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Selection and Sequencing of Therapy for Patients with Newly Diagnosed Metastatic Colorectal Cancer

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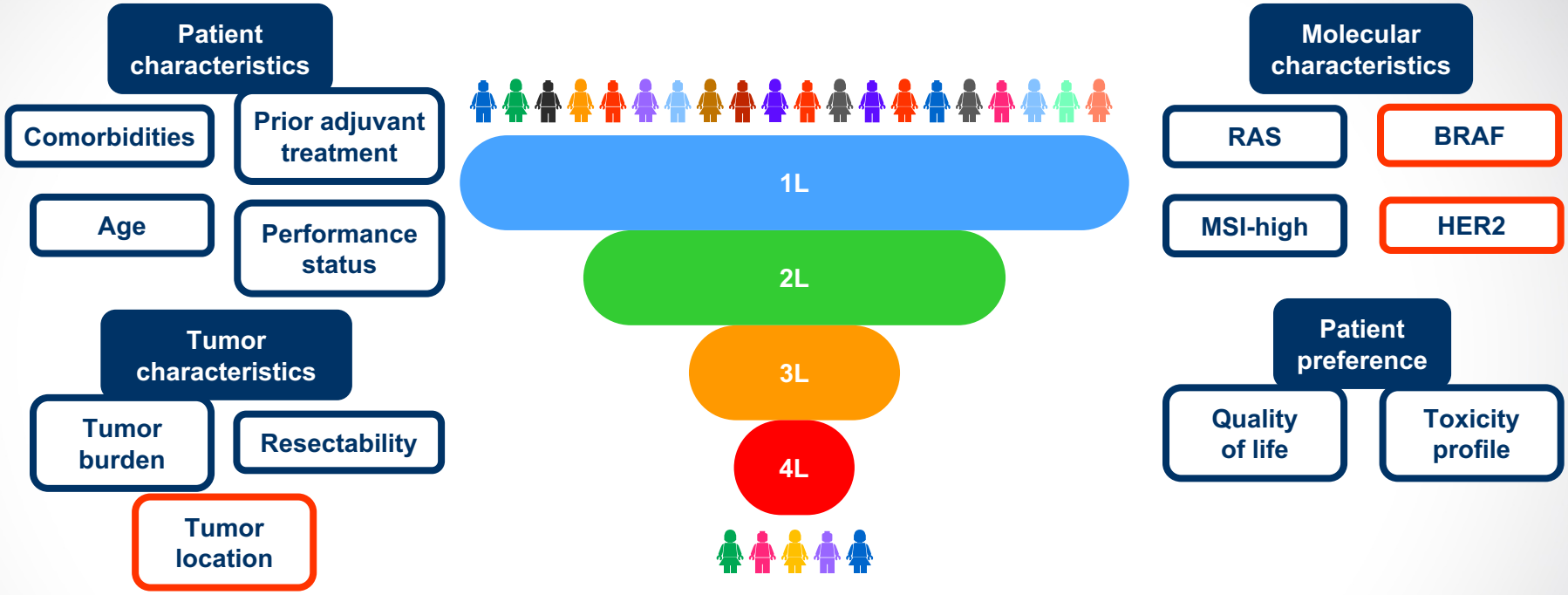
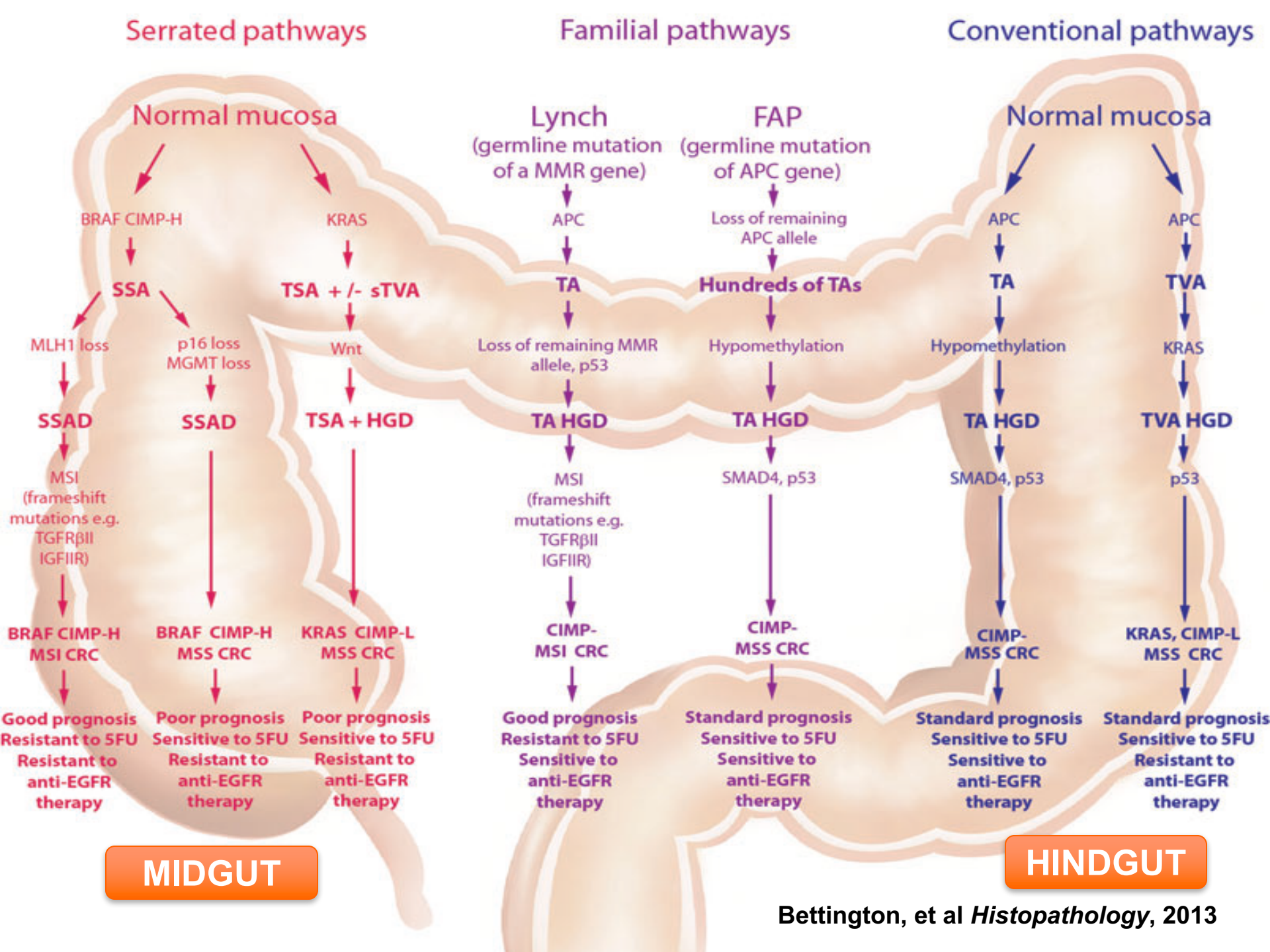
Disclosures

Advisory Committee	Amgen Inc, Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Genentech BioOncology, Roche Laboratories Inc
Contracted Research	Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Eisai Inc, Genentech BioOncology

What influences treatment choices in mCRC?



