XXII Riunione Nazionale I.T.M.O.

Monza, 1 Luglio 2016

Ca colon retto: regimi classici e innovativi

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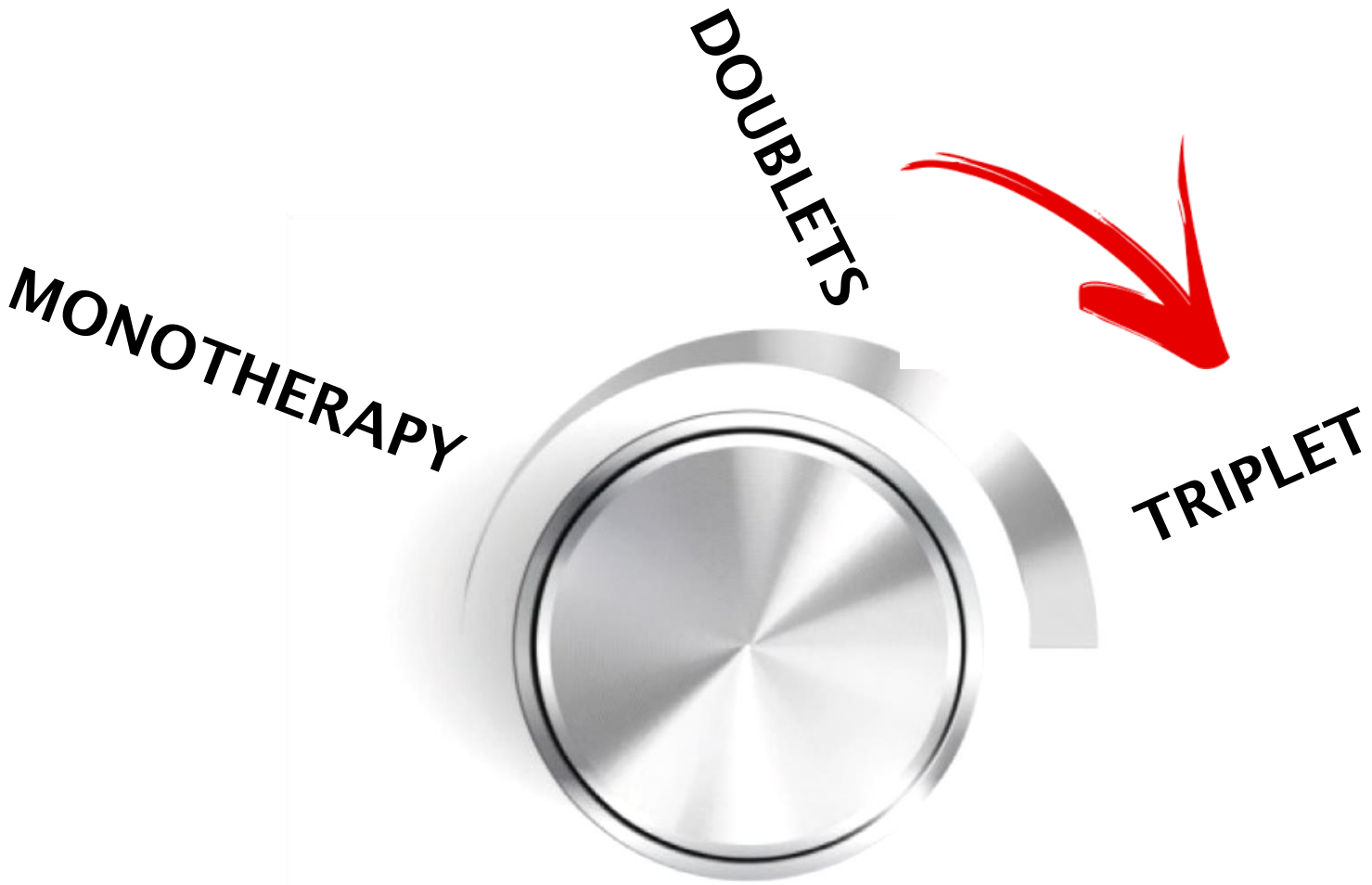
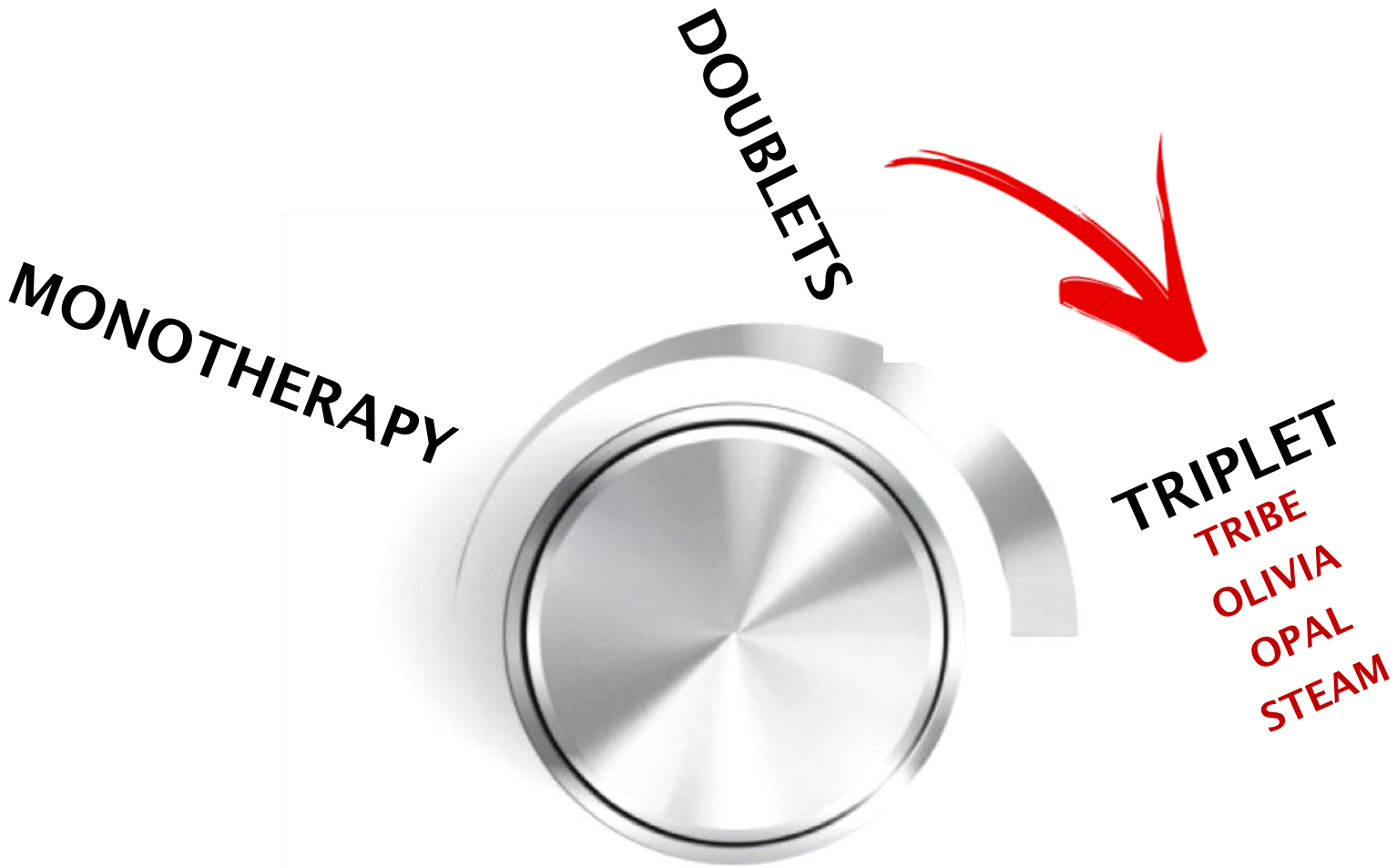
Is mCRC still...

The kingdom of doublets?

