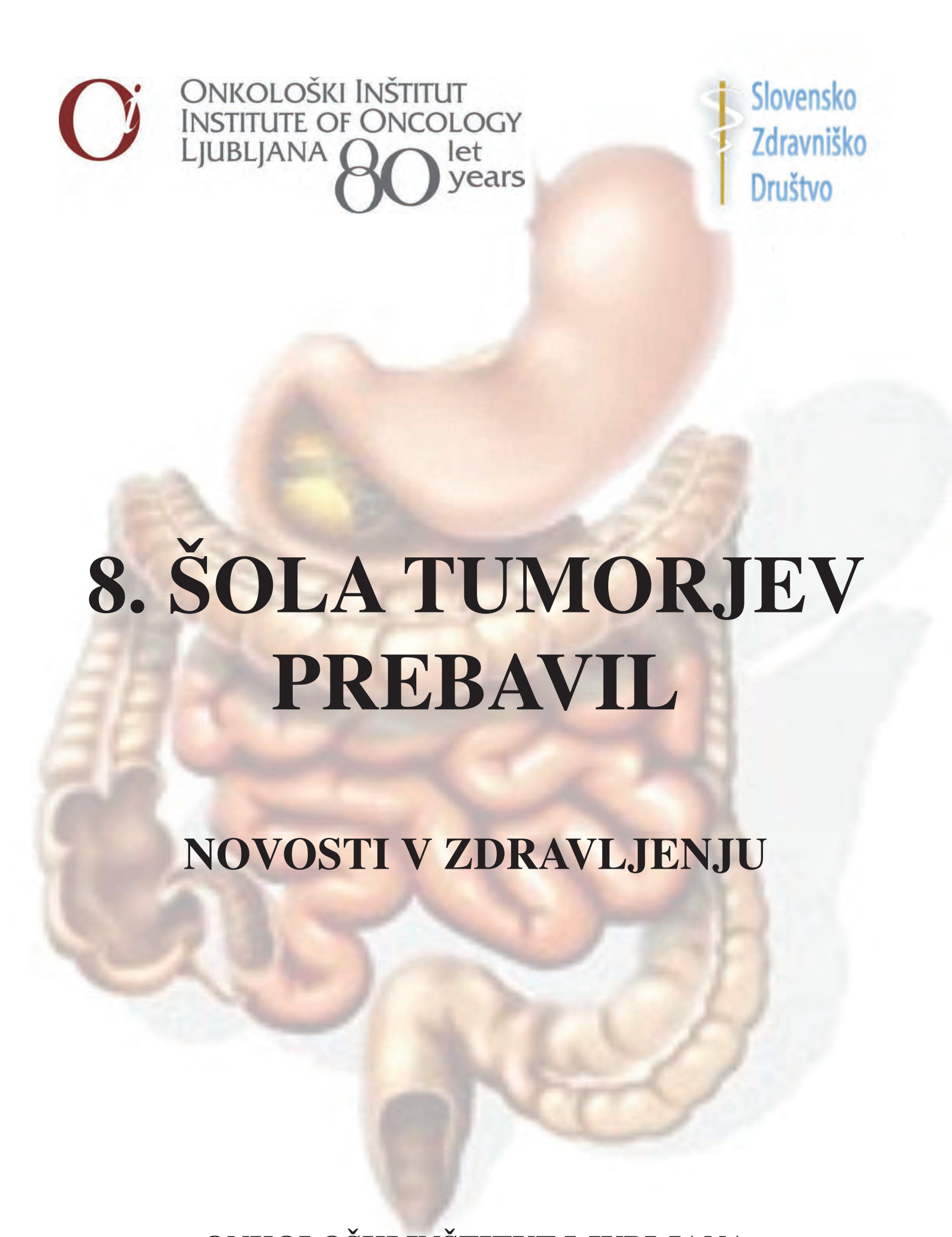
ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA 80 let years

Slovensko Zdravniško Društvo



8. ŠOLA TUMORJEV PREBAVIL

NOVOSTI V ZDRAVLJENJU

ONKOLOŠKI INŠTITUT LJUBLJANA
07. DECEMBER 2018

Strokovni odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
asist. dr. Martina Reberšek, dr.med.
mag. Zvezdana Hlebanja, dr.med.
Marko Boc, dr.med.
asist. dr. Tanja Mesti, dr.med.

Organizacijski odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
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mag. Zvezdana Hlebanja, dr.med.
Marko Boc, dr.med.
asist. dr. Tanja Mesti, dr.med.

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

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

Ljubljana, december 2018

VSEBINA:

PROGRAM SREČANJA: **PETEK, 07.12.2018**

07.00-08.00 REGISTRACIJA

Moderator: izr. prof. Janja Ocvirk, dr.med., asist. dr. Martina Reberšek, dr.med.

08.00-08.30 **SATELITNO PREDAVANJE 1**
08.30-09.00 *Reberšek M.:* Personalizacija zdravljenja raka debelega črevesa in danke
09.00-09.30 *Ocvirk J.:* Vloga imunoterapije pri metastatskem raku debelega črevesa in danke
09.30-10.00 *Velenik V.:* Kompletno preoperativno zdravljenje raka danke
10.00-10.20 **RAZPRAVA**
10.20-10.50 **SATELITNO PREDAVANJE 2**
10.50-11.00 **ODMOR**
11.00-11.30 *Mesti T.:* Novosti v sistemskem zdravljenju HCC
11.30-12.00 *Ocvirk J.:* Novosti v zdravljenju G1, G2 napredovalih tumorjev po progresu
12.00-12.15 **RAZPRAVA**
12.15-12.45 **SATELITNO PREDAVANJE 3**
12.45-13.45 **ODMOR ZA KOSILO**
13.45-14.15 **SATELITNO PREDAVANJE 4**

Moderator: doc. dr. Blaž Trotovšek, dr.med., mag. Zvezdana Hlebanja, dr.med.

14.15-15.30 **Karcinom trebušne slinavke - multidisciplinarni pristop pri bolnikih z omejeno boleznijo**
Boc N.: Pomen slikovne diagnostike
Trotovšek B.: Pomen kirurgije
Oblak I.: Pomen radioterapije
Hlebanja Z.: Pomen sistemske terapije
15.30-15.45 **SATELITNO PREDAVANJE 5**

Moderator: prof. dr. Mirko Omejc, dr.med., dr. Neva Volk, dr.med.

15.45-17.00 **Karcinom želodca - multidisciplinarni pristop pri bolnikih z omejeno boleznijo**
Omejc M.: Pomen kirurgije
Jeromen-Peressutti A.: Pomen radioterapije
Marko B.: Pomen sistemske terapije
Volk N.: Zdravljenje metastatskega karcinoma želodca
RAZPRAVA
17.00-17.15 **ODMOR**
17.15-17.45 **SATELITNO PREDAVANJE 6**

Moderator: dr. Erik Brecelj, dr.med., Marko Boc, dr.med.

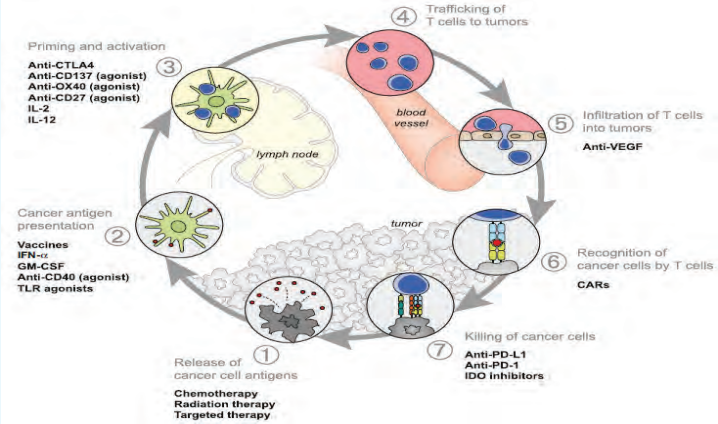
17.45-18.05 *Milanez T.:* Možnosti zdravljenja pri bolnikih s tumorji prebavil in oslabljeno ledvično funkcijo
18.05-18.40 *Brecelj E.:* Karcinoza peritoneja - vloga kirurgije in HIPEC
18.40-19.10 **RAZPRAVA IN ZAKLJUČKI SREČANJA**

PERSONALIZACIJA SISTEMSKEGA ZDRAVLJENJA METASTATSKEGA RAKA DEBELEGA ČREVESA IN DANKE

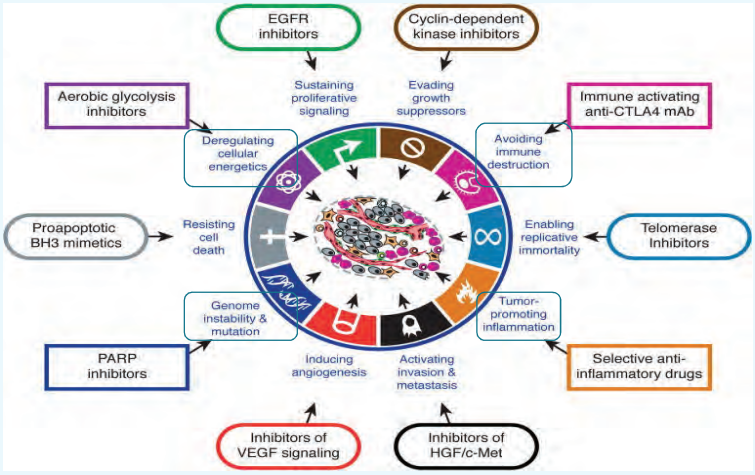
8.ŠOLA TUMORJEV PREBAVIL

Asist.dr. Martina Reberšek, dr.med.
7.december 2018

Protitumorski imunski ciklus



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



Hanahan, et al.Hallmarks of Cancer:The next generation. Cell, 2011

Kaj že vemo:

- *RAS* mutant tumors are long known to be resistant to anti-EGFR therapies. MSI tumors are uniquely sensitive to immune checkpoint inhibitors. This knowledge has set standard indications for cetuximab/panitumumab and pembrolizumab/nivolumab, respectively.
- Molecular heterogeneity of colorectal cancer is substantial. Advances in tumor profiling through both individual alterations and gene signatures is paving the path to emerging matched therapies.
- *BRAFV600E* mutations and *HER2* amplifications show promise in phase 2 clinical trials as predictive biomarkers of efficacy to combination targeted therapies. Rare kinase fusions also confer sensitivity to targeted inhibitors.
- MSI Immune or "MSI-like" and Mesenchymal or "TGFβ active" subtypes or signatures stand out as candidates for new gene expression biomarkers for selection of immune checkpoint inhibitors and targeted combinations, respectively.
- Molecular heterogeneity is also a dynamic process. ctDNA is able to detect emerging genomic alterations in a significant proportion of patients progressing on cetuximab or panitumumab, which are guiding new drug development strategies.

Single gene – tumor cell signals

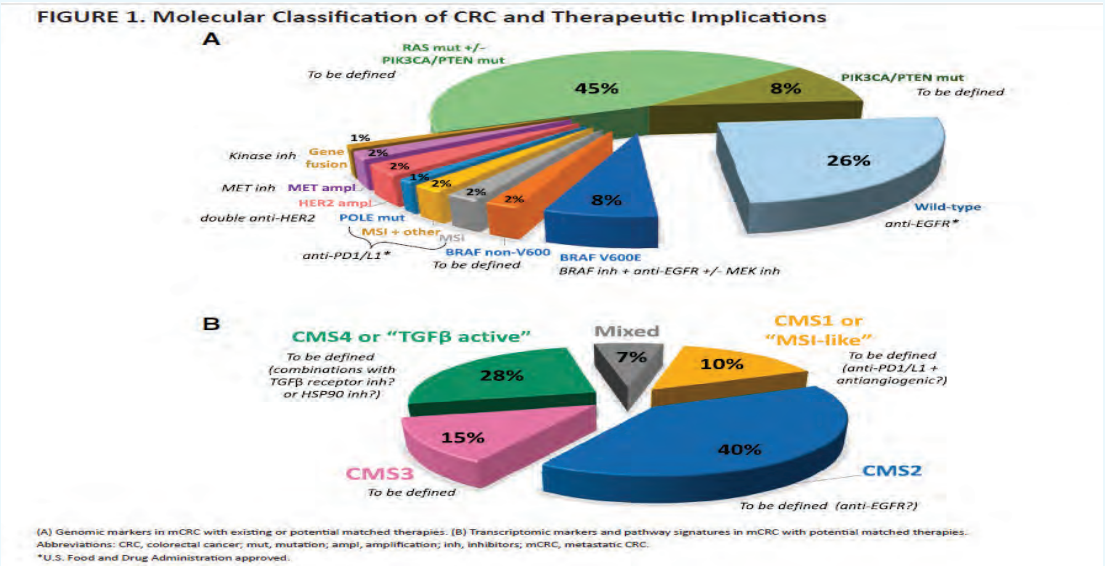
RAS wt (ctDNA)	Rechallenge with anti-EGFR
	Novel anti-EGFR
BRAF ^{V600E} mut	BRAF inh + anti-EGFR +/- MEK inh
HER2 ampl	Double HER2 targeted agents, HER2 ADCs
Oncogenic fusions	Kinase inh

Signatures – microenvironment signals

MSI	anti-PD1/L1
MSI-like	Immuno-targeted combinations?
TGFβ active	Immuno-targeted combinations?
CMS groups	Drug repurposing?

Right versus left

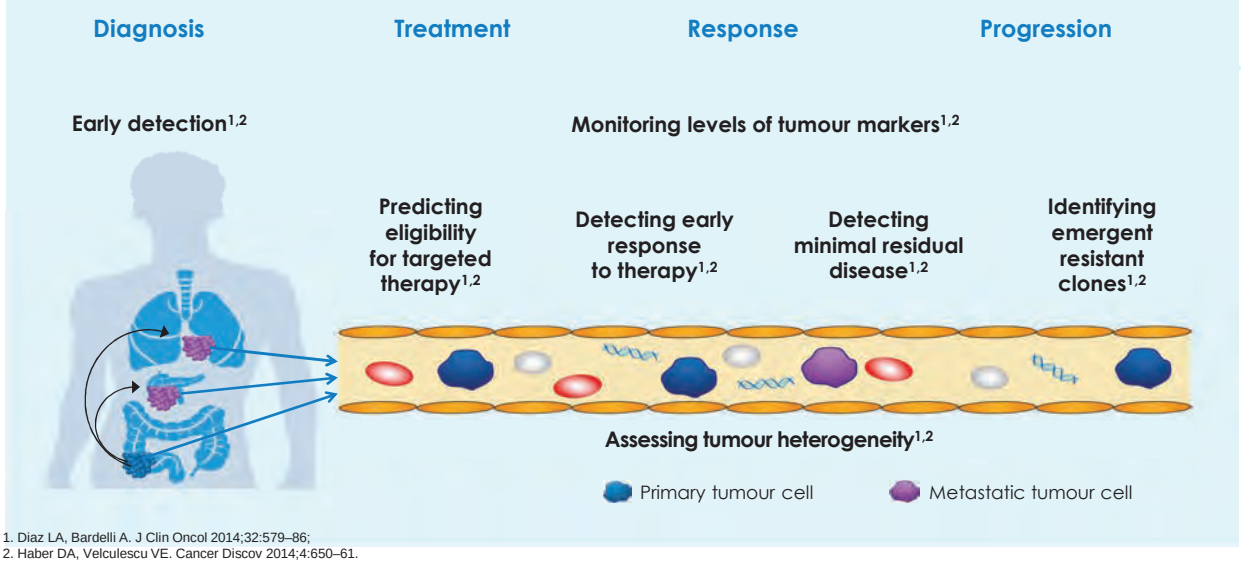
FIGURE 1. Molecular Classification of CRC and Therapeutic Implications



(A) Genomic markers in mCRC with existing or potential matched therapies. (B) Transcriptomic markers and pathway signatures in mCRC with potential matched therapies.
Abbreviations: CRC, colorectal cancer; mut, mutation; ampl, amplification; inh, inhibitors; mCRC, metastatic CRC.
*U.S. Food and Drug Administration approved.

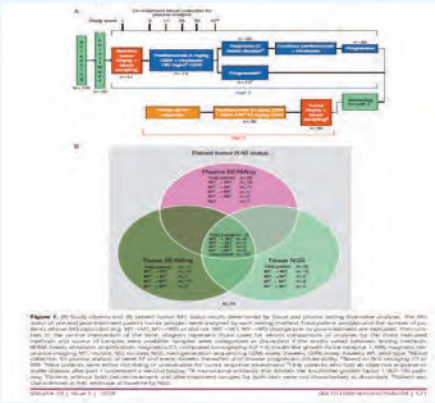
Rodrigo Dienstmann Molecular Subtypes and the Evolution of Treatment Decisions in Metastatic ColorectalCancer. ASCO EDUCATIONAL BOOK, 2018

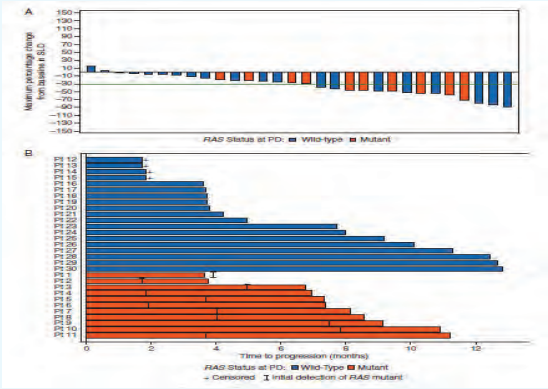
Pomen tekoče biopsije krvi 2018



1. Diaz LA, Bardelli A. J Clin Oncol 2014;32:579–86;
2. Haber DA, Velculescu VE. Cancer Discov 2014;4:650–61.

Reindukcija- CHRONOS študija

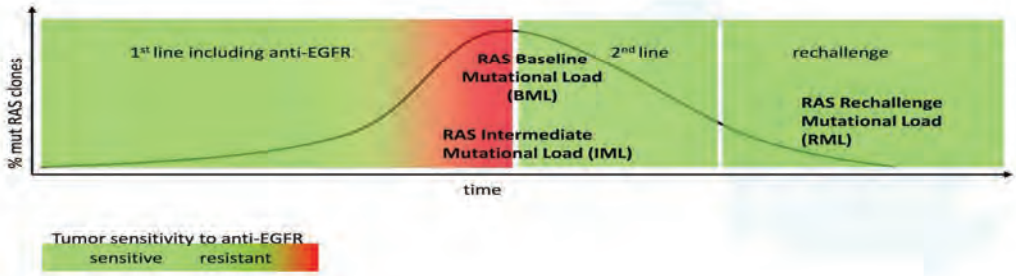




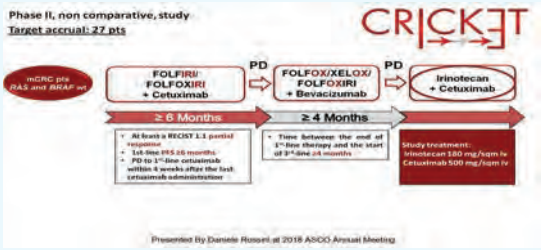
Siena S, et al. Dynamic molecular analysis and clinical correlates of tumor evolution within a phase II trial of panitumumab-based therapy in metastatic colorectal cancer. Annals of Oncology 29: 119–126, 2018.

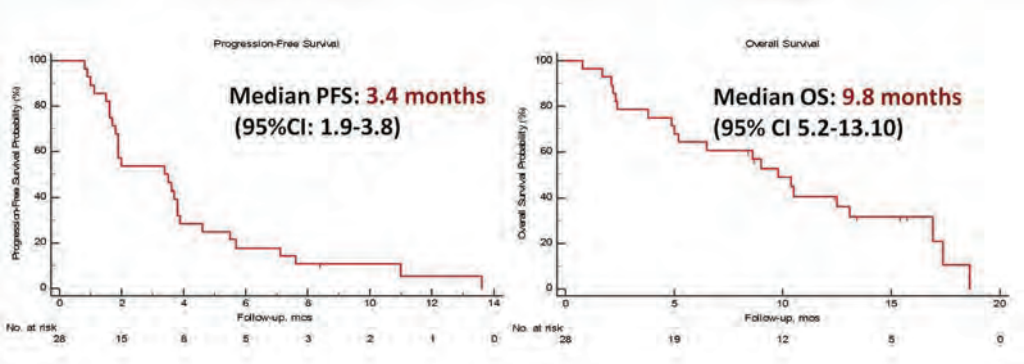
RAS in ctDNA for anti-EGFR rechallenge

CHRONOS trial A PHASE II TRIAL OF RECHALLENGE WITH PANITUMUMAB DRIVEN BY RAS CLONAL-MEDIATED DYNAMIC OF RESISTANCE

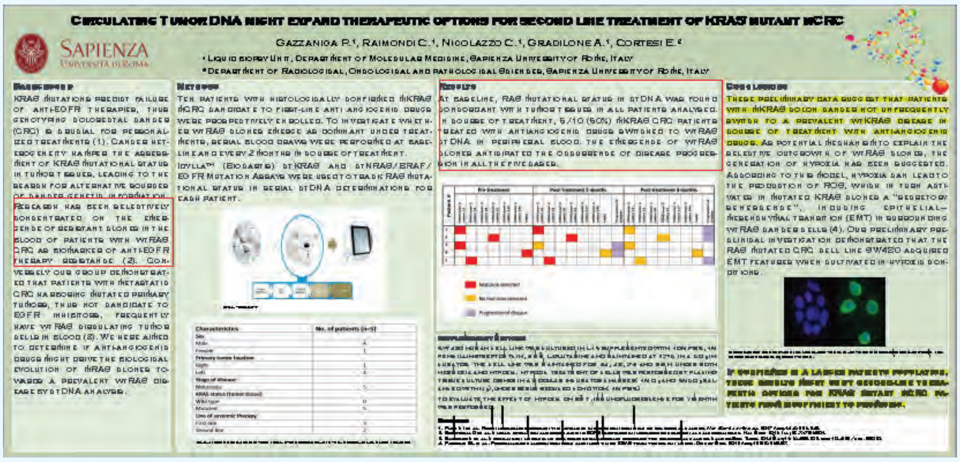


Reindukcija- CRICKET študija



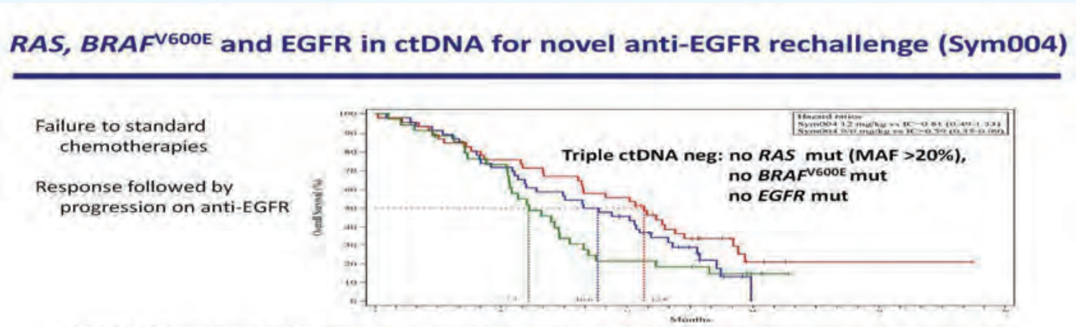


ESMO 2017



Efficacy of Sym004 in Patients With Metastatic Colorectal Cancer With Acquired Resistance to Anti-EGFR Therapy and Molecularly Selected by Circulating Tumor DNA Analyses A Phase 2 Randomized Clinical Trial

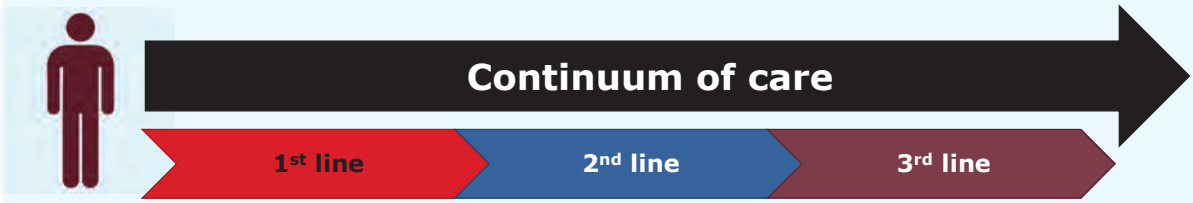
Montagut C, et al. JAMA Oncol 2018



EU & US DN population (N=170)	Sym004 12 mg/kg (N=62)	Sym004 9/6 mg/kg (N=57)	Investigator Choice (N=51)
mOS, months (95% CI)	10.6 m (6.8, 13.1)	12.8 m (9.7, 14.7)	7.3 m (6.3, 8.8)
1-Year Survival Rate, %	46 (31, 59)	56 (40, 69)	21 (9, 36)

Montagut C et al, JAMA Oncol 2018

Future outlook: A more personalized approach to treatment, guided by liquid biopsy in 2018



Establish RAS status at diagnosis by tissue biopsy[1–3]

Re-evaluate RAS status with liquid biopsy* to guide treatment choice[4,5]

Re-evaluate RAS status with liquid biopsy* to guide treatment choice[4,5]

*Using a CE marked test.
1. Van Cutsem E, et al. Ann Oncol 2016;27:1386–1422; 2. NCCN clinical practice guidelines: Colon Cancer, Version 1. 2018; 3. Yoshino T, et al. Ann Oncol 2018;29:44–70; 4. Gazzaniga P, et al. ESMO 2017 (abstract 1672); 5. Gazzaniga P, et al. JCO Precision Oncol 2018; doi: 10.1200/PO.17.00277.

BRAF mutacije

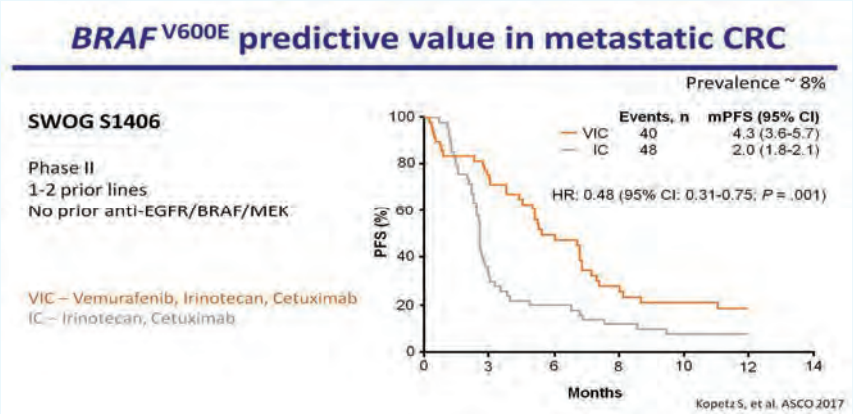
BRAF V600E predictive value in metastatic CRC

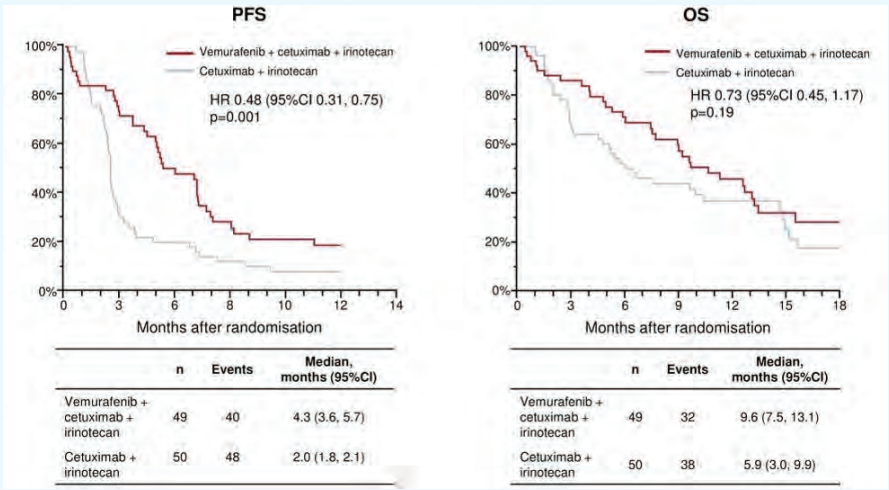
Prevalence ~ 8%

Regimen	N	PR/CR (%)	SD (%)	mPFS (m)
Vemurafenib[1]	21	5	33	2.1
Vemurafenib + Cetuximab[2]	27	4	69	3.7
Dabrafenib + Trametinib[3]	43	12	56	3.5
Dabrafenib + Panitumumab[4]	20	10	80	3.5
Dabrafenib + Trametinib + Panitumumab[4]	91	21	65	4.2
Encorafenib + Cetuximab[5]	42	23	54	3.7
Encorafenib + Alpelisib + Cetuximab[5]	49	32	61	4.3

[1]Kopetz S et al. JCO 2015; [2]Hyman D et al. NEJM 2015; [3]Corcoran R et al JCO 2015; [4]Corcoran R et al. Cancer Discov 2018; [5]Elez et al. ESMO GI 2015

*mt*BRAF V600E



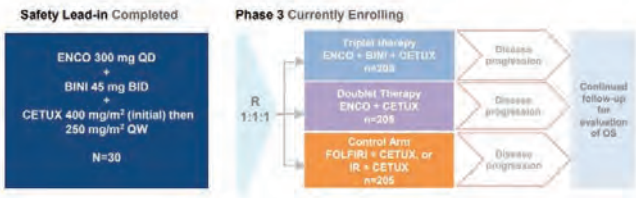


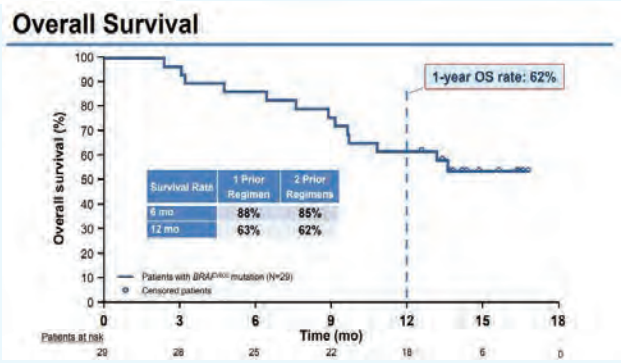
	n	Events	Median, months (95%CI)
Vemurafenib + cetuximab + irinotecan	49	40	4.3 (3.6, 5.7)
Cetuximab + irinotecan	50	48	2.0 (1.8, 2.1)

	n	Events	Median, months (95%CI)
Vemurafenib + cetuximab + irinotecan	49	32	9.6 (7.5, 13.1)
Cetuximab + irinotecan	50	38	5.9 (3.0, 9.9)

SWOG S1406. Kopetz S et al. ASCO 2017.

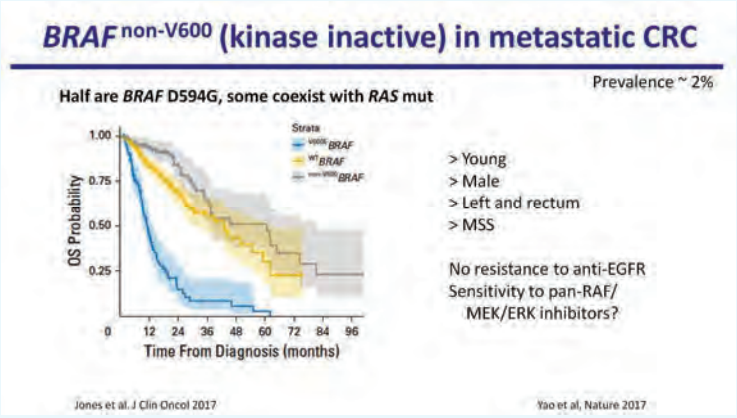
BEACON CRC Phase 3 Study Design[1]





Van Cutsem E et al. ESMO GI 2018.

*mt*BRAF "ne"V600



HER-2 inhibitorji

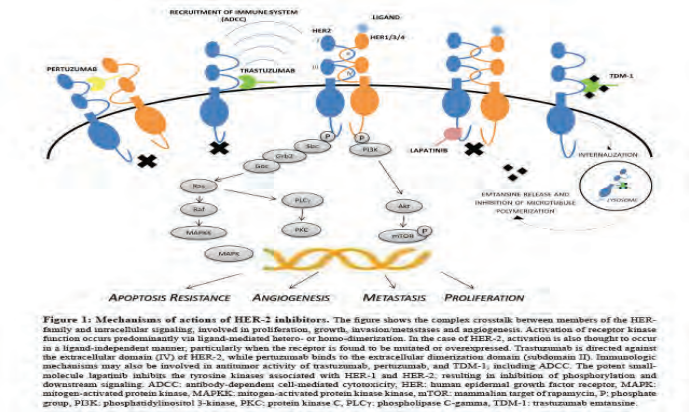


Figure 1: Mechanisms of actions of HER-2 inhibitors. The figure shows the complex crosstalk between members of the HER-family and intracellular signaling, involved in proliferation, growth, invasion/metastases and angiogenesis. Activation of receptor kinase function occurs predominantly via ligand-mediated hetero- or homo-dimerization. In the case of HER-2, activation is also thought to occur in a ligand-independent manner, particularly when the receptor is found to be mutated or overexpressed. Trastuzumab is directed against the extracellular domain (IV) of HER-2, while pertuzumab binds to the extracellular dimerization domain (subdomain II). Immunologic mechanisms may also be involved in antitumor activity of trastuzumab, pertuzumab, and TDM-1, including ADCC. The potent small-molecule lapatinib inhibits the tyrosine kinases associated with HER-1 and HER-2, resulting in inhibition of phosphorylation and downstream signaling. ADCC: antibody-dependent cell-mediated cytotoxicity, HER: human epidermal growth factor receptor, MAPK: mitogen-activated protein kinase, MAPKK: mitogen-activated protein kinase kinase, mTOR: mammalian target of rapamycin, P: phosphate group, PI3K: phosphatidylinositol 3-kinase, PKC: protein kinase C, PLCγ: phospholipase C-gamma, TDM-1: trastuzumab emtansine.

Fanotto V, et al. HER-2 inhibition in gastric and colorectal cancers: tangible achievements, novel acquisitions and future perspectives. Oncotarget, Vol. 7, No. 42, 2016.

HER2 ampl predictive value in metastatic CRC

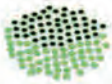
Prevalence ~ 2%

Enrichment clinical/molecular factors

RAS/BRAF wt
Resistance to anti-EGFR therapy
Left colon

2% Prevalence 5-8%

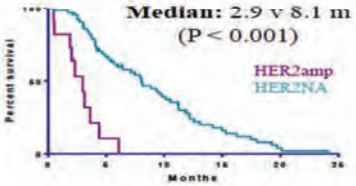
IHC 3+
IHC 2+ and ISH amplification in ≥ **50%** tumor cells



Valtorta et al, Modern Pathology 2017

PFS anti-EGFR 2nd/3rd line setting

MDACC: 14/114 (12%) – IHC/ISH



Raghav et al, ASCO 2016

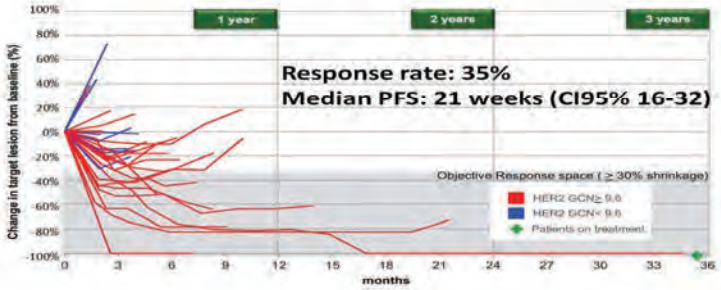
HER2 ampl predictive value in metastatic CRC

Prevalence ~ 2%

HERACLES trial

Phase II
Progression on anti-EGFR
HER2 3+ by IHC or
HER2 2+ by IHC and ISH+

Trastuzumab + Lapatinib



Siena S et al, AACR 2017; Sartore-Bianchi A Lancet Oncol 2017

HERACLES študija

	Patients given trastuzumab and lapatinib (n=27)
Age (years)	62 (50–68)
Sex	
Men	23 (85%)
Women	4 (15%)
ECOG performance status 0–1	27 (100%)
HER2 expression by immunohistochemistry score	
3+	20 (74%)
2+	7 (26%)
Site of primary tumour	
Rectum	7 (26%)
Colon	20 (74%)
Proximal*	4 (20%)
Distal†	16 (80%)
Metastatic disease in multiple sites	26 (96%)
Number of previous lines of therapy	5 (4–6)
Patients with >4 previous lines of therapy	20 (74%)
Previous anti-angiogenesis treatment	20 (74%)
Previous therapy with panitumumab or cetuximab	27 (100%)
Patients eligible to be assessed for sensitivity to panitumumab or cetuximab‡	15 (56%)
Previous response to panitumumab or cetuximab	0
Time on previous treatment (total; months)§	20 (16–24)
By primary site	
Proximal	15 (13–19)
Distal	19 (15–24)
Rectum	23 (20–25)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *Located in caecum, ascending colon, liver flexure, and transverse colon. †Located in splenic flexure, descending colon, and sigmoid colon. ‡Definition of eligibility reported in the appendix (p 16). §Information available for 135 of 136 total previous regimens (treatment holiday excluded).

Table 1: Baseline characteristics

	Patients given trastuzumab and lapatinib (n=27)
Complete response	1 (4%, –3 to 11)
Partial response	7 (26%, 9 to 43)
Stable disease ≥16 weeks*	8 (30%, 13 to 47)
Stable disease <16 weeks	4 (15%, 1 to 27)
Objective response	8 (30%, 14 to 50)
Disease control†	16 (59%, 39 to 78)
Duration of response (weeks)	38 (24 to 94+)
Time to response (weeks)	8 (3 to 16)

Data are n (%, 95% CI) or median (range). Response data are best response according to RECIST 1.1. RECIST=Response Criteria Evaluation in Solid Tumors. *Including one unconfirmed partial response according to RECIST 1.1. †Defined as complete plus partial responses plus stable disease >16 weeks.

Table 2: Responses to treatment

	Grades 1–2	Grade 3
Gastrointestinal		
Diarrhoea	21 (78%)	0
Abdominal pain	4 (15%)	0
Nausea	3 (11%)	0
Vomiting	3 (11%)	0
Dermatological		
Rash	12 (44%)	1 (4%)
Dry skin	8 (30%)	0
Dermatitis	3 (11%)	0
Nail disorder	3 (11%)	0
Pruritus	3 (11%)	0
Erythema	2 (7%)	0
Folliculitis	2 (7%)	0
Metabolic and nutritional disorders		
Fatigue	9 (33%)	4 (15%)
Anorexia	2 (7%)	0
Paronychia	9 (33%)	0
Conjunctivitis	5 (19%)	0
Hand-foot syndrome	2 (7%)	0
Blood bilirubin increase	0	1 (4%)

Data are n (%). Treatment-related adverse events are reported if they occurred in at least 5% of patients or were of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or worse. All 27 patients were included in the analysis. No grade 4 or 5 adverse events occurred.

Table 3: Adverse events

Andrea Sartore-Bianchi,A.et al. ‚Dual-targeted therapy with trastuzumab and lapatinib intreatment-refractory, KRAS codon 12/13 wild-type,HER2-positive metastatic colorectal cancer (HERACLES):a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016; 17: 738–46

HER2 ampl predictive value in metastatic CRC

Prevalence ~ 2%

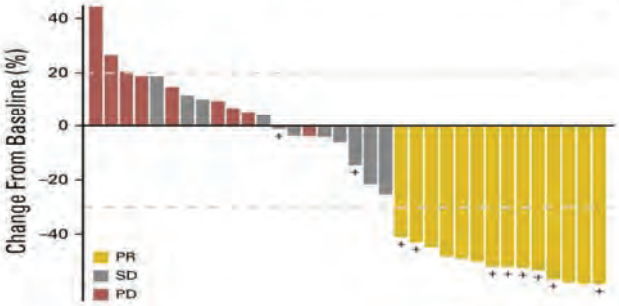
MyPathway trial

Phase II basket trial

HER2 3+ by IHC or
HER2 2+ by IHC and ISH+

Trastuzumab + Pertuzumab

CRC ORR 38% (14/37)



Hainsworth JD et al, J Clin Oncol 2018

Hainsworth JD, et al. **Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. JCO, 2018**

Table 2. Tumor Types and Molecular Alterations

Primary Site	HER2	BRAF	Hedgehog Pathway	EGFR	Total
Lung, non-small-cell	30	21	3	0	54
Colorectal	40	2	0	0	42
Biliary	11*	3	0	1	15
Ovary	8	4	2	0	14
Bladder	13	0	0	0	13
Pancreas	9	4	0	0	13
Uterus	7	0	0	0	7
Breast	2†	0	2	2	6
Salivary gland	5	0	1	0	6
Small intestine	4	0	1	1	6
Prostate	1	3	1	0	5
Unknown primary	1	3	1	0	5
Other (21 tumor types)	20	9	10	5	44
Total	151 (66%)	49 (21%)	21 (9%)	9 (4%)	230

NOTE. N = 230.
Abbreviations: BRAF, murine sarcoma viral (v-raf) oncogene homolog B1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2.
*One patient had a tumor with an RBMS-NRG1 fusion.
†Both had *HER2* mutations without amplification or overexpression.

Table 3. Efficacy of Treatment With Trastuzumab Plus Pertuzumab in Patients With HER2 Amplification/Overexpression

Primary Site	No. of Patients	Response, No. (%)			ORR, % (95% CI)
		CR	PR	SD > 120 Days	
Colorectal	37	0	14 (38)	4 (11)	38 (23 to 55)
Lung, non–small-cell	16	0	2 (13)	2 (13)	13 (2 to 38)
Bladder	9	1 (11)	2 (22)	2 (22)	33 (8 to 70)
Pancreas	9	0	2 (22)	1 (11)	22 (3 to 60)
Biliary	7	0	2 (29)	3 (38)	29 (4 to 71)
Ovary	8	0	1 (13)	0	13 (0 to 53)
Uterus	7	0	0	0	0
Salivary gland	5	0	4 (80)	0	80 (28 to > 99)
Other (11 sites)*	16	1 (6)	1 (6)	3 (19)	13 (2 to 38)
Total	114	2 (2)	28 (25)	16 (14)	26 (19 to 35)

NOTE. N = 114. Includes 12 patients with amplification/overexpression plus mutation.
Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.
*Responses occurred in patients with adenocarcinomas of the prostate (one) and skin (apocrine; one).

HER2 ampl predictive value in metastatic CRC

Prevalence ~ 2%

Ongoing trials

T-DM1	(HERACLES RESCUE)	Phase II
Pertuzumab + T-DM1	(HERACLES B)	Phase II
Tucatinib (HER2 TKI) + trastuzumab	(MONTAINEER)	Phase II
Trastuzumab + Pertuzumab + Capecitabine	(MODUL - maintenance)	Phase II

Gene fusions predictive value in metastatic CRC

Prevalence ~ 1%

Alteration	Prevalence	Targetability evidence	Enrichment
NTRK1 fusion	< 1%	Case reports	(> if right colon, RAS/*BRAF* wt, **MSI**)[1]
ALK fusion	< 1%	Case reports	(> if right colon, RAS/*BRAF* wt, **MSI** colitis-associated)[2]
ROS1 fusion	< 1%	No	(> if right colon, RAS/*BRAF* wt)[3]
RET fusion	< 1%	No	(> if right colon, RAS/*BRAF* wt)[3]

[1]Russo et al, Cancer Discov 2016; [2]Yaeger et al, Gastroenterology [3]Kloosterman et al, Cancer Res

Efficacy of Larotrectinib in *TRK* Fusion– Positive Cancers in Adults and Children

Drilon A, et al. N Engl J Med 2018;378:731-9.

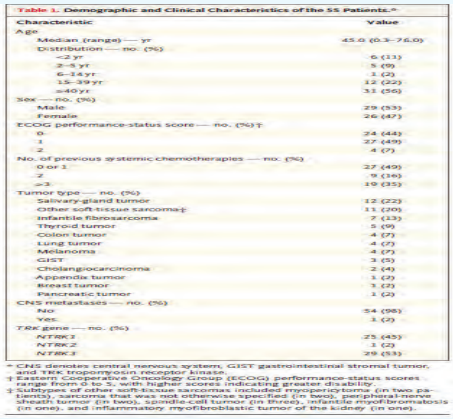


Table 1. Demographic and Clinical Characteristics of the 55 Patients.*

Characteristic	Value
Age	
Median (range) — yr	45.0 (0.3–76.0)
Distribution — no. (%)	
<2 yr	6 (11)
2–5 yr	5 (9)
6–14 yr	1 (2)
15–39 yr	12 (22)
≥40 yr	31 (56)
Sex — no. (%)	
Male	29 (53)
Female	26 (47)
ECOG performance-status score — no. (%)†	
0	24 (44)
1	27 (49)
2	4 (7)
No. of previous systemic chemotherapies — no. (%)	
0 or 1	27 (49)
2	9 (16)
≥3	19 (35)
Tumor type — no. (%)	
Salivary-gland tumor	12 (22)
Other soft-tissue sarcoma‡	11 (20)
Infantile fibrosarcoma	7 (13)
Thyroid tumor	5 (9)
Colon tumor	4 (7)
Lung tumor	4 (7)
Melanoma	4 (7)
GIST	3 (5)
Cholangiocarcinoma	2 (4)
Appendix tumor	1 (2)
Breast tumor	1 (2)
Pancreatic tumor	1 (2)
CNS metastases — no. (%)	
No	54 (98)
Yes	1 (2)
TRK gene — no. (%)	
NTRK1	25 (45)
NTRK2	1 (2)
NTRK3	29 (53)

* CNS denotes central nervous system, GIST gastrointestinal stromal tumor, and TRK tropomyosin receptor kinase.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
‡ Subtypes of other soft-tissue sarcomas included myopericytoma (in two patients), sarcoma that was not otherwise specified (in two), peripheral-nerve sheath tumor (in two), spindle-cell tumor (in three), infantile myofibromatosis (in one), and inflammatory myofibroblastic tumor of the kidney (in one).

Table 2. Overall Response Rate, According to Investigator and Central Assessment.*

Response	Investigator Assessment (N=55)	Central Assessment (N=55)
	percent	
Overall response rate (95% CI)†	80 (67–90)	75 (61–85)
Best response		
Partial response	64‡	62
Complete response	16	13
Stable disease	9	13
Progressive disease	11	9
Could not be evaluated	0	4

* Percentages may not total 100 because of rounding.
† The best overall response was derived from the responses as assessed at specified time points according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
‡ Data include one patient who had a partial response that was pending confirmation at the time of the database lock. The response was subsequently confirmed, and the patient's treatment and response are ongoing.

Efficacy of Larotrectinib in *TRK* Fusion– Positive Cancers in Adults and Children

Drilon A, et al. N Engl J Med 2018;378:731-9.

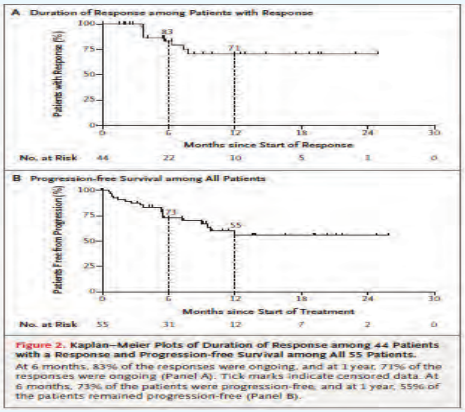


Figure 2. Kaplan–Meier Plots of Duration of Response among 44 Patients with a Response and Progression-free Survival among All 55 Patients.
At 6 months, 83% of the responses were ongoing, and at 1 year, 73% of the responses were ongoing (Panel A). Tick marks indicate censored data. At 6 months, 73% of the patients were progression-free, and at 1 year, 55% of the patients remained progression-free (Panel B).

Table 3. Adverse Events.*

Adverse Event	Adverse Events, Regardless of Attribution					Treatment-Related Adverse Events		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	percent of patients with event							
Increased ALT or AST level	31	4	7	0	42	5	0	10
Fatigue	20	15	2	0	36	0	0	16
Vomiting	24	9	0	0	33	0	0	11
Dizziness	25	4	2	0	31	2	0	25
Nausea	22	7	2	0	31	2	0	16
Anemia	9	9	11	0	29	2	0	9
Diarrhea	15	12	2	0	29	0	0	5
Constipation	24	4	0	0	27	0	0	16
Cough	22	4	0	0	25	0	0	2
Increased body weight	11	5	7	0	24	0	0	11
Dyspnea	9	9	0	0	18	0	0	2
Headache	13	4	0	0	16	0	0	2
Pyrexia	11	2	2	2	16	0	0	0
Arthralgia	13	0	0	0	13	0	0	2
Back pain	5	9	0	0	13	0	0	0
Decreased neutrophil count	0	7	7	0	15	2	0	9

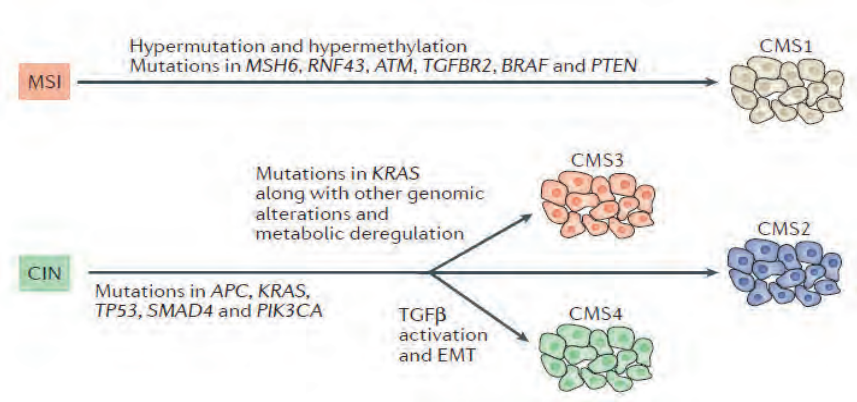
* The adverse events listed here are those that occurred in at least 15% of the patients, regardless of attribution. The relatedness of the treatment to adverse events was determined by the investigators. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

Novel genomic markers in metastatic CRC

Alteration	Prevalence	Targetability evidence	Phase 1
ATM mut (other DDR genes)	< 3%	Preclinical[1]	Veliparib (PARP inh) + irinotecan
MET ampl	< 2%	Preclinical[2,3]	PF-02341066 (MET inh) + binimetinib Sym015

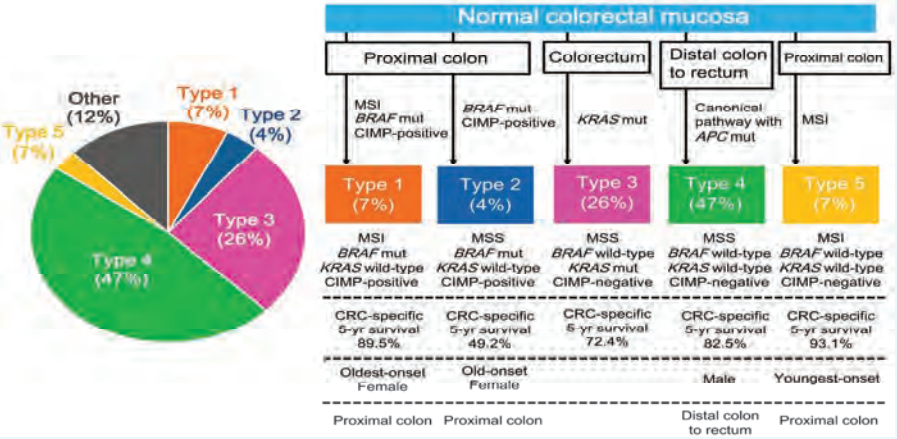
[1]Wang et al, Transl Oncol 2017; [2]Pupo et al Cancer Res 2016, [3]Poulsen et al, Clin Cancer Res 2017

Genetska podtipa CRC



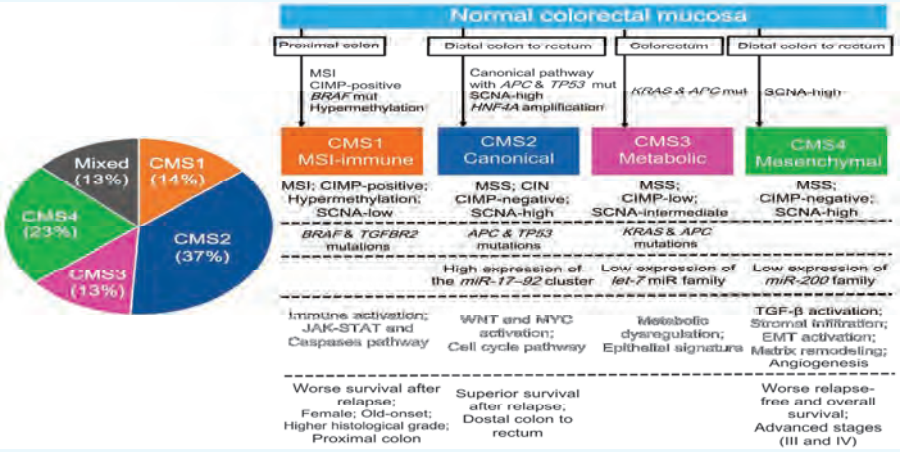
Rodrigo Dienstmann Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. NATURE REVIEWS | CANCER VOLUME 17, FEBRUARY 2017, 79.

Podtipi mCRC glede na mutacije, MSI, CIMP



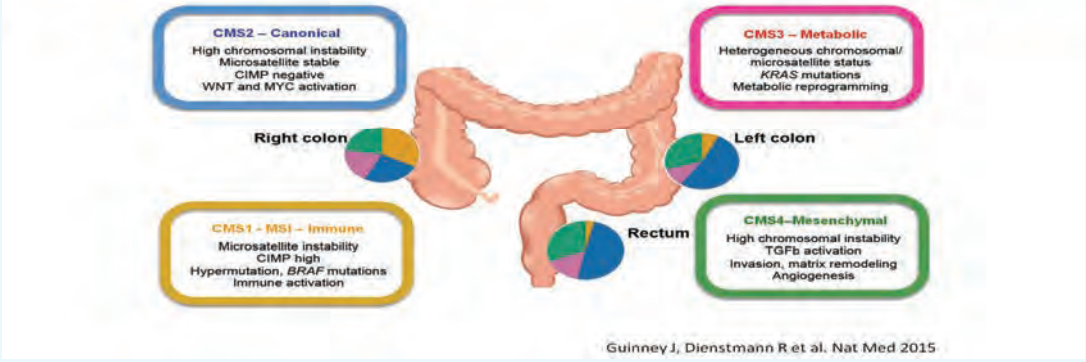
Inamura K. Colorectal Cancers: An Update on Their Molecular Pathology. Cancers 2018

Podtipi CMS



Inamura K. Colorectal Cancers: An Update on Their Molecular Pathology. Cancers 2018

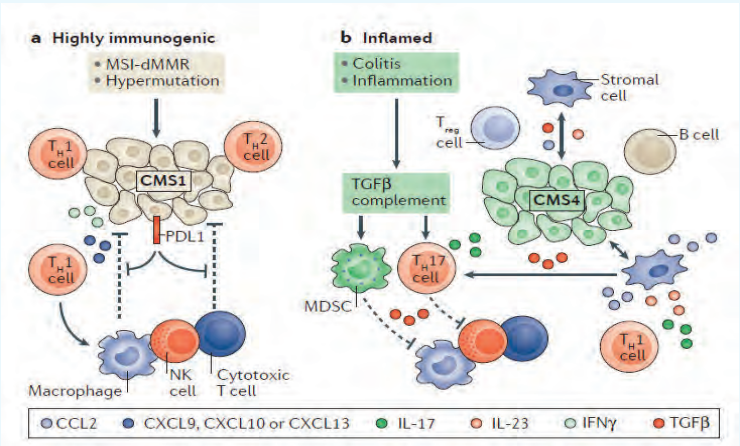
CMS subtypes – clinical and molecular correlates



Guinney J, Dienstmann R et al. Nat Med 2015

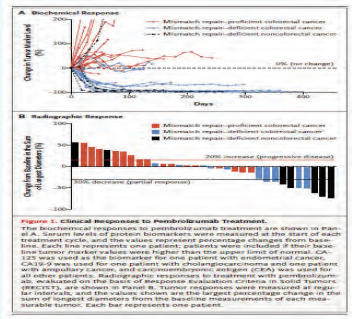
Fenotipi rakov glede na imunsko funkcijo

Immune- ignorant:
- **CMS2**
- **CMS3**



Rodrigo Dienstmann Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. NATURE REVIEWS | CANCER VOLUME 17, FEBRUARY 2017, 79.

POMEN MSI



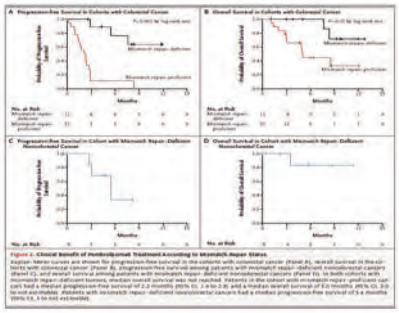


Table 2. Objective Responses According to RECIST Criteria.

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

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

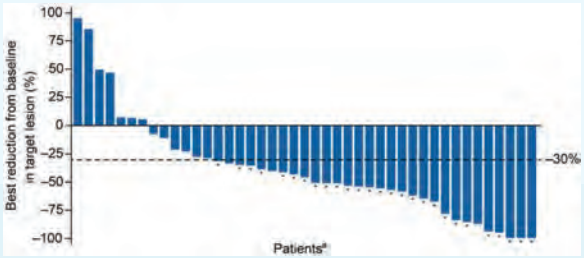
Le DT, et al.PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-20.

CheckMate-142 (phase II): nivolumab + low-dose ipilimumab for 1L MSI-H mCRC

- **Patients with previously untreated MSI-H mCRC (**N=45) were treated with nivolumab + ipilimumab
- **ORR was 60% and DCR was 84%** (INV-assessed)
  - Overall, 7% of patients achieved a CR and 53% of patients achieved a PR
  - Median DoR was NR
  - Responses were observed regardless of tumour PD-L1 expression, BRAF or KRAS mutation status or Lynch Syndrome diagnosis
  - In patients with BRAF MT disease, ORR was 71% and DCR was 88%
- **Median PFS and median OS were NR**
  - **At 12 months, PFS rate was 77% and OS rate was 83%**

Nivolumab: 3mg/kg q2w
Ipilimumab: 1mg/kg q6w
q6w, every 6 weeks

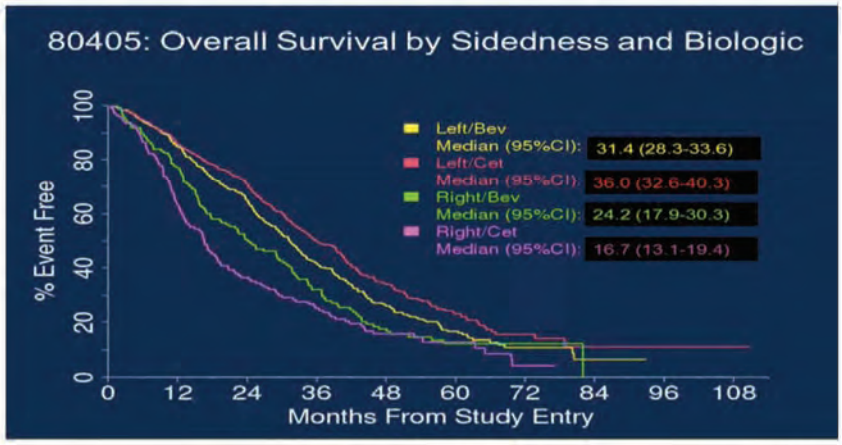
Best reduction in target lesions



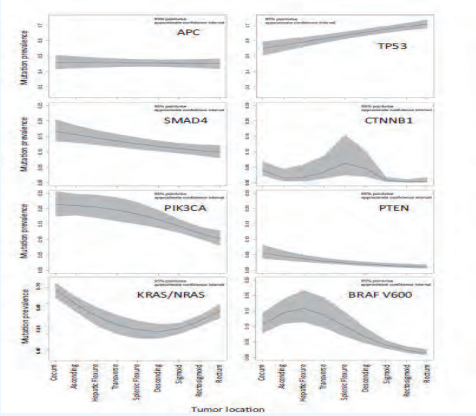
KEYNOTE-177 (phase III trial of pembrolizumab vs CT ± bevacizumab/cetuximab in MSI-H mCRC) is due to read out in early 2019

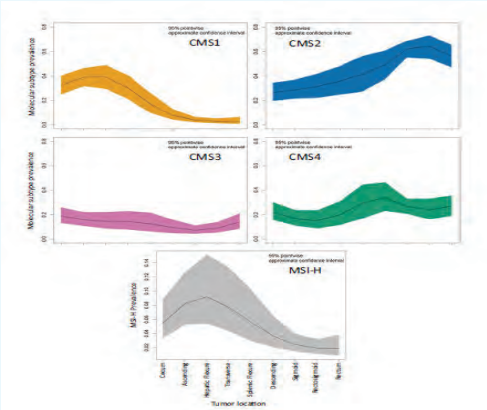
Lenz et al. ESMO 2018. Abstract LBA18_PR

Why right versus left?



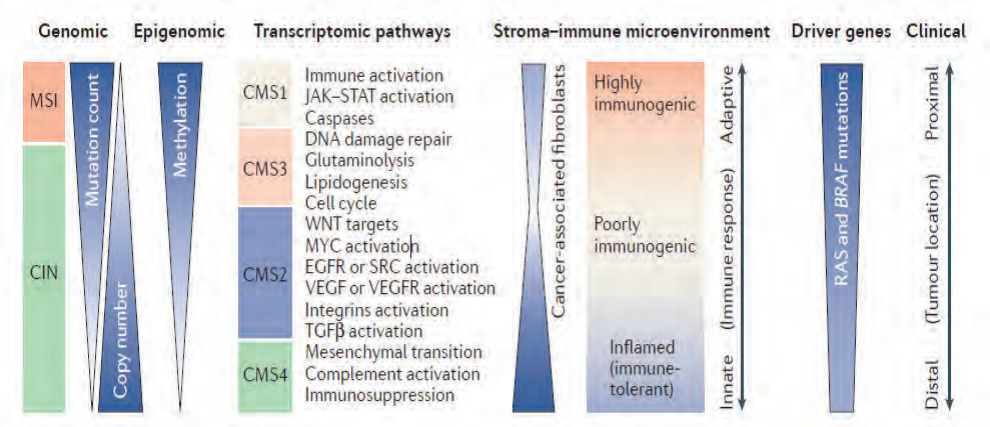
Venook A et al, ASCO 2016



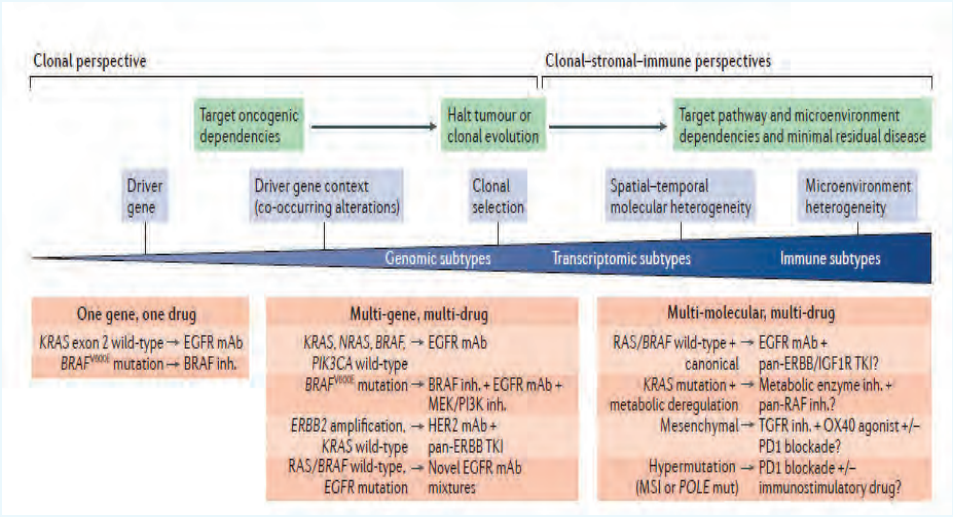


Loree JM et al. Classifying Colorectal Cancer by Tumor Location Rather than Sidedness Highlights a Continuum in Mutation Profiles and Consensus Molecular Subtypes. Clin Cancer Res; 24(5) March 1, 2018.

Podtipi CRC



Dienstmann R, et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. NATURE REVIEWS | CANCER VOLUME 17, FEBRUARY 2017, 79.



