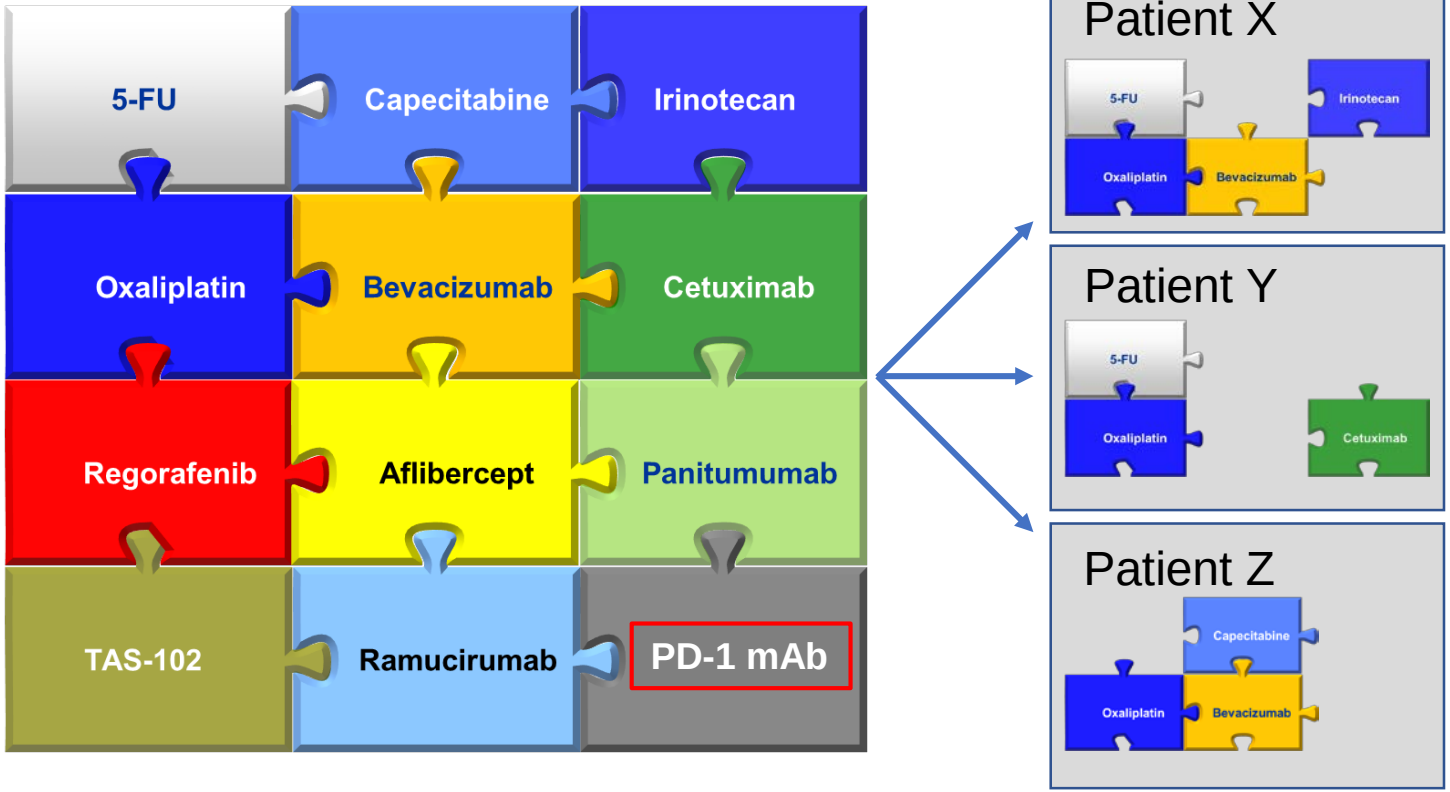
Right Drug for the Right Colorectal Patient: Select the Best Initial Therapy
and
What Comes After 5-FU/OXALI/IRINO?

Axel Grothey

Professor of Oncology

Minnesota -> Tennessee

The Luxury of So Many Options . . .
How Do We Personalize?



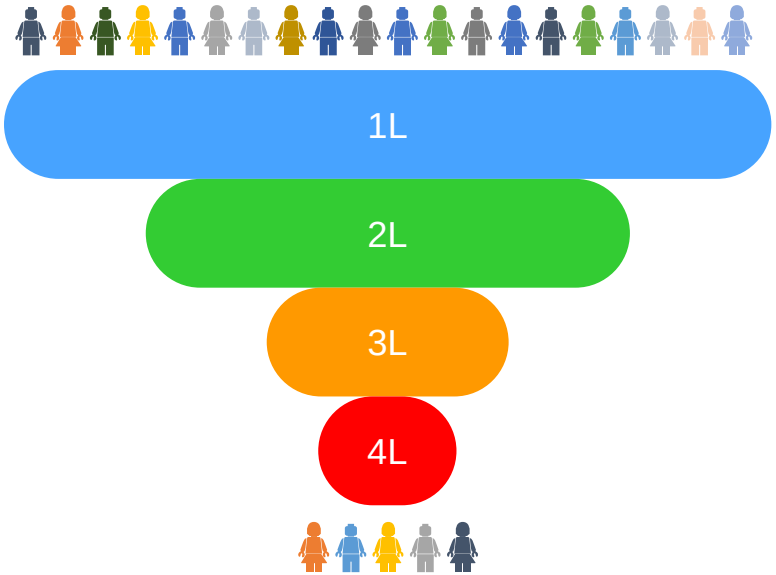
What influences treatment choices in mCRC?

Patient characteristics

- Comorbidities
- Prior adjuvant treatment
- Age
- Performance status

Tumor characteristics

- Tumor burden
- Resectability
- Tumor location



Molecular characteristics

- RAS
- BRAF
- MSI-high
- HER2

Patient preference

- Quality of life
- Toxicity profile

Therapy tailored according to individual patient needs

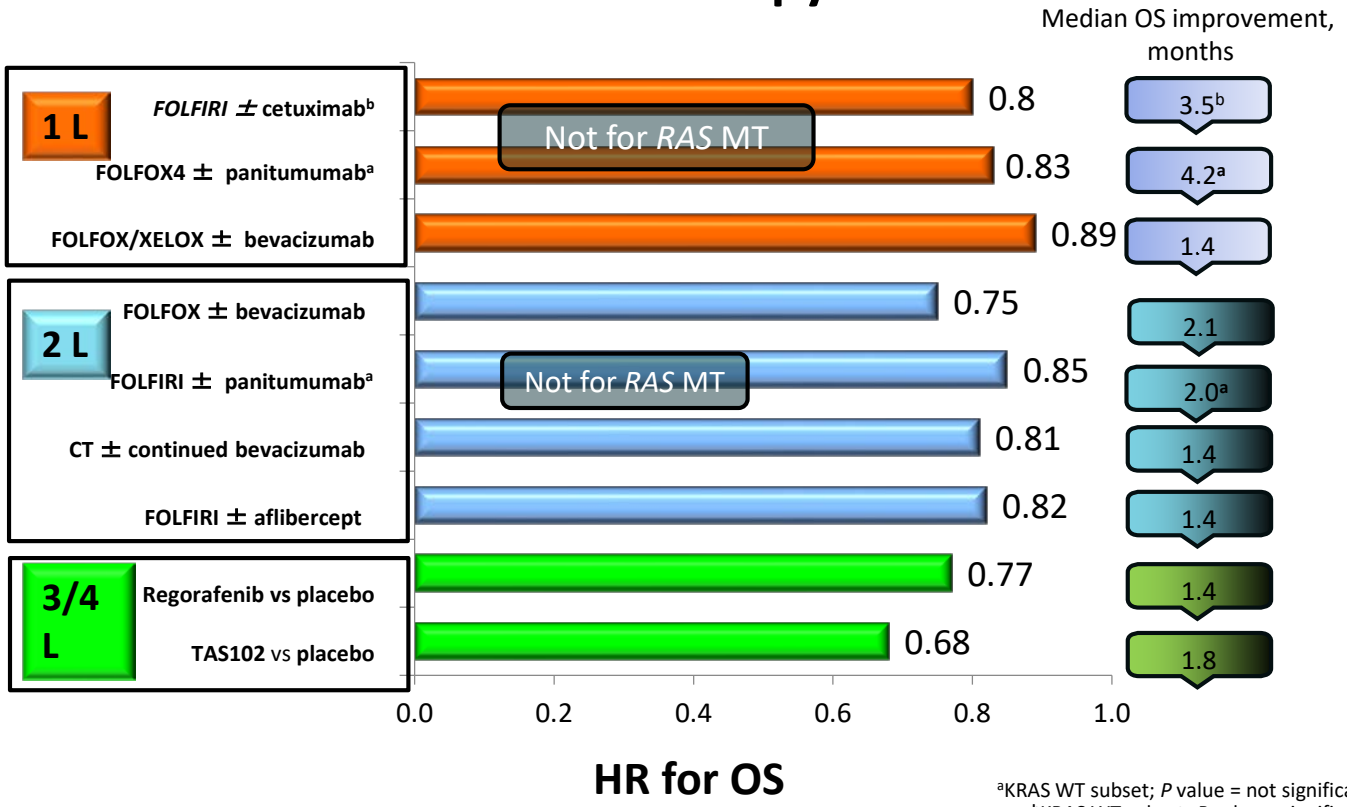
Key points in the medical management of mCRC

- **We can “cure” some patients with limited metastatic disease**
  - Collaboration within a MDT essential
- **For the majority of patients the treatment goal is to extend life and maintain quality of life as long as possible**
- **Patients benefit from access to all active agents**
  - Sequential therapy. It is a marathon, not a sprint
- **We have biomarkers who identify cancers which do NOT respond to certain therapies, i.e. EGFR mAbs**
  - Routine testing for extended RAS/ BRAF mutations, now also HER-2
- **Biomarkers that select patients FOR a specific therapy are emerging**
  - MMR/ MSI-H for immunotherapy, HER-2 and BRAF for targeted approaches

Key Points To Consider

- **Outcome is not driven by first-line therapy for the majority of patients**
  - Importance of subsequent lines of therapy
  - Continuum of care
- **We have refined the patient population which benefits from EGFR mAbs**
  - Better benefit-risk ratio
- **Some patients need special treatment approaches**
  - MSI-H cancers
  - BRAF mutated CRC (V600E vs non-V600E)
  - HER-2 overexpressors

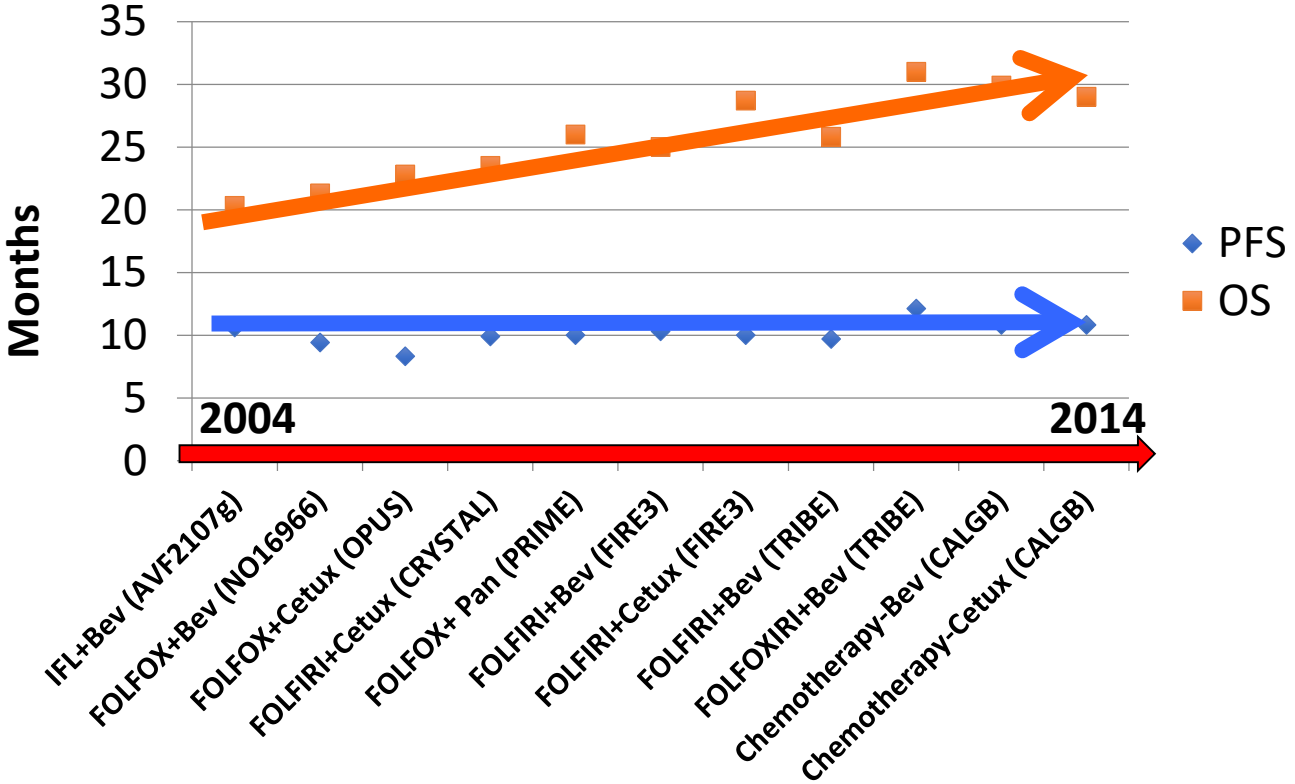
Proportional Impact on Magnitude of OS Benefit Achieved Across Lines of Therapy



[a]KRAS WT subset; *P* value = not significant.
[b]KRAS WT subset; *P* value = significant.

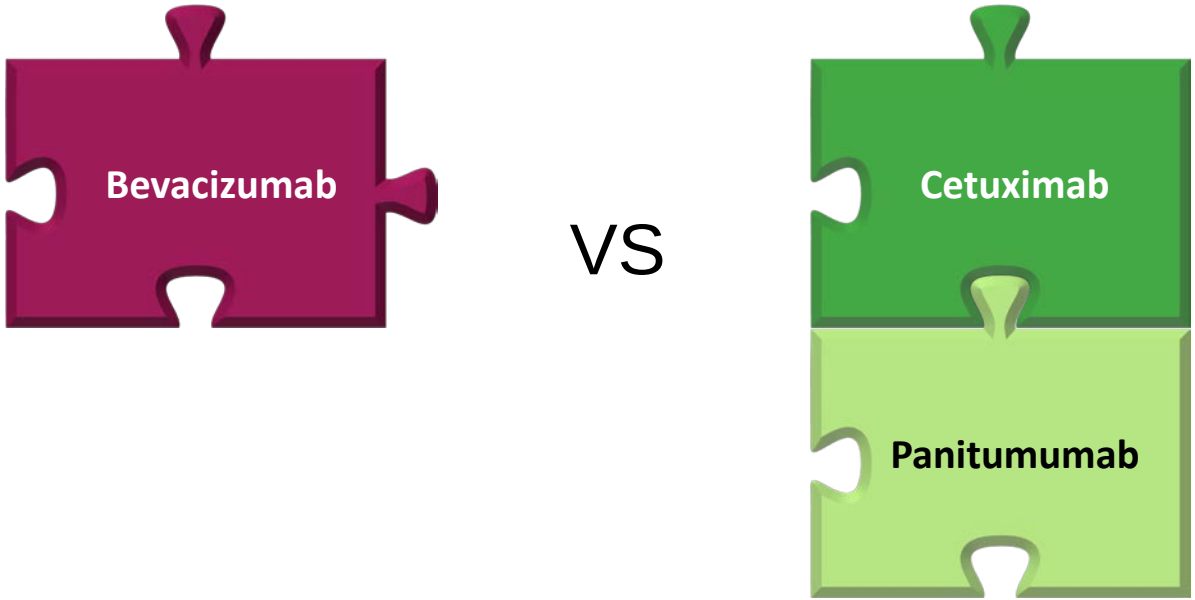
1. Saltz LB, et al. *J Clin Oncol.* 2008;26(12):2013-2019; 2. Douillard, J-Y, et al. *J Clin Oncol.* 2010;28(31):4697-4705; 3. Van Cutsem E, et al. *J Clin Oncol.* 2011;29(15): 2011 -2019; 4. Van Cutsem E, et al. *J Clin Oncol.* 2012;30(28):3499-3506; 5. Bennouna J, et al. *Lancet Oncol*. 2013;14(1):29-37; 6. Giantonio BJ, et al. *J Clin Oncol.* 2007;25(12)1539-1544; 7. Peeters M, et al. *J Clin Oncol* . 2010;28:4706-4713; 8. Grothey A, et al. *Lancet*. 2013;381:303-312. Van Cutsem E, et al. *ESMO 2014*

Although OS Continues to Improve, PFS Has Been Mostly Stable With First-line Therapy in the Chemo-Biologic Era



1. Hurwitz H, et al. *N Engl J Med*. 2004;350(23):2335-2342; 2. Saltz LB, et al. *J Clin Oncol.* 2008;26(12):2013-2019; 3. Bokemeyer C, et al. *Ann Oncol*. 2011;22(7):1535-1546; 4. Van Cutsem E, et al. *J Clin Oncol*. 2011;29(15):2011-2019; 5. Douillard JY, et al. *N Engl J Med*. 2013;369(11):1023-1034; 6. Heinemann V, et al. *J Clin Oncol*. 2013;(suppl 31):abstract LBA3506; 7. Falcone A, et al. *J Clin Oncol*. 2013;(suppl 31):abstract 3505.

