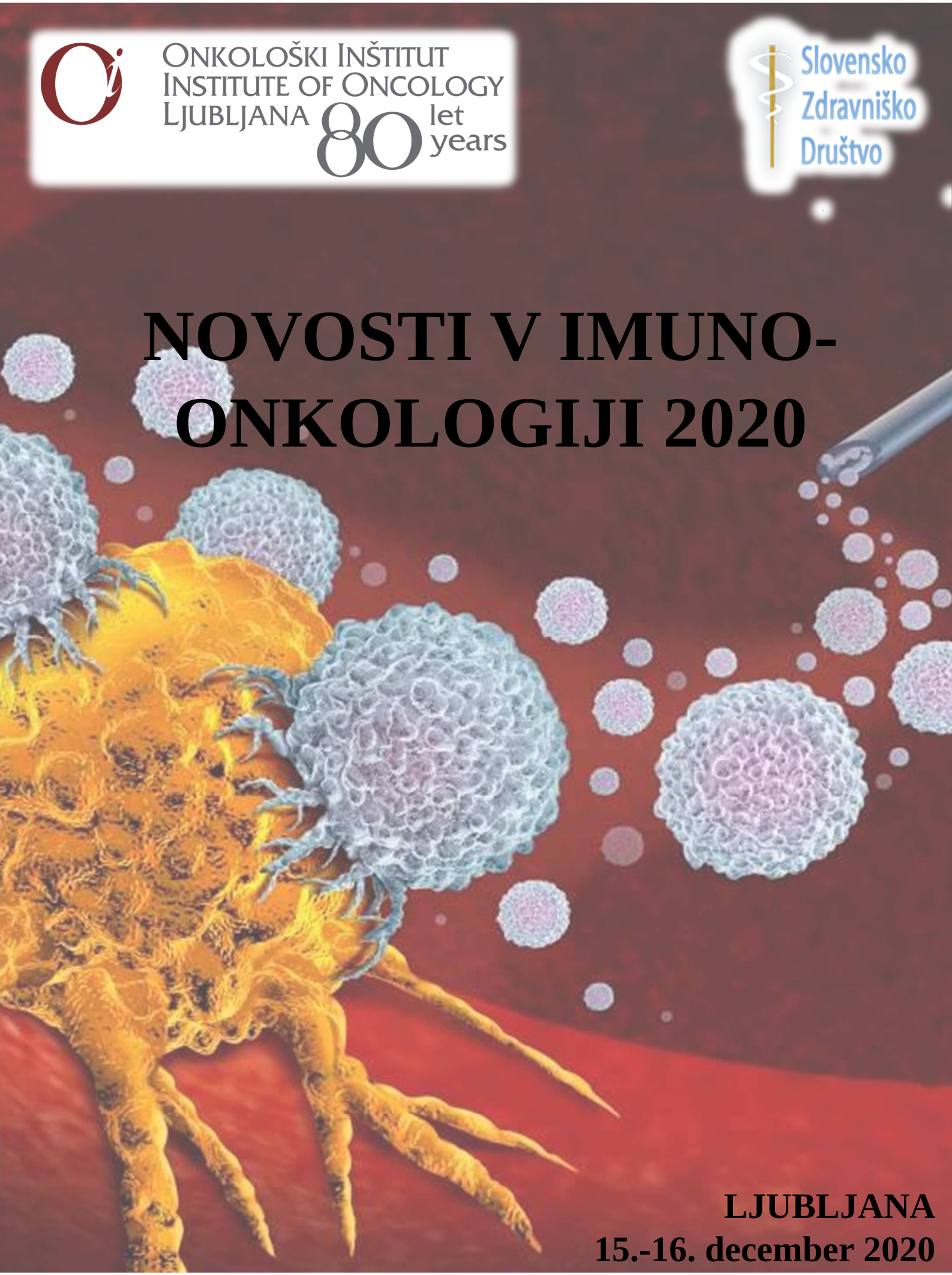
ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA 80 let years

Slovensko Zdravniško Društvo

NOVOSTI V IMUNO-ONKOLOGIJI 2020



LJUBLJANA
15.-16. december 2020

Strokovni odbor:
prof. dr. Janja Ocvirk, dr.med.
doc. dr. Erika Matos, dr.med.
doc. dr. Tanja Mesti, dr.med.

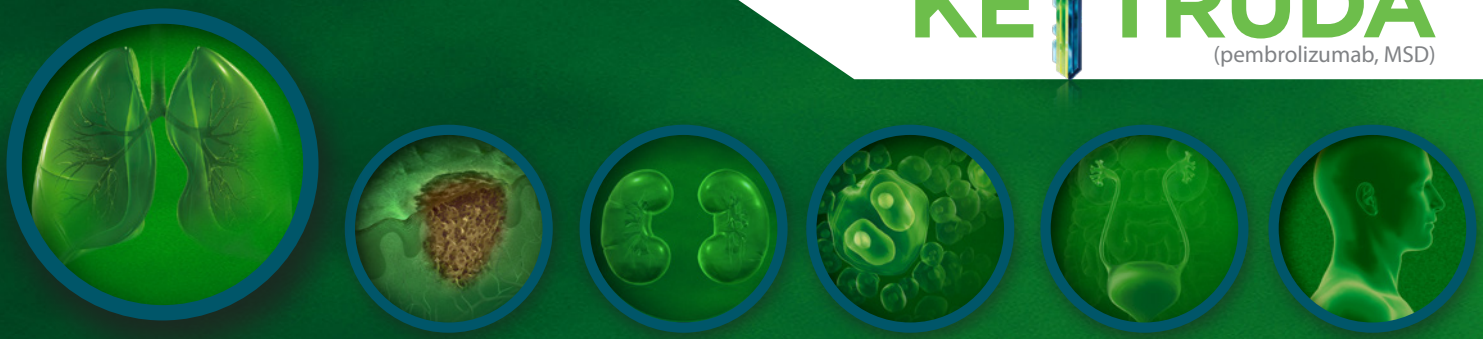
Organizacijski odbor:
prof. dr. Janja Ocvirk, dr.med.
doc. dr. Martina Reberšek, dr.med.
doc. dr. Tanja Mesti, dr.med.
doc. dr. Erika Matos, dr.med.
Marko Boc, dr.med.
Lidija Kristan

Uredniki zbornika:
Marko Boc, dr.med.
prof. dr. Janja Ocvirk, dr.med.
doc. dr. Martina Reberšek, dr.med.

Organizator in izdajatelj (založnik):
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo

Ljubljana, december 2020

KEYTRUDA®
(pembrolizumab, MSD)



Nedrobnocelični pljučni rak[1] | Melanom[1] | Rak ledvičnih celic[1] | Hodgkinov limfom[1] | Urotelijski karcinom[1] | Ploščatocelični karcinom glave in vratu[1]

References: 1. Keytruda EU SmPC

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila!

Ime zdravila: KEYTRUDA 25 mg/ml koncentrat za raztopino za infundiranje vsebuje pembrolizumab.

Terapevtske indikacije: Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za zdravljenje: napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih; za adjuvantno zdravljenje odraslih z melanomom v stadiju III, ki se je razširil na bezgavke, po popolni kirurški odstranitvi; metastatskega nedrobnoceličnega pljučnega raka (NSCLC) v prvi liniji zdravljenja pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS) in brez pozitivnih tumorskih mutacij EGFR ali ALK; lokalno napredovalega ali metastatskega NSCLC pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 (TPS) in so bili predhodno zdravljeni z vsaj eno shemo kemoterapije, bolniki s pozitivnimi tumorskimi mutacijami EGFR ali ALK so pred prejemom zdravila KEYTRUDA morali prejeti tudi tarčno zdravljenje; odraslih bolnikov s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) in zdravljenje z brentuksimabom vedotinom (BV) nista bila uspešna, in odraslih bolnikov, ki za presaditev niso primerni, zdravljenje z BV pa pri njih ni bilo uspešno; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, predhodno zdravljenih s kemoterapijo, ki je vključevala platino; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, ki niso primerni za zdravljenje s kemoterapijo, ki vsebuje cisplatin in imajo tumorje z izraženostjo PD-L1 ≥ 10, ocenjeno s kombinirano pozitivno oceno (CPS); ponovljenega ali metastatskega ploščatoceličnega raka glave in vratu (HNSCC) pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS), in pri katerih je bolezen napredovala med zdravljenjem ali po zdravljenju s kemoterapijo, ki je vključevala platino. Zdravilo KEYTRUDA je kot samostojno zdravljenje ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) indicirano za prvo linijo zdravljenja metastatskega ali neoperabilnega ponovljenega ploščatoceličnega raka glave in vratu pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 1. Zdravilo KEYTRUDA je v kombinaciji s pemetreksedom in kemoterapijo na osnovi platine indicirano za prvo linijo zdravljenja metastatskega neploščatoceličnega NSCLC pri odraslih, pri katerih tumorji nimajo pozitivnih mutacij EGFR ali ALK; v kombinaciji s karboplatinom in bodisi paklitakselom bodisi nab-paklitakselom je indicirano za prvo linijo zdravljenja metastatskega ploščatoceličnega NSCLC pri odraslih; v kombinaciji z aksitinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih. **Odmerjanje in način uporabe**: Testiranje PD-L1 pri bolnikih z NSCLC, urotelijskim rakom ali HNSCC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje izraženosti PD-L1 tumorja z validirano preiskavo, da izberemo bolnike z NSCLC ali predhodno nezdravljenim urotelijskim rakom. Bolnike s HNSCC je treba za samostojno zdravljenje z zdravilom KEYTRUDA ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) izbrati na podlagi izraženosti PD-L1, potrjene z validirano preiskavo. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek za kombinirano zdravljenje je 200 mg na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti sočasno uporabljenih zdravil. Če se uporablja kot del kombiniranega zdravljenja skupaj z intravensko kemoterapijo, je treba zdravilo KEYTRUDA aplicirati prvo. Bolnike je treba zdraviti do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri adjuvantnem zdravljenju melanoma je treba zdravilo uporabljati do ponovitve bolezni, pojava nesprejemljivih toksičnih učinkov oziroma mora zdravljenje trajati do enega leta. Če je aksitinib uporabljen v kombinaciji s pembrolizumabom, se lahko razmisli o povečanju odmerka aksitiniba nad začetnih 5 mg v presledkih šest tednov ali več. Pri bolnikih starih ≥ 65 let, bolnikih z blago do zmerno okvaro ledvic, bolnikih z blago okvaro jeter prilagoditev odmerka ni potrebna. *Odložitev odmerka ali ukinitev zdravljenja*: Zmanjšanje odmerka zdravila KEYTRUDA ni priporočljivo. Za obvladovanje neželenih učinkov je treba uporabo zdravila KEYTRUDA zadržati ali ukiniti, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Kontraindikacije**: Preobčutljivost na učinkovino ali katero koli pomožno snov. **Povzetek posebnih opozoril, previdnostnih ukrepov, interakcij in neželenih učinkov**: Imunsko pogojeni neželeni učinki (pnevmonitis, kolitis, hepatitis, nefritis, endokrinopatije, neželeni učinki na kožo in drugi): Pri bolnikih, ki so prejemali pembrolizumab, so se pojavili imunsko pogojeni neželeni učinki, vključno s hudimi in smrtnimi primeri. Večina imunsko pogojenih neželenih učinkov, ki so se pojavili med zdravljenjem s pembrolizumabom, je bila reverzibilnih in so jih obvladali s prekinitvami uporabe pembrolizumaba, uporabo kortikosteroidov in/ali podporno oskrbo. Pojavijo se lahko tudi po zadnjem odmerku pembrolizumaba in hkrati prizadanejo več organskih sistemov. V primeru suma na imunsko pogojene neželene učinke je treba poskrbeti za ustrezno oceno za potrditev etiologije oziroma izključitev drugih vzrokov. Glede na izrazitost neželenega učinka je treba zadržati uporabo pembrolizumaba in uporabiti kortikosteroide – za natančna navodila, prosimo, glejte Povzetek glavnih značilnosti zdravila Keytruda. Zdravljenje s pembrolizumabom lahko poveča tveganje za zavrnitev pri prejemnikih presadkov čvrstih organov. Pri bolnikih, ki so prejemali pembrolizumab, so poročali o hudih z infuzijo povezanih reakcijah, vključno s preobčutljivostjo in anafilaksijo. Pembrolizumab se iz obtoka odstrani s katabolizmom, zato presnovnih medsebojnih delovanj zdravil ni pričakovati. Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo pembrolizumaba se je treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost pembrolizumaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti za zdravljenje imunsko pogojenih neželenih učinkov. Kortikosteroide je mogoče uporabiti tudi kot premedikacijo, če je pembrolizumab uporabljen v kombinaciji s kemoterapijo, kot antiemetično profilakso in/ali za ublažitev neželenih učinkov, povezanih s kemoterapijo. Ženske v rodni dobi morajo med zdravljenjem s pembrolizumabom in vsaj še 4 mesece po zadnjem odmerku pembrolizumaba uporabljati učinkovito kontracepcijo, med nosečnostjo in dojenjem se ga ne sme uporabljati.

Varnost pembrolizumaba pri samostojnem zdravljenju so v kliničnih študijah ocenili pri 5.884 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom ali HNSCC s štirimi odmerki (2 mg/kg na 3 tedne, 200 mg na 3 tedne in 10 mg/kg na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,3 mesece (v razponu od 1 dneva do 31 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (20 %) in diareja (20 %). Večina poročanih neželenih učinkov pri samostojnem zdravljenju je bila po izrazitosti 1. ali 2. stopnje. Najresnejši neželeni učinki so bili imunsko pogojeni neželeni učinki in hude z infuzijo povezane reakcije. Varnost pembrolizumaba pri kombiniranem zdravljenju s kemoterapijo so ocenili pri 1.067 bolnikih NSCLC ali HNSCC, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg ali 10 mg/kg na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: anemija (50 %), navzea (50 %), utrujenost (37 %), zaprtost (35%), diareja (30 %), nevtropenija (30 %), zmanjšanje apetita (28 %) in bruhanje (25 %). Pri kombiniranem zdravljenju s pembrolizumabom je pri bolnikih z NSCLC pojavnost neželenih učinkov 3. do 5. stopnje znašala 67 %, pri zdravljenju samo s kemoterapijo pa 66 %, pri kombiniranem zdravljenju s pembrolizumabom pri bolnikih s HNSCC 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %. Varnost pembrolizumaba v kombinaciji z aksitinibom so ocenili v klinični študiji pri 429 bolnikih z napredovalim rakom ledvičnih celic, ki so prejemali 200 mg pembrolizumaba na 3 tedne in 5 mg aksitiniba dvakrat na dan. V tej populaciji bolnikov so bili najpogostejši neželeni učinki diareja (54 %), hipertenzija (45 %), utrujenost (38 %), hipotiroidizem (35 %), zmanjšan apetit (30 %), sindrom palmarno-plantarne eritrodisestezije (28 %), navzea (28 %), zvišanje vrednosti ALT (27 %), zvišanje vrednosti AST (26 %), disfonija (25 %), kašelj (21 %) in zaprtost (21 %). Pojavnost neželenih učinkov 3. do 5. stopnje je bila med kombiniranim zdravljenjem s pembrolizumabom 76 % in pri zdravljenju s sunitinibom samim 71 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila

Način in režim izdaje zdravila: H – Predpisovanje in izdaja zdravila je le na recept, zdravilo se uporablja samo v bolnišnicah.

Imetnik dovoljenja za promet z zdravilom: Merck Sharp & Dohme B.V. , Waarderweg 39, 2031 BN Haarlem, Nizozemska.

MSD

Merck Sharp & Dohme inovativna zdravila d.o.o.,
Šmartinska cesta 140, 1000 Ljubljana, tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50
Pripravljeno v Sloveniji, September 2020; SI-KEY-00145 EXP: 09 /2022

Samo za strokovno javnost.

H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila Keytruda, ki je na voljo pri naših strokovnih sodelavcih ali na lokalnem sedežu družbe.

AKTIVNO SODELUJOČI NA SIMPOZIJU NOVOSTI V IMUNO-ONKOLOGIJI 2020:

prof. Alexander Eggermont, PhD, MD, surgical oncologist
General of the Gustave Roussy CCC, Villejuif/Paris-Sud, France

prof. Maximilian J. Hochmair, PhD, MD, pulmonologist
Department of Respiratory and Critical Care Medicine, Vienna North Hospital, Austria

prof. dr. Janja Ocvirk, dr.med., specialistka interne medicine in internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana
Medicinska fakulteta, Univerza v Ljubljani

doc. dr. Cvetka Grašič-Kuhar, dr.med., specialistka interne medicine in internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

doc. dr. Erika Matos, dr.med., specialistka interne medicine in internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

doc. dr. Martina Reberšek, dr.med., specialistka interne medicine in internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

doc. dr. Boštjan Šeruga, dr.med., specialist internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana
Medicinska fakulteta, Univerza v Ljubljani

dr. Breda Škrbinc, dr.med., specialistka interne medicine in internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

mag. Mojca Unk, dr.med., specialistka internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

Marko Boc, dr.med., specialist internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

Marija Ignjatović, dr.med., specialistka internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

Tanja Ovčariček, dr.med., specialistka internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

Nežka Hribernik, dr.med., specialistka internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

Urška Janžič, dr.med., specialistka internistične onkologije
Enota za internistično onkologijo, Univerzitetna klinika Golnik

Marija Ivanović, dr.med., specialistka internistične onkologije
Oddelek za onkologijo, Univerzitetni klinični center Maribor

MODERATORJI SIMPOZIJA:

prof. dr. Janja Ocvirk, dr.med., specialistka interne medicine in internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana
Medicinska fakulteta, Univerza v Ljubljani

doc. dr. Martina Reberšek, dr.med., specialistka interne medicine in internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

dr. Simona Borštnar, dr.med., specialistka interne medicine in internistične onkologije
Sektor internistične onkologije, Onkološki inštitut Ljubljana

Revolucije

zahtevajo strast.

Več kot stoletje postavljamo nove standarde v diagnostiki in zdravljenju številnih bolezni. Danes nam novi viri podatkov in napredna analitika omogočajo, da zagotovimo pravo zdravljenje za pravega bolnika ob pravem času. Zato se povezujemo s tistimi, ki stremijo k istemu cilju in razumejo, da nova znanja služijo ne samo znanosti, temveč predvsem človeštvu.

M-SI-00000051(v2.0)

Informacija pripravljena: september 2020.
DODATNE INFORMACIJE SO NA VOLJO PRI: Roche farmacevtska družba d.o.o., Stegne 13g, 1000 Ljubljana.

TOREK, 15. 12. 2020

Moderator: prof. dr. Janja Ocvirk, dr. med., doc. dr. Martina Reberšek, dr. med.

14.00 - 14.30 Popotnica novostim v imuno-onkologiji 2020
prof. dr. Janja Ocvirk, dr. med.

14.30 - 16.00 Novosti pri zdravljenju melanoma

Letni napredek
Marko Boc, dr. med.

Razprava v obliki panela: napredek in izkušnje v Sloveniji
Marko Boc, dr. med., doc. dr. Martina Reberšek, dr. med., doc. dr. Tanja Mesti, dr. med., prof. dr. Janja Ocvirk, dr. med.

Izkušnje iz tujine
prof. Alexander Eggermont

16.00 - 18.00 Novosti pri kožnih rakih
prof. dr. Janja Ocvirk, dr. med.

Novosti pri zdravljenju rakov hepatobiliarnega sistema
prof. dr. Janja Ocvirk, dr. med., Marija Ignjatović, dr. med.

Novosti pri zdravljenju raka požiralnika, želodca in kolorektalnega raka
doc. dr. Tanja Mesti, dr. med., Nežka Hribernik, dr. med.

Novosti pri biomarkerjih v imuno-onkologiji
doc. dr. Martina Reberšek, dr. med.

Imunoterapija za agnostično zdravljenje raka
Tanja Ovčariček, dr. med.

Razprava

SREDA, 16. 12. 2020

Moderator: dr. Simona Borštnar, dr. med.

14.00 - 15.30 Novosti pri pljučnem raku 2020

Letni napredek
mag. Mojca Unk, dr. med.

Razprava v obliki panela: napredek in izkušnje v Sloveniji
mag. Mojca Unk, dr. med., Urška Janžič, dr. med., Marija Ivanović, dr. med.

Izkušnje iz tujine
dr. Maximilian Hochmair

15.30 – 17.00 **Novosti pri raku dojke**
doc. dr. Erika Matos, dr. med.

Novosti pri raku sečnega mehurja
dr. Breda Škrbinc, dr. med.

Novosti pri raku ledvice
doc. dr. Boštjan Šeruga, dr. med.

Novosti pri zdravljenju raka glave in vratu
doc. dr. Cvetka *Grašič Kuhar, dr. med.*

Razprava

ZLATA SPONZORJA DOGODKA:

Merck Sharp & Dohme inovativna zdravila d.o.o.

Roche, farmacevtska družba d.o.o.

MEDIJSKI SPONZOR DOGODKA:

AdriaSonara d.o.o.
upravljalec spletnega mesta

KAZALO

Zdravilo KEYTRUDA® kot samostojno zdravljenje

OMOGOČA VEČ ČASA

Q6W - samo 9 infuzij letno*

ODMERJANJE NA 6 TEDNOV: MANJ INFUZIJ ZA VAŠE BOLNIKE, VEČ ČASA ZA VAS!

*Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah.[1]

KEYTRUDA®
Pembrolizumab, MSD

Q3W = vsake 3 tedne; Q6W = vsakih 6 tednov

Referenca: 1. Keytruda EU SmPC

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila!
Ime zdravila: KEYTRUDA 25 mg/ml koncentrat za raztopino za infundiranje vsebuje pembrolizumab.
Terapevtske indikacije: Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za zdravljenje: napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih; za adjuvantno zdravljenje odraslih z melanomom v stadiju III, ki se je razširil na bezgavke, po popolni kirurški odstranitvi; metastatskega nedrobnoceličnega pljučnega raka (NSCLC) v prvi liniji zdravljenja pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS) in brez pozitivnih tumorskih mutacij EGFR ali ALK; lokalno napredovalega ali metastatskega NSCLC pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 (TPS) in so bili predhodno zdravljeni z vsaj eno shemo kemoterapije, bolniki s pozitivnimi tumorskimi mutacijami EGFR ali ALK so pred prejemom zdravila KEYTRUDA morali prejeti tudi tarčno zdravljenje; odraslih bolnikov s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) in zdravljenje z brentuksimabom vedotinom (BV) nista bila uspešna, in odraslih bolnikov, ki za presaditev niso primerni, zdravljenje z BV pa pri njih ni bilo uspešno; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, predhodno zdravljenih s kemoterapijo, ki je vključevala platino; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, ki niso primerni za zdravljenje s kemoterapijo, ki vsebuje cisplatin in imajo tumorje z izraženostjo PD-L1 ≥ 10, ocenjeno s kombinirano pozitivno oceno (CPS); ponovljenega ali metastatskega ploščatoceličnega raka glave in vratu (HNSCC) pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS), in pri katerih je bolezen napredovala med zdravljenjem ali po zdravljenju s kemoterapijo, ki je vključevala platino. Zdravilo KEYTRUDA je kot samostojno zdravljenje ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) indicirano za prvo linijo zdravljenja metastatskega ali neoperabilnega ponovljenega ploščatoceličnega raka glave in vratu pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 1. Zdravilo KEYTRUDA je v kombinaciji s pemetreksedom in kemoterapijo na osnovi platine indicirano za prvo linijo zdravljenja metastatskega neploščatoceličnega NSCLC pri odraslih, pri katerih tumorji nimajo pozitivnih mutacij EGFR ali ALK; v kombinaciji s karboplatinom in bodisi paklitakselom bodisi nab-paklitakselom je indicirano za prvo linijo zdravljenja metastatskega ploščatoceličnega NSCLC pri odraslih; v kombinaciji z aksitinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih. **Odmerjanje in način uporabe**: Testiranje PD-L1 pri bolnikih z NSCLC, urotelijskim rakom ali HNSCC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje izraženosti PD-L1 tumorja z validirano preiskavo, da izberemo bolnike z NSCLC ali predhodno nezdravljenim urotelijskim rakom. Bolnike s HNSCC je treba za samostojno zdravljenje z zdravilom KEYTRUDA ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) izbrati na podlagi izraženosti PD-L1, potrjene z validirano preiskavo. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek za kombinirano zdravljenje je 200 mg na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti sočasno uporabljenih zdravil. Če se uporablja kot del kombiniranega zdravljenja skupaj z intravensko kemoterapijo, je treba zdravilo KEYTRUDA aplicirati prvo. Bolnike je treba zdraviti do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri adjuvantnem zdravljenju melanoma je treba zdravilo uporabljati do ponovitve bolezni, pojava nesprejemljivih toksičnih učinkov oziroma mora zdravljenje trajati do enega leta. Če je aksitinib uporabljen v kombinaciji s pembrolizumabom, se lahko razmisli o povečanju odmerka aksitiniba nad začetnih 5 mg v presledkih šest tednov ali več. Pri bolnikih starih ≥ 65 let, bolnikih z blago do zmerno okvaro ledvic, bolnikih z blago okvaro jeter prilagoditev odmerka ni potrebna. *Odložitev odmerka ali ukinitev zdravljenja*: Zmanjšanje odmerka zdravila KEYTRUDA ni priporočljivo. Za obvladovanje neželenih učinkov je treba uporabo zdravila KEYTRUDA zadržati ali ukiniti, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Kontraindikacije**: Preobčutljivost na učinkovino ali katero koli pomožno snov. **Povzetek posebnih opozoril, previdnostnih ukrepov, interakcij in neželenih učinkov**: Imunsko pogojeni neželeni učinki (pnevmonitis, kolitis, hepatitis, nefritis, endokrinopatije, neželeni učinki na kožo in drugi): Pri bolnikih, ki so prejemali pembrolizumab, so se pojavili imunsko pogojeni neželeni učinki, vključno s hudimi in smrtnimi primeri. Večina imunsko pogojenih neželenih učinkov, ki so se pojavili med zdravljenjem s pembrolizumabom, je bila reverzibilnih in so jih obvladali s prekinitvami uporabe pembrolizumaba, uporabo kortikosteroidov in/ali podporno oskrbo. Pojavijo se lahko tudi po zadnjem odmerku pembrolizumaba in hkrati prizadanejo več organskih sistemov. V primeru suma na imunsko pogojene neželene učinke je treba poskrbeti za ustrezno oceno za potrditev etiologije oziroma izključitev drugih vzrokov. Glede na izrazitost neželenega učinka je treba zadržati uporabo pembrolizumaba in uporabiti kortikosteroide – za natančna navodila, prosimo, glejte Povzetek glavnih značilnosti zdravila Keytruda. Zdravljenje s pembrolizumabom lahko poveča tveganje za zavrnitev pri prejemnikih presadkov čvrstih organov. Pri bolnikih, ki so prejemali pembrolizumab, so poročali o hudih z infuzijo povezanih reakcijah, vključno s preobčutljivostjo in anafilaksijo. Pembrolizumab se iz obtoka odstrani s katabolizmom, zato presnovnih medsebojnih delovanj zdravil ni pričakovati. Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo pembrolizumaba se je treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost pembrolizumaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti za zdravljenje imunsko pogojenih neželenih učinkov. Kortikosteroide je mogoče uporabiti tudi kot premedikacijo, če je pembrolizumab uporabljen v kombinaciji s kemoterapijo, kot antiemetično profilakso in/ali za ublažitev neželenih učinkov, povezanih s kemoterapijo. Ženske v rodni dobi morajo med zdravljenjem s pembrolizumabom in vsaj še 4 mesece po zadnjem odmerku pembrolizumaba uporabljati učinkovito kontracepcijo, med nosečnostjo in dojenjem se ga ne sme uporabljati.
Varnost pembrolizumaba pri samostojnem zdravljenju so v kliničnih študijah ocenili pri 5.884 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom ali HNSCC s štirimi odmerki (2 mg/kg na 3 tedne, 200 mg na 3 tedne in 10 mg/kg na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,3 mesece (v razponu od 1 dneva do 31 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (20 %) in diareja (20 %). Večina poročanih neželenih učinkov pri samostojnem zdravljenju je bila po izrazitosti 1. ali 2. stopnje. Najresnejši neželeni učinki so bili imunsko pogojeni neželeni učinki in hude z infuzijo povezane reakcije. Varnost pembrolizumaba pri kombiniranem zdravljenju s kemoterapijo so ocenili pri 1.067 bolnikih NSCLC ali HNSCC, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg ali 10 mg/kg na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: anemija (50 %), navzea (50 %), utrujenost (37 %), zaprtost (35%), diareja (30 %), nevtropenija (30 %), zmanjšanje apetita (28 %) in bruhanje (25 %). Pri kombiniranem zdravljenju s pembrolizumabom je pri bolnikih z NSCLC pojavnost neželenih učinkov 3. do 5. stopnje znašala 67 %, pri zdravljenju samo s kemoterapijo pa 66 %, pri kombiniranem zdravljenju s pembrolizumabom pri bolnikih s HNSCC 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %. Varnost pembrolizumaba v kombinaciji z aksitinibom so ocenili v klinični študiji pri 429 bolnikih z napredovalim rakom ledvičnih celic, ki so prejemali 200 mg pembrolizumaba na 3 tedne in 5 mg aksitiniba dvakrat na dan. V tej populaciji bolnikov so bili najpogostejši neželeni učinki diareja (54 %), hipertenzija (45 %), utrujenost (38 %), hipotiroidizem (35 %), zmanjšan apetit (30 %), sindrom palmarno-plantarne eritrodisestezije (28 %), navzea (28 %), zvišanje vrednosti ALT (27 %), zvišanje vrednosti AST (26 %), disfonija (25 %), kašelj (21 %) in zaprtost (21 %). Pojavnost neželenih učinkov 3. do 5. stopnje je bila med kombiniranim zdravljenjem s pembrolizumabom 76 % in pri zdravljenju s sunitinibom samim 71 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila
Način in režim izdaje zdravila: H – Predpisovanje in izdaja zdravila je le na recept, zdravilo se uporablja samo v bolnišnicah.
Imetnik dovoljenja za promet z zdravilom: Merck Sharp & Dohme B.V. , Waarderweg 39, 2031 BN Haarlem, Nizozemska.

MSD

Merck Sharp & Dohme inovativna zdravila d.o.o.,
Šmartinska cesta 140, 1000 Ljubljana, tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50
Pripravljeno v Sloveniji, December 2020; SI-KEY-00178 EXP: 12/2022
Samo za strokovno javnost.
H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila Keytruda, ki je na voljo pri naših strokovnih sodelavcih ali na lokalnem sedežu družbe.

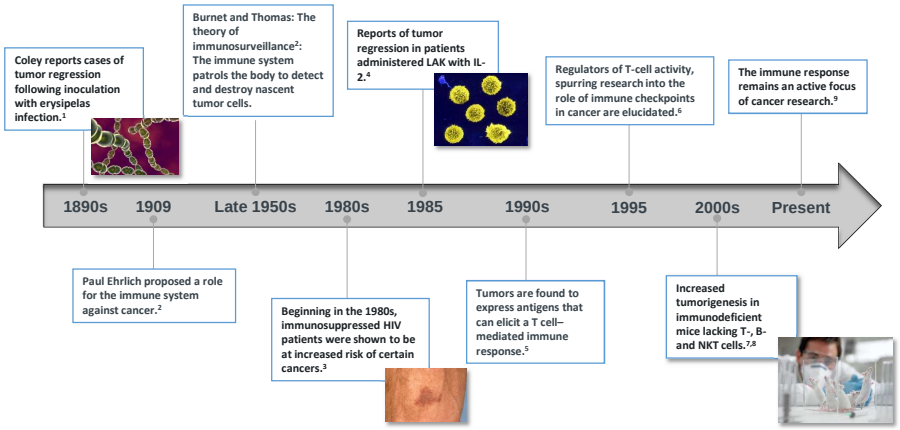
Popotnica novostim v imunoonkologiji 2020

Prof.dr.Janja Ocvirk, dr.med.

Ljubljana, 15.12.2020

Immunotherapy Marks a New Era in Our Fight Against cancer

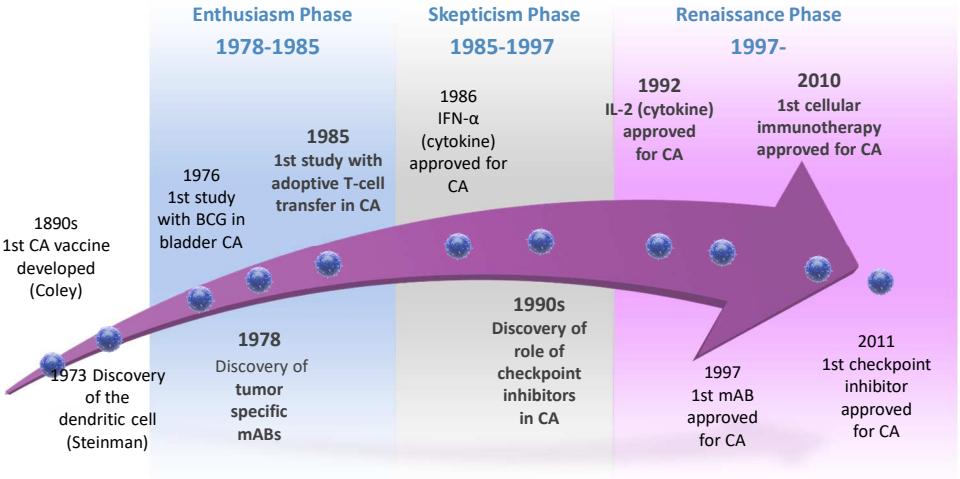
What Have We Learned About the Role of the Immune System in Oncology?



HIV = human immunodeficiency virus; LAK = lymphokine-activated killer; IL-2 = interleukin-2; NKT = natural killer T.

1. Coley WB. *Am J Med Sci.* 1893;105:487–511. **2.** Ichim CV. *J Transl Med.* 20058;3:8. **3.** Levine AM et al. *Curr Probl Cancer.* 1987;11:209–55. **4.** Rosenberg SA et al. *N Engl J Med.* 1985;313:1485–1492. **5**. van der Bruggen P et al. *Science*. 1991;254:1643–1647. **6.** Tivol EA. et al. *Immunity*. 1995;3:541–547. **7**. Vesely MD et al. *Annu Rev Immunol.* 2011;29:235–271. **8.** Shankaran V. et al. *Nature.* 2001;410:1107–1111. **9**. Drake CG *et al. Nat. Rev. Clin. Oncol.* 2014;11: 24–37.

History of Immunotherapy1-5

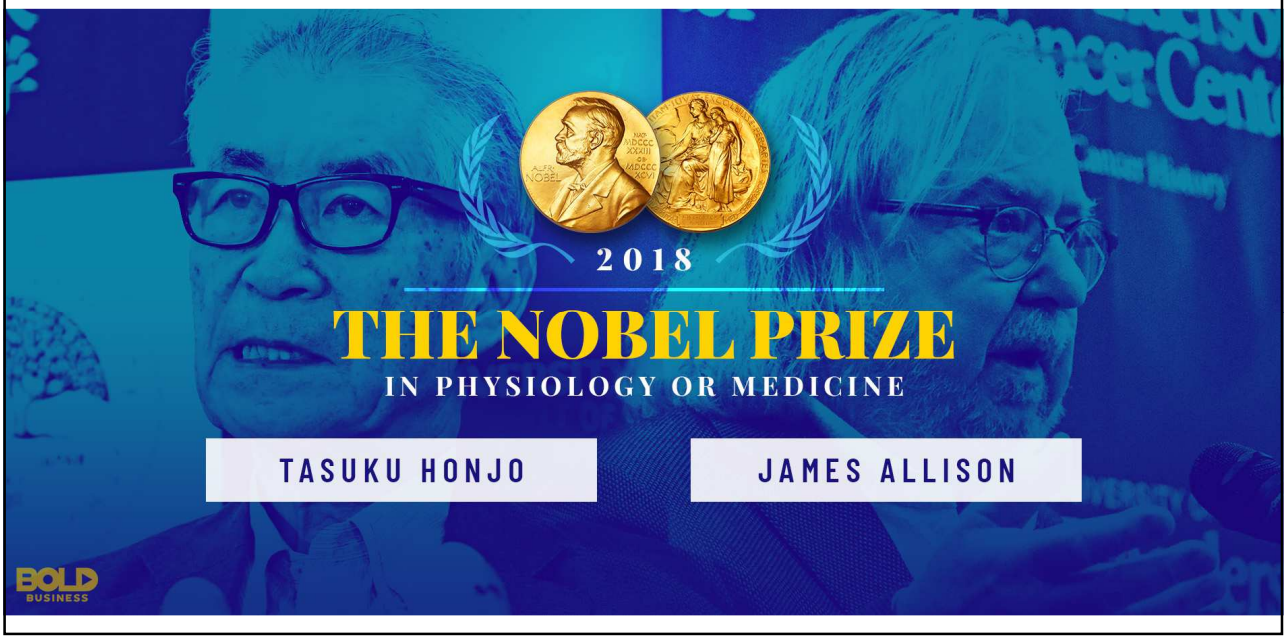


Adapted with permission from Lesterhuis WJ, et al[2] and Kirkwood JM, et al. *J Clin Oncol*. 2008;26(20):3445-3455.

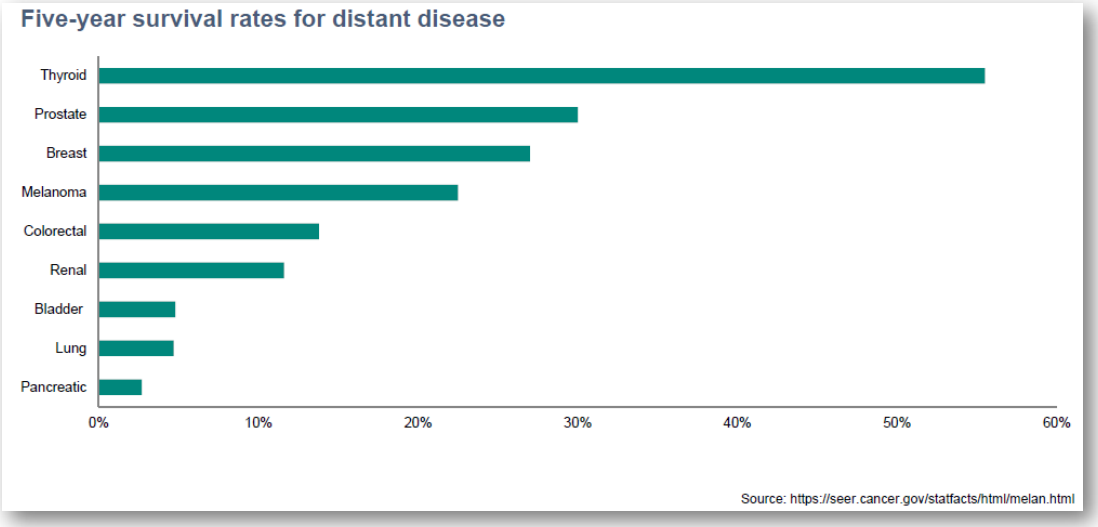
BCG, Bacille Calmette-Guerin; mABs, monoclonal antibodies; CA, cancer; IFN-α, interferon alpha; IL-2, interleukin-2

1. Kirkwood JM, Ferrone S, et al. *CA Cancer J Clin*. 2012;62(5):309-335.
2. Lesterhuis WJ, Punt CJ, et al. *Nat Rev Drug Discov*. 2011;10(8):591-600.
3. Krummel MF, Allison JP. *J Exp Med*. 1995;182(2):459-465.
4. Lotze M. In: *Cancer: Principles & Practice of Oncology*. 9th ed. 2011.
5. Leget GA, Czuczman MS. *Curr Opin Oncol*. 1998;10(6):548-551.

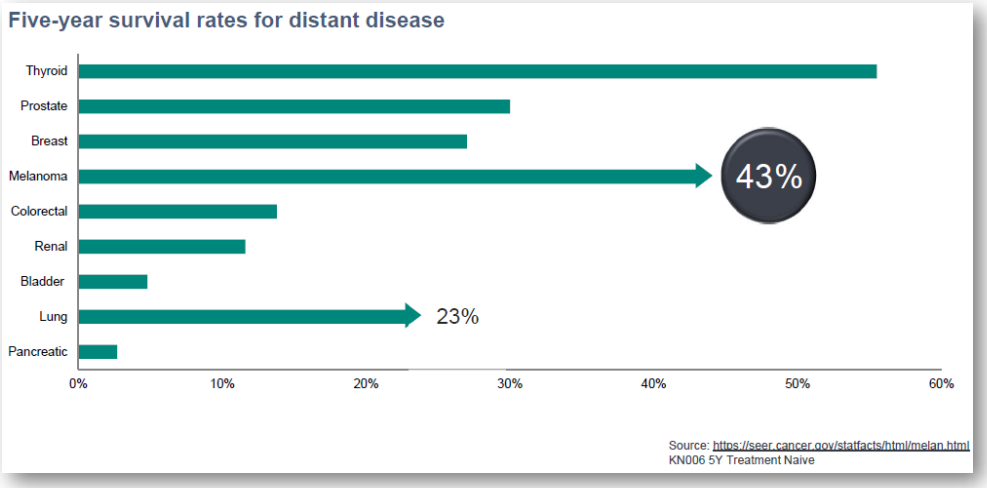
Inhibitorji nadzornih točk- imunoterapija: anti-PD1 and anti-CTLA4



Other than Thyroid, Survival Rates in StIV remain Low (Pre-I/O)



CPIs are transforming cancer outcomes

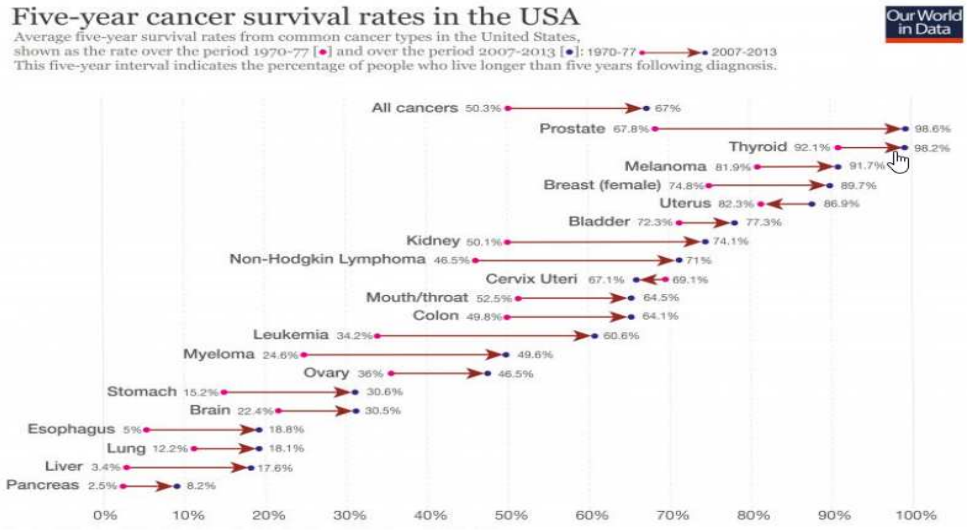


Survival rates for cancer (in any stage) are generally increasing

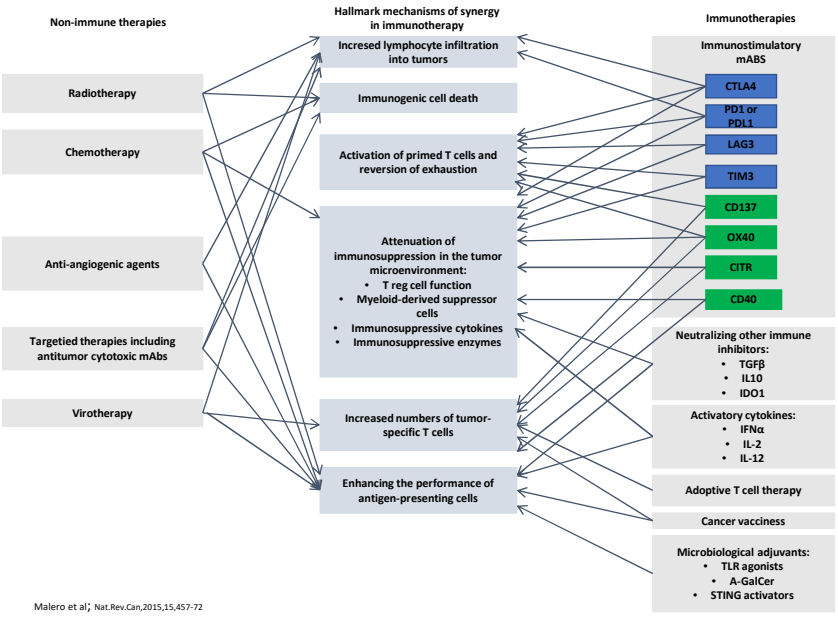
5-year Relative Survival from SEER database

	All Sites	Colon & Rectum	Breast	Lung Cancer
1990-1992	59.9%	61.2%	85.2%	14.0%
1993-1995	61.3%	59.9%	86.3%	14.5%
1996-1998	63.3%	62.4%	88.2%	14.8%
1999-2001	66.0%	65.2%	89.7%	15.5%
2002-2004	67.1%	65.8%	89.9%	16.5%
2005-2008	68.7%	66.7%	90.8%	18.5%
2009-2015	69.3%	66.2%	91.3%	20.7%

Not all cancer sites enjoy the ride of success



Synergy with immunotherapy



Malero et al; Nat.Rev.Can,2015,15,457-72

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Review

Rationally combining immunotherapies to improve efficacy of immune checkpoint blockade in solid tumors

Floris Dammeijer[a,b,1], Sai Ping Lau[b,c,1], Casper H.J. van Eijck[c], Sjoerd H. van der Burg[d], Joachim G.J.V. Aerts[a,b,*]

[a] Department of Pulmonary Medicine, Erasmus Medical Center Rotterdam, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
[b] Erasmus MC Cancer Institute, Erasmus Medical Center Rotterdam, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
[c] Department of Surgery, Erasmus Medical Center Rotterdam, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
[d] Department of Clinical Oncology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands

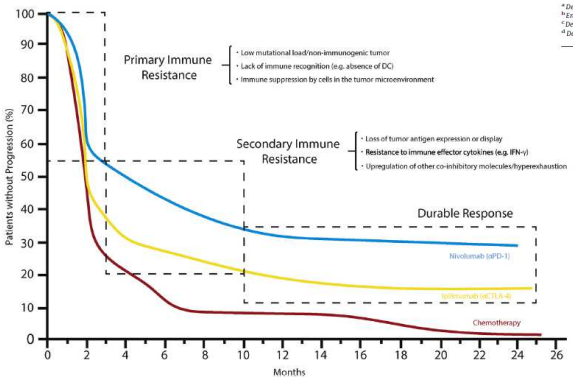
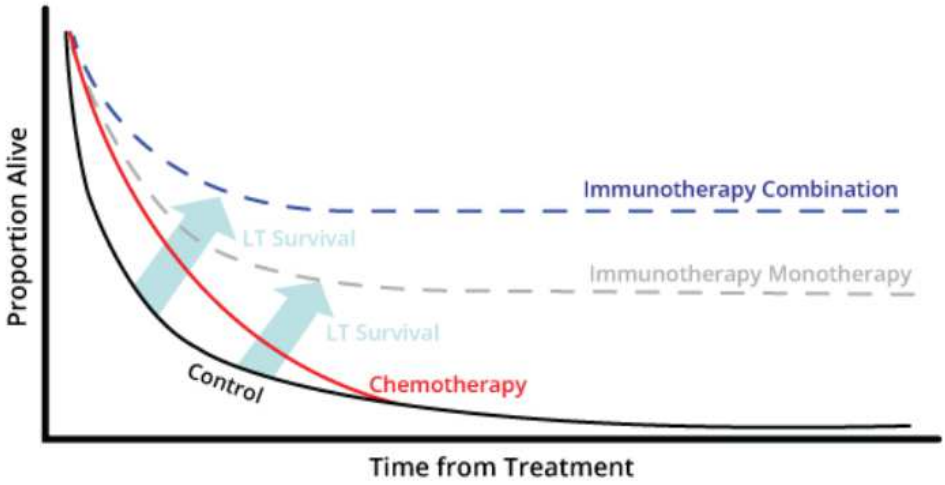


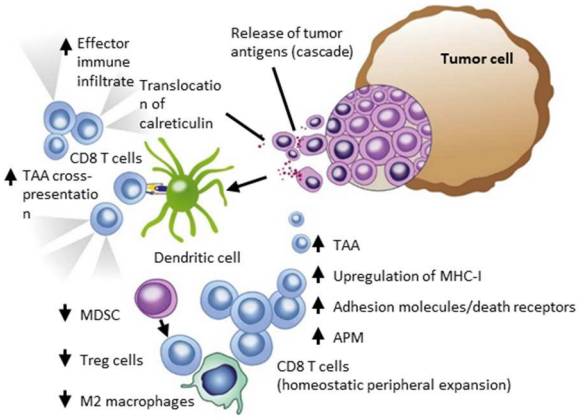
Fig. 1. Progression-free survival curves for chemotherapy, anti-PD-1- and anti-CTLA-4- checkpoint blockers; primary and secondary resistance to immune checkpoint blockade (ICB) therapy precludes patients from achieving durable responses and long-term survival. When patients do not respond to ICBs immediately following start of treatment they experience primary immune resistance. When patients do respond initially but relapse over time, secondary resistance to ICB-treatment has developed. PFS-curves have been derived from the following clinical trials investigating ICB-efficacy in metastatic melanoma: Robert et al. NEJM 2011, Schachter et al. ASCO #9504 2016.



https://obroncology.com/article/accc-iclio-navigating-the-future-of-immuno-oncology-and-whos-going-to-pay-for-it-2/3/

The rationale: CT + Immunotherapy

- **Combining therapies with different mechanisms of action may increase their potential efficacy against tumor cells[1]**
- **Both chemotherapy and immunotherapy have well-established activity in a broad** range of patients[1]
- **Certain chemotherapies have been shown to have immunogenic effects, and may act synergistically with immunotherapy to enhance the tumor killing effect of both agents[2–6]**
- **Combining these as first-line treatment ensures patients receive the potential benefits of these therapies without the "attrition" of patients who clinically decline and may not be able to receive potentially effective treatments[5]**
- **Combinations of immunotherapy agents may lead to additive or synergistic effects and prolonged benefit in a subset of patients with NSCLC**



1. Emens LA, Middleton G. *Cancer Immunol Res*. 2013;3(5):436–443. **2.** Hodge JW et al. *Semin Oncol*. 2012;39:323–339. **3.** Gelbard A et al. *Clin Cancer Res*. 2016;12(6):1897–1905. **4.** Tanaka H et al. *Cancer Res*. 2009;69(17): 6978–6986. **5.** McDonnell AM et al. *Eur J Immunol*. 2015;45(1):49–59. **6.** Lesterhuis WJ et al. *J Clin Invest*. 2011;121(8):3100–3108.

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

Leena Gandhi, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Shirish Gadgeel, M.B., B.S., Emilio Esteban, M.D., Enriqueta Felip, M.D., Ph.D., Flávia De Angelis, M.D., Manuel Domine, M.D., Ph.D., Philip Clingan, M.B., B.S., Maximilian J. Hochmair, Ph.D., Steven F. Powell, M.D., Susanna Y.-S. Cheng, M.D., Helge G. Bischoff, M.D., et al., for the KEYNOTE-189 Investigators*

Article Figures/Media Metrics

May 31, 2018
N Engl J Med 2018; 378:2078-2092
DOI: 10.1056/NEJMoa1801005

Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with *EGFR* mutations or baseline liver metastases in a randomised, open-label phase 3 trial

*Martin Reck, Tony S K Mok, Makoto Nishio, Robert M Jotte, Federico Cappuzzo, Francisco Orlandi, Daniil Stroyakovskiy, Naoyuki Nogami, Delvys Rodríguez-Abreu, Denis Moro-Sibilot, Christian A Thomas, Fabrice Barlesi, Gene Finley, Anthony Lee, Shelley Coleman, Yu Deng, Marcin Kowanetz, Geetha Shankar, Wei Lin, Mark A Socinski, for the IMpower150 Study Group**

15

Rationale for combination – ICI + Anti VEGF

- Hypoxia resulting from altered blood supply support malignant cell escape from immune surveillance and impairs the function of immune effector cells
- Activation of hypoxia-inducible factor 1 alpha upregulates PD-L1 expression in cancer and immune cells
- Hypoxia may result from antiangiogenic therapies too. PD-L1 is preferentially expressed in hypoxic areas, and this can be a key factors in triggering immune evasion
- Production of VEGF in response to the hypoxic state can exert immunosuppressive effects
- Anti VEGF strategies improve tumor specific T cell activity, alleviating tumor hypoxia could improve the outcomes achieved with immune checkpoint inhibitors

Faivre s. et al.J Hepatol. 2020;72:342-352

Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

Ann-Lii Cheng,[1] Shukui Qin,[2] Masafumi Ikeda,[3] Peter R. Galle,[4] Michel Ducreux,[5] Andrew X. Zhu,[6] Tae-You Kim,[7] Masatoshi Kudo,[8] Valeriy Breder,[9] Philippe Merle,[10] Ahmed Kaseb,[11] Daneng Li,[12] Wendy Verret,[13] Derek-Zhen Xu,[14] Sairy Hernandez,[13] Juan Liu,[14] Chen Huang,[14] Sohail Mulla,[15] Ho Yeong Lim,[16] Richard S. Finn[17]

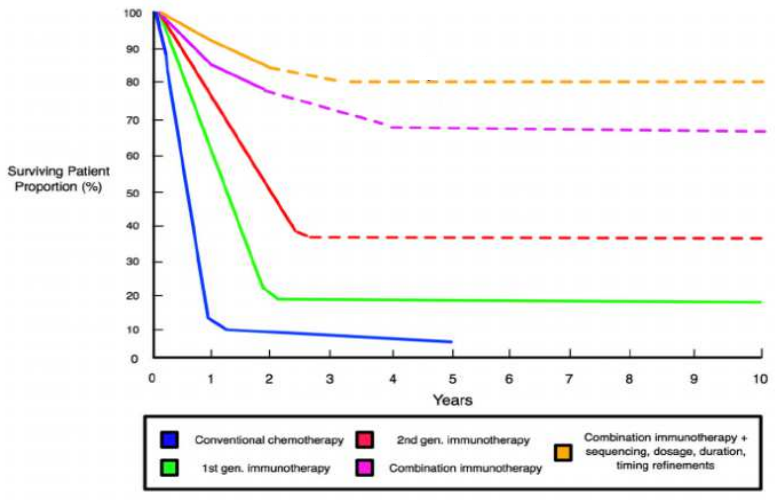
[1]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [2]People's Liberation Army Cancer Center, Jinling Hospital, Nanjing, People's Republic of China; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]University Medical Center Mainz, Mainz, Germany; [5]Gustave Roussy Cancer Center, Villejuif, France; [6]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Seoul National University College of Medicine, Seoul, Korea; [8]Kindai University Faculty of Medicine, Osaka, Japan; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Hospital La Croix-Rousse, Lyon, France;
[11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [13]Genentech, Inc., South San Francisco, CA, USA; [14]Roche Product Development, Shanghai, People's Republic of China; [15]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [17]Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

- The ability to pharmacologically modulate key signaling pathways that drive tumor growth and progression, but do not negatively impact the function of lymphocytes, provides avenues for rational combinatorial approaches to improve the antitumor activity of tumor immunotherapies.
- combining immunotherapy and BRAF-targeted therapies might elicit synergy of effect

Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAF*^{V600} mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial

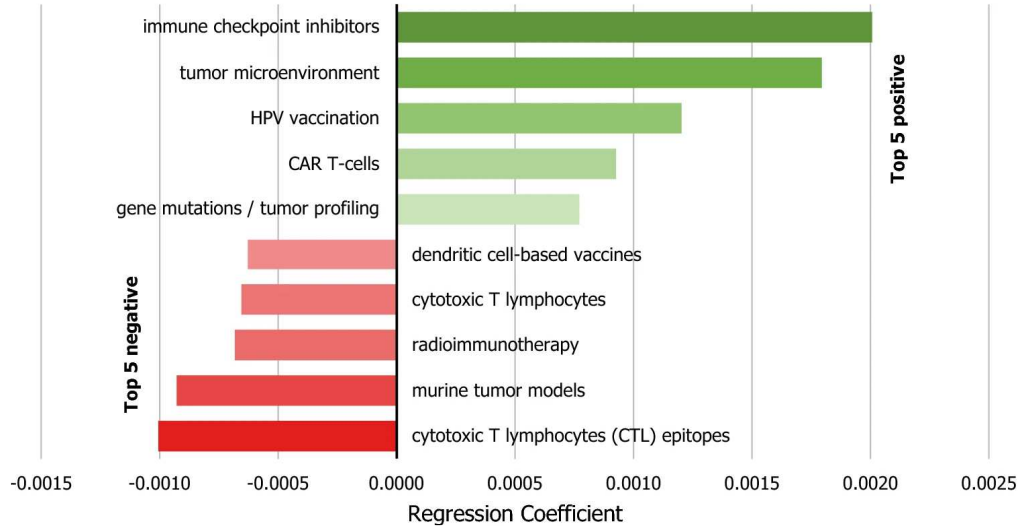
Ralf Gutzmer, Daniil Stroyakovskiy, Helen Gogas, Caroline Robert, Karl Lewis, Svetlana Protsenko, Rodrigo P Pereira, Thomas Eigentler, Piotr Rutkowski, Lev Demidov, Georgy Moiseevich Manikhas, Yibing Yan, Kuan-Chieh Huang, Anne Uyei, Virginia McNally, Grant A McArthur, Paolo A Ascierto**

Correlation of patient survival with different therapies



Frontiers in Oncology, August 2018. Volume 8. Article 315

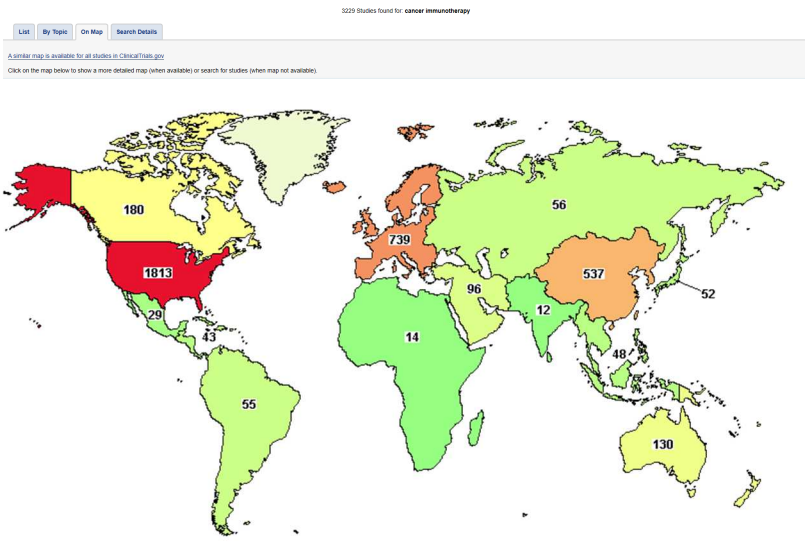
Top five research topics with the higher positive and negative trends



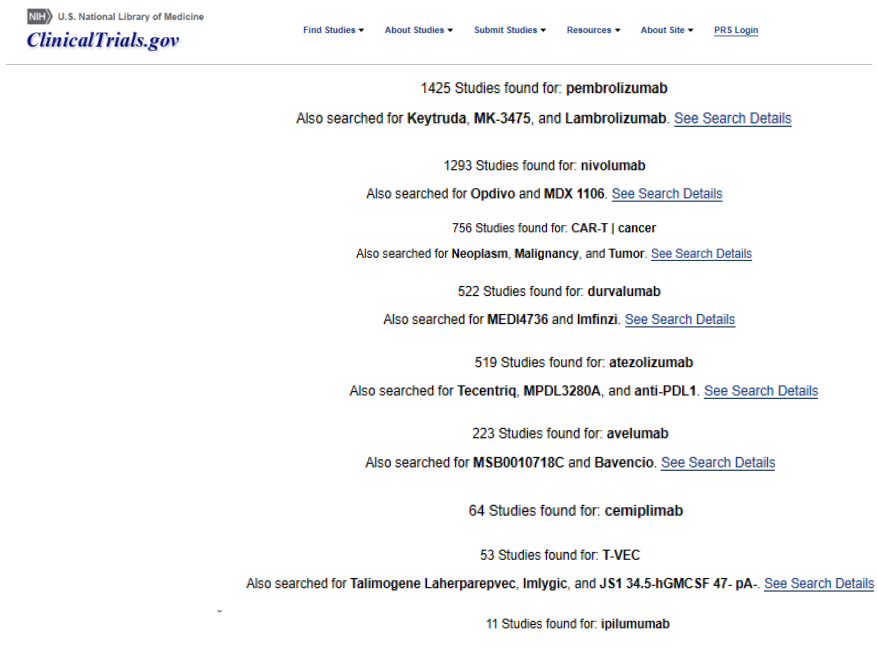
Pouliliou, S., Nikolaidis, C. & Drosatos, G. Current trends in cancer immunotherapy: a literature-mining analysis. *Cancer Immunol Immunother* **69,** 2425–2439 (2020). https://doi.org/10.1007/s00262-020-02630-8

3.226 Immunooncology trials on 10.12.2020

Terms Synonyms	Search Results*	Entire Database**
cancer immunotherapy	273 studies	273 studies
Immuno-Chemotherapy	105 studies	105 studies
Immunotherapy for cancer	14 studies	14 studies
immunotherapy cancer	1 studies	1 studies
immunotherapy	3,146 studies	4,996 studies
immunomodulator	35 studies	212 studies
Immunotherapeutic Agent	24 studies	34 studies
Immunomodulatory Agent	22 studies	90 studies
Immune Modulators	16 studies	61 studies
Biological Response Modifiers	7 studies	16 studies
Immunomodulating Agent	6 studies	21 studies
Immune Mediators	5 studies	21 studies
Immunological therapy	5 studies	7 studies
Immune Regulators	4 studies	14 studies
Biomodulators	3 studies	8 studies
Immunologically Directed Therapy	3 studies	3 studies
Immunopotentiators	2 studies	2 studies
cancer	3,226 studies	88,647 studies



https://www.clinicaltrials.gov/ct2/results/map?term=cancer+immunotherapy&map=



www.ClinicalTrials.gov 10. Dec 2020

Key clinical highlights of I-O from virtual ESMO 2020

GI

KN177 (QoL data) , KN590 (1st in ESCC), CM649 (1st in Gastric Cancer – compete with KN590), CM577 (Adjuvant and 1 line earlier then KN590)

Lung

KN024 (5 yr OS), EMPOWER 1, CM816

Melanoma

KN54, LEAP 004, CM238, COMBI-AD

TNBC

IM 131 (T + N PAC) final OS shows 7.5-mo median OS improvement (clinically meaningful)
IM131 (T+ PAC) failed trial
IM031 (Neoadj) significantly improved pCR rates in ITT (Δ=16.5%) regardless PD- L1 status

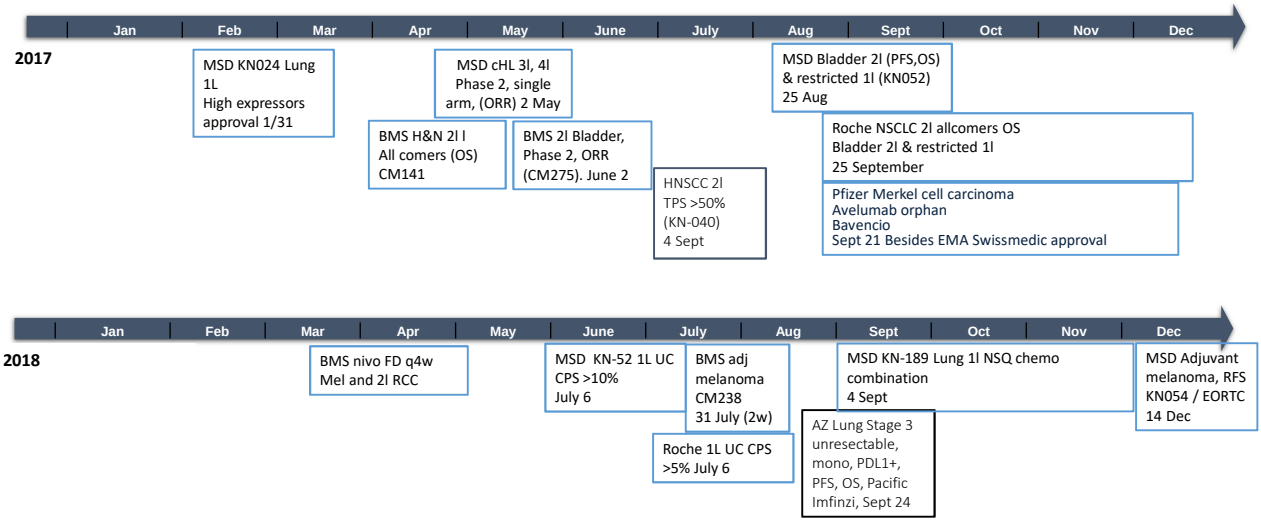
RCC

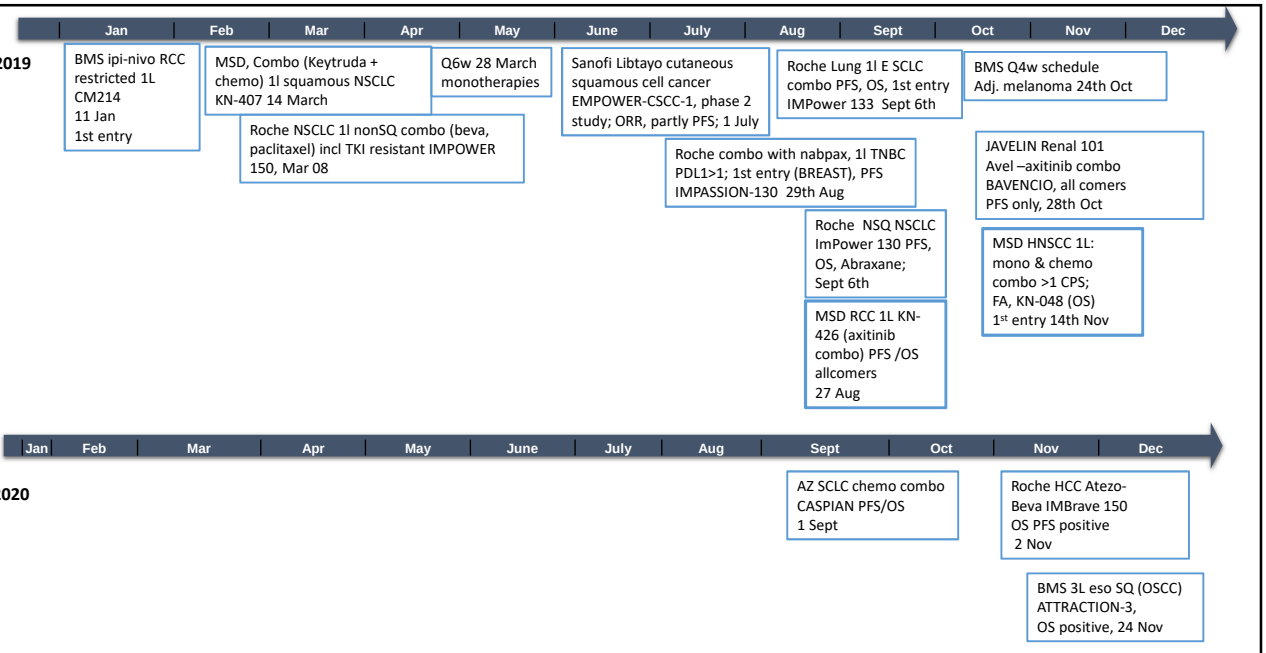
MK6482, KN146, CM9ER

UC & Prostate

KN361, IPATential (Ipatasertib)

Cancer Imunotherapy EMA appovals 2017-2020





Pri zdravljenju adjuvantnega melanoma

JE LEPO DOSEČI TRAJNO REMISIJO

Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za adjuvantno zdravljenje odraslih z melanomom v stadiju III, ki se je razširil na bezgavke, po popolni kirurški odstranitvi.[1]

KEYTRUDA®
(pembrolizumab, MSD)

Referenca: 1. Keytruda EU SmPC

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila!
Ime zdravila: KEYTRUDA 25 mg/ml koncentrat za raztopino za infundiranje vsebuje pembrolizumab.
Terapevtske indikacije: Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za zdravljenje: napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih; za adjuvantno zdravljenje odraslih z melanomom v stadiju III, ki se je razširil na bezgavke, po popolni kirurški odstranitvi; metastatskega nedrobnoceličnega pljučnega raka (NSCLC) v prvi liniji zdravljenja pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS) in brez pozitivnih tumorskih mutacij EGFR ali ALK; lokalno napredovalega ali metastatskega NSCLC pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 (TPS) in so bili predhodno zdravljeni z vsaj eno shemo kemoterapije, bolniki s pozitivnimi tumorskimi mutacijami EGFR ali ALK so pred prejemom zdravila KEYTRUDA morali prejeti tudi tarčno zdravljenje; odraslih bolnikov s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) in zdravljenje z brentuksimabom vedotinom (BV) nista bila uspešna, in odraslih bolnikov, ki za presaditev niso primerni, zdravljenje z BV pa pri njih ni bilo uspešno; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, predhodno zdravljenih s kemoterapijo, ki je vključevala platino; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, ki niso primerni za zdravljenje s kemoterapijo, ki vsebuje cisplatin in imajo tumorje z izraženostjo PD-L1 ≥ 10, ocenjeno s kombinirano pozitivno oceno (CPS); ponovljenega ali metastatskega ploščatoceličnega raka glave in vratu (HNSCC) pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS), in pri katerih je bolezen napredovala med zdravljenjem ali po zdravljenju s kemoterapijo, ki je vključevala platino. Zdravilo KEYTRUDA je kot samostojno zdravljenje ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) indicirano za prvo linijo zdravljenja metastatskega ali neoperabilnega ponovljenega ploščatoceličnega raka glave in vratu pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 1. Zdravilo KEYTRUDA je v kombinaciji s pemetreksedom in kemoterapijo na osnovi platine indicirano za prvo linijo zdravljenja metastatskega neploščatoceličnega NSCLC pri odraslih, pri katerih tumorji nimajo pozitivnih mutacij EGFR ali ALK; v kombinaciji s karboplatinom in bodisi paklitakselom bodisi nab-paklitakselom je indicirano za prvo linijo zdravljenja metastatskega ploščatoceličnega NSCLC pri odraslih; v kombinaciji z aksitinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih. **Odmerjanje in način uporabe**: Testiranje PD-L1 pri bolnikih z NSCLC, urotelijskim rakom ali HNSCC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje izraženosti PD-L1 tumorja z validirano preiskavo, da izberemo bolnike z NSCLC ali predhodno nezdravljenim urotelijskim rakom. Bolnike s HNSCC je treba za samostojno zdravljenje z zdravilom KEYTRUDA ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) izbrati na podlagi izraženosti PD-L1, potrjene z validirano preiskavo. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek za kombinirano zdravljenje je 200 mg na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti sočasno uporabljenih zdravil. Če se uporablja kot del kombiniranega zdravljenja skupaj z intravensko kemoterapijo, je treba zdravilo KEYTRUDA aplicirati prvo. Bolnike je treba zdraviti do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri adjuvantnem zdravljenju melanoma je treba zdravilo uporabljati do ponovitve bolezni, pojava nesprejemljivih toksičnih učinkov oziroma mora zdravljenje trajati do enega leta. Če je aksitinib uporabljen v kombinaciji s pembrolizumabom, se lahko razmisli o povečanju odmerka aksitiniba nad začetnih 5 mg v presledkih šest tednov ali več. Pri bolnikih starih ≥ 65 let, bolnikih z blago do zmerno okvaro ledvic, bolnikih z blago okvaro jeter prilagoditev odmerka ni potrebna. *Odložitev odmerka ali ukinitev zdravljenja*: Zmanjšanje odmerka zdravila KEYTRUDA ni priporočljivo. Za obvladovanje neželenih učinkov je treba uporabo zdravila KEYTRUDA zadržati ali ukiniti, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Kontraindikacije**: Preobčutljivost na učinkovino ali katero koli pomožno snov. **Povzetek posebnih opozoril, previdnostnih ukrepov, interakcij in neželenih učinkov**: Imunsko pogojeni neželeni učinki (pnevmonitis, kolitis, hepatitis, nefritis, endokrinopatije, neželeni učinki na kožo in drugi): Pri bolnikih, ki so prejemali pembrolizumab, so se pojavili imunsko pogojeni neželeni učinki, vključno s hudimi in smrtnimi primeri. Večina imunsko pogojenih neželenih učinkov, ki so se pojavili med zdravljenjem s pembrolizumabom, je bila reverzibilnih in so jih obvladali s prekinitvami uporabe pembrolizumaba, uporabo kortikosteroidov in/ali podporno oskrbo. Pojavijo se lahko tudi po zadnjem odmerku pembrolizumaba in hkrati prizadanejo več organskih sistemov. V primeru suma na imunsko pogojene neželene učinke je treba poskrbeti za ustrezno oceno za potrditev etiologije oziroma izključitev drugih vzrokov. Glede na izrazitost neželenega učinka je treba zadržati uporabo pembrolizumaba in uporabiti kortikosteroide – za natančna navodila, prosimo, glejte Povzetek glavnih značilnosti zdravila Keytruda. Zdravljenje s pembrolizumabom lahko poveča tveganje za zavrnitev pri prejemnikih presadkov čvrstih organov. Pri bolnikih, ki so prejemali pembrolizumab, so poročali o hudih z infuzijo povezanih reakcijah, vključno s preobčutljivostjo in anafilaksijo. Pembrolizumab se iz obtoka odstrani s katabolizmom, zato presnovnih medsebojnih delovanj zdravil ni pričakovati. Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo pembrolizumaba se je treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost pembrolizumaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti za zdravljenje imunsko pogojenih neželenih učinkov. Kortikosteroide je mogoče uporabiti tudi kot premedikacijo, če je pembrolizumab uporabljen v kombinaciji s kemoterapijo, kot antiemetično profilakso in/ali za ublažitev neželenih učinkov, povezanih s kemoterapijo. Ženske v rodni dobi morajo med zdravljenjem s pembrolizumabom in vsaj še 4 mesece po zadnjem odmerku pembrolizumaba uporabljati učinkovito kontracepcijo, med nosečnostjo in dojenjem se ga ne sme uporabljati.
Varnost pembrolizumaba pri samostojnem zdravljenju so v kliničnih študijah ocenili pri 5.884 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom ali HNSCC s štirimi odmerki (2 mg/kg na 3 tedne, 200 mg na 3 tedne in 10 mg/kg na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,3 mesece (v razponu od 1 dneva do 31 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (20 %) in diareja (20 %). Večina poročanih neželenih učinkov pri samostojnem zdravljenju je bila po izrazitosti 1. ali 2. stopnje. Najresnejši neželeni učinki so bili imunsko pogojeni neželeni učinki in hude z infuzijo povezane reakcije. Varnost pembrolizumaba pri kombiniranem zdravljenju s kemoterapijo so ocenili pri 1.067 bolnikih NSCLC ali HNSCC, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg ali 10 mg/kg na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: anemija (50 %), navzea (50 %), utrujenost (37 %), zaprtost (35%), diareja (30 %), nevtropenija (30 %), zmanjšanje apetita (28 %) in bruhanje (25 %). Pri kombiniranem zdravljenju s pembrolizumabom je pri bolnikih z NSCLC pojavnost neželenih učinkov 3. do 5. stopnje znašala 67 %, pri zdravljenju samo s kemoterapijo pa 66 %, pri kombiniranem zdravljenju s pembrolizumabom pri bolnikih s HNSCC 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %. Varnost pembrolizumaba v kombinaciji z aksitinibom so ocenili v klinični študiji pri 429 bolnikih z napredovalim rakom ledvičnih celic, ki so prejemali 200 mg pembrolizumaba na 3 tedne in 5 mg aksitiniba dvakrat na dan. V tej populaciji bolnikov so bili najpogostejši neželeni učinki diareja (54 %), hipertenzija (45 %), utrujenost (38 %), hipotiroidizem (35 %), zmanjšan apetit (30 %), sindrom palmarno-plantarne eritrodisestezije (28 %), navzea (28 %), zvišanje vrednosti ALT (27 %), zvišanje vrednosti AST (26 %), disfonija (25 %), kašelj (21 %) in zaprtost (21 %). Pojavnost neželenih učinkov 3. do 5. stopnje je bila med kombiniranim zdravljenjem s pembrolizumabom 76 % in pri zdravljenju s sunitinibom samim 71 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila
Način in režim izdaje zdravila: H – Predpisovanje in izdaja zdravila je le na recept, zdravilo se uporablja samo v bolnišnicah.
Imetnik dovoljenja za promet z zdravilom: Merck Sharp & Dohme B.V. , Waarderweg 39, 2031 BN Haarlem, Nizozemska.

MSD

Merck Sharp & Dohme inovativna zdravila d.o.o.,
Šmartinska cesta 140, 1000 Ljubljana, tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50
Pripravljeno v Sloveniji, December 2020; SI-KEY-00180 EXP: 12/2022
Samo za strokovno javnost.
H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila Keytruda, ki je na voljo pri naših strokovnih sodelavcih ali na lokalnem sedežu družbe.

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

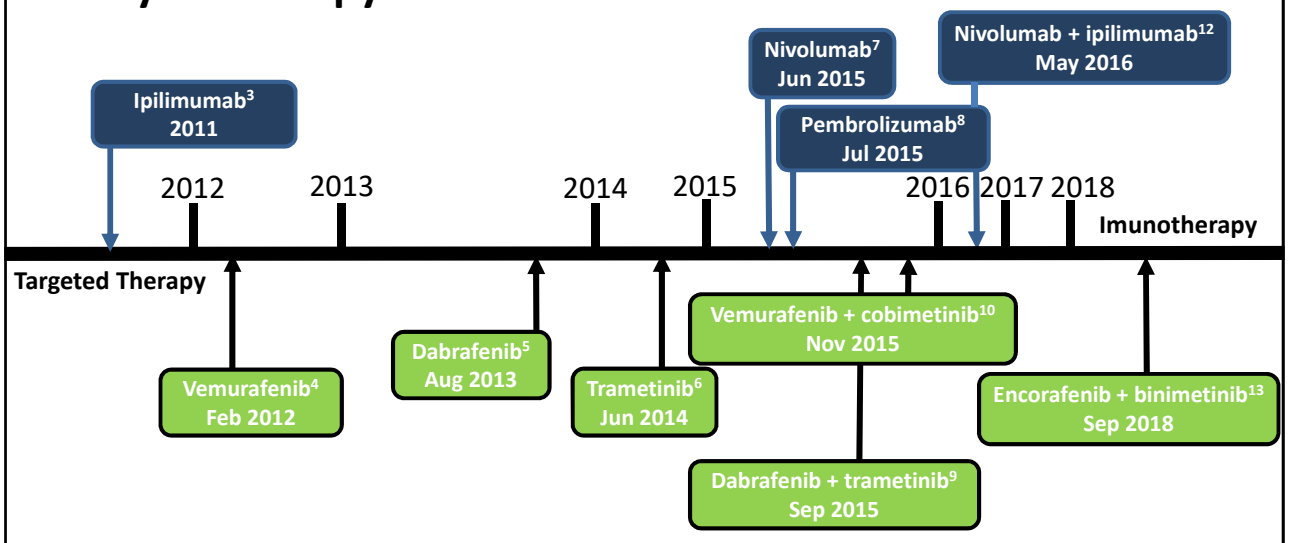
Imuno-onkologija 2020

Novosti pri zdravljenju malignega melanoma

Marko Boc, dr.med.

Ljubljana, 15. december 2020

History of Therapy for Metastatic Melanoma



Bini, binimetinib; cobi, cobimetinib; dab, dabrafenib; enco, encorafenib; ipi, ipilimumab; nivo, nivolumab; OS, overall survival; pembro, pembrolizumab; tram, trametinib; T-VEC, talimogene laherparepvec; vem, vemurafenib.

1. Kirkwood JM, et al. In *Cancer: Principles and Practice of Oncology*. DeVita VT, et al, eds. Philadelphia, PA: Lippincott, 1993; 2. Sabel MS, Sondak VK. *Oncologist*. 2003;8:451-458; 3. https://www.ema.europa.eu/en/medicines/human/EPAR/yervoy; 4. https://www.ema.europa.eu/en/medicines/human/EPAR/zelboraf; 5. https://www.ema.europa.eu/en/medicines/human/EPAR/tafinlar; 6. https://www.ema.europa.eu/en/medicines/human/EPAR/Mekinist; 7. https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo; 8. https://www.ema.europa.eu/en/medicines/human/EPAR/Keytruda; 9. https://www.novartis.com/news/media-releases/novartis-receives-eu-approval-tafinlar-and-mekinist-first-combination-approved-patients-aggressive-form-melanoma; 10. https://www.roche.com/media/releases/med-cor-2015-11-25.htm; 11. https://www.cancer.gov/news-events/cancer-currents-blog/2015/t-vec-melanoma. 12. https://news.bms.com/press-release/cancer/european-commission-approves-first-and-only-immuno-oncology-combination-Bristol; 13. https://www.ema.europa.eu/en/medicines/human/EPAR/braftovi; all accessed 15 June 2020; 14. Robert C, et al. *Lancet Oncol*. 2019;20:1239-1251; 15. Robert C, et al. *N Engl J Med*. 2019;381:626-636; 16. Larkin J, et al. *N Engl J Med*. 2019;381:1535-1546; 17. McArthur G, et al. SMR 2019; 18. Gogas H, et al. ASCO 2020 [abstract 10012].

1. Vloga kombinirane imunoterapije (antiCTLA4 + antiPD1) po progresu na antiPD1 pri BRAFwt bolnikih z mMM?
2. Vloga kombinirane terapije BRAFi+MEKi+antiPD1i pri BRAF mutiranem mMM?
3. Pembrolizumab 200mg/3t vs 400mg/6t?
4. Pembrolizumab – rezultati dolgotrajnega preživetja in reindukcija

antiCTLA4 + antiPD1 po progresu na antiPD1

Ipilimumab (IPI) alone or in combination with anti-PD-1 (IPI+PD1) in patients (pts) with metastatic melanoma (MM) resistant to PD1 monotherapy

Ines Pires da Silva, Tasnia Ahmed, Serigne Lo, Irene LM Reijers, Alison Weppler, Allison Betof, James Randall Patrinely, Patricio Serra-bellver, Celeste Lebbe, Johanna Mangana, Khang Nguyen, Lisa Zimmer, Paolo Ascierto, Dan Stout, Megan Lyle, Olivier Klein, Camille Gerard, Christian U Blank, Alexander A Menzies, Georgina V Long

Melanoma Institute Australia

THE UNIVERSITY OF SYDNEY

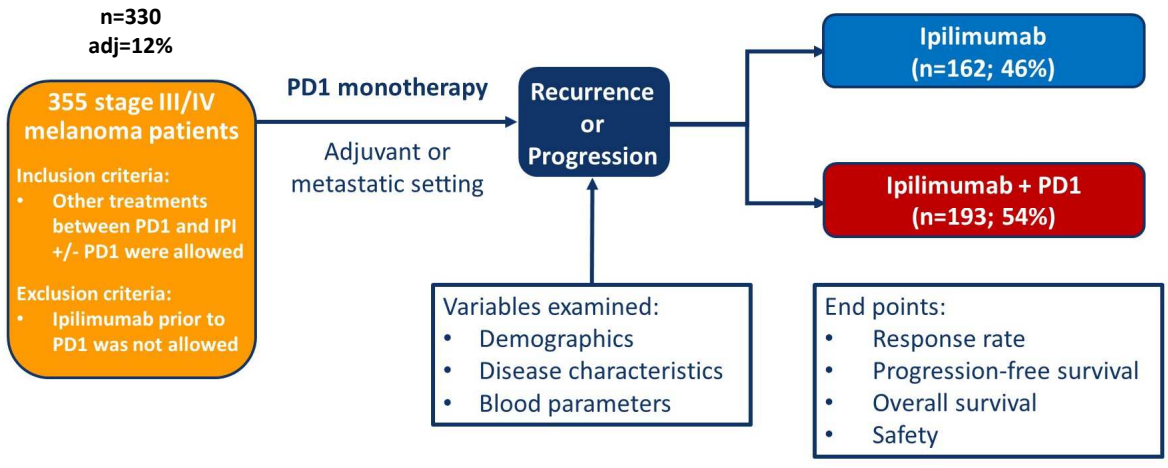
CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD RECIPIENT

Bradley Stuart Beller Endowed Merit Award

Supported by Friends and Family of Dr. and Mrs. Ronald Beller

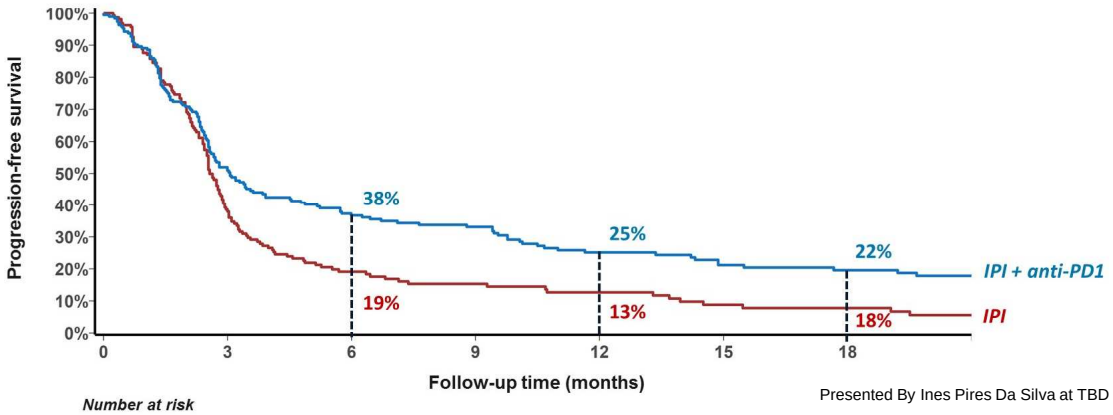
Presented By Ines Pires Da Silva at TBD

Study Design: multicenter retrospective study



Presented By Ines Pires Da Silva at TBD

Progression-free survival



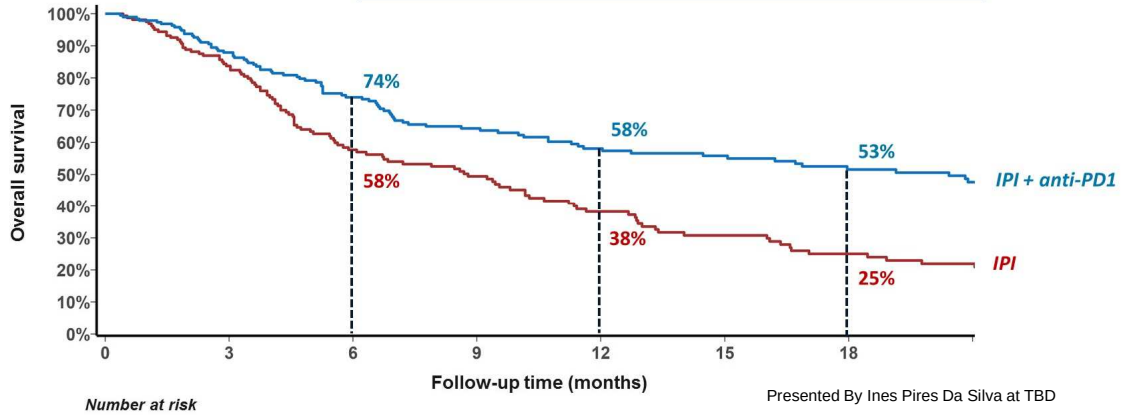
Presented By Ines Pires Da Silva at TBD

Number at risk

IPI	162	60	25	20	13	9	7
IPI+anti-PD1	193	97	63	52	35	27	24

Overall survival

	IPI + anti-PD1 (n=193)	IPI (n=162)	HR (95% CI) IPI + anti-PD1 over IPI	*p-value*
Median OS, months (95% CI)	20.4 (12.7, 34.8)	8.8 (6.1, 11.3)	0.51 (0.38, 0.67)	<0.0001



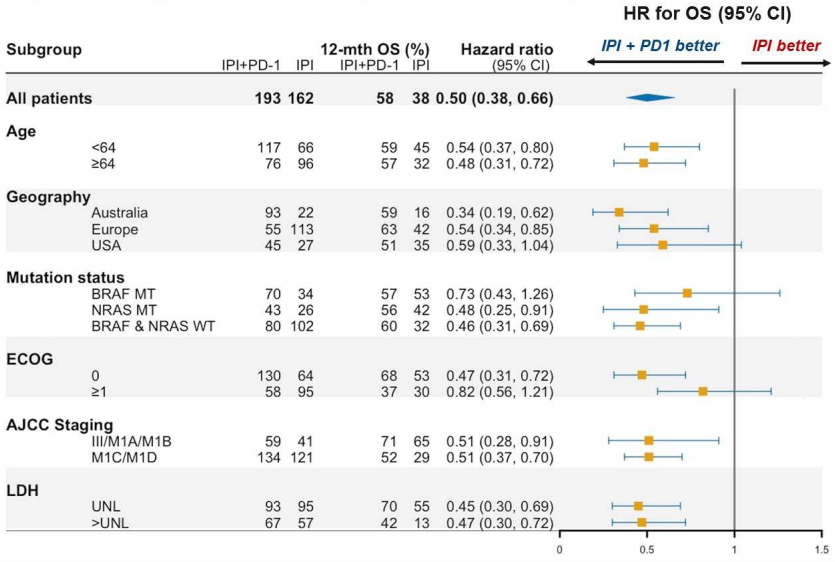
Presented By Ines Pires Da Silva at TBD

Number at risk

IPI	162	131	79	63	43	33	26
IPI+anti-PD1	193	165	125	98	80	69	56

Presented By Ines Pires Da Silva at TBD

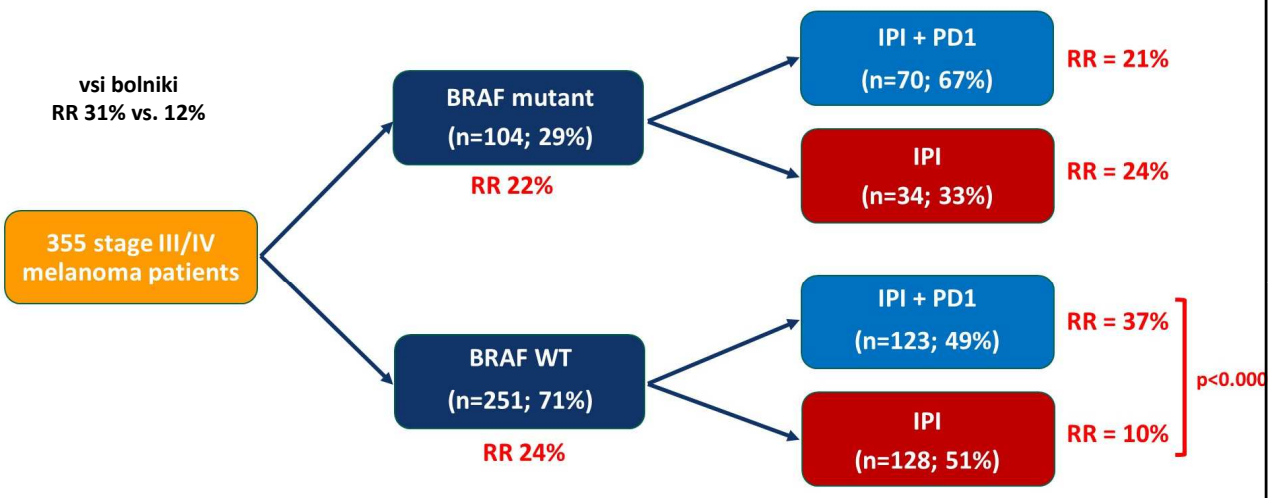
Subgroup analysis for OS (12 months)



Subgroup		12-mth OS (%) IPI+PD-1	IPI	IPI+PD-1	IPI	Hazard ratio (95% CI)
All patients		**193**	**162**	**58**	**38**	**0.50 (0.38, 0.66)**
Age						
	<64	117	66	59	45	0.54 (0.37, 0.80)
	≥64	76	96	57	32	0.48 (0.31, 0.72)
Geography						
	Australia	93	22	59	16	0.34 (0.19, 0.62)
	Europe	55	113	63	42	0.54 (0.34, 0.85)
	USA	45	27	51	35	0.59 (0.33, 1.04)
Mutation status						
	BRAF MT	70	34	57	53	0.73 (0.43, 1.26)
	NRAS MT	43	26	56	42	0.48 (0.25, 0.91)
	BRAF & NRAS WT	80	102	60	32	0.46 (0.31, 0.69)
ECOG						
	0	130	64	68	53	0.47 (0.31, 0.72)
	≥1	58	95	37	30	0.82 (0.56, 1.21)
AJCC Staging						
	III/M1A/M1B	59	41	71	65	0.51 (0.28, 0.91)
	M1C/M1D	134	121	52	29	0.51 (0.37, 0.70)
LDH						
	UNL	93	95	70	55	0.45 (0.30, 0.69)
	>UNL	67	57	42	13	0.47 (0.30, 0.72)

BRAF mutant vs BRAF WT

Presented By Ines Pires Da Silva at TBD



Prior BRAFi RR 13% vs No prior BRAFi RR 22%, p > 0.05%

Conclusion

1. In patients resistant to PD1, IPI combined with PD1 has a higher response rate (32%) and longer PFS (25% at 12 months) and OS (58% at 12 months), yet similar high grade toxicity than IPI alone.

2. Predictive models of response and survival will help forecast patient outcomes when treated with IPI +/- PD1 after progressing on PD1 monotherapy.

Presented By Ines Pires Da Silva at TBD

Significant antitumor activity for low-dose ipilimumab (IPI) with pembrolizumab (PEMBRO) immediately following progression on PD1 Ab in melanoma (MEL) in a phase II trial

Daniel J. Olson[1], Jason J. Luke[2], Andrew S. Poklepovic[3], Madhuri Bajaj[4], Emily Higgs[1], Timothy C. Carll[1], Brian Labadie[1], Thomas Krausz[1], Yuanyuan Zha[1], Theodore Karrison[1], Jose Lutzky[5], Sigrun Hallmeyer[6], Bruce Brockstein[7], Vernon K. Sondak[8], Zeynep Eroglu[8], Thomas F. Gajewski[1], Nikhil I. Khushalani[8]

1. The University of Chicago Comprehensive Cancer Center, Chicago, IL
2. The University of Pittsburgh, Hillman Cancer Center, Pittsburgh, PA
3. VCU Massey Cancer Center, Richmond, VA
4. Illinois Cancer Care, Peoria, IL
5. Mount Sinai Medical Center, Miami Beach, FL
6. Oncology Specialists, SC, Park Ridge, IL
7. NorthShore University Health System, Evanston, IL
8. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

AT THE FOREFRONT UChicago Medicine

CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD RECIPIENT

Presented By Daniel Olson at TBD

Pembro + low-dose ipi after PD1 Ab failure: Study Design

Patient Criteria

- Unresectable or metastatic melanoma
- Confirmed progression on a PD1 Ab immediately prior, or within six months of adjuvant therapy
- Prior BRAF treatment allowed
- Uveal melanoma excluded
- ECOG 0 to 1
- Treated CNS disease allowed

Prior to study enrollment

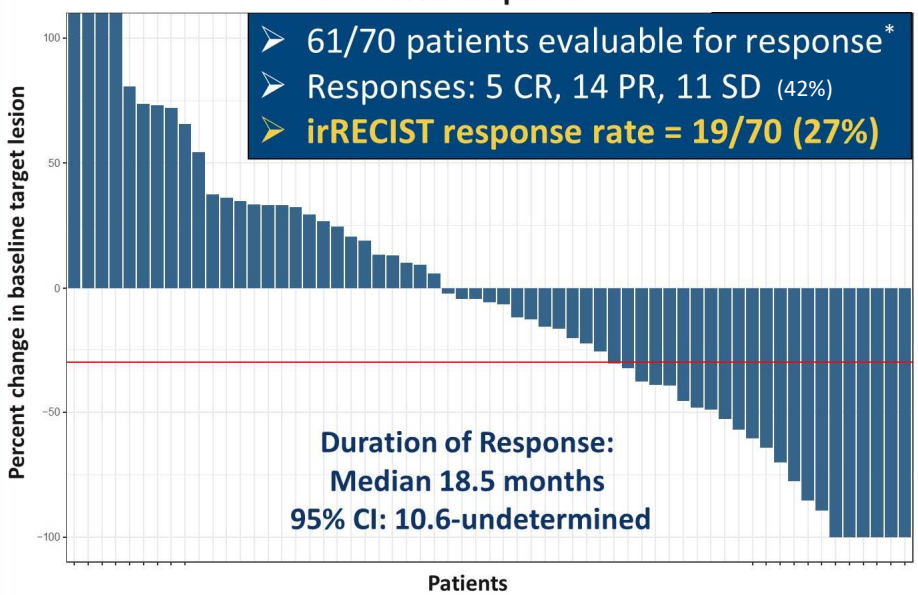
PD1/L1 Ab or non-CTLA4 combination

Study day 1

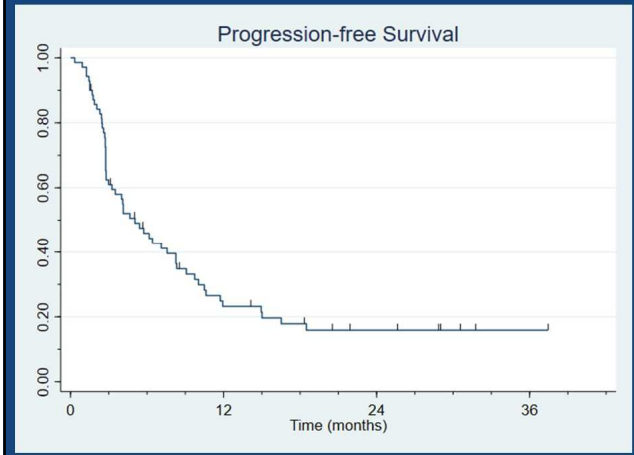
Pembrolizumab 200mg IV Q3 weeks

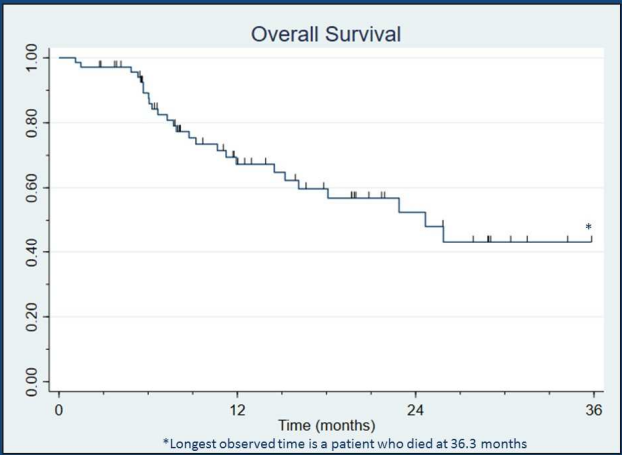
ipilimumab 1mg/kg Q3 weeks x 4 doses

Best Overall Response



Survival Outcomes





Median 5.0 months, 95% CI: 2.8-8.3

Median 24.7 months, 95% CI: 15.2-undetermined

Subgroup response rates

Response by Liver or CNS disease	Response after PD1 Ab adjuvant progression	Response in non-cutaneous melanoma
6/20 (30%)	2/13 (15%)	1/8 (14%)

Response by elevated LDH
8/19 (42%)

Response by BRAF Status	
Mutant	4/19 (26%)
Wild Type	15/48 (31%)

Response by PD-L1 Status*	
PD-L1 +	4/24 (17%)
PD-L1 -	15/39 (38%)

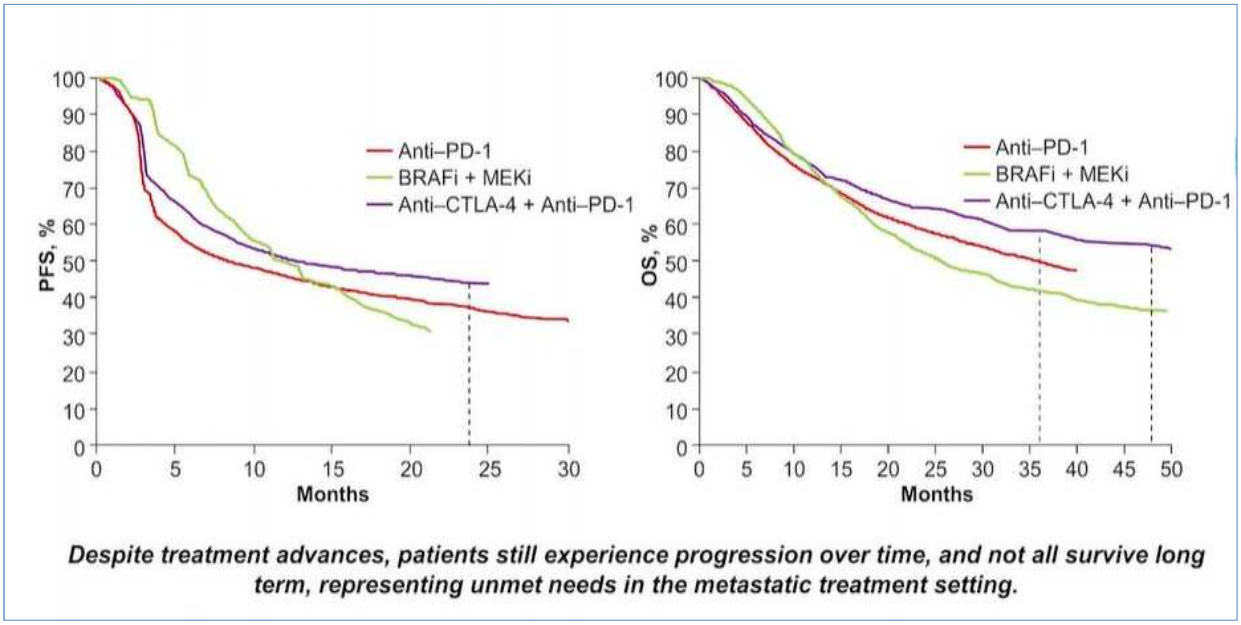
*PD-L1 expression analysis was obtained from historical tumor samples using EIL3N PDL1 Ab; a cut-off of ≥ 1% was used to define PD-L1 positivity as consistent with DAKO 22C3 approach - Gaule, P., et al. JAMA Oncol, 2016

ZAKLJUČEK:

- z kombiniranim zdravljenjem z antiPD1 in antiCTLA4 po progresu na antiPD1 na zdravljenje odgovori do 25% bolnikov

BRAFi + MEKi + antiPD1
(BRAFmt)

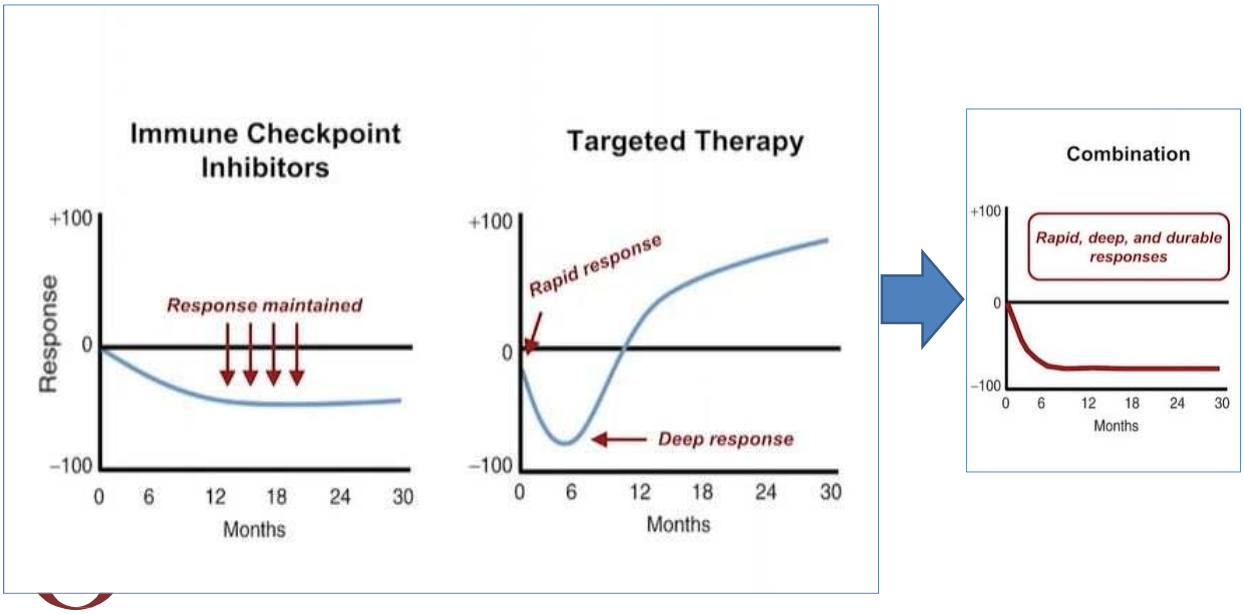
Loss of Tumour Control Over Time



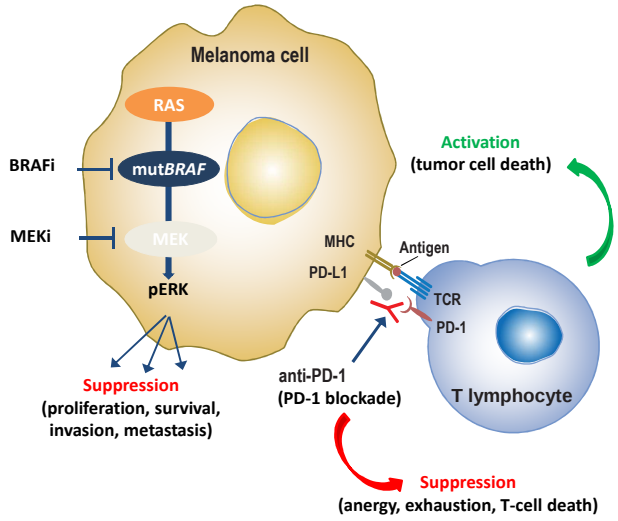
Despite treatment advances, patients still experience progression over time, and not all survive long term, representing unmet needs in the metastatic treatment setting.

Ugurel S, et al. Eur J Cancer 2020;130:126-138.

Tumour response pattern



Wargo JA, et al. Cancer Dis. 2014;4:1377-1386.



- Preclinical data suggest combining an anti–PD-1 antibody with the BRAFi and the MEKi may enhance antitumor activity compared with BRAFi an MEKi alone[1]
- Phase II and III trials have shown that combining IO + TT may improve outcomes in patients with *BRAF* V600–mutant metastatic melanoma[2,3]
- Early clinical findings suggest that BRAFi+MEKi+PD1 may be associated with a higher percentage of patients achieving durable responses[4,5]

IO, immunotherapy; MHC, major histocompatibility complex; mut, mutant; PD-L1, programmed death ligand 1; pERK, phosphorylated extracellular signal-regulated kinase; TCR, T-cell receptor; TT, targeted therapy.

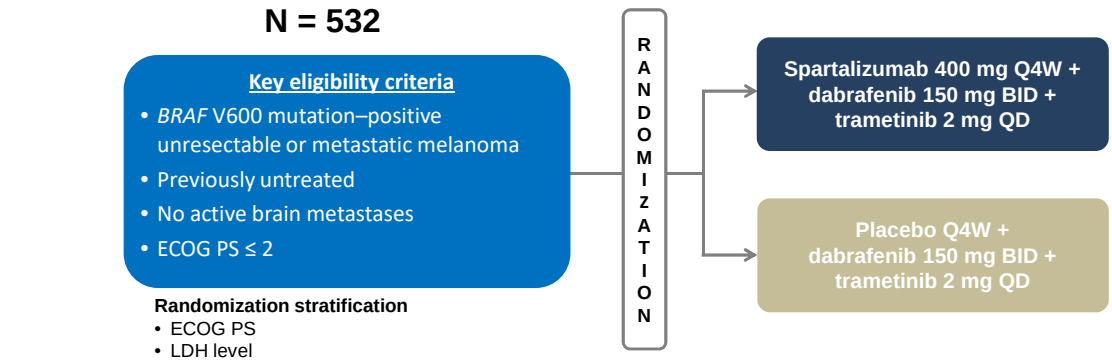
1. Hu-Lieskovan S, et al. *Sci Transl Med*. 2015;7:279ra41; 2. Ferrucci P, et al. SMR 2019; 3. Gutzmer R, et al. *Lancet*. 2020;395:1835-1844; 4. Long G, et al. ASCO 2020 [abstract 10028]; 5. Dummer R, et al. ASCO 2019 [abstract 9515].

VIRTUAL 2020 ESMO congress

Spartalizumab plus dabrafenib and trametinib in patients with previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma: results from the randomized part 3 of the Phase III COMBI-i trial

Paul D. Nathan,[1] Reinhard Dummer,[2] Georgina V. Long,[3] Paolo A. Ascierto,[4] Hussein A. Tawbi,[5] Caroline Robert,[6] Piotr Rutkowski,[7] Oleg Leonov,[8] Caroline Dutriaux,[9] Mario Mandalà,[10] Paul Lorigan,[11] Pier Francesco Ferrucci,[12] Keith T. Flaherty,[13] Jan C. Brase,[14] Steven Green,[15] Tomas Haas,[15] Aisha Masood,[16] Eduard Gasal,[16] Antoni Ribas,[17] Dirk Schadendorf[18]

[1]Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK; [2]Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland; [3]Department of Medical Oncology, Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia; [4]Department of Melanoma, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS "G. Pascale," Napoli, Italy; [5]Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Dermatology Service and Melanoma Research Unit, Gustave Roussy and Paris-Sud-Paris-Saclay University, Villejuif, France; [7]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [8]Department of Medical Oncology, Clinical Oncological Dispensary, Omsk, Russian Federation; [9]Service de Dermatologie, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France; [10]Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; [11]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [12]Cancer Biotherapy Unit, Department of Experimental Oncology, European Institute of Oncology, IRCCS, Milan, Italy; [13]Department of Medicine and Cancer Center, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [14]Precision Medicine, Novartis Pharma AG, Basel, Switzerland; [15]Clinical Development and Analytics, Novartis Pharma AG, Basel, Switzerland; [16]Oncology Clinical Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [17]Department of Medicine, Division of Hematology-Oncology, University of California, Los Angeles, Los Angeles, CA, USA; [18]Department of Dermatology, Comprehensive Cancer Center (Westdeutsches Tumorzentrum), University Hospital Essen, Essen, and German Cancer Consortium, Heidelberg, Germany



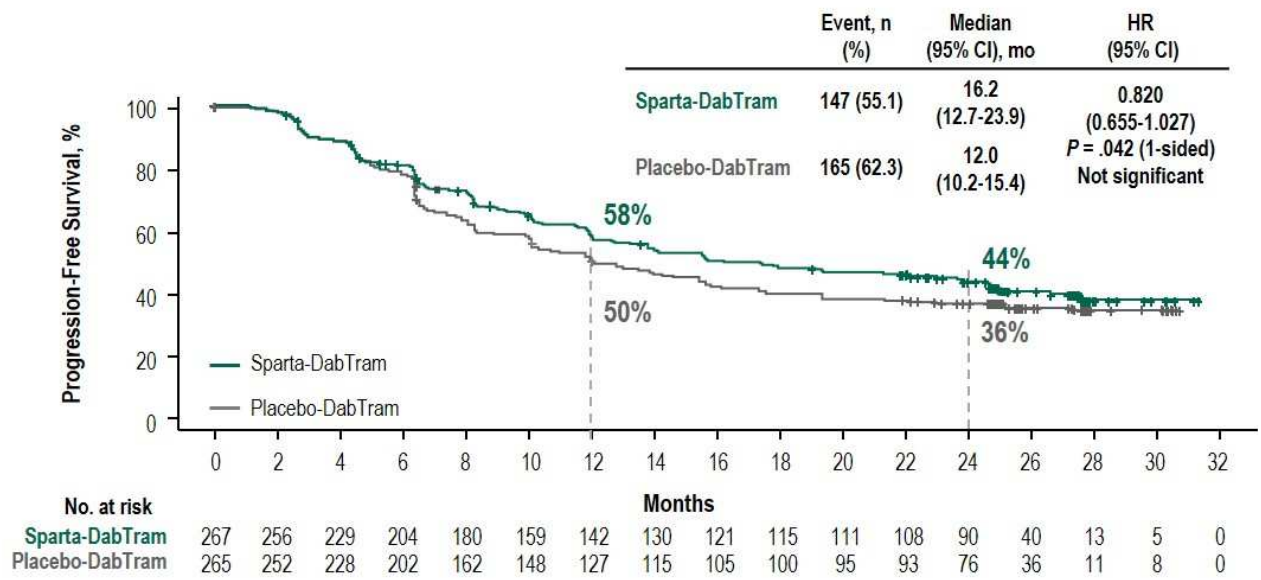
Primary endpoint: Investigator-assessed PFS using RECIST 1.1

Secondary endpoints: OS, ORR, DOR, DCR, safety, PRO, PK

BID, twice daily; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Characteristic	Sparta-DabTram (n = 267)	Placebo-DabTram (n = 265)
Age, median (range), years	56 (20-86)	55 (23-88)
< 65 years, n (%)	189 (70.8)	195 (73.6)
≥ 65 years, n (%)	78 (29.2)	70 (26.4)
ECOG PS, n (%)		
0	195 (73.0)	196 (74.0)
1	67 (25.1)	66 (24.9)
2	5 (1.9)	3 (1.1)
Disease stage, n (%)[a]		
IIIC	16 (6.0)	15 (5.7)
IV M1a	30 (11.2)	42 (15.8)
IV M1b	55 (20.6)	36 (13.6)
IV M1c	166 (62.2)	172 (64.9)
LDH levels, n (%)		
< 1 × ULN	162 (60.7)	161 (60.8)
≥ 1 < 2 × ULN	70 (26.2)	68 (25.7)
≥ 2 × ULN	35 (13.1)	36 (13.6)
Sum of lesion diameters at baseline, median (range), mm	49 (10-266)	48 (10-550)
No. of organ sites with metastases, n (%)		
1-2	145 (54.3)	143 (54.0)
≥ 3	121 (45.3)	122 (46.0)
Unknown	1 (0.4)	0
Prior adjuvant therapy, n (%)	6 (2.2)	4 (1.5)

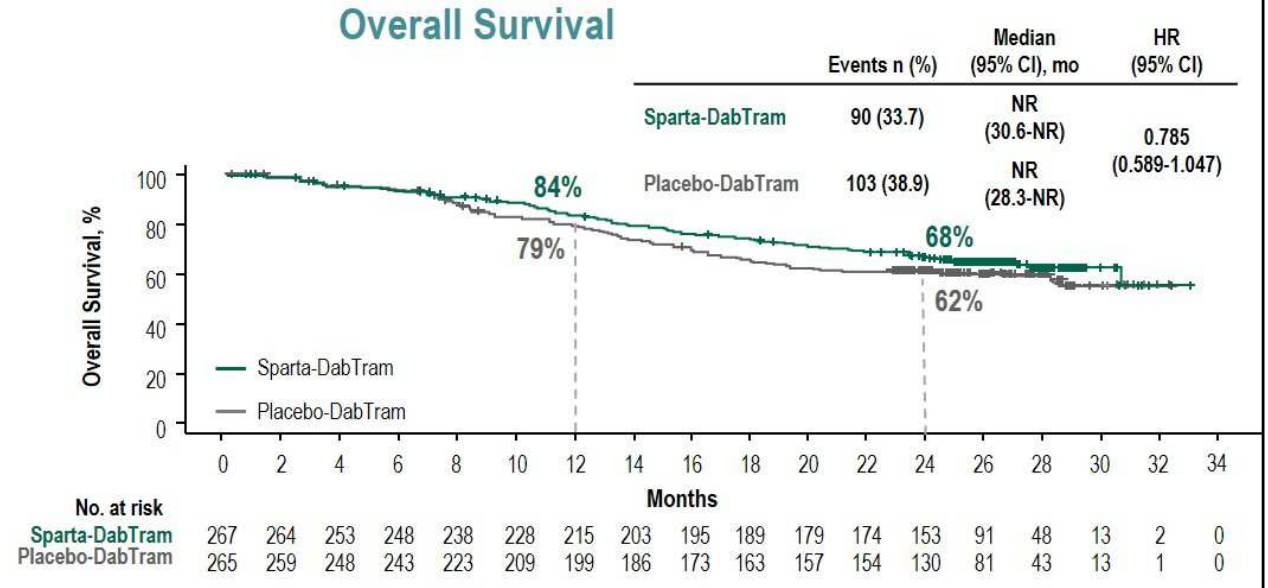
Investigator-Assessed Progression-Free Survival



No. at risk																	
Sparta-DabTram	267	256	229	204	180	159	142	130	121	115	111	108	90	40	13	5	0
Placebo-DabTram	265	252	228	202	162	148	127	115	105	100	95	93	76	36	11	8	0

HR, hazard ratio.

