ESMO Congress 2021

What is the optimal continuum of care in 2021 in metastatic colorectal cancer?

What are best treatment choices for the remaining majority of patients?

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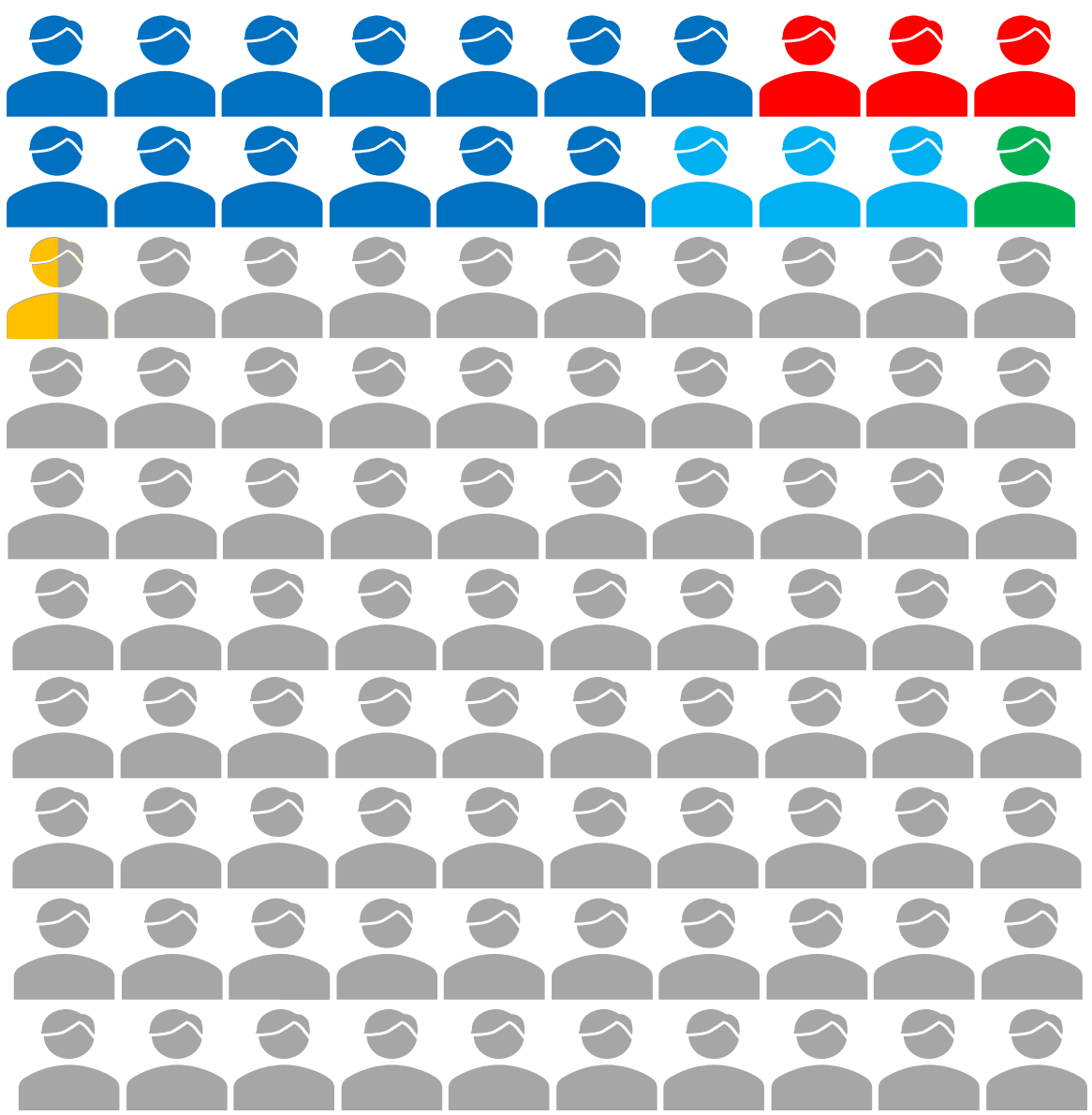
Declaration of interests

- **Honoraria (advisory board member and/or invited speaker):**
  - **Amgen, Bayer, Merck, MSD, Roche, Tesuno, Servier**

- **Research grants:**
  - **Bayer, Merck, Roche, Servier**

CGP analysis of samples from patients enrolled in the TRIBE2 study



13% *BRAF* V600E

3% *KRAS* G12C

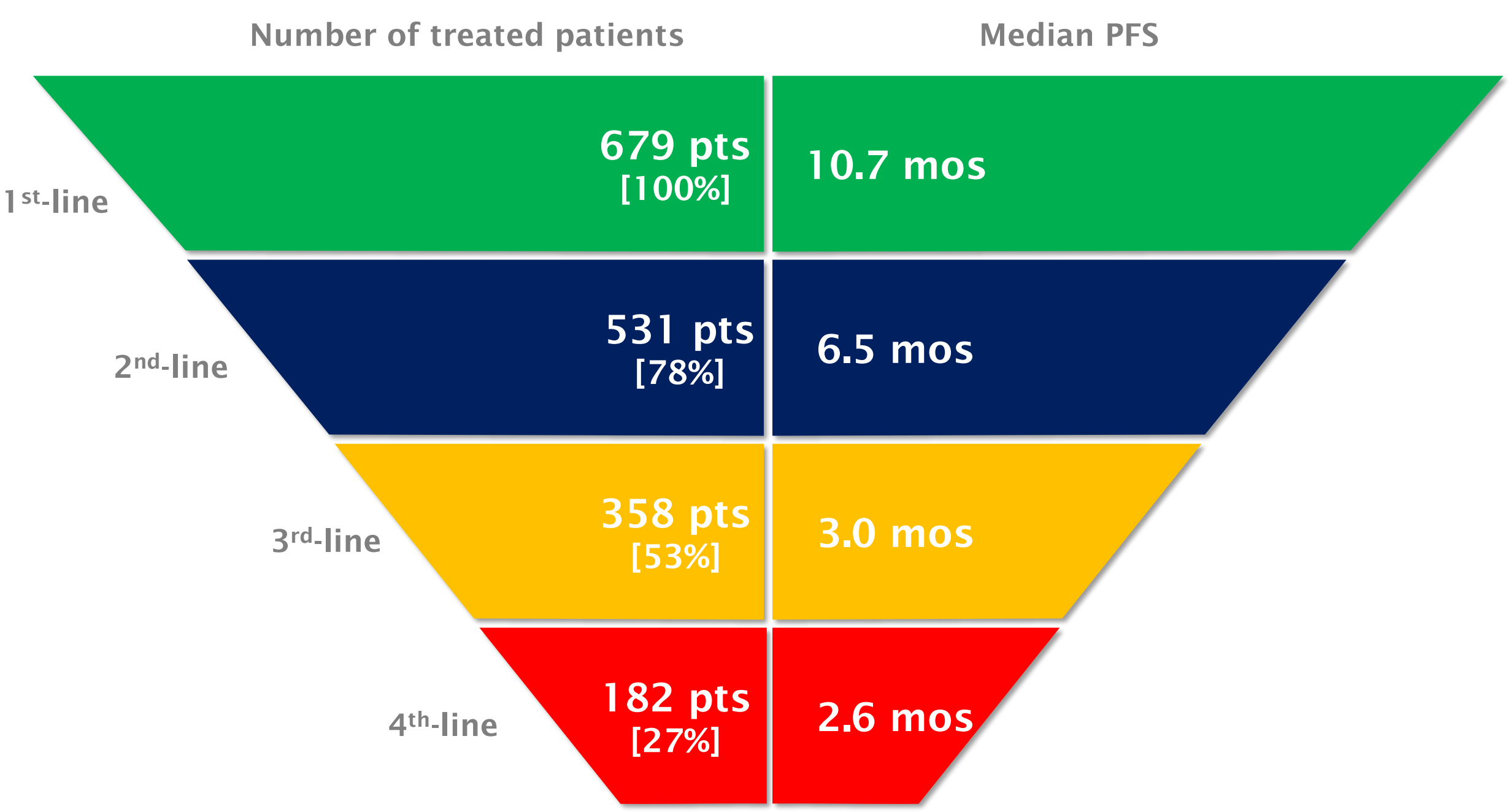
3% MSI-high/dMMR

1% *HER2* amplif

<1% *POLE* mut

79% No actionable alterations

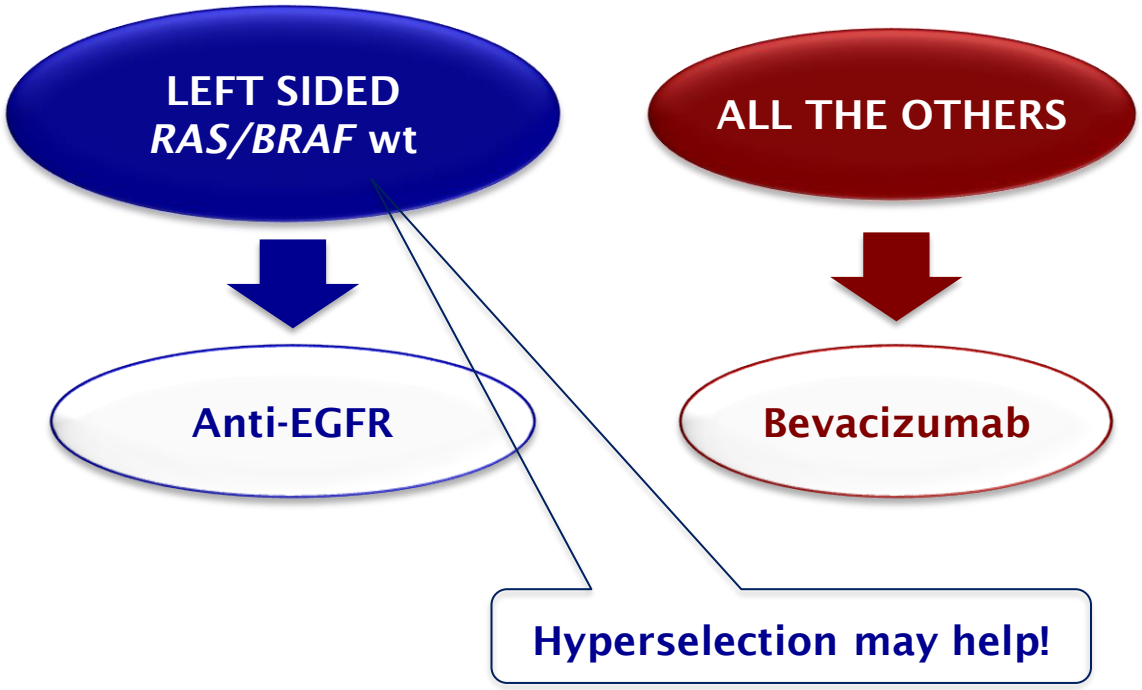
adapted from Antoniotti et al, Eur J Cancer 2021