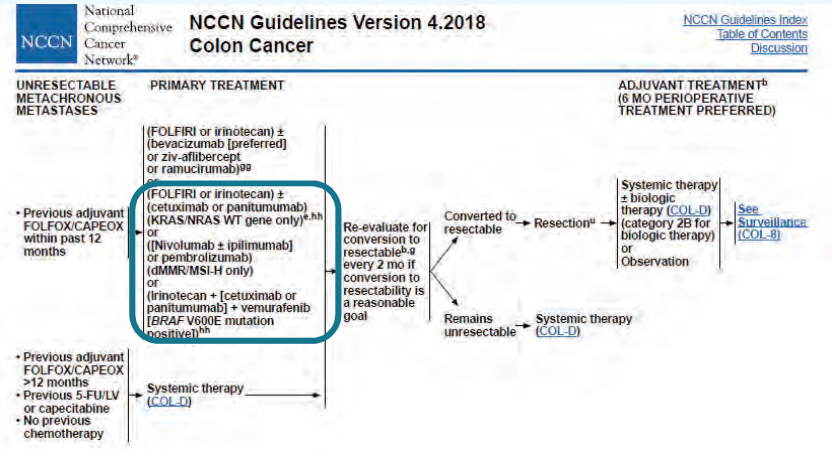
Dienstmann R, et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. NATURE REVIEWS | CANCER VOLUME 17, FEBRUARY 2017, 79.

Umestitev molekularnih testov v klinično prakso

Molecular testing	Objective	Timing	Examples — clinical translation
Next-generation sequencing (mutations, copy number alterations, fusions) and MSI	Target identification for matched therapies	At diagnosis of advanced CRC or progression on standard therapies	*ERBB2* amplification for HER2-targeted therapy, MSI for immune checkpoint inhibitor
ctDNA analysis	Detection of acquired resistance mechanisms and inter-metastatic genomic heterogeneity	At baseline and progression on treatment with targeted therapies	*EGFR* mutations during anti-EGFR therapy for novel EGFR mAb mixtures
	Prediction of radiological tumour progression	During standard therapy	Early change in therapy to alternative rescue regimen[158]
	Detection of minimal residual disease	Post-operative in stage II disease	Personalized adjuvant therapy[159]
Gene-expression classifiers (for example, CMS and supervised predictive signatures)	Subtype identification for matched therapies	Early or advanced-stage CRC (CMS classifier optimized for primary tissue)	Personalized adjuvant therapy for high-risk mesenchymal tumours, target validation in advanced-stage CRC
Immune markers (for example, proteomics in tumour microenvironment, immunophenotype and neoantigen detection)	Identify response and resistance biomarkers	At baseline, on treatment and progression to immunotherapies	Combination of immunotherapies for advanced-stage CRC with MSS

Dienstmann R, et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. NATURE REVIEWS | CANCER VOLUME 17, FEBRUARY 2017, 79.

V klinični praksi- NCCN



Kaj je novega:

- Tekoča bipsija krvi (ctDNA)
- Reindukcija z anti- EGFR inhibitorji glede na ctDNA
- BRAF V600E (zdravljenje v kombinaciji z BRAF inhibitorjem)
- Druge mutacije v BRAF genu
- Kombinirana Imunoterapija pri MSI- H
- TRK inhibitorji
- Anti- HER2 terapija
- Molekularni podtipi- klinična implikacija…..

ZAKLJUČEK: Metastatski kolorektalni karcinom ni en rak, temveč zelo heterogena bolezen,….se nadaljuje……

HVALA ZA POZORNOST

Vloga imunoterapije pri CRC

Janja Ocvirk

Ljubljana, 7.12.2018

Anti-CD27 agonist antibody varlilumab (varli) with nivolumab (nivo) for colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results – Sanborn RE, et al

Study objective

- To assess the efficacy and safety of combination treatment with varlilumab (an anti-CD27 antibody) + nivolumab in patients with CRC or ovarian cancer

Key patient inclusion criteria

- Progressive, recurrent or refractory CRC or ovarian cancer
- No prior anti-PD-L1 therapy
- ≥3 months washout for T-cell direct mAbs
- ≤5 prior regimens for advanced disease

Phase 1	Phase 2
Nivolumab 3 mg/kg q2w + varlilumab escalating doses* q2w Ovarian cancer: n=8 CRC: n=21 (n=29)	Nivolumab 240 mg q2w + varlilumab† Ovarian cancer: n=58 CRC: n=21 (n=79)

PRIMARY ENDPOINT

ORR

SECONDARY ENDPOINTS

PFS, OS, immunogeneity, safety

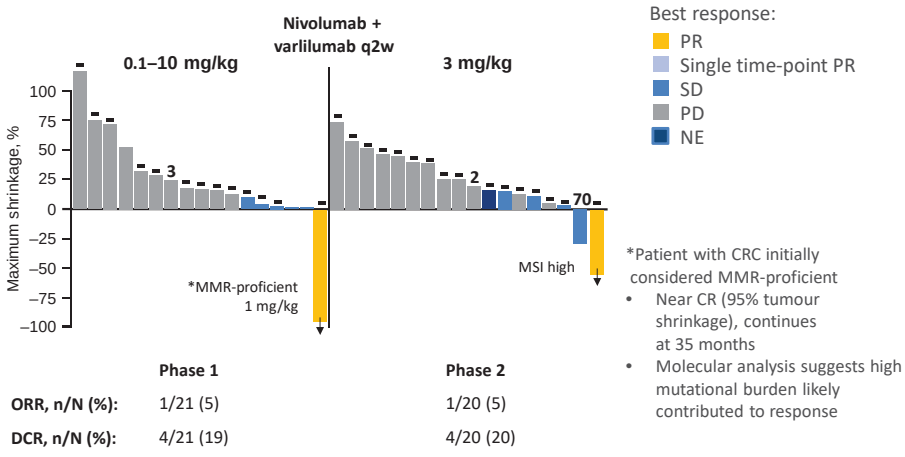
*0.1 mg/kg (n=6), 1 mg/kg (n=15), 10 mg/kg (n=15);
†CRC: 3 mg/kg q2w (n=18), ovarian (n=54): 3 mg/kg q2w (n=18), 3 mg/kg q12w (n=18), 0.3 mg/kg q4w (n=18)

Sanborn RE, et al. J Clin Oncol 2018;36(suppl):abstr 3001

Anti-CD27 agonist antibody varlilumab (varli) with nivolumab (nivo) for colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results – Sanborn RE, et al

Key results

CRC tumour response



*Patient with CRC initially considered MMR-proficient

- Near CR (95% tumour shrinkage), continues at 35 months
- Molecular analysis suggests high mutational burden likely contributed to response

	Phase 1	Phase 2
ORR, n/N (%):	1/21 (5)	1/20 (5)
DCR, n/N (%):	4/21 (19)	4/20 (20)

Sanborn RE, et al. J Clin Oncol 2018;36(suppl):abstr 3001

Anti-CD27 agonist antibody varlilumab (varli) with nivolumab (nivo) for colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results – Sanborn RE, et al

TRAEs in CRC (n=42), n (%)	Grade 3–4	Grade 5
Rash maculo-papular	1 (2)	0
Lymphopenia	5 (12)	0
ALT increased	1 (2)	0
Lipase increased	1 (2)	0
Pneumonitis	0	1 (2)

- No evidence of additional toxicity for combination therapy
- Toxicity profile similar across varlilumab dosing regimens

*Data not shown

Sanborn RE, et al. J Clin Oncol 2018;36(suppl):abstr 3001

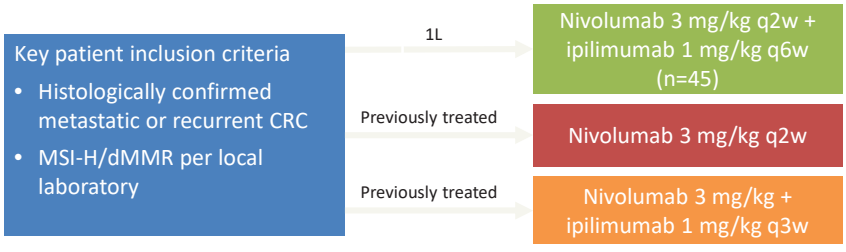
- **Most tumours were PD-L1 negative or low and low TIL***
  - **Therefore, low expectation of response to checkpoint inhibition monotherapy**
- **Varlilumab 3 mg/kg appeared to have better clinical activity vs. other doses***
- **In patients with CRC, durable clinical responses were seen in a patient with MSI-high tumour and one with a high mutational burden**
- **Varlilumab + nivolumab was generally well tolerated at all doses of varlilumab**

Sanborn RE, et al. J Clin Oncol 2018;36(suppl):abstr 3001

: Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

Study objective

- To assess the efficacy and safety of nivolumab + low-dose ipilimumab used as 1L therapy in patients with MSI-H/dMMR mCRC in the CheckMate-142 study



PRIMARY ENDPOINT

- ORR (investigator assessed RECIST v1.1)

SECONDARY ENDPOINTS

- ORR by blinded independent review, DCR*, DoR, PFS, OS and safety

*Patients with a CR, PR or SD for ≥12 weeks divided by the number of treated patients

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

Key result

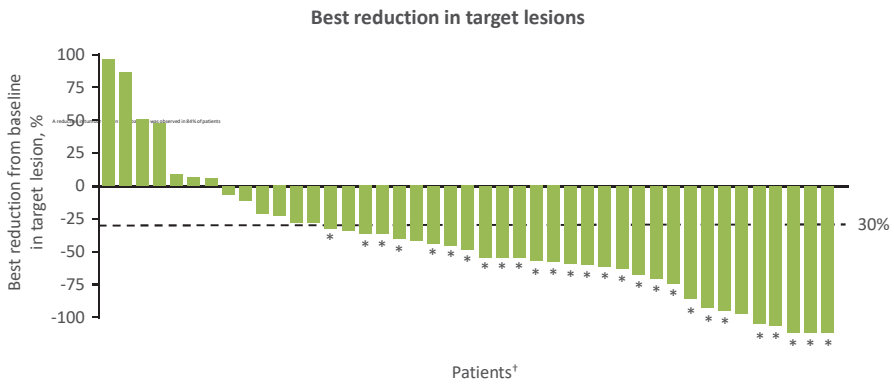
Investigator-assessed	Nivolumab 3 mg/kg q2w + ipilimumab 1 mg/kg q6w (n=45)
ORR*, n (%) [95%CI]	27 (60) [44.3, 74.3]
Best OR, n (%)	
CR	3 (7)
PR	24 (53)
SD	11 (24)
PD	6 (13)
Not determined	1 (2)
DCR, n (%) [95%CI]	38 (84) [70.5, 93.5]
12-month PFS rate, % (95%CI)	77 (62.0, 87.2)
12-month OS rate, % (95%CI)	83 (67.6, 91.7)

- Responses were observed regardless of tumour PD-L1 expression, *BRAF* or *KRAS* mutation status or diagnosis of Lynch syndrome
  - In the 17 patients with a BRAF mutation, ORR was 71% and DCR was 88%

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

Key results (cont.)



*Confirmed response per investigator assessment;
†evaluable patients per investigator assessment

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

Key results (cont.)

	Nivolumab 3 mg/kg q2w + ipilimumab 1 mg/kg q6w (n=45)	
Patients, n (%)	Any grade	Grade 3–4
Any TRAE	35 (78)	7 (16)
Any serious	6 (13)	3 (7)
Any serious TRAE leading to discontinuation	3 (7)	1 (2)
TRAE reported in >10% of patients		
Pruritus	11 (24)	0
Hypothyroidism	8 (18)	1 (2)
Asthenia	7 (16)	1 (2)
Arthralgia	6 (13)	0
Lipase increased	5 (11)	0
Nausea	5 (11)	0
Rash	5 (11)	0

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

Durable clinical benefit with nivolumab (NIVO) plus low-dose ipilimumab (IPI) as first-line therapy in microsatellite instability-high/ mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) – Lenz HJ, et al

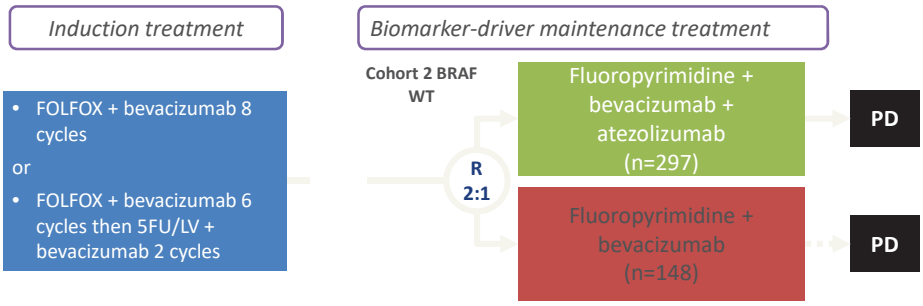
- **In patients with MSI-H/dMMR mCRC, 1L nivolumab + low-dose ipilimumab demonstrated robust and durable clinical benefit and was generally well-tolerated**
- **Nivolumab + low-dose ipilimumab may be a potential new 1L treatment option for this patient population**

Lenz HJ, et al. Ann Oncol 2018;29(suppl 5):abstr LBA18_PR

Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

Study objective

- To assess the efficacy and safety of fluoropyrimidine + bevacizumab + atezolizumab as a 1L maintenance treatment in patients with MSS mCRC in Cohort 2 of the MODUL study (Cohort 1, BRAF mutant; Cohort 3, HER2+; and Cohort 4, HER2-, BRAF WT)



PRIMARY ENDPOINTS

- PFS (RECIST v1.1)

SECONDARY ENDPOINTS

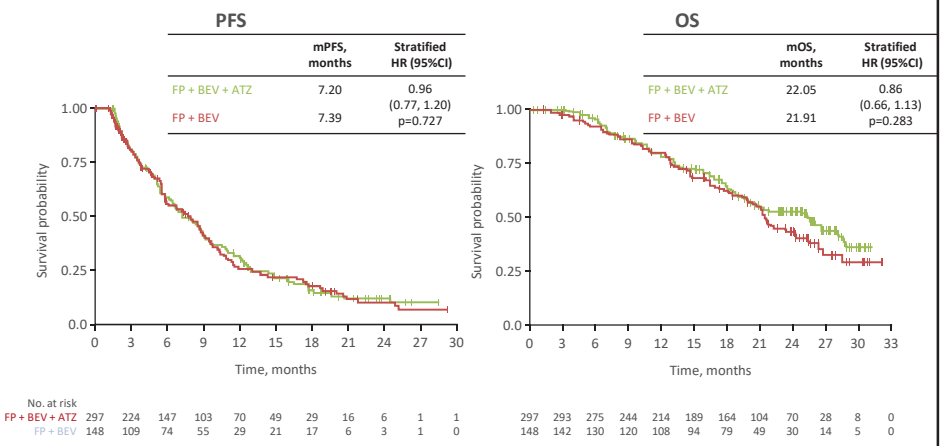
- OS, ORR, DCR, TTR, DoR, change in ECOG and safety

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

LBA19: Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

Key results

PFS and OS (median follow-up 18.7 months)



Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

LBA19: Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

Key results (cont.)

Patients, n (%)	Fluoropyrimidine + bevacizumab + atezolizumab (n=293)	Fluoropyrimidine + bevacizumab (n=143)
TEAE	276 (94.2)	124 (86.7)
Grade ≥3	110 (37.5)	43 (30.1)
Grade 5	3 (1.0)*	1 (0.7)†
Any serious TEAE	28 (9.6)	6 (4.2)
TEAE leading to treatment discontinuation	36 (12.3)	16 (11.2)

*Septic shock, heart attack, recurrent pseudomonas chest infection; †colonic perforation

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

LBA19: Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

- **In patients with BRAF WT mCRC, combining atezolizumab with fluoropyrimidine + bevacizumab as a 1L maintenance therapy did not lead to improvements in survival (PFS and OS)**
- **No new safety signals were identified for atezolizumab + fluoropyrimidine + bevacizumab**

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

Efficacy and safety results from IMblaze370, a randomized phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer – Bendell J, et al

Study objective

- To assess the efficacy and safety of atezolizumab + cobimetinib vs. atezolizumab alone vs. regorafenib in patients with chemotherapy refractory mCRC in the IMblaze370 study

Key patient inclusion criteria

- Unresectable locally advanced or metastatic CRC
- ≥2 prior regimens of cytotoxic chemotherapy
- MSI-H capped at 5%
- ECOG PS 0–1

(n=363)

R 2:1:1

- Atezolizumab 840 mg iv q2w + cobimetinib 60 mg oral 21/7 days (n=183)
- Atezolizumab 1200 mg iv q3w (n=90)
- Regorafenib 160 mg oral 21/7 days (n=90)

Loss of clinical benefit

Stratification

- Extended RAS mutation status (≥50% of patients in each arm)
- Time since diagnosis of first metastasis (<18 vs. ≥18 months)

PRIMARY ENDPOINT

OS for atezolizumab + cobimetinib or atezolizumab vs. regorafenib

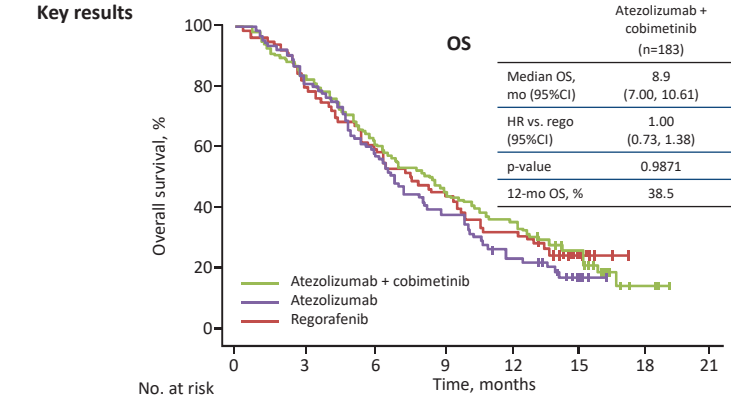
SECONDARY ENDPOINTS

PFS, ORR, DoR

Bendell J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-004

Efficacy and safety results from IMblaze370, a randomized phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer – Bendell J, et al

Key results



	Atezolizumab + cobimetinib (n=183)	Atezolizumab (n=90)	Regorafenib (n=90)
Median OS, mo (95%CI)	8.9 (7.00, 10.61)	7.1 (6.05, 10.05)	8.5 (6.41, 10.71)
HR vs. rego (95%CI)	1.00 (0.73, 1.38)	1.19 (0.83, 1.71)	NA
p-value	0.9871	0.3360*	NA
12-mo OS, %	38.5	27.2	36.6

No. at risk							
Atezolizumab + cobimetinib	183	150	110	83	63	28	3
Atezolizumab	90	73	51	34	22	9	
Regorafenib	90	67	52	40	30	9	

HRs are from stratified log-rank tests. Data cut-off: March 9, 2018. *For descriptive purposes only

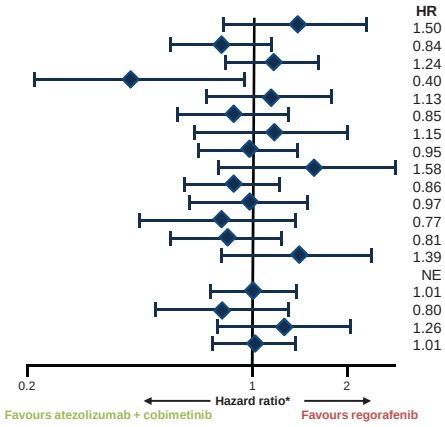
Bendell J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-004

Efficacy and safety results from IMblaze370, a randomized phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer – Bendell J, et al

Key results (cont.)

OS in key subgroups

Subgroup	n	HR
≥65 years	86	1.50
<65 years	187	0.84
White	223	1.24
Non-white	39	0.40
ECOG PS 0	133	1.13
ECOG PS 1	140	0.85
<18 mo since 1st met diagnosis	83	1.15
≥18 mo since 1st met diagnosis	190	0.95
>3 prior tx in met setting	70	1.58
≤3 prior tx in met setting	203	0.86
Left sided tumour	148	0.97
Right sided tumour	72	0.77
RAS mutant	148	0.81
RAS wild-type	104	1.39
MSI high	3	NE
MSI stable/low	250	1.01
PD-L1 high	110	0.80
PD-L1 low	124	1.26
ITT	273	1.01

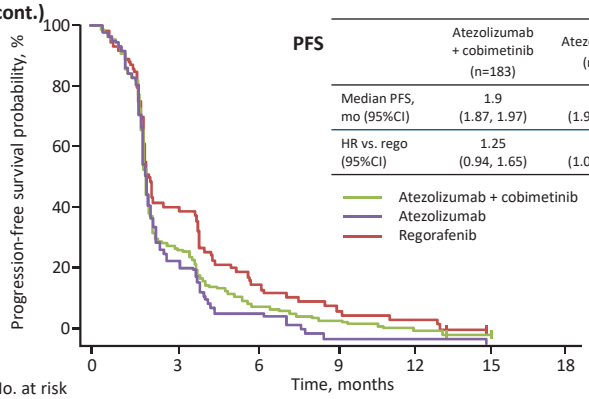


*Unstratified

Bendell J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-004

Efficacy and safety results from IMblaze370, a randomized phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer – Bendell J, et al

Key results (cont.)



PFS

	Atezolizumab + cobimetinib (n=183)	Atezolizumab (n=90)	Regorafenib (n=90)
Median PFS, mo (95%CI)	1.9 (1.87, 1.97)	1.9 (1.91, 2.10)	2.0 (1.87, 3.61)
HR vs. rego (95%CI)	1.25 (0.94, 1.65)	1.39 (1.00, 1.94)	NA

Atezolizumab + cobimetinib
Atezolizumab
Regorafenib

No. at risk						
Atezolizumab + cobimetinib	183	49	18	11	6	1
Atezolizumab	90	22	7	1	1	
Regorafenib	90	33	13	7	5	

Bendell J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-004

Efficacy and safety results from IMblaze370, a randomized phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer – Bendell J, et al

Key results (cont.)

AEs, n (%)	Atezolizumab + cobimetinib (n=179)	Atezolizumab (n=90)	Regorafenib (n=80)
TRAEs	170 (95)	49 (54)	77 (96)
Grade 3–4	80 (45)	9 (10)	39 (49)
Grade 5	2 (1)	0	1 (1)
SAEs	71 (40)	15 (17)	18 (23)
Treatment related	46 (26)	7 (8)	9 (11)
Leading to withdrawal	37 (21)	4 (4)	7 (9)
Leading to dose interruption or modification	109 (61)	18 (20)	55 (69)

Bendell J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-004

Efficacy and safety results from IMblaze370, a randomized phase III study comparing atezolizumab plus cobimetinib and atezolizumab monotherapy vs. regorafenib in chemotherapy-refractory metastatic colorectal cancer – Bendell J, et al

- **In patients with chemotherapy refractory mCRC neither atezolizumab + cobimetinib or atezolizumab alone improved OS compared with regorafenib**
- **The safety profile of atezolizumab + cobimetinib was similar to the safety profiles of the individual agents**

Bendell J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-004

Safety and antitumor activity of pembrolizumab in patients with advanced microsatellite instability–high (MSI-H) colorectal cancer: KEYNOTE-164 – Le D, et al

Study objective

- To assess the efficacy and safety of pembrolizumab in patients with advanced MSI-H CRC in the KEYNOTE-164 study

Key patient inclusion criteria

- Locally advanced, unresectable or metastatic CRC
- dMMR/MSI-H CRC by IHC/PCR
- ≥1 prior line of therapy
- ECOG PS 0–1

(n=63)

Pembrolizumab 200 mg q3w

Treatment for ~2 years (35 cycles) or until PD/toxicity/ withdrawal

PRIMARY ENDPOINT

ORR

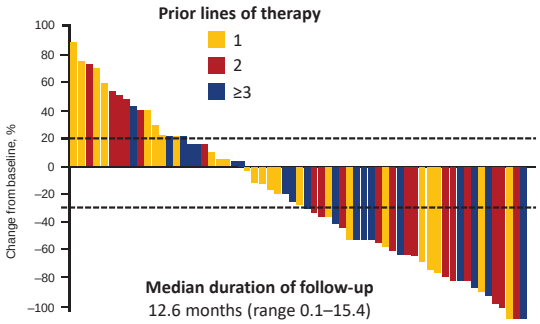
SECONDARY ENDPOINTS

DoR, PFS, OS, safety

Le D, et al. Ann Oncol 2018;29(suppl 5):abstr O-021

Safety and antitumor activity of pembrolizumab in patients with advanced microsatellite instability–high (MSI-H) colorectal cancer: KEYNOTE-164 – Le D, et al

Key results

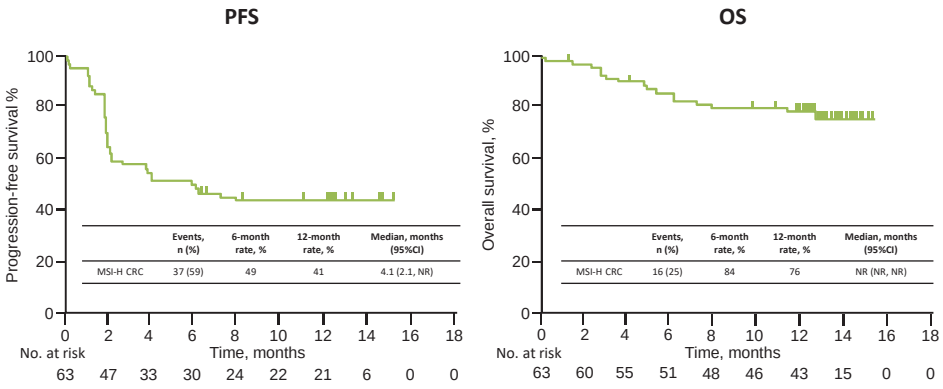


	Pembrolizumab (n=63)
ORR, n (%) [95%CI]	20 (32) [21, 45]
CR	2 (3) [0, 11]
PR	18 (29) [18,41]
SD	16 (25) [15, 38]
PD	25 (40) [28, 53]
DCR	36 (57) [44, 70]
mTTR, months (range)	3.9 (1.8–10.4)
mDoR, months (range)	NR (2.1+–13.2+)
ORR, n/N (%)	
BRAF mutated	1/5 (20)
BRAF WT	13/29 (45)
ORR, n/N (%)	
KRAS mutated	8/22 (36)
KRAS WT	11/34 (32)

Le D, et al. Ann Oncol 2018;29(suppl 5):abstr O-021

Safety and antitumor activity of pembrolizumab in patients with advanced microsatellite instability–high (MSI-H) colorectal cancer: KEYNOTE-164 – Le D, et al

Key results (cont.)

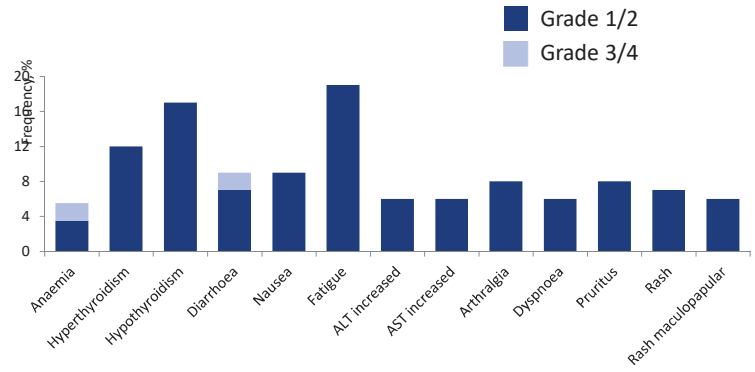


Data cut-off: 12 September 2017

Le D, et al. Ann Oncol 2018;29(suppl 5):abstr O-021

O-021: Safety and antitumor activity of pembrolizumab in patients with advanced microsatellite instability–high (MSI-H) colorectal cancer: KEYNOTE-164 – Le D, et al

Key results (cont.)



Le D, et al. Ann Oncol 2018;29(suppl 5):abstr O-021

Safety and antitumor activity of pembrolizumab in patients with advanced microsatellite instability–high (MSI-H) colorectal cancer: KEYNOTE-164 – Le D, et al

- **In previously treated patients with advanced MSI-H CRC, pembrolizumab demonstrated durable responses and a safety profile comparable to previous studies in patients with solid tumours**

Le D, et al. Ann Oncol 2018;29(suppl 5):abstr O-021

Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

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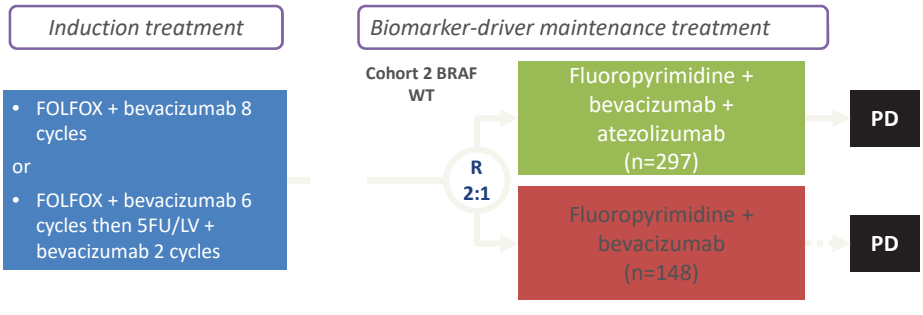


PRIMARY ENDPOINTS

- PFS (RECIST v1.1)

SECONDARY ENDPOINTS

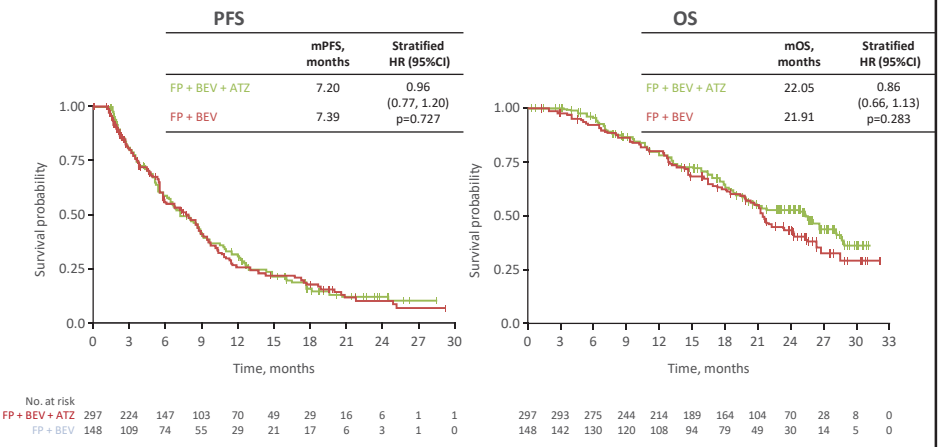
- OS, ORR, DCR, TTR, DoR, change in ECOG and safety

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

Key results

PFS and OS (median follow-up 18.7 months)



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Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

Key results (cont.)

Patients, n (%)	Fluoropyrimidine + bevacizumab + atezolizumab (n=293)	Fluoropyrimidine + bevacizumab (n=143)
TEAE	276 (94.2)	124 (86.7)
Grade ≥3	110 (37.5)	43 (30.1)
Grade 5	3 (1.0)*	1 (0.7)†
Any serious TEAE	28 (9.6)	6 (4.2)
TEAE leading to treatment discontinuation	36 (12.3)	16 (11.2)

*Septic shock, heart attack, recurrent pseudomonas chest infection; †colonic perforation

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

Fluoropyrimidine (FP) + bevacizumab (BEV) + atezolizumab vs FP/BEV in BRAFwt metastatic colorectal cancer (mCRC): Findings from Cohort 2 of MODUL – a multicentre, randomized trial of biomarker-driven maintenance treatment following first-line induction therapy – Grothey A, et al

- **In patients with BRAF WT mCRC, combining atezolizumab with fluoropyrimidine + bevacizumab as a 1L maintenance therapy did not lead to improvements in survival (PFS and OS)**
- **No new safety signals were identified for atezolizumab + fluoropyrimidine + bevacizumab**

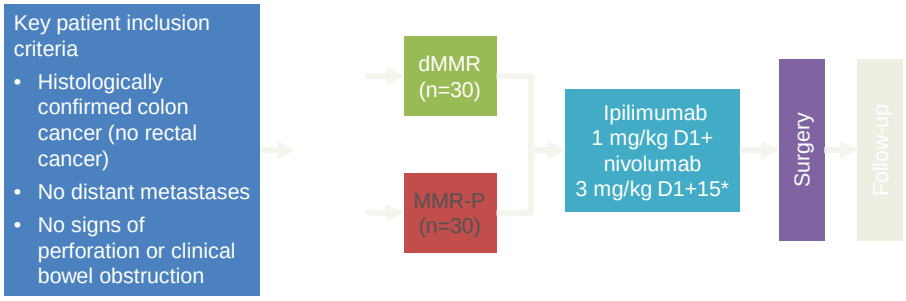
*

Grothey A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA19

Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer – Chalabi M, et al

Study objective

- To assess the efficacy and safety of neoadjuvant ipilimumab + nivolumab in patients with early stage colon cancer



PRIMARY ENDPOINTS

- Safety/feasibility

SECONDARY ENDPOINTS

- Efficacy, association between response and TMB, IFNγ, gene signatures, T-cell infiltration, TCR clonality

*Half of the MMR-P patients received celecoxib and other combinations in addition to study treatment

Chalabi M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA37_PR

Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer – Chalabi M, et al

Key results

- Of 19 patients included, 14 were evaluable; median duration from treatment to surgery was 32 days (IQR 28–35)
- There were no delays to surgery as a result of safety

TRAEs (n=14)	Grade 1/2, n (%)	Grade 3, n (%)
Total	10 (71)	5 (36)
Sarcoid-like reaction	1 (7)	0
Abdominal pain*	0	1 (7)
Rash	0	1 (7)
Dry mouth	4 (29)	0
Infusion reaction	2 (14)	0
Dry skin	1 (7)	0
Arthritis	1 (7)	0
Diarrhoea	1 (7)	0
Abdominal infection	0	1 (7)
Anastomotic leak	0	1 (7)
Pneumonia	0	1 (7)

Post-operative**

*Abdominal pain due to pseudoprogression;
**not attributable to immune checkpoint inhibitor

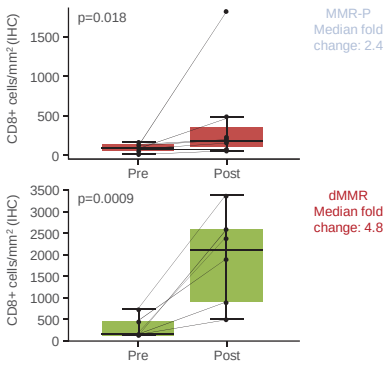
Chalabi M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA37_PR

LBA37_PR: Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer – Chalabi M, et al

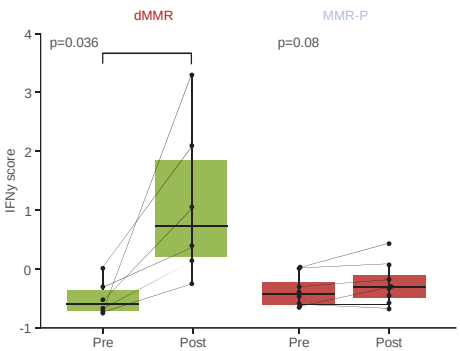
Key results (cont.)

- A major response was observed in all dMMR tumours
- Pre-treatment CD3 infiltration was not predictive of response to treatment

CD8+ T-cells increased in both dMMR and MMR-P tumours



IFNγ score significantly increased post-treatment



Chalabi M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA37_PR

Neoadjuvant ipilimumab plus nivolumab in early stage colon cancer – Chalabi M, et al

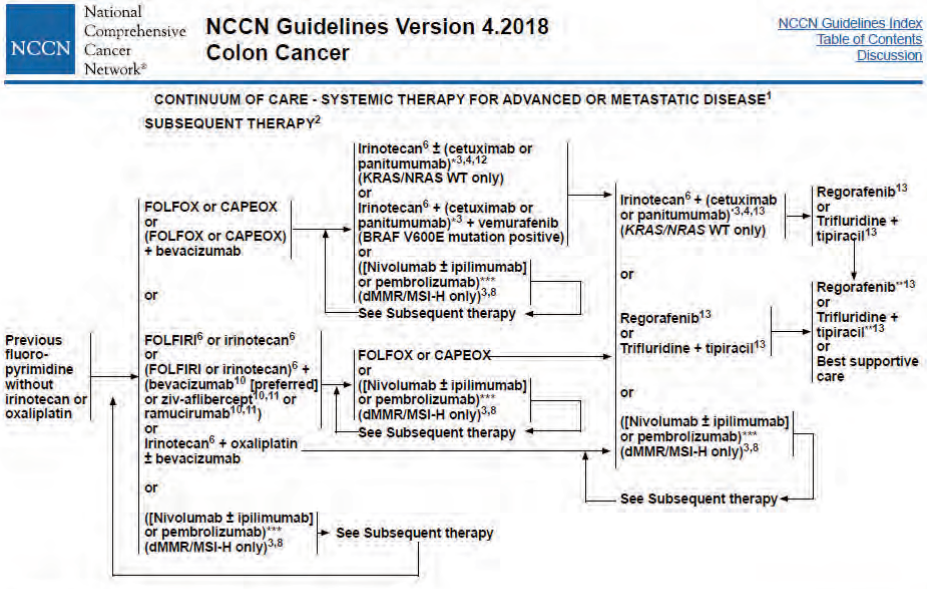
Key results (cont.)

- TCR clonality pre- and post-treatment was not significantly different in dMMR or MMR-P
- Pre-treatment immune gene signatures were not predictive of response to treatment

Conclusions

- **In patients with early stage colon caner, short pre-operative treatment with ipilimumab + nivolumab was safe and associated with major pathological responses in all dMMR tumours**
- **Tumour inflammation measures at pre-treatment were not predictive of response**
- **These findings need to be confirmed in larger trials**

Chalabi M, et al. Ann Oncol 2018;29(suppl 5):abstr LBA37_PR



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 9 of 10)

Capecitabine[8]
Capecitabine 850–1250 mg/m^2 PO twice daily, days 1–14
Repeat every 3 weeks

Capecitabine + bevacizumab[22,¶]
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan
Irinotecan 125 mg/m^2 IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks[23,24]
or Irinotecan 180 mg/m^2 IV over 30–90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300–350 mg/m^2 IV over 30–90 minutes, day 1
Repeat every 3 weeks

Irinotecan + cetuximab (*KRAS/NRAS* WT only)
Cetuximab 400 mg/m^2 first infusion, then 250 mg/m^2 IV weekly[25]
or Cetuximab 500 mg/m^2 IV over 2 hours, day 1, every 2 weeks[13]

Irinotecan + cetuximab + vemurafenib (*BRAF* V600E mutation positive)
Irinotecan 180 mg/m^2 IV every 14 days and cetuximab 500 mg/m^2 IV every 14 days with vemurafenib 960 mg PO twice daily[26]

Irinotecan + panitumumab + vemurafenib (*BRAF* V600E mutation positive)
Irinotecan 180 mg/m^2 IV every 14 days and panitumumab 6 mg/kg IV over 60 minutes every 2 weeks with vemurafenib 960 mg PO twice daily

Cetuximab (*KRAS/NRAS* WT only)
Cetuximab 400 mg/m^2 first infusion, then 250 mg/m^2 IV weekly[25]
or Cetuximab 500 mg/m^2 IV over 2 hours, day 1, every 2 weeks[13]
Panitumumab[27] (*KRAS/NRAS* WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib
Regorafenib 160 mg PO daily on days 1-21[28]
or
First cycle: Regorafenib 80 mg PO daily on days 1-7, then 120 mg PO daily on days 8-14, then 160 mg PO daily on days 15-21[29]
Subsequent cycles: Regorafenib 160 mg PO daily on days 1-21
Repeat every 28 days

Trifluridine + tipiracil[30]
Trifluridine + tipiracil 35 mg/m^2 up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily days 1–5 and 8–12
Repeat every 28 days

Pembrolizumab[31]
Pembrolizumab 2 mg/kg every 3 weeks
or Pembrolizumab 200 mg every 3 weeks

Nivolumab[32]
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every two weeks

Nivolumab + ipilimumab[33]
Nivolumab 3 mg/kg (30 minute IV infusion) and ipilimumab 1 mg/kg (30 minute IV infusion) once every 3 weeks for four doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks

See References on COL-D 10 of 10

¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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

COL-D
9 OF 10

Hvala za pozornost

Kompletno neoadjuvantno zdravljenje raka danke

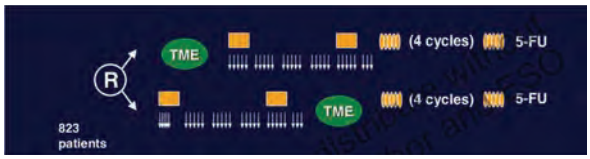
Vaneja Velenik

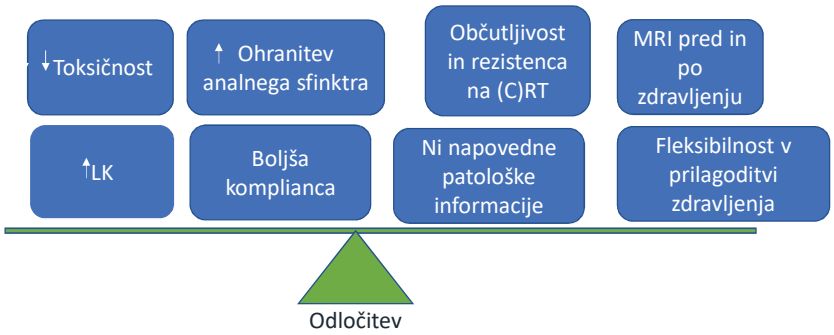
Cilji radikalnega zdravljenja raka danke

- Znižati delež lokalnih ponovitev
- Izboljšati celokupno preživetje in preživetje brez ponovitve bolezni
- Ohranitev analnega sfinktra
- Ohranitev kakovosti življenja in seksualne funkcije

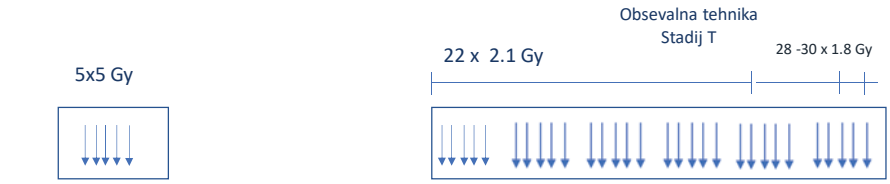
Preoperativna vs. postoperativna CRT

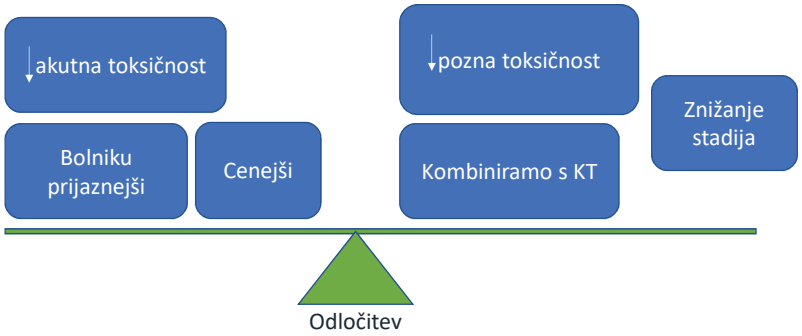
- Sauer R et al, N Engl J Med 2004





Kratek in dolgi režim obsevanja





MRI staging! Kaj meriti?

- Visoko kakovostni MRI za vse rake danke:
  - CRM
  - Ekstramuralna Venska Invazija (EMVI)
  - zajetje levatorjev
  - cT substadij (cT3c and cT3d)
  - cN stadij

MRI staging! Kaj meriti?

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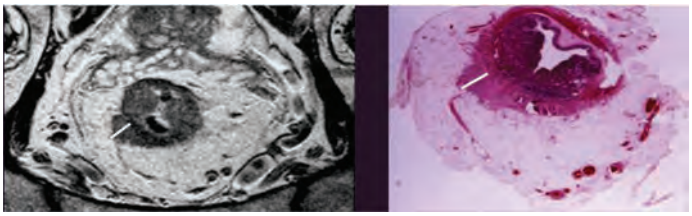
  - Ekstramuralna Venska Invazija (EMVI)
  - zajetje levatorjev
  - cT substadij (cT3c and cT3d)
  - cN stadij

→
- Kururgu poda plan operacije
- Določi potrebo po neoadjuvantni CRT, SCRT ali KT+ CRT/SCRT

MRI staging! Kaj meriti?

- MERCURY, Radiology 2007

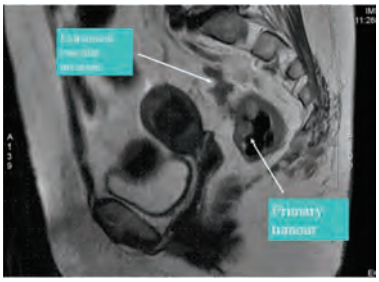


- Taylor et al, MERCURY, Ann of Surgery 2011

MERCURY—MRI-predicted Good Prognosis Patients	Local Recurrence	5-Year Disease-free Survival
Total patients (n = 122)	3.3%	84.7% (95% CI, 76.0%–90.4%)
T3a/b N0, N1, and N2 (n = 58)	1.7%	81% (95% CI, 66.1%–89.8%)
T1,2, or, 3b, N positive disease (n = 22)	0%	95% (95% CI, 69.5%–99.3%) .

MRI staging! Kaj meriti?

- Messenger DE et al, Hum Pathol 2012



- Chand M et al, W J Gastroenterology 2016

Survival outcomes in the presence of venous invasion

Seven studies reported on 5 year survival rates in patients with EMVI positive histology[4,6,13,14,16-18]. The pooled overall survival was 39.5% [Random effects: Event rate 0.395 (0.29, 0.51), $z = -1.9$, $Q = 58.06$, $I^2 = 90\%$] (Figure 3).

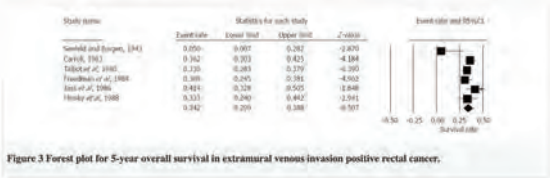


Figure 3 Forest plot for 5-year overall survival in extramural venous invasion positive rectal cancer.

MRI staging! Kaj meriti?

- Nagtegaal ID et al, Am J Surg Pathol 2002 Dutch TME trial unirradiated group (N= 656)

Dutch TME raziskava	3-L lokalna ponovitev	
+CRM ≤ 2 mm	16%	
-CRM > 2 mm	5.8%	P= 0.001

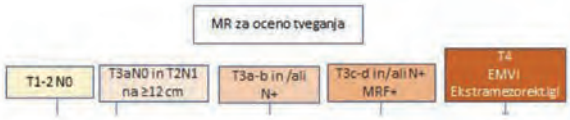
- MERCURY raziskava: CRM potencialno zajet pri 64 pts;
  38/64 ponovitev in 32 smrti;
  5-L OS je bilo 42.2% (62.2% in –CRM; p=0.01)

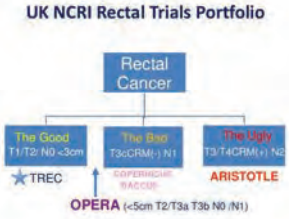
Stratifikacija bolnikov glede na tveganje ponovitve

- Oddaljenost od CRM
- Globina mesorektalne invazije
- Zajetje bezgavk
- EMVI

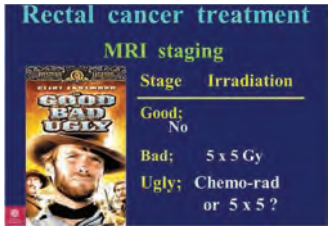
- ”Bad” (=zmerno tveganje) in “Ugly” (=visoko tveganje) tumorji potrebujejo neoadjuvantno radioterapijo

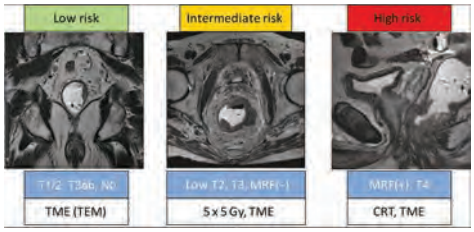
Stratifikacija bolnikov glede na tveganje ponovitve

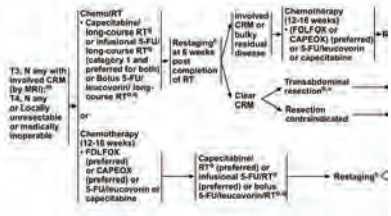


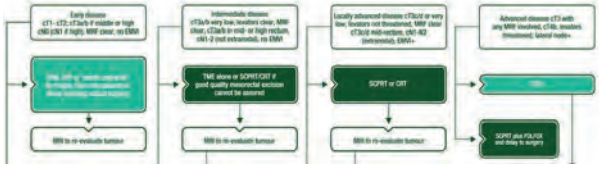


Tveganju ponovitve prilagojeno zdravljenje





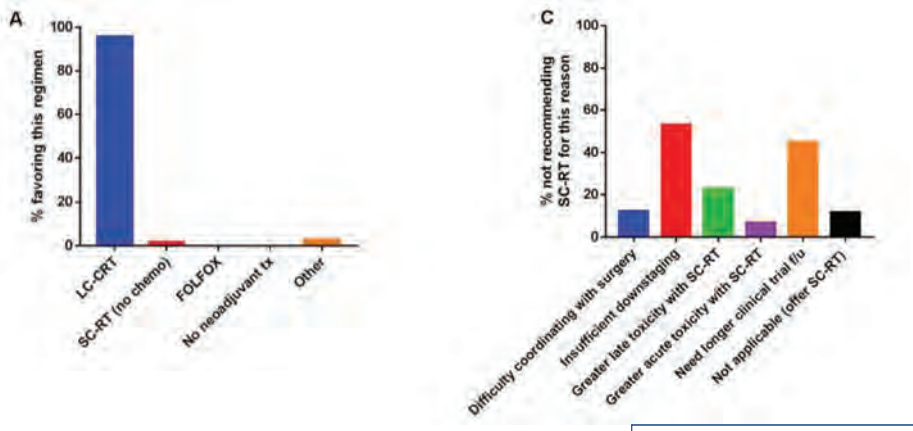




Možnosti zdravljenja

- Kratek režim RT, operacija v nekaj dneh
- Kratek režim RT, odlog do operacije
- Dolg režim CRT, operacija 6-10 tednov po zaključku
- Dolg režim CRT, W&W (NCCN, ESMO)
- neoadjuvantno XELOX/FOLFOX, sledi dolg režim CRT, odlog do operacije (NCCN)
- kratek režim RT, sledi XELOX/FOLFOX, odlog do operacije (ESMO)

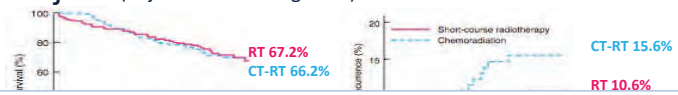
Skandinavci vs. Američani



Mowery YM et al. Cancer, 2016

5x5 Gy ali CRT?

- Poljska (Bujko et al. Br J Surg 2006)



CRT: višji delež pCR
5x5: nižji delež akutne toksičnosti
Ni razlike: ohranitev sfinktra, LK, DM, OS in DFS

pts	163	163	
3-l LRR	7.5.%	4.4.%	0.24
5-l M1	28%	31%	0.85
5-l OS	74%	70%	0.56

5x5 Gy s takojšnjo ali odloženo operacijo

- Meta analiza 10 raziskav (1343 pts)

	Akutna toksičnost	Postop zapleti	pcR	Ohranitev sfinktra	**Preživetje**
Takojšnja op	0%	52.5%		NO	NO
Odložena op	4.2%	39.4%	10% več		

5x5 Gy z odloženo operacijo rutinsko priporočajo starejšim pts neprimernim za KT pri neresektabilnih rakih ali pri zgodnjih rakih pred lokalno ekscizijo

Bujko K et al, Ann Oncol 2016

5x5 Gy s takojšnjo ali odloženo operacijo

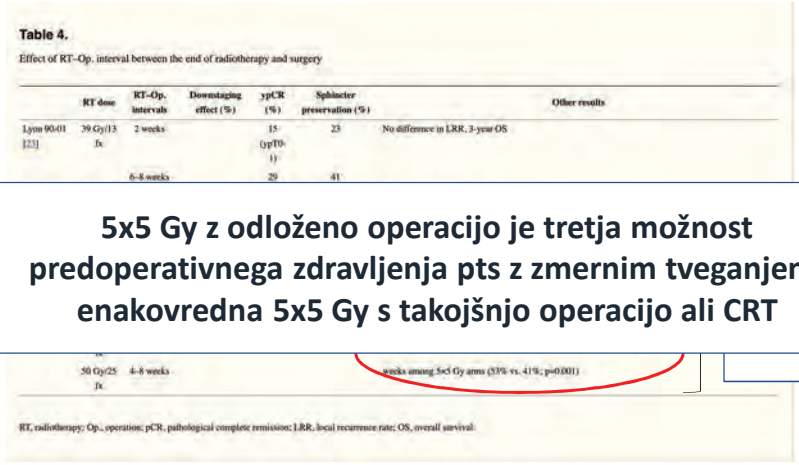


Table 4.

Effect of RT–Op. interval between the end of radiotherapy and surgery

	RT dose	RT–Op. intervals	Downstaging effect (%)	ypCR (%)	Sphincter preservation (%)	Other results
Lyon 90-01 [23]	39 Gy/13 fx	2 weeks		15 (ypT0-1)	23	No difference in LRR, 3-year OS
		6–8 weeks		29	41	
	50 Gy/25 fx	4–8 weeks				weeks among 5×5 Gy arms (33% vs. 41%; p=0.001)

RT, radiotherapy; Op., operation; pCR, pathological complete remission; LRR, local recurrence rate; OS, overall survival.

5x5 Gy z odloženo operacijo je tretja možnost predoperativnega zdravljenja pts z zmernim tveganjem, enakovredna 5x5 Gy s takojšnjo operacijo ali CRT

S, DFS, LR, DM

Wu H et al. Int J Surg 2018

5x5 Gy s takojšnjo ali odloženo operacijo

Int J Surg. 2018 Aug;56:195-202. doi: 10.1016/j.ijsu.2018.05.031. Epub 2018 May 25.

Short-course radiotherapy with immediate or delayed surgery in rectal cancer: A meta-analysis.

Wu H[1], Fang C[1], Huang L[1], Fan C[1], Wang C[2], Yang L[2], Li Y[3], Zhou Z[4].

Author information

5 raziskav na 1244 pts:

- **Odložena op: višji delež pCR, višji delež bolnikov s poop. stadijem 0+I, nižja incidenca pooperativnih zapletov**
- **Ni razlike v OS, deležu ohranitve sfinktra in R0 resekcij**

Wu H et al. Int J Surg 2018

5x5 Gy z odlogom do operacije ali CRT?

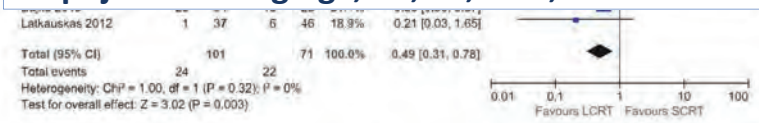
DOI: http://dx.doi.org/10.7314/APJCP.2015.16.14.5755
Short-versus Long-course Preoperative Radiotherapy plus Delayed Surgery for Rectal Cancer: a Meta-analysis

RESEARCH ARTICLE

Short-course Versus Long-course Preoperative Radiotherapy plus Delayed Surgery in the Treatment of Rectal Cancer: a Meta-analy

Shi-Xin Liu[1&s
Tian-Song Zh

CRT: ↑delež pCR
Ni razlike: ohranitev sfinktra, akutna toksičnost, stopnja downstaginga, R0, LR, DM, OS in DFS



Liu SW et al. Asian Pac J Cancer Prev 2015

5x5 Gy z odlogom do operacije ali CRT?

Article in Press

Short-Course Radiotherapy in Neoadjuvant Treatment for Rectal Cancer: A Systematic Review and Meta-analysis

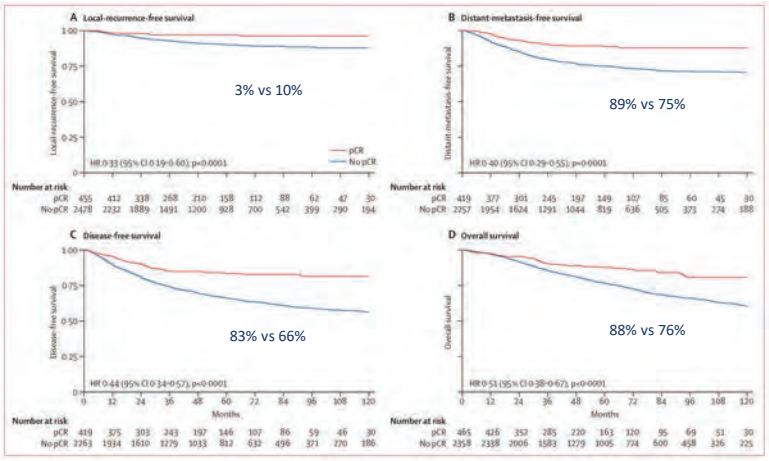
Bin Ma, Peng Gao, Yongxi Song, Xuanzhang Huang, Hongchi Wang, Qingzhou Xu, Shan Zhao, Zhenning Wang

5x5 Gy z odloženo operacijo je lahko izbira, ko pCR ni primarni namen

Ma B et al. Clin Colorectal Cancer 2018

Zakaj pCR?

3105 pts

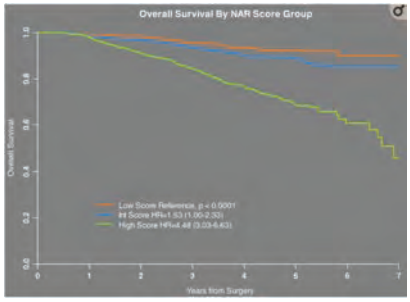


Maas M et al. The Lancet Oncology 2010

"The neoadjuvant rectal (NAR)" točkovalnik

- Na osnovi pN in downstaging T (cT v pT)
- Regres bolezni je boljši napovednik OS kot pCR
- odobren s strani National Cancer Institute kot primarni cilj raziskav faz II, ki proučujejo vpliv neoadjuvantne terapije (uvodne KT ali totalnega neoadjuvantnega zdravljenja

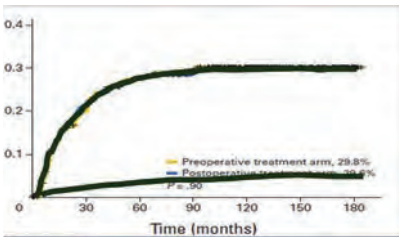
$$NAR = \frac{[5\,pN - 3(cT - pT) + 12]^2}{9.61}$$



George TJ et al. Curr Colorectal Cancer Report 2015

Dejstva

- Lokalna kontrola je REŠENA!
- Okultne metastaze so PROBLEM!
- Preživetje ni izboljšano
- Standard zdravljenja:



DM

LC

CRT	5.5 tednov
Čas do operacije	8 tednov
"Recovery" po operaciji	4 tedne

Skupaj > 4 mesece, da bolnik prejme dostojno kemoterapijo!!!

Omejitve adjuvantne KT

- <u>Čas do pričetka adjuvantne KT</u>
  - Meta-analiza 10 raziskav > 15.000 pts s RDČD
    - Adjuvantna KT mora pričeti 4-6- tednov po operaciji
    - za vsake 4 tedne zamude se zmanjša preživetje za 14%

- <u>Komplianca pts je slaba</u>
  - Do 27% pts je sploh ne prične
  - Manj kot 50% dobi vse predvideno zdravljenje
    - CHRONICLE raziskava: 48% pts zaključilo
    - EORTC 22921 raziskava: 43% pts zaključilo
  - Zaradi pooperativnih zapletov
    - Počasen "recovery"
    - Zapleti z ileostomo
    - Odklonijo zdravljenje

Biagi J et al. JAMA 2011
Bergugom AJ et al. Lancet Oncol 2015

Dobrobit adjuvantne KT je vprašljiva

- Meta-analiza
  - 21 rand. raziskav
  - V vseh 5-FU
  - 9785 pts z/brez adj. KT
  - 1194 pts st. pII in III

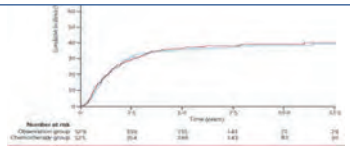
  - Izboljšan OS za 17%
  - Izboljšan DFS za 25%
  - Ni jasno, ali je dobrobit večja pri bolnikih z visokim tveganjem po TNM

Peterson et al. Cochrane database Syst Review 2012

Dobrobit adjuvantne KT je vprašljiv

- Meta-analiza
  - 4 rand. raziskave, ocenjevale OS z/brez adj. KT

Zaključek:
Adjuvantna KT ne doprinese k izidu bolezni
Ali naj dodamo KT k neoadjuvantnemu zdravljenju?



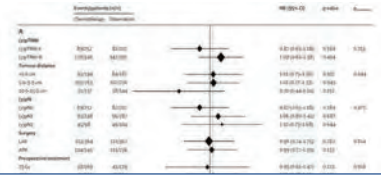
	Observation (n=598)	Chemotherapy (n=598)
Trial		
I-CNR-RT[9]	112 (19%)	133 (22%)
PROCTOR-SCRIPT[6]	204 (34%)	199 (33%)
CHRONICLE[10]	45 (8%)	30 (5%)
EORTC 22921[7]	237 (40%)	236 (39%)
Age (years)	62 (54-68)	61 (55-68)
Sex		
		(67%)
		(33%)
		(28%)
		(22%)
		(49%)
		(61%)
		(39%)
		(32%)
5·0–9·9 cm	256 (43%)	263 (44%)
≥10·0 cm	144 (24%)	137 (23%)
Unknown	11 (2%)	4 (<1%)
(y)pTNM		
II	207 (35%)	252 (42%)
III	391 (65%)	346 (58%)

Data are n (%) or median (IQR). (y)pTNM=(post-neoadjuvant) pathological TNM stage.

Table 2: **Patient characteristics**

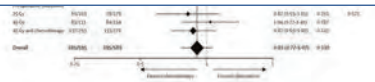
Bergugom AJ et al. Lancet Oncol 2015

Dobrobit adjuvantne KT je vprašljiv



- Meta-analiza
  - 4 rand. raziskave, ocenjevale OS z/brez adj. KT

Ali naj rake danke, ki se nahajajo 10-15 cm od zobate črte pojmujemo kot rake debelega črevesa?



