State-of-the-art first-line therapy for mCRC

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Disclosures

Honoraria (advisory board member and/or invited speaker):

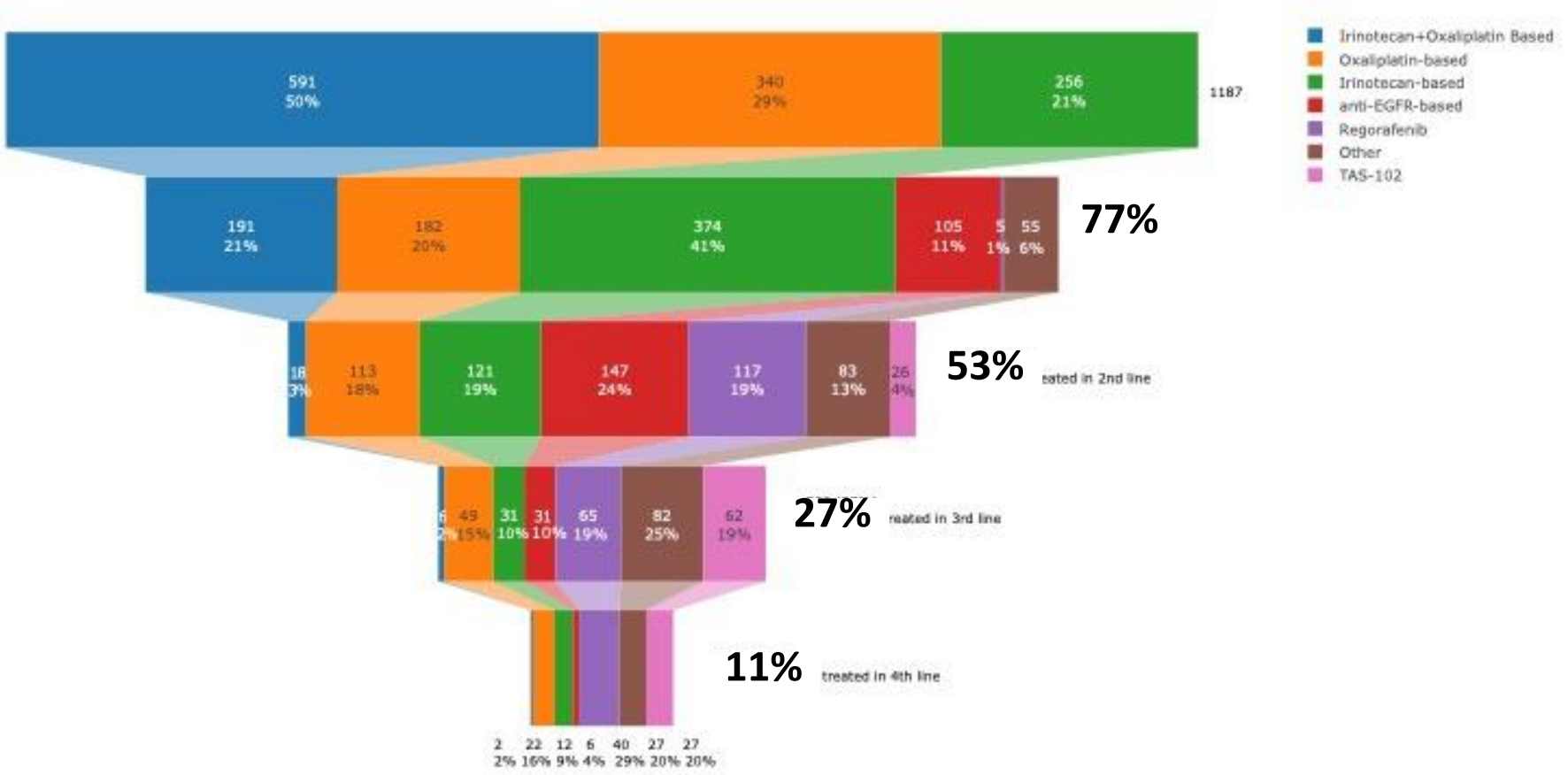
– Amgen, Bayer, Merck, MSD, Nordic Pharma, Pierre Fabre, Roche, Servier

- Research grants:

– Bayer, Merck, Roche, Servier

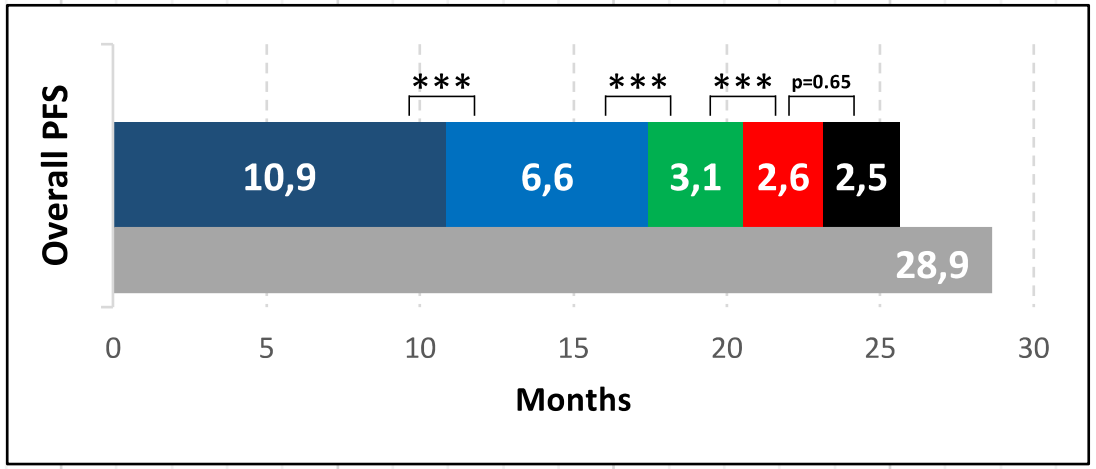
mCRC - starting point #1: the funnel effect

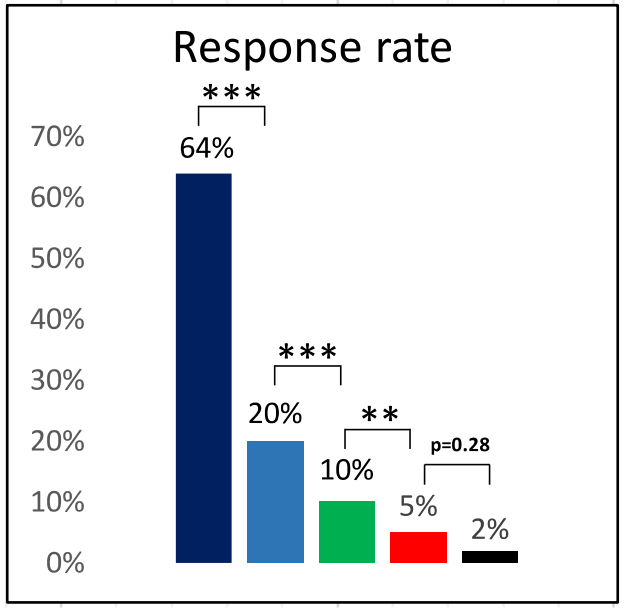
Pts enrolled in the phase III TRIBE and TRIBE2 studies (N=1187)

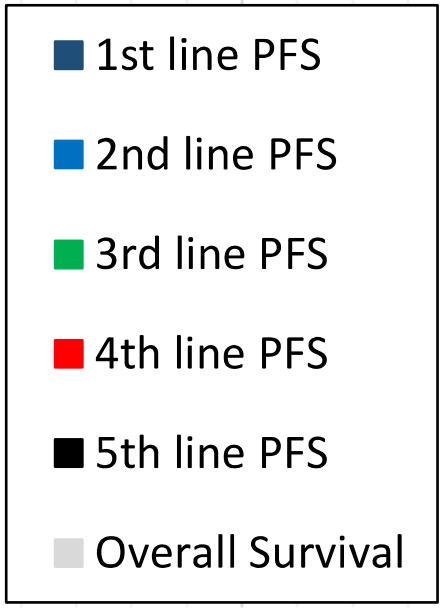


Rossini et al, Eur J Canc '22

mCRC - starting point #2: the funnel effect of efficacy







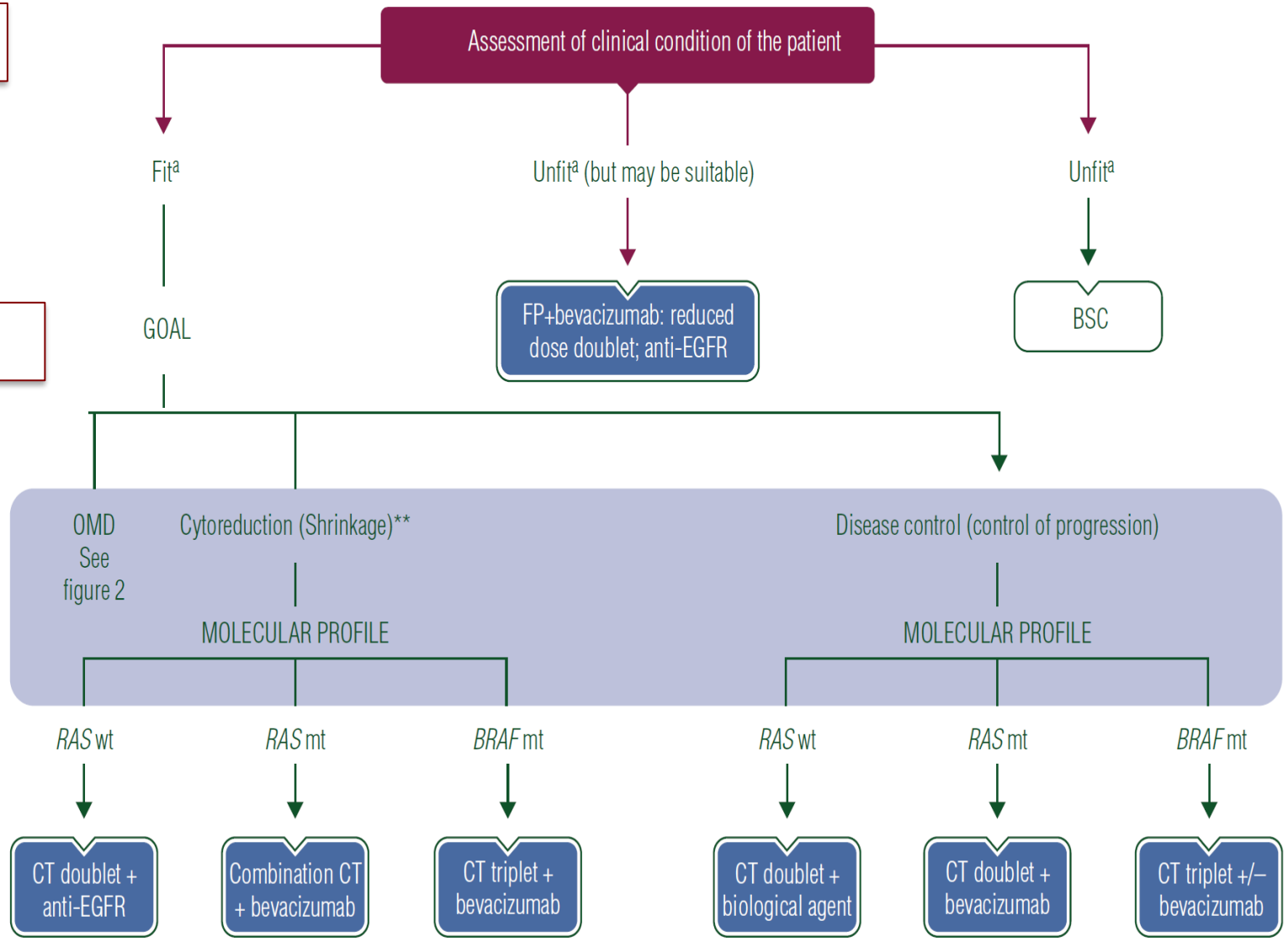
Rossini et al, Eur J Canc '22

Drivers for the choice of the upfront therapy
ESMO Guidelines '16

Patient

Treatment intent

RAS/BRAF



Van Cutsem et al., Ann Oncol '16

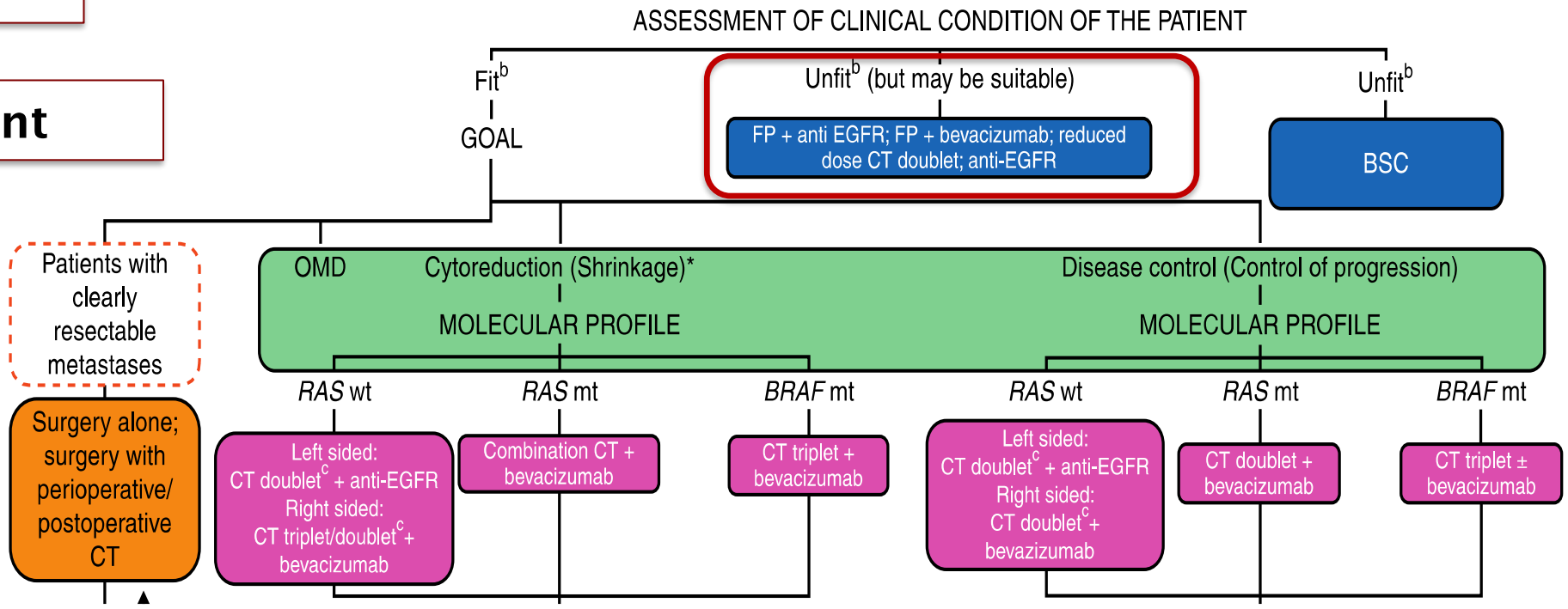
Drivers for the choice of the upfront therapy
ESMO PanAsia Consensus '18

Patient

Treatment intent

RAS/BRAF

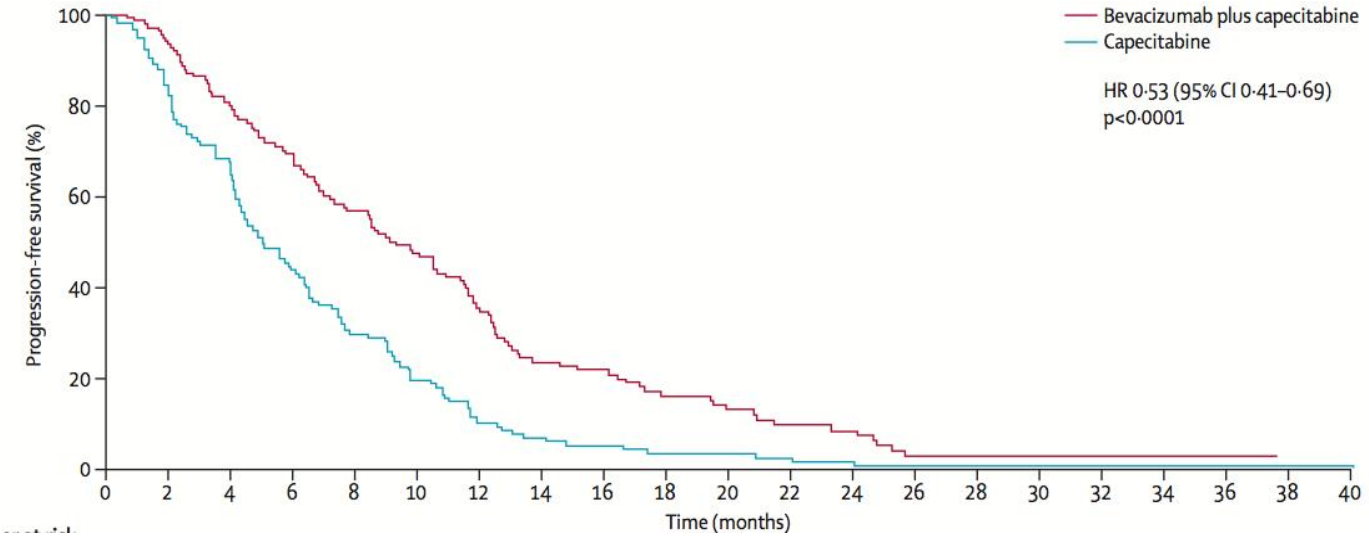
Primary location



Yoshino et al., Ann Oncol '18

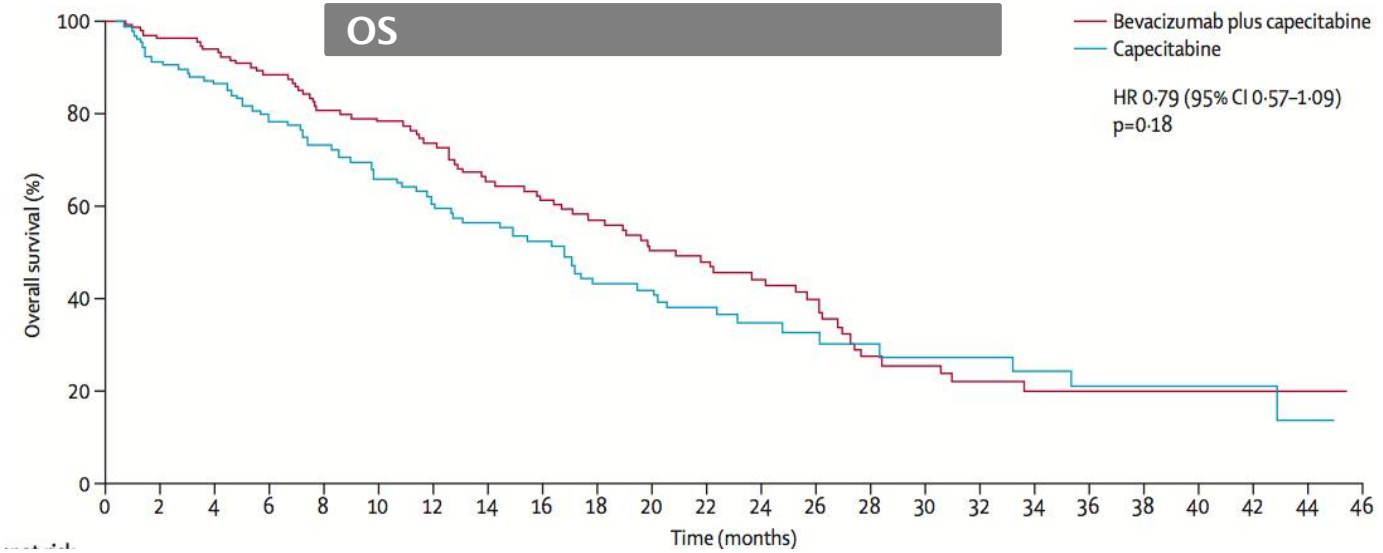
Low intensity CT = monotherapy: a well-established standard

PFS: primary endpoint



Not optimal candidates for a combination chemotherapy with irinotecan or oxaliplatin