TRIBE2 study – unpublished data

Choosing the upfront therapy in MSS mCRC

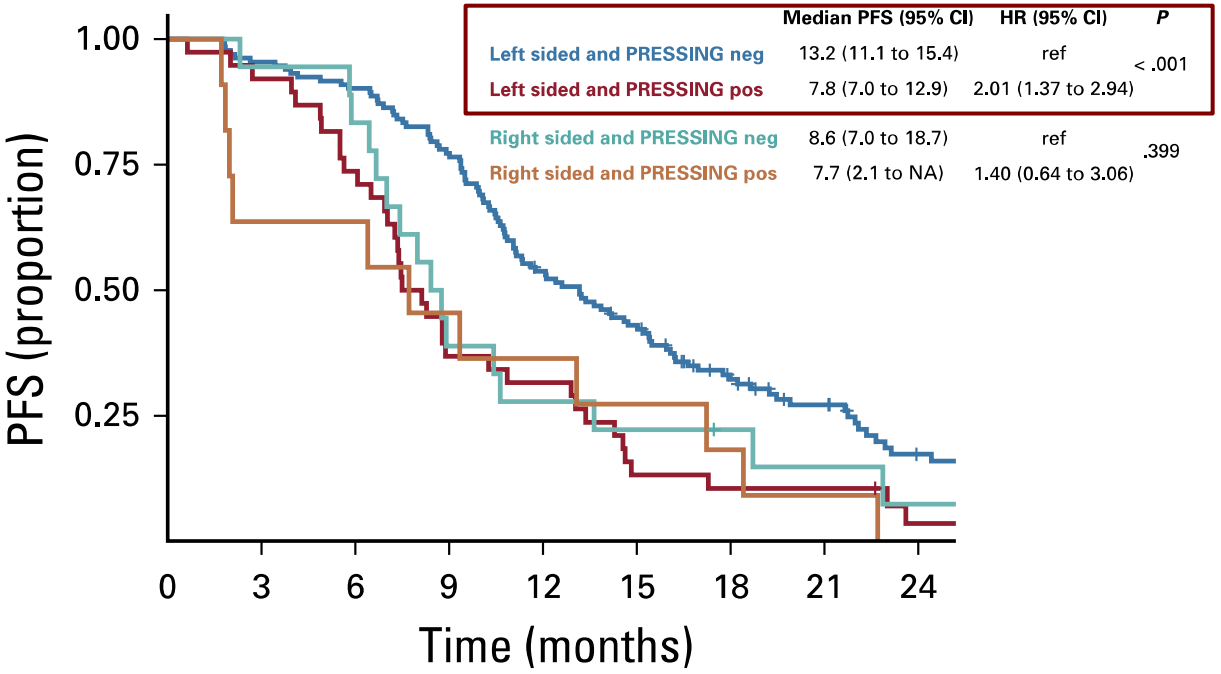
The «best» targeted agent

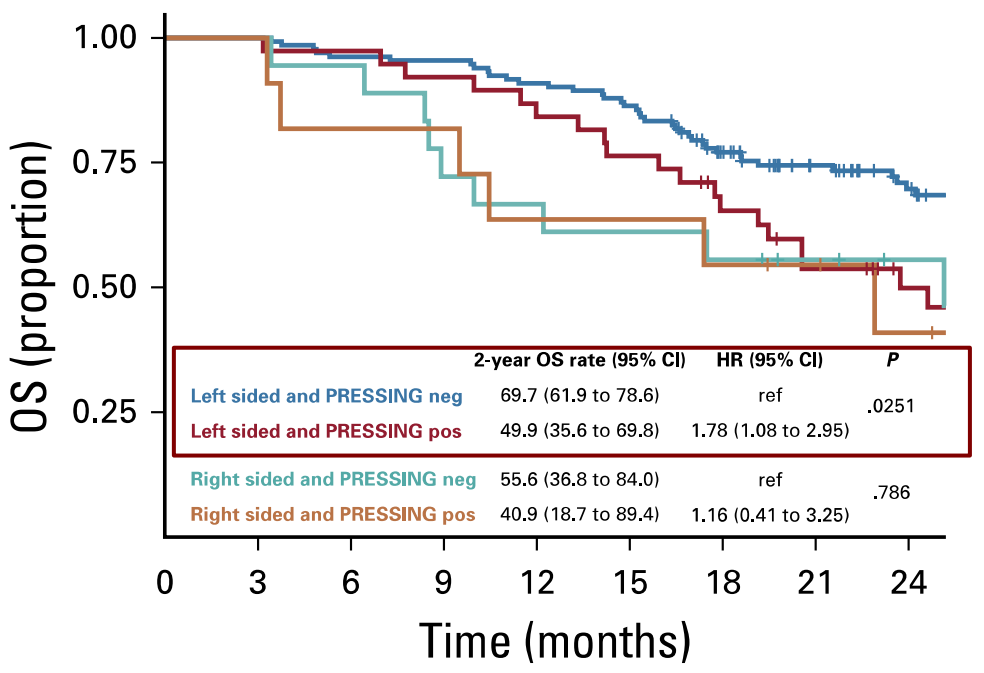


The «best» chemotherapy (intensity)

Prognostic impact of tissue PRESSING panel according to primary side

Post-hoc analysis of the VALENTINO study



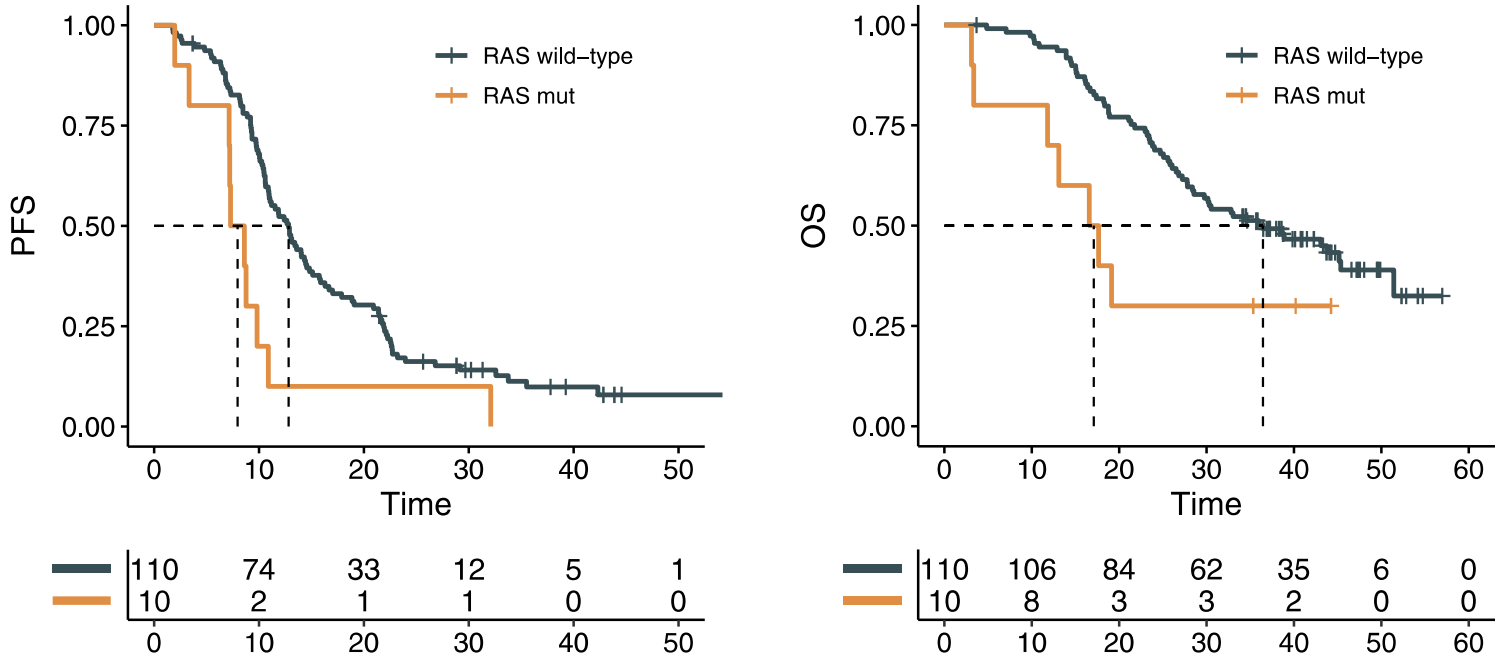


PRESSING panel: ***HER2*** **amplification or mutations;**
MET **amplification;** ***ALK/ROS1/NTRKs*** **and** ***RET*** **fusions;**
PI3K/PTEN/Akt and MAPKs pathways' activating mutations

Morano et al, J Clin Oncol '19

Prognostic impact of ctDNA *RAS* mutations in left-sided *RAS/BRAF* wt HER2-neg MSS mCRC

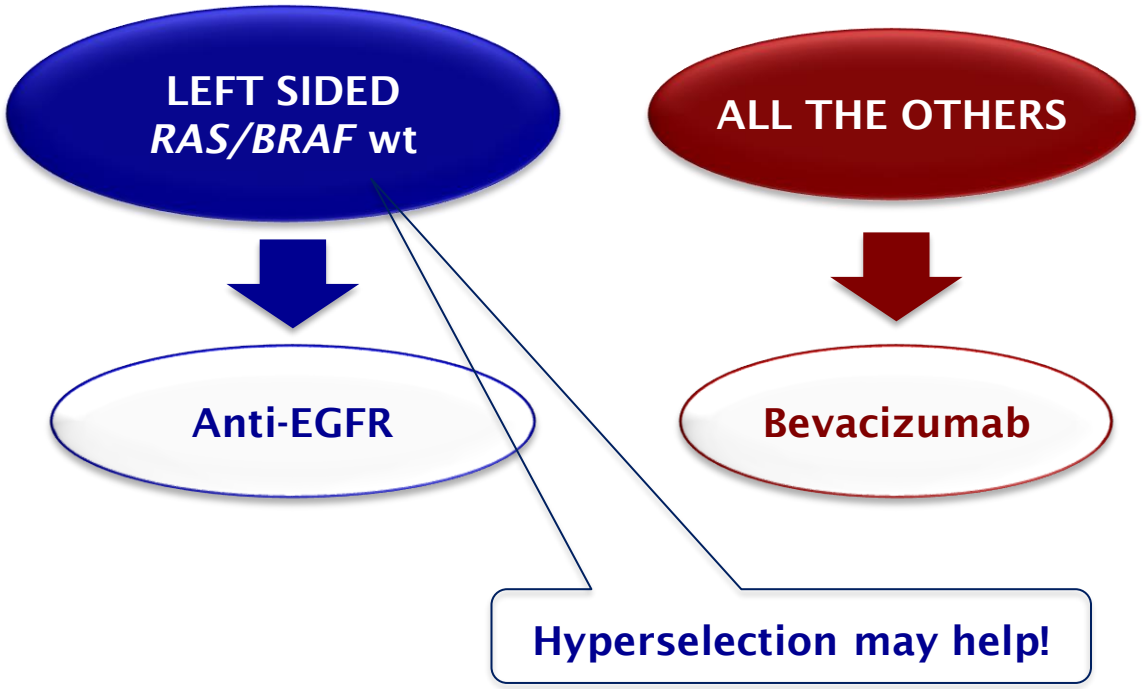
Post-hoc analysis of the VALENTINO study



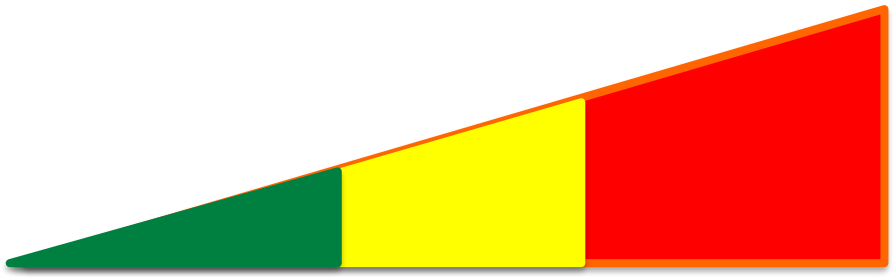
Manca et al, Clin Canc Res '21

Choosing the upfront therapy in MSS mCRC

The «best» targeted agent



The «best» chemotherapy (intensity)



