Key Considerations in the Selection and Sequencing of Therapies for Patients with mCRC; Novel Investigational Approaches

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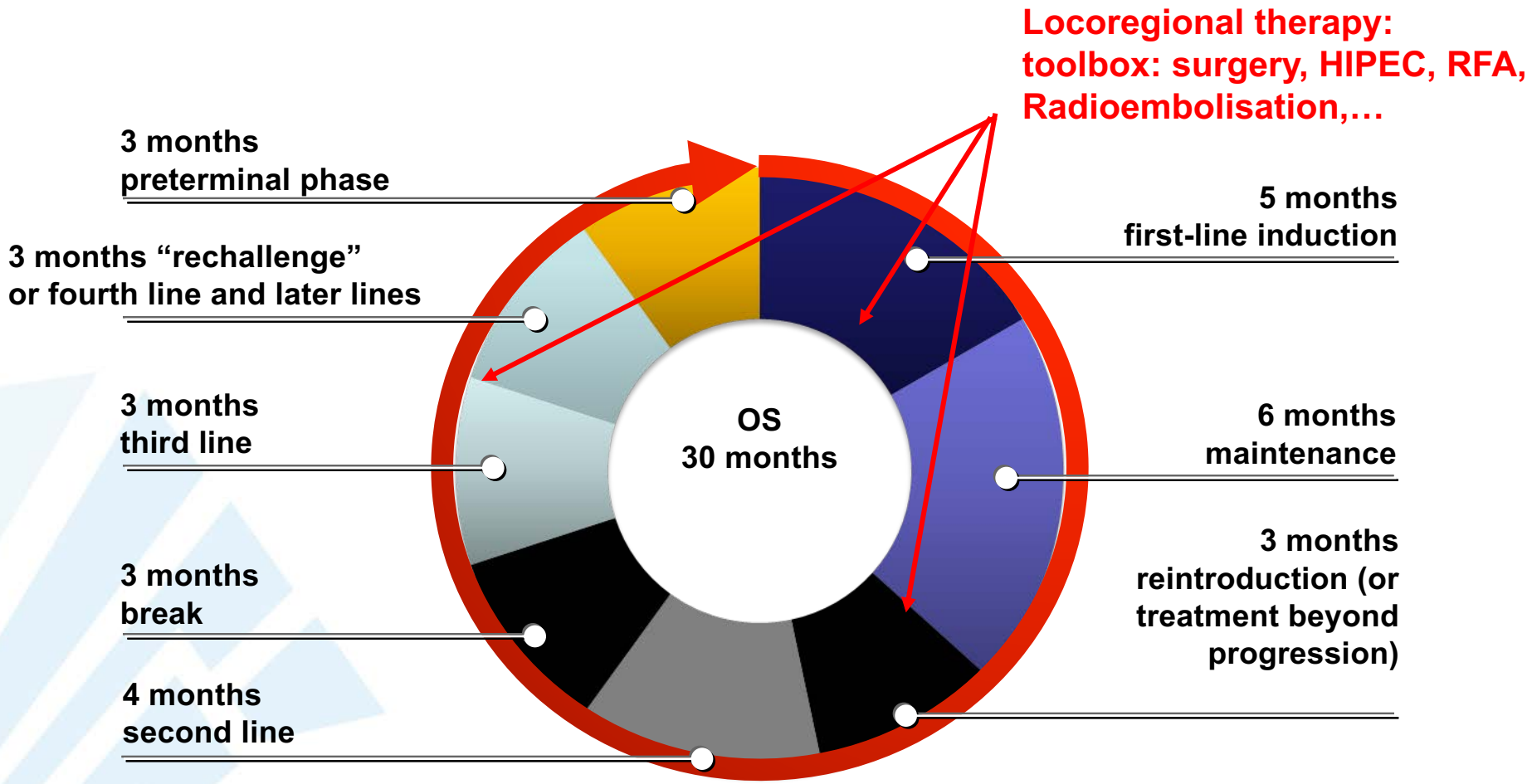
A classical case of mCRC in 2021
CONTINUUM OF CARE

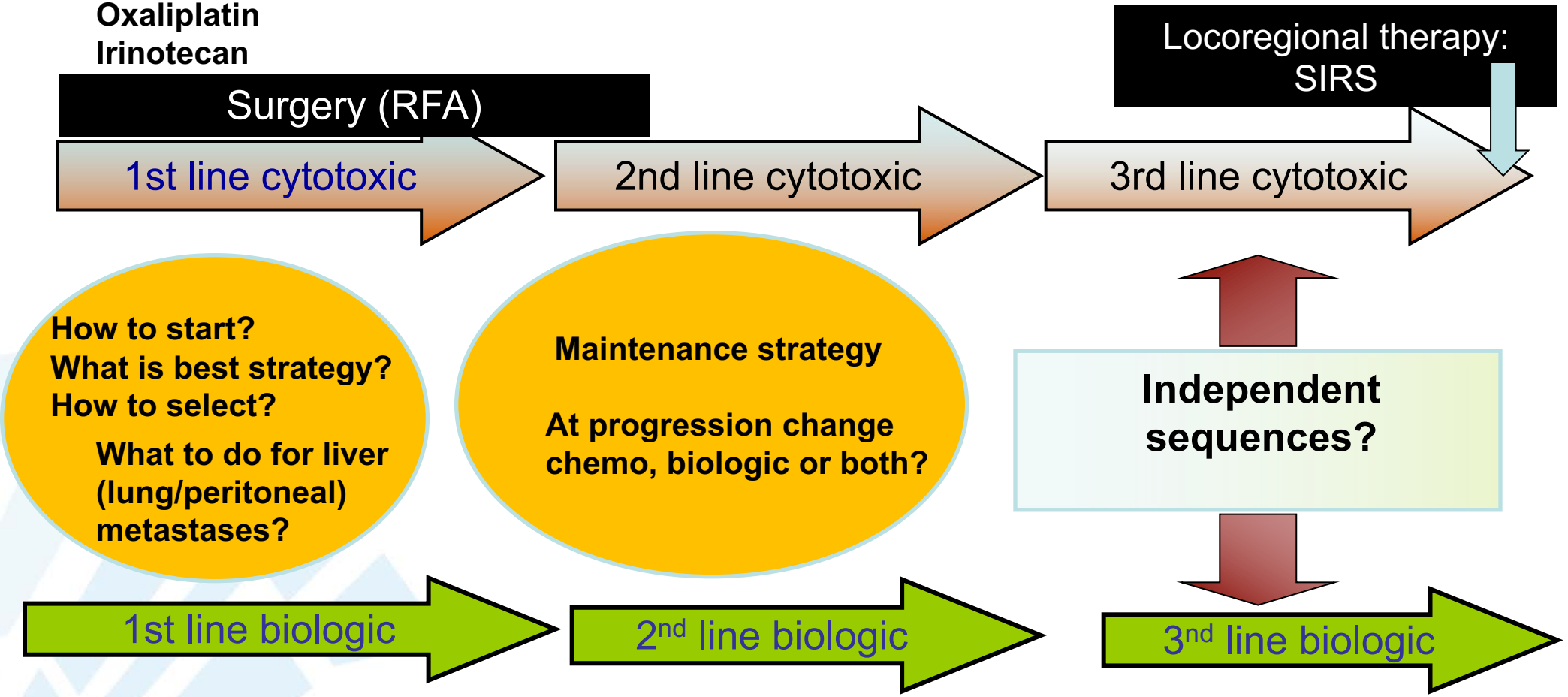


1991: OS 6 months

Courtesy of Eric Van Cutsem, MD, PhD

The continuum of care of mCRC

Fluoropyrimidines: 5FU, capecitabine, S1, Trifluridine/tipiracil = TAS-102
Oxaliplatin
Irinotecan



Bevacizumab/aflibercept/ramucirumab
Cetuximab/panitumumab
Regorafenib
Pembrolizumab/nivolumab ± ipilimumab

Encorafenib (+ binimetinib); vemurafenib; cobimetinib
Trastuzumab + lapatinib or pertuzumab; Trastuzumab/Deruxtecan
Larotrectinib;

Courtesy of Eric Van Cutsem, MD, PhD

Table 4: Drivers for first-line treatment

many are also valid in later line

Tumour characteristics	Patient characteristics	Treatment characteristics
Clinical presentation: Tumour burden Tumour localisation	Age	Toxicity profile
Tumour biology	Performance status	Flexibility of treatment administration
RAS mutation status	Organ function	Socio-economic factors
BRAF mutation status	Comorbidities, patient attitude, expectation and preference	Quality of life

Patient and treatment characteristics become even more relevant in later lines

Courtesy of Eric Van Cutsem, MD, PhD

Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016 Ann Oncol, July 2016

Treatment Options in First-line of mCRC determines later lines of strategy

Regimen	Sidedness restriction	Molecular restriction	Preferred indication
Cape + BEV Or other fluoropyrimidine + BEV	None	None	Elderly patients, low-volume disease and 'not-eligible' for combo cytotoxics
FOLFOX/ CAPOX/ FOLFIRI + BEV	None	None	○ SOC for RAS mutant ○ SOC for Right-sided
FOLFOX/ FOLFIRI + EGFR mAb	Left-sided	RAS/ BRAF wt (HER-2 neg?)	SOC left-sided wt-type cancers
FOLFOXIRI + BEV	None	None	○ Aggressive cancers (w.g. BRAF mut, R-sided) ○ Neoadjuvant
FOLFOXIRI + EGFR mAb	Left-sided	RAS/ BRAF wt (HER-2 neg?)	○ Left-sided cancers with high tumor burden ○ Neoadjuvant
PD-1 antibody: Pembro / IO combo	None	MSI-H/ MMR-D	Pts with MSI-H cancers
BEACON(-like) in future?	None	BRAF V600E mut	Data in first-line pending

Courtesy of Eric Van Cutsem, MD, PhD

Annals of Oncology 0: 1–17, 2017
doi:10.1093/annonc/mdx175
Published online 12 April 2017

SPECIAL ARTICLE

Prognostic and predictive value of primary tumour side in patients with *RAS* wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials†

D. Arnold[1], B. Lueza[2], J.-Y. Douillard[3], M. Peeters[4], H.-J. Lenz[5], A. Venook[6], V. Heinemann[7], E. Van Cutsem[8], J.-P. Pignon[2], J. Tabernero[9], A. Cervantes[10,11] & F. Ciardiello[12]*

- Data and recommendations: First line Ras wild-type mCRC:
  - Left sided tumors have a better prognosis than right sided tumors.
  - Sidedness is predictive in first line treatment of RAS Wt tumours:
    - Left sided tumors benefit more from anti-EGFR antibodies.
    - Right sided tumors benefit slightly more from bevacizumab

- Sidedness concept does not influence my practise in RAS mutant tumors and in pretreated patients