Overall Survival



No. at risk																	
Sparta-DabTram	267	264	253	248	238	228	215	203	195	189	179	174	153	91	48	13	2	0
Placebo-DabTram	265	259	248	243	223	209	199	186	173	163	157	154	130	81	43	13	1	0

- Overall survival could be statistically tested only after the primary endpoint was determined to be statistically significant

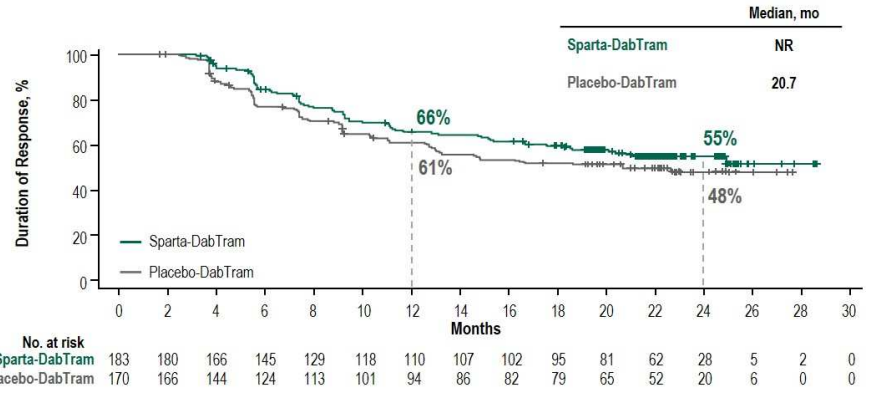
NR, not reached.

Patients, n (%)	Sparta-DabTram n = 267	Placebo-DabTram n = 265
Objective response rate [95% CI][a]	183 (68.5) [62.6-74.1]	170 (64.2) [58.1-69.9]
CR	53 (19.9)	47 (17.7)
PR	130 (48.7)	123 (46.4)
SD	41 (15.4)	58 (21.9)
PD	23 (8.6)	22 (8.3)
Non-CR/non-PD	1 (0.4)	1 (0.4)
Unknown[b]	19 (7.1)	14 (5.3)
DCR	225 (84.3)	229 (86.4)

	Sparta-DabTram (n = 267)	Placebo-DabTram (n = 265)
Patient status, n (%)		
Ongoing[a]	86 (32.2)	82 (30.9)
Discontinued[b]	181 (67.8)	182 (68.7)
Reason for discontinuation of all 3 study drugs, n (%)		
Progressive disease	99 (37.1)	128 (48.3)
Adverse event	51 (19.1)	23 (8.7)
Investigator discretion	13 (4.9)	9 (3.4)
Death	10 (3.7)	8 (3.0)
Withdrawn consent	6 (2.2)	13 (4.9)
Loss to follow-up	1 (0.4)	0
Protocol deviation	1 (0.4)	1 (0.4)

Duration of Response

Median follow-up from the time of randomization to the data cut-off (July 1, 2020) was 27.2 months (range, 24.0-33.6 months)



Patients, n (%)	Sparta-DabTram n = 267		Placebo-DabTram n = 264	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any AE	265 (99.3)	188 (70.4)	256 (97.0)	151 (57.2)
Treatment related	263 (98.5)	146 (54.7)	231 (87.5)	88 (33.3)
Serious AEs	138 (51.7)	91 (34.1)	110 (41.7)	76 (28.8)
Treatment related	106 (39.7)	62 (23.2)	53 (20.1)	29 (11.0)
AEs leading to discontinuation of ≥ 1 study drug	97 (36.3)	58 (21.7)	47 (17.8)	27 (10.2)
Treatment related	85 (31.8)	48 (18.0)	38 (14.4)	19 (7.2)
AEs leading to discontinuation of all 3 study drugs[a]	42 (15.7)	24 (9.0)	24 (9.1)	15 (5.7)
Treatment related	33 (12.4)	16 (6.0)	21 (8.0)	12 (4.5)
AEs leading to dose interruption/adjustment	235 (88.0)	131 (49.1)	192 (72.7)	97 (36.7)
AEs requiring additional therapy	255 (95.5)	118 (44.2)	223 (84.5)	88 (33.3)

- Part 3 of COMBI-i did not meet the primary endpoint, and Sparta-DabTram did not significantly improve investigator-assessed progression-free survival compared with placebo-DabTram
  - –HR, 0.820 (*P* = .042, 1-sided) corresponding to a median progression-free survival of 16.2 months in patients treated with Sparta-DabTram vs 12.0 months in patients who received placebo-DabTram
  - –The control arm (placebo-DabTram) performed better than expected
- While overall survival was not formally tested, a HR of 0.785 was observed in favor of Sparta-DabTram, and the median overall survival had not been reached in either treatment arm
- A higher number of dose modifications (reductions/interruptions) and discontinuations was observed in patients treated with Sparta-DabTram, suggesting increased toxicity
- Additional analyses are ongoing and planned to better understand these results
  - –Further overall survival follow-up may provide additional insights

P Ferrucci KN022 SMR 2019

Updated Survival In Patients With *BRAF*-mutant Melanoma Administered Pembrolizumab, Dabrafenib, And Trametinib

Pier F. Ferrucci[1a]; Paolo A. Ascierto[2a]; Michele Maio[3]; Michele Del Vecchio[4]; Victoria Atkinson[5]; Henrik Schmidt[6]; Jacob E. Schachter[7]; Paola Queirolo[8]; Georgina V. Long[9]; Rosalie Stephens[10]; Inge Marie Svane[11]; Michal Lotem[12]; Mahmoud Abu-Amna[13]; Eduard Gasal[14]; Razi Ghori[15]; Scott J. Diede[15]; Elizabeth Croydon[15]; Antoni Ribas[16]

[a]Both authors contributed equally

[1]Istituto Europeo di Oncologia IRCCS, Milan, Italy; [2]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Naples, Italy; [3]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Brisbane, QLD, Australia; [6]Aarhus University Hospital, Aarhus, Denmark; [7]Ella Lemelbaum Institute for Immuno-Oncology, The Chaim Sheba Medical Center at Tel HaShomer, Cancer Center (Oncology Institute), Ramat Gan, Israel; [8]IEO, European Institute of Oncology IRCCS, Milan, Italy; [9]Melanoma Institute Australia; the University of Sydney; Mater and Royal North Shore Hospitals, Sydney, NSW, Australia; [10]Auckland City Hospital, Auckland, New Zealand; [11]Herlev Hospital, University of Copenhagen, Herlev, Denmark; [12]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [13]Rambam Health Care Campus, Haifa, Israel; [14]Novartis, East Hanover, NJ, USA; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]UCLA and the Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA

P Ferrucci KN022 SMR 2019

KEYNOTE-022 Part 3 Study Design (NCT02130466)

Patients
- Histologically confirmed unresectable or metastatic stage IV *BRAF*$^{V600E/K}$-mutant melanoma
- No prior therapy
- Measurable disease
- ECOG PS 0/1

Stratification factors[a]
- ECOG PS (0 vs 1)
- LDH level (>1.1 × ULN vs ≤1.1 × ULN)

R (1:1)
N = 120

N = 60 → Pembrolizumab 2 mg/kg Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD for up to 2 y[b]

N = 60 → Placebo Q3W + Dabrafenib 150 mg BID + Trametinib 2 mg QD for up to 2 y[b]

- Primary end point: PFS
- Secondary end points: ORR, DOR, and OS
- Data cutoff: Jun 26, 2019

[a]Owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
[b]Trametinib and/or dabrafenib could be continued beyond 2 y per standard of care.

P Ferrucci KN022 SMR 2019

KEYNOTE-022 Part 3 initial analysis

- Pembrolizumab + D + T vs placebo + D + T showed promising antitumor activity in an initial analysis of part 3 of the phase 2 KEYNOTE-022 study with median follow-up of 9.6 mo (range, 2.7-23.4)(data cut-off 15 Feb 2018)[1]

		Events, n	Median,[a] mo (95% CI)	HR[b] (95% CI)[b]	*P* Value[c]
Primary end point	Pembro + D + T	31	16.0 (8.6-21.5)	0.66 (0.40-1.07)	0.043
	Placebo + D + T	41	10.3 (7.0-15.6)		

PFS did not reach statistical significance threshold per study design (required HR for significance ≤0.62, $P \leq 0.025$)

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment. [b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs =1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined. [c]One-sided *P* value based on stratified log-rank test.
1. Ascierto PA et al. *Nat Med*. 2019;25:941-946.

P Ferrucci KN022 SMR 2019

Baseline Characteristics

	Pembro + D + T N = 60	Placebo + D + T N = 60
Age, median (range), y	54 (18-82)	58 (21-83)
Male, n (%)	33 (55)	36 (60)
ECOG PS 0, n (%)	48 (80)	48 (80)
LDH, n (%)		
≤1.1 × ULN	33 (55)	34 (57)
>1.1 × ULN	27 (45)	26 (43)
BRAF mutation, n (%)		
V600E	52 (87)	49 (82)
V600K	8 (13)	11 (18)
PD-L1 status,[a] n (%)		
Positive	47 (78)	44 (73)
Negative[b]	10 (17)	12 (20)

[a]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).
[b]Missing PD-L1 status, 3 (5%) in Pembro + D + T and 4 (7%) in placebo + D + T.
1. Ascierto PA et al. *Nat Med*. 2019;25:941-946. Data cutoff: Feb 15, 2018.

P Ferrucci KN022 SMR 2019

Baseline Characteristics (continued)

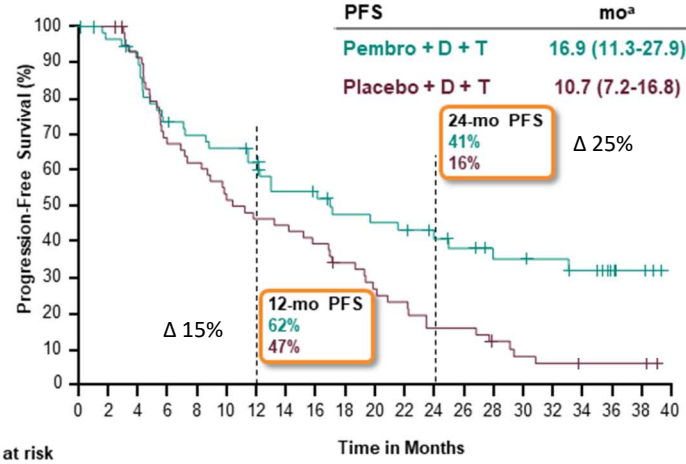
	Pembro + D + T N = 60	Placebo + D + T N = 60
Stage at entry, n (%)		
IIIB/IIIC	1 (2)/ 0 (0)	1 (2)/ 2 (3)
IV	59 (98)	57 (95)
Metastatic stage, n (%)		
M1a/M1b	2 (3)/8 (13)	10 (17)/9 (15)
M1c	49 (82)	38 (63)
No brain metastases, n (%)	59 (98)	59 (98)
No prior radiation, n (%)	51 (85)	54 (90)
Prior therapy, n (%)		
Adjuvant/Neoadjuvant	8 (13)/1 (2)	5 (8)/1 (2)
No prior therapy	51 (85)	54 (90)

[a]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC (22C3 antibody).
[b]Missing PD-L1 status, 3 (5%) in Pembro + D + T and 4 (7%) in placebo + D + T.
1. Ascierto PA et al. *Nat Med*. 2019;25:941-946. Data cutoff: Feb 15, 2018.

P Ferrucci KN022 SMR 2019

Progression-Free Survival

PFS	Median (95% CI), mo[a]	HR (95% CI)[b]
Pembro + D + T	16.9 (11.3-27.9)	0.53 (0.34-0.83)
Placebo + D + T	10.7 (7.2-16.8)	



No. at risk

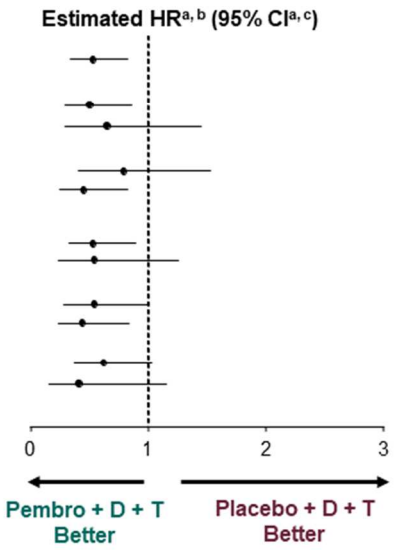
Pembro + D + T	60	55	50	40	38	36	32	27	26	22	21	20	17	15	12	12	11	9	5	3	0
Placebo + D + T	60	60	53	39	36	30	27	26	23	19	14	13	9	9	6	4	3	2	2	2	0

[a]Based on Kaplan-Meier estimate of PFS, per investigator assessment.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
Data cutoff: Jun 28, 2019.

P Ferrucci KN022 SMR 2019

Progression-Free Survival[a] by Subgroups

Subgroup		Event, n/N	HR[a,b]	95% CI[a,c]
Overall		87/120	0.53	(0.34-0.83)
Age				
	<65 y	57/81	0.50	(0.29-0.86)
	≥65 y	30/39	0.65	(0.29-1.45)
Sex				
	Female	38/51	0.79	(0.41-1.53)
	Male	49/69	0.45	(0.25-0.82)
ECOG Status				
	0	64/91	0.53	(0.32-0.89)
	1	23/29	0.54	(0.23-1.25)
LDH				
	LDH ≤1.1 × ULN	43/67	0.54	(0.28-1.01)
	LDH >1.1 × ULN	44/53	0.44	(0.23-0.84)
PD-L1				
	PD-L1 positive	64/91	0.62	(0.37-1.03)
	PD-L1 negative	18/22	0.41	(0.15-1.15)



[a]Based on Kaplan-Meier estimate of PFS, by investigator assessment per RECIST v1.1.
[b]Based on Cox regression model with treatment as covariates and stratified.
[c]Point estimate and nominal 95% confidence interval.
Data cutoff: Jun 26, 2019.

P Ferrucci KN022 SMR 2019

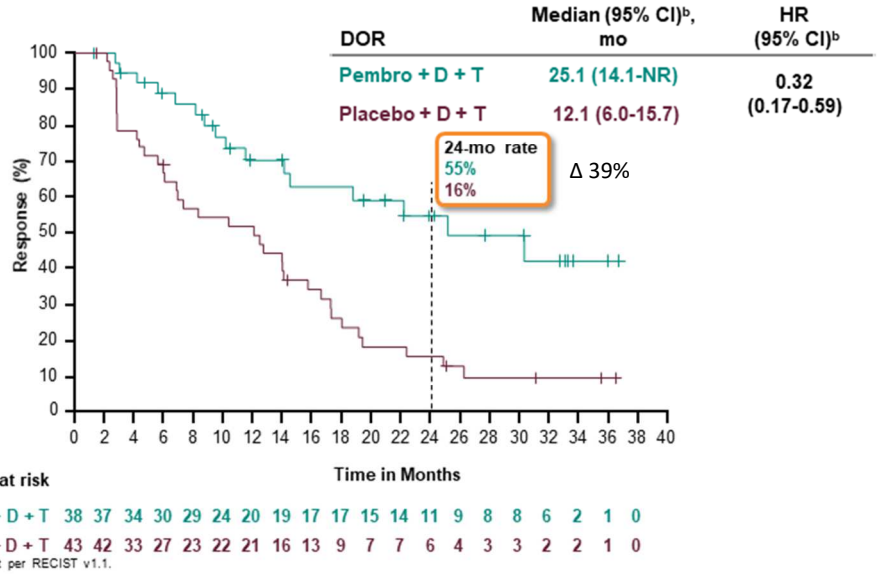
Best Overall Response (investigator review[a], RECIST v1.1)

	Pembro + D + T, n (%) N = 60	Placebo + D + T, n (%) N = 60	Difference in rate[b] % (95% CI)
ORR	38 (63)	43 (72)	–9 (–25 to 8)
CR	12 (20)	9 (15)	5 (–9 to 19)
PR	26 (43)	34 (57)	–14 (–31 to 4)
DCR	51 (85)	56 (93)	–8 (–20 to 4)
SD	13 (22)	13 (22)	1 (–15 to 16)
PD	5 (8)	3 (5)	3 (–7 to 14)
Nonevaluable	2 (3)	0 (0)	3 (–3 to 12)
No assessment	2 (3)	1 (2)	1 (–6 to 10)

[a]Responses are based on investigator best assessment across time points per RECIST v1.1 with confirmation.
[b]Based on Miettinen and Nurimen method stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
Data cutoff: Jun 26, 2019.

P Ferrucci KN022 SMR 2019

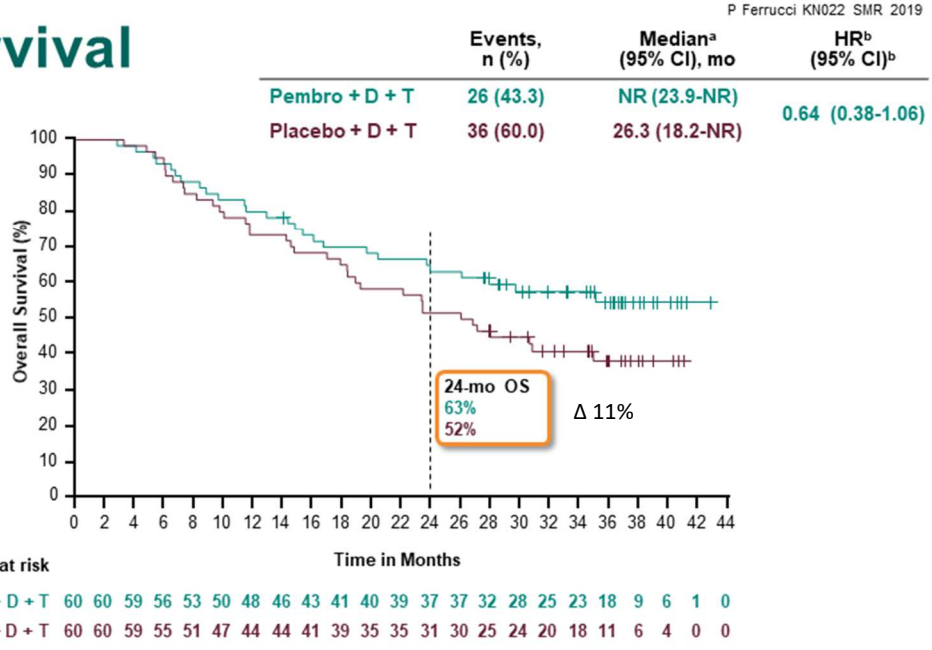
Kaplan-Meier Analysis of Duration of Response[a]



[a]Confirmed response based on investigator assessment per RECIST v1.1.
[b]From Kaplan-Meier method for censored data.
[c]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (LDH >1.1 × ULN vs ≤1.1 × ULN); owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
Data cutoff: Jun 26, 2019.

P Ferrucci KN022 SMR 2019

Overall Survival



[a]Based on Kaplan-Meier estimate of overall survival.
[b]Based on Cox regression model with treatment as a covariate stratified by ECOG PS (0 vs 1) and LDH (>1.1 × ULN vs ≤1.1 × ULN; owing to the small number of patients enrolled in the ECOG PS 1 and LDH ≤1.1 × ULN strata, these strata were combined.
Data cutoff: Jun 26, 2019.

P Ferrucci KN022 SMR 2019

Summary of Adverse Events

	Pembro + D + T n (%) N = 60	Placebo + D + T n (%) N = 60
Any-grade AE	60 (100.0)	58 (96.7)
Grade 3-5	42 (70.0)	27 (45.0)
Led to death[a]	2 (3.3)	0 (0)
Led to discontinuation of ≥1 study drug	28 (46.7)	12 (20.0)
Led to discontinuation of all 3 study drugs	18 (30.0)	10 (16.7)
Treatment-related AE	57 (95.0)	56 (93.3)
Grade 3-5	35 (58.3)	15 (25.0)
Led to death	1 (1.7)	0 (0)
Led to discontinuation of ≥1 study drug	26 (43.3)	11 (18.3)

[a]One patient died due to treatment-related pneumonitis and one died of unknown cause.
Data cutoff: Jun 26, 2019.

P Ferrucci KN022 SMR 2019

Summary and Conclusions

- With longer follow-up, pembrolizumab + D + T vs placebo + D + T continued to show
  - Numerically higher PFS (24-mo rate, 41% vs 16%)
  - Numerically longer DOR (24-mo rate, 55% vs 16%)
  - Numerically higher OS rate (24-mo rate, 63% vs 52%)
- However, these improvements were accompanied by a higher incidence of grade 3-5 TRAEs (58% vs 25%)
  - Higher incidence of discontinuation of ≥1 study drug owing to TRAEs (43% vs 18%)
  - One patient in the pembrolizumab + D +T arm died due to treatment-related pneumonitis
- Role of PD-1 inhibitors as part of triplet therapy with BRAF and MEK inhibitors must be further validated in phase 3 studies

Evaluation of Atezolizumab, Cobimetinib, and Vemurafenib in Previously Untreated Patients With *BRAF*^{V600} Mutation–Positive Advanced Melanoma: Primary Results From the Phase 3 IMspire150 Trial

Grant A. McArthur, M.B., B.S., Ph.D.,[1] Daniil Stroyakovskiy, M.D.,[2] Helen Gogas, M.D., Ph.D.,[3] Caroline Robert, M.D., Ph.D.,[4] Karl Lewis, M.D.,[5] Svetlana Protsenko, M.D.,[6] Rodrigo Pereira, M.D.,[7] Thomas Eigentler, M.D.,[8] Piotr Rutkowski, M.D., Ph.D.,[9] Lev Demidov, M.D.,[10] Georgy Moiseevich Manikhas, M.D.,[11] Yibing Yan,[12] Kuan-Chieh Huang, Ph.D.,[12] Anne Uyei, M.D.,[12] Virginia McNally, Ph.D.,[13] Ralf Gutzmer, M.D.,[14] Paolo Ascierto, M.D.[15]

[1]Melanoma and Skin Service and Cancer Therapeutics Program, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]Moscow City Oncology Hospital #62 of Moscow Healthcare Department, Moscow, Russia; [3]First Department of Medicine, Laiko General Hospital, National and Kapodistrian University of Athens, Greece; [4]Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France; [5]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [6]Department of Chemotherapy and Innovative Technologies, N. N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russia; [7]Hospital das Clinicas, Porto Alegre, Brazil; [8]University Hospital Tübingen, Tübingen, Germany; [9]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [10]N. N. Blokhin Russian Cancer Research Center, Ministry of Health, Moscow, Russia; [11]St. Petersburg Oncology Hospital, St. Petersburg, Russia; [12]Genentech, Inc., South San Francisco, CA, USA; [13]Roche Products Ltd., Welwyn Garden City, UK.; [14]Haut-Tumour-Zentrum Hannover (HTZH), Klinik für Dermatologie, Allergologie und Venerologie, Medizinische Hochschule Hannover (MHH), Hannover, Germany; [15]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale," Naples, Italy.

AACR Annual Meeting 2020

IMspire150 Study Design

- Previously untreated, advanced *BRAF*^{V600} mutation–positive melanoma
- ECOG PS 0 to 1
- Measurable disease by RECIST v1.1

Randomized 514 patients

Randomization stratified by:
- Geographic region and
- Centrally tested LDH level (≤ ULN versus > ULN)

R 1:1

	28-day doublet period; cycle 1		Triple combination period; cycle 2 onward
	Days 1–21	Days 22–28	28-day cycle
Arm 1	Vemurafenib 960 mg BID plus Cobimetinib 60 mg QD	Vemurafenib 720 mg BID plus vemurafenib placebo	Atezolizumab 840 mg on days 1 and 15 plus Vemurafenib 720 mg BID plus vemurafenib placebo BID plus Cobimetinib 60 mg QD on days 1–21
Arm 2	Vemurafenib 960 mg BID plus Cobimetinib 60 mg QD	Vemurafenib 960 mg BID	Atezolizumab placebo on days 1 and 15 plus Vemurafenib 960 mg BID plus Cobimetinib 60 mg QD on days 1–21

Primary endpoint
- Investigator-assessed PFS

Key secondary endpoints
- PFS assessed by an IRC
- Objective response (confirmed by observations at least 4 weeks apart)
- DOR
- OS

BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PS, performance status; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

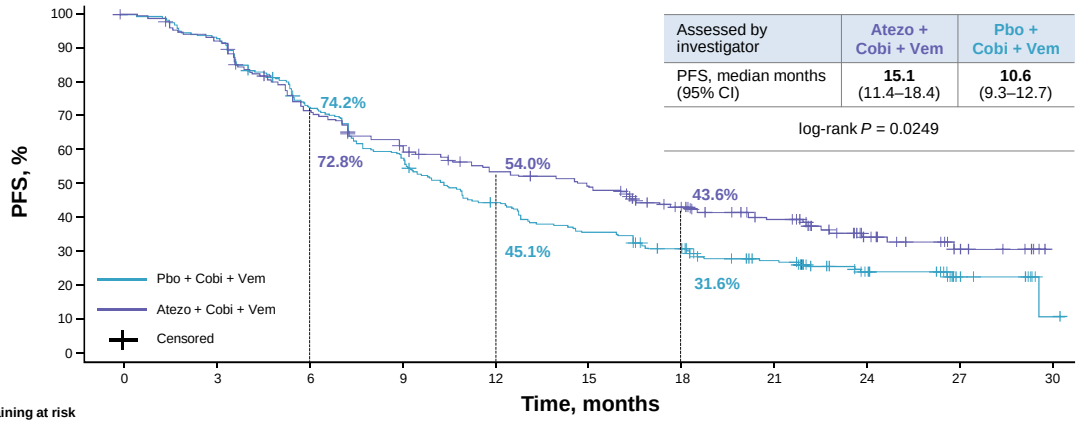
AACR Annual Meeting 2020

5

	Atezolizumab + vemurafenib + cobimetinib n=256	Placebo + vemurafenib + cobimetinib n=258
Median age, years (range)	54.0 (22–87)	53.5 (23–88)
Age		
<65 years	195 (76.2)	199 (77.1)
≥65 years	61 (23.8)	59 (22.9)
Male sex	150 (58.6)	149 (57.8)
Race, white	243 (94.9)	246 (95.3)
Geographic region		
North America	13 (5.1)	14 (5.4)
Europe	203 (79.3)	203 (78.7)
Australia/New Zealand/Other	40 (15.6)	41 (15.9)
ECOG PS		
0	195 (76.2)	198 (76.7)
1	61 (23.8)	56 (21.7)
Unknown	0	4 (1.6)

	Atezolizumab + vemurafenib + cobimetinib n=256	Placebo + vemurafenib + cobimetinib n=258
Disease stage		
IIIC	14 (5.5)	16 (6.2)
IV	242 (94.5)	240 (93.0)
Unknown	0	2 (0.8)
Elevated LDH level (>ULN)	84 (32.8)	85 (32.9)
Stage,* distant metastases at study entry		
M0–M1B	110 (43.0)	93 (36.0)
M1C	145 (56.6)	163 (63.2)
Unknown	1 (0.4)	2 (0.8)
Number of involved organs		
1–3	113 (44.1)	111 (43.0)
>3	143 (55.9)	144 (55.8)
Unknown	0	3 (1.2)
Previously treated brain metastases	5 (2.0)	8 (3.1)
Prior adjuvant therapy	41 (16.0)	30 (11.6)

IMspire150: Primary Endpoint: Investigator-Assessed PFS



Assessed by investigator	Atezo + Cobi + Vem	Pbo + Cobi + Vem
PFS, median months (95% CI)	**15.1** (11.4–18.4)	**10.6** (9.3–12.7)

log-rank *P* = 0.0249

Patients remaining at risk

Pbo + Cobi + Vem	258	230	179	143	107	86	71	51	27	11	1
Atezo + Cobi + Vem	256	229	174	149	123	114	90	66	34	11	

Atezo, atezolizumab; CI, confidence interval; Cobi, cobimetinib; Pbo, placebo; Vem, vemurafenib.

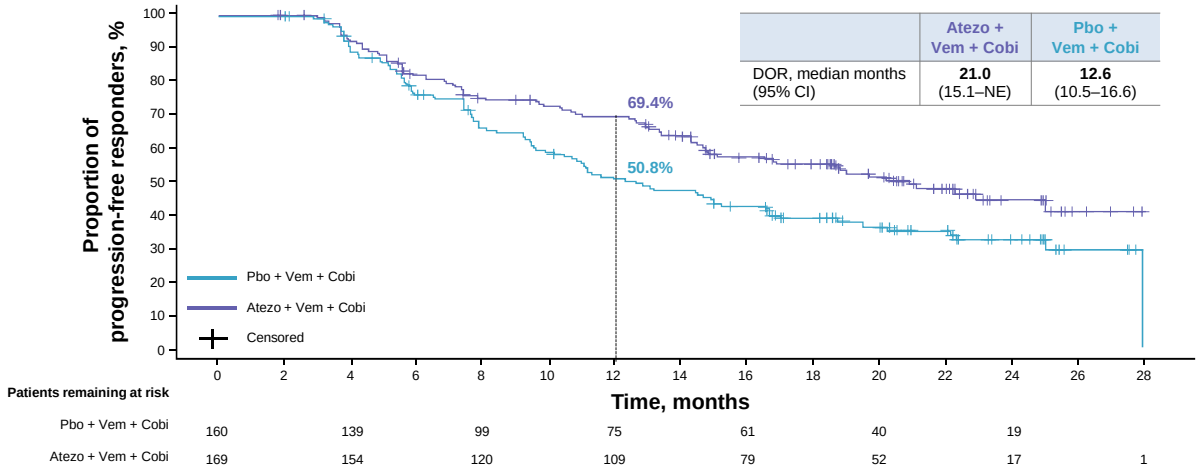
AACR Annual Meeting 2020

9

IMspire150: ORRs

	Atezolizumab + vemurafenib + cobimetinib n=256	Placebo + vemurafenib + cobimetinib n=258
ORR	66.3%	65.0%
Complete response	15.7%	17.1%
Partial response	50.6%	48.0%
Stable disease	22.7%	22.8%

IMspire150: Duration of Response

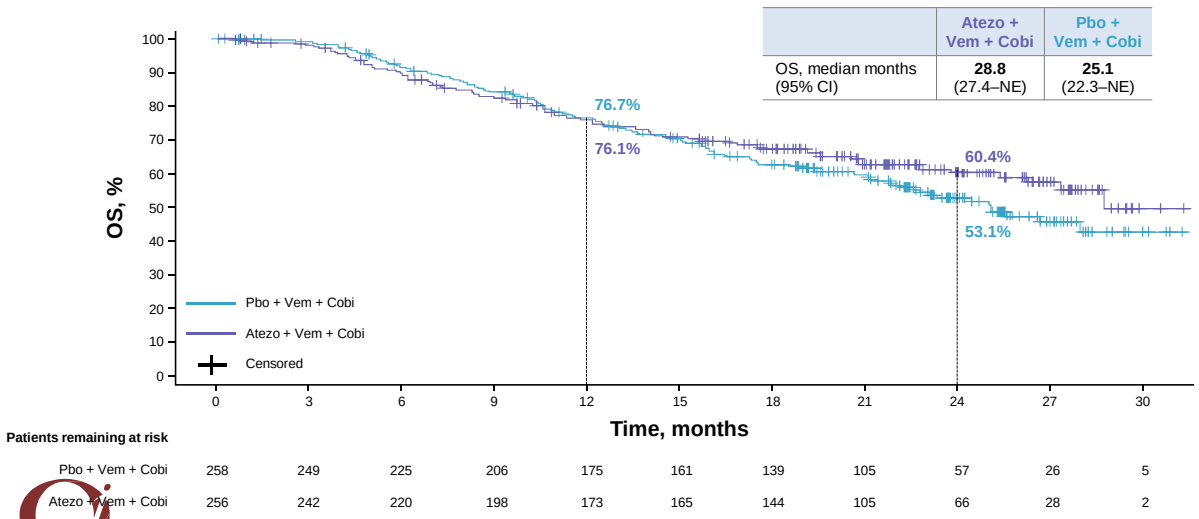


	Atezo + Vem + Cobi	Pbo + Vem + Cobi
DOR, median months (95% CI)	**21.0** (15.1–NE)	**12.6** (10.5–16.6)

- Addition of atezolizumab prolonged DOR

NE, not evaluable.

IMspire150: Overall Survival



Patients remaining at risk

Pbo + Vem + Cobi	258	249	225	206	175	161	139	105	57	26	5
Atezo + Vem + Cobi	256	242	220	198	173	165	144	105	66	28	2

Treatment-Related AEs Leading to Treatment Discontinuation

Preferred terms, n (%)	Atezolizumab + vemurafenib + cobimetinib n=230	Placebo + vemurafenib + cobimetinib n=281
Patients with ≥1 AE, n	29 (12.6)	44 (15.7)
ALT increased	4 (1.7)	4 (1.4)
AST increased	3 (1.3)	1 (0.4)
Hepatitis	3 (1.3)	1 (0.4)
Lipase increased	2 (0.9)	3 (1.1)
Rash	0	4 (1.4)

Grade 5 AEs

Preferred term, n (%)	Atezolizumab + vemurafenib + cobimetinib n=230	Placebo + vemurafenib + cobimetinib n=281
Patients with a grade 5 AE, n	7 (3.0)	7 (2.5)
Sepsis	2 (0.9)	0
Septic shock	1 (0.4)	0
Pneumonia	1 (0.4)	0
Hepatic failure	1 (0.4)*,†	0
Hepatitis fulminant	1 (0.4)*,†	0
Cardiac arrest	1 (0.4)	1 (0.4)
Cardiac failure	0	1 (0.4)
Left ventricular failure	0	1 (0.4)
Cerebrovascular accident	0	1 (0.4)
Hydrocephalus	0	1 (0.4)
Gastrointestinal hemorrhage	0	1 (0.4)
Pulmonary hemorrhage	0	1 (0.4)*

*Treatment-related AEs for any treatment.
†The patients with hepatic failure and fulminant hepatitis had liver lesions at baseline.

Conclusions

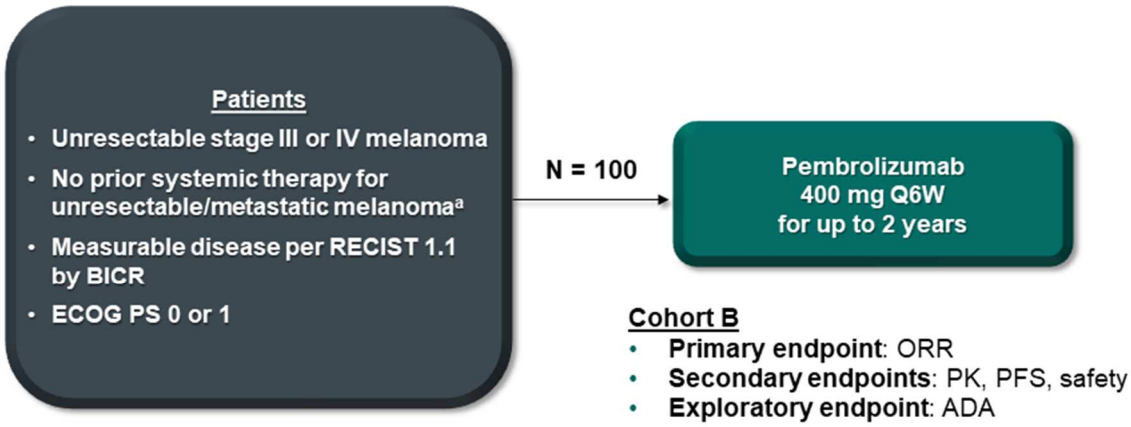
- Atezolizumab combined with vemurafenib and cobimetinib showed a statistically significant and clinically meaningful improvement in investigator-assessed PFS versus placebo plus vemurafenib and cobimetinib
- At the time of this analysis, OS data were not mature but favored the atezolizumab group
- The addition of atezolizumab to vemurafenib and cobimetinib provided a clinically meaningful improvement in DOR versus vemurafenib and cobimetinib alone
- The overall safety profile was consistent with the known risks of each individual study drug and the vemurafenib and cobimetinib combination and no new safety concerns were identified

Pembrolizumab:

200mg/3t vs. 400mg/6t

Lala_KN555_AACR_2020_Oral_Presentation

KEYNOTE-555 Cohort B Study Design (NCT03665597)



[a]BRAF V600 mutant melanoma may have received standard of care targeted therapy (eg, BRAF/MEK inhibitor, alone or in combination). Prior adjuvant or neoadjuvant therapy was permitted if completed ≥4 weeks before randomization.

5

Efficacy: ORR, Interim analysis

ORR of pembrolizumab 400 mg Q6W in metastatic melanoma in KN555 cohort B similar to that observed in previous metastatic melanoma trials[1-3]

Q6W dosing, KN555 Cohort B

N = 44	n	%	95% CI
ORR	**17**	**38.6**	**24.4-54.5**
CR	4	9.1	
PR	13	29.5	
SD	10	22.7	
PD	13	29.5	
NA	4	9.1	

Median follow-up: 6.7 (5.5-8.8) months

Q3W / Q2W dosing, Historical control

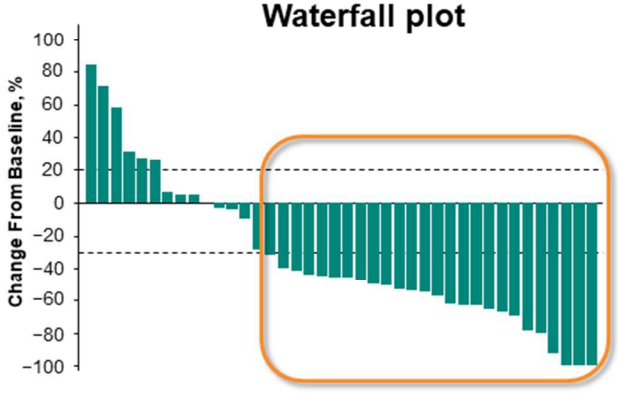
	ORR, %	95% CI
Combined experience (N = 1221)	**35.1**	**32.5-37.9**
KEYNOTE-001 Pembro 2 mg/kg Q3W or 10 mg/kg Q3W or 10 mg/kg Q2W (ipilimumab naïve; N = 313)[1]	39	
KEYNOTE-006 Pembro 10 mg/kg Q3W or 10 mg/kg Q2W (N=556)[2]	36.5	
KEYNOTE-252 Pembro 200 mg Q3W + placebo (N = 352)[3]	31.5	

Response assessed per RECIST v1.1 by BICR. Data cutoff date: Feb 6, 2020.

1. Ribas et al. JAMA. 2016;315(15):1600-9. 2. Schacter et al. Lancet. 2017; 390:1853-1862. 3. Long et al. Lancet Oncol. 2019;20:1083-1097.

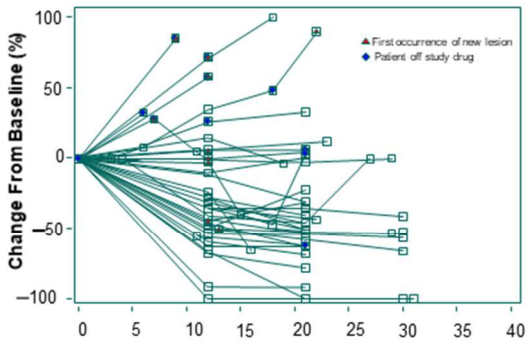
Efficacy: Target Lesion Size Reductions In Individual Patients, Interim Analysis

Waterfall plot



26 of 44 (59%) patients had >30% reduction from baseline in target lesion size

Spider plot



Weeks Since Treatment Initiation

Data cutoff date: Feb 6, 2020.

Safety Summary: Interim Analysis

Safety profile of pembrolizumab 400 mg Q6W is consistent with pembrolizumab 200 mg Q3W safety demonstrated in >12 tumor types[1]

Adverse events	N = 44
Any-grade AE, n (%)	43 (97.7)
Grade 3-4	11 (25.0)
Led to death	0
Led to discontinuation	0
Treatment-related AE, n (%)	30 (68.2)
Grade 3-4	1 (2.3)
Led to death	0
Led to discontinuation	0

Drug exposure	N = 44
Days on therapy, mean (range)	147.5 (1-217)
Number of administrations, mean (range)	4.4 (1-6)

- Low ADA rate (<2%) at Q6W dosing consistent with historical low immunogenicity of pembrolizumab[2]

1. KEYTRUDA® (pembrolizumab) for injection, for intravenous use. Whitehouse Station, NJ, USA: Merck Sharp & Dohme Corp. 2020.2. Van Vugt et al. *J Immunother Cancer.* 2019;7:212. Data cutoff date: Feb 6, 2020.

10

ZAKLJUČEK:

- Aplikacija prembrolizumaba v odmerku 400mg/6t je enako učinkovita in nič bolj toksična kot aplikacija 200mg/3t

Pembrolizumab:

rezultati dolgotrajnega preživetja in reindukcija

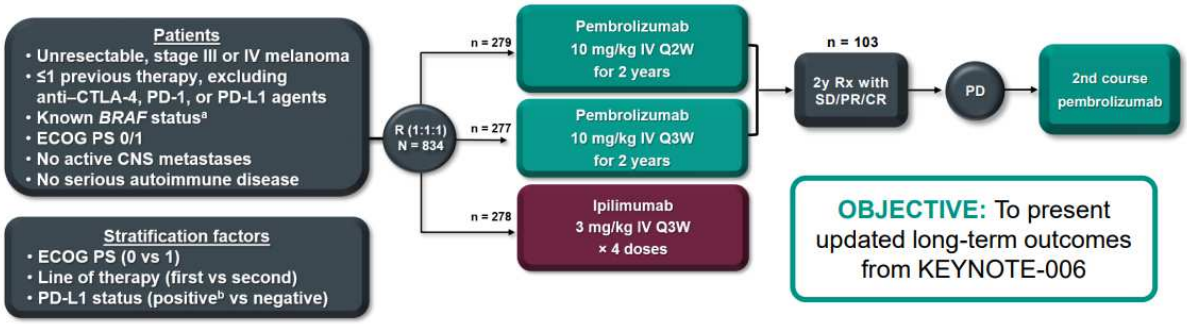
Long-Term Survival From Pembrolizumab Completion and Pembrolizumab Retreatment: Phase 3 KEYNOTE-006 in Advanced Melanoma

G. V. Long[1-4], J. Schachter[5], A. Arance[6], J.-J. Grob[7], L. Mortier[8], A. Daud[9], M. S. Carlino[1,2,10,11], A. Ribas[12], C. M. McNeil[2,13], M. Lotem[14], J. Larkin[15], P. Lorigan[16], B. Neyns[17], C. U. Blank[18], T. M. Petrella[19], O. Hamid[20], E. Jensen[21], C. Krepler[21], S. J. Diede[21], C. Robert[22]

[1]Melanoma Institute Australia, Sydney, NSW, Australia; [2]University of Sydney, Sydney, NSW, Australia; [3]Royal North Shore Hospital, Sydney, NSW, Australia; [4]Mater Hospital, North Sydney, NSW, Australia; [5]Sheba Medical Center, Tel HaShomer Hospital, Tel Aviv, Israel, [6]Hospital Clinic de Barcelona, Barcelona, Spain; [7]Aix Marseille University, Hôpital de la Timone, Marseille, France; [8]Université Lille, Centre Hospitalier Regional Universitaire de Lille, Lille, France; [9]UCSF, San Francisco, CA, USA; [10]Blacktown Hospital, Blacktown, NSW, Australia; [11]Crown Princess Mary Cancer Centre, Westmead Hospital, Sydney, NSW, Australia; [12]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [13]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [14]Sharett Institute of Oncology, Hadassah Hebrew Medical Center, Jerusalem, Israel; [15]Royal Marsden Hospital, London, England; [16]University of Manchester and the Christie NHS Foundation Trust, Manchester, England; [17]Universitair Ziekenhuis Brussel, Brussels, Belgium; [18]Netherlands Cancer Institute, Amsterdam, Netherlands; [19]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [20]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [21]Merck & Co., Inc., Kenilworth, NJ, USA; [22]Gustave Roussy and Paris-Sud University, Villejuif, France

Background & Methods

- KEYNOTE 006: Pembrolizumab significantly improved OS vs ipilimumab in patients with ipilimumab-naive advanced melanoma[1,2]



- Two pembrolizumab arms pooled as similar efficacy[2]
- Patients completing ≥94 weeks of pembrolizumab with SD/PR/CR were considered to have completed 2 years of treatment
- Patients could receive a 2nd course of 1 year of pembrolizumab if progressed after SD/PR/CR
- Data cut-off: July 31, 2019; median follow-up: 66.8 months (range, 65.0-70.4); time from last patient enrolled to data cutoff, 65.0 months

[a]Prior anti-BRAF therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
[b]Defined as ≥1% staining in tumor and adjacent immune cells as assessed by IHC using 22C3 antibody.

Presented by Georgina V. Long

Prior Treatment

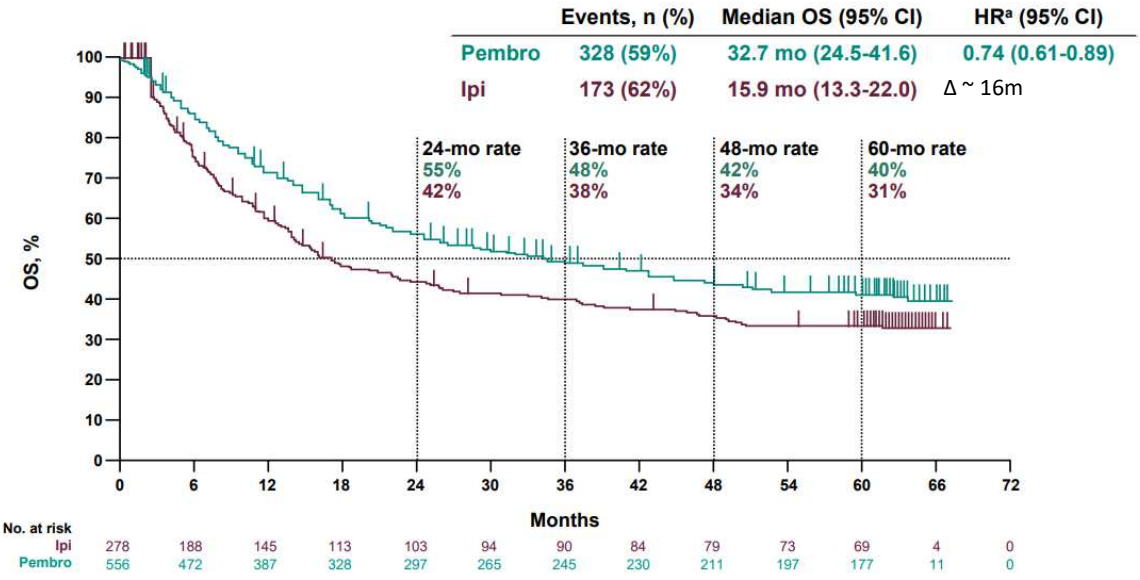
- Eligible patients were treatment-naive or had received 1 prior systemic treatment[a, 2]

	Pembro	Ipi
	n (%)	n (%)
Total Population	**556**	**278**
First line	368 (66)	181 (65)
Second line	187 (34)	97 (35)
Chemotherapy	77 (14)	29 (10)
Immunotherapy	15 (3)	12 (4)
BRAF ± MEK inhibitor	95 (17)	56 (20)

[a]Patients with *BRAF*$^{V600E/K}$ mutation may have received prior BRAF±MEK inhibitor therapy; however BRAF±MEK inhibitor therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or rapidly progressive disease.
Data cut-off: July 31, 2019.

Presented by Georgina V. Long

Overall Survival: Total Population



Data cut-off: July 31, 2019. [a]Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); in instances where there were no patients in one of the treatment groups involved in a comparison for a particular stratum, that stratum was excluded from the treatment comparison.

Presented by Georgina V. Long

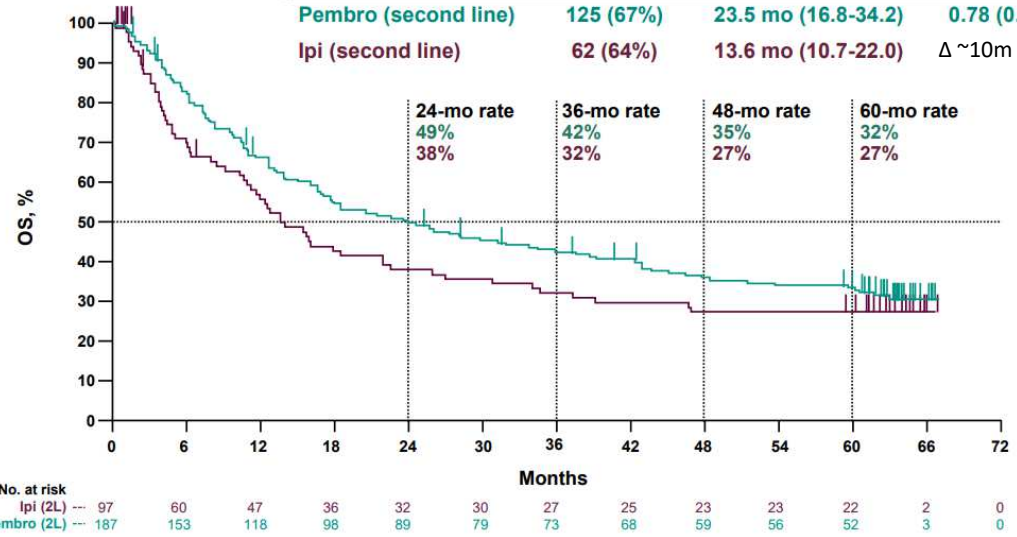
Overall Survival: First Line Patients

Data cut-off: July 31, 2019. [a]Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); in instances where there were no patients in one of the treatment groups involved in a comparison for a particular stratum, that stratum was excluded from the treatment comparison.

Presented by Georgina V. Long

Overall Survival: Second Line Patients

	Events, n (%)	Median OS (95% CI)	HR[a] (95% CI)
Pembro (second line)	125 (67%)	23.5 mo (16.8-34.2)	0.78 (0.57-1.07)
Ipi (second line)	62 (64%)	13.6 mo (10.7-22.0)	Δ ~10m



Data cut-off: July 31, 2019. [a]Based on Cox regression model with treatment as a covariate stratified by line of therapy (1st vs 2nd), PD-L1 status (positive vs negative) and ECOG (0 vs 1); in instances where there were no patients in one of the treatment groups involved in a comparison for a particular stratum, that stratum was excluded from the treatment comparison.

Presented by Georgina V. Long

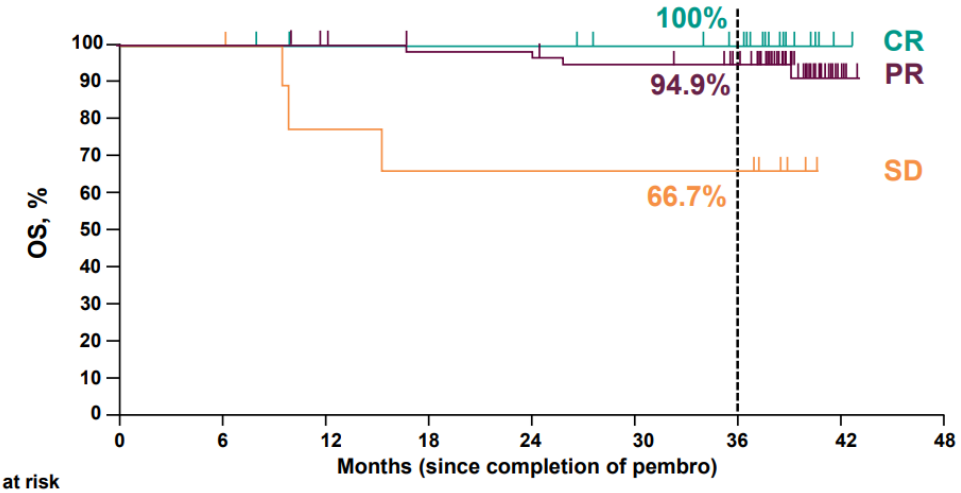
Response

	All Patients		First-line Patients		Second-line Patients	
	Pembro n = 556	Ipi n = 278	Pembro n = 368	Ipi n = 181	Pembro n = 187	Ipi n = 97
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ORR	**235 (42)**	**46 (17)**	**170 (46)**	**31 (17)**	**64 (34)**	**15 (15)**
CR	78 (14)	9 (3)	63 (17)	6 (3)	15 (8)	3 (3)
PR	157 (28)	37 (13)	107 (29)	25 (14)	49 (26)	12 (12)
SD	117 (21)	70 (25)	70 (19)	45 (25)	47 (25)	25 (26)
PD	163 (29)	107 (38)	97 (26)	75 (41)	66 (35)	32 (33)

Response based on investigator assessment per immune-related response criteria.
Data cut-off: July 31, 2019.

Presented by Georgina V. Long

Overall Survival from completion of 2 Years of Pembrolizumab by Best Overall Response (n = 103)[a]



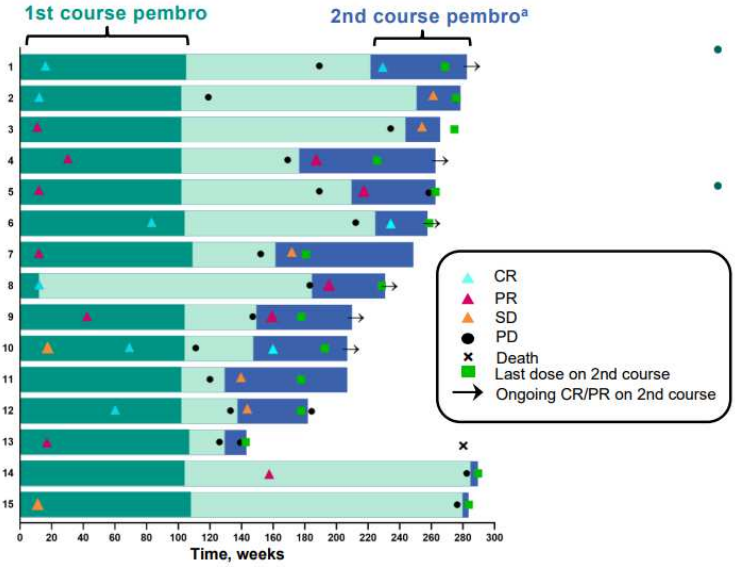
No. at risk

CR	30	30	28	28	28	26	24	1	0
PR	63	63	61	58	58	55	51	4	0
SD	10	9	7	6	6	6	6	0	0

[a]Patients completed ≥94 weeks of pembrolizumab treatment with SD/PR/CR.
Data cut-off: July 31, 2019.

Presented by Georgina V. Long

Patients Who Received Second Course of Pembrolizumab



- 15 pts had 2nd course pembro per trial protocol if:
  - Discontinued with SD/PR/CR in 1st course
  - Had PD after stopping 1st course
- After/during 2nd course
  - 3/15 had CR
  - 4/15 had PR
  - 5/15 had SD
  - 1/15 died
  - 2/15 to be evaluated

[a]For patients 1-13, the blue bar indicates time from start of 2nd course to last scan; at data cutoff, patients 14 and 15 just commenced 2nd course pembrolizumab; imaging was pending.
Data cut-off: July 31, 2019.

Presented by Georgina V. Long

Conclusions

- In this post hoc analysis, pembrolizumab improved OS vs ipilimumab in patients with advanced melanoma regardless of line of therapy (first or second line)
  - 5-year OS rate with 1st line pembrolizumab was 43%
  - CR with 1st line pembrolizumab was 17%
- All patients with a CR who completed 2 years of pembrolizumab were still alive at 5 years
- Retreatment with pembrolizumab at progression in patients with SD/PR/CR provided additional disease control

Acknowledgments
The authors thank the patients and their families and all investigators and site personnel who participated in this study. This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing and/or editorial assistance was provided by Jemimah Walker, PhD, and Doyel Mitra, PhD, of the ApotheCom pembrolizumab team, (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

References

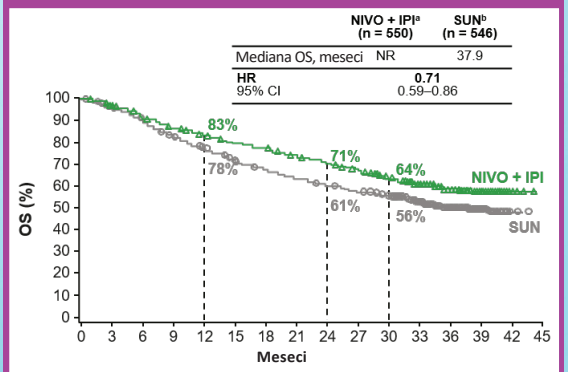
1. Schachter J et al. *Lancet*. 2017;390:1853-1862.
2. Robert C et al. *Lancet Oncol*. 2019;20:1239-1251.

Presented by Georgina V. Long.

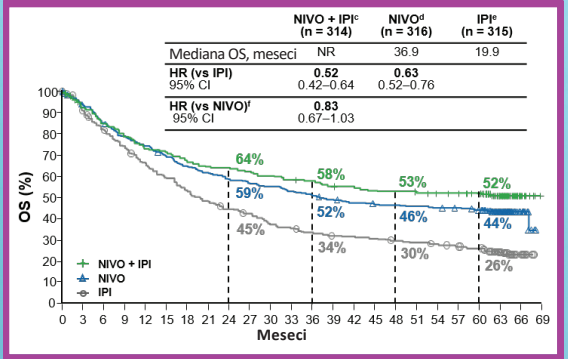
nivolumab + ipilimumab

PODALJŠANO CELOKUPNO PREŽIVETJE PRI VEČIH INDIKACIJAH

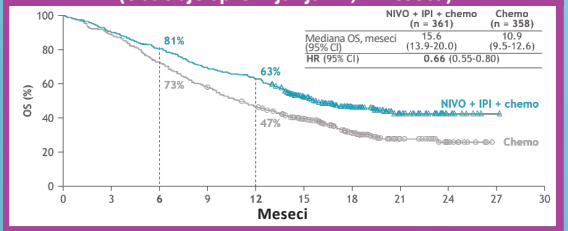
RCC: CheckMate 214 (obdobje spremljanja 30 mesecev)[1]



Melanom: CheckMate 067 (5-letno obdobje spremljanja)[2]



Rak pljuč: CheckMate 9LA (obdobje spremljanja 12,7 meseca)[3]



Povzetek glavnih značilnosti zdravila nivolumab

Povzetek glavnih značilnosti zdravila ipilimumab

1. Tannir NM, et al. ASCO GU 2020; Abstract 609; 2. Larkin J, et al. ESMO 2019; Abstract LBA68; 3. Reck et al. ASCO 2020; Abstract 9501.

OS-celokupno preživetje; NR-ni doseženo; RCC-rak ledvičnih celic; NIVO-nivolumab; IPI-ipilimumab; SUN-sunitinib; HR-razmerje ogroženosti; vs-v primerjavi; n-število bolnikov; CI-interval zaupanja

Samo za strokovno javnost

Mercury koda: IOLR2011782-01

Swixx koda: NM-SI-2020-12-1703 Datum odobritve: DEC2020

THE IMMUNOTHERAPY REVOLUTION

LESSONS FROM MELANOMA

From Advanced to

Adjuvant to Neoadjuvant

Alexander M.M. Eggermont, MD, PhD
Chief Scientific Officer, Board of Directors

Prof Surgical Oncology
University Paris-Saclay, France

Coordinator German NCI Network
Office DKFZ Heidelberg, Germany

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

DISCLOSURE INFORMATION LAST 3 YEARS

Alexander EGGERMONT

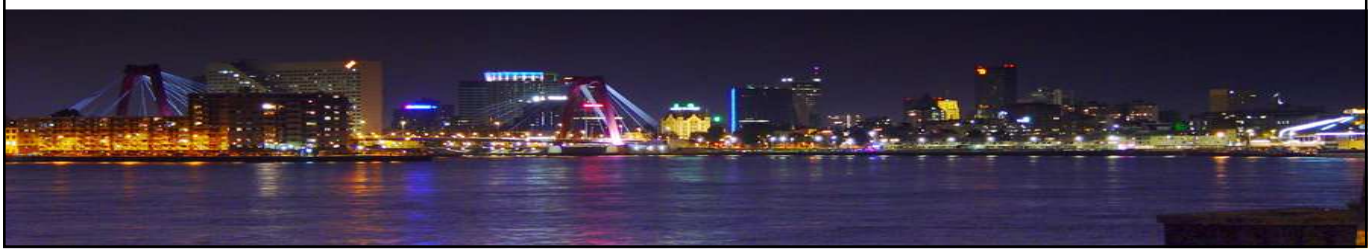
- *Honoraria* : Biocad, BioInvent, BMS, CatalYm, Ellipses, GSK, IO Biotech, Isa Pharmaceuticals, Merck&Co / MSD, Nektar, Novartis, Pfizer, Polynoma, Regeneron, SkylineDx, Stellas
- *Equity*: RiverD, SkylineDx
- *Speaker engagements*: Biocad, BMS, MSD, Novartis

- Positions:
- Chief Scientific Officer: Princess Maxima Center, Utrecht, the Netherlands
- Emeritus Professor Surgical Oncology: Erasmus University Rotterdam Netherlands
- Emeritus Professor Oncology: University Paris-Saclay, France
- Coordinator CCC-Program Deutsche Krebshilfe, Germany
- Coordinating Advisor Multisite National Tumor Centers Program, DKFZ-Heidelberg, Germany

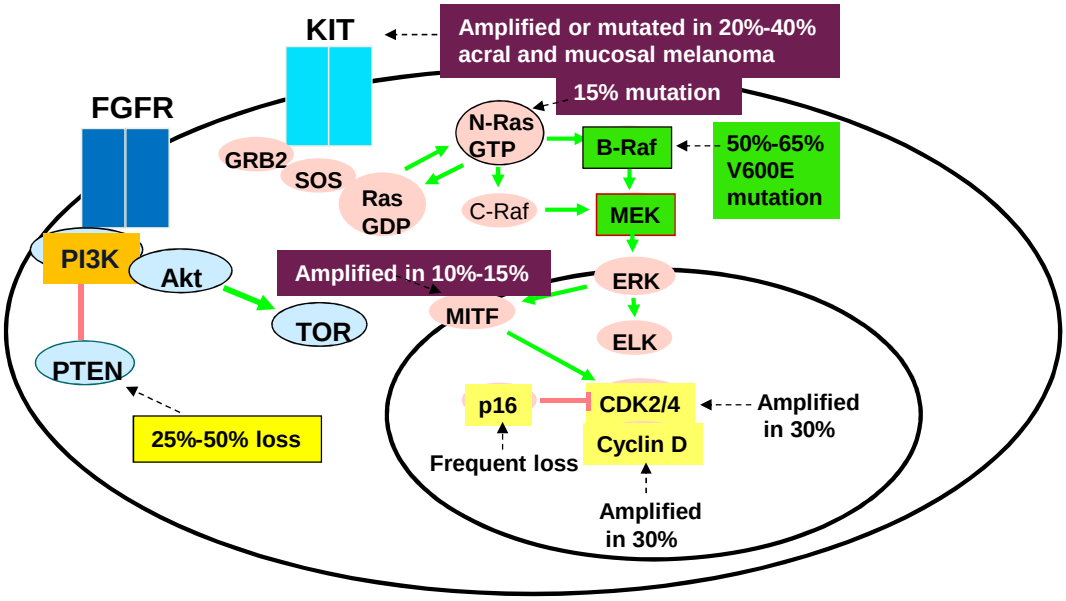
THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION

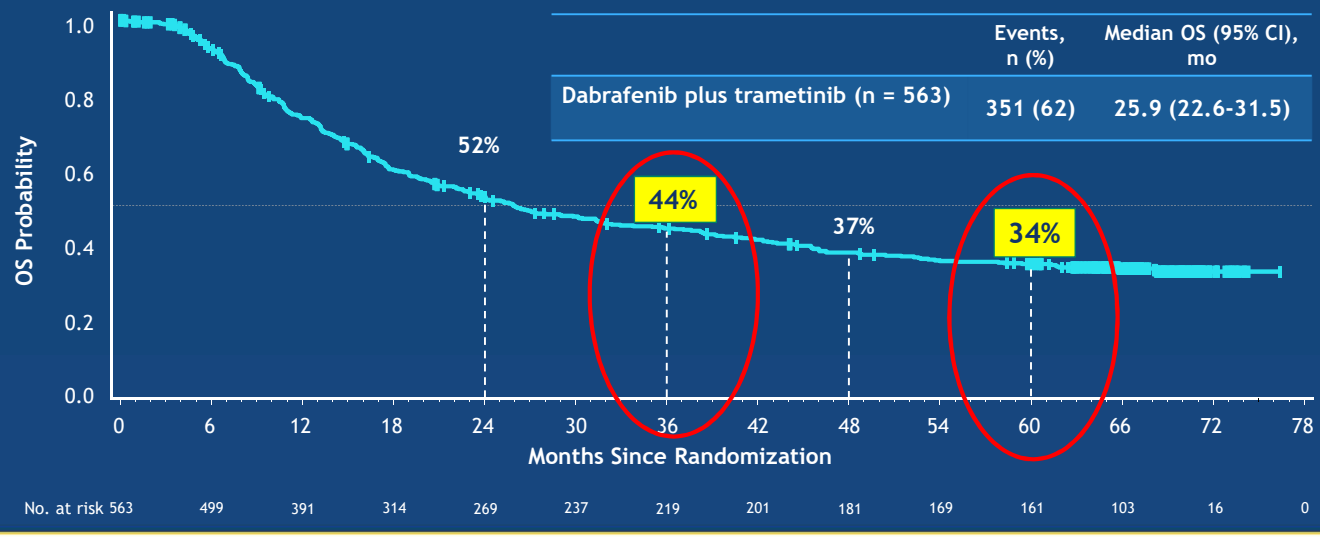


BRAF + MEK Inhibitors Combo



Adapted from Sosman, *Curr. Oncol. Rep*. 11, 405 (2009)

Dabrafenib Plus Trametinib: 3Yr 44% and 5-Yr 34% OS



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 Slides are the property of the author, permission required for reuse.

PRESENTED BY: Paul Nathan

5

THE MELANOMA PARADIGM

MUTATION DRIVEN DRUG DEVELOPMENT

INNOVATIVE IMMUNOMODULATION

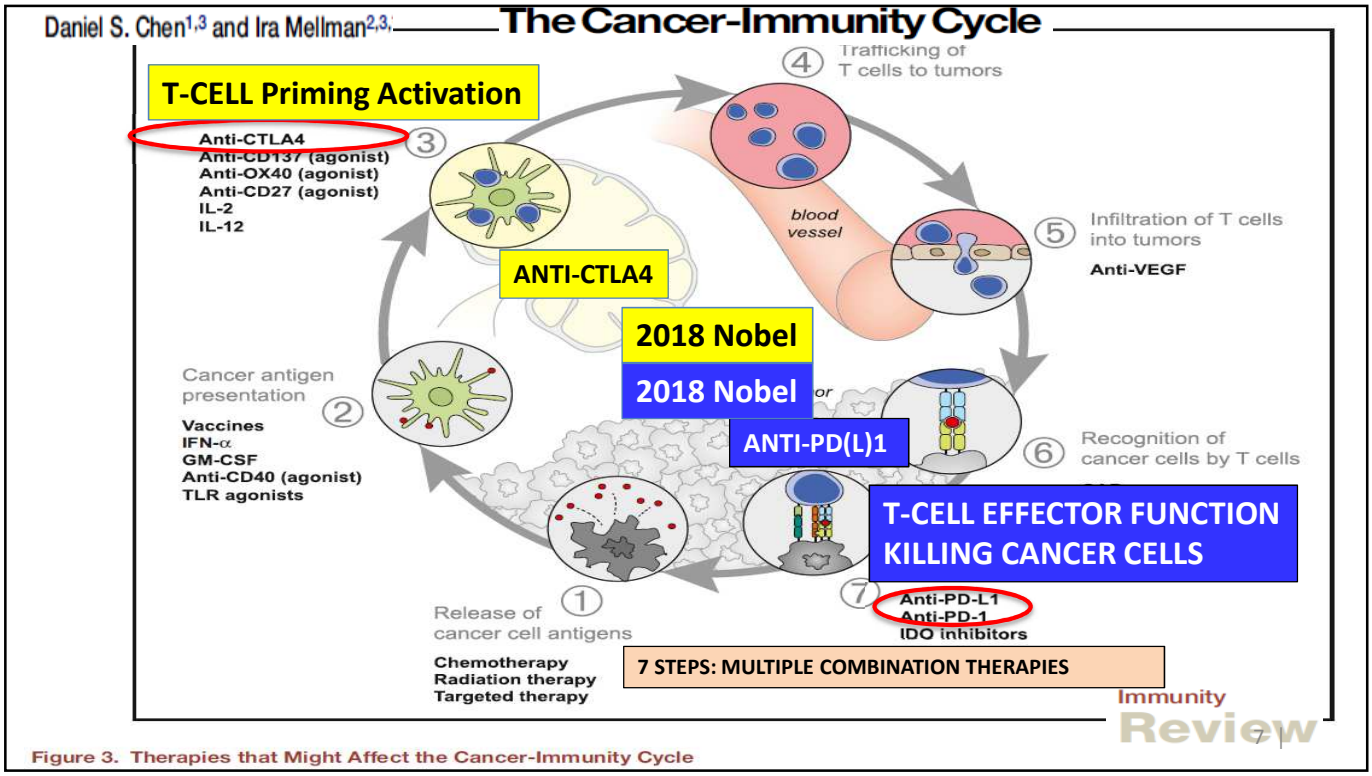
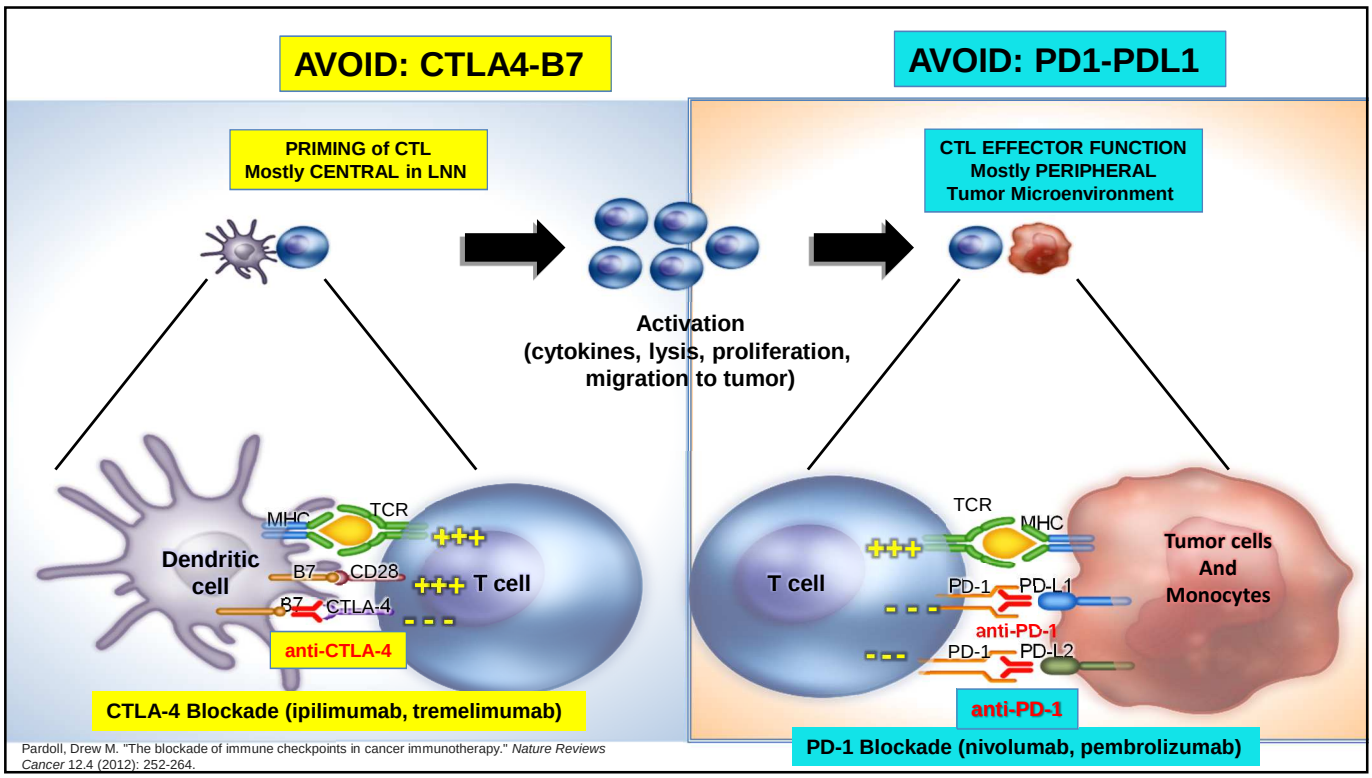


Figure 3. Therapies that Might Affect the Cancer-Immunity Cycle



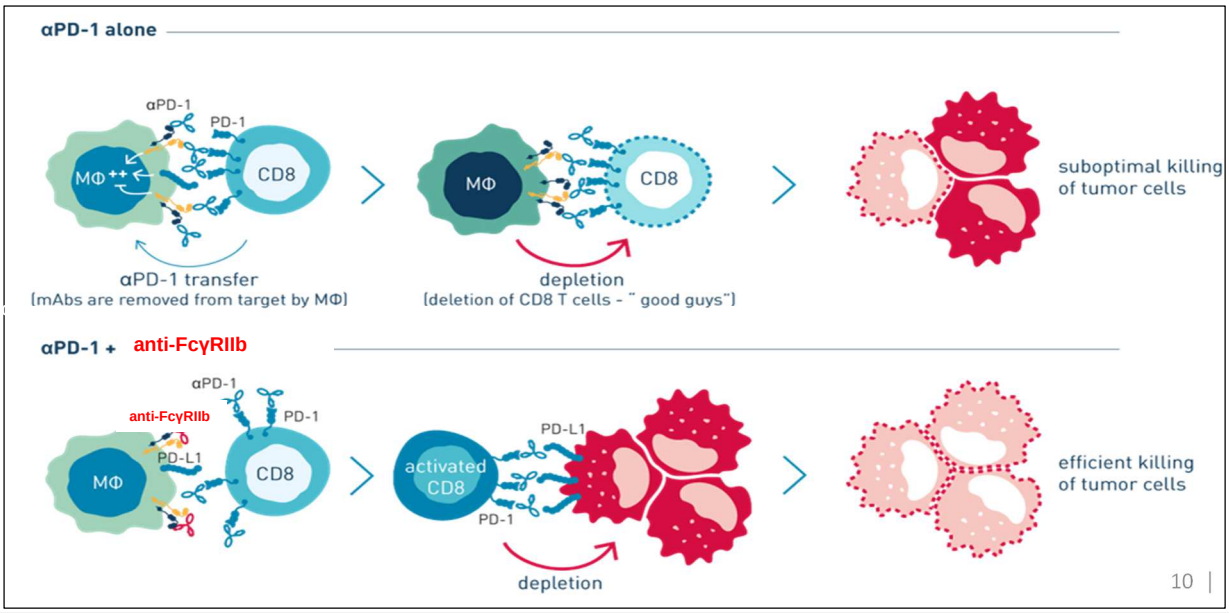
Pardoll, Drew M. "The blockade of immune checkpoints in cancer immunotherapy." *Nature Reviews Cancer* 12.4 (2012): 252-264.

IMMUNE SYSTEM BLOCKED AT MULTIPLE LEVELS

- 1) **CTL PRIMING**
  - e.g. CTLA4 ..... **Unblock: anti-CTLA4**
- 2) **CTL EFFECTOR Function**
  - e.g. PD-1 / PDL-1..... **Unblock: anti-PD1/anti-PDL1**
- 3) **MACROPHAGES in Tumor Infiltrate (TAM)**
  - **e.g. Macrophages; MDSC Unblock: - anti-FcγR**
    - **Fcγ-R modulation: optimize ICI / overcome resistance**
    - **anti-CD47 + anti-SIRPα**
    - M2-M1 repolarization agents (CCR5; CCR5/CCR2) ; **IL-32**
- 4) **Various Immune Escape Mechanisms**
  - e.g.:
    - JAK1/2 mutations and loss Gamma-IFN pathways
    - B2M mutations, Loss MHC Class I molecules, Loss Recognition
    - B-actenin pathway activation : immune exclusion
    - TOX and T-cell exhaustion

9 |

Unblocking Macrophages by anti-FcγRIIb: continued CD8 effector activity



10 |

IMMUNE SYSTEM BLOCKED AT MULTIPLE LEVELS

- 1) **CTL PRIMING**
  - e.g. CTLA4 ..... **Unblock: anti-CTLA4**
- 2) **CTL EFFECTOR Function**
  - e.g. PD-1 / PDL-1..... **Unblock: anti-PD1/anti-PDL1**
- 3) **MACROPHAGES in Tumor Infiltrate (TAM)**
  - **e.g. Macrophages; MDSC** **Unblock: - anti-FcγRII**
    - **Fcγ-R modulation: optimize ICI / overcome resistance**
    - **anti-CD47 + anti-SIRPα**
    - **Fc modulation of anti-PD1 (Prolgolimab)**
    - M2-M1 repolarization agents (CCR5; CCR5/CCR2); **IL-32**
- **4) Various Immune Escape Mechanisms**
  - **e.g.:**
    - **JAK1/2 mutations and loss Gamma-IFN pathways**
    - **B2M mutations, Loss MHC Class I molecules, Loss Recognition**
    - **B-actenin pathway activation : immune exclusion**
    - **TOX and T-cell exhaustion**

11 |

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Dirk Schadendorf, F. Stephen Hodi, Caroline Robert, Jeffrey S. Weber, Kim Margolin, Omid Hamid, Debra Patt, Tai-Tsang Chen, David M. Berman, and Jedd D. Wolchok

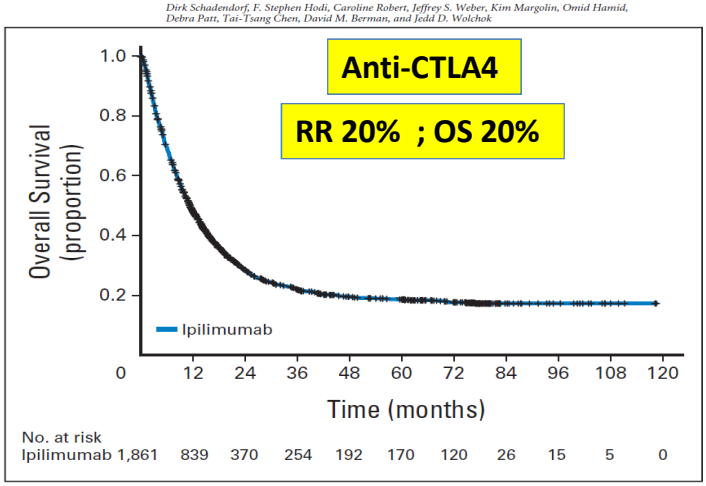
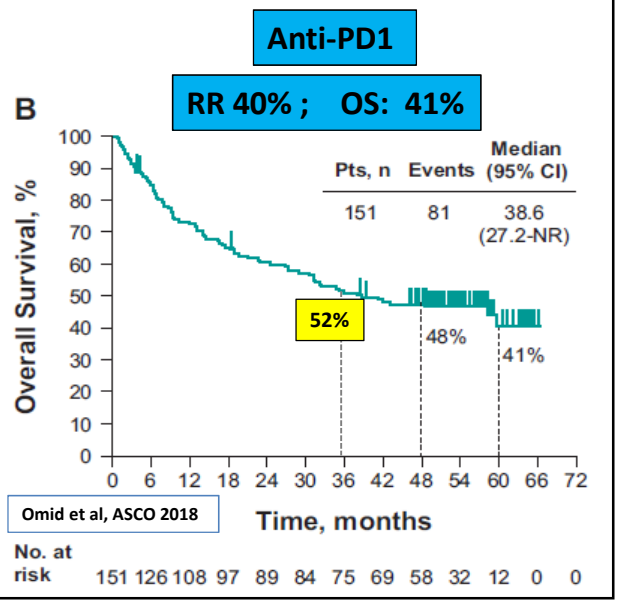


Fig 1. Primary analysis of pooled overall survival (OS) data. Individual patient data were pooled from 10 prospective trials and two retrospective, observational studies of ipilimumab in metastatic melanoma (n = 1,861). Median OS was 11.4 months (95% CI, 10.7 to 12.1 months) with a 3-year survival rate of 22% (95% CI, 20% to 24%). Crosses indicate censored patients.

Phase I Keynote-001 : 3 yr 52% and 5 yr 41% survival Pembrolizumab in advanced melanoma

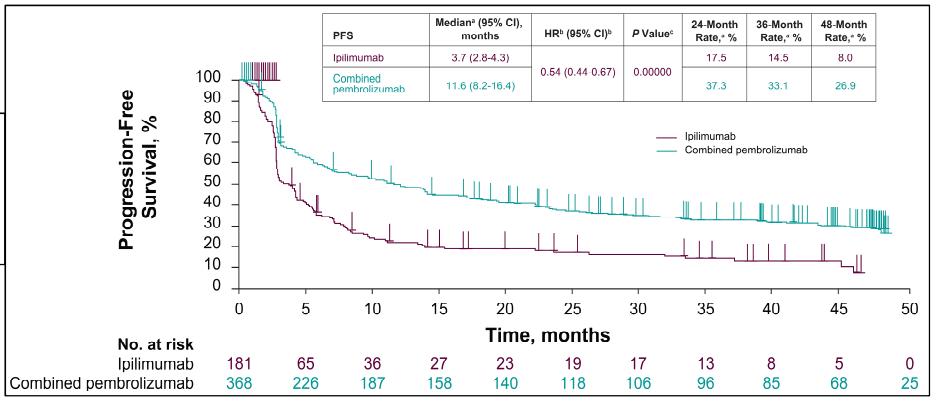


Omid et al, ASCO 2018

KEYNOTE-006: Pembrolizumab vs Ipilimumab
PFS: First-Line Treatment

- **Median PFS:11.6** vs 3.7 mts
- HR, 0.54; P-0.00000

PFS	Median[a] (95% CI), months	HR[b] (95% CI)[b]	*P* Value[c]	24-Month Rate,[a] %	36-Month Rate,[a] %	48-Month Rate,[a] %
Ipilimumab	3.7 (2.8-4.3)	0.54 (0.44 0.67)	0.00000	17.5	14.5	8.0
Combined pembrolizumab	11.6 (8.2-16.4)			37.3	33.1	26.9

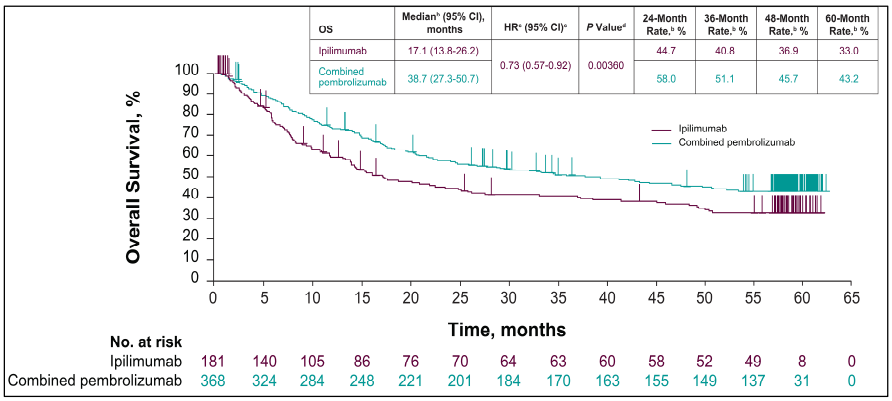


ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; irRC, immune-related response criteria; PD-L1, programmed death ligand 1; PFS, progression-free survival.
[a]From product-limit (Kaplan-Meier) method for censored data.
[b]Based on Cox regression model with treatment as a covariate stratified by line of therapy (first vs second), PD-L1 status (positive vs negative), and ECOG PS (0 vs 1). If no patients are in 1 of the treatment groups involved in a comparison for a particular stratum, that stratum is excluded from the treatment comparison.
[c]1-sided *P* value based on log-rank test.

KEYNOTE-006: Pembrolizumab vs Ipilimumab
OS : First-Line Treatment[a]

- **Median OS 38.7** vs 17.1 mts
- HR, 0.73 ; P= .00360
- **5-year OS : 43.2%** vs 33.0% mts

OS	Median[b] (95% CI), months	HR[c] (95% CI)[c]	*P* Value[d]	24-Month Rate,[b] %	36-Month Rate,[b] %	48-Month Rate,[b] %	60-Month Rate,[b] %
Ipilimumab	17.1 (13.8-26.2)	0.73 (0.57-0.92)	0.00360	44.7	40.8	36.9	33.0
Combined pembrolizumab	38.7 (27.3-50.7)			58.0	51.1	45.7	43.2

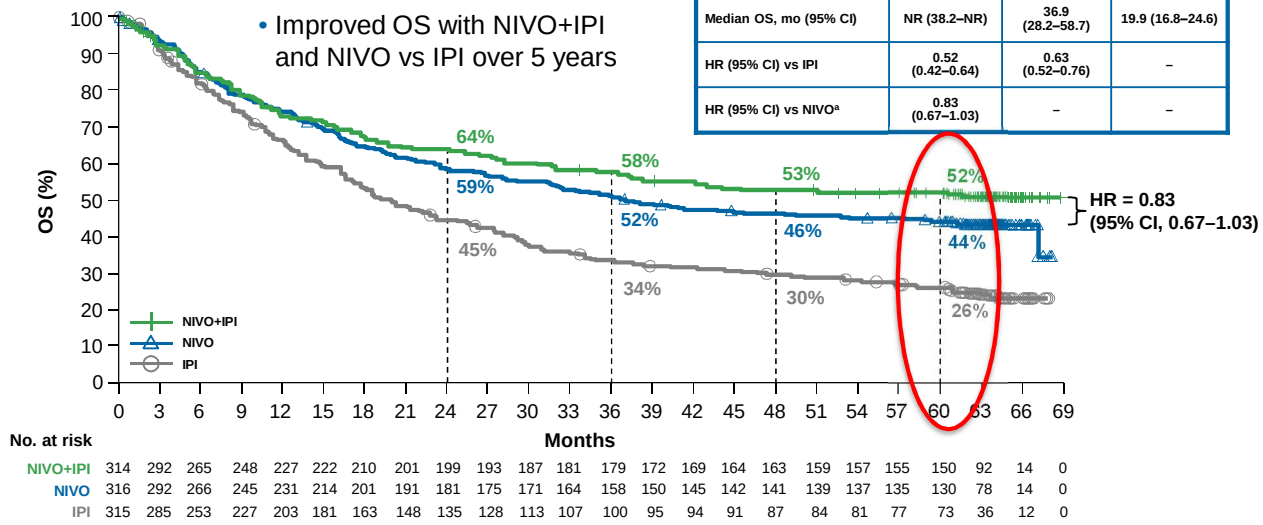


ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1.
[a]Patients excluded from the total population in the combined pembrolizumab and the ipilimumab arms had experienced progression with prior BRAF/MEK inhibitor (n = 95 [17.1%], n = 56 [20.1%]), prior chemotherapy (n = 77 [13.8%], n = 29 [10.4%]), or prior immunotherapy (n = 15 [2.7%], n = 12 [4.3%]).
[b]From product-limit (Kaplan-Meier) method for censored data.
[c]Based on Cox regression model with treatment as a covariate stratified by line of therapy (first vs second), PD-L1 status (positive vs negative), and ECOG PS (0 vs 1). If no patients are in 1 of the treatment groups involved in a comparison for a particular stratum, that stratum is excluded from the treatment comparison.
[d]1-sided *P* value based on log-rank test.

CheckMate 067

Checkmate-067: NIVO + IPI: 5 Year Overall Survival

	NIVO+IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median OS, mo (95% CI)	NR (38.2–NR)	36.9 (28.2–58.7)	19.9 (16.8–24.6)
HR (95% CI) vs IPI	0.52 (0.42–0.64)	0.63 (0.52–0.76)	–
HR (95% CI) vs NIVO[a]	0.83 (0.67–1.03)	–	–



No. at risk																								
NIVO+IPI	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
NIVO	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
IPI	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

[a]Descriptive analysis. 1. Larkin J, et al. Oral presentation at the AACR Annual Meeting; April 1–5, 2017; Washington DC, USA. Abstract CT075; 2. Wolchok JD, et al. *N Engl J Med* 2017;377:1345–1356; 2. Hodi FS, et al. *Lancet Oncol* 2018;19:1480–1492.

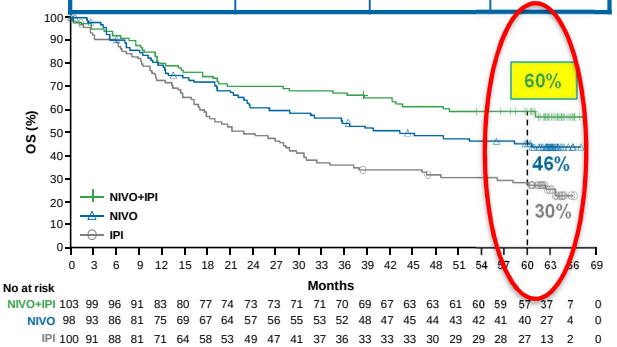
15

CheckMate 067

OS in Patients With *BRAF*-Mutant and Wild-Type Tumors

BRAF Mutant

	NIVO+IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median, mo (95% CI)	NR (50.7–NR)	45.5 (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs IPI	0.44 (0.30–0.64)	0.63 (0.44–0.90)	–
HR (95% CI) vs NIVO[a]	0.70 (0.46–1.05)	–	–

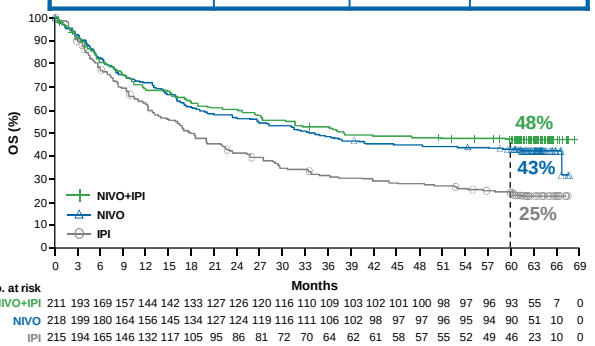


No at risk																								
NIVO+IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	59	57	37	7	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	41	40	27	4	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	13	2	0

• 5-year PFS rates of 38% (NIVO+IPI), 22% (NIVO), and 11% (IPI)

BRAF Wild-Type

	NIVO+IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median, mo (95% CI)	39.1 (27.5–NR)	34.4 (24.1–59.2)	18.5 (14.1–22.7)
HR (95% CI) vs IPI	0.57 (0.45–0.73)	0.64 (0.50–0.81)	–
HR (95% CI) vs NIVO[a]	0.89 (0.69–1.15)	–	–



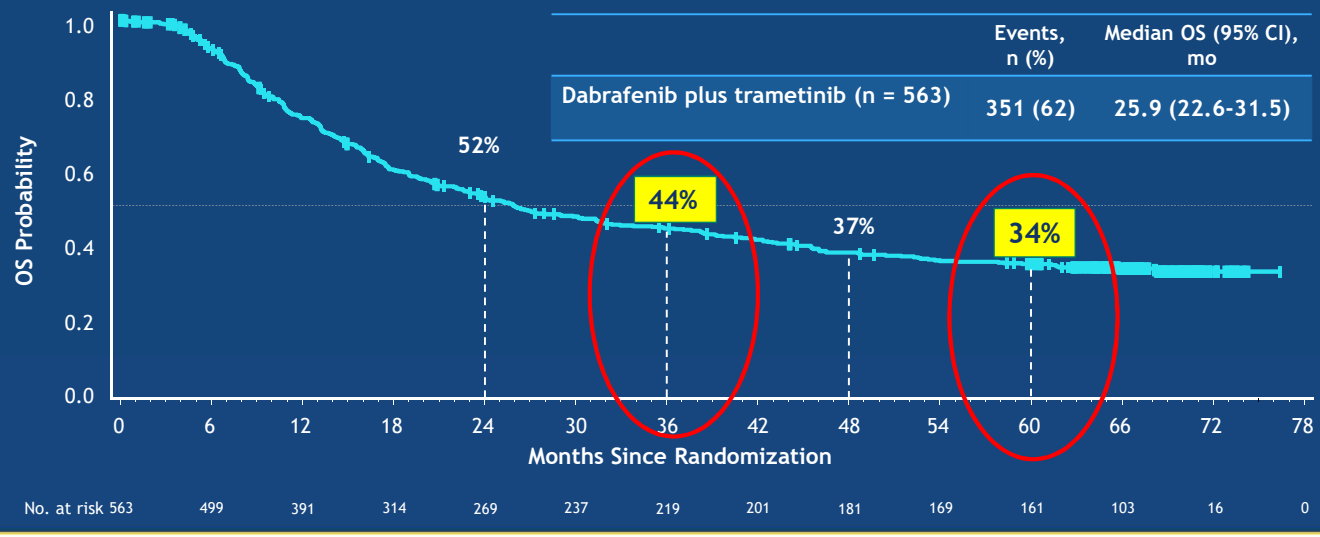
No. at risk																								
NIVO+IPI	211	193	169	157	144	142	133	127	126	120	116	110	109	103	102	101	100	98	97	96	93	55	7	0
NIVO	218	199	180	164	156	145	134	127	124	119	116	111	106	102	98	97	97	96	95	94	90	51	10	0
IPI	215	194	165	146	132	117	105	95	86	81	72	70	64	62	61	58	57	55	52	49	46	23	10	0

• 5-year PFS rates of 35% (NIVO+IPI), 32% (NIVO), and 7% (IPI)

[a]Descriptive analysis.

16

Dabrafenib Plus Trametinib: 3Yr 44% and 5-Yr 34% OS



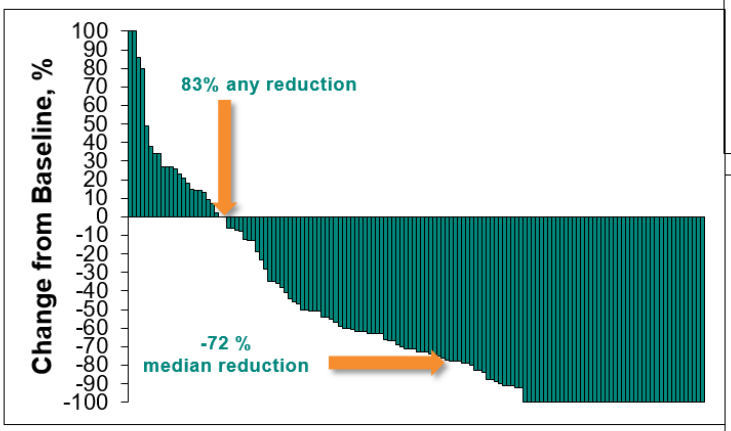
	Events, n (%)	Median OS (95% CI), mo
Dabrafenib plus trametinib (n = 563)	351 (62)	25.9 (22.6-31.5)

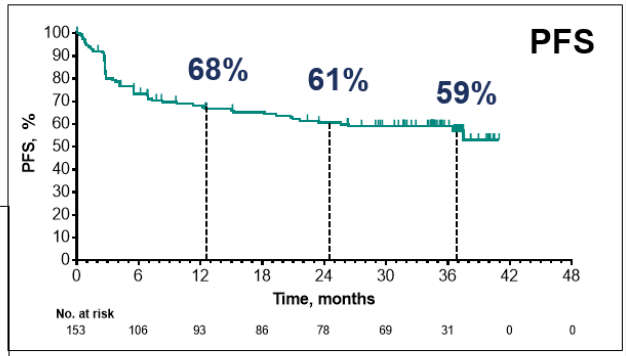
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 Slides are the property of the author, permission required for reuse.

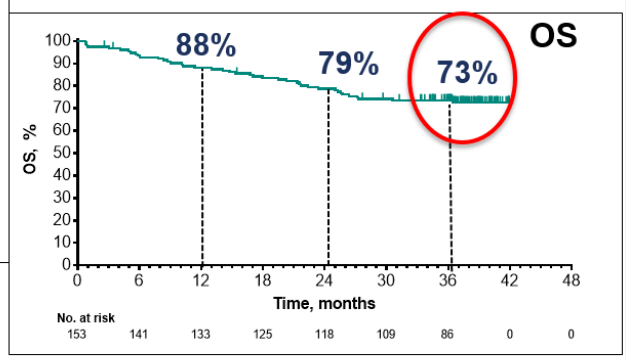
PRESENTED BY: Paul Nathan

17

KEYNOTE-029 3YR DATA
Pembro + Ipilimumab 1mg







Long GV et al ESMO 2018..

TRIPLE THERAPY FOR
BRAFmutant MELANOMA is
about equal to anti-PD1 monotherapy

and
Anti-PD1 + anti-CTLA4
is superior

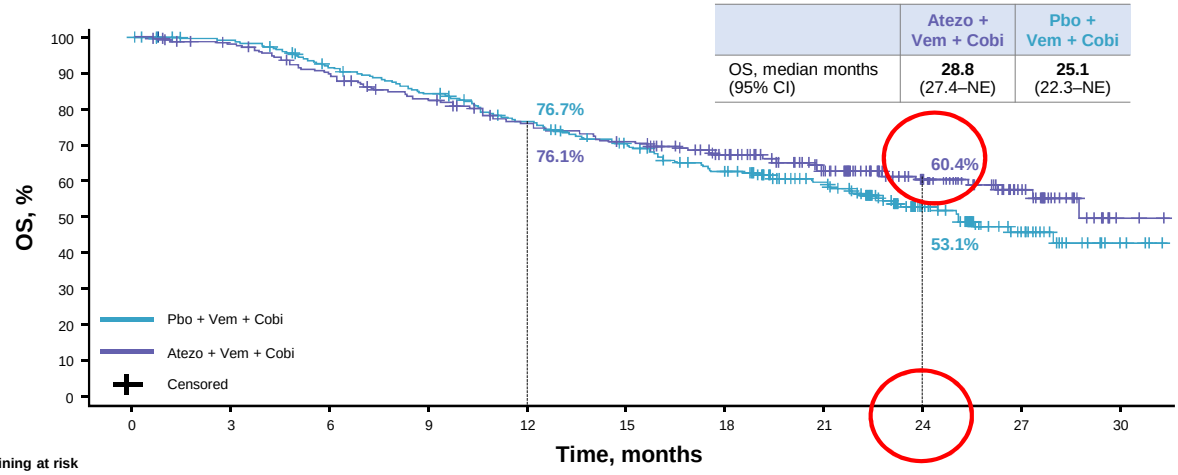
TRIPLE THERAPY FOR
BRAFmutant MELANOMA

Imspire150 positive trial Vemurafenib + Cobimetinib ± Atezolizumab)
COMBI-I negative trial (Dabrafenib + Trametinib ± Spartalizumab)
Difference in median PFS **4.5 months** vs **4.2 months** = 10 days !!

NOT Superior to Anti-PD1 MONOTHERAPY
Clearly Inferior to Anti-PD1 + anti-CTLA4

IMspire150: Overall Survival

	Atezo + Vem + Cobi	Pbo + Vem + Cobi
OS, median months (95% CI)	**28.8** (27.4–NE)	**25.1** (22.3–NE)



Patients remaining at risk

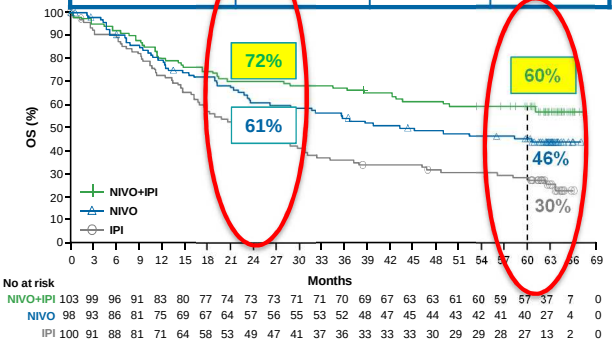
Pbo + Vem + Cobi	258	249	225	206	175	161	139	105	57	26	5
Atezo + Vem + Cobi	256	242	220	198	173	165	144	105	66	28	2

CheckMate 067

OS in Patients With *BRAF*-Mutant and Wild-Type Tumors

BRAF Mutant

	NIVO+IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median, mo (95% CI)	NR (50.7–NR)	45.5 (26.4–NR)	24.6 (17.9–31.0)
HR (95% CI) vs IPI	0.44 (0.30–0.64)	0.63 (0.44–0.90)	–
HR (95% CI) vs NIVO[a]	0.70 (0.46–1.05)	–	–



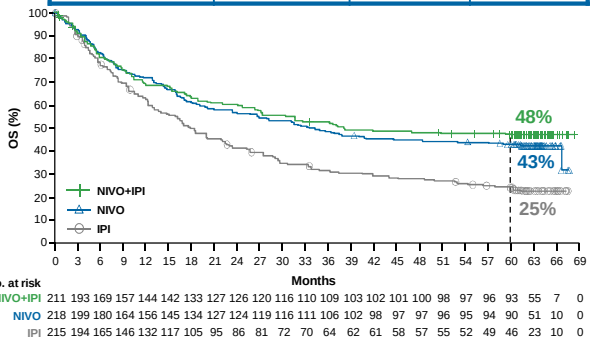
No at risk

NIVO+IPI	103	99	96	91	83	80	77	74	73	73	71	71	70	69	67	63	63	61	60	59	57	37	7	0
NIVO	98	93	86	81	75	69	67	64	57	56	55	53	52	48	47	45	44	43	42	41	40	27	4	0
IPI	100	91	88	81	71	64	58	53	49	47	41	37	36	33	33	33	30	29	29	28	27	13	2	0

- 5-year PFS rates of 38% (NIVO+IPI), 22% (NIVO), and 11% (IPI)

BRAF Wild-Type

	NIVO+IPI (n = 211)	NIVO (n = 218)	IPI (n = 215)
Median, mo (95% CI)	39.1 (27.5–NR)	34.4 (24.1–59.2)	18.5 (14.1–22.7)
HR (95% CI) vs IPI	0.57 (0.45–0.73)	0.64 (0.50–0.81)	–
HR (95% CI) vs NIVO[a]	0.89 (0.69–1.15)	–	–



No. at risk

NIVO+IPI	211	193	169	157	144	142	133	127	126	120	116	110	109	103	102	101	100	98	97	96	93	55	7	0
NIVO	218	199	180	164	156	145	134	127	124	119	116	111	106	102	98	97	97	96	95	94	90	51	10	0
IPI	215	194	165	146	132	117	105	95	86	81	72	70	64	62	61	58	57	55	52	49	46	23	10	0

- 5-year PFS rates of 35% (NIVO+IPI), 32% (NIVO), and 7% (IPI)

[a]Descriptive analysis.

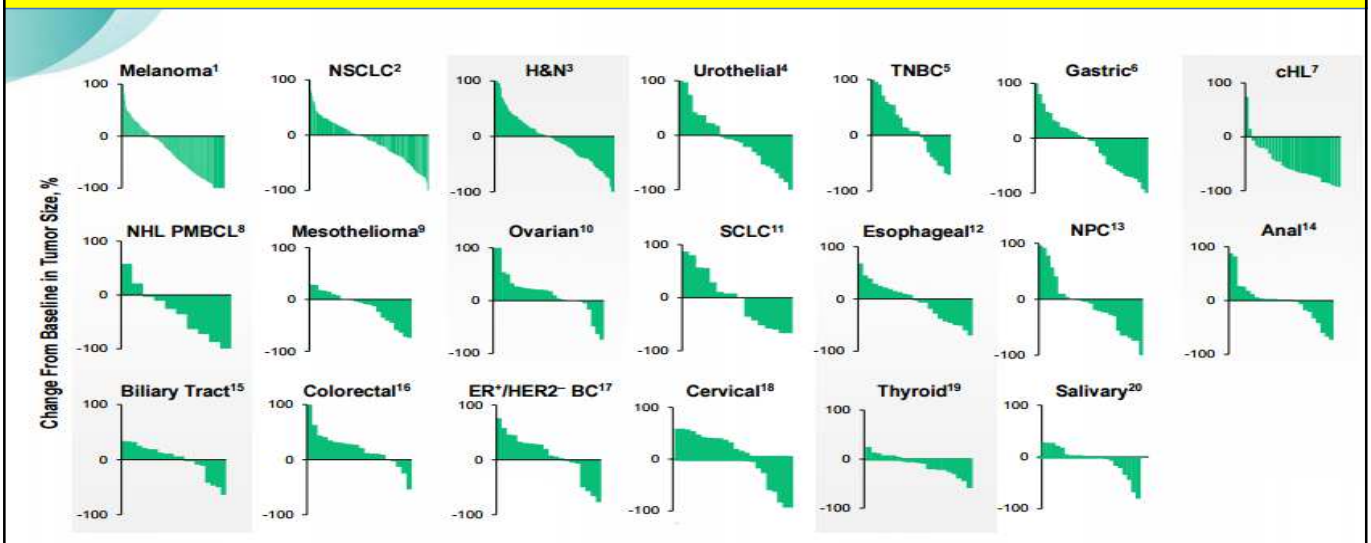
TRIPLE THERAPY FOR BRAFmutant MELANOMA

NOT Superior to Anti-PD1 MONOTHERAPY

Clearly Inferior to Anti-PD1 + anti-CTLA4

Trials should have
Anti-PD1 MONOTHERAPY CONTROL
Anti-PD1 + anti-CTLA4 Positive CONTROL

Anti-PD1 demonstrates broad antitumor activity



1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Bang YJ et al. ASCO 2015; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. ASH Annual Meeting 2014; 8. Alley EA et al. AACR 2015; 9. Varga A et al. ASCO 2015; 10. Ott PA et al. ASCO 2015; 11. Doi T et al. ASCO 2015.

The New Adjuvant Therapy Era results similar to those in advanced melanoma

THE OLD AND NEW ERA
Approved drugs for the adjuvant therapy of stage III melanoma

Old Era (1996–2009)

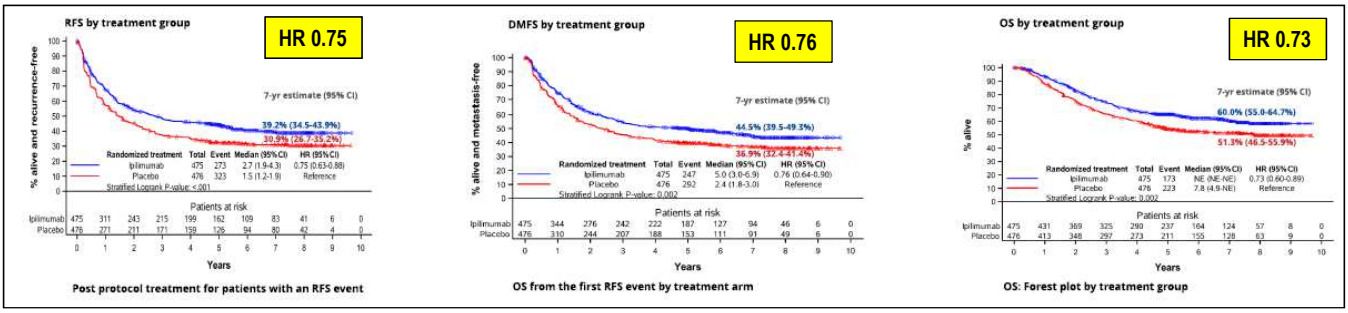
- High-Dose Interferon (IFN)-α2b (US, EU), Low-Dose IFN-α2a (EU), pegylated IFN-α2b (US)[1]

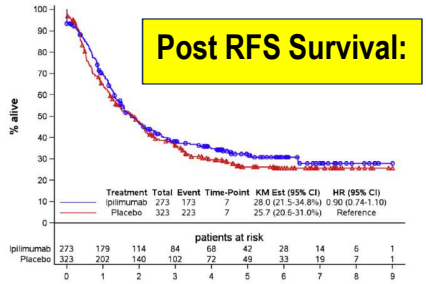
New Era (2015–2018)		**Stage**	**FDA**
Ipilimumab (US)[2,3]	HR_{RFS}(Ipilimumab vs. Placebo)=**0.75**	III	(2015)
Nivolumab[4]	HR_{RFS}(Nivolumab vs. Ipilimumab)=**0.65**	IIIB/IV	(2017)
Dabrafenib plus Trametinib[5,6]	HR_{RFS}(Dab+Tra vs. Placebo)=**0.47**	III	(2018)
Pembrolizumab[7,8]	HR_{RFS}(**Pembrolizumab** vs. **Placebo**)=**0.57**	III	(2018)

3

[1]Eggermont AM, et al. *Lancet* 2014;383:816-27
[2]Eggermont AM, et al. *Lancet Oncology (TLO)* 2015;16:522-30
[3]Eggermont AM, et al. *NEJM 2016; 375: 1845-55;* [3]*Eggermont AM et al. EJC 2019; 119:1-10*
[4]Weber J, et al. *NEJM* 2017;377:1824-35; TLO Ascierto P et al. 2020:
[5]Long GV, et al. *NEJM* 2017;377:1813-23; NEJM Dummer et al. NEJM 2020:
[6]Eggermont AM, et al. *NEJM* 2018;379:1879-1891; Eggermont et al. JCO 2020:Sept 18

EORTC 18071 Ipilimumab vs Placebo
LONG TERM: RFS = DMFS = OS IMPACT





Post RFS Survival:

NO "cross over effect noted of 23% ipilimumab in placebo group after RFS event

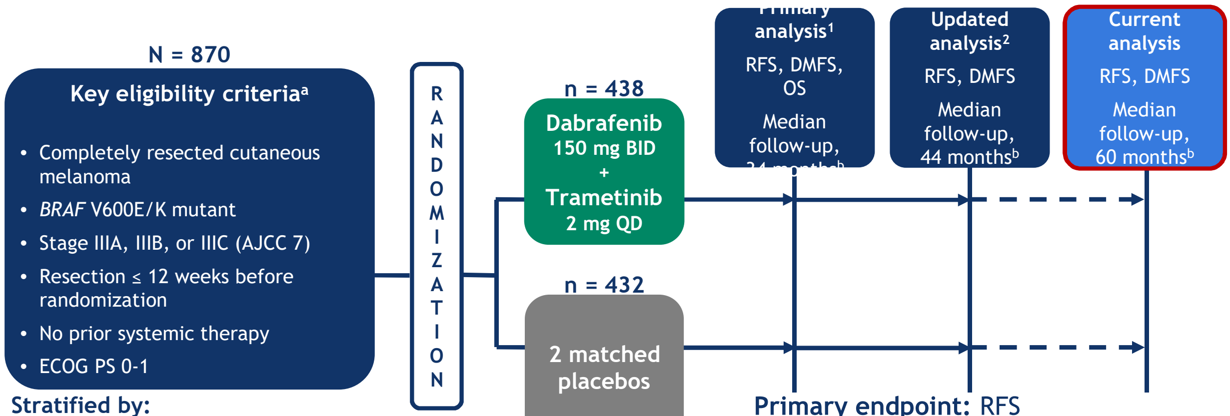
This suggests benefit of adjuvant use of ipilimumab

Eggermont et al, Eur J Cancer 2019;119:1-10

Long-term benefit of adjuvant dabrafenib plus trametinib in patients with resected stage III *BRAF* V600-mutant melanoma: 5-year analysis of COMBI-AD

Axel Hauschild, Reinhard Dummer, Mario Santinami, Victoria Atkinson, Mario Mandalà, John M. Kirkwood, Vanna Chiarion Sileni, James Larkin, Marta Nyakas, Caroline Dutriaux, Andrew Haydon, Caroline Robert, Laurent Mortier, Jacob Schachter, Kohinoor Dasgupta, Eduard Gasal, Monique Tan, Georgina V. Long, Dirk Schadendorf, on behalf of the COMBI-AD Investigators

Study Design



Stratified by:

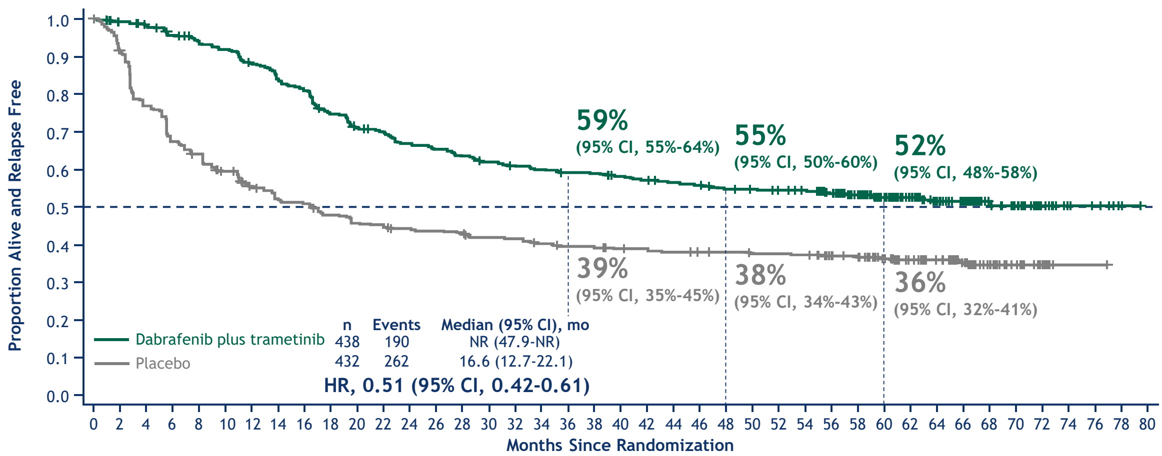
- *BRAF* mutation (V600E or V600K)
- Disease stage (IIIA, IIIB, or IIIC)

Primary endpoint: RFS

Secondary endpoints: OS, DMFS, FFR, safety

AJCC 7, American Joint Committee on Cancer Staging Manual, 7th edition; BID, twice daily; DMFS, distant metastasis-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival.
[a] COMBI-AD is registered at ClinicalTrials.gov (NCT01682083). [b] Median follow-up shown is for the dabrafenib plus trametinib arm.
1. Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; 2. Hauschild A, et al. *J Clin Oncol*. 2018;4:1382-1388.

