Colorectal Cancer: Novel Insights

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The Medical Educator Consortium

Learning Objectives

- Know the current trend for treatment of advanced colorectal cancer
- Know the current status of personalized medicine in advanced CRC
- Know the differences between left vs right sided colon cancer

Impact of CRC

- **CRC US statistics:**
  - 3rd highest incidence rate (~135,000/yr)
  - 2nd highest mortality rate (~49,000/yr)
- **CRC Global statistics:**
  - 3rd highest incidence rate (~ 1.2million/yr)
  - 4th highest mortality rate (~608,000/yr)

- ***The burden of disease is clearly evident…***

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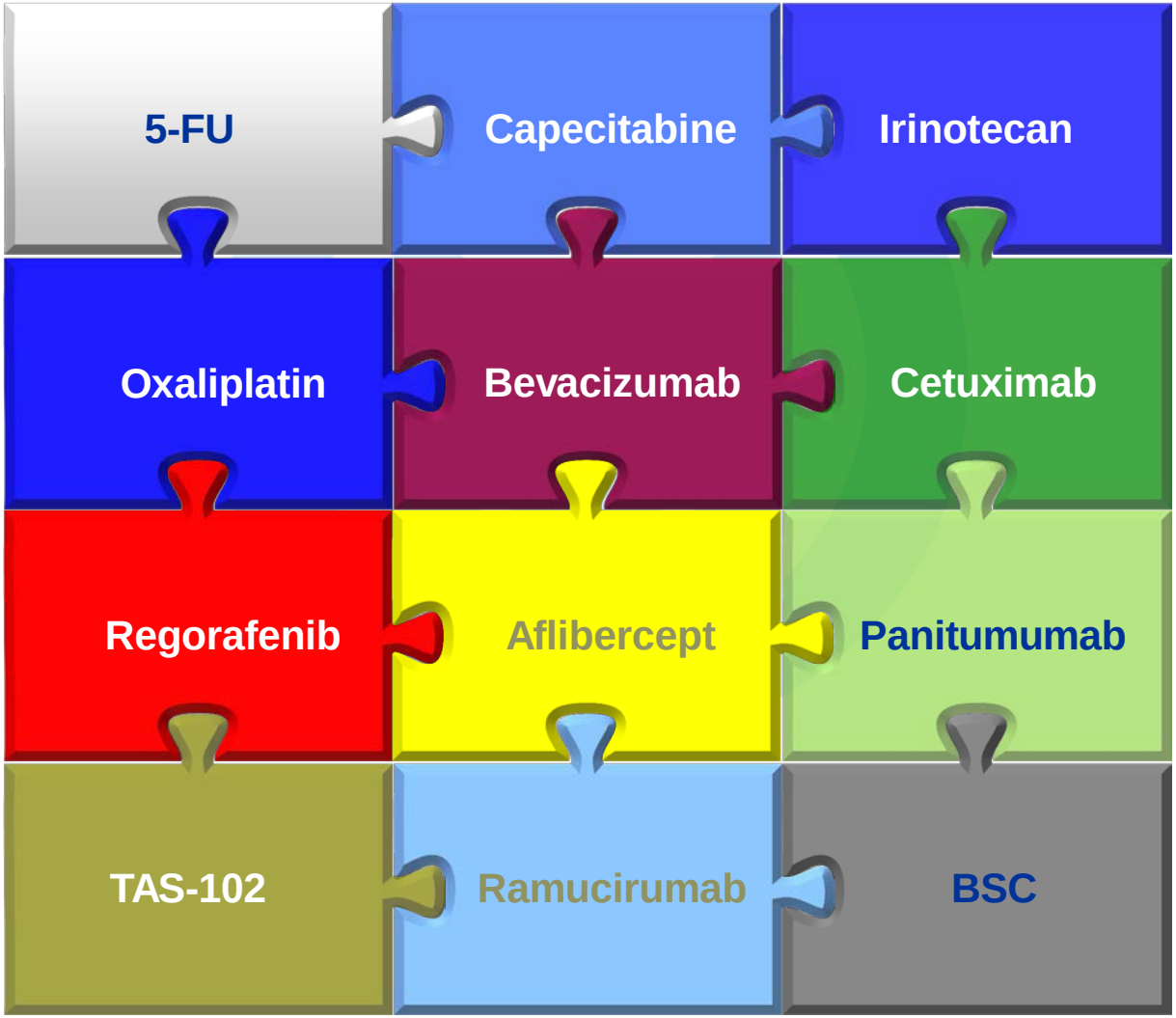
A High Number of Agents Is Currently Available for the Treatment of mCRC



