1° Workshop: Diagnostica Molecolare e Farmaci Innovativi

I “driver” molecolari per i nuovi farmaci a bersaglio: Tumore del Colon-Retto

Trieste 17-18 gennaio 2018

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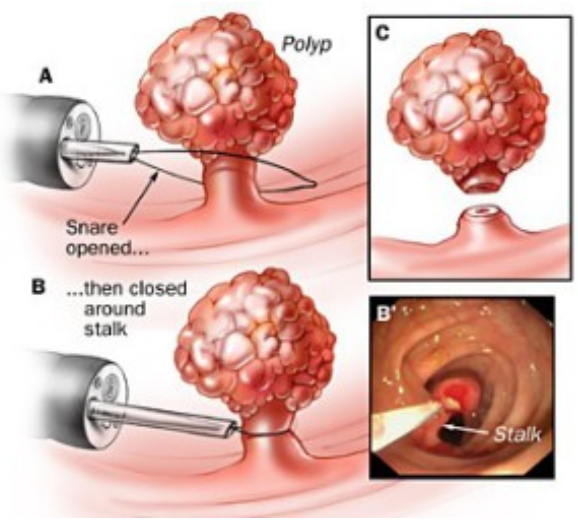
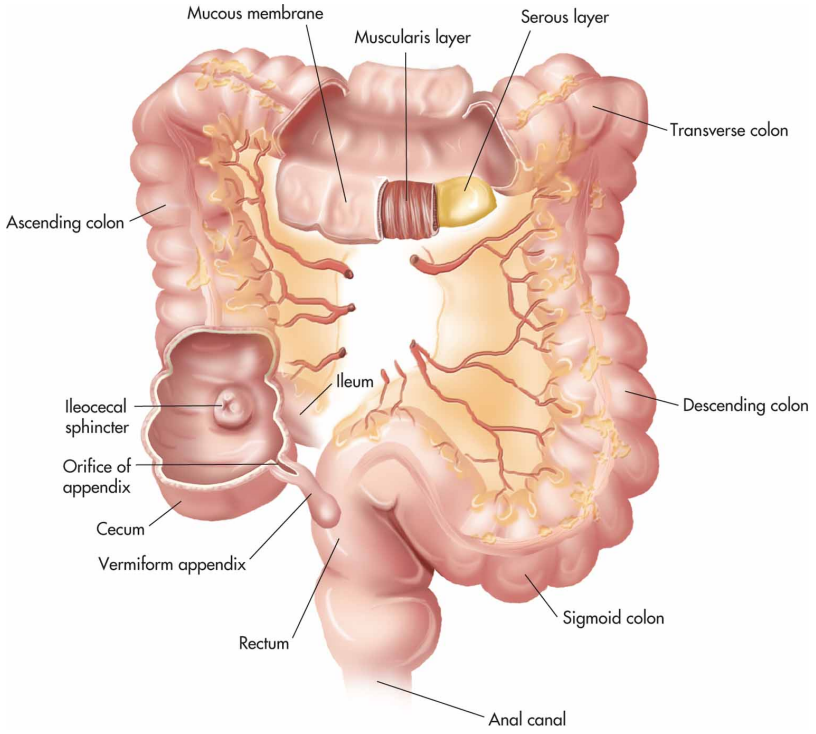
Some time ago…





OUTLINE

Colon cancer

CMS4

EGFR

KRAS Esone 2

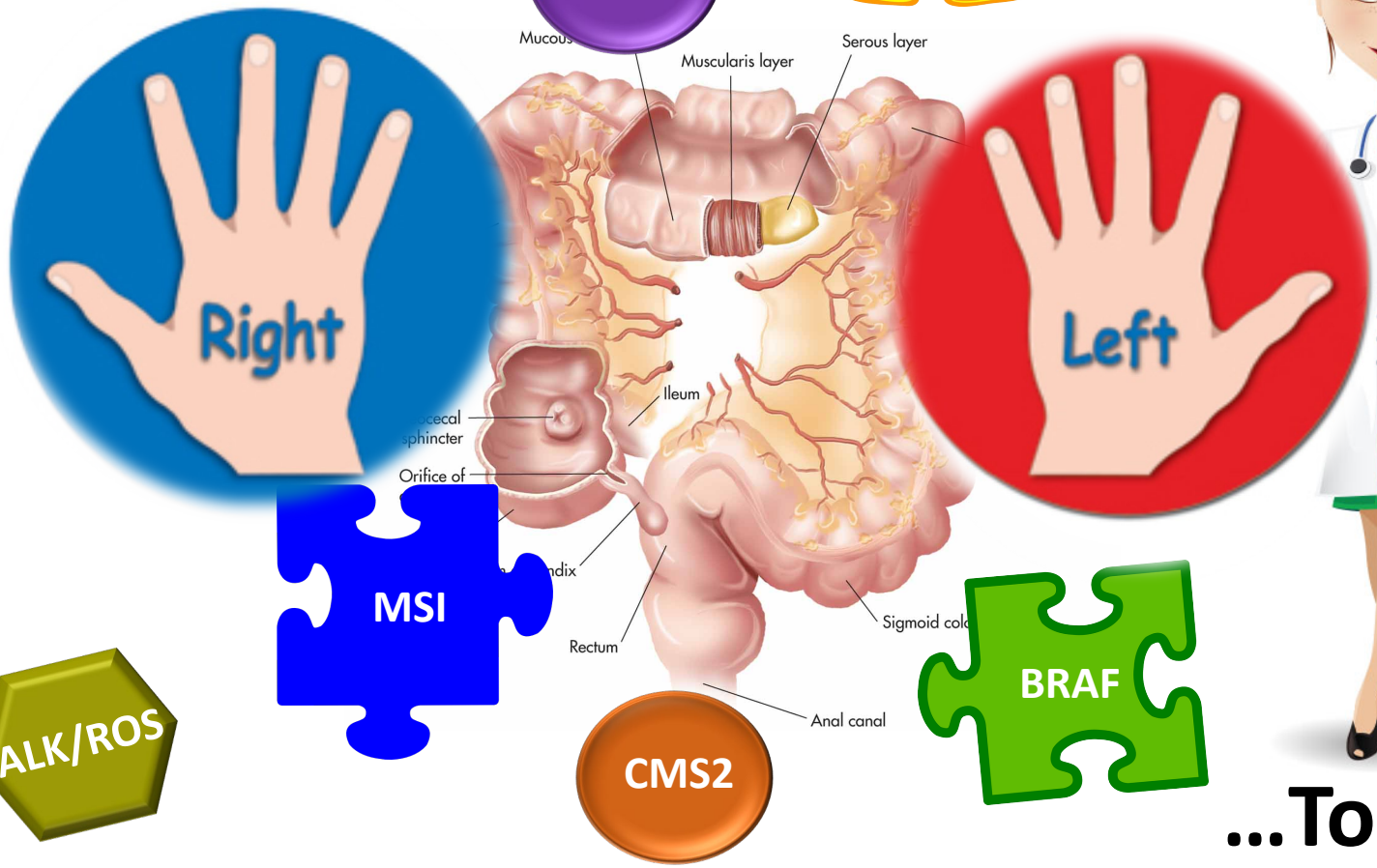
KRAS Esone 3-4

NRAS

MGMT

HER-2

CMS3



C-MET

CMS1

MSI

BRAF

ALK/ROS

CMS2

...Today

OUTLINE

Colon cancer

OUTLINE

Colon cancer

Genomic markers

Biomarkers useful:

- *RAS, BRAF, MSI*

Biomarkers currently not useful:

- EGFR pathway related: *HER2, MET, ALK/ROS1/NTRK and EGFR*
- EGFR pathway unrelated: *MGMT*

Transcriptomic markers

CMS groups

Colorectal cancer

Metastatic setting

Multiple algorythms were developed to direct the management of first line treatment in mCRC

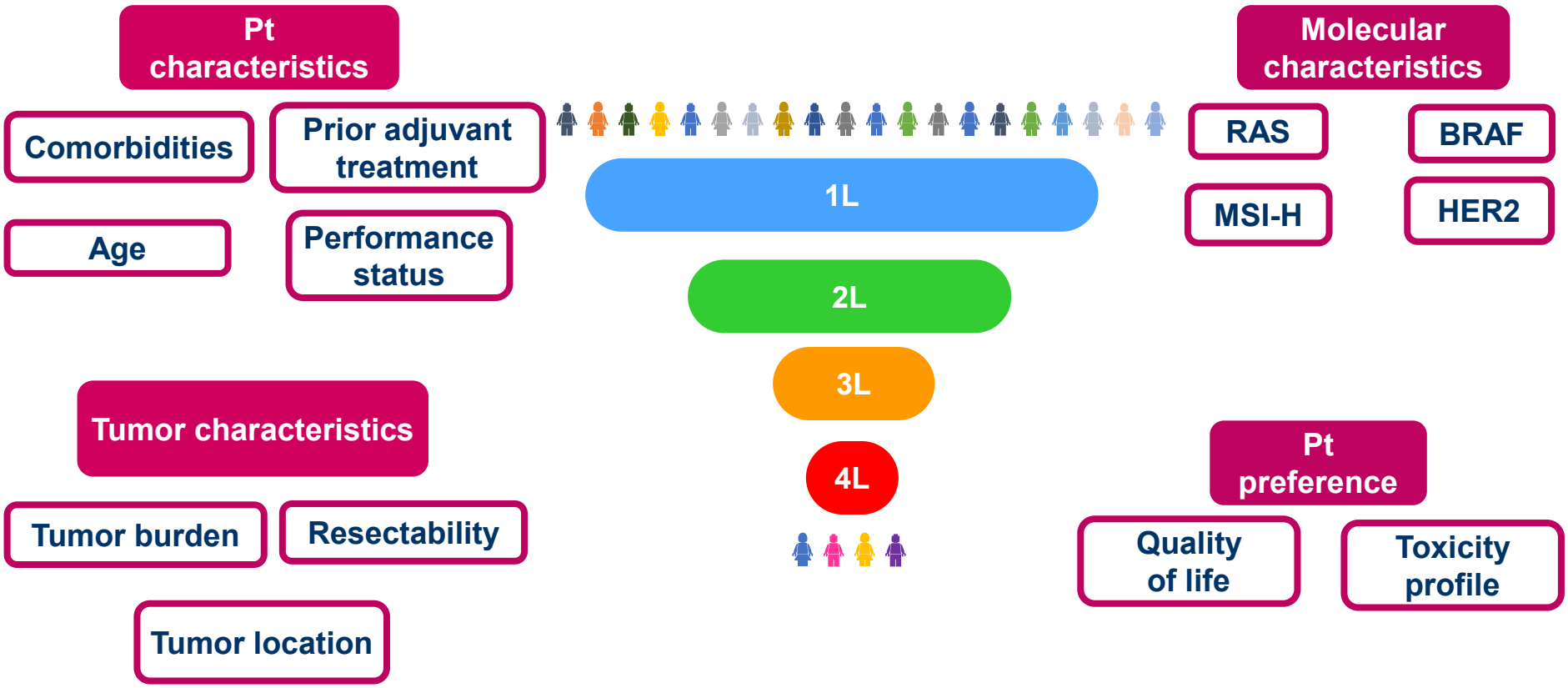
However, data from randomized trials did not clarify the superiority of anti-angiogenic vs anti-EGFR strategy in this setting

In addition, the role of FOLFOXIRI + bevacizumab in the clinical practice is still under debate

Colorectal cancer

Decision making process

Drivers for decision making in 1st line treatment

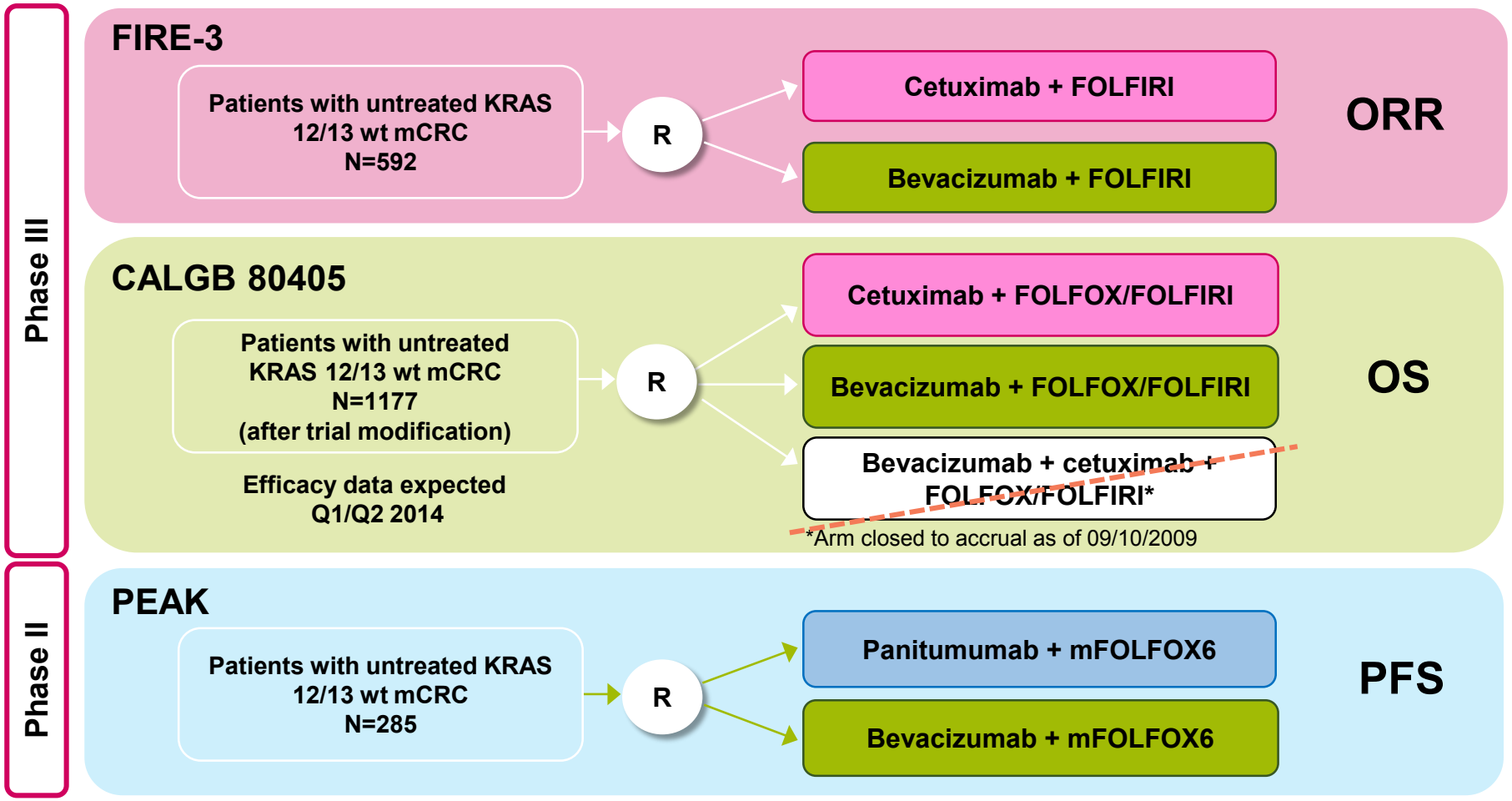


KRAS wt

Colorectal cancer

First line chemotherapy

1st endpoint



Stintzing S, et al. ESMO 2014; Lenz H, et al. ESMO 2014; Schwartzberg

KRAS wt

Colorectal cancer

First line chemotherapy

	RR		PFS		OS	
	CET/PAN	BEV	CET/PAN	BEV	CET/PAN	BEV
FIRE-3 N=400 *RR 1st endpoint*	65%	59%	10.3	10.2	**33.1**	**25.0**
	P=0.18		HR=0.97		**HR=0.70, P=0.006**	
	NEGATIVE		**NEGATIVE**		**POSITIVE**	
CALGB 80405 N=526 *OS 1st endpoint*	**69%**	**54%**	11.4	11.3	32.0	31.2
	P<0.01		HR=1.10		HR=0.90	
	POS/NEG		**NEGATIVE**		**NEGATIVE**	
PEAK N=170 *PFS 1st endpoint*	64%	61%	**13.0**	**10.1**	***41.3***	***28.9***
	NA		**0.029**		***0.058***	
	NA		**"POSITIVE"**		***POS/NEG***	

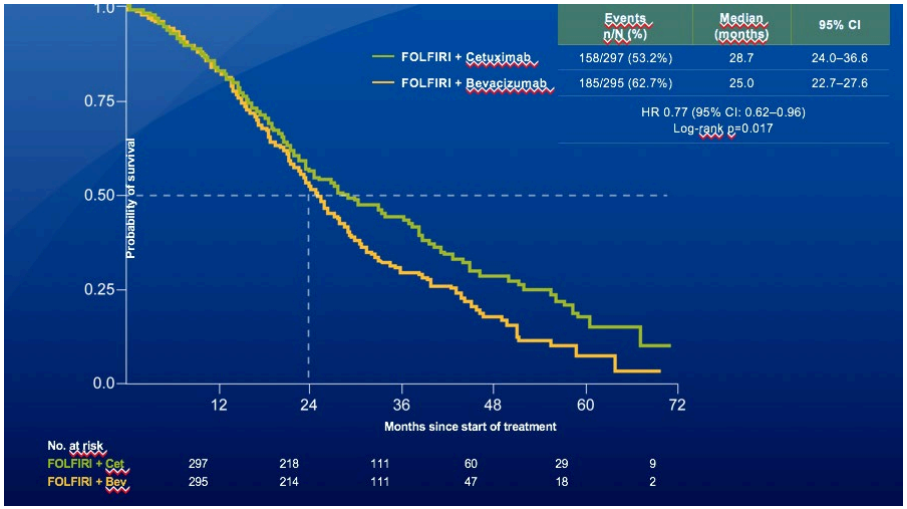
Stintzing S, et al. ESMO 2014; Lenz H, et al. ESMO 2014; Schwartzberg

KRAS wt

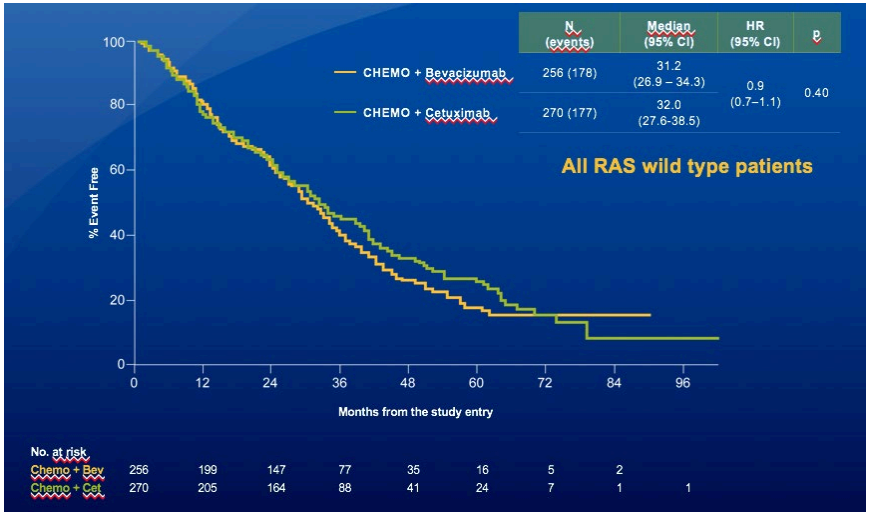
Colorectal cancer

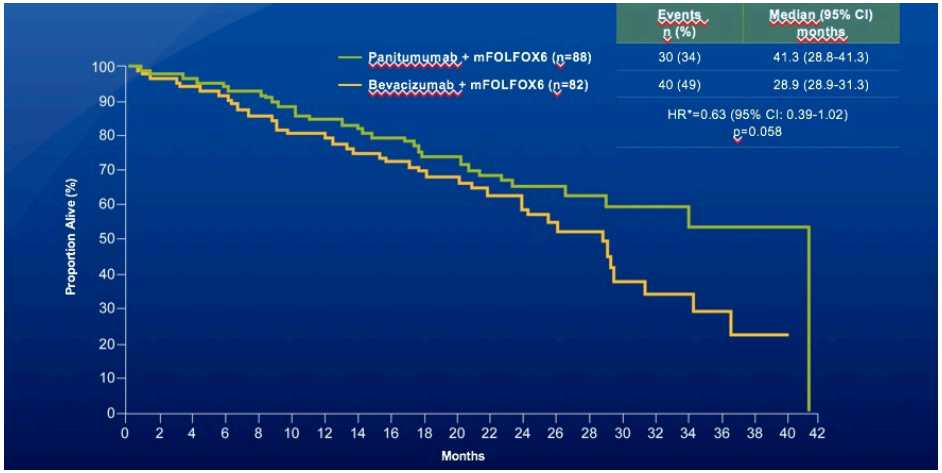
First line chemotherapy

FIRE-3



CALGB





PEAK

Stintzing S, et al. ESMO 2014; Lenz H, et al. ESMO 2014; Schwartzberg

Tumor location

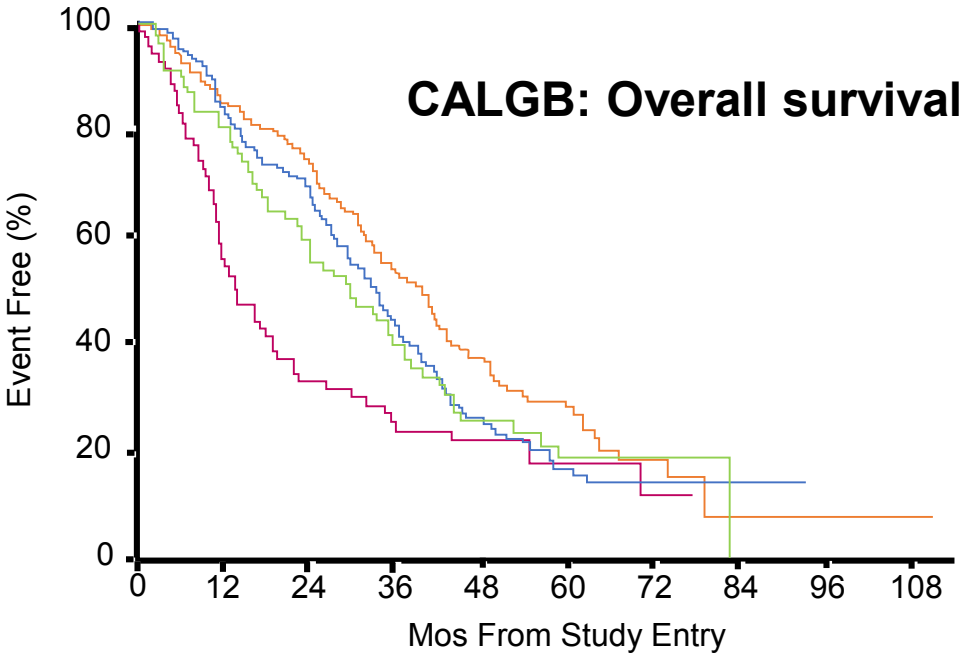
Is sidedness the answer?
Left vs Right

Left vs Right

Worse Prognoses of Right Colon Cancer: an old story

Publication (Study)	Patients N	Molecular selection	Treatment	OUTCOME	RIGHT	LEFT
O' Dwyer JCO 2001 (E2290)	N=1120	None	5FU variations	OS (mos)	10.9	15.8
Brule Eur J Can 2015 (CO.17)	N=399	*KRAS* wt	BSC v. BSC + CET	PFS (mos)	1.9 1.8	1.9 5.4
Loupakis, JNCI 2015	N=2053	None	FILFIRI/BEV FUOX/BEV IFL/BEV	OS (mos)	24.8 18.0 14.6	42.0 23.0 24.0