The Key Question: First-Line Choice of Biologics BEV vs EGFR mAbs



Key Points on anti-VEGF Therapy

- **Duration of VEGF-inhibition matters**
  - **More cytostatic than cytotoxic MoA**
    - Treatment to progression
    - Maintenance strategies
    - Treatment beyond progression
- **Clinical synergism between fluoropyrimidine + bevacizumab**
- **Three positive phase III trials for prolonged VEGF inhibition beyond progression**
  - No compelling arguments for aflibercept or ramucirumab over bevacizumab

VEGFi Beyond PD - Phase III Trials

Agent	Bevacizumab		Ziv-aflibercept		Ramucirumab	
Study	TML		VELOUR		RAISE	
1st Line Tx	Chemo+BEV		FP-Oxali+/- BEV		FP-Oxali+BEV	
	Chemo-BEV	**Chemo**	**FOLFIRI + AFL**	**FOLFIRI + PL**	**FOLFIRI + RAM**	**FOLFIRI + PL**
N pts	409	410	612	614	536	536
mOS (mos)	11.2	9.8	13.5	12.1	13.3	11.7
	HR 0.81 p=0.0062		**HR 0.82** p=0.0032		**HR 0.84** p=0.022	
mPFS (mos)	5.7	4.1	6.9	4.7	5.7	4.5
	HR 0.68 p<0.0001		**HR 0.76 p=0.00007**		**HR 0.79 p=0.0005**	
RR (%)	5.4	3.9	19.8	11.1	13.4	12.5

Bennouna et al., Lancet Oncol 2012
van Cutsem et al., JCO 2012
Tabernero et al., Lancet Oncol 2015

FP = fluoropyrimidine

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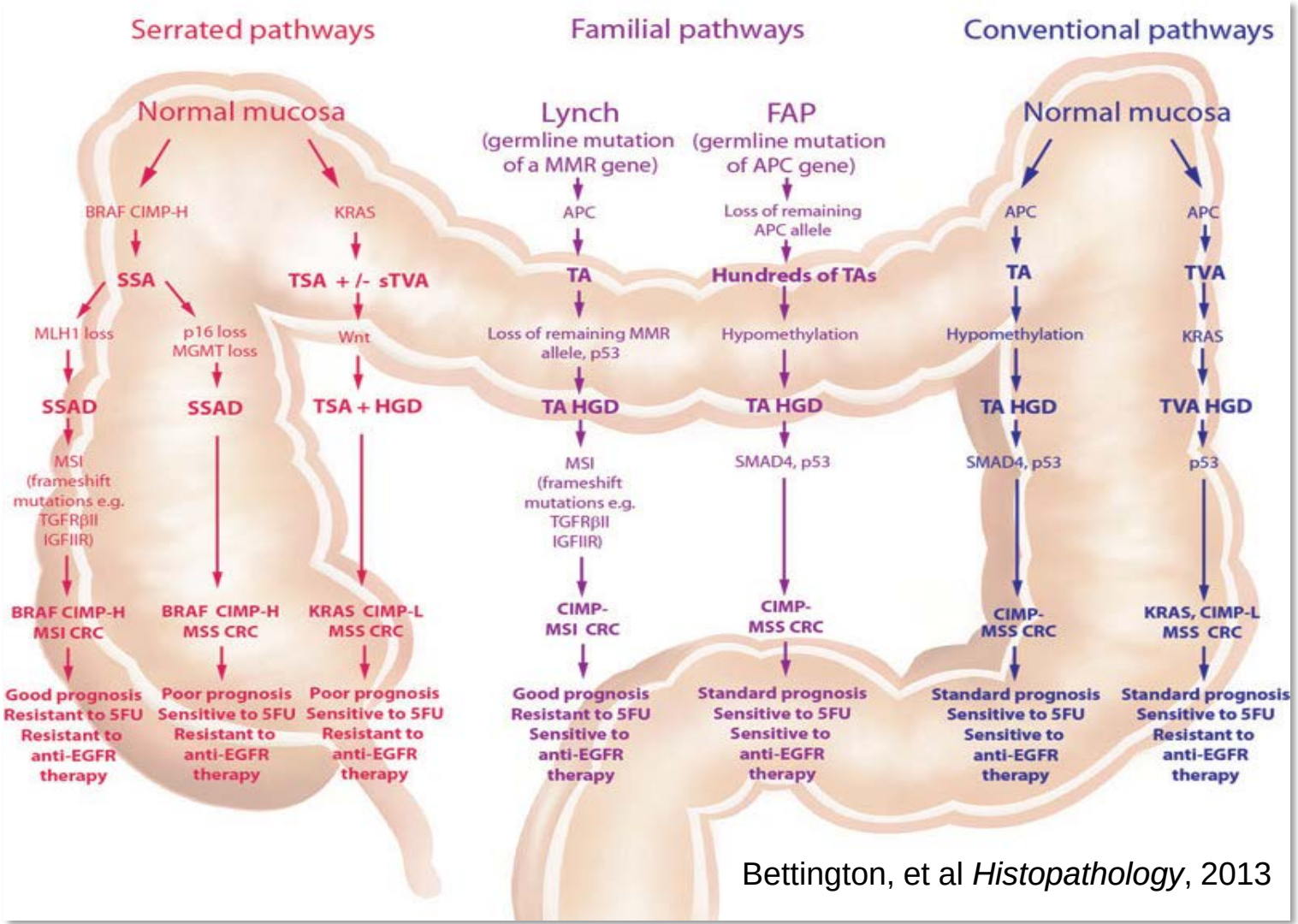
The “Perfect” Candidate for First-Line EGFR mAbs

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%)**



Bettington, et al *Histopathology*, 2013

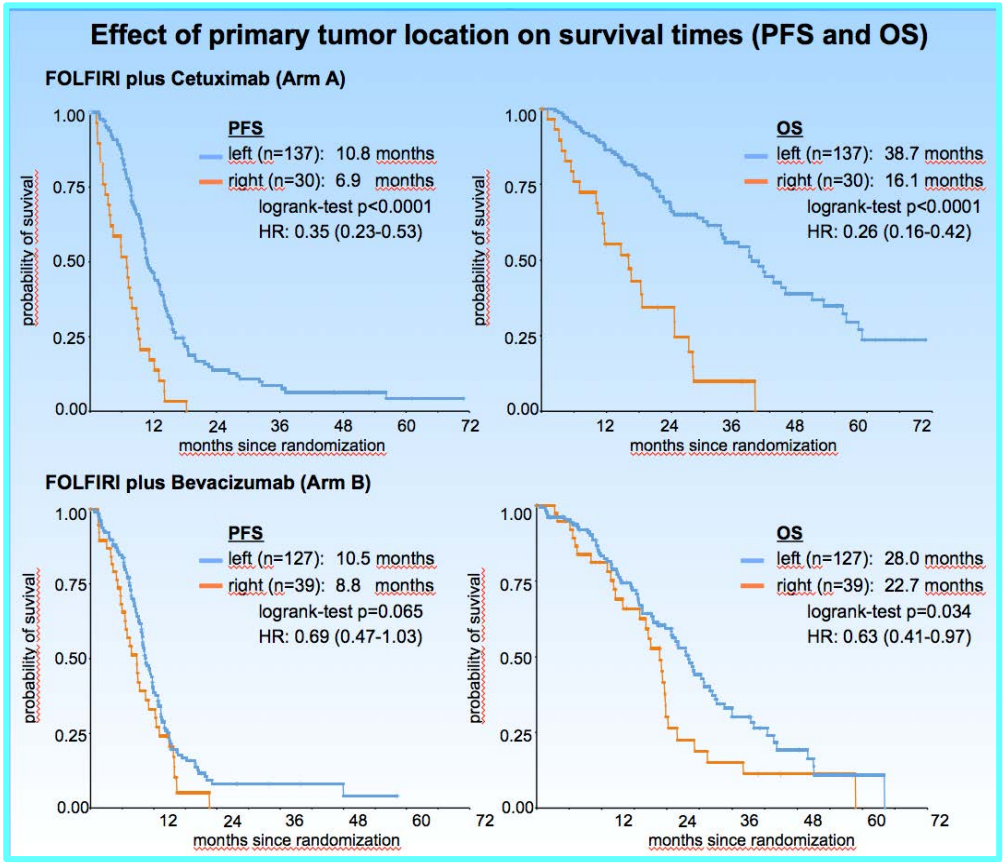
Same Data: Different Perspectives

RAS/ RAF wt	Treatment recommendations	
Location primary	**ESMO**	**NCCN**
Left	EGFR mAbs are Standard of Care in first-line	No clear preference for EGFR mAbs or BEV in first line
Right	EGFR mAbs can be considered in first line if response is goal	No EGFR mAbs in first line and potentially not in any line

Metastatic Colorectal Cancer: Does Side Matter?

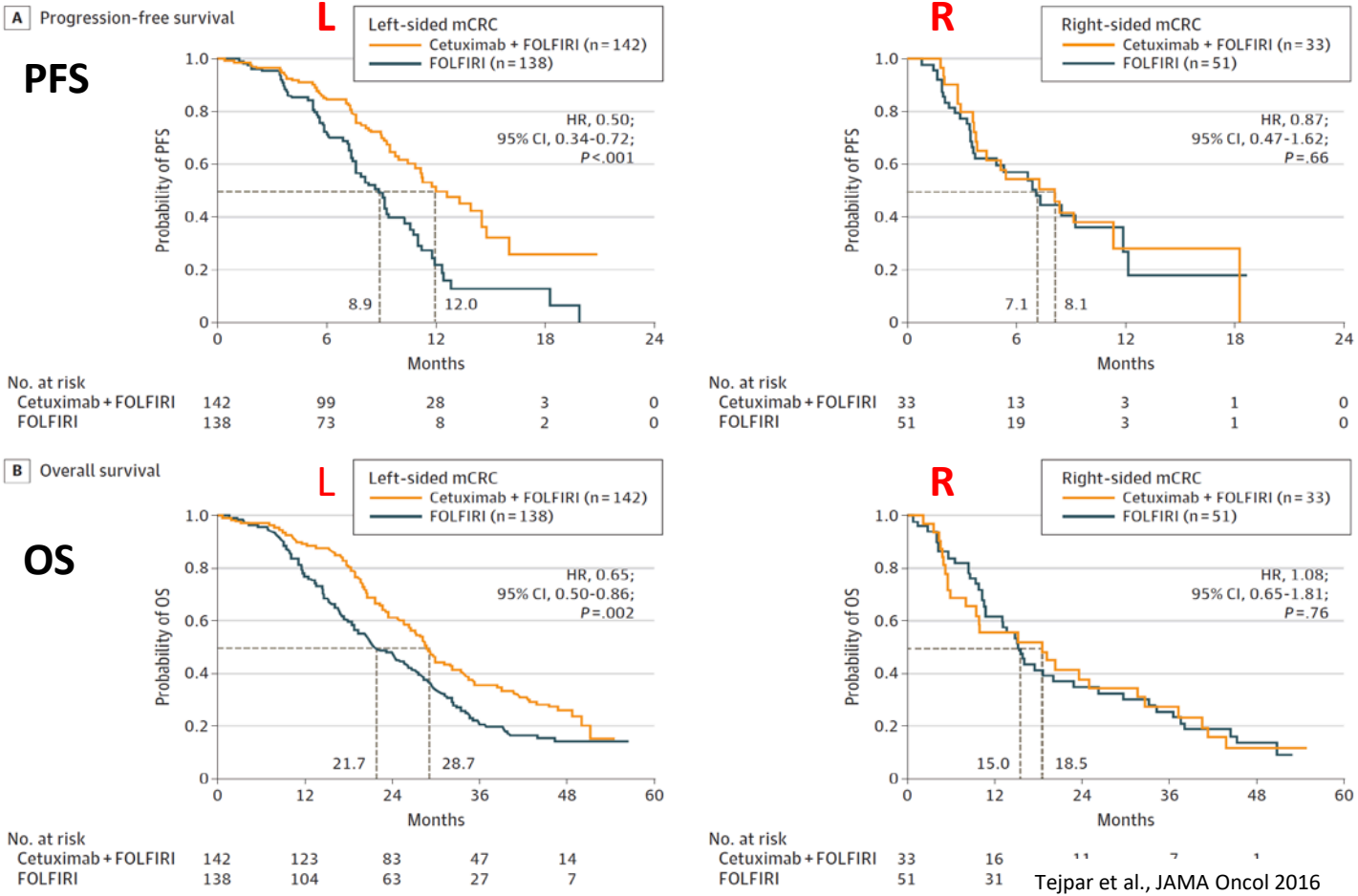
Study	Patients, N	Line of Tx	Molecular Selection	Treatment	Outcome	Right	Left
O'Dwyer, et al. *J Clin Oncol.* 2001. (E2290)	N = 1120	1st	None	5-FU variations	OS (mo)	10.9	15.8
Brulé, et al. *Eur J Cancer.* 2015. (CO.17)	N = 399	3rd/ 4th	*KRAS* WT	BSC vs BSC + CET	PFS (mo)	1.9 1.8	1.9 5.4