Therapy tailored according to individual patient needs



Bettington, et al *Histopathology*, 2013

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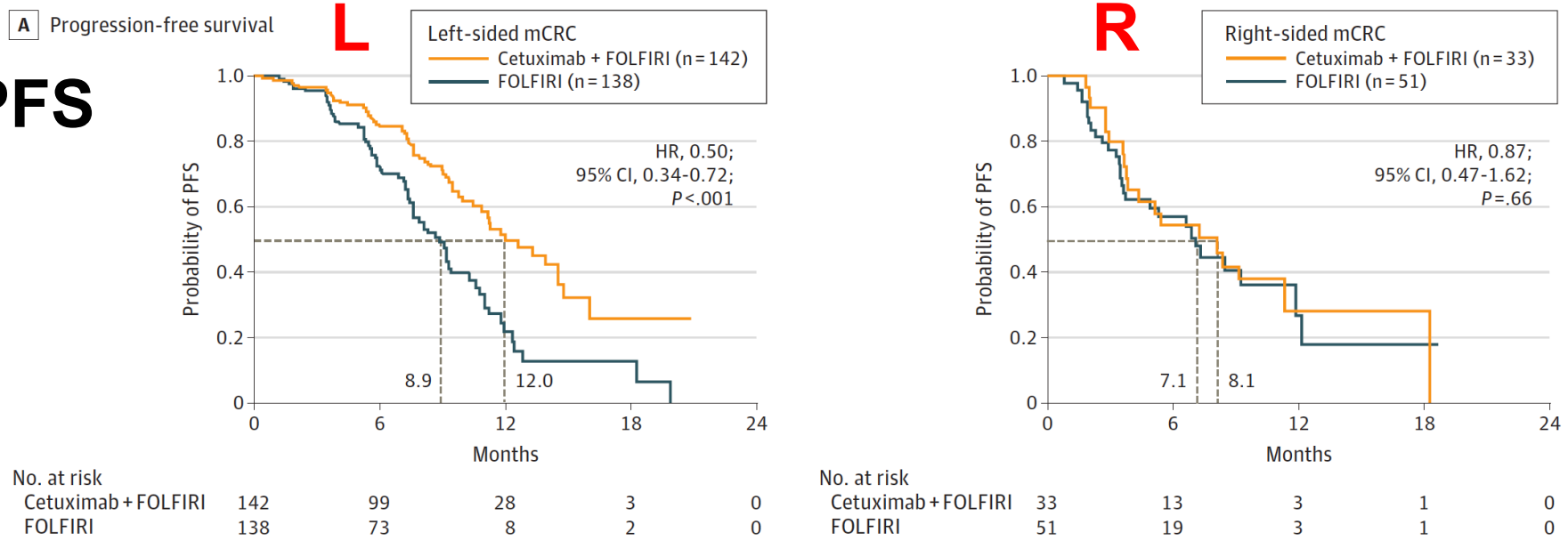
Metastatic Colorectal Cancer: Does Side Matter?

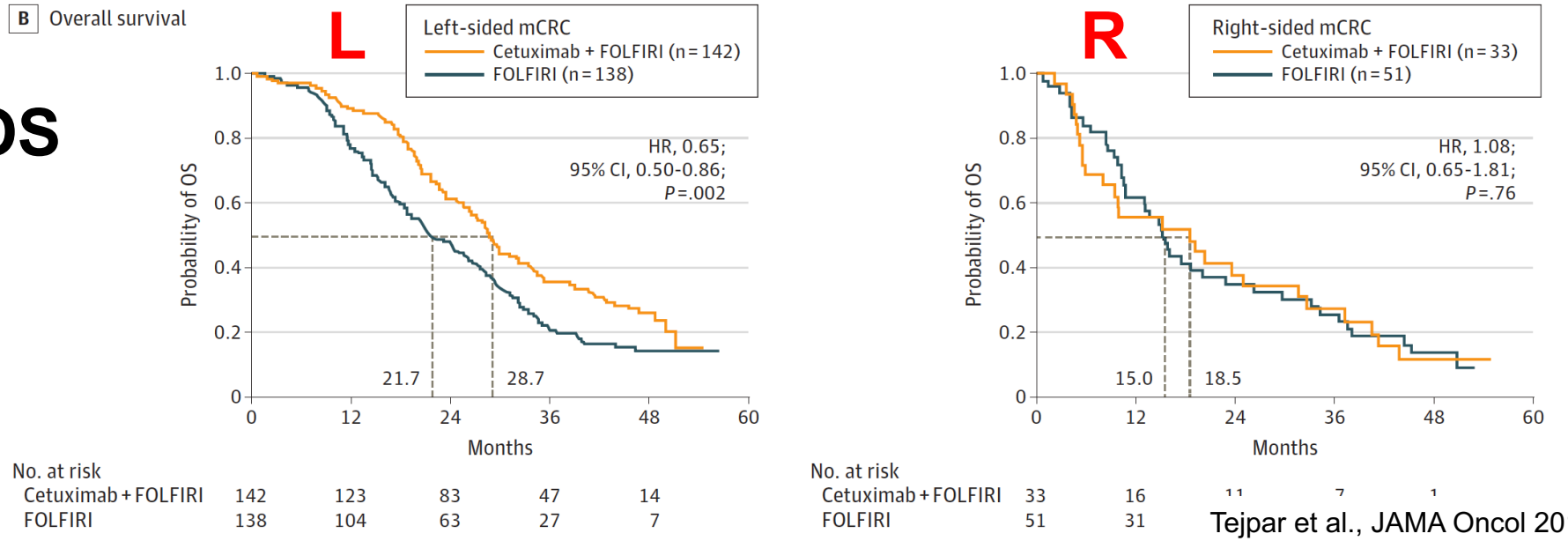
Publication (study)	Patients, N	Treatment	Outcome	Right	Left
O'Dwyer PJ, et al. *J Clin Oncol.* 2001. (E2290)	N = 1120	5-FU variations	OS (mos)	**10.9**	**15.8**
Brulé SY, et al. *Eur J Cancer.* 2015. (CO.17)	N = 399 *KRAS* WT	BSC vs BSC + CET	PFS (mos)	**1.9** **1.8**	**1.9** **5.4**
Loupakis F, et al. *J Natl Cancer Inst.* 2015.	N = 2053	FOLFIRI/BEV FUOX/BEV IFL/BEV	OS (mos)	**24.8** **18.0** **14.6**	**42.0** **23.0** **24.0**