Courtesy of Eric Van Cutsem, MD, PhD

Preferred choices in second line treatment of mCRC

Goal / condition	Molecular	Prefered 2nd line regimen
Cytoreduction (conversion/ symptom relief) Disease stabilization	all WT	1st line doublet + EGFR Ab: doublet + bevacizumab 1st line doublet + bev.: doublet + bevacizumab Oxaliplatin → irinotecan based Irinotecan → oxaliplatin based
	RAS mut	FOLFOX/beva or FOLFIRI/beva alternatives FOLFIRI/aflibercept or (ramucirumab)
	MSI-H	Pembrolizumab / nivolumab ± ipilimumab
	BRAF mut V600E	Cetuximab + encorafenib
	HER2 amplified	Second line or later line? Combination anti-HER2
	NTRK alterations	Second line or later line? NTRK-TKI
	Other: experimental	Trial
"frail"	MSS	○ 5FU or Capecitabine + beva if first line EGFR Ab ○ RAS & BRAF wild type: EGFR Ab ± irinotecan if first line fluoropyrimidine + beva
	MSI-H	Pembrolizumab / nivolumab ± ipilimumab

Courtesy of Eric Van Cutsem, MD, PhD

Adapted and updated from Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus - Ann Oncol, 2016

ESMO consensus guideline:
Third-line treatment

Table 7. Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)[a]

Category	Fit patients[b]					
Treatment goal	Cytoreduction (tumour shrinkage)			Disease control (control of progression)		
Third line						
Preferred choice (s)	CT doublet + EGFR antibody[c,f] or irinotecan + cetuximab[f]	Regorafenib or trifluridine/ tipiracil	Regorafenib or trifluridine/ tipiracil	CT doublet + EGFR antibody[c] or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil
Second choice	EGFR antibody monotherapy[f]			EGFR antibody monotherapy[f]		
Third choice	Regorafenib or trifluridine/ tipiracil			Regorafenib or trifluridine/ tipiracil		

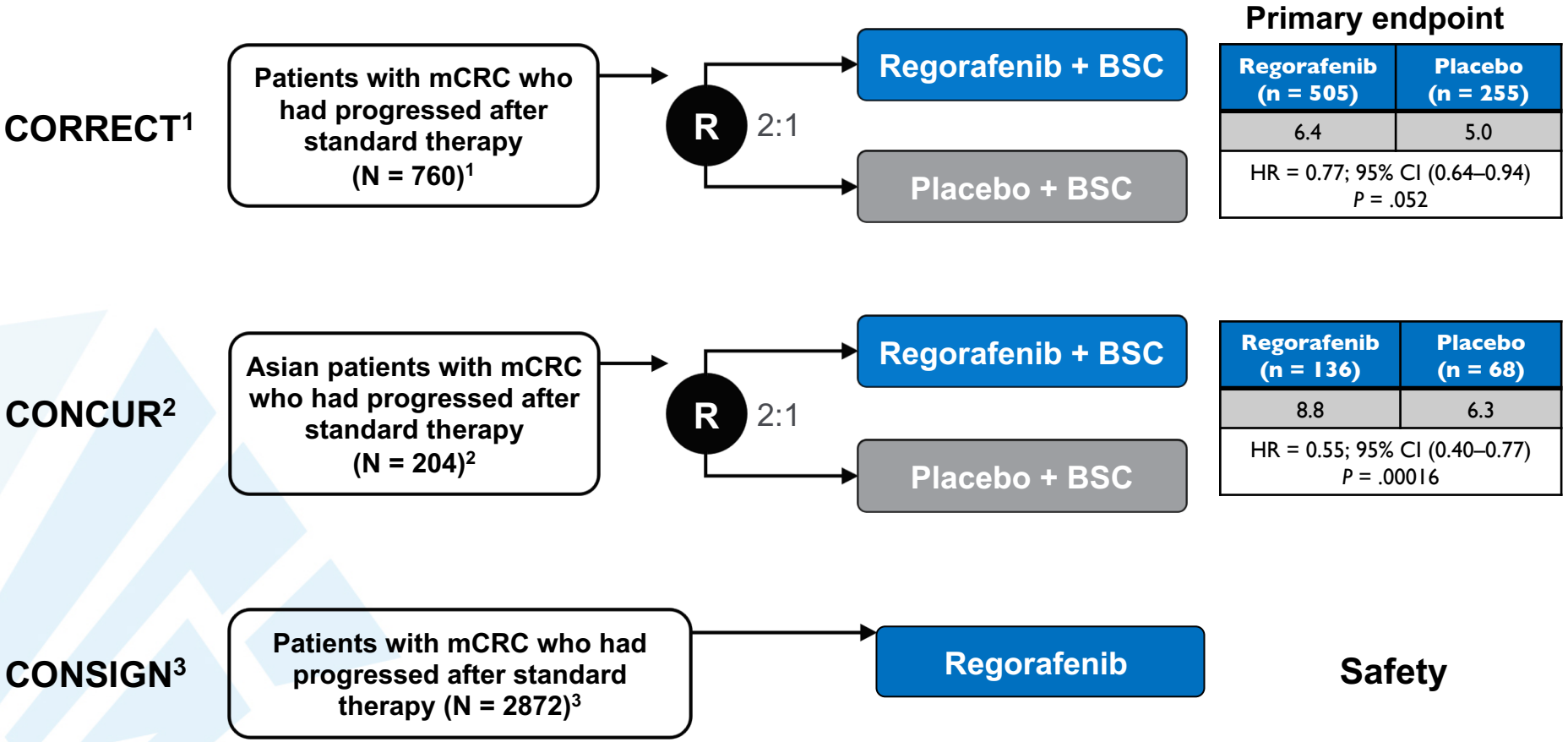
Update based on data:

- **molecular analysis esp. for druggable markers:**
  MSI, BRAF V600E, **HER2, NTRK fusions, POLE mutation: targeted agents or IO agents**

Courtesy of Eric Van Cutsem, MD, PhD

Adapted and updated from Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus - Ann Oncol, 2016

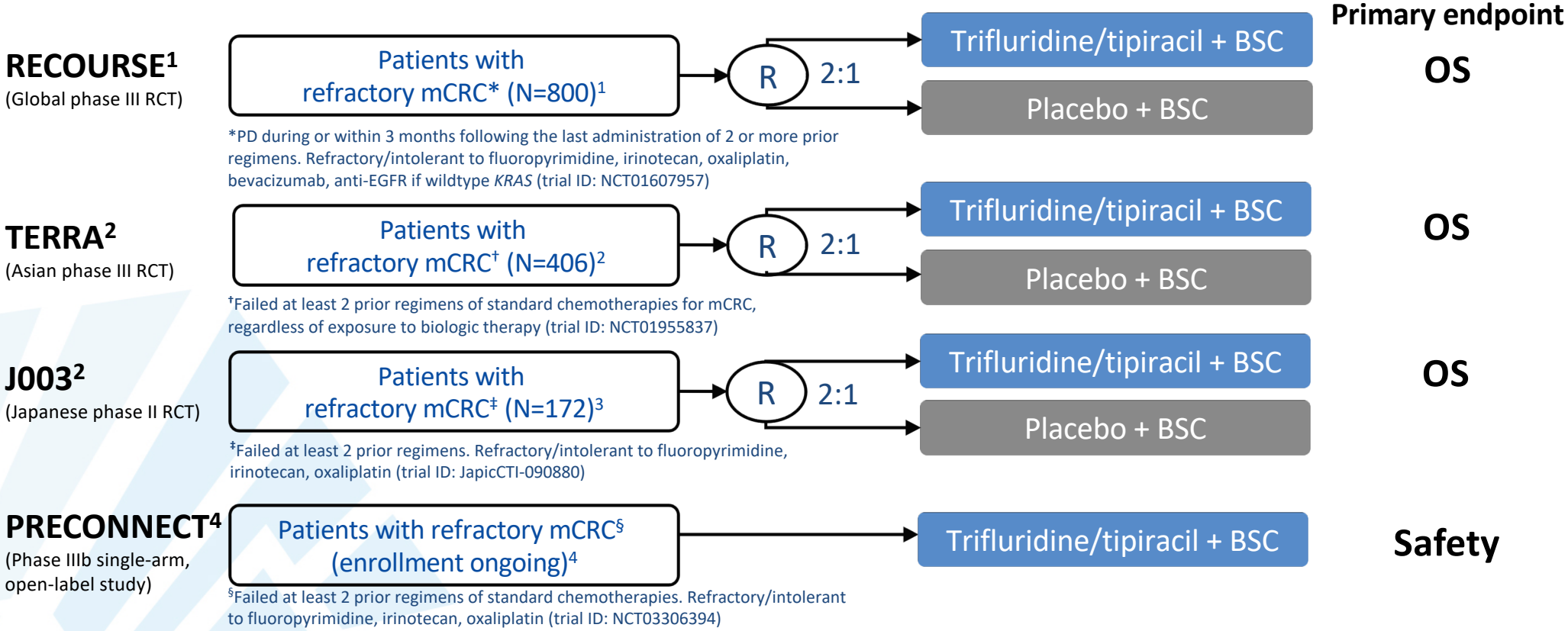
Regorafenib phase III studies



Courtesy of Eric Van Cutsem, MD, PhD

1. Grothey A, Van Cutsem E, et al. Lancet. 2013;381:303-312; 2. Li J, et al. Lancet Oncol. 2015;16:619-629; 3. Van Cutsem E, et al. The Oncologist 2019; 2:185-192.

Trifluridine/tipiracil phase II/III study programs

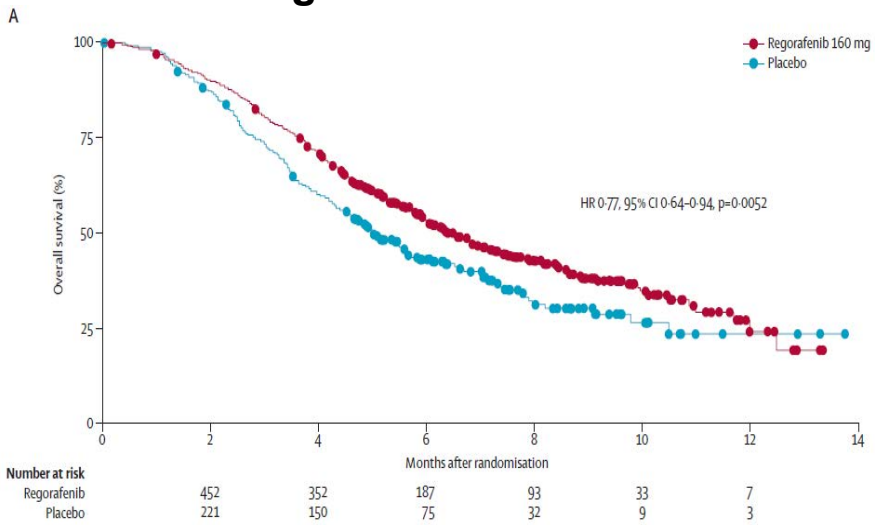


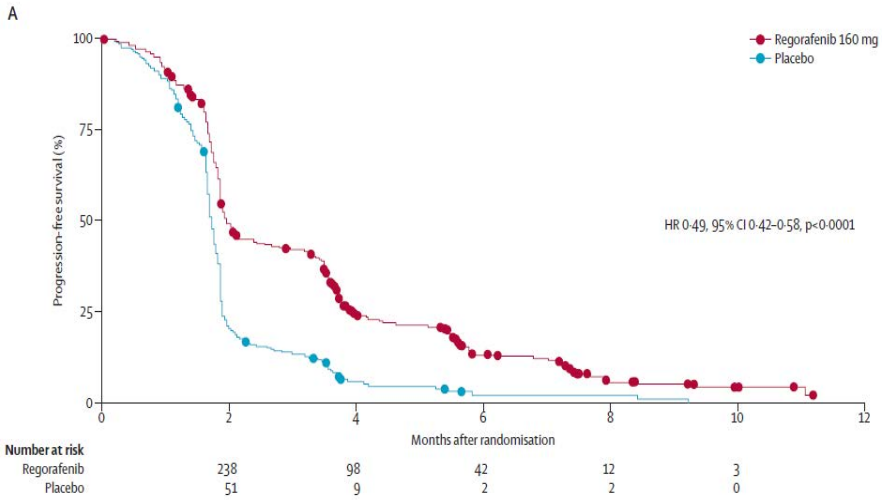
1. Mayer RJ, Van Cutsem E et al. N Engl J Med 2015;372:1909–19; 2. Xu J, et al. J Clin Oncol 2018;36:350–8; 3. Yoshino T, et al. Lancet Oncol 2012;13:993–1001;
4. Falcone A, …Van Cutsem E et al. WCGIC 2018 (Oral and Poster Presentation). Abstract O-013