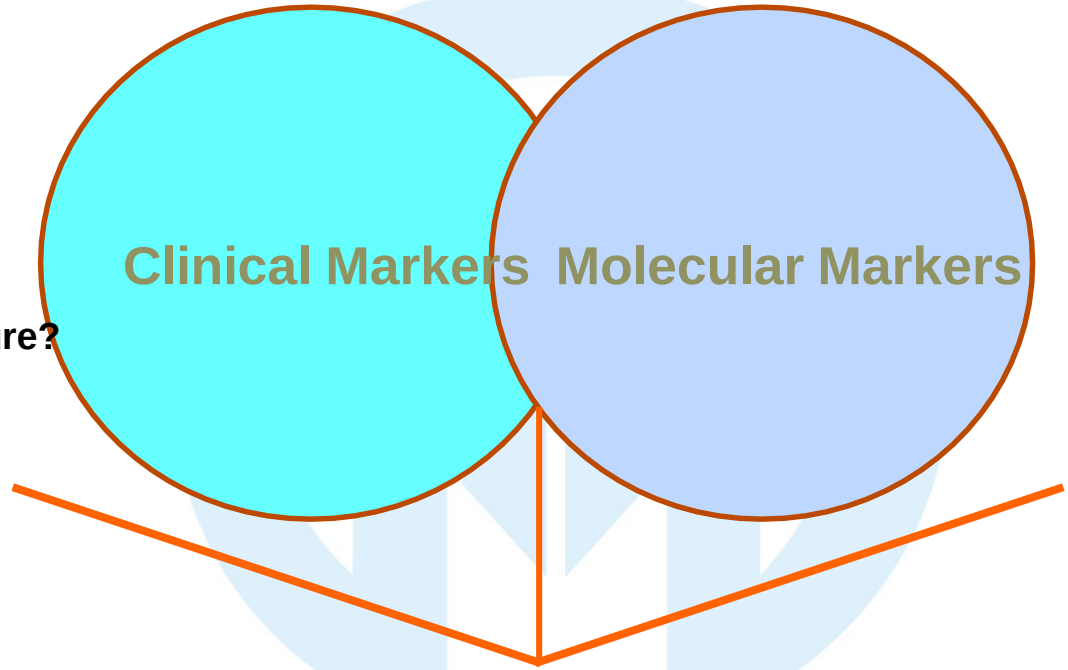
Landscape in mCRC

- Bevacizumab and EGFR mAbs competing for first-line patients in KRAS wt CRC
- Bevacizumab, *ramucirumab* and Aflibercept competing for second-line patients with each other, and with EGFR mAbs in KRAS wt CRC
- Best sequence of therapies (VEGFi vs EGFRi) still to be established
- Regorafenib and TAS 102 as salvage therapy option
- Immunotherapy for pts with MMR deficient/MSI-H tumor