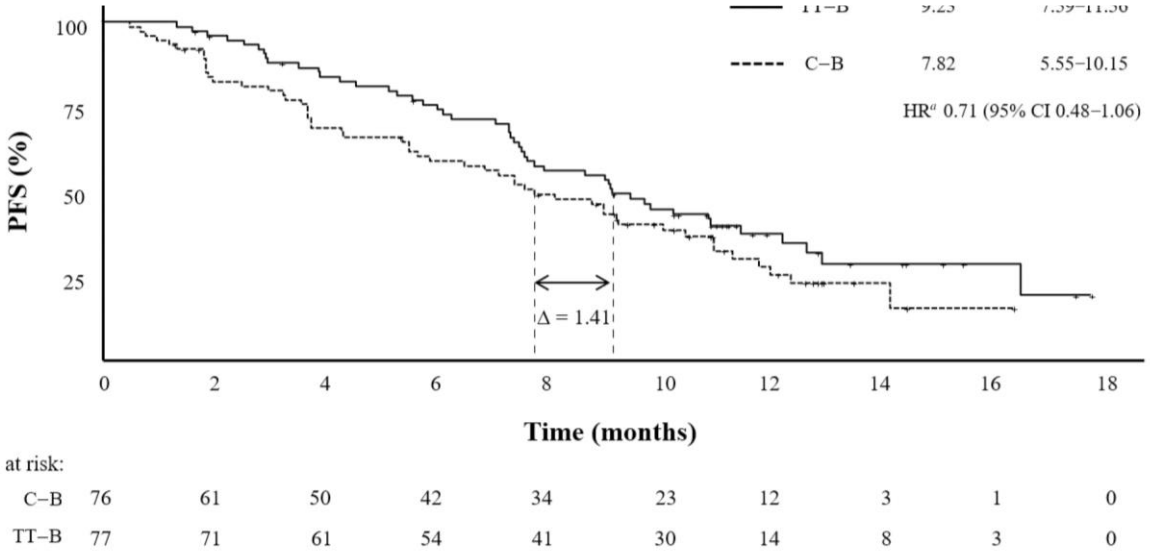
OS



Cunningham et al, Lancet Oncol 2013

Phase II TASCO1 study: TT/bev vs Cape/bev

PFS: primary endpoint

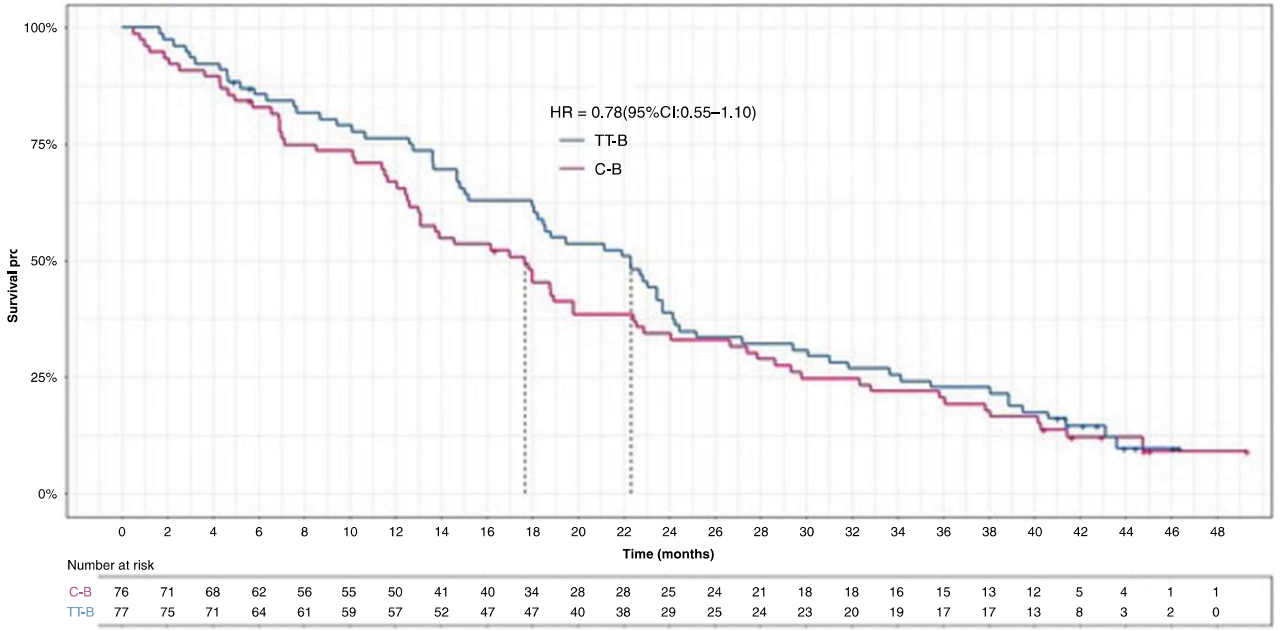


B

Van Cutsem al, Ann Oncol 2020

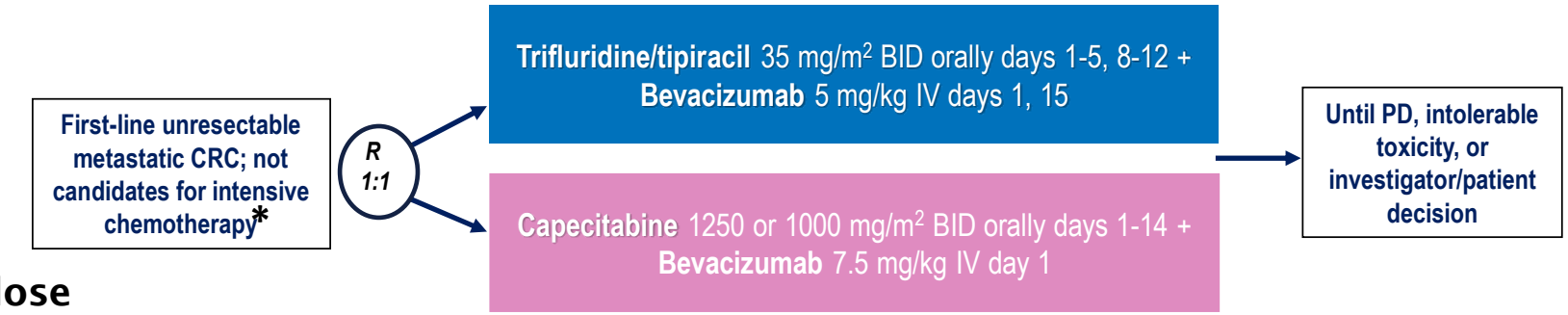
Not eligible for intensive chemotherapy

OS



Van Cutsem al, Br J Canc 2022

Phase III SOLSTICE study: TT/bev vs Cape/bev



*** Standard full dose combination chemotherapy with oxaliplatin or irinotecan**

Main reason for not being candidate for Intensive Therapy*		TT+BEV (n = 425) n	TT+BEV (n = 425) (%)	C+BEV (n = 430) n	C+BEV (n = 430) (%)
Clinical conditions	ECOG	61	(14.3)	67	(15.6)
	Comorbidities	45	(10.6)	40	(9.3)
	Elderly	184	(43.3)	179	(41.6)
Non-clinical conditions	Low tumour burden	52	(12.2)	57	(13.3)
	Patient's preference	77	(18.1)	80	(18.6)
	Other	6	(1.4)	7	(1.6)

* As per investigator's notification
* Each patient can have more than one clinical and/or non-clinica

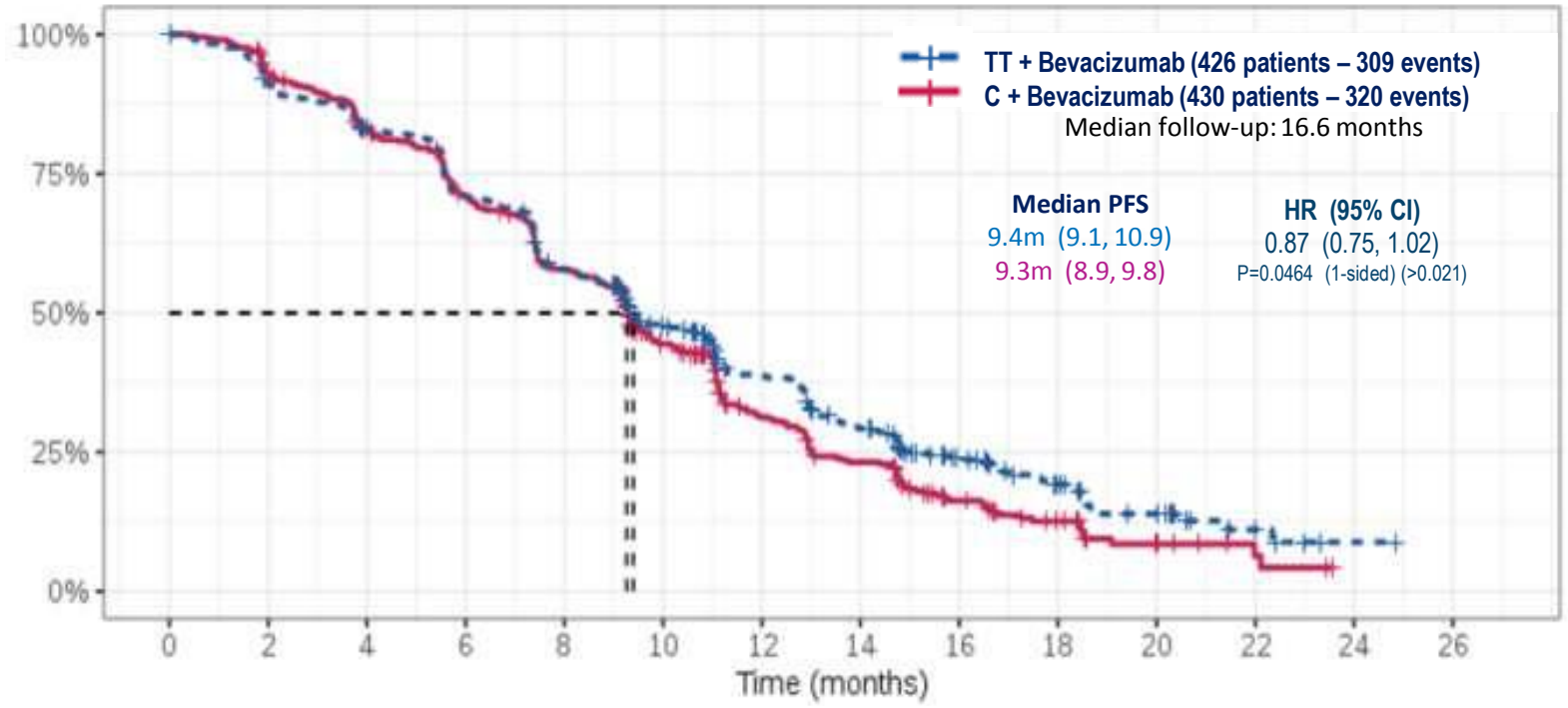
PATIENT CHARACTERISTICS

		TT+BEV (n = 426) n	TT+BEV (n = 426) (%)	C+BEV (n = 430) n	C+BEV (n = 430) (%)
Gender	Male	240	(56.3)	226	(52.6)
Age	Median [range]	73 [27;93]		73 [22;92]	
	□	210	(49.3)	225	(52.3)

André al, ESMO Virtual Plenary Dec '21

Phase III SOLSTICE study: TT/bev vs Cape/bev

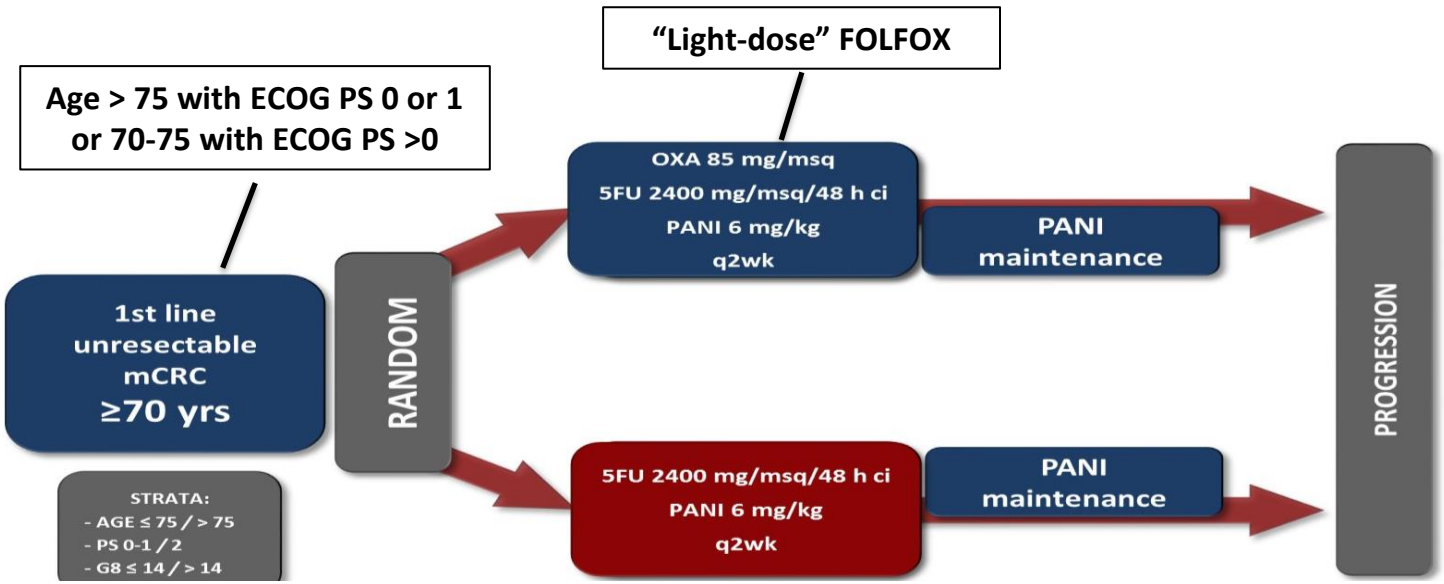
PFS: primary endpoint



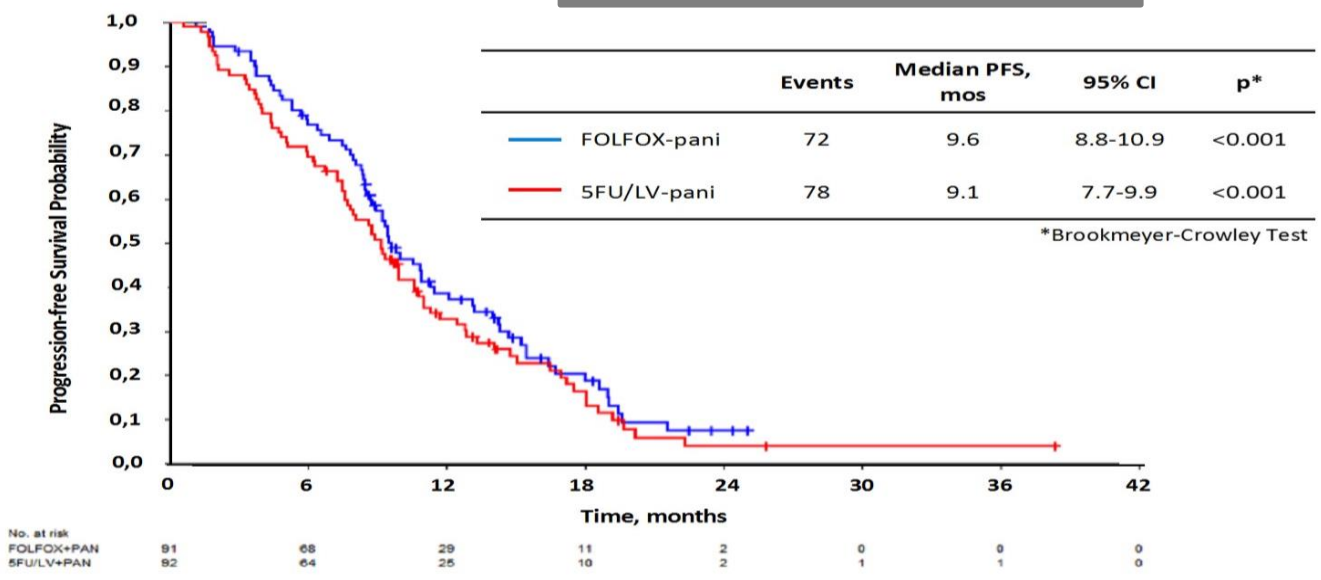
ORR: 36% (TT/bev) and 42% (cape/bev)
DCR: 86% (TT/bev) and 85% (cape/bev)

André al, ESMO Virtual Plenary Dec '21

Phase II PANDA study: 5FU/pan vs «light» FOLFOX/Pan in *RAS/BRAF* wt



PFS: primary endpoint

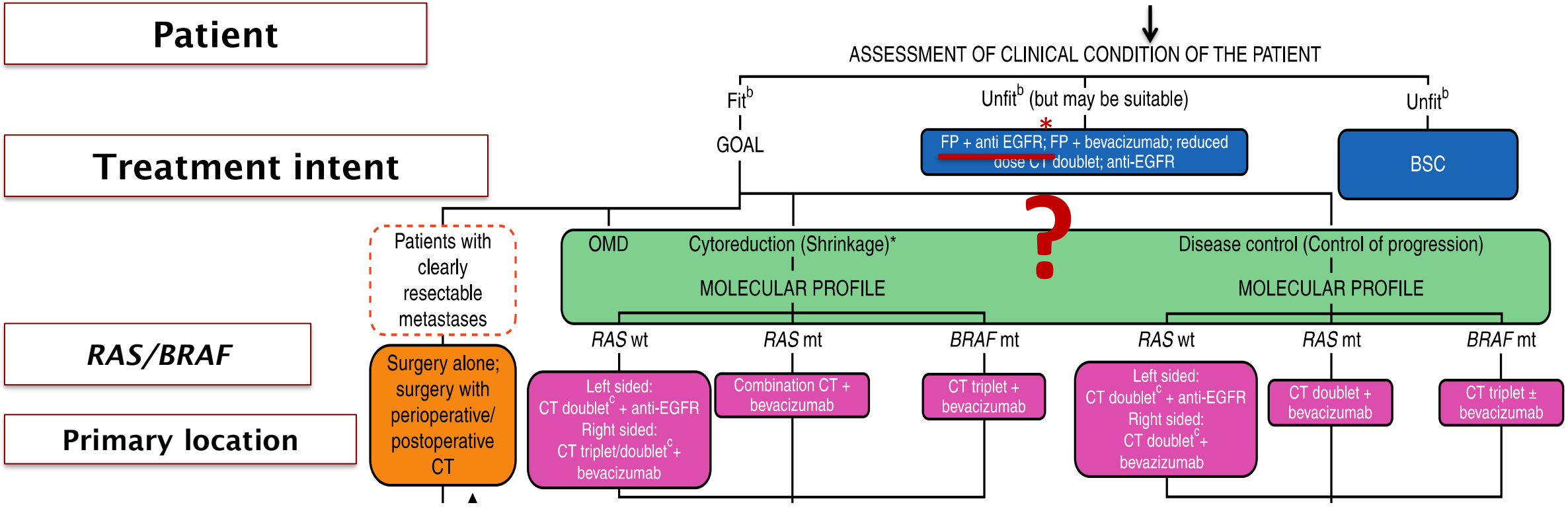


	Events	Median PFS, mos	95% CI	p*
FOLFOX-pani	72	9.6	8.8-10.9	<0.001
5FU/LV-pani	78	9.1	7.7-9.9	<0.001

*Brookmeyer-Crowley Test

ORR: 65% (FOLFOX/pan) and 57% (5FU/pan)
DCR: 88% (FOLFOX/pan) and 86% (5FU/pan)

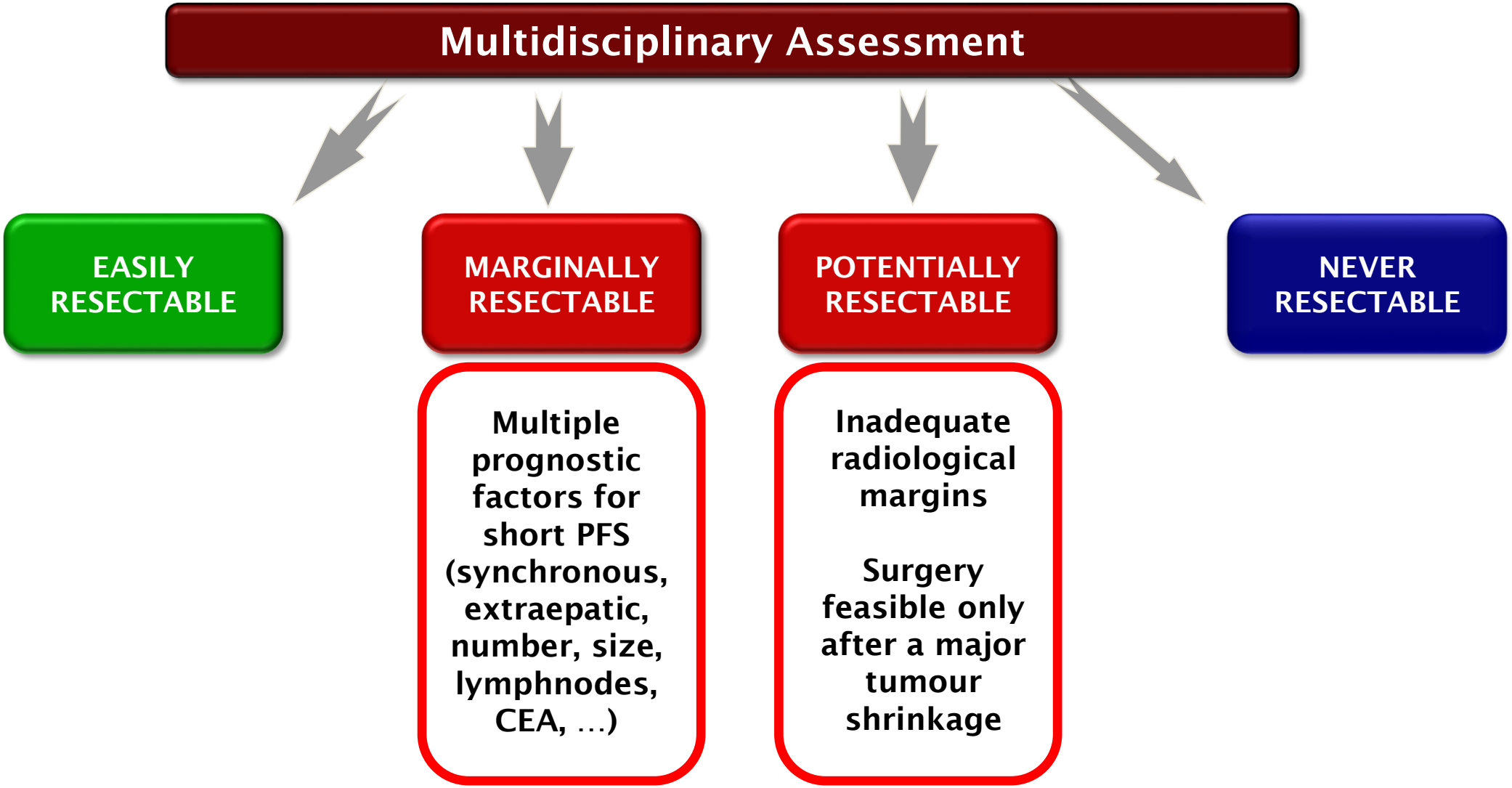
Lonardi et al, ASCO Ann Meet '20



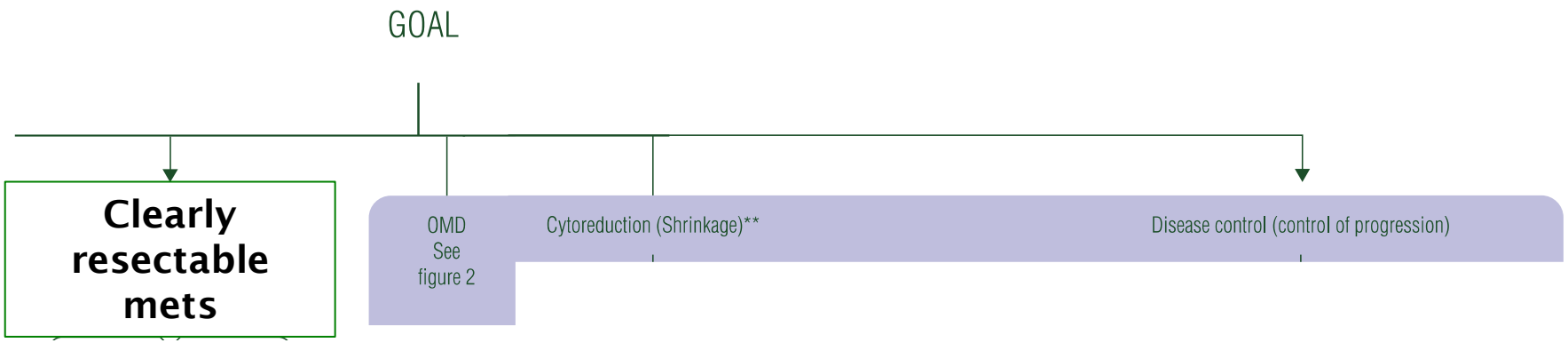
*** According to primary location and *RAS/BRAF* status**

Yoshino et al., Ann Oncol '18

According to our school books…



Clearly resectable metastases: guidelines



Surgery → +/- "adjuvant" oxaliplatin-based chemo
(favourable prognostic criteria)

Oxa-based doublet → Surgery → Oxa-based doublet
(unfavourable prognostic criteria)