Courtesy of Eric Van Cutsem, MD, PhD

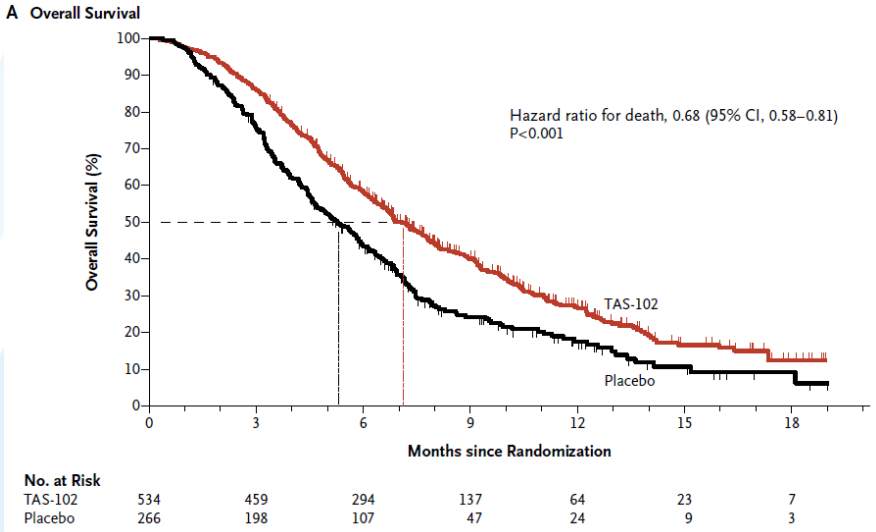
Regorafenib and trifluridine/tipiracil in refractory mCRC:

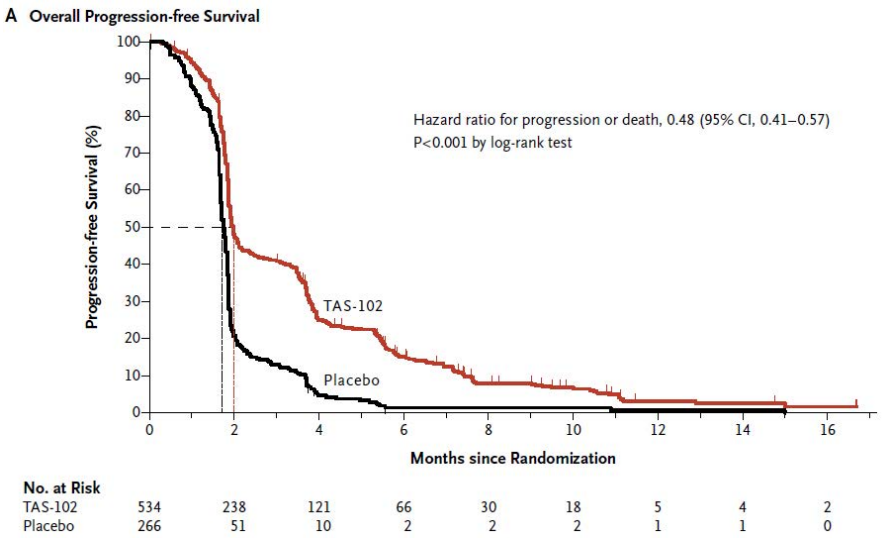
CORRECT: regorafenib





RECOURSE: trifluridine/tipiracil





Courtesy of Eric Van Cutsem, MD, PhD

Grothey, Van Cutsem E et al, Lancet 2013; Mayer R, Van Cutsem E, Ohtsu A et al NEJM, 2015

Optimal Sequence in chemorefractory patients?

Regorafenib ⟶ **Trifluridine/tipiracil**

or

Trifluridine/tipiracil ⟶ **Regorafenib**

Considerations:

- **Different safety pattern**
  - ✓ **Trifluridine/tipiracil: more favourable safety patterns, but what if compared to lower starting dose of regorafenib**
  - ✓ **No predictive markers for benefit, nor clearly differential patient characteristics**
- **More longer responders with regorafenib??**
- **Previous benefit to angiogenesis inhibitors: argument pro regorafenib??**

Courtesy of Eric Van Cutsem, MD, PhD

Ongoing combination trials of TAS-102 in mCRC

Indication	Treatments	Phase	Study status
mCRC, 1L	Trifluridine/tipiracil + bevacizumab vs capecitabine + bevacizumab (TASC01)	Randomized Phase II	Recruitment completed
mCRC, 1L	**Trifluridine/tipiracil + bevacizumab vs capecitabine + bevacizumab (SOLSTICE)**	**Randomized Phase III**	**Recruiting**
mCRC, 2L	Trifluridine/tipiracil + oxaliplatin + bevacizumab or nivolumab	Phase I	In progress
mCRC, 2L	Trifluridine/tipiracil + irinotecan	Phase I	Recruitment completed
mCRC, 3/4L	Trifluridine/tipiracil + nivolumab	Phase II	In progress
mCRC, 3L	**Trifluridine/tipiracil ± bevacizumab (SUNLIGHT)**	**Randomized Phase III**	**Recruiting**
mCRC 3L	PRECONNECT	Phase IIIb	Results available
mCRC, pretreated	Tas-102 + nintedanib Tas-102 + panitumumab	Phase I/II	In progress

Courtesy of Eric Van Cutsem, MD, PhD

Source: https://www.clinicaltrials.gov/

Danish randomized phase II trial: Trifluridine/tipiracil +/- bevacizumab for chemo-refractory mCRC

Patients with mCRC
- Histologically confirmed mCRC
- PD during or after therapy with fluoropyrimidine, irinotecan, oxaliplatin and EGFR-inhibitor (RAS wildtype), prior bevacizumab was optional
- ECOG PS 0–1
- Enrollment between Aug 2017 and Sept 2018

RANDOMIZATION

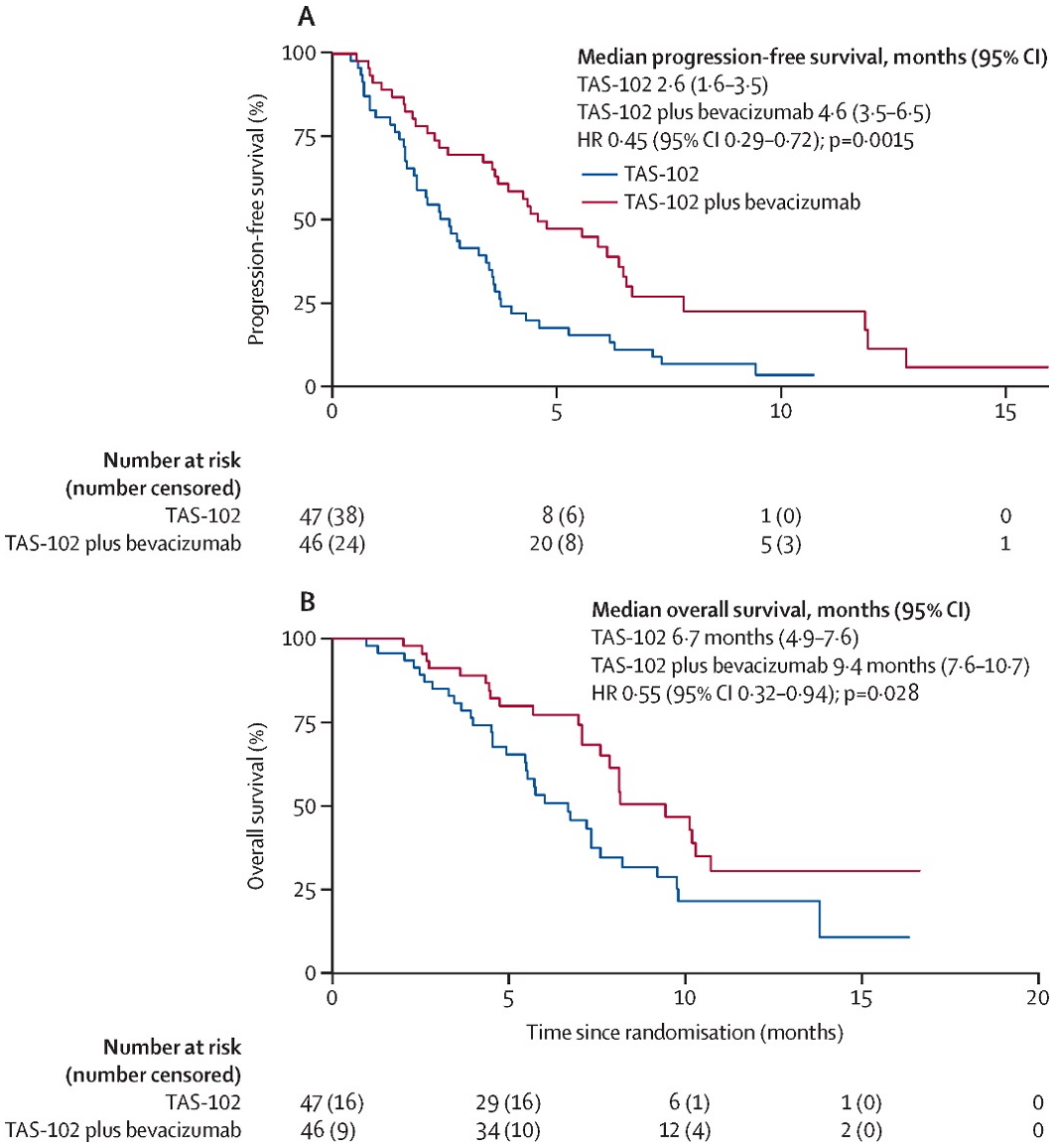
N=80

N=41

Arm A
FTD/TPI 35 mg/m^2 orally twice daily on days 1–5 and 8–12 of a 28-day treatment cycle