CRYSTAL: FOLFIRI +/- Cetuximab

PFS



OS



Tejpar et al., JAMA Oncol 2016

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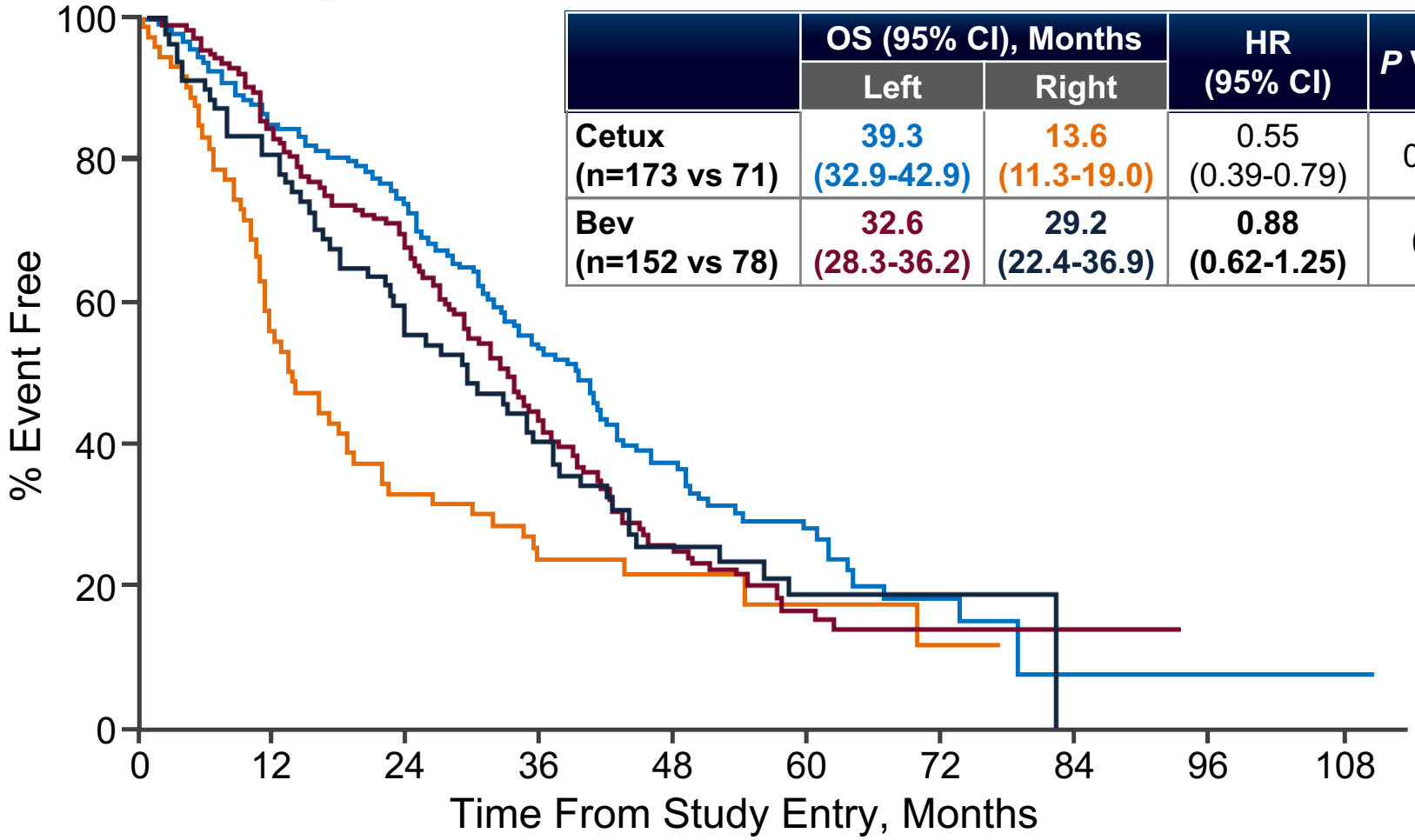
CALGB/SWOG 80405: OS by Tumor Location (*RAS* WT)

	OS (95% CI), Months		HR (95% CI)	*P* Value*
	Left	Right		
Cetux (n=173 vs 71)	39.3 (32.9-42.9)	13.6 (11.3-19.0)	0.55 (0.39-0.79)	0.001
Bev (n=152 vs 78)	32.6 (28.3-36.2)	29.2 (22.4-36.9)	0.88 (0.62-1.25)	0.50



*Adjusted for biologic, protocol CT, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases.

Venook A, et al. Presented at: ESMO. 2016.

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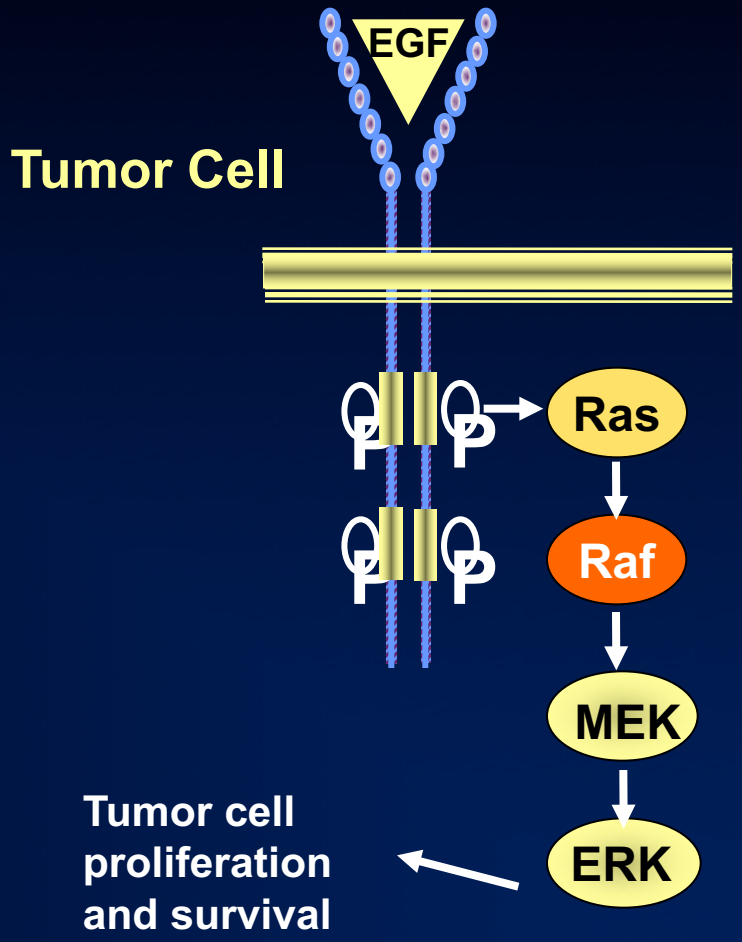
BRAF Mutations in CRC

- BRAF is primary effector of KRAS signaling
- BRAF mutations:
  - Occur most frequently in exon 15 (V600E)
  - Found in 4%-14% of patients with CRC
  - Mutually exclusive with KRAS mutations



Yarden. *Nat Rev Mol Cell Biol*. 2001. Di Nicolantonio. *J Clin Oncol*. 2008. Artale. *J Clin Oncol*. 2008.