FIRE-3: Effect of Location on PFS and OS



Heinemann, et al. ASCO 2014

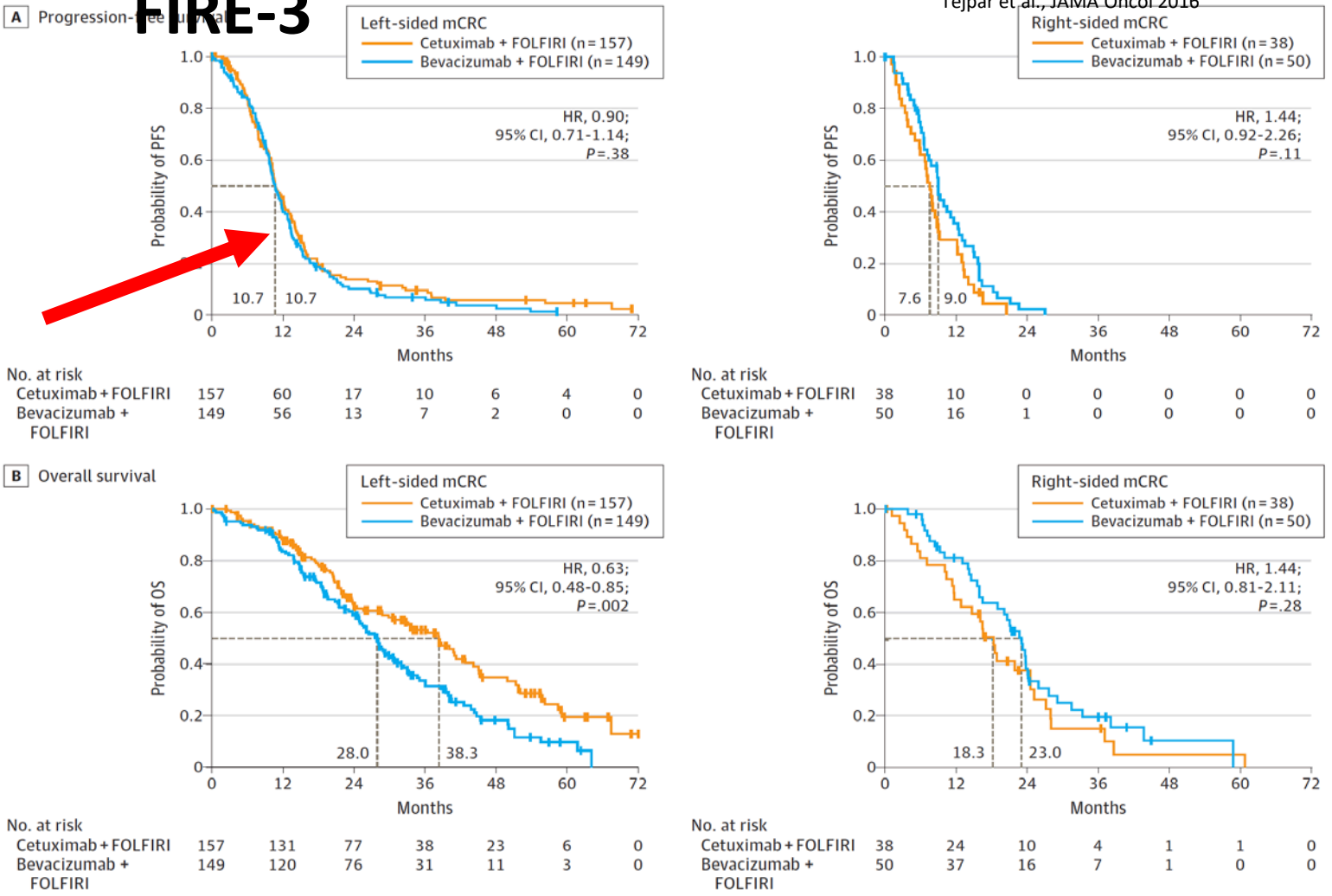
CRYSTAL: FOLFIRI +/- Cetuximab



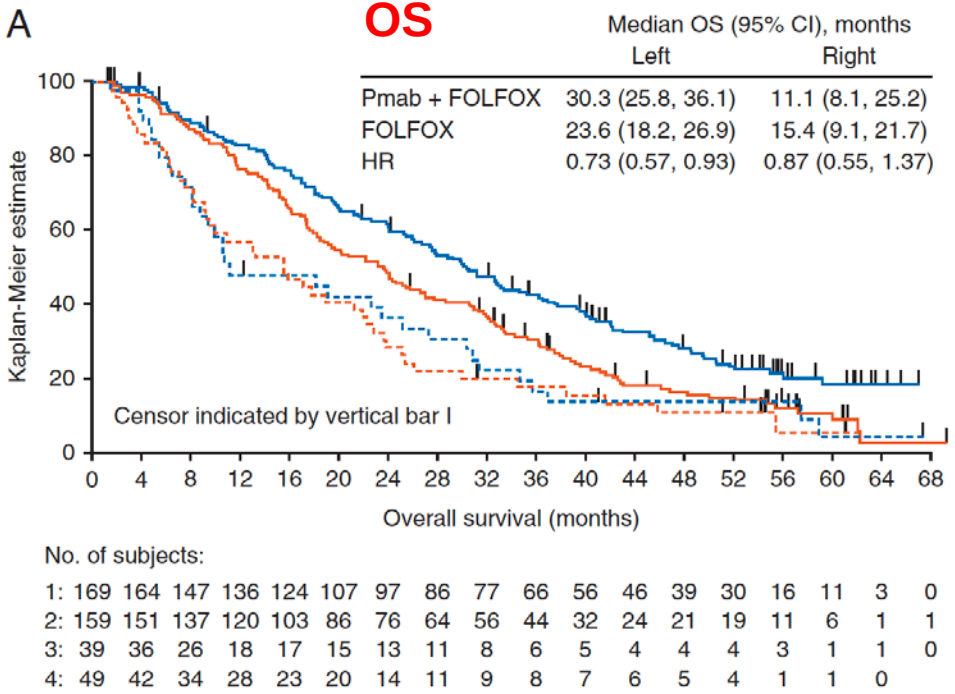
Tejpar et al., JAMA Oncol 2016

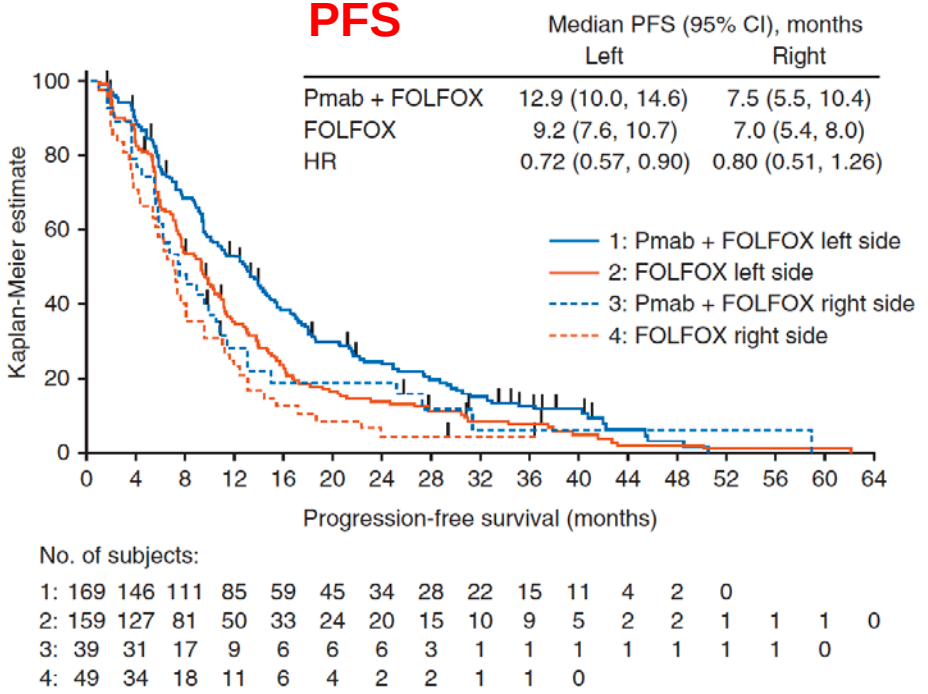
FIRE-3

Tejpar et al., JAMA Oncol 2016



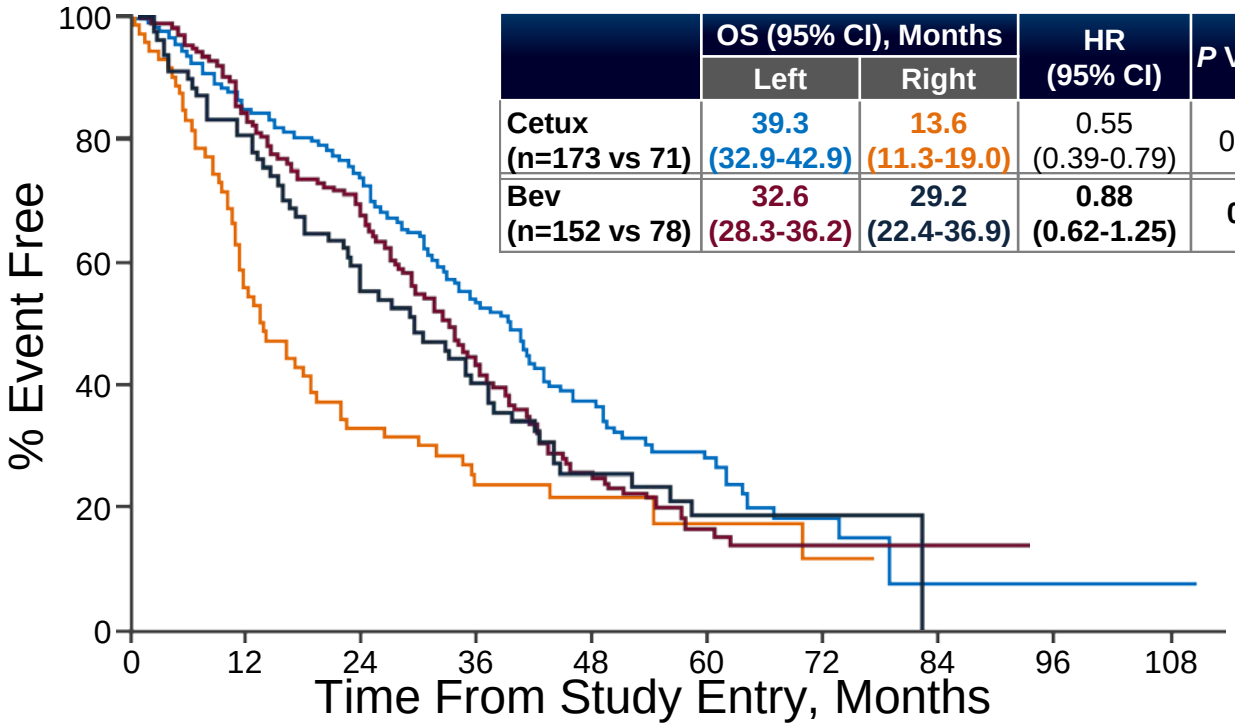
OS and PFS by Sidedness in PRIME





Boeck, et al. Ann Oncol 2017

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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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%)

The Truth on Sidedness

RAS/ RAF wt	Treatment recommendations		
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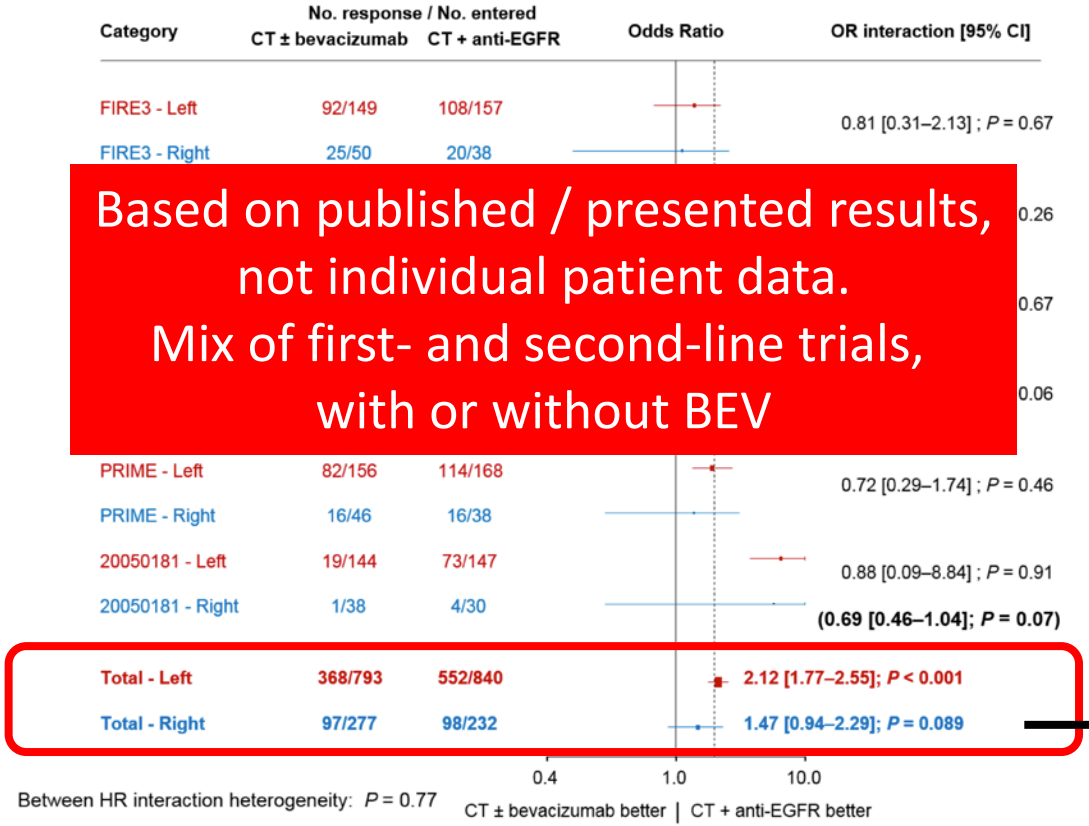
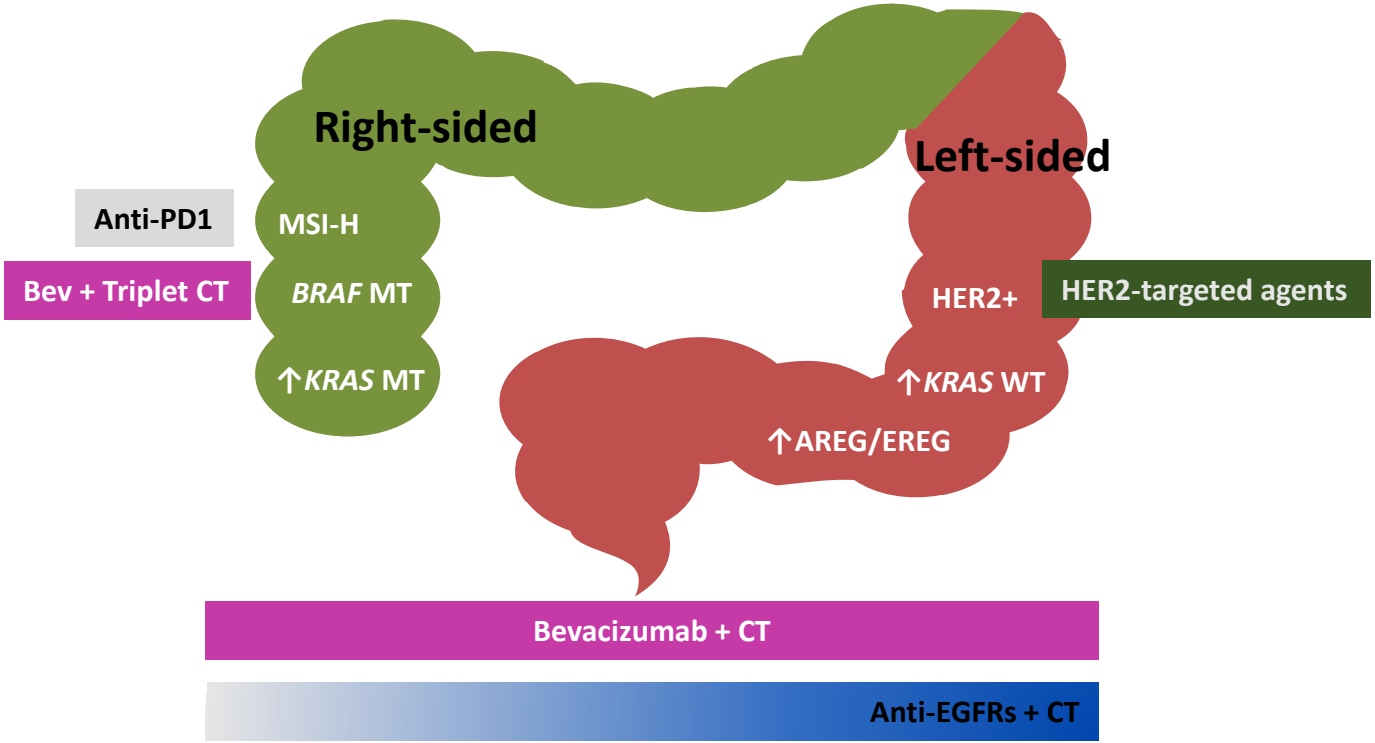
Sidedness and Tumor Response



P=0.089

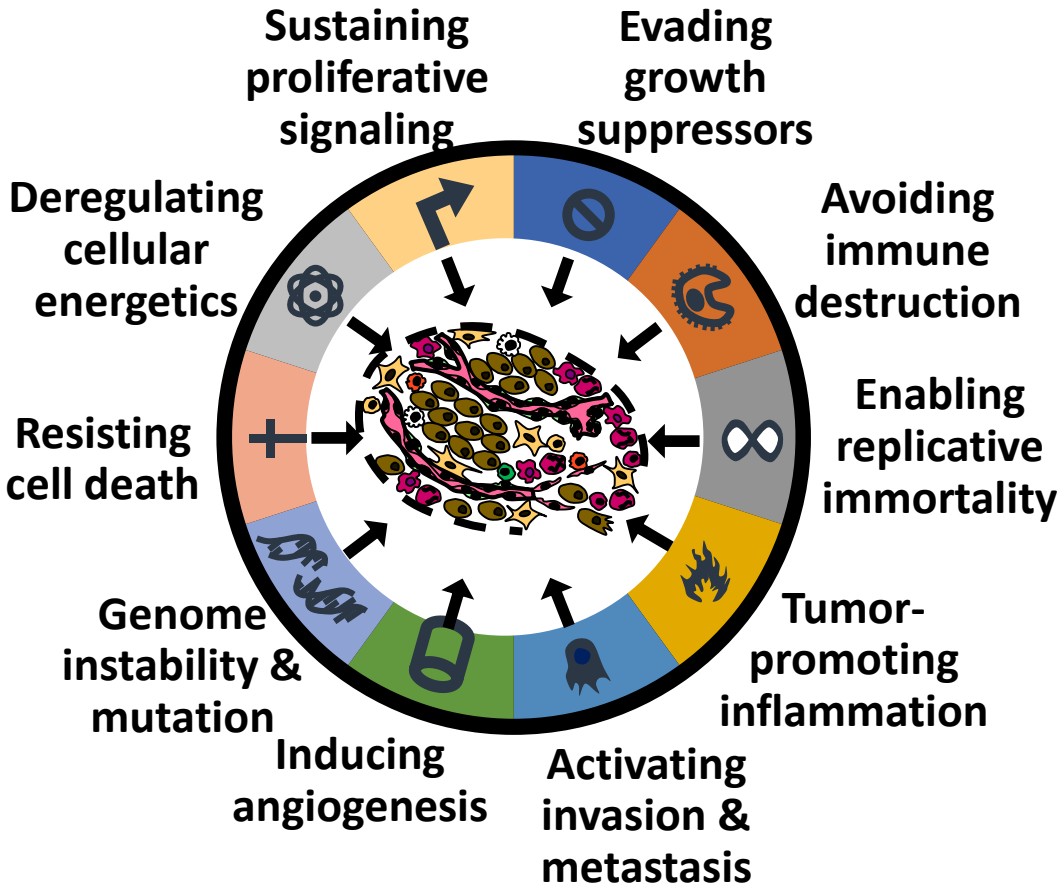
Arnold et al., Ann Oncol 2017

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.

Hallmarks of Cancer – Acquired Capabilities for Tumor Growth and Progression



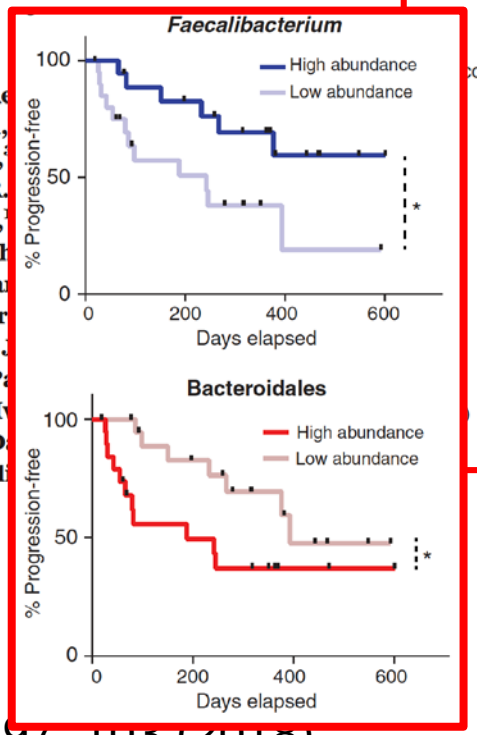
Interaction with "outside world" e.g. microbiome

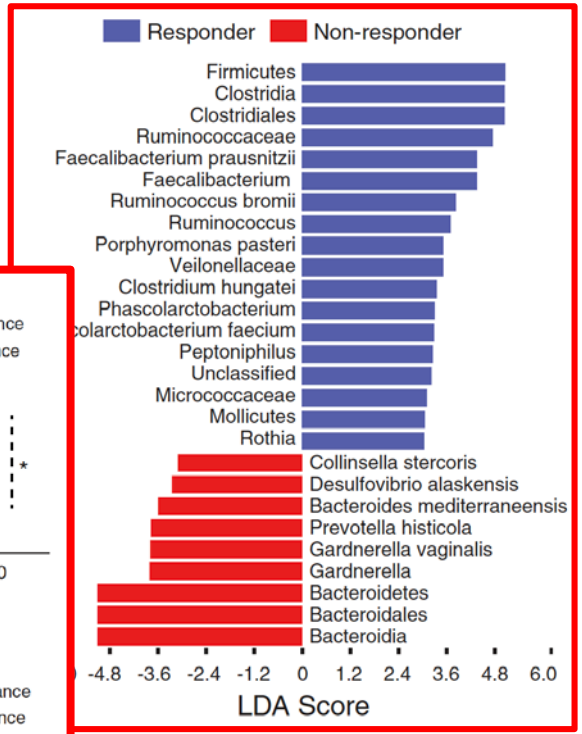
Hanahan D, et al. *Cell.* 2011;144:646-674.