N=39

Arm B
Same dose of FTD/TPI (as Arm A), with bevacizumab 5 mg/kg on day 1 and day 15



Courtesy of Eric Van Cutsem, MD, PhD

Pfeiffer P et al, Lancet Oncol 2020

TASCO1 in first line mCRC:
non-comparative phase II study

- ✓ **First-line mCRC**
- ✓ **Non-eligible for intensive therapy according to investigator judgement**

TT-B
Trifluridine/Tipiracil
35 mg/m² b.i.d. p.o. d1-5, 8-12 q4wks
+
Bevacizumab
5mg/kg IV d1, d15 q4wks
(N=77)

1:1 randomization

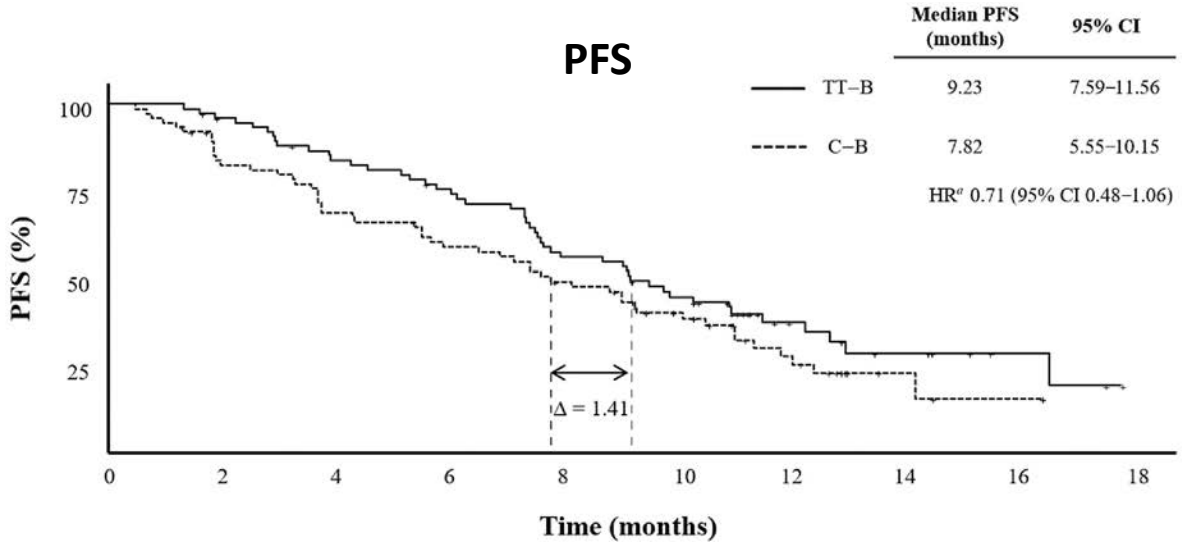
C-B
Capecitabine
1250 or 1000 mg/m² b.i.d. p.o. d1-14 q3wks
+
Bevacizumab
7.5mg/kg IV d1 q3wks
(N=76)

- Multicenter, randomized, open-label, phase II trial
- Stratification: RAS status, ECOG performance status, Country

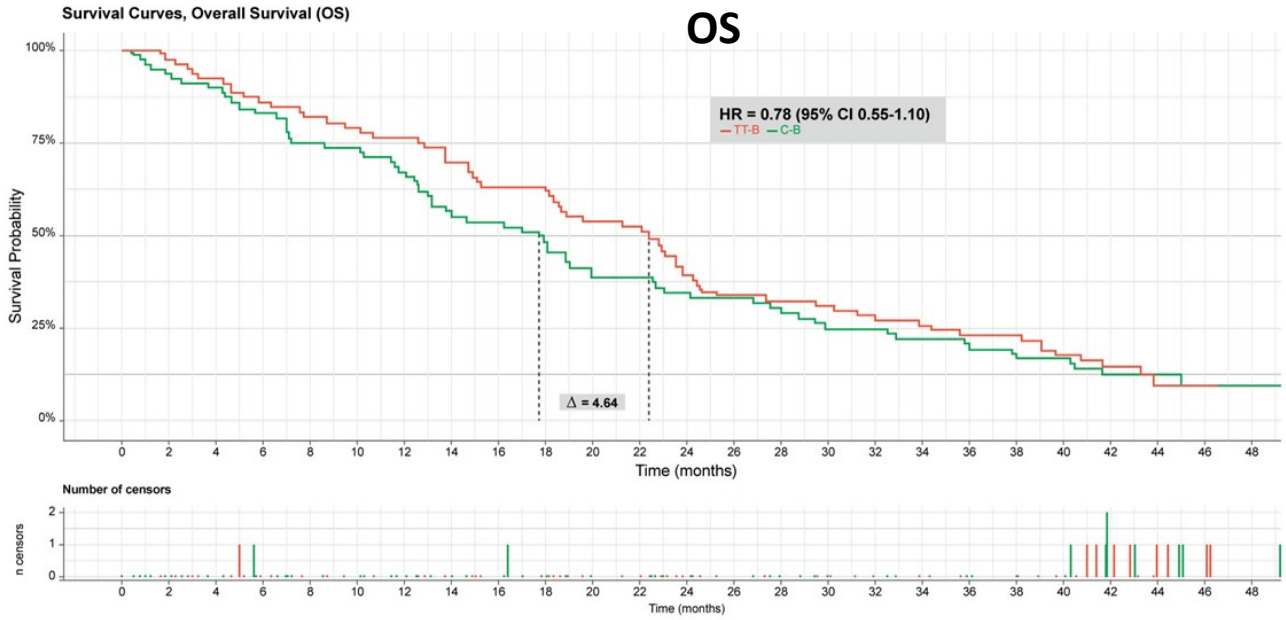
NCT02743221

Courtesy of Eric Van Cutsem, MD, PhD

PFS



OS



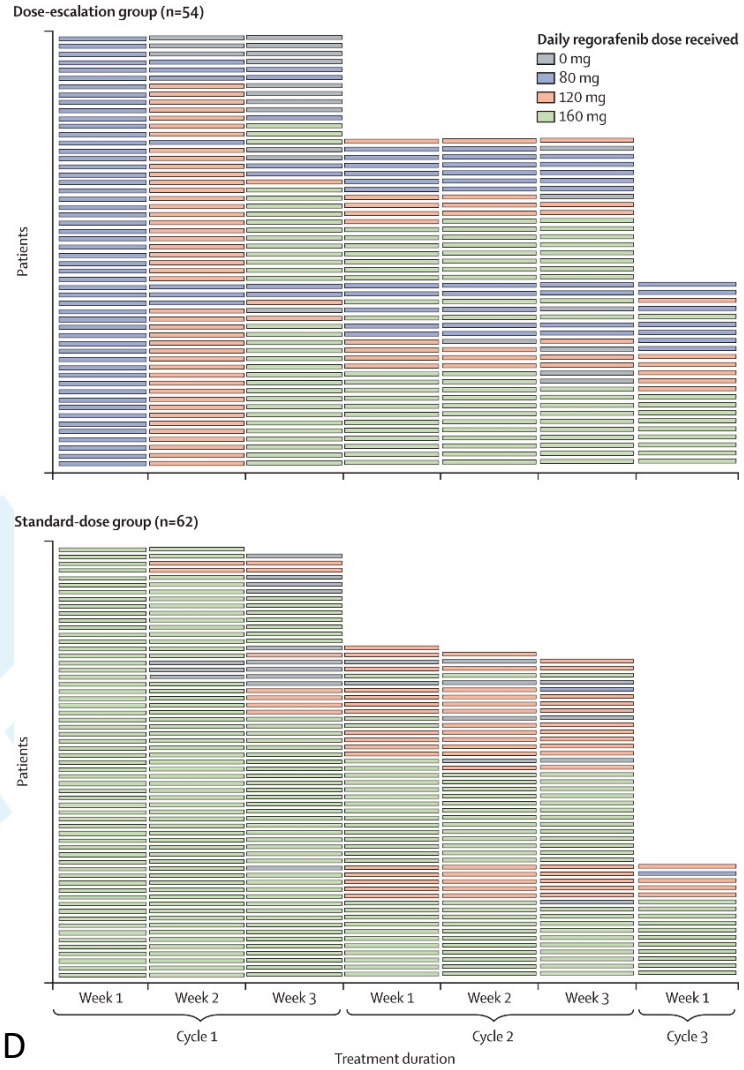
Van Cutsem E et al, Ann Oncol 2020. Van Cutsem E et al, ASCO GI 2021

Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study

Tanios S Bekaii-Saab, Fang-Shu Ou, Daniel H Ahn, Patrick M Boland, Kristen K Ciombor, Erica N Heying, Travis J Dockter, Nisha L Jacobs, Boris C Pasche, James M Cleary, Jeffrey P Meyers, Rodwige J Desnoyers, Jeannine S McCune, Katrina Pedersen, Afsaneh Barzi, E Gabriela Chiorean, Jeffrey Sloan, Mario E Lacouture, Heinz-Josef Lenz, Axel Grothey

