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INSTITUTE OF ONCOLOGY
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15.&16. december 2021

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Ljubljana, december 2021

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SREDA, 15. 12. 2021

Moderator: *prof. dr. Janja Ocvirk, dr. med., doc. dr. Tanja Mesti, dr. med.*

12.00-12.15 **Imuno-terapija v onkologiji v letu 2021. Ali se indikacije širijo?**
prof. dr. Janja Ocvirk, dr. med.

12.15-13.00 **Novosti na področju imuno-terapije kožnih rakov**
prof. dr. Janja Ocvirk, dr. med.

13.00-13.45 **Novosti na področju imuno-terapije rakov glave in vratu**
Prof. dr. Soulieres, dr. med., doc. dr. Cvetka Grašič Kuhar, dr. med.

13.45-14.00 **Odmor**

14.00-14.45 **Novosti na področju imuno-terapije pljučnih rakov**
Prof. dr. Jakopović, dr.med., mag. Mojca Unk, dr. med.

14.45-15.30 **Novosti na področju imuno-terapije raka dojk**
Prof. dr. Cortes, dr. med., dr. Simona Borštnar, dr. med.

15.30-16.15 **Novosti na področju imuno-terapije uroloških rakov**
dr. Breda Škrbinc, dr. med.

16.15-16.30 **Odmor**

16.30-17.00 **Novosti na področju imuno-terapije raka požiralnika in želodca**
Marko Boc, dr. med.

17.00-17.30 **Novosti na področju imuno-terapije rakov hepato-biliarnega trakta in pankreasa**
doc. dr. Martina Reberšek, dr. med.

17.30-18.00 **Novosti na področju imuno-terapije kolo-rektalnega raka**
Marija Ignjatović, dr.med.

ČETRTEK 16. 12. 2021

Moderator*:* *doc. dr. Boštjan Šeruga, dr. med., doc. dr. Martina Reberšek, dr. med, doc. dr. Erika Matos, dr. med.*

9.00-9.30 **Prognostični in prediktivni markerji v imuno-onkologiji**
doc. dr. Boštjan Šeruga, dr. med.

09.30-10.00 **Novosti na področju imuno-terapije ginekoloških rakov**
Mirjana Pavlova, dr. med.

10.00-10.30 **Novosti na področju imuno-terapije drugih rakov**
doc. dr. Erika Matos, dr. med

10.30-11.00 **Faza 1: genska imunoterapija pri BCC**
prof. dr. Maja Čemažar, prof. dr. Gregor Serša

11.30-13.00 **OKROGLA MIZA: Dileme pri zdravljenju z imuno-terapijo v onkologiji**

Razpravljalci: *dr. Maja Ravnik, dr. med., Katja Mohorčič, dr. med., doc. dr. Boštjan Šeruga, dr. med., mag. Mojca Unk, dr. med.*

- **Imunsko pogojeni neželeni učinki:** *doc. dr. Tanja Mesti, dr. med.*
- **Imunosupresivi in imuno-terapija:** *mag. Tomaž Milanez, dr. med.*
- **Prekinitev zdravljenja in re-indukcija imuno-terapije:** *asist. dr. Rok Devjak, dr. med.*

13.00-13.15 **Odmor**

13.15-13.45 **Pseudo-progres: terapevtska zagata v imuno-terapiji**
Nina Boc, dr. med.

11.45-12.15 **Imunoterapija onkraj zaviralcev kritičnih točk**
doc. dr. Tanja Mesti, dr.med.

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Imunoterapija v onkologiji v letu 2021

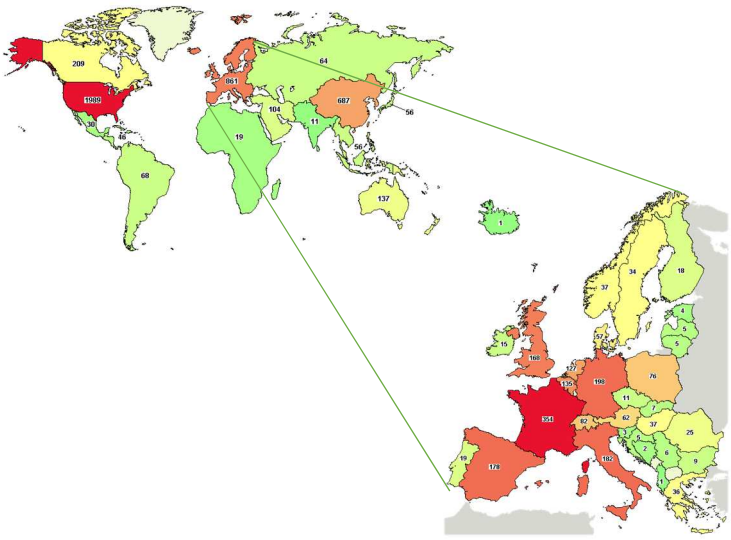
Janja Ocvirk

Registered trials (ClinicalTrials.gov; 8.10.2021)

Cancer immunotherapy: 3,667 ongoing studies

Terms / Synonyms	Search Results*	Entire Database**
cancer immunotherapy	315 studies	315 studies
Immuno-Chemotherapy	125 studies	125 studies
Immunotherapy for cancer	15 studies	15 studies
immunotherapy cancer	1 studies	1 studies
immunotherapy	3,572 studies	5,663 studies
immunomodulator	38 studies	245 studies
Immunomodulatory Agent	27 studies	105 studies
Immunotherapeutic Agent	27 studies	37 studies
Immune Modulators	18 studies	73 studies
Immunomodulating Agent	8 studies	25 studies
Biological Response Modifiers	7 studies	15 studies
Immunological therapy	6 studies	8 studies
Immune Mediators	5 studies	23 studies
Immune Regulators	4 studies	14 studies
Immunologically Directed Therapy	4 studies	4 studies
Biomodulators	3 studies	8 studies
Immunopotentiators	2 studies	2 studies
cancer	3,664 studies	96,288 studies
Neoplasm	3,416 studies	75,952 studies
Tumor	2,875 studies	46,043 studies
Oncology	788 studies	16,759 studies
Malignancy	312 studies	6,697 studies
neoplastic syndrome	19 studies	674 studies
Neoplasia	13 studies	1,126 studies
Neoplastic Disease	1 studies	85 studies
Malignant Growth	--	2 studies
neoplastic growth	--	3 studies

-- No studies found



Source:https://ClinicalTrials.gov

Region Name	Number of Studies	
World	3,667	
Africa [map]	19	
Central America [map]	46	
East Asia [map]	687	
Japan	56	[studies]
Europe [map]	861	
Middle East [map]	104	
North America	2,047	
Canada [map]	209	[studies]
Mexico	30	[studies]
United States [map]	1,989	[studies]
North Asia [map]	64	
Pacifica [map]	137	
South America [map]	68	
South Asia [map]	11	
Southeast Asia [map]	56	

ClinicalTrials.gov

Tumorji pljuč

S Jabbour. ASCO 2021

KEYNOTE-799: Phase 2 Trial of Pembrolizumab Plus Platinum Chemotherapy and Radiotherapy for Unresectable, Locally Advanced, Stage III NSCLC

S.K. Jabbour[1]; K.H. Lee[2]; N. Frost[3]; V. Breder[4]; D.M. Kowalski[5]; I. Alawin[6]; E. Levchenko[7]; N. Reguart[8]; A. Martinez-Marti[9]; B. Houghton[10]; J.-B. Paoli[11]; S. Safina[12]; K. Park[13]; T. Komiya[14]; A. Sanford[15]; V. Boolell[16]; H. Liu[17]; A. Samkari[17]; S.M. Keller[17]; M. Reck[18]

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KEYNOTE-042 5-Year Survival Update: Pembrolizumab Versus Chemotherapy in Patients with Previously Untreated, PD-L1–Positive, Locally Advanced or Metastatic Non–Small-Cell Lung Cancer

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[2]resented at the Society for Immunotherapy of Cancer 36th Annual Meeting 2021 (SITC)
ovember 10 – 14, 2021
Washington, D.C., USA

The following slides are intended for use as a full set for completeness and are a verbatim re-creation of the congress poster

First-line nivolumab + ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year update from CheckMate 743

Solange Peters,[1] Arnaud Scherpereel,[2] Robin Cornelissen,[3] Youssef Oulkhouir,[4] Laurent Greillier,[5] Muhammet Ali Kaplan,[6] Toby Talbot,[7] Isabelle Monnet,[8] Sandrine Hiret,[9] Paul Baas,[10] Anna K. Nowak,[11] Nobukazu Fujimoto,[12] Anne S. Tsao,[13] Aaron S. Mansfield,[14] Sanjay Popat,[15] Xiaoqing Zhang,[16] Nan Hu,[16] David Balli,[16] Jenine K. Sanzari,[16] Gérard Zalcman[17]

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First-Line Pembrolizumab Plus Chemotherapy for Patients With Advanced Squamous NSCLC: 3-Year Follow-Up From KEYNOTE-407

Andrew G. Robinson[1]; David Vicente[2]; Ali Tafreshi[3]; Hector Soto Parra[4]; Julien Mazières[5]; Irfan Cicin[6]; Balazs Medgyasszay[7]; Jeronimo Rodríguez-Cid[8]; Isamu Okamoto[9]; SungSook Lee[10]; Rodryg Ramlau[11]; Vladimir Vladimirov[12]; Ying Cheng[13]; Balazs Halmos[14]; Chih-Chin Liu[15]; Paul Schwarzenberger[15]; Bilal Piperdi[15]; Luis Paz-Ares[16]

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Tumorji glave in vratu

A Phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients unselected for PD-L1 expression in first line metastatic head and neck squamous cell carcinoma (HNSCC)

Abstract # 440

Nivolumab + ipilimumab vs EXTREME regimen as first-line treatment for recurrent/metastatic squamous cell carcinoma of the head and neck: final results of CheckMate 651

Athanassios Argiris,[1,2] Kevin Harrington,[3] Makoto Tahara,[4] Robert L. Ferris,[5] Maura Gillison,[6] Jerome Fayette,[7] Amaury Daste,[8] Piotr Koralewski,[9] Ricard Mesia,[10] Nabil F. Saba,[11] Milena Mak,[12] Miguel Angel Alvarez Avitia,[13] Alexander Guminski,[14] Urs Müller-Richter,[15] Naomi Kiyota,[16] Mustimbo Roberts,[17] Tariq Aziz Khan,[17] Karen Miller-Moslin,[17] Li Wei,[17] Robert Haddad[18]

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Chan KN122 NPC ESMO 2021

Results of KEYNOTE-122: a Phase 3 Study of Pembrolizumab Monotherapy vs Chemotherapy for Platinum-Pretreated, Recurrent or Metastatic Nasopharyngeal Carcinoma

Anthony T.C. Chan[1]; Victor Lee[2]; Ruey-Long Hong[3]; Myung-Ju Ahn[4]; Wan Qin Chong[5]; Sung-Bae Kim[6]; Gwo Fuang Ho[7]; Priscilla B. Caguioa[8]; Nuttapong Ngamphaiboon[9]; Cheryl Ho[10]; Mohamed Amir Shah Abdul Aziz[11]; Quan Sing Ng[12]; Chia-Jui Yen[13]; Nopadol Soparattanapaisarn[14]; Roger Kai-Cheong Ngan[15]; Swee Kiong Kho[16]; Ramona Swaby[17,a]; Sanatan Saraf[17]; Joy Ge[17]; Jianda Yuan[17]; Lillian L. Siu[18]

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Ginekološki raki

Makker_KN775_dMMR_IGCS_2021_Oral

Randomized Phase 3 Study of Lenvatinib Plus Pembrolizumab for Advanced Endometrial Cancer: Subgroup Analysis of Patients with DNA Mismatch Repair-Deficient Tumors

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Pembrolizumab in Patients With Microsatellite Instability-High (MSI-H) Advanced Endometrial Cancer: Updated Results From KEYNOTE-158

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Colombo KN826 ESMO 2021

Pembrolizumab plus Chemotherapy versus Placebo plus Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Randomized, Double-Blind, Phase 3 KEYNOTE-826 Study

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GU raki

Choueiri MK-3475 KN564 AUA 2021

Pembrolizumab vs Placebo as Post Nephrectomy Adjuvant Therapy for Patients with Renal Cell Carcinoma: Randomized, Double-Blind, Phase 3 KEYNOTE-564 Study

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GU raki – nove kombinacije, indikacije

Pembrolizumab Monotherapy for Docetaxel-Pretreated Metastatic Castration-Resistant Prostate Cancer: Updated Analyses With 4 Years of Follow-Up From Cohorts 1-3 of the KEYNOTE-199 Study

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KEYNOTE-365 Cohort C: Pembrolizumab + Enzalutamide in Patients With Abiraterone Acetate–Pretreated Metastatic Castration-Resistant Prostate Cancer—Data After Minimum of 22 Months of Follow-Up

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CheckMate 9KD cohort A2 final analysis: nivolumab plus rucaparib for chemotherapy-naive metastatic castration-resistant prostate cancer

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CheckMate 9KD cohort A1 final analysis: nivolumab plus rucaparib for post-chemotherapy metastatic castration-resistant prostate cancer

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Kidney Cancer Research Summit KCRS21

A phase 3 trial of lenvatinib plus pembrolizumab versus sunitinib as a first-line treatment for patients with advanced renal cell carcinoma: overall survival follow-up analysis (the CLEAR study)

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Conditional survival and 5-year follow-up in CheckMate 214: first-line nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma

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Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma: outcomes by baseline disease characteristics in the phase 3 CheckMate 9ER trial

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First-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma in subgroups based on prior nephrectomy in the CheckMate 9ER trial

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Matching-adjusted indirect comparison of health-related quality of life of nivolumab plus cabozantinib versus pembrolizumab plus axitinib in previously untreated advanced renal cell carcinoma

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Safety and efficacy outcomes with nivolumab plus ipilimumab in patients with advanced renal cell carcinoma and brain metastases: results from the CheckMate 920 trial

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Phase 3 KEYNOTE-045 Trial 5-Year Follow-Up: Pembrolizumab Versus Investigator's Choice of Paclitaxel, Docetaxel, or Vinflunine in Recurrent Advanced Urothelial Cancer

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Pembrolizumab Monotherapy as First-Line Therapy in Advanced Non–Clear Cell Renal Cell Carcinoma: Results After a Minimum of 34 Months of Follow-Up From KEYNOTE-427 Cohort B

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Pembrolizumab Monotherapy as First-Line Therapy in Advanced Clear Cell Renal Cell Carcinoma: Results After a Minimum of 41 Months of Follow-Up From KEYNOTE-427 Cohort A

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Real-world utilization and outcomes of immune-based combination therapies or tyrosine kinase inhibitors for advanced renal cell carcinoma

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WITNESS: Real-world outcomes of patients with advanced renal cell carcinoma treated with nivolumab in France and subgroup analysis of patients receiving concomitant medications at baseline

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Impact of recurrence on health-related quality of life in patients at high risk of recurrence after radical surgery for muscle-invasive urothelial carcinoma: results from the phase 3 CheckMate 274 trial

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Rak dojke

Schmid KN522 ESMO Virtual Plenary 2021

ESMO VIRTUAL PLENARY

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

H. Rugo KN355 ESMO 2021

KEYNOTE-355: Final Results from a Randomized, Double-blind, Phase 3 Study of First-line Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy for Metastatic Triple-Negative Breast Cancer

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Raki prebavil

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

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Zgornja prebavila

Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: CheckMate 649 study

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Nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced esophageal squamous cell carcinoma: first results of the CheckMate 648 study

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CRC

Final Overall Survival for the Phase 3 KN177 Study: Pembrolizumab Versus Chemotherapy in Microsatellite Instability-High/Mismatch Repair Deficient (MSI-H/dMMR) Metastatic Colorectal Cancer (mCRC)

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Single-arm, phase 2 study of regorafenib plus nivolumab in patients with mismatch repair-proficient/microsatellite stable colorectal cancer

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Kožni raki

Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in previously untreated metastatic or unresectable melanoma: Additional efficacy in RELATIVITY-047

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Luke KN716 ESMO 2021

Pembrolizumab Versus Placebo After Complete Resection of High-risk Stage II Melanoma: Efficacy and Safety Results From the KEYNOTE-716 Double-blind Phase 3 Trial

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CheckMate 067: 6.5-year outcomes in patients with advanced melanoma

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Abstract Number 9506

LEAP-004 Study Design (NCT03776136)

Participants

- Unresectable stage III or IV melanoma[a]
- Confirmed PD per iRECIST[1b] on or within 12 wk of last dose of anti–PD-1/L1 given alone or in combination (including with anti–CTLA-4) for ≥2 doses
  - ≤25% with PD on anti–CTLA-4 + anti–PD-1/L1
- No limit to number of previous therapies
- Measurable disease confirmed by blinded, independent central review (BICR)

N ≈ 100 →

Pembrolizumab
200 mg IV Q3W
for up to 35 cycles
+
Lenvatinib
20 mg PO QD

Continued until PD, unacceptable toxicity, or patient or physician decision[c]

End Points

- Primary: ORR per RECIST v1.1[d] by BICR
- Secondary: DOR and PFS per RECIST v1.1[d] by BICR, OS, and safety

[a]Per AJCC 8th edition. [b]In the absence of rapid clinical progression, initial evidence of radiologic PD required confirmation by a second assessment performed ≥4 weeks from first documented radiographic PD. [c]Eligible patients deriving clinical benefit can be treated beyond PD. Participants with CR can discontinue study treatment if they have received it for ≥24 weeks. [d]Modified to follow ≤10 target lesions total and ≤5 target lesions per organ. 1. Seymour L et al. *Lancet Oncol* 2017;18:e143-52.

Arance et al. ASCO 2021 Abstract 9504

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C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous TIL (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)

Patient Population

Unresectable or metastatic melanoma treated with ≥1 prior systemic therapy including a PD-1–blocking antibody and, if BRAF V600 mutation positive, a BRAFi ± MEKi

→ **Cohort 1**
Non-cryopreserved TIL product (Gen 1)
N=30
Closed to enrollment

→ **Cohort 2**
Cryopreserved TIL product (Gen 2)
N=60
Closed to enrollment

→ **Cohort 3**
TIL re-treatment
N=10

→ **Cohort 4 (Pivotal)**
Cryopreserved TIL product (Gen 2)
N=75
Closed to enrollment

Cohort 2 Endpoints

- Primary: Efficacy per investigator-assessed ORR using RECIST 1.1 response criteria
- Secondary: Safety and additional parameters of efficacy

Key Eligibility Criteria

- Radiographic confirmation of progression
- One tumor lesion resectable for TIL generation (~1.5 cm in diameter) and ≥1 target tumor lesion for RECIST 1.1 response assessment
- Age ≥18 years at the time of consent
- ECOG performance status of 0–1

Methods

- Patients were enrolled from April 2017 to January 2019 at 26 sites across the US and EU
- Concomitant anticancer therapy was not permitted
- Imaging-evaluable disease was required
- All responses required confirmation
- Data cutoff: 22 April 2021

BRAFi, BRAF inhibitor; ECOG, Eastern Cooperative Oncology Group; MEKi, MEK inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; TIL, tumor infiltrating lymphocytes.

Presented By: James M. G. Larkin, MD, FRCP, PhD

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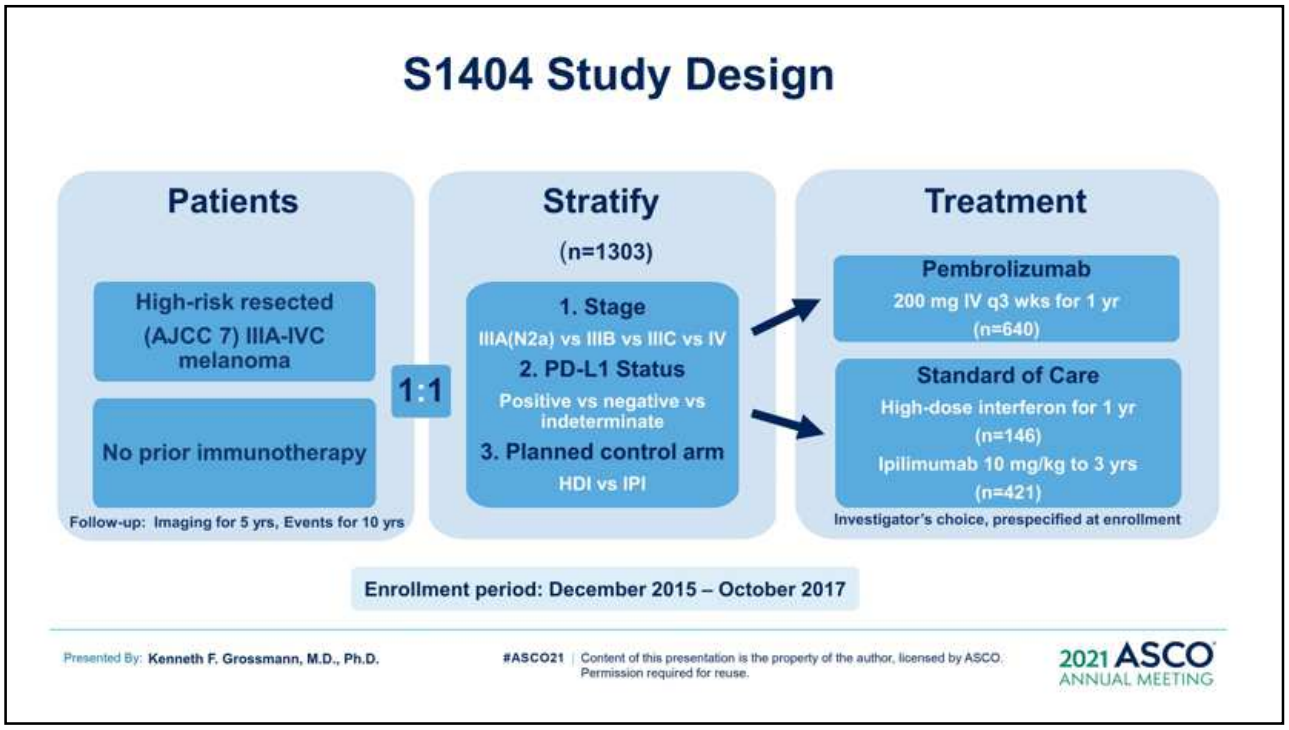
- Širjenje indikacij na druge vrste raka
- Kombinacije z različnimi zdravili – novimi in že uveljavljenimi (imunoterapijo, KT, tarčno terapijo)
- Pomiranje v adjuvantno in neoadjuvantno, zdravljenej, radikalno zdravljenje

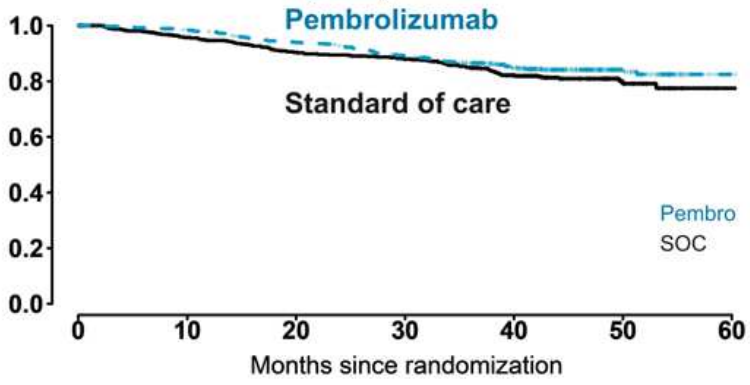
Novosti v imunoterapiji kožnih rakov

Janja Ocvirk

Ljubljana 15-16.12.2021



Overall survival (ITT)



	Total N	N with Events	Hazard Ratio (96.3% CI)
Pembro	648	98	0.84 (0.62, 1.13)
SOC	655	101	

Log-rank p-value = 0.21

Pembro	648	624	587	548	427	108	1
SOC	655	524	485	460	343	86	2

Presented By: **Kenneth F. Grossmann, M.D., Ph.D.**

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Adjuvant Therapy, 2021

Study	RFS	HR for RFS	OS	HR for OS
EORTC 18071[1] Ipilimumab 10mg/kg vs. Placebo	39.2% at 7 years 30.9% at 7 years	**0.75 (0.63-0.88)**	60% at 7 years 51.3% at 7 years	**0.73 (0.60-0.89)**
Combi-AD[2] Dabrafenib+Trametinib vs. Placebo	52% at 5 years 36% at 5 years	**0.51 (0.42-0.61)**	86% at 3 years 77% at 3 years	**0.57 (0.42-0.79)**
CM-238[3] Nivolumab vs. Ipilimumab 10mg/kg	52% at 4 years 41% at 4 years	**0.71 (0.6-0.86)**	78% at 4 years 77% at 4 years	0.87 (0.66-1.14)
Keynote-054[4] Pembrolizumab vs. Placebo	63.7% at 3 years 44.1% at 3 years	**0.56 (0.47-0.68)**		
CM-915[5] Ipilimumab+Nivolumab vs. Nivolumab	64.6% at 2 years 63.2% at 2 years	0.92 (0.77-1.09)		
S1404[6] Pembrolizumab vs. SOC		**0.74 (0.57-0.96)**		0.84 (0.62-1.13)

1: Eggermont et al. Eur J Cancer 2019; 119: 1-10; 2: Hauschild et al. ASCO 2020 Abstract 10001, 3: Weber et al. ESMO 2020 Abstract 10760; 4: Eggermont et al. ASCO 2020 Abstract 10000, 5: Long et al. AACR 2021 Abstract CT004, 6: Grossman et al. ASCO 2021 Abstract 9501

Presented By: **R. Amaria**

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- Adjivantni anti PD1 imajo podaljšano izboljšanje PFS v primerjavi z primerjalno skupino
- Ni izboljšanja OS zaradi nadaljnih linij zdravljenja

Luke KN716 ESMO 2021

Pembrolizumab Versus Placebo After Complete Resection of High-risk Stage II Melanoma: Efficacy and Safety Results From the KEYNOTE-716 Double-blind Phase 3 Trial

Jason J. Luke[1]; Piotr Rutkowski[2]; Paola Queirolo[3]; Michele Del Vecchio[4]; Jacek Mackiewicz[5, 6]; Vanna Chiarion-Sileni[7]; Luis de la Cruz Merino[8]; Muhammad A Khattak[9,10]; Dirk Schadendorf[11]; Georgina V. Long[12,13], Paolo A Ascierto[14]; Mario Mandala[15]; Federica De Galitiis[16]; Vernon Sondak[17]; Richard A. Scolyer[12,18]; John M. Kirkwood[1]; Ke Chen[19]; Nageatte Ibrahim[19]; Sama Ahsan[19]; Alexander M. M. Eggermont[20]

[1]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [3]Istituto Europeo di Oncologia - IRCCS, Milano, Italy; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [5]Poznan University of Medical Sciences, Poznan, Poland; [6]Greater Poland Cancer Center, Poznan, Poland; [7]Istituto Oncologico Veneto, IOV-IRCCS, Padova, Italy; [8]Hospital Universitario Virgen Macarena, Seville, Spain; [9]Fiona Stanley Hospital, Perth, Australia; [10]Edith Cowan University, Perth, Australia; [11]University Hospital Essen & German Cancer Consortium Partner Site, Essen, Germany; [12]Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [13] Royal North Shore & Mater Hospitals, Sydney, Australia; [14]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; [15]University of Perugia, Perugia, Italy; [16]Dermopathic Institute of the Immaculate IDI-IRCCS, Rome, IT; [17]H. Lee Moffitt Cancer Center and Research Institute in Tampa, FL, USA; [18]Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, Australia; [19]Merck & Co., Inc., Kenilworth, NJ, USA; [20]University Medical Center Utrecht & Princess Máxima Center, Utrecht, NL

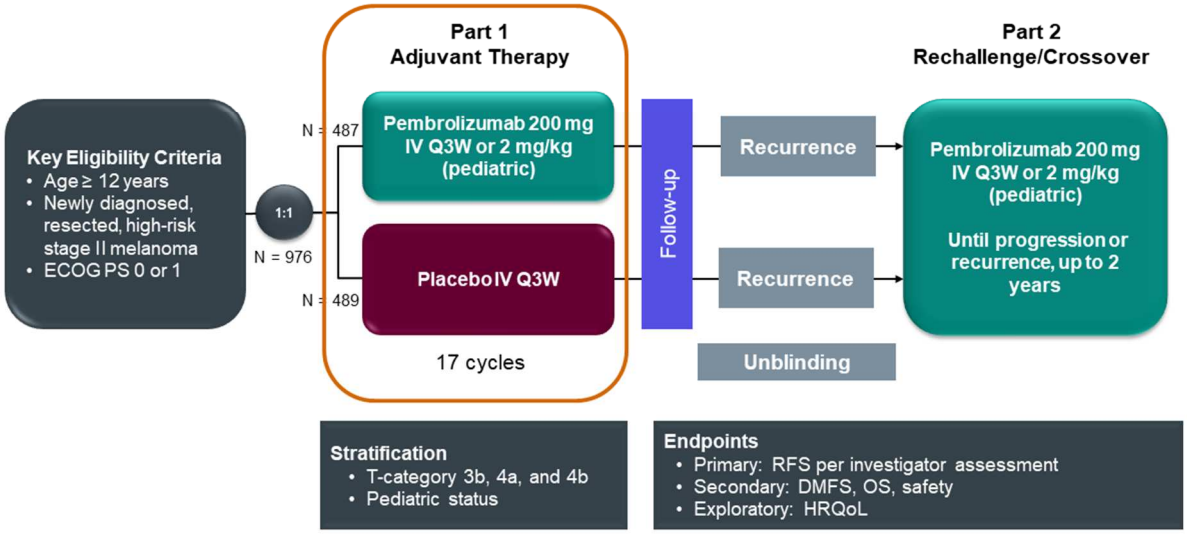
Background

- Patients with stage IIB and IIC melanoma are at high risk of disease recurrence and survival outcomes are similar to stage IIIA and IIIB melanoma[1-3]
- Pembrolizumab prolonged RFS and DMFS versus placebo as adjuvant treatment for stage III melanoma with sustained RFS benefit[4-6]
  - HR for RFS 0.57[4]; HR for DMFS 0.60[5]
  - 3-year follow-up: HR for RFS 0.56; RFS rate of 63.7% vs 44.1%[6]
- Pembrolizumab is approved for adjuvant treatment of patients with melanoma with involvement of lymph nodes following complete resection[7]
- KEYNOTE-716 is the first phase 3, randomized, double-blind study of an anti-PD-1 therapy (pembrolizumab) versus placebo for patients with resected stage IIB and IIC melanoma

DMFS, distant metastasis-free survival; RFS, recurrence-free survival.

1. Koster BD et al. *Clin Cancer Res.* 2017;23:5679-86; 2. Luke JJ et al. *Nat Rev Clin Oncol.* 2017;14:463-82; 3. Gershenwald JE et al. *CA Cancer J Clin.* 2017;67:472-492; 4. Eggermont AMM et al. *New Engl J Med.* 2018;378:1789-01; 5. Eggermont AMM et al. Lan Oncol. 2021;22:643-654; 6. Eggermont AMM et al. *J Clin Oncol.* 2020;38:3925-36; 7. Pembrolizumab: US Prescribing Information 2021. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA.

KEYNOTE-716 Study Design
(NCT03553836)



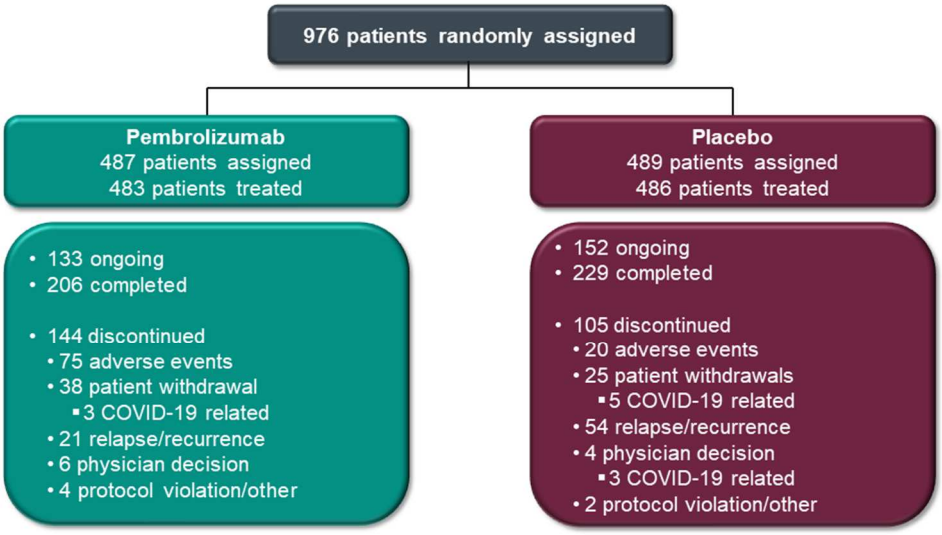
HRQoL, health related quality of life; OS, overall survival; Q3W, every 3 weeks; RFS, time from randomization to recurrence of melanoma at any site (skin, regional lymph nodes or distant) or death from any cause, whichever occurred first.

Assessments

- Efficacy: intention-to-treat population of all randomized patients
- Safety: as-treated population of randomized patients with ≥1 treatment dose
- Disease assessed at 6 months from date of randomization, every 6 months (years 2 to 4), then once in year 5, or as clinically indicated
- HRQoL assessed using the EORTC QLQ-C30 global health status/QoL scale
- First protocol specified analysis: planned to occur after 128 disease recurrence or death events
  - DMC indicated conditions for efficacy were met at first protocol specified interim analysis based on observation of 136 RFS events

EORTC, European Organization for Research and Treatment of Cancer.

Treatment Disposition



Median follow-up was 14.4 months (range, 1.5-26.4) in the pembrolizumab arm and 14.3 months (range, 1.0-26.0) in the placebo arm; Data cut-off: 04Dec2020.

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Baseline Characteristics

Characteristics, n (%)	Pembrolizumab N = 487	Placebo N = 489
Age, median (range), years	60.0 (16-84)	61.0 (17-87)
12-17 years	1 (0.2)	1 (0.2)
≥ 65 years	184 (37.8)	194 (39.7)
Male	300 (61.6)	289 (59.1)
T-Category[a]		
T3b	200 (41.1)	201 (41.1)
T4a	113 (23.2)	116 (23.7)
T4b	172 (35.3)	172 (35.2)
Disease Stage		
IIB	309 (63.4)	316 (64.6)
IIC	171 (35.1)	169 (34.6)

[a]T-category is based on all tumor stages collected on eCRF; Data cut-off: 04Dec2020.

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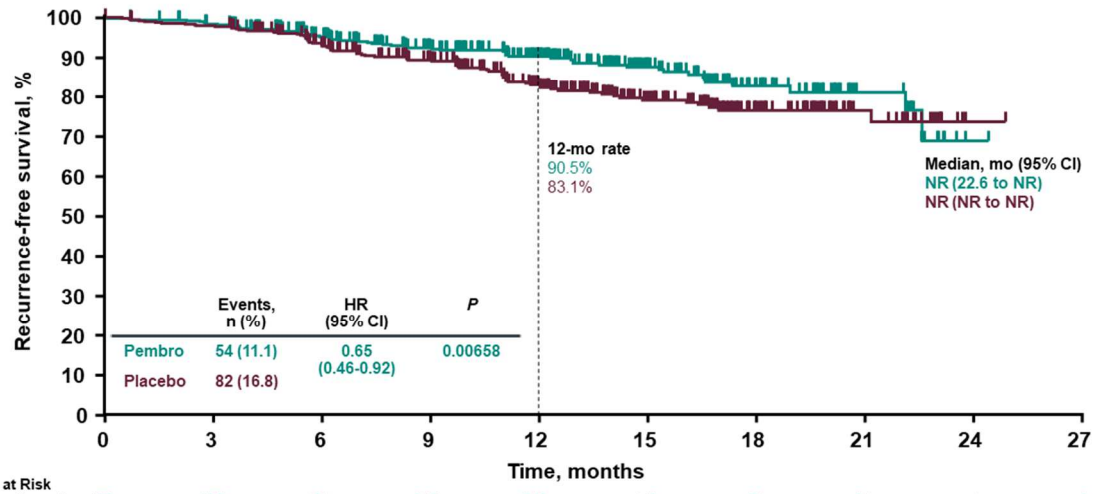
Recurrence-Free Survival (Primary Endpoint)



No. at Risk										
Pembrolizumab	487	465	401	340	249	149	71	21	1	0
Placebo	489	475	400	336	229	149	71	27	1	0

NR, not reached; Data cut-off: 04Dec2020.

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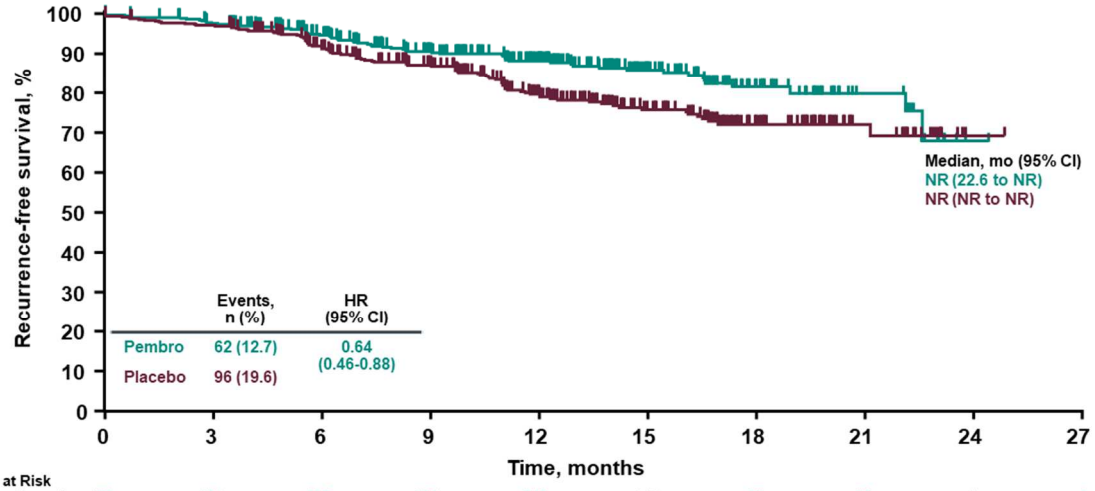
RFS Sensitivity Analysis Including New Primary Melanomas



No. at Risk										
Pembrolizumab	487	461	397	332	242	144	68	20	1	0
Placebo	489	474	396	330	219	142	73	25	1	0

RFS sensitivity analysis including new primary melanomas diagnosed during the study as RFS events; NR, not reached.
Data cut-off: 04Dec2020.

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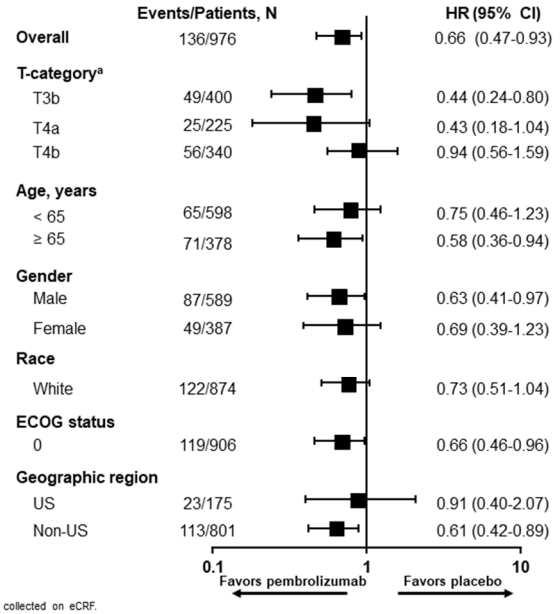
Recurrence-Free Survival in Key Subgroups[a]



[a]Based on actual baseline tumor stages IIB and IIC collected on eCRF.

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Patterns of Recurrence

Event, n (%)	Pembrolizumab N = 487	Placebo N = 489
Patients without an event	433 (88.9%)	407 (83.2%)
Patients with an event[a]	54 (11.1%)	82 (16.8%)
Skin and/or LN regional recurrence	31 (6.4%)	41 (8.4%)
Distant recurrence	23 (4.7%)	38 (7.8%)

LN, lymph node.
[a]Type of first event in recurrence-free survival analysis; Data cut-off: 04Dec2020.

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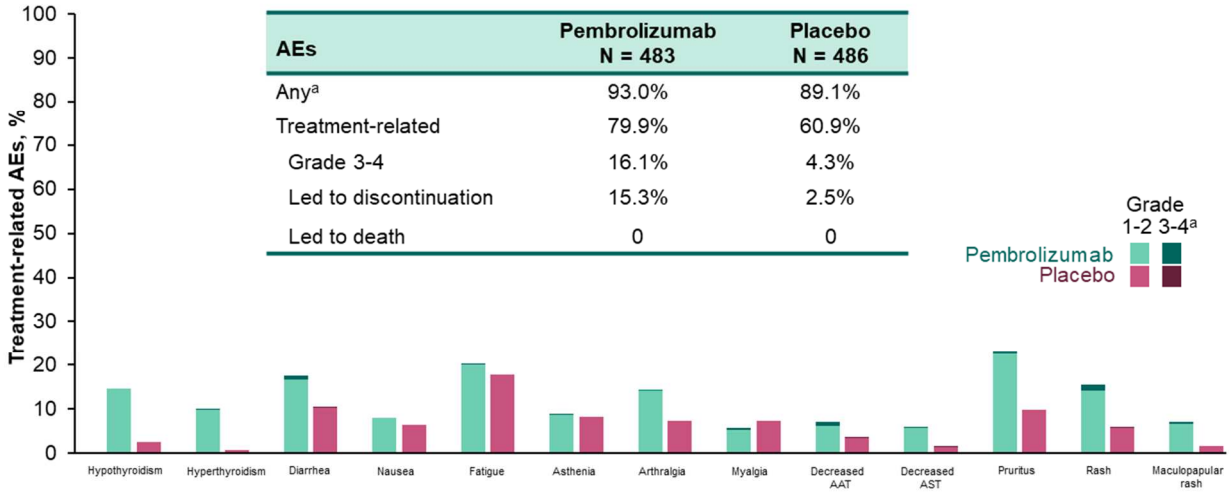
Adverse Events (AEs)

AEs	Pembrolizumab N = 483	Placebo N = 486
Any[a]	93.0%	89.1%
Treatment-related	79.9%	60.9%
Grade 3-4	16.1%	4.3%
Led to discontinuation	15.3%	2.5%
Led to death	0	0



[a]No grade 5 AEs occurred in the pembrolizumab arm; AAT, alanine aminotransferase; AST, aspartate aminotransferase.
Treatment-related events with ≥5% incidence; Data cut-off: 04Dec2020.

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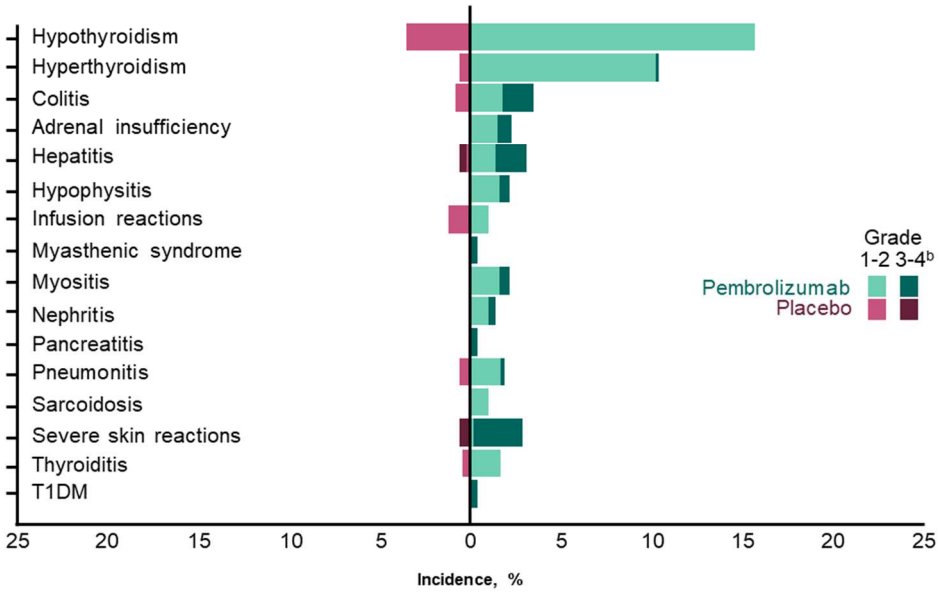
Adverse Events of Interest[a]



T1DM, Type 1 Diabetes Mellitus.
[a]Immune-mediated AEs and infusion reactions occurring in at least 2 patients in decreasing incidence; [b]No grade 5 events occurred in the pembrolizumab arm; Data cut-off: 04Dec2020.

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Hormonal Therapy for Management of Adverse Events of Interest[a]

Patients, n (%)	Pembrolizumab N = 483
Any adverse event of interest	90 (18.6%)
Hypothyroidism	67 (13.9%)
Thyroiditis	6 (1.2%)
Hypophysitis	10 (2.1%)
Adrenal Insufficiency	10 (2.1%)
Type 1 Diabetes Mellitus	2 (0.4%)

[a]HRT with corticosteroids, thyroxine, or insulin in patients with AEs of interest (immune-mediated AEs and infusion reactions); Data cut-off: 04Dec2020.

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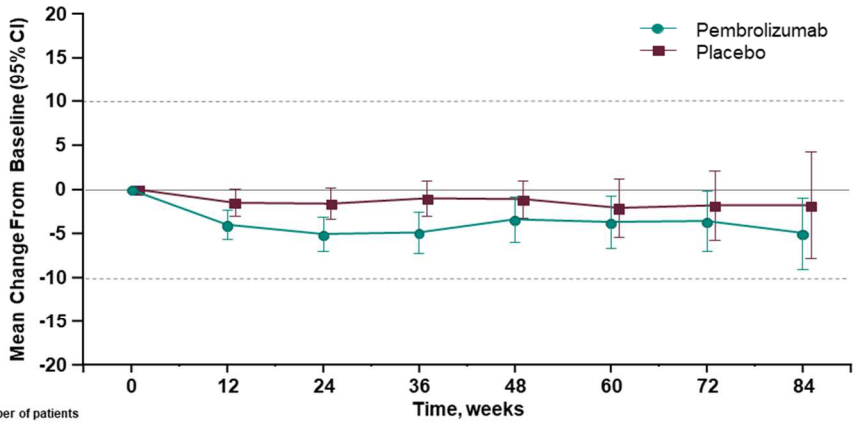
Change in Global Health Status/Quality of Life Over Time



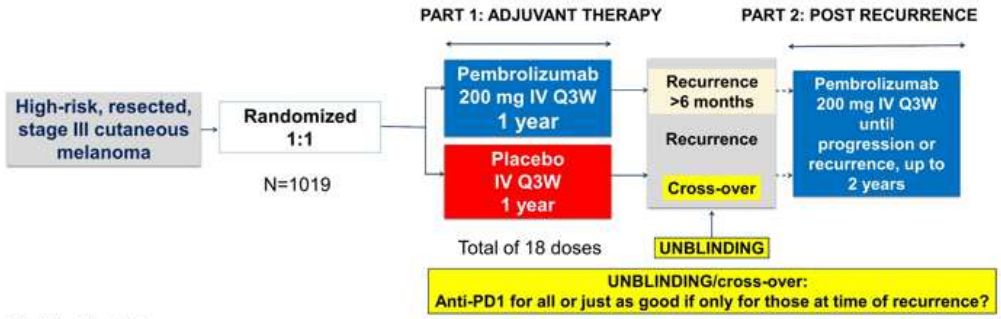
Number of patients								
Pembrolizumab	449	386	327	271	231	156	98	54
Placebo	459	418	339	289	247	141	98	56

- Global health status/quality of life scores were similar between treatment groups at all timepoints

EORTC QLQ-C30 GHS/QoL range of 0 to 100; Horizontal dotted lines indicate the threshold for clinical relevance; Data cut-off: 04Dec2020.

- Adjuvantni Pembrolizumab in statistično značilno zmanjšanje tveganja za ponovitev bolezni ali smrt v primerjavi s placebom pri bolnikih z visoko rizičnem stadiju II (HR 0,65)
- Kakovost življenja je bila podobna v skupini s placebom in pembrolizumabom
- Adjuvantni Pembrolizumab je učinkovito zdravljenej za bolnike stadija II z visokim tveganjem za ponovitev bolezni (IIB, IIC)

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**

Presented By: **A. Eggermont, Abstract 9500**

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EORTC 1325/KEYNOTE-54 Part 2: patient population

	Randomized Placebo N=505	Randomized pembrolizumab N=515
Completion of 1 yr of treatment	**297**	**297**
Recurrence (before/after trt compl.)	**298**	**203**
Recurrence after 6 mts of trt compl.		**47**
Stage at baseline of Part 2, n	**Crossover population N=155**	**Rechallenge population N=20**
III resected (after local, ITM, RLN rec.)	50	7
III/IV various	105	13
III unresected (M0)	10	0
IV (M1)	95	13
IV resected/unresected	12/83	4/9
AJCC-8 M1a	22	4
AJCC-8 M1b	36	5
AJCC-8 M1c	36	4
AJCC-8 M1d	1	0

Presented By: **A. Eggermont, Abstract 9500**

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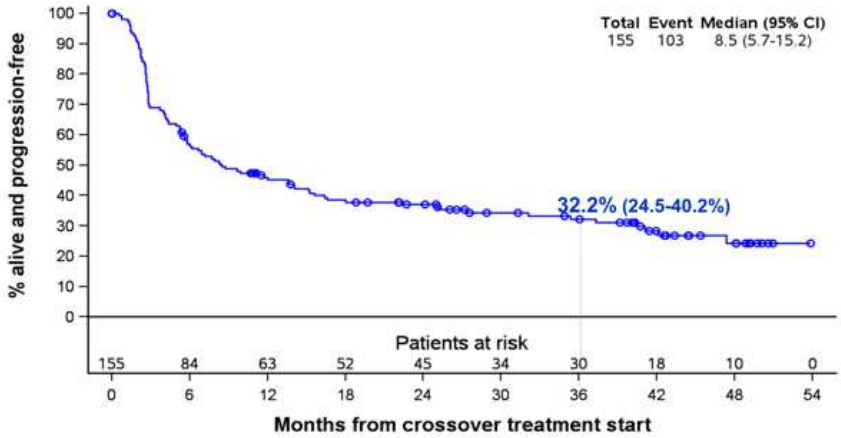
EORTC 1325/KEYNOTE-54
Crossover patients: Recurrence/Progression-free survival



Presented By: A. Eggermont, Abstract 9500

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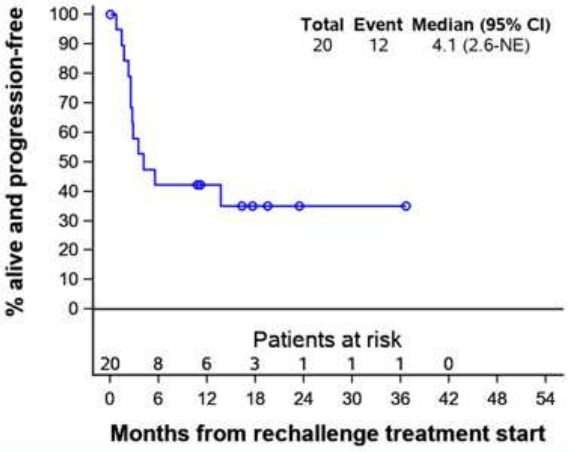
EORTC 1325/KEYNOTE-54
Rechallenged patients

Recurrence/Progression-free survival (N=20)



Patients with measurable advanced disease (N=9)

Best response	Advanced disease N=9 (100%)
CR	1 (11.1)
Stable disease	3 (33.3)
Progressive disease	5 (55.6)

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2021 ASCO ANNUAL MEETING

CheckMate 067: 6.5-year outcomes in patients with advanced melanoma

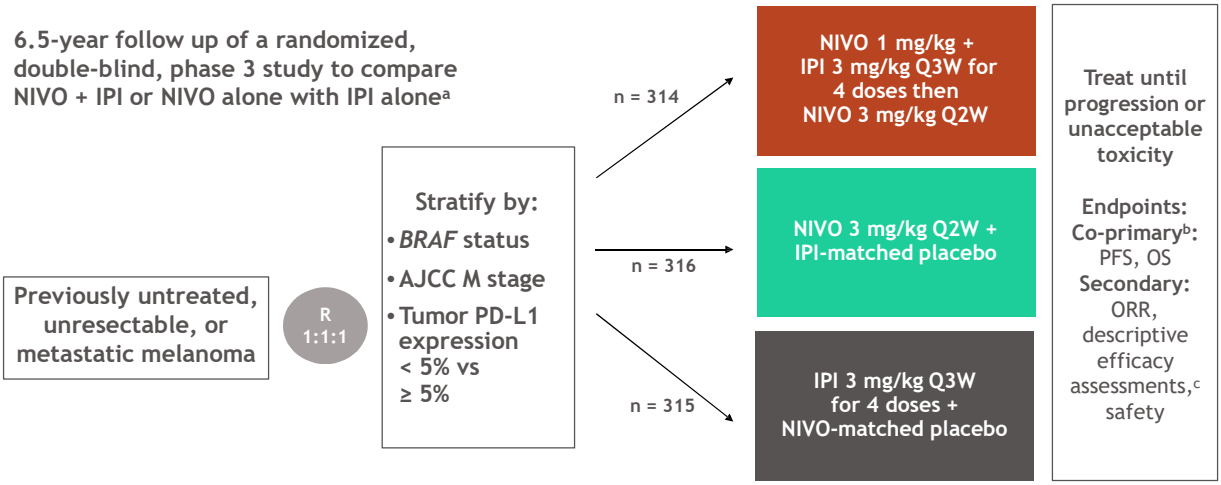
Jedd D. Wolchok,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Jean-Jacques Grob,[4] Piotr Rutkowski,[5] Christopher D. Lao,[6] C. Lance Cowey,[7] Dirk Schadendorf,[8] John Wagstaff,[9] Reinhard Dummer,[10] Pier Francesco Ferrucci,[11] Michael Smylie,[12] Marcus O. Butler,[13] Andrew Hill,[14] Ivan Márquez-Rodas,[15] John B.A.G. Haanen,[16] Tuba Bas,[17] Wim van Dijck,[17] James Larkin,[18,a] F. Stephen Hodi[19,a]

[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [2]Oncology Institute of Veneto IRCCS, Padua, Italy; [3]University of Colorado Cancer Center, Aurora, CO, USA; [4]Aix-Marseille University, APHM Timone France, Marseille, France; [5]Maria Sklodowska-Curie Institute-Oncology Center, Warsaw, Poland; [6]University of Michigan, Ann Arbor, MI, USA; [7]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX, USA; [8]Department of Dermatology, University of Essen, Essen, and German Cancer Consortium, Heidelberg, Germany; [9]The College of Medicine, Swansea University, Swansea, United Kingdom; [10]Universitäts Spital Zurich, Zurich, Switzerland; [11]European Institute of Oncology IRCCS, Milan, Italy; [12]Cross Cancer Institute, Edmonton, Alberta, Canada; [13]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [14]Tasman Oncology Research, Southport, Queensland, Australia; [15]Hospital General Universitario Gregorio Marañon, Madrid, Spain; [16]Netherlands Cancer Institute, Amsterdam, Netherlands; [17]Bristol Myers Squibb, Princeton, NJ, USA; [18]The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; [19]Dana-Farber Cancer Institute, Boston, MA
[a]Co-senior author.

Abstract Number 9506

CheckMate 067: study design

6.5-year follow up of a randomized, double-blind, phase 3 study to compare NIVO + IPI or NIVO alone with IPI alone[a]



Database lock: October 19, 2020; minimum follow-up of 77 months for all patients

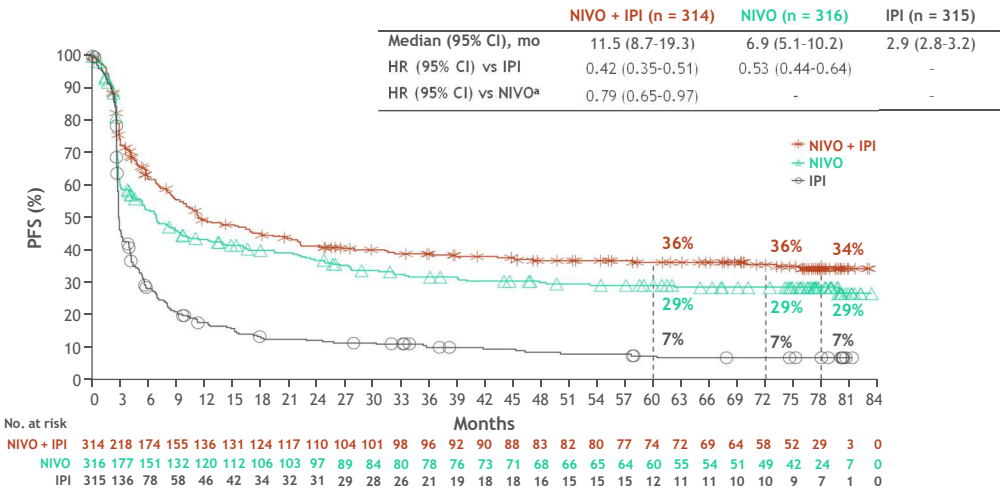
[a]The study was not powered for a comparison between NIVO+IPI and NIVO. [b]NIVO + IPI or NIVO vs IPI alone. [c]NIVO + IPI vs NIVO alone. AJCC, American Joint Committee on Cancer; M stage, metastasis stage; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks.

Response to treatment at 6.5 years

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
ORR (95% CI), %	58 (53-64)	45 (39-51)	19 (15-24)
Best overall response, %			
Complete response	23	19	6
Partial response	36	26	13
Stable disease	12	9	22
Progressive disease	24	38	50
Unknown	6	8	9
Median duration of response (95% CI), months	NR (61.9-NR)	NR (45.7-NR)	19.2 (8.8-47.4)

CI, confidence interval; NR, not yet reached.

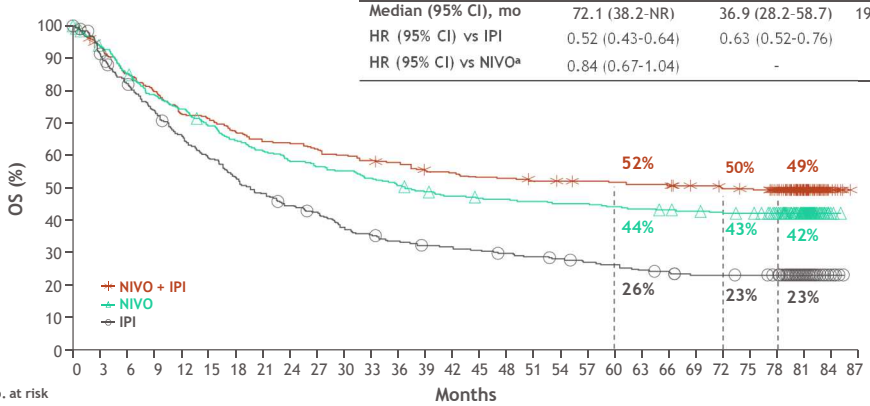
Progression-free survival



[a]Descriptive analysis.

Overall survival

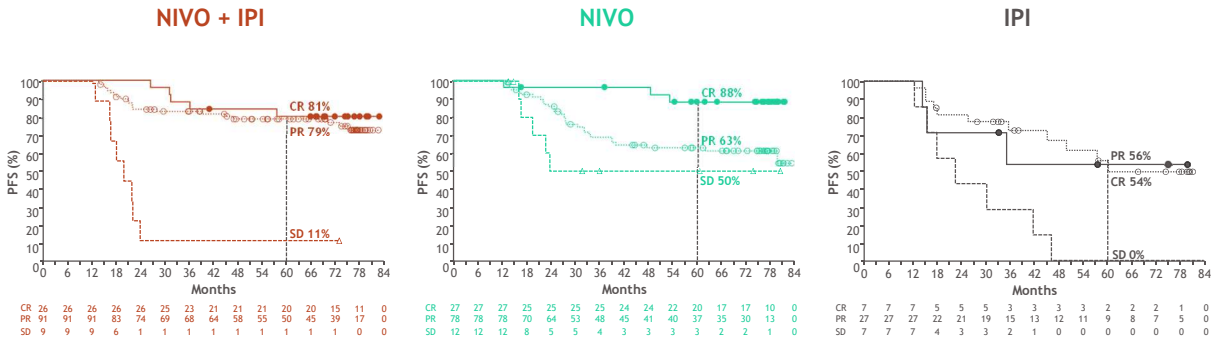
	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs IPI	0.52 (0.43-0.64)	0.63 (0.52-0.76)	-
HR (95% CI) vs NIVO[a]	0.84 (0.67-1.04)	-	-



No. at risk

| | | |

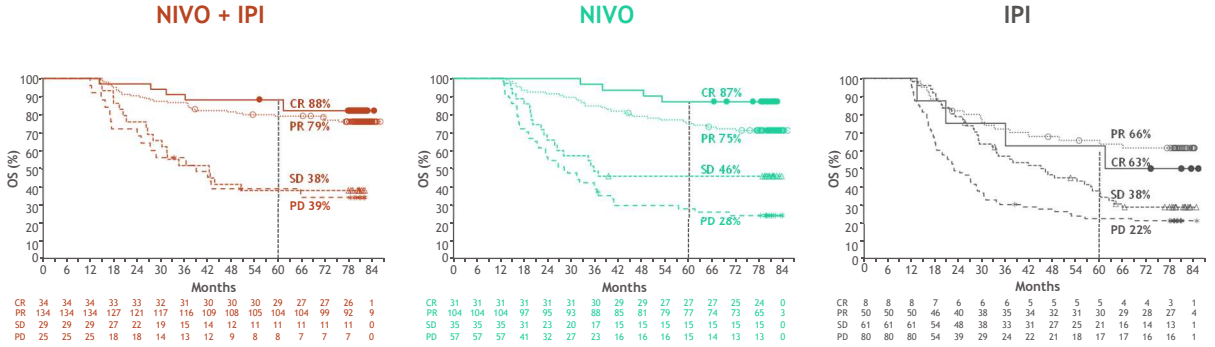
PFS by best overall response, 12-month landmark analysis[a]



- **Patients with a best overall response of a CR, PR, or SD at 12 months were followed for PFS[b]**

[a]To address guarantee-time bias, landmark analysis excluded patients who had an event during the first 12 months.
[b]Since PD is a PFS event, patients with a best overall response of PD were excluded from this analysis.
CR, complete response; PR, partial response; SD, stable disease.

OS by best overall response, 12-month landmark analysis[a]



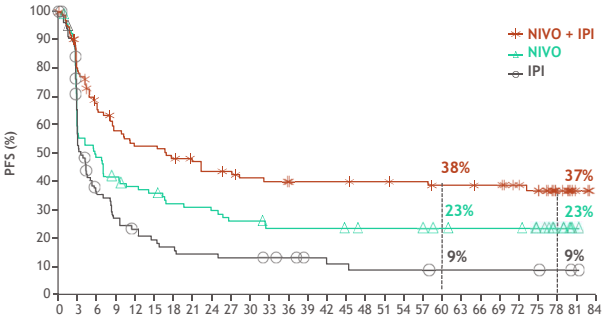
- **Patients with a best overall response of a CR, PR, SD, or PD at 12 months were followed for OS**

[a]To address guarantee-time bias, landmark analysis excluded patients who had an event during the first 12 months.
PD, progressive disease.

PFS by *BRAF* mutation status[a]

BRAF mutant

	NIVO + IPI (n = 103)	NIVO (n = 98)	IPI (n = 100)
Median (95% CI), mo	16.8 (8.3-32.0)	5.6 (2.8-9.5)	3.4 (2.8-5.2)
HR (95% CI) vs IPI HR	0.44 (0.31-0.62)	0.71 (0.51-0.98)	-
(95% CI) vs NIVO[b]	0.62 (0.44-0.89)	-	-



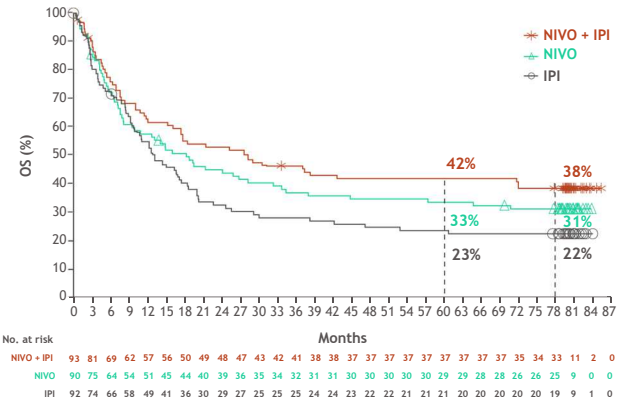
No. at risk

| | | |

OS by presence of baseline liver metastases

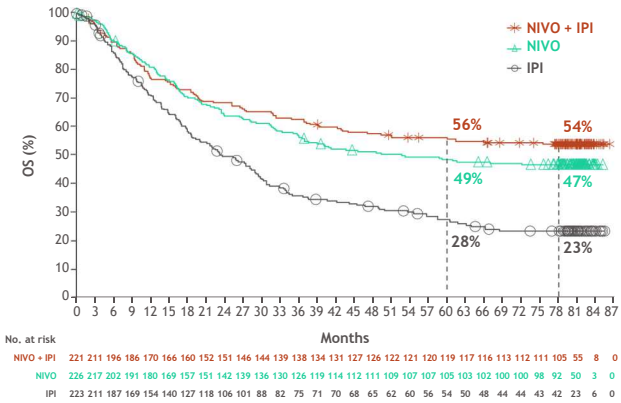
With liver metastases

	NIVO + IPI (n = 93)	NIVO (n = 90)	IPI (n = 92)
Median (95% CI), mo	28.2 (15.2-71.9)	18.2 (8.1-32.3)	13.1 (9.6-18.4)
HR (95% CI) vs IPI	0.66 (0.46-0.93)	0.81 (0.58-1.14)	-
HR (95% CI) vs NIVO[a]	0.81 (0.56-1.16)	-	-



Without liver metastases

	NIVO + IPI (n = 221)	NIVO (n = 226)	IPI (n = 223)
Median (95% CI), mo	NR (50.7-NR)	52.7 (36.0-NR)	23.5 (18.6-29.4)
HR (95% CI) vs IPI	0.47 (0.37-0.60)	0.56 (0.44-0.71)	-
HR (95% CI) vs NIVO[a]	0.84 (0.64-1.09)	-	-



[a]Descriptive analysis.

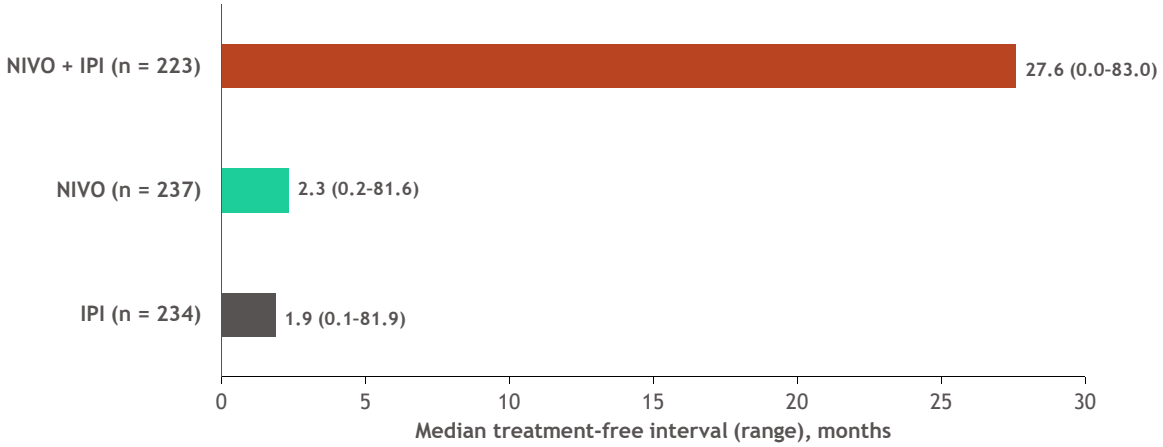
Subsequent therapy at 6.5 years

	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Any subsequent therapy, n (%)[a]	146 (46.5)	188 (59.5)	238 (75.6)
Subsequent systemic therapy	112 (36)	154 (49)	209 (66)
Subsequent immunotherapy	59 (19)	107 (34)	151 (48)
Anti-PD-1 agents	43 (14)	52 (16)	146 (46)
Anti-CTLA-4 agents	23 (7)	92 (29)	19 (6)
BRAF inhibitor	43 (14)	61 (19)	72 (23)
MEK/NRAS inhibitor	34 (11)	44 (14)	42 (13)
Subsequent radiotherapy, n (%)	71 (23)	96 (30)	128 (41)
Subsequent surgery, n (%)	69 (22)	75 (24)	97 (31)
Median time from randomization to subsequent systemic therapy (95% CI), months	NR (59.6-NR)	25.2 (16.0-43.2)	8.0 (6.5-8.7)

[a]Patients may have received more than one type of subsequent therapy, and more than one agent within each type.
CTLA-4, cytotoxic T-lymphocyte-associated-4; MEK, mitogen-activated protein kinase kinase; NRAS, neuroblastoma RAS viral oncogene homolog; PD-1, programmed death 1.

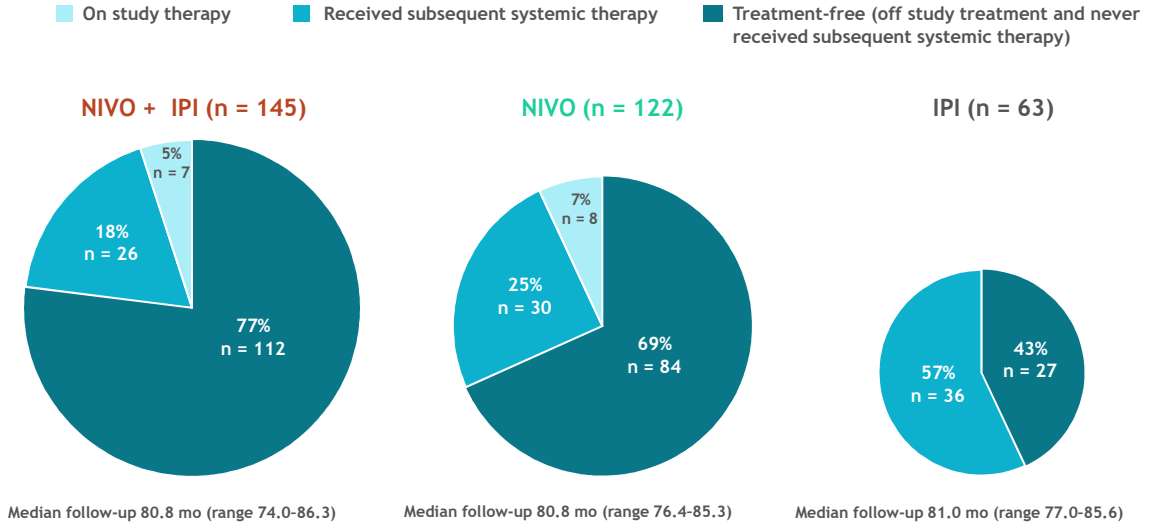
Treatment-free interval following study therapy discontinuation

- Patients analyzed were those who (1) were alive or (2) who died following subsequent systemic therapy



- Median duration of treatment was 3.6 mo (range, 0-80.1) with NIVO + IPI, 8.6 mo (0-79.8) with NIVO, and 3.7 mo (0-49.9) with IPI

Patients alive and treatment-free at 6.5 years



Safety summary

- No new safety signals were observed
- No additional treatment-related deaths were reported since the 36-month analysis

	NIVO + IPI (n = 313)		NIVO (n = 313)		IPI (n = 311)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Treatment-related AE, %	96	59	87	24	86	28
Treatment-related AE leading to discontinuation, %	42	31	14	8	15	13
Treatment-related death,[a] n (%)	2 (1)		1 (< 1)		1 (< 1)	

[a]Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO + IPI (n = 1 each; both occurred > 100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1).
AE, adverse event.

- Ti zreli 6,5-letni rezultati CheckMate 067 z NIVO + IPI vključujejo najdaljšo mediano OS (72,1 meseca) v študiji faze 3 pri bolnikih z napredovalim melanomom. Mediana OS je bila 36,9 meseca z NIVO in 19,9 meseca z IPI
- Trajno klinično korist so opazili v klinično pomembnih podskupinah, vključno z mutacijo BRAF in metastazami v jetrih
- Manj kot polovica bolnikov (47 %), zdravljenih z NIVO + IPI, je prejela kakršno koli naknadno terapijo, pri čemer mediana časa do nadaljnjega zdravljenja še ni dosežena (v primerjavi z 25,2 meseca pri NIVO in 8,0 mesecev z IPI)
- Od bolnikov, ki so bili živi pri 6,5 let, je bilo 77 % zdravljenih z NIVO + IPI in 69 % zdravljenih z NIVO brez nadaljnega zdravljenja

5-year OS Data for Immunotherapy and Targeted Therapy

	5-year OS	5-year OS with baseline LDH > ULN
CM-067 (BRAF mutant)[1,2]		
Ipilimumab + Nivolumab	60%	38%
Nivolumab	46%	28%
Ipilimumab	30%	15%
COLUMBUS[3]		
Encorafenib + Binimetinib	34.7%	9.1%
Encorafenib	34.9%	
Vemurafenib	21.4%	
COMBI-d + COMBI-v[4]		
Dabrafenib + Trametinib	34%	16%

1: Wolchok et al. ASCO 2021 Abstract 9506; 2: Larkin et al. NEJM 2019; 381: 1535-46; 3: Dummer et al. ASCO 2021 Abstract 9507; 4: Nathan et al. J Clin Oncol 2019; 37: 15_suppl Abstract 9507

Presented By: R. Amaria

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2021 ASCO ANNUAL MEETING

- Mediana OS ipi+ nivo je 72 meseca
- 5 letno preživetje binimetiniba +enkorafeniba je podobno dabrafenibu + trametinibu

Anti PD-1 Re-Challenge Data

Study	Type of Initial Response	N	ORR
Keynote 001[1]	CR only	4	50%
Keynote 006[2]	Mix of CR, PR, SD	8	62.5%
Jansen et al. [3]	Mix of CR, PR, SD	19	32%
Betof-Warner et al. [4]	CR only	34	15%
Keynote 054[5]	Adjuvant recurrence	9	11%

1: Hamid et al. Ann Oncol 2019; 30: 582-88; 2: Robert et al. Lancet Oncol 2019; 20: 1239-51; 3: Jansen et al. Ann Oncol 2019; 30: 1154-61; 4: Betof Warner et al. J Clin Oncol 2020; 38: 1655-63; 5: Eggermont et al. ASCO 2021 Abstract 9500

Presented By: R. Amaria

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2021 ASCO ANNUAL MEETING

Study design

- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria
- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0-1

Stratification factors
- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage

N = 714

R 1:1
- RELA 160 mg + NIVO 480 mg fixed-dose combination (FDC) IV Q4W
- NIVO 480 mg IV Q4W

Primary endpoint
- PFS by BICR[d]

Secondary endpoints
- OS
- ORR by BICR[d]

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CTLA-4, cytotoxic T lymphocyte antigen-4; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; Q4W, every 4 weeks; R, randomization.
ClinicalTrials.gov: NCT03470922; Lipson E, et al. Poster presentation at ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract 1302TiP.
[a]Prior adjuvant/neoadjuvant treatment permitted (anti-PD-1 or anti-CTLA-4 permitted if at least 6 months between the last dose and recurrence; interferon therapy permitted if the last dose was at least 6 weeks before randomization); [b]LAG-3 expression on immune cells was determined using an analytically validated IHC assay (LabCorp); [c]PD-L1 expression on tumor cells was determined using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx test; [d]First tumor assessment (RECIST v1.1) performed 12 weeks after randomization, every 8 weeks up to 52 weeks, and then every 12 weeks. Database lock date: March 9, 2021.

Lipson et al. ASCO 2021 Abstract 9503

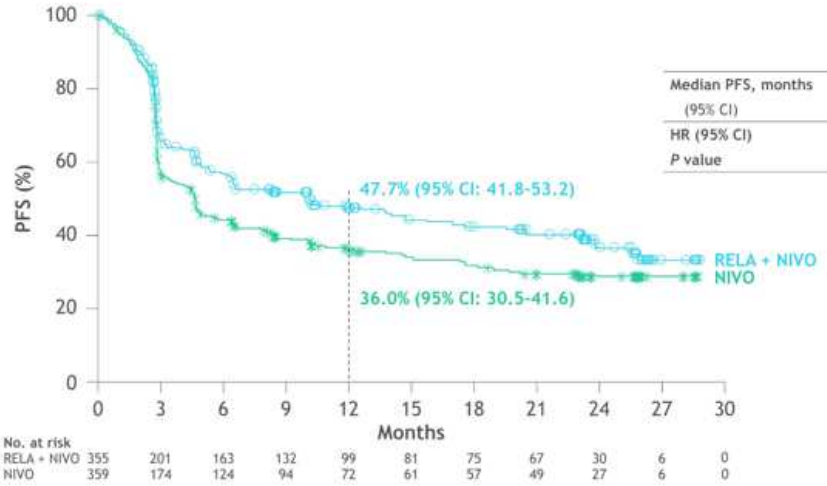
Baseline characteristics

Characteristic		RELA + NIVO (n = 355)	NIVO (n = 359)	Total (N = 714)
Median age, years		63	62	63
Female, n (%)		145 (40.8)	153 (42.6)	298 (41.7)
AJCC v8 M stage, n (%)	M1A	77 (21.7)	107 (29.8)	184 (25.8)
	M1B	85 (23.9)	88 (24.5)	173 (24.2)
	M1C	151 (42.5)	127 (35.4)	278 (38.9)
	M1D	6 (1.7)	11 (3.1)	17 (2.4)
ECOG PS, n (%)	0	236 (66.5)	242 (67.4)	478 (66.9)
	1	119 (33.5)	117 (32.6)	236 (33.1)
Serum LDH level, n (%)	> ULN	130 (36.6)	128 (35.7)	258 (36.1)
	> 2× ULN	32 (9.0)	31 (8.6)	63 (8.8)
Prior neoadjuvant/adjuvant[a], n (%)		33 (9.3)	27 (7.5)	60 (8.4)
Tumor burden[b], median (min.-max.), mm		59.0 (10-317)	54.5 (10-548)	
Stratification factor, n (%)				
LAG-3 expression	≥ 1%	268 (75.5)	269 (74.9)	537 (75.2)
	< 1%	87 (24.5)	90 (25.1)	177 (24.8)
PD-L1 expression	≥ 1%	146 (41.1)	147 (40.9)	293 (41.0)
	< 1%	209 (58.9)	212 (59.1)	421 (59.0)
BRAF mutation status	Mutant	136 (38.3)	139 (38.7)	275 (38.5)
	Wild-type	219 (61.7)	220 (61.3)	439 (61.5)
AJCC M stage	M0/M1any[0][c]	232 (65.4)	237 (66.0)	469 (65.7)
	M1any[1][d]	123 (34.6)	122 (34.0)	245 (34.3)

LDH, lactate dehydrogenase; ULN, upper limit of normal. [a]Most common therapy was interferon; [b]Sum of reference diameters of target lesions in mm; [c]AJCC M stage M0/M1any [LDH not elevated]; [d]AJCC M stage M1any [elevated LDH].

Lipson et al. ASCO 2021 Abstract 9503

RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO FDC vs NIVO



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

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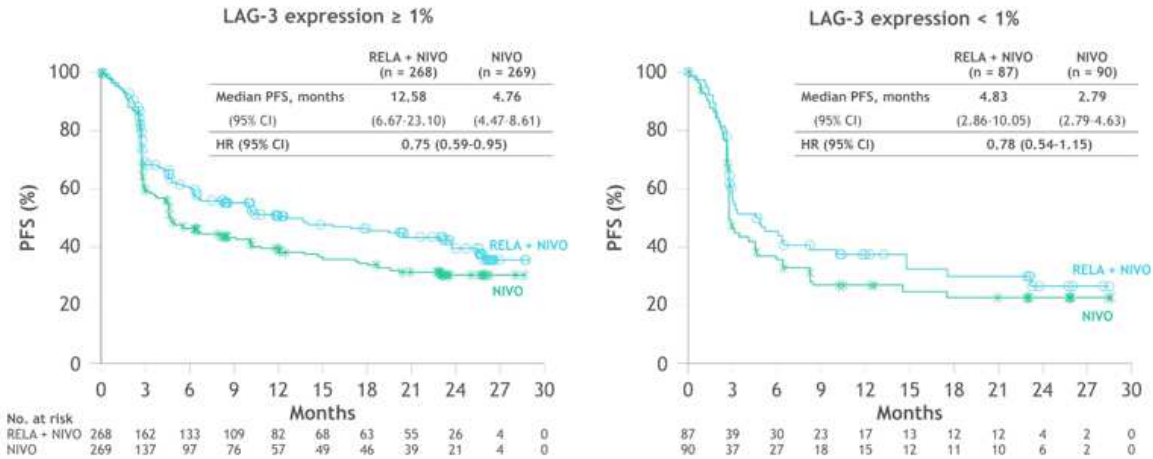
PFS by LAG-3 expression

- PFS benefit favored RELA + NIVO FDC regardless of LAG-3 expression status



Statistical model for HR: unstratified Cox proportional hazard model.

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Immune-mediated adverse events

Immune-mediated AE category[a], n (%)	RELA + NIVO (n = 355)		NIVO (n = 359)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hypothyroidism/thyroiditis	64 (18.0)	0	50 (13.9)	0
Rash	33 (9.3)	2 (0.6)	24 (6.7)	5 (1.4)
Diarrhea/colitis	24 (6.8)	4 (1.1)	11 (3.1)	5 (1.4)
Hyperthyroidism	22 (6.2)	0	24 (6.7)	0
Hepatitis	20 (5.6)	14 (3.9)	9 (2.5)	4 (1.1)
Adrenal insufficiency	15 (4.2)	5 (1.4)	3 (0.8)	0
Pneumonitis	13 (3.7)	2 (0.6)	6 (1.7)	2 (0.6)
Hypophysitis	9 (2.5)	1 (0.3)	3 (0.8)	1 (0.3)
Nephritis and renal dysfunction	7 (2.0)	4 (1.1)	5 (1.4)	4 (1.1)
Hypersensitivity	4 (1.1)	0	4 (1.1)	0

- Additional AE of interest: myocarditis (any grade) occurred in 5 (1.7%) patients with RELA + NIVO and 2 (0.6%) with NIVO. Troponin monitoring was performed for the first 2 months of treatment per protocol

[a]Includes AEs of any grade occurring in ≥ 1% of patients considered by investigators to be potentially immune-mediated that met the following criteria: occurred within 100 days of the last dose, regardless of causality, treated with immune-modulating medication with no clear alternate etiology, or had an immune-mediated component.

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Metastatski melanom

- Ponovna uvedba anti PD1 – podatki so iz majhnih skupin, pa vendar ima lahko ponovna uvedba anti PD1 svoje mesto
- Nivolumab + relatlimab v 1 liniji zdravljenja napredovalega melanoma omogoča učinkovito zdravljenje – 25% izboljšanje PFS (za OS še ni podatkov) in bo to vodilo v spremembo priporočil za zdarvljenej metastatskega melanoma

LEAP-004 Study Design (NCT03776136)

Participants

- Unresectable stage III or IV melanoma[a]
- Confirmed PD per iRECIST[1b] on or within 12 wk of last dose of anti–PD-1/L1 given alone or in combination (including with anti–CTLA-4) for ≥2 doses
  - ≤25% with PD on anti–CTLA-4 + anti–PD-1/L1
- No limit to number of previous therapies
- Measurable disease confirmed by blinded, independent central review (BICR)

N ≈ 100

Pembrolizumab
200 mg IV Q3W
for up to 35 cycles
+
Lenvatinib
20 mg PO QD

Continued until PD, unacceptable toxicity, or patient or physician decision[c]

End Points

- Primary: ORR per RECIST v1.1[d] by BICR
- Secondary: DOR and PFS per RECIST v1.1[d] by BICR, OS, and safety

[a]Per AJCC 8th edition. [b]In the absence of rapid clinical progression, initial evidence of radiologic PD required confirmation by a second assessment performed ≥4 weeks from first documented radiographic PD. [c]Eligible patients deriving clinical benefit can be treated beyond PD. Participants with CR can discontinue study treatment if they have received it for ≥24 weeks. [d]Modified to follow ≤10 target lesions total and ≤5 target lesions per organ. 1. Seymour L et al. *Lancet Oncol* 2017;18:e143-52.

Arance et al. ASCO 2021 Abstract 9504

Baseline Characteristics

Characteristic, n (%)	N = 103
Age, median (range)	63 y (21-85)
Males	55 (53.4%)
ECOG PS 1	41 (39.8%)
LDH >ULN	57 (55.3%)
≥2 × ULN	21 (20.4%)
Brain metastasis (history of or current)	15 (14.6%)
Sum of target lesions, median (range)	95 mm (18-530)

Characteristic, n (%)	N = 103
BRAF^{V600} mutation	38 (36.9%)
PD-L1 positive[a]	66 (64.1%)
Metastatic stage at enrollment	
M0, M1a, or M1b	33 (32.0%)
M1c or M1d	70 (68.0%)
No. of prior lines of therapy	
1	43 (41.7%)
2	26 (25.2%)
≥3	34 (33.0%)

[a]PD-L1 expression assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). Positivity defined as ≥MEL2 (ie, membranous PD-L1 staining in ≥1% of tumor and inflammatory cells).
9 (8.7%) participants had unknown PD-L1 status.
Data cutoff date: Sep 18, 2020.

Arance et al. ASCO 2021 Abstract 9504

BICR-Confirmed Response by RECIST v1.1

	Total Population N = 103
ORR, % (95% CI)	**21.4% (13.9-30.5)**
DCR, % (95% CI)	66.0% (56.0-75.1)
Best overall response, n (%)	
CR	3 (2.9%)
PR	19 (18.4%)
SD	46 (44.7%)
PD	30 (29.1%)
Not assessed[a]	5 (4.9%)

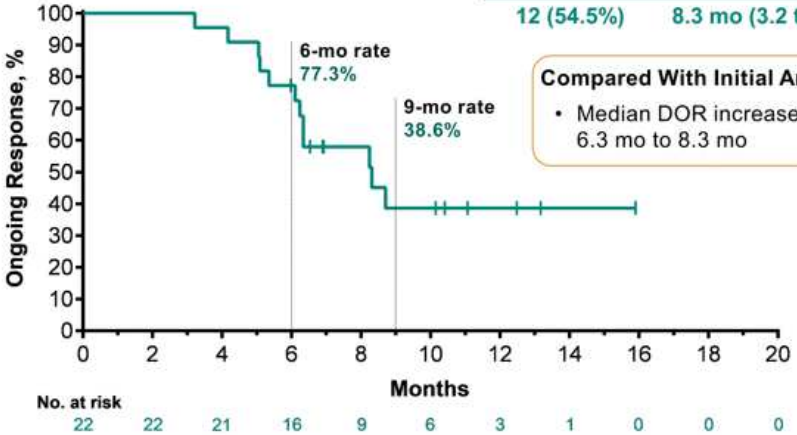
Compared With Initial Analysis[1]
- ORR remained the same
  - 1 additional CR
- DCR increased from 65.0% to 66.0%
  - 1 additional SD

[a]Participants who had no post-baseline imaging assessments. Data cutoff date: Sep 18, 2020.
1. Arance A et al. Ann Oncol 2020;31(suppl_4): S1142-S1215. [Abstr LBA44].

Arance et al. ASCO 2021 Abstract 9504

Duration of BICR-Confirmed Response by RECIST v1.1

Events,[a] n (%)	Median (range)
12 (54.5%)	8.3 mo (3.2 to 15.9+)



Compared With Initial Analysis[1]

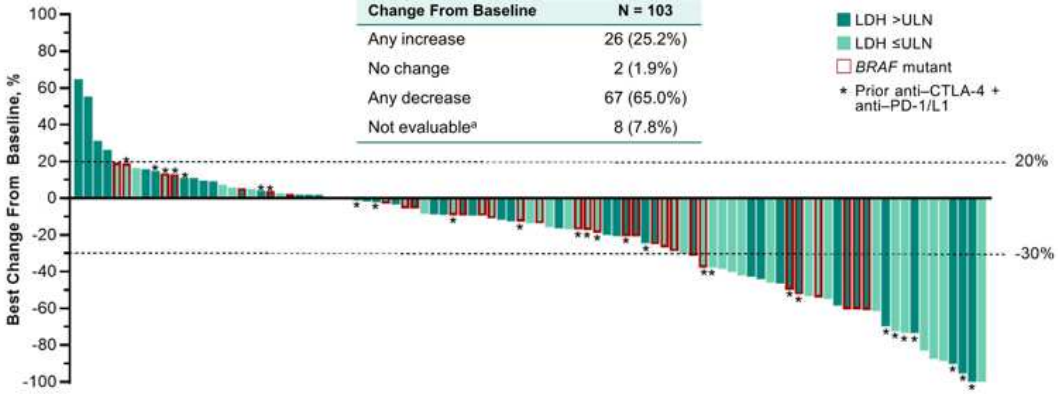
- Median DOR increased from 6.3 mo to 8.3 mo

[a]Patients who died or had PD. Data cutoff date: Sep 18, 2020.

1. Arance A et al. *Ann Oncol* 2020;31(suppl_4): S1142-S1215 [Abstr LBA44].

Best Change From Baseline in Target Lesions (RECIST v1.1 by BICR)

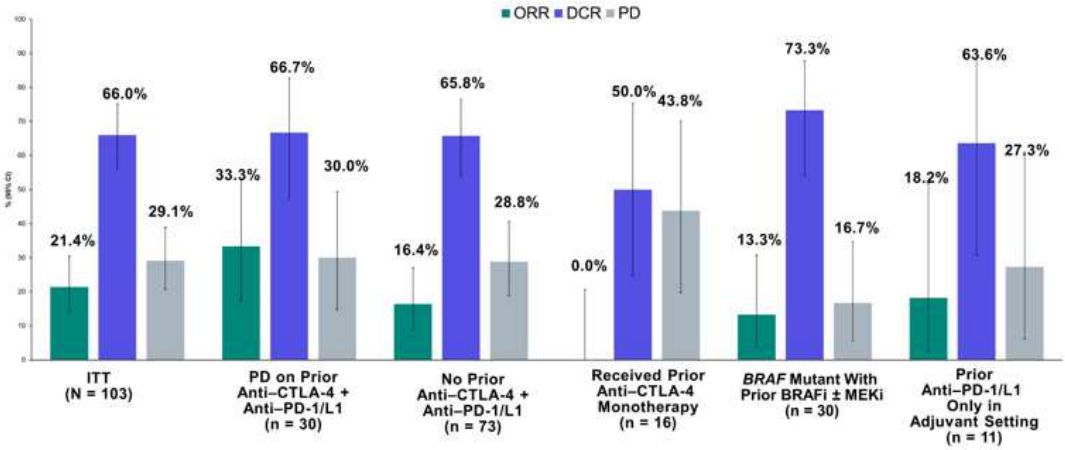
Change From Baseline	N = 103
Any increase	26 (25.2%)
No change	2 (1.9%)
Any decrease	67 (65.0%)
Not evaluable[a]	8 (7.8%)



[a]The 8 participants who did not have ≥1 post-baseline imaging assessment evaluable for change from baseline in target lesions are excluded from the graph.
Data cutoff date: Sep 18, 2020.

Arance et al. ASCO 2021 Abstract 9504

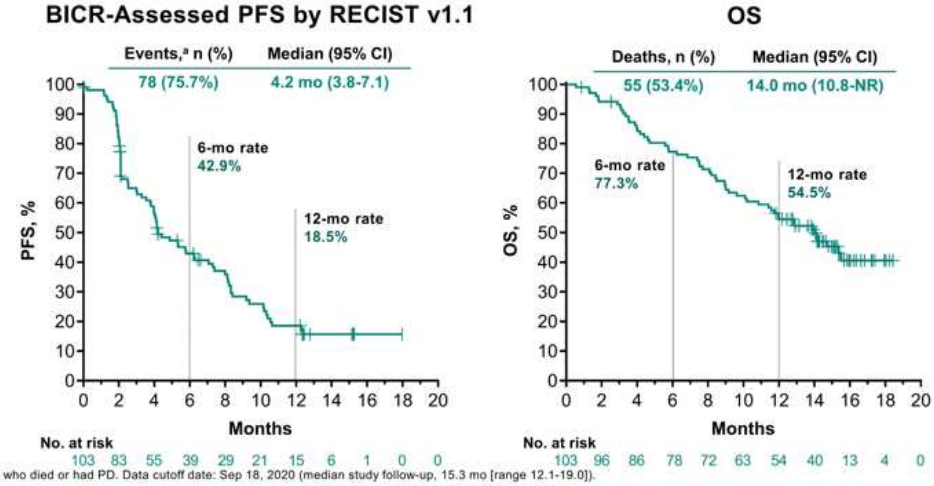
BICR-Confirmed ORR and DCR in Key Subgroups Based on Prior Therapy



Data cutoff date: Sep 18, 2020.

