



**ONKOLOŠKI  
INŠTITUT  
LJUBLJANA**

**INSTITUTE  
OF ONCOLOGY  
LJUBLJANA**



**Slovensko  
zdravniško  
društvo**

**Sekcija za  
internistično  
onkologijo**

**KATEDRA ZA ONKOLOGIJO**

# **13. DAN INTERNISTIČNE ONKOLOGIJE**

**Novosti v sistemskeem zdravljenju  
redkejših solidnih rakov**

**ONKOLOŠKI INŠTITUT LJUBLJANA  
17. NOVEMBER 2017**

**Strokovni odbor:**

izr. prof. dr. Janja Ocvirk, dr.med.  
doc. dr. Cvetka Grašič-Kuhar, dr.med.  
dr. Simona Borštnar, dr.med.  
dr. Breda Škrbinc, dr.med.  
dr. Erika Matos, dr.med.  
prof. dr. Branko Zakotnik, dr.med.

**Organizacijski odbor:**

izr. prof. dr. Janja Ocvirk, dr.med.  
dr. Martina Reberšek, dr.med.  
doc. dr. Cvetka Grašič-Kuhar, dr.med.  
dr. Simona Borštnar, dr.med.  
dr. Breda Škrbinc, dr.med.  
dr. Erika Matos, dr.med.  
prof. dr. Branko Zakotnik, dr.med.  
Marko Boc, dr.med.  
ga. Lidija Kristan

**Uredniki zbornika:**

Marko Boc, dr.med.  
dr. Martina Reberšek, dr.med.  
izr. prof. dr. Janja Ocvirk, dr.med.

**Organizator in izdajatelj (založnik):**

Onkološki inštitut Ljubljana  
Sekcija za internistično onkologijo  
Katedra za onkologijo

Ljubljana, november 2017

## VSEBINA:

Program srečanja.....	4
<i>Zakotnik B.:</i> Obravnavna redkih rakov – projekt »Rare Care Net«.....	5
<i>Grašič-Kuhar C.:</i> Sistemsko zdravljenje raka ščitnice.....	13
<i>Azarija J., Grašič-Kuhar C.:</i> Predstavitev primera (rak ščitnice).....	32
<i>Unk M.:</i> Sistemsko zdravljenje GIST-ov.....	43
<i>Čakš M., Unk M.:</i> Predstavitev primera (GIST).....	59
<i>Čufer T.:</i> Sistemsko zdravljenje timičnega raka.....	69
<i>Janžič U., Čufer T.:</i> Predstavitev primera (timični rak).....	82
<i>Reberšek M.:</i> Sistemsko zdravljenje raka žolčnika in žolčnih vodov.....	93
<i>Fokter-Dovnik N., Boc M.:</i> Predstavitev primera (rak žolčnih vodov).....	115
<i>Ocvirk J.:</i> Sistemsko zdravljenje redkih kožnih rakov (karcinom Merklovih celic, razsejan BCC) .....	120
<i>Ignjatović M., Ocvirk J.:</i> Predstavitev primera (lokalno napredovali BCC) .....	144

## PROGRAM SREČANJA: PETEK, 17.11.2017

07.00-08.30 **REGISTRACIJA UDELEŽENCEV**

08.30-09.15 **SATELITNO PREDAVANJE 1 (ELI LILLY)**

09.15-09.20 *Matos E.:* Uvod

**Moderator: dr. Erika Matos, dr.med., mag. Zvezdana Hlebanja, dr.med.**

09.20-09.30 *Zakotnik B.:* Obravnava redkih rakov – projekt »Rare Care Net«

09.30-10.15 *Grašič-Kuhar C.:* Sistemsko zdravljenje raka ščitnice

*Azarija J., Grašič-Kuhar C.:* Predstavitev primera

10.15-11.00 *Unk M.:* Sistemsko zdravljenje GIST-ov

*Čakš M., Unk M.:* Predstavitev primera

11.00-11.15 **ODMOR S KAVO**

**Moderator: dr. Erika Matos, dr.med., mag. Zvezdana Hlebanja, dr.med.**

11.15-12.00 *Čufer T.:* Sistemsko zdravljenje timičnega raka

*Janžič U., Čufer T.:* Predstavitev primera

12.00-12.45 *Reberšek M.:* Sistemsko zdravljenje raka žolčnika in žolčnih vodov

*Fokter-Dovnik N., Boc M.:* Predstavitev primera

12.45-13.15 **SATELITNO PREDAVANJE 2 (ROCHE)**

13.15-14.15 **KOSILO**

**Moderator: dr. Simona Borštnar, dr.med., Marko Boc, dr.med.**

14.15-15.00 *Škrbinc B.:* Sistemsko zdravljenje nekaterih redkih uroloških rakov (rak penisa, urahus)

*Pavlova-Bojadžiski M., Škrbinc B.:* Predstavitev primera

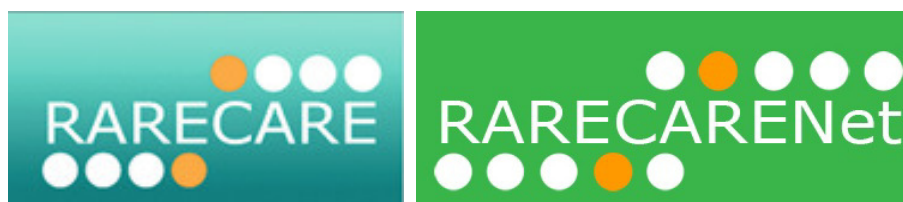
15.00-15.50 *Ocvirk J.:* Sistemsko zdravljenje redkih kožnih rakov (karcinom Merklvovih celic, razsejan BCC)

*Ignjatović M., Ocvirk J.:* Predstavitev primera

15.50-16.00 **ZAKLJUČEK (Matos E.)**

16.00-16.15 **ODMOR**

16.15-16.45 **SKUPŠČINA SEKCIJE ZA INTERNISTIČNO ONKOLOGIJO**



# Redki raki

**B. Zakotnik**

*Dan internistične onkologije 17.11.2017*

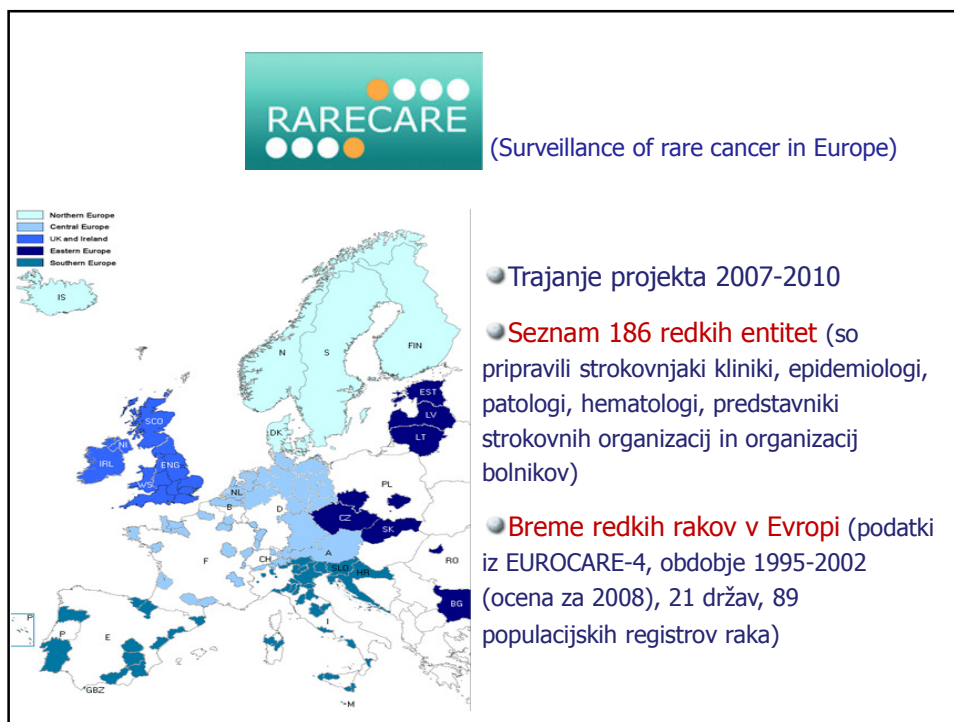
## Vsebina


1. Definicija
2. Incidenca
3. Preživetje
4. Diagnostični problemi
5. Zdravljenje
6. Zaključek

# 1. Definicija




- Redki raki (v sklopu redkih bolezni) izpostavljeni kot posebna entiteta v EU!
- Pri raku prevalenca ni najprimernejše merilo za breme bolezni, odvisna od incidence in preživetja
- **Definicija:** groba incidenčna stopnja  
**< 6/100.000 prebivalcev**  
**(zelo redki <1/100.000)**






**RARECAREnet**



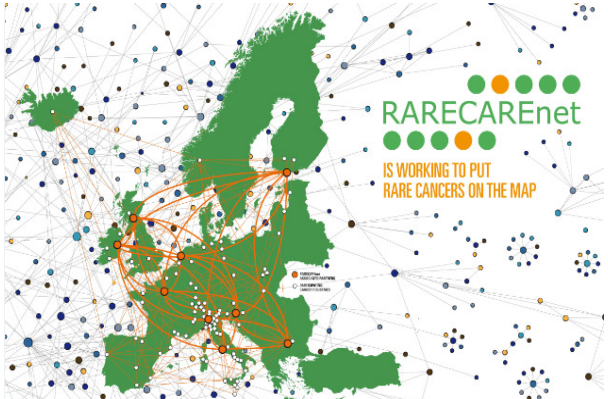
Co-funded by  
the Health Programme  
of the European Union



European  
Commission

Information network on rare cancers (2012-2015)  
<http://www.rarecarenet.eu/>

- analiza kliničnih poti
- obravnava redkih rakov v referenčnih centrih



**RARECAREnet**  
IS WORKING TO PUT  
RARE CANCERS ON THE MAP

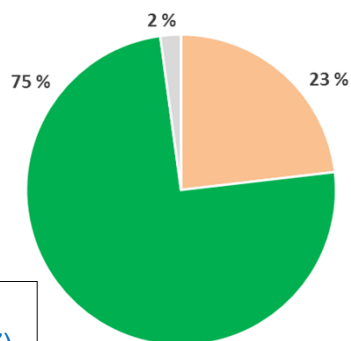
Pilotni projekt s katerim so

- Preučili zdravljenja
- Določili stopnjo centralizacije
- Ocenili povezavo s izidom zdravljenja (preživetje)



## 2. Incidenca

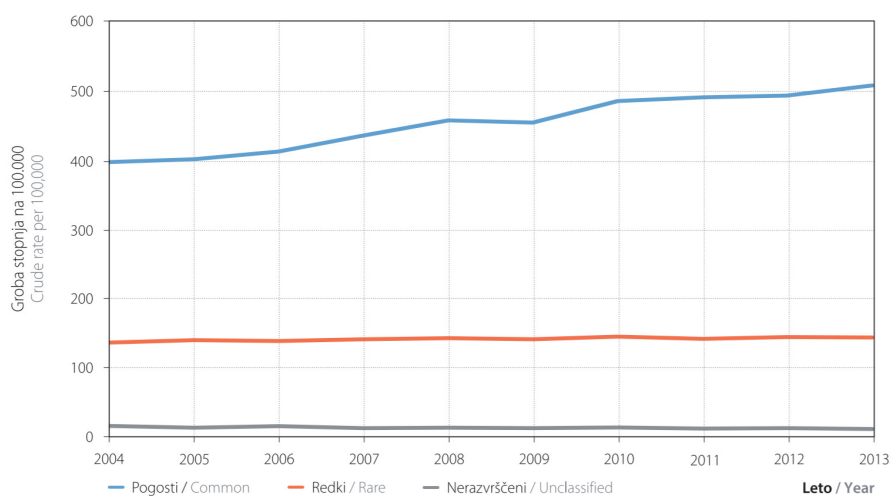
**Incidenca,  
Slovenija 2004-2013**



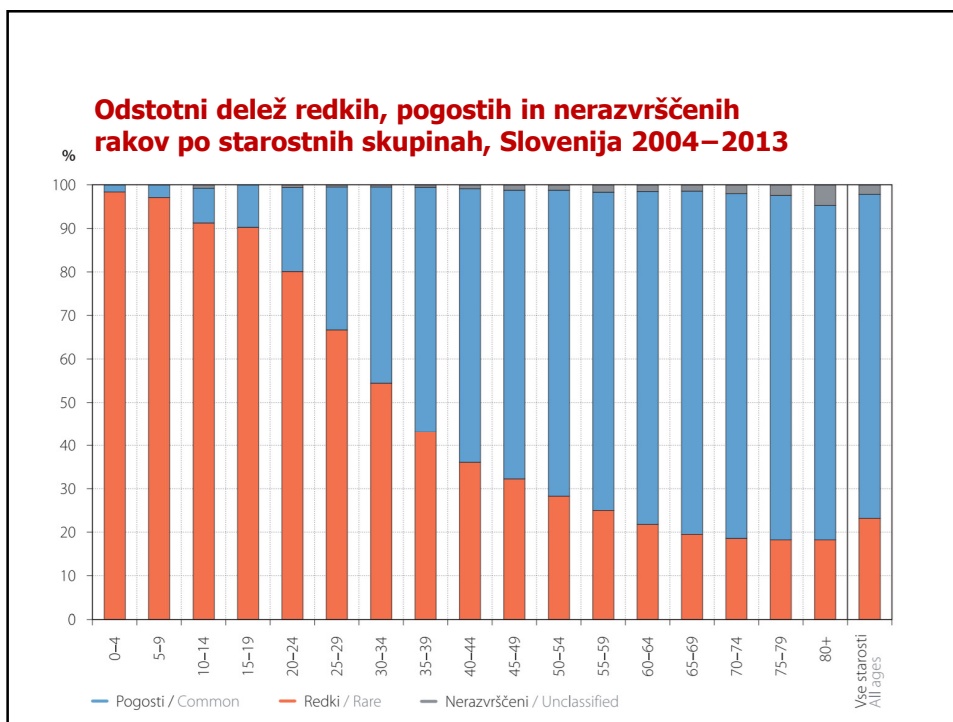
**RareCare :**  
22 % ( EU 27)

Primarna lokacija	Število novih primerov	Delež (%)
Redki raki	28768	23,2
Pogosti raki	92799	74,7
Nerazvrščeni raki	2665	2,1

**Groba letna incidenčna stopnja redkih, pogostih  
in nerazvrščenih rakov, Slovenija 2004–2013**

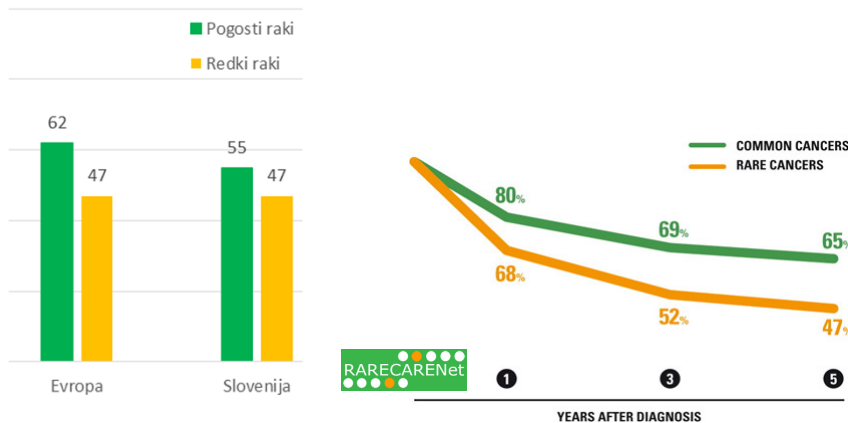






### 3. Preživetje (1)

- Relativno preživetje oseb, ki so zbolele za redko vrsto raka je nižje od preživetja oseb, ki so zbolele za pogosto vrsto raka
- Pri mlajših so razlike v preživetju majhne



### 3. Preživetje (2)

- 5-letno relativno preživetje SLO (2007-2011)

– Rak mod:	98%
– Rak ščitnice:	95%
– Otroški raki:	83% (0-19 let)
– Rak grla:	69%
– Kostni sarkomi:	68%
– Sarkomi mehkih tkiv:	51%
– Rak žrela:	29%

### 4. Diagnostični problemi

- Klinično se redki raki ne razlikujejo od pogostih, zato so problemi podobni (napotitve, čakalne dobe, odločitve o kirurškem zdravljenju brez predhodne diagnoze, stadija,.....)
- **Prvo zdravljenje ni planirano na multidisciplinarnem konziliju (še bolj pomembno za redke rake!)**
- **Histološka diagnoza (konzultacije, dodatni testi, vzorci)**



**čas do diagnoze in zdravljenja ponavadi daljši**

## 5. Zdravljenje

- Plan prvega zdravljenja na multidisciplinarnem konziliju (redosled zdravljenj)
  - Kirurgija: enak princip kot pri drugih rakih (radikalnost), ki lahko predstavlja problem pri določenih lokacijah (baza lobanje, hrbtenica, ...)
  - Obsevanje (indikacija, posebne lokacije)
  - Sistemsko zdravljenje
    - zaradi redkosti velikokrat ni podprto z dokazi
    - investiranje farmacevtske industrije v redke rake (zdravila sirote)
    - klinične raziskave lahko le multicentrične (globalne), z razvojem molekularne biologije (t.i. Basket trials) boljši izgledi
- Ni še utečenih poti (centrov) za drugo mnenje za zelo redke rake (EurocareNet)

## 5. Zaključek

- Obravnava redkih rakov zahteva izkušen multidisciplinarni tim (diagnoza, pravilno zaporedje zdravljenja)
- Zaradi svoje redkosti velikokrat odločitve temeljijo na posameznih primerih
- Principi diagnostike in zdravljenja se bodo v bodoče z novimi dognanji molekularne biologije ter globalnimi raziskavami na tem področju bistveno spremenili

### **Redki raki – pot naprej**

- Posodabljanje podatkov o incidenci redkih rakov na [www.rarecarenet.eu](http://www.rarecarenet.eu)
- JARC (Joint Action on Rare Cancers)
- ERN (European Reference Networks)
- EUCERD (European Committee of Experts on Rare Diseases), priporočila glede referenčnih centrov
- Multicentrične, t.i. Basket raziskave

**Viri informacij:**

<http://www.rarecarenet.eu/>

<http://www.slora.si>

<http://www.onko-i.si/rrs>

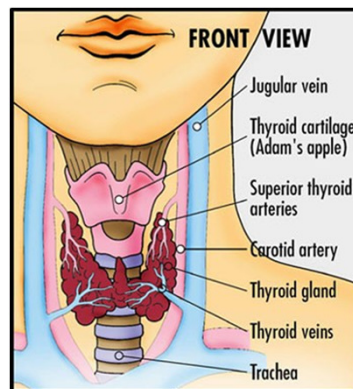
<http://www.onko-i.si>

<http://www.dpor.si>

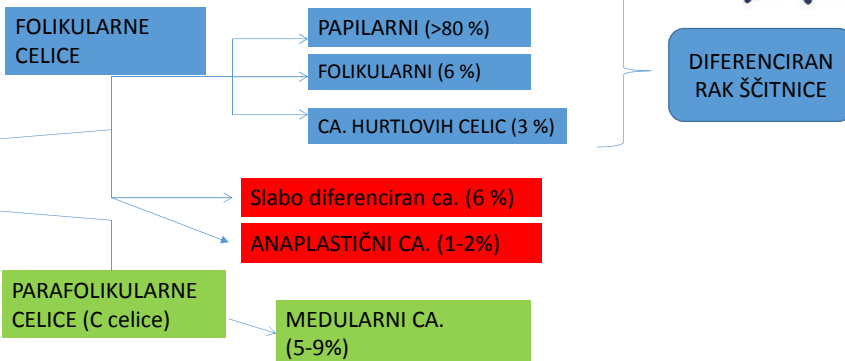
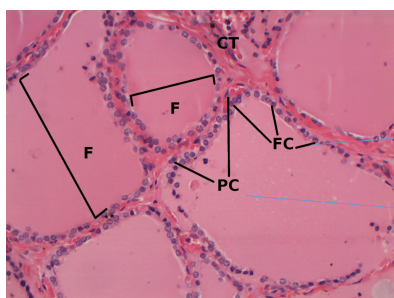


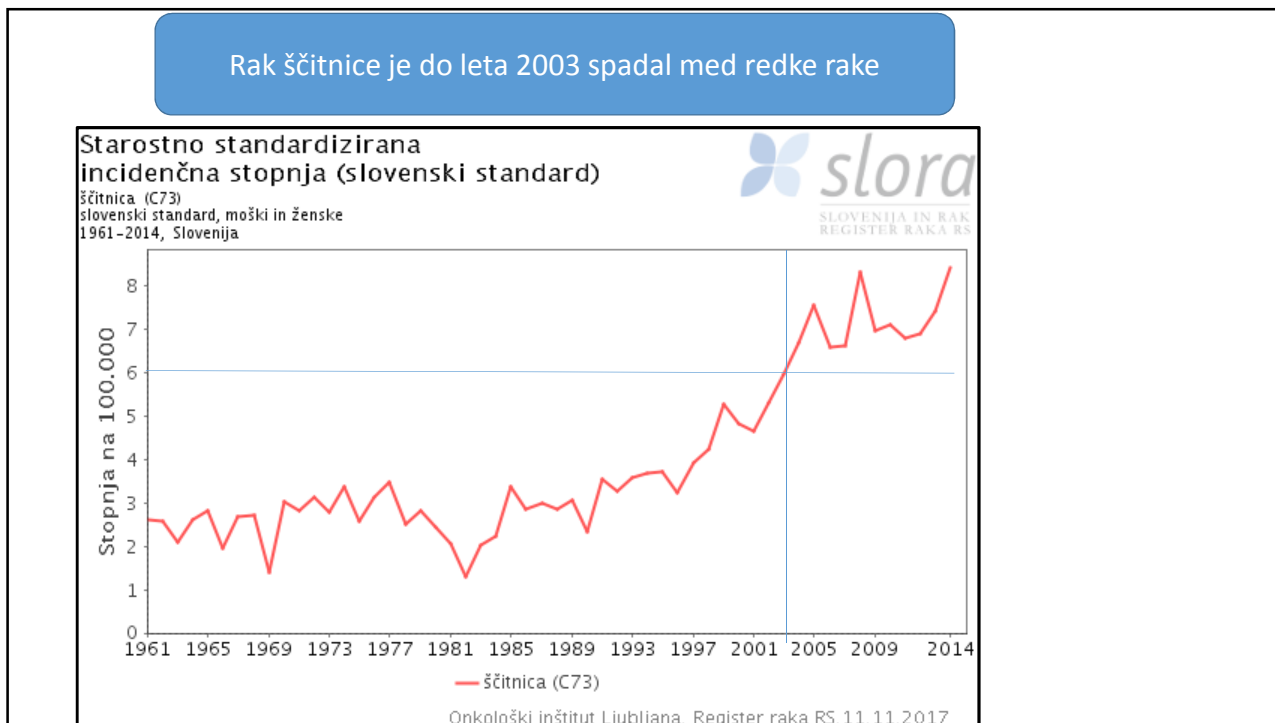
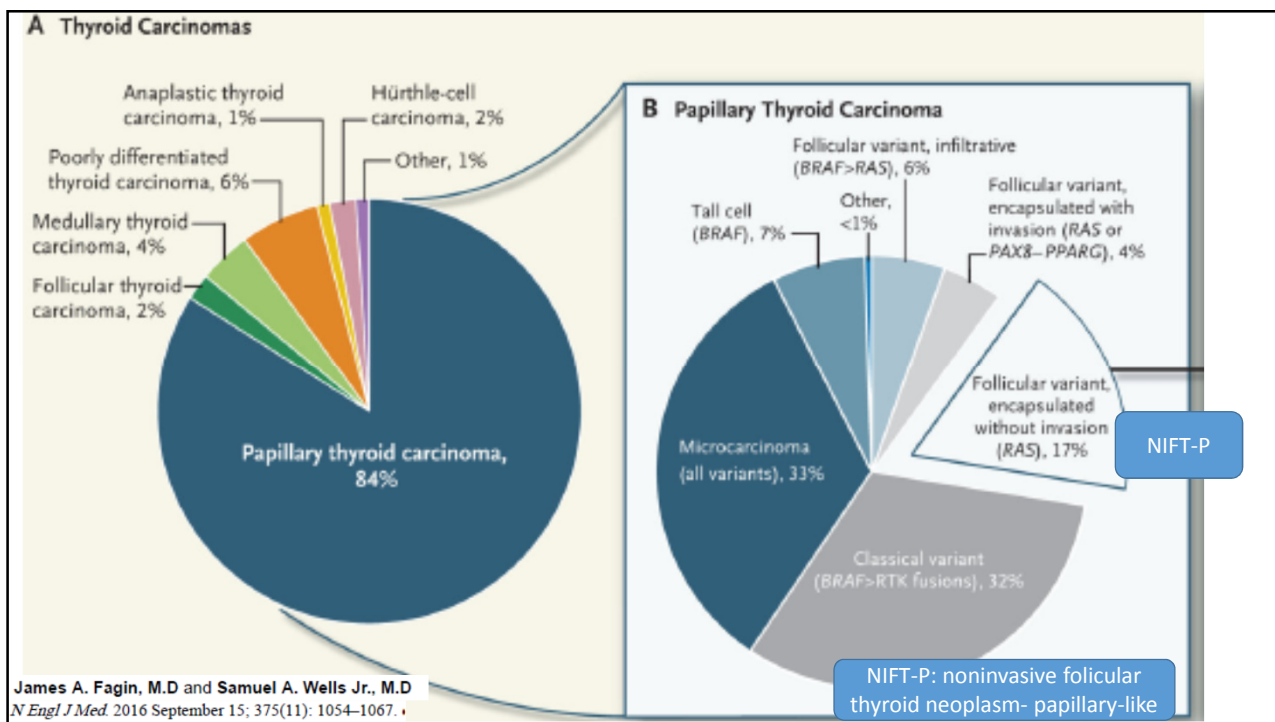
# Sistemsko zdravljenje raka ščitnice

Doc. dr. Cvetka Grašič Kuhar, dr. med.  
Onkološki inštitut Ljubljana



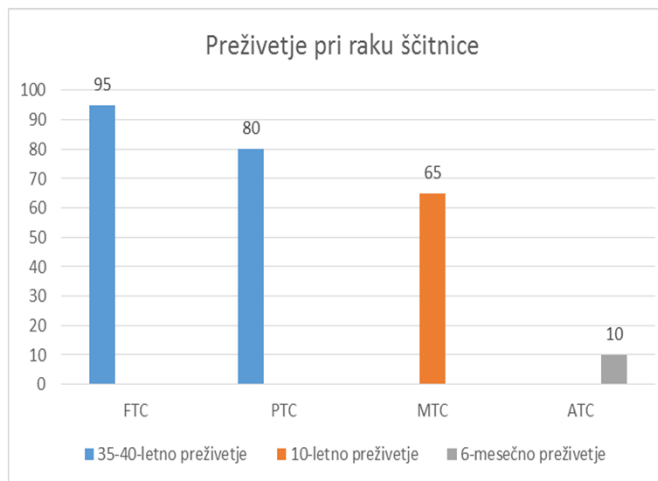
## Rak ščitnice





## Incidenca

- V ZDA se je incidenca povečala 3x (iz 4,9/100.000 na 14,3/100.000 letno)
- Ob tem je smrtnost ostala enaka: 0,5/100.000 letno
- Incidenca se je povečala na račun **papilarnega ca. ščitnice (večinoma mikropapilarnega: T<1 cm; 40 %)**; na avtopsiji najdejo papil. ca ščitnice v 11,5 % (4-36)
- Ostalim entitetam se incidenca ni povečala



## Zdravljenje diferenciranega raka ščitnice (DTC) v omejenem stadiju

- Primarno **kirurško zdravljenje**: totalna tiroidektomija in limfadenektomija
- Visoko rizični: adjuvantna terapija z **radiojodom** (<sup>131</sup>I)
- Nadomestna terapija z levotiroksinom; višji – supresijski - odmerek pri visoko rizičnih (TSH<0,1mU/L), Ca 1200 mg/d, ViD 1000IE/d

Spremljanje bolnikov (detekcija rezidualne bolezni ali ponovitve):

-serumski tiroglobulin (po 6-12 mes) in UZ vratu

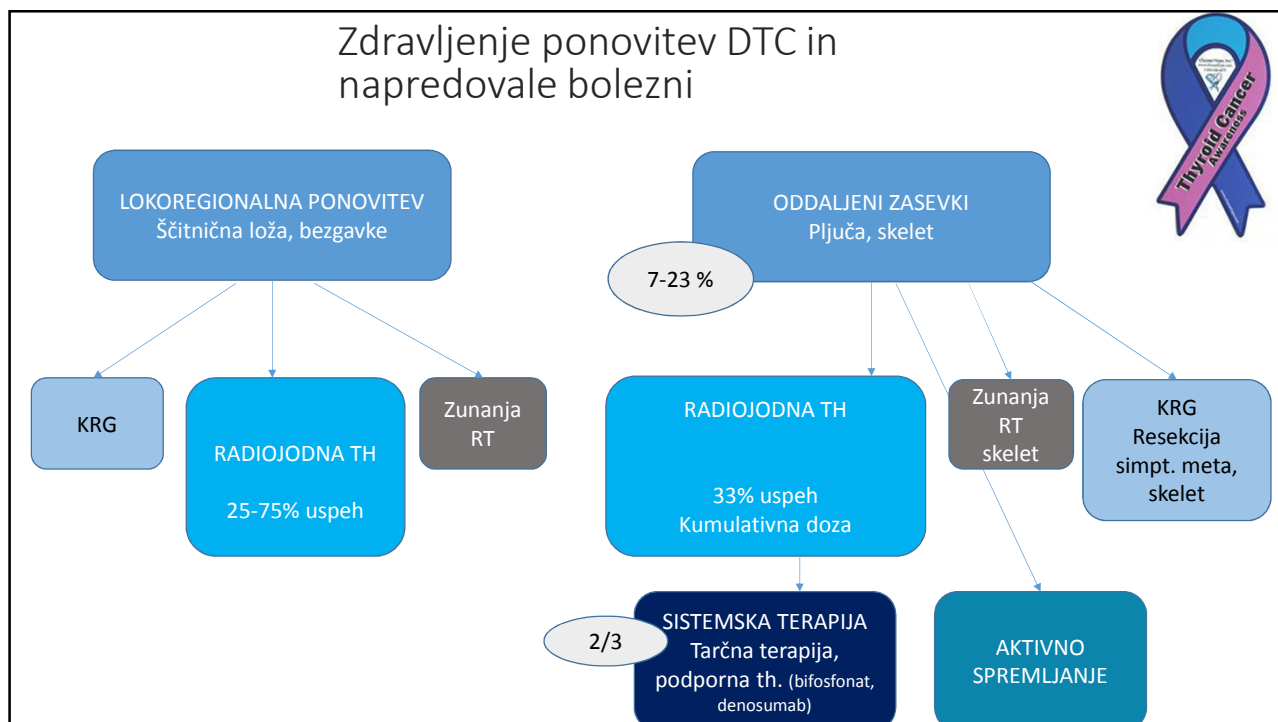
-rhTIROTROPIN; ČE PORASTE >2 ng/ml

KRG

RADIO  
JODNA TH



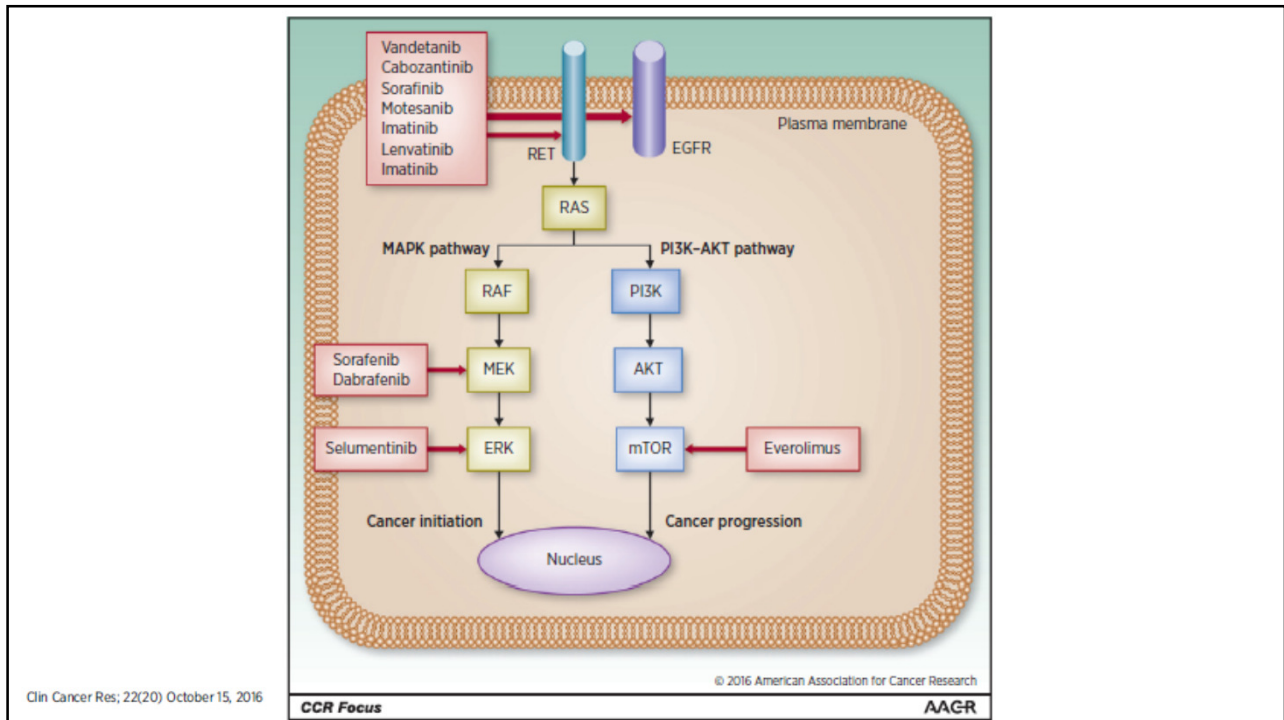
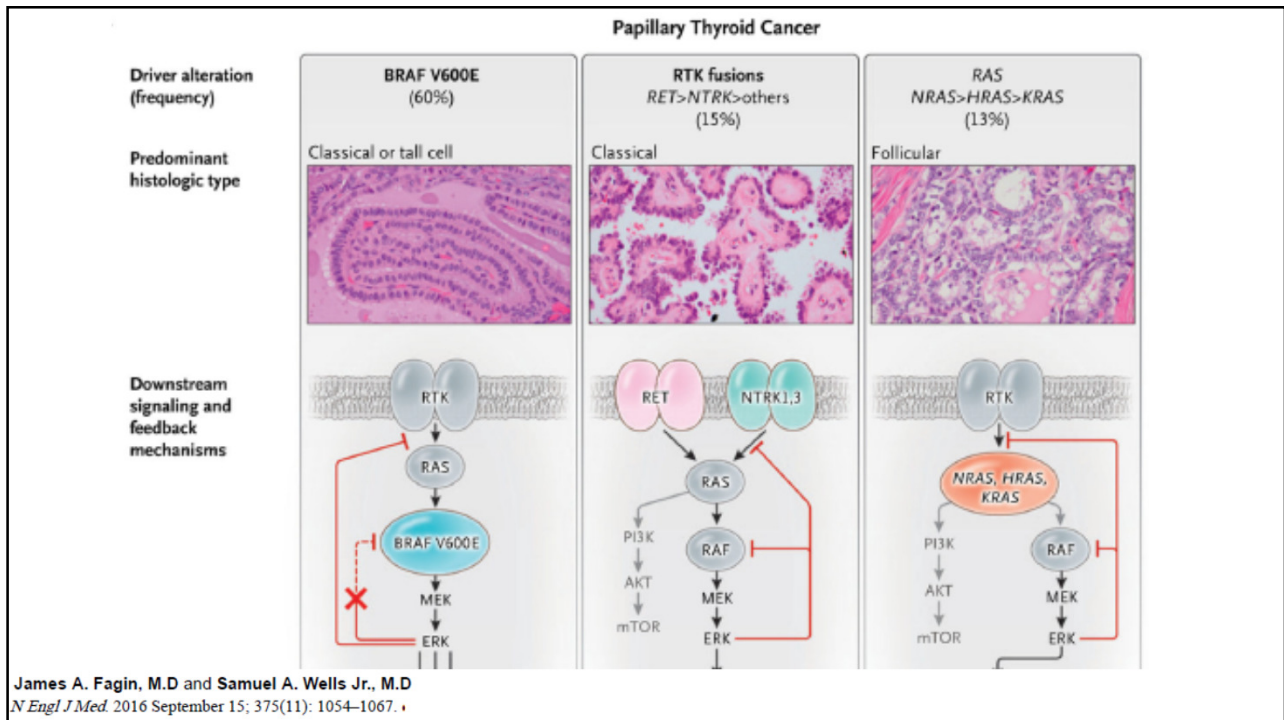
[http://www.nccn.org/professionals/physician\\_gls/pdf/thyroid.pdf](http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf)



## Sistemska terapija pri DTC

- Na radiojod rezistentna bolezen ali dosežena kumulativna doza radiojoda
- simptomatska, progresivna metastatska bolezen
- lokalizirana bolezen, ki ogroža vitalne strukture, kjer lokalna terapija ni možna
- Neresektibilna lokalna bolezen: paliativna RT+nizkodozna KT





## Raziskave faze III na področju tarčne terapije pri DTC

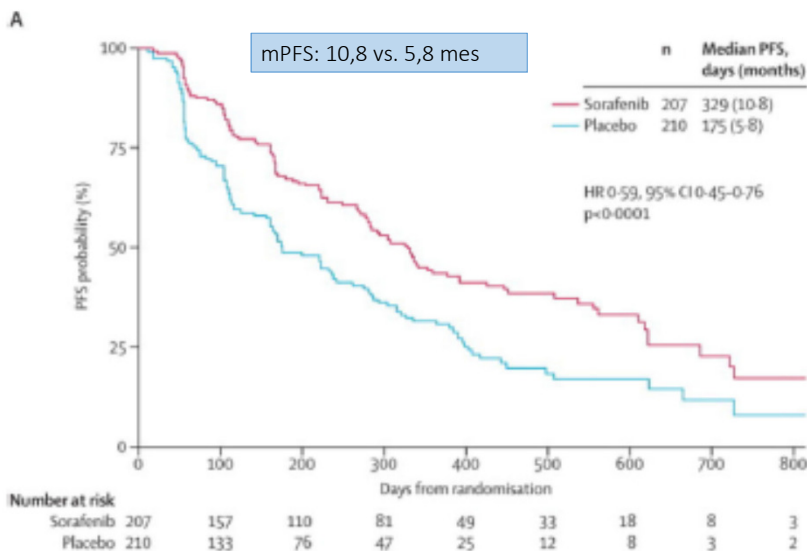
ŠTUDIJA	DECISION	SELECT
VRSTA ŠTUDIJE	Randomizirana, faza III, dvojno slepa, multicentrična	Randomizirana, faza III, dvojno slepa, multicentrična
ŠTUDIJSKE ROKE	Sorafenib (2x400 mg) vs. placebo	Lenvatinib 1x 24 mg vs. placebo
Randomizacija	1:1	2:1
Število bolnikov	417	392
Vključitveni kriteriji	RAI refraktorni bolniki: lokalno napredovali, metastaski (96,4%) Progres po RECIST kriterijih v zadnjih 14 mesecih	RAI refraktorni bolniki s progresivno boleznijo Progres po RECIST kriterijih v zadnjih 13 mesecih
Stanje zmogljivosti bolnika po ECOG	PS 0-1 (PS 2: 3%)	PS 0-3 PS 2-3: 5%/1,5%
Primarni cilj	PFS	PFS
Farmacevtska firma	Bayer	Eisai

## Primerjava raziskav DECISION in SELECT

ZDRAVILO	SORAFENIB	LENVATINIB
TARČE	VEGF 1, 2, 3, RAF (vključno z BRAFV600E,) PDGFR $\beta$ , RET (RET/PTC)	VEGFR 1, 2, 3, FGFR 1-4, PDGFR $\alpha$ , RET, KIT
Izključitveni kriteriji	Prej KT, talidomid ali TKI	Lahko prej 1 TKI (25/21%)
Čas od diagnoze	66 mes	
Analiza biomarkerjev	Serumski tiroglobulin BRAF in RAS (NRAS, HRAS, in KRAS) mutacije	BRAF in RAS mutacije
Srednji čas opazovanja (median FU)	16,2 mes	17,1 mes
Cross-over	Da (71%)	Da (95,6%)
Nadaljnji red th	20/9 %	15,7% L

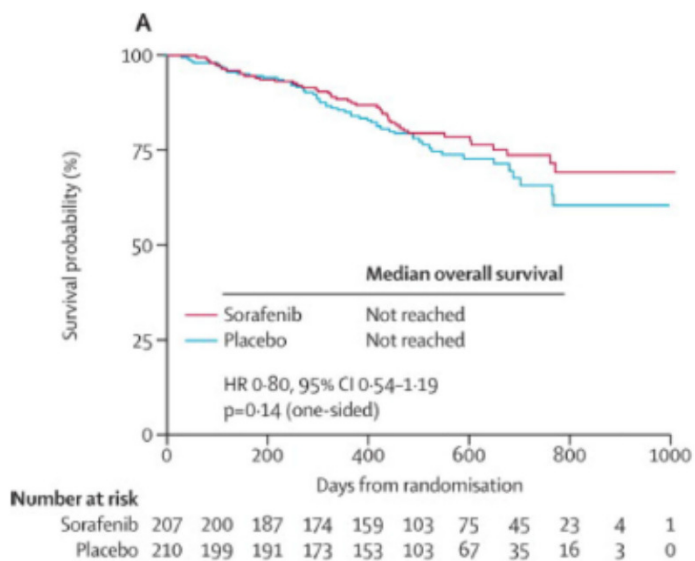
## Raziskava DECISION (sorafenib) - PFS

BRAF in RAS mutaciji nista neodvisni prognostični faktor za PFS

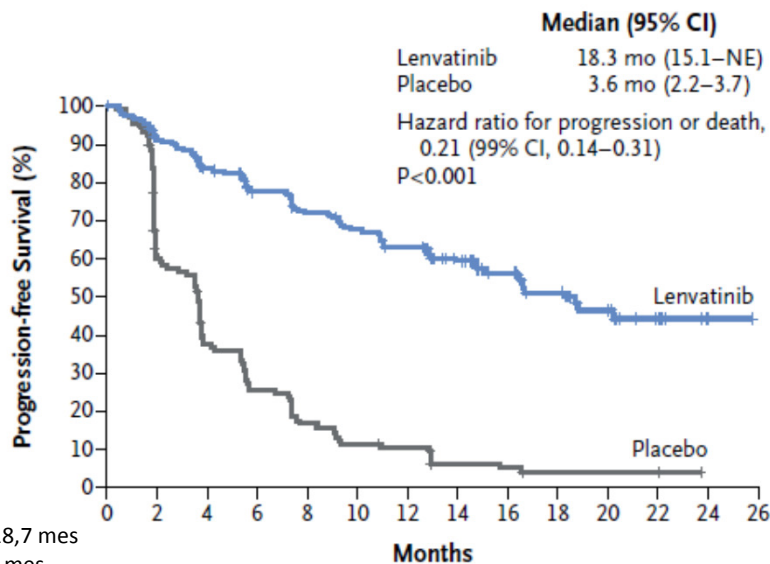


Lancet. 2014 July 26; 384(9940): 319-328.