Dose escalation arm

Standard dose group



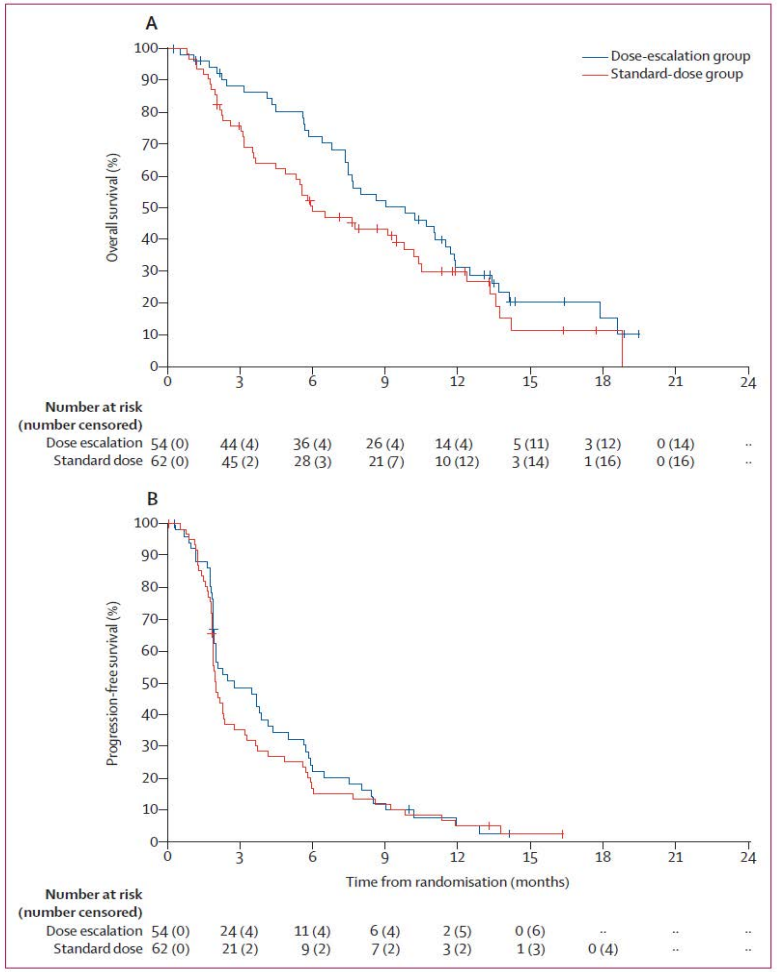
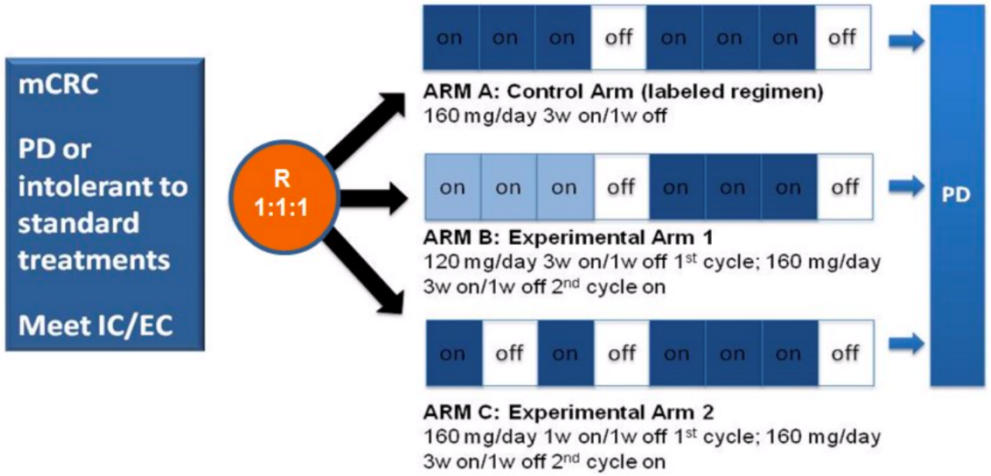


Figure 2: **Overall survival (A) and progression-free survival (B) in the dose-escalation and standard-dose groups**
Censored patients are marked on the curves with a cross.

Courtesy of Eric Van Cutsem, MD, PhD

The Lancet Oncology 2019: DOI: (10.1016/S1470-2045(19)30272-4)

REARRANGE Study: regorafenib optimal dose seeking



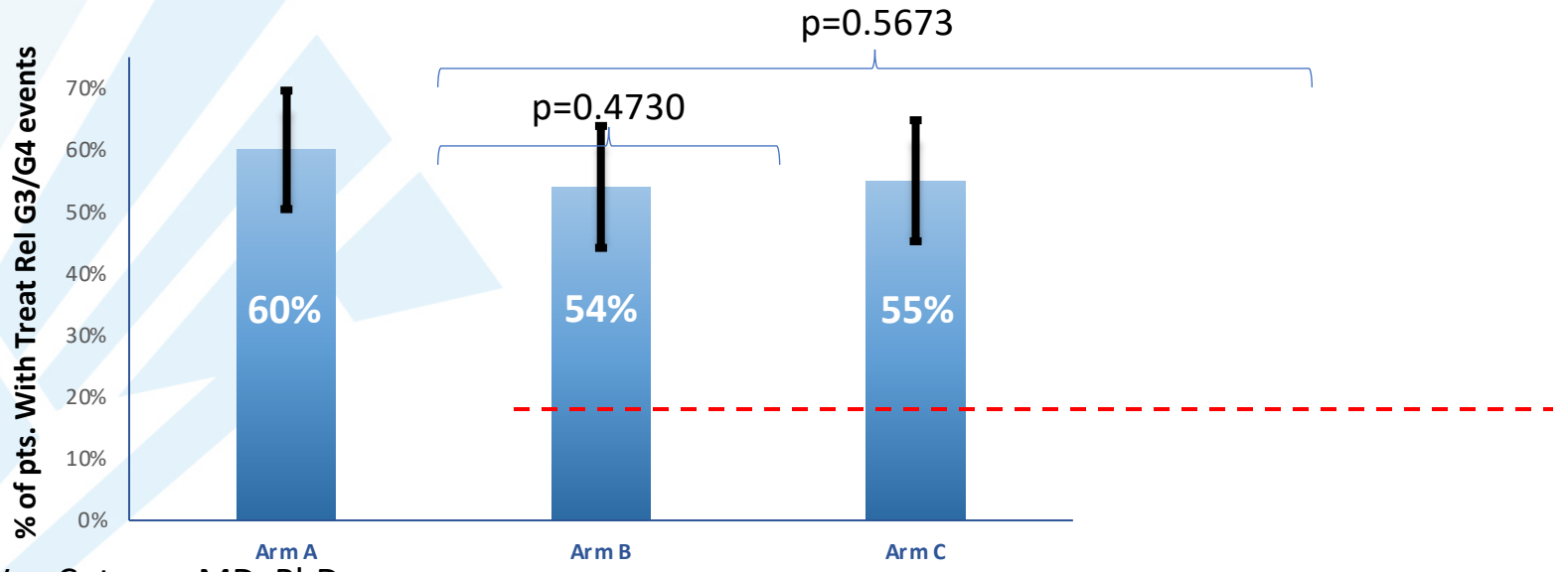
Primary endpoint:

- **Safety** :% of patients having G3/G4 AEs during the entire course of the treatment

Secondary endpoints:

- OS
- PFS
- % of Patients starting C3 on each arm
- Dose intensity
- DCR

Primary Endpoint: Pts having G3/G4 AEs during treatment course



Threshold to reach positivity in the 2 experimental arms

Courtesy of Eric Van Cutsem, MD, PhD

Argiles G et al, ESMO GI/WCGIC 2019

Future: combination studies

❖ **Appealing combinations:**

- ✓ Interesting phase 2 study: trifluridine/tipiracil + bevacizumab
- ✓ Exploring other combinations e.g.
  - ❑ Cobimetinib + atezolizumab
  - ❑ Regorafenib + nivolumab
  - ❑ IO combinations + TKI

❖ **New drugs:**

- ✓ Napabucasin
- ✓ CAR-T-cells
- ✓ ……

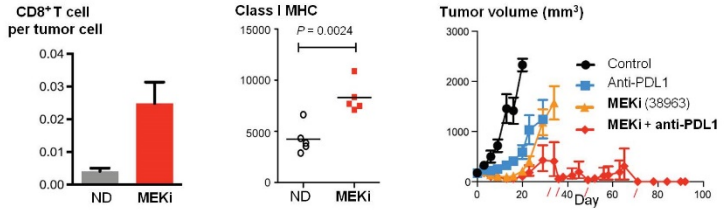
Courtesy of Eric Van Cutsem, MD, PhD

Pfeiffer P et al, Lancet Oncol 2021; Van Cutsem E et al, Ann Oncol 2020; Hara H et al, ESMO GI/WCGIC 2019; Van Cutsem E et al, ESMO GI/WCGIC 2019, Eng C et al, Lancet Oncol 2019

PD-L1 and MEK inhibition in MSS tumors

PD-L1 and MEK Inhibition: A Rational Combination

- MEK inhibition alone can result in **intratumoral T-cell accumulation** and **MHC I upregulation**, and synergizes with an anti-PDL1 agent to promote **durable tumor regression**[1]



- To examine the possible benefits of MEK inhibition with an anti-PDL1 agent, we evaluated cobimetinib + atezolizumab in patients with advanced solid tumors

MHC, major histocompatibility complex; ND, no drug (vehicle alone).
CT26 (KRASmt) CRC models. 1. Ebert et al. *Immunity* 2016.

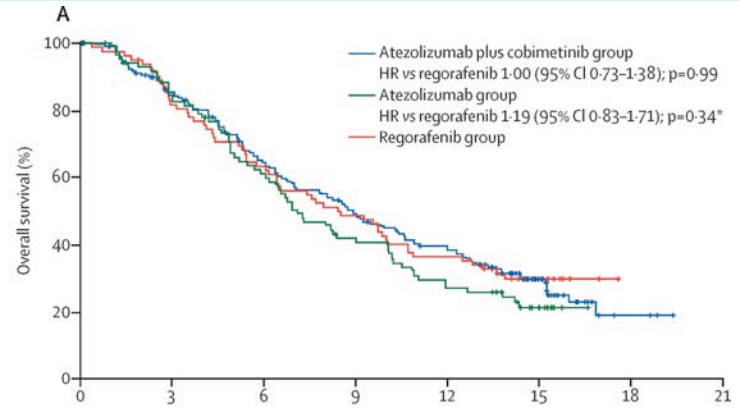
IMblaze study

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

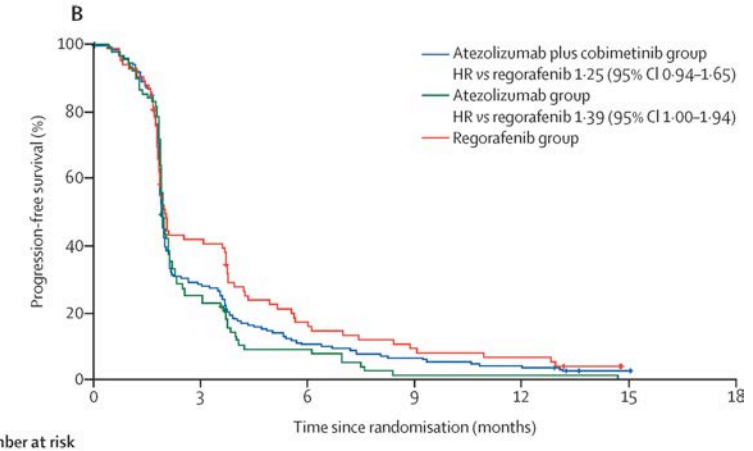
R 2:1:1 N=363

- **Atezolizumab 840 mg IV q2w + cobimetinib 60 mg oral 21/7 days**
- **Atezolizumab 1200 mg IV q3w**
- **Regorafenib 160 mg oral 21/7 days**

Courtesy of Eric Van Cutsem, MD, PhD



Number at risk (numbers censored)							
Atezolizumab plus cobimetinib	183 (7)	150 (4)	110 (1)	83 (2)	63 (22)	28 (19)	3 (3)
Atezolizumab	90 (4)	73 (2)	51 (1)	34 (0)	22 (9)	9 (9)	..
Regorafenib	90 (8)	67 (0)	52 (0)	40 (0)	30 (16)	9 (9)	..



Number at risk (numbers censored)						
Atezolizumab plus cobimetinib	183 (8)	49 (0)	18 (0)	11 (0)	6 (4)	1 (1)
Atezolizumab	90 (2)	22 (2)	7 (0)	1 (0)	1 (0)	..
Regorafenib	90 (10)	33 (1)	13 (0)	7 (0)	5 (3)	..