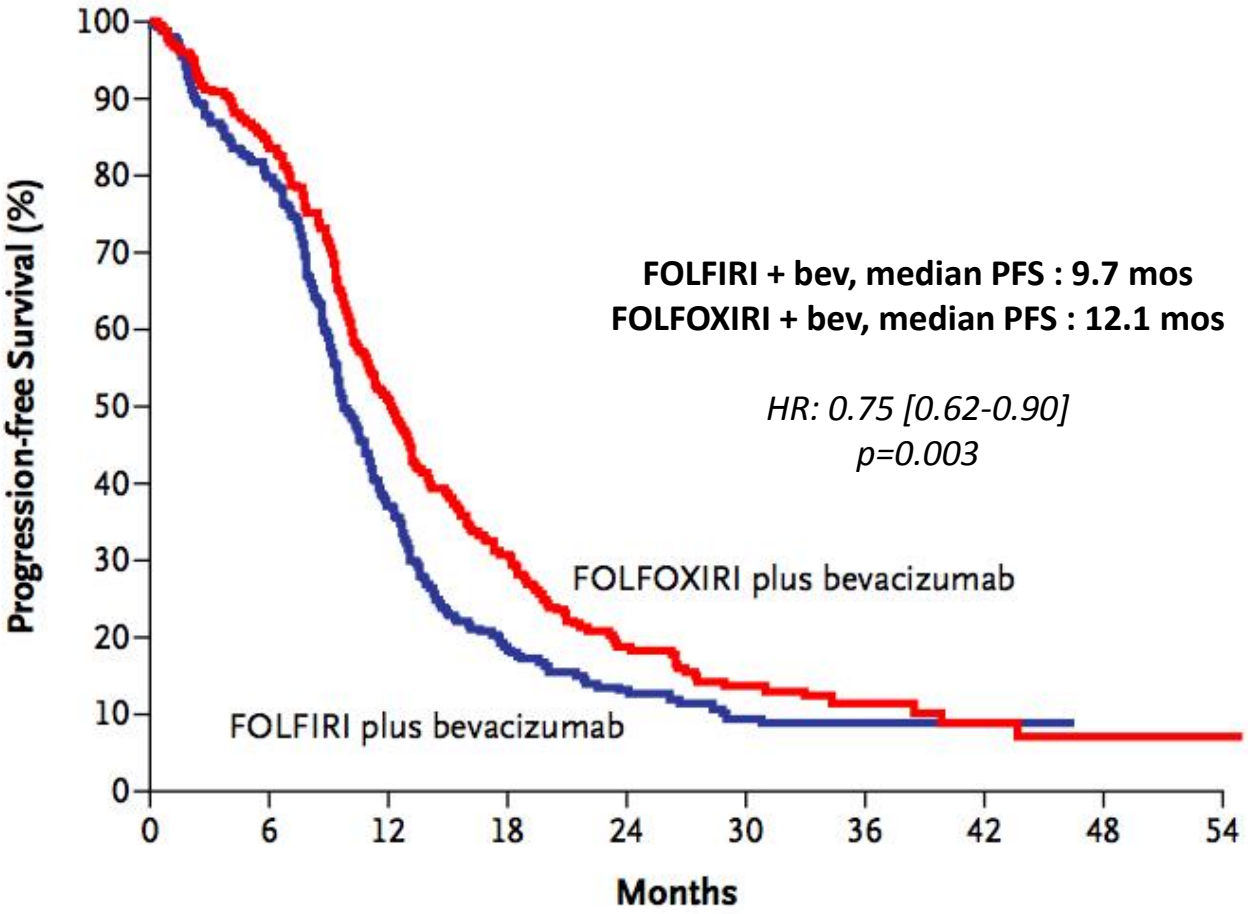
Modulation of chemo-intensity in mCRC



Modulation of chemo-intensity in mCRC…with bev



TRIBE: Primary endpoint - PFS



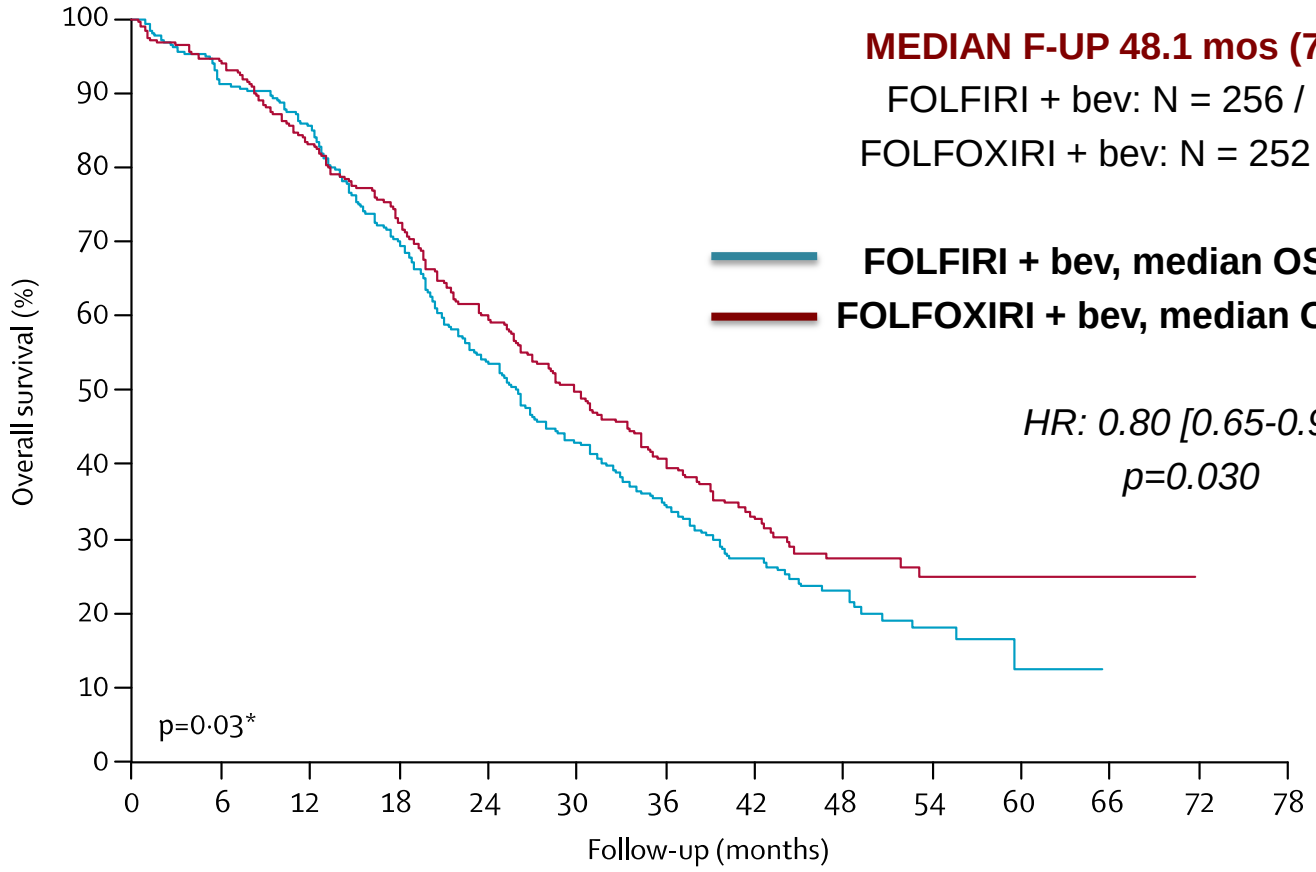
FOLFIRI + bev, median PFS : 9.7 mos
FOLFOXIRI + bev, median PFS : 12.1 mos

HR: 0.75 [0.62-0.90]
p=0.003

No. at Risk										
FOLFIRI plus bevacizumab	256	203	94	46	26	14	7	3	0	0
FOLFOXIRI plus bevacizumab	252	208	125	74	35	21	11	5	2	1

Loupakis et al, NEJM 2014

TRIBE: Secondary endpoint - OS



MEDIAN F-UP 48.1 mos (74% events)

FOLFIRI + bev: N = 256 / Died = 200

FOLFOXIRI + bev: N = 252 / Died = 174

FOLFIRI + bev, median OS : 25.8 mos

FOLFOXIRI + bev, median OS : 29.8 mos

HR: 0.80 [0.65-0.98]

p=0.030

Number at risk

FOLFIRI plus bevacizumab	256	234	219	179	137	109	86	55	31	15	3	0	0	0
FOLFOXIRI plus bevacizumab	252	236	208	181	148	123	95	57	34	19	9	3	0	0

Cremolini et al, Lancet Oncol 2015

TRIBE: Secondary endpoint: Response rate

Best Response, %	FOLFIRI + bev N = 256	FOLFOXIRI + bev N = 252	*p*
Complete Response	3%	5%	
Partial Response	50%	60%	
Response Rate	**53%**	**65%**	***0.006***
Stable Disease	32%	25%	
Progressive Disease	11%	6%	
Not Assessed	4%	4%	

Loupakis et al, NEJM 2014

Consistent results with FOLFOXIRI plus bev

…in previously untreated, unresectable mCRC

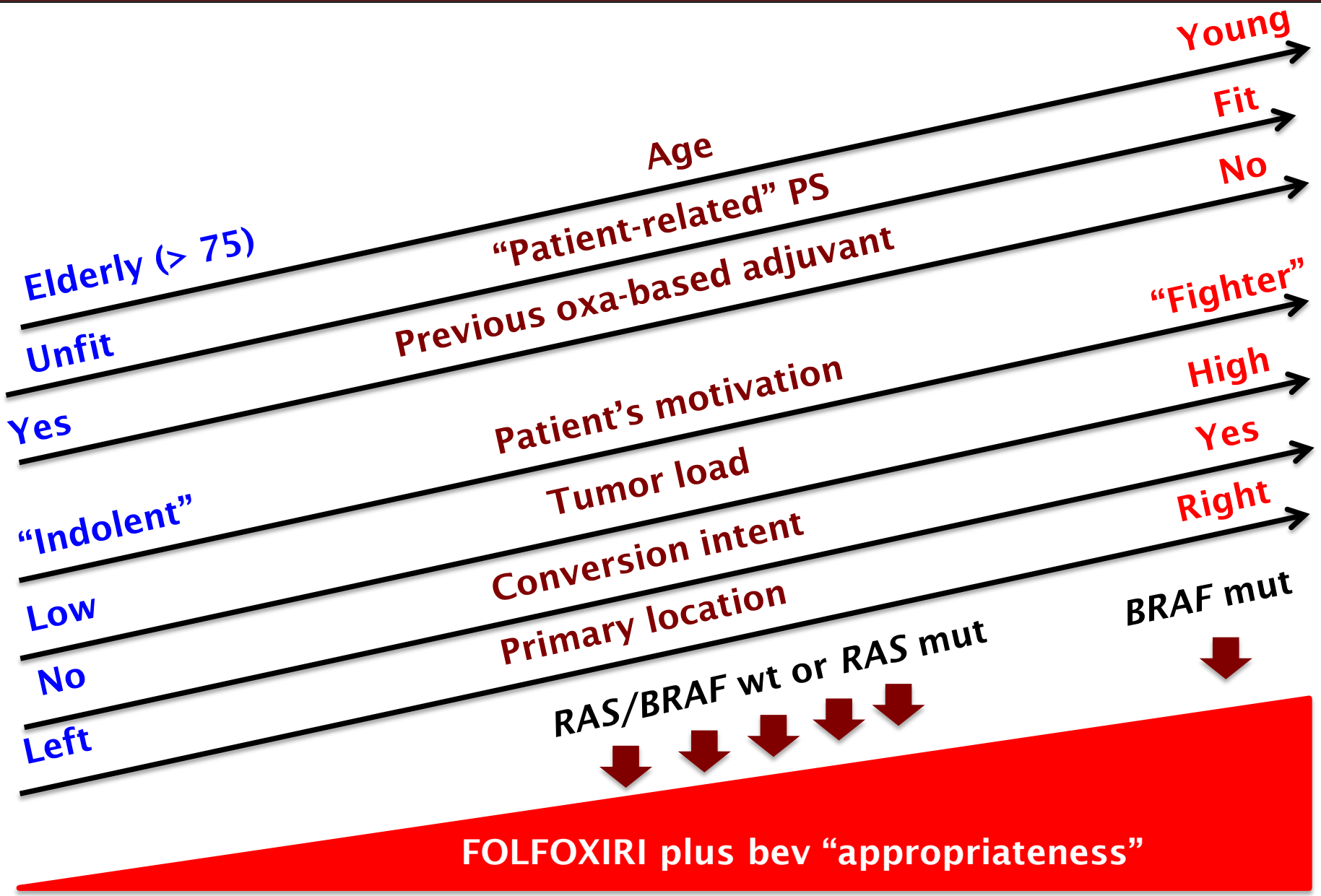
	FOIB N = 57	TRIBE N=252	OPAL N=97	STEAM N=93
Response Rate	77%	65%	64%	60%
Disease Control Rate	100%	90%	87%	91%
Median PFS, mos	13.1	12.3	11.1	11.7
Median OS, mos	30.9	29.8	32.2	Too early