Arance et al. ASCO 2021 Abstract 9504

Progression-Free and Overall Survival



[a]Patients who died or had PD. Data cutoff date: Sep 18, 2020 (median study follow-up, 15.3 mo [range 12.1-19.0]).

Arance et al. ASCO 2021 Abstract 9504

Treatment-Related Adverse Events

Summary

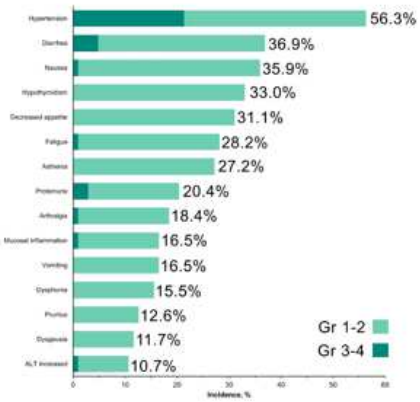
n (%)	N = 103
Any grade	99 (96.1%)
Grade 3-5	47 (45.6%)
Grade 3	42 (40.8%)
Grade 4	4 (3.9%)
Grade 5	1 (1.0%)[a]
Serious	19 (18.4%)
Led to discontinuation[b]	8 (7.8%)
Led to interruption[b]	61 (59.2%)
Led to len dose reduction	58 (56.3%)

Median (range) duration of treatment

- 6.0 mo (0.1-18.2) for len
- 5.6 mo (1 day-18.2 mo) for pembro

[a]Platelet count decreased. [b]Includes participants who discontinued or interrupted both len and pembro, len alone, or pembro alone.
Data cutoff date: Sep 18, 2020.

Incidence ≥10%



Arance et al. ASCO 2021 Abstract 9504

C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous TIL (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)

Patient Population

Unresectable or metastatic melanoma treated with ≥1 prior systemic therapy including a PD-1–blocking antibody and, if BRAF V600 mutation positive, a BRAFi ± MEKi

Cohort 1
Non-cryopreserved TIL product (Gen 1)
N=30
Closed to enrollment

Cohort 2
Cryopreserved TIL product (Gen 2)
N=60
Closed to enrollment

Cohort 4 (Pivotal)
Cryopreserved TIL product (Gen 2)
N=75
Closed to enrollment

Cohort 3
TIL re-treatment
N=10

Cohort 2 Endpoints

- Primary: Efficacy per investigator-assessed ORR using RECIST 1.1 response criteria
- Secondary: Safety and additional parameters of efficacy

Key Eligibility Criteria

- Radiographic confirmation of progression
- One tumor lesion resectable for TIL generation (~1.5 cm in diameter) and ≥1 target tumor lesion for RECIST 1.1 response assessment
- Age ≥18 years at the time of consent
- ECOG performance status of 0–1

Methods

- Patients were enrolled from April 2017 to January 2019 at 26 sites across the US and EU
- Concomitant anticancer therapy was not permitted
- Imaging-evaluable disease was required
- All responses required confirmation
- Data cutoff: 22 April 2021

BRAFi, BRAF inhibitor; ECOG, Eastern Cooperative Oncology Group; MEKi, MEK inhibitor; ORR, objective response rate; PD-1, programmed cell death protein 1; RECIST, Response Evaluation Criteria in Solid Tumors; TIL, tumor infiltrating lymphocytes.

Presented By: James M. G. Larkin, MD, FRCP, PhD

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Objective Response Rate

Response, n (%)	N=66
Objective Response Rate	**24 (36.4)**
Complete response	3 (4.5)
Partial response	21 (31.8)
Stable disease	29 (43.9)
Progressive disease	9 (13.6)
Non-evaluable*	4 (6.1)
Disease control rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, max (months)	2.2, 38.5+

- Mean number of TIL cells infused: 27.3×10^9

- After a median study follow-up of 33.1 months, **median DOR was not reached** (range 2.2, 38.5+ months)

*Not evaluable due to not reaching first assessment
DOR, duration of response; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes

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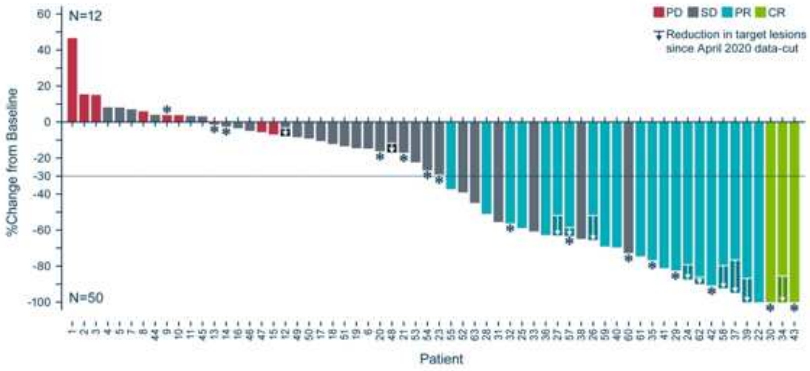
Best Overall Response

- 81% (50/62) of patients had a reduction in tumor burden
- 11 patients (17.7%) had further SOD reduction since April 2020 datacut



*Patients with BRAF V600 mutation. 3 patients had no post-TIL disease assessment due to early death, and 1 due to start of new anticancer therapy
DOR, duration of response; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes

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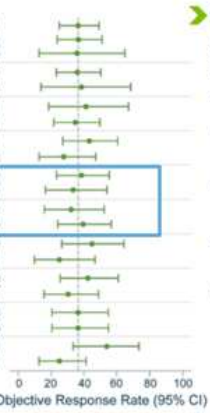
Univariable Analyses: ORR of Lifileucel

Subgroup		n/N	ORR	95% CI*
Overall		24/66	36.4	(24.9, 49.1)
Age Group	<65	19/52	36.5	(23.6, 51.0)
	≥65	5/14	35.7	(12.8, 64.9)
Prior CTLA-4 Use	Yes	19/53	35.8	(23.1, 50.2)
	No	5/13	38.5	(13.9, 68.4)
BRAF Mutation Status	Mutated (V600E or K)	7/17	41.2	(18.4, 67.1)
	Non-Mutated	17/49	34.7	(21.7, 49.6)
Baseline ECOG	0	16/37	43.2	(27.1, 60.5)
	≥1	8/29	27.6	(12.7, 47.2)
Baseline LDH	≤ULN	15/39	38.5	(23.4, 55.4)
	>ULN	9/27	33.3	(16.5, 54.0)
Baseline Brain/Liver Lesion	Yes	9/28	32.1	(15.9, 52.4)
	No	15/38	39.5	(24.0, 56.6)
Cumulative Duration on Anti–CTLA-4	≤Median (2.10 mo)	13/29	44.8	(26.4, 64.3)
	>Median (2.10 mo)	6/24	25.0	(9.8, 46.7)
Cumulative Duration on Anti–PD-1/PD-L1	≤Median (5.06 mo)	14/33	42.4	(25.5, 60.8)
	>Median (5.06 mo)	10/33	30.3	(15.6, 48.7)
Time from Stop of Anti–PD-1 /PD-L1 to TIL infusion	≤Median (4.76 mo)	12/33	36.4	(20.4, 54.9)
	>Median (4.76 mo)	12/33	36.4	(20.4, 54.9)
Baseline Target Lesion SOD	<70 mm	14/26	53.8	(33.4, 73.4)
	≥70 mm	10/40	25.0	(12.7, 41.2)



- ORR was not predicted by any patient or clinical characteristics analyzed, including:
  - Baseline LDH (≤ULN vs >ULN)
  - Baseline ECOG performance status (0 vs ≥1)
  - Baseline brain / liver lesions (yes vs no)
  - Cumulative duration on anti–CTLA-4 (≤median vs >median)
  - Cumulative duration on anti–PD-1 / anti–PD-L1 (≤median vs >median) in a post–PD-1 patient population

*95% CI is calculated using the Clopper-Pearson Exact test.
CTLA-4, cytotoxic T-lymphocyte antigen-4; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; mo, months; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; SOD, sum of diameters; TIL, tumor-infiltrating lymphocytes; ULN, upper limit of normal.

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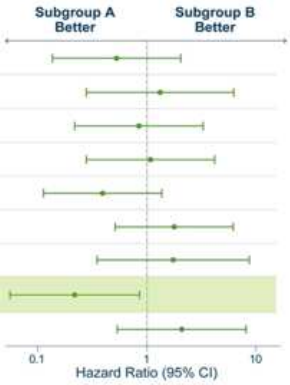
Univariable Analyses*: DOR of Lifileucel

Parameter	Subgroup A vs B	N in Subgroup A	N in Subgroup B	HR (95% CI)
Age Group	<65 vs ≥65	19	5	0.527 (0.136, 2.046)
Prior CTLA-4 Use	Yes vs No	19	5	1.320 (0.280, 6.233)
BRAF Mutation Status	Yes vs No	7	17	0.845 (0.218, 3.278)
Baseline ECOG	0 vs ≥1	16	8	1.079 (0.279, 4.179)
Baseline LDH	≤ULN vs >ULN	15	9	0.393 (0.113, 1.364)
Baseline Brain/Liver Lesion	Yes vs No	9	15	1.776 (0.513, 6.154)
Cumulative Duration on Anti–CTLA-4	≤Median (2.10m) vs >Median	13	6	1.743 (0.350, 8.664)
Cumulative Duration on Anti–PD-1/PD-L1	**≤Median (5.06m) vs >Median**	**14**	**10**	**0.218 (0.056, 0.854)**
Baseline Target Lesion SOD	<70mm vs ≥70mm	14	10	2.083 (0.537, 8.079)



- Although cumulative duration on prior anti–PD-1 / anti–PD-L1 was not associated with achieving a response to lifileucel (ORR), it was associated with DOR

*Univariable Cox proportional hazards regression model was used to estimate hazard ratios with 95% confidence intervals between subgroups on DOR.
CTLA-4, cytotoxic T-lymphocyte antigen-4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; SOD, sum of diameters; TIL, tumor infiltrating lymphocytes; ULN, upper limit of normal.

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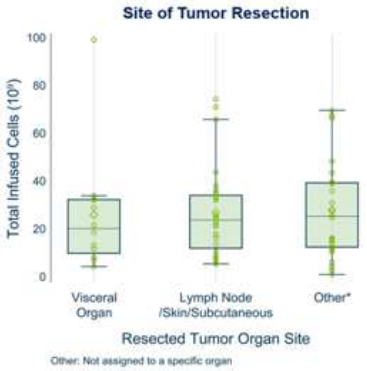
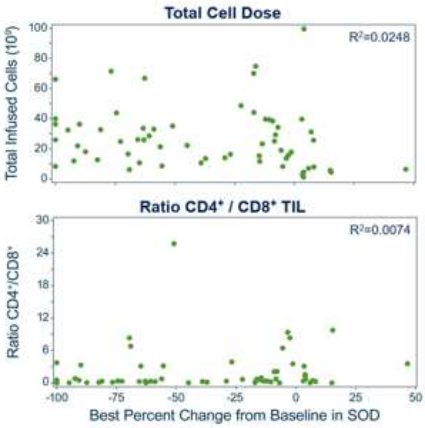
Site of Tumor Resection and Infused Cell Dose





- Appropriate amount of TIL was manufactured regardless of tumor resection site
- Target lesion SOD reductions were seen across the range of total TIL cell doses and CD4⁺ / CD8⁺ TIL ratios

SOD, sum of diameters; TIL, tumor infiltrating lymphocytes

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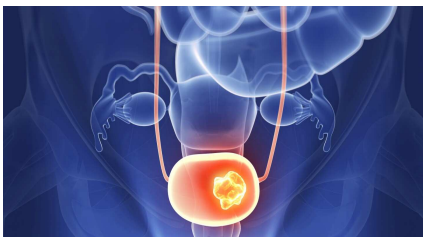
- Pembrolizumab + levantinib omogoča dolgotrajne odgovore pri močno pretretiranih bolnikih, tudi s povišano LDH (55% bolnikov)
- Neželeni učinki G3 so bili obvljadljivi
- Centralno proizvedeni TIL imajo dolgotrajno dobrobit pri bolnikih , ki so rezistentni na anti PD1

Letošnja dognanja:

- Učinkovitost adjuvantnega zdravljenja z anti PD1 se ohranja tudi po daljšem spremljanju
- Adjuvantno zdravljenje bolnikov IIB,C z pembrolizumabom podaljšuje čas do ponovitve bolezni
- Kombinirana imunoterapija v zdravljenju napredovalega melanoma omogoča najdaljša preživetja
- Nivolumab + relatlimab v 1 liniji zdravljenja napredovalega melanoma omogoča učinkovito zdravljenje in verjetno bo to naslednje standardno zdravljenje
- Pembrolizumab + levantinib omogoča dolgotrajne odgovore pri močno pretretiranih bolnikih, tudi z povišano LDH
- Centralno proizvedeni TIL imajo dolgotrajno dobrobit pri bolnikih , ki so rezistentni na anti PD1



NOVOSTI NA PODROČJU IMUNO-TERAPIJE UROLOŠKIH RAKOV V l. 2021

Breda Škrbinc

OIL 15.12.2021

KARCINOM SEČNEGA MEHURJA

- DOPOLNILNO ZDRAVLJENJE
  - CheckMate 274
- RAZSEJANA BOLEZEN
  - JAVELIN bladder 100
  - EVE 301
  - EVE 201
  - TROPHY-U-01

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Genitourinary Cancers Symposium

First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab versus placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma

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Abstract Number 391

Presented By Dean Bajorin at 2021 Genitourinary Cancers Symposium

Study design

- CheckMate 274 is a phase 3, randomized, double-blind, multicenter study of adjuvant nivolumab versus placebo in patients with high-risk MIUC

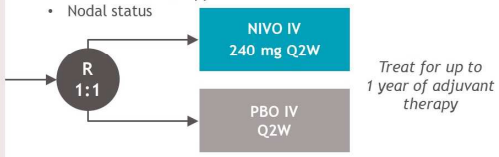
N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



Treat for up to 1 year of adjuvant therapy

Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

[a]Defined by the percent of positive tumor cell membrane staining in a minimum of 100 evaluable tumor cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay.
[b]OS data were not mature at the time of the first planned interim analysis. OS and DSS data are not presented.
DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HRQoL, health-related quality of life; IHC, immunohistochemistry; ITT, intent-to-treat; NUTRFS, non-urothelial tract recurrence-free survival; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; R, randomized.

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CheckMate 274

Patient disposition in all treated patients

	NIVO (N = 351)	PBO (N = 348)
Ongoing treatment, %	6.0	5.7
Completed treatment, %	40.7	37.9
Discontinued treatment, %	53.3	56.3
Reason for treatment discontinuation, %		
Disease recurrence	25.6	42.2
Study drug toxicity	14.0	2.3
Patient request	5.4	1.1
AE unrelated to study drug	4.6	4.3
Patient withdrew consent	1.4	2.0
Death	0	0.3
Other	2.3	4.0

AE, adverse event.

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CheckMate 274

Select baseline demographic and disease characteristics in all randomized patients

	NIVO (N = 353)	PBO (N = 356)
Mean age (range), years	65.3 (30-92)	65.9 (42-88)
Male, %	75.1	77.2
Region, %		
United States	13.9	14.9
Europe	48.2	48.0
Asia	22.7	20.8
Rest of the world	15.3	16.3
ECOG PS,[a] %		
0	63.5	62.1
1	34.6	35.1
2[b]	2.0	2.5
Tumor origin at initial diagnosis, %		
Urinary bladder	79.0	78.9
Upper tract disease	21.0	21.1
Minor histological variants present, %	41.1	39.6
PD-L1 ≥ 1% by IVRS, %	39.7	39.9
Prior neoadjuvant cisplatin, %	43.3	43.5
Pathologic T stage at resection,[c,d] %		
pT0-2	22.7	24.2
pT3	58.4	57.3
pT4a	16.1	17.4
Other	2.5	0.8
Nodal status at resection,[d] %		
N+	47.3	47.2
N0/x with < 10 nodes removed	26.6	27.8
N0 with ≥ 10 nodes removed	25.8	24.7

[a]Not reported for 1 patient in the PBO arm. [b]ECOG PS of 2 was permitted only for patients who did not receive cisplatin-based neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy. [c]The T staging included patients with N+, N0, or NX. [d]Not reported for 1 patient in each arm.
ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice-response system.

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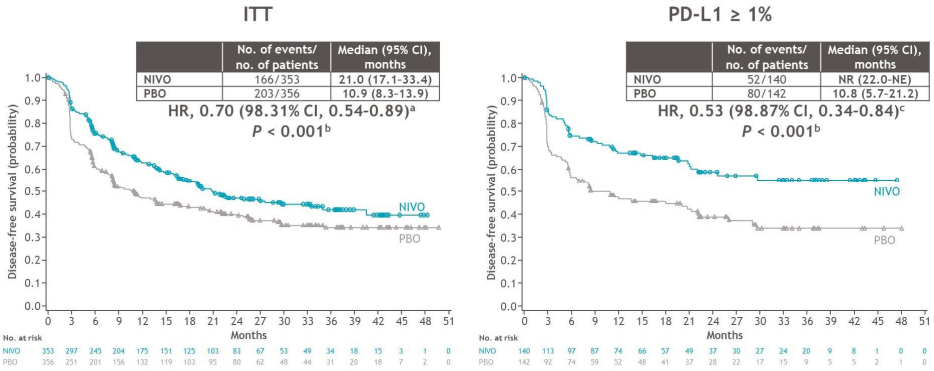
CheckMate 274

Disease-free survival



Minimum follow-up, 5.9 months.
DFS was defined as the time between the date of randomization and the date of first recurrence (local urothelial tract, local non-urothelial tract or distant) or death.
[a]HR, 0.695 (98.31% CI, 0.541-0.894). [b]Based on a 2-sided stratified logrank test. [c]HR, 0.535 (98.87% CI, 0.340-0.842).
CI, confidence interval; NE, not estimable; NR, not reached.

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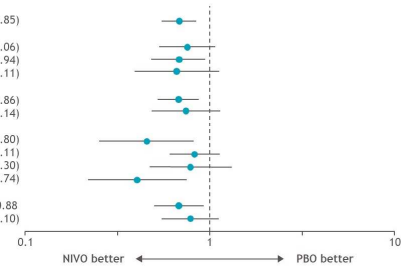
CheckMate 274

Disease-free survival in select subgroups: ITT patients

Subgroup	Nivolumab	Placebo	HR (95% CI)
	no. of events/ no. of patients		
Overall	166/353	203/356	0.70 (0.57-0.85)
Age			
< 65 years	71/155	69/136	0.76 (0.54-1.06)
≥ 65 and < 75 years	63/131	100/164	0.68 (0.49-0.94)
≥ 75 years	32/67	34/56	0.67 (0.40-1.11)
Sex			
Male	122/265	155/275	0.68 (0.53-0.86)
Female	44/88	48/81	0.75 (0.49-1.14)
Region			
US	25/49	36/53	0.45 (0.26-0.80)
Europe	85/170	96/171	0.83 (0.61-1.11)
Asia	35/80	34/74	0.78 (0.47-1.30)
Rest of world	21/54	37/58	0.41 (0.22-0.74)
Baseline ECOG PS			
0	101/224	125/221	0.67 (0.52-0.88
1	64/122	71/125	0.78 (0.55-1.10)



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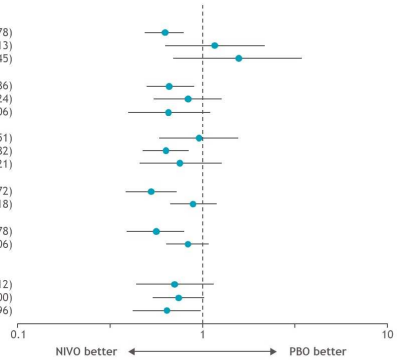
CheckMate 274

Disease-free survival in select subgroups: ITT patients

Subgroup	Nivolumab	Placebo	HR (95% CI)
	no. of events/ no. of patients		
Initial tumor origin			
Urinary bladder	126/279	165/281	0.62 (0.49-0.78)
Renal pelvis	23/44	25/52	1.16 (0.63-2.13)
Ureter	17/30	13/23	1.55 (0.70-3.45)
Pathologic lymph node status			
N+	95/167	115/168	0.65 (0.49-0.86)
N0/x with < 10 nodes removed	44/94	50/99	0.82 (0.54-1.24)
N0 with ≥ 10 nodes removed	27/91	37/88	0.64 (0.39-1.06)
Pathologic status			
pT0-2	36/80	40/86	0.93 (0.58-1.51)
pT3	94/206	119/204	0.62 (0.47-0.82)
pT4a	34/57	40/62	0.74 (0.45-1.21)
Prior neoadjuvant cisplatin			
Yes	69/153	99/155	0.53 (0.39-0.72)
No	97/200	104/201	0.89 (0.67-1.18)
Baseline PD-L1 expression			
≥ 1%	52/139	78/141	0.55 (0.39-0.78)
< 1%	113/210	120/209	0.82 (0.63-1.06)
Time from IUC surgery to randomization, days			
> 30-60	43/79	39/70	0.70 (0.43-1.12)
> 60-90	76/165	93/177	0.73 (0.53-1.00)
> 90-120	45/103	62/95	0.64 (0.42-0.96)



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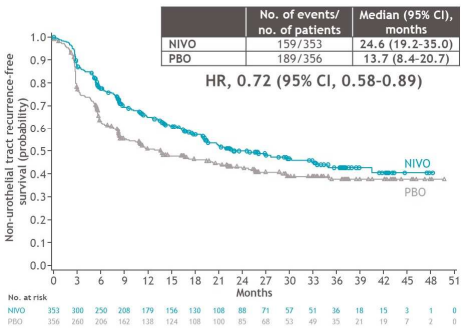
CheckMate 274

Non-urothelial tract recurrence-free survival

ITT

	No. of events/ no. of patients	Median (95% CI), months
NIVO	159/353	24.6 (19.2-35.0)
PBO	189/356	13.7 (8.4-20.7)

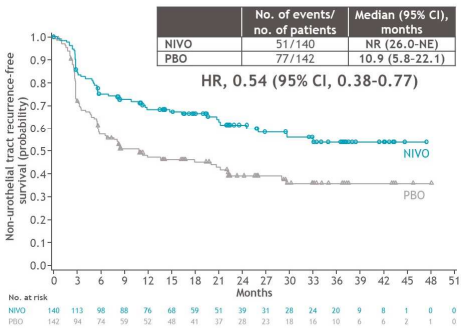
HR, 0.72 (95% CI, 0.58-0.89)



PD-L1 ≥ 1%

	No. of events/ no. of patients	Median (95% CI), months
NIVO	51/140	NR (26.0-NE)
PBO	77/142	10.9 (5.8-22.1)

HR, 0.54 (95% CI, 0.38-0.77)



Minimum follow-up, 5.9 months.
NUTRFS was defined as the time between the date of randomization and the date of first local non-urothelial tract or distant recurrence or death.

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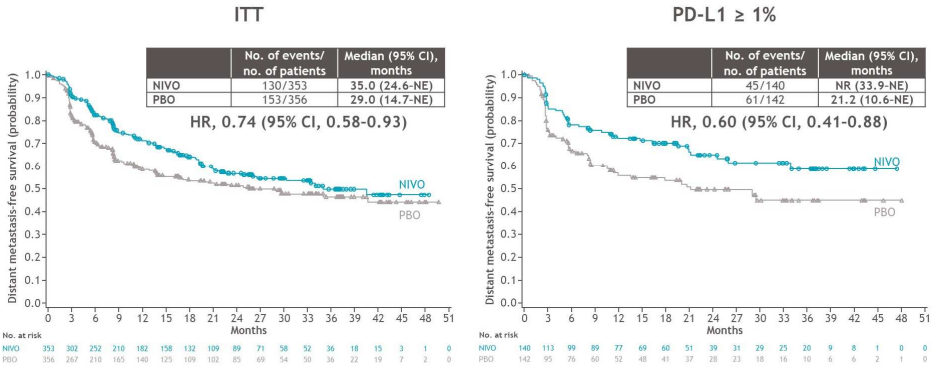
CheckMate 274

Distant metastasis-free survival



Minimum follow-up, 5.9 months.
DMFS was defined as the time between the date of randomization and the date of first distant recurrence (non-local) or date of death.

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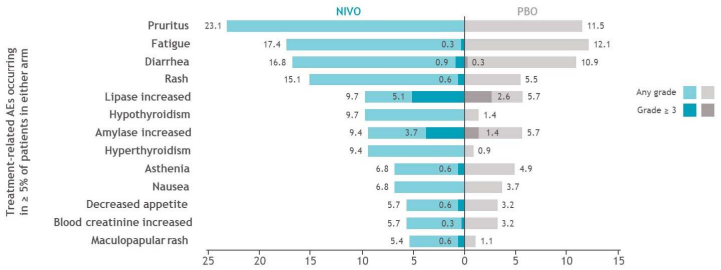
CheckMate 274

Safety summary in all treated patients

	NIVO (N = 351)[a]		PBO (N = 348)[a]	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any-cause AEs, %	98.9	42.7	95.4	36.8
Treatment-related AEs,[b] %	77.5	17.9	55.5	7.2
Treatment-related AEs leading to discontinuation, %	12.8	7.1	2.0	1.4



[a]Includes all treated patients. [b]There were 2 treatment-related deaths due to pneumonitis in the NIVO arm. There were no treatment-related deaths in the PBO arm.
Includes events reported between the first dose and 30 days after the last dose of study therapy.

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CheckMate 274

Treatment-related select AEs

Organ class category, %	NIVO (N = 351)		PBO (N = 348)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin	40.7	1.7	17.8	0
Endocrine	19.1	0.3	3.7	0
Gastrointestinal	18.5	1.7	11.2	0.9
Hepatic	8.3	1.7	4.9	0.3
Renal	7.1	1.1	3.4	0
Pulmonary	5.4	1.4[a]	1.4	0

- The most common grade ≥3 treatment-related select AEs were diarrhea (0.9%), colitis (0.9%), and pneumonitis (0.9%) in the NIVO arm and colitis (0.6%), diarrhea (0.3%), GGT increase (0.3%), and hepatitis (0.3%) in the PBO arm

Select AEs are those with a potential inflammatory mechanism requiring more frequent monitoring and/or specific intervention such as immunosuppressants or endocrine replacement therapy.
[a]One patient with grade 4 treatment-related pneumonitis and 1 patient with grade 3 treatment-related immune-mediated pneumonitis had a fatal outcome.
GGT, gamma-glutamyltransferase.

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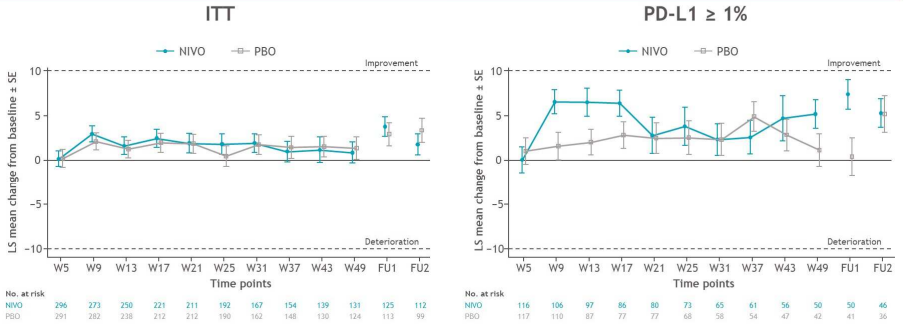
CheckMate 274

Health-related quality of life: change from baseline in EORTC-QLQ-C30 global health status score



- No deterioration in HRQoL with NIVO versus PBO was observed in either the ITT or PD-L1 ≥ 1% populations

Number of patients displayed is the number of patients included in the mixed effects linear regression for repeated measures analysis at each visit. SE is the robust SE calculated using empirical variance estimator.
FU, follow-up visit; LS, least square; SE, standard error.

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CheckMate 274

Summary

- Adjuvant NIVO significantly improved DFS in patients with high-risk MIUC after radical surgery, both in the ITT and PD-L1 ≥ 1% populations
- NUTRFS (secondary endpoint) and DMFS (exploratory endpoint) were also improved with NIVO versus PBO in both study populations
- The safety and tolerability of NIVO monotherapy was consistent with previous reports in other tumor types, including in patients with metastatic UC[1-3]
- No deterioration in HRQoL, as measured by change in EORTC QLQ-C30 global health status score, was observed with NIVO versus PBO
- NIVO is the first systemic immunotherapy to demonstrate a statistically significant and clinically meaningful improvement in outcomes when administered as adjuvant therapy to patients with MIUC[4,5]
- These results support NIVO monotherapy as a new standard of care in the adjuvant setting for patients with high-risk MIUC after radical surgery, regardless of PD-L1 status and prior neoadjuvant chemotherapy

1. Sharma P et al. *Lancet Oncol* 2016;17:1590-1598. 2. Sharma P et al. *Lancet Oncol* 2017;18:312-322. 3. Motzer R et al. *N Engl J Med* 2015;373:1803-1813. 4. Kim HS et al. *Investig Clin Urol* 2018;59:285-296. 5. Hussain MHA et al. *J Clin Oncol* 2020;38(suppl 15):5000.

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Napredovali ca sečnika - Vzdrževalno zdravljenje

Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line chemotherapy in advanced urothelial carcinoma: JAVELIN Bladder 100 phase III results

Thomas Powles,[1] Se Hoon Park,[2] Eric Voog,[3] Claudia Caserta,[4] Begoña P. Valderrama,[5] Howard Gurney,[6] Haralabos Kalofonos,[7] Sinisa Radulovic,[8] Wim Demey,[9] Anders Ullén,[10] Yohann Loriot,[11] Srikala S. Sridhar,[12] Norihiko Tsuchiya,[13] Evgeny Kopyltsov,[14] Cora N. Sternberg,[15] Joaquim Bellmunt,[16] Jeanny B Aragon-Ching,[17] Daniel P. Petrylak,[18] Alessandra di Pietro,[19] Petros Grivas[20]

[1]Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, UK; [2]Sungkyunkwan University Samsung Medical Center, Seoul, Korea; [3]Centre Jean Bernard Clinique Victor Hugo, Le Mans, France; [4]Medical Oncology Unit, Azienda Ospedaliera S. Maria, Terni, Italy; [5]Department of Medical Oncology, Hospital Universitario Virgen del Rocío, Sevilla, Spain; [6]Department of Clinical Medicine, Macquarie University, Sydney, New South Wales, Australia; [7]Medical Oncology, University General Hospital of Patras, Patras, Greece; [8]Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [9]Department of Medical Oncology, AZ KLINA, Brasschaat, Belgium; [10]Patient Area Pelvic Cancer, Theme Cancer, Karolinska University Hospital and Department of Oncology-Pathology, Karolinska Institute, Solna, Sweden; [11]Gustave Roussy, INSERMU981, Université Paris-Saclay Villejuif, France; [12]Princess Margaret Cancer Center, University Health Network, Toronto, Ontario, Canada; [13]Department of Urology, Yamagata University Faculty of Medicine, Yamagata, Japan; [14]State Institution of Healthcare Regional Clinical Oncology Dispensary, Omsk, Russia; [15]Weill Cornell Medicine, Hematology/Oncology, New York, New York, USA; [16]Department of Medical Oncology, Beth Israel Deaconess Medical Center; Harvard Medical School, Boston, Massachusetts, USA; [17]Inova Schar Cancer Institute, Fairfax, Virginia, USA; [18]Yale Cancer Center, New Haven, Connecticut, USA; [19]Pfizer srl, Milano, Italy; [20]Department of Medicine, Division of Oncology, University of Washington; Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

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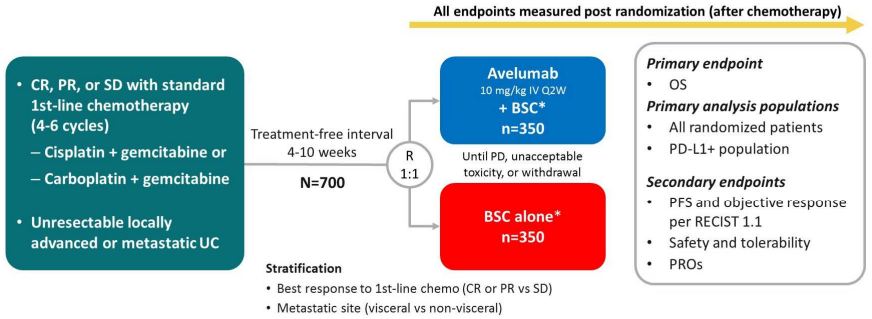
JAVELIN Bladder 100 study design (NCT02603432)



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

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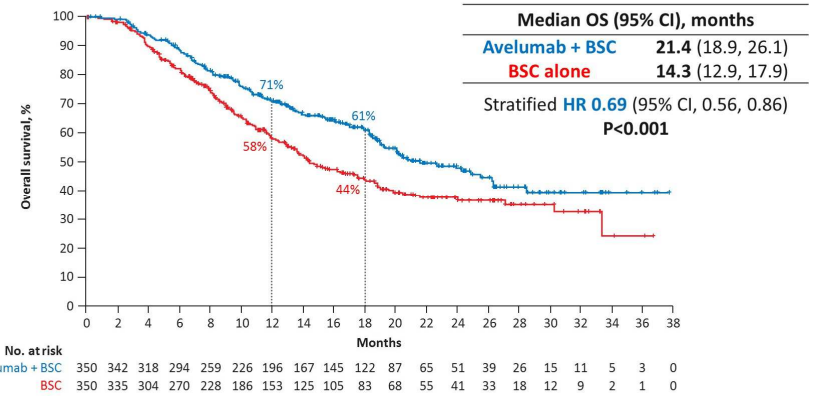
OS in the overall population



OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

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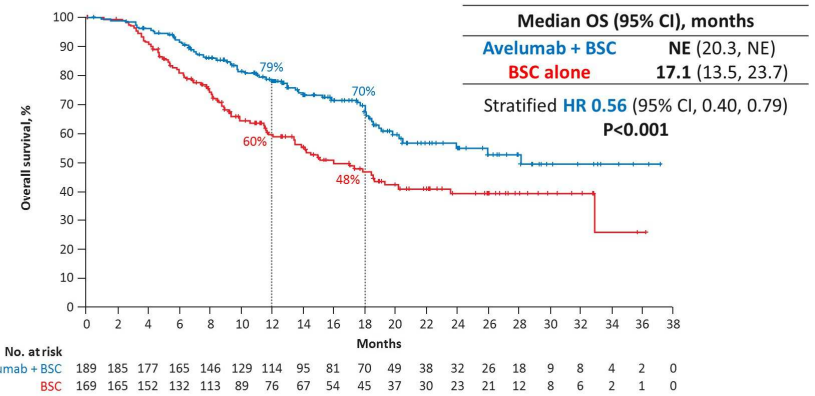
OS in the PD-L1+ population



OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

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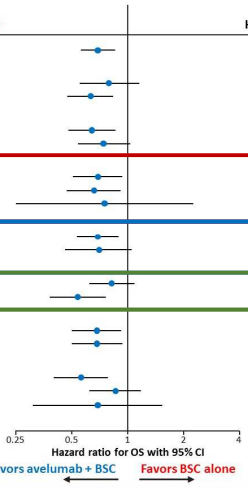
Subgroup analysis of OS in the overall population

Subgroup		Events/patients, n: Avelumab + BSC	Events/patients, n: BSC alone	Hazard ratio (95% CI)
All patients		145/350	179/350	**0.69** (0.56, 0.86)*
Age	<65 years	61/129	53/107	**0.79** (0.55, 1.15)
	≥65 years	84/221	126/243	**0.63** (0.47, 0.83)
ECOG PS score	0	77/213	101/211	**0.64** (0.48, 0.86)
	≥1	68/137	78/139	**0.74** (0.54, 1.03)
1st-line chemotherapy regimen	Gemcitabine + cisplatin	71/183	98/206	**0.69** (0.51, 0.94)
	Gemcitabine + carboplatin	68/147	73/122	**0.66** (0.47, 0.91)
	Gemcitabine + cisplatin/carboplatin	6/20	7/20	**0.75** (0.25, 2.25)
Best response to 1st-line chemotherapy	CR or PR	104/253	127/252	**0.69** (0.53, 0.89)
	SD	41/97	52/98	**0.70** (0.46, 1.05)
Site of baseline metastasis	Visceral	93/191	101/191	**0.82** (0.62, 1.09)
	Nonvisceral	52/159	78/159	**0.54** (0.38, 0.76)
Creatinine clearance	≥60 mL/min	74/181	97/196	**0.68** (0.50, 0.92)
	<60 mL/min	71/168	81/148	**0.68** (0.50, 0.94)
PD-L1 status	Positive	61/189	82/169	**0.56** (0.40, 0.78)
	Negative	76/139	72/132	**0.86** (0.62, 1.18)
	Unknown	8/22	25/49	**0.69** (0.31, 1.53)



Error bars show 95% CI
*Stratified (all other analyses are unstratified)

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JAVELIN Bladder 100: Outcomes by duration of 1L chemotherapy
Baseline characteristics

Duration of 1L chemotherapy	<Q1 (<15.0 wks)		Q1-Q2 (15.0-18.0 wks)		Q2-Q3 (18.0-20.1 wks)		>Q3 (>20.1 wks)	
	Ave + BSC (n=85)	BSC alone (n=86)	Ave + BSC (n=73)	BSC alone (n=72)	Ave + BSC (n=100)	BSC alone (n=111)	Ave + BSC (n=92)	BSC alone (n=79)
Age, median, years	70	69	68	68.5	68	69	68	70
Pooled geographic region, %								
North America	4	9	0	6	6	4	3	8
Europe	66	56	51	50	59	65	67	58
Asia	18	20	34	29	16	15	18	24
Australasia	11	10	11	13	14	13	3	5
Rest of the world	2	5	4	3	5	4	8	5
Site of baseline metastasis, %								
Visceral	51	55	58	57	54	55	57	51
Nonvisceral	49	45	42	43	46	45	43	49
1L chemotherapy regimen, %								
Gemcitabine + cisplatin	41	52	58	61	49	59	62	65
Gemcitabine + carboplatin	54	44	40	38	46	35	28	23
Gemcitabine + cisplatin or carboplatin*	5	3	3	1	5	5	10	13
Best response to 1L chemotherapy, %								
CR or PR	66	65	68	72	79	73	74	77
SD	34	35	32	28	21	27	26	23
PD-L1 status, %								
Positive	52	58	48	43	57	47	58	43
Negative	45	30	40	44	41	36	34	42
Unknown	4	12	12	13	2	17	9	15
ECOG PS, %								
0	48	58	67	60	59	58	70	67
1	52	41	32	39	41	41	30	33
2 or 3	0	1	1	1	0	1	0	0

*Patients who switched platinum regimens while receiving 1L chemotherapy.

- Subgroups with longer exposure to prior chemotherapy appeared to have a higher proportion of patients who had received gemcitabine + cisplatin as 1L regimen; had achieved an objective response (CR or PR) to 1L chemotherapy; and had an ECOG PS score of 0 at randomization
- Observations were similar for subgroups defined by cycles of 1L chemotherapy received
  - Most patients received 4 or 6 cycles of chemotherapy (few received 5 cycles)

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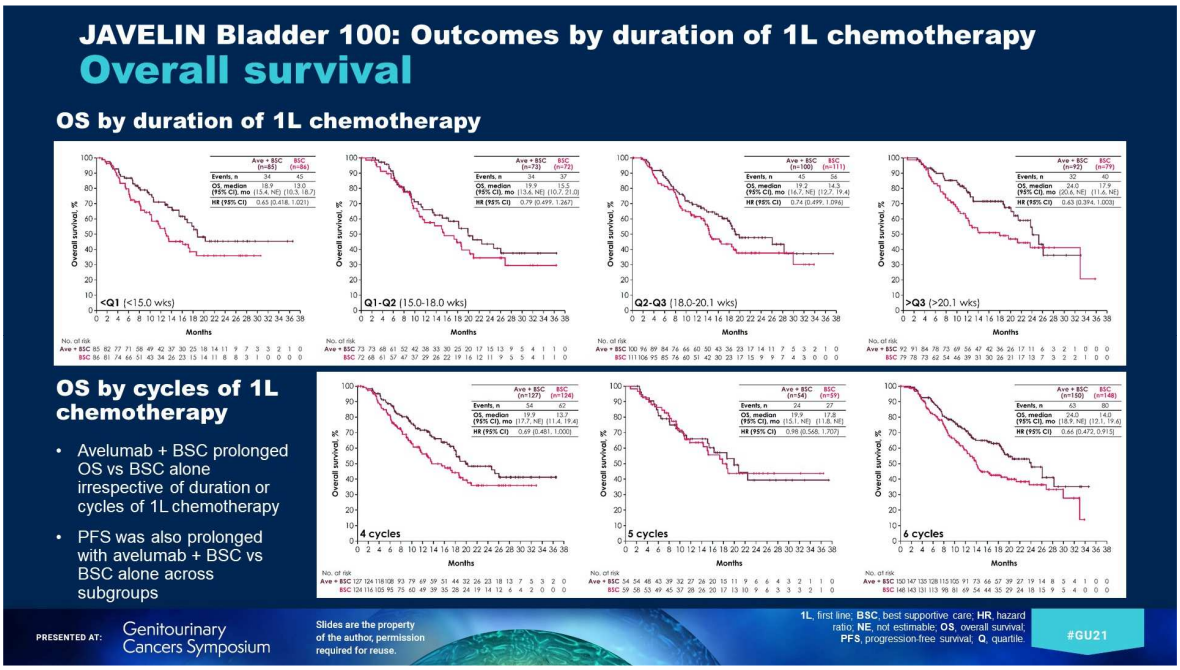

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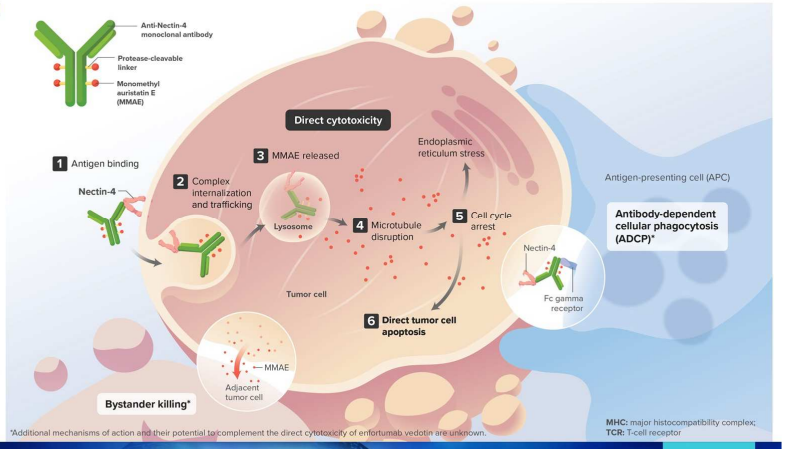
Napredovali ca sečnika – 2.linija in naprej

Enfortumab Vedotin: Nectin-4 Directed Therapy

Mechanism of Action



Enfortumab vedotin is an investigational agent in some settings, and its safety and efficacy have not been established.

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PRESENTED BY: Arjun V. Balar

#GU21

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Primary Results of EV-301: A Phase 3 Trial of Enfortumab Vedotin vs Chemotherapy in Patients With Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

Thomas Powles, MD[1a]; Jonathan E Rosenberg, MD[2a]; Guru P Sonpavde, MD[3]; Yohann Loriot, MD, PhD[4]; Ignacio Durán, MD, PhD[5]; Jae-Lyun Lee, MD, PhD[6]; Nobuaki Matsubara, MD[7]; Christof Vulsteke, MD, PhD[8]; Chunzhang Wu, PhD[9]; Mary Campbell, MD[10]; Maria Matsangou, MBChB, MD[9]; Daniel P Petrylak, MD[11]

[1]Barts Cancer Centre, Queen Mary University of London, London, United Kingdom; [2]Memorial Sloan Kettering Cancer Center, New York City, NY, USA; [3]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [4]Gustave Roussy, Université Paris-Saclay, Villejuif, France; [5]Hospital Universitario Marques de Valdecilla, IDIVAL, Cantabria, Spain; [6]Asan Medical Center and University of Ulsan College of Medicine, Seoul, South Korea; [7]National Cancer Center Hospital East, Chiba, Japan; [8]Center for Oncological Research (CORE), University of Antwerp, Integrated Cancer Center Ghent, Ghent, Belgium; [9]Astellas Pharma, Inc., Northbrook, IL, USA; [10]Seagen Inc., Bothell, WA, USA; [11]Smilow Cancer Center, Yale School of Medicine, New Haven, CT, USA

[a]Dual first authorship; Drs. Powles and Rosenberg contributed equally to this presentation.

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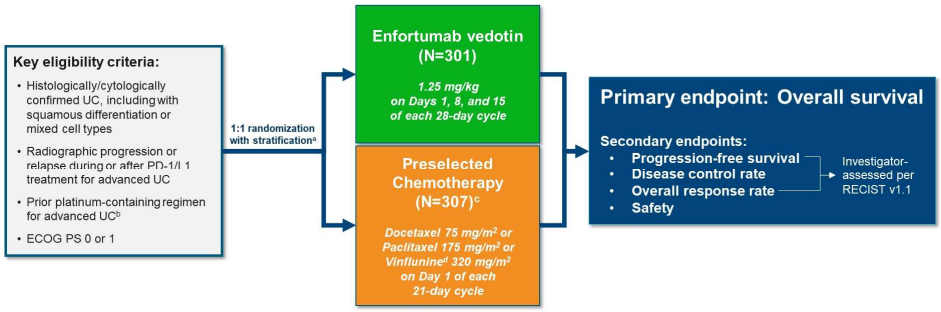
EV-301 Open-Label Phase 3 Trial Design



[a]Stratification variables were ECOG performance status (0 or 1), regions of the world (United States, western Europe, or rest of world), liver metastasis (yes or no).
[b]If used in the adjuvant/neoadjuvant setting, progression must be within 12 months of completion.
[c]Investigator selected prior to randomization.
[d]In countries where approved; overall proportion of patients receiving vinflunine capped at 35%.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1/L1, programmed cell death protein-1/programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; UC, advanced urothelial carcinoma.

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Results – Demographics and Disease Characteristics

Parameter		Enfortumab Vedotin N=301	Chemotherapy N=307
Age, median		68 years	68 years
Male sex		79%	76%
Geographic region	Western Europe	42%	42%
	United States	14%	14%
	Rest of the world	44%	44%
ECOG performance status[b]	0	40%	40%
	1	60%	60%
Bellmunt risk score	0-1	67%	68%
	≥2	30%	31%
Liver metastasis[a]		31%	31%
Prior lines of systemic therapy	1-2	87%	88%
	≥3	13%	12%
Response to prior CPI		20%	16%

[a]Indicates stratification variables: ECOG performance status (0 or 1), regions of the world (US, western Europe, or rest of world), liver metastasis (yes or no).
Abbreviations: CPI, checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group.

Data cut-off: July 15, 2020

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Results – Patient Disposition

Parameter	Enfortumab Vedotin N=301	Chemotherapy N=307
Deaths at the data cut-off date[a]	n=134	n=167
Received study treatment	98%	95%
Median treatment exposure, months (range)	5.0 (0.5, 19.4)	3.5 (0.2, 15.0)
Median follow-up, months (95% CI)	11.1 (10.4, 11.9)	11.1 (10.0, 12.1)
Treatment discontinuation[b]	81%	93%
Progressive disease	59%	59%
Adverse event[c]	14%	15%
Withdrawal by patient	5%	9%
Physician decision	2%	7%

[a]A total of 301 deaths had occurred as of data cut-off date.
[b]Displaying reasons for treatment discontinuation occurring in ≥5% in either arm. Additional reasons for treatment discontinuation in EV vs chemotherapy arms included: death 0.7% vs 0.7%, protocol deviation 0.3% vs 0.3%; loss to follow-up 0% vs 0.3%; other 0.3% vs 2%.
[c]Represents treatment-emergent adverse events leading to treatment discontinuation.
Abbreviations: CI, confidence interval.

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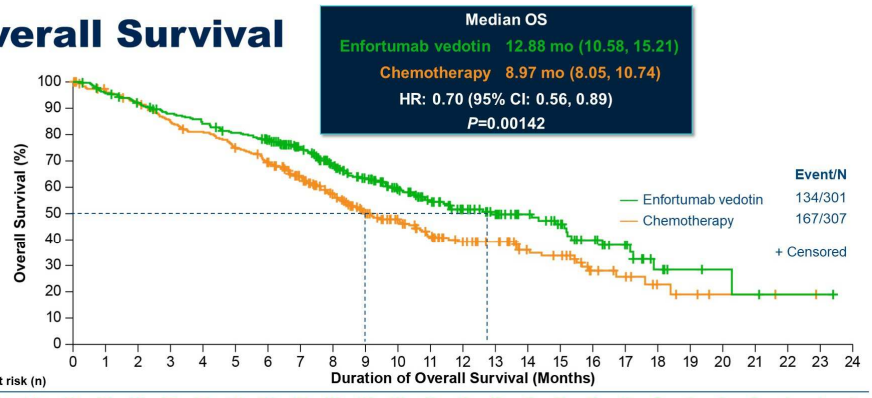
Overall Survival



Patients at risk (n)

Enfortumab vedotin	301	286	272	257	246	234	222	190	158	130	105	85	63	52	42	33	23	15	7	4	3	2	1	1	0
Chemotherapy	307	288	274	250	238	219	198	163	131	101	84	66	51	44	32	29	16	11	6	4	2	2	1	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

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Overall Survival: Subgroup Analyses

		HR (95% CI)	Enfortumab vedotin (Event/N)	Chemotherapy (Event/N)
All subjects		0.70 (0.56, 0.89)	134/301	167/307
Age, group 1	<65 years	0.68 (0.47, 0.99)	49/108	66/111
	≥65 years	0.75 (0.56, 1.00)	85/193	101/196
Sex	Male	0.61 (0.47, 0.79)	101/238	132/232
	Female	1.17 (0.72, 1.89)	33/63	35/75
Region	W Europe	0.76 (0.53, 1.07)	57/126	72/129
	US	0.88 (0.51, 1.54)	25/43	25/44
	Rest of World	0.64 (0.45, 0.92)	52/132	70/134
ECOG PS	0	0.81 (0.53, 1.24)	40/120	46/124
	1	0.67 (0.51, 0.87)	94/181	121/183
Liver metastasis	Yes	0.66 (0.46, 0.96)	53/93	63/95
	No	0.73 (0.55, 0.98)	81/208	104/212
Pre-selected control therapy	Paclitaxel	0.71 (0.49, 1.01)	63/141	59/112
	Docetaxel	0.71 (0.48, 1.04)	41/87	67/117
	Vinflunine	0.77 (0.48, 1.24)	30/73	41/78
Primary site of tumor	Upper tract	0.85 (0.57, 1.27)	44/98	52/107
	Bladder/other	0.67 (0.51, 0.88)	90/203	115/200
Prior lines of systemic therapy	1-2	0.69 (0.54, 0.88)	115/262	147/270
	≥3	0.88 (0.47, 1.64)	19/39	20/37
Best response to prior CPI	Responder	0.63 (0.34, 1.17)	18/61	23/50
	Non-responder	0.76 (0.58, 0.99)	100/207	120/215

Abbreviations: CI, confidence interval; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; US, United States; W, western.

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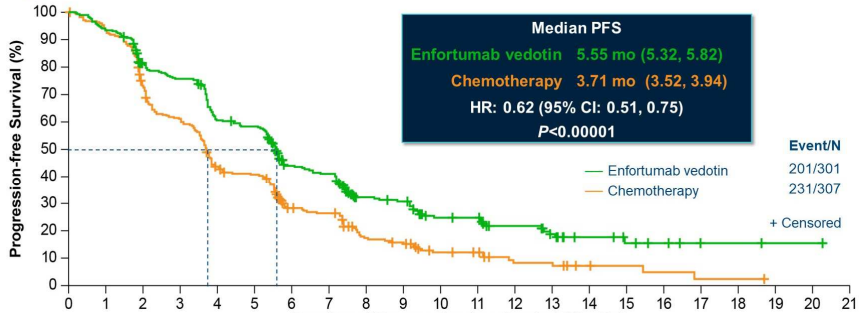
Progression-free Survival



Patients at risk (n)

Enfortumab vedotin	301	269	224	208	165	158	102	95	60	56	38	36	23	17	11	7	5	2	2	1	1	0
Chemotherapy	307	259	200	166	116	107	62	57	33	29	18	16	8	8	4	3	2	1	0	0	0	0

Evaluated in the intent-to-treat population.
Abbreviations: CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Data cut-off: July 15, 2020

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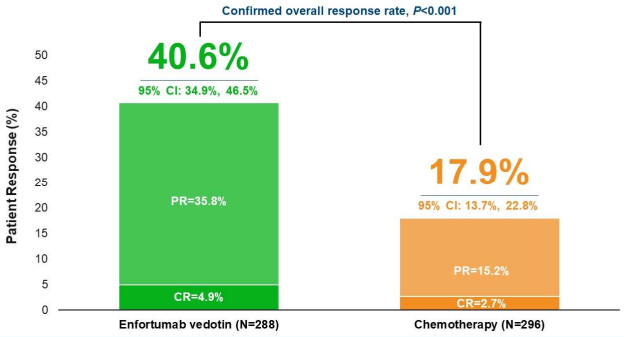
Investigator-Assessed Overall Response



Disease control rate,[a] % (95% CI)	71.9 (66.3, 77.0)	53.4 (47.5, 59.2)	*P*<0.001

Evaluated in the response-evaluable population. Response is as assessed by the investigator per RECIST v1.1.
[a]Indicates the proportion of patients who had a best overall response of confirmed CR, PR, or SD (at least 7 weeks); enfortumab vedotin vs chemotherapy.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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Treatment-Related Adverse Events

Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any adverse event	**94%**	**51%**	**92%**	**50%**
Alopecia	45%	0	36%	0
Peripheral sensory neuropathy	34%	3%	21%	2%
Pruritus	32%	1%	4%	0
Fatigue	31%	6%	23%	4%
Decreased appetite	31%	3%	23%	2%
Diarrhea	24%	3%	16%	2%
Dysgeusia	24%	0	7%	0
Nausea	23%	1%	22%	1%
Rash maculopapular	16%	7%	2%	0
Anemia	12%	3%	20%	8%
Neutrophil count decreased	10%	6%	17%	13%
Neutropenia	7%	5%	8%	6%
White blood cell decreased	5%	1%	11%	7%
Febrile neutropenia	1%	1%	5%	5%
Serious adverse events[a]	23%	-	23%	-
Leading to treatment withdrawal	14%	-	11%	-

TRAEs leading to death, excluding disease progression, occurred in 7 patients (2.4%) treated with EV and 3 (1.0%) treated with chemotherapy.

Evaluated in the safety population; displaying adverse events (AEs) occurring in ≥20% or grade ≥3 AEs occurring in ≥5% of patients in either treatment group. Dashes indicate 'not applicable.'
Treatment-related AEs are events with a reasonable possibility of relationship to treatment (investigator-assessed) or missing relationship and are not time-adjusted.
This slide contains updated data in the chemotherapy arm to adjust for compounded rounding.
[a]AEs that were deemed "serious" in the view of the investigator or sponsor and based upon predefined criteria.
Abbreviations: AE, adverse event; EV, enfortumab vedotin; TRAEs, treatment-related adverse events.

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Adverse Events of Special Interest

Treatment-Related Adverse Event	Enfortumab Vedotin N=296		Chemotherapy N=291	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Skin Reactions[a]	**47%**	**15%**	**16%**	**1%**
Rash	44%	15%	10%	0[c]
Severe cutaneous adverse reactions[b]	20%	5%	8%	1%
Peripheral neuropathy	**46%**	**5%**	**31%**	**2%**
Sensory events	44%	4%	30%	2%
Motor events	7%	2%	2%	0
Hyperglycemia	**6%**	**4%**	**0[c]**	**0**

The majority of TRAEs of special interest were mild-to-moderate in severity.

Evaluated in the safety population; displaying selected TRAEs of special interest to EV. Differences between AE rates in current and prior slide may be due to preferred term groupings.
TRAE are events with a reasonable possibility of relationship to study treatment as assessed by the investigator or missing relationship.
[a]Encompasses rash and severe cutaneous adverse reactions.
[b]Severe cutaneous adverse reactions included the following (by Preferred Term): stomatitis, drug eruption, conjunctivitis, blister, dermatitis bullous, skin exfoliation, erythema multiforme, exfoliative rash, fixed eruption, mouth ulceration, pemphigus, and toxic skin eruption.
[c]One patient had the TRAE that is listed.
Abbreviations: EV, enfortumab vedotin; TRAE, treatment-related adverse event.

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EV-301: Conclusions

Efficacy

Enfortumab vedotin had superior overall survival compared with chemotherapy in patients with advanced UC who had previously received platinum-based chemotherapy and a PD-1/L1 inhibitor

- Enfortumab vedotin showed superior progression-free survival and response rates compared with chemotherapy
- Subgroup analyses also broadly showed benefit in the enfortumab vedotin arm
- Results were consistent with phase 1 and 2 studies

Safety

Enfortumab vedotin demonstrated a tolerable and manageable safety profile

- No new safety signals were identified; safety profile was consistent with prior enfortumab vedotin studies
- Adverse events of special interest (eg, skin reactions, peripheral neuropathy, and hyperglycemia) were generally mild/moderate in severity and consistent with those reported in prior studies

Overall

Enfortumab vedotin is the first drug, beyond chemotherapy and immunotherapy, to show significant survival advantage in previously treated advanced UC

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EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors (NCT03219333)

Arjun V. Balar, Bradley McGregor, Jonathan Rosenberg, Michiel S. van der Heijden, Se Hoon Park, Jae Lyun Lee, Michael R. Harrison, Elisabeth I. Heath, Mark N. Stein, Yohann Loriot, Andrea Necchi, Joyce Steinberg, Shang-Ying Liang, Eric Kim, Janet Trowbridge, Mary Campbell, Daniel P. Petrylak, and Evan Y. Yu

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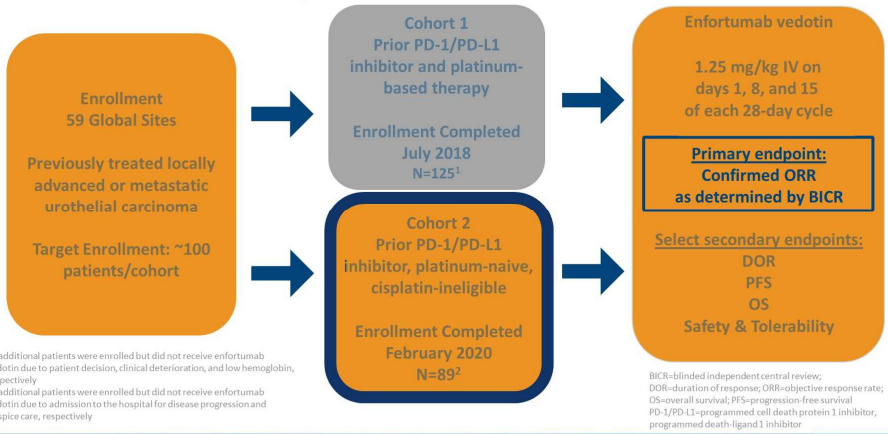
EV-201: Non-Comparative, Pivotal Phase 2 Trial



[1]3 additional patients were enrolled but did not receive enfortumab vedotin due to patient decision, clinical deterioration, and low hemoglobin, respectively
[2]2 additional patients were enrolled but did not receive enfortumab vedotin due to admission to the hospital for disease progression and hospice care, respectively

BICR=blinded independent central review; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival
PD-1/PD-L1=programmed cell death protein 1 inhibitor, programmed death-ligand 1 inhibitor

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EV-201 Cohort 2: Key Eligibility Criteria

- Key inclusion criteria:
  - Locally advanced unresectable or metastatic urothelial carcinoma (including divergent differentiation)
  - Previously treated with a PD-1/PD-L1 inhibitor
  - Ineligible for cisplatin-containing chemotherapy[1] and no prior exposure to platinum-containing chemotherapy in the locally advanced or metastatic setting
  - Progression during or following most recent treatment
- Key exclusion criteria:
  - Ongoing sensory or motor neuropathy ≥Grade 2
  - Active CNS metastases
  - Uncontrolled diabetes mellitus[2]

[1] Defined as meeting any of the following criteria: impaired renal function ([CrCl] ≥30 and <60 mL/min), hearing loss ≥Grade 2, ECOG performance status score >2
[2] Hemoglobin A1C (HbA1c) ≥8% or HbA1c of 7% to <8% with associated diabetes symptoms, polyuria or polydipsia, that were not otherwise explained

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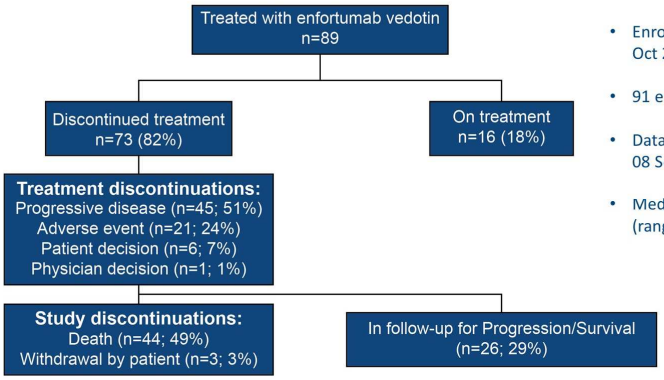
EV-201 Cohort 2: Patient Disposition



- Enrollment from Oct 2017 to Feb 2020
- 91 enrolled[1]
- Data Cutoff date for Primary Analysis: 08 Sept 2020
- Median time on treatment: 6 months (range 0.3-24.6 months)

[1] 2 patients did not receive enfortumab vedotin treatment due to admission to the hospital for disease progression and pursuing hospice care, respectively

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EV-201 Cohort 2: Key Demographics and Disease Characteristics

Characteristic	Patients (N=89)	Characteristic	Patients (N=89)
Median age (range), years	75 (49, 90)	Primary tumor location	
Male sex	66 (74%)	Upper tract[1]	38 (43%)
ECOG performance status		Bladder/other	51 (57%)
0 or 1	78 (88%)	Metastasis sites	
2	11 (12%)	Lymph nodes only	18 (20%)
Body mass index ≥30 kg/m^2	13 (15%)	Visceral disease[2]	70 (79%)
Renal function based on creatinine clearance		Liver	21 (24%)
Normal/Mild decrease ≥60 mL/min	27 (30%)	Received prior PD-1/PD-L1 therapy in first line	87 (98%)
Moderate decrease: ≥30 and <60 mL/min	60 (67%)	Responder[3] to PD-1/PD-L1-containing therapy	22 (25%)
Severe decrease: ≥15 and <30 mL/min	2 (2%)		

[1]Includes renal pelvis and ureter.
[2]Sites of visceral disease include liver, lung, intra-thoracic or intra-abdominal soft tissue, kidney, spleen, ovary, adrenal glands, and bone.
[3]Responses were investigator reported.

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EV-201 Cohort 2: Best Overall Response per BICR

ORR per RECIST v 1.1 assessed by BICR	Patients (N=89) %
Confirmed ORR, 95% CI[1]	52 (40.8, 62.4)
Best overall response[2]	
Confirmed complete response	20
Confirmed partial response	31
Stable disease	30
Progressive disease	9
Not evaluable[3]	9

ORR = Objective Response Rate; RECIST = Response Evaluation Criteria in Solid Tumors; BICR = Blinded Independent Central Review
[1]CI = Confidence Interval, Computed using the Clopper-Pearson method
[2]Best overall response according to RECIST v1.1. Complete response and partial response were confirmed with repeat scans ≥28 days after initial response.
[3]Includes five subjects who did not have response assessment post-baseline, two subjects whose post-baseline assessment did not meet the minimum interval requirement for stable disease, and one subject whose response cannot be assessed due to incomplete anatomy.

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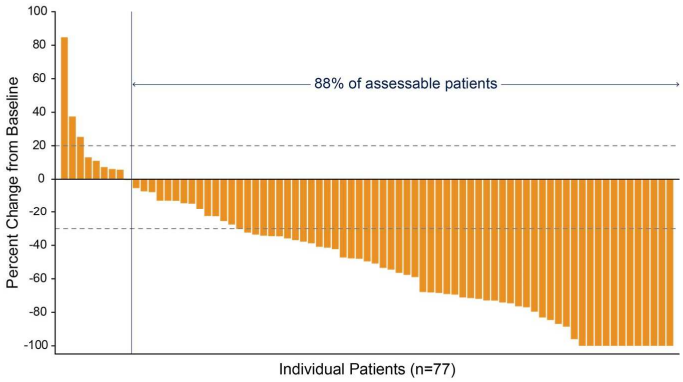
EV-201 Cohort 2: Change in Tumor Measurements per BICR



Data are not available for 12 subjects due to no response assessment post-baseline (n=5), incomplete assessment of target lesions post-baseline (n=1), or no measurable disease at baseline per BICR (n=6).

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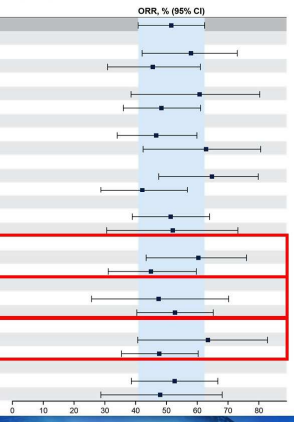
EV-201 Cohort 2: Responses by Subgroup per BICR

Subjects (N=89)

Subgroup	n/N	% (95% CI)
Overall	46/89	52 (40.8, 62.4)
Age		
<75 years	25/43	58 (42.1, 73)
≥75 years	21/46	46 (30.9, 61)
Sex		
Female	14/23	61 (38.5, 80.3)
Male	32/66	48 (36, 61.1)
Race		
White	29/62	47 (34, 59.9)
Non-white	17/27	63 (42.4, 80.6)
ECOG PS		
0	24/37	65 (47.5, 79.8)
1–2	22/52	42 (28.7, 56.8)
Bellmunt risk score		
0–1	34/66	52 (38.9, 64)
≥2	12/23	52 (30.6, 73.2)
Primary tumor sites		
Upper tract	23/38	61 (43.4, 76)
Bladder/Other	23/51	45 (31.1, 59.7)
Liver metastasis		
Yes	10/21	48 (25.7, 70.2)
No	36/68	53 (40.4, 65.2)
Best response to prior CPI		
Responder	14/22	64 (40.7, 82.8)
Non-responder	32/67	48 (35.4, 60.3)
PD-L1 expression		
CPS <10	28/53	53 (38.6, 66.7)
CPS ≥10	13/27	48 (28.7, 68.1)



Responses were observed across all subgroups, including patients:

- with primary tumor sites in the upper tract (ORR=61%)
- with liver metastasis (ORR=48%)
- who did not respond to prior PD-1/PD-L1 inhibitors (ORR=48%)

BICR = Blinded Independent Central Review; ORR = Objective Response Rate; ECOG PS= Eastern Cooperative Oncology Group Performance Score; CPI = Checkpoint Inhibitor; PD-1 = programmed cell death protein 1 inhibitor; PD-L1 = programmed death-ligand 1; CPS = combined positive score

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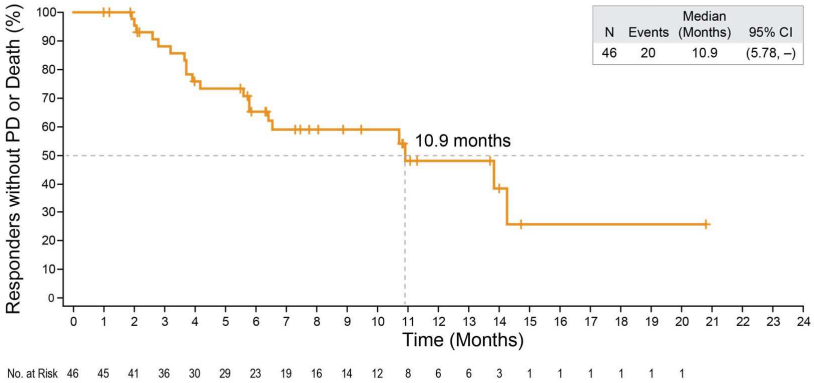
EV-201 Cohort 2: Duration of Response per BICR



BICR = Blinded Independent Central Review; PD = Progressive Disease; CI = Confidence Interval

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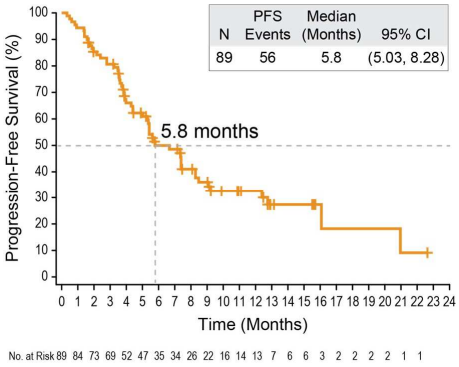
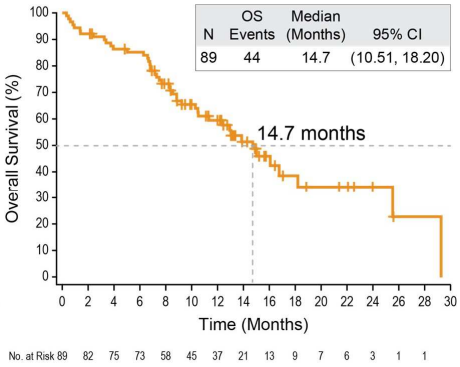
EV-201 Cohort 2: Progression-Free Survival and Overall Survival





Median follow-up: 13.4 months

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EV-201 Cohort 2: Treatment-Related Adverse Events

TRAEs[1] in ≥20% of patients (any Grade) or ≥5% (≥Grade 3)	Patients (N=89) n (%)	
	Any Grade	≥Grade 3
Overall TRAEs	86 (97)	49 (55)
Alopecia	45 (51)	–
Peripheral sensory neuropathy	42 (47)	3 (3)
Fatigue	30 (34)	6 (7)
Decreased appetite	29 (33)	5 (6)
Pruritus	27 (30)	3 (3)
Rash maculo-papular	27 (30)	7 (8)
Dysgeusia	24 (27)	–
Weight decreased	23 (26)	1 (1)
Anemia	22 (25)	5 (6)
Diarrhea	20 (22)	5 (6)
Nausea	20 (22)	1 (1)
Neutropenia	11 (12)	8 (9)
Hyperglycemia	8 (9)	5 (6)
Lipase increased	7 (8)	5 (6)

TRAEs led to discontinuations in 16% of patients
- Peripheral sensory neuropathy was the most common reason (4%)

4 deaths considered to be treatment related by the investigator:
- acute kidney injury
- metabolic acidosis
- multiple organ dysfunction syndrome
- pneumonitis (occurred >30 days of last dose)

3 of these deaths occurred within 30 days of first dose of EV occurred in patients with BMI ≥30 kg/m^2

All 4 deaths: confounded by age (≥75 years) and other comorbidities

[1]Treatment-related Adverse Events

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EV-201 Cohort 2: Treatment-Related Adverse Events of Special Interest

Events categorized based on queries for related MedDRA[1] terms

Skin Reactions
61% any grade, 17% ≥Grade 3
Median Onset = 0.5 months[2]
% resolution/improvement[3] = 80%

- No Grade 5 events, 1 Grade 4 event
- 13 patients with severe cutaneous adverse reactions[4]
  - Most ≤Grade 2, no Grade 4 or 5 events
  - 4 patients with Grade 3 events: stomatitis, skin exfoliation, dermatitis bullous, dermatitis exfoliative generalised
  - 1 discontinuation due to severe cutaneous adverse reaction

Peripheral Neuropathy
54% any grade, 8% ≥Grade 3
Median Onset = 2.4 months
% resolution/improvement[3] = 56%

- PN rate was similar in patients with and without pre-existing PN (53% vs 54%)

Hyperglycemia
10% any grade, 6% ≥Grade 3
Median Onset = 0.5 months[2]
% resolution/improvement[3] = 89%

- Higher rate of HG in patients with pre-existing HG than those without pre-existing HG (20% vs. 7%)
- Higher rate of HG in patients with BMI ≥30 kg/m^2 than those with BMI <30 kg/m^2 (23% vs. 8%)

PN = Peripheral Neuropathy; HG = Hyperglycemia; BMI = Body Mass Index
[1]Medical Dictionary for Regulatory Activities
[2]Most occurred in Cycle 1
[3]Resolution/Improvement as of last follow-up
[4]A range of skin reaction preferred terms, irrespective of grade

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EV-201 Cohort 2: Summary and Conclusions

- Following immunotherapy, cisplatin-ineligible patients need effective treatment options
- The response rates to EV in this study are numerically the highest observed for any regimen in cisplatin-ineligible patients with advanced urothelial carcinoma
  - 52% ORR, with 20% CR rate
  - 10.9 months median duration of response
  - Response rates were consistent across all subgroups
- Tolerable safety profile in an elderly patient population ineligible for cisplatin
- Activity demonstrated in EV-201 Cohort 2 builds upon the overall survival benefit shown in PD-1/PD-L1 inhibitor and platinum-treated patients in EV-301
- These data support continued investigation of EV across the spectrum of urothelial carcinoma and may support a new standard of care for this population with unmet need

ORR = Objective Response Rate; CR = Complete Response
Ongoing enfortumab vedotin trials: **EV-103:** EV alone or in combination with pembrolizumab and/or chemotherapy (NCT03288545) **EV-302:** EV in combination with pembrolizumab vs. chemotherapy alone (NCT04223856)

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original reports

TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitor

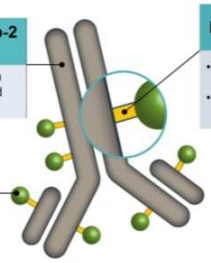
Scott T. Tagawa, MD, MS[1]; Arjun V. Balar, MD[2]; Daniel
Aude Fléchon, MD, PhD[6]; Rohit K. Jain, MD[7]; Neeraj A
Philippe Beuzeboc, MD, PhD[11]; Philip Palmbos, MD,
Cora N. Sternberg, MD[1]; Quan Hong, MD[15]; Trishna G

Sacituzumab Govitecan (SG) Is a Trop-2–Directed Antibody-Drug Conjugate (ADC)

- Trop-2 is an epithelial cell surface antigen highly expressed in UC[1]
- SG is distinct from other ADCs[2-6]:
  - High drug-to-antibody ratio[5]
  - Linker hydrolysis releases SN-38 intracellularly and in the tumor microenvironment[6a]
- SG has shown significant activity across tumor types[3,7-10]
  - Breakthrough therapy designation for mTNBC; accelerated approval submission pending
  - Phase 3 trials ongoing in breast cancer

Humanized Anti-Trop-2 Antibody (hRS7)
- Directed towards Trop-2, an epithelial antigen expressed on many solid tumors

SN-38 Payload
- Metabolite of topoisomerase I inhibitor
- SN-38 more potent than parent compound, irinotecan



Linker for SN-38
- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.6:1)[5]

*Sacituzumab govitecan–bound tumor cells are killed by intracellular uptake of SN-38, and adjacent tumor cells are killed by SN-38 released extracellularly.

mTNBC, metastatic triple-negative breast cancer; pts, patients; Trop-2, trophoblast cell surface antigen 2; UC, urothelial cancer. 1. Avellini et al. *Oncotarget* 2017; 2. Starodub et al. *Clin Cancer Res* 2015; 3. Cardillo et al. *Clin Cancer Res*. 2011; 4. Sharkey et al. *Clin Cancer Res*. 2015; 5. Cardillo et al. *Bioconjugate Chem*. 2015; 6.Govindan et al. *Mol Cancer Ther*. 2013; 7. Faltas et al. *Clin Genitourin Cancer*. 2016; 8. Bardia et al. *J Clin Oncol*. 2017; 9. Bardia et al. *N Engl J Med*. 2019; 10. Tagawa et al. *J Clin Oncol*. 2019.

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4

TROPHY-U-01 Cohort 1 Final Results

TROPHY-U-01 Study Design

TROPHY U-01

Cohort 1 (100 pts): pts with mUC who progressed after prior platinum-based and CPI-based therapies

SG 10 mg/kg → Days 1 and 8, every 21 days

Cohort 2 (40 pts): pts with mUC ineligible for platinum-based therapy and who progressed after prior CPI-based therapies[1]

Cohort 3 (up to 61 pts): mUC CPI-naïve pts who progressed after prior platinum-based therapies

SG days 1 and 8, every 21 days → Pembrolizumab 200 mg day 1, every 21 days

Continue treatment until loss of clinical benefit or unacceptable toxicity

Primary objective:
- ORR by central review

Secondary objectives:
- Safety/tolerability
- DOR
- PFS
- OS

CPI therapy (includes anti-PD-1/anti-PD-L1-based therapies).
CPI, immune checkpoint inhibitor; DOR, duration of response; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; SG, sacituzumab govitecan.
EudraCT Number: 2018-001167-23; ClinicalTrials.gov Number: NCT03547973; IMMU-132-06 study.
1. Petylak, DP et al. J Clin Oncol. 2020;38(suppl), abstract 5027.

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https://www.cua.org/sites/default/files/Flipbooks/CPD/ESMO2020/mobile/index.html#p=39

TROPHY-U-01 Cohort 1 Final Results

Response Assessments

Endpoint	Cohort 1 (N=113)
ORR, n (%) [95% CI]	**31 (27) [19, 37]**
CR, n (%)	6 (5)
PR, n (%)	25 (22)
Median duration of response, mos [95% CI] (Range)	**5.9** [4.70, 8.60] (1.4–11.7)
Median time to onset of response, mos (Range)	1.6 (1.2–5.5)

- ORR, median DOR, and median TTR values were consistent with investigator assessments

[1]Assessments were per Blinded Independent Review Assessment, RECIST 1.1.
CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; TTR, time to response.

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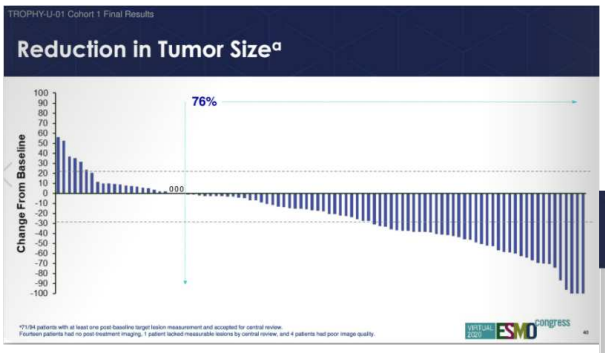

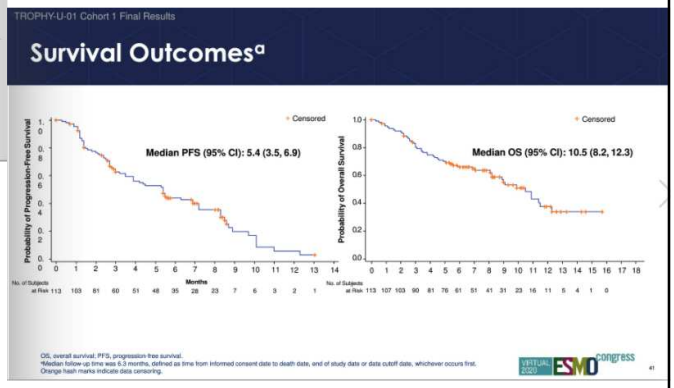

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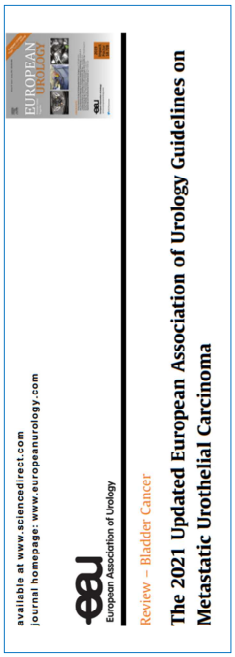


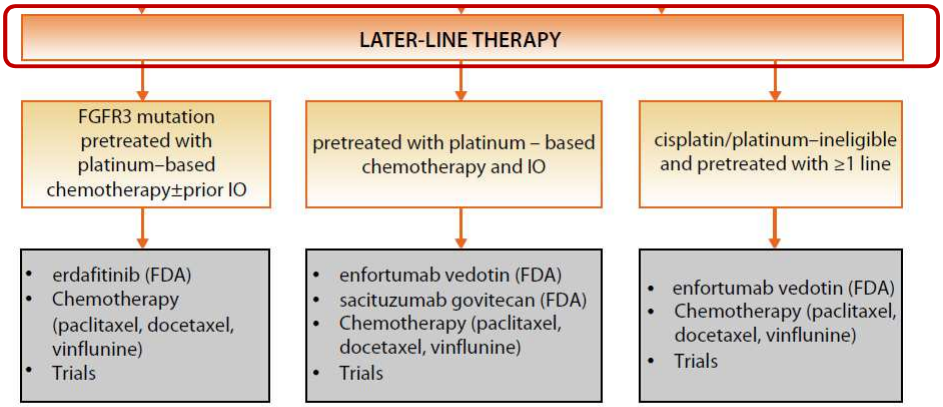
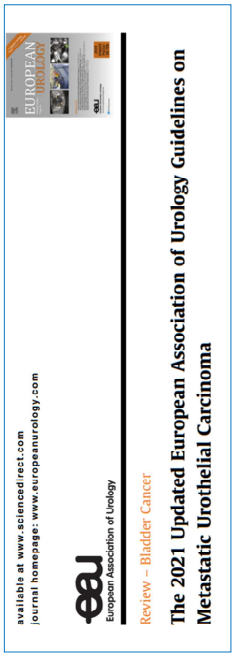


Fig. 1 – Flowchart for the management of metastatic urothelial carcinoma. Treatment within clinical trials is highly encouraged. CR = complete response; DD-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; IO = immunotherapy; PD = progressive disease; PD-L1 = programmed death ligand 1; PR = partial response; PS = performance status; SD = stable disease.



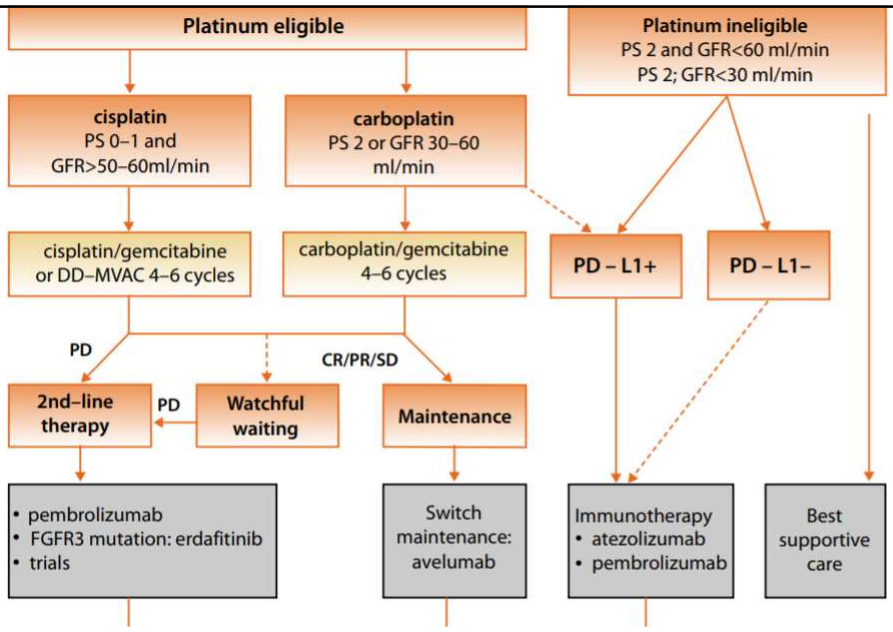


Fig. 1 – Flowchart for the management of metastatic urothelial carcinoma. Treatment within clinical trials is highly encouraged. CR = complete response; DD-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; IO = immunotherapy; PD = progressive disease; PD-L1 = programmed death ligand 1; PR = partial response; PS = performance status; SD = stable disease.

KARCINOM LEDVIČNIH CELIC (RCC)

- **DOPOLNILNO ZDRAVLJENJE**
  - **Keynote 564 (pembrolizumab)**
- **METASTATSKA BOLEZEN**
  - **CLEAR (Lenvatinib+pembrolizumab)**

UVODNA DEJSTVA

65% bolnikov ima primarno lokaliziran RCC, 16% lokalno napredovalo bolezen
40%-50% bolnikov po uspešnem operativnem zdravljenju razvije razsejano bolezen

- Prve raziskave adjuvantnega zdravljenja RCC so vključevale IF vs placebo / opazovanje v različnih odmerkih in različnih časovnih režimih – negativne študije
- Priključitev IL-2 – negativni rezultati

- Adjuvantne študije s TKI
  - ASSURE (sunitinib)
  - PROTECT (pazopanib)
  - ATLAS (axitinib)

  NEGATIVNO
  - S-TRAC (sunitinib) POZITIVNO - primarni cilj DFS 6.8 let sunitinib / 5.6 let placebo (HR 0.76, p=0.03)

Raziskava S-TRACK

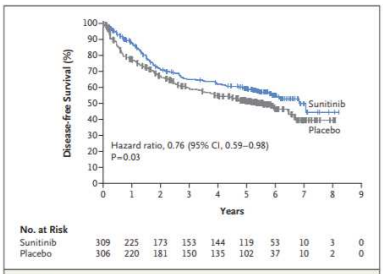


Figure 2. Disease-free Survival.
The median duration of disease-free survival according to independent central review was 6.8 years (95% confidence interval [CI], 5.8 to not reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group. At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group.

Table 3. Adverse Events (Safety Population).*

Event	Sunitinib (N=306)			Placebo (N=304)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	305 (99.7)	148 (48.4)	37 (12.1)	269 (88.5)	48 (15.8)	11 (3.6)
Diarrhea	174 (56.9)	12 (3.9)	0	65 (21.4)	1 (0.3)	0
Palmar–plantar erythrodysesthesia	154 (50.3)	46 (15.0)	3 (1.0)	31 (10.2)	1 (0.3)	0
Hypertension	113 (36.9)	24 (7.8)	0	36 (11.8)	3 (1.0)	1 (0.3)
Fatigue	112 (36.6)	13 (4.2)	2 (0.7)	74 (24.3)	4 (1.3)	0

FDA odobreno dopolnilno zdravljenje – v praksi ni nikoli zaživelo

N Engl J Med 2016;375:2246-54.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2021 VOL. 385 NO. 8

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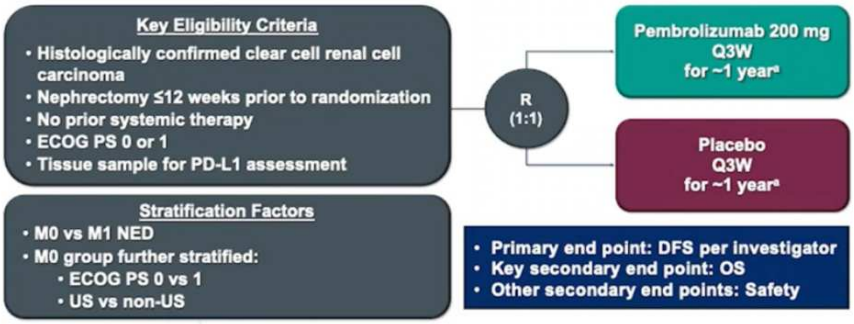
KEYNOTE-564 is a phase III multicenter trial of pembrolizumab versus placebo in patients with histologically confirmed ccRCC. Risk groups were defined as follows:

- Intermediate-high risk disease: pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0 M0
- High-risk disease: pT4, any grade, N0 M0; or pT any stage, any grade, N+ M0
- M1 no evidence of disease: primary tumor + soft tissue metastases completely resected ≤1 year from nephrectomy



https://www.urotoday.com/conference-highlights/eau-2021/eau-2021-kidney-cancer/130671-eau-2021-pembrolizumab-vs-placebo-as-post-nephrectomy-adjuvant-therapy-for-patients-with-rcc-randomized-double-blind-phase-3-keynote-564-study.html

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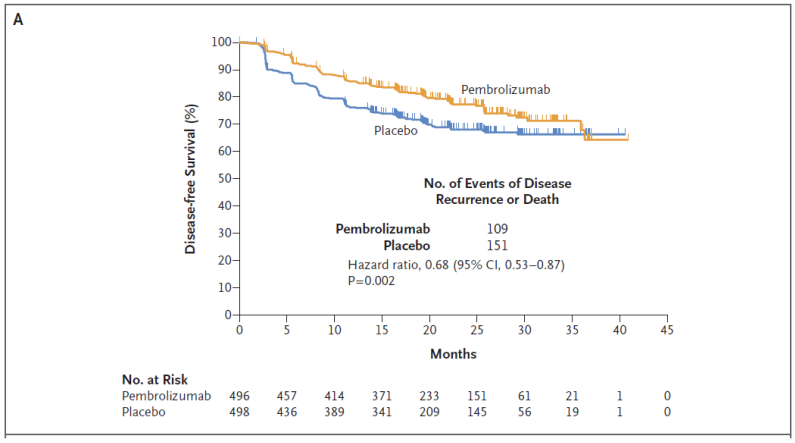

N Engl J Med 2021;385:683-94

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B

Subgroup	No. of Events/No. of Patients	Hazard Ratio for Recurrence or Death (95% CI)
Overall	260/994	0.68 (0.53–0.87)
Age		
<65 yr	166/664	0.62 (0.45–0.84)
≥65 yr	94/330	0.84 (0.56–1.26)
Sex		
Female	79/288	0.75 (0.48–1.16)
Male	181/706	0.66 (0.49–0.89)
ECOG performance-status score		
0	215/847	0.65 (0.49–0.85)
1	45/147	0.91 (0.50–1.63)
PD-L1 combined positive score		
<1	42/237	0.83 (0.45–1.51)
≥1	215/748	0.67 (0.51–0.88)
Geographic region		
North America	65/258	0.87 (0.53–1.41)
European Union	97/375	0.49 (0.32–0.74)
Rest of the world	98/361	0.81 (0.55–1.21)
Metastatic staging		
M0	234/936	0.74 (0.57–0.96)
M1 NED	26/58	0.29 (0.12–0.69)
Type of nephrectomy		
Partial	10/75	0.22 (0.05–1.04)
Radical	250/919	0.72 (0.56–0.93)

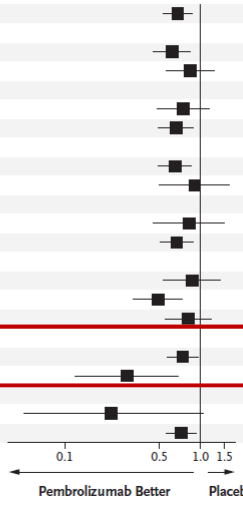

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Table 2. Any-Cause and Treatment-Related Adverse Events (As-Treated Population).*

Event	Pembrolizumab (N=488)	Placebo (N=496)
	no. of patients with event (%)	
Any-cause adverse events		
Adverse event of any grade	470 (96.3)	452 (91.1)
Adverse event of grade 3 to 5	158 (32.4)	88 (17.7)
Discontinuation of pembrolizumab or placebo due to adverse event	101 (20.7)	10 (2.0)
Death due to adverse event	2 (0.4)	1 (0.2)
Serious adverse event	100 (20.5)	56 (11.3)
Discontinuation of pembrolizumab or placebo due to serious adverse event	49 (10.0)	5 (1.0)
Treatment-related adverse events, as assessed by investigator		
Adverse event of any grade	386 (79.1)	265 (53.4)
Adverse event of grade 3 to 5	92 (18.9)	6 (1.2)
Discontinuation of pembrolizumab or placebo due to adverse event	86 (17.6)	3 (0.6)
Death due to adverse event	0	0
Serious adverse event	59 (12.1)	1 (0.2)
Discontinuation of pembrolizumab or placebo due to serious adverse event	37 (7.6)	0

* The as-treated population included all the patients who received at least one dose of pembrolizumab or placebo. Adverse events were recorded from randomization through 30 days after the discontinuation of pembrolizumab or placebo. Serious adverse events were defined as any adverse event that resulted in death, was life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was judged by the investigator to be a serious adverse event. Serious adverse events were recorded from randomization through 90 days after the discontinuation of pembrolizumab or placebo.