Relapse-Free Survival

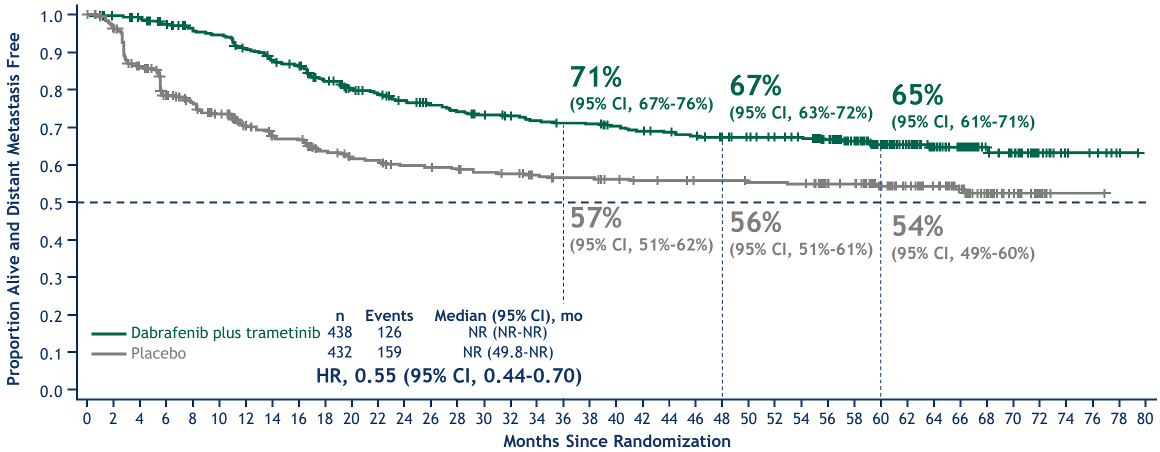


No. at risk																																									
Dabrafenib plus trametinib	438	413	405	391	381	372	354	335	324	298	281	275	262	256	249	242	236	233	229	228	221	217	213	210	204	202	199	195	176	156	133	109	92	80	45	38	17	8	6	2	0
Placebo	432	387	322	280	263	243	219	204	199	185	178	175	168	166	164	158	157	151	147	146	143	140	139	137	136	133	133	132	121	115	99	80	69	56	35	26	13	1	1	0	0

HR, hazard ratio; NR, not reached.

Distant Metastasis-Free Survival

Distant Metastasis as First Relapse Only[a]



No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60	62	64	66	68	70	72	74	76	78	80
Dabrafenib plus trametinib	438	413	407	390	380	373	352	336	327	301	285	278	265	257	251	243	238	234	231	230	223	219	216	212	208	205	201	197	179	158	135	110	93	80	45	38	17	8	6	2	0
Placebo	432	393	329	284	266	247	221	206	202	186	179	176	169	168	165	161	159	153	149	148	145	141	140	138	138	135	135	134	121	116	100	80	69	56	35	26	13	1	1	0	0

[a] Due to informative censoring, patients who had a local or regional first recurrence may not be represented in this analysis. Per protocol, patients with a first relapse at a locoregional site were not required to continue follow-up for distant metastases and were censored at the time of locoregional recurrence if follow-up was not complete.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 *Slides are the property of the author, permission required for reuse.* PRESENTED BY: Axel Hauschild 31

VIRTUAL 2020 ESMO congress

FROM ADJUVANT TO NEOADJUVANT

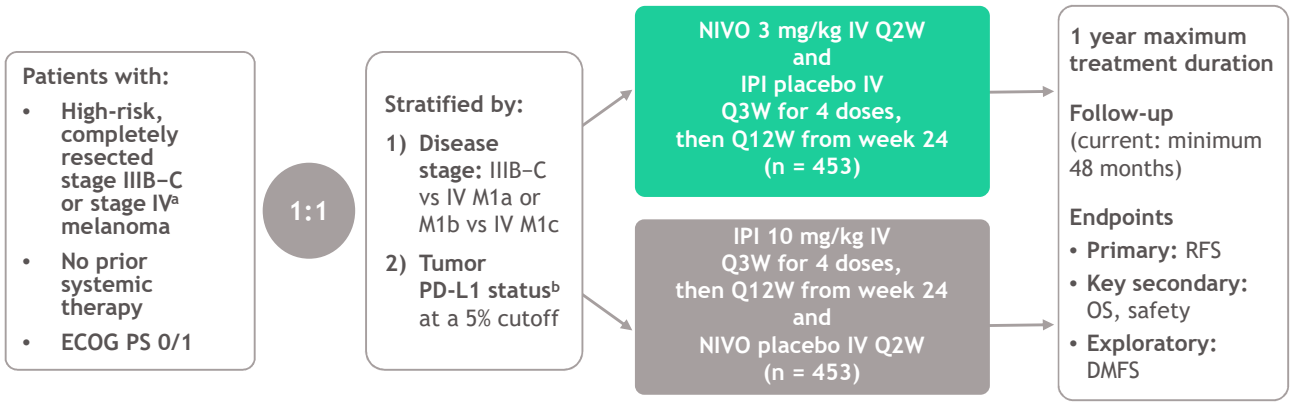
Adjuvant nivolumab vs ipilimumab in resected stage III/IV melanoma: 4-year recurrence-free and overall survival results from CheckMate 238

Jeffrey Weber,[1] Michele Del Vecchio,[2] Mario Mandalá,[3] Helen Gogas,[4] Ana M. Arance,[5] Stephane Dalle,[6] C. Lance Cowey,[7] Michael Schenker,[8] Jean-Jacques Grob,[9] Vanna Chiarion-Sileni,[10] Iván Márquez-Rodas,[11] Marcus O. Butler,[12] Michele Maio,[13] Mark R. Middleton,[14] Luis de la Cruz-Merino,[15] Maurice Lobo,[16] Veerle de Pril,[16] James Larkin,[17*] Paolo A. Ascierto[18*]

Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: final results regarding distant metastasis-free survival results from the EORTC 1325-MG/Keynote 054 double-blinded phase 3 trial

Alexander MM Eggermont, MD, PhD,[1] Christian U Blank, MD, PhD,[2] Mario Mandala, MD,[3] Georgina V Long, MD, PhD,[4] Victoria Atkinson, MD,[5] Stéphane Dalle, MD,[6] Andrew Haydon, MD,[7] Andrey Meshcheryakov, MD,[8] Adnan Khattak, MD,[9] Matteo S Carlino, MD, PhD,[10] Shahneen Sandhu, MD,[11] Susana Puig, MD, PhD,[12] Paolo A Ascierto, MD,[13] Alexander van Akkooi, MD, PhD,[2] Clemens Krepler, MD,[14] Nageatte Ibrahim, MD,[14] Sandrine Marreaud, MD,[15] Michal Kicinski, PhD,[15] Stefan Suciu, PhD,[15] Caroline Robert, MD, PhD[16]

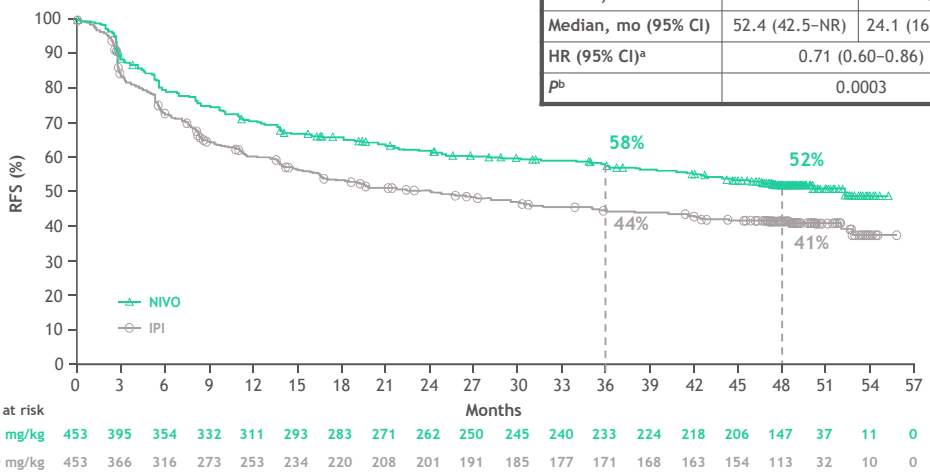
CheckMate 238 study design



NCT02388906. [a]Per American Joint Committee on Cancer, Cancer Staging Manual, Seventh Edition; [b]PD-L1 IHC 28-8 pharmDx assay.
PD-L1, programmed death-ligand 1; PS, performance status.

Primary endpoint: 48-month RFS in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	212	253
Median, mo (95% CI)	52.4 (42.5–NR)	24.1 (16.6–35.1)
HR (95% CI)[a]	0.71 (0.60–0.86)	
P[b]	0.0003	



No. at risk

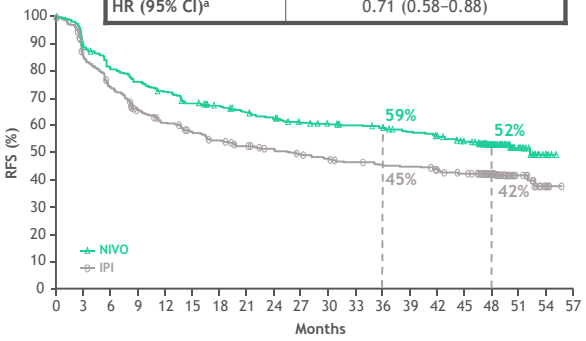
NIVO 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0
IPI 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0

[a]Stratified; [b]Log-rank test. NR, not yet reached.

Subgroup analysis: 48-month RFS by disease stage IIIB–C and stage IV

Stage IIIB–C

	NIVO (n = 370)	IPI (n = 366)
Events, n	170	203
Median, mo (95% CI)	52.4 (42.9–NR)	25.5 (16.6–38.0)
HR (95% CI)[a]	0.71 (0.58–0.88)	

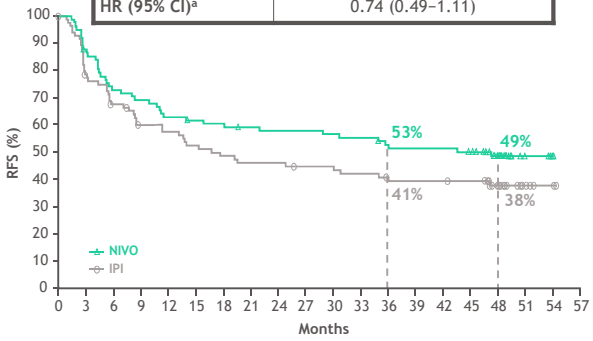


No. at risk

NIVO 3 mg/kg	370	323	294	275	260	244	235	225	217	205	201	197	193	185	179	169	121	33	9	0
IPI 10 mg/kg	366	301	261	226	208	193	182	172	165	157	151	145	141	139	134	126	94	26	7	0

Stage IV

	NIVO (n = 82)	IPI (n = 87)
Events, n	41	50
Median, mo (95% CI)	47.4 (15.9–NR)	16.8 (8.5–47.2)
HR (95% CI)[a]	0.74 (0.49–1.11)	



No. at risk

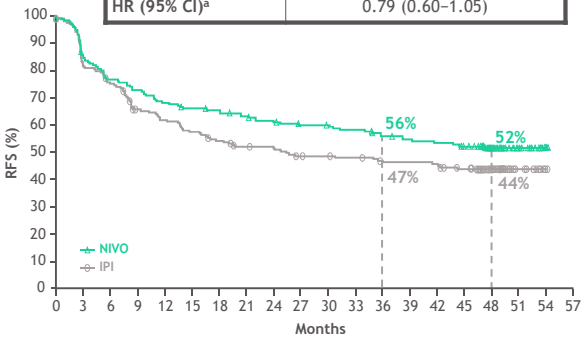
NIVO 3 mg/kg	82	71	59	56	51	49	48	46	45	45	44	43	40	39	39	37	26	4	2	0
IPI 10 mg/kg	87	65	55	47	45	41	38	36	36	34	34	32	30	29	29	28	19	6	3	0

[a]Unstratified.

Subgroup analysis: 48-month RFS by *BRAF* mutation status

BRAF mutant

	NIVO (n = 187)	IPI (n = 194)
Events, n	88	104
Median, mo (95% CI)	NR (35.0–NR)	25.5 (15.9–NR)
HR (95% CI)[a]	0.79 (0.60–1.05)	

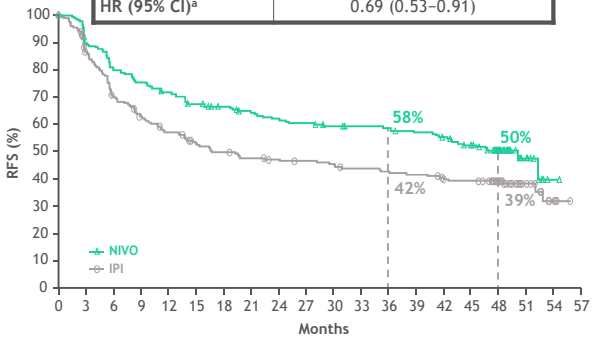


No. at risk

NIVO 3 mg/kg	187	157	142	135	126	121	119	114	110	104	103	100	94	91	89	86	64	19	6	0
IPI 10 mg/kg	194	156	143	120	113	105	98	92	91	84	83	81	77	76	75	69	50	13	2	0

BRAF wild-type

	NIVO (n = 197)	IPI (n = 212)
Events, n	96	123
Median, mo (95% CI)	46.8 (36.3–NR)	16.6 (11.6–35.1)
HR (95% CI)[a]	0.69 (0.53–0.91)	



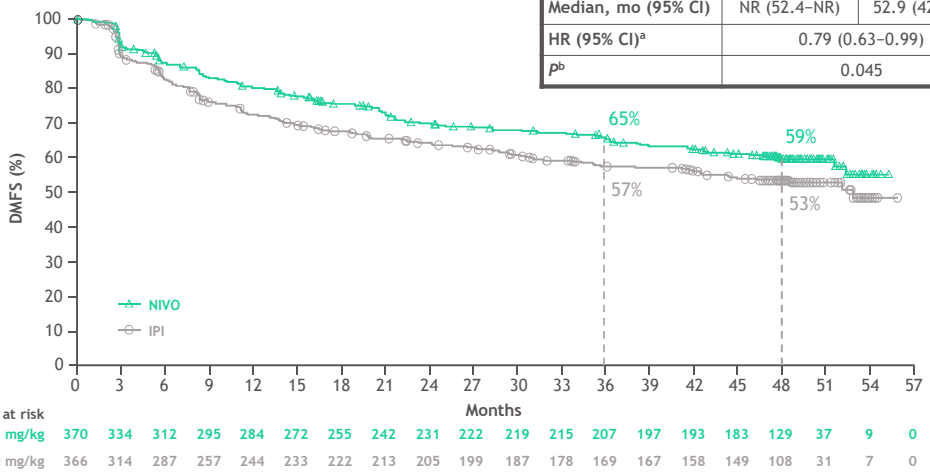
No. at risk

NIVO 3 mg/kg	197	173	155	145	137	128	121	116	111	108	104	102	101	97	93	86	56	11	1	0
IPI 10 mg/kg	212	173	139	122	110	99	93	88	85	83	81	77	75	73	69	66	52	17	7	0

[a]Unstratified.

Exploratory endpoint: 48-month DMFS in all stage IIIB–C patients

	NIVO (n = 370)	IPI (n = 366)
Events, n	142	160
Median, mo (95% CI)	NR (52.4–NR)	52.9 (42.4–NR)
HR (95% CI)[a]	0.79 (0.63–0.99)	
P[b]	0.045	



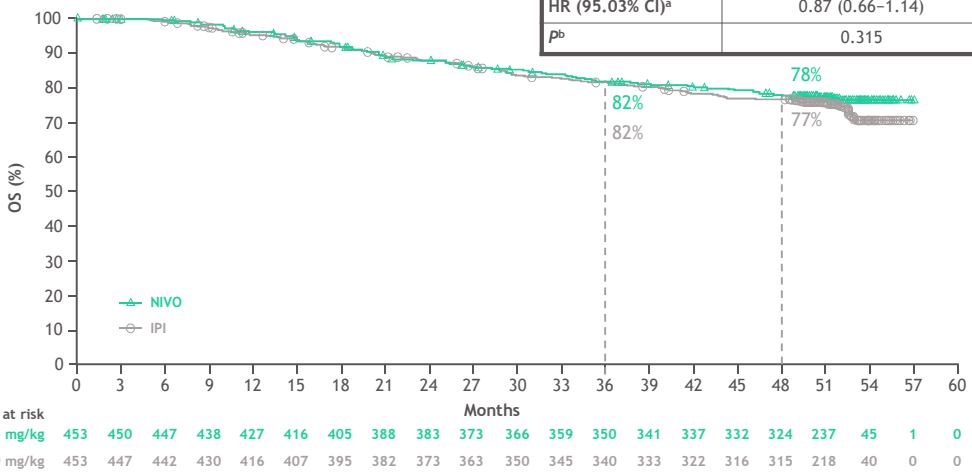
No. at risk																			
NIVO 3 mg/kg	370	334	312	295	284	272	255	242	231	222	219	215	207	197	193	183	129	37	9	0
IPI 10 mg/kg	366	314	287	257	244	233	222	213	205	199	187	178	169	167	158	149	108	31	7	0

[a]Stratified; [b]Log-rank test.

37

Secondary endpoint: 48-month OS in all patients

	NIVO (n = 453)	IPI (n = 453)
Events, n	100	111
Median, mo (95% CI)	NR	NR
HR (95.03% CI)[a]	0.87 (0.66–1.14)	
P[b]	0.315	



No. at risk																				
NIVO 3 mg/kg	453	450	447	438	427	416	405	388	383	373	366	359	350	341	337	332	324	237	45	1	0
IPI 10 mg/kg	453	447	442	430	416	407	395	382	373	363	350	345	340	333	322	316	315	218	40	0	0

- 211 of 302 anticipated events (approximately 73% power)

[a]Stratified; [b]Log-rank test.

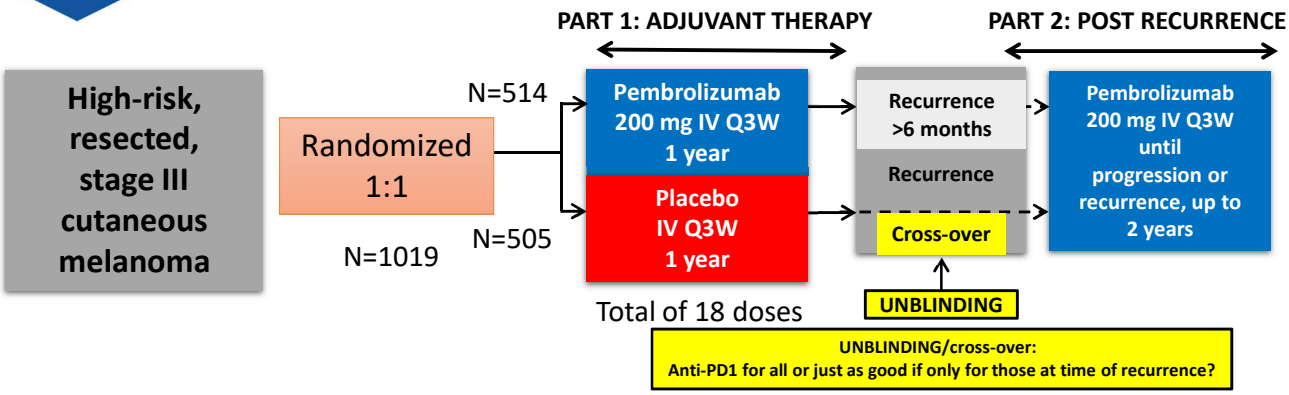
38

Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: final results regarding distant metastasis-free survival results from the EORTC 1325-MG/Keynote 054 double-blinded phase 3 trial

Alexander MM Eggermont, MD, PhD,[1] Christian U Blank, MD, PhD,[2] Mario Mandala, MD,[3] Georgina V Long, MD, PhD,[4] Victoria Atkinson, MD,[5] Stéphane Dalle, MD,[6] Andrew Haydon, MD,[7] Andrey Meshcheryakov, MD,[8] Adnan Khattak, MD,[9] Matteo S Carlino, MD, PhD,[10] Shahneen Sandhu, MD,[11] Susana Puig, MD, PhD,[12] Paolo A Ascierto, MD,[13] Alexander van Akkooi, MD, PhD,[2] Clemens Krepler, MD,[14] Nageatte Ibrahim, MD,[14] Sandrine Marreaud, MD,[15] Michal Kicinski, PhD,[15] Stefan Suciu, PhD,[15] Caroline Robert, MD, PhD[16]

[1] Princess Máxima Center, Utrecht, the Netherlands; [2]Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands; [3]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [4]Melanoma Institute Australia, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, Australia; [5]Princess Alexandra Hospital, University of Queensland, Brisbane, Australia; [6]HCL Cancer Institute, Cancer Research Center of Lyon, Lyon University, Lyon, France; [7]Alfred Hospital, Melbourne, Australia; [8]Federal State Budgetary Institution "Russian Oncology Scientific Centre named after N.N. Blokhin RAMS", Moscow, Russian Federation; [9]Fiona Stanley Hospital/University of Western Australia, Perth, Australia; [10]Westmead and Blacktown Hospitals, Melanoma Institute Australia and the University of Sydney, Australia; [11]Peter Maccallum Cancer Centre, Melbourne, Australia; [12]Hospital Clinic Universitari de Barcelona, Barcelona, Spain; [13]Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; [14]Merck & Co., Inc., Kenilworth, NJ, USA;[15]EORTC Headquarters, Brussels, Belgium; [16]Gustave Roussy Cancer Campus Grand Paris & University Paris-Saclay, Villejuif, France.

EORTC 1325/KEYNOTE-54: Study Design



Stratification factors:

✓ **AJCC-7 Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes

✓ **Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

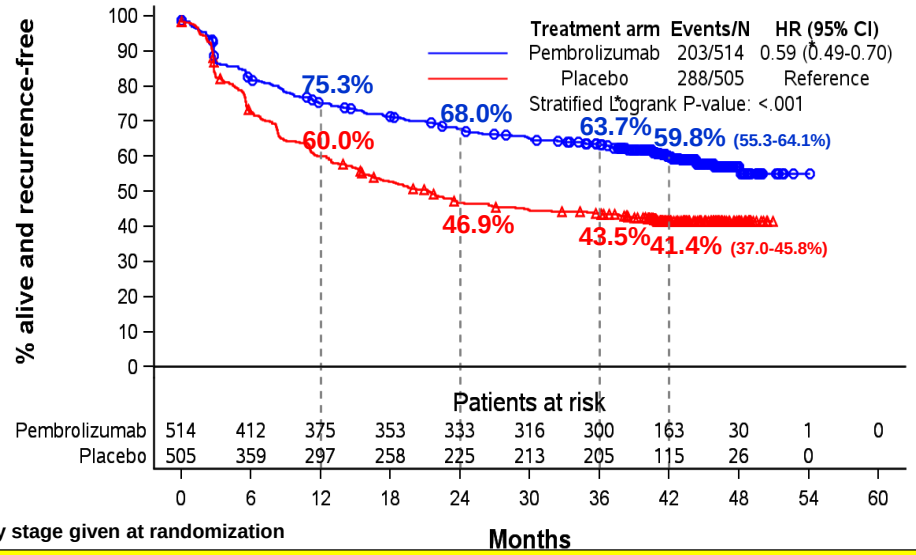
- **RFS (per investigator) in overall ITT population,** and **in patients with PD-L1-positive tumors**

Secondary Endpoints:

- **DMFS and OS** in these 2 populations; **Safety, Health-related quality of life**

Updated RFS analysis (ESMO 2020)

- **Cut-off date** (3-Apr-2020); median duration of follow-up: **3.5** years; **491** RFS events



HR 0.59

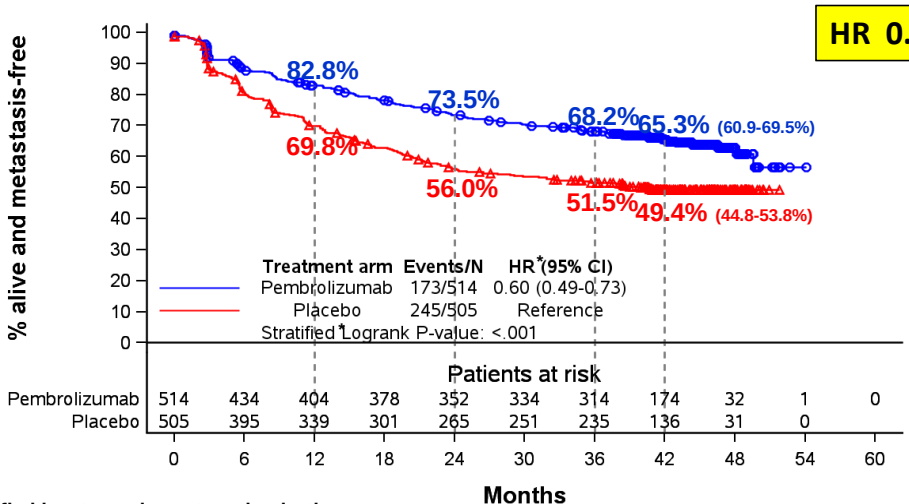
*Stratified by stage given at randomization

** REMINDER: irAEs and Outcome: The occurrence of an irAE was significantly associated with a longer RFS in the pembrolizumab arm (HR = 0.61, 95% CI 0.39-0.95) Eggermont AM, et al. *JAMA Oncology* 2020;6:519-

41

Final DMFS analysis (ESMO 2020)

- **Cut-off date** (3-Apr-2020); median follow-up: **3.5** years; 418 DMFS events (423 planned: ~87% power in the ITT population; targeted HR=0.725)
- **Final DMFS analysis**: split 1-sided α=0.025: 0.014 for the overall ITT population, 0.02 for the PD-L1+ subgroup; if both results are positive results, present the 2-sided 95% CI for the HR



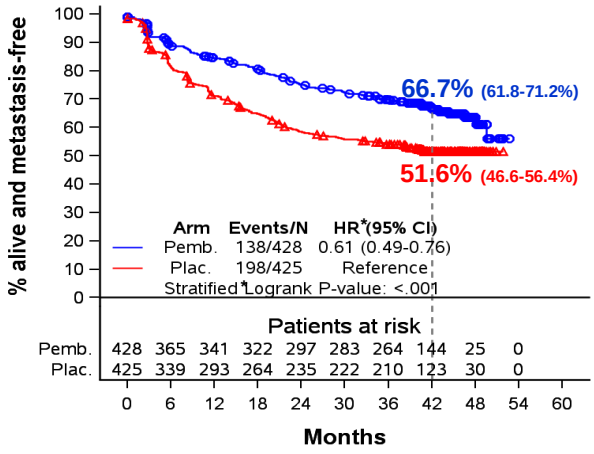
HR 0.60

*Stratified by stage given at randomization

DMFS according to PD-L1 expression

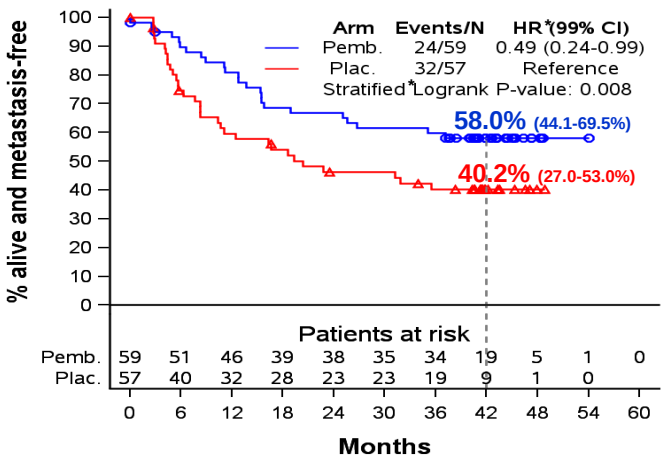
PD-L1 positive (n=853)

HR 0.61



PD-L1 negative (n=116)

HR 0.49

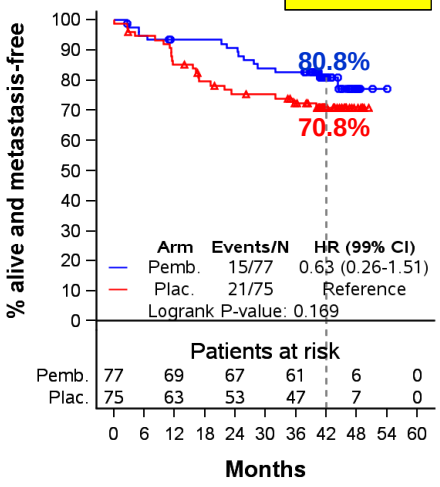


*Stratified by stage given at randomization

DMFS according to AJCC-7 staging

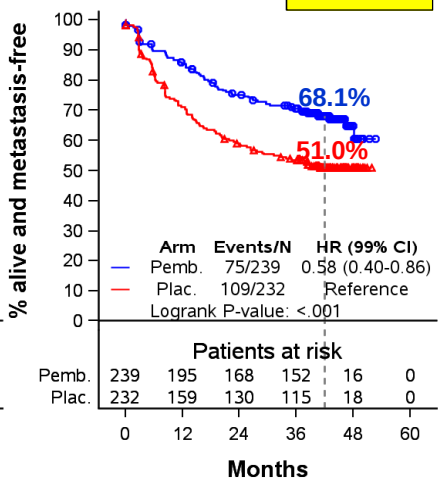
Stage IIIA (n=152)

HR 0.63



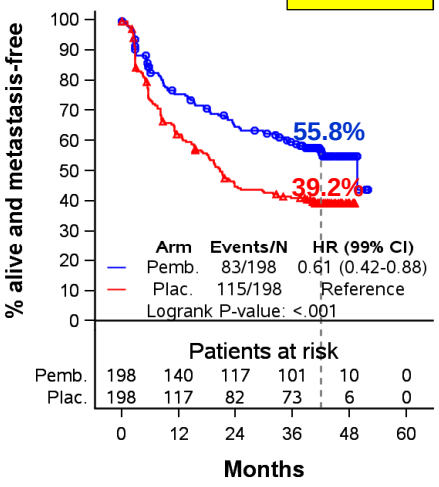
Stage IIIB (n=471)

HR 0.58



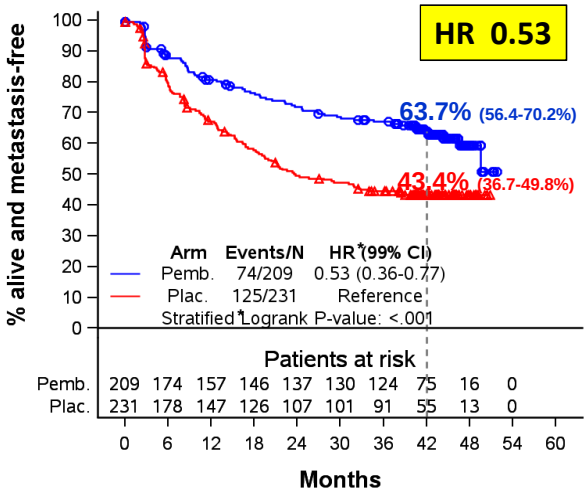
Stage IIIC (n=396)

HR 0.61

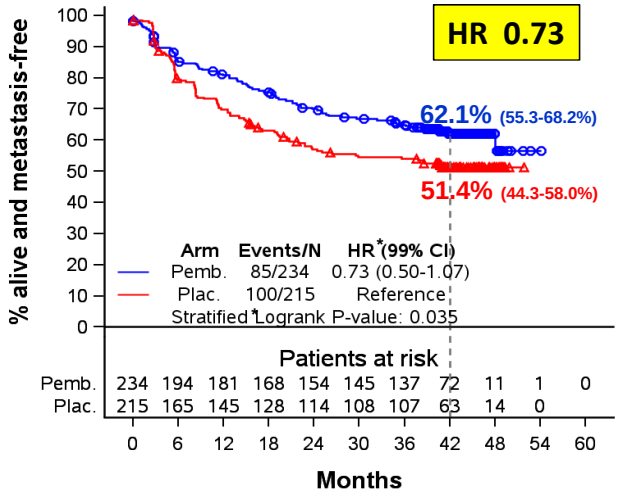


DMFS according to BRAF-V600 E/K mutation status

BRAF-mutated (n=440)



BRAF-WT (n=448)



*Stratified by stage given at randomization

Summary/Conclusions (I)

	HR	~3.5-yr DMFS Rate	Increase
– **Overall population**	**0.60**	**65%** *vs* **49%**	**16%**
– PD-L1 positive	**0.61**	**67%** *vs* **52%**	**15%**
– PD-L1 negative	**0.49**	**58%** *vs* **40%**	**18%**
✓ **BRAF-mutated**	**0.53**	**64%** *vs* **43%**	**20%**

- ✓ This improvement in **BRAF-mutated patients was similar to the COMBI-AD trial (HR=0.53)** for the time to distant metastasis as first type of recurrence)[1]
- ✓ The improvement was similar in **AJCC-7 stage IIIA** (HR 0.63), **IIIB** (HR 0.58), **IIIC** (HR 0.61)

- **OVERALL SURVIVAL BENEFIT WITH ADJUVANT PEMBROLIZUMAB ?**
  - ✓ **Cross-over design in this trial (the ONLY trial to have done so)**
  - ✓ **Additional effective lines of treatment in advanced disease**
- **Question to treat all adjuvantly or treat only those who relapse@relapse remains crucial**

1. Hauschild A, et al. Long-term benefit of adjuvant dabrafenib + trametinib (D+T) in patients (pts) with resected stage III *BRAF* V600-mutant melanoma: five-year analysis of COMBI-AD. 2020 ASCO Virtual Scientific Program; May 29-31. Abstract 10001.

Adjuvant Nivolumab + Ipilimumab vs Nivolimab in Stage IIIB/C + IV

Checkmate 915

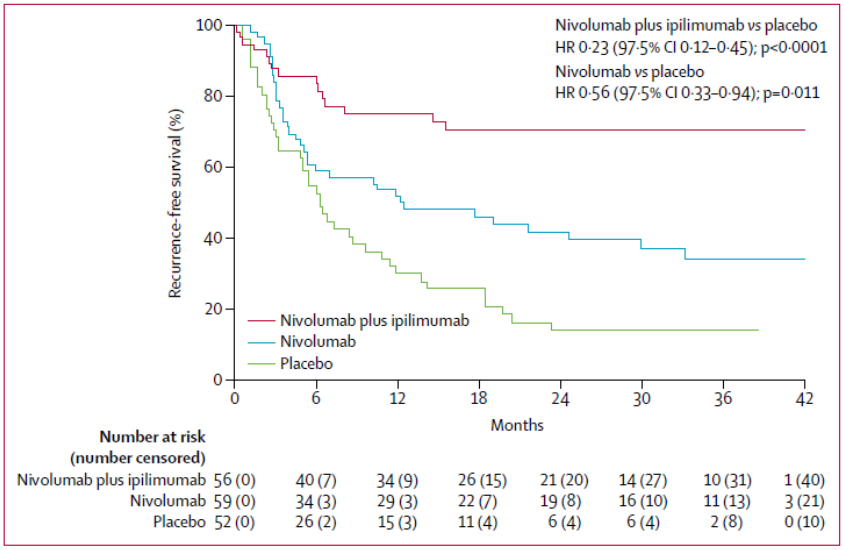
Primary Endpoint:
RFS in PDL-1 negative patient population
Interim Analysis November 2019: Primary endpoint not met
ITT total population analysis October 2020: Primary endpoint not met

MAY 2020:
Positive Randomized Phase II
Nivo+Ipi vs Nivo vs placebo
In Resected Stage IV
(Lancet Zimmer et al, 2020)

Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial

Lancet 2020; 395: 1558–68

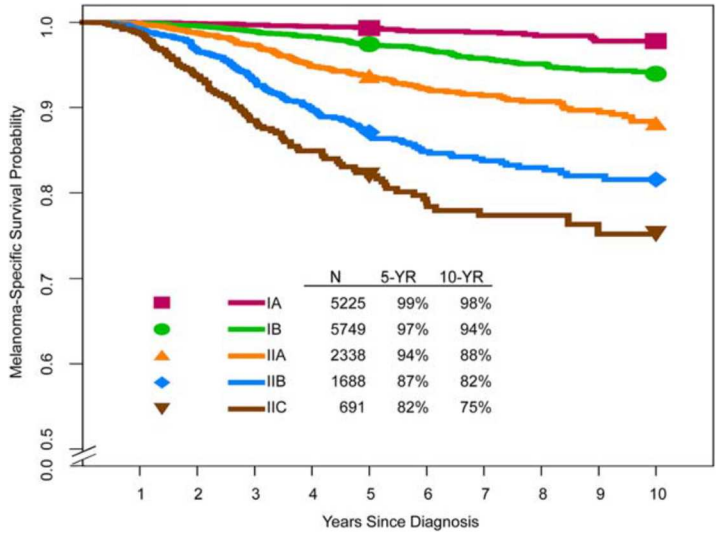
Lisa Zimmer, Elisabeth Livingstone*, Jessica C Hassel, Michael Fluck, Thomas Eigentler, Carmen Loquai, Sebastian Haferkamp, Ralf Gutzmer, Friedegund Meier, Peter Mohr, Axel Hauschild, Bastian Schilling, Christian Menzer, Felix Kieker, Edgar Dippel, Alexander Rösch, Jan-Christoph Simon, Beate Conrad, Silvia Kerner, Christine Windemuth-Kieselbach, Leonora Schwarz, Claus Garbe, Jürgen C Becker, Dirk Schadendorf, on behalf of the Dermatologic Cooperative Oncology Group*



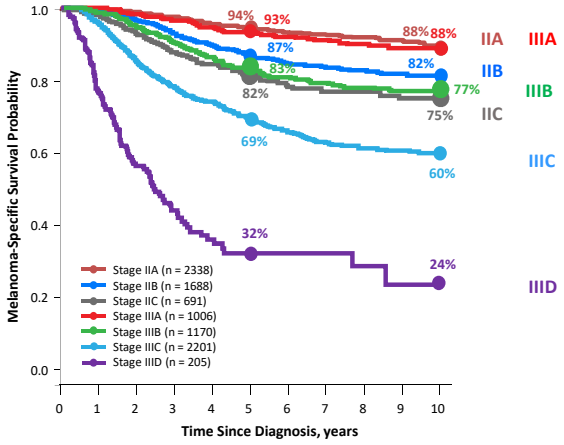
STAGE IIA and Stage IIB/C
Sufficient elevated risk for relapse for adjuvant therapy ?

WE MUST Better IDENTIFY
THOSE WHO WILL RELAPSE

Prognosis Stages I A-B , II A-B-C (AJCC-8)



MSS AJCC-8
Prognosis overlap between Stages IIA-IIIA
Prognosis overlap between Stages IIB-IIIB-IIC



- Patients with stage IIB or IIC disease have a worse prognosis than those with stage IIIA or IIIB disease, respectively[1]
- The large majority of patients with melanoma have tumour thickness categorised as T1 or T2[1]
  - While 10-year survival rates with T1 or T2 tumours are high (> 90%), these tumours account for **over half of future melanoma-related deaths**[2,3]

1. Gershenwald JE, et al. *CA Cancer J Clin.* 2017;67:472-492; 2. Landow SM, et al. *J Am Acad Dermatol.* 2017;76:258-263; 3. Whiteman DC, et al. *J Invest Dermatol.* 2015;135:1190-1193.

Ongoing Trials of Adjuvant Anti–PD-1 Antibodies for Stage IIB/C Melanoma

KEYNOTE-716[1]

N ≈

Key eligibility criteria
- Age ≥ 12 years
- Surgically resected stage IIB/IIC melanoma (AJCC 8)
- Resection within the last 12 weeks
- No prior treatment
- No evidence of metastatic disease by imaging

Part 1: Double Blind

PEMBRO 200 mg[a] Q3W for up to 17 cycles

Placebo Q3W for up to 17 cycles

Recurrence

Unblind

Part 2: Open Label/Crossover

200 mg PEMBRO Q3W[a]
- Up to 17 cycles for recurrence after resection
- Up to 35 cycles for unresectable recurrence

Primary endpoint: RFS

Key secondary endpoints: DMFS, OS, safety

CheckMate 76K[2,3]

N ≈ 1000

Key eligibility criteria
- Age ≥ 12 years
- Completely resected stage IIB/IIC melanoma (AJCC 8)
- Resection within the last 12 weeks
- No prior treatment
- ECOG PS 0-1

Double Blind

NIVO 480mg Q4W for 12 months

2:1

Placebo

Primary endpoint: RFS, safety biomarkers

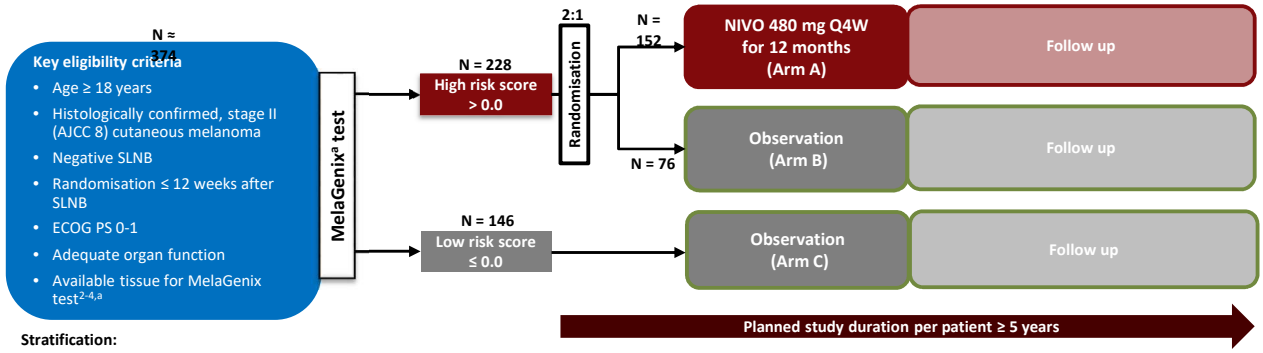
Secondary endpoints: OS, safety, DMFS, ORR, next-line outcomes (eg, PFS2), biomarkers

ECOG PS, Eastern Cooperative Oncology Group performance status; PFS2, progression-free survival on next-line therapy; Q3W, every 3 weeks.
[a] Adult dosage; eligible patients aged 12 to < 18 years receive 2 mg/kg Q3W.
1. Carlino MS, et al. ASCO 2019 [abstract TPS9596]; 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04099251. Accessed 18 May 2020; 3. ClinicalTrialsRegister.eu. https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001230-34/AT. Accessed 18 May 2020.

NivoMela: Adjuvant Treatment of High-Risk Stage II Melanoma[1]

(Investigator Initiated Trial—Sponsor: University Hospital Essen, Prof. Dr. Dirk Schadendorf; CA209-7DL)

Adjuvant NIVO treatment in stage II high-risk melanoma: a randomised, controlled, Phase III trial with biomarker-based risk stratification



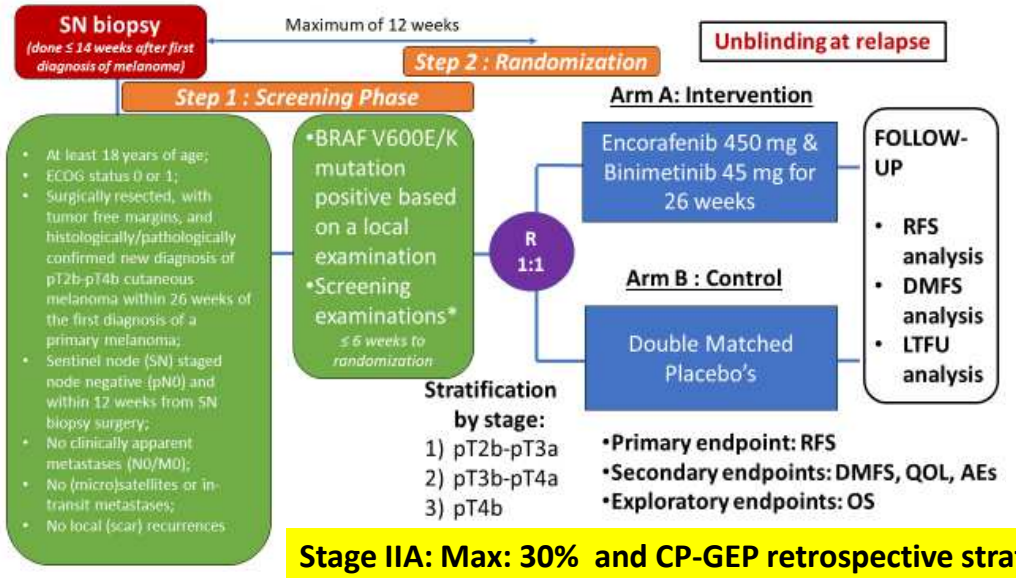
Stratification:
- Tumour stage (IIA vs IIB vs IIC)
- Gender
- Site of primary tumour (extremities vs trunk vs head and neck)

Primary endpoint: RFS (at 36 and 60 months)

Secondary endpoints: DMFS, MSS, and OS (at 36 and 60 months); safety; clinical utility of the MelaGenix GEP score

GEP, gene expression profiling; SLNB, sentinel lymph node biopsy.
[a] MelaGenix is an 11-gene prognostic signature.[2-4]
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04309409. Accessed 19 June 2020; 2. Brunner G, et al. J Cancer Res Clin Oncol. 2013;139:249-258; 3. Brunner G, et al. ASCO 2018 [abstract 9582]; 4. Garbe C, et al. ASCO 2019 [abstract 9518].

EORTC 1902: Stage II A-B-C
Adjuvant Encorafenib + Binimetinib for 6mts vs Placebo



Stage IIA: Max: 30% and CP-GEP retrospective stratification

WHAT TO DO WITH STAGE I-II? (50% of all Melanoma Deaths started as stage I-IIA)

WE MUST IDENTIFY THOSE WHO WILL RELAPSE

Annual # New Melanoma Cases and Annual # Deaths

Clinical Stage	SLNb status	# of cases US[1]	Est # of deaths[2]	Treatment
I/IIA	Negative	62,091	3,942	Surgery, surveillance monitoring
IIB/IIC	Negative	6,012	901	Surgery, surveillance monitoring Adjuvant systemic therapy in clinical trials
III	Positive	21,624	2,379	Surgery, surveillance monitoring Adjuvant systemic therapies approved

~80% of SLN biopsies are negative for metastasis[3]

More than 50% of deaths due to melanoma occur in Stage I/IIA, SLNB-negative patients, generally considered low risk

Unmet need for:

- Identification of patients that can safely forego SLNB
- Identification of high-risk SLNB negative patients (specifically Stage I/IIA)

JCO Precis Oncol 4:319-334. © 2020 by American Society of Clinical Oncology

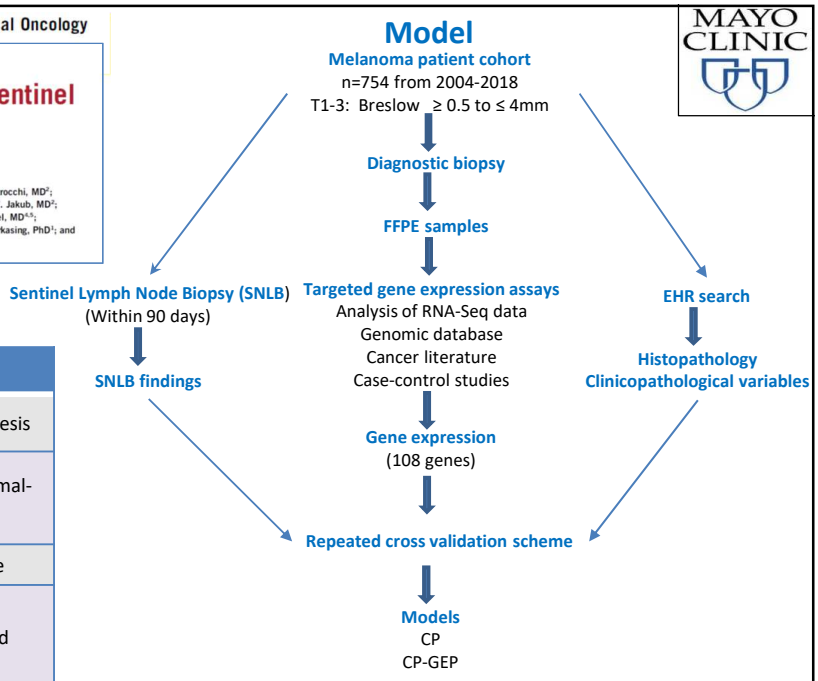
original reports

Model Combining Tumor Molecular and Clinicopathologic Risk Factors Predicts Sentinel Lymph Node Metastasis in Primary Cutaneous Melanoma

Domenico Bellomo, PhD[1]; Suzette M. Arias-Mejias, BA[2]; Chandru Ramana, MS[2]; Joel B. Heim, PhD[2]; Enrica Quattrocchi, MD[2]; Sindhuja Sominidi-Damodaran, MD[2]; Alina G. Bridges, DO[2]; Julia S. Lehman, MD[2]; Tina J. Hieken, MD[2]; James W. Jakub, MD[2]; Mark R. Pittelkow, MD[1]; David J. DiCaudo, MD[3]; Barbara A. Pockaj, MD[3]; Jason C. Sluzevich, MD[4]; Mark A. Cappel, MD[4,5]; Sanjay P. Bagaria, MD[4]; Charles Perniciaro, MD[3]; Félicia J. Tjien-Fooh, MS[1]; Martin H. van Vliet, PhD[1]; Jvalini Dwarkasing, PhD[1]; and Alexander Meves, MD[2]

CP: Breslow and Age

Gene (protein)	Gene Function
MELAN-A (melanoma antigen recognized by T-cells 1)	Melanosome biogenesis
GDF15 (growth differentiation factor 15) TGFBR1 (TGFβ receptor type 1)	Epithelial-mesenchymal-transition (EMT)
CXCL8 (interleukin 8)	Immune response
LOXL4 (lysyl oxidase homolog 4) PLAT (tissue type plasminogen activator) SERPINE2 (glia-derived nexin)	Fibrinolysis/wound healing
ITGB3 (integrin β3)	Angiogenesis



CP-GEP: Predicts SN positivity/negativity : Safely Forgoing SNLB in I-IIA
Identifies SNLB negative patients that will relapse (adjuvant Tx)

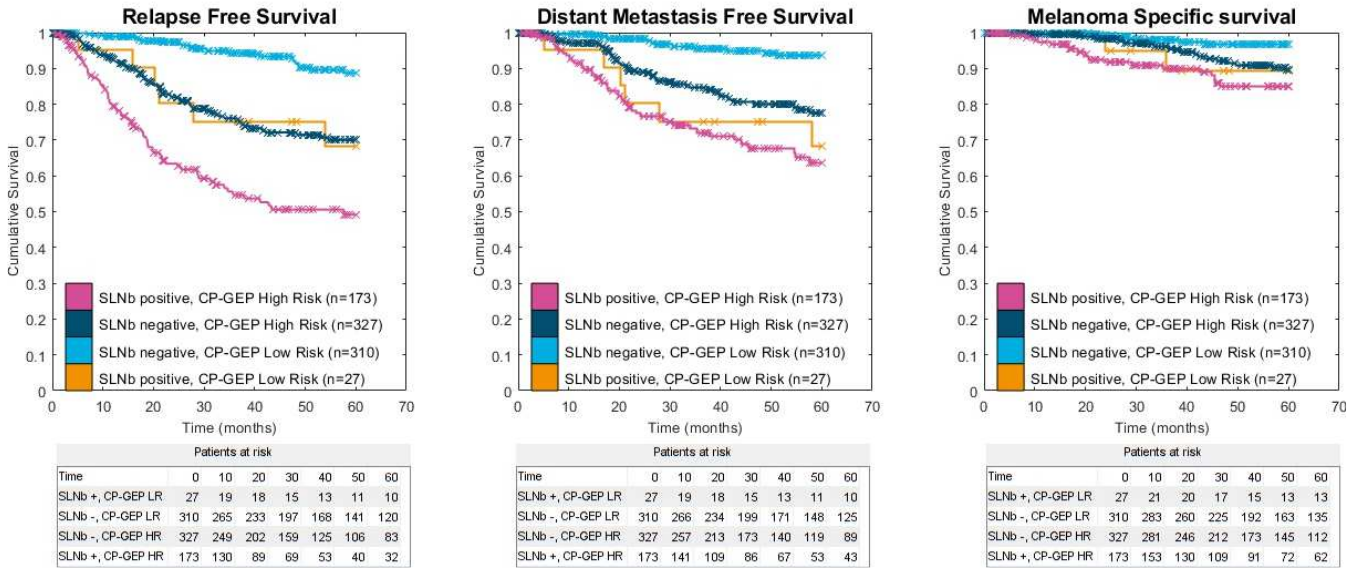
Moving towards new classifiers to identify high risk patients: Clinico-Pathologic + Genomic Profile Classifier

CP-GEP Algorythm
To IDENTIFY Stage I-II patients
with high risk for relapse
~2 out of 3 in stage IIA
~3 out of 4 in stage IB

(Bellomo et al, JCO Prec Med 2020)
(Eggermont et al, Eur J Cancer 2020)

CP-GEP Identifies High Risk SN-negative Candidates for adjuvant therapy

Eggermont A, et al. Eur J Cancer 2020;140:11-18



Patients at risk

Time	0	10	20	30	40	50	60
SLNb +, CP-GEP LR	27	19	18	15	13	11	10
SLNb -, CP-GEP LR	310	265	233	197	168	141	120
SLNb -, CP-GEP HR	327	249	202	159	125	106	83
SLNb +, CP-GEP HR	173	130	89	69	53	40	32

Patients at risk

Time	0	10	20	30	40	50	60
SLNb +, CP-GEP LR	27	19	18	15	13	11	10
SLNb -, CP-GEP LR	310	266	234	199	171	148	125
SLNb -, CP-GEP HR	327	257	213	173	140	119	89
SLNb +, CP-GEP HR	173	141	109	86	67	53	43

Patients at risk

Time	0	10	20	30	40	50	60
SLNb +, CP-GEP LR	27	21	20	17	15	13	13
SLNb -, CP-GEP LR	310	283	260	225	192	163	135
SLNb -, CP-GEP HR	327	281	246	212	173	145	112
SLNb +, CP-GEP HR	173	153	130	109	91	72	62

CP-GEP "COVID INDUCED TRIAL"

Already launched in the Netherlands

All University Medical Centers Participating

SAFELY FORGOING SN-staging in all melanoma T1b-T2a/b that are CP-GEP Negative

NPV : T1 98% ; T2 95%

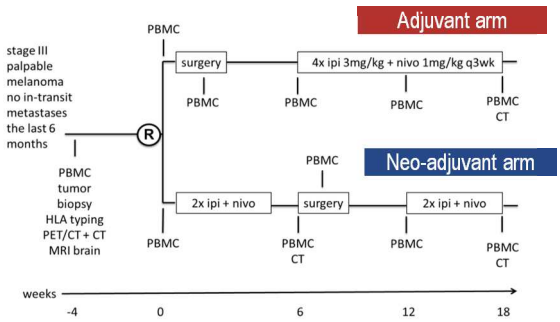
REDUCTION IN > 50% of all SN-Procedures

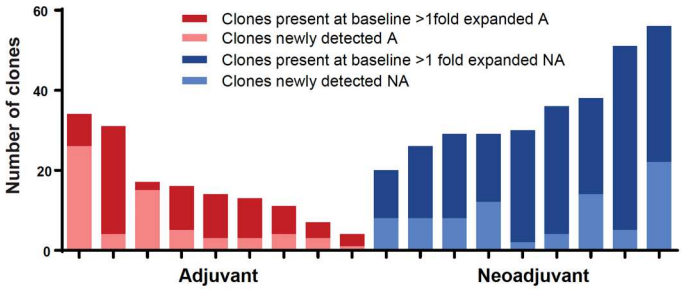
NEXT REVOLUTION
NEOADJUVANT
IMMUNOTHERAPY

NEOADJUVANT
Anti-PD1 + anti-CTLA4

BACKGROUND:

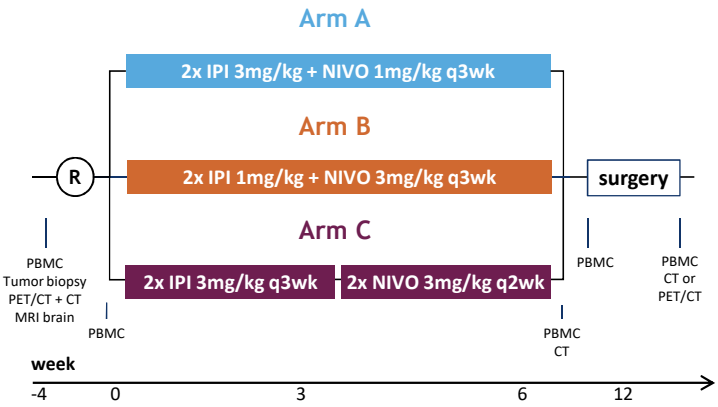
- **Neo-adjuvant Ipilimumab (3mg) plus Nivolumab (1mg)** at standard regimen dosing (**OpACIN** trial) induced high pathological response rates (**pRR, 78%**).
- All responders are **relapse-free** until today (FU 3y).
- Toxicity was high with **90% grade 3/4 toxicities**, making the standard dose unfeasible for broader testing.[1]





[1]Blank, et al. Nat Med 2018

The OpACIN-neo study identified neoadjuvant IPI 1 mg/kg + NIVO 3 mg/kg as the optimal treatment scheme



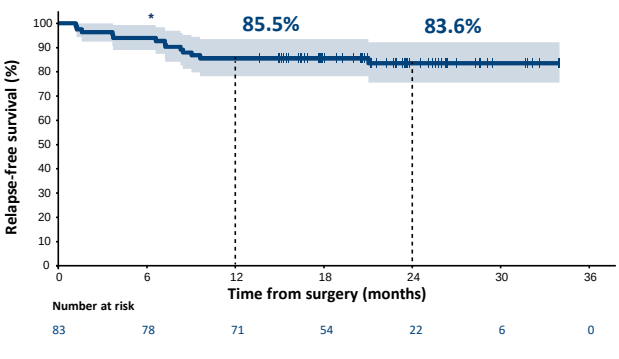
	Grade 3-4 toxicity	Pathologic Response
Arm A	40%	80%
Arm B	20%	77%
Arm C	50%	65%

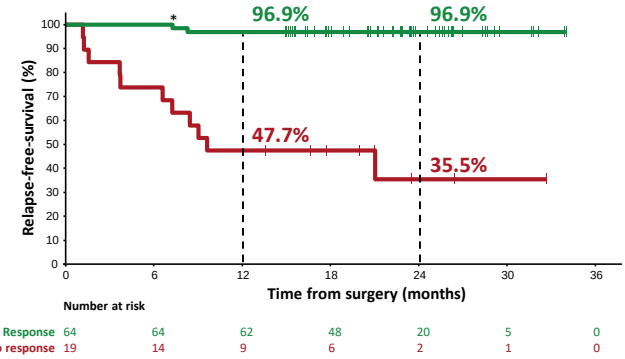
Rozeman et al., Lancet Oncology, 2019

Dosing in Arm A, B, and C based on data from Blank, et al. Nat Med 2018, Long, et al. Lancet Oncol 2017, Meerveld-Eggink et al. Ann Oncol 2017

ASCO 2020 RFS after 2 years follow-up and pathologic response predicts outcome

- **OpACIN-neo:** After a median follow-up of 24.6 months, only 1/64 (2%) patients with pathologic response has relapsed





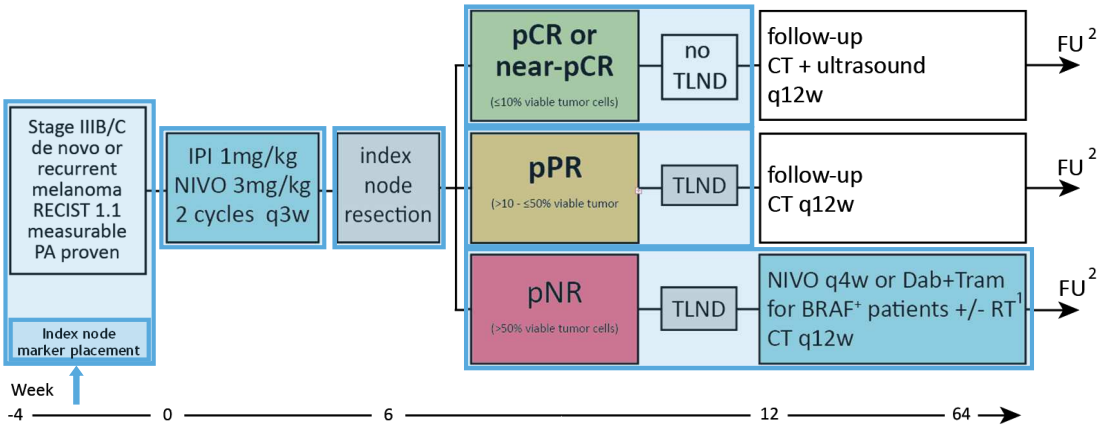
(near-)pCR = (near) pathologic complete response, pPR = pathologic partial response, pNR = pathologic non-response

Rozeman et al., abstract 10015, ASCO 2020

* patient died due to toxicity without signs of melanoma relapse

PRADO: study design (The first 100 pts ; ASCO 2020)

Personalized Response-driven Adjuvant therapy after Combination of Ipilimumab and Nivolumab in stage IIIB/C melanoma



TLND = therapeutic lymph node dissection

1. Adjuvant radiotherapy according to patient's and physician's decision.
2. According to institutes standard.

Objectives & Results of PRADO extension cohort

RESULTS

- PRADO **confirms the high pathologic response rate and safety** observed previously in OpACIN-neo arm B (ipilimumab 1mg/kg + nivolumab 3mg/kg)
  - **Pathologic response rate = 71%**
  - **Grade 3-4 irAE rate = 22% in the first 12 weeks**

- **TLND was omitted in 59 (60%) patients**

NEOADJUVANT IMMUNOTHERAPY: #1 TOPIC NEXT 5 YEARS

Less Surgery, Organ Sparing Approaches

- MELANOMA palpable lymph nodes:
  - Nivolumab 3 + Ipilimumab 1: 70% pathologic CR !!
  - No more TLND in > 50% of patients with palpable nodes in 5 years

- BLADDER CANCER
  - 50% pCR for T3 Bladder Cancers : wait and see
  - Reduction Cystectomies

- MSI Colo-Rectal Cancer
  - 19/20 pCR for MSI CRC ! (Nature Medicine 2020)
  - In future in case of pCR: NO Surgery but Endoscopy + MRI

- LUNG, HEAD&NECK; ESOPHAGEAL and GASTRIC; BREAST, GBM

ODOBRENO V 1L NAPREDOVALEGA ALI NERESEKTABILNEGA HEPATOCELULARNEGA KARCINOMA

UČINKOVITOST, KI OMOGOČA DALJŠE ŽIVLJENJE

TECENTRIQ▼ + AVASTIN® (bevacizumab):
Prva in edina kombinacija z zaviralcem nadzornih imunskih točk, ki je dokazala izboljšanje preživetja v primerjavi s sorafenibom.

- Mediana celokupnega preživetja pri bolnikih zdravljenih s kombinacijo zdravil TECENTRIQ + Avastin ni bila dosežena napram 13,2 mesecev pri bolnikih zdravljenih s sorafenibom (HR=0.58; 95% IZ: 0.42, 0.79; P=0.0006)

TECENTRIQ®
atezolizumab
POVEZANI Z NAMENOM

▼Za to zdravilo se izvaja dodatno spremljanje varnosti, kar označuje navzdol obrnjen črn trikotnik. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Prosimo, da o domnevnih neželenih učinkih, ki jih opazite pri zdravljenju z zdraviloma Tecentriq in Avastin, poročate v skladu s Pravilnikom o farmakovigilanci zdravil za uporabo v humani medicini(Uradni list RS, št. 57/14 in 27/17), na način, kot je objavljeno na spletni strani www.jazmp.si. Izpolnjen obrazec o domnevnem neželenem učinku zdravila pošljite nacionalnemu centru za farmakovigilanco na naslov Javna agencija Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, faks: + 386 (0)8 2000 510 ali na elektronski naslov h-farmakovigilanca@jazmp.si. Za zagotavljanje sledljivosti zdravila je pomembno, da pri izpolnjevanju obrazca o domnevnih neželenih učinkih zdravila navedete številko serije biološkega zdravila.

Indikacija za hepatocelularni karcinom še ni krita iz obveznega zdravstvenega zavarovanja.

Za podrobnejše in posodobljene informacije o zdravilu glejte Povzetek glavnih značilnosti zdravila Tecentriq in zdravila Avastin, ki sta dostopna ob kliku na spodnja spletna naslova ali pod QR kodo, ki jo preberete s pametnim telefonom ali drugo mobilno napravo.

https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_sl.pdf

https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_sl.pdf

Datum priprave: december 2020.
Samo za strokovno javnost.

Dodatne informacije so na voljo pri: Roche farmacevtska družba d.o.o., Stegne 13G, 1000 Ljubljana
M-SI-00000181 (v1.0)

Nemelanomski kožni raki

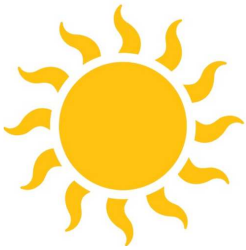
Prof.dr. Janja Ocvirk, dr.med.

NEMELANOMSKI KOŽNI RAK

- BAZALNOCELIČNI KARCINOM (bazaliom)
- SKVAMOZNI KARCINOM (spinaliom)
- REDKI RAKI KOŽE:karcinom Merklovih celic, dermatosarcoma protuberans, mycosis fungoides, Kaposijev sarkom

- Incidenca ~ 2000 /leto
- Manj kot 0,1% smrti zaradi raka

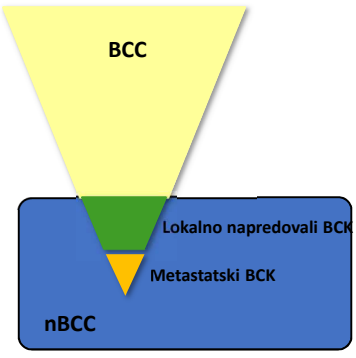
Dejavniki tveganja



Nemelanomski raki

- Kronična izpostavljenost soncu
- Starost
- Industrijski karcinogeni
- Imunosupresija, kronične razjede, stare brazgotine po opeklinah, ionizirajoče sevanje, arzen.
- aktinične keratoze - SCC
- Gorlinov sindrom
- Xeroderma pigmentosum

Klasifikacija bolnikov z BCC



Lokalno napredovali BCC (lnBCKC

- Bolniki, pri katerih lezije niso primerne za operacijo, ali imajo medicinske kontraindikacije za operacijo
- Bolniki, pri katerih bi operacija povzročila znatno obolevnost in/ali deformacijo (npr. vdor v lobanjo, amputacijo, enukleacijo)

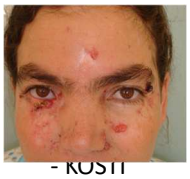
Metastatski BCC (mBCC)

- Včasih se pojavi pri bolnikih z dolgotrajnimi primarnimi lezijami, ki so velike ali se ponavljajo[1]
- Redka, ampak resna oblika BCC (0.0028–0.55% vseh BCK napreduje v mBCC)[1]
- Vključuje oddaljene zasevke (npr. kosti, pljuča in jetra) ali bezgavke[1]
- Slab izid (mediana preživetja: 8–14 mesecev[2,3]; 5-letna stopnja preživetja: 10%[3,4])

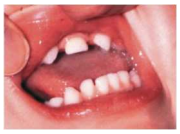
1. Ting PT et al. J Cutan Med Surg 2005;9:10–15
2. von Domarus H, Stevens PJ. J Am Acad Dermatol 1984;10:1043–60
3. Lo JS et al. J Am Acad Dermatol 1991;24:715–19
4. Wong CSM et al. Br Med J 2003;327:794–8

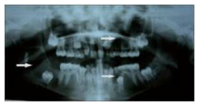
Sy. bazalnoceličnega nevusa (Gorlin Goltz)

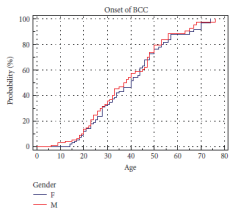
- Redka AD dedna bolezen kože in drugih organov
  (1:19,000, M=Ž, mutacija PTCH gena)[1]
- <u>Od otroštva pojav</u>:
  BCK (lahko več tisoč)
  palmoplantarne diskeratoze
  pogostejši meduloblastom CŽS, ovarijski fibrosarkom
- <u>Druge spremembe</u>:
  keratociste v čeljusti, spina bifida, kifoskolioza
  - ŽIVČNI SISTEM alteracije v EKG-ju, kalcifikacija dure
  - OČI povečan razmik med očmi, katarakta



- KOSTI

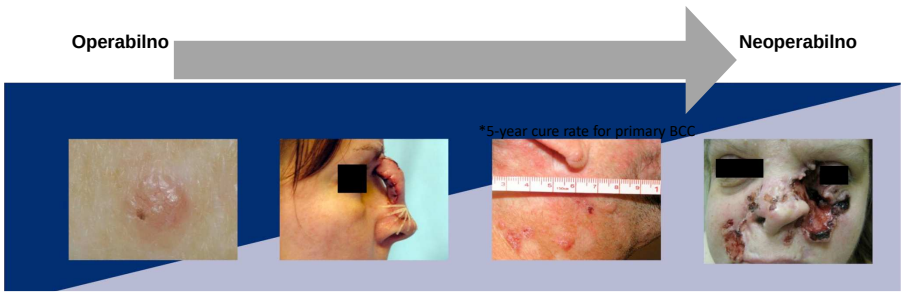






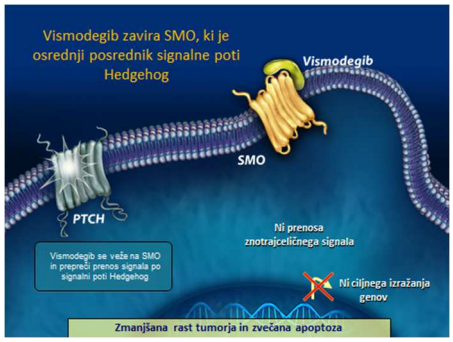
1. Jones E.A et al. Journal of Skin Cancer Volume 2011, Article ID 217378

Operacija in BCC



BCC in signalna pot Hedgehog

- Nenormalna aktivacija signalne poti Hedgehog ima pomembno vlogo v patogenezi in napredovanju BCC
- Zaviralci signalne poti Hedgehog omogočajo novo možnost zdravljenja za bolnike z napredovalim BCC



1. Epstein EH. Nat Rev Cancer 2008;8:743–54
2. Teh MT, et al. Cancer Res 2005; 65: 8597–603

Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial

Nicole Basset-Seguin, Axel Hauschild, Jean-Jacques Grob, Rainer Kunstfeld, Brigitte Dréno, Laurent Mortier, Paolo A Ascierto, Lisa Licitra, Caroline Dutriaux, Luc Thomas, Thomas Jouary, Nicolas Meyer, Bernard Guillot, Reinhard Dummer, Kate Fife, D Scott Ernst, Sarah Williams, Alberto Fittipaldo, Ioannis Xynos, Johan Hansson

Summary
Background The Hedgehog pathway inhibitor vismodegib has shown clinical benefit in patients with advanced basal

Lancet Oncol 2015; 16:729–36

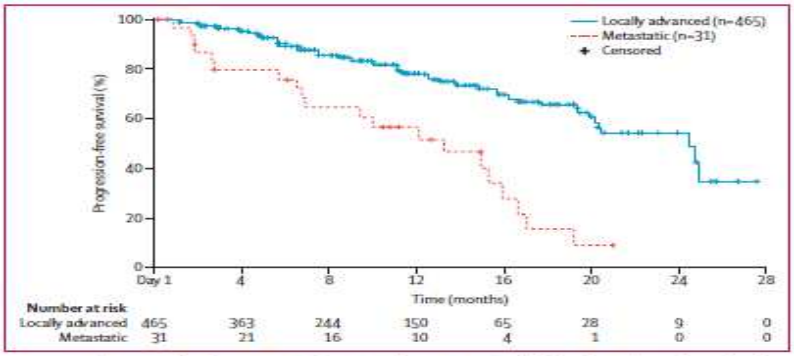
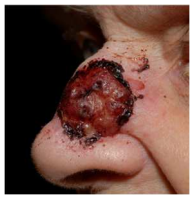
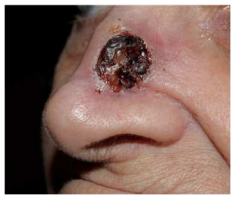
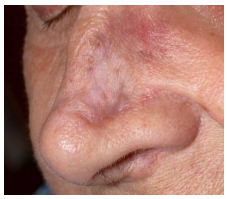


Figure 2: Kaplan-Meier plot of progression-free survival in patients who had histologically confirmed basal cell carcinoma

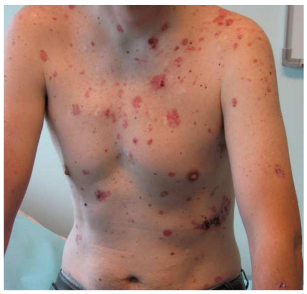
Zdravljenje z vismodegibom


Izhodišče

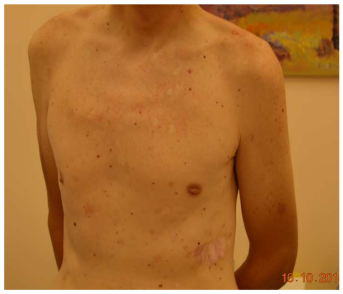

1 mesec

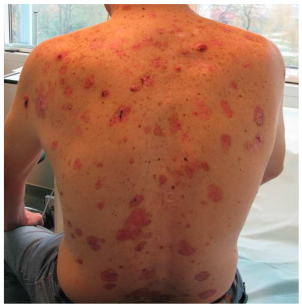

5 mesecev

- 88 stara bolnica – 2 leti krvaveč tumor na nosu; ni primeren za operacijo
- Popolna regresija v 2 mesecih
- Prekinitev zdravljenja kot posledica mišičnih krčev; po prekinitvi zdravljenja so mišični krči izginili

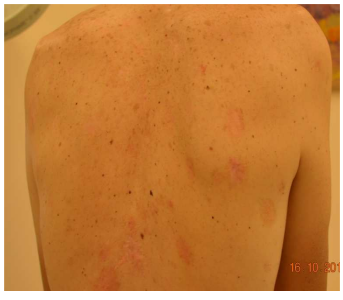

8. 11. 2012

Bolnik z Gorlinovim sindromom (multipli BCC)


16. 10. 2014



Neželeni učinki:
alopecia gr.1
izguba teže gr.2
zvišan CPK gr.1-3



Januar 2020

Maj 2020

74 | ONKOLOGIJA | ISSN 1408-1741 | SMERNICE | LETO XXIII | ŠT. 1 | JUNIJ 2019

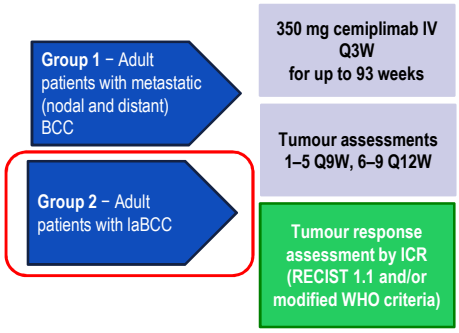
Priporočila za obravnavo bolnikov z bazalnoceličnim karcinomom

Reccomendations for diagnosis, treatment and follow-up of patients with basal cell carcinoma

Ahčan Uroš[1], Bertenjev Igor[2], Benedičič Ana[3], Bremec Toml[4], Dugonik Aleksandra[5], Grošelj Aleš[6], Grebenšek Nataša[7], Hočevar Marko[8], Jančar Boris[8], Luzar Boštjan[9], Mervic Lilijana[10], Ocvirk Janja[8], Pižem Jože[9], Rogl Butina Mirjam[2], Planinšek Ručigaj Tanja[4], Serša Gregor[8], Stojanović Larisa[11], Stopajnik Neža[4], Strojan Primož[8], Tlaker Vesna[12], Žgavec Borut[4]

VIRTUAL 2020 ESMO congress

• Study design and objectives (NCT03132636)



Primary endpoint: overall response rate by ICR

Key secondary endpoints: duration of response, progression-free survival, overall survival, complete response by ICR and safety and tolerability

•Key inclusion criteria

- Histologically confirmed diagnosis of invasive BCC
- Prior progression or intolerance to HHI therapy or no better than stable disease after 9 months on HHI therapy
- At least 1 measurable baseline lesion
- ECOG performance status of 0 or 1

•Key exclusion criteria

- Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression
- Prior anti–PD-1 or anti–PD-L1 therapy
- Concurrent malignancy other than BCC and/or history of malignancy other than BCC within 3 years of date of first planned dose of cemiplimab, except for tumours with negligible risk of metastasis or death

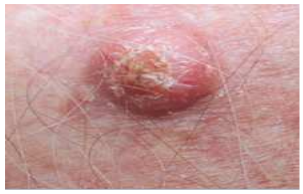
BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; HHI, hedgehog inhibitor; ICR, independent central review; IV, intravenous; laBCC, locally advanced BCC; PD-1, programmed cell death-1; PD-L1, PD-ligand 1; Q3W, every 3 weeks; Q9W, every 9 weeks; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

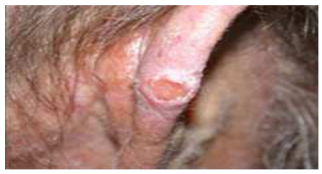
- Cemiplimab je prvo sistemsko zdravljenje, ki je pokazalo klinično korist pri bolnikih z laBCC po terapiji HHI
- 31% ORR in ocenjeno 12-mesečno preživetja 92,3%.
- Varnostni profil je sprejemljiv za populacijo bolnikov. Skladno je z drugimi protitelesi PD-1 in s prejšnjimi poročili o cemiplimabu pri drugih vrstah tumorjev

Ploščatocelični karcinom kože

- Drugi najbolj pogost NMKR (20%)
- Incidenca raste v zadnjih 30 letih (50-200%)
- Glava in vrat 80-90%
- 90% ima dobro prognozo

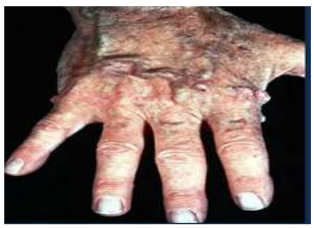
- **Kaj pa preostalih 10%?**

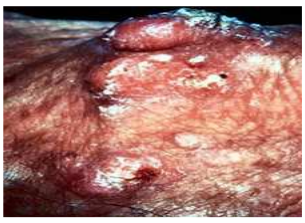


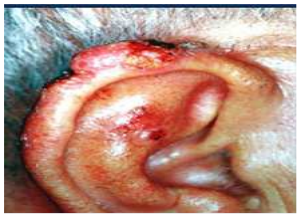


SCC pri transplantiranih bolnikih

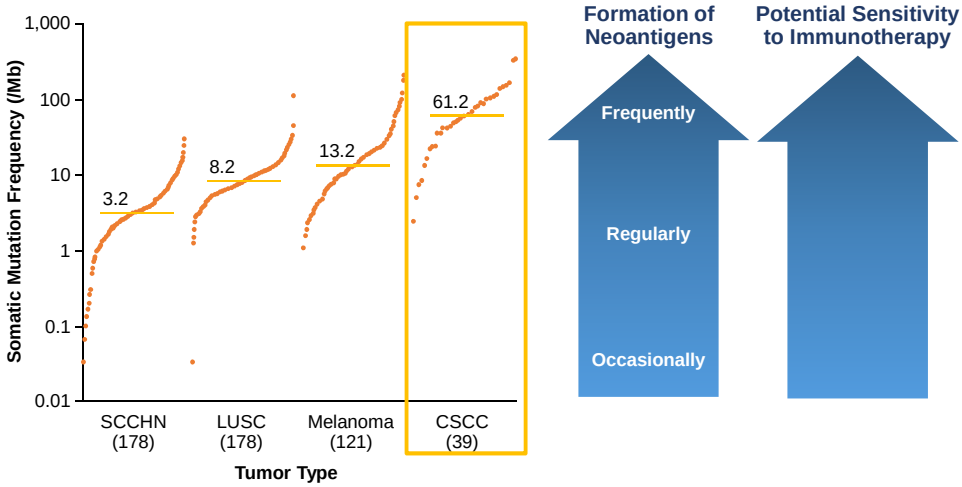
36 x večja incidence kot običajno(BCC: SCC 4: 1)
Agresiven potek - slaba prognoza







Tumor Mutational Burden in CSCC



Red horizontal line and associated number in figurer = median mutations per MB.
CSCC, cutaneous squamous cell carcinoma; LUSC, lung squamous cell carcinoma; Mb, megabase of DNA; SCCHN, Squamous cell carcinoma of the head and neck.
Pickering CR, et al. *Clin Cancer Res*. 2014;20:6582–6592.

Razlogi za imunoterapijo pri CSCC

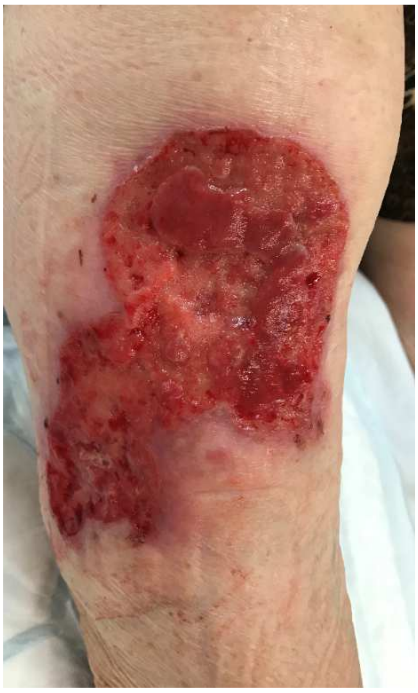
- Velika obremenitev tumorskih mutacij (TMB) in imunogenski rak
  - Visoka TMB lahko prispeva k večji proizvodnji neoantigena, kar lahko poveča antigenost tumorja[1]
- Imunosupresija je dobro opisan dejavnik tveganja za CSCC (zlasti pri bolnikih s presaditvijo organov)[2]
- PD-L1 ekspresijo so ugotovili pri napredovalem CSCC[3]

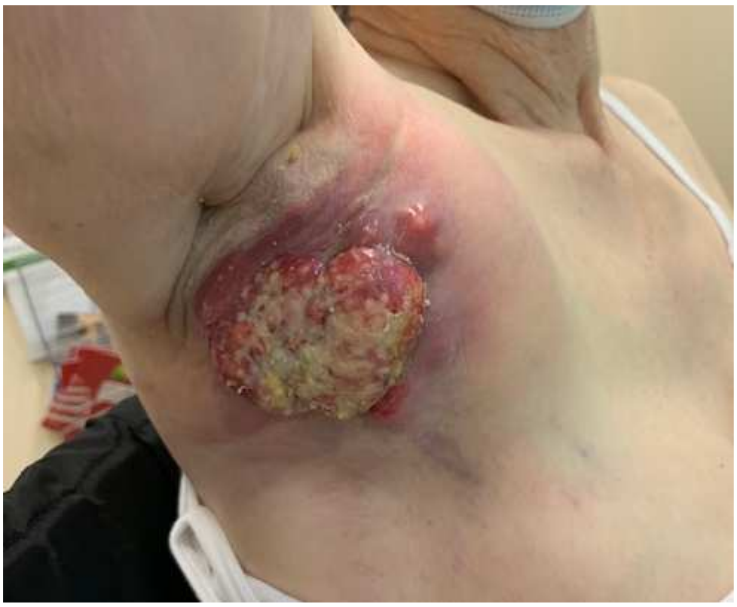
1. Pickering CR, et al. *Clin Cancer Res*. 2014;20:6582-92; 2. Euvrard E, et al. *N Engl J Med*. 2003;348:1681-1691.
3. Slater NA, et al. *J Cutan Pathol*. 2016;43:663-70.

Kandidati za immunotherapijo pri napredovalem CSCC

- Bolniki z napredovalim CSCC

  Lokalno napredovala / metastatska bolezen
- Bolniki, s ponovitvami po predhodnih operacijah
- Bolniki, ki niso kirurški kandidati zaradi obolevnosti / potencialne izčrpanosti ali nizke stopnje zaupanja v jasne meje
- Bolniki, ki niso kandidati za radioterapijo





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

Migden MR, et al. *N Engl J Med*. 2018;379:341-351.

EMPOWER-CSCC-1 Study Design (NCT02760498)

Group 1 – Adult patients with metastatic (nodal and/or distant) CSCC	**Cemiplimab 3 mg/kg Q2W IV, for up to 96 weeks** (retreatment optional for patients with disease progression during follow-up)	**Tumour imaging Q8W for the assessment of efficacy**
Group 2 – Adult patients with locally advanced CSCC		
Group 3 – Adult patients with metastatic (nodal and/or distant) CSCC*	**Cemiplimab 350 mg Q3W IV, for up to 54 weeks**	**Tumour imaging Q9W for the assessment of efficacy**

Tumour response assessment by ICR (RECIST 1.1 for scans; modified WHO criteria for photos)

Key inclusion criteria
- ECOG performance status of 0 or 1
- Adequate organ function
- Groups 1 & 3:
  - At least one lesion measurable by RECIST 1.1
- Group 2:
  - At least one lesion measurable lesion by RECIST 1.1 criteria (for scans) or modified WHO criteria (for photos)
  - CSCC lesion that is not amenable to surgery or radiotherapy per investigator assessment

Key exclusion criteria
- Ongoing or recent (within 5 years) autoimmune disease requiring systemic immunosuppression
- Prior anti–PD-1 or anti–PD-L1 therapy
- History of solid organ transplant, concurrent malignancies (unless indolent or not considered life threatening; for example, basal cell carcinoma), or haematologic malignancies

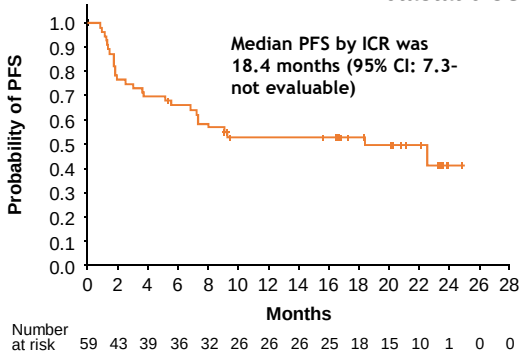
*Data not yet available
CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PD, programmed cell death; PD-L, PD-ligand; Q[n]W, every [n] weeks; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1; WHO, World Health Organisation.

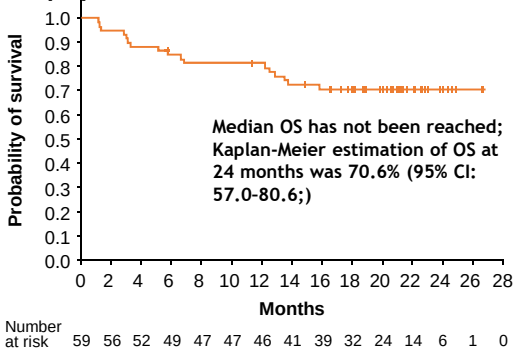
1. Guminski et al. *J Clin Oncol*. 2019:37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. *J Clin Oncol*. 2019:37 (suppl; abstr 6015) [poster presentation].

Group 1: Data cut-off date: September 20, 2018
Group 2: Data cut-off date: October 10, 2018

Kaplan–Meier Estimation Overall Survival, Progression-Free Survival, and Duration of Response in Advanced CSCC Patients

Metastatic CSCC (Group 1)[1]



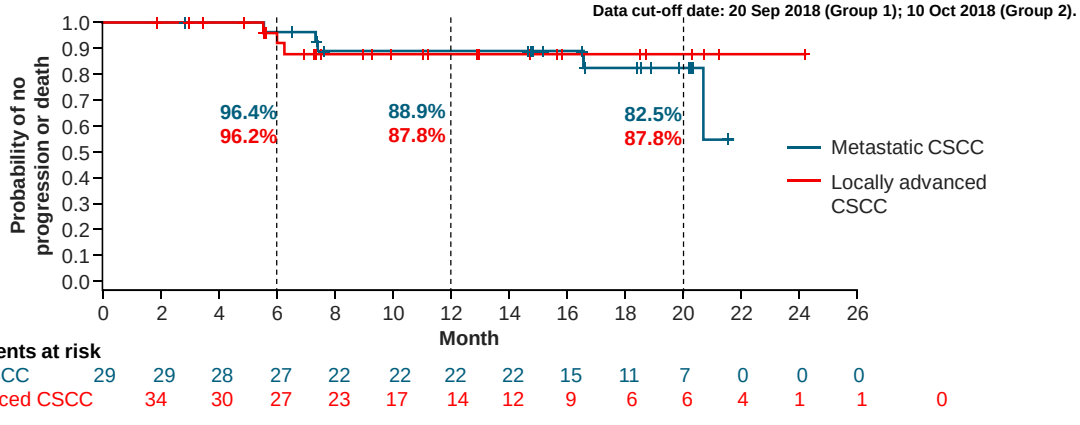


Median DOR not reached

	Locally Advanced CSCC (Group 2)[2]
Median PFS	NR
K-M Estimated PFS at 12 months	58.1% (95% CI: 43.7–70.0)
Median OS	NR
K-M Estimated OS at 12 months	93.2% (95% CI: 84.4–97.1)
Median DOR	NR

Group 1: Median duration of follow-up = 16.5 mos (range 1.1 – 26.6); Group 2: Median duration of follow-up = 9.3 mos (range 0.8 – 27.9)
Data cut-off date: Sept 20, 2018 (Group 1); Oct 10, 2018 (Group 2)
CI, confidence interval; CSCC, cutaneous squamous cell carcinoma; ICR, independent central review; OS, overall survival; PFS, progression-free survival; NR, not reached
1. Guminski et al. J Clin Oncol. 2019:37 (suppl; abstr 9526) [poster presentation]. 2. Migden MR, et al. J Clin Oncol. 2019:37 (suppl; abstr 6015) [poster presentation].

EMPOWER-CSCC-1:Duration of response K-M estimated event-free probability by ICR in responding patients



Number of patients at risk

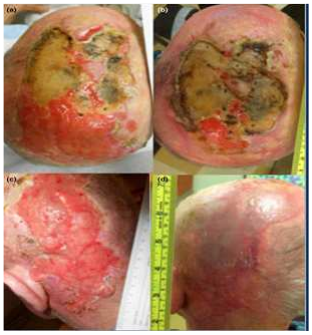
Metastatic CSCC	29	29	28	27	22	22	22	22	15	11	7	0	0	0
Locally advanced CSCC		34	30	27	23	17	14	12	9	6	6	4	1	1	0

Median duration of response has not been reached.

CSCC, cutaneous squamous cell carcinoma; ICR, independent central review.

Cemiplimab v zdravljenju SCC

Pred zdravljenejm

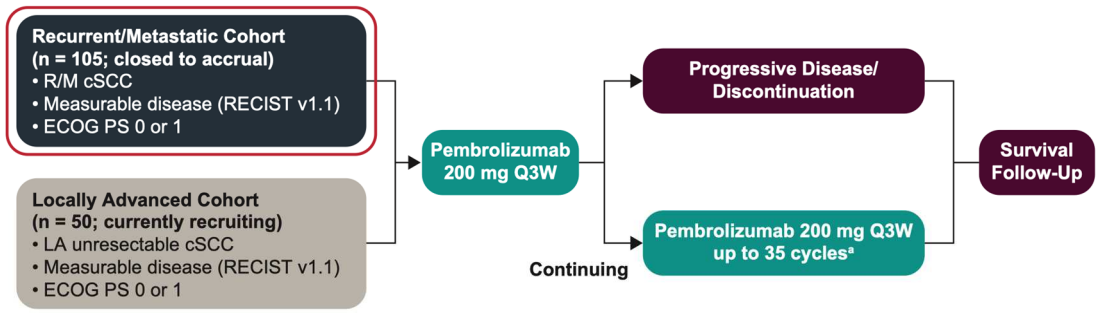


Po zdravljenju

Boradori et al. Br J Dermatol, 2016. 175: 1382-6

Pembrolizumab for Recurrent/Metastatic Cutaneous Squamous Cell Carcinoma: Efficacy and Safety Results From Phase 2 KEYNOTE-629 Study

Studiendesign



Primary end point
• ORR
Secondary end points
• DOR • DCR • PFS • OS • Safety

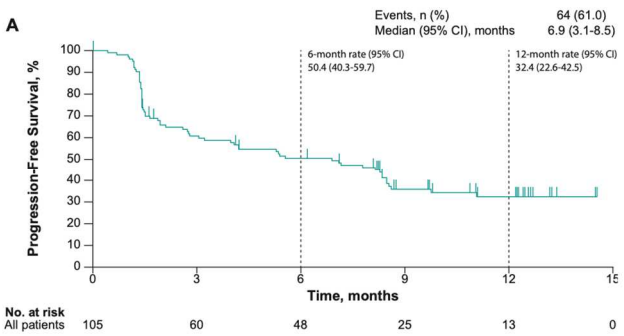
CR, complete response; cSCC, cutaneous squamous cell carcinoma; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; LA, locally advanced; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R/M recurrent and/or metastatic.

[a]Patients who discontinue treatment after achieving CR may be eligible to receive an additional 17 cycles of pembrolizumab if disease progression occurs.

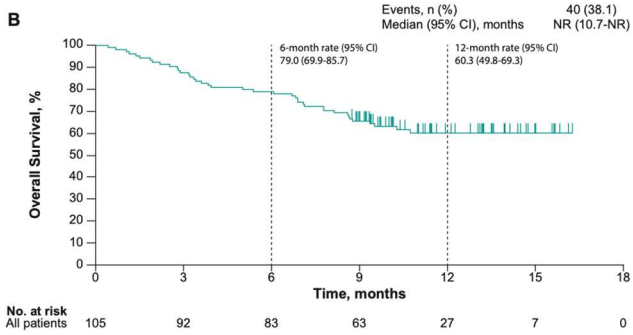
J.-J. Grob et al., KEYNOTE-629 Efficacy and Safety of pembrolizumab in patients with R/M cSCC, Poster presented at ESMO 2019

Pembrolizumab for Recurrent/Metastatic Cutaneous Squamous Cell Carcinoma: Efficacy and Safety Results From Phase 2 KEYNOTE-629 Study

PFS[a] in the R/M Cohort



OS[a] in the R/M Cohort

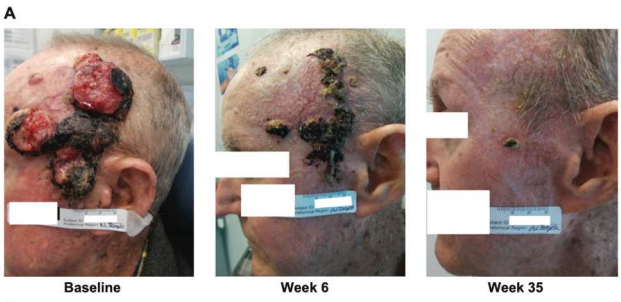


NR, not reached; OS, overall survival; PFS, progression-free survival; R/M, recurrent and/or metastatic.
[a]From product-limit (Kaplan-Meier) method for censored data.

J.-J. Grob et al., KEYNOTE-629 Efficacy and Safety of pembrolizumab in patients with R/M cSCC, Poster presented at ESMO 2019

Pembrolizumab for Recurrent/Metastatic Cutaneous Squamous Cell Carcinoma: Efficacy and Safety Results From Phase 2 KEYNOTE-629 Study

Effects of Pembrolizumab Monotherapy in 2 Patients With R/M cSCC



(A) 80-year-old male patient with cSCC at the temple who previously received surgery, at baseline, after 6 weeks of treatment, and at the most recent follow-up.

(B) 87-year-old female patient with cSCC at the jaw who previously received systemic therapy and radiation, at baseline, after 6 weeks of treatment, and at the most recent follow-up.

cSCC, cutaneous squamous cell carcinoma; R/M, recurrent and/or metastatic.

J.-J. Grob et al., KEYNOTE-629 Efficacy and Safety of pembrolizumab in patients with R/M cSCC, Poster presented at ESMO 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY FOR SQUAMOUS CELL SKIN CANCER

Local Disease Amenable to Surgery
- Systemic therapy is not recommended.

Locally Advanced Disease in Non-Surgical Candidates
- For potential use with RT: (See SCC-3)
  - Options for multidisciplinary team to consider for use in combination with RT for patients who have residual disease and further surgery is not feasible:
    - Clinical trial[1,2]
    - Chemotherapy
- Systemic therapy alone: (See SCC-3)
  - Options for multidisciplinary team to consider for complicated cases of locally advanced disease in which curative surgery and curative RT are not feasible:
    - Cemiplimab-rwlc[1,2] (preferred)
    - Clinical trial[1,2]

Regional Disease (See SCC-4)
- For most cases of fully resected regional disease, adjuvant systemic therapy is not recommended, unless within a clinical trial. (See SCC-4 and SCC-5)
- For patients with completely resected ECE or similar high-risk regional disease, consider RT ± systemic therapy in the context of a clinical trial.
- Options for patients with inoperable or incompletely resected regional disease:
  - For potential use with RT: (See SCC-4 and SCC-5)
    - Cisplatin[3] (category 3)
    - Cisplatin + 5-FU[3] (category 2B)
    - EGFR inhibitors (eg, cetuximab)[3]
    - Carboplatin[3] (category 3)
  - Systemic therapy alone, if curative RT not feasible: (See SCC-4)
    - Cemiplimab-rwlc[1,2] (preferred)
    - Clinical trial[1,2]
    - If ineligible for immune checkpoint inhibitors and clinical trials, consider:
      - Cisplatin[3] (category 2B)
      - Cisplatin + 5-FU[3]
      - EGFR inhibitors (eg, cetuximab)[3]
      - Carboplatin[3] (category 2B)

Regional Recurrence or Distant Metastatic Disease (See SCC-6)
- Cemiplimab-rwlc[1,2] (preferred) if curative surgery and curative RT are not feasible
- Clinical trial[1,2]
- If ineligible for immune checkpoint inhibitors and clinical trials, consider:
  - Cisplatin ± 5-FU[3]
  - EGFR inhibitors (eg, cetuximab)[3]
  - Carboplatin[3] (category 2B)

[1] Recently published phase I–II trial data have shown high response rates (approximately 50%) to cemiplimab-rwlc in patients with locally advanced or metastatic cutaneous squamous cell carcinoma. Preliminary data and the clinical experience of NCCN Panel members suggest that other anti–PD-1 inhibitors may also be effective in this setting.
[2] In solid organ transplant recipients, potential benefit from immune checkpoint inhibitor therapy has to be weighed against a significant risk of organ rejection. For patients receiving immunosuppressive therapy, in consultation with their treating physician, consider dose reduction of the immunosuppressive agent(s) and/or minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors where appropriate. Patients with underlying immunodeficiencies, including CLL, were excluded from the phase I–II cemiplimab-rwlc trial, so the efficacy of cemiplimab-rwlc in this population is unclear.
[3] These options have occasionally produced useful responses, but data supporting efficacy are limited.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ONKOLOŠKI INŠTITUT LJUBLJANA

PLOŠČATOCELIČNI RAK KOŽE

Priporočila za zdravljenje

Barbara Perić, Olga Blatnik, Boštjan Luzar, Jože Pižem, Janja Ocvirk, Marko Hočevar, Primož Strojan, Tomi Bremec, Martina Reberšek

Sistemsko zdravljenje napredovalega neresektabilnega in mcSCC

- cemiplimab (kategorija 2A)
- pembrolizumab*
- vključitev v klinično raziskavo, v kolikor je na voljo.
- v kolikor so kontraindikacije za zaviralce imunskih nadzornih točk:

  karboplatin (kategorija 2B)

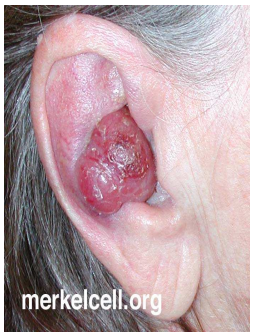
  cisplatin+/-5-FU (kategorija 2A)

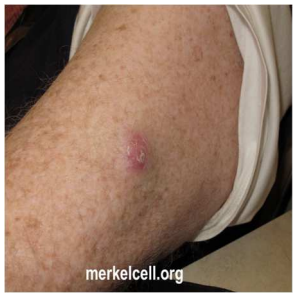
  zaviralci EGFR (cetuksimab) (kategorija 2A).

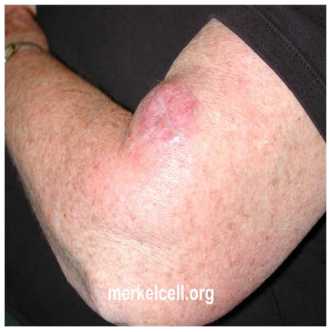
*Po registraciji s strani EMA in umestitvi na B-listo zdravil in s tem zagotovljenega financiranja zdravljenja s strani ZZZS

Rak Merklovih celic

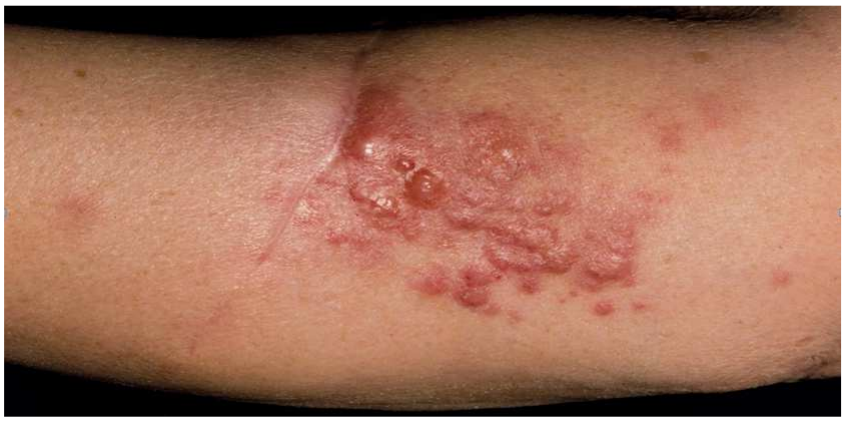
- Rak Merklovih celic (MCC) je redek, agresiven in pogosto smrten nevroendokrini kožni karcinom.
- Naraščajoča incidence (v ZDA se je od 1986 do 2001 potrojila).
- Možna povezava z nedavno odkritim poliomavirusom (80 % celic MCC).
- Pogosto se pojavlja na soncu izpostavljenih predelih kože.







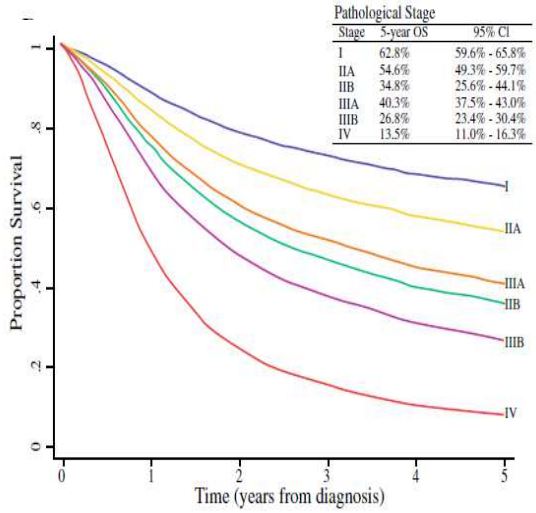
32



ZDRAVLJENJE

- Problem predstavlja visoka stopnja ponovitve bolezni, ki je celo pri bolnikih z lokalno ali regionalno boleznijo 48 %.
- Raziskave so pokazale, da je med bolniki s ponovitvijo bolezni, čas med diagnozo in ponovitvijo le 9 mesecev

PREŽIVETJE



Harms KL et al. Annals of Surgical Onc. 2016:23: 3564-71

35

Razlog za uporabo imunoterapije pri mMCC

- PD-L1 se izraža v MCC tumorskih celicah in infiltratih sosednih imunskih celic[1]
- Disfunkcija MCPyV-specifičnih T celic[2]
  - Nivoji CD8 T celic se zvišajo z večjim tumorskim bremenom
  - Exhausted fenotip (PD-1$^+$, Tim-3$^+$)
- MCPyV-negativni tumorji imajo večje breme mutacij in neoantigenov[3]

1. Lipson EJ, et al. *Cancer Immunol Res*. 2013;1(1):54-63; 2. Afanasiev O, et al. *Clin Cancer Res*. 2014;19(19):5351-60; 3. Goh G, et al. *Oncotarget*. 2016;7(3):3403-15.

Immune Checkpoint Inhibition Trials in MCC: Advanced Metastatic Disease

Drug / Trial	Target	n	Prior chemo	Objective response	Median follow-up	Median PFS	Median OS
Pembrolizumab first-line[1] (NCT02267603) CITN-09	PD-1	26	No	56%	8 mo	Not reached	Not reached
Avelumab first-line[2] (NCT02155647) JAVELIN Merkel 200	PD-L1	29	No	63%	3 mo	Not reached	Not reached
Nivolumab first/second-line[3] (NCT02488759) CheckMate-358	PD-1	15 10	No Yes	73% 1st-L 50% 2nd-L	3+ mo	Not reached	Not reached
Avelumab second-line[4,5] (NCT02155647) JAVELIN Merkel 200	PD-L1	88	Yes	33%	16 mo	3 mo	13 mo

1. Nghiem PT *et al.*: *N Engl J Med* **374**:2542 (2016); 2. D'Angelo SP *et al.*: *ASCO* abstract 9530 (2017); 3. Topalian S *et al.*: *Cancer Res* **77**(13 Suppl): abstract CT074 (2017); 4. Kaufman HL *et al.*: *Lancet Oncol* **17**:1374 (2016); 5. Kaufman H et al.: J Immunother Cancer 6:7 (2018).

- Tudi pri MCC se je imunoterapija izkazala kot zelo učinkovita terapija.
- Učinkovitost imunoterapije je bila dokazana pri MCPyV pozitivnih in MCPyV negativnih tumorjih.
- Preizkušana je bila v prvem, drugem in poznejših redih zdravljenja napredovalega KMC.
- Zdravljenje razsejanega MCC z imunoterapijo: avelumab in pembrolizumab.

Open access Short report

Journal for ImmunoTherapy of Cancer

Efficacy and safety of avelumab treatment in patients with metastatic Merkel cell carcinoma: experience from a global expanded access program

John W Walker [1] Celeste Lebbé,[2] Giovanni Grignani,[3] Paul Nathan,[4] Luc Dirix,[5] Eyal Fenig,[6] Paolo Antonio Ascierto [7] Shahneen Sandhu,[8,9] Rodrigo Munhoz,[10] Elena Benincasa,[11] Sarah Flaskett,[12] Josh Reed,[13] Arne Engelsberg,[14] Subramanian Hariharan,[15] Vijay Kasturi[11]

- Among 240 evaluable patients, the objective response rate was 46.7% (complete response in 22.9%, including 3 of 16 potentially immunocompromised patients), and the disease control rate was 71.2%.
- The median duration of treatment in evaluable patients with response was 7.9 months (range, 1.0–41.7) overall and 5.2 months (range, 3.0–13.9) in immunocompromised patients. No new safety signals were identified.
- .

- The avelumab expanded access program for patients with mMCC demonstrated efficacy and safety in a real-world setting, consistent with the results from JAVELIN Merkel 200, and provided a treatment for patients with limited options.

Sklepi

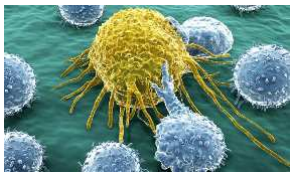
Nemelanomski kožni rak - najpogostejši rak, katerega incidenca narašča

Številne mutacije, ki jih povzroča UV

Operacija je standardna terapija za nezapletene primere

Sklepi

- Kemoterapija nima dokazanega jasnega učinka
- Tarčna terapija pri BCC patched / SMOi inhibitorji so učinkoviti (RR 58%, CR 20-30%)
- Imunoterapija (PD-1 in PD-L1 protitelesa) je učinkovita pri SCC in tumorjih merklovih celic, pa tudi pri BCC



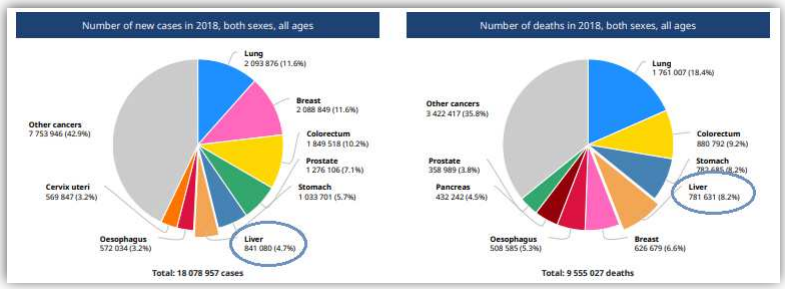
ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Novosti pri zdravljenju rakov hepatobilijarnega sistema

HEPATOCELULARNI KARCINOM

Ljubljana, 15.12.2020

HEPATOCELULARNI CARCINOM ***(HCC)***



- Incidenca:
  - ***5.*** najpogostejši malignom
  - Povečuje se s starostjo (vrh okoli 70. leta)
  - Moški > ženske
- 5 letno preživetje 5-14%
- Mortaliteta: ***4.*** najpogostejši vzrok smrti zaradi malignoma

Globoscan. http://globocan.iarc.fr/old/FactSheets/cancers/liver-new.asp

Barcelona Clinic Liver Cancer DIAGRAM

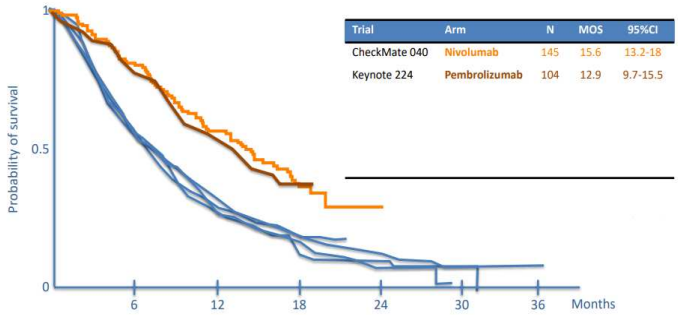
BCLC STADIJ		ECOG PS	VELIKOST/ŠT. TUMORJA, VASKULARNA INVAZIJA	CHILD-PUGH SKOR
0	Zelo zgodnji	0	Solitarni tumor < 2 cm	A
A	Zelo zgodnji	0	Solitarni < 5 cm; 2-3 tumorja < 3 cm	A-B
B	Srednji	0	Multifokalni HCC	A-B
C	Napredovali	1-2	Makrovaskularna invazija; Oddaljeni zasevki	A-B
D	Končni	3-4	Karkoli od zgoraj naštetega	C

Barcelona-Clinic Liver Cancer (BCLC) staging classification and treatment schedule. Adapted from Llovet JM et al., Lancet 2003

	KLINIČNA ŠTUDIJA	Eksperimenatlna vs. Kontrola skupina	PFS (meseci)	OS (meseci)
1. RED	SHARP	Sorafenib vs. Placebo	5.5 vs. 2.8	10.7 vs. 7.9
	REFLECT (neinferiorna)	Lenvatinib vs. Sorefenib	7.4 vs. 3.7	13.6 vs. 12.3
2. RED	RESORECE	Regorafenib vs. placebo	3.1 vs. 1.5	10.6 vs. 7.8
	CELESTIAL	Cabozantinib vs. placebo	5.2. vs 1.9	11.3 vs. 7.2
	REACH	Ramicirumab vs. Placebo	2.8 vs. 1.6	8.5 vs. 7.3

Llovet JM, et al. N Engl J Med. 2008;359(4):378–90
Kudo M, et al. Lancet.2018;391(10126):1163–73
Bruix J, et al. Lancet. 2017;389(10064):56–66
Abou-Alfa GK, et al. N Engl J Med. 2018;379(1):54–63
Zhu AX,, et al. Lancet Oncol. 2019;20:282–96

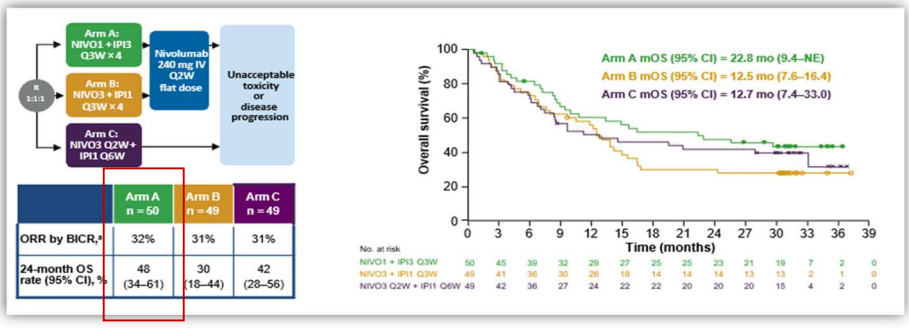
IMUNOTERAPIJA V 2. LINIJI ZDRAVLJENJA



	KLINIČNA ŠTUDIJA	ODGOVOR NA ZDRAVLJENJE	TRAJANJE ODGOVOR	FDA	EMA
FAZA 2	NIVOLUMAB CheckMate 040	14%	16.6 mesecev pri HCV+	22. 9. 2017	Ni odobren
	PEMBROLIZUMAB KeyNote 224	17%	> 6 mesecev 77%	10. 11. 2018	Ni odobren

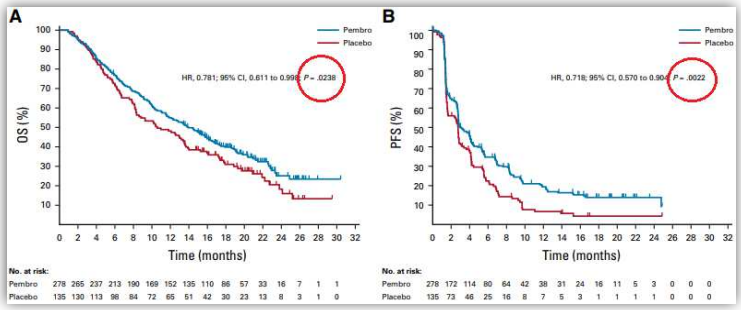
El-Khoueiry A, Sangro B, Yao T, et al. Lancet 2017; Meyer T, et al . Presented at EASL 2018; https://www.onclive.com/web-exclusives/fda-approves-pembrolizumab-for-hcc

IMUNOTERAPIJA V 2. LINIJI ZDRAVLJENJA CheckMate 040: nivolumab + ipilimumab



Sangro B, et al. Presented at AASLD 2019

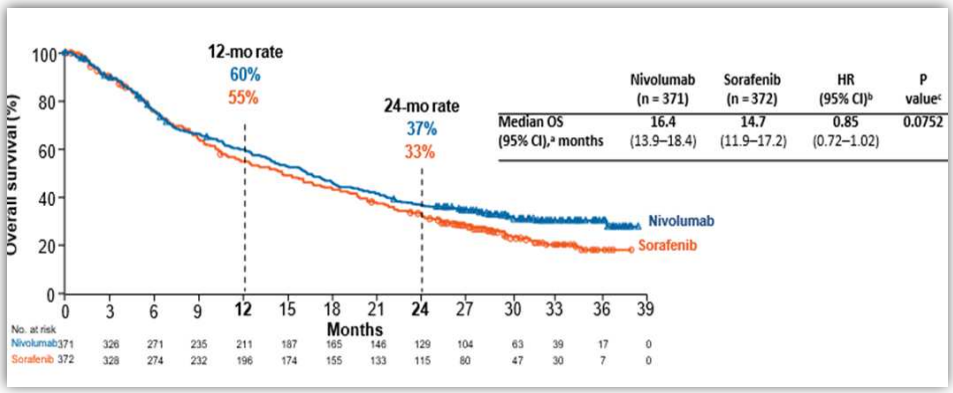
IMUNOTERAPIJA V 2. LINIJI ZDRAVLJENJA KEYNOTE 240 (faza 3)



	Pembrolizumab	Placebo	*P (˝prespecified˝)*	*P*
Celokupno preživetje	13.9 mesecev	10.6 mesecev	***0.0174***	***0.0238***
Čas do napredovanja bolezni	3 mesece	2.8 msecev	***0.002***	***0.0022***

Finn R, et al. Presented at ASCO 2019

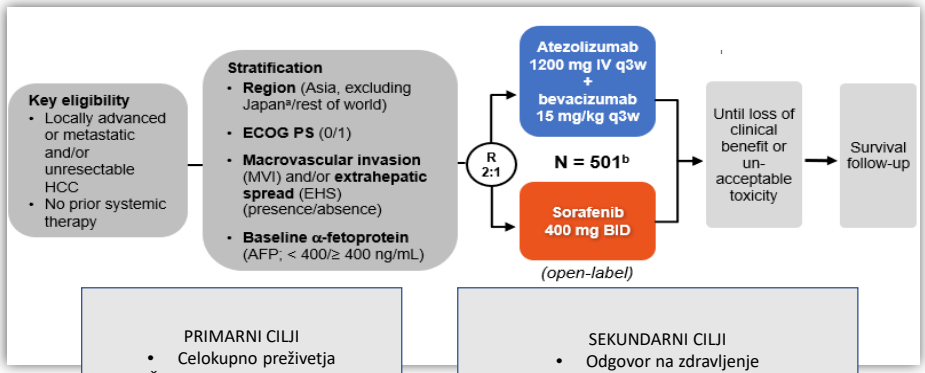
IMUNOTERAPIJA V 1. LINIJI ZDRAVLJENJA CheckMate 459: nivolumab vs. sorafenib



	Nivolumab (n = 371)	Sorafenib (n = 372)	HR (95% CI)[b]	P value[c]
Median OS (95% CI),[a] months	16.4 (13.9–18.4)	14.7 (11.9–17.2)	0.85 (0.72–1.02)	0.0752

Yau T, et al. Presented at ESMO 2019

IMUNOTERAPIJA V 1. LINIJI ZDRAVLJENJA
Imbrave 150
atezolizumab + bevacizumab vs. sorafenib

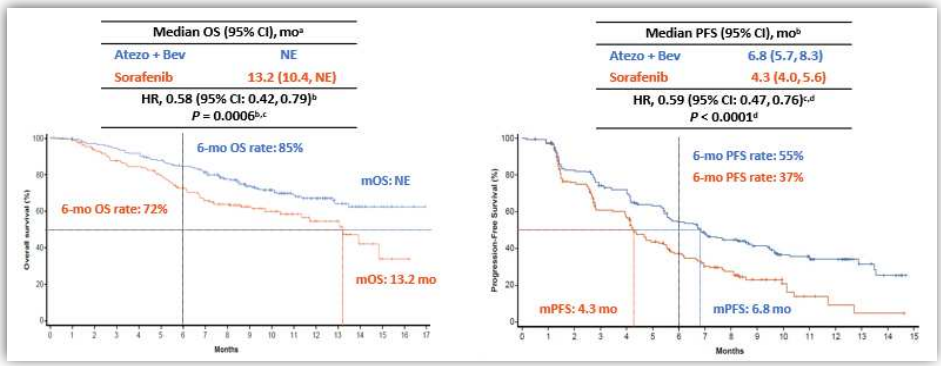


PRIMARNI CILJI
- Celokupno preživetja
- Čas do napredovanja bolezni

SEKUNDARNI CILJI
- Odgovor na zdravljenje
- Kontrola bolezni
- Kvaliteta življenja

Cheng AL, et al. Presented at ESMO Asia 2019

IMUNOTERAPIJA V 1. LINIJI ZDRAVLJENJA
Imbrave 150
atezolizumab + bevacizumab vs. sorafenib



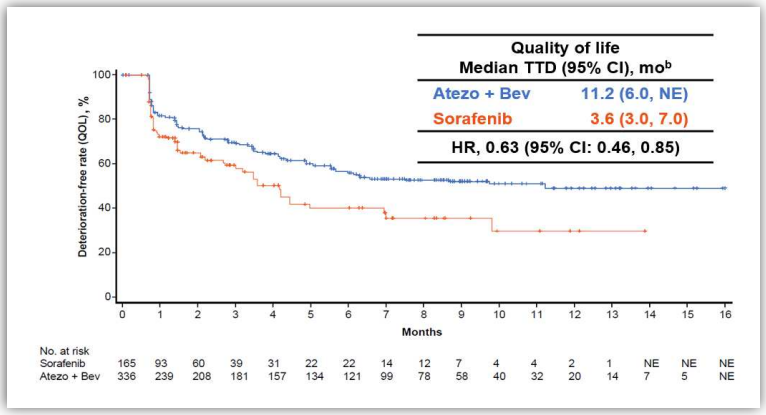
Cheng AL, et al. Presented at ESMO Asia 2019

IMUNOTERAPIJA V 1. LINIJI ZDRAVLJENJA
Imbrave 150
atezolizumab + bevacizumab vs. sorafenib

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n **(%)** (95% CI)	89 **(27)** (23, 33)	19 **(12)** (7, 18)	108 **(33)** (28, 39)	21 **(13)** (8, 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 0.0001**		**< 0.0001**	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Ongoing response, n (%)[c]	77 (87)	13 (68)	84 (78)	13 (62)
Median DOR, months (95% CI)	NE	6.3 (4.7, NE)	NE	6.3 (4.9, NE)
Event-free rate at 6 months, n (%)	88	59	82	63

Cheng AL, et al. Presented at ESMO Asia 2019

IMUNOTERAPIJA V 1. LINIJI ZDRAVLJENJA
Imbrave 150
atezolizumab + bevacizumab vs. sorafenib



Cheng AL, et al. Presented at ESMO Asia 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2020
Hepatocellular Carcinoma
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

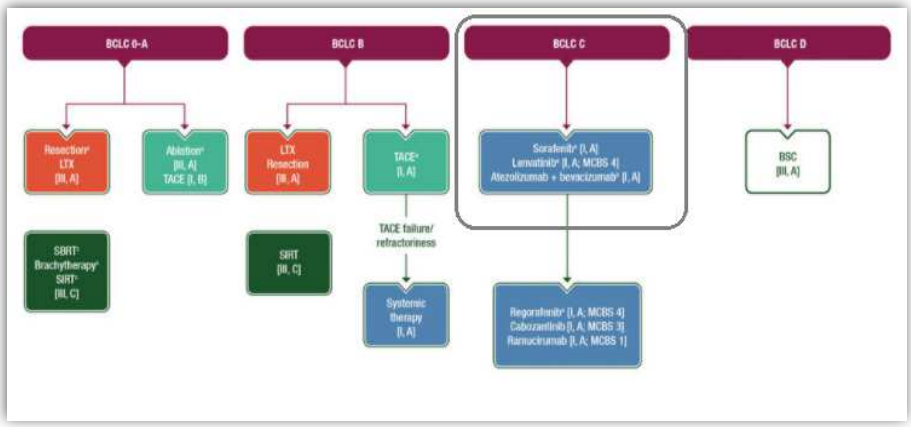
First-line systemic therapy

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Sorafenib (Child-Pugh Class A [category 1] or B7)[a,b,1,2] • Lenvatinib (Child-Pugh Class A only)[3,4] (category 1) • Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[c,d,5]	• None	• Nivolumab[c,6] (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (category 2B) • FOLFOX (category 2B)[e]

Subsequent-line therapy[f] if disease progression[g]

Options

- Regorafenib (Child-Pugh Class A only) (category 1)[h,7]
- Cabozantinib (Child-Pugh Class A only) (category 1)[h,8]
- Ramucirumab (AFP ≥400 ng/mL only) (category 1)[h,9]
- Lenvatinib (Child-Pugh Class A only)
- Nivolumab (Child-Pugh Class A or B)[c,i,10–12]
- Nivolumab + ipilimumab (Child-Pugh Class A only)[c,h,i,14]
- Sorafenib (Child-Pugh Class A or B7)[a,b]
- Pembrolizumab (Child-Pugh Class A only)[c,i,13] (category 2B)



In contrast, the combination of atezolizumab with bevacizumab met both primary endpoints of OS and progression-free survival (PFS) compared with sorafenib, as it was associated with hazard ratios of 0.59 and 0.58 respectively. Based on these data, the combination was approved by the Food and Drug Administration (FDA). Assessment by the European Medicines Agency (EMA) is awaited.