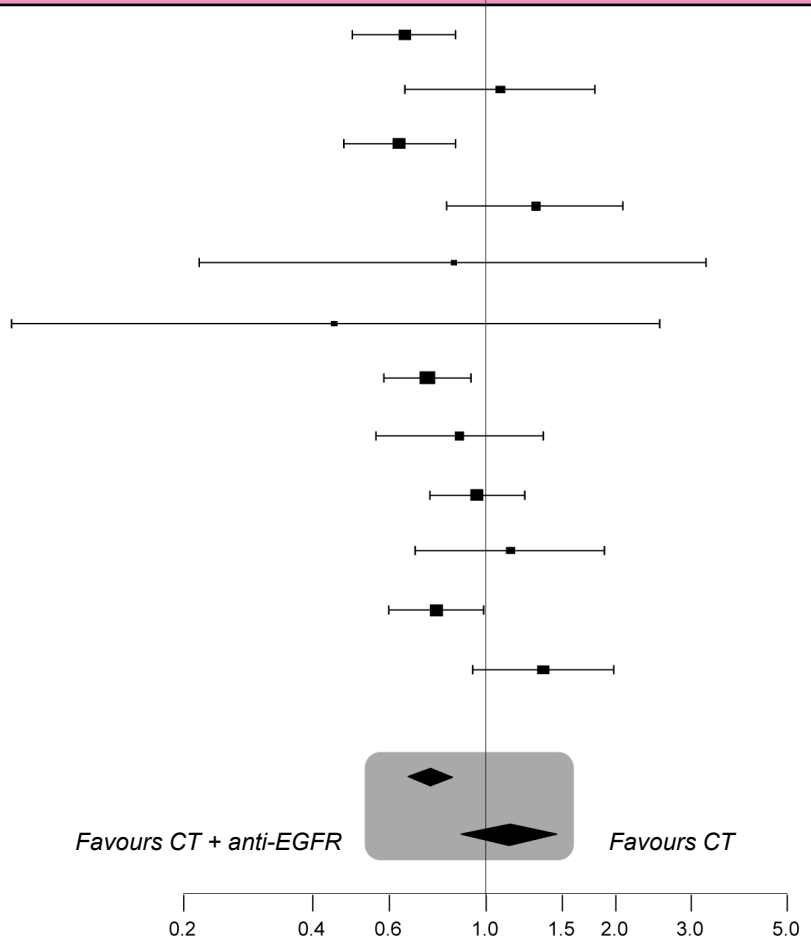
CALGB: Overall survival by sidedness and biologic



	OS (95% CI), Mos		HR (95% CI)	*P* Value
	Left	Right		
Cetuximab (n = 173 vs 71)	39.3 (32.9-42.9)	13.7 (11.3-19.0)	0.55 (0.39-0.79)	.001
Bevacizumab (n = 152 vs 78)	32.6 (28.3-36.2)	29.2 (22.4-36.9)	0.88 (0.62-1.25)	.50

Left vs Right

Trial	HR (95% CI)
CRYSTAL - Left	0.7 (0.5-0.9)
CRYSTAL - Right	1.1 (0.7-1.8)
FIRE3 - Left	0.6 (0.5-0.8)
FIRE3 - Right	1.3 (0.8-2.1)
PEAK - Left	0.8 (0.2-3.3)
PEAK - Right	0.4 (0.1-2.5)
PRIME - Left	0.7 (0.6-0.9)
PRIME - Right	0.9 (0.6-1.4)
181 - Left	1.0 (0.7-1.2)
181 - Right	1.1 (0.7-1.9)
CALGB80405 - Left	0.8 (0.6-1.0)
CALGB80405 - Right	1.4 (0.9-2.0)
Total Left	**0.75 (0.67-0.84)**
Total Right	**1.14 (0.88-1.47)**



Douillard YJ, Pignon JP. ESMO 2016

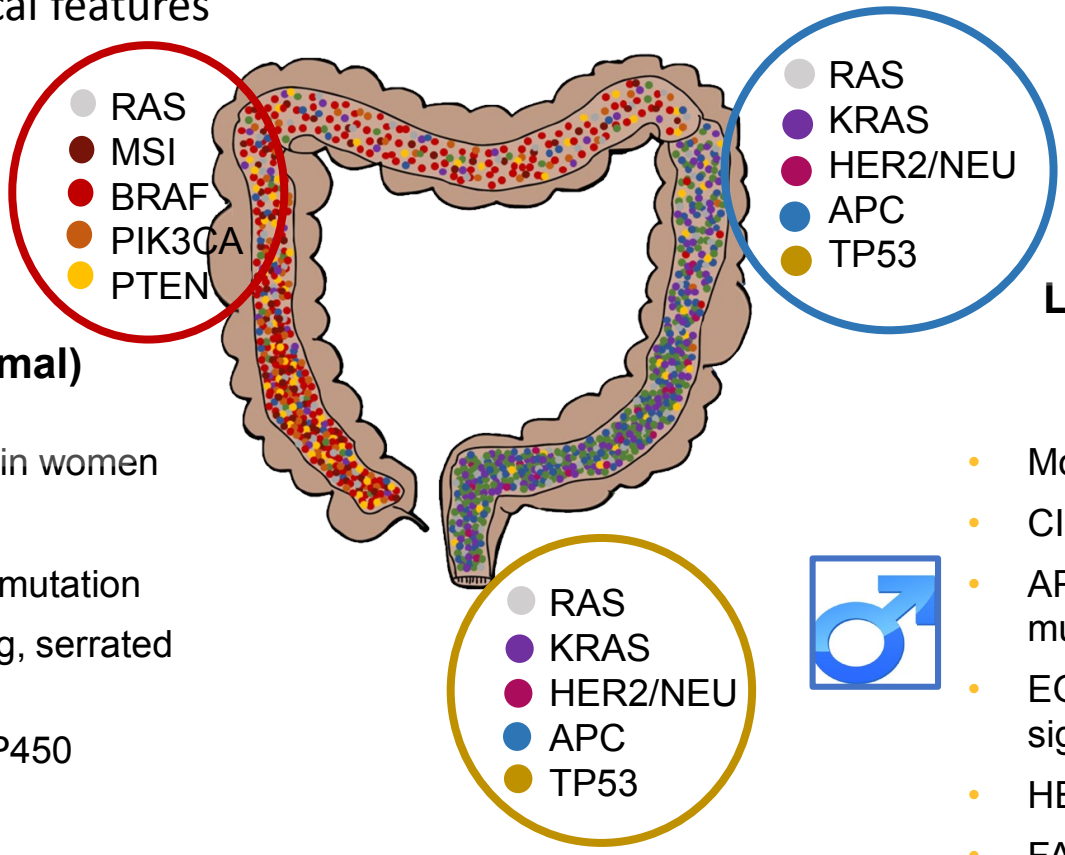
Colorectal cancer

Tumor location

Left vs Right

Different embryogenesis accounts for:

- Different blood supply *(SMA/IMA)*
- Different biological features



Right-sided (proximal) colon cancer

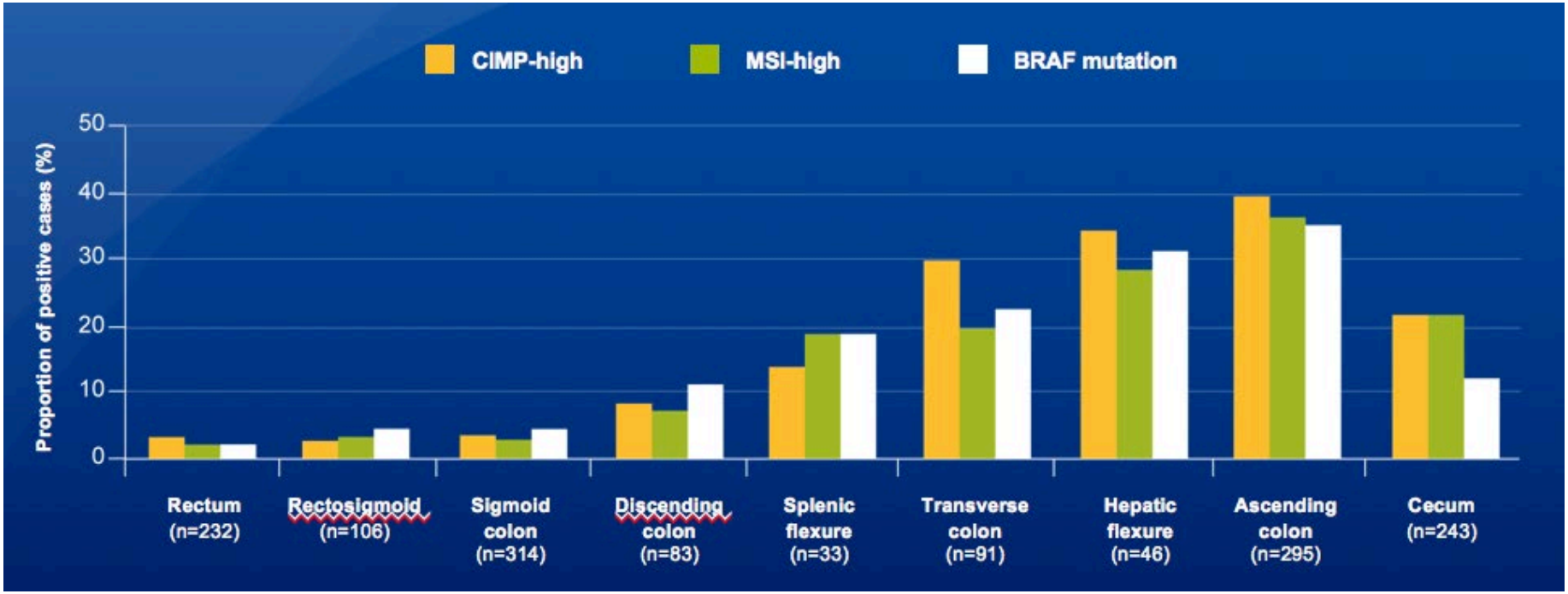
- More common in women
- dMMR/MSI-H
- CIMP+. BRAF mutation
- MAPK signaling, serrated pathway
- Mutagenic CYP450 metabolites
- HNPCC
- CMS1 (Immune)
- CMS3 (Metabolic)

Left-sided (distal) colon cancer

- More common in men
- CIN
- APC, KRAS, DCC, p53 mutations
- EGFR signaling, Wnt signaling
- HER1, HER2 amplification
- FAP
- CMS2 (Canonical)
- CMS4 (Mesenchimal)

Left vs Right

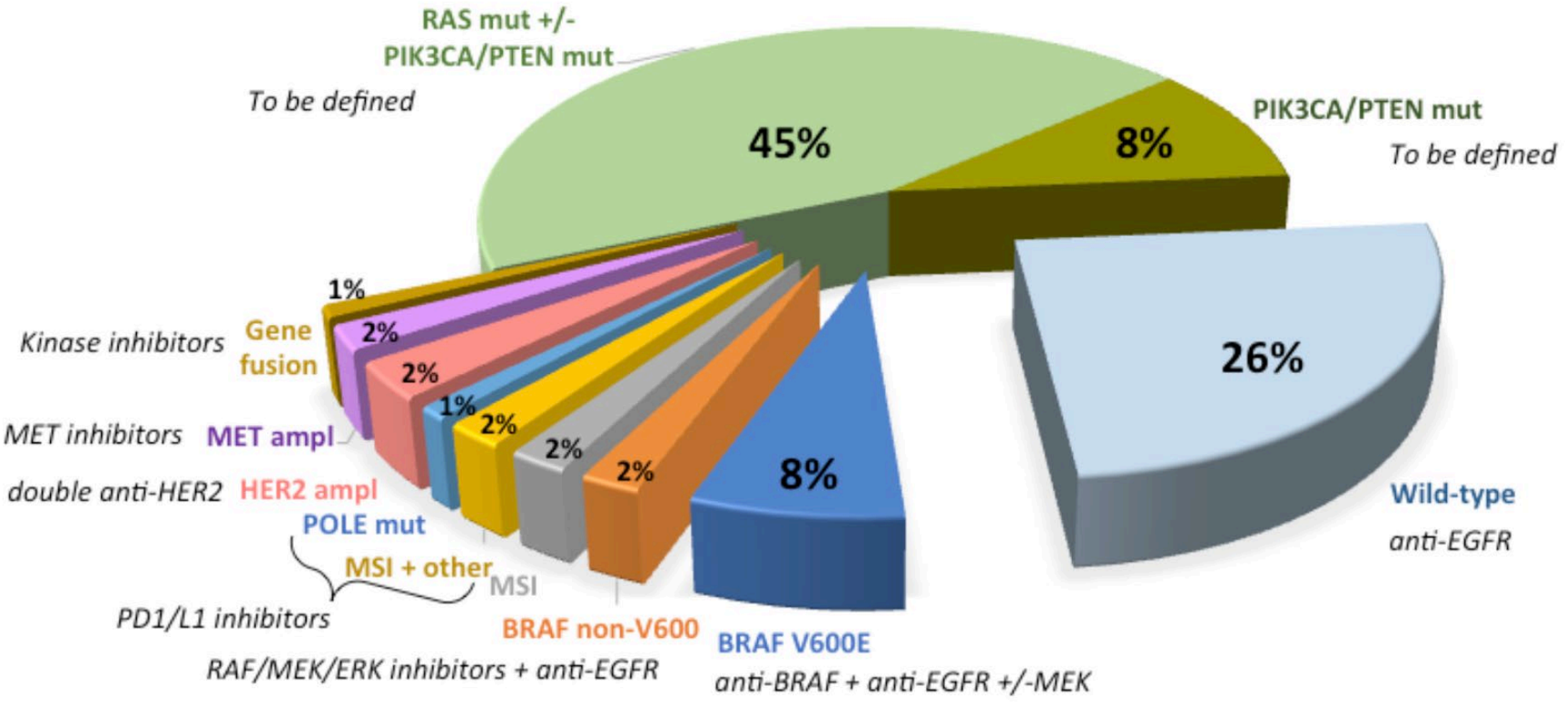
Increase of BRAF mutation and microsatellite instability from the rectum to ascending colon



Yamauchi M et al, Gut 2012

Colorectal cancer

Somatic mutation



Colorectal cancer

RAS mutation

KRAS

- Exon 2 ➡ 35%
- Exon 3 ➡ 4,3%
- Exon 4 ➡ 6,7%

NRAS

- Exon 2 ➡ 3,8%
- Exon 3 ➡ 4,8%
- Exon 4 ➡ 0,5%

PROGNOSTIC ROLE AND PREDICTIVE OF PRIMARY RESISTANCE TO ANTI-EGFRs

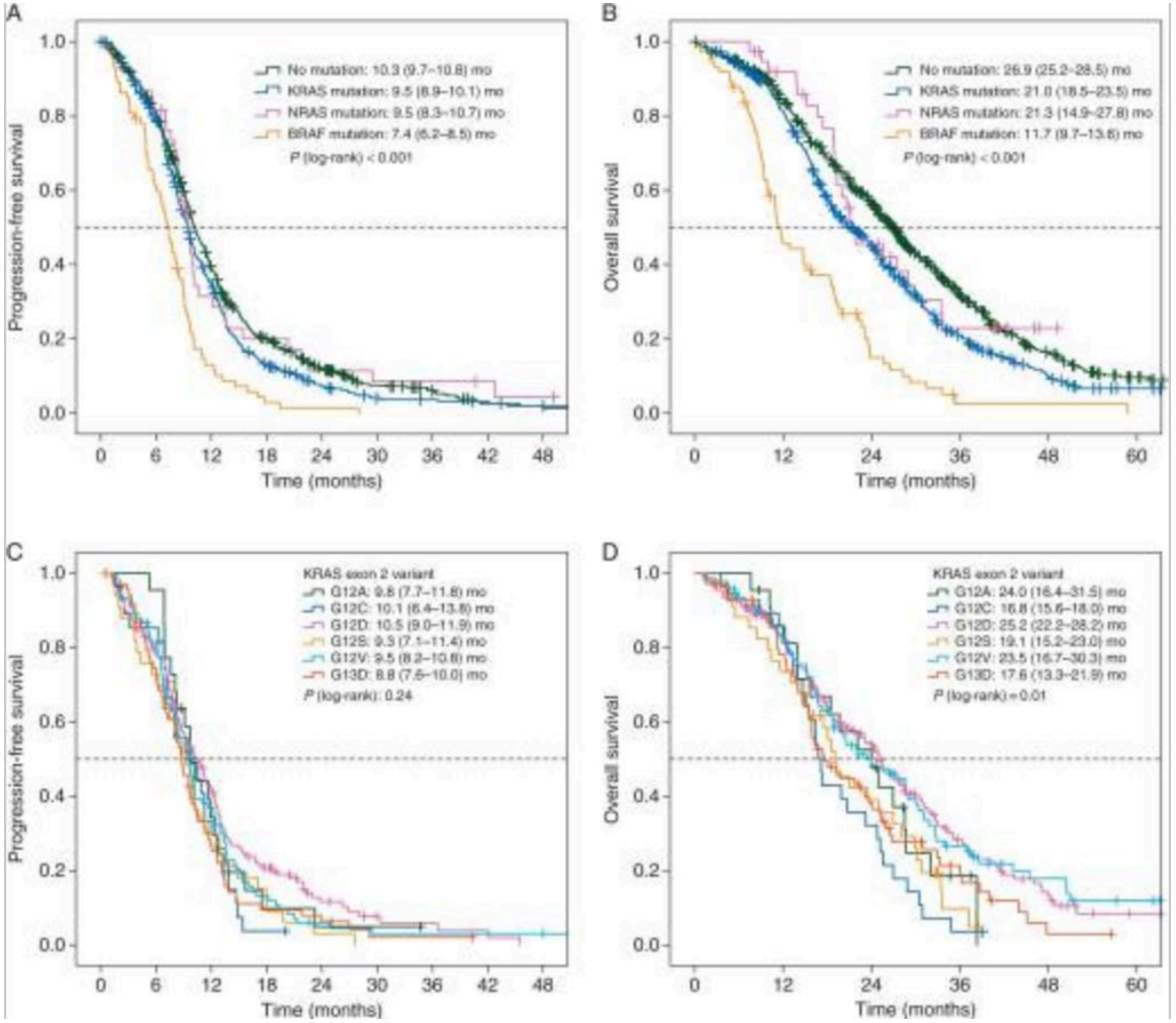
KRAS

Colorectal cancer

Prognostic role

- A total of 1239 patients from five randomized trials (FIRE-1, FIRE-3, AIOKRK0207, AIOKRK0604, RO91) were included into the analysis.