  - Pri tumorjih 10-15 cm nad zobato linijo - značilno boljše DFS in manj pojava DM

Bergugom AJ et al. Lancet Oncol 2015

Razlogi za umestitev KT v neoadjuvantno zdravljenje

- Neoadjuvantna KT omogoča zgodnje zdravljenje mikrometastaz
- Bolniki KT bolje prenašajo kot po operaciji, večina jih zaključi zdravljenje (poop jih 26-57% ne zaključi), zdravljenje je tako učinkovitejše
- Pripomore k večji odzivnosti primarnega tumorja, kar poveča tudi verjetnost uspešne operacije z ohranitvijo sfinktra
  - Patološki stadij ima večjo napovedno vrednost za izhod bolezni kot klinični
    - Caprici C et al. Int J Radiat Oncol Biol Phys 2008
    - Quah et al. Cancer 2008
    - Das P et al. Am J Clin Oncol 2006
    - Kuo Lj et al. Ann Surg Oncol 2007
- Zgodnejše zapiranje ileostome
- Zgodejše odkritje pts, ki ne odgovorijo

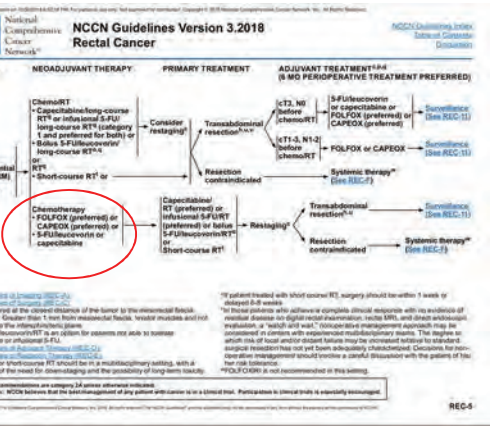
Cercek AJ et al. Lancet JNCC N 2014
Chau I et al. J Clin Oncol 2006
Fernandez-Martos C et al. J Clin Oncol 2010
Schrag D et al. J Clin Oncol 2014

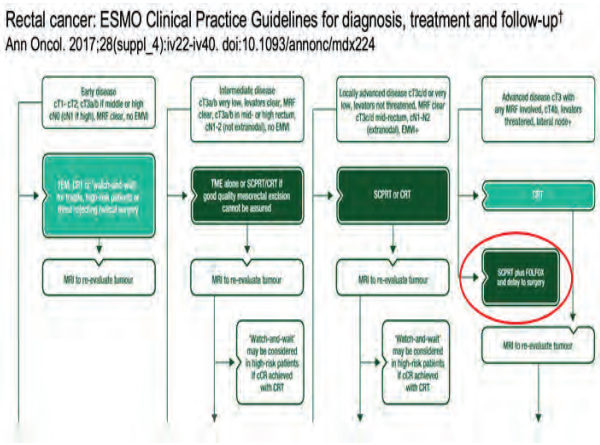
Odgovor metastatskega RDČD na samo KT

Odgovor primarnega tumorja pri zdravljenju metastatskega RDČD (20 pts)			
pCR	> 80%	79-50%	<50%
7 (35%)	4 (29%)	4 (29%)	1 (7%)

Cercek A et al. J Clin Oncol 28: 15s; 2010 (suppl); abstr 481
Cercec A. ASCO GI 2018

KT + CRT **ali** **RT + KT**



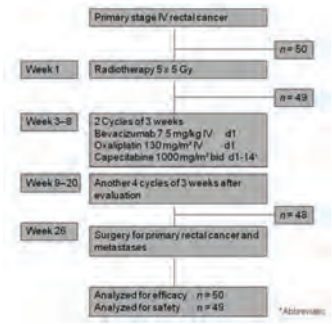


5x5 Gy, konsolidacijska KT, odlog do operacije

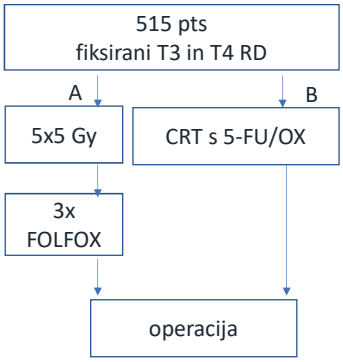
- Nizozemska M1 raziskava (50 pts z resektabilnimi jetrnimi/pljučnimi meta)

  5x5 Gy, nato 6x CAPOX + bevacizumab + odložena operacija > 5 mes
  - > 90% pts dobilo > 4 KT
  - Nizka toksičnost
  - pCR 26%
  - Brez progresa ob KT

- Update 2016: srednji čas sledenja 8.1 (6-9.1) let
  - LR 5.5%
  - OS 32%



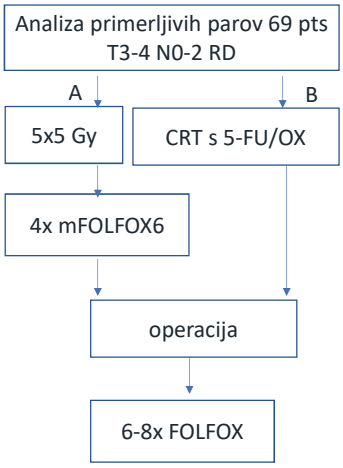
5x5 Gy, konsolidacijska KT, odlog do operacije



	A	B	p
Toksičnost vsi G diareja	75% manj	83%	0.006 <0.001
Redukcija doze RT	0%	8%	<0.001
Podaljšanje časa RT zaradi toksičn.	0	5%	<0.001
R0	77%	71%	0.07
3-L OS	73%	65%	0.046
3-L DFS	53%	52%	n.s.

Bujko K et al. Br J Surg 2006

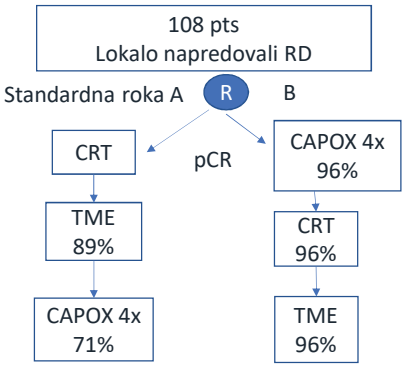
5x5 Gy, konsolidacijska KT, odlog do operacije



	A	B	p
T downstaging	75%	45%	<0.001
3-L OS	96%	89%	
3-L DFS	83%	66%	0.02
3-L DMFS	87%	69%	0.014

Yossef FF et al. IJROBP 2015

Uvodna KT, CRT, odlog do operacije 1



- Ni razlike v pCR 13.5% vs 14.3
- Ni razlike v downstagingu
- Ni razlike v deležu R0 resekcij

- Roka B: komplianca v KT zdravljenju boljša (p<0.001)

- Toksičnost Gradusa 3-4 višja v skupini z adjuvantno KT

Fernandez- Martos C et al. J Clin Oncol 2010

Uvodna KT, CRT, odlog do operacije 2

77 pts
T3 ob ali pod levatorji; T4; T1-4 N2

CAPOX 4x

CRT

TME

CAPOX 4x

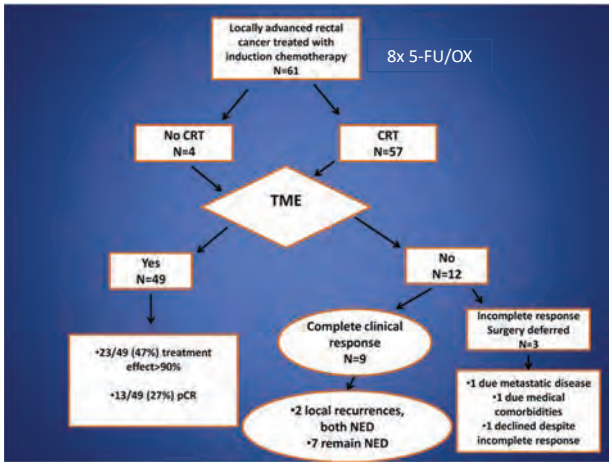
Table 2. Objective Tumor Responses by Imaging

Response	After Chemotherapy (n = 68) No. of Patients	%	After Chemoradiation (n = 70) No. of Patients	%
Complete response	3	4	14	20
Partial response	57	84	54	77
Stable disease	8	12	2	3
Progressive disease	0	0	0	0
Objective response rate, %	88		97	
95% CI	78 to 95		90 to 100	

- Radiološki odgovor: 88% na CAPOX
- Radiološki odgovor na CAPOX +CRT: 97%
- pCR: 24%, R0: 98.8%
- Skoraj popolni odgovor: 48%
- 1-L OS 99%

Chau I et al. J Clin Oncol 2006

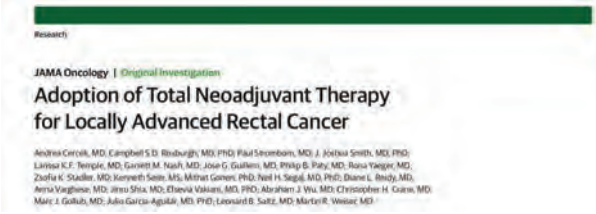
Kompletno neoadjuvantno zdravljenje 3



- Ni G4 toksičnosti po KT + CRT, ni prekinitve
- Vsi pts imeli radiološki odgovor na KT in tudi na CRT, ni progresa med zdravljenjem
- pCR: 21%, cCR: 15% - w&w (skupaj 36%)
- Operirani: downstaging pri 96% pts, pri 47% pts odgovor > 90%,

Cercek AI et al. J Clin Oncol 2006

Kompletno neoadjuvantno zdravljenje 3

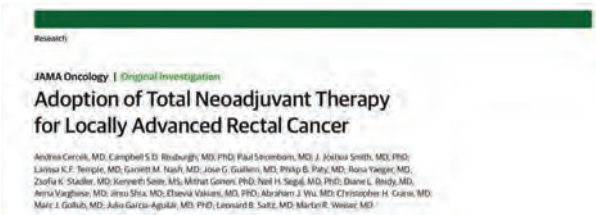

Research

JAMA Oncology | Original Investigation

Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer

- Evaluacija odgovora v večji kohorti
  - 628 pts z lokalno napredovalim RD (T3/4 ali N+), zdravljenih od 2009 do 2015
    - 320 pts dobilo CRT
    - 308 pts dobilo TNT - kompletno neoadjuvantno zdravljenje (FOLFOX/CAPOX, sledi CRT)

Kompletno neoadjuvantno zdravljenje 3


Research

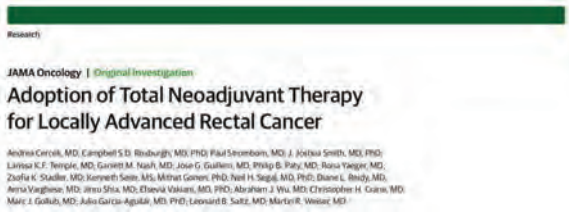
JAMA Oncology | Original Investigation

Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer

- Povprečna prejeta doza 5-FU: TNT 96% vs CRT 88% (p= 0.003)
- Prejeto št. krogov: TNT 95% vs CRT 83% (p= 0.001)

	CRT with Adjuvant CT N=101*	TNT N= 249*	P value
5 FU			
Average Percent of Planned Dose Received (%)	88.4%	95.9%	0.003
Number of cycles administered			
>6 cycles	84 (83)	236 (95)	<0.001
8 Cycles	76 (75)	235 (94)	<0.001
Oxaliplatin			
Average Percent of Planned Dose Received (%)	73%	90%	<0.001
Number of cycles administered			
>6 cycles	64 (63)	214 (86)	<0.001
8 Cycles	42 (42)	195 (78)	<0.001

Kompletno neoadjuvantno zdravljenje 3



Research

JAMA Oncology | Original Investigation

Adoption of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer

Andrea Cercek, MD; Campbell S.D. Roxburgh, MD, PhD; Paul Strombom, MD; J. Joshua Smith, MD, PhD; Larissa K.F. Temple, MD; Garrett M. Nash, MD; Jose G. Guillem, MD; Philip B. Paty, MD; Rona Yaeger, MD; Zsofia K. Stadler, MD; Kenneth Seier, MS; Mithat Gonen, PhD; Nel H. Segal, MD, PhD; Diane L. Reidy, MD; Anna Varghese, MD; Jinru Shia, MD; Efsevia Vakiani, MD, PhD; Abraham J. Wu, MD; Christopher H. Crane, MD; Marc J. Gollub, MD; Julio Garcia-Aguilar, MD, PhD; Leonard B. Saltz, MD; Martin R. Weiser, MD

Group (n)*	All Patients		Surgery within 12 Months		Complete Response (pCR and Sustained eCR) at 12 Months (%)
	N	Sustained eCR (%)†	N	pCR (%)†	
ChemoRT with planned adjuvant chemotherapy					
Stage II	94	9 (10)	82	14 (17)	23 (25)
Stage III	226	10 (4)	214	35 (16)	45 (20)
Total	320	19 (6)	296	49 (17)	68 (21)
TNT					
Stage II	43	23 (5)	20	0	23 (54)
Stage III	265	44 (17)	215	43 (20)	87 (33)
Total	308	67 (22)	235	43 (18)	110 (36)

*Stages are clinical.

†pCR rates are percentages of patients among those who underwent resection within 12 months after completion of neoadjuvant therapy. eCR rates are percentages of patients among all patients in each cohort.

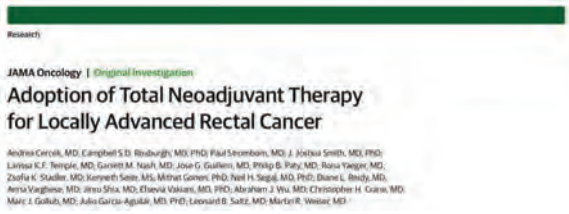
NA, not applicable.

- minimalno invazivna krg TNT 72% vs CRT 47% p<0.001)
- w&w: TNT 24% vs CRT 8%
- Dnevi do zaprtja ileostome:

  CRT + adj KT: **192** (166-243)

  TNT: **89** (71-107) p<0.001

Kompletno neoadjuvantno zdravljenje 3



Research

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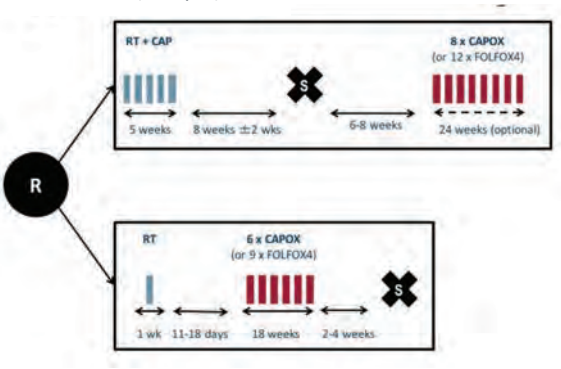
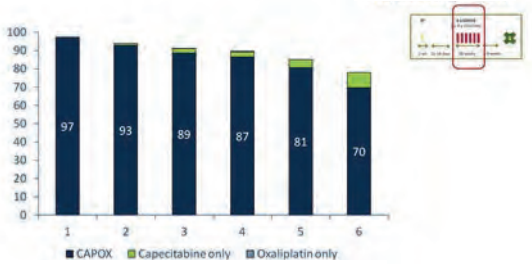
Ameriški ali evropski kompletnega neoadjuvantnega zdravljenja?

RAPIDO (906 pts)





Kompletno predoperativno zdravljenje v slovenskih smernicah

bo predstavljeno na 8. šoli

Zaključki

- Kompletno neoadjuvantno zdravljenje omogoča:
  - Najboljšo komplianco in izvedbo KT
  - Visok klinični in patološki odgovor
  - Umeščeno je v strategije potekajočih raziskav
  - Potencialno ”preveč zdravljenja” nekaterih bolnikov – ključ je dobra selekcija

Nujno je potrebna revizija “The Good, the Bad and the Ugly”

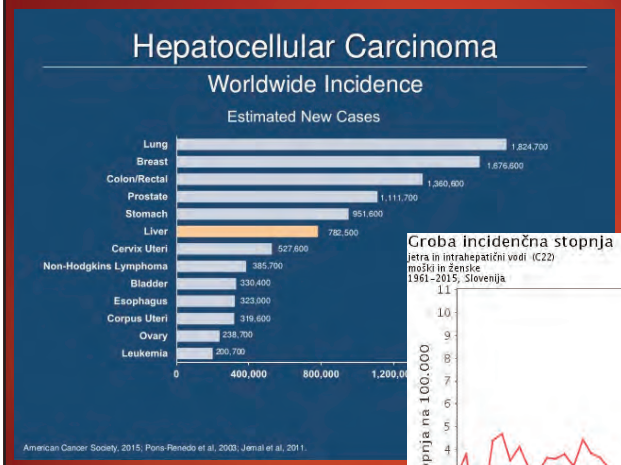
Zaključki

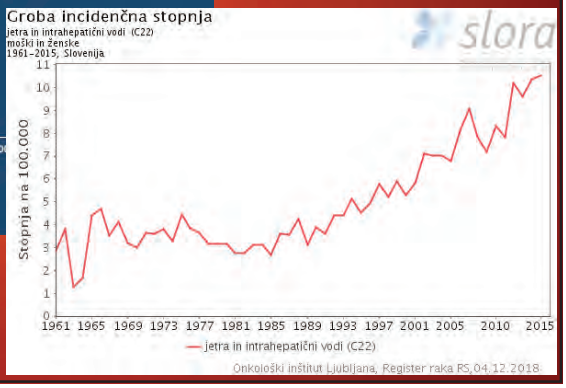
- Namesto stratifikacije bolnikov skupine s samo operacijo ali kratek režim RT ali CRT ali kompletno neoadjuvantno zdravljenje, je ključen namen neoadjuvantne terapije vsake posamezne skupine. Kaj želimo doseči?
  - Lokalno kontrolo?
  - CRM +, downstaging?
  - Da bolnik prejme celotno zdravljenje?
  - Ohranitev organa?

Sistemsko zdravljenje primarnega raka jeter

ASIST.DR.TANJA MESTI, DR.MED.
ONKOLOŠKI INŠTITUT LJUBLJANA

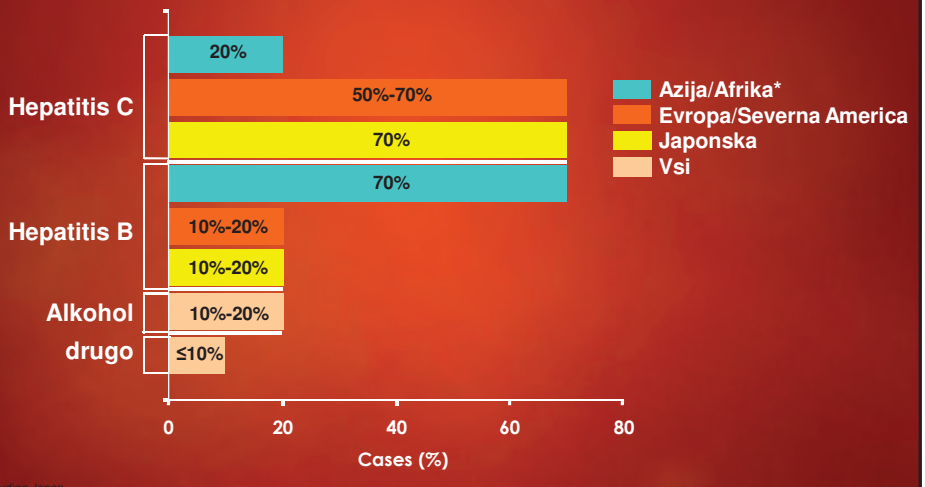
INCIDENCA





UMRLJIVOST

Dejavniki tveganja za HCC – po regijah



*Excluding Japan.
Llovet JM, et al. Lancet. 2003;362:1907-1917.

BCLC staging system

BCLC Staging

BCLC Stage		ECOG PS	Tumor Size/Number, Vascular Involvement, Etc	Child-Pugh Score
0	Very early	0	Solitary <2 cm nodule	A
A	Early	0	Solitary <5 cm nodule or up to 3 nodules each ≤3 cm	A - B
B	Intermediate	0	Large/multinodular	A - B
C	Advanced	1-2	Portal venous invasion and/or extrahepatic spread (N+ or M+)	A - B
D	Terminal	>2	Any of the above	C

BCLC = Barcelona Clinic Liver Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status.
Llovet et al, 1999.

Table 2. Child Pugh Turcotte (CTP) Score

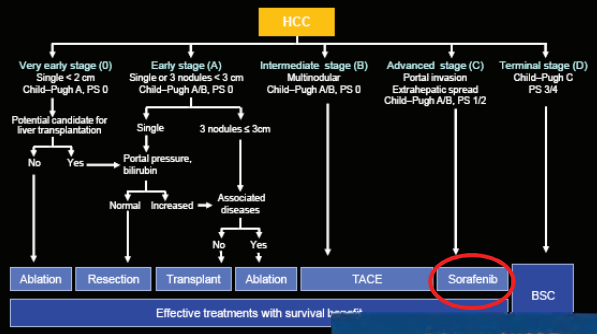
Parameters	Points		
	1	2	3
Serum Bilirubin(mg/dl)	2.0	2-3	>3.0
Serum Albumin(g/dl)	>3.5	2.8-3.5	<2.8
Prothrombin Time (Prolongation (s))	1-4	5-6	>6
Hepatic encephalopathy	None	Minimal	Advanced
Ascites	None	Slight	Moderate

One and two year survival based on CTP Score

Class	1 yr	2 yr
A (5-6 points)	100 %	85 %
B (7-9 points)	80%	60%
C (10-15 points)	45%	35%

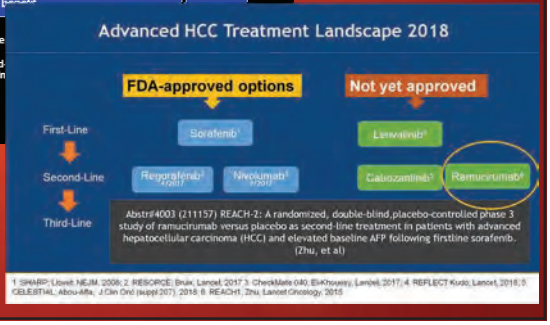
Data from Child CG, Turcotte JG Surgery and portal hypertension. In: Child CG, The liver and portal hypertension. Philadelphia: Saunders; 1964.p.50-64

BCLC Staging and Treatment Strategy



*Note that Child-Pugh classification is not sensitive to accurately identify those liver transplant consideration.
**Patients with end stage cirrhosis due to heavily impaired liver function (Child prognosis high MELD score) should be considered for liver transplantation. In the enlistment criteria.

Bruix J, et al. *Gastroenterol.* 2016;150:835–853.



Kontraindikacije za kirurško zdravljenje

- Izven jetrna bolezen
- Multipli ali bilobarni tumorji
- Napredovala jetrna bolezen
- Zajetje glavnega žolčnega voda
- Prisotnost tromboze debla vene porte ali spodnje vene cave

Absolutne kontraindikacije za cTACE: ESMO priporočila

- Dekompenzirana ciroza (Child–Pugh B ≥8), vključno z:
  - zlatenico
  - klinično encefalopatijo
  - refraktornim ascitesom
- Tumorska masa večjega dela obeh lobusov
- Pomembno zmanjšan portalen venski pretok (npr. Okluzija portalne vene)
- Tehnične kontraindikacije za jetrno intraarterielno zdravljenje (npr. a-v fistula)
- Bilio-enterična anastamoza ali biliarni stenti
- Ledvična insuficienca (klirens kreatinina <30 mL/min)

cTACE, conventional transarterial chemoembolization; ESMO, European Society of Medical Oncology.
Verslype C et al. ESMO guidelines. Ann Oncol 23(Suppl 7):vii41–8. – based on Raoul J-L et al. Cancer Treat Rev 2011;37:212–20

Relativne kontraindikacije za cTACE: mnenje ekspertov

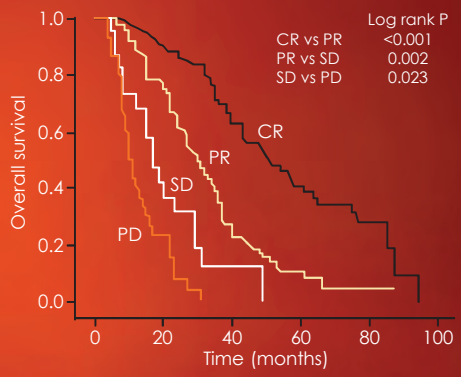
- Tumor ≥10 cm
- Komorbiditeta s slabo funkcijo urganov:
  - Aktivne kardiovaskularne bolezni
  - Aktivne bolezni pljuč
- Nezdravljene varice z virokim tveganjem krvavitve
- Okluzije biliarnega sistema ali papile (stent ali po kirurgiji)

Raoul J-L et al. Cancer Treat Rev 2011;37:212–20

Preživetje in odgovor po mRECIST po TACE

Predictive reponse	OS	
	HR*	P value†
CR	1.0	–
PR	2.75 (1.96– 3.87)	<0.001
SD	6.32 (3.67–10.90)	<0.001
PD	16.06 (9.76–26.43)	<0.001

- C index for mRECIST criteria was 0.72 (95% CI: 0.68–0.76)

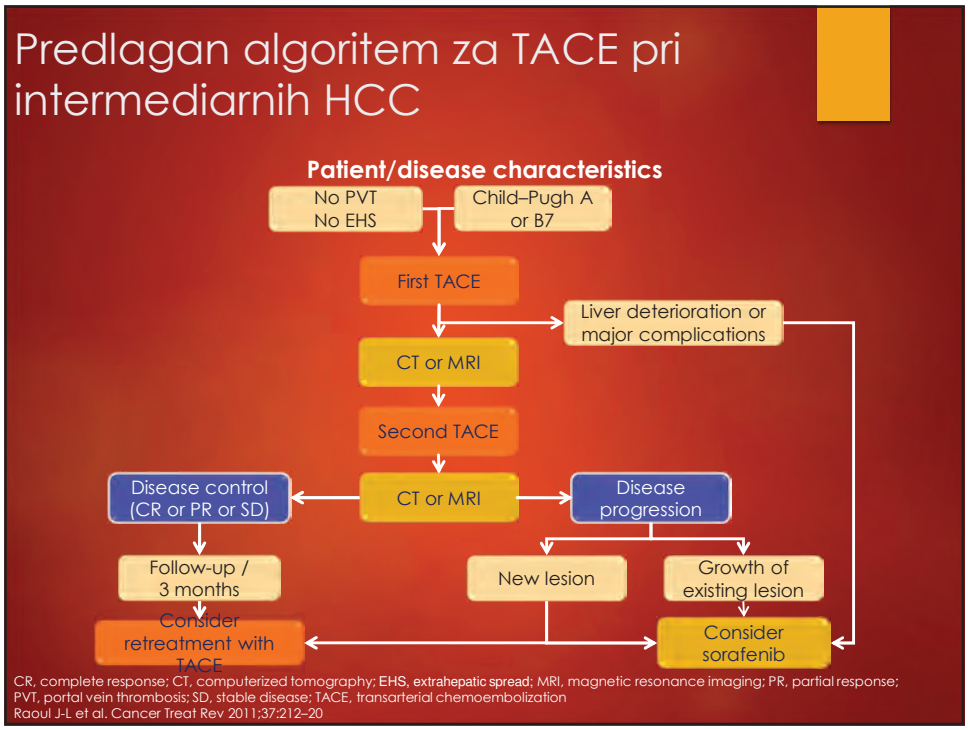


Survival of 332 BCLC stage B patients; tumour responses determined with mRECIST

*Numbers in parentheses are the 95% CIs
†Data were generated from the univariate Cox regression model
BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; CT, computerized tomography; HR, hazard ratio; mRECIST, modified Response Evaluation Criteria In Solid Tumors; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; TTP, time to progression

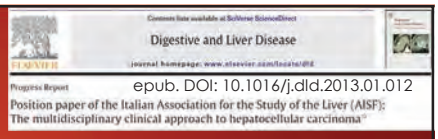
Adapted from Shim JH et al. Radiology 2012;262:708–18

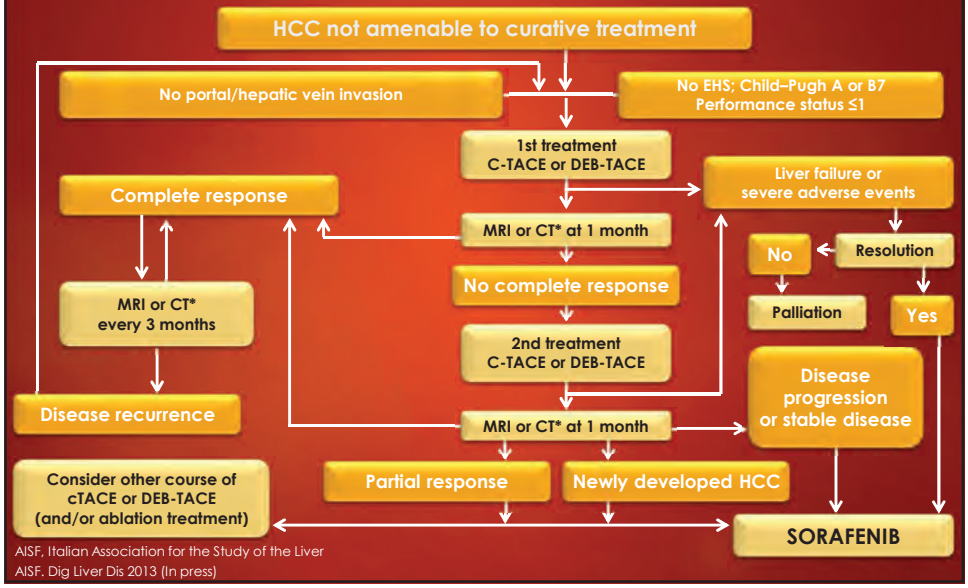
Predlagan algoritem za TACE pri intermediarnih HCC



CR, complete response; CT, computerized tomography; EHS, extrahepatic spread; MRI, magnetic resonance imaging; PR, partial response; PVT, portal vein thrombosis; SD, stable disease; TACE, transarterial chemoembolization
Raoul J-L et al. Cancer Treat Rev 2011;37:212–20

AISF algoritm za TACE (2013)





AISF, Italian Association for the Study of the Liver
AISF. Dig Liver Dis 2013 (In press)

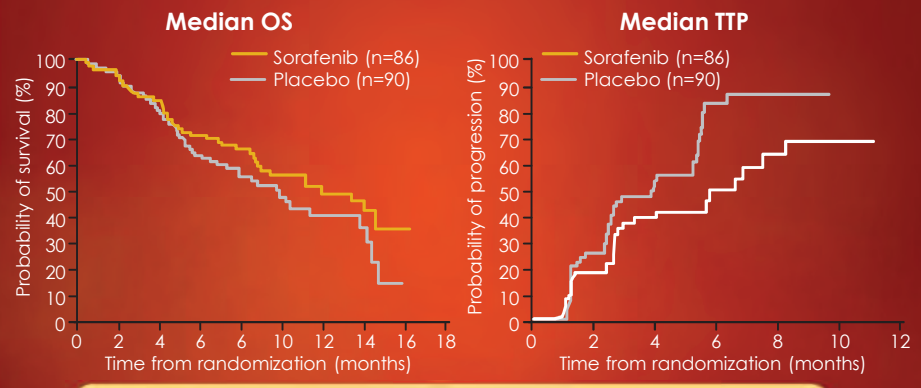
ART točkovnik -Assessment for Retreatment with TACE

- Developed by multivariate regression analysis of
  - baseline characteristics
  - radiological response after 1st TACE (EASL-response criteria)
  - changes of liver function after the 1st TACE
- Determined prior to 2nd TACE in BCLC-A*/B patients, who received ≥ 2x TACE
- Training cohort: n=107 (Vienna), validation cohort: n=115 (Innsbruck)

ART score category	Points	
Absence of radiological tumour response	1	(0 if present)
AST increase >25%	4	(0 if absent)
Increase in CP score by 1 point	1.5	(0 if absent)
Increase in CP score by ≥2 points	3	(0 if absent)

*BCLC-A not suitable for liver transplantation/local ablative treatment
AST, aspartate transaminase; BCLC, Barcelona Clinic Liver Cancer; CP, Child–Pugh; EASL, European Association for the Study of the Liver; TACE, transarterial chemoembolization
Sieghart W et al. Hepatology 2013 Jan 12. doi: 10.1002/hep.26256

Učinkovitost sorafeniba pri bolnikih po TACE



Sorafenib: n=86; placebo: n=90
Median OS: 11.9 vs 9.9 months (HR: 0.75; CI: 0.49–1.14)
Median TTP: 5.8 vs 4.0 months (HR: 0.57; CI: 0.36–0.91)

HR, hazard ratio; OS, overall survival; TTP, time to progression; TACE, transarterial chemoembolization
Bruix J et al. J Hepatol. 2012;57:821–9.

Sorafenib pri bolnikih neprimernih za TACE oz refraktornih na TACE

Intermediaren HCC je zelo raznolika skupina bolnikov

↓

Že izhodiščno niso vsi bolniki primerni za TACE

↓

Bolniku ponudimo naslednjo možno zdravljenje za isti stadij oz nasleden stadij po BCLC ali nasleden prognostičen stadij

↓

Učinkovitost sorafenib pri BCLC-B bolnikih, ki so neprimerni za TACE ali TACE refraktorni (brez odgovora po 2 TACE)

Odločitev o zdravljenju temelji na RR in ART točkovniku

Bolniki z radiološkim odgovorjem na zdravljenje na TACE glede na mRECIST/EASL živijo dalj

↓

Pri vsaki TACE obstaja tveganje za jetrno počkodbo, ki lahko vpliva na prognozo

↓

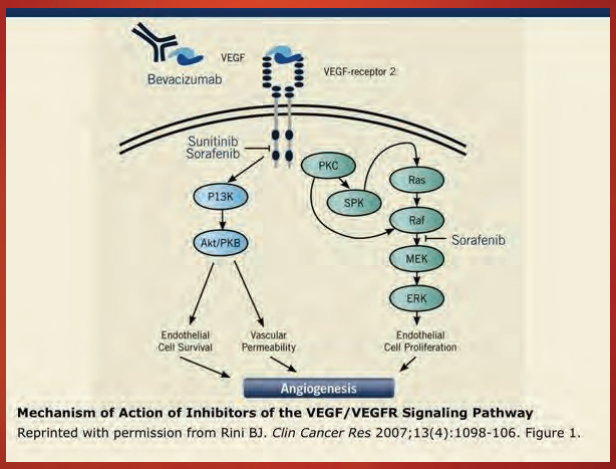
Vrednost ≥2.5 točk po ART točkovniku označuje bolnike, ki zelo verjetno ne bodo imeli dobrobita od naslednje TACE

↓

Sorafenib priporočajo za:

- bolnike z poslabšanjem jetrne funkcije ali pomembnimi NU po 1. TACE
- Progres ali mirovanje bolezni po 2. TACE
- delnem odgovoru po 2 TACE

Sorafenib – mehanizem delovanja



Mechanism of Action of Inhibitors of the VEGF/VEGFR Signaling Pathway
Reprinted with permission from Rini BJ. *Clin Cancer Res* 2007;13(4):1098-106. Figure 1.

SHARP faza III: Sorafenib vs placebo pri napredovalem HCC

Vključitveni kriteriji
- napredoval HCC
- Child–Pugh A status
- ECOG PS 0–2
- Pričakovano preživetje ≥12 mesecev
- Neprimerni ali odpoved lokoregionalnega zdravljenja

Stratifikacija po
- ECOG PS
- Obsežnost tumourja
- Geografska regija

Randomizacija
- 1:1 (n~602)

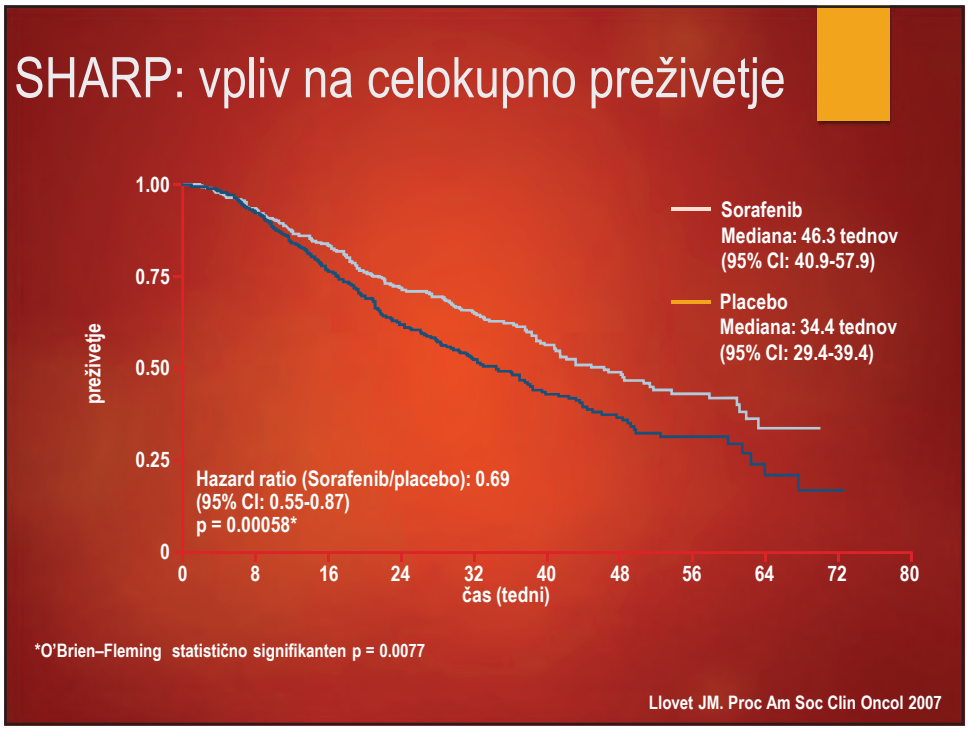
Sorafenib 400 mg b.i.d.

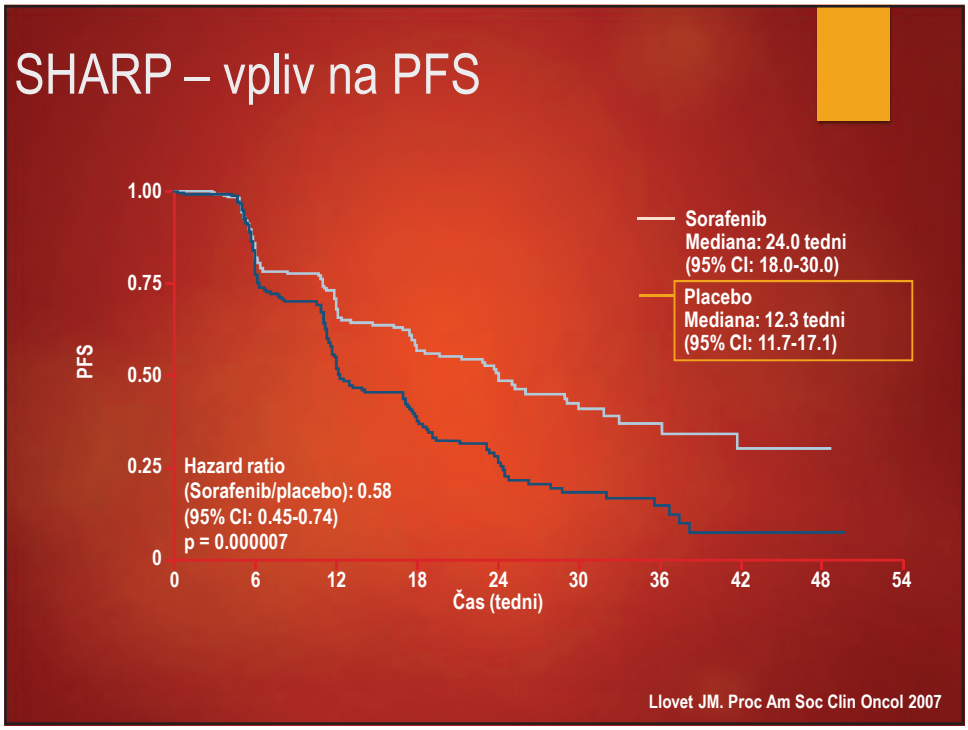
Placebo

Primarni cilj
- OS
- TTSP

Sekundarni cilj
- TTP
- Nadzor bolezni (OR + SD)

- **Zdravljenje do radiografskega ali simptomatskega progresa ali neželenih učinkov, ki so vodili v prekinitev zdravljenja**
- **Cikel zdravljenja – 6 tednov**


SHARP: vpliv na celokupno preživetje
1.00
0.75
0.50
0.25
0
preživetje
Sorafenib
Mediana: 46.3 tednov
(95% CI: 40.9-57.9)
Placebo
Mediana: 34.4 tednov
(95% CI: 29.4-39.4)
Hazard ratio (Sorafenib/placebo): 0.69
(95% CI: 0.55-0.87)
p = 0.00058*
0 8 16 24 32 40 48 56 64 72 80
čas (tedni)
*O'Brien–Fleming statistično signifikanten p = 0.0077
Llovet JM. Proc Am Soc Clin Oncol 2007


SHARP – vpliv na PFS
1.00
0.75
0.50
0.25
0
PFS
Sorafenib
Mediana: 24.0 tedni
(95% CI: 18.0-30.0)
Placebo
Mediana: 12.3 tedni
(95% CI: 11.7-17.1)
Hazard ratio
(Sorafenib/placebo): 0.58
(95% CI: 0.45-0.74)
p = 0.000007
0 6 12 18 24 30 36 42 48 54
Čas (tedni)
Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP - odgovor na zdravljenje

	Sorafenib N = 299	Placebo N = 303
	n (%)	n (%)
Celokupni odgovor		
popoln odg. (CR)	0	0
delni odg. (PR)	7 (2.3)	2 (0.7)
Mirovanje bolezni (SD)	211 (71)	204 (67)
Progres (PD)	54 (18)	73 (24)
Ni bilo določeno	27 (9)	24 (8)
Kontrola bolezni (DCR)**	130 (44)	96 (32)

**DCR = CR + PR + SD vsaj 28 dni od prve evidence

Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP - varnost

	Sorafenib N = 297	Placebo N = 302
Resni neželeni učinki (%)	52	54
Resni neželeni učinki zaradi zdravila (%)	13	9
Neželeni učinki, ki so vodili v ukinitev zdravljenja (%)	32	35

Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP – neželeni učinki

	Sorafenib N = 297		Placebo N = 302	
Neželeni učinki	Vsi (%)	3/4 (%)	vsi (%)	3/4 (%)
Kateri koli	98	39/6	94	24/8
Diareja	55	10/<1	25	2
Bolečina (abdomen)	31	9	26	5/1
Izguba teže	30	2	10	1
Anoreksija	29	3	18	3/<1
Bruhanje	24	1	20	3
Sindrom roka - noga	21	8	3	<1
Izpuščaj	19	1	14	0
Slabost	15	2	11	2
Alopecija	14	0	2	0
Srbečica	14	<1	11	<1
Zaprtje	14	0	10	0
Suha koža	10	0	6	0

Llovet JM. Proc Am Soc Clin Oncol 2007

Sorafenib pri HCC

- Do Sorafeniba je bilo sistemsko zdravljenje HCC skoraj neučinkovito.
- Rezultati SHARP kažejo, da Sorafenib vpliva na preživetje napredovalega, neresektabilnega HCC.
- Sorafenib je prvo učinkovito sistemsko zdravljenje, napredovalega neresektabilnega HCC
- Adjuvanto (post-resekcijsko ali post-ablativno zdr.) v fazi raziskovanja

Rezultati SHARP in vsakodnevne uporabe sorafeniba pri intermediarnem HCC

SHARP[1] BCLC-B subgroup	• **Increased OS and TTP with sorafenib (n=54) vs placebo (n=51)** – Median OS: 14.5 vs 11.4 months (HR: 0.72; 95% CI: 0.38–1.38) – Median TTP: 6.9 vs 4.4 months (HR: 0.47; 95% CI: 0.23–0.96)
SHARP[1] previous TACE subgroup	• **Increased OS and TTP with sorafenib (n=86) vs placebo (n=90)** – Median OS: 11.9 vs 9.9 months (HR: 0.75; 95% CI: 0.49–1.14) – Median TTP: 5.8 vs 4.0 months (HR: 0.57; 95% CI: 0.36–0.91)
SOFIA[2]	• **Good efficacy demonstrated in BCLC-B HCC** – Longer survival in BCLC-B vs BCLC-C patients: 20.6 vs 8.4 months
INSIGHT[3]	• **Good efficacy demonstrated in BCLC-B HCC** – Longer survival in BCLC-B vs BCLC-C patients: 19.6 vs 14.5 months
GIDEON interim analysis[4]	• **Similar safety profile for sorafenib across BCLC stages**

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; TTP, time to progression

1. Bruix J et al. J Hepatol. 2012;57:821–9; 2. Iavarone M et al. Hepatology 2011;54:2055–63; 3. Ganten TM et al. EMSO 2012;poster 77;
4. Lencioni R et al. Eur J Cancer 2011;47 (Suppl 1):abstract 6500

TACE - NOVOSTI

- Two Trials of TACE + systemic therapy
  - TACTICS by Kudo, et al
  - OPTIMIS by Peck-Radosavljevic, et al
- Two trials of systemic therapy alone
  - Keynote-224 by Zhu et al
  - Celestial by Abou-Alfa et al

Presented By Jordan Berlin at 2018 ASCO Annual Meeting

TACE – Novosti: Sorafenib + TACE

Study objective (TACTICS: Abstract 4017 – Kudo M, et al)

- **Primerjava učinkovitosti in varnosti sorafenib ± TACE pri bolnikih s HCC**

Study design

- Patients (n=156) were randomised (1:1) to receive sorafenib 400 mg/day with TACE (n=80) or TACE alone (n=76)

Key results

- The maturity of OS results was 73.6%

	Sorafenib + TACE (n=80)	TACE (n=76)	HR (95%CI)	p-value
Median PFS, months	25.2	13.5	0.59 (0.41, 0.87)	0.006

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

TACE - Novosti

Study objective (Global OPTIMIS: Abstract 4018 – Peck-Radosavljevic M, et al)

- **Evaluacija končnih izidov zdravljenja z TACE pri bolnikih s HCC**

Study design

- In this observational study, patients (n=507) who were eligible for TACE at baseline, eventually progressed to TACE ineligibility after ≥1 TACE and received/did not receive sorafenib upon ineligibility

REZULTATI

- OS je bil 16.2 vs.12.1 mesecev pri tistih, ki so jemali sorafenib potem, ko niso bili vec za TACE vs. tistih, ki niso
- Neustrezna uporaba TACE: 39% (>600) bolnikov niso bili primerni za TACE v času zdravljenja z TACE – 7% zaradi PVT in 7% zaradi EHS
- Pri 11% in 29% bolnikov je prišlo do deterioracije ravni bilirubina in albumina

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

TACE – Novosti
ZAKLJUČEK

- **TACE se prekomerno uporablja. Je skupina, pri kateri sorafenib je boljša izbira.**
- **Po TACE, Sorafenib lahko izboljša tumorsko kontrolo, brez vpliva na OS**

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

Lenvatinib – multikinazni zaviralec

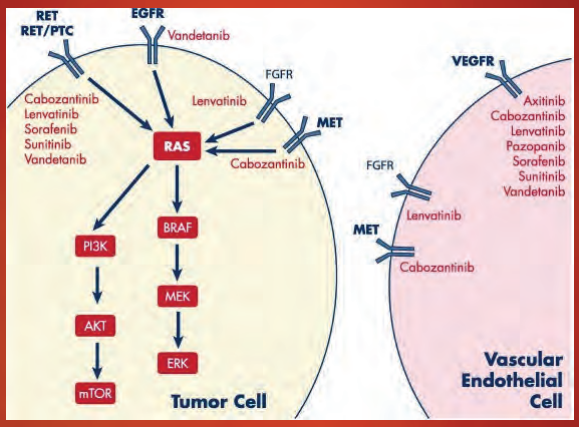
Lenvatinib: A New Option in HCC

- Oral, multitargeted inhibitor of:
  - VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4)
  - FGFR1, 2, 3, and 4
  - PDGFRα, KIT, and RET
- Approved for recurrent or metastatic iodine-refractory thyroid cancer and in renal cell carcinoma in combination with everolimus following prior antiangiogenic therapy

i3Health

Lenvima® prescribing information, 2017.

Lenvatinib – mehanizem delovanja



Lenvatinib: Role in thyroid cancer and other solid tumors; Maria E.CabanillasMouhammed AmirHabra. Cancer Treatment reviews. Volume 42, January 2016, Pages 47-55

REFLECT študija

REFLECT Phase III: Lenvatinib vs Sorafenib as First-Line Therapy

Eligibility
- Unresectable HCC with no prior treatment
- ECOG PS 0 or 1
- BCLC stage B or C
- Child-Pugh A
- Age ≥18 years

Study Design
- Open-label, randomized NI study
- Primary end point: OS
- Secondary end points: PFS, TTP

RANDOMIZE

Lenvatinib 8 or 12 mg daily based on body weight; 8 mg for <60 kg (n=478)

954 pts randomly assigned 1:1 to detect NI in OS

Sorafenib 400 mg twice daily (n=476)

NI = noninferiority; PFS = progression-free survival.
Cheng et al, 2017.

REFLECT - rezultati

REFLECT: Outcomes

Outcomes	Lenvatinib	Sorafenib	HR
Median OS, mo (95% CI)	13.6 (12.1-14.9)	12.3 (10.4-13.9)	0.92 (0.79-1.06)
Median PFS, mo (95% CI)	7.4 (6.9-8.8)	3.7 (3.6-4.6)	0.66 (0.57-0.77)
Median TTP, mo (95% CI)	8.9 (7.4-9.2)	3.7 (3.6-5.4)	0.63 (0.53-0.73)
ORR, n (%)	115 (24%)	44 (9%)	

ORR = overall response rate.
Cheng et al, 2017.

i3Health

REFLECT - AEF

REFLECT: Treatment-Emergent AEs

- Grade 3 and higher events were more common in the lenvatinib arm (57% vs 49%)
- Most common AEs in the lenvatinib arm:
  - Hypertension (42% overall with 23% grade ≥3)
  - Diarrhea (39%)
  - Decreased appetite (34%)
  - Weight loss (31% with 8% grade ≥3)
  - Fatigue (30%)
- Grade 3 HFSR was more common in the sorafenib arm (11% vs 3%)

Cheng et al, 2017.

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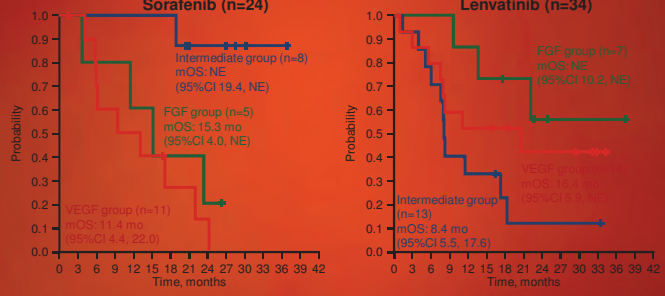
Analiza serumskih biomarkerjev - lenvatinib (LEN) vs sorafenib (SOR) v prvem redu zdravljenja neresektabilnega HCC

ITT population	Lenvatinib	Sorafenib	HR (95%CI)
mOS, months (95%CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)	0.92 (0.79, 1.06)

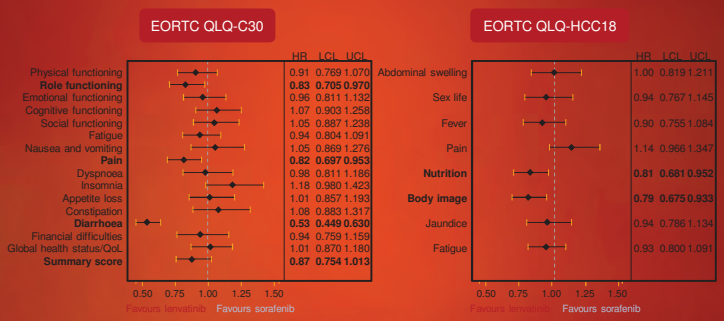
OS by groups identified in the angiogenic and growth factor signature*



*A cluster analysis using expression levels of 38 genes involved in VEGF, FGF and angiopoietin signaling identified 3 groups: (1) VEGF enriched, (2) FGF enriched, (3) FGF/VEGF intermediate

Finn RS, et al. Ann Oncol 2017;28(Suppl 5):Abstr LBA30

Kvaliteta življenja (HRQOL) in kontrola simptomov bolezni - lenvatinib (LEN) vs sorafenib (SOR) v prvem redu zdravljenja neresektabilnega HCC



Vogel A, et al. Ann Oncol 2017;28(Suppl 5):Abstr 6180

ZAKLJUČKI

Prva uspešna študija faze 3 v zadnjih 10 let za prvi red zdravljenja neresektabilnega HCC

Lenvatinib ni inferioren v primerjavi s sorafenibom

Za sorafenib enako, kot za lenvatinib, sta se VEGF in FGF21 izkazala, kot potencijalna prognostična faktorja

V roki, ki je prejemala lenvatinib, boljši OS je bil opazen v skupini z višjo izrazenostjo VEGF in FGF genov

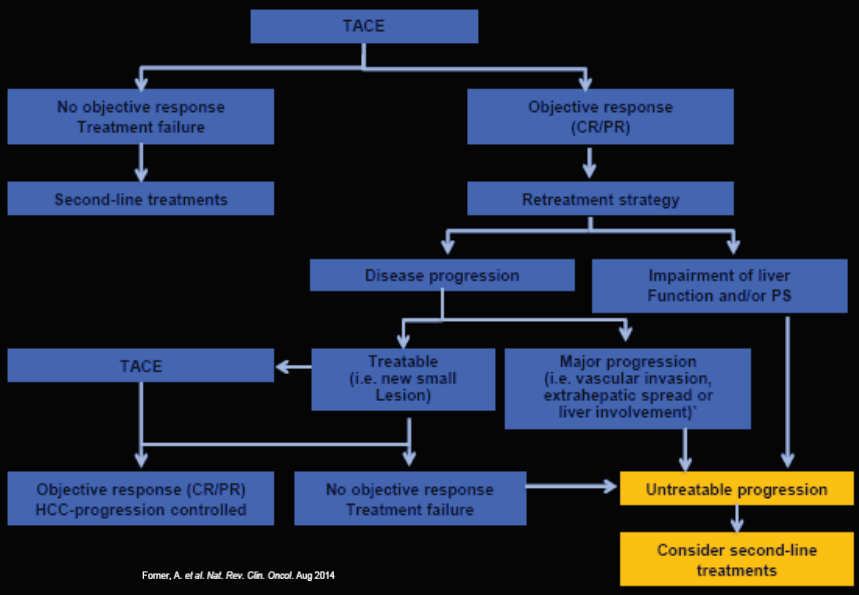
Malo število bolnikov

Kvaliteta življenja ob zdravljenju je upadla ne glede na izbiro zdravila in je bila primerljiva - lenvatinib ali sorafenib

Nekoliko daljši čas do upada organskih funkcij, bolečine, dijareje in nutricije kar se tiče lenvatiniba

Finn RS, et al. Ann Oncol 2017;28(Suppl 5):Abstr LBA30. Vogel A, et al. Ann Oncol 2017;28(Suppl 5):Abstr 6180

The Untreatable Progression Concept



Forner, A. *et al. Nat. Rev. Clin. Oncol.* Aug 2014

RESORCE Trial Design

Clinicaltrials.gov NCT01774344

- HCC patients with documented radiological progression during sorafenib treatment
- Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)

R 2:1

Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

N= 573

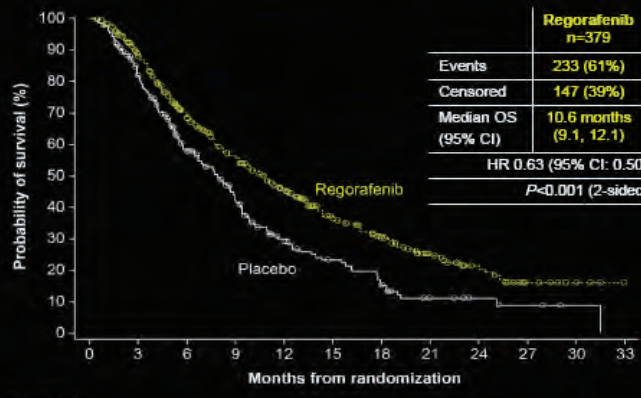
Placebo
(n=194)

- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

ROW, rest of the world; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein

Presented at: 2016 World Congress on GI Cancer; June 28 - July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Regorafenib vs Placebo in Second Line Overall Survival (OS)



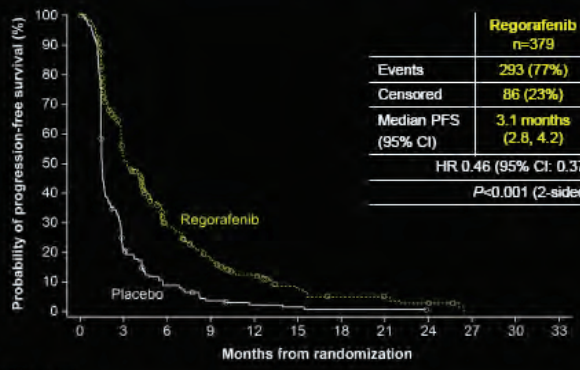
	Regorafenib n=379	Placebo n=194
Events	233 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.63 (95% CI: 0.50, 0.79)		
P<0.001 (2-sided)		

Number at risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

Presented at: 2016 World Congress on GI Cancer; June 28 - July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Progression-free Survival (PFS)



	Regorafenib n=379	Placebo n=194
Events	293 (77%)	181 (93%)
Censored	86 (23%)	13 (7%)
Median PFS (95% CI)	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
HR 0.46 (95% CI: 0.37, 0.56)		
P<0.001 (2-sided)		

Number at risk

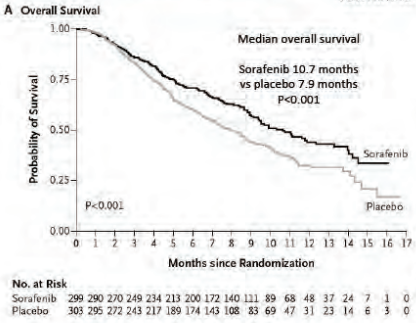
Regorafenib	379	166	76	43	27	14	8	7	4	0	0	0
Placebo	194	37	15	6	3	2	1	1	0	0	0	0

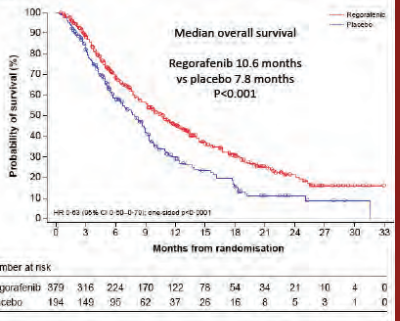
Based on mRECIST

Presented at: 2016 World Congress on GI Cancer; June 28 - July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Sorafenib and regorafenib in advanved HCC

Sorafenib in first line → Progression → Tolerant to sorafenib → Regorafenib in second line





Llovet J, et al. NEJM 2008

Bruix J, et al. Lancet 2016

Key Takeaways

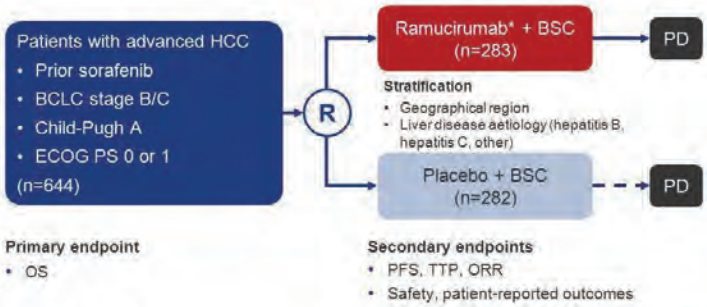
- Sorafenib and regorafenib are the only agents approved for advanced HCC
  - Both are multikinase inhibitors with prominent antiangiogenic effects
  - Sorafenib is approved for first-line treatment
  - Regorafenib is approved for second-line treatment after sorafenib failure or intolerance
- In a head-to-head phase III trial, lenvatinib was shown to be noninferior to sorafenib and may be considered an alternative to sorafenib, particularly in patients with intolerance
- Important to recognize the class-wide side effects of these agents (eg, hand-foot skin reaction, hypertension, diarrhea, weight loss) and employ timely interventions to optimize treatment outcomes

i3Health

REACH – Ramucirumab v drugem redu zdravljenja HCC

LBA16: Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC) following first-line therapy with sorafenib: Results from the randomized phase III REACH study – Zhu A et al.

- **Study objective**
  - To assess the efficacy and safety of ramucirumab after first-line treatment with sorafenib in patients with advanced HCC



Primary endpoint
- OS

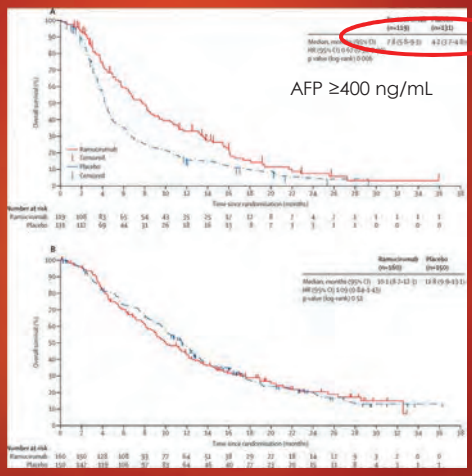
Secondary endpoints
- PFS, TTP, ORR
- Safety, patient-reported outcomes

*8mg/kg, q2w per cycle

Zhu et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA16

Rezultati

- Ramucirumab v drugem redu zdravljenja HCC ni izkazal izboljšanja OS. Opazen je bil učinek na PFS, TTP in ORR.
- RAZEN:



Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial Andrew X Zhu, Joon Oh Park, Baek-Yeol Ryoo, Chia-Jui Yen, Ronnie Poon, Davide Pastorelli,et al. Lancet Oncol 2015; 16: 859–70.