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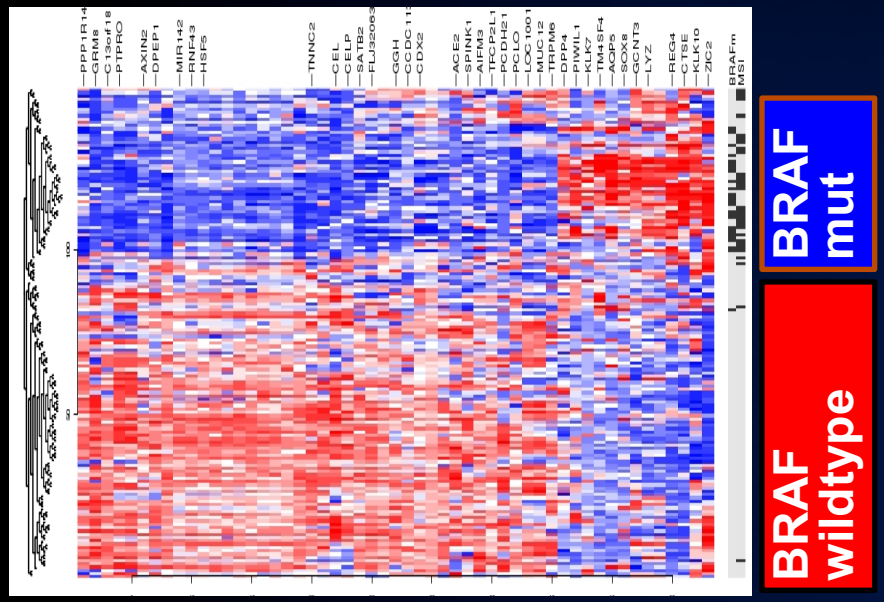
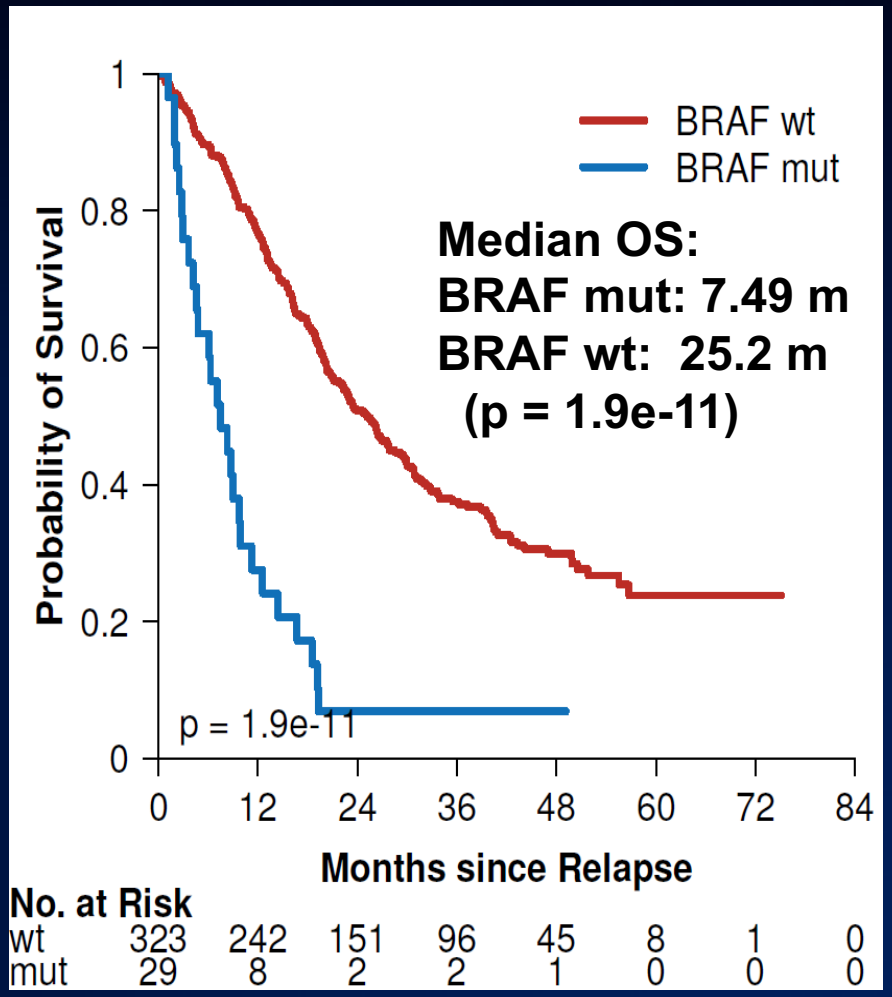
PETACC-3: Survival after relapse according to BRAF mutation status



Tejpar et al, ASCO 2010



Roth, AD et al. JCO 2010

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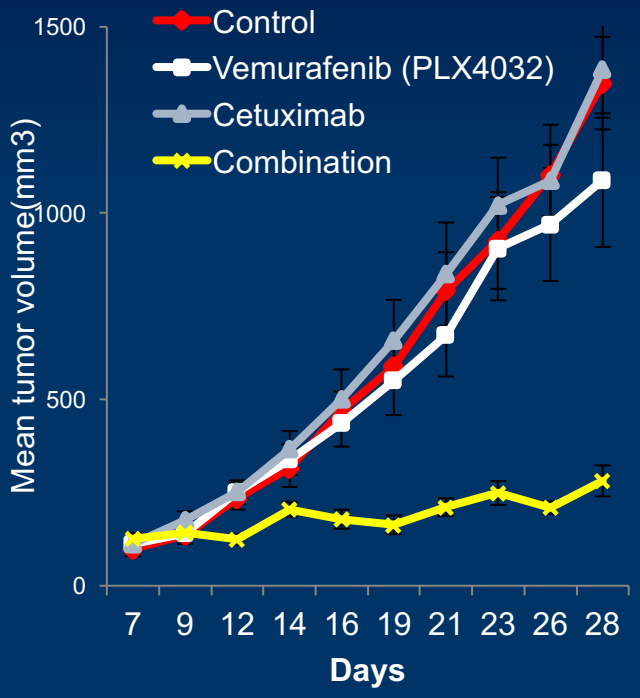
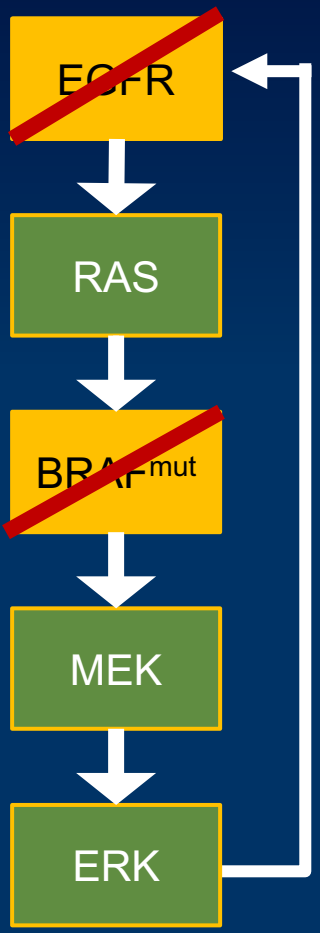
Comparison of RR and PFS for BRAF^{mut} CRC