Masi et al, Lancet Oncol '10, Cremolini et al, Lancet Oncol '15, Stein et al, Br J Canc '15, Bendell et al, ASCO GI '16

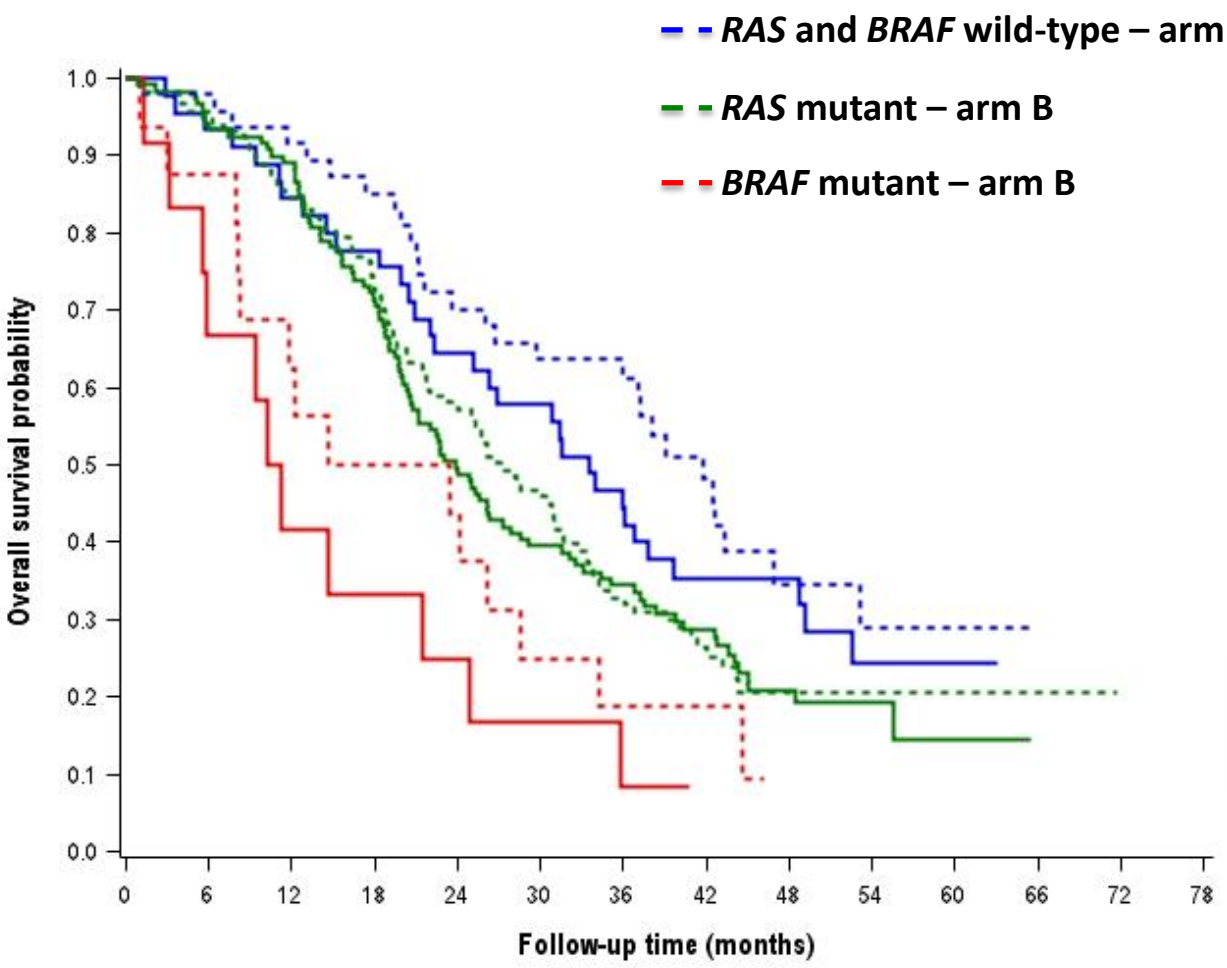
When NOT to go for a triplet plus bev?

- Over 75
- 71-75 ys old with ECOG PS > 0
- Contraindications to 5-FU, Oxaliplatin, Irinotecan or Bevacizumab
- Prior exposure to Oxaliplatin-containing adjuvant

“Decision drivers”



Treatment effect in molecular subgroups - OS



	Events	Median
RAS and *BRAF* wild-type – arm B	28	41.7 months
RAS and *BRAF* wild-type – arm A	32	33.5 months
RAS mutant – arm B	88	27.3 months
RAS mutant– arm A	93	23.9 months
BRAF mutant – arm B	14	19.0 months
BRAF mutant– arm A	11	10.7 months

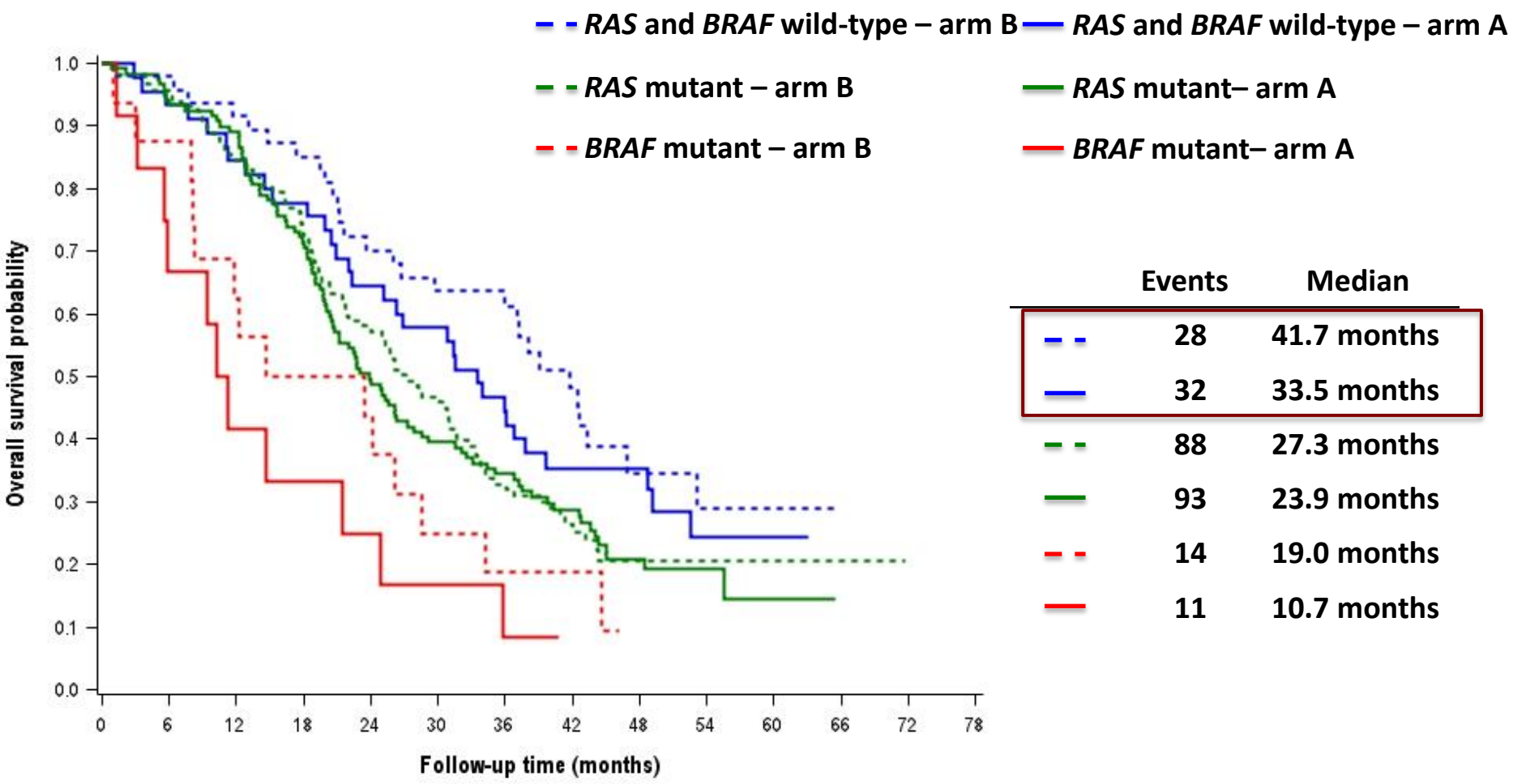
Cremolini et al, Lancet Oncol '15

FOLFOXIRI plus bev in *BRAF* mutant mCRC: summary

Study *Reference*	N	RR	Median PFS	Median OS
FOIB *Masi, Lancet Oncol '10*	10	90%	12.8	23.8
Prospective phase II *Loupakis, EJC'13*	15	60%	9.2	24.1
TRIBE *Cremolini et al, Lancet Oncol'15*	16	56%	7.5	19.0