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Table 3. Any-Cause Adverse Events with an Incidence of at Least 10% in Either Group (As-Treated Population).*

Event	Pembrolizumab (N=488)		Placebo (N=496)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
Fatigue	145 (29.7)	5 (1.0)	120 (24.2)	0
Diarrhea	124 (25.4)	8 (1.6)	111 (22.4)	1 (0.2)
Pruritus	111 (22.7)	1 (0.2)	65 (13.1)	0
Arthralgia	108 (22.1)	2 (0.4)	93 (18.8)	2 (0.4)
Hypothyroidism	103 (21.1)	1 (0.2)	18 (3.6)	0
Rash	98 (20.1)	4 (0.8)	53 (10.7)	2 (0.4)
Nausea	80 (16.4)	2 (0.4)	48 (9.7)	0
Cough	76 (15.6)	0	50 (10.1)	0
Headache	69 (14.1)	0	62 (12.5)	0
Hyperthyroidism	58 (11.9)	1 (0.2)	1 (0.2)	0
Asthenia	50 (10.2)	1 (0.2)	36 (7.3)	1 (0.2)
Increase in blood creatinine level	50 (10.2)	1 (0.2)	42 (8.5)	0
Back pain	49 (10.0)	1 (0.2)	64 (12.9)	1 (0.2)

* No adverse events of grade 4 or 5 occurred in at least 10% of the patients in either group.

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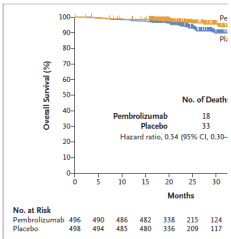

Figure 2. Overall Survival (Intention-to-Treat Population).
Shown are the Kaplan–Meier estimates of overall survival. sent data censored at the last time the patient was known

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https://www.urotoday.com/conference-highlights/eau-2021/eau-2021-kidney-cancer/130671-eau-2021-pembrolizumab-vs-placebo-as-post-nephrectomy-adjuvant-therapy-for-patients-with-rcc-randomized-double-blind-phase-3-keynote-564-study.html

Table 1 – First-line immune checkpoint inhibitor combination trials for clear-cell RCC[a]

Study	N	Experimental arm	Primary endpoint	Risk groups	Median PFS, mo (95% CI)	Median OS, mo (95% CI)
KEYNOTE-426 **NCT02853331** **Median follow-up 30.6 mo** [3,5]	861	Pembrolizumab 200 mg, IV Q3W plus axitinib 5 mg, PO BID vs. sunitinib 50 mg PO QD 4/2 wk	PFS and OS in the ITT by BICR	**IMDC** FAV 31% IMD 56% POOR 13% **MSKCC** Not determined	(ITT) PEMBRO + AXI: 15.4 (12.7–18.9) SUN: 11.1 (9.1-12.5) HR 0.71 (95% CI 0.60–0.84) $p < 0.0001$	(ITT) PEMBRO + AXI: NR SUN: 35.7 (33.3–NE) HR 0.68 (95% CI 0.55–0.85) $p = 0.0003$
JAVELIN 101 **NCT02684006** **Median follow-up 19 mo** [6,7]	886	Avelumab 10 mg/kg IV Q2W + AXI 5 mg PO BID vs sunitinib 50 mg PO QD 4/2 wk	PFS in the PD-L1[+] population and OS in the ITT by BICR	**IMDC** FAV 22% IMD 62% POOR 16% **MSKCC** FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI: 13.8 (10.1–20.7) SUN: 7.0 (5.7–9.6) HR 0.62 (95% CI 0.49–0.78) $p < 0.0001$	(PD-L1+) AVE + AXI: NR SUN: 28.6 (27.4–NE) HR 0.83 (95% CI 0.60–1.15) $p = 0.1301$
IMmotion 151 **NCT02420821** **Median follow-up 24 mo** [8]	915	Atezolizumab 1200 mg fixed dose IV plus bevacizumab 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs sunitinib 50 mg PO QD 4/2 wk	PFS in the PD-L1[+] population and OS in the ITT by IR	**IMDC** Not determined **MSKCC** FAV 20% IMD 69% POOR 12%	(PD-L1+) ATEZO + BEV: 11.2 (8.9–15.0) SUN: 7.7 (6.8–9.7) HR 0.74 (95% CI 0.57–0.96) $p = 0.0217$	(ITT) ATEZO + BEV: 33.6 (29.0–NE) SUN: 34.9 (27.8–NE) HR 0.93 (95% CI 0.76–1.14) $p = 0.4751$
CheckMate214 **NCT02231749** **Minimum follow-up of 48 months** [2,4]	1096	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W vs sunitinib 50 mg PO QD 4/2 wk	PFS and OS in the IMDC intermediate and poor population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC IMD/POOR) NIVO + IPI: 11.2 (8.4–16.1) SUN: 8.3 (7.0–10.8) HR 0.74 (95% CI 0.62–0.88)	(IMDC IMD/poor) NIVO + IPI: 48.1 (35.6-NE) SUN: 26.6 (22.1-33.5) HR 0.65 (0.54–0.78) $p < 0.0001$
CheckMate 9ER **Median follow-up of 18.1 months** **NCT03141177** [1]	651	Nivolumab 240 mg fixed dose IV every 2 wk + cabozantinib 40 mg PO daily vs sunitinib 50 mg PO QD4/2 wk	PFS in the ITT by BICR	IMDC FAV 22% IMD 58% POOR 20% **MSKCC** Not determined	(ITT) NIVO + CABO: 16.6 (12.5–24.9) SUN: 8.3 (7.0–9.7) HR 0.51 (95% CI 0.41–0.64) $p < 0.0001$	(ITT) NIVO + CABO: NR SUN: NR (22.6–NE) HR 0.60 (98.9% CI 0.40–0.89) $p = 0.0010$

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; FAV = favourable; HR = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; mo = months; MSKCC = Memorial Sloan Kettering Cancer Center; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; PO = by mouth; BID = twice a day; QD = once a day; Q2W = every 2 weeks; Q3W = every 3 weeks; SUN = sunitinib; wk = weeks.
[a] Cross trial comparison is not recommended and should occur with caution.

EUROPEANUROLOGY79(2021)339–342

Raziskava CLEAR

The NEW ENGLAND JOURNAL of MEDICINE
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Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

R. Motzer, B. Alekseev, S.-Y. Rha, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, E. Kopyltsov, M.J. Méndez-Vidal, V. Kozlov, A. Alyasova, S.-H. Hong, A. Kapoor, T. Alonso Gordoa, J.R. Merchan, E. Winquist, P. Maroto, J.C. Goh, M. Kim, H. Gurney, V. Patel, A. Peer, G. Procopio, T. Takagi, B. Melichar, F. Rolland, U. De Giorgi, S. Wong, J. Bedke, M. Schmidinger, C.E. Dutcus, A.D. Smith, L. Dutta, K. Mody, R.F. Perini, D. Xing, and T.K. Choueiri, for the CLEAR Trial Investigators*

Study Design

Key eligibility criteria
- Advanced clear-cell RCC
- Treatment-naïve
- Karnofsky performance status ≥70
- Measurable disease
- Adequate organ function

Stratification factors
- **Geographic region:** Western Europe and North America vs Rest of the World
- **MSKCC risk category:** Favorable, Intermediate, or Poor

R (1:1:1)

Lenvatinib 20 mg oral QD + **Pembrolizumab*** 200 mg IV Q3W

Lenvatinib 18 mg oral QD + **Everolimus** 5 mg oral QD

Sunitinib 50 mg oral QD 4 weeks on / 2 weeks off

Primary endpoint
- PFS by IRC per RECIST v1.1

Secondary endpoints
- OS
- ORR by IRC per RECIST v1.1
- Safety
- HRQoL

Key exploratory endpoints
- DOR
- Biomarkers

*Patients could receive a maximum of 35 pembrolizumab treatments.
DOR, duration of response; HRQoL, Health-related quality of life; IRC, Independent Review Committee; MKSCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; R, randomization.

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Baseline Characteristics

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Median age (range) — years	64 (34–88)	62 (32–86)	61 (29–82)
Geographic region — %			
Western Europe and North America	55.8	56.0	55.7
Rest of the World	44.2	44.0	44.3
MSKCC prognostic risk group — %			
Favorable / Intermediate / Poor	27.0 / 63.9 / 9.0	27.5 / 63.6 / 9.0	27.2 / 63.9 / 9.0
IMDC risk group — %			
Favorable / Intermediate / Poor	31.0 / 59.2 / 9.3	31.9 / 54.6 / 11.8	34.7 / 53.8 / 10.4
Sarcomatoid features — %	7.9	6.7	5.9
PD-L1 expression — %			
≥ 1 / < 1 / not available	30.1 / 31.5 / 38.3	32.5 / 33.1 / 34.5	33.3 / 28.9 / 37.8
Prior nephrectomy — %	73.8	72.8	77.0

IMDC, International Metastatic RCC Database Consortium; PD-L1, programmed death ligand 1.

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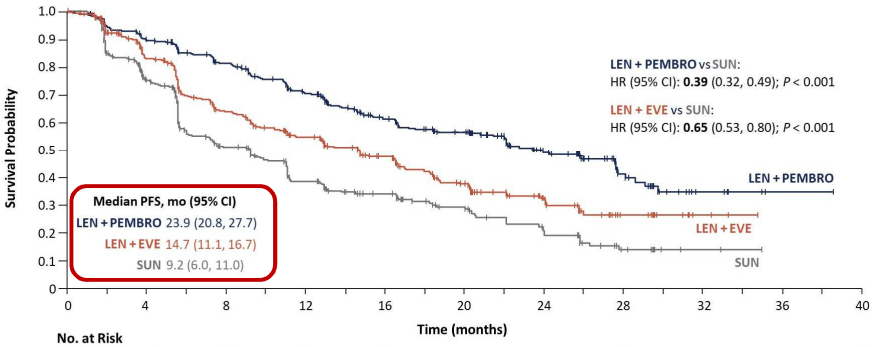
Progression-free Survival*



No. at Risk

355	300	259	213	160	126	80	30	6	1	0
357	259	185	149	105	70	37	13	3	0	
357	218	124	85	62	42	25	9	2	0	

*By Independent Review Committee per RECIST v1.1.

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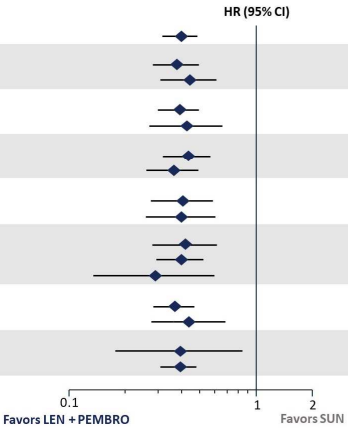
Progression-free Survival* With Lenvatinib Plus Pembrolizumab in Key Subgroups

Subgroup	LEN + PEMBRO	SUN	HR (95% CI)
	Events / no. of patients		
Overall	160/355	205/357	0.39 (0.32–0.49)
Age			
< 65 years	88/194	134/225	0.37 (0.28–0.49)
≥ 65 years	72/161	71/132	0.43 (0.31–0.61)
Sex			
Male	120/255	158/275	0.38 (0.30–0.49)
Female	40/100	47/82	0.42 (0.27–0.66)
Geographic region			
Western Europe and NA	86/198	108/199	0.42 (0.32–0.57)
Rest of the World	74/157	97/158	0.36 (0.26–0.49)
PD-L1 expression			
≥ 1	51/107	78/119	0.40 (0.27–0.58)
< 1	48/112	58/103	0.39 (0.26–0.59)
IMDC risk group			
Favorable	43/110	67/124	0.41 (0.28–0.62)
Intermediate	97/210	110/192	0.39 (0.29–0.52)
Poor	18/33	26/37	0.28 (0.13–0.60)
Prior nephrectomy			
Yes	107/262	163/275	0.37 (0.28–0.47)
No	53/93	42/82	0.44 (0.28–0.68)
Sarcomatoid features			
Yes	19/28	16/21	0.39 (0.18–0.84)
No	141/327	189/336	0.38 (0.31–0.48)



*By Independent Review Committee per RECIST v1.1.
NA, North America.

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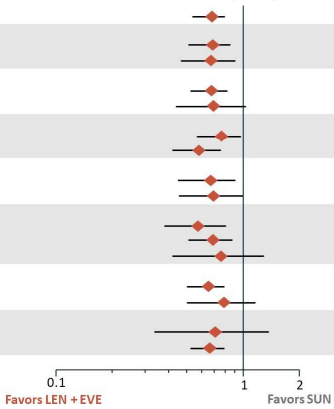
Progression-free Survival* With Lenvatinib Plus Everolimus in Key Subgroups

Subgroup	LEN + EVE	SUN	HR (95% CI)
	Events / no. of patients		
Overall	191/357	205/357	0.65 (0.53–0.80)
Age			
< 65 years	117/201	134/225	0.66 (0.51–0.85)
≥ 65 years	74/156	71/132	0.65 (0.46–0.90)
Sex			
Male	147/266	158/275	0.65 (0.52–0.82)
Female	44/91	47/82	0.67 (0.43–1.03)
Geographic region			
Western Europe and NA	111/200	108/199	0.74 (0.56–0.97)
Rest of the World	80/157	97/158	0.56 (0.42–0.76)
PD-L1 expression			
≥ 1	65/116	78/119	0.64 (0.45–0.90)
< 1	63/118	58/103	0.67 (0.46–0.98)
IMDC risk group			
Favorable	49/114	67/124	0.55 (0.38–0.81)
Intermediate	105/195	110/192	0.67 (0.51–0.88)
Poor	32/42	26/37	0.73 (0.42–1.29)
Prior nephrectomy			
Yes	129/260	163/275	0.63 (0.50–0.80)
No	62/97	42/82	0.76 (0.50–1.15)
Sarcomatoid features			
Yes	19/24	16/21	0.68 (0.33–1.39)
No	172/333	189/336	0.64 (0.52–0.80)



*By Independent Review Committee per RECIST v1.1.

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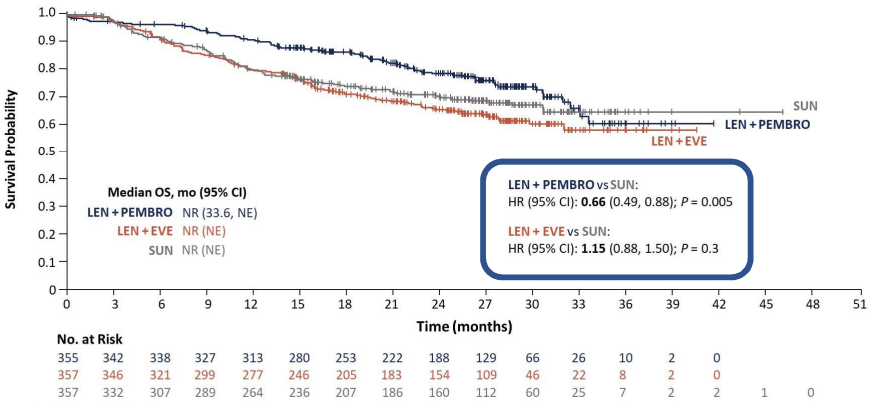
Overall Survival



No. at Risk

355	342	338	327	313	280	253	222	188	129	66	26	10	2	0	
357	346	321	299	277	246	205	183	154	109	46	22	8	2	0	
357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0

NE, not estimable; NR, not reached.

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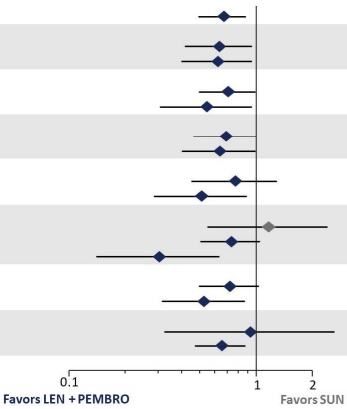
Overall Survival With Lenvatinib Plus Pembrolizumab in Key Subgroups

Subgroup	LEN + PEMBRO (Events / no. of patients)	SUN (Events / no. of patients)	HR (95% CI)
Overall	80/355	101/357	0.66 (0.49–0.88)
Age			
< 65 years	41/194	57/225	0.63 (0.41–0.95)
≥ 65 years	39/161	44/132	0.61 (0.40–0.95)
Sex			
Male	59/255	71/275	0.70 (0.49–0.99)
Female	21/100	30/82	0.54 (0.30–0.94)
Geographic region			
Western Europe and NA	46/198	57/199	0.68 (0.46–1.00)
Rest of the World	34/157	44/158	0.63 (0.40–0.99)
PD-L1 expression			
≥ 1	28/107	36/119	0.76 (0.46–1.27)
< 1	21/112	31/103	0.50 (0.28–0.89)
IMDC risk group			
Favorable	14/110	15/124	1.15 (0.55–2.40)
Intermediate	56/210	60/192	0.72 (0.50–1.05)
Poor	10/33	25/37	0.30 (0.14–0.64)
Prior nephrectomy			
Yes	50/262	66/275	0.71 (0.49–1.03)
No	30/93	35/82	0.52 (0.31–0.86)
Sarcomatoid features			
Yes	9/28	7/21	0.91 (0.32–2.58)
No	71/327	94/336	0.64 (0.47–0.87)



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Confirmed Objective Response Rate*

	LEN + PEMBRO (n = 355)	LEN + EVE (n = 357)	SUN (n = 357)
Objective response rate (95% CI) — %	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Best overall response — %			
Complete response	16.1	9.8	4.2
Partial response	54.9	43.7	31.9
Stable disease	19.2	33.6	38.1
Progressive disease	5.4	7.3	14.0
Unknown / not evaluable	4.5	5.6	11.8
Relative risk versus SUN (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	--
P-value	< 0.001	< 0.001	--

*By Independent Review Committee per RECIST v1.1.

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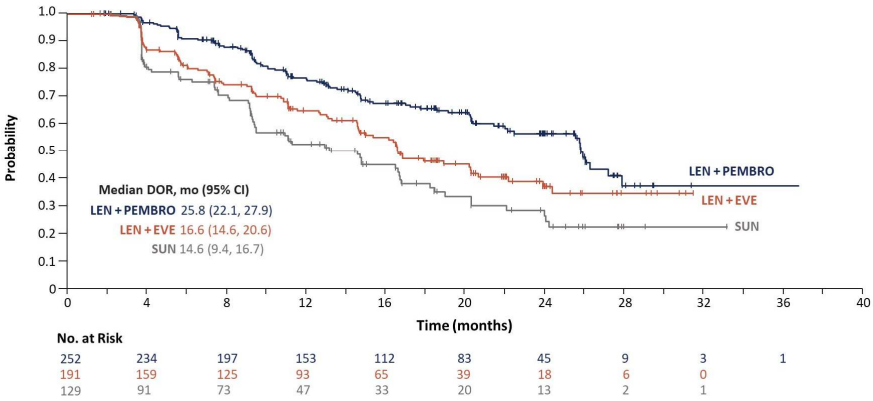
Duration of Response



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Treatment Exposure, Safety, and Discontinuation

	LEN + PEMBRO (n = 352)	LEN + EVE (n = 355)	SUN (n = 340)
Median duration of treatment, months (range)	17.0 (0.1–39.1)	11.0 (0.1–40.0)	7.8 (0.1–37.0)
Patients with any TRAEs (%)	96.9	97.7	92.1
Grade ≥ 3*	71.6	73.0	58.8
Patients with any TRAEs leading to dose reductions (LEN or SUN) (%)	67.3	69.3	49.7
Patients with any grade TRAEs leading to discontinuation (%)			
LEN or SUN	18.5	16.1	10.0
PEMBRO or EVE	25.0	19.2	--
LEN + PEMBRO or LEN + EVE	9.7	13.5	--

*Grade 5 TRAEs were observed in 1.1% of patients in the LEN + PEMBRO arm, 0.8% of patients in the LEN + EVE arm, and 0.3% of patients in the SUN arm.
TRAE, treatment-emergent adverse event.

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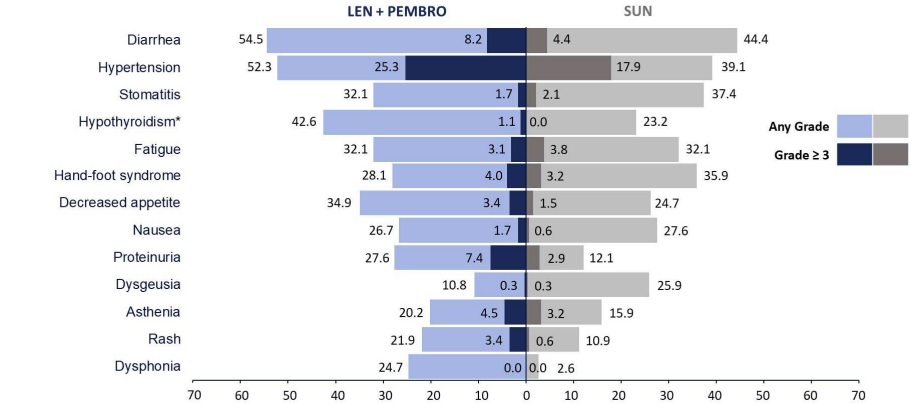
TRAEs With Frequency ≥ 20%



Alanine aminotransferase/aspartate aminotransferase increased in 9.7/9.4% (grade 3: 3.1/2.6%) of patients in the LEN + PEMBRO arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.
*Adverse event of interest for pembrolizumab.

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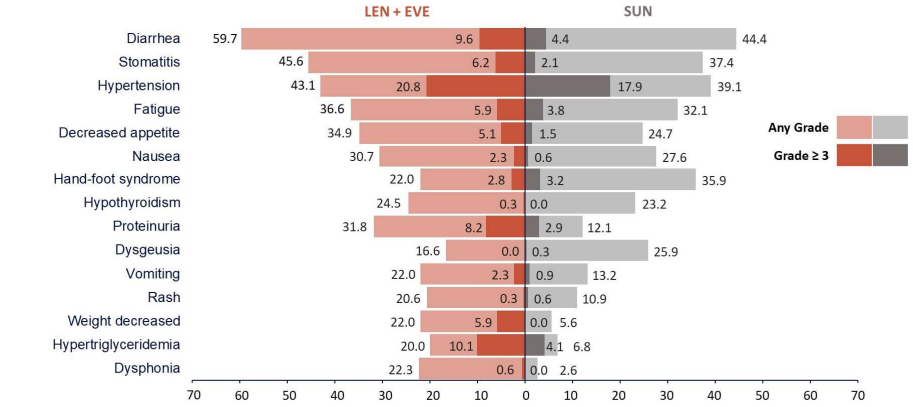
TRAEs With Frequency ≥ 20%



Alanine aminotransferase/aspartate aminotransferase increased in 10.4/11.5% (grade 3: 2.0/1.4%) of patients in the LEN + EVE arm and 8.8/8.8% of patients (grade 3: 1.8/0.6%) in the SUN arm.

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Conclusions

- Lenvatinib plus pembrolizumab demonstrated significant improvements in PFS, OS, and ORR versus sunitinib
- Lenvatinib plus everolimus demonstrated significant improvements in PFS and ORR but not OS versus sunitinib
- The safety profiles of lenvatinib plus pembrolizumab and lenvatinib plus everolimus were consistent with each drug's known profile and manageable, as needed, through dose modifications
- These results support lenvatinib plus pembrolizumab as a potential first-line treatment for patients with advanced RCC

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NCCN Guidelines Version 3.2022
Kidney Cancer

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1)	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Ipilimumab + nivolumab[b] • Pazopanib • Sunitinib	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d] (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b] (category 1) • Ipilimumab + nivolumab[b] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B) • High-dose IL-2[d] (category 3) • Temsirolimus[e] (category 3)

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cabozantinib (category 1) • Lenvatinib + everolimus (category 1) • Nivolumab[b] (category 1)	• Axitinib (category 1) • Axitinib + pembrolizumab[b] • Cabozantinib + nivolumab[b] • Ipilimumab + nivolumab[b] • Lenvatinib + pembrolizumab[b] • Pazopanib • Sunitinib • Tivozanib[g] • Axitinib + avelumab[b] (category 3)	• Everolimus • Bevacizumab[f] (category 2B) • High-dose IL-2 for selected patients[d] (category 2B) • Sorafenib (category 3) • Temsirolimus[e] (category 2B)

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PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[h]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Clinical trial • Cabozantinib • Sunitinib	• Lenvatinib + everolimus • Nivolumab[b] • Pembrolizumab[b]	• Axitinib • Bevacizumab[f] • Bevacizumab[f] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC (See HRCC-D) • Bevacizumab[f] + everolimus • Erlotinib • Everolimus • Pazopanib • Temsirolimus[e] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

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	Standard of care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	Nivolumab/cabozantinib [1b] Pembrolizumab/axitinib [1b]	Sunitinib* [1b] Pazopanib* [1b]
IMDC intermediate and poor risk	Nivolumab/cabozantinib [1b] Pembrolizumab/axitinib [1b] Nivolumab/ipilimumab [1b]	Cabozantinib* [2a] Sunitinib* [1b] Pazopanib* [1b]

Fig. 1 – Updated European Association of Urology guideline recommendations for the first-line treatment of metastatic clear-cell renal cancer. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium. [1b] = based on a randomised controlled phase 3 trial. [2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial. * Pazopanib for intermediate-risk disease only.

KARCINOM PROSTATE

- **KEYNOTE 365**

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SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[ddd,ggg,hhh]

No prior docetaxel/no prior novel hormone therapy[iii]	Prior novel hormone therapy/No prior docetaxel[iii,ooo]
• Preferred regimens ▸ Abiraterone[t,jjj] (category 1[kkk]) ▸ Docetaxel[yy,lll] (category 1) ▸ Enzalutamide[t] (category 1) •Useful in certain circumstances ▸ Sipuleucel-T[yy,mmm] (category 1) ▸ Radium-223[nnn] for symptomatic bone metastases (category 1) •Other recommended regimens ▸ Other secondary hormone therapy[t]	• Preferred regimens ▸ Docetaxel (category 1)[yy] ▸ Sipuleucel-T[yy,mmm] • Useful in certain circumstances ▸ Olaparib for HRRm (category 1)[ppp] ▸ Cabazitaxel/carboplatin[yy,fff] ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy] ▸ Radium-223[nnn] for symptomatic bone metastases (category 1) ▸ Rucaparib for BRCAm[qqq] • Other recommended regimens ▸ Abiraterone[t,jjj] ▸ Abiraterone + dexamethasone[jjj,qqq] ▸ Enzalutamide[t] ▸ Other secondary hormone therapy[t]
Prior docetaxel/no prior novel hormone therapy[iii] • Preferred regimens ▸ Abiraterone[t,jjj] (category 1) ▸ Cabazitaxel[yy] ▸ Enzalutamide[t] (category 1) • Useful in certain circumstances ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy] ▸ Cabazitaxel/carboplatin[yy,fff] ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy] ▸ Radium-223[nnn] for symptomatic bone metastases (category 1) • Other recommended regimens ▸ Sipuleucel-T[yy,mmm] ▸ Other secondary hormone therapy[t]	**Prior docetaxel and prior novel hormone therapy**[iii,ooo] (All systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ▸ Cabazitaxel[yy] (category 1[kkk]) ▸ Docetaxel rechallenge[yy] • Useful in certain circumstances ▸ Olaparib for HRRm (category 1[kkk])[ppp] ▸ Cabazitaxel/carboplatin[yy,fff] ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[yy] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy] ▸ Radium-223[nnn] for symptomatic bone metastases (category 1[kkk]) ▸ Rucaparib for BRCAm[qqq] • Other recommended regimens ▸ Abiraterone[t,jjj] ▸ Enzalutamide[t] ▸ Other secondary hormone therapy[t]

KEYNOTE-365 Cohort B: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer: New data after an additional year of follow-up

Leonard Appleman[1]; Michael Kolinsky[2]; William Berry[3]; Margitta Retz[4]; Loic Mourey[5]; Josep M Piulats[6]; Emanuela Romano[7]; Gwenaelle Gravis[8]; Howard Gurney[9]; Johann de Bono[10]; Martin Boegemann[11]; Urban Emmenegger[12]; Anthony Joshua[13]; Christophe Massard[14]; Srikala Sridhar[15]; Henry Conter[16]; Xin Tong Li[17]; Charles Schloss[17]; Christian Poehlein[17]; Evan Y. Yu[18]

[1]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [2]Cross Cancer Institute, Edmonton, AB, Canada; [3]Duke Cancer Center Cary, Cary, NC, USA; [4]Rechts der Isar University Hospital, Technical University of Munich, Munich Germany; [5]Institut Universitaire du Cancer-Oncopole, Toulouse, France; [6]Catalan Institute of Oncology, Barcelona, Spain; [7]Center of Cancer Immunotherapy, Institut Curie, Paris, France; [8]CLCC Institut Paoli Calmettes, Paris, France; [9]Macquarie University Hospital, Sydney, NSW, Australia; [10]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [11]University Hospital Muenster, Munster, Germany; [12]Sunnybrook Research Institute, Toronto, ON, Canada; [13]Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia; [14]Gustave Roussy Cancer Campus and Paris-Sud University, Villejuif, France; [15]UHN Princess Margaret Cancer Centre, Toronto, ON, Canada; [16]University of Western Ontario, Brampton, ON, Canada; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]University of Washington, Seattle, WA, USA

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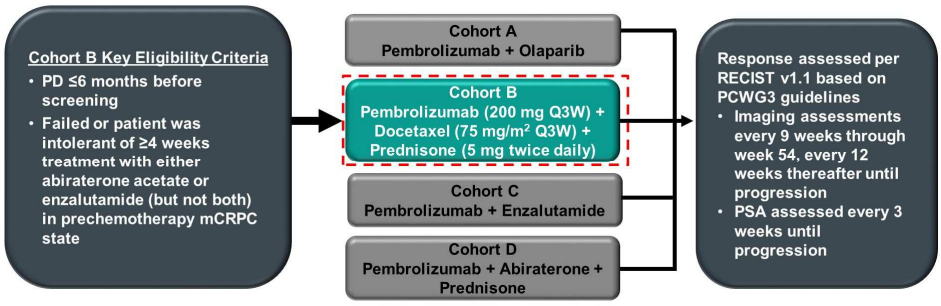
KEYNOTE-365 Study Design



Median Time From Enrollment to Data Cutoff in Cohort B
- **All patients**: 32.4 months (range, 13.9-40.3)

Data cutoff: July 9, 2020.

Primary End Points
- Safety
- PSA response rate
- ORR by RECIST v1.1 (BICR)

Secondary End Points
- DCR
- rPFS by PCWG-modified RECIST v1.1
- OS

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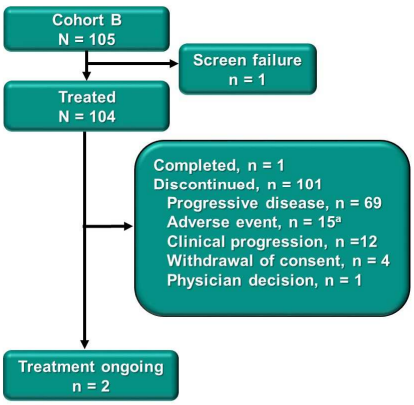
Baseline Characteristics and Disposition



n (%)	Cohort B N = 104
Age	
<65 years	27 (26.0)
≥65 years	77 (74.0)
Median (range), years	68.0 (50-86)
ECOG PS	
0	56 (53.8)
1	48 (46.2)
RECIST 1.1 measurable by BICR	
Yes	52 (50.0)
No	52 (50.0)
Visceral disease[b]	
Yes	26 (25.0)
No	78 (75.0)
PD-L1 status[c]	
Positive	24 (23.1)
Negative	76 (73.1)
Unknown	4 (3.8)

[a]2 treatment-related deaths due to AEs (pneumonitis). [b]Soft tissue (not in brain, bone, or lymph nodes). [c]Defined as combined positive score (tumor and immune cells) ≥1 with the Dako PD-L1 IHC 22C3 pharmDx assay.
Data cutoff: July 9, 2020.

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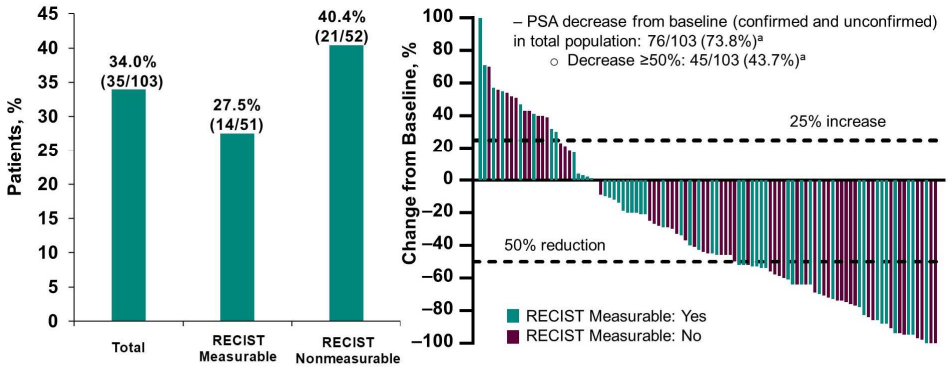
Confirmed PSA Response Rate (≥50% Reduction)[a] and Percentage Change From Baseline[b]



[a]Calculation is based on patients who had nonmissing PSA measurements at baseline; ≥50% PSA decline confirmed by subsequent value ≥3 weeks later. [b]Plot is based on patients who had a PSA measurement at baseline and ≥1 postbaseline PSA measurement (n = 103).
Data cutoff: July 9, 2020.

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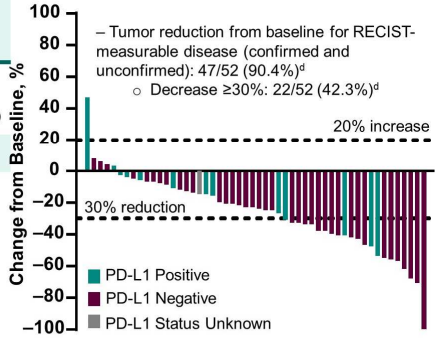
Best Response per RECIST v1.1 by BICR[a,b] and Target Lesion Change from Baseline

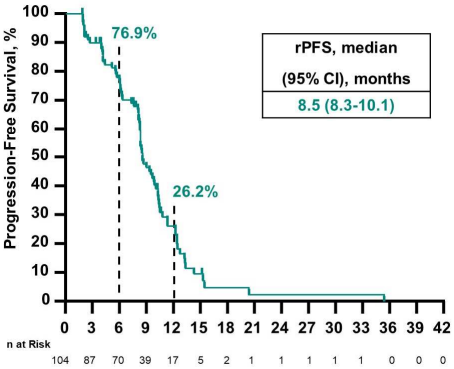
	Measurable Disease n = 52	Nonmeasurable Disease n = 52	Total Population N = 104
ORR,% (95% CI)	**23.1 (12.5-36.8)**	**NA**	**NA**
DCR[c], % (95% CI)	**73.1 (59.0-84.4)**	**78.8 (65.3-88.9)**	**76.0 (66.6-83.8)**
Confirmed best response, n (%)			
CR	0	0	0
PR	12 (23.1)	NA	12 (11.5)
SD of any duration	26 (50.0)	0	26 (25.0)
Non-CR/non-PD	0	41 (78.8)	41 (39.4)
SD or non-CR/non-PD ≥6 months	15 (28.8)	29 (55.8)	44 (42.3)
PD	14 (26.9)	11 (21.2)	25 (24.0)

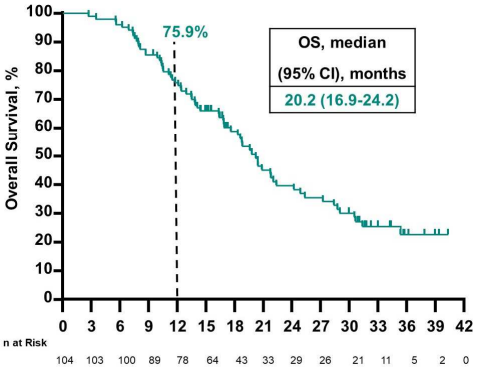


[a]Patients who received ≥1 dose of study drug. [b]Plot is based on patients who had RECIST-evaluable disease at baseline and ≥1 postbaseline measurement (n = 52). [c]Disease control rate (CR +PR +SD or non-CR/non-PD ≥6 months) per RECIST v1.1. [d]Calculation is based on patients who had target lesions at baseline (n = 52).
Data cutoff: July 9, 2020.

Presented By Leonard Appleman at 2021 Genitourinary Cancers Symposium

Kaplan-Meier Estimates of rPFS per PCWG3-Modified RECIST v1.1 and OS





Data cutoff: July 9, 2020.

Presented By Leonard Appleman at 2021 Genitourinary Cancers Symposium

Treatment-Related and Immune-Mediated Adverse Events, Deaths

Treatment-Related AEs With ≥10% Incidence, n (%)	Cohort B N = 104	
	Any Grade	Grade 3-5
Diarrhea	43 (41.3)	3 (2.9)
Fatigue	43 (41.3)	3 (2.9)
Alopecia	42 (40.4)	0 (0)
Dysgeusia	28 (26.9)	0 (0)
Nausea	27 (26.0)	0 (0)
Peripheral neuropathy	23 (22.1)	0 (0)
Asthenia	22 (21.2)	2 (1.9)
Anemia	19 (18.3)	5 (4.8)
Decreased appetite	16 (15.4)	0 (0)
Peripheral edema	15 (14.4)	1 (1.0)
Mucosal inflammation	13 (12.5)	0 (0)
Febrile neutropenia	12 (11.5)	12 (11.5)
Dyspepsia	11 (10.6)	0 (0)
Paresthesia	11 (10.6)	0 (0)

Data cutoff: July 9, 2020.

Immune-Mediated AEs and Infusion Reactions, n (%)	Cohort B N = 104	
	Any Grade	Grade 3-5
Any	34 (32.7)	9 (8.7)
Infusion reaction	10 (9.6)	0 (0)
Hyperthyroidism	9 (8.7)	0 (0)
Pneumonitis	8 (7.7)	4 (3.8)
Colitis	6 (5.8)	4 (3.8)
Hypothyroidism	6 (5.8)	0 (0)
Adrenal insufficiency	1 (1.0)	0 (0)
Severe skin reaction	1 (1.0)	1 (1.0)

- 2 patients died of an AE that the investigator considered related to treatment (both pneumonitis)
- Mean (range) duration on therapy was 7.7 (0.9-23.5) months

Presented By Leonard Appleman at 2021 Genitourinary Cancers Symposium

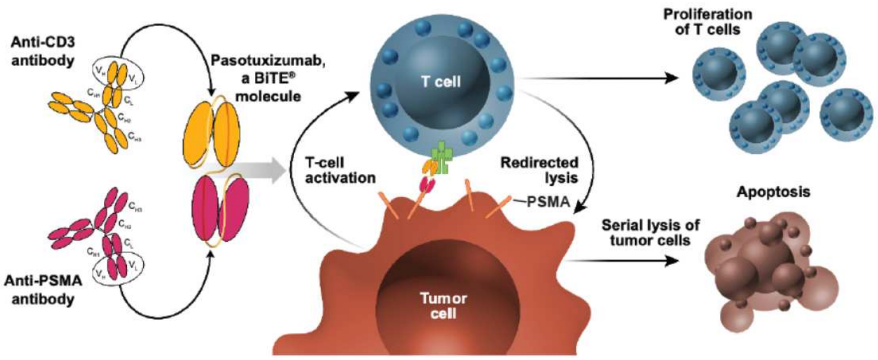
Conclusions

- With 1 year of additional follow-up, encouraging antitumor activity was observed in patients who received combination therapy with pembrolizumab + docetaxel and prednisone
  - Confirmed PSA response rate: Total population, 34.0%
  - ORR in patients with RECIST-measurable disease, 23.1% (95% CI: 12.5%-36.8%)
  - In the total population
    - Median rPFS, 8.5 months (8.3-10.1)
    - Median OS, 20.2 months (16.9-24.2)
- The safety profile was generally consistent with individual profiles of each agent
- The promising rPFS and OS data from this study support further evaluation of pembrolizumab + docetaxel/prednisone in patients with mCRPC previously treated with abiraterone or enzalutamide
  - A randomized phase 3 study of docetaxel + prednisone with and without pembrolizumab in NHA-pretreated patients who have not received chemotherapy for mCRPC is currently enrolling (KEYNOTE-921, NCT03834506)

Presented By Leonard Appleman at 2021 Genitourinary Cancers Symposium

Hummel H-D, et al. Phase 1 Study of Pasotuxizumab (AMG 212/BAY 2010112), a PSMA-targeting BiTE® (Bispecific T-cell Engager) Immune Therapy for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

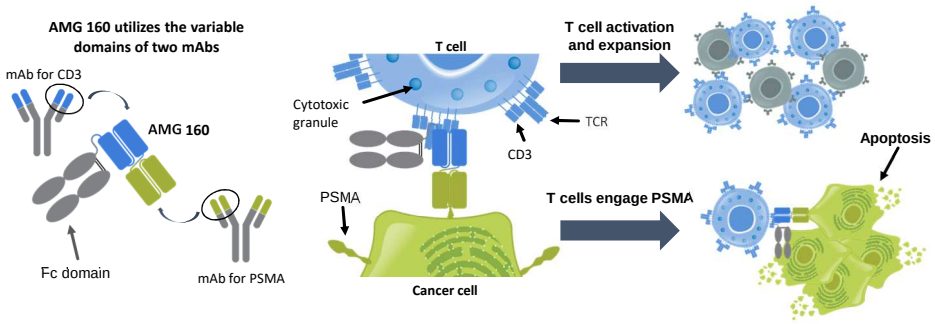
Figure 1: *Pasotuxizumab: A PSMA x CD3 BiTE® Immune Therapy*



BiTE® molecules have been shown to engage T cells to tumor cells and induce T-cell activation, tumor cell lysis, and T-cell proliferation[7-9]

Tran B, et al. Phase 1 Study of AMG 160, a Half-life Extended Bispecific T-cell Engager (HLE BiTE® Immune Therapy) Targeting Prostate-Specific Membrane Antigen (PSMA), in Patients With Metastatic Castration-resistant Prostate Cancer (mCRPC)

Figure 1. AMG 160: A PSMA x CD3 HLE BiTE Immune Therapy



Fc, fragment, crystallizable; mAb, monoclonal antibody; PSMA, prostate-specific membrane antigen; TCR, T cell receptor.

- BiTE molecules such as AMG 160 engage and direct T cells to tumor cells and induce T cell activation, local release of cytokines into the tumor microenvironment, tumor cell lysis, and T-cell proliferation[8-10]

Key Messages

- PSMA is a clinically validated diagnostic and therapeutic target that is highly expressed on prostate cancer cells
- AMG 160 is a novel HLE BiTE immune therapy that targets PSMA-expressing cancer cells by engaging a patient's own immune cells
- We are conducting a phase 1, first-in-human study evaluating AMG 160 as monotherapy and in combination with pembrolizumab in patients with mCRPC
  - NCT03792841 is currently recruiting patients into both Part 1 (AMG 160 monotherapy) and Part 2 (AMG 160 + pembrolizumab) of the study
- For more information, please contact Amgen Medical Information: medinfo@amgen.com

Tran B, et al. Phase 1 Study of AMG 160, a Half-life Extended Bispecific T-cell Engager (HLE BiTE® Immune Therapy) Targeting Prostate-Specific Membrane Antigen (PSMA), in Patients With Metastatic Castration-resistant Prostate Cancer (mCRPC)

A Phase 1 Study of AMG 160, a Half-life Extended Bispecific T-cell Engager (HLE BiTE® Immune Therapy) Targeting Prostate-Specific Membrane Antigen (PSMA), in Patients With Metastatic Castration-resistant Prostate Cancer (mCRPC)

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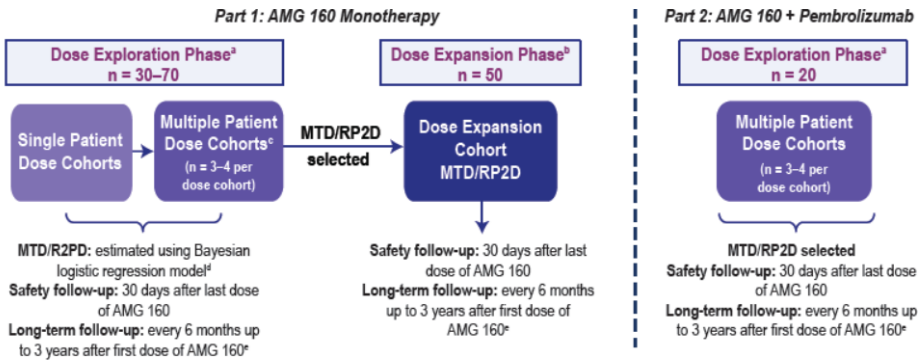
American Society of Clinical Oncology: Genitourinary Cancers Symposium (ASCO GU) 2020
Feb 13 – Feb 15, 2020, San Francisco, California, USA

Abstract TPS261

Methods

Study Design



[a]AMG 160 administered as a short-term intravenous infusion; patients pretreated with dexamethasone and hospitalized for ≥ 72 hours after each AMG 160 infusion in the first treatment cycle.
[b]AMG 160 administered at the MTD or RP2D to confirm safety, PK, and PD at the selected dose and to obtain further safety and efficacy data.
[c]Timing of conversion to multiple-patient cohorts will be determined after evaluation of emerging safety data in single patient cohorts; additional patients (up to 20) may be enrolled in one or more monotherapy dose levels that have been shown to be safe and tolerable (defined as backfill enrollment).
[d]RP2D of AMG 160 may be identified prior to reaching the MTD.
[e]Includes assessment of survival status and/or any subsequent cancer therapies.
mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase 2 dose.

Novosti na področju imunoterapije raka požiralnika in želodca

Marko Boc, dr.med.
Onkološki inštitut Ljubljana

Ljubljana, 15. december 2021

NIVOLUMAB – INDIKACIJE V SMPC

Ploščatocelični karcinom požiralnika (OSCC – oesophageal squamous cell carcinoma)

Zdravilo OPDIVO je v monoterapiji indicirano za zdravljenje neoperabilnega, napredovalega, ponovljenega ali metastatskega ploščatoceličnega karcinoma požiralnika pri odraslih bolnikih po predhodni kombinirani kemoterapiji na osnovi fluoropirimidina in platine.

2. RED

Adjuvantno zdravljenje raka požiralnika (OC – oesophageal cancer) ali ezofagogastričnega stika (GEJC – gastro-oesophageal junction cancer)

Zdravilo OPDIVO je v monoterapiji indicirano za adjuvantno zdravljenje odraslih bolnikov z rakom požiralnika ali ezofagogastričnega stika z ostankom bolezni po predhodni neoadjuvantni kemoradioterapiji

Pri adjuvantnem zdravljenju sme zdravljenje z zdravilom OPDIVO trajati največ 12 mesecev.

ADJ

Adenokarcinom želodca, ezofagogastričnega stika (GEJ – gastro-oesophageal junction) ali požiralnika

Zdravilo OPDIVO je v kombinaciji s kombinirano kemoterapijo na osnovi fluoropirimidina in platine indicirano za prvo linijo zdravljenja odraslih bolnikov s HER2-negativnim, napredovalim ali metastatskim adenokarcinomom želodca, ezofagogastričnega stika ali požiralnika, pri katerih imajo tumorji ekspresijo PD-L1 s kombinirano pozitivno oceno (CPS – combined positive score) ≥ 5.

1. RED

PEMBROLIZUMAB - INDIKACIJE V SMPC

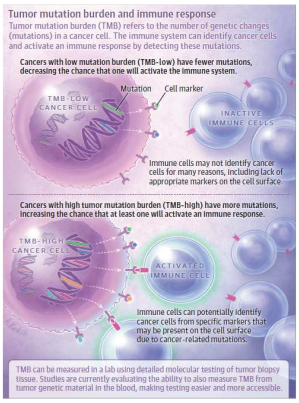
Rak požiralnika

Zdravilo KEYTRUDA je v kombinaciji s kemoterapijo s platino in fluoropirimidinom indicirano za prvo linijo zdravljenja lokalno napredovalega neoperabilnega ali metastatskega raka požiralnika ali HER-2 negativnega adenokarcinoma gastroezofagealnega prehoda pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10

1. RED

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

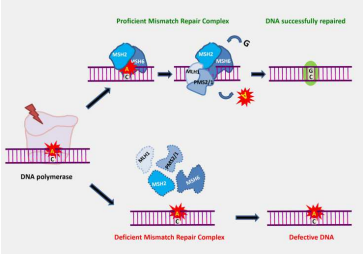
TMB (mutacijsko breme)



Measuring TMB

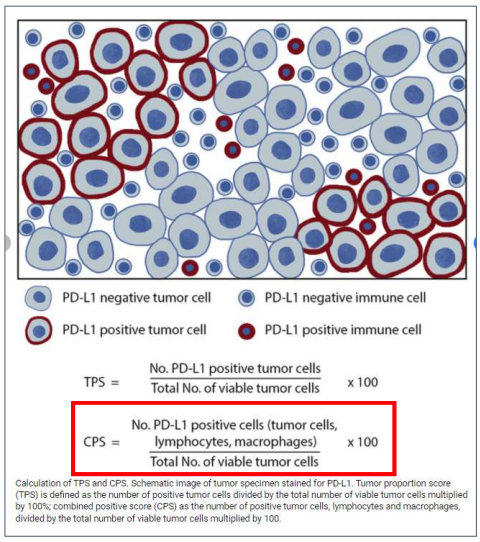
- The TMB can be measured by a laboratory test that uses next-generation sequencing of tumor tissue, which looks broadly for a wide range of mutations.
- Although not as established as measuring TMB from a biopsy sample of tumor tissue, studies are now evaluating measuring TMB from circulating tumor DNA in the plasma, making it potentially possible to test TMB from blood in the future.
- The TMB is reported as the number of mutations seen in a section of DNA and reported as mutations per megabase (mut/Mb).
- Cancers with a TMB of 10 mut/Mb or greater (called TMB-high) may be more likely to respond to drugs called immune checkpoint inhibitors that help activate the immune system to better recognize cancer cells.

MSI/dMMR (MSI-H vs. MSI-L)



Microsatellite instability (MSI) is the **condition of genetic hypermutability (predisposition to mutation)** that results from impaired DNA mismatch repair (MMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally.

CPS SCORE (PD-L1)



E. J. de Ruiter et al. 2020.
E. Puliga et al. 2021.
Michael JF et al. Jama. 2021

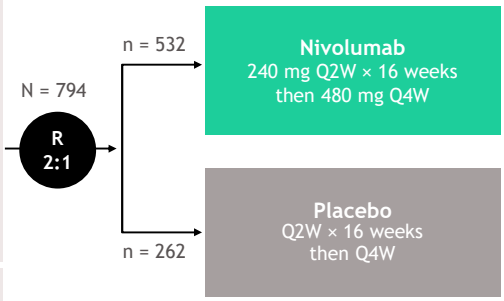
Dopolnilno zdravljenje raka požiralnika:

➡ CheckMate 577

- CheckMate 577 je globalna, dvojno slepa, s placebom kontrolirana študija faze 3[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0–1

Stratification factors
- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Total treatment duration of up to 1 year[d]

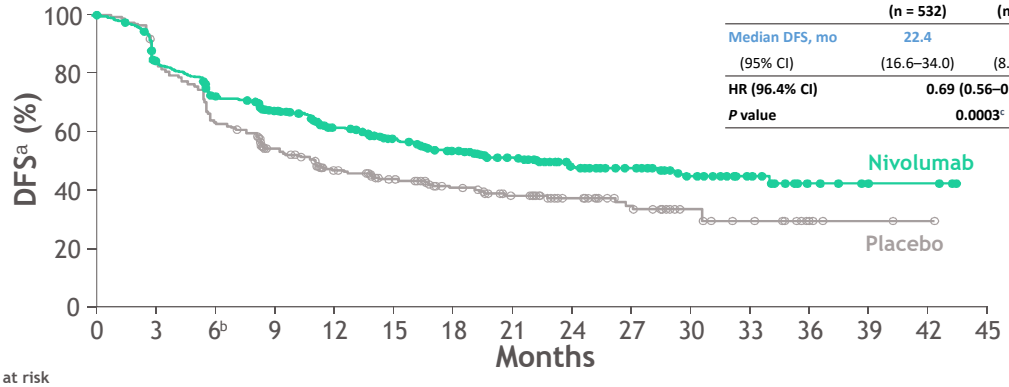
Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2–44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Preživetje brez bolezni (DFS)



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6–34.0)	(8.3–14.3)
HR (96.4% CI)	0.69 (0.56–0.86)	
P value	0.0003[c]	

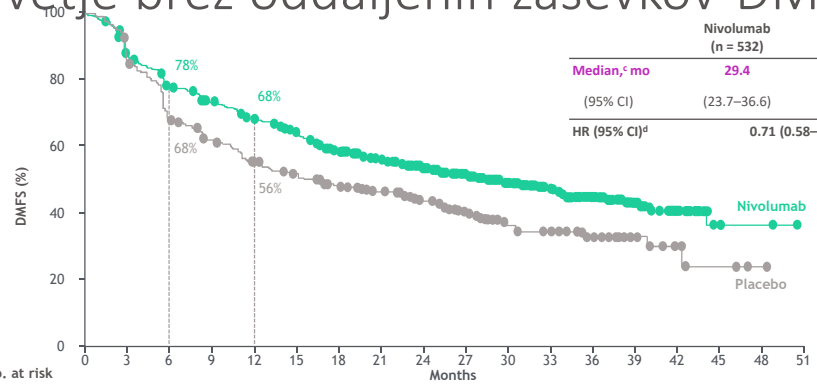
No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the pre-specified interim analysis required the *P* value to be less than 0.036.

CheckMate 577: NIVO, EC/GEJC, adjuvantno; mediana spremljanja, 32.2 meseca

Preživetje brez oddaljenih zasevkov-DMFS[1,a,b]



	Nivolumab (n = 532)	Placebo (n = 262)
Median,[c] mo	29.4	16.6
(95% CI)	(23.7–36.6)	(11.4-24.9)
HR (95% CI)[d]	0.71 (0.58–0.87)	

No. at risk																	
Nivolumab	532	453	400	369	339	307	252	219	181	157	123	93	61	38	22	6	5	0
Placebo	262	222	175	156	136	124	102	88	74	58	38	34	21	12	6	3	1	0

- Nivolumab showed a 29% reduction in the risk of distant recurrence or death versus placebo
  - Compared with earlier results,[2] the HR numerically decreased with longer follow-up (HR, 0.71 [95% CI, 0.58-0.87] from 0.74 [95% CI, 0.60-0.92])

[a]Per investigator assessment; based on Kaplan-Meier estimates. [b]DMFS was censored on the date of last disease assessment. [c]Median DMFS time was computed using the Kaplan-Meier estimate, and a 95% CI for the median was computed based on a log-log transformation of the survivor function. [d]Stratified Cox proportional-hazards model. HR is nivolumab over placebo. 1. Moehler M et al. Poster presentation at ESMO; September 16-21, 2021; Virtual. Abstract 1381P. 2. Kelly RJ et al. *N Engl J Med* 2021;384:1191–1203.

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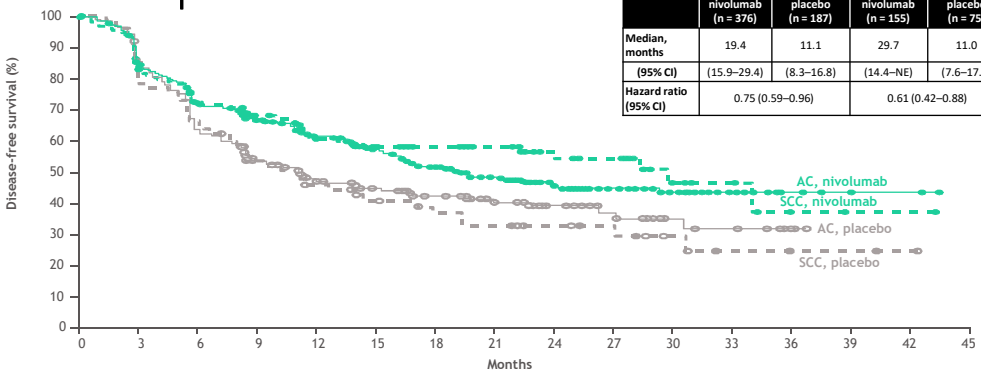
CheckMate 577: NIVO, EC/GEJC, adjuvantno; mediana spremljanja, 24.4 meseca

Preživetje brez ponovitve bolezni glede na histološki tip

	AC, nivolumab (n = 376)	AC, placebo (n = 187)	SCC, nivolumab (n = 155)	SCC, placebo (n = 75)
Median, months	19.4	11.1	29.7	11.0
(95% CI)	(15.9–29.4)	(8.3–16.8)	(14.4–NE)	(7.6–17.8)
Hazard ratio (95% CI)	0.75 (0.59–0.96)		0.61 (0.42–0.88)	



No. at risk																
AC, nivolumab	376	305	257	219	178	151	125	99	65	45	32	16	6	3	2	0
SCC, nivolumab	155	124	106	87	71	61	56	48	27	23	9	6	2	1	1	0
AC, placebo	187	156	114	92	68	57	47	37	26	18	11	9	3	0	0	0
SCC, placebo	75	58	49	34	28	23	18	16	12	10	6	3	2	2	1	0

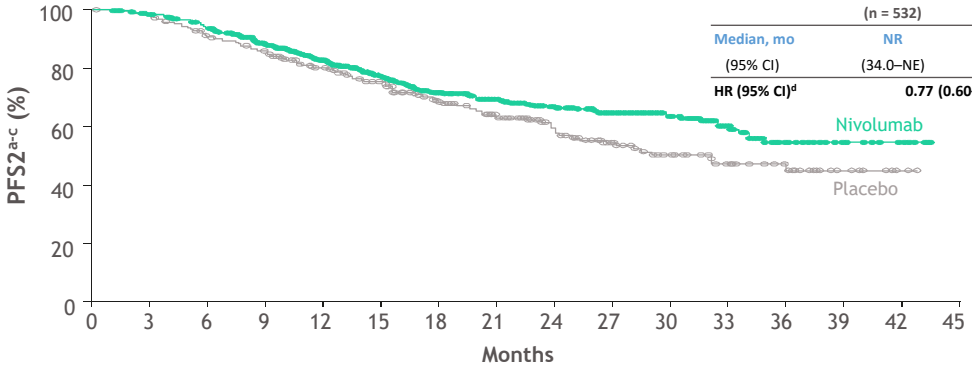
AC, adenocarcinoma; NE, not estimable; SCC squamous-cell carcinoma. Kelly RJ et al. *N Engl J Med* 2021 Apr 1;384:1191-1203.

9

CheckMate 577: NIVO, EC/GEJC, adjuvantno; mediana spremljanja, 24.4 meseca

Preživetje brez napredovanja bolezni-PFS2

	Nivolumab (n = 532)	Placebo (n = 262)
Median, mo	NR	32.1
(95% CI)	(34.0–NE)	(24.2-NE)
HR (95% CI)[d]	0.77 (0.60–0.99)	



No. at risk															
Nivolumab	532	517	487	441	368	301	262	213	174	135	102	61	35	14	6	0
Placebo	262	255	231	215	179	152	118	98	77	58	44	29	19	8	2	0

- PFS2 favored nivolumab versus placebo with HR of 0.77 (95% CI, 0.60–0.99)

[a]Per investigator assessment; based on Kaplan-Meier estimates. [b]PFS2 is defined as the time from randomization to progression after the first subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever is earlier. [c]Patients without a PFS2 event were censored at the date last known alive. [d]Stratified Cox proportional-hazards model. Hazard ratio is nivolumab over placebo. PFS2, progression-free survival 2. Kelly R et al. Oral presentation at ASCO; June 4-8, 2021; Virtual. Abstract 4003.

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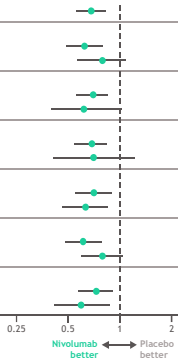
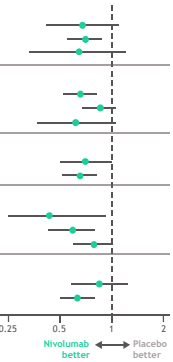
Preživetje brez ponovitve bolezni-DFS (podskupine)[1]

Subgroup	Median DFS, mo		Unstratified HR
	Nivolumab	Placebo	
Overall (N = 794)	22.4	10.4	0.68
Age, years			
< 65 (n = 507)	25.1	9.3	0.63
≥ 65 (n = 287)	19.4	13.9	0.79
Sex			
Male (n = 671)	21.3	10.3	0.70
Female (n = 123)	29.3	11.0	0.62
Race			
White (n = 648)	21.3	10.8	0.69
Asian (n = 117)	29.7	9.7	0.71
ECOG PS			
0 (n = 464)	26.6	11.1	0.71
1 (n = 330)	18.5	9.3	0.64
Tumor location at initial diagnosis			
Esophagus (n = 465)	23.4	8.3	0.61
Gastroesophageal junction (n = 329)	21.4	16.8	0.80
Histologic type			
Adenocarcinoma (n = 563)	19.6	10.4	0.73
Squamous cell carcinoma (n = 230)	29.7	10.6	0.60



Subgroup	Median DFS, mo		Unstratified HR
	Nivolumab	Placebo	
Tumor cell PD-L1 expression[a]			
≥ 1% (n = 129)	28.3	10.2	0.68
< 1% (n = 567)	20.8	11.0	0.70
Indeterminate/nonevaluable (n = 98)	26.6	9.9	0.64
PD-L1 CPS[a,b]			
≥ 5 (n = 371)	29.3	8.5	0.60
< 5 (n = 295)	15.3	11.1	0.85
Indeterminate/nonevaluable/NR (n = 128)	26.6	10.8	0.64
Pathologic lymph node status			
ypN0 (n = 337)	Not reached	27.0	0.71
≥ ypN1 (n = 457)	14.8	7.6	0.65
Pathological tumor status[c]			
ypT0[d] (n = 45)	34.0	5.2	0.40
ypT1 or ypT2 (n = 311)	29.3	9.2	0.59
ypT3 or ypT4 (n = 436)	18.5	11.5	0.80
Time from complete resection to randomization			
< 10 weeks (n = 256)	24.0	12.7	0.85
≥ 10 weeks (n = 538)	21.3	9.3	0.63



- DFS benefit was observed with nivolumab versus placebo across multiple subgroups
  - Compared with earlier results,[2] there was a numerical reduction in HR for multiple subgroups, including GEJC (HR, 0.80 [95% CI, 0.59-1.08] from 0.87 [95% CI, 0.63-1.21]) and adenocarcinoma (HR, 0.73 [95% CI, 0.58-0.91] from 0.75 [95% CI, 0.59-0.96])

[a]PD-L1 expression determined from tumor tissue specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako), which, for most patients, was obtained after completion of CRT. [b]Post hoc analysis. [c]2 patients had unknown pathological tumor status in the nivolumab arm. [d]The lower bound of the 95% CI for this subgroup is 0.18. NR, not reported. 1. Moehler M et al. Poster presentation at ESMO; September 16-21, 2021; Virtual. Abstract 1381P. 2. Kelly RJ, et al. *N Engl J Med* 2021;384:1191–1203.

Varnostni profil[1,2]

Event, n (%)	Nivolumab[a] n = 532		Placebo[a] n = 260	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AEs[b,c]	513 (96)	186 (35)	243 (93)	84 (32)
Serious AEs[c]	160 (30)	109 (20)	80 (31)	53 (20)
AEs leading to discontinuation of nivolumab or placebo[d]	71 (13)	39 (7)	21 (8)	16 (6)
Any TRAEs[b,e]	379 (71)	74 (14)	122 (47)	16 (6)
Serious TRAEs[e]	41 (8)	31 (6)	7 (3)	3 (1)
TRAEs leading to discontinuation of nivolumab or placebo[e]	49 (9)	26 (5)	8 (3)	7 (3)

- The majority of TRAEs were grade 1 or 2
- No new safety signals were identified

[a]Patients who received ≥ 1 dose of study treatment. [b]Events reported between first dose and 30 days after last dose of study drug. [c]There were 8 and 7 grade 5 AEs in the nivolumab and placebo arms, respectively; [d]There were 3 and 2 grade 5 AEs leading to discontinuation in the nivolumab and placebo arms, respectively. [e]Pneumonitis was reported as a serious adverse reaction in ≥ 2% of patients who received nivolumab. One grade 5 nivolumab-related adverse event was recorded (a cardiac arrest in the nivolumab group that was deemed to be not related to nivolumab by the investigator after database lock).[2] Reproduced with permission from 1. Moehler M et al. Poster presentation at ESMO; September 16-21, 2021; Virtual. Abstract 1381P. 2. Nivolumab [package insert]. Princeton, NJ: Bristol Myers Squibb; 2021.

Zdravljenje v prvem redu: GC/GEJC/EC

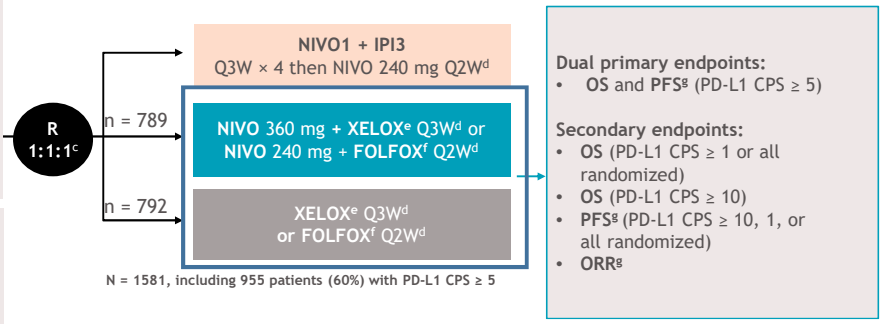
➡ CheckMate 649
➡ KEYNOTE-590

CheckMate 649

- CheckMate 649 je odprta, randomizirana študija faze 3[a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

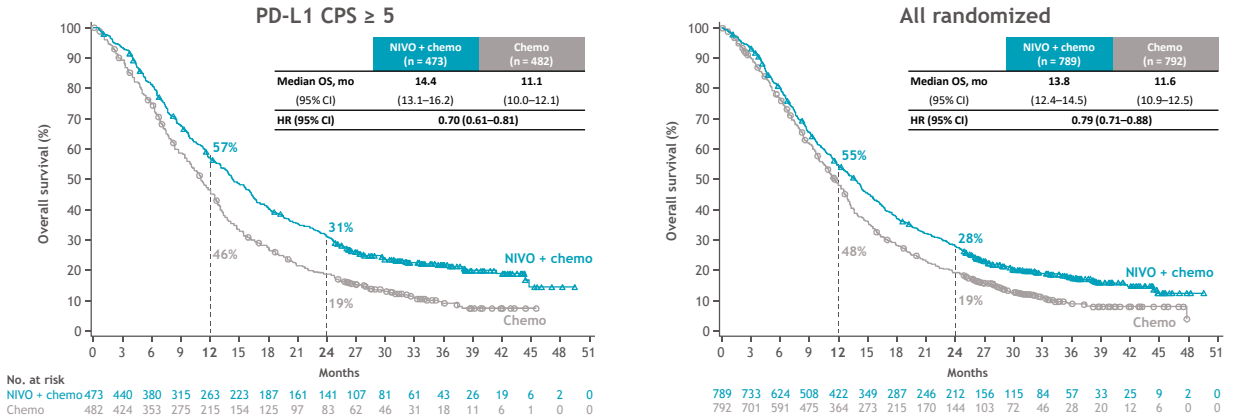
Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

CheckMate 649: NIVO + chemo, GC/GEJC/EAC, 1L; minimum follow-up, 24.0 months

Celokupno preživetje-OS[1]



- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up
  - PD-L1 CPS ≥ 5: 30% reduction in the risk of death and 12% improvement in 24-month OS rate
  - All randomized: 21% reduction in the risk of death and 9% improvement in 24-month OS rate
  - Directionally improved HRs relative to the 12-month follow-up (PD-L1 CPS ≥ 5, 0.71 [98.4% CI, 0.59-0.86]; all randomized, 0.80 [99.3% CI, 0.68-0.94])[2]

1. Janjigian YY et al. Oral presentation at ESMO; September 16-21, 2021; Virtual. Abstract LBA7. 2. Janjigian YY, et al. *Lancet* 2021;398:27-40.

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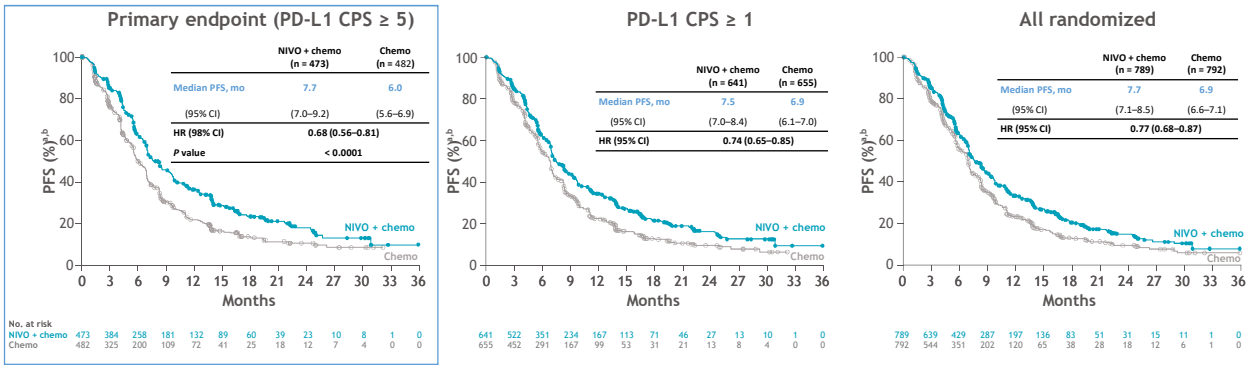
Preživetje brez napredovanja bolezni PFS



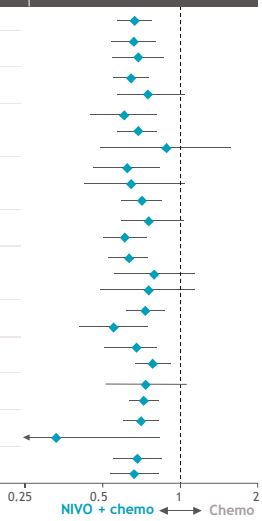
12-mo rate: NIVO + chemo, 36%; chemo, 22% NIVO + chemo, 34%; chemo, 22% NIVO + chemo, 33%; chemo, 23%

- Superior PFS, 32% reduction in the risk of progression or death with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5
- PFS benefit with NIVO + chemo versus chemo in PD-L1 CPS ≥ 1 and all randomized patients

[a]Per BICR assessment; [b]Minimum follow-up 12.1 months.

Celokupno preživetje OS po podskupinah

	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 955)	≥ 65 (n = 403)	14.4	11.1	0.70
Age, years	< 65 (n = 552)	14.8	11.0	0.69
		14.3	11.2	0.72
Sex	Male (n = 680)	14.4	10.8	0.67
	Female (n = 275)	14.4	12.1	0.78
Race	Asian (n = 236)	16.1	11.5	0.63
	White (n = 655)	14.0	11.1	0.71
	Other (n = 64)	9.8	10.6	0.93
Region	Asia (n = 228)	15.6	11.8	0.64
	US/Canada (n = 137)	16.8	12.6	0.67
	ROW (n = 590)	13.6	10.4	0.74
ECOG PS[a]	0 (n = 397)	17.6	13.8	0.79
	1 (n = 557)	12.6	8.8	0.63
Primary tumor location	GC (n = 667)	15.0	10.5	0.66
	GEJC (n = 170)	14.2	13.1	0.84
	EAC (n = 118)	11.2	11.3	0.78
Tumor cell PD-L1[b] expression	< 1% (n = 724)	14.2	11.6	0.75
	≥ 1% (n = 230)	16.2	8.8	0.56
Liver metastases	Yes (n = 408)	13.1	9.8	0.63
	No (n = 518)	15.5	12.0	0.76
Signet ring cell carcinoma	Yes (n = 141)	12.1	9.0	0.71
	No (n = 814)	15.1	11.3	0.69
MSI status[c]	MSS (n = 846)	14.4	11.1	0.73
	MSI-H (n = 34)	Not reached	8.8	0.33
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.71
	XELOX (n = 454)	15.0	11.0	0.69

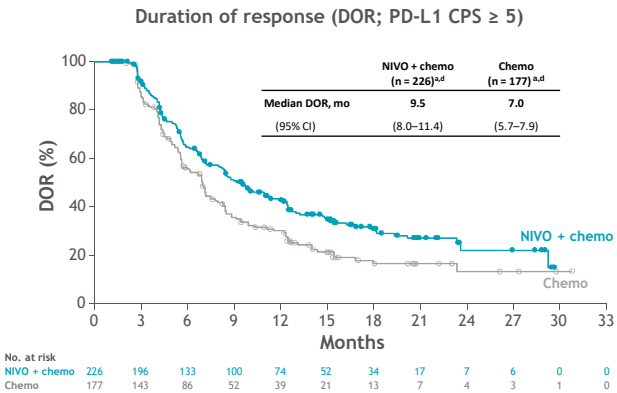


- OS consistently favored NIVO + chemo versus chemo across multiple pre-specified subgroups

[a]Not reported, n = 1; [b]Unknown, n = 1; [c]Not reported/invalid, n = 75.

Odgovor in trajanje odgovora DOR

	PD-L1 CPS ≥ 5	
	NIVO + chemo (n = 378)[a]	Chemo (n = 391)[a]
ORR, %	**60**	**45**
95% CI	55–65	40–50
P value[b]	< 0.0001	
Best overall response,[c] %		
Complete response	**12**	**7**
Partial response	**48**	**38**
Stable disease	28	34
Progressive disease	7	11
Not evaluable	6	10
Median TTR (range), months	1.5 (0.8–10.2)	1.5 (1.0–7.1)



- ORR was higher with NIVO + chemo versus chemo, and responses were more durable

ORR-overall response rate (objektivni odgovor na zdravljenje); TTR-time-to-repair/response (čas do prvega odziva tumorja); DOR-duration of response (trajanje odgovora)

[a]Randomized patients who had target lesion measurements at baseline per BICR assessment; [b]ORR was not formally tested, the pre-specified *P* value is descriptive; [c]Percentages may not add up to 100% due to rounding; [d]Number of responders.

Z zdravljenjem povezani neželeni učinki

Patients, n (%)	All treated[a]			
	NIVO + chemo (n = 782)[b]		Chemo (n = 767)[b]	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAEs[c]	738 (94)	462 (59)	679 (89)	341 (44)
Serious TRAEs[c]	172 (22)	131 (17)	93 (12)	77 (10)
TRAEs leading to discontinuation[c]	284 (36)	132 (17)	181 (24)	67 (9)
Treatment-related deaths	12[d] (2)		4[e] (< 1)	

- The most common any-grade TRAEs (≥ 25%) across both arms were nausea, diarrhea, and peripheral neuropathy
- The incidence of TRAEs in patients whose tumors expressed PD-L1 CPS ≥ 5 was consistent with all treated patients across both arms

TRAE-treatment related adverse events (z zdravljenjem povezane neželeni učinki)

[a]Patients who received ≥ 1 dose of study drug; [b]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [c]There were 4 grade 5 events in the NIVO + chemo arm, 1 case each of cerebrovascular accident, febrile neutropenia, gastrointestinal inflammation, and pneumonia. There were no grade 5 events in the chemo arm; [d]One event each of febrile neutropenia, gastrointestinal bleeding, gastrointestinal toxicity, infection, interstitial lung disease, intestinal mucositis, neutropenic fever, pneumonia, pneumonitis, pulmonitis, septic shock (capecitabine-related), and stroke. [e]One event each of diarrhea-associated toxicity, asthenia and severe hiporexy, pulmonary thromboembolism, and interstitial pneumonia.

Kato KN590 ESMO 2020

KEYNOTE-590 Study Design (NCT03189719)

Key Eligibility Criteria
- Locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic EGJ Siewert type 1 adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)

R (1:1)

Pembrolizumab 200 mg IV Q3W for ≤35 cycles
+
Chemotherapy
5-FU 800 mg/m² IV for days 1-5 Q3W for ≤35 cycles
+ Cisplatin 80 mg/m² IV Q3W for ≤6 cycles

Placebo[a]
+
Chemotherapy
5-FU 800 mg/m² IV for days 1-5 Q3W for ≤35 cycles
+ Cisplatin 80 mg/m² IV Q3W for ≤6 cycles

Stratification Factors
- Asia vs Non-Asia region
- ESCC vs EAC
- ECOG PS 0 vs 1

- **Dual-Primary endpoints: OS and PFS (RECIST v1.1, investigator)**
- **Secondary endpoint: ORR (RECIST v1.1, investigator)**
- **Tumor response assessed at week 9 then Q9W (RECIST v1.1, investigator)**

[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision; EAC, esophageal adenocarcinoma; EGJ, esophagogastric junction, ESCC, esophageal squamous cell carcinoma.

Kato KN590 ESMO 2020

Treatment Disposition

749 patients randomly assigned

Pembrolizumab (Pembro) + Chemotherapy
- 373 assigned
- 370 treated

- 27 ongoing
- 15 completed

- 328 discontinued
  - 204 disease progression
  - 49 adverse events
  - 36 clinical progression
  - 30 patient withdrawals
  - 9 physician decision
  - 0 complete response
  - 0 protocol violation

Placebo + Chemotherapy (Chemo)
- 376 assigned
- 370 treated

- 10 ongoing
- 1 completed

- 359 discontinued
  - 239 disease progression
  - 44 adverse events
  - 41 clinical progression
  - 23 patient withdrawals
  - 10 physician decision
  - 1 complete response
  - 1 protocol violation

22-month recruitment period occurred from 25 Jul 2017 to 03 Jun 2019. At interim analysis median follow-up (from randomization to data cut-off or death) was 10.8 months. Mean (SD) time on therapy was 7.7 months (6.84) vs 5.8 months (4.76) for pembro + chemo vs chemo. 43.5% vs 47.8% of patients in the pembro + chemo vs chemo group had post-study treatment; Data cutoff: July 2, 2020.

Kato KN590 ESMO 2020

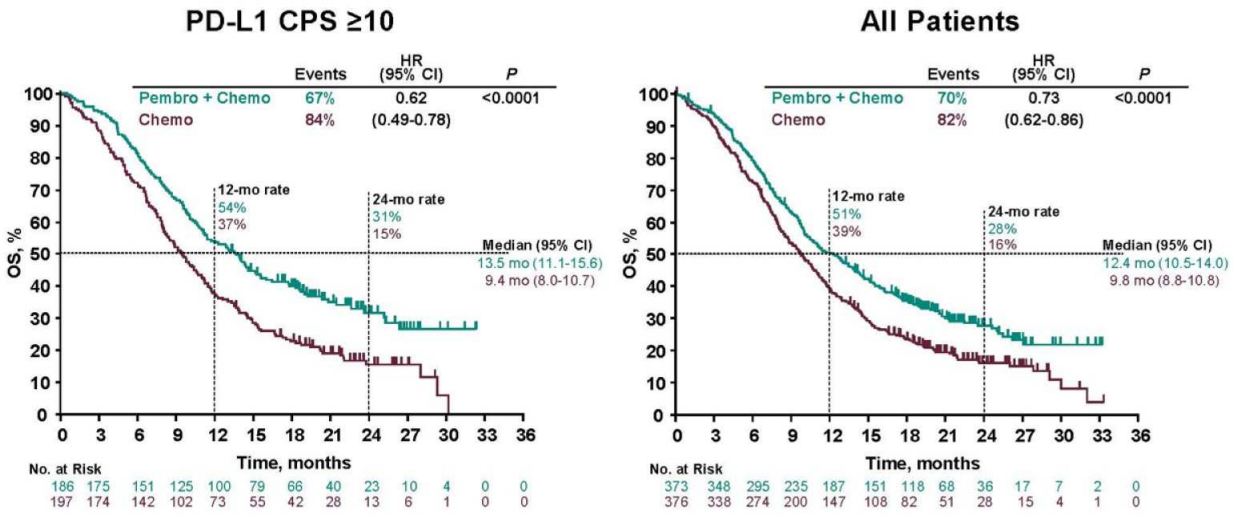
Baseline Characteristics (ITT)

Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally-advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10[a]	186 (49.9)	197 (52.4)

[a]PD-L1 status was not evaluable or missing in 12 patients in the pembro + chemo group and 7 patients in the chemo group.
Data cut-off: July 2, 2020.

Kato KN590 ESMO 2020

Overall Survival

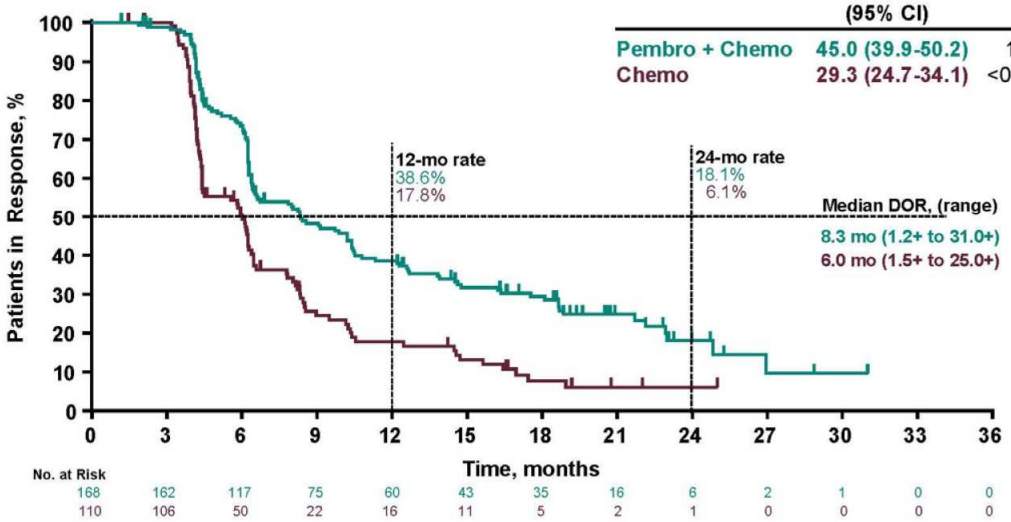


Data cut-off: July 2, 2020.

Kato KN590 ESMO 2020

Response Rate and Duration: All Patients
(RECIST v1.1, investigator)

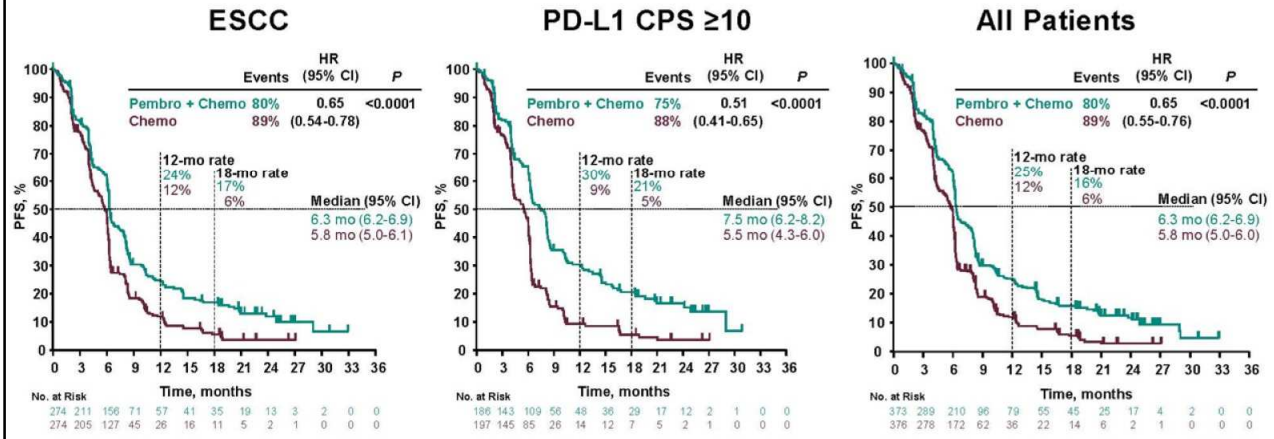
	ORR, % (95% CI)	% difference[a] P
Pembro + Chemo	45.0 (39.9-50.2)	15.8
Chemo	29.3 (24.7-34.1)	<0.0001



[a]Estimate based on Miettinen & Nurminen method stratified by geographic region, histology, and ECOG performance status; Data cut-off: July 2, 2020.

Kato KN590 ESMO 2020

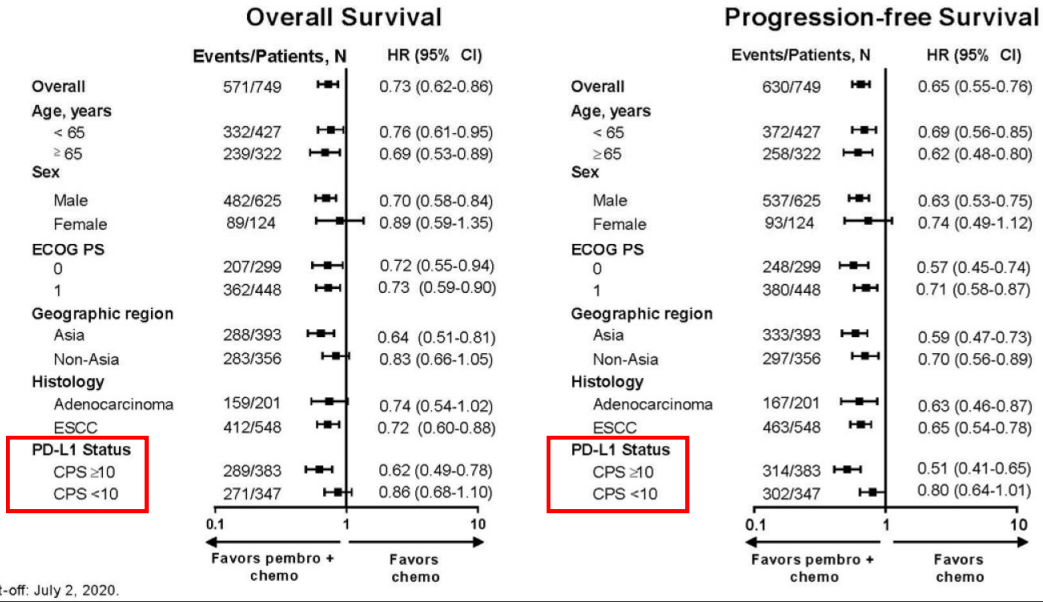
Progression-Free Survival
(RECIST v1.1, investigator)



Data cut-off: July 2, 2020.

Kato KN590 ESMO 2020

Survival in Key Subgroups: All Patients

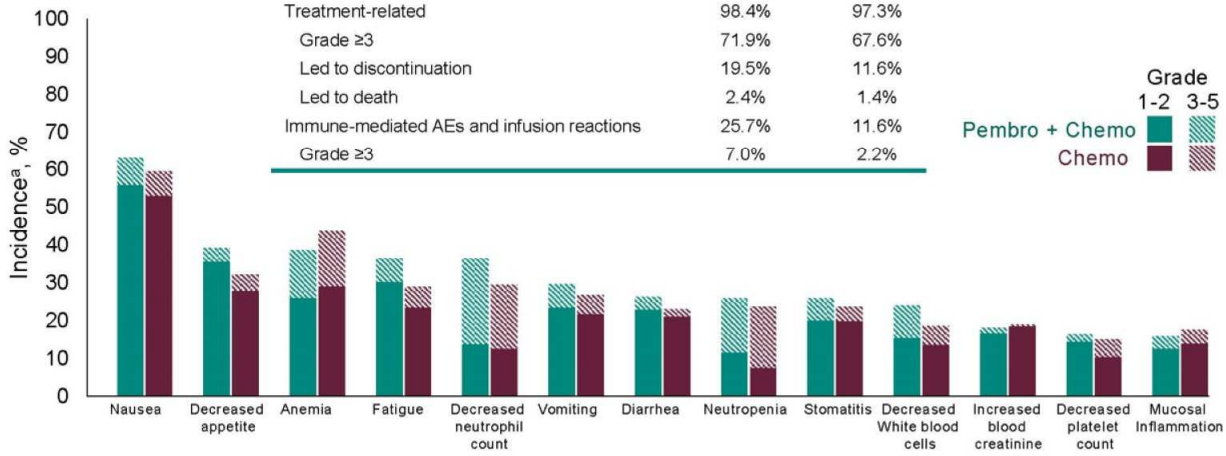


Data cut-off: July 2, 2020.

Kato KN590 ESMO 2020

Adverse Events (AEs) in all Treated Patients

AEs	Pembro + Chemo N = 370	Chemo N = 370
Any	100%	99.5%
Treatment-related	98.4%	97.3%
Grade ≥3	71.9%	67.6%
Led to discontinuation	19.5%	11.6%
Led to death	2.4%	1.4%
Immune-mediated AEs and infusion reactions	25.7%	11.6%
Grade ≥3	7.0%	2.2%



[a]Treatment-related events with ≥15% incidence in any treatment arm; Data cut-off: July 2, 2020.

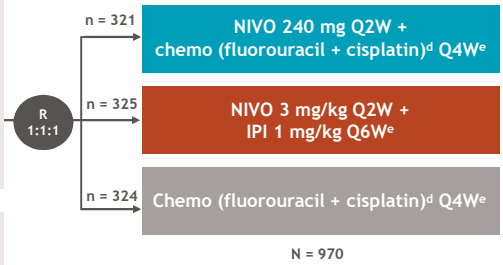
Zdravljenje v prvem redu: ESCC

➡ CheckMate 648

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

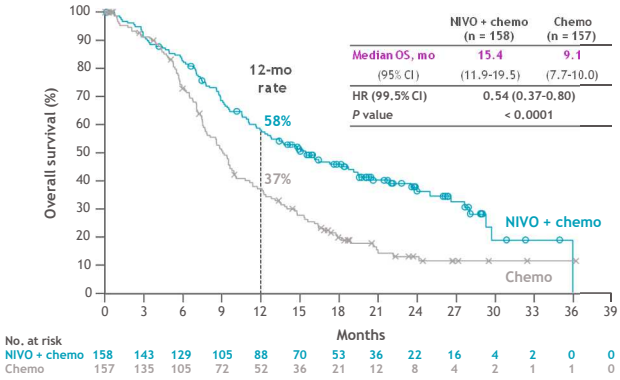
Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m² IV daily (days 1-5) and cisplatin 80 mg/m² IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

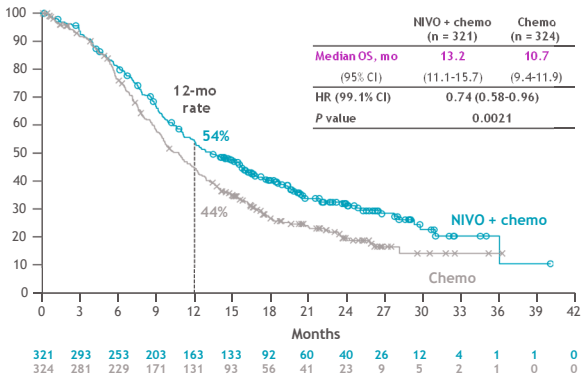
Overall survival: NIVO + chemo vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	< 0.0001	

All randomized[a]



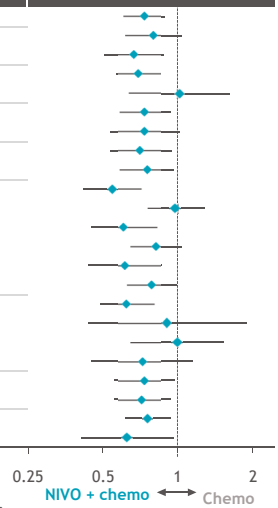
	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

[a]Minimum follow-up 12.9 months.