Tools for Treatment Selection

Age
PS
Comorbidities
Tumor burden
- **Potential for cure?**
- **Symptoms?**

Tumor location



Histologic grade
CEA
KRAS
NRAS
BRAF
MSI/MMR

Patient characteristics

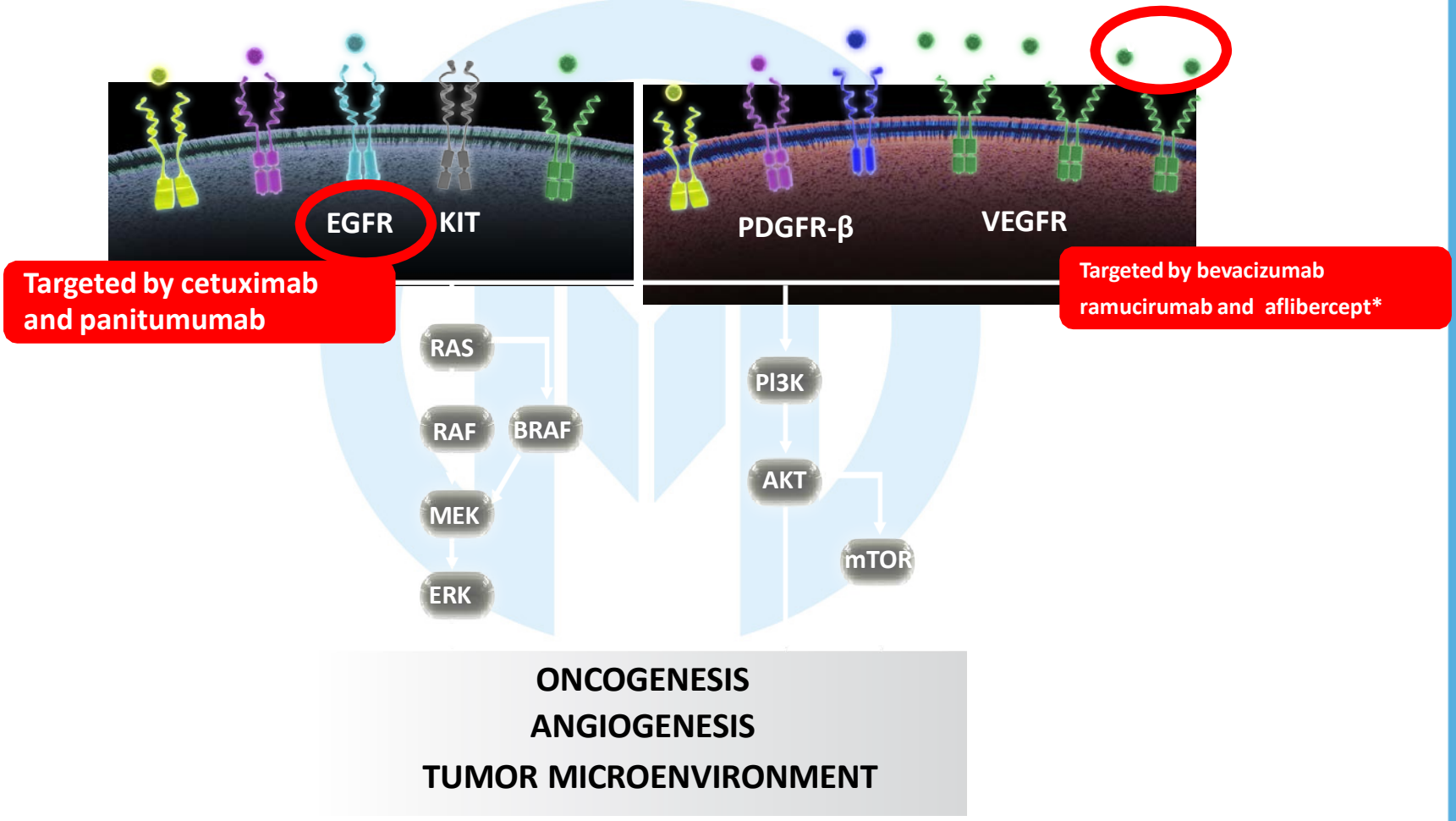
+

Tumor characteristics

Questions

- How can biologics be used to their full potential?
  - Prognostic markers -Biomarker that correlates with clinical outcome ***regardless of therapy***
  - Predictive markers-Biomarker that is associated with the likelihood of ***response to therapy***
- Can a patient population be identified which would benefit most from one specific treatment strategy?