CANCER IMMUNOTHERAPY

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan,[1,2*] C. N. Spencer,[2,3*] L. Nezi,[3*] A. Re
T. V. Karpinets,[3] P. A. Prieto,[1†] D. Vicente,[1] K. Hoffman,
L. Zhao,[3] C. W. Hudgens,[6] D. S. Hutchinson,[7] T. Manzo,
T. Cotechini,[8] T. Kumar,[3] W. S. Chen,[9] S. M. Reddy,[10] R.
J. Galloway-Pena,[11] H. Jiang,[1] P. L. Chen,[9§] E. J. Shpall,
R. F. Chemaly,[11] S. Shelburne,[3,11] L. M. Vence,[5] P. C. Okh
A. G. Swennes,[7] F. McAllister,[14] E. Marcelo Riquelme Sa
E. Le Chatelier,[15] L. Zitvogel,[16] N. Pons,[15] J. L. Austin-Br
E. M. Burton,[1] J. M. Gardner,[1] E. Sirmans,[17] J. Hu,[18] A.
A. Diab,[17] H. Tawbi,[17] I. C. Glitza,[17] W. J. Hwu,[17] S. P. Pa
R. N. Amaria,[17] M. A. Davies,[17] J. E. Gershenwald,[1] P. Hu
L. M. Coussens,[8] Z. A. Cooper,[1,3¶] P. A. Futreal,[3] C. R. Da
J. F. Petrosino,[7] M. T. Tetzlaff,[6,9] P. Sharma,[5,19] J. P. Alli
R. R. Jenq,[3#] J. A. Wargo[1,3#**]





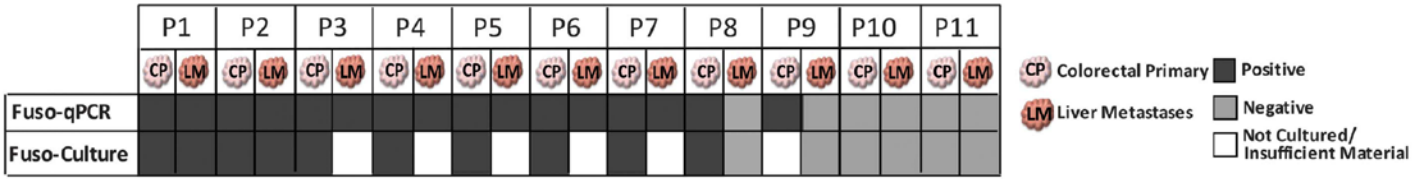
Gopalakrishnan et al., Science 359, 97–103 (2018)

Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer

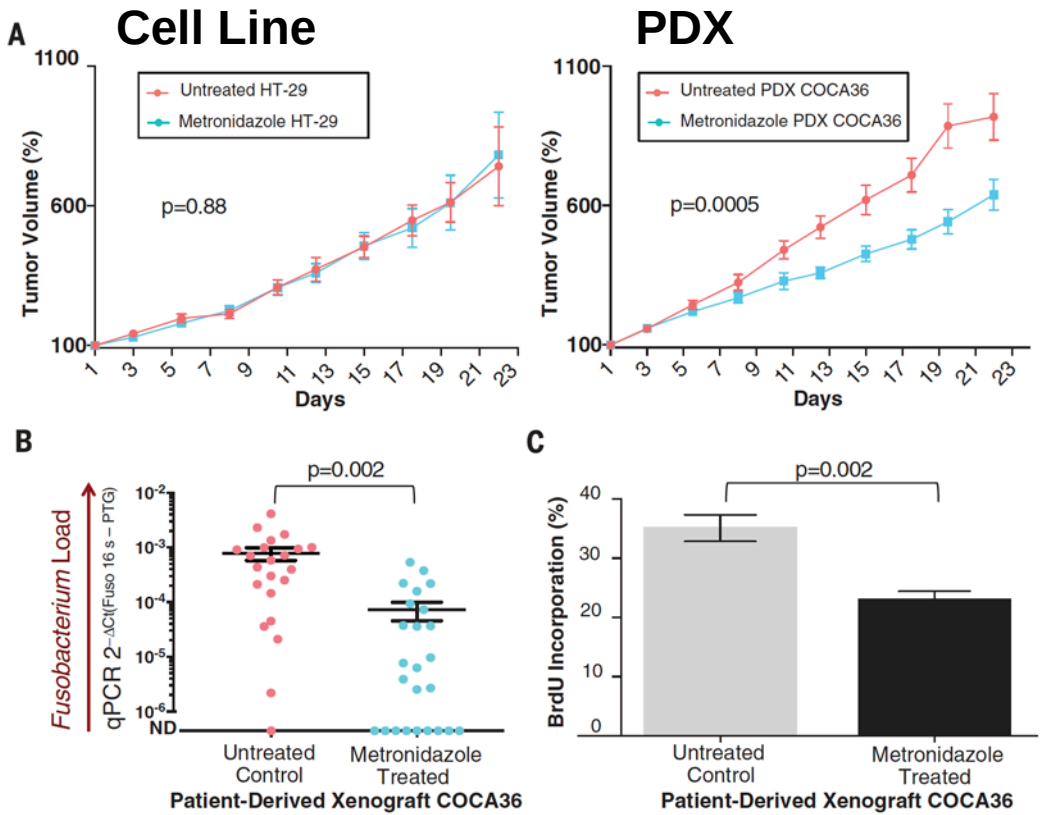
Susan Bullman,[1,2] Chandra S. Pedamallu,[1,2] Ewa Sicinska,[1] Thomas E. Clancy,[3] Xiaoyang Zhang,[1,2] Diana Cai,[1,2] Donna Neuberg,[1] Katherine Huang,[2] Fatima Guevara,[1] Timothy Nelson,[1] Otari Chipashvili,[1] Timothy Hagan,[1] Mark Walker,[2] Aruna Ramachandran,[1,2] Begoña Diosdado,[1,2] Garazi Serna,[4] Nuria Mulet,[4] Stefania Landolfi,[4] Santiago Ramon y Cajal,[4] Roberta Fasani,[4] Andrew J. Aguirre,[1,2,3] Kimmie Ng,[1] Elena Élez,[4] Shuji Ogino,[1,3,5] Josep Tabernero,[4] Charles S. Fuchs,[6] William C. Hahn,[1,2,3] Paolo Nuciforo,[4] Matthew Meyerson[1,2,3]*

Key findings:

- *Fusobacterium nucleatum* commonly found in CRC tiss
- 80% concordance between *FN* colonization in primary ar
- *FN* also found in Xenografts
- Antibiotic therapy reduced tu and proliferation index



Bullman et al., Science 358, 1443–1448 (2017)



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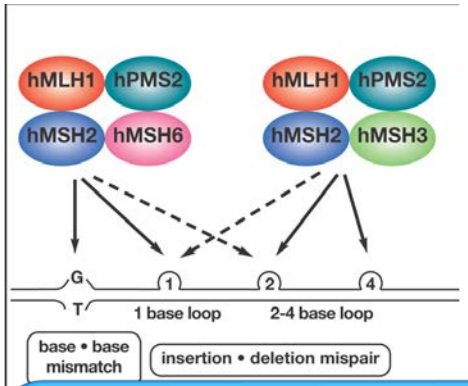
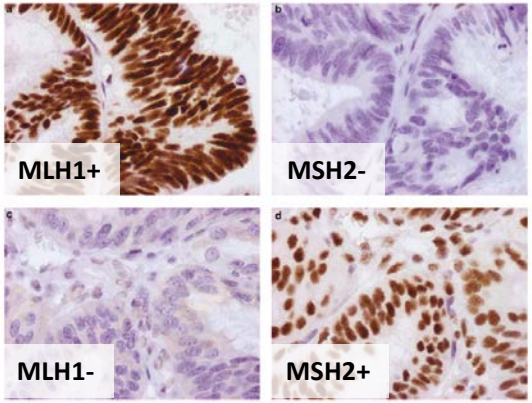
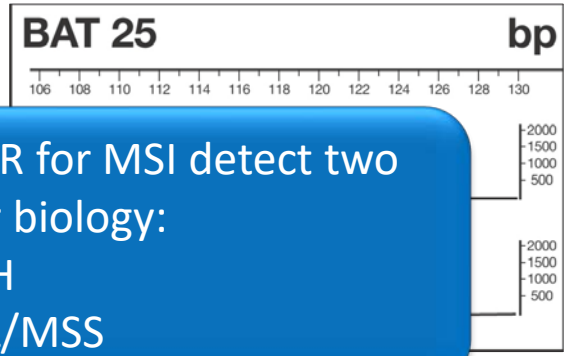
Mismatch Repair Deficiency (MMR-D): Unique Biological Subgroup of Colon Cancer



IHC for MMR protein status





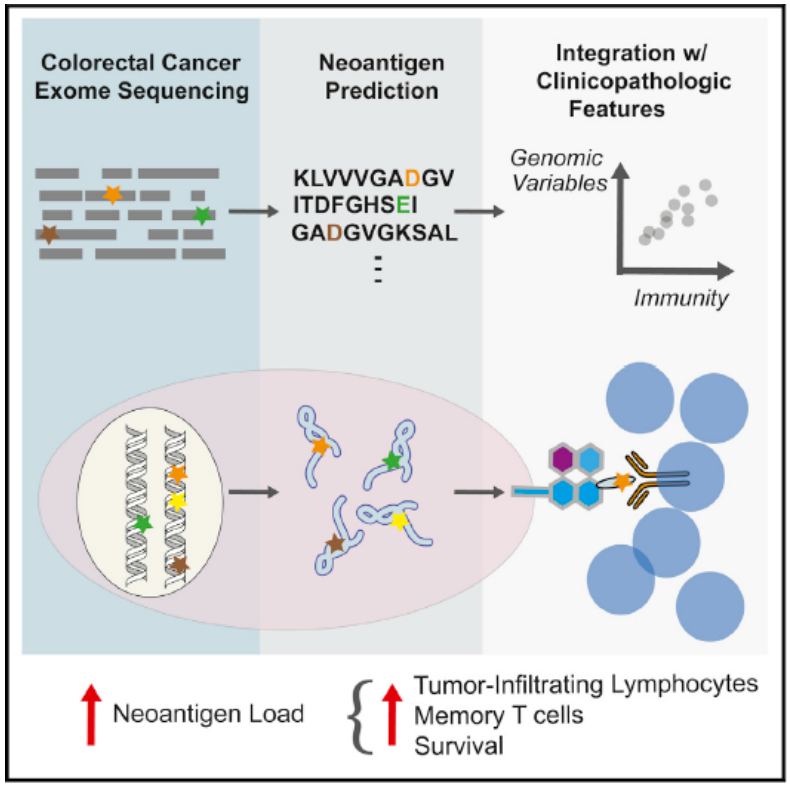
Thus, IHC for MMR proteins and PCR for MSI detect two manifestations of the same tumor biology:

- MMR-D is synonymous with MSI-H
- MMR-P is synonymous with MSI-L/MSS

Imai and
Umetani
Rosen et a

Hypermutation and Immuno-Oncology

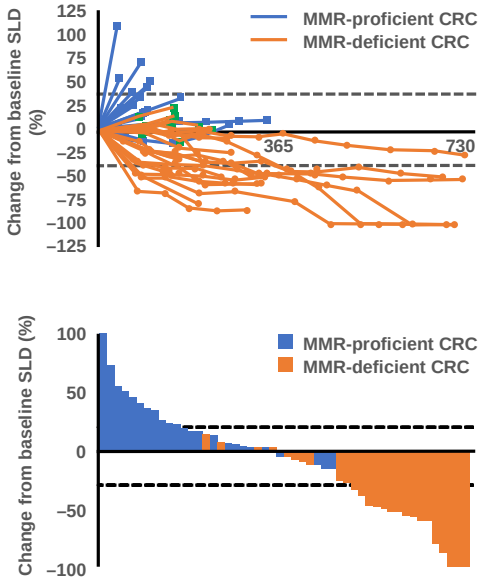
- **In CRC, MSI-H is associated with increases in immune infiltration and expression of immune checkpoint regulators[1,2]**
- **MSI-H is also associated with increased number of mutations per tumor**
- **Tumor mutations produce tumor-specific neoantigens, which when expressed on the tumor cell surface, are a target for T cells**
  - May improve response to immunotherapy
- **Elevated neoantigen load in CRC is associated with improved survival[2]**



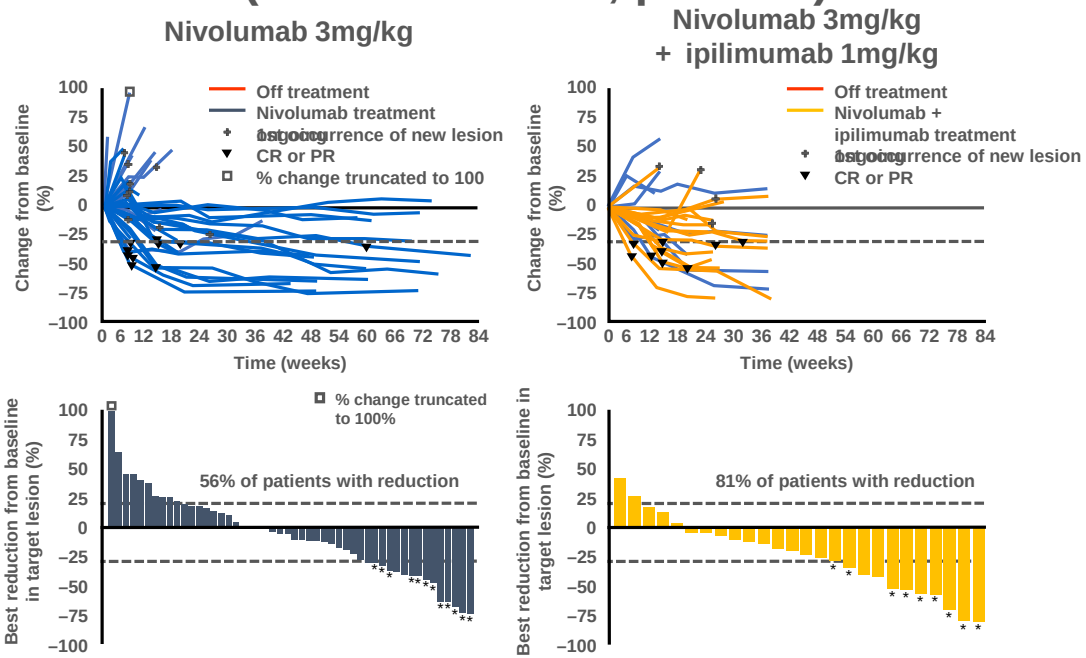
1. Llosa NJ, et al. *Cancer Discov*. 2015;5:43–51.
2. Giannakis M, et al. *Cell Reports*. 2016;15:857–865.

MSI-high tumors 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**

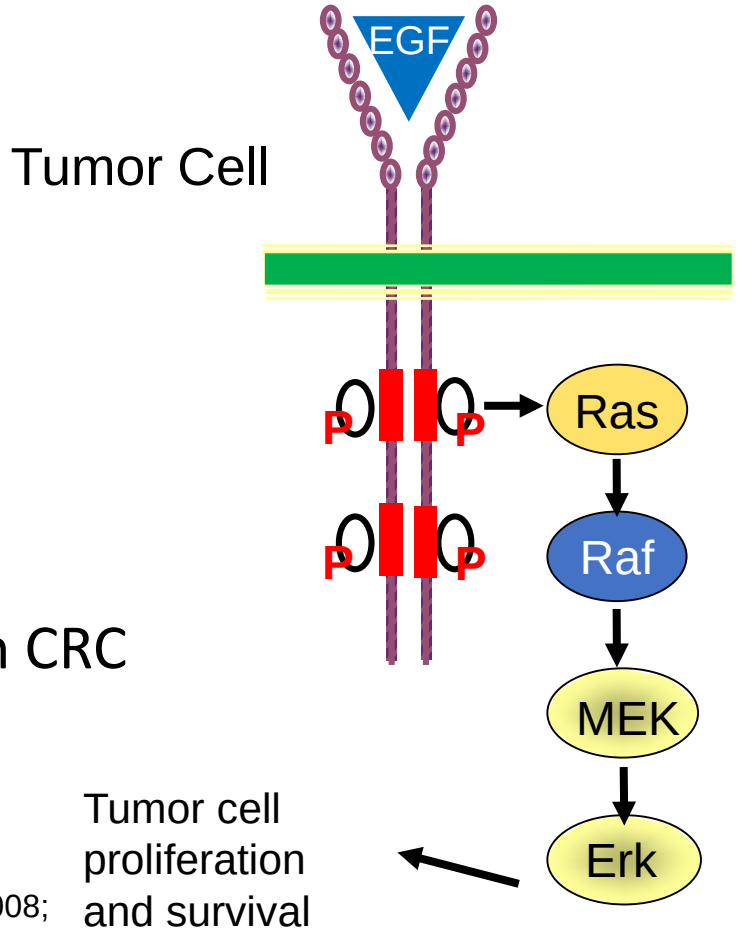
1. Le et al. ASCO 2016; 2.Overman et al. ASCO 2016

Recent FDA Approvals

- **May 23, 2017: Pembrolizumab is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (MMR-D). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.**
- **July 31, 2017: Nivolumab gained accelerated approval for the treatment of patients 12 years and older with mismatch repair deficient (MMR-D) or microsatellite instability high (MSI-H) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.**