Overall survival subgroup analysis: NIVO + chemo vs chemo

Category (all randomized)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 645)		13.2	10.7	0.74
Age, years	< 65 (n = 333)	11.8	10.2	0.80
	≥ 65 (n = 312)	15.1	11.0	0.67
Sex	Male (n = 528)	12.5	10.0	0.70
	Female (n = 117)	15.2	14.8	1.02
Geographic region	Asian (n = 451)	15.5	11.9	0.74
	Non-Asian (n = 194)	10.5	8.5	0.74
ECOG PS[a]	0 (n = 300)	17.3	12.4	0.71
	1 (n = 344)	10.6	9.0	0.76
Tumor cell PD-L1 expression[b]	≥ 1% (n = 314)	15.4	9.2	0.55
	< 1% (n = 329)	12.0	12.2	0.98
	≥ 5% (n = 235)	13.7	9.5	0.61
	< 5% (n = 408)	12.8	11.1	0.82
	≥ 10% (n = 199)	14.7	9.5	0.62
	< 10% (n = 444)	12.3	10.8	0.79
Disease status at study entry	De novo metastatic (n = 371)	13.4	9.4	0.63
	Recurrent - locoregional (n = 46)	14.8	13.5	0.91
	Recurrent - distant (n = 132)	12.3	12.8	1.00
	Unresectable advanced (n = 96)	12.8	12.1	0.73
No. of organs with metastases	≤ 1 (n = 316)	15.7	11.6	0.74
	≥ 2 (n = 329)	11.1	9.6	0.72
Smoking	Current or former (n = 510)	12.3	10.0	0.76
	Never or unknown (n = 135)	15.7	11.1	0.63



- OS favored NIVO + chemo vs chemo across most prespecified subgroups in all randomized patients

[a]Not reported in 1 patient; [b]Indeterminate, not evaluable, or missing (n = 2).

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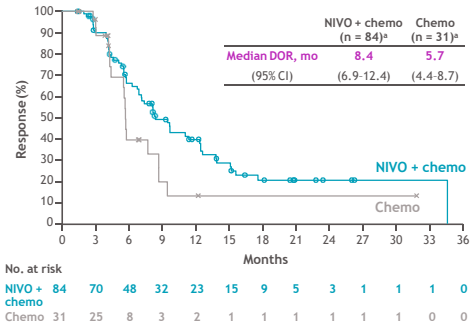
Response and duration of response: NIVO + chemo vs chemo

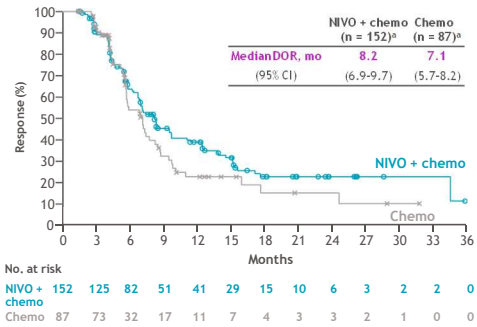
Tumor cell PD-L1 ≥ 1%

Response per BICR	NIVO + chemo (n = 158)	Chemo (n = 157)
ORR, % (95% CI)	53 (45-61)	20 (14-27)
CR	16	5
PR	37	15
SD	25	46
PD	14	15



All randomized

Response per BICR	NIVO + chemo (n = 321)	Chemo (n = 324)
ORR, % (95% CI)	47 (42-53)	27 (22-32)
CR	13	6
PR	34	21
SD	32	46
PD	13	12



[a]Number of responders.

Zdravljenje v drugem redu: ESCC

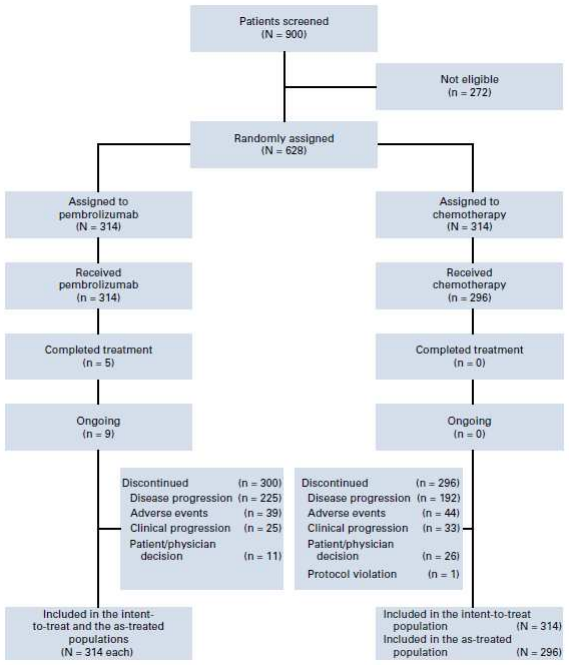
➡ KEYNOTE-181

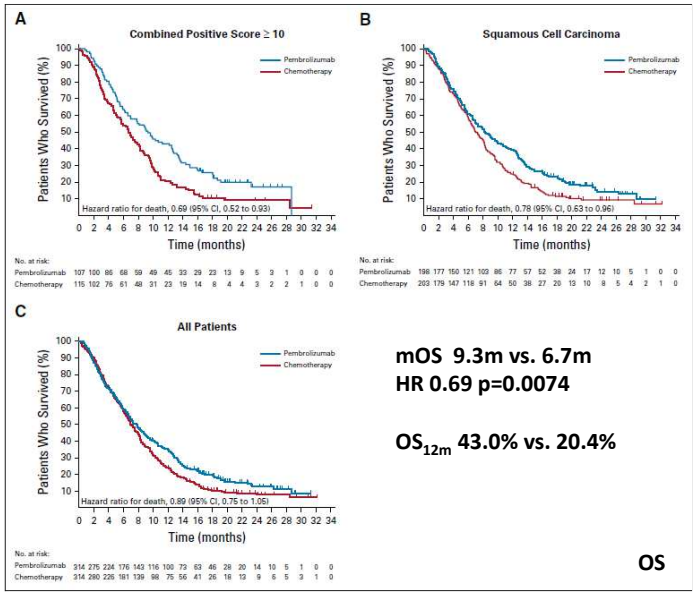
Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer

Takashi Kojima, MD[1]; Manish A. Shah, MD[2]; Kei Muro, MD[3]; Eric Francois[4]; Antoine Adenis, MD, PhD[5]; Chih-Hung Hsu, MD, PhD[6]; Toshihiko Doi, MD, PhD[7]; Toshikazu Moriwaki, MD, PhD[8]; Sung-Bae Kim, MD, PhD[9]; Se-Hoon Lee, MD, PhD[10]; Jaafar Bennouna, MD, PhD[11]; Ken Kato, MD, PhD[12]; Lin Shen, PhD[13]; Peter Enzinger, MD[14]; Shu-Kui Qin, MD[15]; Paula Ferreira[16]; Jia Chen, PhD[17]; Gustavo Girotto, MD[18]; Christelle de la Fouchardiere, MD[19]; Helene Senellart, MD[20]; Raed Al-Rajabi, MD[21]; Florian Lordick[22]; Ruixue Wang, PhD[23]; Shailaja Suryawanshi, PhD[23]; Pooja Bhagia, MD[23]; S. Peter Kang, MD[23]; and Jean-Philippe Metges[24] on behalf of the KEYNOTE-181 Investigators

TABLE 1. Baseline Patient Demographic and Disease Characteristics

Characteristic	Pembrolizumab (N = 314)	Chemotherapy (N = 314)
Age, years, median (range)	63.0 (23-84)	62.0 (24-84)
≥ 65 years	139 (44.3)	133 (42.4)
Male	273 (86.9)	271 (86.3)
Geographic region		
Asia	121 (38.5)	122 (38.9)
Rest of world	193 (61.5)	192 (61.1)
ECOG performance status[a]		
0	126 (40.1)	116 (36.9)
1	187 (59.6)	197 (62.7)
2	1 (0.3)	1 (0.3)
Histology		
Squamous cell carcinoma[b]	198 (63.1)	203 (64.6)
Adenocarcinoma	116 (36.9)	111 (35.4)
PD-L1 combined positive score[c]		
≥ 10	107 (34.1)	115 (36.6)
< 10	201 (64.0)	196 (62.4)
Not evaluable[d]	6 (1.9)	3 (1.0)
Prior adjuvant or neoadjuvant therapy		
Yes	32 (10.2)	32 (10.2)
Disease stage		
Metastatic	290 (92.4)	286 (91.1)
Locally advanced	24 (7.6)	28 (8.9)
No. of prior therapies		
0	2 (0.6)	0 (0.0)
1	303 (96.5)	310 (98.7)
≥ 2	9 (2.9)	4 (1.3)

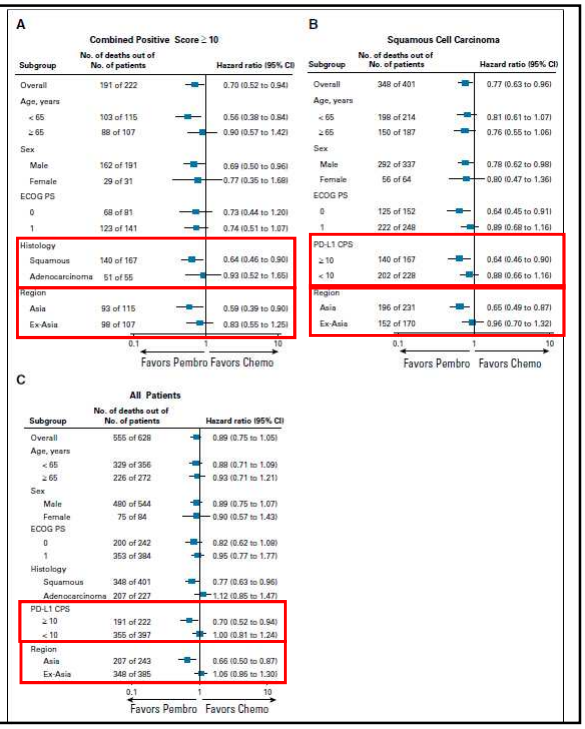


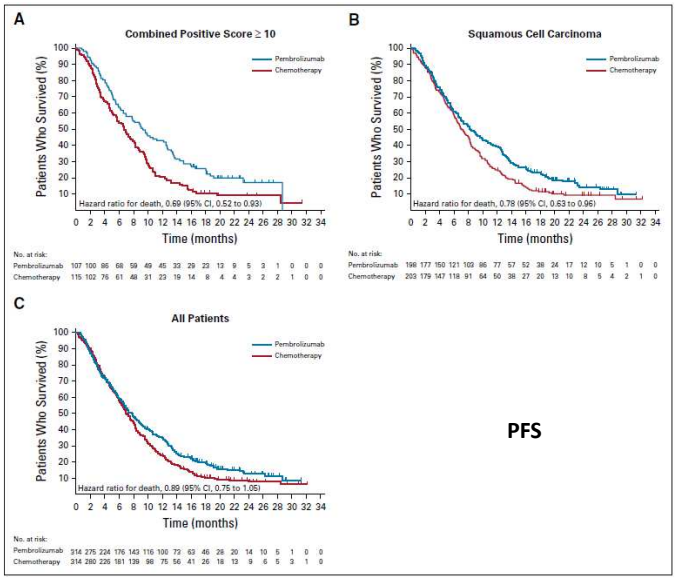


mOS 9.3m vs. 6.7m
HR 0.69 p=0.0074

OS_{12m} 43.0% vs. 20.4%

OS





PFS

TABLE 2. Adverse Events in All Treated Patients

Adverse Event	Pembrolizumab (n = 314)	Chemotherapy (n = 296)
Any	300 (95.5)	288 (97.3)
Treatment related	202 (64.3)	255 (86.1)
Grade 3-5	57 (18.2)	121 (40.9)
Led to discontinuation	19 (6.1)	19 (6.4)
Led to death[a]	5 (1.6)	5 (1.7)

TABLE 3. Treatment-Related Adverse Events in ≥ 10% of Patients in Either Group

	Pembrolizumab (n = 314)		Chemotherapy (n = 296)	
Adverse Event	All Grades	Grade 3-5	All Grades	Grade 3-5
Fatigue	37 (11.8)	2 (0.6)	61 (20.6)	1 (0.3)
Hypothyroidism	33 (10.5)	0 (0.0)	1 (0.3)	0 (0.0)
Decreased appetite	27 (8.6)	2 (0.6)	46 (15.5)	3 (1.0)
Asthenia	22 (7.0)	4 (1.3)	34 (11.5)	3 (1.0)
Nausea	22 (7.0)	0 (0.0)	64 (21.6)	7 (2.4)
Diarrhea	17 (5.4)	2 (0.6)	60 (20.3)	9 (3.0)
Vomiting	10 (3.2)	1 (0.3)	33 (11.1)	6 (2.0)
Anemia	8 (2.5)	4 (1.3)	66 (22.3)	23 (7.8)
Alopecia	2 (0.6)	0 (0.0)	86 (29.1)	1 (0.3)
Neutrophil count decreased	2 (0.6)	1 (0.3)	50 (16.9)	29 (9.8)
Peripheral sensory neuropathy	1 (0.3)	0 (0.0)	50 (16.9)	1 (0.3)
WBC count decreased	1 (0.3)	0 (0.0)	49 (16.6)	30 (10.1)
Neutropenia	0 (0.0)	0 (0.0)	34 (11.5)	21 (7.1)

KEYNOTE-811

KEYNOTE-811 Global Cohort

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)

Patients
- Advanced G/GEJ adenocarcinoma
- No prior therapy in advanced setting
- HER2-positive

Stratification Factors
- Geographic region
- PD-L1 CPS
- Chemotherapy choice

R 1:1
N = 692

Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a] for up to 35 cycles

Placebo IV Q3W + Trastuzumab and FP or CAPOX[a] for up to 35 cycles

Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX dose: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

FDA APPROVED

Janjigian KN811 ASCO 2021.

POŽIRALNIK IN GEP – DOPOLNILNO ZDRAVLJENJE

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Preoperative Chemoradiation
(Infusional fluorouracil[b] can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Definitive Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin[1]
- Fluorouracil[b] and oxaliplatin (category 1)[2,3]
- Fluorouracil and cisplatin (category 1)[11]

Other Recommended Regimens
- Cisplatin with docetaxel or paclitaxel[12-14]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)

Preferred Regimens
- Fluorouracil,[b] leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)[c]
- Fluoropyrimidine and oxaliplatin[b,d]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Postoperative Therapy

Preferred Regimens
- Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)[e,15]

Other Recommended Regimens
- Capecitabine and oxaliplatin[f,16]
- Fluorouracil[b] and oxaliplatin[f]

Preoperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
- Fluorouracil and cisplatin (category 2B)[10]

Postoperative Chemoradiation
- Fluoropyrimidine (infusional fluorouracil[b] or capecitabine) before and after fluoropyrimidine-based chemoradiation[17]

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Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is generally preferred over cisplatin due to lower toxicity.

Preferred Regimens
- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,18]
- HER2 overexpression negative[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥ 5) for adenocarcinoma only (category 1)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) for adenocarcinoma only (category 2B)[e,h,19]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS ≥ 10) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS ≥ 10) (category 1) for adenocarcinoma or squamous cell carcinoma[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS 1-9) for adenocarcinoma only (category 2B)[e,h,20]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin for adenocarcinoma or squamous cell carcinoma[21-23]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin for adenocarcinoma or squamous cell carcinoma[21,24-26]

Other Recommended Regimens
- HER2 overexpression positive adenocarcinoma[g]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[e,h,27]
  - Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[e,h,27]
- Fluorouracil[b,i] and irinotecan[j,28]
- Paclitaxel with or without cisplatin or carboplatin [j,29-33]
- Docetaxel with or without cisplatin [j,34-37]
- Fluoropyrimidine [j,25,38,39] (fluorouracil[b] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b, j,40,41]
- Docetaxel, carboplatin, and fluorouracil (category 2B)[j,42]

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Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Nivolumab for esophageal squamous cell carcinoma (category 1)[e,h,43]
- Pembrolizumab[e,h]
  - For second-line therapy for esophageal squamous cell carcinoma, with PD-L1 expression levels by CPS of ≥10 (category 1)[44]
- Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[45]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[46]
- Docetaxel (category 1)[36,37]
- Paclitaxel (category 1)[31,33,47]
- Irinotecan (category 1)[47-50]
- Fluorouracil[b,i] and irinotecan[48,51,52]
- Trifluridine and tipiracil for third-line or subsequent therapy for EGJ adenocarcinoma (category 1)[53]

Other Recommended Regimens
- Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[54]
- Irinotecan and cisplatin[22,55]
- Fluorouracil and irinotecan + ramucirumab for adenocarcinoma[b,i,56]
- Irinotecan and ramucirumab for adenocarcinoma[57]
- Docetaxel and irinotecan (category 2B)[58]

Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[59,60]
- Pembrolizumab[e,h] for MSI-H or dMMR tumors[61-63]
- Pembrolizumab[e,h] for TMB high (≥10 mutations/megabase) tumors[64]

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Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy • Oxaliplatin is generally preferred over cisplatin due to lower toxicity.
Preferred Regimens • HER2 overexpression positive adenocarcinoma[f] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab (category 1)[a,11] • HER2 overexpression negative[f] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,12] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[13-15] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[13,16-18]
Other Recommended Regimens • HER2 overexpression positive adenocarcinoma[f] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin and trastuzumab[a] and pembrolizumab[g,h,19] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin and trastuzumab[a] and pembrolizumab[g,h,19] • Fluorouracil[b,i] and irinotecan[j,20] • Paclitaxel with or without cisplatin or carboplatin[j,21-25] • Docetaxel with or without cisplatin[j,26-29] • Fluoropyrimidine[j,17,30,31] (fluorouracil[b] or capecitabine) • Docetaxel, cisplatin or oxaliplatin, and fluorouracil[b,j,32,33] • Docetaxel, carboplatin, and fluorouracil (category 2B)[j,34]
Useful in Certain Circumstances • HER2 overexpression negative[f] ‣ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS 1-4) (category 2B)[g,h,12]

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PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred Regimens • Ramucirumab and paclitaxel (category 1)[35] • Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[36] • Docetaxel (category 1)[28,29] • Paclitaxel (category 1)[24,25,37] • Irinotecan (category 1)[37-40] • Fluorouracil[b,i] and irinotecan[38,41,42] • Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[43]
Other Recommended Regimens • Ramucirumab (category 1)[44] • Irinotecan and cisplatin[14,45] • Fluorouracil and irinotecan + ramucirumab[b,i,46] • Irinotecan and ramucirumab[47] • Docetaxel and irinotecan (category 2B)[48]
Useful in Certain Circumstances • Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[49,50] • Pembrolizumab[g,h] for MSI-H or dMMR tumors[51-53] • Pembrolizumab[g,h] for TMB high (≥ 10 mutations/megabase) tumors[54] • Dostarlimab-gxly[g,h,k] for MSI-H or dMMR tumors[55]

Novosti na področju imuno-terapije rakov hepato-biliarnega trakta

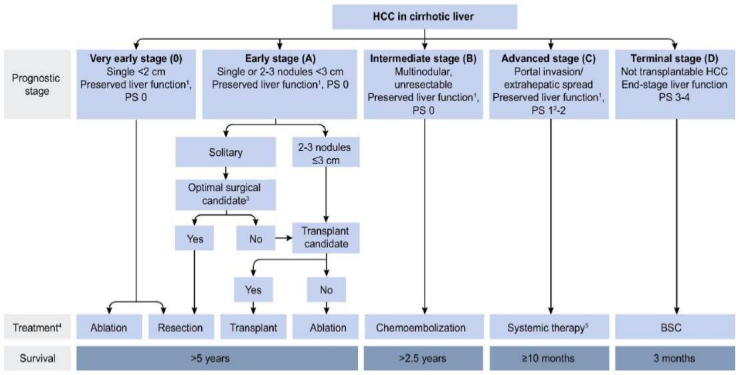
NOVOSTI v IMUNOTERAPIJI pri SOLIDNIH RAKIH LETA 2021
15.in 16.12.2021

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

HCC- imunoterapija

PROGNOSIS

BCLC Algorithm



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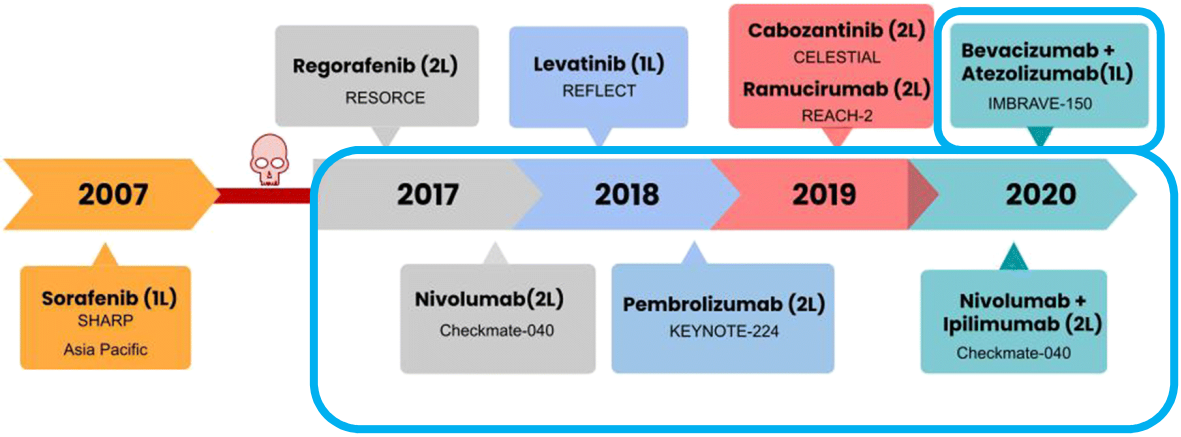
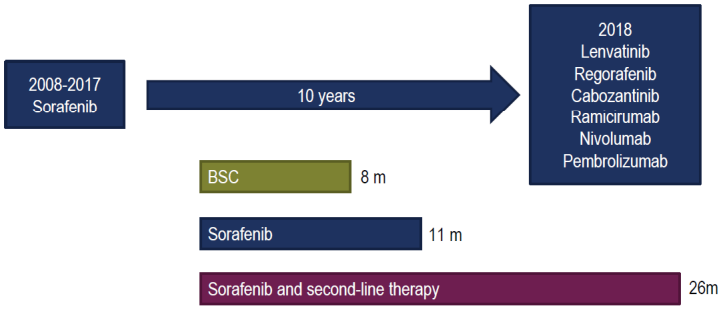
HCC- sistemsko zdravljenje



SYSTEMIC THERAPY

Practice changing clinical research



ESMO

Registracijske klin.raziskave

Table 2 | **Results from randomized controlled trials involving ICIs as systemic therapy for HCC**

Agent (dose)	Number of patients	MVI	EHD	AFP >400 ng/ml	ORR (CR)	mPFS	mOS (95% CI)	HR	Ref.
KEYNOTE-240 (second-line setting)									
Pembrolizumab (200 mg every 3 weeks)	278	13	70	46[a]	18 (2)	3.0	13.9 (11.6–16.0)	0.78	110
Placebo	135	12	69	43[a]	4 (0)	2.8	10.6 (8.3–13.5)		
CheckMate 459 (first-line setting)									
Nivolumab (240 mg every 2 weeks)	371	75[b]	75[b]	33	15 (4)	3.7	16.4 (14.0-18.5)	0.85	112
Sorafenib (400 mg twice a day)	372	70[b]	70[b]	38	7 (1)	3.8	14.8 (12.1-17.3)		
IMbrave150 (first-line setting)									
Atezolizumab (1,200 mg every 3 weeks plus bevacizumab 15 mg/kg every 3 weeks)	336	38	63	38	27 (6)	6.8	NE	0.58	129
Sorafenib (400 mg twice a day)	165	43	56	37	12 (0)	4.3	13.2 (10.4–NE)		

Sangro, B, Sarobe, P, Hervás-Stubbs S, *et al.* Advances in immunotherapy for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol, 2021;* **18**:525–543.

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First-Line Systemic Therapy

Preferred Regimens
- Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1]

Other Recommended Regimens
- Sorafenib (Child-Pugh Class A) [category 1] or B7)[d,e,2,3]
- Lenvatinib (Child-Pugh Class A only)[4,5] (category 1)

Useful in Certain Circumstances
- Nivolumab[b,6] (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B)
- FOLFOX (category 2B)

Subsequent-Line Therapy[g] if Disease Progression[h]

Options
- Regorafenib (Child-Pugh Class A only) (category 1)[i,7]
- Cabozantinib (Child-Pugh Class A only) (category 1)[i,8]
- Ramucirumab (AFP ≥400 ng/mL only) (category 1)[i,9]
- Lenvatinib (Child-Pugh Class A only)
- Sorafenib (Child-Pugh Class A or B7)[d,e]

Other Recommended Regimens
- Nivolumab + ipilimumab (Child-Pugh Class A only)[b,i,13]
- Pembrolizumab (Child-Pugh Class A only)[b,j,k,14] (category 2B)

Useful in Certain Circumstances
- Nivolumab (Child-Pugh Class B only)[b,j,10-12] (category 2B)
- Dostarlimab-gxly[b,j,l,15,16] for MSI-H/dMMR tumors (category 2B)

Imunoterapija pri HCC- zaključki

- **1.linija:**

- kot prva možnost: **atezolizumab+ bevacizumab** (samo pri Child A)
- v posebnih primerih: **nivolumab** (samo pri Child A ali B)

- **2.linija:**

- Kot druga možnost: **nivolumab+ipilimumab** (samo pri Child A)
ali **pembrolizumab** (samo pri Child A)
- V posebnih primerih: **nivolumab** (samo pri Child B)
ali **dostarlimab** v primeru MSI-H

Dostarlimab-gxly is a humanized monoclonal antibody of the **IgG4 isotype that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2**, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

ESMO UpDate marec 2021: BCLC stadiji

Table 4. BCLC staging and treatment options according to level of evidence and approval status

BCLC stage		Treatment (standard of care)	Indication constraints based on tumour burden and liver function	Alternative treatment
0-A	Single tumour any size or up to three nodules ≤3 cm Preserved liver function ECOG PS 0	Resection [III, A] Transplantation [III, A] Thermal ablation [III, A] TACE [I, A]	Adequate size and function of remnant liver Size ≤5 cm, number of nodules ≤3 Size ≤3 cm, not adjacent to vessels or bile duct Contraindications against resection and thermal ablation. Bridging to transplantation	SBRT [III, C] HDR brachytherapy [III, C] SIRT [III, C]
B	Multinodular Preserved liver function ECOG PS 0	TACE [I, A]	Size 5-10 cm, tumour nodules accessible to supra-selective catheterisation	Transplantation [III, A] Resection [III, A] Systemic therapy (not suitable for local therapies) [I, A] SIRT (liver confined, good liver function, no systemic therapy feasible)
C	Portal invasion Extrahepatic spread Preserved liver function ECOG PS 0-2	Atezolizumab plus bevacizumab (first line) [I, A; ESMO-MCBS v1.1 score: 5] Option: Sorafenib (first line) [I, A; ESMO-MCBS v1.1 score: 4] Lenvatinib (first line) [I, A][a] Standard after sorafenib: Cabozantinib [I, A; ESMO-MCBS v1.1 score: 3] Regorafenib[b] [I, A; ESMO-MCBS v1.1 score: 4] Ramucirumab[c] [I, A; ESMO-MCBS v1.1 score: 1] Option after atezolizumab plus bevacizumab/lenvatinib: Sorafenib [V, C] Lenvatinib [V, C] Cabozantinib [V, C] Regorafenib[b] [V, C] Ramucirumab[c] [V, C]	Child–Pugh A Child–Pugh A Tolerability to sorafenib, (regorafenib) AFP ≥400 ng/ml for ramucirumab	SIRT (liver confined, good liver function, no systemic therapy feasible)
D	End-stage liver function ECOG PS 3-4	BSC [III, A]		

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; HDR, high dose rate; PS, performance status; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor.
[a] Noninferiority to sorafenib established; no evaluable benefit.
[b] Regorafenib is not recommended in TKI-naïve patients.
[c] Ramucirumab is only recommended in patients with an AFP level ≥400 ng/ml.

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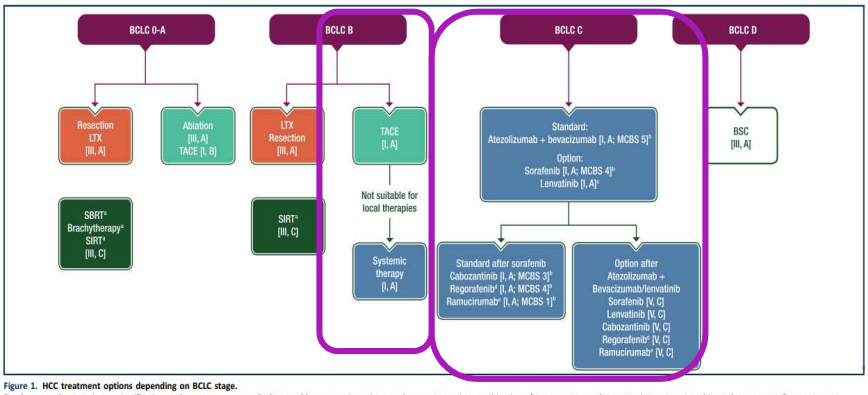


Figure 1. HCC treatment options depending on BCLC stage.
Purple: general categories or stratification; red: surgery; green: radiotherapy; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management.
AFP, a-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; EMA, European Medicines Agency; HCC, hepatocellular carcinoma; LTX, liver transplantation; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor.
[a] Nonstandard, alternative treatment.
[b] ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since January 1, 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/scale-evaluation-forms-v1.0-v1.1/scale-evaluation-forms-v1.1).
[c] Noninferiority to sorafenib established; no evaluable benefit.
[d] Regorafenib is not recommended in TKI-naïve patients.
[e] Ramucirumab is only recommended in patients with an AFP level ≥400 ng/ml.

RAKI BILIARNEGA TRAKTA (RBT)- imunoterapija

Sistemsko zdravljenje

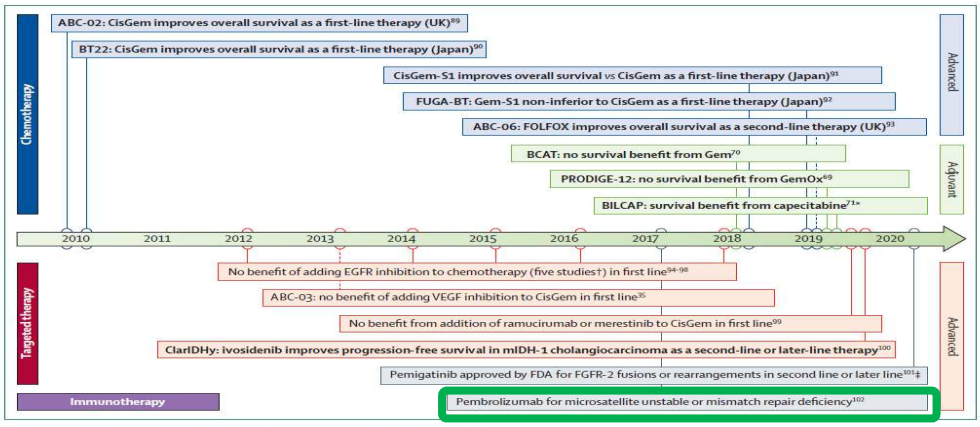


Figure 3: **Timeline of developments in systemic therapy of biliary tract cancer**
Randomised controlled studies are presented, with randomised phase 3 studies in bold and randomised phase 2 in non-bold font. CisGem-S1 and ABC-06 have been presented as abstracts (final publication pending). Grey boxes signify licensed therapies. The timeline shows the year of final publication. ABC=Advanced Biliary tract Cancer. CisGem=cisplatin and gemcitabine. GemOx=gemcitabine and oxaliplatin. EGFR=epidermal growth factor receptor. VEGF=vascular endothelial growth factor. mIDH-1=mutated isocitrate dehydrogenase-1. FDA=Food and Drug Administration. FGFR-2=fibroblast growth factor receptor-2. *In prespecified sensitivity analysis (not by intention to treat). †One phase 3 study and four phase 2 studies. ‡Orphan drug, breakthrough therapy, and priority review designation (based on phase 2 study).

Valle JW, et al. Biliary tract cancer. Lancet 2021; 397: 428–44.

KEYNOTE 158- MSI-H

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

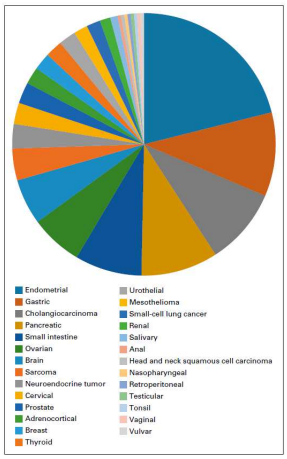
Aurelien Marabelle, MD, PhD[1]; Dung T. Le, MD[2]; Paolo A. Ascierto, MD[3]; Anna Maria Di Giacomo, MD[4]; Ana De Jesus-Acosta, MD[5]; Jean-Pierre Delord, MD, PhD[6]; Ravit Geva, MD, MSc[7]; Maya Gottfried, MD[7]; Nicolas Penel, MD, PhD[8]; Aaron E. Hansen, MBBS[9]; Sarina A. Piha-Paul, MD[10]; Toshihiko 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[19]; Scott K. Pruitt, MD, PhD[20]; and Luis A. Diaz Jr, MD[1,4]

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)
Colorectal	34 (14.6)
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

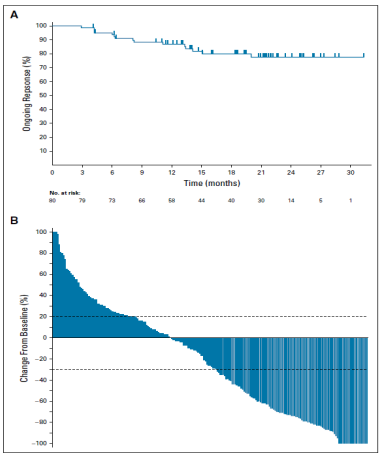
Response	Evaluable Patients (N = 233)
Objective response	
No. (%; 95% CI)	80 (34.3; 28.3 to 40.8)
Median time to response, months (range)*	2.1 (1.3-10.6)
Median duration of response, months† (range)	NR (2.9-31.3+)
Best overall response, No. (%)	
Complete response	23 (9.9)
Partial response	57 (24.5)
Stable 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)

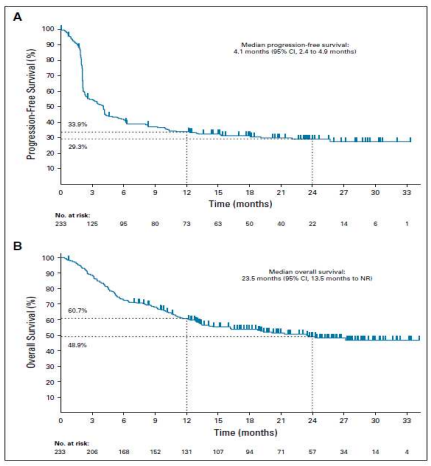
TABLE 4. Incidence of Adverse Events

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.

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

- MSI-H:ORR na pembrolizumabu

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[5]; Jean-Pierre Delord, MD, PhD[6]; Ravit Geva, MD, MSc[7]; Maya Gottfried, MD[8]; Nicolas Penel, MD, PhD[9]; Aaron R. Hansen, MBBS[10]; Sarina A. Piha-Paul, MD[11]; Toshihiko Doi, MD, PhD[12]; 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[19]; Scott K. Pruitt, MD, PhD[20]; and Luis A. Diaz Jr, MD[21]

Eligible patients with histologically/cytologically confirmed MSI-H/dMMR advanced noncolorectal cancer who experienced failure with prior therapy received pembrolizumab 200 mg once every 3 weeks for 2 years or until disease progression, unacceptable toxicity, or patient withdrawal.

TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
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)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
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. 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 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**

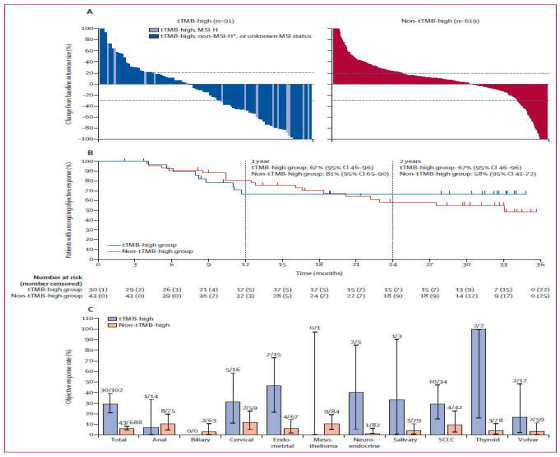
Marabelle A, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020

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

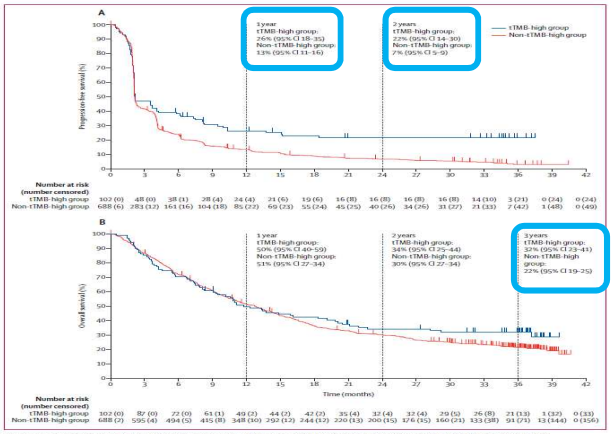


Figure 3: Progression-free survival per RECIST (version 1.1) by independent central review (A) and overall survival (B) in the efficacy population
Vertical lines on each curve denote censored patients. RECIST=Response Evaluation Criteria in Solid Tumors. tTMB=high=high tissue tumour mutational burden.

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

Trenutna potekajoče klinične raziskave z imunoterapijo in RBT

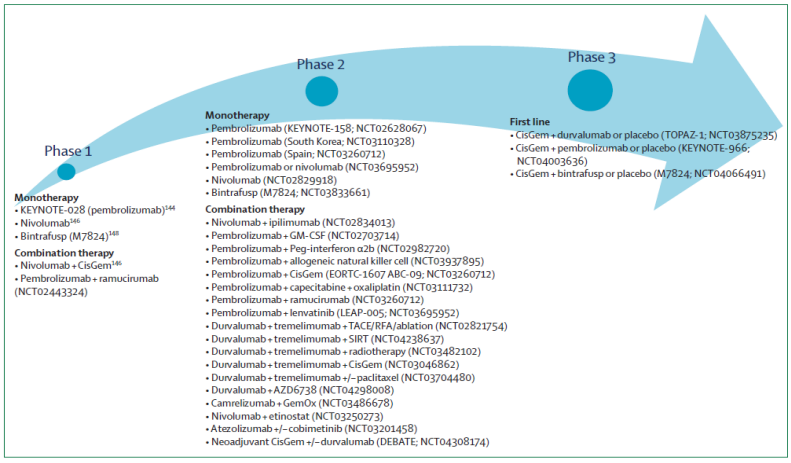


Figure 4: **Clinical trial development of immunotherapy in biliary tract cancer**
CisGem=cisplatin and gemcitabine. GemOx=gemcitabine and oxaliplatin.

Bintrafusp Alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 monoclonal antibody blocking PD-L1. It binds to and neutralizes activated TGF beta and binds to PD-L1. This prevents TGF beta- and PD-L1-mediated signalling, and increases natural killer (NK) cell and cytotoxic T-lymphocyte (CTL) activities.

Valle JW, et al. Biliary tract cancer. Lancet 2021; 397: 428–44.

NCCN

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
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 (category 2B) • Capecitabine + cisplatin (category 2B) • Capecitabine + oxaliplatin • Gemcitabine + albumin-bound paclitaxel • 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] • For MSI-H/dMMR tumors: ‣ Pembrolizumab[d,e,9]

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression

		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] • For MSI-H/dMMR tumors/TMB-H tumors: ‣ Pembrolizumab[d,e,g,9,13,14] fusions or rearrangements: ‣ Pemigatinib[15] ‣ Infigratinib[16] • For cholangiocarcinoma with *IDH1* mutations ‣ Ivosidenib[17] • For *BRAF*-V600E mutated tumors ‣ Dabrafenib + trametinib[18,19] Nivolumab[v,u,x,y] (category 2B) • Lenvatinib + pembrolizumab[e,g,21] (category 2B) • For MSI-H/dMMR tumors ‣ Dostarlimab-gxly[e,g,h,22,23] (category 2B)

[d] There are limited clinical trial data to support pembrolizumab in this setting. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744-750.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] Treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction.
[g] For patients who have not been previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[h] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

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.

BIL-C

Imunoterapija pri RBT- zaključki

1.linija:

<u>V posebnih primerih:</u>

- MSI-H/dMMR → pembrolizumab

2.linija:

<u>V posebnih primerih:</u>

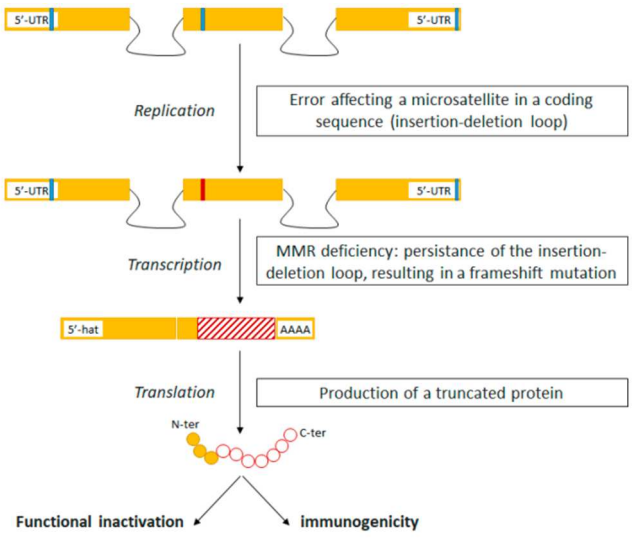
- MSI-H/dMMR/TMB-H → pembrolizumab
- Nivolumab
- Levantinib + pembrolizumab
- MSI-H/dMMR/TMB-H → dostarlimab

NOVOSTI NA PODROČJU IMUNO-TERAPIJE KOLOREKATLANEGA RAKA

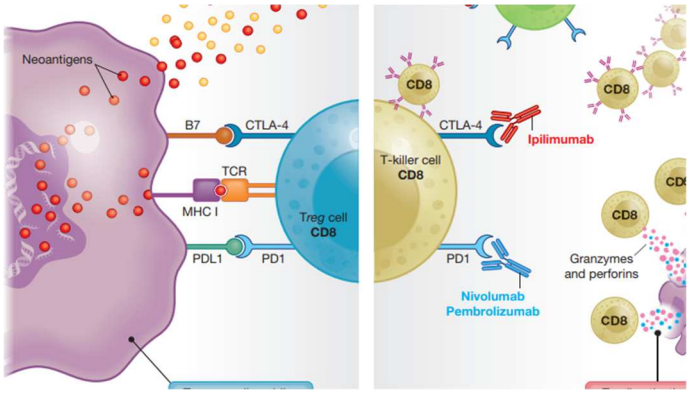
MARIJA IGNJATOVIĆ, DR. MED.

MIKROSATELINTNA NESTABILNOST (MSI)

"MOLEKULARNI INDIKATOR OKVARE MMR-JA DNA MOLEKULE"



- Veliko mutacijsko breme
- Neoantigeni
- Dobra infiltracija z limfociti



MSI/dMMR KOLOREKTALNI KARCINOM (KRK)

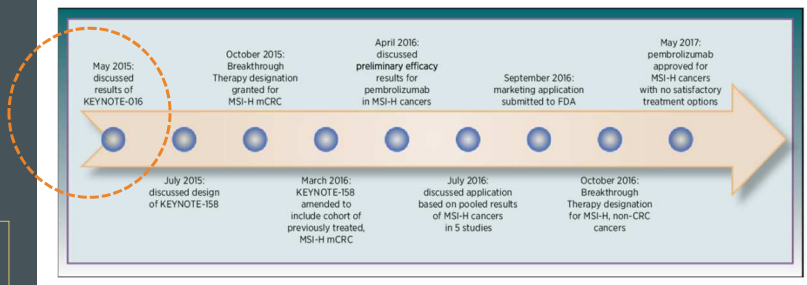
Lokalizirani KRK: 10-18%
Metastatski KRK 3-5%

Mucinozni/pečatnocelični/slabo diferencirani/nediferencirani; številni intraepitelijski limfociti; peritumorski Cronu podoben limfocitni infiltrati

Desni kolon

Boljša prognoza kot MSS/pMMR tumorji

KRK IN IMUNOTERAPIJA



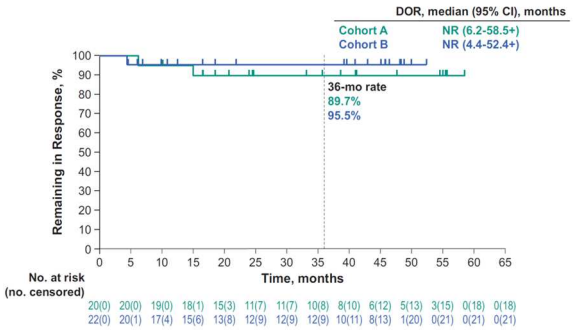
	MSI/dMMR KRK (n=11)	MSI/dMMR neKRK (n=9)	MSS/pMMR KRK (n=21)
Odgovor na zdravljenje	40%	71%	0%

Klinična raziskava in zdravilo	n	Odgovor na zdravljenje (%)	Čas do napredovanja bolezni (%)		Celokupno preživetje (%)	
			Po 1 letu	Po 2 letih	Po 1 letu	Po 2 letih
KN-016, pembrolizumab	28	57	-	-	-	-
KN-164, pembrolizumab kohorta A (≥2 red zdravljenja)	61	33	34	31	72	55
KN-164, pembrolizumab kohorta B (≥1 red zdravljenja)	63	33	41	37	76	63
CM-142, nivolumab kohorta A	74	33	44	-	-	-
CM-142, nivolumab + ipilimumab kohorta B	119	61	71	60	85	74
NCT02227667, durvalumab	11	27	36	-	-	-
GARNET, dostarlimab	69	36	-	-	-	-

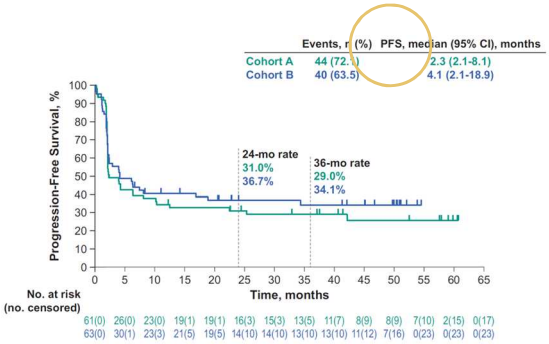
IMUNOTERAPIJA V 2. ALI POZNEJŠEM REDU ZDRAVLJENJA METASTATSKEGA KRK

ESMO 2021

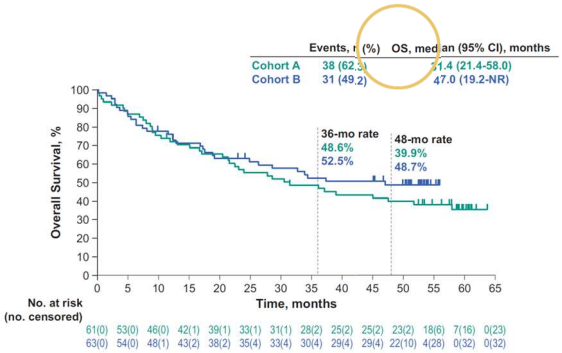
	Cohort A n = 61		Cohort B n = 63	
	n	% (95% CI)[a]	n	% (95% CI)[a]
ORR	20	32.8 (21.3-46.0)	22	34.9 (23.3-48.0)
DCR				
CR	3	4.9 (1.0-13.7)	9	14.3 (6.7-25.4)
PR	17	27.9 (17.1-40.8)	13	20.6 (11.5-32.7)
SD	11	18.0 (9.4-30.0)	13	20.6 (11.5-32.7)
PD	28	45.9 (33.1-59.2)	25	39.7 (27.6-52.8)
Nonevaluable	2	3.3 (0.4-11.3)	3	4.8 (1.0-13.3)
DCR (CR + PR + SD)	31	50.8 (37.7-63.9)	35	55.6 (42.5-68.1)
DOR,[b] median (range), months	NR (6.2-58.5+)		NR (4.4-52.4+)	
DOR ≥36 months,[b] %	89.7		95.5	



ESMO 2021

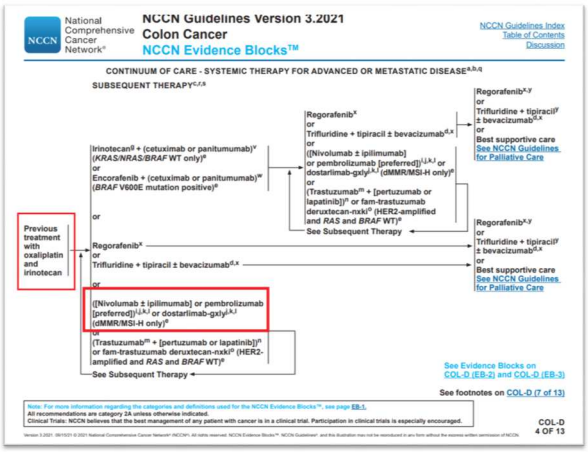


	Po 1 letu	Po 2 letih	Po 3 letih
Kohorta A	34%	31%	29%
Kohorta B	41%	37%	34%



	Po 1 letu	Po 2 letih	Po 3 letih	Po 4 letih
Kohorta A	72%	55%	49%	40%
Kohorta B	76%	63%	52.5%	49%

- Prv randomizirana raziskava SAMCO



ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

PRIPOROČILA ZA OBRAVNAVO BOLNIKOV Z RAKOM DEBELEGA ČREVESA IN DANKE

DRUGI RED TERAPIJE:

Imunoterapija z zaviralci imunskih kontrolnih točk v primeru MSI-H*:

-anti- PD-1 monoterapija: nivolumab, pemrolizumab

-anti –PD-1 v kombinaciji z anti CTLA-4: nivolumab+ipilimumab

First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study

Klinična raziskava in zdravilo	n	odgovor na zdravljenje (%)	kotrola bolezni (%)	čas do napredovanja bolezni (%)	celokupno preživetje (%)
CM-142, nivolumab + ipilimumab, kohorta 3	45	69	84	74 (po 2 letih)	79 (po 2 letih)

IMUNOTERAPIJA V 1. REDU ZDRAVLJENJA METASTATSKEGA KRK

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*

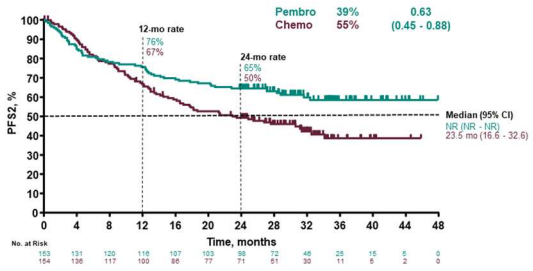
		SEKUNDARNI CILJI				PRIMARNA CILJA	
pembrolizumab vs. KT +/- antiVEGF ali EGFR inhibitor	n	odgovor na zdravljenje (%)	trajanje odgovor (%)	čas do napredoavanja bolezni 2 (%)	kvaliteta življenja	čas do napredovanja bolezni (meseci)	celokupno preživetje
	307	44 vs. 33	83 vs. 35			16.5 vs 8.2	

IMUNOTERAPIJA V 1. REDU ZDRAVLJENJA METASTATSKEGA KRK

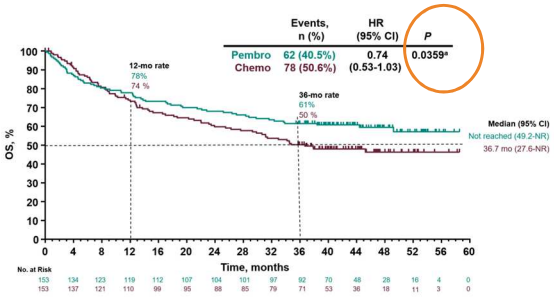
ASCO GI 2021

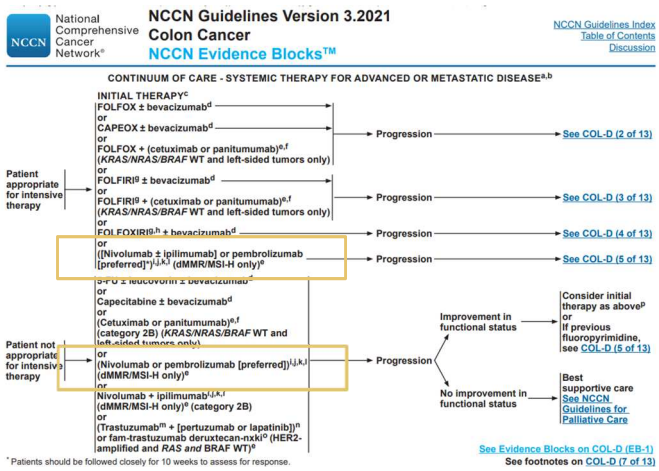
Patients, n (%)	Pembrolizumab N = 153	Chemotherapy N = 154
Crossed over from SOC to pembrolizumab	0	56 (36.4)
Did not cross over but received subsequent anti-cancer therapies*	44 (28.8)	44 (28.6)
Pembrolizumab*	6 (3.9)	14 (9.1)
Nivolumab	0	4 (2.6)
Durvalumab	0	2 (1.3)
Nivolumab + Ipilimumab	0	3 (1.9)
Atezolizumab + Bevacizumab	0	1 (0.6)
Avelumab	0	1 (0.6)
Anti-PD-L1 unspecified	0	2 (1.3)
FOLFIRI/XELIRI	4 (2.6)	2 (1.3)
FOLFIRI + Bevacizumab	7 (4.6)	3 (1.9)
FOLFIRI + Panitumumab	1 (0.7)	1 (0.6)
FOLFOXIRI/FOLFOXIRI + Bevacizumab	2 (1.3)	0
XELIRI/Irinotecan + Cetuximab	2 (1.3)	0
FOLFOX	7 (4.6)	1 (0.6)
FOLFOX/XELOX + Bevacizumab	9 (5.9)	2 (1.3)
FOLFOX + Panitumumab	1 (0.7)	0
5-Fluorouracil	1 (0.7)	0
5-Fluorouracil + Bevacizumab	0	3 (1.9)
Panitumumab	1 (0.7)	2 (1.3)
ICOS inhibitor + Pembrolizumab	1 (0.7)	0
Other**	2 (1.3)	3 (1.9)

Čas do napredovanja bolezni 2

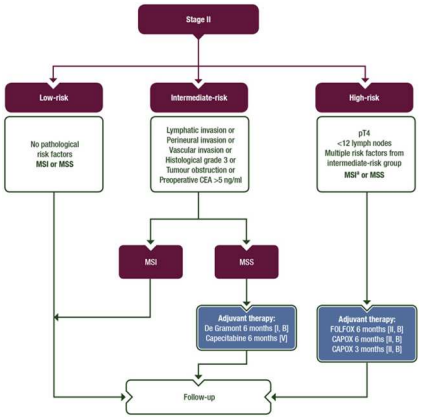


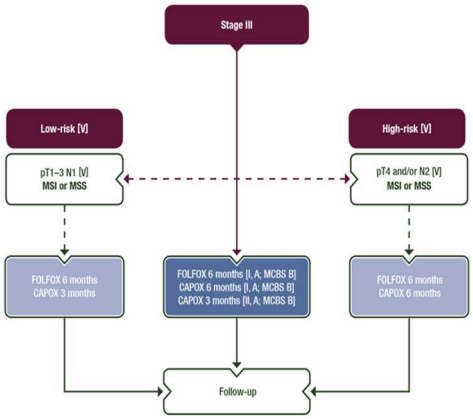
ASCO 2021





IMUNOTERAPIJA V ADJUVANTNEM ZDRAVLJENJU KRK





IMUNOTERAPIJA V ADJUVANTNEM ZDRAVLJENJU KRK

NCT02912559	ATOMIC	III	stage III; dMMR	FOLFOX+/– atezolizumab (anti-PDL1)	recruiting
NCT03827044	POLEM	III	stage III;dMMR or POLE mutant	fluoropyrimidine-based chemotherapy +/– avelumab (anti-PDL1)	recruiting
NCT03832569	-	II	resected R0 tumor with persistent ctDNA; dMMR	Pembrolizumab (anti-PD1) or placebo	recruiting
NCT04165772	-	II	advanced rectal cancer; dMMR	Dostarlimab (anti-PD1) followed by chemoradiotherapy and surgery	recruiting

IMUNOTERAPIJA V NEOADJUVANTNEM ZDRAVLJENJU KRK

Study Description Go to

Brief Summary:

In this exploratory study, patients with stage 1-3 adenocarcinoma of the colon with no signs of distant metastases will be treated with short-term immunotherapy + COX2-inhibitors. This treatment will be given during the window period until surgical resection of the tumor. The duration of treatment will be approximately 6 weeks.

Condition or disease	Intervention/treatment	Phase
Colon Carcinoma	Drug: Nivolumab Drug: Ipilimumab Drug: Celecoxib 200mg	Phase 2

Detailed Description:

In this single-center, open-label, exploratory study, the investigators will enroll 60 patients within two years, including 30 patients with MSS tumors and 30 patients with MSI tumors. Patients with MSS tumors will be randomized to either group 1 or 2. Patients with MSI tumors will all be allocated to group 1.

Patients in group 1 will be treated with a single dose of ipilimumab 1mg/kg on day 1 and two cycles of nivolumab 3mg/kg on day 1 and 15, respectively.

Patients in group 2 will be treated with a single dose of ipilimumab 1mg/kg on day 1, two cycles of nivolumab 3mg/kg one day 1 and 15 and celecoxib daily until the day before surgery.

IMUNOTERAPIJA V NEOADJUVANTNEM ZDRAVLJENJU KRK

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi, Lorenzo F. Fanchi, ... John B. Haanen + Show authors

	Patološki odgovor na zdravljenje (%)	Patološki popolni odgovor na zdravljenje (%)
dMMR	100	60
pMMR	27	0

ZAKLJUČKI MSI KRK

- Sedanjost: zdravljenja metastatske bolezni (monoimunoterapija & kombinirana imunoterapija)
- Prihodnost: (neo)adjuvantna imunoterapija…

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ONKOLOŠKI INŠTITUT LJUBLJANA

Prognostični in prediktivni biomarkerji v imuno-onkologiji

Doc. dr. Boštjan Šeruga, dr. med.
Sektor internistične onkologije, Onkološki inštitut Ljubljana in Univerza v Ljubljani

Novosti v imunoterapiji 2021

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ONKOLOŠKI INŠTITUT LJUBLJANA

Izhodišča

- **Kaj je prognostični in kaj prediktivni biomarker (BM)?**
- **Primeri v Imuno-onkologiji: PD-L1 in TMB**
- **Kombinacije BM in multi-parametrični modeli BM**
- **Zaključki**

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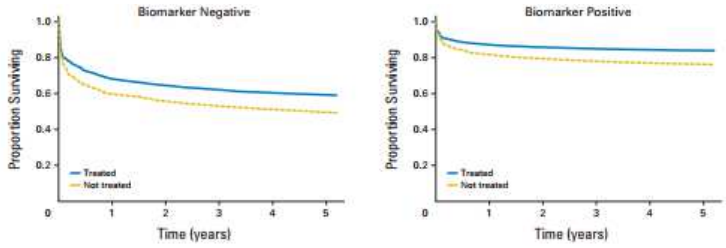
ONKOLOŠKI INŠTITUT LJUBLJANA

Prognostični biomarker

- **Prognostični BM napoveduje izhod bolezni ne glede na vrsto zdravljenja**
- **Če novo zdravljenje učinkovito, imajo korist tako BM+ kot tudi BM- bolniki**
- **V multivariatni analizi BM neodvisno napoveduje izhod, stat. test interakcije med BM in zdravljenjem je <u>negativen</u>**



Ballman, J Clin Oncol, 2021

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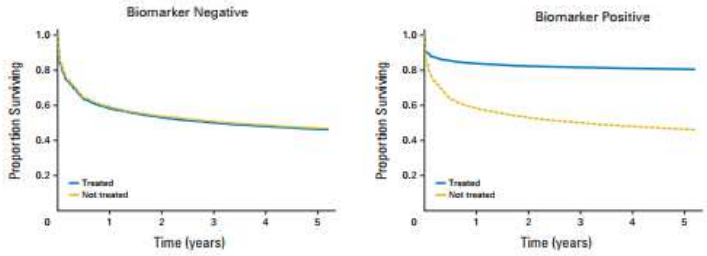
ONKOLOŠKI INŠTITUT LJUBLJANA

Prediktivni biomarker

- **BM je prediktiven, če se učinek zdravljenja razlikuje med BM+ in BM- bolniki**
- **Za dokaz prediktivnega BM vedno potrebi vsaj dve skupini bolnikov (randomizacija)**
- **Stat. test interakcije med zdravljenjem in BM je <u>pozitiven</u>**



Ballman, J Clin Oncol, 2021

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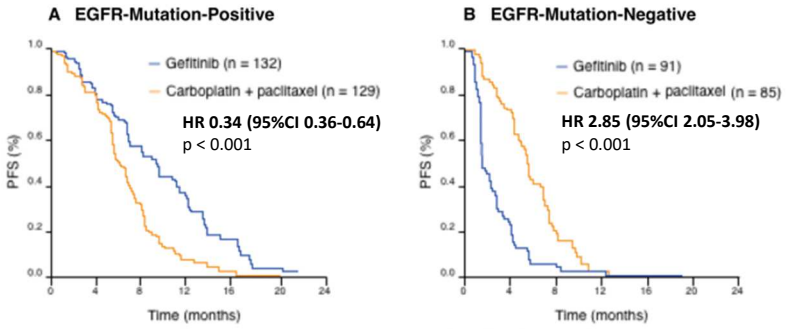
Kvalitativna interakcija

Test interakcije: p < 0.001

Gefitinib je boljši kot KT za EGFR+

Gefitinib je slabši kot KT za EGFR-



Kvalitativna interakcija jasno določi indikacijo za zdravljenje

Mok et al, NEJM, 2009

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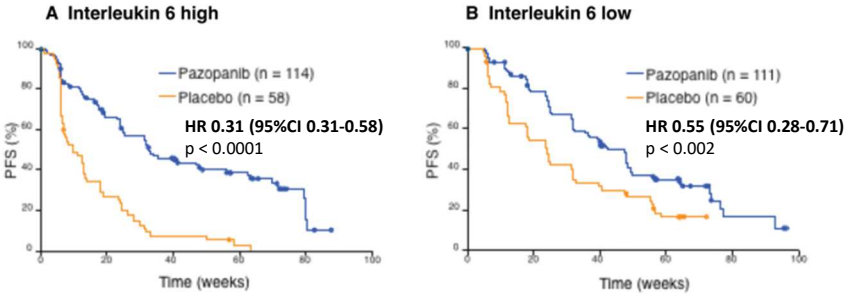
ONKOLOŠKI INŠTITUT LJUBLJANA

Kvantitativna interakcija

Test interakcije: p=0.009

Korist pri BM+ in BM-, korist večja pri IL-6 high kot IL-6 low



Odločitev ali je BM koristen za odločitev glede zdravljenje je težja

Tran et al, Lancet Oncol 2012

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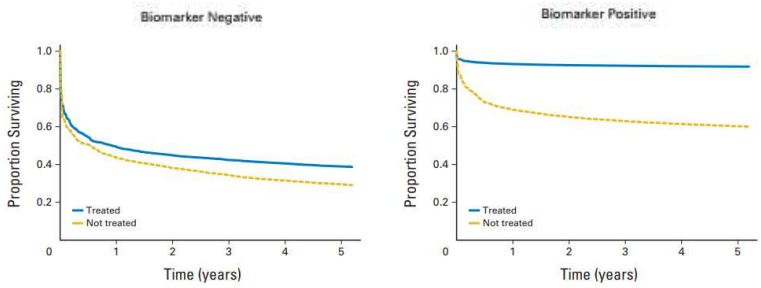
ONKOLOŠKI INŠTITUT LJUBLJANA

Prognostični in prediktivni biomarker

- **Prognostični BM: različen izhod glede na BM, ne glede na zdravljenje**
- **Prediktivni BM: različen učinek zdravljenja glede na izraženost BM**



Ballman, J Clin Oncol, 2021

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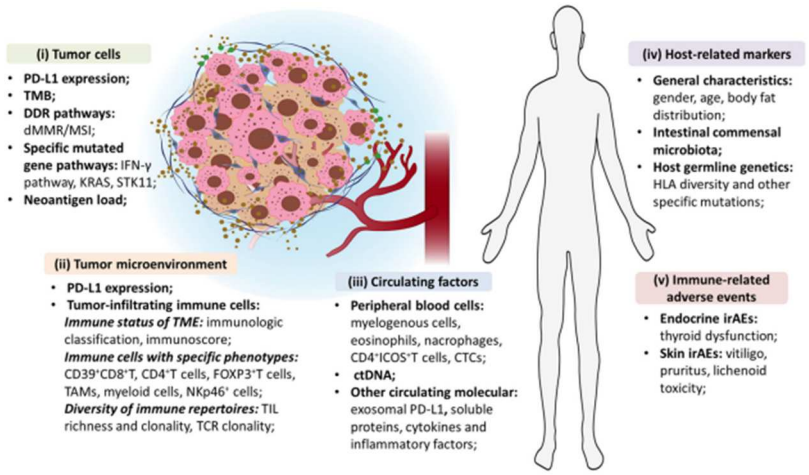
ONKOLOŠKI INŠTITUT LJUBLJANA

Potencialni biomarkerji v imuno-onkologiji



Bai et al, Biomarker Research, 2020

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ONKOLOŠKI INŠTITUT LJUBLJANA

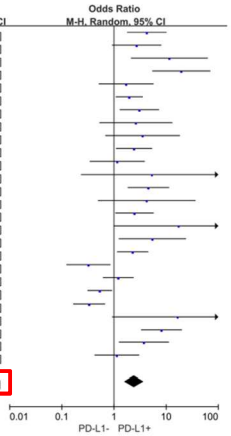
PD-L1 and Survival in Solid Tumors: A Meta-Analysis

Pin Wu[1,3], Dang Wu[3], Lijun Li[4], Ying Chai[1]*, Jian Huang[2,3]*

- **N=3107, 28 publikacij, 52.5% bolnikov PD-L1+**

Study or Subgroup	PD-L1- Events	PD-L1- Total	PD-L1+ Events	PD-L1+ Total	Weight	Odds Ratio M-H, Random, 95% CI
Boorjian, S. A et al.(2008)	115	140	14	27	4.6%	4.27 [1.79, 10.20]
Chen, L., et al. (2014)	11	17	33	82	4.1%	2.72 [0.92, 8.08]
Chen, X. L et al.(2009)	13	22	2	18	2.9%	11.56 [2.12, 63.13]
Chen, Y. B., et al. (2012)	24	51	3	69	3.7%	19.56 [5.43, 70.41]
Cho, Y. A et al.(2011)	12	19	13	26	3.9%	1.71 [0.51, 5.74]
Gao, Q et al.(2009)	99	180	23	60	5.1%	1.97 [1.08, 3.57]
Geng, Y., et al. (2014)	24	35	27	65	4.6%	3.07 [1.29, 7.31]
Hamanishi, J et al.(2007)	20	22	38	48	3.1%	2.63 [0.53, 13.19]
Hino, R et al.(2010)	23	25	26	34	3.0%	3.54 [0.68, 18.39]
Hou, J. et al.(2014)	27	41	31	70	4.7%	2.43 [1.09, 5.40]
Karim, R et al.(2009)	78	93	18	22	3.8%	1.16 [0.34, 3.90]
Liu, Y et al.(2013)	3	11	0	6	1.4%	5.35 [0.23, 122.96]
Loos, M et al.(2011)	53	64	19	37	4.5%	4.56 [1.83, 11.40]
Mansfield, A. S., et al. (2014)	6	64	1	42	2.3%	4.24 [0.49, 36.57]
Mu, C. Y et al.(2011)	20	51	12	58	4.6%	2.47 [1.06, 5.78]
Nakanishi, J et al(2007)	19	19	32	46	1.5%	17.40 [0.98, 308.28]
Ohigashi, Y et al.(2005)	12	23	3	18	3.3%	5.45 [1.24, 24.09]
Shi, S. J. et al.(2013)	56	79	33	64	4.9%	2.29 [1.15, 4.56]
Taube, J. M et al.(2012)	35	56	36	43	4.4%	0.32 [0.12, 0.86]
Ukpo, O. C et al.(2013)	75	97	62	84	5.0%	1.21 [0.61, 2.39]
Velcheti, V et al.(2014)-Greek cohort	100	219	44	72	5.2%	0.53 [0.31, 0.92]
Velcheti, V et al.(2014)-Yale University cohort	44	98	39	55	4.9%	0.33 [0.17, 0.68]
Wang, Y et al.(2009)	14	14	23	36	1.5%	16.66 [0.92, 302.04]
Wu, C et al.(2006)	42	59	10	43	4.5%	8.15 [3.30, 20.14]
Wu, K et al.(2009)	30	36	20	35	4.1%	3.75 [1.24, 11.30]
Xylinas, E et al.(2014)	50	72	16	24	4.3%	1.14 [0.42, 3.05]
Total (95% CI)		**1607**		**1184**	**100.0%**	**2.43 [1.60, 3.70]**
Total events	1005		578			

Heterogeneity: Tau² = 0.80; Chi² = 106.23, df = 25 (P < 0.00001); I² = 76%
Test for overall effect: Z = 4.18 (P < 0.0001)



Wu et al, PLOS One 2015

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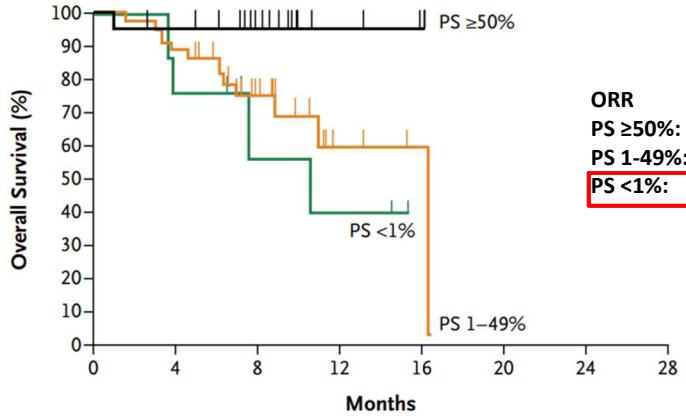
ONKOLOŠKI INŠTITUT LJUBLJANA

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S.,

No Previous Treatment



ORR
PS ≥50%: 45.2%
PS 1-49%: 16.5%
PS <1%: 10.7%

NEJM, 2016

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.I. Motzer. N.M. Tannir. D.F. McDermott. O. Arén Frontera. B. Melichar. T.K. Choueiri. E.R. Plimack. P. Barthélémy.

	PD-L1 <1%		PD-L1 ≥1%	
Outcome	**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

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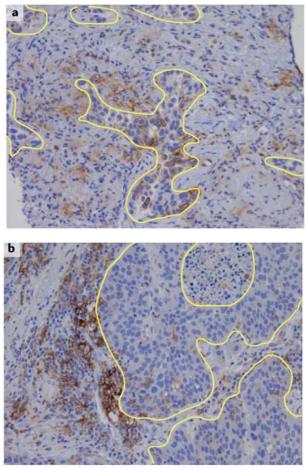
Točkovanje PD-L1

Različne celice, različni testi…



$$\text{TPS (\%)} = \frac{\text{Number of PD-L1-stained tumour cells}}{\text{Total number of viable tumour cells}} \times 100\% \text{ (for 22C3 or SP263)}$$

$$\text{TC (\%)} = \frac{\text{Number of PD-L1-stained tumour cells}}{\text{Total number of viable tumour cells}} \times 100\% \text{ (for SP142)}$$

$$\text{IC (\%)} = \frac{\text{Area of tumour infiltrated by PD-L1-stained immune cells}}{\text{Total tumour area}} \times 100\% \text{ (for SP142)}$$

$$\text{CPS} = \frac{\text{Number of PD-L1-stained cells (tumour cells, lymphocytes and macrophages)}}{\text{Total number of viable tumour cells}} \times 100 \text{ (for 22C3)}$$

Doroshow et al, Nat Rev Clin Oncol 2021

PD-L1 kot kriterij za zdravljenje

KEYNOTE-355	TNBC	Pembrolizumab + chemotherapy VS Placebo + chemotherapy	2020	1st	CPS[a] ≥ 10	IHC 22C3	566	PFS, OS	Median PFS: 9.7 vs. 5.6 m
IMpower110	adult patients with NSCLC	Atezolizumab VS Platinum-based chemotherapy	2020	1st	TC ≥ 50% or IC ≥ 10%	SP142	277	OS	Median OS: 20.2 vs 13.1 m Median PFS: 8.1 vs. 5.0 m
CHECKMATE-227 (Part 1a)	NSCLC	Nivolumab+ ipilimumab VS Platinum-doublet chemotherapy	2020	1st	TC ≥ 1%	IHC 28-8	396	OS	Median OS: 17.1 vs. 14.9 m
KEYNOTE-181	ESCC[a]	Pembrolizumab VS Chemotherapy	2019	2nd	CPS ≥10	IHC 22C3	85	OS	Median OS: 10.3 vs. 6.7 m
KEYNOTE-180		Pembrolizumab		3rd			121	ORR, response duration	ORR: 20%
KEYNOTE-042	NSCLC	Pembrolizumab V.S Carboplatin-containing chemotherapy	2019	1st	TPS[d] ≥ 1%	IHC 22C3	637	OS	Median OS: TPS ≥ 1%: 16.7 vs. 12.1 m TPS ≥ 20%: 17.7 vs. 13.0 m TPS ≥ 50%: 20 vs. 12.2 m
IMpassion130	TNBC	Atezolizumab + nab-paclitaxel VS Placebo + nab-paclitaxel	2019	1st	IC ≥ 1%	SP142	451	PFS, OS	Median OS: 7.4 vs. 4.8 m
KEYNOTE-048 subgroups	HNSCC	Pembrolizumab VS Cetuximab plus chemotherapy	2019		CPS ≥ 1	IHC 22C3	301	OS	Median OS: CPS ≥1: 12.3 vs. 10.3 m CPS ≥ 20: 14.9 vs. 10.7 m
KEYNOTE-158	Cervical cancer	Pembrolizumab	2018	2nd	CPS ≥ 1	IHC 22C3	98	ORR	ORR:14.3%[b]
KEYNOTE-059	Gastric/GEJ	Pembrolizumab	2017	3rd	CPS ≥ 1	IHC 22C3	259	ORR	Overall ORR: 11.6% PD-L1+:15.5% PD-L1-: 6.4%
NCT01693562	Urothelial carcinoma	Durvalumab	2017	2nd	TC or IC≥ 25%	SP263	191	ORR	Overall ORR: 17.8% PD-L1+:27.6% PD-L1-: 5.1%

Različne cut-off vrednosti zaradi statističnih razlogov

Lei et al, Frontiers in Oncology, 2021

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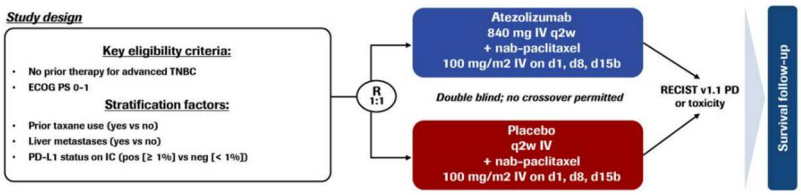
Primer 1: IMpassion 130

IMpassion130: First phase III cancer immunotherapy in mTNBC study to demonstrate clinical benefit in PD-L1+ patients



- Co-primary endpoints: PFS and OS in the ITT and PD-L1+ populations
- Prevalence of patients with PD-L1+ status: 41% in both treatment arms
- First OS IA: median follow-up: 12.9 months, 43% of death events had occurred (clinical cutoff April 17 2018)
- Second OS IA: median follow-up 18.0 months, 59% of death events (clinical cutoff Jan 2 2019)

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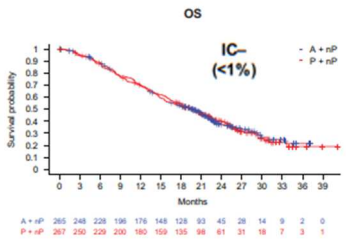
ONKOLOŠKI INŠTITUT LJUBLJANA

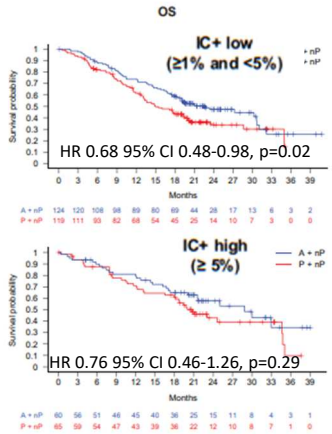
Atezolizumab and *nab*-Paclitaxel in Advanced Triple-Negative Breast Cancer: Biomarker Evaluation of the IMpassion130 Study

Leisha A. Emens, MD, PhD,[1,*] Luciana Molinero, PhD,[2] Sherene Loi, MD, PhD,[3] Hope S. Rugo, MD,[4]

BM-



BM+



Samo BM+ skupina ima korist od IT → Kvalitativna interakcija?

JNCI, 2021

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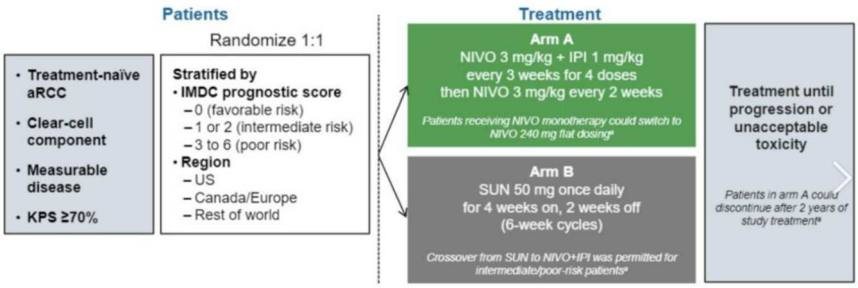
ONKOLOŠKI INŠTITUT LJUBLJANA

Primer 2: CheckMate 214



Primary endpoints: ORR, PFS (both per IRRC), and OS in IMDC intermediate- and poor-risk patients
Secondary endpoints: ORR, PFS (both per IRRC), and OS in any-risk patients (ITT); safety in all treated patients
Exploratory endpoints: ORR, PFS (both per IRRC), and OS in IMDC favorable-risk patients

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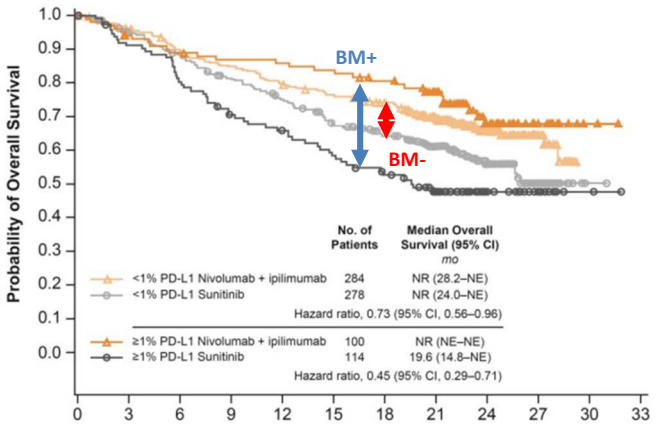
ONKOLOŠKI INŠTITUT LJUBLJANA

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma

R.J. Motzer, N.M. Tannir, D.F. McDermott, O. Arén Frontera, B. Melichar, T.K. Choueiri, E.R. Plimack, P. Barthélémy,



Obe skupini imata lahko korist od imunoterapije → Kvantitativna interakcija ?

NEJM, 2018

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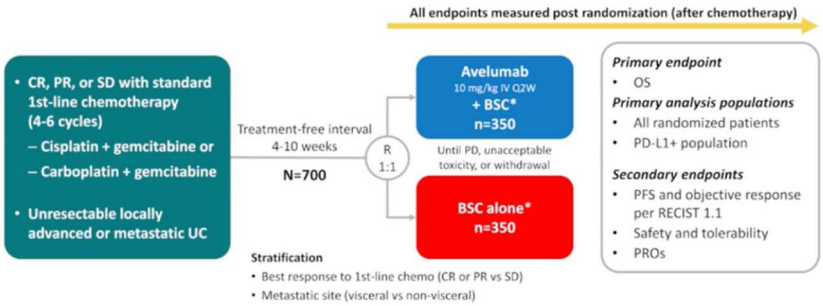
Primer 3: JAVELIN Bladder 100



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ONKOLOŠKI INŠTITUT LJUBLJANA

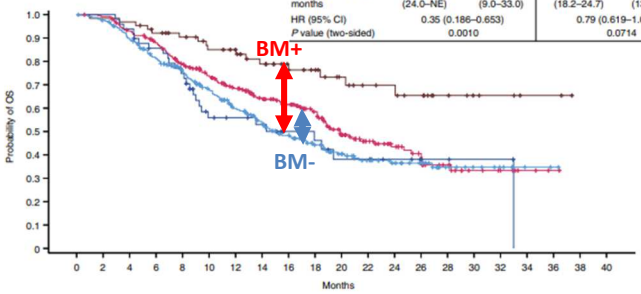
Avelumab maintenance in advanced urothelial carcinoma: biomarker analysis of the phase 3 JAVELIN Bladder 100 trial

Thomas Powles[1], Srikala S. Sridhar[2], Yohann Loriot[3], Joaquim Bellmunt[4], Xinmeng Jasmine Mu[5]

Test interakcije p=0.0163

PD-L1 na tumorskih celicah

	PD-L1 high		PD-L1 low	
	Avelumab/BSC (n = 64)	BSC (n = 49)	Avelumab/BSC (n = 260)	BSC (n = 249)
Events, n	16	26	120	127
Median (95% CI), months	NE (24.0–NE)	17.9 (9.0–33.0)	19.9 (18.2–24.7)	15.0 (13.3–18.7)
HR (95% CI)	0.35 (0.186–0.653)		0.79 (0.619–1.020)	
P value (two-sided)	0.0010		0.0714	



Potencialno uporaben biomarker?

Nature Medicine, 2021

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ONKOLOŠKI INŠTITUT LJUBLJANA

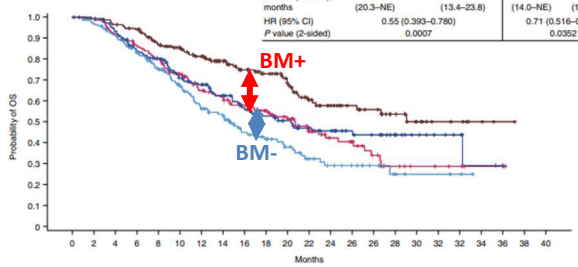
Avelumab maintenance in advanced urothelial carcinoma: biomarker analysis of the phase 3 JAVELIN Bladder 100 trial

Thomas Powles[1], Srikala S. Sridhar[2], Yohann Loriot[3], Joaquim Bellmunt[4], Xinmeng Jasmine Mu[5]

Test interakcije p=0.35

PD-L1 na imunskih celicah

	Avelumab/BSC		BSC	
	PD-L1 high (n = 173)	PD-L1 low (n = 151)	PD-L1 high (n = 153)	PD-L1 low (n = 145)
Events, n	56	80	70	83
Median (95% CI), months	NE (20.3–NE)	18.9 (13.4–23.8)	18.5 (14.0–NE)	13.4 (10.4–17.3)
HR (95% CI)	0.55 (0.393–0.780)		0.71 (0.516–0.977)	
P value (2-sided)	0.0007		0.0352	



Neuporaben prediktiven biomarker!!!

Nature Medicine, 2021

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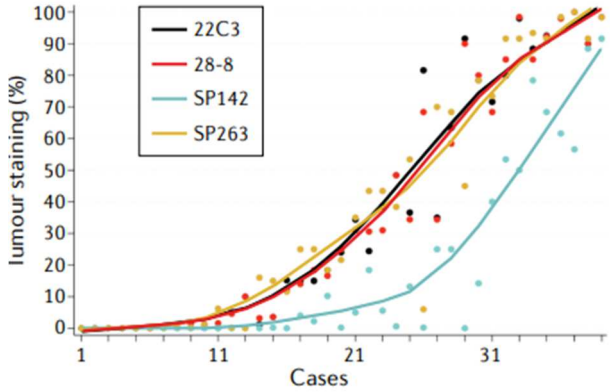
ONKOLOŠKI INŠTITUT LJUBLJANA

Analitična primerjava deleža PD-L1+ tumorskih celic



SP 142 slabše občutljiv za PD-L1 na tumorskih celicah

Hirsch et al, J Thor Oncol, 2017

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ONKOLOŠKI INŠTITUT LJUBLJANA

Kaj določa izraženost PD-L1 v tumorskem tkivu?

- **Starost vzorca**
  - **Starejši vzorci (> 3leta) pogosteje PD-L1-**
- **Primarni tumor vs. Zasevek**
  - **Pri NSCLC lahko neujemanje , pri raku dojke v zasevkih nižja izraženost PD-L1 kot v primarnem tumorju**
- **Čas odvzema tkiva**
  - **Zdravljenje lahko zmanjša izraženost PD-L1 pri NSCLC, ne pri urotelnem raku**
- **Tip vzorca (histo vs. cito)**
  - **Cito ni primerna za določitev izraženosti na imunskih celicah, sicer v vzorcu potrebnih vsaj 100 tumorskih celic**
- **Predanalitične metode**

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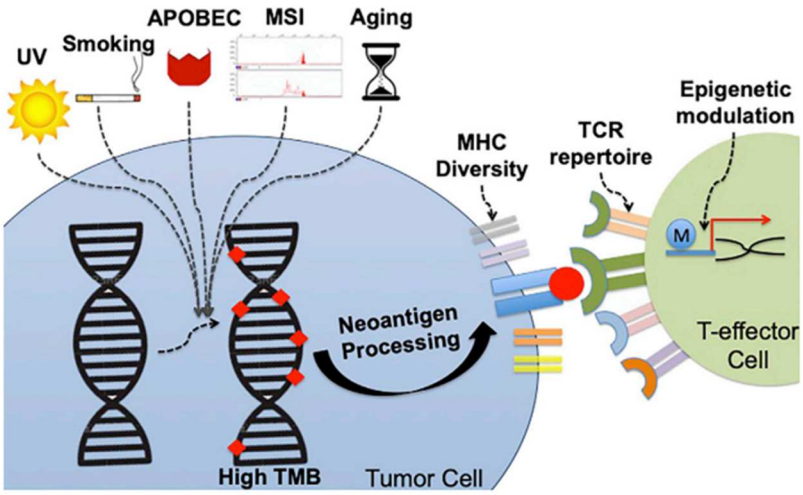
ONKOLOŠKI INŠTITUT LJUBLJANA

Kaj vpliva na TMB kot potencialen BM?



APOBEC: apolipoprotein B mRNA-editing citidin deaminaza

Jardim et al, Cancer Cell, 2021

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ONKOLOŠKI INŠTITUT LJUBLJANA

High Tumor Mutational Burden Correlates with Longer Survival in Immunotherapy-Naïve Patients with Diverse Cancers

Paul Riviere[1,2], Aaron M. Goodman[1,3], Ryosuke Okamura[1], Donald A. Barkauskas[4], Theresa J. Whitchurch[1],

N=1415, nezdravljeni z imunoterapijo

Table 3. Univariate and multivariate analyses of survival from locally advanced or metastatic disease (excluding patients treated with immunotherapy; $N = 1{,}415$ patients).[a]

Variable	Group	Patients, *N* (%)	Median survival (weeks)	HR OS (95% CI)	*P*[b] univariate
Age, y	<60	826 (58%)	250	Reference Group	
	≥60	589 (42%)	170	1.57 (1.33–1.84)	**3.83×10^{-8}**
Sex	Women	716 (51%)	189	Reference Group	
	Men	699 (49%)	172	1.07 (0.91–1.25)	0.41
Ethnicity	African-American	53 (4%)	257	1.03 (0.67–1.60)	**5.1×10^{-3}**
	Asian	137 (10%)	170	1.31 (1.02–1.68)	
	Hispanic	194 (14%)	213	0.95 (0.75–1.21)	
	Other	60 (4%)	92	1.80 (1.26–2.58)	
	NHW	971 (69%)	212	Reference Group	
Smoking history	No	848 (60%)	234	Reference Group	
	Yes	567 (40%)	187	1.22 (1.05–1.43)	0.01
Tumor type	Brain[b]	150 (11%)	697	0.61 (0.46–0.80)	**1.65×10^{-8}**
	Breast	136 (10%)	214	0.86 (0.67–1.11)	
	Colon/rectum	141 (10%)	174	0.91 (0.69–1.19)	
	Hematologic	201 (14%)	707	0.48 (0.37–0.63)	
	Lung	160 (11%)	146	1.15 (0.89–1.48)	
	Cutaneous	90 (6%)	535	0.59 (0.40–0.86)	
	Other	537 (38%)	177	Reference Group	
TMB level	Low (≤5 mutations/Mb)	960 (68%)	238	Reference Group	
	Intermediate (≥6 and <20 mutations/Mb)	348 (25%)	174	1.44 (1.21–1.71)	**1.8×10^{-4}**
	High (≥20 and <50 mutations/Mb)	58 (4%)	195	1.12 (0.75–1.67)	
	Very high (≥50 mutations/Mb)	49 (3%)	350	0.73 (0.43–1.25)	

Mol Cancer Ther; 19(10) October 2020

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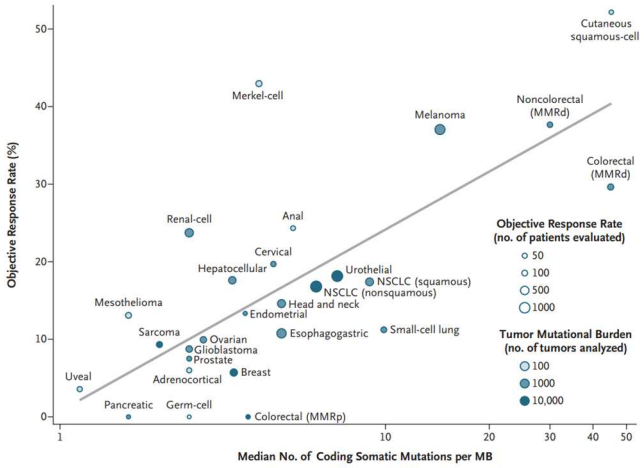
ONKOLOŠKI INŠTITUT LJUBLJANA

Korelcija med TMB in odgovorom na zdravljenje

27 različnih rakov, Pozitivna korelacija med ORR in log (TMB) (r=0.74, p<0.0001)



Yarchoan et al, NEJM, 2017

FDA approves pembrolizumab for adults and children with TMB-H solid tumors

FDA U.S. FOOD & DRUG ADMINISTRATION

On June 16, 2020, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

A total of 102 patients (13%) had tumors identified as TMB-H, defined as TMB ≥10 mut/Mb. The ORR for these patients was 29% (95% CI: 21,39), with a 4% complete response rate and 25% partial response rate. The median DoR was not reached, with 57% of patients having response durations ≥12 months and 50% of patients having response durations ≥24 months.

