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Metastatic Colon Cancer

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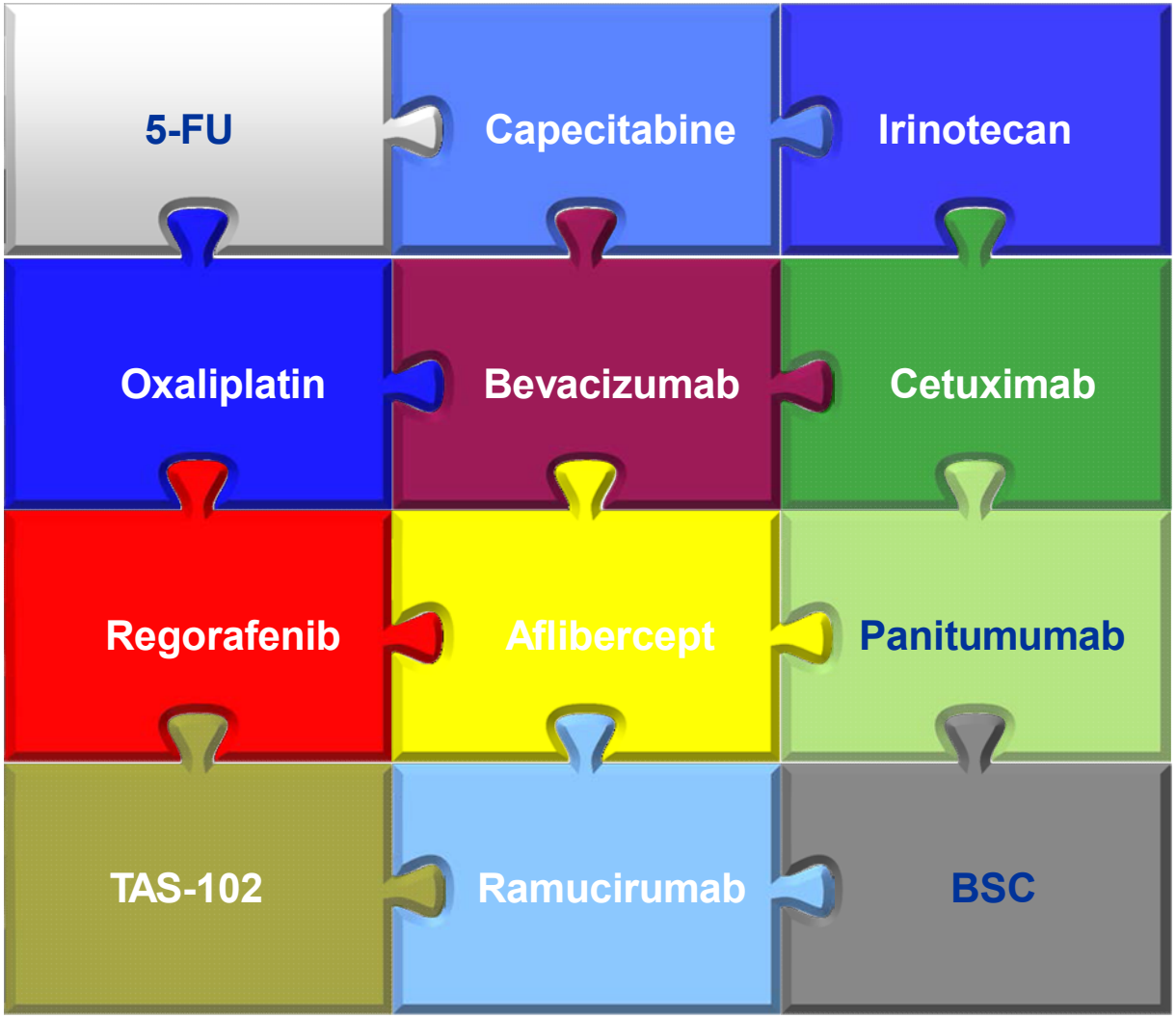
Multiple agents in mCRC and multiple opportunities



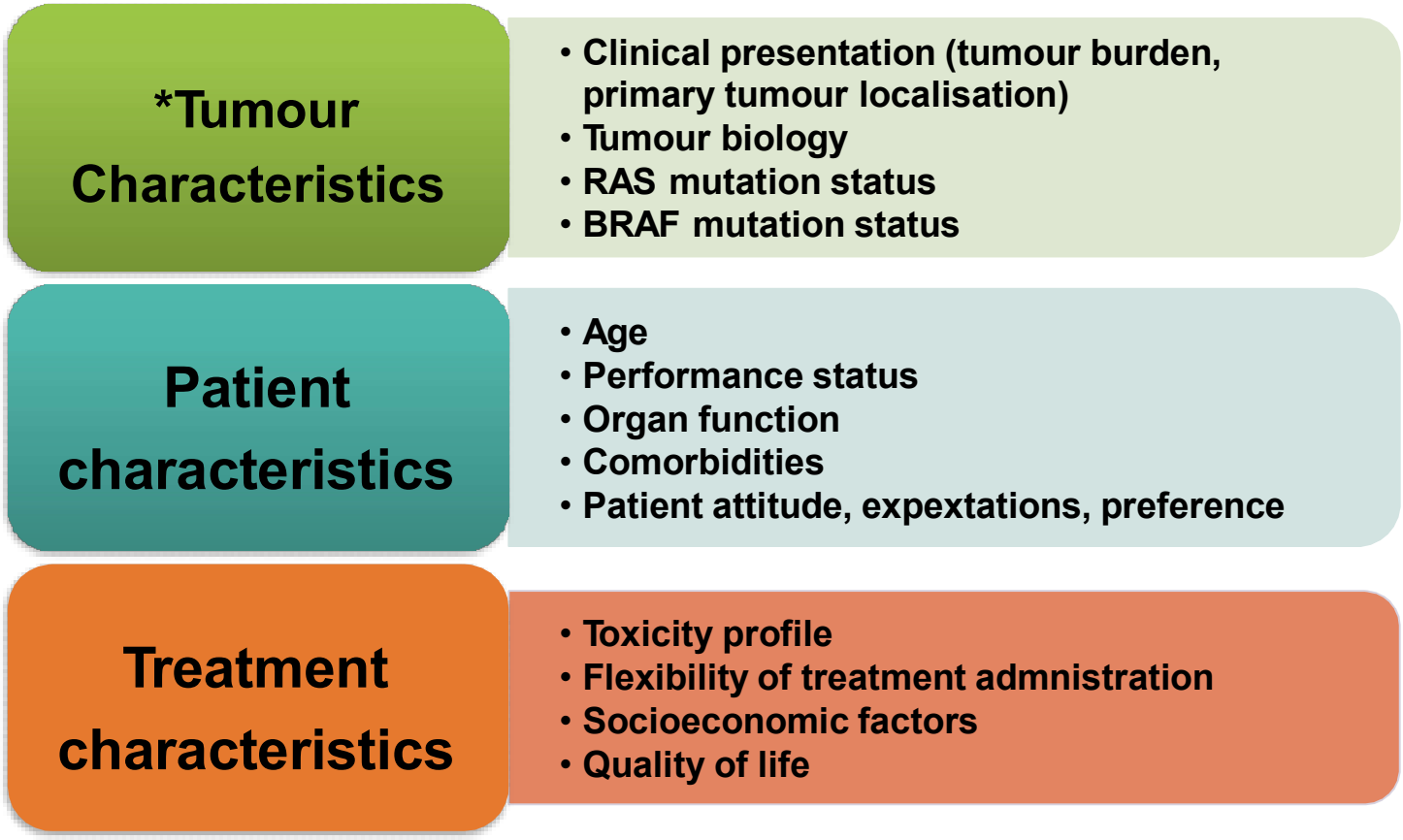
Cytotoxics in Colon Cancer

- Single agents
  - 5-FU, Capecitabine, Irinotecan, TAS-102, and Oxaliplatin
- FOLFOX = FOLFIRI
- CAPOX = FOLFOX
- Predictors of Efficacy:
  - Not really
- Predictors of Toxicity
  - Irinotecan (UGTA1A), fluoropyrimidines (DPD).

Biologics in mCRC

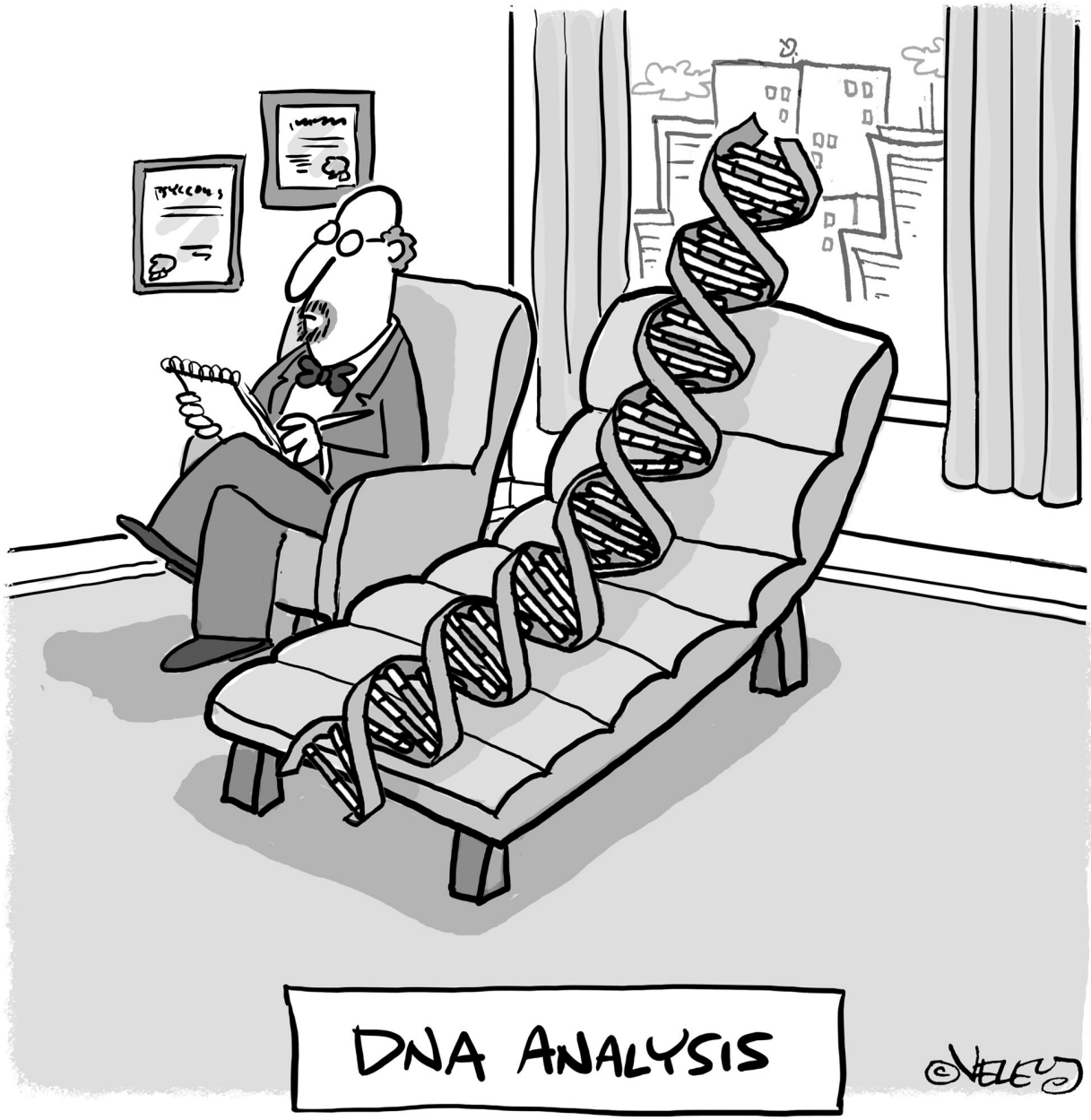
- Bevacizumab or EGFR mAbs in combination with cytotoxic chemotherapy first-line KRAS wt CRC
- Bevacizumab in combination with cytotoxic chemotherapy first-line KRAS Mut CRC
- Bevacizumab, *ramucirumab* , Ziv-Aflibercept, EGFR mAbs in combination with cytotoxic chemotherapy second-line in KRAS wt CRC
- Best sequence of therapies (VEGFi vs EGFRi) still to be established
- Regorafenib and TAS 102 as salvage therapy option
- Braf Inhibitors in BRAF mutant tumors
- HER 2 Inhibitors in HER 2 + tumors
- Immunotherapy In MMRd/MSIh