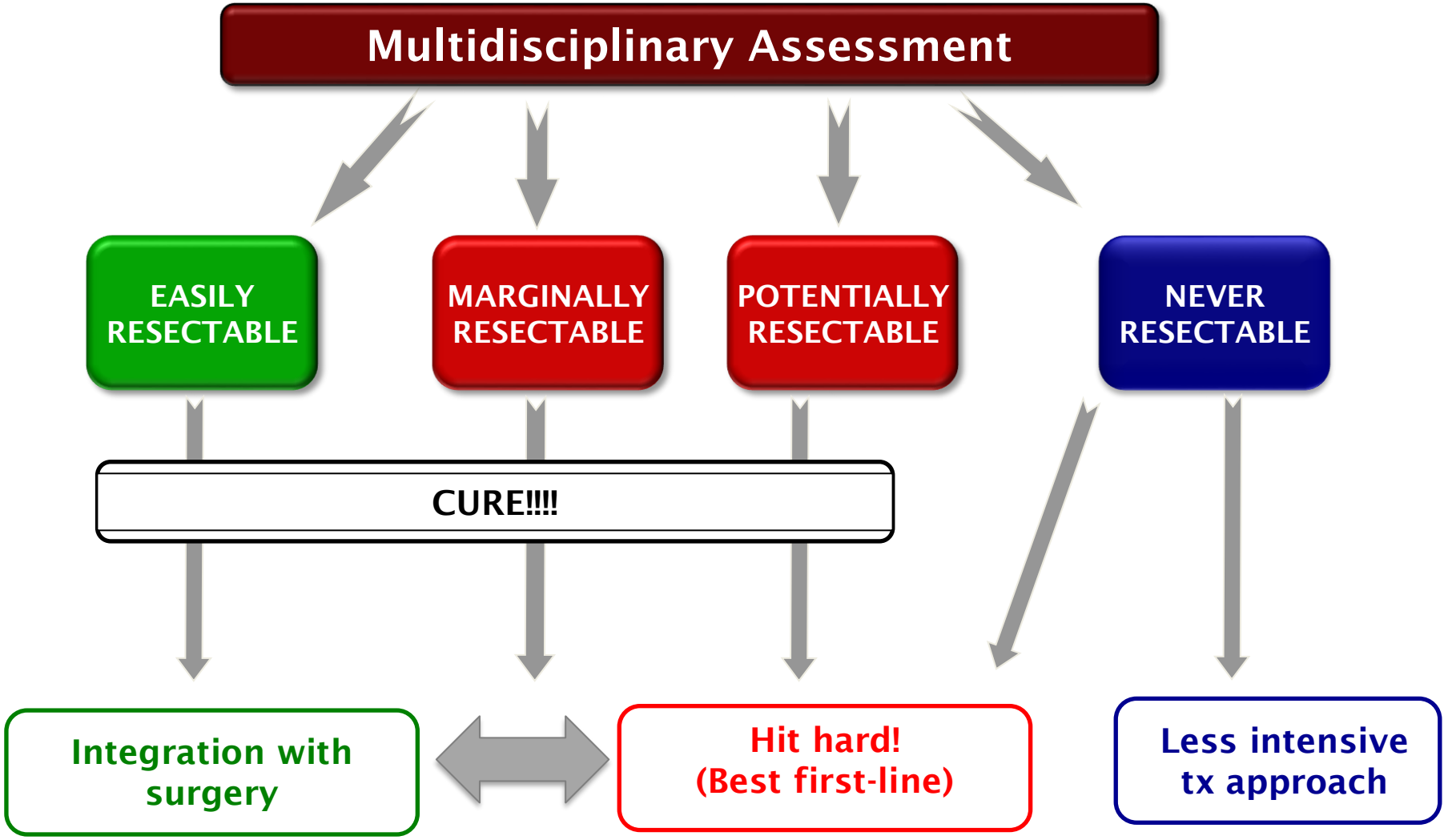
<u>No targeted agents</u>

Clinical Prognostic Models

MIND THE GAP

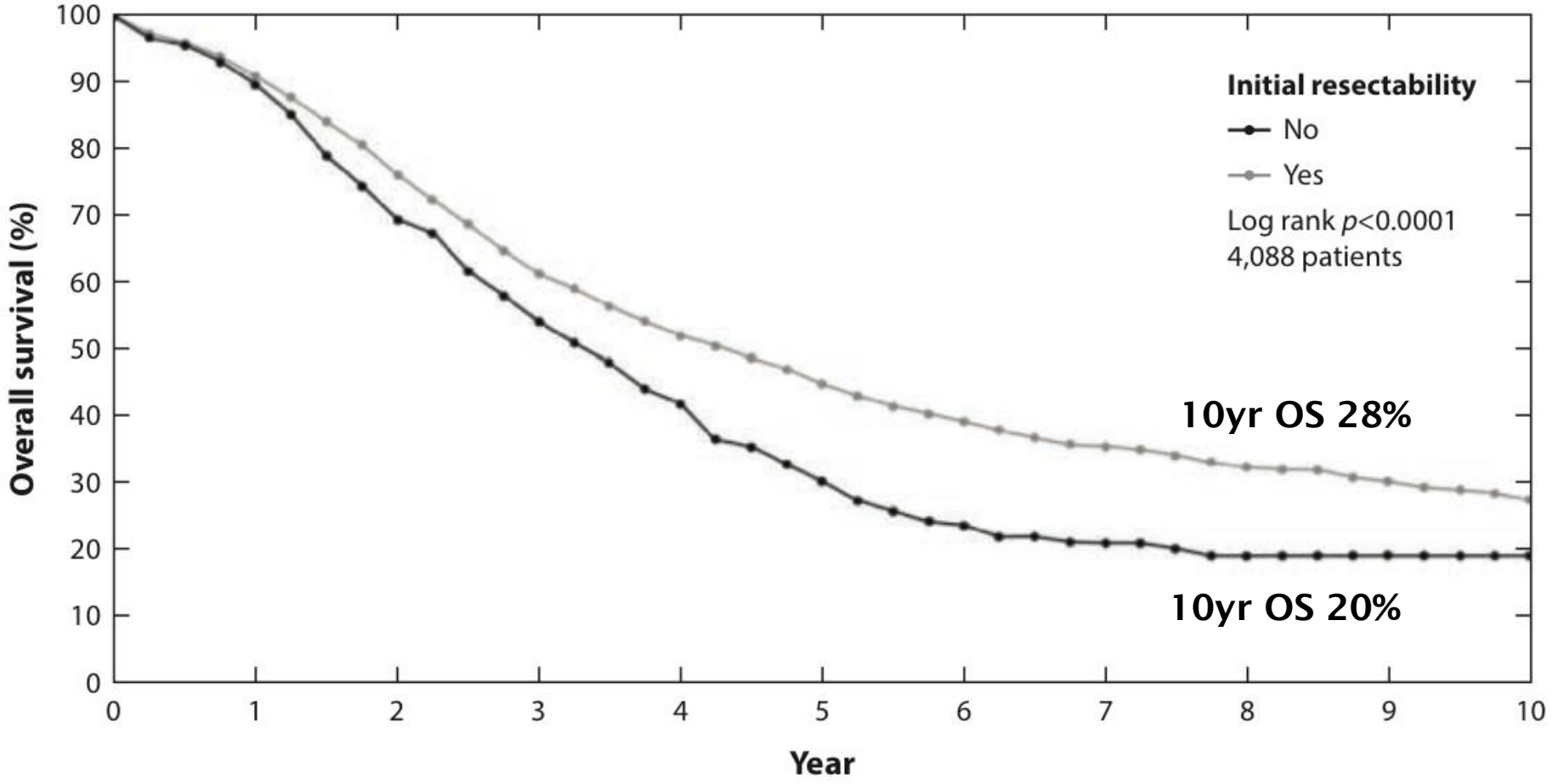
	Rees	Malik	Minagawa	Konopke	Nordlinger	Fong	Zakaria	Yamaguchi	Iwatsuki	Tan	Schindl	Tanaka	Lise	Ueno	Nagashima
Number of met‘s	+	+	+	+	+	+	-	+	+	-	+	-	+	+	+
Nodal status	+	-	+		+	+	-	+	-	+	+	-	+	+	+
Max. size of met‘s	+	-	-	-	+	+	-	+	+	-	-	-	-	-	+
Interval primary-met‘s		-	-		+	+	-		+					+	+
CEA	+	-	+	+	-	+	-			-	+		-	-	-
Extrahep. spread	+		-			+		+	+			-			+
Positive margins	+	-				+	-		+						
Poorly diff. tumour	+		-						-	+	-	+		-	
Serosal invasion					+							-		-	+
Hepat. lymph nodes			+				+								
Bilobar spread	-		-		-	-	-		+	-	-	+		-	-

Spelt et al, Eur J Cancer Surg 2012


Multidisciplinary Assessment
EASILY RESECTABLE
MARGINALLY RESECTABLE
POTENTIALLY RESECTABLE
NEVER RESECTABLE
CURE!!!!
Integration with surgery
Hit hard! (Best first-line)
Less intensive tx approach

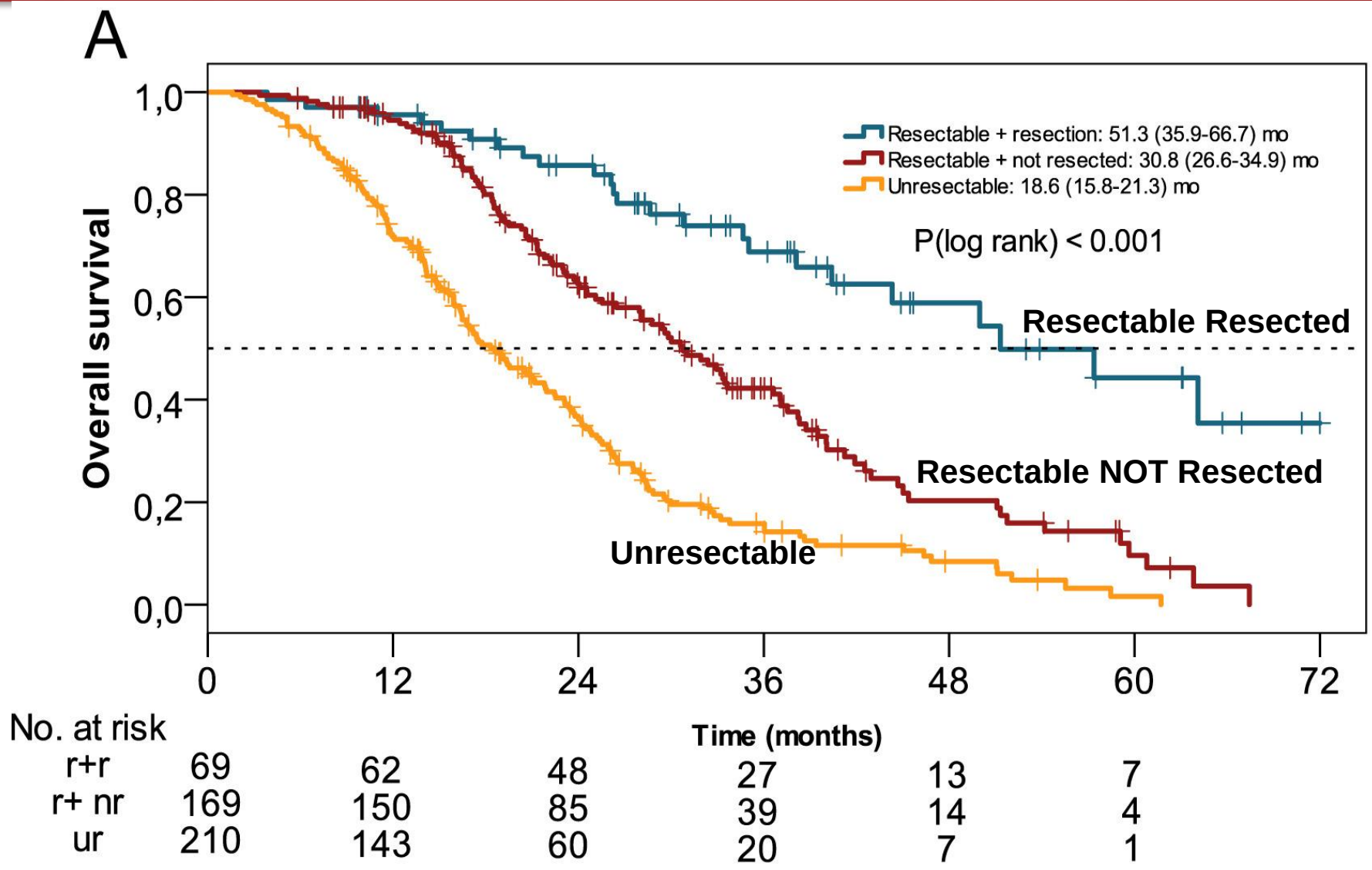
To cure? …Yes, WE CAN!

Survival following hepatectomy for colorectal liver metastases



Jones and Poston, Annu Rev Med 2017

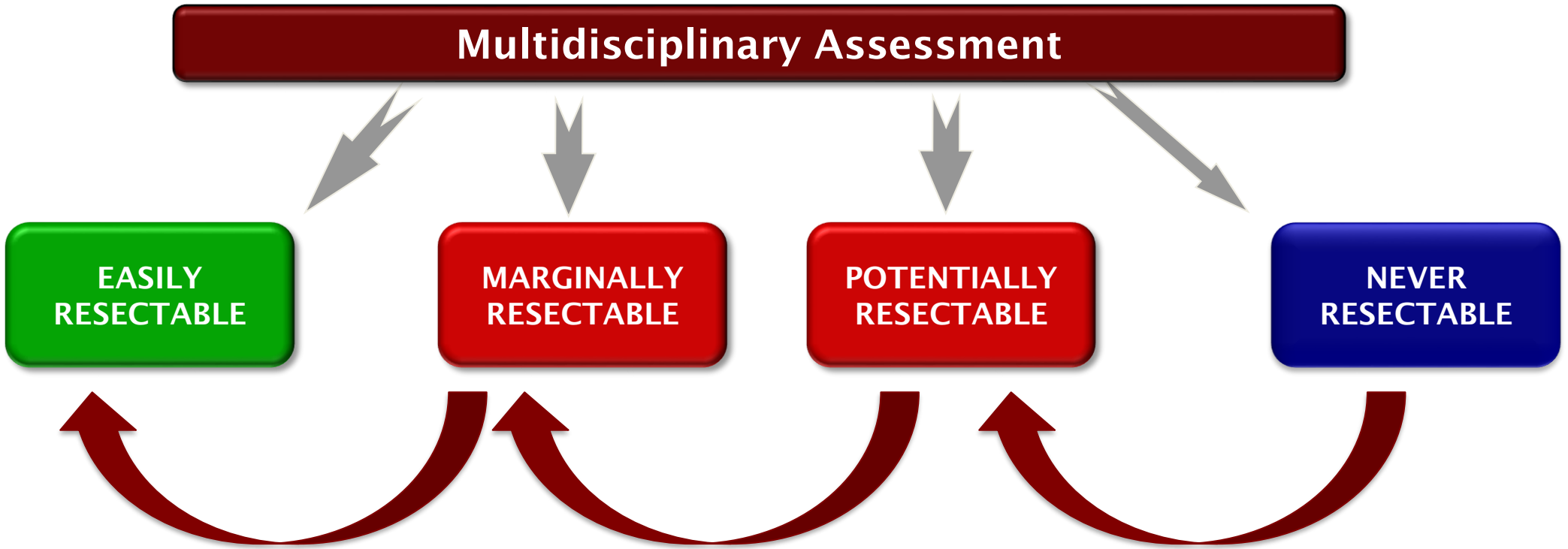
Overall survival according to surgical treatment in FIRE-3

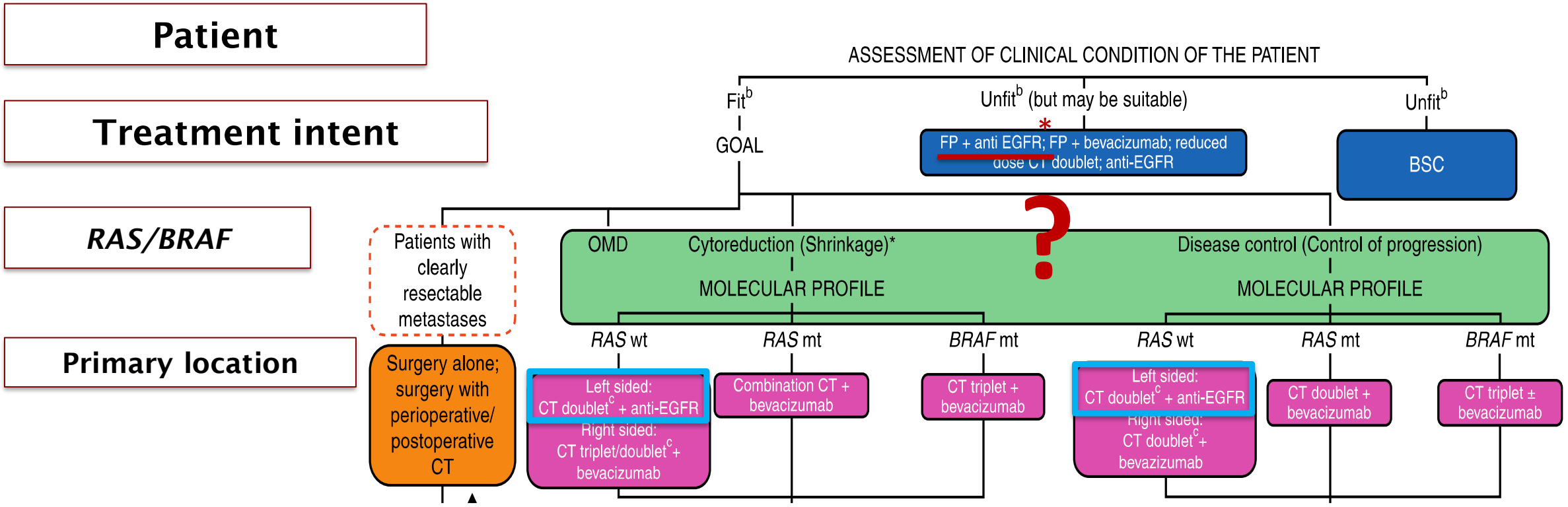


Modest, EJC 2017

Surgeons are “raising the bar” of resectability

As a consequence…



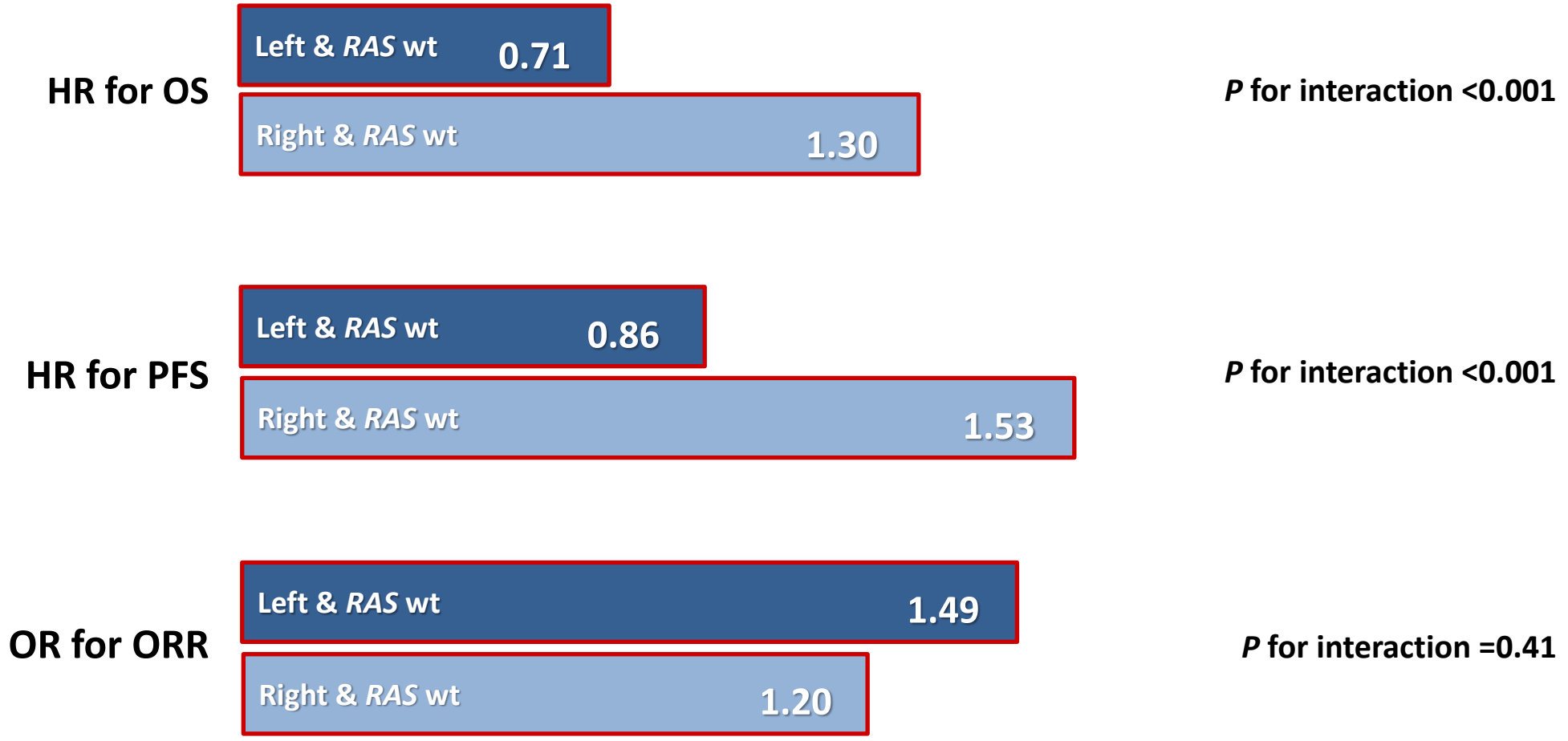


*** According to primary location and *RAS/BRAF* status**

Yoshino et al., Ann Oncol '18

Primary tumor location matters

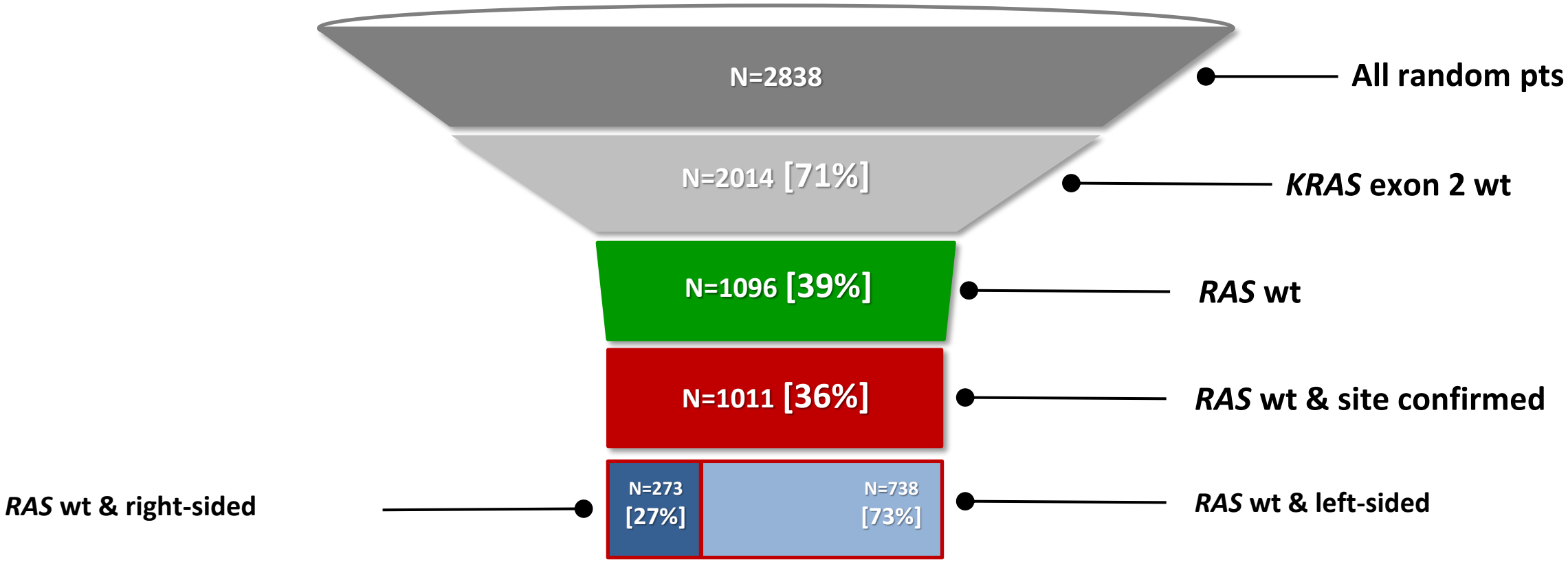
Pooled analysis of the FIRE-3, CALGB80405 and PEAK trial