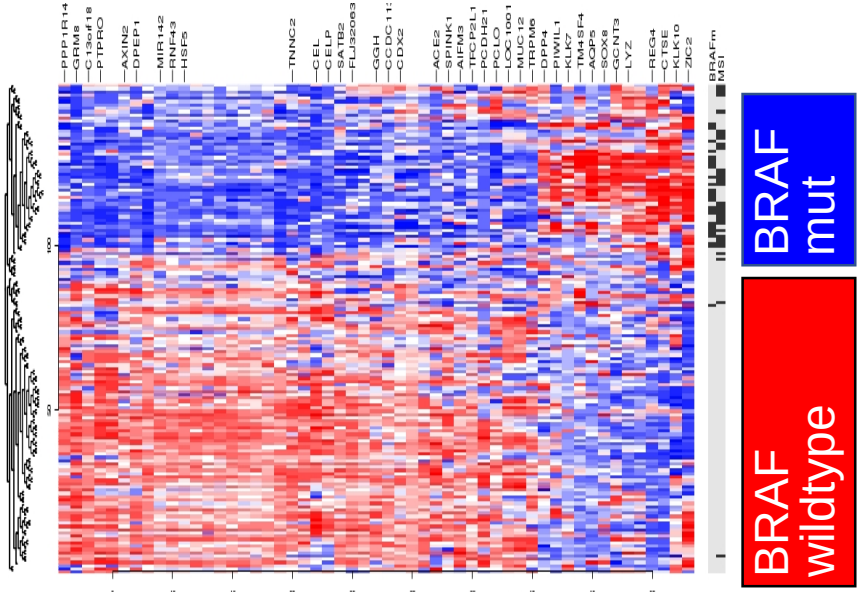
BRAF Mutations in CRC

- **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

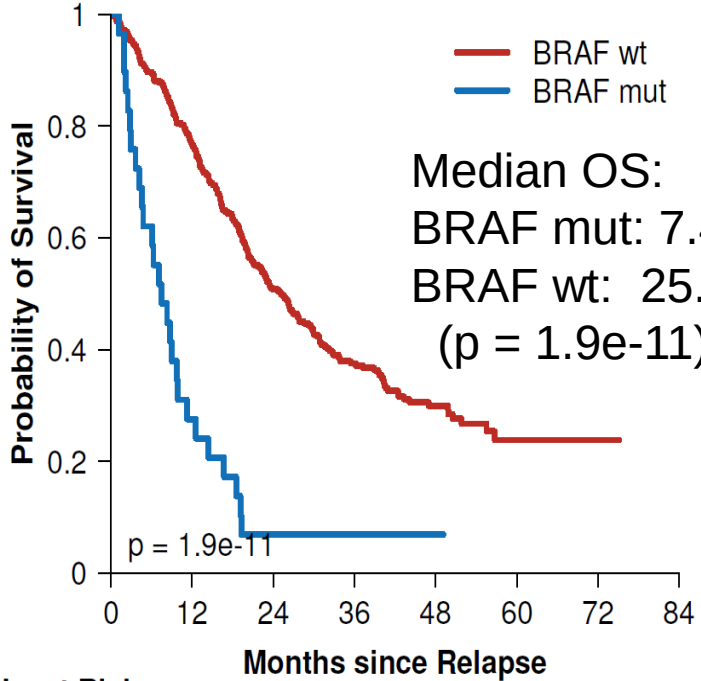


Yarden. *Nat Rev Mol Cell Biol*. 2001; Di Nicolantonio. *J Clin Oncol*. 2008; Artale. *J Clin Oncol*. 2008.

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



Tejpar et al, ASCO 2010

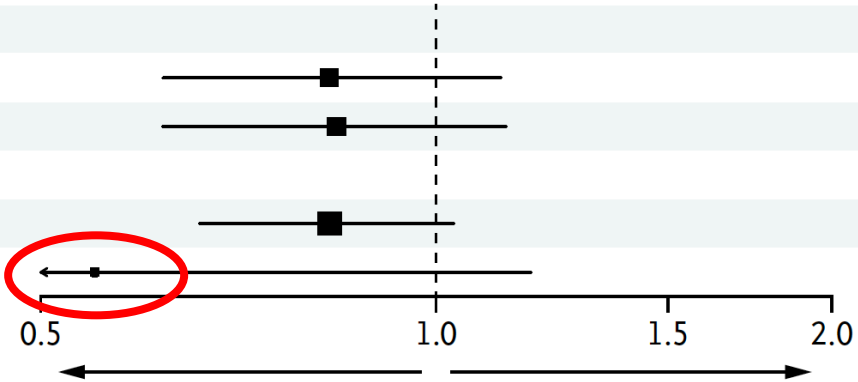


Median OS:
BRAF mut: 7.49 m
BRAF wt: 25.2 m
(p = 1.9e-11)

Roth et al. JCO 2010

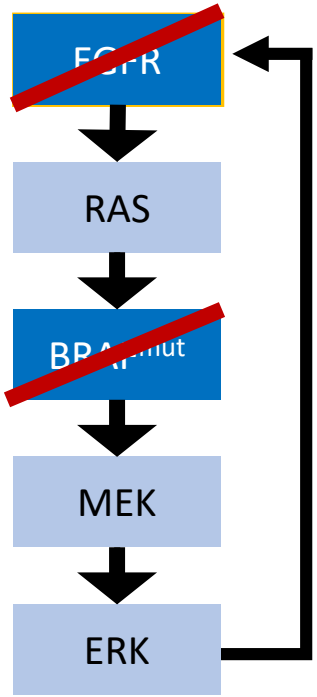
FOLFOXIRI + BEV in BRAF V600E mut mCRC

Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value
KRAS			0.97
Nonmutated	193	0.83	
Mutated	200	0.84	
BRAF			0.32
Nonmutated	365	0.83	
Mutated	28	0.55	

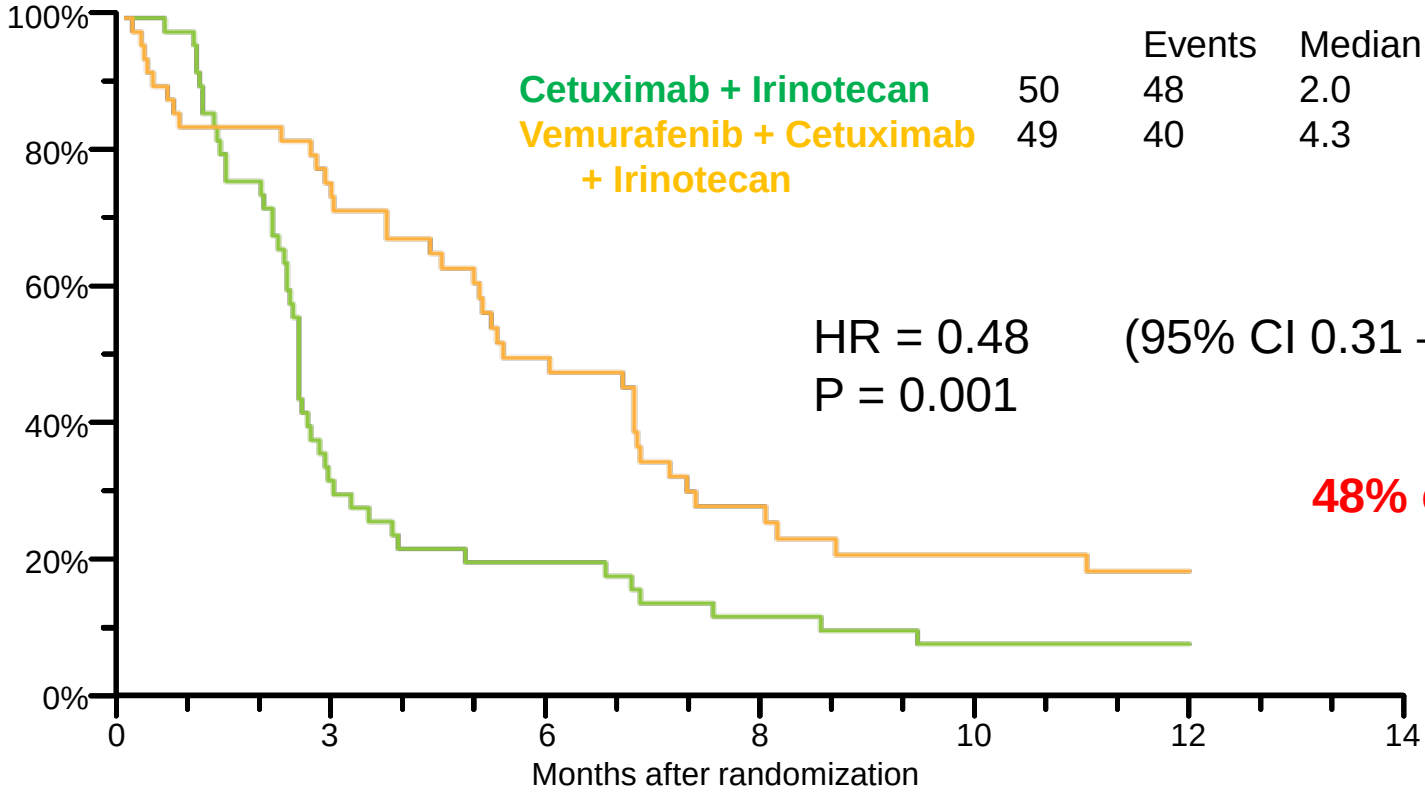


Loupakis et al., NEJM 2014

Rationale for combined BRAF and EGFR blockade



S1406: PFS – Cetux+Irino +/- Vemurafenib



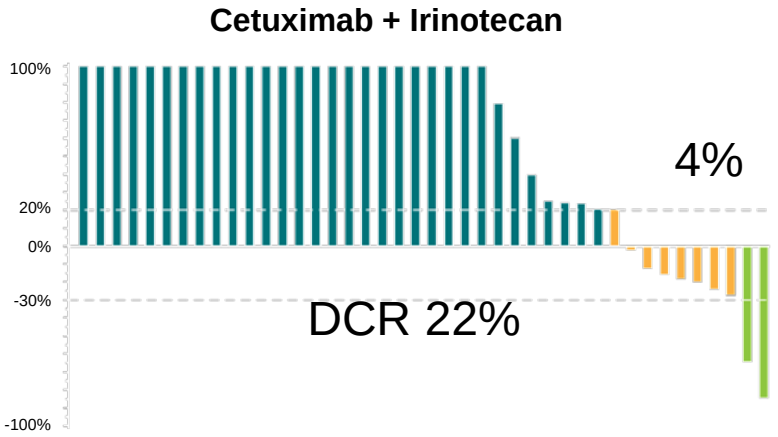
		Events	Median	95% Conf Int
Cetuximab + Irinotecan	50	48	2.0	(1.8 – 2.1)
Vemurafenib + Cetuximab + Irinotecan	49	40	4.3	(3.6 – 5.7)

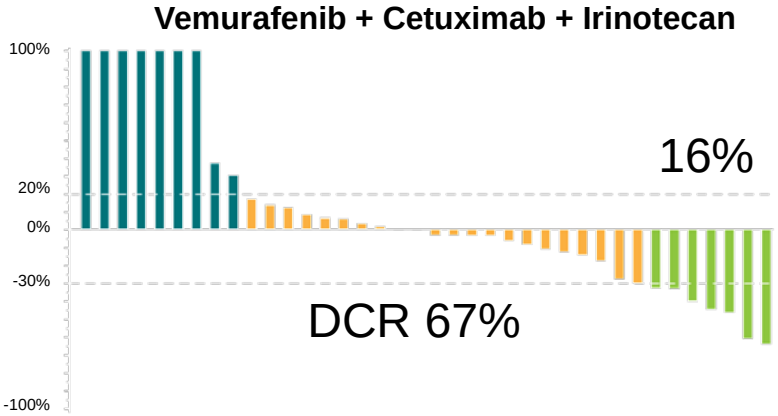
HR = 0.48 (95% CI 0.31 – 0.75)
P = 0.001

48% cross-over

Kopetz et al., ASCO 2017

S1406: RR/OS – Cetux+Irino +/- Vemurafenib





OS (mos)

	N	Median	95% CI
Cetuximab + Irinotecan	50	**5.9**	(3.0 – 9.9)
Vemurafenib + Cetuximab + Irinotecan	49	**9.6**	(7.5 – 13.1)

HR = 0.73 (95% CI 0.45 – 1.17)
P=0.19

Kopetz et al., ASCO 2017

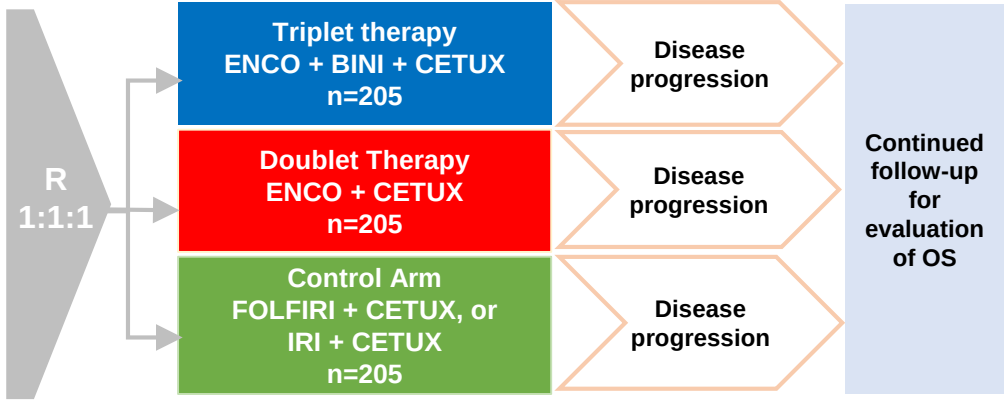
BEACON CRC Phase 3 Study Design[1]

Safety Lead-in Completed

ENCO 300 mg QD
+
BINI 45 mg BID
+
CETUX 400 mg/m^2 (initial), then 250 mg/m^2 QW

N=30

Phase 3 Currently Enrolling



1. Clinicaltrials.gov/ct2/show/NCT02928224; https://clinicaltrials.gov/ct2/show/NCT02928224 (February 2018).

Van Cutsem et al., ESMO GI 2018

BEACON SLI: Confirmed Best Overall Response

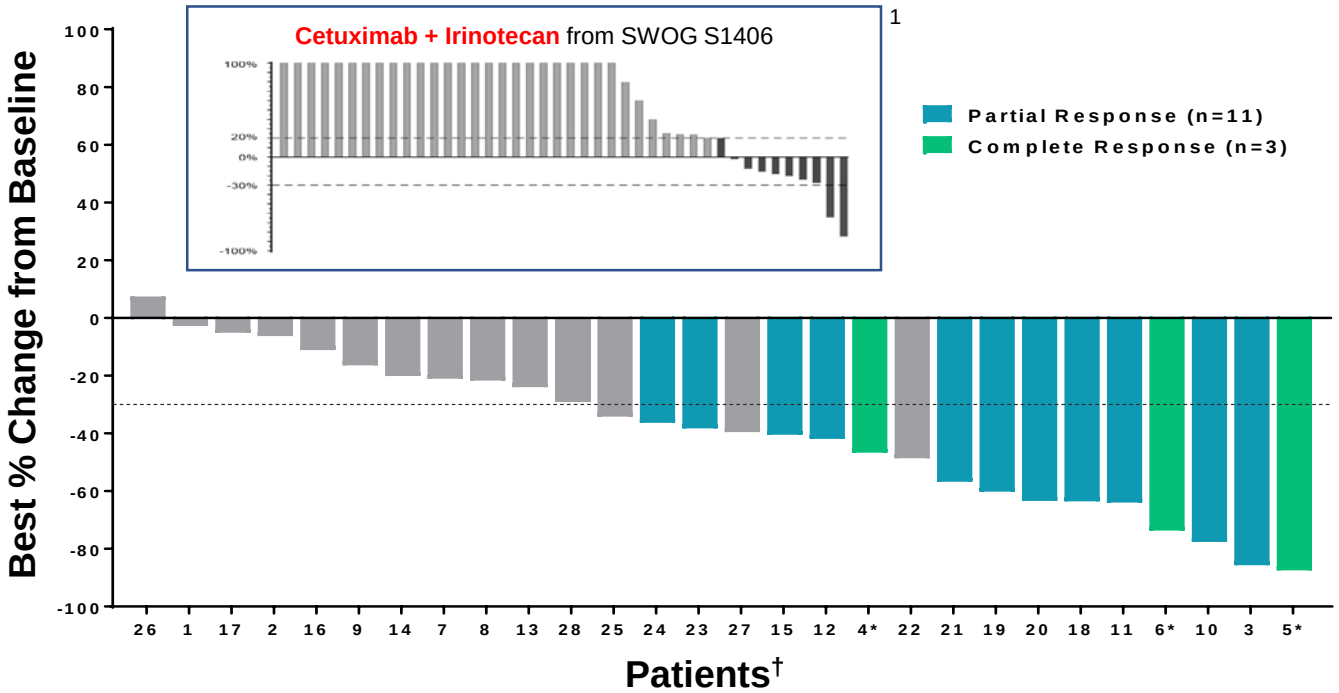
CONFIRMED BEST OVERALL RESPONSE*	PATIENTS (N=29)†
ORR (CR + PR)	**14 (48%)** **(95% CI 29%–67%)**
CR	3 (10%)
PR	11 (38%)
SD	13 (45%)
PD	0
Not evaluable for response‡	2 (7%)

- **ORR for patients with 1 and 2 prior regimens were 62% and 31% respectively**
- **43% of responders have response ≥6 months**
- **Median DOR: 5.5 mo (95% CI, 4.1–NR)**
- **Median PFS: 8.0 months**

*Local assessed confirmed responses per RECIST 1.1
†Patients with *BRAF*^{V600E} mutations.
‡Non-responders per intent-to-treat analysis.