## Raziskava DECISION (sorafenib) – celotno preživetje



## Raziskava SELECT – lenvatinib - PFS

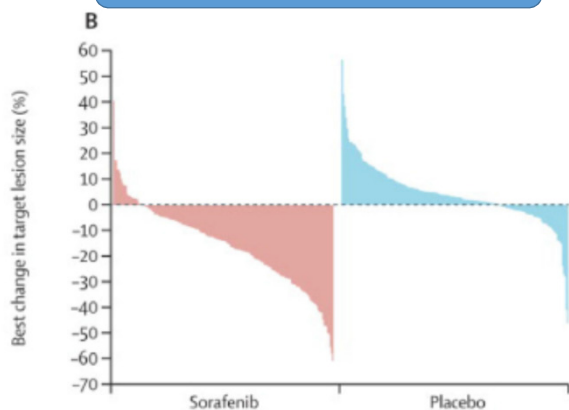


No prior TKI: PFS L 18,7 mes  
Prior TKI: PFS L 15,1 mes  
PFS neodvisen od BRAF, RAS mutacij!

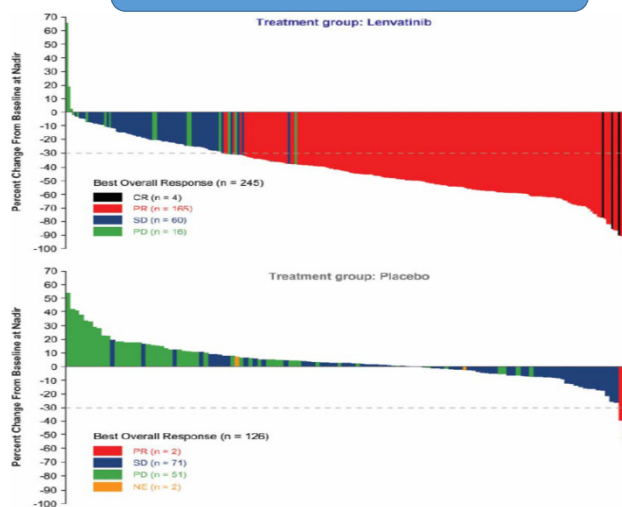
N Engl J Med 2015;372:621-30.

## Prikaz zmanjšanja tarčnih lezij – ‚waterfall plot‘

Raziskava DECISION– sorafenib



Raziskava SELECT – lenvatinib



### Primerjava učinkovitosti in compliance v testni roki

	Sorafenib vs. placebo	Lenvatinib vs. placebo
CR	0%	1,5%
PR	12,2 vs. 0,5%	63,2 vs. 1,5%
SD	SD>6 mes 41,8 vs. 33,2%	23% SD>23 tednov 15,3 vs. 30%
PD	?	6,9 vs. 39,7%
Evaluacija ni možna	?	5,5%
Srednje trajanje odgovora pri PR	10,2 mes.	
Srednje trajanje zdravljenja	10,6 vs. 6,5 mes	13,8 vs. 3,9 mes
Srednja dnevna doza zdravila	651 mg vs. 793 mg	17,2 mg (82% dose interruption , 67% dose reduction)

## Medularni rak ščitnice

- Sporadični (75-80 %)
- Familiarni (20-25 %); MEN 2A, 2B, FMTC
- Tvori kalcitonin
- Etiologija:
  - vsi familiarni: 'germline' RET mutacija
  - Sporadični:
    - v 50-60 % somatska RET mutacija
    - RAS mutacija
    - Prekomerna izraženost VEGFR1, 2

## Zdravljenje MTC

- KRG: totalna tiroidektomija + bilateralna disekcija bezgavk na vratu (T> 1cm, bezgavke bilateralno, familiarni rak)
- Genska okvara: **profilaktična tiroidektomija** (priporočljiva starost odvisno od rizičnosti kodona RET mutacije)
- **Ev.** dopolnilna RT, če R1, R2 resekcija, visok N stadij, ECE, če grozi obstrukcija dihal
- 3 mesece po KRG: CEA, kalcitonin (če > 150pg/ml)
  - Če nista zvišana: ozdravljen bolnik; kontrole 1x letno (CEA, kalcitonin, fizikalni pregled, UZ vratu)
  - Če zvišana po KRG: slikovna diagnostika: KRG rezidualne bolezni, če INOP.: RT, če KRG, RT in možna in simptomatska bolezen: TKI
  - Če asimptomatska: spremljanje CEA, kalcitonina na 3-6 mes. (podvojitveni čas; kalkulator)

## Sistemsko zdravljenje medularnega raka ščitnice (MTC)

- V poštev pride v primeru:
  - inoperabilna lokalna ponovitev bolezni in/ali inoperabilne metastatske bolezni
  - primarno metastatska ali lokalno napredovala bolezen (sporadični MTC)
- Srednje preživetje bolnika z metastasko boleznijo je 3 leta, indolenten potek
- Kdaj začeti zdravljenje:
  - Ob dg.? (asimptomatski bolniki)
  - Ob simptomih?
  - Ob dokazanem radiološkem progresu?

Metastaze velikosti vsaj 1-2 cm  
Rast vsaj 20 % letno

Multiple metastaze s simptomi, ki jih ne moremo zdraviti z OP, RT

## Indikacije za sistemsko zdravljenje

- **Klinično pomemben progres** bolezni v zadnjih 12-14 mesecih
- **Simptomatsko tumorsko breme**, ki ga ne moremo obvladati z lokalizirano terapijo
- Prizadetost **vitalnih organov ali funkcij** zaradi tumorja
- Huda neznosna **diareja**

Metastaze velikosti vsaj 1-2 cm  
Rast vsaj 20 % letno

Multiple metastaze s simptomi,  
ki jih ne moremo zdraviti z OP,  
RT

Samo **porast tumorskih markerjev** ni indikacija za uvedbo sistemske terapije!

## Sistemsko zdravljenje

- Podporna (na simptome orientirana) terapija
- Tarčna terapija
- Sistemska kemoterapija



## TARČNA TERAPIJA



- VANDETANIB
- CABOZANTINIB
- SUNITINIB
- SORAFENIB
- Klinične raziskave
  - PAZOPANIB...
  
- per os th., male molekule

## Raziskava ZETA



- Multicentrična raziskava faze III (2006-07), dvojno slepa, kontrolirana s placebo
- vandetanib 300 mg vs. placebo (2:1); n=331
- Lokalno napredovala neresektabilna bolezen/ metastatska bolezen
  - hereditarni in sporadični
- I. cilj: PFS

Vandetanib in Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer: A Randomized, Double-Blind Phase III Trial

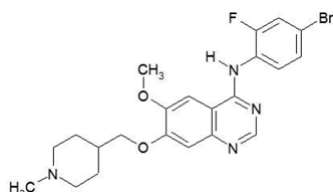
Samuel A. Wells Jr, Bruce G. Robinson, Robert F. Gagel, Henning Dralle, James A. Fagin, Massimo Santoro, Eric Baudin, Rossella Elisai, Barbara Jarzab, James R. Vasselli, Jessica Read, Peter Langmuir, Anderson J. Ryan, and Martin J. Schlumberger

J Clin Oncol 30:134-141. © 2011.



# Vandetanib

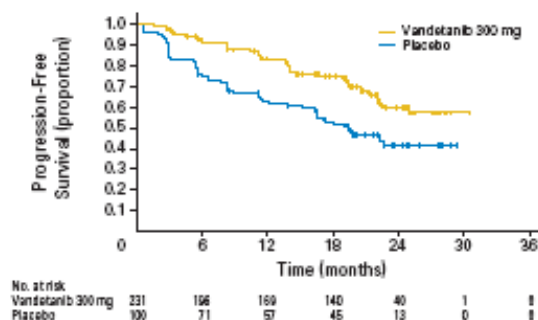
- Mala molekula



- Multi-kinazni inhibitor (RET, EGFR)
- Antiangiogeno delovanje (VEGFR-1, VEGFR-2)

RET: Rearranged during Transfection

## Primarni cilj raziskave ZETA



*J Clin Oncol* 30:134-141. © 2011.

**HR 0,46 (95% IZ 0,31-0.69), p<0.001**

**Srednji PFS: 30,5 mes. vs. 19,3 mes.**

**Mediano trajanje zdravljenja: 90 vs. 40 tednov**

## Sekundarni cilji raziskave ZETA

Sekundarni cilj	vandetanib	placebo	OR	p
Objektivni odgovor (CR+PR)	45%	13%	5,48	<0,001
Klinična kontrola bolezni (CR+PR+SD)	87%	71%	2,64	0,001
Biokemični odgovor: kalcitonin	69%	3%	72,9	<0,001
Biokemični odgovor: CEA	52%	2%	52	<0,001

*J Clin Oncol 30:134-141. © 2011.*

## Neželeni učinki zdravljenja

### Vandetanib:

- GIT: diareja; že simptom MTC (hiperkalcitonin.), nauzea...
- Kožni: izpuščaj (rash), akne, suha koža...
- Inapetenca, slabo počutje
- Podaljšanje QT dobe ( $t_{1/2}$ = 19 dni!) (imeti pri sebi kartico z opozorilom!), torsades de pointes
- G3: diareja 11%, art. hipertenzija 9%, pod. QTc 8%, fatigue 6%
- Znižanje doze: 35% vs. 3%
- Prekinitev zdravljenja: 12% vs. 3%
- Vandetanib: 5 smrti

**Table 4. Common Adverse Events (safety population)**

Adverse Event	Vandetanib (300 mg) (n = 231)		Placebo (n = 99)	
	No.	%	No.	%
<i>Any grade occurring with an incidence <math>\geq</math> 10% overall</i>				
Diarrhea	130	56	26	26
Rash	104	45	11	11
Nausea	77	33	16	16
Hypertension	73	32	5	5
Fatigue	55	24	23	23
Headache	59	26	9	9
Decreased appetite	49	21	12	12
Acne	46	20	5	5
Asthenia	34	14	11	11
Vomiting	34	14	7	7
Back pain	21	9	20	20
Dry skin	35	15	5	5
Insomnia	30	13	10	10
Abdominal pain	33	14	5	5
Dermatitis acneiform	35	15	2	2
Cough	25	10	10	10
Nasopharyngitis	26	11	9	9
ECG QT prolonged*	33	14	1	1
Weight decreased	24	10	9	9

*J Clin Oncol 30:134-141. © 2011.*

## Celotno preživetje – ni razlike

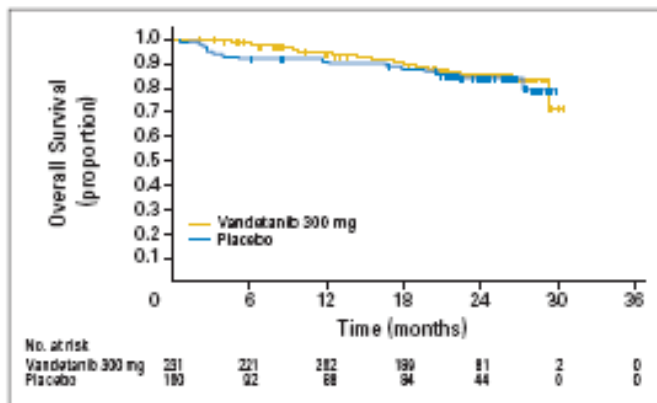


Fig 3. Kaplan-Meier curve of overall survival (intention-to-treat population; all randomly assigned patients).

Ob progresu so možen cross-over na vandetanib (93%)!

*J Clin Oncol 30:134-141. © 2011.*

## Raziskava EXAM



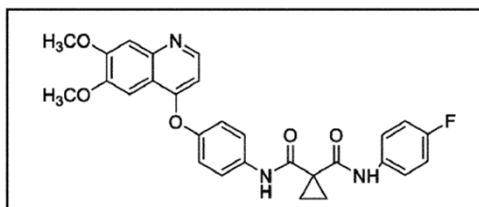
- Multicentrična raziskava faze III (2008-2011), dvojno slepa, kontrolirana s placebom
- **Cabozantinib 140 mg vs. placebo (2:1); n=330**
- Lokalno napredovala neresektabilna bolezen/ metastatska bolezen
- Radiološki PROGRES BOLEZNI po RECIST-u (v zadnjih 14. mes)
- I. cilj: PFS Ob progresu ni bil dovoljen cross-over!

Elisei J et al. J Clin Oncol  
2013; 31: 3639-46.

# Cabozantinib

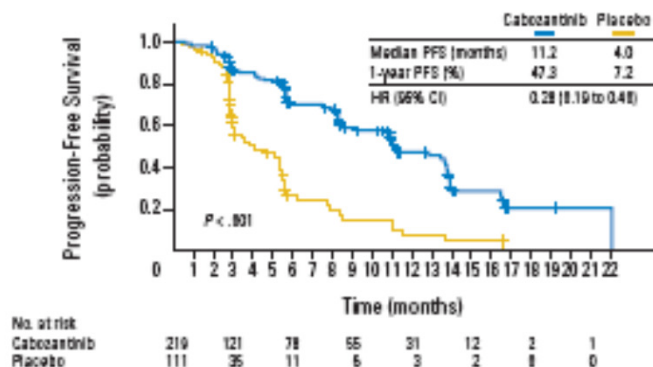


- Mala molekula



- Multi-kinazni inhibitor (RET, MET)
- Antiangiogeno delovanje (VEGFR-2)

## Primarni cilj raziskave EXAM



Objektivni RR:  
27% vs. 0%

**HR 0,28 (95% IZ 0,19-0.40), p<0.001;**  
 -srednji PFS: 11,2 mes. vs. 4,0 mes.;  
 -1-letni PFS (%): 47,3% vs. 7,2%  
 -mediano trajanje odgovora 14,6 mes  
 -mediano trajanje zdravljenja: 204 vs. 105 dni  
**Učinek neodvisen od RET mutacije!**

Elisei J et al. J Clin Oncol  
2013; 31: 3639-46.

## Neželeni učinki



### Povezani s kinaznim delovanjem

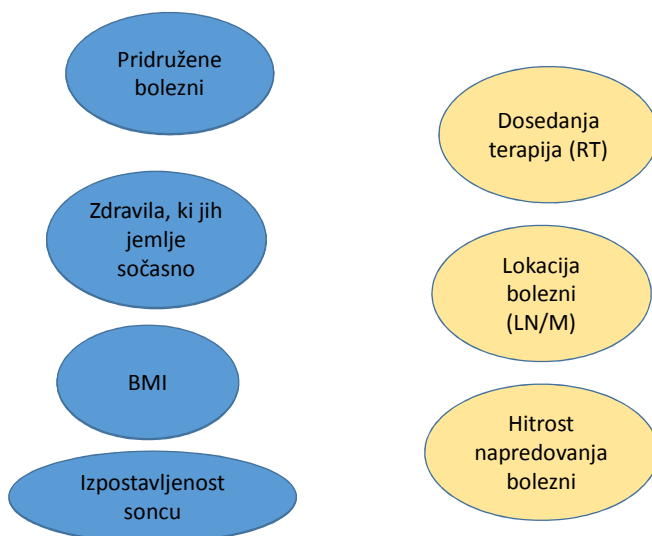
- Kožni: palmarno-plantarna eritrodizesteziya
- Diareja
- splošna oslabelost (fatigue)
- vpliv na krvno sliko: nevtropenija, trombopenija
- elektrolitne motnje: K, Na, Mg, P, Ca,
- patološki jetrni testi!

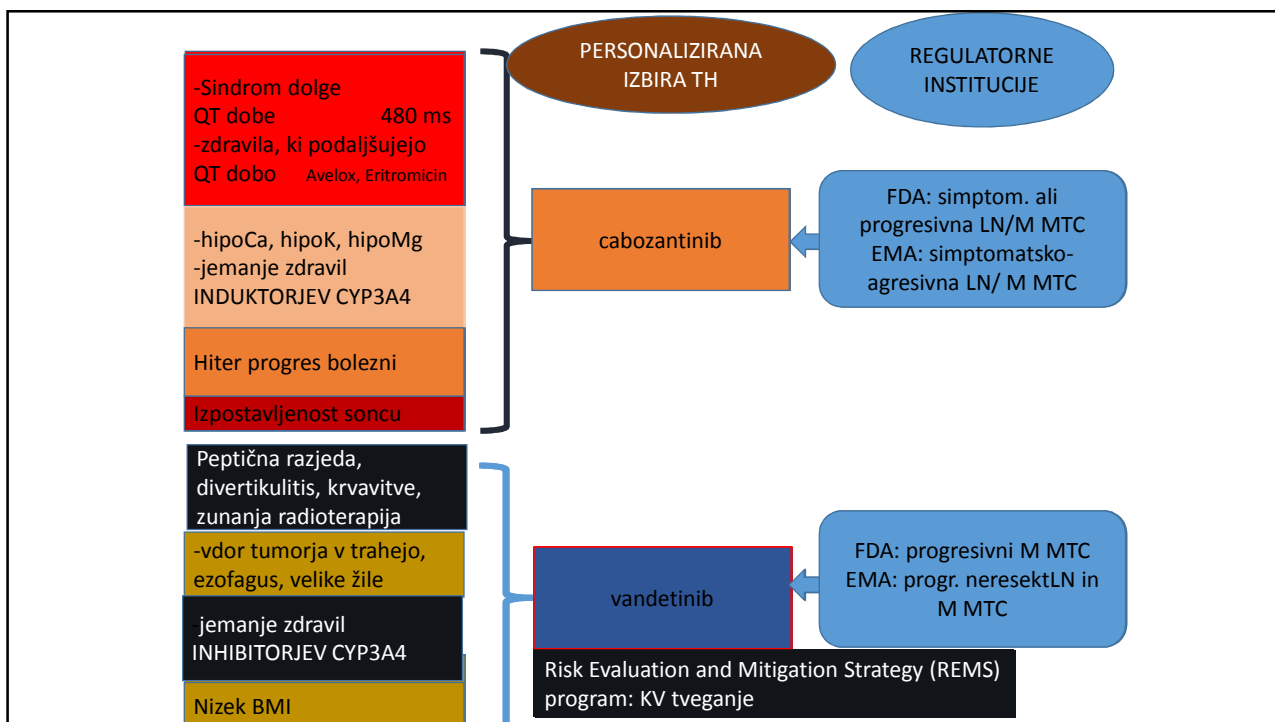
### Povezani z antiangiogenim delovanjem

- fistule, perforacije GIT
- hude krvavitve
- venska tromboza
- arterijska hipertenzija
- AE G3/4: 69% vs 33%
- SEA: 42% vs. 23%
- ↓ doze: 79%!!!

Elisei J et al. J Clin Oncol 2013; 31: 3639-46.

## Odločitev o izbiri tarčne terapije





## Best Supportive Care from the Conservative/ Non-Surgical Perspective and Its Costs in the Treatment of Patients with Advanced Medullary Thyroid Cancer: Results of a Delphi Panel

Michael C. Kreissl<sup>a,b</sup> Christian Jacob<sup>c</sup> Dagmar Führer<sup>d</sup> Wolfram Karges<sup>e</sup>  
 Markus Luster<sup>f</sup> Michael P. Lux<sup>g</sup> Klaus Mann<sup>d</sup> Thomas Mittendorf<sup>e</sup>  
 Matthias Schott<sup>h</sup> Christine Spitzweg<sup>i</sup> Hans-Joachim Schmoll<sup>k</sup>

Oncol Res Treat 2014;37:316-322

**Table 2. Costs of BSC in advanced MTC**

Medications/BSC measures	Percentage of use	Weighted cost			
		Based on DDD (€)	Per day, €	Per month (30 days), €	Per year (365 days), €
<b>Medications</b>					
Antidiarrheals	56.67	2.30	1.30	39.10	475.74
Analgesics (excluding opiates)	39.44	1.45	0.57	17.16	208.74
Opiates	31.11	3.06	0.95	28.58	347.68
Bisphosphonates	27.78	12.97	3.60	108.10	1,315.19
Antiemetics	21.67	1.68	0.36	10.89	132.50
Antithrombotics	21.11	0.68	0.14	4.32	52.51
Other medications targeting functional gastrointestinal disorders	17.22	0.49	0.08	2.51	30.56
Antidepressants	9.44	0.69	0.07	1.95	23.77
Sedatives	8.11	0.67	0.05	1.63	19.84
Diuretics	5.63	0.20	0.01	0.33	4.01
Laxatives	5.56	0.76	0.04	1.27	15.45
Antiepileptics	4.22	2.58	0.11	3.26	39.70
Neuroleptics	3.11	3.82	0.12	3.56	43.35
Immunostimulants	0.89	66.33	0.59	17.71	215.48
<b>Other services</b>					
Physiotherapy	29.22	3.94	1.15	34.54	420.21
Palliative radiotherapy	28.75	3.65	1.05	31.48	383.02
Enteral nutrition	16.11	66.57	10.72	321.73	3,914.42
Occupational therapy	15.33	5.00	0.77	23.00	279.77
Psychotherapy	11.11	2.41	0.27	8.02	97.56
Palliative surgery	10.33	21.56	2.23	66.80	812.76
Oxygen support	2.78	1.14	0.14	34.21	416.23
<b>Total costs, €</b>			<b>25.32</b>	<b>760.15</b>	<b>9,248.49</b>

BSC = Best supportive care, DDD = defined daily dose.

**Somatostatinski analogi za kontrolo diareje!**

## Kdaj sistemska KT

- Po progresu na vandetanib, cabozantinib: sunitinib ali sorafenib (raziskave faze II, n= 15-20) ali klinična raziskava
- Kemoterapija: po progresu na tarčno terapijo (NCCN)
- MTC spada med **nevroendokrine tumorje**, ki secernirajo kalcitonin, CEA...
- Dakarbazin (monoterapija ali kombinacija);
- Odgovor na th: <20%

## Zaključki



- LN/M medularni rak ščitnice je lahko dolgo indolentna bolezen
- Zdravljenje s tarčnimi zdravili je indicirano ob **simptomatskem radiološko dokazanem progresu**
- individualizirana izbira tarčne terapije glede na dosedanje bolezni, lokacijo bolezni, sočasno jemanje drugih zdravil
- Pri nas vandetanib in cabozantinib nista na voljo; v tem primeru glede na mnenje konzilija indiciramo sunitinib ali sorafenib; KT

# Primer bolnika z rakom ščitnice

Jelena Azarija

**J.B., l. 1955, ♂**

**Februar 1995:** pregled pri tireologu zaradi rezistence levo na vratu

Klinični pregled: tipen nodus v levem ščitničnem lobusu, ki je fiksiran na trahejo in premičen pri požiranju; brez tipno povečanih bezgavk na vratu

UZ ščitnice: povečan levi ščitnični reženj, v spodnjem delu je neostro omejeno nehomogeno hipoehogeno področje

Punkcija gomolja - citološki izvid: suspektno za folikularni maligni proces

Laboratorij: Tg 1.5, TSH 0.93, aTG in aTPO negativna



## J.B., I. 1955, ♂

**Marec 1995:** pregledan na Onkološkem inštitutu

Punkcija gomolja - citološki izvid: posamezne skupine celic sumljive za papilarni karcinom, vendar procesa ni možno zanesljivo opredeliti

Scintigrafija ščitnice s  $^{99m}\text{Tc}$ : hladen nodus v levem lobusu ščitnice

RTG p/c: bp

Laboratorij: bp

## Primarno zdravljenje

**Maj 1995:** totalna tiroidektomija

Histološki izvid: **folikularni karcinom** v levem ščitničnem režnju, **multicentričen** (velikost?), **slabo diferenciran**, z blago do zmerno mitotsko aktivnostjo, **vrašča v ovojnico**, vendar se **ne širi izven** ščitnice, prisotna **obsežna vaskularna invazija**, nahaja se **v medialnem resekcijskem robu**.

D lobus, obščitnice, LNN (0/1): brez malignih celic.

**Junij 1995:** ablacija z  $^{131}\text{I}$  (100 mCi) + ščitnični hormoni v supresijskem odmerku

**Julij 1995:** obsevanje predela ščitnice in zgornjega mediastinuma (TD 45 Gy)

**Papilarni ali folikularni rak - Mlajši od 45 let**

Stadij I	katerikoli T	katerikoli N	M0
Stadij II	katerikoli T	katerikoli N	M1

**Papilarni ali folikularni rak – 45 let ali starejši**

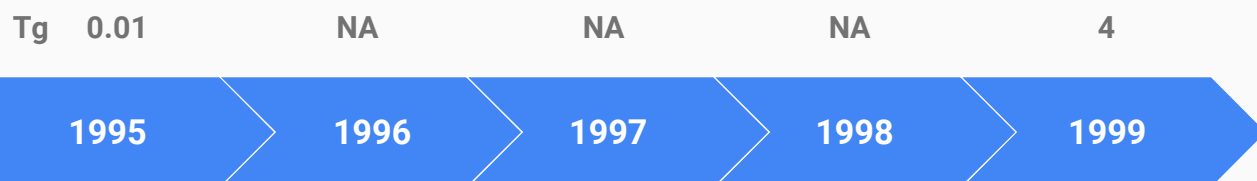
Stadij I	T1	N0	M0
Stadij II	T2	N0	M0
Stadij III	T3	N0	M0
	T1, T2, T3	N1a	M0
Stadij IV-A	T1, T2, T3	N1b	M0
	T4a	N0, N1	M0
Stadij IV-B	T4b	katerikoli N	M0
Stadij IV-C	katerikoli T	katerikoli N	M1

pT2/T3 N0 M0

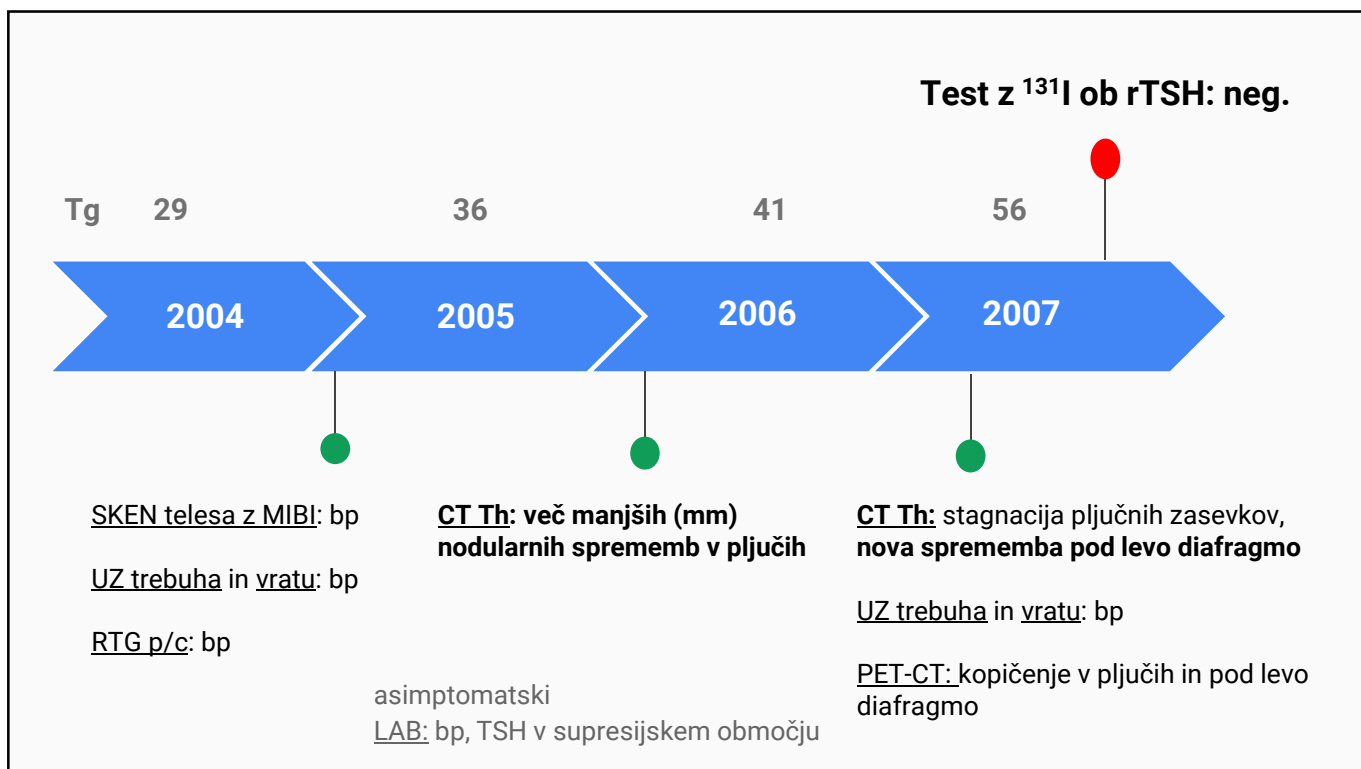
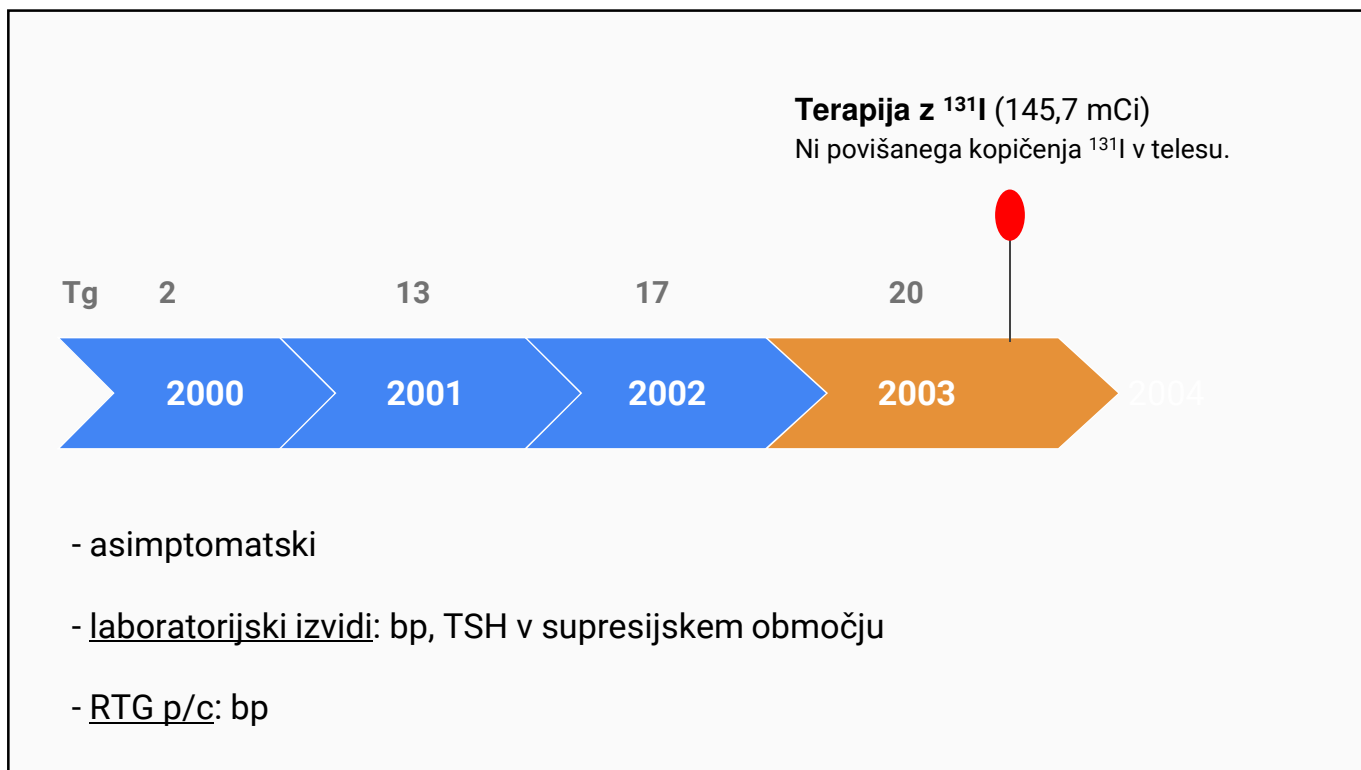
**stadij I**