Regimen	Response rate	PFS	Citation
Single/Doublet BRAF/MEK			
Vemurafenib	5%	2.1 months	Kopetz, ASCO ’10
Dabrafenib	11%	NR	Falchook, Lancet ‘08
Encorafenib	16%	NR	Gomez-Roca, ESMO ‘14
Dabr +Tramet	12%	3.5 months	Corcoran, ASCO ‘14
Doublet with EGFR			
Vem + Panit	13%	3.2 months	Yeager et al CCR ’14
Vem + Cetux	20%	3.2 months	Tabernero et al ASCO ‘14
Encoraf + Cetux	23%	4.0 months	Tabernero et al ESMO ‘14
Dabr + Panit	10%	3.4 months	Atreya, ASCO ‘15
Triplet with EGFR			
Vem + Cetux + Irinotecan	35%	7.7 months	Hong, ASCO ‘15
Dabr + Tramet + Panit	26%	4.1 months	Atreya, ASCO ‘15
Encoraf + Cetux + Alpelisib	32%	4.4 months	Tabernero et al ESMO ’14

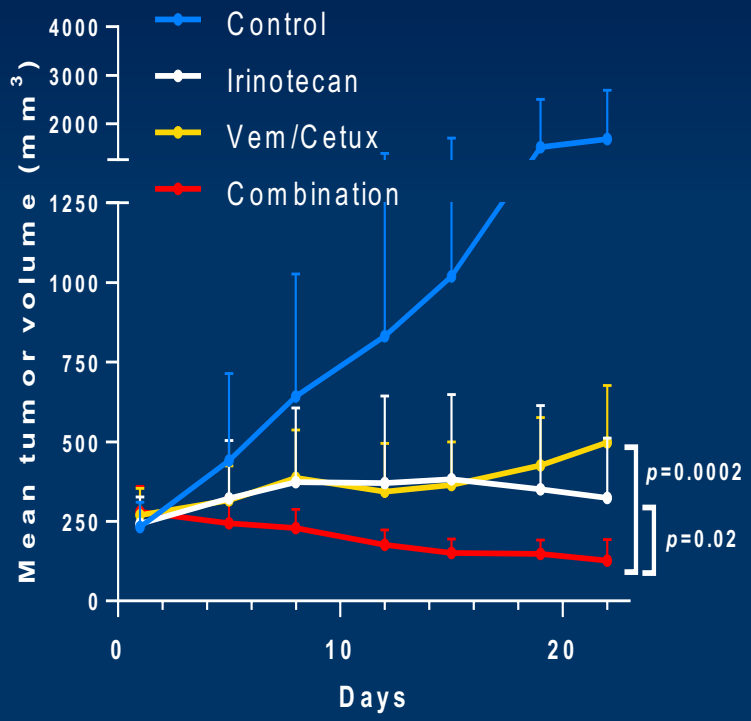
Rationale for dual BRAF and EGFR blockade

Synergy of EGFRi/BRAFi





Benefit of Irinotecan



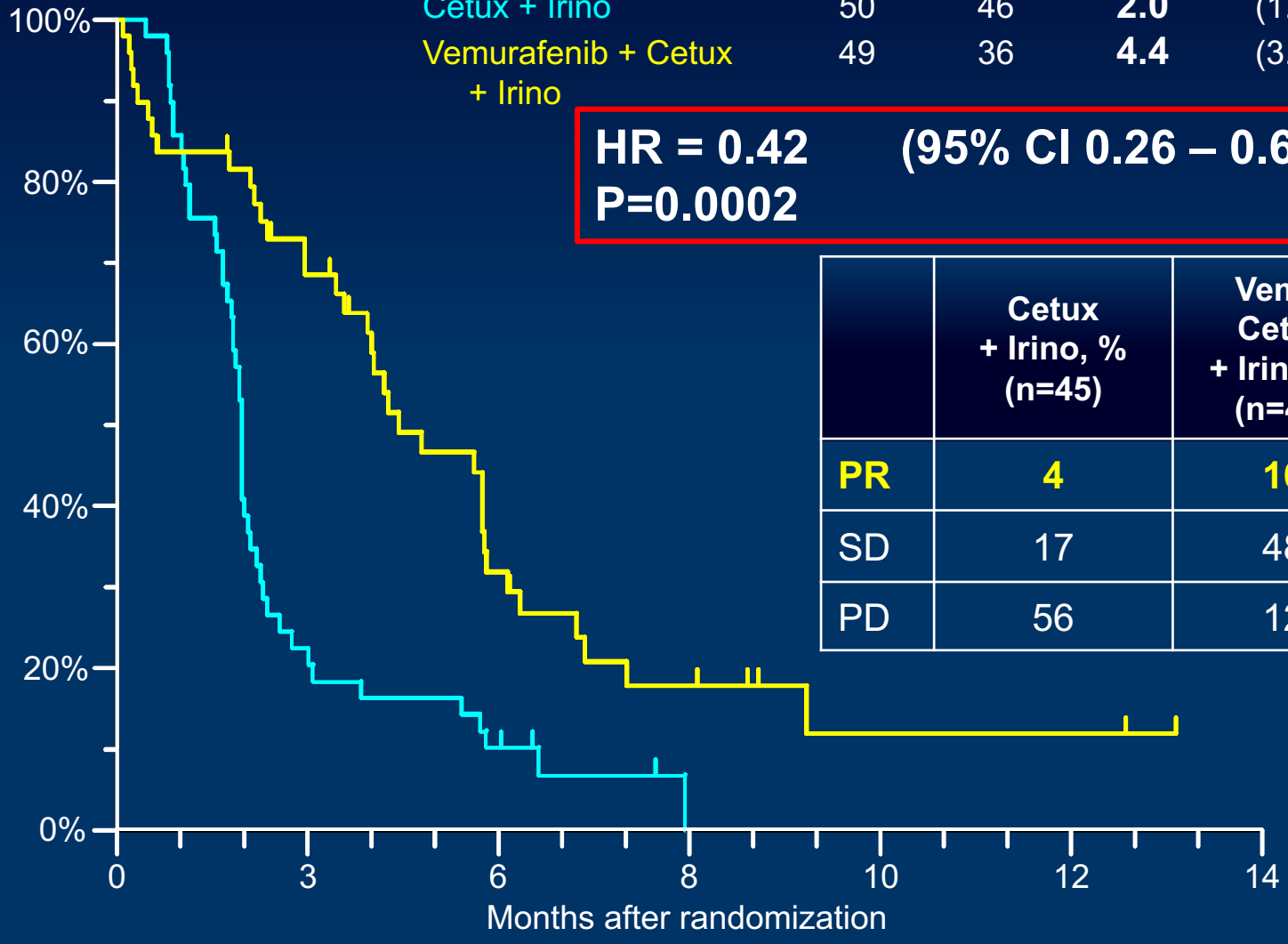
[1]Hong et al Cancer Disc '16

Kopetz S, et al. Presented at: ASCO. 2016 (abstr 3506).