Data are from different trials, not suitable for direct comparison

Treatment effect in molecular subgroups - OS



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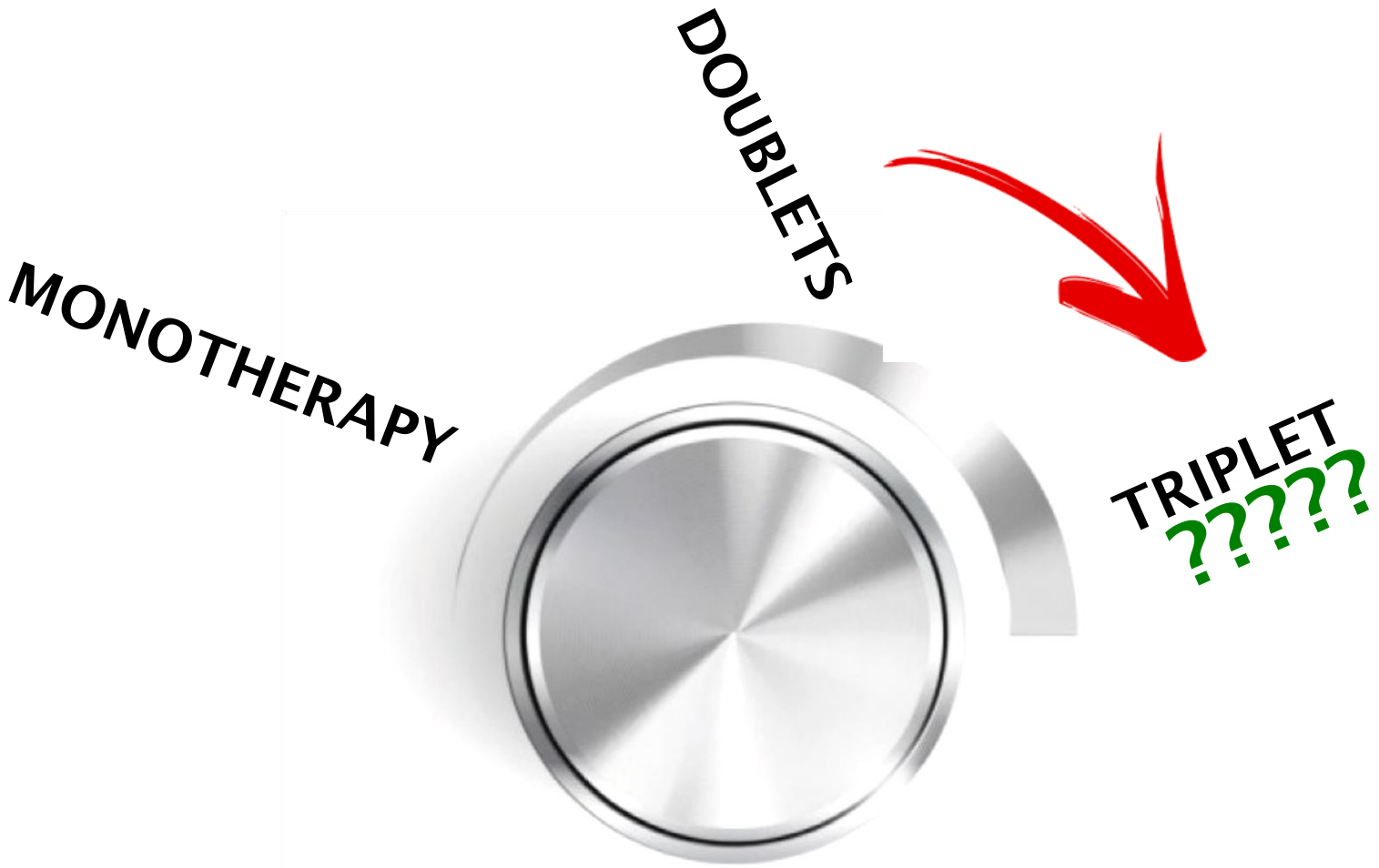
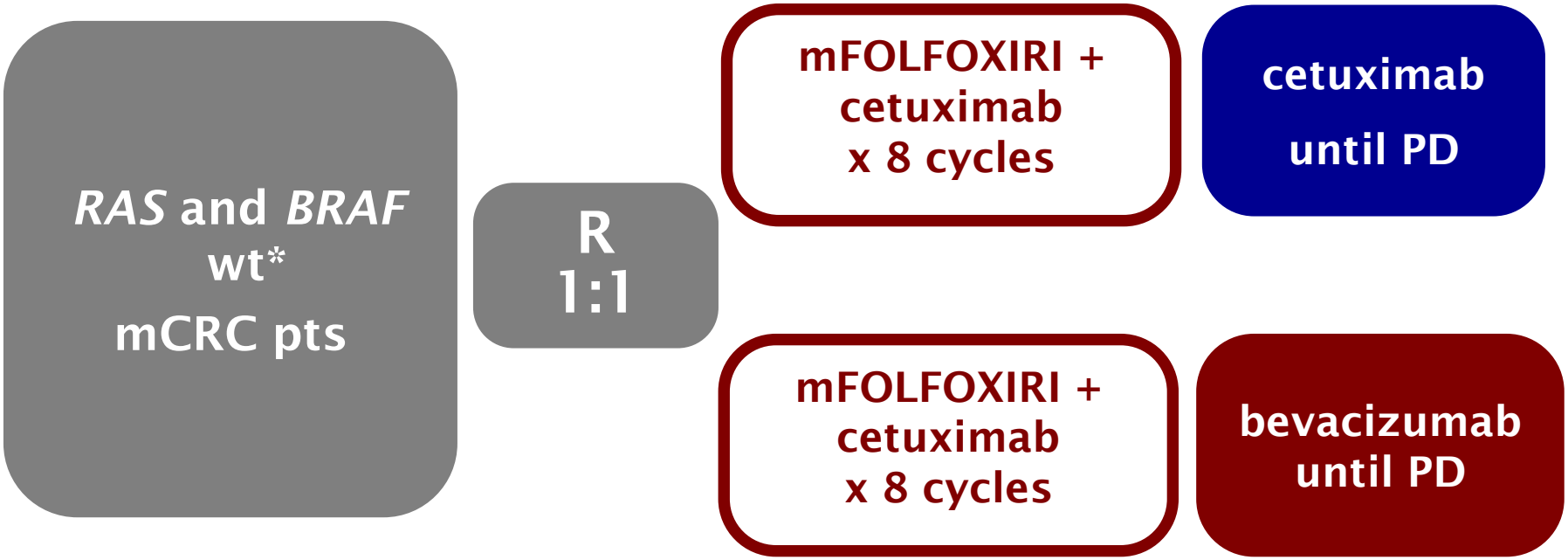
Cremolini et al, Lancet Oncol '15

Modulation of chemo-intensity in mCRC…with anti-EGFRs



MACBETH trial



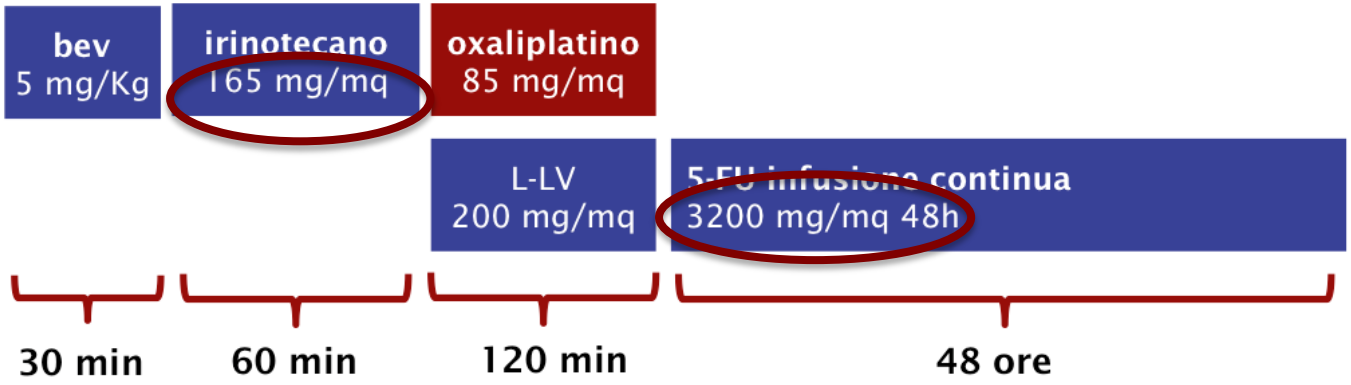
Primary endpoint: 10 months – progression free rate

***KRAS* 12, 13 and 61 wt until Oct 2013, then *RAS* and *BRAF* wt**

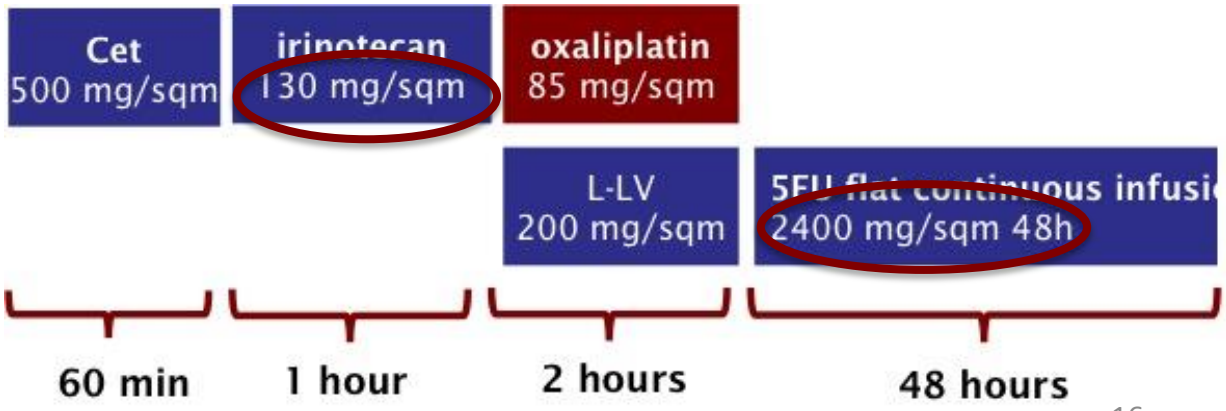
G.O.N.O
Gruppo Oncologico del Nord Ovest

Modified FOLFOXIRI regimen

“Classic” FOLFOXIRI



modified FOLFOXIRI



Toxicity Profile

G3/4 adverse events, % patients	Arm A N = 59	Arm B N = 57	All N = 116
Nausea	1.7%	0%	**0.9%**
Vomiting	3.4%	1.0%	**2.6%**
Diarrhea	20.3%	15.8%	**18.1%**
Stomatitis	6.8%	5.3%	**6.0%**
Neutropenia	28.8%	33.3%	**31.0%**
Febrile neutropenia	3.4%	1.8%	**2.6%**
Neurotoxicity	6.7%	0%	**3.5%**
Asthenia	10.1%	8.8%	**9.5%**
Skin rash	18.6%	12.3%	**15.5%**
Venous Thrombosis	1.7%	3.5%	**2.6%**
Arterial Thrombosis	1.7%	0%	**0.9%**

Antoniotti et al., ASCO Ann Meet '16

Primary endpoint: 10m-PFR – mITT population

	Arm A N = 59	Arm B N = 57
N pts observed at 10 months	50	52
N pts progression-free at 10 months	26	23

"…if at least 33 pts out of 53 per arm will be alive and progression-free at 10 months."