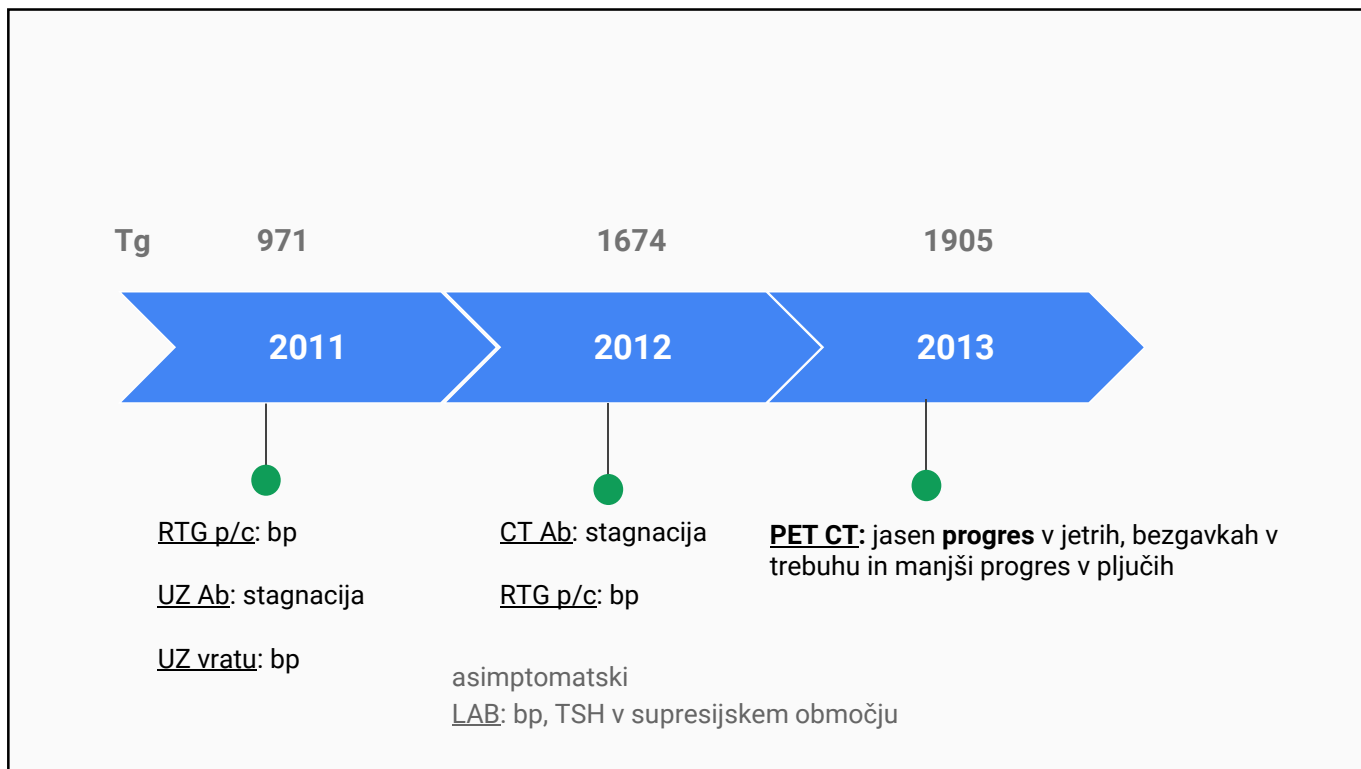
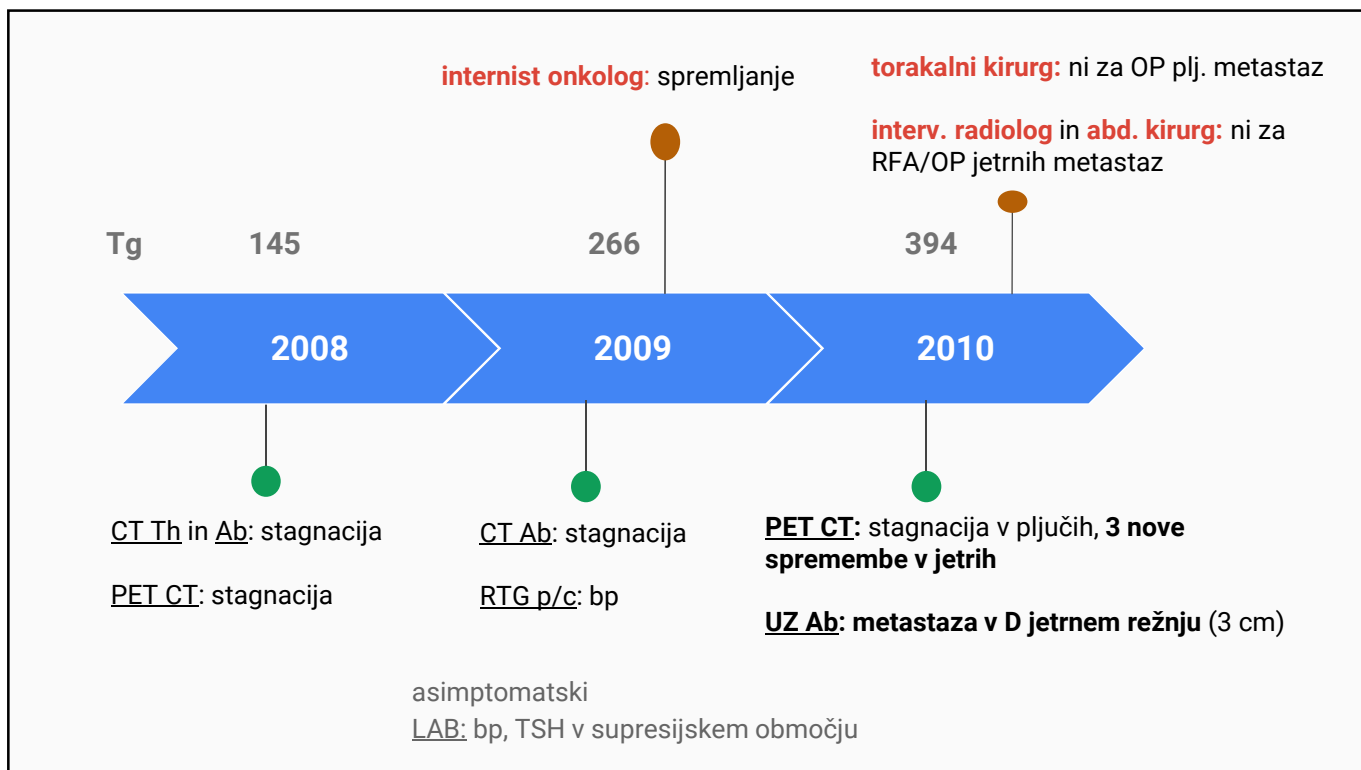
7. izdaja TNM klasifikacij

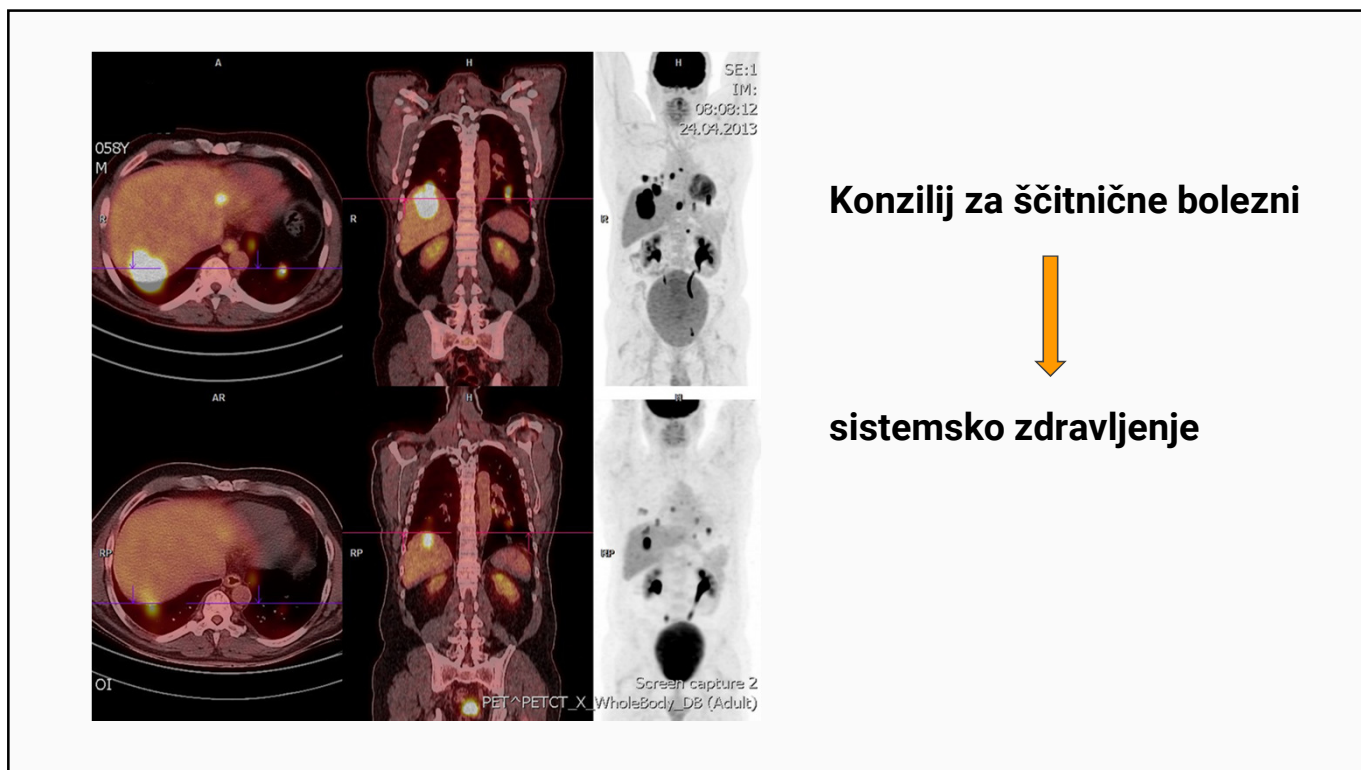
## Sledenje



- asimptomatski
- laboratorijski izvidi: bp, TSH v supresijskem območju
- RTG p/c: bp







## Sistemsko zdravljenje

**Maj 2013:** pregled pri internistu onkologu

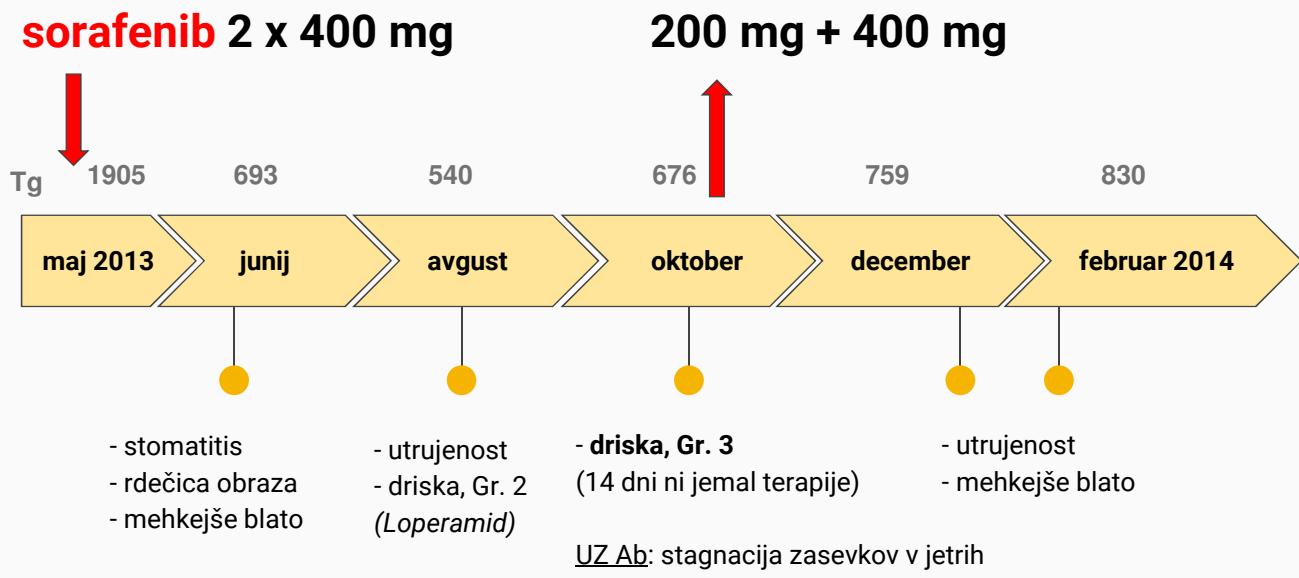
Anamneza:

- en mesec trajajoča nepojasnjena nevrološka simptomatika (težave z L okončinama - hemipareza, nevrogeni mehur), v obravnavi pri **nevrologu** (CT glave, MRI glave in Th-L hrbtenice, EMG, LP, onkonevronska Ig: bp)
- drugih težav ne navaja

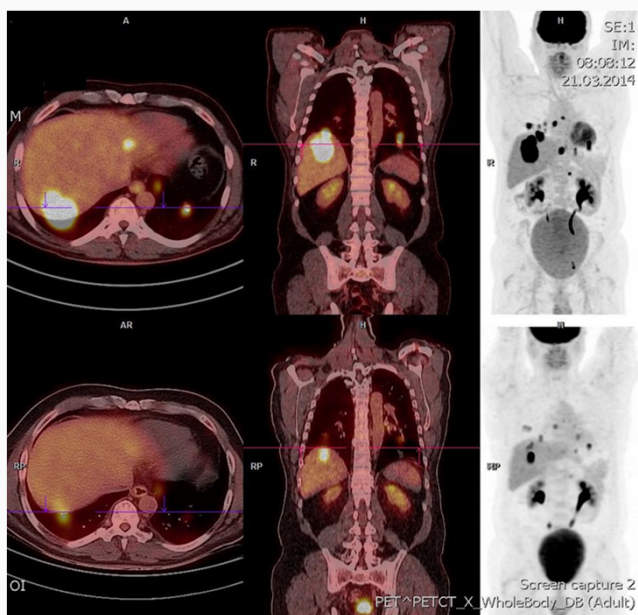
Klinični pregled: v mejah normale

Laboratorij: **Tg 1905**, preostali izvidi bp

# 1. linija zdravljenja



# Progres bolezni



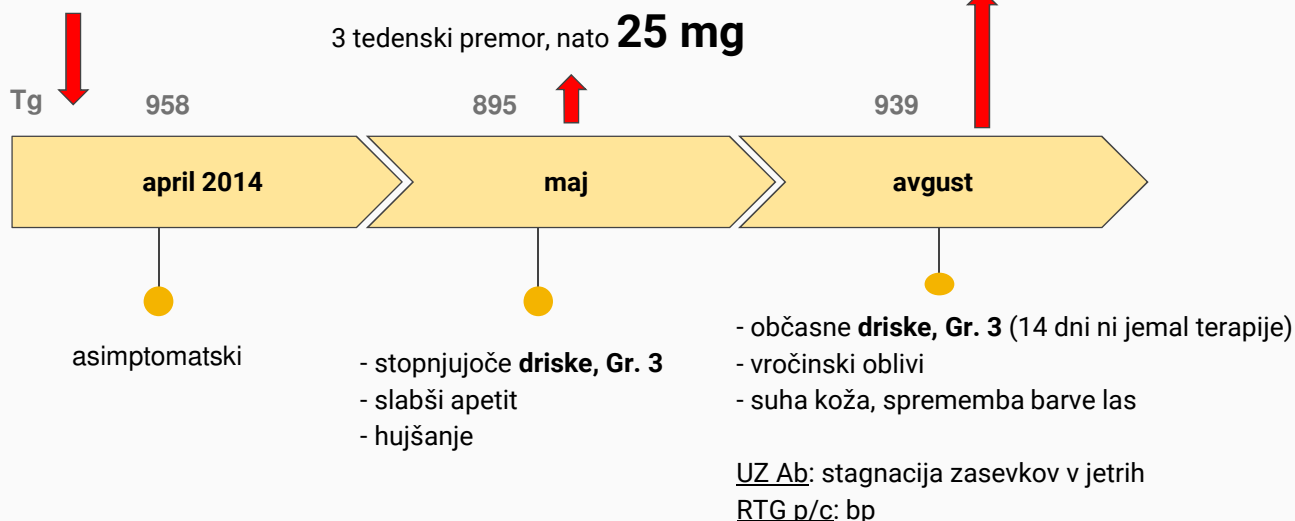
## PET-CT (marec 2014):

- progres v jetrih in pljučih
- nove patološke bezgavke v Ab

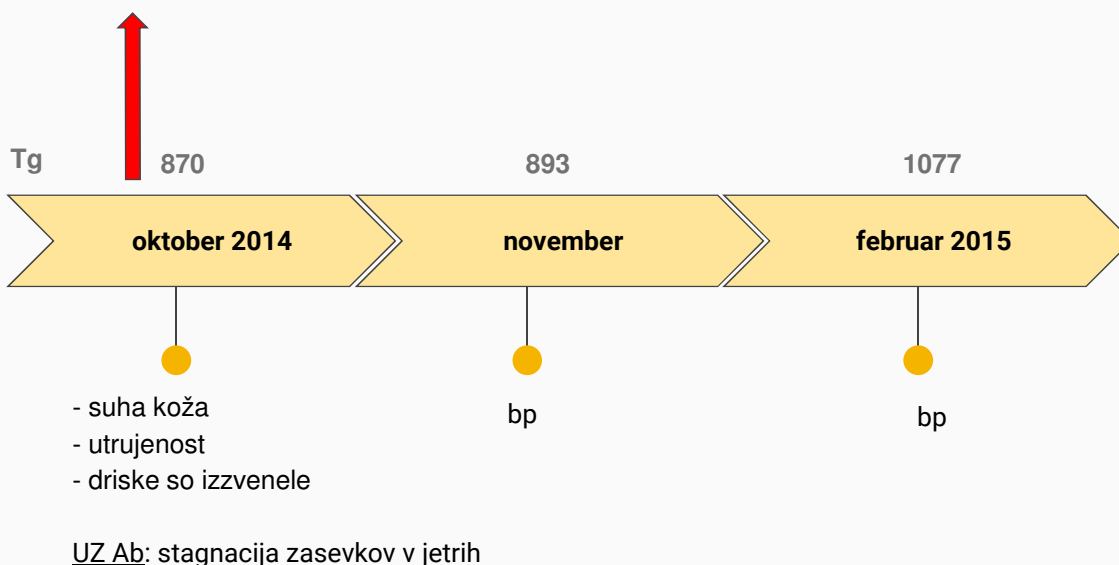
## 2. linija zdravljenja

**sunitinib 37.5 mg**

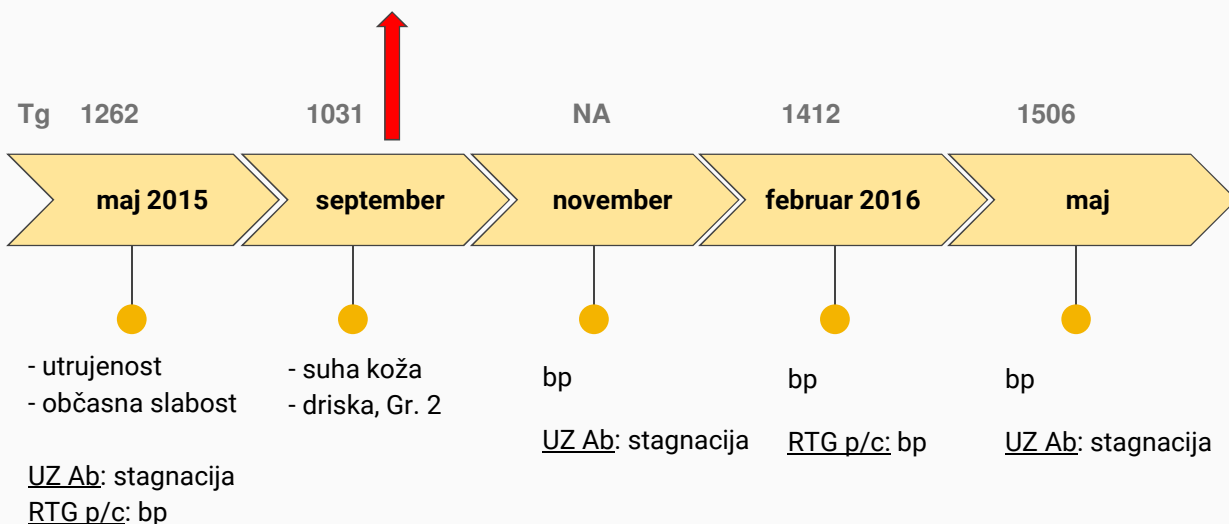
**25 mg 4 tedne - 1 teden pavze**



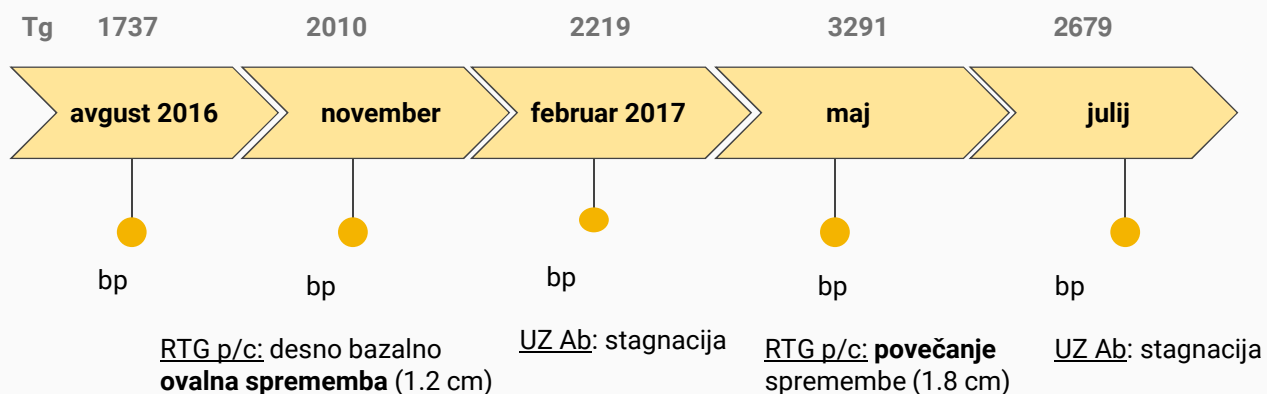
**sunitinib 25 mg 3 tedne - 12.5 mg 1 teden - 1 teden pavze**



**sunitinib 25 mg 1 teden - 12.5 mg 1 teden - še 1 x ponovit shemo - 3 tedni pavze**



**sunitinib 25 mg 1 teden - 12.5 mg 1 teden - še 1 x ponovit shemo - 3 tedni pavze**





**Oktober 2017**

Anamneza: 1 teden trajajoča dispneja, občasna bolečina za prsnico, suh kašelj, huda utrujenost

Status: blažje prizadet, dispnoičen v mirovanju, FR<sub>D</sub> 17/min, SaO<sub>2</sub> 97 %, RR 150/110 mmHg, FR<sub>S</sub> 70/min. Preostali status bp.

Laboratorij: Tg 2889, LDH 5.57, preostali izvidi bp.



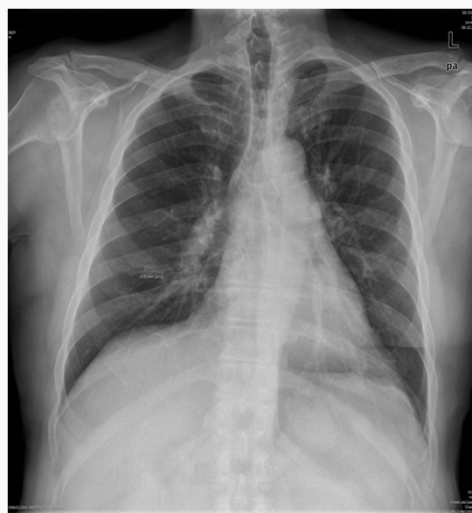
**pljučna embolija / a. ishemija miokarda?**

EKG: inverzni T valovi in ST denivelacije v V1-V3

RTG p/c: povečana oba pljučna hilusa, nodularna sprememba v pljučih v stagnaciji



napoten na Internistično prvo pomoč



Dg: **obsežna pljučna embolija** z jahajočim trombom na odcepišču obeh glavnih pljučnih arterij (brez znakov za obremenitev desnega srca) ob **GVT D goleni**

## Zadnji pregled: 6.11.2017

Anamneza: Okreva po pljučni emboliji, je na terapevtskih odmerkih NMH. Počutje je zadovoljivo, nima večjih sopojavov zdravljenja s sunitinibom.

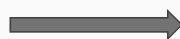
Status: v mejah normale

Laboratorij: **Tg 2935, AST 0.97, ALT 1.91**, preostali izvidi bp



Nadaljuje z ustaljeno shemo sunitiniba.

Ob naslednji kontroli: UZ Ab, RTG p/c.



**Zamenjava terapije?**

# Hvala za pozornost!

13. dan internistične onkologije  
NOVOSTI V SISTEMSKEM ZDRAVLJENJU REDKEJŠIH SOLIDNIH RAKOV

# SISTEMSKO ZDRAVLJENJE GASTROINTESTINALNIH STROMALNIH TUMORJEV (GIST)

Mag. M. Unk, dr.med.

Onkološki inštitut Ljubljana, 17.11.2017

## Uvod

- Mazur in Clarck 1983
- Mezenhimalni tumor
- Mezoderm prebavnega trakta
- Pod 1% vseh tumorjev prebavil
- Hirota et al 1998: KIT mutacija
- Cajalove intersticijske celice (? prekurzor)

## Epidemiologija

- Incidenca 1/100000/leto (klinično pomembni, >1 cm)
- moški > ženske
- Starost 40-80 let (srednja ~ 60 let)
- Večina sporadični
- V sklopu sindromov (Carneyeva triada, Carney Stratakis sindrom, neurofibromatoza I)
- Familialno (AD mut KIT)

Eisenberg et al. Ann Surg Oncol 2004; Gold et al. Ann Surg 2006; DeMateo et al. Ann Surg 2000; Takazawa et al. Am J Surg Pathol 2005.

## Lokacija

- Želodec: 50%
- Požiralnik: 5%
- Tanko črevo: 25%
- Debelo črevo in rektum: 10%
- Ekstraintestinalno: 10%

Rubin et al, Clin Can cer Res 2003

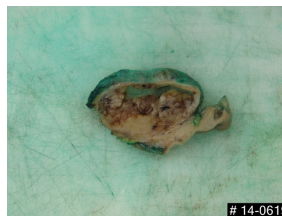


Z dovoljenjem: A. Klevišar, OI

## Klinična slika

- Nespecifična
- Odvisna od mesta
- V prebavilih: krvavitev
- Ostalo:
  - masa v trebuhu
  - bolečina
  - distenzija
  - obstrukcija
- Asimptomatski: 30%

Miettinen et al. Hum Pathol 1999.



Z dovoljenjem: O. Blatnik, OI



Z dovoljenjem: A. Klevišar, OI

## Diagnoza

- Klinične, radiološke in patohistološke značilnosti
- CT s kontrastom (slikovna preiskava izbora)
- Endo UZ za manjše tumorje
- MRI: rektalni GIST
- PET CT
- Predoperativna biopsija:
  - ponavadi ne („seeding“, krvavitev)
  - endoskopska biopsija: potrditev dg, manj krvavitev

Naključno odkrita subepitelijska sprememba:

- Ni jasnih priporočil
- Na endoUZ pod 2 cm, ponovi čez 3 mesece; dinamika
- če izrašča iz mišičnine in je nad 3 cm; verjetno GIST; op
- Če izrašča iz mišičnine; ABTI in cKIT
- ? Mase med 2 in 3 cm
- Rektum, vagina

Blay et al. Ann Oncol 2005

## Patohistologija

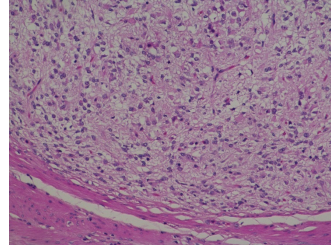
- **Makroskopska slika:** dobro omejen, belkasto siva, slatinasta površina, ulceracija v 50%

- **Diagnoza:** morfologija in imunohistokemija

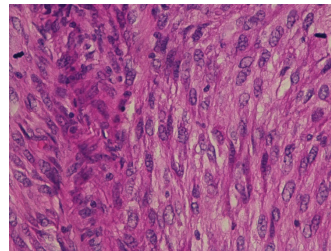
Vretenaste celice

IHC: CD117 (5% je neg), DOG1

Molekularna analiza gena cKIT, PDGFR $\alpha$ , bRAF



Z dovoljenjem: O. Blatnik, OI



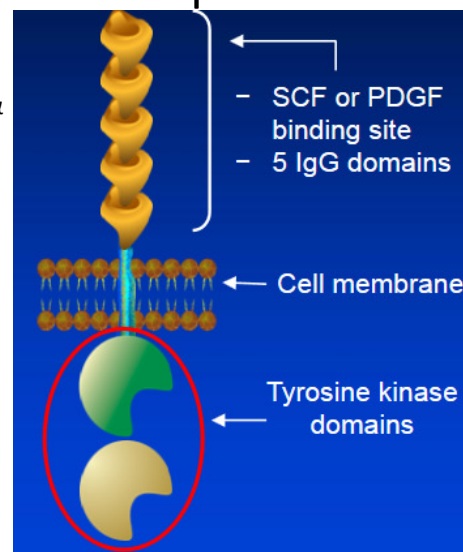
Z dovoljenjem: A. Klevišar, OI

## Genetska osnova GIST: KIT – PDGFR $\alpha$ receptor

### Tirozinska kinaza tipa 3

- Vezava liganda na KIT ali PDGFR $\alpha$  sproži kaskado reakcij...
  - proliferacija
  - antiapoptoza
- Ekstracelularna domena
  - SCF za KIT
  - PDGF za PDGFR $\alpha$
- Intracelularna domena
  - dve tirozin kinazi
  - več avtofosforilacijskih mest

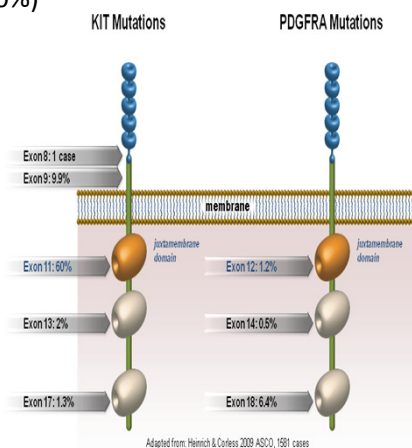
SCF: stem cell factor  
Taylor et al. Haematol Oncol Clin North Am 2000; Corless et al. Annu Rev Pathol 2008.



## Molekularni podtipi GIST

- KIT mutacija
  - 80% (exon 11- 70%, ekson 9- 10%)
- PDGFR mutacija – 10 %
- SDH-B pomanjkanje
- Raf V600E
- NF1
- Ras
- PI3K
- Prekomerno izražanje IGF-1R
- Wild type

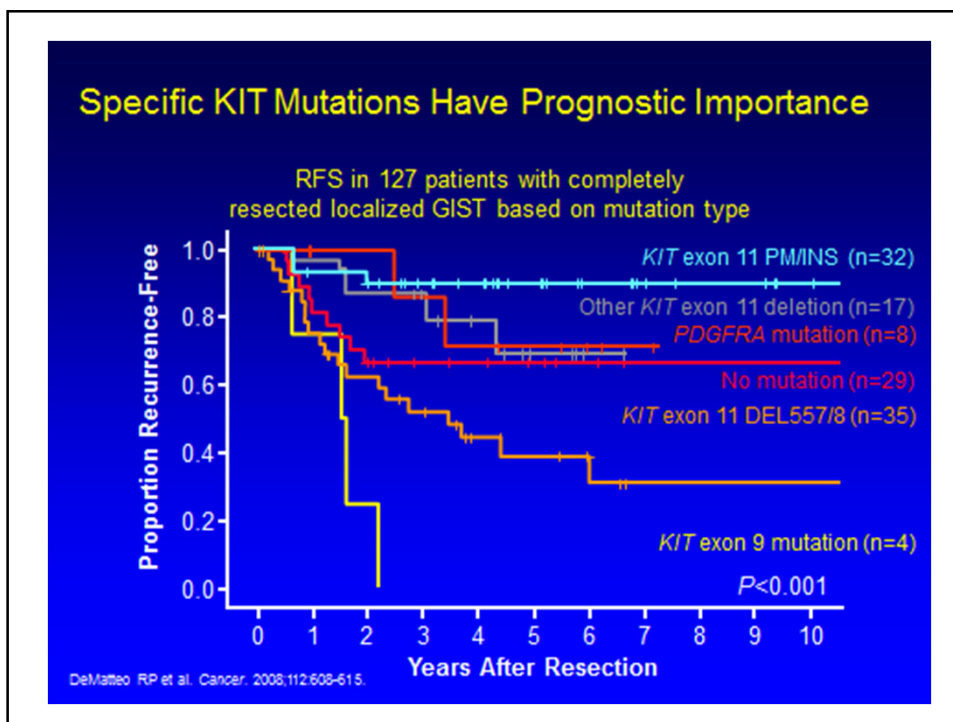
Blay et al. Discover Med 2012



## Maligni potencial

- Ocena malignega potenciala: izziv
- Morfologija vpliva na maligni potencial:
  - mitoze
  - lokacija
  - velikost
- Vpliv rupture tumorja ob operaciji
- Tip mutacije prediktivni dejavnik za odgovor na zdravljenje metastatske bolezni (? Adj)

Fletcher et al. Hum Pathol. 2002; Demetri et al. J Natl Compr Cancer Netw. 2007; Miettinen et al. Ach Pathol Lab Med. 2006; Debiec-Rychter et al. Eur J Cancer. 2006; Heinrich MC et al. J Clin Oncol. 2003;21:4342-4349.



## Vloga sistemskega zdravljenja

- Omejena bolezen:

- Adjuvantno
- Neoadjuvantno

Statistično pomembno tveganje za ponovitev bolezni 50% (nomogram)

- Velikost
- Mitotična aktivnost
- Lokacija
- Molekularna analiza

- Metastatska bolezen:

- 1. red
- 2. red
- 3. red

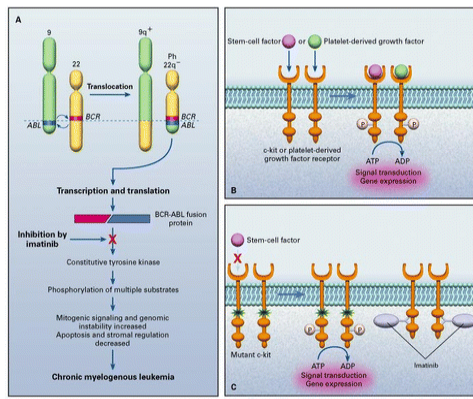
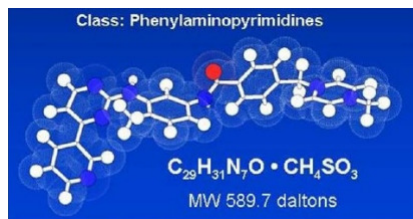
Miettinen et al. Arch Pathol Lab Med 2006



# Imatinib

- Specifični inhibitor tirozin kinazne aktivnosti **abl** (Abelson proto-onkogen), **c-kit** **PDGF-R** (platelet derived growth factor receptor)
- Vezava na isto mesto kot ATP

Hantighel et al. Leukemia Lymphoma 2008.  
 Maley et al. EJC 2002; Savage et al. NEJM 2002.



The New England Journal of Medicine

**Brief Report**

**EFFECT OF THE TYROSINE KINASE INHIBITOR STI571 IN A PATIENT WITH A METASTATIC GASTROINTESTINAL STROMAL TUMOR**

HEIKO JOENSU, M.D., PETER J. ROBERTS, M.D., MAARIT SARLOAO-RIKALA, M.D., LEIF C. ANDERSSON, M.D., PEKKA TERUJARTIALA, M.D., DAVID TUVESON, M.D., PH.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPOVILLE, M.D., SASA DIMITRIJEVIC, PH.D., BRIAN DRUKER, M.D., AND GEORGE D. DEMETRI, M.D.


phosphatidylinositol 3-kinase and mitogen-activated protein kinases. Gastrointestinal stromal tumors are notoriously unresponsive to cancer chemotherapy, and there is no effective therapy for advanced, metastatic disease.<sup>6</sup>

We used STI571 (Gleevec, Novartis, Basel, Switzerland),<sup>7</sup> an inhibitor of the tyrosine kinase activity of c-kit, in a patient with a gastrointestinal stromal tumor.