Low intensity CT: monotherapy

- More a «need» according to patients' tumor-unrelated conditions than a choice based on disease indolence

- Capecitabine + bevacizumab : for long the most evidence-based standard

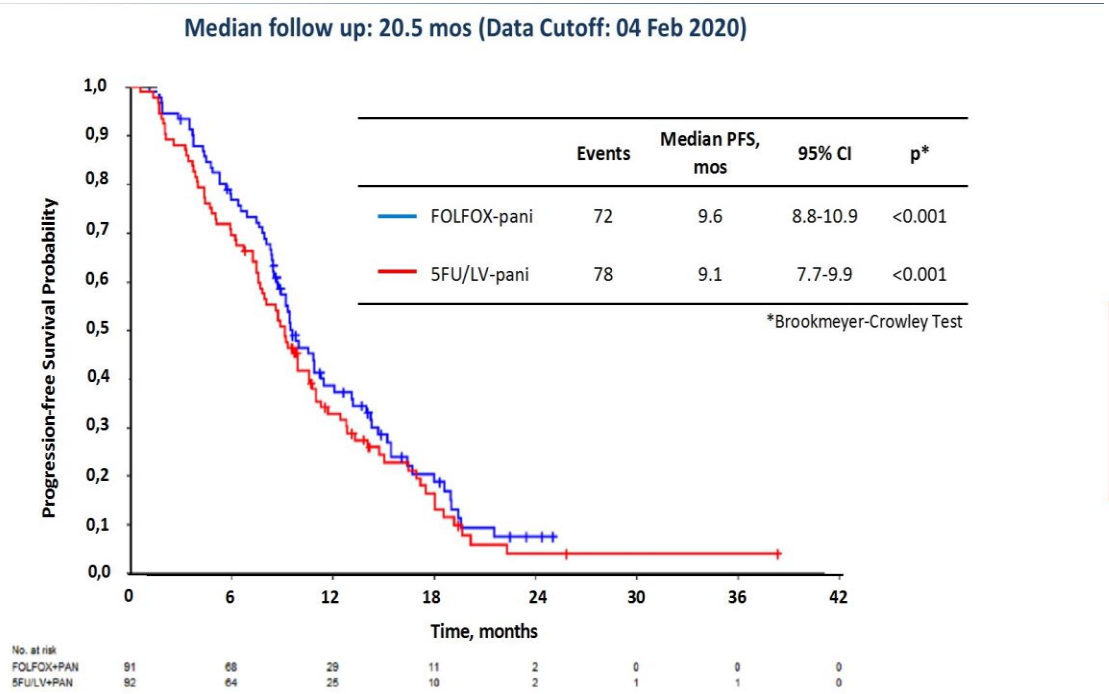
Cunningham et al, Lancet Oncol '13

- 5FU/LV + anti-EGFR : an option for pts with (left-sided) *RAS/BRAF* wt tumours

Lonardi et al, ASCO Ann Meet '20

PANDA: 5FU/LV+pan vs «light» FOLFOX+pan

Age > 75 with ECOG PS 0 or 1 or 70-75 with ECOG PS >0



Grade 3-4 toxicities	ARM A FOLFOX + PANI N= 92	ARM B 5FU/LV + PANI N= 91
Neutropenia	9.8 %	1.1 %
Diarrhea	16.3 %	1.1 %
Stomatitis	9.8 %	4.4 %
Neurotoxicity	3.3 %	-
Fatigue	6.5 %	4.4 %
Skin rash	25.0 %	24.2 %
Hypomagnesemia	3.3 %	7.7 %

ORR: 65% (arm A) and 57% (arm B)
DCR: 88% (arm A) and 86% (arm B)

Lonardi et al, ASCO Ann Meet '20

Low intensity CT: monotherapy

- More a «need» according to patients' tumor-unrelated conditions than a choice based on disease indolence

- Capecitabine + bevacizumab : for long the most evidence-based standard

Cunningham et al, Lancet Oncol '13

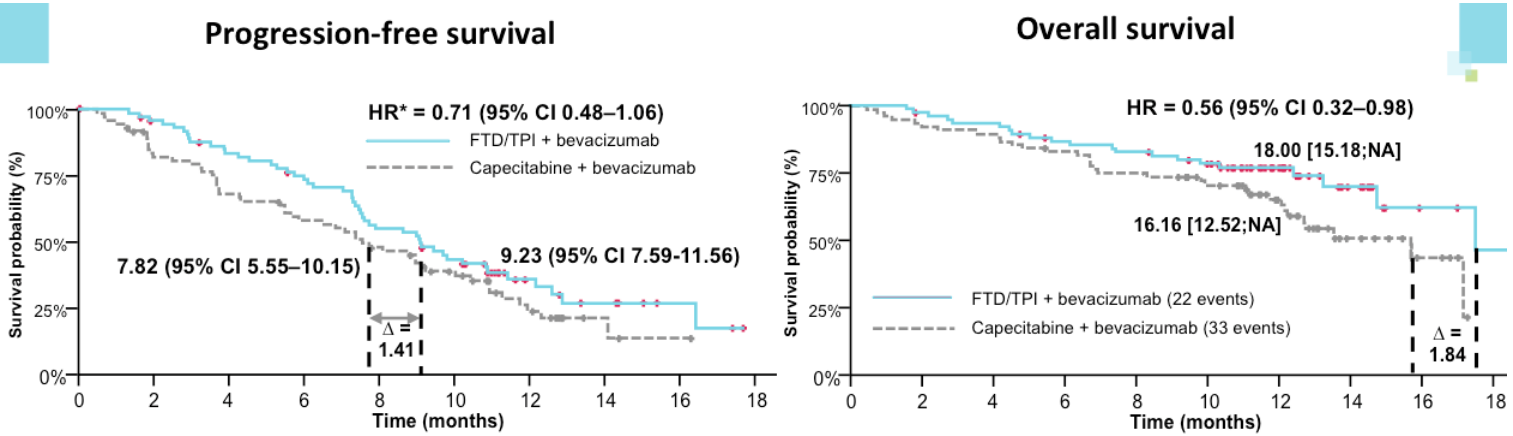
- 5FU/LV + anti-EGFR : an option for pts with (left-sided) *RAS/BRAF* wt tumours

Lonardi et al, ASCO Ann Meet '20

- News on the horizon: FTD/TPI + bev?

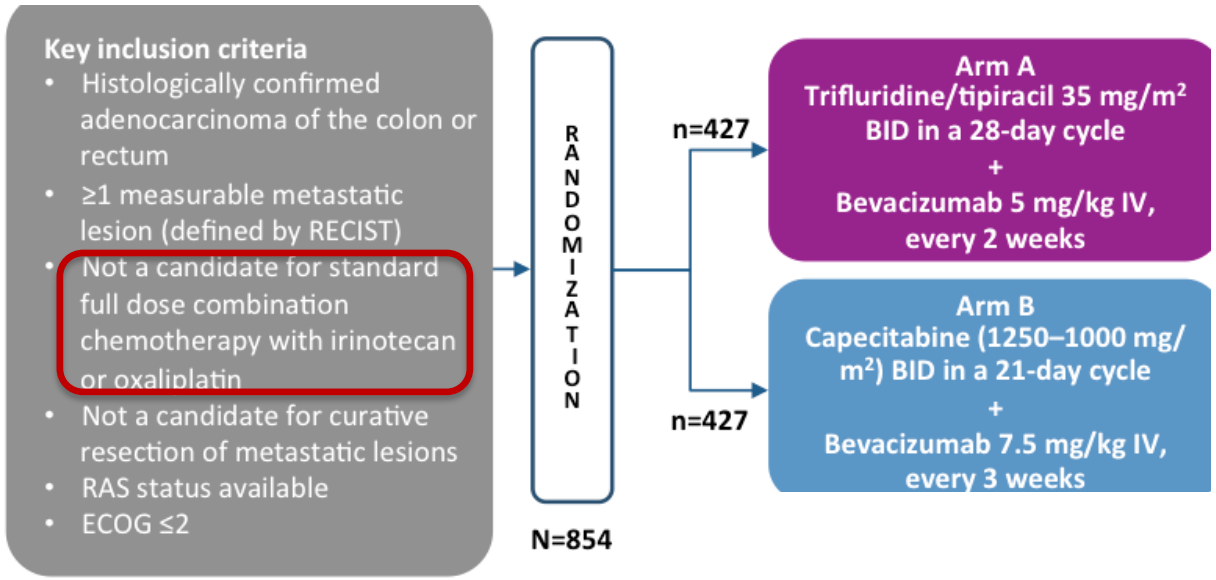
On the horizon…from TASCO-1 to SOLSTICE

Phase II TASCO-1



Van Cutsem et al, Ann Oncol '20

Phase III SOLSTICE – accrual completed

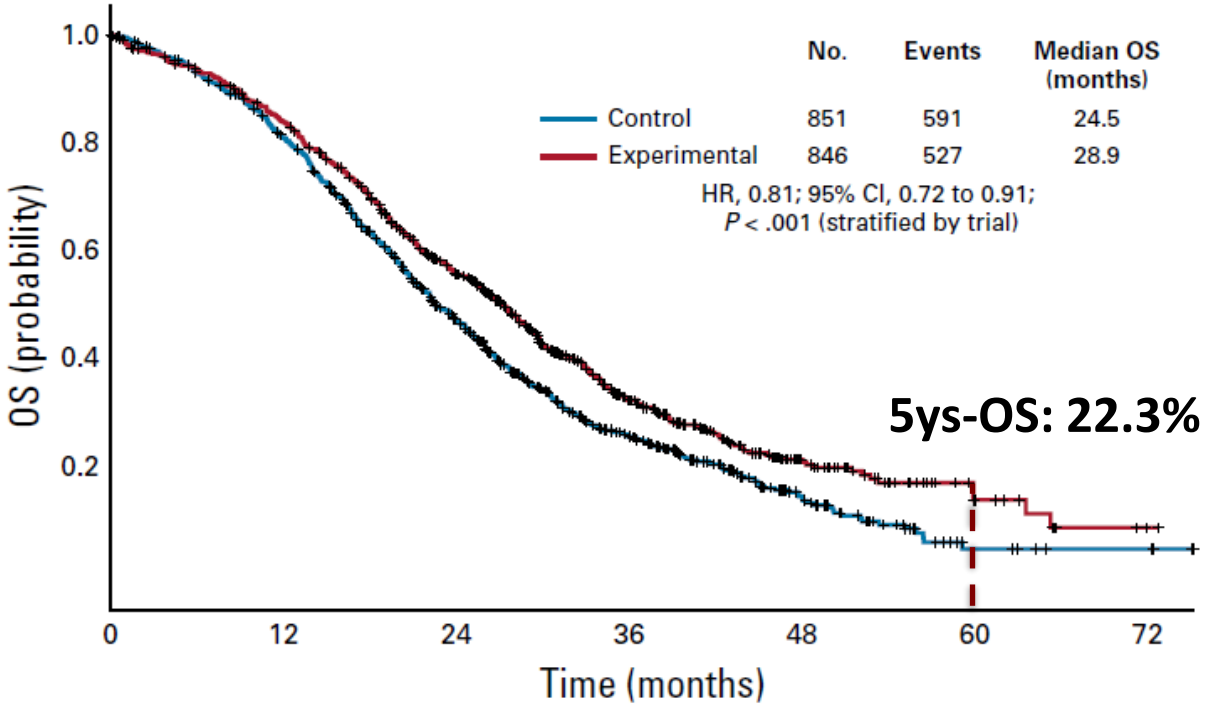


André et al, Fut Oncol '20

Higher intensity CT: FOLFOXIRI

- **FOLFOXIRI/bev provides a clinically relevant benefit versus doublets/bev at the price of increased chemo-related toxicity**