Drivers for first line treatment choices in metastatic colorectal cancer



The Goals of Systemic Therapy

- Extending OS
- Maintaining quality of life as long as possible
- Tumour response; especially if the pt is symptomatic or potentially resectable
  - Consider intensity of therapy/toxicities
  - Consider patient wishes
  - Which situation needs more aggressive and which a more gentle therapy?


DNA ANALYSIS

Molecular Pathology and Biomarkers

RAS testing

- ***RAS* is a predictive biomarker for therapeutic choices** involving EGFR antibody therapies in the metastatic disease setting .
- ***RAS* testing is mandatory prior to treatment** with EGFR-targeted monoclonal antibodies cetuximab and panitumumab .
- Primary or metastatic colorectal tumour tissue can be used for *RAS* testing.
- ***RAS* analysis** should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).
- **Turnaround time for *RAS* testing** (expanded *RAS* analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.

Molecular Pathology and Biomarkers

BRAF testing

- Tumour BRAF mutation status should be assessed alongside the assessment of tumour RAS mutational status for prognostic assessment (and/or potential selection for clinical trials)

MSI testing

- MSI testing in the metastatic disease setting can assist clinicians in genetic counselling
- MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC

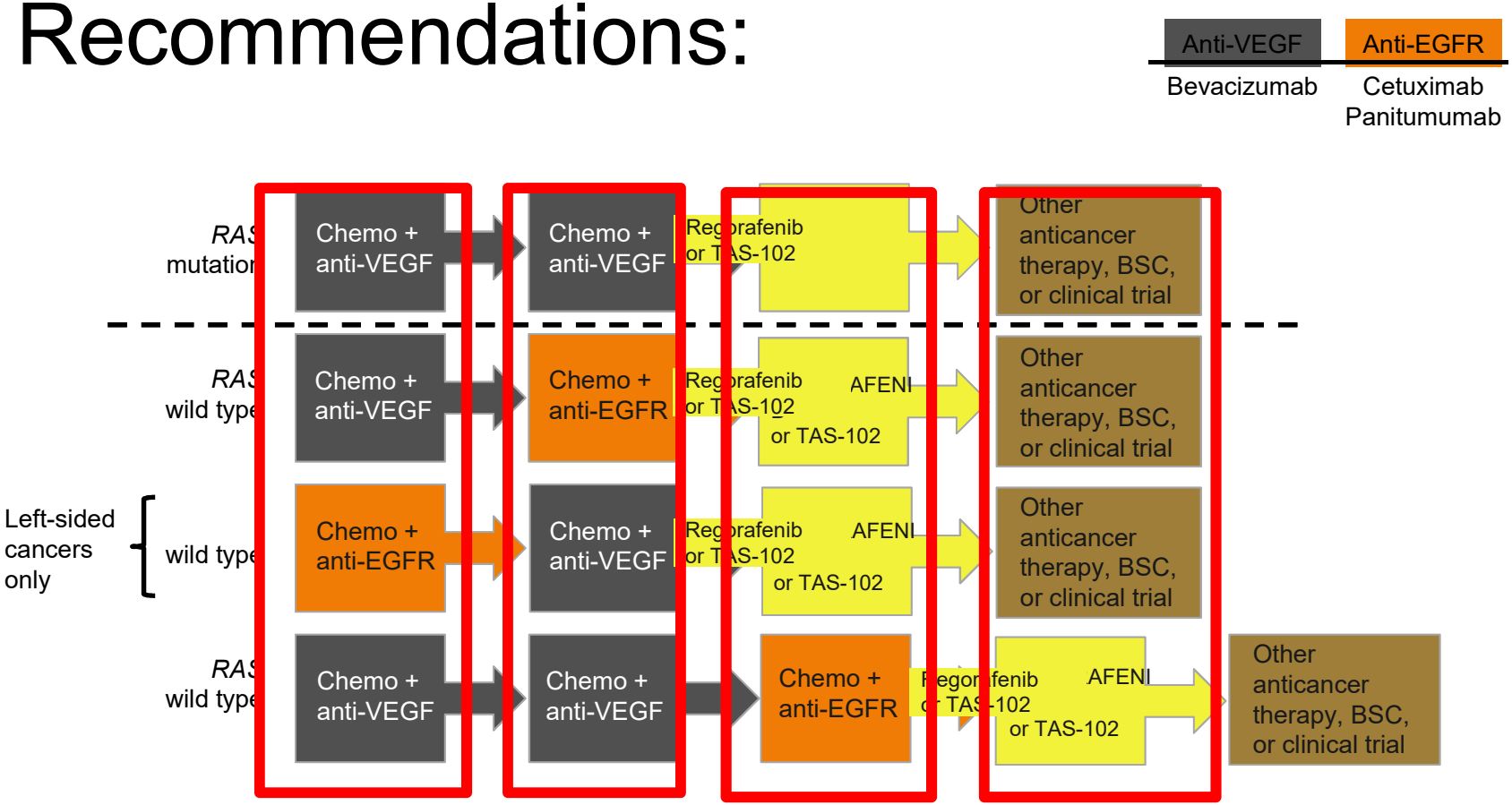
HER 2 Testing

Molecular Pathology and Biomarkers

Emerging technologies

- Although CTC number correlates with prognosis in patients with mCRC, the clinical utility of CTC assessments is not yet clear and therefore cannot be recommended .
- The utility of liquid ctDNA biopsies to guide treatment decisions may be considered as an alternative when tissue is not available.
  - Reproducible RAS testing
- Whole genome, whole exome and whole transcriptome analysis are generaly done in the research setting .

mCRC Treatment Decision Recommendations:

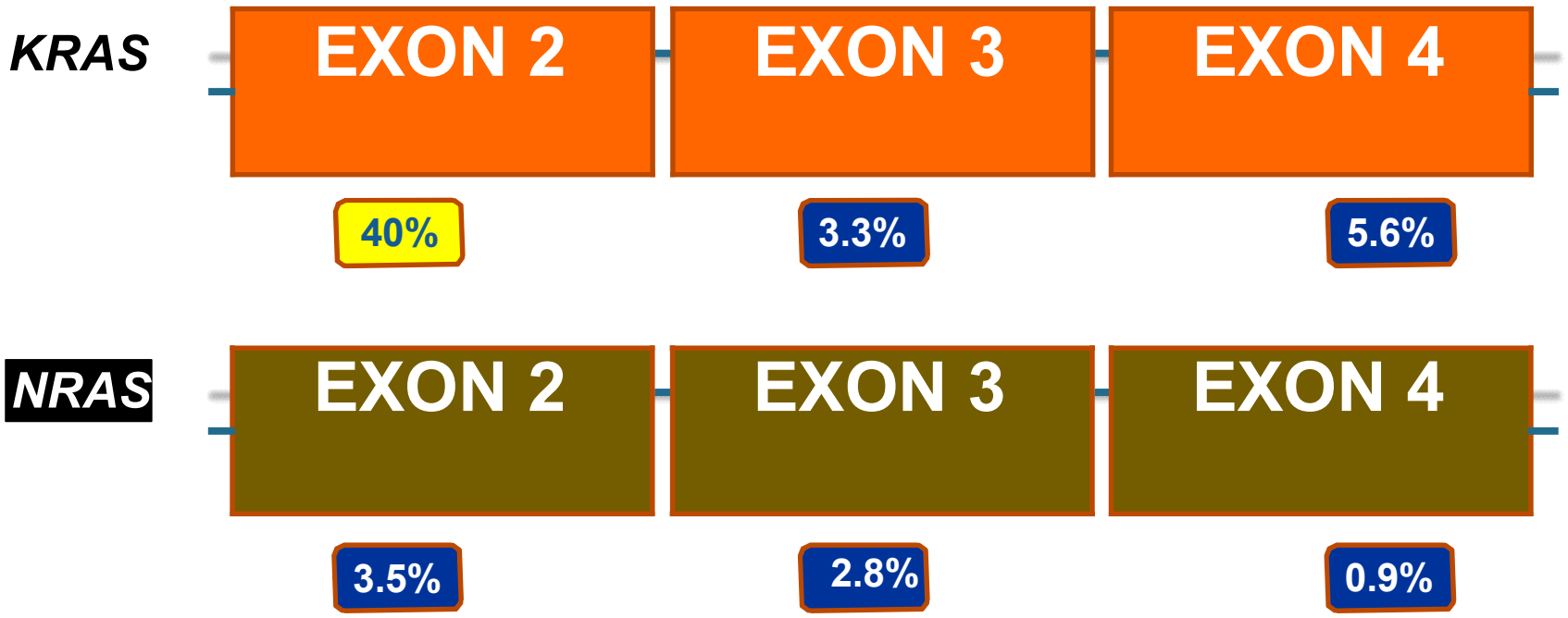


Bevacizumab added to chemotherapy in metastatic CRC

	PFS months	OS months
IFL	6.8 → 8.8	15.1 → 20.3
FOLFOX$^{2nd\text{-}line}$	4.7 → 7.3	10.8 → 12.9
FOLFIRI	7.6 → 11.2	23.1 → NR
FOLFOX/XELOX	8.0 → 9.4	19.9 → 21.3^{NS}