**CASE REPORT**


In October 1996, a 50-year-old, previously healthy woman presented with mild abdominal discomfort and a large mass in the upper abdomen. Two tumors, 6.5 and 10 cm in diameter, were removed from the stomach by proximal gastric resection, and the greater omentum and mesocolic peritoneum were removed because of the presence of multiple metastatic nodules 1 to 2 mm in diameter. Histologic examination of the specimens revealed more than 20 cells undergoing mitosis per 10 high-power fields and identified the masses as a gastrointestinal stromal tumor. The diagnosis was confirmed by immunostaining for CD117, and a c-kit mutation consisting of a deletion of 15 bp from exon 11 was de-

**A**



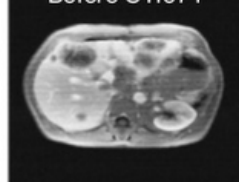
Before STI571

**B**

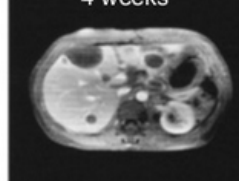


4 weeks

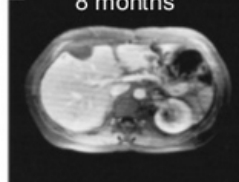
**Before STI571**



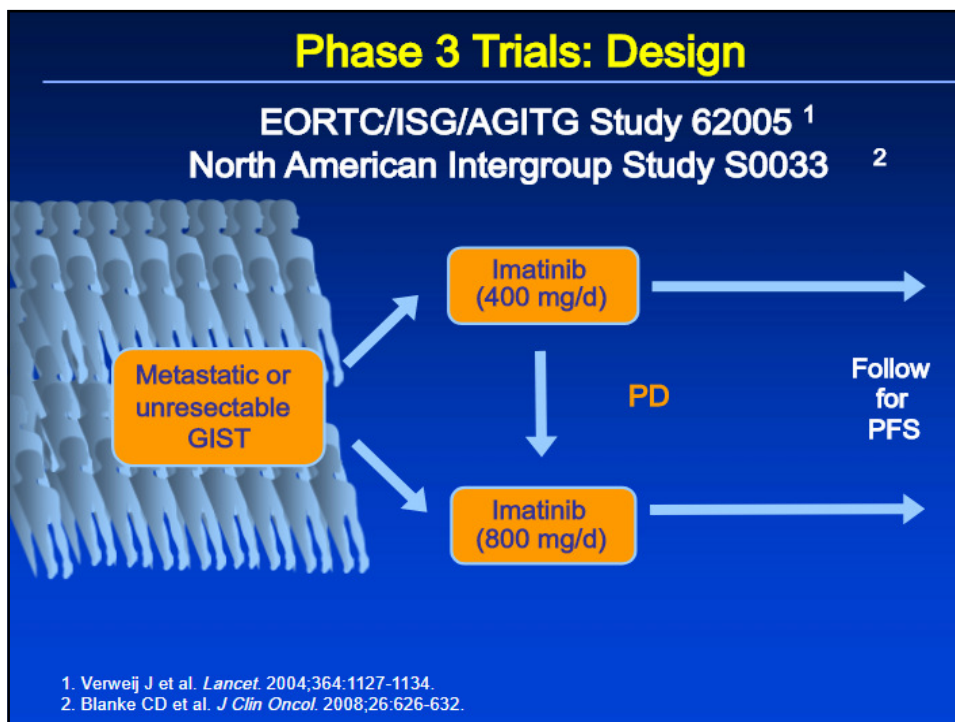
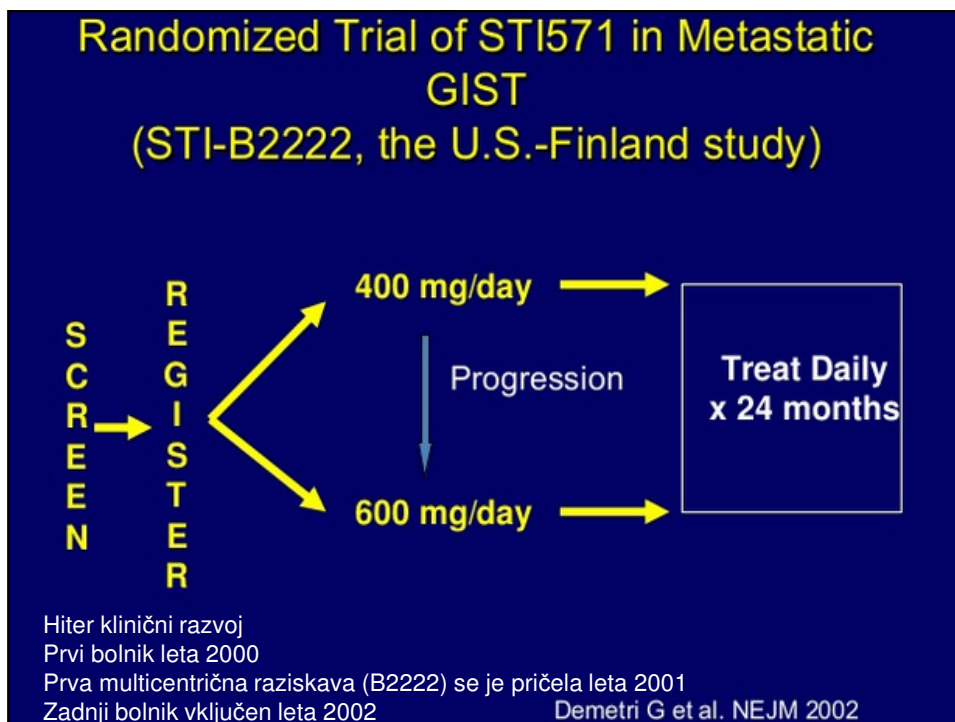
**4 weeks**

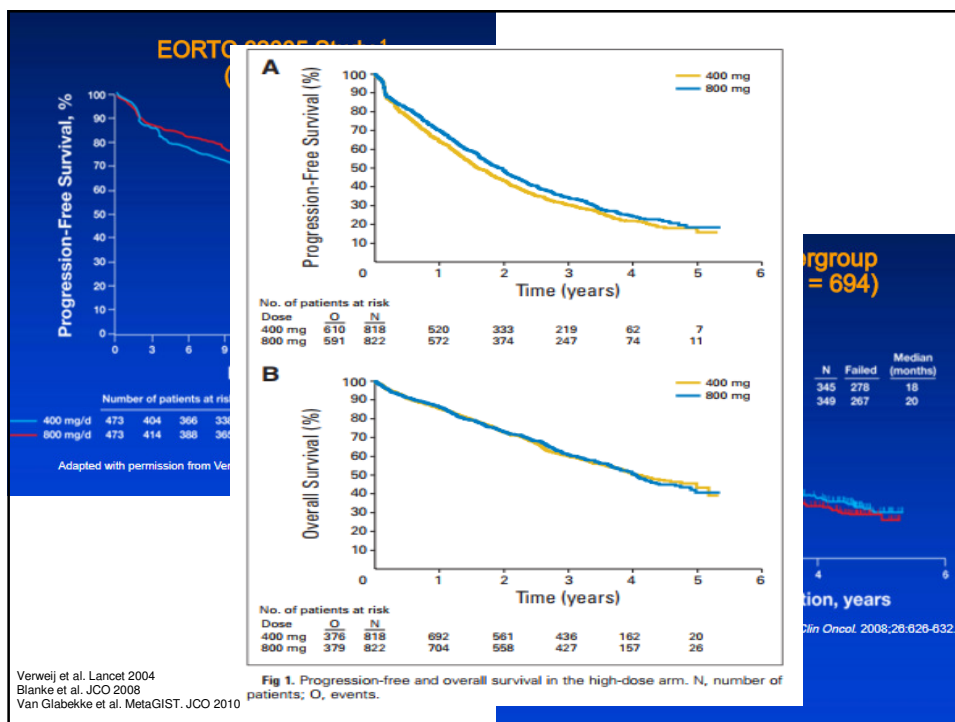


**8 months**



NEJM 2001;344:1052-6 (Apr 5)





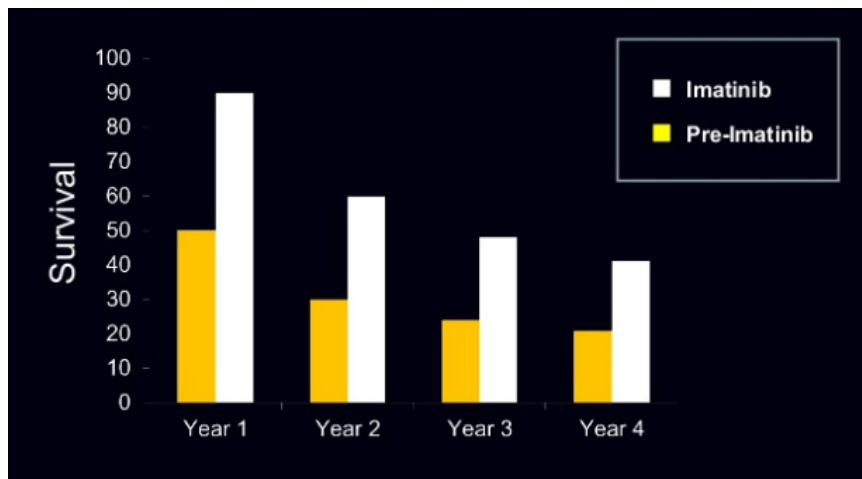
## Metastatski GIST in odgovor na imatinib



raziskava	odgovor (CR, PR, SD)	progres (P)	neocenljivo
B2222	123 (84%)	17 (12%)	7 (5%)
EORTC	794 (84%)	103 (11%)	49 (5%)
S0033	375 (69%)	79 (15%)	86 (16%)
skupaj	1292 (79%)	199 (12%)	142(9%)

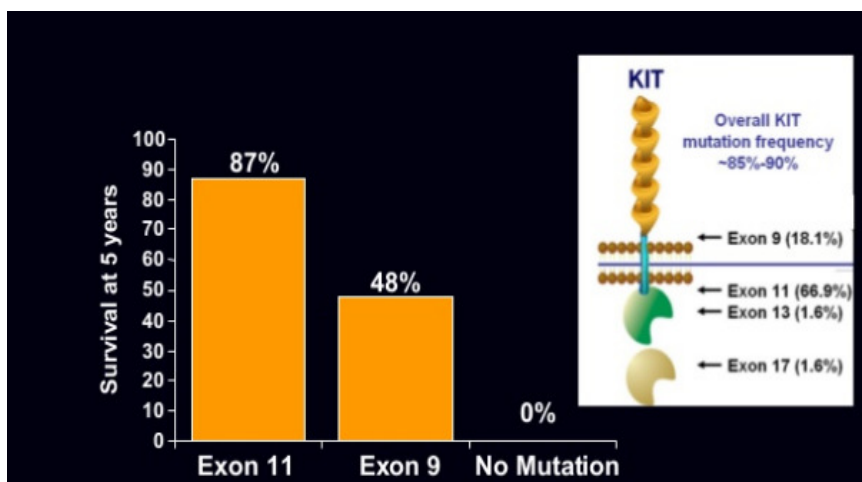
Demetri et al. NEJM 2002; Blanke et al. JCO 2008; Verweij et al. Lancet 2005.

## Preživetje metastatskega GIST pred in po imatinibu



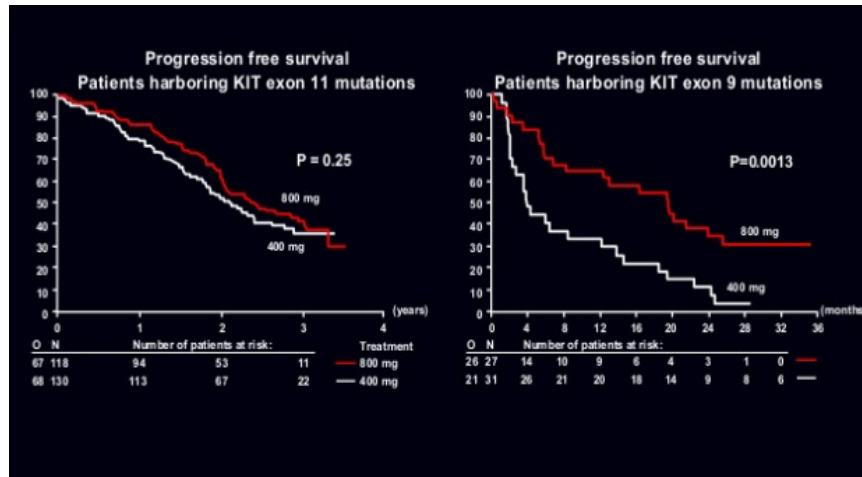
Artinyan and Ellenhorn. Cancer Epidemiol Biomarkers Prev 17:2194

## Imatinib pri napredovalem GIST



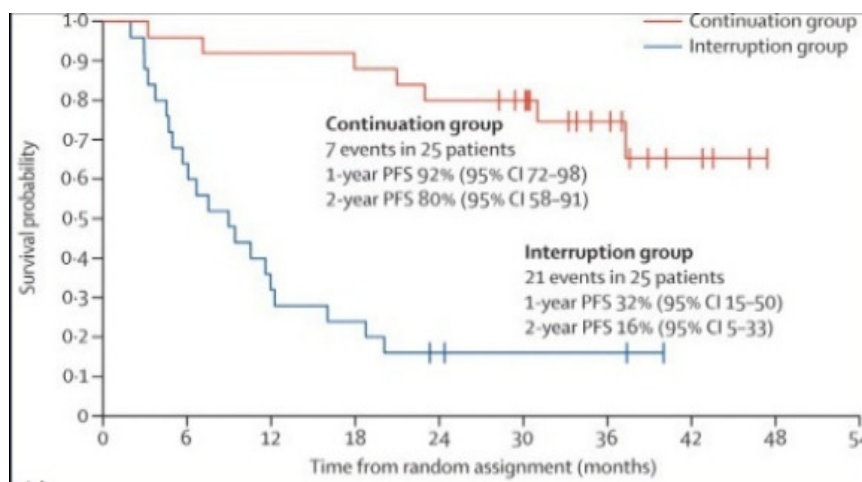
Blanke et al. Proc Am Soc Clin Oncol 2007

## Vpliv odmerka imatiniba na čas do napredovanja bolezni

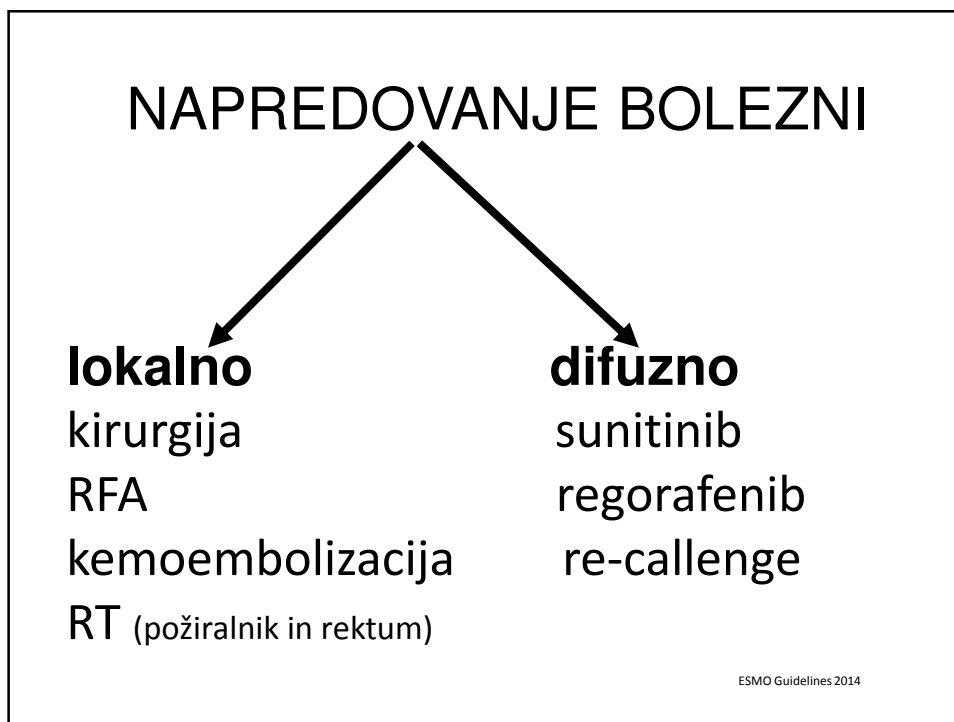


Debiec-Rychter et al. Eu J Cancer 2006

## Trajanje zdravljenja z imatinibom pri metastatski bolezni



Le Cesne et al. Lancet Oncol 2010



## Na imatinib odporen metastatski GIST

Odobren za zdravljenje bolnikov z GIST, katerim je bolezen napredovala tekom zdravljenja z imatinibom ali pa imatiniba ne prenašajo

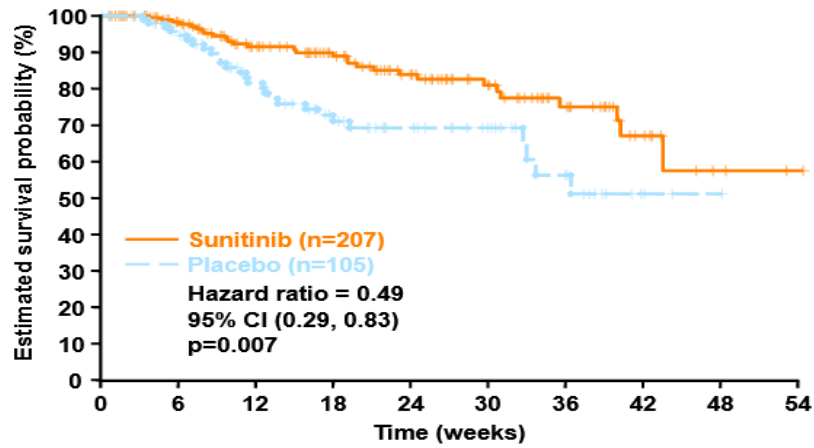
SUNITINIB

Zaviralec različnih receptorских tirozinskih kinaz

Antitumorsko in antiangiogeno delovanje

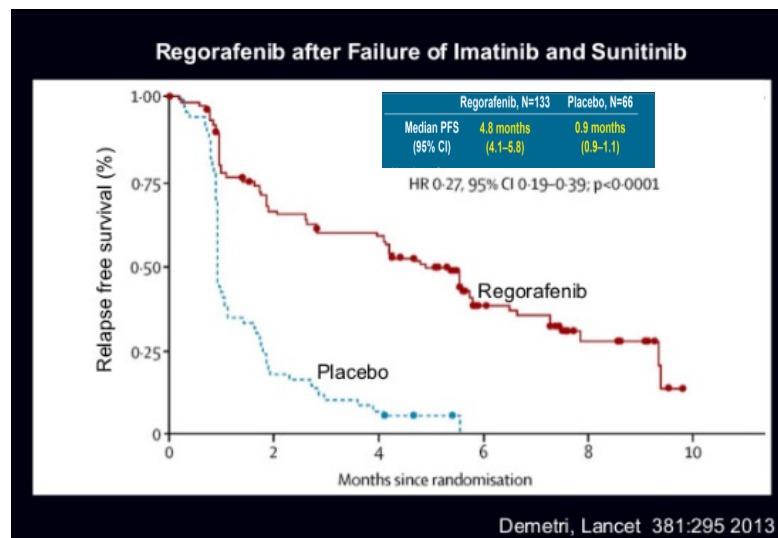
Demetri GD, et al. Lancet. 2006;368:1329-1338.

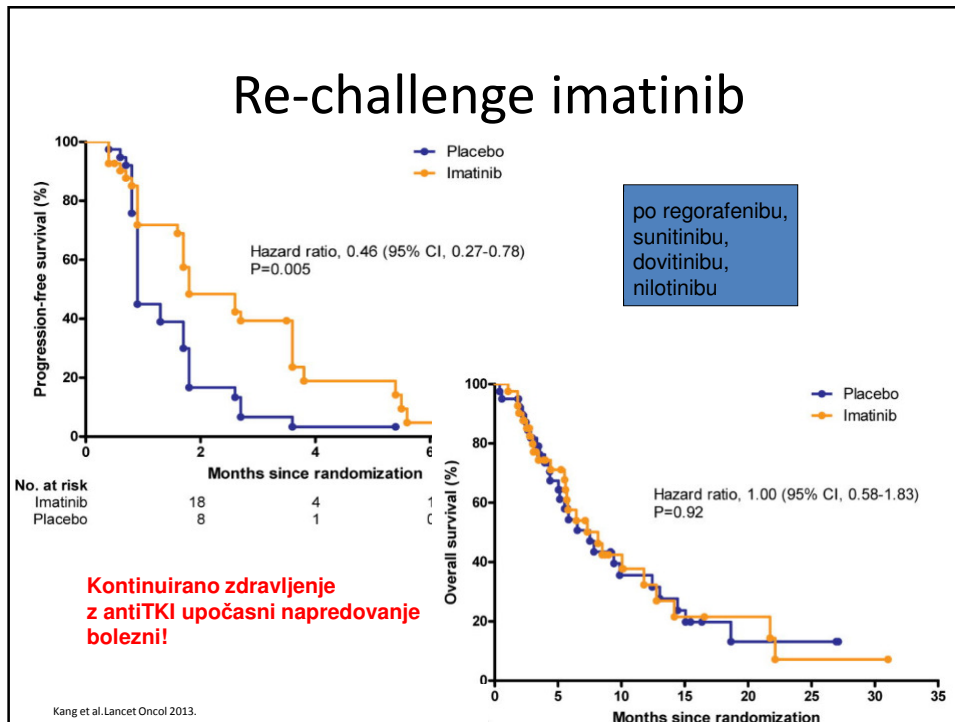
## Preživetje



Demetri et al. Lancet.2006.

## Napredovanje po imatinibu in sunitinibu- GRID





## Dopolnilno sistemsko zdravljenje



# ACOSOGZ9001

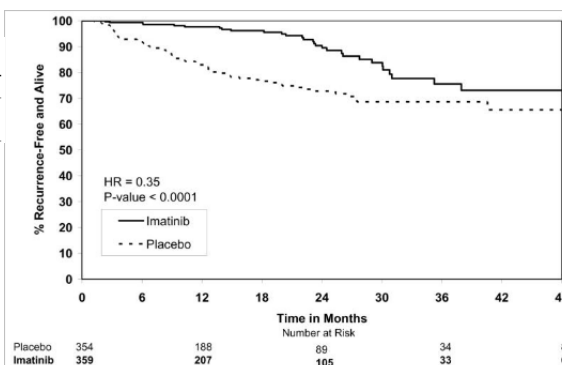
- 713 bolnikov, CD117 pozitivnih, GIST  $\geq 3$  cm
- Imatinib 400mg/dan vs placebo
- Izboljšanje PFS po srednjem spremljanju 20 mesecev
- Brez razlik v preživetju

Summary of RFS and OS results.

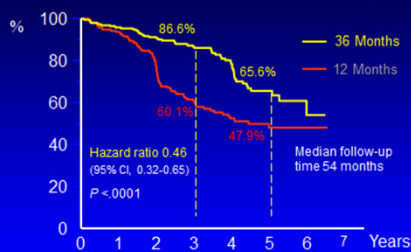
Outcome	No. of pts	No. of events	HR (95% CI)	p-value
RFS (primary)	713	100 (14.0%)	0.35 (0.22 to 0.53)	< 0.0001
OS (secondary)	713	13 (1.8%)	0.66 (0.22 to 2.03)	0.4714

dobrobit PFS je največja pri velikih tumorjih (nad 10 cm), saj imajo ti bolniki več kot 50% tveganje za ponovitev bolezni v 2 letih

Dimateo et al. Lancet 2009.



## SSGXVIII: Recurrence-free survival (ITT)



	0	1	2	3	4	5	6	7
36 Months of imatinib	198	184	173	133	82	39	8	0
12 Months of imatinib	199	177	137	88	49	27	10	0

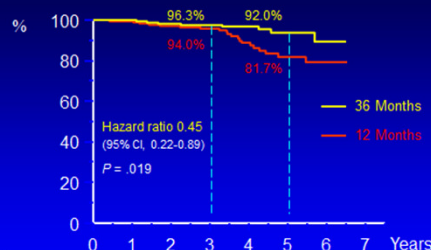
## SSGXVIII<sup>1</sup>

785 bolnikov z velikim tveganjem za ponovitev<sup>2</sup>  
 36 proti 12 mesecev imatiniba  
 Izboljšanje časa do ponovitve bolezni  
 Izboljšanje preživetja  
 Varno zdravljenje

Kateri bolniki so najbolj primerni?  
**MUTACIJE!**

1. Joensuu et al. JAMA 2012.  
 2. Fletcher et al. Hum pathol 2002

## SSGXVIII: Overall survival (ITT)



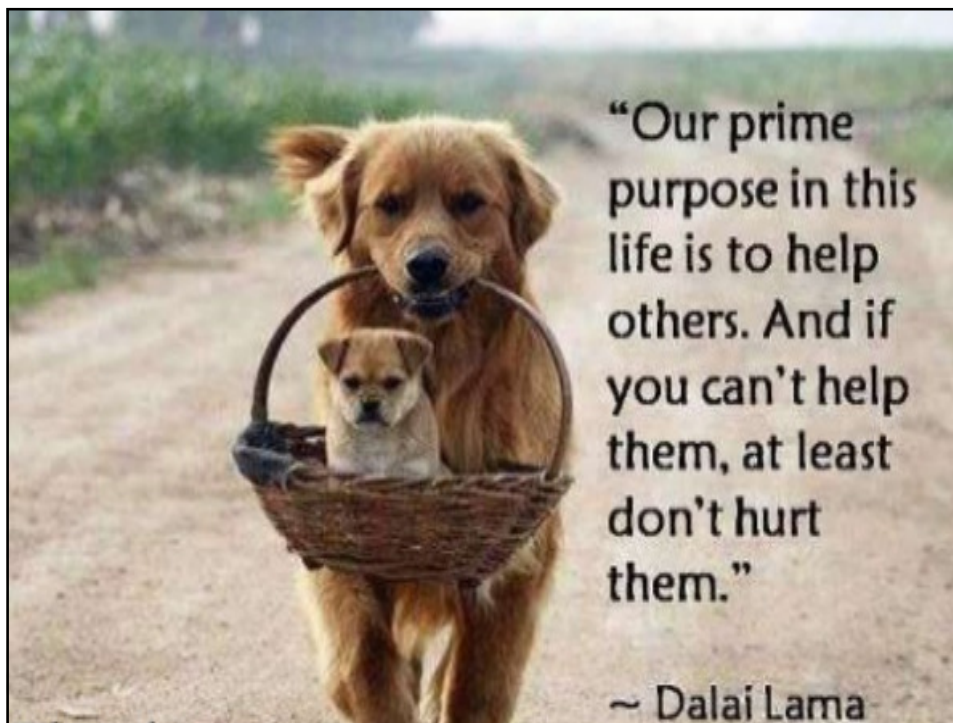
	0	1	2	3	4	5	6	7
36 Months of imatinib	198	192	184	152	100	56	13	0
12 Months of imatinib	199	188	176	140	87	46	20	0


## Neoadjuvantni imatinib

- Kdaj?
    - Inoperabilni ali mejno operabilni
    - Operacija bi imela veliko posledic (multivisceralna)
    - Eventuelno resektabilna metastatska bolezen
- RTOG0132/ACRIN6665
- faza II; ali tumor nad 5 cm (A) ali primarno M1 (B)  
in do 2 cm velik tumor

Eisenberg et al. J Surg Oncol 2009; Wang et al. ASCO 2011.

	Group A	Group B
Response to pre-operative therapy (RECIST)	7% PR, 83% SD, 10% unknown	4.5% PR, 91% SD, PD 4.5%
Estimated 2-year PFS	82.7%	77.3%
Estimated 5-year PFS	57%	30%
Estimated 2-year OS	93.3%	90.9%
Estimated 5-year OS	77%	68%
Type of resection	R0 77% R1 15% R2 8%	R0 58% R1 5% R2 32% Unspecified 5%





## Klinični primer: metastatski GIST

DNEVI INTERNISTIČNE ONKOLOGIJE 2017

Pripravila: Marina Čakš, dr. med

Mentorica: mag. Mojca Unk, dr. med

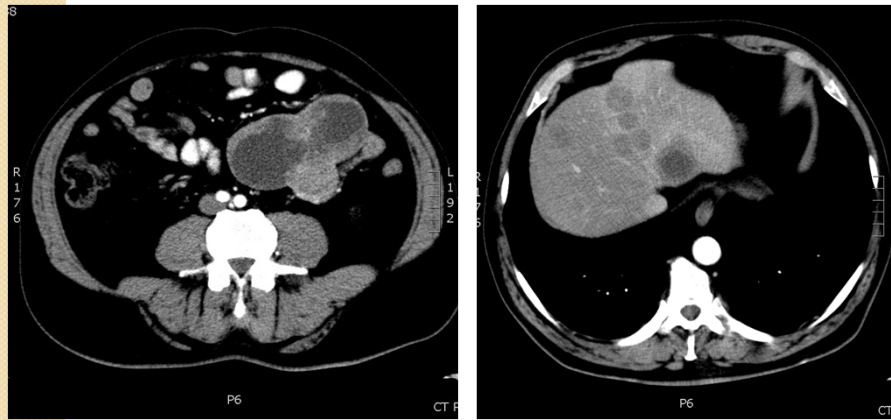


## Predstavitev bolnika

- 62-letni bolnik
- Brez spremljajočih bolezni
- Nekadilec
- V družini rak na debelem črevesju pri teti
  
- Simptomi in znaki: slabost, melena, anemija

## Diagnostika

- CT trebuha: TU v predelu tankega črevesja, zasevki v jetrih

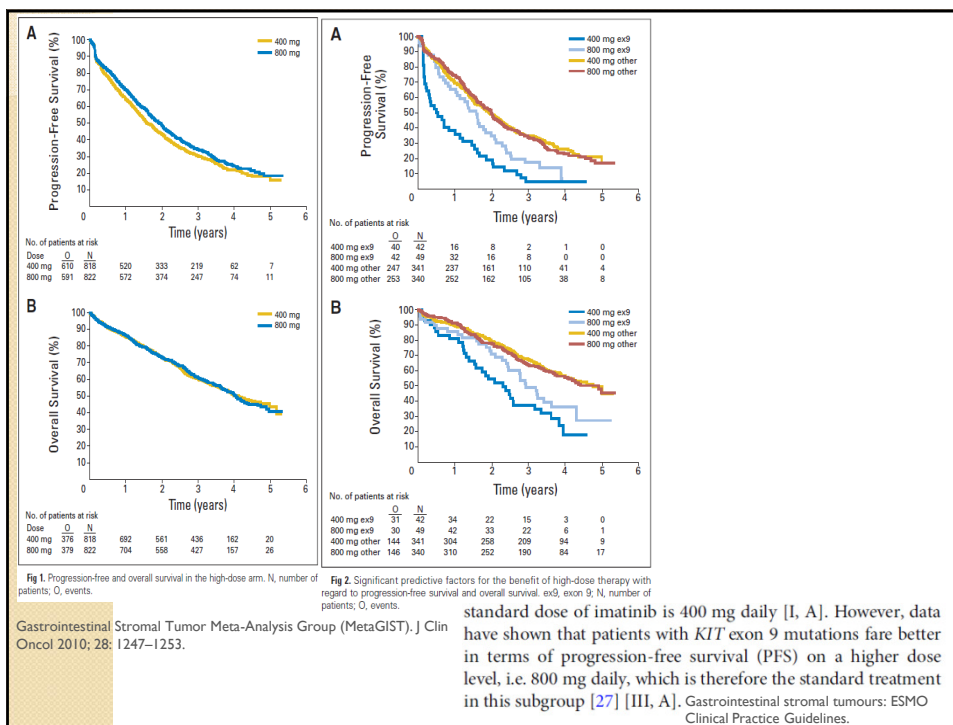


## Diagnostika

- Operacija zaradi krvavitve iz tumorja (11.9.2012): eksplorativna laparotomija, ekscizija tumorja, resekcija dela jejunuma.
- DG: GIST, 10x8,5x6 cm, 40 mitoz/10 polj velike povečave, CD117+; citološka punkcija spremembe v jetrih: metastaza GISTa
- Naknadna določitev mutacij iz primarnega tumorja: prisotna cKIT mutacija na exonu 11

## I.VPRAŠANJE: Za kakšno zdravljenje bi se odločili?

- imatinib 400 mg/d
- imatinib 800 mg/d
- sunitinib
- študijsko zdravljenje
- KT



## Sistemsko zdravljenje I. reda

- **Imatinib** 400 mg/d
- Po 9 mesecih zdravljenja delna remisija bolezni
- NU imatiniba: krči v mišicah, mialgije GI diareja GI, edem GI (periorbitalni), utrujenost oz. oslabelost GI
- Po 21 mesecih difuzen progres bolezni v jetrih, PS I

## 2. vprašanje: Kaj bi naredili zdaj?

- imatinib 800 mg/d
- sunitinib 37,5 mg/d
- sunitinib 50 mg (4t on+2t off)
- klinična raziskava
- RFA

## Povišanje odmerka imatiniba

### EORTC 62005<sup>1</sup>

- 133 bolnikov, crossover na 800 mg
- odgovor: 2% PR, 27% SD
- mPFS: 81 dni

### SOO33<sup>2</sup>

- 77 bolnikov, crossover na 800 mg
- odgovor: 3% PR, 28% SD
- mPFS: 5m

#### Možna razlaga:

- exon 9 mutacija
- nezadostna koncentracija zdravila v krvi <sup>3</sup>

<sup>1</sup>Zalberg et al., Eur J Cancer 2005; 41(11): 1751-1757.

<sup>2</sup>Blanke et al., J Clin Oncol 2008; 26(4): 626-632.

<sup>3</sup>Demetri et al., J Clin Oncol 2009; 27(19): 3141-3147

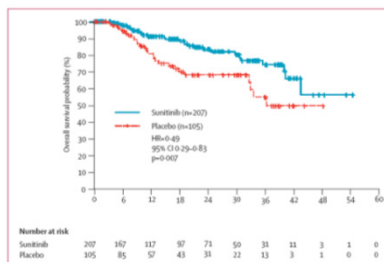
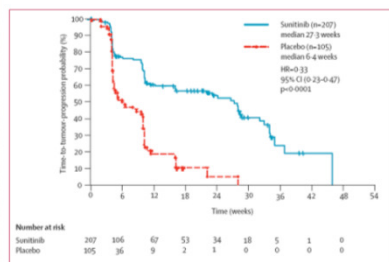
## Sistemsko zdravljenje

- **Imatinib 800 mg/d**
- Najboljši odgovor stagnacija bolezni
- NU: mialgije GI, edem GI (periorbitalni)
  
- Po 6 mesecih zdravljenja difuzen progres bolezni v jetrih, pojav anemije, PS I

### Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial



George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali



Demetri GD et al., Lancet. 2006;368:1329-1338.

### 3. vprašanje: Za kakšen odmerek sunitiniba bi se odločili?

- sunitinib 50 mg; 4 t on+ 2 t off
- sunitinib 37,5 mg/d



In the case of confirmed progression or rare intolerance on imatinib (after attempts to manage side-effects also through expert advice, also exploiting dose reductions and possibly plasma level assessment), standard second-line treatment is another tyrosine kinase inhibitor, sunitinib [34] [I, B]. The drug was proved effective in terms of PFS following a '4 weeks on-2 weeks off' regimen. Data have been provided that a continuously dosed daily oral regimen with a lower daily dose (37.5 mg) is effective and well tolerated, although no formal comparison has been carried out within a randomised clinical trial. This schedule can therefore be considered an alternative on an individualised basis [35] [III, B].

Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines

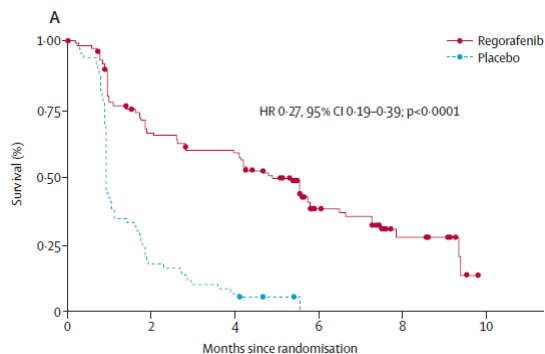
## Sistemsko zdravljenje 2. reda

- **Sunitinib 37,5 mg/d**
- Po dveh mesecih zdravljenja dosežena delna remisija bolezni
- NU: diareja G2, sprememba barve kože, HFS GI, hipotiroidizem, trombocitopenija GI, AH
- Po 18 mesecih zdravljenja difuzen progres bolezni v jetrih, PS I

### Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial



George D Demetri, Peter Reichardt, Yoon-Koo Kang, Jean-Yves Blay, Piotr Rutkowski, Hans Gelderblom, Peter Hohenberger, Michael Leahy, Margaret von Mehren, Heikki Joensuu, Giuseppe Badalamenti, Martin Blackstein, Axel Le Cesne, Patrick Schöffski, Robert G Maki, Sebastian Bauer, Binh Bui Nguyen, Jianming Xu, Toshirou Nishida, John Chung, Christian Kappeler, Iris Kuss, Dirk Laurent, Paolo G Casali, on behalf of all GRID study investigators\*



## Sistemsko zdravljenje 3. reda

- **Regorafenib** 160 mg/d (3+1), zaradi NU doza po 3 mesecih nižana na 120 mg/d (3+1)
- Po 2 mescih stagnacija bolezni
- NU: Diareja G3, HFS G1, utrujenost oz. oslabelost, AH, sprememba glasu
- Bolečine v trebuhu ob pavzi: modifikacija sheme jemanja (krajša pavza)
- Po 15 mesecih zdravljenja progres bolezni v jetrih

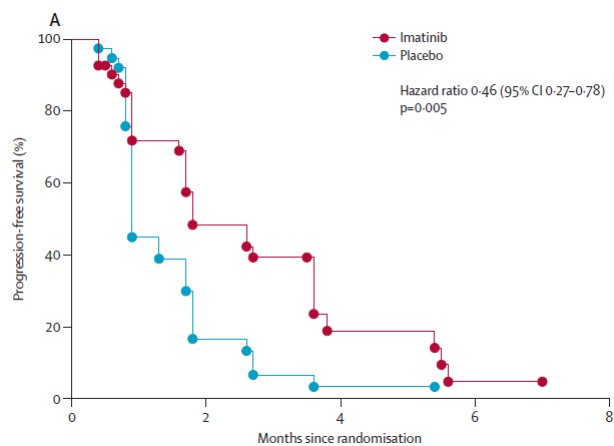
#### 4. vprašanje: Za kakšno zdravljenje bi se odločili zdaj?

- ponovno povišanje odmerka regorafeniba
- ponovna uvedba imatiniba
- klinična raziskava
- BSC

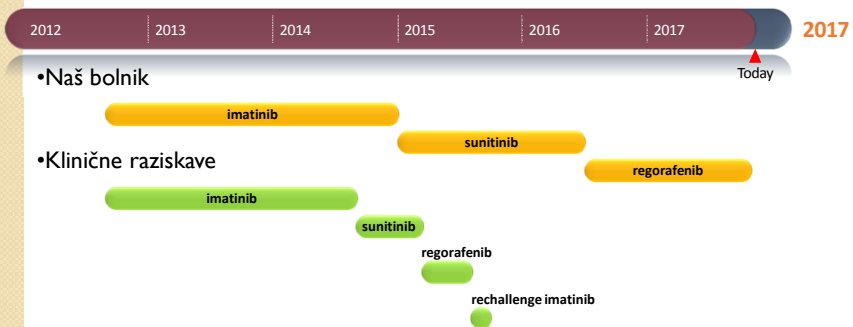
#### Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial



Yoon-Koo Kang, Min-Hee Ryu, Changhoon Yoo, Baek-Yeol Ryoo, Hyun Jin Kim, Jong Jin Lee, Byung-Ho Nam, Nikhil Ramaiya, Jyothi Jagannathan, George D Demetri



# Zaključek



# Sistemsko zdravljenje timičnih rakov (TR)

prof.dr. Tanja Čufer, dr.med  
 Urška Janžič, dr. med  
 Univerzitetna klinika Golnik  
 Medicinska Fakulteta, Univerza Ljubljana

13. Dnevi Internistične onkologije, Ljubljana, 2017

## Epidemiologija

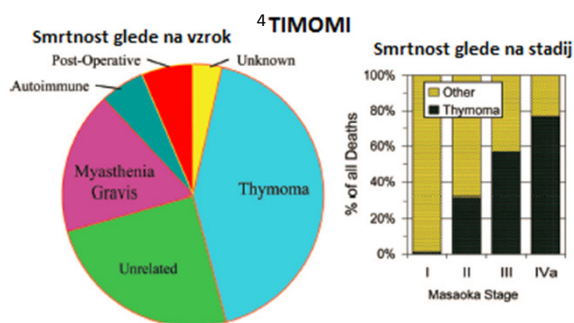
### Incidenca timičnih rakov (TR):

- <sup>1</sup>IACR: 1-5/1.000.000
- <sup>2</sup>SLO (2010 – 2014) 26 primerov (5.2/leto) = 0.28/100.000
- <sup>3</sup>UK Golnik (2010 – 2016) 26 primerov (3.7/leto)

### 5-letno preživetje:

- Timomi 90%
- Timični karcinomi 55%

ESMO definicija redkih rakov < 3 / 100.000



<sup>1</sup> <https://www.iacr.com>; <sup>2</sup> <https://www.onko-i.si/trs/>;

<sup>3</sup> <http://www.klinika-golnik.si/dejavnost-bolniscice/klinicna-dejavnost/onkoloska-uejavnost/register-raka-pijuc.pnp>

<sup>4</sup> Huang L, et al. JTO. 2010.; <sup>5</sup> Strobel P, et al. JCO 2004.