IPD-metanalysis of 5 random trials - Age < 70 with ECOG PS 0-2 or 70-75 with ECOG PS 0



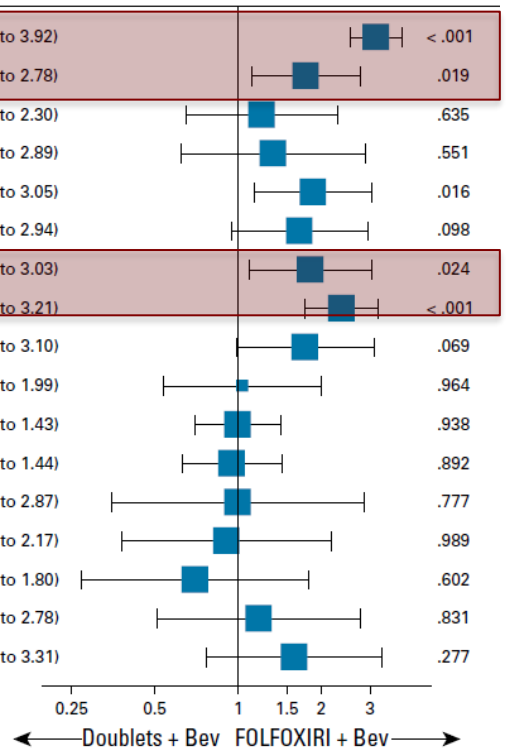
5ys-OS: 22.3% vs 10.7%

Cremolini et al, J Clin Oncol '21

Higher intensity CT: FOLFOXIRI

- **FOLFOXIRI/bev provides a clinically relevant benefit versus doublets/bev at the price of increased chemo-related toxicity**

Grade 3-4 Toxicity	Doublets + Bev No. Events of Total (%)	FOLFOXIRI + Bev No. Events of Total (%)	OR (95% CI)	P
Neutropenia	180 of 836 (21.5)	384 of 838 (45.8)	3.16 (2.54 to 3.92)	< .001
Febrile neutropenia	31 of 836 (3.7)	53 of 838 (6.3)	1.76 (1.12 to 2.78)	.019
Anemia	17 of 836 (2.0)	21 of 838 (2.5)	1.22 (0.65 to 2.30)	.635
Thrombocytopenia	10 of 836 (1.2)	14 of 838 (1.7)	1.34 (0.62 to 2.89)	.551
Nausea	25 of 836 (3.0)	46 of 838 (5.5)	1.87 (1.14 to 3.05)	.016
Vomiting	20 of 836 (2.4)	33 of 838 (3.9)	1.67 (0.95 to 2.94)	.098
Mucositis	24 of 836 (2.9)	43 of 838 (5.1)	1.83 (1.10 to 3.03)	.024
Diarrhea	70 of 836 (8.4)	149 of 838 (17.8)	2.37 (1.75 to 3.21)	< .001
Neurotoxicity	19 of 836 (2.3)	33 of 838 (3.9)	1.75 (0.99 to 3.10)	.069
Neurotoxicity (oxa-population)*	19 of 583 (3.3)	20 of 587 (3.4)	1.04 (0.54 to 1.99)	.964
Arterial hypertension	65 of 836 (7.8)	65 of 838 (7.8)	1.00 (0.70 to 1.43)	.938
Venous thromboembolism	48 of 836 (5.7)	46 of 838 (5.5)	0.95 (0.63 to 1.44)	.892
Arterial thrombosis	6 of 836 (0.7)	6 of 838 (0.7)	1.00 (0.35 to 2.87)	.777
Proteinuria	11 of 836 (1.3)	10 of 838 (1.2)	0.91 (0.38 to 2.17)	.989
Bleeding	10 of 836 (1.2)	7 of 838 (0.8)	0.70 (0.27 to 1.80)	.602
Intestinal perforation	9 of 836 (1.1)	11 of 838 (1.3)	1.19 (0.51 to 2.78)	.831
Toxic death	12 of 836 (1.4)	19 of 838 (2.3)	1.60 (0.77 to 3.31)	.277

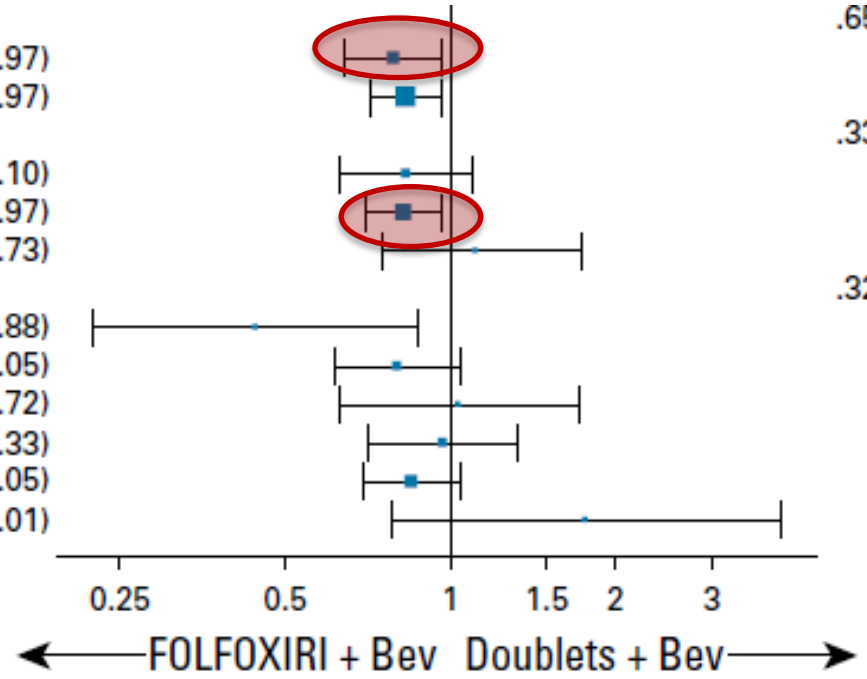


Cremolini et al, J Clin Oncol '21

Higher intensity CT: FOLFOXIRI

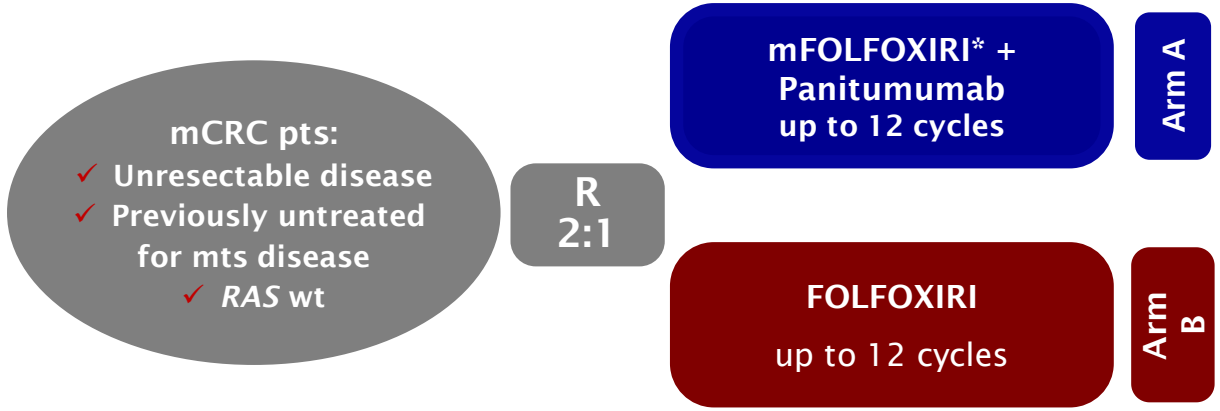
- **FOLFOXIRI/bev provides a clinically relevant benefit versus doublets/bev at the price of increased chemo-related toxicity**

Tumor site				.656
Right	185 of 255 (72.5)	193 of 295 (65.4)	0.79 (0.64 to 0.97)	
Left/rectum	367 of 535 (68.6)	317 of 496 (63.9)	0.83 (0.72 to 0.97)	
RAS and *BRAF* status				.337
RAS-BRAF wt	107 of 172 (62.2)	99 of 177 (55.9)	0.83 (0.63 to 1.10)	
RAS mut	316 of 430 (73.5)	289 of 422 (68.5)	0.82 (0.70 to 0.97)	
BRAF mut	43 of 54 (79.6)	53 of 61 (86.9)	1.11 (0.75 to 1.73)	
Site-*RAS/BRAF*				.320
Right-*RAS/BRAF* wt	21 of 31 (67.7)	21 of 44 (47.7)	0.44 (0.22 to 0.88)	
Right-*RAS* mut	110 of 149 (73.8)	113 of 168 (67.3)	0.80 (0.62 to 1.05)	
Right-*BRAF* mut	33 of 40 (82.5)	34 of 39 (87.2)	1.04 (0.63 to 1.72)	
Left-*RAS/BRAF* wt	79 of 134 (59.0)	78 of 132 (59.1)	0.97 (0.71 to 1.33)	
Left-*RAS* mut	199 of 273 (72.9)	173 of 250 (69.2)	0.85 (0.69 to 1.05)	
Left-*BRAF* mut	9 of 13 (69.2)	19 of 22 (86.4)	1.77 (0.78 to 4.01)	



Cremolini et al, J Clin Oncol '21

Triplet/pan : VOLFI trial



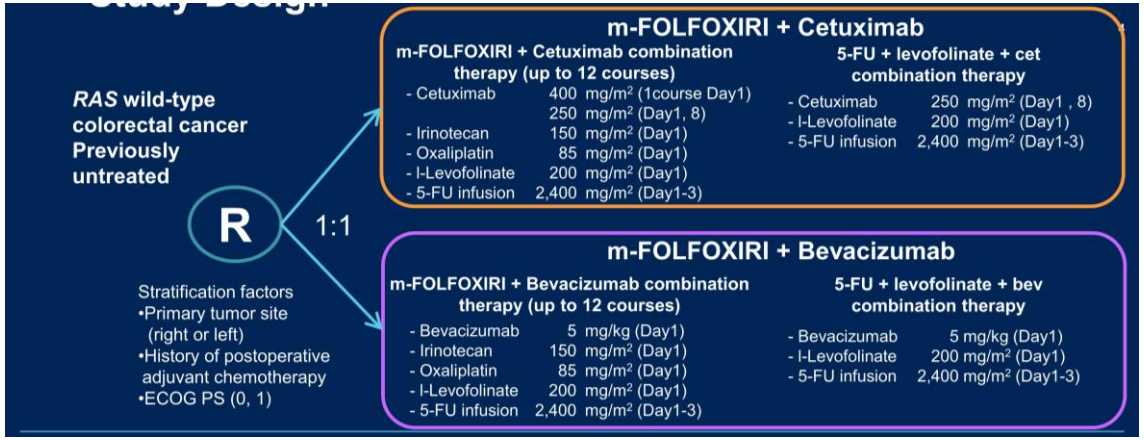
*irinotecan 150mg/sqm; oxaliplatin 85 mg/sqm; LV 200 mg/sqm; 5FU: 3000 mg/sqm