Van Cutsem et al., ESMO GI 2018

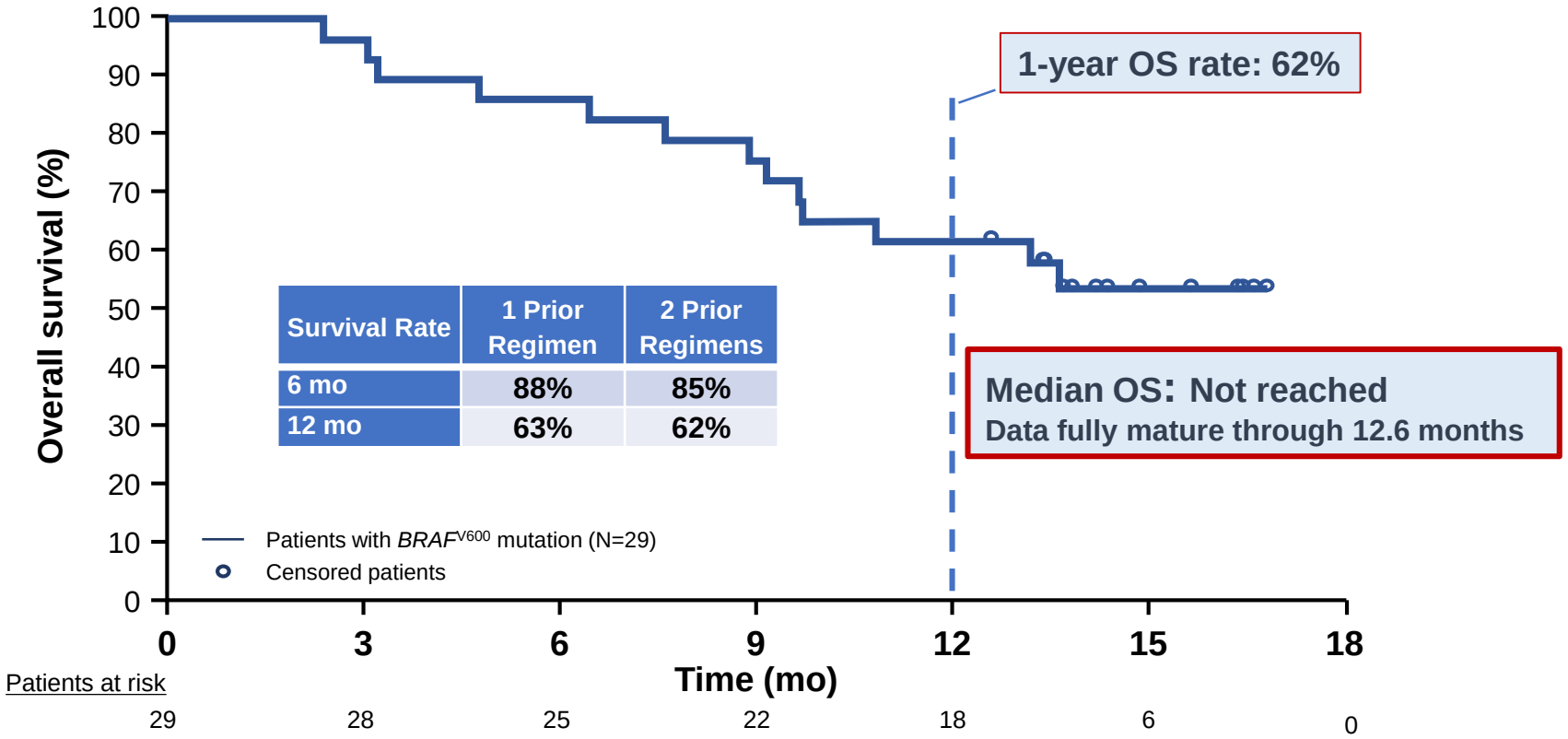
Best Percentage Change in Tumor Measurements from Baseline



*Patients with lymph node disease with decreases in short axis dimensions consistent with RECIST 1.1 defined Complete Response.
†One patient had no baseline sum of longest diameters and is not presented.
1. Kopetz S, et al. *J Clin Oncol*. 2017;35:Abstr 3505, with permission.

Van Cutsem et al., ESMO GI 2018

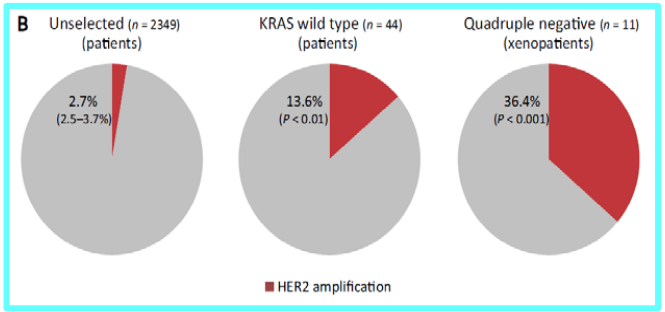
BEACON SLI: Overall Survival

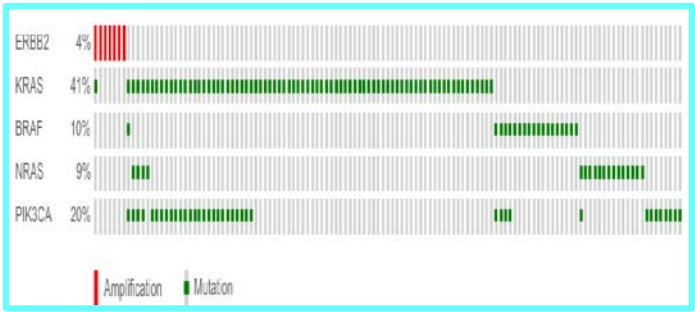


Van Cutsem et al., ESMO GI 2018

HER-2 Amplification in CRC

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**

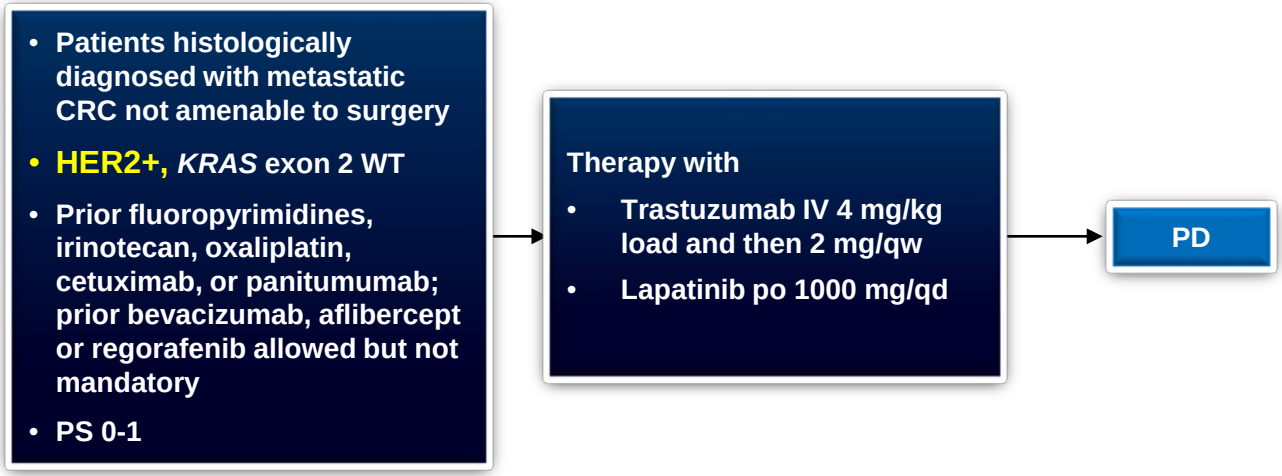




- 5.3% HER2 amplification seen in HERACLES Study (screened = 836)[1]
- HER2 amplification enriched in KRAS, NRAS, BRAF, and PIK3CA WT tumors[2]

[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)

HERACLES: Trastuzumab + Lapatinib



- **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 de novo resistant patients and upon PD**

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

Sartore-Bianchi, et al. Lancet Oncol 2016

HERACLES: Trastuzumab + Lapatinib

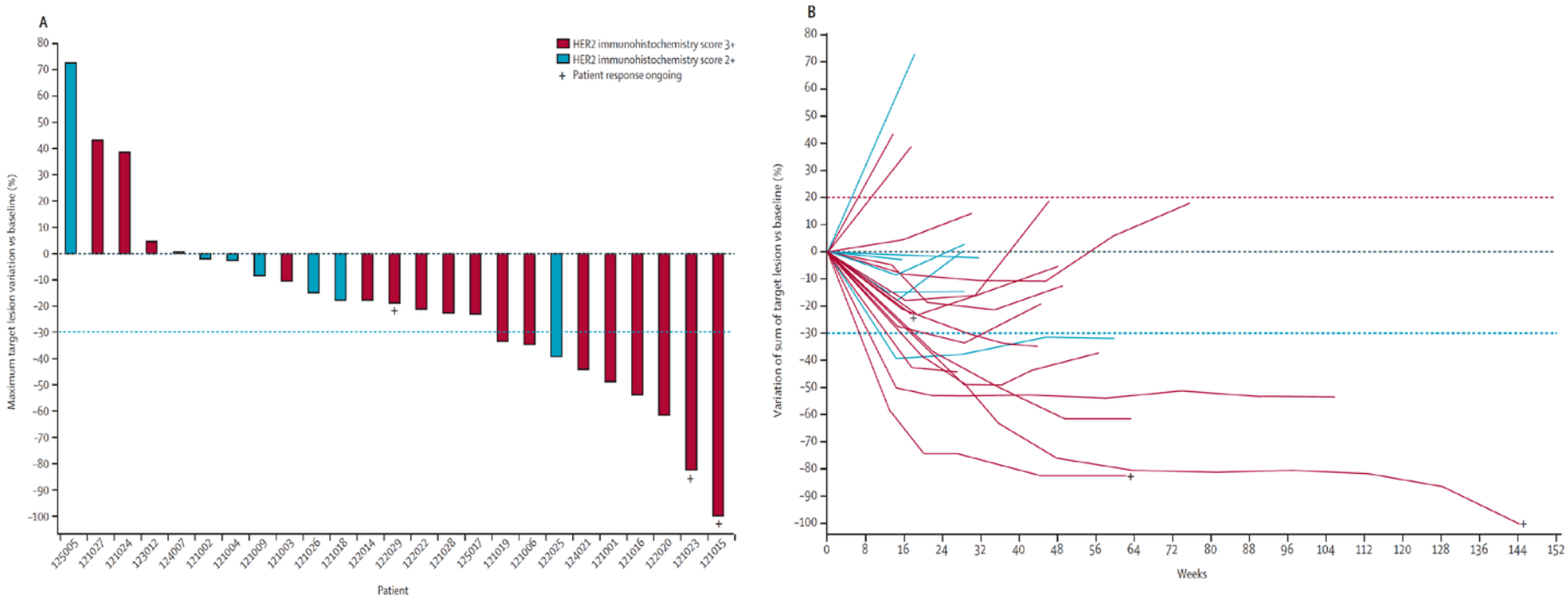
Best Response (RECIST 1:1 by Central Rev)	N	%
Responses (PR + CR)	**8**	**30**
Complete response	1	4
Partial response	7	26
Stable disease ≥4 mos	**8**	**30**
Stable disease <4 mos	4	15
Progressive disease	7	25
Total	27	100

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

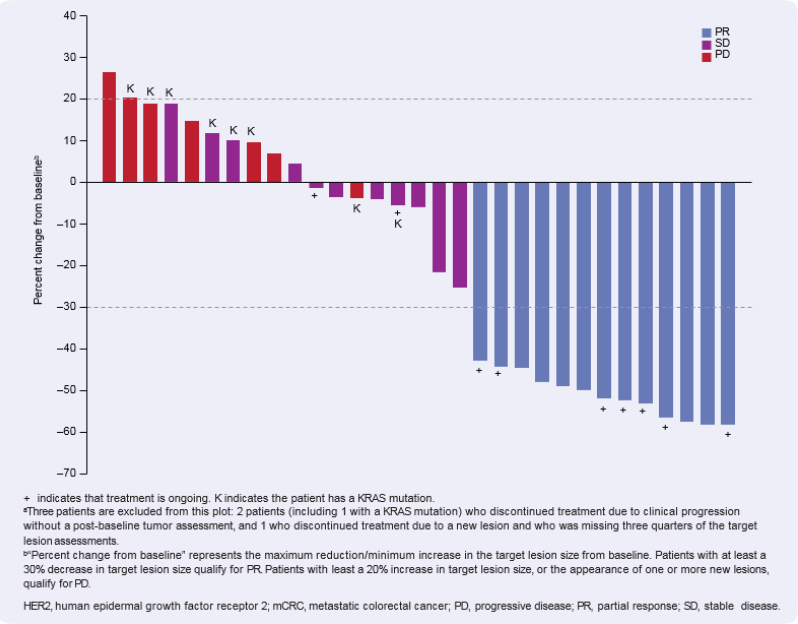
HERACLES: Responses



Sartore-Bianchi, et al. Lancet Oncol 2016

MyPathway: Trastuzumab + Pertuzumab in HER-2 pos CRC

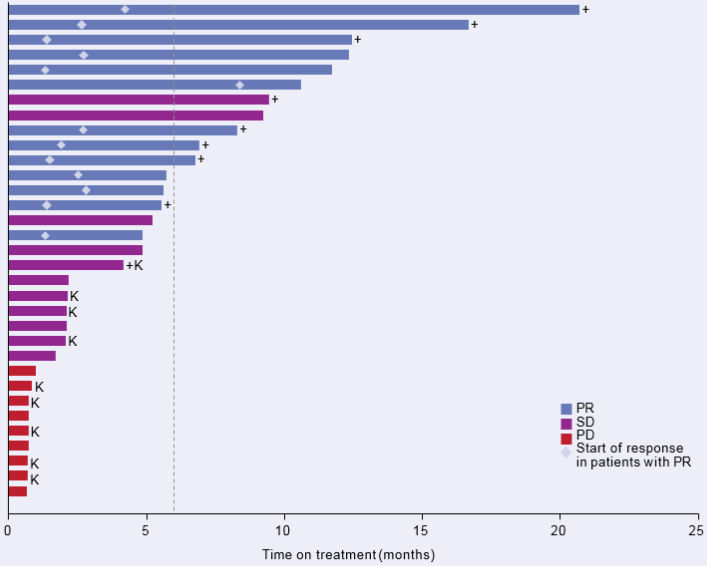
Figure 2. Best percent change from baseline in target lesion size in patients with HER2-amplified/overexpressed mCRC (n=31)[a]



+ 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.