Irino/ Cetux +/- vemurafenib: PFS

	N	Events	Median	95% CI
Cetux + Irino	50	46	**2.0**	(1.8 – 2.1)
Vemurafenib + Cetux + Irino	49	36	**4.4**	(3.6 – 5.7)

HR = 0.42 (95% CI 0.26 – 0.66)
P=0.0002



	Cetux + Irino, % (n=45)	Vem + Cetux + Irino, % (n=43)	P
PR	**4**	**16**	**0.001**
SD	17	48	0.001
PD	56	12	0.001

Kopetz S, et al. Presented at: ASCO. 2016 (abstr 3506).

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Prevalence of Non-V600E BRAF mutations in CRC

	MC	MDA	FM	Totals	All BRAF mut %	% of all BRAF mut which are non-V600	% of total CRC which are non-V600
Total CRC Cases	1014	2276	6353	9643	1147/9643 11.9%		
Total BRAF Mutations	137	334	469	940			
Non-V600 BRAF	27	54	126	207		207/940 22%	207/9643 2.1%

Outcomes data available for 101 pts with non-V600E BRAF mut

Jones et al., *in press*

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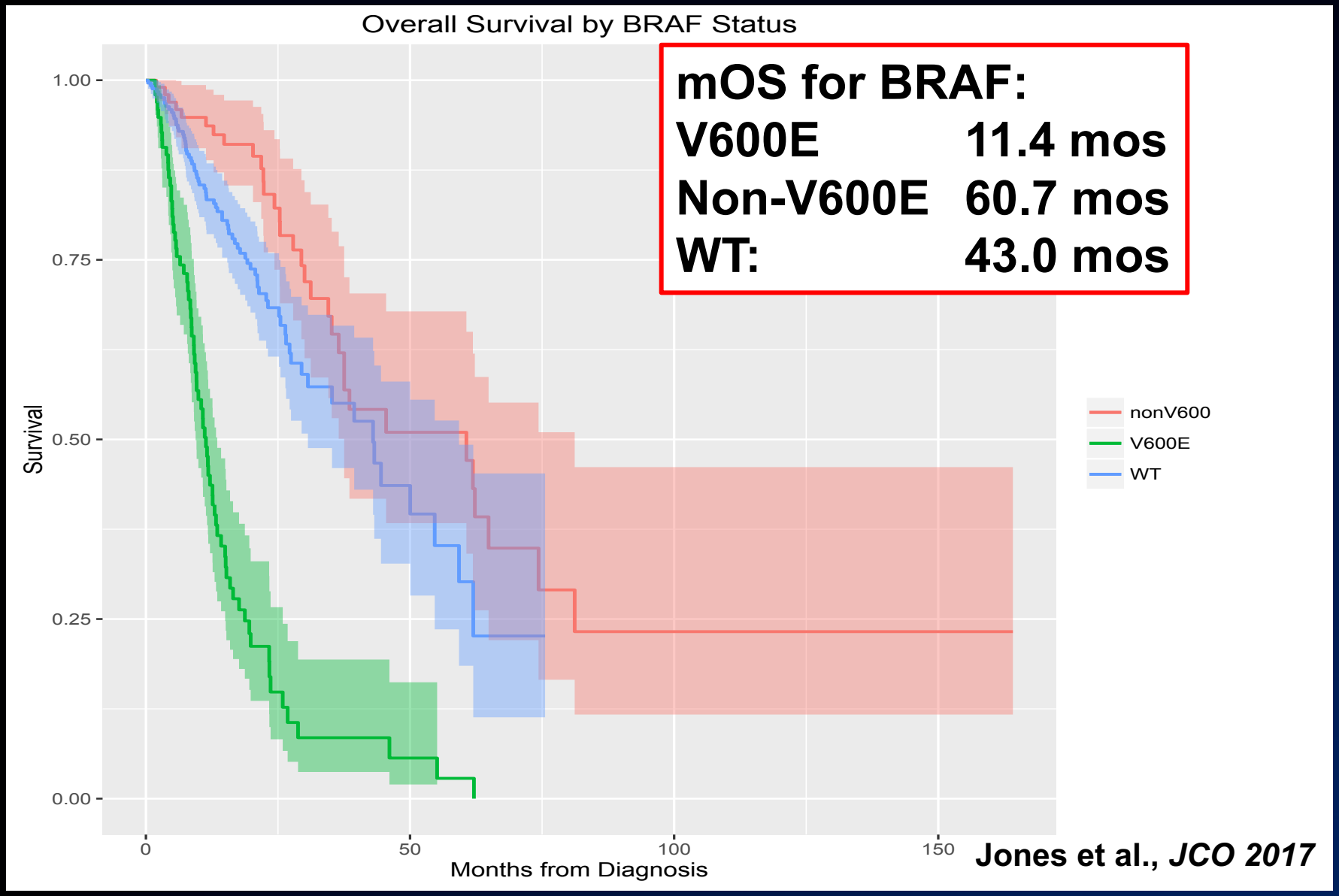
OS dependent on BRAF mutation