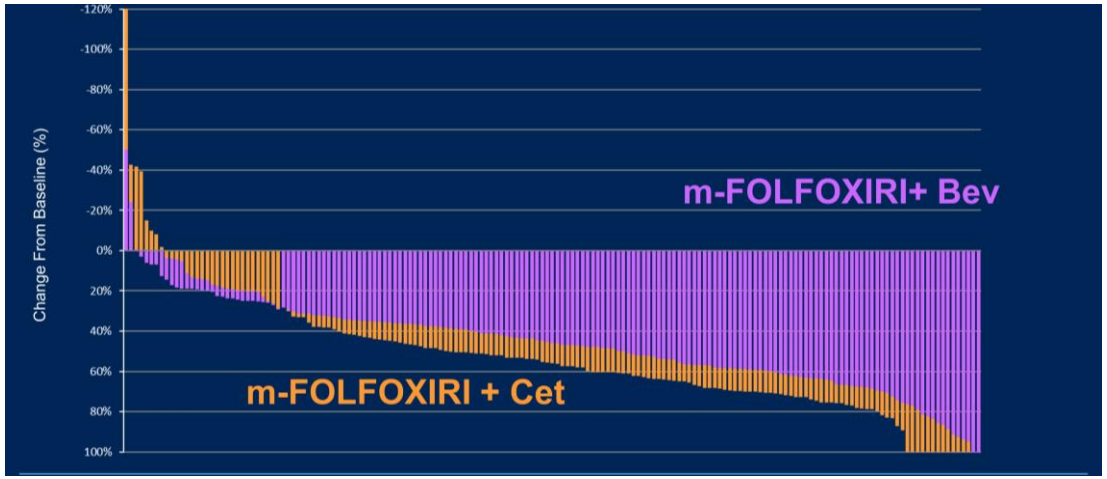
Primary endpoint: Objective Response Rate

	mFOLFOXIRI+pan N=63	FOLFOXIRI N=33	OR	*p*
Response Rate	85.7%	60.6%	3.90	0.0096
***RAS/BRAF* wt**	N=43 / 86.0%	N=17 / 64.7%	3.36	0.0806
Left-sided tumors	N=53 / 90.6%	N=25 / 68.0%	4.52	0.0210
Right-sided tumors	N=10 / 60.0%	N=8 / 37.5%	2.50	0.64
Progression-free Survival	10.8 mos	10.5 mos	1.11	0.66
Resection Rate (potentially resectable cohort, n=31)	70.0%	36.4%	-	0.13

Modest et al, J Clin Oncol '19

Triplet/cet : DEEPER trial

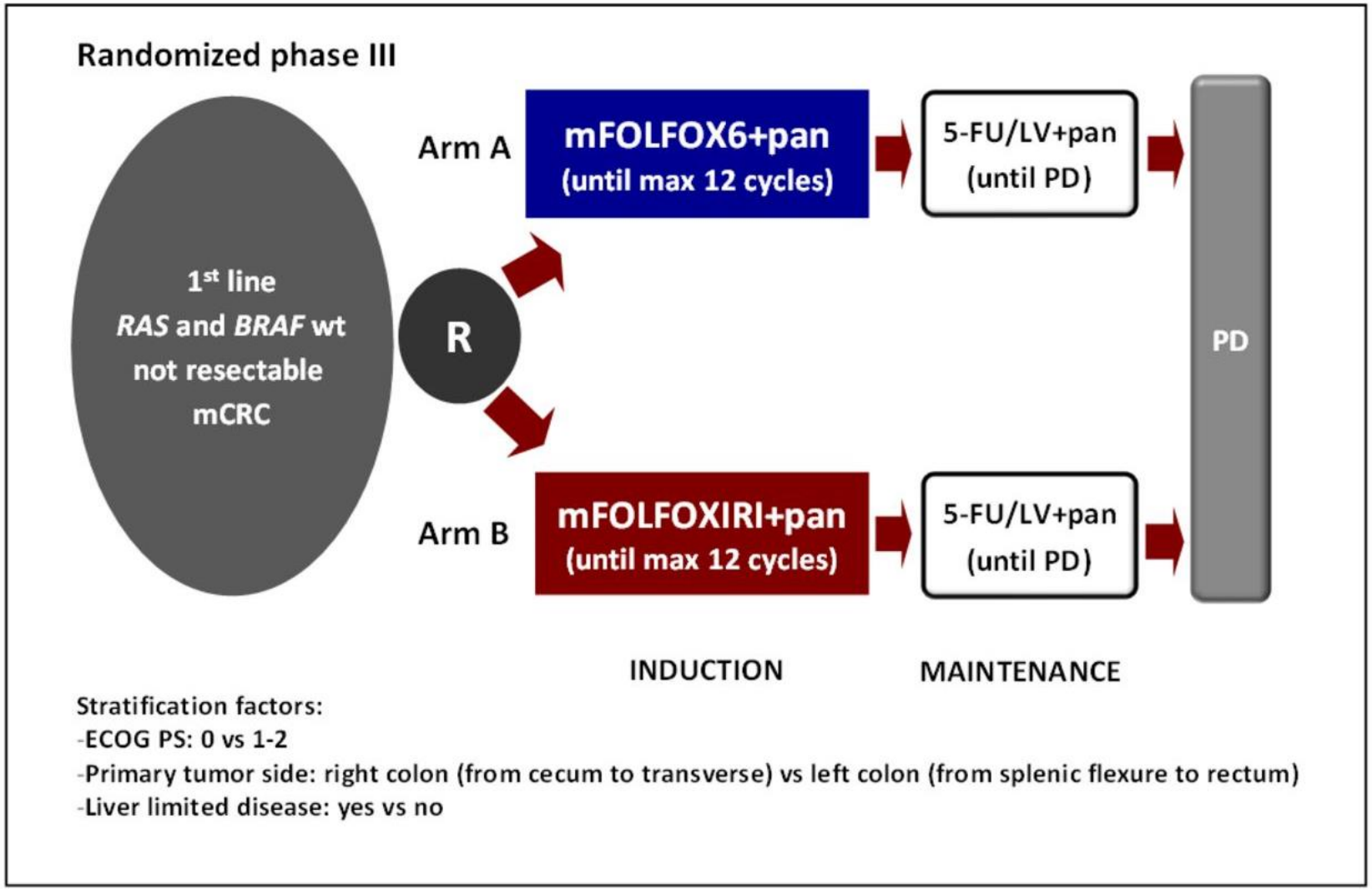




	mFOLFOXIRI+cetux N=158	mFOLFOXIRI + bev N=162	*p*
Depth of response (median)	57.4%	46%	0.0010
Left-sided subgroup (N= 131/137)	60.3%	46.1%	0.0007
Right-sided subgroup (N=27/25)	50.0%	41.2%	0.466
RECIST Response Rate	69.1%	71.7%	0.605
Disease Control Rate	90.9%	95.4%	0.096
R0 resection rate	28.6%	30.6%	0.673
Progression-free Survival (mos)	12.7	10.5	-
Overall Survival (mos)	37.6	36.4%	-

Tsuji et al, ASCO Ann Meet '21

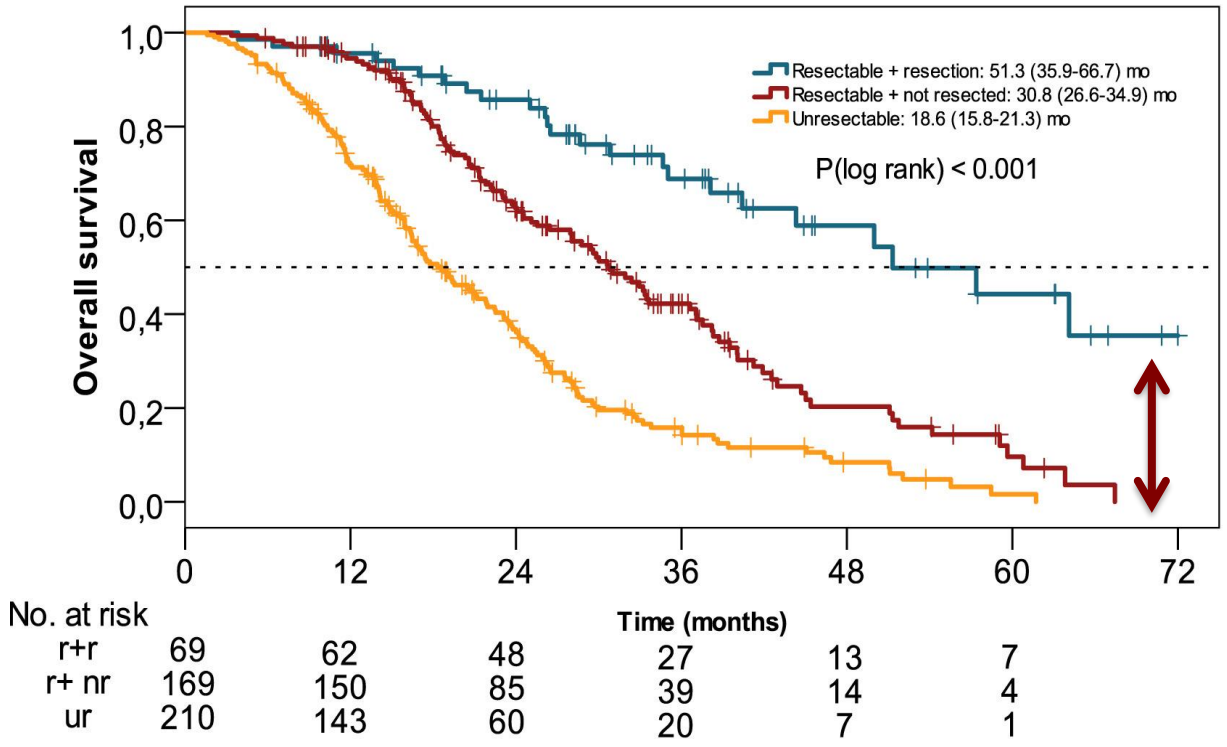
Is there any added value for intensified chemo with anti-EGFRs? TRIPLETE study



Borelli et al., ESMO Open '18

At the time of best response

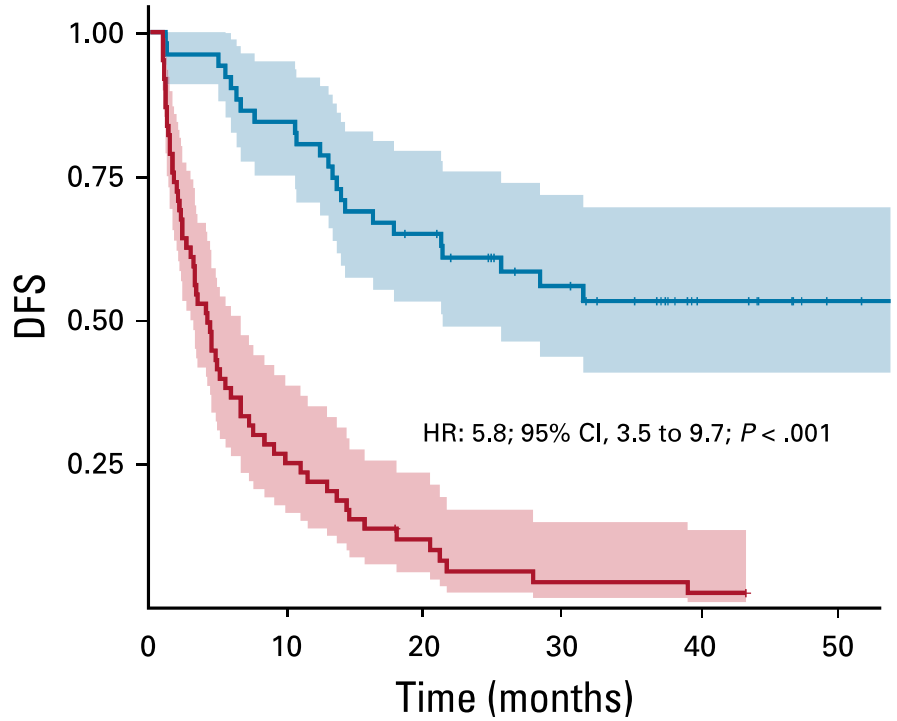
Is surgery technically feasible and oncologically sound?