Eng C et al, Lancet Oncol 2019

Ongoing I/O combination trials in MSS CRC investigate strategies to turn “cold” tumors” into “hot”

	Anti-PD-L1			Anti-PD-1	
	4 trials Atezolizumab	6 trials Durvalumab	4 trials Avelumab	15 trials Nivolumab	15 trials Pembrolizumab
Ph1	+ Cobimetinib + bevacizumab[1]	+ Cabozantinib[5] + Selumetinib ± tremelimumab[6]		+ Regorafenib[14]	+ Maraviroc[27] + Romidepsin ± chemotherapy[28] + Grapiprant[29] + Binimetinib[30] + Pemetrexed + oxaliplatin[40]
Ph1/2	+ Imprime PGG + bevacizumab or isatuximab or selicrelumab + bevacizumab vs regorafenib[2]		+ Regorafenib[10]	+ Regorafenib[15] + Copanlisib[16] + ONC201[17] + Binimetinib ± ipilimumab[18] + GO-004 GRT-C901/GRT-R902 ± ipilimumab[23] + Guadecitabine[26]	+ Epacadostat + azacitidine/INCB057643/ INCB059872[31] + Poly–ICLC[32] + Napabucasin[33] + Regorafenib[34] + EDP1503[35] + Birinapant[41] + Entinostat[39]
Ph2	+ Bevacizumab + chemotherapy[3] + Bevacizumab + chemotherapy[4]	+ Trametinib[7] + Azacitidine[8] + Monalizumab[9]	+ Cetuximab + chemotherapy[11] + eFT508[12] + Cetuximab + FOLFOX[13]	+ Relatlimab[19] + Panitumumab + ipilimumab[20] + Ipilimumab[21] + BNC105 or BBI608[22] + BNC105 or napabucasin[24] + Ipilimumab + temozolomide[25]	+ Navarixin[36] + Vicriviroc[37] + Bevacizumab + capecitabine[38]

1. NCT02876224; 2. NCT03555149; 3. NCT03721653; 4. NCT03698461; 5. NCT03539822; 6. NCT02586987; 7. NCT03428126; 8. NCT02811497; 9. NCT02671435; 10. NCT03475953; 11. NCT03608046; 12. NCT03258398; 13. NCT03174405; 14. NCT03712943; 15. NCT03406871; 16. NCT03711058; 17. NCT03791398; 18. NCT03271047; 19. NCT03642067; 20. NCT03442569; 21. NCT03693846; 22. NCT03647839; 23. NCT03639714; 24. NCT03647839; 25. NCT03832621; 26. NCT03576963; 27. NCT03274804; 28. NCT02512172; 29. NCT03658772; 30. NCT03374254; 31. NCT02959437; 32. NCT02834052; 33. NCT02851004; 34. NCT03657641; 35. NCT03775850; 36. NCT03473925; 37. NCT03631407; 38. NCT03396926; 39. NCT02437136; 40. NCT03626922; 41. NCT02587962. ClinicalTrials.gov searched in June 2019. Studies may include combinations with additional agents.

Courtesy of Eric Van Cutsem, MD, PhD

REGONIVO (SO-007: #96 ESMO GI2020)

Dose escalation cohort:"3+3" design

Regorafenib
Level 1: **80** mg/day
21 on 7 days off
+Nivolumab 3 mg/kg
q2w

N = 3～6

Regorafenib
Level 2: **120** mg/day
21 on 7 days off
+Nivolumab 3 mg/kg
q2w

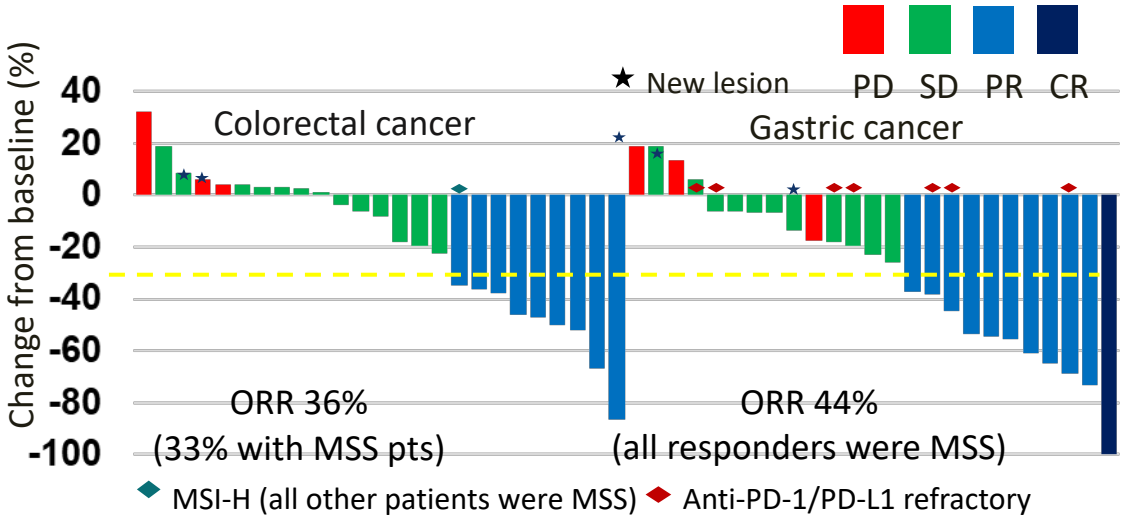
N = 3～6

Regorafenib
Level 3: **160** mg/day
21 on 7 days off
+Nivolumab 3 mg/kg
q2w

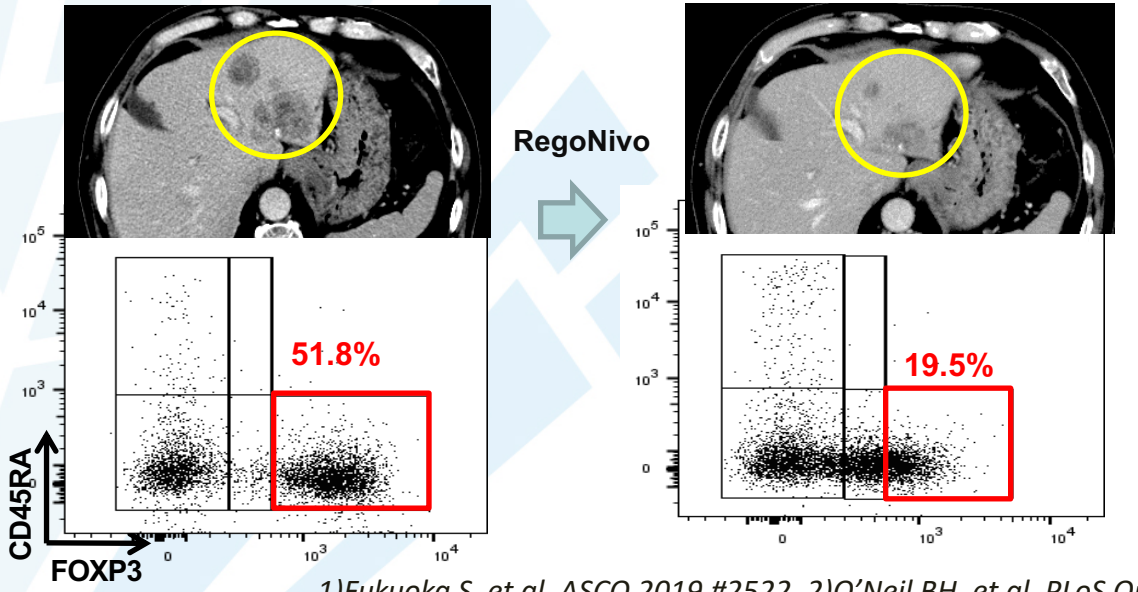
N = 3～6

Expansion cohort

Total N = 36 (Colorectal cancer, Gastric cancer)



Proof-of-Concept; Depletion of Tregs



Summary (CIT in MSS)

	REGONIVO[1]	KEYNOTE-028[2]	CheckMate 142[3]		IMblaze370[4]		CCTG CO.26[5]
Regimen	Nivo/REG	Pembro	Nivo1/Ipi3	Nivo3/Ipi1	Atezo/Cobi	Atezo	Durva/Treme
N	25	23	10	10	183	90	119
MSS	96%	96%	100%	100%	93%	92%	98%
ORR	36% (MSS 33%)	4%	10%	0%	2.7%	2.2%	-
DCR	88%	20%	-	-	26.2%	21.1%	-
PFS	6.3m	1.8m	2.3m	1.31m	1.9m	1.9m	1.8m
OS	NR	5.3m	11.5m	3.73m	8.9m	7.1m	6.6m

1)Fukuoka S, et al. ASCO 2019 #2522. 2)O'Neil BH, et al. PLoS One 2017. 3)Overman MJ, et al. ASCO 2016. 4)Bendell J, et al. WCGC 2018. 5) Chen E, et al. ASCO-GI 2019. Hoff S, et al. ESMO 2017 #1198P. Hara H, et al. WCGC 2019 SO-007: #96.

Courtesy of Eric Van Cutsem, MD, PhD

Phase I/IB study of Regorafenib and Nivolumab in Mismatch Repair (MMR) Proficient Advanced Refractory Colorectal Cancer

As of 3/2/2020, 28 patients were treated

Patients

- Histologically confirmed refractory CRC
- MMR proficient.
- Failed/ intolerant to standard chemotherapy.