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ONKOLOŠKI INŠTITUT LJUBLJANA

Primeri kliničnih raziskav za TMB

Cancer Type (N)	TMB and Response Relationship*	Assay Type	Treatment Strategy	Comments	Reference
NSCLC (34 pts)	*TMB high (≥ 200 mut per tumor) versus low (<200 mut per tumor)* *RR: 59% versus 12% (p = 0.01)* *PFS: not reached versus 3.4 months, HR 0.91 (95%CI 0.08–0.47, p < 0.001)*	WES	ICI	Design: exploratory analysis of prospective phase I trial Keynote 001 (NCT01295827) Drug: pembrolizumab Higher TMB had a positive correlation with RR and PFS	(Rizvi et al., 2015)
NSCLC (312 pts)	*Nivo versus chemotherapy comparison* High TMB (≥ 243 mut): RR 47% versus 28%; PFS HR 0.62 (95% CI 0.38–1.0); OS HR 1.10 (95% 0.64–1.88) Medium and low TMB (<243 mut): RR 23% versus 33%; PFS HR 1.82 (95% CI 1.30–2.55); OS HR 9.99 (95% CI 0.71–1.40)	WES	ICI	Design: exploratory analysis of randomized phase III trial CheckMate 026 (NCT02041533) Drug: Nivo TMB was predictive of RR and PFS, but not OS	(Carbone et al., 2017)
NSCLC (102 pts)	*TMB high (≥ 13.5 mut/Mb) versus low* RR: 25% versus 20% PFS: HR 0.54 (95% CI 0.3–0.97) OS: HR 0.45 (0.17–1.16)	NGS Foundation Medicine	ICI	Design: exploratory analysis of prospective phase II trial (NCT01846416) Drug: atezolizumab Higher TMB was associated with RR and PFS in both unselected and PD-L1-selected patients	(Kowanetz et al., 2017)
NSCLC (371pts)	*TMB high (≥ 17.1 mut/Mb) versus low* RR: 29% versus 16% PFS: HR 0.5 (95% CI 0.38–0.67) OS: HR 0.7 (0.49–1.0)	NGS Foundation Medicine	ICI	Design: exploratory analysis of prospective phase II trial (NCT02031458) Drug: atezolizumab TMB was associated with RR, PFS, and OS	(Kowanetz et al., 2017)
NSCLC (92 pts)	*Atezolizumab versus docetaxel comparison* TMB high (≥ median = 15.8 mut/Mb): RR 20% versus 8%; OS = HR 0.5 (95%CI 0.15–1.67); PFS = HR 0.49 (95% CI 0.19–1.3) All evaluable patients: RR 13% versus 15%; OS = HR 0.65 (95% CI 0.38–1.12); PFS 0.98 (95%CI 0.63–1.53)	NGS Foundation Medicine	ICI	Design: exploratory analysis of randomized phase II trial (NCT01903993) Drug: atezolizumab Higher TMB was an independent predictor of improved RR, PFS, but not OS	(Kowanetz et al., 2017)
NSCLC (444 pts)	*TMB high (≥ 20 mut/Mb) versus intermediate/low (<20 mut/Mb)* Median duration of therapy: 7.5 versus 4.6 months (p = 0.001) Median OS: not reached versus 10 months (p = 0.10)	NGS Foundation Medicine	ICI	Design: retrospective analysis of Flatiron Health Database Drug: Nivo Higher TMB was predictive of benefit in the multivariable analysis	(Singal et al., 2017)
NSCLC (75 pts)	*TMB above (>158 mutations) versus below median (≤ 158 mutations)* RR: 51% versus 13% (p = 0.0005) DCB: 65% versus 34% (p = 0.011) PFS: 17.1 versus 3.7 months, HR 0.41 (95% CI, 0.23–0.73; p = 0.0024)	WES	ICI + ICI	Design: exploratory analysis of single phase II trial (CheckMate 012) (NCT01454102). Drug: Ipi plus Nivo TMB and PD-L1 were demonstrated to present independent predictive value four outcome	(Hellmann et al., 2018c)

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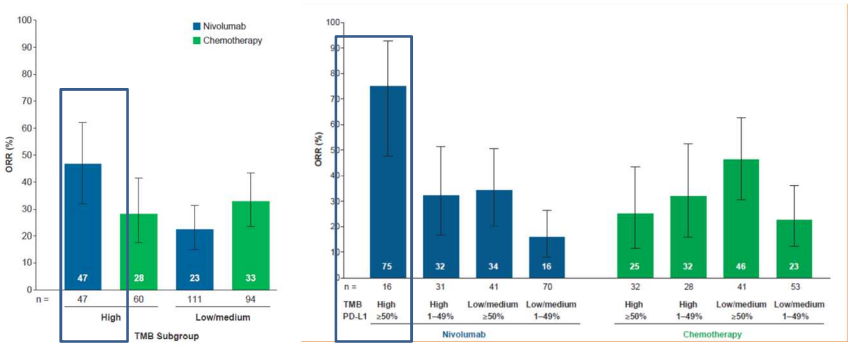
ONKOLOŠKI INŠTITUT LJUBLJANA

First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer

D.P. Carbone, M. Reck, L. Paz-Ares, B. Creelan, L. Horn, M. Steins, E. Felip, M.M. van den Heuvel, T.-E. Ciuleanu,

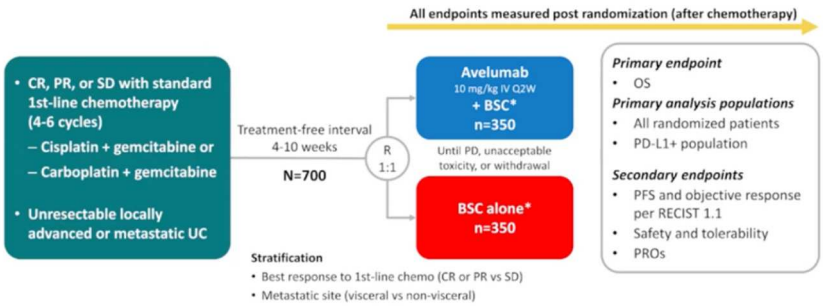
Kombinacija TMB in PD-L1



Kombinacija obeh BM lahko boljše napove odgovor na zdravljenje kot posamezen BM

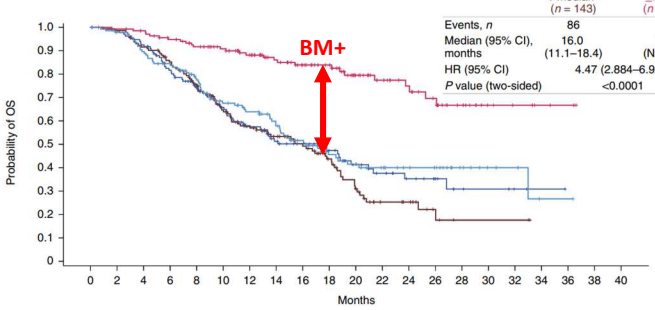
NEJM, 2017

Primer : JAVELIN Bladder 100



Multi-parametrični prediktivni model

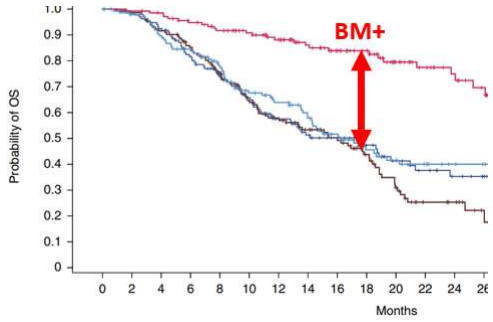
- **Upoštevane genomske alteracije (n=120) in genski podpis genov vključenih v imunski odgovor in rast tumorja (N=444)**



	Avelumab + BSC >median (n = 143)	Avelumab + BSC ≤median (n = 138)	BSC >median (n = 134)	BSC ≤median (n = 140)
Events, n	86	27	69	68
Median (95% CI), months	16.0 (11.1–18.4)	NE (NE–NE)	17.3 (11.5–21.0)	16.2 (14.0–20.2)
HR (95% CI)	4.47 (2.884–6.927)		1.10 (0.787–1.540)	
P value (two-sided)	<0.0001		0.5734	

Optimalen prediktivni biomarker?

Powles et al, Nature Medicine 2021



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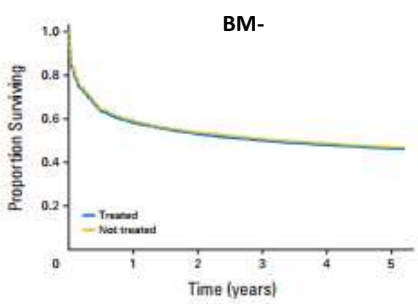
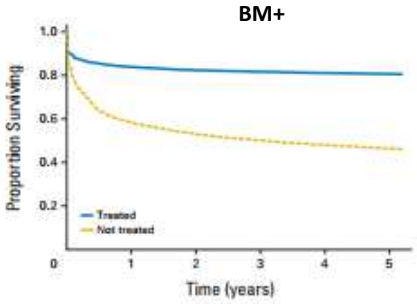




Univerza v Ljubljani

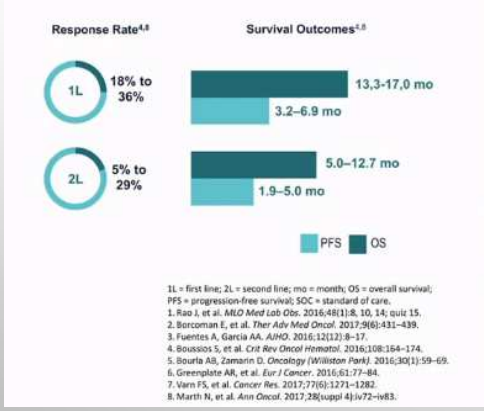
ONKOLOŠKI INŠTITUT LJUBLJANA

Zaključki

- **IT večini bolnikov s solidnimi raki ne koristi, zdravljenje predstavlja velik finančni strošek in je lahko tudi zelo toksično**
- **Pomen prognostičnih BM v I-O jasnejši kot pomen prediktivnih dejavnikov**
- **PD-L1 in TMB najboljša približka prediktivnih BM v I-O**
- **Obetajo multi-parametrični prediktivni modeli**

IMUNOTERAPIJA PRI ZDRAVLJENJU NAPREDOVALEGA KARCINOMA MATERNIČNEGA VRATU

MIRJANA PAVLOVA BOJADŽISKI, DR MED



- 1 LINIJA PLATINA/PACLITAXEL +/- BEVACIZUMAB
- NI SOC V 2L+
- POTREBA PO NOVEJŠE TERAPIJE Z BOLJŠIM IN DALJŠIM UČINKOM ZA BOLNICE Z NAPREDOVALIM KARCINOMOM MATERNIČNEGA VRATU , POSEBEJ PRI RELAPSIH
- POTREBA PO BOLJŠEM RAZUMEVANJU TUMORSKE BIOLOGIJE IN INTERAKCIJA Z TUMORSKIMI CELICAMI

Imunoterapija novi mejnik

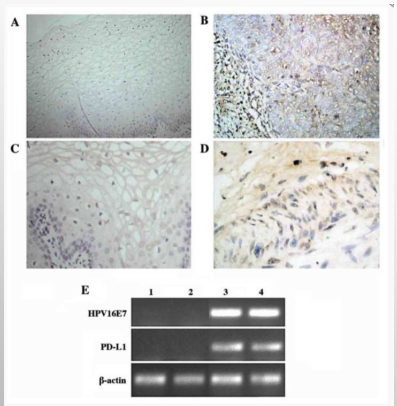


Figure 1. - Expression of HPV16E7 and PD-L1 in cervical tissues. Immunohistochemical staining and RT-PCR analyses were used to detect the protein and mRNA levels of HPV16E7 and PD-L1. Representative images of HPV16E7 staining in (A) normal cervical tissues and (B) cervical cancer tissues (magnification, ×40). Representative images of PD-L1 staining in (C) normal cervical tissues and (D) cervical cancer tissues (magnification, ×40). (E) mRNA expression levels of HPV16E7 and PD-L1, as detected by RT-PCR analysis. Lanes 1 and 2, normal cervical tissues; lanes 3 and 4, cancerous cervical tissues. HPV16E7, human papillomavirus 16 E7 oncoprotein; PD-L1, programmed death-ligand 1; RT-PCR, reverse transcription-polymerase chain reaction.

- HPV infekcija
- PDL1 je solidni biomarker HPV okužbe cerviksa
- PDL1 je značilno upregulated pri karcinomu cerviksa (IHC)

Ploščatocelični karcinom materničnega vratu 54-80%

Adenokarcinomu materničnega vratu 64%

- Vezava PD-1 na imunskih celicah z njegovim ligandom PD-L1 na tumorskih celicah sproži zavoro aktivacije in proliferacije imunskih celic ter vodi v programirano celično smrt (apoptozo) ali inaktivacijo predhodno že aktiviranih T-celic, kar omogoči nadaljnjo rast in širjenje tumorja.
- Preprečevanje vezave PD-1/PDL-1 imunoterapevtski cilj ki bi lahko omogočil povrnitev funkcije limfocitov oz bi telesu pomagal prepoznati tumorske celice kot tujke

Liu c et al ,Molecular Medicine Reports 2017,
Increased expression of PD-L1 by the human papillomavirus 16 E7 oncoprotein inhibits anticancer immunity

Neoantigeni pri različnih tumorjih
Možna uporaba kot biomarker

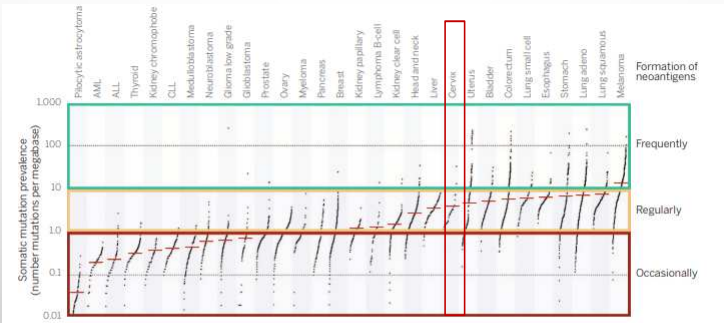


Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (50). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

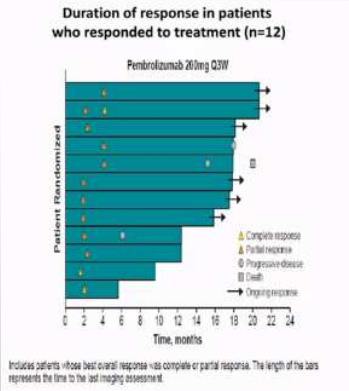
Alexandrov et al, Nature 2013
Schumacher et al, Science 2015

KEYNOTE 158 : multikohortna, multicentrična študija faza 2 – kohorta s karcinomom materničnega vratu

TABLE 2. Antitumor Activity Assessed by RECIST v1.1 per Independent Central Review

Antitumor Activity	Total Population (N = 98)*	PD-L1–Positive Population: Total (n = 82)	PD-L1–Positive Population: Previously Treated (n = 77)†	PD-L1–Negative Population (n = 15)
ORR	12 (12.2)	12 (14.6)	11 (14.3)	0 (0.0)
95% CI	6.5 to 20.4	7.8 to 24.2	7.4 to 24.1	0.0 to 21.8
DCR	30 (30.6)			
95% CI	21.7 to 40.7			
Best overall response				
CR	3 (3.1)			
PR	9 (9.2)			
SD	18 (18.4)			
Progressive disease	55 (56.1)			
Not able to be evaluated‡	5 (5.1)			
Not able to be assessed§	8 (8.2)			
Time to response, months‖				
Median	2.1			
Range	1.6-4.1			
Duration of response, months‖¶				—
Median	NR	NR	NR	
Range	≥ 3.7 to ≥ 18.6	≥ 3.7 to ≥ 18.6	4.1 to ≥ 18.6	
Estimated rate of response duration, months‖¶				—
≥ 6	10 (90.9)	10 (90.9)	10 (90.9)	
≥ 9	9 (90.9)	9 (90.9)	9 (90.9)	
≥ 12	7 (79.5)	7 (79.5)	7 (79.5)	

FDA odobritev- Juni 2018: bolnice z rekurentnim ali metastatskim karcinomom materničnega vratu ki je progrediral med ali po zdravljenju s KT na podlagi platine in s tumorji ki izražajo CPS ≥ 1



Chung et al JCO 2019

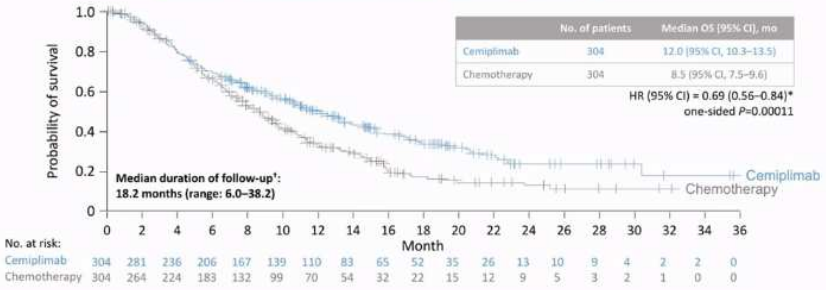
CHECKMATE 358 : nivolumab imunoterapija pri tumorjih povezanih z virusi
1 cilj raziskave ORR

	All patients (N = 24)	Cervical (n = 19)	Vaginal/ Vulvar (n = 5)	0 prior systemic therapies in R/M setting (n = 7)	≥1 prior systemic therapies in R/M setting (n = 17)
Best overall response, n (%)					
Complete response	1 (4.2)	1 (5.3)	0	0	1 (5.9)
Partial response	4 (16.7)	4 (21.1)	0	2 (28.6)	2 (11.8)
Stable disease	12 (50.0)	8 (42.1)	4 (80.0)	3 (42.9)	9 (52.9)
Progressive disease	7 (29.2)	6 (31.6)	1 (20.0)	2 (28.6)	5 (29.4)
ORR, n (%) [95% CI]	5 (20.8) [7.1, 42.2]	5 (26.3) [9.1, 51.2]	0 [0.0, 52.2]	2 (28.6) [3.7, 71.0]	3 (17.6) [3.8, 43.4]
Disease control rate, n (%)	17 (70.8)	13 (68.4)	4 (80.0)	5 (71.4)	12 (70.6)
Duration of response, median (range), months	NR[a] (0.0–5.8+)	NR[a] (0.0–5.8+)	NA		

Hollebecque et al Journal of Clinical Oncology 2017 35.15 supplement 5504-5504

EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9: Overall survival

Overall Population: efficacy regardless histology



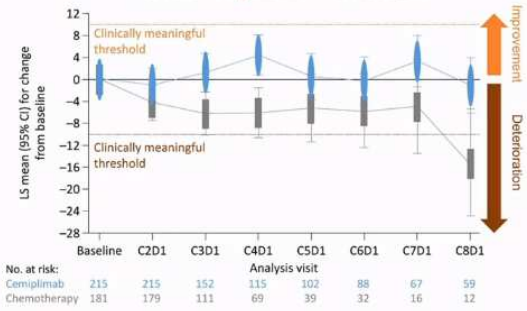
	No. of patients	Median OS [95% CI], mo
Cemiplimab	304	12.0 [95% CI, 10.3–13.5]
Chemotherapy	304	8.5 [95% CI, 7.5–9.6]

HR (95% CI) = 0.69 (0.56–0.84)*
one-sided *P*=0.00011

*Stratified by geographic region (North America vs Asia vs ROW) and Histology (SCC vs AC) according to interactive web response system. †From randomisation to data cutoff date.
Data cutoff date: 4 Jan 2021.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival; ROW, rest of world; SCC, squamous cell carcinoma.

Mean change from baseline in GHS/QoL scale

Overall Population: GHS/QoL

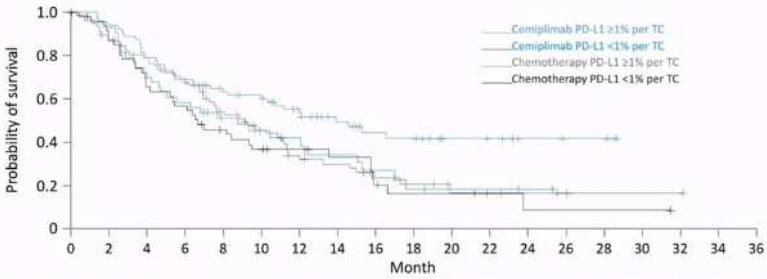


Overall (SE)
Cemiplimab: 1.01 (1.54)
Chemotherapy: −6.81 (2.12)
Difference: 7.81, one-sided nominal *P*=0.00040

- Overall population: Significant difference in favour of cemiplimab over IC chemotherapy
- Patients receiving cemiplimab improved or maintained GHS/QoL from baseline
- Patients receiving chemotherapy generally showed deterioration in these scores

*MMRM analysis included only the first 8 cycles as the sample size was too small for robust analysis thereafter (<10 patients in the IC chemotherapy group). Data cutoff date: 4 Jan 2021.
C, cycle; CI, confidence interval; D, day; GHS, Global Heath Status; IC, investigator's choice; LS, least squares; MMRM, mixed-model repeated measure; QoL, quality of life; SE, standard error.

Overall survival by PD-L1 status*



No. at risk:																			
Cemiplimab PD-L1 ≥1% per TC	82	78	65	55	45	39	30	22	16	15	10	9	4	3	3	0	0	0	0
Cemiplimab PD-L1 <1% per TC	44	41	30	25	18	13	11	9	6	4	3	3	1	0	0	0	0	0	0
Chemotherapy PD-L1 ≥1% per TC	80	69	58	50	36	28	20	16	10	8	5	5	4	2	1	1	1	0	0
Chemotherapy PD-L1 <1% per TC	48	40	30	26	19	15	12	10	6	4	4	2	1	1	1	1	0	0	0

*Associations between efficacy outcomes and PD-L1 expression (detected using the SP263 monoclonal antibody) in tumor cells was evaluated using exploratory analyses. Of 608 randomized patients, 254 had valid baseline PD-L1 samples: cemiplimab (n=126) and chemotherapy (n=128).
Data cutoff date: 4 Jan 2021.
PD-L1, programmed cell death-ligand 1; TC, tumor cells.

KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study

Key Eligibility Criteria
- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

R 1:1

Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Placebo IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Stratification Factors
- Metastatic disease at diagnosis (yes vs no)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)
- Planned bevacizumab use (yes vs no)

End Points
- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Secondary:** ORR, DOR, 12-mo PFS, and safety
- **Exploratory:** PROs assessed per EuroQol EQ-5D-5L VAS

[a]Paclitaxel: 175 mg/m². Cisplatin: cisplatin 50 mg/m². Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of via tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

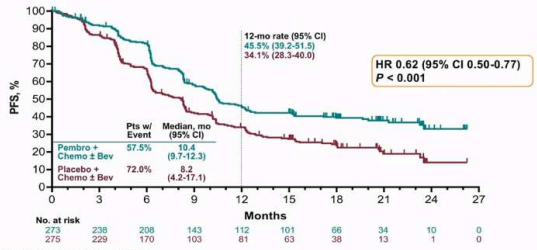
Baseline Characteristics, All-Comer Population

	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Age, median (range)	51 y (25-82)	50 y (22-79)
ECOG PS 1	128 (41.6%)	139 (45.0%)
Squamous cell carcinoma	235 (76.3%)	211 (68.3%)
PD-L1 CPS		
<1	35 (11.4%)	34 (11.0%)
≥1 to <10	115 (37.3%)	116 (37.5%)
≥10	158 (51.3%)	159 (51.5%)
Prior therapy		
Chemoradiation or radiation with surgery	71 (23.1%)	79 (25.6%)
Chemoradiation or radiation only	156 (50.6%)	142 (46.0%)
Surgery only	23 (7.5%)	24 (7.8%)
None	58 (18.8%)	64 (20.7%)

	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Stage at initial diagnosis (FIGO 2009/NCCN 2017 criteria)		
I	67 (21.8%)	58 (18.8%)
II	85 (27.6%)	93 (30.1%)
III	5 (1.6%)	8 (2.6%)
IIIA	4 (1.3%)	8 (2.6%)
IIIB	46 (14.9%)	42 (13.6%)
IVA	7 (2.3%)	4 (1.3%)
IVB	94 (30.5%)	96 (31.1%)
Disease status at study entry		
Metastatic[b]	58 (18.8%)	64 (20.7%)
Persistent or recurrent with distant metastases	199 (64.6%)	179 (57.9%)
Persistent or recurrent without distant metastases	51 (16.6%)	66 (21.4%)
Bevacizumab use during the study	196 (63.6%)	193 (62.5%)

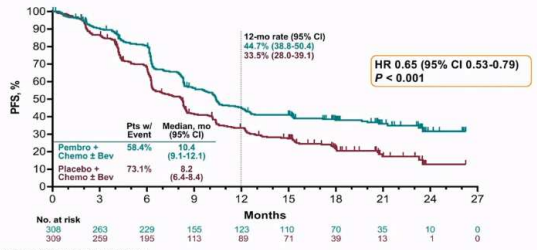
The treatment regimen in both arms included chemo ± bev.
ncludes participants with para-aortic lymph node involvement. These participants were diagnosed with stage IVB disease and entered the study with no prior treatment for cervical cance
ata cutoff date: May 3, 2021

PFS: PD-L1 CPS ≥1 Population

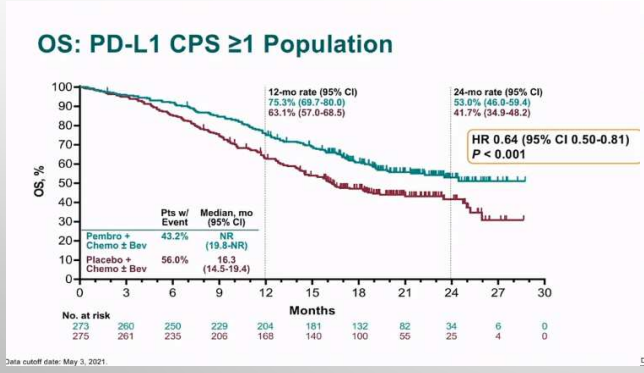


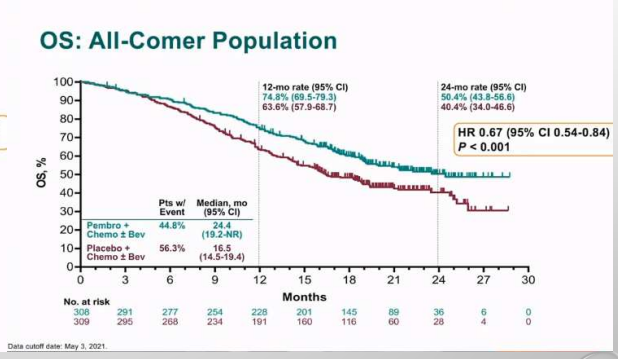
Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021

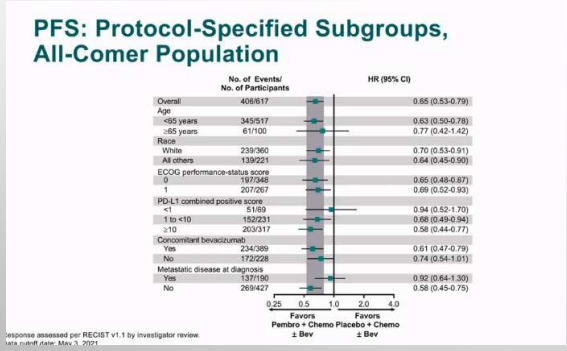
PFS: All-Comer Population

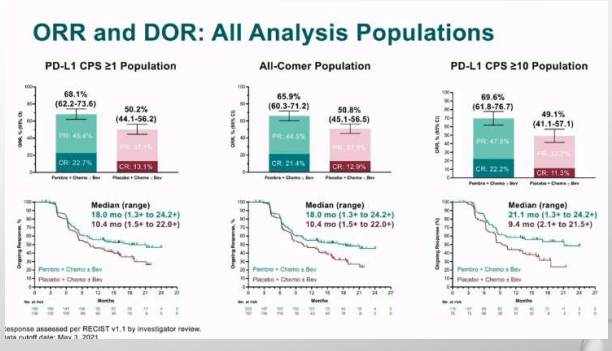


Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021


OS: PD-L1 CPS ≥1 Population
12-mo rate (95% CI)
75.3% (69.7-80.0)
63.1% (57.0-68.5)
24-mo rate (95% CI)
53.0% (46.0-59.4)
41.7% (34.9-48.2)
HR 0.64 (95% CI 0.50-0.81)
P < 0.001
OS, %
Pts w/ Event
Median, mo (95% CI)
Pembro + Chemo ± Bev
43.2%
NR (19.8-NR)
Placebo + Chemo ± Bev
56.0%
16.3 (14.5-19.4)
Months
No. at risk
273 260 250 229 204 181 132 82 34 6 0
275 261 235 206 168 140 100 55 25 4 0
Data cutoff date: May 3, 2021.


OS: All-Comer Population
12-mo rate (95% CI)
74.8% (69.5-79.3)
63.6% (57.9-68.7)
24-mo rate (95% CI)
50.4% (43.8-56.6)
40.4% (34.0-46.6)
HR 0.67 (95% CI 0.54-0.84)
P < 0.001
OS, %
Pts w/ Event
Median, mo (95% CI)
Pembro + Chemo ± Bev
44.8%
24.4 (19.2-NR)
Placebo + Chemo ± Bev
56.3%
16.5 (14.5-19.4)
Months
No. at risk
308 291 277 254 228 201 145 89 36 6 0
309 295 268 234 191 160 116 60 28 4 0
Data cutoff date: May 3, 2021.


PFS: Protocol-Specified Subgroups, All-Comer Population
No. of Events/ No. of Participants
HR (95% CI)
Overall 406/617 0.65 (0.53-0.79)
Age
<65 years 345/517 0.63 (0.50-0.78)
≥65 years 61/100 0.77 (0.42-1.42)
Race
White 239/360 0.70 (0.53-0.91)
All others 139/221 0.64 (0.45-0.90)
ECOG performance-status score
0 197/346 0.65 (0.48-0.87)
1 207/267 0.69 (0.52-0.93)
PD-L1 combined positive score
<1 51/69 0.94 (0.52-1.70)
1 to <10 152/231 0.68 (0.49-0.94)
≥10 203/317 0.58 (0.44-0.77)
Concomitant bevacizumab
Yes 234/389 0.61 (0.47-0.79)
No 172/228 0.74 (0.54-1.01)
Metastatic disease at diagnosis
Yes 137/190 0.92 (0.64-1.30)
No 269/427 0.58 (0.45-0.75)
0.25 0.5 1.0 2.0 4.0
Favors Pembro + Chemo ± Bev
Favors Placebo + Chemo ± Bev
Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.


ORR and DOR: All Analysis Populations
PD-L1 CPS ≥1 Population
All-Comer Population
PD-L1 CPS ≥10 Population
68.1% (62.2-73.6)
50.2% (44.1-56.2)
65.9% (60.3-71.2)
50.8% (45.1-56.5)
69.6% (61.8-76.7)
49.1% (41.1-57.1)
Median (range)
18.0 mo (1.3+ to 24.2+)
10.4 mo (1.5+ to 22.0+)
21.1 mo (1.3+ to 24.2+)
9.4 mo (2.1+ to 21.5+)
Pembro + Chemo ± Bev
Placebo + Chemo ± Bev
Months
Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

Adverse Events and Exposure

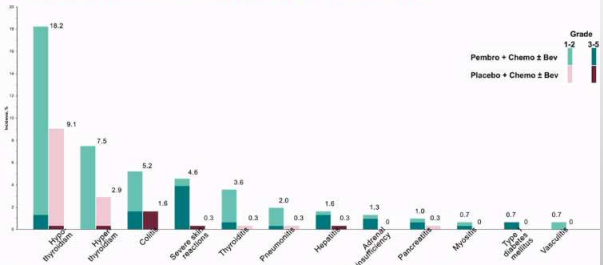
	All-Cause AEs		Treatment-Related AEs[a]		Immune-Mediated AEs[b]	
	Pembro Arm[c] (N = 307)	Placebo Arm[c] (N = 309)	Pembro Arm[c] (N = 307)	Placebo Arm[c] (N = 309)	Pembro Arm[c] (N = 307)	Placebo Arm[c] (N = 309)
Any grade	305 (99.3%)	307 (99.4%)	298 (97.1)	300 (97.1)	104 (33.9%)	47 (15.2%)
Grade 3-5	251 (81.8%)	232 (75.1%)	210 (68.4)	198 (64.1)	35 (11.4%)	9 (2.9%)
Serious	153 (49.8%)	131 (42.4%)	93 (30.3)	71 (23.0)	22 (7.2%)	7 (2.3%)
Led to death	14 (4.6%)	14 (4.5)	2 (0.7)[d]	4 (1.3)[e]	1 (0.3%)[d]	0
Led to discontinuation						
Any treatment	115 (37.5%)	82 (26.5%)	96 (31.1)	69 (22.3)	16 (5.2%)	1 (0.3%)
All treatment	18 (5.9%)	15 (4.9%)	10 (3.3)	6 (1.9)	3 (1.0%)	0

Median no. of cycles, pembro vs placebo arm
- Any treatment: 14 vs 11
- Pembrolizumab or placebo: 13 vs 11
- Chemotherapy: 6 vs 6
- Bevacizumab: 13 vs 11

Treatment duration, pembro vs placebo arm
- Median: 10.0 mo vs 7.7 mo
- Mean: 11.8 mo vs 9.4 mo

[a]Per investigator assessment. [b]Events were considered regardless of attribution to treatment by the investigator. [c]The treatment regimen in each arm included chemo ± bev. [d]Encephalitis autoimmune (also immune-mediated) and intestinal perforation. [e]Embolism, female genital tract fistula, large intestine perforation, and pulmonary sepsis.
Data cutoff date: May 3, 2021.

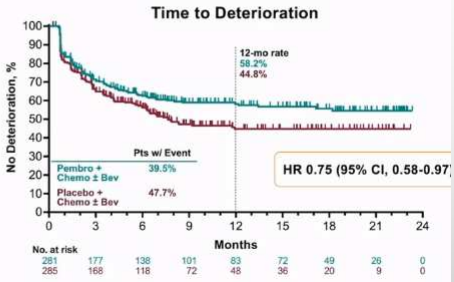
Immune-Mediated AEs, Incidence ≥2 Patients in Either Arm

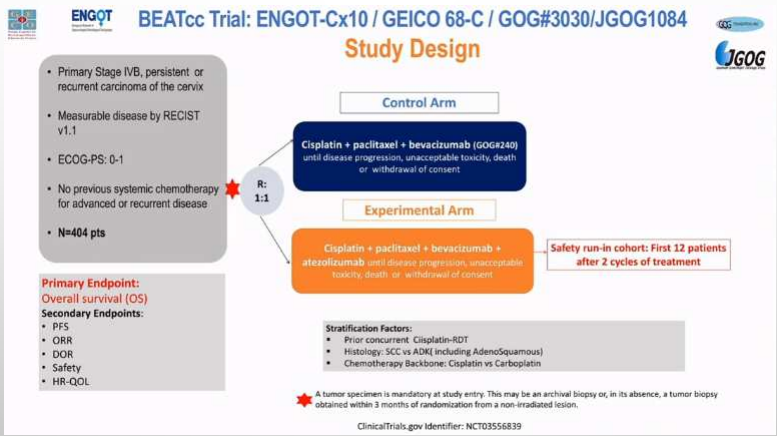


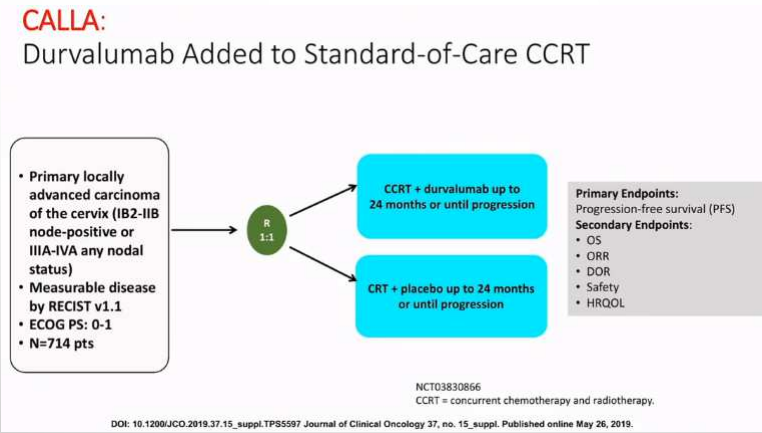
[a]Events were considered regardless of attribution to treatment by the investigator. Related terms were included in addition to the specific terms listed.
Data cutoff date: May 3, 2021.

EuroQol EQ-5D-5L VAS, All-Comer Population

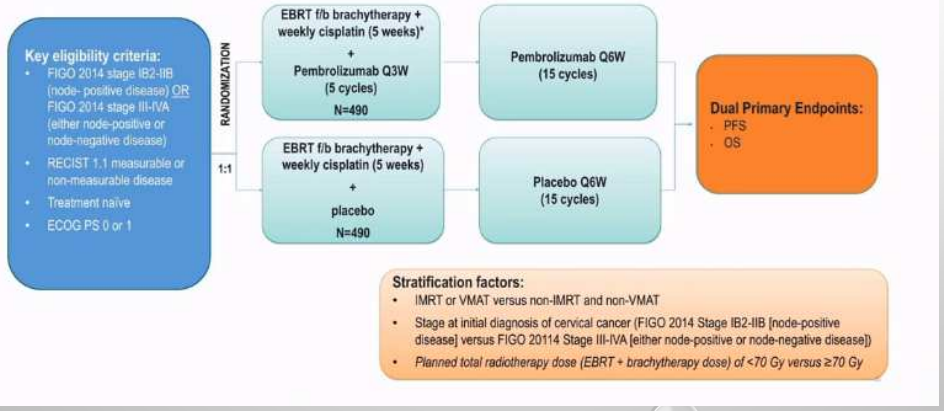
- Administered before study treatment at cycles 1-14 and every other cycle thereafter
  - Compliance between baseline and wk 30[+]: ≥94.0% with pembro + chemo ± bev, ≥88.9% with placebo + chemo ± bev
- Analysis population: all treated participants with ≥1 available PRO assessment
- Time to deterioration: time from first EQ-5D-5L VAS assessment to first onset of a ≥10-point decrease in score from baseline with confirmation under the right censoring rule or death, whichever occurred first



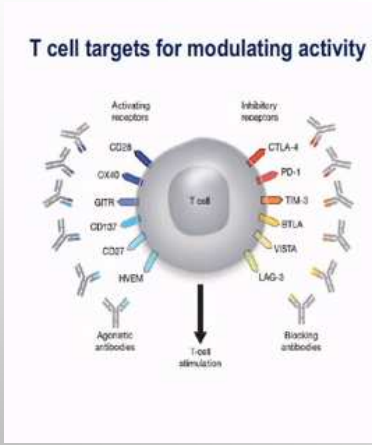

ENGOT
BEATcc Trial: ENGOT-Cx10 / GEICO 68-C / GOG#3030/JGOG1084
Study Design
JGOG
• Primary Stage IVB, persistent or recurrent carcinoma of the cervix
• Measurable disease by RECIST v1.1
• ECOG-PS: 0-1
• No previous systemic chemotherapy for advanced or recurrent disease
• N=404 pts
R: 1:1
Control Arm
Cisplatin + paclitaxel + bevacizumab (GOG#240) until disease progression, unacceptable toxicity, death or withdrawal of consent
Experimental Arm
Cisplatin + paclitaxel + bevacizumab + atezolizumab until disease progression, unacceptable toxicity, death or withdrawal of consent
Safety run-in cohort: First 12 patients after 2 cycles of treatment
Primary Endpoint:
Overall survival (OS)
Secondary Endpoints:
• PFS
• ORR
• DOR
• Safety
• HR-QOL
Stratification Factors:
• Prior concurrent Cilisplatin-RDT
• Histology: SCC vs ADK(including AdenoSquamous)
• Chemotherapy Backbone: Cisplatin vs Carboplatin
A tumor specimen is mandatory at study entry. This may be an archival biopsy or, in its absence, a tumor biopsy obtained within 3 months of randomization from a non-irradiated lesion.
ClinicalTrials.gov Identifier: NCT03556839

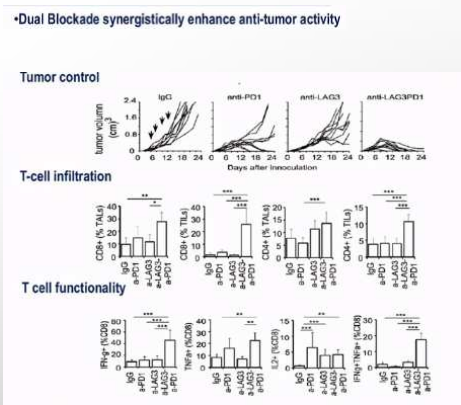

CALLA:
Durvalumab Added to Standard-of-Care CCRT
• Primary locally advanced carcinoma of the cervix (IB2-IIB node-positive or IIIA-IVA any nodal status)
• Measurable disease by RECIST v1.1
• ECOG PS: 0-1
• N=714 pts
R 1:1
CCRT + durvalumab up to 24 months or until progression
CRT + placebo up to 24 months or until progression
Primary Endpoints:
Progression-free survival (PFS)
Secondary Endpoints:
• OS
• ORR
• DOR
• Safety
• HRQOL
NCT03830866
CCRT = concurrent chemotherapy and radiotherapy.
DOI: 10.1200/JCO.2019.37.15_suppl.TPS5597 Journal of Clinical Oncology 37, no. 15_suppl. Published online May 26, 2019.

ENGOT-CX11/GOG-3047/KEYNOTE-A18
Pembrolizumab in Newly Diagnosed LACC at High Recurrence Risk



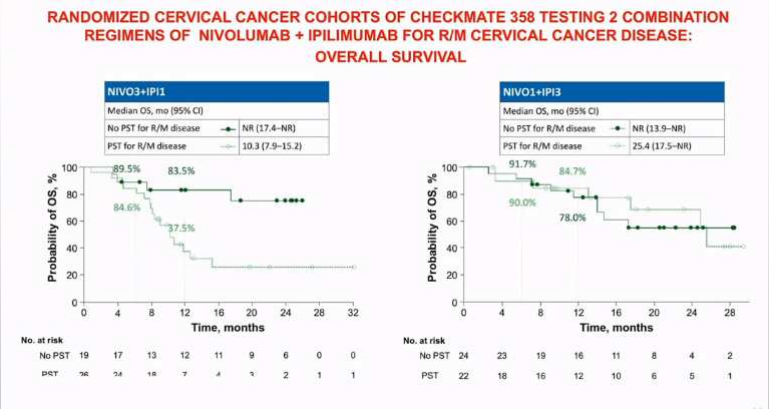
Kako lahko izboljšamo učinkovitost inhibitorjev kontrolnih točk pri karcinomu maternicnega vratu?





Domenica Lorrusso ESGO 2021 Scientific session
Ruea Yea Huang et al Oncotarget 2015 6: 27359-27377

CHECKMATE 358 – kohorta s karcinomom maternično vratu



Balstilimab (anti-PD-1) Alone and in Combination with Zalifrelimab (anti-CTLA-4)

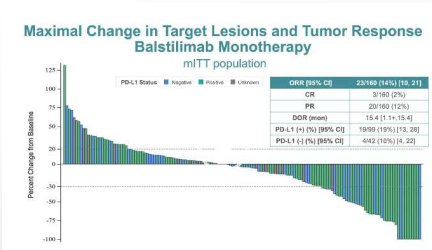
for Recurrent/Metastatic (R/M) Cervical Cancer (CC)

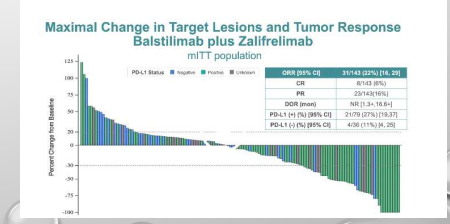
Preliminary Results of Two Independent Ph2 Trials

(NCT03104699 and NCT03495882)

Tumor Response

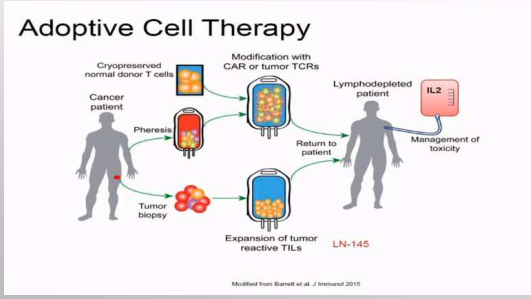
	Balstilimab Only		Balstilimab + Zalifrelimab	
	mITT (N=160)	≥1 Prior chemotherapy (N=138)	mITT (N=143)	≥1 Prior chemotherapy (N=119)
Objective Response Rate (ORR), n (%)	**23 (14%)**	**18 (13%)**	**31 (22%)**	**24 (20%)**
Complete Response	3 (2%)	3 (2%)	8 (6%)	6 (5%)
Partial Response	20 (12%)	15 (11%)	23 (16%)	18 (15%)
Duration of Response, median (mon) [range obs]	15.4 [1.1+,15.4]	15.4 [1.3+,15.4]	NR [1.3+,16.6+]	NR [1.3+,15.4+]
ORR by tumor histology				
SCC # responders/# treated (%)	18/100 (18%)	13/83 (16%)	29/106 (27%)	22/82 (27%)
AdenoCa/AdnoSq # responders/# treated (%)	5/59 (8%)	5/55 (9%)	2/37 (5%)	2/37 (5%)





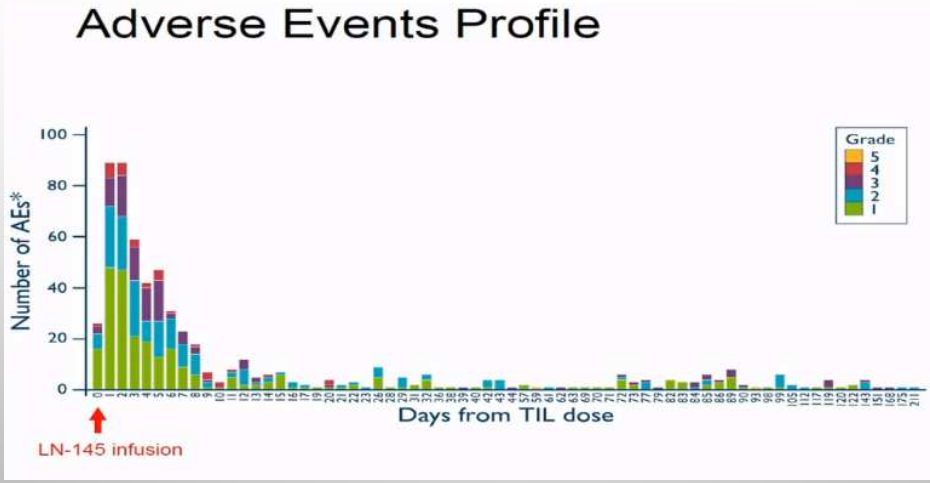
O' Malley ESMO Virtual congress 2020

LN 145 raziskava



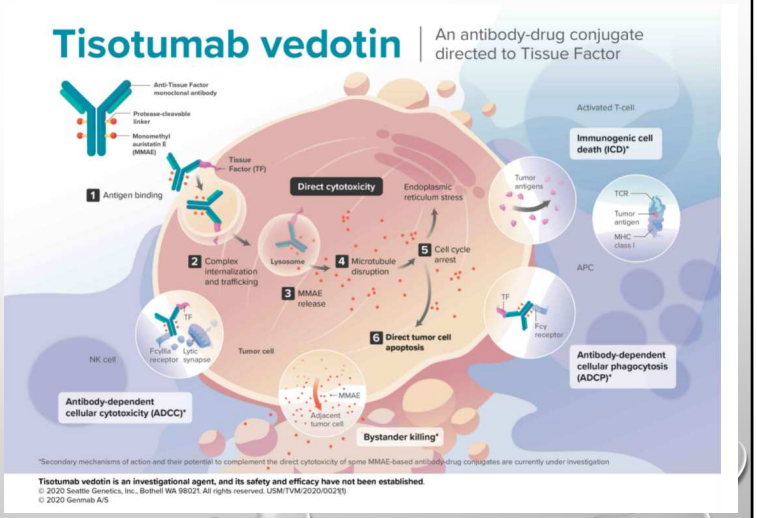
LN-145 for Recurrent / Metastatic Cervical Cancer

RESPONSE (RECIST v1.1)	PATIENTS, N=27 n (%)
Objective Response Rate (ORR)	**12 (44.4%)**
Complete Response (CR)	3 (11.1%)
Partial Response (PR)	9 (33.3%)
Stable Disease (SD)	11 (40.7%)
Progressive Disease (PD)	4 (14.8%)
Non-Evaluable	0
Disease Control Rate (DCR)	23 (85.2%)
Median Duration of Response (DOR)	**Not Reached**
Min, Max (range)	2.6+ to 9.2+ months



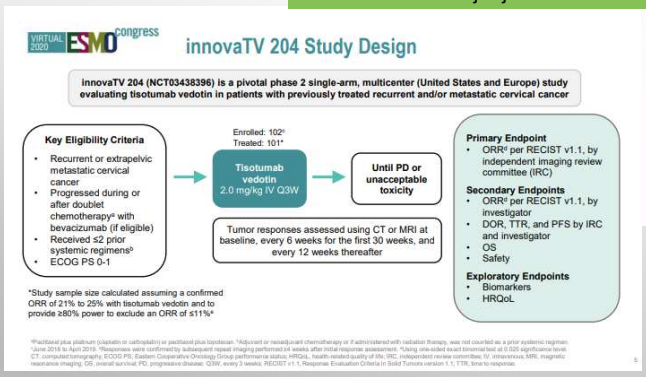
TISOTUMAB VEDOTIN

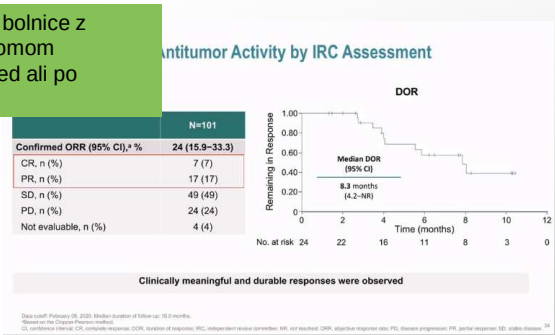
- Tisotumab vedotin je konjugirano zdravilo iz protiteles, ki ga sestavlja monoklonsko protitelo, usmerjeno proti tkivnemu faktorju (TF), ki se kovalentno veže na antimikrotubulno učinkovino monometil avristatin E (MMAE).
- Tkivni faktor je aberantno izražen pri cervikalnem karcinomu in ostalih solidnih rakih ter je povezan s tumorsko patofiziologijo in slabšo prognozo
- Tisotumab vedotin ima številne antitumorske učinke



INNOVATV 204/GOG-3023/ENGOT-cx6 študija

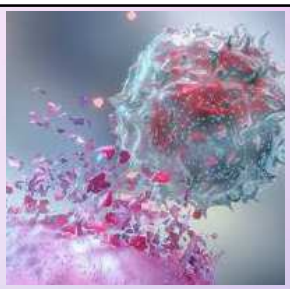
FDA odobritev - september 2021 za bolnice z rekurentnim ali metastatskim karcinomom materničnega vratu, ki progredira med ali po sistemskem zdravljenju 1. reda





ZAKLJUČKI

- REKURENTNI KARCINOM MATERNIČNEGA VRATU – POTREBA PO NOVE MOŽNOSTI ZDRAVLJENJA ZARADI SLABE PROGNOZE
- KARBOPLATIN-PAKLITAXEL-PEMBROLIZUMAB+-BEVACIZUMAB NOVI SOC V 1. LINIJI
- CEMIPLIMAB- BOLJŠI OS V 2.L IN 3.L
- POTREBNE RAZISKAVE S KOMBINACIJO IMUNOTERAPIJE IN KONKOMITANTNE KTRT
- ADC TISOTUMAB VEDOTIN IN LN 145 OBETAVNE STRATEGIJE



IMUNOTERAPIJA PRI ZDRAVLJENJU KARCINOMA MATERNIČNEGA TELESA

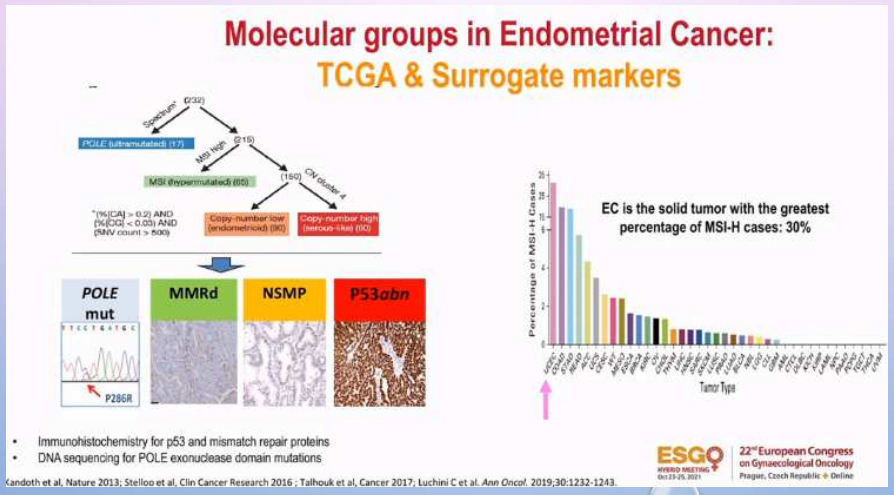
MIRJANA PAVLOVA BOJADŽISKI,DR MED

- Najpogostejši rak rodil pri ženskah v razvitem svetu
  417.000 novih primerov in 87000 smrtnih izidov 2020
  -V Sloveniji letno obravnavamo 350 bolnic z rakom maternicnega telesa

- Diagnosticiran v zgodnjem stadiju 5 letno splošno preživetje- 95% po izhodiščni terapiji
- Bolnice diagnosticirane v napredovalem stadiju - 5 letno splošno preživetje 17%

- Nedavno, terapevtske možnosti za bolnice s ponovitvami ali metastatsko boleznijo so bile omejene
- 1. Linija zdravljenja dvojček na osnovi platine- karboplatin/paklitaxel
- Brez standardnega zdravljenja v 2. liniji, najpogostejši pristop:
  monoterapija (paklitaxel, doxorubicin...) ali hormonsko zdravljenje mOS ≤ 12 mesecev

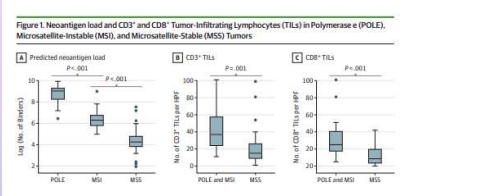
- Mesto imunoterapije

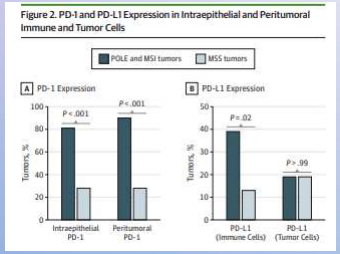


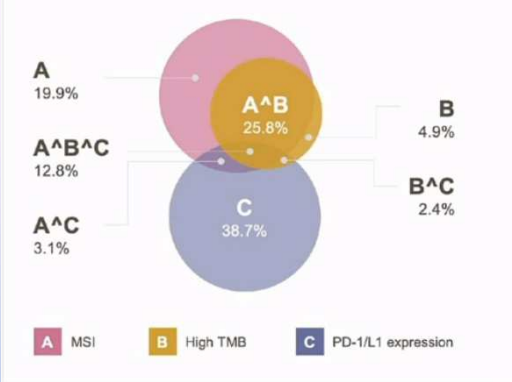
Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017; Luchini C et al. *Ann Oncol.* 2019;30:1232-1243.

PODLAGA ZA IMUNOTERAPIJO PRI ZDRAVLJENJU RAKA MATERNIČNEGA TELESA

PRILAGODITEV NA PODLAGI MOLEKULARNE KLASIFIKACIJE







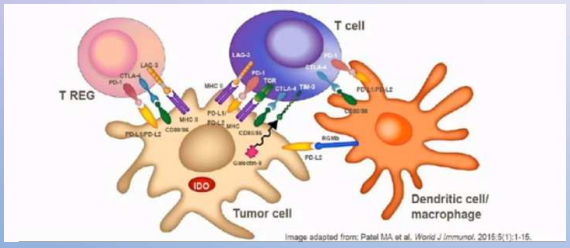
Za bolnice z karcinomom maternicnega telesa prekrivanje med MSI-h in TMB , je MSI-H/d MMR učinkovit biomarker glede benefita od imunoterapije

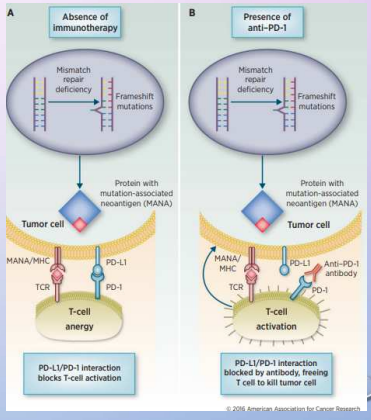
Howitt BE Jama Oncology 2015, Luchini C Annals of Oncology 2019

BLOKADA KONTROLNIH TOČK

MEHANIZEM DELOVANJA PRI dMMR/MSI-H tumorjih

- Močna ekspresija PD-1, PDL-1,CTLA-4, LAG-3,IDO
- Povečana invazija citotoksičnih T limfocitov (CD3+,CD8+)
- Povečana prisotnost T celice pomagalke tip 1 in izražanje kemokinov
- Povečana prisotnost T spominskih celicah





Dudley JC Clin.Cancer Research 2016 ; 22.813-820, Patel Ma et al World Journal of Immunology 2015;5.1-15

IMUNOTERAPIJA Z ZAVIRALCI KONTROLNIH TOČK PRI KARCINOMU MATERNIČNEGA TELESA

MONOTERAPIJA

Avelumab

Humanizirano monoklonsko protitelo IgG1, usmerjeno proti imunomodulacijskemu proteinskemu ligandu PD-L1 celične površine ki blokira interakcijo z receptorji PD1 in B7.1

Durvalumab

Humano monoklonsko protitelo IgG1, usmerjeno proti imunomodulacijskemu proteinskemu ligandu PD-L1 celične površine ki blokira interakcijo z receptorji PD1 in B7.1

Pembrolizumab

Humanizirano IgG4 monoklonsko protitelo proti receptorjem programirane celične smrti 1(PD-1) ki blokira interakcijo z ligandi PD-L1 in PD-L2

Dostarlimab

Humanizirano monoklonsko protitelo proti receptorjem programirane celične smrti 1 (PD1), ki blokira interakcijo z ligandmi PDL-1 in PD-L2

PEMBROLIZUMAB odobren v ZDA za bolnice z neresktabilnim, metastaskim MSI-H,dMMR ali TMB-H ki so progredirali po prejšnjo linijo in nimajo alternativne možnosti zdravljenja

DOSTARLIMAB odobren v ZDA in EU za bolnice z dMMR napredovali/ponavljajoč karcinom maternicnega telesa

KEYNOTE-158

PEMBROLIZUMAB PRI MSI-H kohorti z karcinomom maternicnega telesa

Odprta, multikohortna študija faze 2 tipa košara

Patients with advanced endometrial cancer
- **MSI-H by PCR or IHC**
- Progression after ≥1 standard therapy
- Measurable disease
- ECOG PS of 0 or 1

(N = 49)

→ **Pembrolizumab 200 mg every 3 wk** → Up to 24 months (35 cycles), or until PD or unacceptable toxicity

Primary endpoint: ORR by ICR

Secondary endpoints: DoR, PFS, OS, safety

Basket cohort with exploratory biomarker objective: Association between response to pembrolizumab treatment and tTMB (tumour mutation burden):
- tTMB-high (≥10 mutations per megabase)
- non-tTMB-high (<10 mutations per megabase)

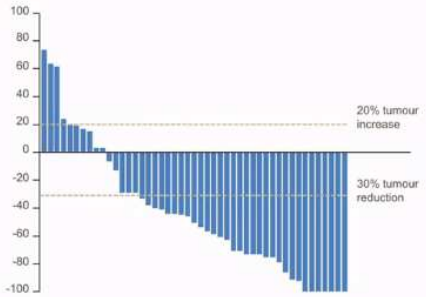
Marabelle A, et al. *J Clin Oncol* 2020;38:1–10.

ESGO HYBRID MEETING Oct 23-25, 2021 | 22nd European Congress on Gynaecological Oncology Prague, Czech Republic + Online

KEYNOTE 158: kohorta z karcinomom maternicnega telesa

Efficacy

Efficacy outcome	Pembrolizumab-treated patients [N = 49]
ORR, % (95% CI)	**57.1 (42.2, 71.2)**
CR, n (%) PR, n (%)	8 (16.3) 20 (40.8)
Median PFS, months (95% CI)	25.7 (4.9, NR)
Median OS, months (95% CI)	NR (27.2, NR)
Median DoR, months (range)	NR (2.9, 27.0+)



At the data cutoff for this analysis (December 6, 2018), median follow-up duration was 13.4 months (range: 0.4–34.2 months); 114 patients were being followed at the data cut-off, with study treatment ongoing in 36 patients (15.5%)

ESGO HYBRID MEETING | 22nd European Congress on Gynaecological Oncology

GARNET ŠTUDIJA

The GARNET study
Dostarlimab in EC Cohorts

- GARNET (NCT02715284) is a phase 1, single-arm study of dostarlimab (TSR-042) monotherapy in multiple tumor types
- In part 2B, dostarlimab was dosed at the RTD determined from Part 1 and 2A
  - 500 mg IV Q3W for 4 cycles, then 1000 mg IV Q6W until disease progression
- MMR status was determined by local immunohistochemistry
- Primary endpoint: ORR and DOR

Key inclusion/exclusion criteria for cohorts A1 and A2:
- Patients must have progressed on or after platinum doublet therapy
- Patients must have received ≤2 prior lines of treatment for recurrent or advanced disease
- Patients must have measurable disease at baseline
- Patients must be anti–PD-(L)1 naïve

*Cohort enrollment includes 3 patients with MMRunk/MSI-H disease; †Cohort enrollment includes 16 patients with MMRunk/MSS disease
DOR; duration of response; IHC, immunohistochemistry; MMR, mismatch mutation repair; MSI, microsatellite instability; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; PCR, polymerase chain reaction; PD-L1, programmed cell death (ligand) 1; PROC, platinum-resistant ovarian cancer; Q3W, every 3 weeks; Q6W, every 6 weeks; RTD, recommended therapeutic dose.

GARNET : Dostarlimab in cohort A1:
Efficacy in dMMR endometrial cancer patients

Variable	dMMR EC n = 103
Follow-up time, median, mo	**16.3**
Objective response rate, n (%, 95% CI)	**46 (44.7, 34.9-54.8)**
Complete response, n (%)	11 (10.7)
Partial response, n (%)	35 (34.0)
Stable disease, n (%)	13 (12.6)
Progressive disease, n (%)	39 (37.9)
Not evaluable, n (%)	3 (2.9)
Not done, n (%)	2 (1.9)
Disease control rate, n (%, 95% CI)	**59 (57.3, 47.2-67.0)**
Response ongoing, n (%)	**41 (89.1)**
Duration of response, median (range), mo	**Not reached (2.63-28.09+)**
KM estimated probability of remaining in response	
At 6 mo, %	97.8
At 12 mo, %	90.6
At 18 mo, %	79.2

Oaknin A et al. Presented at ESMO Annual Meeting; September 2020; Madrid, Spain. Abstract LBA-3594.

Antitumor Activity by RECIST v1.1 by Prior lines of therapy

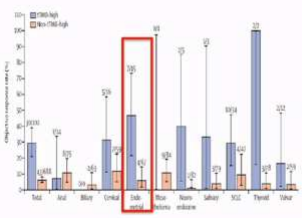
Variable	dMMR/MSI-H EC, N=105	
	1 prior line (n=66)	≥2 prior lines (n=39)
Objective response, n (%)	33 (50.0%) (95% CI, 37.4–62.6)	14 (35.9%) (95% CI, 21.2–52.8)
Best confirmed response, n (%)		
CR	6 (9.1%)	5 (12.8%)
PR	27 (40.9%)	9 (23.1%)
SD	9 (13.6%)	4 (10.3%)
PD	19 (28.8%)	20 (51.3%)
NE	5 (7.6%)	1 (2.6%)
Disease control, n (%)	42 (63.6%)	18 (46.2%)
Duration of response, months	Not reached	Not reached

Oaknin A. et al. Presented at IGCS 2021

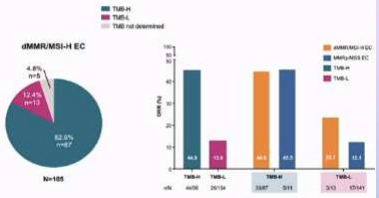
CR, complete response; dMMR, mismatch repair deficient; EC, endometrial cancer;MSI-H, microsatellite instability high;; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Beyond dMMR/MSI-H as biomarker: TMB

KEYNOTE-158



GARNET



- 10 mutations/megabase (FDA-approved threshold) was used as the threshold for TMB-H status.

Marabelle A et al;Lancet Oncol. 2020 Oct;21(10):1353-1365; Oaknin A. et al. Presented at ESMO 2021

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pMMR/MSS karcinomi maternicnega telesa

Omejena učinkovitost

Study	Drug	N	ORR(%)
KEYNOTE 158: Marabelle (2019)	Pembrolizumab	107	11%
GARNET: Oaknin (2020)	Dostarlimab	94	13%
PHAEDRA: Antill (2019)	Durvalumab	36	3%
Konstantinopoulos (2019)	Avelumab	16	6%

Marabelle A, et al. *J Clin Oncol*. 2020;38(1);1-10. Oaknin A, et al. *Ann Oncol*. 2020;31(Suppl_4): Abstract LBA36; Antill et al., J Clin Oncol 2019 (ASCO 2019; 5501) ; Konstantinopoulos PA et al. *J Clin Oncol*. 2019

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KOMBINACIJA

ANTIANGIOGENA TERAPIJA

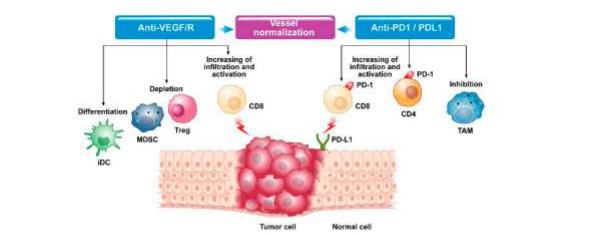
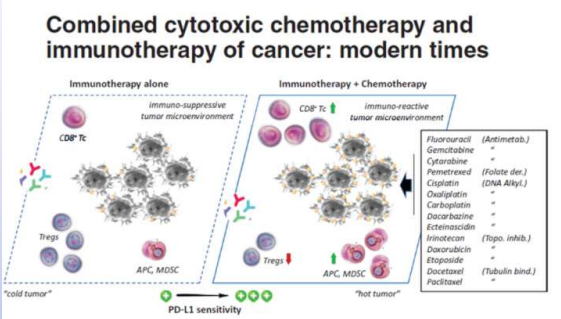


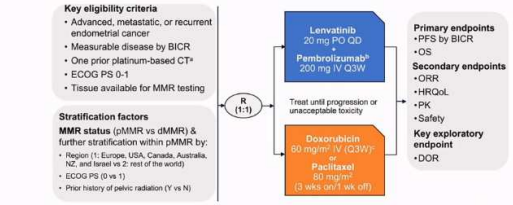
Figure 1. Modifications in the tumor microenvironment after combined anti-VEGF and anti-PD1/PDL1 therapy. iDC = immature dendritic cell; MDSC = myeloid-derived suppressor cell; Treg = regulatory T cell; CD8 = linfociti T CD8; CD4 = linfociti T CD4; TAM = Tumor-associated macrophage; PD-1 = programmed cell death protein 1; PD-L1 Programmed death-ligand 1.

KEMOTERAPIJA



KEYNOTE- 775

KEYNOTE-775: Phase 3 trial to compare the efficacy and safety of lenvatinib + pembrolizumab vs. treatment of physician's choice in participants with advanced EC: Study Design



[a]Patients may have received up to two prior platinum-based CT regimens if given in the neoadjuvant or adjuvant treatment setting. [b]Maximum of 35 doses. [c]Maximum cumulative dose of 500 mg/m².
BICR, Blinded Independent Central Review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; DOR, duration of response; HRQoL, health-related quality of life; pMMR, mismatch repair-proficient; ORR, objective response rate; PK, pharmacokinetics.

Makker V. et al. Presented as SGO 2021 Virtual Meeting

ClinicalTrials.gov Identifier: NCT03517449

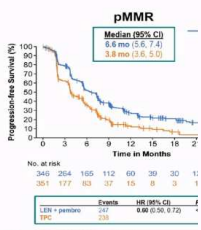
KEYNOTE-775: Baseline Characteristics

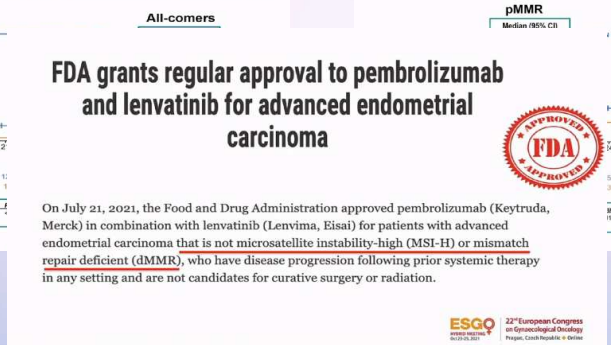
	LEN + PEMBRO (n = 411)	TPC (n = 416)
Median age (range), years	64 (30-82)	65 (35-86)
MMR status: pMMR / dMMR (%)	84.2 / 15.8	84.4 / 15.6
Prior history of pelvic radiation (%)	40.9	41.6
ECOG 0 / 1 (%)[a]	59.9/39.9	57.9/42.1
Race: White / Black / Asian / other[b] (%)	63.5 / 4.1 / 20.7 / 1.2	59.1 / 3.4 / 22.1 / 1.7
Histology at diagnosis (%)[c]		
Endometrioid carcinoma[d] High-grade / Low-grade / Not specified	22.9/14.4/21.9	21.6/13.0/26.4
Serous carcinoma	25.1	27.6
Clear cell carcinoma	7.3	4.1
Mixed cell carcinoma	5.4	3.8
Prior lines of systemic Tx 1 / 2 (%)	72.3 / 25.1	66.6 / 30.3
Prior lines of platinum-based Tx 1 / 2 (%)	79.3 / 20.2	75.7 / 24.3
Neo-adjuvant or adjuvant (%)	54.5	60.3

[a]0.2% of patients in the lenvatinib plus pembrolizumab group had an ECOG score deviation of 3. [b]Includes American Indian or Alaska native, native Hawaiian or other Pacific islander. 4.8% of patients in the LEN + pembro group and 13.8% of patients in the TPC group were missing information on race. [c]Other histology at diagnosis included mucinous, undifferentiated, and neuroendocrine. LEN + PEMBRO: 1.7%; TPC: 0.98%. Histology was undescribed for 5% patients in the LEN + PEMBRO arm, and 0.7% in the TPC arm. [d]Endometrioid Histology includes Low Grade, High Grade, Endometrioid, and Endometrioid with Squamous Differentiation. Tx, treatment.

Makker V. et al. Presented as SGO 2021 Virtual Meeting

KEYNOTE-775: Progression-free Survival: pMMR and All Comers





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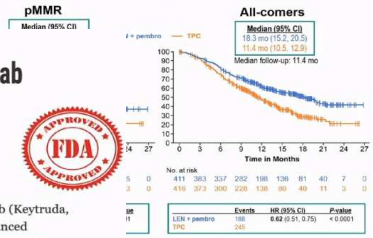
KEYNOTE-775: Overall Survival: pMMR and All Comers



FDA grants regular approval to pembrolizumab and lenvatinib for advanced endometrial carcinoma

On July 21, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) in combination with lenvatinib (Lenvima, Eisai) for patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

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	pMMR patients		All-comer patients	
No. of patients	346	351	411	416
Objective response rate (%) (95% CI)	30.3 (25.5–35.5)	15.1 (11.5–19.3)	31.9 (27.4–36.6)	14.7 (11.4–18.4)
Best overall response (%)				
Complete response	5.2	2.6	6.6	2.6
Partial response	25.1	12.5	25.3	12.0
Stable disease	48.6	39.6	47.0	40.1
Progressive disease	15.6	30.8	14.8	29.6
Not evaluable / assessed	0.6 / 4.9	2.0 / 12.5	1.2 / 5.1	1.9 / 13.7
Difference (%) vs TPC	15.2	--	17.2	--
P-value	<0.001	--	<0.001	--
Median duration of response (range) (mo)	9.2 (1.6*–23.7*)	5.7 (0.0*–24.2*)	14.4 (1.6*–23.7*)	5.7 (0.0*–24.2*)
Median time to response (range) (mo)	2.1 (1.5-9.4)	3.5 (1.0-7.4)	2.1 (1.5-16.3)	2.1 (1.0-7.4)

*No progressive disease reported at the last disease assessment.

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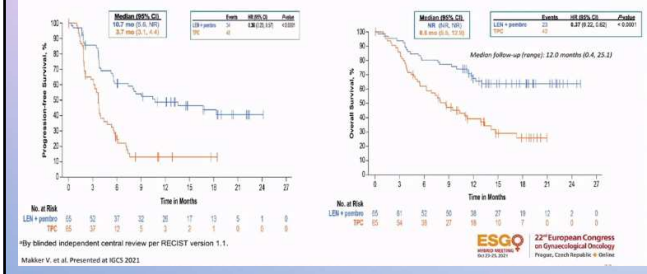
dMMR SKUPINA

KEYNOTE-775:Exploratory Analysis in the dMMR population
PFS[a] and OS



[a]By blinded independent central review per RECIST version 1.1.

Makker V. et al. Presented at IGCS 2021

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KEYNOTE-775:Exploratory Analysis in the dMMR population
Objective Responses[a]

	LEN + pembro (n = 65)	TPC (n = 65)
Objective response, % (95% CI)	40.0 (28.0–52.9)	12.3 (5.5–22.8)
Difference vs TPC, %; *P*-value	27.7; 0.0002	--
Best overall response, %		
Complete response	13.8	3.1
Partial response	26.2	9.2
Stable disease	38.5	43.1
Progressive disease	10.8	23.1
Not evaluable / assessed	4.6 / 6.2	1.5 / 20.0
Median duration of response, months (range)	NR (2.1[b]–20.4[b])	4.1 (1.9[b]–15.6[b])
Median time to response, months (range)	2.9 (1.7–16.3)	1.9 (1.8–3.7)
Disease control rate[c], %	73.8	47.7

[a]By blinded independent central review per RECIST version 1.1; [b]No progressive disease reported by the time of the last disease assessment. [c]The proportion of participants who have best overall response of complete response, partial response, or stable disease achieved at ≥ 7 weeks after randomization.

Makker V. et al. Presented at IGCS 2021

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ENGOT-en9/MK-7902-001/LEAP-001

Ongoing phase 3 study of pembrolizumab + lenvatinib vs chemotherapy in newly diagnosed endometrial cancer[a,b]

Patients with advanced or recurrent endometrial cancer
- Newly diagnosed
- Stage III/IV or recurrent

(N ~ 720)

R (1:1)

Pembrolizumab 200 mg IV every 3 wk **+ Lenvatinib** 20 mg PO daily

Paclitaxel 175 mg/m² IV every 3 wk **+ Carboplatin** AUC 6 IV every 3 wk

- Enrollment started in April 2019 and is ongoing
- Estimated primary completion date is April 2023

Stratified by: MMR status (MMRd vs MMRp);
MMRp patients further stratified by ECOG PS, measurable disease, and prior chemoradiation

Primary endpoints: PFS, OS
Secondary endpoints: ORR, HRQoL, safety and tolerability, PK
Exploratory endpoints: DoR, DCR, CBR

Clincaltrials.gov. NCT03884101.

Marth C, et al. *J Clin Oncol*. 2020;38(15_suppl): Abstract TPS6106;

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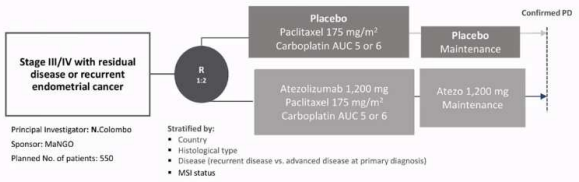
ENGOT-EN7/AtTEnd: Atezolizumab Trial in Endometrial cancer (ATTEND) - MaNGO



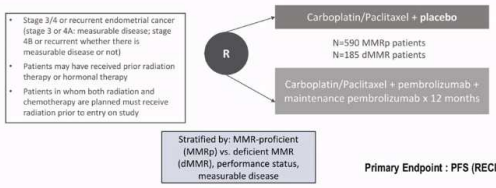
Principal Investigator: N.Colombo
Sponsor: MaNGO
Planned No. of patients: 550

Stratified by:
- Country
- Histological type
- Disease (recurrent disease vs. advanced disease at primary diagnosis)
- MSI status

ClinicalTrials.gov Identifier: NCT03603184

Primary Endpoints: PFS and OS

NRG-GY018: Randomized, placebo-controlled phase 3 study of Pembrolizumab in addition to Carboplatin and Paclitaxel in pts with advanced or recurrent EC

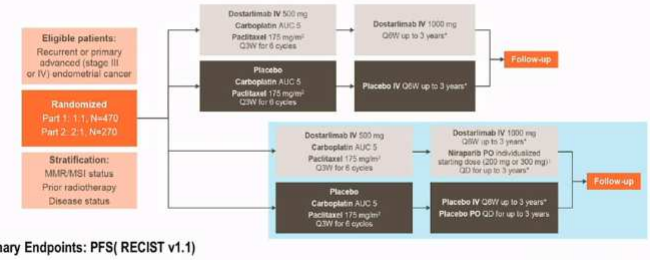


Stratified by: MMR-proficient (MMRp) vs. deficient MMR (dMMR), performance status, measurable disease

Primary Endpoint : PFS (RECIST 1.1)

ClinicalTrials.gov Identifier: NCT03914612

ENGOT-EN6/GOG-3031/ /NSGO-RUBY): Phase 3 Study of Dostarlimab + Chemotherapy in Recurrent or Primary Advanced EC



Primary Endpoints: PFS(RECIST v1.1)

https://clinicaltrials.gov/ct2/show/NCT03981796.

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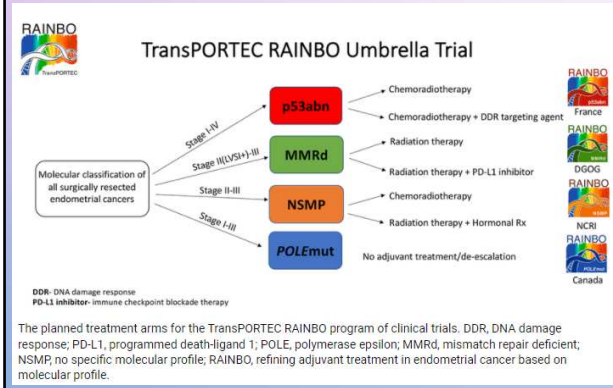
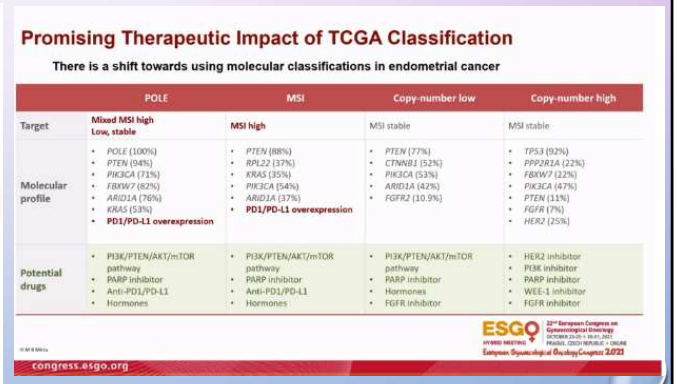
PRIHODNOST



The planned treatment arms for the TransPORTEC RAINBO program of clinical trials. DDR, DNA damage response; PD-L1, programmed death-ligand 1; POLE, polymerase epsilon; MMRd, mismatch repair deficient; NSMP, no specific molecular profile; RAINBO, refining adjuvant treatment in endometrial cancer based on molecular profile.



Promising Therapeutic Impact of TCGA Classification

There is a shift towards using molecular classifications in endometrial cancer

	POLE	MSI	Copy-number low	Copy-number high
Target	Mixed MSI high Low, stable	MSI high	MSI stable	MSI stable
Molecular profile	• *POLE* (100%) • *PTEN* (94%) • *PIK3CA* (71%) • *FBXW7* (82%) • *ARID1A* (76%) • *KRAS* (53%) • **PD1/PD-L1 overexpression**	• *PTEN* (88%) • *RPL22* (37%) • *KRAS* (35%) • *PIK3CA* (54%) • *ARID1A* (37%) • **PD1/PD-L1 overexpression**	• *PTEN* (77%) • *CTNNB1* (52%) • *PIK3CA* (53%) • *ARID1A* (42%) • *FGFR2* (10.9%)	• *TP53* (92%) • *PPP2R1A* (22%) • *FBXW7* (22%) • *PIK3CA* (47%) • *PTEN* (11%) • *FGFR* (7%) • *HER2* (25%)
Potential drugs	• PI3K/PTEN/AKT/mTOR pathway • PARP inhibitor • Anti-PD1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • PARP inhibitor • Anti-PD1/PD-L1 • Hormones	• PI3K/PTEN/AKT/mTOR pathway • PARP inhibitor • Hormones • FGFR inhibitor	• HER2 inhibitor • PI3K inhibitor • PARP inhibitor • WEE-1 inhibitor • FGFR inhibitor

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ZAKLJUČKI

Karcinom materničnega telesa ima visok delež TMB-H in dMMR - utemeljitev za terapijo z zaviralci kontrolnih točk

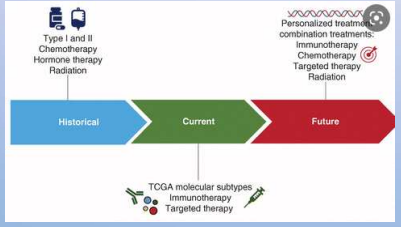
MSI-H dMMR fenotip izstopa kot prediktivni biomarker za terapijo z zaviralci kontrolnih točk

Dostarlimab (Jemperli) – edini zaviralec kontrolnih točk odobren s strani EMA

Učinkovitost zaviralcev imunskih točk pri pMMR/MSS je omejena

Kombinacija **Lenvatinib/pembrolizumab** se je pokazala bolj učinkovita (PFS,OS) v primerjavi s kemoterapijo – FDA odobrena za tumorje ki **niso** dMMR/MSI

Smo v obdobju novih terapij, pravega napredka v področju ponavljajočega/napredovalega karcinoma materničnega telesa



Novosti na področju imunoterapije drugih rakov

16.12.2021

dr. Erika Matos, dr. med.

Novosti na področju imunoterapije zdravljenja raka neznanega izvora

Vloga ZIKT pri zdravljenju raka neznanega izvora

Uvod (1)

- Vse več bolnikov z RNI je zdravljenjih z ZIKT:
  - V okviru kliničnih raziskav
  - V okviru FDA odobrene indikacije (agnostično zdravljenje):
    - MSI-H (stanje genetske hipermutabilnosti-nagnjenost k nabiranju mutacij)
    - dMMR (okvara proteinov za popravljanje neujemanja DNK)
    - TMB-H (breme somatskih mutacij na kodirajočo enoto-magabazo)
  - "off-label"

Olivier T et al. Canc Treat Rev 2021; 97: 102204.

RNI - rak neznanega izvora
ZIKT – zaviralci imunskih kontrolnih točk

Uvod (2)

- RNI je histološko potrjen rak, pri keterem anatomski izvor kljub izčrpni diagnostiki ostane nerazpoznan
  - 15% rakov je ob prvi prezentaciji t.i. MUO (malignancy of unknown origin)
  - 2-5% jih ostane RNI (ESMO guidelines)
- RNI je heterogena skupina bolezni, ki ima nekatere skupne značilnosti:
  - Bolezen je razsejana, ob odkritju
    - intrinzično agresivno vedenje tumorja z možnostjo zgodenje diseminacije
  - Odsotnost, zakritost, majhnost, izginotje izvornega mesta
  - Nepredvidljiv vzorec metastaziranja
  - Slab odziv na standardno, citostatsko zdravljenje

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.
Fizzazi K et al. Ann Oncol 2015; 26(Suppl 5): v133-138.

Uvod (3)

Prognostično ugodna skupina (15-20%)

9 specifičnih entitet

- G3 nevroendokrini karcinomi neznanega izvora
- G1 nevroendokrini karcinomi neznanega izvora
- Karcinoza peritoneja pri Ž (serozni papilarni tip)
- Izolirana prizadetost bezgavk pri Ž
- SCC v bezgavkah na vratu (razen scl lož)
- RNI s kolorektalnim profilom (IHK ali molekularno)
- Izolirana metastatska lokalizacija
- Blastni zasevki v skeletu pri moškem in/ali povišana PSA vrednost
- SCC izolirano v ingvinalnih bezgavkah

Prognostično ne-ugodna skupina (80%)

mOS ~ 1 leto

- Prognostični model (-i), ki to skupino deli v bolj/manj ugodno:
  - Model 1:
    - PS= 0, 1, LDH= N, odsotnost zasevkov v jetrih
    - mOS: 12 mes vs 4 mes (overestimation!)
    - Pomoč pri odločiti o zdravljenju
      - Empirična KT
      - BSC
  - Model 2:
    - Belci, ženske, pod 65 let, poročene, SCC, zdravljenje z RT

Abeloff's Clinical Oncology (6th Edition) 2020; Cancer of Undefined Site of Origin 1694-702.
Fizzazi K et al. Ann Oncol 2015; 26(Suppl 5): v133-138.

Randén M, Rutqvist L-E, Johansson HCancer patients without a known primary: incidence and survival trends in Sweden 1960-2007. Acta Oncol 48(6): 915-920

Article in Acta oncologica (Stockholm, Sweden) · May 2009
DOI: 10.1080/02841860902862503 · Source: PubMed

Prognoza bolnikov z RNI je slaba in se v zadnjih desetletjih ni pomembno izboljšala.

Prognostično neugodna skupina

Table 1
Randomized clinical trials studying specifically CUP.

Author (year) (number of patients)	Histology	Regimens	Median overall survival (months)	Response rate	p
Woods *et al.* (1980) [75] (n = 47)	Adenocarcinoma, undifferentiated	5-Fluorouracil, cyclophosphamide, methotrexate	1.6	4.5%	NS
		Doxorubicin, mitomycin-C	4.1	36%	
Shildt *et al.* (1983) [76] (n = 36)	Adenocarcinoma	5-Fluorouracil	3.4	0%	NS
		Doxorubicin, 5-fluorouracil, cyclophosphamide	3.1	0%	
Milliken *et al.* (1987) [78] (n = 101)	Adenocarcinoma, undifferentiated	Doxorubicin, mitomycin-C	4.1	42%	NS
		Cisplatin, bleomycin, vinblastin	5.7	32%	
Eagan et al. (1987) [77] (n = 55)	Carcinoma (50/55 adenocarcinomas)	Doxorubicin, mitomycin-C	5.5	14%	NS
		Cisplatin, doxorubicin, mitomycin-C	4.6	27%	
Falkson *et al.* (1998) [79] (n = 84)	Adenocarcinoma, undifferentiated	Cisplatin, epirubicin, mitomycin-C	9.4	50%	0.05
		Mitomycin-C	5.4	17%	
Dowell *et al.* (2001) [80] (n = 34)	Adenocarcinoma, undifferentiated	Paclitaxel, 5-fluorouracil, leucovorin	8.2	19%	NS
		Carboplatin, etoposide	6.4	19%	
Assersohn *et al.* (2003) [81] (n = 88)	Carcinoma	5-Fluorouracil	6.6	11.6%	NS
		5-Fluorouracil, mitomycin-C	4.7	20%	
Culine *et al.* (2003) [83] (n = 80)	Carcinoma	Cisplatin, gemcitabine	8	55%	NS
		Cisplatin, irinotecan	6	38%	
Palmeri *et al.* (2006) [11] (n = 66)	Carcinoma	Cisplatin, gemcitabine, vinorelbine	13.6	48.5%	NS
		Cisplatin, paclitaxel, gemcitabine	9.6	42.3%	
Huebner *et al.* (2009) [84] (n = 92)	Adenocarcinoma, undifferentiated	Carboplatin, paclitaxel	11	23.8%	NS
		Gemcitabine, vinorelbine	6.9	20%	
Hainsworth *et al.* (2010) [85] (n = 198)	Carcinoma	Paclitaxel, carboplatin, etoposide then gefitinib	7.4	18%	NS
		Gemcitabine, irinotecan then gefitinib	8.5	18%	
Gross-Goupil et al. (2012) [86] (n = 52)	Carcinoma	Cisplatin	8	16%	NS
		Cisplatin, gemcitabine	11	19%	
Hainsworth *et al.* (2015) [74] (n = 89)	Carcinoma	Carboplatin, paclitaxel, belinostat	12.4	45%	NS OS
		Carboplatin, paclitaxel	9.1	21%	P less than 0.02 ORR
Hayashi *et al.* (2019) [88] (n = 130)	Carcinoma	Carboplatin, paclitaxel	12.5	41.2%	NS
		Site-specific therapy	9.8	34.7%	
Fizazi *et al.* (2019) [89] (n = 243)	Carcinoma	Cisplatin, gemcitabine	10	NA	NS
		Site-specific therapy	10.7		

p = p-value for statistical significance for overall survival; NS = not statistically significant, OS = overall survival, ORR = overall response rate, NA = not available

Olivier T et al. Canc Treat Rev 2021; 97: 102204. Redefining cancer of unknown primary: Is precision medicine really shifting the paradigm?

RNI in empirično (citostatsko) zdravljenje

Prognostično neugodna skupina

- KT-dvojčki (na osnovi platine in/ali taksanov)
  - Izbirana osnovi izkušenj, dostopnosti zdravil, toksičnega profila in stanja bolnika (spremljajoče bolezni)
- Sistematični pregled randomiziranih raziskav:
  - Nobena shema zdravljenja se ni izkazala za učinkovitejši
  - Nakazan trend k izboljšanju preživetju za kombinacijo platina/taksan
- Metanaliza:
  - 32 raziskav
  - Trend boljšega preživetja za sheme na osnovi platine ali taksanov
- F3: Trojček (pakli/karbo/etopozid) vs dvojček (gem/irino)
  - Ni bolj učinkovit, je bolj toksičen

Fizzazi K et al. Ann Oncol30 (Suppl 5); 2019: v851–v934.
Golfinopoulos V et al. Cancer Treat Rev 2009; 35:570-3.
Lee J et al. Br J Cancer 2013;108:39-48.
Amela EY et al. Crit.Rev. Oncol. Hematol. 2012; 84:213-23.

Korak naprej

Prognostično neugodna skupina

Iskanje tkivnega izvora

(Tissue of Origin Classifier Assay)

- Analiza genskega izražanja tumorskih celic, profil miRNA, metilacijski status DNA in primerjava s tumorji znanega izvora.
- Tumorske cc. vsaj deloma ohranijo dedni zapis izvornega tkiva.
- Hipoteza: prepoznava tkivnega izvora omogoče bolj usmerjeno zdravljenje, ki je bolj učinkovito.
- Najverjetnejši tkivni izvor odkrit pri 80-85% bolnikov.

Can Precision Medicine Change The Paradigm?

Obsežno genomsko profiliranje

(tarčno zdravljenje, imunoterapija)

- Metoda: NGS
- Iskanje molekularnih posebnosti tumorja
  - Za nekatere (~30%) že poznamo usmrejno zdravljenje na osnovi rezultatov molekularne analize genoma (targetable alterations)
- Molekularni podpis RNI?
  - Biologija RNI slabo poznana
  - Več hipotez nastanka
  - Kromosomska nestabilnost
    - Značilnost metastaz RNI

Olivier T et al. Canc Treat Rev 2021; 97: 102204.

Pomen iskanja tkivnega izvora (1)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

LATE-BREAKING AND DEFERRED PUBLICATION ABSTRACTS

BIOMARKERS

LBA15_PR **A phase III trial of empiric chemotherapy with cisplatin and gemcitabine or systemic treatment tailored by molecular gene expression analysis in patients with carcinomas of an unknown primary (CUP) site (GEFCAPI 04)**

K. Fizazi[1], A. Maillard[2], N. Penel[3], G. Baciarello[1], D. Allouache[4], G. Daugaard[5], A. Van de Wouw[6], G. Soler[7], E. Vauleon[8], L. Chaigneau[9], R. Janssen[10], F. Losa Gaspa[11], R. Morales Barrera[12], C. Balana[13], D. Tosi[14], B. Chauffert[15], C.A. Schnabel[16], G. Martineau[17], S. Culine[18], I. Borget[19]

F3, randomizirana, N= 243

92-genski RT-PCR mRNA profiliranje

- Najpogosteje propoznan tkivni izvor: pankreatiko-biliarni trakt (19%), SCC (11%), hipernefrom (8%), pljuča (8%)
- 91/123 (skup B): usmrejeno zdravljenje
- PFS: 5.3 mes (skup A) vs 4.6 mes (skup B); HR 0.95 (0.72-1.25); p=0.7
- OS: 10.0 mes (skup A) vs 10.7 mes (mes) (skup B); HR 0.92 (0.69-1.23)
- V proučevani skupini je bilo >50% bolnikov s tumoji, za katere učinkovitega zdravljenja ne poznamo in bi bili ne glede na randomizacijo zdravljenji s shemo GC.

Fizzazi K et al. Ann Oncol30 (Suppl 5); 2019: v851–v934.