Holch et al, Eur J Canc '17

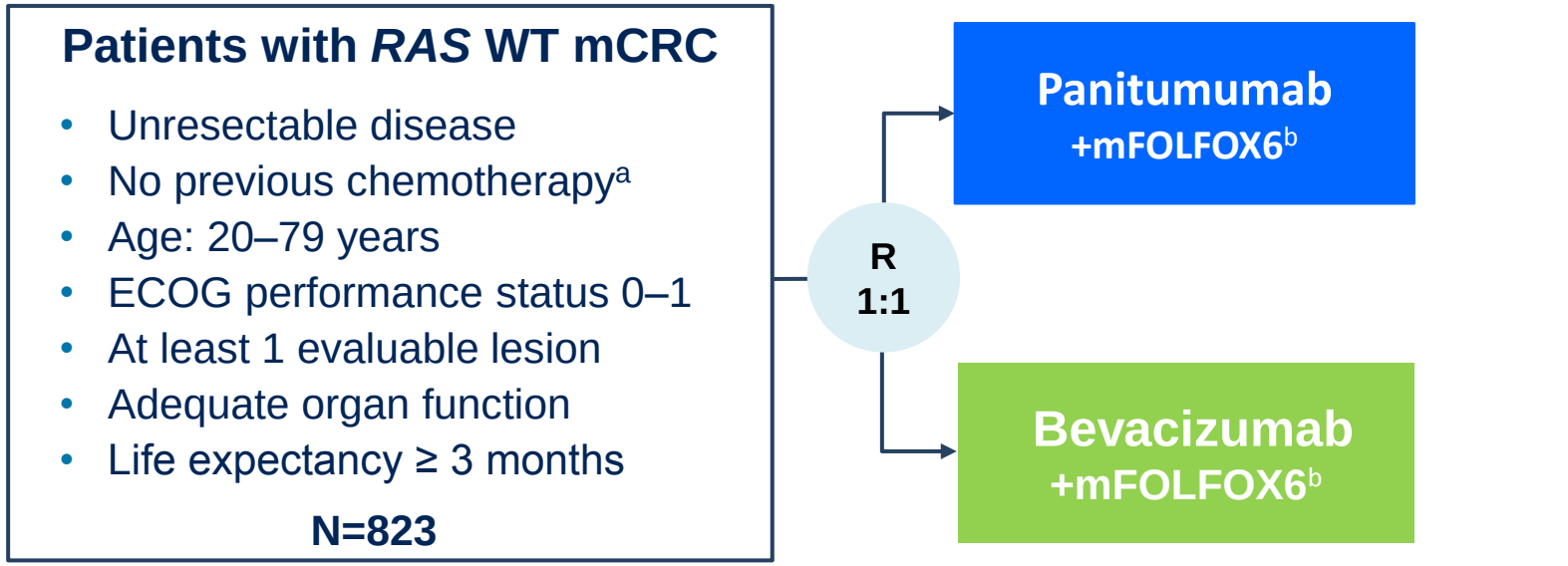
Right *versus* left in *RAS* wt mCRC

Pooled analysis of the FIRE-3, CALGB80405 and PEAK trial
From ITT to subgroups



Phase III PARADIGM trial: mFOLFOX6/pan vs mFOLFOX6/bev in *RAS* wt

Phase 3, randomized, open-label, multicenter study (NCT02394795)

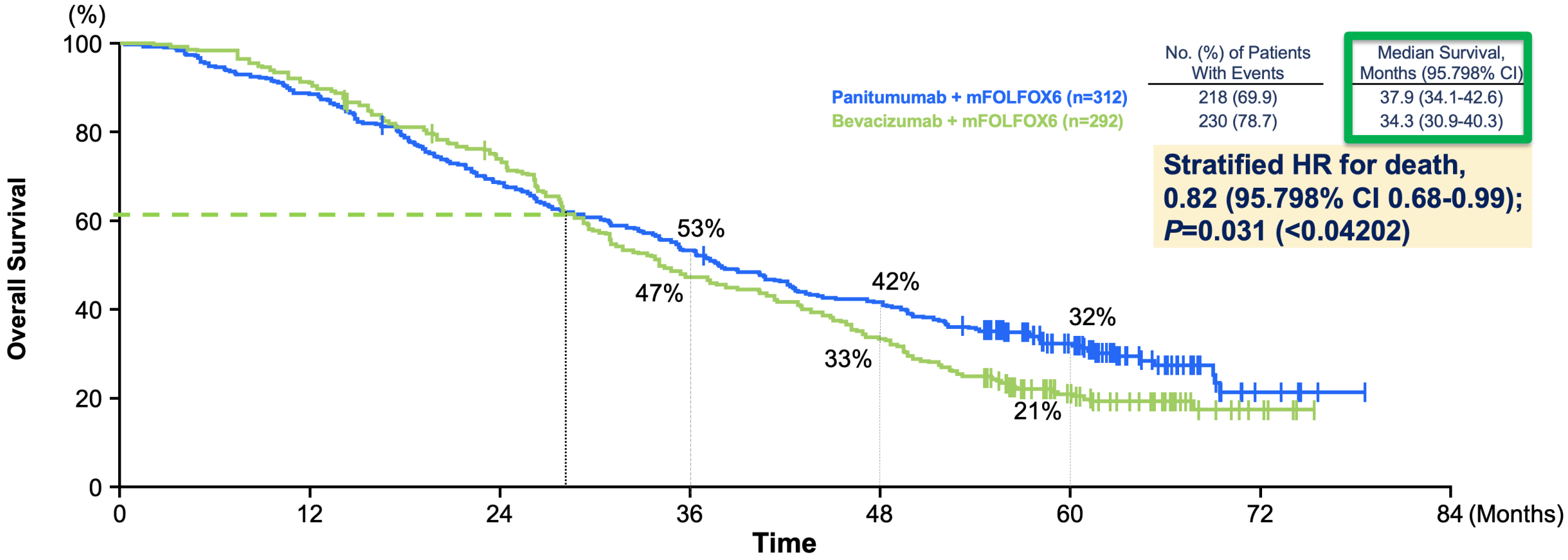


Stratification factors

- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

Yoshino et al, ASCO '22

Primary endpoint: OS in left-sided

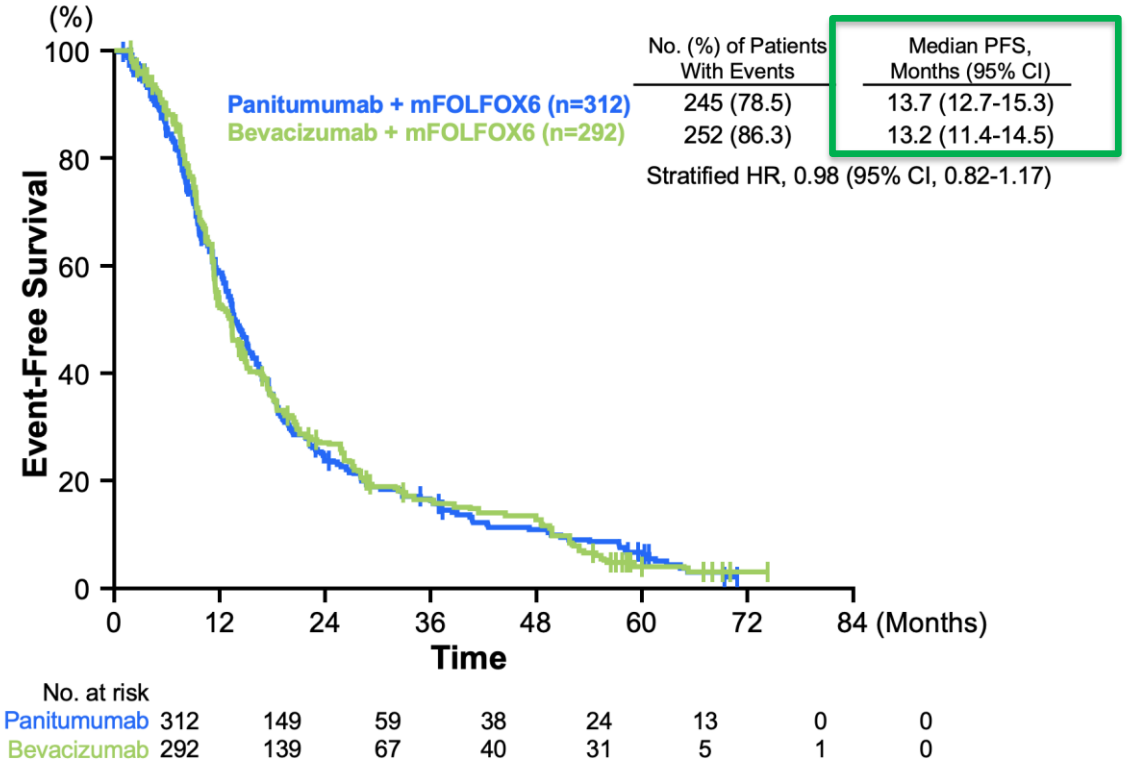


No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

Yoshino et al, ASCO '22

Secondary endpoints: RR and PFS in the left-sided

Parameter	Left-sided Population	
	Panitumumab + mFOLFOX6 (n=308)	Bevacizumab + mFOLFOX6 (n=287)
Response rate, % (95% CI)	80.2 (75.3–84.5)	68.6 (62.9–74.0)
Difference (95% CI)	11.2 (4.4–17.9)	
Disease control rate, % (95% CI)	97.4 (94.9–98.9)	96.5 (93.7–98.3)
Median duration of response,* months (95%CI)	13.1 (11.1–14.8)	11.2 (9.6–13.1)
Curative resection rate,† % (95% CI)	18.3 (14.1–23.0)	11.6 (8.2–15.9]



Yoshino et al, ASCO '22

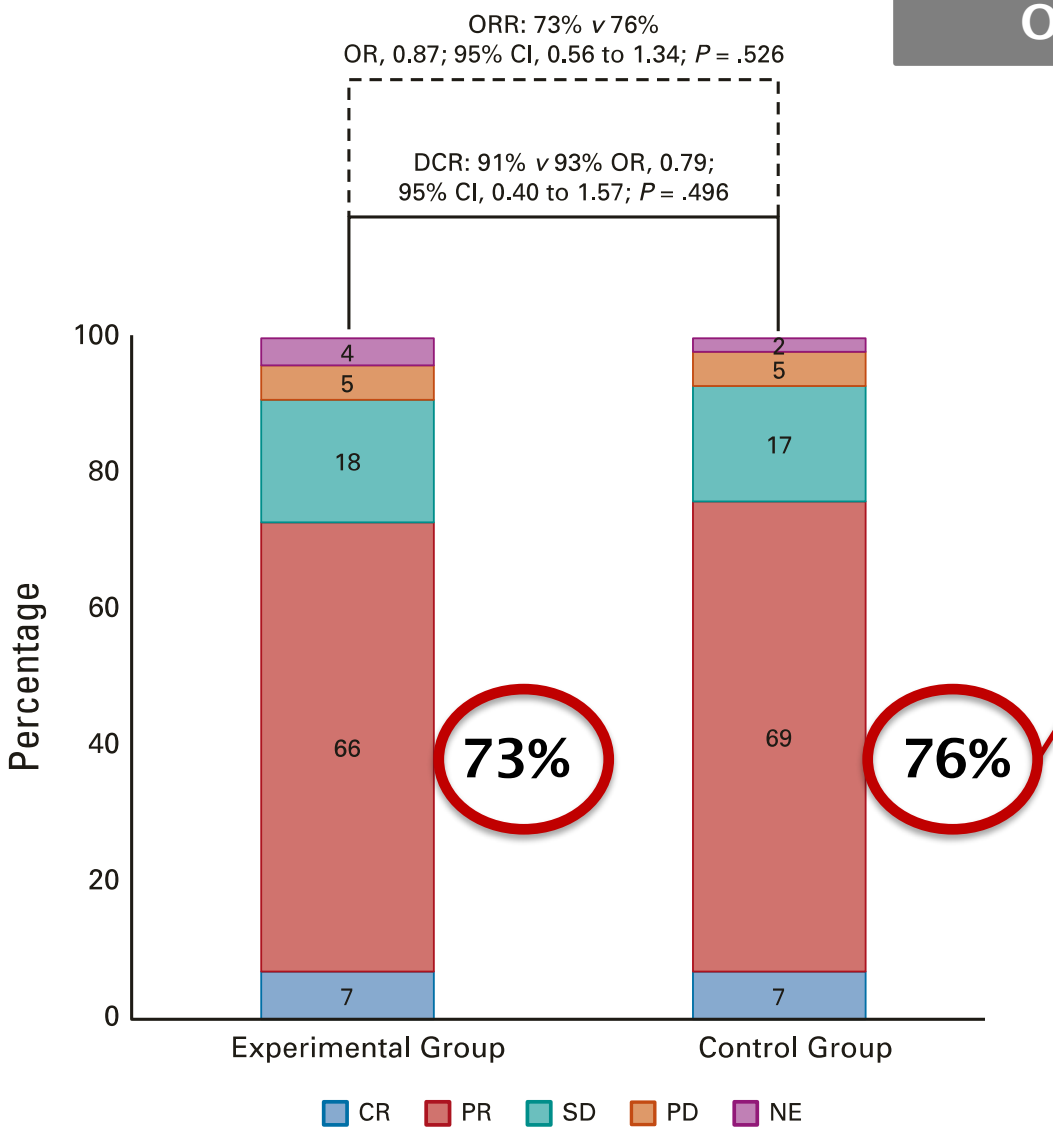
Doublets plus anti-EGFR in RAS wt left-sided mCRC

	mPFS (mos)	mOS (mos)	ORR (%)
TRIPLETE** [mFOLFOX6/pan] n=191	13.6	NA	75.9
PARADIGM [mFOLFOX6/pan] n=312	13.7	37.9	80.2
FIRE-3 [FOLFIRI/cet] n=157	10.7	38.3	68.8
CALGB80405 [chemo doublet*/cet] N=173	12.7	39.3	69.4
PEAK [mFOLFOX6/pan] n=53	14.6	43.4	64.1

*FOLFOX or FOLFIRI at investigator choice; ***RAS* and *BRAF* wt

Arnold et al, Ann Oncol '17; Holch et al, Eur J Can '17; Yoshino et al, ASCO '22; Rossini et al, J Clin Oncol '22

Phase III TRIPLETE trial: mFOLFOXIRI/pan vs mFOLFOX6/pan in *RAS/BRAF* wt



ORR: primary endpoint

Expected ORR in control group: 60%*

To detect a ≥ 15% increase in ORR in arm B

2-sided alpha-error= 0.05; beta-error=0.10

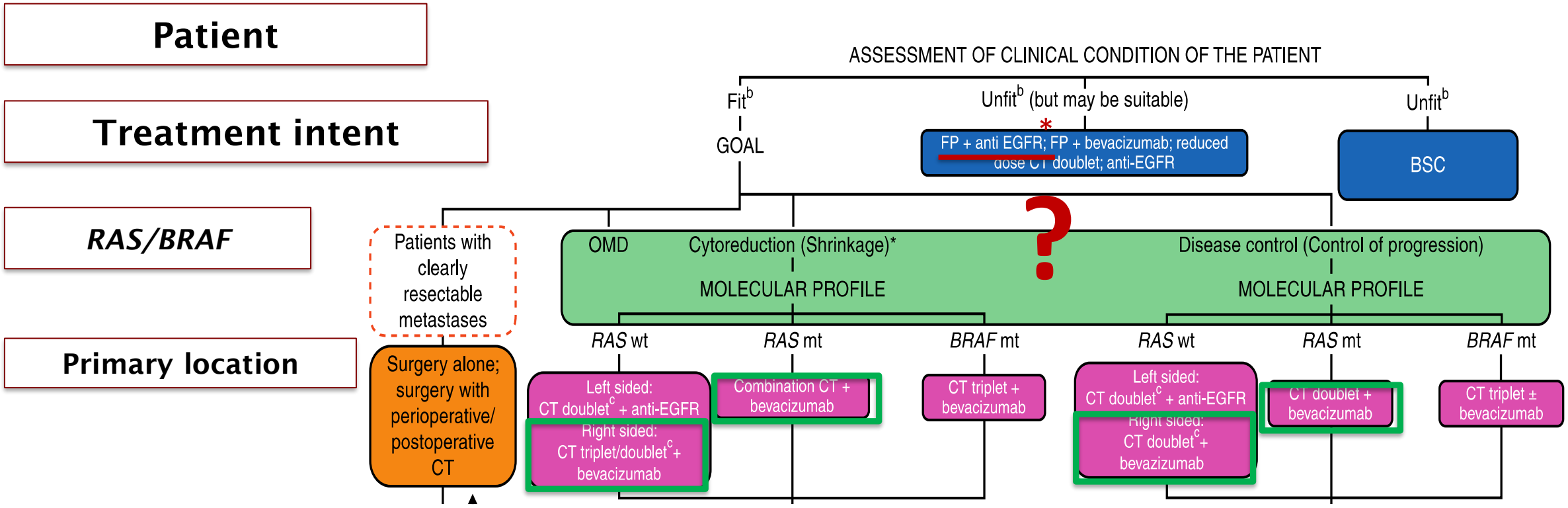
1:1 randomization ratio

→ 432 patients to be randomized

***Douillard et al, Nejm '13*

Left-sided primary tumor: 88%

Rossini et al, J Clin Oncol '22



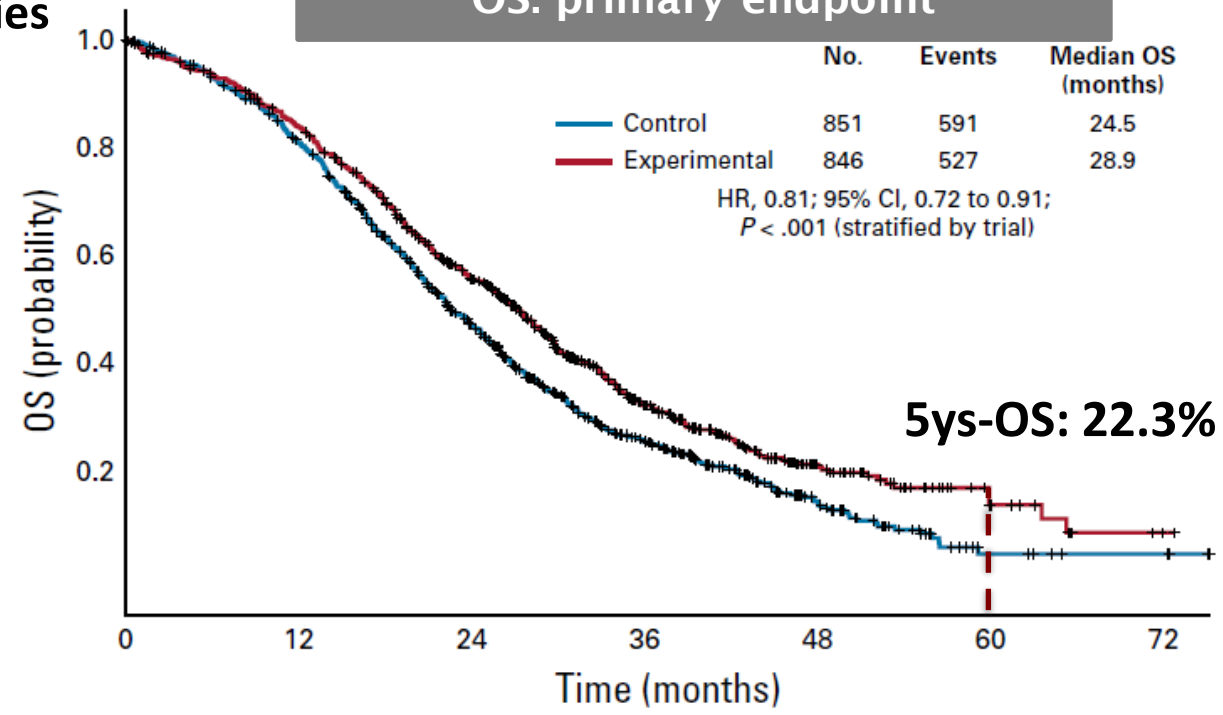
*** According to primary location and *RAS/BRAF* status**

Yoshino et al., Ann Oncol '18

IPD-based metanalysis: FOLFOXIRI/bev vs doublets/bev

Metanalysis of 5 random studies
N= 1697

OS: primary endpoint



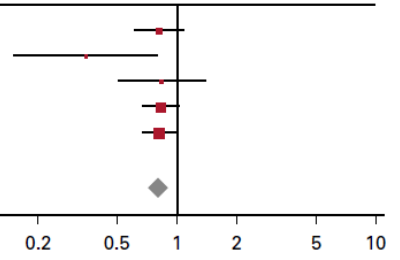
5ys-OS: 22.3% vs 10.7%

No. at risk:

Control	851	677	377	169	55	9	4
Experimental	846	704	446	190	60	15	2

Study or Subgroup	LogHR	SE	FOLFOXIRI + Bev Total	Doublet + Bev Total	Weight, %	HR IV, Fixed, 95% CI
CHARTA	−0.1972	0.1433	121	121	17.6	0.82 [0.62 to 1.09]
OLIVIA	−1.0498	0.4222	41	39	2.0	0.35 [0.15 to 0.30]
STEAM	−0.1708	0.2534	93	95	5.6	0.84 [0.51 to 1.39]
TRIBE	−0.1791	0.1039	252	256	33.5	0.84 [0.68 to 1.02]
TRIBE2	−0.2009	0.0935	339	340	41.3	0.82 [0.68 to 0.98]
Total (95% CI)			846	851	100.0	0.81 [0.72 to 0.91]

Heterogeneity: χ^2, 4.09; df = 4; P = .39; I^2 = 2%
Test for overall effect: Z = 3.47; P = .0005



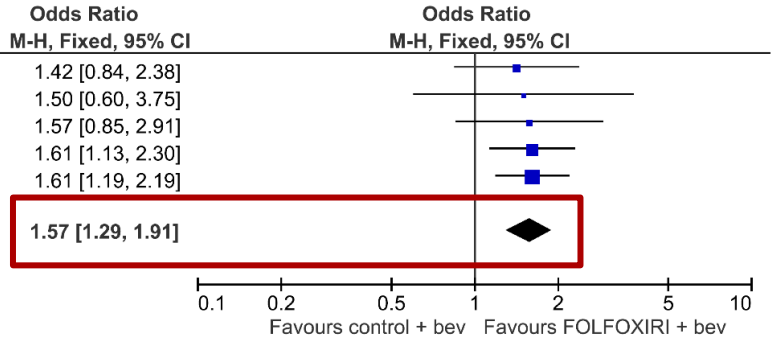
Cremolini et al, J Clin Oncol '20

IPD-based metanalysis: FOLFOXIRI/bev vs doublets/bev

ORR: secondary endpoint

Study or Subgroup	FOLFOXIRI + bev Events	Total	Doublet + bev Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CHARTA	79	121	69	121	14.9%	1.42 [0.84, 2.38]
OLIVIA	28	41	23	39	4.7%	1.50 [0.60, 3.75]
STEAM	67	93	59	95	10.2%	1.57 [0.85, 2.91]
TRIBE	161	252	134	256	29.9%	1.61 [1.13, 2.30]
TRIBE2	210	338	171	339	40.3%	1.61 [1.19, 2.19]
Total (95% CI)		**845**		**850**	**100.0%**	**1.57 [1.29, 1.91]**
Total events	545		456			

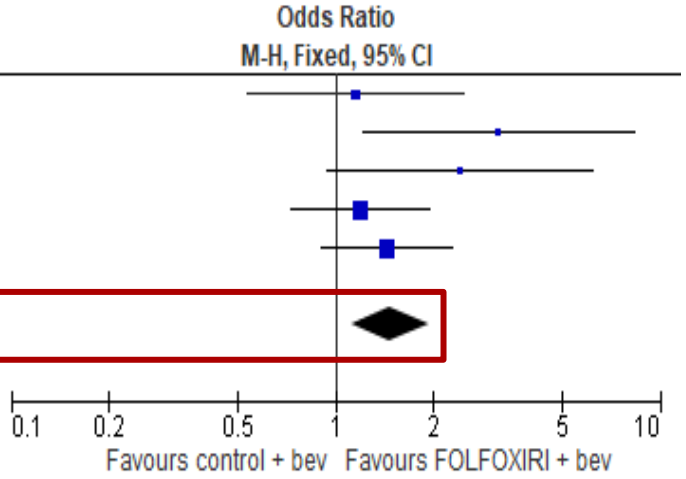
Heterogeneity: Chi² = 0.21, df = 4 (P = 1.00); I² = 0%
Test for overall effect: Z = 4.54 (P < 0.00001)



R0 resection rate : secondary endpoint

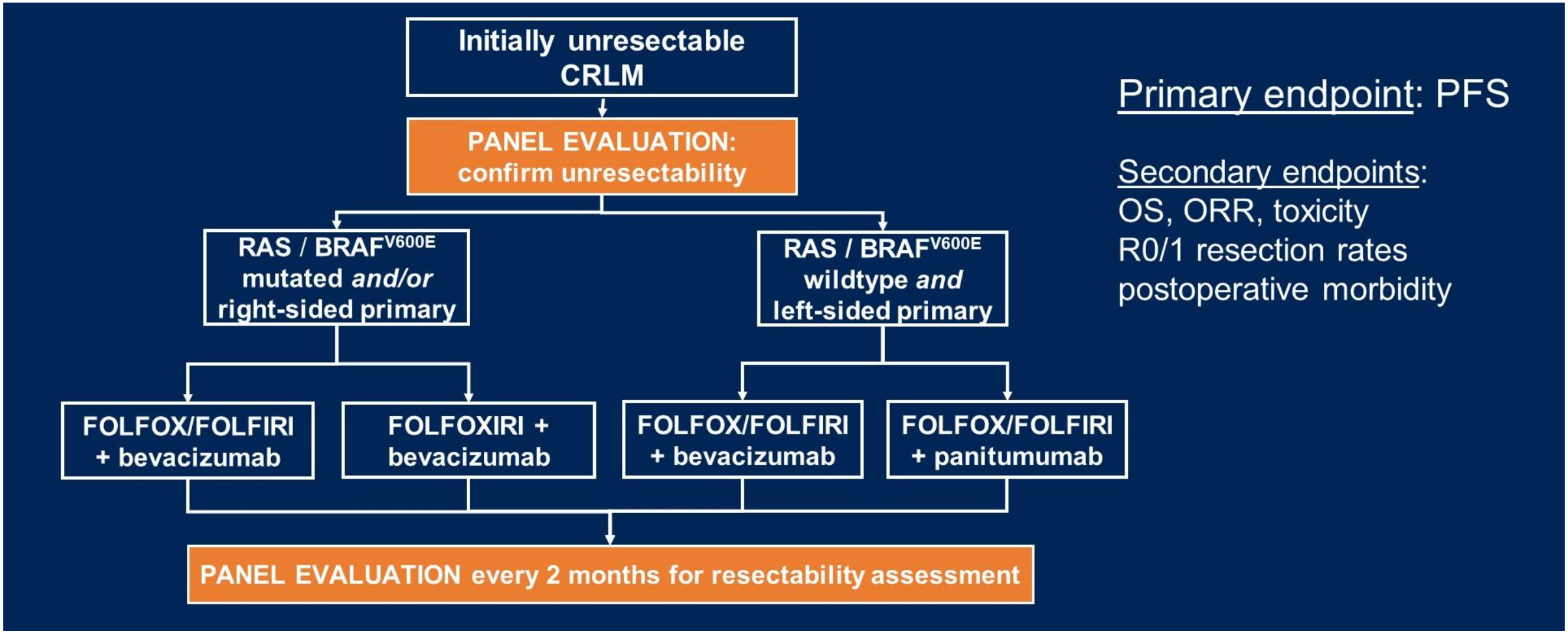
Study or Subgroup	FOLFOXIRI + bev Events	Total	Doublet + bev Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CHARTA	16	121	14	120	14.9%	1.15 [0.54, 2.48]
OLIVIA	20	41	9	39	5.8%	3.17 [1.21, 8.33]
STEAM	15	93	7	95	7.1%	2.42 [0.94, 6.24]
TRIBE	40	252	35	256	35.6%	1.19 [0.73, 1.95]
TRIBE2	48	339	35	340	36.6%	1.44 [0.90, 2.29]
Total (95% CI)		**846**		**850**	**100.0%**	**1.48 [1.12, 1.95]**
Total events	139		100			

Heterogeneity: Chi² = 4.61, df = 4 (P = 0.33); I² = 13%
Test for overall effect: Z = 2.74 (P = 0.006)



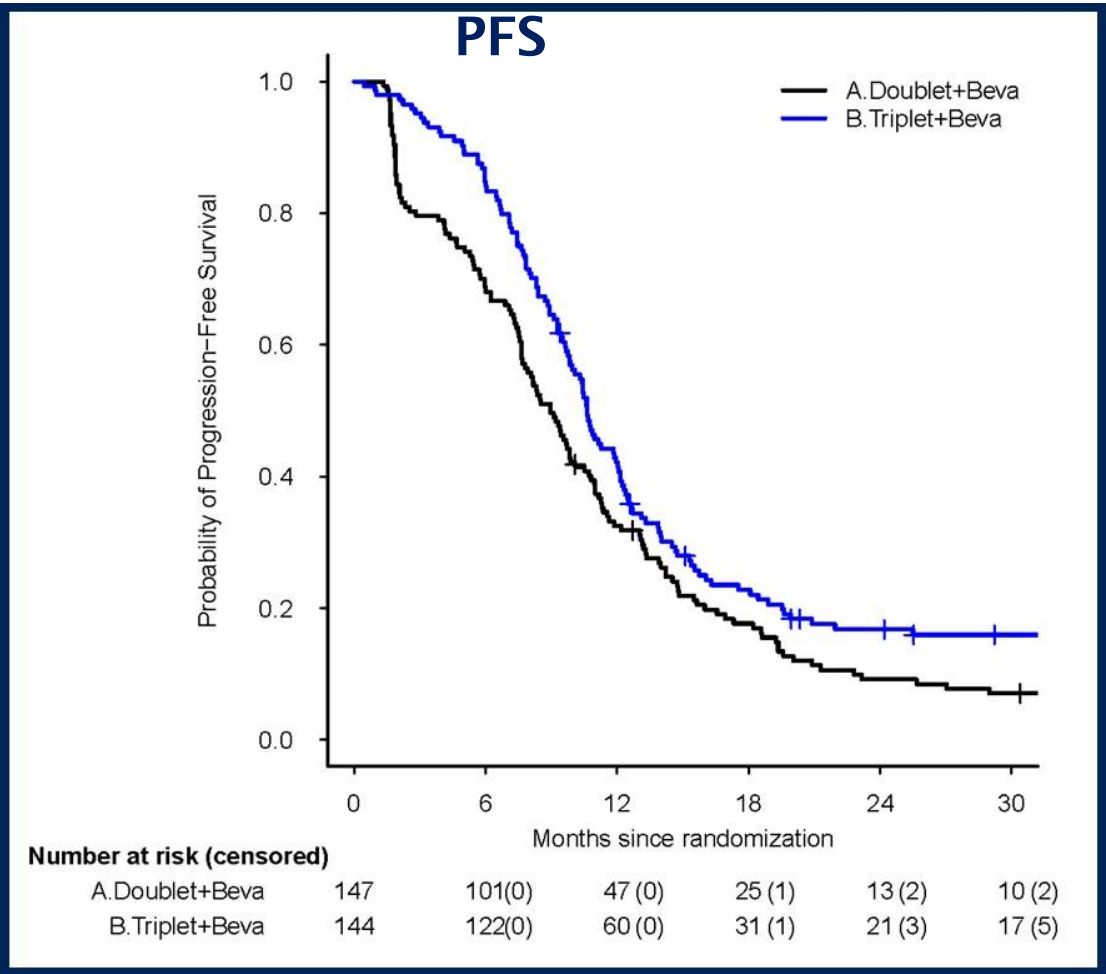
Cremolini et al, J Clin Oncol '20

CAIRO-5: study design



Punt et al, ASCO '22

CAIRO-5: results



Median follow up 41 months

FOLFOX/FOLFIRI + bevacizumab 9.0 months
FOLFOXIRI + bevacizumab 10.6 months

HR 0.77, 95% CI 0.60-0.99, p=0.038

Data on overall survival not yet mature

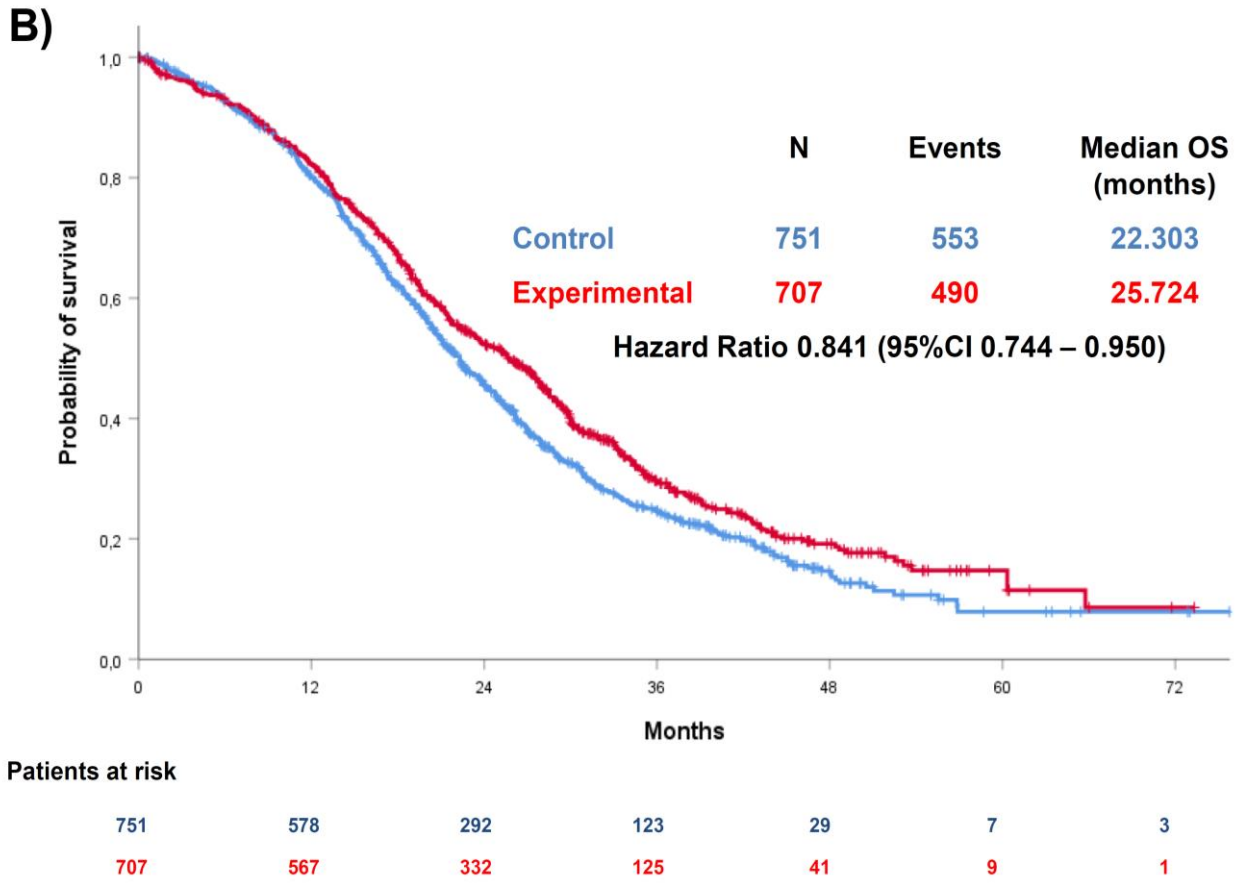
ORR: 54% vs 33%, p<0.001
R0/1 resection rate: 51% vs 37%, p=0.02

Punt et al, ASCO '22

IPD-based metanalysis: FOLFOXIRI/bev vs doublets/bev

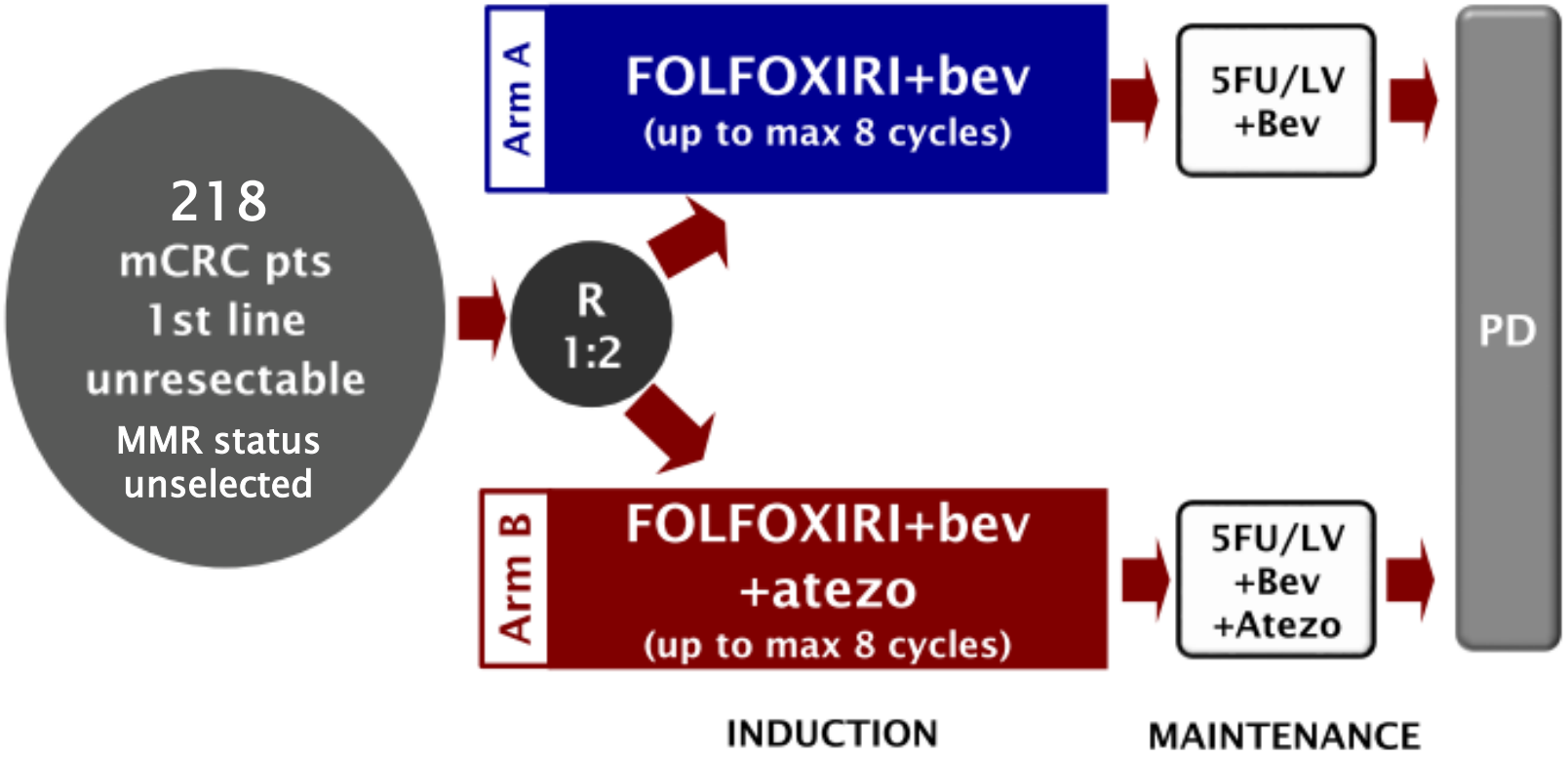
Metanalysis of 5 random studies
N= 1697

Subgroup of patients not undergoing R0 resection
N=1458



Cremolini et al, J Clin Oncol '20

AtezoTRIBE study design



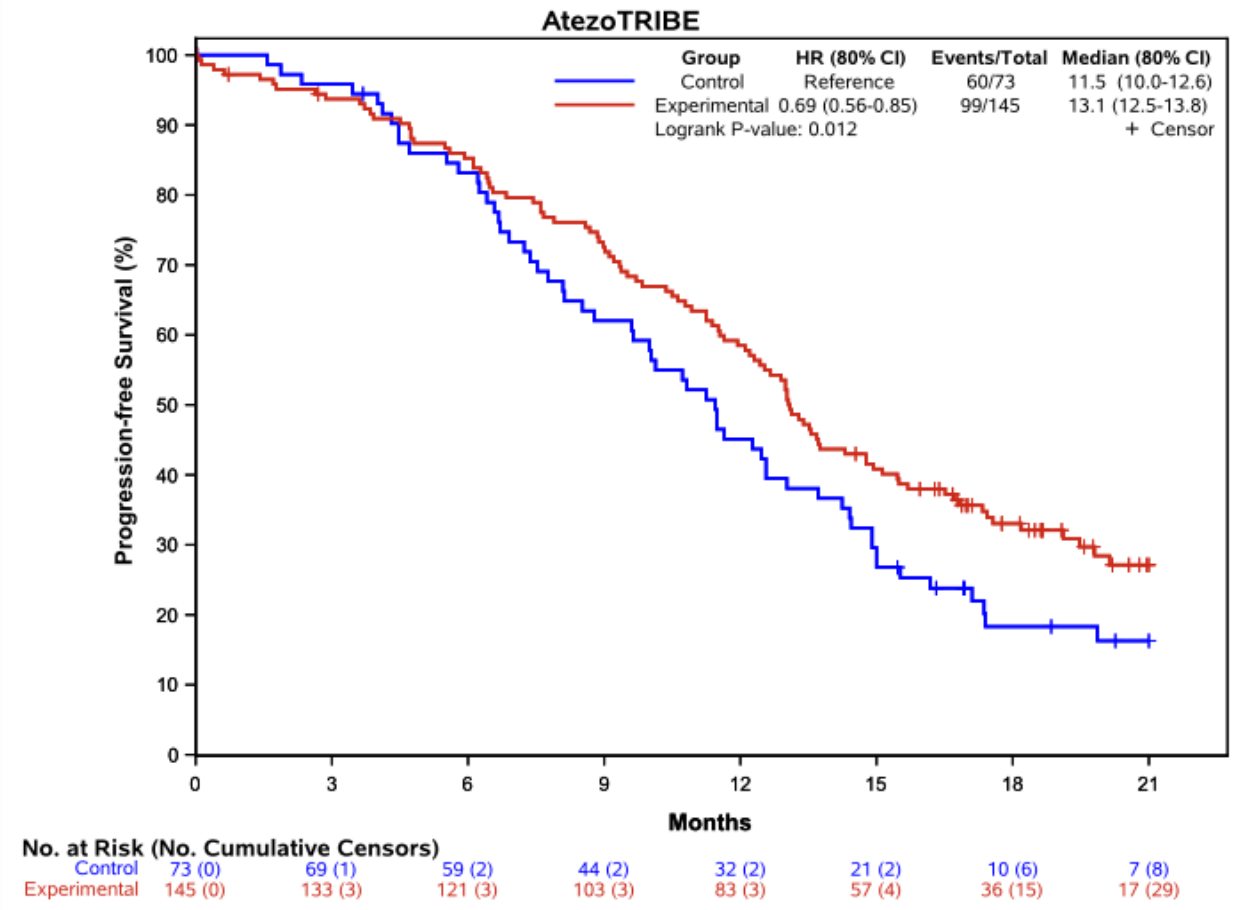
Stratification factors:

- Center
- PS 0 vs 1-2;
- primary tumor location (right vs left or rectum);
- Previous adjuvant CT