Phase I

N= 12

Nivolumab

240mg IV q2wk and regorafenib according to dose escalation of 80mg, 120 mg or 160mg 21 days on 7 days off

Expanded Cohort

N=16(goal=40)

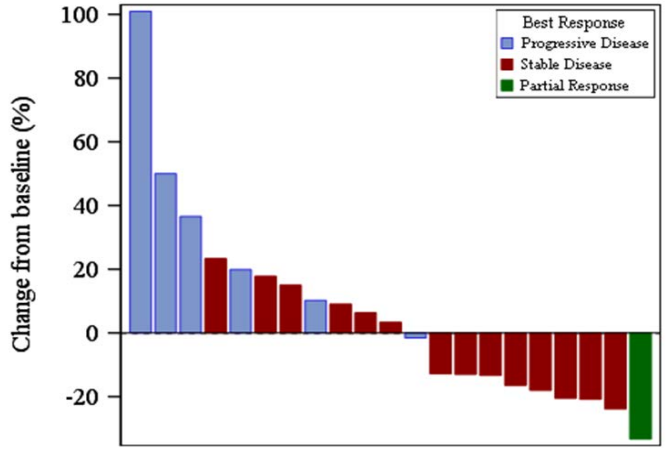
Nivolumab

240mg IV

Q2wk for 16 wks then 480 mg q4wk and dose of regorafenib based on MTD

Best Overall Response	N = 21
CR	0
PR (unconfirmed)	1 (4.8%)
SD	14 (66.7%)
DCR	15 (71.4%)
PD	6 (28.6%)

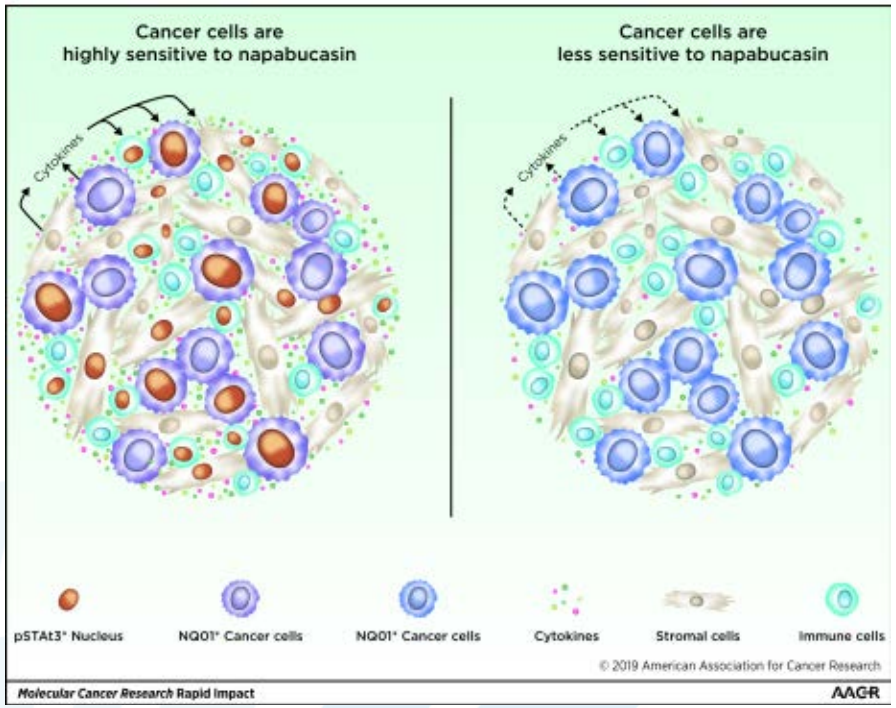
7 patients were not evaluable for RR (3 DLTs, 3 consent withdrawal and 1 clinical progression)



Courtesy of Eric Van Cutsem, MD, PhD

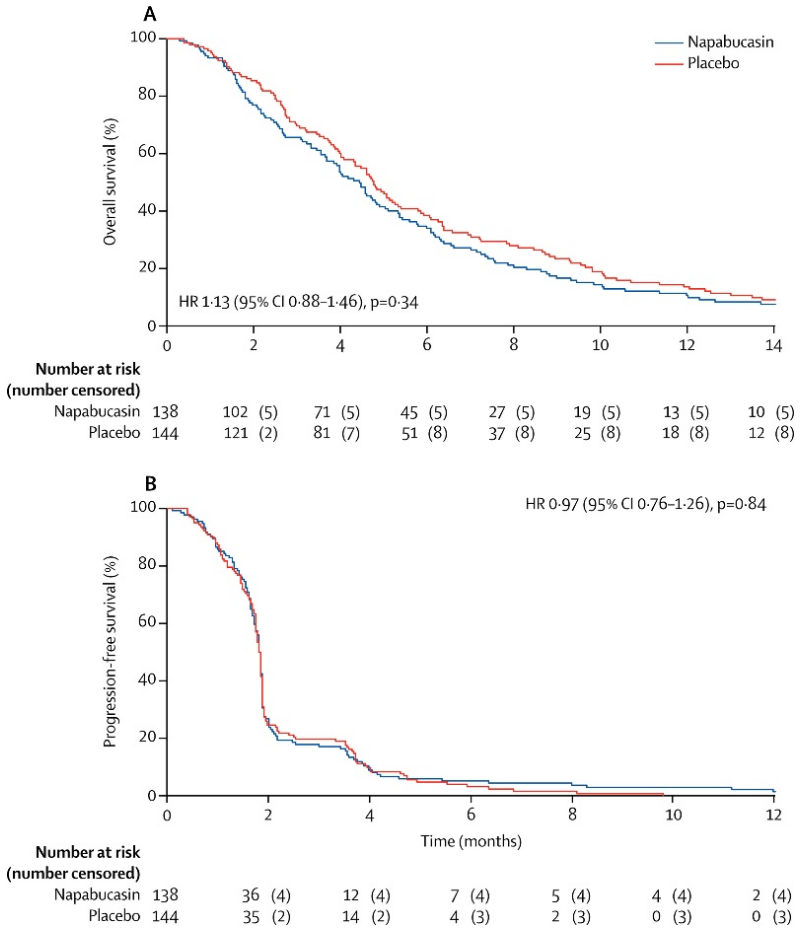
Kim R et al, Ann Oncol 2020, ESMO GI/WCGIC abstr 0-20

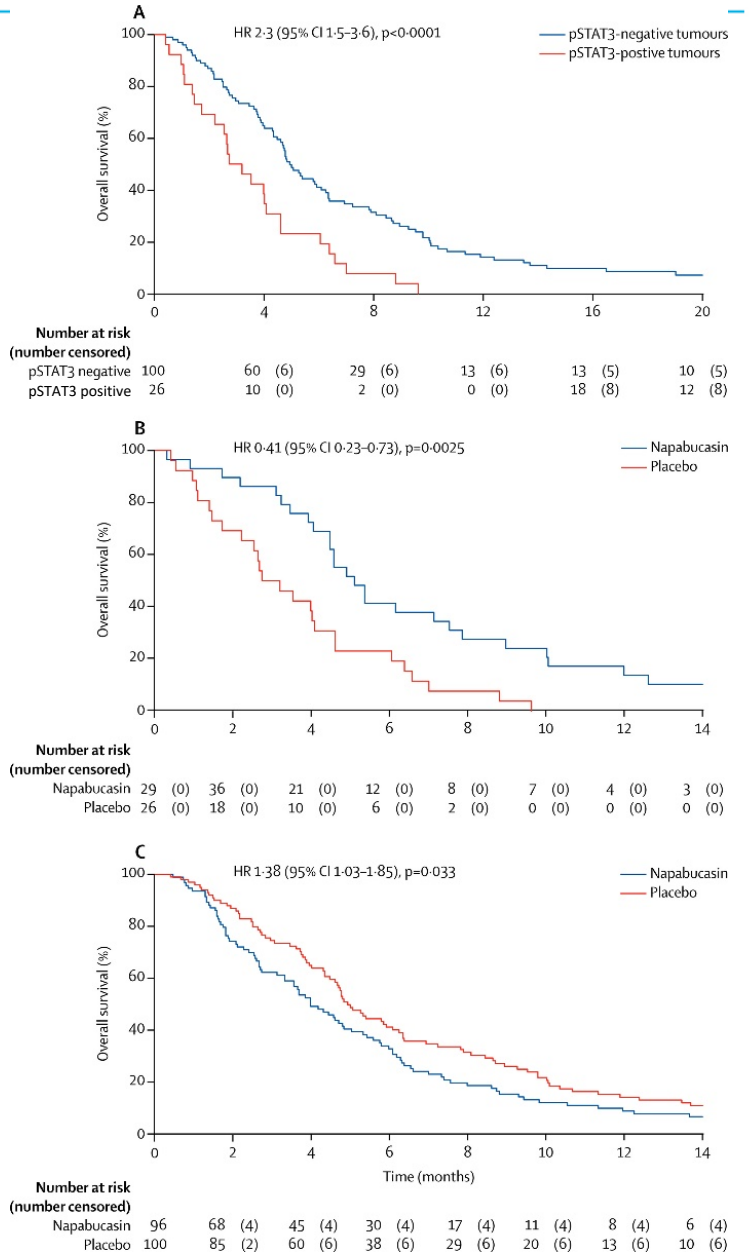
Napabucasin versus placebo in refractory advanced colorectal cancer: a randomised phase 3 trial



Napabucasin:

- ✓ **a cancer stemness inhibitor**
- ✓ **STAT3 inhibitor**





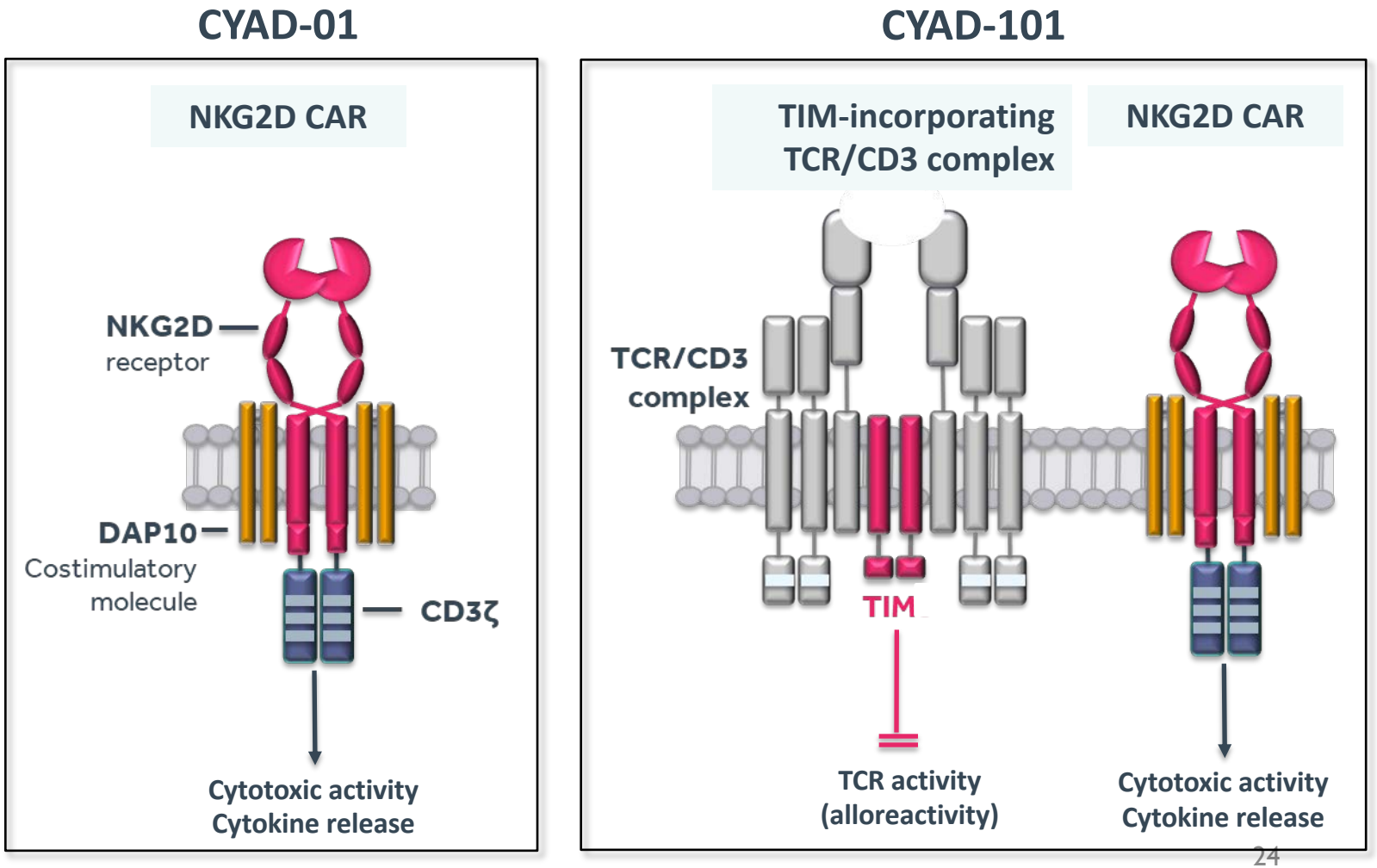
Chang Y et al, Molecular Cancer Research 2019