REACH-2: Randomizirana, dvojno slepa placebo – kontrolirana študija faze 3 ramucirumab versus placebo v drugem redu zdravljenja napredovalega HCC in povišanim alfa-fetoproteinom (AFP) po prvem redu zdravljenja s sorafenibom

Study objective

- To assess the benefit of ramucirumab in patients with HCC and baseline AFP ≥400 ng/mL in the REACH-2 study

Key patient inclusion criteria
- HCC with BCLC stage C or B, refractory or unamenable to locoregional therapy
- Prior sorafenib
- Child-Pugh A
- Baseline AFP ≥400 ng/mL
- ECOG PS 0–1

(n=292)

R 2:1

Ramucirumab 8 mg/kg iv q2w + BSC (n=197) → PD/ toxicity

Placebo + BSC (n=95) → PD/ toxicity

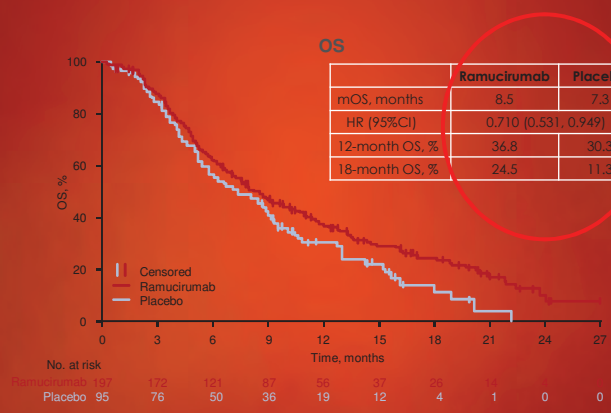
Stratification
- Macrovascular invasion (yes vs. no)
- ECOG PS (0 vs. 1)
- Geographic region (Americas, Europe, Australia vs. Asia [except Japan] vs. Japan)

PRIMARY ENDPOINT
- OS

SECONDARY ENDPOINTS
- PFS, TTP, ORR, safety

Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4003

REACH-2: Randomizirana, dvojno slepa placebo – kontrolirana študija faze 3 ramucirumab versus placebo v drugem redu zdravljenja napredovalega HCC in povišanim alfa-fetoproteinom (AFP) po prvem redu zdravljenja s sorafenibom



OS

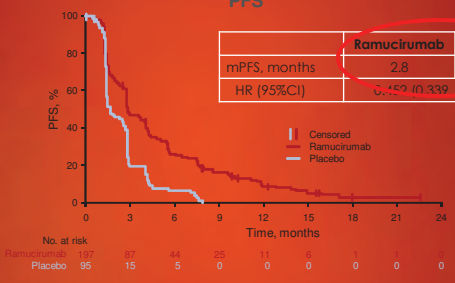
	Ramucirumab	Placebo	p-value
mOS, months	8.5	7.3	-
HR (95%CI)	0.710 (0.531, 0.949)		0.0199
12-month OS, %	36.8	30.3	0.293
18-month OS, %	24.5	11.3	0.0187

Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4003

REACH-2: Randomizirana, dvojno slepa placebo – kontrolirana študija faze 3 ramucirumab versus placebo v drugem redu zdravljenja napredovalega HCC in povišanim alfa-fetoproteinom (AFP) po prvem redu zdravljenja s sorafenibom

PFS

	Ramucirumab	Placebo	p-value
mPFS, months	2.8	1.6	-
HR (95%CI)	0.452 (0.339, 0.603)		<0.0001



	Ramucirumab (n=197)	Placebo (n=95)	p-value
ORR, n (%) [95%CI]	9 (4.6) [1.7, 7.5]	1 (1.1) [0.0, 3.1]	0.1697
DCR	118 (59.9) [53.1, 66.7]	37 (38.9) [29.1, 48.8]	0.0006

Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4003

REACH-2: Randomizirana, dvojno slepa placebo – kontrolirana študija faze 3 ramucirumab versus placebo v drugem redu zdravljenja napredovalega HCC in povišanim alfa-fetoproteinom (AFP) po prvem redu zdravljenja s sorafenibom

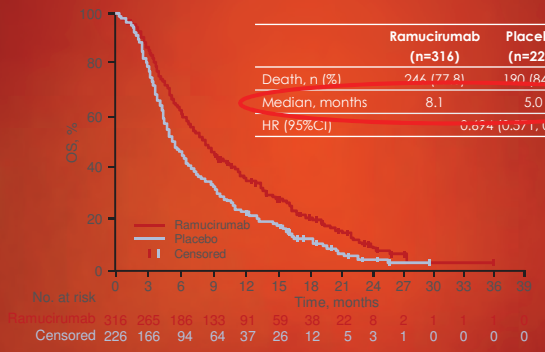
TRAE, n (%)	Ramucirumab (n=197)	Placebo (n=95)
Discontinuation due to TRAE	21 (10.7)	3 (3.2)
Dose adjustment due to AE	68 (34.5)	13 (13.7)
Deaths due to TRAE	3 (1.5)	0
≥1 TRAE in ≥15% patients in ramucirumab arm		
Any grade	191 (97.0)	82 (86.3)
Grade ≥3	116 (58.9)	42 (44.2)

Zaključki

- **Ramucirumab je pokazal značilni učinek v smislu OS vs. Placebo pri bolnikih z HCC in AFP ≥400 ng/mL po PD ali intoleranci na sorafenib**
  - **Klinično značilen učinek tudi glede PFS in DCR**
- **Ramucirumab se dobro prenaša**
- **REACH-2 je prva pozitivna študija z značilnim učinkom na OS pri bolnikih s slabo prognozo - HCC + AFP ≥400 ng/mL**

Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4003

Izpeljana Analiza - REACH-2 in REACH UČINKOVITOST



	Ramucirumab (n=316)	Placebo (n=226)	Difference	p-value
Death, n (%)	246 (77.8)	190 (84.1)		
Median, months	8.1	5.0	3.1	
HR (95%CI)	0.674 (0.571, 0.842)			0.0002

No heterogeneity in treatment effect observed across both studies

A random effect Wald model after adjusting for study (as random effect) produced a similar treatment result (HR 0.680; p=0.0002)

Zhu A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-001

Izpeljana Analiza - REACH-2 in REACH
UČINKOVITOST

	Ramucirumab (n=316)	Placebo (n=226)	p-value
PFS			
Median, months	2.8	1.5	
HR (95%CI)	0.572 (0.472, 0.694)		<0.0001
ORR, n (%) [95%CI]	17 (5.4) [2.9, 7.9]	2 (0.9) [0.0, 2.1]	0.0064
DCR, n (%) [95%CI]	178 (56.3) [50.9, 61.8]	84 (37.2) [30.9, 43.5]	<0.001

Zhu A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-001

Izpeljana Analiza - REACH-2 in REACH
VARNOST

Grade >3 AEs of special interest occurring in ≥3% of patients, n (%)	Ramucirumab (n=316)	Placebo (n=223)
Liver injury/failure	63 (19.9)	59 (26.5)
Ascites	15 (4.7)	9 (4.0)
Bleeding/haemorrhage events	15 (4.7)	15 (6.7)
GI haemorrhage events	11 (3.5)	12 (5.4)
Hypertension	40 (12.7)	8 (3.6)

ZAKLJUČKI

- **Bolniki z napredovalim HCC in AFP ≥400 ng/mL, ramucirumab podaljša OS vs. placebo**
- **Ramucirumab ima varnosni profil v konzistenci z ostalimi študijami z ramucirumabom in ga bolniki dobro prenašajo**
- **Pri bolnikih s HCC in povišanim AFP po sorafenibu v prvem redu zdravljenja, je ramucirumab nova potencijalno učinkovita opcija zdravljenja**

Zhu A, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-001

Cabozantinib (C) versus placebo (P) pri bolnikih z napredovalim HCC po sorafenibu: randomizirana študija faze 3 - CELESTIAL študija

Study objective

- To assess the efficacy and safety of cabozantinib vs. placebo in patients with advanced HCC after prior systemic therapy

Key patient inclusion criteria
- Advanced HCC
- Child-Pugh score A
- Received prior sorafenib
- Progressed after ≥1 prior systemic treatment for HCC
- Received ≤2 prior systemic regimens for advanced HCC
- ECOG PS 0–1

(n=760)

R 2:1

Cabozantinib 60 mg/day (n=470) → Loss of clinical benefit/ toxicity

Placebo (n=237) → Loss of clinical benefit/ toxicity

Stratification
- Disease aetiology (HBV, HCV, other)
- Geographic region (Asia, other)
- Presence of extrahepatic spread and/or macrovascular invasion (EHS/MVI)

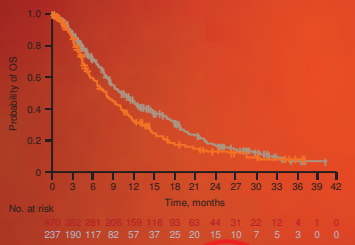
PRIMARY ENDPOINT
- OS

SECONDARY ENDPOINTS
- PFS, ORR

Abou-Alfa G, et al. J Clin Oncol 2018;36(Suppl 4S):Abstr 207

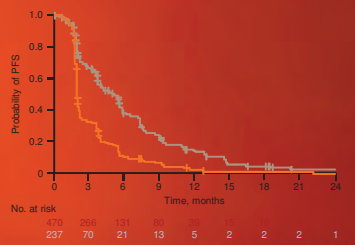
Odgovor na zdravljenje - CELESTIAL študija

OS and PFS



	mOS, months (95%CI)	No. of deaths
Cabozantinib (n=470)	10.2 (9.1, 12.0)	317
Placebo (n=237)	8.0 (6.8, 9.4)	167

HR 0.76 (95%CI 0.63, 0.92); p=0.0049*



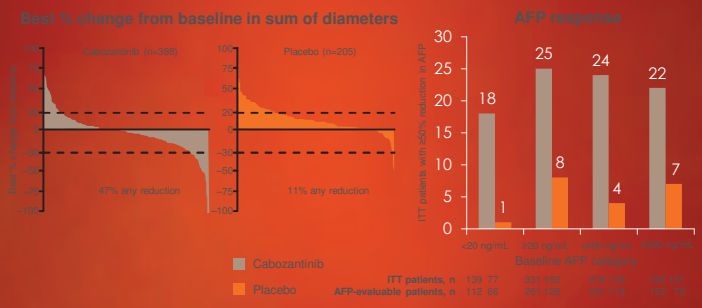
	mPFS, months (95%CI)	No. of deaths
Cabozantinib (n=470)	5.2 (4.0, 5.5)	349
Placebo (n=237)	1.9 (1.9, 1.9)	205

HR 0.44 (95%CI 0.36, 0.52); p<0.0001

*Critical p-value ≤0.021 for second interim analysis

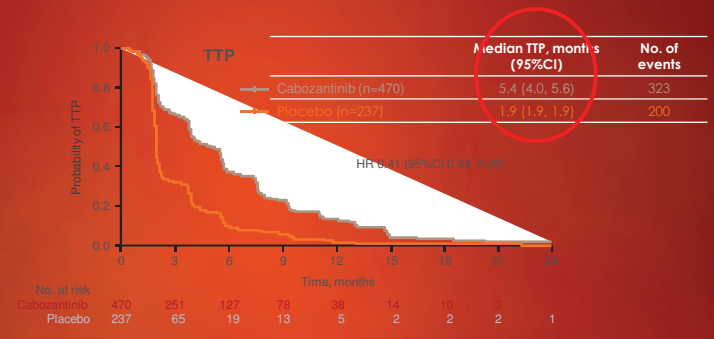
Abou-Alfa G, et al. J Clin Oncol 2018;36(Suppl 4S):Abstr 207

Evaluacija tumorskega odgovora, AFP ter TTP – CELESTIAL študija



Merle P, et al. Ann Oncol 2018;29(suppl 5):abstr O-011

Evaluacija tumorskega odgovora, AFP ter TTP – CELESTIAL študija



	Median TTP, months (95%CI)	No. of events
Cabozantinib (n=470)	5.4 (4.0, 5.6)	323
Placebo (n=237)	1.9 (1.9, 1.9)	200

- Zmanjšanje odmerka - 62% in 13% (cabozantinib vs placebo)
- Prekinitev zaradi TRAEs -16% in 3% (cabozantinib vs placebo)

Merle P, et al. Ann Oncol 2018;29(suppl 5):abstr O-011

STRANSKI UČINKI - CELESTIAL študija

	Cabozantinib (n=467)	Placebo (n=237)
Median duration of exposure, months (range)	3.8 (0.1–37.3)	2.0 (0–27.2)
Median average daily dose, mg	35.8	58.9
Any dose reduction, %	62	13
Discontinuation due to TRAEs, %	16	3
Grade 3/4 AEs, %	**Cabozantinib (n=467)**	**Placebo (n=237)**
Any	68	36
Palmar-plantar erythrodysesthesia	17	0
Hypertension	16	2
AST increased	12	37
Fatigue	10	4
Diarrhoea	10	2
Asthenia	7	2
Decreased appetite	6	<1
Anaemia	4	5

Abou-Alfa G, et al. J Clin Oncol 2018;36(Suppl 4S):Abstr 207

ZAKLJUČKI – CELESTIAL študija

- **Pri bolnikih z napredovalim HCC, cabozantinib značilno podaljša OS, PFS and ORR po prvem redu zdravljenja s sorafenibom**
- **Varnosti profil cabozantiniba je bil sprejemljiv, stopnja prekinitve je bila nizka**
- **Cabozantinib je lahko nova opcija zdravljenja napredovalega HCC po prvem redu zdravljenja**

Abou-Alfa G, et al. J Clin Oncol 2018;36(Suppl 4S):Abstr 207

IMUNOTERAPIJA

Nivolumab in sorafenib-experienced patients with advanced hepatocellular carcinoma with or without chronic hepatitis: CheckMate 040 study

- Phase 1 / 2 using nivolumab 3 mg/kg every 2 weeks in patients with advanced HCC progressor or intolerant to sorafenib
- Primary endpoint: objective response rate

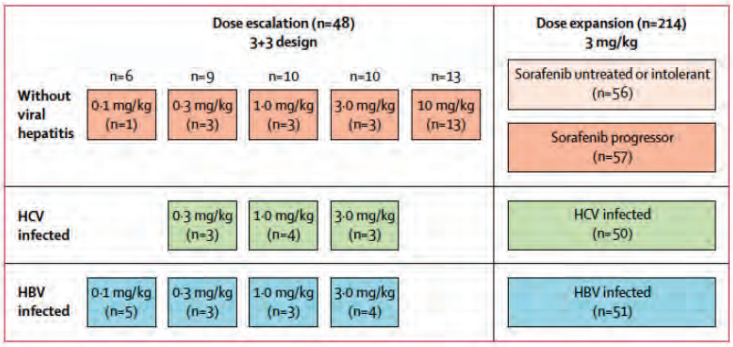
Inclusion criteria
Child Pugh A patient
Advanced HCC
Progression after 1 prior line of systemic therapy or intolerant to sorafenib

Exclusion criteria
Any history of hepatic encephalopathy
Prior or current clinically significant ascites

El Khoueiry AB, et al. Lancet 2017

IMUNOTERAPIJA

Nivolumab in sorafenib-experienced patients with advanced hepatocellular carcinoma with or without chronic hepatitis: CheckMate 040 study



El Khoueiry AB, et al. Lancet 2017

IMUNOTERAPIJA NIVOLUMAB

Nivolumab in HCC (CheckMate-040): Efficacy in Dose-Escalation Cohort

- No correlation between PD-L1 expression and response

Discontinued, n (%)	Uninfected (n = 23)	HCV (n = 10)	HBV (n = 15)	Total (N = 48)
Objective response	**3 (13)**	**3 (30)**	**1 (7)**	**7 (15)**
▪ CR	2 (9)	1 (10)	0	3 (6)
▪ PR	1 (4)	2 (20)	1 (7)	4 (8)
▪ SD	13 (57)	5 (50)	6 (40)	24 (50)
▪ PD	6 (26)	2 (20)	7 (47)	15 (31)
▪ Not evaluable	1 (4)	0	1 (7)	2 (4)
Ongoing response	1 (33)	0	0	1 (14)

El Khoueiry A, et al. ASCO 2016. Abstract 4012

Slide credit: clinicaloptions.com

Checkmate 040 : nivolumab pri napredovalem HCC ZAKLJUČKI

- Nivolumab 3 mg/kg vodi v objektivne odgovore pri 16% bolnikov po RECIST 1.1 (15% of PR and 1% of CR)
- Nadzor bolezni -68%
- Srednje preživetje 15 mesecev
- Sprejemljiv varnostni profil
- Randomizirane raziskave faze III – primerjava sorafeniba in nivolumaba pri napredovalem HCC (Checkmate 459)

El Khoueiry AB, et al. Lancet 2017

IMUNOTERAPIJA PEMBROLIZUMAB

Pembrolizumab (pembro) in Patients with Advanced Hepatocellular Carcinoma (HCC): KEYNOTE-224 Update

Andrew A. Zhu,[1] Richard S. Finn,[2] Josep Edeline,[3] Stephanie Cattan,[4] Isabelle Ogasawara,[5] Daniel Palmer,[6] Chris Verslype,[7] Vittorina Zagonel,[8] Laetitia Fartoux,[9] Ansh Vogel,[10] Debasish Sarker,[11] Gordon Verset,[12] Stephen L. Chan,[13] Jennifer Knox,[14] Bruno Daniele,[15] Andrea L. Webber,[16] Scot W. Ebbinghaus,[16] Junshui Ma,[16] Abby B. Siegel,[16] Ann-Lii Cheng,[17] Masatoshi Kudo[18]

Study Design

- Key eligibility criteria
  - ≥18 y
  - Pathologically confirmed HCC
  - Progression on or intolerance to sorafenib treatment
  - Child Pugh class A
  - ECOG PS 0-1
  - BCLC Stage C or B disease
  - Predicted life expectancy >3 mo

→ Pembrolizumab 200 mg Q3W for 2y or until PD, intolerable toxicity, withdrawal of consent or investigator decision → Survival follow-up

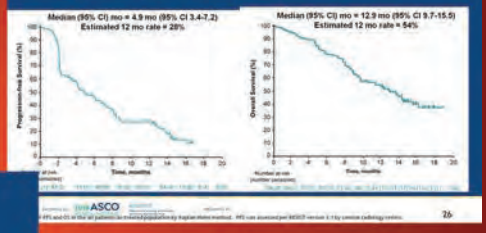
- Response assessed Q9W
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability

2018 ASCO

24

IMUNOTERAPIJA PEMBROLIZUMAB

Progression-free and overall survival



2018 ASCO

26

Response per RECIST version 1.1 by independent central review

	Total N=104
ORR, n (%, 95%CI)*	18 (17, 11-26)
BOR, n (%)†	
CR	1 (1)
PR	17 (16)
SD	46 (44)
PD	34 (33)
No assessment‡	6 (6)
DCR, n (%, 95%CI)§	64 (62, 52-71)
Median time to response, mo (IQR)¶	2.1 (2.1-4.1)
Median DOR, mo (range)¶‖	Not reached (3.1-14.6+)
Response duration ≥9 mo, n (%)¶‖	12 (77)

PDL-1 overexpressers may do better, but so may older women from the US

2018 ASCO

25

	Pembrolizumab (n=104)
Median OS, months (95%CI)	12.9 (9.7, 15.5)
Median PFS, months (95%CI)	4.9 (3.4, 7.2)
ORR, n (%)	18/104 (17)

Kudo M, et al. J Clin Oncol 2018;36(suppl):abstr 4017
Peck-Radosavljevic M, et al. J Clin Oncol 2018;36(suppl):abstr 4018
Abou-Alfa GK, et al. J Clin Oncol 2018;36(suppl):abstr 4019
Zhu AX, et al. J Clin Oncol 2018;36(suppl):abstr 4020

IMUNOTERAPIJA ZAKLJUČKI

Conclusions on pembro

- Pembrolizumab looks like nivolumab in HCC
  - RR 14.3% (N) vs 18% (P)
  - Both appear to have > 50% have response duration >12 months
- The reason we get excited about immune therapy is not the response rate
  - Frankly that is poor
  - But we like the tail of the curve
- PDL1 data do not eliminate a group of non-responders so become a minor predictive marker if accurate

2018 ASCO ANNUAL MEETING 27

HCC - DRUGI RED ZDRAVLJENJA

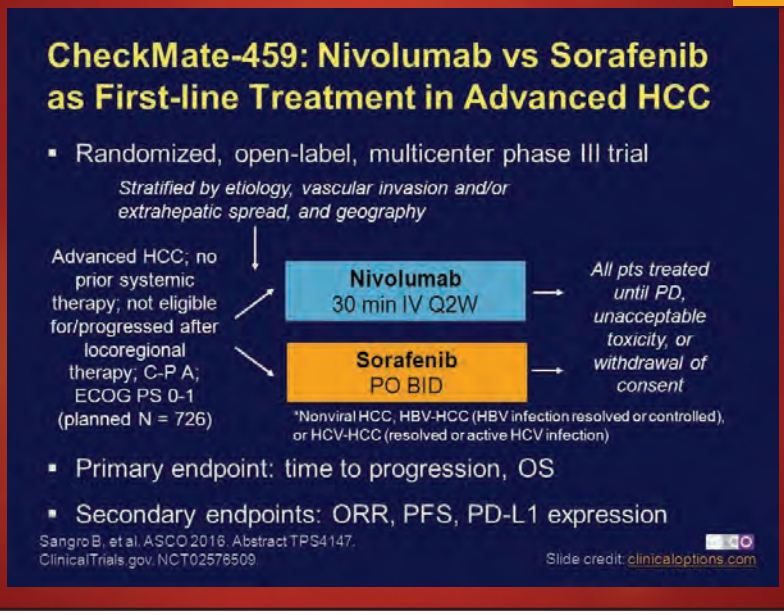
Landscape-Second line therapy for HCC

		Total N	PFS benefit	OS benefit	RR
CHECKMATE040 (SINGLE ARM)	Nivolumab*	154	NA	NA median OS +15 mo*	14%
RESOURCE	Regorafenib* v placebo	573 (2:1)	+1.6 mo HR 0·46 (0.37-0.56); p<0·0001	+2.8 mo HR 0.63 (0.50-0.79) p<0.0001)	11%
CELESTIAL**	Cabozantinib v placebo	707 (2:1)	+3.3 mo HR=0.44 [0.36-0.52]; P < 0.001	+2.2 mo HR=0.76 (0.63-0.92) P = 0.0049	4%
REACH1	Ramucirumab v placebo	565	+0.7mo HR 0.63 [0.52-0.75]; p<0.0001	NO	7%
REACH 2 (AFP≥400)	**Ramucirumab v placebo**	**292 (2:1)**	**+1.2 mo HR 0.452 (0.339, 0.603) p< 0.0001**	**+1.2 mo HR 0.71 (0.531, 0.949); p=0.0199**	**4.6%**
Pooled REACH 1 / 2 (AFP≥400 subgroup)	*Ramucirumab v placebo*	*542*	*NA*	*+3.1 mo HR 0.694 (0.571, 0.842) P=0.0002*	*NA*

2018 ASCO ANNUAL MEETING

*FDA approved
** included 2nd and 3rd line; 2nd line update: Kelley, et al. Abstr #4088 ASCO 2018

NIVOLUMAB vs SORAFENIB



HVALA

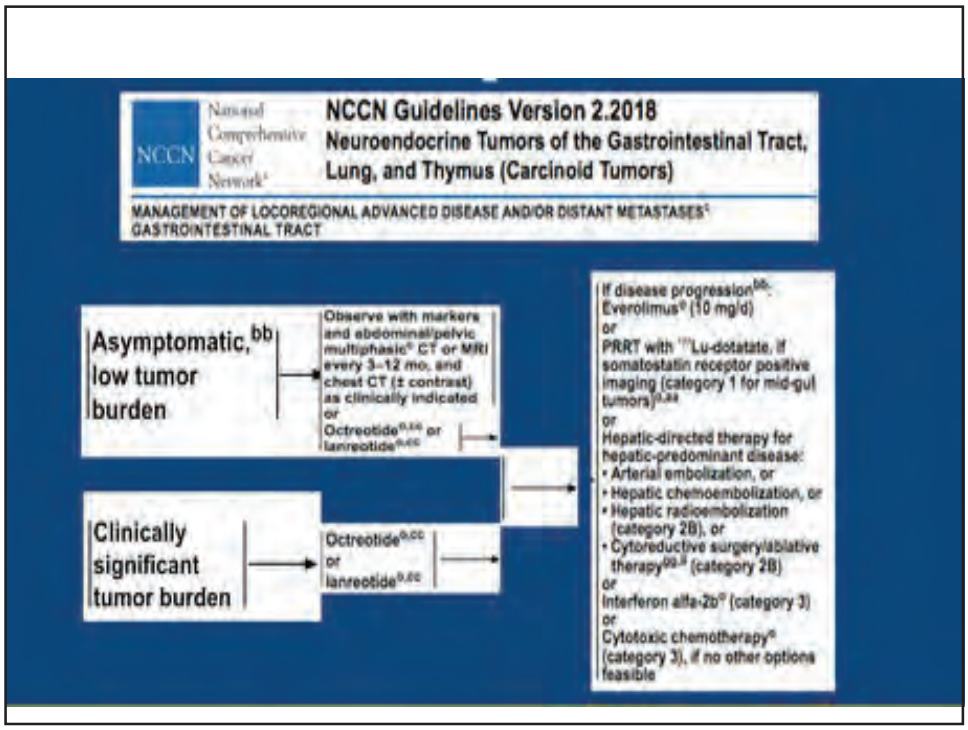
Novosti v zdravljenju napredovalih nevroendokrinih tumorjev po progresu

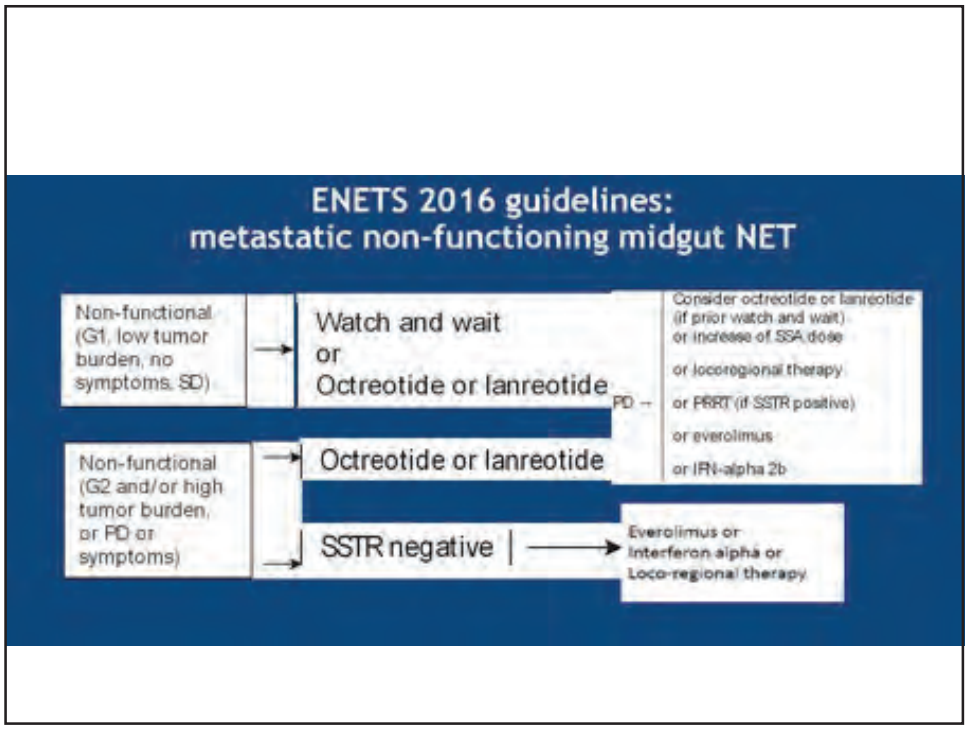
Janja Ocvirk

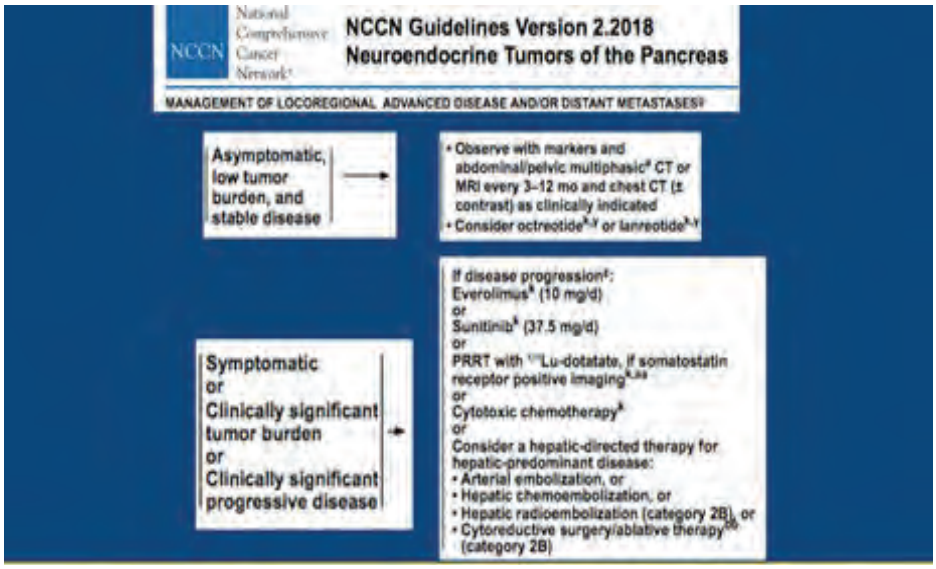
Ljubljana, 7.12.2018

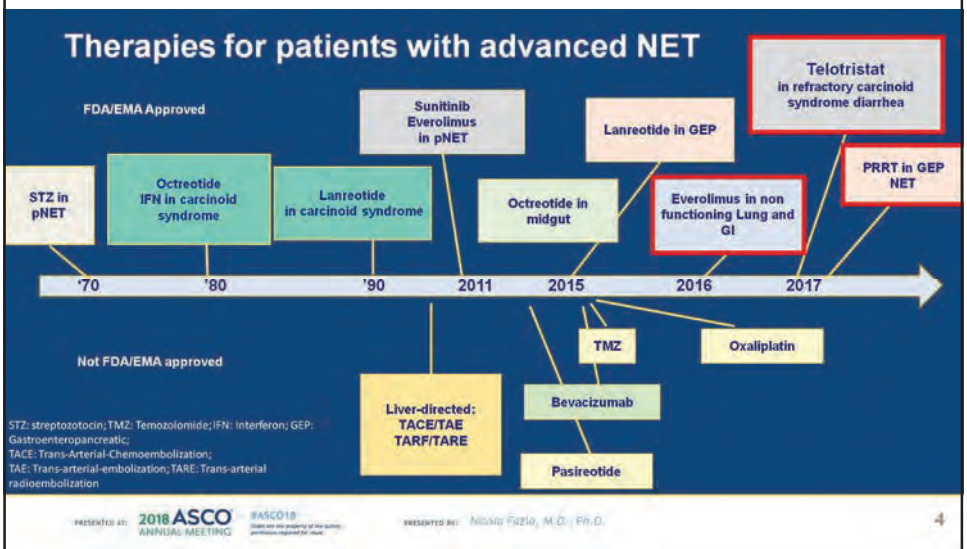
Zdravljenje napredovalega pan NET 2018

www.nccn.org

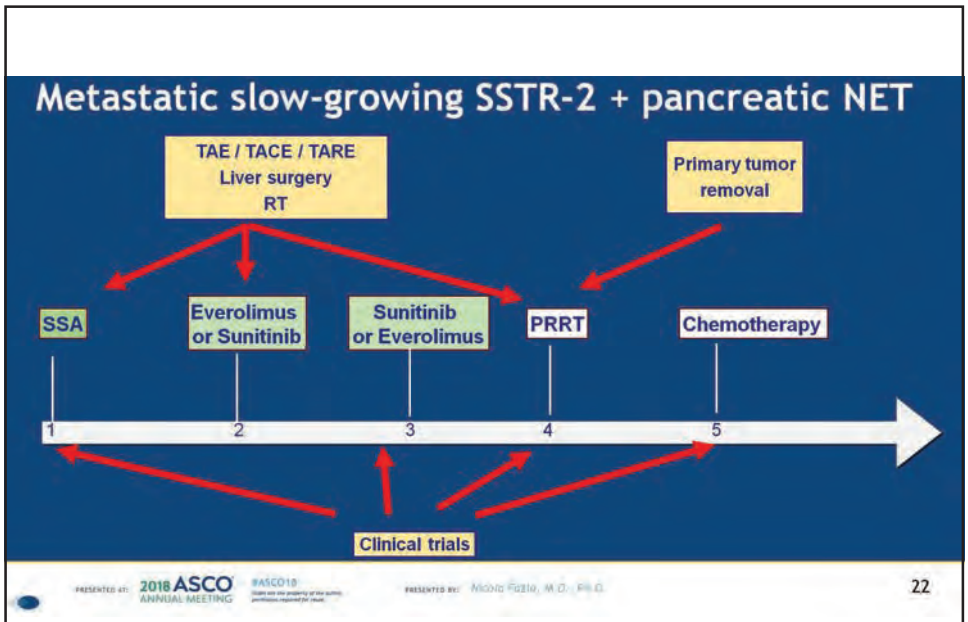

NCCN Guidelines Version 2.2018
Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)
MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES
GASTROINTESTINAL TRACT
Asymptomatic, low tumor burden
Observe with markers and abdominal/pelvic multiphasic CT or MRI every 3–12 mo, and chest CT (± contrast) as clinically indicated
or
Octreotide or lanreotide
Clinically significant tumor burden
Octreotide or lanreotide
If disease progression:
Everolimus (10 mg/d)
or
PRRT with Lu-dotatate, if somatostatin receptor positive imaging (category 1 for mid-gut tumors)
or
Hepatic-directed therapy for hepatic-predominant disease:
• Arterial embolization, or
• Hepatic chemoembolization, or
• Hepatic radioembolization (category 2B), or
• Cytoreductive surgery/ablative therapy (category 2B)
or
Interferon alfa-2b (category 3)
or
Cytotoxic chemotherapy (category 3), if no other options feasible


ENETS 2016 guidelines:
metastatic non-functioning midgut NET
Non-functional (G1, low tumor burden, no symptoms, SD)
Watch and wait
or
Octreotide or lanreotide
PD →
Consider octreotide or lanreotide (if prior watch and wait)
or increase of SSA dose
or locoregional therapy
or PRRT (if SSTR positive)
or everolimus
or IFN-alpha 2b
Non-functional (G2 and/or high tumor burden, or PD or symptoms)
Octreotide or lanreotide
SSTR negative
Everolimus or Interferon alpha or Loco-regional therapy

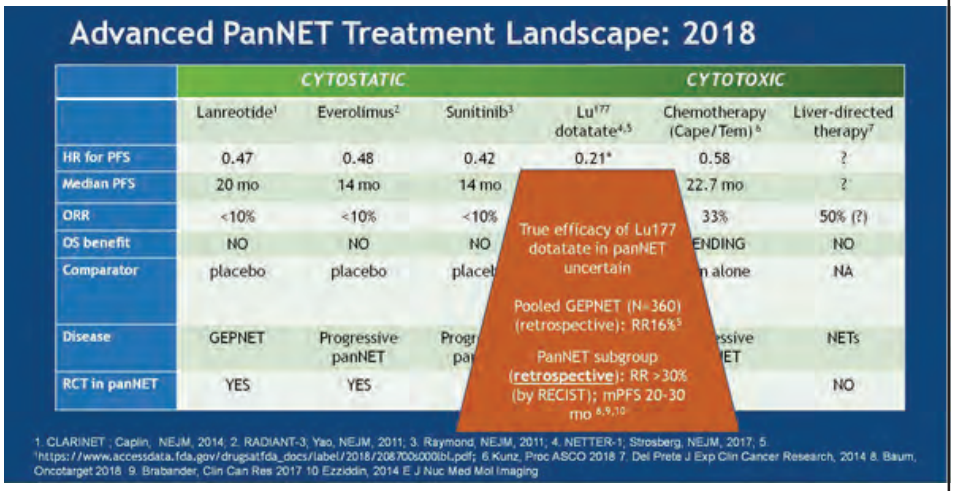




Presented By Nicola Fazio at 2018 ASCO Annual Meeting



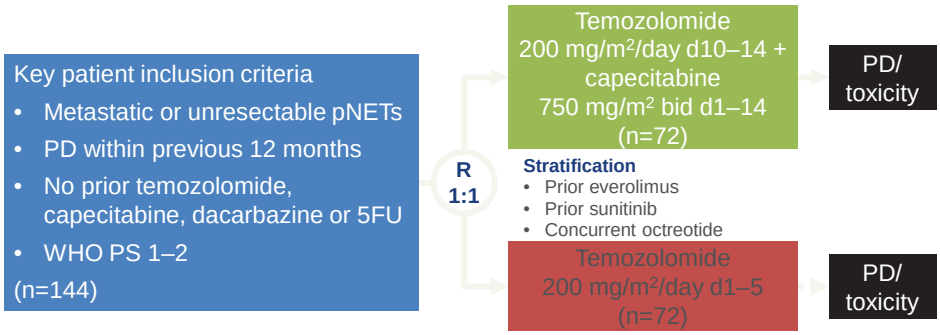
Presented By Nicola Fazio at 2018 ASCO Annual Meeting



A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al

Study objective

- To assess the efficacy and safety of temozolomide alone or combined with capecitabine in patients with advanced pancreatic neuroendocrine tumours (pNETs)



PRIMARY ENDPOINT

- PFS – local review

SECONDARY ENDPOINTS

- ORR, OS, safety

Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

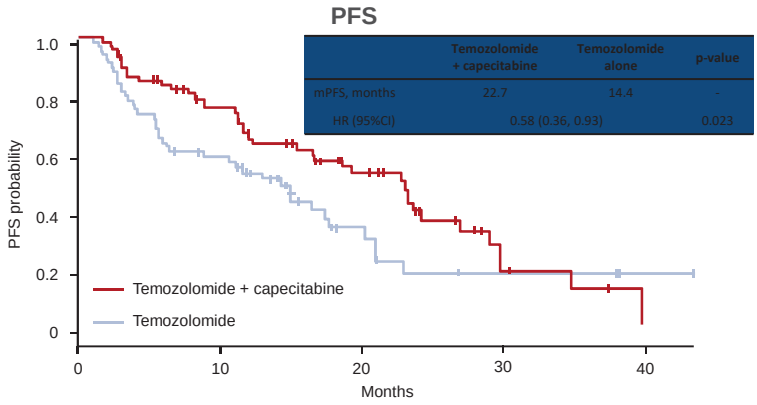
A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al

Baseline characteristics	Temozolomide + capecitabine (n=72)	Temozolomide alone (n=72)
Gender, female, %	45.8	43.1
Median age, years	62.5	59.5
Time from diagnosis, months	34.0	24.4
WHO grade*		
Grade 1	**68.1**	**45.1**
Grade 2	**31.9**	**54.9**
Sites of metastasis		
Liver	93.1	93.1
Bone	11.1	12.5
Lung	13.9	6.9
Peritoneum	9.7	5.6
Prior treatment		
Everolimus	36.1	34.7
Sunitinib	11.1	12.5
Concurrent octreotide	52.8	54.2

*Imbalance, p=0.013

Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al



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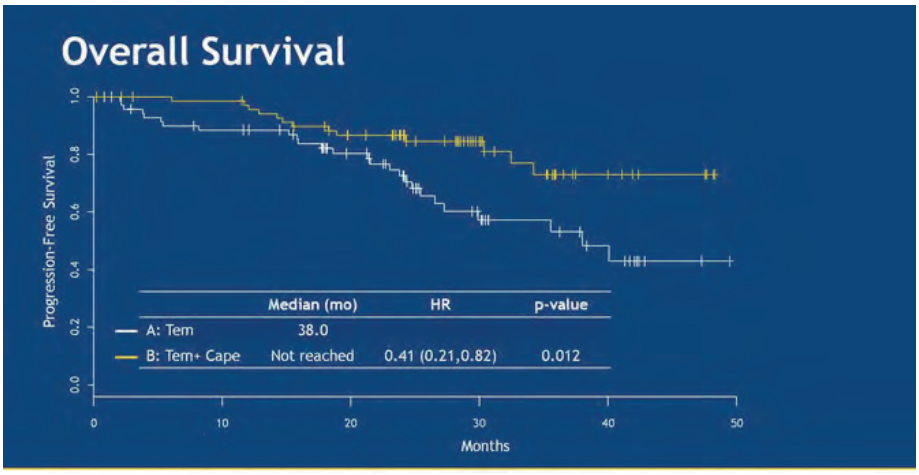
A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al



Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al

	Temozolomide + capecitabine	Temozolomide alone	HR (95%CI); p-value
mOS, months	Not reached	38.0	0.41 (0.21, 0.82); 0.012

Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211) – Kunz PL, et al

	Temozolomide + capecitabine	Temozolomide alone
ORR, %	33.3	27.8
p-value	0.47	
DCR, %	81.9	68.1
Median response duration, months	12.1	9.7

%	Temozolomide + capecitabine	Temozolomide	p-value
Worst degree* for all TRAEs grade 3–4	44	22	0.007

*Highest grade patients achieved across all toxicities reported

Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

Safety Profile (CTCAE v4.0)

AE Category	AE Term	Temozolomide (N= 68)	Temozolomide + Capecitabine (N= 71)	p-value
Worst degree for all treatment-related, Grade 3-4 AEs*				
		22%	44%	p=0.007
Treatment related, Grade 3-4 AEs ≥ 5%				
Hematologic	Neutropenia	4%	13%	
	Lymphopenia	4%	5%	
	Thrombocytopenia	13%	8%	
Gastrointestinal	Nausea	0	8%	
	Vomiting	0	8%	
	Diarrhea	0	8%	
Constitutional	Fatigue	1%	8%	

*Worst degree is highest grade a patient achieved across all toxicities reported

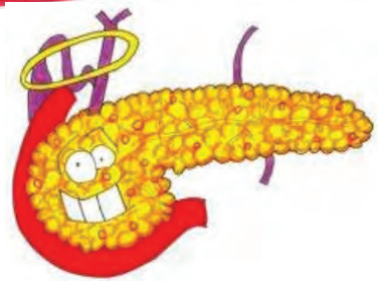
There were no Grade 5 related AES

Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

Conclusions

- Temozolomid + kapecitabin je pri bolnikih z naprednimi pNET pokazal izboljšan PFS v primerjavi s temozolomidom
- ORR je bil v primerjavi z večino odobrenih terapij visok, vendar med zdravljenjem ni bilo bistvene razlike
- AE so bile pričakovane, pri stopnjah, ki so se podvojile v kombinaciji
- To je prva prospektivna randomizirana klinična raziskava s temi zdravili in prikazuje najdaljši PFS, ki se poroča za pNET usmerjeno terapijo

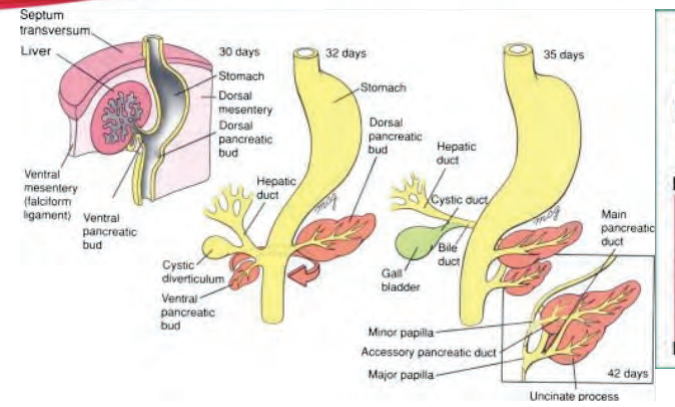
Kunz PL, et al. J Clin Oncol 2018;36(suppl):abstr 4004

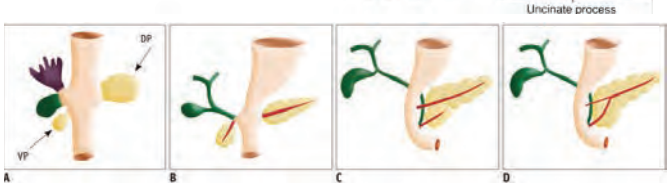


SLIKOVNA DIAGNOSTIKA PRI RAKU TREBUŠNE SLINAVKE

Nina Boc, dr. med.

RAZVOJ IN LEGA V ABDOMNU

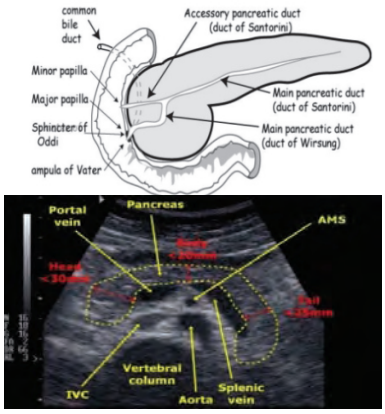


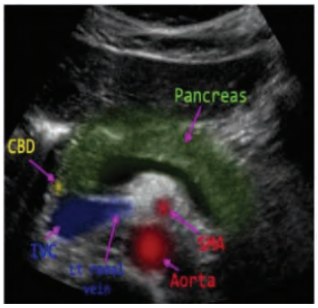


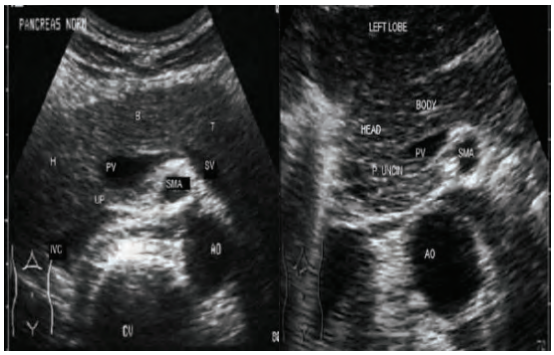
Razvojne anomalije pankreasa:

- Agenezija
- Pancreas divisum
- Annularni pancreas
- Ektopični pankreas
- Kongenitalne ciste

UZ ANATOMIJA



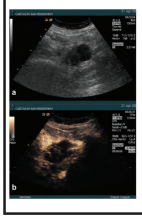




UZ PREISKAVA

PREDNOSTI:
- Najbolj uporabna neinvazivna začetna preiskava
- Poceni (45€)
- lahko bedside
- Doppler UZ – za oceno prehodnosti žilja
- Mesto obstrukcije (v 90% bolnikov)
- FNA

OMEJITVE:
- Preiskovalec
- Senzitivnost 80-90% vs. CT/MR do 100%
- Slabo pripravljen bolnik – meteorizem
- Diagnostičen pri ca. Papile Vateri le 24%
- Slabo vidne zelo povrhnje in zelo globoke spremembe



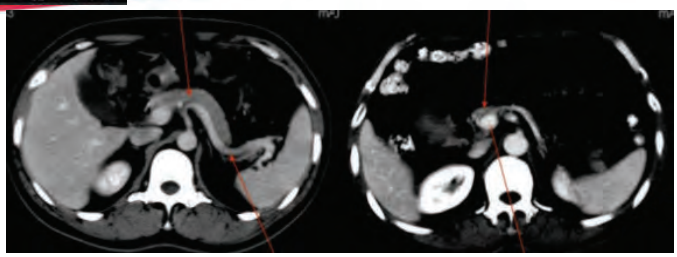
CEUS – 9 priporočil
- Za cistične lezije pankreasa
- lahko loči med adenoca in NET
- Dobro oceni odnos do žilja…

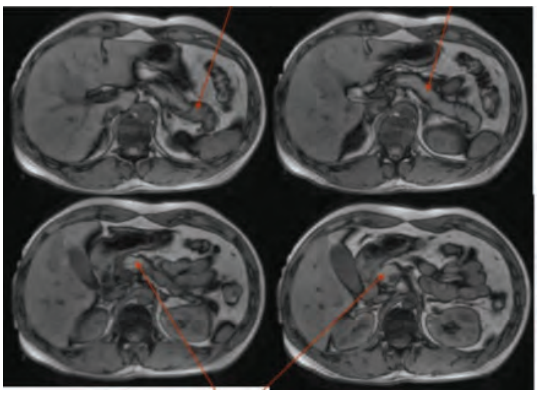
The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Short Version)

ENDO UZ
- Zelo odvisna od preiskovalca
- Možnost FNA
- Zelo senzitivna za detekcijo prizadetosti velikih žil
- Identifikacija tumorjev <1 cm
- Najbolj senzitivna za ca. Papile Vateri
  - Senzitivnost 97%
  - Ocena T stadija 72%
  - Ocena N stadija 47%
  - Ocena prizadetosti žilja 100%
- Možnost stentiranja biliarnih poti
- Nizka senzitivnost za oddaljene metastaze

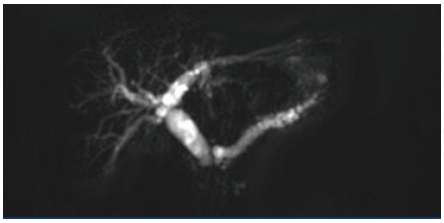
LAPAROSKOPSKI UZ
- bolj specifičen in natančen pri oceni resektabilnosti kot laparoskopija (88% in 89% vs. 50 in 65%)

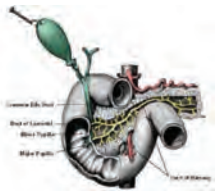
CT/MR ANATOMIJA





MRCP – MR CholangioPancreatography





CT PREISKAVA

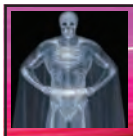
PREDNOSTI

- Različne faze obarvanja s kontrastom (nativna, arterijska, pankreatična, venska faza)
- Hitra preiskava, dobra prostorska ločljivost
- Senzitivnost 75-100%, specifičnost 70-100% (tumorji <2 cm senzitivnost 68–77%)
- 11% izodenznih – le posredni znaki → razširjen pankreatični vod in/ali holedohus – double duct sign, atrofija repa pankreasa, efekt mase in izguba lobularnega izgleda parenhima pankreasa
- Dobra ocena resektabilnosti: – senzitivnost in specifičnost 63 in 100% (neresektabilni razsoj, invazija v prileţne organe, predvsem pa vaskularna invazija)

SLABOSTI

- Sevanje, obremenitev z jodnim kontrastom (vsi nefrotoksični, alergije, tiortoksikoza)
- Cena 210€


REVIEW ARTICLE
Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature



MR PREISKAVA

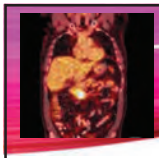
PREDNOSTI

- Boljša prostorska ločljivost kot CT + difuzija (gostoceličnost→malignom)
- Različne faze obarvanja s kontrastom
- MRI in MRCP senzitivnost 100%, specifičnost 83%,PPV 94%,NPV 100% in natančnost pri oceni resektabilnosti 95%
- Ni sevanja

SLABOSTI

- MRCP 15 min, MR zgornjega abdomna vsaj 30 min
- Segrevanje tkiv, implantanti
- Cena 260€

REVIEW ARTICLE
Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature

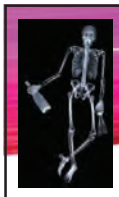


FDG PET-CT

- Senzitivnost 90% - 95% and specifičnost 82% - 100% (CT Senzitivnost 75-100%, specifičnost 70-100%)
- PET-CT nima dodane vrednosti pri oceni lokalne bolezni in regionalnih LN (približno enako natančna ocena 84-85%)
- Za oceno razširjenosti izven abdomna in progresa je PET-CT bolj senzitivna 90% vs. 80% CT

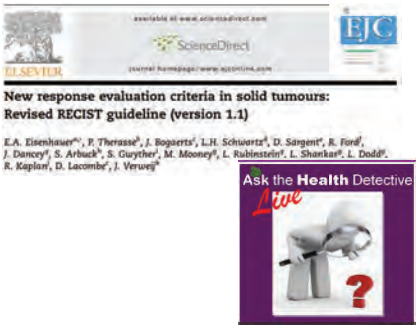
- Cena 1068€

REVIEW ARTICLE
Multimodality imaging of pancreatic ductal adenocarcinoma: a review of the literature



VLOGA RADIOLOGA

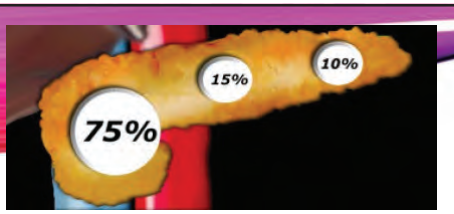
- Lokalni staging
- Razširjenost bolezni
- Evaluacija učinka terapije
- Spremljanje (po kirurškem zdravljenju ali cističnih sprememb)



international union against cancer — Pancreas — UICC

T1	Tumour 2 cm or less	M category unchanged	
T1a	Tumour 0.5 cm or less		
T1b	Tumour greater than 0.5 cm and less than 1 cm	Stage	
T1c	Tumor greater than 1 cm but no more than 2 cm	Stage IA T1	N0 M0
T2	Tumour more than 2 cm but no more than 4 cm	Stage IB T2	N0 M0
T3	Tumour more than 4 cm in greatest dimension	Stage IIA T3	N0 M0
T4	Tumour involves coeliac axis, superior mesenteric artery and/or common hepatic artery	Stage IIB T1, T2, T3	N1 M0
		Stage III T1, T2, T3	N2 M0
		T4	Any N M0
N1	Metastases in 1 to 3 nodes	Stage IV Any T	Any N M1
N2	Metastases in 4 or more nodes		

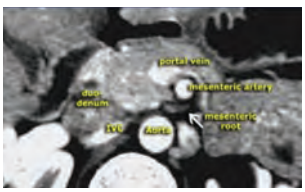
WWW.UICC.ORG

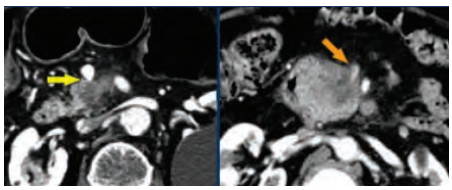


LOKALNI STAGING

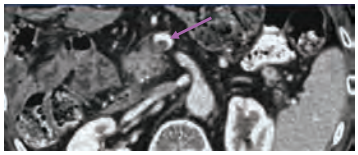
- Ocena resektabilnosti
- DD. Fokalni pankreatitis, limfom, metastaze

Resectable	Irresectable
Peripancreatic lnn	Para-aortal, truncal, mesenterial lnn
Limited ingrowth in fat or duodenum	Ingrowth stomach, colon, mesocolon
Ingrowth gastroduodenal artery	Ingrowth portal vein, a.hepatica, tr. coeliacus
< 180° vessel contact	> 180° vessel contact
	Liver, peritoneal metastases

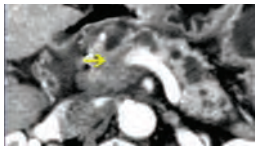




Tear drop – najbolj zanesljiv znak neresektabilnosti



Tumorski tromb



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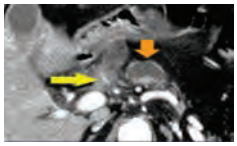


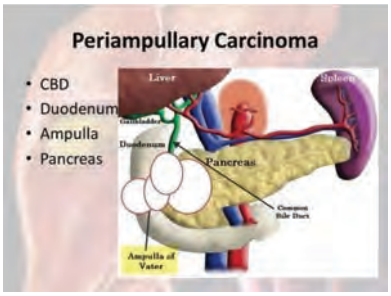
Preraščanje a.hepatike

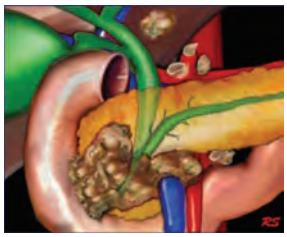
PERIAMPULARNI CA.

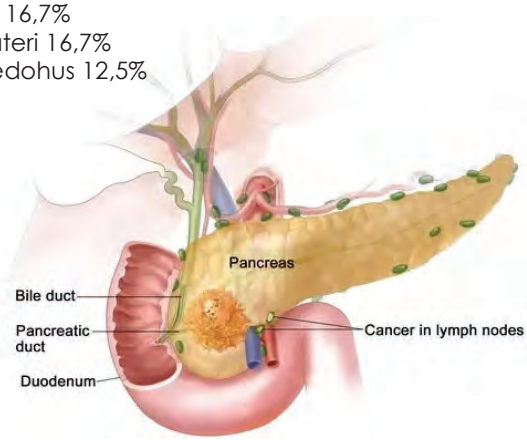
- Tumorji, ki izvirajo iz distalnega holedohusa in ampule ležijo v glavi pankreasa enako kot tumorji glave pankreasa
- Incidenca
  - Glava pankreasa 54,1%
  - Duodenum 16,7%
  - Ampulla Vateri 16,7%
  - Distalni holedohus 12,5%

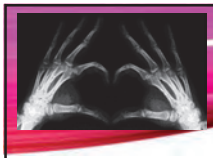
Table 2: Symptoms of present series in comparison to other series.

Symptoms	Tarazi (1986)[7]	Robertson (1987)[8]	Present series
Jaundice	78%	93%	100%
Loss of appetite	70.6%	NM	77.08%
Pain Abdomen	57.9%	47%	58.33%
Pruritus	34.1%	NM	85.41%





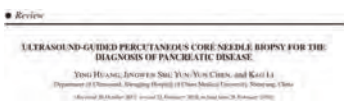




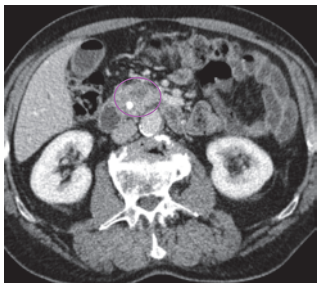
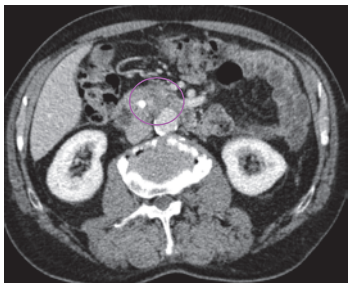
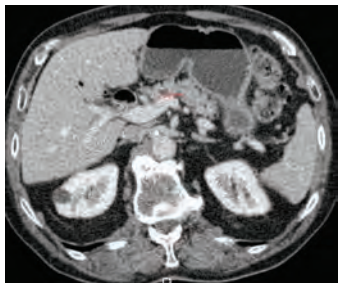
BIOPSIJE

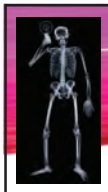
- EUS FNA – 1% pankreastitis, 2,6% krvavitev, bolečina 3%; neustrezni vzorci 6-20%
- Transabdominalni UZ FNA – 20G (0,8 mm) komplikacije v 7% 18G (1mm) komplikacije v 15% → krvavitev intraabdominalno, makrohematurija, pankreatitis, exocrine leak in biopsija prileznega organa
- DIB senzitivnost za malignom 78.1% in natančnost 81% - komplikacije okrog 21,4%
- Karcinoza peritoneja EUS FNA vs. perkutana FNA 2,2% vs 16,6%

Gastrointest Endosc. 2003 Nov;58(5):690-5
Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA.
Micames C[1], Jowell PS, White R, Paulson E, Nelson R, Morse M, Hurwitz H, Pappas T, Tyler D, McGrath K.

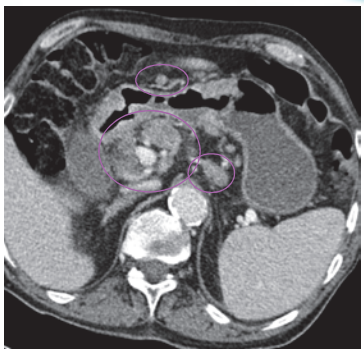
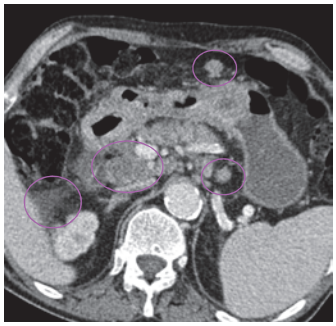
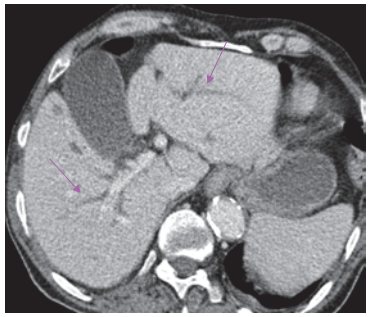
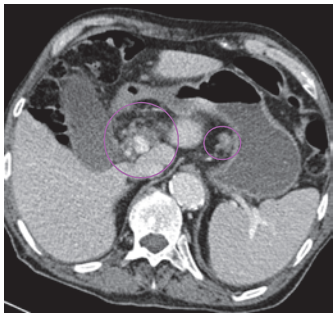

• Review
ULTRASOUND-GUIDED PERCUTANEOUS CORE NEEDLE BIOPSY FOR THE DIAGNOSIS OF PANCREATIC DISEASE

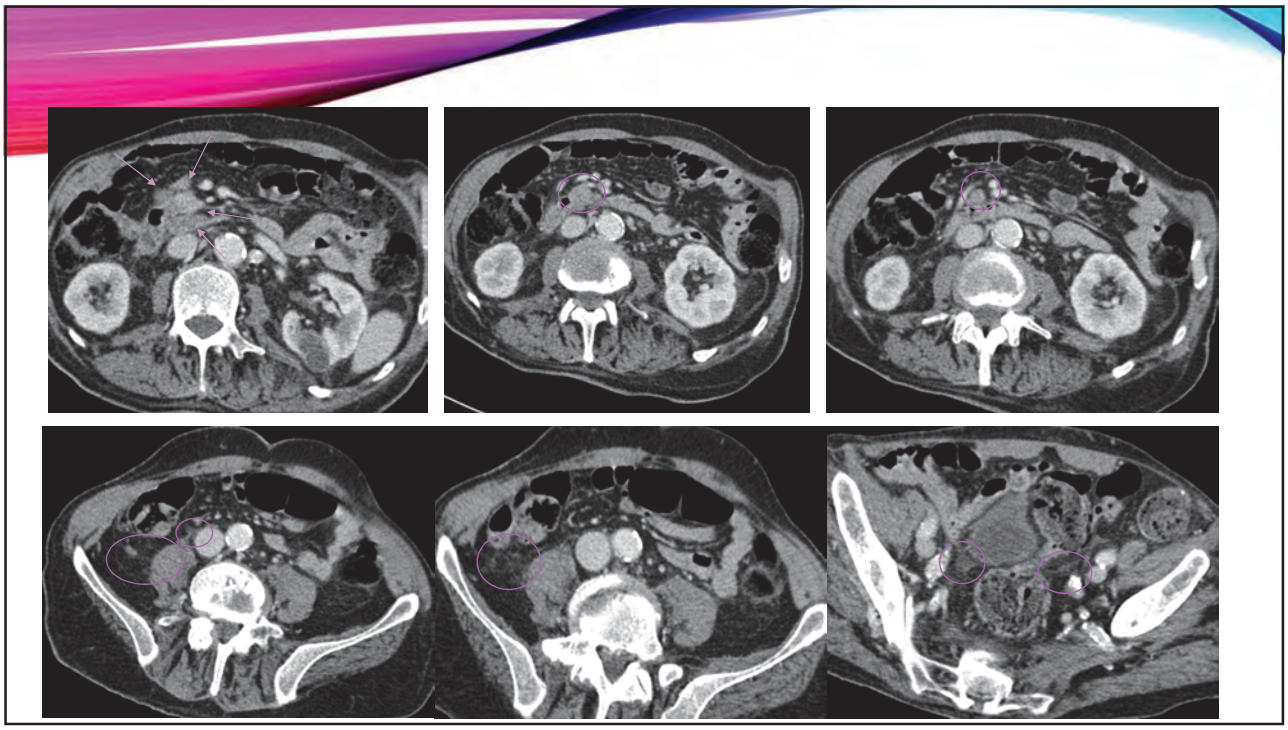
75 letni moški

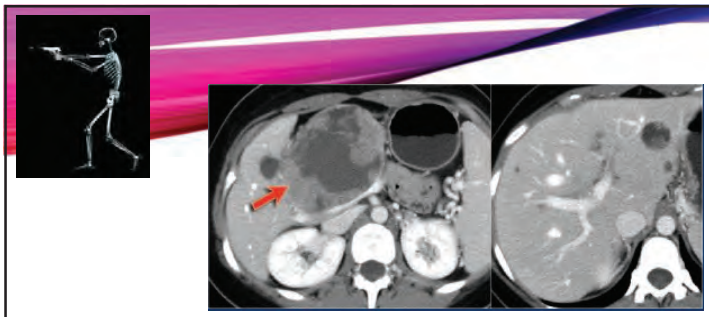






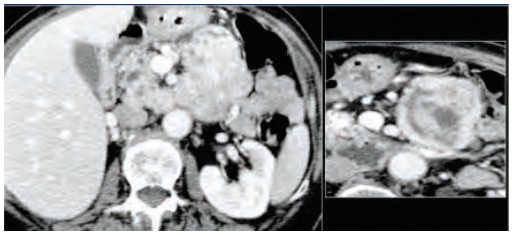
Ocena razširjenosti bolezni

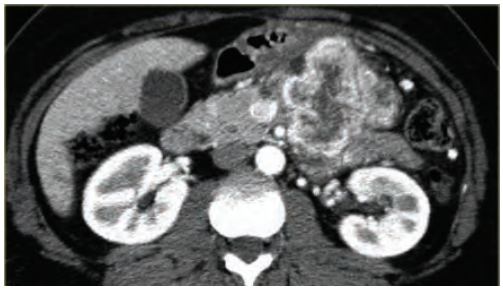




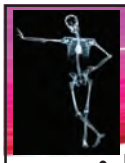
Pseudopapilarna neoplazma+m. v jetrih



Neuroendokrini tumor s cistično degeneracijo



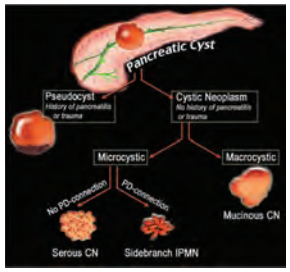
Neuroendokrini tumor s centralno nekrozo

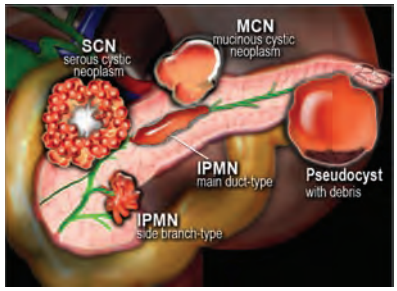


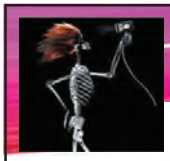
CISTIČNE LEZIJE PANKREASA

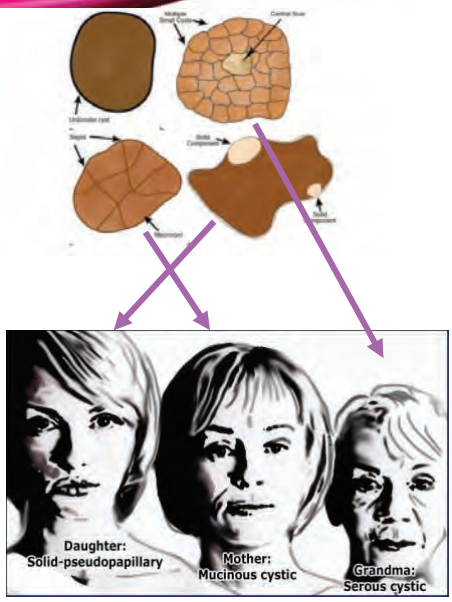
- Pseudociste
- Cistične neoplazme pankreasa – debelorobe ciste, zadebeljene septe, nodularna obarvanja, razširjen pankreatični vod
  - Serozni cistadenom
  - Mucinozna cistična neoplazma
  - IPMN
  - Solidni pseudopapilarni tumor
  - Ostali – redki: limfangiom, paragangliom…
- Solidne pankreatične lezije s cistično degeneracijo
  - Adenokarcinom pankreasa
  - Cistični insulinom, glukagonom, gastrinom
  - Metastaze
  - Cistični teratom
- Prave epitelijske ciste – von Hippel-Lindau, policistična bolezen ledvic, cistična fibroza
- Samo serozne cistične neoplazme nimajo malignega potenciala

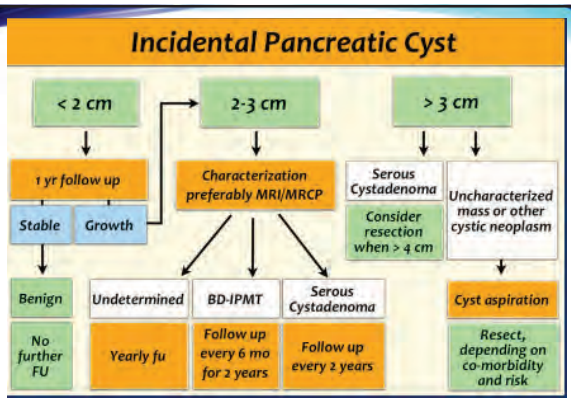
European evidence-based guidelines on pancreatic cystic neoplasms



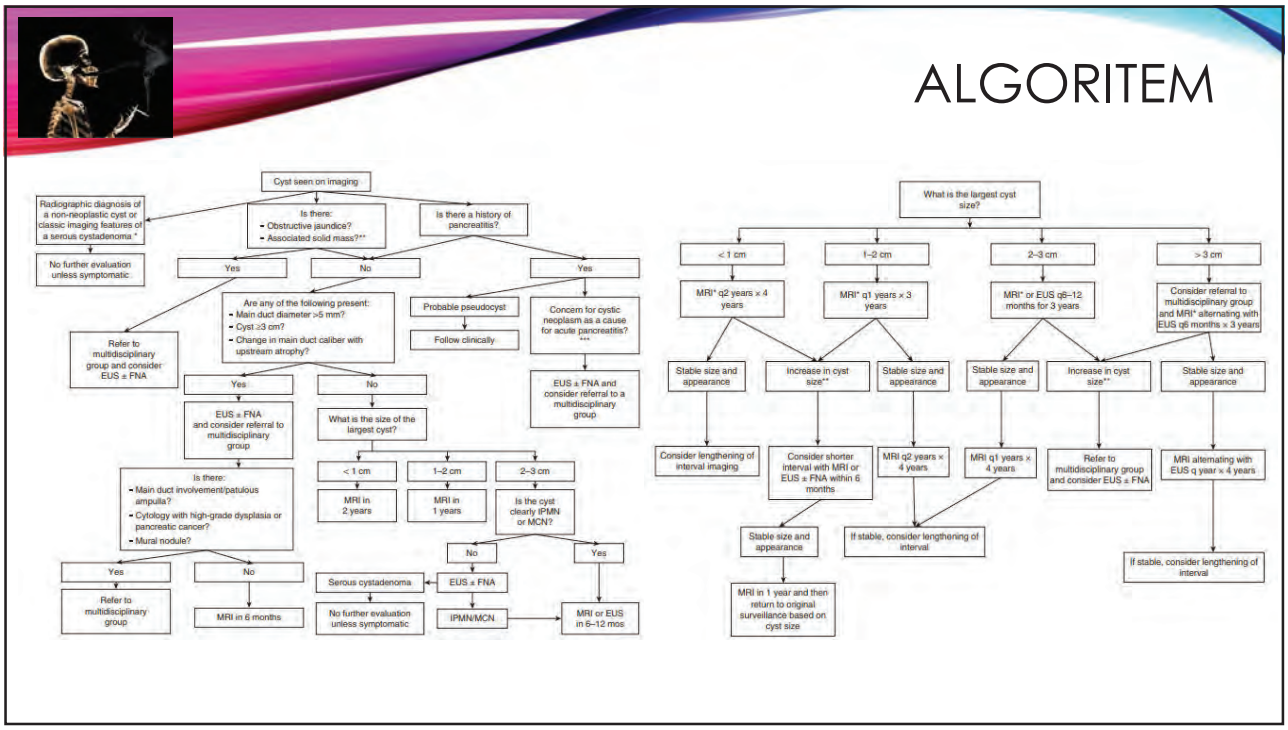


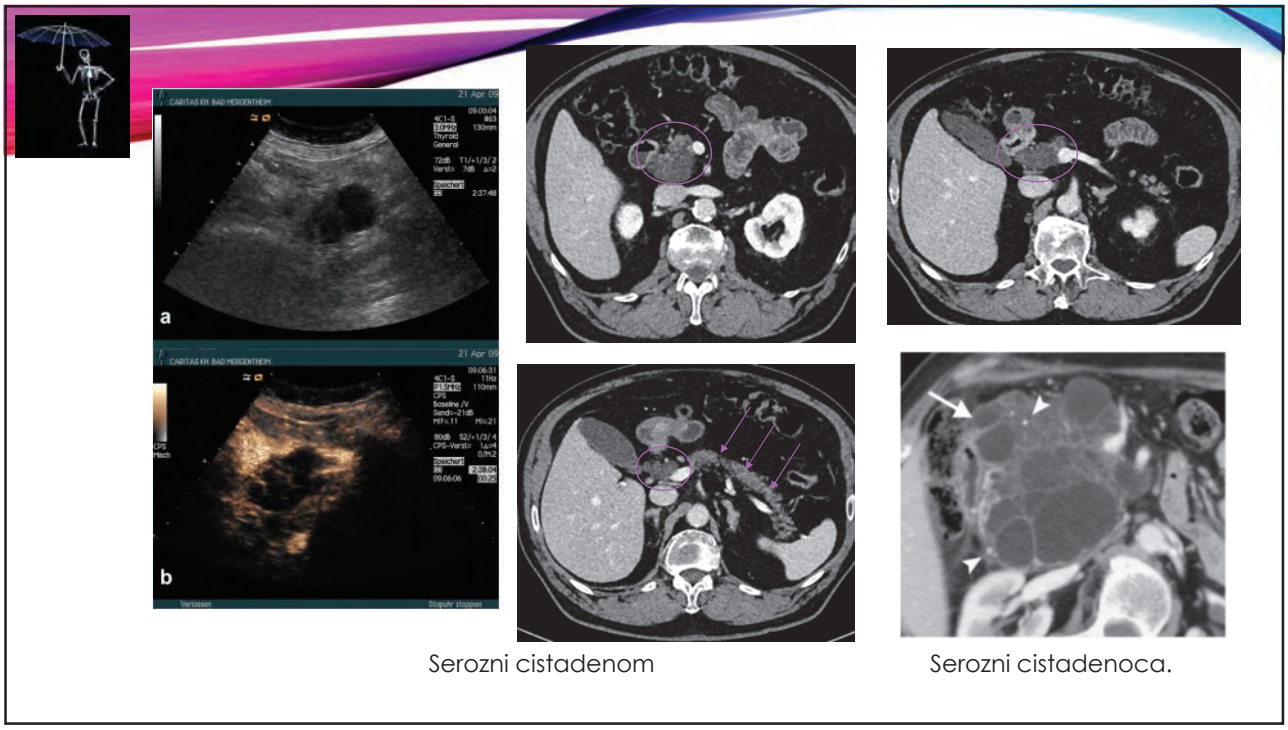






		Age - Gender	Imaging
	**SCN** Benign	75% women 60-70 y **Grandma**	Lobulated microcystic 18% central scar with Ca^{++}
	**MCN** Malignant potential	99% women 40-50 y **Mother**	Macrocystic Usually 1 cyst 25% peripheral Ca^{++} 95% in tail and body
	**Main-duct IPMN** Malignant potential	M=W 60-80 y	Dilated Pancreatic duct Protruding papil of Vater
	**Side-branch IPMN** Malignant potential	M=W 60-80 y	Bunch of grapes connection to PD





Serozni cistadenom

Serozni cistadenoca.