Pomen iskanja tkivnega izvora (2)

- Ali je prepoznava tkivnega izvora iz vidika izida bolezni pri bolniku z RNI pomembna/smiselna?
  - GEFCAPI 04: NE
  - Približno 20% bolnikov v raziskavi je imelo pankreatiko-biliarni profil tumorja. To so tumorji, za katere nimamo poznanega učinkovitega zdravljenja.
  - Zaključek raziskave: Iskanje tkivnega izvora in usmrejno zdravljenje je najverjetneje povezano z boljšim izidom pri določenih podskupinah bolnikov z RNI:
    - Kolo-rektalni profil RNI,
    - RNI s profilom hipernefroma,
    - RNI s profilom pljučnega raka.

Ann Oncol30 (Suppl 5); 2019: v851–v934.
Rassy E et al. Crit Rev Oncol 2020; 147.

Korak naprej

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

Prognostično neugodna skupina

Iskanje tkivnega izvora

(Tissue of Origin Classifier Assay)

- Analiza genskega izražanja tumorskih celic, profil miRNA, metilacijski status DNA in primerjava s tumorji znanega izvora.
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- Molekularni podpis RNI?
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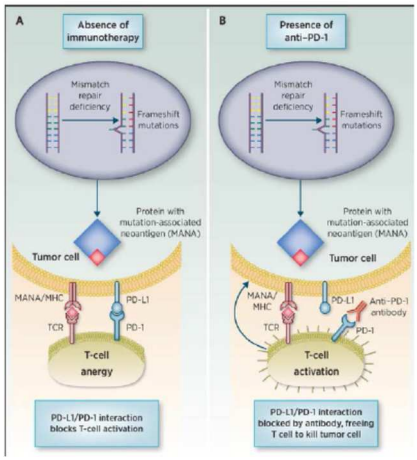
  - Več hipotez nastanka
  - Kromosomska nestabilnost
    - Značilnost metastaz RNI

Olivier T et al. Canc Treat Rev 2021; 97: 102204.

Imunsko mikro-okolje RNI (1)

- Tumorji z dMMR, MSI-H ali TMB-H so bolj imunogeni ⇒ pričakovana večja dobrobit zdravljenja z ZIKT
  - dMMR tu celice: visoka ekspresija PD-L1
  - Običajno v teh tumorjih dokazana visoka infiltracija s TIL: visoka ekspresija PD1, CTLA4 in Lag3
- Izraženost PD-L1 je nezadosten prediktivni bio-marker za odgovor na imunoterapijo (podatki iz zdravljenja različnih rakov znanega izvora).
- TMB se je v nekaterih raziskavah pokazal za bolj zanesljiv bio-marker odziva na zdravljenje z ZIKT.



Olivier T et al. Canc Treat Rev 2021; 97: 102204.

Imunsko mikro-okolje RNI (2)

- imunsko mikro-okolje RNI je slabo poznano
- N= 92; prisotnost CD8+ TIL (IHK) nima prognostične vloge
- N= 303; NGS, pri 32% prisotni bio-markerji odgovora na zdravljenje z ZIKT
- N=389; analiza 592 genov; 28% bolnikov ima izražen vsaj en potencialni prediktivni bio-marker odgovora na zdravljenje z ZIKT

Table 3
Investigational predictive biomarkers of response to immune checkpoint inhibitors in CUP.

Ross *et al.* (2021) [58] (n = 303)	PD-L1 expression ≥ 50%: 14% TMB high: 11.6% MSI-high: 1%
Galatica *et al.* (2018) [66] (n = 389)	TMB High : 11.8% MSI-H : 1.8% PD-L1 expression ≥ 5%: 22.5%

TMB high: Tumor mutational burden ≥ 16 mutations/megabase.
MSI-H : microsatellite instability high

Olivier T et al. Canc Treat Rev 2021; 97: 102204.
Ross JS et al. Oncologist 2021; 26:e394-402.
Galactica Z et al. Eur J Cancer 2018; 94:179-86.

Imunsko mikro-okolje RNI (3)

- Incidenca bolnikov z RNI, ki imajo dokazan MSI-H profil, je globalno nizka.

Table 3
Investigational predictive biomarkers of response to immune checkpoint inhibitors in CUP.

Ross *et al.* (2021) [58] (n = 303)	PD-L1 expression ≥ 50%: 14% TMB high: 11.6% MSI-high: 1%
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Olivier T et al. Canc Treat Rev 2021; 97: 102204.
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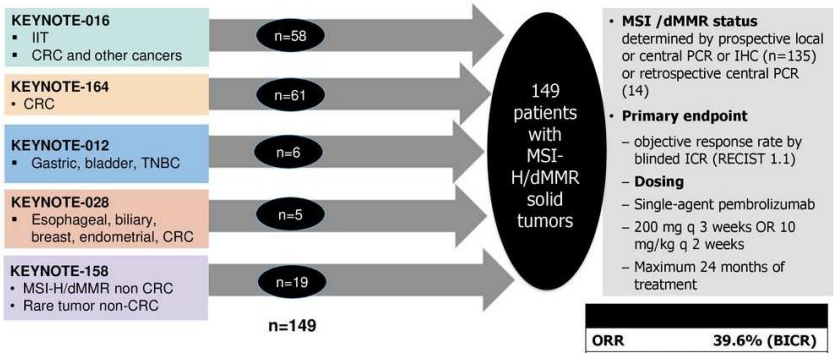
Galactica Z et al. Eur J Cancer 2018; 94:179-86.

Pembrolizumab: FDA odobritev za agnostično zdravljenje (1)

- Maj 2017: solidni, neoperabilen, metastatski rak (MSI-H, dMMR), ki je napredovalo predhodnem zdravljenju oziroma zanj nimamo druge učinkovite možnosti zdravljenja

Primarni cilj: ORR= 39,6%
78% odgovor traja ≥ 6 mes.
11 CR, 48 PR



Merck Sharp & Dohme: KEYTRUDA (pembrolizumab) full prescribing information. Whitehouse Station, NJ, Merck Sharp & Dohme Corp., 2018

Pembrolizumab: FDA odobritev za agnostično zdravljenje (2)

- Junij 2020: širitev indikacije, FDA odobritev za zdravljenje solidnih neoperabilnih, metastatskih rakov z dokazanim TMB-H, po progresu na standardno zdravljenje in brez alternativnih možnosti zdravljenja (TMB-H≥10)

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

N= 1066
13% (N=105) bolnikov TMB-H
Primarni cilj: ORR
30% za TMB-H vs 6% za TMB-nonH

Marabelle AM et al. Lancet Oncol 2020; 21: 1353–65

NivoCUP

- Anekdotični opisi učinkovitosti ZIKT pri RNI
- NivoCUP:
  - Učinkovitost ZIKT pri RNI (slaba prognostična skupina)
  - N= 56; (80% (N=45) že predhodno zdravljenih, do 3 linije)
  - Primarni cilj: ORR
    - N=45: ORR= 22% (2 bolnika CR, 9 bolnikov PR)
    - N=56: mPFS= 5,1 mes, OS= 15,9 mes
  - Zaključek: Nivolumab nakazuje učinkovitost pri izbranih bolnkih z RNI. Potrebujemo prediktivne bio-markerje.

Olivier T et al. Canc Treat Rev 2021; 97: 102204.
Tanizaki J et al. JCO 2020; 38(suppl.15, Abst. 106)

Aktivne raziskave: ZIKT pri RNI

Vključevanje v klinične raziskave, ki proučujejo zdravljnje bolnikov z RNI je težavno:

- Vključitveni kriteriji, heterogenost bolnikov
- Slab PS ob postavitvi diagnoze
- Količina in kakovost tumorskih vzorcev

Trenutno so aktivne 4 klinične raziskave: vloga ZIKT pri RNI

Ongoing recruiting trials specifically designed for CUP patients.

Trial name	NTC	Title	Phase	Arms	Setting
CUPSICO	NCT03498521	A Phase II Randomized Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site	II	Mutliples arms : - Platinum-based- molecularly guided therapy	First line poor prognosis CUP
CheCUP	NCT04131621	Nivolumab/Ipilimumab in Second Line CUP-syndrome	II	Single arm	Second line poor prognosis CUP
CUPem	NCT03752333	Trial of Pembrolizumab in Cancer of Unknown Prima	II	Single arm	2 cohorts: first line and second line settings
CUP	NCT03391973	Pembrolizumab in Patients With Poor-Prognosis Carcinoma of Unknown Primary Site	II	Single arm	First line poor prognosis CUP

Olivier T et al. Canc Treat Rev 2021; 97: 102204.

Klinična raziskava CUPISCO

U.S. National Library of Medicine
ClinicalTrials.gov

A Phase II Randomized Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site (CUPISCO)

ClinicalTrials.gov Identifier: NCT03498521

- Primarni cilj: PFS
- Sekundarni cilji: RR, OS, CBR QoL
- Proučuje učinkovitost zdravljenja, izbranega na osnovi molekularne analize tumorja v primerjavi s KT na osnovi platine.
- Ekperimentalna zdravila: širok nabor zdravil, ki imajo dokazano učinkovitost pri različnih genomskih alteracijah.
- Izbor terapije, prepoznavanje t.i.”driver” genomskih aberacij. V odločitev o vrsti zdravljenja je vključen MTB.
- Vključevanje počasno, 55% “screen failure”

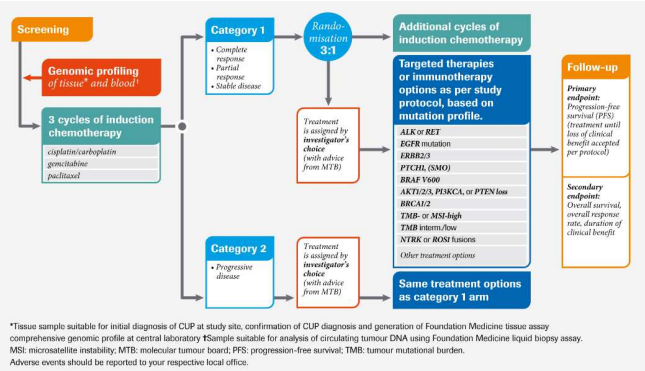
Intervention/treatment

Drug: Alectinib
Drug: Vismodegib
Drug: Ipatasertib
Drug: Olaparib
Drug: Erlotinib
Drug: Bevacizumab
Drug: Vemurafenib
Drug: Cobimetinib
Drug: Trastuzumab Subcutaneous (SC)
Drug: Pertuzumab
Drug: Atezolizumab
Drug: Carboplatin
Drug: Paclitaxel
Drug: Cisplatin
Drug: Gemcitabine
Drug: Entrectinib
Drug: Ivosidenib
Drug: Pemigatinib

Pauli C et al. Oncologist 2021;26:e769–e779.

Klinična raziskava CUPISCO

- Cilj: Učinkovitost, varnost zdravljenja RNI na osnovi molekularne analize tu.genoma.
- Izbor zdravljenja sloni na rezultat CGP (FMT*)
- N=790; F 2, globalna, 162 centrov
- Po 3-eh ciklih indukcijske KT na osnovi platine (dvojček):
  - Responder-ji: R (eksperimentalno zdravljenje ali nadaljevanje KT)
  - Non-responder-ji: eksperimentalno zdravljenje (eksploratorna analiza).



Predviden zaključek: Junij 2023.

https://cup-syndrome.com/en/home/cupisco-study.html
*FMT: Foundation Medicine Tissue or liquid Test

Zarkavelis G et al. ESMO open 2019; 4(Suppl2).
Pauli C et al. Oncologist 2021;26:e769–e779.

Zaključki

- ZIKT so potencialno učinkovita zdravila za zdravljenje malignih bolezni različnega izvora
  - Anekdotični opisi učinkovitosti pri RNI
  - Raziskave, ki so v teku, bodo morda bolje opredelile pomen imunoterapije pri RNI
- Neskončno iskanje origa v (dobi personalizirane medicine) ni smislno.
- Potrebujemo prediktivne bio-markerje, s pomočjo katerih se bomo bolj zanseljivo odločali o optimalnem zdravljenju posameznega bolnika.
  - dMMR/MSI-H/TMB-H so prediktivni biomarkerji za odgovor na ZIKT v okviru tumor agnostičnega zdravljenja.
- FDA odobrila zdravljenje s pembrolizumabom za solidne rake dMMR/MSI-H/TMB-H neodvisno od origa, po progresu na standardno zdravljenje
  - Trenutno edina uradna indikacija za zdravljenje RNI z ZIKT.

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Genska imunoterapija pri BCC: Klinična študija faze I

Maja Čemažar, Gregor Serša

Novosti v imunoterapiji pri solidnih rakih leta 2021

REPUBLIC OF SLOVENIA
MINISTRY OF EDUCATION, SCIENCE AND SPORT

EUROPEAN UNION
EUROPEAN REGIONAL DEVELOPMENT FUND
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SmartGene.si

Nova generacija genske terapije za zdravljenje raka: od genov do proizvodnje

A new gene based cancer treatment modality with a paradigm shift in immunotherapy.

2018 – 2021

Javni razpis „Spodbujanje izvajanja raziskovano-razvojnih projektov (TRL 3-6)“
Prednostno področje: Zdravje-medicina
Prednostno podpodročje: Zdravljenje raka

REPUBLIC OF SLOVENIA
MINISTRY OF EDUCATION, SCIENCE AND SPORT

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PARTNERJI:

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY LJUBLJANA

COBIK

JAFRAL
passion for biosolutions

University of Ljubljana
Faculty of Electrical Engineering

pio
Clean visions.

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

University of Ljubljana
Veterinary Faculty

OPIS VLOGE PARTNERJEV, NJIHOVA EKSPERTIZA

- Onkološki inštitut Ljubljana je celovit center za zdravljenje raka, ki obsega bolnišnico, specializirano za onkologijo, in predklinični oddelek za raziskave rakavih obolenj.
- COBIK je zasebni raziskovalni zavod na področju biotehnologije. Ima ekspertizo na področju bioprocesništva, razvoja analitskih in diagnostičnih metod, razvoja antibakterijskih učinkovin in razvoja cepiv.
- JAFRAL d.o.o. je podjetje, ki ponuja proizvodnjo biomolekul po naročilu ter izvaja pogodbene raziskave na področju razvoja bioloških zdravil.
- ISKRA PIO d.o.o. je družba za projektiranje in izdelavo opreme za čiste in čistilne tehnologije.
- Univerza v Ljubljani, Fakulteta za elektrotehniko preučuje biofizikalne mehanizme elektroporacije, njene aplikacije v biologiji biotehnologiji in medicini ter razvoj elektrod in sistemov za generiranje pulzov.

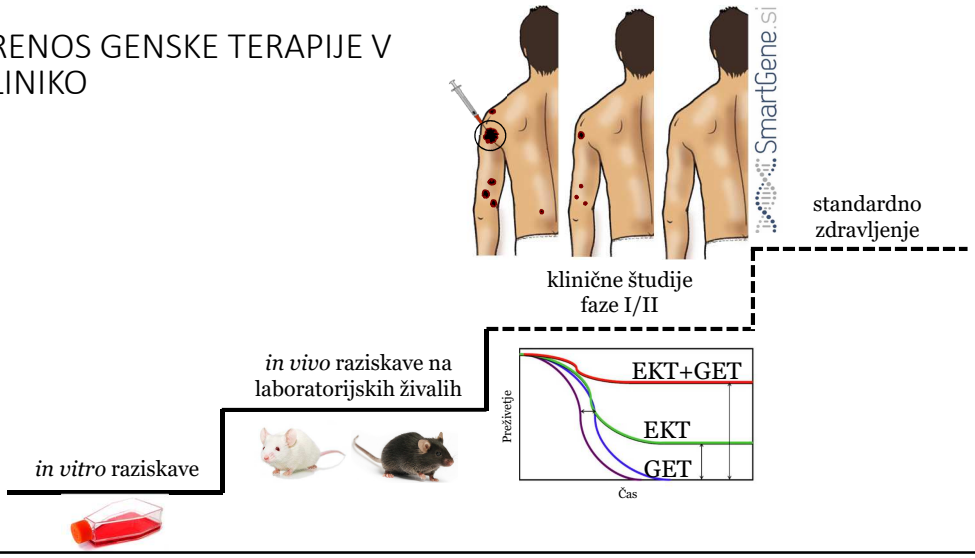
SODELUJOČI IZVAJALCI PROJEKTA, NJIHOVA EKSPERTIZA

- Univerzitetni klinični center Ljubljana, Oddelek za otorinolaringologijo in cervikofacialno kirurgijo je klinična in raziskovalna ustanova na področju zdravljenja raka v področju glave in vratu z bogatimi kliničnimi izkušnjami zdravljenja z elektrokemoterapijo.

- Univerza v Ljubljani, Veterinarska fakulteta, Klinika za male živali je klinična ustanova za zdravljenje malignih tumorjev pri psih in mačkah, ki ima veliko izkušenj tudi z elektrokemoterapijo in gensko terapijo.

NAMEN PROJEKTA – TRANSLACIJA V KLINIKO

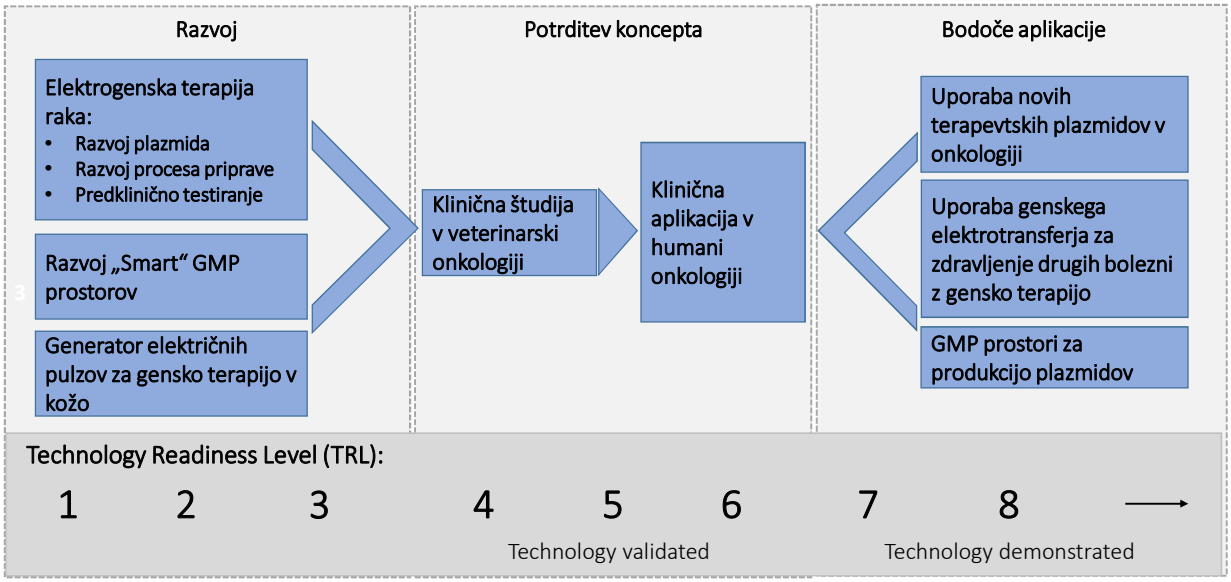
- PRENOS GENSKE TERAPIJE V KLINIKO



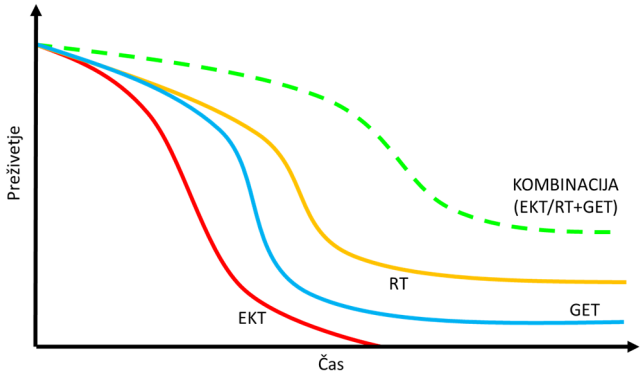
CILJI SmartGene.si PROJEKTA

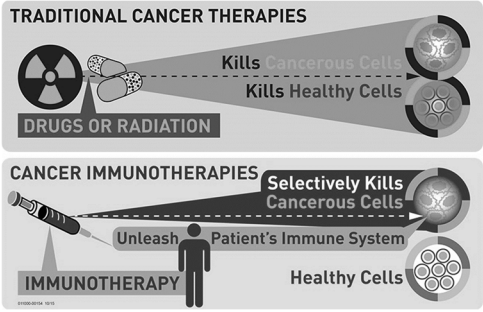
- Konstrukcija in testiranje plazmidnega vektorja za IL-12 in novih plazmidnih DNA vektorjev s terapevtskimi geni
- Inovativen terapevtski pristop s kombinacijo elektrokemoterapije (ECT) in terapije z genskim elektroprenosom (GET)
- Nova naprava za elektroporacijo za prenos plazmidne DNA v celice kože
- Inovativen proces proizvodnje plazmidne DNA
- „Smart“ GMP proizvodnih prostorov
- GMP proizvodnja plazmidne DNA
- Klinična študija
- Translacijska raziskovalna platforma na področju zdravljenja raka

CILJI PROJEKTA SmartGene.si



NAJNOVEJŠA STRATEGIJA JE KOMBINACIJA ABLATIVNIH TEHNIK ZDRAVLJENJA RAKA Z IMUNOTERAPIJO



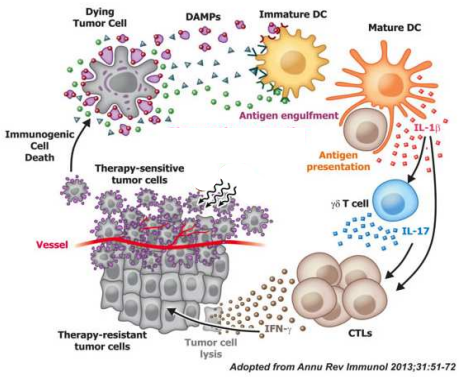


CILJI IMUNOTERAPIJE:

- ✓ Spodbujanje lokalnega odgovora tumorja
- ✓ Sistemski učinek
- ✓ Rezultat: povečanje preživetja bolnikov

EKT SPODBUDI TUDI LOKALNI IMUNSKI ODGOVOR, TAKO KOT RADIOTERAPIJA

EKT inducira imunogeno celično smrt.



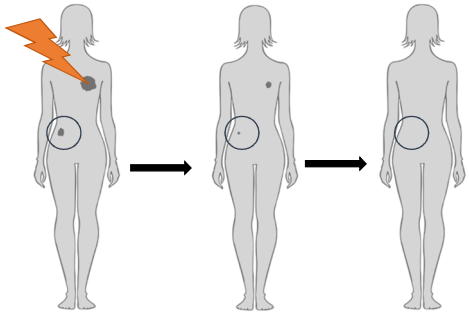
Problem: Kako nadgraditi lokalne ablativne tehnike, kot sta EKT in RT, v sistemska zdravljenja?

KAKO SPREMENITI LOKALNO ZDRAVLJENJE V LOKOREGIONALNO ALI SISTEMSKO?

Cilj: Doseči protitumorski učinek na oddaljenih, lokalno ne-zdravljenih tumorjih.

Kako:

- Lokalni imunski odziv ablativnih zdravljenj lahko smatramo za in situ vakcinacijo.
- Ta lokalni imunski odgovor lahko spodbudimo z
  - zaviralci imunskih točk,
  - Imunostimulacijo.

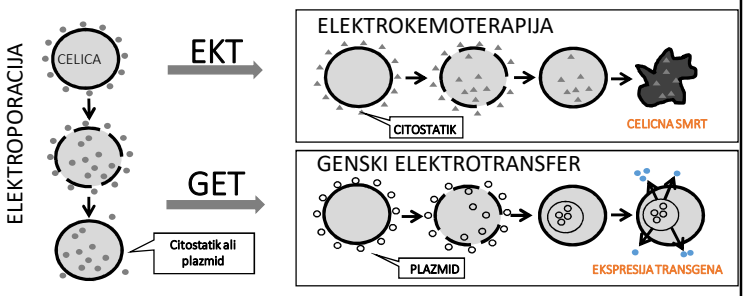


Hipoteza:

EKT ali RT imata in situ vakcinacijski učinek, ki ga lahko spodbudimo z imunostimulacijo z interlevkinom 12.

ELEKTROPORACIJA KOT DOSTAVNI SISTEM ZA DOSTAVO CITOSTATIKOV IN PLAZMIDOV

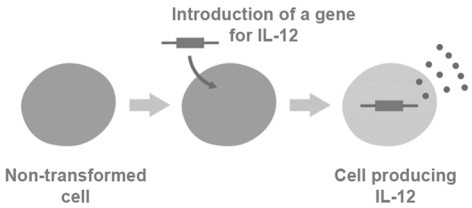
- Elektrokemoterapija je že uveljavljena lokalna ablativna tehnika.
- Genski elektroprenos pa je novejša modaliteta zdravljenja za dostavo plazmidov v tkiva.

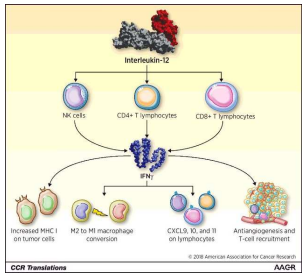


GENSKA TERAPIJA

je lahko nov terapevtski pristop za imunoterapijo

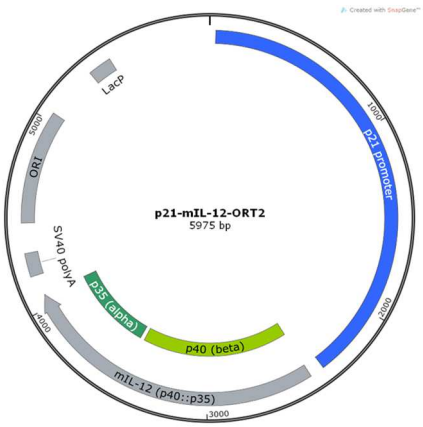
- Plazmidna DNA lahko nosi zapis za imuno-modulatorni protein.
- Odličen kandidat je Interleukin 12 (IL-12), ki ima imunostimulatorno in protitumorsko delovanje.
  - Interlevkin 12 (IL-12) je citokin z imunomodulatornim delovanjem.
  - Deluje tudi anti-angiogeno.
  - Njegova protitumorska učinkovitost je znana, je pa toksičen v večjih odmerkih.





PLAZMID za IL-12

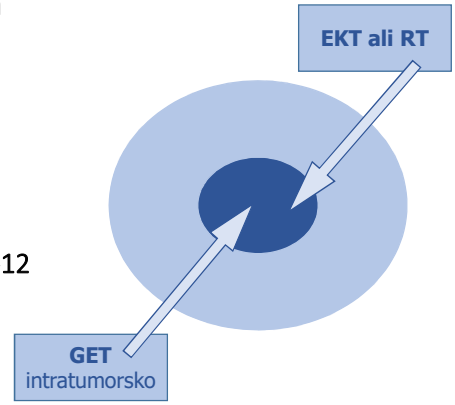
- Pripravljen imamo plazmid z zapisom za IL-12, ki ima dobro protitumorsko učinkovitost, tako za miši, pse in ljudi.
- Prednosti plazmida so:
  - Plazmid z ORT tehnologijo, ki ne potrebuje dodajanja antibiotikov.
  - Izražanje IL-12 je pod kontrolo tumorsko specifičnega in z genotoksičnim stresom (radio-, kemoterapija) inducibilnega promotorja p21.



NAŠA IDEJA: Kombinacija EKT ali RT z lokalno gensko terapijo, ki bi imela sistemski učinek na oddaljene tumorje

Razviti nov terapevtski pristop za zdravljenje raka na osnovi kombinacije:

- Lokalne ablativne tehnike
  - Elektrokemoterapija (EKT)
  - Radioterapija (RT)
- Genska imunoterpija
  - Genski elektrotransfer (GET) plazmida z zapisom za IL-12

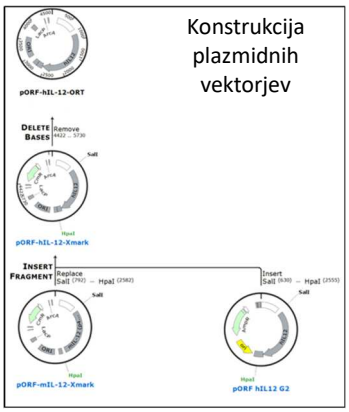


CILJI SmartGene.si projekta

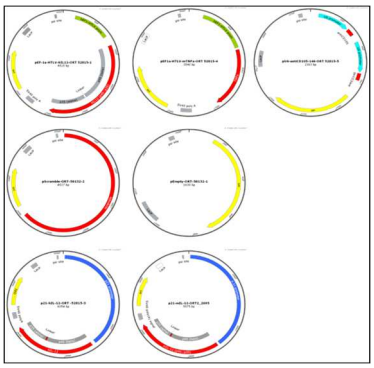
- Konstrukcija in testiranje plazmidnega vektorja za IL-12 in novih plazmidnih DNA vektorjev s terapevtskimi geni
- Inovativen terapevtski pristop s kombinacijo elektrokemoterapije (ECT) in terapije z genskim elektroporenosom (GET)
- Nova naprava za elektroporacijo za prenos plazmidne DNA v celice kože
- Inovativen proces proizvodnje plazmidne DNA
- „Smart“ GMP proizvodnjih prostorov
- GMP proizvodnja plazmidne DNA
- Klinična študija
- Translacijska raziskovalna platforma na področju zdravljenja raka

Konstrukcija in testiranje plazmidnega vektorja za IL-12 in novih plazmidnih DNA vektorjev s terapevtskimi geni

Konstrukcija plazmidnih vektorjev



Sekveniranje in anotacija



Pred-klinično testiranje novih plazmidov in elektroporatorja

In vitro

FaDu CT26

In vivo

Ne-klinična študija za odobritev klinične študije faze I

Zasnovana na podlagi:

- Smernic EMA za napredna zdravljenja
  - EMA/CAT/80183/2014 (Quality, preclinical and clinical aspects of gene therapy medicinal products),
  - EMA/CAT/852602/2018 (Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials),
  - EMEA/CHMP/GTWP/125459/2006 (Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products),
  - EMA/CPMP/ICH/286/1995 (ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals),
  - EMA/CHMP/ICH/646107/2008 (ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals),
  - EMEA/273974/2005 (Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors),
  - CPMP/BWP/3088/99 (Note for Guidance on the Quality, Preclinical and Clinical aspects of gene transfer medicinal products),
  - CPMP/SWP/1042/99 Rev 1 Corr (Guideline on repeated dose toxicity),
  - Reflection paper: Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products.

- Znanstvenega nasveta EMA/CHMP/SAWP/19705/2020 na podlagi naših vprašanj in predstavitve/sestanka z eksperti na EMA-i.
- Pravilnika o načelih dobre laboratorijske prakse (Uradni list RS, št. 38/00 in 2/04)

Ne-klinična študija SMG-01

Vodja študije: prof. Maja Čemažar

Oddelek za eksperimentalno onkologijo, OIL

Glavna raziskovalca:
dr. Maša Bošnjak, mag. farm.; poverjena faza študije: izvedba *in vitro* testiranja
dr. Boštjan Markelc, univ. dipl. biol.; poverjena faza študije: izvedba *in vivo* testiranja

Oddelek za patologijo, OIL

Glavna raziskovalka: dr. Gorana Gašljević, dr. med.; poverjena faza študije: izvedba histopatološkega testiranja

Klinika za male živali, Veterinarska fakulteta, Univerza v Ljubljani

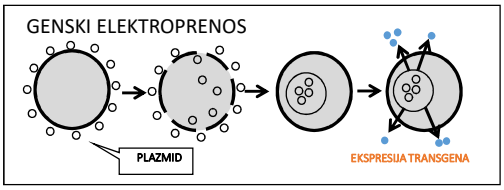
Glavna raziskovalka: prof. Nataša Tozon, dr. vet. med.; poverjena faza študije: izvedba preiskav krvne slike in biokemijskih parametrov

Oseba za zagotavljanje kakovosti: dr. Tanja Jesenko, univ. dipl. biokem.,

Ne-klinična študija SMG-01

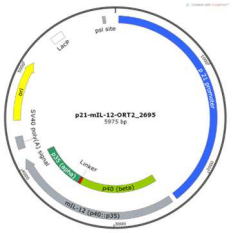
Genski prenos (GET) plazmida phIL12:

- farmakodinamika
- farmakokinetika
- toksičnost
- imunogenost



Za dovajanje električnih pulzov smo uporabili generator električnih pulzov CLINIPORATOR™, ki ima dovoljenje za uporabo v kliničnem okolju z oznako CE.

Zaradi biološke neaktivnosti humanega IL-12 v miših smo pripravili tudi analog plazmida phIL12, ki ima zamenjan humani gen za IL-12 z mišjim - plazmid **pmIL12**



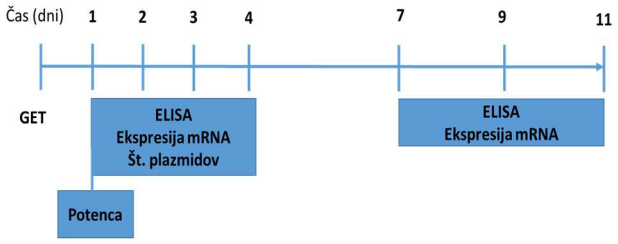
Ne-klinična študija SMG-01

Z ***in vitro* študijami** smo določili biološko aktivnost proteinov, ki nastajata iz plazmidov phIL12 in pmIL12, stopnjo izražanja transgenov in število kopij plazmidne DNA v celicah.

Vse in vitro študije s phIL12 so bile izvedene na humani celični liniji ploščatoceličnega karcinoma žrela FaDu

Vse *in vitro* študije s pmIL12 so bile izvedene na mišji celični liniji raka debelega črevesa CT26

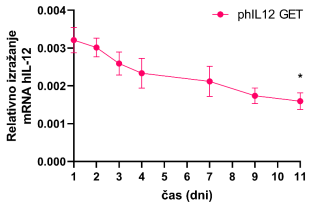
Potek *in vitro* poskusov in analiz.

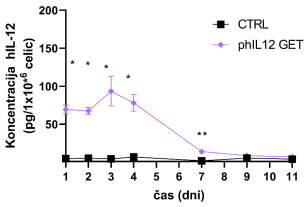


Ne-klinična študija SMG-01

In vitro študije s phIL12 na humani celični liniji FaDu

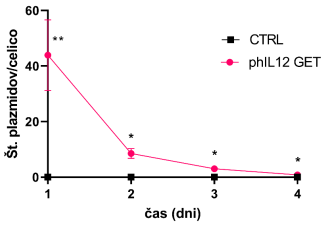
Stopnja izražanja mRNA

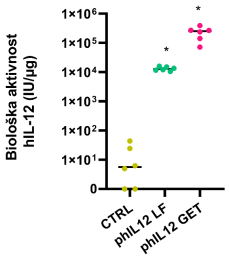




Stopnja izražanja: proteini

Število kopij plazmida



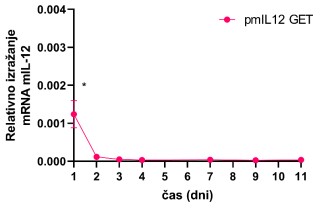


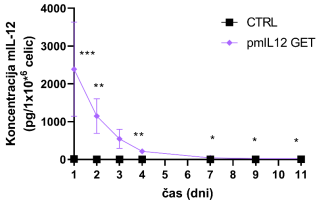
Biološka aktivnost

Ne-klinična študija SMG-01

In vitro študije s pmIL12 na mišji celični liniji CT26

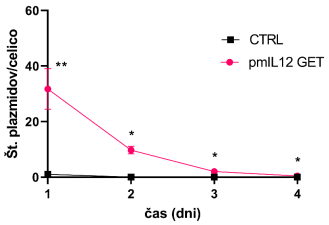
Stopnja izražanja mRNA

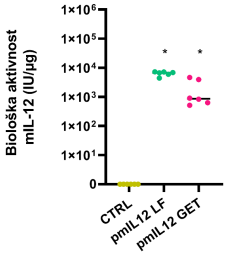




Stopnja izražanja: proteini

Število kopij plazmida





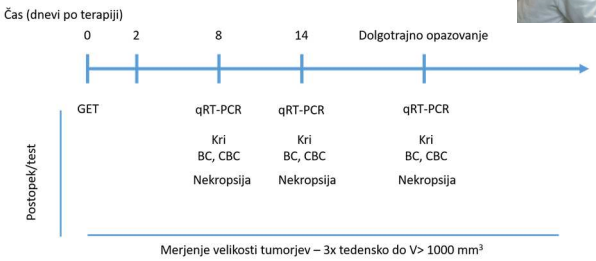
Biološka aktivnost

Ne-klinična študija SMG-01

Z ***in vivo* študijami** smo določili učinkovitost zdravila, farmakokinetiko, toksičnost, toleranco in imunogenost plazmida pmIL12. Študije so bile izvedene na mišjih tumorjih CT26.

			Št miši/skupino			
	Skupine (skupno število)		Časovna točka (dnevi po zadnji terapiji)			
		Doza	2	8	14	Dolgotrajno opazovanje
1	Naïvne miši	0	10	5	0	
2	CTRL	0	10	15	0	6
3	pmIL12 nizka doza	0.5 mg/mL	10	15	10	12
4	pmIL12 srednja doza	1 mg/mL	10	15	10	12
5	pmIL12 visoka doza	2 mg/mL	10	15	10	12

Potek *in vivo* poskusov in analiz.



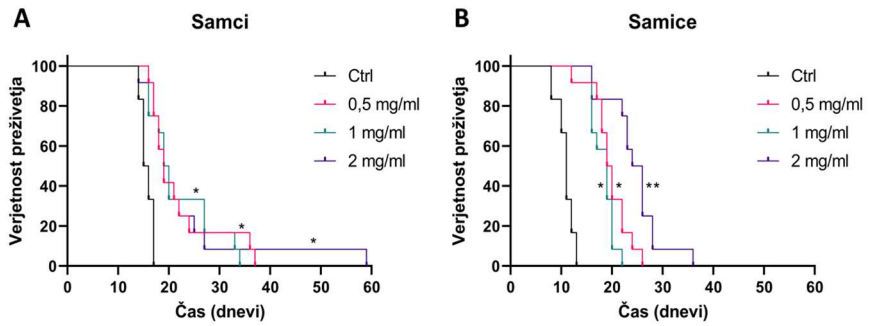
Vse študije smo izvedli na samcih in samicah.

V študiji smo uporabili 220 miši vsakega spola.

Ne-klinična študija SMG-01

Farmakodinamika

Učinkovitost delovanja plazmida pmIL12 na laboratorijskih živalih glede na dozo

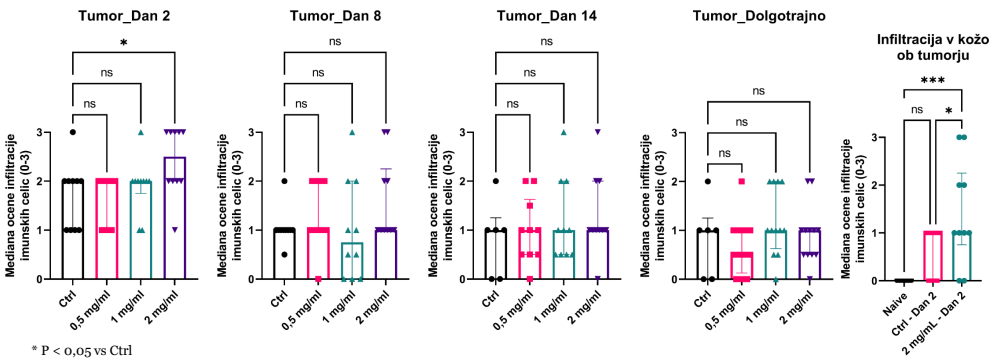


* - P< 0,05 vs Ctrl, ** - P< 0,05 vs Ctrl, 0,5 mg/ml in 1 mg/ml.

Ne-klinična študija SMG-01

Farmakodinamika

Infiltracija imunskih celic v tumor po vnosu plazmida pmIL12



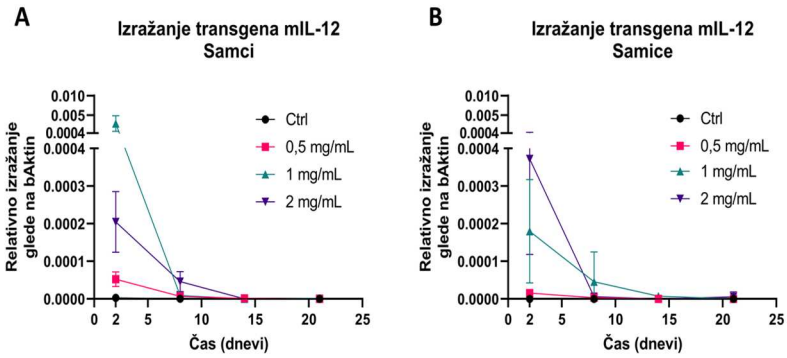
* P < 0,05 vs Ctrl

*P < 0,05 vs Naive
*** P < 0,001 vs Naive

Ne-klinična študija SMG-01

Farmakokinetika

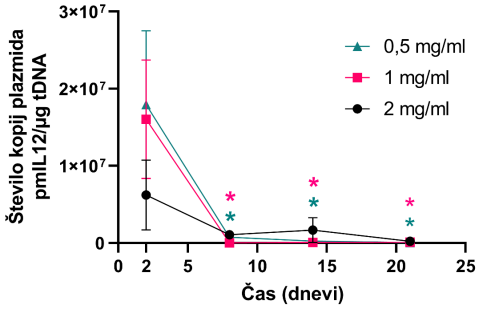
Kinetika izražanja transgena v tumorjih



Ne-klinična študija SMG-01

Farmakokinetika

Prisotnost števila kopij plazmida v koži nad in okoli tumorja



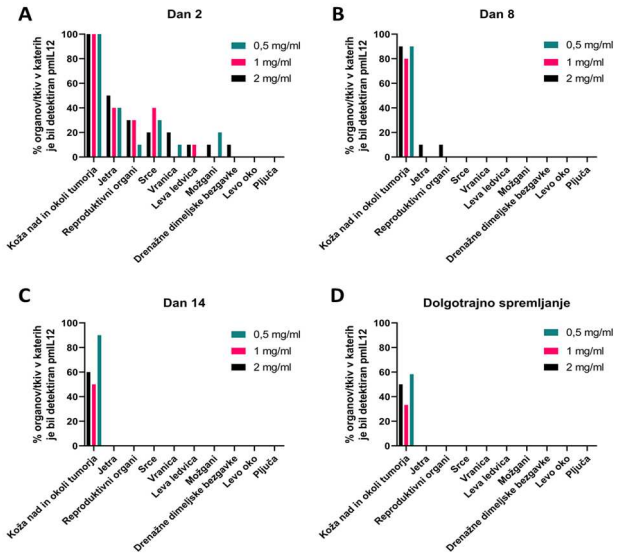
* - P < 0,05 vs Dan 2 0.5 mg/ml, * - P < 0,05 vs Dan 2 1 mg/ml.

Ne-klinična študija SMG-01

Farmakokinetika

Distribucija plazmida pmIL12 po organih

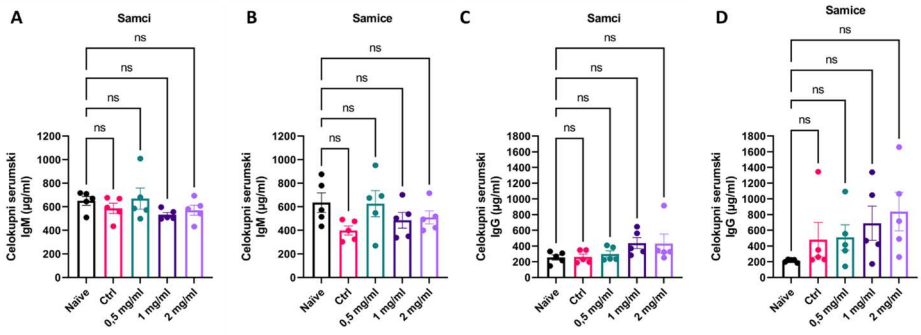
Zaporedna številka	Organ/tkivo	Trajanje zadrževanja pmIL12
1	Koža nad in okoli tumorja	dolgotrajno
2	Jetra	8 dni
3	Reproduktivni organi	8 dni
4	Srce	2 dni
5	Vranica	2 dni
6	Leva ledvica	2 dni
7	Možgani	2 dni
8	Drenažne dimeljske bezgavke	2 dni
9	Levo oko	Ni bil zaznan
10	Pljuča	Ni bil zaznan



Ne-klinična študija SMG-01

Toksikologija

Celokupna serumska količina IgM in IgG protiteles po vnosu plazmida



Ne-klinična študija SMG-01

Toksikologija

Krvna slika, biokemija in histopatologija v mejah normale

Organi na katerih je bila opravljena histopatološka analiza.

Zaporedna številka	Organ/tkivo
1	Koža nad in okoli tumorja
2	Jetra
3	Reproduktivni organi
4	Srce
5	Vranica
6	Leva ledvica
7	Možgani
8	Drenažne dimeljske bezgavke
9	Levo oko
10	Pljuča

Parametri, ki smo jih določevali z analizo krvi.

	CBC	BC
Zaporedna številka	Parameter	Parameter
1	WBC	Glukoza
2	RBC	Sečnina
3	HGB	Kreatinin
4	HCT	Celokupne beljakovine
5	MCV	Albumini
6	MCH	Holesterol
7	MCHC	Žolčne kisline
8	CHCM	Kalcij
9	RDW	Anorganski fosfat
10	HDW	Alanin aminotransferaza (ALT)
11	PLT	Aspartat aminotransferaza (AST)
12	MPV	Alkalna fosfataza (AP)
13	CH	Kreatinin kinaza (CK)
14	PCT	gama-glutamil transpeptidaza (GGT)
15	%NEUT	Natrij
16	%LYMPH	Kalij
17	%MONO	Klorid
18	%EOS	Celokupne beljakovine
19	%BASO	
20	%LUC	
21	#NEUT	
22	#LYMPH	
23	#MONO	
24	#EOS	
25	#BASO	
26	#LUC	

Zaključki

Ne-klinična študija SMG-01

Oddaja prve vloge na EMA: Avgust 2019
Prvi Online sestanek z EMA: September 2019
Sestanek v Amsterdamu na EMA: 14. 01. 2020

Oddaja vloge za poskuse na živalih na UVHVVR: 06. 02. 2020
Odobritev vloge za poskuse na živalih: 26. 02. 2020
Številka dovoljenja: U3401-6/2020/9
Oddaja vloge na KSOPKR: 24.06. 2020
Odobritev vloge na KSOPKR: 2.7.2020
Trajanje dela v laboratorijih: Oktober 2020 – Maj 2021

Število udeleženih raziskovalcev: 22

Število novih obrazcev ter SOP-jev: 103

Število shranjenih in procesiranih vzorcev:
- *in vitro* študije: 1655
- *in vivo* študije: 7558

CILJI SmartGene.si projekta

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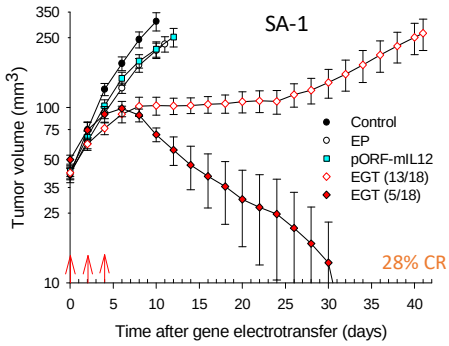
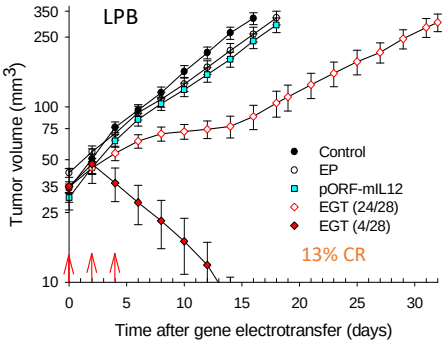
- Translacijska raziskovalna platforma na področju zdravljenja raka

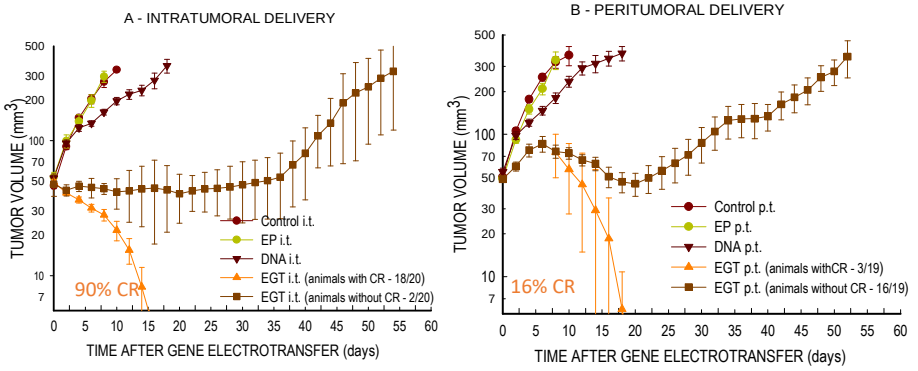
ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Protitumorski učinek *mIL-12* genskega elektrotransferja v mišico na podkožne tumorje miši





Protitumorsko delovanje of *mIL-12* genskega elektrotransferja; primerjava intra in peritumoralnega injiciranja



Intratumoral EGT resulted in high level of complete responses (18/20 tumors) with significant inhibition of tumor growth in the remaining 2 tumors.

Peritumoral EGT resulted in lower complete response rate (3/19 tumors), with remaining 16/19 showing significant delay in tumor growth.

Pavlin et al. Cancer Biol Ther 2009; 8:2112-2120

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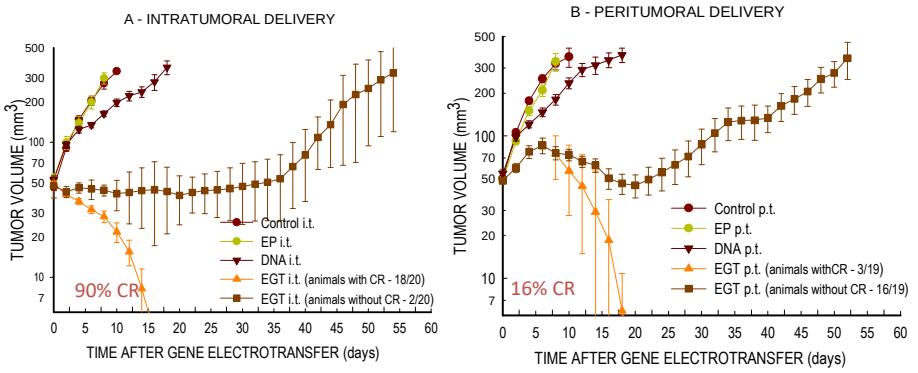

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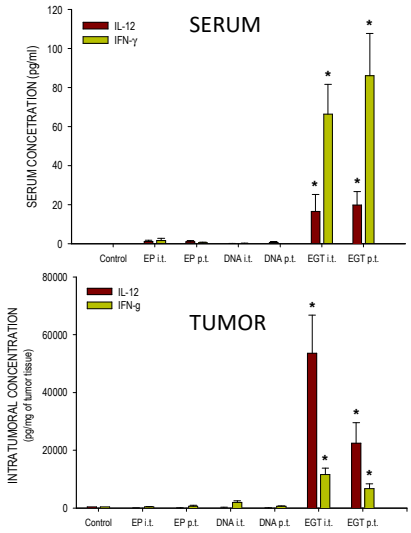
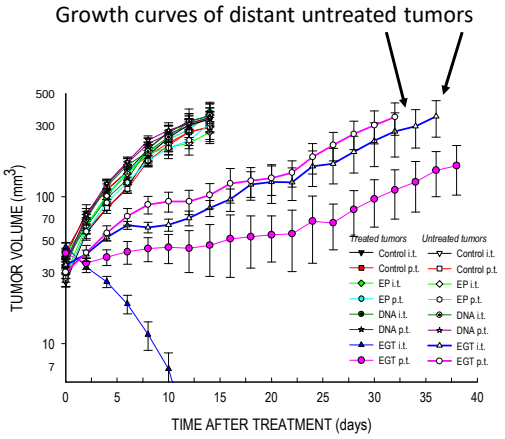
Peritumoral EGT resulted in lower complete response rate (3/19 tumors), with remaining 16/19 showing significant delay in tumor growth.

Pavlin et al. Cancer Biol Ther 2009; 8:2112-2120

Genski elektrotransfer lokalno, inducira lokalno in sistemsko izločanje citokinov IL-12 and IFN-γ in ima lokalni in sistemski protitumorski učinek





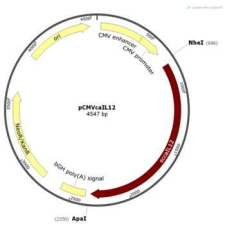
Pavlin et al. Cancer Biol Ther 2009; 8:2112-2120

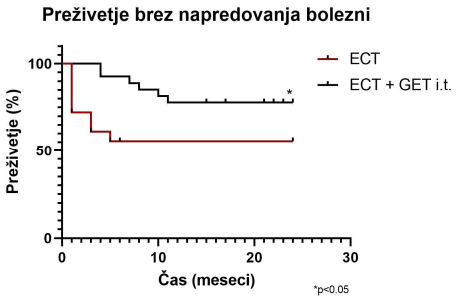
Onkološki inštitut Institute of Oncology Ljubljana

University of Ljubljana Veterinary Faculty

Inovativen terapevtski pristop s kombinacijo elektrokemoterapije (EKT) in terapije z genskim elektroporenosom (GET)

- Predklinično testiranje v veterinarski medicini.
- Intratumoralna aplikacija plazmidne DNA (pCMVcaIL-12).
- 25 psov s kožnim tumorjem (mastocitom).





Terapija: intratumoralna aplikacija cisplatina in plazmida pCMVcaIL-12, električni pulzi 1300 V/cm, 100 µs, 5 kHz.

CILJI SmartGene.si projekta

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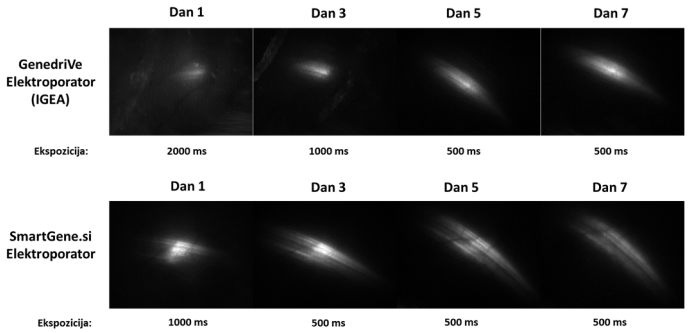
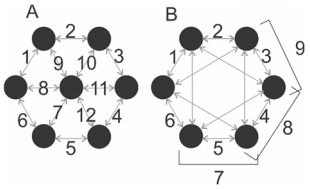
University of Ljubljana
Faculty of Electrical Engineering

Nova naprava za elektroporacijo za prenos plazmidne DNA v celice kože

University of Ljubljana
Faculty of Electrical Engineering

- Nova, inovativna ročka za dovajanje električnih pulzov.
- Neinvazivna transfekcija v kožo.





Klasična shema dovajanja pulzov A). Alternativna shema dovajanja pulzov B).

SmartGene elektroporator z aplikatorjem.

CILJI SmartGene.si projekta

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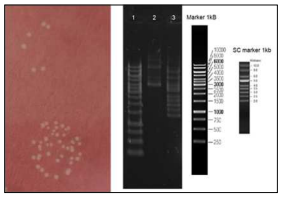
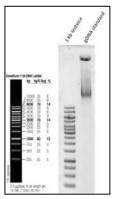
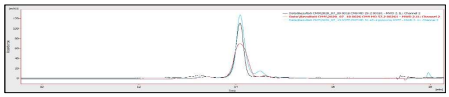
Inovativen proces proizvodnje plazmidne DNA

- Priprava osnovne in delovne celične banke izbranih bakterijskih sevov ter priprava zalog standarda okarakterizirane plazmidne in genomske DNA.
- Razvoj in optimizacija pripravljalnih procesov proizvodnje plazmida na laboratorijski skali.
- Prenos iz laboratorijske skale na pilotno skalo proizvodnje.
- Razvoj in optimizacija zaključnih procesov proizvodnje plazmida.
- Integracija s pripravljalnimi procesi ter prenos iz laboratorijskega na pilotni nivo.

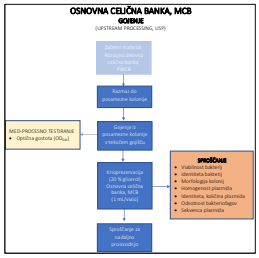




Specifikacije celične banke za GMP okolje za proizvodnjo p21-hIL12-ORT ter agarozna gelska elektroforeza pripravljenega gDNA standarda.



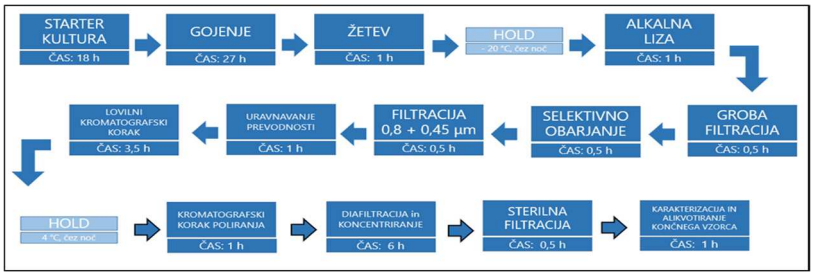
Kromatogrami plazmidov izoliranih iz različnih produkcijskih sevov.



Proces GMP priprave MCB iz razvojne delovne celične banke (RWCB).

Inovativen proces proizvodnje plazmidne DNA

- Razvoj več analitskih metod za medprocesno spremljanje procesa.
- Razvoj metod za določanje čistosti zdravilne učinkovine.
- Združitev vseh procesnih korakov v funkcionalen sistem integrirane proizvodnje.
- Umestitev med-procesne kontrole z razvitimi analitskimi metodami.
- Priprava standardnih operativnih postopkov (SOP) vseh procesnih korakov za integrirano proizvodnjo plazmida na pilotni skali.
- Priprava standardnih operativnih postopkov (SOP) vseh analitskih metod.
- Prenos na GMP proizvodno raven.



Shema integriranega bioprocesa z dvema korakoma ustavitve.

Cilji SmartGene.si projekta

- Konstrukcija in testiranje plazmidnega vektorja za IL-12 in novih plazmidnih DNA vektorjev s terapevtskimi geni
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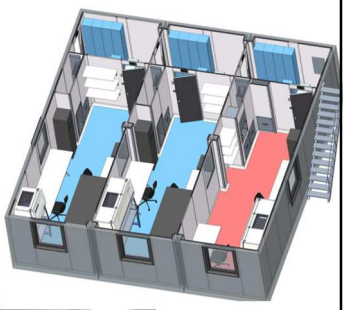
Clean visions.

„Smart“ GMP proizvodnih prostorov

Umeščena potrebna tehnološka oprema, ki je bila razporejena z ozirom na tehnološki proces skupaj s konzorcijskim partnerjem Jafral glede na predviden proizvodni proces (Cobik) in proizvodnjo kliničnega materiala (OI) ter v skladu s predvidenimi prototipnimi omejitvami prostora.

Koncept "SMART" GMP modularnih čistih prostorov



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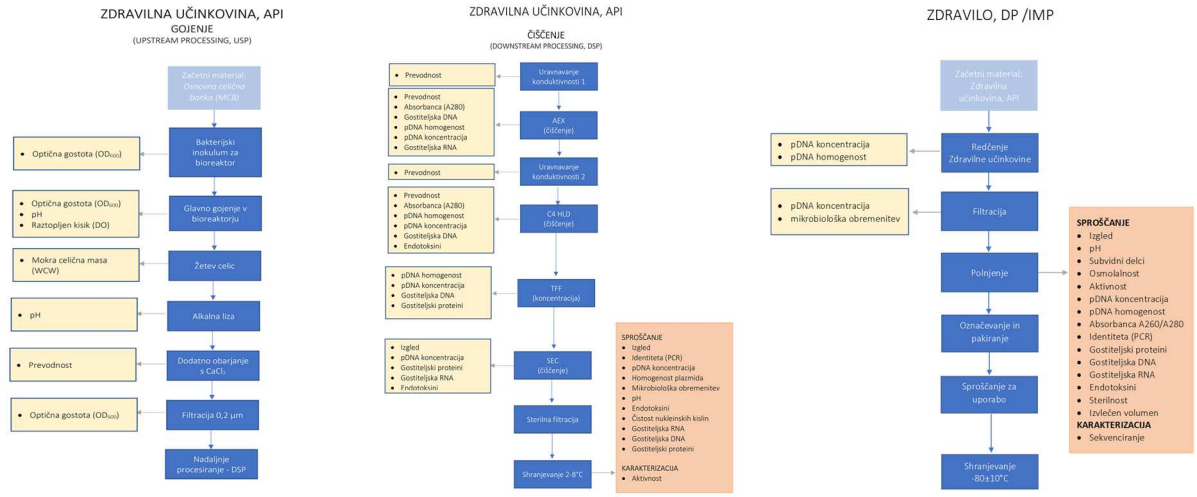
GMP proizvodnja plazmidne DNA



Shematski prikaz gojenja (USP) za pripravo zdravilne učinkovine (API).

Shematski prikaz korakov čiščenja (DSP) za pripravo zdravilne učinkovine.

Shematski prikaz priprave zdravila (DP/IMP).

CILJI SmartGene.si projekta

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Klinična študija

- Priprava protokola za fazo I.
- Tri naraščajoče doze plazmida z zapisom za IL-12 (phIL12).
- Aplikacija v monoterapiji.

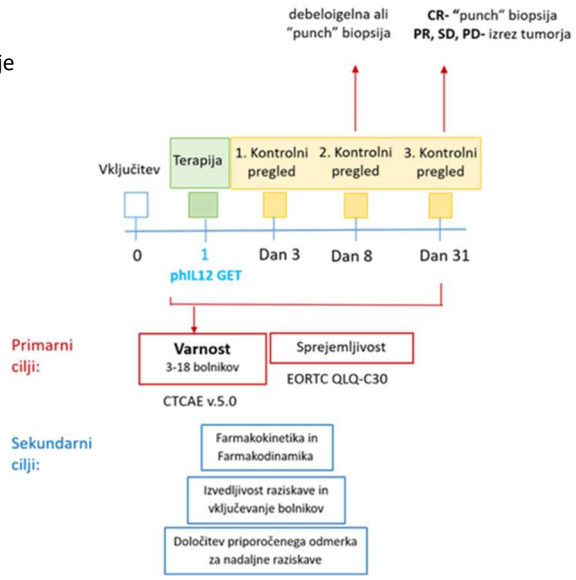
- Protokoli, pripravljeni po zahtevah Komisije Republike Slovenije za medicinsko etiko (KME) in Komisije za protokole na Onkološkem inštitutu Ljubljana (KSOPKR).
- Evropska agencija za zdravila (EMA) poda mnenje o primernosti klinične študije (EMA/CHMP/SAWP/19705/2020).
- Javna agencija Republike Slovenije za zdravila in medicinske pripomočke (JAZMP) izda dovoljenje za izvajanje klinične študije.
- Prijava študije v dve svetovni bazi kliničnih študij ClinicalTrials.gov in ISRCTN register.
- Iniciacija študije - oktober 2021.

Klinična študija

Shema postopkov klinične študije faze I; genska terapija s phIL12

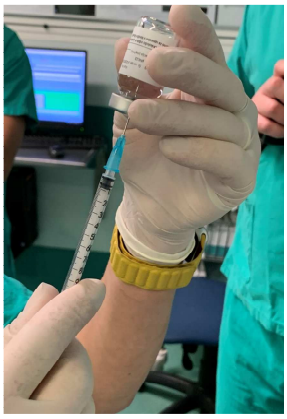
Bazalno celični karcinom (BCC) na glavi ali vratu
Enkratna terapija z GET IL-12

Cilji:
Varnost
Izvedljivost



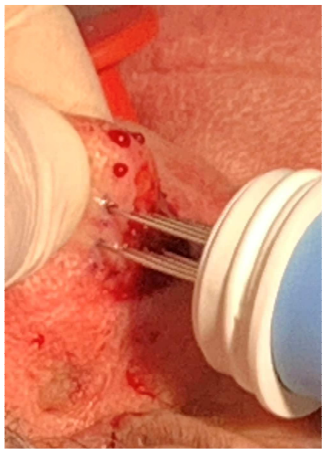
Postopek zdravljenja:
Priprava plazmida za injiciranje

- Plazmid je pripravljen po GMP postopku, ki je odobren od JAZMP
- Redčenje in priprava raztopine plazmida v brizgi za injiciranje poteka v kirurški sobi, ki je registrirana za delo z GSO



Postopek zdravljenja:
Aplikacija električnih pulzov – genski elektroprenos

Električne pulze se dovede s pomočjo vzporedno igelnih elektrod in pulze generira v IGEA generatorju
Električne pulze se dovede tolikokrat da se pokrije celoten volumen tumorja



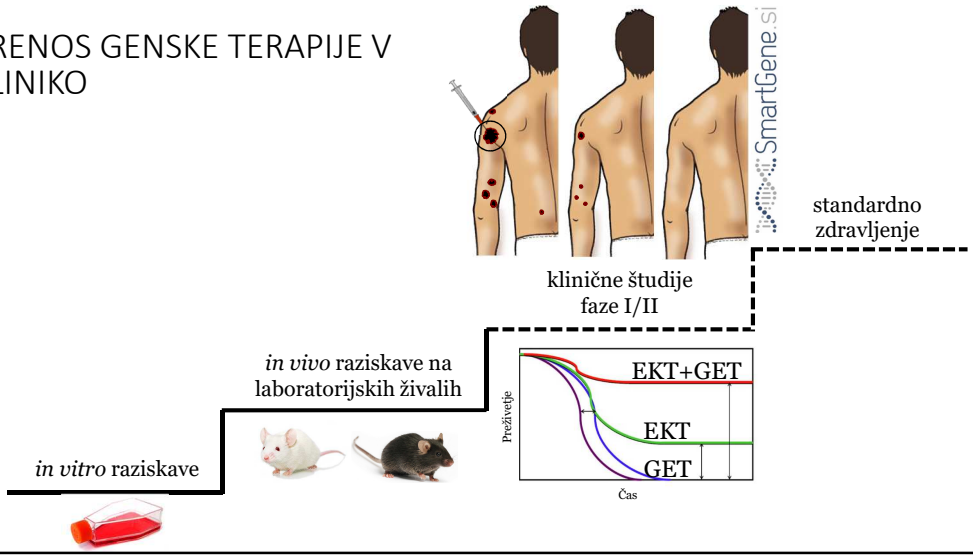
Varnost in učinkovitost

- Pri prvem pacientu nismo zabeležili stranskih učinkov do 10. dneva po terapiji
- Učinek terapije še ni viden, nastala je krasta, z nekoliko vnetim robnim tkivom

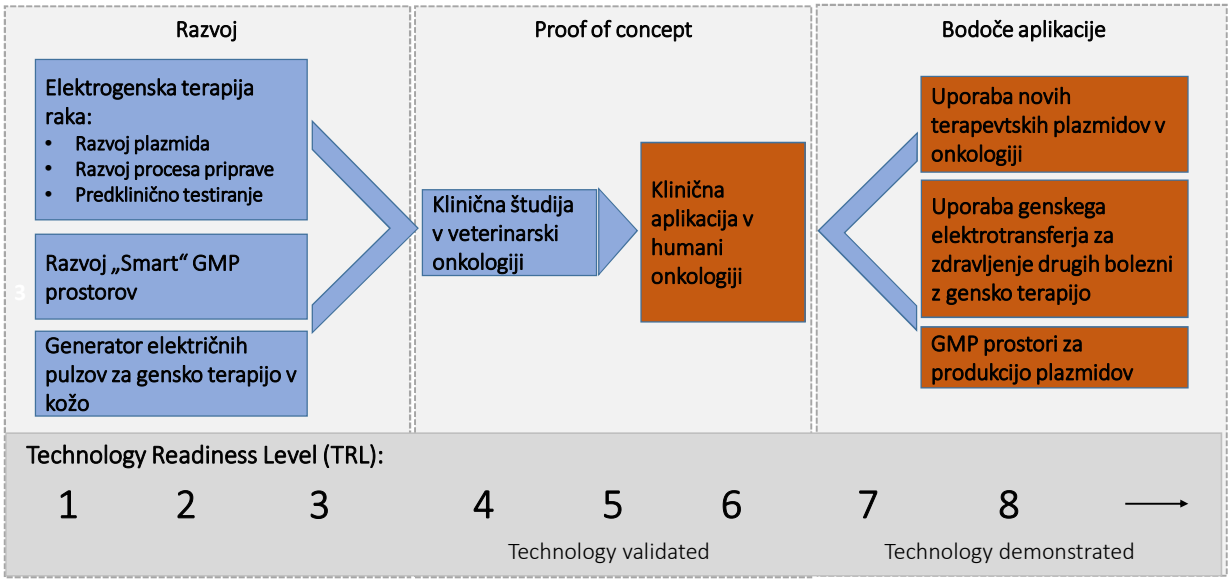
Ekipa v kirurški dvorani

NAMEN PROJEKTA – TRANSLACIJA V KLINIKO

- PRENOS GENSKE TERAPIJE V KLINIKO



KAKO OD TU NAPREJ: SmartGene.si



Uporaba v kombinirani terapiji

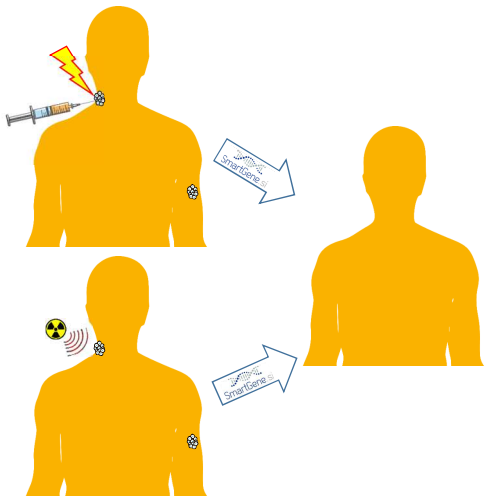
ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Kombinacija

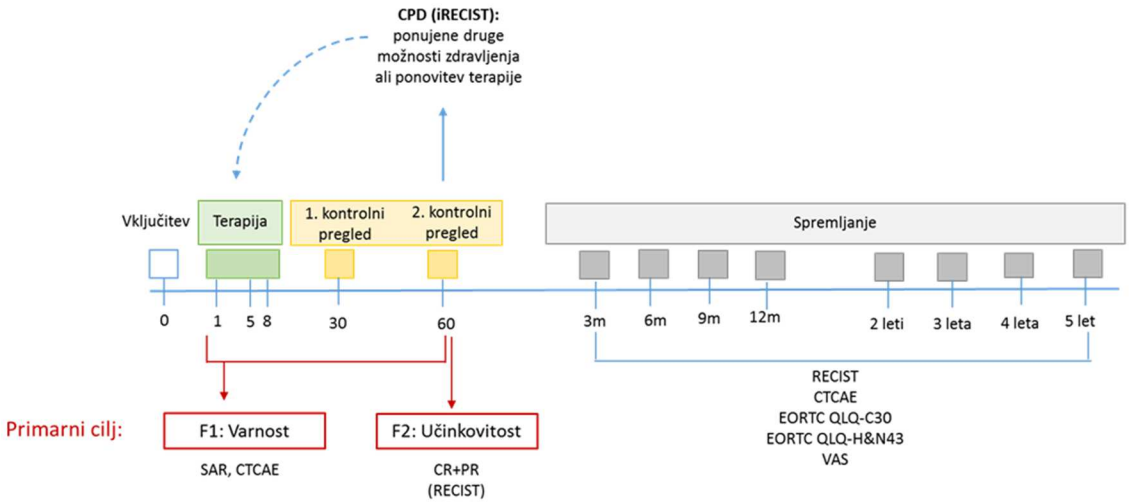
- Lokalna ablativna terapija (EKT / RT)
- GET plazmida za IL-12 intratumorsko

Cilj

- Transformirati lokalno terapijo v loko-regionalno ali sistemsko



Uporaba v kombinirani terapiji - možni klinični protokol



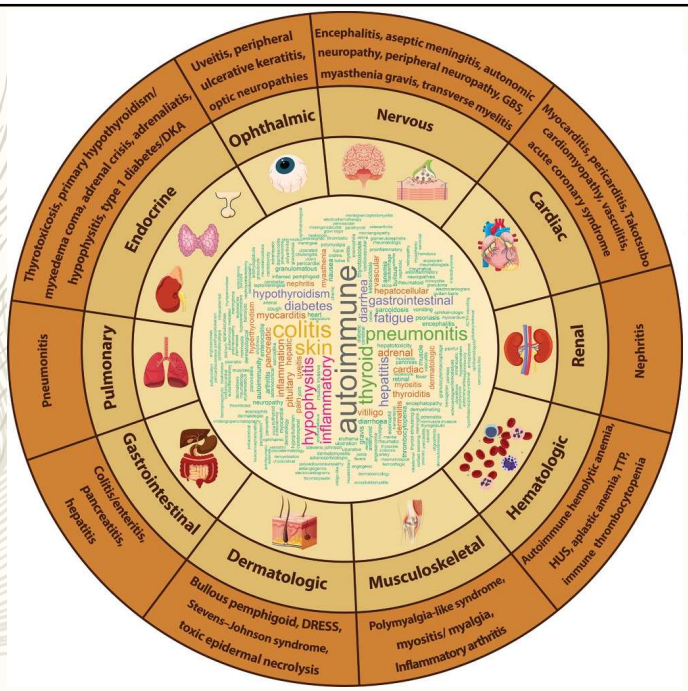
PLATFORMA ZA TRANSLACIJO GENSKE TERAPIJE
In vitro
In vivo
Veterina
Klinika
Klinična aplikacija za zdravljenje raka in drugih bolezni.
Klinična aplikacija za vakcinacije

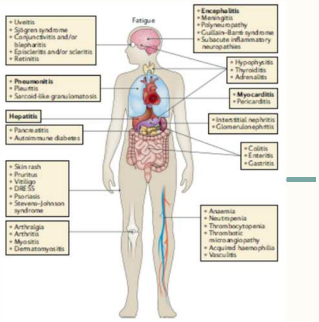
Imunsko pogojeni neželeni učinki

Doc. Dr. Tanja Mesti, dr. med.

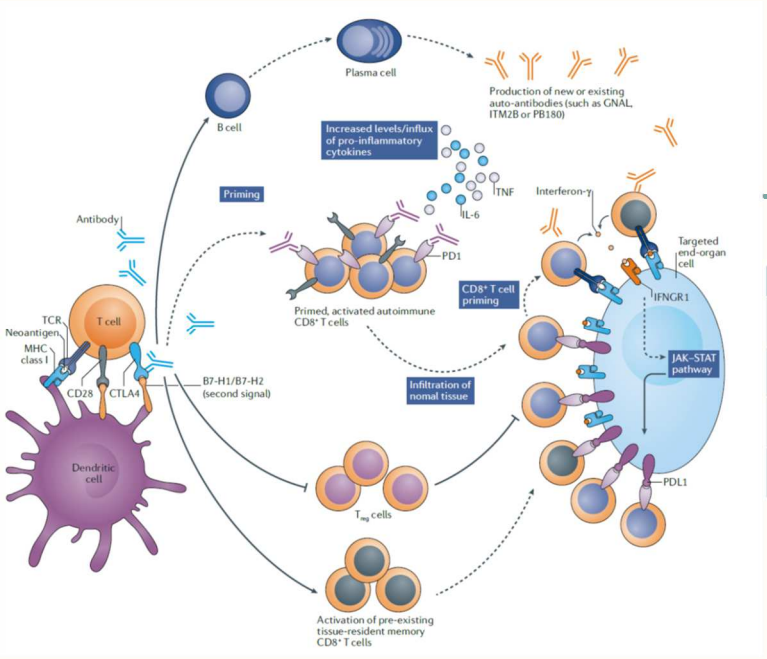
Novosti v Imunoterapiji pri solidnih rakih leta 2021

16.12.2021





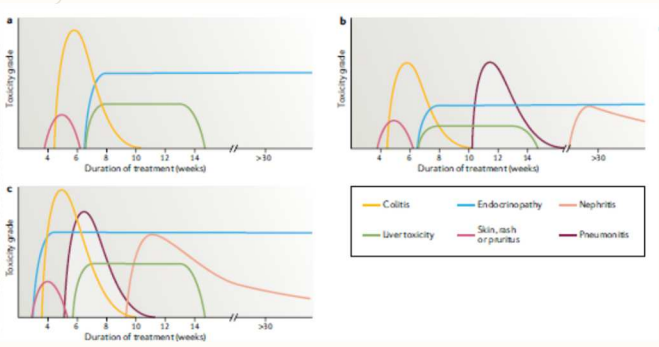
Mehanizem irAE



Mechanism	On/off target
Expansion of existing autoantibodies by B cells	On target
Disinhibition of T cells that destroy normal tissue	On target
Secretion of high levels of cytokines by T cells	On target
Binding of ICI antibodies to tissue and complement fixation	Off target

https://doi.org/10.1038/s41573-021-00259-5

Kinetika toksičnosti



a) CTLA4 inh; b) PD1/PDL1 inh; c) PD1 + CTLA4 inh

Frekvenca

Table 1 | Frequencies of treatment-related irAEs in selected cohorts

Study details		Any-grade adverse events (grade ≥3 adverse events)							
Study	Dose (n)	Diarrhoea	Colitis	Pulmonary	Rash	Neurological	Endocrinopathy	Hepatic	Renal
Ipilimumab									
EORTC 18071 (REF.[17])	10 mg/kg, 3-weekly (471)	41.2% (9.8%)	15.5% (8.2%)	–	34.2% (1.1%)	4.5% (1.9%)	37.8% (2.8%)	24.4% (10.9%)	–
Hodi et al.[146]	3 mg/kg, 3-weekly (131)	27.5% (4.6%)	7.6% (5.3%)	–	19.1% (0.8%)	–	7.6% (3.8%)	3.8% (0%)	–
Nivolumab									
CheckMate 066 (REF.[21])	3 mg/kg, 2-weekly (206)	16% (1%)	1% (0.5%)	1.5% (0%)	15% (0.5%)	–	7.3% (1%)	3.4% (1.5%)	1.9% (0.5%)
CheckMate 057 (REF.[147])	3 mg/kg, 2-weekly (287)	8% (1%)	1% (0.3%)	4.9% (1.4%)	9% (3.5%)	0.3% (0.3%)[a]	10.5% (0%)	10.8% (1.4%)	2% (0%)
Pembrolizumab									
KEYNOTE-010 (REF.[148])	2 mg/kg, 3-weekly (339)	7% (1%)	1% (1%)	5% (2%)	9% (0.3%)	–	15% (1%)	0.3% (0.3%)	–
KEYNOTE-010 (REF.[148])	10 mg/kg, 3-weekly (343)	6% (0%)	1% (0.3%)	4% (2%)	13% (0.3%)	–	16.5% (2%)	1% (0%)	–
KEYNOTE-054 (REF.[149])	200 mg, 3-weekly (509)	19.1% (0.8%)	3.7% (2%)	4.7%[b] (0.8%)	16.1% (0.2%)	–	23.4% (1.8%)	1.8% (1.4%)	0.4% (0.4%)
Ipilimumab plus nivolumab									
CheckMate 067 (REF.[150])	3 mg/kg ipilimumab plus 1 mg/kg nivolumab, 3-weekly (313)	45% (9%)	13% (8%)	7% (1%)	30% (3%)	–	34% (6%)	33% (20%)	7% (2%)
CheckMate 214 (REF.[7])	1 mg/kg ipilimumab plus 3 mg/kg nivolumab, 3-weekly (547)	27% (4%)	–	–	22% (1%)	–	16% (0.4%)[c]	–	–
CheckMate 227 (REF.[151])	1 mg/kg 6-weekly ipilimumab plus 3 mg/kg 2-weekly nivolumab (576)	16.3% (1.6%)	1% (0.5%)	3% (2%)	16.7% (1.6%)	–	12.3% (1%)[c]	3.5% (3%)	–
Avelumab									
JAVELIN Solid Tumour[148]	10 mg/kg, 2-weekly (184)	7% (0%)	–	1% (1%)	–	1% (1%)[d]	7% (0%)	1.6% (1.1%)[e]	–
JAVELIN Merkel 200 (REF.[152])	10 mg/kg, 2-weekly (88)	10% (0%)	–	1% (0%)	13% (0%)	–	7% (0%)	6.8% (2%)[e]	1% (0%)
Atezolizumab									
OAK[153]	1,200 mg, 3-weekly (609)	15.4% (0.7%)	0.3% (0%)	1% (0.7%)	–	–	–	0.3% (0.3%)	–
Durvalumab									
ATLANTIC[130]	10 mg/kg, 2-weekly (444)	0.7% (0.2%)[f]	0.4% (0%)[f]	2% (0.7%)[f]	0.7% (0.2%)[f]	–	10.1% (0.5%)[f]	0.7% (0.7%)[f]	–

irAE, immune-related adverse event. [a]Encephalitis. [b]Sarcoidosis in 1.4%. [c]All hypothyroidism. [d]Monoplegia. [e]Transaminase increase (treatment related or unrelated). [f]Adverse events of special interest that required the use of systemic steroids, other immunosuppressants or endocrine therapy, and with no clear other cause; therefore, the percentages reported here probably do not reflect the true rate of irAEs of any grade because any irAEs events that were not managed with such treatments, for example, would have been excluded.

Martins, F., Sofiya, L., Sykiotis, G.P. *et al*. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* **16,** 563–580 (2019). https://doi.org/10.1038/s41571-019-0218-0

Smrtnost

Study details		Treatment-related deaths	
Study	Dose (n)	Deaths (%)	Causes of death
Ipilimumab			
EORTC 18071 (REF.[17])	10 mg/kg, 3-weekly (471)	5 (1.1)	Colitis in three patients, myocarditis in one patient and multiple organ failure associated with Guillain–Barré syndrome in one patient
Hodi et al.[146]	3 mg/kg, 3-weekly (131)	2 (1.4)	Colitis in one patient and liver failure in one patient
Nivolumab			
CheckMate 066 (REF.[21])	3 mg/kg, 2-weekly (206)	0	–
CheckMate 057 (REF.[147])	3 mg/kg, 2-weekly (287)	1 (0.5)	Encephalitis
Pembrolizumab			
KEYNOTE-010 (REF.[148])	2 mg/kg, 3-weekly (339)	3 (0.9)	Pneumonitis in two patients and pneumonia in one patient
KEYNOTE-010 (REF.[148])	10 mg/kg, 3-weekly (343)	3 (0.9)	Myocardial infarction in one patient, pneumonia in one patient and pneumonitis in one patient
KEYNOTE-054 (REF.[149])	200 mg, 3-weekly (509)	1 (0.2)	Myositis
Ipilimumab plus nivolumab			
CheckMate 067 (REF.[150])	3 mg/kg ipilimumab plus 1 mg/kg nivolumab, 3-weekly (313)	2 (0.6)	Liver failure in one patient and myocarditis in one patient
CheckMate 214 (REF.[7])	1 mg/kg ipilimumab plus 3 mg/kg nivolumab, 3-weekly (547)	8 (1.5)	Aplastic anaemia, haemophagocytic lymphohistiocytosis, lower gastrointestinal haemorrhage, liver failure, lung infection, pneumonia, pneumonitis and unexplained sudden death each in one patient
CheckMate 227 (REF.[151])	1 mg/kg 6-weekly ipilimumab plus 3 mg/kg 2-weekly nivolumab (576)	7 (1.2)	Pneumonitis in three patients and acute tubular necrosis, cardiac tamponade, circulatory collapse and myocarditis each in one patient
Avelumab			
JAVELIN solid tumour[148]	10 mg/kg, 2-weekly (184)	0	–
JAVELIN Merkel 200 (REF.[152])	10 mg/kg, 2-weekly (88)	0	–
Atezolizumab			
OAK[153]	1,200 mg, 3-weekly (609)	0	–
Durvalumab			
ATLANTIC[130]	10 mg/kg, 2-weekly (444)	0	–

Pristop in zdravljenje

- Izključiti drugo etiologijo
- Gradus
- Lokacija
- ESMO in NCCN smernice

CLINICAL PRACTICE GUIDELINES

An ESMO Product

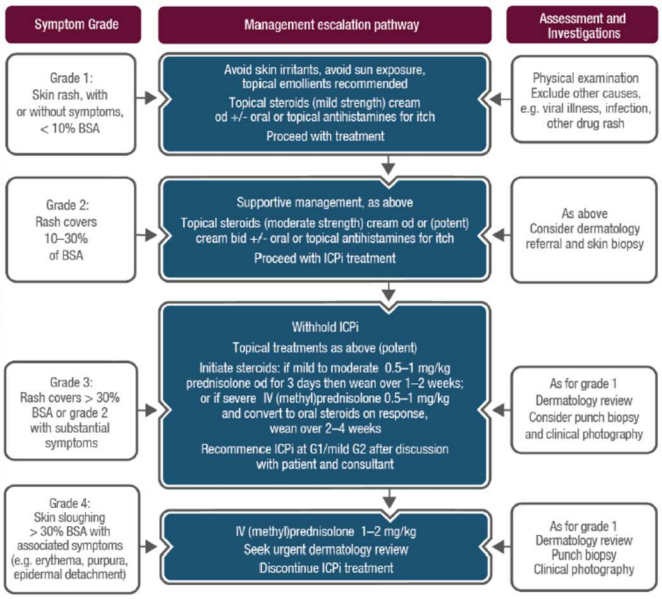
Management of toxicities from immunotherapy

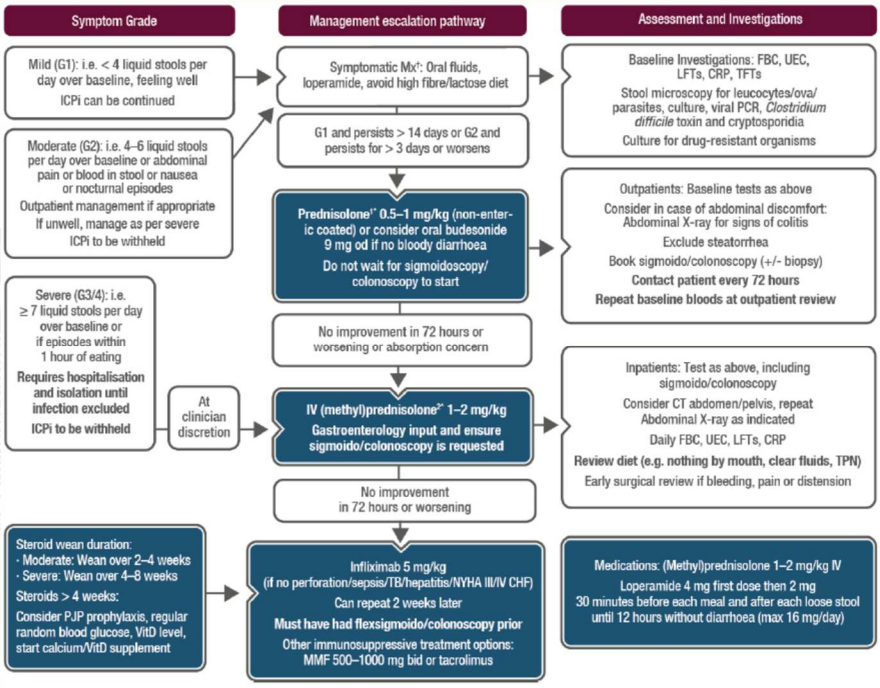
ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan, on behalf of the ESMO Guidelines Committee

*For details of author affiliations, correspondence and versions, please see the full version at esmo.org/Guidelines/Supportive-and-Palliative-Care

ESMO





Summary of recommendations	
Time frame	A range of neurological events have been described with a time of onset from 6 to 13 weeks
Assessment	Progression of the underlying cancer, seizure activity, infection and metabolic derangement should be ruled out as causes and nerve conduction studies and lumbar puncture may assist in diagnosis
Management	• Early consultation with a neurologist is advised • For all but mild (grade 1) neurological symptoms, ICPi therapy should be withheld until the cause is determined • Prednisolone 0.5–1 mg/kg should be considered for moderate symptoms • High-dose oral prednisolone 1–2 mg/kg or IV equivalent is recommended for significant neurological toxicity • Plasmapheresis or IVIg may be required for the treatment of myasthenia and GBS

Guillain-Barréjev sindrom

ZDRAVLJENJE

- Grade ≥2–3 colitis indicates a need to withhold ICIs and start steroid therapy immediately. Infliximab should be considered in the absence of symptomatic improvements within 2–5 days. Delayed endoscopic examination is correlated with an increased risk of treatment-refractoriness[10].
- Hospitalization should be considered in patients with grade ≥3 irAEs and tailored regarding comorbidities, frailty status and kinetics of evolution in patients with lower-grade irAEs.
- Tapering of steroids should be considered after 48 hours of consistent symptom improvement and extended over 4–6 weeks to avoid flare phenomena related to the long half-life of ICIs.

Neželeni učinek	Izrazitost	Prilagoditev zdravljenja
Imunsko pogojen	Blaga	Simptomatsko zdravljenje
	Zmerna	Zadržati zdravljenje z zaviralci nadzornih točk in predpisati kortikosteroid v odmerku 1 mg/kg/dan – po potrebi odmerek zviševati.
	Huda	Zadržati zaviralec nadzornih točk, kortikosteroid i.v. (2mg/kg/d po potrebi zviševati). Lahko tudi imunosupresivna terapija, če se simptomi ne uredijo v 5-7 dnevih.
	Ponavljajoči se neželeni učinki 3 ali 4 stopnje	Trajna ukinitev zdravljenja.

Korelacija irAE z učinkom ICI

Characteristics		irAE cohort n (%)	NirAE cohort n (%)
Number		38 (38)	61 (62)
Age mean		67.4	61.6
Sex	Male	18 (47.4)	37 (60.7)
	Female	20 (52.6)	24 (39.3)
Treatment	Naive	34 (89.5)	51 (83.6)
	Previously treated	4 (10.5)	10 (16.4)
Immunotherapy	Pembrolizumab	34 (89.5)	52 (85.2)
	Nivolumab	2 (5.3)	5 (8.2)
	Nivolumab + ipilimumab	2 (5.3)	4 (6.6)
BRAF status	BRAF mutated	10 (26.3)	17 (27.9)
	BRAF wild type	21 (55.3)	27 (44.3)
	Not reported	7 (18.4)	17 (27.9)
M1a/b	Cohort a and b	22 (57.9)	35 (57.4)
M1c/d	Cohort c and d	16 (42.1)	26 (42.6)
LDH	increased	7 (18.4)	15 (24.6)
LDH	normal	31 (81.6)	46 (75.4)

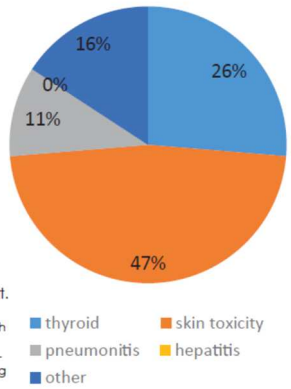


FIGURE 1. Distribution of immune-related adverse events by type in the irAE cohort.

irAE cohort = patients with metastatic melanoma who developed immune-related side effects during immunotherapy

Radiol Oncol 2021; 55(3): 354-361.

Korelacija irAE z učinkom ICI

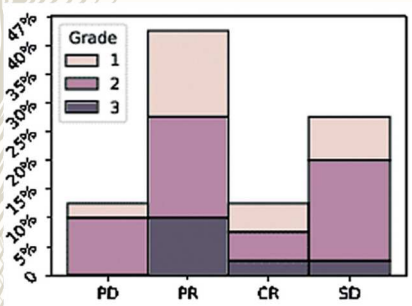


FIGURE 4. Correlation between the treatment response and the grade (1-3) of the immune-related side effect adverse events in the irAE cohort presented as a percentage (%).

CR = complete response; PD = partial response; PR = progression of disease; SD = stable disease

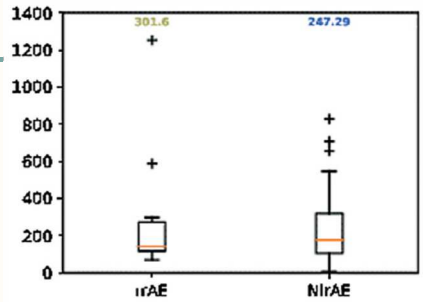


FIGURE 6. Progression-free survival difference in patients with metastatic melanoma between the two cohorts, cohort with immune-related adverse events (irAEs) and cohort with no immune-related adverse events (NirAEs), presented in days. The orange line indicates the median, while the patients who belong to the fourth quartile are represented with plus signs ("+").