- PFS and OS were significantly influenced by molecular subgroups



D.P. Modest Ann Oncol 2016

KRAS

Predictive role

Mutant *RAS* and outcome with anti-EGFR

	PRIME[1,2]			OPUS[3,4]			CRYSTAL[5,6]		
	Treatment	PFS	OS	Treatment	PFS	OS	Treatment	PFS	OS
***KRAS* Ex2 WT**	Panitumumab + FOLFOX4 (n = 325)	**10.0**	**23.9**	Cetuximab + FOLFOX4 (n = 82)	**8.3**	**22.8**	Cetuximab + FOLFIRI (n = 316)	**9.9**	**23.5**
	FOLFOX4 (n = 331)	**8.6**	**19.7**	FOLFOX4 (n = 97)	**7.2**	**18.5**	FOLFIRI (n = 350)	**8.4**	**20.0**
		HR 0.80*	**HR 0.88**		**HR 0.57***	**HR 0.86***		**HR 0.70***	**HR 0.80***
***KRAS* Ex2 MT**	Panitumumab + FOLFOX4 (n = 221)	**7.4**	**15.5**	Cetuximab + FOLFOX4 (n = 77)	**5.5**	**13.4**	Cetuximab + FOLFIRI (n = 214)	**7.4**	**16.2**
	FOLFOX4 (n = 219)	**9.2**	**19.2**	FOLFOX4 (n = 59)	**8.6**	**17.5**	FOLFIRI (n = 183)	**7.7**	**16.7**
		HR 1.27*	**HR 1.17**		**HR 1.72***	**HR 1.29**		**HR 1.17**	**HR 1.04**
No *RAS* MT	Panitumumab + FOLFOX4 (n = 259)	**10.1**	**25.8**	Cetuximab + FOLFOX4 (n = 38)	**12.0**	**19.8**	Cetuximab + FOLFIRI (n = 178)	**11.4**	**28.4**
	FOLFOX4 (n = 253)	**7.9**	**20.2**	FOLFOX4 (n = 49)	**5.8**	**17.8**	FOLFIRI (n = 189)	**8.4**	**20.2**
		HR 0.72*	**HR 0.77***		**HR 0.53***	**HR 0.94***		**HR 0.56***	**HR 0.69***
Any *RAS* MT	Panitumumab + FOLFOX4 (n = 272)	**7.3**	**15.5**	Cetuximab + FOLFOX4 (n = 92)	**5.6**	**13.5**	Cetuximab + FOLFIRI (n = 246)	**7.4**	**16.4**
	FOLFOX4 (n = 276)	**8.7**	**18.7**	FOLFOX4 (n = 75)	**7.8**	**17.8**	FOLFIRI (n = 214)	**7.5**	**17.7**
		HR 1.31*	**HR 1.21***		**HR 1.54***	**HR 1.29**		**HR 1.10**	**HR 1.05**

Before the first line of metastatic colorectal carcinoma

The Right

Timing

KRAS

Colorectal cancer

Is liquid biopsis needed?

CAPRI-GOIM trial:

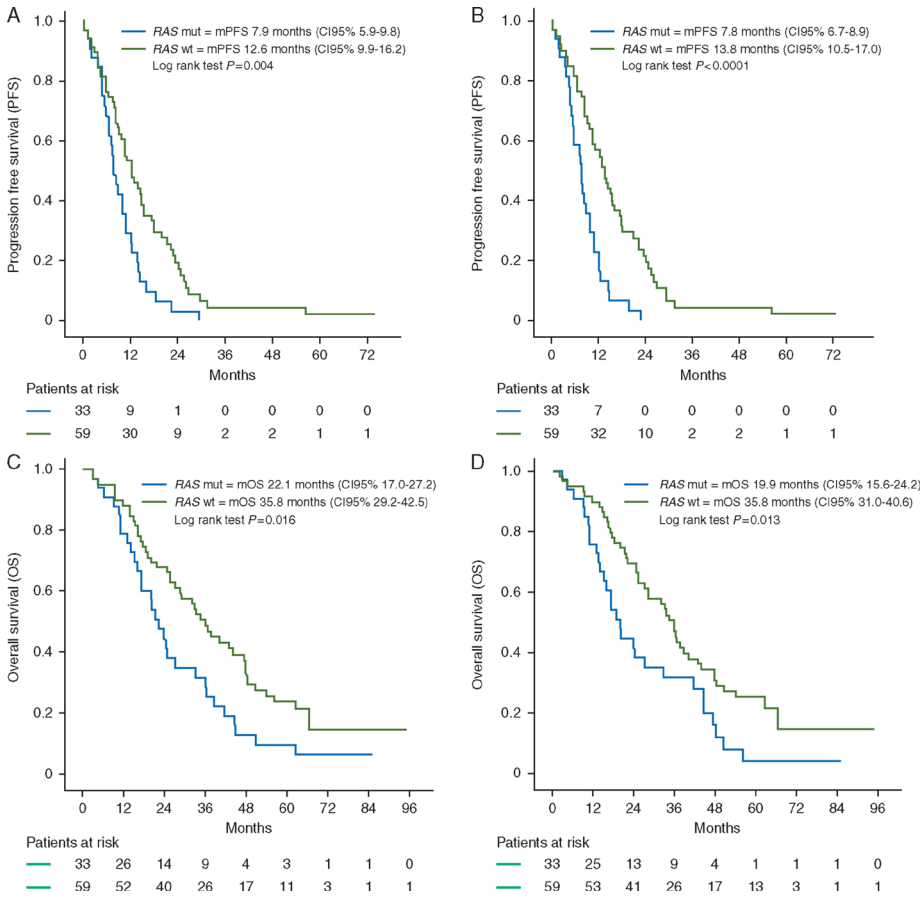
RAS wt, evaluable for both tissue and plasma NGS

New RAS in tissue or plasma associated with shorter PFS and OS

1) Was tissue-based analysis sensitive enough as compared to plasma-based analysis?

2) Can we improve the prediction primary resistance?

Plasma KRAS/NRAS mutational status (n)				
	N	n	Rate (%)	95 % CI
Concordance	92	72	78,3	69,8 ; 86,7
Sensitivity	33	23	69,7	54,0 ; 85,4
Specificity	59	49	83,1	73,5 ; 92,6
PPV	33	23	69,7	54,0 ; 85,4
NPV	59	49	83,1	73,5 ; 92,6



Low concordance between NGS on tissue and plasma

- 10% false negatives in tissue (all detected by ultradeep-seq)
- 10% false negatives in plasma (few detected by ddPCR)

KRAS

Colorectal cancer

Is liquid biopsis needed?

CAPRI-GOIM trial:

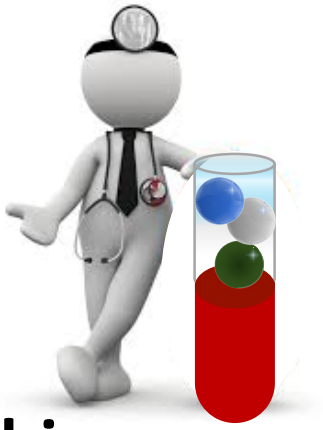
RAS wt, evaluable for both tissue and plasma NGS

OPEN QUESTION:

Cases with lower RAS MAF/fractional abundance may have initial benefit (debulking) and may just develop acquired resistance more rapidly?

Is this a mirror of CRC heterogeneity?

What to do in practice? Leave anti-EGFR at later lines?



Or do we just need to apply ultra-sensitive tecniques on tissue biopsies?

Which is the clinically relevant RAS minor allele fraction (MAF)/fractional abundance?

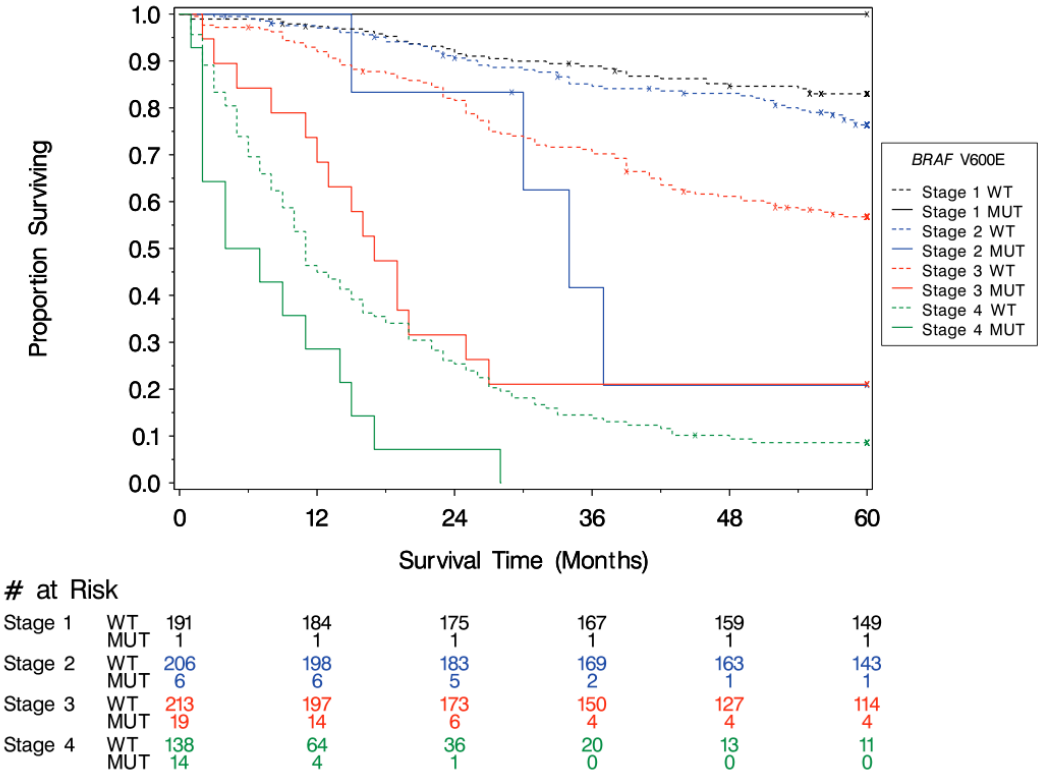
Liquid biopsy needs to be implemented in clinical trials as strategy-defining tool

BRAF

Colorectal cancer

Prognostic role

- BRAF mutation occurs at a rate of 8–10% in mCRC patients and is notably associated with a poor prognosis. Until now, optimal therapy has remained a matter of controversial debate.



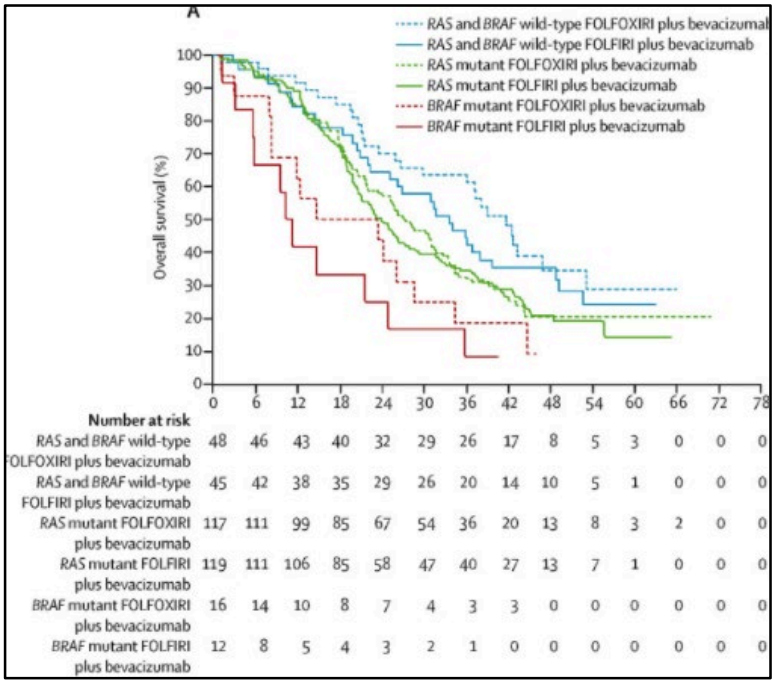
PROGNOSTIC ROLE ACROSS ALL DISEASE STAGES

Roth JCO '10; Richman et al, JCO '09

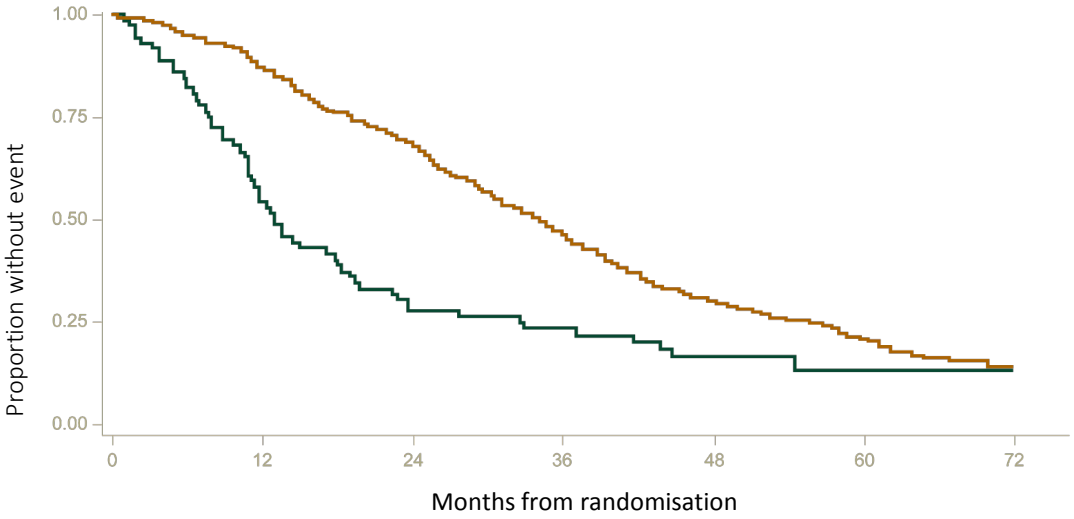
BRAF

Colorectal cancer

Prognostic role



BRAF	Median OS (95% CI)
Mutant n=72	12.9 mo (11.1–19.0)
Wildtype n=432	34.2 mo (31.0–36.4)



HR_{adj} 1.67 (95% CI 1.20-2.33), p=0.0035

Without adjusting for sidedness: HR_{adj} 1.82 (95% CI 1.37-2.44), p=0.0001

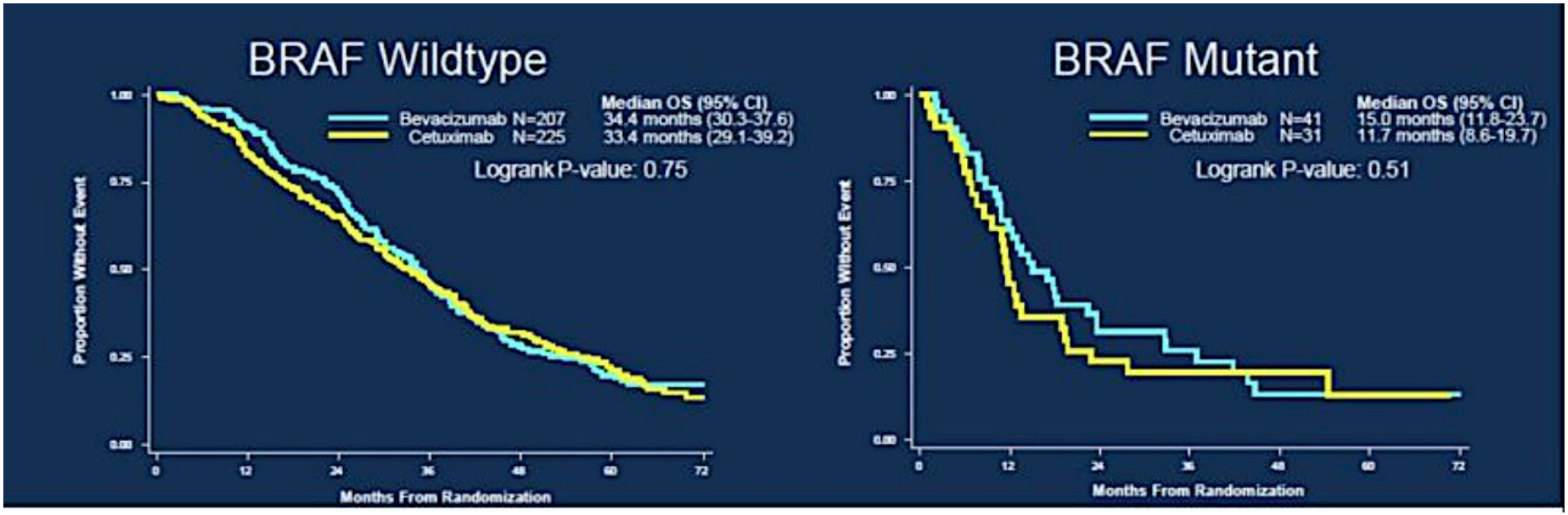
Innocenti F, et al JCO 35, 2017

BRAF

Colorectal cancer

Predictive role

Interaction of BRAF status with biologics



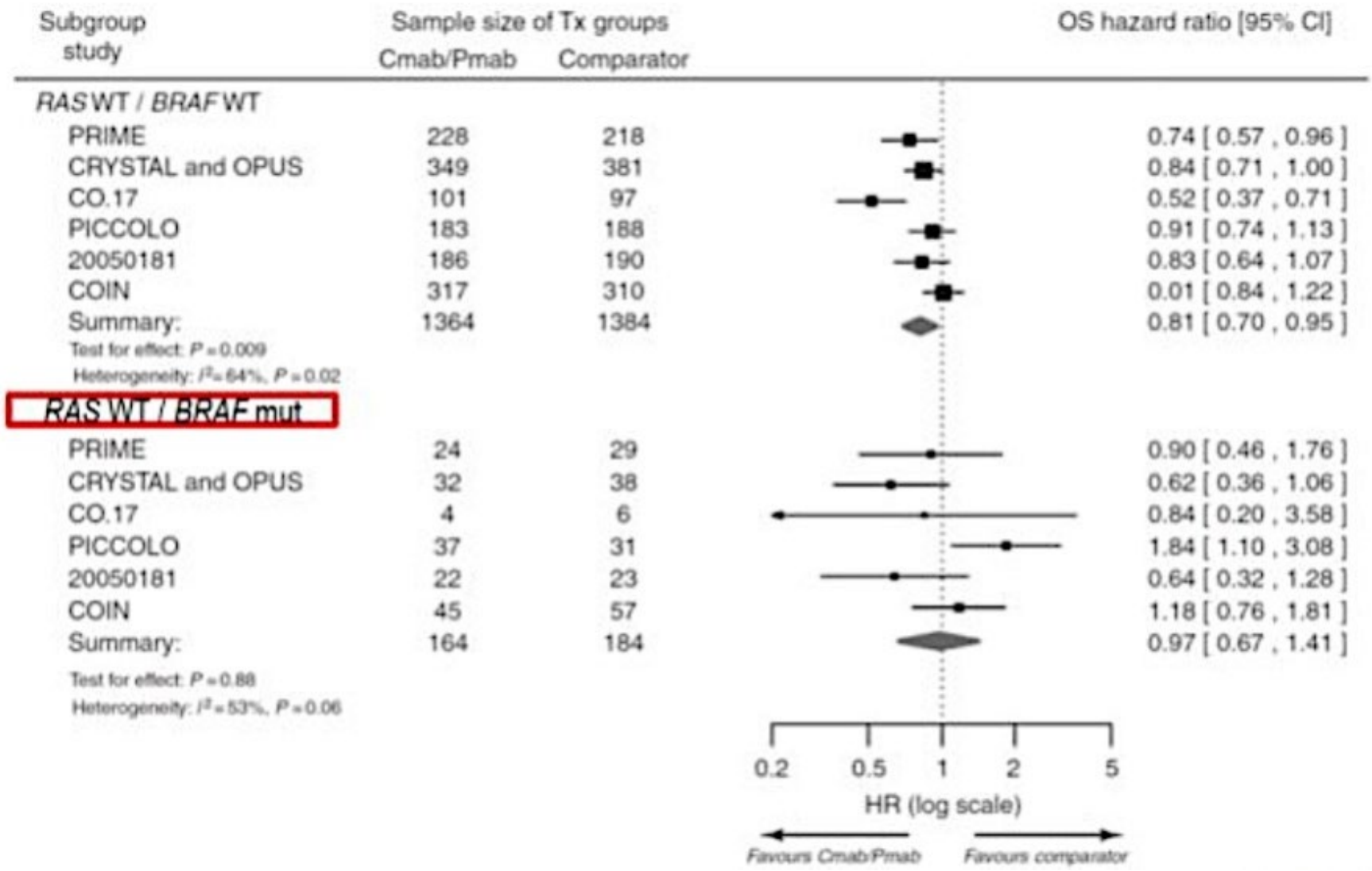
NO CLEAR ROLE FOR PREDICTIVE ROLE

Innocenti F. et al, ASCO 2017

BRAF

Colorectal cancer

Predictive role

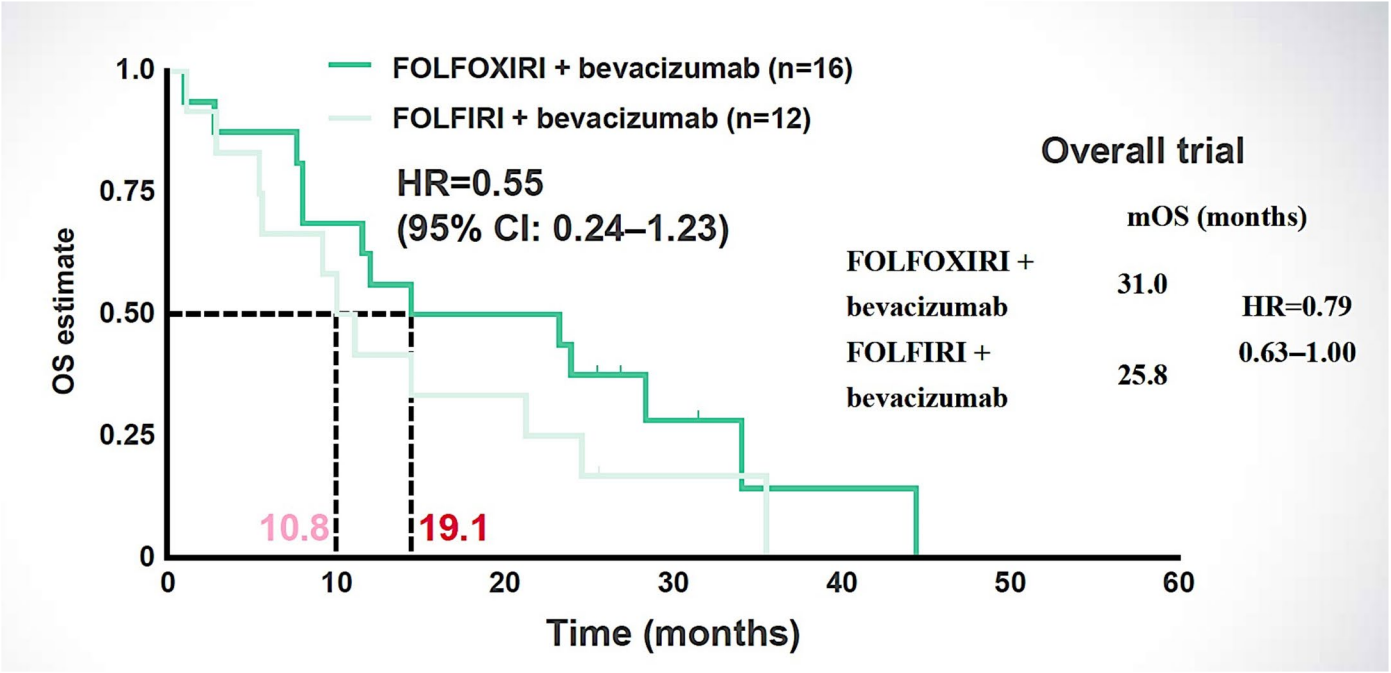


Rowland A et al, BJC 2016

BRAF

Predictive role

TRIBE, benefit of more intensive tratment for pts with BRAF mutation



Treatment with a chemotherapy triplet plus bevacizumab may be an appropriate treatment for patients with BRAF mutations

Loupakis et al, ASCO 2014

BRAF

Colorectal cancer

Other mutations

Not all BRAF mutations are the same

BRAF mutation		Kinase activity
	Wild type	Neutral
Class 1	V600E	High
	V600K	High
	V600D	High
	V600R	High
	V600M	Intermediate
Class 2	K601E	High
	K601N	High
	K601T	High
	L597Q	High
	L597V	Intermediate
	G469A	High
	G469V	High
	G469R	Intermediate
	G464V	Intermediate
	G464E	Intermediate
	Fusions*	High
Class 3	D287H	Low
	V459L	Low
	G466V	Low
	G466E	Low
	G466A	Low
	S467L	Low
	G469E	Low
	N581S	Low
	N581I	Low
	D594N	None
	D594G	None
	D594A	None
	D594H	None
	F595L	Low
	G596D	Low
	G596R	Low

Non-V600 mut

NO specific recommendation for non-V600 mutated cases!