## Klinična slika

- Starost najpogosteje 50 – 60 let
- Blago tiščanje, težka sapa, kašelj, bolečina v prsnem košu, SVC
- Okoli 30% bolnikov s timomi ima paraneoplastični sindrom, najpogostejši je miastenija gravis (10-15% bolnikov z miastenijo gravis ima TR)

Organski sistem	Paraneoplastični sindrom	Preiskave
Živčnišiščni	Miastenija gravis Periferna nevropatija Polimiozitis	Acetilholinska protitelesa ANA, ANCA
Hematološki	Aplazija eritrocitov Pancitopenija Hemolitična anemija	KKS, DKS, retikulociti
Avtoimuni	SLE RA Sjogrenov sindrom	ANA, ANCA
Endokrini	Multiple endokrine neoplazme Cushingov sindrom.	Hormoni (kortizol, ACTH, LH, FSH, TSH, T3, T4)
Motnje imunske pomanjkljivosti	Hipogamaglobulinemija Sy. pomanjkanja T-celic	Elektroforeza, imunoelektroforeza
Koža	Pemfigus Lichen planus	

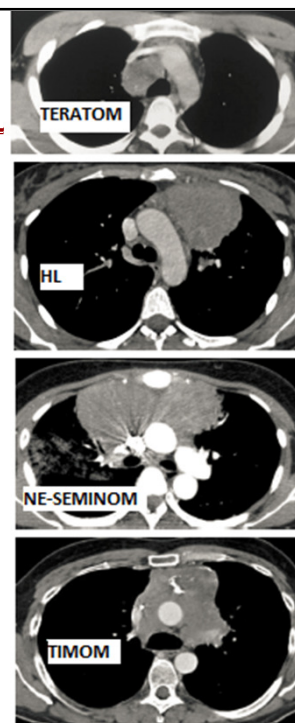
## Diagnostični postopki

- CT prsnega koša s kontrastom (MRI, za opredelitev vraščanja v perikard, plevro)
- Krvne preiskave (KKS, DKS, LDH, AFP, beta-HCG, acetilholinska protitelesa in nuklearna protitelesa, ostalo glede na paraneoplastično simptomatiko)
- Pridobitev tkiva:
  - Debeloigelnna biopsija (izogibati se plevri)
  - Če je tumor dobro omejen in je predvidena radikalna resekcija predhodna biopsija ni potrebna
- PET-CT samo izjemoma, pri timičnem karcinomu za iskanje oddaljenih metastaz

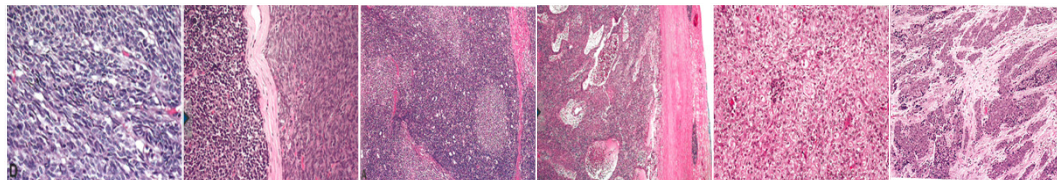
**Najpogostejši vzrok mase v sprednjem mediastinumu po 40. letu je timična neoplazma!**

Girard N, et al. Ann Oncol 2015.

[https://www.nccn.org/professionals/physician\\_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx)



## Patolomorfološke značilke in prognoza



	TIMOM A	TIMOM AB	TIMOM B1	TIMOM B2	TIMOM B3	TIMIČNI KARCINOM
<b>Značilnosti</b>	Ovalne / vretenaste tumorske celice, malo limfocitov	Del tumorja z vretenastimi celicami, del bogat z limfociti	Podobnost z normalnim timusom; bogat z limfociti	Tumor z veliko limfociti in poligonalnimi tumorskimi celicami	Predominantno epitelijske celice, ki rastejo v plahtah, vmes posamični T limfociti	Porušena normalna arhitektura, skoraj nič limfocitov, najpogosteje SCC tip
<b>Možnost ponovitve v 5-L po RO resekciji</b>	5%	3%	11%	14%	23%	38%
<b>Možnost ponovitve v 10-L po RO resekciji</b>	9%	3%	14%	32%	29%	28%
<b>5-L OS</b>	90%	90%	96%	NR	89%	57-65%

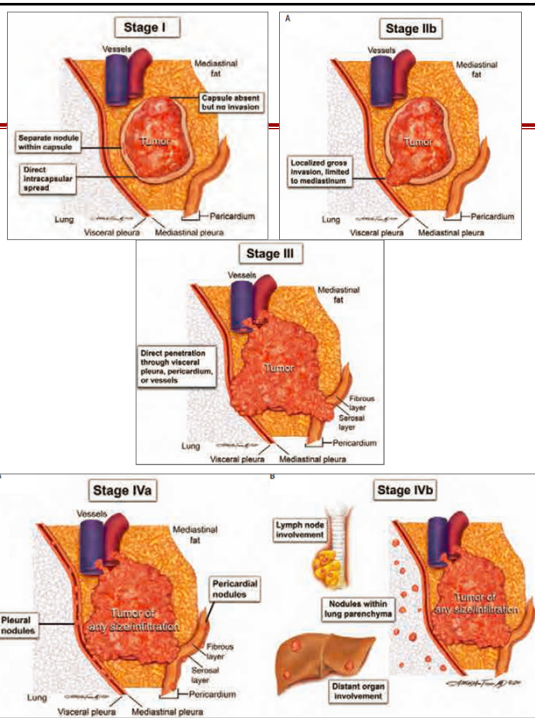
Travis DW, et al. WHO 2015.

## Stadij: Masaoka-Koga sistem

Temelji na KIRURGIJI =  
pooperativni / patološki stadij

STADIJ	Značilnosti
<b>I</b>	V celoti enkapsuliran tumor
<b>Ila</b>	Mikroskopska transkapsularna invazija
<b>Ilb</b>	Makroskopska invazija v timično in okolno maščevje ali v stiku (brez preraščanja) z mediastinalno plevro ali perikardom
<b>III</b>	Makroskopska invazija v sosednji organ (perikard, velike žile, pljuča)
<b>IVa</b>	Plevralni ali perikardialni zasevki
<b>IVb</b>	Limfogeni ali hematogeni zasevki

Detterbeck F, et al. JTO 2014.



## Stadiji: IASLC – ITMIG

Osnova v 8. klasifikaciji TNM, v povezavi z izidi zdravljenja pri bolnikih.

STADIJ	TNM	Odgovarjajoči Masaoka-Koga stadij
I	T1a 1b N0M0	I, IIA, IIB, III
II	T2N0M0	III
IIIA	T3N0M0	III
IIB	T4N0M0	III
IVA	T any N0-1 M0-1a	IVA, IVB
IVB	T any N0-2 M0-1b	IVB

Carter BW, et al. Radio Graphics 2017.

T (tumor)	
T1a	Enkapsuliran ali ne-enkapsuliran tumor z ali brez vraščanja v okolno maščevje
T1b	Invazija v mediastinalno plevro
T2	Vraščanje v perikard
T3	Vraščanje v pljuča, prsno steno, frenični živec, brahiocefalno veno, v.cave sup., ali hilarne (ekstraperikardilane) pljučne žile
T4	Vraščanje v toraklano aorto, žile loka, glavno pljučno arterijo, trahejo, požiralnik, miokard
N (bezgavke)	
N0	Brez zasevkov v bezgavkah
N1	Zasevki v sprednjih (peritimičnih) bezgavkah
N2	Zasevki v globokih intratorakalnih ali cervikalnih bezgavkah
M (zasevki)	
M0	Brez zasevkov
M1a	Plevralni ali perikardialni zasevki
M1b	Zasevki v pljučih ali drugih solidnih organih

## Kirurško zdravljenje

- Kirurško zdravljenje je temeljno zdravljenje vseh timičnih rakov, razen stadija IV
- Mediana sternotomija, minimalno invazivna krg samo za stadij I
- **Kompletna timektomija** (cel timus + okolno maščevje)
- Če je tumor **infiltrativen v okolico – en bloc odstranitev** vseh prizadetih struktur (žile, živci, perikard, plevra)
- Kjer je sum na ostanek, se položijo krg. sponke (za vodenje RT)
- Zmrzli rezi niso potrebni

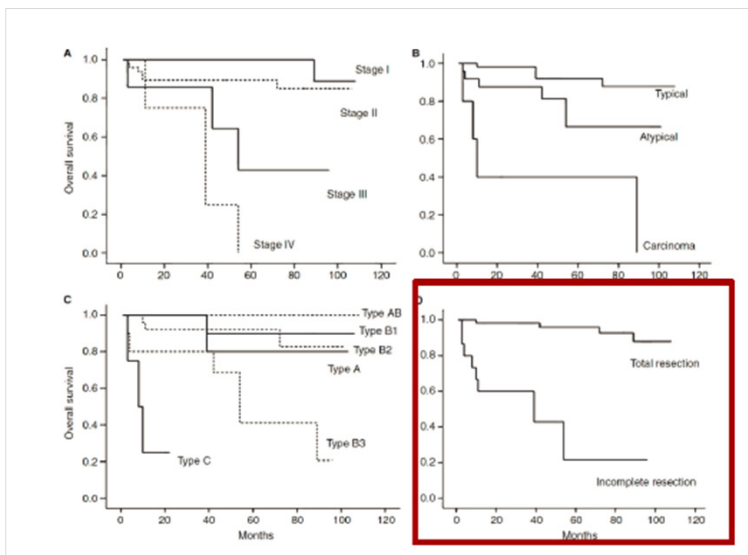


Girard N, et al. Ann Oncol 2015.; Detterbeck F, et al. JTO 2011.; [https://www.nccn.org/professionals/physician\\_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx)



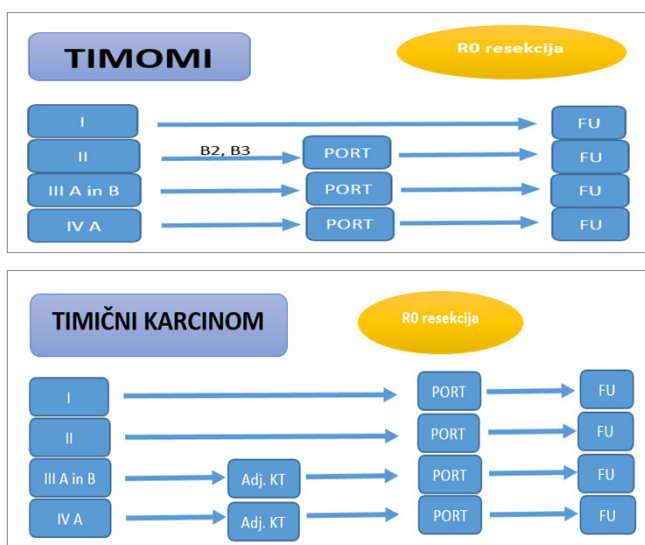
## Prognostični dejavniki

- Starost
- Histologija
- Stadij
- R0 operacija = najpomembnejši prognostični dejavnik!!!



Rossi G, et al. Histopathology 2008.

## Pooperativno zdravljenje

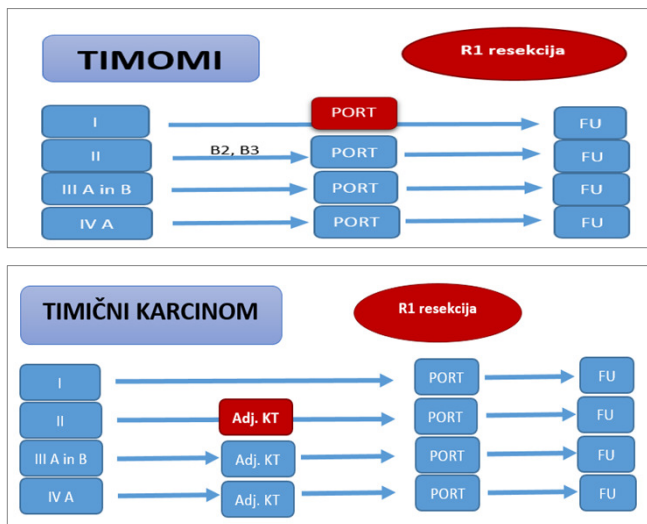


Girard N, et al. Ann Oncol 2015; [https://www.nccn.org/professionals/physician\\_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx)

### Sledenje:

- Klinični pregled na 3 mesece,
- CT toraksa
  - vsake 6-12 mesecev prve 2 leti
  - nato 1x letno do dopolnjenih 5 let za TC in 10 let za timom

## Pooperativno zdravljenje



### Sledenje :

- Klinični pregled na 3 mesece,
- CT toraksa
  - vsake 6-12 mesecev prve 2 leti
  - nato 1x letno do dopolnjenih 5 let za TC in 10 let za timom

Girard N. et al. Ann Oncol 2015.; [https://www.nccn.org/professionals/physician\\_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx)

## Vloga pooperativne RT

- Zmanjšanje lokalnih ponovitev iz 30% na < 5%
- Največja dobit pri stadiju II-III
- Podatki so iz retrospektivnih študij velikih med-institucijskih baz

	Št. pacientov	Histologija	Stadij	PORT	Rezultat
<sup>1</sup> Jackson	3031 1025	T TC	I - IV	47% 54%	HR OS T: 0.8 HR OS TC: 0.79
<sup>2</sup> Rimner	1263	T	II - III	55%	5-L OS: 95% vs. 90% 10-L OS: 90% vs. 79%
<sup>3</sup> Boothe	1156	T + TC	II - III	42%	5-L OS: 83% vs. 79%
<sup>4</sup> Omasa	1100 155	T TC	II - III	52% 30%	5-L OS T st.II: 96% vs 96% 5-L OS T st. III: 93% vs 90% 5-L OS TC st.II: 91% vs 87% 5-L OS TC st.III: 65% vs 64%

T – timom; TC – timični karcinom; PORT – pooperativna radioterapija

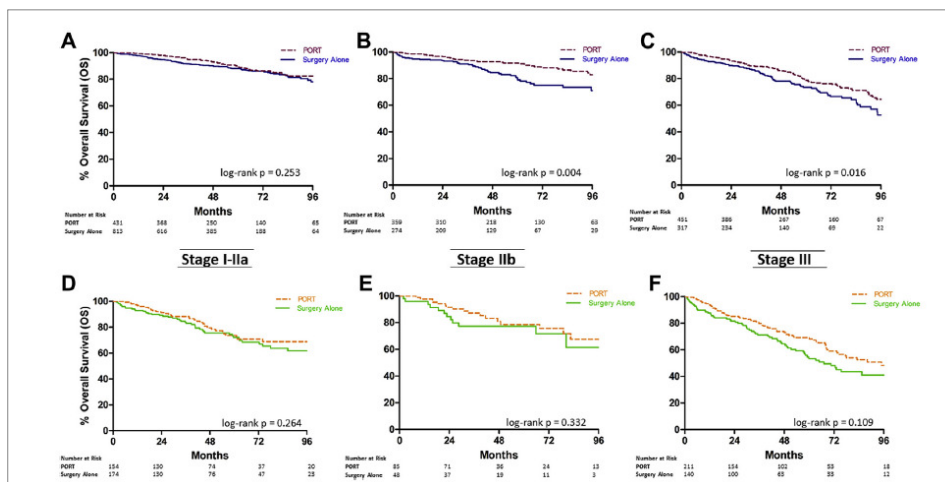
1 Jackson MW, et al. JTO 2017.; 2 Rimner A, et al. JTO 2016.; 3 Boothe D, et al. JTO 2016.; 4 Omasa M, et al. Cancer 2015.

## Učinkovitost PORT glede na histološki tip in stadij

Velika ameriška observacijska raziskava, 3013 bolnikov s timomom in 1025 bolnikov s timičnim karcinomom

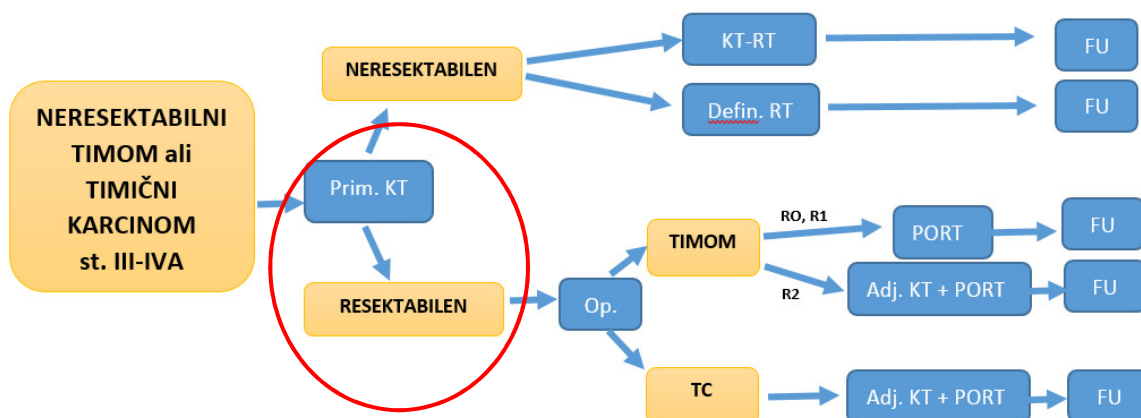
Timom

Timični karcinom



Jackson MW, et al. JTO 2017.

## Zdravljenje inoperabilnih timičnih rakov

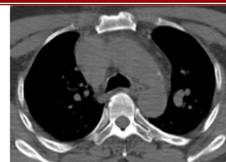


Girard N, et al. Ann Oncol 2015.; [https://www.nccn.org/professionals/physician\\_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx)

## Primarna / indukcijska KT

Primary chemotherapy regimen	Subjects n	Tumour		Design	Response rate	
		Type	Stage			
<b>Chemotherapy</b>						
MACCHARINI [78]	CEE	7	T/TC	III	Phase II	100
BERRUTI [79]	ADOC	6	T	III-IVA	Phase II	83
REA [80]	ADOC	16	T	III-IVA	Retrospect	100
BERRUTI [81]	ADOC	16	T	III-IVA	Phase II	81
VENUTA [82]	CEE	15	T/TC	III	Retrospect	66
BRETTI [83]	ADOC/PE	25	T/TC	III-IVA	Retrospect	72
KIM [74]	CAPP	22	T	III/IVA	Phase II	77
LUCCHI [84]	CEE	36	T/TC	III-IVA	Retrospect	67
JACOT [85]	CAP	5	T/TC	III-IVA	Retrospect	75
YOKOI [86]	CAMP	14	T/TC	III, IV	Retrospect	93
KUNITOH [87]	CODE	21	T	III	Phase II	62
PARK [88]	DDP-Docetaxel	27	T/TC	IIIV	Phase II	63
<b>Chemoradiation</b>						
LOEHRER [72]	CAP/54 Gy	23	T/TC	III-IVA	Phase II	70
WRIGHT [37]	PE, ADOC, CAP, CEE/45-60 Gy	10	T/TC	III-IVA	Retrospect	40

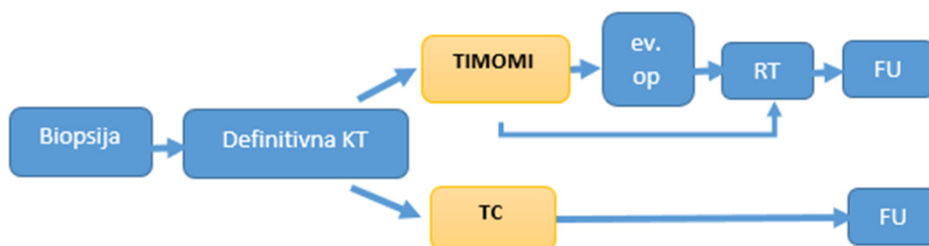
RR 80% → operacija



Delež kompletne resekcije 14% – 78%

Girard N, et al. Eur Resp Rev 2013.

## Zdravljenje metastatskih timičnih rakov, stadij IVB



Girard N, et al. Ann Oncol 2015; [https://www.nccn.org/professionals/physician\\_gls/default.aspx](https://www.nccn.org/professionals/physician_gls/default.aspx)

## Definitivna KT za metastatske timične rake

Study	No. of Patients	Period of Accrual (years)	Tumor Type	Design	Regimen	Agents	Doses	Response Rate (%)
Single-agent chemotherapy								
Bonami et al 1992 <sup>27</sup>	21	4	T/TC	Phase II	Cisplatin		50 mg/m <sup>2</sup> /3 weeks	10
Highley et al 1999 <sup>28</sup>	15	12	T/TC	Retrosip	Ifosfamide		1.5g/m <sup>2</sup> × 5 days/3 weeks	46
Loehrer et al 2006 <sup>29</sup>	27	1	T/TC	Phase II	Pemetrexed		500 mg/m <sup>2</sup> /3 weeks	17
Combination chemotherapy								
Fornasiero et al 1990 <sup>30</sup>	32	11	T	Retrosip	ADOC	Doxorubicin Cisplatin Vincristin	40 mg/m <sup>2</sup> /3 weeks 50 mg/m <sup>2</sup> /3 weeks 0.6 mg/m <sup>2</sup> /3 weeks	91
Loehrer et al 1994 <sup>31</sup>	30	9	T/TC	Phase II	CAP	Cyclophosphamide Cisplatin Doxorubicin	700 mg/m <sup>2</sup> /3 weeks 50 mg/m <sup>2</sup> /3 weeks 50 mg/m <sup>2</sup> /3 weeks	51
Giaccone et al 1996 <sup>32</sup>	16	6	T	Phase II	PE	Cyclophosphamide Cisplatin Etoposide	500 mg/m <sup>2</sup> /3 weeks 60 mg/m <sup>2</sup> /3 weeks 120 mg/m <sup>2</sup> × 3/3 weeks	56
Loehrer et al 2001 <sup>33</sup>	34	2	T/TC	Phase II	VIP	Etoposide Ifosfamide Cisplatin	75 mg/m <sup>2</sup> × 4 days/3 weeks 1.2 g/m <sup>2</sup> × 4 days/3 weeks 20 mg/m <sup>2</sup> × 4 days/3 weeks	32
Lemma et al 2011 <sup>34</sup>	46	7	T/TC	Phase II	Carbo-Px	Carboplatin Paclitaxel	AUC 5/3 weeks 225 mg/m <sup>2</sup> /3 weeks	43
Palmieri et al 2011 <sup>35</sup>	15	3	T/TC	Phase II	CAP-GEM	Capecitabine Gemcitabine	650 mg/m <sup>2</sup> bid × 14 days/3 weeks 1000 mg/m <sup>2</sup> × 2 days/3 weeks	40
Okuma et al 2011 <sup>36</sup>	9	8	TC	Retrosip	Cisplatin-Irinotecan	Cisplatin Irinotecan	80 mg/m <sup>2</sup> /4 weeks 60 mg/m <sup>2</sup> × 3 days/4 weeks	56

**KT z antraciklini:**  
ORR 50-90%  
mOS 37-48 mes

**KT brez antraciklinov:**  
ORR 30-50%  
mOS 31-51 mes

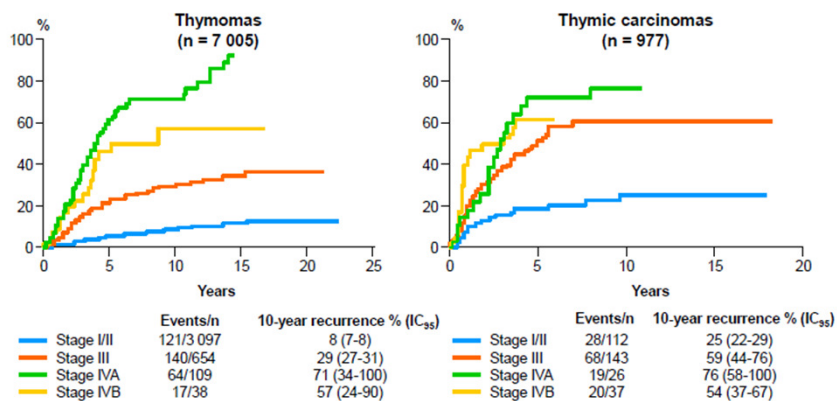
**KT za TC:**  
karboplatin-paclitaxel  
ORR 36%, mPFS 7.5 mes  
(Hirai Fet et al, Ann Oncol 2014)

Povzeto po Girard N, ASCO Educational Book, 2012.

## Ukrepanje ob ponovitvi bolezni

ITMIG retrospective database

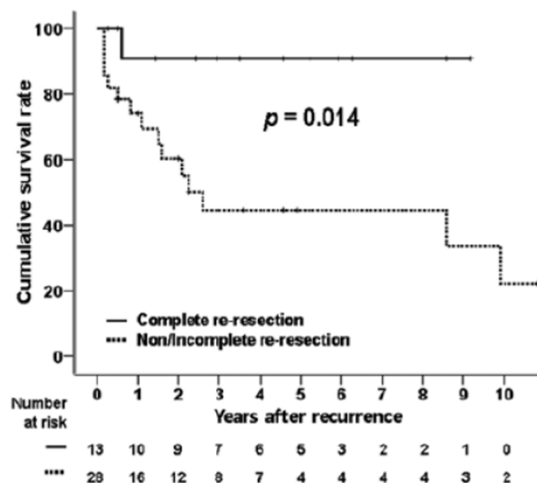
Cumulative incidence of recurrences in Masaoka-Koga groups



Detterbeck, et al. WCLC 2013..

## Operativni poseg

- DA, v kolikor je možna **KOMPLETNA RESEKCIJA**
- Sicer je preživetje enako (slabo) kot če ne bi bilo kirurške intervencije
- Kompletna vs. nekompletna res.:  
5-L OS: 91% vs. 45% (P=0.014)



Bae E, et al. JTO 2012.

## Druga linija KT

KT ali shema	Študija	Histologija	Št. pacientov	ORR	mPFS (m)	mOS (m)
<sup>1</sup> Pemetrexed	Faza II	T	16	0%	1.2	NR
		TC	11	17%	11.2	29
<sup>2</sup> Amrubicin	Faza II	T	14	18%	8.7	NR
		TC	19	11%	8.5	18.1
<sup>3</sup> Kapecitabin + Gemcitabin	Faza II	T	8	40%	11	1-yr OS 90%
		TC	22	38%	6	2-yr OS 66%
<sup>4</sup> Pemetrexed	Retrospektiva	T	6	17%	13.8	20.1
		TC	10	10%	6.5	12.7
<sup>5</sup> Etopozid p.o.	Retrospektiva	T	5	15%	53	98
		TC	8	13%	4	22

<sup>1</sup> Loehrer PJ, et al. ASCO 2006.; <sup>2</sup> Wakelee H, et al. ASCO 2015.; <sup>3</sup> Palmieri G, et al. Future Onc 2014.; <sup>4</sup> Liang Y, et al. Lung Cancer 2015.; <sup>5</sup> Boutros CF, et al. Lung Cancer 2013.

## Tarčna terapija

- Sunitinib
- Sorafenib
- Imatinib
- Everolimus
- Dasatinib
- Lucitanib
- Erlotinib
- Selumetinib
- CDK 4/6 inhibitorji
- Belinostat
- ...

▪ Prekomerna ekspresija KIT (izražanje proteina CD117):

- 2% T
- 87% TC

▪ C-KIT mutacije:

- 12% TC

▪ Boljši odgovor na:

- Imatinib
- Sunitinib
- Sorafenib

Mutation	Exon
E490K	9
Y553N	11
W557R	11
V559A	11
V560del	11
L576P	11
P577-D579del	11
D579del	11
H697Y	14
D820E	17

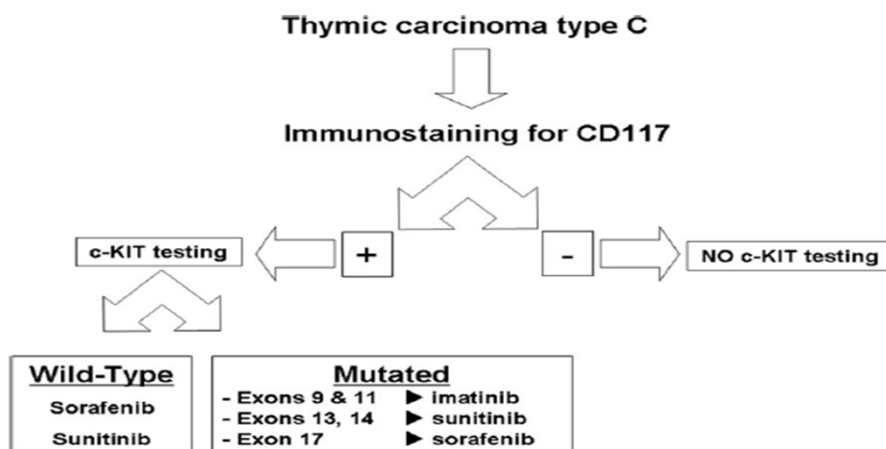
MOLECULAR AND CLINICAL ONCOLOGY, 2016

### *c-Kit* mutation-positive advanced thymic carcinoma successfully treated as a mediastinal gastrointestinal stromal tumor: A case report

FUMIHIKO HIRAI, MAKOTO EDAGAWA, SHINICHIRO SHIMAMATSU, RYO TOYOZAWA, GOUJI TOYOKAWA, KANAME NOSAKI, MASAFUMI YAMAGUCHI, TAKASHI SETO, MITSUHIRO TWAKENYOYAMA and YUKITO ICHINOSE

Schirosi L, et al. Ann Oncol 2012.

## Algoritem zdravljenja TC s tarčnimi zdravili



Povzeto po Schirosi L, et al. Ann Oncol 2012.

## Tarčna terapija - OKTREETID

- 50% timomov izraža visok nivo somatostatinskih receptorjev na OctreoScan-u
- Dodatno so pri timomih v 83% prisotni tudi steroidni receptorji → s steroidi je mogoče doseči „timolitični efekt“ = uničenje limfocitne populacije (NU: okužbe, ↑ tveganje za miastenijo gravis)

	GKK	TIMOMI			TIMIČNI KARCINOMI		
		n	CR+PR (%)	SD (%)	n	CR+PR (%)	SD (%)
1 Palmieri	+	10	40	40	3	33	33
2 Loehrer	+/-	32	38	34	5	0	60
3 Schalke	+	17	88	0	0	NA	NA


<sup>1</sup> Palmieri I, et al. Cancer 2002.; <sup>2</sup> Loehrer P, et al. JCO 2004.; <sup>3</sup> Schalke A, et al. ASCO 2012.

## Imunoterapija: Pembrolizumab pri bolnikih s ponovitvijo timičnega karcinoma, faza II

Timični karcinomi, N = 40	
Odgovor	
CR	1/40 (2.5%)
PR	8/40 (20%)
SD	21/40 (52%)
PD	10/40 (25%)
mPFS	4.2 mes
mOS	24.9 mes
NU G 3/4	6/40 (15%)

Giaccone G, et al. Abstract 8573. ASCO 2017.

**EORTC-ETOP NIVOTHYM**

etop 

**Primary objective:**  
To detect activity of nivolumab as single agent as second line treatment for **type B3 thymoma and thymic carcinoma**

Eligible patients → Nivolumab 240 mg IV q2 weeks

**Primary endpoint: PFS rate at 6 months**

**Secondary endpoints:**

- ORR and DCR, Duration of response
- OS
- QOL
- Safety

PIs: N. Girard, S. Peters



# Pomembno je sodelovanje v kliničnih registrih in raziskavah!

**Screening Patients with Thoracic Malignancy for Efficient Clinical Trial Access**

**14MIG Solid tumour panel v1**  
 Panel footprint: 2.2 Mb  
 Panel features: 478

Category	Count
Genes (all exons)	328
Copy number variants	111
Other	29
Other	10

**Function (genes)**

- Signalling
- Transcription factor
- Transcriptional control
- Apoptosis
- DNA damage response
- Cell cycle control
- Miscellaneous/Unknown
- Immune-related
- Structural components

**Online molecular portrait Prospective clinical data 500-1000 tumors / yr**

Central Biobank Biobank

## KLINIČNI PRIMER: Kontinuirano vodenje in zdravljenje pacienta s timičnim karcinomom

Dnevi internistične onkologije 2017

Pripravila: Urška Janžič, dr.med.

Mentorica: prof. dr. Tanja Čufer, dr.med.



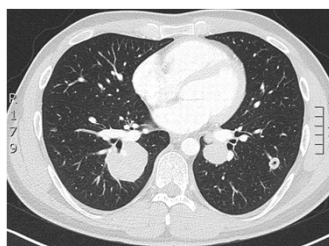
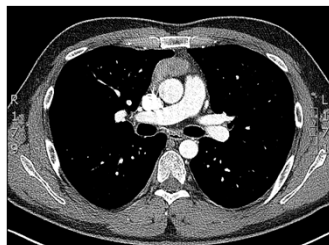
## KLINIČNI PRIMER

- 29-letni moški
- Podiplomski študent, fizično aktiven, nekadilec
- Sicer zdrav, brez redne terapije
- Družinska anamneza negativna za rakava obolenja
- Simptomi: 4 mesece trajajoč suh kašelj
- Klinični pregled brez posebnosti
- PS po WHO 1

## KLINIČNI PRIMER - nadaljevanje

### SLIKOVNA DIAGNOSTIKA:

- Na RTG pc vidna masa v sprednjem mediastinumu
- CT prsnega koša: tumorska masa v zg. mediastinumu brez vraščanja v okolno maščevje, perikard ali plevro in več okroglih lezij po pljučih obojestransko
- CT abdomna in CŽS brez posebnosti
- B-HCG < 0.1; AFP = 1.5



### PATOHISTOLOŠKA DG:

- Timični karcinom
- IHC: CD5+, CD117+, AE1/AE3+ EMA+, vimentin -, LCA-, S100-

**Anatomski stadij T1aN0M1b po IASLC-ITMIG klas.  
Klinični stadij IVb**

## Klinični stadij timičnih neoplazem – nova IASLC / ITMIG klasifikacija

T1aN0M1b

Category	Description
T1a	Encapsulated or unencapsulated tumor, with or without extension into mediastinal fat
T1b	Invasion of mediastinal pleura
T2	Invasion of pericardium
T3	Involvement of lung, chest wall, phrenic nerve, brachiocephalic vein, SVC, or hilar (extrapericardial) pulmonary vessels
T4	Invasion of thoracic aorta, arch vessels, main pulmonary artery, trachea, esophagus, or myocardium

Category	Description
N0	No lymph node metastasis
N1	Involvement of anterior (perithymic) lymph nodes
N2	Involvement of deep intrathoracic or cervical lymph nodes

Category	Description
M0	No metastasis
M1a	Pleural or pericardial metastatic nodule(s)
M1b	Pulmonary intraparenchymal metastatic nodule or distant-organ metastasis

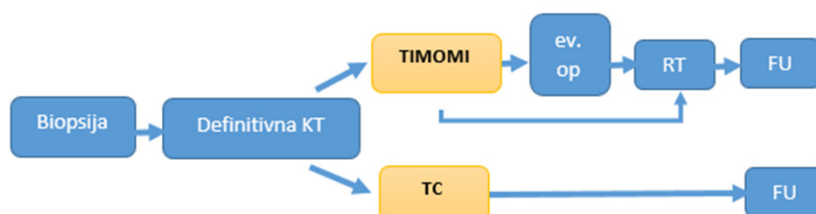
Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	T any	N1	M0
	T any	N0, N1	M1a
IVB	T any	N2	M0, M1a
	T any	N any	M1b

Carter BW, et al. RadioGraphics. 2017

**VPRAŠANJE 1:**  
**Kakšno vrsto zdravljenja bi predlagali mlademu  
pacientu z metastatskim timičnim  
karcinomom?**

1. Preoperativna KT + operacija + RT
2. Definitivna kemoterapija
3. Kemo-radioterapija
4. Operacija + radioterapija

**Principi zdravljenja metastatskega  
timičnega karcinoma**



Girard N, et al. Ann of Oncol. 2015

## KT sheme za 1. linijo zdravljenja timičnih neoplazem

Study	No. of Patients	Period of Accrual (years)	Tumor Type	Design	Regimen	Agents	Doses	Response Rate (%)
Single-agent chemotherapy								
Bonomi et al 1992 <sup>27</sup>	21	4	T/TC	Phase II	Cisplatin		50 mg/m <sup>2</sup> /3 weeks	10
Highley et al 1999 <sup>28</sup>	15	12	T/TC	Retrosip	Ifosfamide		1.5g/m <sup>2</sup> × 5 days/3 weeks	46
Loehrer et al 2006 <sup>29</sup>	27	1	T/TC	Phase II	Pemetrexed		500 mg/m <sup>2</sup> /3 weeks	17
Combination chemotherapy								
Fornasiero et al 1990 <sup>30</sup>	32	11	T	Retrosip	ADOC	Doxorubicin Cisplatin Vincristin	40 mg/m <sup>2</sup> /3 weeks 50 mg/m <sup>2</sup> /3 weeks 0.6 mg/m <sup>2</sup> /3 weeks	91
Loehrer et al 1994 <sup>31</sup>	30	9	T/TC	Phase II	CAP	Cyclophosphamide Cisplatin Doxorubicin	700 mg/m <sup>2</sup> /3 weeks 50 mg/m <sup>2</sup> /3 weeks 50 mg/m <sup>2</sup> /3 weeks	51
Giaccone et al 1996 <sup>32</sup>	16	6	T	Phase II	PE	Cyclophosphamide Cisplatin Etoposide	500 mg/m <sup>2</sup> /3 weeks 60 mg/m <sup>2</sup> /3 weeks 120 mg/m <sup>2</sup> × 3/3 weeks	56
Loehrer et al 2001 <sup>33</sup>	34	2	T/TC	Phase II	VIP	Etoposide Ifosfamide Cisplatin	75 mg/m <sup>2</sup> × 4 days/3 weeks 1.2 g/m <sup>2</sup> × 4 days/3 weeks 20 mg/m <sup>2</sup> × 4 days/3 weeks	32
Lemma et al 2011 <sup>34</sup>	46	7	T/TC	Phase II	Carbo-Px	Carboplatin Paclitaxel	AUC 5/3 weeks 225 mg/m <sup>2</sup> /3 weeks	43
Palmeri et al 2011 <sup>35</sup>	15	3	T/TC	Phase II	CAP-GEM	Capotecabine Gemcitabine	450 mg/m <sup>2</sup> bid × 14 days/3 weeks 1000 mg/m <sup>2</sup> × 2 days/3 weeks	40
Okuma et al 2011 <sup>36</sup>	9	8	TC	Retrosip	Cisplatin-Irinotecan	Cisplatin Irinotecan	80 mg/m <sup>2</sup> /4 weeks 60 mg/m <sup>2</sup> × 3 days/4 weeks	56

**KT z antraciklini:**  
ORR 50-90%  
mOS 37-48 mes

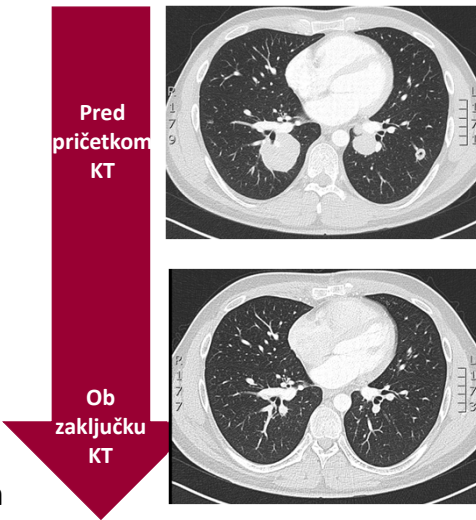
**KT brez antraciklinov:**  
ORR 30-50%  
mOS 31-51 mes

**KT za TC: karboplatin-paclitaxel CR+PR: 36% + SD: 59%, mPFS 7.5 mes (Hirai F. et al, Ann Oncol 2014)**

Povzeto po Girard N, ASCO Educational Book, 2012.