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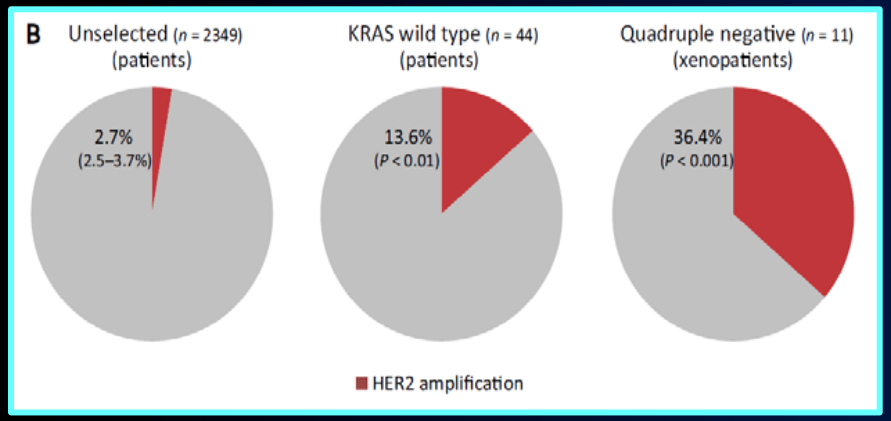
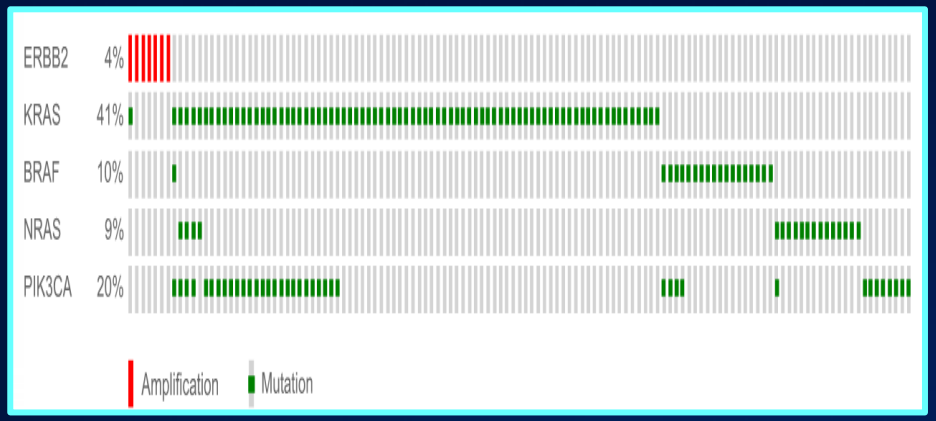
HER-2 Amplification in CRC

HER2 overexpression and amplification is seen in a distinct subset of mCRC

Study	N	Positive Rate	IHC 2+	IHC 3+	FISH Concordance
Nathanson et al. Int J Cancer '03	139	IHC: 5 (4%) FISH: 4 (3%)	2	3	K = 0.85
Ooi et al. Mod Pathol '04	244	IHC: 8 (3%) FISH: 8 (3%)	2	6	100%
Marx et al. Human Path '10	1439	IHC: 39 (3%) FISH: 36 (3%)	12	27	100%
Summary IHC	**1822**		**16**	**36**	**Good**





- 5.3% HER2 amplification seen in HERACLES Study (screened = 836)[1]
- HER2 amplification enriched in KRAS, NRAS, BRAF, and PIK3CA WT tumors[2]

[1]Siena et al. GI ASCO 2015 [2]Bertotti et al. Cancer Discovery 2011;1:508-523. [2]Kuwada et al. Int. J. Cancer: 109, 291–301 (2004)

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HERACLES: Trastuzumab + Lapatinib

- Patients histologically diagnosed with metastatic CRC not amenable to surgery
- **HER2+**, *KRAS* exon 2 WT
- Prior fluoropyrimidines, irinotecan, oxaliplatin, cetuximab, or panitumumab; prior bevacizumab, aflibercept or regorafenib allowed but not mandatory
- PS 0-1

→

Therapy with
- Trastuzumab IV 4 mg/kg load and then 2 mg/qw
- Lapatinib po 1000 mg/qd

→ PD

(Enrolled n=24; evaluable n=23)

- Primary endpoint: ORR (RECIST 1.1 with central independent radiological review)
- Secondary endpoints: TTP, safety
- Translational: HER2 ctDNA in plasma (ddPCR); HER2 ectodomain in serum (ELISA); NGS in tissue and plasma in patients with de novo resistant disease and upon PD

ddPCR=Droplet Digital PCR; NGS=next-generation sequencing.

Sartore-Bianchi, et al. Lancet Oncol 2016

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HERACLES: Response

Best Response (RECIST 1:1 by Centralized Revision)	N	%
Responses (PR + CR)	**8**	**30**
Complete response	1	4
Partial response	7	26
Stable disease ≥4 mos	**8**	**30**
Stable disease <4 mos	4	15
Progressive disease	7	25
Total	27	100

60% DCR

Primary endpoint met in advance with 8/27 objective responses (as per protocol, 6/27 needed to declare the study positive)

Sartore-Bianchi, et al. Lancet Oncol 2016

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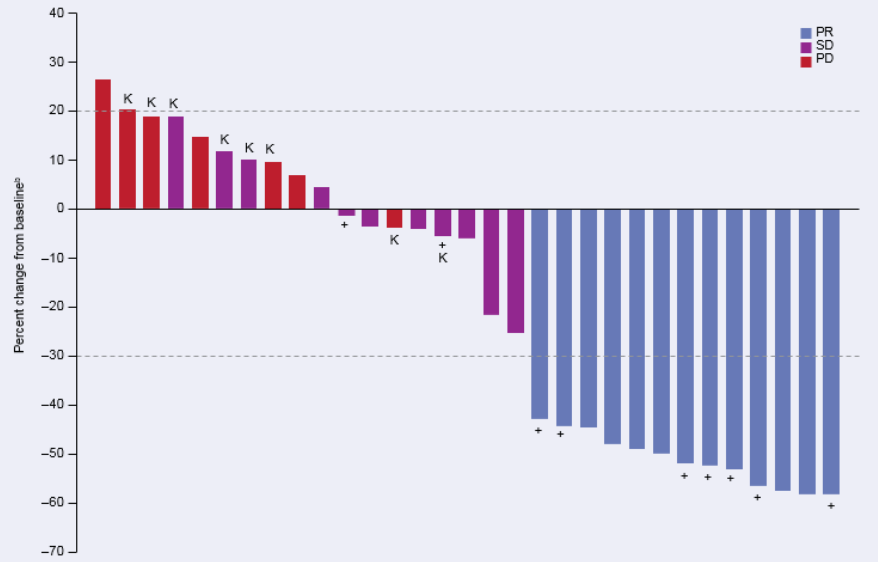
MyPathway: Trastuzumab + Pertuzumab in HER-2 pos CRC

Figure 2. Best percent change from baseline in target lesion size in patients with HER2-amplified/overexpressed mCRC (n=31)[a]