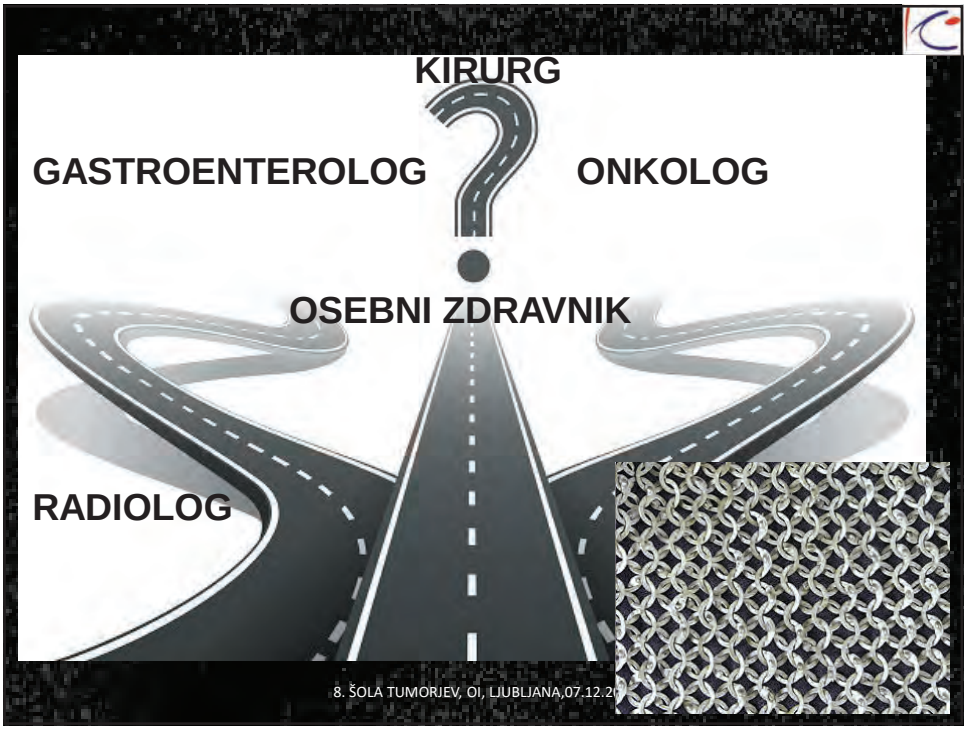
TAKE HOME

- Pomen radiologije – ocenjujemo spremembe glede na vzorce, morfološki izgled, način obarvanja; ocena perfuzije, ocena gostoceličnosti - ne delamo pa z mikroskopom!
- Najbolj racionalna izbira slikovno-diagnostične preiskave
- Pomen multidisciplinarnega pristopa

Kirurško zdravljenje raka trebušne slinavke

Doc. Dr. Blaž Trotovšek, dr.med.

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.



OSEBNI ZDRAVNIK

The Truth

Test Score:	Has the disease	Does not have the disease	
Positive	True Positives (TP) a	False Positives (FP) b	$PPV = \frac{TP}{TP + FP}$
Negative	False Negatives (FN) c	True Negatives (TN) d	$NPV = \frac{TN}{TN + FN}$

Sensitivity $\frac{TP}{TP + FN}$ **Specificity** $\frac{TN}{TN + FP}$

Or, $\frac{a}{a + c}$ $\frac{d}{d + b}$

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

GASTROENTEROLOG

		Condition (as determined by "Gold standard")		
		Positive	*Negative*	
Test outcome	*Positive*	True Positive	False Positive (Type I error, P-value)	→ Positive predictive value
	Negative	False Negative (Type II error)	True Negative	→ Negative predictive value
		↓ Sensitivity	↓ Specificity	

" That's our Gastro Specialist."

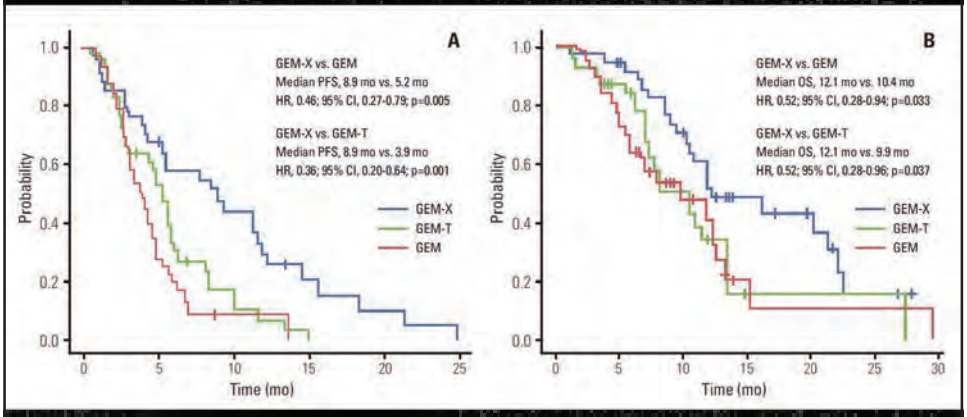
- V kakšnem stadiju najpogosteje odkrije bolezen?
- Kako dolgo traja diagnostična obravnava bolnika z rakom trebušne slinavke?

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

ONKOLOG

- Kako uspešno je onkološko zdravljenje raka trebušne slinavke?
  - 5-letno preživetje ob RT in KT ter drugih interventnih onkoloških zdravljenjih BREZ KIRURŠKEGA POSEGA?
  - Kakšen je odstotek bolnikov, ki prejmejo neoadjuvantno KT (? Učinkovitost)
  - Kakšen odstotek down-staginga lahko pričakujemo ob uporabi najsodobnejših shem KT?

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.



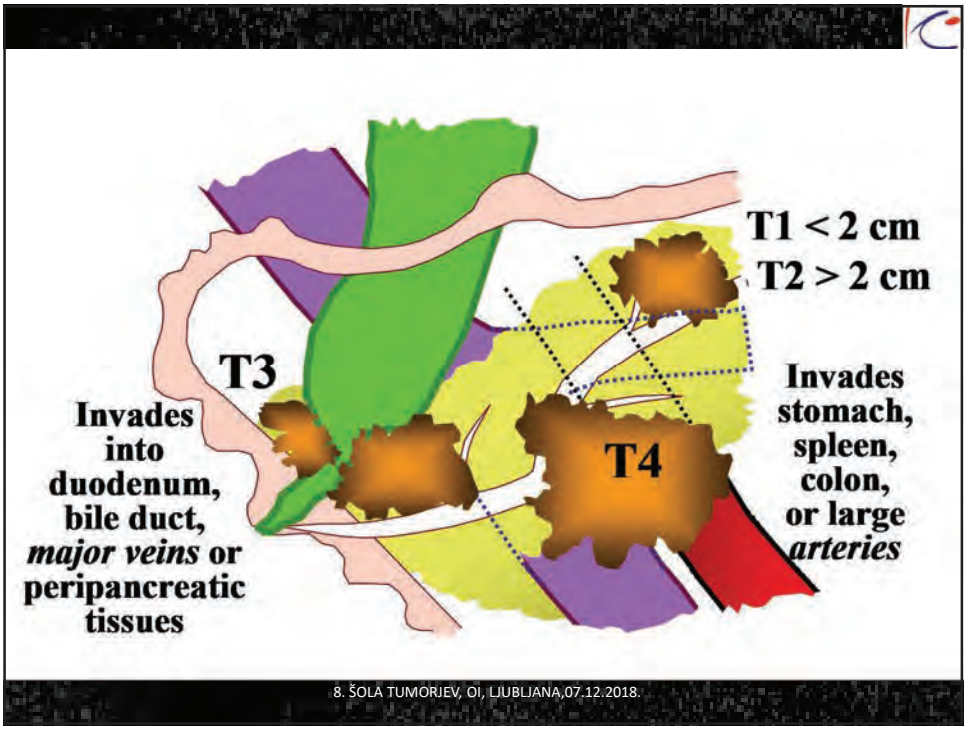
8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Incidenca raka (brez primerov registriranih samo iz zdravniških poročil o vzroku smrti) po stadiju,

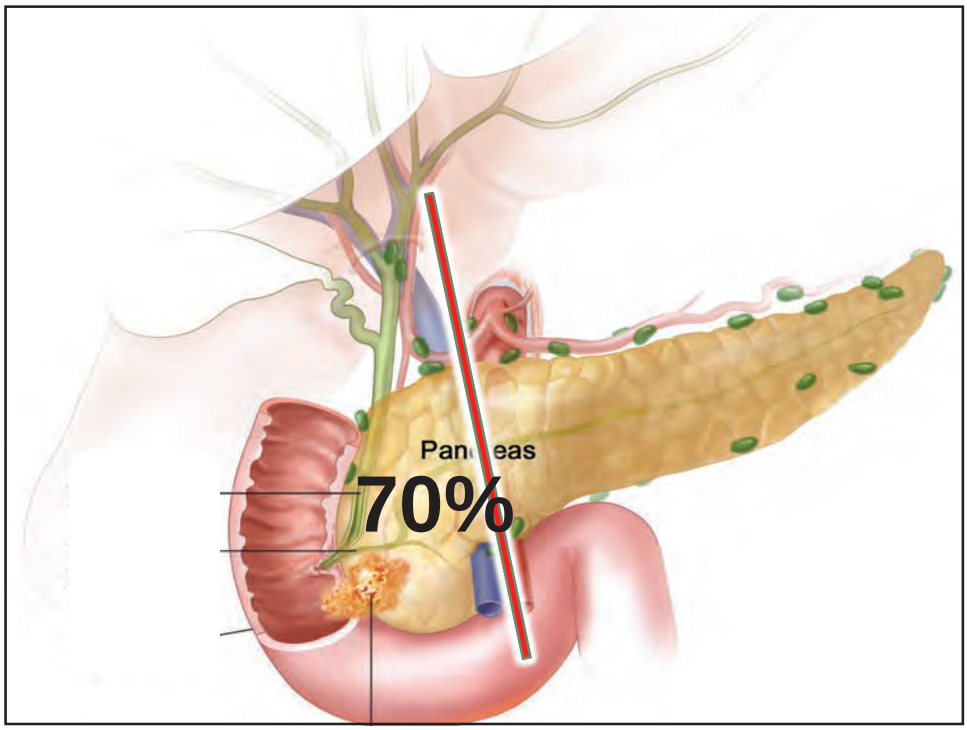
Šifra MKB ICD code	Primarna lokacija Primary site		Spol Sex	Število novih primerov Number of new cases	Stadij							
					Omejen		Razširjen		Razsejan		Neznan	
					Število	%*	Število	%*	Število	%*	Število	%*
					Stage							
					Localized		Regional		Distant		Unknown	
					Number	%*	Number	%*	Number	%*	Number	%*
C25	Trebušna slinavka	2014	M	213	13	6,1	62	29,1	132	62,0	6	2,8
	Pancreas		Ž	179	20	11,2	75	41,9	81	45,3	3	1,7

- Omejen (37/392)
  - T1-2 (N0, M0)
- Regionalno razširjena bolezen (137/392)
  - T3-4, TxN1, M0
- Oddaljeno razširjena bolezen (218/392)
  - TxN1M1, TxN2M0

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.



8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.



Pancreas Cancer Staging*

7th EDITION

Definitions

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ1**
- T1 Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

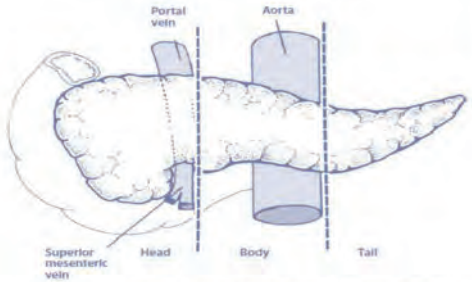
Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1



Tumors of the head of the pancreas are those arising to

Notes

* Endocrine AND exocrine tumors are now staged by a single pancreatic staging system.

** Also includes the "Panin" classification.

8th Edition od 1.1.2018

American Cancer Society®

Table 1. Staging System for Pancreatic Cancer

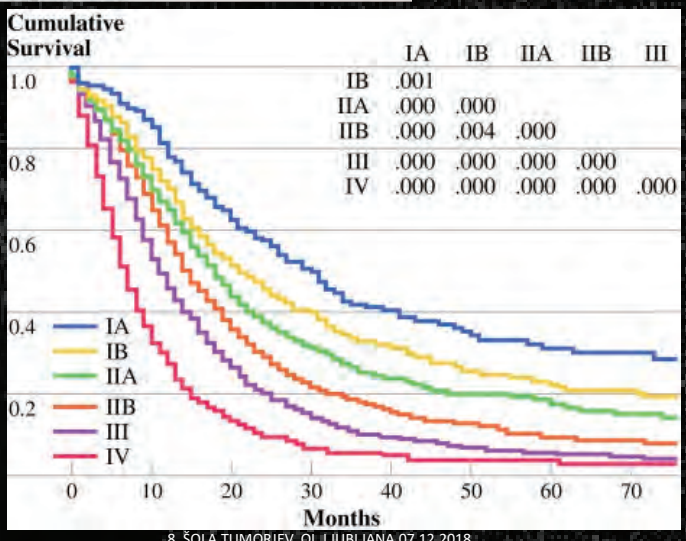
Stage	Characteristics	Median Survival (Months)
IA	Tumor < 2 cm and limited to pancreas No lymph node involvement	24.1
IB	Tumor > 2 cm and limited to pancreas No lymph node involvement	20.6
IIA	Tumor extends beyond the pancreas (no superior mesenteric artery or celiac axis involvement) No lymph node involvement	15.4
IIB	Any size tumor with regional lymph node involvement	12.7
III	Tumor involves the superior mesenteric artery or celiac axis ± lymph node involvement No distance metastasis	10.6
IV	Any size tumor ± lymph node involvement Distance metastasis	4.5

Source: References 5, 11-13.

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Impact of Tumor Grade on Prognosis in Pancreatic Cancer: Should We Include Grade in AJCC Staging?

Article – Annals of Surgical Oncology - September 2010



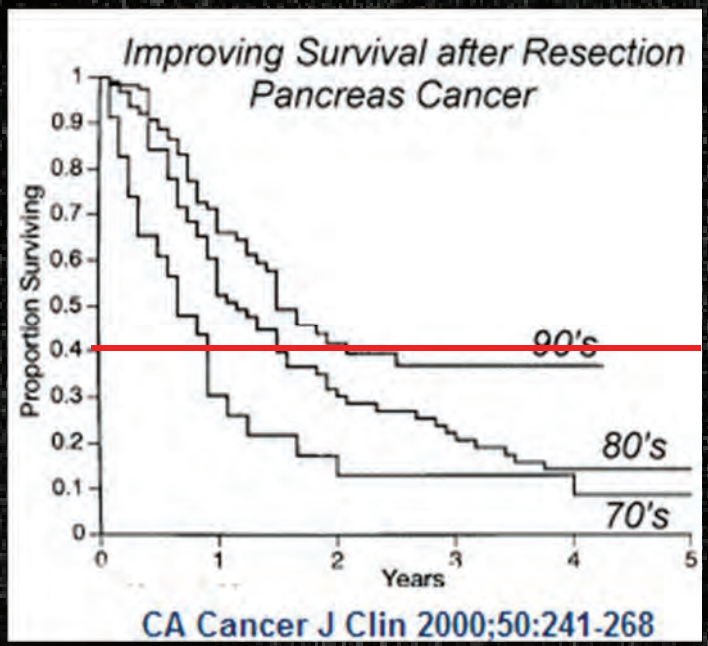
8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

American Cancer Society®

Preživetje glede na vrsto

STADIJ	5-LETNO PREŽIVETJE (%)	
	ADENOCA	NET
IA	14	61
IB	12	
IIA	7	41
IIB	5	
III	3	41
IV	1	16

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.



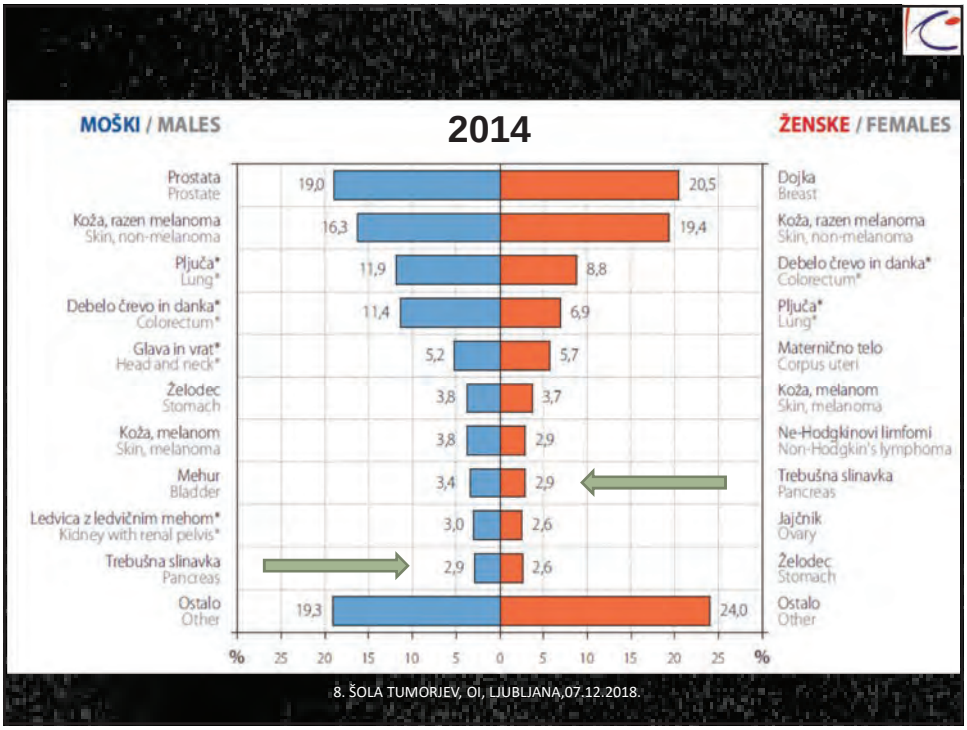
8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Kirurg

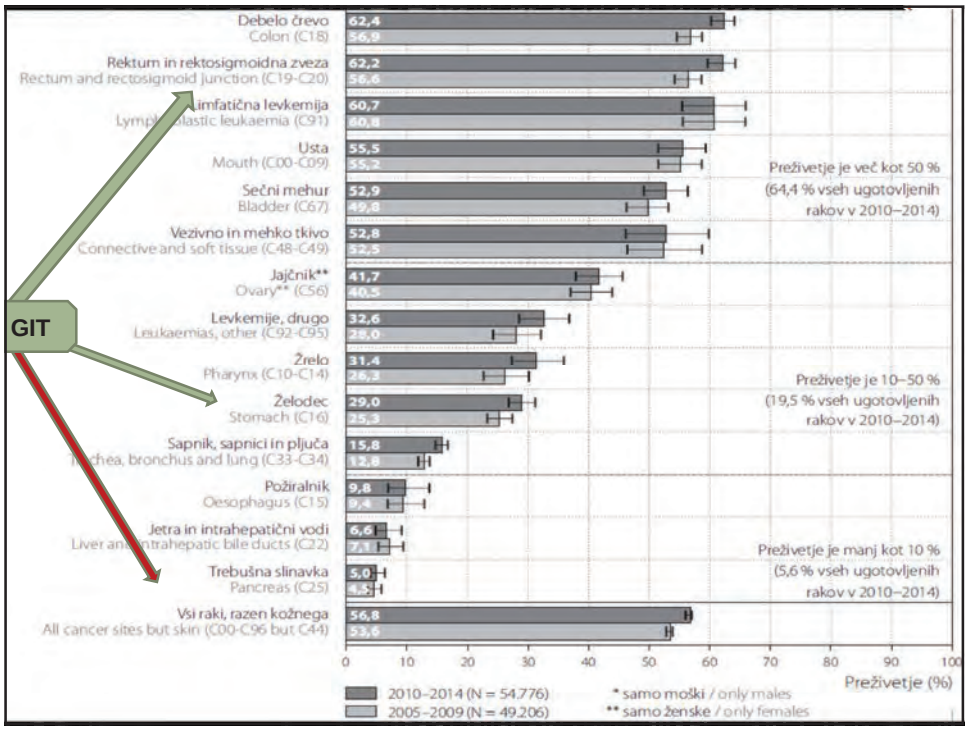
- 40% - 5-letno preživetje ob R0 resekciji
- 50% - 40 mesečno preživetje ob R0 resekciji

- Stopnja zapletov po posegu ≈40%
  - Narašča pri starejših
  - Ob spremljajočih boleznih
  - Pri bolj kompleksnih posegih
  - RESEKCIJE ŽIL

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.



8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

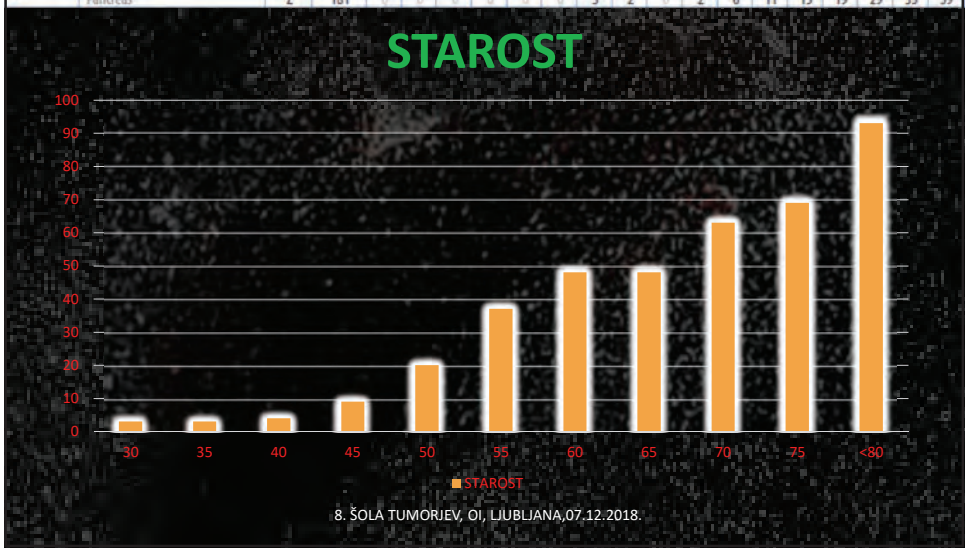


Šifra MKB ICD code	Primarna lokacija Primary site	Spol Sex	Povprečne letne opazovane vrednosti 2005–2009 Average annual observed values 2005–2009 Število Number	Incidenčna stopnja na 100.000 Incidence rate per 100,000	Povprečne letne opazovane vrednosti 2010–2014 Average annual observed values 2010–2014 Število Number	Incidenčna stopnja na 100.000 Incidence rate per 100,000	Ocena za 2017 Estimation for 2017 Število (95 % napovedni interval) Number (95% prediction interval)		Incidenčna stopnja na 100.000 (95 % napovedni interval) Incidence rate per 100,000 (95% prediction interval)	
C16	Želodec	M	290	29,2	294	28,9	290	246–335	28	24–33
	Stomach	Ž	180	17,6	181	17,4	171	137–205	16	13–20
C18	Debelo črevo	M	440	44,2	514	50,5	548	475–621	53	46–61
	Colon	Ž	353	34,5	386	37,2	392	335–450	38	32–43
C19–C20	Rektum in rektosigmoidna zveza	M	364	36,6	409	40,2	430	373–487	42	36–48
	Rectum and rectosigmoid junction	Ž	246	24,0	229	22,1	210	173–247	20	17–24
C22	Jetra in intrahepatični vodi	M	113	11,4	138	13,6	164	130–198	16	13–19
	Liver and intrahepatic bile ducts	Ž	44	4,3	51	4,9	57	38–77	6	4–7
C23–C24	Žolčnik in žolčevodi	M	64	6,5	74	7,3	91	65–116	9	6–11
	Gallbladder and billiary tract	Ž	106	10,3	104	10,0	105	77–133	10	7–13
C25	Trebušna slinavka	M	154	15,5	183	18,0	229	189–269	22	18–26
	Pancreas	Ž	165	16,1	176	17,0	185	148–221	18	14–21

> 400

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Šifra MKB ICD code	Primarna lokacija Primary site	Spol Sex	Vse starosti All ages	Starost Age																
				0–	5–	10–	15–	20–	25–	30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80+
C25	Trebušna slinavka Pancreas	M	216	0	0	0	0	0	0	0	1	4	7	14	26	33	29	34	34	34
		Ž	181	0	0	0	0	0	0	3	2	0	2	6	11	15	19	29	35	59



Kaj lahko sodobna kirurgija ponudi?

- CEFALIČNA PANKREATODUODENEKTOMIJA
  - Sec. Whipple
  - PP
- DISTALNA PANKREATEKTOMIJA
  - RAMPS A
  - RAMPS P
- TOTALNA PANKREATEKTOMIJA

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Cilji sodobne kirurgije

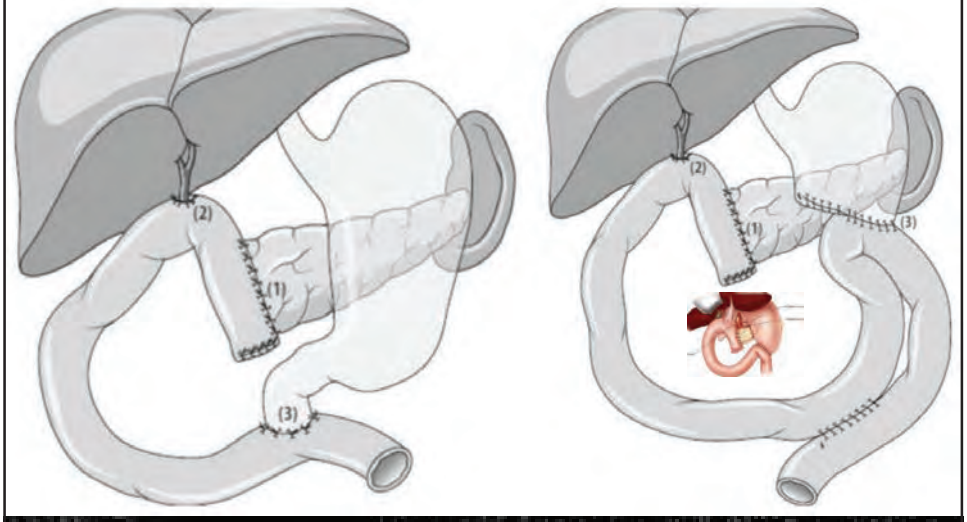
- R0 resekcija
  - Limfadenektomija
  - Resekcija žil
- Zmanjšanje pogostosti zapletov (<40%)
- Preživetje 5 let ≈ 40% in ↑
- Umrljivost < 5%
- Uvajanje laparoskopske in robotske kirurgije

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Tradicija WP

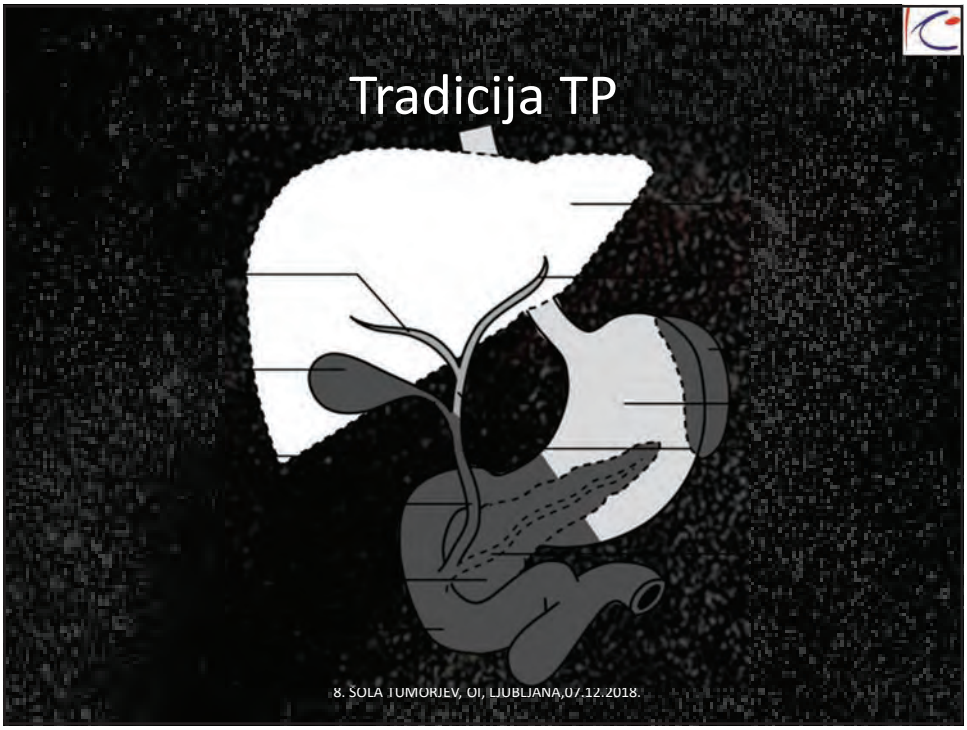
8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

PPPD V WP - rekonstrukcija

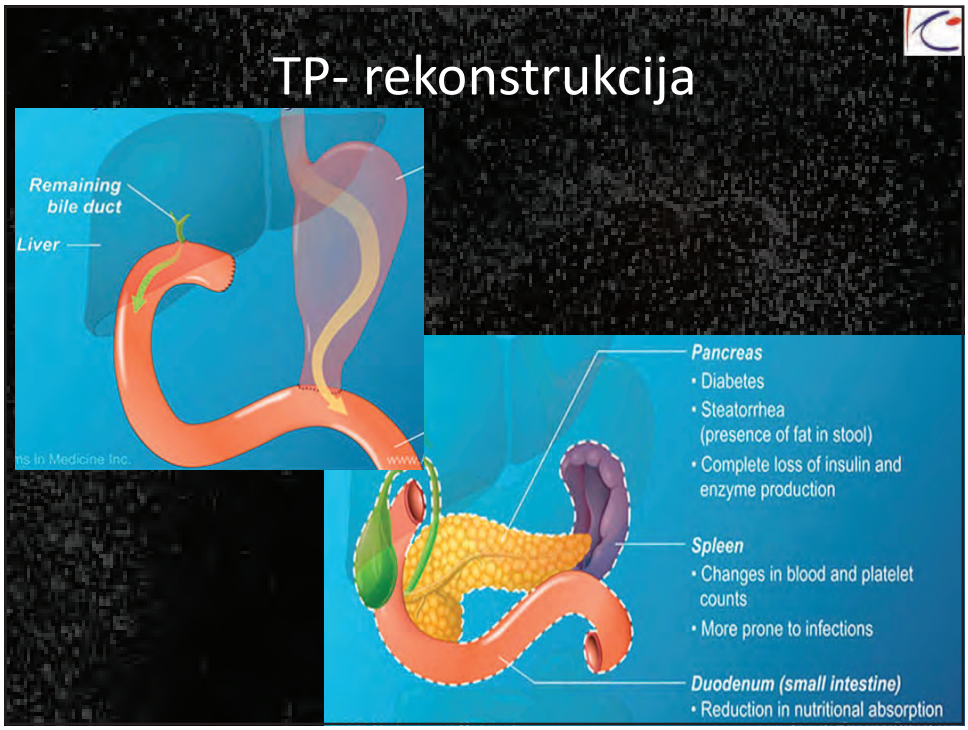


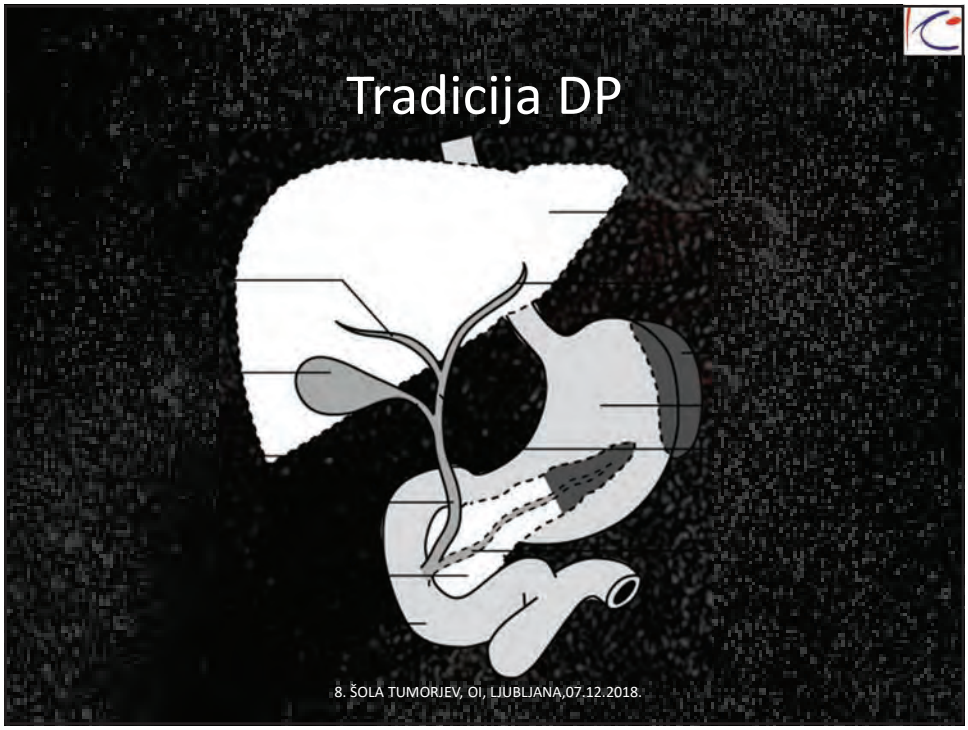
8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Tradicija TP

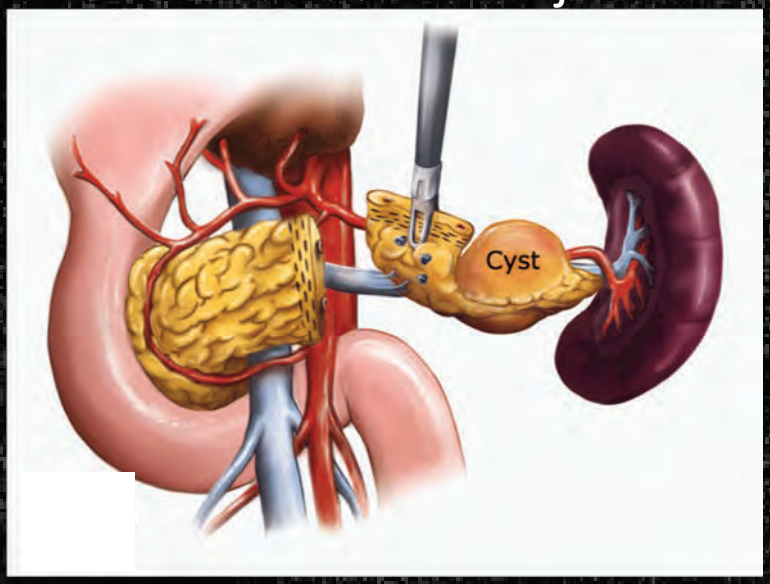


8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.


TP- rekonstrukcija
Remaining bile duct
Liver
Pancreas
• Diabetes
• Steatorrhea (presence of fat in stool)
• Complete loss of insulin and enzyme production
Spleen
• Changes in blood and platelet counts
• More prone to infections
Duodenum (small intestine)
• Reduction in nutritional absorption

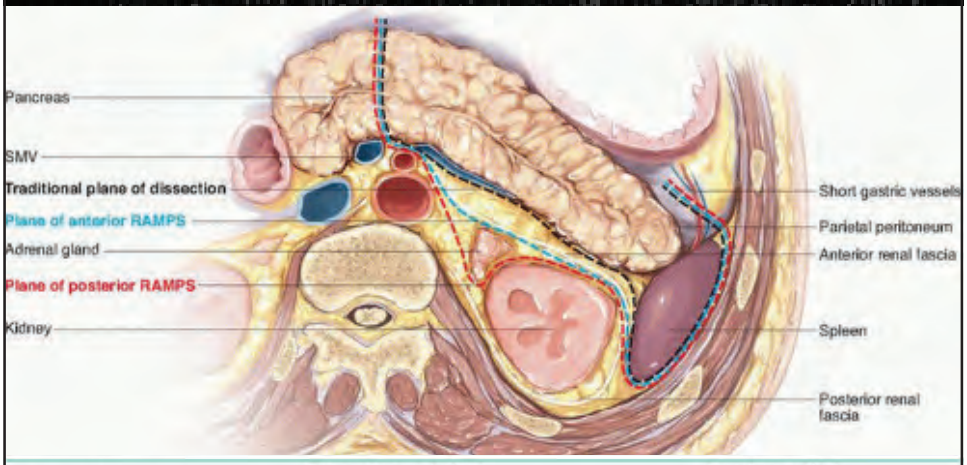

Tradicija DP
8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

TP- rekonstrukcija



8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

NOVOSTI-RAMPS



Surgical procedure	No.	Disease-free survival (%)				Overall survival (%)			
		1 yr	2 yr	3 yr	P-value	1 yr	2 yr	3 yr	P-value
RAMPS	12	100	83.3	55.6	0.048	70.7	56.6	42.4	0.197
DP	11	54.5	54.5	27.3		63.6	36.4	27.3	
Total	23	79.5	70.7	42.4		67.5	47.2	34.4	

Preko tradicionalnih meja

- Resekcija PV in VMS
- Resekcija arterij
- Ekstenzivna limfadenektomija
- Multivisceralne resekcije
- Resekcija zasevkov
- Resekcija pri recidivu

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Preko tradicionalnih meja

- Zaradi pozne ugotovitve ACP je samo 20% bolnikov kandidatov za kirurško zdravljenje.
- Kirurgija je edino potencialno kurativno zdravljenje.
- Dejavniki, ki ↓ resektabilnost so:
  - Jetrni zasevki,
  - Širjenje v oddaljene bezgavke,
  - Invazija posteriornega robu P, SMA, TC, VP+VMS+L.

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Preko tradicionalnih meja

Habermehl D, Kessel K, Welzel T et al (2012) Neoadjuvant chemoradiation with gemcitabine for locally advanced pancreatic cancer. Radiat Oncol 2(7):28

- Obeti neoadjuvantne KT RT
  - Po zaključku je bilo ≈ 40% R0
  - Mediano preživetje 22,1% (11,2 brez R)

Resekcija PV in VMS

- Infiltracija PV je pogosta.
- Je neodvisna od biološkega potenciala – odvisna je od lokacije in velikosti tumorja.
- Vedno ko lahko dosežemo R0
- V 50% je prisotno histološko zgolj vnetje, čeprav se zdi da gre za preraščanje.
- OB/UM (42/6 ns)
- Vpliv na preživetje (+) ali ?

Resekcija PV in VMS

- **Napravimo jo vedno ko lahko dosežemo R0**
- Rekonstrukcija
  - Patch,
  - End to end,
  - Interponat (naravni ali umetni)

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Resekcija arterij

- Pri < 7% bolnikov se naredi,
- Ugotovljena pre-operativno (obsežna zajetost) je kontraindikacija
- Intra-operativno ugotovljena = manjša → OP
- Serije majhne, a je vse bolj popularna.
- OB/UM sta zvišani
- Z resekcijo arterij dosežemo zelo visok delež R0 resekcij (≈90%).

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Resekcija arterij

- Ni pomembnejšega vpliva na preživetje.
- Primerna pri izbranih bolnikih (WHO 0, mlajši).
  - Pri teh je preživetje enako kot, če ne bi bilo zajete arterije.

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Ekstenzivna limfadenektomija

- 30% bolnikov ima zasevke v retroperitonealnih bezgavkah – ki jih ne odstranimo z regionalno limfadenektomijo.
- Pri ACP so bezgavke prizadete pri 75% in perinevralna invazija je prisotna v 65%.
- Obolevnost je ↑
- NE VPLIVA NA PREŽIVETJE!!

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Multiorganske resekcije

- Za doseganje R0
- OB/UM (68%/3%)
- 5-letno preživetje 22%, 10 let 18%
- Mediano preživetje 20 mesecev
- DA, vendar za skrbno izbrane bolnike

Resekcija zasevkov

- Malo podatkov
- Mediano celokupno preživetje po resekciji:
  - Jetra 14 mesecev
  - Aortokavalne bezgavke 27 mesecev
- DA pri solitarni metastazi
  - Preživetje bolnikov po R0 resekciji enega zasevka je enako kot pri tistih, kjer metastaz preoperativno ne ugotovimo.

Resekcija pri recidivu

- Recidivi so pogosti (do 72% - J zasevki do 62%)
- Vzrok: 50 odstotkov ima R1 - + zadnji rob
- DA
  - Mlajši od 65,
  - Metahroni recidiv (>9mesecev),
  - Kadar je omejen recidiv na pankreas.

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Preko tradicionalnih meja

- Obstaja veliko možnosti.
- Vrednost je vprašljiva in potrebne bodo dobro zastavljene študije za razjasnitev vpliva sodobnih tehnik na preživetje bolnikov.

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Zaključki

- Preživetje kirurških bolnikov se postopoma, a vztrajno izboljšuje.
- Kandidati za radikalno kirurško zdravljenje so bolniki z omejeno in lokalno razširjeno boleznijo.
  - V skupino bolnikov z lokalno razširjeno boleznijo je usmerjenega največ kirurškega truda da dosežemo radikalno odstranitev bolezni.
- Pri razsejani bolezni le paliativno kirurško zdravljenje.

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Zaključki

- Cilj je R0 resekcija.
- Pomemben napovedni dejavnik preživetja:
  - Kirurg,
  - Center.
- Cilji kirurškega posega, ki mora biti prilagojen posamezniku, so:
  - Daljše preživetje,
  - Izboljšana kvaliteta življenja,
  - Zmanjšanje pogostosti zapletov.

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

Zaključki

- Nejasni vplivi:
  - Nekaterih agresivnih kirurških postopkov,
  - Neoadjuvantnega zdravljenja s:
    - KT
    - RT
- **Rezultati kirurškega zdravljenja se bodo v prihodnje lahko bistveno izboljšali le z napredkom pri drugih komplementarnih metodah zdravljenja.**

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

TAKE HOME

- INFORMIRANJE LAIČNE in STROKOVNE JAVNOSTI
- ZGODNEJŠA PREPOZNAVA
- KLINIČNA POT do POSEGA (max 30 dni)
- V RS največ 2 specializirana centra
  - S HPB - konzilijem
  - S celotno paleto možnosti zdravljenja
  - Licenciranje kirurgov (omejitev števila)

8. ŠOLA TUMORJEV, OI, LJUBLJANA,07.12.2018.

POMEN RADIOTERAPIJE PRI RAKU TREBUŠNE SLINAVKE

Doc.dr.Irena Oblak, dr.med.

KARCINOM TREBUŠNE SLINAVKE

- Incidenca narašča;
- Prognoza bolnikov se zadnjih 20 let ni bistveno spremenila;
- Le slabih 5% bolnikov vključenih v raziskave;
- 15-20% bolnikov ima ob DG omejeno obliko raka, resektabilno bolezen;
- 30% bolnikov ima ob DG lokalno napredovalo bolezen in 50% oddaljene zasevke;
- Po OP se bolezen ponovi lokalno v 50-80%, z oddaljenimi zasevki v 75%;
- 5-letno preživetje <5% , po R0 OP 20%.

Vloga RT pri raku trebušne slinavke

- Adjuvantno zdravljenje
- Neoadjuvantno zdravljenje
- Definitivna RT pri lokalno napredovalem raku
- Ponovitev bolezni
- Paliativno zdravljenje

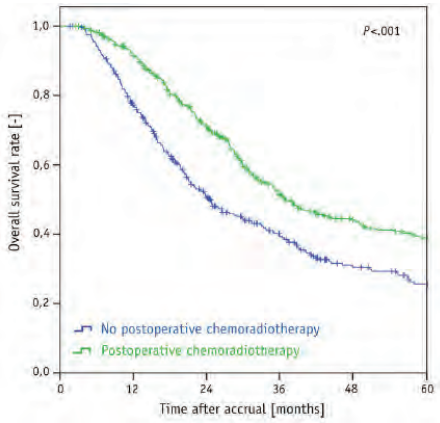
VLOGA RT V SKLOPU ADJUVANTNEGA ZDRAVLJENJA

- Kontradiktorni izsledki raziskav;
- Korist adjuvantne RT?;
- Pri izbranih bolnikih po R+ resekciji ali N+ = ↑rizični za LR

1. *Morganti AG, Falconi M, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. Int J Radiat Oncol Biol Phys 2014;*
2. *Kooby DA, Gilespie TW, et al. Impact od adjuvant radiotherapy on survival after pancreatic cancer resection: an appraisal of data from the national cancer data base. Ann Surg Oncol 2013; 20: 3634-42.*
3. *RTOG trial 0848 še teče- zaključena 2020*

Ajuvantna RT+KT

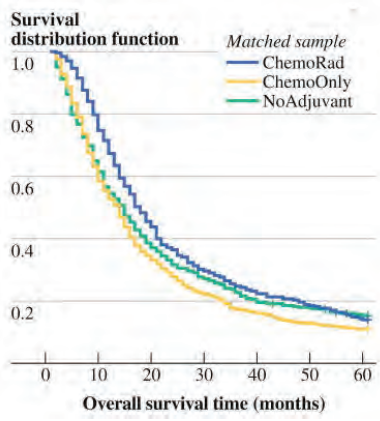
- 1995-2008: 1.120 bolnikov po OP;



Morganti AG, Falconi M, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. Int J Radiat Oncol Biol Phys 2014;

Ajuvantna RT+KT

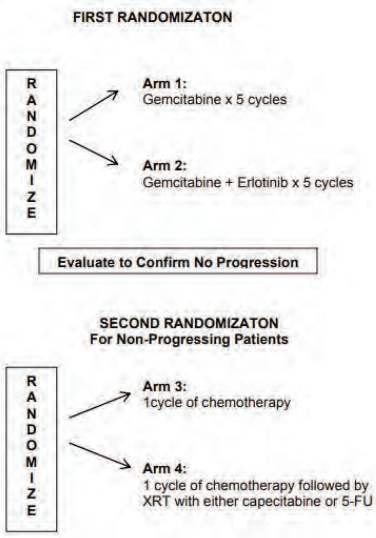
- 1982-2002: 11.526 bolnikov po OP;
- RT mora biti del adjuvantnega zdravljenja



Kooby DA, Gilespie TW, et al. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: an appraisal of data from the national cancer data base. Ann Surg Oncol 2013

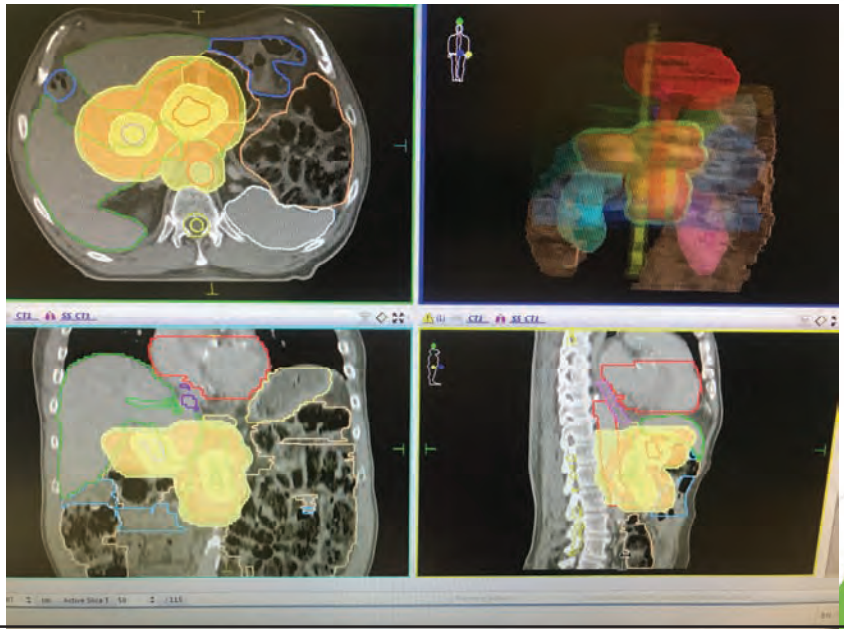
Adjuvantno zdravljenje z RT

- 1000 bolnikov po OP glave trebušne slinavke;
- Rezultati 2020



RTOG trial 0848

Primer poOP RT



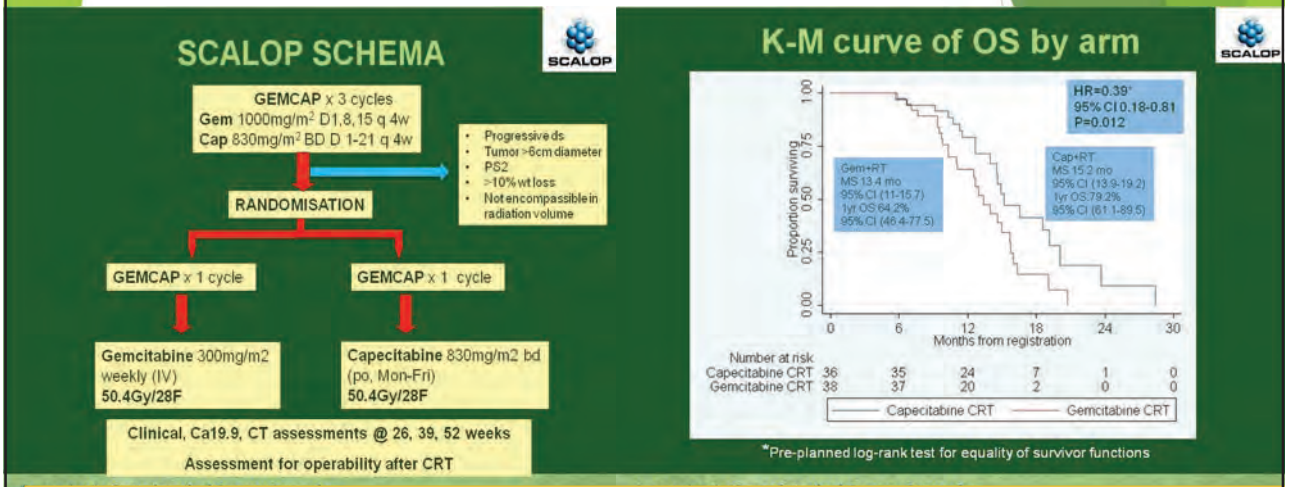
VLOGA RT V SKLOPU NEOADJUVANTNEGA ZDRAVLJENJA PRI MEJNO RESEKTABILNIH TU

4-6 mesecev KT ⟶ RT+KT (derivati 5-FU) (Scalop trial) ali SBRT

- Poveča verjetnost R0 resekcije;
- VMAT> 3-D konformalna RT (50,4Gy v 28 fr): boljša D distrubucija, eskaliranje D, ↓SE;
- GTV +1 cm, ABC sistem;
- SBRT 25-30Gy v 5-6 frakcijah (↓OTT-manj prekinitve sistemske TH).

Katz MH, Crane CH, et al. Management of bordeline resektable pancreatic cancer. Semin Radiat oncol 2014

Ob RT derivati 5-FU> Gemcitabin



RT s kapecitabinom podobne učinkovitosti kot z gemcitabinom , vendar ↓toksična

SCALOP raziskava: Mukherjee, ASCO GI 2013

VLOGA RT V SKLOPU DEFINITIVNEGA ZDRAVLJENJA PRI LOKALNO NAPREDOVALIH TU

- KT+RT>KT
- Odloži lokalni progres,ni ↑OS
- Predvsem za bolnike, kjer ni možno, da postanejo OP

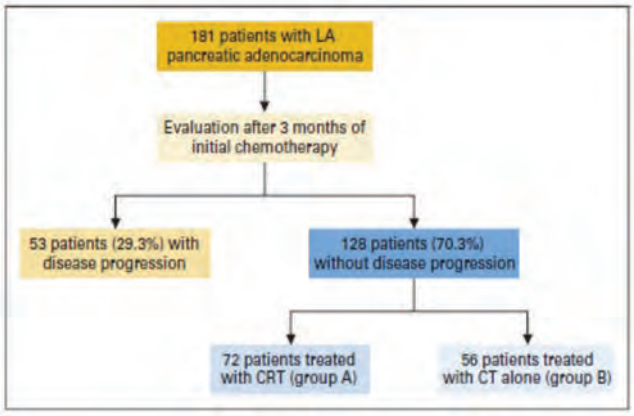
a). 4-6 mesecev KT → RT+KT ali SBRT- če M0

b). Če ni kandidat za KT: RT+KT ali SBRT- če M0

1.Tempero MA, Malafa MP, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines J Natl Compr Canc Netw. 2014;12:1083-1093.
2.LAP07 raziskava: Hammel P, Huguet F, et al. Effect of chemoradiotherapy vs chemotherapy on survival. JAMA 2016

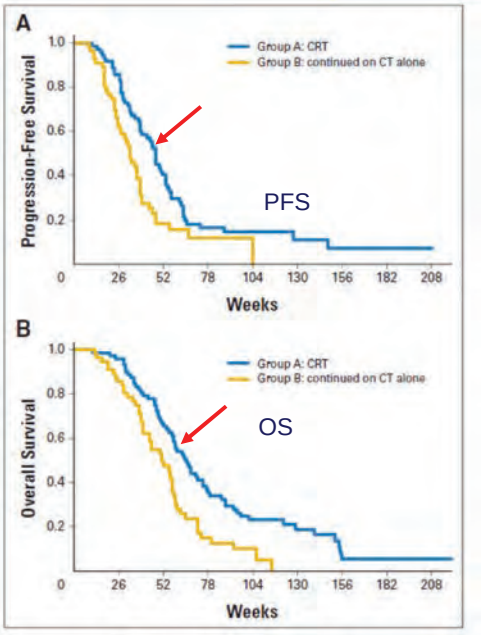
Radiokemoterapija pri lokalno napredovalem raku trebušne slinavke

Retrospektivna analiza



RT+KT bi lahko bila pomembna po uvodni KT za vsaj stabilizacijo bolezni

Huguet JCO 2007



RT pri lokalno napredovalem raku trebušne slinavke

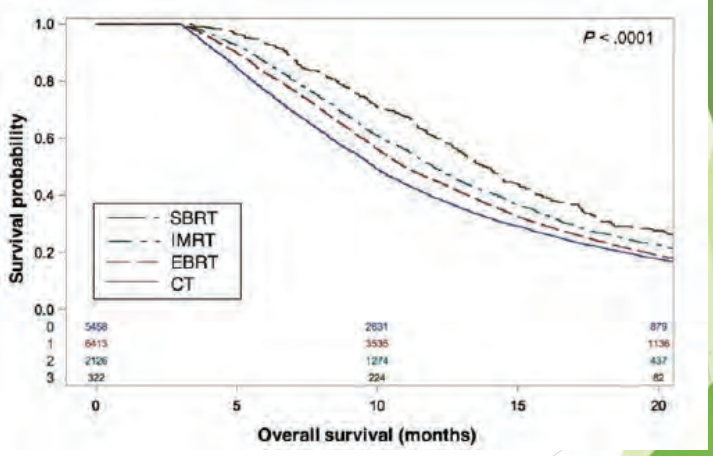
14.331 bolnikov:

a. 38 %KT,

b. 44% KT+3-D RT,

c. 15% KT+IMRT,

d. 3% KT+SBRT



De Geus SWL, Eskander MF, et al. Stereotactic Body Radiotherapy for Unresected Pancreatic Cancer: A Nationwide Review. Cancer 2017

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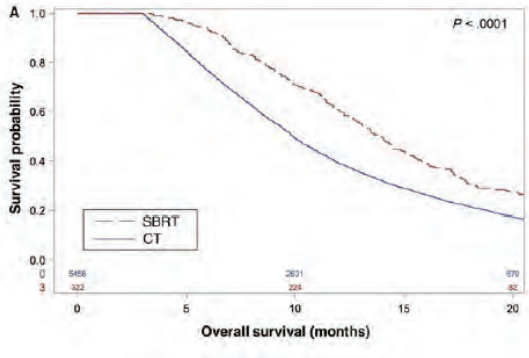

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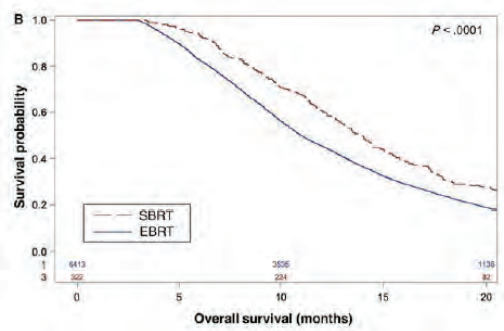

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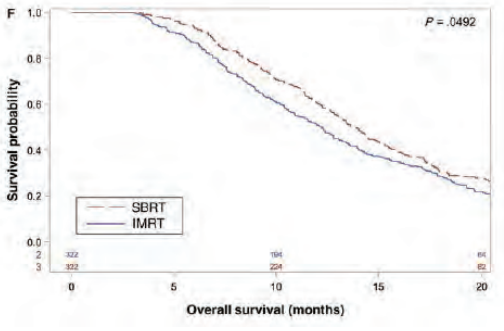

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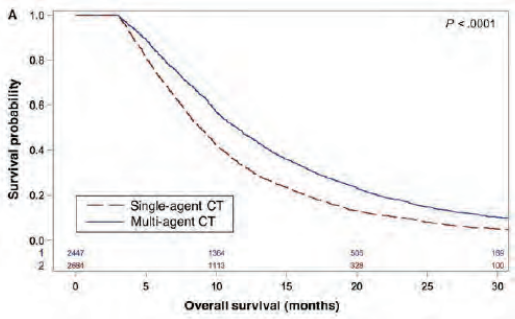


De Geus SWL, Eskander MF, et al. Stereotactic Body Radiotherapy for Unresected Pancreatic Cancer: A Nationwide Review. Cancer 2017

VLOGA RT V SKLOPU ZDRAVLJENJA LOKALNE PONOVITVE BOLEZNI ALI V SKLOPU „SECOND LINE“ ZDRAVLJENJA

a). KT+/- RT

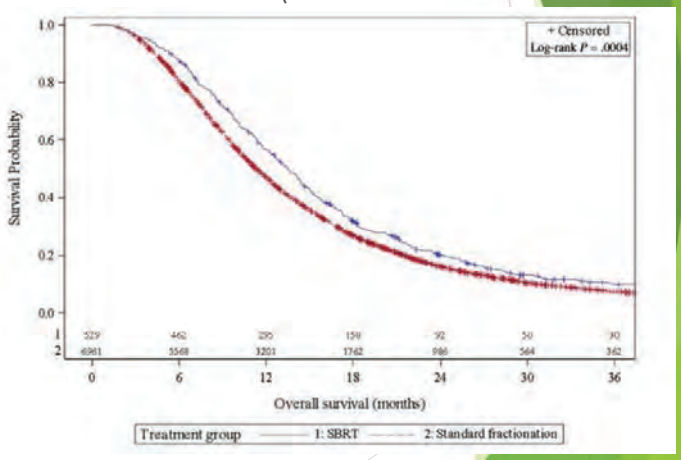
b). SBRT

VLOGA RT V SKLOPU PALIATIVNEGA ZDRAVLJENJA

- Protibolečinsko
- Hemostiptično
- Zmanjšanje obstrukcije,…

SBRT

- SBRT>konvencionalno RT: ↑mediano S in OS_2 ((21.7% vs 16.5%)



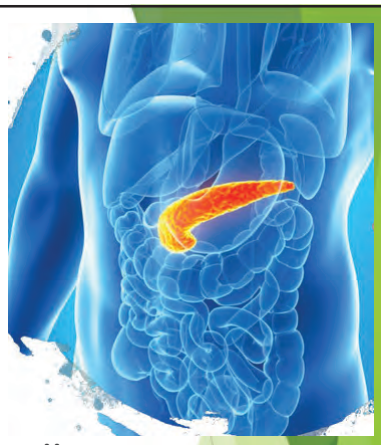
Zhong J, Patel K, *et al*. **Outcomes for Patients With Locally Advanced Pancreatic Adenocarcinoma Treated With Stereotactic Body Radiation Therapy Versus Conventionally Fractionated Radiation** *2017*

SBRT

Indikacije:

- Neresektabilen TU ali recidiv;
- Velikost lezije <5cm;
- >2mm stran od želodca ali dvanajstnika;
- Brez znakov M+;
- V okviru neoadjuvantnega zdravljenja (KT);
- PS 0-2 po WHO

SBRT



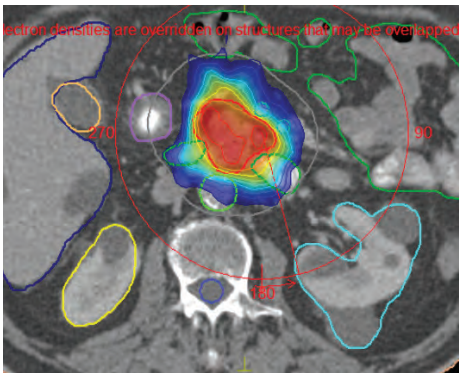
Kontraindikacije:

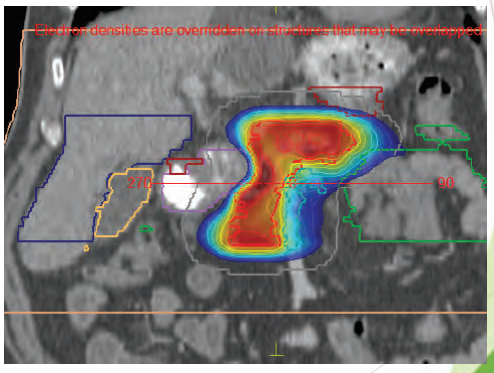
- Predhodnje obsevanje trebuha;
- M+;
- Gastrična ali duodenalna obstrukcija oz invazija;
- Sočasna KT;
- Imunosupresivna TH.