POVEZANI Z NAMENOM

TECENTRIQ® ▼
atezolizumab

ZDRAVILO TECENTRIQ JE INDICIRANO ZA ZDRAVLJENJE RAZLIČNIH VRST RAKA:

- NEDROBNOCELIČNI RAK PLJUČ
- DROBNOCELIČNI RAK PLJUČ
- TROJNO NEGATIVNI RAK DOJK
- UROTELIJSKI KARCINOM
- HEPATOCELULARNI KARCINOM

Skrajšan povzetek glavnih značilnosti zdravila Tecentriq

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Kako poročati o neželenih učinkih, si poglejte skrajšani povzetek glavnih značilnosti zdravila pod „Poročanje o domnevnih neželenih učinkih".

Ime zdravila: Tecentriq 840 mg/1200 mg koncentrat za raztopino za infundiranje. **Kakovostna in količinska sestava:** 840 mg: ena 14-ml viala s koncentratom vsebuje 840 mg atezolizumaba. 1200 mg: ena 20-ml viala s koncentratom vsebuje 1200 mg atezolizumaba. Po redčenju je končna koncentracija razredčene raztopine med 3,2 mg/ml in 16,8 mg/ml. Atezolizumab je humanizirano monoklonsko protitelo IgG1 z inženirsko obdelano domeno Fc, ki je pridobljeno iz celic jajčnika kitajskega hrčka s tehnologijo rekombinantne DNA in deluje na ligand za programirano celično smrt 1 (PD-L1). **Terapevtske indikacije:** Urotelijski karcinom (840 mg in 1200 mg): Zdravilo Tecentriq je kot monoterapija indicirano za zdravljenje odraslih bolnikov z lokalno napredovalim ali razsejanim urotelijskim karcinomom, ki: so bili predhodno zdravljeni s kemoterapijo na osnovi platine ali niso primerni za zdravljenje s cisplatinom in katerih tumorji izražajo PD-L1 v ≥ 5 %. Nedrobnocelični rak pljuč (le za 1200 mg): Zdravilo Tecentriq je v kombinaciji z bevacizumabom, paklitakselom in karboplatinom indicirano kot prva linija zdravljenja odraslih bolnikov z razsejanim nepločastoceličnim nedrobnoceličnim rakom pljuč (NDRP). Pri bolnikih z EGFR mutiranim ali ALK pozitivnim NDRP je zdravilo Tecentriq v kombinaciji z bevacizumabom, paklitakselom in karboplatinom indicirano le, ko so izčrpana ustrezna tračna zdravljenja. Nedrobnocelični rak pljuč (840 mg in 1200 mg): Zdravilo Tecentriq je kot monoterapija indicirano za zdravljenje odraslih bolnikov z lokalno napredovalim ali razsejanim NDRP, ki so bili predhodno zdravljeni s kemoterapijo. Bolniki z EGFR mutiranim ali ALK pozitivnim NDRP morajo pred uvedbo zdravila Tecentriq prejeti tudi tračna zdravljenja. Nedrobnocelični rak pljuč (le za 1200 mg): Zdravilo Tecentriq je v kombinaciji z nab-paklitakselom in karboplatinom indicirano kot prva linija zdravljenja odraslih bolnikov z razsejanim nepločastoceličnim NDRP, ki ni EGFR mutiran ali ALK pozitiven. Drobnocelični rak pljuč (le za 1200 mg): Zdravilo Tecentriq je v kombinaciji s karboplatinom in etopozidom indicirano kot prva linija zdravljenja odraslih bolnikov z razsejanim drobnoceličnim rakom pljuč (DRP). Hepatocelularni karcinom (le za 1200 mg): Zdravilo Tecentriq je v kombinaciji z bevacizumabom indicirano za zdravljenje odraslih bolnikov z napredovalim ali neresektabilnim hepatocelularnim karcinomom (HCC), ki predhodno še niso prejemali sistemskega zdravljenja. Rak dojk (le za 840 mg): Zdravilo Tecentriq je v kombinaciji z nab-paklitakselom indicirano za zdravljenje odraslih bolnikov z inoperabilnim lokalno napredovalim ali razsejanim trojno negativnim rakom dojk (TNRD), katerih tumorji izražajo PD-L1 v ≥ 1 % in predhodno še niso prejemali kemoterapije zaradi razsejane bolezni. **Odmerjanje in način uporabe:** Zdravilo Tecentriq morajo uvesti in nadzorovati zdravniki z izkušnjami pri zdravljenju raka. Testiranje PD-L1 pri bolnikih z urotelijskim karcinomom in TNRD: bolnike s predhodno nezdravljenim urotelijskim karcinomom in TNRD je treba za zdravljenje izbrati na podlagi tumorskega izražanja PD-L1, potrjenega z validirano preiskavo. Odmerjanje: *Zdravilo Tecentriq v monoterapiji:* 840 mg: priporočeni odmerek zdravila Tecentriq je 840 mg intravensko na vsaka dva tedna ali 1680 mg intravensko na vsake štiri tedne. 1200 mg: priporočeni odmerek zdravila Tecentriq je 1200 mg intravensko na vsake tri tedne. *Zdravilo Tecentriq v kombinaciji: Prva linija zdravljenja nepločastoceličnega NDRP: Zdravilo Tecentriq v kombinaciji z bevacizumabom, paklitakselom in karboplatinom:* Med uvodno fazo je priporočeni odmerek zdravila Tecentriq 1200 mg v intravenski infuziji, čemur sledijo bevacizumab, paklitaksel in nato karboplatin na tri tedne, skupno štiri ali šest ciklov. Uvodni fazi zdravljenja sledi faza vzdrževanja brez kemoterapije, med katero se na tri tedne uporabi zdravilo Tecentriq v odmerku 1200 mg v intravenski infuziji, ki mu sledi bevacizumab. *Zdravilo Tecentriq v kombinaciji z nab-paklitakselom in karboplatinom:* Med uvodno fazo je priporočeni odmerek zdravila Tecentriq 1200 mg v intravenski infuziji, čemur sledita nab-paklitaksel in nato karboplatin na vsake tri tedne, skupno štiri ali šest ciklov. Uvodni fazi zdravljenja sledi faza vzdrževanja brez kemoterapije, med katero se zdravilo Tecentriq v odmerku 1200 mg v intravenski infuziji aplicira na tri tedne. *Prva linija zdravljenja razsejanega DRP: Zdravilo Tecentriq v kombinaciji s karboplatinom in etopozidom:* Med uvodno fazo je 1. dan cikla priporočeni odmerek zdravila Tecentriq 1200 mg v intravenski infuziji, čemur sledita najprej karboplatin in nato etopozid v intravenski infuziji. Etopozid v intravenski infuziji se aplicira tudi 2. in 3. dan. Ta shema se aplicira na vsake tri tedne v skupno štirih ciklih. Uvodni fazi sledi faza vzdrževanja brez kemoterapije, med katero se zdravilo Tecentriq v odmerku 1200 mg v intravenski infuziji aplicira na tri tedne. *Zdravilo Tecentriq v kombinaciji z nab-paklitakselom v 1. liniji razsejanega TNRD:* Priporočeni odmerek zdravila Tecentriq je 840 mg v intravenski infuziji, ki ji sledi 100 mg/m² nabpaklitaksela. V vsakem 28-dnevnem ciklu se zdravilo Tecentriq uporabi 1. in 15. dan, nab-paklitaksel pa 1., 8. in 15. dan. *Hepatocelularni karcinom: Zdravilo Tecentriq v kombinaciji z bevacizumabom:* Priporočeni odmerek zdravila Tecentriq je 1200 mg, ki mu sledi bevacizumab 15 mg/kg telesne mase, dan z intravensko infuzijo vsake 3 tedne. *Trajanje zdravljenja:* zdravljenje z zdravilom Tecentriq je priporočljivo nadaljevati, dokler je klinično koristno ali dokler se ne pojavijo neobvladljivi toksični učinki. *Zapozneli ali izpuščeni odmerki:* v primeru izpuščenega načrtovanega odmerka zdravila Tecentriq je treba odmerek dati čim prej. Urnik dajanja zdravila je treba nato prilagoditi ustreznemu presledku med odmerki. *Prilagoditev odmerka med zdravljenjem:* odmerkov zdravila Tecentriq ni priporočljivo zmanjševati. *Zapoznitev odmerka ali prenehanje uporabe* glede na neželeni učinek je opisano v SmPC. Posebne populacije bolnikov: *Starejši:* glede na populacijsko farmakokinetično analizo bolnikom v starosti ≥ 65 let odmerka zdravila Tecentriq ni treba prilagoditi. Način uporabe: zdravilo Tecentriq je namenjeno za intravensko uporabo. Infuzij se ne sme dajati kot hiter intravenski odmerek ali bolus. Začetni odmerek zdravila Tecentriq je treba dati v 60 minutah. Če bolnik prvo infuzijo dobro prenese, je mogoče vse nadaljnje infuzije dati v 30 minutah. **Kontraindikacije:** Preobčutljivost na atezolizumab ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Sledljivost: Za izboljšanje sledljivosti bioloških zdravil je treba lastniško ime in številko serije uporabljenega zdravila jasno zabeležiti v bolnikovi dokumentaciji. Imunsko pogojeni neželeni učinki: Večina imunsko pogojenih neželenih učinkov, ki so se pojavili med zdravljenjem z atezolizumabom, je bila po prekinitvi atezolizumaba in uvedbi kortikosteroidov in/ali podpornega zdravljenja reverzibilna. Opazili so imunsko pogojene neželene učinke, ki vplivajo na več kot en organski sistem. Imunsko pogojeni neželeni učinki, povezani z atezolizumabom, se lahko pojavijo po zadnjem odmerku atezolizumaba. Pri sumu na imunsko pogojene neželene učinke je treba opraviti temeljito oceno za potrditev etiologije oziroma izključitev drugih vzrokov. Glede na izrazitost neželenega učinka je treba uporabo atezolizumaba odložiti in uvesti kortikosteroide. Atezolizumab je treba trajno prenehati uporabljati pri vseh imunsko pogojenih neželenih učinkih 3. stopnje, ki se ponovijo, in pri vseh imunsko pogojenih neželenih učinkih 4. stopnje, z izjemo endokrinopatij, ki jih je mogoče nadzorovati z nadomestnimi hormoni. Imunsko pogojeni pnevmonitis: v kliničnih preskušanjih atezolizumaba so opažali primere pnevmonitisa, vključno s smrtnimi primeri. Bolnike je treba spremljati glede znakov in simptomov pnevmonitisa ter izključiti druge možne vzroke, razen imunsko pogojenega pnevmonitisa. Imunsko pogojeni hepatitis: v kliničnih preskušanjih atezolizumaba so opazili primere hepatitisa, nekatere s smrtnim izidom. Bolnike je treba spremljati glede znakov in simptomov hepatitisa. Vrednosti AST, ALT in bilirubina je treba spremljati pred začetkom zdravljenja z atezolizumabom, redno med zdravljenjem in kot je potrebno glede na klinično oceno. Imunsko pogojeni kolitis: v kliničnih preskušanjih atezolizumaba so opažali primere diareje ali kolitisa. Bolnike je treba spremljati glede znakov in simptomov kolitisa. Imunsko pogojene endokrinopatije: v kliničnih preskušanjih atezolizumaba so opažali hipotiroidizem, hipertiroidizem, insuficienco nadledvičnih žlez, hipofizitis in sladkorno bolezen tipa 1, vključno z diabetično ketoacidozo. Bolnike je treba spremljati glede znakov in simptomov endokrinopatij. Imunsko pogojeni meningoencefalitis: v kliničnih preskušanjih z atezolizumabom so opažali meningoencefalitis. Bolnike je treba spremljati glede znakov in simptomov meningitisa ali encefalitisa. V primeru meningitisa ali encefalitisa je treba zdravljenje z atezolizumabom trajno ukiniti ne glede na njuno stopnjo. Imunsko pogojene nevropatije: pri bolnikih, zdravljenih z atezolizumabom, so opažali miastenijski sindrom/miastenijo gravis ali Guillain-Barréjev sindrom, ki je lahko življenje ogrožujoč. Bolnike je treba spremljati glede znakov in simptomov motoričnе in senzorične nevropatije. V primeru miastenijskega sindroma/miastenije gravis ali Guillain-Barréjevega sindroma je treba zdravljenje z atezolizumabom trajno prekiniti ne glede na njihovo stopnjo. Imunsko pogojeni pankreatitis: v kliničnih preskušanjih z atezolizumabom so opazili pankreatitis, vključno z zvišanjem amilaze in lipaze v serumu. Bolnike je treba nadzorovati glede znakov in simptomov, ki kažejo na akutni pankreatitis. Imunsko pogojeni miokarditis: v kliničnih preskušanjih z atezolizumabom so opazili miokarditis. Bolnike je treba nadzorovati glede znakov in simptomov, ki kažejo na miokarditis. Imunsko pogojeni nefritis: v kliničnih preskušanjih z atezolizumabom so opazili nefritis. Bolnike je treba nadzorovati glede sprememb v delovanju ledvic. Imunsko pogojeni miozitis: V kliničnih preskušanjih z atezolizumabom so opazili primere miozitisa, vključno s smrtnimi primeri. Bolnike je treba nadzorovati glede znakov in simptomov, ki kažejo na miozitis. Z infundiranjem povezane reakcije: pri zdravljenju z atezolizumabom so opažali z infundiranjem povezane reakcije. Pri bolnikih, ki imajo z infundiranjem povezane reakcije 1. ali 2. stopnje, je treba hitrost infundiranja zmanjšati ali zdravljenje prekiniti. Pri bolnikih, ki imajo z infundiranjem povezane reakcije 3. ali 4. stopnje, je treba zdravljenje z atezolizumabom trajno ukiniti. Bolniki, ki imajo z infundiranjem povezane reakcije 1. ali 2. stopnje, lahko še naprej prejemajo atezolizumab pod natančnim nadzorom; v poštev pride premedikacija z antipiretikom in antihistaminikom. Bolniki, ki niso bili vključeni v klinična preskušanja: v klinična preskušanja niso bili vključeni bolniki z naslednjimi stanji: z anamnezo avtoimunske bolezni, anamnezo pnevmonitisa, simptomatskimi možganskimi zasevki, okužbo z virusom HIV, s hepatitisom B ali hepatitisom C, pomembnimi srčno-žilnimi boleznimi ter bolniki z nezadostnim hematološkim delovanjem in delovanjem končnih organov. Prav tako v klinična preskušanja niso bili vključeni bolniki, ki so bili v obdobju 28 dni pred vključitvijo v študijo cepljeni z živim oslabljenim cepivom, ki so v obdobju 4 tednov pred vključitvijo v študijo dobili sistemska imunostimulacijska sredstva ali v obdobju 2 tednov sistemska imunosupresivna zdravila ali so v obdobju 2 tednov pred začetkom študijskega zdravljenja prejemali zdravljenje s peroralnimi ali intravenskimi antibiotiki. Kartica za bolnika: Vsi zdravniki, ki predpisujejo zdravilo Tecentriq, morajo biti dobro seznanjeni z Informacijami za zdravnika in Smernicami za vodenje bolnikov. Zdravnik, ki predpiše zdravilo, se mora z bolnikom pogovoriti o tveganjih zdravljenja z zdravilom Tecentriq. Bolniku je treba dati kartico za bolnika in mu naročiti, naj jo ima vedno pri sebi. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Formalnih študij farmakokinetičnega medsebojnega delovanja zdravil z atezolizumabom niso izvedli. Ker se atezolizumab odstrani iz obtoka s katabolizmom, ni pričakovati presnovnih medsebojnih delovanj med zdravili. Uporabi sistemskih kortikosteroidov ali imunosupresivov se je pred uvedbo atezolizumaba treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost atezolizumaba. Vendar pa se sistemske kortikosteroide ali druge imunosupresivne lahko uporabi po začetku zdravljenja z atezolizumabom za zdravljenje imunsko pogojenih neželenih učinkov. **Neželeni učinki:** povzetek neželenih učinkov, ki so se v kliničnih preskušanjih pojavili bolnikom, zdravljenim z atezolizumabom. *Zelo pogosti:* okužba sečil, okužba pljuč, anemija, trombocitopenija, nevtropenija, levkopenija, hipotiroidizem, zmanjšan apetit, periferna nevropatija, glavobol, hipertenzija, kašelj, dispneja, navzea, bruhanje, diareja, zaprtost, izpuščaj, srbenje, alopecija, artralgija, bolečina v hrbtu, mišično-skeletna bolečina, zvišana telesna temperatura, utrujenost, astenija in periferni edem. *Pogosti:* sepsa, zvišanje alkalne fosfataze v krvi, zvišanje kreatinina v krvi, trombocitopenija, limfopenija, z infundiranjem povezane reakcije, hipertiroidizem, hipotiroidizem, hipokaliemija, hiponatriemija, hiperglikemija, hipomagneziemija, sinkopa, omotica, hipotenzija, pnevmonitis, hipoksija, zamašenost nosu, nazofaringitis, disfonija, bolečine v trebuhu, kolitis, disfagija, orofaringealna bolečina, stomatitis, disgevzija, zvišanje AST, zvišanje ALT, hepatitis, suha koža, proteinurija, gripi podobna bolezen in mrzlica. Poročanje o domnevnih neželenih učinkih: Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na: Javna agencija Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel.: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. Za zagotavljanje sledljivosti zdravila je pomembno, da pri izpolnjevanju obrazca o domnevnih neželenih učinkih zdravila navedete številko serije biološkega zdravila. **Režim izdaje zdravila:** H **Imetnik dovoljenja za promet:** Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Nemčija. Verzija: 6.0/20

DODATNE INFORMACIJE SO NA VOLJO PRI: Roche farmacevtska družba d.o.o., Stegne 13G, 1000 Ljubljana

Samo za strokovno javnost.

M-SI-00000182 (v1.0) Datum priprave informacije: december 2020

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Imunoterapija hlangiokarcinomov

Prof.dr. Janja Ocvirk, dr.med.

Ljubljana, 15.12.2020

Zdi se, da je holangiokarcinom povezan z imunskim sistemom, karcinogeneza pa s kroničnimi parazitskimi okužbami in avtoimunskimi stanji, kot je primarni sklerozirajoči holangitis[1-2]

Imunski regulatorni protein PD-1 je v intrahepatičnem tkivu holangiokarcinoma je bolj izražen v primerjavi s sosednjim tkivom[3]

Bolniki z CD45RO + infiltrirajočimi se imunskimi celicami in zunajhepatičnem holangiokarcinomu so imeli daljše preživetje brez ponovitve bolezni in celotno preživetje kot ostali holangiokarcinomi[4]

Klinična učinkovitost je bila dokazana s pembrolizumabom pri refraktornih BTC kot del raziskave KEYNOTE -28[5]

1. Sripa B el al. *PLoS Med* 2007 **2**. Tyson GL *Hepatology* 2011 3. Ye Y et al. *Journal of Surgical Oncology* 2009. 4. R.Kim et al. *Oncotarget (in press)* 2018 5. Bang et al ESMO 2015, Abstract 525

Pembrolizumab (MK-3475, anti-PD-1) in Cholangiocarcinoma: KEYNOTE-028

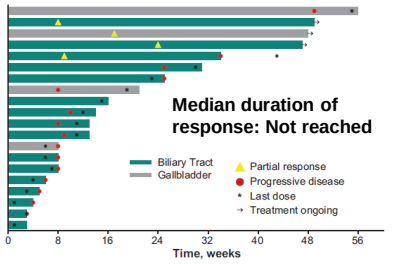
Screened 87 patients:

- 41% tumor PD-L1+
- Enrolled 24

Outcomes:

- Partial response 17%
- Stable disease 17%
- Treatment-related grade 3 AE: 17%

Figure 4. Duration of exposure to pembrolizumab and summary of best overall response assessed per RECIST v1.1 by investigator review in patients who had ≥1 postbaseline tumor assessment (n = 20).



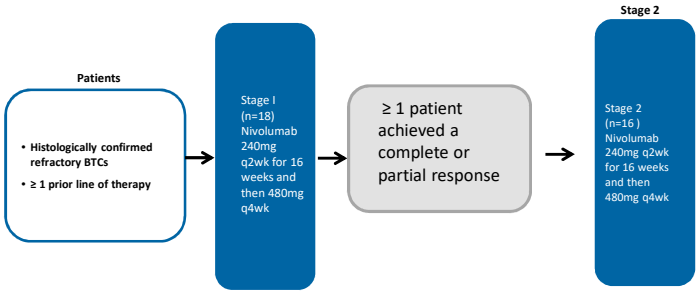
Bang et al ESMO 2015, Abstract 525

JAMA Oncology | Original Investigation

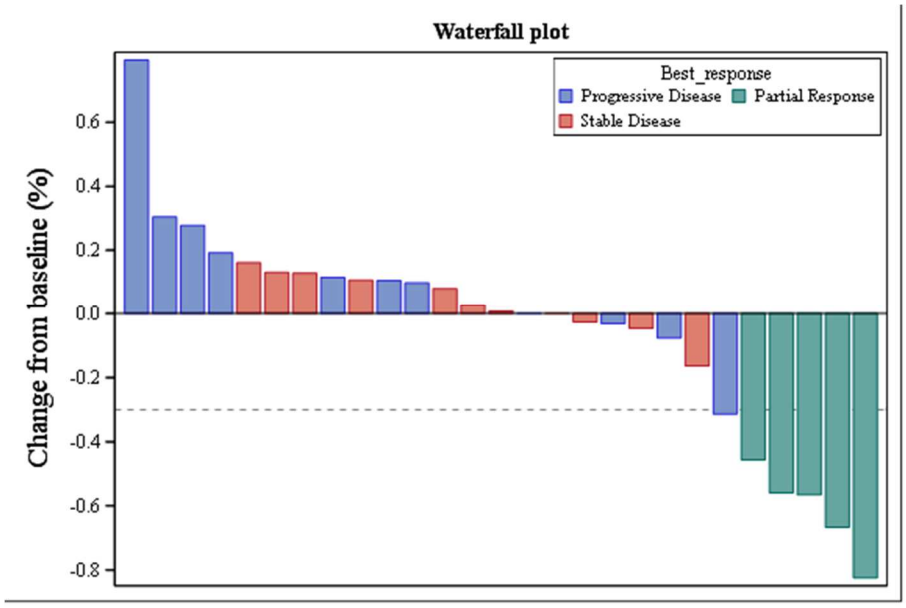
A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer

Richard D. Kim, MD; Vincent Chung, MD; Olatunji B. Alese, MD; Bassell F. El-Rayes, MD; Daneng Li, MD; Taymeyah E. Al-Toubah, BS; Michael J. Schell, PhD; Jun-Min Zhou, BS; Amit Mahipal, MD; Baek Hui Kim, MD; Dae Won Kim, MD

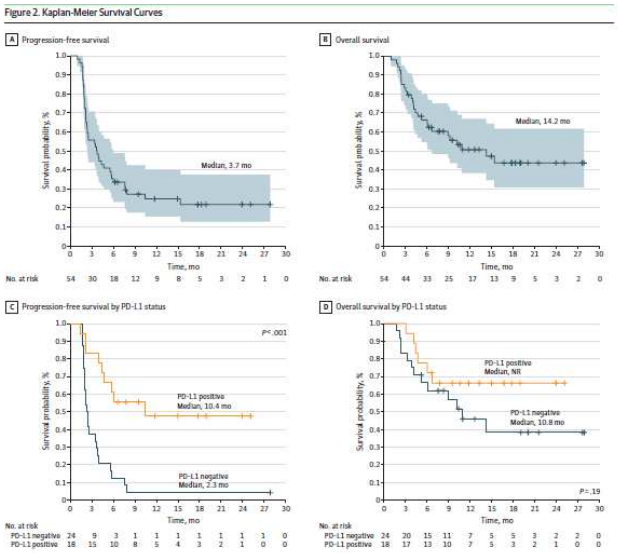
34 patients were treated



Primary endpoint: ORR per investigator assessment
Secondary endpoint: PFS, OS and safety and tolerability
Other endpoints: biomarkers



JAMA Oncol. 2020;6(6):888-894. doi:10.1001/jamaoncol.2020.0930



JAMA Oncol. 2020;6(6):888-894. doi:10.1001/jamaoncol.2020.0930

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW ARTICLE

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

F. Mosele[1], J. Remon[2], J. Mateo[3], C. B. Westphalen[4], F. Barlesi[1], M. P. Lolkema[5], N. Normanno[6], A. Scarpa[7], M. Robson[8], F. Meric-Bernstam[9], N. Wagle[10], A. Stenzinger[11], J. Bonastre[12,13], A. Bayle[1,12,13], S. Michiels[12,13], I. Bièche[14], E. Rouleau[15], S. Jezdic[16], J-Y. Douillard[16], J. S. Reis-Filho[17], R. Dienstmann[18] & F. André[1,19,20*]

[1]Department of Medical Oncology, Gustave Roussy, Villejuif, France; [2]Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Delfos, HM Hospitales, Barcelona; [3]Clinical Research Program, Vall Hebron Institute of Oncology (VHIO) and Vall d'Hebron University Hospital, Barcelona, Spain; [4]Comprehensive Cancer Center Munich and Department of Medicine III, University Hospital, LMU Munich, Munich, Germany; [5]Department of Medical Oncology, Erasmus MC Cancer Center, Rotterdam, the Netherlands; [6]Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori, 'Fondazione G. Pascale' — IRCCS, Naples; [7]ARC-Net Research Centre and Department of Diagnostics and Public Health — Section of Pathology, University of Verona, Verona, Italy; [8]Breast Medicine and Clinical Genetics Services, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York; [9]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston; [10]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [11]Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; [12]Department of Biostatistics and Epidemiology, Gustave Roussy, University Paris-Saclay, Villejuif; [13]Oncostat U1018, Inserm, University Paris-Saclay, labeled Ligue Contre le Cancer, Villejuif; [14]Department of Genetics, Institut Curie, Paris Descartes University, Paris; [15]Cancer Genetic Laboratories, Department of Medical Biology and Pathology, Gustave Roussy Cancer Campus, Villejuif, France; [16]Scientific and Medical Division, European Society for Medical Oncology, Lugano, Switzerland; [17]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA; [18]Oncology Data Science Group, Molecular Prescreening Program, Vall dHebron Institute of Oncology, Barcelona, Spain; [19]Inserm, Gustave Roussy Cancer Campus, UMR981, Villejuif; [20]Paris Saclay University, Orsay, France

ESMO recommendations

Next-generation sequencing (NGS) allows sequencing of a high number of nucleotides in a short time frame at an affordable cost. While this technology has been widely implemented, there are no recommendations from scientific societies about its use in oncology practice. The European Society for Medical Oncology (ESMO) is proposing three levels of recommendations for the use of NGS. **Based on the current evidence, ESMO recommends routine use of NGS on tumour samples in advanced** non-squamous non-small-cell lung cancer (NSCLC), prostate cancers, ovarian cancers and c**holangiocarcinoma.** In these tumours, large multigene panels could be used if they add acceptable extra cost compared with small panels. In colon cancers, NGS could be an alternative to PCR. In addition, based on the KN158 trial and considering that patients with endometrial and small-cell lung cancers should have broad access to anti-programmed cell death 1 (anti-PD1) antibodies, it is recommended to test tumour mutational burden (TMB) in cervical cancers, well- and moderately-differentiated neuroendocrine tumours, salivary cancers, thyroid cancers and vulvar cancers, as TMB-high predicted response to pembrolizumab in these cancers.

Table 10. List of genomic alterations level I/II/III according to ESCAT in advanced cholangiocarcinoma (CC)

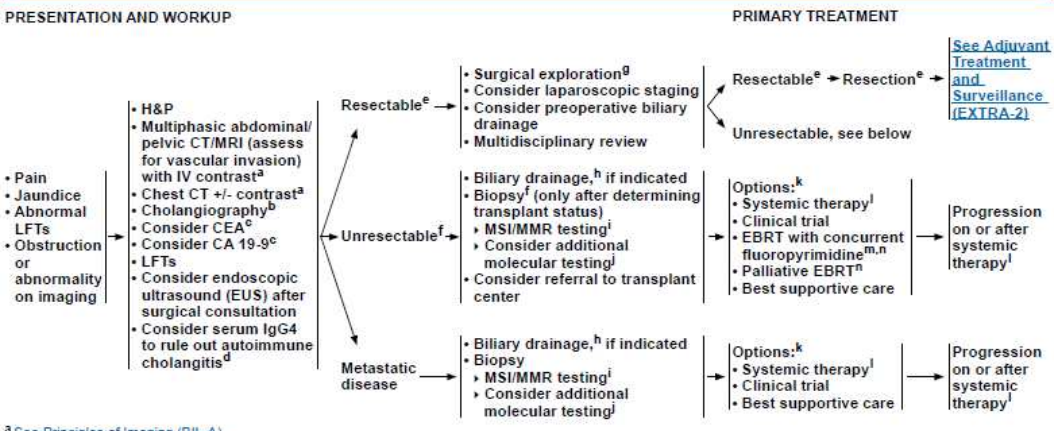
Gene	Alteration	Prevalence	ESCAT	References
IDH1	Mutations	20%	IA	Abou-Alfa G. K, et al. *Ann Oncol.* 2019[129]
FGFR2	Fusions	15%	IB	Vogel A, et al. *Ann Oncol.* 2019[130]
	MSI-H	2%	IC	Marabelle A, et al. *J Clin Oncol.* 2020[131]
NTRK	Fusions	2%	IC	Doebele RC, et al. *Lancet Oncol.* 2020[50]
BRAF^{V600E}	Mutations	5%	IIB	Wainberg Z, et al. *J Clin Oncol.* 2019[132]
ERBB2	Amplifications Mutations	10% 2%	IIIA	Javle MM, et al. *J Clin Oncol.* 2017[133]
PIK3CA	Hotspot mutations	7%	IIIA	André F, et al. *N Engl J Med.* 2019[72]
BRCA 1/2	Mutations	3%	IIIA	De Bono J, et al. *N Engl J Med.* 2020[93]
MET	Amplifications	2%	IIIA	Camidge D, et al. *J Clin Oncol.* 2018[52]

ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets.

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2020
Biliary Tract Cancers: Extrahepatic Cholangiocarcinoma

NCCN Guidelines Index
Table of Contents
Discussion



[a] See Principles of Imaging (BIL-A).

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2020
Biliary Tract Cancers

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Gemcitabine + cisplatin[4] (category 1)	• 5-fluorouracil + oxaliplatin • 5-fluorouracil + cisplatin • Capecitabine + cisplatin • Capecitabine + oxaliplatin • Gemcitabine + albumin-bound paclitaxel (cholangiocarcinoma only) • Gemcitabine + capecitabine • Gemcitabine + oxaliplatin • Gemcitabine + cisplatin + albumin-bound paclitaxel[1] (category 2B) • Single agents: › 5-fluorouracil › Capecitabine › Gemcitabine	• For *NTRK* gene fusion-positive tumors: › Entrectinib[5–7] › Larotrectinib[8] • For MSI-H/dMMR tumors: › Pembrolizumab[d,e,9]

Subsequent-line Therapy for Biliary Tract Cancers if Disease Progression

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances[f]
• FOLFOX[10]	• FOLFIRI[11] (category 2B) • Regorafenib[12] (category 2B) • See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above[f]	• For *NTRK* gene fusion-positive tumors: › Entrectinib[5–7] › Larotrectinib[8] • For MSI-H/dMMR tumors: › Pembrolizumab[d,e,9] • For cholangiocarcinoma with *FGFR2* fusions or rearrangements: › Pemigatinib[13] • For cholangiocarcinoma with *IDH1* mutations › Ivosidenib[14]

Zaključki – sistemsko zdarvljenje

- **Neo- adjuvantno zdarvljenej (samo karcinom žolčnika):**
fluoropirimidini, gemcitabin ali kombo z platina derivati
- **Adjuvantno zdarvljenje:**
- Kapecitabin monoterapija
- Vloga radioterapije v kombinaciji s sistemskim zdarvljenjem potrebuje zaključke prospektivnih randomiziranih kliničnih raziskav faze IIIs
- **Metastatska bolezen:**
- 1st linija: gemcitabin + cisplatin (PS ECOG 0-1), gemcitabin mono (PS ECOG 2)
- 2nd liniaj: folfox, (tarčna terapija: regorafenib)
-**Imunoterapija (nivolumab, pembrolizuamb): MSI- H**
-**Entrectinib, larotrectinib pri z NTRK fuzijon pozitivnih tumorjih**

A Global Phase III Study of Durvalumab or Placebo in Combination With Gemcitabine/Cisplatin in Patients With 1st Line Advanced Biliary Tract Cancer

Pembrolizumab (MK-3475) Plus Gemcitabine/Cisplatin Versus Placebo Plus Gemcitabine/Cisplatin for First-Line Advanced and/or Unresectable Biliary Tract Carcinoma (BTC) (MK-3475-966/ KEYNOTE-966)

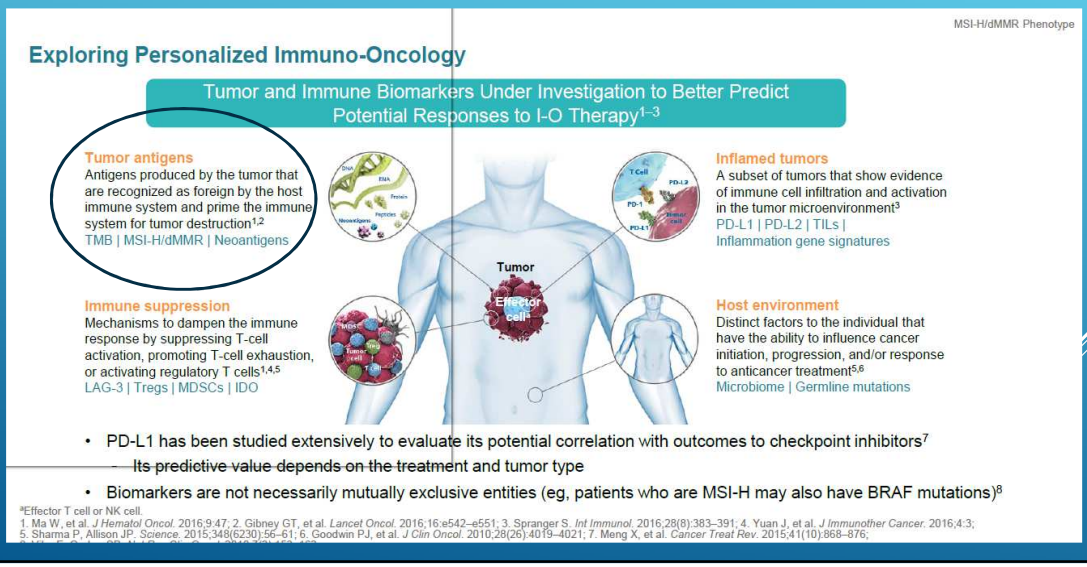
IMUNOTERAPIJA V ZDRAVLJENJU RDČD - 2020

Doc.dr.Tanja Mesti, dr.med.

Novosti v Imuno-onkologiji 2020

15 December 2020

BIOMARKERJI



BIOMARKERJI

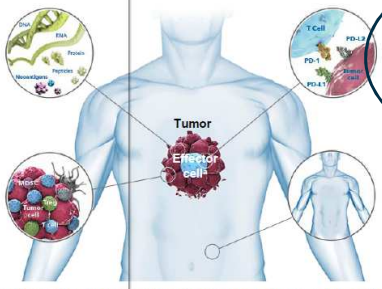
MSI-H/dMMR Phenotype

Exploring Personalized Immuno-Oncology

Tumor and Immune Biomarkers Under Investigation to Better Predict Potential Responses to I-O Therapy[1–3]

Tumor antigens
Antigens produced by the tumor that are recognized as foreign by the host immune system and prime the immune system for tumor destruction[1,2]
TMB | MSI-H/dMMR | Neoantigens

Inflamed tumors
A subset of tumors that show evidence of immune cell infiltration and activation in the tumor microenvironment[3]
PD-L1 | PD-L2 | TILs | Inflammation gene signatures



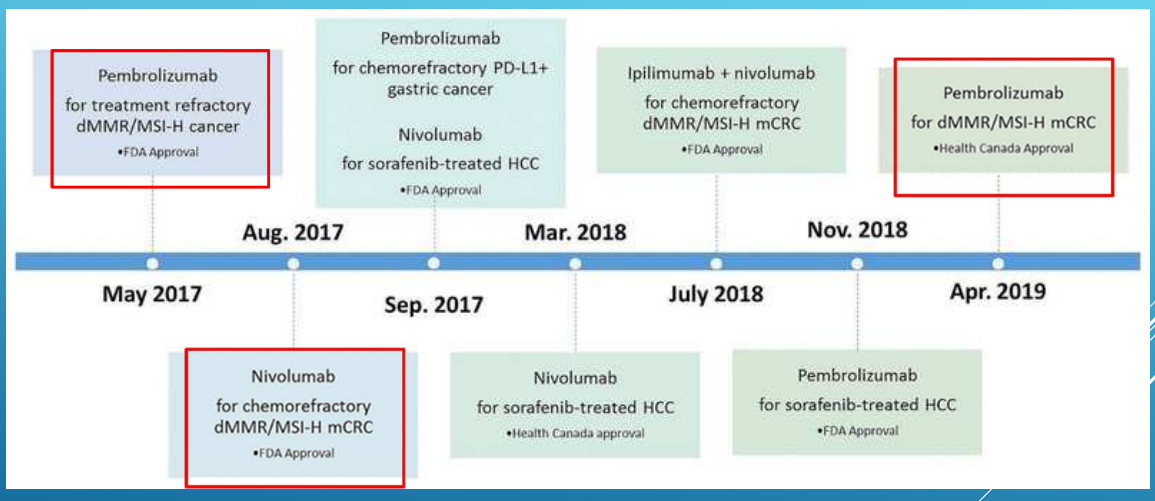
Immune suppression
Mechanisms to dampen the immune response by suppressing T-cell activation, promoting T-cell exhaustion, or activating regulatory T cells[1,4,5]
LAG-3 | Tregs | MDSCs | IDO

Host environment
Distinct factors to the individual that have the ability to influence cancer initiation, progression, and/or response to anticancer treatment[5,6]
Microbiome | Germline mutations

- PD-L1 has been studied extensively to evaluate its potential correlation with outcomes to checkpoint inhibitors[7]
  - Its predictive value depends on the treatment and tumor type
- Biomarkers are not necessarily mutually exclusive entities (eg, patients who are MSI-H may also have BRAF mutations)[8]

[a]Effector T cell or NK cell.

1. Ma W, et al. *J Hematol Oncol.* 2016;9:47; 2. Gibney GT, et al. *Lancet Oncol.* 2016;16:e542–e551; 3. Spranger S. *Int Immunol.* 2016;28(8):383–391; 4. Yuan J, et al. *J Immunother Cancer.* 2016;4:3; 5. Sharma P, Allison JP. *Science.* 2015;348(6230):56–61; 6. Goodwin PJ, et al. *J Clin Oncol.* 2010;28(26):4019–4021; 7. Meng X, et al. *Cancer Treat Rev.* 2015;41(10):868–876;



U.S. Food and Drug Administration (FDA) and Health Canada approvals for checkpoint inhibitors in gastrointestinal cancers up to 30 June 2019. It should be noted that, in Canada, Health Canada approval does not necessarily imply drug access on a provincial formulary. dMMR/MSI-H = deficient mismatch repair/high microsatellite instability; mCRC = metastatic colorectal cancer; HCC = hepatocellular carcinoma.

Pembrolizumab Versus Chemotherapy for Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer: The Phase 3 KEYNOTE-177 Study

Thierry André,[1] Kai-Keen Shiu,[2] Tae Won Kim,[3] Benny Vittrup Jensen,[4] Lars Henrik Jensen,[5] Cornelis Punt,[6] Denis Smith,[7] Rocio Garcia-Carbonero,[8] Manuel Benavides,[9] Peter Gibbs,[10] Christelle de la Fouchardiere,[11] Fernando Rivera,[12] Elena Elez,[13] Johanna Bendell,[14] Dung T. Le,[15] Takayuki Yoshino,[16] Ping Yang,[17] Mohammed Farooqui,[18] Patricia Marinello,[18] and Luis A. Diaz Jr[19]

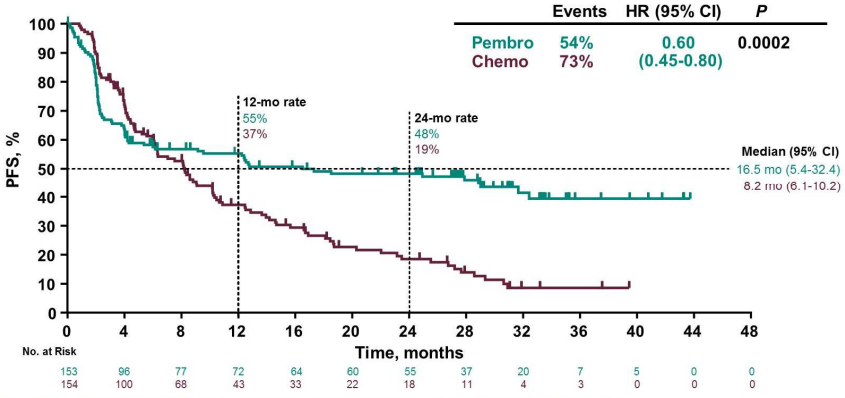
[1]Sorbonne Université and Hôpital Saint Antoine, Paris, France; [2]University College Hospital, NHS Foundation Trust, London, United Kingdom; [3]Asan Medical Center, University of Ulsan, Seoul, Republic of Korea; [4]Herlev and Gentofte Hospital, Herlev, Denmark; [5]University Hospital of Southern Denmark, Vejle, Denmark; [6]Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands; [7]Bordeaux University Hospital, Bordeaux, France; [8]Hospital Universitario 12 de Octubre, Imas12, CNIO, UCM, Madrid, Spain; [9]Hospital Regional Universitario de Malaga, Malaga, Spain; [10]Western Health, St Albans, Australia; [11]Léon Bérard Center, Lyon, France; [12]Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Spain; [13]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [15]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [16]National Cancer Center Hospital East, Kashiwa, Japan; [17]MSD China, Beijing, China; [18]Merck & Co., Inc. Kenilworth, NJ, USA; [19]Memorial Sloan Kettering Cancer Center, New York, NY, USA

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Thierry Andre, MD

ČAS DO PROGRESA

Progression-Free Survival



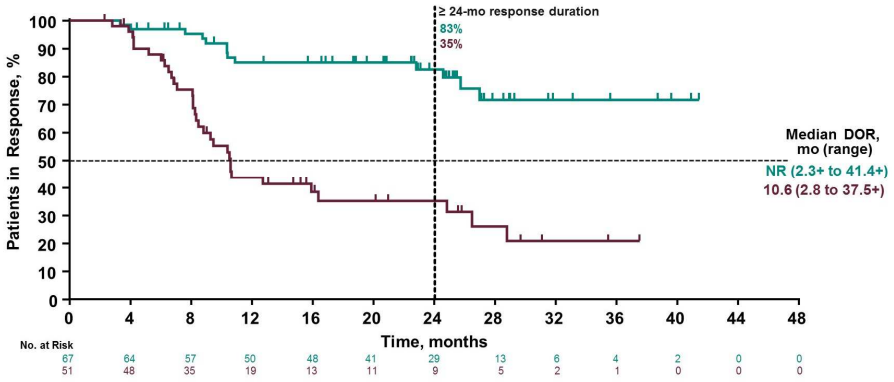
Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Thierry Andre, MD

ODGOVOR

Duration of Response



Duration of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

VARNOSTNI PROFIL

Immune-Mediated AEs and Infusion Reactions

	Pembrolizumab N = 153		Chemotherapy N = 143	
All	31%		13%	
Grade ≥3	9%		2%	
Discontinued	7%		0	
Died	0		0	
Incidence >0%	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Hypothyroidism	12%	0	2%	0
Colitis	7%	3%	0	0
Hyperthyroidism	4%	0	0	0
Pneumonitis	4%	0	1%	0
Adrenal insufficiency	3%	1%	0	0
Hepatitis	3%	3%	0	0
Infusion reactions	2%	0	8%	1%
Hypophysitis	1%	0	0	0
Myocarditis	0	0	1%	0
Myositis	1%	0	0	0
Nephritis	1%	0	0	0
Pancreatitis	1%	1%	0	0
Severe skin reactions	1%	1%	1%	1%
Thyroiditis	1%	0	0	0
Type 1 Diabetes Mellitus	1%	1%	0	0

Based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness; Data cutoff: 19Feb2020.

Summary and Conclusions

- Pembrolizumab provided a clinically meaningful and statistically significant improvement in PFS versus chemotherapy in patients with MSI-H mCRC
  - Median PFS: 16.5 vs 8.2 months
  - HR 0.60, 95% CI 0.45-0.80; *P* = 0.0002
  - 24-month PFS rates: 48.3% vs 18.6%
- Responses were more durable with pembrolizumab versus chemotherapy
  - Overall response rate: 43.8% vs 33.1% (*P* = 0.0275)
  - Median duration of response: not reached vs 10.6 months
- Improved safety profile with pembrolizumab versus chemotherapy
  - Lower incidence of grade ≥3 treatment-related events (22% vs 66%)
- Pembrolizumab should be new standard-of-care as first-line therapy in patients with MSI-H mCRC

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

Background: Pembro monotherapy significantly improved PFS vs standard of care (SOC) chemotherapy as first-line treatment in pts with MSI-H or dMMR mCRC in the phase III KEYNOTE-177 (NCT02563002) study. HRQoL results are reported.

Methods: Pts with confirmed MSI-H/dMMR mCRC with no prior systemic therapy for mCRC were randomized 1:1 to pembro 200 mg Q3W for up to 2 y or investigator's SOC choice of mFOLFOX6 or FOLFIRI Q2W ± bevacizumab or cetuximab. EORTC QLQ-C30, EORTC QLQ-CR29, and EQ-5D-3L were administered at baseline and at various time points up to 1 y or end of treatment, whichever came first, and at 30 days after treatment discontinuation. Data from pts receiving ≥1 dose of study treatment and completing ≥1 HRQoL assessment were analyzed. Least-squares mean (LSM) score change from baseline to prespecified wk 18, 95% CI, and nominal 2-sided *P* values were calculated. Time to deterioration (TTD; ≥10-point decline from baseline) was assessed by Kaplan-Meier method and Cox regression model. HRs, 95% CIs, and nominal 1-sided *P* values are provided.

Results: Data for 294 pts (152, pembro; 142 SOC) were available for HRQoL analyses. Compliance at baseline was >90% in pembro and SOC arms for all 3 questionnaires and remained high at wk 18 (>85% and >75%, respectively). LSM change from baseline to wk 18 showed clinically meaningful improvement in QLQ-C30 global health status (GHS)/QoL (LSM difference: 8.96; 95% CI, 4.24-13.69; *P*=0.0002) and EQ-5D VAS (LSM difference: 7.38; 95% CI, 2.82-11.93; *P*=0.0016) for pts receiving pembro vs SOC. Prolonged TTD for pts receiving pembro vs SOC was observed for GHS/QoL (HR, 0.61; 95% CI, 0.38-0.98; *P*=0.0195), physical functioning (HR, 0.50; 95% CI, 0.32-0.81; *P*=0.0016), social functioning (HR, 0.53; 95% CI, 0.32-0.87; *P*=0.0050), and fatigue (HR, 0.48; 95% CI, 0.33-0.69; *P*≤0.0001).

Conclusions: Pembro monotherapy demonstrated clinically meaningful improvements in HRQoL vs SOC chemotherapy in pts with previously untreated MSI-H/dMMR mCRC.

Clinical trial identification: NCT02563002.

3960 **Health-related quality of life (HRQoL) in patients (pts) treated with pembrolizumab (pembro) vs chemotherapy as first-line treatment in microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR) metastatic colorectal cancer (mCRC): Phase III KEYNOTE-177 study**

T. André[1], M. Amonkar[2], J. Norquist[2], K-K. Shiu[3], T.W. Kim[4], B.V. Jensen[5], L.H. Jensen[6], C.J. Punt[7], D. Smith[8], R. Garcia-Carbonero[9], I. Sevilla[10], C. de la Fouchardiere[11], F. Rivera[12], E. Elez[13], L.A. Diaz[14], T. Yoshino[15], E. Van Cutsem[16], P. Yang[2], M.Z.H. Farooqui[2], D. Le[17]

https://doi.org/10.1016/j.annonc.2020.08.507

- NIVOLUMAB
- 2L mono data: CheckMate 142 phase 2 multicohort trial examined nivolumab monotherapy. Patients with MSI-H/dMMR mCRC were enrolled after ≥ one prior therapy line. The dose of nivolumab was 3 mg/kg (Q2W). On July 31, 2017, nivolumab received approval by the US FDA [1-2].

ODGOVOR

Deepening of Response With Longer Follow-Up[1]

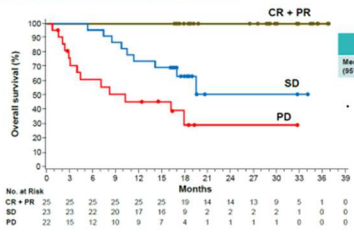
	All patients N = 74[a]	
	13-Month follow-up[b,2]	21-Month follow-up[b]
ORR, n (%) [95% CI]	24 (32) [22.0, 44.3]	25 (34) [23.2, 45.7]
Best overall response, n (%)		
CR	2 (3)	7 (9)
PR	22 (30)	18 (24)
SD	25 (34)	23 (31)
PD	21 (28)	22 (30)
Not determined	4 (5)	4 (5)
Disease control, n (%)[c]	47 (64)	46 (62)

- CR rates increased in all patients with longer follow-up
- Similar trends in CR were observed in groups A and B[d]

[a]ISKDA data. [b]Defined here as the time from first dose to data cutoff. [c]Patients with a CR, PR, or SD for ≥ 12 weeks. [d]Group A patients received ≥ 3 prior chemotherapies, including a fluoropyrimidine, oxaliplatin, and irinotecan. Group B patients did not receive treatment with all 3 of these chemotherapies (fluoropyrimidine, oxaliplatin, and irinotecan).
1. Overman MJ, et al. Oral presentation at ASCO-GI 2018; 2. Overman MJ, et al. *Lancet Oncol* 2017;18:1182–1191.

CELOKUPNO PREŽIVETJE

Overall Survival by Best Overall Response



	CR + PR n = 25	SD n = 23	PD n = 22
Median OS (95%CI), months	NR (NE)	NR (14.3, NE)	10.3 (3.0, NE)

- Best overall response to nivolumab treatment correlated with overall survival

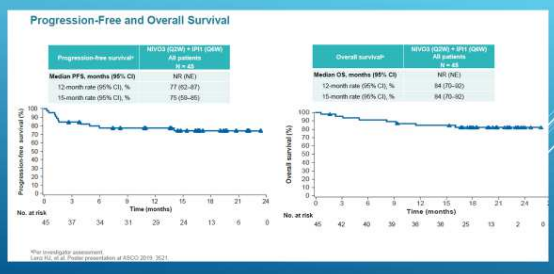
Overman MJ, et al. Oral presentation at ASCO-GI 2018.

1.Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study [published correction appears in Lancet Oncol. 2017 Sep;18(9):e510]. Lancet Oncol. 2017;18(9):1182-1191. [http://dx.doi.org/10.1016/S1470-2045(17)30422-9]; 2. FDA News release. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-nivolumab-accelerated-approval-msi-h-or-dmmr-colorectal-cancer]

- NIVOLUMAB + IPILIMUMAB
- 2L+ combo data: Cohort C2 of the CheckMate 142 trial evaluated nivolumab and ipilimumab (from second line) among MSI-H/dMMR CRC patients. After four initial cycles of nivolumab (3mg/kg) combined with ipilimumab 1mg/kg (Q3W), patients received nivolumab 3mg/kg (Q2W) until progression. On July 10, 2018, nivolumab plus low-dose ipilimumab obtained accelerated approval from the US FDA [3-4].

ČAS DO PROGRESA IN CELOKUPNO PREŽIVETJE

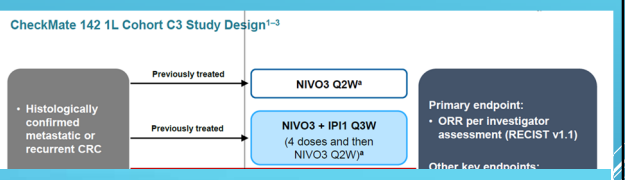
Progression-Free and Overall Survival



	NIVO3 (Q2W) + IPI1 (Q6W) All patients N = 45		NIVO3 (Q2W) + IPI1 (Q6W) All patients N = 45
Median PFS, months (95% CI)	NR (NE)	Median OS, months (95% CI)	NR (NE)
12-month rate (95% CI), %	77 (62–87)	12-month rate (95% CI), %	84 (70–92)
15-month rate (95% CI), %	75 (58–85)	15-month rate (95% CI), %	84 (70–92)

[a]Per investigator assessment.
Lenz HJ, et al. Poster presentation at ASCO 2018. 3521.

CheckMate 142 1L Cohort C3 Study Design[1–3]



ODGOVOR

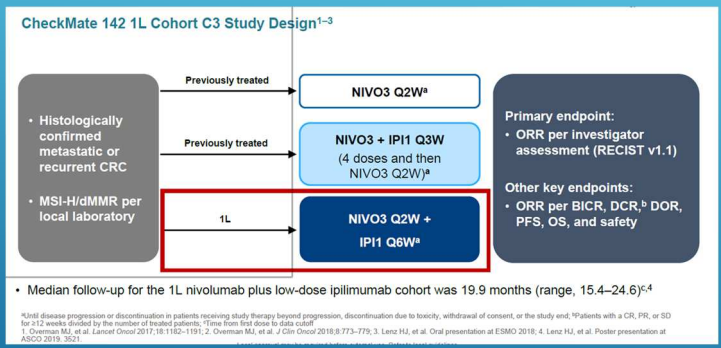
Response, Disease Control, and Durability[a]

	NIVO3 (Q2W) + IPI1 (Q6W) N = 45	
	BICR assessed	Investigator assessed
ORR[1], n (%) [95% CI]	26 (58) [42–72]	29 (64) [49–78]
Best overall response, n (%)[a]		
Complete response	8 (18)	4[c] (9)
Partial response	18 (40)	25 (56)
Stable disease	10 (22)	9 (20)
Progressive disease	7 (16)	6 (13)
Not determined	2 (4)	1 (2)
DCR[1], n (%) [95% CI]	35 (78) [63–89]	38 (84) [71–94]
Median TTR (range), months	1.6 (1.2–16.3)	2.6 (1.2–13.8)
Median DOR (range), months	NR (3.3+ to 20.8+)	NR (1.4+ to 20.8+)

[a]Median follow-up of 19.9 months. [b]Patients with CR or PR divided by the number of treated patients. [c]One patient was incorrectly reported as CR instead of PR. CR was based on surgical pathology and not RECIST v1.1. [d]Patients with a CR, PR, or SD for ≥ 12 weeks divided by the number of treated patients.
Lenz HJ, et al. Poster presentation at ASCO 2018. 3521.

3. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. J Clin Oncol. 2018;36(8):773-779. Doi:10.1200/JCO.2017.76.9901 [http://dx.doi.org/10.1200/JCO.2017.76.9901]; 4. FDA News release. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-ipilimumab-msi-h-or-dmmr-metastatic-colorectal-cancer]

- NIVOLUMAB + IPILIMUMAB
- 1L combo (recently presented) data: Cohort 3 of the CheckMate 142 trial, MSI-H/dMMR CRC patients were enrolled after no prior line of therapy. Dosing was different; patients received nivolumab 3 mg/kg (Q2W) and ipilimumab 1mg/kg (Q6W) until progression. Primary endpoint was ORR (per investigator assessment). At a mFU of 19.9 months, investigator-assessed ORR was 64% (49–78), with a 9% complete response rate. The mTTR was 2.6 months (1.2–13.8). The mDOR was not achieved (from 1.4+ to 20.8+ months). At a mFU of 29 months (presented at ASCO 2020) ORR (investigator-assessed) increased from 60% to 69%, and CR rate increased from 7% to 13% [5-7].



[a]Until disease progression or discontinuation in patients receiving study therapy beyond progression, discontinuation due to toxicity, withdrawal of consent, or the study end; [b]Patients with a CR, PR, or SD for ≥12 weeks divided by the number of treated patients; [c]Time from first dose to data cutoff.
1. Overman MJ, et al. *Lancet Oncol* 2017;18:1182–1191; 2. Overman MJ, et al. *J Clin Oncol* 2018;8:773–779; 3. Lenz HJ, et al. Oral presentation at ESMO 2018; 4. Lenz HJ, et al. Poster presentation at ASCO 2019. 3521.

5.Lenz HJ, van Cutsem E, Limon ML, Wong KY, Hendlisz A, Aglietta M, Garcia-Alfonso P, Neyns B, Luppi G, Cardin D, Dragovich T, Shah U, Atasoy A, Postema R, Boyd Z, Ledeine J, Overman M, Lonardi S. Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/mismatch repair deficient (MSI-H/DMMR) metastatic colorectal cancer (mCRC): Oral presentation at ESMO 2018; Abstract 3298. https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress/Durable-Clinical-Benefit-With-Nivolumab-NIVO-Plus-Low-Dose-Ipilimumab-IPI-as-First-Line-Therapy-in-Microsatellite-Instability-High-Mismatch-Repair-Deficient-MSI-H-dMMR-Metastatic-Colorectal-Cancer-mCRC; 6.Lenz HJ, Lonardi S, Zagonel V, Van Cutsem E, Limon ML, Wong M, Hendlisz A, Aglietta M, Garcia-Alfonso P, Neyns B, Cardin DB, Spallanzani A, Dragovich T, Shah U, Atasoy A, Ledeine JM, Overman M, Lenz HJ, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) as first-line (1L) therapy in microsatellite instability-high/DNA mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Clinical update. Poster presentation at ASCO 2019. 3521. [Available from: https://doi.org/10.1200/JCO.2019.37.15_suppl.3521]; 7.Lenz HJ, Lonardi S, Zagonel V, Van Cutsem E, Limon ML, Wong M, Hendlisz A, Aglietta M, Garcia-Alfonso P, Neyns B, Cardin DB, Spallanzani A, Dragovich T, Shah U, Atasoy A, Ledeine JM, Overman M. Nivolumab + low-dose ipilimumab as first-line therapy in microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 2-year clinical update. ASCO GI 2020 Gastrointestinal Cancers Symposium, Abstract Number 4040 https://meetinglibrary.asco.org/record/182822/abstract

DOUBLET EGFR + PD-L1 INHIBITORS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

3970 **Avelumab plus cetuximab in pre-treated RAS wild type metastatic colorectal cancer patients as a rechallenge strategy: The phase II CAVE (cetuximab-avelumab) mCRC study**

E. Martinelli[1], G. Martini[1], T. Troiani[1], F. Pietrantonio[2], A. Avallone[3], N. Normanno[4], A. Nappi[3], E. Maiello[5], A. Falcone[6], G. Santabarbara[7], C. Pinto[8], D. Santini[9], D. Ciardiello[1], M. Terminiello[1], C. Borrelli[1], S. Napolitano[1], D. Renato[1], V. Famiglietti[1], L. Esposito[1], F. Ciardiello[1]

Background: Rechallenge strategies with anti-epidermal growth factor receptor (EGFR) drugs have been evaluated in patients (pts) with refractory RAS/BRAF wild type (WT) mCRC after response to anti-EGFR based 1st line therapy. Given the role of cetuximab in enhancing antibody-dependent cellular cytotoxicity (ADCC) and promoting expression of MHC class II molecules on dendritic cells, its association with anti-PD-L1 avelumab may be a relevant rechallenge strategy in RAS WT mCRC.

Methods: CAVE mCRC, a single arm multi-centre phase II study, aims to evaluate the efficacy of avelumab and cetuximab in RAS WT mCRC pts treated in first line with chemotherapy (CT) in combination with anti-EGFR drugs and who achieved a complete (CR) or partial response (PR). Primary endpoint is median overall survival (mOS), secondary endpoints are overall response rate (ORR) according to RECIST 1.1, progression free survival (PFS) and safety profile. This study seeks to demonstrate a mOS of 11 months (mo) for the experimental combination in comparison with historical mOS of 8.0 mo with standard third line treatments, which corresponds to an improvement in mOS of 37,5 %.

Results: From August 10, 2018 to February 21, 2020, 77 pts have been enrolled and started treatment with avelumab 10 mg/kg q14 and cetuximab at 400 mg/m^2 and subsequently 250 mg/m^2 weekly until progression of disease (PD) or unacceptable toxicity. Kaplan-Meier curves estimated for the whole intention-to-treat (ITT) population (77 pts): mOS was 13.1 mo (95% Confidence Interval CI, 7.4-18.8 mo; 32 events); mPFS, 3.6 mo (95% CI, 3.3-3.9 mo; 62 events). Among 65 pts evaluable for response, 1 pt (1.5%) experienced CR, 3 pts (4.6%) PR, 32 pts stable disease (SD) (49.2%); 29 pts PD (44.6%). Pts with PFS≥ 6 mo were 12/65 (18.5%). Grade-3 adverse events were reported in 16/77 pts (22%), the most common being skin rash 10/77 (13%) and diarrhoea 3/77 (4%).

Conclusions: At this preliminary analysis, avelumab plus cetuximab as a rechallenge strategy is effective and well tolerated in chemorefractory RAS/BRAF WT mCRC pts. The final analysis for OS will be presented at the ESMO 2020 congress.

Clinical trial identification: EudraCT 2017-004392-32.

https://doi.org/10.1016/j.annonc.2020.08.509

TRIPLET EGFR + PD-L1 INHIBITORS + CHEMOTH

ASCO20 Virtual EDUCATION PROGRAM

Avelumab and cetuximab in combination with FOLFOX in patients with previously untreated metastatic colorectal cancer (MCRC): Final results of the phase II AVETUX trial (AIO-KRK-0216).

Alexander Stein, Mascha Binder, Eray Goekkurt **et al.**

- ITT included 39 pts.
- ORR was 79.5%, including 6 complete (CR) and 25 partial responses (PR). Further 5 stable diseases were noted, thus disease control rate was 92.3%; 2 pts had progression and 1 was not evaluable. Early tumor shrinkage (ETS) rate (≥20% after 8 weeks) was 79.5% (1 CR, 27 PR and 3 SD with ≥20% - < 30%). In MSI-H pts 1 PR and 1 SD and in the 3 low RAS mut pts 2 PR were noted. Panel sequencing was feasible with 153 mutations detected, showing an immediate ctDNA drop within 4 weeks of treatment, mirroring the high rate of early tumor response. Notably, the 4 pts with fever had a high T cell infiltration in the tumor. Final data including the primary endpoint and translational data will be presented at the meeting.
- **Conclusions:** The AVETUX regimen was feasible producing a high rate of responses in MSS pts mainly occurring within the first 8 weeks. The noted ORR/ETS of 79.5% warrants further evaluation in a randomized trial.
- Clinical trial information: NCT03174405.

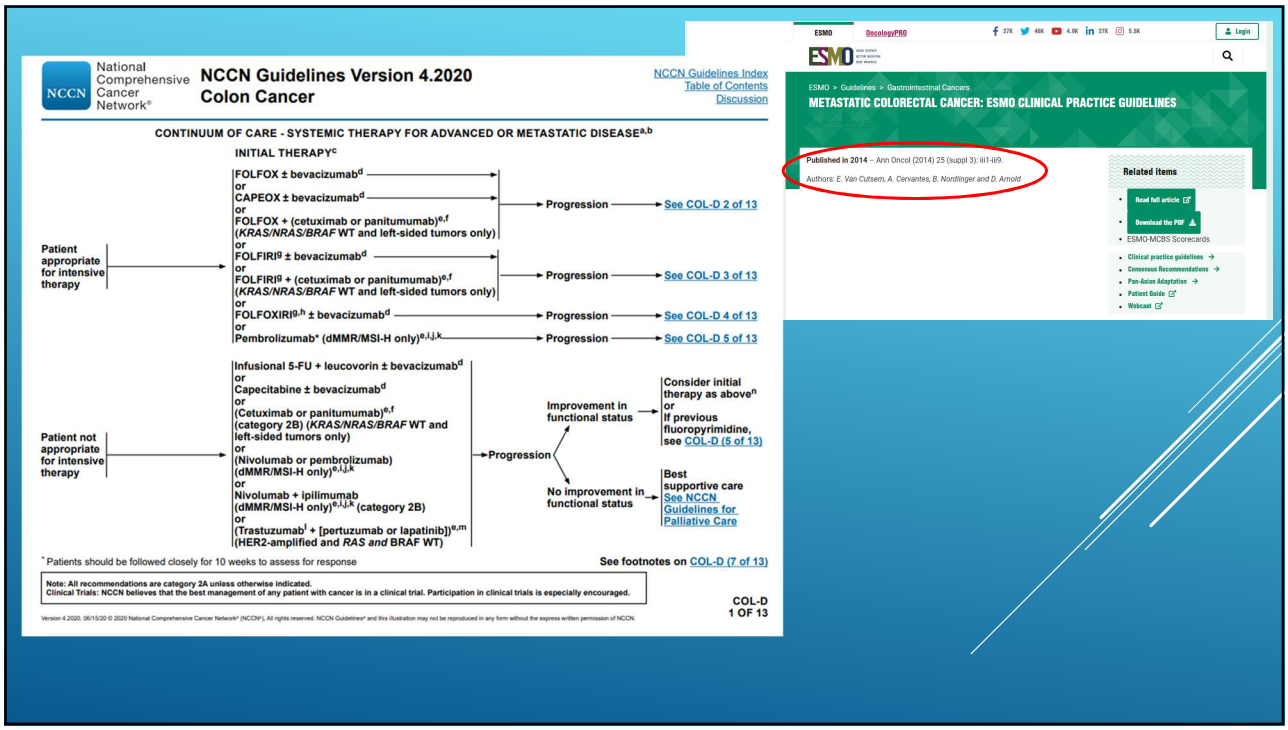
https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.96

DOUBLET TKI + PD-L1 INHIBITORS
REGOMUNE: A PHASE 2 STUDY COMBINING REGORAFENIB AND AVELUMAB

ASCO20 Virtual EDUCATION PROGRAM

- REGOMUNE phase 1/2 study evaluating the efficacy and safety of the combination regorafenib and avelumab
- 48 patients with non-MSI-high mCRC were enrolled. Patients were treated with regorafenib (160 mg once daily, 3 weeks on/1 week off) plus avelumab (10 mg/kg every 2 weeks) until progression of disease. Median follow-up was 7.2 months.
- A total of 12 patients (30%) had a reduction in tumour burden. Best response was stable disease for 23 patients (57.5%) and progressive disease for 17 patients (42.5%).
- Median PFS was 3.6 months, median OS was 10.8 months.
- Increased tumour infiltration by CD8-positive T cells at day 1 of the second treatment cycle was significantly associated with better PFS and OS (P=0.011). Combining low TAM infiltration and low distance between tumour cells and CD8-positive T cells enabled the identification of a subgroup of patients (25%) who are more likely to benefit from the regorafenib plus avelumab combination: median PFS 5.3 months versus 1.9 months (P=0.037); median OS not reached versus 5.3 months (P=0.02).
- Almost all patients (87%) experienced grade ≥3 adverse events. The most common grade ≥3 adverse events were palmar-plantar erythro-dysesthesia syndrome (29.8%), hypertension (23.4%), and diarrhoea (12.8%). No death was related to the treatment.

Cousin S, et al. ASCO Virtual Meeting, 29-31 May 2020, Abstract 4019


National Comprehensive Cancer Network
NCCN Guidelines Version 4.2020
Colon Cancer
NCCN Guidelines Index
Table of Contents
Discussion
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]
INITIAL THERAPY[c]
Patient appropriate for intensive therapy
FOLFOX ± bevacizumab[d]
or
CAPEOX ± bevacizumab[d]
or
FOLFOX + (cetuximab or panitumumab)[e,f] (KRAS/NRAS/BRAF WT and left-sided tumors only)
or
FOLFIRI[g] ± bevacizumab[d]
or
FOLFIRI[g] + (cetuximab or panitumumab)[e,f] (KRAS/NRAS/BRAF WT and left-sided tumors only)
or
FOLFOXIRI[g,h] ± bevacizumab[d]
or
Pembrolizumab* (dMMR/MSI-H only)[e,i,j,k]
Progression
See COL-D 2 of 13
See COL-D 3 of 13
See COL-D 4 of 13
See COL-D 5 of 13
Patient not appropriate for intensive therapy
Infusional 5-FU + leucovorin ± bevacizumab[d]
or
Capecitabine ± bevacizumab[d]
or
(Cetuximab or panitumumab)[e,f] (category 2B) (KRAS/NRAS/BRAF WT and left-sided tumors only)
or
(Nivolumab or pembrolizumab) (dMMR/MSI-H only)[e,i,j,k]
or
Nivolumab + ipilimumab (dMMR/MSI-H only)[e,i,j,k] (category 2B)
or
(Trastuzumab[l] + [pertuzumab or lapatinib])[e,m] (HER2-amplified and RAS and BRAF WT)
Progression
Improvement in functional status
Consider initial therapy as above[n]
or
If previous fluoropyrimidine, see COL-D (5 of 13)
No improvement in functional status
Best supportive care
See NCCN Guidelines for Palliative Care
* Patients should be followed closely for 10 weeks to assess for response
See footnotes on COL-D (7 of 13)
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
COL-D
1 OF 13
Version 4.2020, 06/15/20 © 2020 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.
ESMO
OncologyPRO
Login
ESMO > Guidelines > Gastrointestinal Cancers
METASTATIC COLORECTAL CANCER: ESMO CLINICAL PRACTICE GUIDELINES
Published in 2014 – Ann Oncol (2014) 25 (suppl 3): iii1-iii9.
Authors: E. Van Cutsem, A. Cervantes, B. Nordlinger and D. Arnold
Related items
Read full article
Download the PDF
ESMO-MCBS Scorecards
Clinical practice guidelines
Consensus Recommendations
Pan-Asian Adaptation
Patient Guide
Webcast

Neulasta® Onpro INJEKTOR OMOGOČA *BOLJŠI NADZOR* NAD ZDRAVLJENJEM VAŠIH BOLNIKOV...

...saj v 97 % injiciranj zagotavlja uporabo pegfilgrastima v ustreznem časovnem okviru v skladu **z veljavnimi smernicami.**[1,3]

Optimalno učinkovitost granulocitne kolonije spodbujajočih faktorjev (G-CSF) dosežemo z aplikacijo v času med 24 ur in 72 ur po zadnjem odmerku kemoterapije.[2,3]

NEULASTA® 6 mg raztopina za injiciranje (pegfilgrastim) – SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA
Samo za strokovno javnost. Pred predpisovanjem si preberite celoten Povzetek glavnih značilnosti zdravila.
SESTAVA ZDRAVILA: Ena napolnjena injekcijska brizga vsebuje 6 mg pegfilgrastima v 0,6 ml (10 mg/ml) raztopine za injiciranje. **TERAPEVTSKE INDIKACIJE:** Skrajšanje trajanja nevtropenije in zmanjšanje incidence febrilne nevtropenije pri odraslih bolnikih, zdravljenih s citotoksično kemoterapijo za maligne bolezni (z izjemo kronične mieloidne levkemije in mielodisplastičnih sindromov). **ODMERJANJE IN NAČIN UPORABE:** Zdravljenje z zdravilom Neulasta® morajo uvesti in nadzorovati zdravniki, izkušeni v onkologiji in/ali hematologiji. Za vsak cikel kemoterapije priporočajo en 6 mg odmerek (eno napolnjeno injekcijsko brizgo) zdravila Neulasta®, ki je dana vsaj 24 ur po citotoksični kemoterapiji. Varnost in učinkovitost zdravila Neulasta® pri otrocih še nista bili dokazani in priporočil o odmerjanju ni mogoče dati. Pri bolnikih z okvaro ledvic in s končno odpovedjo ledvic odmerka ni treba spreminjati. Zdravilo Neulasta® se injicira subkutano z napolnjeno injekcijsko brizgo za ročno injiciranje, ali z napolnjeno injekcijsko brizgo in injektorjem, ki se pritrdi na telo, za avtomatično injiciranje. Ročno dane injekcije se morajo dati v stegno, trebuh ali zgornji del roke. Injektor je treba napolniti s priloženo napolnjeno injekcijsko brizgo. Injektor je treba namestiti na nepoškodovano, nerazdraženo kožo na zadnji strani nadlakta ali na trebuhu. Približno 27 ur po namestitvi injektorja na bolnikovo kožo, bo injektor v teku približno 45 minut injiciral zdravilo Neulasta®. **KONTRAINDIKACIJE**: Preobčutljivost na učinkovino ali katerokoli pomožno snov. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI**: Sledljivost: Za izboljšanje sledljivosti granulocitne kolonije spodbujajočih faktorjev (G-CSF) je treba v bolnikovi dokumentaciji jasno zabeležiti zaščiteno ime uporabljenega zdravila. Pri bolnikih z *de novo* akutno mieloično levkemijo (AML) omejeni klinični podatki kažejo primerljiv učinek pegfilgrastima in filgrastima na čas do okrevanja po hudi nevtropeniji. Dolgoročni učinki pegfilgrastima pri AML niso ugotovljeni, zato ga je treba pri tej populaciji bolnikov uporabljati previdno. Varnost in učinkovitost pegfilgrastima nista raziskani pri bolnikih z mielodisplastičnim sindromom, s kronično mielogeno levkemijo in s sekundarno AML, zato ga pri takšnih bolnikih ne smete uporabljati. Posebno pozornost je treba nameniti razlikovanju diagnoze blastne transformacije kronične mieloične levkemije od AML. Varnost in učinkovitost uporabe pegfilgrastima pri bolnikih z *de novo* AML, mlajših od 55 let in s citogenetiko t(15;17), nista ugotovljeni. Varnosti in učinkovitosti pegfilgrastima niso raziskovali pri bolnikih, ki prejemajo kemoterapijo v velikih odmerkih. Tega zdravila ne smete uporabljati za zvečevanje odmerka citotoksične kemoterapije preko uveljavljenih shem odmerjanja. Neželene reakcije na pljučih: Bolj ogroženi so lahko bolniki z nedavno anamnezo pljučnih infiltratov ali pljučnice. Pojav pljučnih znakov, kot so kašelj, zvišana telesna temperatura in dispneja v povezavi z radiološkimi znaki pljučnih infiltratov, in poslabšanje pljučne funkcije skupaj z zvečanim številom nevtrofilcev utegnejo biti preliminarni znaki sindroma akutne dihalne stiske (ARDS -'*Acute Respiratory Distress Syndrome*'). V takih primerih je treba pegfilgrastim po presoji zdravnika prenehati dajati in poskrbeti za ustrezno zdravljenje. Glomerulonefritis: Na splošno so primeri glomerulonefritisa minili po zmanjšanju odmerka ali prenehanju uporabe filgrastima ali pegfilgrastima. Priporočljivo je spremljanje laboratorijskih izvidov urina. Sindrom kapilarne prepustnosti: Bolnike, ki se jim pojavijo simptomi sindroma kapilarne prepustnosti, je treba natančno kontrolirati in deležni morajo biti standardnega simptomatskega zdravljenja, ki lahko vključuje potrebo po intenzivni negi. Splenomegalija in ruptura vranice: Skrbno je treba spremljati velikost vranice (s kliničnim pregledom, ultrazvokom). Na diagnozo rupture vranice moramo misliti pri bolnikih, ki poročajo o bolečini v zgornjem levem delu trebuha ali v predelu lopatice. Trombocitopenija in anemija: Zdravljenje s samim pegfilgrastimom ne prepreči trombocitopenije in anemije, ker se hkrati vzdržuje mielosupresivna kemoterapija s polnimi odmerki po predpisani shemi. Priporočajo redno spremljanje števila trombocitov in hematokrita. Posebna previdnost je potrebna med uporabo posameznih kemoterapevtikov ali njihovih kombinacij, za katere je znano, da povzročajo hudo trombocitopenijo. Napaka pri uporabi zdravila kot posledica odpovedi pripomočka: V primeru odpovedi ali nepravilnega delovanja injektorja obstaja tveganje za napako pri uporabi zdravila, zlasti za injiciranje le delnega odmerka ali za izpuščen odmerek pegfilgrastima. V primeru delnega ali izpuščenega odmerka obstaja večje tveganje za učinke, kot so nevtropenija, febrilna nevtropenija in/ali okužbe, kakor bi bilo, če bi bil odmerek pravilno injiciran. Zdravstveni delavec mora poskrbeti, da je bolnik deležen ustreznega usposabljanja o injektorju ter da ve, da se mora v primeru suma na odpoved injektorja ali njegovo nepravilno delovanje nemudoma posvetovati z zdravstvenim delavcem, saj bo morda potreben nadomesten odmerek. Izčrpna navodila za uporabo za zdravstvene delavce in bolnike so navedena v navodilu za uporabo. Bolnik mora dobiti tudi opozorilno kartico za bolnika. Srpastocelična anemija: Pri bolnikih s srpastocelično dispozicijo ali s srpastocelično anemijo je bila uporaba pegfilgrastima povezana s srpastocelično krizo, zato se mora pri teh bolnikih pegfilgrastim predpisovati previdno in spremljati ustrezne klinične parametre in laboratorijski status in biti pozoren na morebitno povezavo tega zdravila z zvečanjem vranice in vazookluzivno krizo. Levkocitoza: Zaradi kliničnih učinkov zdravila Neulasta® in zaradi možnosti levkocitoze je treba med zdravljenjem redno kontrolirati število belih krvnič. Če število levkocitov po pričakovanem najmanjšem številu preseže 50 x 10^9/l, je treba nemudoma prenehati z zdravljenjem s tem zdravilom. Preobčutljivost: Dokončno prenehajte z zdravljenjem s pegfilgrastimom pri bolnikih s klinično signifikantno preobčutljivostjo. Pegfilgrastima ne dajajte bolnikom z anamnezo preobčutljivosti na pegfilgrastim ali filgrastim. V primeru resne alergijske reakcije je treba poskrbeti za ustrezno zdravljenje in pazljivo spremljanje bolnika še nekaj dni. Stevens-Johnsonov sindrom: V povezavi z zdravljenjem s pegfilgrastimom so redko poročali o Stevens-Johnsonovem sindromu (SJS), ki je lahko smrtno nevaren ali smrten. Če se je pri bolniku ob uporabi pegfilgrastima pojavil SJS, se pri tem bolniku nikoli več ne sme ponovno uvesti zdravljenja s pegfilgrastimom. Imunogenost: Kot pri vseh terapevtskih beljakovinah obstaja možnost imunogenosti. Stopnja nastajanja protiteles proti pegfilgrastimu je na splošno nizka. Vezavna protitelesa se pojavijo po pričakovanjih pri vseh bioloških zdravilih, vendar jih doslej niso povezali z nevtralizacijskim delovanjem. Aortitis: Po dajanju G-CSF zdravim osebam in bolnikom z rakom so poročali o aortitisu. Aortitis so v večini primerov diagnosticirali s slikanjem s CT, na splošno pa je minil po ukinitvi G-CSF. Ostala opozorila: Varnosti in učinkovitosti zdravila Neulasta® za mobilizacijo matičnih krvotvornih celic pri bolnikih ali zdravih dajalcih niso primerno ovrednotili. Pokrovček igle pri napolnjeni injekcijski brizgi vsebuje suho naravno gumo (derivat lateksa), ki lahko povzroča alergične reakcije. Za namestitev injektorja je uporabljeno akrilno lepilo. Bolnikom, ki imajo reakcije na akrilna lepila, lahko uporaba tega pripomočka povzroči alergijsko reakcijo. Povečana hemopoetična aktivnost kostnega mozga zaradi zdravljenja z rastnimi dejavniki je bila povezana s prehodnimi pozitivnimi izvidi pri slikanju kosti, kar je treba upoštevati pri interpretaciji izvidov na podlagi slikanja kosti. Zdravilo Neulasta® vsebuje sorbitol. Bolniki z redko prirojeno motnjo intolerance za fruktozo ne smejo dobiti tega zdravila. To zdravilo vsebuje manj kot 1 mmol (23 mg) natrija na 6 mg odmerek, kar v bistvu pomeni "brez natrija". **MEDSEBOJNO DELOVANJE ZDRAVIL IN DRUGE OBLIKE INTERAKCIJ**: Zaradi možne občutljivosti hitro se delečih mieloidnih celic za citotoksično kemoterapijo je treba pegfilgrastim dati vsaj 24 ur po aplikaciji citotoksične kemoterapije. Sočasne uporabe zdravila Neulasta® s katerimkoli kemoterapevtskim zdravilom pri bolnikih niso ovrednotili. **NEŽELENI UČINKI:** Zelo pogosti (≥ 1/10): glavobol, navzea, bolečina v kosteh. Pogosti (≥ 1/100 do < 1/10): trombocitopenija, levkocitoza, kontaktni dermatitis, mišično-skeletna bolečina (mialgija, artralgija, bolečina v okončini, bolečina v hrbtu, mišično-skeletna bolečina, bolečina v vratu), bolečina na mestu injiciranja, reakcije na mestu aplikacije, bolečina v prsih, ki ne izvira od srca. Občasni (≥ 1/1.000 do < 1/100): srpastocelična kriza, splenomegalija, ruptura vranice, preobčutljivostne reakcije, anafilaksija, zvišanje sečne kisline, sindrom kapilarne prepustnosti, sindrom akutne dihalne stiske, pljučne neželene reakcije (intersticijska pljučnica, pljučni edem, pljučni infiltrati in pljučna fibroza), hemoptiza, Sweetov sindrom (akutna febrilna dermatoza), kožni vaskulitis, glomerulonefritis, reakcije na mestu injiciranja, zvišanje laktat-dehidrogenaze in alkalne fosfataze, prehodno zvišanje jetrnih funkcijskih testov za ALT ali AST. Redki (≥ 1/10.000 do < 1/1.000): aortitis, pljučna hemoragija, Stevens-Johnsonov sindrom. **NAČIN IN REŽIM PREDPISOVANJA TER IZDAJE ZDRAVILA**: Predpisovanje in izdaja zdravila je le na recept s posebnim režimom: Napolnjena injekcijska brizga – H/Rp, injektor, ki se pritrdi na telo – ZZ. **IMETNIK DOVOLJENJA ZA PROMET:** Amgen Europe B.V., 4817 ZK Breda, Nizozemska. Dodatna pojasnila lahko dobite v lokalni pisarni: Amgen zdravila d.o.o., Šmartinska 140, SI-1000 Ljubljana. **DATUM ZADNJE REVIZIJE BESEDILA:** November 2019. **DATUM PRIPRAVE INFORMACIJE:** December 2020. Podrobni podatki o tem zdravilu so na voljo na spletni strani Evropske agencije za zdravila http://www.ema.europa.eu/. **Literatura: 1.** Metz M. et al. ADMINISTRATION OF PEGFILGRASTIM PROPHYLAXIS VIA PREFILLED SYRINGE (NEULASTA®) OR ON-BODY INJECTOR (OBI). German Cancer Congress 2020: 19 - 22 February, Berlin. Poster number: 458. **2.** Burris, H. A. et al. Pegfilgrastim on the Same Day Versus Next Day of Chemotherapy in Patients With Breast Cancer, Non–Small-Cell Lung Cancer, Ovarian Cancer, and Non-Hodgkin's Lymphoma: Results of Four Multicenter, Double-Blind, Randomized Phase II Studies. J. Oncol. Pract. 6, 133–140 (2010).. **3.** Klastersky, J. et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann. Oncol. 27, v111–v118 (2016).

SI-NEU-1220-00001

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

IMUNOTERAPIJA PRI RAKU ŽELODCA IN POŽIRALNIKA

Novosti v imuno-onkologiji 2020

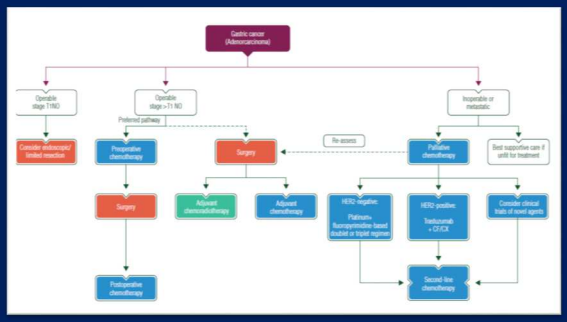
Nežka Hribernik, dr. med.

Ljubljana, 15.12.2020

VSEBINA PREDAVANJA:

- IMUNOTERAPIJA V ESMO SMERNICAH
- MSI/dMMR podskupina tumorjev
- Klinične raziskave z IT v prvem, drugem redu zdravljenja ter pri kemorezistentni obliki
- IT v sklopu radikalnega zdravljenja
- Prediktivni označevalci

ESMO PRIPOROČILA



- Zenkrat še brez omembe IT.
- Ali imamo že dovolj trdnih dokazov za spremembe?

Management of advanced/metastatic disease

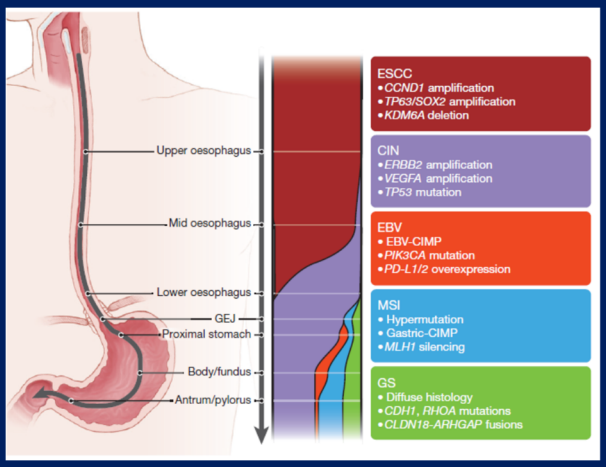
Patients with metastatic oesophageal cancer can be considered for different options of palliative treatment depending on the clinical situation. Single-dose brachytherapy may be a preferred option even after external RT, since it provides better long-term relief of dysphagia with fewer complications than metal stent placement [I, B].

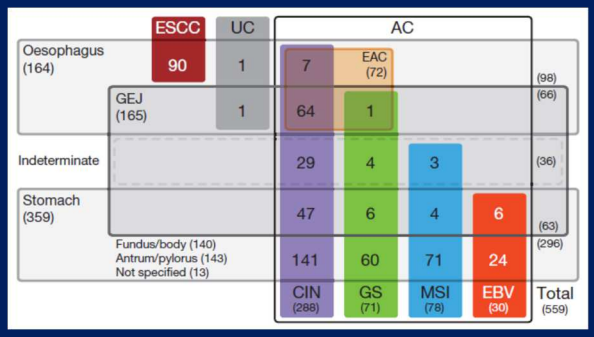
Chemotherapy is indicated for palliative treatment in selected patients, particularly for patients with AC who have a good PS [III, B].

In squamous cell oesophageal cancer, the value of palliative combination chemotherapy is less proved. Therefore, BSC or palliative monotherapy should also be considered [II, B].

ESMO guidelines, Ann Oncol 2016.

MOLEKULARNA KLASIFIKACIJA – PRIHODNOST?

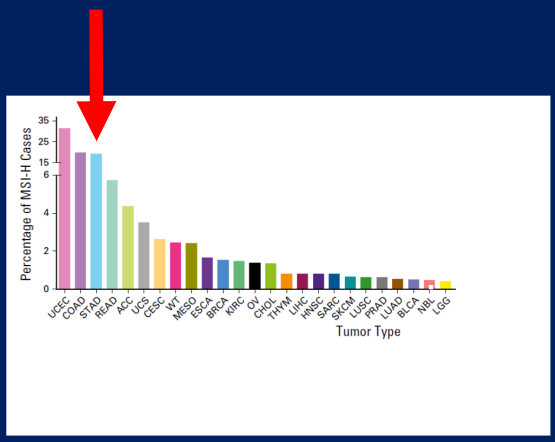




Adenokarcinom in skvamozni karcinom požiralnika sta različni entiteti, v kliničnih raziskavah pa še vedno pogosto skupaj.

CGARN Nature 2017.

MSI/dMMR podskupina



- Adenokarcinom želodca/GEP med pogostejšimi med vsemi raki z MSI/dMMR (poleg endometrijskega raka in RDČD)
- Omejena oblika: 8-22% (dobra prognoza)
- Razsejana oblika: 7% (slaba prognoza ob standardnem citostatskem zdravljenju)
- MSI/dMMR je prediktiven, tumor-agnostičen označevalec učinkovitosti IT.

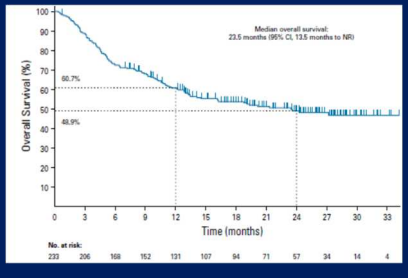
Bonneville R, et al. JCO 2017.

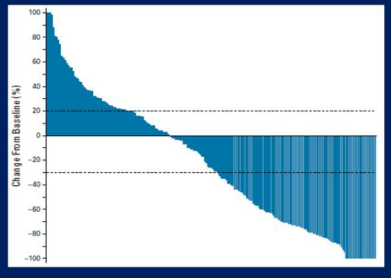
PD-1 ZAVIRALEC PEMBROLIZUMAB PRI MSI/dMMR BOLNIKIH Z RAZSEJANO OBLIKO RAKA

KN-158 (f.2)

- Visok ORR
- Dolgotrajni odgovori
- Dober toksični profil

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)

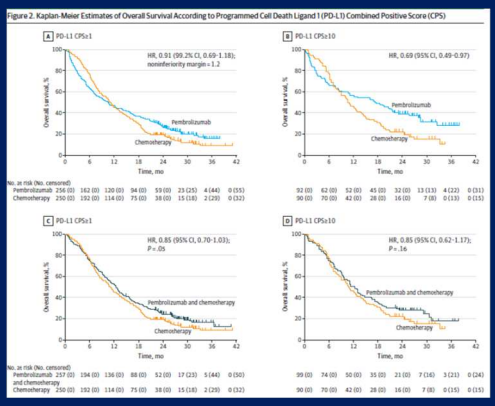




Marabelle A, et al. JCO 2019.

IMUNOTERAPIJA V 1. REDU ZDRAVLJENJA
KN-062 (f.3): PD-1 zaviralec pembrolizumab + KT

- Bolniki z meta/recidivantnim HER2- adenokarcinomom želodca/GEP
- ECOG PS 0 ali 1
- 1. red ST, CPS ≥ 1
- KT vs. KT + pembro vs. pembro
- Azijska in neazijska populacija!

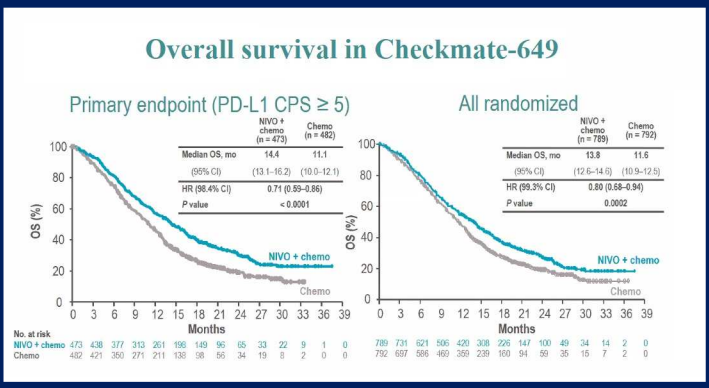


- Pembro + KT NI *superiorno* napram KT
- Pembro NI *superioren* napram KT
- Pembro statistično *non-inferioren* napram KT*
- Vključeni tudi bolniki z MSI

Shitara K, et al. JAMA Oncol 2020.

IMUNOTERAPIJA V 1. REDU ZDRAVLJENJA
CM-649 (f.3): PD-1 zaviralec nivolumab + KT

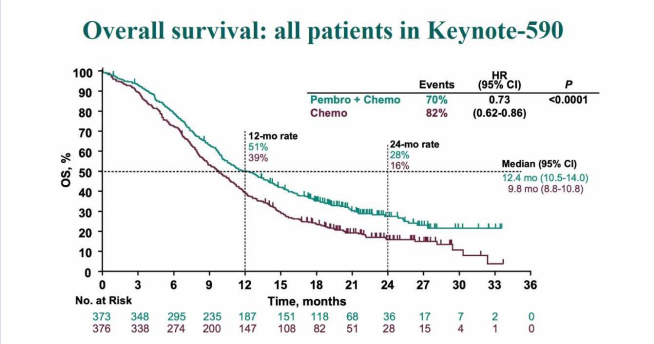
- bolniki z meta/recidivantnim HER2- adenokarcinomom želodca/GEP/požiralnika
- ECOG PS 0 ali 1
- 1. red ST,
- KT + nivo vs. KT
- Večina neazijska populacija!
- 60% CPS ≥ 5



Moehler M, et al. ESMO congress 2020.

IMUNOTERAPIJA V 1. REDU ZDRAVLJENJA
KN-590 (f.3): PD-1 zaviralec pembrolizumab + KT

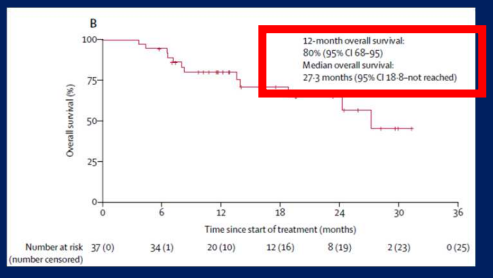
- Bolniki z metastatskim karcinomom požiralnika/GEP (skvamozni in žlezni)
- ECOG PS 0 ali 1
- KT + pembro vs. KT,
- Največja korist pri PD-L1+ /CPS

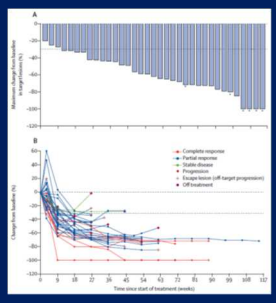


Enzinger PC, et al. ESMO congress 2020.

IMUNOTERAPIJA V 1. REDU ZDRAVLJENJA
ClinicalTrials.gov, NCT02954536 (f.2): PD-1 zaviralec pembrolizumab + trastuzumab + KT

- bolniki z meta/recidivantnim HER2+ adenokarcinomom želodca/GEP
- ECOG PS 0 ali 1





N = 37
RR: 90%

- KN-811 (f.3) v teku

Janjigian Y, et al. Lancet Oncol 2020.

IMUNOTERAPIJA V 2. REDU ZDRAVLJENJA
KN-061 (f.3): PD-1 zaviralec nivolumab napram KT

- Bolniki z razsejanim adenokarcinomom želodca/GEP
- ECOG PS 0 ali 1
- pembro vs. pakli (primerjalna roka brez ramucirumaba)
- CPS ≥ 1 (prvih 489 bolnikov neodvisno glede na CPS)

- Pembro ne izboljša preživetja napram KT v PD-L1 pozitivni skupini.
- Pembro je *inferioren* v PD-L1 negativni skupini.
- Pembro je *superioren* v skupini CPS ≥ 10 in MSI (podanaliza, *underpowered**)

CPS < 1

	Pembrolizumab	Paclitaxel
Events/Pts	87/99	86/96
	HR (95% CI): 1.20 (0.89–1.63)	
Median OS, mo (95% CI)	4.8 (3.9–6.1)	8.2 (6.8–10.6)

MSI-H

	Pembrolizumab	Paclitaxel
	HR 0·42, 95% CI 0·13–1·31	
Median OS, mo (95% CI)	Not reached	8.1 (2-16.7)

CPS ≥ 10

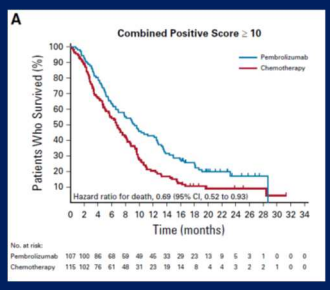
	Pembrolizumab	Paclitaxel
Events/Pts	34/53	46/55
	HR (95% CI): 0.64 (0.41–1.02)	
Median OS, mo (95% CI)	10.4 (5.9–17.3)	8.0 (5.1–9.9)

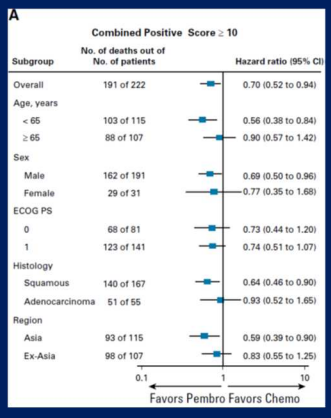
Shitara K, et al. ASCO post 2020.

IMUNOTERAPIJA V 2. REDU ZDRAVLJENJA
KN-181 (f.3): PD-1 zaviralec pembrolizumab napram KT

- Bolniki z razsejanim karcinomom požiralnika (skvamozni in žlezni)
- ECOG PS 0 ali 1
- Pembro vs. KT

<u>CPS ≥ 10</u>
OS 9.3 mo vs 6.7 mo,
HR 0.69 (95% CI 0.51-0.93),
p = 0.0074



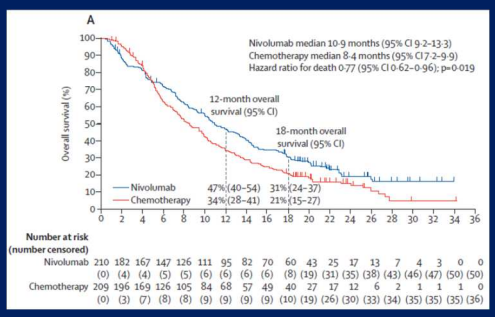


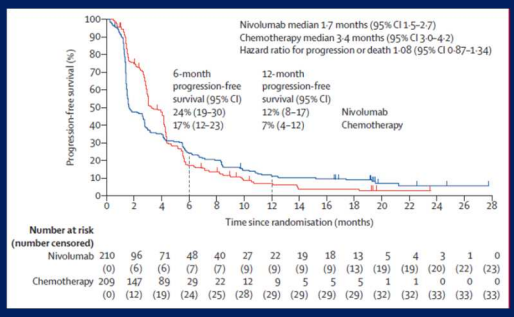
- Samo skvamozni CPS korist od PD-1 zaviralca

Takashi K, et al. JCO 2020.

IMUNOTERAPIJA V 2. REDU ZDRAVLJENJA
ATTRACTION-3 (f.3): PD-1 zaviralec nivolumab napram KT

- Bolniki z razsejanim skvamoznim karcinomom požiralnika
- ECOG PS 0 ali 1; skoraj vsi azijci
- Nivolumab vs. KT (taksani)

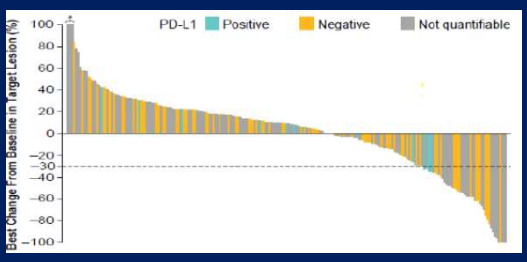


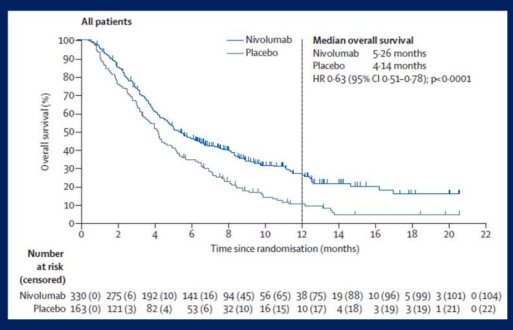


Kojima T et al. Lancet 2019

IMUNOTERAPIJA PRI KEMOREFRAKTARNIH
ATTRACTION-02 (f.3): PD-1 zaviralec nivolumab

- bolniki z metastatskim/recidivantnim adenokarcinomom želodca/GEP, PS 0 ali 1
- po ≥ 2 redih ST
- Nivolumab 3mg/kg /2t napram placebu; Azijska populacija
- ORR = 12%





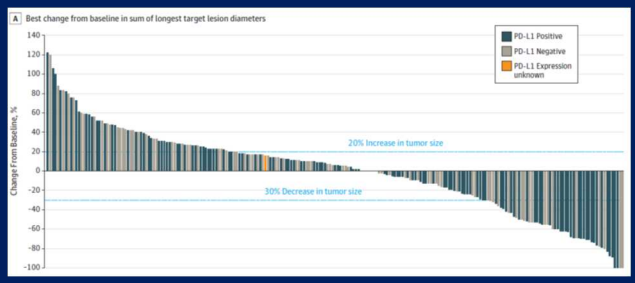
Kang TK, et al. Lancet 2017.

IMUNOTERAPIJA PRI KEMOREFRAKTARNIH
KN-059 (f.2): PD-1 zaviralec pembrolizumab

- bolniki z metastatskim/recidivantnim adenokarcinomom želodca/GEP, PS 0 ali 1
- po ≥ 2 redih KT
- Pembrolizumab 200 mg/3t; do PD ali 24 mesecev ali nesprejemljive toksičnosti

Table 1. Objective Tumor Response

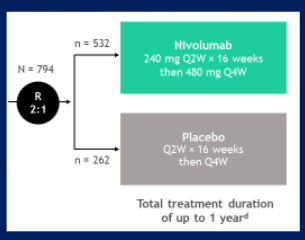
	Participants (n = 259)	
Best Overall Response[a]	No.	% (95% CI)
Objective response (CR+PR)	30	11.6 (8.0-16.1)
Disease control (CR+PR+SD ≥2 mo)	70	27.0 (21.7-32.9)
CR	6	2.3 (0.9-5.0)
PR	24	9.3 (6.0-13.5)
SD	42	16.2 (11.9-21.3)
Progressive disease	145	56.0 (49.7-62.1)
Nonevaluable	7	2.7 (1.1-5.5)
No assessment[b]	35	13.5 (9.6-18.3)
Duration of response, median (range), mo	8.4 (1.6+ to 17.3+)[c]	

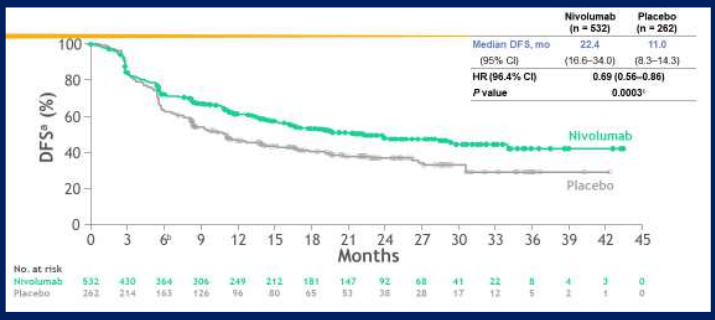


Fuchs CS, et al. JAMA Oncology 2018.

IMUNOTERAPIJA PRI RADIKALNEM ZRAVLJENJU
CM-577 (f.3): PD-1 zaviralec nivolumab

- Stadij II/III karcinom požiralnika/GEP (skvamozni in žlezni)
- Po neoadjuvanti KRT + kirurški resekciji (R0)
- ECOG PS 0 ali 1





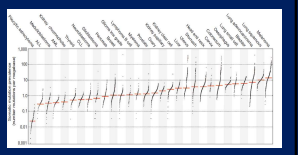
Ronan JK, et al. ESMO congress 2020.

PREDIKTIVNI OZNAČEVALCI SO KLJUČNA POT DO USPEHA

- IT **NI** UČINKOVITA PRI **VSEH** BOLNIKIH Z RAZSEJANIM RAKOM ŽELODCA IN POŽIRALNIKA.

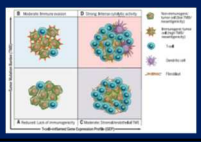
- PREDIKTIVNI OZNAČEVALCI:
  - MSI/dMMR – vsekakor!
  - TMB – KN-158 (ni vključevala raka želodca in požiralnika!)

→ OZNAČEVALCA TUMORSKIH AG. (POSLEDICA SOMATSKIH MUTACIJ)



  - CPS SCORE (PD-L1) - 1% ali 5% ali 10 %?, heterogenost tumorja (bx), različna protitelesa …
  - genski profil izražanja T celic

→ OZNAČEVALCA VNETJA (MIKROOKOLJE)



Alexandrov BL, et al. Nature 2013. Cristescu R, et al. Science 2018.

ZAKLJUČKI

- Zdravljenje bolnikov z karcinomom želodca in požiralnika se v zadnjih letih spreminja, imunoterapija postaja del njihovega specifičnega sistemskega zdravljenja.
- MSI/dMMR je jasno prediktiven označevalec za korist anti-PD-1 terapije. **Vsi bolniki z razsejanim rakom želodca/GEP morajo biti testirani na MSI/MMR.**
- Potrebujemo še druge dobre prediktivne označevalce, s katerimi bomo prepoznali podskupine bolnikov, pri katerih je IT učinkovita.
- **V klinične raziskave z imunoterapijo so bili vključeni bolniki v ECOG PS 0 ali 1. Podatkov za bolnike v PS 2 ali več nimamo.**

GC IMMUNOTHERAPY BIOMARKERS OF RESPONSE

Response rates to anti-PD-1 monotherapy are low for most patients (~12%)
Biomarkers for increased response rates to anti-PD-1 in clinical trials include:

	Prevalence	ORR	HR vs paclitaxel in KN061
Microsatellite instability	3-5%	>50%	HR 0·42, mOS not reached
High tumour mutational burden *dependent on assay	~18%	30-40%	0.34-0.45 mOS 16 months - not reached
High PD-L1 expression CPS ≥ 5 CPS ≥ 10 *dependent on assay	 ~30% ~20%	 ~25%	 0.72 : mOS 10.4 months 0.69 : mOS 10.4 months

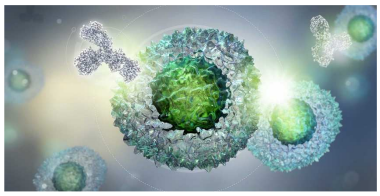
EBV positivity has been associated with variably increased response rates, but is quite rare

#4 "CPS SCORE"

- "CPS score" je uporablja pri zdravljenju adenokarcinomu želodca/GEP za izračun izražanja proteina PD-L1.

$$\text{CPS} = \frac{\text{\# of PD-L1-positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# of tumor cells}} \times 100$$

- PD-L1 IHK 22C3 pharmDx je test, ki je indiciran za bolnike z adenokarcinomo želodca/GEP, ki so kandidati za zdravljenje s pembrolizumabom.



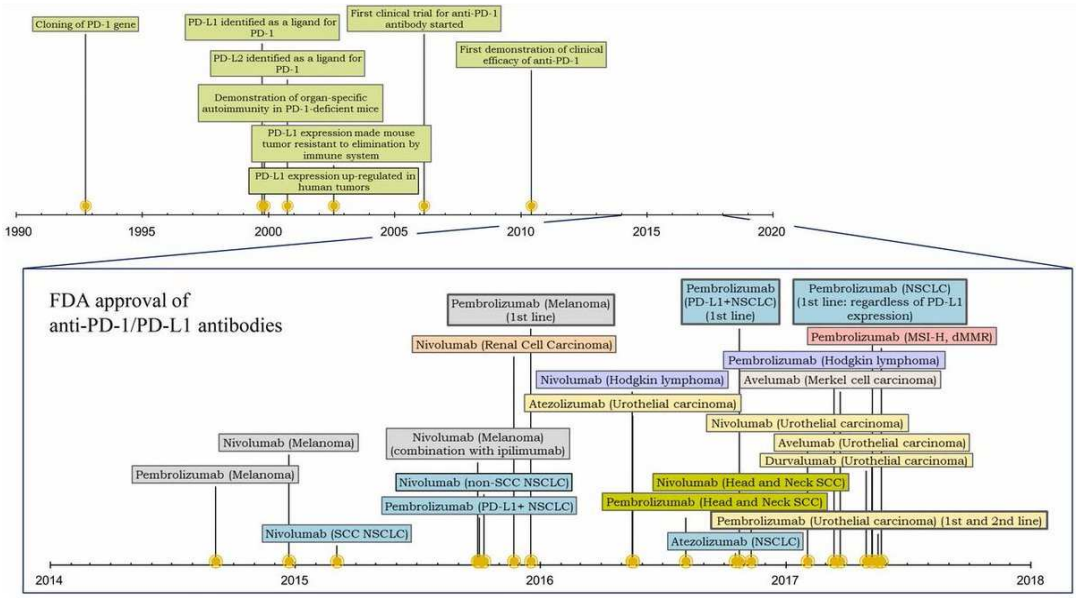
Novosti v biomarkerjih v imunoterapiji

15.12.2020

Doc.dr.Martina Reberšek, dr.med.
Sektor internistične onkologije
Onkološki inštitut Ljubljana

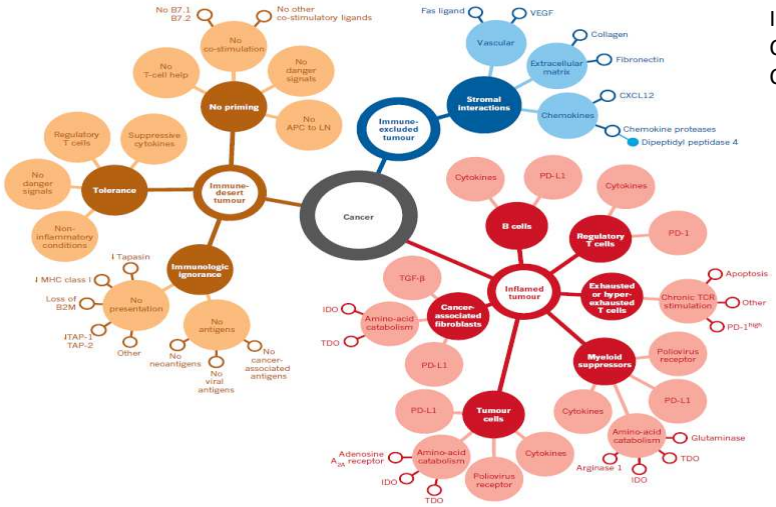
Mejniki.....