Jonker D et al, Lancet Gastroenterology Hepatology 2018

Courtesy of Eric Van Cutsem, MD, PhD

Two NKG2D CAR T-cells: autologous CYAD-01 and allogeneic CYAD-101

- **NKG2D** is an activating receptor expressed on natural killer (NK) cells which binds up to eight ligands expressed on a broad range of malignancies and absent in normal tissues
- **CYAD-01** are **<u>autologous</u>** (patient's own cells) NKG2D-CD3ζ chimeric antigen receptor (CAR) T-cells
- **CYAD-101** are **<u>allogeneic</u>** (healthy donor-derived) NKG2D-CD3ζ CAR T-cells co-expressing a TCR inhibitory molecule (TIM) to reduce the alloreactivity



Courtesy of Eric Van Cutsem, MD, PhD

Van Cutsem E et al, Ann Oncol 2019, ESMO GI/WCGIC S-009

SHRINK and ALLOSHRINK
Phase I clinical studies in mCRC

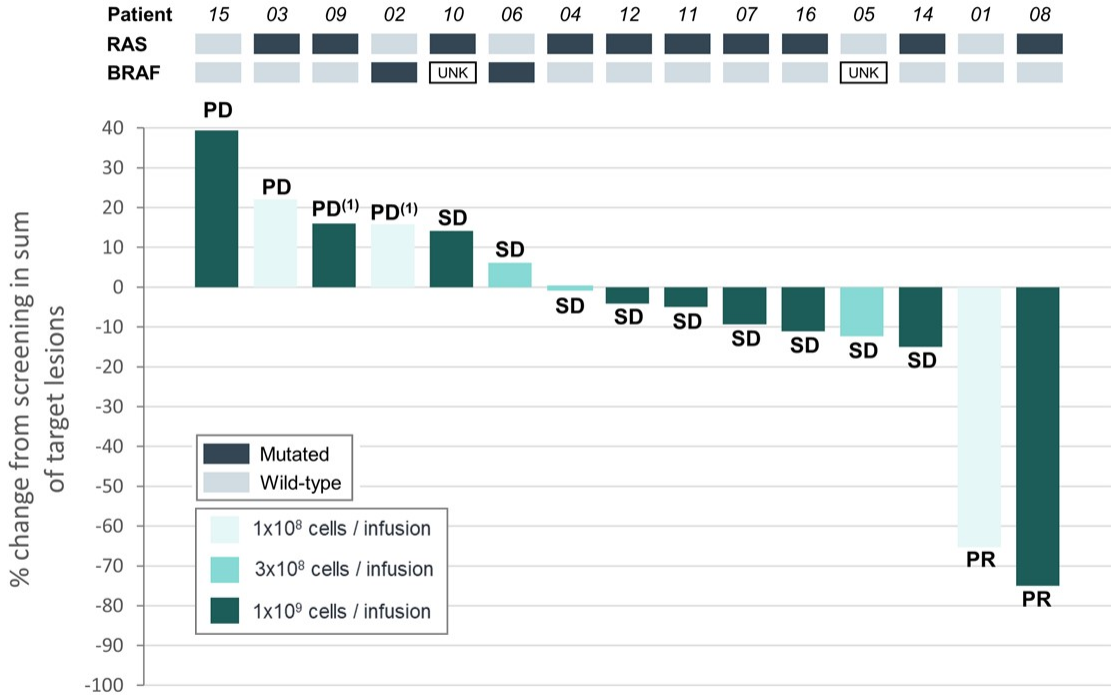
	SHRINK study (NCT03310008)	ALLOSHRINK study (NCT03692429)
Investigational product	Autologous (patient's derived cells) CYAD-01	Allogeneic (healthy donor's derived cells) CYAD-101
Patient population	1. Unresectable mCRC and ○ Recurrent/progressing after at least 1 metastatic line, ○ Due to receive FOLFOX chemotherapy (re-challenge). 2. mCRC with resectable liver metastases and ○ Due to receive 1st line metastatic neoadjuvant FOLFOX treatment, ○ No evidence of extra-hepatic metastases, ○ Primary tumor resected or resectable.	1. Unresectable mCRC and ○ Recurrent/progressing after at least 1 metastatic line, ○ Due to receive FOLFOX chemotherapy (re-challenge).
Study design	• Apheresis at D-21 to produce CAR T-cells • Concurrent administration of six FOLFOX cycles • 3 CYAD-01 infusions Q2W at Day 3 of the 2nd, 3rd and 4th FOLFOX chemotherapy cycles • Potential consolidation cycle of 3 CYAD-01 infusions with or without concurrent FOLFOX if no progression after 1st cycle of treatment	• [no apheresis !] • Concurrent administration of six FOLFOX cycles • 3 CYAD-101 infusions Q2W at Day 3 of the 1st, 2nd and 3rd FOLFOX chemotherapy cycles
Doses	• 3 dose-levels (dose escalation, 3+3 design) ○ $1x10^8$, $3x10^8$ and $1x10^9$ **CYAD-01** per injection	• 3 dose-levels (dose escalation, 3+3 design) ○ $1x10^8$, $3x10^8$ and $1x10^9$ **CYAD-101** per injection

Courtesy of Eric Van Cutsem, MD, PhD

Van Cutsem E et al, Ann Oncol 2019, ESMO GI/WCGIC S-009

Updated data from the alloSHRINK Phase 1 First-in-Human Study evaluating CYAD-101, an innovative Non-Gene-Edited Allogeneic CAR-T, in mCRC

Results – change of target lesions



PR: Partial response; SD: Stable disease; PD: Progressive disease; UNK: Unknown. (1) Progression of non-target lesions.

- At the highest CYAD-101 dose level (n = 9), **6 patients** have shown some evidence of **tumor control** by RECIST 1.1 criteria
- The **median progression free-survival** is **3.94 months** (range: 1.2-8.1 months)
- The **overall survival** is **10.58 months** (range: 1.9-18.7 months)

PRESENTED AT: Gastrointestinal Cancers Symposium

PRESENTED BY: Hans Prenen, University Hospital Antwerp

#GI21

Courtesy of Eric Van Cutsem, MD, PhD

CASE SCENARIO 1:

Male patient, born in 1966

- 12-2017: sigmoid adenocarcinoma with livermetastases, multipele, not-resectable
- ECOG 0; normal organ function.
- Start FOLFOX + bevacizumab . Objective response
  CEA: decrease from 600 to 8.7
- 08-2018: chemo break – no maintenance chemo
- 12-2018: progression.

- Inclusion in phase 3 trial: FOLFIRI +/- napabucin
- Initial response, but after 9 months slight progression
- 09-2019: reintroduction: FOLFOX-bevacizumab.
- 03-2020: increase of CEA and progression of liver metastases and a few small lung metastases.

Courtesy of Eric Van Cutsem, MD, PhD

CASE SCENARIO 1:

Male patient, born in 1966

- **Second opinion in Leuven:**

- ECOG 1; normal organ function
  Tumor: N-RAS mutation, MSS, BRAF wild type, HER-2 neg, NTRK negative

- 06-2020: Start trifluridine/tipiracil (TAS-102) + bevacizumab in Leuven.
- Till 12-2020: Tumor stabilisation ; very good clinical condition

Courtesy of Eric Van Cutsem, MD, PhD

CASE SCENARIO 2:

Male patient, born in 1966
Banker; fighter and very motivated

- 06-2014: rectum adenocarcinoma. Pre-opstaging MRI: cT3N0M0
  Neo-adjuvant chemoradiotherapy (50Gy, continuous infusion 5FU). pTN3N0MO
  postoperative adjuvant chemotherapy 5FU/LV 4 months till early 2015.

- 03-2016: elevated CEA & liver metastases – bilobar with localisation close to central vessels – not resectable.
  Inclusion in Module study – induction with 8 cycli Folfox/bevacizumab
  Objective response after 4 and confirmed (deeper response) afeter 8 courses.

- 30/06/2016: laparoscopic microwaveablation of 4 levermetastases (S7, S5/8, S8, S6)
  Postoperative mFOLFOX-bevacizumab.
- 9/2016: No evidence of disease – stop chemo

- 04/2017: increased CEA: 3 small lung metastases & 2 new liver metastases: reintroduction of mfolfox + bevacizumab

Courtesy of Eric Van Cutsem, MD, PhD

CASE SCENARIO 2:

Male patient, born in 1966

- 06/2017: after 4 cycli: response of liver metastases (segment 4b and 7) and decrease of 3 lung metastases in right lung lower lobe, right mid lobe, and left lower lobe
  - ✓ Laparoscopic right hemihepatectomy (intentention 2 stage lung resection)
  - ✓ 08/2017: ct thorax - abdomen: no livermetastases, growth of 3 lungmetastases
  - ✓ 09/2017: Bilateral thoracoscopic wedge resection (right lung lower lobe, right mid lobe, and left lower lobe) of 3 lung metastases (histology adenocarcinoma , R0 resection)

- Postoperative mFOLFOX-bevacizumab till 01/2018: NED.

Courtesy of Eric Van Cutsem, MD, PhD

CASE SCENARIO 2:

Male patient, born in 1966

- 05/2018: Relapse with 2 small lung metastases and 2 liver metastases (oligometastastatic)
  ECOG PS: 0; Normal organ function
  Tumor: MSS - KRAS mutation; BRAF wt;
  no other druggable alterations

- Inclusion in Canstem303c study (Folfiri +bevacizumab + BBI-608 (napabucasin)
  Partial response of lung metastases and disappearance of liver metastases
- 11/2018: Thorascopic resection of 2 lung metastases: right lung (wedge)
  NED

Courtesy of Eric Van Cutsem, MD, PhD

CASE SCENARIO 2:

Male patient, born in 1966

- 04/2019: progression - inclusion in alloSHRINK study (Folfox 6 cycles till July 2019 + CAR-T cells CYAD-101 3 administrations)
- 06/2019: partial response
- 12/2019: persisting response

- 3/2020: progression: reintroduction of FOLFOX/bevacizumab : regression
  9/2020: chemo break

- 12/2020: WHO: 0 and normal organ function, but progression of lung and liver metastases:
  reintroduction of FOLFOX/bevacizumab
  February 2021: treatment ongoing
  ECOG PS: 0
  toxicity: fatigue Gr 1 and PNP grade 1

Courtesy of Eric Van Cutsem, MD, PhD