Tolerance na sosednje organe

Organ	Volume	Dose
Duodenum	< 1cc	36Gy
Spinal cord	< 1cc	18Gy
Kidneys	< 35%	15Gy
Stomach, SI	< 3cc	36Gy
Healthy liver	> 700cc	21Gy

Primer bolnika





Atene, november 2018

SBRT INOPERABILNEGA CA PANKREASA

2013

RESEARCH Open Access

SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience

Angelo Tozzi[1], Tiziana Comito[1], Filippo Alongi[1,2*], Pierina Navarria[1], Cristina Iftode[1], Pietro Mancosu[1], Giacomo Reggiori[1], Elena Clerici[1], Lorenza Rimassa[1], Alessandro Zerbi[1], Antonella Fogliata[2], Luca Cozzi[2], Stefano Tomatis[1] and Marta Scorsetti[1]

- Januar 2010 - oktober 2011;
- **30 bolnikov** z **inoperabilnim ali recidivnim adenocarcinomom pancreasa;**
- KT z gemcitabinom pred SBRT;
- predpisana doza **45Gy v 6 frakcijah po 7.5Gy.**

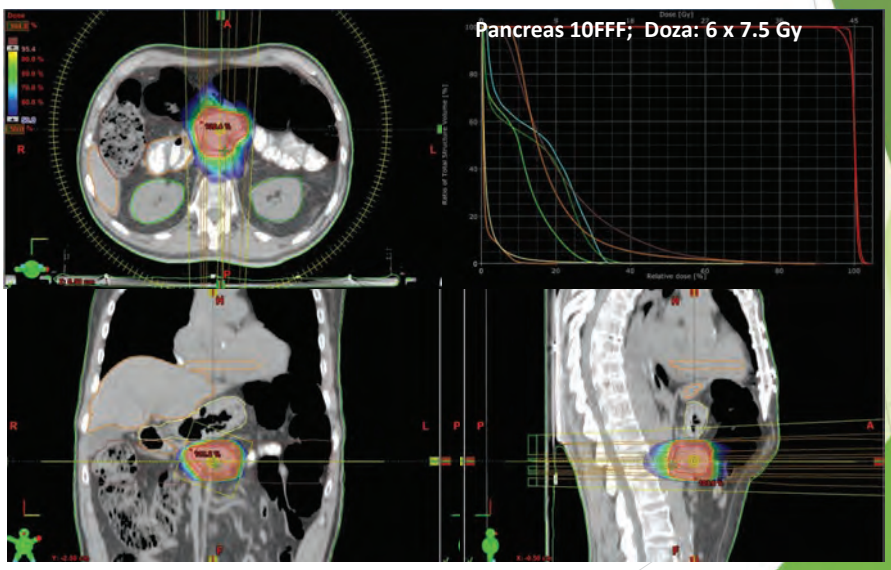
Rezultati

- **Srednji čas sledenja 11 mesecev (2–28 mesecev);**
- **LC 91% pri 6 mesecih, 85% pri 1 letu.**

Restrikcije

MEDULA	D1cc<18 Gy
LEDVICA	V15Gy <35%
DUODENUM	V36Gy<1cc
ŽELODEC	V36Gy<1cc
TANKO ČREVO	V36Gy<3cc
JETRA	(Vcela jetra – V21Gy)>700cc

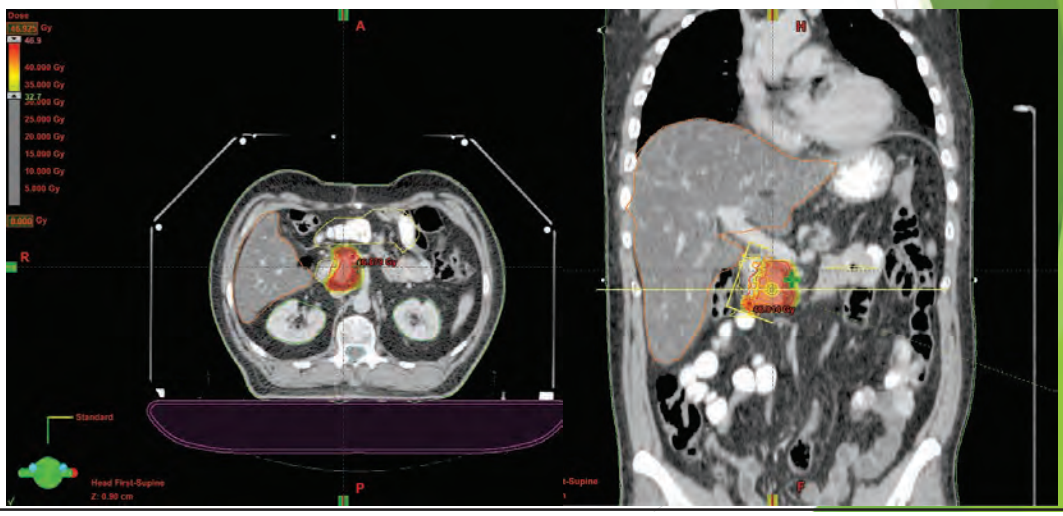
SBRT KARCINOMA PANCREASA



Milano, 2016

SBRT KARCINOMA PANCREASA

Bolnik: 56 let. Neresektabilni adenokarcinom pankreasa;
GEM + FOLFIRI in RT (**45Gy v 6 frakcijah**) -> OP (R0).




“
Hvala lepa
”

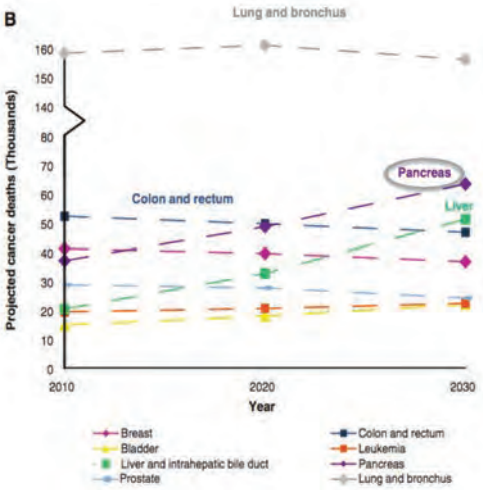
KARCINOM TREBUŠNE SLINAVKE - MULTIDISCIPLINARNI PRISTOP PRI BOLNIKIH Z OMEJENO BOLEZNIJO, POMEN SISTEMSKE TERAPIJE

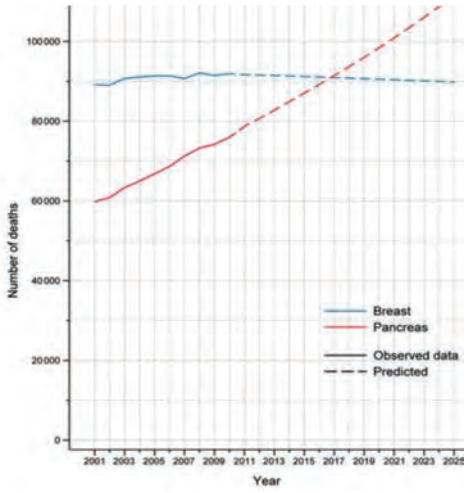
Mag. Zvezdana Hlebanja, dr. med.
Specialistka internistične onkoligije
Onkološki inštitut

UVOD

- cca 85% bolnikov diagnosticiramo v napredovali fazi bolezni
- 15-20% bolnikov primernih za operacijo
- cca 80% bolnikov, ki so operirani in adjuvantno zdravljeni, metastazira
- ozdravljenih <5% bolnikov
- srednje OS = 23 mesecev
- srednje OS, stadij IV, brez zdravljenja = 3 mesece
- 5-letno preživetje <10%
- incidenca je skoraj enaka umrljivosti in strmo narašča

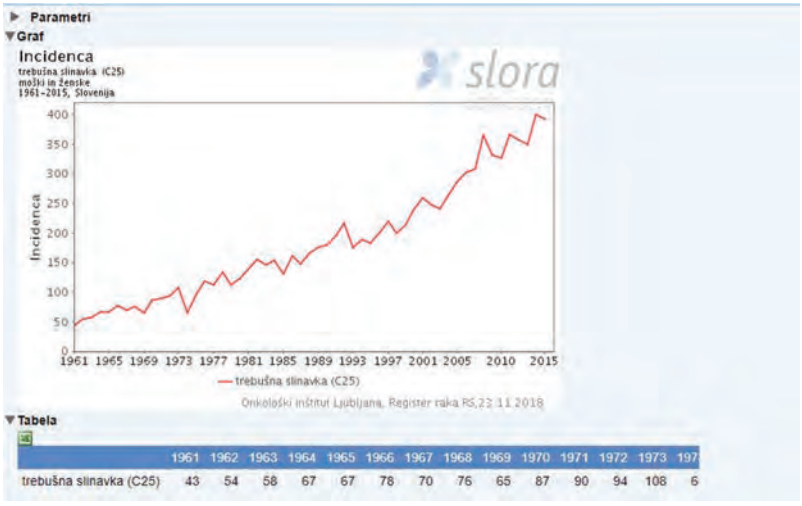
RAK TREBUŠNE SLINAVKE, 2. VZROK SMRTI LETA 2020





INCIDENCA V SLOVENIJI (REGISTER RAKA 2015)

- Zahrbten, pozno odkrit, hitro potekajoč, smrten!



ZDRAVLJENJE

- zahteva multidisciplinarni pristop
- edino kurativno zdravljenje je kirurško
- odvisno je od razširjenosti bolezni, PS bolnika, komorbidnosti in preferenc bolnika
- nujno je agresivno zdavljenje bolečine in drugih z rakom povezanih simptomov - zgodnja vključitev v paliativno oskrbo!

ZDRAVLJENJE OMEJENE BOLEZNI (BREZ ODDALJENIH METASTAZ)

- adjuvantno (post-operativno)

- neoadjuvantno (pred-operativno):
  - potencialno resektabilna bolezen,
  - mejno resektabilna bolezen,
  - lokalno napredovala bolezen

ADJUVANTNO ZDRAVLJENJE

- priporočeno za vse bolnike po R0 resekciji (ki niso prejeli neoadjuvantnega zdravljenja), tudi T1N0
- začne naj se 8-12 tednov po operaciji (do primernega okrevanja po operaciji)
- pred začetkom adjuvantne kemoterapije opravimo:
  - restaging CT
  - določimo tumorske markerje (CA 19-9)

IZBIRA ADJUVANTNE TERAPIJE

- bolnikom informacije o potekajočih kliničnih študijah
- priporočamo 6 mesecev mFolfirinox (za PS=0-1)
- lahko GEM/CAP (PS>1)
- gemzar mono je razumna opcija, pri PS>1, oz ko gre za komorbidnost, ki preprečuje agresivno terapijo
- nosilci BRCA mutacij naj bodo zdravljeni adjuvantno, enako kot ostali
- vloga adjuvantne radio-kemoterapije ostaja kontaverzna:
  - EU večinoma le kemoterapija,
  - ZDA dopušča kemoterapijo in radiokemoterapijo (ASCO: po 6 mesecih adjuvantne gemcitabin vsebujoče kemoterapije dodatek radiokemoterapije - pri N+,R1)

ADJUVANTNO ZDRAVLJENJE - PREGLED ŠTUDIJ

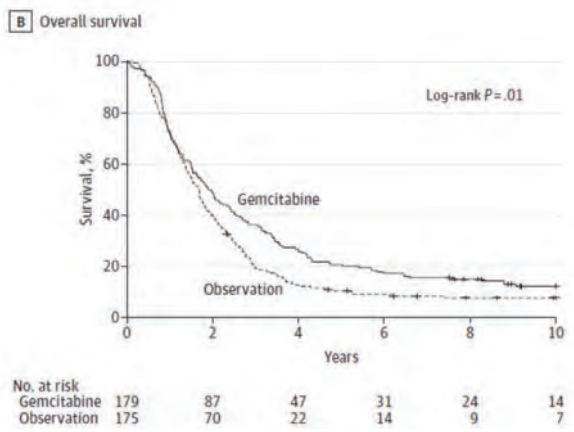
Table 2. Adjuvant Therapy for Pancreatic Cancer.*

Study	No. of Patients	Treatment	Survival	P Value
GITSG[58]	43	Observation Fluorouracil plus radiotherapy	10% at 2 yr 20% at 2 yr	0.007
EORTC[59]	218	Observation Fluorouracil plus radiotherapy	26% at 2 yr 34% at 2 yr	0.10
ESPAC-1[60]	289	Observation Chemoradiotherapy	16.9 mo (median)† 13.9 mo	
		Fluorouracil Chemoradiotherapy plus fluorouracil	21.6 mo 19.9 mo	
CONKO-01[61]	368	Observation Gemcitabine	10.4% at 5 yr 20.7% at 5 yr	0.01
ESPAC 3[62]	1088	Fluorouracil Gemcitabine	23.0 mo (median) 23.6 mo	0.39
RTOG 9704[63]	451	Fluorouracil plus radiotherapy Gemcitabine plus radiotherapy	22% at 5 yr 18% at 5 yr	0.12
JASPAC-01[64]	378	S-1 (oral fluoropyrimidine) Gemcitabine	70% at 2 yr 53% at 2 yr	<0.001

* CONKO-01 denotes Charité Onkologie 01, EORTC European Organization for Research and Treatment of Cancer, ESPAC European Study Group for Pancreatic Cancer, GITSG Gastrointestinal Tumor Study Group, JASPAC-01 Japan Adjuvant Study Group of Pancreatic Cancer, and RTOG 9704 Radiation Therapy Oncology Group 9704.
† The estimated 5-year survival rate was 10% among patients who received chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy (P=0.05). The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (P=0.009).

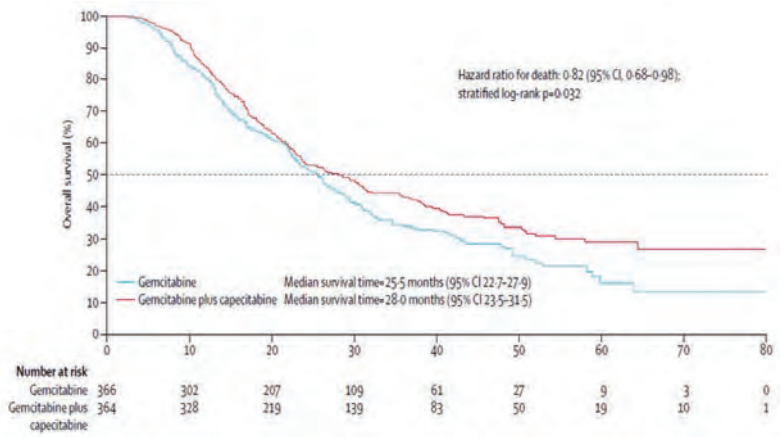
ADJUVANTNI GEMCITABIN / CONKO - 001

- registracijska študija, ki je dokazala izboljšanje celokupnega preživetja za 24% glede na opazovano skupino

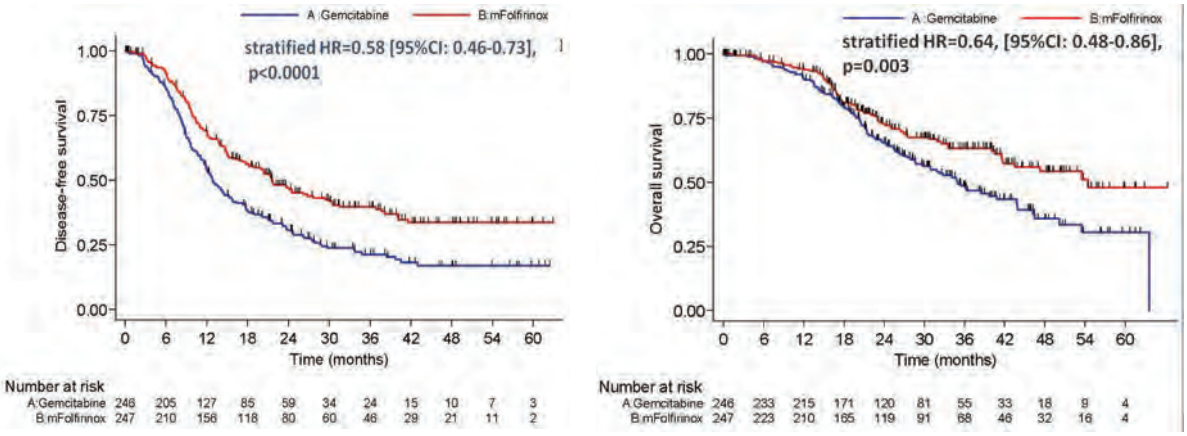


ADJUVANTNA KEMOTERAPIJA / ESPAC-4

- nov standard adjuvantne kemoterapije (GEM/CAP) do leta 2018



ADJUVANTNA KEMOTERAPIJA ASCO 2018 / PRODIGE



Nov standard adjuvantne kemoterapije (mFolfirinox)

ADJUVANTNO ZDRAVLJENJE

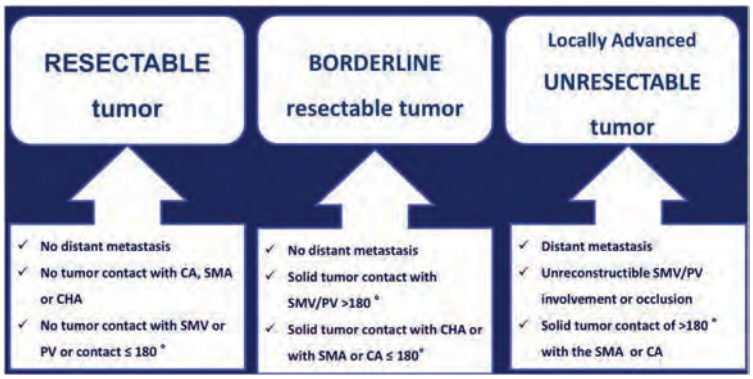
- naj sledi optimalni kirurgiji (izkušeni centri z velikim številom opravljenih operacij, specializirani kirurgi), LE R0 RESEKCIJA ZAGOTAVLJA MOŽNOST PREŽIVETJA
- adjuvantna terapija ostaja standard zdravljenja, čeprav se proučujejo možnosti neoadjuvantne terapije
- adjuvantno zdravimo bolnike v dobri psihofizični kondiciji, za tiste v odlični priporočamo mFolfirinox, sicer GEM/CAP ali gemzar

NEO-ADJUVANTNO ZDRAVLJENJE

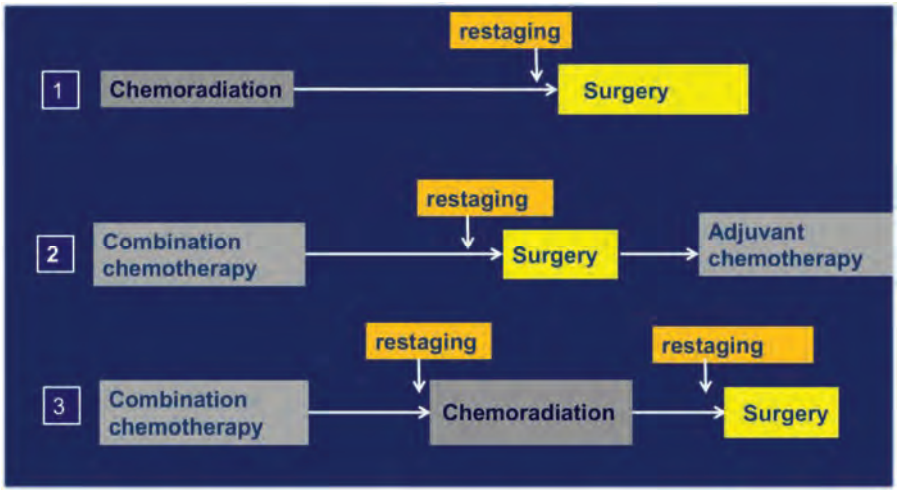
- nizek %R0 resekcij
- slabo preživetje tudi po radikalni resekciji in adjuvantni kemoterapiji
- dejstvo je, da prodaljšano okrevanje po Whipplovi resekciji prepreči pravočasno uvedbo adjuvantnega zdravljenja pri ¼ bolnikov
- od tod razmišljanje o uvedbi predoperativnega zdravljenja pri nemetastatskih bolnikih
- redki bolniki s tumorji manjšimi od 2cm in negativnimi bezgavkami verjetno tovrstnega zdravljenja ne potrebujejo in so kandidati za takojšnjo operacijo
- načini neo-adjuvantnega zdravljenja niso dorečeni (terapevtske prakse v ZDA in EU se razlikujejo)

NEO-ADJUVANTNO ZDRAVLJENJE

- ločimo:
  - potencialno resektabilno boleznen,
  - mejno resektabilno boleznen,
  - lokalno napredovalo boleznen



TRENUTNE MOŽNOSTI ZDRAVLJENJA



ZDRAVLJENJE MEJNO RESEKTABILNEGA OZ LOKALNO NAPREDOVALEGA CA PANKRESA

Regimen	Stage	Study Design	N	ORR, %	Resection rate, %	R0 resections, %	1-year PFS, %
FOLFIRINOX[1]	BL or unresectable	Retro-spective	18	---	39	28	83
FOLFIRINOX[2]	laPC	Retro-spective	16	50	---	---	---
FOLFIRINOX[3]	laPC or BL	Registry	23	34	---	---	75
FOLFIRINOX[4]	laPC or BL	Retro-spective	43	---	54	42	---
FOLFIRINOX[5]	BL or unresectable	Phase II	32	37	41	---	---
FOLFIRINOX[6]	laPC	Phase II[b]	8	63	37	---	---
Nab-paclitaxel + gemcitabine[7]	BL or resectable	Phase II	16	31[c]	56[d]	89[e]	---

NEO-ADJUVANTNO ZDRAVLJENJE LOKALNO NAPREDOVALEGA CA PANKREASA

- cca 40% bolnikov
- ni standardnih pristopov
- možnosti: obsevanje, kemoterapija, radiokemoterapija in kombinacije
- splošna navodila: inicialna kemoterapija (ločimo bolnike, ki gredo hitro v progres) - prihranimo nepotrebno obsevanje
- incialna kemoterapija:
  - gem + nab pacli = standard
  - ob PS = 0-1, N bilirubin, brez komorbidnosti = mFolfirinox

BOLNIKI, KI NE METASTAZIRAJO MED INICIALNO KEMOTERAPIJO

- če razmišljamo o resekciji, priporočamo, da se inicialni kemoterapiji doda radiokemoterapija (ne priporočamo senzibilizacije z gemcitabinom) - izboljšano možnost R0 resekcije
- alternativa (ob uporabi mFolfirinoxa) je nadaljevanje zdravljenja s kemoterapijo do maksimalnega odgovora (ni jasno, če dodatek obsevanja tako kompleksi kemoterapiji izboljša odstotek R0 resekcij)
- bolniki, ki so odgovorili na inicialno zdravljenje naj bodo eksplorirani

BOLNIKI, KI NE METASTAZIRAJO MED INICIALNO KEMOTERAPIJO

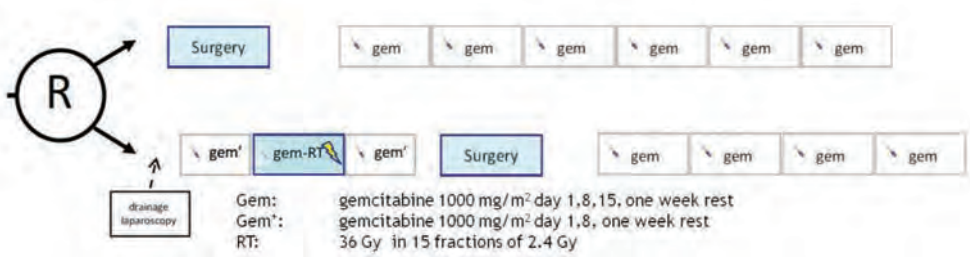
- če niso kandidati za eksploracijo po inicalni kemoterapiji priporočamo nadaljevanje kemoterapije (raje kot dodatek radiokemoterapije)
- radiokemoterapijo dodamo le pri tistih, ki ne prenašajo več kemoterapije (za boljšo lokalno kontrolo in ohranjanje PS)

NEO-ADJUVANTNO ZDRAVLJENJE MEJNO RESEKTABILNEGA CA PANKREASA

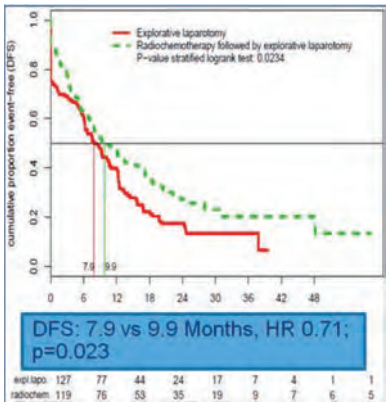
- v to skupino sodijo bolniki, kjer je možnost neradikalne resekcije visoka, največkrat zaradi vaskularne invazije (zlasti AMS)
- ni standardnih pristopov
- za bolnike v izrazito dobri psihofizični kondiciji, ki so seznanjeni z možnostjo nezagotovljene dobrobiti tovrstnega zdravljenja, priporočamo inicialno kemoterapijo, ki ji sledi radiokemoterapija in nato resekcija - raje kot primarno operacijo (NCCN, ESMO)

- NEO-ADJUVANTNO ZDRAVLJENJE POTENCIALNO RESEKTABILNIH CA PANKREASA: za veliko večino priporočamo neoadjuvantno zdravljenje, ki mu sledi operacija, izjema so tumorji <= 2cm brez prizadetih bezgavk

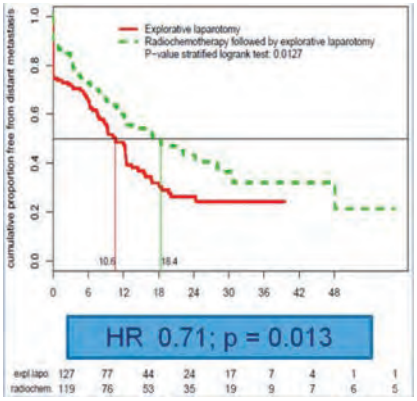
DOBROBIT NEO-ADJUVANTNEGA ZDRAVLJENJA PRED ADJUVANTNIM (PREOPANC ŠTUDIJA, ASCO 2018)



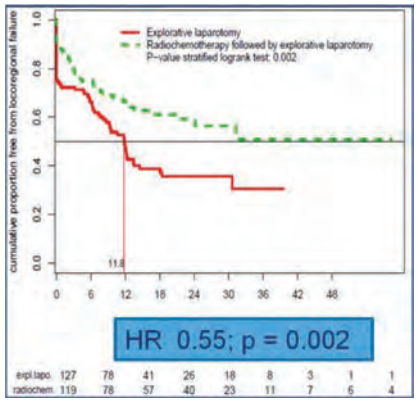
PREOPANC ŠTUDIJA - DFS



Overall DFS

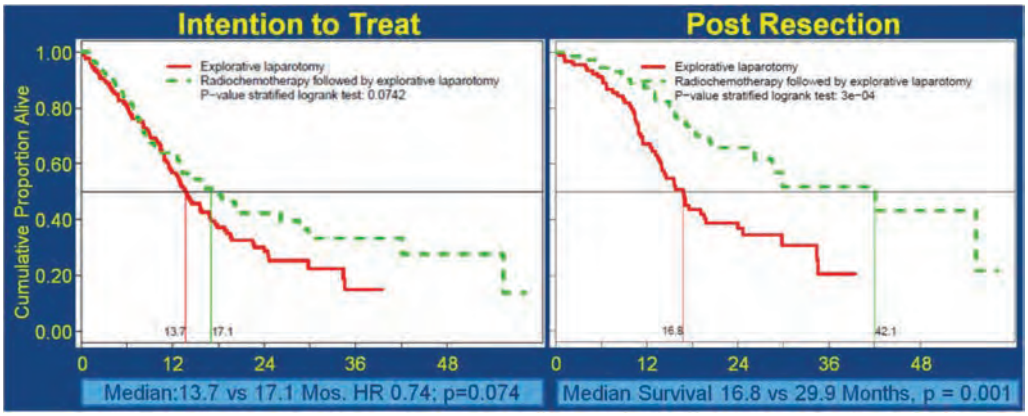


Distant Metastasis Free Interval



Locoregional Recurrence Free Interval

PREOPANC ŠTUDIJA - OS



ZAKLJUČKI

- **adjuvantno kemoterapijo**, naj dobe vsi bolniki po R0 resekciji, ki niso bili deležni neo-adjuvantnega zdravljenja (tudi T1N0)
- vrsta adjuvantne kemoterapije je odvisna od PS: odličen PS - mFolfirinix, raje od GEM-CAP ali GEM MONO
- vloga adjuvantne radiokemoterapije ni dorečena
- **Neo-adjuvantno zdravljenje** obeta, vendar še vedno ni prepričljivih podatkov iz randomiziranih študij
- najboljši režim neo-adjuvantnega zdravljenja ni dorečen, ostaja multidisciplinarni izziv
- zaenkrat še največ obeta inicialna kemoterapija, ki ji lahko sledi radiokemoterapija in nato operacija
- mfolfirinox je obetajoč režim predoperativnega zdravljenja za bolnike v izrazito dobrem PS
- podporno zdravljenje bolečine, hujšanja, depresije, biliarne obstrukcije, insuficience pankreasa, ter preprečevanje tromemboličnih zapletov mora biti zagotovljeno ves čas

Rak želodca - kirurgija

Omejc M

Klinični oddelek za abdominalno kirurgijo, Klinični center Ljubljana

RAK ŽELODCA

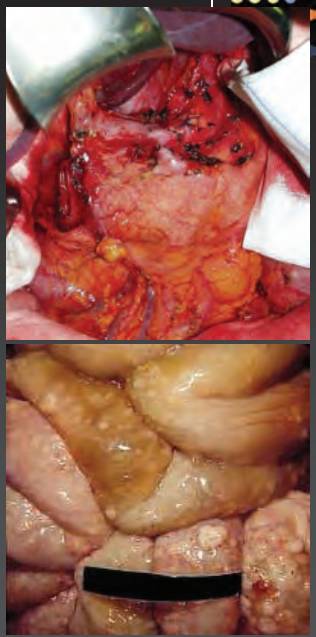
- lokalna kontrola raka:

  temelj zdravljenja

- recidiv po omejeni kirurški resekciji

  lokalni/regionalni recidiv: **50% - 80%**

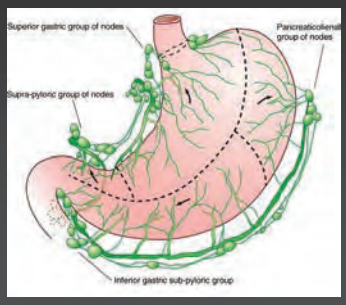
  ⇨ ležišče želodca
  ⇨ regionalne bezgavke
  ⇨ anastomoza
  ⇨ krn dvanajstnika



Gunderson LL et al. Int J Radiation Oncol Biol, 1981

Napredovanje tumorja

↑ globina vraščanja v steno želodca - ↑ prizadetost regionalnih bezgavk - ↓ 5 letno preživetje



Cilj lokalne kontrole so zasevki v bezgavkah

"The surgery of cancer is not the surgery of organs; it is the surgery of the lymphatic system".

Sir Berkeley Moynihan

Depth		(n)	LN	Liver	Perit.	5YSR
pT1	M	1063	3.3	0.0	0.0	93.3
	SM	881	17.4	0.1	0.0	88.9
pT2	MP	436	46.4	1.1	0.5	81.3
	SS	325	63.7	3.4	2.2	65.8
pT3	SE	1232	78.9	6.3	17.8	35.5
pT4	SI	724	89.8	15.5	41.6	10.1
Overall		4683	47.8	4.5	11.5	60.3

Incidence of metastasis and 5-YSR according to the depth of tumor invasion
Patients operated on between 1972 -91, NCCH

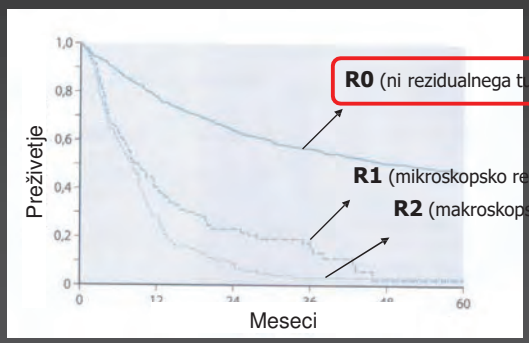
Neresektabilnost

- Oddaljene metastaze
- Vraščanje/preraščanje v glavne žile (aorta, truncus celiakus, art. hepatika, proks. del art. lienalis)
- ? LUAE (distalno vraščanje v art. lienalis)
- ? Whipple (vraščanje v glavo trebušne slinavke)

laparoskopija ev. neoadjuvant.

***R0** resekcija*

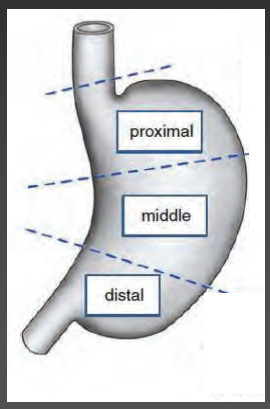
Odstranitev večjega dela ali vsega želodca s tumorjem z zadostnim varnostnim robom v zdravo v oralni in v aboralni smeri ter v »tretji dimenziji« (okolne oporne strukture, limfna pota in bezgavke ter sosednji organi).



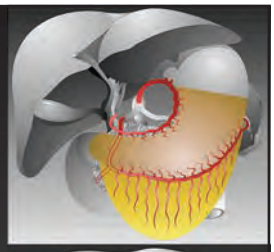
Totalna / subtotalna gastrektomija

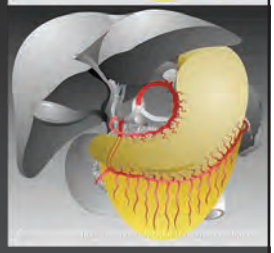
Obseg resekcije odvisen od:

- lokalizacije tumorja
- histološkega tipa *(Lauren)*
- cTNM stadij



Resekcija



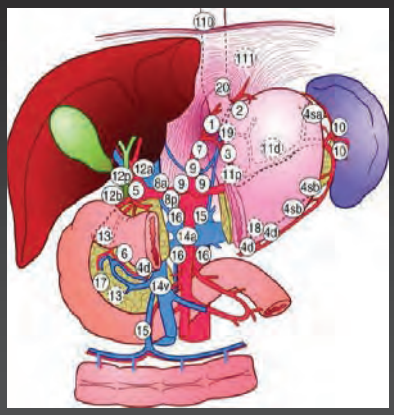


- Tu v distalni tretjini želodca
  - subtotalna resekcija (intestinalni tip raka)
  - totalna gastrektomija (difuzni tip raka)
  - D2 limfadenektomija
- Tu v srednji tretjini želodca
  - totalna gastrektomija in D2 limfadenektomija
- Tu v proksimalni tretjini želodca
  - razširjena gastrektomija vključno z odstranitvijo distalnega dela požiralnika, limfadenektomija

Bezgavke

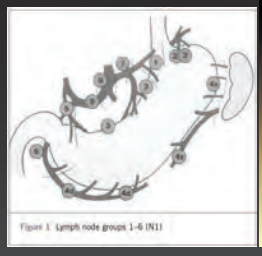
N1: perigastrične bezgavke
ob mali krivini želodca
1, 3, 5
ob veliki krivini želodca
2, 4, 6

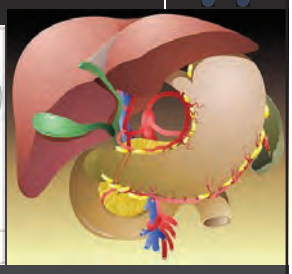
N2: bezgavke ob
art. gastriki sin. *(7)*
art. hepatiki com. *(8)*
truncus celiakus *(9)*
hilusu vranice *(10)*
art. lienalis *(11)*



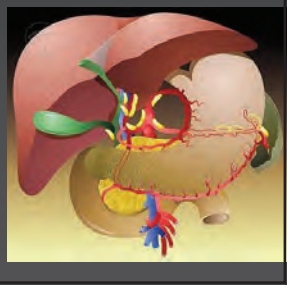
Limfadenektomija – odstranitev bezgavk

- D1 limfadenektomija:
  odstranitev perigastričnih bezgavk





- D2 limfadenektomija:
  perigastrične + bezgavke ob trunkus celiakusu, art. hepatiki komunis, art. lienalis in v hilusu vranice



Ali obseg limfadenektomije vpliva na preživetje ?

"Stage migration"

"When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."

Will Rogers

- ↑ razširjena limfadenektomija = ↑ zanesljiv stadij
- "Upstaging"
- Izboljšano "stage-specific" preživetje pri razširjeni limfadenektomiji (D2, D3)

D1 vs. D2: retrospektivne študije

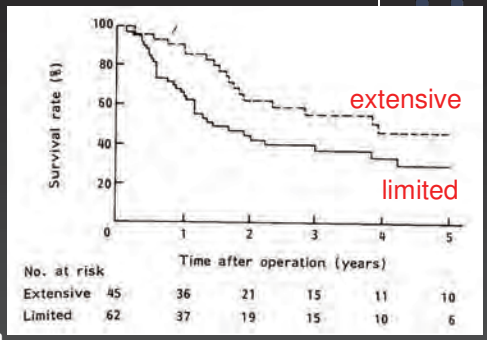
- *Pacelli, G. Br J Surg. 1993*

  1 inštitucija
  2 kirurški ekipi

n=320

n=157 razširjena limfadenektomija
n=163 omejena limfadenektomija

5 letno preživetje: stadij III 48.7 vs. 29.8%. *(p=0.02)*



D1 vs. D2: nerandomizirane študije

Siewert 1998 - Annals of Surgery

- n=1654
- Prospektivna, nerandomizirana
- Obseg limfadenektomije definiran s številom bezgavk v resektatu

- planirano za vse D2, retrospektivno inadekvatne resekcije D1

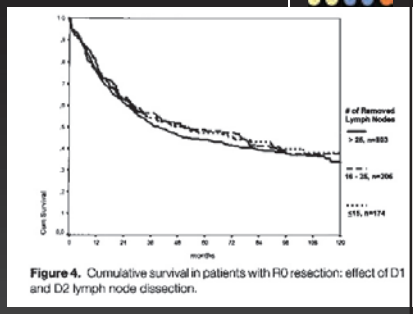


Figure 4. Cumulative survival in patients with R0 resection: effect of D1 and D2 lymph node dissection.

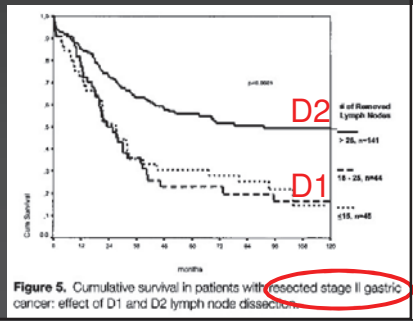


Figure 5. Cumulative survival in patients with resected stage II gastric cancer: effect of D1 and D2 lymph node dissection.

D1 vs. D2: randomizirane (RCT) študije

*Bonenkamp: 1995/1999 - Lancet /*NEJM

- n=711
- preoperativna randomizacija
- follow up: mediana 6 let

	D1 (n=380)	D2 (n=331)
Mortaliteta	15 (4%)	32 (10%)
Morbiditeta	94 (25%)	142 (43%)
Reoperacije	8%	18%
Hospitalizacija (dnevi)	18	25

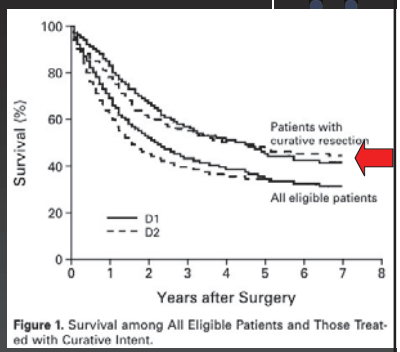


Figure 1. Survival among All Eligible Patients and Those Treated with Curative Intent.

Overall survival - <u>no benefit</u>

↑ poperacijske komplikacije in smrtnost v D2 *(p<0.005)*

Hartgrink HH et al. J Clin Oncol. 2004 Jun 1;22(11

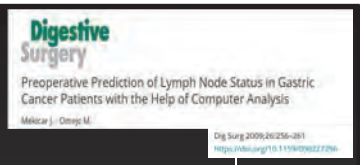
D2 ali D1 ?

Visoka pooperativna smrtnost zakrije dolgoročne učinke zdravljenja

"If postoperative death is excluded, the 11 year survival data favor the D2 dissection".

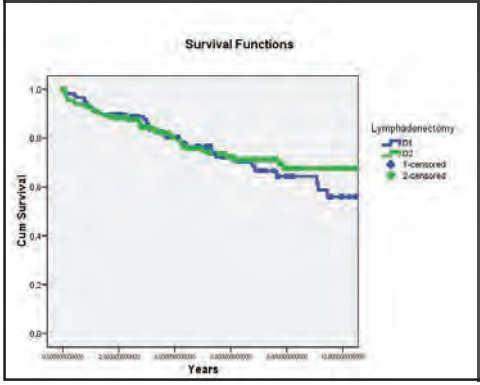
van de Velde CJH, 2004

5-letno preživetje (UKC Ljubljana)



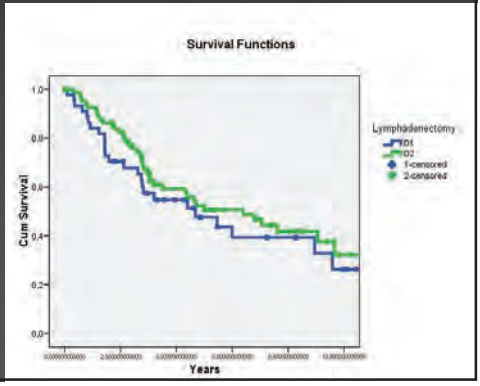
- Stage I+II (N0)
  - D1 : n = 122, 78%
  - D2 : n = 153, 77%

  p = ns



- Stage I+II (N1 in N2)
  - D1 : n = 47, 49%
  - D2 : n = 84, 51%

  p = ns

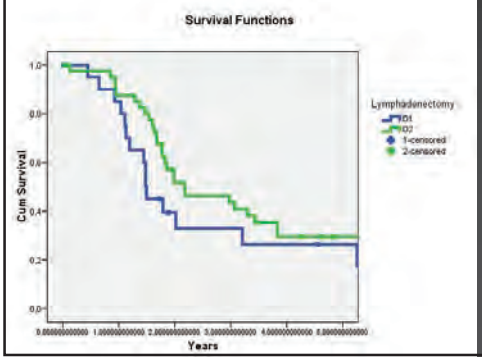


5-letno preživetje (UKC Ljubljana)

Digestive Surgery
Preoperative Prediction of Lymph Node Status in Gastric Cancer Patients with the Help of Computer Analysis

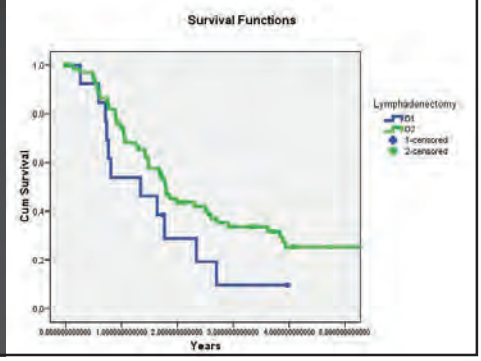
- Stage III (N0 in N1)
  - D1 : n = 20, 27%
  - D2 : n = 40, 33%

  p = 0.107



- Stage III (N2)
  - D1 : n = 13, 10%
  - D2 : n = 66, 30%

  p = 0.034



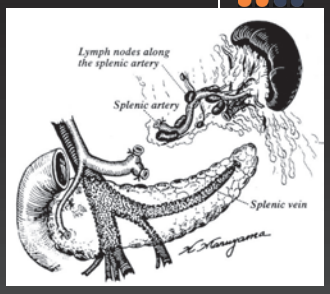
Limfadenektomija

Digestive Surgery
Preoperative Prediction of Lymph Node Status in Gastric Cancer Patients with the Help of Computer Analysis

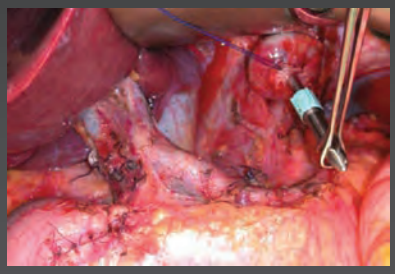
- D2 limfadenektomija je varna operacija: izkušen kirurg, izogibanje splenektomije in resekcije pankreasa. Pooperativna smrtnost se ne razlikuje med D1/D2 skupinama bolnikov.
- Boljša lokalna kontrola tumorja in bolj zanesljiv staging.
- Potencialna korist v podskupini bolnikov z okultno boleznijo v D2 bezgavkah. Boljše 5 letno preživetje bolnikov v stadiju III pri katerih je bila narejena D2 limfadenektomija.

Razširjene/multivisceralne resekcije

- **Vranica**
  - splenektomija le pri raku v zgornji tretjini želodca, raku na strani velike krivine v srednji tretjini v napredovalih stadijih (S3, S4).

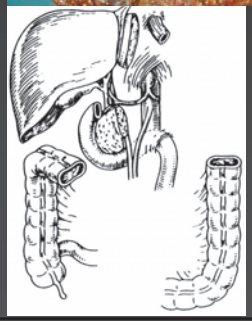


- **Pankreas**
  - ***pancreas-preserving total gastrectomy***
  - resekcija pankreasa le v primeru direktnega vraščanja tumorja

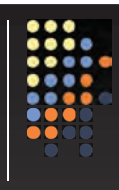


Razširjene/multivisceralne resekcije

- **T4 tumor: R0 resekcija**
  - vranico, rep trebušne slinavke, del jeter (2. in 3. segment), del transverzuma, desni kolon s transverzumom, dvanajstnik z glavo trebušne slinavke.
  - LUAE (eksenteracija levega zgornjega kvadranta).



Klasična / laparoskopska resekcija

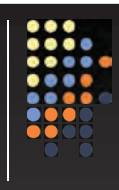


- Lap. distalna resekcija: early gastric cancer
- *West vs. East: stage, BMI, age*

Hu Y, et al. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. J Clin Oncol 2016; 34:1350.

Honda M, et al. Long-term Outcomes of Laparoscopic Versus Open Surgery for Clinical Stage I Gastric Cancer: The LOC-1 Study. Ann Surg 2016; 264:214.

ZAKLJUČEK



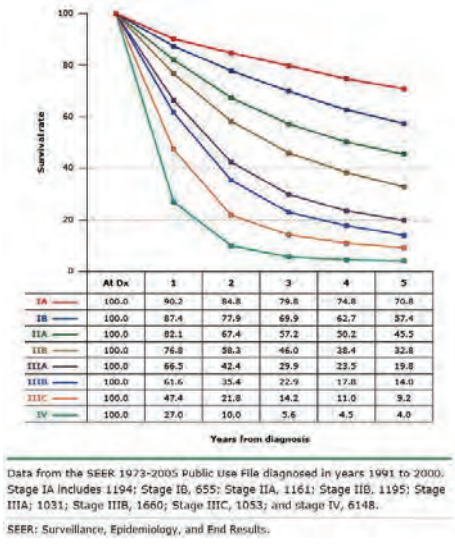
- kirurgija - temelj zdravljenja raka želodca
- izboljšanje rezultatov možno ob zgodnejšem odkrivanju
- pooperativna smrtnost in obolevnost odvisna od izkušenj kirurga, inštitucije.
- multidisciplinarni pristop (kirurgija, radioterapija, kemoterapija, …)

RAK ŽELODCA
obsevanje

Paliativna RT

- *Tey et al.: palliative radiotherapy for gastric cancer: a systematic review and meta-analysis, 2016*
- **Hemostiptični efekt: 74%** Ni razlik v BED ≥ 39Gy *vs* BED < 39Gy!
- **Protibolečinski efekt: 67%**
- **Izboljšanje simptomov obstrukcije: 68%**
- Stranski učinki s strani GIT G3-4: < 15%
- Trajanje efekta: 1,5-11,4 mesecev

Celokupno preživetje pri zgolj operiranih



	At Dx	1	2	3	4	5
IA	100.0	90.2	84.8	79.8	74.8	70.8
IB	100.0	87.4	77.9	69.9	62.7	57.4
IIA	100.0	82.1	67.4	57.2	50.2	45.5
IIB	100.0	76.8	58.3	46.0	38.4	32.8
IIIA	100.0	66.5	42.4	29.9	23.5	19.8
IIIB	100.0	61.6	35.4	22.9	17.8	14.0
IIIC	100.0	47.4	21.8	14.2	11.0	9.2
IV	100.0	27.0	10.0	5.6	4.5	4.0

Years from diagnosis

Data from the SEER 1973-2005 Public Use File diagnosed in years 1991 to 2000. Stage IA includes 1194; Stage IB, 655; Stage IIA, 1161; Stage IIB, 1195; Stage IIIA; 1031; Stage IIIB, 1660; Stage IIIC, 1053; and stage IV, 6148.

SEER: Surveillance, Epidemiology, and End Results.

Washington et al Ann Surg Oncol, 2010

Multimodalen pristop

Vsebina

vloga obsevanja

- Kdaj
- Kako
- Pogled naprej

KDAJ ?

Pooperativno

Predoperativno

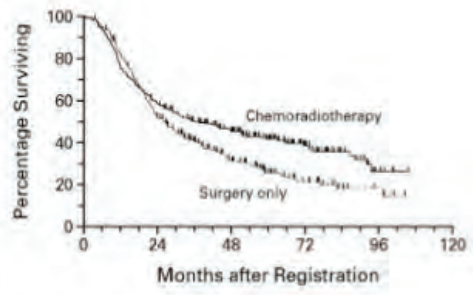
Macdonalds JS et al., 2001: Chemoradioterapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction

resecirani Ca GEJ ali želodca
stadij Ib-IV
n=556

randomizacija

opazovanje
n= 275

poop RTKT
(5FU/LV, 45Gy)
n= 281



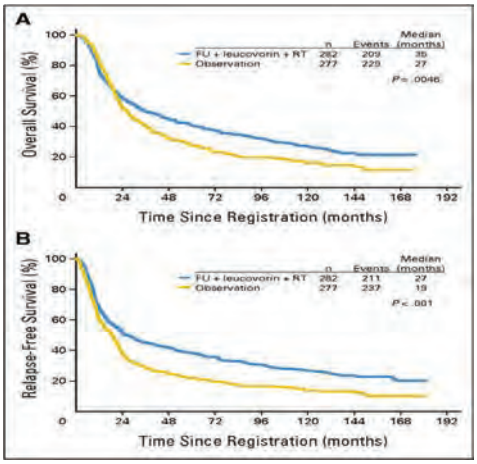
Macdonald et al., NEJM 2001

median OS: 27m *vs* 36m
3-yr OS: 50% *vs* 41%
3-yr DFS: 48% *vs* 31%

Le pri 10% D2 disekcija

2D obsevalna tehnika

Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection



Smalley S R et al. JCO 2012

Lee J et al., 2012: Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial.

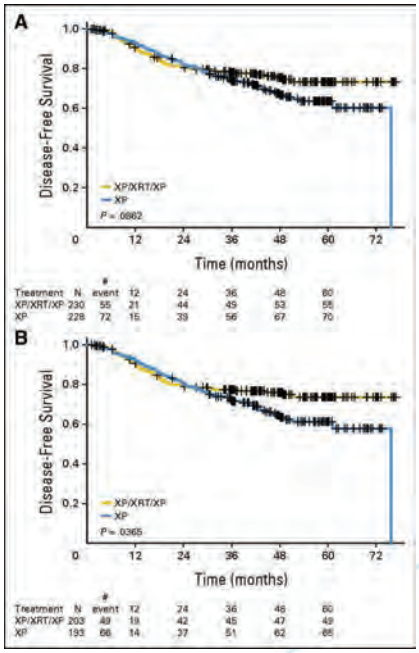
Adenokarcinom želodca
D2 disekcija
n=458

→ randomizacija

→ KT (x+cis)

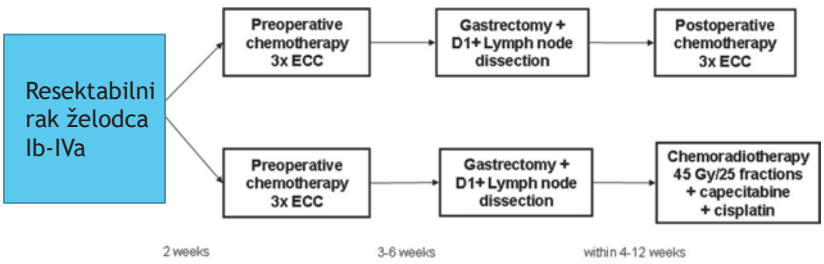
→ KT (x+cis) → KTRT (x, 45Gy)

ARTIST study

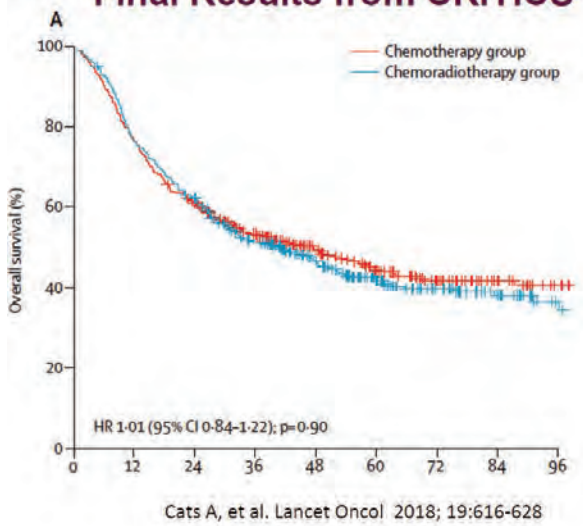


Lee J et al. JCO 2012;30:268-273

Verheij et al, 2016 Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS study)



Final Results from CRITICS



Cats A, et al. Lancet Oncol 2018; 19:616-628

CRITICS study

	CT	CRT
5-year OS, %	41.3	40.9
p-value	0.99	
Grade ≥3 AEs	**CT**	**CRT**
Haematological, %	44	34
p-value	0.01	
Gastrointestinal, %	37	42
p-value	0.14	

Zdravljenje dokončalo 46% bolnikov v KT roki in 55% v KTRT roki.

Pri bolnikih z resektabilnim rakom želodca ni razlike v OS.

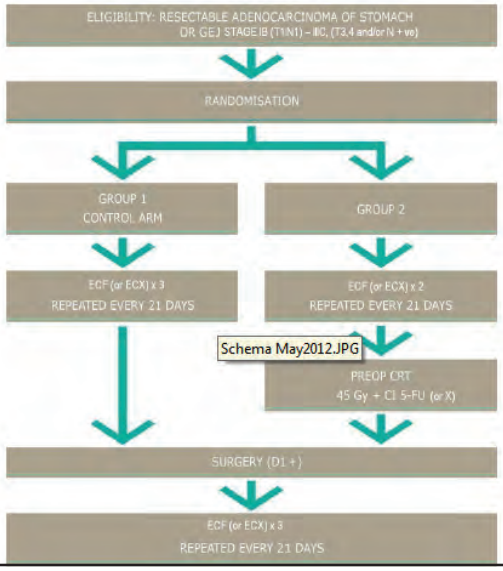
Stadij pT2N0 R0 resekcija ?

- *NCCN:* pooperativna RTKT pri visoko rizičnih: slabo diferencirani, limfovaskularna/perinevralna invazija, <50 let, neadekvatna (D2) disekcija
- *ESMO:* ni posebnih priporočil za ta stadij (adj. RTKT ali KT)

Predoperativno zdravljenje

- Zmanjševanje tumorja (neresektabilni tumorji!), boljša oksigeniranost tkiv, manjši volumni, manjša toksičnost, večja komplianca, kontrola mikrometastaz
- Še ni objavljenih rezultatov raziskav faze III, ki bi potrdile dobrobit dodatka RT k predoperativni KT
- TOP GEAR študija-poteka

TOPGEAR: a randomised phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG).

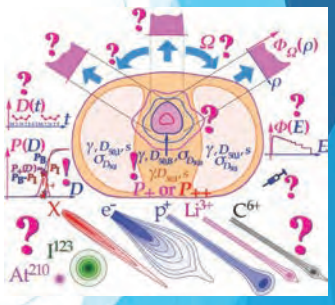


Vmesna analiza (Leong et al, 2017):

- 93% bolnikov prejme vse predoperativne KT cikle v KT roki in 98% v RTKT roki; pooperativno 65% *vs* 53%
- ni razlik v deležu bolnikov, ki so operirani
- ni razlik v pooperativnih komplikacijah
- ni razlik v GI ali hematološki toksičnosti G3/4
- predoperativna RTKT je varna

NA KAKŠEN NAČIN

- Vrisovanje tarčnih volumnov
- Sodobne (bolj konformne tehnike obsevanja): IMRT, VMAT
- Ustrezen IGRT



Vrisovanje tarčnih volumnov - pooperativno

- R0 resekcija: nimamo tumorja (GTV); samo CTV in PTV
- R1 / R2: boostiramo ostanek - če ga lahko določimo
- Kaj vključimo v CTV???
- PTV: geometrično konstruiran volumen (upoštevanje premikov)

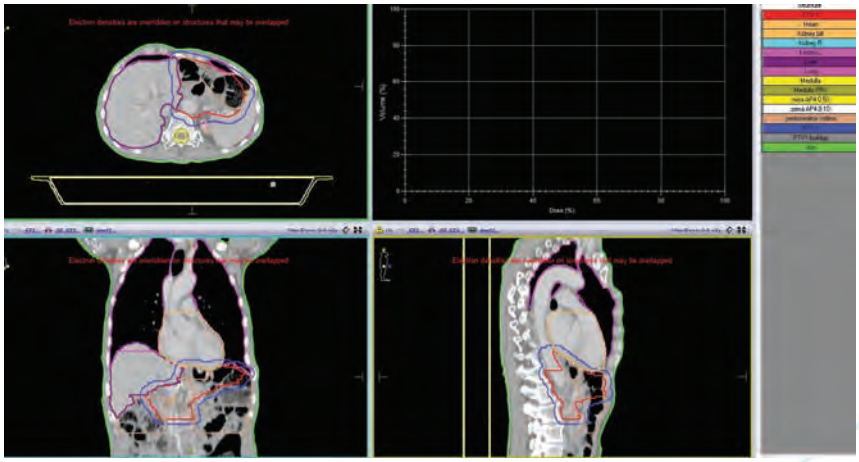
Pooperativni CTV

Ležišče tumorja

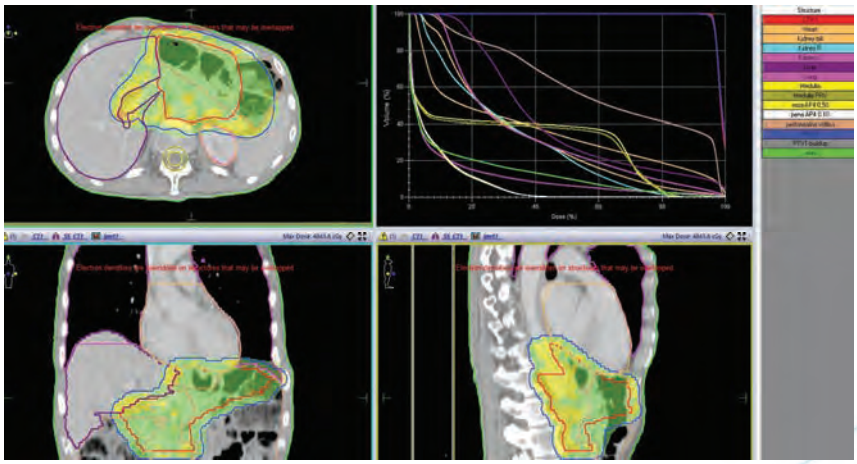
Ostanek želodca?