## KLINIČNI PRIMER - nadaljevanje

- **FEBRUAR 2013:** prične s KT po shemi karboplatin - paclitaxel (7 ciklov)
- Klinično: prenehanje kašlja
- Radiološki učinek - CT toraksa: zmanjšanje primarnega tumorja in izginotje pljučnih metastaz
- Operativna odstranitev edine preostale tumorske mase – (timektomija)
- Patohistološki izvid: brez vitalnih tumorskih celic – dosežena pCR



**VPRAŠANJE 2:**  
**Ali bi pacientu z metastatskim timičnim  
 karcinomom po doseženi patološki kompletni  
 remisiji in odstranitvi primarnega tumorja  
 priporočali RT?**

1. Da
2. Ne

**Vloga kooperativne RT (PORT) pri timičnih  
 karcinomih (retrospektivne analize)**

	Št. pacientov	mFU (meseci)	Stadij*	Op + PORT (%)	5-letno preživetje PORT vs. No PORT
<sup>1</sup> SEER databaza	187	39	I – IV	56	57% vs. 54%
<sup>1</sup> Fu	329	36	I – IV	68	<b>75% vs. 44%</b>
<sup>1</sup> Mao	54	72	I – III	46	79% vs. 66%
<sup>1</sup> Omasa	155	57	I – III	52	91% vs. 87% st. II <b>65% vs 64% st. III</b>
<sup>1</sup> Song	76	44	I – IVa	64	70% vs. 57%
<sup>1</sup> Ruffini	137	68	I – IVb	66	60% vs. 50 % s KT 69% vs. 61% brez KT
<sup>1</sup> Weissferdt	65	50	I - IV	51	66% vs. 70%
<sup>2</sup> Ahmad ITMIG group	1042	53	I - IV	48	NR <b>HR 0.454</b>
<sup>3</sup> Jackson	1025	57	I - IV	54	NR <b>HR 0.79</b>

*Večina vključenih pacientov je imela zgodnejši stadij bolezni (I – III)  
 Signifikantni rezultati so odebeljeni*

<sup>1</sup> Hamaji M, et al. J Thor Surg. 2016  
<sup>2</sup> Ahmad U, et al. Gen Thor Surg. 2015.  
<sup>3</sup> Jackson MW, et al. JTO. 2017.

### KLINIČNI PRIMER - nadaljevanje

- Pacient po doseženi pCR v rednem sledenju (klin. pregled na 3 mesece in CT na 6 mesecev)
- Po 16 mesečnem prostem intervalu
  - Klinično: utrujenost
  - Radiološko CT toraksa: pljučni zasevki
- Še vedno fizično dobro zmogljiv, PS 1, brez pridruženih bolezni ali redne terapije

### VPRAŠANJE 3: Kaj je najprimernejši naslednji korak?

1. Rebiopsija in dodatno molekularno testiranje
2. 2. linija KT
3. Tarčno zdravljenje
4. Vključitev v klinično študijo

## Možnosti zdravljenja timičnega karcinoma v 2. liniji

### ESMO smernice (2015)

#### Recurrences

- Recurrences of thymic epithelial tumours should be managed according to the same strategy as newly diagnosed tumours [IV, A].
- Complete resection of recurrent lesions, when achievable, is recommended.
- Several consecutive lines of chemotherapy may be administered when the patient presents with tumour progression. The re-administration of a previously effective regimen should be considered [IV, B].
- Preferred regimens for second-line treatment include carboplatin plus paclitaxel, and platin plus etoposide [III, B]; capecitabine plus gemcitabine is an option [III, B].
- Options for subsequent lines include pemetrexed [III, B] and oral etoposide.
- In patients with octreoscan-positive thymoma not eligible to receive additional chemotherapy, octreotide alone or with prednisone may represent a valuable option [III, B].

#### Targeted agents

- *KIT* sequencing (exons 9–17) is an option for refractory thymic carcinomas in the setting of potential access to specific inhibitors, particularly in the context of clinical trials [IV, B].
- It is not recommended to administer imatinib in the absence of a *KIT*-sensitising mutation [III, E].
- Sunitinib is an option as second-line treatment of thymic carcinomas independently from *KIT* status [III, A].
- Everolimus may represent an option for refractory tumours [III, B].

### NCCN smernice 2017

**SECOND-LINE CHEMOTHERAPY**  
 Sunitinib (Thymic carcinomas only)<sup>7</sup>  
 Pemetrexed<sup>8</sup>  
 Everolimus<sup>9</sup>  
 Paclitaxel<sup>10-11</sup>  
 Octreotide (including LAR) +/- prednisone<sup>12</sup>  
 Gemcitabine<sup>13</sup>  
 5-FU and leucovorin<sup>14</sup>  
 Etoposide<sup>4</sup>  
 Ifosfamide<sup>15</sup>

Girard N, et al. Ann of Oncol. 2015  
<https://www.nccn.org>

## KT za 2. linijo zdravljenja timičnih karcinomov

### Ponoviti KT za 1.linijo:

- CAP<sup>6</sup>
- Karboplatin + paclitaxel
- Cisplatin - etopozid

### 2.linija KT za timične karcinome

KT ali shema	Študija	Št. pacientov	ORR	mPFS (m)	mOS (m)
<sup>1</sup> Pemetrexed	Faza II	11	17%	11.2	29
<sup>2</sup> Amrubicin	Faza II	19	11% (+68% SD)	8.5	18.1
<sup>3</sup> Kapecitabin + Gemcitabin	Faza II	8	38%	6	1-yr OS 90% 2-yr OS 66%
<sup>4</sup> Pemetrexed	Retrospektiva	16	10% (+50% SD)	6.5	12.7
<sup>5</sup> Etopozid p.o.	Retrospektiva	13	13% (+63% SD)	9	22

<sup>1</sup> Loehrer PJ, et al. Abstract 7079. ASCO 2006

<sup>2</sup> Wakelee H, et al. Abstract 7580. ASCO 2015.

<sup>3</sup> Palmieri G, et al. Future Onc. 2014.

<sup>4</sup> Liang Y, et al. Lung Cancer. 2015.

<sup>5</sup> Boutros CF, et al. Lung Cancer. 2013

<sup>6</sup> Lara PN, et al. Chest. 1996



## Tarčna terapija za ≥ 2. linijo zdravljenja timičnih karcinomov

- Sunitinib
- Sorafenib
- Imatinib
- Everolimus
- Dasatinib
- Lucitanib
- Erlotinib
- Selumetinib
- CDK 4/6 inhibitorji
- Belinostat
- ...

Schiroso L, et al. Ann Oncol 2012.

- Prekomerna ekspresija KIT (izražanje proteina CD117):

- 2% T
- 87% TC

- C-KIT mutacije:

- 12% TC

- Boljši odgovor na:

- Imatinib
- Sunitinib
- Sorafenib

Mutation	Exon
E490K	9
Y553N	11
W557R	11
V559A	11
V560del	11
L576P	11
P577-D579del	11
D579del	11
H697Y	14
D820E	17

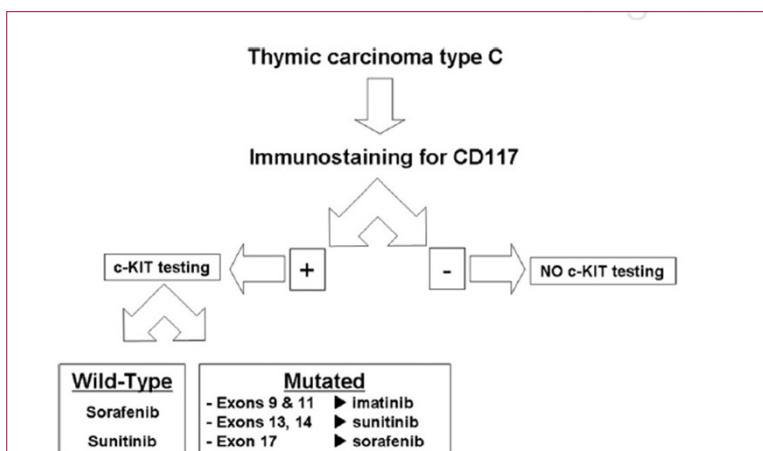
MOLECULAR AND CLINICAL ONCOLOGY, 2016

### **c-Kit mutation-positive advanced thymic carcinoma successfully treated as a mediastinal gastrointestinal stromal tumor: A case report**

FUMIHIKO HIRAI, MAKOTO EDAGAWA, SHINICHIRO SHIMAMATSU, RYO TOYOZAWA, GOUJI TOYOKAWA, KANAME NOSAKI, MASAFUMI YAMAGUCHI, TAKASHI SETO, MITSUHIRO TWAKENOYAMA AND YUKITO ICHINOSE

## CD117 ekspresija, c-KIT mutacije

### PREDLAGAN ALGORITEM ZDRAVLJENJA TC S TARČNIMI ZDRAVILI:



Schiroso L, et al. Ann Oncol. 2012

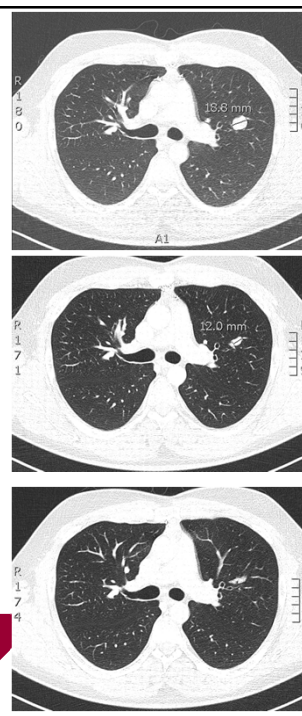
## KLINIČNI PRIMER - nadaljevanje

- Dodatna molekularna analiza: CD117 +, vendar cKIT mutacije negativne (z IHC in PCR)
- JUNIJ 2014: prične z 2.linijo KT po shemi CAP (7 ciklov)
- Klinično: izboljšanje simptomatike
- Radiološko: izginotje vseh lezij, razen ene v LZR (celokupno PR)
- Radikalno obsevanje lezije v LZR s 54 Gy
- Sledenje

Pred  
pričetkom  
2. linije KT

PR

Po RT  
edine  
preostale  
metastaze



## KLINIČNI PRIMER - nadaljevanje

- Po PFS 18 mesecev hud glavobol, ki ne mine
- CT in MRI CŽS: solitarna metastaza desno z edenom
- CT prsnega koša in abdominalna: brez znakov progressa bolezni izven CŽS
- FEBRUAR 2016: operativna odstranitev tumorja v CŽS + obsevanje na ležišče tumorja s 45 Gy
- Dodatna patohistološka analiza možg. zasevka: timični karcinom  
→ Z NGS najdene c-KIT mutacije (mutacija Y553N na exonu 11)



## KLINIČNI PRIMER - nadaljevanje

- Od maja 2016 do danes je pacient v sledenju
- Na MRI prsnega koša je vidna počasna rast zgolj ene lezije v pljučih v DZR (12 mm v 30 mesecih)
- Kljub dvema progresoma bolezni je pacient v obravnavi že več kot **55 mesecev**, trenutno v zelo dobri psihofizični kondiciji, polno zaposlen in aktiven
- Vprašanje, ki se poraja: Kako ukrepati ob naslednjem sistemskem progresu bolezni?

## CD117 ekspresija, c-KIT mutacije



### Prekomerna ekspresija KIT (izražanje proteina CD117):

- 2% T
- 87% TC

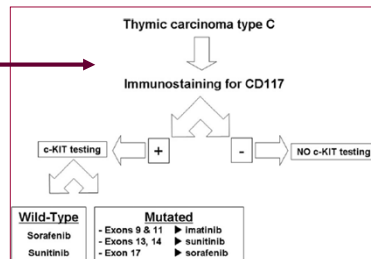
### C-KIT mutacije:

- 12% TC

### Boljši odgovor na:

- Imatinib
- Sunitinib
- Sorafenib

Mutation	Exon
E490K	9
Y553N	11
W557R	11
V559A	11
V560del	11
L576P	11
P577-D579del	11
D579del	11
H697Y	14
D820E	17



Imatinib

Schiroso L, et al. Ann Oncol. 2012;

## CD117 ekspresija, c-KIT mutacije



Reference	Age/sex	Histologic type	c-KIT mutation	Stage	Therapy	Drug	Clinical response
Strobel et al. [7]	54/M	TC, squamous cell, G3	V560del ex11	Metastatic	None	Imatinib	SD (6 months)
Bisagni et al. [10]	46/M	TC, squamous cell, G3	D820E ex17	pT3, N2, M1	S + CT + RT	Sorafenib	PR (>15 months)
Disel et al. [13]	47/F	TC, squamous cell, G3	del577-578-579 ex11	IVA	CT + RT	Sorafenib	SD
Buti et al. [14]	48/M	TC, squamous cell, G3	Y553N	IV	CT	Imatinib	PR (>8 months)
Li et al. [19]	46/M	TC, squamous cell, G3	ND	IV	CT	Sorafenib	SD (>9 months)
Chuah et al. [20]	NA	Type-B2	ND	I	Imatinib + CT	Dasatinib	LR
Hamada et al. [21]	Case 1: 62/M	Atypical carcinoid	None	Invasive	CT	Imatinib	Good clinical response
	Case 2: 58/M	Atypical carcinoid	ND	Invasive	S + RT	Nessuno	Recurrence and metastasis
Giaccone et al. [22]	Case 1: 36/M	TC	ND	IVB	CT	Imatinib	PD
	Case 2: 67/M	Type-B3	None	IVA	S + RT + CT	Imatinib	SD
	Case 3: 47/M	Type-B2/3	ND	IVA	CT	Imatinib	SD
	Case 4: 76/M	TC	ND	IVB	None	Imatinib	PD
	Case 5: 36/M	TC	ND	IVB	CT	Imatinib	PD
	Case 6: 71/M	TC	None	IVB	None	Imatinib	PD
	Case 7: 69/F	TC, squamous cell type	None	IVB	None	Imatinib	PD
Strobel et al. [23]	Case 1: 35/M	TC, squamous cell type	None	IVB	CT + imatinib	Sunitinib	PR
	Case 2: 69/M	TC, squamous cell type	None	IVA	S + RT + CT	Sunitinib	PR
	Case 3: 77/M	TC, squamous cell type	None	II	S	Sunitinib	PR
	Case 4: 28/F	TC, undifferentiated	None	IVB	CT + RT	Sunitinib	PR (2 months)
Palmieri et al. [24]	15 cases	4 type B2	None	NA	NA	Imatinib	PD
		2 type B2/B3	None	NA	NA	Imatinib	PD
		6 type B3	None	NA	NA	Imatinib	1 SD
		3 TC	None	NA	NA	Imatinib	PD

Schiroli L, et al. Ann Oncol. 2012

## Kaj pa imunoterapija?

### Pembrolizumab in Patients with Recurrent Thymic Carcinoma: Results of a Phase II Study

Giuseppe Giaccone, Jillian Thompson, Colleen McGuire, Maria Manning, Binshakar Kallakury, Jeffrey Chahine, Deepa S. Subramanian, Stephen V. Liu, Geoffrey Gibney, Chul Kim, Justine M. McCutcheon

Lombardi Comprehensive Cancer Center, Georgetown University, Washington DC USA

ASCO  
Abstract #8573

#### Responses (n=40 eligible)

Complete response 1  
 Partial response 8  
 Stable disease 21 (1 unconfirmed PR)  
 Progressive disease 10  
 Response rate 22.5% (95%CI 9.6% - 35.4%)

#### PFS, OS, DOR

Median PFS: 4.2 months  
 Median survival: 24.9 months  
 Median duration of response (from first measurement): 22.7 months  
 Median duration of stable disease (from start): 6.8 months



Giaccone G, et al. Abstract 8573. ASCO 2017.

#### Adverse Events

- Median 6 cycles (1-35)
- Mostly mild AEs
- 6 patients had severe irAEs
- Female gender more commonly associated with autoimmune disorders (4/6, P=.026)
- 3 patients interrupted treatment because of irAEs (all responders) and 3 because of progression around the time of the irAE
- 5 patients developed hypothyroidism and 1 hyperthyroidism

### NIVOTHYM: Nivolumab for patients with advanced type B3 thymoma and thymic carcinoma

= EORTC academic group trial - starts recruiting in Jan 2018

# Sistemsko zdravljenje karcinoma žolčnika in žolčevodov

## DIO 2017

ASIST.DR.MARTINA REBERŠEK, DR.MED.  
SEKTOR INTERNISTIČNE ONKOLOGIJE  
ONKOLOŠKI INŠTITUT LJUBLJANA  
17.11.2017

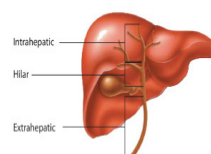
## Klasifikacija

### Razdelitev:

- Karcinom žolčnika
- Intrahepatični holangiokarcinom
- Perihilarni holangiokarcinom (Klatskinov tumor)
- Distalni (ekstrahepatični) holangiokarcinom

- ≈2% vseh GIT tumorjev
- Karcinom žolčnega epitelijskega tkiva, ki lahko vznikne kjerkoli v žolčnem vejevju
- HISTOLOŠKO: 90% adenoCa, 10% SCC

Figure 1: Classification of Cholangiocarcinoma



Reproduced with permission from Patel T. Cholangiocarcinoma. Nat Clin Pract Gastroenterol Hepatol 2006;3:33-42.

## Epidemiologija (1)

Tabela 8: Incidenca raka (brez primerov registriranih samo iz zdravniških poročil o vzroku smrti) po stadiju, lokaciji in spolu, Slovenija 2014.

Table 8: Cancer incidence (without cases registered from death certificates only) by stage, by site and by sex, Slovenia 2014.

Šifra MKB ICD code	Primarna lokacija Primary site	Spol Sex	Število novih primerov Number of new cases	Stadij							
				Omejen		Razširjen		Razsejan		Neznan	
				Število	%*	Število	%*	Število	%*	Število	%*
				Stage							
Localized		Regional		Distant		Unknown					
Number	%*	Number	%*	Number	%*	Number	%*	Number	%*		
C22	Jetra in intrahepatični vodi Liver and intrahepatic bile ducts	M	141	57	40,4	40	28,4	37	26,2	7	5,0
		F	7	67	20	79,9	13	19,4	33	49,3	1
C23	Žolčnik Gallbladder	M	22	8	36,4	5	22,7	9	40,9	0	0
		F	2	46	12	26,1	12	26,1	22	47,8	0
C24	Drugi in neopredeljeni deli biliarnega trakta Biliary tract, other and unspecified parts	M	74	17	23,0	35	47,3	19	25,7	3	4,1
		F	7	67	11	16,4	36	53,7	19	28,4	1

Rak v Sloveniji 2014. Ljubljana: Onkološki inštitut Ljubljana, Epidemiologija in register raka, Register raka Republike Slovenije, 2017.

## Epidemiologija (2)

Tabela 11a: Število in deleži bolnikov (brez primerov registriranih samo iz zdravniških poročil o vzroku smrti), v Sloveniji zbolelih leta 2014, ki so bili v okviru prvega kurativnega zdravljenja operirani, zdravljeni s sistemskim zdravljenjem ali obsevani.

Table 11a: Number of patients (without cases registered from death certificates only) diagnosed in Slovenia in 2014, that were treated by primary curative surgery, systemic therapy or radiotherapy during their first treatment.

Šifra MKB ICD code	Primarna lokacija Primary site	Število novih primerov Number of new cases	Število kakorkoli zdravljenih* Number of all treated*		Število operiranih Number of treated by surgery		Število zdravljenih s sistemskim zdravljenjem Number of treated systemic therapy		Število obsevanih Number of treated by radiotherapy	
			Število Number	%**	Število Number	%**	Število Number	%**	Število Number	%**
C00–C96	Vse lokacije All sites	13728	11109	80,9	8514	62,0	3994	29,1	3102	22,6
C00–C14	Usta in žrelo Mouth and pharynx	352	328	93,2	190	54,0	21	6,0	256	72,7
C15	Požiralnik Oesophagus	111	73	65,8	20	18,0	32	28,8	52	46,8
C16	Želodec Stomach	452	284	62,8	216	47,8	149	33,0	79	17,5
C18	Debelo črevo Colon	809	708	87,5	687	84,9	185	22,9	9	—
C19–C20	Rektum in rektosigmoidna zveza	502	517	87,3	477	79,7	103	32,6	199	33,6
C22	Jetra in intrahepatični vodi Liver and intrahepatic bile ducts	208	64	30,8	31	14,9	33	15,9	3	—
C23–C24	Žolčnik in žolčevodi Gallbladder and biliary tract	209	86	41,1	79	37,8	12	—	3	—
C25	Prejunašnica Pancreas	392	140	35,7	76	19,4	87	22,2	13	—

Rak v Sloveniji 2014. Ljubljana: Onkološki inštitut Ljubljana, Epidemiologija in register raka, Register raka Republike Slovenije, 2017.

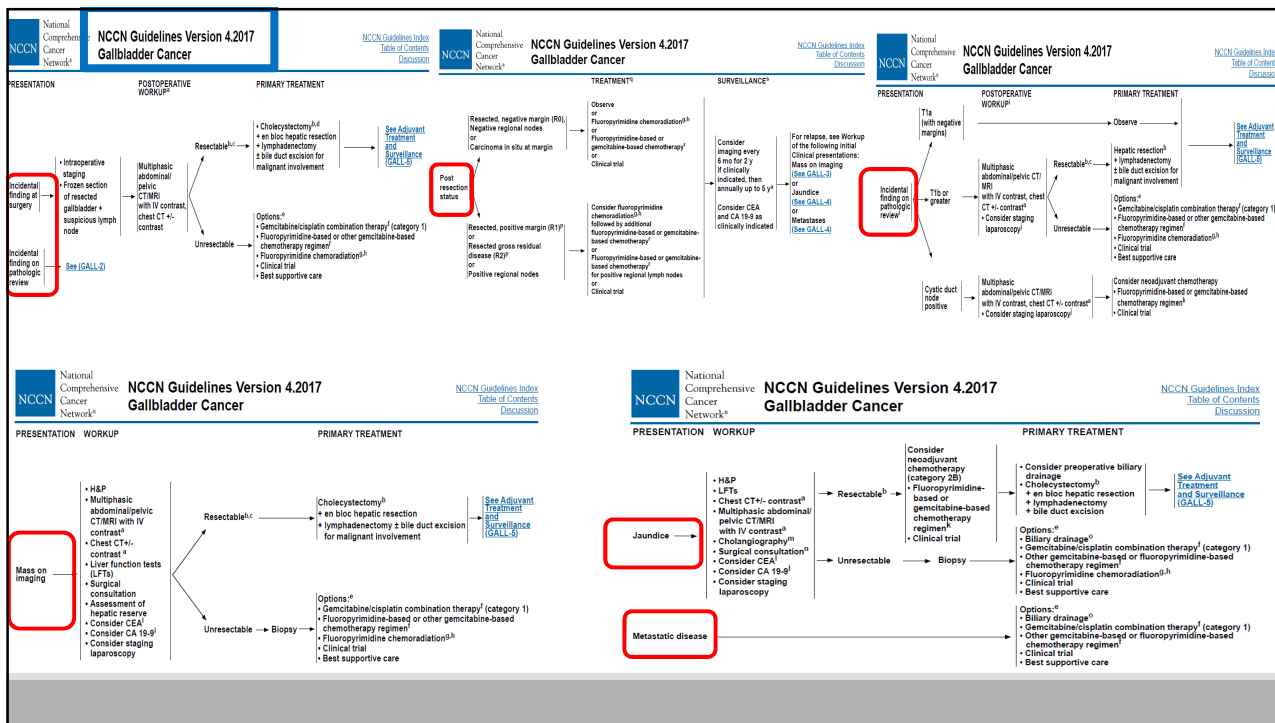
# KLINIČNA SLIKA

## SIMPTOMI

- Pruritus (66%)*
- Bolečina pod DRL (30-50%)*
- Hujšanje (30-50%)*
- Povišana tel. T(20%)*
- Temen urin, belo blato*
- Redko holangitis*

## ZNAKI

- Zlatenica (90%)*
- Hepatomegalija (25-40%)*
- Masa pod DRL (10%)*
- Courvoisier-jev znak (redko)*



### NCCN Guidelines Version 4.2017 Intrahepatic Cholangiocarcinoma

**Post resection status**

- No residual local disease (R0 resection)
  - Options:
    - Observe
    - Clinical trial
    - Fluoropyrimidine-based or gemcitabine-based chemotherapy<sup>1</sup>
- Microscopic margins (R1) or Positive regional nodes
  - Options:
    - Clinical trial
    - Fluoropyrimidine chemoradiation<sup>1,2</sup>
    - Fluoropyrimidine-based or gemcitabine-based chemotherapy<sup>1</sup>
- Residual local disease<sup>3</sup> (R2 resection)
  - Options:
    - Clinical trial<sup>4</sup>
    - Fluoropyrimidine-based or gemcitabine-based chemotherapy regimen<sup>1</sup>
    - Locoregional therapy (category 2B)<sup>5</sup>
    - Best supportive care

**SURVEILLANCE<sup>6</sup>**

- Consider multiphasic abdominal/pelvic CT/MRI with IV contrast<sup>7</sup> and chest CT +/- contrast<sup>8</sup> every 6 mo for 2 y if clinically indicated, then annually up to 5 years

**PRESENTATION**

**WORKUP**

- H&P
- Multiphasic abdominal/pelvic CT/MRI with IV contrast<sup>7</sup>
- Chest CT +/- contrast<sup>8</sup>
- Consider CEA<sup>9</sup>
- Consider CA 19-9<sup>9</sup>
- LFTs
- Surgical consultation<sup>10</sup>
- Esophagogastroduodenoscopy (EGD) and colonoscopy
- Consider viral hepatitis serologies
- Consider biopsy<sup>9</sup>
- Consider AFP

**PRIMARY TREATMENT**

- Resectable<sup>11</sup>
  - Consider staging laparoscopy<sup>12</sup>
  - Resection<sup>13</sup>
  - Consider lymphadenectomy for accurate staging
- Unresectable<sup>14</sup>
  - Options:
    - Gemcitabine/cisplatin combination therapy<sup>1</sup> (category 1)
    - Clinical trial
    - Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen<sup>1</sup>
    - Fluoropyrimidine chemoradiation<sup>1</sup>
    - Locoregional therapy (category 2B)<sup>5</sup>
    - EBRT<sup>15</sup>
    - Arterially directed therapies<sup>16</sup>
    - Best supportive care
- Metastatic disease
  - Options:
    - Gemcitabine/cisplatin combination therapy<sup>1</sup> (category 1)
    - Clinical trial
    - Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen<sup>1</sup>
    - Locoregional therapy (category 2B)<sup>5</sup>
    - Best supportive care

**Isolated intrahepatic mass<sup>17</sup>**  
(Imaging characteristics consistent with malignancy but not consistent with hepatocellular carcinoma)  
*(See recent guidelines for Occult Primary Cancers)*

### NCCN Guidelines Version 4.2017 Extrahepatic Cholangiocarcinoma

**Post resection status**

- Resected, negative margin (R0), Negative regional nodes or Carcinoma in situ at margin
  - Options:
    - Observe or Fluoropyrimidine chemoradiation<sup>18</sup> or Fluoropyrimidine-based or gemcitabine-based chemotherapy<sup>19</sup> or Clinical trial
- Resected, positive margin (R1)<sup>20</sup> or Resected gross residual disease (R2) or Positive regional nodes
  - Options:
    - Consider fluoropyrimidine chemoradiation<sup>18</sup> followed by additional fluoropyrimidine-based or gemcitabine-based chemotherapy<sup>19</sup> or Fluoropyrimidine-based or gemcitabine-based chemotherapy<sup>19</sup> for positive regional lymph nodes or Clinical trial

**SURVEILLANCE<sup>21</sup>**

- Consider imaging every 6 mo for 2 y if clinically indicated, then annually up to 5 years<sup>22</sup>

**PRESENTATION**

**WORKUP**

- H&P
- Multiphasic abdominal/pelvic CT/MRI (assess for vascular invasion) with IV contrast<sup>23</sup>
- Chest CT +/- contrast<sup>24</sup>
- Cholangiography<sup>25</sup>
- Consider CEA<sup>26</sup>
- Consider CA 19-9<sup>26</sup>
- LFTs
- Consider endoscopic ultrasound (EUS) after surgical consultation
- Consider serum IgG4 to rule out autoimmune cholangitis

**PRIMARY TREATMENT**

- Unresectable<sup>27</sup>
  - Biliary drainage,<sup>28</sup> if indicated
  - Biopsy<sup>29</sup> (only after determining transplant status)
  - Consider referral to transplant center
- Resectable<sup>30</sup>
  - Surgical exploration<sup>31</sup>
  - Consider laparoscopic staging
  - Consider preoperative biliary drainage
- Metastatic disease
  - Biliary drainage,<sup>28</sup> if indicated
  - Biopsy

**Options:**

- Gemcitabine/cisplatin combination therapy<sup>1</sup> (category 1)
- Clinical trial
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen<sup>1</sup>
- Fluoropyrimidine chemoradiation<sup>18</sup>
- Best supportive care

**Isolated extrahepatic mass<sup>32</sup>**  
(Pain, jaundice, abnormal LFTs, obstruction or abnormality on imaging)

## J. W. Valle, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up- TNM AJCC

Table 1. Continued

Cholangiocarcinoma				Cholangiocarcinoma - perihilar				Cholangiocarcinoma - distal				Gallbladder cancer			
Cholangiocarcinoma - intrahepatic				Cholangiocarcinoma - perihilar				Cholangiocarcinoma - distal				Gallbladder cancer			
Primary tumour (T)				Primary tumour (T)				Primary tumour (T)				Primary tumour (T)			
				Distant metastasis present											
Stage grouping				Stage grouping				Stage grouping				Stage grouping			
Stage 0	T1a	N0	M0	Stage 0	T1a	N0	M0	Stage 0	T1a	N0	M0	Stage 0	T1s	N0	M0
Stage I	T1	N0	M0	Stage I	T1	N0	M0	Stage IA	T1	N0	M0	Stage I	T1	N0	M0
Stage II	T2	N0	M0	Stage II	T2a-b	N0	M0	Stage IB	T2	N0	M0	Stage II	T2	N0	M0
Stage III	T3	N0	M0	Stage IIIA	T3	N0	M0	Stage IIA	T3	N0	M0	Stage IIIA	T3	N0	M0
Stage IVA	T4	N0	M0	Stage IIIB	T1-3	N1	M0	Stage IIB	T1	N1	M0	Stage IIIB	T1-3	N1	M0
Stage IVB	Any T	N1	M0	Stage IVA	T4	N0-1	M0	Stage IIB	T2	N1	M0	Stage IVA	T4	N0-1	M0
				Stage IVB	Any T	N2	M0	Stage IIB	T3	N1	M0	Stage IVB	Any T	N2	M0
								Stage III	T4	Any N	M0				
								Stage IV	Any T	Any N	M1				

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control. Edge et al. [20]. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL, USA. The original source for this material is the AJCC Cancer Staging Handbook, 7th edition (2010) published by Springer Science and Business Media LLC, www.springer.com.



## Onkološko specifično zdravljenje

---

- kirurško
- radioterapija
- **sistemska terapija:**
  - adjuvantno sistemsko zdravljenje
  - sistemsko zdravljenje metastatske bolezni

## Adjuvantna sistemska terapija (1)

---

- redki raki
- podatki iz retrospektivnih analiz, kliničnih primerov in klin.raziskav faze II

### Only Older Randomized Adjuvant Therapy Trial

- Japanese study, randomly assigned patients with: extrahepatic biliary cancer, gallbladder cancer, periampullary cancer or pancreas cancer to chemotherapy post-op vs surgery alone
  - Chemotherapy was 5FU and MMC x 1 dose then oral 5FU
  - Only gallbladder came out positive
  - Problem: were these 5 trials or 5 subset analyses?

## Adjuvantna sistemska terapija (2)

### Adjuvantna kemoterapija:

- BILCAP faza III: kapecitabin vs. kontrola
- Prodigee-12 faza III: GEMOX vs. kontrola
- ACTICCA-1 faza III: gem/cis vs. kontrola

### Adjuvantna kemoradioterapija lahko izboljša preživetje (drenaža žolča)<sup>1</sup>

- mOS 9m vs. 3 m
- Rezultati retrospektivnih analiz


1. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 2012; 30: 1934-1940.

## Adjuvant capecitabine for biliary tract cancer: the **BILCAP** randomized study


**Primrose JN**, Fox RP, Palmer D, Prasad R, Mirza D, Anthony A, Corrie P, Falk S, Wasan H, Ross P, Wall L, Wadsley J, Evans J, Stocken D, Prasad R, Cunningham D, Garden OJ, Stubbs C, Valle JW and Bridgewater J on behalf of the BILCAP investigators

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17  
Slides are the property of the author. Permission required for reuse.