Overview of EGFR and VEGFR Growth Signaling Pathways



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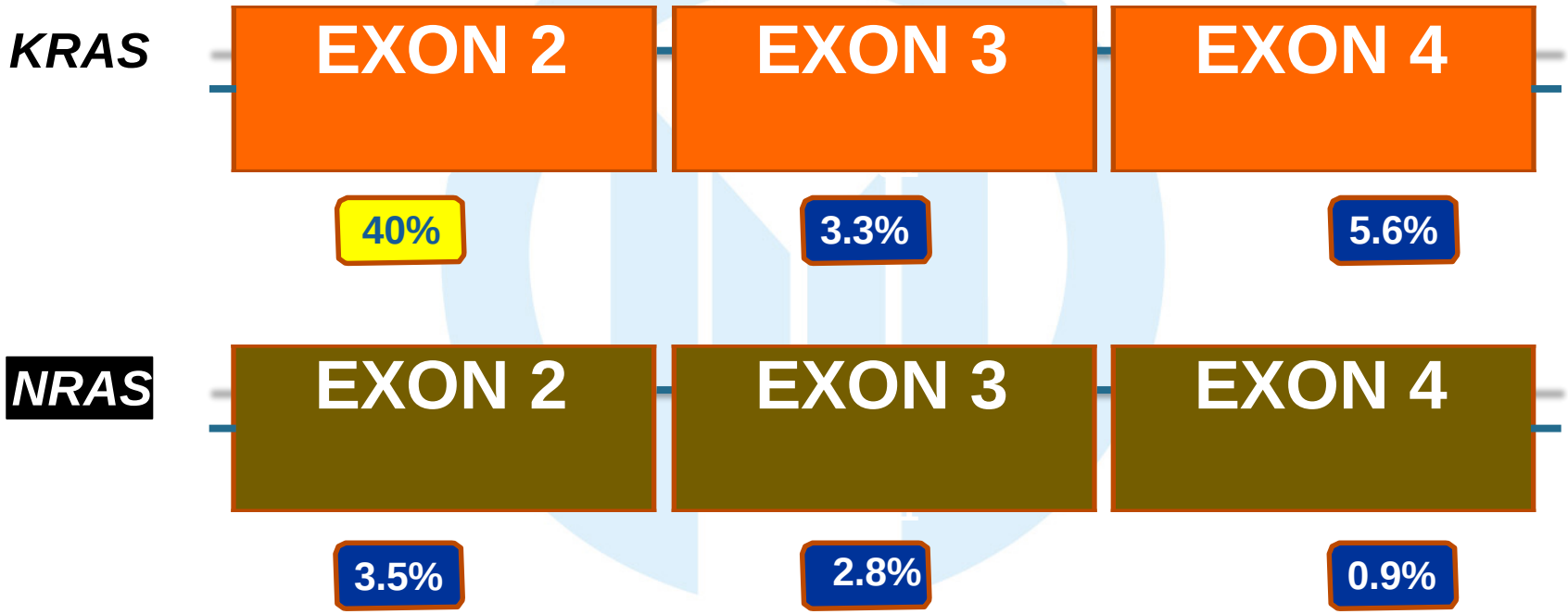
Biomarkers for anti- VEGF Drugs

Spectrum of ras mutations



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Updated Analysis of PRIME study