Hurwitz, NEJM, 2006; Giantonia, JCO, 2007; Fuchs, JCO, 2007; Saltz, JCO, 2008

CRC RAS mutations

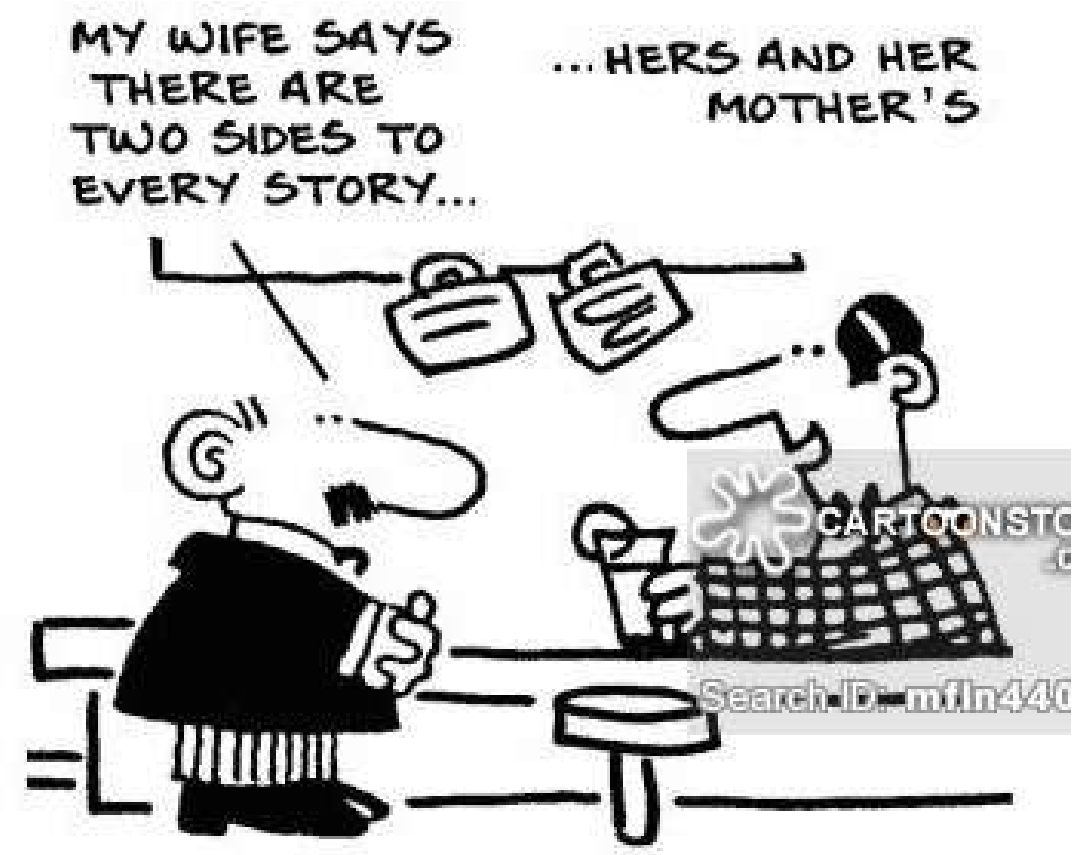


1st-line EGFR: Efficacy
KRAS *wild type*

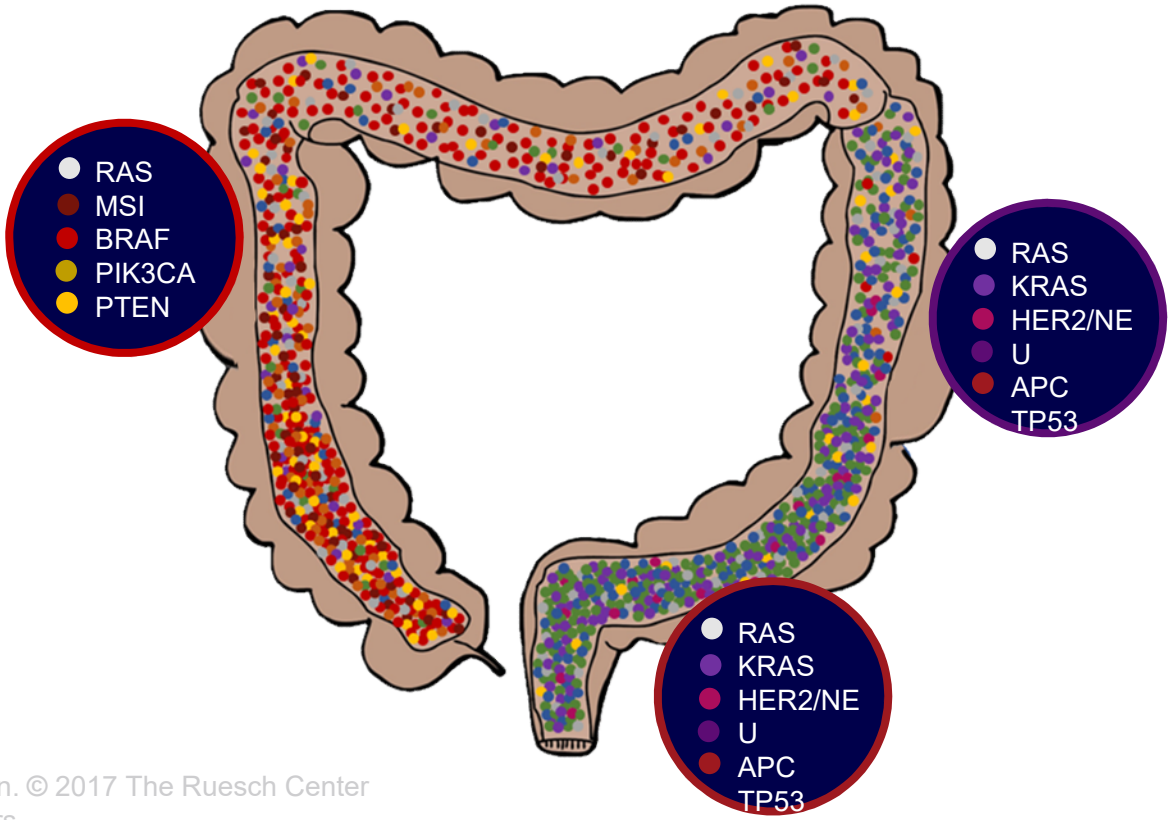
	Comparative Regimens	Median PFS, Mos	Median OS, Mos
CRYSTAL[1]	FOLFIRI/Cetux vs FOLFIRI	**9.9 vs 8.4**	**23.5 vs 20.0**
OPUS[2]	FOLFOX4/Cetux vs FOLFOX4	**8.3 vs 7.2**	**22.8 vs 18.5**
PRIME[3-5]	FOLFOX4/Pmab vs FOLFOX4	**9.6 vs 8.0**	**23.8 vs 19.4**
	FOLFOX4/Pmab vs FOLFOX4 (KRAS/NRAS WT)	**10.1 vs 7.9**	**26.0 vs 20.2**
COIN[6]	FOLFOX/XELOX/Cetux vs FOLFOX/XELOX	**8.6 vs 8.6**	**17.0 vs 17.9**

1. Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-2019. 2. Bokemeyer C, et al. Ann Oncol. 2010;22:1535-1546. 3. Douillard JY, et al. J Clin Oncol. 2010;28:4697-4705. 4. Douillard JY, et al. ASCO 2013. Abstract 3620. 5. Douillard JY, et al. N Engl J Med. 2013;369:1023-1034. 6. Maughan TS, et al. Lancet. 2011;377:2103-2114.