Median follow-up: 25.5 months

Secondary endpoint: Response rate

Best Response, %	Arm A N = 59	Arm B N = 57	All N = 116
Complete Response	5%	4%	4%
Partial Response	63%	72%	67%
Response Rate	**67.8%**	**75.4%**	**71.6%**
Stable Disease	24%	14%	19%
Disease Control Rate	**92%**	**89%**	**91%**
Progressive Disease	3%	4%	3%
Not Assessed	5%	6%	6%

RECIST response rate and disease control rate in evaluable patients were 76% and 96%, respectively

Antoniotti et al., ASCO Ann Meet '16

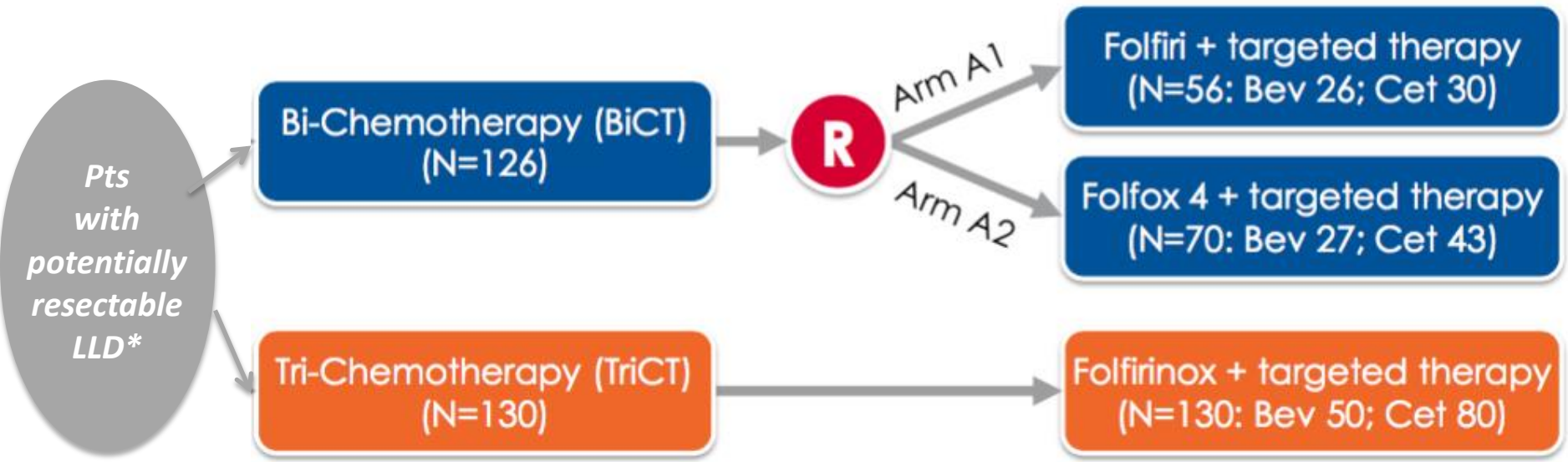
Secondary endpoint: Resection of Metastases

	Arm A N = 59	Arm B N = 57	All N = 117
Secondary surgery with radical intent	45.8%	29.8%	**37.9%**
R0 secondary surgery	32.2%	22.8%	**27.6%**

Liver-only subgroup	N = 28	N = 24	N=52
Secondary surgery with radical intent	71.4%	58.3%	**65.4%**
R0 secondary surgery	53.6%	45.8%	**50.0%**

Antoniotti et al., ASCO Ann Meet '16

Prodige-14 (Methep-2): study design



***Unresectable liver mets for technical (<30% residual liver) or oncological reasons (>5 bilobar lesions)**

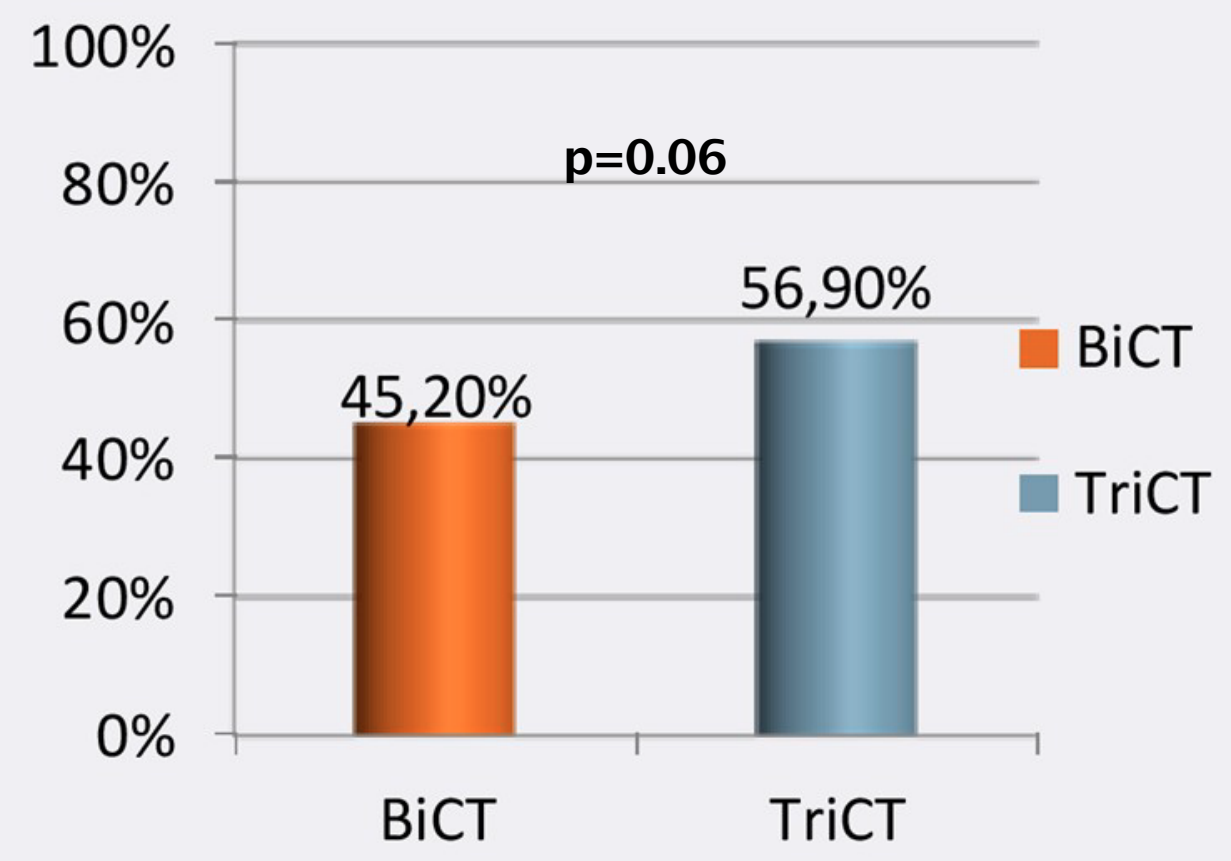
Primary endpoint: R0/R1 resection rate

H0: R0/R1 resection rate with BiCT = 50%
H1: R0/R1 resection rate with TriCT = 70%
2sided-alpha error: 0.05; beta-error: 0.10