1



## Study overview



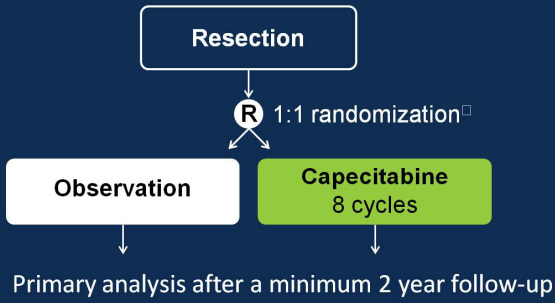
- Two arm, open label, randomized, controlled clinical trial

**Interventions**

- Observation
- Capecitabine (1250mg/m<sup>2</sup>) twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles)

**Outcome measures**

- Primary; overall survival (OS)
- Secondary;
  - Relapse free survival (RFS)
  - Toxicity
  - Quality of life\*
  - Health economics




\*EORTC QLQ-C30 & LMC-21 (latter for patients with colorectal liver metastasis)  
 □Minimized on surgical centre, tumour site, type of resection (R0/R1) & performance status (ECOG PS 0-2)


PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by Professor John Primrose

4



## Baseline characteristics



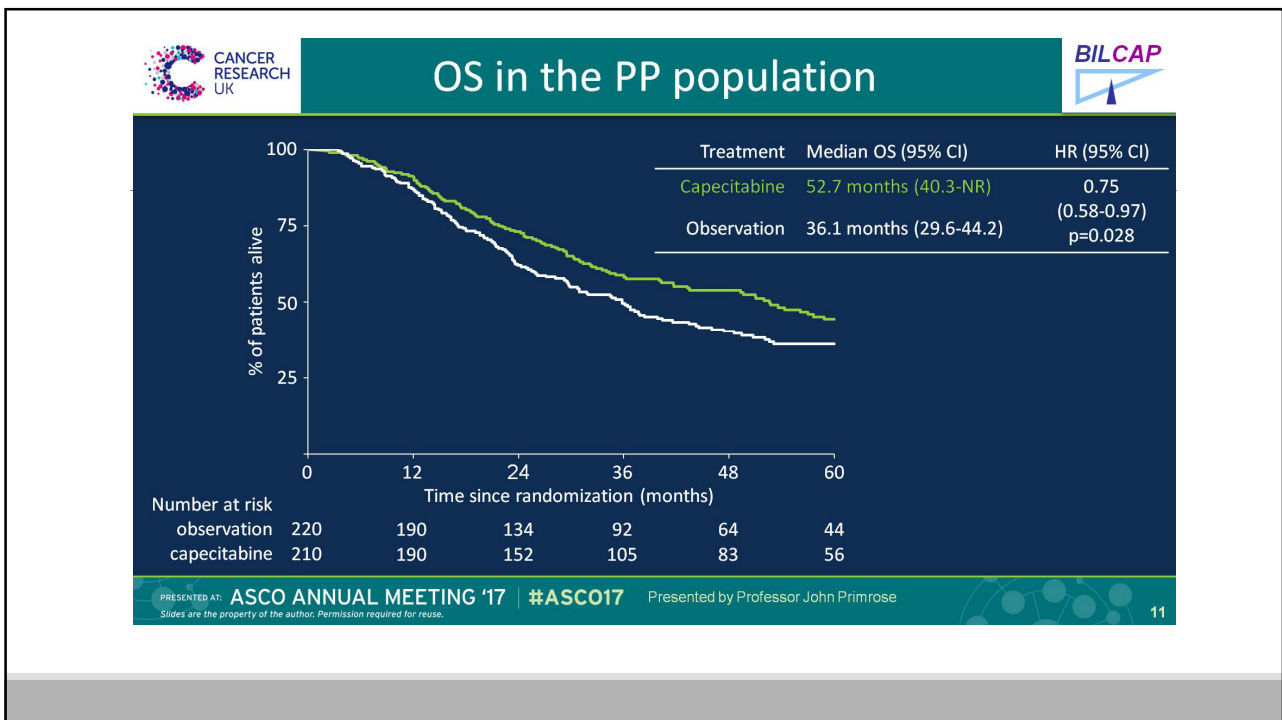
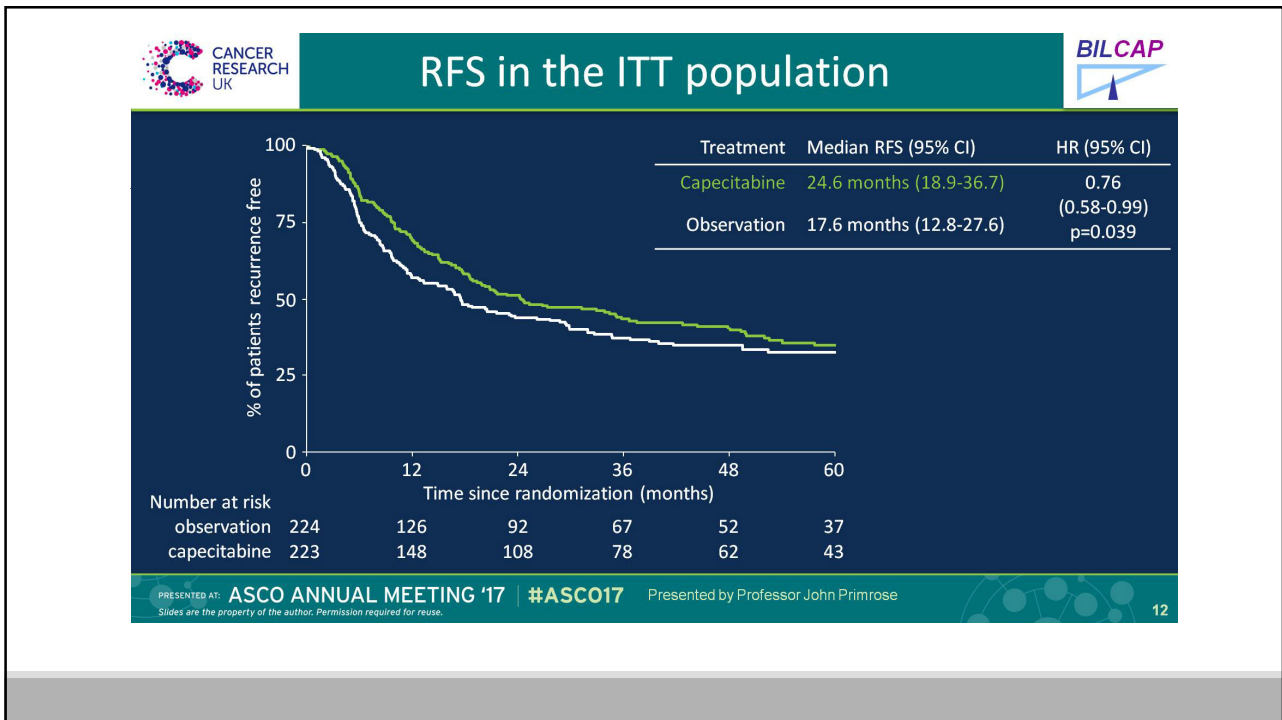
		Observation arm (n=224)	Capecitabine arm (n=223)
Gender	Male	113 (50%)	111 (50%)
Age	Median years (inter-quartile range)	64 (55-69)	62 (55-68)
Tumour site	Intrahepatic CC	41 (18%)	43 (19%)
	Hilar CC	63 (28%)	65 (29%)
	Muscle invasive gall bladder carcinoma	40 (18%)	39 (17%)
Lower common bile duct CC		80 (36%)	76 (34%)
Resection status	R0	140 (63%)	139 (62%)
	R1	84 (38%)	84 (38%)
ECOG performance status	0	101 (45%)	100 (45%)
	1	116 (52%)	116 (52%)
	2	7 (3%)	7 (3%)
Tumour size	Median mm (inter-quartile range)	25 (20-44)	25 (19-45)
Lymph node status	N0	108 (48%)	100 (45%)
	N1	102 (46%)	108 (48%)
	NX	14 (6%)	15 (7%)

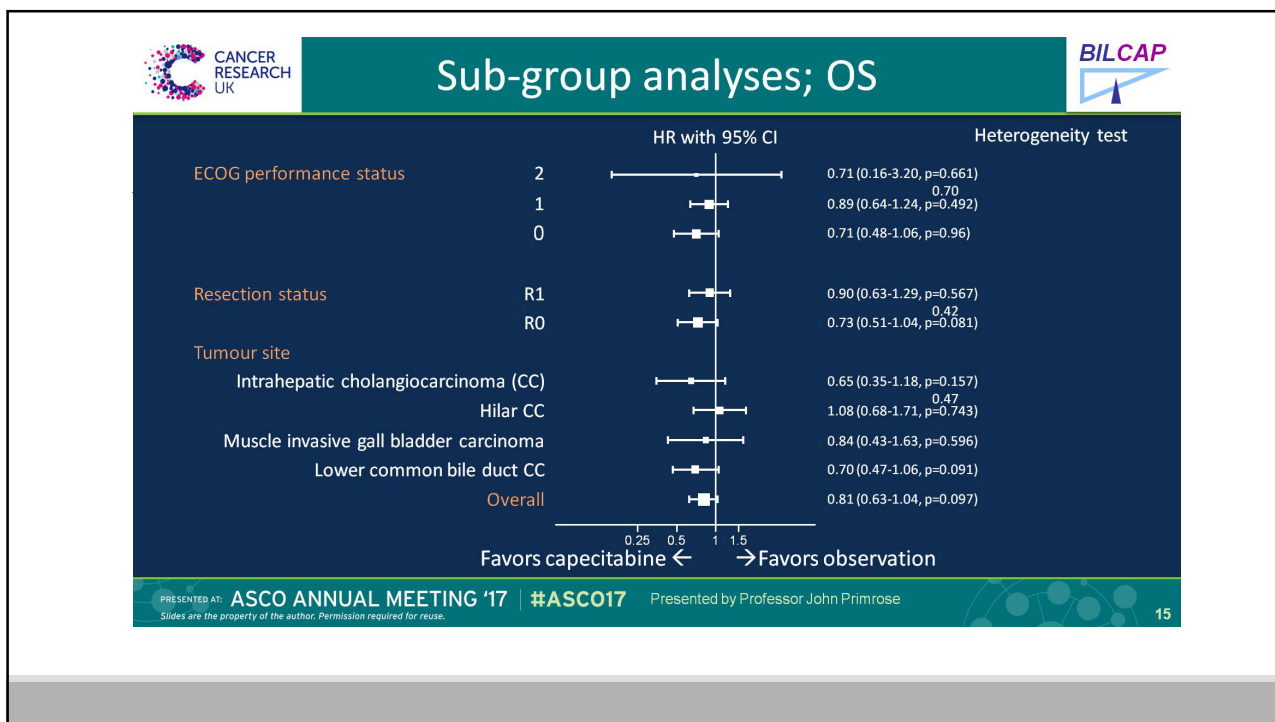
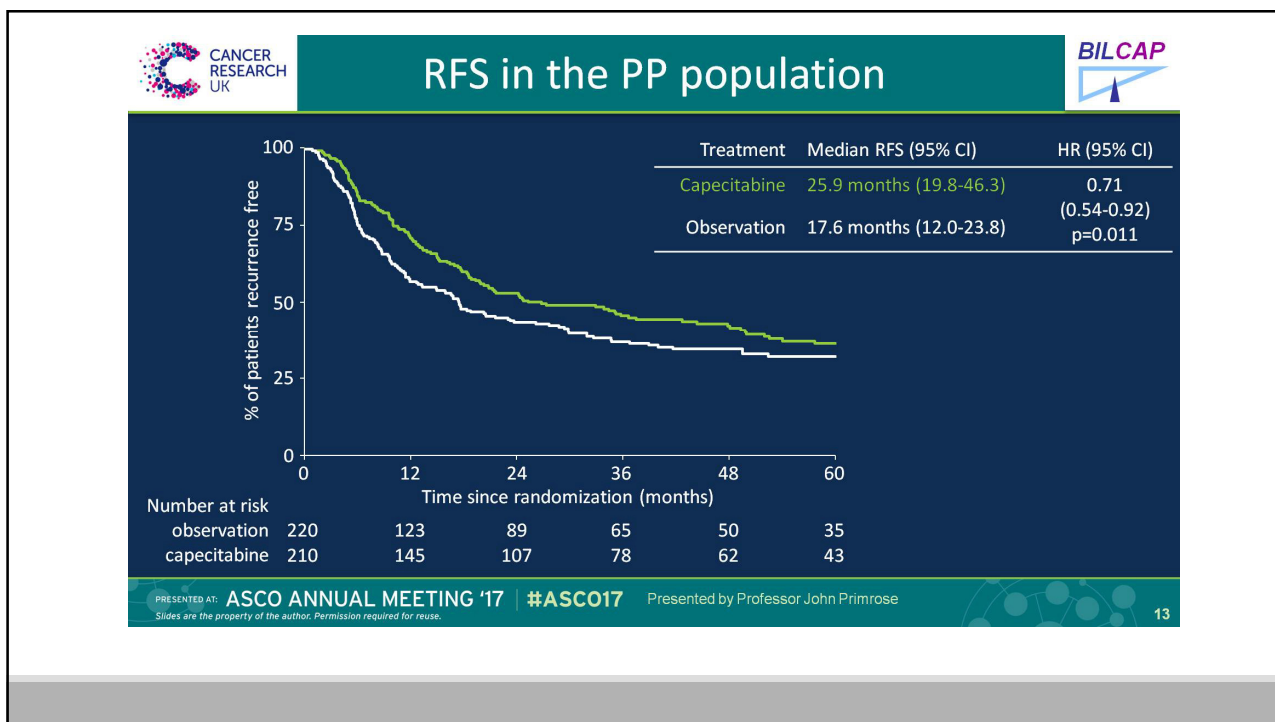
Values shown are n (%) for categorical data, and median (IQR) for continuous measures


PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by Professor John Primrose

8








CANCER RESEARCH UK

Toxicity



The safety population was conditional on receiving capecitabine (n=213)

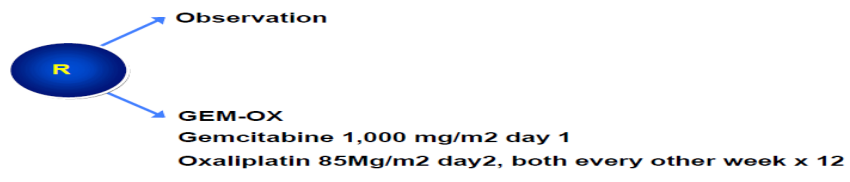
There were no deaths related to chemotherapy

Toxicity type	Grade 3/4
Fatigue	16 ( 7.5 %)
Plantar palmar erythema	44 (20.7 %)
Diarrhea	16 ( 7.5 %)
Nausea	2 ( 0.9 %)
Mucositis/stomatitis	2 ( 0.9 %)
Vomiting	1 ( 0.5 %)
Neutropenia	4 ( 1.9 %)
Bilirubin	3 ( 1.4 %)
Thrombocytopenia	1 ( 0.5 %)
Alopecia	0

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17 Presented by: Professor John Primrose

Adjuvant GEMOX: Study Design

Prodige 12- Accord 18 (UNICANCER GI)



Randomized phase III design

Edeline, J, et al. ASCO GI, 2017, abstract 225

AIM: whether GEMOX would improve RFS vs surveillance while maintaining health-related quality of life.

One hundred and ninety-six patients were enrolled; median follow-up was 44.3 months. Relapse events occurred in 54 patients with GEMOX and in 64 patients under surveillance. Median RFS was 30.4 months with GEMOX vs 22 months with surveillance; 4-year RFS rates were 39.3% and 33.2%, respectively. The differences were not significant.

Edeline J, Bonnetain F, Philip JM, et al. Gemox versus surveillance following surgery of localized biliary tract cancer: Results of the PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial. *J Clin Oncol.* 2017;35(suppl):45-Abstract 225.

## Baseline Characteristics

Characteristic	GEMOX N= 94	Surveillance N = 99
M:F	59.6%/40.4%	50.5%/49.5%
ECOG PS: 0	53.2%	63.6%
1	39.4%	31.3%
2	5.3%	2.0%
IHC	43.6%	45.5%
Perihilar	10.6%	5.1%
Extrahepatic	27.7%	28.3%
Gallbladder	18.1%	21.2%
Pre-op Tx: Portal vein Embo	20.2%	23.2%
Biliary drain	11.7%	9.1%
Tumor characteristics: Node + R1	37.2%	36.4%
Perineural invasion	13.8%	12.1%
Perineural invasion	54.3%	45.5%
Vascular Emboli	26.6%	29.3%

Edeline, J, et al. ASCO GI, 2017, abstract 225

Vanderbilt-Ingram Cancer Center

## Outcomes

- **Primary endpoint, RFS**
  - HR 0.83, p = 0.31
  - Median Gem-OX 30.4 months vs 22.0 Months for surveillance
  - 4-year RFS: 39.3% vs 33.2%
  - Forrest Plot
    - All subsets to left of 1 except Extrahepatic cholangiocarcinoma which was wildly to the right

Edeline, J, et al. ASCO GI, 2017, abstract 225

Vanderbilt-Ingram Cancer Center

- Health-related quality of life scores did not differ at 1-year and 2-year time points.
- Grade 4 adverse events occurred among 17% of patients receiving GEMOX and 9.1% of patients under surveillance. One patient died from each group.

# Sistemsko zdravljenje metastatske bolezni (1)

## Gemcitabine

Reference	Schedule	# of patients	Response Rate	TTP	Overall Survival
Penz, et al	2200/m2 Q o week	32	22%	5.6 mos	11.5 mos
Valencak, et al	1200/m2 Qw x3	24	4%	3.5 mos	6.8 mos
Kubicka, et al	1000/m2 qw x3	23	30%	4.4 mos	N/A
Arroyo, et al	1000/m2 qw x3	39	36%	N/A	6.5 mos

These and other trials are all summarized in Scheitauer W. Semin Oncol 29:6 (suppl 20), 40-45, 2002

# Sistemsko zdravljenje metastatske bolezni (2)

## Gemcitabine + 5-FU

Reference	Gemcitabine + _____	# of pts	Response Rate	TTP or PFS	Overall Survival
Murad (Am J Clin Oncol 26: 151-4, 2003)	Bolus 5-FU	9 pts	33%	TTP	9 months
Jacobson D ASCO 2003	Bolus 5-FU with LV	42 pts	9.5%	3.8 months	6.8 months
Hsu C, et al ASCO 2003	Bolus 5-FU	26 pts	19%	4.2 months	7.3 months
Knox J, et al GI Symposium, 2004	Capecitabine	35 pts	26%	6.8 months	10.3 months

2<sup>nd</sup> study of gem-cape in 57 pts, RR18%, OS 7 months

<sup>7</sup>  
Vanderbilt-Ingram Cancer Center



## Sistemsko zdravljenje metastatske bolezni (3)

### Gemcitabine + platinums

Reference	Type of platinum	# of pts	RR	Survival
Thengprasert, et al GI ASCO	Cisplatin	24	33%	13 mos
Reyes-Vidal, et al GI ASCO (GOCCHI trial)	Cisplatin	42	48%	7 mos
ASCO 2003	Carboplatin	13	30%	N/A
EORTC	Oxaliplatin	33 (1 <sup>st</sup> line)	36%	14.3 months

## Sistemsko zdravljenje metastatske bolezni (4)

### Sistemska terapija:

- **Faza III UK ABC-02:** cisplatin/gemcitabine vs. gemcitab- mOS: 11.7 mesecev cisplatin/  
Gemcitabin vs. 8.1 mesecev gemcitabin (95% CI: 0.53-0.79; P<0.001)

- **Meta-analiza**<sup>1</sup>: kombinacija kemoterapije učinkovitejša od monokemoterapije neodvisno od starosti (<65 vs ≥65 let), spola, mesta primarnega tumorja (intrahepatični vs ekstrahepatični vs karcinom žolčnika), stadija bolezni (lokoregionalni vs metastatski) in predhodne terapije (operacija vs stent), razen v primeru PS ECOG 2 vs 0,1 → gemcitabin monoterapija, v primeru led. insuficience oksaliplatin

### Kemoradioterapija

- **Nerandomizirane klinične raziskave:** mOS 9- 14 mesecev

- **Faza III FFCD 9902:** KT (5-FU, cis)RT (50 Gy) vs KT (GEMOX): DFS 5.8 m vs 11 m; OS 13.5 m vs 20 m

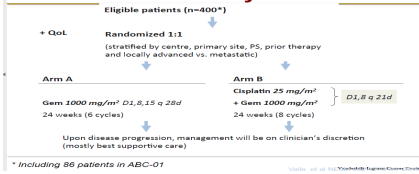
<sup>1</sup> Valle JW, Furuse J, Jitlal M et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann Oncol 2014; 25: 391–398.

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthony, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators\*

ABC-02 - Study schema



ABC-02 statistical methods

**Primary endpoint:** OVERALL SURVIVAL: ITT analysis (pre-planned ABC-01 and ABC-02)

**Secondary endpoints:**

- Progression-free survival
- Toxicity
- Quality of life (EORTC QLQ C-30)

**Sample size:**

- Powered to detect increase in median survival from 8 to 11 months
- n=354 patients (315 OS events), n=400 to allow for drop-out
- Log-rank test with 80% power and two-sided  $\alpha$  5% level

**Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.\***

Variable	Gemcitabine (N=200)	Cisplatin plus Gemcitabine (N=204)	P Value
Age — yr			
Median	63.2	63.9	0.88
Range	23.4–84.8	32.8–81.9	
Sex — no. (%)			
Female	108 (52.4)	108 (52.9)	0.92
Male	98 (47.6)	96 (47.1)	
Extent of disease — no. (%)			
Locally advanced	49 (23.8)	55 (27.0)	0.46
Metastatic	157 (76.2)	149 (73.0)	
Primary tumor site — no. (%)			
Gallbladder	76 (36.9)	73 (35.8)	0.87
Bile duct	119 (57.8)	122 (59.8)	
Ampulla	11 (5.3)	9 (4.4)	
Type of tumor — no. (%)			
Adenocarcinoma	191 (92.7)	186 (91.2)	0.27
Carcinoma, type not specified	12 (5.8)	17 (8.3)	
Adenosquamous carcinoma	2 (1.0)	0	
Squamous-cell carcinoma	1 (0.5)	0	
Carcinosarcoma	0	1 (0.5)	
ECOG performance-status score — no. (%)			
0	64 (31.1)	66 (32.4)	0.72
1	117 (56.8)	111 (54.4)	
2	24 (11.7)	27 (13.2)	
Unknown	1 (0.5)	0	
Previous therapy — no. (%)			
No	50 (24.3)	50 (24.5)	0.96
Yes	156 (75.7)	154 (75.5)	
Type of previous therapy — no. (%)			
Curative surgery	48 (23.3)	37 (18.1)	0.20
Palliative surgery	40 (19.4)	37 (18.1)	0.74
Laparotomy	49 (23.5)	48 (23.5)	0.99
Biliary stenting	92 (44.7)	93 (45.6)	0.83
Radiotherapy	5 (2.4)	3 (1.3)	0.48
Adjuvant chemotherapy	5 (2.4)	3 (1.3)	0.74
Photodynamic therapy	1 (0.5)	1 (0.5)	1.00
Other therapy	81 (39.3)	76 (37.3)	0.14

\* ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 to 5, with lower scores indicating a higher level of functioning.

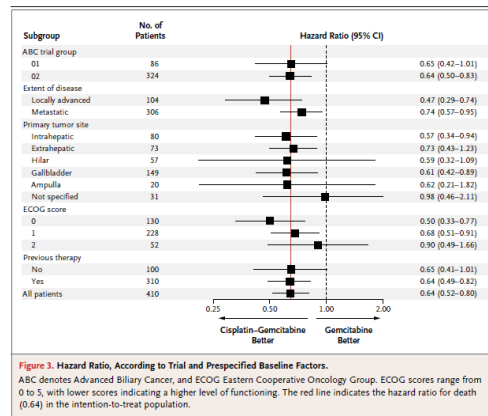
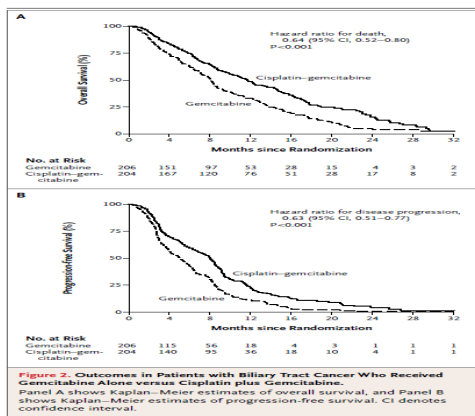
N Engl J Med 2010;362:1273-81.

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthony, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators\*

OS, PFS



N Engl J Med 2010;362:1273-81.

ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthony, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iversen, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators\*

NEŽELENI UČINKI

**Table 2. Grade 3 or 4 Toxic Effects during Treatment, According to Treatment Group.**

Variable	Gemcitabine (N=199)	Cisplatin plus Gemcitabine (N=199) <i>number (percent)</i>	P Value
<b>Hematologic toxic effects</b>			
Decreased white-cell count	19 (9.5)	31 (15.7)	0.07
Decreased platelet count	13 (6.5)	17 (8.6)	0.44
Decreased hemoglobin level	6 (3.0)	15 (7.6)	0.04
Decreased neutrophil count	33 (16.6)	50 (25.3)	0.03
Any hematologic toxic effect	47 (23.6)	64 (32.3)	0.05
<b>Liver function</b>			
Increased alanine aminotransferase level	34 (17.1)	19 (9.6)	0.03
Other abnormal liver function	39 (19.6)	26 (13.1)	0.08
Any abnormal liver function	54 (27.1)	33 (16.7)	0.01
<b>Nonhematologic toxic effects</b>			
Alopecia	0	2 (1.0)	0.16
Anorexia	5 (2.5)	6 (3.0)	0.75
Fatigue	33 (16.6)	37 (18.7)	0.58
Nausea	7 (3.5)	8 (4.0)	0.78
Vomiting	11 (5.5)	10 (5.1)	0.65
Impaired renal function	2 (1.0)	3 (1.5)	0.83
<b>Infection</b>			
Without neutropenia	23 (11.6)	12 (6.1)	0.05
With neutropenia	14 (7.0)	20 (10.1)	0.28
Biliary sepsis	8 (4.0)	8 (4.0)	0.99
Any type	38 (19.1)	36 (18.2)	0.82
Deep-vein thrombosis	1 (0.5)	4 (2.0)	0.18
Thromboembolic event	3 (1.5)	7 (3.5)	0.20
Other	62 (31.2)	66 (33.3)	0.64
Any	100 (50.3)	108 (54.5)	0.39
Any grade 3 or 4 toxic effect	137 (68.8)	140 (70.7)	0.69

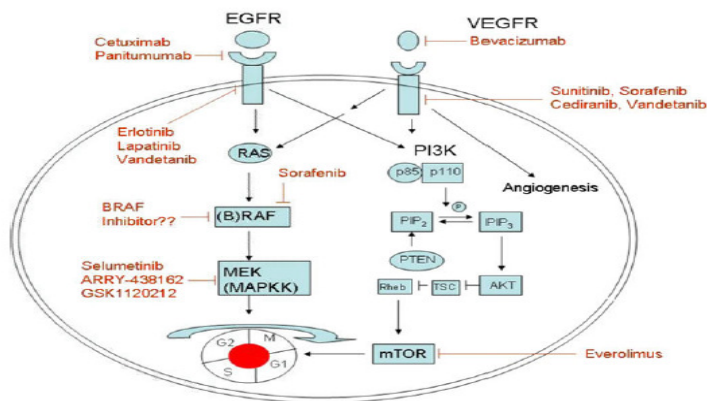
N Engl J Med 2010;362:1273-81.

NOVOSTI v sistemskem zdravljenju

- Tarčna zdravila ?
- Imunoterapija ?



## Signalne poti in tarčne terapije pri rakah biliarnega trakta



Faris JE, et al. Targeted therapy for biliary tract cancers. J Hepatobiliary Pancreat Sci (2012) 19:326–336

## Tarčna zdravila (1)

Table 1 Clinical trials with targeted therapies in advanced biliary tract cancers

Agent	Trial design	Line	#Pts	CR (%)	PR (%)	ORR (%)	PFS	OS
<b>EGFR</b>								
Erlotinib monotherapy [31]	Single-arm PII	1st/2nd	43	0	8	8	TTP 2.6 months	7.5 months
GEMOX ± erlotinib [32]	Randomized PII	1st	135/133	NR	NR	NR	5.8 vs. 4.2 months	9.5 vs. 9.5 months
GEMOX ± cetuximab [36]	Randomized PII	1st	36	NR	NR	NR	4 months: 61 vs. 44%	NR
GEMOX/cetuximab [35]	Single-arm PII	1st	30	10	53	63	8.8 months	15.2 months
GEMOX/capecitabine/panitumumab [39]	Single-arm PII	Any	42	2.4	31	33	8.3 months	9.8 months
<b>HER2</b>								
Lapatinib monotherapy [45]	Single-arm PII	1st/2nd	17	0	0	0	1.8 months	5.2 months
<b>VEGF</b>								
GEMOX/bevacizumab [51]	Single-arm PII	1st	35	0	40	40	7 months	12.7 months
Sorafenib monotherapy [52]	Single-arm PII	Any	46	0	2.2	2.2	2.3 months	4.4 months
Sorafenib monotherapy [53]	Single-arm PII	First	31	0	0	0	3 months	9 months
Gemcitabine ± sorafenib [54]	Randomized PII	First	62	0	7	7	2.9 months	9.4 months
Sunitinib monotherapy [55]	Single-arm PII	Previously treated	56	0	8.9	8.9	1.7 months	4.8 months
<b>MEK</b>								
Selumetinib monotherapy [61]	Single-arm PII	Any	28	0	12	12	3.7 months	9.8 months
<b>Combination</b>								
Erlotinib/bevacizumab [33]	Single-arm PII	First	49	0	18.4	18.4	TTP 4.4 months	9.9 months

EGFR epidermal growth factor receptor, GEMOX gemcitabine and oxaliplatin, HER2 human epidermal growth factor receptor 2, VEGF vascular endothelial growth factor, MEK mitogen-activated protein kinase/extracellular-signal regulated kinase

Faris JE, et al. Targeted therapy for biliary tract cancers. J Hepatobiliary Pancreat Sci (2012) 19:326–336

## Tarčna zdravila (2)

Table 2. Planned or ongoing clinical trials using targeted agents

Agents	Trial type	Line of therapy	Country	Target #pts	NCT#
<b>EGFR</b>					
GEMOX ± cetuximab	Randomized PII	1st line	Taiwan	120	01267344
GEMOX ± erlotinib	Randomized PIII	1st line	Korea	180	01149122
GEMOX + erlotinib	PIb	1st line	USA	22	00987766
GEMOX + panitumumab	Single-arm PII	1st line	USA	30	01308840
GEMOX/capecitabine ± panitumumab	Two arm PI based on KRAS	Any	Denmark	70	00779454
GEMOX ± panitumumab	Randomized PII	1st line	Italy	18	01389414
Gemcitabine/irinotecan + panitumumab	Single-arm PII	1st line	USA	45	00948935
Gemcitabine/cisplatin ± panitumumab	Randomized PII	1st line	Germany	92	01320254
<b>MEK</b>					
ARRY-438162	PI	2nd/subsequent	USA	95	00959127
GSK112012, GSK1120212 + gemcitabine	PI	Any line	Japan	21	01324258
Gemcitabine/cisplatin/selumetinib	PI/II	Any line	UK	18	01242605
<b>mTOR</b>					
Everolimus	Single-arm PII	1st line	Australia	27	00973713
<b>VEGF</b>					
mFOLFOX6 + bevacizumab	PII	1st line	USA	24	00881504
Gemcitabine/capecitabine/bevacizumab	Single-arm PII	1st line	USA	50	01007552
mFOLFOX6 + cediranib	Single-arm PII	1st line	USA	25	01229111
Gemcitabine/cisplatin ± cediranib	Randomized PII	1st line	UK	136	00939848
GEMOX/sorafenib	Single-arm P/II	Any line for PI 1st line for PII	USA	58	00955721
Gemcitabine ± vandetanib, vandetanib	Randomized PII	1st line	Italy	174	00753675
Gemcitabine/capecitabine/vandetanib	Phase I	Any line	USA	28	00551096

EGFR epidermal growth factor receptor, GEMOX gemcitabine and oxalipatin, MEK mitogen-activated protein kinase/extracellular-signal regulated kinase, mTOR mammalian target of rapamycin, VEGF vascular endothelial growth factor, mFOLFOX6 5-fluorouracil, oxalipatin, leucovorin

Faris JE, et al. Targeted therapy for biliary tract cancers. J Hepatobiliary Pancreat Sci (2012) 19:326–336

## Tarčna zdravila (3)

Table 4. Completed EGFR inhibitor trials in BTC/GEMOX

Treatment	Phase	No. of subjects	ORR	mPFS (m)	mOS (m)	Reference
GEMOX	III	268	16% 30%	4.2	9.5	Lee et al, 2012
GEMOX + erlotinib				5.8	9.5	
GEMOX	II	150	29% 23%	5.5	12.4	Malka et al, 2012
GEMOX + cetuximab				6.1	11	
GEMOX	II	122	17% 27%	4.1	9.8	Chen et al, 2013
GEMOX + cetuximab				6.7	10.6	
GEMOX	II	31	45%	10.6	20.3	Hezel et al, 2010
Panitumumab						
GEMOX	II	30	63%	8.8	15.2	Gruenberger et al, 2010
Cetuximab						
Gemcitabine	II	34	18%	7.8	14.5	Rubovszky et al, 2013
Capecitabine						
Cetuximab						
GEMOX	II	46	33%	8.3	10	Jensen et al, 2012
Capecitabine						
Panitumumab						
Gemcitabine	II	31	31%	9.7	12.7	Sohal et al, 2013
Irinotecan						
Panitumumab						
Erlotinib (2nd line)	II	42	8%	2.6	7.5	Philip et al, 2006

Abbreviations: BTC = biliary tract cancer, EGFR = epidermal growth factor receptor, GEMOX = in combination with gemcitabine and oxalipatin, mOS = median overall survival, mPFS = median progression free survival, ORR = objective response rate.

British Journal of Cancer (2014) 111, 430–436 | doi: 10.1038/bjc.2014.343

O-019

Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

Hendrik-Tobias Arkena HT, et al. (1)



- Ramucirumab 8 mg/kg i.v. 1. in 8. dan
- Pembrolizumab 200 mg i.v. 1.dan/3 tedne

“The primary objective was to assess the safety and tolerability of ramucirumab plus pembrolizumab; preliminary efficacy will be examined.”

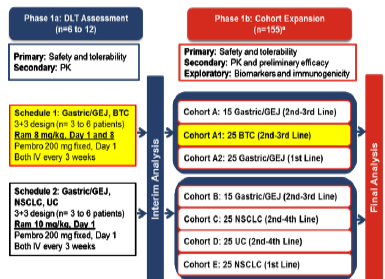
O-019

Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

Hendrik-Tobias Arkena HT, et al. (2)

**METHODS**

**JVDF (NCT02443324) Phase 1a/b Study Design (n=164)**



<sup>a</sup>Patients may continue treatment for up to 35 cycles, until confirmed progressive disease or discontinuation for any other reason.  
 DLT=dose-limiting toxicity; PK=pharmacokinetics; Ram=ramucirumab; Pembro=pembrolizumab

**RESULTS**

**Baseline Demographics**

		Cohort A1 n=28
Age	Median, yr (range)	63 (35-78)
		16 (62)
Race, n (%)	White	23 (88)
Sex, n (%)	Female	10 (69)
ECOG PS, n (%)	1	14 (54)
Prior systemic therapy, n (%)	2 prior lines	9 (35)
Disease Stage	Metastatic	21 (81)
	Intrahepatic CC	11 (42)
	Extrahepatic CC	8 (31)
Site of primary tumor, n (%)	Gallbladder	4 (15)
	Ampulla of Vater	1 (4)
	Other	2 (8)
	Low	3 (12)
	Intermediate	10 (38)
	High	4 (15)
	Unknown <sup>a</sup>	9 (35)
	Positive	12 (46)
	Negative	11 (42)
PD-L1 status, n (%)	Pending	2 (8)
	Not available	1 (4)

<sup>a</sup>Unknown included patients with non-evaluable tissue, not yet evaluated, or missing tissue sample at time of data cut.

CC=cholangiocarcinoma

O-019  
 Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

Hendrik-Tobias Arkena HT, et al. (3)

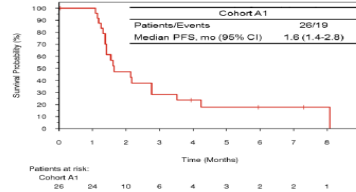
Treatment Exposure

	Cohort A1 n=26
Median follow-up duration, mo (95% CI)	5.3 (2.6-6.2)
<b>Ramucirumab</b>	
Median duration of therapy, months (IQR)	2.1 (1.4-3.8)
Median number of cycles, n (IQR)	3 (2-5)
Patients completing ≥ 3 cycles, n (%)	15 (58)
<b>Pembrolizumab</b>	
Median duration of therapy, months (IQR)	2.1 (1.4-4.1)
Median number of cycles, n (IQR)	3 (2-6)
Patients completing ≥ 3 cycles, n (%)	16 (62)

One treatment cycle is equal to 3 weeks. IQR=interquartile range

All treated patients	Cohort A1 n=26
Best overall response, n (%)	-
Complete response	1 (4)
Partial response	9 (35)
Stable disease	12 (46)
Not Evaluable	4 (15)
Objective response rate	4%
Disease control rate	38%
Duration of stable disease, mo (95% CI)	3.9 (2.2-8.1)

Progression-free Survival



O-019  
 Ramucirumab plus pembrolizumab in previously treated advanced or metastatic biliary tract cancer: A multi-disease phase 1 study

Hendrik-Tobias Arkena HT, et al. (4)

Overview of Adverse Events

	Cohort A1 n=26	
	TEAE	TRAE
Number of patients, n (%)		
Any Grade	26 (100)	22 (85)
Grade ≥3	17 (65)	11 (42)
SAE	14 (54)	6 (23)
Discontinued due to AE/SAE	1 (4) <sup>a</sup>	1 (4) <sup>a</sup>
AE leading to death on study treatment	-	-
AE leading to death within 30 days of discontinuation from study treatment	-	-

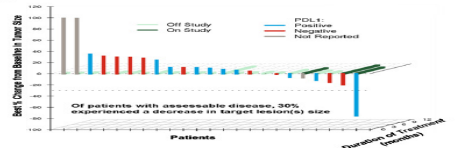
<sup>a</sup>Transaminases increased (grade 3) TEAE=treatment-emergent adverse event. TRAE=treatment-related adverse event.

Treatment-related Adverse Events (22 patients)

Treatment-related AE, pts (%)	Cohort A1, n=26	
Any	Any Grade	Grade 3/4
Any	22 (85)	11 (42)
Serious	6 (23)	6 (23)
Occurring in ≥ 2 patients	10 (38)	-
Fatigue <sup>a</sup>	7 (27)	-
Nausea	3 (12)	-
Decreased appetite	3 (12)	-
Stomatitis	3 (12)	-
Pyrexia	3 (12)	-
Vomiting	2 (8)	-
Treatment-related AE of interest <sup>b</sup> , pts (%)	Any Grade	Grade 3/4
Occurring in ≥ 2 patients	8 (31)	5 (19)
Hypertension	5 (19)	1 (4)
Bleeding/hemorrhage event <sup>c</sup>	4 (15)	-
Endocrine disorder <sup>d</sup>	4 (15)	-
Diarrhea	3 (12)	-
Infection related reaction	3 (12)	-
Transaminases increased <sup>e</sup>	3 (12)	2 (8)
CTCAE <sup>f</sup>	2 (8)	-

<sup>a</sup>Independently pre-identified for ramucirumab and pembrolizumab: neutropenia, constipation, renal impairment, renal hemorrhage, edema, cerebrovascular hemorrhage, PDL1, and rash/dermatitis  
<sup>b</sup>Independently pre-identified for pembrolizumab: renal hemorrhage, edema, cerebrovascular hemorrhage, PDL1, and rash/dermatitis  
<sup>c</sup>Transaminases (aspartate aminotransferase and alanine aminotransferase)  
<sup>d</sup>Transaminases (aspartate aminotransferase and alanine aminotransferase)  
<sup>e</sup>Transaminases (aspartate aminotransferase and alanine aminotransferase)  
<sup>f</sup>Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

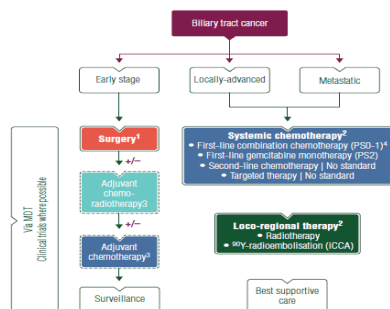
Response and Duration of Treatment



CONCLUSIONS

- At this interim evaluation, the combination of ramucirumab with pembrolizumab did not reveal any unexpected safety signals in patients with advanced or metastatic biliary tract cancer.
- In this heavily pretreated patient population with advanced or metastatic biliary tract cancer, limited antitumor activity was observed with the studied regimen.
- Additional overall survival follow-up and biomarker data will guide the future development of this combination in advanced or metastatic biliary tract cancer.

J. W. Valle, et al. On behalf of the **ESMO** Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



<sup>1</sup> Special considerations:  
 • Need for pre-operative biliary drainage  
 • Avoid percutaneous biopsy in resectable disease  
 • Assess Future Liver Remnant  
 • Assess need for Portal Vein Embolisation  
 • Neoadjuvant approach (selected cases)  
 • Completion surgery for incidental gallbladder cancer of T-stage T1b and above  
<sup>2</sup> Option of salvage surgery should be considered in responding patients with initially inoperable disease  
<sup>3</sup> Level of recommendation IVC  
<sup>4</sup> Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

**Figure 1.** Algorithm for the management of patients with biliary tract cancer. MDT, multidisciplinary team; PS, performance status; ICCA, intrahepatic cholangiocarcinoma.

Annals of Oncology 27 (Supplement 5): v28–v37, 2016 doi:10.1093/annonc/mdw324

J. W. Valle, et al. On behalf of the ESMO Guidelines Committee Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

- Treatment**
- Curative**
- Radical surgery (with lymphadenectomy) is the only curative treatment of BTC; the exact nature and extent of surgery will depend on tumour subtype/ location and should be agreed at a specialist hepatobiliary multidisciplinary tumour board
  - Surgery involving hepatic resection will need to take into account the future liver remnant and may require portal vein embolisation
  - For patients with incidentally diagnosed GBC (post-cholecystectomy), reoperation with radical intent should be considered for stage T1b and above (± resection of port sites)
  - Adjuvant therapy (radiotherapy, chemoradiotherapy or chemotherapy alone) may be offered to patients on the understanding that the evidence base is weak and only after risk-benefit assessment participation in clinical trials should be encouraged
  - Neoadjuvant therapy and liver transplant (Mayo Clinic protocol) in early stage hilar CCA remains investigational; participation in clinical trials should be encouraged
  - Patients with initially inoperable, non-metastatic disease should be re-discussed at the multidisciplinary tumour board with a view to salvage surgery in the event of a good response to systemic and/or loco-regional treatment, including participation in clinical trials
- Palliative**
- Systemic chemotherapy is the treatment of choice for patients with locally advanced or inoperable disease; combination chemotherapy for PS 0-1 patients and monotherapy for PS 2 patients
  - Cisplatin/gemcitabine is the reference chemotherapy regimen for good PS (0-1) patients; oxaliplatin may be substituted for cisplatin where there is a concern about renal function
  - Gemcitabine monotherapy may be considered for PS 2 patients
  - There is no established second-line chemotherapy regimen; patients should be encouraged to participate in clinical trials
  - There is no established evidence to support the use of targeted therapies; patients should be encouraged to participate in clinical trials
  - Radiotherapy may be considered in patients with localised disease, after first-line chemotherapy; patients should be encouraged to participate in clinical trials
  - Radioembolisation may be considered in patients with inoperable ICCA, usually after first-line chemotherapy; patients should be encouraged to participate in clinical trials



## Zaključki (1)

---

- slaba prognoza
- pomen diagnostike
- prvo zdravljenje kiruško

## Zaključki (2)- vloga sistemske terapije

---

- **Adjuvantno zdravljenje:**

- kapecitabin novo standardno sistemsko zdravljenje
- vloga radioterapije v kombinaciji s sistemsko kemoterapijo- prospektivne klin.raziskave

- **Metastatska bolezen:**

- 1.red: gemcitabin+cisplatin (PS0-1), gemcitabin mono (PS 2)
- 2.red: ni standardne terapije
- tarčno zdravljenje: ni standardne terapije

- **Imunoterapija:** prve klinične raziskave v poteku



HVALA ZA POZORNOST

# Rak žolčnega voda

*Predstavitev primera*

Nina Fokter Dovnik, dr.med.