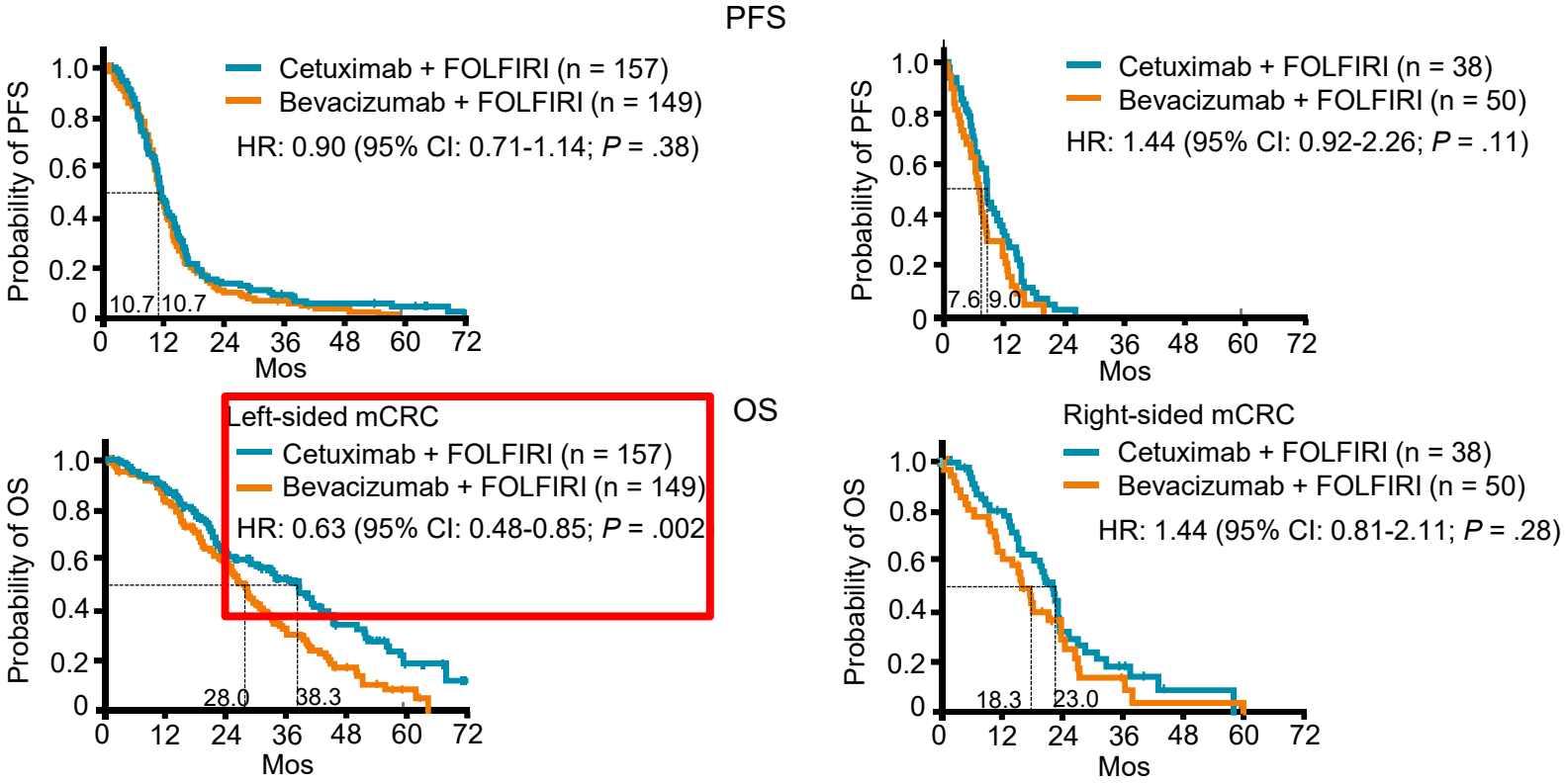
Two Sides Of A Story



Molecular Heterogeneity by Sidedness

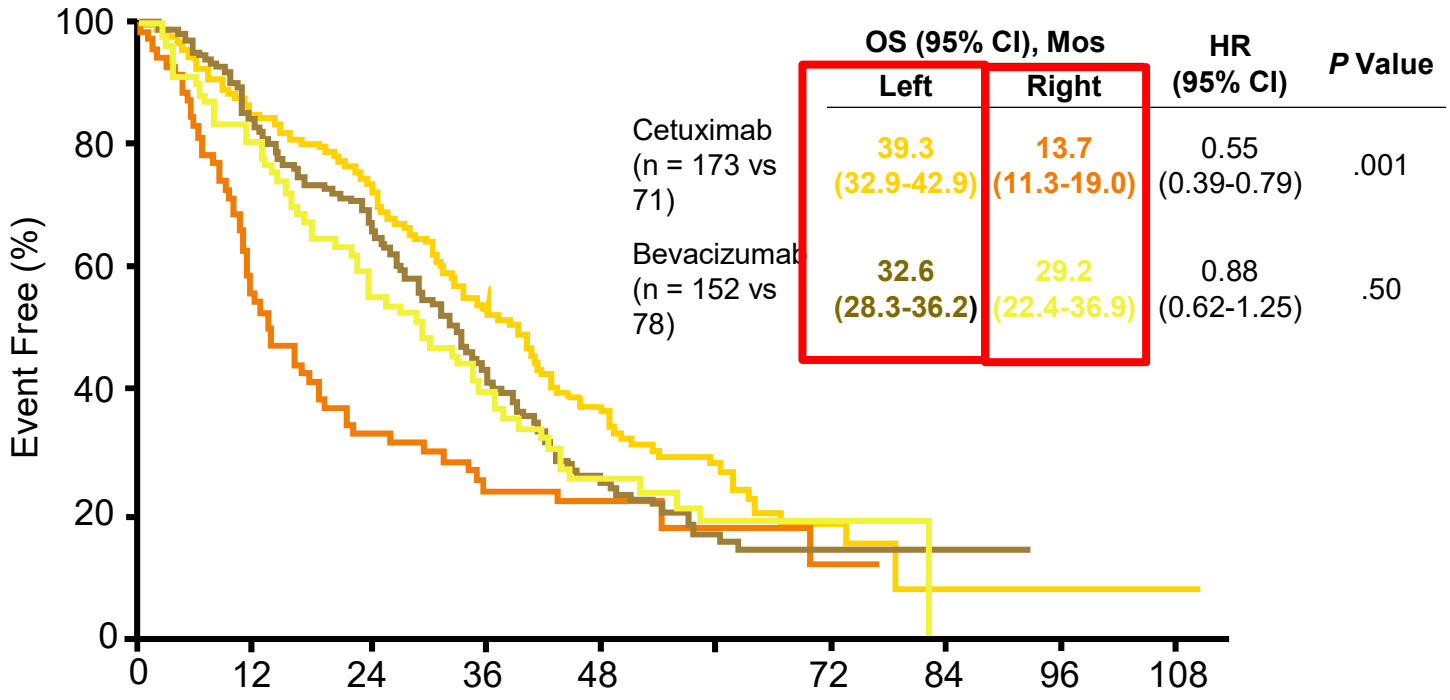


FIRE-3 (FOLFIRI + Bevacizumab or Cetuximab): PFS and OS by Tumor Location



Tejpar S, et al. JAMA Oncol. 2016;3:194-201.

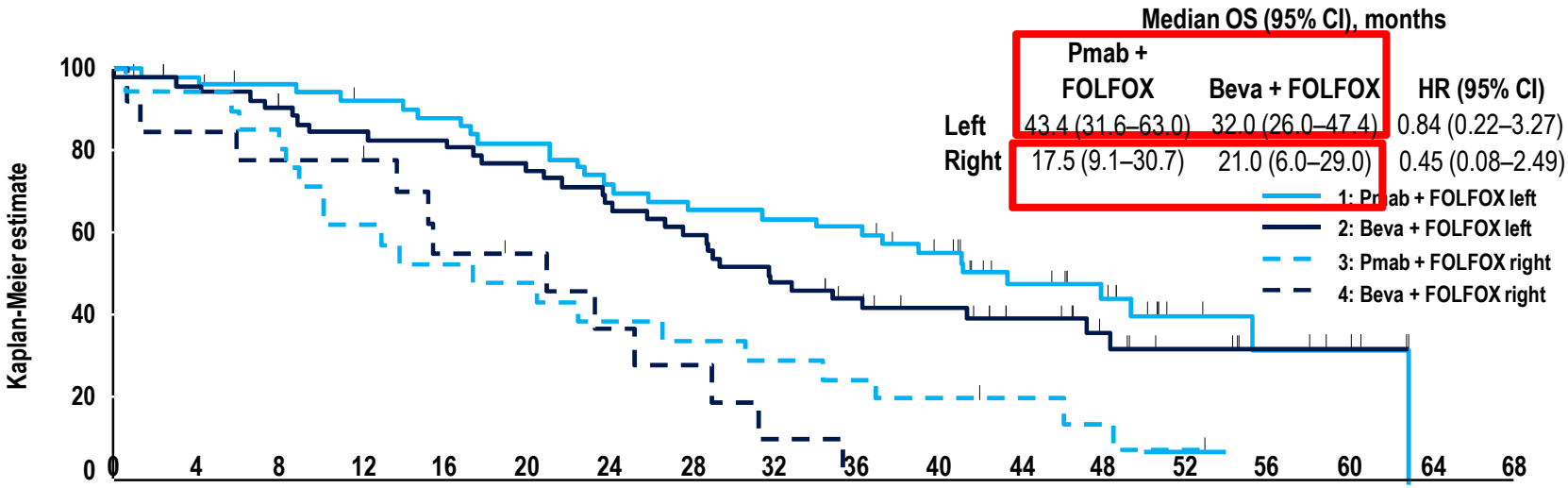
CALGB/SWOG 80405 (FOLFIRI/FOLFOX + Bev or Cetuximab): OS by Tumor Location (*RAS* WT)



	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

Venook A, et al. ESMO 2016. Abstract.

Right versus Left: PEAK – OS



No. of subjects:

1:	53	51	49	46	44	41	36	33	32	31	25	17	13	6	3	2	0
2:	54	51	48	44	43	40	35	31	26	21	17	13	10	5	3	2	0
3:	22	21	18	13	11	10	8	7	6	5	4	3	2	1	0		
4:	14	12	11	11	7	6	4	3	1	0							

Censor indicated by vertical bar

Beva, bevacizumab; HR, hazard ratio; OS, overall survival; Pmab, panitumumab

Take Home Points

- Left sided primary colorectal cancers have better prognosis than right sided colon cancers
- Right sided colorectal cancers do not benefit from anti-EGFR therapy but do benefit from bevacizumab
- Left sided tumors benefit from both bevacizumab and anti-EGFR therapy

Randomised trials of triplet chemotherapy plus bevacizumab

Trial	Setting	n	Treatment arms		mPFS (p value)	mOS (p value)
			Induction	Maintenance		
TRIBE	1st line	508	FOLFOXFIRI-Bev vs	5FU-Bev	12.1 vs	29.8 vs
Loupakis,			FOLFIRI-Bev		9.7	25.8
2014					(p=0.003)	(p=0.03)
OLIVIA	1st line	80	FOLFOXIRI-Bev vs	NA	18.6 vs	NR vs
Gruenberger,	(unresectable		FOLFOX-Bev		11.5	32.2
2014	liver only				(not reported)	(not reported)
	disease)					
STEAM	1st line	280	cFOLFOXIRI-Bev vs	5FU –Bev or	11.86 vs	34 vs
Hurwitz, 2017			sFOLFOXIRI-Bev vs	Capecitabine-Bev	11.37 vs	28 vs
			FOLFOX-Bev		9.46	31
					(p=0.01)	n.s.
CHARTA	1st line	250	FOLFOXIRI-Bev vs	5FU-Bev or	12 vs	28 vs
Schmoll, 2018			FOLFOX-Bev	Capecitabine-Bev	10.3	24
					(p=0.19)	(p=0.21)

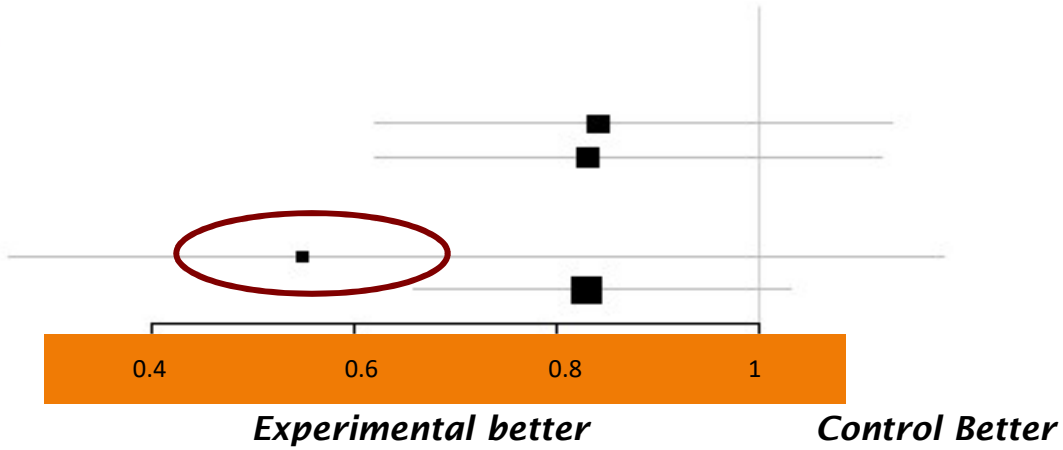
Loupakis, NEJM 2014; Greunberger, Ann Oncol 2014; Hurwitz, ASCO 2017; Schmoll, ESMO GI 2018

TRIBE: Resection of Metastases (ITT Population)

	FOLFIRI + Bev, % (n=256)	FOLFOXIRI + Bev, % (n=252)	*P* Value
Secondary surgery with radical intent	21	26	0.210
R0 secondary surgery	12	15	0.327
Liver-only subgroup	**(n=46)**	**(n=59)**	
Secondary surgery with radical intent	41	39	1.000
R0 secondary surgery	28	32	0.823