Korelacija irAE z učinkom ICI

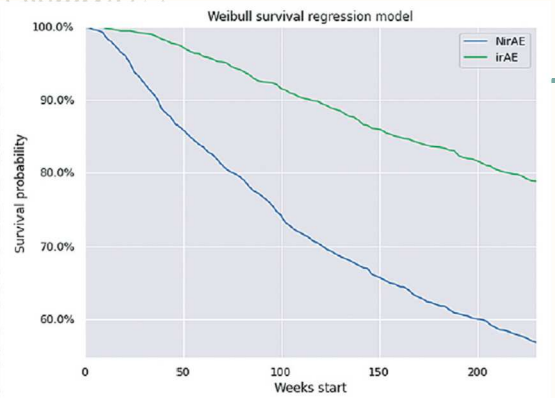


FIGURE 7. Difference in progression-free survival between the irAE and NirAE cohorts, with a significant increase in the survival probability from less than 60% for the NirAE cohort to almost 80% for the irAE cohort.

irAE cohort = patients with metastatic melanoma who developed immune-related adverse events during immunotherapy; NirAE cohort = patients with metastatic melanoma who did not develop immune-related adverse events during immunotherapy

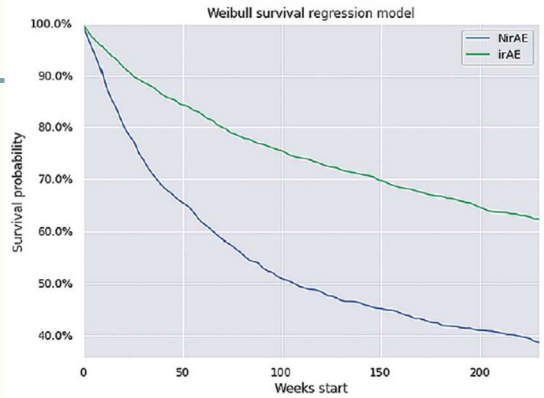


FIGURE 8. Difference in progression-free survival between the irAE and NirAE cohorts with increased LDH, with a significant increase in the survival probability from less than 40% for the NirAE cohort to more than 60% for the irAE cohort.

irAE cohor = patients with metastatic melanoma who developed immune-related adverse events during immunotherapy; NirAE cohort = patients with metastatic melanoma who did not develop immune-related adverse events during immunotherapy

S. Hussaini et al.

Korelacija irAE z učinkom ICI

- 51 študija
- 15 – 1019 bolnikov
- 46.5% irAE, G3/4 ↑ORR/↓OS
  - ❑ Melanom
  - ❑ NSCLC
  - ❑ Rak ledvic
  - ❑ Rak glave in vratu
  - ❑ GIT (MSJ-H mCRC, GEJ in želodec)

↑PFS in OS

Cancer Treatment Reviews 92 (2021) 102134

https://doi.org/10.1016/j.ctrv.2020.102134

S. Hussaini et al.

Korelacija irAE z učinkom ICI

- ❑ MELANOM (nivo, pembro, nivo/ipi)
- ORR 37.67% vs 23.44%
- PFS (3 študije, n 143), 17.61 vs 2.23 mes.
- OS (7 študij, n 1474), 15.24 vs 8.94 mes.
- Driska in izpuščaj
- ❑ NSCLC (nivo, pembro, atezo)
- ORR (9 študij, n 1817), 41.49% vs 18.01%
- PFS (9 študije, n 2117), 8.97 vs 3.06 mes.
- OS (8 študij, n 1347), 19.07 vs 7.45 mes.

Cancer Treatment Reviews 92 (2021) 102134

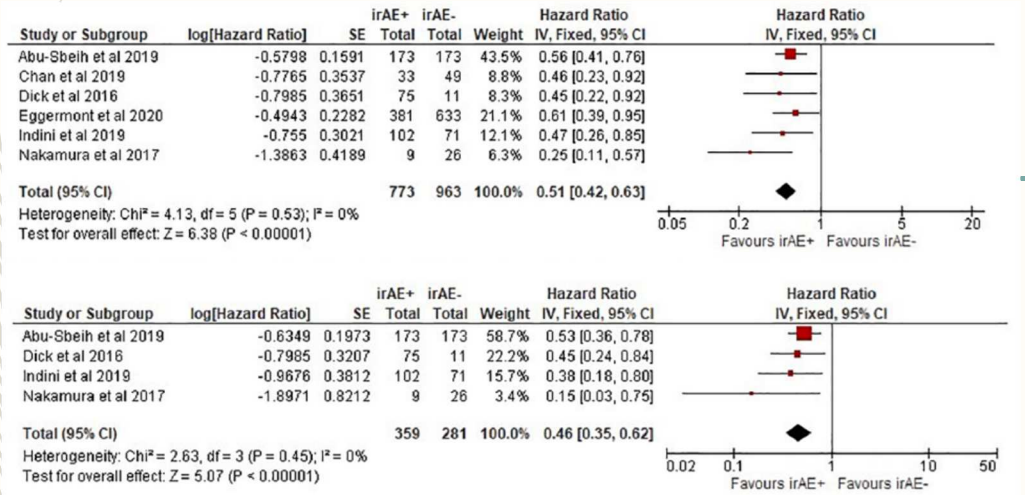


Fig. 1. Forest plots for (a) progression free survival (PFS) in advanced melanoma patients that developed irAEs versus patients that did not, (b) overall survival (OS) in advanced melanoma patients that developed irAEs versus patients that did not, (c) progression free survival (PFS) in advanced NSCLC patients that developed irAEs versus patients that did not, (d) overall survival (OS) in advanced NSCLC patients that developed irAEs versus patients that did not.

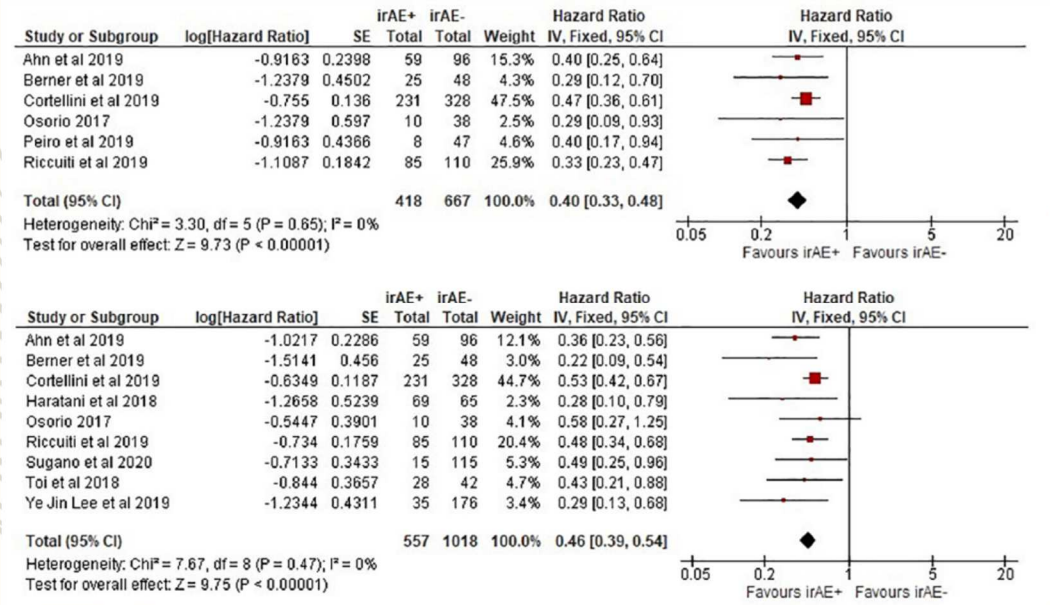


Fig. 1. Forest plots for (a) progression free survival (PFS) in advanced melanoma patients that developed irAEs versus patients that did not, (b) overall survival (OS) in advanced melanoma patients that developed irAEs versus patients that did not, (c) progression free survival (PFS) in advanced NSCLC patients that developed irAEs versus patients that did not, (d) overall survival (OS) in advanced NSCLC patients that developed irAEs versus patients that did not.

NOVOSTI v IMUNOTERAPIJI pri SOLIDNIH RAKIH LETA 2021

Prekinitev zdravljenja in re-indukcija imuno-terapije

asist. dr. Rok Devjak, dr. med.

16.12.2021

Smernice za obravnavo irAE

- American Society for Clinical Oncology (ASCO),
- European Society for Medical Oncology (ESMO),
- National Comprehensive Cancer Network (NCCN),
- Society for Immunotherapy of Cancer (SITC)

Terminologija

- CTCAE v5

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE.

Stopnja dokazov priporočil

Table 1 Summary of 'The Oxford Levels of Evidence 2' (Adapted from OCEBM Levels of Evidence Working Group)

Level 1	Level 2	Level 3	Level 4	Level 5
Systematic review or meta-analysis	Randomized trial or observational study with dramatic effect	Non-randomized, controlled cohort, or, follow-up study	Case series, case-control, or, historically controlled study	Mechanism-based reasoning

OCEBM, Oxford Centre for Evidence-Based Medicine.

Vzročnost neželenega učinka (AE)

- Ključna za ustrezno ukrepanje
- Izziv v realnem življenju
  - Polifarmacija/polimorbidnost bolnikov
  - Sheme onkoloških zdravljenj so kompleksne: ICI kombinacije
- Vidik planiranja nadaljevanja sistemskega zdravljenja

Neželeni učinek

- AE – katerikoli neželeni učinek (tudi nepovezan) z zdravljenjem
- TRAE – neželeni učinek povezan z zdravljenjem (ICI + druga zdravila)
- irAE – katerikoli neželeni učinek, ki je verjetno imunološkega izvora in je nastal med ali po zdravljenji z ICI

Pojavnost irAE

- antiPD-(L)1 inhibitorji so razvili irAEs v 74% (14% grade ≥3),
- anti-CTLA-4 inhibitorjiso razvili irAE v 89% (34% grade ≥3),
- Kombinacija ICIs so razvili irAE v 90% (55% grade ≥3).4

Int J Cancer. 2019 Aug 1;145(3):639-648. doi: 10.1002/ijc.32132. Epub 2019 Feb 4.

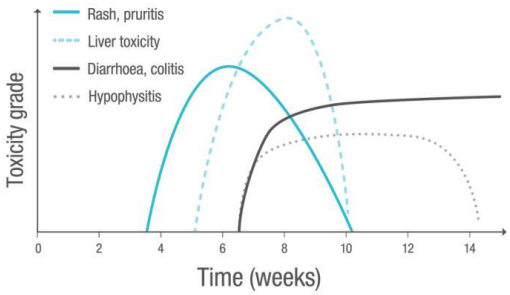
A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors

Patrick Arnaud-Coffin [1 2 3], Denis Maillet [1 2], Hui K Gan [4 5 6], Jean-Jacques Stelmes [7], Benoit You [1 2 3], Stephane Dalle [2 3 8], Julien Péron [1 2 3 9 10]

Nastanek – časovni okvir

Incidence and epidemiology

Time to onset and resolution of occurrence of immuno-related adverse events following Ipilimumab treatment



Weber JS et al. J Clin Oncol 2012;30:2691–2697. Reprinted with permission. ©2012 American Society of Clinical Oncology. All rights reserved.

Nastanek – časovni okvir

- irAE lahko nastanejo relativno kmalu po pričetku zdravljenja z ICI in tudi po zaključki 6-12 mesecev po prenehanju
- Trajanje: izredno variabilno, nekateri celo doživljensko (tip 1 diabetes, motnje v delovanju ščitnice)

Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691–7.
Davies M, Duffield EA. Duffield EA: safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. *Immunotargets Ther* 2017;6:51–71.
Couey MA, Bell RB, Patel AA, *et al*. Delayed immune-related events (dire) after discontinuation of immunotherapy: diagnostic hazard of autoimmunity at a distance. *Journal for ImmunoTherapy of Cancer* 2019;7:165.

irAE – osnovni principi oskrbe

- Tipično gre za kombinacijo ukrepov:
  - Prekinitev (začasna ali trajna glede stopnjo in vrsto irAE) zdravljenja z ICI
  - Uporaba imunosupresivnih zdravil (tipično kortikosteroidov in/ali drugih imunosupresivnih zdravil)
  - Reindukcija ICI?
- Zmanjševanje odmerka ICI po priporočilih nima vloge pri oskrbi irAE

irAE – osnovni principi oskrbe

- **Gradus 1:** v kolikor ni drugače priporočeno je potrebno tovrstne irAE slediti za eventuelno poslabšanje simptomov, zdravljenj z ICI se lahko nadaljuje

irAE – osnovni principi oskrbe

- **Gradus 2:** v kolikor ni drugače priporočeno je potrebno pri bolnikih irAE gradusa 2 zdravljenje z ICI začasno prekiniti in zdraviti s kortikosteroidi glede na vrsto neželenega učinka

irAE – osnovni principi oskrbe

- **Gradus 3:**
  - glede na specifična navodila pri posameznem irAE,
  - konzultacija ustreznega subspecialista,
  - za večino irAE je zdravljenje hospitalno
  - Načeloma trajna prekinitev zdravljenja z ICI

Re-challenge

- Ko irAE ustrezno izzvenijo (Gradus 1 ali manj ob prednisone ≤10 mg ekvivalentu dnevno) je možen re-challenge.
- Faktorji, ki na to vplivajo so kompleksni

Re-challenge – študija 1

- 93 bolnikov po gradus 2-4 irAE
- Različne lokalizacije
- Isti ali drug ICI
- 55% jih je utrpelo ponoven neželen učinek

Original Investigation FREE

June 6, 2019

Evaluation of Readministration of Immune Checkpoint Inhibitors After Immune-Related Adverse Events in Patients With Cancer

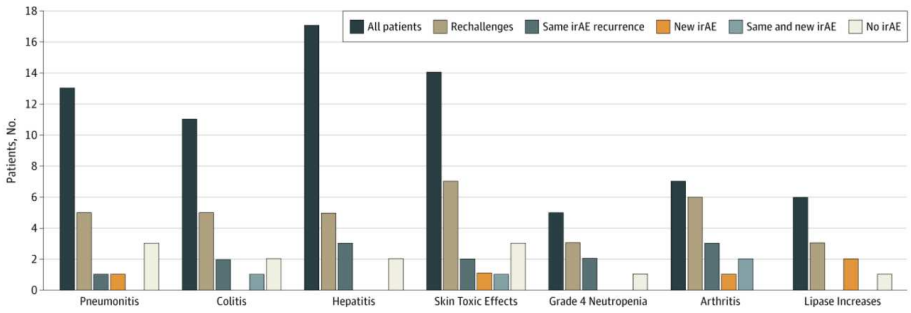
Audrey Simonaggio, MD[1]; Jean Marie Michot, MD[1,2]; Anne Laure Voisin, MD[3]; et al

Author Affiliations | Article Information

JAMA Oncol. 2019;5(9):1310-1317. doi:10.1001/jamaoncol.2019.1022

Re-challenge – študija 1

- Bolniki so razvili enak irAE ali drug
- Noben od irAE ob re-challenge ni bil višjega gradusa kot ob prvem pojavu.



Re-challenge – študija 2

- 482 bolnikkov z metastatskim NSCLC
- 68 (14%) bolnikov imelo irAE gradusa 2 ali več, 38 bolnikov je bilo ponovno zdravljenih
- Od teh jih je 52% jih je ponovno razvilo irAE: 26% enakega in 26% drugega
- Večina je bila blagih ir AE
- **2 z zdravljenjem povezani**

Smrti v rechallenge skupini.

Cancer Immunol Res. 2018 Sep;6(9):1093-1099. doi: 10.1158/2326-6066.CIR-17-0755. Epub 2018 Jul 10.

Safety and Efficacy of Re-treating with Immunotherapy after Immune-Related Adverse Events in Patients with NSCLC

Fernando C Santini [1 2], Hira Rizvi [3], Andrew J Plodkowski [4], Andy Ni [5], Mario E Lacouture [6], Maya Gambarin-Gelwan [7], Olivia Wilkins [1], Elizabeth Panora [8], Darragh F Halpenny [4], Niamh M Long [4], Mark G Kris [1 9], Charles M Rudin [1 3 9], Jamie E Chaft [1 9], Matthew D Hellmann [10 9 11]

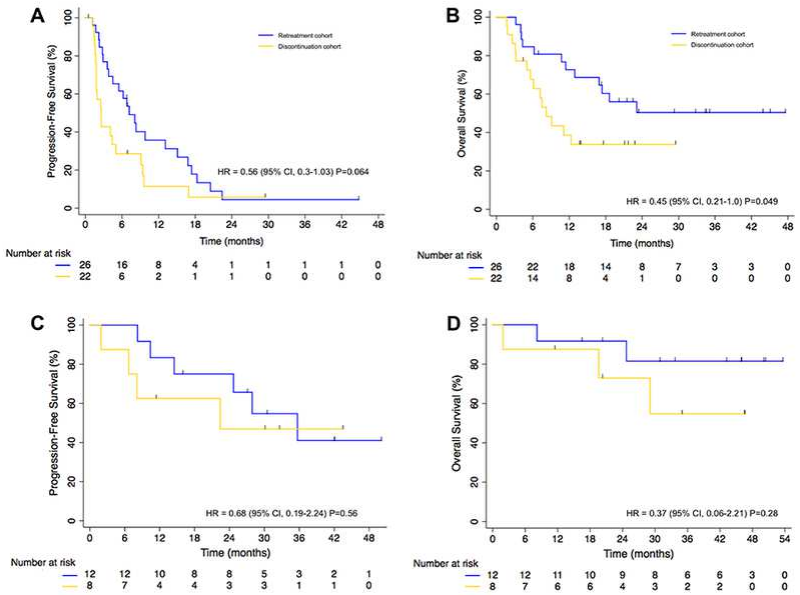
Affiliations + expand

PMID: 29991499 PMCID: PMC6125223 DOI: 10.1158/2326-6066.CIR-17-0755

Free PMC article

Re-challenge – študija 2

- Vpliv na OS in PFS?
  - Bolniki brez objektivnega odgovora pred irAE
  - Bolniki z obejktivni odgovorom pred irAE



Zaključki

- The decision to re-challenge patients with ICIs may be complex. Factors that may cause clinicians to lean away from re-challenge include severe or lifethreatening irAEs, requirement for prolonged or multiple immunosuppressants, and a history of longterm ICI therapy and/or patients with complete responses or prolonged clinical benefit.

PSEUDO-PROGRES: TERAPEVTSKA ZAGATA V IMUNO-TERAPIJI

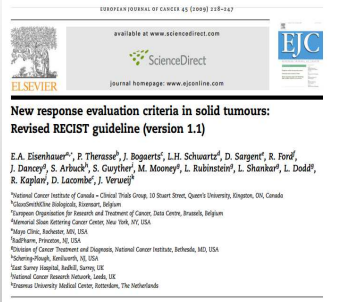
NINA BOC, DR. MED.

RADIOLOŠKI KRITERIJI ZA OCENJEVANJE UČINKA TERAPIJE

- Osnovni
  - RECIST 1.0 in 1.1 (Response Evaluation Criteria in Solid Tumors 2000/2009)
  - WHO 1979
  - Volumetric
- Funkcionalni kriteriji v radiologiji
  - EORTC - F^{18} FDG PET/CT
  - PERCIST 2009
- Specifični kriteriji
  - CHOI, CHESON (RECIL 2017 - **New** response evaluation criteria in lymphoma), MASS, CHUN, RANO

RECIST 1.1 - 2009

- **R**esponse **E**valuation **C**riteria **I**n **S**olid **T**umors
- Standardizirana ocena učinka terapije za solidne tumorje
- RECIST je kombinacija kvalitativne in kvantitativne ocene
- Temelji na konceptu tarčnih in netarčnih lezij
  - Tarčne lezije so kvantitativna ocena
  - Netarčne lezije so kvalitativna ocena


EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

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ELSEVIER

EJC

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer[a,*], P. Therasse[b], J. Bogaerts[c], L.H. Schwartz[d], D. Sargent[e], R. Ford[f], J. Dancey[g], S. Arbuck[h], S. Gwyther[i], M. Mooney[g], L. Rubinstein[j], L. Shankar[k], L. Dodd[l], R. Kaplan[i], D. Lacombe[c], J. Verweij[m]

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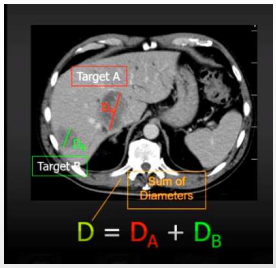
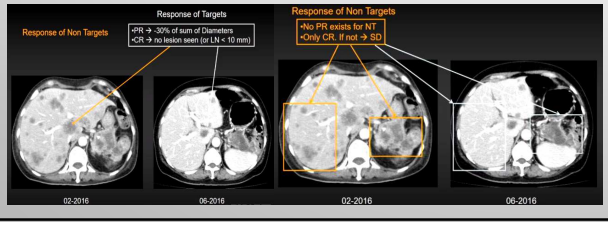
[h]Schering-Plough, Kenilworth, NJ, USA
[i]East Surrey Hospital, Redhill, Surrey, UK
[j]National Cancer Research Network, Leeds, UK
[k]Erasmus University Medical Center, Rotterdam, The Netherlands

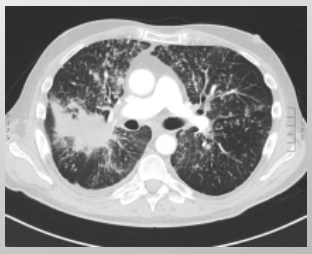
Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Guidelines (version 1.1)

OSNOVNA OCENA PREISKAV

- BASELINE – Osnova za primerjavo
  - Tarče – vsota najdaljših premerov
  - Opis netarčnih lezij in ostalih sprememb
- EVALUACIJA
  - Tarče – vsota najdaljših premerov in primerjava s prvo preiskavo pred zdravljenjem ali NADIR
  - Netarčne lezije
  - Ocena ev. novo nastalih sprememb







RECIST KLASIFIKACIJA LEZIJ

- TARČNE LEZIJE
  - Merljive lezije ≥10 mm (spiralni CT kolimacija 5 mm)
  - 5 lezij, max. 2 na organ
  - Bezgavke >15 mm
- NETARČNE LEZIJE
  - Nemerljive lezije in ostale (sledimo kvalitativno)
  - Lezije <20 mm na rtg pc, lezije <10 mm na CT
  - LN 10-14 mm
  - Lezije v skeletu
  - Predhodno obsevane lezije
  - Ascites, plevralni izliv, cistične lezije, vnetni karcinom dojke, karcinoza mening
- NOVE LEZIJE

Target Lesions	Non- Target Lesions and New Lesions
• Recommended ➢ CT (preferred) ➢ MRI • Accepted ➢ Clinical Examination ➢ Chest X Ray ➢ Mammogram ➢ Ultrasound	• Recommended ➢ CT (preferred) ➢ MRI • Accepted ➢ Clinical Examination ➢ X Ray ➢ Ultrasound ➢ Endoscopy

- Za oceno učinka terapije – enaka preiskava kot predhodna
- Scintigrafija skeleta, PET, angiografija, tumorski markerji, citologija/histologija niso del RECIST

TARČNE LEZIJE

- IZBIRA TARČNIH LEZIJ:

Morajo biti jasno MERLJIVE

DEFINICIJA MERLJIVIH LEZIJ
- Velikost - Spiralni CT
  - If slice collimation <5mm, minimum lesion size is **10 mm**
  - If slice collimation >5mm, minimum lesion size is 2 x collimation
    ex. Slice collimation = 7mm, minimum lesion size = 14mm
  - Lezije >20 mm na rtg pc

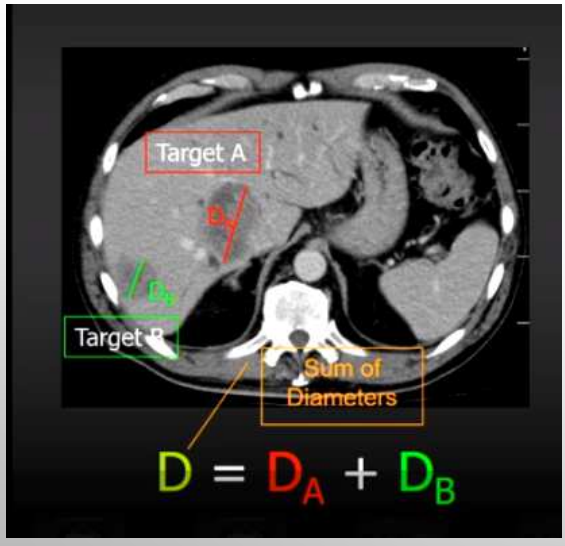
Morajo biti jasne METASTAZE

DEFINICIJA JASNIH METASTAZ
- Izberemo dobro omejene
- Vedno daljši premer
- Vedno v isti fazi slikanja ali na isti sekvenci na MRI
- Vedno samo lezije za katere smo prepričani, da so metastaze
- Izogibamo se lezijam, ki so mobilne (v mezenteriju)

Moramo izbirati glede na DISTRIBUCIJO

DISTRIBUCIJA
- Največ 5 lezij
- Največ 2 na organ

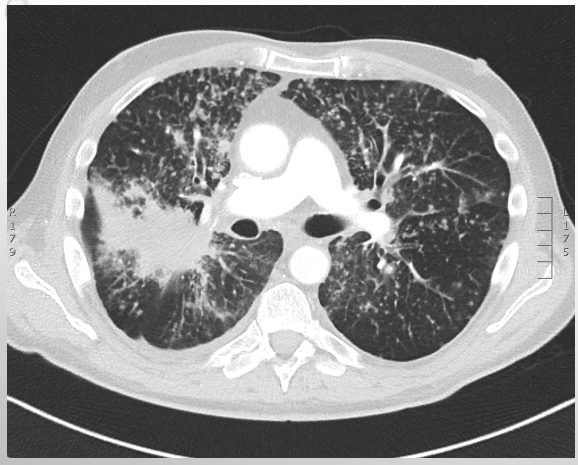
RECIST 1.1



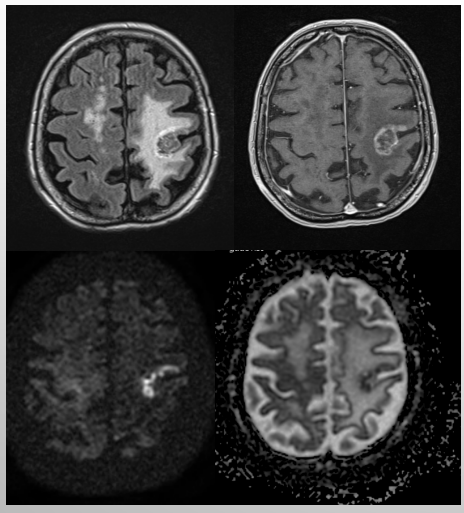
NETARČNE LEZIJE

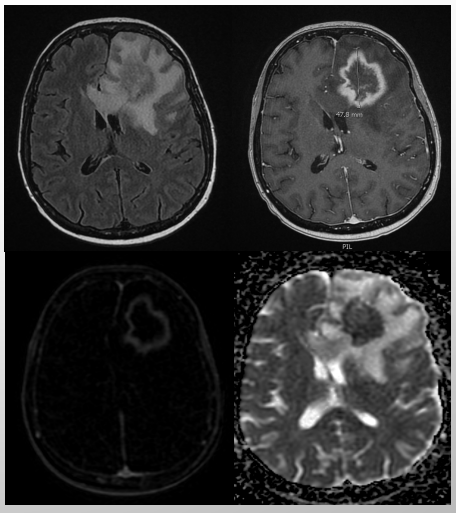
1. Vse, ki niso tarčne
   - Vse metastaze <10mm (daljši premer), bezgavke 10-14mm (krajši premer)
   - Tudi merljive lezije, ki jih nismo izbrali za tarčne
   - Lezije, ki so lahko (ne pa zagotovo) metastaze
2. Nemerljive lezije
   - Ascites
   - Perikardialni izliv
   - Plevralni izliv
   - Cistične lezije
   - Skeletne lezije
   - Noduli mlečnega stekla v pljučih
   - Leptomeningealni razsoj
   - Vnetni karcinom dojke
   - Limfangiokarcinomatoza
   - Obsevane lezije

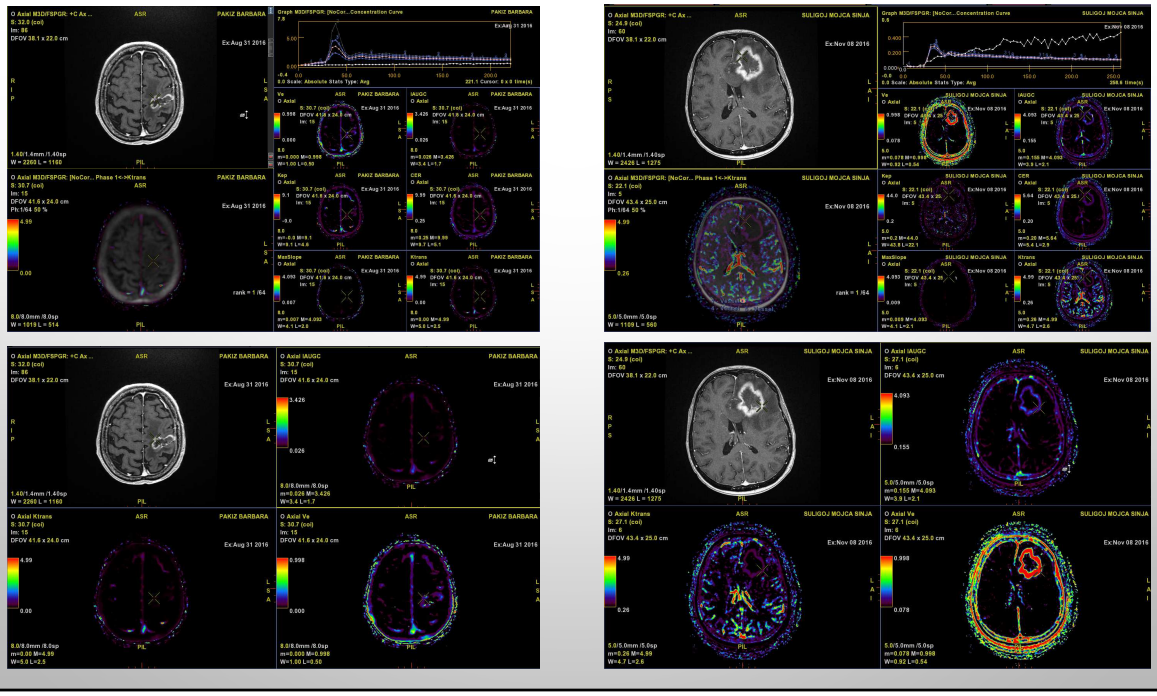
POSEBNOSTI
- Litične skeletne metastaze z mehkotkivno komponento >10 mm so lahko merljive lezije
- Sklerotične metastaze so vedno nemerljive/netarčne
- Cistične metastaze so lahko tarčne, vendar če imamo možnost, rajši izberemo necistične metastaze



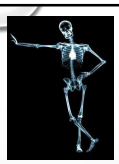
NETARČNE LEZIJE – OBSEVANE LEZIJE







ODGOVOR NA TERAPIJO



Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	SD(Non-CR/non-PD)	No	PR
PR	CR or SD	No	PR
SD	CR or SD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes (PD)	PD

Novonastale lezije:

- Vse, ki se na novo pojavijo tudi v obsevanem področju
- Vse, ki se ponovno pojavijo (prehodno pa so izginile)
- Za novo lezijo ni pomembna velikost

1. CR – complete response – popoln odgovor
- popolno izginotje tarčnih in netarčnih lezij in ln<10mm

2. PR – partial response – delni odgovor
- >= 30% zmanjšanje vsote premerov tarčnih lezij
- Netarčne letije v stagnaciji ali popoln regres
- Ni novonastalih lezij

3. SD – stable disease – stabilna bolezen
- Niti PR niti PD

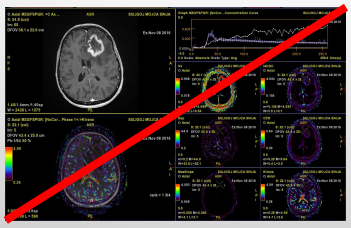
4. PD – progressive disease – progres bolezni
- >= 20% povečanje vsote premerov tarčnih lezij (skupno vsaj >5mm) + netarčne lezije karkoli
- Vsaka novonastala lezija (ne glede na velikost)
- Progres netarčnih lezij

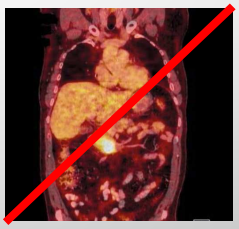
OMEJITVE RECIST PRIPOROČIL

- MORFOLOGIJA TUMORJA:
  - Zlivajoče metastaze, nepravilni robovi
  - Cirkumferentna rast – mezoteliomi
  - Podolgovate lezije (> 1,5-2x daljše)
- UNIDIMENZIONALNE MERITVE
  - Metastaze lahko spreminjajo obliko → lahko je volumsko precej manjše, unidimenzinalno pa ni večje razlike
- Asimetrična rast tumorjev
- Velikost – subcentimeterski tumorji
- Izbira reprezentativne meje tumorja
- Nepredvidljivo obnašanje tumorjev

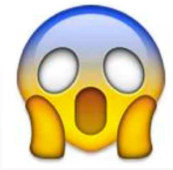
FUNKCIONALNE SPREMEMBE?

- RECIST:
  - TEMELJI SAMO NA VELIKOSTI
  - NE UPOŠTEVA METABOLNE FUNKCIJE
  - NE UPOŠTEVA PERFUZIJSKIH PARAMETROV

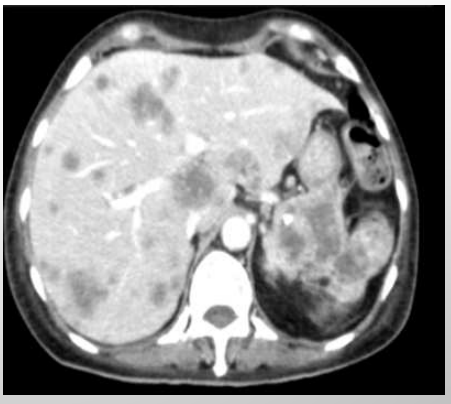




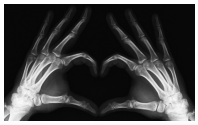
PROGRES BOLEZNI



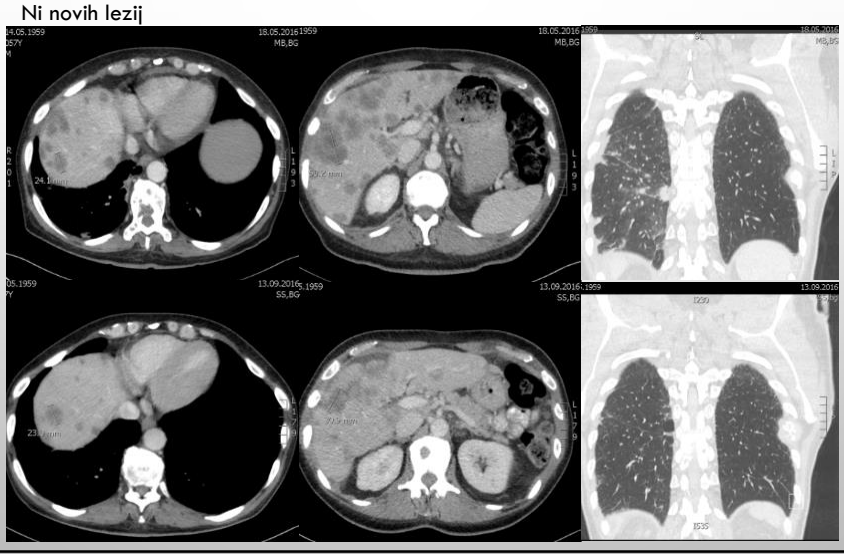
Povečanje seštevka premerov tarčnih lezij za >20%
Vsaka novo nastala lezija



DELNI REGRES BOLEZNI



Zmanjšanje seštevka premerov tarčnih lezij za >30%
Netarčne lezije, ki so nespremenjene ali so se zmanjšale
Ni novih lezij



RECIST IS SIMPLE, USING RECIST IS NOT

NOVA ZDRAVILA - NOVI KRITERIJI

	Original irRC	irRECIST	iRECIST
BL: Definition of TL	WHO+ 5 cutaneous target	RECIST 1.1 criteria	RECIST 1.1 criteria
BL: Definition of NTL	Non specified	RECIST 1.1 criteria	RECIST 1.1 criteria
BL: Definition of LN	Not specified	RECIST 1.1 criteria	RECIST 1.1 criteria
FU: TL and measurable NL	Sum of TL and NL (≥5×5 mm; up to 5 /organ 5 new cutaneous and 10 visceral lesions)	Sum of TL and NL (>10mm for non nodal, > 15mm for nodal lesions, 2/organ up to 5)	irCR, irSD, irPR uPD separately for TL, NTL and NL
FU: NTL	Only to define irCR	irCR and Non-irCR/Non-irPD	irCR, Non-irCR/Non-uPD, uPD
FU: Non measurable NL	Prevent for irCR	PD if unequivocal PD Prevent for irCR	
irRC	4 weeks confirmation	4 weeks confirmation after the first PD	4 -8 weeks after the first PD

Seymour L on behalf of the RECIST working group Lancet oncol 2017;18:e143-52

Clin Cancer Res. 2009 Dec 1;15(23):7412-20. doi: 10.1158/1078-0432.CCR-09-1624. Epub 2009 Nov 24.
Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria.
Wolchok JD[1], Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS.

J Clin Oncol. 2015 Nov 1;33(31):3541-3. doi: 10.1200/JCO.2015.61.6870. Epub 2015 Aug 10.
Pseudoprogression and Immune-Related Response in Solid Tumors.
Chiou VL[1], Burotto M[2].

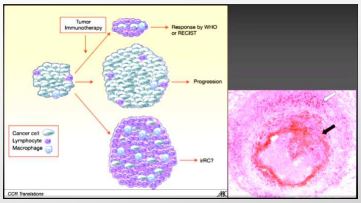
Lancet Oncol. 2017 Mar;18(3):e143-e152. doi: 10.1016/S1470-2045(17)30074-8. Epub 2017 Mar 2.
iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics.
Seymour L[1], Bogaerts J[2], Perrone A[3], Ford R[4], Schwartz LH[5], Mandrekar S[6], Lin NU[7], Litière S[2], Dancey J[8], Chen A[9], Hodi FS[7], Therasse P[10], Hoekstra OS[11], Shankar LK[12], Wolchok JD[13], Ballinger M[14], Caramella C[15], de Vries EG[16], RECIST working group.

REVIEW | Open Access
Hyperprogression: A novel response pattern under immunotherapy
Xue-jiao Han, Aqu Alu, Yi-nan Xiao, Yu-quan Wei, Xia-wei Wei

iRECIST

- Temelji na kriterijih RECIST 1.1
- Ima prefix ‚i'
- Glavna razlika = progres bolezni
  1. radiološko ugotovljeni progres bolezni → iUPD (unconfirmed progression disease)

opravimo kontrolno preiskavo čez 4-8 tednov

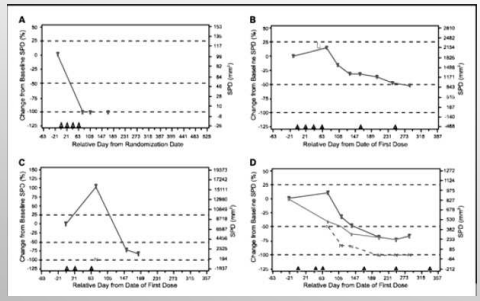


v kolikor potrdimo, da je bolezni več kot na prvi preiskavi → confirmed progression disease (iCPD)

- Vsak naslednji prvi progres pomeni iUPD in ponovimo preiskavo čez 4-8 tednov

PSEVDO-PROGRES

- Pri 5 - 7% bolnikov
- Mlajši bolniki – bolj odziven imunski sistem
- Lahko povezan s kliničnim poslabšanjem
- Najpogosteje okrog 12 tedna

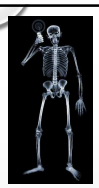


POTRDITEV PROGRESA

- 4-8 tednov
- Nishino et al 103 bolniki z melanomom – 4% pseudoprogresov
  - Srednji čas od prve preiskave do zmanjšanja tumorskega bremena 6,8 mes (3,4-6,9mes)
- RANO working group (neuro-oncology) priporoča 3 mesečni zamik za potrditev progresa bolezni

Herbst RS et al. Nature.2014 Nov 27;515(7528):563-7, Nishino M at al Clin Cancer res
Hodi F J Clin Oncol 2016; 34: 1510-1517; Nishino M Clin Oncol 2017

HIPERPROGRES (HPD)



- Pri cca 9-29% bolnikov
- Potencialni prediktivni faktorji za HPD: ↑ LDH, > 2x povečanje tumorja

Table 1

Definitions of hyperprogressive disease (HPD)

Publication	Unit and calculation	HPD definition
Champiat *et al.* (3)	TGR = Δ tumor volume/Δ time (months)	RECIST-defined PD and $TGR_{post} \geq 2\ TGR_{pre}$
Saada-Bouzid *et al.* (7)	TGK = Δ sum of tumor diameters/Δ time (months)	$TGK_{post}/TGK_{pre} \geq 2$
Ferrara *et al.* (4)	TGR = Δ tumor volume/Δ time (months)	RECIST-defined PD and $TGR_{post} \geq TGR_{pre}$ +50%
Karo *et al.* (8)	TGR = Δ tumor volume/Δ time (months)	Time to treatment failure <2 months and >50% increase in tumor burden and $TGR_{post} \geq 2\ TGR_{pre}$

HPD, hyperprogressive disease; PD, progressive disease; RECIST, response evaluation criteria in solid tumors; TGK, tumor growth kinetics; TGR, tumor growth rate.

Stopnja rasti tumorja (TGR) - ▲ volumna tumorja/▲ časa (mes)
- HPD >2x TGR

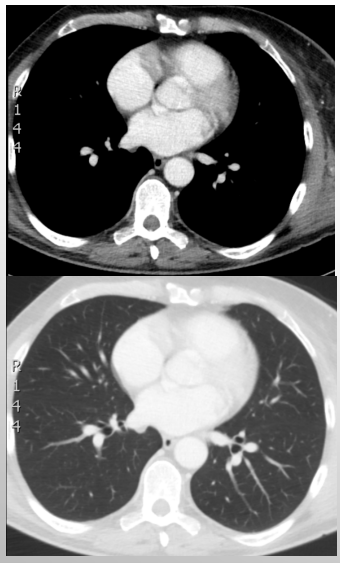
Kinetika rasti tumorja TGK - ▲vsote premerov/▲ časa (mes)
- HPD >2x TGK

V <2mes za > 50% povečanje tumorskega bremena

Jong Yeob Kim et. Al., Hyperprogressive Disease during Anti-PD-1 (PDCD1) / PD-L1 (CD274) Therapy: A Systematic Review and Meta-Analysis, Cancers (Basel).2019 Nov;11(11):1699

Borcoman et.al., Patterns of response and progression to immunotherapy, DOI: 10.1200/EDBK_200643 *American Society of Clinical Oncology Educational Book* 38 (May 23, 2018) 169-178.

PSEVDOPROGRES? Ali HIPERPROGRES? – radiološko iUPD



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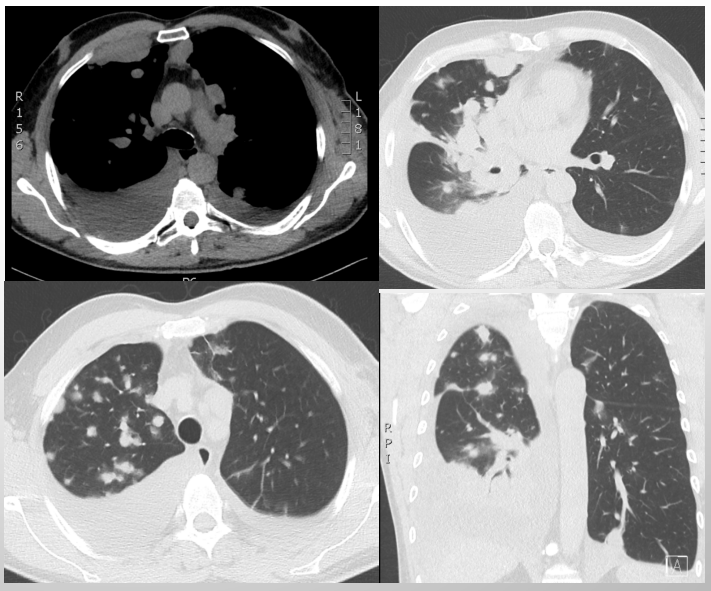
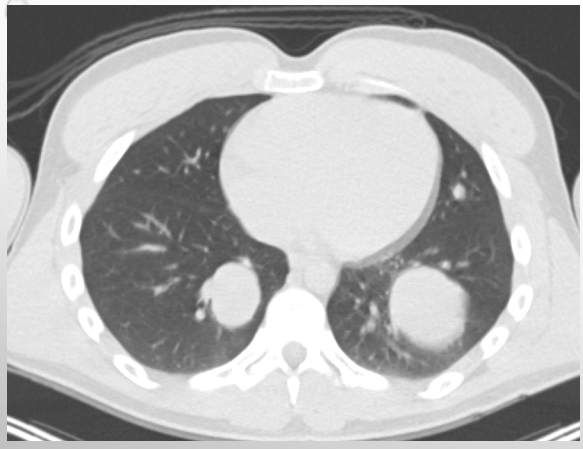
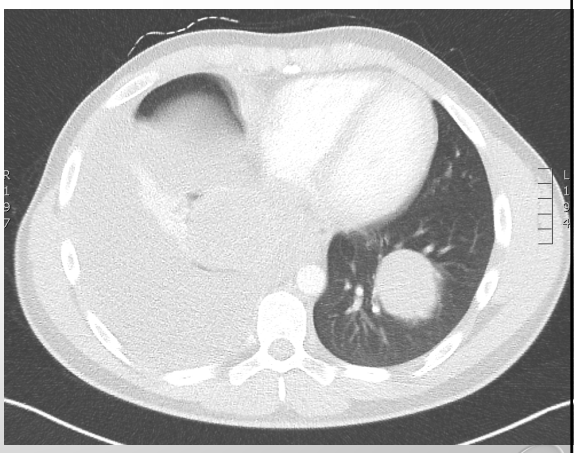


Po 2 aplikacijah pembrolizumaba

PSEVDOPROGRES? ALI HIPERPROGRES? – radiološko iUPD

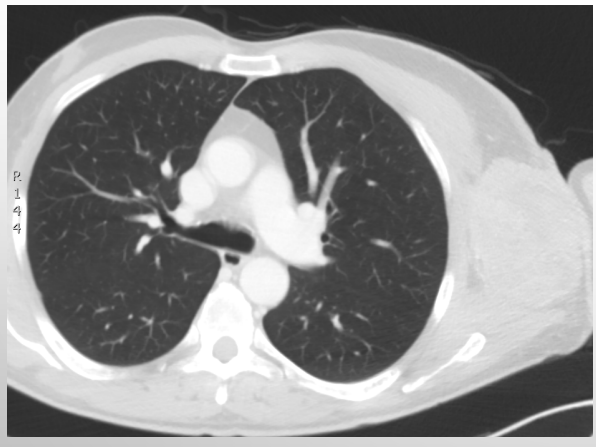


4.10.2017

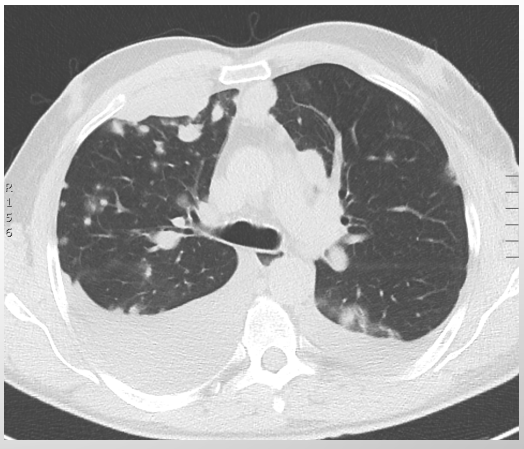


3.1.2018

PSEVDOPROGRES? ALI HIPERPROGRES? – radiološko iUPD



11.10.2017



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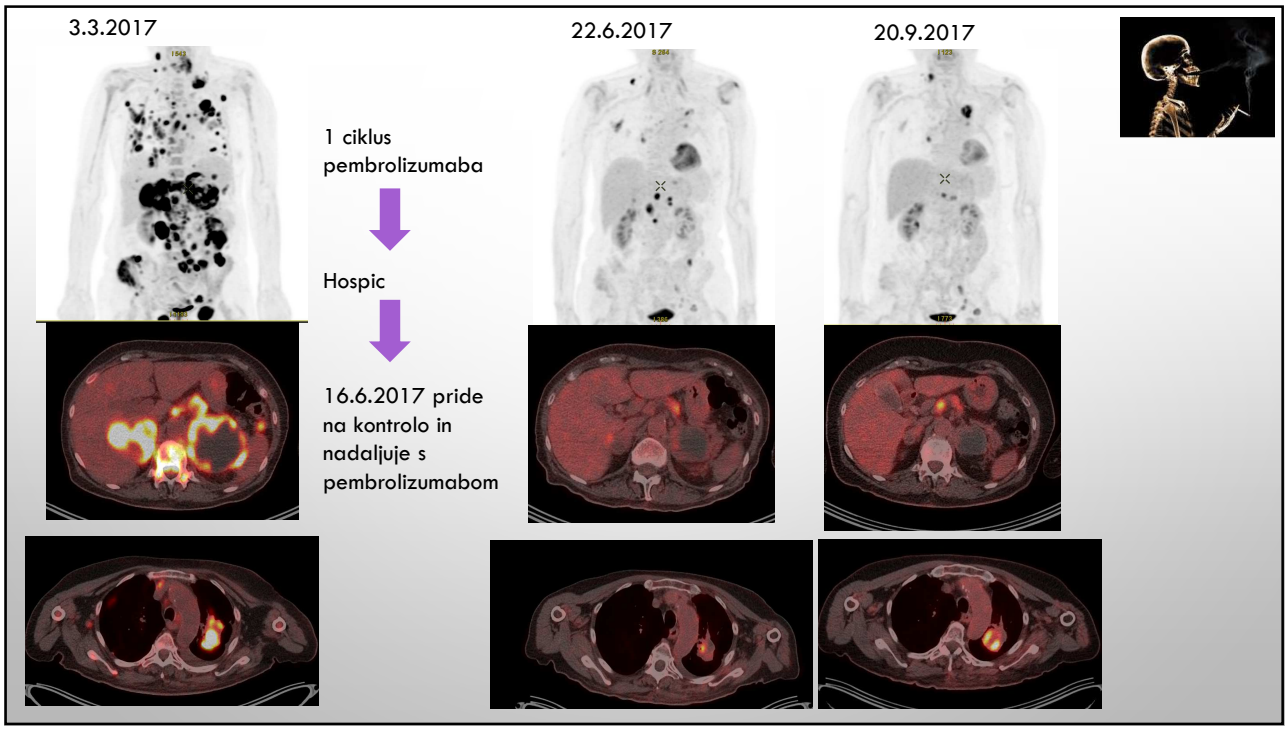
3.3.2017
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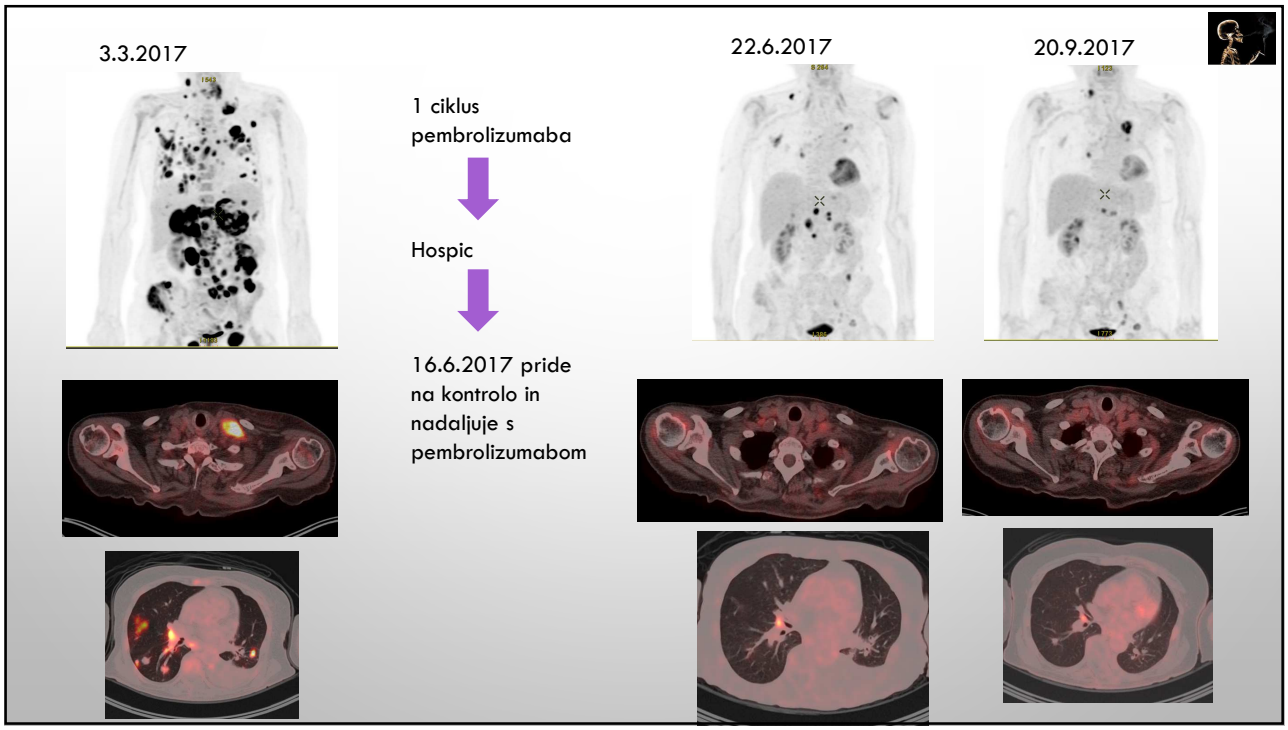
20.9.2017
1 ciklus pembrolizumaba
Hospic
16.6.2017 pride na kontrolo in nadaljuje s pembrolizumabom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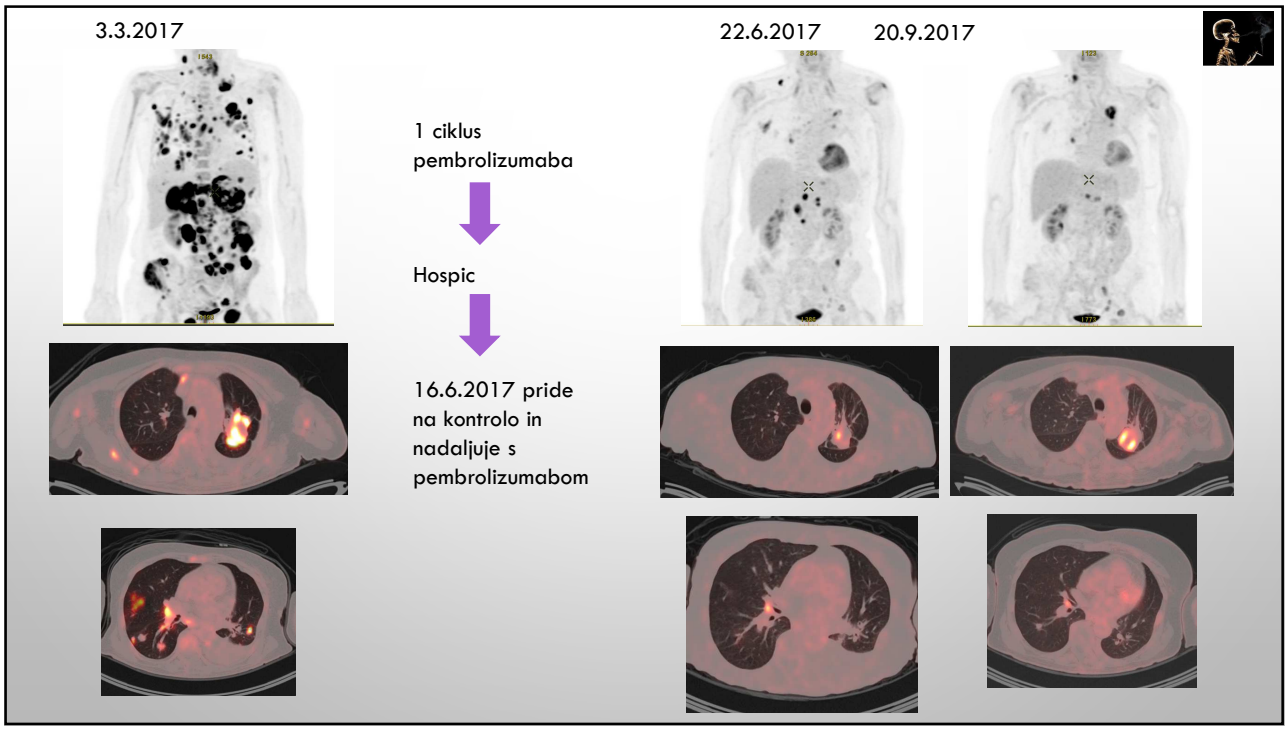
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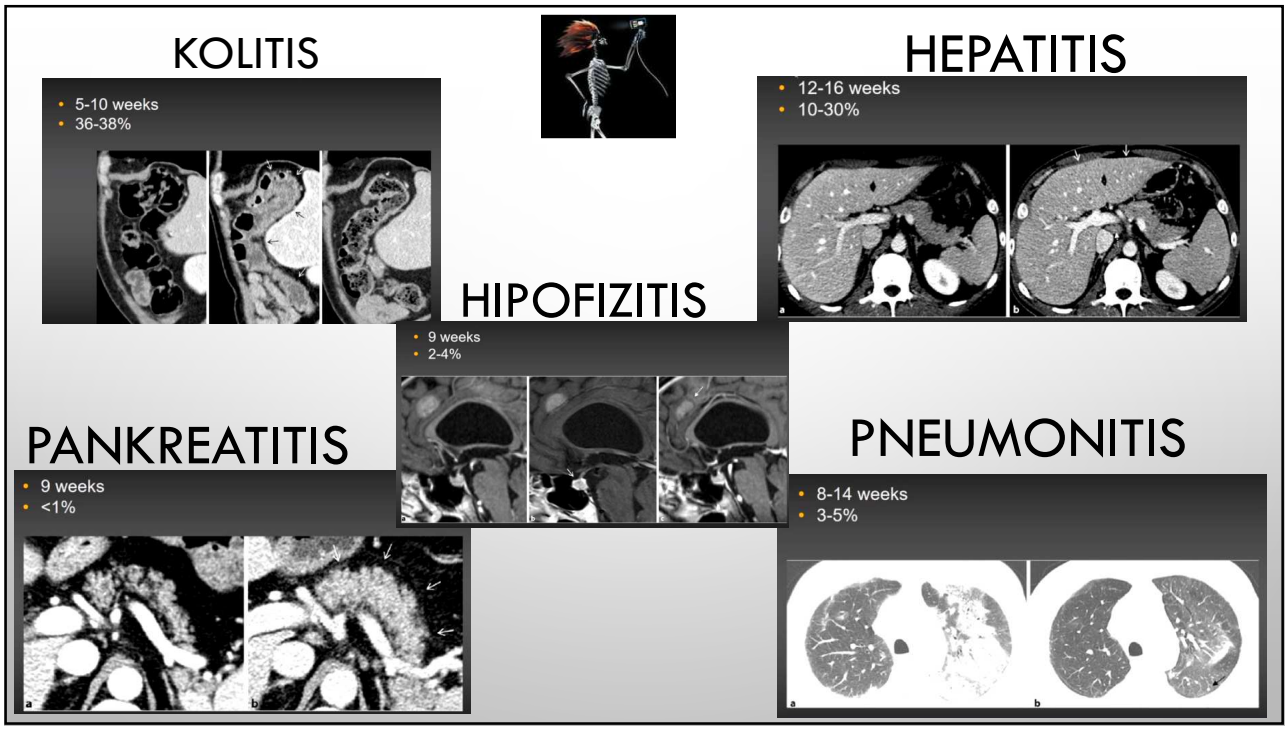
KOLITIS
5-10 weeks
36-38%
HEPATITIS
12-16 weeks
10-30%
HIPOFIZITIS
9 weeks
2-4%
PANKREATITIS
9 weeks
<1%
PNEUMONITIS
8-14 weeks
3-5%

ZAKLJUČEK

- Novo zdravljenje → novi vzorci radiološkega odgovora na terapijo → novi kriteriji za ocenjevanje učinka terapije → iRECIST
  - Kasnejše zmanjšanje tumorskega bremena
  - Časovno daljše trajanje odgovora
  - PSEVDO-PROGRES – najprej povečanje sprememb, nato zmanjšanje
- Novi spektri stranskih učinkov

- Pomen slikovne diagnostike = ocena sprememb glede na vzorce in značilnosti → ne delamo pa z mikroskopom!

Imunosupresijska zdravljenja in imunoterapija

Tomaž Milanez

Izhodišča

- T –celična aktivacija povezana z zdravljenjem z zaviralci imunskih nadzornih točk (ZINT) pri bolnikih z rakom **vzpodbuja** vnetje in imunsko povezane neželene dogodke/učinke (vzročnost je velikokrat vprašljiva !)
- Pojavnost neželenih dogodkov v registracijskih študijah je verjetno podcenjena
- Zdravljenje (ukrepi) neželenih dogodkov/učinkov povezanih z ZINT **ne temelji na visoki stopnji dokazov** (soglasje strokovnjakov)
  - EULAR priporočila
  - Celosten/multidisciplinaren pristop skupaj z bolnikom !
  - Presoja
- **Kortikosteroidi so temeljna zdravila** pri obvladovanju z imunoterapijo povezanih neželenih dogodkov/učinkov
  - nizki odmerki v.s visoki odmerki

Izhodišča

- Imunosupresijska zdravljenja
  - Zdravila
  - Invazivna vrsta zdravljenj
  - Kombinacije zdravljenj
- Imunosupresijsko zdravljenje neželenih dogodkov, ki so povezani z zdravljenjem ZINT
  - Pojavnost neželenih dogodkov ob zdravljenju z ZINT je podcenjena
  - Smrtnost ob zdravljenju z ZINT je do 1,3 %
    - 10-15% neželenih dogodkov je hujše stopnje
  - Prizadetost srčne mišice-miokarditis, perikarditis
  - Prizadetost CŽS, perifenega živčevja
  - Prizadetost mišic
  - Prizadetost kože
  - Prizadetost krvnih celic-TMA

Izhodišča

- "Dvojno" delovanje immunosupresivov
- Sinergistično delovanje ? (Infliximab+ZINT, Tacrolimus +ZINT)
- Uvedba in nadaljevanje zdravljenja z ZINT pri bolnikih z rakom ki se zdravijo zaradi avtoimunih bolezni
  - Sekvenčno imunosupresivno zdravljenje
  - Antagonizem in sinergizem imunosupresijskega zdravljenja z ZINT
- Nadaljevanje zdravljenja z ZINT pri bolnikih z neželenimi učinki-dogodki povezanimi z ZINT
- Zdravljenje z ZINT pri bolniki z rakom in s presajenim organom
  - Čvrsti organi (ledvica, srce, jetra)
  - Študija: Faza I tacrolimus + prednisolone 10mg +ZINT

Razdelitev zdravil za zdravljenje sistemskih vnetnih boleznih povezanih z avtoimunostjo

- Konvencionalni sintentizirani imunomodulirajoči antirevmatiki
  - Ciklofosfamid
  - Antimetaboliti
  - Sulfasalazin…….

Zdravila za zdravljenje sistemskih vnetnih boleznih povezanih z avtoimunostjo

- Zdravila ki neposredno vplivajo na delovanje in sintezo citkinov ter na prenos informacij
  - Zaviralci dejavnika tumorske nekroze (anti TNF-α)
    - Etanercept
    - Infliximab
    - Adalimumab
    - Certolizumab
    - Golimumab
  - Zaviralci IL-1
    - Anakinra
    - Canakinumab
    - Rinolacept

Zdravila za zdravljenje sistemskih vnetnih boleznih povezanih z avtoimunostjo

- Zdravila ki neposredno vplivajo na delovanje, sintezo citkinov in na prenos informacij
  - Zaviralci IL-6
    - Tocolizumab
    - Sarilumab
  - Zaviralci IL-17
    - Secukinumab
    - Ixekizumab
    - Ustekinumab

Zdravil za zdravljenje sistemskih vnetnih boleznih povezanih z avtoimunostjo

- Zaviralno na kostimulacijo T limfocitov
  - Abatacept (vezava na CD80 in CD86 selektivno zavira kostimulacijsko pot)
- Propadanje Limfocitov B
  - Rituximab (RTX)
  - Belimumab (anti B Limfocitni stimulator-preprečuje stimulacijo B limfocitov)

- **Tarčna zdravila**
  - Zaviralci Janus Kinaze (ang.Janus Kinase inhibitors)
    - Tofacitinib
    - Baricitinib
    - Upadacitinib

Zdravila za zdravljenje sistemskih vnetnih boleznih povezanih z avtoimunostjo

- Zaviralci dejavnika tumorske nekroze (anti TNF-α)
  - **Infliximab**

- Infliximab: TNF-α zaviralec (zaviralec dejavnik tumorske nekroze α):
  - imunosupresivno zdravljenje za različne avtoimune bolezni in stanja
  - vprašanje zmanjšanja učinkovitosti terapije z ZINT (antagonizem)
- Sekvenca zdravljenja s TNF-α zaviralci (npr. infliximab in tocolizumab)
- Infliximab- TNF-α zaviralec
  - Minimalni vpliv na T-celice v tumorskem tkivu v.s glikortikoidi, ki imajo že pri nizkih odmerkih potencial zmanjšati učinkovitost ZINT
  - Na mišjih modelih TNF-α zaviralci sinergistični učinek z ZINT pri zdravljenju raka
  - Ne priporoča se zdravljenje pri bolnikih s hepatitisom in s srčnim popuščanjem
- Phase I investigator initiated trial (TICIMEL): kombinirano zdravljenje ZINT s TNF zaviralci

Glukokortikoidi

- ***Protivnetno in imunosupresijsko delovanje***
  - Manjše dostopanje levkocitov do vnetišč
  - Manjše vnetno delovanje vnetnih in endotelijskih celic
  - Zmanjšana aktivnost <u>predvsem T-limfocitov</u> v imunskem odzivu
  - Zaviranje humoralnih posrednikov vnetja in imunskega odziva

- **Delovanje glukokortikoidov**
  - Transaktivacija-genomski učinek (nastajanje protivnetnih snovi)
  - Transpresija-genomski učinek (protivnetni učinek)/zavora sinteze IL-1,IL-2, IL-6 in dejavnika tumorske nekroze α)
  - Specifični ne-genomski učinki
    - -vpliv preko citoplazemskega receptorja (zavora sinteze IL-1, IL-6 in G-CSF)
    - .preko membranskega receptorja (monociti, limfociti B9
  - <u>*Nespecifični ne-genomski učinek*</u>
    - Npr. <u>*Veliki pulzni odmerki glukokortikoidov*</u>/sprememba prometa kationov ter protonov, zmanjšanje energetske presnove vnetnic- hitro zmanjšanje imunskega in vnetnega delovanja limfocitov -hiter imunosupresijski in protivnetni učinek

Ciklofosfamid

- 4-hidroksiciklfsfamid –alikilirajoče zdravilo-način delovanja
  - zlom verige DNA-motnja v podvojevanju DNA-citostatičen učinek, apoptoza
  - Zavirajoč učinek na limfocite, zavira celično in humoralno imunost
    - Zavira delovanje limfocitov B, limfocitov T , nastajanje protiteles
    - Ima tudi protivneten učinek

Azatioprin

- Azatioprin se v organizmu pretvori v 6-merkaptopurin-tioinozin monofosfat
- zavrejo sintezo purinov-motnja v sintezi DNA (antimetabolit)
  - Delovanje azatioprina oz. aktivnih metabolitov je najbolj izraženo na limfocitih (nimajo reševalne poti sinteze nukleotidov)
  - Presnovki ovirajo sintezo RNA
  - Apoptoza limfocitov
  - Slabšajo možnost aktivacije T
  - Zavirajo delovanja encima inozin monofosfat dehidrogenazo

Mikofenolat mofetil in mikofenolna kislina

- Mikofenolna kislina zavira proliferacijo limfocitov T in B pri antigenskem vzpodbujanju
- Ključni način imunosupresivnega delovanja→mikofenolna kislina zavira sintezo purinov in posledično motnjo v podvojevanju DNA
  - Zavora proliferacije limfocitov T in B pri antigenskem vzpodbujanju
  - Zaviranje nastajanja protiteles v celicah B
  - Deluje predvsem na poznejši del odgovora na antigensko vzpodbujanje (zgodnje- izločanje IL 1 in IL 2)
  - Dokaj specifična za limfocite T in B
    - druge celice imajo rešilno pot sinteze purinov
    - Selektivnost delovanja je tudi posledica na encim inozin monofosfat dehidrogenazo tip 2

Zaviralca kalcinevrina-ciklosporin in takrolimus

- **Zaviralci kalcinevrina imunski učinki**
  - Ciklosporin → vezava na ciklofilin
  - Takrolimus →vezava za beljakovino FK
  - Zaviralca kalcinevrina zmanjšata izločanje IL-2 sorazmerno s koncentracijo zdravila
  - zmanjšajo tvorbo interlevkina IL-2 in zmanjšajo izražanje receptorja IL-2- zmanjšana aktivacija limfocitov
- **Zaviralci kalcinevrina in neimunski učinki**
  - Vpliv na prepustnost in na naboj glomerulskega filtra
  - Spreminjata delovanje podocitov
  - Zmanjšata velikost glomerulne filtracije

Sirolimus in everolimus

- **Imunosupresijski učinek sirolimusa in everolimusa je posledica zaviranja citoplazemskega mTORC**
  - vpliva na uravnavanje rasti zorenja in delitve limfocitov ter drugih imunokompetentnih celic (mTORC 1)
  - Kronična izpostavljenost vpliva na integriteo citoskeleta-življensko dobo limfocitov T in B (mTORC2)

Poliklonska protilimfocitna protitelesa

- Ključna vloga pri presaditvi čvrstih organov in krvotvornih matičnih celic
  - poliklonski protitimocitni globulini vežejo se na različne površinske antigene limfocitov T (način priprave : Imunizacija kuncev: limfocite za imunizacijo iz odstranjenih priželjcev)
  - monoklonski protilimfocitni globulini
    - Muromonab-CD3 (OKT3)-mišje monoklonsko protitelo proti CD3-na limfocitu T
    - Alemtuzumab –humanizirano monoklonsko protitelo proti CD52 –na limfocitih T in B
- Način delovanja
  - Limfociti T
    - Liza
    - Vezava na antigene(kostimulacijske, adhezijske, kemotaktične dejavnike)
    - Posledica porušeno ravnovesje regulacija/citotoksičnost
  - Limfociti B
    - Vezava na antigene(preprečuje diferenciacijo v plazmatke=manj protiteles)

Intravenski Imunoglubulini

- Interakcije s celičnimi in humoralnimi mehanizmi
- Polispecifični Ig-iz plazme več tisoč dajalcev
  - Raznovrstna protitelesa: specifična za različne antigene
- **Način delovanja**
  - Vsebujejo antiidiopatska protitelesa-vezava na Limfocite B isti idiotopi-uničenje avtoreaktivnih klonov
  - Vezava na idiotope krožečih avtoprotiteles (npr. protitelesa proti citoplazmi nevtrofilcev)
  - Fc regija IgG vezava na s komplementom neonatalnim receptorjem
  - Z zaviralnim receptorjem na makrofagih
  - **Glukortikoidi povečajo učinek glukokortikoidov-smiselna sočasna uporaba**
  - **IVIg zmanjšajo odpornost na glukokortikoide-smiselna sočasna uporaba**

- **Indikacije način delovanja: splošno**
  - Primarne in sekundarne imunske pomanjkljivosti: nadomeščanje manjkajočih Ig
  - Avtoimunske in vnetne bolezni: imunomodulatorni in protivnetni učinek
  - *Protivnetni učinek: IVIg v visokih odmerkih: 2g/kgTT v enem ali dveh-petih odmerkih (npr.400mg/kg/TT zaporedoma 5 dni-lahko ponovimo mesečni intervali*
  - Provnetni učinek: IVIg v nizkih odmerkih

Rituximab (RTX)

- Vloga limfocitov B v avtoimunih reakcijah
  - procesiranje in predstavitev (avto)antigenov celicam T
  - Nastanku citokinov
  - Diferenciacija v plazmatke (izdelovanje -(avto)protiteles)
  - Arhitektura limfatičnega tkiva
- Monoklonsko protitelo –vezava na CD20 antigen na limfocith B
- Način delovanja
  - Izginotje oz. deplecija limfocitov B
    - Od komplementa odvisna citotoksičnost
    - Učinkovitost je odvisna od regulatornih beljakovin:več jih je večja odpornost na RTX
  - Ustavitev celičnega ciklusa in apoptoza limfocita B
  - Od protiteles odvisna celična toksičnost
    - Antitumorski učinek

Terapevtska afereza

- **Z izmenjavo plazme in imunsko adsorbcijo poiskušamo vplivati na**
  - **prekinitev patoloških procesov**
  - Zmanjšanje okvare tkiv
  - Restitucijo organa z njegovo funkcijo
  - Napram imunosupresivnem zdravljenju hitrejše odstranjevanje protiteles (razpolovni čas IG 21 dni= kombinacija zdravljenja)
    - Kombinacija imunosupresivnega zdravljenja in plazmafereze
    - Brez imunosupresijkega zdravljenja –rebound učinek

- Imunska adsorbcija-adbsorbcijske kolumne-vezava
  - Ig
  - Imunski kompleksi

- Plazmafereza- odstrani del bolnikove plazme
  - Avtoprotitelesa
  - Imunski kompleksi, endotoksini, kriglobulini
  - ZINT?
  - učinkovine zdravil
  - Zamenjava plazme/albuminov (1-1,5x količina cirkulirajoče volumna plazme 4% telesne mase)

Terapevtska afereza

- **Splošne indikacije**
  - Razpolovni čas snovi je tako dolg, da je endogena pot odstranjevanja iz telesa pomembno daljša od zunajtelesnega odstranjevanja
  - Snov je tako škodljiva ali akutno toksična oziroma odporna proti konvencionalnem zdravljenju-hitra odstranitev
  - Molekulska masa snovi je večja od 15kDa in zato ni možno odstranjevanje s purifikacijsko metodo
    - **Hemofiltracija**
    - **Visoka polprepustna hemodializa**

Plazmafereza (PF)

- Izventelesni krvni obtok-žilni pristop
- Odstrani del bolnikove plazme
  - Avtoprotitelesa
  - Imunski kompleksi, endotoksini, krioglobulini
  - Zamenjava plazme/albuminov (1-1,5x količina cirkulirajoče volumna plazme 4% telesne mase= 3l plazme)
  - Odstranjevanje pomembne količine RTX! (47%-54%)-zamakniti PF

Imunska adsorbcija

- Plazma se ločeno od krvnih celic obdela v sekundarnih plazmafiltrih/adsorbcijskih kolumnah-vežejo se molekule
- Očiščeno plazmo vrnemo bolniku
- Odstranjuje-na kolumnah adsorbcijska snov-stafilokokna beljakovina A-s fragmentom Fc:
  - Imunoglobuline
    - Velika afiniteta: IgG1, IgG2, IgG4
    - Majhna afiniteta:IgG3, IgA, IgM
  - Imunske komplekse
- Količina obdelane plazme je okoli 10l-
  - Visoka učinkovitost odstranjevanja IgG
  - Ob okužbi prenehati z zdravljenjem

Zaključki

- Imunuspresijska zdravljenja
- Dvojno delovanje imunosupresijskega zdravljenja
- Kortikosteroidi so temelj zdravljenja z ZINT povezanimi neželenimi dogodki/učinki
  - Najmanjši še možen odmerek glikokortikoidov: prednisone 10mg/dan oz. ekvivalent
  - Pulzno zdravljenje pri življenjsko ogrožajočih dogodkih ob ZINT (nesepecifični-negenomski učinek)
  - Glukokortikoidi + IVIgG = boljši učinek zdravljenja
- Infliksimab (anti TNF alfa) verjetno ne vpliva na protitumorsko učinkovitost zdravljenja z ZINT

- Pri potencialno življenjsko ogrožajočih neželenih dogodkih povezanih z zdravljenjem z ZINT je potrebno hitro in "polno" (zavora T celičnega, humoralnega in citokinskega odgovora) in kombinirano (imunosupresivi in plazmafereza) imunosupresijsko zdravljenje ne glede na potencialno vplivanje na slabšo učinkovitost protirakavega zdravljenja

- Zdravljenje posebnih skupin bolnikov z rakom z ZINT
  - potrebujejo imunosupresivno zdravljenje
  - ne potrebujejo imunosupresivno zdravljenje

DOGODEK "NOVOSTI V IMUNOTERAPIJI PRI SOLIDNIH RAKIH 2021"
SO PODPRLE NASLEDNJE DRUŽBE:

ZLATI SPONZOR:

MSD

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(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 in pediatričnih bolnikov, starih 3 leta ali več, s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) ni bila uspešna, ali po najmanj dveh predhodnih zdravljenjih kadar ASCT ne pride v poštev kot možnost zdravljenja; 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 in za prvo linijo zdravljenja metastatskega kolorektalnega raka z visoko mikrosatelitsko nestabilnostjo (MSI-H – microsatellite instability-high) ali s pomanjkljivim popravljanjem neujemanja pri podvojevanju DNA (dMMR - mismatch repair deficient) pri odraslih. 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 ali v kombinaciji z lenvatinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih; v kombinaciji s kemoterapijo s platino in fluoropirimidinom je indicirano za prvo linijo zdravljenja lokalno napredovalega neoperabilnega ali metastatskega raka požiralnika ali HER-2 negativnega adenokarcinoma gastroezofagealnega prehoda pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10; v kombinaciji s kemoterapijo je indicirano za zdravljenje lokalno ponovljenega neoperabilnega ali metastatskega trojno negativnega raka dojk pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10 in predhodno niso prejeli kemoterapije za metastatsko bolezen; v kombinaciji z lenvatinibom je indicirano za zdravljenje napredovalega ali ponovljenega raka endometrija (EC) pri odraslih z napredovalo boleznijo med ali po predhodnem zdravljenju s kemoterapijo, ki je vključevala platino, v katerih koli terapevtskih okoliščinah, in ki niso kandidati za kurativno operacijo ali obsevanje. **Odmerjanje in način uporabe:** Testiranje PD-L1: Če je navedeno v indikaciji, je treba izbiro bolnika za zdravljenje z zdravilom KEYTRUDA na podlagi izraženosti PD-L1 tumorja potrditi z validirano preiskavo. Testiranje MSI-H/dMMR pri bolnikih s CRC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje MSI-H/dMMR statusa tumorja z validirano preiskavo, da se izbere bolnike s CRC. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA pri odraslih je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje pri pediatričnih bolnikih s cHL, starih 3 leta ali več, je 2 mg/kg telesne mase (do največ 200 mg) na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti zdravil 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 (in do maksimalnega trajanja zdravljenja, če je le to določeno za indikacijo). 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. V primeru uporabe v kombinaciji z lenvatinibom je treba zdravljenje z enim ali obema zdraviloma prekiniti, kot je primerno. Uporabo lenvatiniba je treba zadržati, odmerek zmanjšati ali prenehati z uporabo, v skladu z navodili v povzetku glavnih značilnosti zdravila za lenvatinib, in sicer za kombinacijo s pembrolizumabom. 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 6.185 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom, HNSCC ali CRC s štirimi odmerki (2 mg/kg telesne mase na 3 tedne, 200 mg na 3 tedne in 10 mg/kg telesne mase na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,6 mesece (v razponu od 1 dneva do 47 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (21 %) in diareja (21 %). 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 2.033 bolnikih z NSCLC, HNSCC, rakom požiralnika ali TNBC, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg telesne mase ali 10 mg/kg telesne mase na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: anemija (52 %), navzea (52 %), utrujenost (37 %), zaprtost (34 %), nevtropenija (33 %), diareja (32 %), zmanjšanje apetita (30 %) in bruhanje (28 %). Pojavnost neželenih učinkov 3. do 5. stopnje je pri bolnikih z NSCLC pri kombiniranem zdravljenju s pembrolizumabom znašala 67 % in pri zdravljenju samo s kemoterapijo 66 %, pri bolnikih s HNSCC pri kombiniranem zdravljenju s pembrolizumabom 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %, pri bolnikih z rakom požiralnika pri kombiniranem zdravljenju s pembrolizumabom 86 % in pri zdravljenju samo s kemoterapijo 83 % ter pri bolnikih s TNBC pri kombiniranem zdravljenju s pembrolizumabom 78 % in pri zdravljenju samo s kemoterapijo 74 %. Varnost pembrolizumaba v kombinaciji z aksitinibom ali lenvatinibom pri napredovalem RCC in v kombinaciji z lenvatinibom pri napredovalem EC so ocenili pri skupno 1.456 bolnikih z napredovalim RCC ali napredovalim EC, ki so v kliničnih študijah prejemali 200 mg pembrolizumaba na 3 tedne skupaj s 5 mg aksitiniba dvakrat na dan ali z 20 mg lenvatiniba enkrat na dan, kot je bilo ustrezno. V teh populacijah bolnikov so bili najpogostejši neželeni učinki diareja (58 %), hipertenzija (54 %), hipotiroidizem (46 %), utrujenost (41 %), zmanjšan apetit (40 %), navzea (40 %), artralgija (30 %), bruhanje (28 %), zmanjšanje telesne mase (28 %), disfonija (28 %), bolečine v trebuhu (28 %), proteinurija (27 %), sindrom palmarno-plantarne eritrodizestezije (26 %), izpuščaj (26 %), stomatitis (25 %), zaprtost (25 %), mišično-skeletna bolečina (23 %), glavobol (23 %) in kašelj (21 %). Neželenih učinkov od 3. do 5. stopnje je bilo pri bolnikih z RCC med uporabo pembrolizumaba v kombinaciji z aksitinibom ali lenvatinibom 80 % in med uporabo sunitiniba samega 71 %. Pri bolnicah z EC je bilo neželenih učinkov od 3. do 5. stopnje med uporabo pembrolizumaba v kombinaciji z lenvatinibom 89 % in med uporabo kemoterapije same 73 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. Za dodatne informacije o varnosti v primeru uporabe pembrolizumaba v kombinaciji glejte povzetke glavnih značilnosti zdravila za posamezne komponente kombiniranega zdravljenja. **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

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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.

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 prednodno 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 in pediatričnih bolnikov, starih 3 leta ali več, s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) ni bila uspešna, ali po najmanj dveh predhodnih zdravljenjih kadar ASCT ne pride v poštev kot možnost zdravljenja; 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 in za prvo linijo zdravljenja metastatskega kolorektalnega raka z visoko mikrosatelitsko nestabilnostjo (MSI-H – *microsatellite instability-high*) ali s pomanjkljivim popravljanjem neujemanja pri podvojevanju DNA (dMMR - *mismatch repair deficient*) pri odraslih. 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 ali v kombinaciji z lenvatinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih; v kombinaciji s kemoterapijo s platino in fluoropirimidinom je indicirano za prvo linijo zdravljenja lokalno napredovalega neoperabilnega ali metastatskega raka požiralnika ali HER-2 negativnega adenokarcinoma gastroezofagealnega prehoda pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10; v kombinaciji s kemoterapijo je indicirano za zdravljenje lokalno ponovljenega neoperabilnega ali metastatskega trojno negativnega raka dojk pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10 in prednodno niso prejeli kemoterapije za metastatsko bolezen; v kombinaciji z lenvatinibom je indicirano za zdravljenje napredovalega ali ponovljenega raka endometrija (EC) pri odraslih z napredovalo boleznijo med ali po prednodnem zdravljenju s kemoterapijo, ki je vključevala platino, v katerih koli terapevtskih okoliščinah, in ki niso kandidati za kurativno operacijo ali obsevanje. **Odmerjanje in način uporabe:** Testiranje PD-L1: Če je navedeno v indikaciji, je treba izbiro bolnika za zdravljenje z zdravilom KEYTRUDA na podlagi izraženosti PD-L1 tumorja potrditi z validirano preiskavo. Testiranje MSI-H/dMMR pri bolnikih s CRC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje MSI-H/dMMR statusa tumorja z validirano preiskavo, da se izbere bolnike s CRC. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA pri odraslih je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje pri pediatričnih bolnikih s cHL, starih 3 leta ali več, je 2 mg/kg telesne mase (do največ 200 mg) na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti zdravil 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 (in do maksimalnega trajanja zdravljenja, če je le to določeno za indikacijo). 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. V primeru uporabe v kombinaciji z lenvatinibom je treba zdravljenje z enim ali obema zdraviloma prekiniti, kot je primerno. Uporabo lenvatiniba je treba zadržati, odmerek zmanjšati ali prenehati z uporabo, v skladu z navodili v povzetku glavnih značilnosti zdravila za lenvatinib, in sicer za kombinacijo s pembrolizumabom. 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 6.185 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom, HNSCC ali CRC s štirimi odmerki (2 mg/kg telesne mase na 3 tedne, 200 mg na 3 tedne in 10 mg/kg telesne mase na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,6 mesece (v razponu od 1 dneva do 47 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (21 %) in diareja (21 %). 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 2.033 bolnikih z NSCLC, HNSCC, rakom požiralnika ali TNBC, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg telesne mase ali 10 mg/kg telesne mase na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: anemija (52 %), navzea (52 %), utrujenost (37 %), zaprtost (34 %), nevtropenija (33 %), diareja (32 %), zmanjšanje apetita (30 %) in bruhanje (28 %). Pojavnost neželenih učinkov 3. do 5. stopnje je pri bolnikih z NSCLC pri kombiniranem zdravljenju s pembrolizumabom znašala 67 % in pri zdravljenju samo s kemoterapijo 66 %, pri bolnikih s HNSCC pri kombiniranem zdravljenju s pembrolizumabom 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %, pri bolnikih z rakom požiralnika pri kombiniranem zdravljenju s pembrolizumabom 86 % in pri zdravljenju samo s kemoterapijo 83 % ter pri bolnikih s TNBC pri kombiniranem zdravljenju s pembrolizumabom 78 % in pri zdravljenju samo s kemoterapijo 74 %. Varnost pembrolizumaba v kombinaciji z aksitinibom ali lenvatinibom pri napredovalem RCC in v kombinaciji z lenvatinibom pri napredovalem EC so ocenili pri skupno 1.456 bolnikih z napredovalim RCC ali napredovalim EC, ki so v kliničnih študijah prejemali 200 mg pembrolizumaba na 3 tedne skupaj s 5 mg aksitiniba dvakrat na dan ali z 20 mg lenvatiniba enkrat na dan, kot je bilo ustrezno. V teh populacijah bolnikov so bili najpogostejši neželeni učinki diareja (58 %), hipertenzija (54 %), hipotiroidizem (46 %), utrujenost (41 %), zmanjšan apetit (40 %), navzea (40 %), artralgija (30 %), bruhanje (28 %), zmanjšanje telesne mase (28 %), disfonija (28 %), bolečine v trebuhu (28 %), proteinurija (27 %), sindrom palmarno-plantarne eritrodizestezije (26 %), izpuščaj (26 %), stomatitis (25 %), zaprtost (25 %), mišično-skeletna bolečina (23 %), glavobol (23 %) in kašelj (21 %). Neželenih učinkov od 3. do 5. stopnje je bilo pri bolnikih z RCC med uporabo pembrolizumaba v kombinaciji z aksitinibom ali lenvatinibom 80 % in med uporabo sunitiniba samega 71 %. Pri bolnicah z EC je bilo neželenih učinkov od 3. do 5. stopnje med uporabo pembrolizumaba v kombinaciji z lenvatinibom 89 % in med uporabo kemoterapije same 73 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. Za dodatne informacije o varnosti v primeru uporabe pembrolizumaba v kombinaciji glejte povzetke glavnih značilnosti zdravila za posamezne komponente kombiniranega zdravljenja. **Način in režim izdaje zdravila:** H – Predpisovanje in izdaja zdravila je le na recept, zdravilo se uporablja samo v **bolnišnicahlmetnik 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.,
Ameriška ulica 2, 1000 Ljubljana, tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50
Pripravljeno v Sloveniji, november 2021; SI-KEY-00352 EXP: 11/2023
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.

ZDRAVILO TECENTRIQ JE INDICIRANO ZA ZDRAVLJENJE RAZLIČNIH VRST RAKA:

NEDROBNOCELIČNI RAK PLJUČ

DROBNOCELIČNI RAK PLJUČ

TROJNO NEGATIVNI RAK DOJK

UROTELIJSKI KARCINOM

HEPATOCELULARNI KARCINOM

Vir: 1. Povzetek glavnih značilnosti zdravila Tecentriq je dosegljiv na povezavi: https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_sl.pdf

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: 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: Zdravilo Tecentriq je v kombinaciji z bevacizumabom, paklitakselom in karboplatinom indicirano v prvi liniji zdravljenja odraslih bolnikov z razsejanim nepoločatoceličnim 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 tarčna zdravljenja. Zdravilo Tecentriq je v kombinaciji z nab-paklitakselom in karboplatinom indicirano kot prva linija zdravljenja odraslih bolnikov z razsejanim nepoločatoceličnim NDRP, ki ni EGFR mutiran ali ALK pozitiven. Zdravilo Tecentriq je kot monoterapija indicirano v prvi liniji zdravljenja odraslih bolnikov z razsejanim nedrobnoceličnim rakom pljuč (NDRP), pri katerih je PD-L1 izražen na ≥ 50 % tumorskih celic (TC) ali ≥ 10 % imunskih celic (IC), ki infiltrirajo tumor, ter nimajo EGFR mutiranega ali ALK pozitivnega NDRP. 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 tarčna zdravljenja. Drobnocelični rak pljuč: Zdravilo Tecentriq je v kombinaciji s karboplatinom in etopozidom indicirano kot prva linija zdravljenja odraslih bolnikov z razsejanim drobnoceličnim rakom pljuč (DRP). Trojno negativni rak dojk: 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. Hepatocelularni karcinom: 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. **Odmerjanje in način uporabe:** Zdravilo Tecentriq morajo uvesti in nadzorovati zdravniki z izkušnjami pri zdravljenju raka. Odmerjanje: priporočeni odmerek zdravila Tecentriq je 840 mg, danim intravensko na dva tedna, ali 1200 mg, danim intravensko na tri tedne, ali 1680 mg, danim intravensko na štiri tedne, kot je navedeno v celotnem Povzetku glavnih značilnosti zdravila Tecentriq. *Zdravilo Tecentriq v kombinaciji:* kadar zdravilo Tecentriq dajete v kombinaciji, glejte tudi celotne informacije za predpisovanje zdravil, ki se uporabljajo v kombinaciji. *Prilagoditev odmerka med zdravljenjem:* odmerkov zdravila Tecentriq ni priporočljivo zmanjševati. *Zapoznitev odmerka ali prenehanje uporabe* glede na neželeni učinek je opisano v SmPC. 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. Bolnike je treba spremljati glede znakov in simptomov pnevmonitisa ter izključiti druge možne vzroke, razen imunsko pogojenega pnevmonitisa. 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. Bolnike je treba spremljati glede znakov in simptomov kolitisa in endokrinopatij, meningitisa ali encefalitisa. V primeru meningitisa ali encefalitisa je treba zdravljenje z atezolizumabom trajno ukiniti ne glede na njuno stopnjo. Bolnike je treba spremljati glede znakov in simptomov motorične 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. Bolnike je treba nadzorovati glede znakov in simptomov, ki kažejo na akutni pankreatitis. Bolnike je treba nadzorovati glede znakov in simptomov, ki kažejo na miokarditis. Imunsko pogojeni nefritis: Bolnike je treba nadzorovati glede sprememb v delovanju ledvic. 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. Pri bolnikih, ki so prejemali atezolizumab, so poročali o imunsko pogojenih hudih kožnih neželenih učinkih, vključno s primeri Stevens-Johnsonovega sindroma (SJS) in toksične epidermalne nekrolize (TEN). Bolnike je treba spremljati glede sumov na hude kožne neželene učinke in izključiti druge vzroke. V primeru suma na hude kožne neželene učinke je treba bolnike napotiti k specialistu po nadaljnjo diagnozo in zdravljenje. Uporabo atezolizumaba je treba odložiti pri bolnikih s sumom na SJS ali TEN. Pri potrjenem SJS ali TEN je treba trajno prenehati z uporabo atezolizumaba. Kartica za bolnika: 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 imunosupresive lahko uporabi po začetku zdravljenja z atezolizumabom za zdravljenje imunsko pogojenih neželenih učinkov. **Neželeni učinki:** *Informacije o varnosti atezolizumaba v monoterapiji:* najpogostejši neželeni učinki (> 10 %) so bili utrujenost, zmanjšan apetit, navzea, zvišana telesna temperatura, izpuščaj, kašelj, diareja, dispneja, mišično-skeletna bolečina, bolečina v hrbtu, astenija, bruhanje, srbenje, artralgija, okužba sečil in glavobol. *Varnost atezolizumaba v kombinaciji z drugimi učinkovinami:* najpogostejši neželeni učinki (≥ 20 %) so bili anemija, nevtropenija, navzea, utrujenost, trombocitopenija, diareja, izpuščaj, alopecija, zaprtost, zmanjšan apetit in periferna nevropatija. 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: 5.0/21**

M-SI-00000349(v1.0) Datum priprave informacije: november 2021

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

Samo za strokovno javnost.