Marko Boc, dr.med.

13. dan internistične onkologije, Onkološki inštitut, 17. 11. 2017

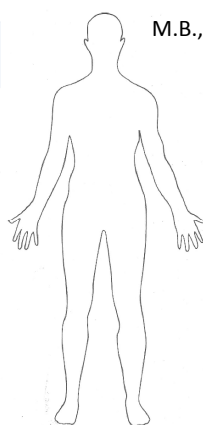
## Anamneza

Družinska anamneza: bp.

Brez pridruženih bolezni

Brez redne terapije,  
brez alergij

Bivši kadilec,  
prekomerno uživa alkohol



M.B., 67 let

Ikterus  
Hujšanje

Rezistenca pod DRL

## Diagnostične preiskave

### Laboratorij

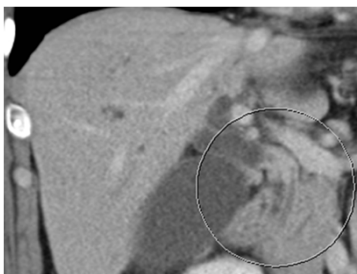
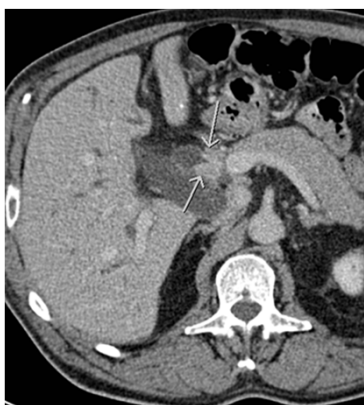
- Bilirubin cel. 184.3  $\mu\text{mol/L}$
- GGT 15,02  $\mu\text{kat/L}$
- AF 6,06  $\mu\text{kat/L}$
- ALT 2,66  $\mu\text{kat/L}$
- AST 1,87  $\mu\text{kat/L}$
- CA 19-9 525,7 KU/L

### CT trebuha

- Povečan žolčnik
- Razširjeni intrahepatalni žolčni vodi
- Zadebeljena stena holedohusa v srednjem delu z zoženim lumnom

### ERCP + krtačenje

- Stenoza holedohusa v višini izstopišča cistikusa
- Razširjeni proksimalni žolčni vodi
- Citološki izvid: adenokarcinom



## Vprašanje 1

Kakšno zdravljenje bi priporočili bolniku v tem trenutku?

- A. Neoadjuvantno kemoterapijo
- B. Neoadjuvantno kemoradioterapijo
- C. Operacijo
- D. Definitivno kemoradioterapijo
- E. Paliativno sistemsko zdravljenje

## Operacija in histološki izvid

- 15. 9. 2017: pankreatikoduodenektomija po Whipple
- Pooperativni potek brez pomembnih zapletov
- Histološki izvid:
  - invazivni žlezni karcinom žolčnega voda, biliarni tip, večinoma G2, mestoma G3
  - tumor 1,8 cm, plitvo infiltrira preko stene žolčnega voda v tkivo pankreasa
  - obsežna peri- in intranevralna invazija, invazija v limfne žile
  - žarišča BilIN visoke stopnje
  - 1/28 bezgavk pozitivnih
  - izrezano v zdravo (R0)
  - pT3N1

## Vprašanje 2

Bi po operaciji priporočili še kakšno zdravljenje?

- A. Dopolnilno kemoterapijo
- B. Dopolnilno radioterapijo
- C. Dopolnilno kemoradioterapijo
- D. Opazovanje

## Dopolnilno sistemsko zdravljenje



Kapcitabin 1250 mg/m<sup>2</sup>  
1.-14. dan, vsakih 21 dni  
8 ciklov

## Vprašanje 3

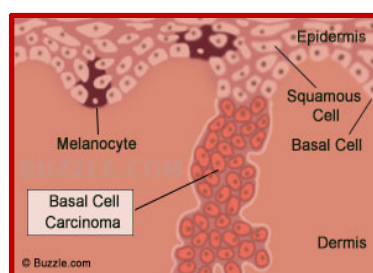
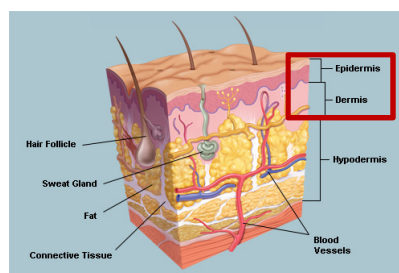
Kakšna je bila razlika v srednjem celokupnem preživetju bolnikov v ITT analizi raziskave BiCap?

- A. 14 dni
- B. 2 meseca
- C. 6 mesecev
- D. 16 mesecev
- E. 24 mesecev

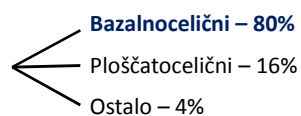
# Sistemsko zdravljenje nemelanomskih kožnih rakov

Janja Ocvirk

## UVOD – anatomija kože in kožni rak



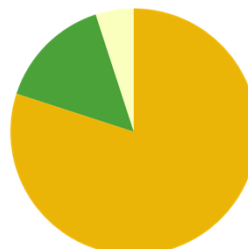
Melanom  
Nemelanomski rak kože





## Bazalnocelični karcinom

- Bazalnocelični karcinom (BCK) raste iz bazalne plasti povrhnjice in je najpogosteje diagnosticiran maligni tumor ter najpogostejša oblika kožnega raka pri beli populaciji<sup>1-4</sup>
- Tveganje za pojav BCK pri beli populaciji je 30%<sup>1,2</sup>
- Slabo poročanje v registrih
- Glavni vzrok za pojav BCK je izpostavljenost UV sevanju, ki vodi do kumulativnih poškodb DNK in mutacije genov<sup>1-5</sup>



80% glava in vrat  
15% trup  
5% okončnine

1. Rubin AI et al. N Engl J Med 2005;353:2262-9
2. Wong CSM et al. Br Med J 2003;327:794-8
3. Roewert-Huber J et al. Br J Dermatol 2007;157:47-51
4. Lear JT et al. J R Soc Med 1998;91:585-8
5. Caro J, Low JA. Clin Cancer Res 2010;16:3335-9

3

## Bazalnocelični karcinom – *histološki podtipi*

- nodularni (60%)
- površinski (30%)
- infiltrirajoči
- morfeiformni (sklerozirajoči)



Update of the Guideline on Basal Cell Carcinoma. European Dermatology Forum.  
[http://www.euroderm.org/images/stories/guidelines/guideline\\_Basal\\_Cell\\_Carcinoma-update2012%20.pdf](http://www.euroderm.org/images/stories/guidelines/guideline_Basal_Cell_Carcinoma-update2012%20.pdf)

4

## Zdravljenje bazalnoceličnega karcinoma

- Kiretaža in kavterizacija, kriokirurgija
- Krema imiquimod (Aldara®)

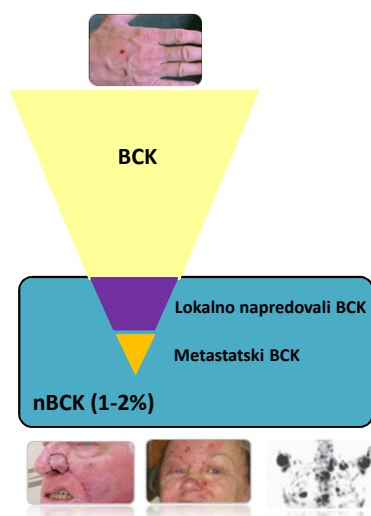
- **Kirurška ekscizija**
- **Elektrokemoterapija**
- **Obsevanje**
- **Tarčno zdravilo Erivedge®**

nBCK



5

## Napredovali bazalnocelični karcinom



### Lokalno napredovali BCK (lnBCK)

- **Agresivna** oblika bolezni s **poškodbo lokalnih tkiv**
- Pogoste **ponovitve** po operaciji
- Operacija bi povzročila **deformacijo**



### Metastatski BCK (mBCK)

- **Redka, a resna** oblika BCK
- Vključuje prisotnost **metastaz** (npr. bezgavke, kosti, pljuča, jetra)<sup>1</sup>
- **Slab izid** (mediana preživetja: 8–14 mesecev<sup>2,3</sup>; 5-letna stopnja preživetja: 10%<sup>3,4</sup>)

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

6

## Kriteriji za opredelitev napredovale oblike BCK

- Velikost lezije  $\geq 10$  mm
- Vrašćanje tumorja v okolna tkiva in strukture
- Kirurško zdravljenje/obsevanje je kontraindicirano zaradi lege tumorja ali bi vodilo v znatno obolevnost/deformacijo/izgubo funkcije
- Dve ali več ponovitev lezije na enakem mestu



1

1. Basset-Seguín N. et al. Mol Cancer Ther 2015; 1-9

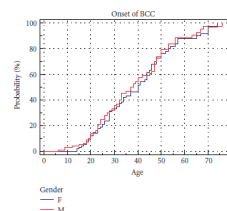
7

## Sy. bazalnoceličnega nevusa (Gorlin Goltz)

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



- KOSTI



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

8

## Tveganje za lokalno ponovitev

Tveganje za lokalno ponovitev	Majhno	Veliko
Trup, okončine	<20 mm	≥20mm
Lica, čelo, skalp, vrat	<10 mm	≥10mm
Centralni del obraza, veke, obrvi, periorbitalno, nos, ustnice, brada, mandibularno, uhlji in okrog uhljev, temporalno, spolovilo, roke, stopala	<6 mm	≥6mm
Klinična omejenost	Dobra	Slaba
Primarni vs. rekurentni	Primarni	Rekurentni
Predhodna radioterapija	Ne	Da
Imunosupresija	Ne	Da
Histološki podtip	Nodularni, superficialni	Mikronodularni, morfeiformni, infiltrativni
Perinevralna invazija	Ne	Da
Metoda zdravljenja	Kirurška (popolna ekscizija)	Lokalne destruktivne metode, nepopolna ekscizija

9

## Kaj preostane bolniku, ko so vse možnosti zdravljenja izčrpane?



Puig S. Clin Transl Oncol DOI 10.1007/s12094-014-1272-9

10

## BCK in signalna pot Hedgehog



- Pot celične rasti in diferenciacije, ki nadzira tvorbo organov v embrionalnem razvoju<sup>1</sup>
- Signalna pot Hedgehog je v večini tkiv odraslega neaktivna
- Nenormalna aktivacija signalne poti pomembno BCK<sup>1</sup>
- Zaviralci signalne poti Hedgehog omogočajo novo možnost zdravljenja za bolnike z napredovalim



1. Epstein EH. Nat Rev Cancer 2008;8:743-54

## Raziskava ERIVANCE BCC - učinkovitost

Izidi	(30-mesečna analiza)		
	mBCK (n=33)	InBCK (n=63)	Total (n=96)
Mediana trajanja odgovora, meseci 95%CI	14,8 5,6 - 17,0 (n=16)	26,2 9,0 - 37,6 (n=38)	16,1 9,5 - 26,2 (n=54)
Objektivni odgovor, n (%) 95% CI	16 (48,5) 30,8 - 66,2	38 (60,3) 47,2 - 71,7	54 (56,3) 45,7 - 66,4
Popolni odgovor	0	20	20
Delni odgovor	16	18	34
Stabilna bolezen	14	15	29
Napredovanje bolezni	2	6	8

Sekulic A, Poster presentation ASCO 2014

## Raziskava ERIVANCE BCC - varnost

Neželeni dogodek <sup>a</sup>	NCI CTCAE Stopnja (n = 104)					
	n (%)	Total	1	2	3	4
Mišični krči	74 (71,2)	45 (43,3)	23 (22,1)	6 (5,8)	0 (0)	0 (0)
Alopecija	69 (66,3)	49 (47,1)	20 (19,2)	NA	NA	NA
Sprememba okusa	58 (55,8)	32 (30,8)	26 (25,0)	NA	NA	NA
Izguba teže	54 (51,9)	29 (27,9)	16 (15,4)	9 (8,7)	0 (0)	0 (0)
Utrujenost	45 (43,3)	33 (31,7)	7 (6,7)	4 (3,8)	1 (1,0)	1 (1,0)
Slabost	34 (32,7)	25 (24,0)	9 (8,7)	0 (0)	0 (0)	0 (0)
Zmanjšan apetit	29 (27,9)	19 (18,3)	7 (6,7)	3 (2,9)	0 (0)	0 (0)

<sup>a</sup> NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Neželeni učinki se po intenzivnosti razvrščajo od stopnje 1 do stopnje 5, kjer pomeni stopnja 1 blage neželene učinke, stopnja 2,3,4 po intenzivnosti rastejo vse do stopnje 5, ki pomeni smrt zaradi neželenega učinka zdravila.

Sekulic A, Poster presentation ASCO 2014

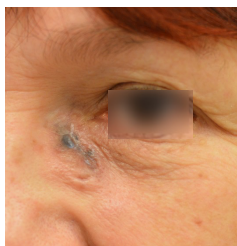
13

## primer z Onkološkega inštituta

23. 9. 2013



19. 12. 2013



31. 7. 2014



- Hitri odgovor na zdravljenje
- Neželeni učinki: alopecija gr. 2 po enem letu zdravljenja, zvišan CPK gr.1, mišični krči gr.1

14

**primer z Onkološkega inštituta****8. 11. 2012**

Bolnik z Gorlinovim sindromom (multipli BCK)

**16. 10. 2014**

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

**Rak Merklovih celic**

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

## INCIDENCA

- Stopnja incidence karcinoma Merklvih celic se razlikuje glede na geografsko področje in varira med 0.2-1.6 primerov na 100.000 prebivalcev
- Najvišjo incidenco beležijo na Novi Zelandiji in Avstraliji (1.6/100.000), v Združenih državah Amerike je nekoliko nižja (0.8/100.000), v Evropi pa le 0.2-0.4 primerov na 100.000 prebivalcev.
- Incidenca je močno povečana pri starostnikih (srednja starost ob diagnozi je 75 let)
- Večja je tudi pri moških kot pri ženskah.
- Večja pri bolnikih na imunosupresivni terapiji (HIV, transplantacija...)

## ETIOLOGIJA IN NASTANEK BOLEZNI

Poznamo dva vzroka za nastanek KMC:

- Preko onkoproteinov enkodiranih z polioma virusom Merklvih celic (MCPyV)
- Akumulacija mutacij povzročenih z UV sevanjem. Pogosteje pri imunosupresiranih bolnikih







National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 1.2018 Merkel Cell Carcinoma

### Staging continued

American Joint Committee on Cancer (AJCC)  
TNM Staging Classification for Merkel Cell Carcinoma  
(8th ed., 2016)

#### AJCC Prognostic Stage Groups

##### Clinical (cTNM)

Tis	NO	MO	O
T1	NO	MO	I
T2-3	NO	MO	IIA
T4	NO	MO	IIB
T0-4	N1-3	MO	III
T0-4	Any N	M1	IV

##### Pathological (pTNM)

Tis	NO	MO	O
T1	NO	MO	I
T2-3	NO	MO	IIA
T4	NO	MO	IIB
T1-4	N1a(sn) or N1a	MO	IIIA
T0	N1b	MO	IIIA
T1-4	N1b-3	MO	IIB
T0-4	Any N	M1	IV

### PRINCIPLES OF SYSTEMIC THERAPY<sup>1</sup>

#### Local Disease:

- Adjuvant chemotherapy not recommended

#### Regional Disease:

- Clinical trial (preferred)
- Adjuvant chemotherapy not routinely recommended as survival benefit has not been demonstrated in available retrospective studies, but could be used on a case-by-case basis if clinical judgement dictates
  - › Cisplatin ± etoposide
  - › Carboplatin ± etoposide

#### Disseminated Disease:

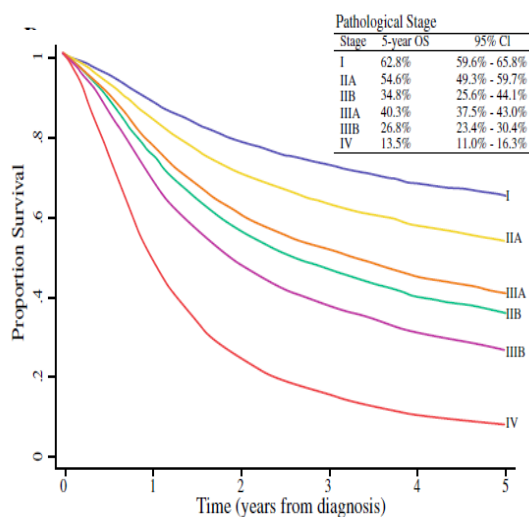
- Clinical trial (preferred)
- Avelumab<sup>2</sup>
- Pembrolizumab<sup>2</sup>
- Nivolumab<sup>2</sup>
- As clinical judgment dictates for patients with contraindications to checkpoint immunotherapy:
  - › Cisplatin ± etoposide
  - › Carboplatin ± etoposide
  - › Topotecan
  - › (CAV): Cyclophosphamide, doxorubicin (or epirubicin), and vincristine

<sup>1</sup>When available and clinically appropriate, enrollment in a clinical trial is recommended. The literature is not directive regarding the specific chemotherapeutic agent(s) offering superior outcomes, but the literature does provide evidence that Merkel cell carcinoma is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.

<sup>2</sup>Preliminary data from non-randomized trials in patients with MCC demonstrate that rates of durable response are improved with PD-1/VPD-L1 blockade compared with cytotoxic therapy. The safety profiles for checkpoint immunotherapies are significantly different from cytotoxic therapies. Consult prescribing information for recommendations on detection and management of immune-related adverse events associated with checkpoint immunotherapies. Clinician and patient education is critical for safe administration of checkpoint immunotherapies.

**ZDRAVLJENJE**

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

**PREŽIVETJE**

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

## Role of chemo for metastatic MCC

*Becker et al, ESMO 2016*

### Treatment results in pre-treated pts.:

- CR;PR;SD: 0%, 8,8%, 8,8%
- DOR (median): 1.9 mon
- PFS (median): 3.0 mon
- OS (median): 5.3 mon
- PFS and OS (at 1 year): 0% (!)
- No PRs/SDs in immunocompromised patients!

### Razlog za uporabo imunoterapije pri mMCC

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

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

## Avelumab for metastatic MCCs

*Kaufman et al, Lancet Oncol; 17: 1374-85 (2016)*

- Multicentric phase 2 study (JAVELIN 200) on the use of a PD-L1 antibody, avelumab (10mg/kg; 2-weekly)
- 88 MCC patients (stage IV; chemo-resistant)
- Mean age: 72.5 years
- 66% PD-L1-positive; 52% MCPv-positive
- Median follow-up time: 10.4 months
- Primary trial endpoint: Response rate (RECIST criteria)

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17  
Slides are the property of the author. Permission required for reuse.

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

## Avelumab for metastatic MCC

*Kaufman et al, Lancet Oncol; 17: 1374-85 (2016)*

### Outcome of JAVELIN 200 trial (second-line)

- CR; PR; SD: 9%; 23%; 10%
- Not evaluable: 20%
- 23/28 patients presented ongoing remissions
- Median PFS//OS: 2.8 mon//11.3 mon
- ORR (PD-L1-pos. vs. neg.): 34.5% vs. 18.8%
- ORR (MCPv-pos. vs. neg.): 35.5% vs. 26.1%
- Toxicity: CTC grade 3 only in 4/88 patients (5%)

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17  
Slides are the property of the author. Permission required for reuse.

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

## First-line avelumab treatment in patients with metastatic Merkel cell carcinoma (mMCC): preliminary data from an ongoing study

S. P. D'Angelo<sup>1</sup>, J. S. Russell<sup>2</sup>, J. Hassel<sup>3</sup>, C. Lebbé<sup>4</sup>, B. Chmielowski<sup>5</sup>, G. Rabinowits<sup>6</sup>, P. Terheyden<sup>7</sup>, I. Brownell<sup>8</sup>, I. Zwiener<sup>9</sup>, M. Bajars<sup>10</sup>, M. Hennessy<sup>11</sup>, H. L. Kaufman<sup>12</sup>

<sup>1</sup>Memorial Sloan Kettering Cancer Center & Weill Cornell Medical College, New York, New York, USA; <sup>2</sup>H. Lee Moffitt Cancer Center, Tampa, Florida, USA; <sup>3</sup>Universitätsklinikum Heidelberg, Heidelberg, Germany; <sup>4</sup>Saint Louis Hospital, Paris, France; <sup>5</sup>UCLA Medical Center, Los Angeles, California, USA; <sup>6</sup>Dana-Farber Cancer Institute, Boston, Massachusetts, USA; <sup>7</sup>University of Lübeck, Lübeck, Germany; <sup>8</sup>National Cancer Institute, Bethesda, Maryland, USA; <sup>9</sup>Merck KGaA, Darmstadt, Germany; <sup>10</sup>Merck Serono SIA, Riga, Latvia; <sup>11</sup>EMD Serono, Inc, Billerica, Massachusetts, USA; <sup>12</sup>Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey, USA

Poster presentation at the 53<sup>rd</sup> ASCO Annual Meeting, June 2-6, 2017; Chicago, IL, USA.

45

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

**Table 2. BOR by RECIST v1.1 per IERC**

	Patients with ≥13 weeks of follow-up, confirmed* BOR (n=16)	Patients with ≥6 weeks of follow-up, unconfirmed BOR (n=25)
BOR, n (%)		
CR	3 (18.8)	3 (12.0)
PR	7 (43.8)	14 (56.0)
Stable disease	2 (12.5)	2 (8.0)
Progressive disease	3 (18.8)	5 (20.0)
Non-evaluable	1 (6.3) <sup>†</sup>	1 (4.0) <sup>†</sup>
ORR, %	62.5	68.0
95% CI	(35.4-84.8)	(46.5-85.1)

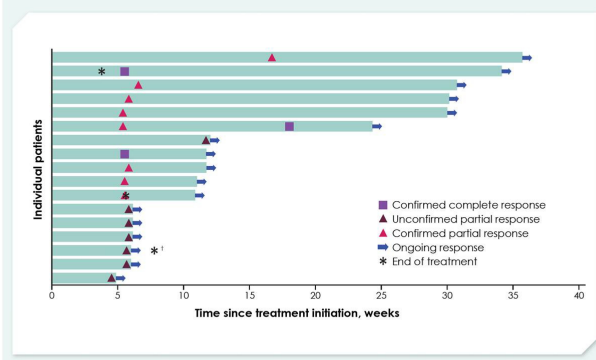
\* Response criteria met again in repeat assessment performed ≥5 weeks after initial documentation of CR or PR.

<sup>†</sup> Died prior to tumor assessment.

46

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

**Figure 3. Time to and duration of response in patients with ≥6 weeks of follow-up**



<sup>1</sup> Patient started a new treatment after discontinuing avelumab for an adverse event and is therefore nonevaluable for further study assessment; response cannot be confirmed.

47

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

## Merkel Cell Carcinoma: Pembrolizumab

*Nghiem et al, N Engl J Med 2016*

- Multicentric US phase-2 trial in MCC on Pembrolizumab (2mg/kg; 3-weekly)
- First-line therapy in 26 metastatic MCC pts (92% with stage IV)
- Mean age: 70.5 years; 62% males
- 17/26 pts (65%) were MCPyV-positive

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17  
Slides are the property of the author. Permission required for reuse.

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

# Merkel Cell Carcinoma: Pembrolizumab

*Nghiem et al, N Engl J Med 2016*

- 14/25 ORR (56%), “confirmed responses”
- 4 CR (16%), 10 PR (40%); 12/14 responses ongoing after 33 weeks of follow-up
- 4/26 pts (15%) with CTC-grade 3/4 adverse events
- 2/26 pts with grade 4 (1x myocarditis + 1x liver enzyme elevation), but ongoing PR/CR despite discontinuation
- Median PFS: 9 mon, Median OS: not reached

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17  
Slides are the property of the author. Permission required for reuse.

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

## Primerjava rezultatov študij: avelumab, pembrolizumab in nivolumab

	Avelumab - JAVELIN	Pembrolizumab	Nivolumab
<b>TARGET POPULATION</b>	Stage IV - ALL Total N=200 1L N=112 2L N=52 3L N=26 4L+ N=10	Stage IIIB (N=2) Stage IV (N=24) Total N=26 1L N=26 (now increasing to 50)	Unresectable local or Stage IV Total N=25 1L N=15 2L N=7 3L N=3
<b>STUDY DESIGN</b>	Phase 2 single arm Global including Europe	Phase 2 single arm, US only	Phase 2 single arm Global including Europe
<b>CLINICAL ASSESSMENT</b>	6 week intervals	12 week intervals after starting therapy 9 week intervals thereafter	8 week intervals
<b>RESPONSE ASSESSMENT</b>	All responses were assessed by an independent review committee	Only patients who had a response were assessed by a central radiologic review	By Investigator assessment
<b>STRENGTH OF TRIAL</b>	Largest Study in MCC	Signal finding study with small data set	Signal finding MCC cohort part of a large multi-tumour cohort study
	Pivotal study with longer follow-up intended for regulatory submission worldwide	Increase in cohort to 50 patients Approval in US likely Approval in Europe UNLIKELY	Strategy is in adjuvant setting

34



## ZAKLJUČEK

- Tudi pri MCC se je imunoterapija izkazala kot zelo učinkovita terapija.
- Učinkovitost imunoterapije je bila dokazana pri MCPyV pozitivnih in MCPyV negativnih tumorjih.
- Preizkušana je bila v prvem, drugem in poznejših redih zdravljenja napredovalega KMC.
- Zaenkrat je za zdravljenje razsejanega MCC z imunoterapijo, s strani FDA (ZDA) ter s strani Evropske agencije za zdravila, odobreno le zdravilo avelumab.

## SCC

- Drugi najbolj pogost NMKR (20%)
- Incidenca v zadnjih 30 letih narašča (50-200%)
- Večina na glavi in vratu 80-90%
- Večinoma vznikne iz prekuzorskih lezij, a tudi na novo
- 90% jih ima odlično prognozo



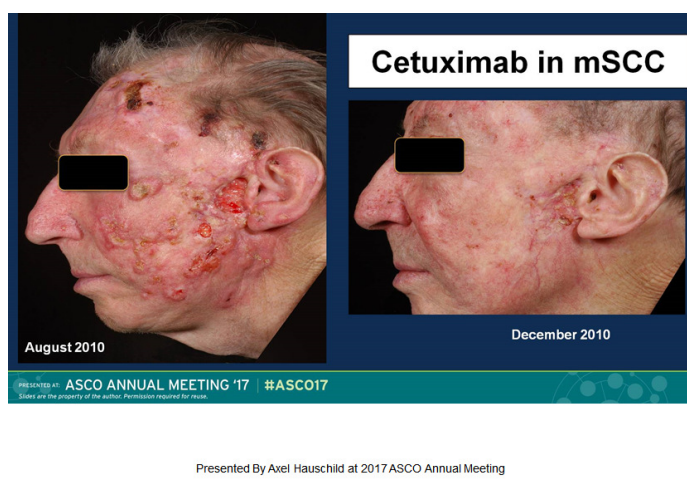


## SCC pri transplantiranih bolnikih

36 x višje incidenca kot običajno (BCC:SCC 4:1)  
Agresivno obnašanje – slaba prognoza

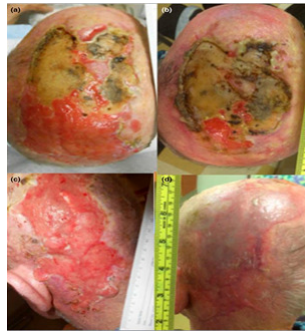


- Omejena bolezen – kirurgija, elektrokemoterapija
- Radioterapija
- Napredovala bolezen - lokalno in sistemsko
- Kemoterapija na osnovi cisplatina – ni standardnih shem, kratko trajanje remisij – 3 mesece
- Tarčna terapija: cetuximab (RR 21%), Panitumumab (31%)



## PD 1 protitelesa pri SCC

Pred zdravljenjem



Po zdravljenju

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

## REGN2810, a Fully Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy

**Kyriakos Papadopoulos**,<sup>1</sup> Taofeek Owonikoko,<sup>2</sup> Melissa Johnson,<sup>3</sup> Irene Braña,<sup>4</sup> Marta Gil Martin,<sup>5</sup> Raymond Perez,<sup>6</sup> Victor Moreno,<sup>7</sup> April Salama,<sup>8</sup> Emiliano Calvo,<sup>9</sup> Nelson Yee,<sup>10</sup> Howard Safran,<sup>11</sup> Antonio Gonzalez Martin,<sup>12</sup> Raid Aljumaily,<sup>13</sup> Daruka Mahadevan,<sup>14</sup> Kosalai Mohan,<sup>15</sup> Chetachi Emeremni,<sup>15</sup> Elizabeth Stankevich,<sup>15</sup> Israel Lowy,<sup>15</sup> Matthew Fury,<sup>15</sup> Jade Homsj<sup>16</sup>

<sup>1</sup>South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; <sup>2</sup>Emory Winship Cancer Institute, Atlanta, GA, USA; <sup>3</sup>Sarah Cannon Research Institute, Nashville, TN, USA; <sup>4</sup>Vall D'Hebron Institute of Oncology, Barcelona, Spain; <sup>5</sup>Institut Català d'Oncologia, Barcelona, Spain; <sup>6</sup>University of Kansas, Fairway, KS, USA; <sup>7</sup>START Madrid Fundacion Jimenez Diaz, Madrid, Spain; <sup>8</sup>Duke University Medical Center, Durham, NC, USA; <sup>9</sup>START Madrid, Hospital Madrid Norte Sanchinarro, Madrid, Spain; <sup>10</sup>Penn State Cancer Institute, Hershey, PA, USA; <sup>11</sup>Miriam Hospital, Providence, RI, USA; <sup>12</sup>MD Anderson Cancer Center, Madrid, Spain; <sup>13</sup>University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; <sup>14</sup>University of Arizona Cancer Center, Tucson, AZ, USA; <sup>15</sup>Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; <sup>16</sup>Banner MD Anderson Cancer, Gilbert, AZ, USA.

PRESENTED AT: **ASCO ANNUAL MEETING '17 #ASCO17** Presented by: Kyri Papadopoulos  
Slides are the property of the author. Permission required for reuse.

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

### Ongoing Pivotal Phase 2 CSCC Study (NCT02760498)

Enrollment

**Group 1 (N=53)<sup>†</sup>**

- Metastatic (nodal & distant) CSCC

**Group 2 (N=76)**

- Unresectable locally advanced CSCC

**Group 3 (N = 53)**

- Metastatic (nodal & distant) CSCC

**Regimen:**  
3 mg/kg REGN2810 every 14 days

Tumor assessment at the end of each 8 week cycle

**Regimen:**  
350 mg REGN2810 every 21 days  
(PK-equivalent exposure for all ongoing REGN2810 studies)

**Primary Endpoint:** Objective Response Rate by Central Review in each Group  
**Study Sites Locations:** US, Australia, Germany

<sup>†</sup>Fully enrolled.  
CSCC, cutaneous squamous cell carcinoma, PK, pharmacokinetic.

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17
Presented by: Kyri Papadopoulos

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

### Investigator Assessed Preliminary Response Rate by RECIST 1.1 (Intention-To-Treat Population) is 46.2%

Investigator assessment	Cohort 7 (N=10), n (%)	Cohort 8 (N=16), n (%)	Overall (N=26), n (%)
Complete response	0	2 (12.5)	2 (7.7)
Partial response	6 (60.0) <sup>†</sup>	4 (25.0)	10 (38.5)
Stable disease	1 (10.0)	5 (31.3)	6 (23.1)
Progressive disease	2 (20.0)	4 (25.0)	6 (23.1)
Not evaluated	1 (10.0)	1 (6.3)	2 (7.7)


**ORR (CR + PR + one unconfirmed PR) = 46.2% (12/26 patients; 95% CI:26.6–66.6)**  
**DCR (ORR + SD) = 69.2% (18/26 patients; 95% CI: 48.2–85.7)**

<sup>†</sup>Includes 5 confirmed partial responses and 1 unconfirmed partial response.  
CR, complete response; DCR, disease control rate; ORR, overall response rate;  
PD, progressive disease; PR, partial response; SD, stable disease;  
RECIST, Response Evaluation Criteria In Solid Tumors.

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17
Presented by: Kyri Papadopoulos

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

**CSCC EXPANSION COHORTS WERE OPENED IN THE PHASE 1 STUDY OF REGN2810**




4/1/16 5/13/16

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17  
Slides are the property of the author. Permission required for reuse.

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

**CSCC EXPANSION COHORTS WERE OPENED IN THE PHASE 1 STUDY OF REGN2810**



4/1/16 5/13/16

PRESENTED AT: ASCO ANNUAL MEETING '17 #ASCO17  
Slides are the property of the author. Permission required for reuse.

Presented By Axel Hauschild at 2017 ASCO Annual Meeting

## Zaključki

- NMKR – so najbolj pogosti raki
- Incidenca raste
- Številne mutacije pri UV induciranih rakih
- Kirurgija ej standardno zdravljenje pri nezahtevnih primerih
- Omejena vloga radioterapije kljub radiosenzitivnosti pri KMC

- Ni jasnega dobrobita kemoterapije
- Tarčna terapija glede na mutacije (SCC EGFRi in panHERi; BCC patched/SMOi) je učinkovita (RR 58%, CR 20-30%)
- Imunoterapija (PD-1 in PD-L1 protitelesa) so učinkovita pri KMC in veliko obetajo tudi pri SCC in BCC

# LOKALNO NAPREDOVALI BCC (CASE REPORT)

Marija Ignjatović, dr.med.  
Izred.prof.dr.Janja Ocvirk, dr.med.

## ANAMNEZA

- Maj 2017: 92 letni bolnik
- Dosedanje bolezni
  - Po prebolelem AMI (2008)
  - AH
  - Putika
- Nekdanji dolgoletni kadilec
- Poklic???



## SEDANJA BOLEZEN

- ◉ Plastična kirurgija → operiran zaradi BCC desnega nosnega krila (kdaj???)
  
- ◉ ORL
  - Julij 2012 → (verjetno recidiv) BCC desnega nosnega krila → operacija s kritjem defekta
  - Oktober 2014 → eksofitičen recidiv BCC med korenomo nosu in desnim medialnim očesnim kotom, vel.15x15 mm → operacija s kritjem defekta
  - Julij 2015 → ponovni recidiv BCC, adherenten na kost, vel.20mm, ektropij spodnje desne veke, epifora

## ORL KONZILIJ

- ◉ Ponovna operacija?
- ◉ EKT?
- ◉ RT?

## RT

- ◉ 10x4 Gy (5.8-18.8.2015)
- ◉ 1.kontrola po zaključenem obsevanju → *ni rezidualnega tumorja*
- ◉ Zadnja kontrola s strani radioterapevta → defekt brez okolnega infiltrata
- ◉ Nadaljne kontrole...

## APRIL 2017: PONOVNI RECIDIV BCC

- ◉ ORL konzilij
  - Operacija ≠ mutilantna
  - RT ≠ že bil obsevan
  - **ST = vismodegib**

## MAJ 2017: INT. ONKOLOG



## MAJ 2017: INT. ONKOLOG

- ◉ PS po WHO 2, blago dehidriran, brez evidentnih znakov srčnega popuščanja
- ◉ Laboratorij:
  - Kreatinin 278
  - Sečnina 21.4
  - Kalij 5.3
- ◉ Lasix 40 mg/dan → ex
- ◉ Hidracija

## MAJ 2017: INT. ONKOLOG

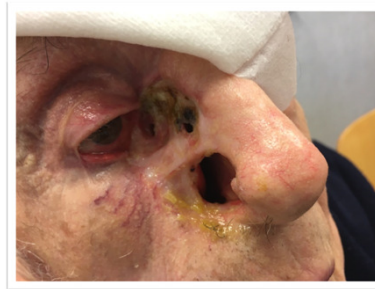
- Kontrolni laboratorij čez 1 teden:
  - Kreatinin 235
  - Sečnina 14.9
- Vismodegib  
150 mg/dan
- Kontrola na 4 tedne

PHARMACOKINETICS:	
Half-life (hours)	less than 2-4 days; bioavailability 52%; pH dependent solubility (reduced solubility with increasing pH)
Distribution	membrane phospholipidosis
cross blood brain barrier?	no information found
Volume of distribution	10-21 L
plasma protein binding	greater than 99%, primarily to albumin and alpha 1 acid glycoprotein
Metabolism	via oxidation, glucuronidation, and pyridine ring cleavage in liver; unchanged drug accounts for greater than 90% of circulating compound
active metabolite(s)	no information found
parenteral metabolism	no information found
Excretion	slow elimination
Urine	6%
Feces	82% (primarily as unchanged drug)
terminal half life	4 days
clearance	17 ml/min

## VISMODEGIB (NAJPOGOSTEJŠI STRANSKI UČINKI)

- Utrujenost
- Izguba okusa ✓
- Izguba apetita ✓
- Izguba TT ✓
- Mišični krči
- Alopecija
- Hepatopatija

OKTOBER 2017 → KONTROLNI PREGLED 5 MESECEV PO ZAČETKU ZDRAVLJENJA



PRED ZAČETKOM ZDRAVLJENJA

5 MESECEV KASNEJE



## **SIMPOZIJI SO PODPRLE NASLEDNJE DRUŽBE:**

ROCHE

ELI LILLY

MERCK

NOVARTIS

MSD

SERVIER

BAYER

BOEHRINGER INGELHEIM

EWOPHARMA

PFIZER

AMGEN

PHARMASWISS

TAKEDE