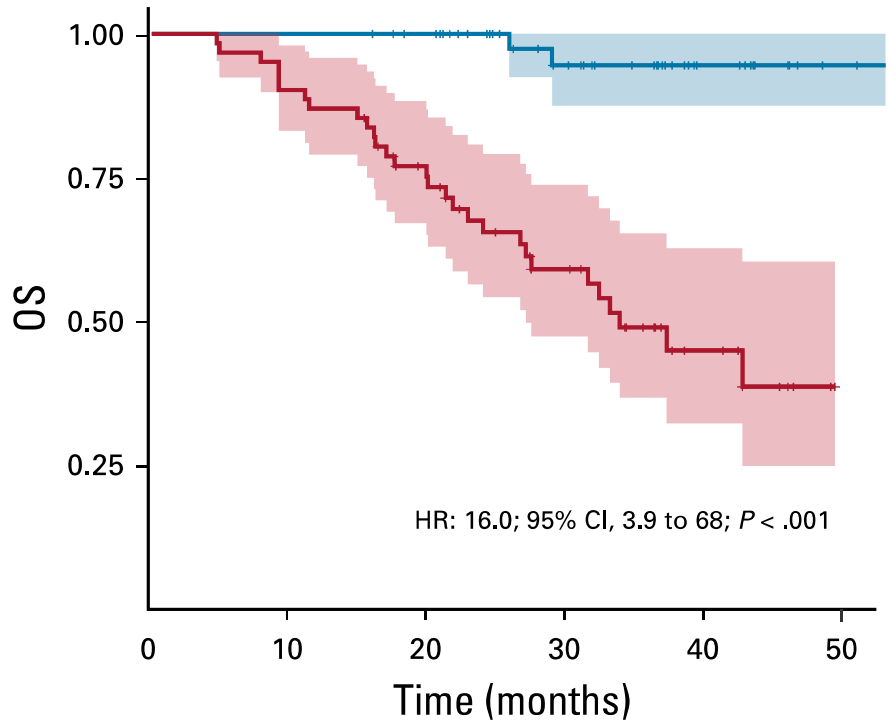
Modest et al, Eur J Can '15

Throwing light on the «adjuvant» therapy

Detection of ctDNA in 112 radically resected mCRC patients



ctDNA-negative	51	43	32	22	9	2
ctDNA-positive	61	15	6	2	1	0



ctDNA-negative	51	51	48	32	13	3
ctDNA-positive	61	55	41	25	9	0

Loupakis et al, JCO Precision Oncol '21

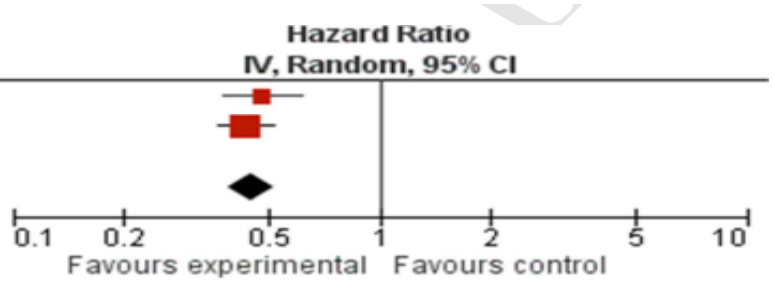
Treatment de-intensification in unresectable pts

Fluoropyrimidine/bev better than holiday

(AIO KRK0207 – CAIRO 3)

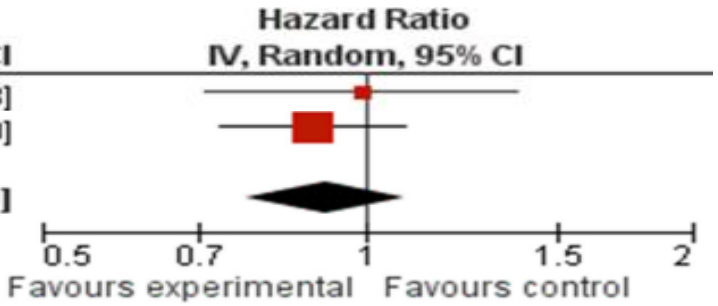
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
AIO KRK 0207 - Combi	-0.7381	0.1242	34.8%	0.48 [0.37, 0.61]
CAIRO 3	-0.84397007	0.09065533	65.2%	0.43 [0.36, 0.51]
Total (95% CI)			**100.0%**	**0.45 [0.39, 0.51]**

Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 11.02 (P < 0.00001)



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
AIO KRK 0207 - Combi	-0.01005034	0.16961535	26.2%	0.99 [0.71, 1.38]
CAIRO 3	-0.11653382	0.10111254	73.8%	0.89 [0.73, 1.09]
Total (95% CI)			**100.0%**	**0.92 [0.77, 1.09]**

Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)



Stein, Clin Col Canc '15

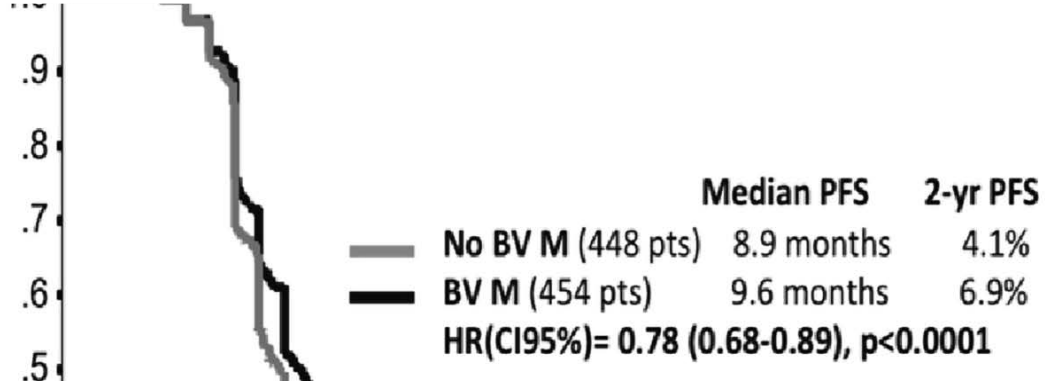
Treatment de-intensification in unresectable pts

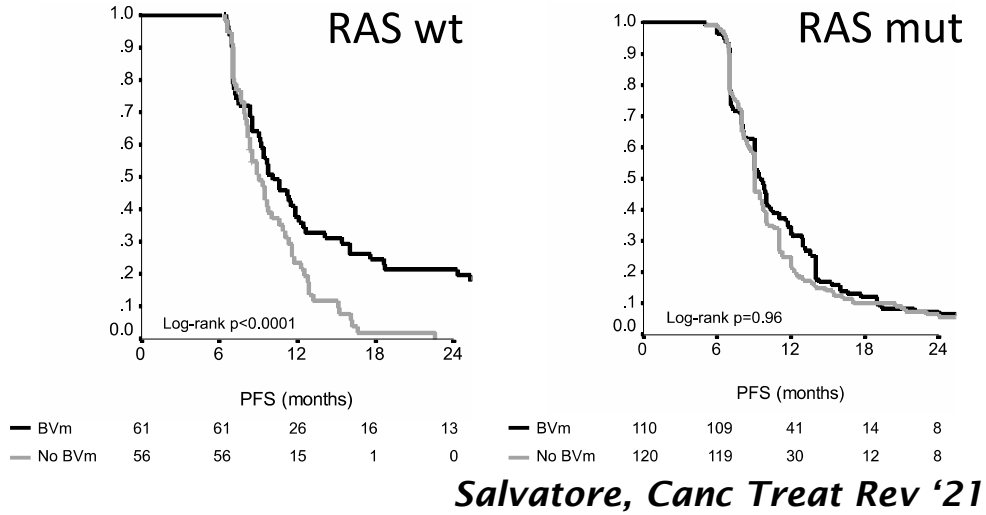
Fluoropyrimidine/bev better than holiday

(AIO KRK0207 – CAIRO 3)

Limited/No impact of bev alone versus holiday

(AIO KRK0207 – PRODIGE-9 – SAKK-41/06)

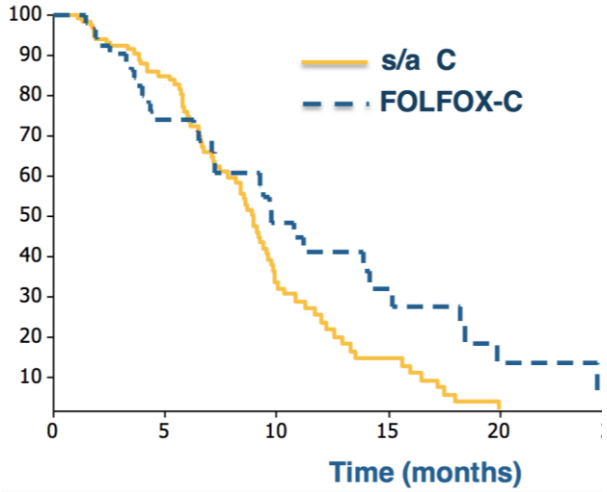




Salvatore, Canc Treat Rev '21

Maintenance after 1st-line anti-EGFR: what we already knew

Anti-EGFR maintenance not inferior to combined treatment until PD



MACRO2:
Cet = FOLFOX/cet
(KRAS ex2 wt!)