Ychou et al., ASCO Ann Meet '16

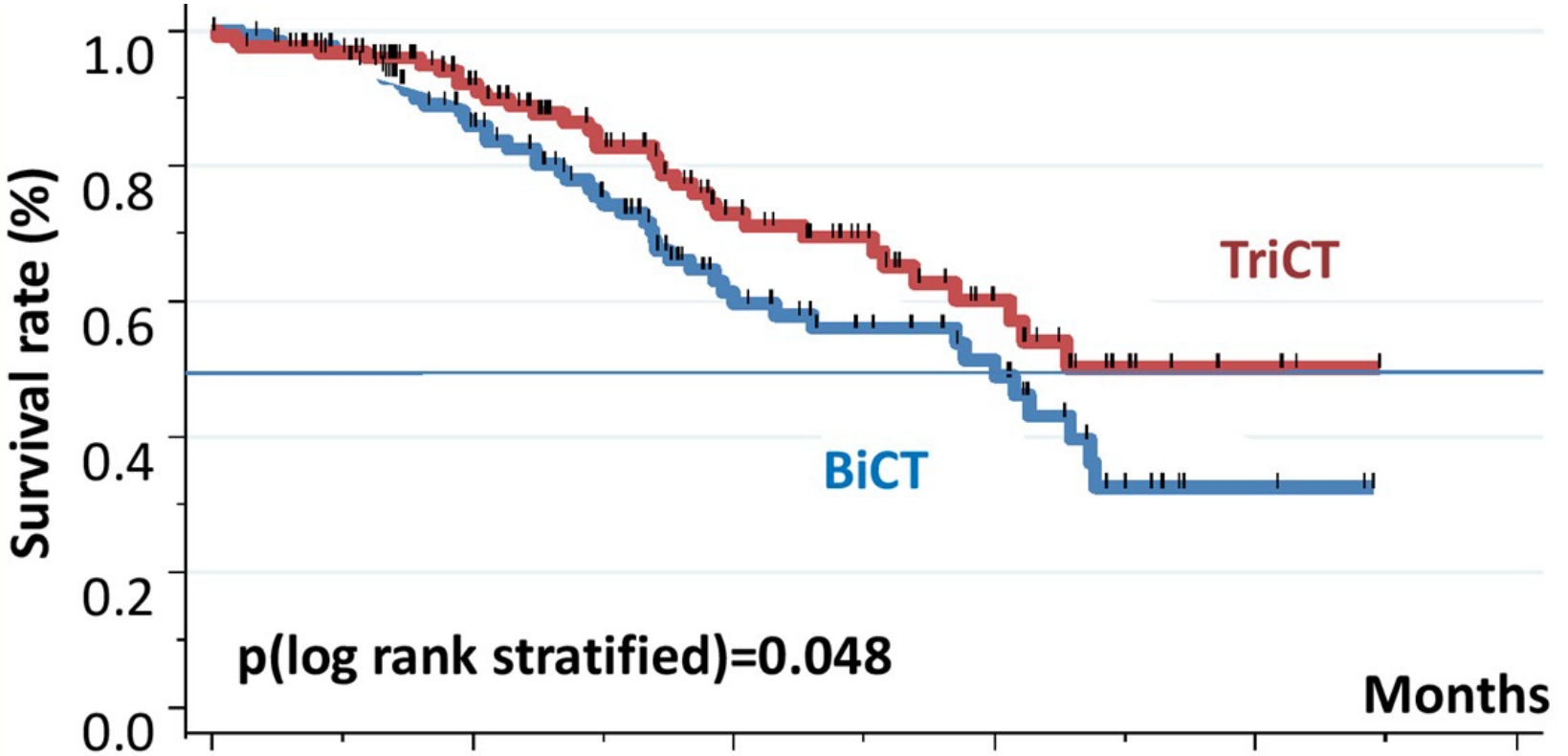
Prodige-14 (Methep-2): primary endpoint

R0/R1 resection rate



Ychou et al., ASCO Ann Meet '16

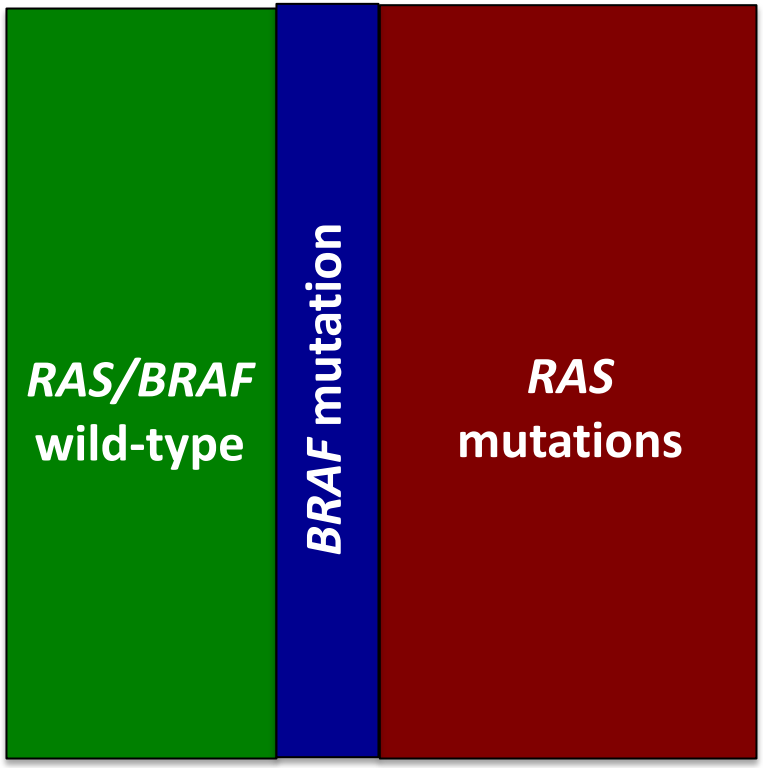
Prodige-14 (Methep-2): secondary endpoint OS



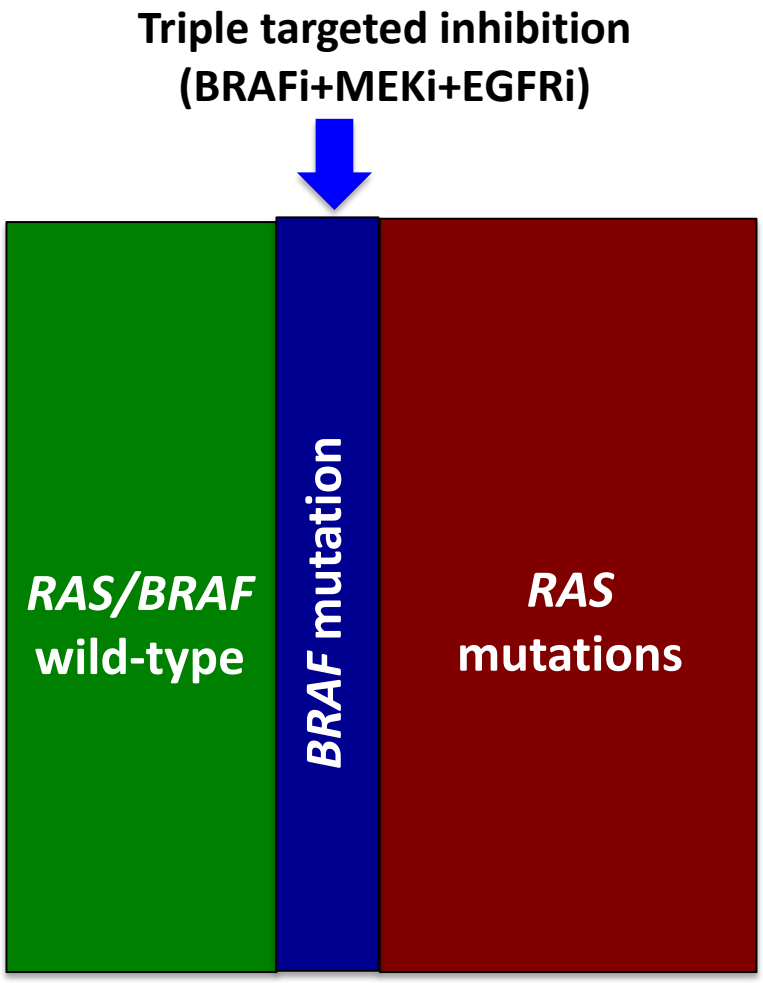
Number at risk	12	24	36	48	60
BiCT 126	80	37	21	3	0
TriCT 127	90	46	20	3	0

Ychou et al., ASCO Ann Meet '16

Innovative regimens in the next future

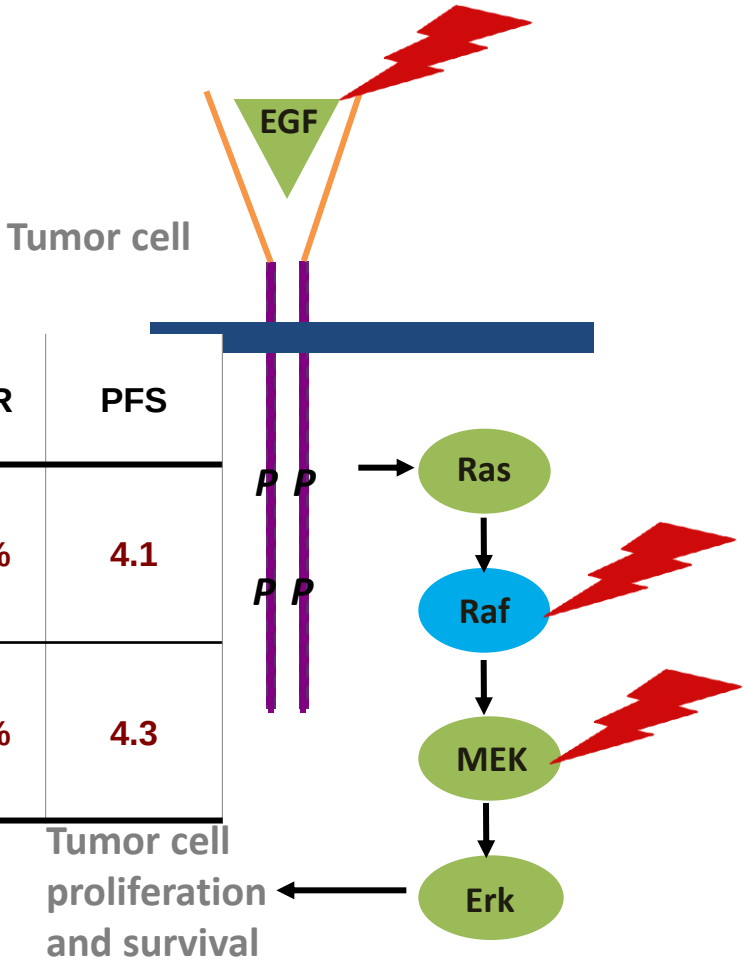


Innovative regimens in the next future



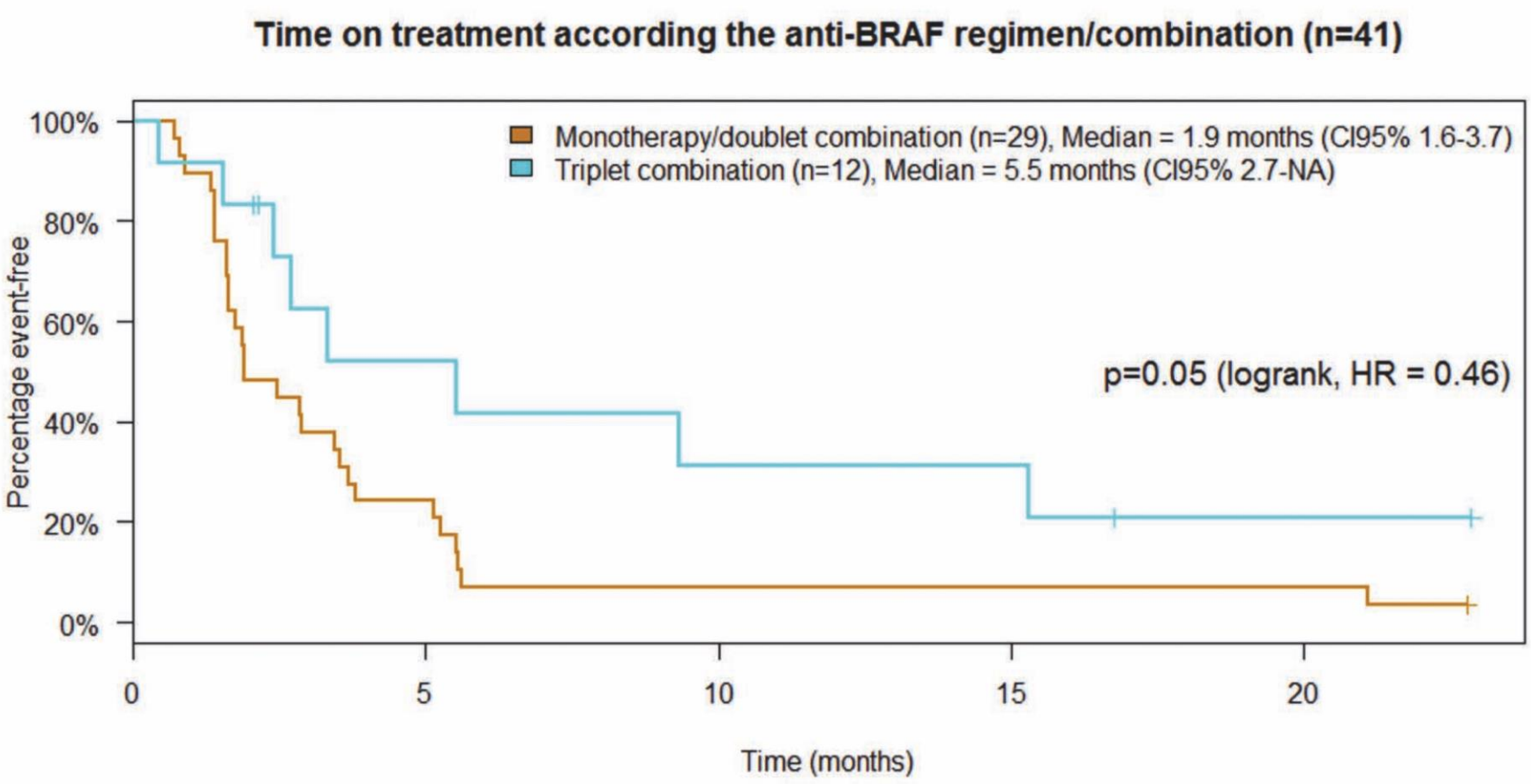
Targeted approaches: BRAFi + MEKi/PIK3CAi + EGFRi