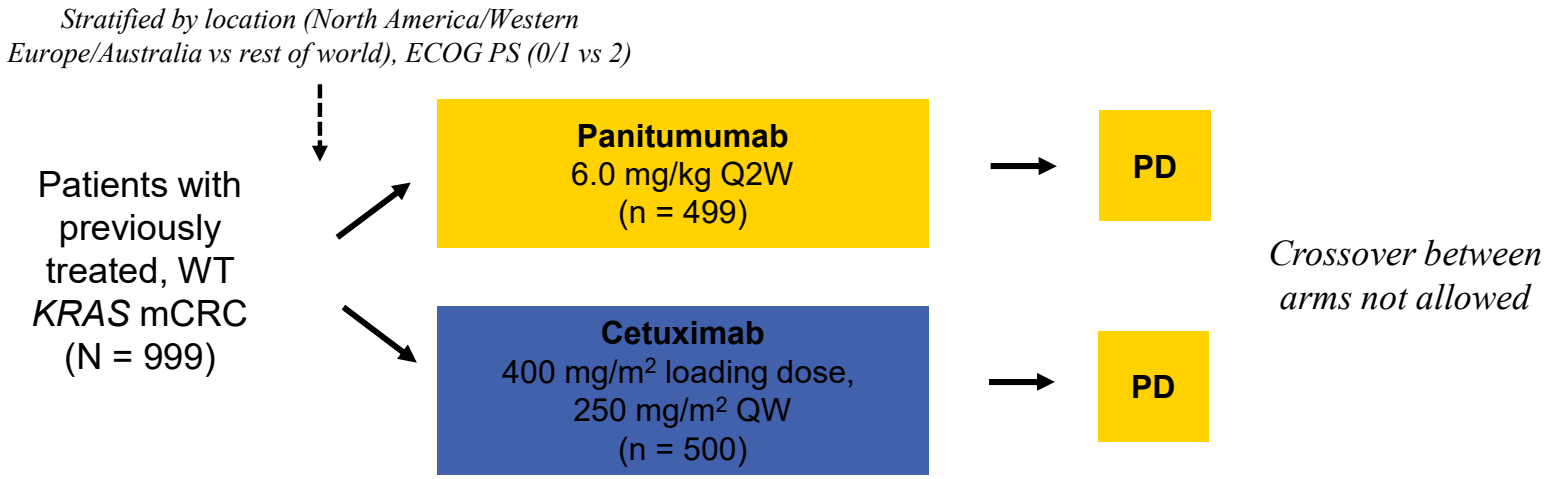
Subgroup analyses of PFS – molecular characteristics

Factor	N	HR	p
KRAS status			
mut	200	0.84	0.973
wt	193	0.83	
BRAF status			
mut	28	0.55	0.323
wt	365	0.83	



Cremolini C et al. Lancet Oncology Online August 2015

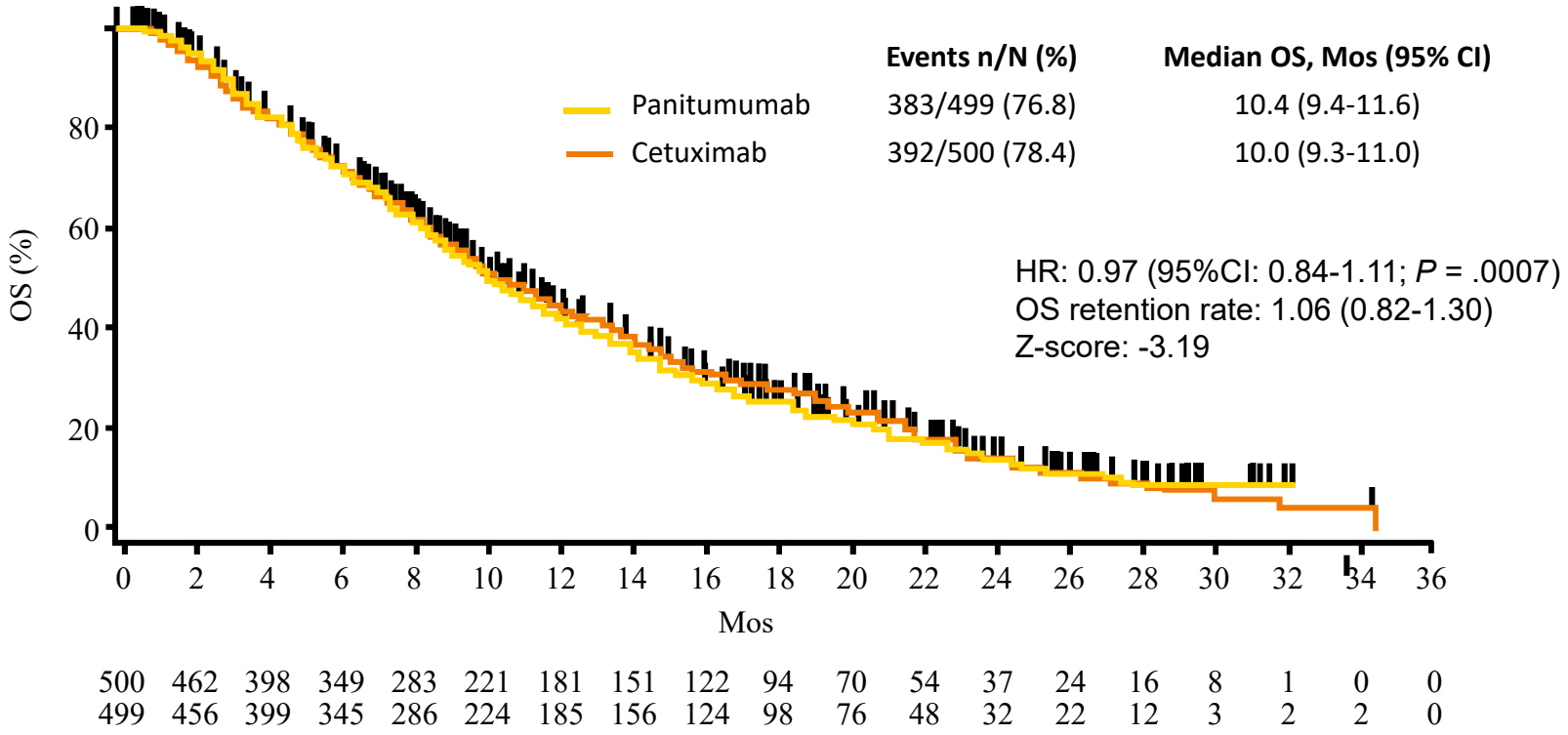
Phase III ASPECCT: Panitumumab vs Cetuximab in KRAS-WT mCRC



- Primary endpoint: OS

Price TJ, et al. Lancet Oncol. 2014;15:569-579.

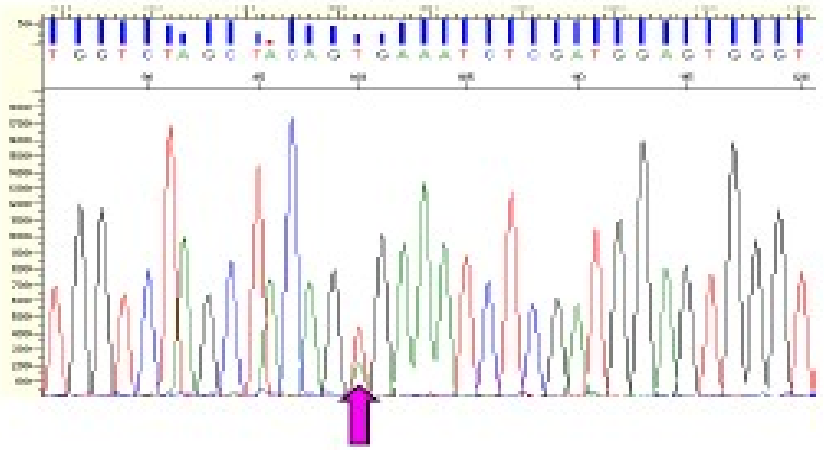
Phase III ASPECCT: OS



BRAF

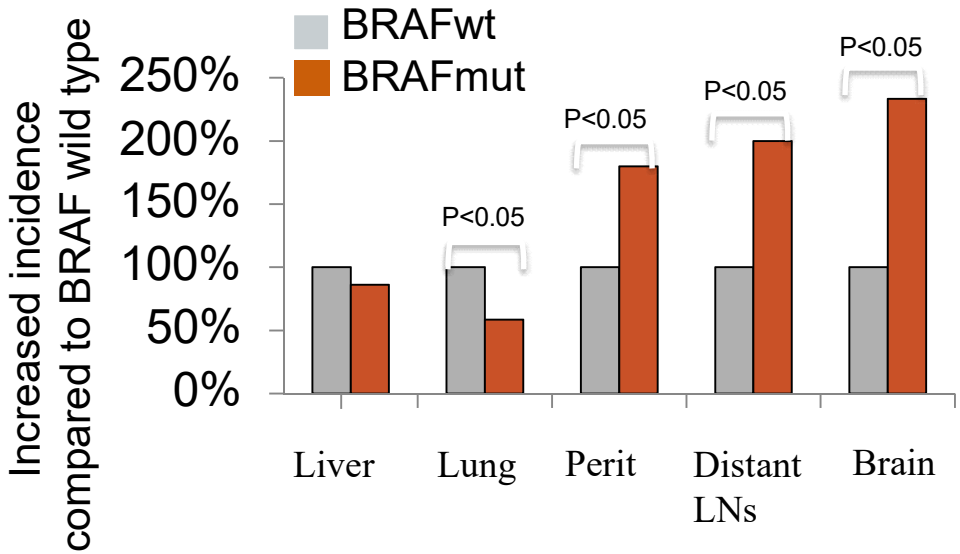
BRAF gene mutations

Exon 15, codon 600 (mutation V600E)



BRAF Characteristics

- Origin: serrated adenoma
- Hyper-methylated
- ~30% Microsatellite unstable
- RAS wild-type
- Ascites, peritoneal & lymph node metastases