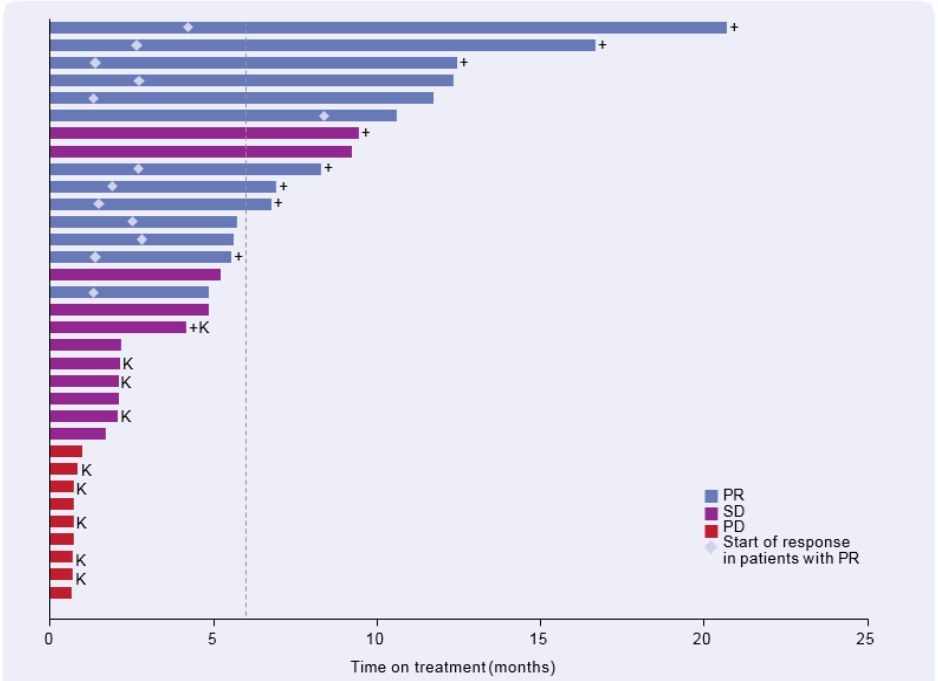
+ indicates that treatment is ongoing. K indicates the patient has a KRAS mutation.

[a]Three patients are excluded from this plot: 2 patients (including 1 with a KRAS mutation) who discontinued treatment due to clinical progression without a post-baseline tumor assessment, and 1 who discontinued treatment due to a new lesion and who was missing three quarters of the target lesion assessments.

[b]"Percent change from baseline" represents the maximum reduction/minimum increase in the target lesion size from baseline. Patients with at least a 30% decrease in target lesion size qualify for PR. Patients with least a 20% increase in target lesion size, or the appearance of one or more new lesions, qualify for PD.

HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 1. Time on treatment for patients with HER2-amplified/overexpressed mCRC (n=34)



+ indicates that treatment is ongoing. K indicates the patient has a KRAS mutation. Dashed line indicates 6 months.

HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; PD, progressive disease; PR, partial response; SD, stable disease.

N = 31, RR 42%

Hurwitz et al., ASCO GI 2017

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HER-2 Amplification in CRC

- Resistance marker for EGFR antibodies
- Defines patients who are candidates for HER-2 targeted therapy

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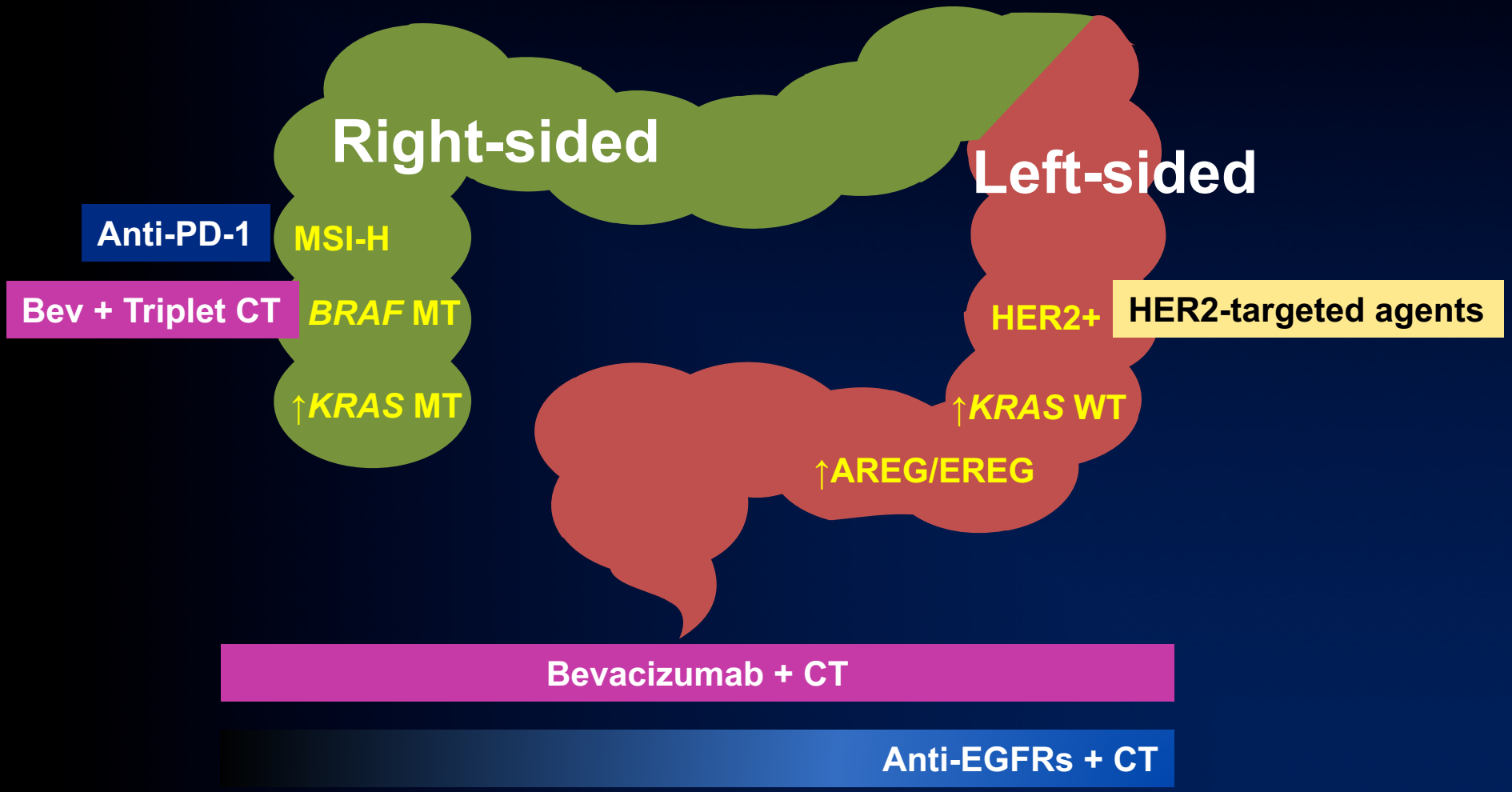
Primary Tumor Location and Potential Treatments



Bufill JA. *Ann Intern Med.* 1990;113:779-788; Missiaglia E, et al. ASCO 2013. Abstract 3526; Brule SY, et al. ASCO 2013. Abstract 3528; The Cancer Genome Atlas Network. *Nature.* 2012490:61-70; Bendardaf R, et al. *Anticancer Res.* 2008;28:3865-3870.

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The "Perfect" Candidate for First-Line EGFR mAbs

Negative selection (mutually exclusive)

- KRAS/ NRAS/ HRAS exon 2, 3, 4 wild-type - 55%
- No BRAF V600E mutation - 8%
- No HER-2 amplification -2.5%

Further exclusion criteria (not mutually exclusive)

- Right-sided cancers 30%
- (Low EGFR ligand expression 60%)