Primary endpoint: PFS

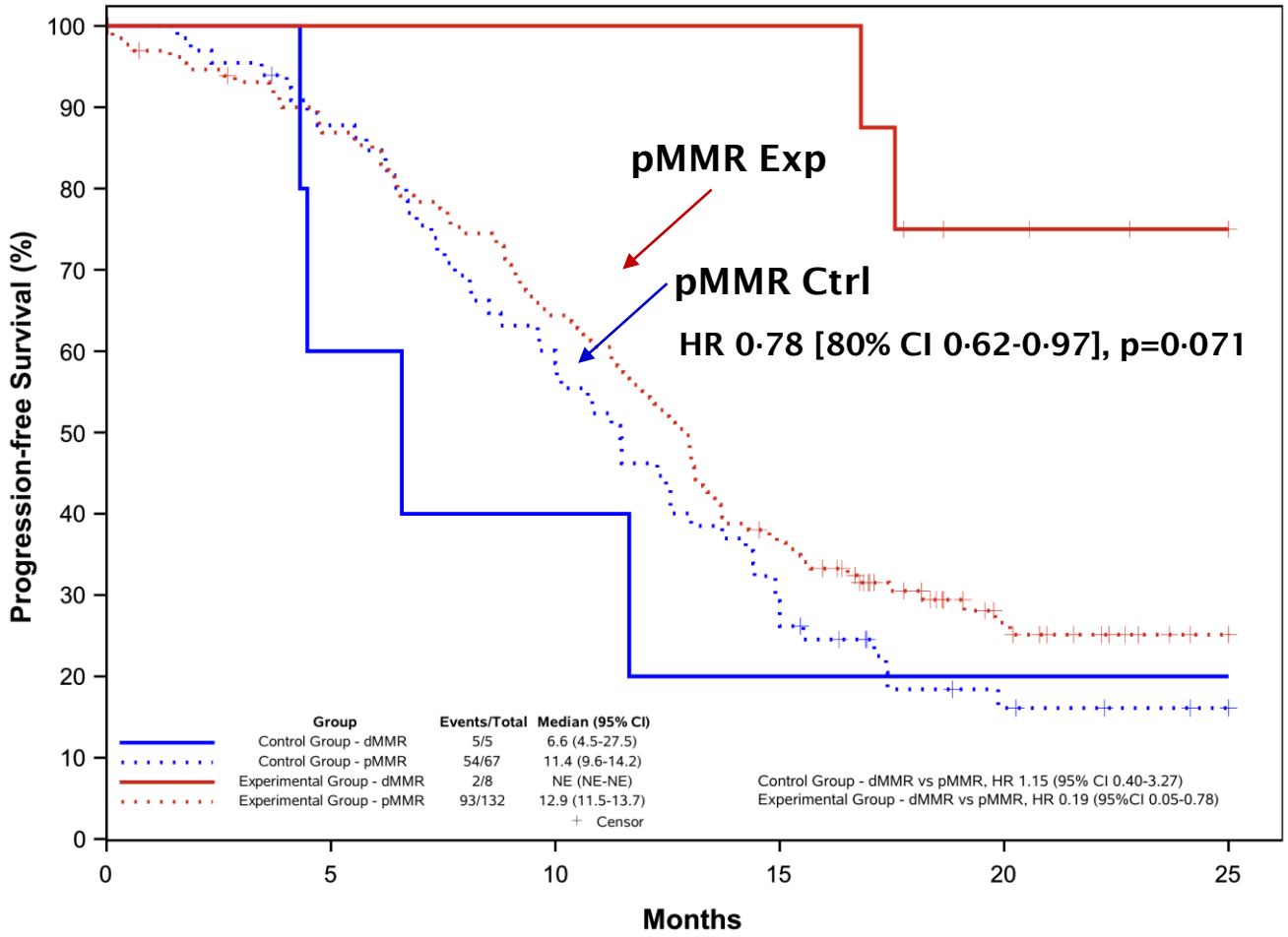
Phase II ATEZOTRIBE trial: FOLFOXIRI/bev/atezo vs FOLFOXIRI/bev

PFS: primary endpoint



Antoniotti et al, Lancet Oncol '22

PFS according to MMR status



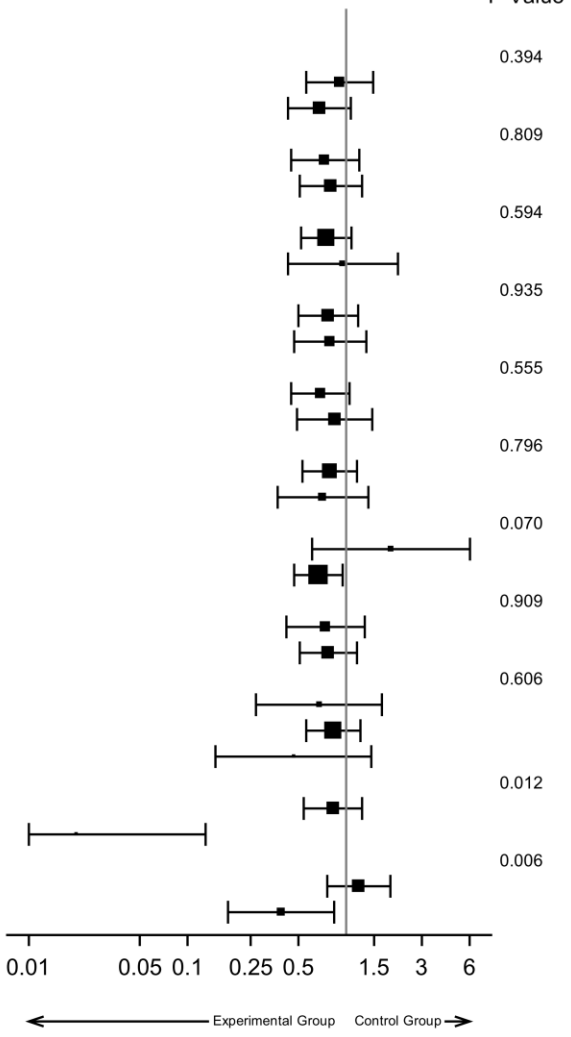
No. at Risk (No. Cumulative Censors)

Control Group - dMMR	5 (0)	3 (0)	2 (0)	1 (0)	1 (0)	1 (0)
Control Group - pMMR	67 (0)	57 (2)	39 (2)	19 (2)	7 (7)	4 (10)
Experimental Group - dMMR	8 (0)	8 (0)	8 (0)	8 (0)	4 (2)	2 (4)
Experimental Group - pMMR	132 (0)	112 (3)	83 (3)	46 (4)	18 (22)	7 (32)

Antoniotti et al, Lancet Oncol '22

PFS – subgroup analyses – pMMR cohort

Subgroup	Control Group Events/N (%)		Experimental Group Events/N (%)		HR (95% CI)	P Value
Age						0.394
< 60 years	24/30	(80.0)	48/66	(72.7)	0.91 (0.56, 1.48)	
≥ 60 years	30/37	(81.1)	45/66	(68.2)	0.68 (0.43, 1.07)	
Gender						0.809
Female	24/31	(77.4)	44/56	(78.6)	0.73 (0.45, 1.21)	
Male	30/36	(83.3)	49/76	(64.5)	0.80 (0.51, 1.26)	
ECOG PS						0.594
0	45/56	(80.4)	75/111	(67.6)	0.75 (0.52, 1.08)	
1	9/11	(81.8)	18/21	(85.7)	0.95 (0.43, 2.12)	
Primary Tumor Site						0.935
Left colon or rectum	32/39	(82.1)	56/76	(73.7)	0.77 (0.50, 1.19)	
Right colon	22/28	(78.6)	37/56	(66.1)	0.79 (0.47, 1.34)	
Surgery on Primary Tumor						0.555
No	21/27	(77.8)	33/52	(63.5)	0.69 (0.45, 1.05)	
Yes	33/40	(82.5)	60/80	(75.0)	0.85 (0.49, 1.46)	
Liver-Only disease						0.796
No	39/47	(83.0)	71/95	(74.7)	0.79 (0.53, 1.17)	
Yes	15/20	(75.0)	22/37	(59.5)	0.71 (0.37, 1.38)	
Time to mets						0.070
Metachronous	4/8	(50.0)	11/18	(61.1)	1.92 (0.61, 6.03)	
Synchronous	50/59	(84.7)	82/114	(71.9)	0.67 (0.47, 0.95)	
N. of mets sites						0.909
Single	19/27	(70.4)	30/57	(52.6)	0.74 (0.42, 1.31)	
Multiple	35/40	(87.5)	63/75	(84.0)	0.77 (0.51, 1.17)	
RAS and BRAF status						0.606
Wild-Type	7/9	(77.8)	14/20	(70.0)	0.68 (0.27, 1.68)	
RAS Mutated	39/49	(79.6)	73/102	(71.6)	0.83 (0.56, 1.23)	
BRAF Mutated	8/9	(88.9)	5/9	(55.6)	0.47 (0.15, 1.44)	
TMB						0.012
Low	35/42	(83.3)	55/76	(72.4)	0.83 (0.54, 1.26)	
High	1/1	(100)	2/6	(33.3)	0.02 (0.01, 0.13)	
Immunoscore® IC						0.006
Low	29/36	(80.6)	53/64	(82.8)	1.20 (0.76, 1.90)	
High	13/16	(81.3)	14/31	(45.2)	0.39 (0.18, 0.84)	



Antoniotti et al, Lancet Oncol '22

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Primary Tumor Site						0.935
TMB						0.012
Low	35/42	(83.3)	55/76	(72.4)	0.83 (0.54, 1.26)	
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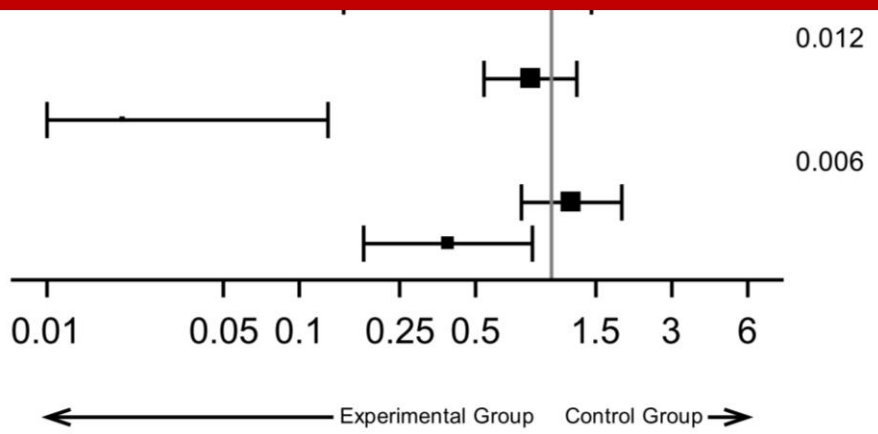


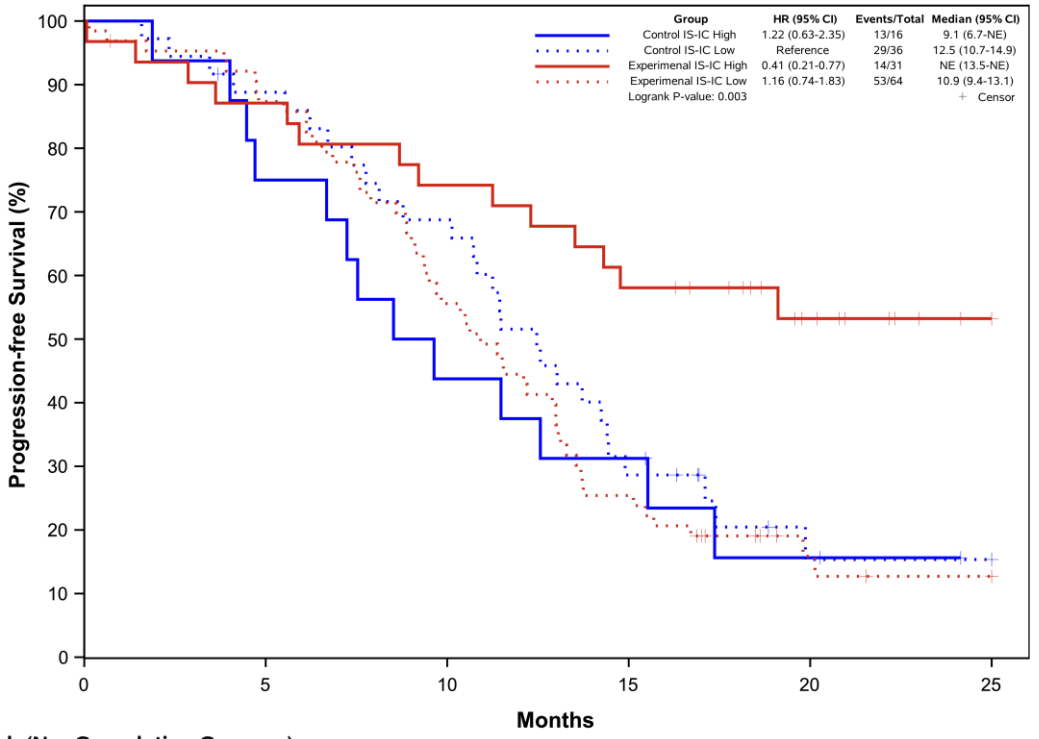
BRAF Mutated 8/9 (88.9) 5/9 (55.6) 0.47 (0.15, 1.44)
TMB 0.012
Low 35/42 (83.3) 55/76 (72.4) 0.83 (0.54, 1.26)
High 1/1 (100) 2/6 (33.3) 0.02 (0.01, 0.13)
Immunoscore® IC 0.006
Low 29/36 (80.6) 53/64 (82.8) 1.20 (0.76, 1.90)
High 13/16 (81.3) 14/31 (45.2) 0.39 (0.18, 0.84)
0.01 0.05 0.1 0.25 0.5 1.5 3 6
Experimental Group Control Group

classic Immunoscore vs Immunoscore IC

	Immunoscore	Immunoscore IC
What	CD3+ and CD8+ cell densities	CD8+ and PD-L1+ cell densities and proximity between them
Where	Tumour core and invasive margin	Tumour core
How	IHC and digital pathology	

PFS – pMMR cohort – subgroup analysis according to IS-IC status

IS-IC



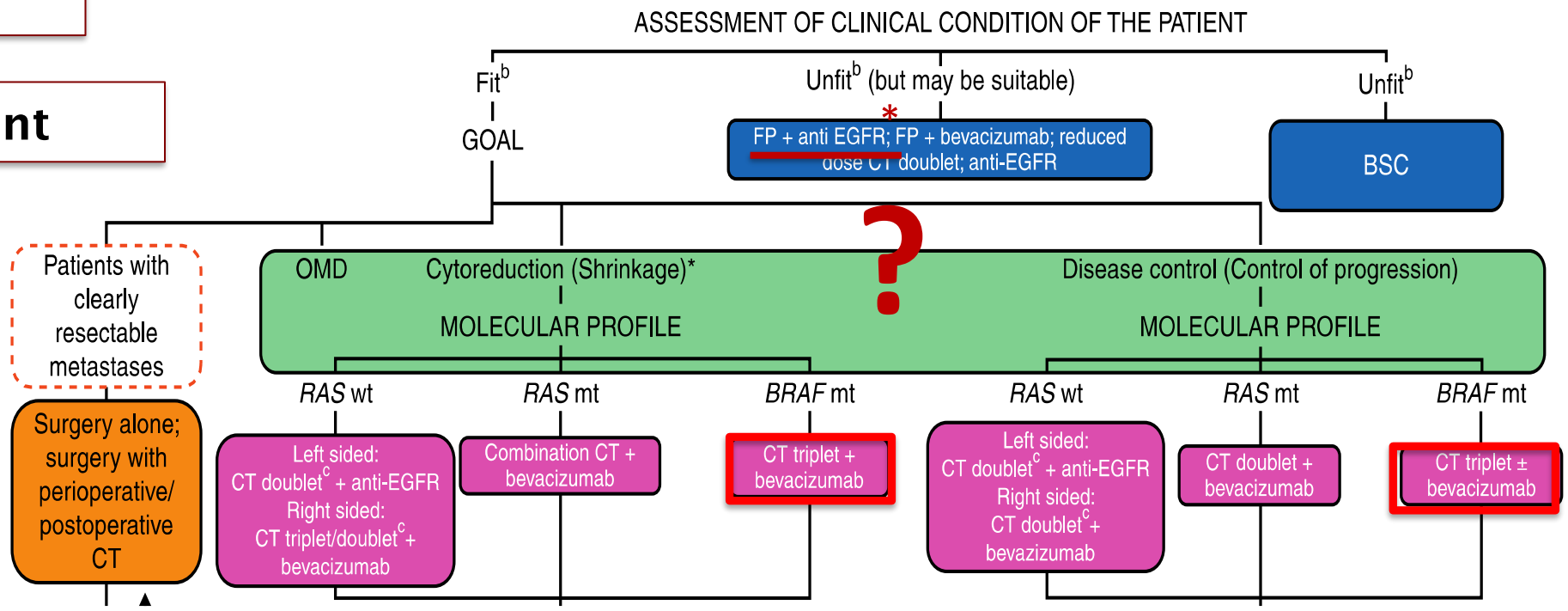
Antoniotti et al, Lancet Oncol '22

Patient

Treatment intent

RAS/BRAF

Primary location

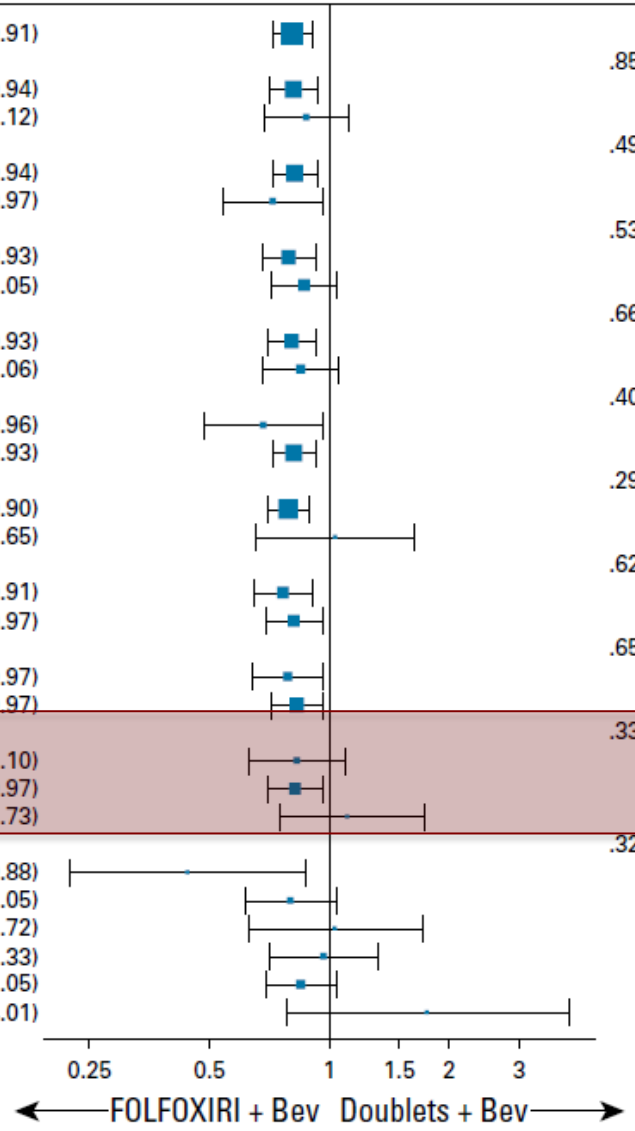


*** According to primary location and *RAS/BRAF* status**

Yoshino et al., Ann Oncol '18

FOLFOXIRI/bev vs doublets/bev – Subgroup analyses

Subgroup	Doublets + Bev No. Events of Total (%)	FOLFOXIRI + Bev No. Events of Total (%)	HR (95% CI)	P
Intention to treat population	591 of 851 (69.4)	527 of 846 (62.3)	0.81 (0.72 to 0.91)	
ECOG PS				.855
0	441 of 656 (67.2)	398 of 667 (59.7)	0.82 (0.71 to 0.94)	
1-2	149 of 192 (77.6)	126 of 175 (72.0)	0.88 (0.69 to 1.12)	
Age, years				.492
< 70	493 of 722 (68.3)	436 of 707 (61.7)	0.82 (0.72 to 0.94)	
> 70	98 of 129 (76.0)	91 of 139 (65.5)	0.72 (0.54 to 0.97)	
Sex				.533
Male	376 of 518 (72.6)	307 of 489 (62.8)	0.80 (0.68 to 0.93)	
Female	215 of 333 (64.6)	220 of 357 (61.6)	0.87 (0.72 to 1.05)	
Liver only				.665
No	441 of 596 (74.0)	358 of 543 (65.9)	0.81 (0.70 to 0.93)	
Yes	150 of 254 (59.1)	168 of 300 (56.0)	0.85 (0.68 to 1.06)	
Time to metastases				.408
Metachronous	83 of 130 (63.8)	57 of 130 (43.8)	0.69 (0.49 to 0.96)	
Synchronous	508 of 720 (70.6)	470 of 716 (65.6)	0.82 (0.72 to 0.93)	
Previous adjuvant				.296
No	552 of 790 (69.9)	492 of 782 (62.9)	0.79 (0.70 to 0.90)	
Yes	39 of 61 (63.9)	35 of 63 (55.6)	1.04 (0.66 to 1.65)	
Primary resection				.623
No	284 of 386 (73.6)	267 of 400 (66.8)	0.77 (0.65 to 0.91)	
Yes	307 of 465 (66.0)	260 of 445 (58.4)	0.82 (0.69 to 0.97)	
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)	