Tran et al, *Cancer* 2011

BRAF MUTATION IN MSI PATIENTS

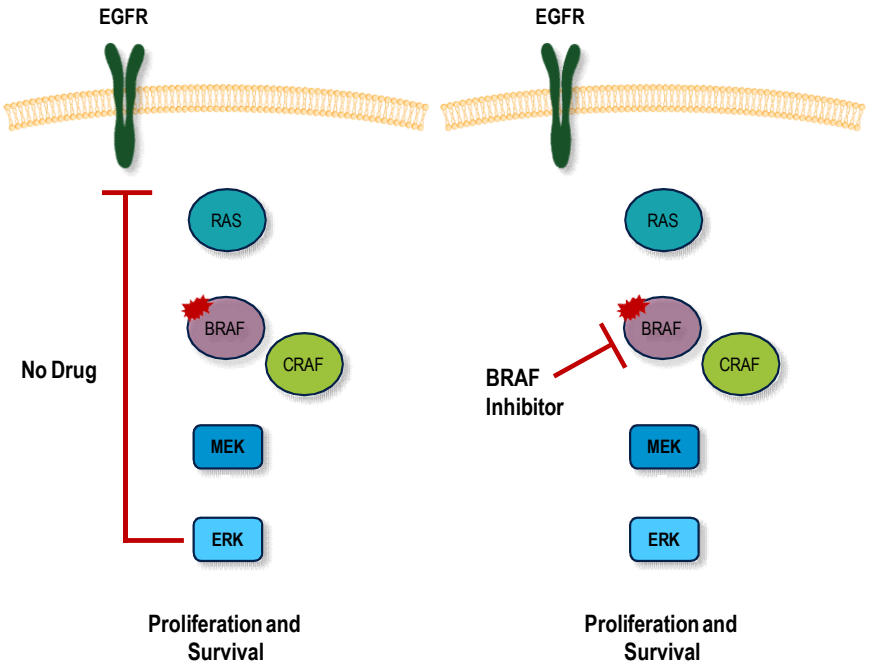
Checkmate 142 study

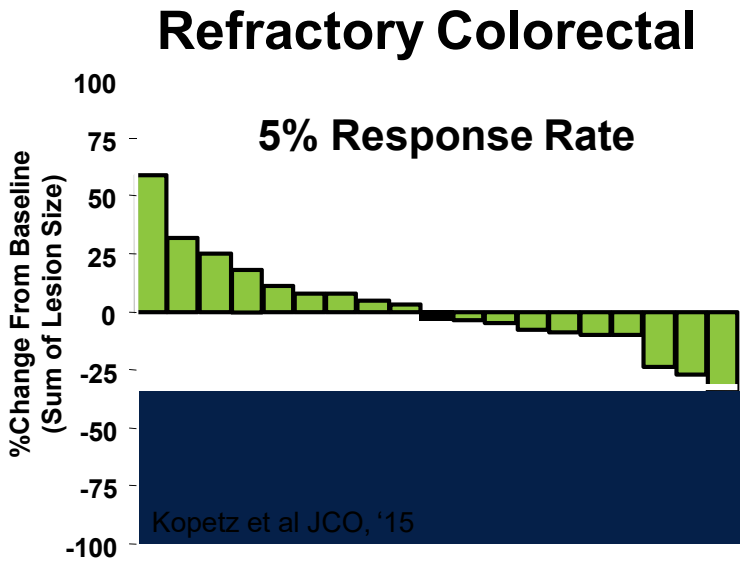
	Objective response	Disease control for ≥12 weeks
Mutation status		
BRAF mutant (n=12)	3 (25%)	9 (75%)
KRAS mutant (n=26)	7 (27%)	16 (62%)
Both *BRAF* and *KRAS* wild type (n=29)	12 (41%)	23 (79%)

- No effect of *BRAF* mutation tumour growth control with nivolumab
- But completely different population of patients….

Overman NJ et al. Lancet Oncol 2017; Published online

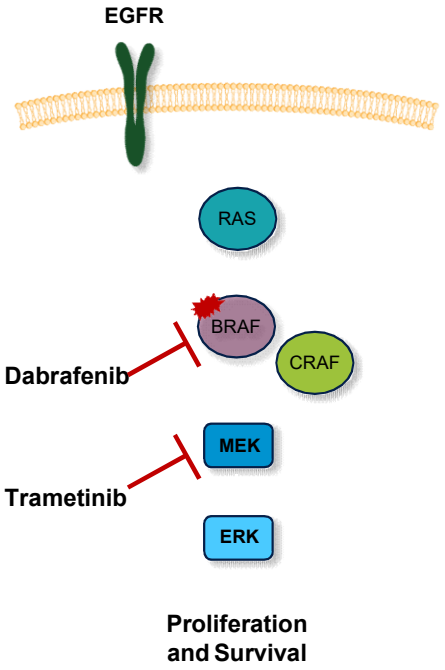
7. Clinical trials with BRAF inhibitors

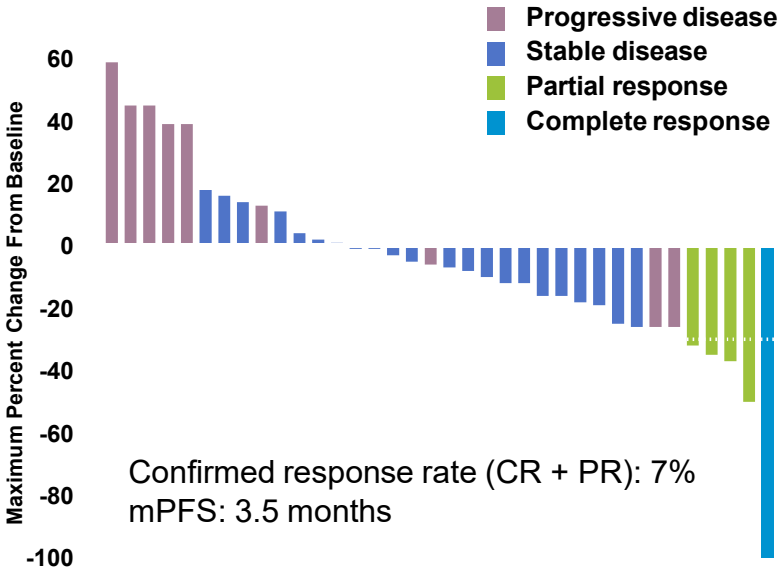




Vemurafenib monotherapy: not effective in BRAF(V600E) mCRC

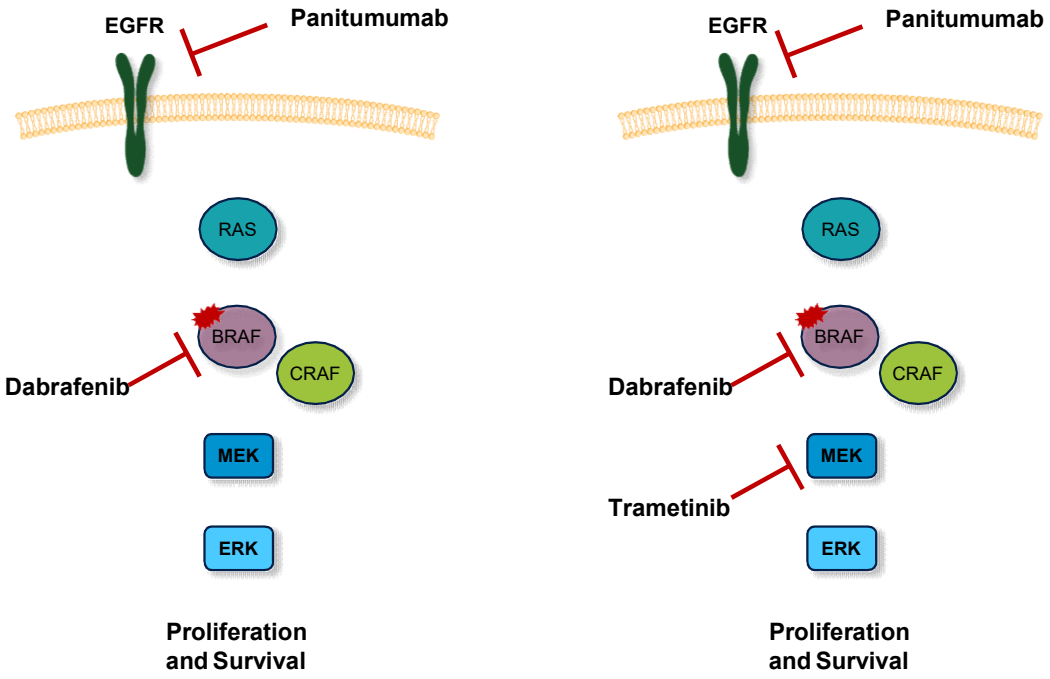
Dabrafenib + trametinib: limited activity in BRAFm CRC





Corcoran, Atreya et al, J Clin Oncol 2015

Can Targeting EGFR Overcome Resistance to BRAF + MEK Inhibitors in *BRAF*-mutant CRC?



Prahallad A, et al. *Nature* 2012;
Corcoran RB, et al. *Cancer Discov* 2012

BRAF V600E Mutation: Treatment Outcomes

Regimen	RR, %	mPFS, mo
Single/Doublet BRAF/MEK		
Vemurafenib[1]	5	2.1
Dabrafenib[2]	11	NR
Encorafenib[3]	6	4
Dabrafenib + Trametinib[4]	12	3.5
Doublet with EGFR		
Vemurafenib + Panitumumab[5]	13	3.2
Vemurafenib + Cetuximab[6]	20	3.2
Encorafenib + Cetuximab[7]	19	3.7
Dabrafenib + Panitumumab[8]	10	3.4
Triplet with EGFR		
Vemurafenib + Cetuximab + Irinotecan[9]	35	7.7
Dabrafenib +Trametinib + Panitumumab[8]	26	4.1
Encorafenib + Cetuximab + Alpelisib[7]	18	4.2

VIC x IC

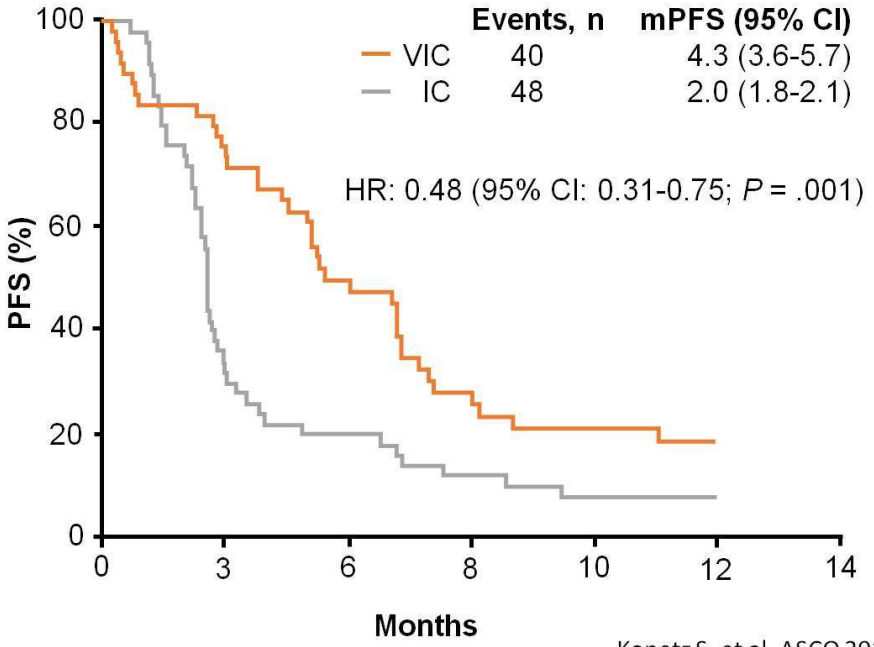
BRAF ^{V600E} predictive value in metastatic CRC