Anastomoza, bezgavčne lože

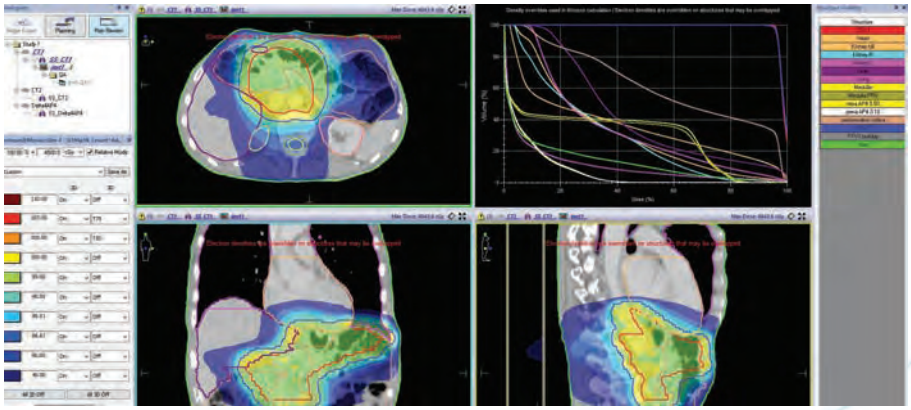
Primer 1: 74-letni bolnik po primarni totalni gastrektomiji, pT3N2



Področje visokih doz (95%-107% izodoza)



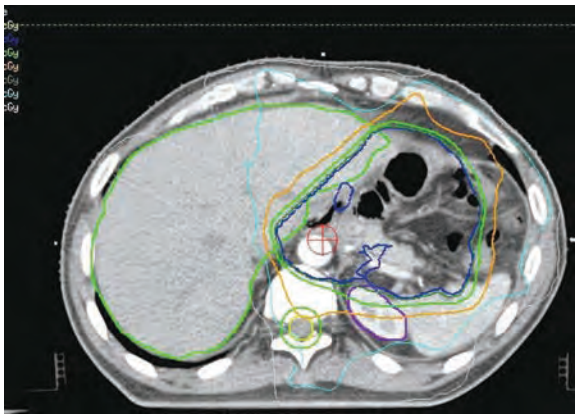
Visokodozno in nizkodozno področje



Vrisovanje tarčnih volumnov- predoperativno

- GTV T (tumor), GTV N (bezgavke)
- CTV (možnost mikroskopskega širjenja v želodcu in bezgavkah)
- PTV

Rak želodca



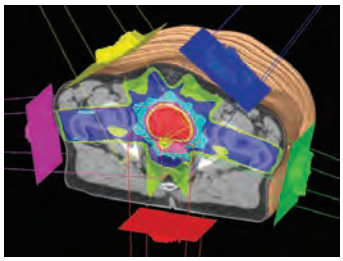
- Številni rizični organi
- Velika obsevalna polja
- Premiki (dihanje, bitje srca, peristaltika, polnost želodca)

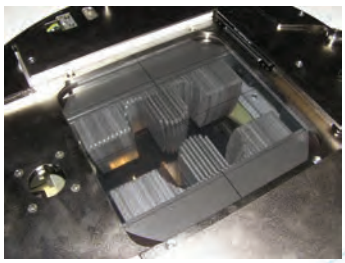
IMRT (Intesity Modulated RadioTherapy

- več žarkovnih snopov

- gibanje lističev MLC-spreminjanje intenzitete žarkovnega snopa

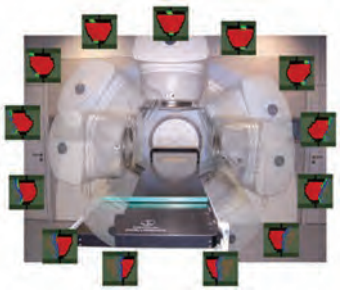
- **rezultat:** večji indeks konformnosti različni deli tarčnih volumnov so obsevani z različno dozo

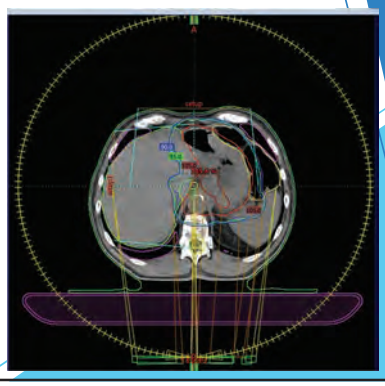




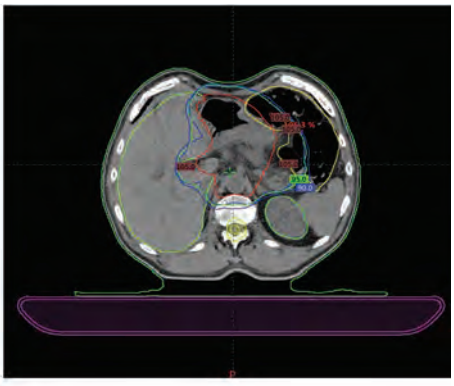
VMAT (Volumetric Modulated Arc Therapy)

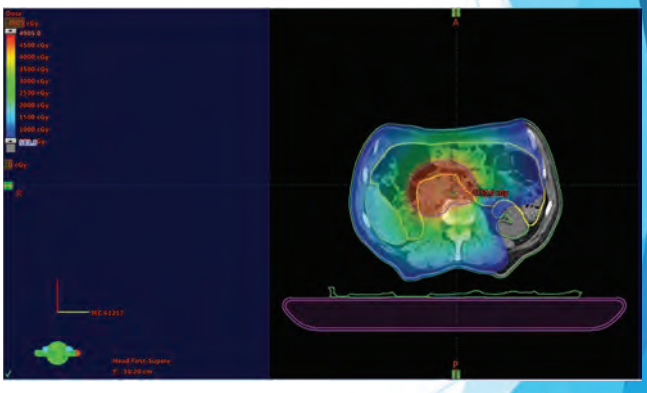
- rotacija glave obsevalnika za 360°
- med proženjem žarka se ves čas spreminja **oblika** obsevalnega polja, **hitrost** izsevane **doze** in **hitrost vrtenja** glave obsevalnika
- **rezultat:** -konformnost in zaščita rizičnih organov primerljiva z IMRT (ali še boljša)
  - bistveno krajši čas obsevanja
  - manjše število monitorskih enot sevanja



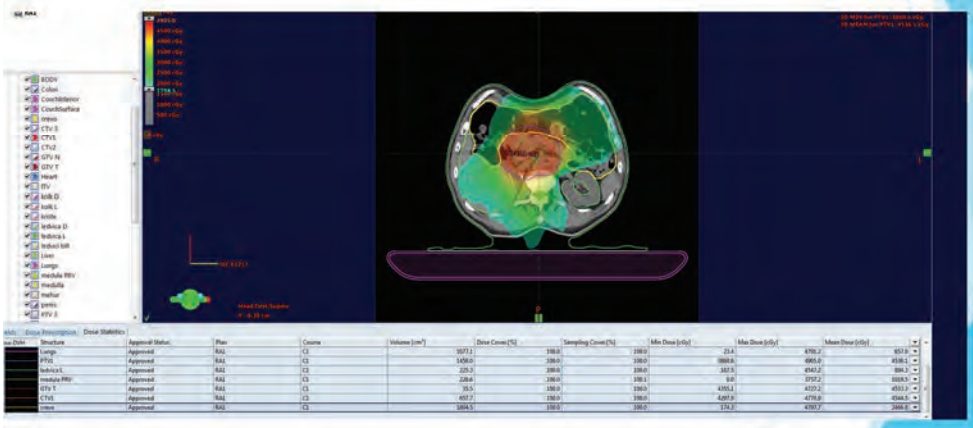


Primer 2: 76-letni bolnik, cT3N+ rak želodca; solitarna leva ledvica





- VMAT tehnika
- Dmean na levo ledvico 8 Gy



Doprinos IMRT/VMAT

Dozimetrične študije: IMRT/VMAT omogočata nižje doze na rizične organe in zagotavljata večji indeks konformnosti in homogenosti.

- **Wieland et al, 2004: -** AP PA *vs* 3D *vs* IMRT
  - IMRT. manjša doza na ledvice (predvsem levo)
- **Zhiping et al, 2013: -** IMRT *vs* VMAT
  - VMAT: višji CI in HI; nižji V13, V18 in Dmean za ledvice
  - IMRT: nižji V30 in Dmean za jetra
- **Zhang et al, 2015: -** 3D *vs* IMRT *vs* VMAT
  - višji CI in HI pri IMRT in VMAT
  - VMAT: najnižja Dmax medule, V30 jeter in V20 ledvic; Dmean pa je za vse enaka
- **Hawrylewicz et al, 2015: -** 3D *vs* IMRT (predop RTKT)
  - največja razlika v dozi na ledvice (predvsem levo!) in medulo

doprinos v kliničnih rezultatih

?

3D *vs* IMRT

Minn et al 2010: ni razlik v GI toksičnosti G≥2
manj prekinitev RT
manjši upad ledvične funkcije

Liu et al, 2014: 3D (45Gy) *vs* IMRT (50,4Gy): ni razlik v toksičnosti ne v preživetju

Suprya et al 2015: ni razlik v toksičnosti, ne v OS ali LC

Wang et al, 2016: ni razlik v OS

Pogled naprej

- ARTIST II: vloga adjuvantne RTKT pri N+ bolezni
- CRITICS II: predoperativno zdravljenje- izboljšati komplianco
- Sodobne RT tehnike
- Markerji, ki nakazujejo radiosenzitivnost (senzitivnost: E2F-1, HER2; rezistentnost: CHK1)

PERIOPERATIVNO SISTEMSKO ZDRAVLJENJE ZGODNJEGA RAKA ŽELODCA

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

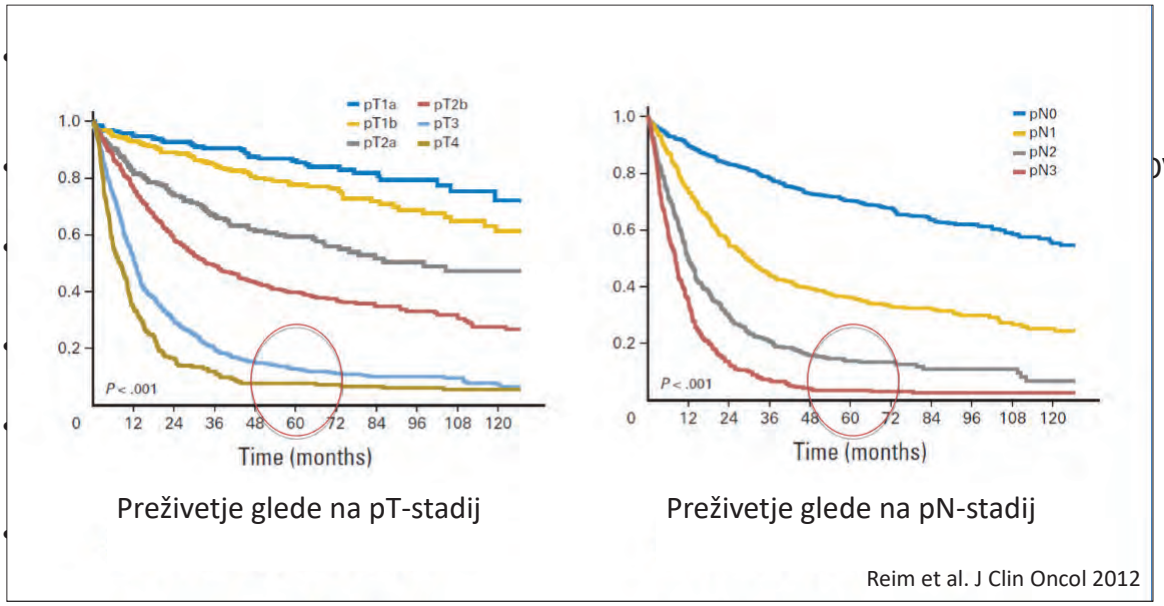
8. ŠOLA TUMORJEV PREBAVIL
Ljubljana, 07. december 2018

RAK ŽELODCA JE AGRESIVNA BOLEZEN

- SKORAJ **2/3** BOLNIKOV ODKRIJEMO Z LOKALNO NAPREDOVALO BOLEZNIJO (T3-T4)
  - V 85% PRIZADETE TUDI LOKALNE BEZGAVKE
- PRI **40-65%** BOLNIKOV, KI SO ZDRAVLJENI Z NAMENOM OZDRAVITVE SE BOLEZEN PONOVI
- **mS = 24m** PRI BOLNIKIH ZDRAVLJENIH Z NAMENOM OZDRAVITVE
  - S_{5L} 20-30%
- **mS = 8m** PRI BOLNIKIH ZDRAVLJENIH Z PALIATIVNIMI POSEGI
- **mS = 5-6m** PRI BOLNIKIH Z NAPREDOVALIMI KARCINOMI, KI NISO DELEŽNI NOBENEGA ZDRAVLJENJA
- BOLNIKI Z METASTATSKO BOLEZNIJO
  - mS 8-11m, S_{5L} <10%

World Journal of Gastroenterology. **20** (7): 1635–49.
Ann Surg. 2005 Jan; 241(1): 27–39.

RAK ŽELODCA JE AGRESIVNA BOLEZEN



Preživetje glede na pT-stadij

Preživetje glede na pN-stadij

Reim et al. J Clin Oncol 2012

World Journal of Gastroenterology. **20** (7): 1635–49.
Ann Surg. 2005 Jan; 241(1): 27–39.

PRED ZAČETKOM ZDRAVLJENJA

OBRAVNAVA NA MULTIDISCIPLINARNEM KONZILIJU (KIRURG, INTERNIST ONKOLOG, RADIOTERAPEVT, RADIOLOG)

NAČRT ZDRAVLJENJA

Smyth EC et al. Ann Oncol (2016) 27 (suppl 5): v38-v49

SISTEMSKO ZDRAVLJENJE RAKA ŽELODCA

1. **Lokalna/regionalno omejena bolezen**
   - Perioperativna kemoterapija (KT➔OP➔KT)
   - Dopolnilna kemoterapija (OP ➔ KT)
   - Predoperativna (KT/RT➔OP)
   - Dopolnilna kemo-radioterapija (OP➔KT/RT)

Z NAMENOM OZDRAVITVE

2. **Lokalno napredovala/neresektabilna in metastatska bolezen**

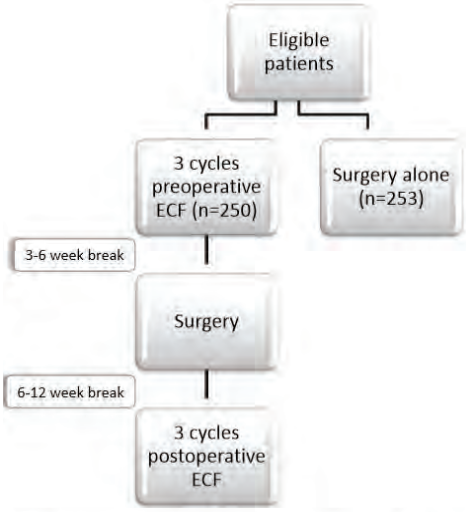
PALIATIVNO

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca - CILJI

- Zmanjšanje tumorja ➔ več radikalnih resekcij oz. odstranitev lokalne bolezni v celoti
- Zgodnje zdravljenje mikrozasevkov

Večja verjetnost ozdravitve, manj lokalnih relapsov, podaljšanje časa brez bolezni in izboljšanje celokupnega preživetja

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca raziskave faze III - MAGIC (n=503)



Eligibility criteria
Stage ≥ II gastric, gastroesophageal junction, or lower oesophageal adenocarcinoma (after 1999)
No metastases
ECOG 0-1

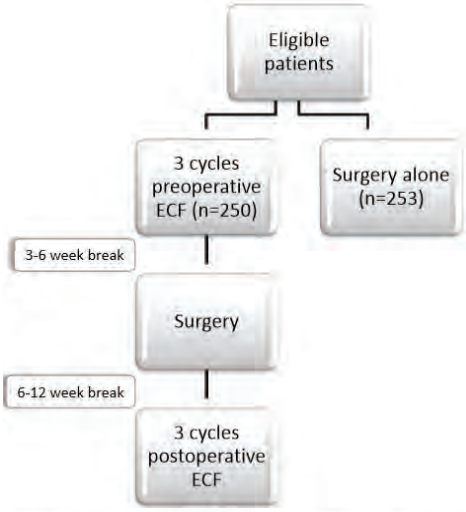
MAGIC preoperative patient characteristics

	Surgery alone	Chemo + surgery
Median age	62	62
Sex		
Male	191 (75%)	205 (82%)
Female	62 (25%)	45 (18%)
Site of disease		
Gastric	187 (74%)	185 (74%)
Oesophagus	36 (14%)	37 (15%)
GOJ	30 (12%)	28 (11%)

ECF, epirubicin 50mg/m2, cisplatin 60mg/m2 and continuous 5-fluorouracil 200mg/m2/d

Cunningham D et al. *N Engl J Med* 2006;355:11-20.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca raziskave faze III - MAGIC (n=503)



MAGIC post-operative patient characteristics

	Surgery alone	Chemo + surgery
Surgery		↑ curative resections
Curative	66/250 (66%)	169/244 (69%)
Palliative	70/250 (28%)	44/244 (18%)
Other	17/250 (6%)	27/244 (13%)
ypT stage		↑ early T stage
T1	16/193 (8%)	27/172 (16%)
T2	55/193 (29%)	62/172 (36%)
T3	106/193 (55%)	75/172 (44%)
T4	16/193 (8%)	8/172 (4%)
ypN Stage (gastric)		↑ early N stage
N0	42/156 (27%)	42/135 (31%)
N1	68/156 (43%)	72/135 (53%)
N2	34/156 (23%)	19/135 (14%)
N3	12/156 (8%)	2/135 (2%)

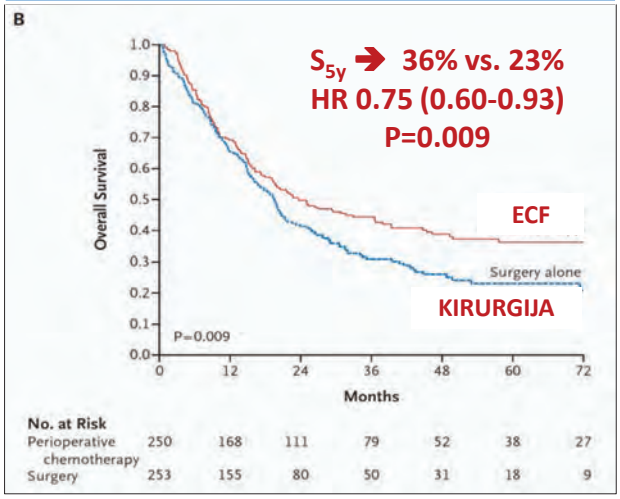
Perioperativna terapija vodi v „DOWNSTAGING“.

ECF, epirubicin 50mg/m2, cisplatin 60mg/m2 and continuous 5-fluorouracil 200mg/m2/d

Cunningham D et al. *N Engl J Med* 2006;355:11-20.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca raziskave faze III - MAGIC (n=503)

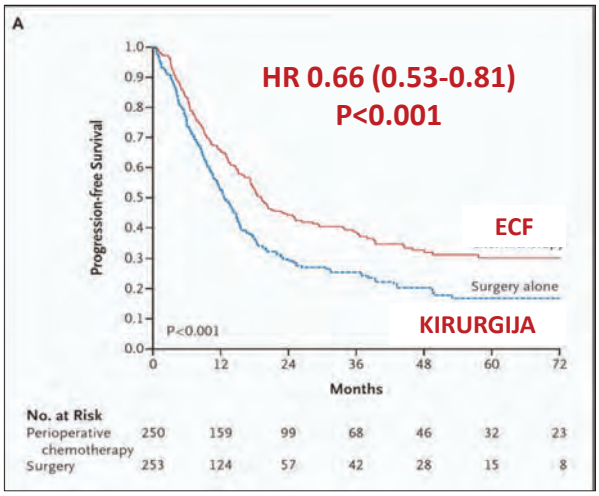
OS



S_{5y} ➔ 36% vs. 23%
HR 0.75 (0.60-0.93)
P=0.009

ECF
Surgery alone
KIRURGIJA

PFS

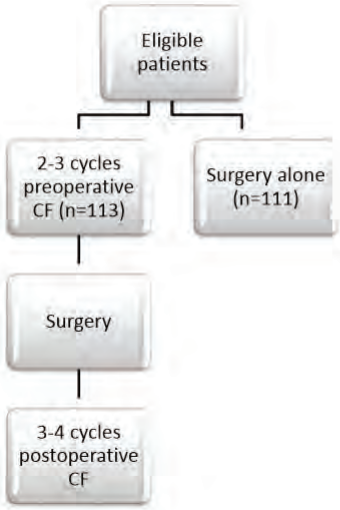


HR 0.66 (0.53-0.81)
P<0.001

ECF
Surgery alone
KIRURGIJA

Cunningham D et al. *N Engl J Med* 2006;355:11-20.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca raziskave faze III - FNCLCC (n=224)



Eligibility criteria
Lower oesophageal or GOJ adenocarcinoma (gastric after 1998)
No metastases
ECOG 0-1

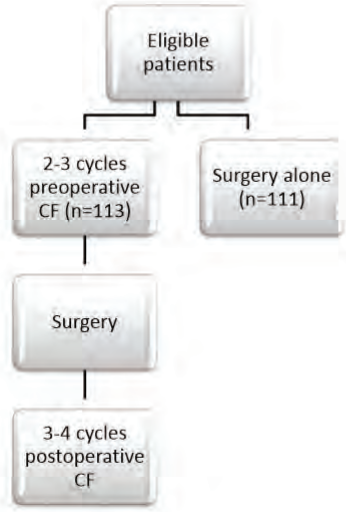
FFCD/ACCORD preoperative patient characteristics

	Surgery alone	Chemo + surgery
Median age	63	63
Sex		
Male	91 (82%)	96 (85%)
Female	20 (18%)	17 (15%)
Site of disease		
Gastric	28 (13%)	27(9%)
Oesophagus	15 (25%)	10 (24%)
GOJ	70 (62%)	74(67%)

CF, cisplatin 100mg/m2 and continuous 5-fluorouracil 800mg/m2/d day 1-5 q 28d

Ychou M et al. *JCO* 2011;29:1715-21.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca raziskave faze III - FNCLCC (n=224)



FFCD/FNCLCC post-operative patient characteristics		
	Surgery alone	Chemo + surgery
Surgery		↑ curative surgery
No resection	11 (10%)	7 (6%)
R0	81(74%)	95(87%)
R1	6 (5%)	4 (4%)
R2	11(10%)	2(2%)
Rx	1(1%)	1(1%)
ypT stage		↑ early T stage
T0	(8%)	3 (3%)
T1-2	(29%)	38 (39%)
T3-4	(55%)	57 (58%)
ypN Stage (gastric)		↑ early N stage
N0	17 (20%)	32(33%)
N+	68 (80%)	66(67%)

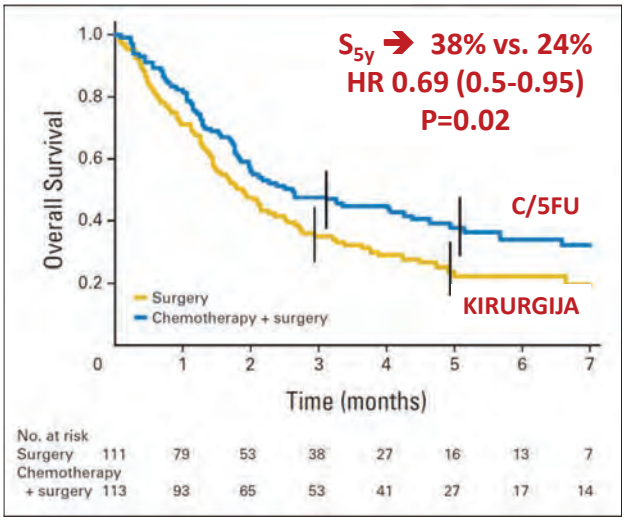
Perioperativna terapija vodi v „DOWNSTAGING“.

CF, cisplatin 100mg/m2 and continuous 5-fluorouracil 800mg/m2/d day 1-5 q 28d

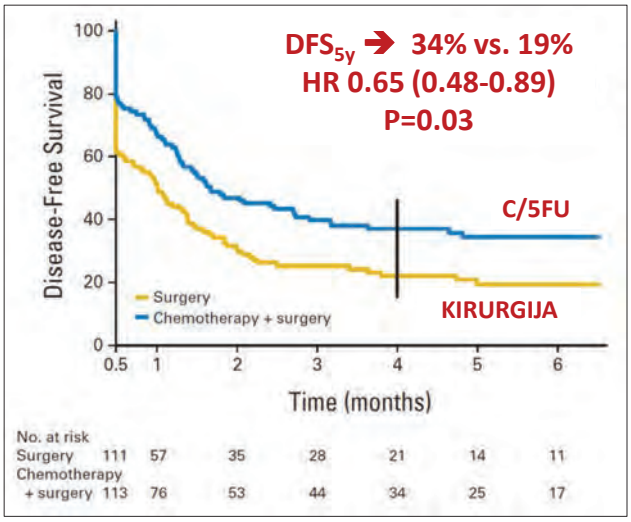
Ychou M et al. *JCO* 2011;29:1715-21.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca raziskave faze III - FNCLCC (n=224)

OS



DFS



Ychou M et al. *JCO* 2011;29:1715-21.

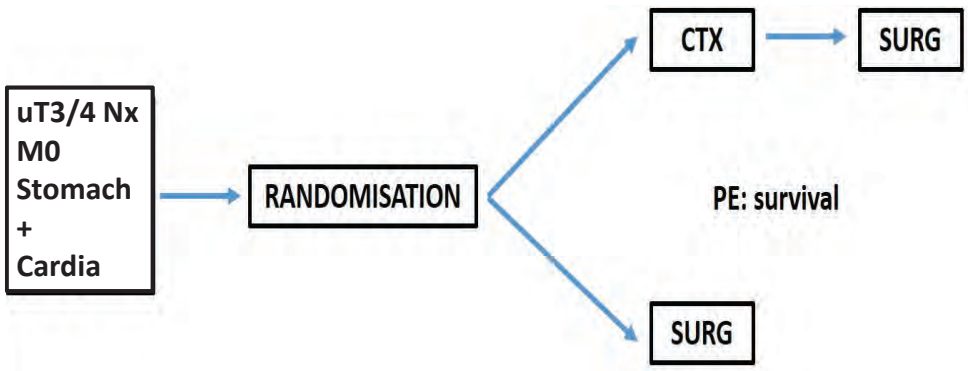
Peri-operativna kemoterapija pri zdravljenju karcinoma želodca – raziskave faze III. – MAGIC & FNCLCC

1. ~10% BOLNIKOV NE BO ZAKLJUČILO CELOTNE PRED-OPERATIVNE KT
2. ~ 50% BOLNIKOV NI SPOSOBNIH PO-OPERATIVNE KT

	MAGIC 3 cycles ECF	FFCD/FNCLCC 2-3 cycles CF
Pre-operative chemotherapy	3 cycles: n= 215 (91%)	1 cycle: n=11 (10%) 2 cycles: n=85 (75%) 3 cycles: n= 13 (12%) 87% had minimum 2 cycles
Surgery	229 (92%)	109 (97%)
Post-operative chemotherapy	Any chemotherapy: n=137 (55%) 3 cycles: n= 104 (42%)	Any chemotherapy: n=54 (50%) 1 cycle: n=6 (6%) 2 cycles: n=7 (6%) 3 cycles: n= 16 (15%) 4 cycles: n=25 (23%)

Ychou M et al. *JCO* 2011;29:1715-21.
Cunningham D et al. *N Engl J Med* 2006;355:11-20.

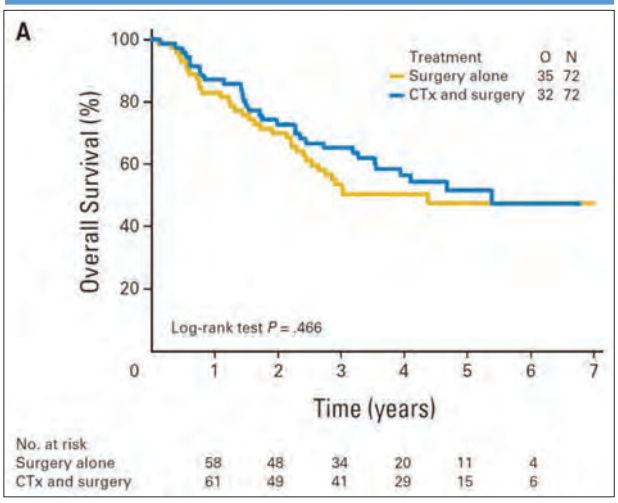
Peri-operativna kemoterapija pri zdravljenju karcinoma želodca – raziskave faze III – EORTC 40954



Schuhmacher C et al. *JCO* 2010;28:5210-5218.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca – raziskave faze III – EORTC 40954

OS



mOS: **KT + kirurgija 65m**
kirurgija 53m
HR 0.84, NS (p=.466)

R0 **81.9% vs. 66.7%, p=.036**

$SURG_{group}$ >N+ (76.5% vs. 61.4%, p=.018)
$postOP_{kompl}$ > CTX_{group} (27.1% vs. 16.2%, NS)

Schuhmacher C et al. *JCO* 2010;28:5210-5218.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
Epirubicin? – MRC OE5

Histologically confirmed adenoCa of lower oesophagus and EGJ (Type I and II)

MDT-resectable desease following EUS and CT

(T1/2 N0 excluded)

→ RANDOM → 2xCF → SURG

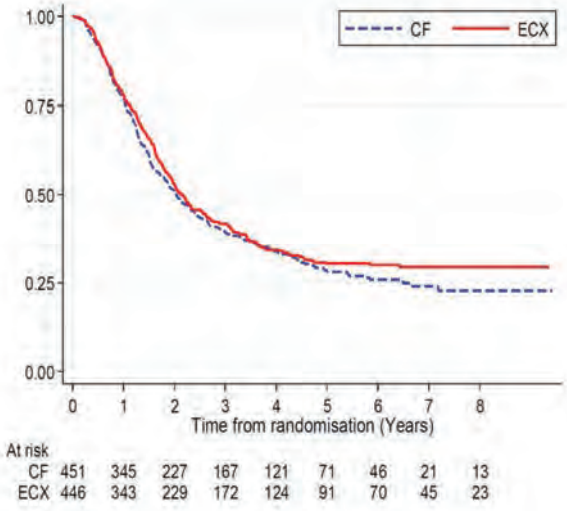
RANDOM → 4xECX → SURG

CF: 2x 3w cycles of cisplatin (80mg/m^2 D1) and 5FU (1g/m^2 D1-4)

ECX: 4x 3w cycles of epirubicine (50mg/m^2 D1) , cisplatine (60mg/m^2 D1) and capecitabine (1250mg/m^2 daily)

Alderson D et al. *ASCO* 2015;#4002.

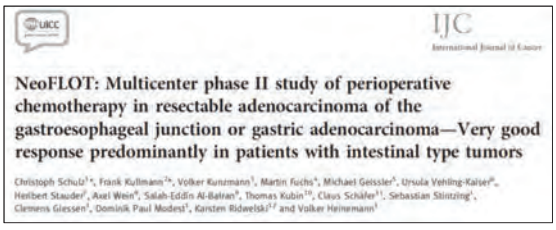
Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
Epirubicin? – MRC OE5



Median survival (95% CI)	
CF	2.02 (1.80, 2.38) ys
ECX	2.15 (1.93, 2.53) ys
HR	0.92 (0.79, 1.08)
P-value	0.8582
3-year survival (95% CI)	
CF	39% (35%, 44%)
ECX	42% (37%, 46%)

Alderson D et al. *ASCO* 2015;#4002.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – NeoFLOT



NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma—Very good response predominantly in patients with intestinal type tumors

Christoph Schulz[1]*, Frank Kullmann[2]*, Volker Kunzmann[3], Martin Fuchs[4], Michael Geissler[5], Ursula Vehling-Kaiser[6], Heribert Stauder[7], Axel Wein[8], Salah-Eddin Al-Batran[9], Thomas Kubin[10], Claus Schäfer[11], Sebastian Stintzing[1], Clemens Giessen[1], Dominik Paul Modest[1], Karsten Ridwelski[12] and Volker Heinemann[1]

mFU = 24.5 meseca
mDFS = 32.9 meseca
mOS = NR

S_{1L} = 79.3%
PFS_{1L} = 67.2%

Schulz et al, Int. J. Cancer, 2015

Table 2. Pathology report (per-protocol analysis)

Pathology report	No. of specimen (N = 50)	%
Resection rate[1]		
R0	43	86.0
R1	3	6.0
R2	0	0
Rx	2	4.0
Posttherapeutic tumor classification		
T0	10	20.0
T1	6	12.0
T2	8	16.0
T3	20	40.0
T4	4	8.0
Unknown	2	4.0
Post-therapeutic lymph node classification		
N0	27	54.0
N1	8	16.0
N2	8	16.0
N3	5	10.0
Unknown	2	4.0
Distant metastasis classification		
M0	47	94.0
M1	3	6.0
Mx	0	0
Histologic regression grade (Becker *et al.*, 2003)		
Grade 1a	10	20.0
Grade 1b	10	20.0
Grade 2	13	26.0
Grade 3	15	30.0
Unknown	2	4.0
Pathological remission rate		
Complete (pCR)	10	20.0
Lymph nodes		
Median number of lymph nodes analysed 23 (range 10–50)		
Median number of positive lymph nodes 0 (range 0–25)		

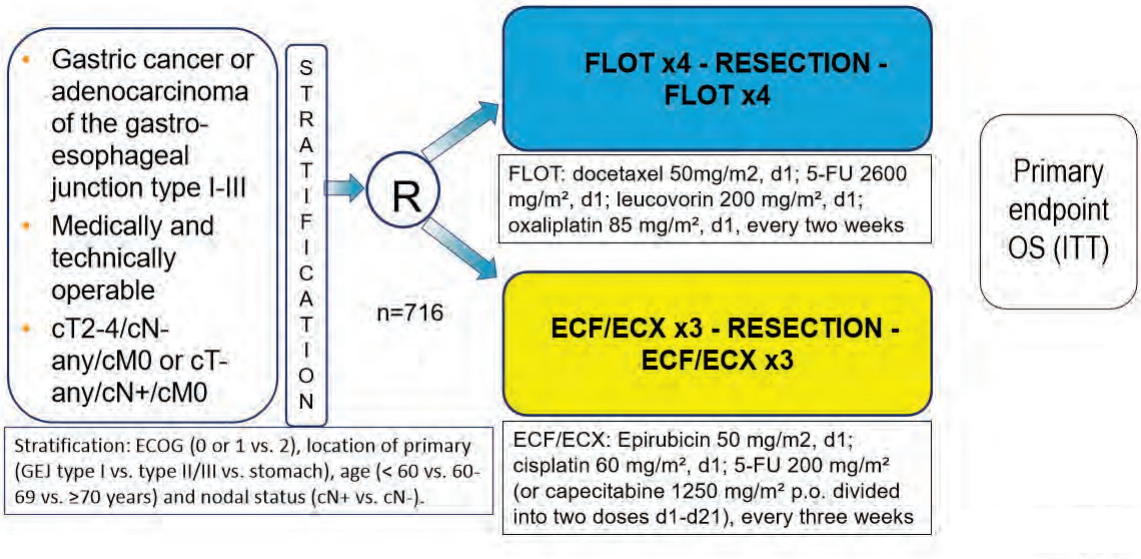
[1]In 2 patients functional inoperability was observed during surgery.

Table 3. Toxic effects according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4

Toxicity	All Grades No. of patients (N = 58)	%	Grades 3–4 No. of patients (N = 58)	%
Hematological toxicity[1]				
Neutropenia	24	41.1	17	29.3
Leukopenia	39	67.2	14	24.1
Thrombocytopenia	9	15.4	1	1.7
Anemia	11	18.9	1	1.7
Febrile neutropenia	1	1.7	1	1.7
Gastrointestinal toxicity				
Nausea	39	67.2	2	3.4
Vomiting	25	43.1	2	3.4
Diarrhea	35	48.3	7	12.1
Constipation	9	15.5	0	0
Mucositis	24	41.4	4	6.9
Hepatic toxicity				
Elevated AST (GOT)	8	13.8	0	0
Elevated ALT (GPT)	7	12.1	1	1.7
Elevated GGT	7	12.1	2	3.4
Other toxicity				
Fatigue	25	43.1	0	0
Fever	6	10.3	0	0
Sepsis[2]	2	3.4	2	3.4
Loss of appetite	20	34.5	1	1.7
Loss of weight	6	10.3	0	0
Alopecia	22	37.9	0	0
Neurosensory toxicity	37	63.8	3	5.2

[1]Seven of 58 patients received a secondary prophylaxis with G-CSF.
[2]These 2 patients died from sepsis after application of study medication. There the NCI-CTC grade is 5.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – FLOT4



al Batran et al, ASCO 2017

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – FLOT4

	ECF/ECX (n=360)	FLOT (n=356)	
Resection surgery	313/360(87%)	336/356 (94%)	0.001
R0 resection rate	276/360 (77%)	300/356 (84%)	0.011
Any surgical complication	188/341 (55%)	188/345 (55%)	
Median duration hospital stay	16 days	15 days	
Death 90 days	26 (8%)	16 (5%)	

✓ **PERI-OPERATIVNA KT PO SHEMI FLOT POVEČA DELEŽ RESECIRANIH BOLNIKOV IN BOLNIKOV Z DOSEŽENO R0 RESEKCIJO V PRIMERJAVI Z KT PO SHEMI ECF/ECX**

✓ **MORBIDITETA IN MORTALITETA SE OB KT PO SHEMI FLOT NE POVEČA**

al Batran et al, ASCO 2017

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – FLOT4

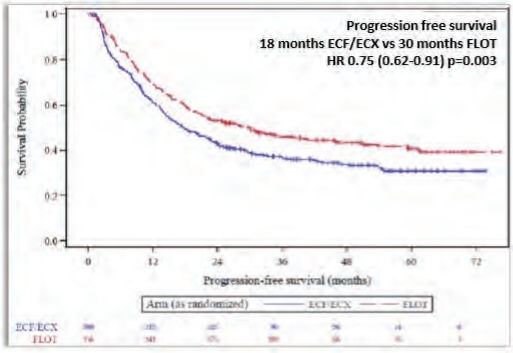
	ECF/ECX (n=360)	FLOT (n=356)	
ypT stage			
≤T1	**53 (15%)**	**88(25%)**	**0.001**
T2	44 (12%)	44(12%)	
T3	175 (49%)	165(46%)	
T4	47(13%)	37(10%)	
NA	41(11%)	22(6%)	
ypN stage			
N0	**146(41%)**	**174(49%)**	**0.029**
N1	44(12%)	55(16%)	
N2	54(15%)	47(13%)	
N3	73(20%)	57(16%)	
NA	43(12%)	23(7%)	

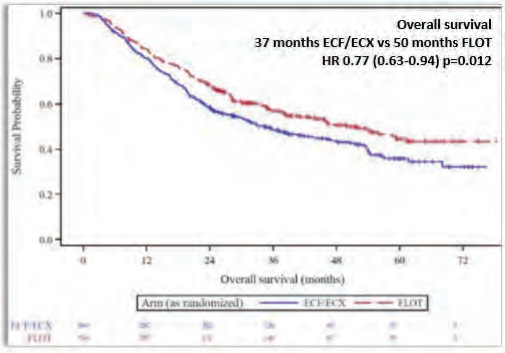
✓ **PERI-OPERATIVNA KT PO SHEMI FLOT POVEČA DELEŽ BOLNIKOV Z PO-OPERATIVNO NIŽJIM STADIJEM BOLEZNI V PRIMERJAVI Z KT PO SHEMI ECX/ECF**

✓ **pCR 15.6% vs. 5.8% (** Pauligk et al. *ASCO* 2015;#4016. **)**

al Batran et al, ASCO 2017

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – FLOT4





Projected PFS rates		
	ECF/X	FLOT
2 year	43%	53%
3 year	37%	46%
5 year	31%	41%

Projected OS rates		
	ECF/X	FLOT
2 year	59%	68%
3 year	48%	57%
5 year	36%	45%

✓ **PERI-OPERATIVNA KT PO SHEMI FLOT PODALJŠA CELOKUPNO PREŽIVETJE IN PREŽIVETJE BREZ BOLEZNI Z KT PO SHEMI ECX/ECF**

al Batran et al, ASCO 2017

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – FLOT4

Grade 3-4 >5%	ECF/ECX (N=354)	FLOT (N=354)	P-value (Chi-Square)
Diarrhea	13 (4%)	34 (10%)	0.002
Vomiting	27 (8%)	7 (2%)	<0.001
Nausea	55 (16%)	26 (7%)	0.001
Fatigue	38 (11%)	25 (7%)	
Infections	30 (9%)	63 (18%)	<0.001
Leukopenia	75 (21%)	94 (27%)	
Neutropenia	139 (39%)	181 (51%)	0.002
Sensory	7 (2%)	24 (7%)	0.002
Thromboembolic	22 (6%)	9 (3%)	0.03
Anemia	20 (6%)	9 (3%)	0.04

al Batran et al, ASCO 2017

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – FLOT4

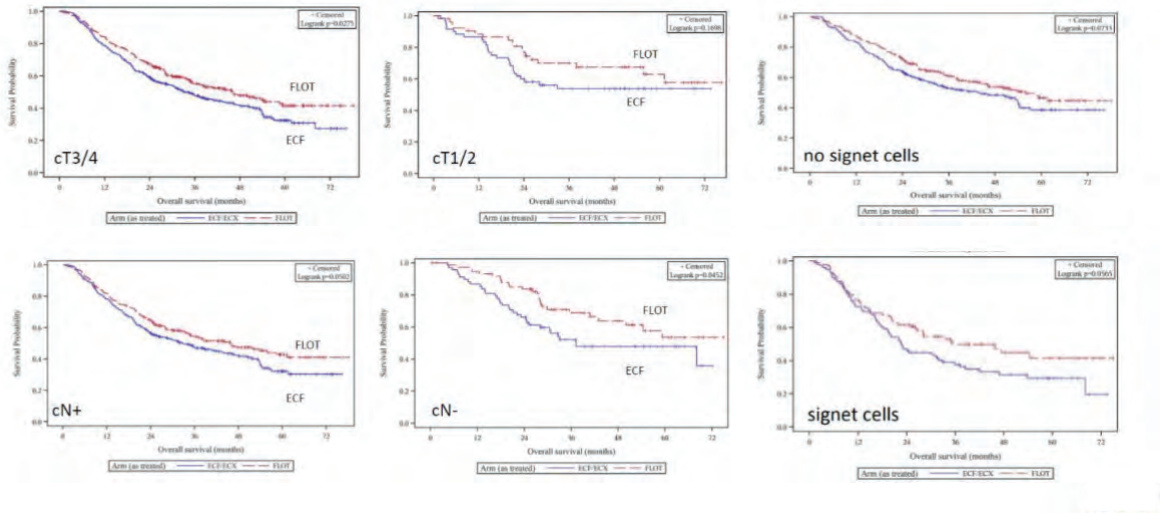
	ECF/ECX (n=360)	FLOT (n=356)
Completed pre-operative chemo	327 (91%)	320 (90%)
Surgery	340 (94%)	336 (94%)
Started post-operative chemo Completed protocol post-op chemo	187 (52%) 133 (37%)	213 (60%) 162 (46%)

✓ **BOLNIKI ZDRAVLJENI Z PERI-OPERATIVNO KT PO SHEMI FLOT V VEČJEM ODSTOTKU KONČAJO POST-OPERATVINO KT**

✓ **BOLNIKI, KI PRIČNEJO PO-OPERATIVNO KT PO SHEMI FLOT, JO TUDI V VEČJEM ODSTOTKU KONČAJO**

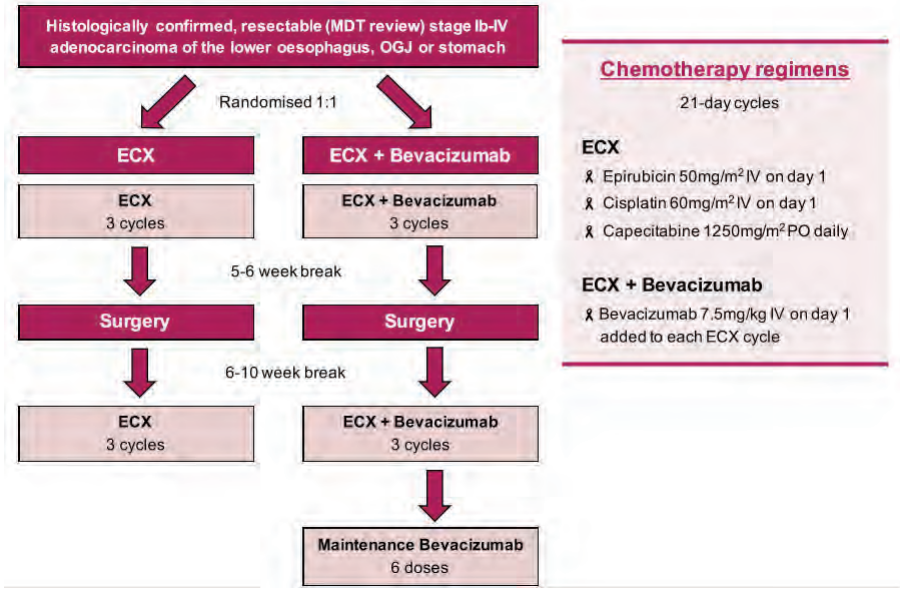
al Batran et al, ASCO 2017

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – FLOT4



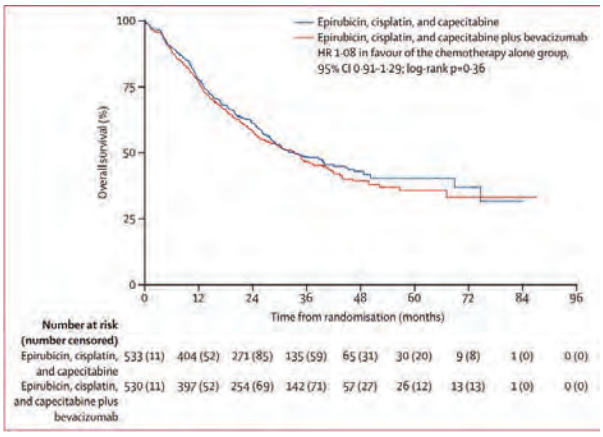
al Batran et al, ASCO 2017

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
DODATEK BEVACIZUMABA – ST03 MAGIC



Lancet Oncol 2017; 18: 357–70

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
DODATEK BEVACIZUMABA – ST0-3/MAGIC-B



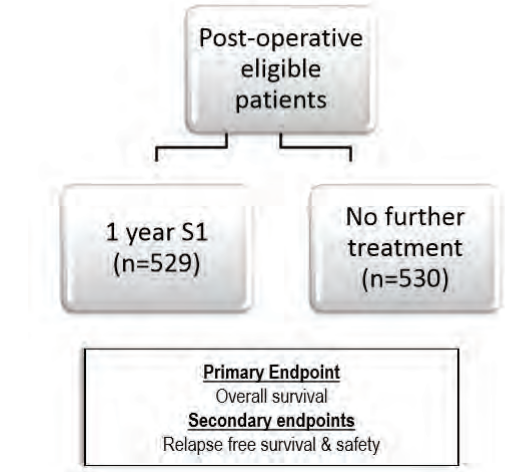
Overall survival		
Median OS	ECX	33.97 months
	ECX+B	34.46 months
Hazard Ratio		**1.067**
(95% CI)		**(0.8911 to 1.279)**
Log-rank p-value		**0.4784**

3-year overall survival (95% CI)	
ECX	48.9% (43.6% to 53.8%)
ECX+B	47.6% (42.3% to 52.7%)

- ✓ **DODATEK BEVACIZUMABA SISTEMSKI KT V PERIOPERATIVNO NE DOPRINESE K UČINKOVITOSTI TERAPIJE, TAKO GLEDE PREŽIVETJA, KOT TUDI GLEDE ODGOVORA NA ZDRAVLJENJE IN ŠTEVILA R0 RESEKCIJ**
- ✓ **ENAKO ZAENKRAT VELJA TUDI ZA OSTALA PREIZKUŠENA TARČNA ZDRAVILA (TRASTUZUMAP, PERTUZUMAB, ITD.)**

Lancet Oncol 2017; 18: 357–70.
Annals of Oncology 27 (Supplement 5): v38–v49, 2016 doi:10.1093/annonc/mdw350.

Dopolnilna KT pri zdravljenju karcinoma želodca
ACTS-GC



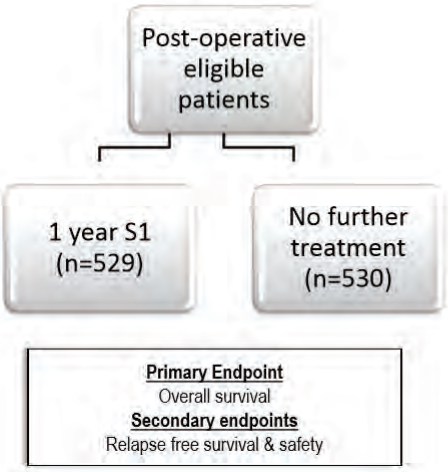
Eligibility criteria
Stage ≥ II (no T1), IIIA or IIIB gastric adenocarcinoma
D2 resection minimum

ACTS-GC patient characteristics		
	Surgery alone	Chemo + surgery
Median age	63	63
Sex Male Female	 369 (70%) 161(30%)	 367 (71%) 162(29%)
Stage of cancer II III IV	 282 (53%) 213 (40%) 35 (7%)	 264 (50%) 224 (42%) 40(8%)

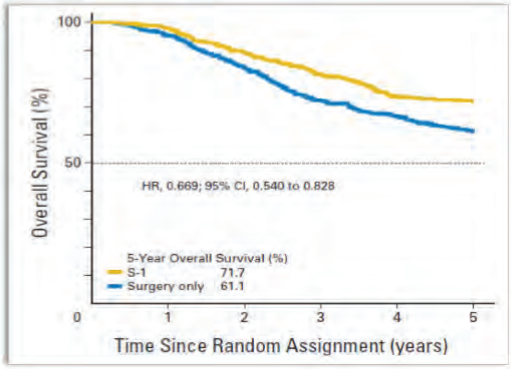
S1, 40mg/m2/d x 28 days followed by 2 week break x 1 year

Sakuramotoet al, N EnglJ Med. 2007 Nov 1;357(18):1810-20.

Dopolnilna KT pri zdravljenju karcinoma želodca ACTS-GC



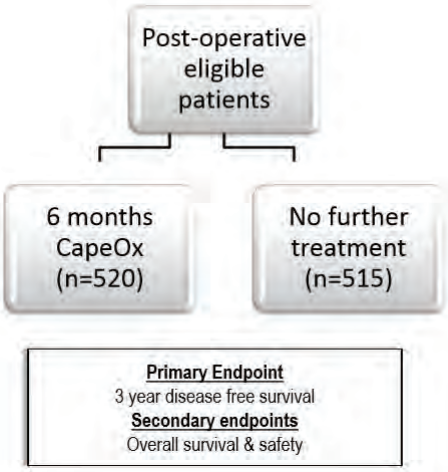
Updated 5 year survival S1 vs surgery alone
All patients 5 year OS 72% vs. 61%
Stage II 5 year OS 84% vs 71%
Stage IIIA 5 year OS 67% vs 57%
Stage IIIB 5 year OS 50% vs 44%



S1, 40mg/m2/d x 28 days followed by 2 week break x 1 year

Sakuramotoet al, N EnglJ Med. 2007 Nov 1;357(18):1810-20.

Dopolnilna KT pri zdravljenju karcinoma želodca CLASSIC



Eligibility criteria
Stage ≥ II, IIIA or IIIB gastric adenocarcinoma
D2 resection minimum

CLASSIC patient characteristics		
	Surgery alone	Chemo + surgery
Median age	56	56
Sex Male Female	 358 (70%) 157(30%)	 373 (72%) 147(28%)
Stage of cancer II III IV	 261 (51%) 253 (49%) 1 (<1%)	 253(49%) 266(51%) 0 (0%)

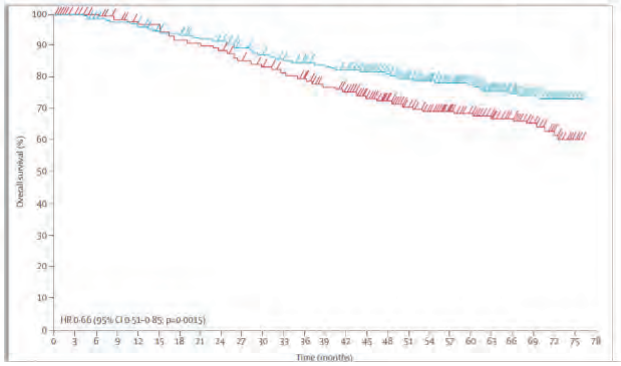
CapeOx, capecitabine 1000 mg/m2 bd D1-14 , plus oxaliplatin 130 mg/m2 iv D1 q3wks

Banget al, Lancet. 2012 Jan 28;379(9813):315-21.

Dopolnilna KT pri zdravljenju karcinoma želodca CLASSIC

Primary Endpoint
3 year disease free survival
Secondary endpoints
Overall survival & safety

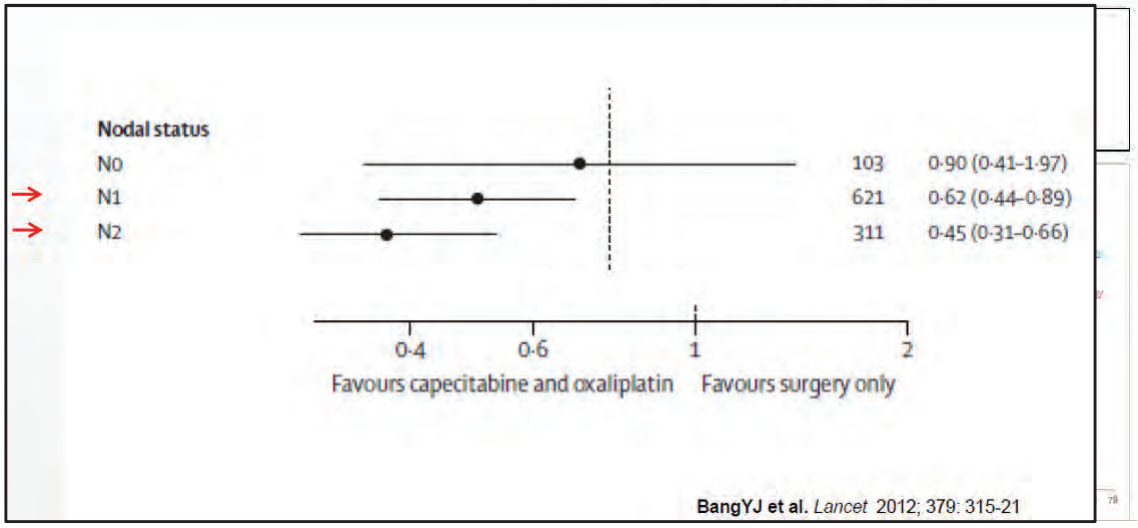
5 year updated survival CapeOx vs surgery alone
All patients 5 year OS 78% vs 69%
Stage II 5 year OS 88% vs 79%
Stage IIIA 5 year OS 70% vs 63%
Stage IIIB 5 year OS 66% vs 45% (compare ACTS GC 50% vs. 44%)



CapeOx, capecitabine 1000 mg/m2 bd D1-14 , plus oxaliplatin 130 mg/m2 iv D1 q3wks

Noh et al, Lancet Oncol. 2014 Nov;15(12):1389-96.

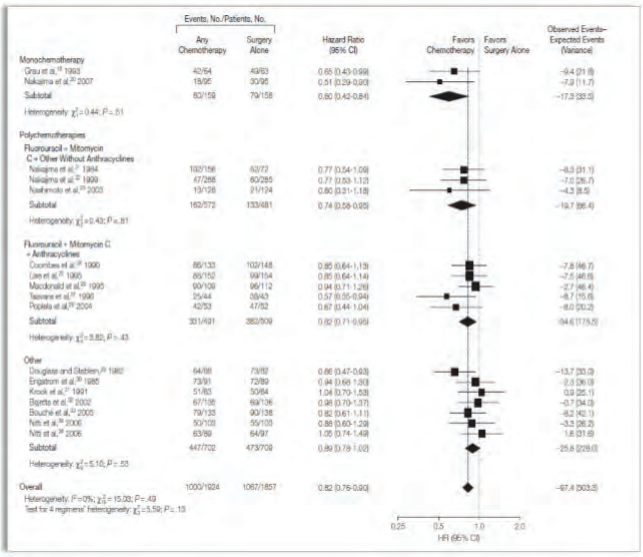
Dopolnilna KT pri zdravljenju karcinoma želodca CLASSIC



CapeOx, capecitabine 1000 mg/m2 bd D1-14 , plus oxaliplatin 130 mg/m2 iv D1 q3wks

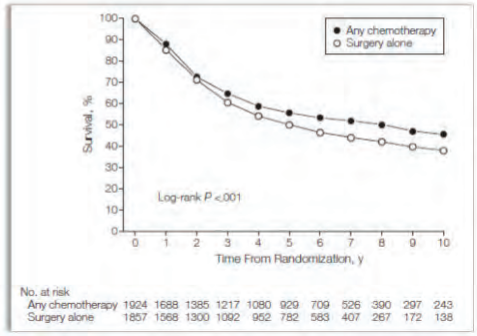
Noh et al, Lancet Oncol. 2014 Nov;15(12):1389-96.

Dopolnilna KT pri zdravljenju karcinoma želodca
neazijska populacija



Meta-analiza GASTRIC skupine:

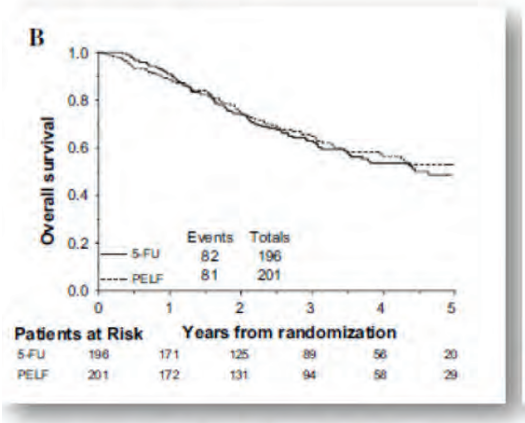
Samo 5,8% absolutna dobrobit na 5L preživetje pri dopolnilni KT (55.3% vs. 49.6%), HR 0.82, p<.001



Paolettiet al, JAMA. 2010 May 5;303(17):1729-37.

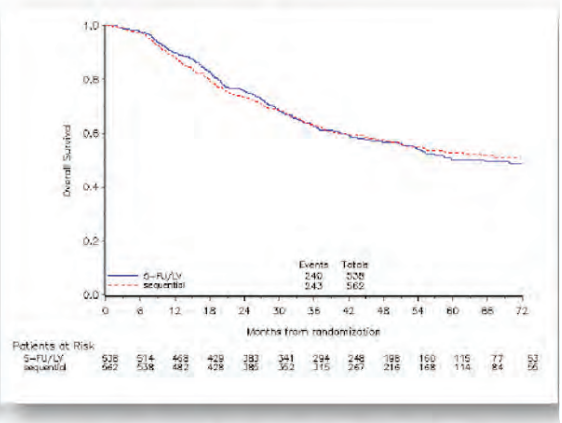
Dopolnilna KT pri zdravljenju karcinoma želodca
intenziviranje KT

GISCAD Study



Cascinu et al., *J Nat Canc Inst* 2007; 99: 601-607

ITACA-S Study

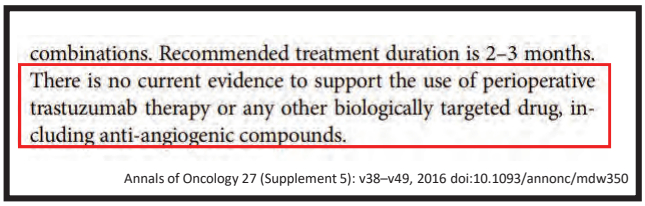


Bajetta et al., *Ann Oncol.* 2014; 25: 1373-8

✓ **INTENZIVIRANJE ADJUVANTNE SISTEMSKE KT NE PRINAŠA DOBROBITI**

PERIOPERATIVNO SISTEMSKO ZDRAVLJENJE - ZAKLJUČKI

- **Peri-operativna kemoterapija je standard zdravljenja pri lokaliziranem adenokarcinomu želodca stadija ≥ IB:**
  - Perioperativna KT po shemo FLOT predstavlja nov standard perioperativnega sistemskega zdravljenja pri operabilnem zgodnjem raku želodca
    - Dodatek **TAXANOV** izboljša odgovor peri-operativne kemoterapije, signifikantno podaljša čas do ponovitve bolezni in celokupno preživetje (projekcija 5L preživetja 45%)
  - Peri-operativna kemoterapija pri bolnikih, ki niso primerni za „trojček“, naj vključuje derivat platine in fluoropirimidin,
  - Dodatek epirubicina je opcijski (toksični profil), vendar imamo največ dokazov učinkovitosti peri-operativne kemoterapije pri shemah, ki vključujejo cisplatin/fluorouracil ± epirubicin,
- **Z peri-operativno kemoterapijo:**
  - Dosežemo „downstaging“ bolezni
  - Povečamo verjetnost R0 resekcije
  - Podaljšamo čas do ponovitve bolezni
  - Podaljšamo celokupno preživetje bolnikov



combinations. Recommended treatment duration is 2–3 months. There is no current evidence to support the use of perioperative trastuzumab therapy or any other biologically targeted drug, including anti-angiogenic compounds.

Annals of Oncology 27 (Supplement 5): v38–v49, 2016 doi:10.1093/annonc/mdw350

POOPERATIVNO SISTEMSKO ZDRAVLJENJE - ZAKLJUČKI

- **Pri bolnikih stadija ≥ IB ki so bili operirani brez pred-operativne kemoterapije oz. niso kandidati za po-operativno KT-RT prihaja v poštev dopolnilno zdravljenje**
  - S-1 in XELOX pri Azijski populaciji,
  - 5,8% absolutna dobrobit dopolnilnih kemoterapevtskih shem na osnovi 5FU pri ne-azijski populaciji

8. ŠOLA TUMORJEV PREBAVIL

Novosti v zdravljenju

Zdravljenje metastatskega karcinoma želodca

Dr. Neva Volk, dr. med.
Onkološki inštitut
Sektor za internistično onkologijo

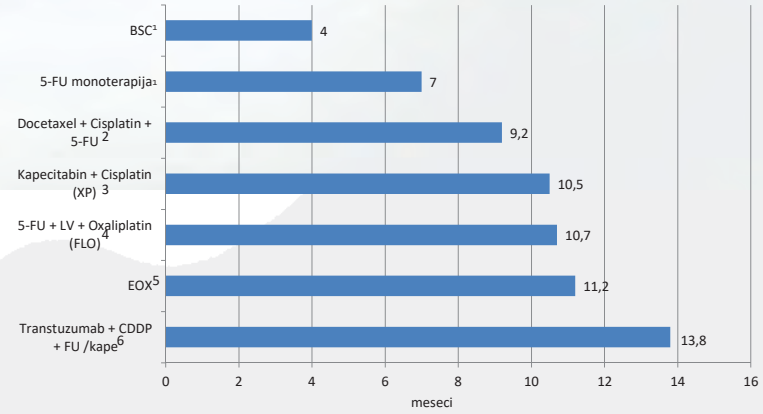
Cilji zdravljenja metastatskega raka želodca (mRŽ)

Podaljšanje preživetja

Kvaliteta življenja

Zmanjšanje simptomov
Čim manj sopojavov zdravljenja

Preživetje pri mRŽ



1. WagnerAD, et al. J Clin Oncol 2006;24:2903–9. 2. van Cutsem E, et al. J Clin Oncol 2006;24:4991–4997. 3.Kang YK et al, Ann Oncol 2009; 20:666–73. 4. Al Batran SE, et al. J Clin Oncol 2008;26:1435–1442. 5. Cunningham D, et al. N Engl J Med 2008;358:36-46. 6. Bang YJ, et al. Lancet 2010;376:687–697. BSC: Best supportive care; CDDP, cisplatin; EOX: Epirubicin/Oxaliplatin/Capecitabine; 5-FU, 5-fluorouracil.