Study *Reference*	N	RR	DCR	PFS
Dabrafenib + Trametinib + Panitumumab *Atreya, ASCO Ann Meet '15*	35	26%	60%	4.1
Encorafenib + Alpelisib + Cetuximab *Elez, WCGIC '15*	28	32%	94%	4.3



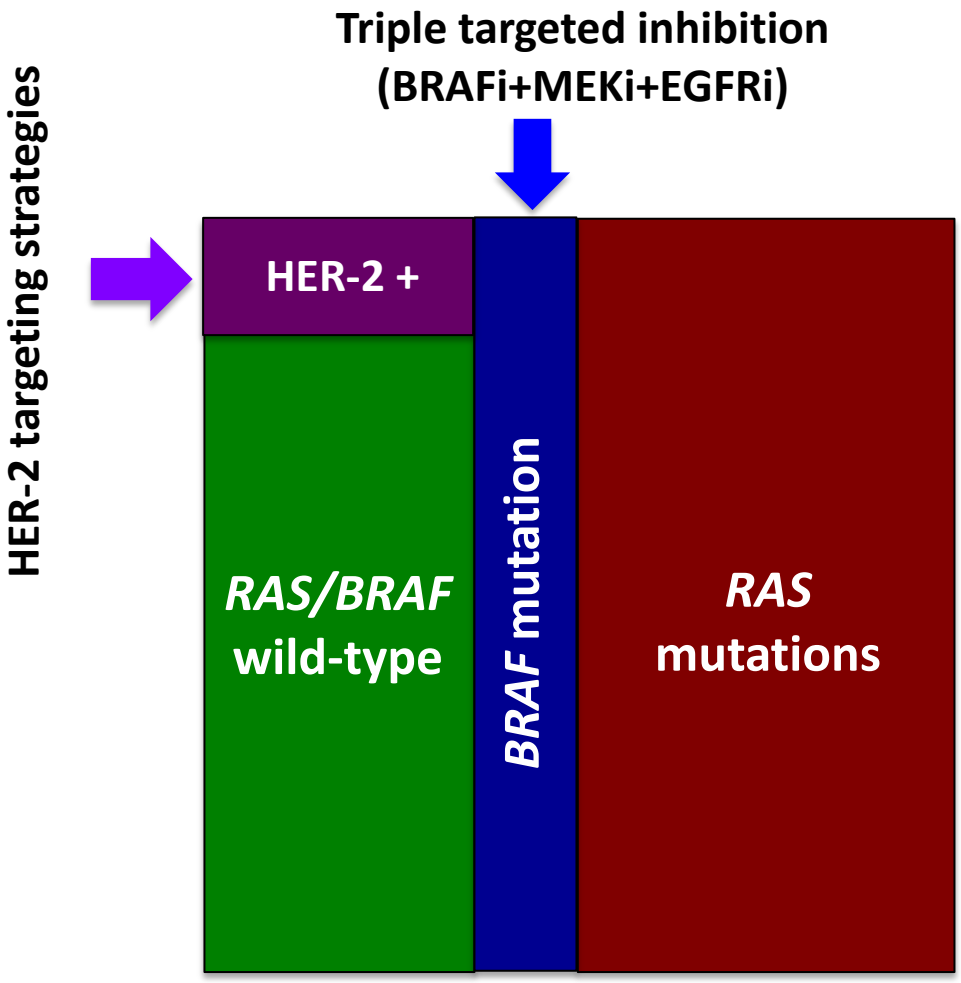
Triple combinations are the most promising approach

Comparison of patients treated with BRAFi monotherapy or BRAFi-including combinations in early clinical trials at Vall d'Hebron Institute of Oncology



Sanz-Garcia et al, ASCO GI'16

Innovative regimens in the next future



HERACLES trial

27 HER-2 +, *KRAS* wt mCRC pts progressed after fluoropyr, oxaliplatin, irinotecan and an anti-EGFR moAb

Trastuzumab + Lapatinib

PD

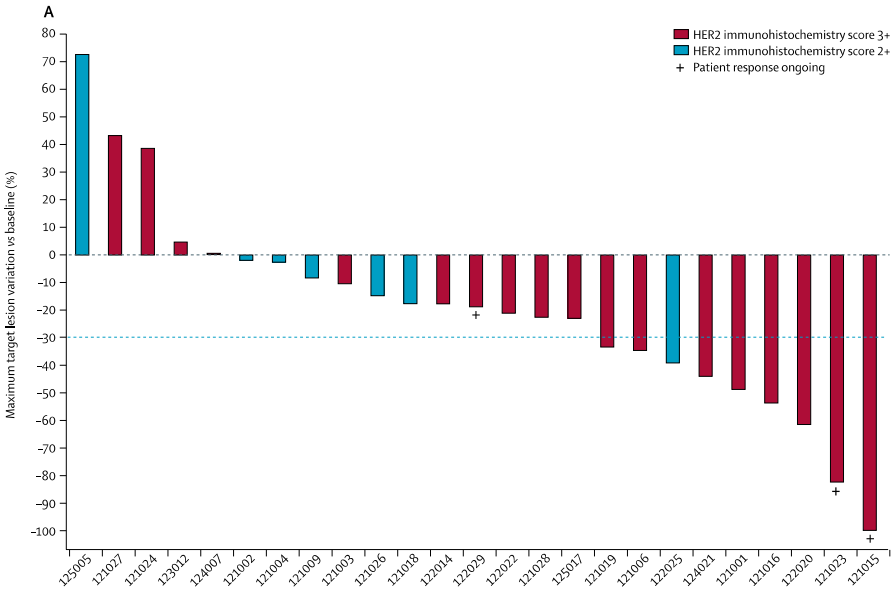
Phase II, primary endpoint: ORR (Recist 1.1)

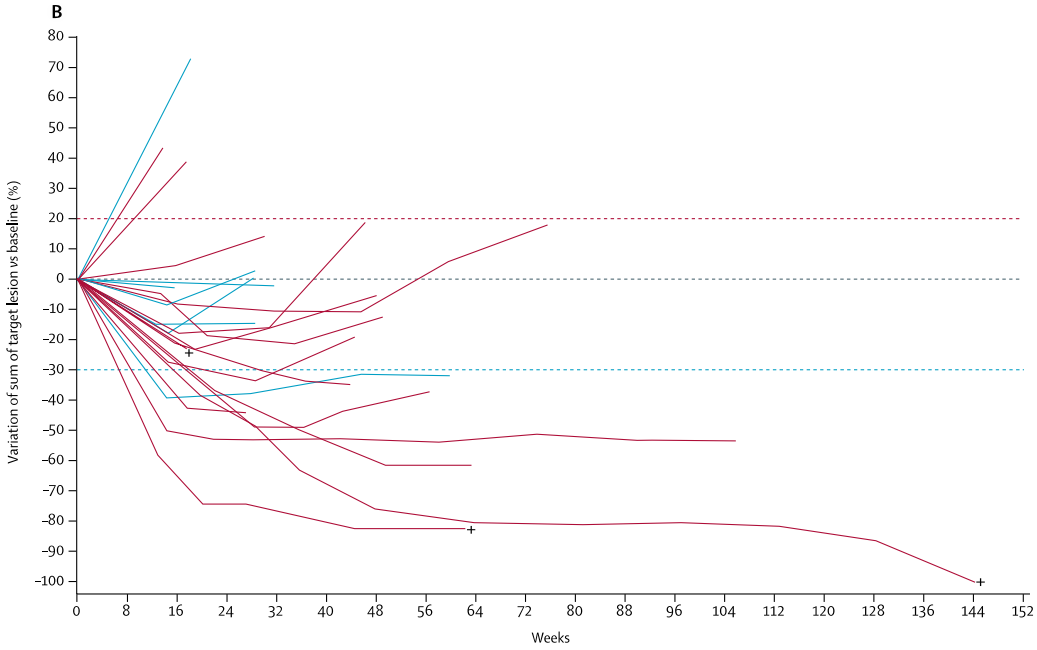
H0: ORR: 10%
H1: ORR> 30%
α: 0.05; β:0.15
At least 6 responders out of 27 pts

	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)