Class II:
More similar to BRAF V600

Class III:
Kinease dead mut or low transforming activity

Yaeger et al, Nature 2017

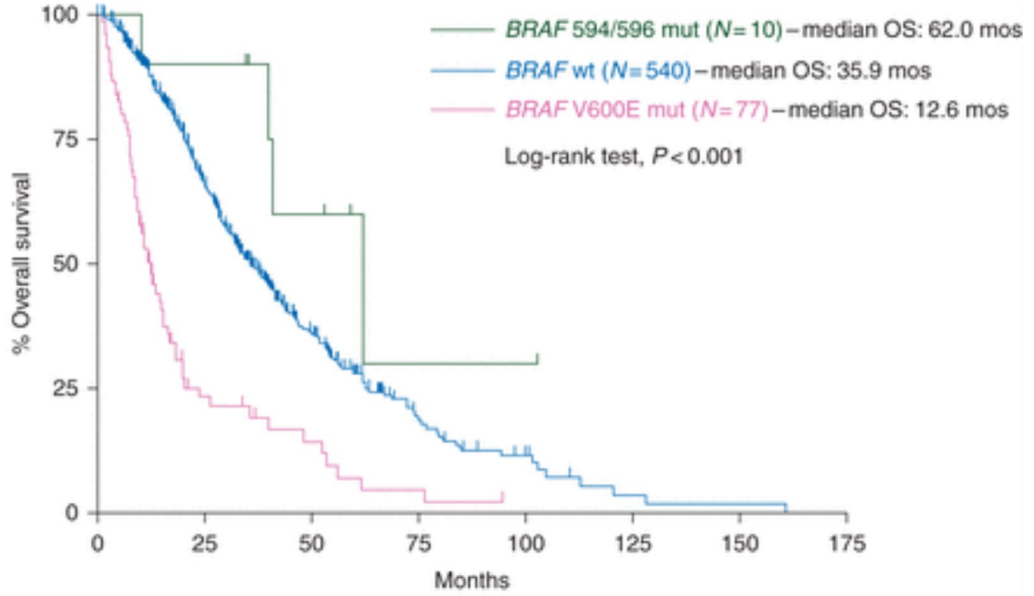
BRAF

Colorectal cancer

Other mutations

Not all BRAF mutations are the same

- Patients with codon 594 and 596 mutated
- Longer OS in confront of BRAF V600E
- Median OS BRAFV600E: 12.06 mo
- Median OS non BRAF V600E: 62 mo



HR for death according to BRAF mutational status:

	HR	p-value
BRAF 594/596 vs BRAF V600E	0.36 [0.20–0.64]	0.002*
BRAF 594/596 vs BRAF wt	0.55 [0.29–1.05]	0.081
BRAF V600E vs BRAF wt	5.70 [3.74–8.69]	<0.001*

*Statistically significant, OS = overall survival, wt = wild type, HR = hazard ratio

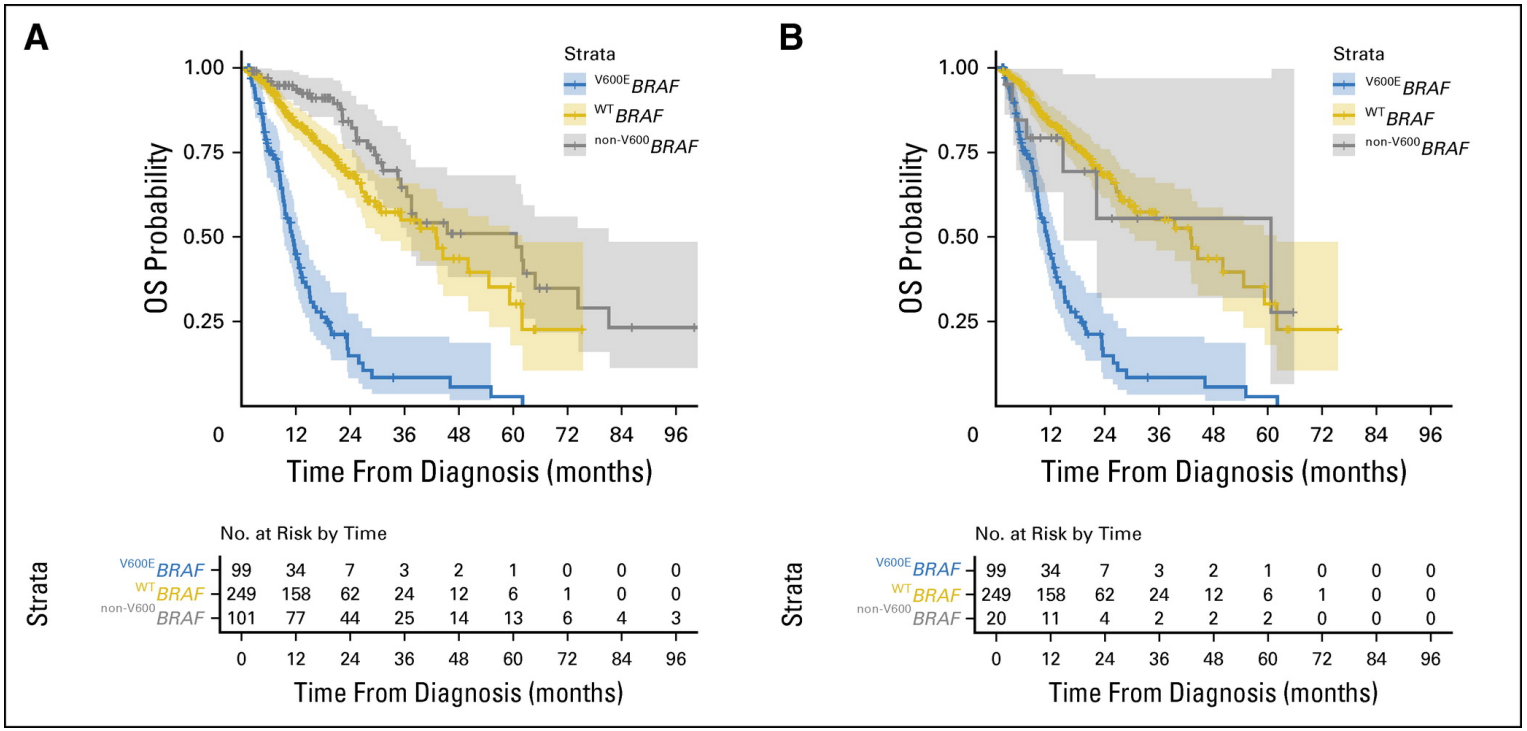
Cremolini C. et al, Ann Oncol 2015

BRAF

Other mutations

Not all BRAF mutations are the same

- 9643 patients (Mayo Clinic, Foundation Medicin, MD Anderson)
- NGS analysis
- Prevalence of any BRAF mutation 10%
- Prevalence of non-V600E BRAF mutation 2,2% (20% of BRAF mutation)



- mOS V600E BRAF mt 11.4 mo
- mOS non-V600E BRAF mt 60.7 mo

Jones J. C et al. JCO 2017

Before the first line of metastatic colorectal carcinoma

The Right

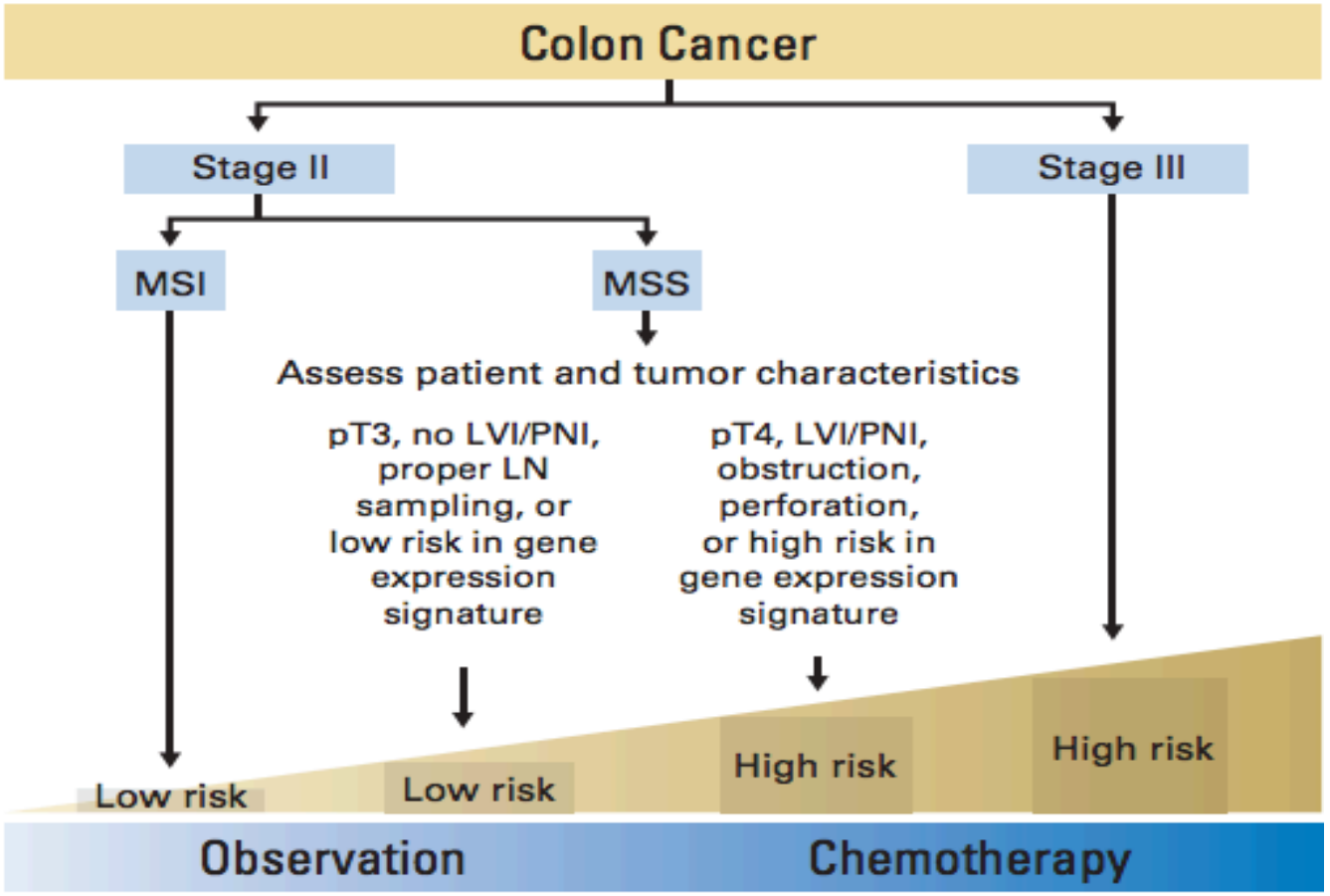
Timing

Colorectal cancer

Adjuvant setting

MSI

Approximately 15% of early colorectal cancers display a high degree of microsatellite instability (MSI-H), due to a deficient DNA mismatch repair system

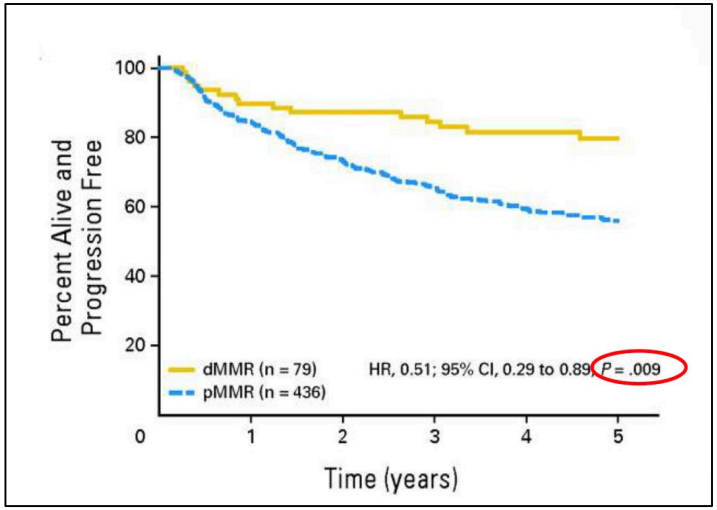


Dienstmann R, Salazar R, Tabernero J. J Clin Oncol. 2015;33(16):1787 - 96)(3)

Colorectal cancer

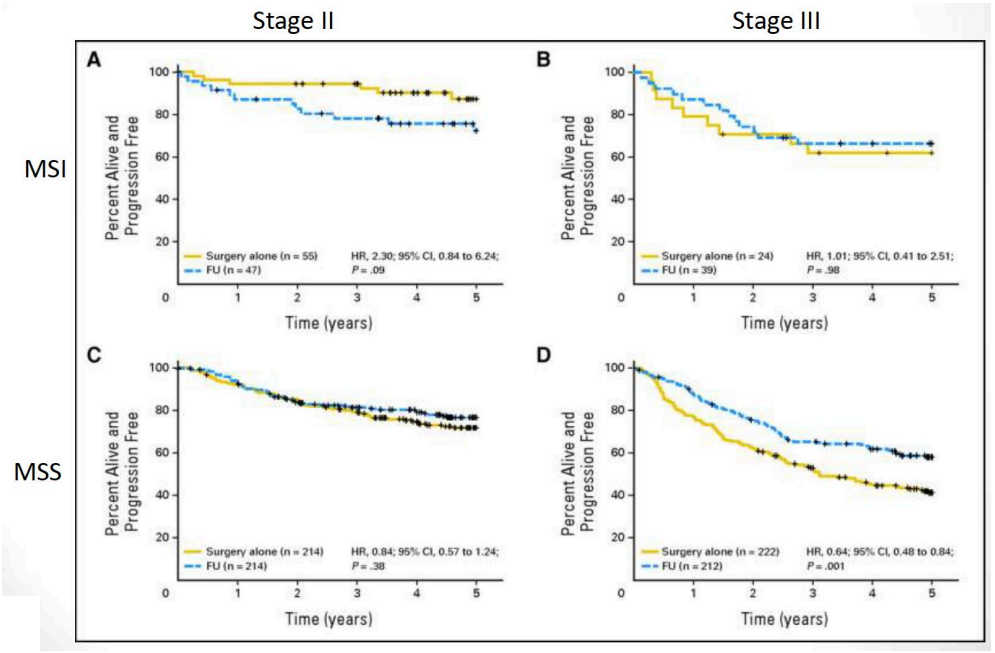
Adjuvant setting

MSI



MSI identifies Stage II and III patients with low risk of recurrence

MSI identifies Stage II patients who do not benefit from fluorouracil treatment



Stage II: prognostic and predictive role
Stage III: prognostic role, but not clinical impact, no predictive role

JCO 2010; 28:3219-3226

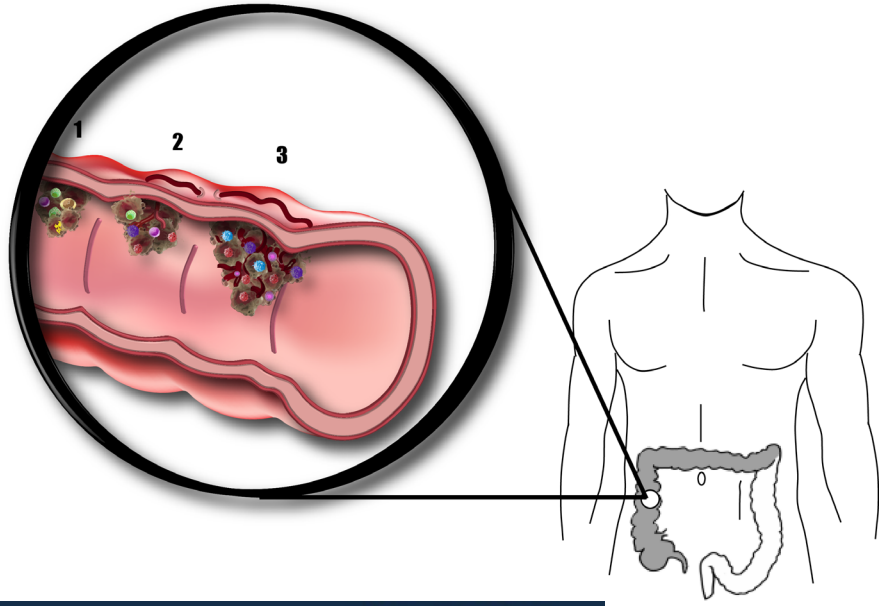
MSI

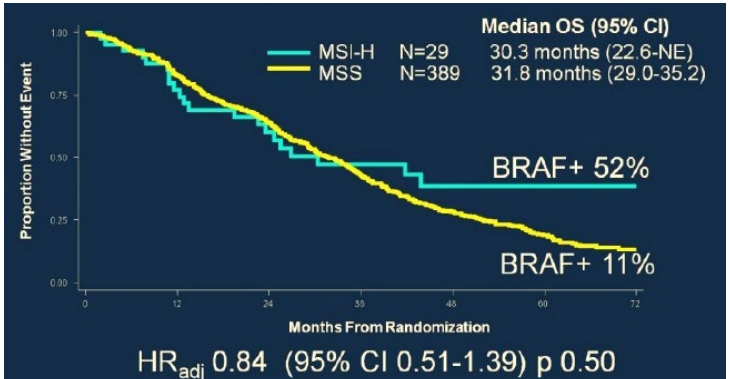
Colorectal cancer

Colon cancer

- MSI-H status is found in approximately 4% of metastatic CRC
- MSI-H CRC is known to have an exceptionally high mutation burden

Principal immune cells	Protumorogenic effect	Antitumorogenic effect
NK cells	Limited	- Release cytotoxic cytoxines - Directly kill cancer cells
T CD8+	Release cancer promoting cytokines	- Kill cancer cells via direct lysis - Cytotoxic response
T CD4+	Release cancer promoting cytokines	Stimulate production and activity CTLs
Dendritic cells	Suppress T cell function thorugh expression of CTLA-4	- Antigen presentation to T cells - Release cytotoxic cytokines
MDSCs	Release immunosuppression molecular mediators	Limited
Macro-phages	M2: - Block immunesurveillance - Recruit immuno-suppressive cells	M1 act as effector cells in Th1 responses
MSCs	Inhibit: - lymphocytes proliferation - DCs maturation - down-regulate MHC Recruit M2	Limited
Treg	Suppress the host immune-respons	Suppress chronic inflammation





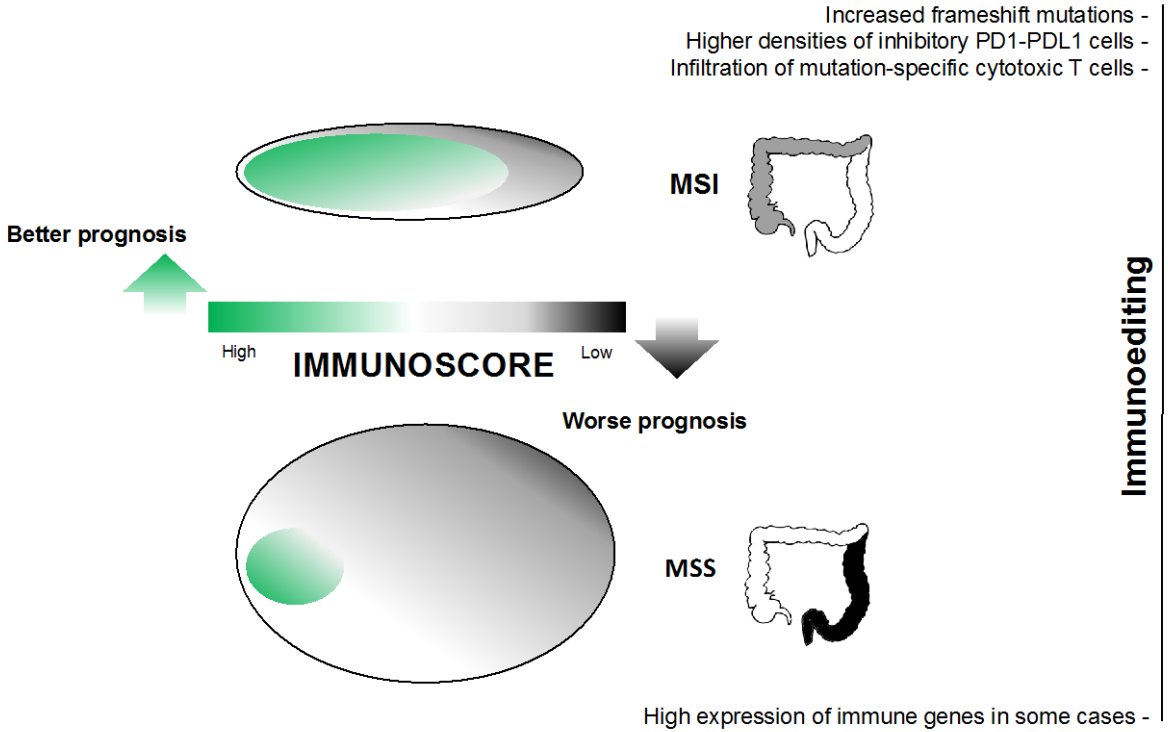
Stage IV: prognostic? Maybe predictive? Yes

Basile D. et al., Exp. Op. on Biol. Ther. 2017,
Innocenti et al., ASCO 2017

MSI

Colorectal cancer

Metastatic setting



Increased presence of tumor-specific neoantigens in hypermutated tumors is associated with an increased quantity of TILs and overexpression of PD-1 and PD-L1

Figure 2. Immunoscore, gene profile, tumor location and prognosis in colorectal cancer
The figure summarizes the overlapping of immune and molecular classification and differences in clinical presentation and prognosis. A high immunoscore is more frequent in right side MSI tumors and is correlated with good prognosis. On the other hand, left side MSS tumors commonly show a low immunoscore and worse prognosis.