RAS and BRAF Status

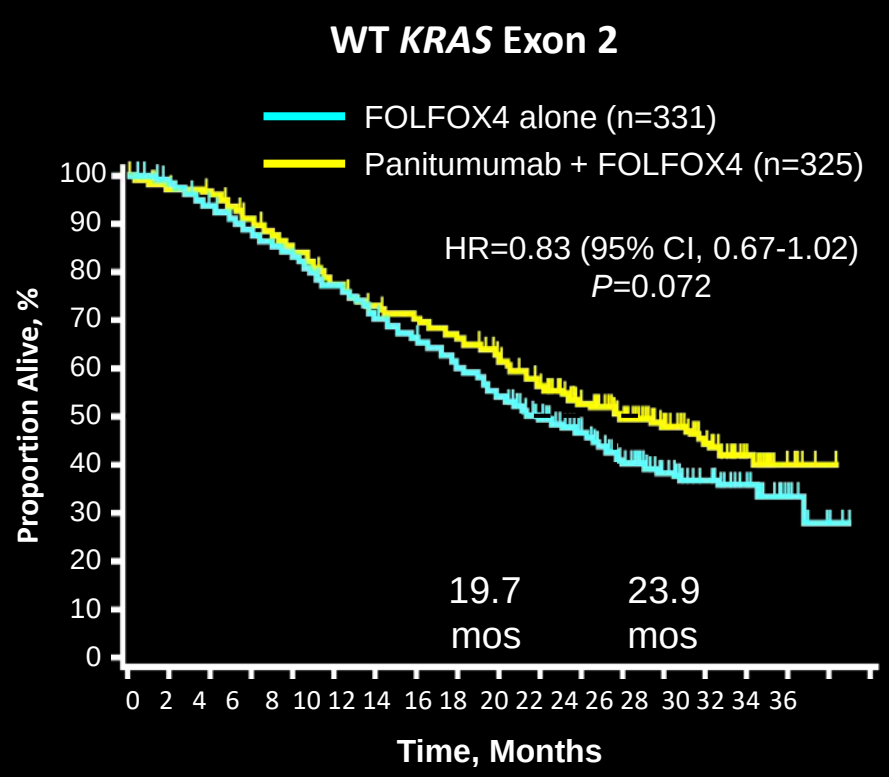
	Panitumumab + FOLFOX4	FOLFOX4 Alone	Total
KRAS exon 2 (codons 12/13)			
Wild-type	325	331	656
Mutant	221	219	440
Wild-type *KRAS* exon 2 tumors tested for *RAS* and *BRAF*	N = 320	N = 321	N = 641
Wild-type *KRAS* exon 2/mutant other *RAS* – n (%)	51 (16)	57 (18)	108 (17)
KRAS exon 3 (codon 61) – n (%)			
Wild-type	308 (96)	306 (95)	614 (96)
Mutant	10 (3)	14 (4)	24 (4)
Failure	2 (1)	1 (0)	3 (0)
KRAS exon 4 (codons 117/146) – n (%)			
Wild-type	288 (90)	296 (92)	584 (91)
Mutant	21 (7)	15 (5)	36 (6)
Failure	11 (3)	10 (3)	21 (3)
NRAS exon 2 (codons 12/13) – n (%)			
Wild-type	308 (96)	307 (96)	615 (96)
Mutant	8 (3)	14 (4)	22 (3)
Failure	4 (1)	0 (0)	4 (1)
NRAS exon 3 (codon 61) – n (%)			
Wild-type	305 (95)	305 (95)	610 (95)
Mutant	12 (4)	14 (4)	26 (4)
Failure	3 (1)	2 (1)	5 (1)
NRAS exon 4 (codons 117/146) – n (%)			
Wild-type	316 (99)	313 (98)	629 (98)
Mutant	0 (0)	0 (0)	0 (0)
Failure	4 (1)	8 (2)	12 (2)
BRAF exon 15 (codon 600) – n (%)			
Wild-type	286 (89)	280 (87)	566 (88)
Mutant	24 (8)	29 (9)	53 (8)
Failure	10 (3)	12 (4)	22 (3)