- ≈1990- odkritje: specifični T-celični proteinski receptorji - PD-1 in CTLA-4 – zmanjšujejo citotoksični odziv
- Ipilimumab-anti-CTLA-4 monoklonalno protitelo: prva registrirana imunoterapija, za 1.indikacijo napredovalega melanoma 2011
- 2016: imunoterapija kot napredek v zdravljenju raka
- 2018 Nobelova nagrada za imunoterapijo: dr.James Allison, dr.Tasuko Honjo



Tipi rakov glede na imunsko funkcijo

Immune- desert
CT+IO
CT→IO



Immune- excluded
CT+IO
CT→IO

Inflamed
IO →CT
CT+IO

Chen DS, Mellman I. Elements of cancer immunity and the cancer–immune set point. Nature, vol.541, 2017.

Imunoterapija:

Table 1. Different forms of immunotherapy used to manage cancer.

Form of immunotherapy	Example(s)	Tumor type(s) where used
Cytokines	IL2, interferon-α	Melanoma, renal
Vaccines	Sipuleucel-T	Prostate
	BCG[a]	Noninvasive bladder
Antibodies	Rituximab	B-cell lymphoma
	Trastuzumab[b]	Breast, stomach
Adoptive cell transfer	Tisagenlecleucel	Acute lymphoblastic leukemia
ICIs	Ipilimumab, pembrolizumab, nivolumab	Melanoma, lung, kidney, urothelial, Merkel cell carcinoma, Hodgkin lymphoma

[a] BCG, Bacillus Calmette-Guerin.
[b] Acts in part via an immune mechanism, i.e., via antibody-dependent cell-mediated cytotoxicity.

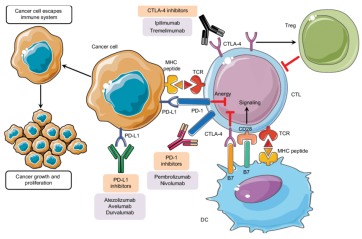
Duffy MJ, et al. Biomarkers for Predicting Response to Immunotherapy with Immune Checkpoint Inhibitors in Cancer Patients. Clinical Chemistry,2019

Imunoterapija z zaviralci imunskih kontrolnih točk - anti-PD-1, -PD-L1 in -CTLA-4 inhibitorji

Table 2. ICIs in clinical use or undergoing clinical trials together with their targets.[a]

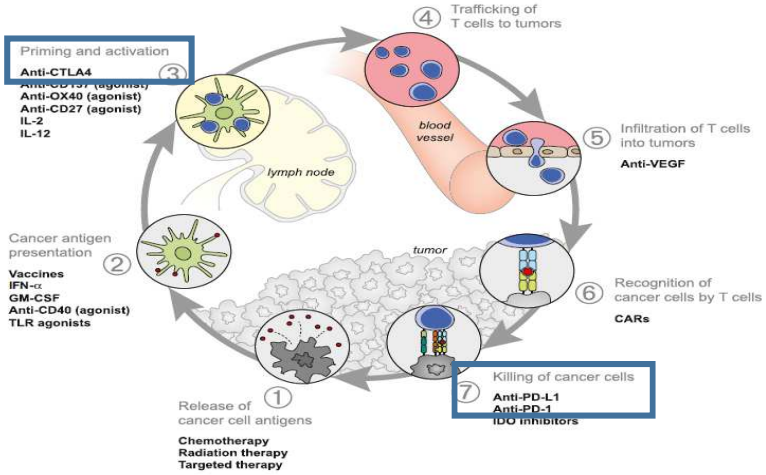
Inhibitor	Type of antibody	Target	Cancer(s) where indicated
Ipilimumab	IgG1	CTLA4	Melanoma
Tremelimumab	IgG2	CTLA4	Mesothelioma[b]
Pembrolizumab	IgG4	PD-1	NSCLC, HNSCC[c], Hodgkin lymphoma, MSI-defective, gastric, urothelial cancer
Nivolumab	IgG4	PD-1	Melanoma, kidney, NSCLC, HNSCC, HCC, Hodgkin lymphoma, urothelial cancer, MSI-defective tumors
Atezolizumab	IgG1	PD-L1	NSCLC, urothelial cancer,
Atezolizumab plus nab-paclitaxel	IgG1	PD-L1	Triple-negative breast cancer
Durvalumab	IgG1	PD-L1	NSCLC, urothelial cancer
Avelumab	IgG1	PD-L1	Merkel cell carcinoma, urothelial cancer

[a] Data reviewed from (*1–3*).
[b] Orphan approval only.
[c] HNSCC, head and neck squamous cell cancer; HCC, hepatocellular cancer.



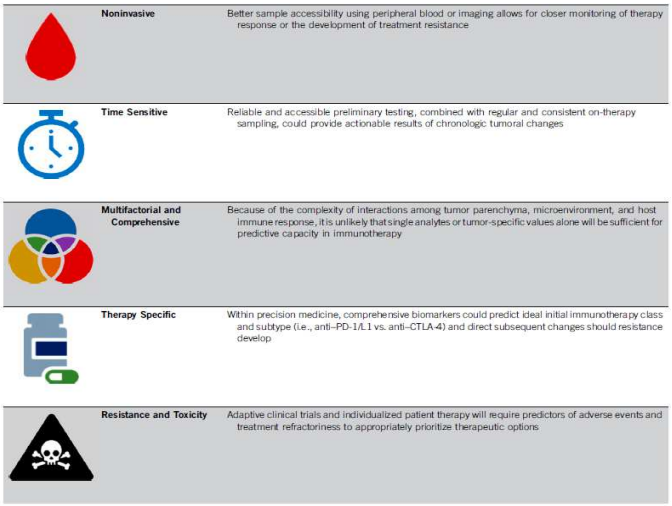
Duffy MJ, et al. Biomarkers for Predicting Response to Immunotherapy with Immune Checkpoint Inhibitors in Cancer Patients. Clinical Chemistry,2019

Mesta delovanja sistemske onkološke terapije v imunskem protitumorskem ciklusu



Chen DS, Mellman I. Oncology Meets Immunology:TheCancer-Immunity Cycle. Immunity 39, July 25, 2013 ª2013 Elsevier Inc

Idealni biomarkerji v imunoterapiji.....



McKean WB, et al. Biomarkers in Precision Cancer Immunotherapy: Promise and Challenges *American Society of Clinical Oncology Educational Book* 40, 2020

Vzroki za napake v validaciji biomarkerjev

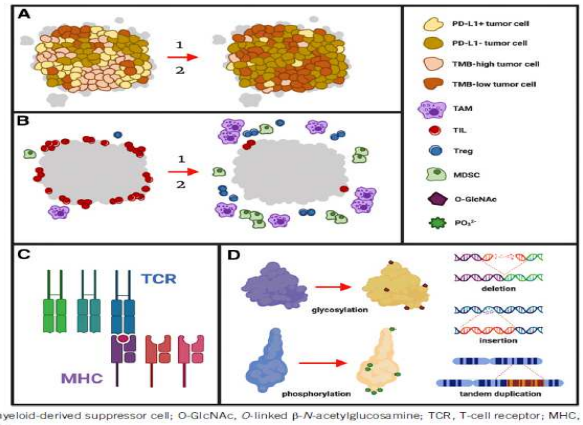


FIGURE 1. Sources of Biomarker Error
(A) Intratumoral (and intrapersonal) cellular heterogeneity remains a significant limitation in biomarker validity. Further dynamic alterations in clonal composition under the pressure of time (1) and therapy (2) prohibit pretreatment biomarker accuracy. (B) Patient host immunity and surrounding tumor microenvironment remain highly individualized and responsive to progressive cytokine (1) and/or treatment (2) exposures. These multiple variables abrogate the accuracy of single biomarker tests. (C) HLA allelic polymorphism and TCR selection generate significant variety among patient antigen processing and presentation. (D) Post-translational protein modifications or novel mutations such as indels and copy number alterations generate neoantigens that may remain undetected by traditional biomarkers.
Abbreviations: TMB, tumor mutation burden; TAM, tumor-associated macrophage; TIL, tumor-infiltrating lymphocyte; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; O-GlcNAc, *O*-linked β-*N*-acetylglucosamine; TCR, T-cell receptor; MHC, major histocompatibility complex.
Created with Biorender.

McKean WB, et al. Biomarkers in Precision Cancer Immunotherapy: Promise and Challenges *American Society of Clinical Oncology Educational Book* 40, 2020

Potencialni biomarkerji za imunoterapijo

Topni faktorji: serumski proteini
Tumor specifični faktorji: receptorji, mikrookolje
Genomski faktorji bolnika

Type	Source	Biomarker	Clinical Significance
Soluble	Serum	IL-6	High levels are prognostic for HD IL-2 treatment failure and shorter OS in metastatic RCC[13]
		CRP	High levels predict resistance to HD IL-214; decreasing levels during ipilimumab therapy are associated with disease control and survival[18]
		VEGF	High levels are an independent predictor for lack of response to HD IL-2[15] and are associated with decreased OS[16]
		LDH	Low pretreatment levels predict benefit from ipilimumab[17]; decreasing levels during ipilimumab therapy are associated with disease control and survival[18]
		sCD25	High levels predict resistance to ipilimumab[19]
		NY-ESO-1 antibody	Seropositivity has greater likelihood to respond to CTLA-4 blockade[29,30]
Cellular	Peripheral blood	Neutrophils/leukocytes	High counts are prognostic for HD IL-2 treatment failure and shorter OS[21]
		Lymphocytes	Immediate lymphocytosis is associated with response to HD IL-2 therapy[26]
		$CD8^+$ T cells	Presence is associated with clinical benefit to CTLA-4 blockade[30]
		ALCs	Increasing counts during ipilimumab therapy are associated with an improved OS[18,27]; however, this may occur in all patients regardless of benefit[27]
		Eosinophils	Increasing counts during ipilimumab therapy are associated with an improved OS[23]
		$CD4^+ICOS^+$ T cells	Increase in frequency after ipilimumab[46]
		MDSCs	Low frequency predicts benefit from ipilimumab therapy[25]
	Tumor	PD-L1	Refer to Table 2
	TILs	$CD4^+ICOS^{high}$ T cells	Increased frequency correlates with clinical benefit in ipilimumab[41,44-46]
		$CD8^+$ T cells	PD-1/PD-L1 expression on these cells predicts response to PD-1 blockade[47,55,57]
Genomic	Tumor	Tumor mutation loads	Predict clinical benefit to ipilimumab[8,75] and PD-1 blockade[7]
		MMR	Predicts clinical benefit to PD-1 blockade[76,77]

Abbreviations: IL, interleukin; HD, high-dose; OS, overall survival; RCC, renal cell carcinoma; CRP, C-reactive protein; LDH, lactate dehydrogenase; NY-ESO-1, NY-esophageal cancer 1; ALC, absolute lymphocyte count; ICOS, inducible T-cell costimulator; MDSC, myeloid-derived suppressor cell; TIL, of tumor-infiltrating lymphocyte; MMR, mismatch repair.

Kristen R, et al. Biomarkers for Immunotherapy: Current Developments and Challenge. American Society of Clinical Oncology Educational Book 2016

Značilnosti in klinična povezava biomarkerjev z imunoterapijo

TABLE 1. Characteristics and Clinical Correlates of Biomarkers in Cancer Immunotherapy

Biomarker	Immunotherapy	Malignancy	Example Tests	Clinical Utility	Tissue Source
PD-L1	Checkpoint inhibition	Multiple	TPS,[19] CPS,[20-24] IC expression[25]	CR/PR[26] ORR[21,23-25,27,28] DCB/DOR[21,23] PFS[28] OS[19,20,28]	Tumor, infiltrating lymphocytes/ macrophages
TMB	Checkpoint inhibition	Multiple	ΔTMB[12]	CR/PR[13,25,29] ORR[9,30-32] DCB/ DOR[30,33,34] PFS[9,30,31,34] OS[12,13,31,34]	Tumor
MMR/MSI	Checkpoint inhibition	Multiple	N/A	ORR[35] PFS[35] OS[35]	Tumor
Aneuploidy	Checkpoint inhibition	Multiple	SCNA level[36]	CR/PR[37] OS[36]	Tumor
TIL	Checkpoint inhibition	Multiple	Immunoscore,[38-40] CTLA-4^{hi}PD-1^{hi},[41] T_{RM},[42,43] PD-1^{T},[44] 4PD1^{hi},[45] CYT[12,46]	CR/ PR[12,41,44,47,48] ORR[49,50] PFS[41,50] OS[42,44,48]	Infiltrating lymphocytes
GEP	Checkpoint inhibition	Multiple	IFN-γ signature,[51-55] IMPRES,[56] TIDE,[57] immunophenoscore[58]	CR/PR[52,53,55-58] ORR[54] PFS[53-57] OS[51,54-57]	Tumor, infiltrating lymphocytes
mIHC/IF	Checkpoint inhibition	Melanoma, MCC, NSCLC	N/A	CR/PR[47,59,60] ORR[50] DCB/DOR[61] PFS[50,59,61] OS[59,61]	Tumor, infiltrating lymphocytes
PET/CT imaging	Checkpoint inhibition	Multiple	Immune-PET[62] (i.e., ^{89}ZR-desferrioxamine), ^{18}F-FDG[62,63]	CR/PR[63,64] PFS[64] OS[64]	N/A
Circulating CAR T cells	Adoptive cell therapy	B-cell precursor ALL, DLBCL	N/A	ORR[65] DFS[66]	Peripheral blood
Peripheral lymphocytes	Checkpoint inhibition, adoptive cell therapy, T-cell engagers	Multiple	Treg,[67] CD27^{+}CD45RO^{-}CD8^{+},[68] RLC[69]	CR/PR[67,68] OS[69]	Peripheral blood

TABLE 1. Characteristics and Clinical Correlates of Biomarkers in Cancer Immunotherapy (Continued)

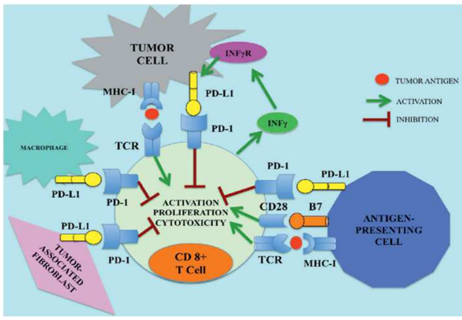
Biomarker	Immunotherapy	Malignancy	Example Tests	Clinical Utility	Tissue Source
Proinflammatory cytokines	Checkpoint inhibition, adoptive cell therapy	Melanoma, B-cell precursor ALL, CLL, NHL	IFN-γ, IL-13, MIP-1α, IL-6, IL-8, sCD25, IL-17, sCD163, CXCL5	Toxicity[70-77]	Peripheral blood
Autoantibodies	Checkpoint inhibition	Multiple	Anti-thyroglobulin, anti-GAD65, anti-IA2, anti-insulin, anti-ZnT8	Toxicity[78,79]	Peripheral blood

Abbreviations: TPS, tumor proportion score; CPS, combined positive score; IC, infiltrating immune cell; CR, complete response; PR, partial response; ORR, objective or overall response rate; DCB, durable clinical benefit; DOR, duration of response; PFS, progression-free survival; OS, overall survival; TMB, tumor mutation burden; ΔTMB, change in TMB; MMR/MSI, mismatch repair/microsatellite instable; N/A, not applicable; SCNA, somatic copy number alteration; TIL, tumor-infiltrating lymphocyte; T_{RM}, tissue-resident memory T cell; PD-1^{T}, intratumoral CD8^{+} T cell PD-1 elevation; 4PD1^{hi}, unconventional PD-1–expressing CD4^{+}FOXP3^{-} subpopulation; CYT, cytolytic score; IMPRES, immune-predictive score; GEP, gene expression profile; IFN-γ, interferon gamma; TIDE, tumor immune dysfunction and exclusion; mIHC, multiplex immunohistochemical; IF, immunofluorescence; MCC, Merkel cell carcinoma; NSCLC, non–small cell lung cancer; FDG, fluorodeoxyglucose; CAR, chimeric antigen receptor; ALL, acute lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; DFS, disease-free survival; Treg, regulatory T cell; RLC, relative lymphocyte count; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; IL-13, interleukin-13; MIP-1α, macrophage inflammatory protein 1α; IL-6, interleukin-6; IL-8, interleukin-8; sCD25, soluble interleukin-2 receptor; IL-17, interleukin 17; sCD163, soluble cluster of differentiation 163; CXCL5, CXC motif chemokine 5; GAD65, glutamic acid decarboxylase 65; IA2, α-islet antigen 2; ZnT8, zinc transporter 8.

McKean WB, et al. Biomarkers in Precision Cancer Immunotherapy: Promise and Challenges *American Society of Clinical Oncology Educational Book* 40, 2020

PD-L1(1)

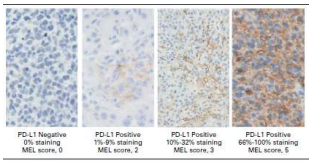
- Definicija: ligand programirane celične smrti 1 (PD-L1)
- Vloga pri zaščiti tkiv pred vnetji in avtoimunimi reakcijami
- ↑ekspresija PD-L1 na tumorskih celicah→ povezava z limfociti T →inhibicija aktivnosti imunskega sistema → tumorska rast in progresija
- Vezava anti- PD-1/PD-L1 monoklonalnih protiteles na PD-1/PD-L1 →reaktivacija aktivnosti limfocitov T →protitumorski učinek imunskih celic



PD-L1 (2)

- Določanje:

- Imunohistokemično



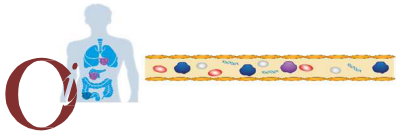
- Različni diagnostični testi s protitelesi za PD-L1

Table 3. Assays for PD-L1, together with the situations in which they are approved by the US FDA for clinical use.

Test	Company	FDA approval	ICI therapy	Cancer[a]
PD-L1 IHC 22C3 pharma Dx	Dako/Agilent Technologies	Companion[b]	Pembrolizumab in patients with untreated and previously treated NSCLC patients	NSCLC
PD-L1 IHC 28-8 pharma Dx assay	Dako/Agilent Technologies	Complementary[c]	Nivolumab in second-line treatment of NSCL patients	NSCLC
PD-L1 IHC SP 142	Ventana	Complementary	Atezolizumab in patients with progressive NSCLC, also in patients with urothelial cancer	NSCLC, urothelial
PD-L1 IHC SP263	Ventana	Complementary	Durvalumab in patients with urothelial cancer	Urothelial

[a] Refers to advanced or metastatic cancers.
[b] A companion diagnostic provides information that is essential for the safe and effective use of a corresponding therapeutic product.
[c] A complementary diagnostic can be used to assist but not determine treatment decision making.

- Tekočinska biopsija



Duffy MJ, et al. Biomarkers for Predicting Response to Immunotherapy with Immune Checkpoint Inhibitors in Cancer Patients. Clinical Chemistry,2019

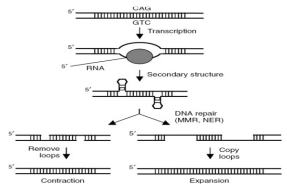
Korelacija ekspresije PD-L1 z odgovorom na zdravljenje

TABLE 2. Summary of PD-L1 Expression and Response to Therapy in Various Clinical Trials

First Author	Tumor Type	Therapy	Cutoff (%)	Biomarker Results
Topalian[48]	Advanced melanoma, NSCLC, CRPC, RCC, and CRC	Pembrolizumab	5	0 of 17 patients with PD-L1–negative tumors had objective response
Borghaei[51]	Advanced nonsquamous NSCLC	Nivolumab vs. docetaxel	1, 5, and 10	Nivolumab had superior efficacy to docetaxel, greater with higher tumor membrane PD-L1 expression
Muro[80]	Gastric	Pembrolizumab	1	Tumor PD-L1 expression was associated with ORR
Taube[53]	Melanoma, NSCLC, RCC, CRC, CRPC	Nivolumab	5	Tumor cell PD-L1 expression correlated with objective response
Disis[68]	Recurrent/refractory ovarian cancer	Avelumab	1	Trend toward better response rates in PD-L1–positive tumors
Garon[49]	Advanced NSCLC	Pembrolizumab	50	PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy
Powles[69]	Bladder	Atezolizumab (anti–PD-L1)	1, 5, and 10	PD-L1–positive tumors at > 5% had particularly high response rates
Weber[66]	Advanced melanoma progressed on anti–CTLA-4 therapy	Nivolumab vs. investigator's choice	5	Higher response rates with nivolumab correlated with positive tumor PD-L1 expression, but patients with PD-L1–negative tumors still had benefit
Weber[65]	Advanced melanoma progressed on prior therapy/CTLA-4 therapy	Nivolumab	1 and 5	PD-L1 positivity correlated significantly with better response but negativity did not rule out response
Kefford[67]	Melanoma	Pembrolizumab	1	PD-L1 positivity associated with improved ORR and PFS, but activity observed in patients with low PD-L1 expression
Robert[70]	Metastatic melanoma	Nivolumab vs. dacarbazine	5	Nivolumab-treated patients had improved objective response rate and overall survival, regardless of PD-L1 status
Motzer[71]	Metastatic RCC	Nivolumab	1 and 5	Response rates were higher with greater PD-L1 expression (≥ 5%), but those with lower expression (< 5%) also had meaningful responses
Brahmer[50]	Advanced progressed squamous NSCLC	Nivolumab vs. docetaxel	1, 5, and 10	Expression of PD-L1 was neither prognostic nor predictive of benefit
Herbst[57]	Advanced melanoma, NSCLC, RCC, and other	Atezolizumab	5	Response correlated with PD-L1 expression by tumor-infiltrating immune cells, but correlation between response and PD-L1 expression by tumor cells was not significant

Spencer KR, et al. Biomarkers for Immunotherapy: Current Developments and Challenge. American Society of Clinical Oncology Educational Book 2016

MSI (1)



- Mikrosateliti so kratki odseki DNK (1-6 nukleotidov), ki se tandemsko ponavljajo skozi genom- v genih in medgenskih področjih- promotorske regije, terminalne regije, introni in kodirajoči eksoni)
- Mikrosatelitna nestabilnost- MS se pojavi takrat ko genom izgubi ali pridobi ≥ ponovitev
- DNK popravljalni mehanizem za popravljanje napak- sistem za popravljanje neujemanja DNK- MMR

- **DOLOČANJE:**
- imunohistokemično – za dMMR
- polimerazna verižna reakcija- PCR- za MSI-H
- sekvenciranje naslednje generacije- NGS- za MSI-H

MSI (2)

<u>Imunohistokemično barvanja za 4 MMR proteine v vzorcu tumorja:</u>

- MLH1 ohranjena/izguba ekspresije
- MSH2 ohranjena/izguba ekspresije
- MSH6 ohranjena/izguba ekspresije
- PMS2 ohranjena/izguba ekspresije

- IHK barvanja so/niso pokazala izgube ekspresije pMMR /dMMR proteinov – verjetnost da gre za MSI –H tumor (v sklopu Lynch sindroma) je velika/majhna.
- Število mutacij in predvidene mutacije kot neoantigeni višje v dMMR tumorju v primerjavi s pMMR
- Zarodne ali somatske mutacije teh 4 genov ali hipermetilacija promotorskega MLH1 gena vodijo v dMMR- defekt v izražanju proteinov za popravljanje neujemanja DNK- "dMMR" in nesposobnost popravljanja napak med DNK replikacijo
- Te napake se zgodijo v glavnem v MS regijah, zato te tumorje imenujemo visoko mikrosatelitno nestabilne- MSI-H

MSI (3)

- **MSI-H:** v večini solidnih rakov, prevalenca različna pri različnih rakih
- Prevalenca MSI-H≈ 5%bolnikov
- Prevalenca MSI-H >10%bolnikov s CRC in z endometrijskim karcinomom
- Prevalenca MSI-H <2%bolnikov z glioblastomom, rakom dojke, NSCLC

- **MSI-H**:CRC- imunohistokemično ali PCR (polimerazna verižna reakcija) ali NGS,ostali raki- imunohistokemično ali z NGS (sekvenciranje naslednje generacije:tarčno sekvenciranje- pokritost tarčnih regij> 500x)

dMMR, MSI-H

Rates of dMMR or MSI-H in advanced/metastatic cancer across 2 different panels, expressed as a percentage

Tumor type	Fraction with mismatch repair abnormalities	
	Assessed by dMMR (Le, 2017)[1]	Assessed by MSI-H (Middha, 2017)[2]
Biliary	1	1.3
Bladder	NR	3.1
Brain tumors	<1	–
Breast	<1	–
Cervical	<1	–
Colorectal	3	8.3
Endometrial	6	16.2
Esophagus and esophagogastric junction	–	2.5*
Gastric adenocarcinoma	3	2.5*
Hepatocellular	–	–
Lung, non-small cell	<1	<1
Lung, small cell	1	1.1
Neuroendocrine tumors	1	2.1¶
Ovarian	<1	–
Pancreatic	1	<1
Prostate	1	1.7
Sarcoma, uterine	<1	2
Skin, melanoma	NR	–
Skin, Merkel cell	NR	NR
Skin, oculomelanoma	NR	3.1
Small bowel	1	15.6
Soft tissue sarcoma, nonuterine	–	<1
Thyroid carcinoma	2	<1
Unknown primary	1	2

dMMR: deficient mismatch repair; MSI-H: high levels of microsatellite instability; NR: not reported.
* Esophagogastric tumors, nongastrointestinal stromal tumors.
¶ Gastrointestinal.

Overman MJ, et al.Tissue-agnostic cancer therapy: DNA mismatch repair deficiency, tumor mutational burden, and response to immune checkpoint blockade in solid tumors. UpToDate, Sept 2020

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

MSI-H

Imunoterapija z zaviralci imunskih kontrolnih točk- **monoterapija**

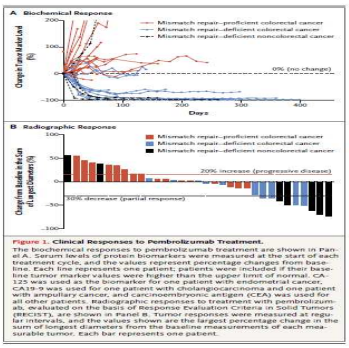


Figure 1. Clinical Responses to Pembrolizumab Treatment.
The biochemical responses to pembrolizumab treatment are shown in Panel A. Serum levels of protein biomarkers were measured at the start of each treatment cycle, and the values represent percentage changes from baseline. Each line represents one patient; patients were included if their baseline tumor marker values were higher than the upper limit of normal. CA-125 was used for one patient with ovarian cancer, CA19-9 was used for one patient with cholangiocarcinoma and one patient with ampullary cancer, and carcinoembryonic antigen (CEA) was used for all other patients. Radiographic responses to treatment with pembrolizumab, evaluated on the basis of Response Evaluation Criteria in Solid Tumors (RECIST), are shown in Panel B. Tumor responses were measured at regular intervals, and the values shown are the largest percentage change in the sum of longest diameters from the baseline measurements of each measurable tumor. Each bar represents one patient.

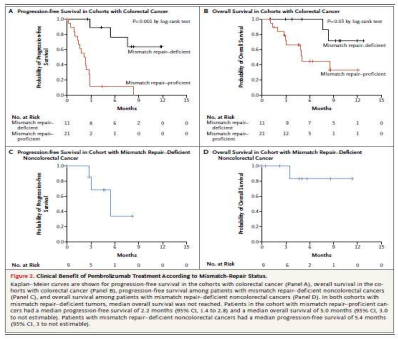


Figure 2. Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status.
Kaplan–Meier curves are shown for progression-free survival in the cohorts with colorectal cancer (Panel A), overall survival in the cohorts with colorectal cancer (Panel B), progression-free survival among patients with mismatch repair–deficient noncolorectal cancers (Panel C), and overall survival among patients with mismatch repair–deficient noncolorectal cancers (Panel D). In both cohorts with mismatch repair–deficient tumors, median overall survival was not reached. Patients in the cohort with mismatch repair–proficient cancers had a median progression-free survival of 2.2 months (95% CI, 1.4 to 2.8) and a median overall survival of 5.0 months (95% CI, 3.0 to not estimable). Patients with mismatch repair–deficient noncolorectal cancers had a median progression-free survival of 5.4 months (95% CI, 3 to not estimable).

Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

Le DT, et al.PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-20.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

MSI- H

Imunoterapija z zaviralci imunskih kontrolnih točk-**kombinacija**

Table 2. ORR, Best Overall Response, and DCR per Investigator Assessment (N = 119)

Response	No. (%)	95% CI
ORR	65 (55)	45.2 to 63.8
Best overall response		
Complete response	4 (3)	
Partial response	61 (51)	
Stable disease	37 (31)	
Progressive disease	14 (12)	
Not determined	3 (3)	
Disease control for ≥ 12 weeks	95 (80)	71.5 to 86.6

Abbreviations: DCR, disease control rate; ORR, objective response rate.

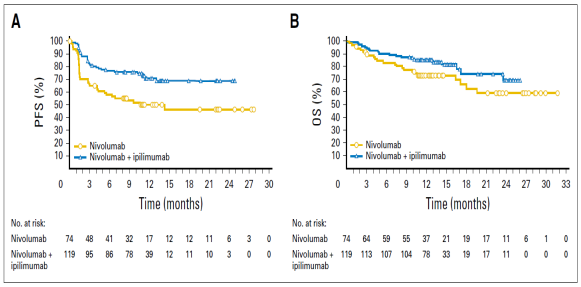


Fig 3. Kaplan-Meier plots of (A) progression-free survival (PFS) per investigator assessment and (B) overall survival (OS) in patients treated with nivolumab plus ipilimumab in the analyses presented herein or nivolumab in the monotherapy cohort of CheckMate-142 from an analysis that had a similar median follow-up (potential time on study from first dose to data cutoff: 13.4 months).[11]

Overman MJ, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer. J Clin Oncol 36:773-779.

KEYNOTE 158- MSI

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

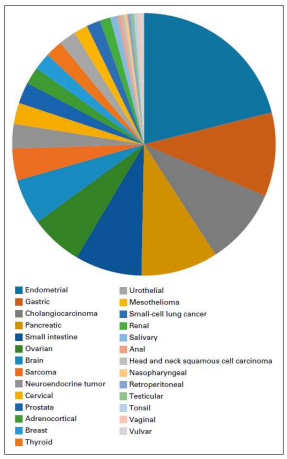
Aurelien Marabelle, MD, PhD[1]; Dung T. Le, MD[2]; Paolo A. Ascierto, MD[3]; Anna Maria Di Giacomo, MD[4]; Ana De Jesus-Acosta, MD[2]; Jean-Pierre Delord, MD, PhD[5]; Ravit Geva, MD, MSc[6]; Maya Gottfried, MD[7]; Nicolas Penel, MD, PhD[8]; Aaron E. Hansen, MBBS[9]; Sarina A. Piha-Paul, MD[10]; Toshihiko Doi, MD, PhD[11]; Bo Gao, MBBS, PhD[12]; Hyun Cheol Chung, MD, PhD[13]; Jose Lopez-Martin, MD, PhD[14]; Yung-Jue Bang, MD, PhD[15]; Ronnie Shapira Frommer, MD[16]; Manisha Shah, MD[17]; Razi Ghori, PhD[18]; Andrew K. Joe, MD[18]; Scott K. Pruitt, MD, PhD[18], and Luis A. Diaz Jr, MD[19]

TABLE 1. Baseline Demographics and Disease Characteristics

Demographic or Characteristic	Evaluable Patients (N = 233)
Median age, years (range)	60.0 (20-87)
≥ 65	87 (37.3)
Sex	
Male	96 (41.2)
Female	137 (58.8)
ECOG performance status	
0	113 (48.5)
1	120 (51.5)
Disease stage	
MX	1 (0.4)
M0	10 (4.3)
M1	212 (91.0)
Unknown	10 (4.3)
Brain metastases	4 (1.7)
Median sum of target lesions at baseline, mm (range)	65.8 (10.2-394.5)
Prior (neo) adjuvant therapy	55 (23.6)
Prior lines of therapy for recurrent/ metastatic disease	
0*	7 (3.0)
1	87 (37.3)
2	61 (26.2)
3	41 (17.6)
≥ 4	37 (15.9)
Cancer type of primary diagnosis	
Endometrial	49 (21.0)
Gastric	24 (10.3)
Cholangiocarcinoma	22 (9.4)
Pancreatic	22 (9.4)
Small intestine	19 (8.2)
Ovarian	15 (6.4)
Brain	13 (5.6)
Sarcoma	9 (3.9)
Neuroendocrine tumor	7 (3.0)
Cervical	6 (2.6)
Prostate	6 (2.6)
Adrenocortical	5 (2.1)
Breast	5 (2.1)
Thyroid	5 (2.1)
Urothelial	5 (2.1)
Mesothelioma	4 (1.7)
Small-cell lung cancer	4 (1.7)
Renal	3 (1.3)

(continued in next column)

Demographic or Characteristic	Evaluable Patients (N = 233)
Salivary	2 (0.9)
Anal	1 (0.4)
Head and neck squamous cell carcinoma	1 (0.4)
Nasopharyngeal	1 (0.4)
Retroperitoneal	1 (0.4)
Testicular	1 (0.4)
Tonsil	1 (0.4)
Vaginal	1 (0.4)
Vulvar	1 (0.4)



Marabelle A, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020 Jan 1;38(1):1-10.

Odgovor na zdravljenje in ipNU

TABLE 2. Best Overall Response per RECIST Version 1.1 by Independent Central Radiologic Review

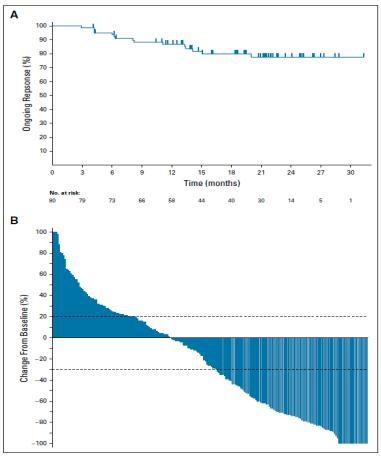
Response	Evaluable Patients (N = 233)
Objective response	
No. (%; 95% CI)	80 (34.3; 28.3 to 40.8)
Median time to response, months (range)*	2.1 (1.3-10.6)
Median duration of response, months† (range)	NR (2.9-31.3+)
Best overall response, No. (%)	
Complete response	23 (9.9)
Partial response	57 (24.5)
Stable disease	42 (18.0)
Progressive disease	92 (39.5)
Nonevaluable	2 (0.9)
No assessment‡	17 (7.3)
Kaplan-Meier estimate of patients with extended duration of response, months†, No. (%)	
≥ 12	58 (86.9)
≥ 18	40 (79.9)
≥ 24	14 (77.6)

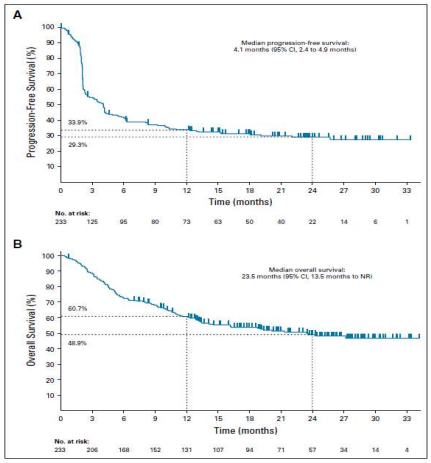
TABLE 4. Incidence of Adverse Events

Adverse Event	Patients (N = 233) Any Grade, No. (%)	Grade 3-4*, No. (%)
Treatment-related adverse events		
Any	151 (64.8)	34 (14.6)
Occurring in ≥ 5% of patients		
Fatigue	34 (14.6)	2 (0.9)
Pruritus	30 (12.9)	0
Diarrhea	28 (12.0)	0
Asthenia	25 (10.7)	1 (0.4)
Hypothyroidism	19 (8.2)	0
Arthralgia	18 (7.7)	0
Nausea	15 (6.4)	0
Rash	12 (5.2)	0
Immune-mediated adverse events and infusion reactions†		
Hypothyroidism	21 (9.0)	0
Hyperthyroidism	12 (5.2)	1 (0.4)
Pneumonitis	9 (3.9)	3 (1.3)
Colitis	9 (3.9)	2 (0.9)
Hepatitis	4 (1.7)	2 (0.9)
Severe skin reactions	3 (1.3)	3 (1.3)
Myositis	3 (1.3)	0
Type 1 diabetes mellitus	2 (0.9)	1 (0.4)
Infusion reactions	2 (0.9)	0
Nephritis	2 (0.9)	0
Guillain-Barre syndrome	1 (0.4)	1 (0.4)
Pancreatitis	1 (0.4)	1 (0.4)

Marabelle A, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020 Jan 1;38(1):1-10.

Trajanje odgovora in OS, PFS





mFU 13.4 mesecev
ORR 34.3%
mPFS 4.1 mesecev
mOS 23.5 mesecev

Marabelle A, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020 Jan 1;38(1):1-10.

KEYNOTE -177: pembrolizumab pri MSI-H metastatskem raku debelega črevesa in danke

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2020 VOL. 383 NO. 23

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*

KEYNOTE-177
- demografski podatki

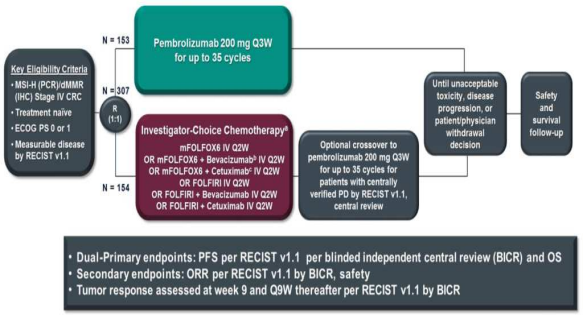


Table 1. Demographic and Patient Characteristics at Baseline.*

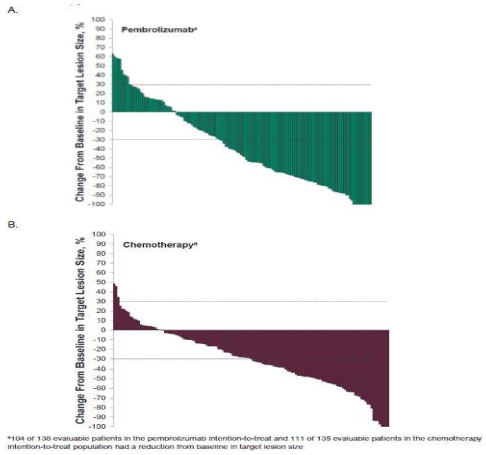
Characteristic	Pembrolizumab (N = 153)	Chemotherapy† (N = 154)
Median age (range) — yr	63.0 (24–93)	62.5 (26–90)
≥65 years of age — no. (%)	73 (48)	71 (46)
Male sex — no. (%)	71 (46)	82 (53)
ECOG performance-status score of 0 — no. (%)‡	75 (49)	84 (55)
MSI-H§ — no. (%)	153 (100)	153 (99)
Region — no. (%)		
Asia	22 (14)	26 (17)
Western Europe or North America	109 (71)	113 (73)
Rest of world	22 (14)	15 (10)
Primary tumor location — no. (%)		
Right side	102 (67)	107 (69)
Left side	46 (30)	42 (27)
Other site or site missing¶	5 (3)	5 (3)
Stage — no. (%)		
Recurrent metachronous‖	80 (52)	74 (48)
Newly diagnosed with metastatic disease	73 (48)	80 (52)
Prior systemic therapy — no. (%)		
Adjuvant	33 (22)	37 (24)
Neoadjuvant with or without adjuvant systemic therapy	5 (3)	8 (5)
None	115 (75)	109 (71)
Mutation status — no. (%)		
BRAF, *KRAS*, *NRAS* all wild type	34 (22)	35 (23)
KRAS or *NRAS* mutant	33 (22)	41 (27)**
$BRAF^{V600E}$ mutant	34 (22)	43 (28)**
Could not be evaluated for *BRAF*, *KRAS*, or *NRAS*††	52 (34)	38 (25)

Andre T, et al. Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer. N Engl J Med 2020;383:2207-18.

KEYNOTE-177
- odgovor na zdravljenje

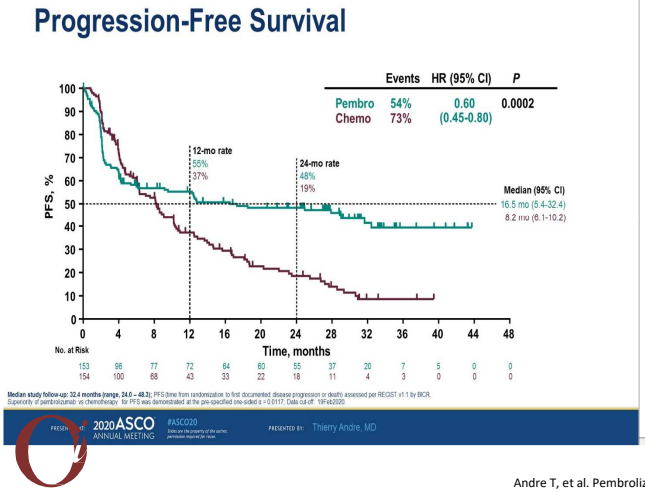
Table 2. Antitumor Activity in the Intention-to-Treat Population.

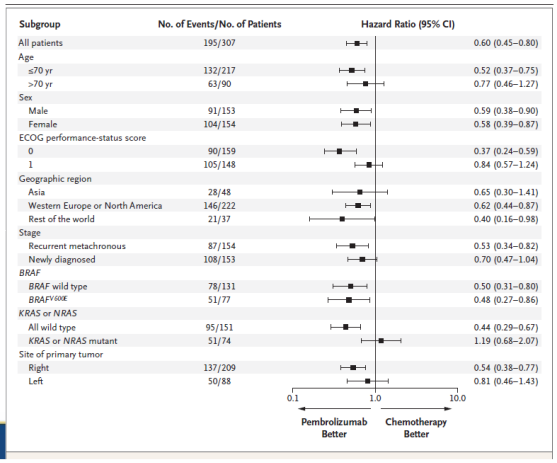
Variable	Pembrolizumab (N = 153)	Chemotherapy (N = 154)
Overall response*		
No. of patients	67	51
% (95% CI)	43.8 (35.8 to 52.0)	33.1 (25.8 to 41.1)
Best response — no. (%)†		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Progressive disease	45 (29.4)	19 (12.3)
Could not be evaluated or no assessment made‡	9 (5.9)	19 (12.3)
Median time to response (range) — mo	2.2 (1.8 to 18.8)	2.1 (1.7 to 24.9)
Median duration of response (range) — mo§	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)
Response duration of ≥24 months — %§	82.6	35.3



Andre T, et al. Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer. N Engl J Med 2020;383:2207-18.

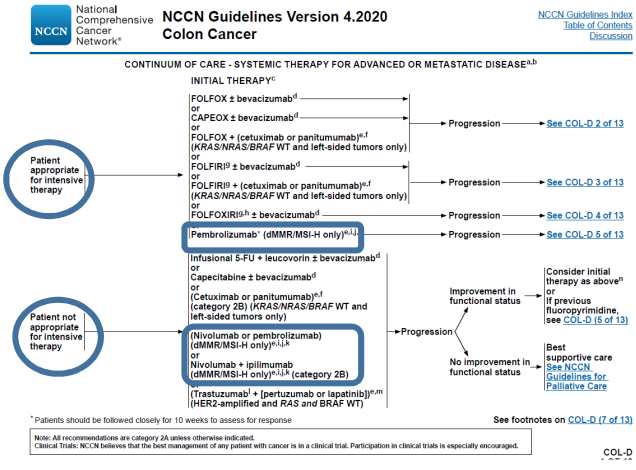
KEYNOTE-177
PFS



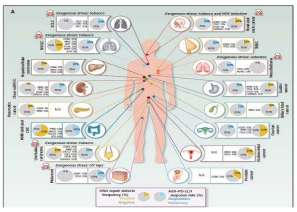


Andre T, et al. Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer. N Engl J Med 2020;383:2207-18.

MSI-H pri raku debelega črevesa in danke



Tumorsko mutacijsko breme- TMB



- **Tumorsko mutacijsko breme (TMB):** je opredeljeno kot skupno število nesinonimnih mutacij na kodirno območje tumorskega genoma
- Večje kot je TMB- večja sposobnost generiranja neoantigenov, bolj je tumor imunogen →večja verjetnost za odgovora na imunoterapijo
- Visok TMB povezan s predobstoječim imunskim odzivom in ekspresijo PD-1/PDL1
- Glavna determinanta imunskega odgovora je vezava neoantigena na MHC1 in prepoznava tega kompleksa s strani receptorja limfocita T
- Določanje: NGS

Prevalenca somatskih mutacij pri različnih rakih

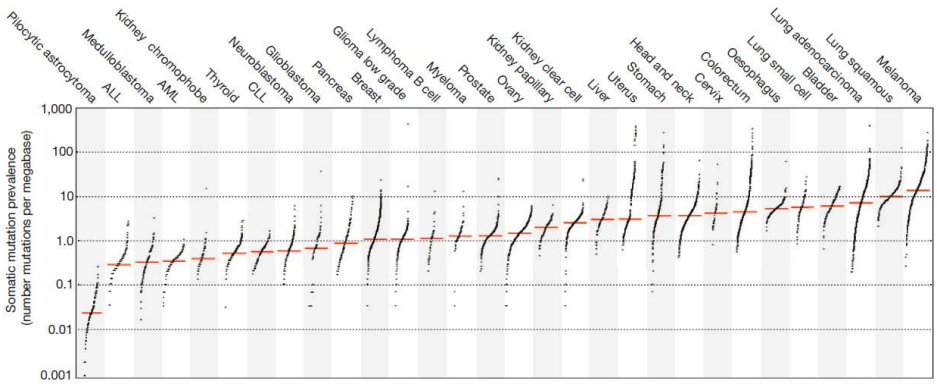
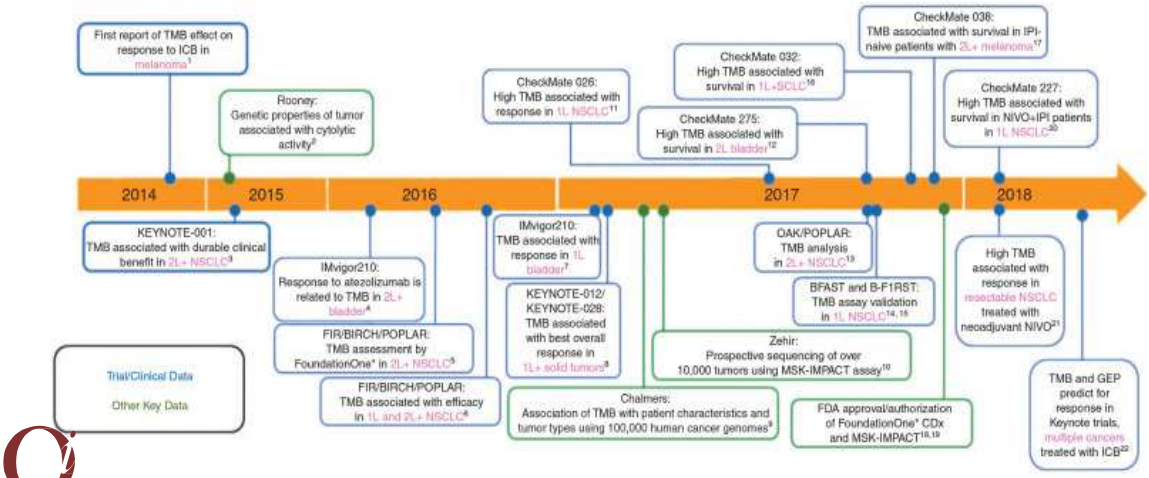


Figure 1 | The prevalence of somatic mutations across human cancer types. Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We thank G. Getz and colleagues for the design of this figure[26]. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

Alexandrov BL, et al. Signatures of mutational processes in human cancer. Nature, Vol.500,2013.

TMB



ESMO

ANNALS OF ONCOLOGY

REVIEW ARTICLE

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

F. Mosele[1], J. Remon[2], J. Mateo[3], C. B. Westphalen[4], F. Barlesi[5], M. P. Lolkema[6], N. Normanno[7], A. Scarpa[8], M. Robson[9], F. Meric-Bernstam[10], N. Wagle[11], A. Stenzinger[12], J. Bonastre[13,14], A. Bayle[14,15,16], S. Michiels[14,15], I. Bièche[14], E. Rouleau[14], S. Jezdic[17], J-Y. Douillard[18], J. S. Reis-Filho[19], R. Dienstmann[20] & F. André[1,15,20]*

Table 2. Summary recommendations

Tumour types	General recommendations for daily practice	Recommendation for clinical research centres	Special considerations for patients
Lung adenocarcinoma	Tumour multigene NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included') and if they report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions in the panel	It is highly recommended that clinical research centres perform multigene sequencing in the context of molecular screening programmes in order to increase access to innovative drugs and to speed up clinical research. This is particularly relevant in breast, pancreatic and hepatocellular cancers where level II–IV alterations are numerous.	Using large panels of genes could lead to few clinically meaningful responders, not detected by small panels or standard testings. In this context and outside the diseases where large panels of genes are recommended, ESMO acknowledges that a patient and a doctor could decide together to order a large panel of genes, pending no extra cost for the public health care system, and if the patient is informed about the low likelihood of benefit.
Squamous cell lung cancers	No current indication for tumour multigene NGS		
Colon cancers	Multigene tumour NGS can be an alternative option to PCR if it does not result in additional cost.		
Gastric cancers	No current indication for tumour multigene NGS		
Pancreatic cancers	No current indication for tumour multigene NGS		
Hepatocellular carcinoma	No current indication for tumour multigene NGS		
Cholangiocarcinoma	Multigene tumour NGS could be recommended to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included') and if they report accurate ranking of alterations.		
Others	Tumour multigene NGS can be used in ovarian cancers to determine somatic *BRCA1/2* mutations. In this latter case, larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included') and if they report accurate ranking of alterations. Large panel NGS can be used in carcinoma of unknown primary. It is recommended to determine TMB in cervical cancer, salivary cancer, thyroid cancers, well-to-moderately differentiated neuroendocrine tumours, vulvar cancer, pending drug access (and in TMB-high endometrial and SCL cancers if anti-PD1 antibody is not available otherwise).		

KEYNOTE 158- TMB

Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study

Aurélien Marabelle, Marwan Fakih, Juanita Lopez, Manisha Shah, Ronnie Shapira-Frommer, Kazuhiko Nakagawa, Hyun Cheol Chung, Hedy L Kindler, Jose A Lopez-Martin, Wilson H Miller Jr, Antoine Italiano, Steven Kao, Sarina A Piha-Paul, Jean-Pierre Delord, Robert R McWilliams, David A Fabrizio, Deepti Aurora-Garg, Lei Xu, Fan Jin, Kevin Norwood, Yung-Jue Bang

	Safety population (n=105)*	Efficacy population	
		tTMB-high group (n=102)	Non-tTMB-high group (n=688)
Age, years	61 (55–68)	61 (55–68)	61 (53–69)
Sex			
Men	35 (33%)	35 (34%)	253 (37%)
Women	70 (67%)	67 (66%)	435 (63%)
ECOG performance status			
0	44 (42%)	42 (41%)	277 (40%)
1	60 (57%)	59 (58%)	409 (59%)
2	1 (1%)	1 (1%)	2 (<1%)
Brain metastases	6 (6%)	6 (6%)	17 (2%)
Disease stage			
M0	10 (10%)	9 (9%)	72 (10%)
M1	95 (90%)	93 (91%)	616 (90%)
Sum of longest diameters of target lesions, mm	84·2 (44·2–137·3)	88·3 (44·2–141·0)	83·4 (46·7–152·7)
PD-L1 status			
Positive	69 (66%)	68 (67%)	383 (56%)
Negative	30 (29%)	29 (28%)	274 (40%)
Not evaluable	5 (5%)	5 (5%)	30 (4%)
Missing	1 (1%)	0	1 (<1%)
MSI-H status			
MSI-H	14 (13%)	14 (14%)	0
Non-MSI-H†	83 (79%)	81 (79%)	672 (98%)
Missing	8 (8%)	7 (7%)	16 (2%)
Previous therapies for recurrent or metastatic disease			
No systemic chemotherapy	1 (1%)	1 (1%)	23 (3%)
Previous adjuvant, neoadjuvant or definitive therapy‡	0	0	8 (1%)
One line	45 (43%)	44 (43%)	257 (37%)
Two lines	40 (38%)	38 (37%)	187 (27%)
Three lines	6 (6%)	6 (6%)	107 (16%)
Four or more lines	13 (12%)	13 (13%)	106 (15%)

(Table 1 continues in next column)

	Safety population (n=105)*	Efficacy population	
		tTMB-high group (n=102)	Non-tTMB-high group (n=688)
(Continued from previous column)			
Tumour types§			
Anal	14 (13%)	14 (14%)	75 (11%)
Biliary	0	0	63 (9%)
Cervical	16 (15%)	16 (16%)	59 (9%)
Endometrial	15 (14%)	15 (15%)	67 (10%)
Mesothelioma	1 (1%)	1 (1%)	84 (12%)
Neuroendocrine	5 (5%)	5 (5%)	82 (12%)
Salivary	3 (3%)	3 (3%)	79 (11%)
Small-cell lung	34 (32%)	34 (33%)	42 (6%)
Thyroid	2 (2%)	2 (2%)	78 (11%)
Vulvar	15 (14%)	12 (12%)	59 (9%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. M0=no metastases. M1=metastases present. MSI-H=high microsatellite instability. tTMB-high=high tissue tumour mutational burden. *All participants in the safety population were assessed as having tTMB-high status. †Comprises patients with tumours with low microsatellite instability or were microsatellite stable. ‡Received adjuvant or neoadjuvant alone without recurrence for less than 12 months since completing the therapy or received definitive therapy alone, which cannot be considered a line of therapy. §The 14 MSI-H tumours were endometrial (n=10), cervical (n=2), thyroid (n=1), and salivary (n=1).

Table 1: **Baseline demographics and clinical characteristics**

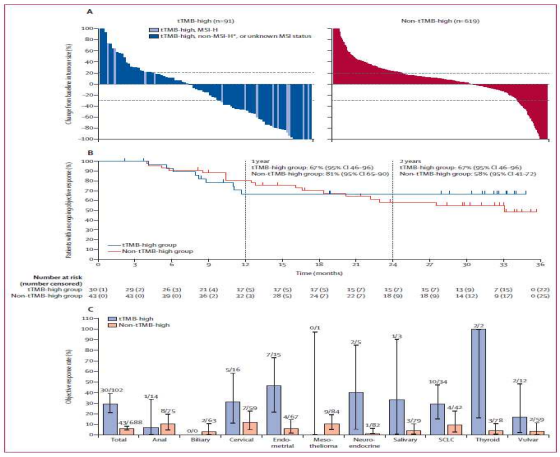
Marabelle A, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020

Odgovor na zdravljenje

	tTMB-high (n=102)	tTMB-high (excluding MSI-H; n=81)*	Non-tTMB-high (n=688)
Best response			
Complete response	4 (4%)	3 (4%)	11 (2%)
Partial response	26 (25%)	20 (25%)	32 (5%)
Stable disease	14 (14%)	11 (14%)	227 (33%)
Non-complete response or non-progressive disease†	0	0	3 (<1%)
Progressive disease	48 (47%)	38 (47%)	349 (51%)
Not evaluable‡	1 (1%)	1 (1%)	13 (2%)
Not assessed§	9 (9%)	8 (10%)	53 (8%)
Objective response rate	29% (21–39)	28% (19–40)	6% (5–8)

Data are n (%) or % (95% CI). MSI-H=high microsatellite instability. RECIST=Response Evaluation Criteria in Solid Tumors. tTMB-high=high tissue tumour mutational burden. *Excludes 14 patients who were MSI-high and seven additional patients who had missing MSI status. †Patients without measurable disease per central review at baseline who did not have a complete response or progressive disease. ‡Patients who did not have a post-baseline imaging assessment evaluable for response. §Patients who did not have post-baseline imaging.

Table 2: **Objective response (per RECIST version 1.1), assessed by independent central review in the efficacy population**



Marabelle A, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020

PFS in OS

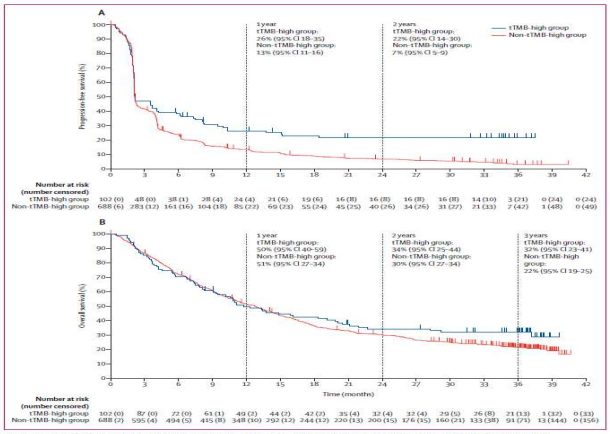


Figure 2: Progression-free survival per RECIST (version 1.1) by independent central review (A) and overall survival (B) in the efficacy population
Vertical lines on each curve denote censored patients. RECIST=Response Evaluation Criteria in Solid Tumors. tTMB-high=high tissue tumour mutational burden.

Marabelle A, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020

TMB 10 ≥ mut/Mb:

- Junij 2020 FDA: indikacija za pembrolizumab za zdravljenje odraslih in pediatričnih bolnikov z neresektabilnimi ali metastatskimi solidnimi raki v primeru “TMB-high” (≥10 mut/Mb), po predhodnem progresu na prvo zdravljenje brez možnosti nadaljnje učinkovite terapije

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

EDITORIAL

The FDA approval of pembrolizumab for patients with TMB >10 mut/Mb: was it a wise decision? No

There are 12 reasons why the US FDA's approval of pembrolizumab for patients with ≥10 mutations/megabase (mut/Mb) progressing on one prior line without satisfactory alternatives is an unwise decision.

associated with a 46% RR[9] for PD-1/PD-L1 drugs. Lowering the cut off to 10 mut/Mb means a lower RR, but more prescriptions.

5. *Overall survival was longer in the TMB-low cohort, i.e.*

Prednosti in slabosti biomarkerjev v imunoterapiji z zaviralci imunskih kontrolnih točk

Table 5. Some advantages and disadvantages of the most widely investigated biomarkers for predicting response to ICI.

Assay	Advantages	Disadvantages
PD-L1	Easy and cheap to assay, widely available, can be automated	Multiple assays exist, different assays used in different settings, lack of assay standardization, optimum cutoff point is unknown and may vary depending on type of therapy and tumor type being treated, relative importance of tumor cell vs stromal staining unclear and may vary depending on tumor type, accuracy for predicting response to ICI appears to depend on tumor type
MSI-H/dMMR	Can be used in all solid tumor types. Two types of assay already in clinical use (PCR for determining MSI status and IHC for determining dMMR)	Overall, MSI-H/dMMR is relatively rare in tumors (≤5%). It is especially rare in cancers such as melanoma, breast, and NSCLCs. Best method for determining MSI status is unclear
TMB	Applicable to most solid tumors and multiple ICIs, potentially can be measured in blood, allows the simultaneous detection of other potential predictive biomarkers (e.g., KRAS for predicting lack of benefit from anti-EGFR antibodies in CRC)	Expensive and time-consuming (especially WES), slow turnaround time for results, optimum cutoff point not established and may vary depending on tumor type, optimum panel of genes to be tested is unknown, requires high quality DNA, which may not always be possible

Duffy MJ, et al. Biomarkers for Predicting Response to Immunotherapy with Immune Checkpoint Inhibitors in Cancer Patients. Clinical Chemistry,2019

Potencialni biomarkerji v imunoterapiji z zaviralci imunskih kontrolnih točk

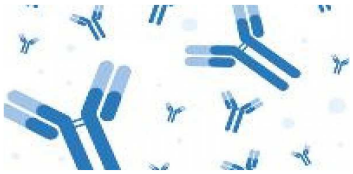
Table 4. Emerging biomarkers for predicting response, resistance, toxicity, and hyperprogression associated with administration of checkpoint inhibitors.

Biomarker	End point	Cancer	Reference number
CD8+ T cells[a]	Response	Melanoma	(69)
Specific gene signatures	Response	Melanoma, NSCLC	(65, 70)[b]
Interferon-γ	Response	Melanoma	(71)
PD-L1 amplification	Response	Multiple	(72)
Gut microbiome	Response or resistance[c]	Melanoma	(73)
IDO1[d]	Resistance	NSCLC, melanoma	(74)
JAK mutations	Resistance	Multiple	(75)
Cytox score[e]	Toxicity	Melanoma	(66)
MDM2/MDM4, EGFR mutations	Hyperprogression	Multiple	(67)

[a] Located at invasive tumor margin.
[b] Reference 70 relates to an IFN-γ-related mRNA profile, whereas reference 65 relates to immunopredictive score (IMPRES).
[c] Increased abundance of bacteria of the *Ruminococcaceae* family was associated with response, whereas a high relative abundance of the Bacteroidales order correlated with resistance.
[d] IDO1, indoleamine 2, 3-dioxygenase.
[e] Measures the concentration of 11 circulating cytokines (G-CSF, GM-CSF, fractalkine, FGF-2, IFNα2, IL12p70, IL1a, IL1B, IL1RA, IL2, and IL13).

Duffy MJ, et al. Biomarkers for Predicting Response to Immunotherapy with Immune Checkpoint Inhibitors in Cancer Patients. Clinical Chemistry,2019

…2020….



Biomarkerji v imunoterapiji z zaviralci imunskih kontrolnih točk:

- Izraženost PD-L1
- Visoka mikrosatelitna nestabilnost- MSI- H
- Tumorsko mutacijsko breme- TMB

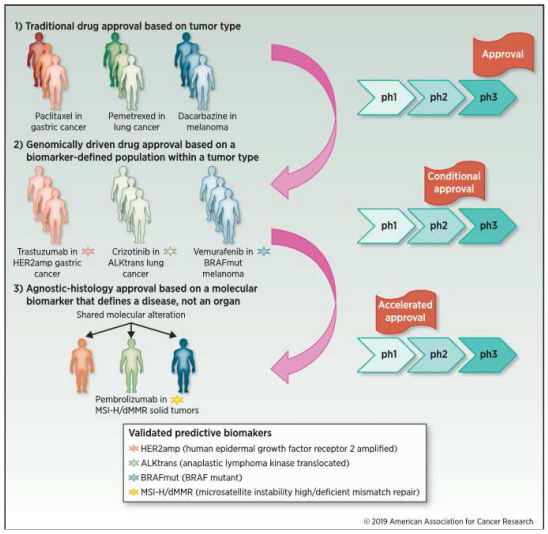
…..v prihodnosti…..celovito imunsko profiliranje tumorjev za razvoj prediktivnih biomarkerjev za usmerjeno individualizirano izbiro vrste in kombinacije imunoterapije pri posameznem bolniku

IMUNOTERAPIJA ZA AGNOSTIČNO ZDRAVLJENJE RAKA

Tanja Ovčariček, dr.med

Novosti v imuno-onkologiji
December 2020

Never mind what or where it is, just look for the target



- Zdravljenje usmerjeno na histologijo in izvor raka-“one fits all“
- Tarčno zdravljenje pri podskupinah določenih vrst raka glede na prisotnost biomarkerja (genomska)
- „basket“ raziskave: agnostično zdravljenje na podlagi molekularnega biomarkerja, ni vezano na izvor raka ali histologijo

FDA-Approved Immune Checkpoint Inhibitor Indications in Solid Tumors

HNSCC
1L: pembro + platinum chemo
1L if PD-L1 CPS ≥ 1: pembro
2L+ after platinum chemo: nivo or pembro

Malignant Melanoma
Adj: ipi, nivo, or pembro
1L+: ipi, nivo ± ipi, or pembro

Merkel Cell Carcinoma
1L+: avelumab
2L+: pembro

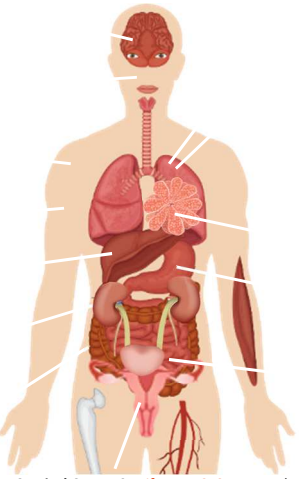
Cutaneous SCC
1L: cemiplimab-rwlc
1L+: pembro

HCC
2L+ after sorafenib: nivo ± ipi, pembro
1L: atezo + bevacizumab

Advanced RCC
1L: nivo + ipi, pembro + axitinib, avelumab + axitinib
2L+ after antiangiogenic therapy: nivo

MSI-H or dMMR Cancers
1L in CRC: pembro
2L+ in CRC: nivo ± ipi
2L+ in CRC: pembro
2L+ tumor agnostic: pembro

TMB-H Cancers
2L+ tumor agnostic: pembro



Cervical Cancer 2L+ if PD-L1 CPS ≥ 1: pembro
Endometrial 2L+ if *NOT* MSI-H or dMMR: pembro + lenvatinib

SCLC
1L, extensive stage: atezo + carboplatin/etoposide, durva + platinum/etoposide
2L+ after platinum chemo: nivo, pembro

NSCLC
Unresectable stage III after CRT: durva
Metastatic/unresectable stage III if PD-L1 TPS ≥ 1%: pembro
1L if PD-L1 TC ≥ 50% or IC ≥ 10%: atezo
1L nonsqNSCLC: pembro + pemetrexed/platinum; atezo + carboplatin/paclitaxel/bevacizumab or carboplatin/nab-paclitaxel
1L sqNSCLC: pembro + carboplatin/(nab)paclitaxel
1L: nivo + ipi + platinum-doublet chemo
1L if PD-L1 TC ≥ 1%: nivo + ipi
2L+ if PD-L1 TPS ≥ 1%: pembro
2L+: nivo, atezo

TNBC
1L if PD-L1 IC ≥ 1%: atezo + nab-paclitaxel

Gastric, Esophageal, and GEJ Adenocarcinoma
2L+ squamous esophageal if PD-L1 CPS ≥ 10: pembro
2L+ squamous esophageal: nivo
3L+ gastric or GEJ if PD-L1 CPS ≥ 1: pembro

Locally Advanced or Metastatic Urothelial Cancer
1L if ineligible for any platinum: pembro or atezo
1L if PD-L1 CPS ≥ 10 and ineligible for cisplatin chemo: pembro
1L if PD-L1 IC ≥ 5% and ineligible for cisplatin chemo: atezo
Maintenance after 1L platinum chemo: avelumab
After platinum chemo: pembro, atezo, avelumab, durva, or nivo

BCG-unresponsive NMIBC: pembro

Atezolizumab PI. Avelumab PI. Cemiplimab-rwlc PI. Durvalumab PI. Ipilimumab PI. Nivolumab PI. Pembrolizumab PI. PD-L1 IHC 28-8 PharmDx PMA.

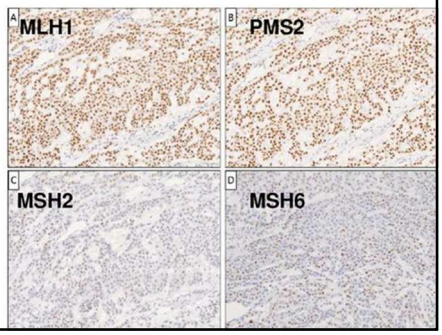
MSI(angl, microsatellite instability)-mikrosatelitna nestabilost je fenomen, za katerega so značilne majhne delecije ali insercije v kratkih ponavljajočih se zaporedjih v tumorski DNA

MMR (angl, missmatch repair genes): geni, ki kodirajo proteine za popravljanje neujemanja DNA

- MSI-H fenotip: Stanje genetske hipermutabilnosti-nagnjenost k nabiranju mutacij
- MSI-H fenotip nastane zaradi napak v genih, ki kodirajo proteine za popravljanje neujemanja DNA (MMR), gre za dMMR
- Najpogostejše različice v MMR genih nastanejo zaradi:

1. Mutacije v genih MLH1, MSH2,3,6, PMS2
2. Hipermetilacija promotorja MLH1
3. Epigenetsko utišanje MSH2
4. Utišanje genov vključenih v popravljalne mehanizme (MMR) z miRNA

- Status MMR določamo IHK, MSI pa z NGS/PCR metodo

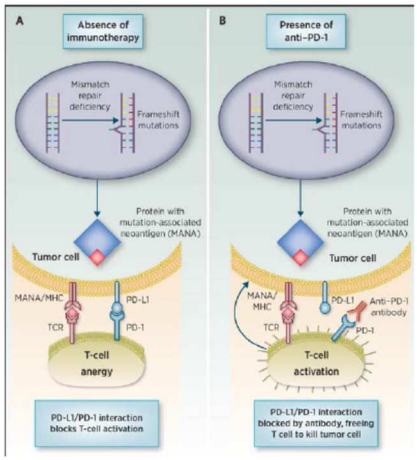


Hipoteza:tu z dMMR in MSI-H so bolj imunogeni in pričakovana večja dobrobit zdravljenja s PD-1/PD-L1 i

1. Tu z napakami v MMR imajo 10-100 več mutacij, večja izpostavitev neoantigenov na površini rakaste celice, večja vzdraženost imunskega sistema

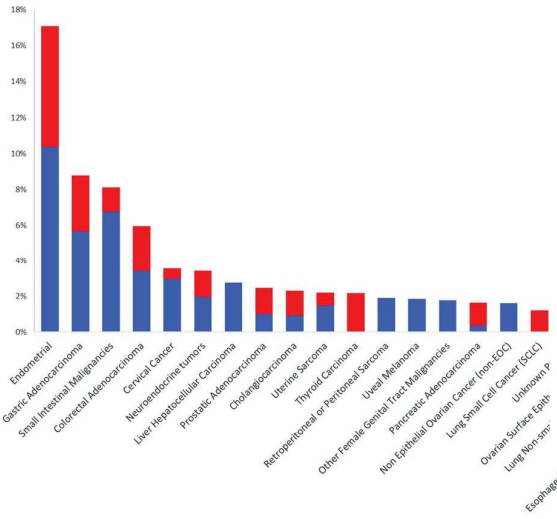
2. dMMR tu celice: visoka ekspresija PD-L1

3. Običajno v teh tumorjih dokazana visoka infiltracija s TIL: visoka ekspresija PD1, CTLA4 in Lag3



Dudley JC, Clin Cancer Res 2016

Pogostost dMMR (12009 vzorcev)



MSI-H Among Tumor Types:

Table 1. Cancers with an MSI-H frequency greater than 10%

Tumor type	Frequency, % (*n*)	Study
Colorectal cancer	13% (1066)	Hampel et al. (72)
Endometrial	22% (543), 33% (446)	Zighelboim et al. (73), Hampel et al. (74)
Gastric	22% (295)	TCGA (75)
Hepatocellular carcinoma	16% (37)[a]	Chiappini et al. (76)
Ampullary carcinoma	10% (144)	Ruemmele et al. (77)
Thyroid	63% (30)[a]	Mitmaker et al. (78)
Skin (sebaceous tumors)	35% (20)[a], 60% (25)[a]	Cesinaro et al. (79), Kruse et al (80)
Skin (melanoma)	11% (56)[a]	Palmieri et al. (81)

Lee et al. The Oncologist 2016;21:1200–1211

Dung T. Le et al. Science 2017

KEYNOTE-016: potrditev hipoteze-pembrolizumab učinkovit za zdravljenje dMMR rakov

The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Dung T. Le, M.D., Jennifer N. Uram, Ph.D., Hao Wang, Ph.D., Bjarne R. Bartlett, B.S., Holly Kemberling, R.N., Aleksandra D. Eyring, M.Pharm., Andrew D. Skora, Ph.D., Brandon S. Luber, Sc.M., Nilofer S. Azad, M.D., Dan Laheru, M.D., Barbara Biedrzycki, Ph.D., C.N.R.P., Ross C. Donehower, M.D., Atif Zaheer, M.D., George A. Fisher, M.D., Ph.D., Todd S. Crocenzi, M.D., James J. Lee, M.D., Ph.D., Steven M. Duffy, M.D., Richard M. Goldberg, M.D., Albert de la Chapelle, M.D., Ph.D., Minori Koshiji, M.D., Ph.D., Feriyl Bhaijee, M.D., Thomas Huebner, M.D., Ralph H. Hruban, M.D., Laura D. Wood, M.D., Ph.D., Nathan Cuka, M.D., Drew M. Pardoll, M.D., Ph.D., Nickolas Papadopoulos, Ph.D., Kenneth W. Kinzler, Ph.D., Shibin Zhou, M.D., Ph.D., Toby C. Cornish, M.D., Ph.D., Janis M. Taube, M.D., Robert A. Anders, M.D., Ph.D., James R. Eshleman, M.D., Ph.D., Bert Vogelstein, M.D., and Luis A. Diaz, Jr., M.D.

May 30, 2015 | DOI: 10.1056/NEJMoa1500596

KEYNOTE-016

- 41 bolnikov : 3 kohorte
- Pembrolizumab 10 mg/kg na 2 tedna
- Primarni cilj: ORR, iPFS

Le DT et al. N Engl J Med 2015

Table 1. Demographic and Baseline Characteristics of the Patients.*

Characteristic	Mismatch Repair–Deficient Colorectal Cancer (N=11)	Mismatch Repair–Proficient Colorectal Cancer (N=21)	Mismatch Repair–Deficient Noncolorectal Cancer (N=9)	P Value†
Median age (range) — yr	46 (24–65)	61 (32–79)	57 (34–92)	0.02
Sex — no. (%)				0.72
Female	5 (45)	8 (38)	4 (44)	
Male	6 (55)	13 (62)	5 (56)	
Race — no. (%)‡				0.66
White	8 (73)	17 (81)	8 (89)	
Black	1 (9)	3 (14)	0	
Other	2 (18)	1 (5)	1 (11)	
ECOG performance status — no. (%)§				0.07
0	0	6 (29)	2 (22)	
1	11 (100)	15 (71)	7 (78)	
Cancer type — no. (%)				>0.99
Colon	9 (82)	18 (86)	0	
Rectal	2 (18)	3 (14)	0	
Ampullary or cholangiocarcinoma	0	NA	4 (44)	
Endometrial	0	NA	2 (22)	
Small bowel	0	NA	2 (22)	
Gastric	0	NA	1 (11)	
Histologic grade — no. (%)				0.20
Well or moderately differentiated	7 (64)	18 (86)	4 (44)	
Poorly differentiated	4 (36)	3 (14)	3 (33)	
Other	0	0	2 (22)	
Stage IV cancer — no. (%)	11(100)	21 (100)	9 (100)	>0.99
Liver metastases — no. (%)	6 (55)	11 (52)	6 (67)	>0.99
Median time since initial diagnosis (range) — mo	31 (6–95)	58 (27–192)	23 (2–105)	0.07
Previous therapies — no. (%)				0.89
1	0	0	1 (11)	
2	3 (27)	4 (19)	5 (56)	
3	3 (27)	5 (24)	1 (11)	
>4	5 (45)	12 (57)	2 (22)	
Detected germline mutation or known Lynch syndrome — no. (%)				<0.001
Yes	9 (82)	0	4 (44)	
No	2 (18)	21 (100)	4 (44)	
Unknown	0	0	1 (11)	
BRAF wild type — no. (%)				0.64
Yes	8 (73)	11 (52)	4 (44)	
No	0	1 (5)	0	
Unknown	3 (27)	9 (43)	5 (56)	
KRAS wild type — no. (%)				0.72
Yes	6 (55)	13 (62)	4 (44)	
No	5 (45)	8 (38)	1 (11)	
Unknown	0	0	4 (44)	

* NA denotes not applicable.
† P values are for the comparison between the cohort with mismatch repair–deficient colorectal cancer and the cohort with mismatch repair–proficient colorectal cancer.
‡ Race was self-reported.
§ Eastern Cooperative Oncology Group (ECOG) performance status is a measure of a patient's ability to perform activities of daily living; values range from 0 to 5, with higher scores indicating greater impairment.

KEYNOTE-016: ORR

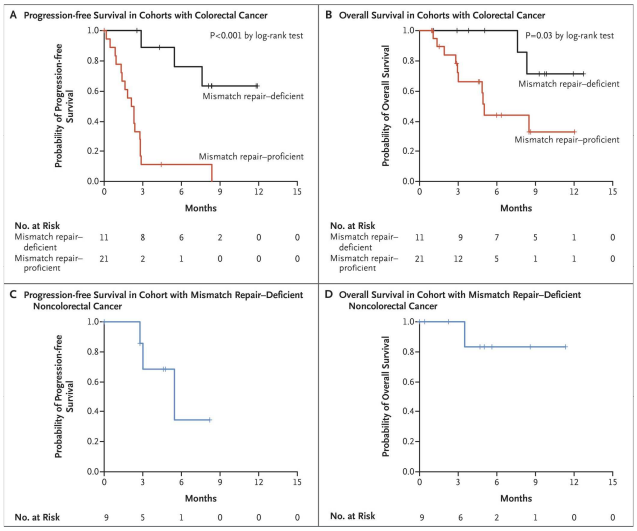
Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.
† One patient had a partial response at 12 weeks.
‡ Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.
§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.
¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.

Le DT et al. N Engl J Med 2015

KEYNOTE-016: PFS/OS



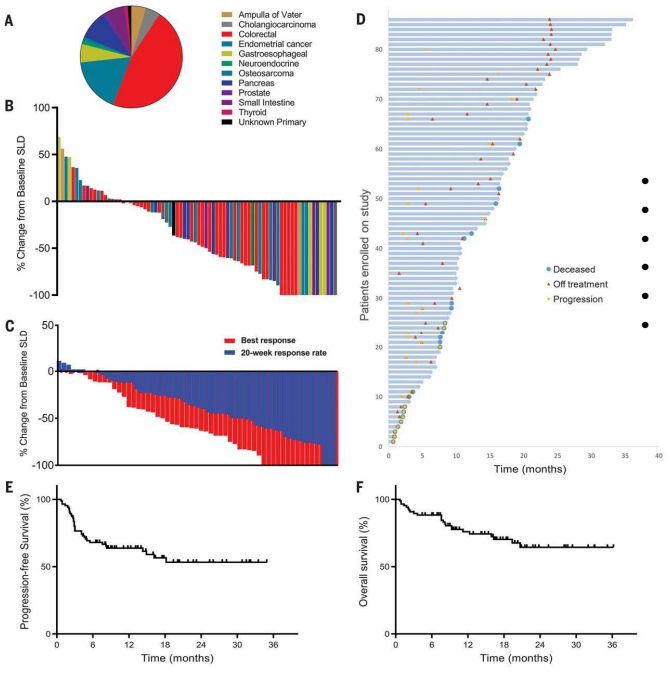
Le DT et al. N Engl J Med 2015

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

by Dung T. Le, Jennifer N. Durham, Kellie N. Smith, Hao Wang, Bjarne R. Bartlett, Laveet K. Aulakh, Steve Lu, Holly Kemberling, Cara Wilt, Brandon S. Luber, Fay Wong, Nilofer S. Azad, Agnieszka A. Rucki, Dan Laheru, Ross Donehower, Atif Zaheer, George A. Fisher, Todd S. Crocenzi, James J. Lee, Tim F. Greten, Austin G. Duffy, Kristen K. Ciombor, Aleksandra D. Eyring, Bao H. Lam, Andrew Joe, S. Peter Kang, Matthias Holdhoff, Ludmila Danilova, Leslie Cope, Christian Meyer, Shibin Zhou, Richard M. Goldberg, Deborah K. Armstrong, Katherine M. Bever, Amanda N. Fader, Janis Taube, Franck Housseau, David Spetzler, Nianqing Xiao, Drew M. Pardoll, Nickolas Papadopoulos, Kenneth W. Kinzler, James R. Eshleman, Bert Vogelstein, Robert A. Anders, and Luis A. Diaz

Science
Volume 357(6349):409-413
July 28, 2017

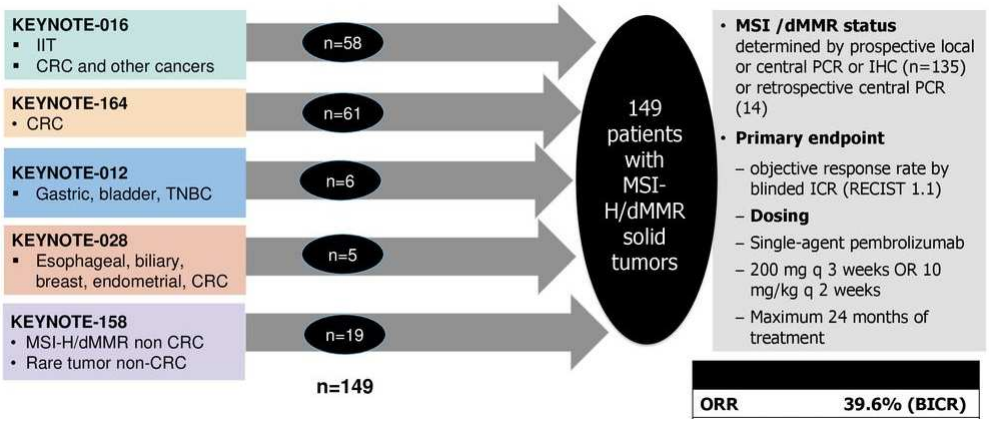
86 bolnikov, 12 različnih solidnih rakov dMMR



- ORR: 53%
- CR: 21%
- Klinični učinek (SD+PR+CR):77%
- 24 msc- PFS: 53%
- 24 msc -OS: 64%
- 11 bolnikov s CR po 2 letih zdravljenje prekinjeno, brez progresa (mFU 8.3 msc)

Dung TL, et al. Science 2017

2017: FDA odobritev za zdravljenje napredovalega solidnega raka dMMR/MSI-H po progresu na standardno zdravljenje ali če ni drugih alternativ zdravljenja, enaka agnostična odobritev še na Japonskem



Merck Sharp & Dohme: KEYTRUDA (pembrolizumab) full prescribing information. Whitehouse Station, NJ, Merck Sharp & Dohme Corp., 2018

Pooled ORR Results for Patients with MSI-H/dMMR Cancer

	N=149
Objective response rate	
ORR (95% CI)	39.6% (31.7, 47.9)
Complete response rate	7.4%
Partial response rate	32.2%
Response duration	
Median in months (range)	NR (1.6+, 22.7+)
% with duration ≥6 months	78%

		Objective response rate		DOR range
	N	n (%)	95% CI	(months)
CRC	90	32 (36%)	(26%, 46%)	(1.6+, 22.7+)
Non-CRC	59	27 (46%)	(33%, 59%)	(1.9+, 22.1+)

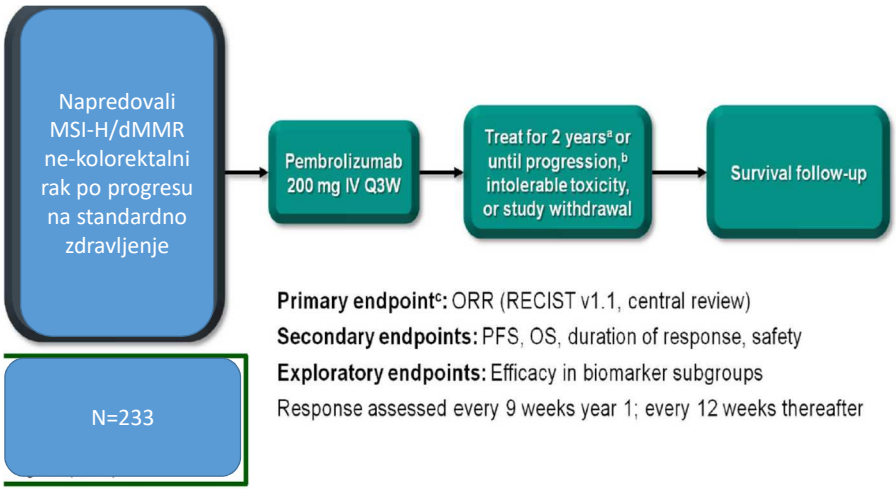
Merck Sharp & Dohme: KEYTRUDA (pembrolizumab) full prescribing information. Whitehouse Station, NJ, Merck Sharp & Dohme Corp., 2018

Keynote-158

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

Aurelien Marabelle, MD, PhD[1]; Dung T. Le, MD[2]; Paolo A. Ascierto, MD[3]; Anna Maria Di Giacomo, MD[4]; Ana De Jesus-Acosta, MD[2]; Jean-Pierre Delord, MD, PhD[5]; Ravit Geva, MD, MSc[6]; Maya Gottfried, MD[7]; Nicolas Penel, MD, PhD[8]; Aaron R. Hansen, MBBS[9]; Sarina A. Piha-Paul, MD[10]; Toshihiko Doi, MD, PhD[11]; Bo Gao, MBBS, PhD[12]; Hyun Cheol Chung, MD, PhD[13]; Jose Lopez-Martin, MD, PhD[14]; Yung-Jue Bang, MD, PhD[15]; Ronnie Shapira Frommer, MD[16]; Manisha Shah, MD[17]; Razi Ghori, PhD[18]; Andrew K. Joe, MD[18]; Scott K. Pruitt, MD, PhD[18]; and Luis A. Diaz Jr, MD[19]

Raziskava KEYNOTE-158: MSI-H/dMMR



Primary endpoint[c]: ORR (RECIST v1.1, central review)
Secondary endpoints: PFS, OS, duration of response, safety
Exploratory endpoints: Efficacy in biomarker subgroups
Response assessed every 9 weeks year 1; every 12 weeks thereafter

Marabelle A, JCO 2020

Raziskava KEYNOTE-158: MSI-H/dMMR

Cancer type of primary diagnosis	
Endometrial	49 (21.0)
Gastric	24 (10.3)
Cholangiocarcinoma	22 (9.4)
Pancreatic	22 (9.4)
Small intestine	19 (8.2)
Ovarian	15 (6.4)
Brain	13 (5.6)
Sarcoma	9 (3.9)
Neuroendocrine tumor	7 (3.0)
Cervical	6 (2.6)
Prostate	6 (2.6)
Adrenocortical	5 (2.1)
Breast	5 (2.1)
Thyroid	5 (2.1)
Urothelial	5 (2.1)
Mesothelioma	4 (1.7)
Small-cell lung cancer	4 (1.7)
Renal	3 (1.3)

TABLE 2. Best Overall Response per RECIST Version 1.1 by Independent Central Radiologic Review

Response	Evaluable Patients (N = 233)
Objective response	
No. (%; 95% CI)	80 (34.3; 28.3 to 40.8)
Median time to response, months (range)*	2.1 (1.3-10.6)
Median duration of response, months† (range)	NR (2.9-31.3+)
Best overall response, No. (%)	
Complete response	23 (9.9)
Partial response	57 (24.5)
Stable disease	42 (18.0)
Progressive disease	92 (39.5)
Nonevaluable	2 (0.9)
No assessment‡	17 (7.3)
Kaplan-Meier estimate of patients with extended duration of response, months†, No. (%)	
≥ 12	58 (86.9)
≥ 18	40 (79.9)
≥ 24	14 (77.6)

- ORR: 34.3%
- mPFS: 4.1 msc
- mOS: 23.5 msc

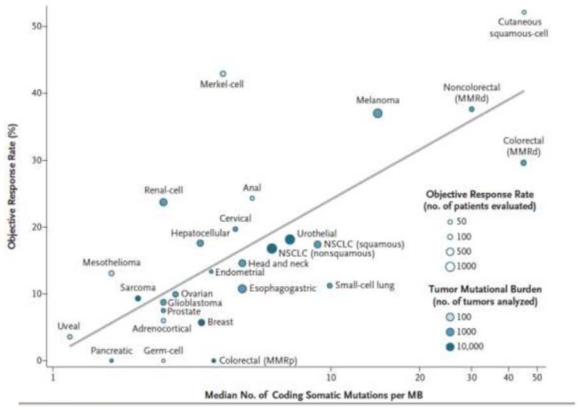
Marabelle A, JCO 2020

TMB: mutacijsko breme tumorja

- TMB meri število somatskih mutacij na kodirajočo enoto- megabazo in predstavlja surogat bremena neoantigenov-bolj imunogene
- Retrospektivne analize prospektivnih raziskav (KEYNOTE-010, 042-NSCLC), metaanaliza, ki je vključila raziskave na 27 različnih tumorjih, so potrdili pozitivno prediktivno vrednost TMB-H za odgovor na terapijo s PD-1 in PD-L1 i

Marcus L, et al. Clin Cancer Res 2019.

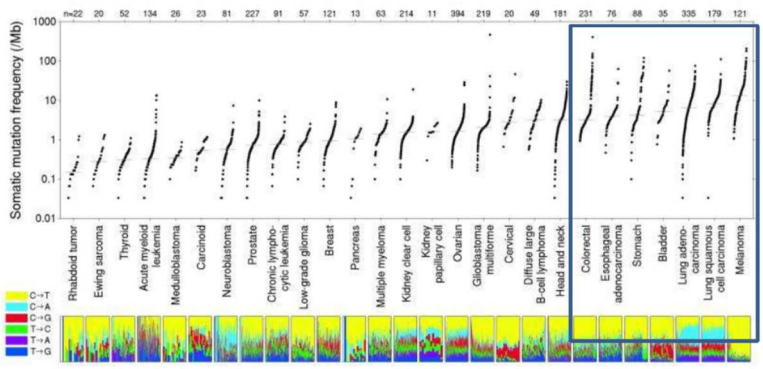
TMB-neodvisni prediktivni biomarker za zdravljenje z PD-1 in PD-L1 inhibitorji (metaanaliza)



Yarchoan M, et al. N Engl J Med 2017

TMB v različnih tumorjih

Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs



Lawrence MS, et al. Nature 2013

KEYNOTE-158-TMB:

Patients
- Unresectable and/or metastatic cancer
- Progression on or intolerance to standard therapy
- ECOG PS 0 or 1
- ≥1 measurable lesion
- Evaluable tumor sample for biomarker assessment

Pembrolizumab 200 mg IV Q3W
for 2 years or until PD, intolerable toxicity, or withdrawal[a]

Biomarker Assessments
- TMB
  - Assessed in FFPE tumor samples (tissue TMB, or tTMB) using the FoundationOne CDx™ assay (version 3.3)
  - TMB-high defined as ≥10 mut/Mb (prespecified[a])
- MSI
  - Determined retrospectively by PCR of 5 mononucleotide loci[b] performed at a central laboratory
  - MSI-H defined as allelic loci size shifts in ≥2 of 5 analyzed loci

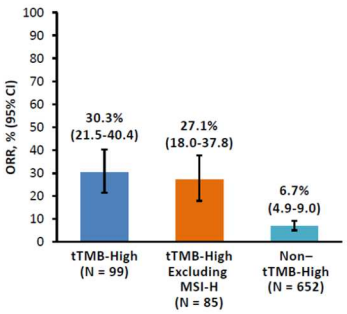
Included cancers
- Cohort A: anal squamous cell carcinoma
- Cohort B: biliary adenocarcinoma
- Cohort C: well or moderately differentiated neuroendocrine tumors
- Cohort D: endometrial carcinoma
- Cohort E: cervical squamous cell carcinoma
- Cohort F: vulvar squamous cell carcinoma
- Cohort G: small-cell lung cancer
- Cohort H: malignant pleural mesothelioma
- Cohort I: papillary or follicular thyroid carcinoma
- Cohort J: salivary gland carcinoma
- Cohort K: MSI-H solid tumors, excluding colorectal cancer (cohort excluded from this analysis)

- 13% bolnikov TMB-H
- ORR.

Protocol-Specified Study End Points
- Primary: ORR assessed per RECIST v1.1 by independent central review
- Secondary: DOR and PFS assessed per RECIST v1.1 by independent central review, OS, safety
- Exploratory: relationship between TMB and efficacy

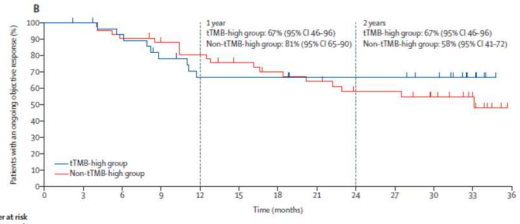
Primarni cilj: ORR, sekundarni cilj: DoR

TMB-H dober prediktivni faktor za odgovor na pembrolizumab ne glede na vrsto raka, PD-L1 in MSI status



Best Response	tTMB-High N = 99	tTMB-High Excl. MSI-H N = 85	Non–tTMB-High N = 652
CR	4.0%	3.5%	1.7%
PR	26.3%	23.5%	5.1%
SD	14.1%	15.3%	33.6%
Non-CR/ non-PD	0%	0%	0.5%
PD	46.5%	48.2%	50.3%
Not evaluable[a]	0%	0%	2.3%
Not assessed[b]	9.1%	9.4%	6.6%

	Safety population (n=105)*	Efficacy population	
		tTMB-high group (n=102)	Non-tTMB-high group (n=688)
(Continued from previous column)			
Tumour types§			
Anal	14 (13%)	14 (14%)	75 (11%)
Biliary	0	0	63 (9%)
Cervical	16 (15%)	16 (16%)	59 (9%)
Endometrial	15 (14%)	15 (15%)	67 (10%)
Mesothelioma	1 (1%)	1 (1%)	84 (12%)
Neuroendocrine	5 (5%)	5 (5%)	82 (12%)
Salivary	3 (3%)	3 (3%)	79 (11%)
Small-cell lung	34 (32%)	34 (33%)	42 (6%)
Thyroid	2 (2%)	2 (2%)	78 (11%)
Vulvar	15 (14%)	12 (12%)	59 (9%)

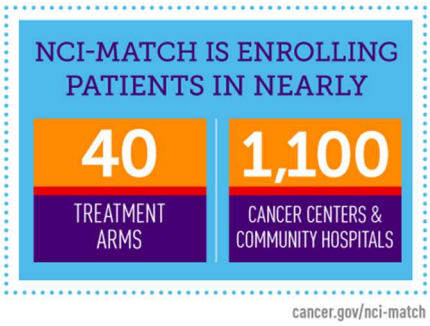


- mFU:33 msc
- mDoR TMB-H: NR
- mDoR non-TMB-H: 33.1 msc

Marabelle A, et al. Lancet 2020

Junij 2020: pembrolizumab odobritev FDA za zdravljenje napredovalih solidnih rakov z visokim TMB (TMB-H≥10, FoundationOneDx) po progresu na standardno zdravljenje in brez alternativnih možnosti zdravljenja

Velika raziskava-basket trial: NCI-MATCH trial: Molecular Analysis for Therapy Choice



Protokol Z1D: nivolumab pri pretretiranih nekolorektalnih tumorjih dMMR (tu brez FDA odobritve za nivolumab): 4900 bolnikov IHC za MLH1 in MSH2 (2%), vključenih 42 bolnikov

TABLE 1. Tumor Histologies of the 42 Evaluable Patients

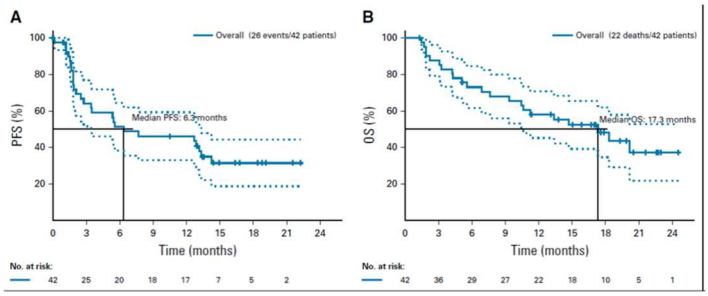
Histology	No. of Patients
Endometrioid endometrial adenocarcinoma	7
Endometrioid endometrial adenocarcinoma variants*	6
Adenocarcinoma of prostate†	5
Uterine carcinosarcoma/malignant mixed Müllerian tumor	4
Adenocarcinoma of esophagus/esophagogastric junction	3
Cholangiocarcinoma‡	3
Ductal carcinoma of breast	3
Pancreatic neuroendocrine carcinoma	1
Other§	10

Konkordanca dMMR in NGS za MSI-H=89%

Azad NS. JCO 2020

NCI-MATCH trial-Z1D: nivolumab

- ORR: 36%
- CR: 7%



Azad NS. JCO 2020

ZAKLJUČEK

- Tumor agnostično zdravljenje usmerjeno na molekularni biomarker in ne histologijo oziroma izvor raka
- dMMR/MSI-H/TMB-H so prediktivni biomarkerji za odgovor na PD-1 inhibitorje-agnostično zdravljenje
- FDA odobrila zdravljenje s pembrolizumabom za solidne rake dMMR/MSI-H/TMB-H, po progresu na standardno zdravljenje

Zdravilo Alunbrig se uporablja kot monoterapija za zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim pljučnim rakom (NSCLC – non small cell lung cancer), pozitivnim na anaplastično limfomsko kinazo (ALK), ki še niso bili zdravljeni z inhibitorjem ALK. [1]

SKRAJŠANI POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Pred predpisovanjem preberite celoten povzetek glavnih značilnosti zdravila (SmPC).

Ime zdravila: ALUNBRIG 30 mg filmsko obložene tablete; ALUNBRIG 90 mg filmsko obložene tablete; ALUNBRIG 180 mg filmsko obložene tablete

Kakovostna in količinska sestava: ALUNBRIG 30 mg filmsko obložene tablete. Ena filmsko obložena tableta vsebuje 30 mg brigatiniba. ALUNBRIG 90 mg filmsko obložene tablete. Ena filmsko obložena tableta vsebuje 30 mg brigatiniba. ALUNBRIG 180 mg filmsko obložene tablete. Ena filmsko obložena tableta vsebuje 30 mg brigatiniba.Indikacije: Zdravilo Alunbrig se uporablja kot monoterapija za zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim pljučnim rakom (NSCLC – non small cell lung cancer), pozitivnim na anaplastično limfomsko kinazo (ALK), ki še niso bili zdravljeni z inhibitorjem ALK. Zdravilo Alunbrig se uporablja kot monoterapija za zdravljenje odraslih bolnikov z napredovalim NSCLC pozitivnim na ALK, ki so bili predhodno zdravljeni z zdravilom krizotinib. Odmerjanje/način uporabe: Priporočeni začetni odmerek je 90 mg enkrat na dan prvih 7 dni, nato pa 180 mg enkrat na dan. Če se jemanje zdravila Alunbrig prekine za 14 dni ali dlje iz drugega razloga kot so neželeni učinki, je treba zdravljenje nadaljevati z odmerkom 90 mg enkrat na dan za obdobje 7 dni, preden se odmerek poveča na predhodno toleriran odmerek. Če odmerek ni bil zaužit ali se je po zaužitju pojavilo bruhanje, se dodatnega odmerka ne sme zaužiti in je potrebno naslednji odmerek zaužiti ob predhodno načrtovanem času. Prilagoditve odmerka: Huda okvara jeter: priporočljiv zmanjšan začetni odmerek 60 mg enkrat na dan v prvih 7 dneh, ter nato 120 mg enkrat na dan. Huda okvara ledvic: priporočljiv zmanjšan začetni odmerek 60 mg enkrat na dan v prvih 7 dneh, ter nato 90 mg enkrat na dan. Starejši: odmerka ni treba prilagajati. Kontraindikacije: Preobčutljivost na učinkovino ali katero koli pomožno snov. Posebna opozorila in previdnostni ukrepi (pri uporabi brigatiniba): Neželeni učinki na pljuča Pri bolnikih lahko pride do hudih, življenjsko nevarnih in smrtnih neželenih učinkov na pljučih, vključno z značilnostmi, ki so enake kot pri IPB/pnevmonitisu. Večina neželenih učinkov na pljuča je bila opažena v prvih 7 dneh zdravljenja. Neželeni učinki na pljuča stopnje 1-2 so bili odpravljeni s prekinitvijo zdravljenja ali spremembo odmerka. Višja starost in kratek interval (manj kot 7 dni) med zadnjim odmerkom krizotiniba in prvim odmerkom zdravila Alunbrig sta bila neodvisno povezana s povečano stopnjo teh neželenih učinkov na pljuča. Nekateri bolniki so zaradi pnevmonitisa zboleli kasneje med zdravljenjem z zdravilom Alunbrig. Bolnike je zlasti v prvem tednu zdravljenja treba skrbno spremljati zaradi novih ali poslabšanih simptomov dihal (npr. dispneja, kašelj itd.). Bolnike, pri katerih so se pojavili znaki pnevmonitisa s poslabšanimi simptomi bolezni dihal, je treba nemudoma pregledati. Če sumite na pnevmonitis, je treba odmerjanje zdravila Alunbrig začasno prekiniti, bolnika pa oceniti glede morebitnih drugih vzrokov simptomov (npr. pljučna embolija, napredovanje tumorja, infekcijska pljučnica). Odmerek je treba ustrezno spremeniti. Hipertenzija: treba je redno nadzorovati krvni tlak. Bradikardija: Redno je treba spremljati srčni utrip in krvni tlak. Motnje vida: Bolnikom je treba svetovati, naj poročajo o kakršnih koli simptomih motenj vida. Zvišanje kreatin fosfokinaze (CPK): Bolnikom je treba svetovati, naj poročajo o kakršnih koli nepojasnjenih bolečinah v mišicah, občutljivosti ali šibkosti mišic. Zvišanje encimov trebušne slinavke: treba je redno nadzorovati koncentracijo amilaze in lipaze. Hepatotoksičnost: pojavilo se je zvišanja jetrnih encimov (aspartat-aminotransferaza, alanin-aminotransferaza) in bilirubin. Glede na resnost laboratorijsko odkritih nepravilnosti je treba zdravljenje začasno prekiniti in ustrezno spremeniti odmerek. Medsebojno delovanje zdravil: Izogibati se je treba sočasni uporabi zdravila Alunbrig z močnimi zaviralci CYP3A. Če se sočasni uporabi močnih zaviralcev CYP3A ni mogoče izogniti, je treba odmerek zdravila Alunbrig zmanjšati s 180 mg na 90 mg ali z 90 mg na 60 mg. Po prekinitvi uporabe močnega zaviralca CYP3A je treba zdravljenje z zdravilom Alunbrig nadaljevati z odmerkom, ki ga je bolnik prenašal pred začetkom uporabe močnega zaviralca CYP3A. Izogibati se je treba sočasni uporabi zdravila Alunbrig z močnimi in zmernimi induktorji CYP3A. Plodnost: Ženskam v rodni dobi je treba svetovati, naj med zdravljenjem in vsaj 4 mesece po zadnjem odmerku uporabljajo učinkovito nehormonsko kontracepcijo. Moškim s partnericami v rodni dobi je treba svetovati, naj uporabijo učinkovito kontracepcijo med zdravljenjem in vsaj 3 mesece po zadnjem odmerku zdravila Alunbrig. Laktoza Zdravilo Alunbrig vsebuje laktozo monohidrat. Bolniki z redko dedno intoleranco za galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila.

Medsebojno delovanje z drugimi zdravili in druge oblike interakcij: Učinkovine, ki lahko zvišajo koncentracijo brigatiniba v plazmi: Zaviralci CYP3A brigatinib je substrat CYP3A4/5. Sočasna uporaba večkratnih odmerkov itrakonazola, ki je močan zaviralec CYP3A, je povečala koncentracijo brigatiniba v krvi.Sočasni uporabi močnih zaviralcev CYP3A z zdravilom Alunbrig, vključno z nekaterimi protivirusnimi zdravili (npr. indinavirjem, nelfinavirjem, ritonavirjem, sakvinavirjem), makrolidnimi antibiotiki (npr. klaritromicinom, telitromicinom, troleandomicinom), antimikotiki (npr. ketokonazolom, vorikonazolom), mibefradilom in nefazodonom, se je treba izogibati. Zmerni zaviralci CYP3A (npr. diltiazem in verapamil) lahko povečajo AUC brigatiniba za približno 40%. Pri kombinaciji z zmernimi zaviralci CYP3A prilagajanje odmerka ni potrebno. Grenivka ali sok grenivke lahko prav tako zviša koncentracije brigatiniba v plazmi in se ji je treba izogibati. Zaviralci CYP2C8: brigatinib je substrat CYP2C8. Sočasna uporaba večkratnih odmerkov gemfibrozila, ki je močan zaviralec CYP2C8, je zmanjšala koncentracijo brigatiniba v krvi. Pri sočasnem odmerjanju močnih zaviralcev CYP2C8 prilagajanje odmerka ni potrebno.Zaviralci P-gp in BCRP: Pri sočasni uporabi z zaviralci P-gp in BCRP prilagajanje odmerka zdravila Alunbrig ni potrebno. Učinkovine, ki lahko znižajo koncentracijo brigatiniba v plazmi: Induktorji CYP3:. sočasna uporaba večkratnih odmerkov rifampicina, je zmanjšala koncentracijo brigatiniba v krvi. Treba se je izogibati sočasni uporabi močnih induktorjev CYP3A z zdravilom Alunbrig, vključno z rifampicinom, karbamazepinom, fenitoinom, rifabutinom, fenobarbitalom in šentjanževko. Zmerni induktorji CYP3A lahko zmanjšajo AUC brigatiniba za približno 50%. Izogibati se je treba sočasni uporabi zmernih induktorjev CYP3A z zdravilom Alunbrig, vključno z, vendar ne omejeno na efavirenz, modafinil, bosentan, etravirin in nafcilin. Učinkovine, katerim lahko brigatinib spremeni koncentracijo v plazmi: Substrati CYP3A: brigatinib je induktor CYP3A4. Zmanjša lahko koncentracije v plazmi pri sočasno uporabljenih zdravilih, ki se v glavnem presnavljajo s CYP3A. Zato je treba pri sočasni uporabi zdravila Alunbrig s substrati CYP3A z ozkim terapevtskim indeksom (npr. alfentanilom, fentanilom, kinidinom, ciklosporinom, sirolimusom, takrolimusom) izogibati, ker se lahko zmanjša njihova učinkovitost. Zdravilo Alunbrig lahko inducira tudi druge encime in transporte (npr. CYP2C, P-gp) preko enakih mehanizmov, ki so odgovorni za indukcijo CYP3A (npr. aktivacija pregnanskega X receptorja). Transportni substrati: Sočasna uporaba brigatiniba s substrati P-gp (npr. digoksin, dabigatran, kolhicin, pravastatin), BCRP (npr. metotreksat, rosuvastatin, sulfasalazin), organskim kationskim prenašalcem 1 (OCT1), proteini za ekstruzijo več zdravil in toksinov 1 (Mate1), in 2K (MATE2K) lahko poveča njihovo koncentracijo v plazmi. Bolnike je treba skrbno spremljati, ko je zdravilo Alunbrig sočasno uporabljeno s substrati teh transporterjev z ozkim terapevtskim indeksom (npr. digoksin, dabigatran, metotreksat). Plodnost, nosečnost in dojenje: Ženske v rodni dobi/Kontracepcija za moške in ženske Ženskam v rodni dobi je treba svetovati, naj ne zanosijo in vsaj 4 mesece po zadnjem odmerku uporabijo učinkovito nehormonsko kontracepcijo in moškim, naj med zdravljenjem ne zaplodijo otroka. Moškim s partnericami v rodni dobi je treba svetovati, naj uporabijo učinkovito kontracepcijo med zdravljenjem in vsaj 3 mesece po zadnjem odmerku zdravila Alunbrig. Nosečnost: V primeru jemanja zdravila Alunbrig med nosečnostjo, lahko to povzroči okvaro ploda. Če se zdravilo Alunbrig uporablja med nosečnostjo ali če bolnica zanosi med jemanjem tega zdravila, je treba bolnico seznaniti s potencialno nevarnostjo za plod. Dojenje: Ni znano, ali se zdravilo Alunbrig izloča v materino mleko.Plodnost: Na voljo ni nobenih podatkov o vplivu zdravila Alunbrig na plodnost. Neželeni učinki: Najpogostejši neželeni učinki (≥25%), o katerih so poročali pri bolnikih, ki so se zdravili z zdravilom Alunbrig pri priporočenem režimu odmerjanja, so zvišana AST, hiperglikemija, hiperinsulinemija, anemija, zvišana CPK, navzea, povečana lipaza, zmanjšano število limfocitov, povečana ALT, diareja, povečana amilaza, utrujenost, kašelj, glavobol, povečana alkalna fosfataza, hipofosfatemija, zvišana vrednost APTT, izpuščaj, bruhanje, dispneja, hipertenzija, zmanjšano število belih krvnih celic, mialgija in periferna nevropatija. Najpogostejši resni neželeni učinki (≥2%), o katerih so poročali pri bolnikih, zdravljenih z zdravilom Alunbrig pri priporočenem režimu odmerjanja, razen pri učinkih, povezanih z napredovanjem neoplazme, so bili pnevmonitis, pljučnica in dispneja. Za podroben profil neželenih učinkov zdravila Alunbrig in medsebojno delovanje z drugimi zdravili glejte celoten povzetek glavnih značilnosti zdravila. O katerem koli domnevnem neželenem učinku zdravila morate poročati na Javno agencijo Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. Posebna navodila za shranjevanje: Za shranjevanje zdravila niso potrebna posebna navodila. Imetnik dovoljenja za promet z zdravilom: Takeda Pharma A/S, Dybendal Alle 10. 2630 Taastrup, Danska. Datum zadnje revizije besedila: 01. apr. 2020. Datum priprave informacije: april 2020. Režim izdaje zdravila: Rp/Spec. Dodatne informacije so na voljo pri: Takeda GmbH, Podružnica Slovenija, Bleiweisova cesta 30, Ljubljana, tel: 059 082 480.

1. Povzetek glavnih značilnosti zdravila ALUNBRIG, www.europa.ema.eu, Datum revizije besedila: 07. sep. 2020.

SAMO ZA STROKOVNO JAVNOST
C-APROM/SI/BRI/0005 Datum priprave: oktober 2020

Takeda GmbH, Podružnica Slovenija
Bleiweisova cesta 30, 1000 Ljubljana, Slovenija
tel.: + 386 (0) 59082480
www.takeda.com

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Novosti pri pljučnem raku 2020

Letni napredek

mag. Mojca Unk, dr. med.
Sektor internistične onkologije
Onkološki inštitut Ljubljana

Novosti v imuno-onkologiji 2020
15.12. - 16.12.2020
Onkološki inštitut Ljubljana

Kaj je novega?