Basile D. et al., Exp. Op. on Biol. Ther. 2017

Colorectal cancer

Immunotherapy

MSI

Pembrolizumab

Histologically proven metastatic or locally advanced colorectal cancer

Measurable disease

Patients with colon cancer must have received **at least two prior cancer therapy regimens**

ECOG Performance Status of 0-1

No prior anti-PD-1/PD-L1/PD-L2, anti-CD137, anti-OX-40, anti-CD40, anti-CTLA4

Type of response	MSI (n=10)	MSS (n=18)
Complete Response	0%	0%
Partial Response	40%	0%
Objective Response Rate	40%	0%
Disease Control Rate	90%	11%

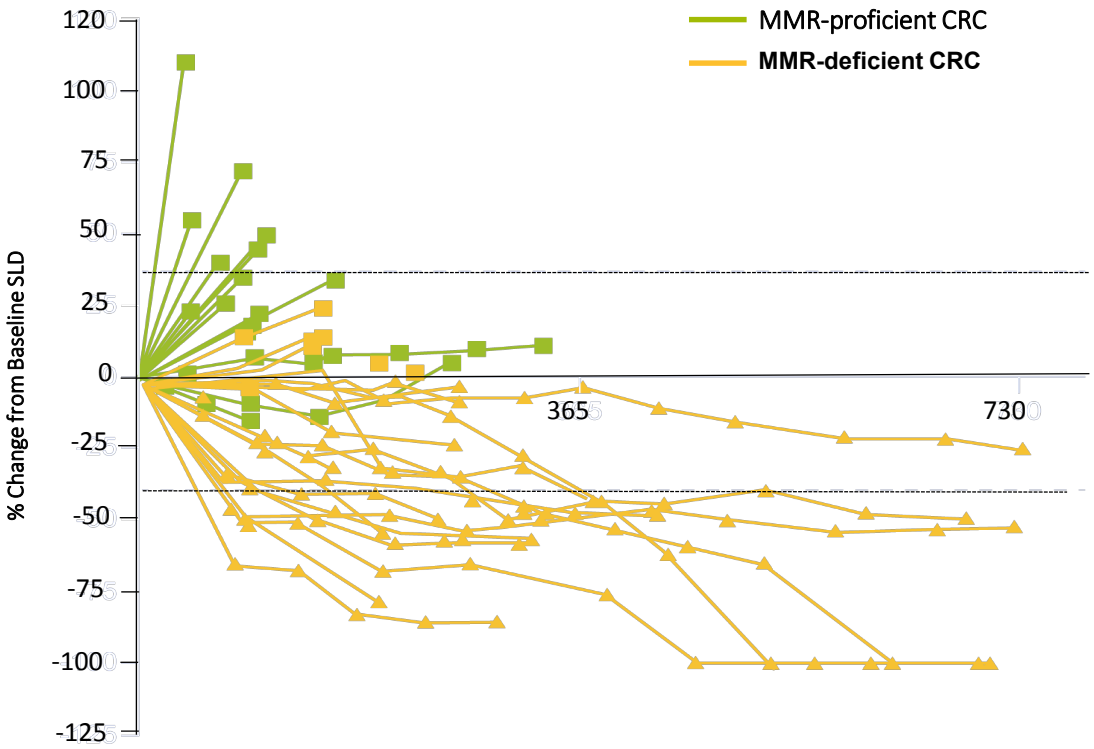
Le DT, et al. ASCO 2016

MSI

Colorectal cancer

Immunotherapy

Pembrolizumab in dMMR CRC



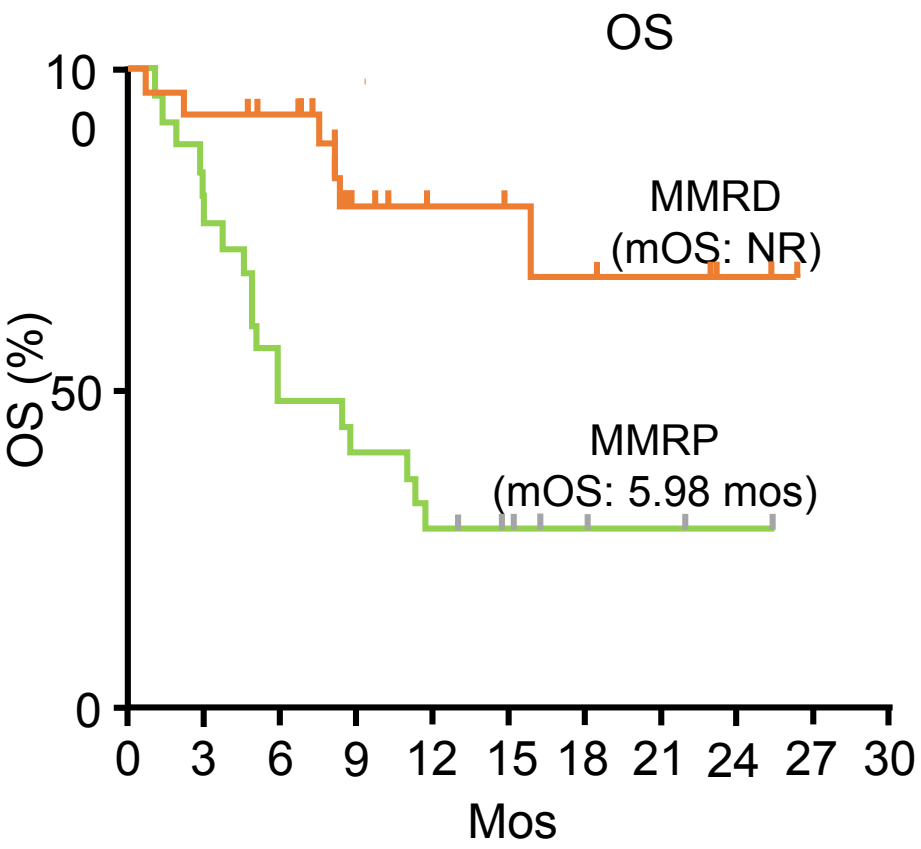
Type of Response-no (%)	MMR-deficient CRC n=28
Complete Response	3 (11)
Partial Response	13 (46)
Stable Disease (Week 12)	9 (32)
Progressive Disease	1 (4)
Not Evaluable[1]	2 (7)
Objective Response Rate (%)	16 (57)
95% CI	39-73
Disease Control Rate (%)	25 (89)
95% CI	73-96
Median Follow-up (mos)	9.3

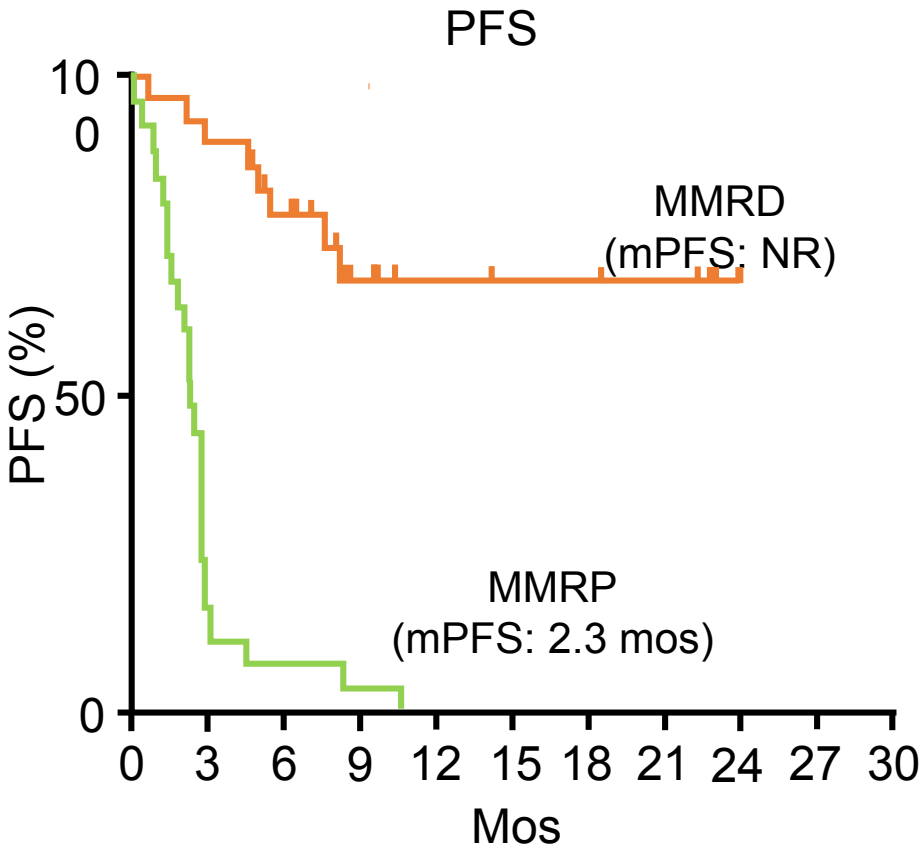
[1]Patients were considered not evaluable if they did not undergo a 12 week scan

Le DT, et al. ASCO 2016

MSI

Pembrolizumab: MSI-H vs not MSI-H





MSI

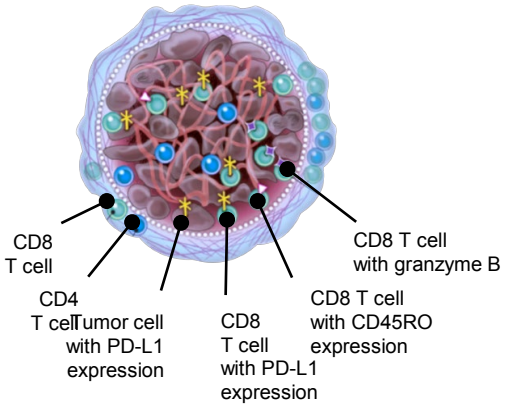
Colorectal cancer

Immunotherapy

How we can enhance immunotherapy?

Combination strategies?

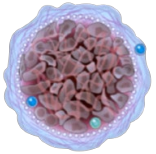
Immunogenic (HOT) tumor microenvironment



Immunogenic tumor microenvironment

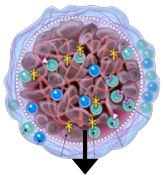
Immune checkpoint therapy and durable clinical benefit

Non-immunogenic (COLD) tumor microenvironment



Non-immunogenic tumor microenvironment

Combination therapies with agents that create immunogenic tumor microenviroment and immune checkpoint therapy



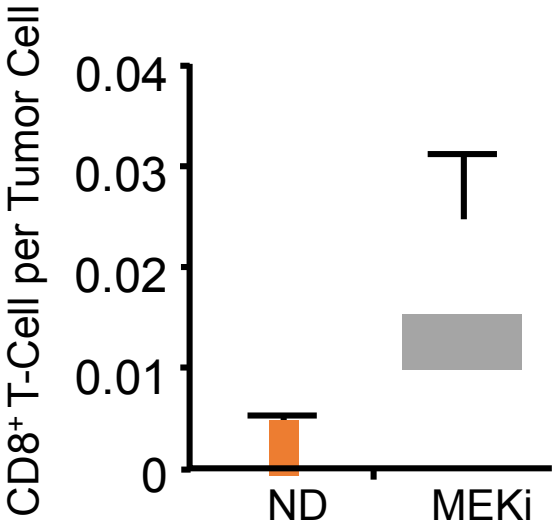
Durable clinical benefit

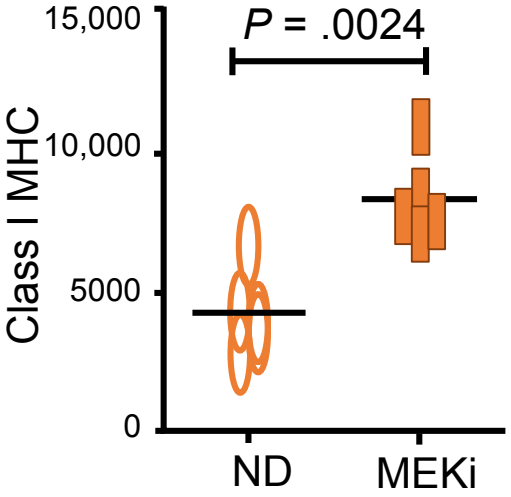
MSI

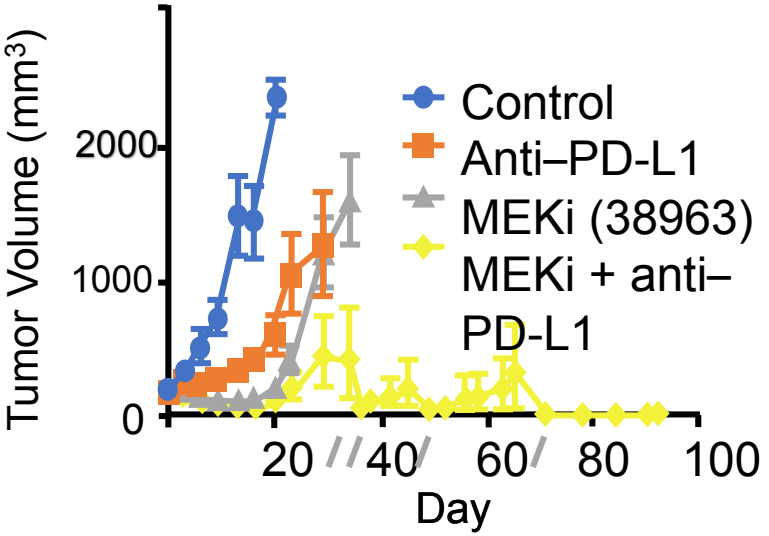
Colorectal cancer

Immunotherapy

- MEK inhibition alone can result in intratumoral T-cell accumulation and MHC I upregulation, and synergizes with an anti–PD-L1 agent to promote durable tumor regression[1]





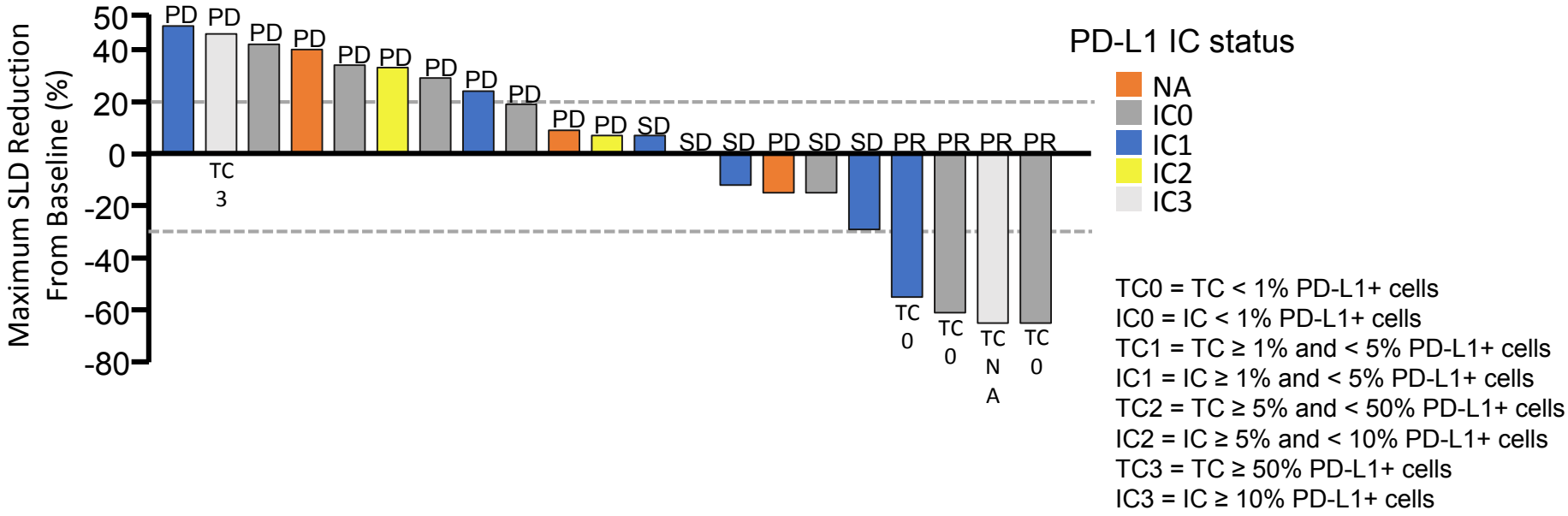


- To examine the possible benefits of MEK inhibition in combination with an anti–PD-L1 agent, it is evaluated cobimetinib + atezolizumab in pts with advanced solid tumors[2]

1. Ebert PJ, et al. Immunity. 2016;44:609-621.
2. 2. Bendell J, et al. ASCO 2016. Abstract 3502.

MSI

Phase Ib Study: Change in Tumor Burden With Cobimetinib + Atezolizumab



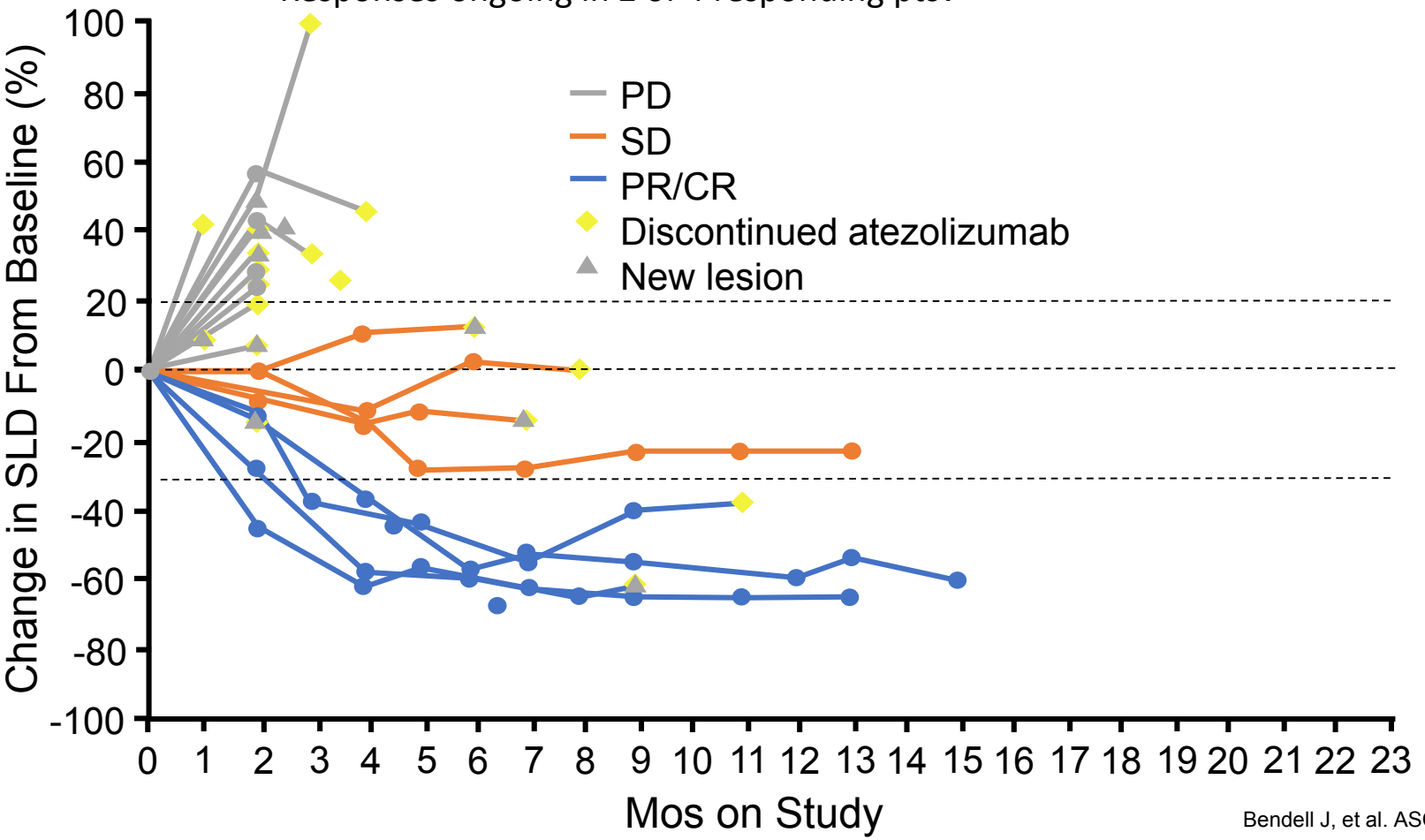
- 4 pts had PR (confirmed per RECIST v1.1)
- MSI status of CRC pts examined by NGS-based scoring: 3 of 4 responders were MMRP (not MSI-H); 1 responder had unknown MSI status and was not evaluable
- Tumor volume reduction not associated with PD-L1 status: TC3 (n = 1; PD), TC0 (n = 18), NA (n = 4)

Bendell J, et al. ASCO 2016. Abstract 3502.