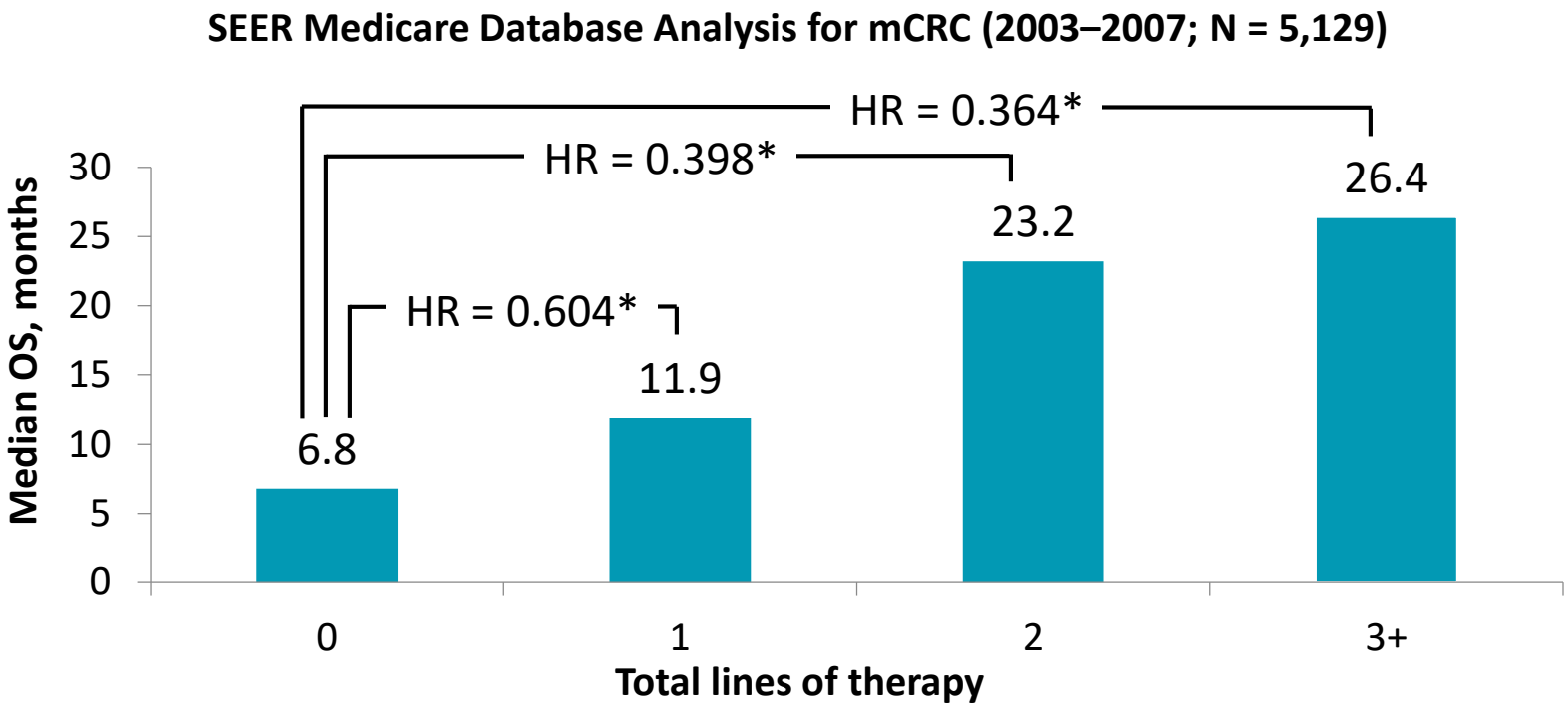
N = 31, RR 42%

Hurwitz et al., ASCO GI 2017

HER-2 Amplification in CRC

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

Median Survival Increases With Increased Lines of Therapy



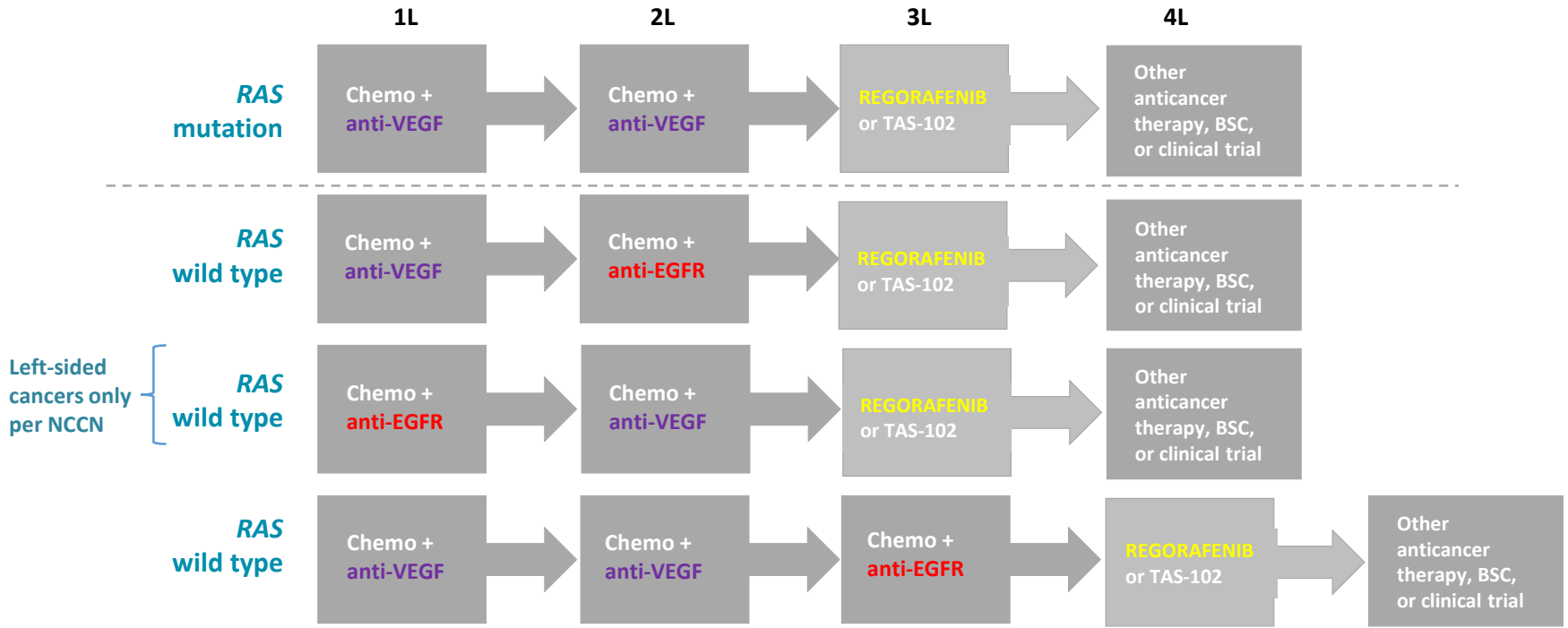
- Patients should be exposed to all active and approved agents during their treatment

*P <.001.

HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.

Hanna N, et al. *J Clin Oncol.* 2014;32(suppl 3):abstract 559.

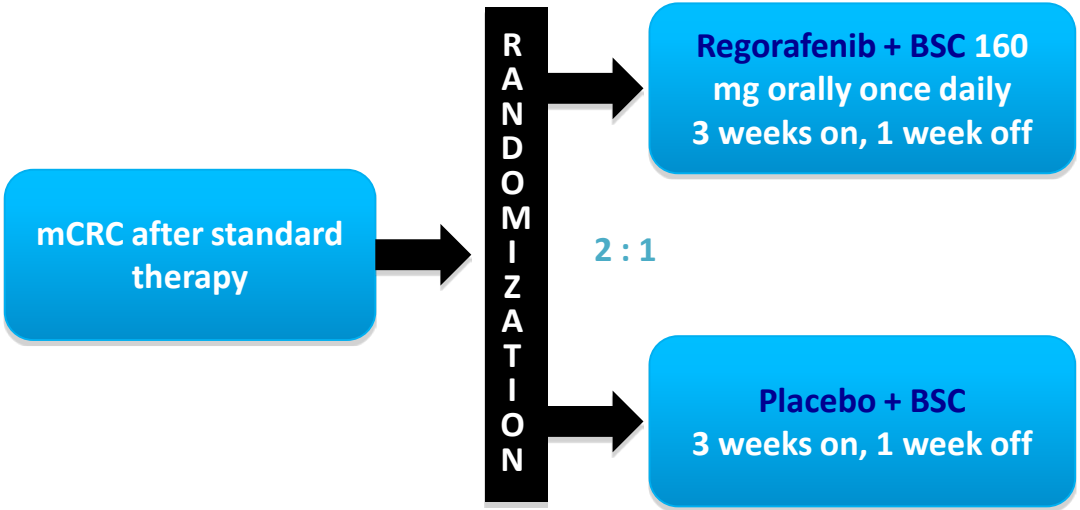
NCCN and ESMO mCRC Guidelines



BSC, best supportive care; EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; VEGF, vascular endothelial growth factor. Figure adapted from
NCCN Clinical Practice Guidelines. Colon cancer. V2.2017; NCCN Clinical Practice Guidelines. Rectal cancer. V3.2017; Van Cutsem E, et al. *Ann Oncol.* 2016;27(8):1386-1422.

Regorafenib Studies Design

CORRECT[1] and CONCUR[2] Phase III Trials



Multicenter, randomized, double-blind, placebo-controlled, phase III

– 2:1 randomization

Trial populations

– CORRECT—global outside of Asia

– CONCUR—Asia

Grothey A, Van Cutsem E, et al. *Lancet.* 2013;381(9863):303-312; Li J, et al. *Lancet Oncol.* 2015;16(6):619-629.

Patient Eligibility for Regorafenib Phase III Trials

CORRECT[1]	CONCUR[2]
Adenocarcinoma of the colon or rectum	
ECOG performance status 0–1	
Measurable or nonmeasurable disease	
Adequate bone marrow, liver, and renal function	
Signed informed consent	
Disease progression during/within 3 months after last administration of or intolerance to approved standard therapies, which had to include (if licensed) • Fluoropyrimidine, oxaliplatin, irinotecan • Bevacizumab • Cetuximab or panitumumab (if *KRAS* wild-type)	Disease progression during/within 3 months after the last standard therapies (or within 6 months of stopping adjuvant oxaliplatin) or have stopped standard treatment because of unacceptable toxicity • Prior anti-VEGF or anti-EGFR targeted therapy allowed, but not mandatory
Age ≥18 years	Asian adults ≥18 years of age

Grothey A, Van Cutsem E, et al. *Lancet.* 2013;381(9863):303-312; Li J, et al. *Lancet Oncol.* 2015;16(6):619-629.

52% of Patients in CORRECT and 61% in CONCUR Received 3 or Fewer Prior Therapies for mCRC

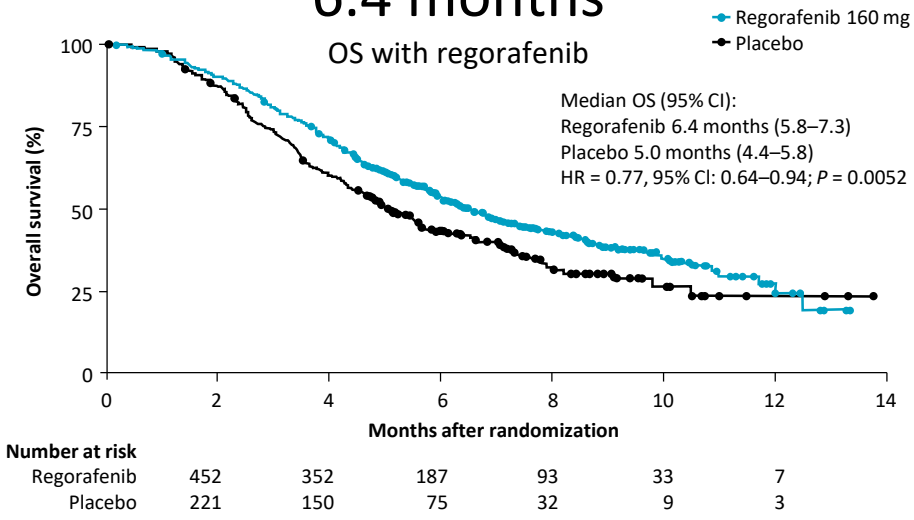
CORRECT[1]		Regorafenib 160 mg + BSC (n = 505)	Placebo + BSC (n = 255)
Prior therapies for metastatic disease*	≤3	52%†	53%†
	≥4	49%	47%
Prior targeted therapy‡	Any	100%	100%
Trial Geography – Global			

CONCUR[2]		Regorafenib 160 mg + BSC (n = 136)	Placebo + BSC (n = 68)
Prior therapies for metastatic disease*	≤3	62%	60%
	≥4	38%	40%
Prior targeted therapy‡	Any	59%	62%
Trial Geography – Asia			

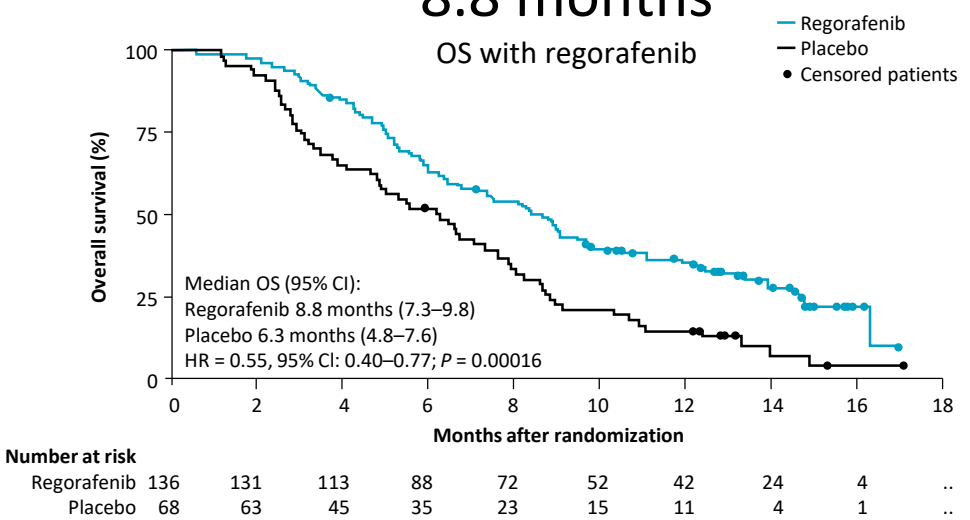
*Previous therapies included fluoropyrimidines, oxaliplatin, irinotecan, and bevacizumab, and if *KRAS* wildtype, anti-EGFR.
†Five patients on placebo (2%) and 16 patients on regorafenib (3%) had received only 1 prior therapy for metastatic disease.
‡In CONCUR, some patients did not have access to targeted therapies; in contrast, all patients in CORRECT had received bevacizumab, and an anti-EGFR agent had been utilized for all *KRAS* wildtype cases.
Grothey A, Van Cutsem E, et al. *Lancet.* 2013;381(9863):303-312; Li J, et al. *Lancet Oncol*. 2015;16(6):619-629.

Significant Improvements in OS with Regorafenib in 2 Randomized Phase III Trials: CORRECT and CONCUR

6.4 months



8.8 months



CORRECT[1]: 23% reduction in the risk of death (primary endpoint)

CONCUR[2]: 45% reduction in the risk of death (primary endpoint)

1. Grothey A, Van Cutsem E, et al. *Lancet.* 2013;381(9863):303-312; 2. Li J, et al. *Lancet Oncol.* 2015;16(6):619-629.

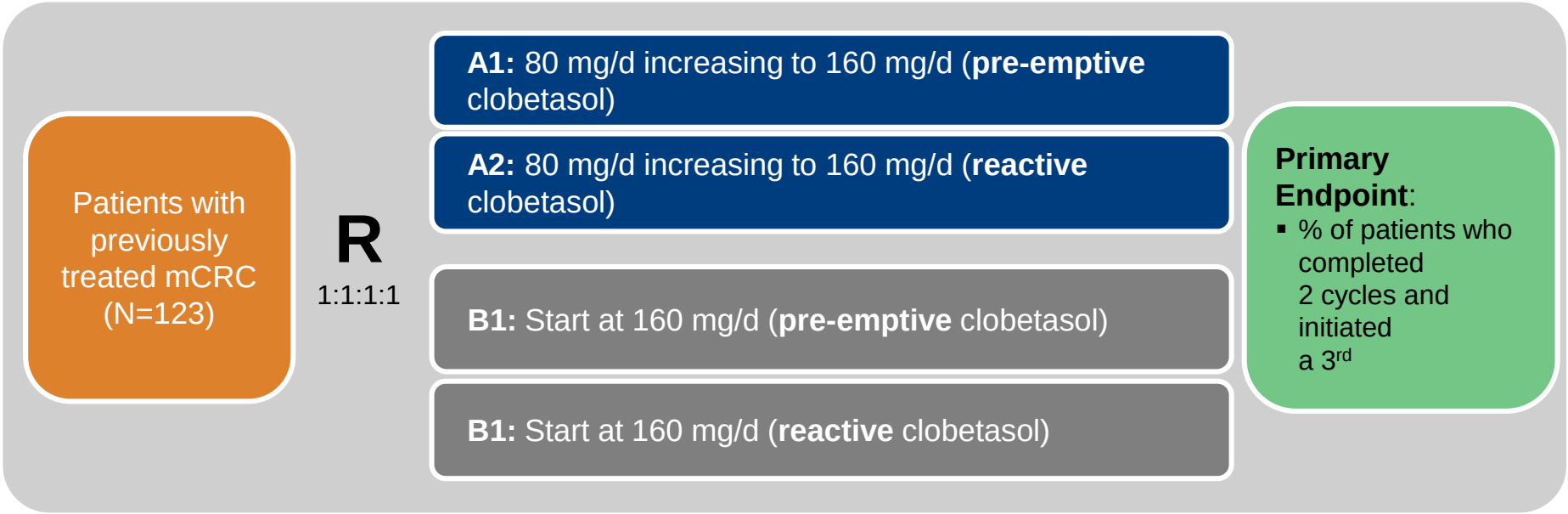
Drug-Related Treatment-Emergent Adverse Events Occurring in ≥10% of Patients

Adverse Event, %	Regorafenib (n = 500)			Placebo (n = 253)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hand-foot skin reaction	46.6	16.6	0	7.5	0.4	0
Fatigue	47.4	9.2	0.4	28.1	4.7	0.4
Hypertension	27.8	7.2	0	5.9	0.8	0
Diarrhea	33.8	7.0	0.2	8.3	0.8	0
Rash/desquamation	26.0	5.8	0	4.0	0	0
Anorexia	30.4	3.2	0	15.4	2.8	0
Mucositis, oral	27.2	3.0	0	3.6	0	0
Thrombocytopenia	12.6	2.6	0.2	2.0	0.4	0
Fever	10.4	0.8	0	2.8	0	0
Nausea	14.4	0.4	0	11.1	0	0
Bleeding	11.4	0.4	0	2.8	0	0
Voice changes	29.4	0.2	0	5.5	0	0
Weight loss	13.8	0	0	2.4	0	0

*Grade 5 drug-related AEs: 1.0% in regorafenib arm vs 0% in placebo arm

Grothey A, Van Cutsem E, et al. *Lancet*. 2013;381:303-312.

Phase II ReDOS Study:
Overview

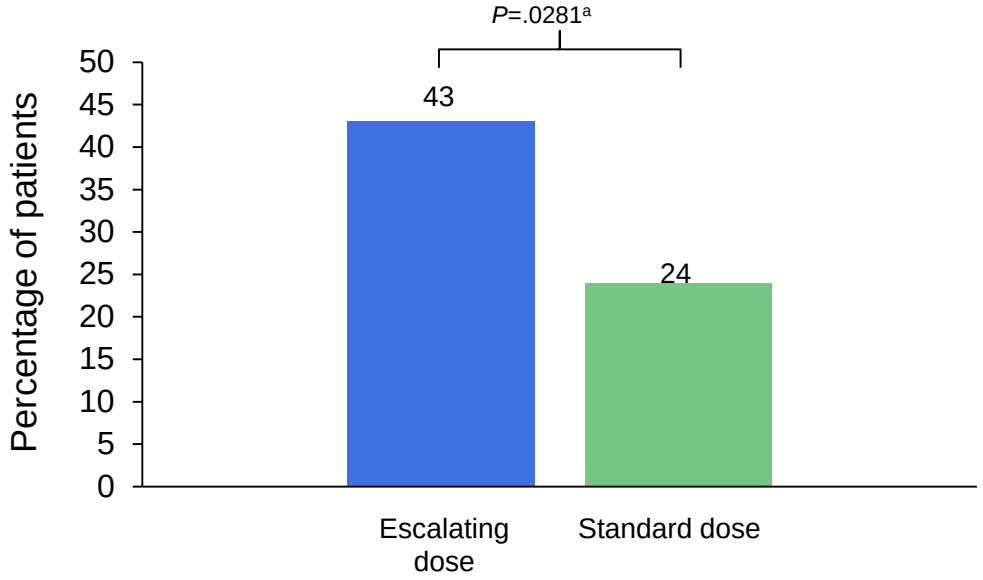


- Other endpoints: OS, PFS, TTP

OS, overall survival; PFS, progression-free survival; TTP, time-to-progression.