NOV STANDARD ZA mOS PRI UROTELIJSKEM KARCINOMU

BAVENCIO® avelumab 20 mg/ml koncentrat za raztopino za infundiranje

Zdravilo BAVENCIO je indicirano kot monoterapija za VZDRŽEVALNO ZDRAVLJENJE V PRVI LINIJI za odrasle bolnike z lokalno napredovalim ali metastatskim urotelijskem karcinomom, ki jim po kemoterapiji na osnovi platine bolezen ni napredovala.[1]

mOS 22,1 meseca*[1] z zdravilom BAVENCIO® + BSC

v primerjavi z

mOS 14,6 meseca*[1] z BSC samo

HR = 0,70 (95 % CI: 0,56-0,86), dvostranska vrednost p = 0,0008

Samo za strokovno javnost
Merck, d.o.o., Letališka cesta 29c, 1000 Ljubljana.
Pfizer Luxemburg SARL, Branch Office Ljubljana.
Letališka cesta 29a, 1000 Ljubljana.

Ni za nadaljno distribucijo.
Prosimo, da se pred predpisovanjem in izdajanjem morebitno omejenih zdravil seznanite s celotnimi povzetki glavnih značilnosti zdravila.

UC = (urothelial caracinoma) urotelijski karcinom

*Datum zaključka zajema podatkov: 19. januar 2020. V skupini z zdravilom BAVENCIO + BSC je zdravljenje mediano trajalo 25,3 tedna (razpon: 2,0 – 173,9) in v skupini z BSC 13,1 tedna (razpon: 0,1 – 168,4).[2]

BSC = (best supportive care) najboljša podporna oskrba, CI = (confidence interval) interval zaupanja, mOS = (median overall survival) mediano celokupno preživetje, HR = (hazard ratio) razmerje ogroženosti.

1. Povzetek glavnih značilnosti zdravila Bavencio, oktober 2021.
2. Merck: interni podatki.

MERCK Pfizer

SI-AVEBL-00008; 11/2021

Skrajšan povzetek glavnih značilnosti zdravila

Bavencio 20 mg/ml koncentrat za raztopino za infundiranje

Sestava: 1 ml koncentrata vsebuje 20 mg avelumaba. Avelumab je humano monoklonsko protitelo IgG1, usmerjeno proti imunomodulacijskemu proteinskemu ligandu PD-L1 celične površine, ki je pridobljeno s tehnologijo rekombinantne DNA v celicah jajčnika kitajskega hrčka. **Terapevtske indikacije:** Zdravilo Bavencio je indicirano kot monoterapija za zdravljenje odraslih bolnikov z metastatskim karcinomom Merklovih celic (KMC). Zdravilo Bavencio je indicirano kot monoterapija za vzdrževalno zdravljenje prve izbire za odrasle bolnike z lokalno napredovalim ali metastatskim urotelijskim karcinomom (UK), ki jim po kemoterapiji na osnovi platine bolezen ni napredovala. Zdravilo Bavencio je v kombinaciji z aksitinibom indicirano kot zdravilo prve izbire za zdravljenje odraslih bolnikov z napredovalim karcinomom ledvičnih celic (KLC). **Odmerjanje in način uporabe:** Priporočeni odmerek zdravila Bavencio v monoterapiji je 800 mg, ki se daje intravensko, v obliki 60minutnega infundiranja, na vsaka 2 tedna. Dajanje zdravila Bavencio naj se nadaljuje v skladu s priporočenim načrtom do napredovanja bolezni ali nesprejemljive toksičnosti. Bolnike je treba pred prvimi 4 infuzijami zdravila Bavencio premedicirati z antihistaminikom in paracetamolom. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Bolnike je treba spremljati zaradi pojava znakov in simptomov neželenih učinkov, povezanih z infundiranjem, vključno s pireksijo, mrzlico, pordevanjem, hipotenzijo, dispnejo, piskajočim dihanjem, bolečinami v hrbtu, bolečinami v trebuhu in urtikarijo. Pri neželenih učinkih 3. ali 4. stopnje, povezanih z infundiranjem, je treba infundiranje ustaviti in avelumab trajno ukiniti. Pri neželenih učinkih 1. stopnje, povezanih z infundiranjem, je treba hitrost infundiranja zmanjšati za 50 % hitrosti prvotnega infundiranja. Pri bolnikih z neželenimi učinki 2. stopnje, povezanimi z infundiranjem, je treba z infundiranjem začasno prekiniti, dokler se neželeni učinki ne vrnejo na 1. stopnjo ali izzvenijo, nato pa z infundiranjem nadaljevati s 50 % počasnejšo hitrostjo infundiranja. Pri ponovnem pojavu neželenih učinkov 1. ali 2. stopnje, povezanih z infundiranjem, lahko bolnik avelumab prejema še naprej, ob natančnem spremljanju, po ustrezni spremembi hitrosti infundiranja in premedikaciji s paracetamolom in antihistaminikom. Pri sumu na imunsko pogojene neželene učinke je treba z ustrezno oceno potrditi njihovo etiologijo ali izključiti druge vzroke. Na podlagi resnosti neželenega učinka je treba uporabo avelumaba odložiti in bolniku dati kortikosteroide. **Interakcije:** Študij medsebojnega delovanja z avelumabom niso izvedli. Avelumab se primarno presnavlja po kataboličnih poteh, zato se ne pričakuje, da bi prišlo do farmakokinetičnega medsebojnega delovanja avelumaba z drugimi zdravili. **Neželeni učinki:** Najpogostejši neželeni učinki avelumaba so bili utrujenost (30,0 %), navzea (23,6 %), driska (18,5 %), zaprtost (18,1 %), zmanjšan apetit (17,6 %), reakcije, povezane z infundiranjem (15,9 %), bruhanje (15,6 %) in zmanjšanje telesne mase (14,5 %). Najpogostejši neželeni učinki stopnje ≥ 3 so bili anemija (5,6 %), hipertenzija (3,9 %), hiponatriemija (3,6 %), dispneja (3,5 %) in bolečine v trebuhu (2,6 %). Resni neželeni učinki so bili imunsko pogojeni neželeni učinki in učinki, povezani z infundiranjem. **Posebna navodila za shranjevanje:** Shranjujte v hladilniku (2 °C – 8 °C). Ne zamrzujte. Shranjujte v originalni ovojnini za zagotovitev zaščite pred svetlobo. **Pakiranje:** Velikost pakiranja je 1 steklena viala z 10 ml koncentrata v škatli. **Način in režim izdaje:** H-Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. **Imetnik dovoljenja za promet:** Merck Europe B.V., Amsterdam, Nizozemska.
Datum zadnje revizije besedila: oktober 2021

Pred predpisovanjem zdravila natančno preberite celoten Povzetek glavnih značilnosti zdravila.

O domnevnem neželenem učinku lahko poročate neposredno nacionalnemu centru za farmakovigilanco, na način, kot je objavljeno na spletni strani www.jazmp.si.

Samo za strokovno javnost.

Podrobnejše informacije so na voljo pri predstavniku imetnika dovoljenja za promet z zdravilom:
Merck d.o.o., Letališka cesta 29c, 1000 Ljubljana, tel.: 01 560 3810, faks: 01 560 3830, el. pošta: info@merck.si

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IMF durvalu

50 mg/ml koncent

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegov Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

Imfinzi 50 mg/ml koncentrat za raztopino za infundiranje

SESTAVA: 1 ml koncentrata za raztopino za infundiranje vsebuje 50 mg durvalumaba. Ena viala z 2,4 ml koncentrata vsebuje 120 mg durvalumaba. Ena viala z 10 ml koncentrata vsebuje 500 mg durvalumaba. **INDIKACIJE:** Zdravilo Imfinzi je kot samostojno zdravljenje indicirano za zdravljenje lokalno napredovalega, neoperabilnega nedrobnoceličnega raka pljuč (NSCLC – "non small cell lung cancer") pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 na tumorskih celicah in pri katerih bolezen ni napredovala po kemoradioterapiji na osnovi platine. Zdravilo Imfinzi je v kombinaciji z etopozidom in bodisi karboplatinom bodisi cisplatinom indicirano za prvo linijo zdravljenja odraslih z razsejanim drobnoceličnim rakom pljuč (ES SCLC – "extensive stage small cell lung cancer"). **ODMERJANJE IN NAČIN UPORABE:** Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje na področju zdravljenja raka. Bolnike z lokalno napredovalim nedrobnoceličnim rakom pljuč je treba za zdravljenje izbrati na podlagi izraženosti PD-L1, ugotovljene z validirano testno metodo. Odmerjanje: Priporočeni odmerek zdravila Imfinzi pri samostojnem zdravljenju je 10 mg/kg na 2 tedna ali 1500 mg na 4 tedne do napredovanja bolezni, nesprejemljivih toksičnih učinkov ali največ 12 mesecev . Bolniki s telesno maso 30 kg ali manj morajo prejemati odmerke na podlagi telesne mase, in sicer 10 mg/kg na 2 tedna ali 20 mg/kg na 4 tedne kot samostojno zdravljenje, dokler se telesna masa ne poveča na več kot 30 kg. V kombinaciji s kemoterapijo je priporočeni odmerek zdravila Imfinzi 1500 mg v kombinaciji s kemoterapijo na 3 tedne (21 dni) 4 cikluse in nato 1500 mg na 4 tedne kot samostojno zdravljenje. Zdravilo Imfinzi se uporablja v intravenski infuziji, ki traja 1 uro. Povečevanje ali zmanjševanje odmerka ni priporočljivo. Glede na individualno varnost in prenašanje je lahko potrebna odložitev odmerka ali prenehanje uporabe zdravila. V primeru domnevnih imunsko pogojenih neželenih učinkov je treba opraviti ustrezno ovrednotenje za potrditev etiologije oziroma izključitev druge etiologije. Glede na resnost neželenega učinka je treba prenehati uporabljati zdravilo IMFINZI in pričeti z dajanjem kortikosteroidov. Če se stanje ne izboljša ali se poslabša, pride v poštev povečanje odmerka kortikosteroidov in/ali dodatna uporaba sistemskih imunosupresivov. Po izboljšanju na ≤ 1. stopnjo je treba začeti s postopnim zmanjševanjem kortikosteroida in ga zmanjševati v obdobju vsaj 1 meseca. Po odložitvi uporabe je mogoče zdravilo Imfinzi znova začeti uporabljati v času 12 tednov, če se neželeni učinki izboljšajo na ≤ 1. stopnjo in je odmerek kortikosteroida zmanjšan na ≤ 10 mg prednizona ali ekvivalenta na dan. Zdravilo IMFINZI je treba dokončno ukiniti, če se imunsko pogojeni neželeni učinki 3. stopnje (močno izraženi) ponavljajo in pri katerih koli imunsko pogojenih neželenih učinkih 4. stopnje (življenjsko nevarni), razen pri endokrinopatijah, ki jih nadziramo z nadomestnimi hormoni. Pri ne imunsko pogojenih neželenih učinkih, v primeru 2. ali 3. stopnje izraženosti, odložite uporabo zdravila IMFINZI do izboljšanja neželenih učinkov na ≤ 1. stopnjo ali na izhodiščno raven. Z uporabo zdravila Imfinzi je treba prenehati v primeru neželenih učinkov 4. stopnje (razen v primeru laboratorijskih nepravilnosti 4. stopnje, pri katerih naj odločitev o prekinitvi uporabe zdravila temelji na spremljajočih kliničnih znakih oziroma simptomih in na klinični presoji zdravnika). Zdravilo Imfinzi je namenjeno za intravensko uporabo. Dati ga je treba kot raztopino za intravensko infundiranje v obdobju 1 ure. **KONTRAINDIKACIJE:** Preobčutljivost na učinkovino (učinkovine) ali katero koli pomožno snov. **OPOZORILA IN PREVIDNOSTNI UKREPI:** Za izboljšanje sledljivosti bioloških zdravil je treba jasno zabeležiti lastniško ime in številko serije uporabljenega zdravila. Imunsko pogojeni pnevmonitis: Pri bolnikih, ki so prejemali zdravilo Imfinzi, sta se pojavila imunsko pogojeni pnevmonitis ali interstICijska bolezen pljuč, opredeljeno kot potreba po uporabi sistemskih kortikosteroidov in brez jasne druge etiologije. Pri bolnikih, zdravljenih z radioterapijo pljuč, je pogost radiacijski pnevmonitis in klinična slika pnevmonitisa in radiacijskega pnevmonitisa je zelo podobna. V študiji PACIFIC sta se pri bolnikih, ki so opravili zdravljenje z najmanj 2 cikloma sočasne kemoradioterapije od 1 do 42 dni pred začetkom preizkušanja, pnevmonitis ali radiacijski pnevmonitis pojavila pri 161 (33,9 %) bolnikih v skupini z zdravilom Imfinzi in pri 58 (24,8 %) bolnikih v skupini s placebom, vključno s 3. stopnjo (3,4 % in 3,0 %) in 5. stopnjo (1,1 % in 1,7 %). Bolnike je treba spremljati glede znakov in simptomov pnevmonitisa ali radiacijskega pnevmonitisa. Imunsko pogojeni hepatitis: Pri bolnikih, ki so prejemali zdravilo Imfinzi, se je pojavil imunsko pogojeni hepatitis, opredeljen kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Imunsko pogojeni kolitis: Pri bolnikih, ki so prejemali zdravilo Imfinzi, sta se pojavila imunsko pogojeni kolitis ali driska, opredeljeno kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Imunsko pogojene endokrinopatije: Imunsko pogojeni hipotiroidizem, hipertiroidizem in tiroiditis: Pri bolnikih, ki so prejemali zdravilo Imfinzi, so se pojavili imunsko pogojeni hipotiroidizem, hipertiroidizem in tiroiditis; hipertiroidizmu lahko sledi hipotiroidizem. Bolnike je treba spremljati glede nenormalnih izvidov delovanje ščitnice pred zdravljenjem in redno med zdravljenjem ter kot je potrebno glede na klinično oceno. Imunsko pogojeni hipotiroidizem, hipertiroidizem in tiroiditis je treba obravnavati in ukrepati, kot je priporočeno v povzetku glavnih značilnosti zdravila. Imunsko pogojena adrenalna insuficienca: Pri bolnikih, ki so prejemali zdravilo Imfinzi, se je pojavila imunsko pogojena adrenalna insuficienca. Bolnike je treba spremljati glede kliničnih znakov in simptomov adrenalne insuficience. Imunsko pogojena sladkorna bolezen tipa 1: Pri bolnikih, ki so prejemali zdravilo Imfinzi, se je pojavila imunsko pogojena sladkorna bolezen tipa 1, ki sa lahko najprej kaže kot diabetična ketoacidoza, ki je lahko smrtno nevarna, če je dovolj zgodaj ne odkrijemo. Bolnike je treba spremljati glede kliničnih znakov in simptomov sladkorne bolezni tipa 1. Imunsko pogojeni hipofizitis/hipopituitarizem: Pri bolnikih, ki so prejemali zdravilo Imfinzi, sta se pojavila imunsko pogojena hipofizitis ali hipopituitarizem. Bolnike je treba spremljati glede kliničnih znakov in simptomov hipofizitisa ali hipopituitarizma. Imunsko pogojeni nefritis: Pri bolnikih, ki so prejemali zdravilo Imfinzi, se je pojavil imunsko pogojeni nefritis, opredeljen kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Imunsko pogojeni izpuščaj: Pri bolnikih, ki so prejemali zdravilo Imfinzi, se je pojavil imunsko pogojeni izpuščaj ali dermatitis (vključno s pemfigoidom), opredeljen kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Pri bolnikih, ki so bili zdravljeni z zaviralci PD-1, so poročali o pojavljanju Stevens-Johnsonovega sindroma ali toksične epidermalne nekrolize. Drugi imunsko pogojeni neželeni učinki: Glede na mehanizem delovanja zdravila Imfinzi se lahko pojavijo še drugi potencialno imunsko pogojeni učinki. Naslednji imunsko pogojeni neželeni učinki so bili opaženi pri bolnikih, ki so prejemali samostojno zdravljenje z zdravilom Imfinzi: miastenija gravis, miokarditis, miozitis, polimiozitis, meningitis, encefalitis, Guillain Barrějev sindrom, imunska trombocitopenija in neinfektivni cistitis. V programu kliničnih študij so pri bolnikih poročali o primerih pankreatitisa. Bolnike je treba spremljati glede znakov in simptomov in ukrepati, kot je priporočano za druge imunsko pogojene neželene učinke. Z infundiranjem povezane reakcije: Bolnike je treba spremljati glede znakov bolnikih, ki so prejemali zdravilo Imfinzi, so bil Bolniki, ki niso bili vključeni v klinična preizkušan naslednjimi značilnostmi: izhodiščno oceno zmo tirano avtoimunsko boleznijo v 2 letih pred za anamnezo hudih imunsko pogojenih neželenih nosupresijo, razen fiziološkega odmerka sistem ekvivalenta); neobvladanimi sočasnimi bolezni C ali HIV; bolniki, ko so prejeli živo oslabljeno cep Imfinzi ali v 30 dneh po začetku. Dokler takšni bolnikov uporabljati previdno ter po skrbnem in posameznega bolnika. Varnost sočasnega prof iom Imfinzi pri bolnikih z ES SCLC ni znana. **MI** Razen fizioloških odmerkov sistemskih kortikos pred uvedbo durvalumaba ni priporočljivo upor vov, kar lahko vplivajo na farmakodinamično a mogoče kortikosteroide ali druge imunosupresi za zdravljenje imunsko pogojenih neželenih učin kinetičnih (PK) študij medsebojnega delovanja z katabolizem beljakovin preko retikuloendotelijsk vanja, zato ni pričakovati presnovnih medsebolj bojna delovanja med durvalumabom in kemoter da sočasno zdravljenje z durvalumabom no v cisplatina. Poleg tega populacijska farmakokine rapijo ne vpliva pomembno na farmakokinetiko **NJE:** Ženske v rodni dobi morajo med zdravljenj odmerku durvalumaba uporabljati učinkovito k nosečnicah ni. Glede na mehanizem delovanja v alogenskem modelu nosečnosti pri miših je bil ča izgubo plodov. Pri nosečnici uporabljeni du uporabljati med nosečnostjo in pri ženskah v r med zdravljenjem in vsaj še 3 mesece po zadnj izloča v materinem mleku. Pri človeku protitele sorpcije in škode za novorojenčka ni znana. To izključiti. Odločiti se je treba, ali naj ženska preku bom oziroma sploh ne začne zdravljenja z njim, in koristi zdravljenja za žensko. Podatkov o mo živalih ni. **NEŽELENI UČINKI:** Ugotovitve o var meljijo na kumulativnih podatkih 3006 bolnikov: i v odmerku 10 mg/kg na 2 tedna ali v odmerku (> 10 %) so bili kašelj/produktivni kašelj (21,5 % temperatura (13,8 %), okužbe zgornjih dihal (13 in hipotiroidizem (10,1 %). Ugotovitve o varnosti jo na podatkih 265 bolnikov z SCLC. Zdravilo Im kombinaciji s kemoterapijo in nato pri samosto učinki (> 20 %) so bili nevtropenija (48,7 %), an alopecija (31,3 %), trombocitopenija (21,1 %) i nem zdravljenju: Zelo pogosti neželeni učinki: o ven kašelj, driska, bolečine v trebuhu, izpuščaj, leni učinki: pljučnica, zobne okužbe in okuž hipertiroidizem, pnevmonitis, disfonija, zvišan vrednosti alanin aminotransferaze, nočno znoje v krvi, disurija, periferni edemi, z infundiranjem adrenalna insuficienca, intersticijska bolezen Redki neželeni učinki: sladkorna bolezen tipa 1, astenija gravis, meningitis, miokarditis, pemfig Imfinzi v kombinaciji s kemoterapijo: Zelo pogos panija, levkopenija, zmanjšan apetit, kašelj/prod las, utrujenost. Pogosti neželeni učinki: okužbe ustnih mehkih tkiv, febrilna nevtropenija, pan adrenalna insuficienca, pnevmonitis, driska, bol tat aminotransferaze ali zvišanje vrednosti alani matitis, mialgija, zvišanje vrednosti kreatinina v neželeni učinki: gripa, sladkorna bolezen tipa **VSEBINA OVOJNINE:** 2,4 ml koncentrata v ste in sivo snemno aluminijsko zaporo; viala vsebuj ml koncentrata v steklani viali iz stekla tipa 1 z zaporo; viala vsebuje 500 mg durvalumaba. Pak **NAČIN IZDAJANJA ZDRAVILA:** H - Predpisov **DATUM REVIZIJA BESEDILA:** oktober 2021 (S **IMETNIK DOVOLJENJA ZA PROMET:** AstraZe

Pred predpisovanjem, prosimo, preberite cel
Datum priprave informacije: november 2021.
Dodatne informacije so na voljo pri družbi
AstraZeneca UK Limited, Podružnica v Sloveniji
Verovškova 55, Ljubljana.

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 ishemičnih možganskožilnih bolezni ter optimatizirati obvladovanje dejavnikov tveganja, kot so hipertenzija, diabetes ali dislipidemija, skladno s standardno oskrbo. 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. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** 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. **Plodnost, 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 je kontraindicirano pri nosečnicah in ženskah , ki bi lahko zanosile in se ne sme uporabljati med dojenjem. **Neželeni učinki:** Hipotiroidizem, zmanjšan apetit, hiperholesterolemija, hipertrigliceridemija, disgevzija, ishemične možganskožilne bolezni, konvulzije, ishemična bolezen srca, podaljšanje intervala QT, vročinski oblivi, hipertenzija, driska, kožni izpuščaj, srbenje, alopecija, 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 zadnje revizije besedila:** 18. november 2021

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-198062/231121

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BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

Inlyta 1 mg/3 mg/5 mg/7 mg filmsko obložene tablete
Sestava in oblika zdravila: Ena tableta vsebuje 1 mg, 3 mg, 5 mg oz. 7 mg aksitiniba. **Indikacije:** Zdravljenje napredovalega karcinoma ledvičnih celic (RCC) pri odraslih bolnikih, pri katerih predhodno zdravljenje s sunitinibom ali citokinom ni bilo uspešno. **Odmerjanje in način uporabe:** Zdravljenje mora izvajati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Priporočeni odmerek je 5 mg dvakrat na dan. Zdravljenje naj traja, dokler je mogoče opaziti klinično korist oz. do pojava nesprejemljive toksičnosti, ki je ni mogoče obvladovati s sočasno uporabljanimi zdravili ali prilagajanjem odmerka. Če bolnik bruha ali izpusti odmerek, ne sme vzeti dodatnega odmerka; naslednji predpisan odmerek je treba vzeti ob običajnem času. *Prilagajanja odmerka*: Pri bolnikih, ki aksitinib v začetnem odmerku 5 mg dvakrat na dan prenašajo brez neželenih učinkov > 2. stopnje dva tedna zapored, je odmerek mogoče zvečati na 7 mg dvakrat na dan, razen če je krvni tlak pri bolniku > 150/90 mmHg ali če jemlje antihipertenzive. Kasneje je z uporabo enakih meril pri bolnikih, ki prenašajo 7 mg dvakrat na dan, odmerek mogoče zvečati na največ 10 mg dvakrat na dan. Za obvladovanje nekaterih neželenih učinkov bo morda treba začasno ali trajno prekiniti zdravljenje in/ali zmanjšati odmerek na 3 mg dvakrat na dan in nato na 2 mg dvakrat na dan. Prilagajanje odmerka glede na bolnikovo starost, raso, spol ali telesno maso ni potrebno. *Sočasno zdravljenje z močnimi zaviralci CYP3A4/5:* Lahko zveča plazemske koncentracije aksitiniba. V primeru sočasne uporabe močnega zaviralca CYP3A4/5, je odmerek aksitiniba priporočljivo zmanjšati na približno polovico odmerka; morda bo potrebna začasna ali trajna prekinitev zdravljenja z aksitinibom. Če prekinemo sočasno uporabo močnega zaviralca, je treba razmisliti o vrnitvi na odmerek aksitiniba, ki je bil uporabljen pred uvedbo močnega zaviralca CYP3A4/5. *Sočasno zdravljenje z močnimi induktorji CYP3A4/5:* Lahko zmanjša plazemske koncentracije aksitiniba. V primeru sočasne uporabe močnega induktorja CYP3A4/5 je odmerek aksitiniba priporočljivo postopoma zvečati in bolnika skrbno nadzorovati glede pojava toksičnosti. Morda bo treba začasno ali trajno prekiniti zdravljenje in/ali zmanjšati odmerek aksitiniba. Če prekinemo sočasno uporabo močnega induktorja, je treba takoj začeti uporabljati odmerek aksitiniba, ki je bil uporabljen pred uvedbo močnega induktorja CYP3A4/5. *Okvara ledvic:* Prilagajanje odmerka ni potrebno; o uporabi pri bolnikih z očistkom kreatinina < 15 ml/min ni podatkov. *Okvara jeter:* Prilagajanje odmerka ni potrebno pri bolnikih z blago okvaro jeter (razred A po Child-Pughu). Zmanjšanje odmerka je priporočljivo pri bolnikih z zmerno okvaro jeter (razred B). Zdravila se ne sme uporabljati pri bolnikih s hudo okvaro jeter (razred C). *Pediatrična populacija*: Varnost in učinkovitost pri otrocih < 18 let nista bili dokazani; podatkov ni na voljo. *Način uporabe:* Peroralna uporaba. Tablete je treba pogoltniti cele, s kozarcem vode, dvakrat na dan, v približno 12-urnih časovnih presledkih, s hrano ali brez nje. **Kontraindikacije:** Preobčutljivost na aksitinib ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** *Dogodki srčnega popuščanja*: Poročali so o dogodkih srčnega popuščanja. Med zdravljenjem je treba redno spremljati znake ali simptome srčnega popuščanja. Obravnava dogodkov srčnega popuščanja lahko zahteva začasno ali stalno prekinitev zdravljenja z aksitinibom in/ali zmanjšanje odmerka. *Hipertenzija:* O hipertenziji so poročali zelo pogosto. Pred začetkom zdravljenja mora biti krvni tlak ustrezno urejen; bolnike je treba spremljati in po potrebi uporabiti standardno antihipertenzivno zdravljenje. V primeru trdovratne hipertenzije (kljub uporabi antihipertenzivov) je treba odmerek aksitiniba zmanjšati, pri hudi hipertenziji pa zdravljenje začasno prekiniti in ga ponovno uvesti z manjšim odmerkom, ko se krvni tlak normalizira. Pri hudi ali trdovratni arterijski hipertenziji in simptomih sindroma posteriorne reverzibilne encefalopatije je treba razmisliti o diagnostičnem slikanju možganov z uporabo magnetne resonance. *Motnje delovanja ščitnice*: Poročali so o primerih hipotiroidizma in, v manjšem obsegu, hipertiroidizma. Delovanje ščitnice je treba spremljati pred začetkom zdravljenja in v rednih časovnih presledkih med zdravljenjem. *Venski in arterijski embolični in trombotični dogodki:* Poročali so o venskih in arterijskih emboličnih in trombotičnih dogodkih. Previdna uporaba pri bolnikih s tveganjem za pojav teh dogodkov ali anamnezo teh dogodkov. *Zvišanje ravni hemoglobina ali hematokrita:* Med zdravljenjem lahko pride do zvišanj ravni hemoglobina ali hematokrita, njuno raven je treba spremljati pred začetkom zdravljenja in v rednih časovnih presledkih med zdravljenjem. *Krvavitve:* Poročali so o pojavu krvavitev. Pri bolnikih z znaki nezdravljenih možganskih metastaz ali nedavne aktivne krvavitve v prebavilih se zdravila ne sme uporabljati. Če je pri krvavitvi potreben zdravniški posег, je treba z odmerjanjem aksitiniba začasno prekiniti. *Anevrizme in arterijske disekcije:* Uporaba zaviralcev poti VEGF pri bolnikih s hipertenzijo ali brez nje lahko spodbudi nastanek anevrizem in/ali disekcij arterij. Pred uvedbo aksitiniba je treba to tveganje skrbno preučiti pri bolnikih z dejavniki tveganja, kot sta hipertenzija ali anamneza anevrizme. *Perforacija prebavil in nastanek fistule*: Poročali so o pojavu perforacij prebavil in fistul. Med zdravljenjem je potrebno redno spremljanje glede morebitnega pojava simptomov perforacije prebavil ali nastanka fistule. *Zapleti pri celjenju ran*: Zdravljenje z aksitinibom je treba prekiniti najmanj 24 ur pred načrtovanim kirurškim posegom; odločitev glede ponovne uvedbe zdravljenja po posegu mora temeljiti na klinični presoji ustreznosti celjenja rane. *Sindrom posteriorne reverzibilne encefalopatije (PRES)*: Poročali so o primerih PRES. Pri bolnikih z znaki ali simptomi PRES je treba zdravljenje začasno ali trajno prekiniti. Varnost ponovne uvedbe zdravljenja pri bolnikih, pri katerih je v preteklosti prišlo do PRES, ni znana. *Proteinurija:* Poročali so o proteinuriji, vključno s proteinurijo 3. in 4. stopnje izraženosti. Pred začetkom zdravljenja in v rednih časovnih presledkih med zdravljenjem je priporočljivo spremljanje glede pojava proteinurije; ob pojavu zmerne do hude proteinurije je treba zmanjšati odmerek ali začasno prekiniti zdravljenje. Zdravljenje je treba trajno prekiniti, če se pri bolniku pojavi nefrotski sindrom. *Neželeni učinki na jetra:* Zvišanja ravni ALT, AST in bilirubina v krvi. Pred začetkom zdravljenja in v rednih časovnih presledkih med njim je treba spremljati rezultate preiskav delovanja jeter. *Zdravilo vsebuje laktozo:* 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:** *Zaviralci CYP3A4/5:* Sočasna uporaba z močnimi zaviralci (npr. ketokonazol, itrakonazol, klaritromicin, eritomicin, atazanavir, indinavir, nefazodon, nelfinavir, ritonavir, sakvinavir in telitromicin) ter uživanje grenivk lahko zveča plazemske koncentracije aksitiniba. Priporočljiva je izbira sočasno uporabljanih zdravil, ki ne zavirajo ali minimalno zavirajo CYP3A4/5. Če je treba sočasno uporabljati močan zaviralec CYP3A4/5, je odmerek aksitiniba priporočljivo prilagoditi. *Zaviralci CYP1A2 in CYP2C19:* Zaradi tveganja, da se plazemske koncentracije aksitiniba povečajo, je potrebna previdnost. *Induktorji CYP3A4/5:* Sočasna uporaba aksitiniba z močnimi induktorji (npr. rifampicin, deksametazon, fenitoin, karbamazepin, rifabutin, rifapentin, fenobarbital in šentjanževka) lahko zmanjša plazemske koncentracije aksitiniba. Priporočljiva je izbira sočasno uporabljanih zdravil, ki ne inducirajo ali minimalno inducirajo CYP3A4/5. Če je treba sočasno uporabljati močan induktor CYP3A4/5, je odmerek aksitiniba priporočljivo prilagoditi. **Plodnost, nosečnost in dojenje:** Ne sme se uporabljati med nosečnostjo, razen če klinično stanje ženske zahteva zdravljenje s tem zdravilom. Ženske v rodni dobi morajo uporabljati kontracepcijo med zdravljenjem in še en teden po njem. V obdobju dojenja se ne sme uporabljati. Lahko neugodno vpliva na sposobnost razmnoževanja in plodnost pri ljudeh. **Vpliv na sposobnost vožnje in upravljanja strojev:** Ima blag vpliv na sposobnost vožnje in upravljanja strojev. Med zdravljenjem se lahko pojavijo učinki, kot je npr. omotica in/ali utrujenost. **Neželeni učinki:** Najpogostejši (≥ 20 %) neželeni učinki so bili driska, hipertenzija, utrujenost, zmanjšan apetit, navzea, zmanjšana telesna masa, hripavost, sindrom palmarno-plantarne eritrodisestezije (sindrom dlani-podplati), krvavitev, hipotiroidizem, bruhanje, proteinurija, kašelj in zaprtje. Ostali zelo pogosti (≥ 1/10 bolnikov) neželeni učinki so: glavobol, disgevzija, dispneja, bolečine v trebuhu, stomatitis, dispepsija, izpuščaj, suha koža, artralgija, bolečine v okončinah, astenija, vnetje sluznice. **Način in režim izdaje:** Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Izjemoma se lahko uporablja pri nadaljevanju zdravljenja na domu ob odpustu iz bolnišnice in nadaljnjem zdravljenju. **Imetnik dovoljenja za promet:** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgija. **Datum zadnje revizije besedila:** 29.07.2021

Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Literatura: 1. Melichar B, Poprach A, Kubackova K, et al. Efficacy and tolerability of axitinib in metastatic renal cell carcinoma (mRCC): Comparison of Czech clinical registry and AXIS trial data. ECC. 25–29 September 2015. Vienna, Austria. Poster: 2615. **2.** Matias M, Le Teuff G, Albiges L, et al. Real world prospective experience of axitinib in metastatic renal cell carcinoma in a large comprehensive cancer centre. Eur J Cancer. 2017;79:185–192. **3.** Rossetti S, Romano FJ, D'Aniello C, et al. Activity of second line axitinib in metastatic renal cell carcinom (mRCC) patients treated with sunitinib: Results from SAX Italian real world trial. J Clin Oncol. 2017;35(15_suppl):e16054. **4.** Povzetek glavnih značilnosti zdravila Inlyta, 29.7.2021.

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YERVOY 5 mg/ml koncentrat za raztopino za infundiranje (ipilimumab) Pred predpisovanjem zdravila, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila (SmPC).

SESTAVA ZDRAVILA: En ml koncentrata vsebuje 5 mg ipilimumaba. 10-ml viala vsebuje 50 mg ipilimumaba; 40-ml viala vsebuje 200 mg ipilimumaba. Na trgu morda ni vseh navedenih pakiranj. **TERAPEVTSKE INDIKACIJE:** Yervoy je **v monoterapiji** indiciran za zdravljenje napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih in mladostnikih, starih 12 let in starejših, **v kombinaciji z nivolumabom** pa za zdravljenje napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih. Yervoy je **v kombinaciji z nivolumabom** indiciran za prvo linijo zdravljenja odraslih z napredovalim karcinomom ledvičnih celic s srednje ugodnim ali slabim prognostičnim obetom, za prvo linijo zdravljenja odraslih z neoperabilnim malignim mezoteliomom plevre in za zdravljenje odraslih z rakom debelega črevesa in danke s pomanjkljivim popravljanjem neujemanja ali z visoko stopnjo mikrosatelitne nestabilnosti po predhodni kombinirani kemoterapiji na osnovi fluoropirimidina. Yervoy je **v kombinaciji z nivolumabom in 2 cikloma kemoterapije** na osnovi platine indiciran za prvo linijo zdravljenja metastatskega nedrobnoceličnega pljučnega raka pri odraslih s tumorji brez senzitizacijske mutacije EGFR ali translokacije ALK. **ODMERJANJE IN NAČIN UPORABE:** Zdravljenje mora uvesti in nadzirati zdravnik z izkušnjami pri zdravljenju raka. *YERVOY v monoterapiji*: **Melanom:** *Odrasli in mladostniki, stari 12 let in starejši:* Priporočeni odmerek za indukcijsko zdravljenje je 3 mg/kg v obliki 90-minutne i.v. infuzije, ki ga bolnik prejme na vsake 3 tedne, vsega skupaj 4 odmerke. Med indukcijskim zdravljenjem morajo bolniki glede na prenašanje zdravila prejeti vse 4 odmerke, ne glede na pojav novih lezij ali razrast obstoječih. *YERVOY v kombinaciji z nivolumabom:* **Melanom:** Priporočeni odmerek pri prvih 4 odmerkih je 3 mg/kg ipilimumaba v kombinaciji z 1 mg/kg nivolumaba, ki ju bolnik prejme i.v. vsake 3 tedne. Zdravljenje se nato nadaljuje z drugo fazo, v kateri bolnik prejema nivolumab v monoterapiji i.v. v odmerku bodisi 240 mg vsaka 2 tedna **ali** 480 mg vsake 4 tedne. **Karcinom ledvičnih celic in rak debelega črevesa in danke s pomanjkljivim popravljanjem neujemanja (dMMR) ali z visoko stopnjo mikrosatelitne nestabilnosti (MSI-H):** Priporočeni odmerek pri prvih 4 odmerkih 1 mg/kg ipilimumaba v kombinaciji s 3 mg/kg nivolumaba, ki ju bolnik prejme i.v. vsake 3 tedne. Zdravljenje se nato nadaljuje z drugo fazo, v kateri bolnik prejema nivolumab v monoterapiji i.v. v odmerku 240 mg vsaka 2 tedna **ali** 480 mg vsake 4 tedne (le pri zdravljenju karcinoma ledvičnih celic). Za priporočene odmerke in čase infundiranja pri i.v. aplikaciji ipilimumaba v kombinaciji z nivolumabom glejte celotni SmPC. **Maligni mezoteliom plevre:** Priporočeni odmerek je 1 mg/kg ipilimumaba, ki ga bolnik prejme vsakih 6 tednov v obliki 30-minutne i.v. infuzije, v kombinaciji z nivolumabom v odmerku 360 mg v obliki 30-minutne i.v. infuzije vsake 3 tedne. Pri bolnikih brez napredovanja bolezni zdravljenje traja do 24 mesecev. *YERVOY v kombinaciji z nivolumabom in kemoterapijo:* **Nedrobnocelični pljučni rak:** Priporočeni odmerek je 1 mg/kg ipilimumaba, ki ga bolnik prejme v obliki 30-minutne i.v. infuzije vsakih 6 tednov, v kombinaciji z nivolumabom v odmerku 360 mg v obliki 30-minutne i.v. infuzije vsake 3 tedne in kemoterapijo na osnovi platine vsake 3 tedne. Po dokončanju 2 ciklov kemoterapije se zdravljenje nadaljuje z ipilimumabom v odmerku 1 mg/kg, ki ga bolnik prejme i.v. vsakih 6 tednov, v kombinaciji z nivolumabom v odmerku 360 mg vsake 3 tedne. Zdravljenje je priporočljivo, dokler bolezen ne napreduje, se ne pojavijo nesprejemljivi toksični učinki ali do 24 mesecev pri bolnikih brez napredovanja bolezni. Glede navodil za trajno ukinitev zdravljenja ali zadržanja odmerkov glejte celotni SmPC. Način uporabe: Yervoy je namenjen za i.v. uporabo. Aplicirati ga je treba v obliki 30-minutne ali 90-minutne i.v. infuzije, odvisno od odmerka. Lahko se ga daje i.v. brez predhodnega redčenja ali pa se ga predhodno razredči z 9 mg/ml raztopino natrijevega klorida za injiciranje ali 50 mg/ml raztopino glukoze za injiciranje do koncentracije med 1 in 4 mg/ml. **Yervoya se ne sme dajati v obliki hitre i.v. ali bolus injekcije.** Pri uporabi v kombinaciji z nivolumabom ali v kombinaciji z nivolumabom in kemoterapijo je treba najprej aplicirati nivolumab, sledi aplikacija Yervoya, nato pa še kemoterapija na isti dan. Pri infundiranju vsakega zdravila je treba uporabiti drugo infuzijsko vrečko in filter. **KONTRAINDIKACIJE:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Yervoy se pri otrocih, mlajših od 12 let, ne sme uporabljati. Pri starejših in bolnikih z okvaro ledvic odmerka ni potrebno prilagajati. Pri bolnikih, ki imajo pred začetkom zdravljenja vrednosti aminotransferaze ≥ 5x ZNV ali bilirubina > 3x ZNV, je treba Yervoy uporabljati previdno. Pri uporabi ipilimumaba v kombinaciji z drugimi zdravili pred začetkom zdravljenja preberite tudi SmPC-je drugih zdravil. Pri uporabi nivolumaba v kombinaciji z ipilimumabom je bila pojavnost imunsko pogojenih neželenih učinkov večja kot pri uporabi nivolumaba v monoterapiji. Bolnike je treba kontinuirano nadzirati glede pojava neželenih učinkov za srce in pljuča, pa tudi glede kliničnih znakov, simptomov in laboratorijskih nepravilnosti, ki kažejo na motnje elektrolitov in dehidracijo. Bolnike je treba neprestano nadzirati (še vsaj do 5 mesecev po aplikaciji zadnjega odmerka), saj se neželeni učinki ipilimumaba v kombinaciji z nivolumabom lahko pojavijo kadarkoli, tudi po ukinitvi zdravljenja. Če se ne ugotovi drugačne etiologije, je treba drisko, pogostejše odvajanje blata, krvavo blato, zvišane vrednosti testov delovanja jeter, kožni izpuščaj in endokrinopatije obravnavati kot vnetne in povezane z uporabo ipilimumaba. Zgodnje odkritje in ustrezno ukrepanje sta nujna za zmanjšanje pojavnosti življenjsko nevarnih zapletov. V primeru hudih imunsko pogojenih neželenih učinkov bo morda potrebno zdravljenje z visokimi odmerki sistemskih kortikosteroidov z ali brez sočasnega dodatnega zdravljenja z imunosupresivi. Za ipilimumab specifične smernice za ukrepanje v primeru pojava imunsko pogojenih neželenih učinkov za zdravljenje v monoterapiji ali v kombinaciji z nivolumabom glejte celotni SmPC. Zdravilo vsebuje natrij, kar je potrebno upoštevati pri bolnikih, ki so na dieti z nadzorovanim vnosom natrija. Sočasna uporaba ipilimumaba in vemurafeniba ni priporočljiva. Pri uporabi ipilimumaba po predhodni uporabi vemurafeniba je potrebna previdnost. Yervoya ne uporabljajte pri nosečnicah, doječih materah in pri ženskah v rodni dobi, ki ne uporabljajo učinkovite kontracepcije, razen v primeru, ko klinična korist odtehta možno tveganje. **INTERAKCIJE:** Ipilimumab je humano monoklonsko protitelo, ki se ne presnavlja z encimi citokroma P450 (CYP) ali drugimi presnovnimi encimi. Uporabi sistemskih kortikosteroidov v izhodišču, pred začetkom zdravljenja z ipilimumabom, se je treba izogibati, saj lahko vplivajo na farmakodinamsko aktivnost in učinkovitost ipilimumaba. Sistemske kortikosteroide in druga imunosupresivna zdravila se lahko uporablja po začetku zdravljenja z ipilimumabom za zdravljenje imunsko pogojenih neželenih učinkov. Bolnike, ki potrebujejo sočasno zdravljenje z antikoagulanti, je treba skrbno nadzirati. **NEŽELENI UČINKI:** *Ipilimumab v monoterapiji (melanom)*: zelo pogosti (≥ 1/10): zmanjšanje apetita, driska, bruhanje, slabost, izpuščaj, srbenje, utrujenost, reakcija na mestu injiciranja, zvišana telesna temperatura; pogosti (≥ 1/100 do < 1/10): bolečina zaradi raka, anemija, limfopenija, hipopituitarizem (vključno s hipofizitisom), hipotiroidizem, dehidracija, hipokaliemija, zmedenost, periferna senzorična nevropatija, omotica, glavobol, letargija, zamegljen vid, bolečina v očesu, hipotenzija, zardevanje, vročinski oblivi, dispneja, kašelj, gastrointestinalna krvavitev, kolitis, zaprtost, gastroezofagealni refluks, bolečine v trebuhu, vnetje sluznic, nenormalno delovanje jeter, dermatitis, rdečina, vitiligo, urtikarija, ekcem, alopecija, nočno znojenje, suha koža, artralgija, mialgija, mišično-skeletna bolečina, mišični krči, mrzlica, astenija, edem, bolečina, gripi podobna bolezen, zvišanje vrednosti alanin-aminotransferaze, zvišanje vrednosti aspartat-aminotransferaze, zvišanje vrednosti alkalne fosfataze v krvi, zvišanje vrednosti bilirubina v krvi, zmanjšanje telesne mase; občasni (≥ 1/1.000 do < 1/100): sepsa, septični šok, okužba sečil, okužba dihal, paraneoplastični sindrom, hemolitična anemija, trombocitopenija, eozinofilija, nevtropenija, preobčutljivost, insuficienca nadledvične žleze, sekundarna insuficienca skorje nadledvične žleze, hipertiroidizem, hipogonadizem, hiponatriemija, alkaloza, hipofosfatemija, sindrom tumorske lize, hipokalciemija, spremembe duševnega stanja, depresija, zmanjšanje libida, Guillain-Barréjev sindrom, meningitis (aseptični), avtoimunska nevropatija osrednjega živčevja (encefalitis), sinkopa, nevropatija možganskih živcev, možganski edem, periferna nevropatija, ataksija, tremor, mioklonus, disartrija, uveitis, krvavitve v steklovino, iritis, očesni edem, blefaritis, zmanjšanje ostrine vida, občutek tujka v očesu, konjunktivitis, aritmija, atrijska fibrilacija, vaskulitis, angiopatija, periferna ishemija, ortostatska hipotenzija, odpoved dihanja, sindrom akutne dihalne stiske, infiltracija pljuč, pljučni edem, pljučnica, alergijski rinitis, perforacija v prebavilih, perforacija debelega črevesa, perforacija črevesa, peritonitis, gastroenteritis, divertikulitis, pankreatitis, enterokolitis, želodčna razjeda, razjeda debelega črevesa, stomatitis, ezofagitis, ileus, odpoved jeter, hepatitis, hepatomegalija, zlatenica, toksična epidermalna nekroliza, levkocitoklastični vaskulitis, luščenje kože, spremembe barve las, revmatična polimialgija, miozitis, artritis, mišična šibkost, odpoved ledvic, glomerulonefritis, avtoimunski nefritis, renalna tubularna acidoza, hematurija, neinfektivni cistitis, amenoreja, odpoved več organov, sindrom sistemskega vnetnega odziva, infuzijske reakcije, zvišanje vrednosti gama-glutamiltransferaze, zvišanje vrednosti kreatinina v krvi, zvišanje vrednosti tirotropina, zmanjšanje vrednosti kortizola v krvi, zmanjšanje vrednosti kortikotropina v krvi, zvišanje vrednosti lipaze, zvišanje vrednosti amilaze v krvi, pozitivna protijedrna protitelesa, zmanjšanje vrednosti testosterona v krvi; redki (≥ 1/10.000 do < 1/1.000): avtoimunsko vnetje ščitnice, vnetje ščitnice, miastenija gravis, Vogt-Koyanagi-Haradov sindrom, serozni odstop mrežnice, temporalni arteritis, proktitis, multiformni eritem, psoriaza, reakcija na zdravilo z eozinofilijo in sistemskimi simptomi (DRESS), polimiozitis, proteinurija, znižanje vrednosti tirotropina v krvi, znižanje vrednosti tiroksina, nenormalne vrednosti prolaktina v krvi; zelo redki (< 1/10.000); anafilaktična reakcija; neznana pogostnost (ni mogoče oceniti iz razpoložljivih podatkov): hemofagocitna limfohistiocitoza, zavrnitev presadka čvrstega organa, pemfigoid. *Ipilimumab v kombinaciji z nivolumabom:* **Melanom:** najpogostejši neželeni učinki (≥ 10 %) so bili naslednji: izpuščaj, utrujenost, driska, srbenje, navzea, zvišana telesna temperatura, zmanjšanje apetita, hipotiroidizem, kolitis, bruhanje, artralgija, bolečina v trebuhu, glavobol in dispneja. Večinoma so bili blagi do zmerni. **RCC in dMMR ali MSI-H CRC:** najpogostejši neželeni učinki (≥ 10 %) so bili: utrujenost, driska, mišično-skeletna bolečina, izpuščaj, srbenje, navzea, kašelj, zvišana telesna temperatura, bolečina v trebuhu, artralgija, zmanjšanje apetita, okužba zgornjih dihal, bruhanje, glavobol, dispneja, hipotiroidizem, zaprtost, edem (vključno s perifernim edemom), omotica, hipertiroidizem, suha koža in hipertenzija. Večina neželenih učinkov je bila blagih do zmernih. **MPM:** najpogostejši neželeni učinki (≥ 10 %) so bili: utrujenost, driska, izpuščaj, mišično-skeletna bolečina, navzea, zmanjšanje apetita, srbenje, zaprtost in hipotiroidizem. Večina neželenih učinkov je bila blagih do zmernih. *Ipilimumab v kombinaciji z nivolumabom in kemoterapijo:* najpogostejši neželeni učinki so bili naslednji: utrujenost, navzea, izpuščaj, driska, srbenje, zmanjšanje apetita, hipotiroidizem in bruhanje. Večina neželenih učinkov je bila blagih do zmernih. Za celoten seznam neželenih učinkov in podrobnejši opis imunsko pogojenih neželenih učinkov, prosimo, glejte celoten SmPC.

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.

IMETNIK DOVOLJENJA ZA PROMET Z ZDRAVILOM: Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irska. **PREDSTAVNIŠTVO IMETNIKA DOVOLJENJA ZA PROMET:** Swixx Biopharma d.o.o., Pot k sejmišču 35, 1231 Ljubljana - Črnuče. **NAČIN IN REŽIM IZDAJE:** H. **DATUM PRIPRAVE INFORMACIJ:** september 2021.

OPDIVO® 10 mg/ml koncentrat za raztopino za infundiranje (nivolumab) Pred predpisovanjem zdravila, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila (SmPC). **SESTAVA ZDRAVILA:** En ml koncentrata vsebuje 10 mg nivolumaba. Zdravilo je na voljo v viali s 4 ml koncentrata (40 mg nivolumaba), 10 ml koncentrata (100 mg nivolumaba) ali 24 ml koncentrata (240 mg nivolumaba). Na trgu morda ni vseh navedenih pakiranj. **TERAPEVTSKE INDIKACIJE:** Opdivo je v **monoterapiji ali kombinaciji z ipilimumabom** pri odraslih indiciran za zdravljenje napredovalega (neoperabilnega ali metastatskega) melanoma; **v kombinaciji z ipilimumabom** za: prvo linijo zdravljenja napredovalega karcinoma ledvičnih celic s srednje ugodnim ali slabim prognostičnim obetom, prvo linijo zdravljenja neoperabilnega malignega mezotelioma plevre, zdravljenje raka debelega črevesa in danke s pomanjkljivim popravljanjem neujemanja ali visoko stopnjo mikrosatelitne nestabilnosti po predhodni kombinirani kemoterapiji na osnovi fluoropirimidina; **v kombinaciji s kabozantinibom** za prvo linijo zdravljenja napredovalega karcinoma ledvičnih celic; **v monoterapiji** za: adjuvantno zdravljenje melanoma, ki se je razširil na bezgavke, ali za zdravljenje bolnikov z metastatsko boleznijo po popolni kirurški odstranitvi, zdravljenje lokalno napredovalega ali metastatskega nedrobnoceličnega pljučnega raka po predhodni kemoterapiji, zdravljenje napredovalega karcinoma ledvičnih celic po predhodnem zdravljenju, zdravljenje odraslih s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom po avtologni presaditvi matičnih celic (ASCT) in zdravljenju z brentuksimabom vedotinom, zdravljenje ponovljenega ali metastatskega ploščatoceličnega karcinoma glave in vratu, pri katerih je bolezen napredovala med zdravljenjem ali po zdravljenju na osnovi platine, zdravljenje lokalno napredovalega, neoperabilnega ali metastatskega urotelijskega karcinoma po neuspešnem predhodnem zdravljenju, ki je vključevalo platino, zdravljenje neoperabilnega, napredovalega, ponovljenega ali metastatskega ploščatoceličnega karcinoma požiralnika po predhodni kombinirani kemoterapiji na osnovi fluoropirimidina in platine, adjuvantno zdravljenje raka požiralnika ali ezofagogastričnega stika z ostankom bolezni po predhodni neoadjuvantni kemoradioterapiji; **v kombinaciji z ipilimumabom in 2 cikloma kemoterapije** na osnovi platine za prvo linijo zdravljenja metastatskega nedrobnoceličnega pljučnega raka s tumorji brez senzitizacijske mutacije EGFR ali translokacije ALK; **v kombinaciji s kombinirano kemoterapijo na osnovi fluoropirimidina in platine** za prvo linijo zdravljenja odraslih s HER2-negativnim, napredovalim ali metastatskim adenokarcinomom želodca, ezofagogastričnega stika ali požiralnika, pri katerih imajo tumorji ekspresijo PD-L1 s kombinirano pozitivno oceno. **ODMERJANJE IN NAČIN UPORABE:** Zdravljenje mora uvesti in nadzirati zdravnik z izkušnjami pri zdravljenju raka. Če je pri indikaciji navedeno, mora izbira bolnika za zdravljenje z Opdivom temeljiti na ekspresiji PD-L1 tumorja, kar je treba potrditi z validiranim testom. *Opdivo v monoterapiji:* Priporočeni odmerek Opdiva je 240 mg nivolumaba vsaka 2 tedna **ali** 480 mg vsake 4 tedne, odvisno od indikacije. Melanom (napredovali melanom ali adjuvantno zdravljenje) in Karcinom ledvičnih celic: 240 mg vsaka 2 tedna v obliki 30-minutne i.v. infuzije ali 480 mg vsake 4 tedne v obliki 60-minutne i.v. infuzije. Rak požiralnika ali ezofagogastričnega stika (adjuvantno zdravljenje): 240 mg vsaka 2 tedna v obliki 30 minutne i.v. infuzije ali 480 mg vsake 4 tedne v obliki 30 minutne i.v. infuzije prvih 16 tednov in nato 480 mg vsake 4 tedne v obliki 30 minutne i.v. infuzije. Nedrobnocelični pljučni rak, Klasični Hodgkinov limfom, Ploščatocelični karcinom glave in vratu, Urotelijski karcinom, Ploščatocelični karcinom požiralnika: 240 mg vsaka 2 tedna v obliki 30-minutne i.v. infuzije. Če je pri bolnikih z melanomom, karcinomom ledvičnih celic, rakom požiralnika ali ezofagogastričnega stika shemo zdravljenja z odmerkom 240 mg vsaka 2 tedna treba zamenjati s shemo zdravljenja z odmerkom 480 mg vsake 4 tedne, je prvi 480-mg odmerek treba aplicirati 2 tedna po zadnjem 240-mg odmerku. Če je shemo zdravljenja z odmerkom 480 mg vsake 4 tedne treba zamenjati s shemo zdravljenja z odmerkom 240 mg vsaka 2 tedna, je prvi 240 mg odmerek treba aplicirati 4 tedne po zadnjem 480-mg odmerku. *Opdivo v kombinaciji z ipilimumabom:* Melanom: Priporočeni odmerek je 1 mg/kg nivolumaba v kombinaciji s 3 mg/kg ipilimumaba, ki ju bolnik prejme i.v. vsake 3 tedne, in sicer prve 4 odmerke. Zdravljenje se nato nadaljuje z drugo fazo, v kateri bolnik prejema nivolumab v monoterapiji i.v. v odmerku 240 mg vsaka 2 tedna **ali** 480 mg vsake 4 tedne. V fazi zdravljenja v monoterapiji je prvi odmerek nivolumaba treba aplicirati: 3 tedne po zadnjem odmerku kombinacije nivolumaba in ipilimumaba, če se uporablja odmerek 240 mg vsaka 2 tedna; ali 6 tednov po zadnjem odmerku kombinacije nivolumaba in ipilimumaba, če se uporablja odmerek 480 mg vsake 4 tedne. Maligni mezoteliom plevre: Priporočeni odmerek nivolumaba je 360 mg, ki ga bolnik prejme vsake 3 tedne v obliki 30-minutne i.v. infuzije, v kombinaciji z ipilimumabom v odmerku 1 mg/kg, ki pa ga bolnik prejme v obliki 30-minutne i.v. infuzije vsakih 6 tednov. Pri bolnikih brez napredovanja bolezni zdravljenje traja do 24 mesecev. Karcinom ledvičnih celic in rak debelega črevesa in danke s pomanjkljivim popravljanjem neujemanja (dMMR) ali z visoko stopnjo mikrosatelitne nestabilnosti (MSI-H): Priporočeni odmerek je 3 mg/kg nivolumaba v kombinaciji z 1 mg/kg ipilimumaba, ki ju bolnik prejme i.v. vsake 3 tedne, in sicer prve 4 odmerke. Zdravljenje se nato nadaljuje z nivolumabom v monoterapiji i.v. v odmerku 240 mg vsaka 2 tedna ali odmerku 480 mg vsake 4 tedne (le pri zdravljenju karcinoma ledvičnih celic). V fazi zdravljenja v monoterapiji je 1. odmerek nivolumaba treba aplicirati: 3 tedne po zadnjem odmerku kombinacije nivolumaba in ipilimumaba, če se uporablja odmerek 240 mg vsaka 2 tedna; ali 6 tednov po zadnjem odmerku kombinacije nivolumaba in ipilimumaba, če se uporablja odmerek 480 mg vsake 4 tedne (le pri zdravljenju karcinoma ledvičnih celic). *Opdivo v kombinaciji s kabozantinibom:* Karcinom ledvičnih celic: Priporočeni odmerek nivolumaba je 240 mg, ki ga bolnik prejme i.v. vsaka 2 tedna, ali 480 mg, ki ga bolnik prejme i.v. vsake 4 tedne, v kombinaciji s kabozantinibom v odmerku 40 mg, ki ga bolnik jemlje peroralno vsak dan. *Opdivo v kombinaciji z ipilimumabom in kemoterapijo:* Nedrobnocelični pljučni rak: Priporočeni odmerek je 360 mg nivolumaba, ki ga bolnik prejme v obliki 30-minutne i.v. infuzije vsake 3 tedne, v kombinaciji z ipilimumabom v odmerku 1 mg/kg v obliki 30-minutne i.v. infuzije vsakih 6 tednov in kemoterapijo na osnovi platine vsake 3 tedne. Po dokončanju 2 ciklov kemoterapije se zdravljenje nadaljuje z nivolumabom v odmerku 360 mg, ki ga bolnik prejme i.v. vsake 3 tedne, v kombinaciji z ipilimumabom v odmerku 1 mg/kg vsakih 6 tednov. Zdravljenje je priporočljivo, dokler bolezen ne napreduje, se ne pojavijo nesprejemljivi toksični učinki ali do 24 mesecev pri bolnikih brez napredovanja bolezni. *Opdivo v kombinaciji s kemoterapijo:* Adenokarcinom želodca, ezofagogastričnega stika ali požiralnika: Priporočeni odmerek je 360 mg nivolumaba, ki ga bolnik prejme v obliki 30-minutne i.v. infuzije v kombinaciji s kemoterapijo na osnovi fluoropirimidina in platine vsake 3 tedne ali 240 mg nivolumaba, ki ga bolnik prejme v obliki 30-minutne i.v. infuzije v kombinaciji s kemoterapijo na osnovi fluoropirimidina in platine vsaka 2 tedna. Zdravljenje z nivolumabom je priporočljivo dokler bolezen ne napreduje, se ne pojavijo nesprejemljivi toksični učinki ali do 24 mesecev pri bolnikih brez napredovanja bolezni. *Trajanje zdravljenja:* Zdravljenje z Opdivom mora trajati, dokler je prisotna klinična korist oziroma dokler bolnik zdravljenje prenaša (in najdaljši čas zdravljenja, če je le ta pri indikaciji posebej naveden). Pri adjuvantnem zdravljenju sme zdravljenje z Opdivom trajati največ 12 mesecev. Pri zdravljenju z Opdivom v kombinaciji s kabozantinibom mora zdravljenje z Opdivom trajati dokler bolezen ne napreduje, se ne pojavijo nesprejemljivi toksični učinki ali do 24 mesecev pri bolnikih brez napredovanja bolezni. Zdravljenje s kabozantinibom se mora nadaljevati dokler bolezen ne napreduje ali se ne pojavijo nesprejemljivi toksični učinki. Glejte SmPC za kabozantinib. Poročali so o atipičnih odzivih (npr. prehodno povečanje velikosti tumorja ali pojav manjših novih sprememb na začetku zdravljenja v prvih nekaj mesecih, nato pa je sledilo zmanjšanje tumorja). Pri klinično stabilnih bolnikih z znaki napredovanja bolezni na začetku zdravljenja, je zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom priporočljivo nadaljevati, dokler se napredovanje bolezni ne potrdi. Povečanje ali zmanjšanje odmerka Opdiva pri zdravljenju v monoterapiji ali kombinaciji z drugimi zdravili ni priporočljivo. Na osnovi varnosti ali prenašanja zdravila pri posameznem bolniku bo morda potrebno odmerek aplicirati z zamikom ali zdravljenje ukiniti. Glede smernic za trajno ukinitev zdravljenja ali zadržanje odmerka ali zdravljenje imunsko pogojenih neželenih učinkov glejte celoten SmPC. Pri uporabi nivolumaba v kombinaciji z drugimi zdravili za odmerjanje drugih zdravil glejte ustrezen SmPC. Bolniki, ki se zdravijo z Opdivom, morajo prejeti opozorilno kartico za bolnika. Bolnike je treba seznaniti s tveganji, povezanimi z zdravljenjem z Opdivom. Pri uporabi Opdiva v kombinaciji z ipilimumabom je treba v primeru zadržanja aplikacije enega zdravila zadržati tudi aplikacijo drugega zdravila. Če se po prekinitvi zdravljenje nadaljuje, je treba kombinirano zdravljenje ali zdravljenje z Opdivom v monoterapiji nadaljevati na osnovi ocene pri posameznem bolniku. Kadar se Opdivo uporablja v kombinaciji s kemoterapijo, za odmerjanje drugih zdravil, ki se jih uporablja v kombinaciji, glejte ustrezen SmPC. Povečanje/zmanjšanje odmerka Opdiva ni priporočljivo. Če se zdravljenje s katerim koli zdravilom zadrži, se zdravljenje z drugimi zdravili lahko nadaljuje. Če se po prekinitvi zdravljenja, zdravljenje nadaljuje, je treba kombinirano zdravljenje, zdravljenje z Opdivo v monoterapiji ali zdravljenje samo s kemoterapijo nadaljevati na osnovi ocene pri posameznem bolniku. Če se Opdivo uporablja v kombinaciji s kabozantinibom, se prilagoditve zdravljenja nanašajo tudi na Opdivo. Za ukrepe v primeru zvišanja vrednosti jetrnih encimov pri bolnikih z RCC, ki se zdravijo z Opdivom v kombinaciji s kabozantinibom, prosimo, glejte SmPC. *Pediatrična populacija:* Varnost in učinkovitost Opdiva pri otrocih, mlajših od 18 let, nista bili dokazani. *Starostniki:* Odmerka ni treba prilagajati. *Okvara ledvic:* Pri bolnikih z blago ali zmerno okvaro ledvic odmerka ni treba prilagajati. Pri bolnikih s hudo okvaro ledvic je na voljo premalo podatkov. *Okvara jeter:* Pri bolnikih z blago okvaro jeter odmerka ni treba prilagajati. Pri bolnikih z zmerno ali hudo okvaro jeter je treba Opdivo uporabljati previdno. Način uporabe: Opdivo je namenjen le za i.v. uporabo. Aplicirati ga je treba v obliki 30-minutne ali 60-minutne i.v. infuzije, odvisno od odmerka. Zdravilo je treba infundirati preko sterilnega, nepirogenega linijskega filtra, ki minimalno veže proteine, z velikostjo por 0,2-1,2 µm. Zdravila se ne sme aplicirati v obliki hitre i.v. ali bolus injekcije. Opdiva se ne sme infundirati sočasno z drugimi zdravili preko iste intravenske linije. Celotni potrebni odmerek Opdiva se lahko infundira neposredno v obliki raztopine s koncentracijo 10 mg/ml ali pa se ga predhodno razredči z 0,9-% (9 mg/ml) raztopino natrijevega klorida za injiciranje ali s 5-% (50 mg/ml) raztopino glukoze za injiciranje. Pri uporabi zdravila v kombinaciji z ipilimumabom in/ali kemoterapijo je treba najprej aplicirati Opdivo, sledi aplikacija ipilimumaba (če je predvidena), nato pa še kemoterapija na isti dan. Pri infundiranju vsakega zdravila je treba uporabiti drugo infuzijsko vrečko in filter. **KONTRAINDIKACIJE:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Vrednotenje statusa PD-L1: Pri vrednotenju statusa PD-L1 tumorja je pomembno, da se uporabi dobro validirano in robustno metodologijo. Imunsko pogojeni neželeni učinki: Pri uporabi nivolumaba v kombinaciji z drugimi zdravili pred začetkom zdravljenja preberite tudi SmPC-je drugih zdravil. Pri uporabi nivolumaba v kombinaciji z ipilimumabom je bila pojavnost imunsko pogojenih neželenih učinkov večja kot pri uporabi nivolumaba v monoterapiji. Pri uporabi Opdiva v kombinaciji s kabozantinibom je bila pogostnost imunsko pogojenih neželenih učinkov podobna kot pri uporabi nivolumaba v monoterapiji. Smernice za ukrepanje v primeru pojava imunsko pogojenih neželenih učinkov veljajo tudi pri uporabi Opdiva v kombinaciji, razen kadar je posebej navedeno drugače. Večina imunsko pogojenih neželenih učinkov se je izboljšala ali izzvenela z ustreznim zdravljenjem, vključno z uvedbo kortikosteroidov, in prilagoditvami zdravljenja. Možen je tudi sočasen pojav imunsko pogojenih neželenih učinkov, ki prizadenejo več kot le en organski sistem. Pri kombiniranem zdravljenju so poročali tudi o neželenih učinkih za srce in pljuča, vključno s pljučno embolijo. Bolnike je treba kontinuirano nadzirati glede pojava neželenih učinkov za srce in pljuča, pa tudi glede kliničnih znakov, simptomov in laboratorijskih nepravilnosti, ki kažejo na motnje elektrolitov in dehidracijo, pred uvedbo zdravljenja in periodično med zdravljenjem. V primeru pojava življenje ogrožajočih ali ponovitve hudih neželenih učinkov za srce in pljuča je treba zdravljenje z nivolumabom v kombinaciji z ipilimumabom ukiniti. Bolnike je treba neprestano nadzirati (vsaj do 5 mesecev po zadnjem odmerku), saj se neželeni učinki nivolumaba ali nivolumaba v kombinaciji z ipilimumabom lahko pojavijo med zdravljenjem ali po ukinitvi zdravljenja. Na osnovi resnosti neželenega učinka je treba zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom zadržati in uvesti zdravljenje s kortikosteroidi. Če se za zdravljenje neželenega učinka uporabi imunosupresivno zdravljenje s kortikosteroidi, je treba po izboljšanju uvesti vsaj 1-mesečno postopno zmanjševanje odmerka. Pri hitrem zmanjševanju odmerka se neželeni učinek lahko poslabša ali ponovi. Če se stanje kljub uporabi kortikosteroida poslabša ali ne izboljša, je treba dodatno uvesti še nekortikosteroidno imunosupresivno zdravljenje. Dokler bolnik prejema imunosupresivne odmerke kortikosteroidov ali drugih zdravil za zaviranje imunske odzivnosti, se zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom ne sme nadaljevati. Pri bolnikih, ki se zdravijo z zdravili za zaviranje imunske odzivnosti, je treba profilaktično uporabljati antibiotike za preprečevanje oportunističnih okužb. Če se kateri koli resni imunsko pogojeni neželeni učinek ponovi, ali pojavi kateri koli resni imunsko pogojeni neželeni učinek, ki ogrozi življenje, je treba zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom trajno ukiniti. *Imunsko pogojeni pnevmonitis:* Bolnike je treba nadzirati glede pojava znakov in simptomov pljučnice, kot so radiografske spremembe, dispneja in hipoksija. *Imunsko pogojeni kolitis:* Bolnike je treba nadzirati glede pojava driske in dodatnih simptomov kolitisa, kot so bolečina v trebuhu in sluz ali kri v blatu. Poročali so o okužbi/reaktivaciji okužbe s citomegalovirusom. Za izključitev okužb in drugih vzrokov driske je treba izvesti ustrezne laboratorijske teste in dodatne preiskave. Ob potrditvi imunsko pogojenega kolitisa, neodzivnega na kortikosteroide, je treba razmisliti o dodatku alternativnega zaviralca imunske odzivnosti k zdravljenju s kortikosteroidi ali zamenjavi kortikosteroidnega zdravljenja. *Imunsko pogojeni hepatitis:* Bolnike je treba nadzirati glede pojava znakov in simptomov hepatitisa, kot so zvišanje vrednosti aminotransferaz in skupnega bilirubina. *Imunsko pogojeni nefritis in okvara delovanja ledvic:* Bolnike je treba nadzirati glede pojava znakov in simptomov nefritisa ali okvare delovanja ledvic. Večina bolnikov je imela le asimptomatsko zvišano vrednost serumskega kreatinina. *Imunsko pogojene endokrinopatije:* Bolnike je treba nadzirati glede pojava kliničnih znakov in simptomov endokrinopatij, hiperglikemije in sprememb delovanja ščitnice (ob uvedbi zdravljenja, periodično med zdravljenjem in kot je indicirano na osnovi kliničnega pregleda). Pri bolnikih se lahko pojavijo utrujenost, glavobol, spremembe duševnega stanja, bolečina v trebuhu, neobičajno odvajanje blata in hipotenzija ali nespecifični simptomi, ki lahko spominjajo na druge vzroke, kot so zasevki v možganih ali osnovna bolezen. Če se ne ugotovi drugačne etiologije, je treba znake in simptome endokrinopatij obravnavati kot imunsko pogojene. *Imunsko pogojeni neželeni učinki na kožo:* V primeru hudega izpuščaja je treba uvesti zdravljenje z visokim odmerkom kortikosteroidov. V primeru pojava simptomov ali znakov SJS ali TEN je treba zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom ukiniti, bolnika pa napotiti k ustreznemu specialistu na nadaljnje preiskave in zdravljenje. Če se med zdravljenjem z nivolumabom pri bolniku pojavi SJS ali TEN, je zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom priporočljivo trajno ukiniti. Pri bolnikih z resnimi ali smrtno nevarnimi kožnimi neželenimi učinki pri predhodnem zdravljenju raka z drugimi zdravili za imunsko stimulacijo je treba možnost uporabe nivolumaba previdno pretehtati. *Drugi imunsko pogojeni neželeni učinki,* o katerih so poročali pri bolnikih, ki so se v kliničnih preskušanjih zdravili z nivolumabom v monoterapiji ali nivolumabom v kombinaciji z ipilimumabom v različnih odmerkih in zaradi različnih vrst tumorjev: pankreatitis, uveitis, demielinizacija, avtoimunska nevropatija (vključno s parezo obraznega in abducentnega živca), Guillain-Barréjev sindrom, miastenija gravis, miastenijski sindrom, aseptični meningitis, encefalitis, gastritis, sarkoidoza, duodenitis, miozitis, miokarditis in rabdomioliza. V obdobju trženja zdravila so poročali o primerih sindroma Vogt-Koyanagi-Harada, hipoparatiroidizma in neinfektivnega cistitisa. Na osnovi resnosti neželenega učinka je treba zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom zadržati in uvesti zdravljenje s kortikosteroidi. Po izboljšanju in postopnem zmanjšanju odmerka kortikosteroida se zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom lahko nadaljuje. Če se kateri koli resni imunsko pogojeni neželeni učinek ponovi, ali pojavi kateri koli resni imunsko pogojeni neželeni učinek, ki ogrozi življenje, je treba zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom trajno ukiniti. V primeru pojava znakov in simptomov toksičnosti za mišice je treba bolnika skrbno nadzirati in ga brez odlašanja napotiti k ustreznemu specialistu. Na osnovi resnosti toksičnosti za mišice je treba zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom zadržati ali ukiniti in uvesti ustrezno zdravljenje. Pri diagnostiki miokarditisa je potrebna velika mera previdnosti. Bolnike s srčnimi ali srčno-pljučnimi simptomi je treba ovrednotiti glede možnega miokarditisa. V primeru suma na miokarditis je treba takoj uvesti zdravljenje z visokimi odmerki kortikosteroidov, se nemudoma posvetovati s kardiologom in opraviti diagnostične preiskave v skladu s trenutnimi kliničnimi smernicami. Če se diagnoza miokarditisa potrdi, je treba zdravljenje z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom zadržati ali trajno ukiniti. Zdravljenje z nivolumabom lahko poveča tveganje za zavrnitev pri prejemnikih presadkov čvrstih organov. Hemofagocitno limfohistiocitozo (HLH) so opazili pri zdravljenju z nivolumabom v monoterapiji in v kombinaciji z ipilimumabom. Pri zdravljenju z nivolumabom v monoterapiji ali v kombinaciji z ipilimumabom je potrebna previdnost. Če je HLH potrjena, je treba zdravljenje z nivolumabom v monoterapiji ali v kombinaciji z ipilimumabom prekiniti in uvesti zdravljenje za HLH. Infuzijske reakcije: V primeru pojava hude ali življenje ogrožajoče infuzijske reakcije je treba infundiranje nivolumaba ali nivolumaba v kombinaciji z ipilimumabom prekiniti in uvesti ustrezno zdravljenje. Bolniki z blago ali zmerno infuzijsko reakcijo se lahko zdravijo z nivolumabom ali nivolumabom v kombinaciji z ipilimumabom, vendar pa jih je med infundiranjem treba skrbno nadzirati, za preprečevanje infuzijskih reakcij pa uporabiti premedikacijo v skladu z lokalnimi smernicami. Za bolezen specifični previdnostni ukrepi: Glejte celoten SmPC glede stanja bolnikov pri posamezni indikaciji, ki so jih iz kliničnih preskušanj izključili ali pri katerih so potrebni za bolezen specifični previdnostni ukrepi. Pri teh skupinah bolnikov je potrebna posebna previdnost. Pri bolnikih, ki so na dieti z nadzorovanim vnosom natrija, je treba upoštevati, da Opdivo vsebuje natrij. Nosečnost in dojenje: Uporaba nivolumaba ni priporočljiva pri nosečnicah in ženskah v rodni dobi, ki ne uporabljajo učinkovite kontracepcije, razen v primeru, ko klinična korist odtehta možno tveganje. Učinkovito kontracepcijo je treba uporabljati še vsaj 5 mesecev po zadnjem odmerku nivolumaba. Ni znano, ali se nivolumab izloča v materino mleko. Odločiti se je treba med prenehanjem dojenja in prenehanjem zdravljenja z nivolumabom, pri čemer je treba pretehtati prednosti dojenja za otroka in prednosti zdravljenja za mater. **INTERAKCIJE:** Nivolumab je humano monoklonsko protitelo, zato ni pričakovati, da bi zaviranje ali indukcija presnovnih encimov, zaradi sočasne uporabe drugih zdravil, vplivala na farmakokinetiko nivolumaba. Pred uvedbo zdravljenja z nivolumabom se je treba izogniti uporabi sistemskih kortikosteroidov in drugih zdravil za zaviranje imunske odzivnosti zaradi njihovega možnega vpliva na farmakodinamično aktivnost. Po uvedbi zdravljenja z nivolumabom pa se sistemske kortikosteroide in druga zdravila za zaviranje imunske odzivnosti lahko uporablja za zdravljenje imunsko pogojenih neželenih učinkov. Zdravljenje z nivolumabom lahko poveča tveganje za hudo GVHD in smrt pri bolnikih, ki so imeli predhodno alogensko HSCT, predvsem tistih z GVHD v anamnezi. Pri teh bolnikih je potrebno ovrednotiti razmerje med možno koristjo in tveganjem zdravljenja z nivolumabom. **NEŽELENI UČINKI:** *Nivolumab:* zelo pogosti (≥ 1/10): okužba zgornjih dihal, zmanjšanje apetita, glavobol, dispneja, kašelj, driska, bruhanje, navzea, bolečina v trebuhu, zaprtost, izpuščaj, srbenje, mišično-skeletna bolečina, artralgija, utrujenost, zvišana telesna temperatura, edem, limfopenija, hiperglikemija, anemija, zvišanje vrednosti AST, hiponatriemija, hipoalbuminemija, zvišanje vrednosti alkalne fosfataze, zvišanje vrednosti ALT, zvišanje vrednosti lipaze, hiperkaliemija, zvišanje vrednosti amilaze, hipokalciemija, levkopenija, hipomagneziemija, nevtropenija, trombocitopenija, hipokaliemija, hipoglikemija, hiperkalciemija; pogosti (≥ 1/100 do < 1/10): pljučnica, bronhitis, infuzijska reakcija, preobčutljivost (vključno z anafilaktično reakcijo), hipotiroidizem, hipertiroidizem, tiroiditis, dehidracija, periferna nevropatija, omotica, zamegljen vid, suhe oči, tahikardija, atrijska fibrilacija, hipertenzija, pnevmonitis, plevralni izliv, kolitis, stomatitis, suha usta, vitiligo, suha koža, eritem, alopecija, artritis, odpoved ledvic (vključno z akutno odpovedjo ledvic), bolečina, bolečina v prsnem košu, zvišanje vrednosti skupnega bilirubina, hipernatriemija, hipermagneziemija, zmanjšanje telesne mase; občasni (≥ 1/1.000 do < 1/100): eozinofilija, sarkoidoza, insuficienca nadledvičnih žlez, hipopituitarizem, hipofizitis, diabetes, metabolična acidoza, polinevropatija, avtoimunska nevropatija (vključno s parezo obraznega in abducentnega živca), uveitis, bolezni perikardija, aritmija (vključno z ventrikularno aritmijo), pljučni infiltrati, pankreatitis, gastritis, hepatitis, holestaza, multiformni eritem, luskavica, rozacea, urtikarija, revmatična polimialgija, tubulointersticijski nefritis; redki (≥ 1/10.000 do < 1/1.000): aseptični meningitis, histiocitni nekrotizirajoči limfadenitis (Kikuchijev limfadenitis), diabetična ketoacidoza, hipoparatiroidizem, Guillain-Barréjev sindrom, demielinizacija, miastenijski sindrom, encefalitis, miokarditis, vaskulitis, razjeda dvanajstnika, toksična epidermalna nekroliza, Stevens-Johnsonov sindrom, Sjogrenov sindrom, miopatija, miozitis (vključno s polimiozitisom), rabdomioliza, neinfektivni cistitis. Za seznam neželenih učinkov neznane pogostnosti, prosimo, glejte celoten SmPC. *Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg) pri zdravljenju RCC in dMMR ali MSI H CRC:* zelo pogosti (≥ 1/10): okužba zgornjih dihal, hipotiroidizem, hipertiroidizem, zmanjšanje apetita, glavobol, omotica, hipertenzija, dispneja, kašelj, driska, bruhanje, navzea, bolečina v trebuhu, zaprtost, izpuščaj, srbenje, suha koža, mišično-skeletna bolečina, artralgija, utrujenost, zvišana telesna temperatura, edem (vključno s perifernim edemom), zvišanje vrednosti AST, zvišanje vrednosti ALT, zvišanje vrednosti skupnega bilirubina, zvišanje vrednosti alkalne fosfataze, zvišanje vrednosti lipaze, zvišanje vrednosti amilaze, zvišanje vrednosti kreatinina, hiperglikemija, hipoglikemija, limfopenija, levkopenija, nevtropenija, trombocitopenija, anemija, hiperkalciemija, hipokalciemija, hiperkaliemija, hipokaliemija, hipomagneziemija, hiponatriemija; pogosti (≥ 1/100 do < 1/10): pljučnica, bronhitis, konjunktivitis, infuzijska reakcija, preobčutljivost, insuficienca nadledvičnih žlez, hipofizitis, tiroiditis, diabetes, dehidracija, periferna nevropatija, zamegljen vid, tahikardija, pnevmonitis, plevralni izliv, kolitis, stomatitis, pankreatitis, suha usta, gastritis, hepatitis, eritem, alopecija, urtikarija, artritis, mišični krči, mišična šibkost, odpoved ledvic (vključno z akutno odpovedjo ledvic), bolečina, bolečina v prsnem košu, mrzlica, hipermagneziemija, hipernatriemija, zmanjšanje telesne mase; občasni (≥ 1/1.000 do < 1/100): aseptični meningitis, eozinofilija, sarkoidoza, diabetična ketoacidoza, hipopituitarizem, metabolična acidoza, polinevropatija, avtoimunska nevropatija (vključno s parezo obraznega in abducentnega živca), miastenija gravis, encefalitis, uveitis, aritmija (vključno z ventrikularno aritmijo), miokarditis, Stevens-Johnsonov sindrom, vitiligo, multiformni eritem, psoriaza, revmatična polimialgija, miozitis (vključno s polimiozitisom), rabdomioliza, tubulointersticijski nefritis, neinfektivni cistitis. Za seznam neželenih učinkov neznane pogostnosti, prosimo, glejte celoten SmPC. *Nivolumab (3 mg/kg) + ipilimumab (1 mg/kg) pri zdravljenju MPM:* zelo pogosti (≥ 1/10): hipotiroidizem, zmanjšanje apetita, driska, navzea, zaprtost, izpuščaj, srbenje, mišično-skeletna bolečina, utrujenost, zvišanje vrednosti AST, zvišanje vrednosti ALT, zvišanje vrednosti alkalne fosfataze, zvišanje vrednosti lipaze, zvišanje vrednosti amilaze, zvišanje vrednosti kreatinina, hiperglikemija, limfopenija, anemija, hiperkalciemija, hipokalciemija, hiperkaliemija, hipokaliemija, hiponatriemija, hipomagneziemija; pogosti (≥ 1/100 do < 1/10): infuzijska reakcija, preobčutljivost, hipertiroidizem, insuficienca nadledvičnih žlez, hipofizitis, hipopituitarizem, pnevmonitis, kolitis, pankreatitis, hepatitis, artritis, akutna odpoved ledvic, odpoved ledvic, zvišanje vrednosti skupnega bilirubina, hipoglikemija, levkopenija, nevtropenija, trombocitopenija, hipernatriemija, hipermagneziemija; občasni (≥ 1/1.000 do < 1/100): tiroiditis, encefalitis, miokarditis, miozitis, neinfektivni cistitis. Za seznam neželenih učinkov neznane pogostnosti, prosimo, glejte celoten SmPC. *Nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) pri zdravljenju melanoma:* zelo pogosti (≥ 1/10): hipotiroidizem, zmanjšanje apetita, glavobol, dispneja, kolitis, driska, bruhanje, navzea, bolečina v trebuhu, izpuščaj, srbenje, artralgija, utrujenost, zvišana telesna temperatura, zvišanje vrednosti AST, zvišanje vrednosti ALT, zvišanje vrednosti skupnega bilirubina, zvišanje vrednosti alkalne fosfataze, zvišanje vrednosti lipaze, zvišanje vrednosti amilaze, zvišanje vrednosti kreatinina, hiperglikemija, hipoglikemija, limfopenija, levkopenija, nevtropenija, trombocitopenija, anemija, hipokalciemija, hiperkaliemija, hipokaliemija, hipomagneziemija, hiponatriemija; pogosti (≥ 1/100 do < 1/10): pljučnica, okužba zgornjih dihal, eozinofilija, infuzijska reakcija, preobčutljivost, insuficienca nadledvičnih žlez, hipopituitarizem, hipofizitis, hipertiroidizem, tiroiditis, dehidracija, periferna nevropatija, omotica, uveitis, zamegljen vid, tahikardija, hipertenzija, pnevmonitis, pljučna embolija, kašelj, stomatitis, pankreatitis, zaprtost, suha usta, hepatitis, vitiligo, suha koža, eritem, alopecija, urtikarija, mišično-skeletna bolečina, odpoved ledvic (vključno z akutno odpovedjo ledvic), edem (vključno s perifernim edemom), bolečina, hiperkalciemija, hipermagneziemija, hipernatriemija, zmanjšanje telesne mase; občasni (≥ 1/1.000 do < 1/100): bronhitis, sarkoidoza, diabetična ketoacidoza, diabetes, Guillain-Barréjev sindrom, polinevropatija, nevritis, pareza peronealnega živca, avtoimunska nevropatija (vključno s parezo obraznega in abducentnega živca), encefalitis, aritmija (vključno z ventrikularno aritmijo), atrijska fibrilacija, miokarditis, plevralni izliv, predrtje črevesa, gastritis, duodenitis, psoriaza, spondiloartropatija, Sjogrenov sindrom, artritis, miopatija, miozitis (vključno s polimiozitisom), rabdomioliza, tubulointersticijski nefritis, neinfektivni cistitis, bolečina v prsnem košu; redki (≥ 1/10.000 do < 1/1.000): toksična epidermalna nekroliza, Stevens-Johnsonov sindrom. Za seznam neželenih učinkov neznane pogostnosti, prosimo, glejte celoten SmPC. *Nivolumab + ipilimumab + kemoterapija:* zelo pogosti (≥ 1/10): hipotiroidizem, zmanjšanje apetita, navzea, driska, bruhanje, izpuščaj, srbenje, utrujenost, anemija, trombocitopenija, levkopenija, limfopenija, nevtropenija, zvišanje vrednosti alkalne fosfataze, zvišanje vrednosti aminotransferaz, zvišanje vrednosti kreatinina, zvišanje vrednosti amilaze, zvišanje vrednosti lipaze, hipokaliemija, hipomagneziemija, hiponatriemija; pogosti (≥ 1/100 do < 1/10): konjunktivitis, pljučnica, okužba dihal, febrilna nevtropenija, infuzijska reakcija, preobčutljivost, hipertiroidizem, insuficienca nadledvičnih žlez, hipofizitis, tiroiditis, dehidracija, hipoalbuminemija, hipofosfatemija, periferna nevropatija, omotica, suhe oči, pnevmonitis, dispneja, kašelj, zaprtost, stomatitis, bolečina v trebuhu, kolitis, suha usta, pankreatitis, hepatitis, alopecija, suha koža, eritem, urtikarija, mišično-skeletna bolečina, artralgija, artritis, odpoved ledvic (vključno z akutno odpovedjo ledvic), zvišana telesna temperatura, edem (vključno s perifernim edemom), zvišanje vrednosti skupnega bilirubina, zvišanje vrednosti tiroideo stimulirajočega hormona; občasni (≥ 1/1.000 do < 1/100): eozinofilija, hipopituitarizem, hipoparatiroidizem, polinevropatija, avtoimunska nevropatija (vključno s parezo obraznega in abducentnega živca), encefalitis, zamegljen vid, episkleritis, tahikardija, atrijska fibrilacija, bradikardija, hipertenzija, plevralni izliv, psoriaza, Stevens-Johnsonov sindrom, vitiligo, mišična oslabelost, mišični krči, revmatična polimialgija, nefritis, neinfektivni cistitis, mrzlica, bolečina v prsnem košu, zvišanje vrednosti gama- glutamiltransferaze. Za seznam neželenih učinkov neznane pogostnosti, prosimo, glejte celoten SmPC. *Nivolumab + kemoterapija:* zelo pogosti(≥ 1/10): okužba zgornjih dihal, zmanjšanje apetita, periferna nevropatija, glavobol, kašelj, driska, stomatitis, bruhanje, navzea, bolečina v trebuhu, zaprtost, sindrom palmarno-plantarne eritrodisestezije, izpuščaj, mišično-skeletna bolečina, utrujenost, zvišana telesna temperatura, edem (vključno s perifernim edemom), anemija, trombocitopenija, levkopenija, limfopenija, nevtropenija, zvišanje vrednosti aminotransferaz, zvišanje vrednosti skupnega bilirubina, zvišanje vrednosti kreatinina, hipernatriemija, hiponatriemija, hiperkaliemija, hipokaliemija, hipokalciemija, hipoglikemija, hiperglikemija, zvišanje vrednosti lipaze, zvišanje vrednosti alkalne fosfataze, zvišanje vrednosti amilaze; pogosti (≥ 1/100 do < 1/10): pljučnica, febrilna nevtropenija, eozinofilija, preobčutljivost, infuzijska reakcija, hipotiroidizem, hipertiroidizem, parestezija, omotica, suhe oči, zamegljen vid, tahikardija, tromboza, hipertenzija, pnevmonitis, dispneja, kolitis, suha usta, srbenje, hiperpigmentacija kože, alopecija, suha koža, eritem, artralgija, mišična oslabelost, odpoved ledvic, hiperkalciemija; občasni (≥ 1/1.000 do < 1/100): hipopituitarizem, insuficienca nadledvičnih žlez, hipofizitis, sladkorna bolezen, Guillain-Barréjev sindrom, uveitis, miokarditis, pankreatitis, hepatitis, nefritis, neinfektivni cistitis. Za seznam neželenih učinkov neznane pogostnosti, prosimo, glejte celoten SmPC. *Nivolumab + kabozantinib:* zelo pogosti (≥ 1/10): okužba zgornjih dihal, hipotiroidizem, hipertiroidizem, zmanjšanje apetita, paragevzija, omotica, glavobol, hipertenzija, disfonija, dispneja, kašelj, driska, bruhanje, navzea, zaprtost, stomatitis, bolečina v trebuhu, dispepsija, sindrom palmarno-plantarne eritrodisestezije, izpuščaj, srbenje, mišično-skeletna bolečina, artralgija, mišični krči, proteinurija, utrujenost, zvišana telesna temperatura, edem, anemija, trombocitopenija, levkopenija, limfopenija, nevtropenija, zvišanje vrednosti alkalne fosfataze, zvišanje vrednosti ALT, zvišanje vrednosti AST, zvišanje vrednosti skupnega bilirubina, zvišanje vrednosti kreatinina, zvišanje vrednosti amilaze, zvišanje vrednosti lipaze, hipokaliemija, hipomagneziemija, hiponatriemija, hipokalciemija, hiperkalciemija, hipoglikemija, hipofosfatemija, hiperglikemija, hiperkaliemija, hipermagneziemija, hipernatriemija, zmanjšanje telesne mase; pogosti (≥ 1/100 do < 1/10): pljučnica, eozinofilija, preobčutljivost (vključno z anafilaktično reakcijo), insuficienca nadledvičnih žlez, dehidracija, periferna nevropatija, tinitus, suhe oči, zamegljen vid, atrijska fibrilacija, tahikardija, tromboza, pnevmonitis, pljučna embolija, plevralni izliv, epistaksa, kolitis, gastritis, bolečina v ustni votlini, suha usta, hemoroidi, hepatitis, alopecija, suha koža, eritem, sprememba barve las, artritis, odpoved ledvic, akutna okvara ledvic, bolečina, bolečina v prsnem košu, zvišanje vrednosti holesterola v krvi, hipertrigliceridemija; občasni (≥ 1/1.000 do < 1/100): z infuzijo povezana preobčutljivostna reakcija, hipofizitis, tiroiditis, avtoimun encefalitis, Guillain-Barréjev sindrom, miastenijski sindrom, uveitis, miokarditis, pankreatitis, perforacija tankega črevesa, glosodinija, psoriaza, urtikarija, miopatija, osteonekroza čeljusti, fistula, nefritis; redki (≥ 1/10.000 do < 1/1.000): neinfektivni cistitis. Za seznam neželenih učinkov neznane pogostnosti, prosimo, glejte celoten SmPC. Za Povzetek varnostnega profila in podrobnejši opis izbranih neželenih učinkov prosimo glejte celoten SmPC.

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.

IMETNIK DOVOLJENJA ZA PROMET Z ZDRAVILOM: Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Irska. **PREDSTAVNIŠTVO IMETNIKA DOVOLJENJA ZA PROMET:** Swixx Biopharma d.o.o., Pot k sejmišču35, 1231 Ljubljana - Črnuče; **NAČIN IN REŽIM IZDAJE:** H. **DATUM PRIPRAVE INFORMACIJ:** november 2021.

Bristol Myers Squibb™

Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown
Corporate Park 2, Dublin 15, D15 T867, Irska

SAMO ZA STROKOVNO JAVNOST.

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