MSI

Phase Ib Study: Change in Tumor Burden With Cobimetinib + Atezolizumab

- Median DoR: not reached (range: 5.4 to 11.1+ mqos)
- Responses ongoing in 2 of 4 responding ptsv



Bendell J, et al. ASCO 2016. Abstract 3502.

EGFR pathways related
EGFR pathways unrelated

HER2, MET, ALK/ROS1/NTRK and EGFR
MGMT

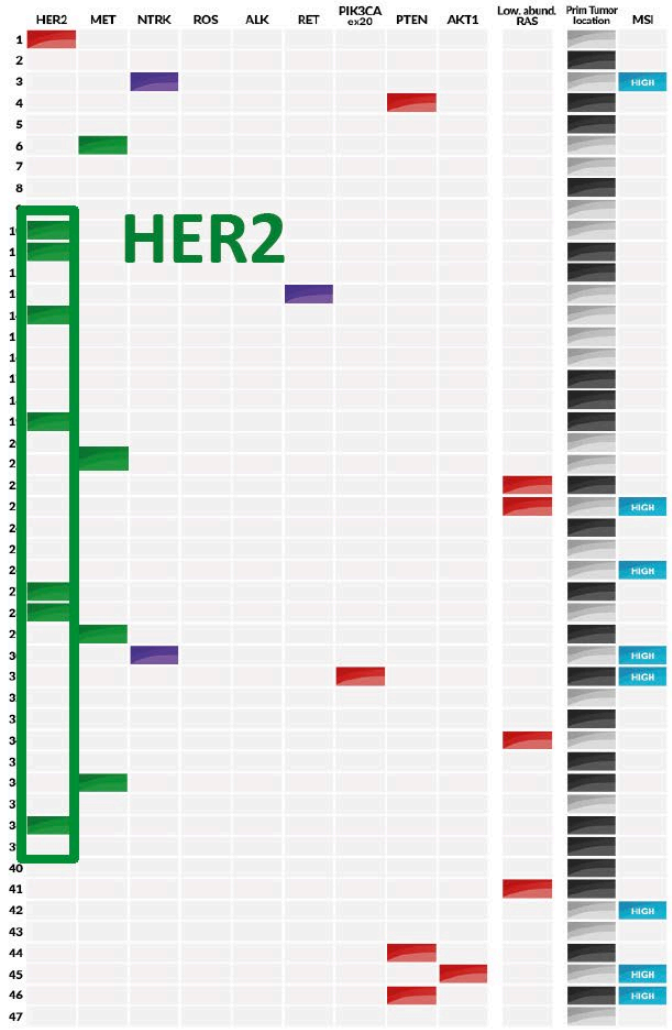
HER2

Metastatic setting

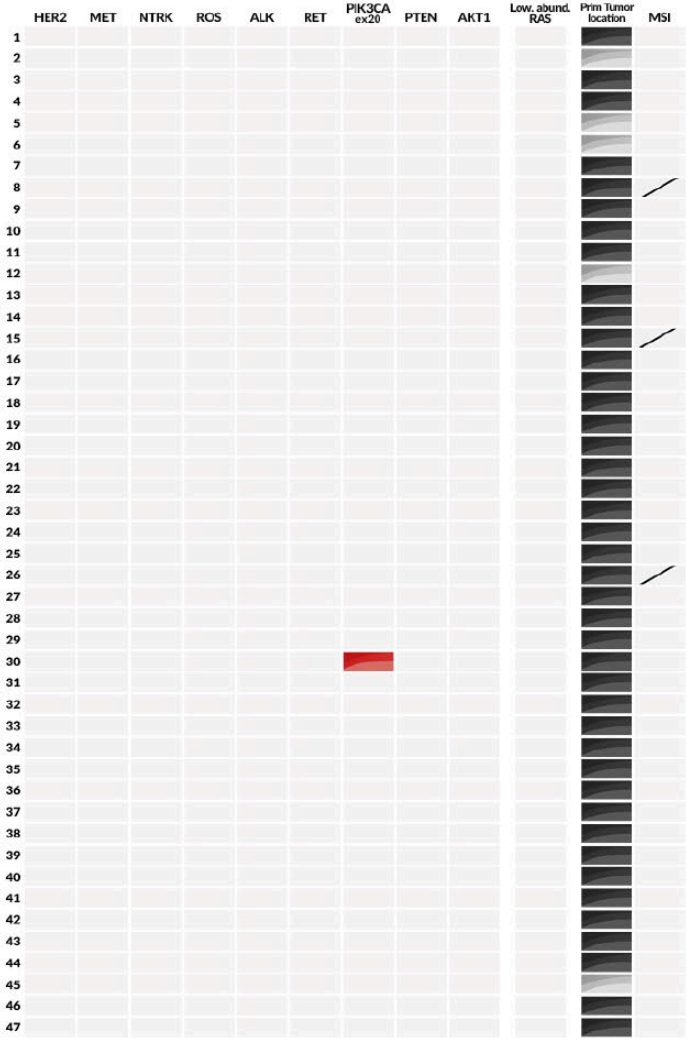
EGFR pathways-related

PRESSING STUDY

Resistant group



Sensitive group



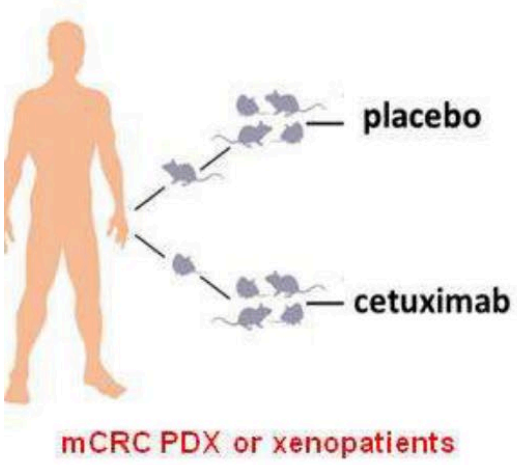
Cremolini et al, Ann Oncol 2017

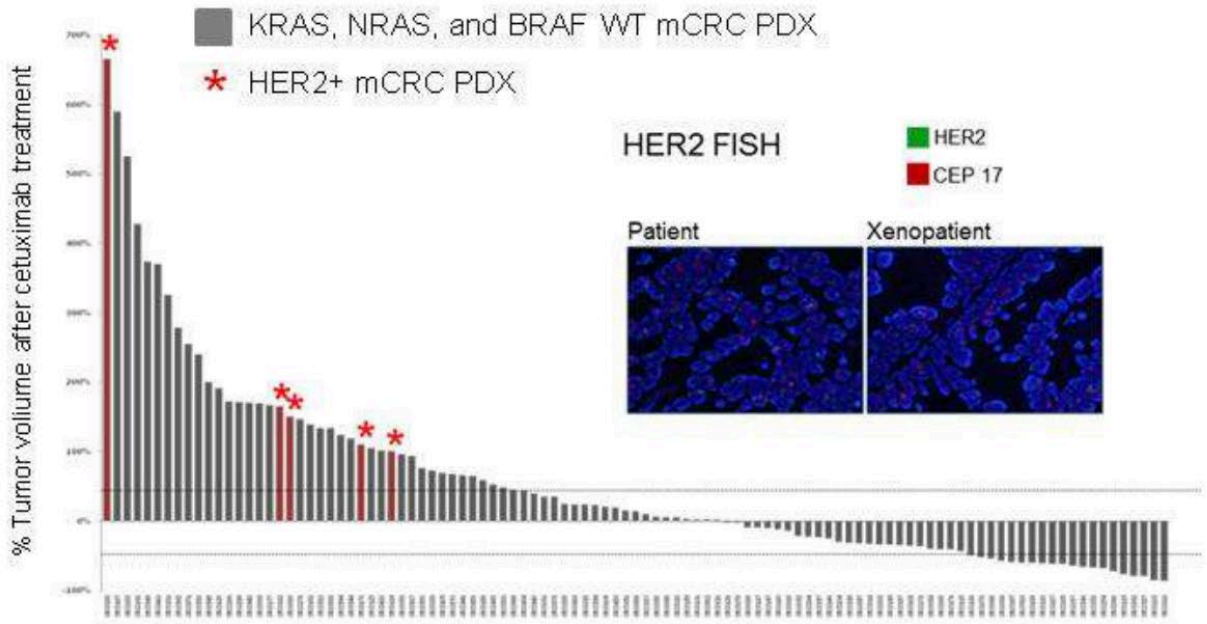
HER2

Metastatic setting

EGFR pathways-related

HER2 amplification is a driver of resistance to cetuximab in mCRC patient-derived xenografts (xenopatients)





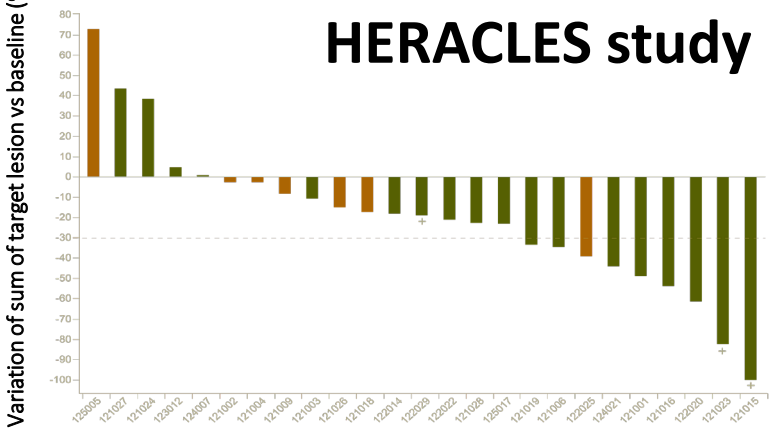
Bertolotti A. et a, Cancer Discovery, 2011

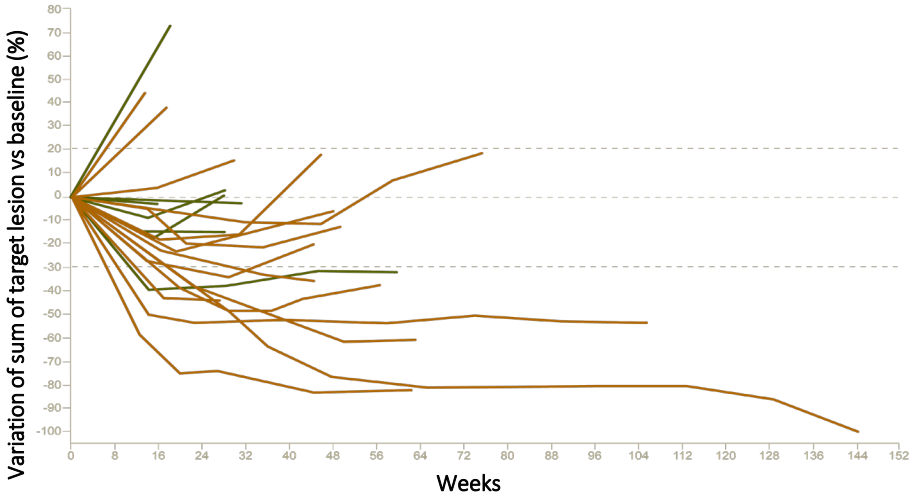
HER2

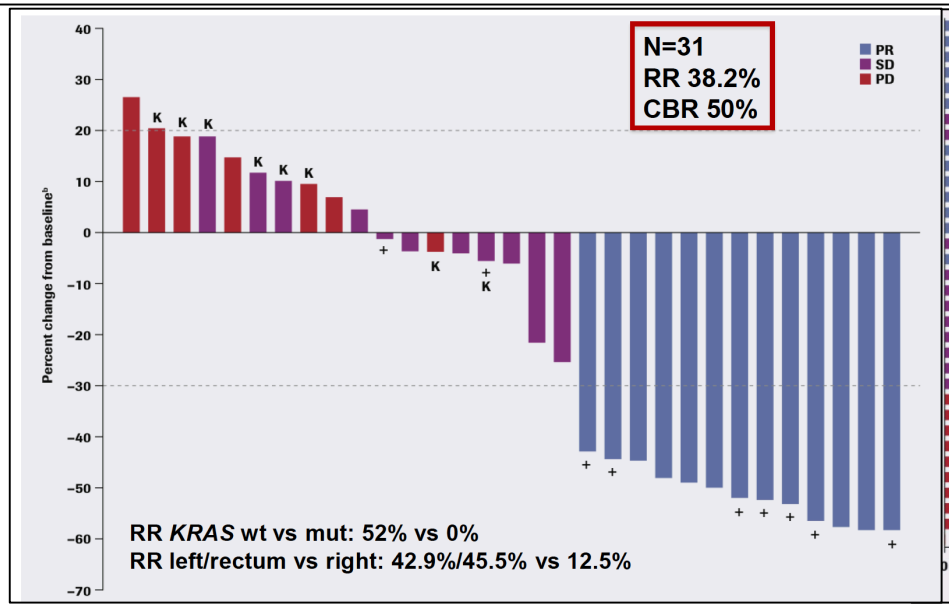
Metastatic setting

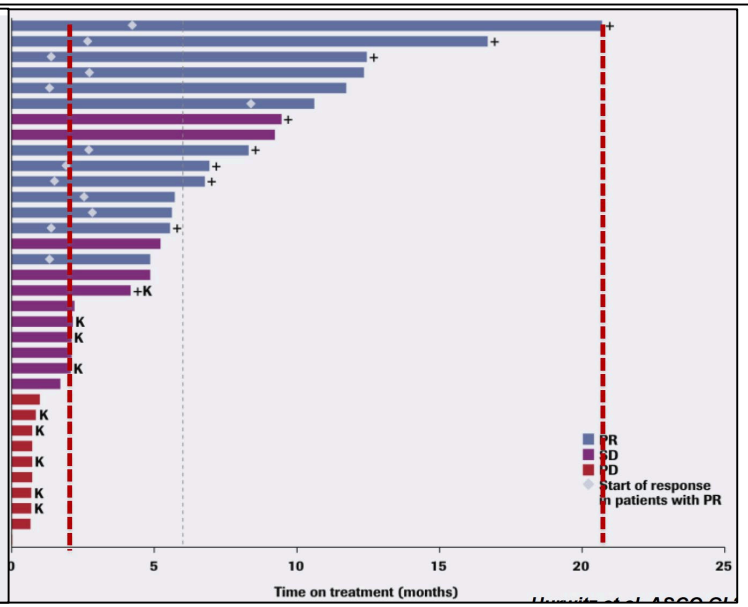
EGFR pathways-related

HERACLES study









Sartore-Bianchi et al. Lancet Oncol 2016

HER2

Metastatic setting

EGFR pathways-related

Study	Tx	*KRAS* wt N	RR %	Median duration of response	DCR %	PFS mos	OS mos
MyPathway	Trastuz+Pertuz	25	52%	10.3	68%	5.7	14.0
Heracles	Trastuz+Lapat	27	30%	9.5	59%	5.3	11.5

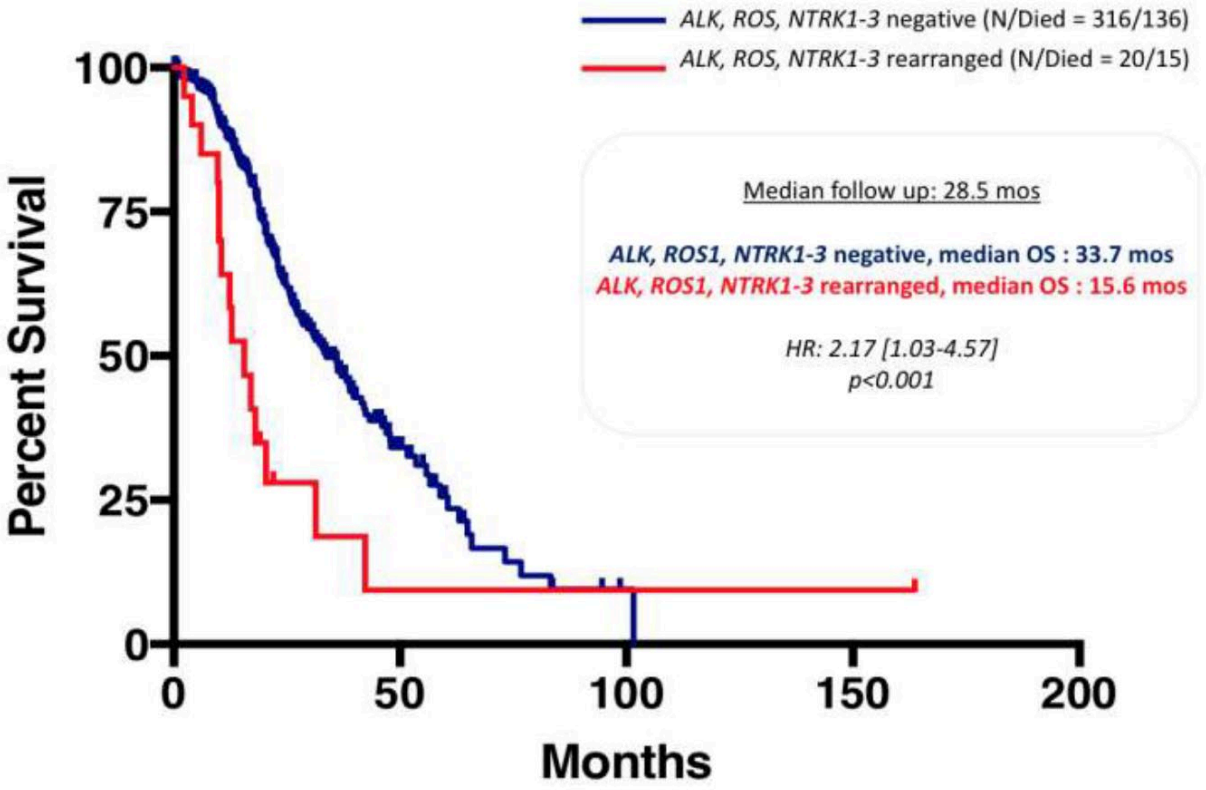
Hurwitz et al. ASCO GI 2017 #676
Sartore-Bianchi et al. Lancet Oncol 2016

ALK/ROS1/NTRK

Metastatic setting

EGFR pathways-related

- ALK/ROS1/NTRK occur in 1,5% of mCRC patients



Pietrantonio et al. ASCO GI 2017 #589

EGFR

Metastatic setting

EGFR pathways-related

88 RAS/BRAF WT mCRC
II/III line therapy
Cetuxumab-irinotecan

Sideness
Right vs Left

EGFR GCN
<2.12 vs 2.12

EGFR prom
m vs unm

Univariate analysis	88 pts	ORR (%)	PFS (m)	OS (m)
Right colon	27.3%	4.2	3.0	8
Left colon	72.7%	35.9	6.76	13.6
		P= 0.003	P < 0.0001	P < 0.0001
EGFR GCN <2.12	36.4%	6.2	3.5	8.5
EGFR GCN >2.12	63.6%	39.3	6.5	14.0
		P= 0.0009	P=0.0006	P< 0.0001
EGFR promother meth	50%	0.1	3	8
EGFR promother unmeth	50%	45.5	7.67	17
		P=0.0001	P< 0.0001	P>0.0001

Multivariate analysis	ORR (%)	PFS (m)	OS (m)
EGFR GCN	P= 0.0082	P= 0.0048	P=0.0001
EGFR promother meth	P= 0.0025	P < 0.001	P< 0.0001

Demurtas L. et al, BJC 2017

C-MET

Metastatic setting

EGFR pathways-related

C-MET 2%

Primary endpoint: ORR. Secondary endpoints: PFS, OS, safety, biomarker evaluation.
The treatment had to be considered effective if ≥ 5 confirmed PR were observed among 41 patients.