- (Neo)adjuvantno zdravljenje
- Kombinacija imunoterapije z obsevanjem
- Imunoterapija pri razširjeni bolezni

(NEO)ADJUVANTNA IMUNOTERAPIJA

Neoadjuvantna imunoterapija- prvi rezultati

Avtor (klinična raziskava)	NDRP stadij	Neoadjuvantna Io+/- KT	Št cikl.	N	Primarni cilj	Brez op po neoadj (%)	MPR (%)
Forde et al	I-IIIa	nivolumab	2	22	varnost	0	45
Kwiatkovski et al (LCMC3)	Ib-IIIb	atezolizumab	2	101	MPR	11	19
Cascone et al (NEOSTAR)	I-IIIa	nivolumab vs nivolumab/ipilimumab	3*	44	MPR	11	17 vs 33 (ITT) 19 vs 44 (ocenljivi)
Li et al	Ia-IIIb	sintilimab	2	40	varnost	7,5	40,5
Shu et al	Ib-IIIa	atezolizumab+karboplatin+nabpaklitaksel	4	14	MPR	21,4	50
Provencio et al (NADIM)	IIIa	nivolumab+karboplatin+paklitaksel	3	46#	PFS pri 2l	0	83

NDRP- nedrobnocelični rak pljuč; MPR- major pathological response; PFS- čas do napredovanja bolezni; * 3 ciklusi nivolumaba z/brez 1 odmerka ipilimumaba;# preliminarni rezultati za 41 bolnikov

Prirejeno po Uprety et al. Journal of Thoracic Oncology 2020

Neoadjuvantna imunoterapija- potekajoče raziskave

Raziskava	shema	Stadij	N	Faza	Cilj
MK3475-223	Pembro različne sheme→op	I-II	28	1	toksičnost MPR
TOP 1501	Pembro 200mg 2x→op Pembro 200 mg 4x	IB-IIIA	32	2	možnost kirurškega zdravljenja
PRICNEPS	Atezo 1200 mg 1x→op	IB-IIIA (brez N2)	60	2	toksičnost
SAKK 16/14	KTx3→durva 750 mg 2x→op→durva 750 mg 1 leto	IIIA (N2)	68	2	čas brez dogodka (EFS)
IONESCO	Durva 750 mg 3x→op	IB-II	81	2	R0
Columbia University	KT+atezo 1200 mg 4x→op	IB-IIIA	30	2	MPR
KeyNote617	KT+pembro 200 mg/placebo 4x→op→pembro/placebo 13x	II-IIIB	786	3	čas brez dogodka (EFS) preživetje (OS)
CheckMate 816	KT+nivo 360 mg 3x→op vs KT 3x→op	IB-IIIA	350	3	čas brez dogodka (EFS) pCR
ImPower 030	KT+atezo 1200 mg/placebo 4x→op→atezo/placebo 16x	II-IIIB (cT3N2)	374	3	MPR čas brez dogodka (EFS)
AEGEAN	KT+durva 1500 mg/placebo 3x→op→durva/placebo 12x	IIA-IIIB	300	3	MPR

MPR- major pathological response; pCR- pathological complete response; R0- operacija v zdravo

www.clinicaltrials.gov

Adjuvantna imunoterapija- potekajoče raziskave

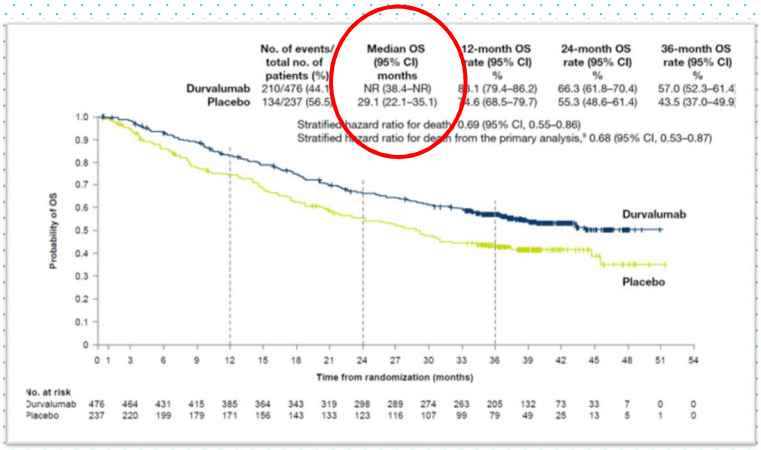
Raziskava	shema	stadij	N	Faza	Cilj
PEARLS	Op+/- KT→pembro vs placebo	Ib-IIIA	1080	3	DFS
BR31	Op +-/ KT→durva vs placebo	Ib-IIIA	1360	3	DFS DFS pri PD-L1+
ANVIL	Op+/- KT→nivo vs opazovanje	Ib-IIIA	903	3	DFS, OS
ImPower 010	Op+KT→atezo vs BSC	Ib-IIIA	1280	3	DFS

DFS- preživetje brez bolezni; OS- celokupno preživetje

www.clinicaltrials.gov

IMUNOTERAPIJA V KOMBINACIJI Z OBSEVANJEM

PACIFIC



Antonia et al., N Eng J Med. 2018; Gray et al. JTO 2019

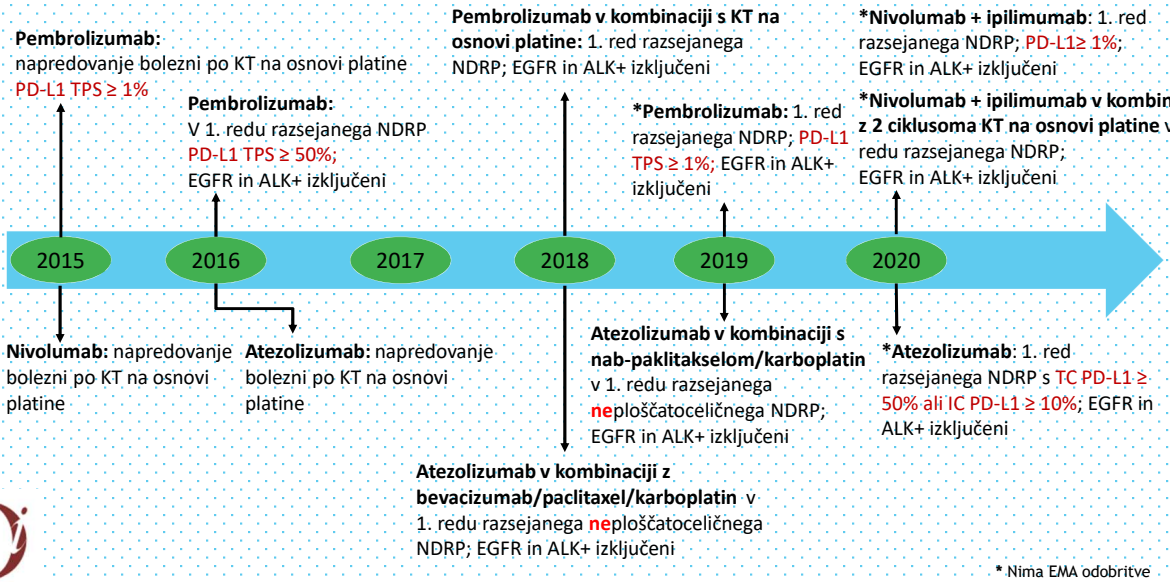
Imunoterapija v kombinaciji z obsevanjem- potekajoče raziskave

Namen	Klinična raziskava	zdravilo	n	faza	shema
Definitivno obsevanje					
	PACIFIC 2	durvalumab	328	3	sočasno IO+KT+RT→adjuvantno IO
	HCRN LUN 14-179	pembrolizumab	93	2	KT-RT→adjuvantno IO
	NICOLAS	nivolumab	78	2	sočasno IO+KT+RT→adjuvantno IO
	NCT03102242	atezolizumab	63	2	indukcijsko IO→KT+RT→adjuvantno IO
Neoadjuvantno obsevanje					
	NCT03237377	durvalumab +/- tremelimumab	32	2	neoad IO+RT→operacija
	NCT03053856	pembrolizumab	37	2	neoad KT+RT→operacija→adjuvantno IO
Adjuvantno obsevanje					
	NCT02572843	durvalumab	68	2	neoadj IO→operacija→RT→adjuvantno IO

www.clinicaltrials.gov

IMUNOTERAPIJA PRI RAZSEJANI BOLEZNI

Pregled ključnih kliničnih raziskav z imunoterapijo pri razsejanem nedrobnoceličnem raku pljuč



* Nima EMA odobritve

2. red zdravljenja: ESMO smernice

- **Nivolumab:** že zdravljen NDRP ploščatocelični podtip in neploščatocelični podtip
- **Pembrolizumab:** že zdravljen NDRP in PD-L1 nad 1%
- **Atezolizumab:** že zdravljen NDRP po enem ali dveh redih zdravljenja

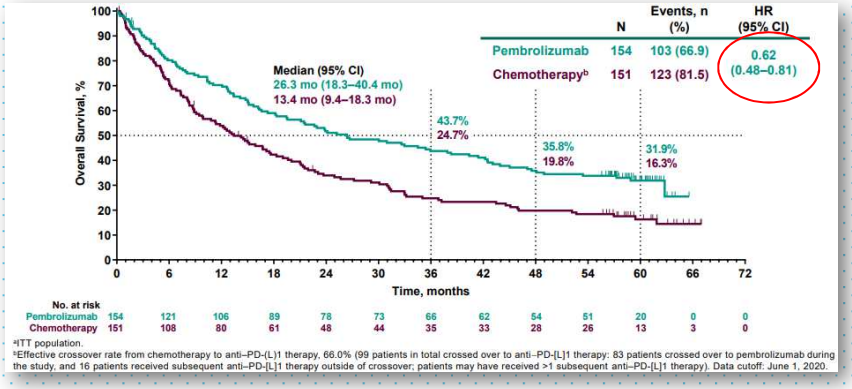
1. red zdravljenja: možnosti

Imunoterapija	Bolniki	Raziskava	Zdravljenje
Monoterapija	NDRP brez EGFR,ALK	KN024; *KN042	Pembrolizumab
		*ImPower110	Atezolizumab
Kombinacija kemoimunoterapija	Neploščatocelični, Brez EGFR,ALK	KN189	Platina+pemetreksed+pembrolizumab
		*ImPower132	Platina+pemetreksed+atezolizumab
	Neploščatotelični, izčrpani TKI pri EGFR, ALK dovoljeni	ImPower130	Karboplatin+nabpaklitaksel+atezolizumab
		ImPower150	Karboplatin+paklitaksel+atezolizumab+bevacizumab
	Ploščatocelični NDRP	KN407	Karboplatin+(nab)paklitaksel+pembrolizumab
Kombinacija imunoterapij	NDRP, brez EGFR,ALK	*CheckMate9LA	Kemoterapija+nivolumab/ipilimumab
		*CheckMate227	Nivolumab/ipilimumab

* Nima EMA odobritve

Pembrolizumab-monoterapija

KeyNote024

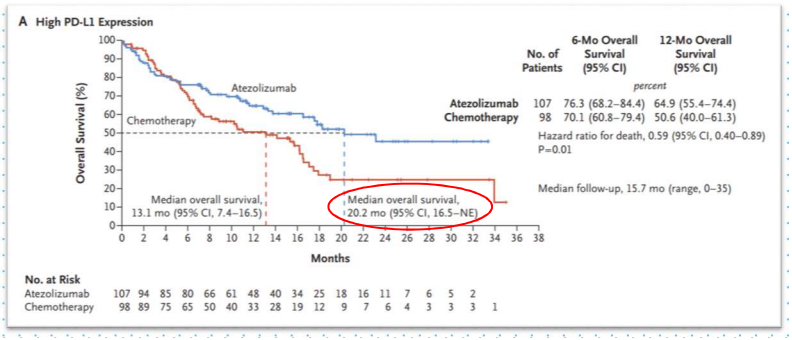


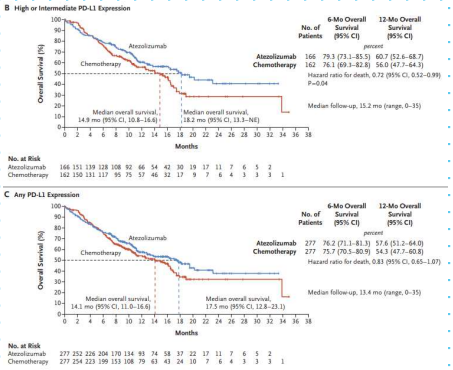
[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

Brahmer et al. ESMO 2020

Atezolizumab monoterapija

ImPower110

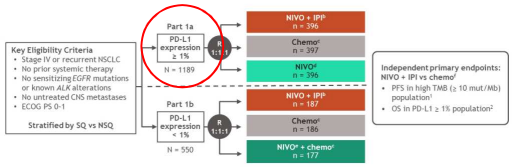


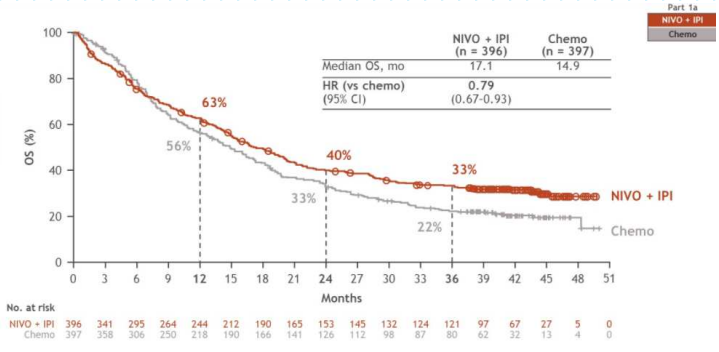


Herbst et al. NEJM 2020

Nivolumab-ipilimumab kombinacija

CheckMate 227: 3-letna posodobitev





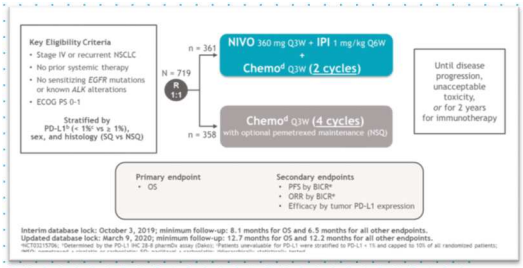
Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Among patients who were alive at 2 years, subsequent systemic therapy was received by 35% in the NIVO + IPI arm and 76% in the chemo arm; subsequent immunotherapies were received by 13% and 71%, respectively, and subsequent chemotherapy was received by 28% and 30%, respectively.

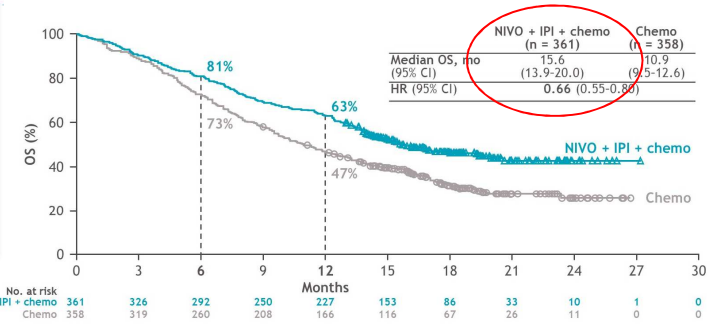
Ramalingam et al. ASCO 2020

Nivolumab-ipilimumab KT kombinacija

Interim analiza:
HR 0,69; p=0,0006

CheckMate 9LA (12-m FU)





Dobrobit:
- Ploščatocelični, neploščatocelični
- Vsi PD-L1

Minimum follow-up: 12.7 months.
[a]Patients remaining in follow-up were censored on the last date they were known to be alive; 47% of patients in the NIVO + IPI + chemo arm and 32% of patients in the chemo arm were censored. Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 40% in the chemo arm; subsequent immunotherapy was received by 5% and 30%, and subsequent chemotherapy by 29% and 22%, respectively. Among patients with BICR-confirmed disease progression on study, subsequent systemic therapy was received by 40% in the NIVO + IPI + chemo arm and 44% in the chemo arm; subsequent immunotherapy was received by 7% and 34%, and subsequent chemotherapy by 38% and 24%, respectively

Reck et al. ASCO 2020

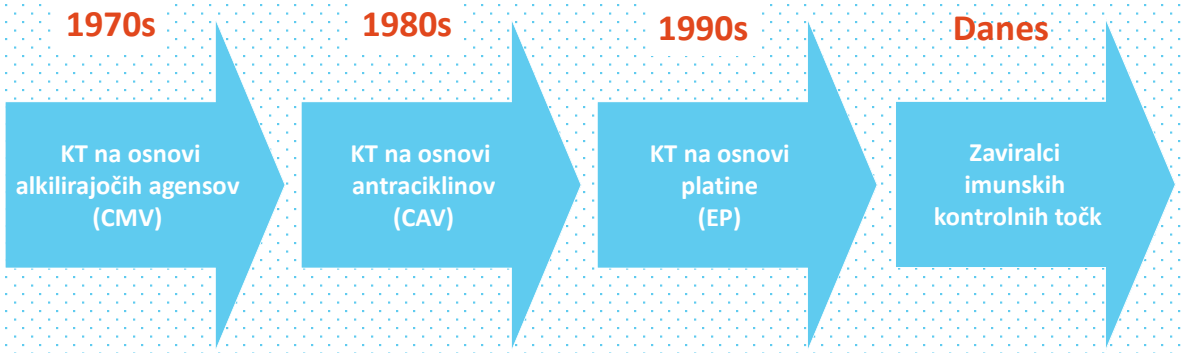
Imunoterapija trenutno predstavlja 1. red zdravljenja večine bolnikov z razsejanim nedrobnoceličnim rakom pljuč.

Pri bolnikih, ki nimajo onkogenih mutacij (EGFR, ALK, ROS1,..) se postavlja glavno vprašanje, ali dodamo kemoterapijo k imunoterapiji ali ne.

Agresivna bolezen,
z veliko bremena;
Simptomatski bolnik

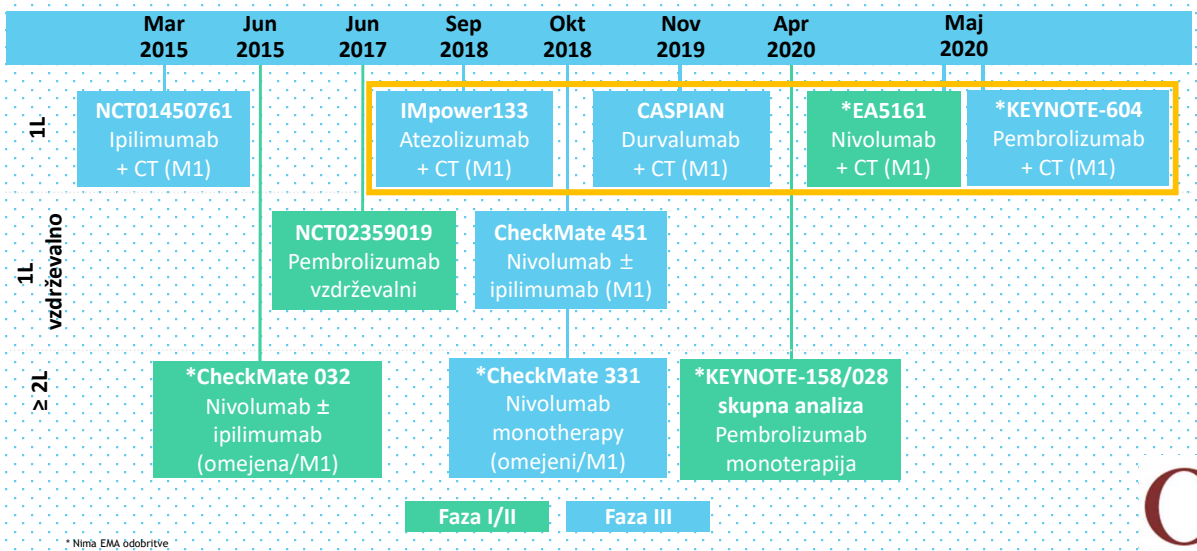
		ORR
	raziskava	PD-L1 ≥ 50 %
monoterapija	KN024	45 %
		PD-L1 ≥ 50 %
kombinacija	KN189 KN407 ImPower150	61 % 60,3 % 69 %

Razvoj sistemske terapije pri drobnoceličnem raku pljuč



Sabari, Nat Rev Clin Oncol. 2017;14:549. Saleh. Immunotherapy. 2019;11:457.

Pregled ključnih kliničnih raziskav z imunoterapijo pri drobnoceličnem raku pljuč

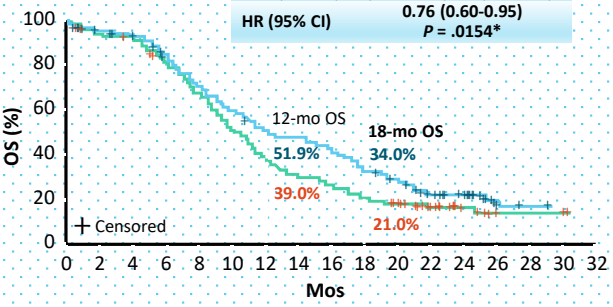


* Nima EMA odobritve

IMpower133 in CASPIAN: preživetje (OS)

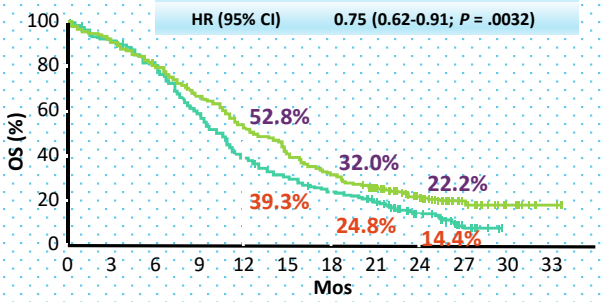
IMpower133: Dodatek atezolizumaba h KT podaljša OS [1]

	Atezolizumab + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mos (95% CI)	12.3 (10.8-15.8)	10.3 (9.3-11.3)
HR (95% CI)	**0.76 (0.60-0.95) *P* = .0154***	



CASPIAN: Dodatek durvalumab h KT podaljša OS [2]

	Durvalumab + EP (n = 268)	EP (n = 269)
Median OS, mos (95% CI)	12.9 (11.3-14.7)	10.5 (9.3-11.2)
HR (95% CI)	**0.75 (0.62-0.91; *P* = .0032)**	

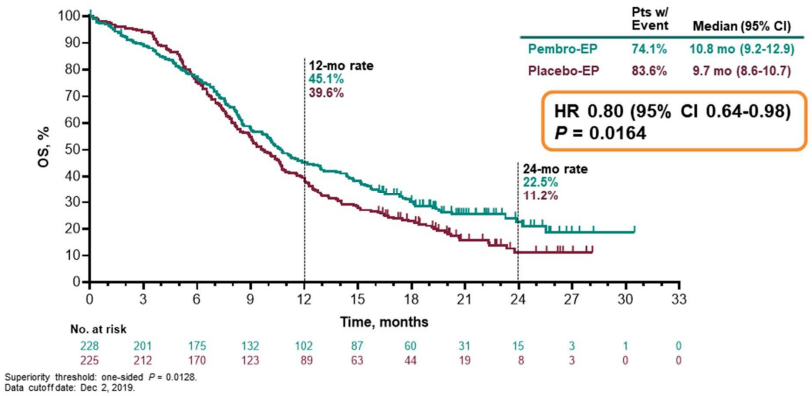


1. Horn. AACR 2020. Abstract 9759. 2. Paz-Ares. ASCO 2020. Abstr 9002.

*Descriptive purposes only. Data cutoff: January 24, 2019.

KeyNote 604

Celokupno preživetje



Superiority threshold: one-sided $P = 0.0128$.
Data cutoff date: Dec 2, 2019.

Rudin et al. ASCO 2020

Zaključek

- Imunoterapija je dramatično spremenila zdravljenje in izhod bolezni nedrobnoceličnega raka pljuč; od zgodnejšega stadija do razsejane bolezni. To ne velja za drobnocelični rak pljuč.
- Razsejana bolezen: imunoterapija v monoterapiji ali v kombinaciji s kemoterapijo
- Prihodnost:
  - Vloga pri „mutiranih“ NDRP
  - Personalizacija zdravljenja z uporabo biomarkerjev
  - Trajanje zdravljenja, ukrepi ob napredovanju bolezni na imunoterapiji
  - Kombinacija z obsevanjem pri lokalno napredovali obliki
  - Rezultati randomiziranih raziskav v neoadjuvantnem obdobju bolezni

Foreign center experience

Maximilian J. Hochmair

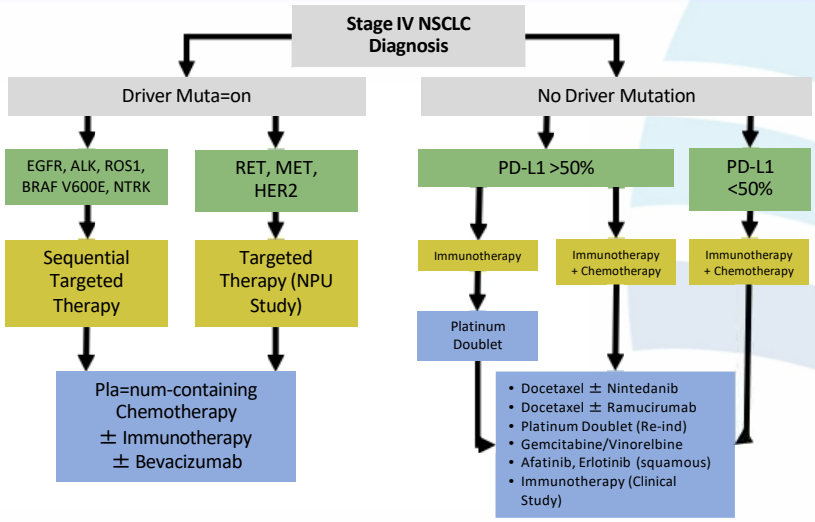
Wiener Gesundheitsverbund
Klinik Floridsdorf

1990‘s: A thoracic oncologist‘s life was simple...

Lung cancer → **Platinum + Etoposide**

→Very few treatment options

Treatment NSCLC



All lungcancer patients are all different

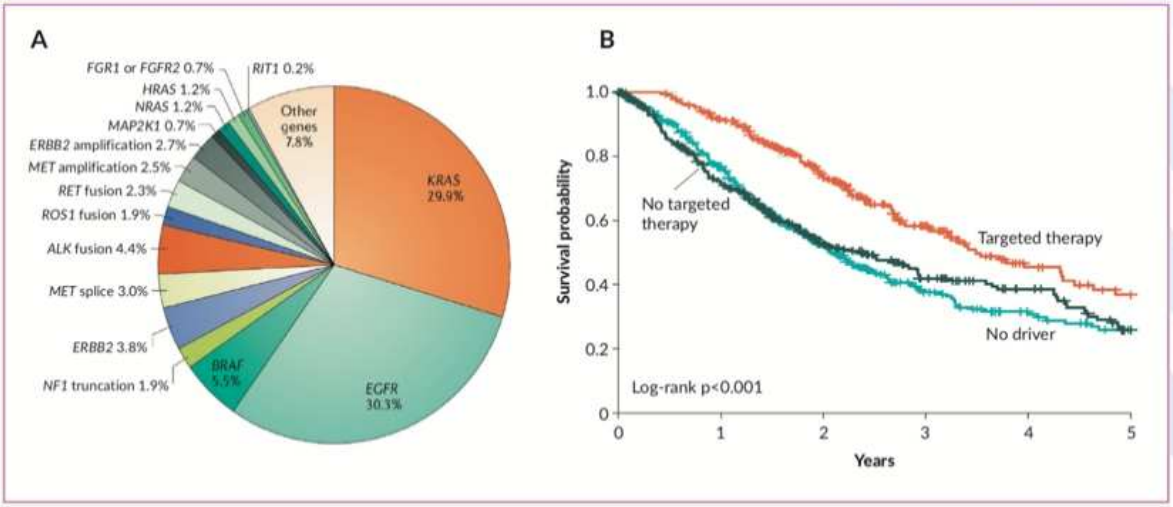
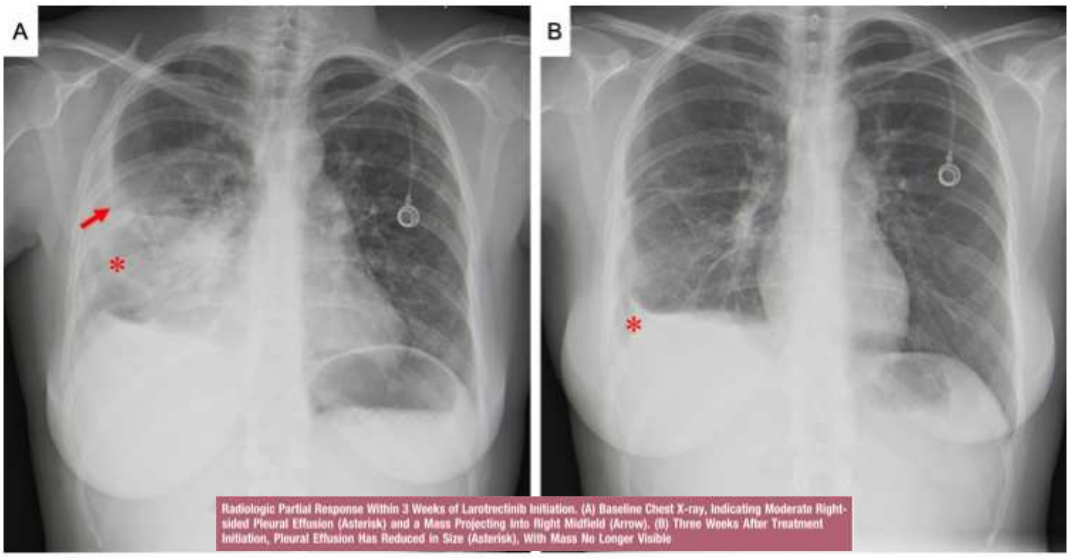


Figure 1. A) Distribution of oncogenic driver mutations in NSCLC (adapted from Skoulidis F et al. 2019[1]); **B) OS targeted versus non-targeted treatment** (adapted from Kris MG et al. 2014[2]); and **C) History of *EGFR*-mutant positive (EGFR M+) NSCLC** (adapted from Rotow J et al. 2017[23]).

Hochmair et al, Review, healthbook TIMES Oncology Hematology 2020

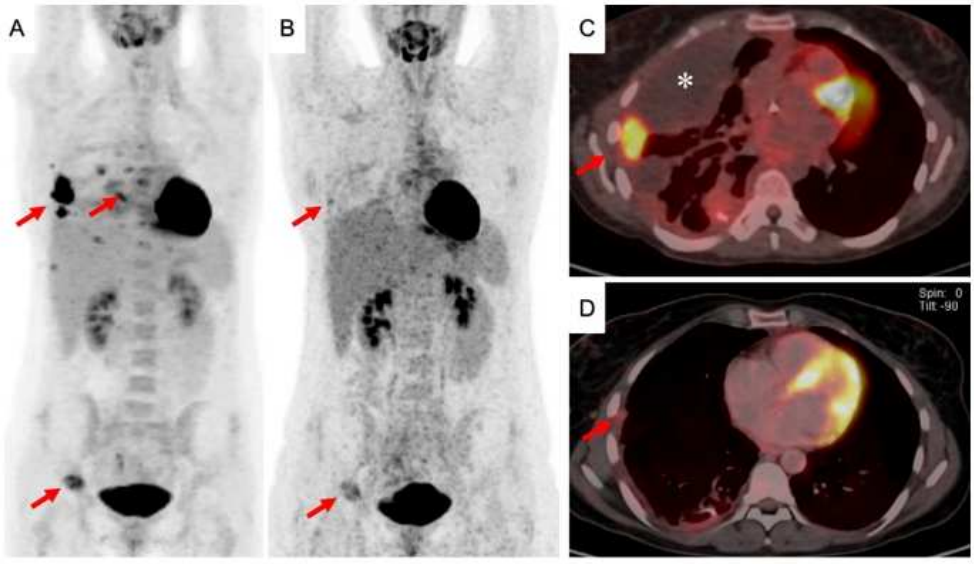
First NTRK pos patient in Austria May 2019



Radiologic Partial Response Within 3 Weeks of Larotrectinib Initiation. (A) Baseline Chest X-ray, Indicating Moderate Right-sided Pleural Effusion (Asterisk) and a Mass Projecting Into Right Midfield (Arrow). (B) Three Weeks After Treatment Initiation, Pleural Effusion Has Reduced in Size (Asterisk), With Mass No Longer Visible

Hochmair, Clinical Lung Cancer 2019

Rapide Improvement

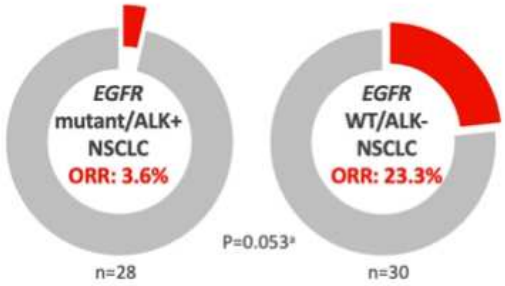


Hochmair, Clinical Lung Cancer 2019

Immunotherapy in patients with EGFR + und ALK + NSCLC

- *ALK* rearrangements are associated with a lower response to immune checkpoint inhibitors

ORR to PD-1/PD-L1 inhibitors from retrospective analysis[1]

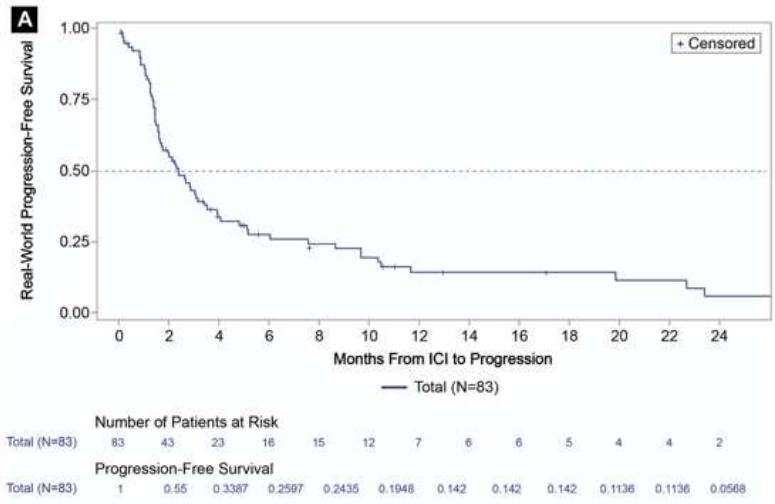


ORR and PFS in patients receiving durvalumab as a ≥third-line treatment[2]

	EGFR mutant/ALK+ NSCLC, PD-L1 ≥25%	*EGFR* WT/ALK- NSCLC, PD-L1 ≥25%	*EGFR* WT/ALK- NSCLC, PD-L1 ≥90%
ORR (%)	12.2	16.4	30.9
PFS (months)	1.9	3.3	2.4

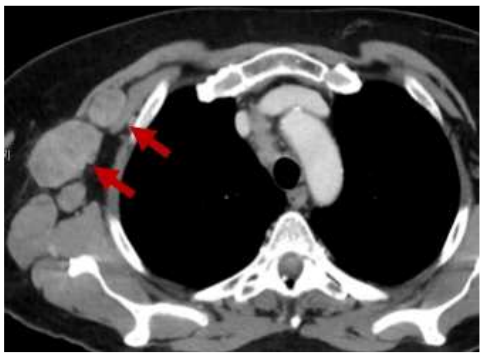
[a]Fisher's exact test
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; WT, wild type
1. Gainor JF, et al. *Clin Cancer Res*. 2016;22:4585-4593; 2. Garassino MC, et al. *Lancet Oncol*. 2018;19:521-536

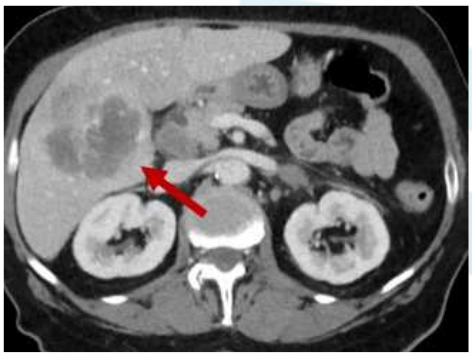
Real World Daten – IO bei ALK pos pat



Jahanzeb , CLC 2020

♀ - 65 a – NSCLC T3 N2 M1c - PDL1 50% - all biomarker neg
PFS 1- No relevant comorbidities





Question

What would be you recommondation?

1. Cisplatin/Pemetrexed/Pembrolizumab
2. Carboplatin/Pemetrexed/Pembrolizumab
3. Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab
4. Platin/Pemeterxed/Nivolumab/Ipililumab (Checkmate 9LA)
5. Nivolumab/Ipilimumab (Checkmate 227)
6. Pembrolizumab alone
7. Atezolizumab alone
8. Others

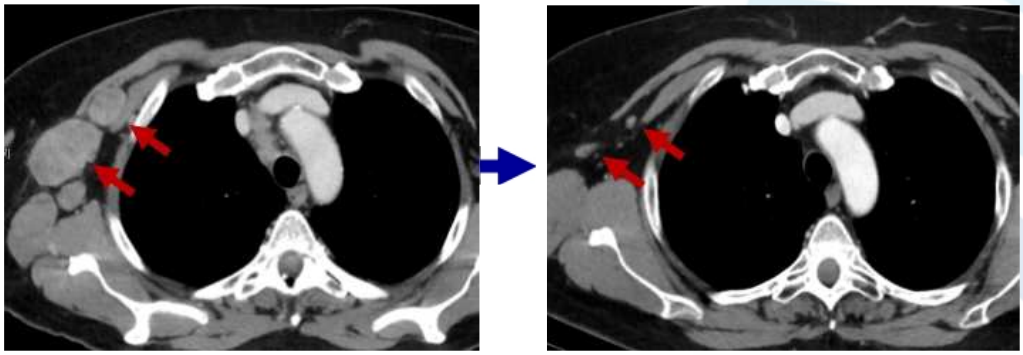
Question

What would be you recommondation?

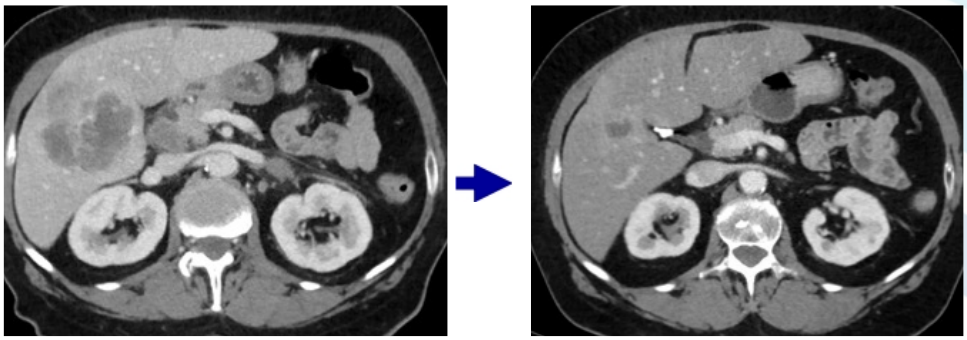
1. Cisplatin/Pemetrexed/Pembrolizumab
2. Carboplatin/Pemetrexed/Pembrolizumab
3. Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab
4. Platin/Pemeterxed/Nivolumab/Ipililumab (Checkmate 9LA)
5. Nivolumab/Ipilimumab (Checkmate 227)
6. Pembrolizumab alone
7. Atezolizumab alone
8. Others

♀ - 65 a - PDL1 50% - PFS 41 months

Ongoing



♀ - 65 a - PDL1 50% - PFS 41 months
ongoing



Gandhi KN189 AACR 2018

KEYNOTE-189: Randomized, Double-Blind, Phase 3 Study of Pembrolizumab or Placebo plus Pemetrexed and Platinum as First-Line Therapy for Metastatic NSCLC

Leena Gandhi, Delvys Rodríguez-Abreu, Shirish Gadgeel, Emilio Esteban, Enriqueta Felip, Flávia De Angelis, Manuel Domine, Philip Clingan, Maximilian J. Hochmair, Steven Powell, Susanna Yee-Shan Cheng, Helge G. Bischoff, Nir Peled, Francesco Grossi, Ross R. Jennens, Martin Reck, Rina Hui, Edward B. Garon, Michael Boyer, Belén Rubio-Viqueira, Silvia Novello, Takayasu Kurata, Jhanelle E. Gray, John Vida, Ziwen Wei, Jing Yang, Harry Raftopoulos, M. Catherine Pietanza, Marina C. Garassino

Gandhi, NEJM 2018

Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)

Key Eligibility Criteria
- Untreated stage IV nonsquamous NSCLC
- No sensitizing *EGFR* or *ALK* alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors
- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

R (2:1)

N = 410: Pembrolizumab 200 mg + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles → Pembrolizumab 200 mg Q3W for up to 31 cycles + Pemetrexed 500 mg/m² Q3W

N = 206: Placebo (normal saline) + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles → Placebo (normal saline) for up to 31 cycles + Pemetrexed 500 mg/m² Q3W

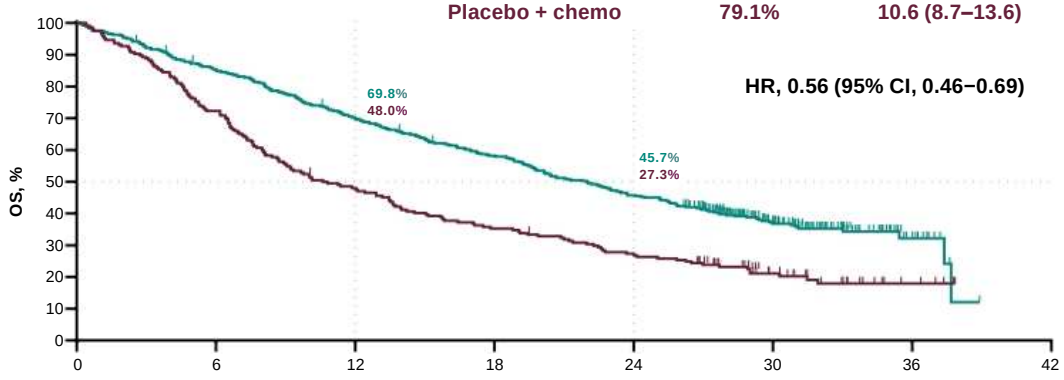
PD[b] → Pembrolizumab 200 mg Q3W for up to 35 cycles

[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

Overall Survival[a]

	Events, %	Median (95% CI) OS, mo
Pembro + chemo	62.9%	22.0 (19.5–24.5)
Placebo + chemo	79.1%	10.6 (8.7–13.6)

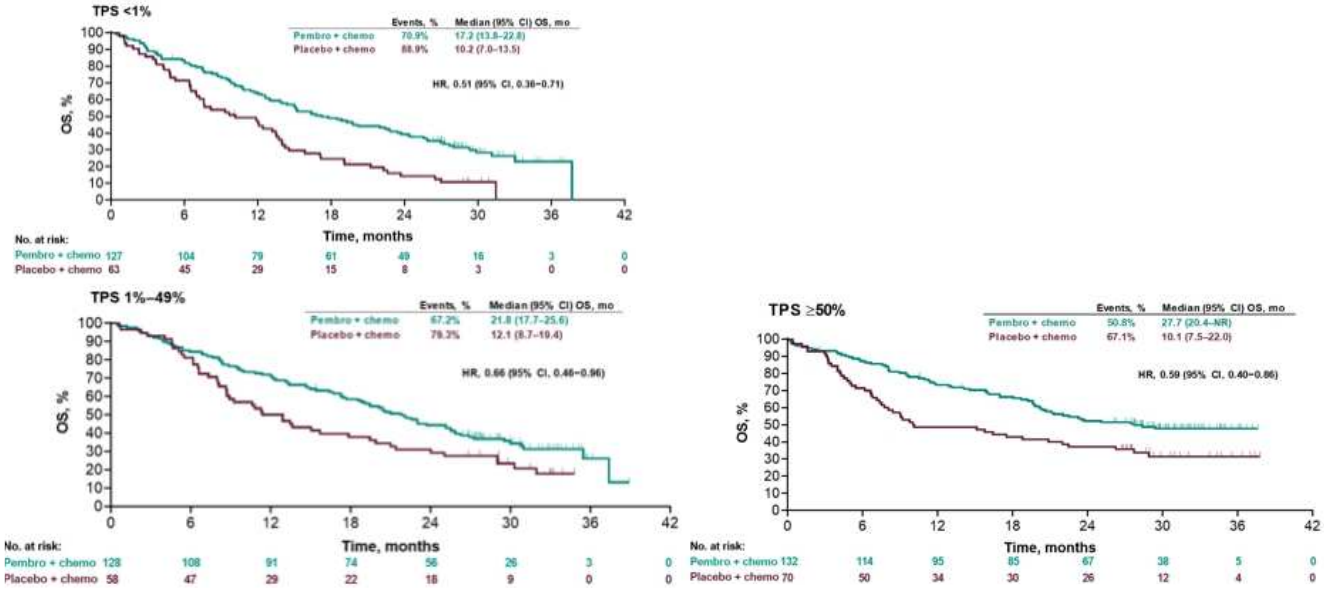
HR, 0.56 (95% CI, 0.46−0.69)



No. at risk:								
Pembro + chemo	410	347	283	234	184	86	12	0
Placebo + chemo	206	149	98	72	55	25	5	0

[a]Kaplan-Meier estimate using ITT population.
Chemo, chemotherapy with pemetrexed + platinum; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Pembro, pembrolizumab.
Data cutoff 20 May 2019

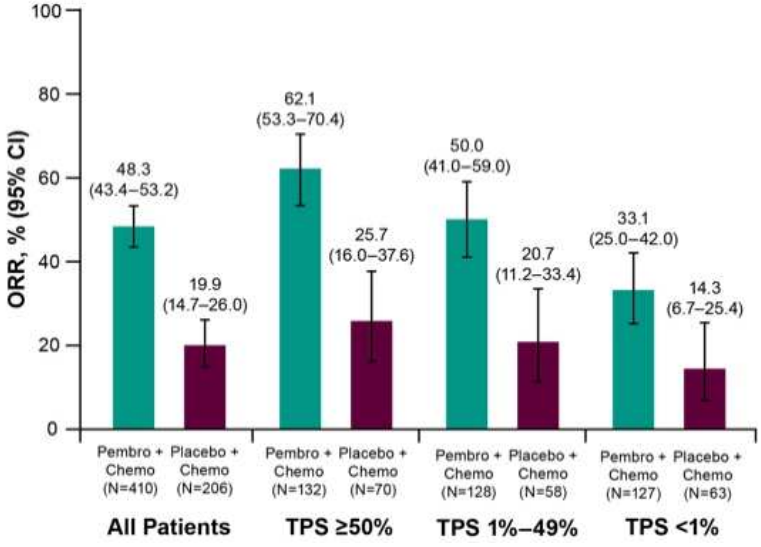
Overall Survival by PD-L1 Status[a]



[a]Kaplan-Meier estimate using ITT population.
Data cutoff 20 May 2019

Objective Response Rate

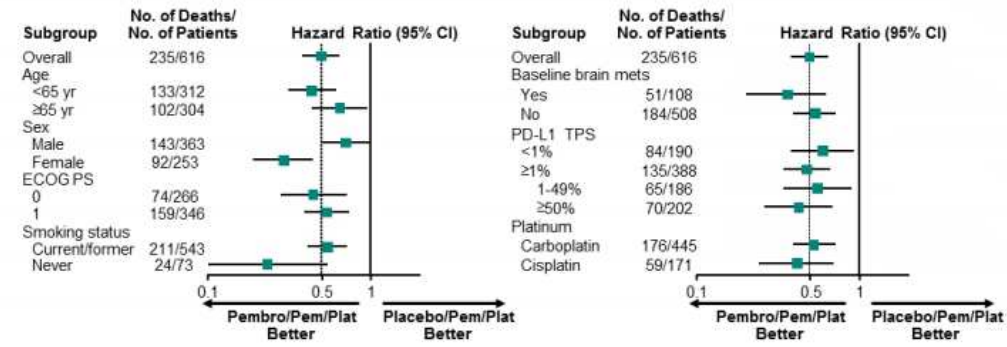
Per RECIST v1.1 By BICR



Data cutoff 20 May 2019

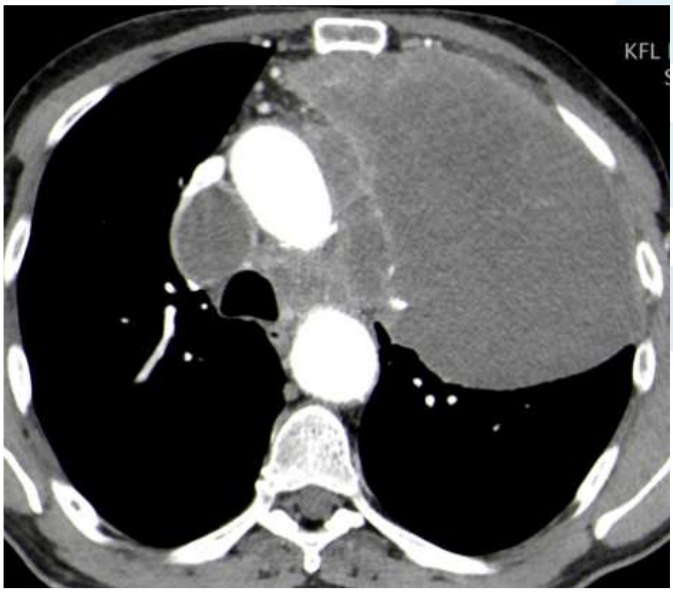
Gandhi KN189
AACR 2018

Overall Survival in Key Subgroups

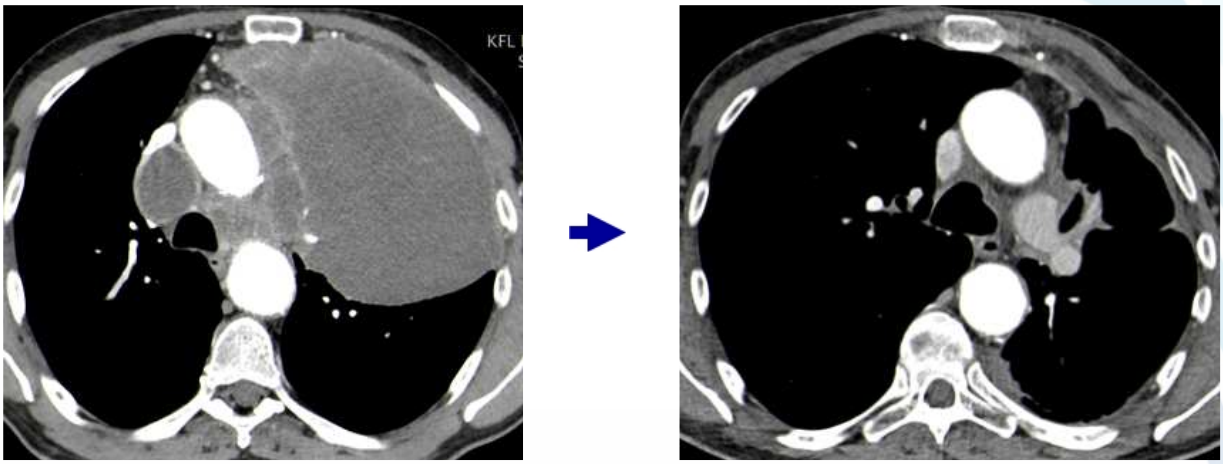


Data cutoff date: Nov 8, 2017.

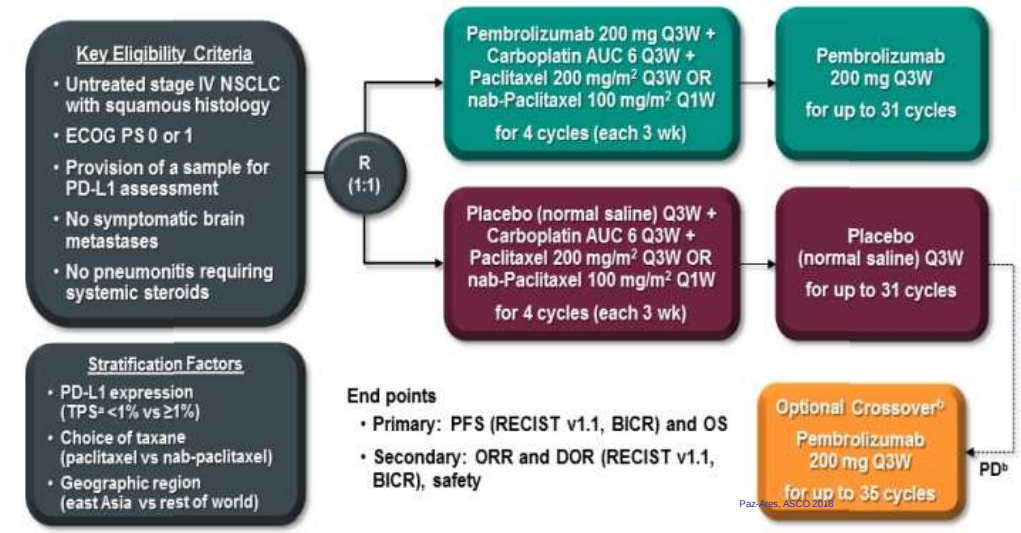
62 a – male - PDL1 1% - NSCLC non squamous Biomarker neg



62 a – male - PDL1 1% - NSCLC non squamous
PFS > 15 months



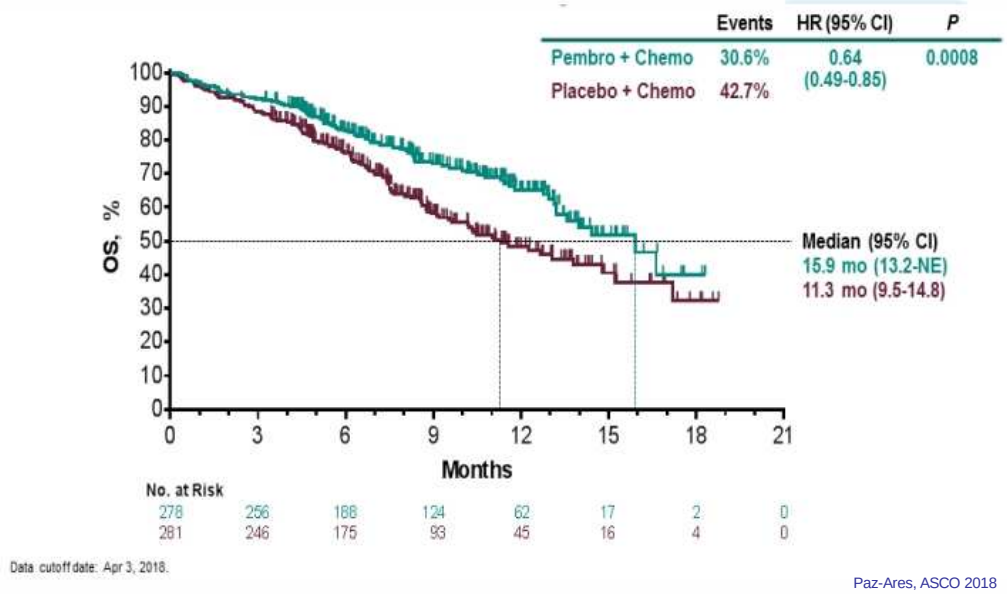
KEYNOTE 407



BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

Paz-Ares, ASCO/NEJM 2018

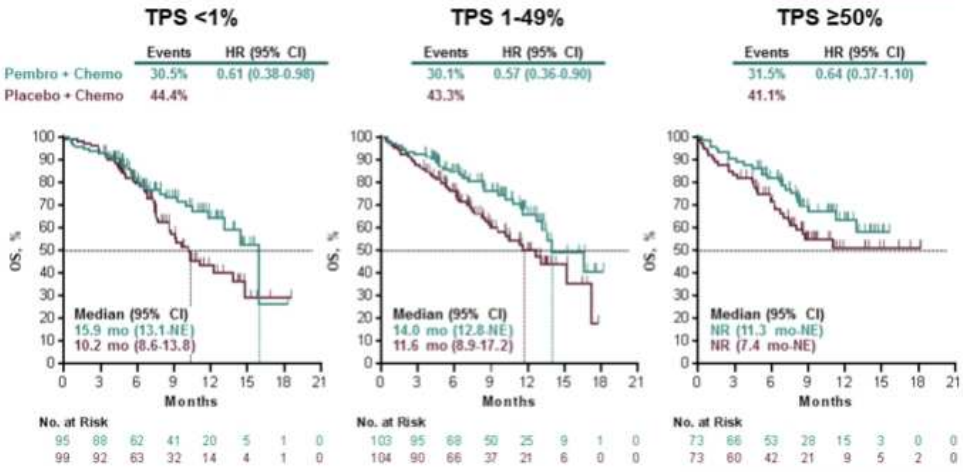
OS



Data cutoff date: Apr 3, 2018.

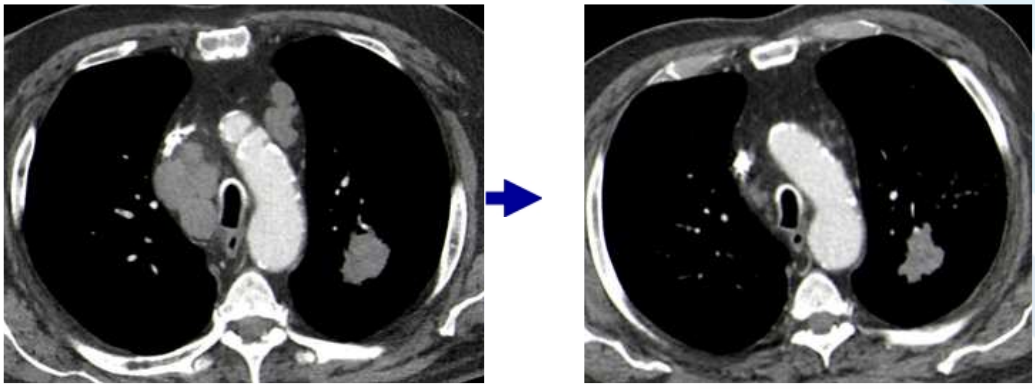
Paz-Ares, ASCO 2018

OS and PDL1 Status

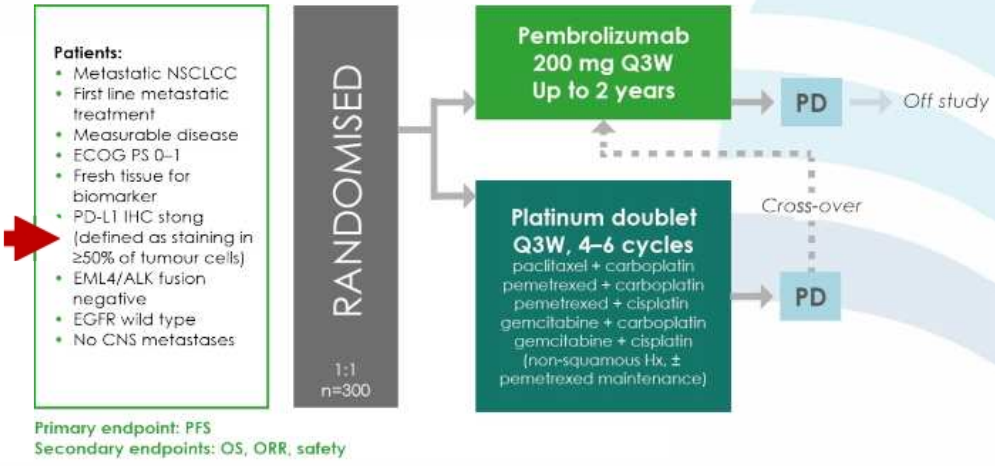


Paz-Ares, ASCO 2018

68 a, male, 50 PY, NSCLC (squamous – PDL1 1%)
T4 N3 pM1a – Carbo/Pac/Pem starting 1/2019

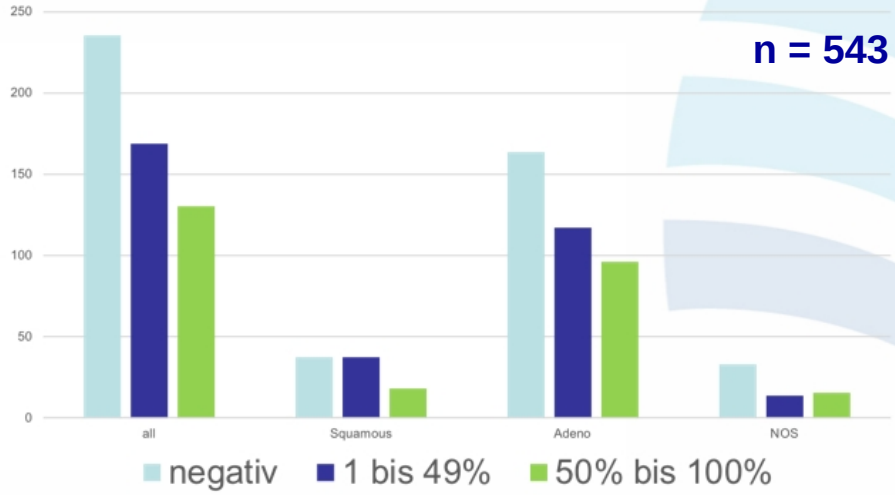


KEYNOTE-024
Study design



Reck, ESMO 2016

PD-L1 Testing Pathology

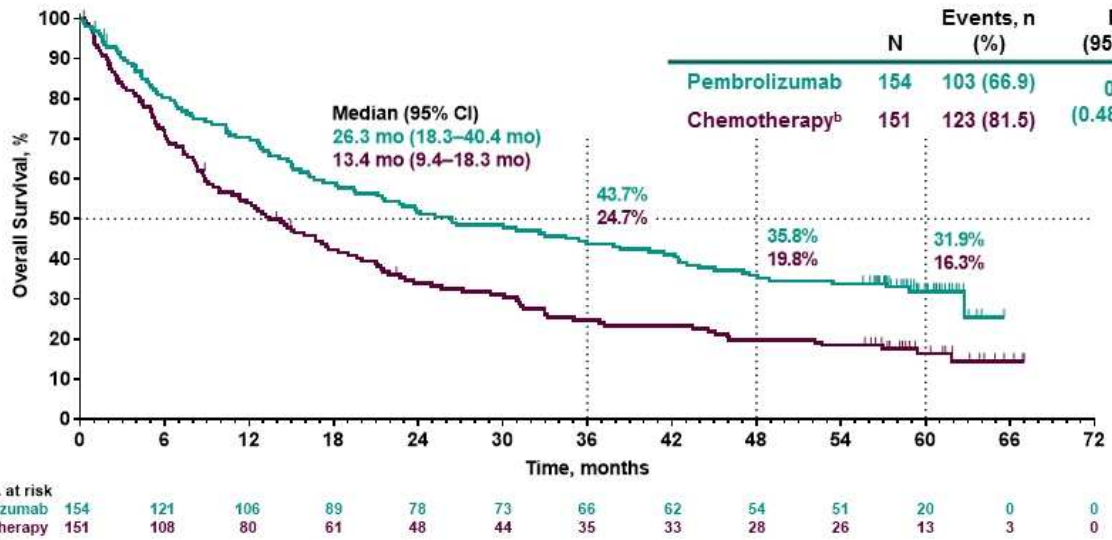


n = 543

Testing with Ventana SP 263 and Abcam 28.8
Pathology OWS, WCLC 2016

J Brahmer. ESMO 2020

Overall Survival[a]



	N	Events, n (%)	HR (95% CI)
Pembrolizumab	154	103 (66.9)	0.62 (0.48–0.81)
Chemotherapy[b]	151	123 (81.5)	

No. at risk

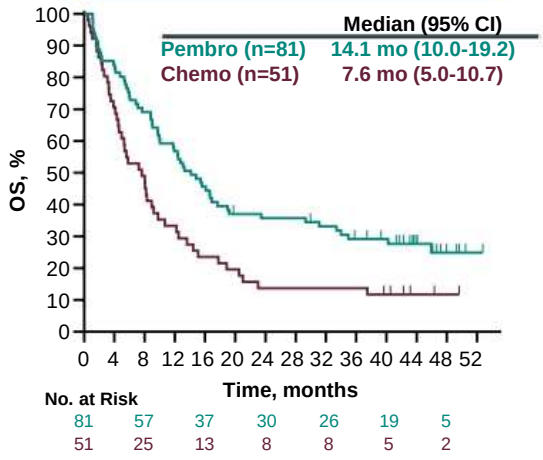
Pembrolizumab	154	121	106	89	78	73	66	62	54	51	20	0	0
Chemotherapy	151	108	80	61	48	44	35	33	28	26	13	3	0

[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

Clinical Utility for OS (KEYNOTE-010[a]): tTMB Cutpoint of 175 mut/exome

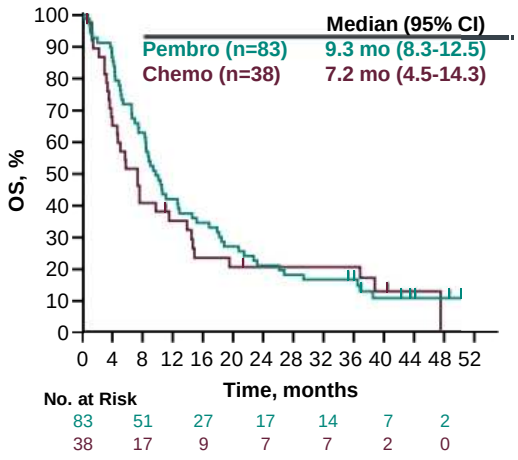
tTMB ≥ 175/mut/exome

HR 0.56 (95% CI 0.38-0.83)



tTMB < 175 mut/exome

HR 0.85 (95% CI 0.56-1.30)

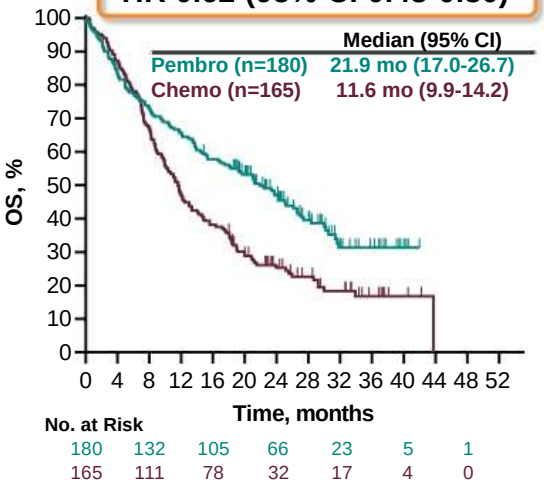


[a]All patients were PD-L1- (PS 1%). D : M 16, 2018.

Clinical Utility for OS (KEYNOTE-042[a]): tTMB Cutpoint of 175 mut/exome

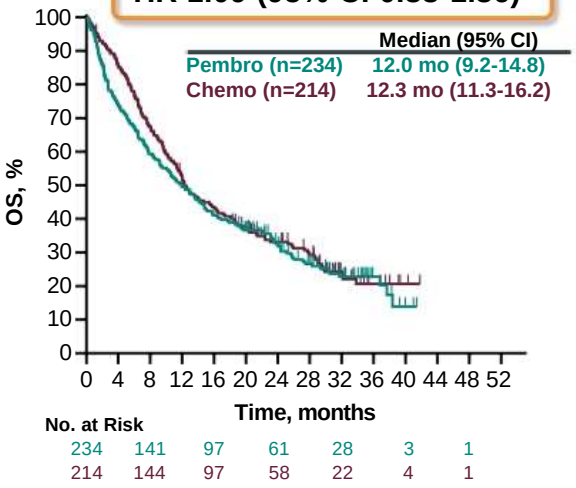
tTMB ≥ 175/mut/exome

HR 0.62 (95% CI 0.48-0.80)



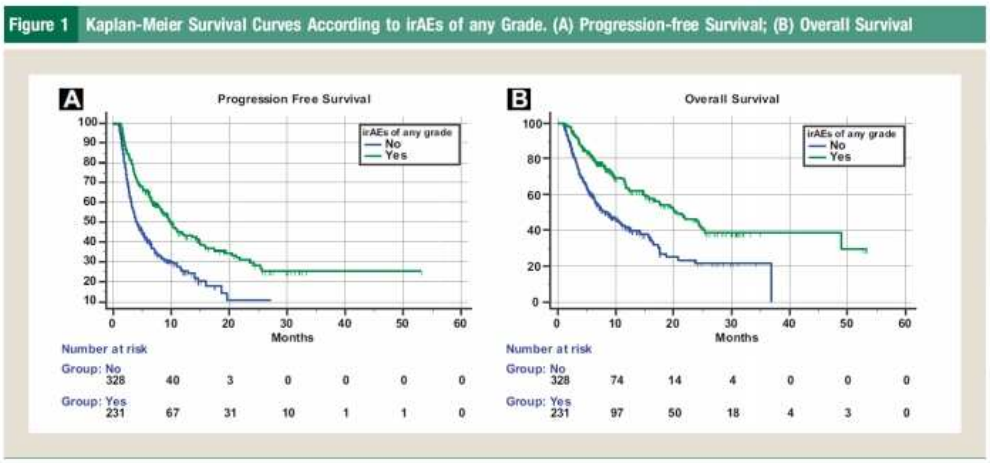
tTMB < 175 mut/exome

HR 1.09 (95% CI 0.88-1.36)



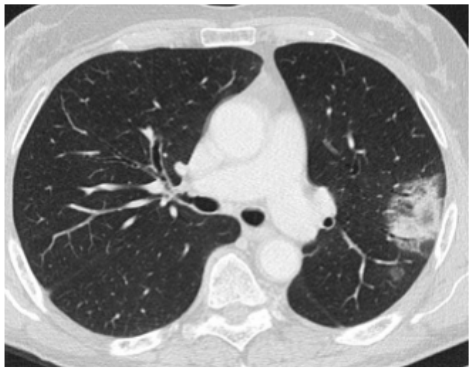
[a]All patients were PD-L1- (TPS 1%). D : S 4, 2018.

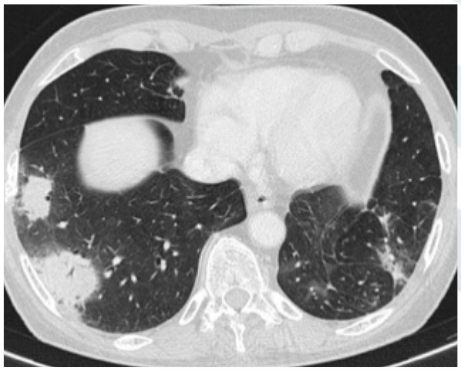
Same results with PD1 Inhibitor



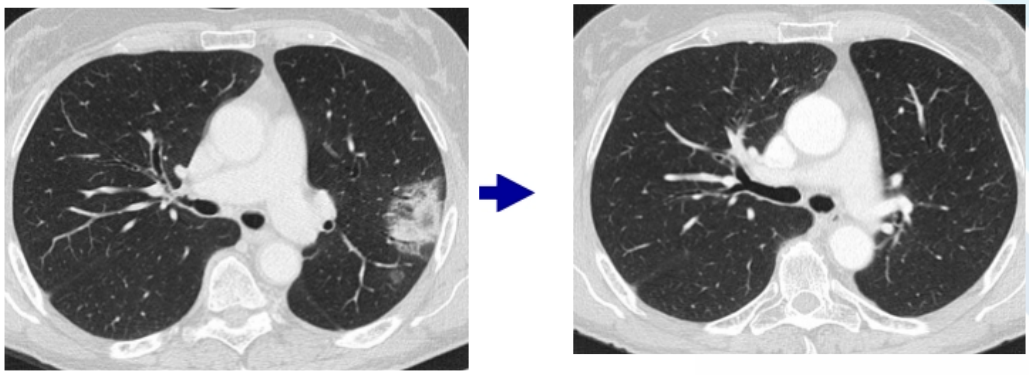
Cortellini, et al. Clinical Lung Cancer. https://doi.org/10.1016/j.cllc.2019.02.006

Early detection is important



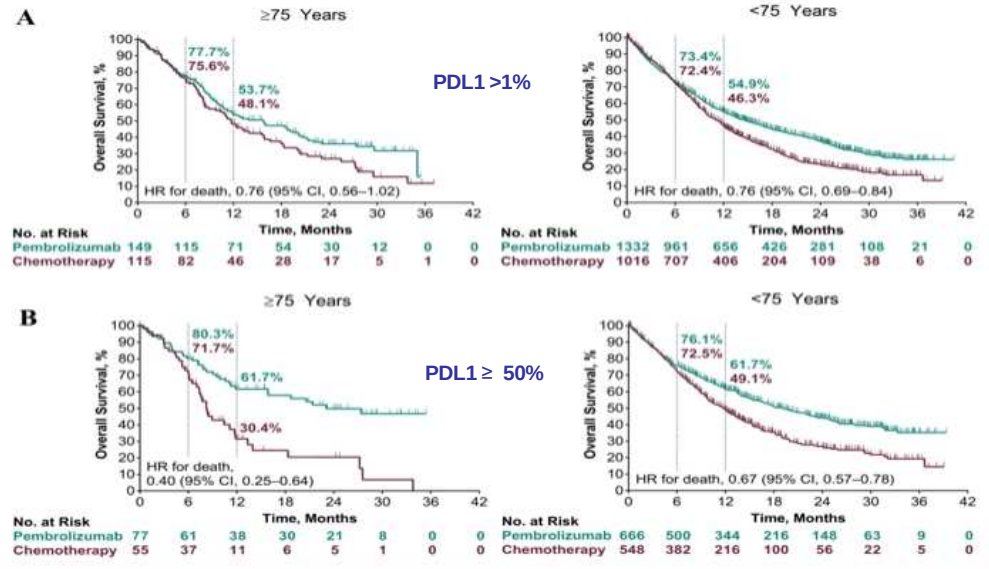


Cortison helps



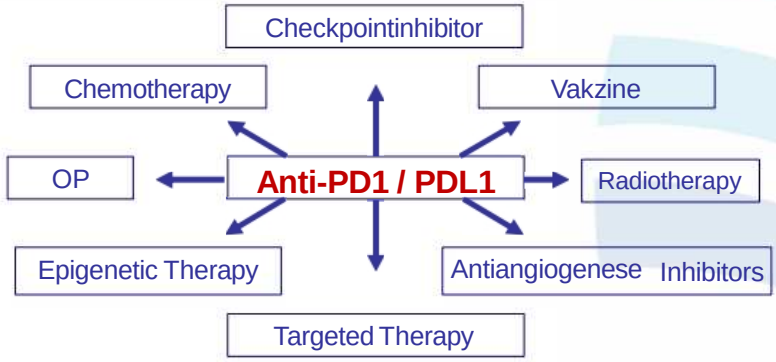
OS in older pat ≥ 75 y comperable with overall population

polled analysis from KEYNOTE 10/24/42



Nosaki, Lung Cancer 2019

Combination treatments



VIRTUAL 2020 ESMO congress

PACIFIC: TRIAL DESIGN

Phase 3, Randomised, Double-blind, Placebo-controlled, Multicentre, International Trial

- Unresectable Stage III NSCLC without progression after definitive platinum-based cCRT* (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumour tissue for PD-L1 testing†

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomised

1–42 days post-cCRT

R

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

2:1 randomisation, stratified by age, sex, and smoking history

Placebo
q2w for up to 12 months
N=237

Primary endpoints
- PFS by BICR using RECIST v1.1‡
- OS

Key secondary endpoints
- ORR, DoR, and TTDM by BICR using RECIST v1.1
- Safety
- PROs

- Updated analyses of OS and PFS (~4 years after the last patient was randomised; planned exploratory update)
  - Treatment effects for the ITT population were estimated using a stratified log-rank approach (with trial stratification factors)
  - Treatment effects for patient subgroups were estimated from unstratified Cox proportional-hazards models (with treatment as the only covariate)

NCT02125461. *Radiation dosage typically 60–66 units of gray in 30–33 fractions. †Using the Ventana SP263 immunohistochemistry assay.
‡Defined as the time from randomisation (which could occur up to 6 weeks post-cCRT) to the date of objective disease progression or death by any cause in the absence of progression.
BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; ITT, intent to treat; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

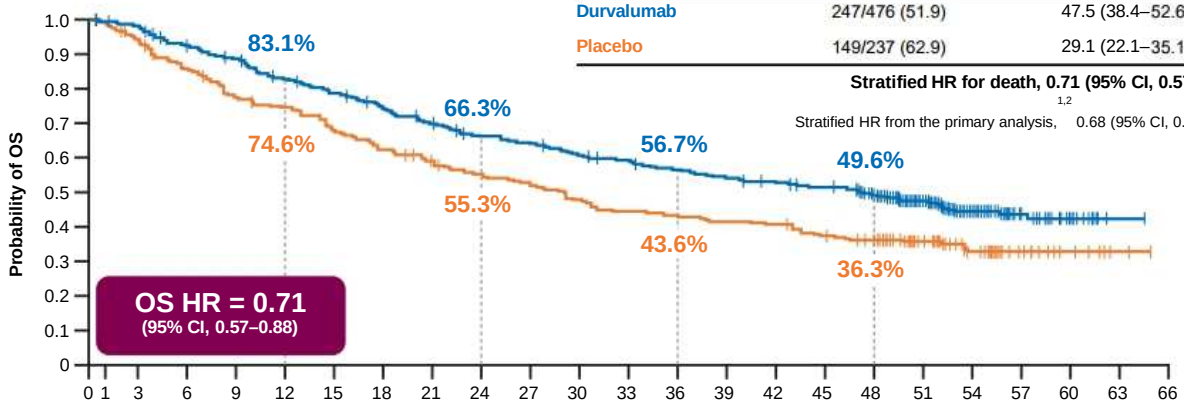
36

UPDATED OS (ITT)

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)

Stratified HR for death, 0.71 (95% CI, 0.57–0.88)[1,2]

Stratified HR from the primary analysis, 0.68 (95% CI, 0.53–0.87)



No. at risk

Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

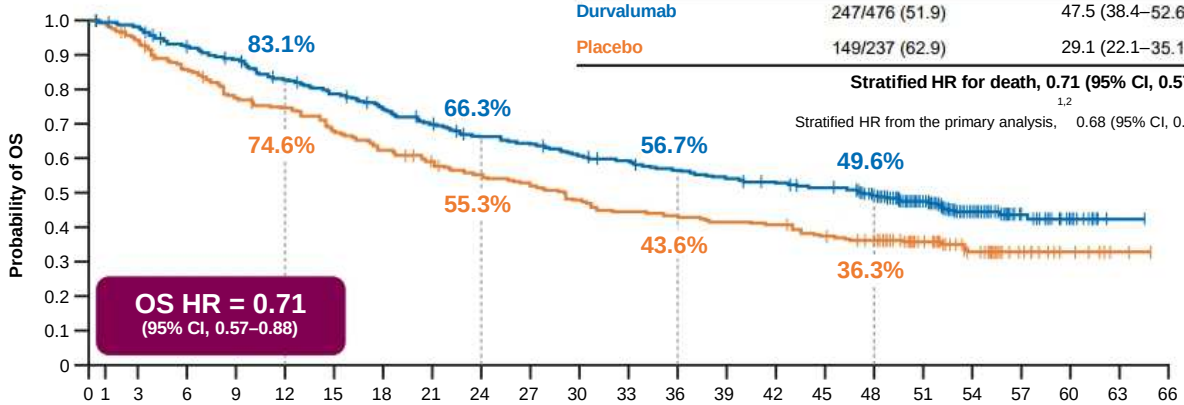
Data cutoff: 20 March 2020 (median follow up, 34.2 months [range, 0.2–64.9]). CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.
1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020 [Accessed August 2020]. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf.

UPDATED OS (ITT)

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	247/476 (51.9)	47.5 (38.4–52.6)
Placebo	149/237 (62.9)	29.1 (22.1–35.1)

Stratified HR for death, 0.71 (95% CI, 0.57–0.88)[1,2]

Stratified HR from the primary analysis, 0.68 (95% CI, 0.53–0.87)



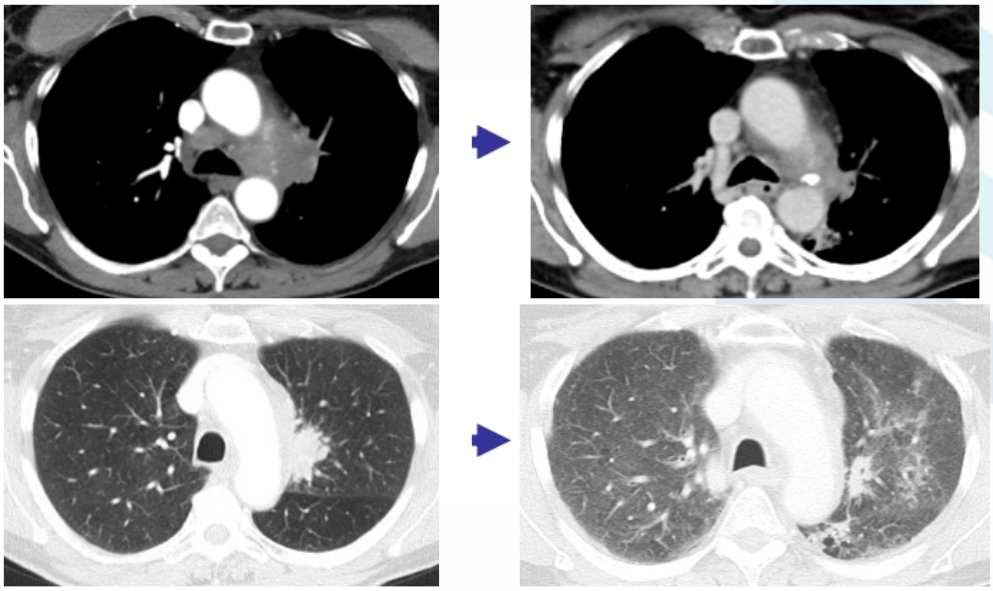
No. at risk

Durvalumab	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

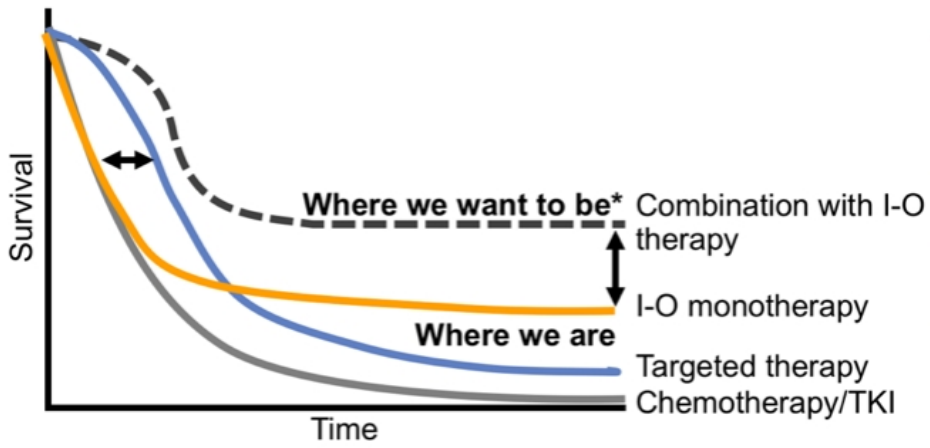
Data cutoff: 20 March 2020 (median follow up, 34.2 months [range, 0.2–64.9]). CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.
1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020 [Accessed August 2020]. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf.

64 female - smoker

NSCLC Adeno Ca PDL1 80% - Cisplatin/Pemetrexed + Radiotherapy
followed by Durvalumab



Combination of therapies



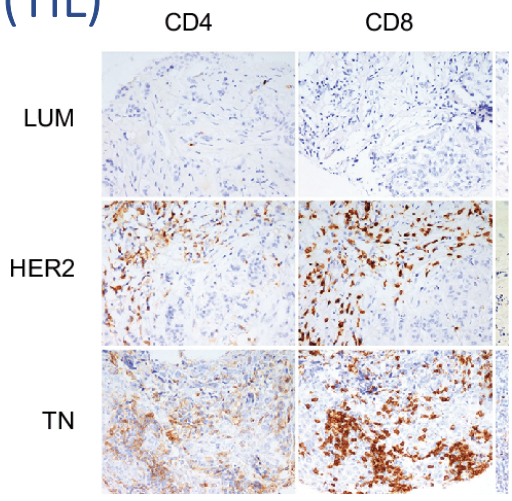
Vloga imunoterapije pri raku dojk

doc. dr. Matos Erika, dr.med.

16.12.2020

Rak dojk – hladni tumorji (TIL)

- Nizka infiltracija z imunskimi celicami (TIL)
- Vsi podtipi: 10% (mediana)
  - TNBC 20-25 %
  - HER2+ 15-20%
  - ER+/PR+ 5-10%
- Pri TNBC in HER2+ raku višji TIL boljši izhod.
  - Za 10% višji TIL vpliva na:
    - Boljši odgovor na predoperativno zdravljenje
    - ⇒ Zmanjšano tveganje za ponovitev bolezni
    - Izboljšanje celokupnega preživetja



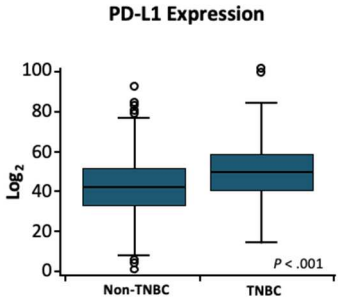
Garbar C, et all. Cancer Manag Res 2018

Rak dojk – hladni tumorji (PD1, PDL-1)

- PDL-1/PD1 izraženost po podtipih

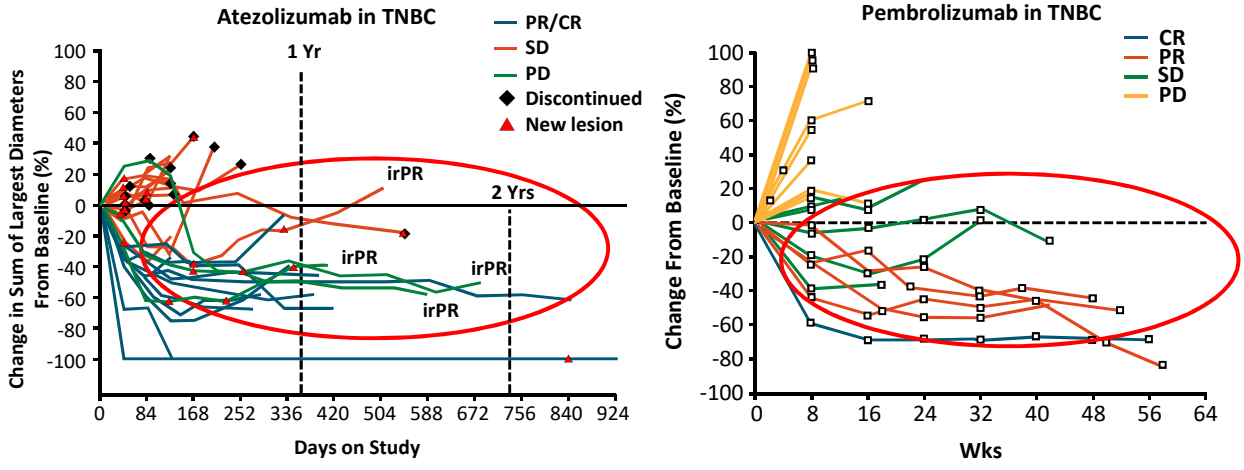
Breast cancer subtypes (n = 116)	PD-1 expression/hpf (TILs; % and range)	PD-L1 (tumor cells; %)	Concurrent PD-1 PD-L1 expressior
Luminal tumors (n = 58)			
Luminal A (n = 33)	25% (1–>10)	33%	13%
Luminal B (n = 25)	44% (1–20)	33%	17%
HER2 positive (n = 5)	60% (1–9)	20%	20%
Triple-negative (n = 53)	70% (1–20)[a]	59%[a]	45%[a]

Abbreviation: hpf, high-power fields.
[a]Significantly higher than in luminal tumors.



Gatalica Z, et all. Cancer Epidemiol Biomarkers Prev 2014; Mittendorf et all. Cancer Immunol Res. 2014

PD-1/PDL-1 blokada pri TNBC



Emens et all. JAMA Oncol. 2019; Nanda et all. JCO. 2016

Imunoterapija pri mTNBC

Impassion 130

Impassion 131

Keynote 355

IMpassion130

Vključitveni kriteriji

- Histološko potrjen metastatski/inoperabilni (LA) TNBC
- Brez predhodne terapije za napredovali TNBC
  - Predhodna terapija s taksani dovoljena: (neo)adj. zdravljenja s prostim intervalom ≥ 12 mesecev
- ECOG PS 0-1
- Primernost za zdravljenje s taksani v monoterapiji
- PD-L1 testiranje tkiva tumorja

(N = 902)

R 1:1

Dvojno slepa raziskava

Atezolizumab + *nab*-paclitaxel

Placebo + *nab*-paclitaxel

Zdravljenje do progresa ali hudih NU

Stratifikacijski kriteriji

- Jetrne metastaze (da/ne)
- (Neo)adj. zdravljenje s taksani (da/ne)
- PD-L1 IC status (poz/neg)

Primarna cilja:

- PFS in OS (v ITT in PD-L1+ skupini)

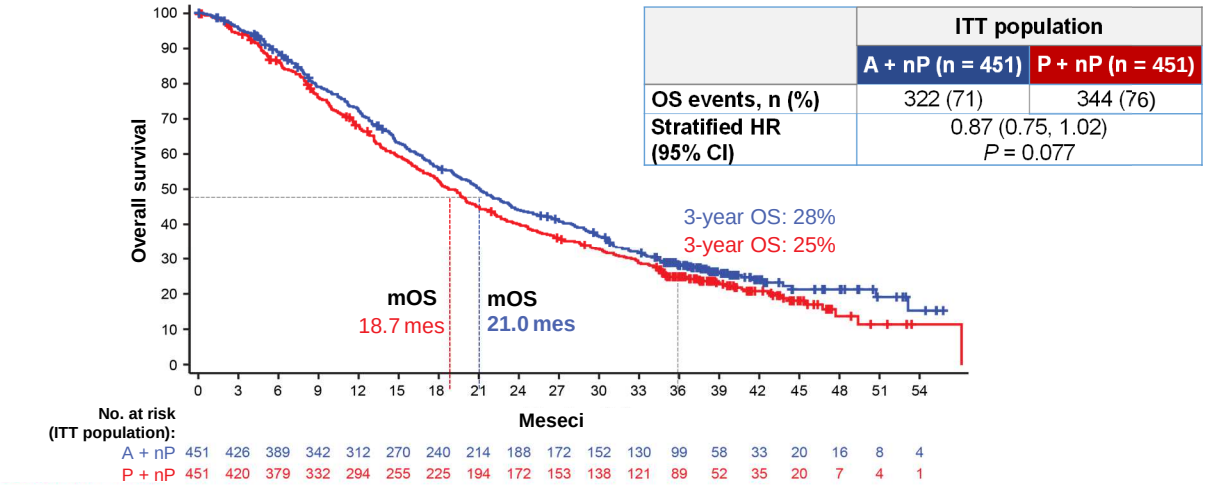
Emens LA. ESMO 2020.
Schmid, NEJM 2018.

Značilnosti bolnikov

Characteristic	ITT population	
	Atezolizumab + *nab*-paclitaxel (n = 451)	Placebo + *nab*-paclitaxel (n = 451)
Median age (range), years	55 (20-82)	56 (26-86)
≥ 65 years, n (%)	104 (23)	115 (26)
Race, n (%)[a] White Asian Black/African American	 308 (68) 85 (19) 26 (6)	 301 (67) 76 (17) 33 (7)
ECOG PS 1, n/N (%)	193/450 (43)	179/450 (40)
PD-L1 IC+, n (%)[b]	185 (41)	184 (41)
Metastatic disease, n/N (%)	404/450 (90)	408/450 (91)
Liver metastases, n (%)	126 (28)	118 (26)
Prior taxane therapy, n (%)	231 (51)	230 (51)

Emens LA. ESMO 2020.
Schmid, NEJM 2018.

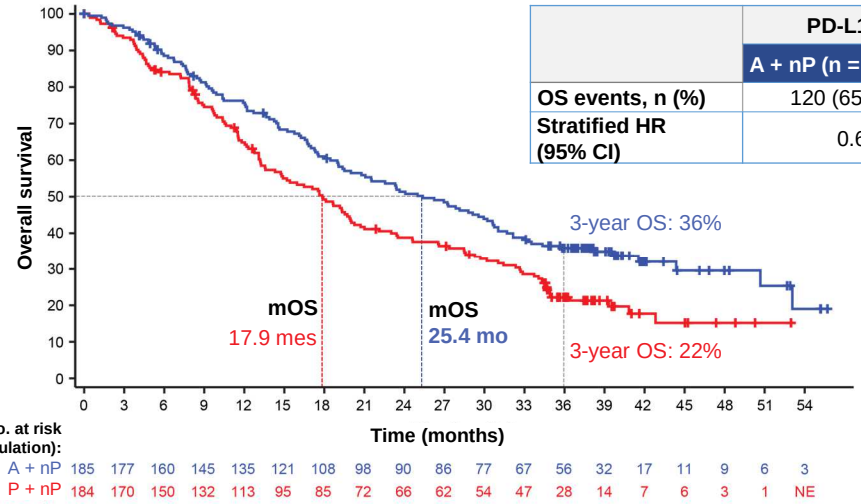
IMpassion130: OS v ITT skupini



	ITT population	
	A + nP (n = 451)	P + nP (n = 451)
OS events, n (%)	322 (71)	344 (76)
Stratified HR (95% CI)	0.87 (0.75, 1.02) *P* = 0.077	

Emens LA. ESMO 2020.

IMpassion130: OS (PD-L1 IC+ podskupina)

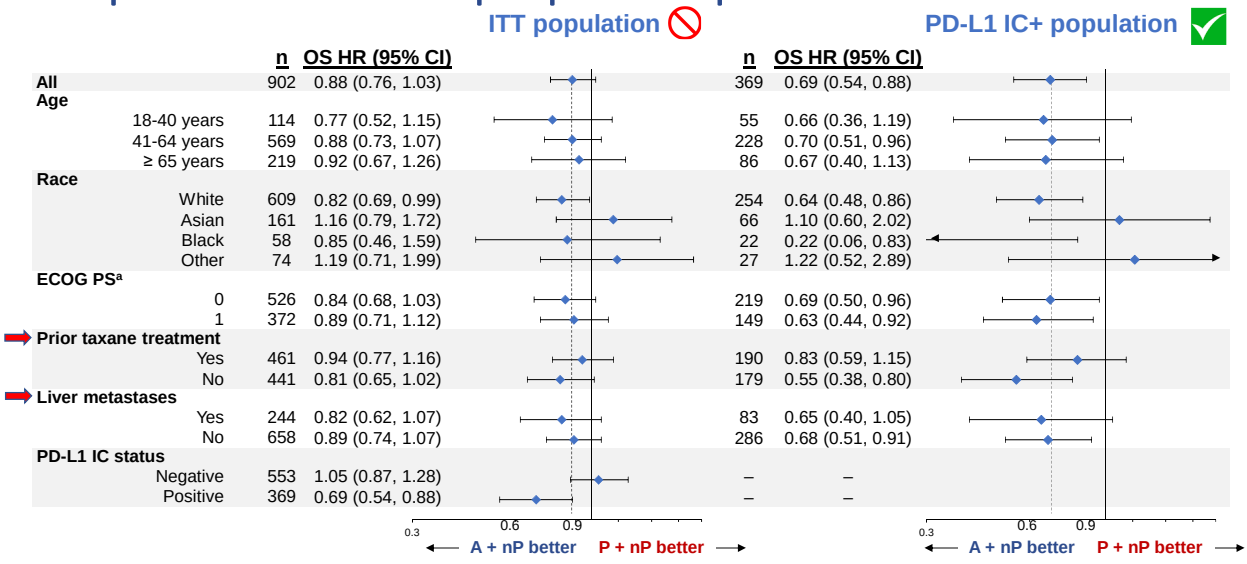


	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)	

ΔmOS=7,5 mes.

Emens LA. ESMO 2020.

IMpassion130: OS po podskupinah



Emens LA. ESMO 2020.

IMpassion130: varnost

Safety-evaluable population[a]	Atezolizumab + *nab*-paclitaxel (n = 460)		Placebo + *nab*-paclitaxel (n = 430)	
	Atezolizumab	*nab*-paclitaxel	Placebo	*nab*-paclitaxel
Treatment exposure, n (%)				
Up to 24 months	60 (13)	35 (8)	19 (4)	14 (3)
≥ 24 months	38 (8)	22 (5)	3 (1)	6 (1)
Deaths	322 (70)		337 (78)	
All-Grade AEs[b]	457 (99)		421 (98)	
Grade 3-4	233 (51)		183 (43)	
Treatment-related Grade 3/4 AEs	191 (42)		129 (30)	
Grade 5 AEs	6 (1)		3 (1)	
Treatment-related Grade 5 AEs[c]	2 (< 1)		1 (< 1)	
Serious AEs	110 (24)		80 (19)	
Treatment-related serious AEs	58 (13)		31 (7)	
AE leading to any treatment withdrawal[d]	88 (19)		36 (8)	
AE leading to atezolizumab/placebo withdrawal	37 (8)		4 (1)	
AE leading to *nab*-paclitaxel withdrawal	85 (19)		36 (8)	
AESI[e]	270 (59)		179 (42)	
Grade 3-4 AESI	39 (9)		20 (5)	

Emens LA. ESMO 2020.

IMpassion130: Atezolizumab NU

AE (medical concept), n (%)[a]	Atezolizumab + *nab*-paclitaxel (n = 460)		Placebo + *nab*-paclitaxel (n = 430)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hepatitis (diagnosis)[b]	11 (2)	7 (2)	7 (2)	1 (< 1)
Hypothyroidism	84 (18)	0	19 (4)	0
Hyperthyroidism	22 (5)	1 (< 1)	5 (1)	0
Adrenal insufficiency	5 (1)	1 (< 1)	0	0
Pneumonitis	18 (4)	2 (< 1)	1 (< 1)	0
Colitis	7 (2)	2 (< 1)	3 (1)	1 (< 1)
Pancreatitis[c]	2 (< 1)	1 (< 1)	0	0
Diabetes mellitus	1 (< 1)	1 (< 1)	3 (1)	2 (< 1)
Hypophysitis	1 (< 1)	1 (< 1)	0	0
Myositis	3 (1)	1 (< 1)	1 (< 1)	1 (< 1)
Rash	165 (36)	5 (1)	112 (26)	2 (1)
Severe cutaneous reactions	4 (1)	1 (< 1)	3 (1)	0

Emens LA. ESMO 2020.

IMpassion131

Vključitveni kriteriji
- Metastatski ali inoperabilen (LA) TNBC
- Brez predhodnega zdravljenja napredovale TNBC
- Prost interval od (neo)adj. zdravljenja ≥ 12 mesecev
- Primernost za zdravljenje s taksani
- Merljiva bolezen
- ECOG PS 0/1

R
2:1

Atezolizumab 840 mg d1 & 15 + paklitaksel 90 mg/m² d1, 8 & 15

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paklitaksel 90 mg/m² d1, 8 & 15

Stratifikacijski kriteriji
- Predhodno zdravljenje s taksani (da/ne)
- PD-L1 status tumorja (IC <1%/≥1%)
- Jetrne metastaze (da/ne)

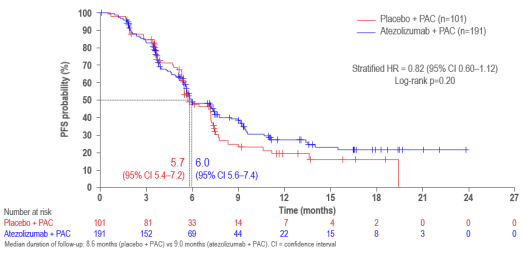
Primarni cilji: PFS v PDL-1 poz.
Sekundarni cilji: OS, ORR, PFS po 12 mes, PROs, varnost,translacijske raziskave

Miles D et al. ESMO 2020.

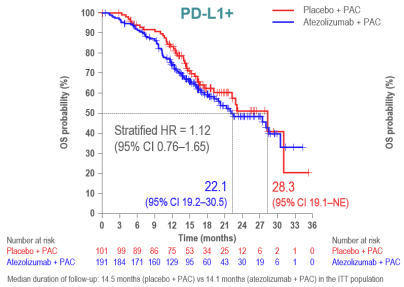
IMpassion131

- Primarni cilj **ni bil dosežen**: dodajanje atezolizumaba k paklitakselu ni pomembno izboljšalo PFS pri bolnikih z PD-L1+ mTNBC
- Ni statistično pomembnega podaljšanja OS (sekundarni cilj)

PFS pri PD-L1 poz. skupini



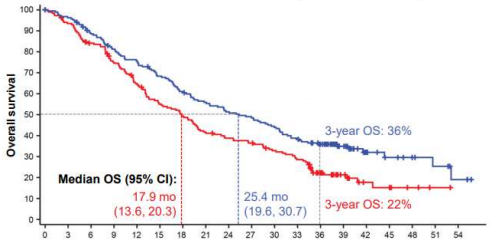
OS pri PD-L1 poz. skupini



Miles D et al. ESMO 2020.

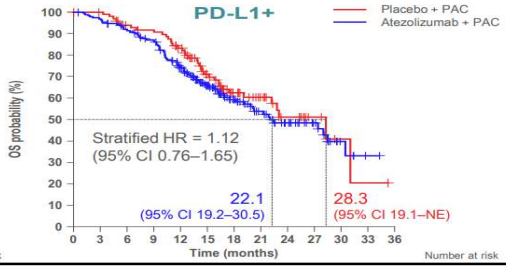
OS in the PD-L1 IC+ population

IMpassion 130



Nab-paklitaksel

IMpassion 131



Paklitaksel

Z dovoljenjem B.Šeruga

ESMO 2020.

KEYNOTE-355

*Kemoterapija po izboru onkologa:

- Nab-paclitaxel 100 mg/m² IV na dan 1, 8, 15 (/28 dni)
- Paclitaxel 90 mg/m² IV on na dan 1, 8, 15 (/28 dni)
- Gem 1000 mg/m² + carbo AUC 2 na dan 1, 8 (/21 dni)

Vključitveni kriteriji

- Metastatski ali inoperabilni (LA) TNBC
- Brez predhodnega zdravljenja napredovale TNBC
- Prost interval od adj. zdravljenja ≥ 6 mesecev

(N = 847)

Pembrolizumab 200 mg IV Q3W + chemotherapy* (n = 566)

Placebo + chemotherapy* (n = 281)

Zdravljenje do progresa, hudih NU ali do prejetih 35 ciklov th

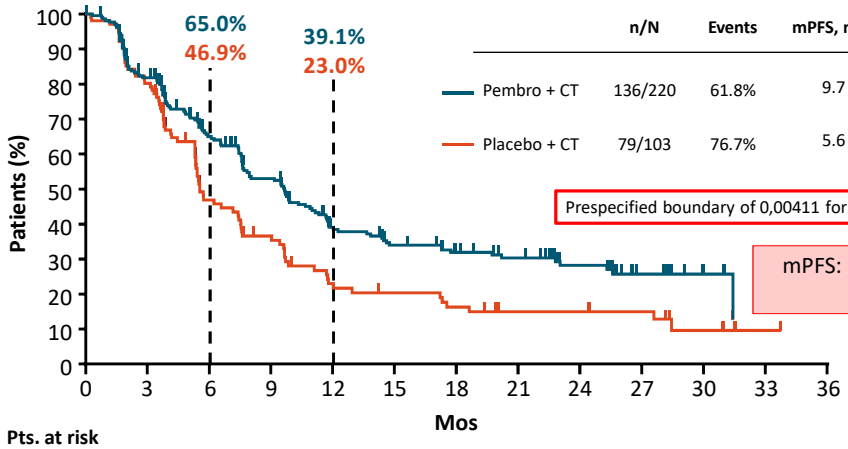
Stratifikacijski kriterji

- Vsta kemoterapije (taksani vs gem/karbo);
- PD-L1 status (PD-L1 CPS ≥ 1, CPS < 1);
- Predhodno zdravljenje z enako vrsto kemoterapije (da/ne)

Dva primarna cilja:
PFS in OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, ITT)
Sekundarni cilji: ORR, DoR, DCR, varnost

Cortez J et al. Lancet 2020

KEYNOTE-355: PFS v skupini PD-L1 CPS ≥ 10



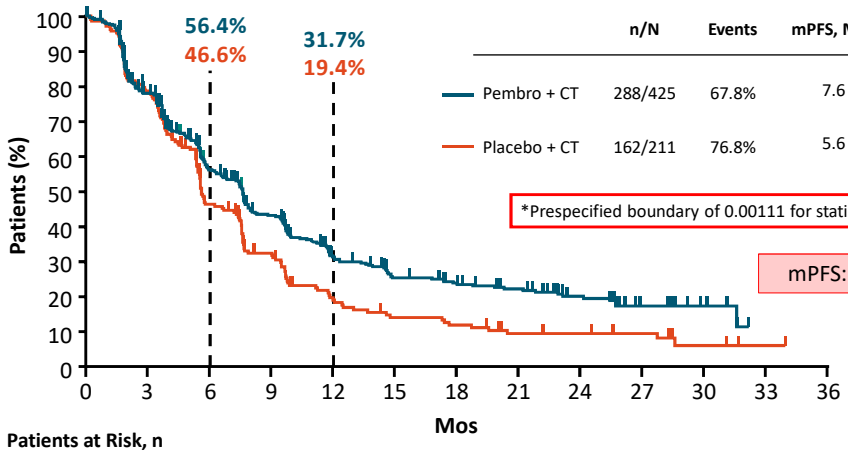
	n/N	Events	mPFS, mos	HR (95% CI)	*P* value (one-sided)
Pembro + CT	136/220	61.8%	9.7	0.65 (0.49-0.86)	0.0012
Placebo + CT	79/103	76.7%	5.6		

Prespecified boundary of 0,00411 for statistical significance met.

mPFS: 9,7 mes vs. 5,6 mes.
Δ4,1 mes.

Cortez J et al. Lancet 2020

KEYNOTE-355: PFS v skupini PD-L1 CPS ≥ 1



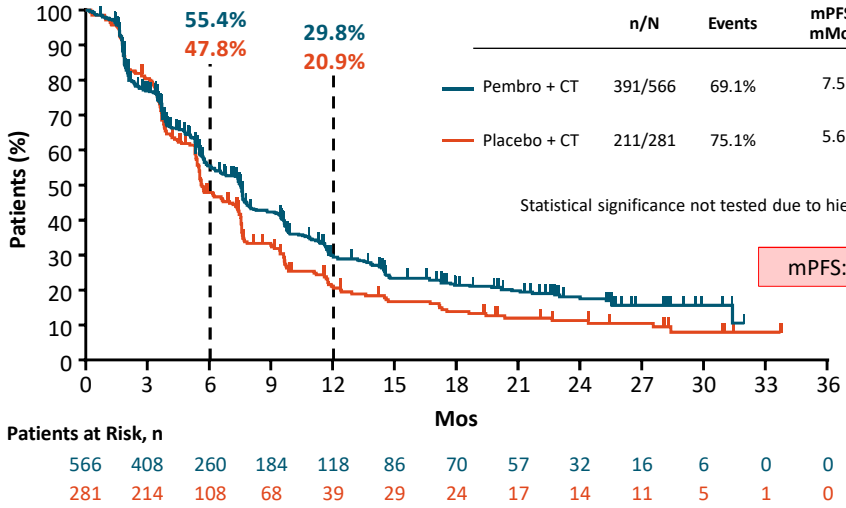
	n/N	Events	mPFS, Mos	HR (95% CI)	*P* Value (one-sided)
Pembro + CT	288/425	67.8%	7.6	0.74 (0.61-0.90)	00014*
Placebo + CT	162/211	76.8%	5.6		

*Prespecified boundary of 0.00111 for statistical significance not met

mPFS: 7,6 mes vs. 5,6 mes.

Cortez J et al. Lancet 2020

KEYNOTE-355: PFS v skupini ITT



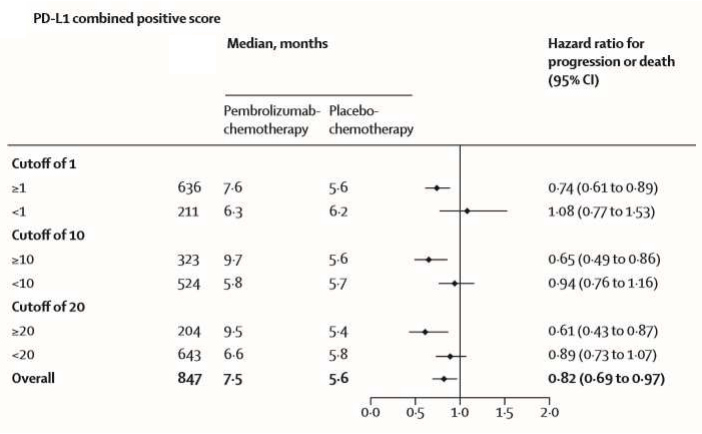
	n/N	Events	mPFS, mMos	HR (95% CI)
Pembro + CT	391/566	69.1%	7.5	0.82 (0.69-0.97)
Placebo + CT	211/281	75.1%	5.6	

Statistical significance not tested due to hierarchical testing strategy

mPFS: 7,5 mes vs. 5,6 mes.

Cortez J et al. Lancet 2020

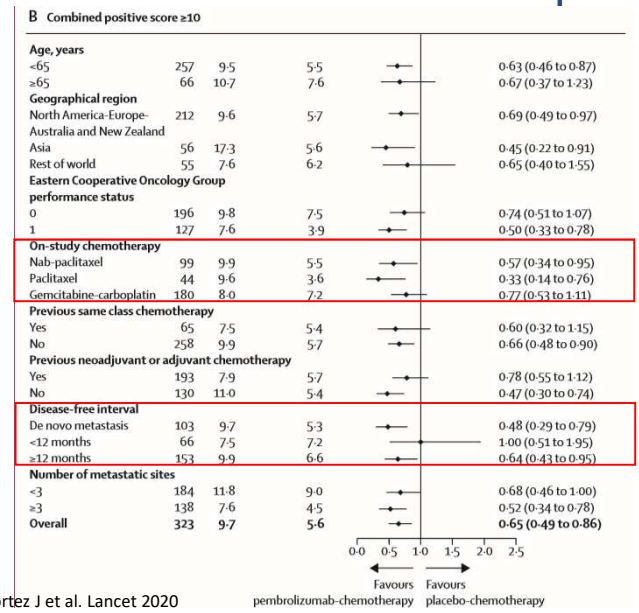
KEYNOTE-355: Je pomemben CPS?



Učinek pembrolizumaba sovpada z izraženostjo PDL-1 (višji CPS, večja dobrobit).

Cortez J et al. Lancet 2020

KEYNOTE-355: PFS v skupini PD-L1 CPS ≥ 10



Dodatek pembrolizumaba h KT je konzistenten v vseh izhodiščno definiranih podskupinah, ne glede na:

- Vrsto KT-partnerja (! Ne pred-definirana analiza, nima moči)
- Prosti interval (nizko število <12 mes)

Cortez J et al. Lancet 2020

KEYNOTE-355: varnost

	Pembrolizumab–chemotherapy group (n=562)		Placebo-chemotherapy group (n=281)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event*	554 (99%)	438 (78%)	276 (98%)	207 (74%)
Treatment-related adverse event†				
Total	541 (96%)	383 (68%)	267 (95%)	188 (67%)
Anaemia	275 (49%)	92 (16%)	129 (46%)	41 (15%)
Neutropenia	231 (41%)	167 (30%)	107 (38%)	84 (30%)
Nausea	221 (39%)	9 (2%)	115 (41%)	4 (1%)
Alopecia	186 (33%)	5 (1%)	94 (33%)	3 (1%)
Fatigue	160 (28%)	16 (3%)	83 (30%)	7 (2%)
Neutrophil count decreased	125 (22%)	98 (17%)	74 (26%)	57 (20%)
Alanine aminotransferase increased	115 (20%)	33 (6%)	46 (16%)	13 (5%)
Immune-mediated adverse event‡				
Total	144 (26%)	29 (5%)	17 (6%)	0
Hypothyroidism	87 (15%)	2 (<1%)	9 (3%)	0
Hyperthyroidism	27 (5%)	1 (<1%)	3 (1%)	0
Pneumonitis	14 (2%)	6 (1%)	0	0
Colitis	10 (2%)	2 (<1%)	4 (1%)	0
Severe skin reactions	10 (2%)	10 (2%)	1 (<1%)	0

Ni novih/nepričakovanih NU.
NU, povezani s pembrolizumabom so redki, blagi:

- G3 ali več: kožna toksičnost

Cortez J et al. Lancet 2020

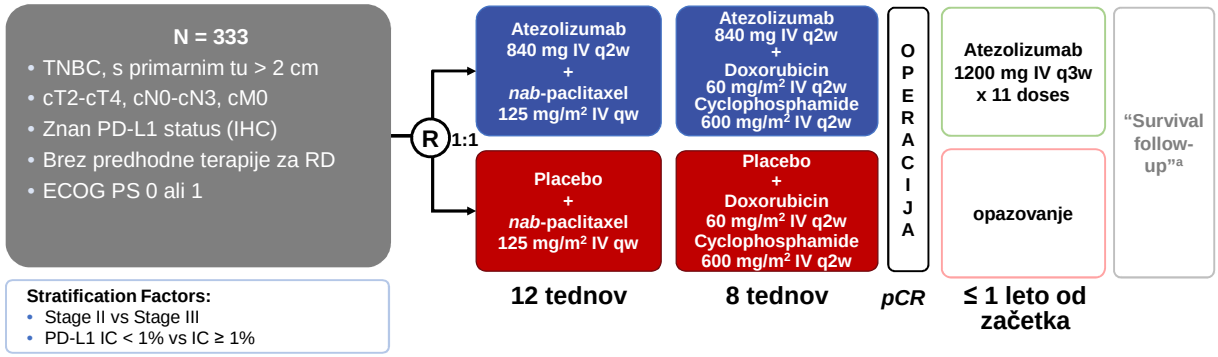
Imunoterapija pri zgodnjem TNBC

Impassion 031

Keynote 522

IMpassion031: atezolizumab neoadjuvantno

Randomizirana, mednarodna, dvojno slepa raziskava s placebo kontrolno skupino, F3

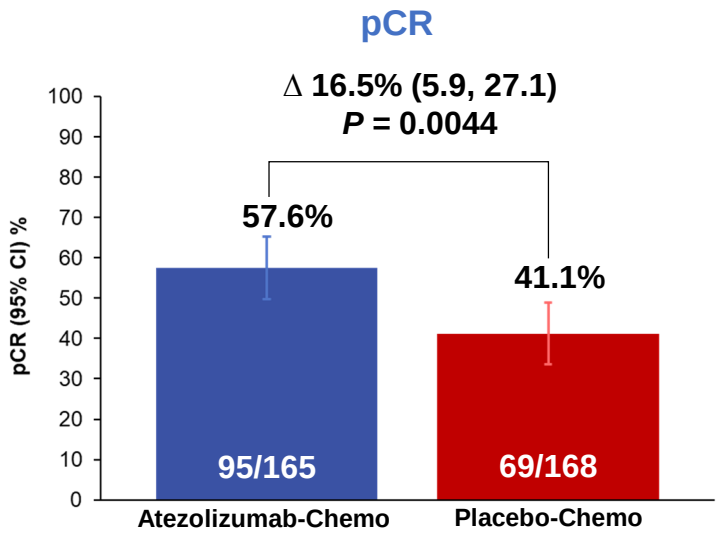


Primarni cilji: pCR v ITT populaciji in PD-L1+(IC ≥ 1%) subpopulaciji

Sekundarni cilji: EFS, DFS, and OS in ITT and in PD-L1+ subpopulaciji (po oceni raziskovalcev), varnost, PRO

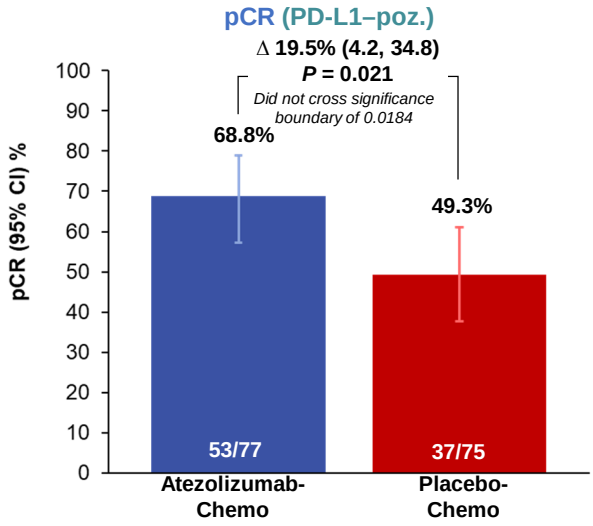
Mittendorf EA et al. Lancet 2020

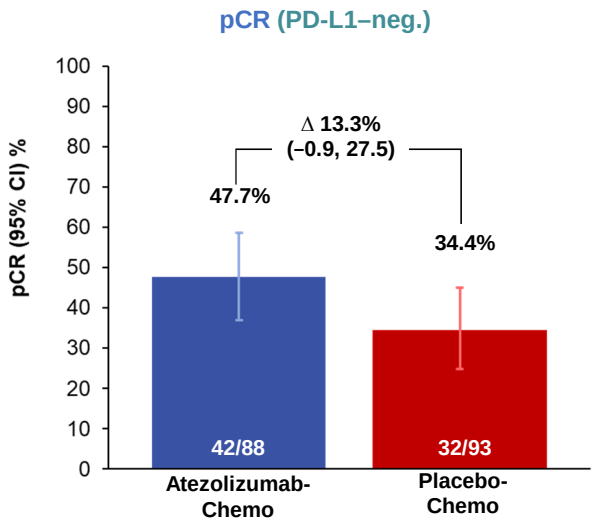
IMpassion031: pCR v ITT populaciji



Mittendorf EA, et all. Lancet 2020

IMpassion031: pCR glede na PD-L-1





Mittendorf EA, et all. Lancet 2020

IMpassion031: varnost

	Atezolizumab-Chemo (n = 164)	Placebo-Chemo (n = 167)
Number of patients ≥ 1 AE, n (%)	163 (99.4)	167 (100)
Grade 3-4, n (%)	103 (62.8)	101 (60.5)
Treatment-related Grade 3-4 AE	93 (56.7)	89 (53.3)
Grade 5, n (%)	1 (0.6)	1 (0.6)
Serious AE, n (%)	50 (30.5)	30 (18.0)
Treatment-related SAE	37 (22.6)	26 (15.6)
AE leading to any treatment discontinuation, n (%)	37 (22.6)	33 (19.8)
Of atezolizumab/placebo	21 (12.8)	19 (11.4)
Of nab-paclitaxel	27 (16.5)	23 (13.8)
Of doxorubicin	8 (4.9)	10 (6.0)
Of cyclophosphamide	8 (4.9)	10 (6.0)

- NU ob zdravljenju več v skupini z atezolizumabom.
- Prekinitev zdravljenja zaradi G3-4 NU podobno v obeh skupinah.