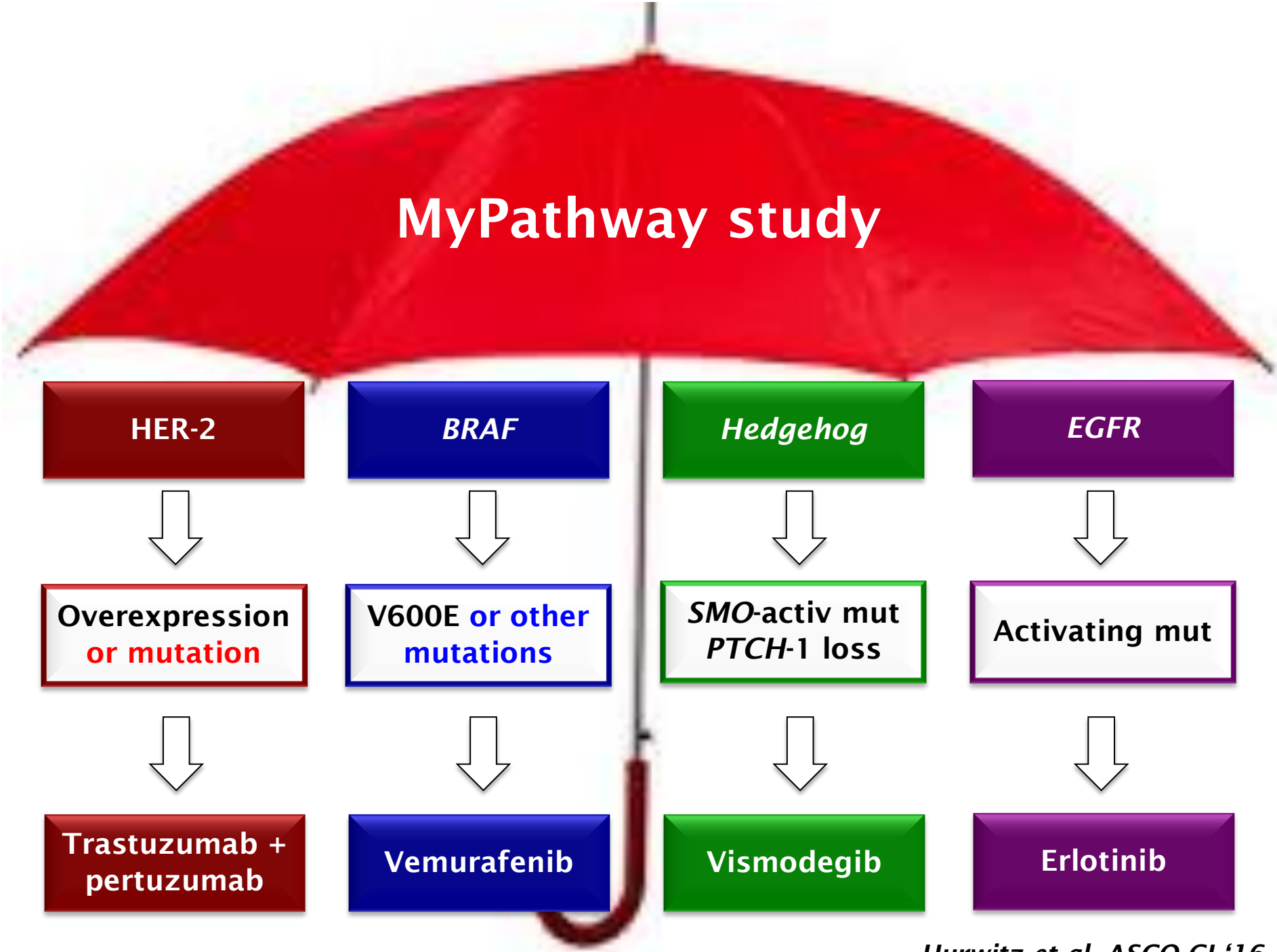
Sartore Bianchi et al, Lancet Oncology '16

Clinically relevant and durable responses



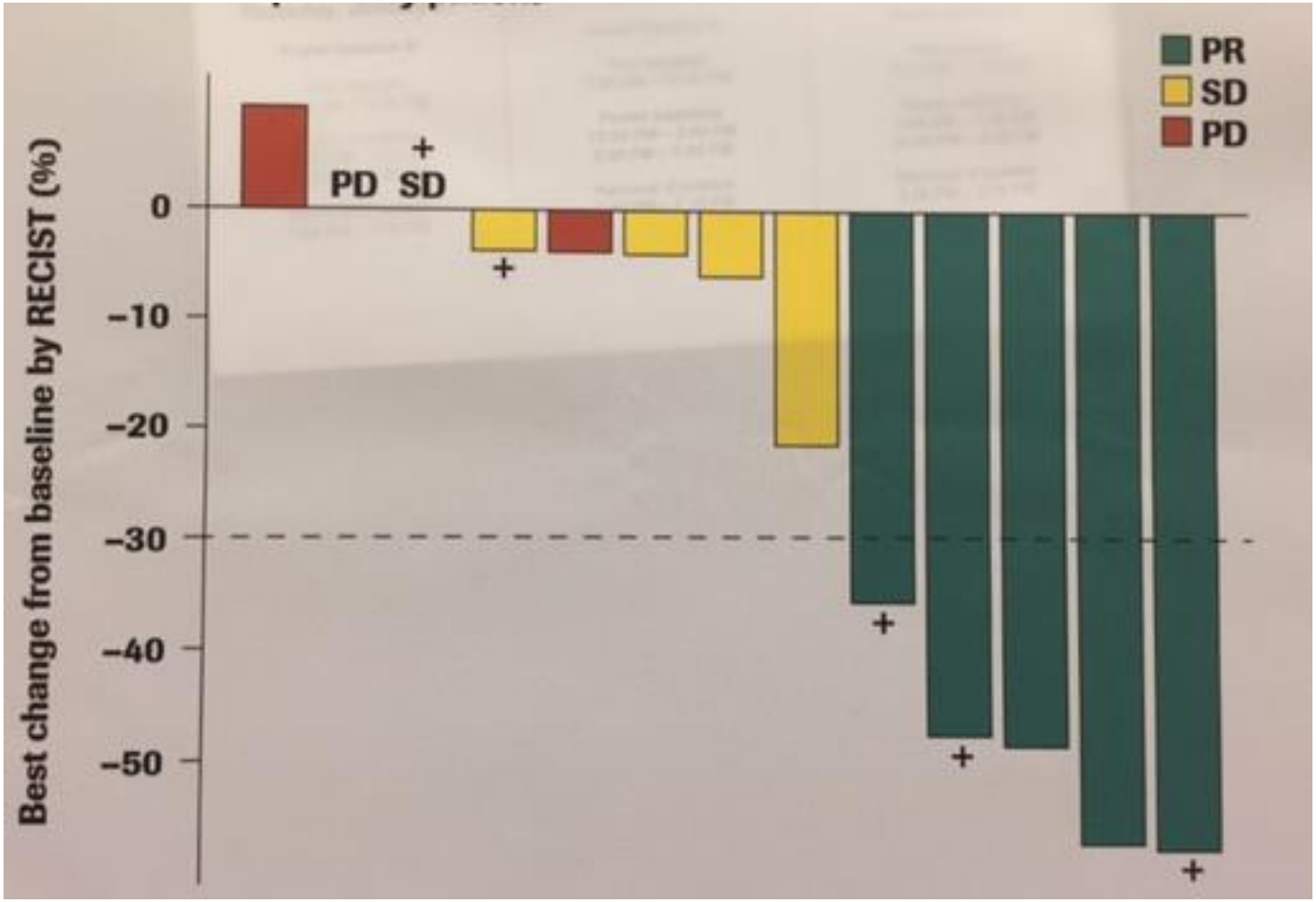


Sartore Bianchi et al, Lancet Oncology '16



Hurwitz et al, ASCO GI '16

ORR in HER-2+ mCRC

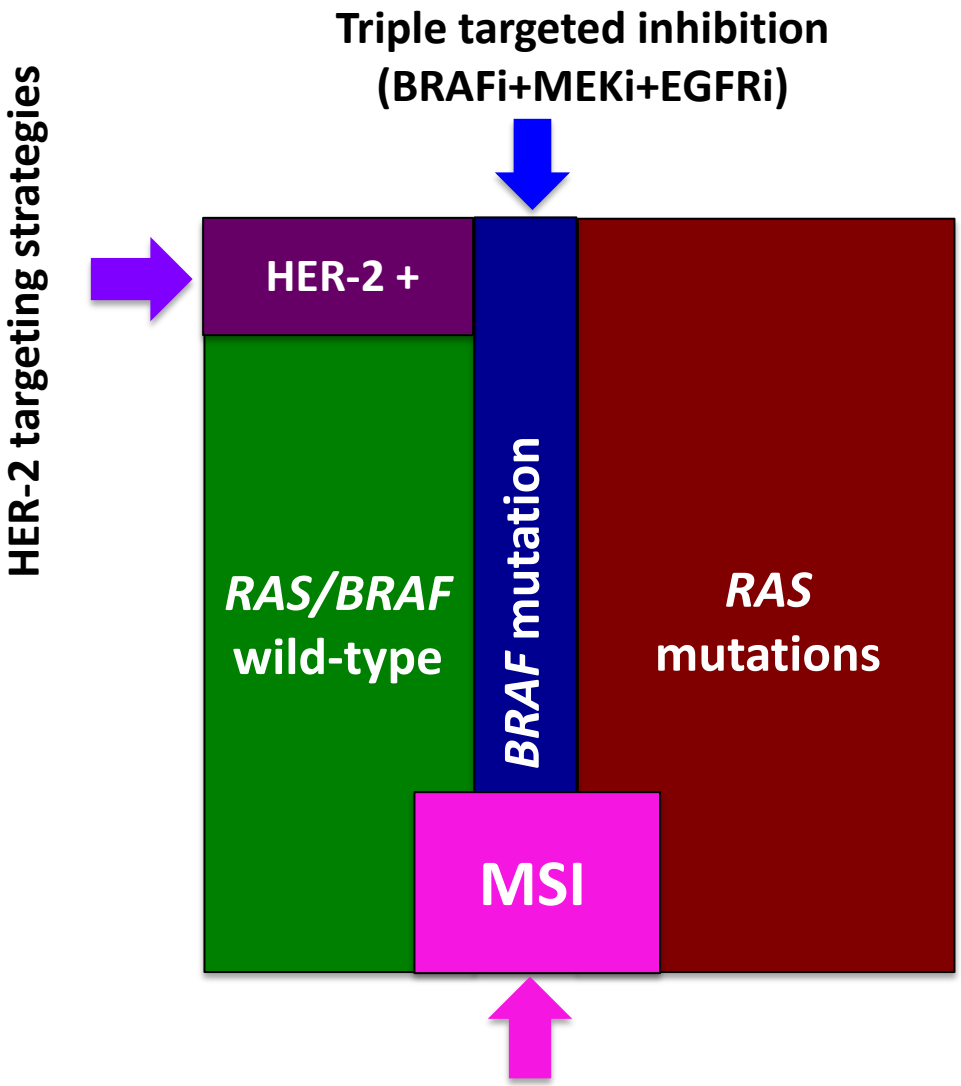


ORR: 5/13

DCR: 10/13

Hurwitz et al, ASCO GI '16

Innovative regimens in the next future



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