Endpoint	N= 42 (%)	Median duration months (range)
Best Responce		
Complete Response	1 (2.4)	16.6
Partial Response	3 (7.3)	5.5 (1.6-17.8)
Stable Disease	14 (34.1)	3.3 (1.2-7.5)
Progressive Disease	21 (51.2)	-
Not Evaluable	2 (4.9)	-
Overall Response Rate (CR+PR)	4 (9.8)	11 (1.6-17.8)
Disease Control Rate (CR + PR + SD)	18 (43.9)	3.6 (1.2-17.8)

Rimassa L et al, ESMO GI 2017

MGMT

Metastatic setting

EGFR pathways-unrelated

Phase II clinical trials with alkylating agents in mCRC

Ref.	Schedule	*n*(MGMT-m)	RR (MGMT-m)	DCR (MGMT-m)	PFS mo (MGMT-m)	OS mo (MGMT-m)
Amatu *et al* Clin Cancer R. 2013	DTIC 250 mg/m2 per day, d 1-4 q21d	68 (26)	3% (8%)	12% (44%)	1.7 (NR)	/
Hochauser *et al* Mol Can Ther 2013	TMZ 150 mg/m2 per day 7 d on/7 d off	372 (37)	3% (3%)	44% (44%)	/	/
Pietrantonio *et al* *Ann Oncol 2014*	TMZ 150 mg/m2 per day d 1-5, q28d	323 (32)	12% (12%)	31% (31%)	1.8 (1.8)	8.4 (8.4)
Pietrantonio *et al* *Target Oncol. 2016*	TMZ 75 mg/m2 per day, d 1-21 q28d	214 (21)	24% (24%)	30% (30%)	2.2 (2.2)	/
Amatu *et al* *Ann Oncol 2016*	TMZ 200 mg/m2 days 1-5 q28	150 (29)	3.4% (3.4%)	48% (48)	2.6 (2.6)	6.2 (6.2)
Calegari *et al* *Br J Cancer 2017*	TMZ 150-200 mg/m2 d 1-5, q28d	225 (41)	10% (10%)	32% (32%)	1.9 (1.9)	5.1 (5.1)

Metastatic setting

HER2, ALK/ROS1/NTRK, EGFR, MGMT

HER2, ALK/ROS1/NTRK, EGFR
in RAS wt refractory patients to anti EGFR therapy

MGMT may be represent, in the future, a target pathway for temozolomide-based therapy

The Right
Timing

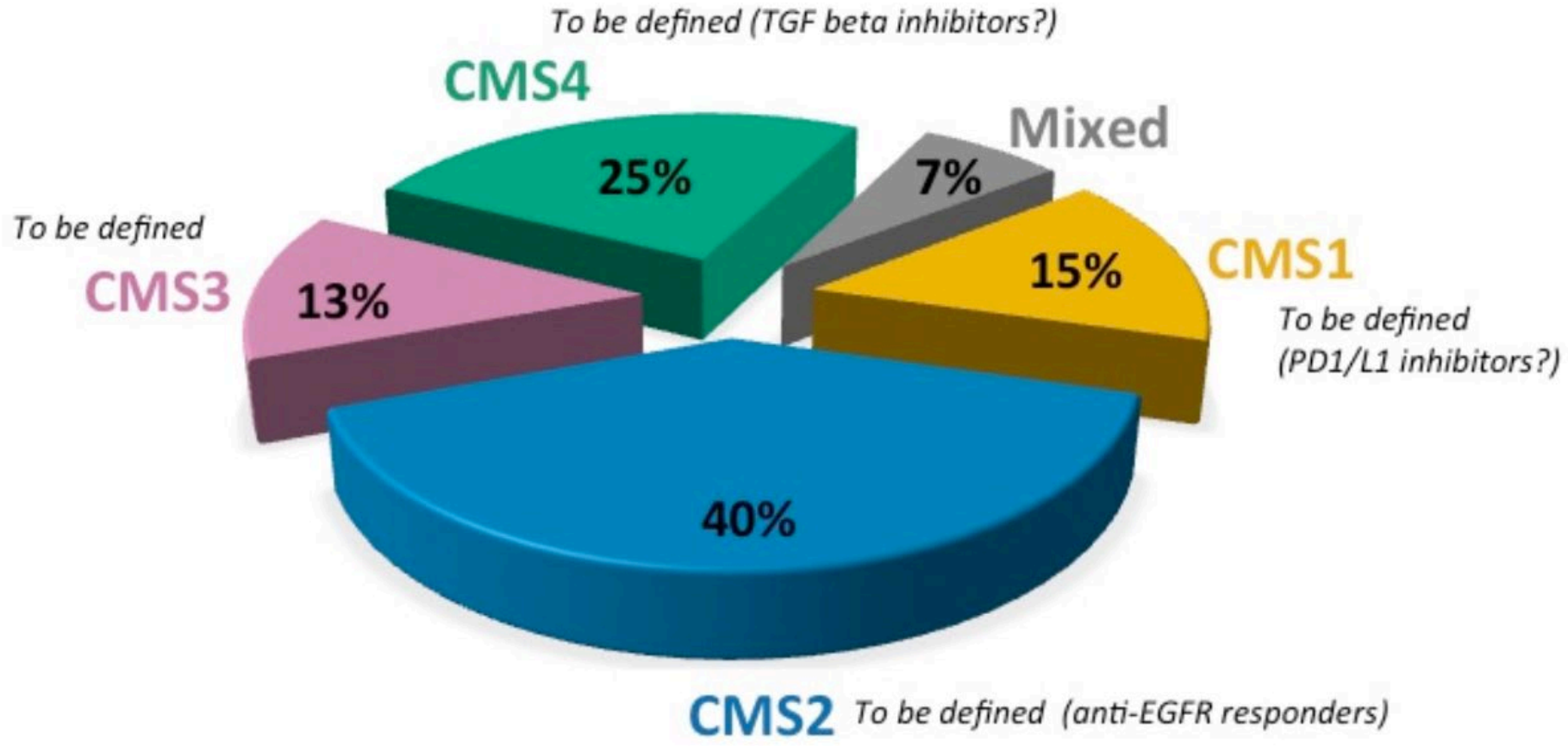
Transcriptomic markers

CMS groups

CMS

Metastatic setting

EGFR pathways-unrelated



Guinney J. Nat. Med. 2015

Metastatic setting

EGFR pathways-unrelated

CMS

CMS in FIRE-3

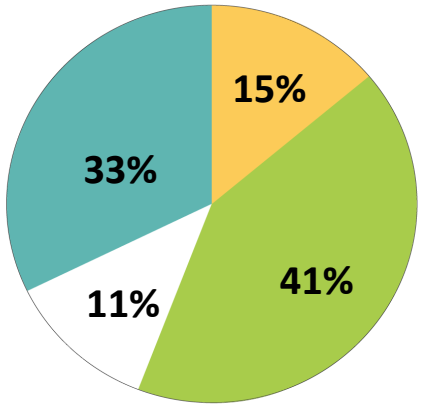
OS according to CMS in RAS wt across all treatment groups