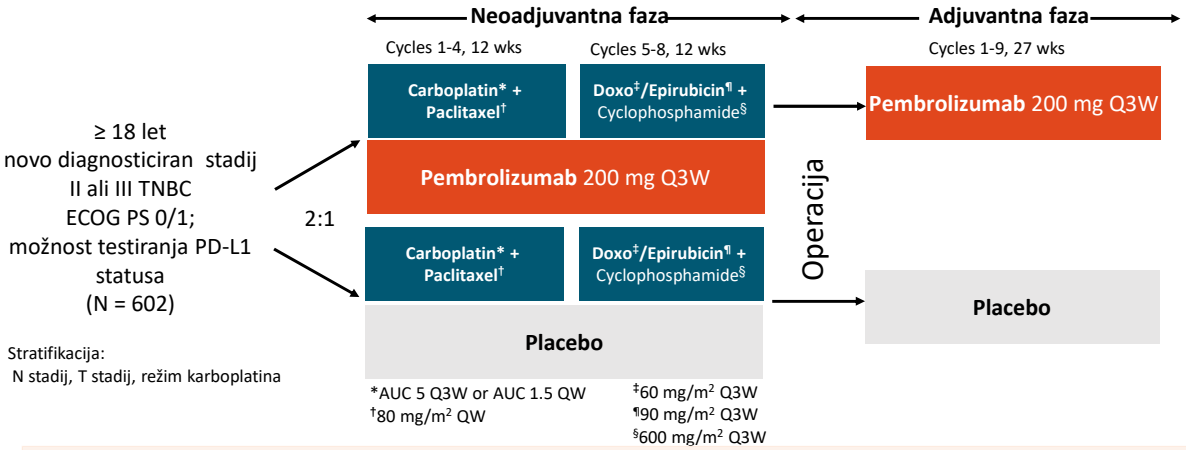
Mittendorf EA, et all. Lancet 2020

IMpassion031: varnost (imunsko pogojeni NU)

Summary, n (%)	Atezolizumab-Chemo (n = 164)		Placebo-Chemo (n = 167)	
All AESIs	115 (70.1)		101 (60.5)	
Grade 3-4 AESI	24 (14.6)		20 (12.0)	
Serious AESI	11 (6.7)		5 (3.0)	
AESI requiring systemic corticosteroids	21 (12.8)		16 (9.6)	
Specific AESIs, n (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Hepatitis	2 (1.2)	0	1 (0.6)	0
Hypothyroidism	11 (6.7)	0	2 (1.2)	0
Hyperthyroidism	5 (3.0)	0	0	0
Adrenal insufficiency	0	0	1 (0.6)	0
Pneumonitis	2 (1.2)	1 (0.6)	2 (1.2)	0
Colitis	1 (0.6)	1 (0.6)	1 (0.6)	0
Guillain-Barré syndrome	0	0	2 (1.2)	1 (0.6)
Diabetes	1 (0.6)	0	1 (0.6)	0
Encephalitis[b]	1 (0.6)	1 (0.6)	0	0
Myositis	1 (0.6)	1 (0.6)	0	0
Rash	80 (48.8)	6 (3.7)	82 (49.1)	6 (3.6)
Infusion-related reactions	17 (10.4)	1 (0.6)	11 (6.6)	1 (0.6)
Ocular inflammatory toxicity	2 (1.2)	0	0	0
Severe cutaneous reactions	0	0	1 (0.6)	0

Mittendorf EA, et all. Lancet 2020

KEYNOTE-522

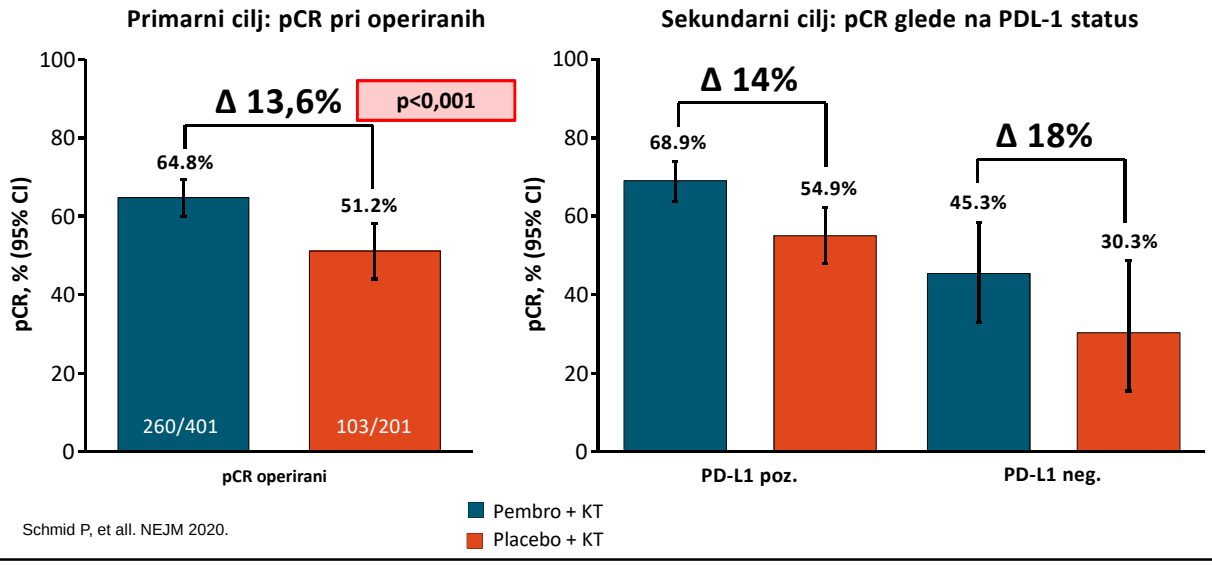


Primarni cilji: pCR pri operiranih (n=602), EFS v ITT

Sekundarni cilji: pCR vseh bolnikov, OS, pCR in EFS po podskupinah (glede na CPS), RCB, EFS glede na pCR, varnost

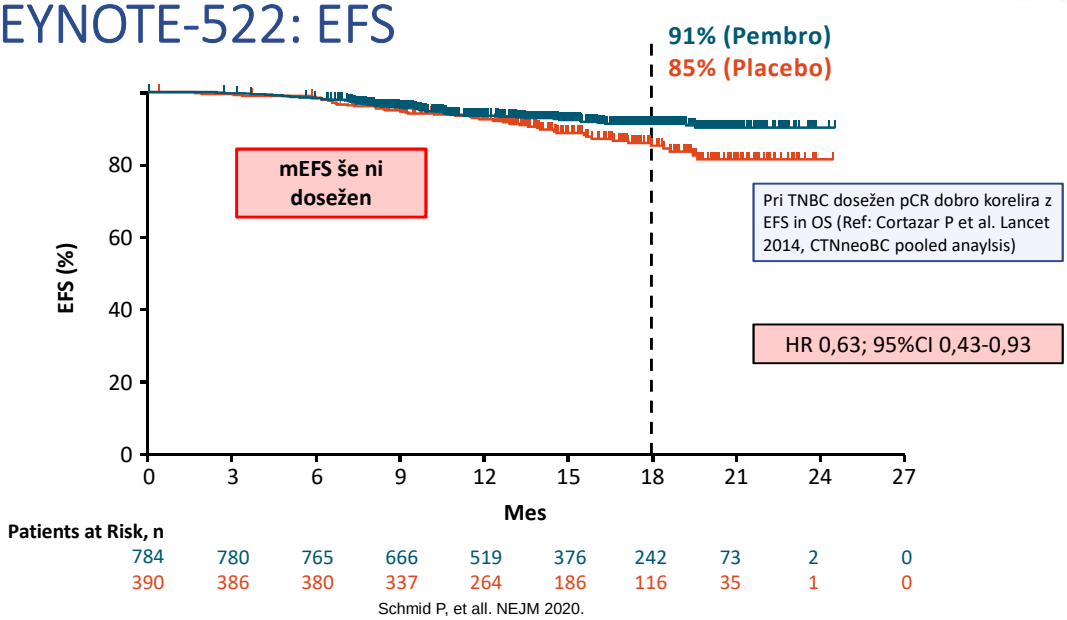
Schmid P, et all. NEJM 2020.

KEYNOTE-522: pCR



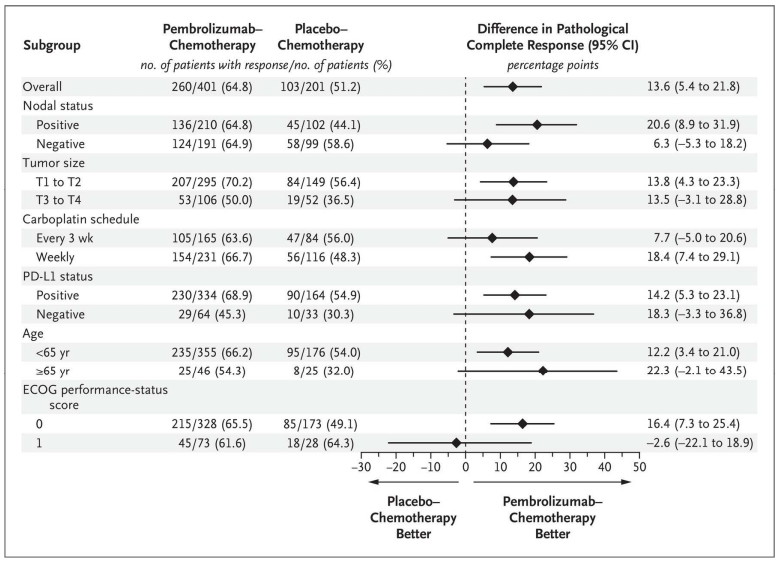
Schmid P, et all. NEJM 2020.

KEYNOTE-522: EFS



Schmid P, et all. NEJM 2020.

KEYNOTE-522: pCR po podskupinah



Schmid P, et all. NEJM 2020.

KEYNOTE-522: varnost

Event	Pembrolizumab–Chemotherapy (N=781)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related adverse event†	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Elevated alanine aminotransferase level	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)
Adverse event of interest‡	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Infusion reaction	132 (16.9)	20 (2.6)	43 (11.1)	4 (1.0)
Hypothyroidism	107 (13.7)	3 (0.4)	13 (3.3)	0
Hyperthyroidism	36 (4.6)	2 (0.3)	4 (1.0)	0
Severe skin reaction	34 (4.4)	30 (3.8)	4 (1.0)	1 (0.3)
Adrenal insufficiency	18 (2.3)	10 (1.3)	0	0

Schmid P, et all. NEJM 2020.

Koliko h KT doda imunoterapija?

	KN 522 Pembrolizumab	IMpassion 31 Atezolizumab
Karboplatin	**DA**	**NE**
N+	**51.7%**	**33.9%**
PD-L1+	**83% (CPS≥1)**	**45% (IC ≥1%)**
pCR	**65% vs. 51% Δ 14%**	**57% vs. 41% Δ 16%**
pCR PD-L1+ **pCR PD-L1-**	**69% vs. 55%** **45% vs. 30%**	**68% vs. 49%** **47% vs. 34%**
LN+ **LN-**	**65% vs. 44%** **65% vs. 59%**	**57% vs 31%** **58% vs. 49%**

Z dovoljenjem B.Šeruga

Raziskava NeoTRIP

- Randomizirana raziskava faze III

Bolniki s eTNBC, "high-risk" (T1cN1, T2N1, or T3N0) ali lokalno napredovalim rakom (ene) dojke (N = 280)

→ **Atezolizumab** 1200 mg Day 1 Q3W for 8 cycles + **Carboplatin** AUC2 + **nab-Paclitaxel** 125 mg/m^2 Day 1, Day 8 Q3W; 8 cycles (n = 138)

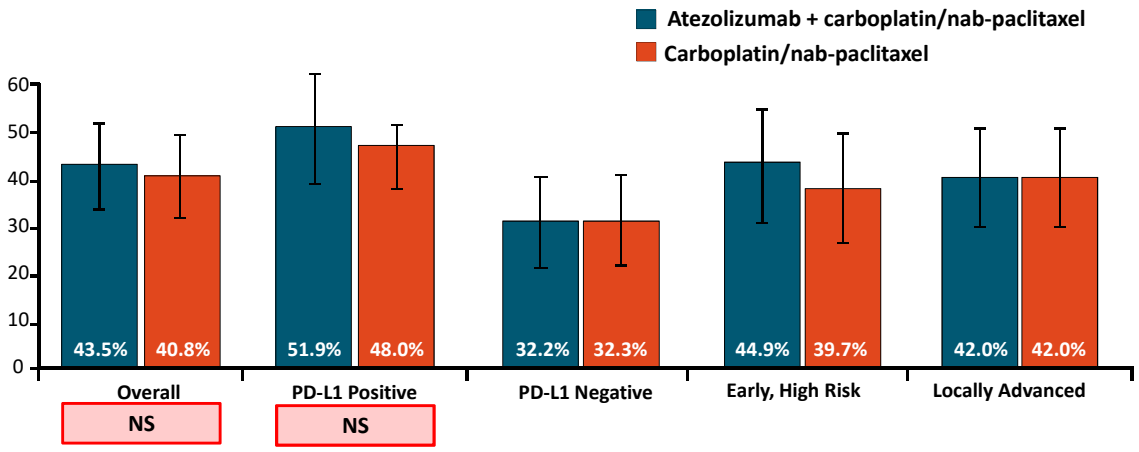
→ **Carboplatin** AUC2 + **nab-Paclitaxel** (125 mg/m^2) Day 1, Day 8 Q3W; 8 cycles (n = 142)

→ **Operacija, ki ji sledi dopolnilno zdravljenje z antraciklini 4x**

- Primarni cilj: EFS po 5 letih
- Sekundarni cilj: EFS glede na PDL-1 status, delež pCR, varnost, biomarkerji odgovora na zdravljenje (dinamika infiltracije s TIL in izraženosti PDL-1 tekom zdravljenja; TILs≥40% na d1c2 prediktor odgovora na zdravljenje z imunoterapijo)

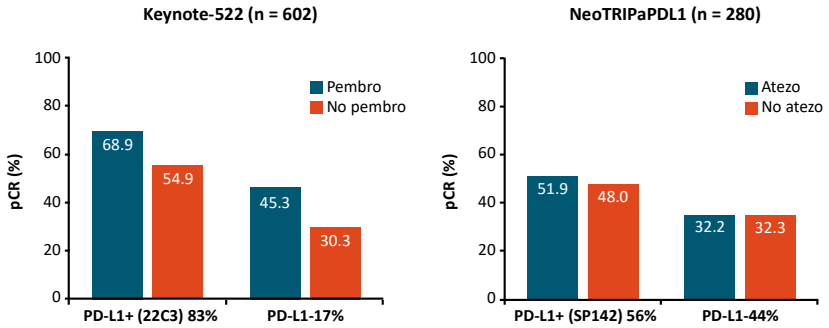
Gianni. SABCS 2019.

NeoTRIP: delež pCR



Gianni. SABCS 2019.

PD-L1 + status napoveduje višji delež pCR Ali napove tudi koristi od imunoterapije?



MVA, ki je vključevala stadij in PD-L1 status je pokazala, da je edini neodvisni napovedni dejavnik pCR izraženost PDL-1, ne glede na obliko zdravljenja.

Schmid P, et all. NEJM 2020, Gianni. SABCS 2019. Abstr GS3-04

NeoTrip: Dinamika TILs in PD-L1 med zdravljenjem (1)

- N=228
- Določitev TIL v stromi in znotraj tumorja
- Določitev PD-L1 na IC, TC
- Dinamika v času zdravljenja (izhodiščno, po 1. ciklu IT → povezava s pCR)
- Ali TILs ≥ 40% po 1 ciklu napoveduje višji pCR?

Bianchini G. Ann Oncol 2020 (ESMO 2020)

NeoTrip: Dinamika TILs in PD-L1 med zdravljenjem (2)

- Tako izhodiščno višji TILs kot PD-L1 je povezan z višjim pCR v skupini, zdravljeni z atezolizumabom
- Samo izhodiščni PD-L1 (ne tudi izhodiščni TILs) je povezan z višjim pCR v skupini s placebom (samo KT)

	Atezo (pCR)	Placebo (pCR)	Δ
PD-L1 (≥10%)	87%	72%	15%
PD-L1 (<10%, ≥1%)	56,2%	44%	12%
PD-L1 < 1%	**35,1%**	**41,1%**	**-6%**

p=0,032

- TILs so se stat. pomembno povišali na d1c2 v obeh skupinah (atezo in placebo) (p<0,0001)
  - TILs na d1c2 so bili kot prediktivni marker za pCR bolj povedni kot izhodiščna vrednost ali ΔTILs
  - TILs ≥ 40% na d1c2 v obeh skupinah napoveduje višji pCR
- PD-L1 se stat. pomembno poviša na d1c2 v skupini z atezo: 45,4%→74,7% (p=0,03)
- PD-L1 se stat. pomembno zniža na d1c2 v skupini s placebom: 52,7%→37,9% (p=0,0001)

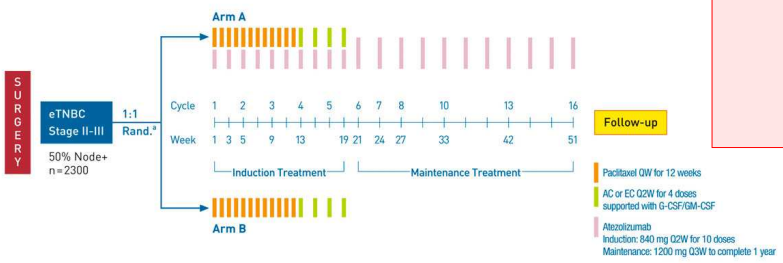
Bianchini G. Ann Oncol 2020 (ESMO 2020)

ONKOLOŠKI INŠTITUT LJUBLJANA

Raziskava ALEXANDRA/IMpassion030

Faza III, randomizirana, multicentrična, odprta
Standardna adj. KT (taksani in antraciklini) ± atezolizumab in eTNBC

Primarni cilj:
iDFS v ITT
Sekundarni cilji:
iDFS glede na PDL-1 status,
glede na N-status,
OS,
varnost,
HRQoL



Notes: The study population will be enriched for patients with node-positive disease such that the final population will contain no more than 50% of node-negative patients. Node-negative patients with tumors ≤ 2 cm in size are not eligible to participate in this study. G-CSF/pegylated G-CSF/GM-CSF will be used with each dose of AC/EC. In the induction period, 1 cycle = 4 weeks; in the maintenance period, 1 cycle = 3 weeks.

* Randomization should occur no more than 8 weeks after definite surgery, and study drug administration should begin within 1 week after randomization but no sooner than 2 weeks after surgery.

McArthur HL, JCO 2019.

Imunoterapija pri ne-TNBC

MEDIOLA

NCT02849496 (atezo+olaparib)

KATE2

Raziskava MEDIOLA

Olaparib and durvalumab in patients with germline *BRCA*-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study

PARPi + antiPDL-1
N= 34
Primarni cilj: varnost, prenosljivost
Različno solidni raki z dokazano zarodno mutacijo v BRCA1/2 genu

- Zdravljenje je prenosljivo.

NU >=G3: 32% (anemija, nevtropenija)
iRAE: diareja (3%), hipotiroidizem (15%)

- Dodatek imunoterapije morda izboljša učinkovitost PARPi (po 12 tednih pri 80% še ni PD)

Domchek SM et al. Lancet Oncol 2020

NCT02849496

Trial in progress: A phase II open-label, randomized study of PARP inhibition (olaparib) either alone or in combination with anti-PD-L1 therapy (atezolizumab) in homologous DNA repair (HDR) deficient, locally advanced or metastatic non-HER2-positive breast cancer.

Check for updates

Patricia LoRusso, Mary Josephine Paula Pilat, Cesar Augusto Santa-Maria, Roisin M. Connolly, Erin Elizabeth Roesch, Anosheh Afghahi, ...

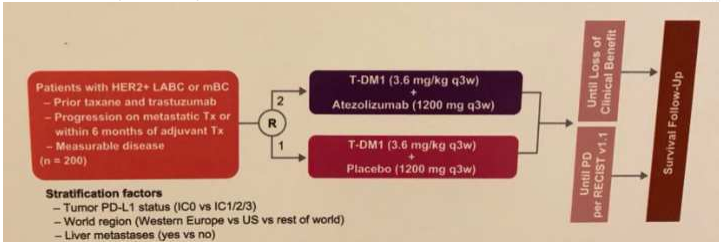
Randomizirana, odprta, F2
N=81 bolnikov
Stadij III/IV, HER2 negativen RD
Znana okvara v genih za homologno rekombinacijo

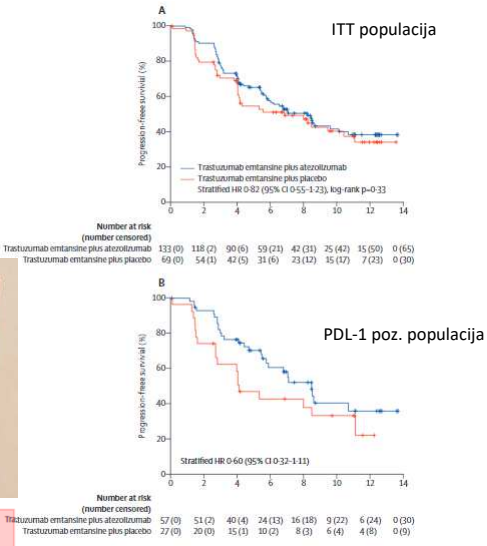
Primerni cilj: PFS
Sekundarni cilji: ORR, DoR
Δ v izraženosti PDL-1, dinamika TIL, ΔTMB v BRCA1/2

Raziskava KATE2

Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial

N=202 (133; 69)





Dodatek atezolizumaba k T-DM1 ni klinično pomembno podaljšal PFS. Zdravljenje je bilo povezano z več NU.

Emens LA et al Lancet Oncol 2020

Zaključki

- Rak dojk je (tradicionalno) veljal za “imunsko hladno bolezen”.
  - Pri nekaterih podtipih raka dojk (TNBC, HER2poz.) ugotavljamo visoko mutacijsko breme in bogato infiltracijo s TIL ⇒ pričakujemo odgovor od imunoterapije (v komibnaciji s kemoterapijo).
- Kako imunsko hladne tumorje spremeniti v imunsko vroče, je eno od pomembnih vprašanj.
- Kateri so biokemični označevalci odgovora na zdravljenje z imunoterapijo.
  - Izraženost PDL-1: mešani rezultati
  - TIL in TMB: potrebujemo še razultate raziskav
- Imunoterapija bo verjetno pomembna oblika zdavljenja za določeno podskupino bolnic z rakom dojk. V teku so številne klinčne raziskave, ki bodo razkrile podskupine bolnic z rakom dojk, za katere bo imunoterapija učinkovito zdravljenje.

LIBTAYO®
(cemiplimab)

Prva terapija za zdravljenje odraslih bolnikov z metastatskim ali lokalno napredovalim ploščatoceličnim karcinomom kože (PCKK), ki niso kandidati za kurativni kirurški poseg ali kurativno obsevanje. [1,2]

Zaviralec PD-1:
spodbuja bolnikov imunski protitumorski odziv za izboljšanje rezultatov zdravljenja [3]

PD-1, receptor programirane celične smrti 1

Pred predpisovanjem prosimo preberite celoten povzetek glavnih značilnosti zdravila.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.
Ime zdravila: LIBTAYO 350 mg koncentrat za raztopino za infundiranje. **Sestava:** En mililiter koncentrata vsebuje 50 mg cemiplimaba. Ena viala vsebuje 350 mg cemiplimaba v 7 ml raztopine. **Terapevtske indikacije:** Zdravilo LIBTAYO je kot samostojno zdravljenje (monoterapija) indicirano za zdravljenje odraslih bolnikov z metastatskim ali lokalno napredovalim ploščatoceličnim karcinomom kože (mPCKK ali lnPCKK), ki niso kandidati za kurativni kirurški poseg ali kurativno obsevanje. **Odmerjanje in način uporabe:** Zdravljenje mora uvesti in nadzorovati zdravnik, izkušen na področju zdravljenja raka. *Priporočeni odmerek:* Priporočeni odmerek cemiplimaba je 350 mg na 3 tedne v 30-minutni intravenski infuziji. Zdravljenje se sme nadaljevati do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. *Prilagoditve odmerka:* Zmanjšanja odmerka niso priporočena. Glede na varnost in prenašanje pri posameznem bolniku je lahko potrebna odložitev odmerka ali prenehanje uporabe. Za priporočene prilagoditve za obvladovanje neželenih učinkov glejte celoten Povzetek glavnih značilnosti zdravila. *Posebne populacije: Pediatrična populacija:* Varnost in učinkovitost zdravila LIBTAYO pri otrocih in mladostnikih, mlajših od 18 let, nista ugotovljeni. *Starejše osebe, okvara ledvic, okvara jeter:* odmerka ni treba prilagoditi. *Način uporabe:* Zdravilo LIBTAYO je namenjeno intravenski uporabi. Daje se v intravenski infuziji v obdobju 30 minut po intravenski liniji, ki vsebuje sterilen, nepirogen filter (v sami liniji ali kot dodatek), ki malo veže beljakovine (velikost por od 0,2 do 5 mikronov). Po isti infuzijski liniji se ne sme istočasno dajati drugih zdravil. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** *Sledljivost:* Za izboljšanje sledljivosti bioloških zdravil je treba čitljivo zabeležiti ime in serijsko številko uporabljenega zdravila. *Imunsko pogojeni neželeni učinki:* Med uporabo cemiplimaba so opažali hude imunsko pogojene neželene učinke, tudi s smrtnim izidom. Pri bolnikih, zdravljenih s cemiplimabom ali drugimi zaviralci PD-1/PD-L1, se lahko sočasno pojavijo imunski neželeni učinki, ki vplivajo na več telesnih sistemov, na primer miozitis in miokarditis ali miastenija gravis. Za obvladanje imunsko pogojenih neželenih učinkov je treba prilagoditi odmerek cemiplimaba, nadomestno hormonsko zdravljenje (če je klinično indicirano) in kortkosteroide. Odvisno od izrazitosti neželenega učinka je treba uporabo cemiplimaba začasno prekiniti ali za stalno prenehati. *Imunsko pogojeni pnevmonitis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeni pnevmonitis, opredeljen s potrebo po uporabi kortikosteroidov in brez jasne alternativne etiologije, vključno s primeri s smrtnim izidom. *Imunsko pogojeni kolitis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeno drisko ali kolitis, opredeljena s potrebo po uporabi kortikosteroidov in brez jasne alternativne etiologije. *Imunsko pogojeni hepatitis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeni hepatitis, opredeljen s potrebo po uporabi kortikosteroidov in brez jasne alternativne etiologije, vključno s primeri s smrtnim izidom. *Imunsko pogojene endokrinopatije:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojene endokrinopatije, opredeljene kot med zdravljenjem nastale endokrinopatije brez jasne alternativne etiologije. *Ščitnične motnje (hipotiroidizem/ hipertiroidizem):* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojene ščitnične motnje. *Hipofizitis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeni hipofizitis. *Nadledvična insuficienca:* Pri bolnikih, ki so prejemali cemiplimab, so opažali nadledvično insuficienco. *Sladkorna bolezen tipa 1:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeno sladkorno bolezen tipa 1, vključno z diabetično ketoacidozo. *Imunsko pogojeni neželeni učinki na kožo:* Med zdravljenjem s cemiplimabom so poročali o imunsko pogojenih neželenih učinkih na kožo, opredeljenih s potrebo po uporabi sistemskih kortikosteroidov in brez jasne alternativne etiologije; med njimi so bili hudi neželeni učinki na kožo, na primer Stevens-Johnsonov sindrom (SJS) in toksična epidermalna nekroliza (TEN) (v nekaterih primerih s smrtnim izidom), in druge kožne reakcije, na primer izpuščaj, multiformni eritem in pemfigoid. *Imunsko pogojeni nefritis:* Pri bolnikih, ki so prejemali cemiplimab, so opažali imunsko pogojeni nefritis, opredeljen s potrebo po uporabi kortikosteroidov in brez jasne alternativne etiologije. Drugi imunsko pogojeni neželeni učinki: Pri bolnikih, ki so prejemali cemiplimab, so opažali še druge življenjsko nevarne in smrtne imunsko pogojene neželene učinke, med njimi paraneoplastični encefalomielitis, meningitis in miozitis. Zdravljenje s cemiplimabom lahko pri prejemnikih presadkov parenhimskih organov poveča tveganje za zavrnitev. V obdobju po prihodu na trg so pri bolnikih, ki so prejemali druge zaviralce PD-1/PD-L1 obenem z alogensko presaditvijo hematopoetskih matičnih celic, poročali o primerih bolezni presadka proti gostitelju. Z infundiranjem povezane reakcije: Cemiplimab lahko povzroči resne ali življenjsko nevarne z infundiranjem povezane reakcije. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo cemiplimaba se je treba izogibati – razen fizioloških odmerkov sistemskih kortikosteroidov (≤ 10 mg/dan prednizolona ali enakovredno) – ker lahko motijo farmakodinamično aktivnost in učinkovitost cemiplimaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti po začetku zdravljenja s cemiplimabom za zdravljenje imunsko pogojenih neželenih učinkov. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi morajo med zdravljenjem s cemiplimabom in vsaj še 4 mesece po zadnjem odmerku cemiplimaba uporabljati učinkovito kontracepcijo. Cemiplimab ni priporočljiv med nosečnostjo in za ženske v rodni dobi, ki ne uporabljajo učinkovite kontracepcije, razen če klinična korist odtehta možno tveganje. Če se ženska odloči za zdravljenje s cemiplimabom, ji je treba svetovati, da med zdravljenjem s cemiplimabom in vsaj še 4 mesece po zadnjem odmerku ne sme dojiti. **Vpliv na sposobnost vožnje in upravljanja strojev:** Po zdravljenju s cemiplimabom so poročali o utrujenosti. **Neželeni učinki:** Zelo pogosti: driska, izpuščaj, pruritus, utrujenost. Pogosti: z infundiranjem povezane reakcije, hipotiroidizem, hipertiroidizem, dispneja, stomatitis, hepatitis, artralgija, mišično-skeletna bolečina,artritis, zvišana alanin-aminotransferaza, zvišana aspartat-aminotransferaza, zvišana alkalna fosfataza v krvi, zvišan kreatinin v krvi. Občasni: sjögrenov sindrom, imunsko pogojena trombocitopenična purpura, sladkorna bolezen tipa 1, nadledvična insuficienca, hipofizitis, tiroiditis, praneoplastični encefalomielitis, kronična vnetna demielinizirajoča poliradikulonevropatija, encefalitis, meningitis, Guillain-Barréjev sindrom, vnetje osrednjega živčevja, periferna nevropatija, miastenija gravis, keratitis, miokarditis, perikarditis, šibkost mišic, revmatska polimialgija, nefritis. **Preveliko odmerjanje:** V primeru prevelikega odmerjanja naj se bolnike natančno kontrolira glede znakov in simptomov neželenih učinkov in uvede ustrezno simptomatsko zdravljenje. **Način in režim izdaje zdravila:** H-Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. **Imetnik dovoljenja za promet z zdravilom:** Regeneron Ireland Designated Activity Company (DAC), Europa House, Harcourt Centre, Harcourt Street, Dublin 2, Irska. **Datum zadnje revizije besedila:** 07 2020

SAMO ZA STROKOVNO JAVNOST

REGENERON | SANOFI GENZYME

Sanofi and Regeneron are collaborating in the global development and commercialization for LIBTAYO (cemiplimab).

MAT-SI-2000079-3.0-10/2020

1. Libtayo (cemiplimab) Povzetek glavnih značilnosti zdravila, www.ema.europa.com, datum zadnjega podaljšanja 31.07.2020
2. www.nice.org.uk, technology appraisal guidance TA592. dostop 07.08.2019. 3. www.cancer.gov/publications/dictionaries/cancer-terms/def/pd-1, dostop 07.08.2019

NOVOSTI PRI RAKU SEČNEGA MEHURJA

BREDA ŠKRBINC

NOVOSTI V IMUNO-ONKOLOGIJI 2020

OIL 15.- 16.12.2020

Urotelni karcinom še do pred 10 let povsem neraziskan rak, nepoznana tu biologija, raziskav malo

- 30 let nobenih sprememb / napredka v zdravljenju

- Spoznanja o biologiji raka na sploh in na modelih drugih vrst raka
- Spoznanja o imunologiji raka
  - TMB in povezava z imunologijo raka
- Nove tehnike tehnike molekularne diagnostike
- Raziskave vloge imunoterapije v zdravljenju urotelnega raka
- Molekularna klasifikacija
- Raziskave racionalnega pristopa k sistemskemu zdravljenju urotelnega ca
  - Napovedni dejavniki odziva ne zdravljenja
  - Racionalne sekvence in kombinacije KT, imunoterapije in tarčnih zdravil

Imunoterapija in rak sečnega mehurja

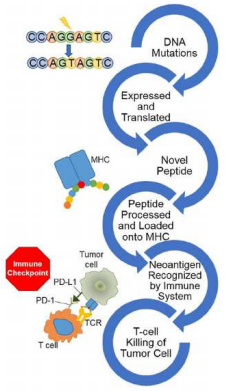


Figure 1. Rationale for the use of both microsatellite instability–high/mismatch repair deficiency and tumor mutational burden as immune checkpoint inhibitor biomarkers. Large numbers of mutations produce numerous altered peptides. Of these, a subset are expressed and processed successfully by the major histocompatibility complex, resulting in neoantigens to which the immune system can generate an antitumor response.

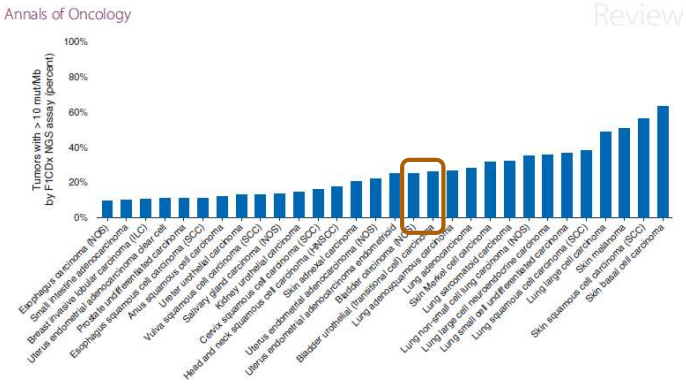


Figure 4. Impact of TMB pan-cancer: percent of solid tumors with TMB ≥10 mut/Mb. Analysis of top 30 solid tumor types selected from 104,814 total cases sorted by percent of cases with TMB ≥10 mut/Mb according to the Foundation Medicine database. TMB is defined as the number of somatic synonymous and non-synonymous base substitutions and indels divided by the region over which it was counted. Only cancer types with at least 100 total cases are reported. The average across all solid tumor types was 13.3%.

Metastatski urotelni ca

TMB – povezava z možnostjo zdravljenja z imunoth s CPI
Raziskave CPI v zdravljenju mBC

- Anti PD-L1
  - Atezolizumab
- Anti PD1
  - Pembrolizumab
  - Nivolumab
  - Avelumab
  - Durvalumab
- Anti CTL4
  - Ipilimumab
  - tremelilumab

Odobreni za Klinično prakso

Metastatski urotelni ca 2. linija

- Anti PD-L1
  - Atezolizumab
- Anti PD1
  - Pembrolizumab
  - Nivolumab
  - Avelumab
  - Durvalumab

Odobreni za Klinično prakso

Metastatski urotelni ca 1. linija
Cisplatin ineligable - PD1/PD-L1 poz

- Anti PD-L1
  - Atezolizumab
- Anti PD1
  - Pembrolizumab

Metastatski urotelni ca

TABLE 2. Pivotal Clinical Trials of Immune Checkpoint Inhibitors for Advanced Urothelial Cancer

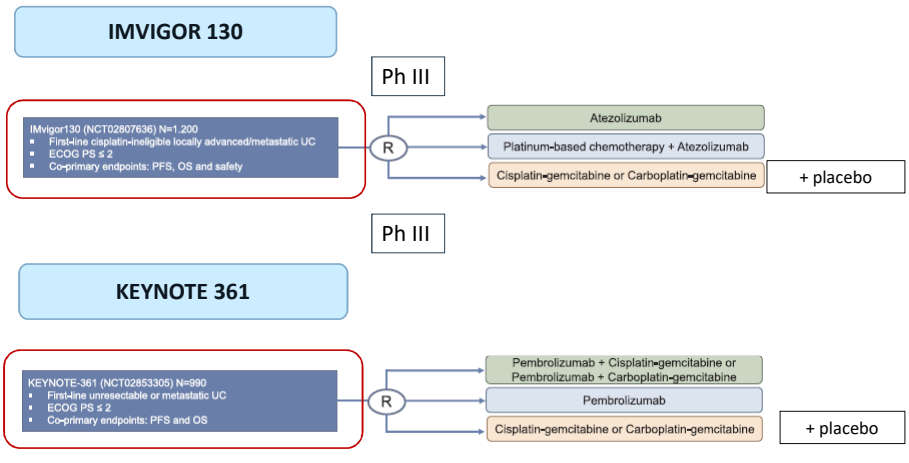
STUDY	MONTH/YEAR	ELIGIBILITY	NO.	PHASE	INTERVENTION	PRIMARY ENDPOINT (95% CI)
Rosenberg 2016[120] (IMvigor210)	05/2016	Platinum-ineligible or refractory	311	2	Atezolizumab	ORR: All, 15% (11%-19%); IC1/IC2/IC3, 18% (13%-24%); IC2/IC3, 26% (18%-36%)
Sharma 2007[122] (CheckMate-032)	11/2016	Platinum-ineligible or refractory	78	1/2	Nivolumab	ORR: All, 24% (15%-35%)
Balar 2017[123] (IMvigor210)	01/2017	First-line, cisplatin-ineligible[a]	119	2	Atezolizumab[a]	ORR: All, 23% (%16-31%); PD-L1 ≥ 5%, 28% (14%-47%); PD-L1 < 5%, 22% (14%-32%)
Bellmunt 2017[124] (KEYNOTE-045)	03/2017	Platinum-ineligible or refractory	542	3	Pembrolizumab vs chemotherapy	OS: All, HR, 0.73 (0.59-0.91; P = .002); CPS ≥ 10, HR, 0.57 (0.37-0.88; P = .005); CPS < 10, HR, 0.89 (0.61-1.05)
Apolo 2017,[125] Patel 2018[126] (JAVELIN Solid Tumor trial)	07/2017; 01/2018	Platinum-ineligible or refractory	242	1b	Avelumab	ORR: All, 17% (11%-24%); PD-L1 ≥ 5, 24% (14%-36%); PD-L1 < 5, 13% (7%-23%)
Powles 2017[127]	09/2017	Platinum-ineligible or refractory	191	1/2	Durvalumab	ORR: All, 17% (11%-24%); PD-L1 ≥ 25%, 28% (19%-38%); PD-L1 < 25%, 9% (4%-15%)
Balar 2017[128] (KEYNOTE-052)	11/2017	First-line, cisplatin-ineligible[b]	370	2	Pembrolizumab[b]	ORR: All, 24% (20%-29%); CPS ≥ 10, 39% (28%-50%); CPS 1-10, 20% (14%-28%); CPS < 1, 11% (4%-21%)

Abbreviations: CheckMate-032, A Study of Nivolumab by Itself or Nivolumab Combined With Ipilimumab in Patients With Advanced or Metastatic Solid Tumors (ClinicalTrials.gov identifier NCT01928394); CPS, combined positive score (percentage of tumor and immune cells with PD-L1 expression × 100); IC, immune cell group (corresponding to level of PD-L1 expression on tumor cells); IMvigor210, A Study of Atezolizumab in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer (Cohort 2) (ClinicalTrials.gov identifier NCT02108652); JAVELIN Solid Tumor trial, Avelumab in Metastatic or Locally Advanced Solid Tumors (ClinicalTrials.gov identifier NCT01772004); KEYNOTE-045, A Study of Pembrolizumab (MK-3475) Versus Paclitaxel, Docetaxel, or Vinflunine for Participants With Advanced Urothelial Cancer (ClinicalTrials.gov identifier NCT02256436); KEYNOTE-052, Study of Pembrolizumab (MK-3475) in Participants With Advanced Urothelial Cancer (ClinicalTrials.gov identifier NCT02335424); ORR, objective response rate; OS, overall survival.
[a]The data monitoring committee of this study found early deaths in patients harboring <5% PD-L1 expression, thus approval was restricted to first-line cisplatin-ineligible patients harboring ≥5% PD-L1 expression.
[b]The data monitoring committee of this study found early deaths in patients who had a CPS < 10, thus approval was restricted to first-line cisplatin-ineligible patients who had a CPS ≥ 10.

Faza III-IMVIGOR 211: Atezo vs CTX

CA CANCER J CLIN 2020;70:404–423

Metastatski urotelni ca



Lancet 2020; 395: 1547–57

Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial

Metastatski urotelni ca

IMvigor130 (NCT02807636) N=1.200
- First-line cisplatin-ineligible locally advanced/metastatic UC
- ECOG PS ≤ 2
- Co-primary endpoints: PFS, OS and safety

R

- Atezolizumab
- Platinum-based chemotherapy + Atezolizumab
- Cisplatin-gemcitabine or Carboplatin-gemcitabine

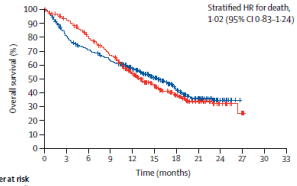
B A C

+ placebo

Kaplan-Meier estimates of overall survival for groups B and C.

D

	Number of events/ number of patients	Median overall survival (95% CI), months
Atezolizumab monotherapy (group B)	191/360	15·7 (13·1–17·8)
Placebo + platinum-based chemotherapy (group C)	198/359	13·1 (11·7–15·1)

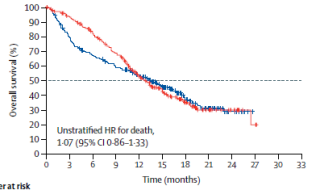


Number at risk (number censored)												
Atezolizumab monotherapy (group B)	360 (0)	285 (10)	245 (14)	216 (16)	173 (41)	120 (75)	72 (107)	42 (128)	16 (153)	NE	NE	NE
Placebo + platinum-based chemotherapy (group C)	359 (0)	322 (13)	274 (19)	224 (24)	158 (48)	103 (79)	62 (107)	35 (128)	15 (147)	3 (158)	NE	NE

Kaplan-Meier estimates of overall survival for groups B and C for patients with PD-L1 IC0/1 tumours.

F

	Number of events/ number of patients	Median overall survival (95% CI), months
Atezolizumab monotherapy (group B)	158/272	13·5 (11·1–16·4)
Placebo + platinum-based chemotherapy (group C)	156/274	12·9 (11·3–15·0)



Number at risk (number censored)												
Atezolizumab monotherapy (group B)	272 (0)	210 (7)	175 (10)	152 (12)	124 (27)	85 (49)	48 (74)	28 (87)	11 (103)	NE	NE	NE
Placebo + platinum-based chemotherapy (group C)	274 (0)	246 (10)	212 (16)	173 (20)	116 (40)	73 (62)	41 (83)	21 (98)	10 (109)	2 (116)	NE	NE

Lancet 2020; 395: 1547–57

FDA no longer considered the benefit-risk profile favorable for all cisplatin-ineligible patients. Therefore, **on June 18, 2018, the *indication for both agents* was modified to include only patients who are not eligible for cisplatin-containing chemotherapy *and who have high expression of PD-L1* or are not eligible for any platinum-containing chemo-therapy regardless of the level of PD-L1 expression**

The Oncologist 2019;24:563–569

Metastatski urotelni ca

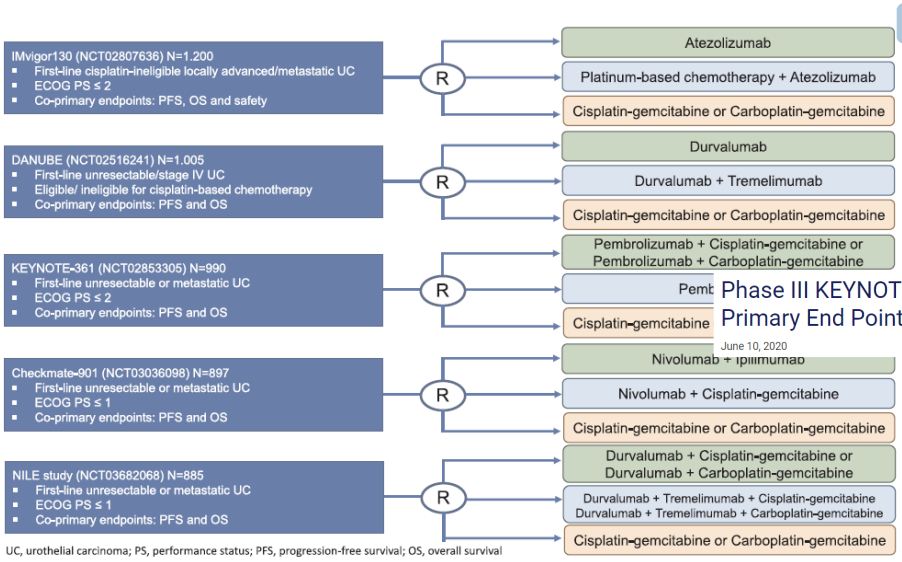
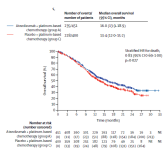


Fig. 2. Key first-line Phase III trials of anti-PD1/PD-L1 antibodies in urothelial carcinoma.



Phase III KEYNOTE-361 Trial Fails to Meet Primary End Points

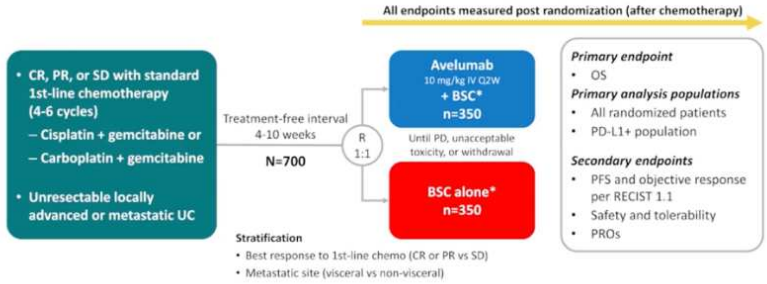
June 10, 2020

Cancer Treatment Reviews 76 (2019) 10–21

PD-L1 poz

Metastatski urotelni ca

JAVELIN Bladder 100 study design (NCT02603432)

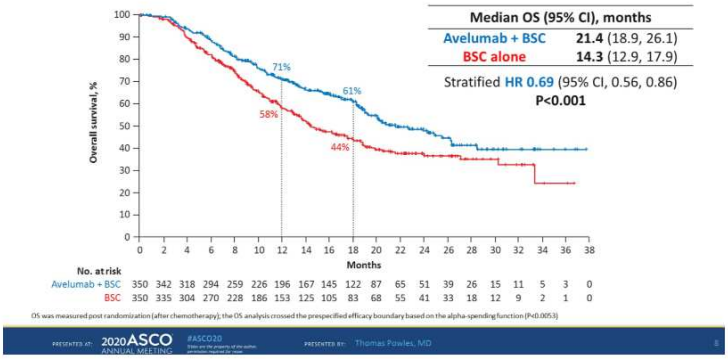


PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; CR, complete response; IV, intravenous; PR, partial response; PRO, patient reported outcome; Q2W, every 2 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease

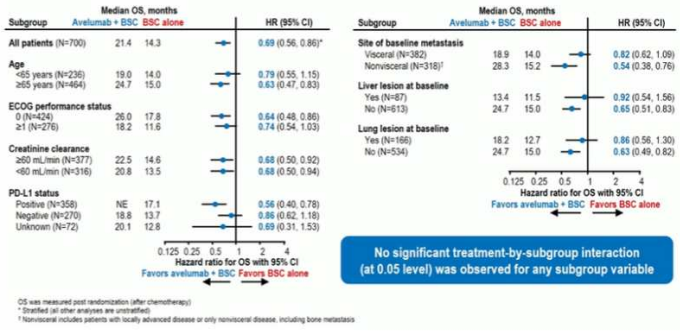
*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

OS in the overall population



Metastatski urotelni ca

OS benefit with avelumab 1L maintenance was observed across additional prespecified subgroups



Metastatski urotelni ca

CPI v zdravljenju metastatskega urotelnega ca v 2020

- Anti PD-L1
  - Atezolizumab
- Anti PD1
  - Pembrolizumab
  - Nivolumab
  - Avelumab
  - Durvalumab
- Anti CTL4
  - Ipilimumab
  - tremelilumab

Odobreni za Klinično prakso

Metastatski urotelni ca 2. linija

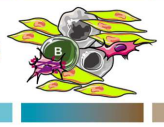
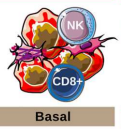
- Anti PD-L1
  - Atezolizumab
- Anti PD1
  - Pembrolizumab
  - Nivolumab
  - Avelumab
  - Durvalumab

Odobreni za Klinično prakso

Metastatski urotelni ca 1. linija
Cisplatin ineligable / PDL1 poz

- Anti PD-L1
  - Atezolizumab
- Anti PD1
  - Pembrolizumab
  - Avelumab vzdrževalno

Molekularna opredelitev MIBC

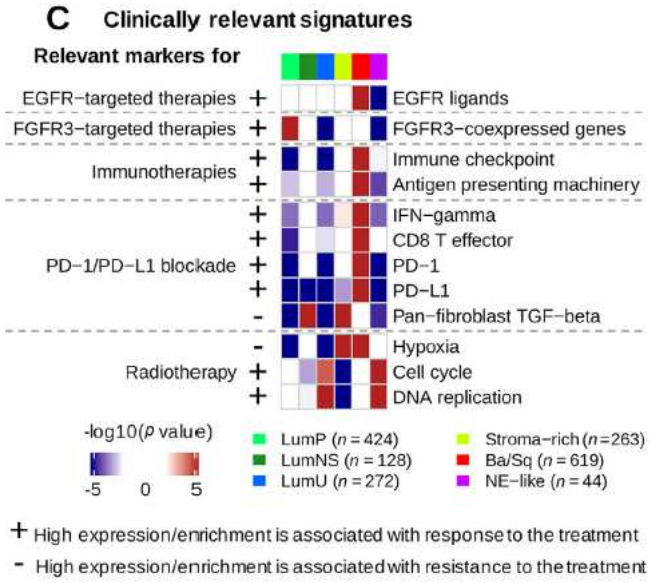
% of MIBC	24%	8%	15%	15%	35%	3%
Class Name	Luminal Papillary (LumP)	Luminal Non-Specified (LumNS)	Luminal Unstable (LumU)	Stroma-rich	Basal/Squamous (Ba/Sq)	Neuroendocrine-like (NE-like)
						
Differentiation	Urothelial / Luminal				Basal	Neuroendocrine
Oncogenic mechanisms	FGFR3 + PPARG + CDKN2A -	PPARG +	PPARG + E2F3 +, ERBB2 + Genomic instability Cell cycle +		EGFR +	TP53 -, RB1 -, Cell cycle +
Mutations	*FGFR3* (40%), *KDM6A* (38%)	*ELF3* (35%)	*TP53* (76%), *ERCC2* (22%) TMB +, APOBEC +		*TP53* (61%), *RB1* (25%)	*TP53* (94%) *RB1* (39%)*
Stromal infiltrate		Fibroblasts		Smooth muscle Fibroblasts Myofibroblasts	Fibroblasts Myofibroblasts	
Immune infiltrate				B cells	CD8 T cells NK cells	
Histology	Papillary morphology (59%)	Micropapillary variant (36%)			Squamous differentiation (42%)	Neuroendocrine differentiation (72%)
Clinical	T2 stage +	Older patients + (80+)			Women + T3/T4 stage +	
Median overall survival (years)	4	1.8	2.9	3.8	1.2	1

* 94% of these tumors present either RB1 mutation or deletion

EUROPEAN UROLOGY 77 (2 0 2 0) 4 20– 4 33

A Consensus Molecular Classification of Muscle-invasive Bladder Cancer

A Consensus Molecular Classification of Muscle-invasive Bladder Cancer



EUROPEAN UROLOGY 77 (2 0 2 0) 4 20– 4 33

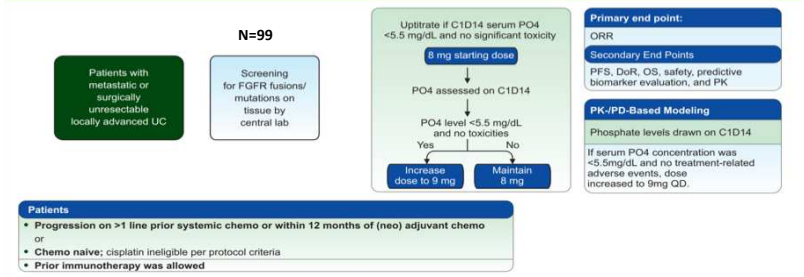
Metastatski urotelni ca

ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Erdafitinib

Raziskava **BCL2001**

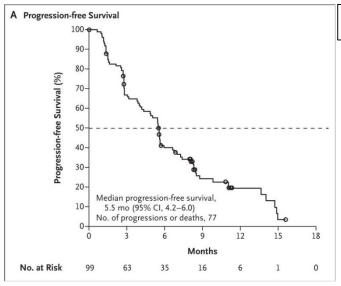


***Raziskava* BCL2001**

Erdafitinib: FGFR-inhibitor

Metastatski urotelni ca

FGFR 2/3 mutacije - fuzije



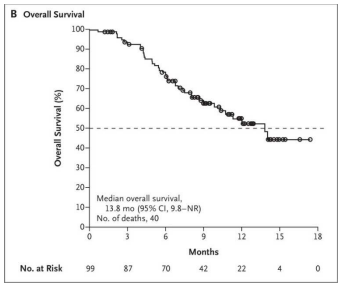


Table 2. Antitumor Activity of Erdafitinib in the 99 Patients in the Selected-Regimen Group.*

Variable	Value	Rate of Response (95% CI)
		percent
Response per investigator assessment — no. of patients†		
Any objective response	40	40 (31–50)
Complete response	3	3
Partial response	37	37
Stable disease	39	39
Progressive disease	18	18
Could not be evaluated or unknown	2	
Median time to response — mo	1.4	
Median duration of response (95% CI) — mo	5.6 (4.2–7.2)	
Response per independent radiologic assessment — no. of patients†		
Objective response	34	34 (25–44)
Complete response	3	3
Partial response	31	31
Response according to previous treatment — no./total no.		
No chemotherapy	5/12	42
Progression or relapse after chemotherapy	35/87	40
Immunotherapy	13/22	59
Response according to number of previous systemic treatments — no./total no.		
0	4/11	36 (8–65)
1	17/45	38 (24–52)
2	11/29	38 (20–56)
3	6/10	60 (10–90)
≥4	2/4	50 (1–99)
Response according to presence or absence of visceral metastasis — no./total no.		
Present	30/78	38 (28–49)
Bone	10/21	48 (26–69)
Liver	7/20	35 (14–56)
Lung	23/57	40 (28–53)
Lymph node only	4/12	33 (7–60)
Upper tract disease‡	10/23	43 (23–64)
Lower tract disease§	30/76	39 (29–51)
Absent	10/21	48 (26–69)
Response according to daily dose of erdafitinib — no./total no.		
8 mg	20/58	34 (22–47)
8 mg with dose escalation to 9 mg	20/41	49 (34–64)
Response according to genetic alteration — no./total no.		
FGFR3 mutation	36/74	49 (37–60)
FGFR2/3 fusion	4/25	16 (2–30)

N Engl J Med 2019;381:338-48

***Raziskava* BCL2001**

Erdafitinib – neželeni učinki zdravljenja

Metastatski urotelni ca

Table 3. Adverse Events in the 99 Patients in the Selected-Regimen Group.*

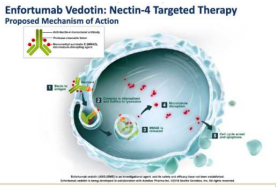
Adverse Event	Any Grade	Grade 1	Grade 2	Grade ≥3
		number of patients (percent)		
Hyperphosphatemia	76 (77)	53 (54)	21 (21)	2 (2)
Stomatitis	57 (58)	21 (21)	26 (26)	10 (10)
Diarrhea	50 (51)	31 (31)	15 (15)	4 (4)
Dry mouth	45 (46)	34 (34)	11 (11)	0
Decreased appetite	38 (38)	18 (18)	20 (20)	0
Dysgeusia	37 (37)	23 (23)	13 (13)	1 (1)
Fatigue	32 (32)	12 (12)	18 (18)	2 (2)
Dry skin	32 (32)	24 (24)	8 (8)	0
Alopecia	29 (29)	23 (23)	6 (6)	0
Constipation	28 (28)	19 (19)	8 (8)	1 (1)
Hand–foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Anemia	20 (20)	9 (9)	7 (7)	4 (4)
Asthenia	20 (20)	2 (2)	11 (11)	7 (7)
Nausea	20 (20)	13 (13)	6 (6)	1 (1)
Dry eye	19 (19)	14 (14)	4 (4)	1 (1)
Onycholysis	18 (18)	6 (6)	10 (10)	2 (2)
Alanine aminotransferase increased	17 (17)	13 (13)	2 (2)	2 (2)
Paronychia	17 (17)	3 (3)	11 (11)	3 (3)
Blurred vision	17 (17)	10 (10)	7 (7)	0
Nail dystrophy	16 (16)	5 (5)	5 (5)	6 (6)
Urinary tract infection	16 (16)	0	11 (11)	5 (5)
Vomiting	13 (13)	10 (10)	1 (1)	2 (2)
Hyponatremia	12 (12)	1 (1)	0	11 (11)
Hematuria	10 (10)	7 (7)	1 (1)	2 (2)
Dyspnea	8 (8)	4 (4)	2 (2)	2 (2)
Nail disorder	8 (8)	4 (4)	1 (1)	3 (3)
Acute kidney injury	6 (6)	2 (2)	2 (2)	2 (2)
Cataract	6 (6)	3 (3)	1 (1)	2 (2)
Colitis	5 (5)	1 (1)	2 (2)	2 (2)
General deterioration in physical health	5 (5)	0	1 (1)	4 (4)
Keratitis	5 (5)	0	2 (2)	3 (3)
Aphthous ulcer	4 (4)	2 (2)	0	2 (2)
Increase in γ-glutamyltransferase	3 (3)	1 (1)	0	2 (2)
Urosepsis	3 (3)	0	0	3 (3)

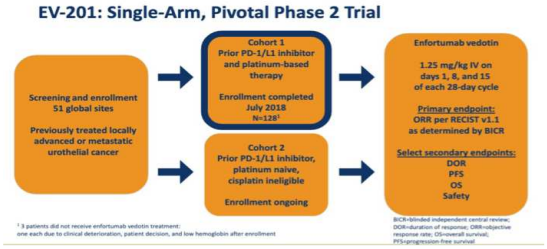
N Engl J Med 2019;381:338-48

Metastatski urotelni ca

Enfortumab vedotin

- Kombinacija humanega monoklonskega protitelesa proti nectinu 4 in monometil auristatina E (delovanje na mikrotubule)
- Tarča je nectin 4, transmembranski protein, visoko izražen na površini celic urotelnega karcinoma

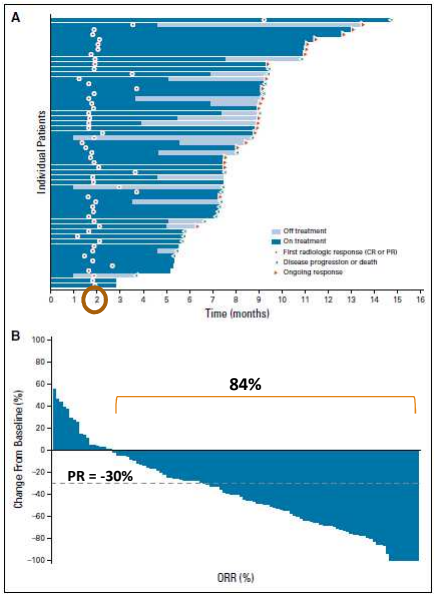




Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy

Metastatski urotelni ca

Enfortumab vedotin – EVE 201



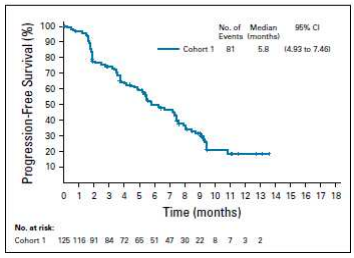


FIG A5. Kaplan-Meier estimate of progression-free survival per blinded independent central review in the full analysis set.

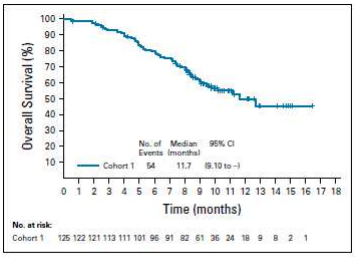


FIG A6. Kaplan-Meier estimate of overall survival in the full analysis set.

J Clin Oncol 37:2592-2600.

Enfortumab vedotin-EVE 201 – neželeni učinki zdravljenja

Metastatski urotelni ca

TABLE 3. Summary of Adverse Events in Patients Receiving Enfortumab Vedotin

Variable	Patients (N = 125)	
Any adverse event	125 (100)	
Treatment-related adverse events	117 (94)	
Grade ≥ 3 treatment-related adverse events	68 (54)	
Treatment-related serious adverse events	24 (19)	
Treatment-related adverse events resulting in treatment discontinuation	15 (12)	
Treatment-related adverse events leading to death*	0 (0)	
Treatment-related adverse events occurring in ≥ 20% (preferred term)	Any Grade	Grade ≥ 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Rash maculopapular	27 (22)	5 (4)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0

NOTE. Data are presented as No. (%).

*There were no treatment-related deaths during the 30-day safety reporting period. One death as a result of interstitial lung disease that occurred outside the safety reporting period was reported as treatment related.

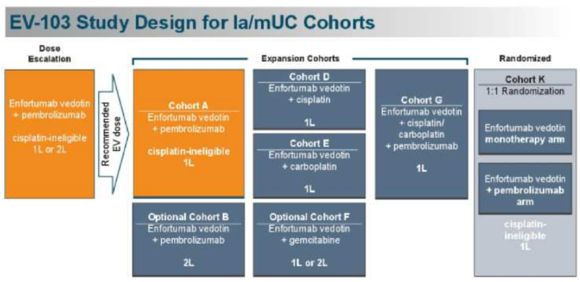
Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy

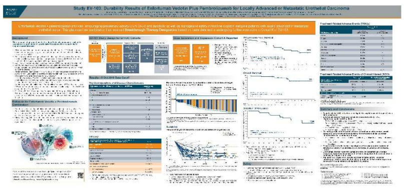
Jonathan E. Rosenberg, MD[1,2]; Peter H. O'Donnell, MD[3]; Arjun V. Balar, MD[4]; Bradley A. McGregor, MD[5]; Elisabeth I. Heath, MD[6]; Evan Y. Yu, MD[7,8]; Matthew D. Galsky, MD[9]; Noah M. Hahn, MD[10]; Elaina M. Gartner, MD[11]; Juan M. Pinelli, PA-C, MMSc[11]; Shang-Ying Liang, PhD[11]; Amal Melhem-Bertrandt, MD[12]; and Daniel P. Petrylak, MD[13]

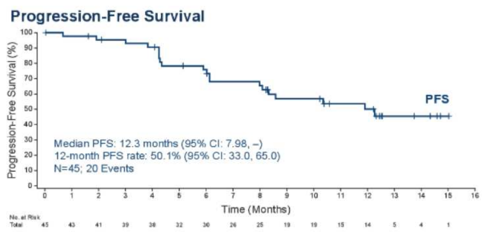
J Clin Oncol 37:2592-2600.

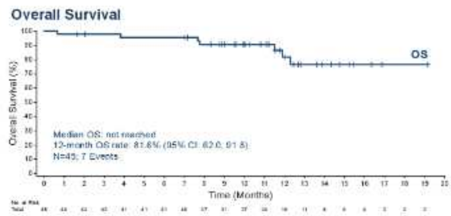
ASCO 2020: Study EV-103: Durability Results of Enfortumab Vedotin plus Pembrolizumab for Locally Advanced or Metastatic Urothelial Carcinoma

Metastatski urotelni ca

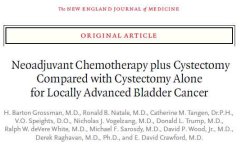








PERIOPERATIVNO ZDRAVLJENJE



ORIGINAL ARTICLE

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

H. Barton Grossman, M.D., Ronald B. Natale, M.D., Catherine M. Tangen, Dr.P.H., V.O. Speights, D.O., Nicholas J. Vogelzang, M.D., Donald L. Trump, M.D., Ralph W. deVere White, M.D., Michael F. Sarosdy, M.D., David P. Wood, Jr., M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.

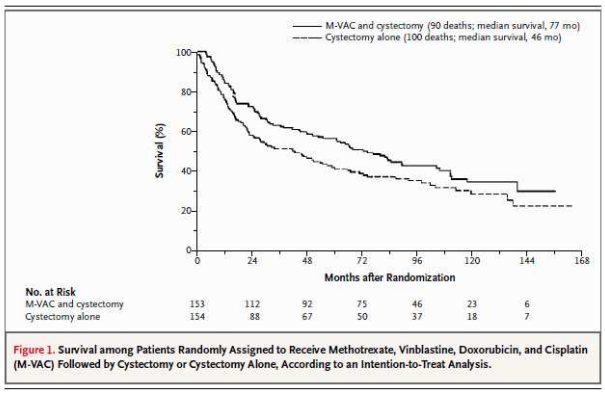


Figure 1. Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis.

MVAC – 14% izboljšanje 5 letnega OS

Table 2.
Criteria for Cisplatin Ineligibility

Table 2. Criteria for Cisplatin Ineligibility

Performance status	ECOG ≥2; KPS ≤60%–70%
Renal function	Creatinine clearance <60 mL/min
Hearing	Hearing loss of 25 dB at 2 contiguous frequencies; CTCAE grade ≥2
Neuropathy	CTCAE grade ≥2
Heart function	NYHA class ≥III

Abbreviations: KPS, Karnofsky performance status; NYHA, New York Heart Association.

N Engl J Med 2003;349:859-66.

Mišično invazivni urotelni ca

PURE-01 - pembrolizumab

Opportunity window trial

- Fit and planned for cystectomy
- Predominant (i.e., 50% at least) UC histology
- cT ≤3bN0 stage
- Residual disease after TURB (surgical opinion, cystoscopy or radiological presence)
- GFR ≥20 mL/min (Cockcroft–Gault formula)
- ECOG-PS 0–1

3 x 3 weekly cycles of pembrolizumab 200 mg IV

Additional DD-MVAC x 4 cycles in non-responding patients (investigator choice)

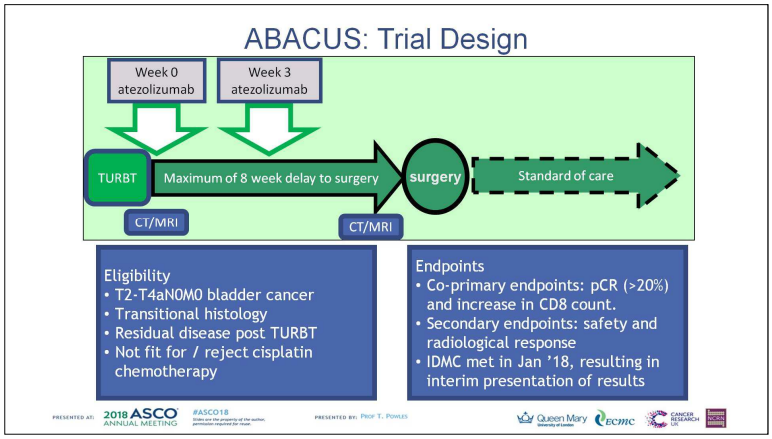
Pre-post treatment tissue/blood sample collection for biomarker analyses

Pre-post treatment imaging: multiparametric bladder MRI (mpMRI); FDG-PET/CT scan, T/A CT scan

- Cystectomy
- Post-cystectomy management according to EAU guidelines
- Survival data collected until 2-years post cystectomy

Primary endpoint – pT0 at the time of radical cystectomy in the ITT population

ABACUS - atezolizumab



Presented By Thomas Powles at 2018 ASCO Annual Meeting

	GU14-188 Gem+Pembro	NABUCCO Ipi/Nivo	ABACUS Atezolizumab	PURE-01 Pembrolizumab	BLASST-1 Nivolumab+Gem-Cis	GU 14-188 PEMBRO+ GEM-CIS
Target population	Cis-ineligible	Cis-ineligible/refusal	Cis-ineligible/refusal	Cis-eligible/ineligible	Cis-eligible	Cis-eligible
N	37	24	88	114	41	40
cT2	43%	0	73%	43%	90%	51%
cT3/T4	57%	58%	27%	57%	7%	44%
cN+	0	42%	0	0	3%	0
pT0N0 rate	45.2%	46%	31% (includes CIS)	37%	49% (includes CIS)	39.5%
pT≤1N0 rate	51.6%	58%		55%	66%	
RFS	67 %	92%	79%	91%	Not mature	80%
Gr 3-4 AEs	84%	54% (irAE)	11%	Initial report 5% (N=43)	24%	
RC withheld due to TRAE	No	Yes 4%	Yes 3%	No	No	2.5%
Biomarkers	Not reported	PD-L1,TMB, TGF-BETA, CD8, TLS, B cell	PDL1, TMB, TGF-BETA, CD8, GZMB	PD-L1, TMB Immune gene signatures	PD-L1, TMB, Immune gene signatures	PD-L1

Powlles Thomas et al. Nature Medicine 2019, Necchi Andrea et al. J Clin Oncol 2018, Gupta, Shilpa GU ASCO 2020 Hoimes C et al. ESMO 2018

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: SHILPA GUPTA

9

Presented By Shilpa Gupta at TBD

Phase III Neoadjuvant IO Trials in MIBC

Single-Agent Therapy	Country	Eligibility	Cisplatin Eligibility	Trial Identifier	Status
• Pembrolizumab > RC vs RC alone (KEYNOTE-905)	Multicenter international	T2-4aN0M0	No	NCT03924895	Recruiting
• Nivolumab > RC vs RC alone	Multicenter international	T2-4aN0M0	No	NCT04209114	Not yet recruiting
Immune Combination Therapy					
• Nivolumab + NKTR-214 > RC vs RC alone	Multicenter international	T2-4aN0M0	No	NCT04209114	Not yet recruiting
Chemoimmunotherapy Combinations					
• Gem/Cis + pembrolizumab vs Gem/Cis (KEYNOTE-866)	Multicenter international	T2-4aN0M0	Yes	NCT03924856	Recruiting
• Gem/Cis + durvalumab vs Gem/Cis (NIAGARA)	Multicenter international	T2-4aN0M0	Yes	NCT03732677	Recruiting
• Gem/Cis + nivolumab ± BMS-986205 vs Gem/Cis (ENERGIZE)	Multicenter international	T2-4aN0M0	Yes	NCT03661320	Recruiting

Slide Courtesy: Andrea Necchi

Presented By Shilpa Gupta at TBD

Mišično invazivni urotelni ca
ADJUVANTNO ZDRAVLJENJE

IMvigor010 Study Design

Key eligibility[a]
- **High-risk MIUC (bladder, renal pelvis, ureter)**
- **Radical cystectomy/nephroureterectomy with LN dissection** within ≤ 14 weeks
  - **ypT2-T4a or ypN+** for patients treated with **NAC**[b]
  - **pT3-T4a or pN+** for patients **not treated with NAC**[b]
- No postsurgical radiation or AC
- If no prior NAC given, patient had to be ineligible for, or declined, cisplatin-based AC
- ECOG PS 0-2
- **Tissue sample for PD-L1 testing**

R 1:1

Atezolizumab 1200 mg q3w *(16 cycles or 1 year)*

No crossover allowed

Observation[c] q3w

Disease recurrence/ survival follow-up

Tumor assessments: q12w for years 1-3, (q24w for years 4-5 and at year 6)

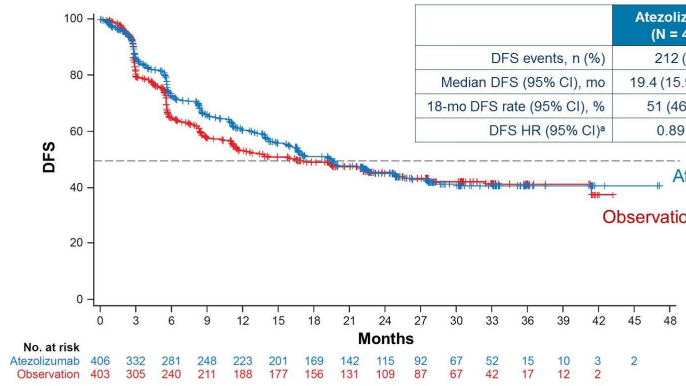
Stratification factors
- Number of LNs resected (< 10 vs ≥ 10)
- Prior NAC (Yes vs No)
- LN status (+ vs –)
- Tumor stage (≤ pT2 vs pT3/pT4)
- PD-L1 status[a] (IC0/1 vs IC2/3)

- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Exploratory analyses:** Biomarkers including PD-L1 status
- **Safety**

AC, adjuvant chemotherapy; DFS, disease-free survival; ITT, intention to treat; LN, lymph node; MIUC, muscle-invasive UC. [a]Protocol amendments broadened eligibility to "all-comers" (initially, only PD-L1–selected patients were enrolled [IC2/3: PD-L1 expression on tumor-infiltrating immune cells (IC) ≥ 5% of tumor area [VENTANA SP142 IHC assay]) and to patients with MIUC (initially, only patients with muscle-invasive bladder cancer were enrolled). [b]Upper-tract UC staging: ypT2-4 or ypN+ (with NAC) and pT3-4 or pN+ (without NAC). [c]Alternating clinic visits and phone calls.

Presented By Maha Hussain at TBD

DFS in ITT Population

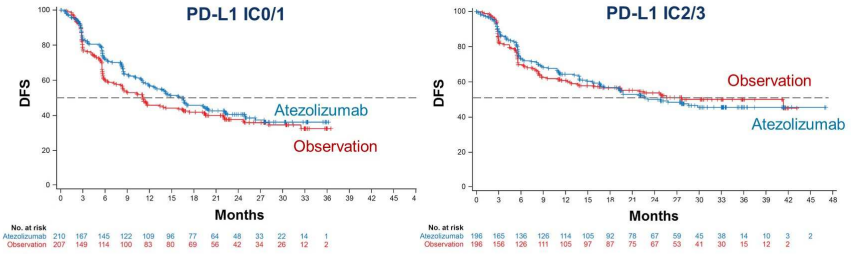


	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a] Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b] 2-sided.

Presented By Maha Hussain at TBD

DFS by PD-L1 Status



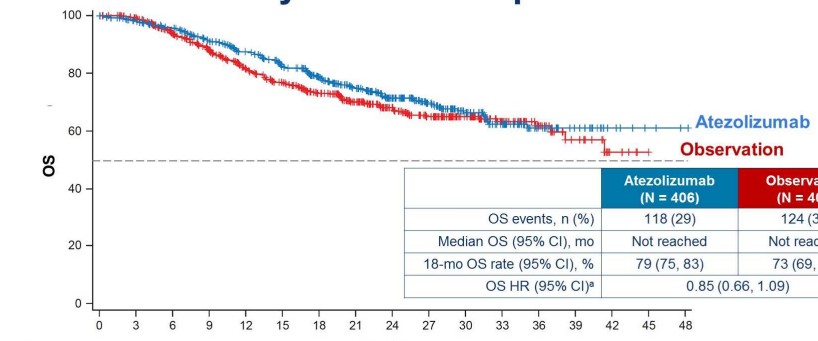
	Atezolizumab (n = 210)	Observation (n = 207)
DFS events, n (%)	118 (56)	120 (58)
HR (95% CI)[a]	0.81 (0.63, 1.05)	

Atezolizumab (n = 196)	Observation (n = 196)
94 (48)	88 (45)
1.01 (0.75, 1.35)	

Data cutoff: November 30, 2019. IC2/3, PD-L1–expressing IC on ≥ 5% of tumor area (VENTANA SP142 assay); IC0/1, < 5%. [a] Stratified by tumor stage and nodal status.

Presented By Maha Hussain at TBD

Interim OS Analysis in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)[a]	0.85 (0.66, 1.09)	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). [a] OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

Presented By Maha Hussain at TBD

IMvigor010: Conclusions

- IMvigor010 is the first Phase III study evaluating the benefit of an adjuvant CPI in MIUC
- The safety profile for atezolizumab monotherapy was consistent with that in prior studies in the advanced setting, with no new safety concerns
  - Higher frequencies of AESIs (mainly Grade 1-2), and treatment discontinuation due to AEs (mainly skin and gastrointestinal) were seen, while corticosteroid use was lower in IMvigor010
- IMvigor010 did not meet its primary endpoint of DFS
  - No pre-specified subgroups (including higher PD-L1 status) showed treatment benefit with atezolizumab
  - OS follow-up is ongoing; additional exploratory biomarker and subgroup analyses may warrant further study
- Other clinical trials with atezolizumab as monotherapy and combination therapy are underway in the metastatic, non-muscle invasive, and bladder-preservation UC settings

Presented By Maha Hussain at TBD

Bristol Myers Squibb

CheckMate-274 - nivolumab

Mišično invazivni urotelni ca – adjuvantno zdravljenje

See All Press Releases > Sign up for Email Alerts >

Opdivo (nivolumab) Significantly Improves Disease Free-Survival vs. Placebo as Adjuvant Therapy for Patients with High-Risk, Muscle-Invasive Urothelial Carcinoma in Phase 3 CheckMate -274 Trial

09/24/2020

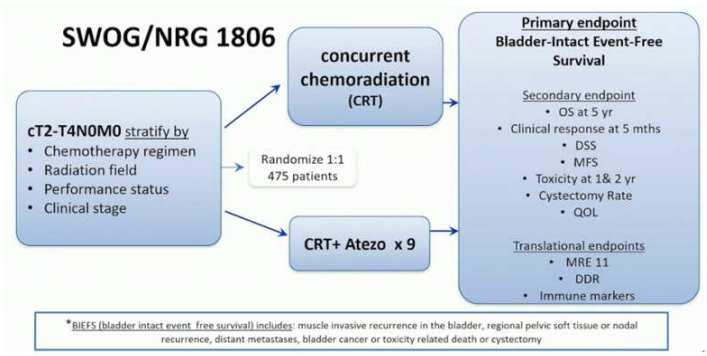
CATEGORY: Corporate/Financial News

In an interim analysis, CheckMate -274 met primary endpoints of disease-free survival in both all randomized patients and in patients whose tumor cells express PD-L1 ≥1%

Opdivo *has now demonstrated clinically meaningful efficacy in the adjuvant treatment of three tumor types, including bladder cancer, melanoma and esophageal/gastroesophageal junction cancer*

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced that CheckMate -274, a pivotal Phase 3 trial evaluating *Opdivo* (nivolumab) after surgery in patients with high-risk, muscle-invasive urothelial carcinoma, met its primary endpoints of improving disease-free survival (DFS) versus placebo in both all randomized patients and in patients whose tumor cells express PD-L1 ≥1% (programmed death-ligand 1). CheckMate -274 is the first and only Phase 3 trial in which immunotherapy has reduced the risk of relapse in the adjuvant setting for these patients.The safety profile of *Opdivo* was consistent with previously reported studies in solid tumors.

MIBC - OHRANITVENO ZDRAVLJENJE



Ne-mišično iinvazivni karcinom sečnega mehurja

- ***NMIBC*** **– 70% novo odkritega urotelnega ca**
  - **heterogena bolezen, pogosti recidivi**
  - **5 letno OS 90%**
  - **zahtevno, intenzivno sledenje (pogoste cistoskopije in biopsije /resekcije recidivov)**
  - **na BCG rezistentni recidivi - cistektomija**
  - **15% - 20% NMIBC visokega gradusa progrediira v MIBC (CIS, papillary HG)**

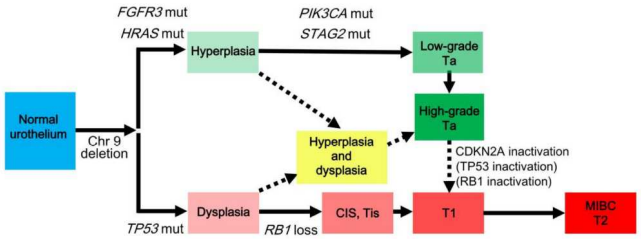


Figure 2. Potential pathways of the tumorigenesis and tumor progression of bladder cancer [2,6,25].

Cancers 2018, 10, 100; doi:10.3390/cancers10040100

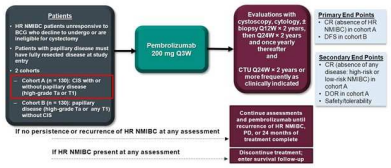
Ne-mišično invazivni urotelni karcinom

PD-1/PD-L1 Inhibitors for NMIBC: Selected Trials

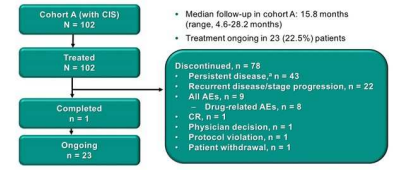
Trial ID	Phase	Regimen	Population
NCT02844816 (SWOG 1605)	II	Atezolizumab IV Infusion	BCG-resistant
NCT02625961 (Keynote 057)	II	Pembrolizumab IV Infusion	BCG-resistant
NCT02901548	II	Durvalumab IV Infusion	BCG-resistant CIS
NCT03317158 (ADAPT-Bladder)	I/II	Durvalumab IV Infusion Durvalumab + BCG Durvalumab + XRT	BCG-resistant
NCT03106610	I	Nivolumab IV Infusion	BCG-resistant
NCT02792192	I	Atezolizumab +/- BCG	BCG-naïve (or resistant)
Pending	I/II	Durvalumab + BCG	BCG-naïve

https://grandroundsinurology.com/checkpoint-inhibitors-for-nmibc/

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



Patient Disposition: Cohort A CIS ± Papillary Disease



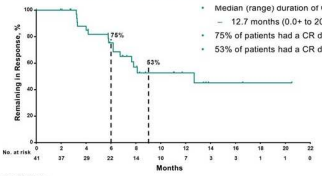
[a]Includes patients in cohort A with CIS at baseline who at month 3 also had CIS ± papillary tumor.

Overall Response Rate at Month 3[a]

Response	Total Population (N = 102)		
	n	%	95% CI
CR	41	40.2	30.6-50.4
Non-CR	57	55.9	45.7-65.7
Persistent[b]	41	40.2	30.6-50.4
Recurrent[c]	6	5.9	2.2-12.4
NMIBC stage progression[d]	9	8.8	4.1-16.1
Non-bladder malignancy[e]	1	1.0	0.0-5.3
Progression to T2	0	0	NA-NA
Nonevaluable[f]	4	3.9	1.1-9.7

[a]Summary of overall responses of HR NMIBC per central assessment at month 3 in all patients who received ≥1 dose of trial treatment, had baseline evaluations, and also had ≥1 postbaseline disease assessment. [b]Defined as patients with CIS at baseline who at month 3 also had CIS ± papillary tumor. [c]Defined as pathologically confirmed appearance of papillary tumor (high-grade Ta or T1) without CIS at month 3.[d]Increase in stage from CIS and/or high-grade Ta at baseline to T1 disease. [e]Defined as presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. Patient developed new liver lesions, as seen on imaging, and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. [f]Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were considered not evaluable for efficacy.
Database cutoff: September 14, 2018.

Duration of Response for Patients Who Achieved CR at Month 3[a]



• Median (range) duration of CR
– 12.7 months (0.0+ to 20.5+ months)
• 75% of patients had a CR duration ≥6 months
• 53% of patients had a CR duration ≥9 months

[a]1 month = 30.4367 days.
Database cutoff: September 14, 2018.

Incidence of Grades 3 or 4[a] Treatment-related AEs, n (%)	N = 102
Any	13 (12.7)
Hyponatremia	3 (2.9)
Arthralgia	2 (2.0)
Adrenal insufficiency	1 (1.0)
Cholestatic hepatitis	1 (1.0)
Hypophosphatemia	1 (1.0)
Hypophysitis	1 (1.0)
Decreased lymphocyte count	1 (1.0)
Malaise	1 (1.0)
Pruritus	1 (1.0)
Pulmonary embolism	1 (1.0)
Dermatitis	1 (1.0)
Syncope	1 (1.0)
Type 1 diabetes mellitus	1 (1.0)

Presented By Arjun Balar at 2019 Genitourinary Cancers Symposium

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author; permission required for reuse.

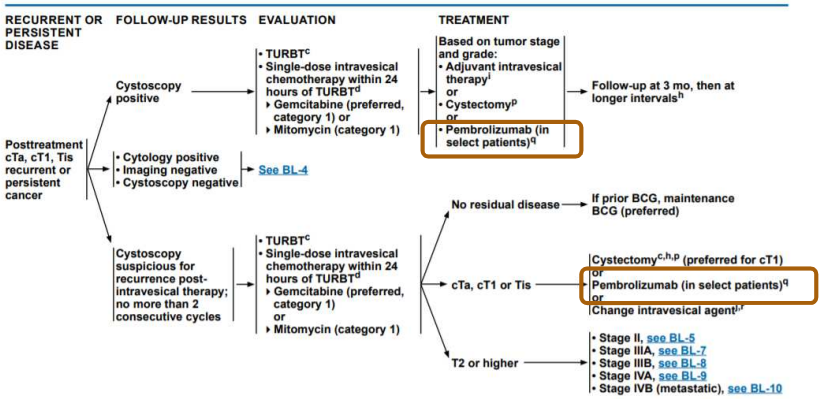
PRESENTED BY: SHILPA GUPTA

23

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2020 Non-Muscle Invasive Bladder Cancer

NCCN Guidelines Index
Table of Contents
Discussion



[c] See Principles of Surgical Management (BL-B).
[d] Most efficacious in patients with low grade, low-volume Ta urothelial cancer. See Principles of Intravesical Treatment (BL-F).
[h] See Follow-Up (BL-E).
[i] Indications for adjuvant induction therapy: Based on probability of recurrence and progression to muscle-invasive disease, such as size, number, and grade.
[i] See Principles of Intravesical Treatment (BL-F).
[p] If not a cystectomy candidate, and recurrence is cTa or cT1, consider concurrent chemoradiotherapy (category 2B for cTa, category 2A for cT1) or a clinical trial. See Principles of Systemic Therapy (BL-G 5 of 7).
[q] Pembrolizumab is indicated for the treatment of patients with BCG-unresponsive, high-risk, non-muscle invasive bladder cancer with Tis with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
[r] Valrubicin is approved for BCG-refractory carcinoma in situ.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BL-3

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2020
Bladder Cancer

NCCN Guidelines Index
Table of Contents
Discussion

BLADDER CANCER: NON-UROTHELIAL AND UROTHELIAL WITH VARIANT HISTOLOGY

Mixed Histology:
- Urothelial carcinoma plus squamous, adenocarcinoma, micropapillary, nested, plasmacytoid, and sarcomatoid should be identified because of the potential to have a more aggressive natural history.
- These are usually treated in a similar manner to pure urothelial carcinoma of the bladder.
- Micropapillary,[1,2] plasmacytoid,[3] and sarcomatoid histologies are generally at higher risk for progression to muscle-invasive disease and a more aggressive approach should be considered.

Pure Squamous:
- No proven role for neoadjuvant/adjuvant chemotherapy for pure squamous cell carcinoma of the bladder.
- Local control with surgery or RT and best supportive care recommended.
- For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with paclitaxel, ifosfamide, and cisplatin may be considered.[4]
- Consider postoperative RT in selected cases (positive margins).[5]

Pure Adenocarcinoma Including Urachal:
- No proven role for neoadjuvant/adjuvant chemotherapy for pure adenocarcinomas of the bladder including urachal carcinoma.
- Local control with surgery or RT and best supportive care recommended.
- For urachal carcinoma with localized disease, a partial or complete cystectomy with en bloc resection of the urachal ligament with umbilicus and lymph node dissection is recommended.
- For node-positive disease, consider chemotherapy with colorectal regimen (FOLFOX [oxaliplatin, leucovorin, and 5-FU] or GemFLP [5-FU, leucovorin, gemcitabine, and cisplatin]). Consider post-chemotherapy surgical consolidation in responding disease.
- For advanced disease, clinical trial preferred. For selected patients, combination chemotherapy with a 5-FU–based regimen (FOLFOX or GemFLP) or ITP (paclitaxel, ifosfamide, and cisplatin). Alternatively, combination paclitaxel and platinum may be considered.[4,6]
- For non-urachal pure adenocarcinoma, consider additional metastatic workup. See NCCN Guidelines for Occult Primary.

Any Small-Cell Component (or neuroendocrine features):
- Concurrent chemoradiotherapy or neoadjuvant chemotherapy followed by local treatment (cystectomy or radiotherapy) is recommended for any patient with small-cell component histology with localized disease regardless of stage.
- Neoadjuvant chemotherapy
  - Standard cisplatin eligible
    - ◊ Etoposide + cisplatin[7]
    - ◊ Alternating ifosfamide + doxorubicin with etoposide + cisplatin[8-10]
  - Standard cisplatin ineligible
    - ◊ Etoposide + carboplatin[11]
- Metastatic chemotherapy
  - Standard cisplatin eligible
    - ◊ Etoposide + cisplatin[7]
  - Standard cisplatin ineligible
    - ◊ Etoposide + carboplatin[11]
  - Alternate regimen for select patients
    - ◊ Alternating ifosfamide + doxorubicin with etoposide + cisplatin[8-10]

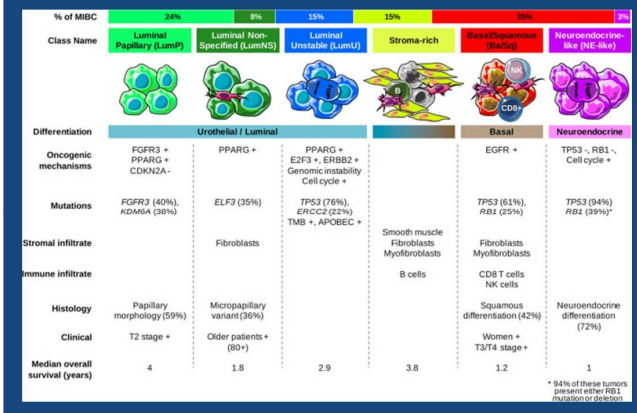
Primary Bladder Sarcoma:
- Treatment as per NCCN Guidelines for Soft Tissue Sarcoma.

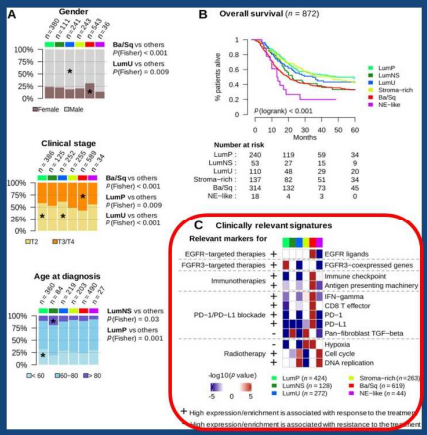
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

BL-D
1 OF 2

MIBC is a molecularly diverse disease with heterogeneous clinical outcomes





Aurélie Kamoun et al. Eur Urology 2020

Presented By Shilpa Gupta at TBD

ZAUSTAVITE NAPREDOVANJE BOLEZNI IN PODALJŠAJTE PREŽIVETJE

Pri bolnikih z mHSPC, zdravljenje samo z ADT ni dovolj.

ZDRAVILO ERLEADA® JE SEDAJ ODOBRENO TUDI ZA ZDRAVLJENJE BOLNIKOV S HORMONSKO OBČUTLJIVIM, METASTATSKIM RAKOM PROSTATE (mHSPC).[1]

Zgodnja uporaba zdravila ERLEADA+ADT v primerjavi z ADT pomembno podaljša preživetje bolnikov in zmanjša tveganje za napredovanje bolezni, hkrati pa prihrani druge oblike zdravljenja za kasnejše stadije bolezni.[1-3]

Skrajšan povzetek glavnih značilnosti zdravila ERLEADA®

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih. **Ime zdravila:** Erleada 60 mg filmsko obložene tablete. **Kakovostna in količinska sestava:** 60 mg apalutamida; pomožne snovi: brezvodni koloidni silicijev dioksid, premreženi natrijev karmelozat, hipromeloza acetat sukcinat, magnezijev stearat, mikrokristalna celuloza, mikrokristalna celuloza (silicifirana), črni in rumeni železov dioksid, makrogol, polivinilalkohol (delno hidroliziran), smukec, titanov dioksid. **Indikacije:** Zdravljenje odraslih moških z nemetastatskim, na kastracijo odpornim rakom prostate (nmCRPC), pri katerih obstaja veliko tveganje za razvoj metastatske bolezni. Za zdravljenje odraslih moških s hormonsko občutljivim metastatskim rakom prostate (mHSCP) v kombinaciji z zdravljenjem z odtegnitvijo androgenov. **Odmerjanje in način uporabe:** Priporočeni odmerek je 240 mg (štiri 60-miligramske tablete) v enkratnem peroralnem odmerku na dan. Med zdravljenjem je treba pri bolnikih, ki niso bili kirurško kastrirani, nadaljevati medicinsko kastracijo z analogom gonadoliberina. V primeru izpuščenega odmerka je treba zdravilo vzeti čimprej še isti dan, naslednji dan pa naj odmerjanje nadaljuje po običajnem razporedu. Dodatnih tablet za nadomestitev pozabljenega odmerka se ne sme vzeti. Če se pri bolniku pojavijo toksični učinki ≥ 3. stopnje ali nesprejemljivi neželeni učinki, je treba uporabo zdravila prekiniti začasno in ne dokončno, dokler se simptomi ne izboljšajo na ≤ 1. stopnjo oziroma na začetno stopnjo, nato pa z zdravljenjem nadaljevati z enakim ali manjšim odmerkom (180 mg ali 120 mg), če je potrebno. Starejšim bolnikom, bolnikom z blago do zmerno okvaro ledvic ali jeter odmerka ni treba prilagajati. Pri bolnikih s hudo okvaro ledvic je potrebna previdnost, pri bolnikih s hudo okvaro jeter pa uporaba ni priporočljiva. Tablete je treba pogoltniti cele in se jih lahko jemlje s hrano ali brez nje. Apalutamid ni namenjen za uporabo pri pediatrični populaciji. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov, nosečnice in ženske, ki bi lahko zanosile. **Posebna opozorila in previdnostni ukrepi:** Uporaba zdravila ni priporočljiva pri bolnikih z anamnezo konvulzij ali drugimi predispozicijskimi dejavniki, med drugim tudi pri bolnikih s poškodbo možganov, nedavno kapjo (v zadnjem letu), pri bolnikih s primarnimi možganskimi tumorji ali metastazami v možganih. Pri bolnikih, ki so prejemali apalutamid je prišlo do padcev in zlomov, zato je treba pred uvedbo zdravljenja pri bolnikih oceniti tveganje za zlome in padce, bolnike pa spremljati po ustaljenih smernicah in premisliti o uporabi učinkovin, ki delujejo na kosti. Bolnike je treba spremljati tudi glede znakov in simptomov ishemične bolezni srca in optimatizirati obvladovanje dejavnikov tveganja za srčno-žilne bolezni. Sočasni uporabi apalutamida z zdravili, ki so občutljivi substrati več presnovnih encimov ali prenašalcev, se je načeloma treba izogibati, če je terapevtski učinek teh zdravil za bolnika zelo pomemben in njihovega odmerjanja ni mogoče enostavno prilagajati na osnovi spremljanja učinkovitosti ali koncentracij v plazmi. Sočasni uporabi z varfarinom ali kumarinskimi antikoagulansi se je treba izogibati. Če se predpiše apalutamid, je treba pri bolnikih s klinično pomembnimi boleznimi srca in ožilja spremljati dejavnike tveganja kot so hiperholesterolemija, hipertrigliceridemija ali druge srčno presnovne bolezni. Zdravljenje z odtegnitvijo androgenov lahko podaljša interval QT. **Interakcije:** Apalutamid je induktor encimov in prenašalcev in lahko povzroči povečan obseg odstranjevanja številnih pogosto uporabljanih zdravil. Pri sočasnem odmerjanju tega zdravila s katerim od močnih zaviralcev CYP2C8 ali močnih zaviralcev CYP3A4 začetnega odmerka ni treba prilagajati, premisliti pa velja o zmanjšanju odmerka zdravila Erleada na osnovi prenašanja zdravila. Ni pričakovati, da bi induktorji CYP3A4 ali CYP2C8 klinično pomembno vplivali na farmakokinetiko apalutamida in aktivnih frakcij. . Pri sočasni uporabi s substrati CYP2B6 je treba spremljati neželene učinke in oceniti izgubo učinka substrata ter za zagotovitev optimalnih plazemskih koncentracij morda prilagoditi odmerek substrata. Sočasna uporaba z zdravili, ki se primarno presnavljajo s CYP3A4 (kot so darunavir, felodipin, midazolam in simvastatin), s CYP2C19 (kot sta diazepam in omeprazol) ali s CYP2C9 (kot sta varfarin in fenitoin), lahko povzroči zmanjšanje izpostavljenosti tem zdravilom. Pri sočasni uporabi s substrati UDP-glukuronil transferaze je potrebna previdnost. Pri sočasni uporabi s substrati P-gp, BCRP ali OATP1B1 je potrebna ocena obsega zmanjšanja učinka ter za zagotovitev optimalnih plazemskih koncentracij morda prilagoditi odmerek substrata. Ni mogoče izključiti možnosti, da apalutamid in njegov N-desmetil presnovek zavirata prenašalce OCT2,OAT3 in MATE. Pri preiskovancih z mHSPC, ki so prejemali levprorelinijev acetat (analog GnRH), sočasna uporaba apalutamida ni bistveno vplivala na izpostavljenost leuprolidu v stanju dinamičnega ravnovesja. Skrbna presoja je potrebna tudi pri sočasni uporabi z zdravili, za katera je ugotovljeno, da podaljšujejo interval QT, oziroma z zdravili, ki lahko izzovejo Torsades de pointes. **Nosečnost in dojenje:** Ni znano, ali so apalutamid ali njegovi presnovki prisotni v spermi, zato lahko to zdravilo škoduje plodu v razvoju. Bolniki, ki imajo spolne odnose z žensko v rodni dobi, morajo med zdravljenjem in še 3 mesece po zadnjem odmerku zdravila Erleada uporabljati kondome skupaj s še katero od drugih visoko učinkovitih metod kontracepcije. Zdravilo se ne sme uporabljati med dojenjem. **Neželeni učinki:** Hipotiroidizem, zmanjšan apetit, hiperholesterolemija, hipertrigliceridemija, disgevzija, konvulzije, ishemična bolezen srca, podaljšanje intervala QT, vročinski oblivi, hipertenzija, driska, kožni izpuščaj, srbenje, TEN, zlomi, artralgija, mišični krči, utrujenost, zmanjšanje telesne mase, padci. Za popoln seznam neželenih učinkov glejte Povzetek glavnih značilnosti zdravila. **Imetnik DzP:** Janssen-Cilag International NV, Turnhoutseweg 30, 2340 Beerse, Belgija **Predstavnik imetnika DzP v Sloveniji**: Johnson & Johnson d.o.o., Šmartinska cesta 53, Ljubljana.
Režim izdajanja zdravila: Rp/Spec. **Datum odobritve:** 12. 11. 2020
Povzetek glavnih značilnosti zdravila s podrobnejšimi informacijami o zdravilu je dostopen pri predstavniku imetnika dovoljenja za promet.

Viri:
1. Povzetek glavnih značilnosti zdravila ERLEADA® (apalutamid).
2. Chi KN, et al. N Engl J Med. 2019;81(1):13–24
3. Chi KN, et al. N Engl J Med. 2019;81(1):13–24. Supplementary information.

CP-198062/091220

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Janssen, farmacevtski del Johnson & Johnson d.o.o., Šmartinska cesta 53, 1000 Ljubljana,
tel: 01 401 18 00, e-mail: info@janssen-slovenia.si

Erleada® ▼
(apalutamid) tablete

Univerza v Ljubljani

Onkološki inštitut Ljubljana

Novosti v zdravljenju napredovalega raka ledvičnih celic

Doc. dr. Boštjan Šeruga, dr.med.
Sektor internistične onkologije
Onkološki inštitut Ljubljana in Univerza v Ljubljani
Ljubljana, Slovenija

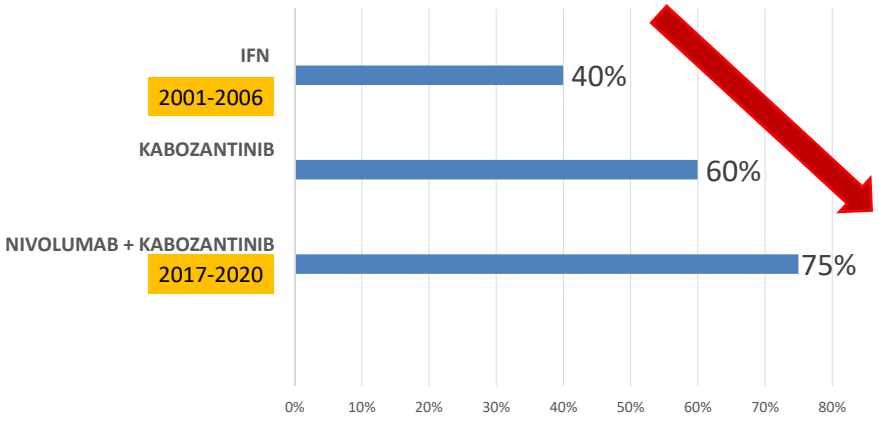
Ljubljana, 16.12.2020

Univerza v Ljubljani

Onkološki inštitut Ljubljana

Napredek v zdravljenju karcinoma ledvičnih celic

2-letno preživetje vseh bolnikov (vseh pognostičnih skupin)



IFN: Interferon

Choueiri T, Check Mate 9ER,ESMO 2020; Gore ME, Lancet 2010

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Imunobiologija karcinoma levičnih celic

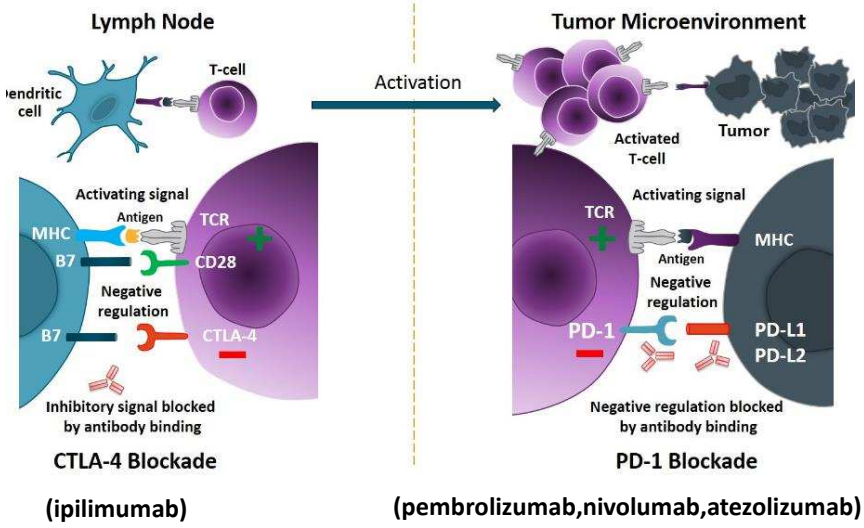
- **Infiltracija tumorja s CD8 T-limfociti je povezana s <u>slabšo</u> prognozo bolezni**
  - **z bolj intenzivno infiltracijo s CD8 T-limfociti povezana tudi večja izraženost PD-L1**
  - **večje breme mutacij → manj intenzivna infiltracija z limfociti**
- **Relativno <u>nizko</u> bremenu mutacij v tumorju (1.1 mutacija/megabazo)**
  - **rel. delež indel mutacij visok → premik bralnega okvirja → velika količina neoantigenov**
  - **reaktivirani endogeni retrovirus vgrajen v genom → več virusnih neoantigenov → imunogenost**
  - **rak testis antigen (CSAG2)**

Drake and Stein, JCO, 2018

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Kombinirana imunoterapija (zavora inhibitornih signalov v imunski sinapsi)

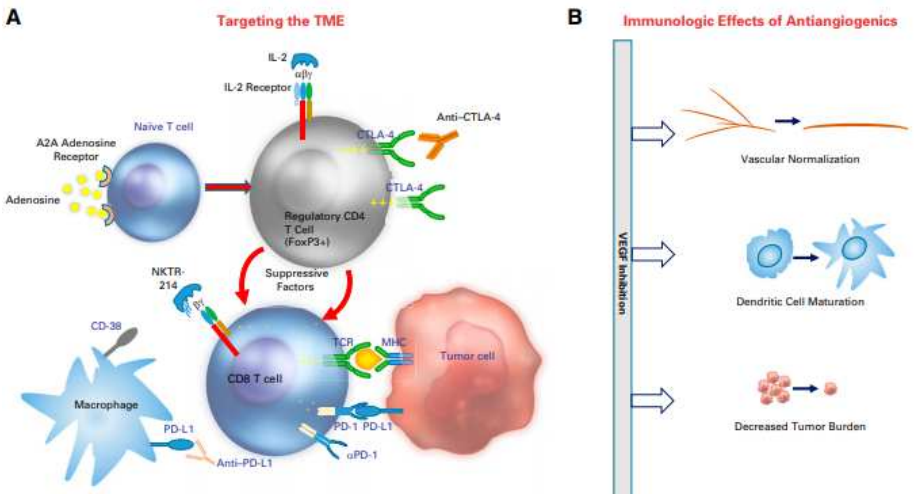


AAAS; https://science.sciencemag.org/content/359/6382/1350; 02.11.2020

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Imunoterapija in tarčna zdravila



Drake CG, Stein MN: The Immunobiology of Kidney Cancer; Journal of Clinical Oncology 36, no. 36 (December 20, 2018) 3547-3552.

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Klinične raziskave faze III v 1. liniji zdravljenja

Raziskava	Primerjava	Primarni izid
CheckMate 214 Motzer et al, NEJM, 2018	Ipilimumab+Nivolumab vs. Sunitinib	OS, ORR, PFS pri bolnikih s srednje ugodno in neugodno prognozi
Keynote 426 Rini et al, NEJM, 2019	Pembrolizumab+Axitinib vs. Sunitinib	OS in PFS v ITT populaciji
Javelin Renal 101 Motzer et al, NEJM, 2018	Avelumab+Axitinib vs. Sunitinib	OS in PFS pri PD-L1+
Immotion 151 Rini et al, Lancet, 2019	Atezolizumab+Bevacizumab vs. Sunitinib	PFS pri PD-L1+ OS v ITT populaciji
CheckMate 9ER Choueiri et al, ESMO 2020	Nivolumab+Kabozantinib vs. Sunitinib	PFS v ITT populaciji

CheckMate 214 - protitumorska aktivnost
(srednje ugoden in neugoden prognostičen obet)

27.5% PD-L1+

Outcome	PD-L1 <1%		PD-L1 ≥1%	
	Nivolumab + Ipilimumab N=284	Sunitinib N=278	Nivolumab + Ipilimumab N=100	Sunitinib N=114
Objective response rate,* % (95% CI)	37 (32–43)	28 (23–34)	58 (48–68)	22 (15–31)
	P=0.0252†		P<0.001†	
Best overall response,* %				
Complete response	7	1	16	1
Partial response	30	27	42	21
Stable disease	36	47	19	40
Progressive disease	20	13	14	25
NA	7	12	9	13

* IRRC-assessed.
† Exploratory analyses.

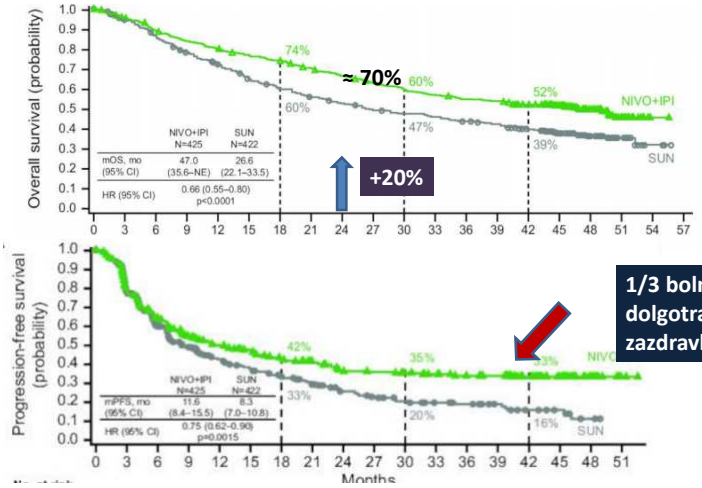
Motzer et al, NEJM, 2018

Univerza v Ljubljani

Onkološki inštitut Ljubljana

Kombinirana imunoterapija izboljša preživetje pri najbolj bolnih

Srednje ugodna/neugodna prognostična skupina



1/3 bolnikov dolgotrajno zazdravljenih

Motzer RJ et al, J Immunother Cancer, 2020

Univerza v Ljubljani

Imunoterapija in sarkomatoidni karcinom

ONKOLOŠKI INŠTITUT LJUBLJANA

Table 2. Investigator-assessed best overall response per RECIST v1.1

Outcome	Sarcomatoid intermediate/poor risk		All intermediate/poor risk[18]	
	NIVO+IPI N = 60	SUN N = 52	NIVO+IPI N = 425	SUN N = 422
Confirmed ORR (95% CI), %	56.7 (43.2–69.4)	19.2 (9.6–32.5)	41.9 (37.1–46.7)	29.4 (25.1–34.0)
Confirmed BOR, %				
Complete response	18.3	0	11.3	1.2
Partial response	38.3	19.2	30.6	28.2
Stable disease	8.3	42.3	25.9	41.2
Progressive disease	25.0	28.8	24.9	19.0
Unable to determine/not reported	10.0	9.6	7.3	10.4

OS probability, % (95% CI)	NIVO+IPI N = 60	SUN N = 52
12 month	79.7 (67.1–87.9)	55.8 (41.3–68.0)
24 month	58.4 (44.6–69.9)	34.6 (22.1–47.4)
30 month	53.0 (39.2–64.9)	28.8 (17.3–41.4)

, confidence interval; HR, hazard ratio; NE, not estimable.

Univerza v Ljubljani

KEYNOTE 426- protitumorska aktivnost (vsi bolniki)

ONKOLOŠKI INŠTITUT LJUBLJANA

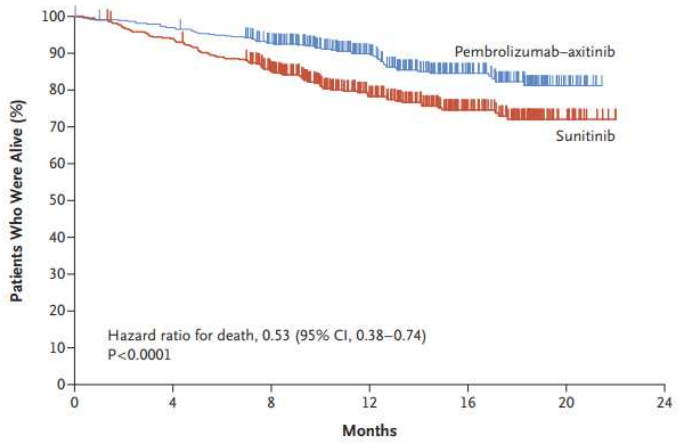
Table 2. Summary of Confirmed Objective Response.*

Variable	Pembrolizumab–Axitinib (N=432)	Sunitinib (N=429)
Objective response rate — % (95% CI)†	59.3 (54.5 to 63.9)	35.7 (31.1 to 40.4)
Best overall response — no. (%)		
Complete response	25 (5.8)	8 (1.9)
Partial response	231 (53.5)	145 (33.8)
Stable disease	106 (24.5)	169 (39.4)
Progressive disease	47 (10.9)	73 (17.0)
Could not be evaluated‡	8 (1.9)	6 (1.4)
Not assessed§	15 (3.5)	28 (6.5)
Median time to response (range) — mo¶	2.8 (1.5 to 16.6)	2.9 (2.1 to 15.1)
Median duration of response (range) — mo‖	Not reached (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

Univerza v Ljubljani

KEYNOTE 426 - skupno preživetje (vsi bolniki)

ONKOLOŠKI INŠTITUT LJUBLJANA



Rini et al, NEJM, 2019

Univerza v Ljubljani

KEYNOTE 426 Preživetje v podskupinah bolnikov

ONKOLOŠKI INŠTITUT LJUBLJANA

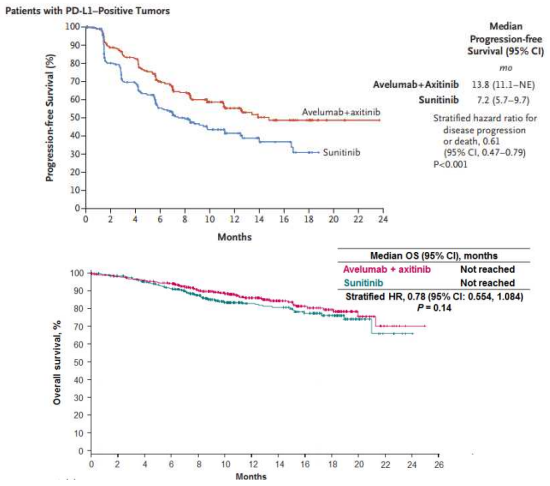
Podskupina	12-mesečno preživetje		
	Pembrolizumab+ Axitinib	Sunitinib	
IMDC Prognostični obet			
Ugoden	95%	94%	Δ 1%
Srednje ugoden	91%	77%	Δ 14%
Slab	70%	45%	Δ 25%
PD-L1 CPS			
≥ 1%	90%	78%	
< 1%	92%	78%	

IMDC denotes International Metastatic Renal Cell Carcinoma Database Consortium

Rini et al, NEJM, 2019

Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

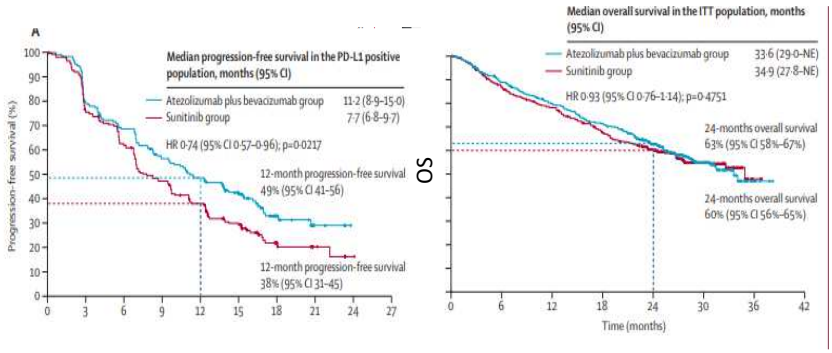
Robert J. Motzer, M.D., Konstantin Penkov, M.D., Ph.D., John Haanen, Ph.D., Brian Rini, M.D.,



NEJM, 2019

Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial

Brian I Rini, Thomas Powles, Michael B Atkins, Bernard Escudier, David F McDermott, Cristina Suarez, Sergio Bracarda, Walter M Stadler, Frede Donskov,

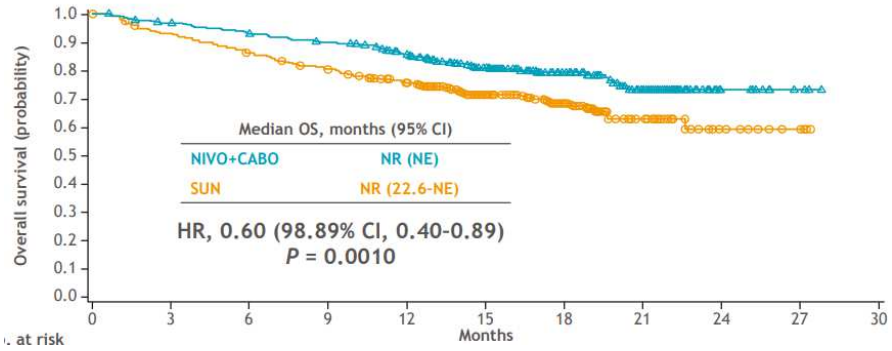


Lancet, 2019

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

CheckMate 9ER
(skupno preživetje pri vseh bolnikih)



Choueiri TK et al, Annals of Oncology (2020) 31 (suppl_4), S1142-S1215

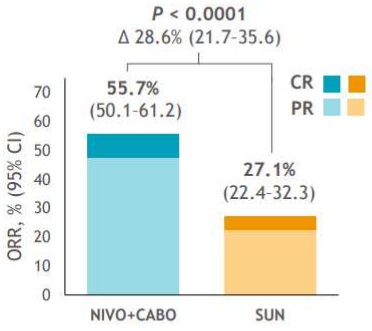
Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

CheckMate 9ER -Protitumorski učinek

CheckMate 9ER

Objective response and best overall response per BICR



Outcome, %	NIVO+CABO (n = 323)	SUN (n = 328)
Complete response	8.0	4.6
Partial response	47.7	22.6
Stable disease	32.2	42.1
Progressive disease	5.6	13.7
Not evaluable/not assessed[a]	6.5	17.1
Median time to response (range), months[b]	2.8 (1.0-19.4)	4.2 (1.7-12.3)
Median duration of response (95% CI), months[b]	20.2 (17.3-NE)	11.5 (8.3-18.4)

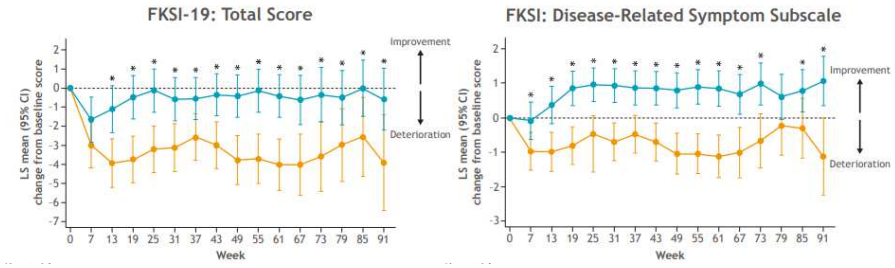
- ORR favored NIVO+CABO over SUN across subgroups including by IMDC risk status, tumor PD-L1 expression (≥ 1% vs < 1%), and bone metastases

BICR-assessed ORR and BOR by RECIST v1.1.
[a]Includes patients who were never treated, those who discontinued/died before disease assessment, those without measurable disease at baseline per BICR, or other reason not reported/specified; [b]Median time to and duration of response were calculated for patients who had a complete or partial response (n = 180 with NIVO+CABO, n = 89 patients with SUN).