SAPPHIRE:
FU/pan =
FOLFOX/pan

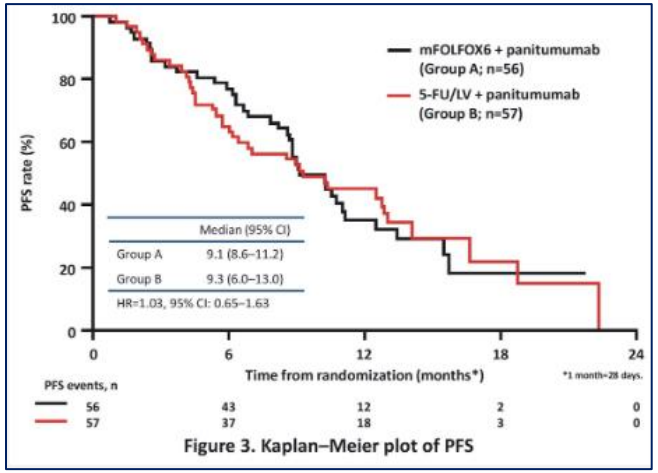


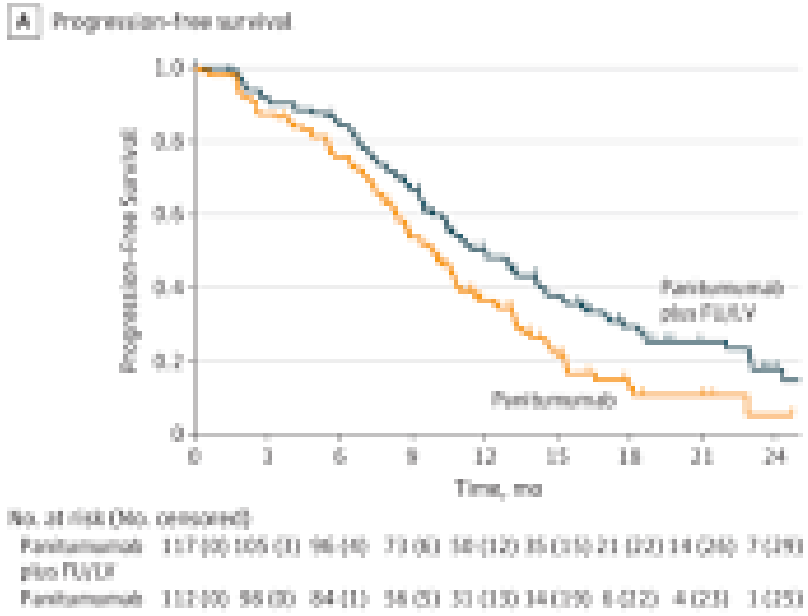
Figure 3. Kaplan–Meier plot of PFS

Maintenance after 1st-line anti-EGFR: what we already knew

Anti-EGFR maintenance not inferior to combined treatment until PD

5FU/LV + pan better than pan as maintenance

VALENTINO:
Pan < FU/pan

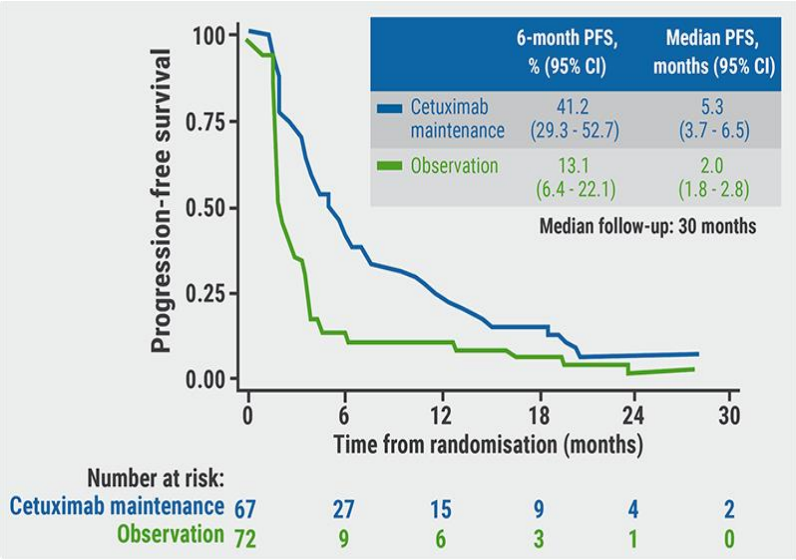


Maintenance after 1st-line anti-EGFR: what we already knew

Anti-EGFR maintenance not inferior to combined treatment until PD

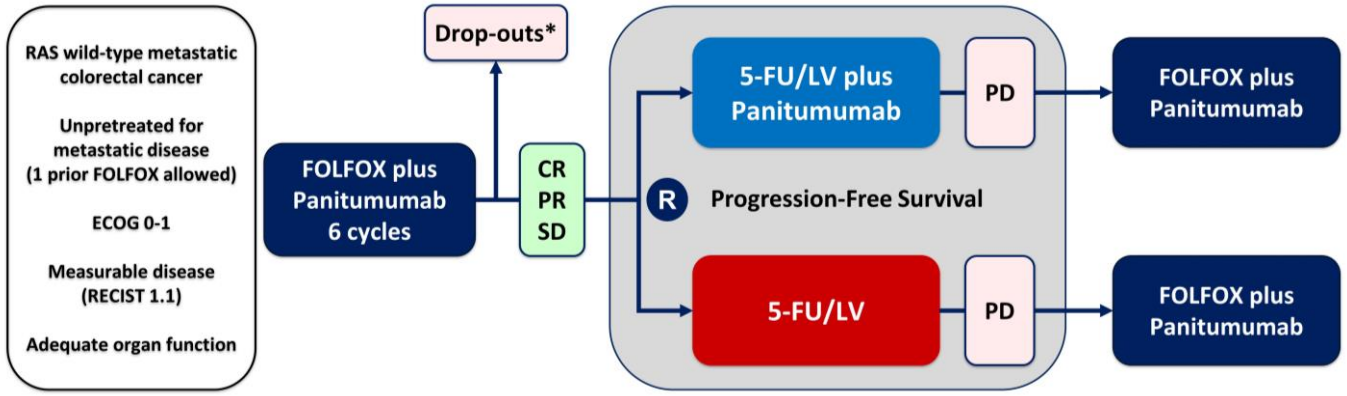
5FU/LV + pan better than pan as maintenance

Cetuximab better than observation

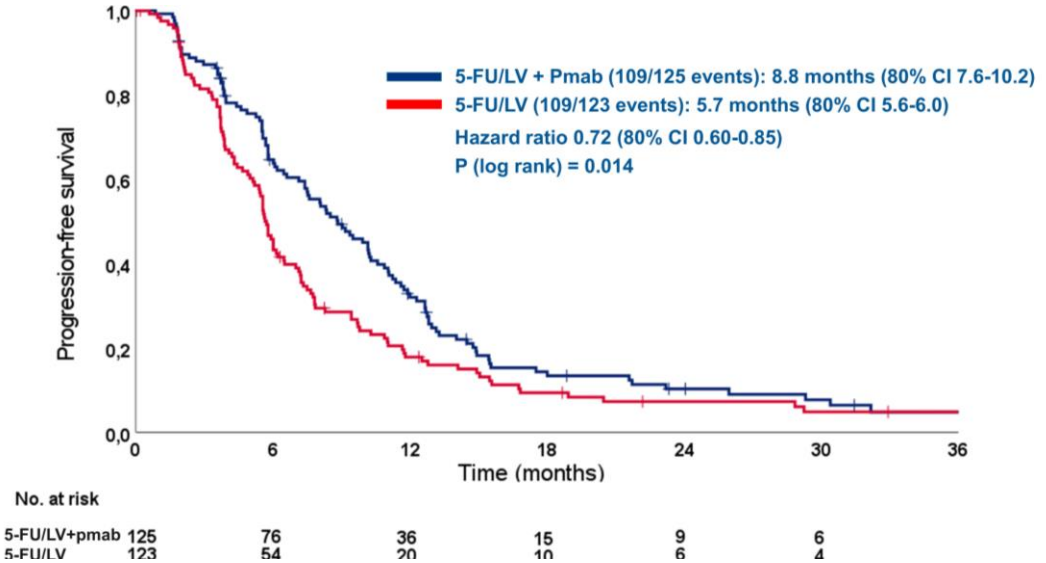


PRODIGE28:
Full holiday < cet

Another piece in the puzzle: PANAMA



Primary endpoint: PFS

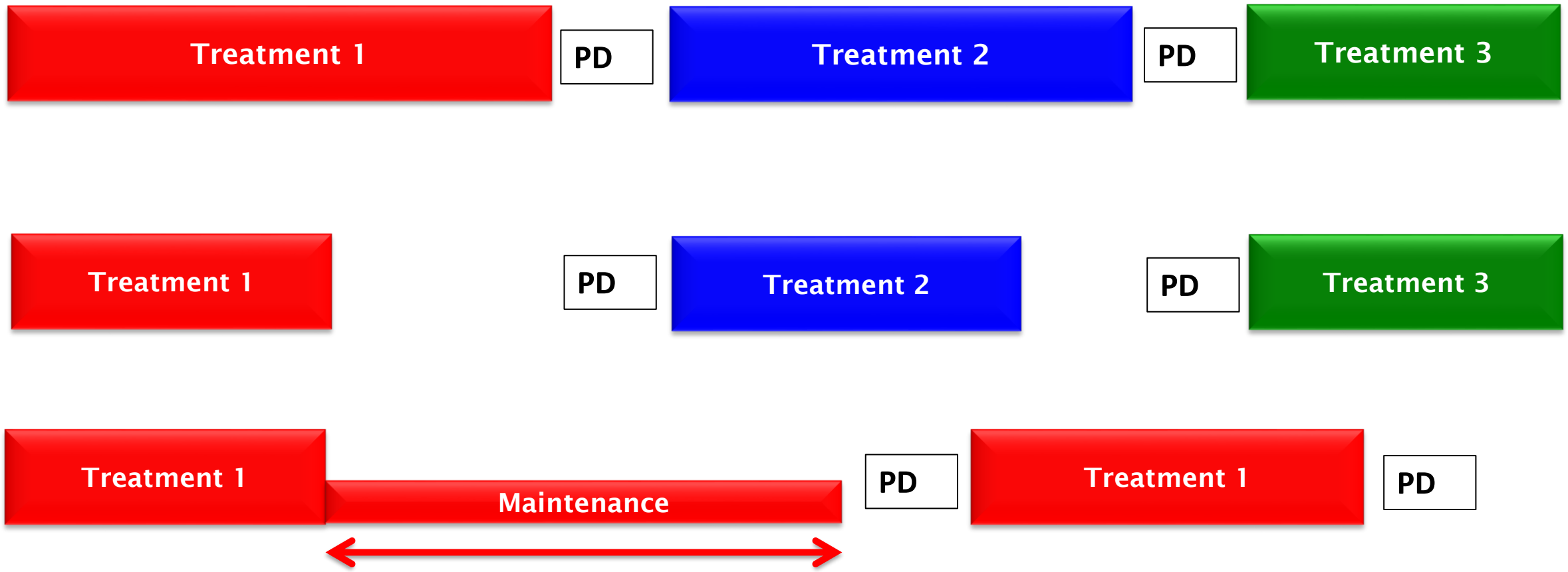


Modest et al, ASCO Ann Meet '21

…and the winner is…

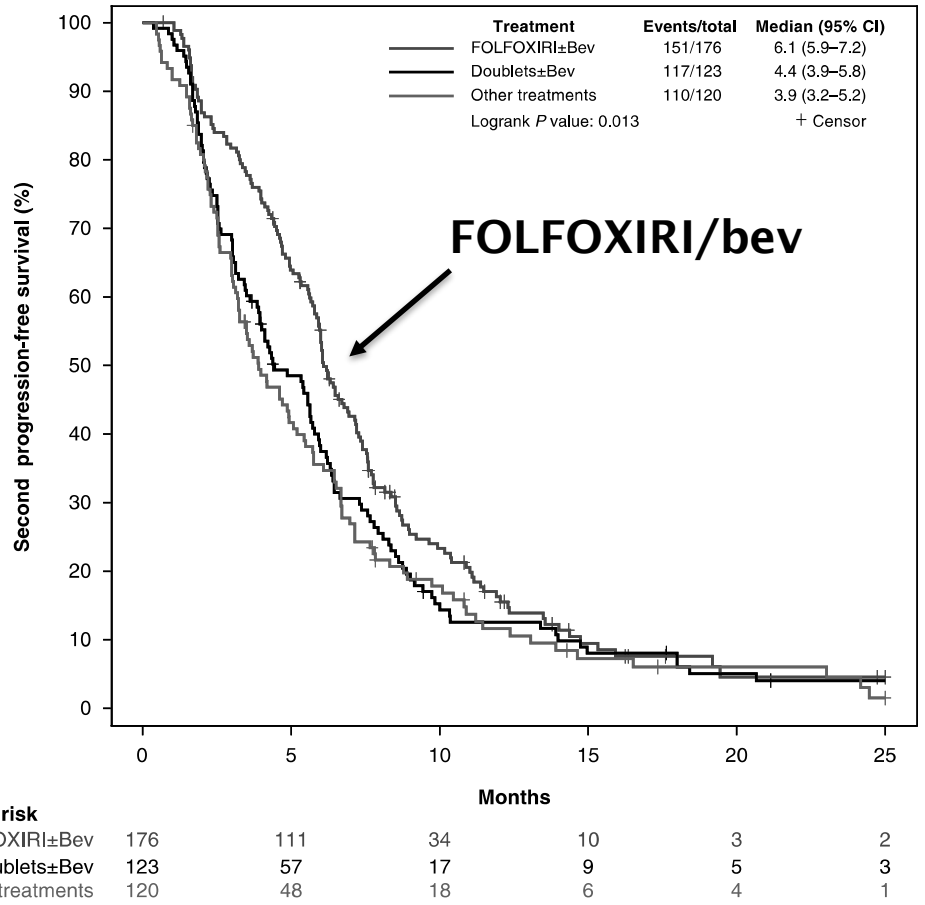
Fluoropyrimidine
+ targeted agent

Treatment strategies in mCRC



Treatments after progression to FOLFOXIRI/bev

Pooled analysis of TRIBE and TRIBE2
Pts treated with FOLFOXIRI/bev who experienced 1st PD (N=524)