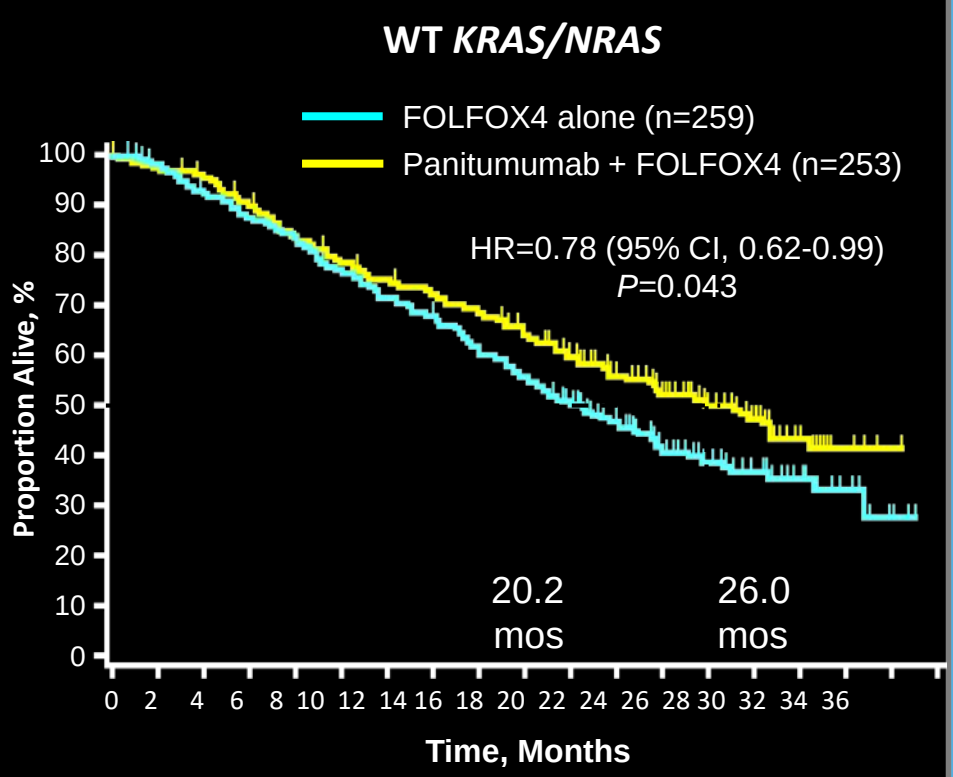
KRAS exon 2 codon 12/13	**40%**
KRAS exon 3 codon 61	4%
KRAS exon 4 codon 117/146	6%
NRAS exon 2 codon 12/13	3%
NRAS exon 3 codon 61	4%
BRAF exon 15 codon 600	8%