Algoritem zdravljenja mRŽ ESMO 2016

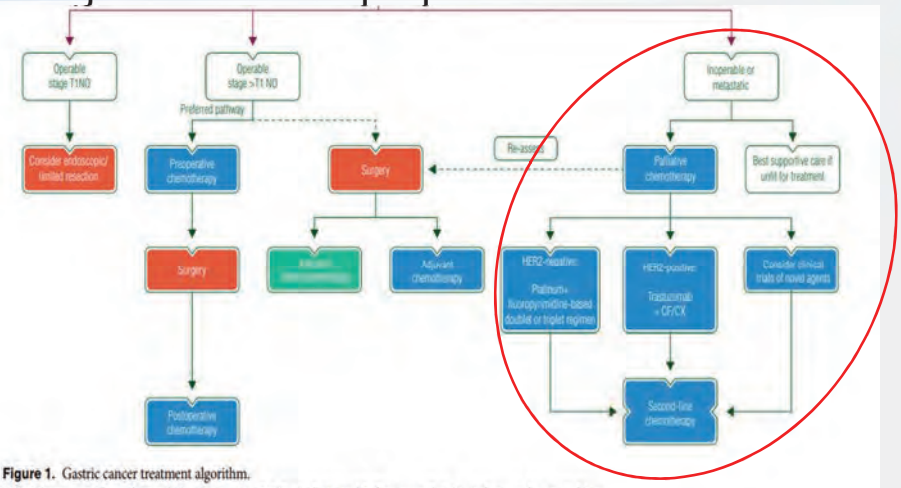
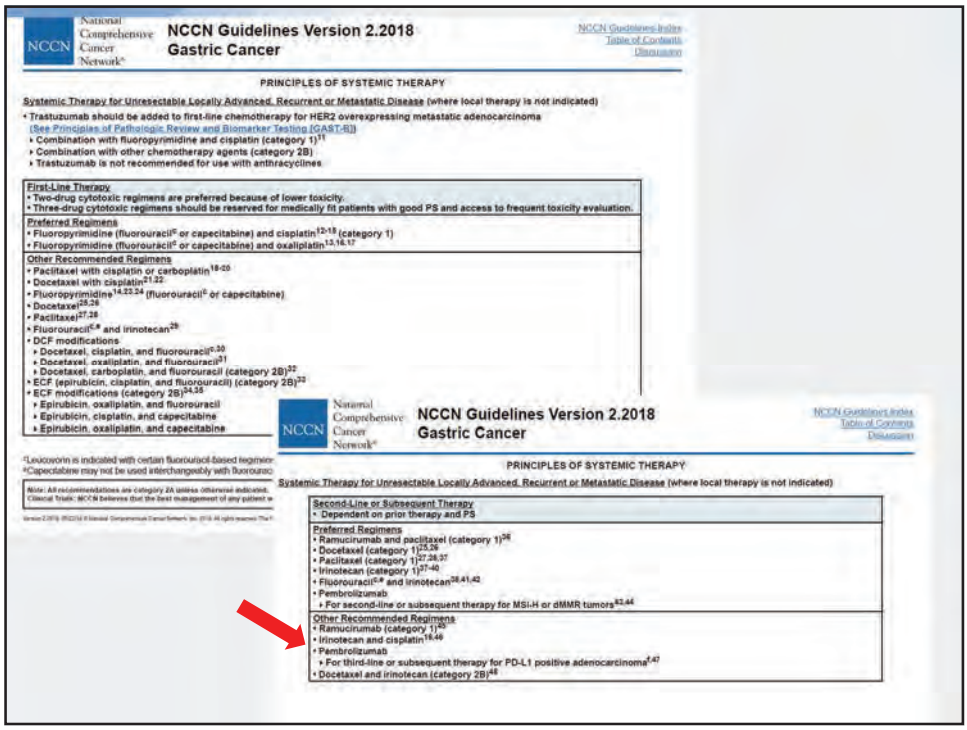


Figure 1. Gastric cancer treatment algorithm.
HER2, human epidermal growth factor receptor 2; CF, cisplatin and 5-fluorouracil; CX, cisplatin and capecitabine

Ann Oncol (2016) 27 (suppl 5): v38-v49



NCCN Guidelines Version 2.2018
Gastric Cancer

PRINCIPLES OF SYSTEMIC THERAPY

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

- Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma (See Principles of Pathologic Review and Biomarker Testing (GAST-B))
  - Combination with fluoropyrimidine and cisplatin (category 1)[11]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy
- Two-drug cytotoxic regimens are preferred because of lower toxicity.
- Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

Preferred Regimens
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and cisplatin[12-18] (category 1)
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and oxaliplatin[13,16,17]

Other Recommended Regimens
- Paclitaxel with cisplatin or carboplatin[19-20]
- Docetaxel with cisplatin[21,22]
- Fluoropyrimidine[14,23,24] (fluorouracil[c] or capecitabine)
- Docetaxel[25,26]
- Paclitaxel[27,28]
- Fluorouracil[c,e] and irinotecan[29]
- DCF modifications
  - Docetaxel, cisplatin, and fluorouracil[c,30]
  - Docetaxel, oxaliplatin, and fluorouracil[31]
  - Docetaxel, carboplatin, and fluorouracil (category 2B)[32]
- ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[33]
- ECF modifications (category 2B)[34,35]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine

[c]Leucovorin is indicated with certain fluorouracil-based regimens.
[e]Capecitabine may not be used interchangeably with fluorouracil.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient is

NCCN Guidelines Version 2.2018
Gastric Cancer

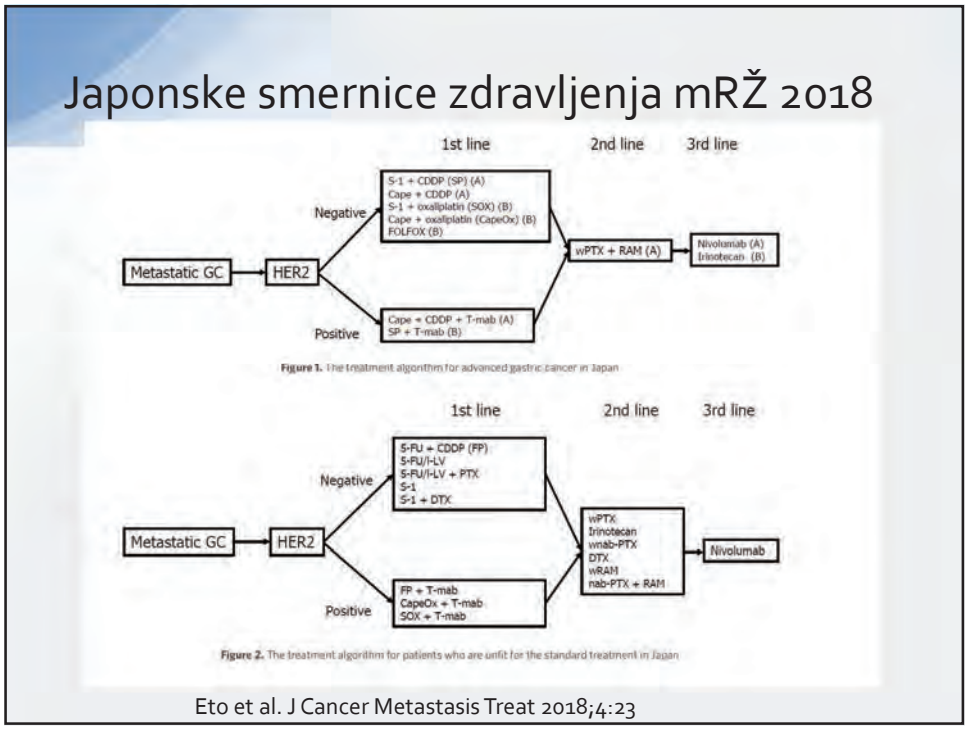
PRINCIPLES OF SYSTEMIC THERAPY

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

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

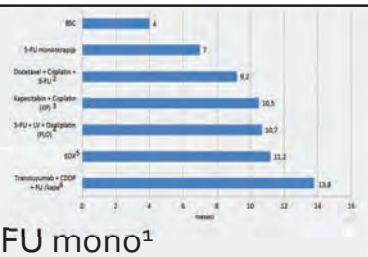
Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[36]
- Docetaxel (category 1)[25,26]
- Paclitaxel (category 1)[27,28,37]
- Irinotecan (category 1)[37-40]
- Fluorouracil[c,e] and irinotecan[28,41,42]
- Pembrolizumab
  - For second-line or subsequent therapy for MSI-H or dMMR tumors[43,44]

Other Recommended Regimens
- Ramucirumab (category 1)[45]
- Irinotecan and cisplatin[18,46]
- Pembrolizumab
  - For third-line or subsequent therapy for PD-L1 positive adenocarcinoma[47]
- Docetaxel and irinotecan (category 2B)[48]



Eto et al. J Cancer Metastasis Treat 2018;4:23

mRŽ prva linija
Standardno zdravljenje



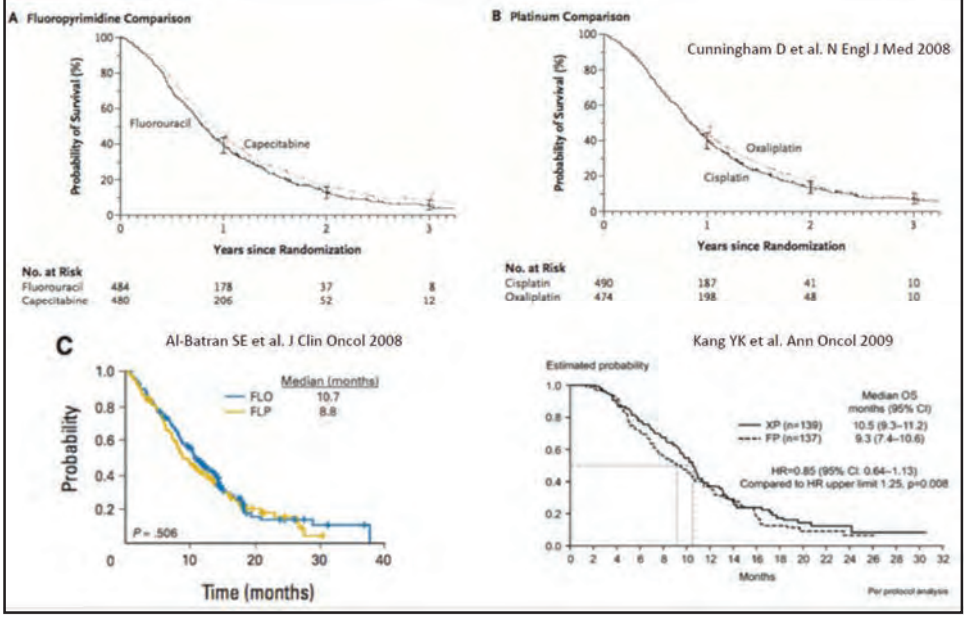
- Kombinacije učinkovitejše kot 5-FU mono[1]

Standard: kombinacija derivat platine + fluoropirimidin[2]

- Oxaliplatin enako učinkovit kot cisplatin[2-4]
- Kapecitabin in S-1 enako učinkovita kot 5-FU[2,5,6]

1.Wagner AD et al. Cochrane Database Syst Rev. 2017;8:CD004064. Epub 2017 Aug 29
2.Wagner AD et al. Cochrane Database Syst Rev 2010
3. Al-Batran SE et al. J Clin Oncol 2008; 4.Yamada Y et al. Ann Oncol 2014;
5. Kang YK et al. Ann Oncol 2009; 6. Ajani JA et al. J Clin Oncol 2010

5Fu vs kapecitabin in oksaliplatin vs cisplatin



Kombinacija z epirubicinom?
Ne!

„Whether the survival benefit for three-drug combinations including cisplatin, 5-FU, and epirubicin as compared to the same regimen without epirubicin is still valid when second-line therapy is routinely administered and when cisplatin is replaced by oxaliplatin and 5-FU by capecitabine is questionable. Furthermore, the magnitude of the observed survival benefits for the three-drug regimens is not large enough to be clinically meaningful as defined recently by the American Society for Clinical Oncology (Ellis 2014). „*

*Wagner AD et al. Cochrane Database Syst Rev. 2017;8:CD004064. Epub 2017 Aug 29

Kombinacija z irinotekanom?
Da!

- „In contrast to the comparisons in which a survival benefit was observed by adding a third drug to a two-drug regimen at the cost of increased toxicity, the comparison of regimens in which another chemotherapy was replaced by irinotecan was associated with a survival benefit (of borderline statistical significance), but without increased toxicity. For this reason irinotecan/5-FU-containing combinations are an attractive option for first-line treatment.“

*Wagner AD et al. Cochrane Database Syst Rev. 2017;8:CD004064. Epub 2017 Aug 29

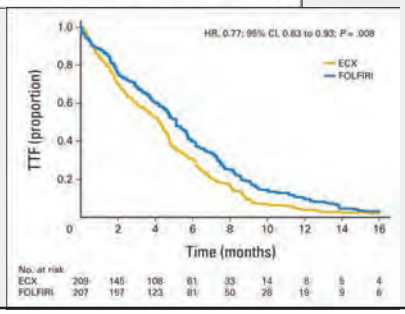
FFCD-GERCOR-FNCLCC 03-17 f. III

FOLFIRI vs ECF ; mRŽ

Table 2. Efficacy Results for PFS and OS

Variable	ECX Arm (n = 209) No.	ECX Arm (n = 209) %	ECX Arm (n = 209) 95% CI	FOLFIRI Arm (n = 207) No.	FOLFIRI Arm (n = 207) %	FOLFIRI Arm (n = 207) 95% CI	P
PFS, months							.96*
Median	5.29			5.75			
Range	4.53-6.31			5.19-6.74			
24-month survival		5.03	2.46 to 8.97		2.76	1.01 to 6.03	
OS, months							.95*
Median	9.49			9.72			
Range	8.77-11.14			8.54-11.27			
24-month survival		11.17	7.03 to 16.36		10.71	6.51 to 16.09	

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; FOLFIRI, fluorouracil, leucovorin, and irinotecan; OS, overall survival; PFS, progression-free survival.
*Log-rank test.



Guimbaud R et al. J Clin Oncol 2014 32:31, 3520-3526

Kombinacija s taksani?

DA!

Docetaxel poveča učinkovitost , a tudi toksičnost
(V325 faza III: DCF vs. CF)*
RR 37% vs. 25% p=0.01
TTP 5.6 vs. 3.7 mes. p<0.01
OS 9.2 vs. 8.6 mes. p=0.02

Gr. 3-4 toksičnost:
nevtropenija 82% vs. 57%
febrilna nevtropenija 29% vs. 12%

*Van Cutsem et al. J Clin Oncol 2006; 24: 4991-7

Modificirani DCF

Table 1. Randomly Assigned Treatment

Drug	Dose (mg/m²)	Schedule
Arm A (mDCF)		
Docetaxel	40	Day 1 IVPB (60 minutes)
Leucovorin	400	Day 1 IVPB (30 minutes)
Fluorouracil	400	Day 1 IVP
Fluorouracil	1,000 (per day)	IVCI daily × 2 days
Cisplatin	40	Day 2 or 3 IVPB (30 minutes)
Arm B (parent DCF plus G-CSF)		
Docetaxel	75	Day 1 IVPB (60 minutes)
Cisplatin	75	Day 1 IVPB (60 minutes)
Fluorouracil	750 (per day)	IVCI daily × 5 days
Neulasta*	6 mg	Subcutaneous on day 8, 9, or 10
Neupogen*	300 or 480 μg†	Subcutaneous × 7 days (days 10 to 17)

NOTE. Eligible patients were randomly assigned to receive mDCF (arm A) or parent DCF with growth factor support (arm B). Arm A treatment was repeated every 2 weeks, with one cycle considered 6 weeks (ie, three treatments). Arm B treatment was repeated every 3 weeks, with one cycle considered every 6 weeks (ie, two treatments).
Abbreviations: DCF, docetaxel, cisplatin, and fluorouracil; G-CSF, granulocyte colony-stimulating factor; IVCI, intravenous continuous infusion; IVP, intravenous push; IVPB, intravenous piggyback; mDCF, modified docetaxel, cisplatin, and fluorouracil.
*Either neulasta or neupogen was administered, not both.
†300 μg for weight ≤ 60 kg; 480 μg for weight > 60 kg.

Table 1. Randomly Assigned Treatment

Published in: Manish A. Shah; Yelena Y. Janjigian; Ronald Stoller; Stephen Shibata; Margaret Kemeny; Smitha Krishnamurthi; Yungpo Bernard Su; Allyson Ocean; Marinela Capanu; Bhoomi Mehrotra; Paul Ritch; Charles Henderson; David P. Kelsen; ***Journal of Clinical Oncology*** **2015,** 33, 3874-3879.
DOI: 10.1200/JCO.2015.60.7465

Toksičnost mDCF (gr. 2-4)

Table 3. Grade 2 to 4 Toxicities Possibly, Probably, or Definitely Related to Treatment

	No. (%)							
	Arm A (mDCF; n = 54)				Arm B (DCF + G-CSF; n = 31)			
Toxicity	Grade 2	Grade 3	Grade 4	Total Grades 3 to 4	Grade 2	Grade 3	Grade 4	Total Grades 3 to 4
Nonhematologic								
Allergy or hypersensitivity	4 (7)	3 (6)	0	3 (6)	0	0	0	0
Anorexia	8 (15)	0	0	0	2 (6)	4 (13)	0	**4 (13)**
Dysgeusia	5 (9)	0	0	0	1 (3)	0	0	0
Nausea	10 (19)	1 (2)	0	1 (2)	9 (29)	7 (23)	0	**7 (23)**
Vomiting	3 (6)	1 (2)	0	1 (2)	8 (26)	6 (19)	0	**6 (19)**
Dehydration	3 (6)	3 (6)	0	3 (6)	4 (13)	3 (10)	0	3 (10)
Diarrhea	6 (11)	3 (6)	0	3 (6)	8 (26)	1 (3)	0	1 (3)
Mucositis	7 (13)	0	0	0	13 (42)	4 (13)	0	**4 (13)**
Fatigue	22 (41)	6 (11)	0	**6 (11)**	17 (55)	4 (13)	0	**4 (13)**
Neuropathy	13 (24)	2 (4)	0	2 (4)	4 (13)	4 (13)	0	**4 (13)**
Alopecia	9 (17)	0	0	0	3 (10)	0	0	0
Electrolytes								
Hypomagnesemia	10 (19)	1 (2)	0	1 (2)	7 (23)	3 (10)	1 (3)	**4 (13)**
Hypophosphatemia	3 (6)	7 (13)	0	**7 (13)**	2 (6)	10 (32)	0	**10 (32)**
Hypokalemia	1 (2)	5 (9)	0	5 (9)	3 (10)	3 (10)	1 (3)	**4 (13)**
Thromboembolism	2 (4)	4 (7)	7 (13)	**11 (20)**	4 (13)	2 (6)	4 (13)	**6 (19)**
Hemorrhage	0	0	0	0	0	1 (3)	0	1 (3)
GI perforation	0	0	0	0	0	1 (3)	0	1 (3)
AST or ALT elevation	0	2 (3)	0	2 (3)	1 (3)	0	0	0
Hematologic								
Hemoglobin	30 (56)	5 (9)	1 (2)	**6 (11)**	14 (45)	12 (39)	0	**12 (39)**
Thrombocytopenia	10 (19)	2 (4)	0	2 (4)	2 (8)	1 (3)	0	1 (3)
Leucopenia	19 (35)	19 (35)	5 (9)	**24 (44)**	7 (23)	9 (29)	6 (19)	**15 (48)**
Neutropenia (without fever)	9 (17)	20 (37)	10 (19)	**30 (56)**	4 (13)	5 (16)	9 (29)	**14 (45)**
Febrile neutropenia	0	2 (4)	3 (6)	5 (9)	0	2 (6)	3 (10)	**5 (16)**

NOTE. Bold font indicates toxicity occurring in > 10% of study population.
Abbreviations: DCF, docetaxel, cisplatin, and fluorouracil; G-CSF, granulocyte colony-stimulating factor; mDCF, modified docetaxel, cisplatin, and fluorouracil.

Table 3. Grade 2 to 4 Toxicities Possibly, Probably, or Definitely Related to Treatment

Published in: Manish A. Shah; Yelena Y. Janjigian; Ronald Stoller; Stephen Shibata; Margaret Kemeny; Smitha Krishnamurthi; Yungpo Bernard Su; Allyson Ocean; Marinela Capanu; Bhoomi Mehrotra; Paul Ritch; Charles Henderson; David P. Kelsen; ***Journal of Clinical Oncology*** **2015,** 33, 3874-3879.
DOI: 10.1200/JCO.2015.60.7465
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Učinkovitost mDCF

Table 4. Efficacy Measures for Arms A and B

Efficacy	Arm A (mDCF)	Arm B (DCF + G-CSF)	*P*
Median No. of cycles	5.7	4.0	
Range	3.4-6.8	2.5-6.3	
6-month PFS, %*	63	53	
SD, %	48-75	34-69	
6-month TTF, %	56	51	
SD, %	42-68	32-67	
Median PFS, months	9.7	6.5	.2†
95% CI	5.8 to 11.6	3.9 to 9.4	
Median OS, months	18.8	12.6	.007†
95% CI	14.9 to 24.5	6.7 to 16	
1-year survival, %	63	55	
SD, %	48-74	36-70	
2-year survival, %	30	12	
SD, %	15-46	3-26	
Objective response rate (CR + PR)	49	33	.2‡
SD, %	35-63	17-53	

Abbreviations: CR, complete response; DCF, docetaxel, cisplatin, and fluorouracil; G-CSF, granulocyte colony-stimulating factor; mDCF, modified docetaxel, cisplatin, and fluorouracil; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, standard deviation; TTF, time to treatment failure.
*One patient in arm A and two patients in arm B were inevaluable for primary end point.
†Log-rank test.
‡Fischer's exact test.

Published in: Manish A. Shah; Yelena Y. Janjigian; Ronald Stoller; Stephen Shibata; Margaret Kemeny; Smitha Krishnamurthi; Yungpo Bernard Su; Allyson Ocean; Marinela Capanu; Bhoomi Mehrotra; Paul Ritch; Charles Henderson; David P. Kelsen; ***Journal of Clinical Oncology*** **2015,** 33, 3874-3879.
DOI: 10.1200/JCO.2015.60.7465

FLOT

Docetaxel 50mg/m² + modif. FOLFOX (oxaliplatin 85 mg/m², leukovorin 200 mg/m², FU 2600 mg/m² 24h infuzija na 2 tedna

RR 53%
TTP 5.3 mes.
OS 11.3 mes.

Al Batran et al. Ann Oncol. 2008 Nov;19(11):1882-7. doi: 10.1093/annonc/mdn403. Epub 2008 Jul 31.

Posebne skupine

- Oligometastatska bolezen

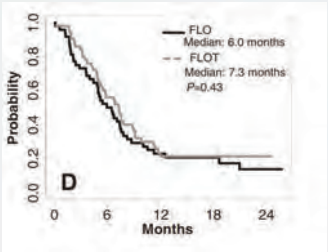
	Locally advanced resectable	Oligometastatic	Metastatic
Clinical definition	T3-T4 and/or N+	M1 with retroperitoneal lymph nodes and/or one potentially resectable incurable site	M1 patients other than oligometastatic
Prevalence	30-40%	Unknown	40-50%
Treatment strategy	Perioperative FLOT	Neoadjuvant FLOT followed by surgery ± adjuvant FLOT	Platinum-fluoropyrimidine-based doublet or triplet
Median OS	50 months	31.3 months	9-11 months
3-year OS	57%	NA	< 10%

Neoadjuvantna KT!
ESMO: eksperimentalno

Salati M et al. Eur J Surg Oncol. 2018 Nov 10. pii: S0748-7983(18)31997-8. doi: 10.1016/j.ejso.2018.11.006. [Epub ahead of print]

Starostniki z mRŽ

FLOT65+ (N 143)FLO/FLOT



- FLOT več toksičnosti gr 3- 4
- Poslabšanje QoL

- Trojčki z docetakselom – ne pri starejših

Al-Batran et al. Eur J Cancer. 2013;49:835–42.

Raziskave s tarčnimi zdravili

Recent phase 3 of new agents for GC

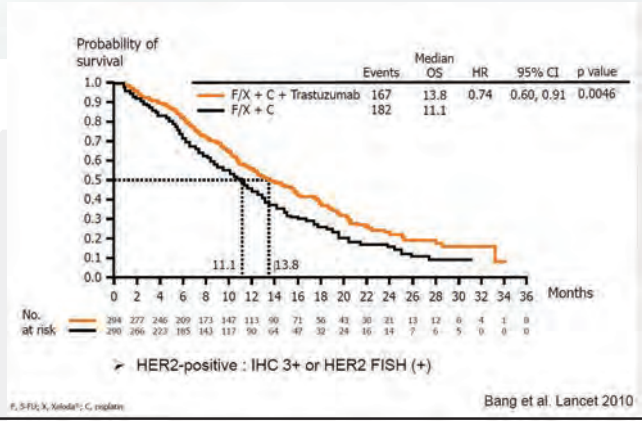
Target	Trial/Author	Line	Screening	Agent	control	Endpoint	Results	difference mOS (HR)
HER2	ToGA	1st	HER2	Trastuzumab	(+chemo)	OS	Positive	+2.7 (HR 0.74)
HER2	Logic	1st	HER2(FISH)	Lapatinib	PBO (+chemo)	OS	Negative	+1.7 (HR 0.91)
HER2	JACOB	1st	HER2	Pertuzumab	PBO (+Chemo+T)	OS	Negative	+3.3 (0.84)
HER2	TyTAN	2nd	HER2(FISH)	Lapatinib	(+chemo)	OS	Negative	+3 (HR 0.84)
HER2	GATSBY	2nd	HER2	T-DM1	Taxanes	OS	Negative	-0.7 (HR 1.15)
EGFR	REAL-3	1st	-	Panitumumab	(+chemo)	OS	Negative	-2.5 (HR 1.37)
EGFR	EXPAND	1st	-	Cetuximab	PBO (+chemo)	PFS	Negative	-1.3 (HR 1.0)
EGFR	ENRICH	2nd	EGFR(IHC)	Nimotuzumab	(+chemo)	OS	Negative	
mTOR	GRANITE-1	2nd/3rd	-	Everolimus	PBO	OS	Negative	+1.05 (HR 0.9)
mTOR	GRANITE-2	2nd	-	Everolimus	PBO (+chemo)	OS	Negative	+1.0 (HR 0.92)
HGF	RILOMET1	1st	MET(IHC)	Rilotumumab	PBO (+chemo)	OS	Negative	-2.9 (HR 1.36)
MET	METgastric	1st	MET(IHC)	Onartuzumab	PBO (+chemo)	OS	Negative	-0.3 (HR 0.82)
VEGF-A	AVAGAST	1st	-	Bevacizumab	PBO (+chemo)	OS	Negative	+2 (HR 0.87)
VEGFR2	RAINFALL	1st	-	Ramucirumab	PBO (+chemo)	OS	Negative	+0.4 (HR 0.96)
VEGFR2	REGARD	2nd	-	Ramucirumab	PBO	OS	Positive	+1.4 (HR 0.776)
VEGFR2	RAINBOW	2nd	-	Ramucirumab	PBO (+chemo)	OS	Positive	+2.2 (HR 0.807)
VEGFR2	Li, et al	3rd	-	Apatinib	PBO	OS	Positive	+1.8 (HR 0.71)
PARP	GOLD	2nd	ATM(IHC)	Olaparib	PBO (+chemo)	OS	Negative	+1.9 (HR 0.79)
STAT3	BRIGHTER	2nd	-	Napabucasin	PBO(+chemo)	OS	Negative	+0.3 (HR 1.01)
PD1	Keynote061	2nd	PDL1 (IHC)	Pembrolizumab	Paclitaxel	OS	Negative	+0.8 (HR 0.82)
PD1	JAVELIN300	3rd	-	Avelumab	Irl/taxanes/BSC	OS	Negative	
PD1	ATTRACTION-2	3rd-	-	Nivolumab	PBO	OS	Positive	+1.2 (HR 0.63)

Only 5 / 22 positive trials
Difference in median survival: 1.2~2.7ms (vs. placebo)

Presented By Kohei Shitara at 2018 ASCO Annual Meeting

HER2-pozitivni rak želodca

- HER2 pozitivni: ~16%
- Proksimalni > distalni
- Intestinalni >> difuzni
- TOGA



Tarčna zdravila v prvi liniji zdravljenja mRŽ – povzetek raziskav f. III

Trial	Chemotherapy	Biological	HR OS	P value	Increase in median survival
ToGA[1]	Cisplatin+5-FU/ capecitabine	Trastuzumab	0.74	0.04	+2.8 months
AVAGAST[2]	Cisplatin+ capecitabine	Bevacizumab	0.87	0.10	+2.0 months
EXPAND[3]	Cisplatin+ capecitabine	Cetuximab	1.00	0.95	-1.3 months
REAL-3[4]	Oxaliplatin+ epirubicin + capecitabine	Panitumumab	1.37	0.013	-2.5 months
RILOMET-1[5]	Cisplatin+ epirubiicin+ capecitabine	Rilotumumab	--	--	Stopped in futility analysis
METGASTRIC[6]	FOLFOX6	Onartuzumab	1.06	0.83	-0.6 months

1. Bang YJ, et al. Lancet 2010;376:687–697. 2. Van Cutsem E, J Clin Oncol 2012;30 (17):2119–2127. 3. Lordick F, Lancet Oncol 2013;14:490–499. 4. Waddell T, Lancet Oncol 2013;14:481–489. 5. Cunigham ASCO 2015,. 6. Shah M. J Clin Oncol 2015;33(15)

Anti HER 2 zdravila pri mRŽ

povzetek raziskav f. III (trastuzumab, lapatinib, TDM-1, pertuzumab)

TRIAL	Chemotherapy backbone	Line of therapy number	HR OS	P value	Response rate	Increase in median survival
ToGA[1]	Cisplatin+5-FU/ capecitabine	First 584	0.74	0.04	51% vs 37% p=0.0017	**+2.8 months**
LOGiC[2]	Oxaliplatin/ capecitabine +/- Lapatinib	First 545	0.91	0.35	53% vs 39% p=0.031	**+1.7 months**
TyTAN[3]	Paclitaxel+/- Lapatinib	Second 261	0.84	0.20	27% vs 9% p=0.001	**+2.1 months**
GATSBY[4]	TDM-1 vs Taxane	Second 345	1.15	0.85	NP	**- 0,7 months**
JACOB[5]	Cisplatin+5-FU/ cap/Trastu +/- Pertuzumab	First 780	0.84	0.056	56% vs 48%	**3.3 months**

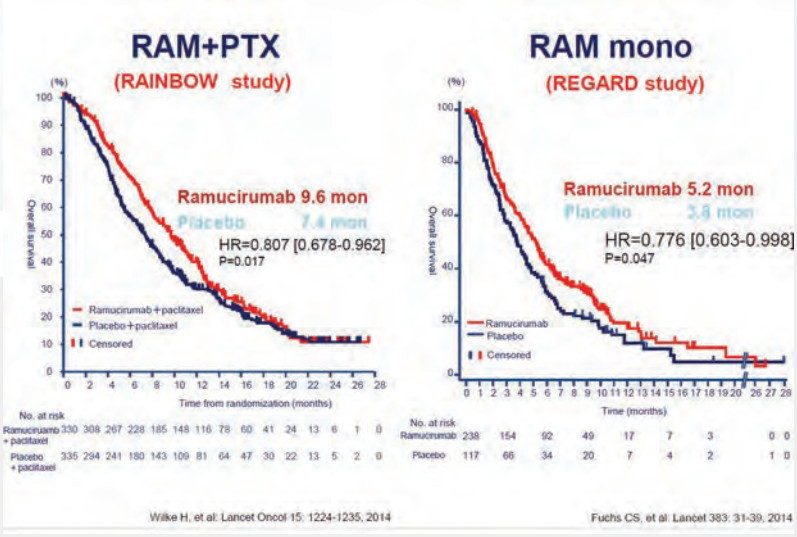
1. Bang YJ, et al. Lancet 2010;376:687–697.2. Hecht JR, et al. ASCO abstract 2013 LBA4001.
3. Satoh N, et al. J Clin Oncol 2014; 32:2039–2049. 4. Kang YK et al. ASCO GI 2016 5. Tabernero j, et al. ESMO 2017

mRŽ - druga linija: citostatsko in tarčno vs. podporno zdravljenje

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	Gain in median survival
Thuss-Patience, et al.[1]	2011	40 1:1	Irinotecan	0.48	0.0023	2.4 months
Kang, et al.[2]	2012	193 2:1	Irinotecan Docetaxel	0.65	0.004	1.3 months
Ford, et al.[3]	2014	168 1:1	Docetaxel	0.67	0.01	1.6 months
Otshu, et al[4]	2013	656 2:1	Everolimus	0.90	0.124	0.9 months
Fuchs, et al[5]	2014	355 2:1	Ramucirumab	0.77	0.047	1.4 months

1. Thuss-Patience PC, et al. Eur J Cancer 2011;47:2306–2314. 2. Kang JH, et al. J Clin Oncol 2012;30:1513–1518. 3. Ford HE, et al. Lancet Oncol 2014;15:78–86. 4. Otshu A, et al. J Clin Oncol 2013;31:3935–3943. 5. Fuchs CS, et al. Lancet 2014;383:31–39.

mRŽ – druga linija: ramucirumab



mRŽ- druga linija: primerjava dveh aktivnih zdravljenj

Trial author	Year	Patients (n)	Treatment	HR OS	P value	Gain in median survival
Hironaka, et al.[1]	2013	223	Irinotecan vs paclitaxel	1.13	0.38	0.9 months for paclitaxel
Wilke et al.[2]	2014	665	Paclitaxel+/- ramucirumab	0.80	0.017	2.2 months

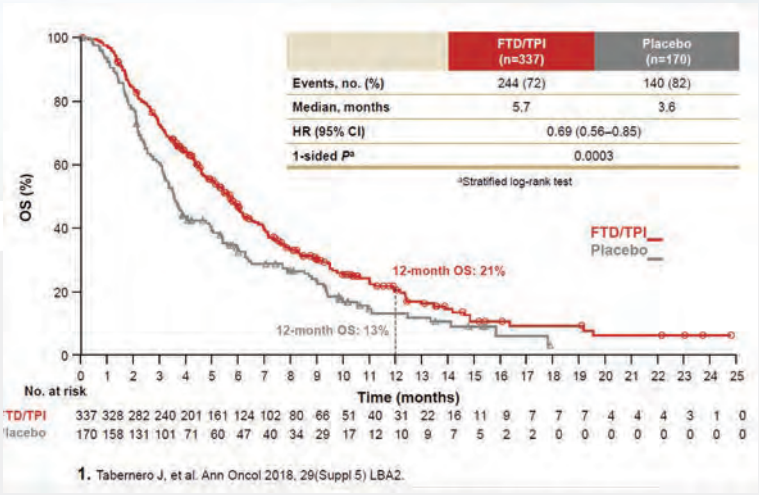
1. Hironaka S, et al. J Clin Oncol 2013;31:4438–4444.
2. Wilke H, et al. Lancet Oncol 2014;15:1224–1235.

mRŽ - tretja linija ? Trifluridin/tipiracil?

Trial author	Year	Patients random (n)	Treatment	Response rate (%)	HR OS	P value	Gain in median survival
Tabernero et al.[1]	2018	507 2:1	Trifluridin/Tipiracil (TAS102)	NR SD 58%	0.69	0.0003	5.7 vs 3,6 2.1 months

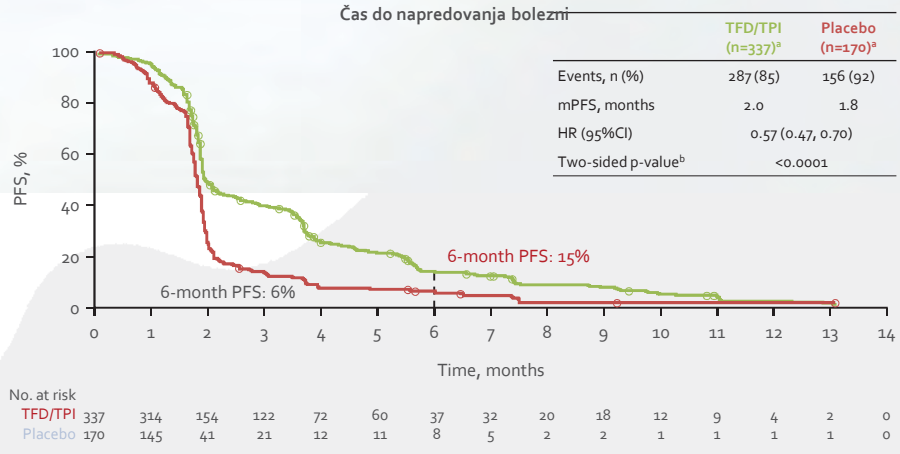
1. Tabernero J, et al. Ann Oncol 2018; 29(Suppl 5) LBA2.

TAGS - randomizirana, dvojno slepa raziskava f.3: TAS-102 vs placebo pri bolnikih z refraktornim mRŽ



1. Tabernero J, et al. Ann Oncol 2018; 29(Suppl 5) LBA2.

TAGS: randomizirana, dvojno slepa raziskava f.3: TAS-102 vs placebo pri bolnikih z refraktornim mRŽ



[a]ITT population; [b]stratified log-rank test

Arkenau H, et al. Ann Oncol 2018;29(suppl 5):abstr LBA25

TAGS: Neželeni učinki

NUZ: TFD/TPI 81%, placebo 57%
Gradus ≥3: 53% 13%

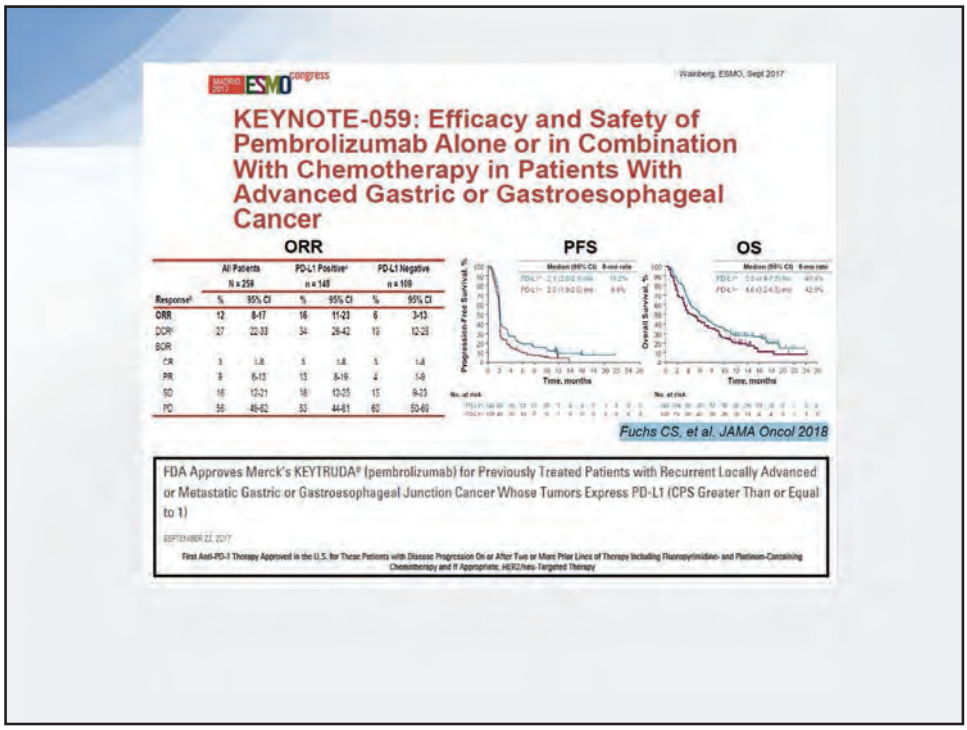
Najpogostejši NU gr. ≥3, ki so se pojavili pri >10% bolnikov z TFD/TPI:

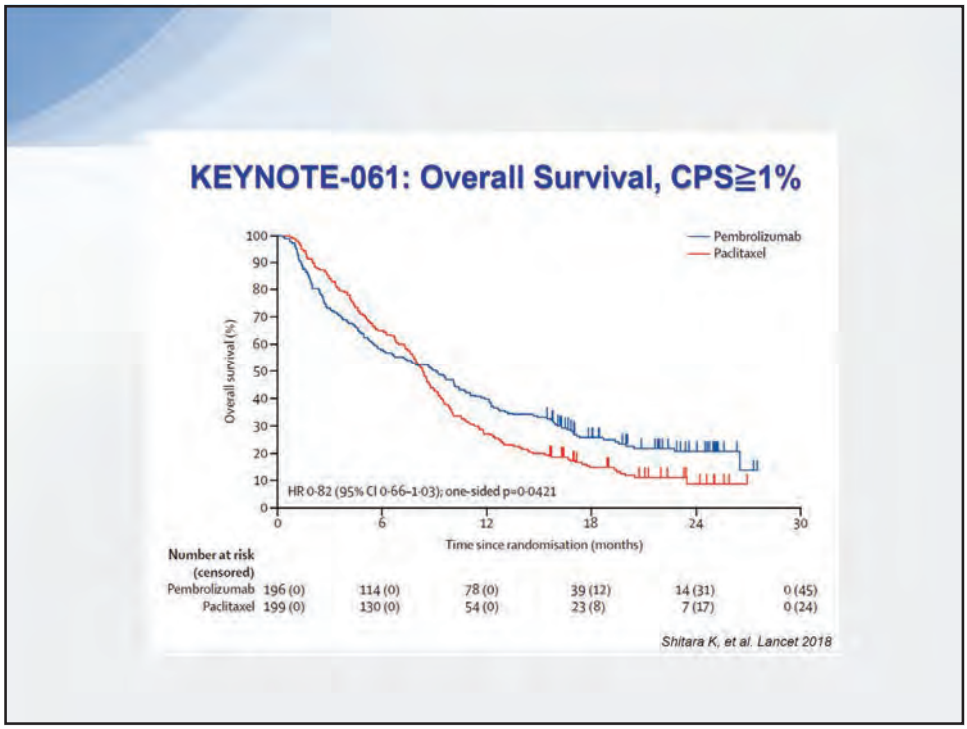
neutropenija (34%)
anemija (19%)

mRŽ: imunoterapija v drugi ali kasnejši liniji;randomizirane raziskave f. III - podporno vs. aktivno zdravljenje

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	mOS and Gain in median survival
Shitara, et al.[1] **KEYNOTE-061** **Second line**	2018	592 1:1	**Pembrolizumab** vs wk Paclitaxel	0.82	ns	9.1 vs 8.3 0.8 months
Bang, et al.[2] **JAVELIN 300** **Third or further lines**	2018	371 1:1	**Avelumab** vs Investigator choice of Chemotherapy	1.10	ns	4,6 vs 5.0 -0.4 months
Kang, et al[3] **ATTRACTION-2** **Third or further lines**	2017	493 2:1	**Nivolumab** vs BSC	0.63	0.0001	5.26 vs 4.14 1.12 months

1. Shitara, K. et al. Lancet 2018; 392:123–133. 2. Bang YJ, et al. Ann Oncol 2018; doi: 10.1093/annonc/myd264
3. Kang JK, et al. Lancet 2017;390:2461-2471.


ESMO congress
Wainberg, ESMO, Sept 2017
KEYNOTE-059: Efficacy and Safety of Pembrolizumab Alone or in Combination With Chemotherapy in Patients With Advanced Gastric or Gastroesophageal Cancer
ORR
PFS
OS
Fuchs CS, et al. JAMA Oncol 2018
FDA Approves Merck's KEYTRUDA® (pembrolizumab) for Previously Treated Patients with Recurrent Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer Whose Tumors Express PD-L1 (CPS Greater Than or Equal to 1)


KEYNOTE-061: Overall Survival, CPS≧1%
Pembrolizumab
Paclitaxel
Overall survival (%)
HR 0·82 (95% CI 0·66–1·03); one-sided p=0·0421
Time since randomisation (months)
Number at risk (censored)
Pembrolizumab 196 (0) 114 (0) 78 (0) 39 (12) 14 (31) 0 (45)
Paclitaxel 199 (0) 130 (0) 54 (0) 23 (8) 7 (17) 0 (24)
Shitara K, et al. Lancet 2018

ATTRACTION-2: mRŽ in mGEP -učinkovitost in varnost v 3L nivolumab vs. placebo (ATTRACTION-2) po dveh letih opazovanja

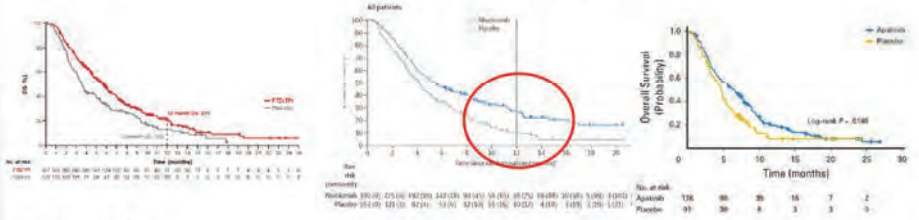
- n=493; randomizacija 2:1 nivolumab 3 mg/kg iv (q2w) ali placebo

	Nivolumab (n=330)	Placebo (n=163)	HR (95%CI); p-value
mOS, mes (95%CI)	5.26 (4.60, 6.37)	4.14 (3.42, 4.86)	0.62 (0.51, 0.76) <0.0001
mPFS, mes (95%CI)	1.61 (1.54, 2.30)	1.45 (1.45, 1.54)	0.60 (0.49, 0.75) <0.0001

- Pri večini bolnikov na nivolumabu, ki so preživeli dve leti - CR ali PR (19/29 [65.5%]), vsi bolniki v skupini na placebu (3/3 [100%]) - SD
- Brez resnih varnostnih zapletov v 2 letih

Satoh T, et al. Ann Oncol 2018;29(suppl 5):abstr 617PD

TAS-102 vs Nivolumab vs Apatinib Overall Survival



Median OS
5.7 mo vs 3.6 mo
HR 0.69

5.3 mo vs 4.1 mo
0.63

6.5 mo vs 4.7 mo
0.71

Imunoterapija pri mRŽ

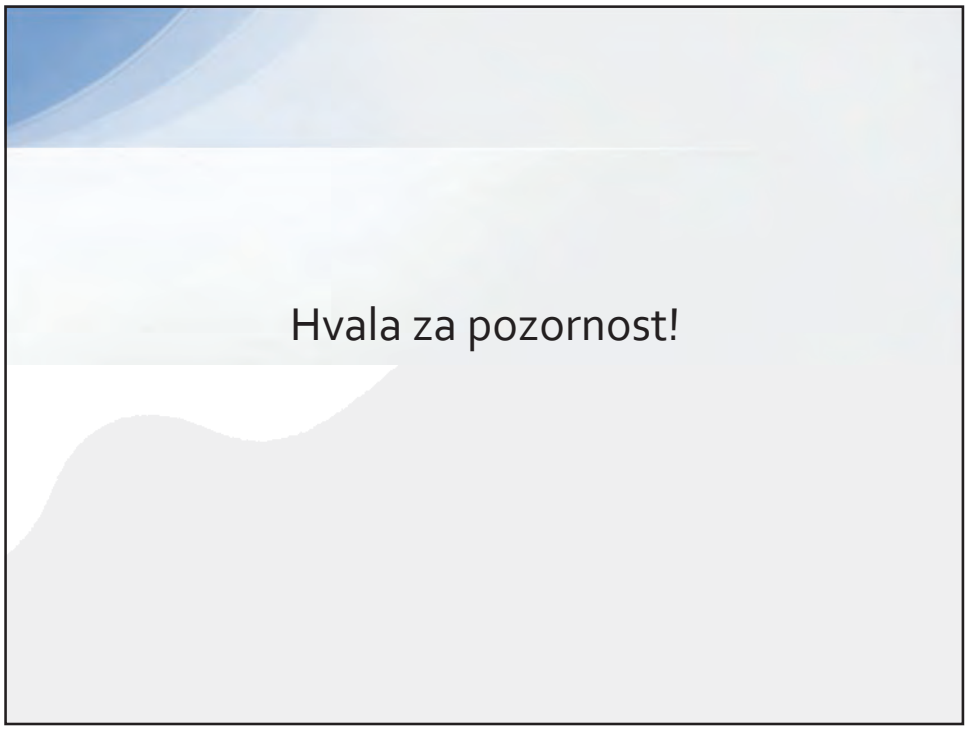
- Učinkovita pri nekaterih bolnikih z mRŽ
- MSI status & PD-L1 ekspresija - kot prediktivni marker za optimalno izbiro bolnikov
- Potekajo f. III raziskave kombinacije zaviralcev nadzornih točk in citostatikov

Standardno zdravljenje mRŽ

1 linija:
fluororopirimidin + der. platine
(+trastuzumab pri HER2+)

2. linija
ramucirumab + paklitaksel
(mono taksan, irinotekan, ramucirumab)

(≥3. linija)
(?TAS 102, nivolumab, apatinib)


Hvala za pozornost!

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

8. ŠOLA TUMORJEV PREBAVIL

Erik Brecelj

Onkološki inštitut

KARCINOZA PERITONEJA PRI KOLOREKTALNEM RAKU:

- **prisotna v 10-15% pri postavitvi diagnoze**
- **kasneje se razvije pri 20-25% bolnikov**
- **druga najbolj pogosta lokalizacija metastaz**

V 25% EDINA LOKALIZACIJA RAZŠIRJENEGA KOLOREKTALNEGA RAKA

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

KARCINOZA PERITONEJA; TNM KLASIFIKACIJA:

Distant metastasis (M)	
M0	No distant metastasis by imaging or other studies, no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis
M1a	Metastasis confined to 1 organ or site (eg, liver, lung, ovary, nonregional node) without peritoneal metastasis
M1b	Metastasis to two or more sites or organs without peritoneal metastasis
M1c	**Metastasis to the peritoneal surface alone or with other site or organ metastases**

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

KARCINOZA PERITONEJA – RIZIČNI DEJAVNIKI:

- karcinomi desnega kolona
- mlajši bolniki
- napredovali T stadij s penetracijo tumorja
- višji N status
- slabo diferencirani in mucinozni tumorji
- obstruktivni tumorji, perforacija

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

KARCINOZA PERITONEJA – RIZIČNI DEJAVNIKI ZA METAHRONE METASTAZE

- tumorji desnega kolona
- mlajši bolniki od 60 let
- stadij T4, N2
- metastaze v bezgavke z manj kot 12 odstranjenimi bezg.
- urgentna operacija
- R1 resekcija
- mucinozni in pečatnocelični karcinomi

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

KARCINOZA PERITONEJA nekoč

- inoperabilna, terminalna, paliativna bolezen…
- preživetje v mesecih
- samo s paliativnimi kirurškimi posegi

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

Paul H. Sugarbaker

Paul H. Sugarbaker; KARCINOZA JE LOKOREGIONALNA BOLEZEN

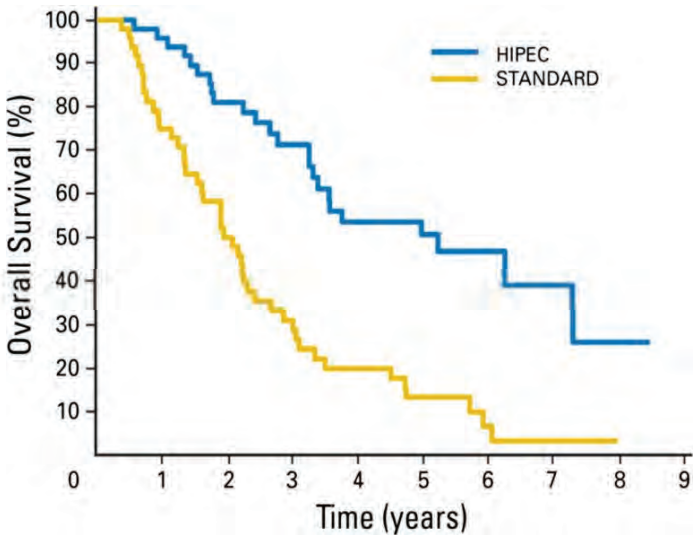
- **citoreduktivna kirurgija z odstranitvijo karcinoze s peritonektomijo in resekcijo posameznih organov**
- **intraperitonealna kemoterpija s hipertermijo - HIPEC**

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

RAZLIČNE OBLIKE INTRAPERITONEALNE KEMOTERAPIJE

- **EPIC** (early postoperative intraperitoneal chemotherapy)
- **SPIC** (sequential postoperative intraperitoneal chemotherapy)
- **HIPEC** (hyperthermic intraperitoneal chemotherapy)

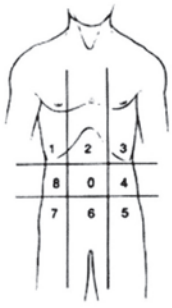
Karcinoza peritoneja - vloga kirurgije in HIPEC-a



J Clin Oncol. 2009 Feb 10;27(5):681-5. doi: 10.1200/JCO.2008.19.7160. Epub 2008 Dec 22.
Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin.
Elias D[1], Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, Ferron G, Guilloit JM, Meeus P, Goéré D, Bonastre J.

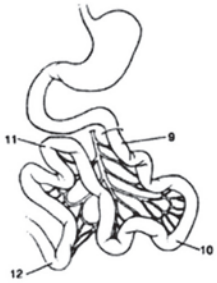
Karcinoza peritoneja - vloga kirurgije in HIPEC-a

PCI indeks

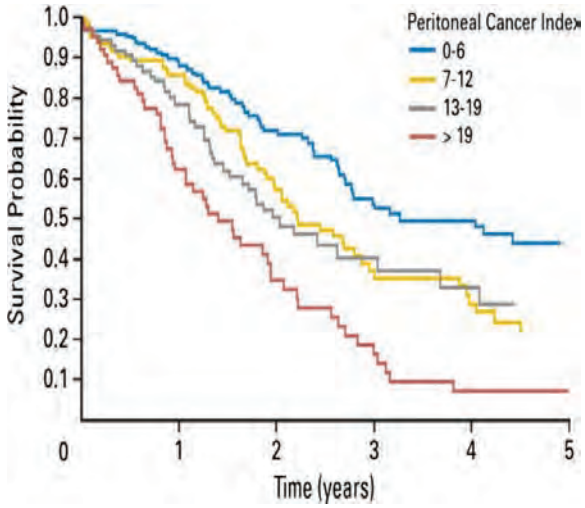


Regions	Lesion Size
0 Central	___
1 Right Upper	___
2 Epigastrium	___
3 Left Upper	___
4 Left Flank	___
5 Left Lower	___
6 Pelvis	___
7 Right Lower	___
8 Right Flank	___
9 Upper Jejunum	___
10 Lower Jejunum	___
11 Upper Ileum	___
12 Lower Ileum	___
PCI	☐

Lesion Size Score
LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm
or confluence



Karcinoza peritoneja - vloga kirurgije in HIPEC-a



J Clin Oncol. 2010 Jan 1;28(1):63-8. doi: 10.1200/JCO.2009.23.9285. Epub 2009 Nov 16.
Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study.
Elias D[1], Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, Lorimier G, Dubè P, Glehen O.

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

PRODIGE 7; prospektivna randomizirana multicentrična faza III študija

citoreduktivna peritonektomija **s HIPEC-om z oksaliplatinom** s kemoterapijo pred in po operaciji

citoreduktivno kirurgijo s kemoterapijo pred in po operaciji

	HIPEC SKUPINA	SAMO KIRURGIJA	p
število	*133*	*132*	
med. preživetje	41,7 mes.	41,2 mes.	0,995
čas do pon.	13,1 mes.	11,1 mes.	0,486
poop. smrt.	1,5%	1,5%	
morbiditeta 30.d.	=	=	
morbiditeta 60.d.	24,1%	13,6%	0.003

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

ZAPLETI

- pooperativni zapleti; 12-64%
- smrtnost; 0-12%
- v izkušenih centrih so zapleti primerljivi z večjimi abdominalnimi posegi
- komplikacije zaradi kemoterapije; nevtropenija, ledv. insuficienca, srčne aritmije

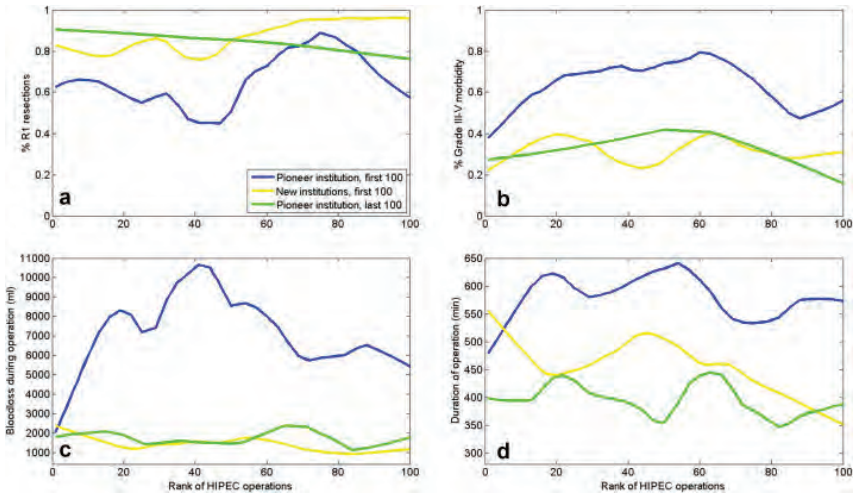
- UČNA KRIVULJA !!!

Verwaal VJ, van RS, de BE, van Sloothen GW, van TH, Boot H, et al. **Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer.** J Clin Oncol 2003 Oct 15;21(20):3737-43.

8% smrtnost

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

UČNA KRIVULJA



Eur J Surg Oncol. 2016 Feb;42(2):244-50. doi: 10.1016/j.ejso.2015.08.162. Epub 2015 Sep 3.
Cytoreduction and hyperthermic intraperitoneal chemotherapy: The learning curve reassessed.
Kuijpers AM[1], Hauptmann M[2], Aalbers AG[3], Nienhuijs SW[4], de Hingh IH[4], Wiezer MJ[5], van Ramshorst B[5], van Ginkel RJ[6], Havenga K[6], Verwaal VJ

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

IZBIRA BOLNIKOV ZA ZDRAVLJENJE S PERITONEKTOMIJO

ZA	PROTI
brez hude komorbiditete	slabo diferencirani karcinomi
z brez ali milimi simptomi	bolniki z multiplimi bilobarnimi jetrnimi metastazami
brez progresa bolezni med kemoterapijo	kahektični bolni ???
dobro ali srednje diferencirani karcinomi	
brez extraabdominalnih metastaz	
z do tri metastazami na jetrih ležečih periferno	
brez biliarne ali ureteralne obstrukcije	
brez metastaz v gastrohepatičnem ligamentu >5 cm	
brez infiltracije v mezenterij tankega črev. ali pankreas	
ne več kot ena stenoza na črevesju	
PCI index < 20	

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

CC (completeness of cytoreduction)

Oceni ostanek bolezni po operaciji;

- **CC-0 ni makroskopskega ostanka bolezni**
- **CC-1 ostanek manj kot 2,5 mm**
- **CC-2 ostanek med 2,5 mm in 2,5 cm**
- **CC-3 ostanek več kot 2,5 cm**

CC-0 močan pozitiven prognostični dejavnik

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

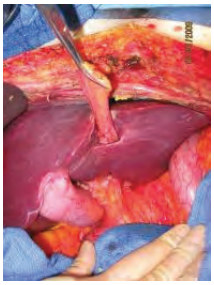
PONOVITEV BOLEZNi; pogosta, prognoza slaba

IZBOLJŠANJE ZDRAVLJENJA;

- izbor bolnikov
- boljša kirurgija
- boljša diagnostika
- „second look“ kirurgija
- profilaktični HIPEC

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

IZBOLJŠANJE ZDRAVLJENJA; BOLJŠA KIRURGIJA



J Surg Oncol. 2010 Mar 1;101(3):251-2. doi: 10.1002/jso.21478.
Pont hepatique (hepatic bridge), an important anatomic structure in cytoreductive surgery.
Sugarbaker PH[1].

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

IZBOLJŠANJE ZDRAVLJENJA; BOLJŠA DIAGOSTIKA

- ocena obsega karcinoze pred operacijo težka
- CT plus MRI boljše kot samo CT

- ICG-FGS (Indocyanine green fluorescence guided surgery) intraoperativno za slabo vidne metastaze po peritoneju, verjetno v prihodnje

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

TABLE 1 RISK OF RECURRENCE IN FUNCTION OF CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS OF TUMORS

	Estimated incidence of peritoneal metastases observed in follow-up
Clinical characteristic	
Peritoneal nodules detected during primary cancer resection	70%
Ovarian metastases	60%
Perforation through the primary cancer	50%
Adjacent organ or structure invasion	20%
Signet-ring histology	20%
Fistula formation	20%
Obstruction of primary cancer	20%
Histopathological characteristic	
Positive resection margin	80%
Positive cytology before or after resection	40%
Positive imprint cytology	40%
Positive lymph nodes at or near resection margin	20%
T3/T4 mucinous cancer	40%

Second-look surgery plus hyperthermic intraperitoneal chemotherapy for patients with **colorectal cancer** at high risk of peritoneal carcinomatosis: Does it really save lives?
Cortes-Guiral D, Elias D, Cascales-Campos PA, Badía Yébenes A, Guijo Castellano I, León Carbonero AI, Martín Valadés JI, Garcia-Foncillas J, Garcia-Olmo D
World J Gastroenterol. 2017 Jan 21;23(3):377-381. doi: 10.3748/wjg.v23.i3.377

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

„SECOND LOOK“ KIRURGIJA

VISOKO RIZIČNI BOLNIKI (ASIMPTOMATSKI);

- **omejena sinhrona karcinoza pri primarni operaciji**
- **bolnice z metastazami v ovarije**
- **bolniki s perforiranim primarnim tumorjem**

1 LETO PO PRVI OPERACIJI REOPERACIJA – 55% PONOVITEV !

Elias D, Goere D, Di PD, Boige V, Malka D, Kohneh-Shahri N, et al. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. Ann Surg 2008 Mar;247(3):445-50

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

IZBOLJŠANJE ZDRAVLJENJA

ProphyloCHIP multicentrična faza III študij

- **Rizični bolniki 6 mesecev po KT ;**

SPREMLJANJE

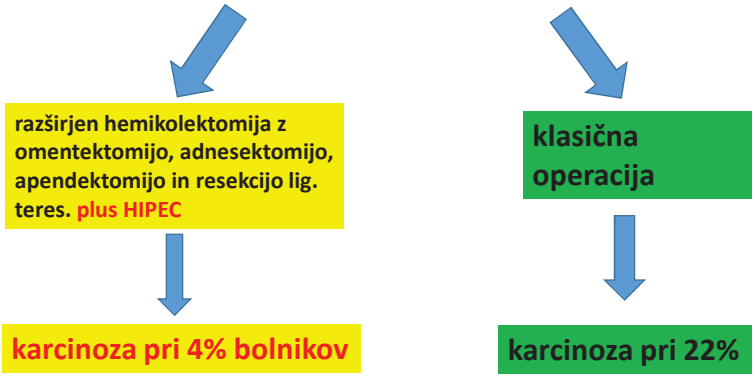
vers.

REOPERACIJA S HIPEC-om

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

IZBOLJŠANJE ZDRAVLJENJA; PROFILAKTIČNI HIPEC

MUCINOZNIMI IN PEČATNOCELIČNIMI KARCINOMI



Sammartino P, Sibio S, Biacchi D, Cardi M, Accarpio F, Mingazzini P, et al. Prevention of Peritoneal Metastases from Colon Cancer in High-Risk Patients: Preliminary Results of Surgery plus Prophylactic HIPEC. Gastroenterol Res Pract 2012;2012:141585

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

IZBOLJŠANJE ZDRAVLJENJA; PROFILAKTIČNI HIPEC; COLOPEC ŠTUDIJA

PREDVIDEVAJO ZNIŽANJE RIZIKA KARCINOZE IZ 25% NA 10%

Klaver CE, Musters GD, Bemelman WA, Punt CJ, Verwaal VJ, Dijkgraaf MG, et al. **Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial**. BMC Cancer 2015 May 24;15:428.

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

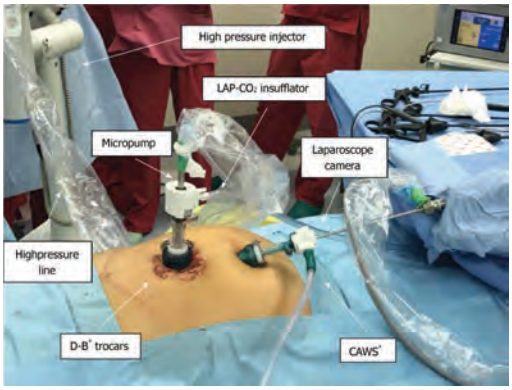
INTRAPERITONEALNA KEMOTERAPIJA PRI INOPERABILNI KARCINOZI

- **zmanjša simptome bolezni**
- **zmanjša oličino ascitesa**

- **podatki iz retrospektivnih študij**

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

PIPAC (pressurized intraperitoneal aerosol chemotherapy)



Karcinoza peritoneja - vloga kirurgije in HIPEC-a

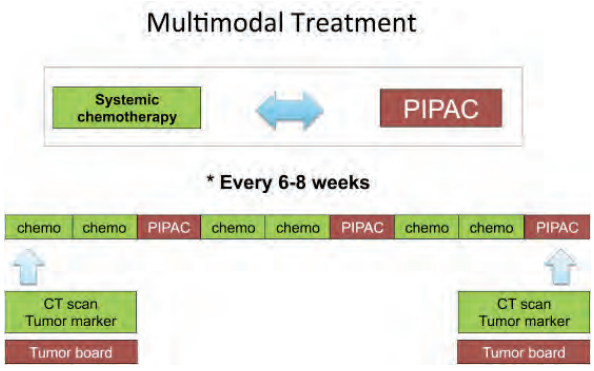
PIPAC (pressurized intraperitoneal aerosol chemotherapy)

- aplikacija citostatika kot aerosola pod pritiskom v abdomen
- pri paliativnih bolnikih
- zmanjša simptome (npr. ascites)
- zniža PCI
- neoadjuvantna terapija pri inoperabilnih karcinozah ?

POTREBNE RANDOMIZIRANE ŠTUDIJE

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

PIPAC (pressurized intraperitoneal aerosol chemotherapy)



Multicentric initial experience with the use of the pressurized intraperitoneal aerosol chemotherapy (**PIPAC**) in the management of unresectable peritoneal carcinomatosis.
Alyami M, Gagniere J, Sgarbura O, Cabelguenne D, Villeneuve L, Pezet D, Quenet F, Glehen O, Bakrin N, Passot G.
Eur J Surg Oncol. 2017 Nov;43(11):2178-2183

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

ZAKLJUČEK

- peritonektomija s HIPEC- om izboljša preživetje
- je del multidisciplinarnega zdravljenja s sistemsko terapijo
- dobra selekcija bolnikov je ključna, kirurgija najbolj pomembna
- smiselno zdraviti bolnike z nizkim PCI

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

ZAKLJUČEK

- „second look“ peritonektomija s HIPEC-om in profilaktični HIPEC obetata boljše rezultate zdravljenja
- vloga intraperitonealne kemoterapije pri paliativnih bolnikih?
- REZULTATI RANDOMIZIRANIH ŠTUDIJ ?

Karcinoza peritoneja - vloga kirurgije in HIPEC-a

NAJLEPŠA HVALA

SIMPOZIJ SO PODPRLE NASLEDNJE DRUŽBE:

NOVARTIS

ROCHE

SERVIER

ELI LILLY

BAYER

SANOFI

AMGEN

MSD

MERCK

TEVA

MEDIAS INTERNATIONAL

ABBOTT