80% received a treatment after PD

Better **FOLFOXIRI/bev reintro** if:

- PR/CR during FOLFOXIRI/bev
- OIFI > 4 mos

Rossini et al, Br J Canc '20

Later lines of tx: Which is the best option?

Phase III options

Anti-EGFR Re-treatment in mCRC

Study	Study type	N	Tx line	RR, %	Median PFS	Median OS
Santini et al, 2012	Retrospective	39	3-7	53.8	6.6	NR
Nogueira et al, 2016	Retrospective	15	3	13.3	3.5	NR
Tanioka et al, 2018	Retrospective	14	3-6	21.4	4.4	NR
TRECC	Retrospective	68	3+	42.6	6.6	24.4
Rossini et al, 2020	Retrospective	86	3+	19.8	3.8	10.2
CRICKET	Phase II	28	3	21.4	3.4	9.8
E-RECHALLENGE	Phase II	33	3+	15.6	2.9	8.6
JACCRO CC-08	Phase II	34	3	2.9	2.4	8.1
CAVE (cetuximab + avelumab)	Phase II	77	3	7.8	3.6	11.6
WJOG8916G (panitumumab + FTD/TPI)	Phase II	56	3+	3.6	2.4	9.8

Santini et al, Ann Oncol '12, Nogueira et al, Ann Oncol '16, Tsuji et al, ESMO '16, Tanioka et al, Oncol Lett '18, Cremolini et al, JAMA Oncol '18, Karani et al, ASCO '19, Takahashi et al, ESMO WCGI '21

Anti-EGFR Re-treatment in mCRC

Study	Study type	N	Tx line	RR, %	Median PFS	Median OS
CRICKET	Phase II	28	3	21.4	3.4	9.8
CRICKET (ctDNA *RAS* wt)	-	13	3	**31**	4	12.5
E-RECHALLENGE	Phase II	33	3+	15.6	2.9	8.6
E-RECHALLENGE (ctDNA *RAS/BRAF/PIK3CA/EGFR* wt)	-	24	3+	**50**	7	NR
CAVE (cetuximab + avelumab)	Phase II	77	3	7.8	3.6	11.6
CAVE (ctDNA RAS/BRAF wt)	-	48	3	**8.5**	4.1	17.3
WJOG8916G (panitumumab + FTD/TPI)	Phase II	56	3+	3.6	2.4	9.8
WJOG8916G (ctDNA *RAS/BRAF/PIK3CA/ERBB2/MET* wt)	-	21	3+	**9.5**	5.5	14.2

Cremolini et al, JAMA Oncol '18, Karani et al, ASCO '19, Nakamura et al, ESMO '19, Ohhara et al, ASCO GI '19, Takahashi et al, ESMO WCGI '21; Masuishi, ESMO WCGI '21; Mariani et al., ASCO '21, Sartore-Bianchi et al., ASCO '21

Anti-EGFR Re-treatment in mCRC

Study	Study type	N	Tx line	RR, %	Median PFS	Median OS
CRICKET	Phase II	28	3	21.4	3.4	9.8
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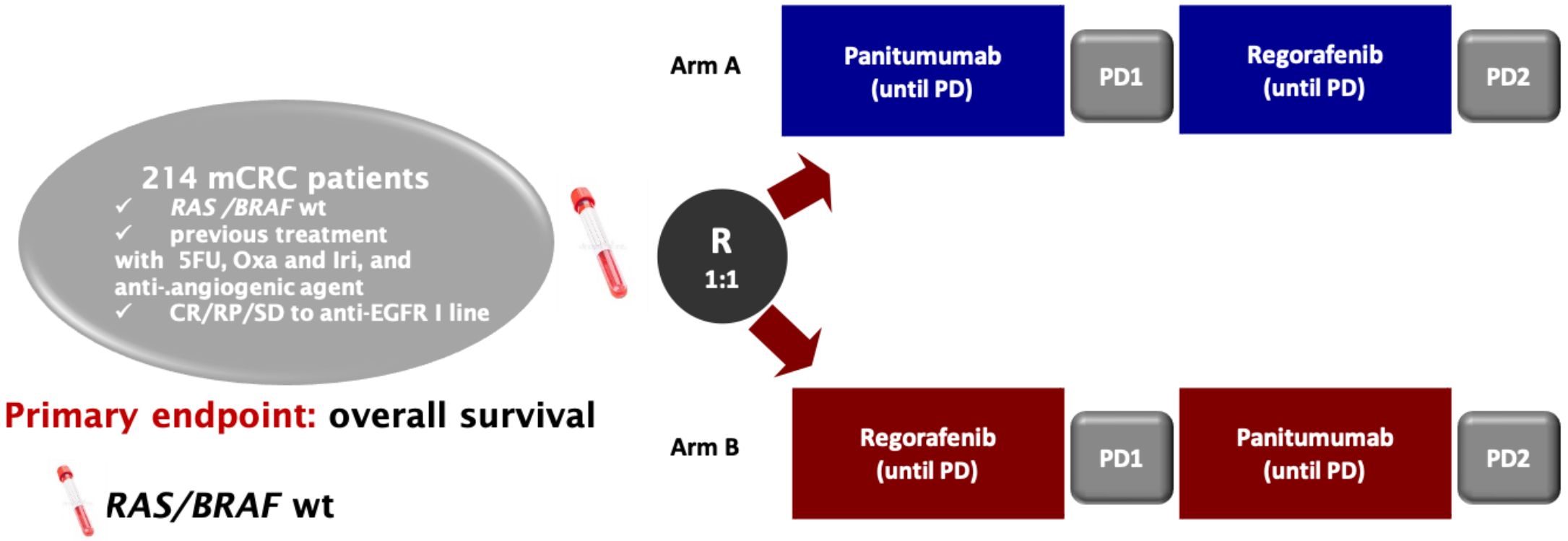
WJOG8916G (ctDNA *RAS/BRAF/PIK3CA/ERBB2/MET* wt)	-	21	3+	**9.5**	5.5	14.2
Mariani et al, 2021 (ctDNA *RAS/BRAF* wt)	Prospective	14	3+	**27.3**	3	7
CHRONOS (ctDNA *RAS/BRAF/EGFR* wt)	Phase II	27	3+	**30**	16.4	NR

Cremolini et al, JAMA Oncol '18, Karani et al, ASCO '19, Nakamura et al, ESMO '19, Ohhara et al, ASCO GI '19, Takahashi et al, ESMO WCGI '21; Masuishi, ESMO WCGI '21; Mariani et al., ASCO '21, Sartore-Bianchi et al., ASCO '21

Later lines of tx: Which is the best option?

Phase III options

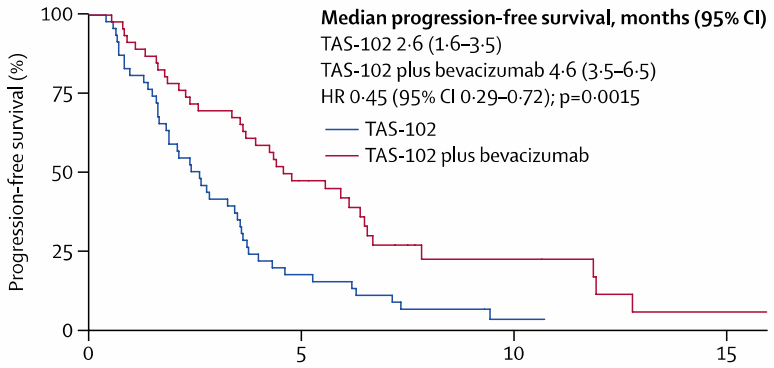
PARERE



Moretto et al, Clin Col Canc '21

On the horizon…from Danish trial to SUNLIGHT

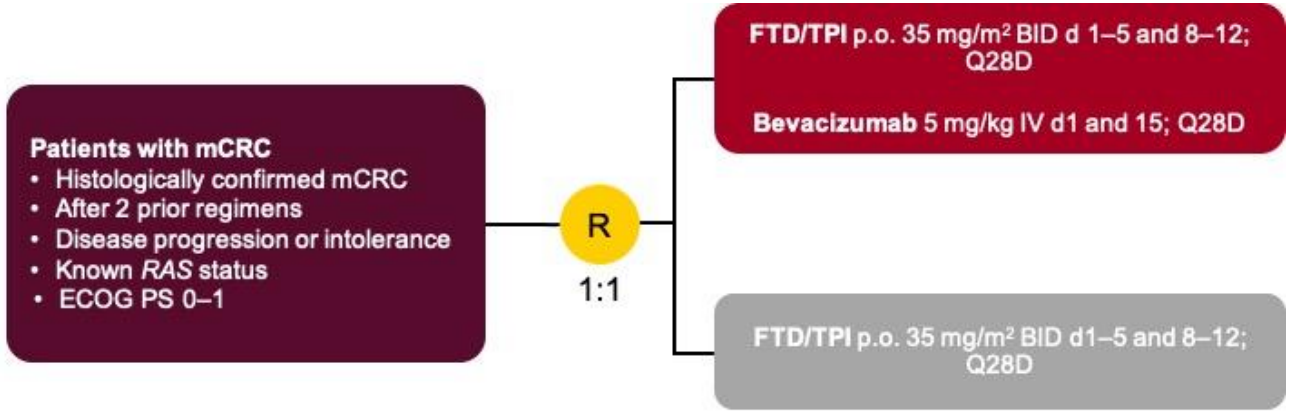
Phase II Danish trial



Number at risk (number censored)				
TAS-102	47 (38)	8 (6)	1 (0)	0
TAS-102 plus bevacizumab	46 (24)	20 (8)	5 (3)	1

Pfeiffer et al, Lancet Oncol '20

Phase III SUNLIGHT – Accrual completed



Primary endpoint: Overall survival

Secondary endpoints: PFS, DCR, ORR, Safety, QoL

Tabernero et al, Fut Oncol '21

Thank you!