17%

Oliner et al., ASCO 2013

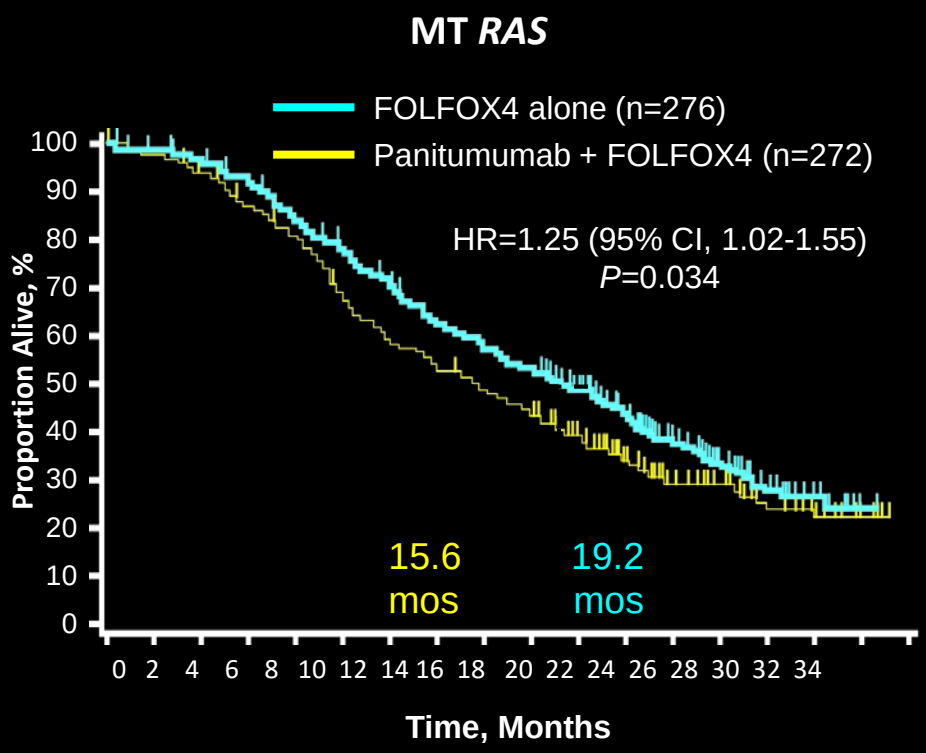
PRIME Biomarker Analysis: OS in Patients With WT *KRAS* Exon 2 and WT *RAS* mCRC

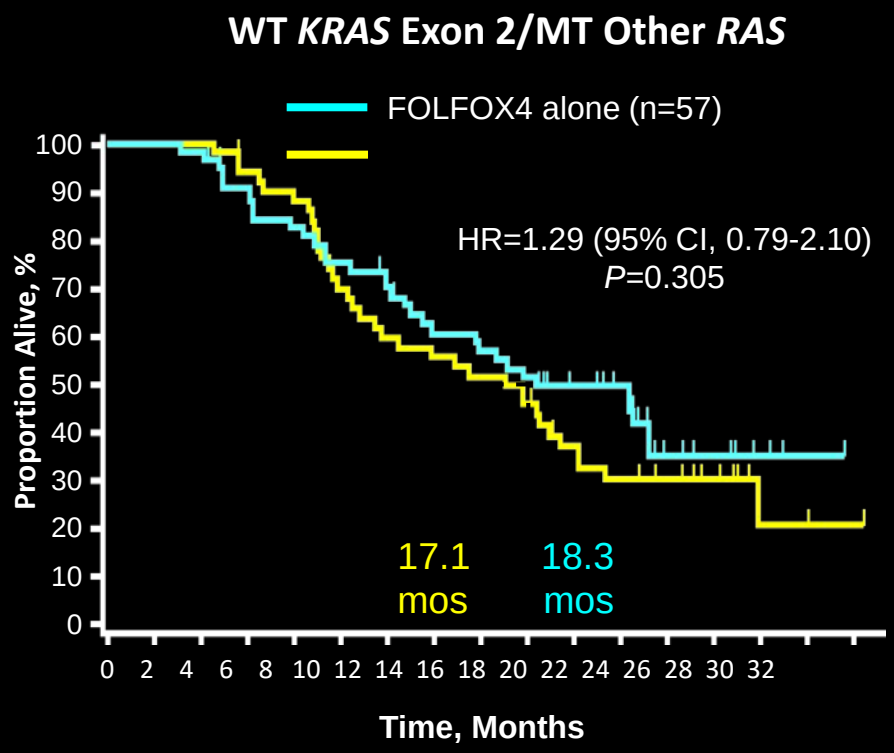




Oliner J, et al. ASCO. 2013 (abstr 3511).