Prevalence ~ 8%

SWOG S1406

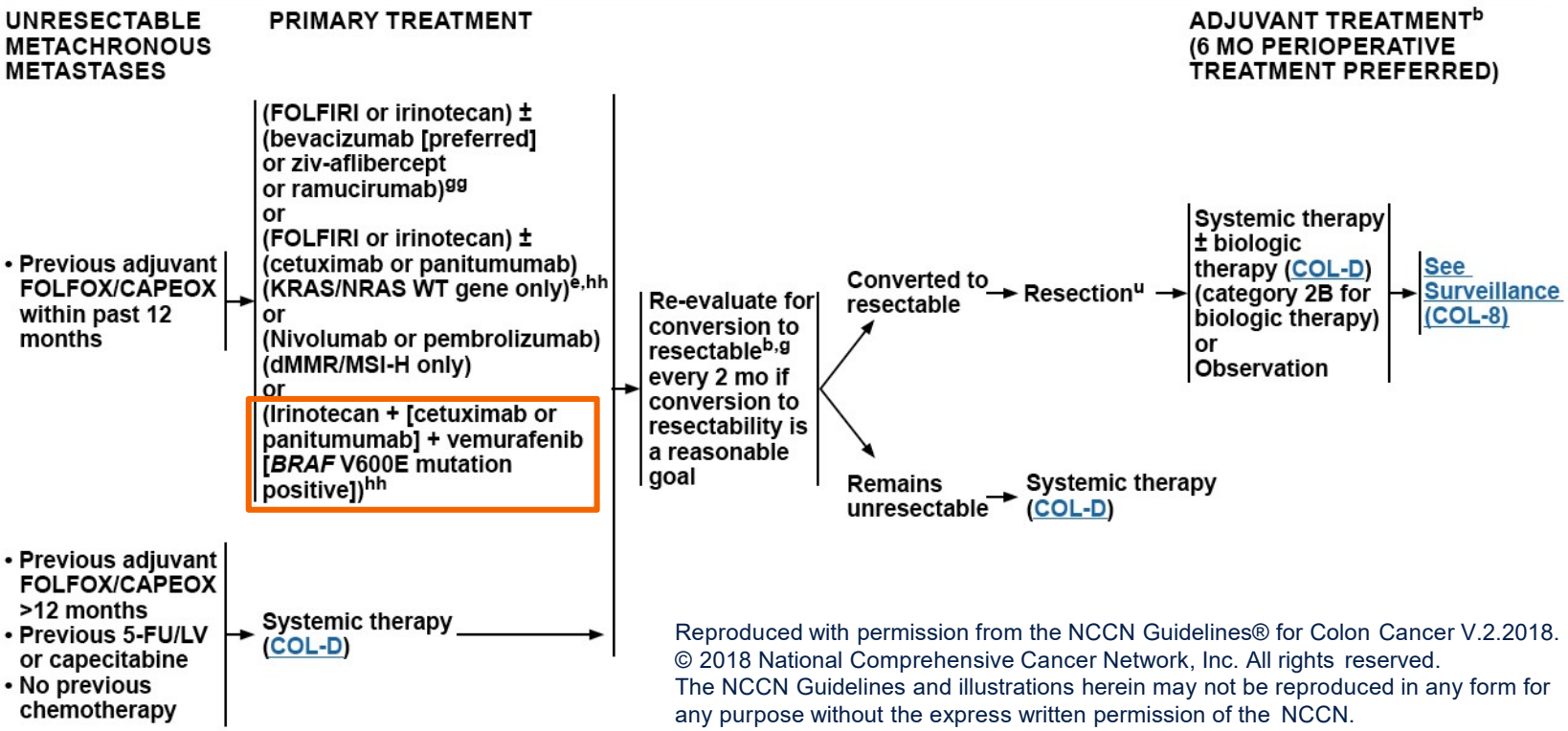
Phase II
1-2 prior lines
No prior anti-EGFR/BRAF/MEK

VIC – Vemurafenib, Irinotecan, Cetuximab
IC – Irinotecan, Cetuximab



Kopetz S, et al. ASCO 2017

NCCN Guidelines Version 2.2018
Colon Cancer



HER2 Aberrations in CRC:

- Dimerization activates MAPK and PI3K pathways
- Overexpression, amplifications and mutations upregulate HER2 signaling
- Amplification: 5,4% of CRC
- Mutation: 2,8% of CRC
- Resistance to EGFR may lead to higher expression rates.

Yonesaka Sci Trans Med 2011 Bertotti Can Disc 2012
Kavuri Can Disc 2015
Valtoria et al. Modern Pathology 2017

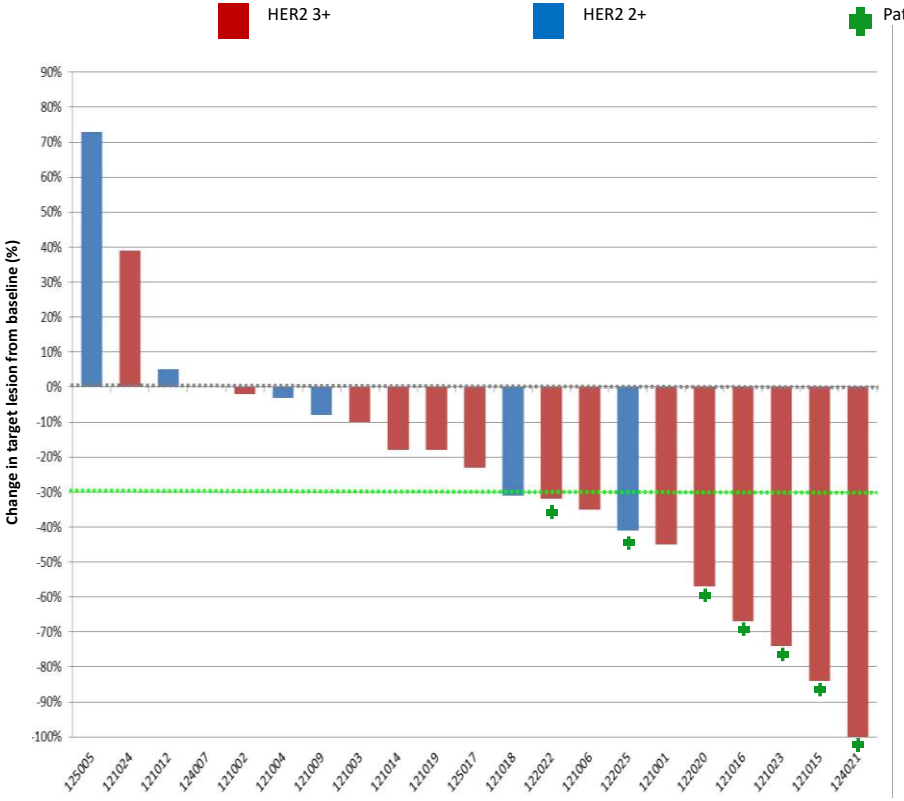
Heracles Results

- 23 evaluable pts treated with lapatinid + trastuzumab:
- 2F/21M, median age 63 (r = 40-86), ECOG PS ≤ 1, median prior regimens 5 (r = 3-8).
- Primary endpoint was met with 8/23 Response [ORR = 35% (95% CL 20-55)]; 7/8
- ORs were observed in HER2 IHC3+ pts.
- Responses lasted: 8+, 12+, 14+, 24, 24.5+ 32, 54+ and 55+ weeks. Median time to progression was 5.5 months (95% CL 3.7-9.8).