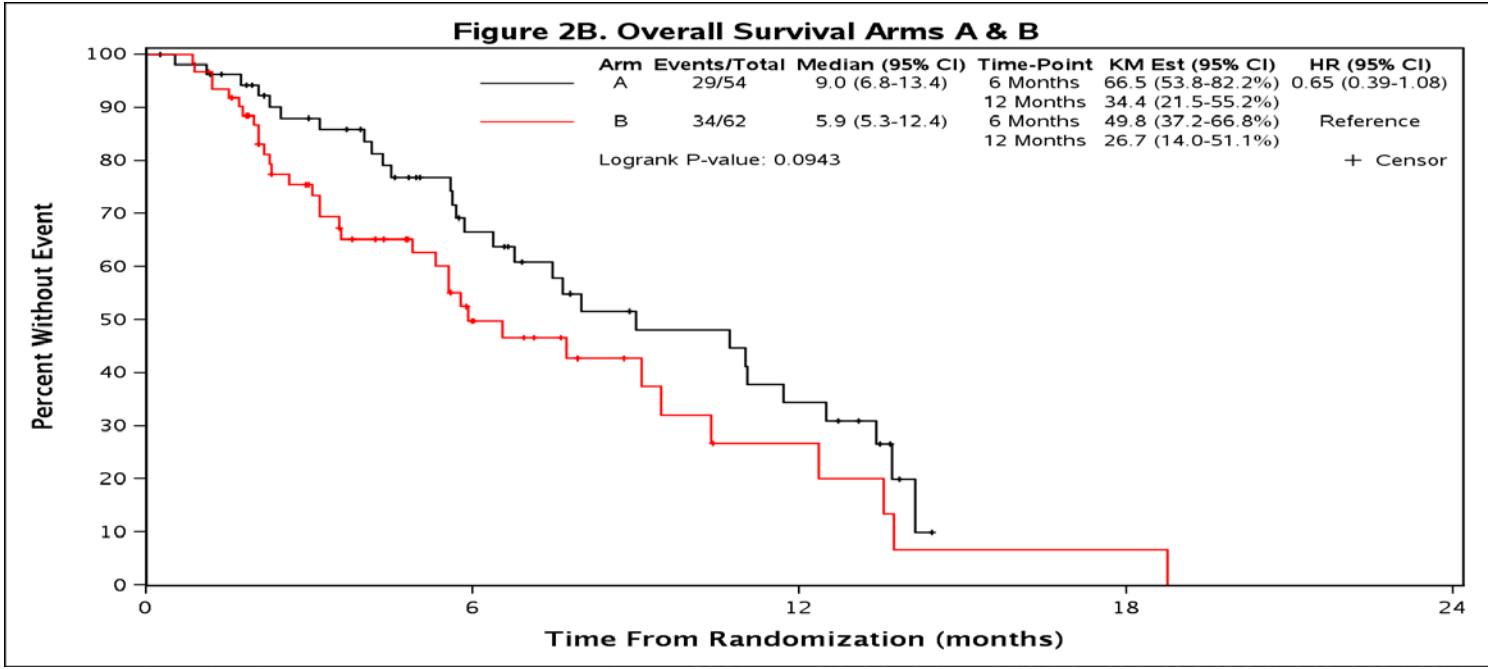
Data on File, ACCRU.

Phase II ReDOS Study:
Percentage of Patients Starting Cycle 3 (primary endpoint)



[a]Fisher's exact test (1-sided)

Phase II ReDOS Study:
OS (secondary endpoint)



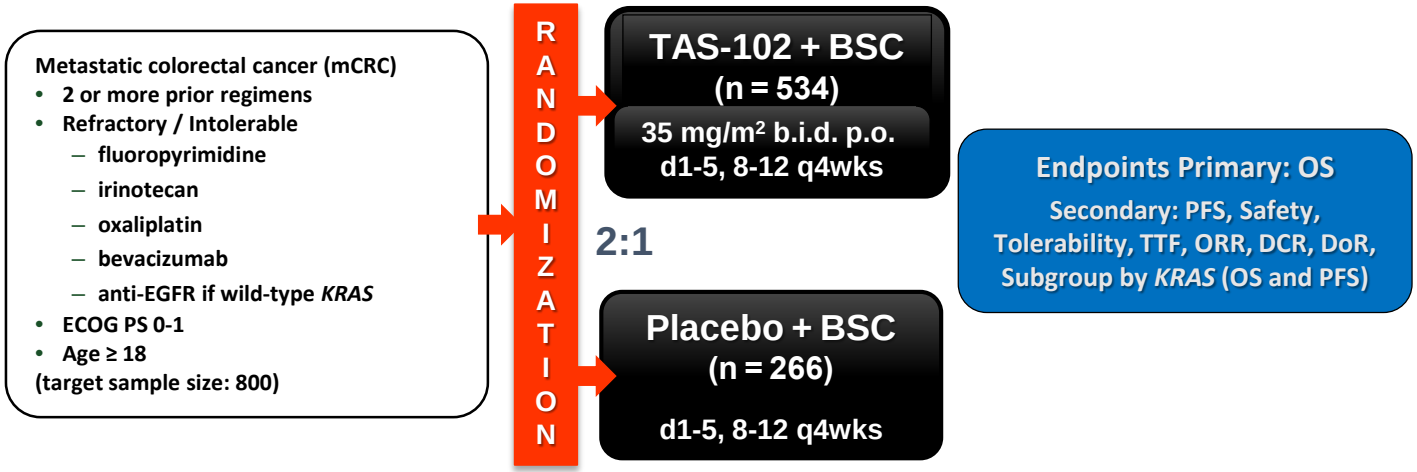
HR, hazard ratio; KM est, Kaplan-Meier estimate; OS, overall survival.

Data on File, ACCRU.

TAS-102 Global Randomized Phase III study

RECOURSE: Refractory Colorectal Cancer Study

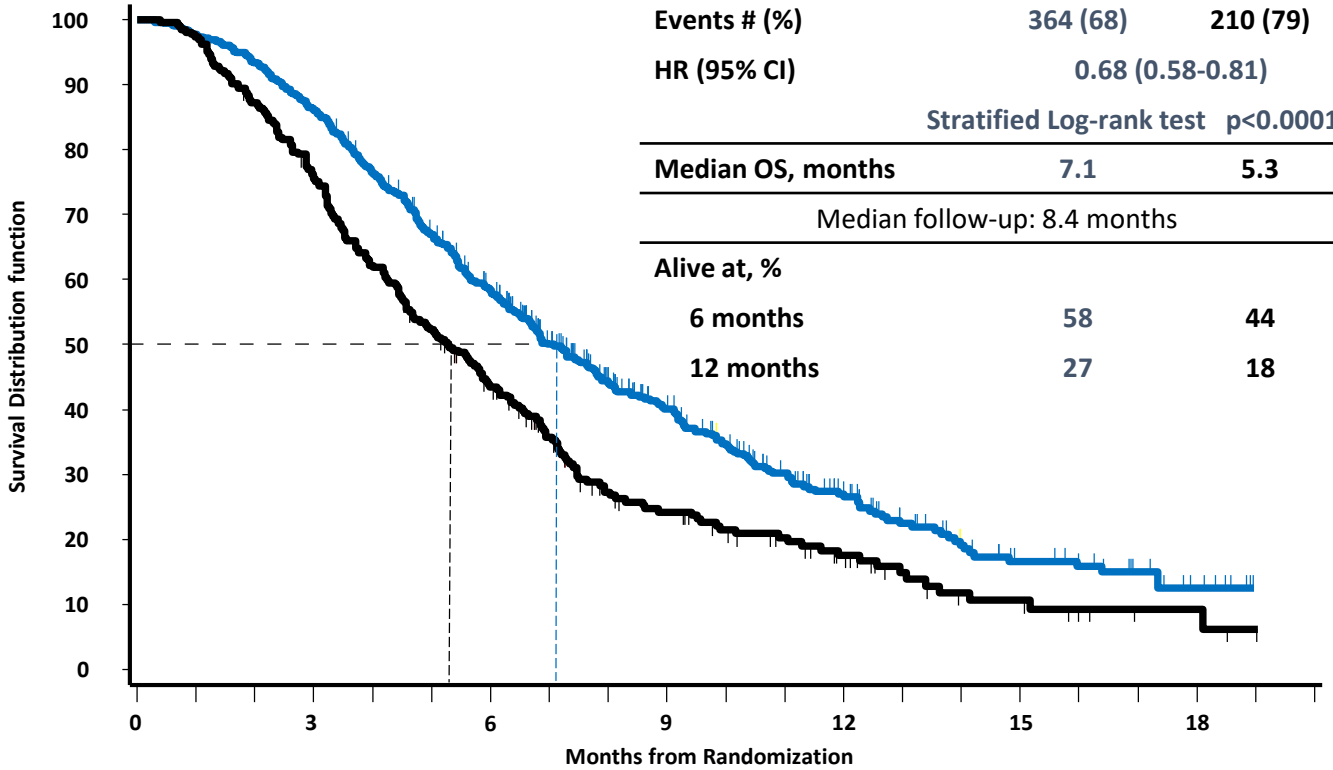
(NCT01607957)



- Treatment continuation until progression, intolerant toxicity or patient refusal
- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification: *KRAS* status, time from diagnosis of metastatic disease, geographical region
- Sites: 13 countries, 114 sites
- Enrollment: June 2012 to October 2013

Mayer et al., NEJM 2015

TAS-102 Overall Survival



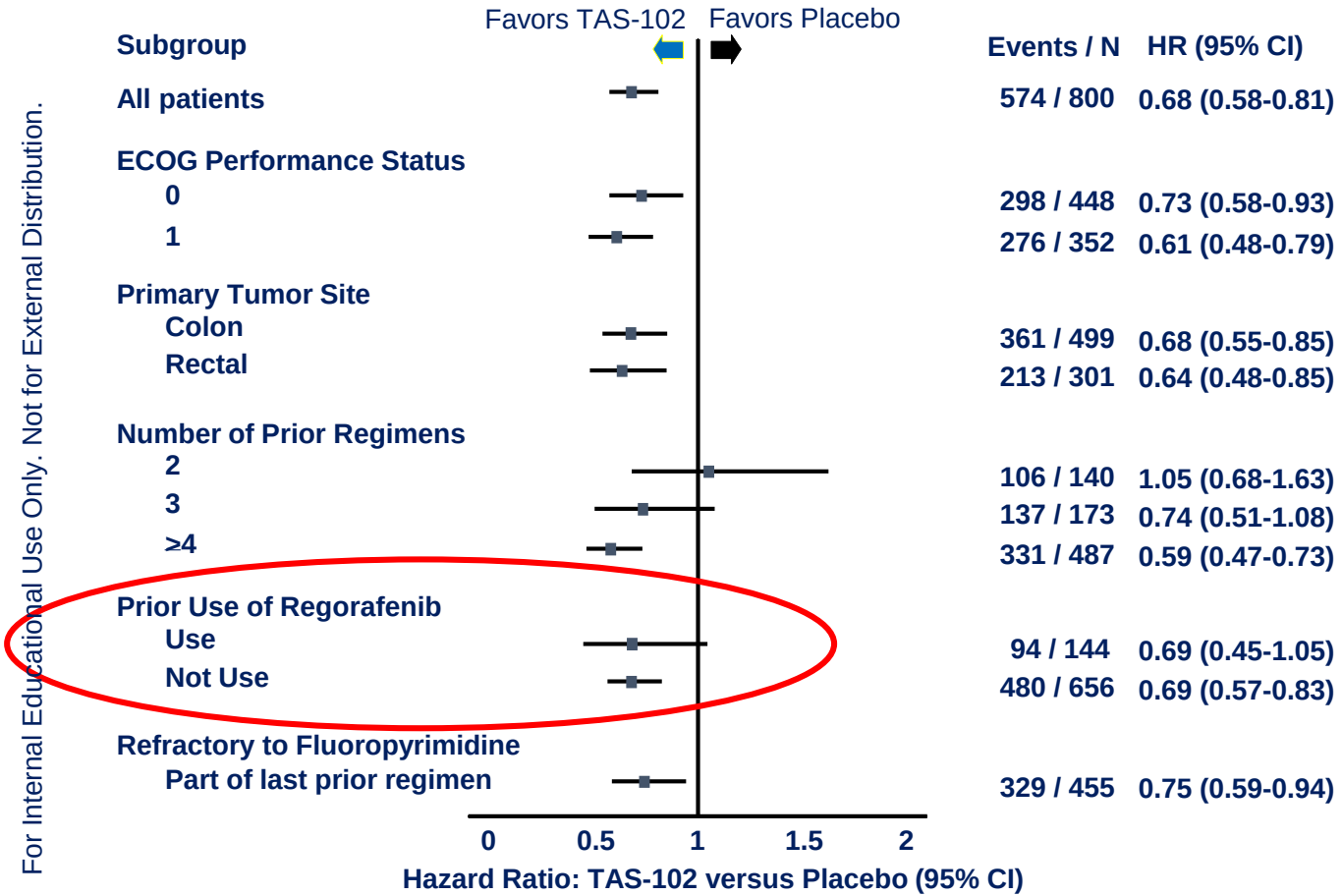
	TAS-102 N=534	Placebo N=266
Events # (%)	364 (68)	210 (79)
HR (95% CI)	0.68 (0.58-0.81)	
	Stratified Log-rank test	p<0.0001
Median OS, months	7.1	5.3
Median follow-up: 8.4 months		
Alive at, %		
6 months	58	44
12 months	27	18

N at Risk:

TAS-102	534	459	294	137	64	23	7
Placebo	266	198	107	47	24	9	3

Mayer et al., NEJM 2015

RECOURSE: OS Subgroup Analyses



Mayer R and Van Cutsem E, et al. *N Engl J Med.* 2015;372:1909-1919.

Why Regorafenib before TAS-102?

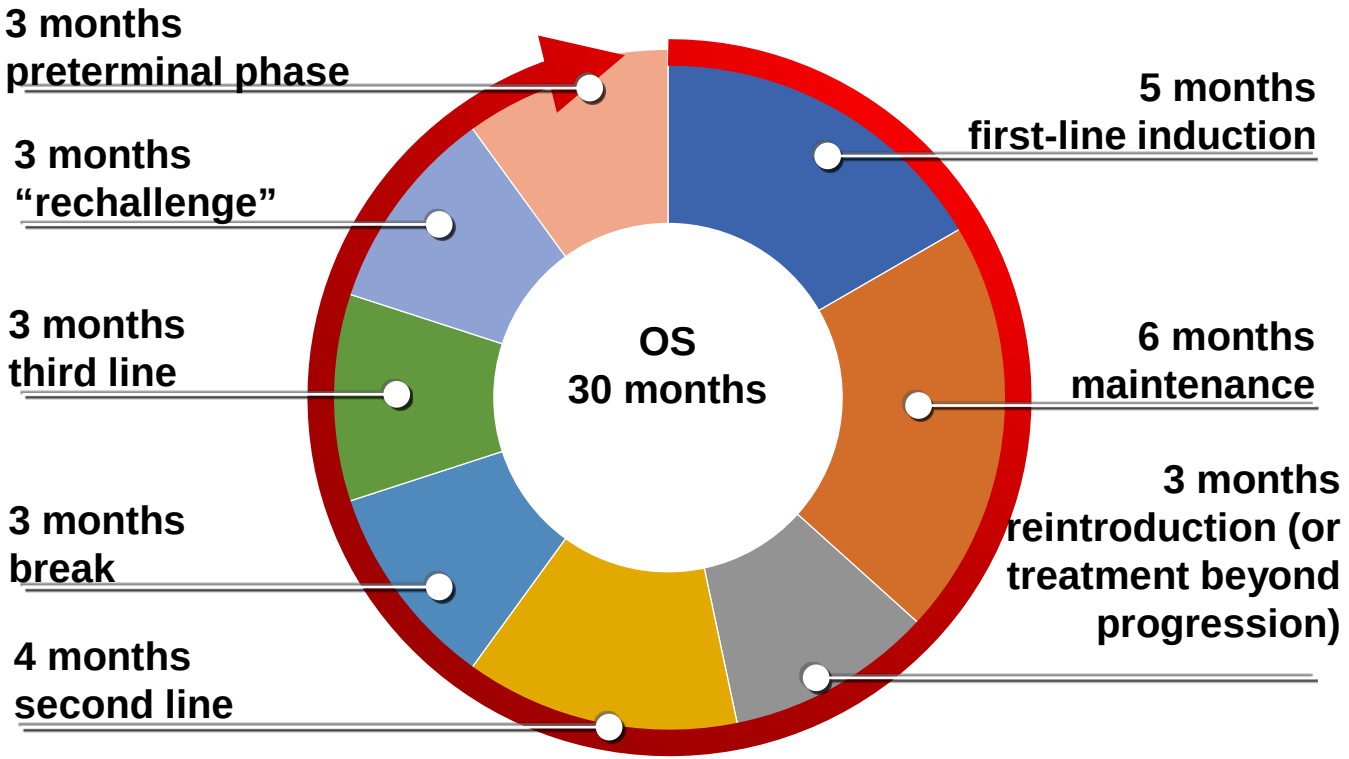
- **Patients benefit from access to all active agents, i.e. Regorafenib AND TAS-102**
- **Regorafenib appears to provide more benefit in less pretreated patients**
- **Regorafenib should not be used in PS2+ patients**
  - Do not let PS deteriorate before Regorafenib
- **Side-effects can be managed**
- **Cytotoxic therapy (e.g. TAS-102) can be active after Regorafenib**
- **We have data on TAS-102 after Regorafenib**

Riechelmann R, Grothey A. Lancet Oncol. 2015

Conclusions

- **Survival of patients with mCRC has significantly improved in the last decade**
  - Survival gains are not driven by advances in first-line therapy, but by incremental additions of effects of subsequent treatment lines
- **In spite of advances in molecular profiling, sidedness is currently an independent prognostic (and for EGFR mAbs, predictive) factor in mCRC**
- **Subgroups of patients are being identified which warrant a specific treatment intervention**
- **Regorafenib and TAS-102 are later-line treatment options**

2018: A classical case of mCRC



Courtesy: Alberto Sobrero