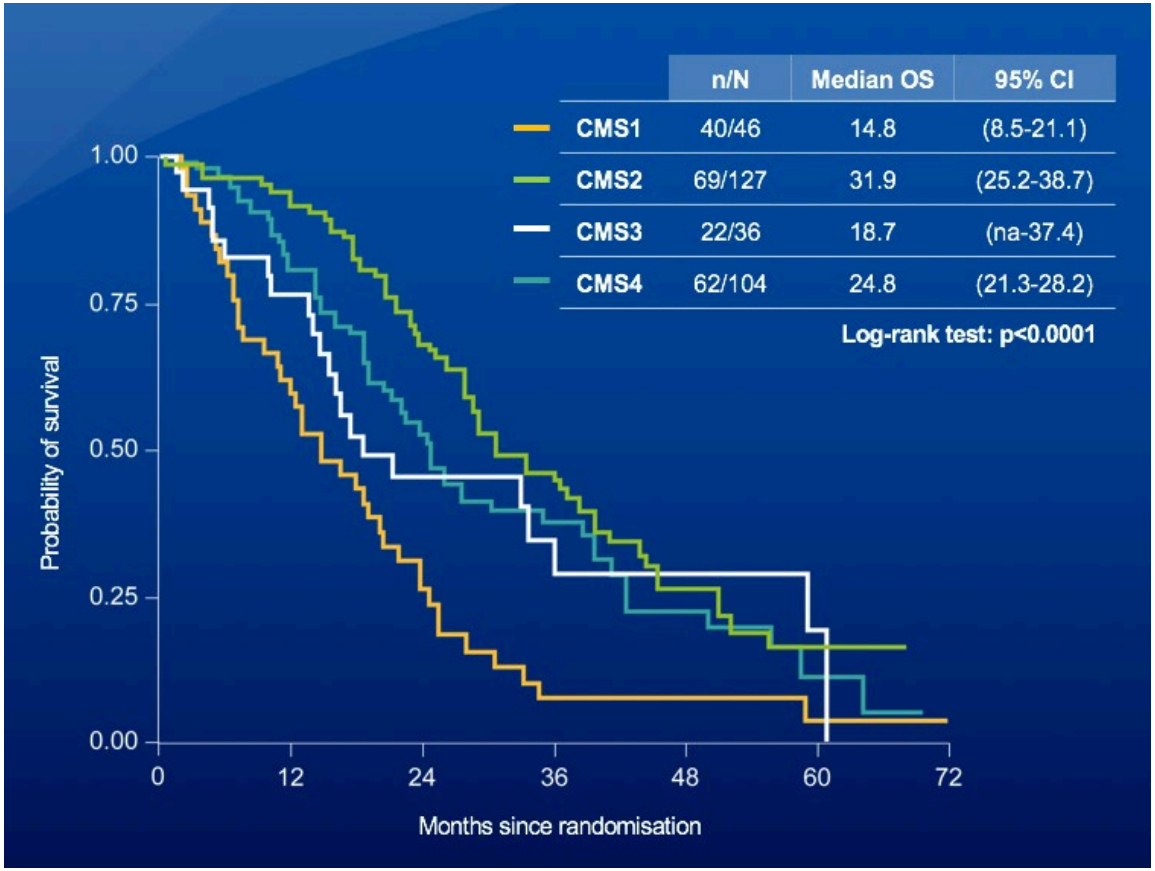
CMS1: Immune

CMS2: Canonical

CMS3: Metabolic

CMS4: Mesenchymal





Stintzing S, et, JCO 2017

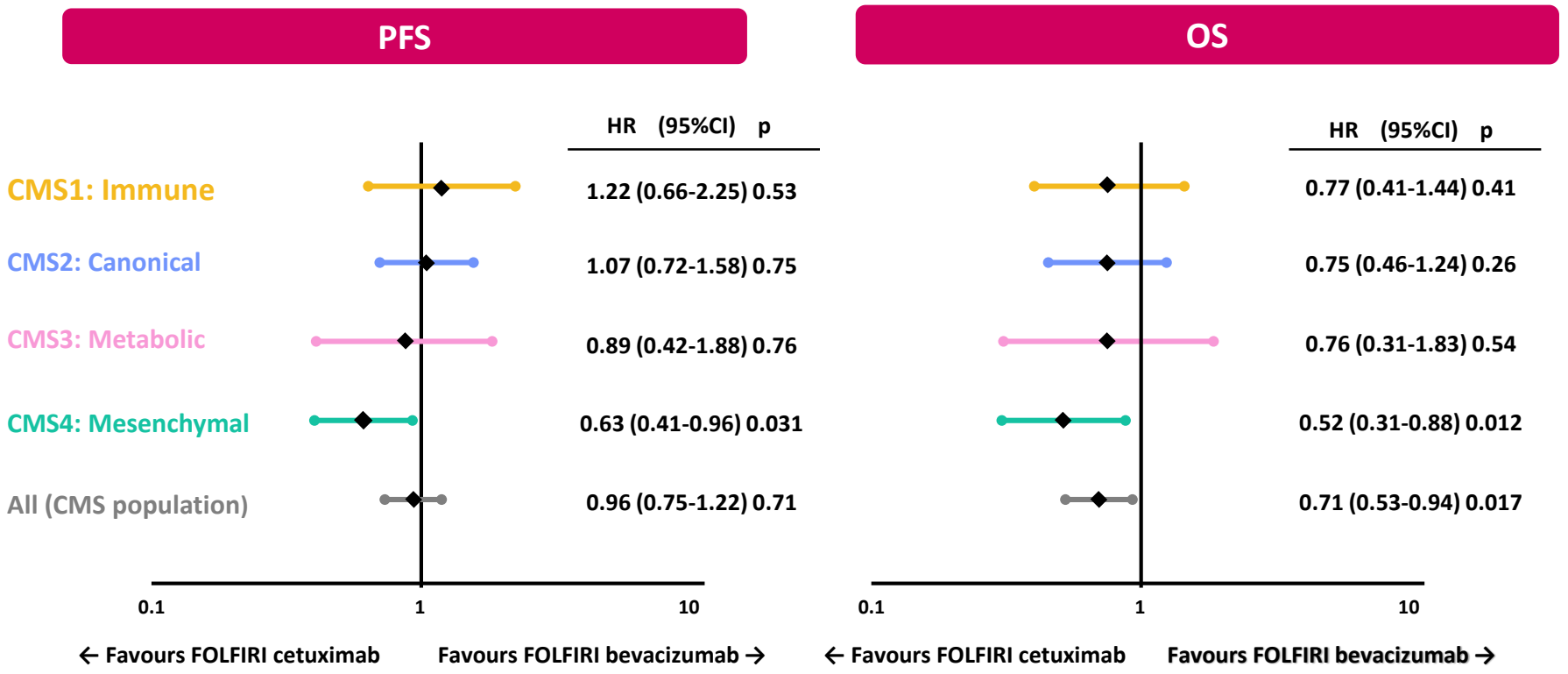
CMS

Metastatic setting

EGFR pathways-unrelated

CMS in FIRE-3

FOLFIRI cetuximab vs FOLFIRI bevacizumab



Stintzing S, et, JCO 2017

CMS

Metastatic setting

EGFR pathways-unrelated

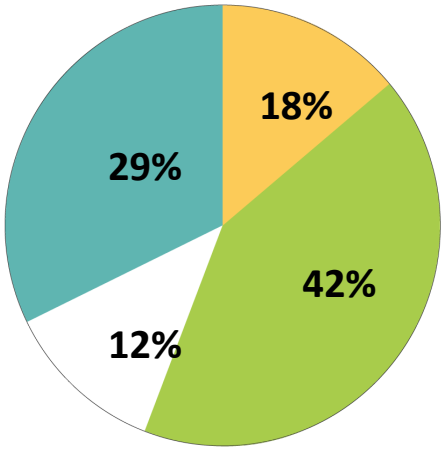
CMS in CALGB

CMS1: Immune

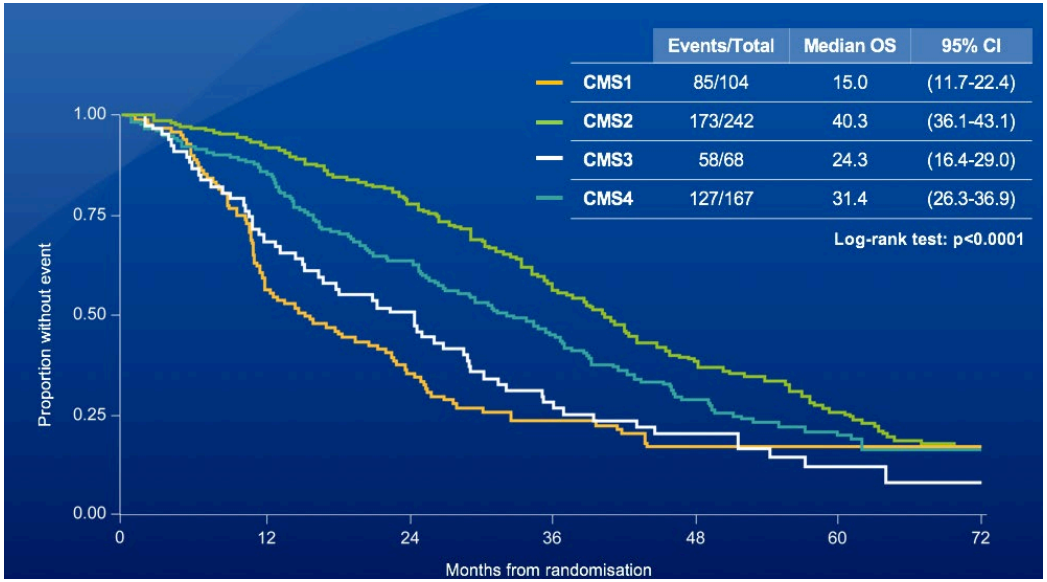
CMS2: Canonical

CMS3: Metabolic

CMS4: Mesenchymal



OS in RAS wild type



Lenz HJ, et al JCO 35, 2017

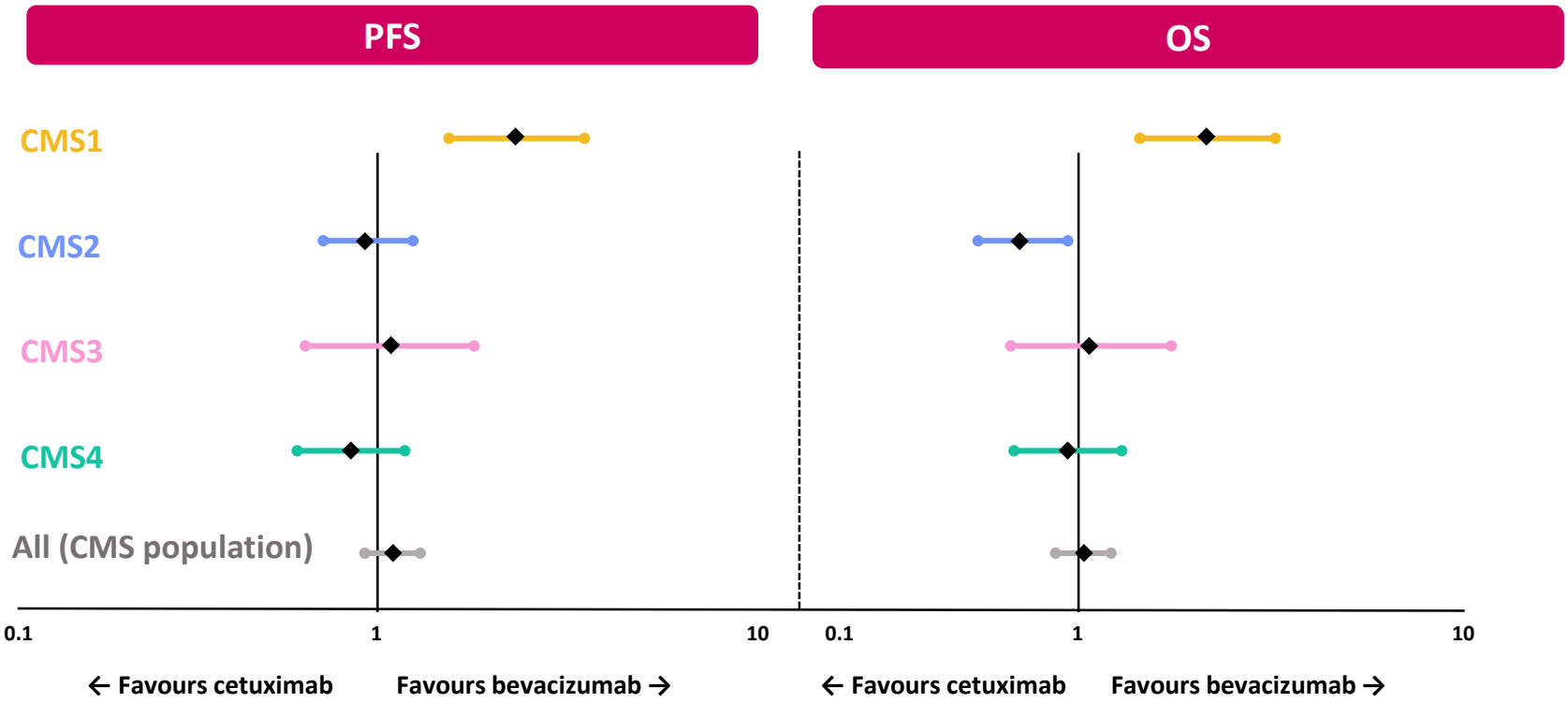
Metastatic setting

Transcriptomic markers

CMS

CMS in CALGB

FOLFIRI cetuximab vs FOLFIRI bevacizumab



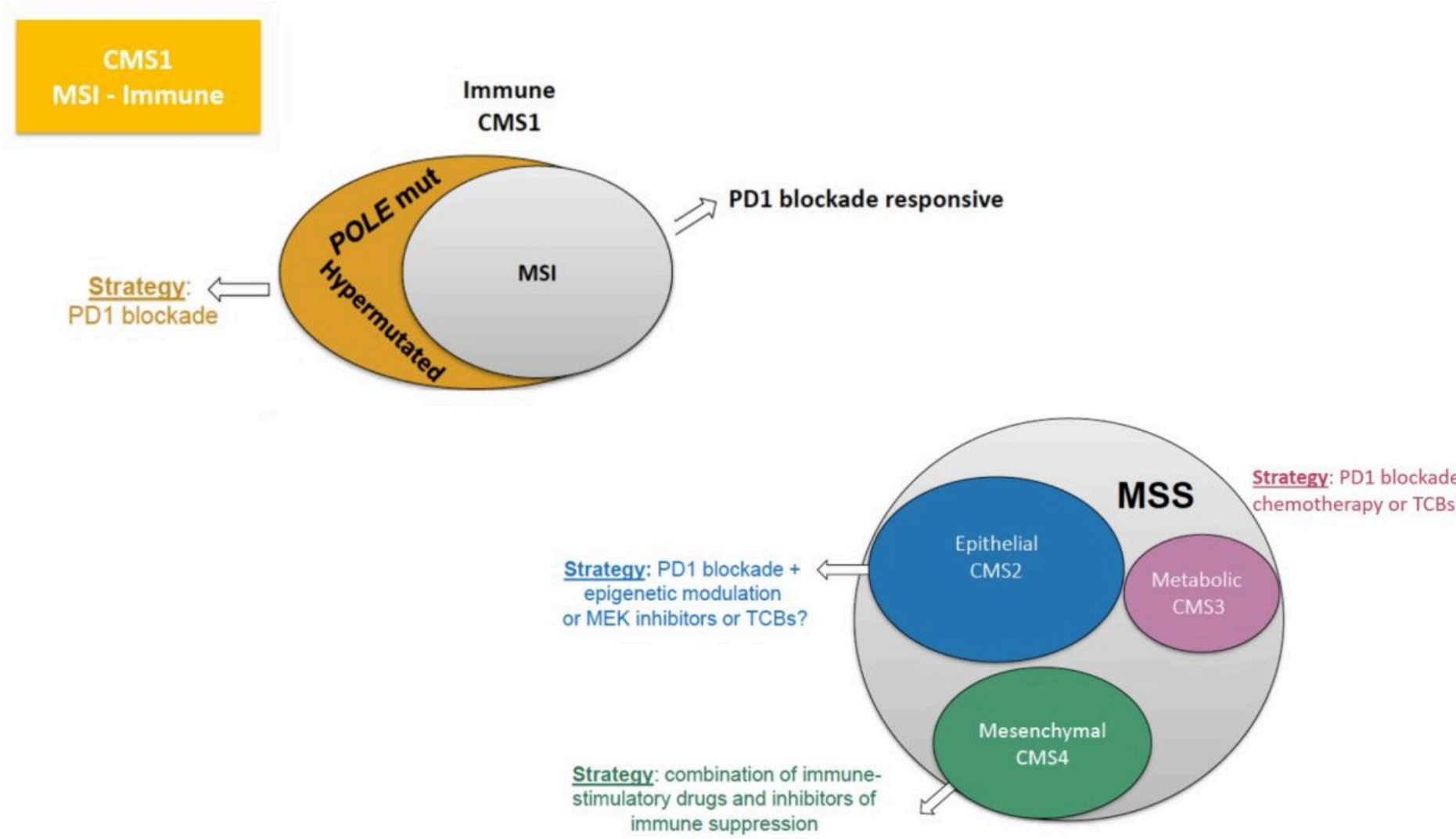
Lenz HJ, et al JCO 35, 2017

CMS

Metastatic setting

Treatment strategies in CMS

EGFR pathways-unrelated



Tabernero J. ESMO 2017

Metastatic setting

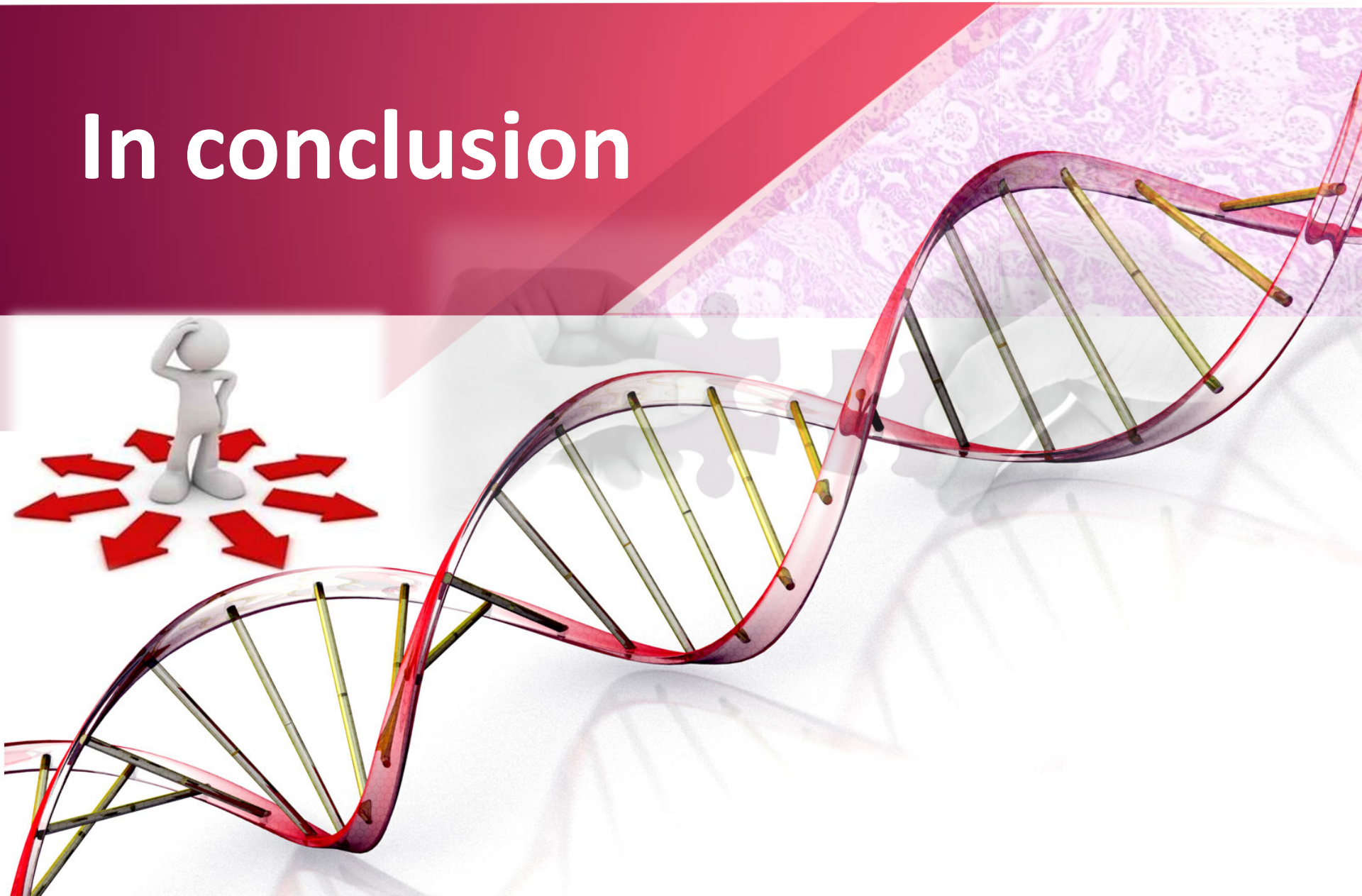
CMS groups

CMS has a strong prognostic role, but its predctive role doesn't appear clear and currently, its determination is difficult in clinical practice

The Right

Timing

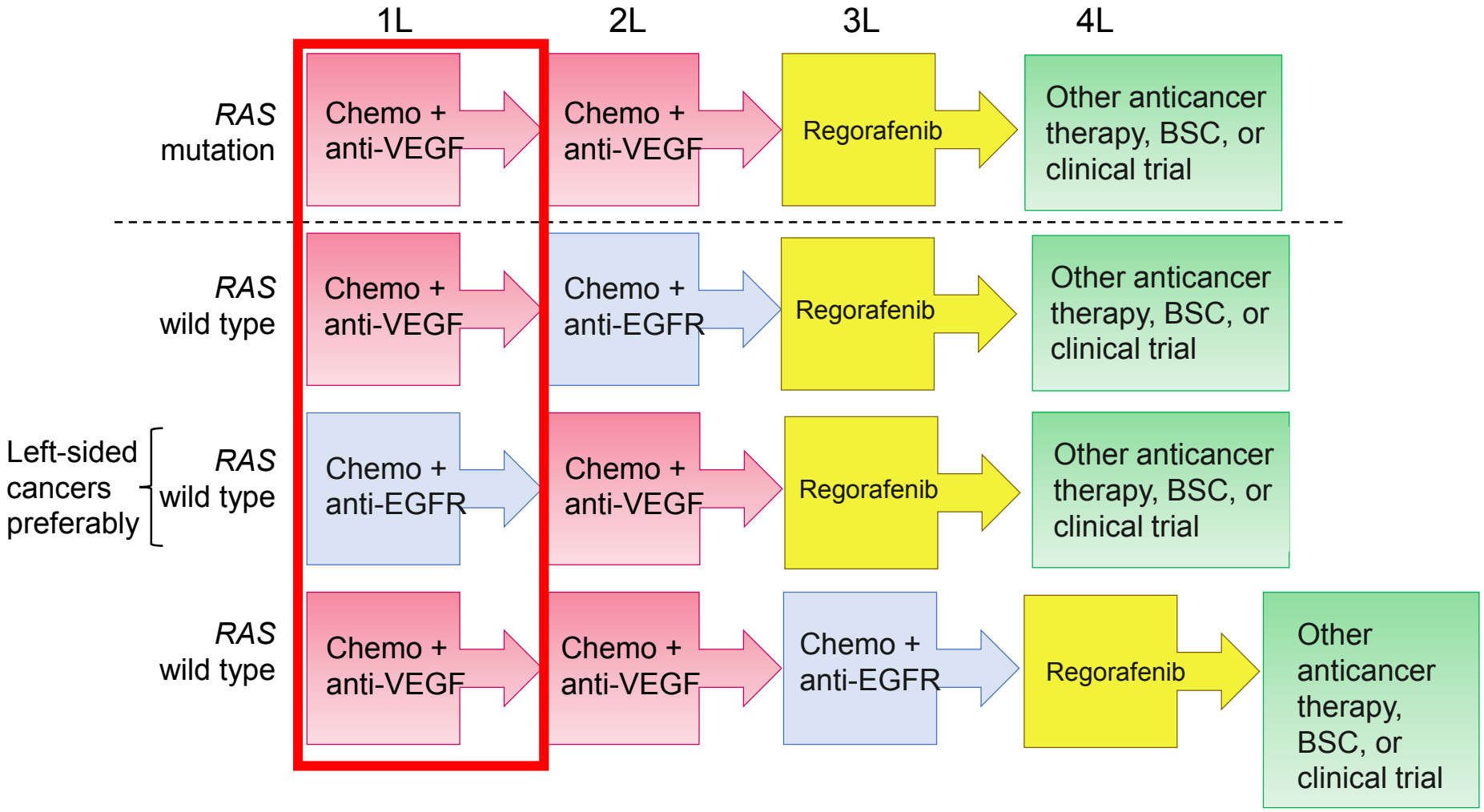
In conclusion



First line

Colorectal cancer

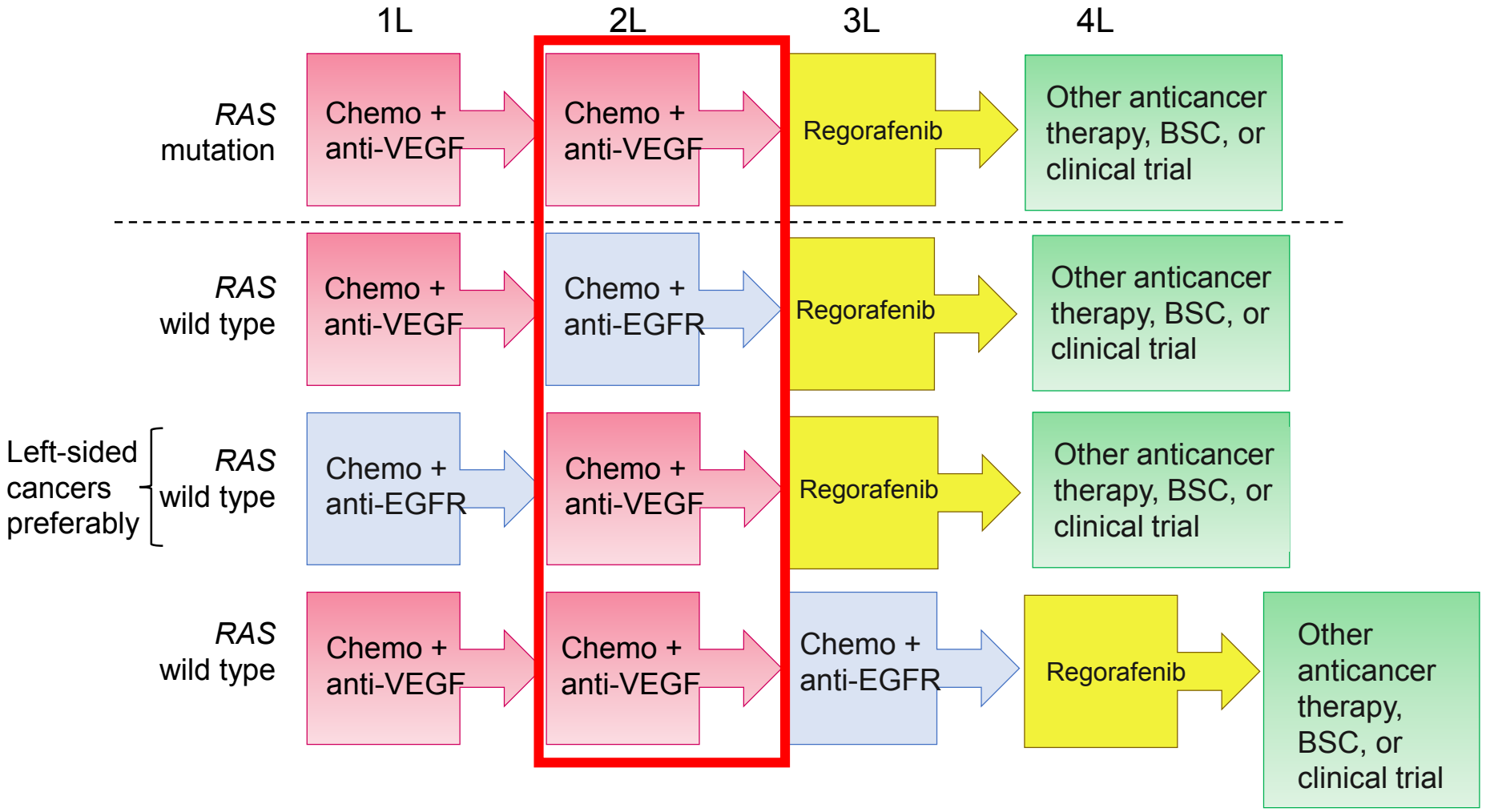
The better strategies



First line

Colorectal cancer

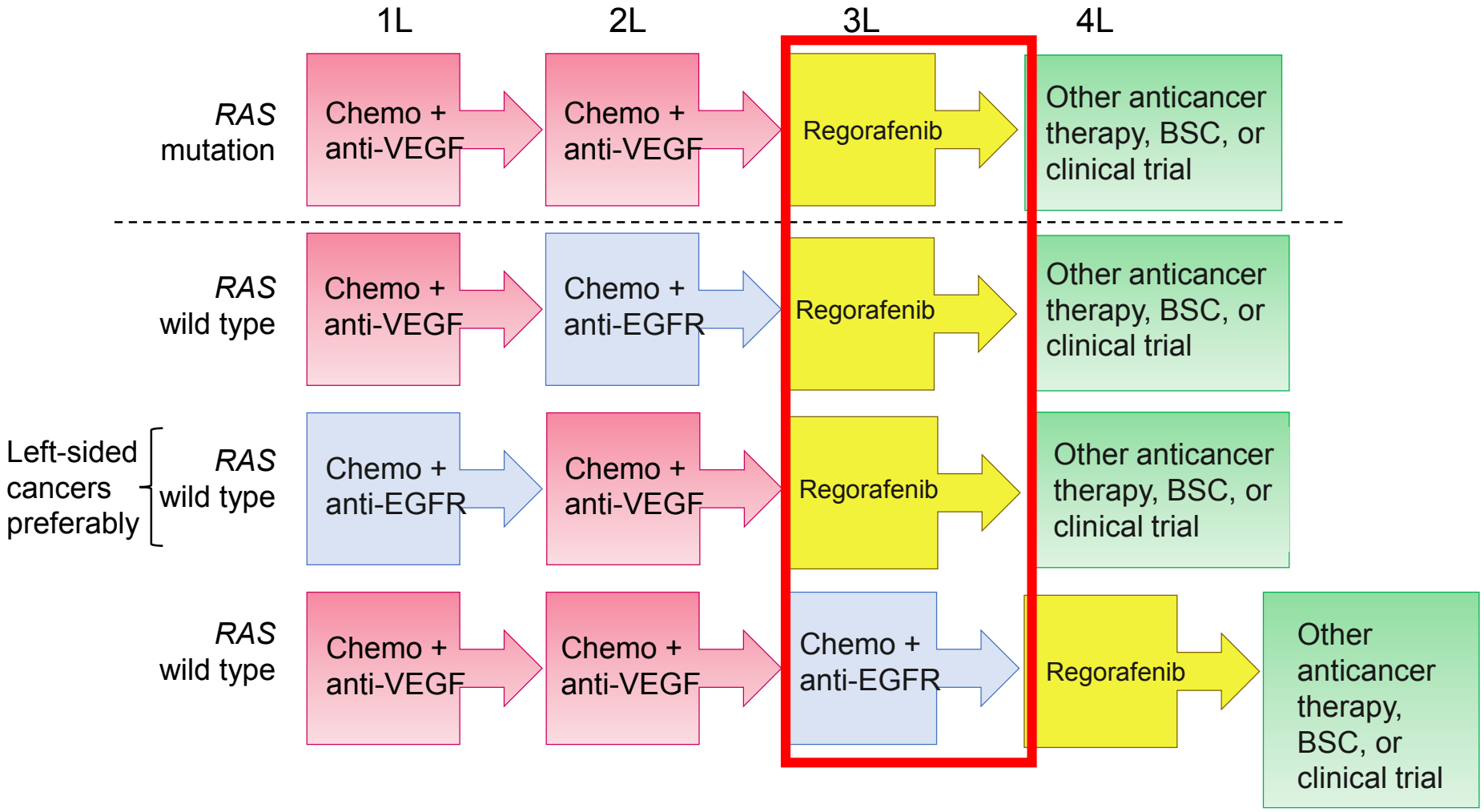
The better strategies



First line

Colorectal cancer

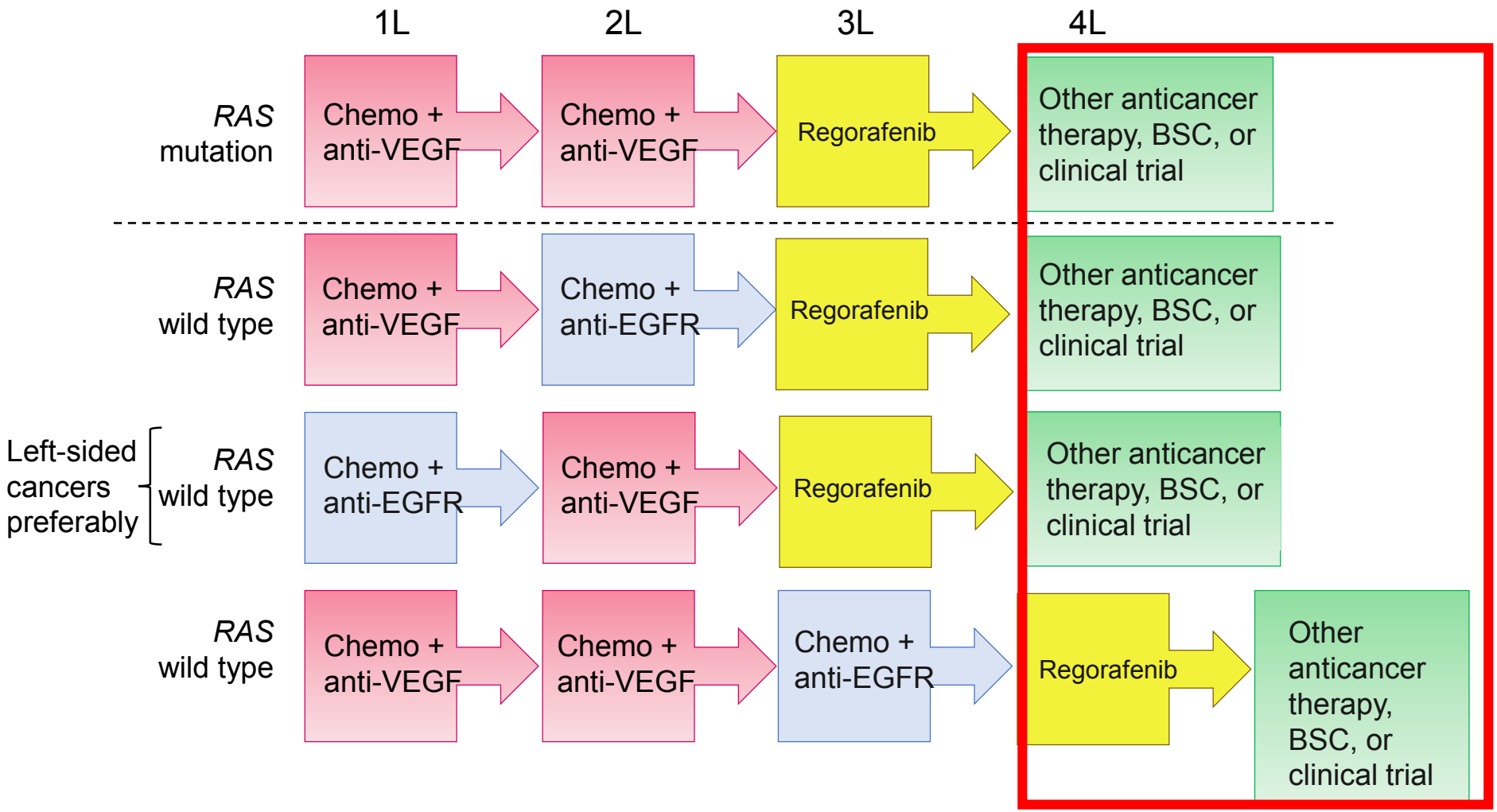
The better strategies



First line

Colorectal cancer

The better strategies



Grazie per l'attenzione!

Trieste 17-18 gennaio 2018

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