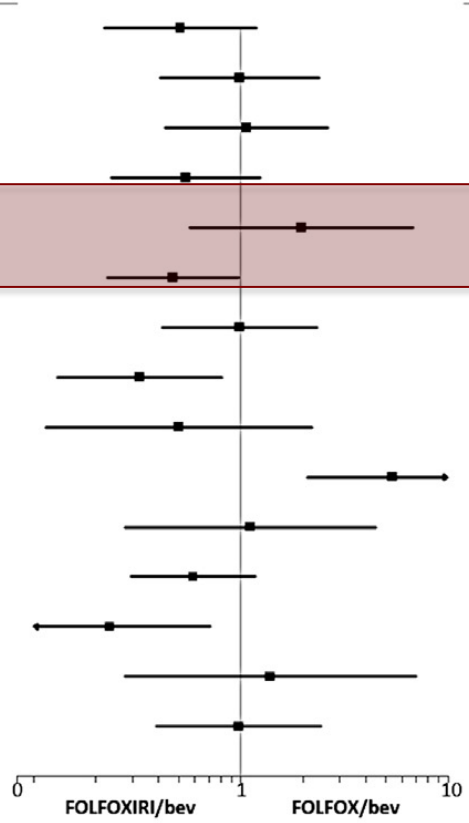


Cremolini et al, J Clin Oncol '20

FOLFOXIRI/Bev vs FOLFOX/bev in *BRAF* mut mCRC according to primary tumor site

Subgroup analysis of the TRIBE2 study

Subgroup	Level	FOLFOX /bev (n)	FOLFOXIRI /bev (n)	FOLFOX /bev (event)	FOLFOXIRI /bev (event)	P-value	P interaction	Hazard ratio (95%CI)
BM subtype	BM1	11	13	11	11	0.12	0.29	0.51 (0.22-1.18)
	BM2	11	11	10	10	0.98		0.99 (0.41-2.38)
Wnt activation	LD	10	9	10	9	0.9	0.28	1.06 (0.43-2.63)
	LI	12	15	11	12	0.15		0.54 (0.24-1.24)
Primary tumor site	left colon or rectum	5	8	4	7	0.29	0.05	1.96 (0.56-6.78)
	right colon	17	16	17	14	0.04		0.47 (0.23-0.97)
Gender	F	12	11	11	10	0.97	0.08	0.99 (0.42-2.33)
	M	10	13	10	11	0.02		0.32 (0.13-0.81)
ECOG performance	0	20	16	19	13	0.36	<0.01	0.50 (0.11-2.19)
	1	2	8	2	8	<0.01		5.39 (2.09-13.94)
Surgery at baseline	no	3	6	3	6	0.89	0.42	1.11 (0.28-4.46)
	yes	19	18	18	15	0.13		0.59 (0.29-1.17)
Semplified score	low	7	8	7	7	0.01	0.09	0.23 (0.08-0.71)
	high	2	7	2	6	0.69		1.38 (0.27-6.96)
	intermediate	12	9	11	8	0.96		0.98 (0.39-2.43)



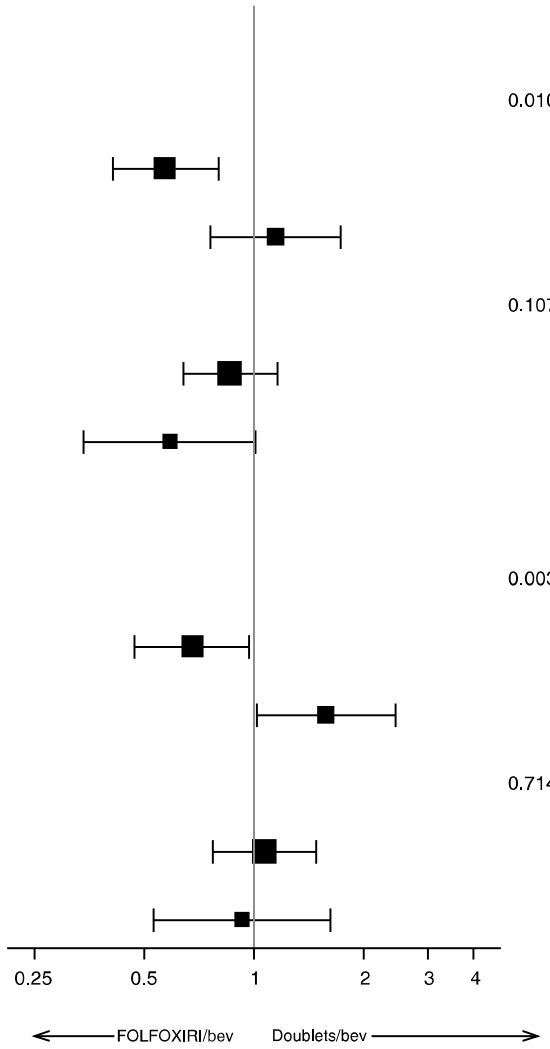
Moretto et al, Eur J Canc '21

FOLFOXIRI/Bev vs doublets/bev in *BRAF* mut mCRC according to primary tumor site

Pts selected according to ECOG PS and age criteria from the real-life BRAF BeCool dataset

N= 296

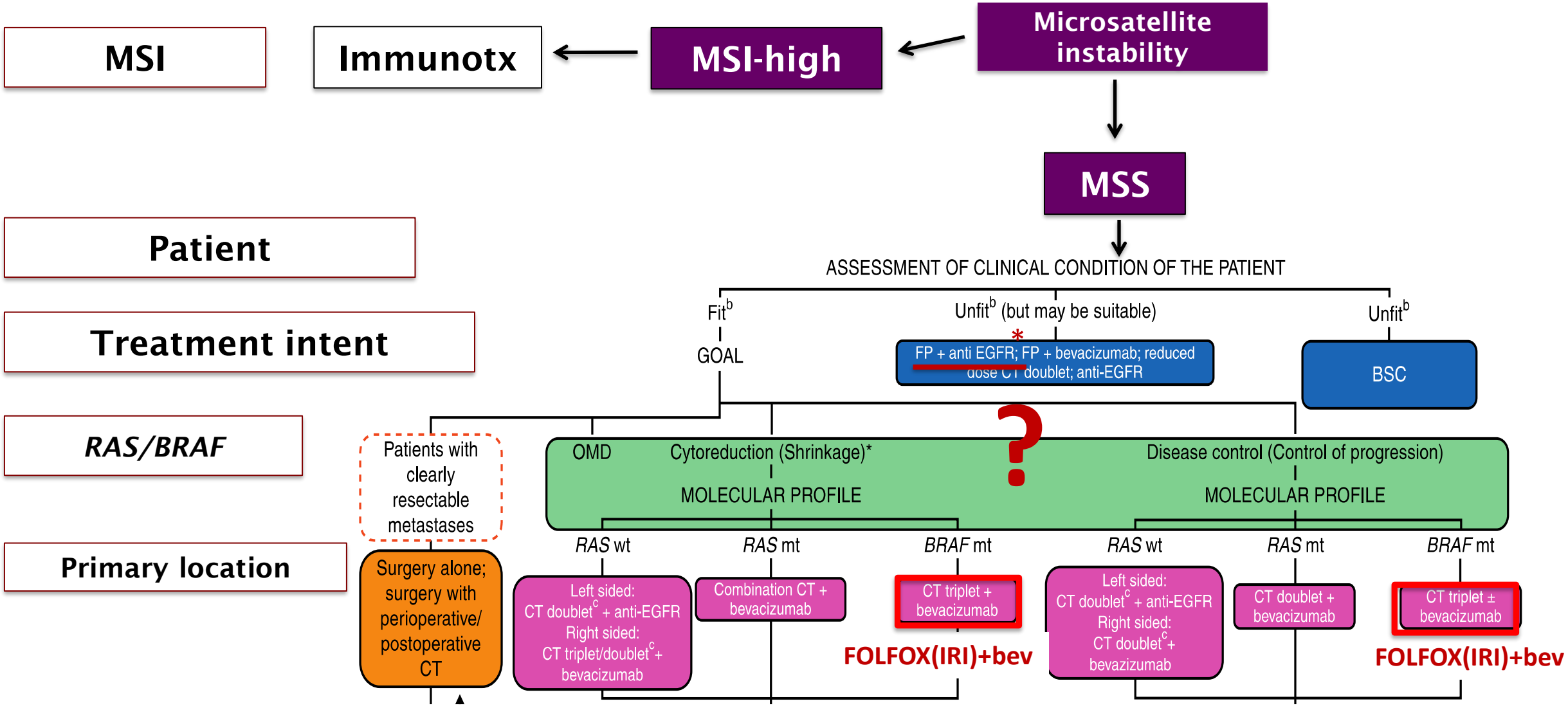
Subgroup	Doublets/bev events/N (%)		FOLFOXIRI/bev events/N (%)		HR (95% CI)	*P* value
Progression-free survival						
Sidedness						0.010
Right	91/107	(85.0)	56/72	(77.8)	0.57 (0.41, 0.80)	
Left	53/64	(82.8)	43/52	(82.7)	1.15 (0.76, 1.73)	
ECOG-PS						0.107
0	95/116	(81.9)	81/100	(81.0)	0.86 (0.64, 1.16)	
1–2	50/56	(89.3)	18/24	(75.0)	0.59 (0.34, 1.01)	
Overall survival						
Sidedness						0.003
Right	79/107	(73.8)	47/72	(65.3)	0.68 (0.47, 0.97)	
Left	44/64	(68.8)	40/52	(76.9)	1.58 (1.02, 2.45)	
ECOG-PS						0.714
0	80/116	(69.0)	69/100	(69.0)	1.07 (0.77, 1.48)	
1–2	44/56	(78.6)	18/24	(75.0)	0.93 (0.53, 1.62)	



0.010

0.003

Moretto et al, Br J Canc '22

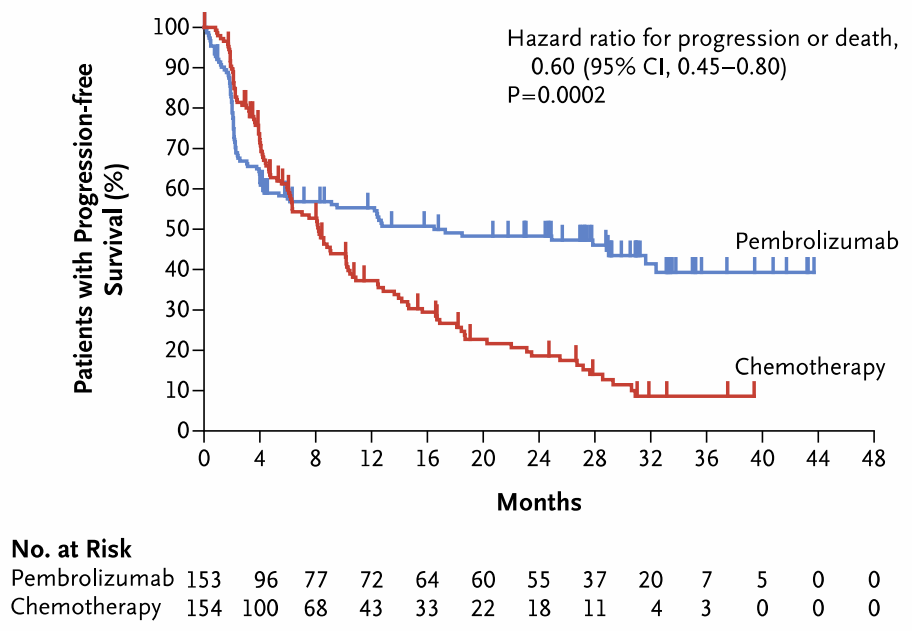


*** According to primary location and *RAS/BRAF* status**

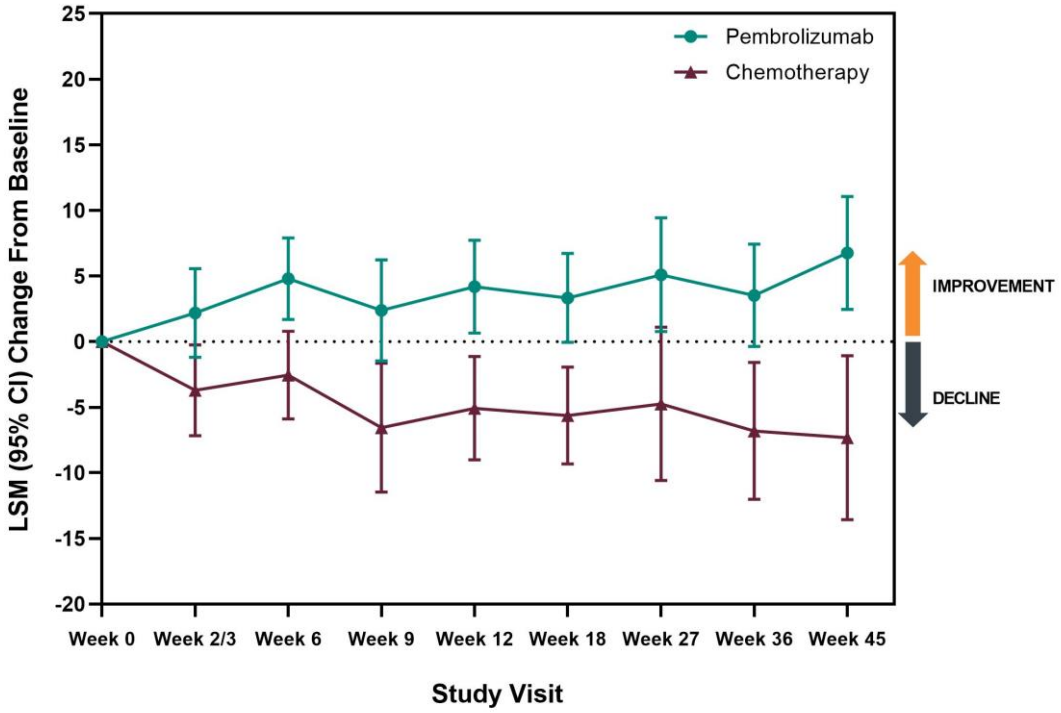
Yoshino et al., Ann Oncol '18

Phase III KEYNOTE 177 trial: pembro vs doublet/biologic in dMMR

PFS: co-primary endpoint



QOL: secondary endpoint



André et al, Lancet Oncol '21

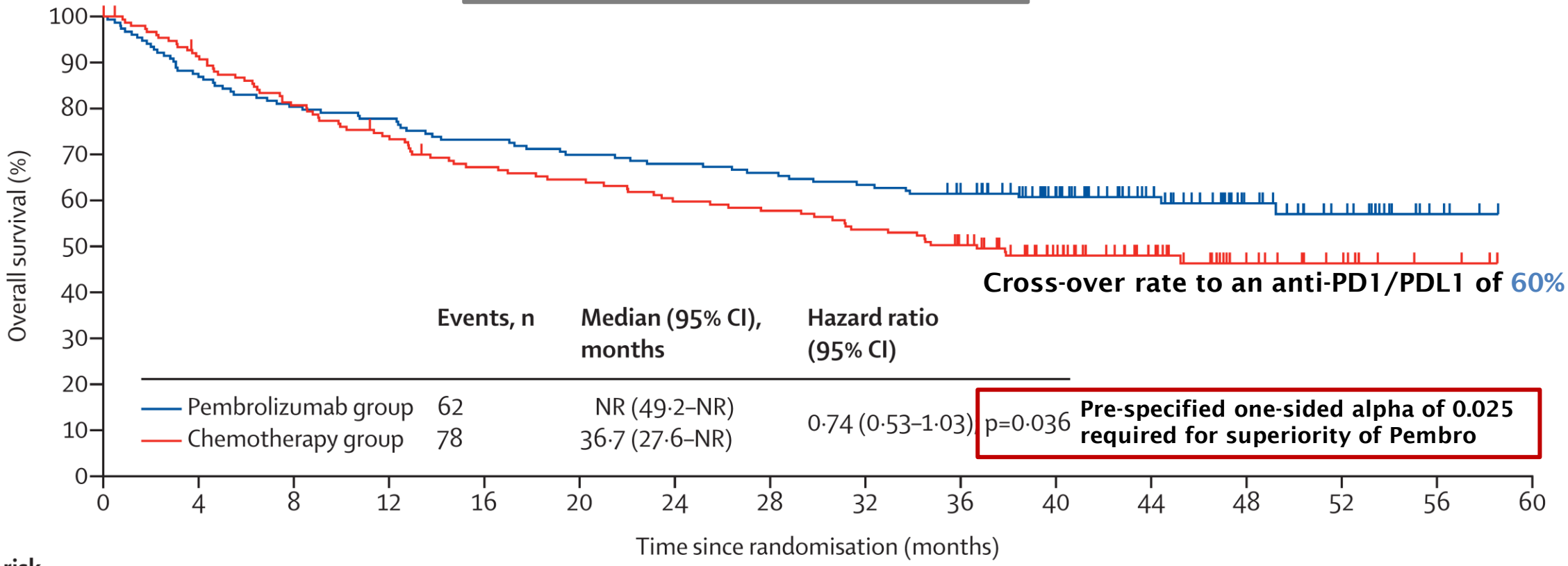
ORR: secondary endpoint

43.8% vs 33.1%, p=0.028

André et al, N Engl J Med '20

Phase III KEYNOTE 177 trial: pembro vs doublet/biologic in dMMR

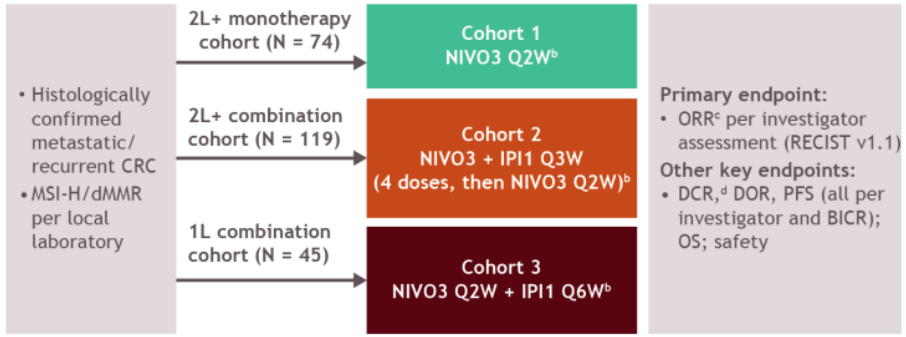
OS: co-primary endpoint

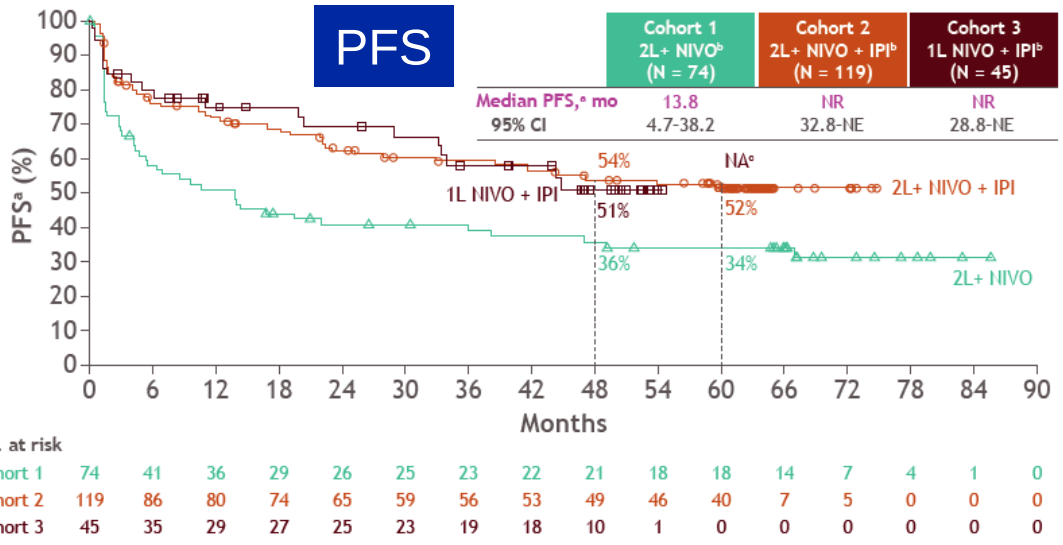


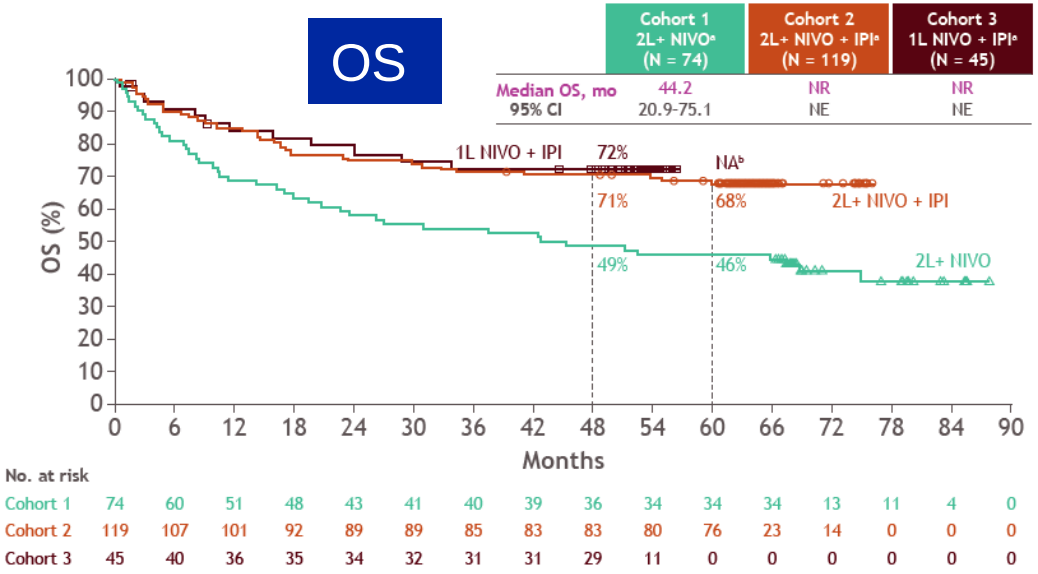
Number at risk (number censored)															
Pembrolizumab group	153 (0)	134 (0)	123 (0)	119 (0)	112 (0)	107 (0)	104 (0)	101 (0)	97 (2)	92 (23)	70 (45)	48 (64)	28 (75)	16 (78)	4 (91)	0 (91)
Chemotherapy group	154 (4)	137 (4)	121 (5)	110 (6)	99 (6)	95 (6)	88 (6)	85 (6)	79 (9)	71 (24)	53 (41)	36 (58)	18 (65)	11 (73)	3 (76)	0 (76)

Diaz et al, Lancet Oncol 2022

Phase II CheckMate142 trial: nivo3+ipi1 in first-line MSI-high



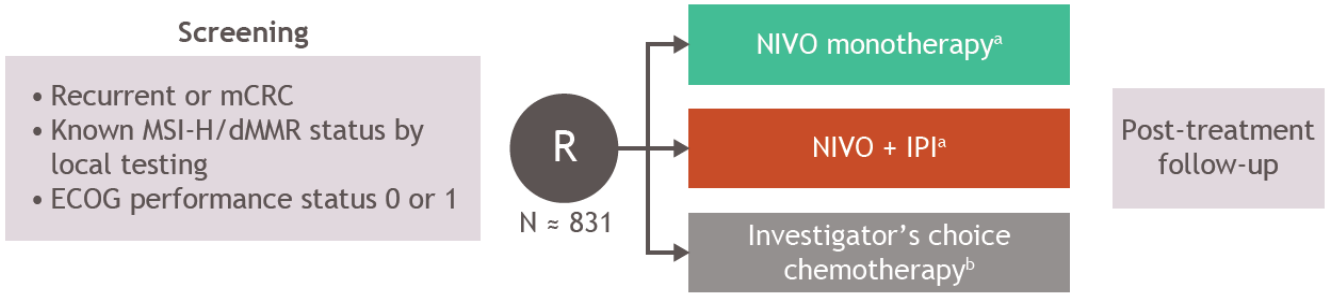




Overman et al, ASCO Ann Meet 2022

Combo ICIs better than ICI monotherapy in first-line MSI-high?