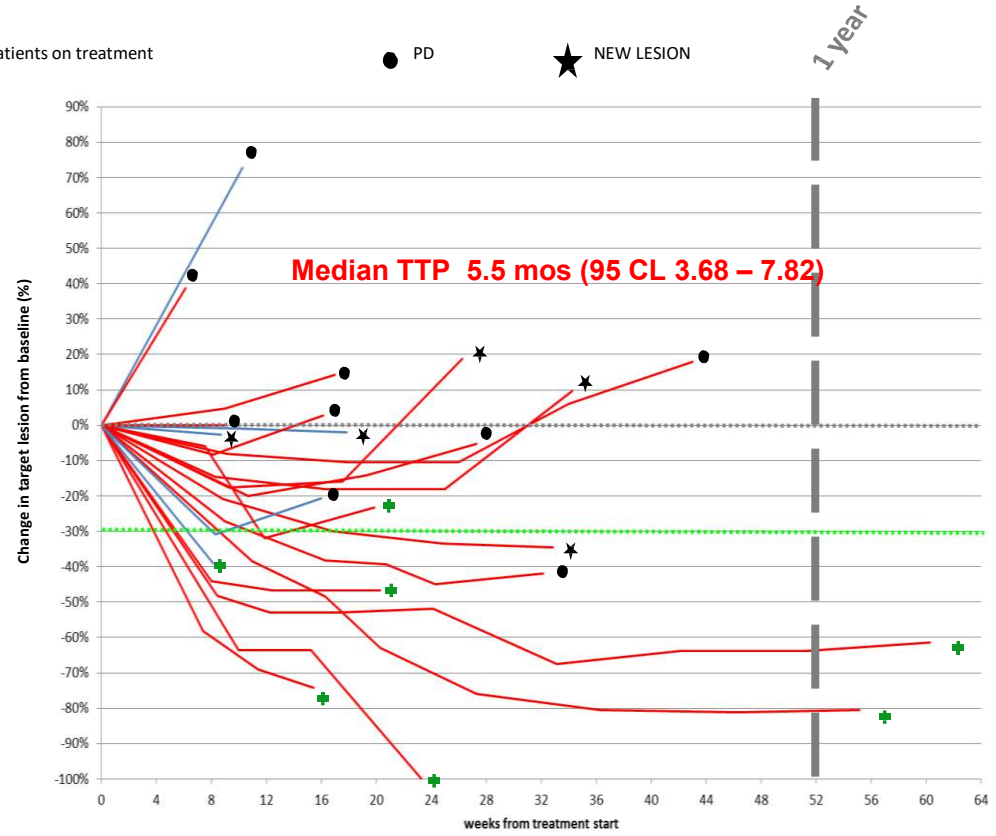
Sartore-Bianchi.: Lancet Onc2016

Responses by HER2 IHC Score

Waterfall plot



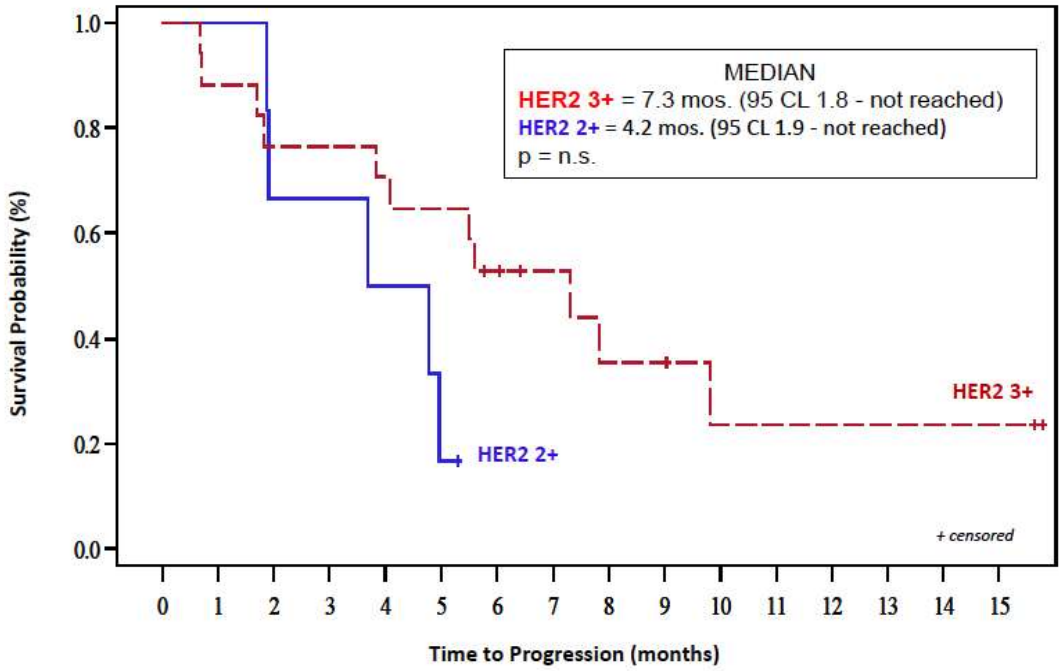
Spaghetti plot



*3 patients are not shown: 122026 (IHC 2+), not assessed yet; 121011 (IHC 3+) and 121013 (IHC 3+) early clinical PD.

Sartore-Bianchi.: Lancet Onc2016

Time To Progression



At risk:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HER2 2+	6	6	4	4	3	1	0									
HER2 3+	17	15	13	13	12	11	8	6	4	4	2	2	2	2	2	2

Sartore-Bianchi.: Lancet Onc2016

Trastuzumab + Pertuzumab

- My pathway: phase II basket trial
- 37 CRC pts with HET2 3+ or 2+ by IHC and ISH +. 14 (38%) PRs
- Ongoing trials:
  - Heracles rescue (TDM-1), Heracles B (pertuzumab +TDM1, Montaineer (Tucatinib + trastuzumab), MODUL (Cape, trastuzumab, pertuzumab)

Hainsworth J et al, JCO 2018
Siena S et al, AACR 2017

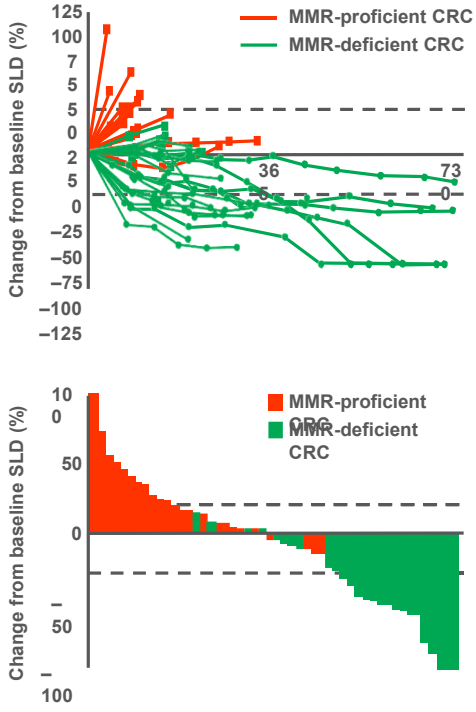
Other Gene Alterations CRC

- Fusions:
  - ALK, NTRK1, ROS 1, RET
- ATM (and other DNA repair) Mutation
  - Velaparib + Irinotecan
- MET Amplification
  - PF-02341066 + binimetinib

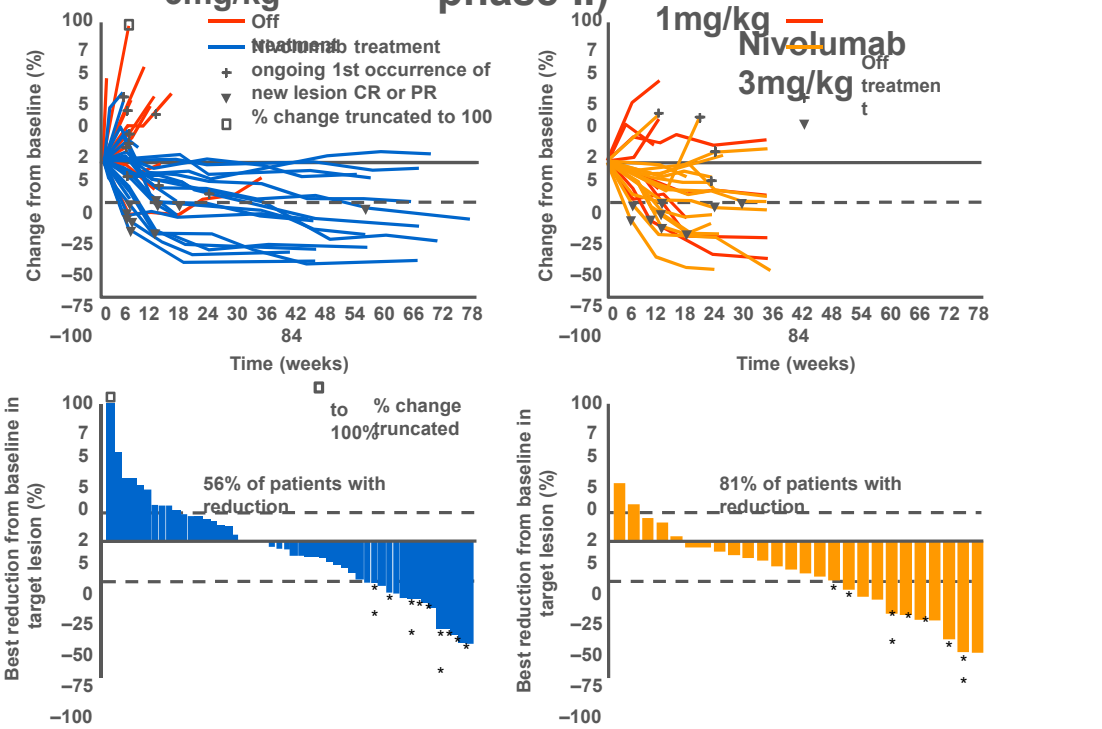
CHECKPOINT INHIBITORS

MSI-high tumours are responsive to PD-1 inhibitors

Pembrolizumab (KEYNOTE 016, phase II)[1,*]



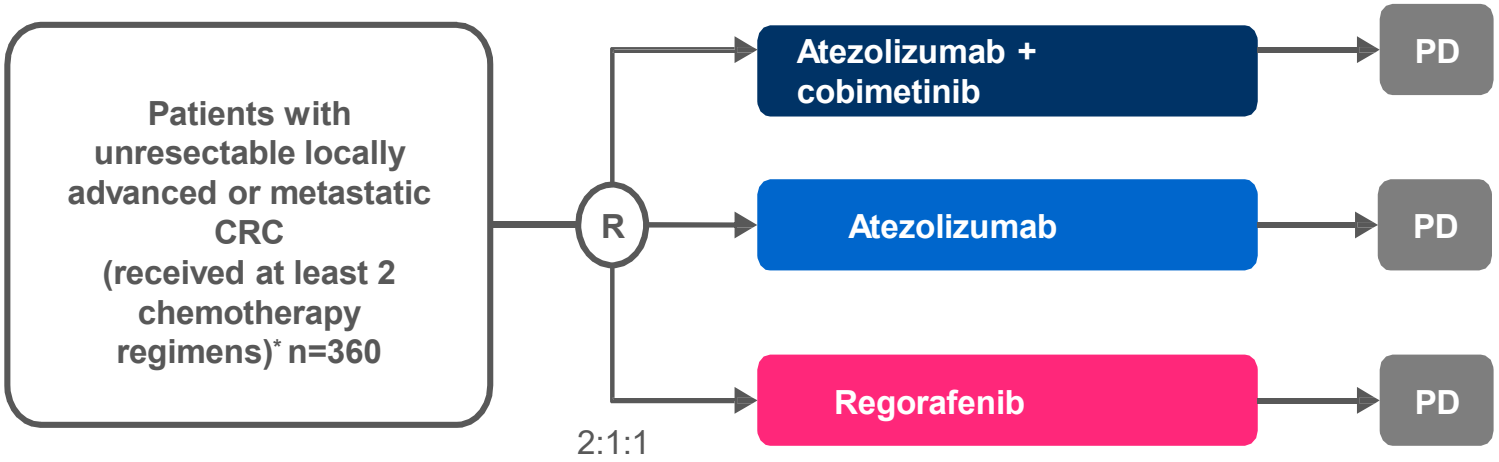
Nivolumab ± ipilimumab (CheckMate-142, phase II)[2]



*Lynch Syndrome (yes/no/unknown): MMR-deficient CRC = 54/7/39; MMR-proficient CRC = 0/100/0

1. Le et al. ASCO 2016; 2.Overman et al. ASCO 2016

Phase III trial of Cobimetinib and Atezolizumab in chemotherapy-refractory mCRC (COTEZO – IMBlaze 370)



- Primary endpoint = OS

*Experienced disease progression or was intolerant to at least two systemic chemotherapy regimens including fluoropyrimidines, irinotecan, or oxaliplatin

Bendel J, Ann Onc 29, suppl_5, 2018

Phase III trial of Cobimetinib and Atezolizumab in chemotherapy- refractory mCRC

- Median OS (363 patients)
  - 8.9 mo atezolizumab+cobimetinib vs 8.5 mo with regorafenib (HR, 1.00 [95% CI: 0.73, 1.38] P = 0.987)
  - 7.1 mo with atezolizumab monotherapy (HR vs regorafenib, 1.19 [95% CI: 0.83, 1.71]).
- No Change PFS

Bendel J, Ann Onc 29, suppl_5, 2018

Conclusions

- Survival of patients with mCRC continues to improve thanks to incremental additional effects of subsequent treatment lines
- Patients should receive all active agents to derive full benefits
- Molecular driven subgroups are leading to individualization of treatment
- Immunotherapy activity in MSI-High tumors is stablished.
- Targeted Therapy and immunotherapy combo are emerging options
- Biomarkers to predict benefit from IO are desperately needed.

Thank you