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Kombinacija tarčnih zdravil in imunoterapije izboljša kakovost življenja

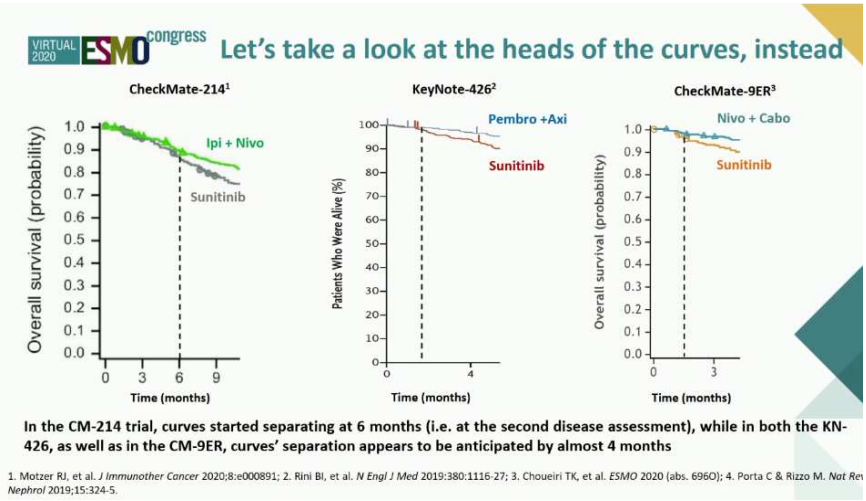


UroToday; https://www.urotoday.com/conference-highlights/esmo-2020/kidney-cancer/124542-esmo-virtual-congress-2020-nivolumab-cabozantinib-vs-sunitinib-in-first-line-treatment-for-advanced-renal-cell-carcinoma-first-results-from-the-randomized-phase-3-checkmate-9er-trial.html; 02.11.2020.

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Katera kombinacija učinkuje prej?



Porta C, ESMO, 2020

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Odprta vprašanja 1

VIRTUAL 2020 ESMO congress

Given all the above, how to practically decide?

Presently, the only possible, though highly empiric, driver of our therapeutical choice could the biological aggressiveness of the tumor

- **In the case of a very aggressive disease, the use of an immune checkpoint inhibitor plus a VEGFR-TKI seems a very reasonable choice, in order to try to control disease growth, while waiting for the tail effect of immunotherapy**
- **Otherwise, one could head for the long-term benefit of the immune combo, as well as for complete responses (= cure?), trying to spare the additional toxicities deriving from the continuous use of the VEGFR-TKI**

As far as safety, we should consider that the trade-off between efficacy and safety a 1st line patient is willing to accept is usually unbalanced in favor of efficacy

Porta C, ESMO, 2020

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Odprta vprašanja 2

VIRTUAL 2020 ESMO congress

Open questions worthwhile of investigation

What about the possibility of using the VEGFR-TKI just for a limited period of time, at the beginning of the combined treatment?

- **Indeed, stopping it after few months would spare the patients the chronic toxicities induced by multikinase inhibition, realistically a very important issue, especially when achieving a deep response; hopefully, prospective studies will be able to address this issue**

As far as the immune combo, what about considering reinduction doses of Ipilimumab during Nivolumab maintenance, in case of progression (expecially if not massive)?

If the use of a VEGFR-TKI such as Cabozantinib is really able to positively modulate the tumor microenvironment[1-3], what about exploring different schedules of the available combinations?

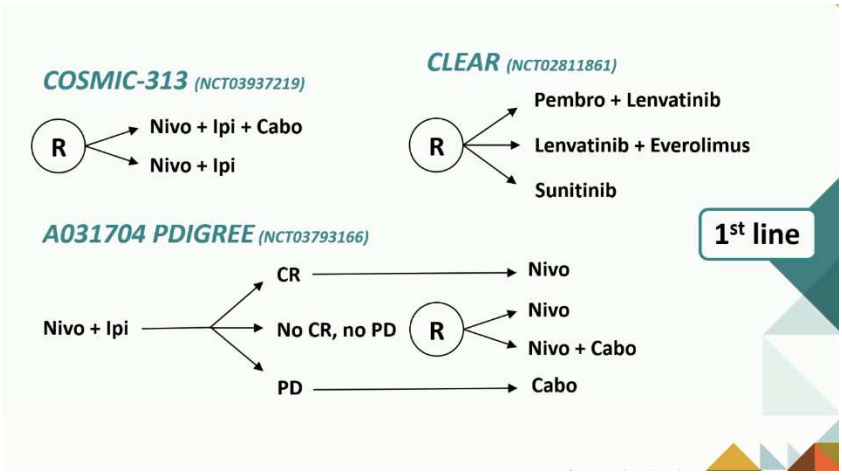
1. Mennitto A, et al. *J Clin Med* 2020;9:930; 2. Bracarda S, et al. *Crit Rev Oncol Hematol* 2019;139:149-57; 3. Bergerot P, et al. *Mol Cancer Ther* 2019;18:2185-93.

Porta C, ESMO, 2020

Univerza v Ljubljani

ONKOLOŠKI INŠTITUT LJUBLJANA

Kaj obeta bližnja prihodnost?



UroToday; https://www.urotoday.com/conference-highlights/esmo-2020/kidney-cancer/124546-esmo-virtual-congress-2020-invited-discussant-first-results-from-the-randomized-phase-3-checkmate-9er-trial.html; 02.11.2020.

Novosti pri zdravljenju raka glave in vratu

Doc. dr. Cvetka Grašič Kuhar, dr. med.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J.-P. Machiels[1,2†], C. René Leemans[3†], W. Golusinski[4], C. Grau[5], L. Licitra[6] & V. Gregoire[7], on behalf of the EHNS Executive Board*, ESMO Guidelines Committee* and ESTRO Executive Board*

Available online 23 October 2020

RELAPSED / METASTATIC DISEASE

Local treatment if possible (RT, surgery)
Systemic treatment

Table 2. Personalised medicine in SCCHN

Biomarker	Method	Validated use	LoE, GoR
p16	p16 IHC	1. Surrogate marker for HPV-induced oropharyngeal cancer 2. Prognostic factor for oropharyngeal cancer	I, A
PD-L1	PD-L1 IHC (FDA-approved test)	First-line recurrent/metastatic disease to identify patients that may benefit from pembrolizumab monotherapy	I, A

FDA, Food and Drug Administration; GoR, grade of recommendation; HPV, human papilloma virus; IHC, immunohistochemistry; LoE, level of evidence; PD-L1, programmed death-ligand 1.

Machiels J.-P. Ann Oncol 2020

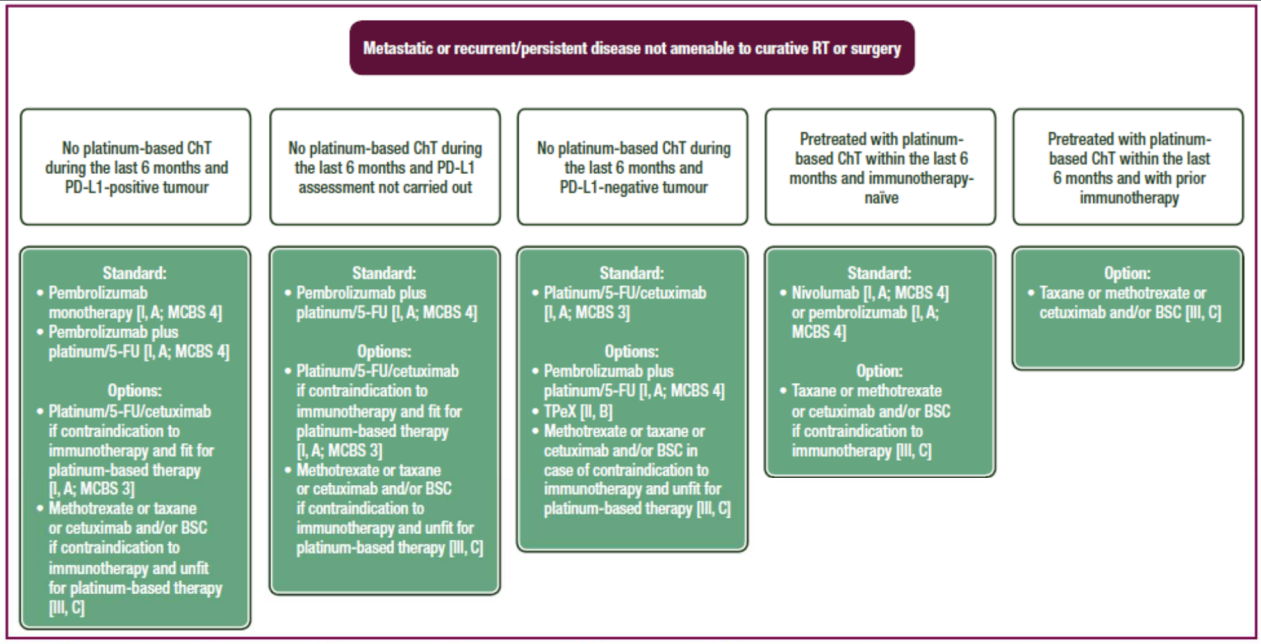


Figure 5. Management of recurrent and/or metastatic disease not amenable to curative RT or surgery.
5-FU, 5-fluorouracil; BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; PD-L1, programmed death-ligand 1; RT, radiotherapy; T, tumour; TPeX, cisplatin/docetaxel/cetuximab.

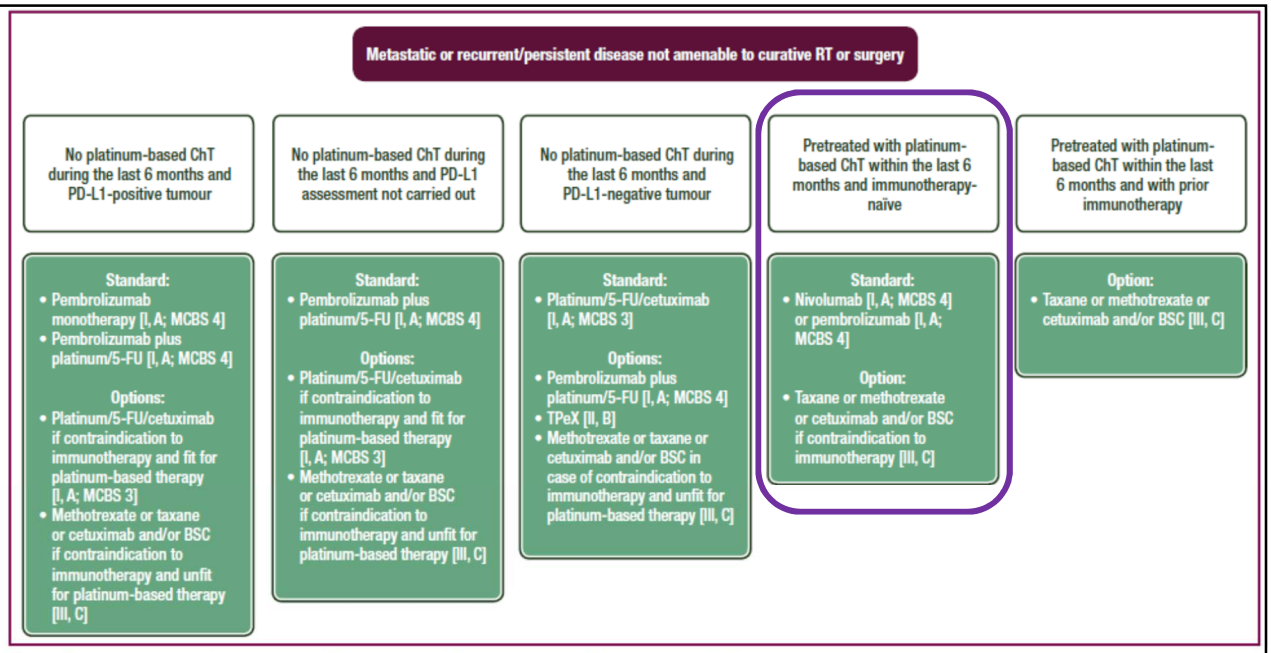


Figure 5. Management of recurrent and/or metastatic disease not amenable to curative RT or surgery.
5-FU, 5-fluorouracil; BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; PD-L1, programmed death-ligand 1; RT, radiotherapy; T, tumour; TPeX, cisplatin/docetaxel/cetuximab.

Table 1. Features of the two phase 3 trials assessing efficacy of antiprogrammed death 1 checkpoint inhibitors in pretreated recurrent and or metastatic squamous cell carcinoma of the head and neck CHECKMATE-141 and KEYNOTE-040

	CHECKMATE-141 [16••]	KEYNOTE-040 [19••]
Experimental arm (2:1 / 1:1)	Nivolumab, 3-mg/kg IV, d1 = d15 *N* = 240	Pembrolizumab 200-mg IV, d1 = d22 *N* = 247
Standard single agent arm	Methotrexate 40–60-mg/m^2 IV weekly Docetaxel 30–40 mg/m^2 weekly Cetuximab 400-mg/m^2 IV then 250 mg/m^2 weekly *N* = 121	Methotrexate 40–60-mg/m^2 IV weekly Docetaxel 75 mg/m^2 every 3 weeks Cetuximab 400-mg/m^2 IV then 250 mg/m^2 weekly *N* = 248
Main inclusion criteria	2nd-line RM and beyond Platinum refractory allowed PD-L1 status optional	2nd and 3rd line Had recurrence or progression within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease PD-L1 status mandatory
Stratification criteria	Prior cetuximab	PS HPV status PD-L1 status
Efficacy in the ITT population OS PFS (median)	Median: 7.5 vs. 5.1 m, *P* = 0.01 1-year OS rate: 36.0 vs. 16.6% 2.0 vs. 2.3	Median: 8.4 vs. 6.9 m, *P* = 0.016 1-year OS rate: 37.0 vs. 26.5% 2.1 vs. 2.3 m
Efficacy in PD-L1 positive Median OS	TPS ≥ 1%: 8.7 vs. 4.6 months	TPS ≥ 50%: 11.6 vs. 6.6 m (EMA) CPS ≥ 1%: 8.7 vs. 7.1 m
Overall response rate	13.3 vs. 5.8%	14.6 vs. 10.1%
Safety Grade 3–5 adverse events	13.1 vs. 35.1%	13 vs. 36%

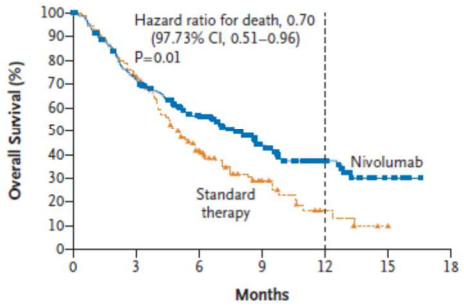
Curr Opin Oncol 2019, 31:146–151

CHECKMATE-141: NIVOLUMAB

N=361

A Overall Survival

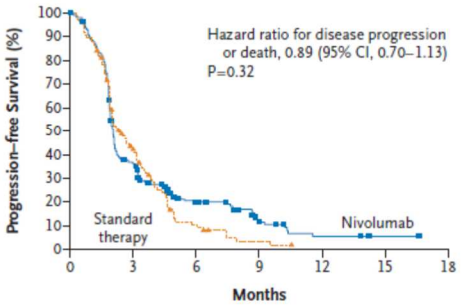
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

B Progression-free Survival

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Nivolumab	240	190	2.0 (1.9–2.1)
Standard Therapy	121	103	2.3 (1.9–3.1)



No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Standard therapy	121	43	9	2	0	0	0

mOS: 7.5 vs. 5.1 months

Nivolumab doubled OS at 1 year of FU

This article was published on October 9, 2016, at NEJM.org.

FDA approvement in Nov 2016

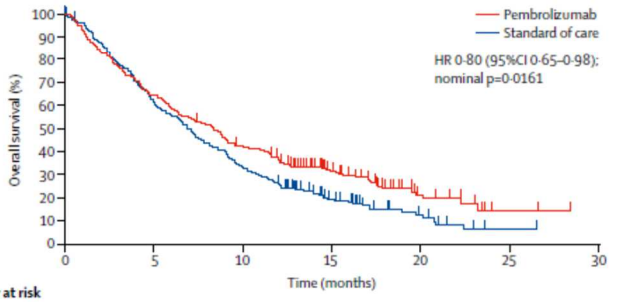
Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study

Keynote-012; phase Ib: durable response to pembrolizumab; FDA approval in August 2016

Ezra E W Cohen, Denis Soulières, Christophe Le Tourneau, José Dinis, Lisa Licitra, Myung-Ju Ahn, Ainara Soria, Jean-Pascal Machiels, Nicc
Ranee Mehra, Barbara Burtness, Pingye Zhang, Jonathan Cheng, Ramona F Swaby, Kevin J Harrington, on behalf of the KEYNOTE-040 i

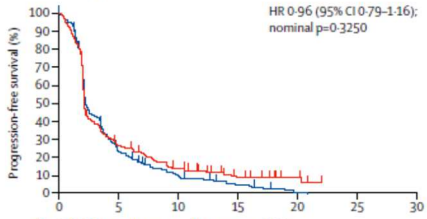
Lancet 2019; 393: 156–67

A

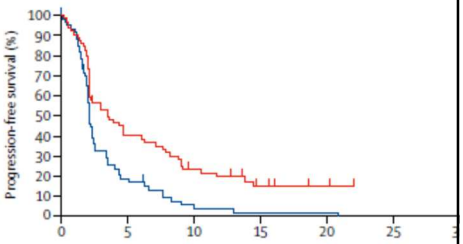


Number at risk (number censored)							
Pembrolizumab	247 (0)	160 (0)	103 (2)	48 (33)	14 (55)	2 (64)	0 (66)
Standard of care	248 (0)	151 (3)	82 (3)	34 (19)	10 (35)	1 (40)	0 (41)

E Total population



C PD-L1 tumour proportion score ≥50%



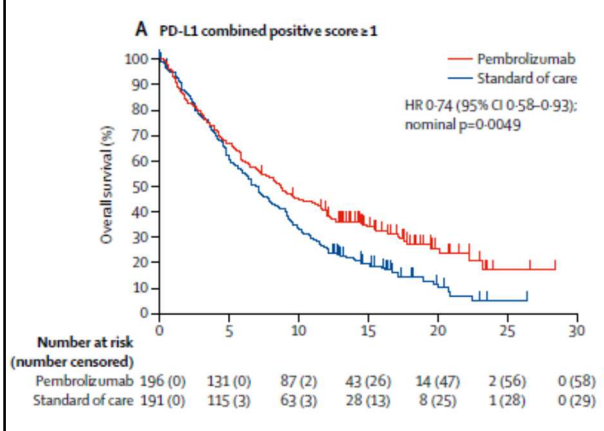
N=495

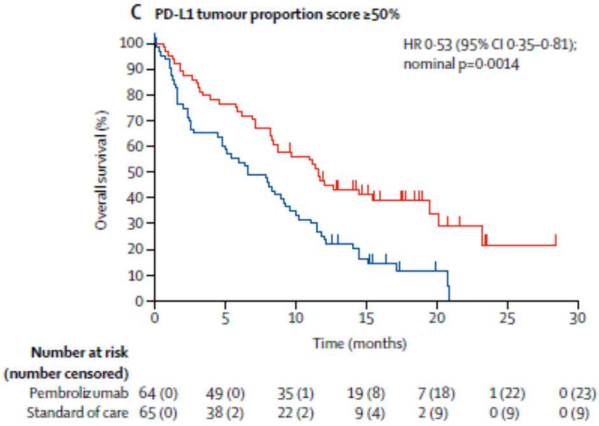
mOS: 8·4 months vs. 6·9 months

Confounding effect of subsequent ICI in the standard arm (13%) vs. pembro (5%) on OS data

KEYNOTE-040

Lancet 2019; 393: 156–67





70% of pts CPS≥1

8.7 vs 7.1 months
40% vs. 26% 1yS

26% of pts TPS≥50%

mOS: 11.6 vs. 6.6 months
47% vs. 25% 1yS

EMA indication!

9

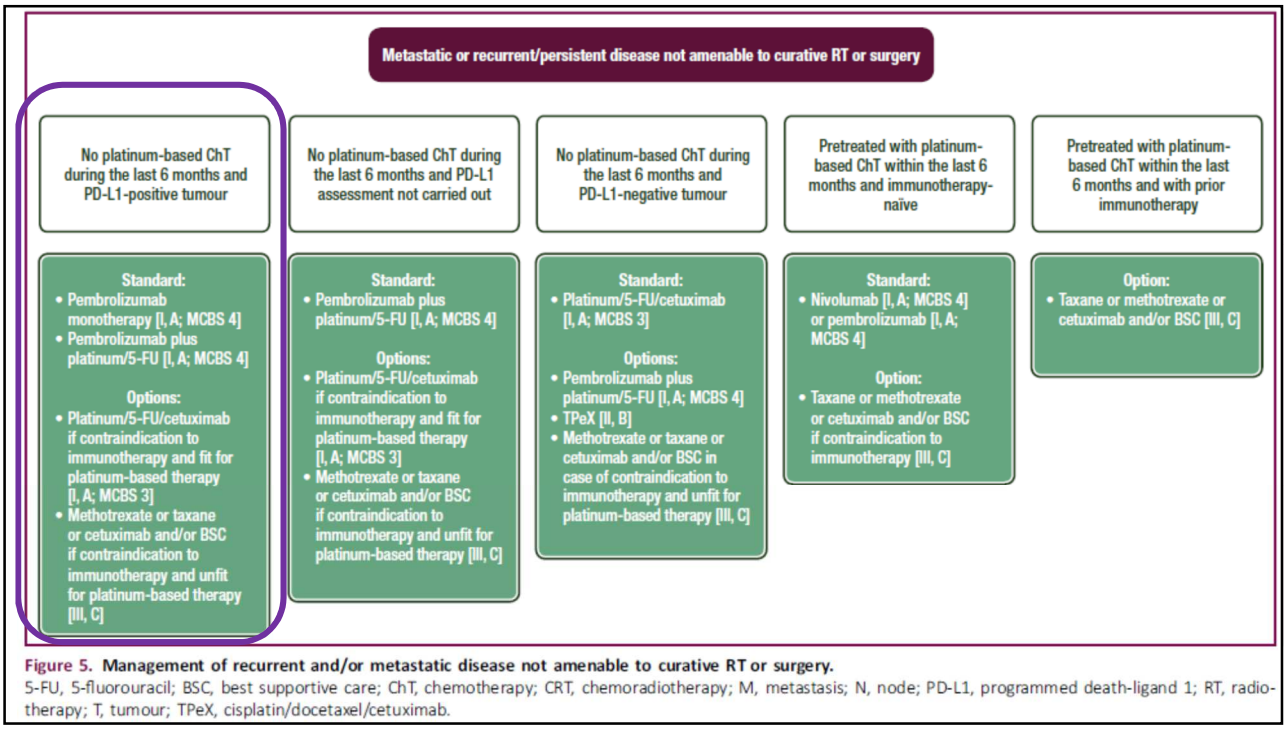
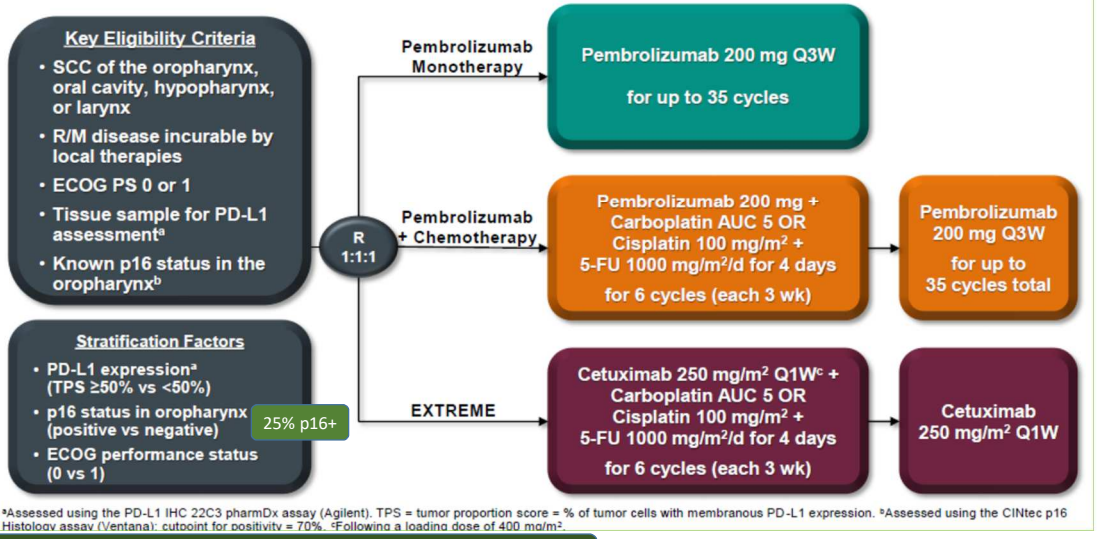


Figure 5. Management of recurrent and/or metastatic disease not amenable to curative RT or surgery.
5-FU, 5-fluorouracil; BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; PD-L1, programmed death-ligand 1; RT, radiotherapy; T, tumour; TPeX, cisplatin/docetaxel/cetuximab.

N=882

MUNICH 2018 ESMO congress

KEYNOTE-048 Study Design (NCT02358031)



25% p16+

[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Prospectively used a biomarker PD L1 expression: CPS

11

Rischin KN048 ASCO 2019

Study End Points: Pembrolizumab vs EXTREME and Pembrolizumab + Chemotherapy vs EXTREME

Primary
- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - OS
  - PFS[b]

Secondary
- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - PFS[b] rates at 6 and 12 mo
  - ORR[b]
  - Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)[c]
- Total population
  - Safety and tolerability

Key Exploratory
- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - Duration of response[b]

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
[b]Assessed per RECIST v1.1 by blinded, independent central review.
[c]To be presented at a later date.

Efficay and adverse effects

www.thelancet.com Published online October 31, 2019 https://doi.org/10.1016/S0140-6

	subgroup	Pembro	Pembro+chemo	Extreme
ORR	CPS≥20 CPS≥1 Total population	23% 19% 16%	43% 36.5%	36.1% 34.9% 36.3%
PFS	CPS≥20 CPS≥1 Total population	3.4 vs. 5.0 months 3.2 vs. 5.0 months	HR 0.76 (0.58-1.01) HR 0.84 (0.69-1.02) HR 0.92 (0.77-1.10) 4.9 vs. 5.1 months	
OS	CPS≥20 CPS≥1 Total population	 14.9 vs. 10.7 months HR 0.74 12.3 vs. 10.3 months HR 0.83 (0.70-0.99) 11.5 vs. 10.7 months	HR 0.60 (0.45-0.82) 14.7 vs. 11 months HR 0.65 (0.53-0.80) 13.6 vs. 10.4 months HR 0.72 (0.60-0.87) 13 vs. 10.7 months	
DOR		20.9 vs 4.5 months	7.1 vs. 4.2 months	
AE G3-5		54.7%	85.1%	83.3%

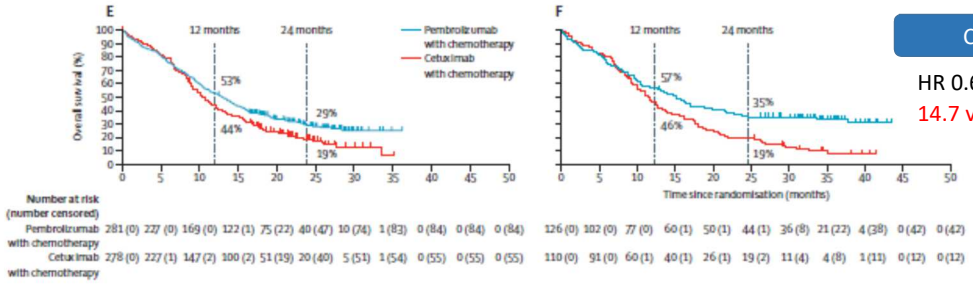
KEYNOTE-048

OS: Pembro +chemo vs. Extreme

KEYNOTE-048

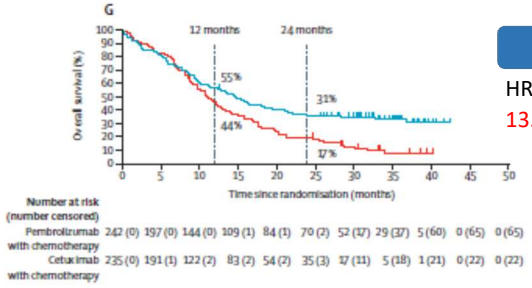
Total population

HR 0.72 (0.60-0.87)
13 vs. 10.7 months



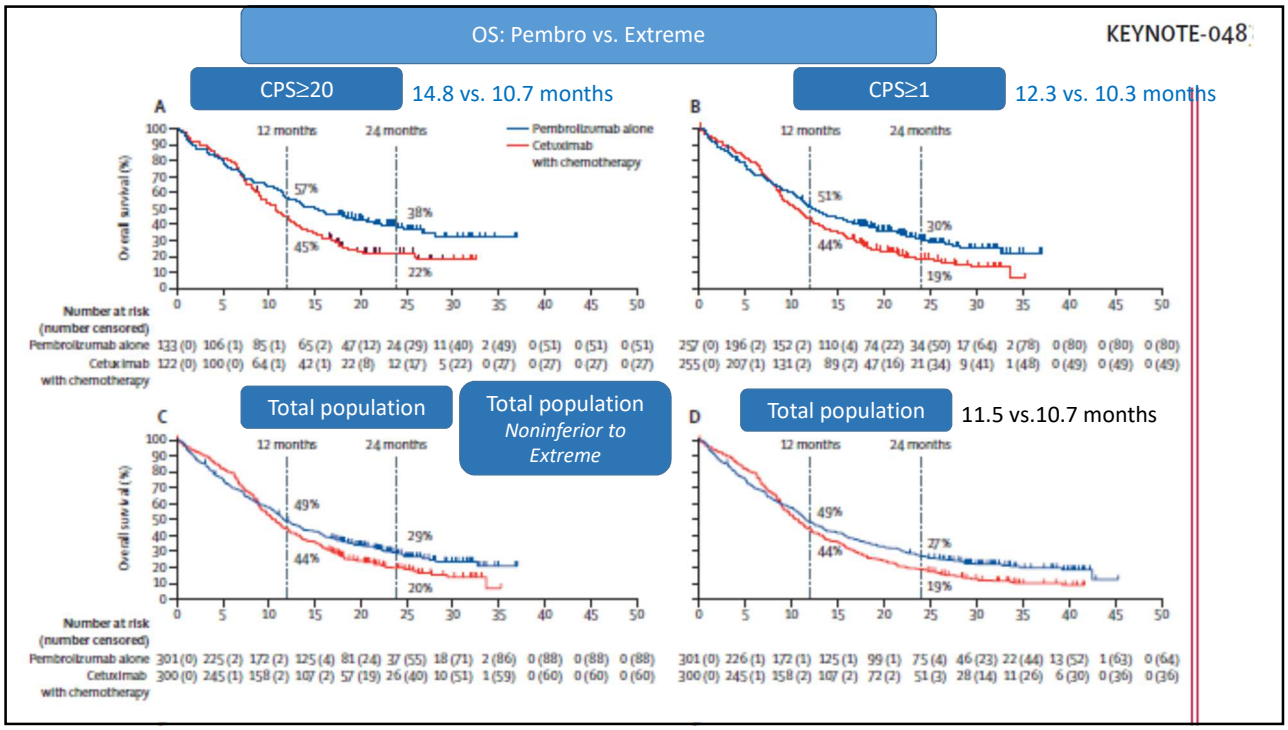
CPS≥20

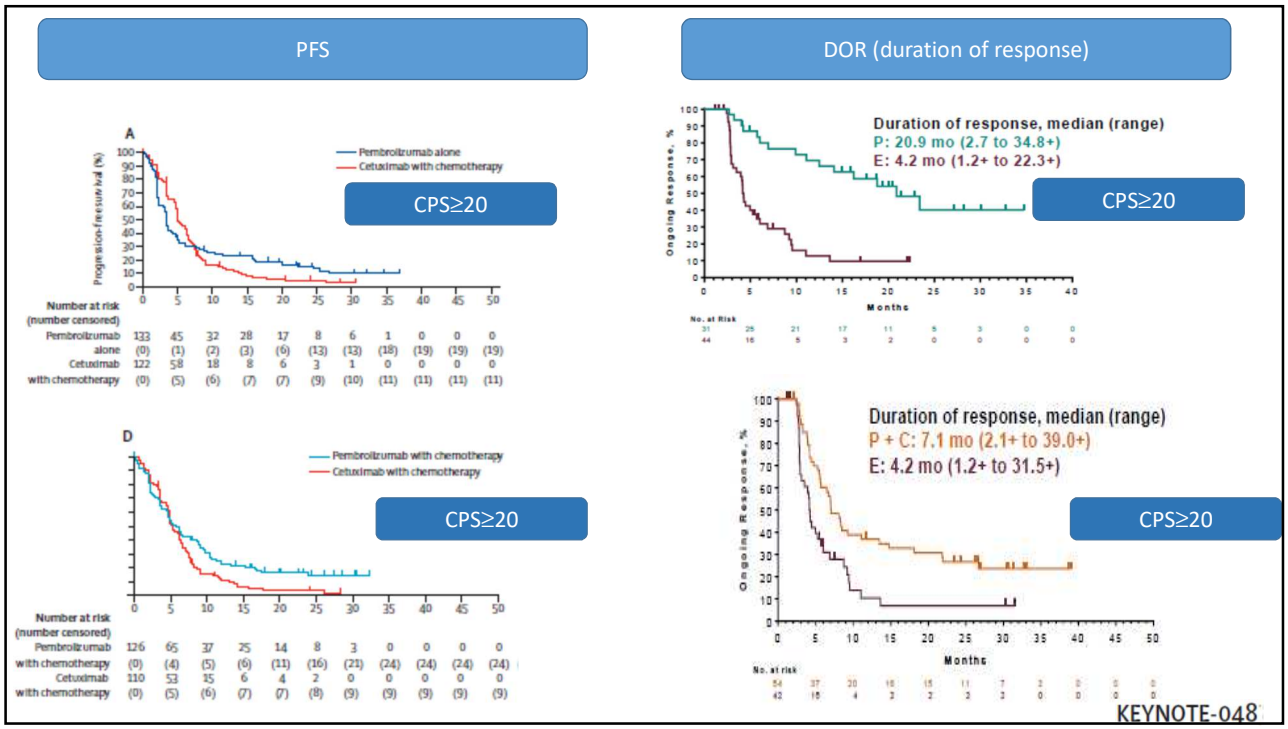
HR 0.60 (0.45-0.82)
14.7 vs. 11 months



CPS≥1

HR 0.65 (0.53-0.80)
13.6 vs. 10.4 months


OS: Pembro vs. Extreme
KEYNOTE-048
CPS≥20
14.8 vs. 10.7 months
CPS≥1
12.3 vs. 10.3 months
Total population
Total population
Noninferior to
Extreme
Total population
11.5 vs.10.7 months
Pembrolizumab alone
Cetuximab
with chemotherapy
12 months
24 months
Overall survival (%)
Number at risk
(number censored)


PFS
DOR (duration of response)
CPS≥20
Duration of response, median (range)
P: 20.9 mo (2.7 to 34.8+)
E: 4.2 mo (1.2+ to 22.3+)
Duration of response, median (range)
P + C: 7.1 mo (2.1+ to 39.0+)
E: 4.2 mo (1.2+ to 31.5+)
Pembrolizumab alone
Cetuximab with chemotherapy
Pembrolizumab with chemotherapy
Cetuximab with chemotherapy
Ongoing Response, %
Months
KEYNOTE-048

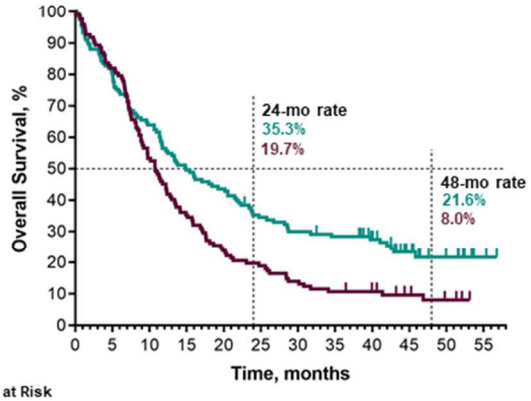
R Greil KN048 ESMO 2020

OS: Pembrolizumab vs EXTREME

4-letni OS

PD-L1 CPS ≥20

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembrolizumab	75.9%	14.9 (11.5-20.6)	0.61 (0.46-0.81)	0.00034
EXTREME	91.0%	10.8 (8.8-12.8)		

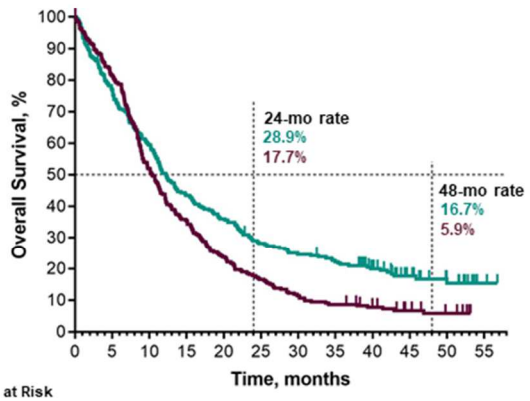


No. at Risk

Pembro	133	107	85	66	58	45	39	36	30	17	9	2
EXTREME	122	100	65	43	29	23	17	13	11	7	4	0

PD-L1 CPS ≥1

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembrolizumab	81.7%	12.3 (10.8-14.8)	0.71 (0.61-0.89)	0.00080
EXTREME	92.9%	10.4 (9.0-11.7)		



No. at Risk

Pembro	257	197	152	111	92	71	62	55	40	22	12	2
EXTREME	255	207	132	90	60	42	29	22	16	10	6	0

CI, confidence interval; HR, hazard ratio.
[a]Nominal, unadjusted one-sided *P* value based on log-rank test. Data cutoff: February 18, 2020.

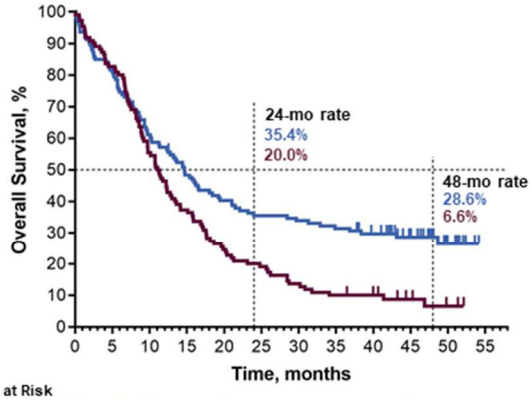
R Greil KN048 ESMO 2020

OS: Pembrolizumab + Chemo vs EXTREME

4-letni OS

PD-L1 CPS ≥20

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembro + Chemo	71.4%	14.7 (10.3-19.3)	0.62 (0.46-0.84)	0.00082
EXTREME	91.8%	11.1 (9.2-13.0)		

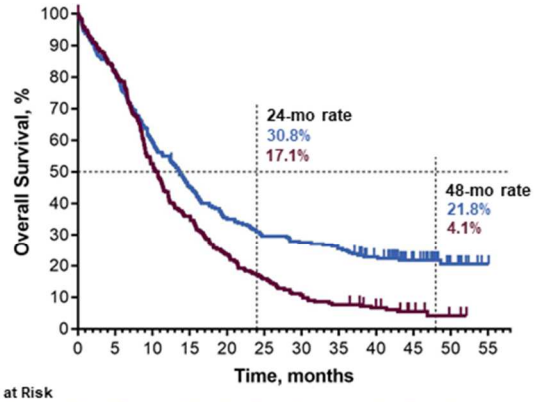


No. at Risk

Pembro + Chemo	126	102	77	60	50	44	42	39	33	22	7	0
EXTREME	110	91	61	41	27	21	15	11	9	5	2	0

PD-L1 CPS ≥1

	Events	Median OS, mo (95% CI)	HR (95% CI)	*P* value[a]
Pembro + Chemo	78.1%	13.6 (10.7-15.5)	0.64 (0.53-0.78)	0.00001
EXTREME	94.0%	10.6 (9.1-11.7)		



No. at Risk

Pembro + Chemo	242	197	144	109	84	71	66	61	48	29	9	1
EXTREME	235	191	123	84	55	37	25	18	12	6	2	0

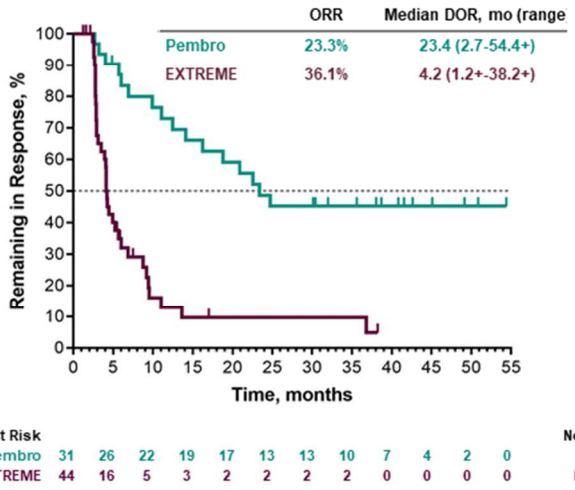
[a]Nominal, unadjusted one-sided p-value based on log-rank test. Data cutoff: February 18, 2020.

R Greil KN048 ESMO 2020

DOR: Pembrolizumab vs EXTREME

4-letni rezultati trajanja odgovora

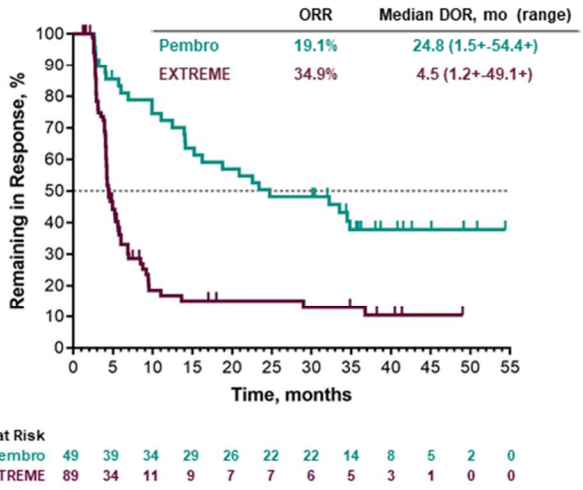
PD-L1 CPS ≥20



No. at Risk

Pembro	31	26	22	19	17	13	13	10	7	4	2	0
EXTREME	44	16	5	3	2	2	2	2	0	0	0	0

PD-L1 CPS ≥1



No. at Risk

Pembro	49	39	34	29	26	22	22	14	8	5	2	0
EXTREME	89	34	11	9	7	7	6	5	3	1	0	0

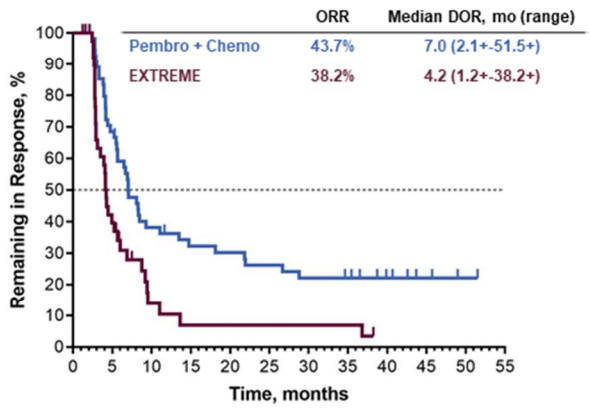
ORR, overall response rate.
Data cutoff: February 18, 2020.

R Greil KN048 ESMO 2020

DOR: Pembrolizumab + Chemo vs EXTREME

4-letni rezultati trajanja odgovora

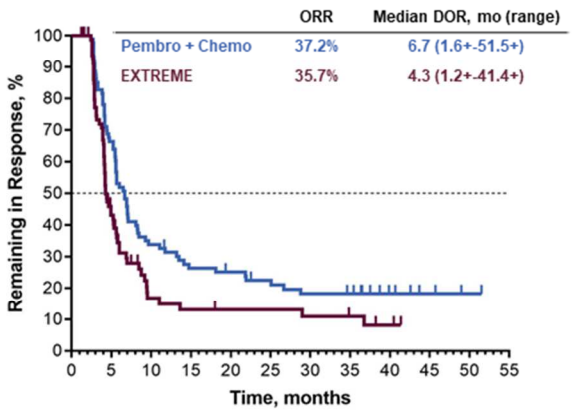
PD-L1 CPS ≥20



No. at Risk

Pembro + Chemo	55	37	20	16	15	13	11	10	6	3	1	0
EXTREME	42	15	4	2	2	2	2	2	0	0	0	0

PD-L1 CPS ≥1



No. at Risk

Pembro + Chemo	90	56	28	21	19	16	13	12	6	3	1	0
EXTREME	84	31	9	7	6	6	5	4	2	0	0	0

Data cutoff: February 18, 2020.

FDA approval:

-pembrolizumab+ChT as 1st line treatment regardless of PD-L1 expression

-pembrolizumab alone for pts with CPS≥1

EMA approval:

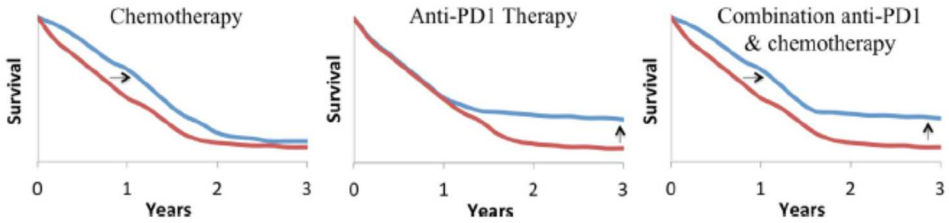
-pembrolizumab with or without ChT as 1st line treatment only for patients with a CPS ≥1

When choose 'chemo-free' approach with pembrolizumab monotherapy?

- Consider in patients with **CPS ≥ 1**,
- especially **when a rapid tumour shrinkage is not needed (e.g. pulmonary metastases only)**

When choose pembrolizumab+chemo (cisplatin or carboplatin plus 5-FU)?

- **In cases where rapid response is critical**
  - Symptomatic disease
  - Bulky locoregional disease (risk of bleeding or airway obstruction)
- **Preferred for lower PD-L1 expression**



JD Cramer, Oral Oncology 2019

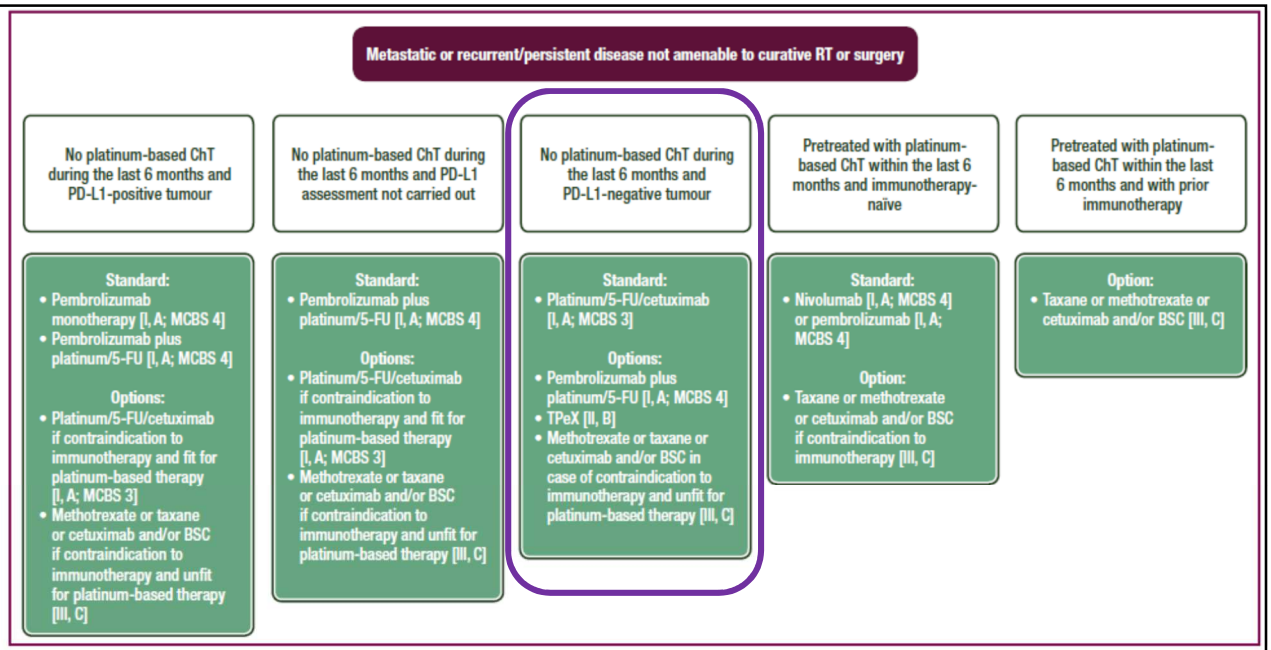


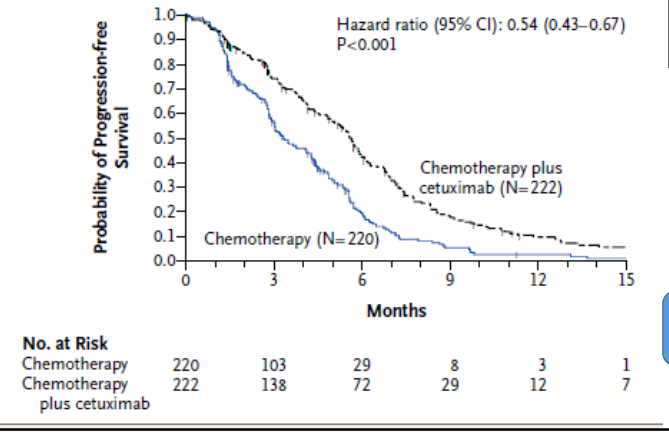
Figure 5. Management of recurrent and/or metastatic disease not amenable to curative RT or surgery.
5-FU, 5-fluorouracil; BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; PD-L1, programmed death-ligand 1; RT, radiotherapy; T, tumour; TPeX, cisplatin/docetaxel/cetuximab.

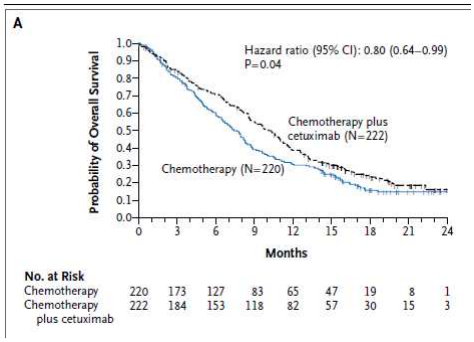
N Engl J Med 2008;359:1116-27.

EXTREME study

Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Ricard Mesia, M.D., Fernando Rivera, M.D., Ph.D., Eva Remenar, M.D., Andrzej Kawecki, M.D., Ph.D., Sylvie Rottey, M.D., Ph.D., Jozsef Erfan, M.D., Dmytro Zabolotnyy, M.D., Ph.D., Heinz-Roland Kienzer, M.D., Didier Cupissol, M.D., Frederic Peyrade, M.D., Marco Benasso, M.D., Ihor Vynnychenko, M.D., Ph.D., Dominique De Raucourt, M.D., Carsten Bokemeyer, M.D., Armin Schueler, M.S., Nadia Amellal, M.D.,





mPFS 3.3 vs. 5.6 months

RR: 20 vs. 36%

mOS 7.4 vs. 10.1 months

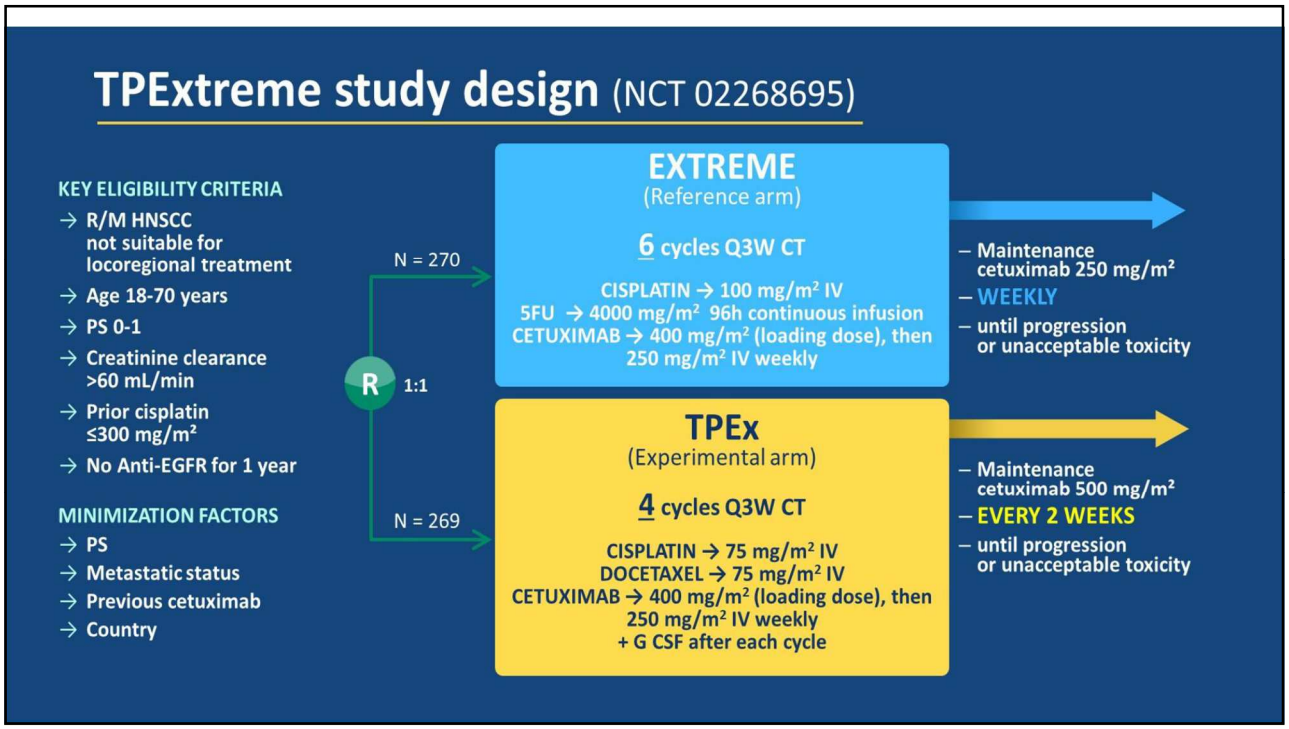
24

EXTREME regimen

In the first-line treatment of recurrent SCCHN:
-for patients with contraindications to immune checkpoint inhibitors [I, A]
-in patients with a tumour not expressing PD-L1 [II, B].

As a second-line treatment after progression on an immune checkpoint inhibitor
-in fit patients considered eligible for platinum-based ChT [IV, B].

Similarly, TPEx can be considered as a treatment alternative to EXTREME for some patients (DPD deficiency)



Overall Survival

Median OS higher than expected:
14.5 months in TPEx arm and
13.4 months in EXTREME arm

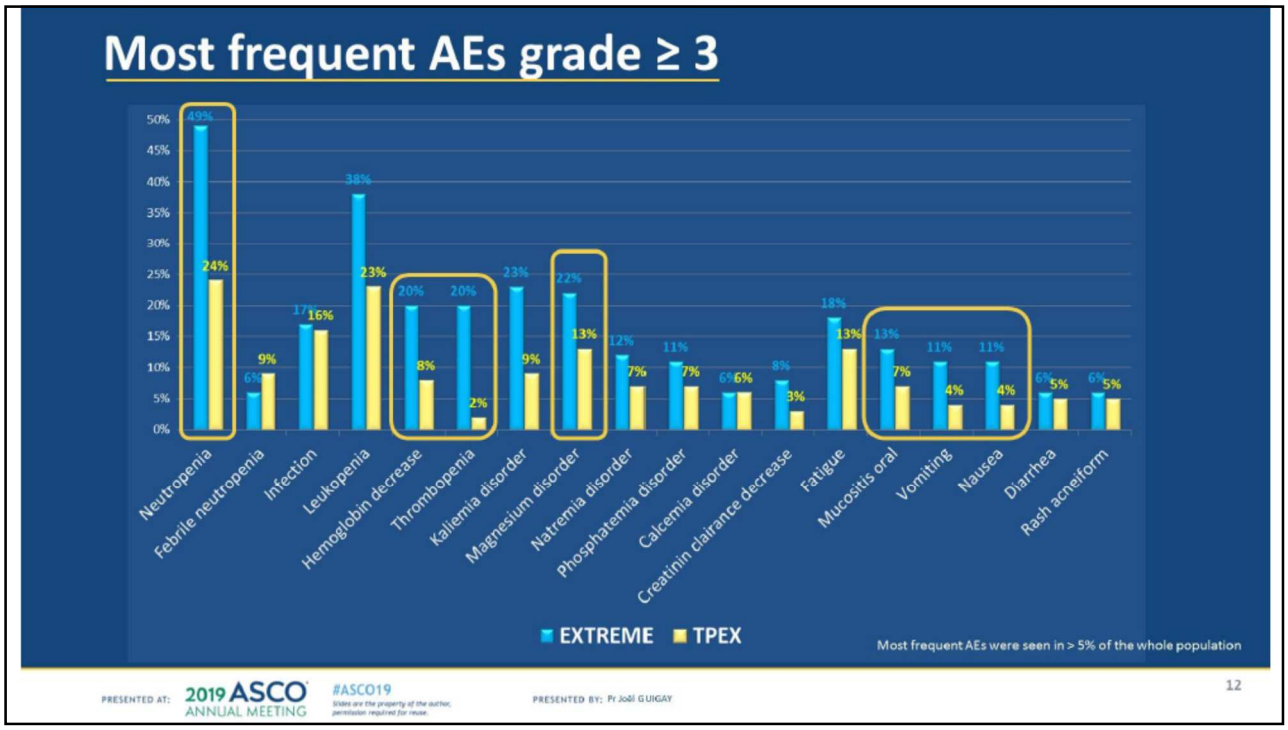
Hazard ratio TPEx vs EXTREME:
HR=0.87 (95% CI: 0.71-1.05)
p-value=0.15

Progression Free Survival and ORR 12 wks

- 486 events, 247 in the EXTREME arm and 239 in the TPEx arm
- **HR = 0.88 (95%CI:0.74-1.06), p-value = 0.17**

- **ORR (CR+PR) at 12 weeks according to local evaluation**

→ **46% (123 / 269) in the TPEx arm**
→ **40% (109 / 270) in the EXTREME arm**



Potekajoče raziskave pri ponovljenem/metastatskem raku glave in vratu

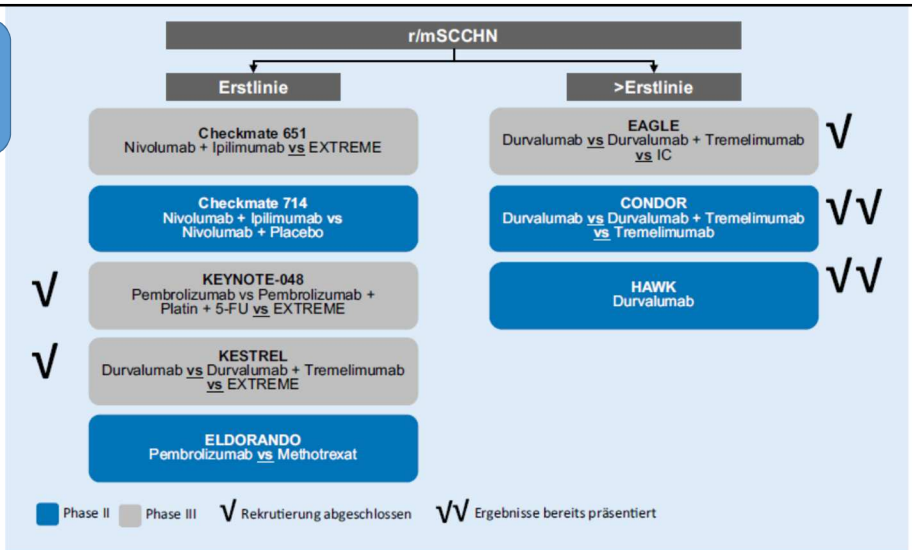


Abb. 2 ▲ Laufende immunonkologische (IO-)Studien beim r/mSCCHN. Erläuterung zu den Studien s. Text. *r/m* „recurrent/metastatic", rezidivierend/metastasierend; *SCCHN* „squamous cell carcinoma of the head and neck", Kopf-Hals-Plattenepithelkarzinom; *vs* versus; *5-FU* 5-Fluouracil; *IC* „investigator's choice", Entscheidung des Therapeuten: Methotrexat, Docetaxel oder Cetuximab

HNO 2019 · 67:221–235
https://doi.org/10.1007/s00106-018-(

Stefan Kasper[1] · Timon Hussain[2] · Isabel Virchow[1] · Martin Stuschke[3] · Stephan Lang[2]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study

R. L. Ferris[1*], R. Haddad[2], C. Even[3], M. Tahara[4], M. Dvorkin[5], T. E. Ciuleanu[6], P. M. Clement[7], R. Mesia[8], S. Kutukova[9], L. Zholudeva[10], A. Daste[11], J. Caballero-Daroqui[12], B. Keam[13], I. Vynnychenko[14], C. Lafond[15], J. Shetty[16], H. Mann[17], J. Fan[16], S. Wildsmith[17], N. Morsli[17], J. Fayette[18] & L. Licitra[19*]

Available online 12 April 2020

Durvalumab: anti PD-L1 antibody
Tremelimumab, an anti-CTLA-4 monoclonal antibody

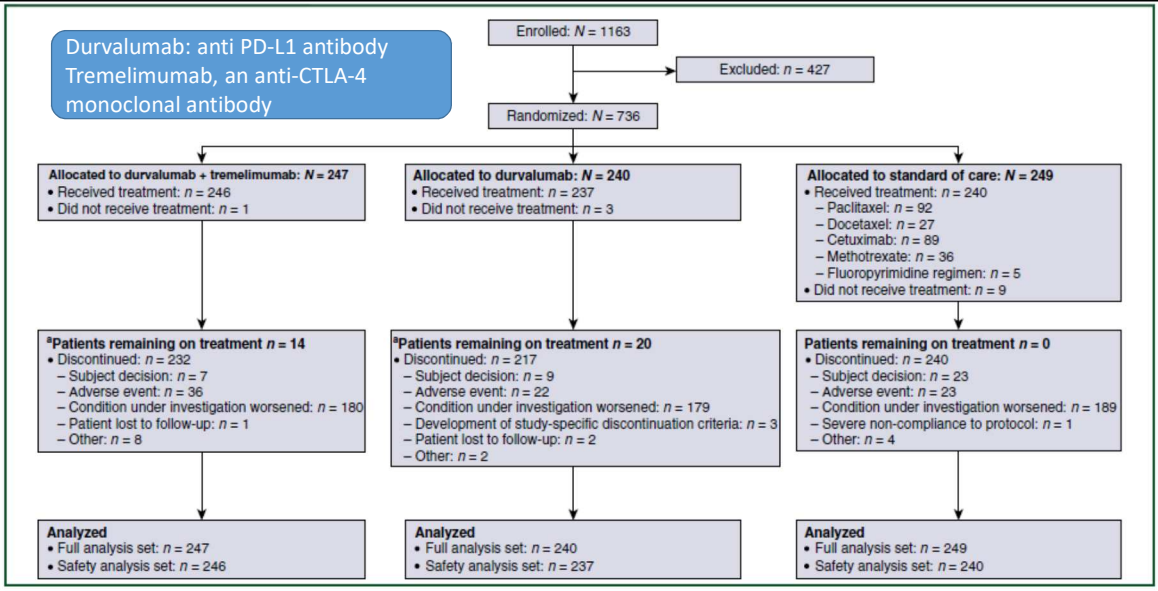
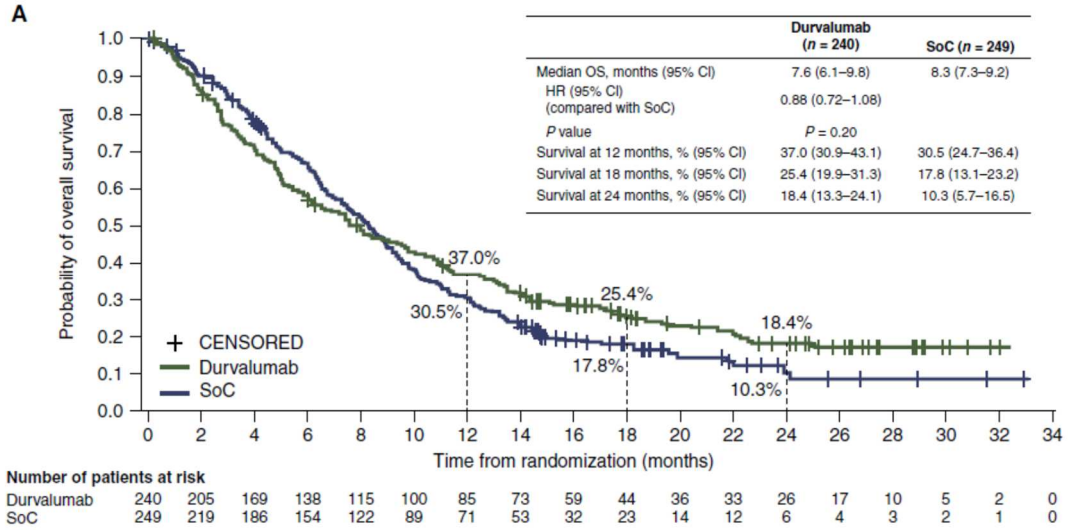


Figure 1. CONSORT diagram.

Dual primary end points were OS for durvalumab versus SoC and OS for durvalumab plus tremelimumab versus SoC.

A

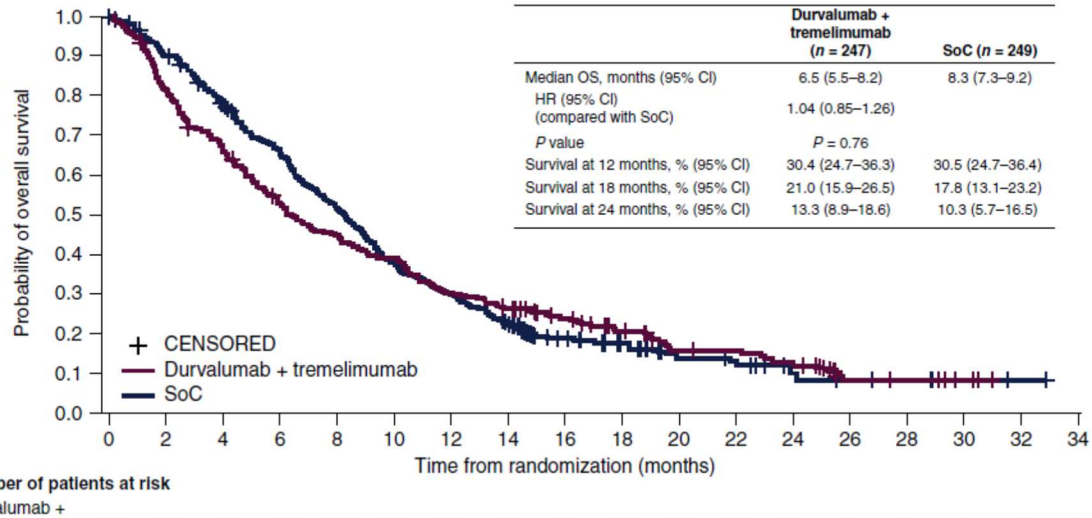


	Durvalumab (*n* = 240)	SoC (*n* = 249)
Median OS, months (95% CI)	7.6 (6.1–9.8)	8.3 (7.3–9.2)
HR (95% CI) (compared with SoC)	0.88 (0.72–1.08)	
P value	*P* = 0.20	
Survival at 12 months, % (95% CI)	37.0 (30.9–43.1)	30.5 (24.7–36.4)
Survival at 18 months, % (95% CI)	25.4 (19.9–31.3)	17.8 (13.1–23.2)
Survival at 24 months, % (95% CI)	18.4 (13.3–24.1)	10.3 (5.7–16.5)

Number of patients at risk

Durvalumab	240	205	169	138	115	100	85	73	59	44	36	33	26	17	10	5	2	0
SoC	249	219	186	154	122	89	71	53	32	23	14	12	6	4	3	2	1	0

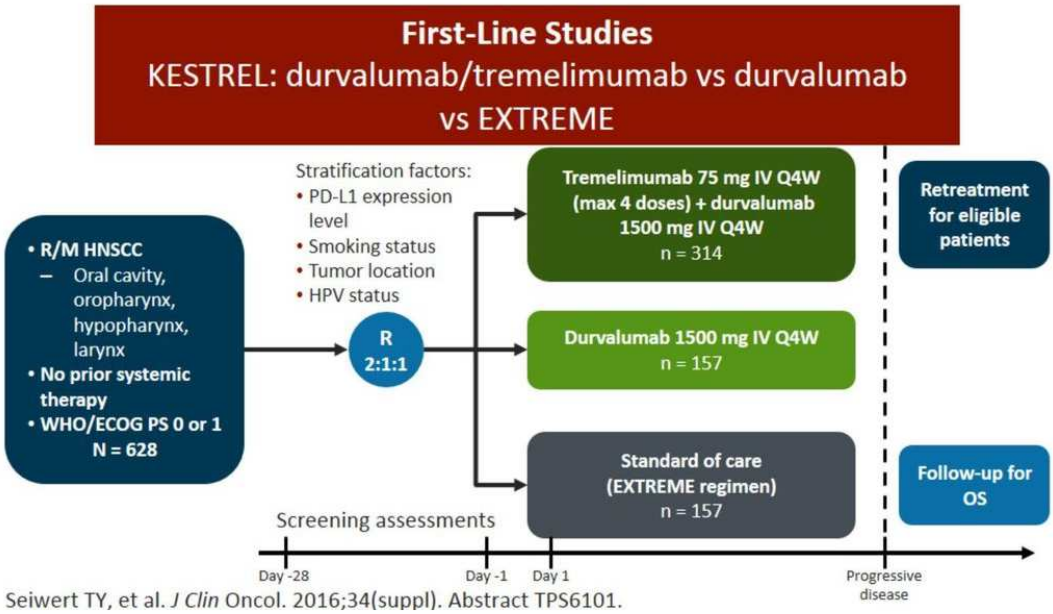
B



	Durvalumab + tremelimumab (*n* = 247)	SoC (*n* = 249)
Median OS, months (95% CI)	6.5 (5.5–8.2)	8.3 (7.3–9.2)
HR (95% CI) (compared with SoC)	1.04 (0.85–1.26)	
P value	*P* = 0.76	
Survival at 12 months, % (95% CI)	30.4 (24.7–36.3)	30.5 (24.7–36.4)
Survival at 18 months, % (95% CI)	21.0 (15.9–26.5)	17.8 (13.1–23.2)
Survival at 24 months, % (95% CI)	13.3 (8.9–18.6)	10.3 (5.7–16.5)

Number of patients at risk

Durvalumab + tremelimumab	247	200	165	127	108	94	73	63	48	37	25	24	20	8	7	3	0	0
SoC	249	219	186	154	122	89	71	53	32	23	14	12	6	4	3	2	1	0



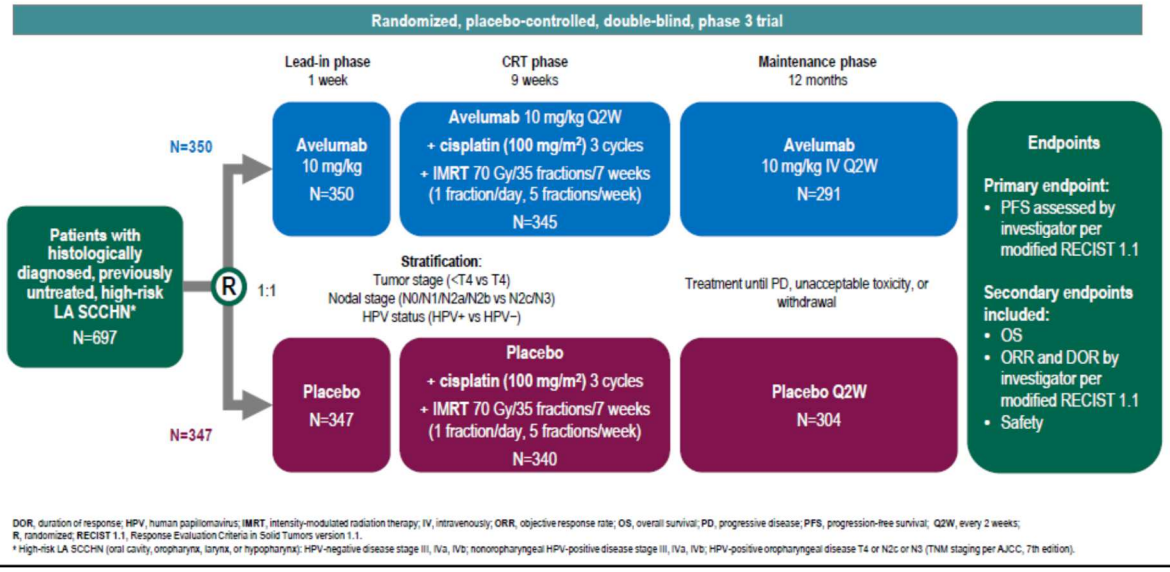
Seiwert TY, et al. *J Clin* Oncol. 2016;34(suppl). Abstract TPS6101.

Immunotherapy combined with radiation - concomitant treatment

Study	Inclusion criteria	Treatment arms	Recruitment
JAVELIN	Stage III-IVB HPV- HNSCC or T4 or N2c/N3 HPV+ OPSCC	Avelumab+cisplatin/RT vs cisplatin/RT	Accrual completed N=697
GORTEC 2017-01 (REACH)	Stage III-IVB HNSCC	Cisplatin eligible: avelumab+cetuximab/RT vs. cisplatin/RT Cisplatin ineligible: avelumab+cetuximab/RT vs. cetuximab/RT	Ongoing Planned N= 688
NRG HN-004	Phase II/III Cisplatin ineligible: stage III-IVB oral cavity/larynx/hypopharinx HNSCC or HPV- OPC SCC	Durvalumab/RT vs. cetuximab/RT	Ongoing Planned N=523
NRG HN-005	Phase II/III: HPV+ non-smoking associated OPSCC	Nivolumab/reduced dose RT (60 Gy) vs. cisplatin/reduced dose RT (60 Gy) vs. cisplatin/standard dose RT (70 Gy)	Ongoing Planned N=711
KEYNOTE-412	HNSCC, oral cavity need to be unresectalbe	Pembrolizumab+cisplatin/RT vs. cisplatin/RT	Acrcrual compalted N=780
NCT0334971	LA HNSCC	Cisplatin eligible: nivolumab+cisplatin/RT vs. cisplatin/RT Cisplatin ineligible: nivolumab/RT vs. cetuximab/RT	Active, not recruiting Planned N=1046

VIRTUAL ESMO congress 2020

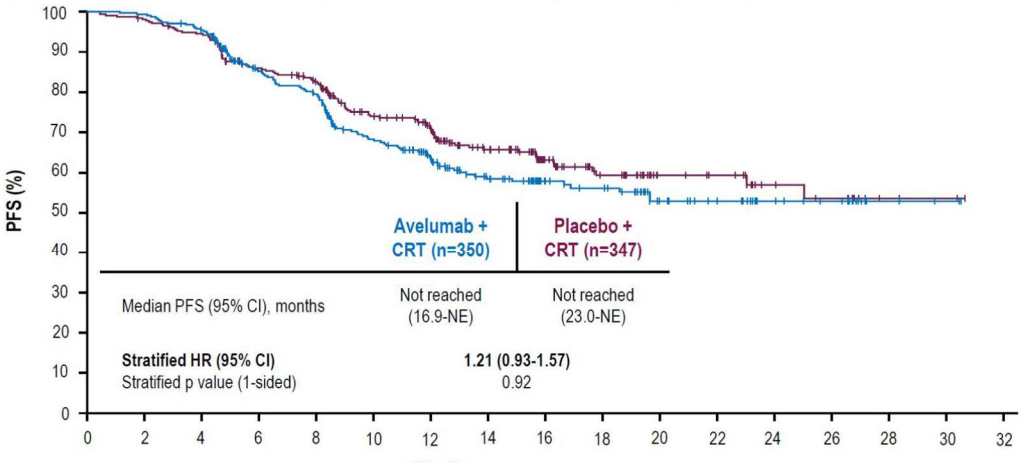
JAVELIN Head & Neck 100: study design



DOR, duration of response; HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q2W, every 2 weeks; R, randomized; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

VIRTUAL ESMO congress 2020

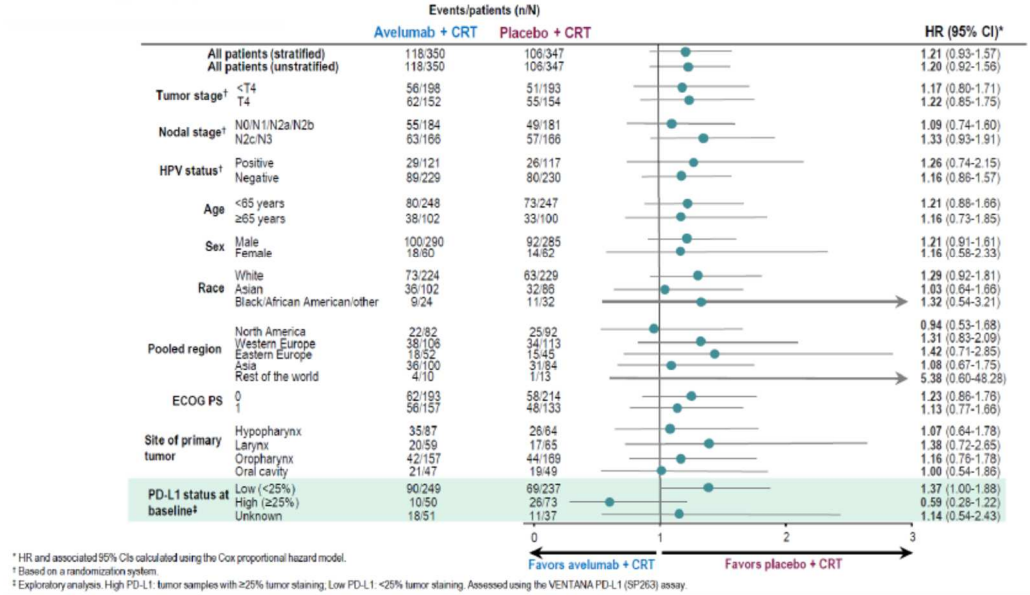
Primary endpoint: PFS by investigator per modified RECIST 1.1



At risk																	
Avelumab + CRT	350	303	289	239	222	176	143	107	69	63	41	33	22	18	4	2	0
Placebo + CRT	347	303	291	257	241	200	172	121	75	56	31	28	18	15	3	2	0

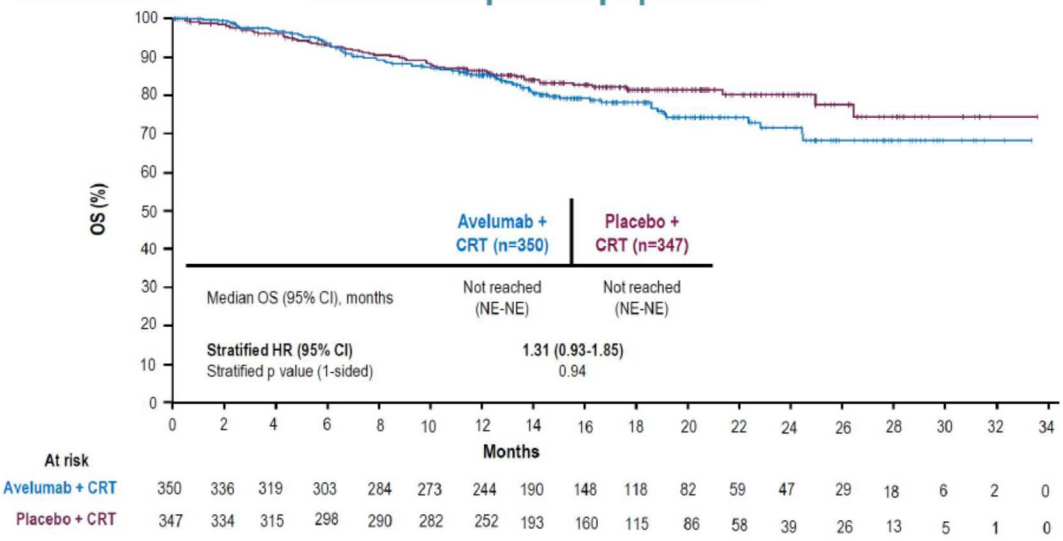
NE, not estimable.

PFS in subgroups



* HR and associated 95% CIs calculated using the Cox proportional hazard model.
† Based on a randomization system.
‡ Exploratory analysis. High PD-L1: tumor samples with ≥25% tumor staining; Low PD-L1: <25% tumor staining. Assessed using the VENTANA PD-L1 (SP263) assay.

OS: overall patient population



VIRTUAL 2020 ESMO congress

Treatment-related AEs

	Avelumab + CRT (n=348)		Placebo + CRT (n=344)	
	All grades	Grade 3/4	All grades	Grade 3/4
Any TRAE, %*	**98**	**66/14**	**99**	**63/11**
Mucosal inflammation	41	14	37	13
Radiation skin injury	39	5	40	5
Dysphagia	38	14	40	14

	Avelumab + CRT (n=348)	Placebo + CRT (n=344)
Serious TRAEs, %	36	32
TRAEs leading to discontinuation of avelumab/placebo, %	7	3
TRAEs leading to discontinuation of cisplatin, %	21	19
TRAEs leading to discontinuation of IMRT, %	<1	<1

VIRTUAL 2020 ESMO congress

Immune-related AEs

	Avelumab + CRT (n=348)		Placebo + CRT (n=344)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any irAE, %	**35**	**5**	**26**	**2**
Thyroid disorders	25	1	17	<1
Rash	10	1	8	<1

Avelumab–cetuximab–radiotherapy versus standards of care in locally advanced squamous-cell carcinoma of the head and neck: The safety phase of a randomised phase III trial GORTEC 2017-01 (REACH)

European Journal of Cancer 141 (2020) 21–29

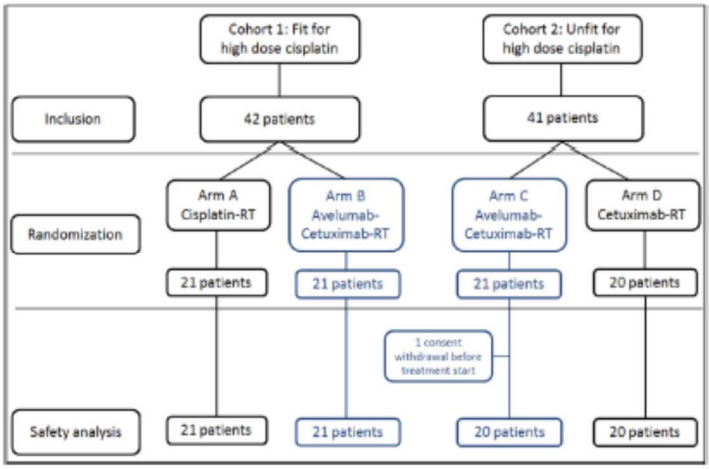


Fig. 1. Trial profile.

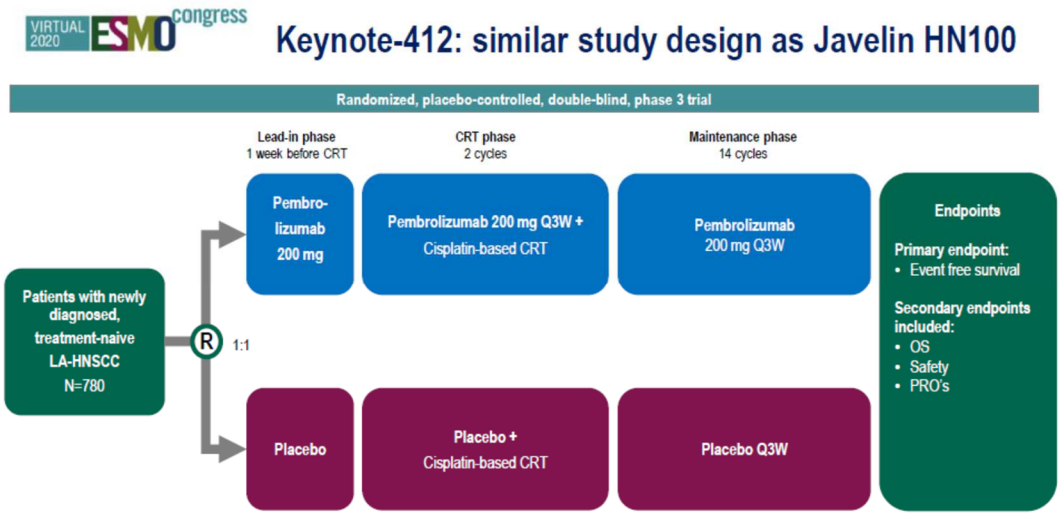
Safety acceptable, the study goes on

European Journal of Cancer 141 (2020) 21–29

Table 3
Number (%) of patients with adverse events by grade in experimental and SOC arms.

Characteristics	Arm A (SOC cisplatin)	Arms B + C (experimental)	Arm D (SOC cetuximab)
Any grade	21 (100%)	41 (100%)	20 (100%)
Grade I	20 (95%)	39 (95%)	20 (100%)
Grade II	20 (95%)	41 (100%)	16 (80%)
Grade III	18 (86%)	35 (85%)	19 (95%)
Grade IV	2 (10%)	5 (12%)	2 (10%)
Grade V	1 (5%)	0 (0%)	0 (0%)

SOC, standard of care.



PembroRad: study design

Randomized, open label, phase 2 trial

GORTEC

Patients unfit for high dose cisplatin
Non-operated stage III-Iva-b
SCC of oral cavity, oro/hypopharynx and larynx
Non-metastastatic

R

1:1

Arm A:
cetuximab 400 mg/m² loading dose and 250 mg/m² weekly + IMRT 69.96 Gy in 33 fractions
N=65

Arm B:
Pembrolizumab 200 mg Q3W + IMRT69.96 Gy in 33 fractions
N=66

Stratification:
N-stage (N0-1 vs N2-3)
P16 status and tumor site
(OPC positive vs OPC negative or non OPC)

Endpoints

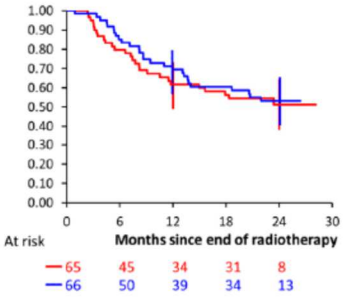
Primary endpoint:
- Locoregional control at 15 months

Secondary endpoints included:
- PFS
- Locoregional progression and distant metastases
- OS
- Acute adverse events
- Delayed toxicity
- Compliance

Pembro-RT does not improve outcome versus Cetux-RT

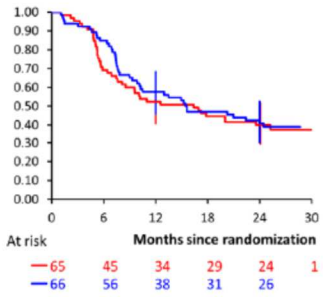
LRC

15 months:
Cetux-RT 59% (95% CI 45%-72%)
Pembro-RT 60% (95% CI 46%-72%)
OR = 1.05, p=0.91



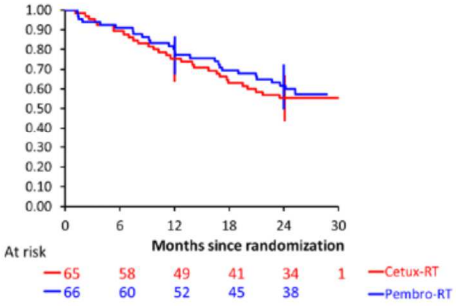
PFS

2 years:
Cetux-RT 40%
Pembro-RT 42%
HR = 0.83 (95% CI 0.53-1.29)



OS

2 years:
Cetux-RT 55%
Pembro-RT 62%
HR = 0.83 (95% CI 0.49-1.40)



VIRTUAL 2020 ESMO congress

STUDY DESIGN

Double-blind, placebo-controlled, Randomized Phase II

Part A
N=14
Dose escalation Phase I*
Primary endpoint
Definition of MTD/RP2D

RP2D
200mg QD

Part B
N=96 (ITT)

R
1:1

Xevinapant + CRT n=48

Placebo + CRT n=47

- **Xevinapant/Placebo** D1- D14 every 21 days for 3 cycles
- **CDDP** 100mg/m² every 21 days, for 3 cycles
- **IMRT** 2Gy 5d/week over 7 weeks (total dose 70Gy)

Stratified by
- N0-N1 vs N2-N3
- Primary tumor site (OPC vs non-OPC)
  - If OPC, by HPV/p16 status

Primary endpoint
- Locoregional control rate at 18 months after CRT (Δ>20% between arms with 0.8 power at 0.2 significance level)

Main secondary endpoints
- PFS
- Duration of LRC
- Overall survival

Main inclusion criteria:
- Previously untreated, unresectable stage III, IVA & IVB LA-SCCHN
- Oral cavity
- Hypopharynx
- Larynx
- Oropharynx-HPV/p16 both negative or positive

ClinicalTrials.gov Identifier: NCT02022098.
* Tao et al. ESTRO 2016

VIRTUAL 2020 ESMO congress

Background information[1] – presented at ESMO 2019

Baseline characteristics
- Well balanced between arms
- Over 80% of OPC were HPV/p-16 negative
- All have heavy smoking history
- Over 80% Stage IV

→ **High-risk patients**

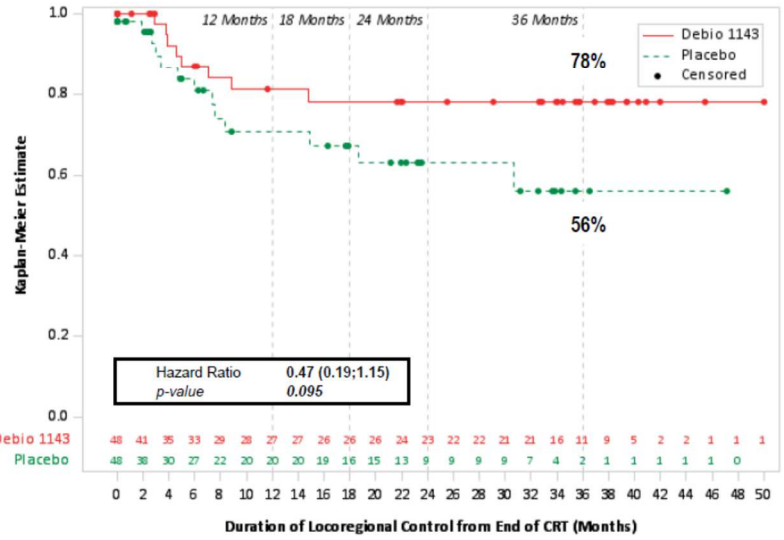
Treatment compliance
- Overall treatment exposure was comparable between arms
- Identical CDDP dose intensity
- Comparable RT doses

→ **Good treatment compliance**

1. Sun et al. Lancet Oncolol. 2020; In press

Duration of LRC - 3-year follow up

As per investigator - ITT



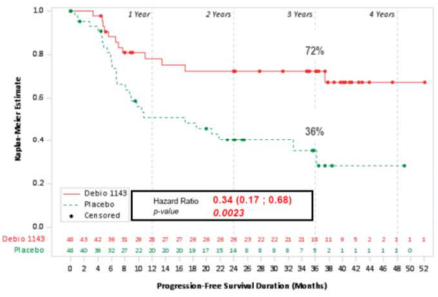
Median

› not reached in either arm

Improvement in line with 2-year results

Duration of PFS - 3-year follow up

As per investigator, with censoring for late events* – ITT



Median PFS

› Placebo: 16.9 months (95%CI: 6.8 - 36.1)

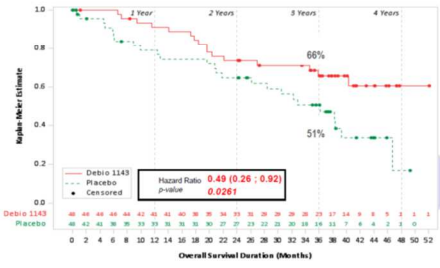
› Xevinapant: Not reached (95%CI: 37.4- NR)

Statistically significant, clinically compelling PFS improvement

* Late events: those occurring after m censored to avoid assumption of non- before PD identified (FDA guidance)

Duration of OS - 3-year follow up*

ITT



Median OS

› Placebo is 36.1 months

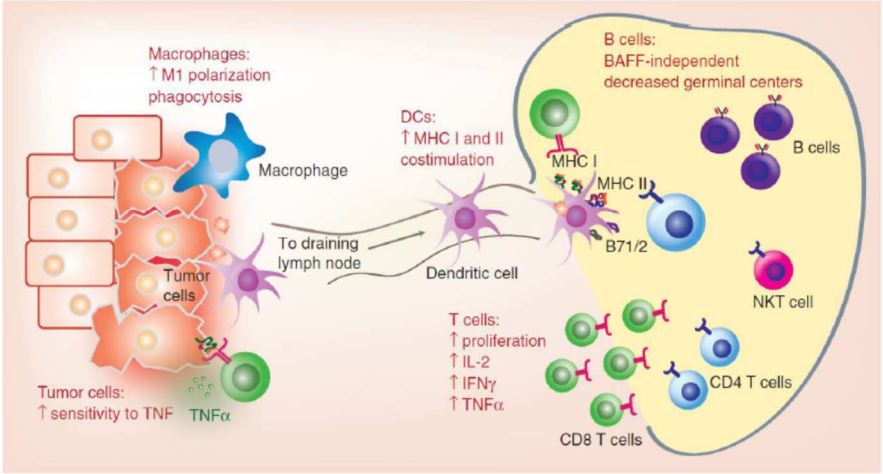
› Not reached for xevinapant

OS improvement is statistically significant

* 5 year FU ongoing

VIRTUAL 2020 ESMO congress

IAP antagonists activate innate and adaptive immunity



Dougan SK. Immunotherapy 2018;10:787-96.

Immunotherapy combined with radiation - neo/adjuvant treatment

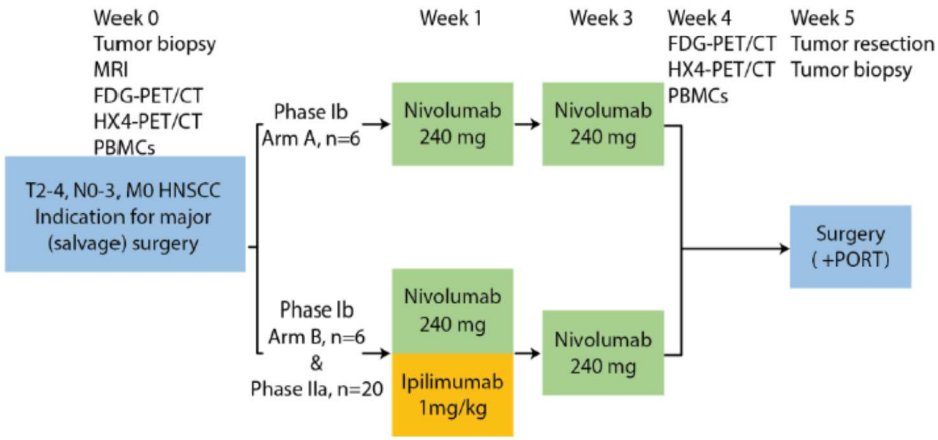
Study	Inclusion criteria	Treatment arms	Recruitment
KEYNOTE-689	Stage III-IVA oral cavity/larynx/hypopharxnx and HPV- OPSCC or stage III HPV+ OPSCC	Neoadjuvant + adjuvant pembrolizumab added to surgery and standard risk-based adjuvant therapy Vs. surgery and standard risk-based adjuvant therapy	Ongoing Planned N=704
WO420424	HNSCC requiring multimodality therapy	Adjuvant atezolizumab vs. placebo after definitive local therapy (surgery or RT)	Ongoing Planned N=400
ECOG ACRIN EA3161	Phase II/III Intermediate risk HPV+ OPSCC	Nivolumab+cisplatin/RT vs. cisplatin/RT	Ongoing, planned N=744

Neoadjuvantne študije

	Zhong 2012	Licitra 2003	Schoenfeld 2020	IMCISION 2020	Zinner 2020
Lokalizacija	Ustna votlina	Ustna votlina	Ustna votlina	Vse lokaliz.	Vse lokaliz.
Stadij	T1-4 N0-2c	T2-4 N0-2c	T2-4 N0-2c	T2-4 N0-3	Stadij III-IV (HPV neg.) Stadij II-III (HPV poz.)
Vrsta indukcijske terapije	TPF	PF	Nivo/Ipi	Nivo/Ipi	Nivo/Karbo-pakli
Skoraj pCR (>=90%)	28%	33%	20%	31%	42%
Toksičnost gradusa 3/4	31%	35% (3 gradus 5)	30% (irAE)	30% (irAE)	37%

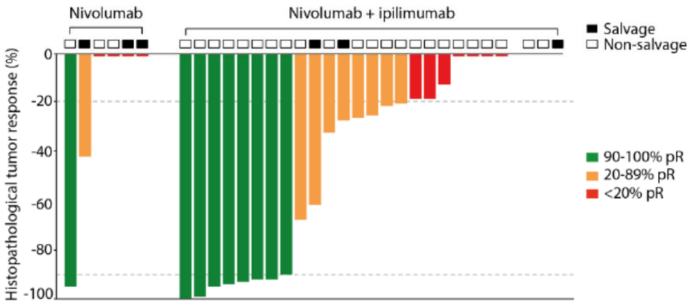
VIRTUAL 2020 ESMO congress

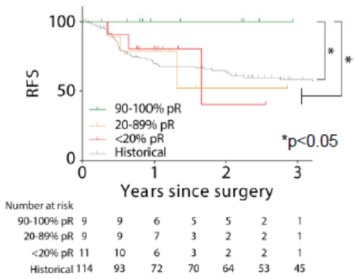
*IM*CISION trial design



VIRTUAL 2020 ESMO congress

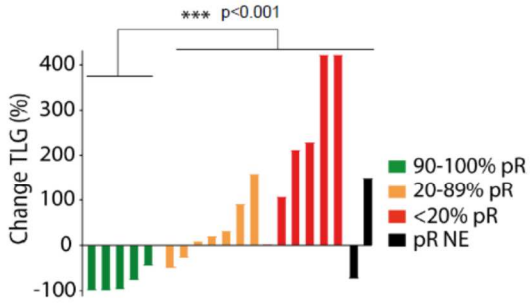
Nivolumab w/wo ipilimumab induces 31% (near) complete responses (CRs) at the primary tumor site, with superior (100%) RFS at 14mo FU

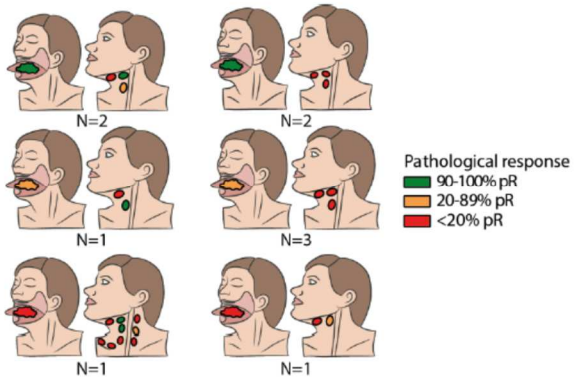




VIRTUAL 2020 ESMO congress

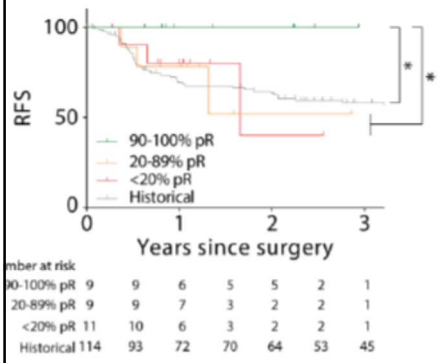
FDG-PET %change in total lesion glycolysis (δTLG) identifies (near)CRs to neoadjuvant ICB in a 4-week timeframe





VIRTUAL ESMO congress 2020

Patients with pCR have better disease control with Nivo/Ipi, but also with PF: Will induction with Nivo/Ipi impact on overall survival?



*p<0.05

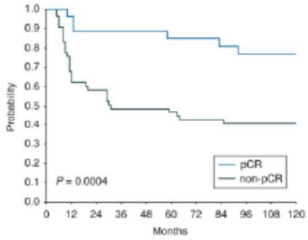


Figure 3. Disease-free survival in the induction chemotherapy arm according to pathological complete response (pCR) achievement.

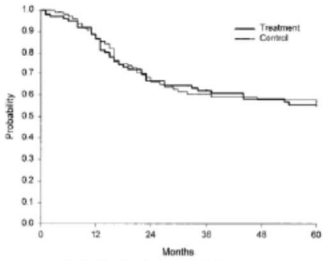


Fig 4. Overall survival curves by treatment arm.

Bossi et al. Annals of Oncology 2014

KARCINOM NAZOFARINKSA

Anti-PD1 monotherapy in recurrent/metastatic NPC patients

	Eligibility criteria	Treatment	n	PD-L1 ≥ 1	ORR	PFS (median, mo)	OS (median, mo)
KEYNOTE-028 Hsu C, JCO 2017[1]	NPC PD-L1 CPS (22C3) ≥ 1	Pembrolizumab	24	41/44 (93%) (CPS, 22C3)	25.9%	6.5	16.5
NCI-9742 Ma BBY, JCO 2018[2]	NPC, WHO type II or III	Nivolumab	45	TC: 18/45% (40%) IC: 10/45 (22%) (22C3)	20.5%	2.8	17.8
CHECKMATE 358 Delord JP, ASCO 2017[3]	NPC, WHO type II or III EBER(+), EBV DNA (+)	Nivolumab	24	TC: 11/24 (45.8%)	20.8%	2.4	NA
Fang WF, Lancet Oncol 2018[4]	NPC, WHO criteria	Camrelizumab (SHR-1210)	91	NA	34%	5.6	NA
Wang FH, ASCO 2018[5]	NPC	Toripalimab (JS001)	190	TC: 45.6%	25.2%	NA	NA
Shen L, JITC 2020[6]	NPC	Tislelizumab (BGB-A317)	21	TC: 16/20 (80%) (SP263)	43%	10.4	NA

NA: not available

1. Hsu C, et al. *J Clin Oncol* 2017;35:4050-4056; **2.** Ma BBY, et al. *J Clin Oncol* 2018;36:1412-1418; **3.** Delord JP, et al, *J Clin Oncol* 2017;35(15 supp):#6025; **4.** Fang WF, Lancet Oncol 2018; 19: 1338-50; **5.** Wang FH, *J Clin Oncol* 2019;37(15 supp):#2556; **6.** Shen L, *J Immunother Cancer*. 2020; 8(1): e000437; **7.** Lim DWT, et al. *Cancer Res* 2019 (79) (13 Supp)

Study Design

Single arm, phase II, multi-center study
(Singapore, Taiwan)

Eligibility Criteria

- Recurrent/metastatic, undifferentiated NPC
- Detectable plasma EBV DNA
- Measurable disease per RECIST 1.1
- ECOG PS 0/1
- No more than 1 line prior palliative chemotherapy

→ **Nivolumab** 3mg/kg q2w
Ipilimumab 1mg/kg q6w
Every 6 weeks a cycle

→ Until clinical deterioration or unacceptable toxicity

→ Survival follow-up

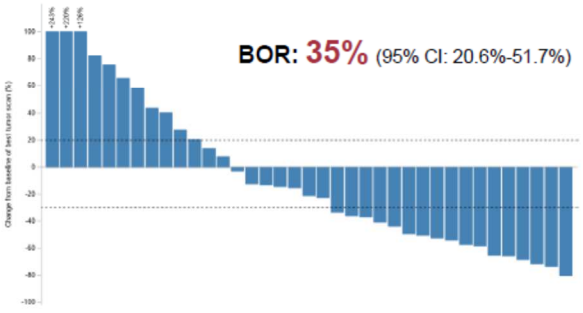
Sample size estimate: Simon optimal 2-stage design
- To investigate if the BOR is at least 45% with a no-interest BOR rate of 25%, at 80% power and 10% significance level.
- Stage I: 15 patients, stage II: 11 patients.
- An additional 14 patients were recruited for the clinical efficacy and safety estimates (per protocol).

Primary endpoint: best objective response rate

Investigator-initiated trial (NCT03097939)
PI: Darren Wan-Teck Lim (NCCS)

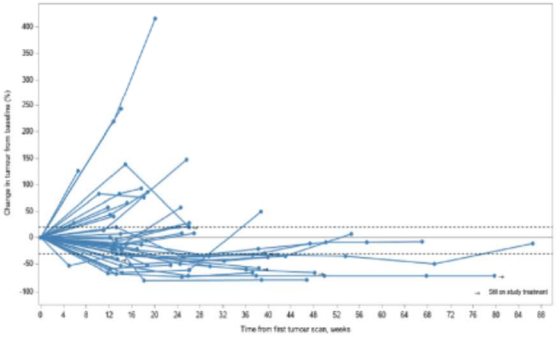
Results

Best objective response rate (BOR) and duration of response



BOR: 35% (95% CI: 20.6%-51.7%)

	Nivolumab + ipilimumab N=40, n (%)
Partial response (PR)	14 (35.0)
Stable disease (SD)	7 (17.5)
Progressive disease (PD)	17 (42.5)
Not done (ND)	1 (2.5)
Not evaluable (NE)	1 (2.5)



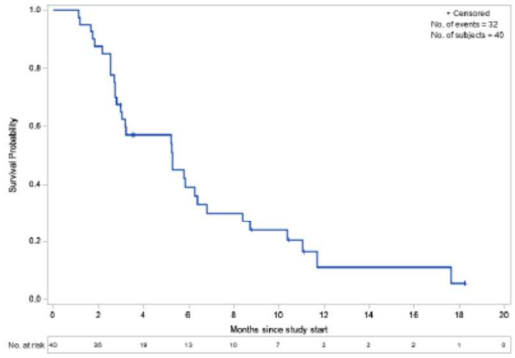
Duration of response:
median **5.9** (95% CI, 3.95 - 8.97) **months**

Results

Survival analysis

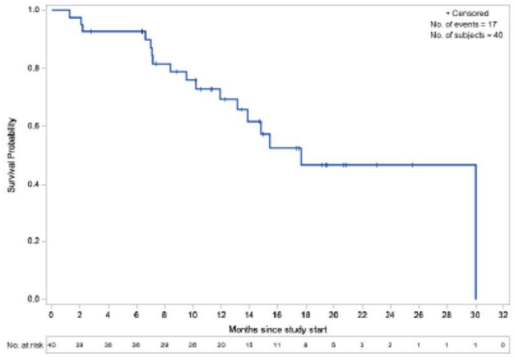
Progression-free survival
Median (95% CI)

5.3 (3.0 – 6.4) months



Overall Survival
Median (95% CI)

17.6 (13.1, 30.0) months



Study Design

Key eligibility criteria:
- Histologically confirmed R/M NPC (WHO class 2/3; Stage IVb)
- Progressed on ≥2 lines of chemotherapy
- ECOG PS of 0 or 1
- At least one measurable lesion per RECIST 1.1

→ **Camrelizumab** 200 mg, iv, q2w →

Primary endpoint:
- ORR per IRC

Secondary endpoints:
- ORR per INV; DoR; DCR; TTR; PFS; OS
- Safety

Single-arm, Open-label, Multicenter Phase 2 Clinical Trial (NCT03558191; CTR20180865)
Treatment until disease progression, unacceptable toxicity, patient withdrawal, or investigator decision.
Tumor assessments by RECIST v1.1.

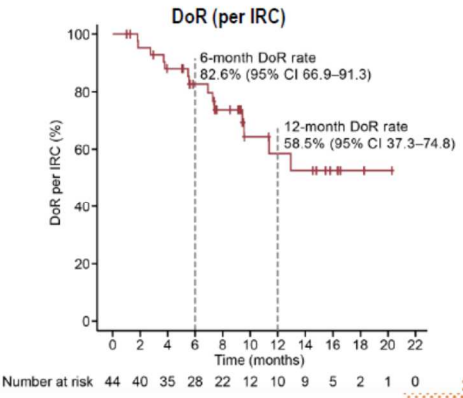
Enrollment period: From Aug 14, 2018 to Dec 30, 2019, 156 eligible patients were enrolled.
Data cut-off date: Jun 30, 2020
Median follow-up duration: 10.9 months (range 0.7-22.3)

ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; DoR, duration of response; DCR, disease control rate; TTR, time to response; PFS, progression-free survival; OS, overall survival; IRC, independent review committee; INV, investigator.

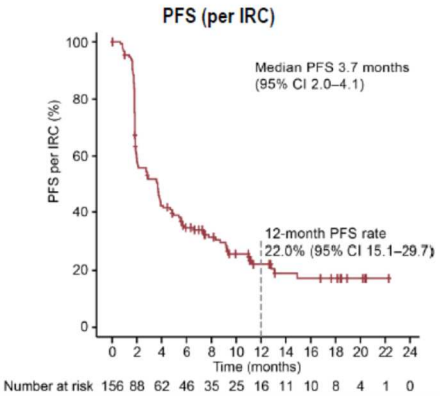
Primary endpoint: ORR

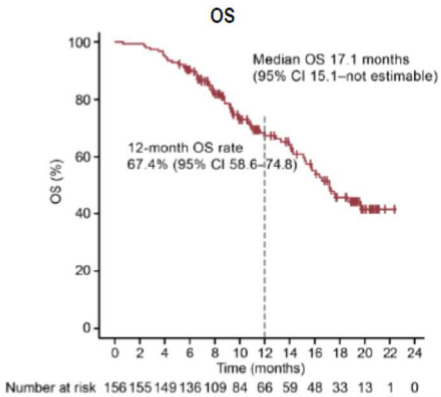
	Per IRC (n=156)	Per INV (n=156)
Best overall response		
Complete response	1 (0.6%)	2 (1.3%)
Partial response	43 (27.6%)	35 (22.4%)
Stable disease	41 (26.3%)	47 (30.1%)
Progressive disease	67 (43.0%)	67 (43.0%)
Not assessable	4 (2.6%)	5 (3.2%)
ORR	44 (**28.2%**, 21.3–36.0)	37 (**23.7%**, 17.3–31.2)
DCR	85 (**54.5%**, 46.3–62.5)	84 (**53.9%**, 45.7–61.9)
12-month DoR rate	58.5% (37.3–74.8)	62.2% (40.1–78.3)

Data are n (%), n (%, 95% CI), or % (95% CI).



PFS and OS





Biomarkerji za ICI

Hot Topic

Biomarkers for immunotherapy response in head and neck cancer

Niki Gavrielatou[a], Stergios Doumas[b], Panagiota Economopoulou[a], Periklis G. Foukas[c], Amanda Psyrri[a,*]

Cancer Treatment Reviews 84 (2020) 101977

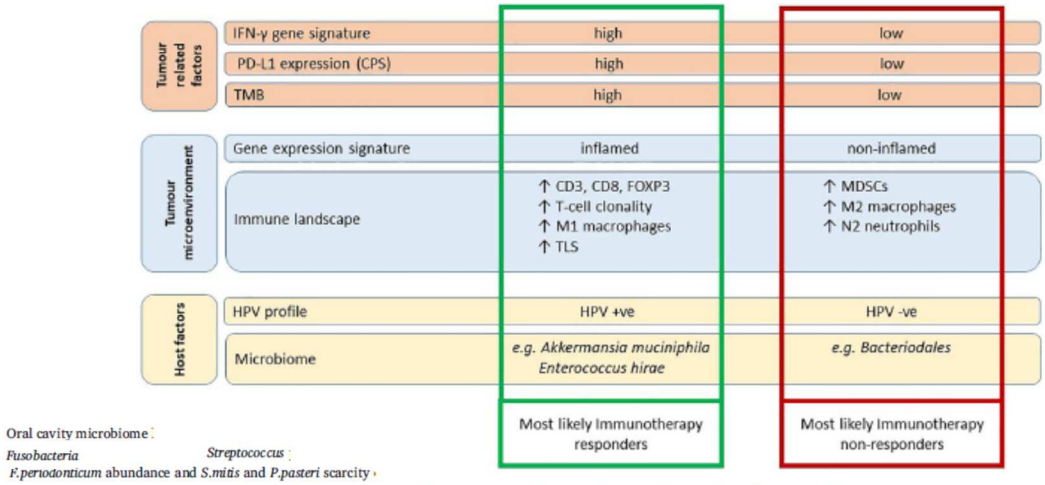


Fig. 1. Strategies to optimize response to immunotherapy depicted in the cancer immunity cycle.

Zaključki

- Ključno pri izbiri zdravljenja R/M SCHNC z zaviralci kontrolnih točk je selekcija
  - Rezistenca na cisplatin
  - Izraženost PD-L1
  - Bolnik: PS, delovanje ključnih organov (ledvice, jetra, kostni mozeg)
  - Razširjenost bolezni (oligometastatska, razširjena, mesto metastaz)
  - Ogroženost življenjskih funkcij

SIMPOZIJ SO PODPRLE NASLEDNJE DRUŽBE:

ZLATA SPONZORJA:

Merck Sharp & Dohme inovativna zdravila d.o.o.

Roche, farmacevtska družba d.o.o.

OSTALI SPONZORJI:

JANSSEN

MERCK

PFIZER

AMGEN

TAKEDA

BRISTOL MYERS SQUIBB

ELI LILLY

SANOFI

MEDIJSKI PARTNER DOGODKA:

ADRIASONARA D.O.O.
upravljalec spletnega mesta

Onkološki Inštitut
Institute of Oncology
Ljubljana

Strokovna knjižnica za onkologijo

8 čitalniških mest

5.300 knjig

6.000 e-revij

vsak delovni dan od 8. do 15. ure
www.onko-i.si/strokovna_knjiznica