CheckMate 8HW

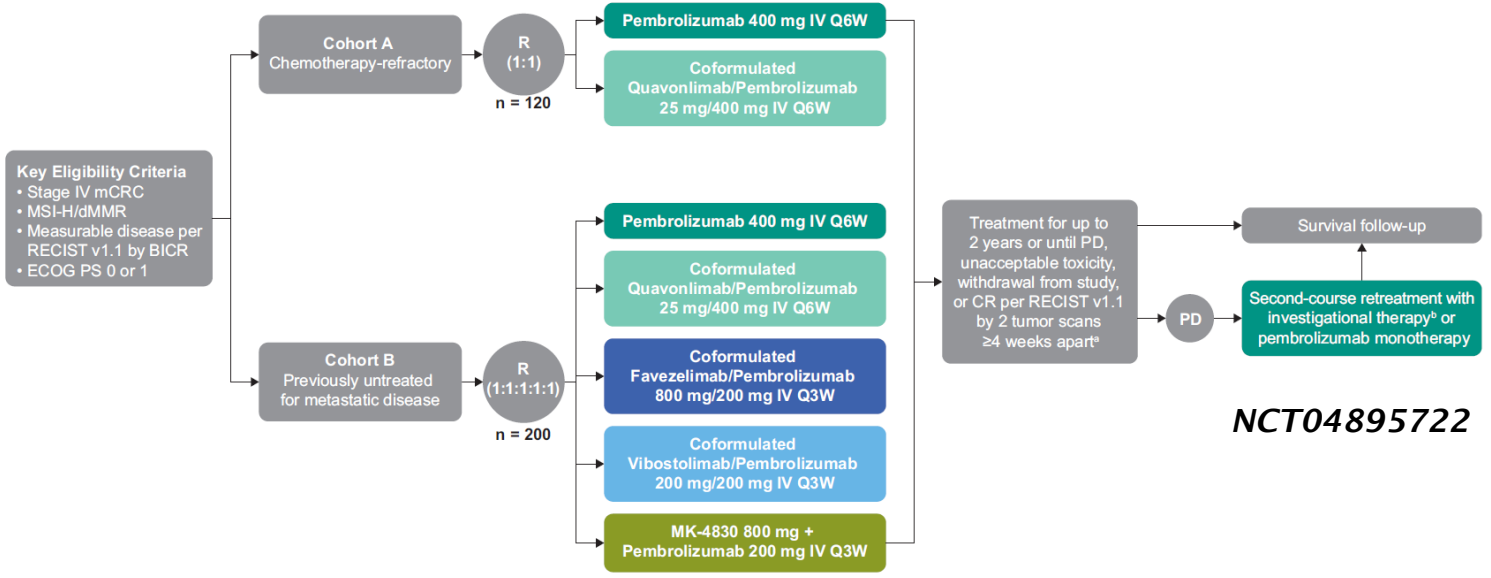


[a]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms; [b]Patients receiving investigator's choice chemotherapy are eligible to receive NIVO + IPI upon progression.
R, randomization.

NCT04008030

Dual primary endpoints[b]
PFS by BICR (NIVO + IPI vs NIVO across all lines)
PFS by BICR (NIVO + IPI vs chemotherapy in the first-line setting)

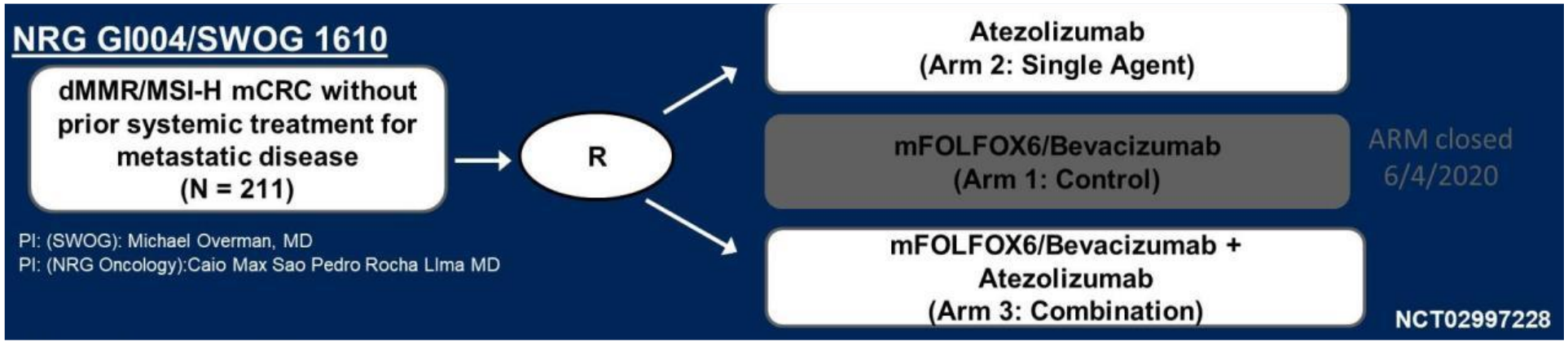
MK C08

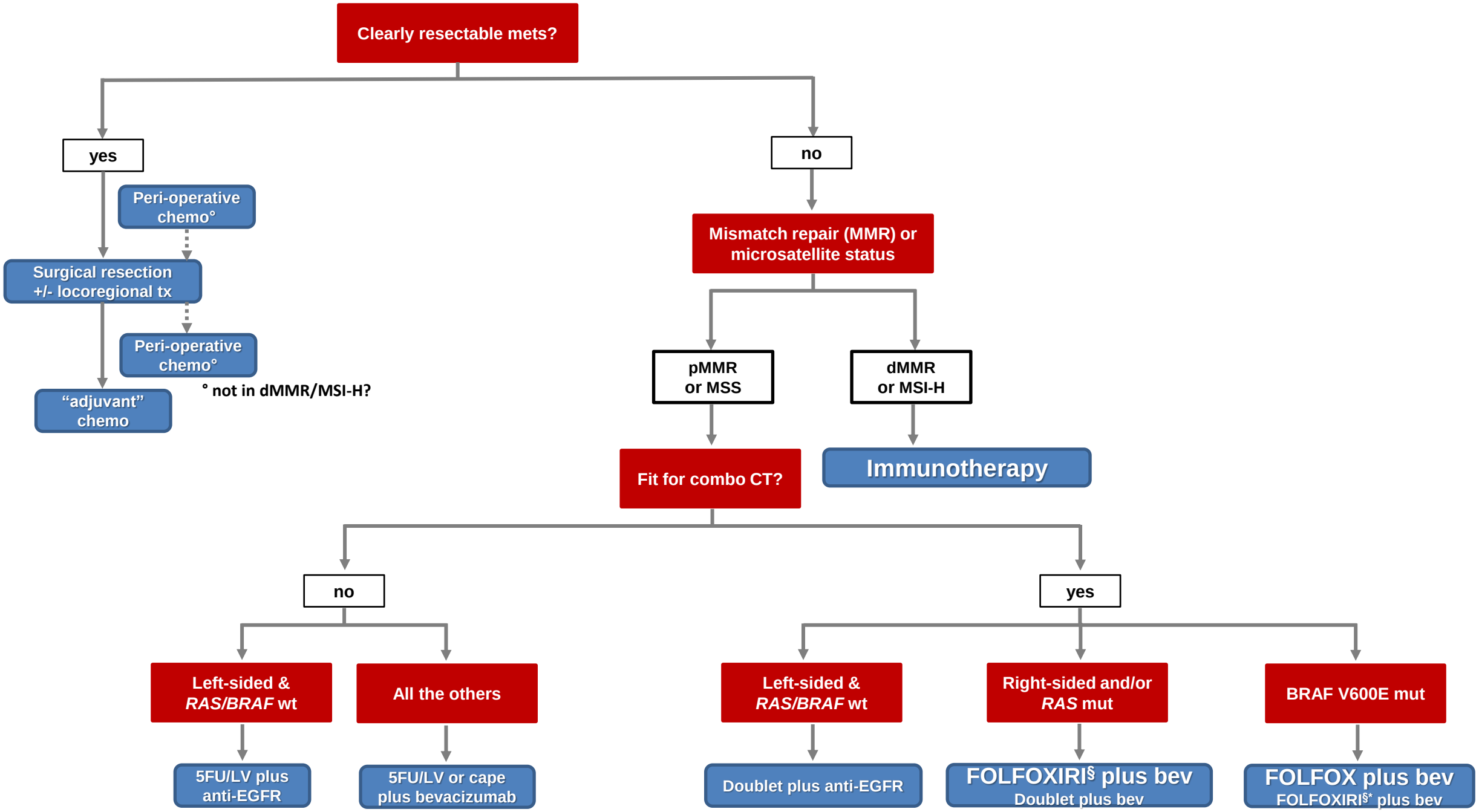


NCT04895722

Does chemo + bevacizumab add something?

NRG GI004/SWOG 1610

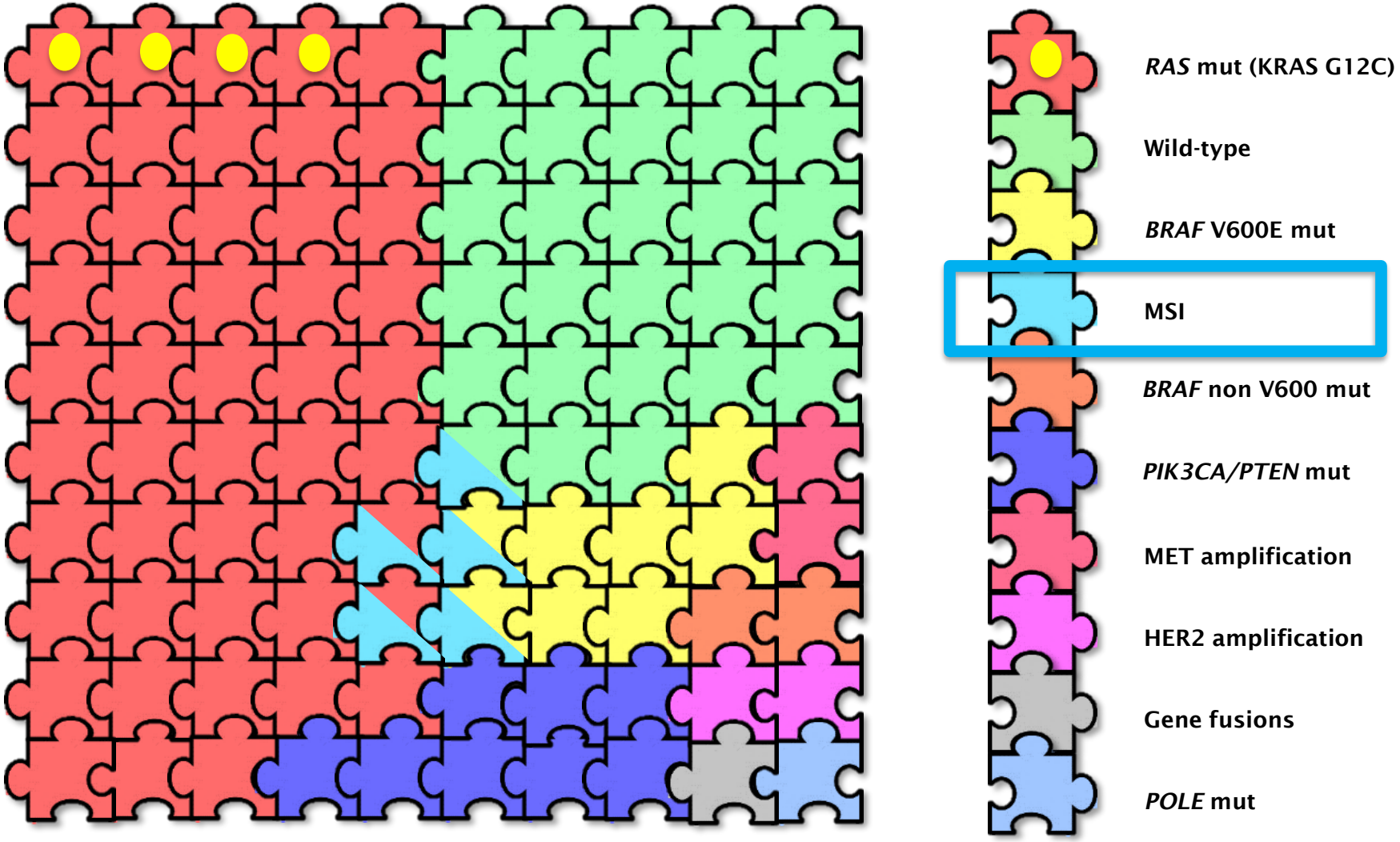




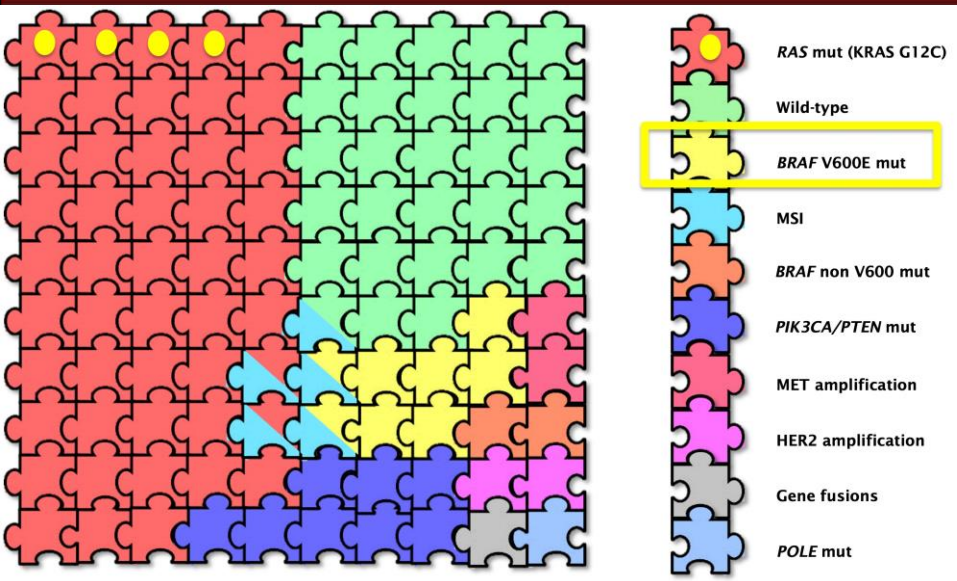
§ only if <75 years old (71-75 years old with ECOG Performance Status 0); * mainly if right-sided.

Is anything missing?

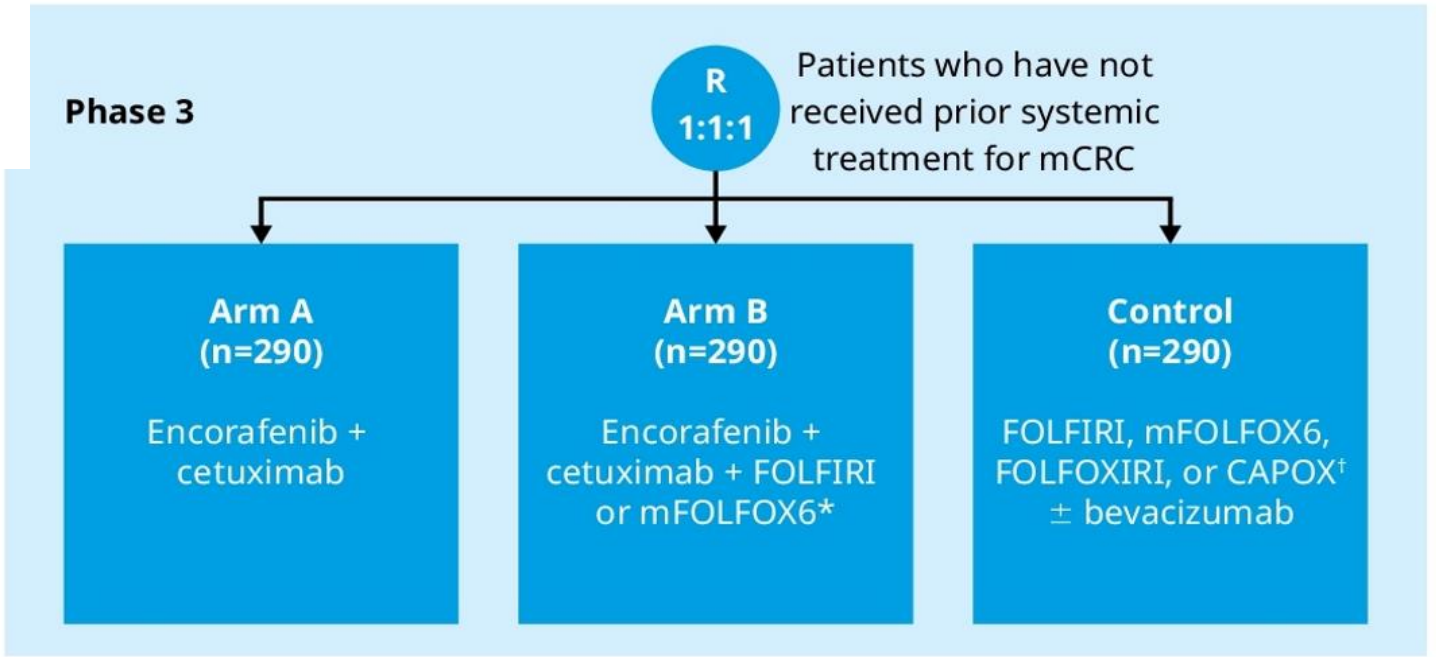
Molecularly defined subgroups and targeted treatments



But… on the horizon

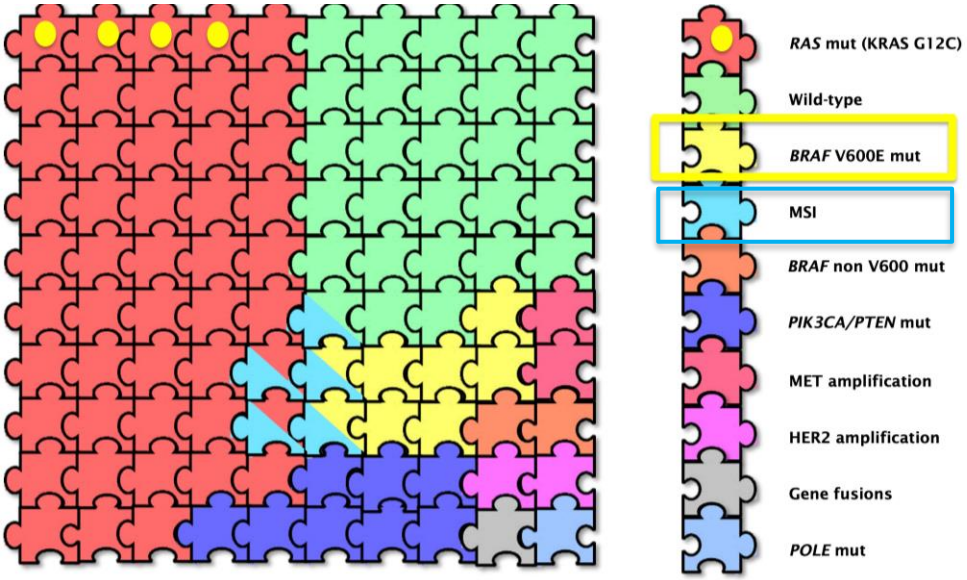


Phase III BREAKWATER study



NCT04607421

But… on the horizon



Phase II SEAMARK studynew al

Patient Population

- Previously untreated Stage IV mCRC
- Documented *BRAF* V600E mutation and MSI-H/dMMR status as previously determined by local laboratory assays
- Measurable disease per RECIST v1.1
- ECOG PS ≤ 1

Randomized Phase 2
N = 104

Randomization 1:1
(stratified by ECOG PS: 0 vs 1)

Triplet Arm (Arm A)
Encorafenib (300 mg QD) +
Cetuximab (500 mg/m² Q2W) +
Pembrolizumab (400 mg IV Q6W up to 24 months)
N = 52

Control Arm (Arm B)
Pembrolizumab (400 mg IV Q6W up to 24 months)
N = 52

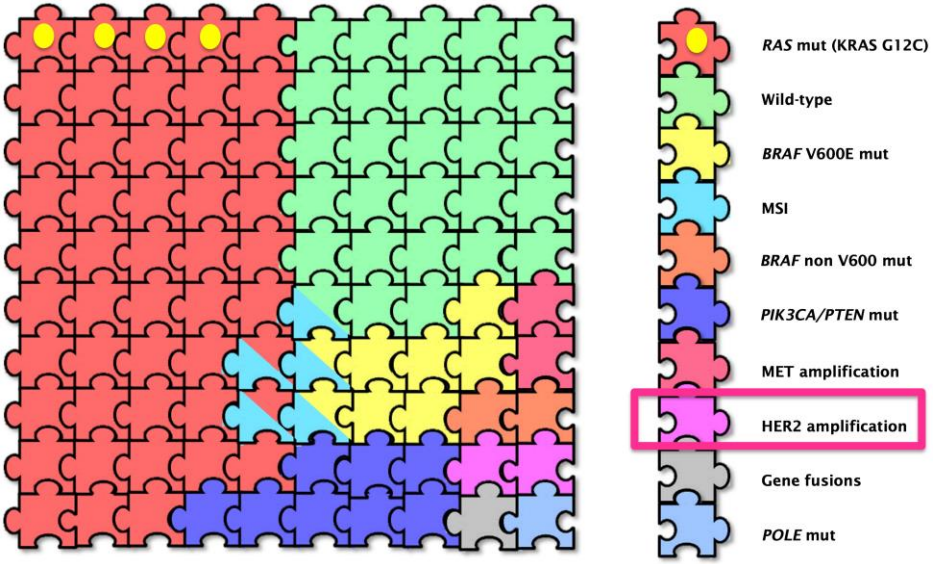
Treat until disease progression, unacceptable toxicity, withdrawal of consent/assent, or death, whichever occurs first *

Post Treatment
- Safety Follow-up
- Disease Follow-up (until PD, if applicable)
- Survival Follow-up (every 12 weeks)

Primary Endpoint	PFS per investigator according to RECIST v1.1
Secondary Endpoints	OS, OR, DOR, Safety/tolerability, central confirmation of *BRAF*/MSI status, PROs

NCT05217446

But… on the horizon



Phase III MOUNTAINEER-3 study

Study Population
Measurable disease per RECIST 1.1
ECOG PS 0-1
HER2+, RAS wild-type, Metastatic CRC, no prior treatment in the metastatic setting,
but may have received adjuvant treatment if completed >6 months prior to enrollment (Cycle 1 Day 1)

↓

Randomization*
1:1

↓

Tucatinib Experimental Arm
Tucatinib 300 mg PO BID
Trastuzumab 8 mg/kg loading dose, then 6 mg/kg IV (Q3W)
mFOLFOX6 (Q2W)

Standard of Care Control Arm
mFOLFOX6 (Q2W), or
mFOLFOX6 (Q2W) + bevacizumab (Q2W), or
mFOLFOX6 (Q2W) + cetuximab (QW)

Primary endpoint: PFS

NCT05253651

Thank you!