PRIME Biomarker Analysis: OS in Patients With MT *RAS* or WT *KRAS* Exon 2/MT Other *RAS*





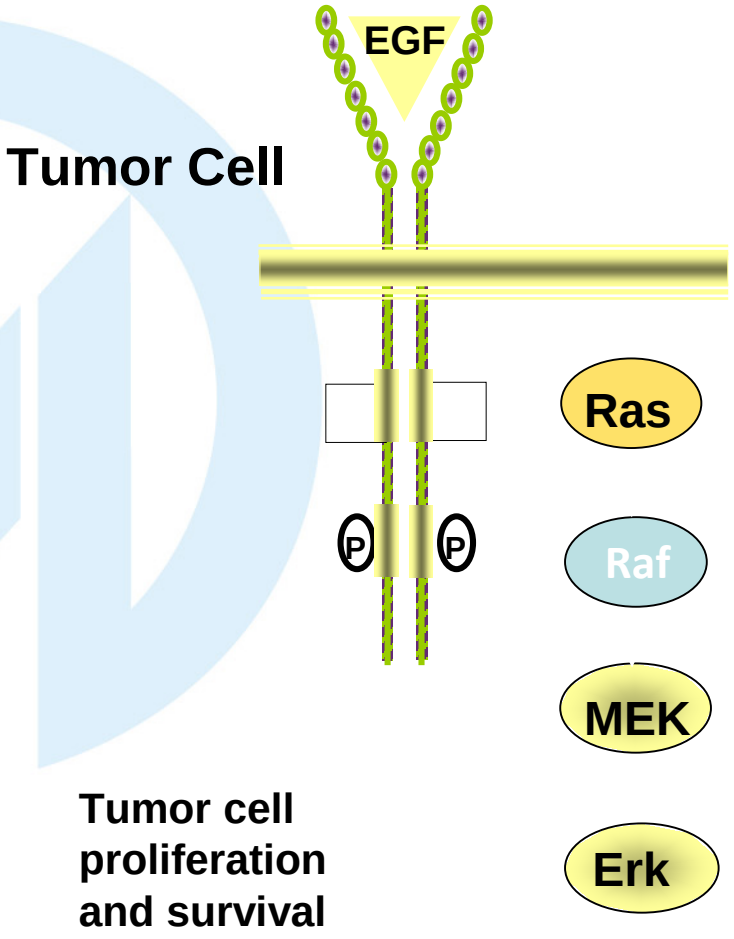
Oliner J, et al. ASCO. 2013 (abstr 3511).

Take home point

- testing for these additional codons could help screen 20% more patients with mCRC for treatment with EGFR inhibitors
- This method could help to more accurately select patients who will benefit from EGFR inhibitors.
- NCCN now recommends testing for all RAS mutations

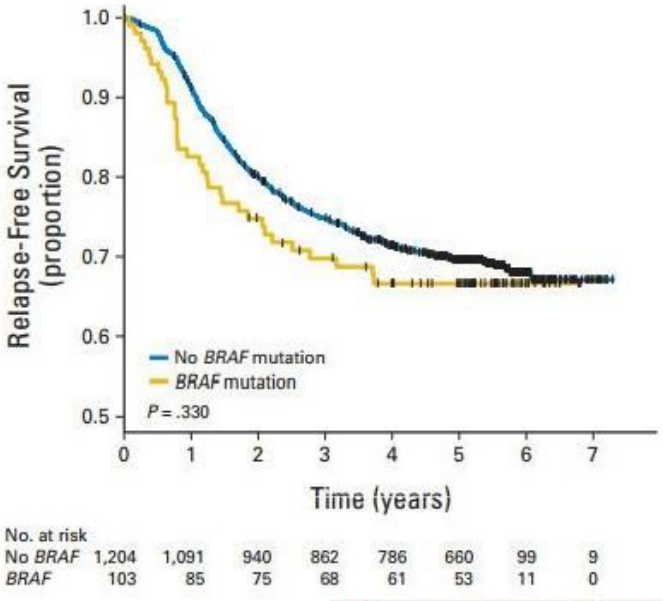
BRAF Mutations in CRC

- 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



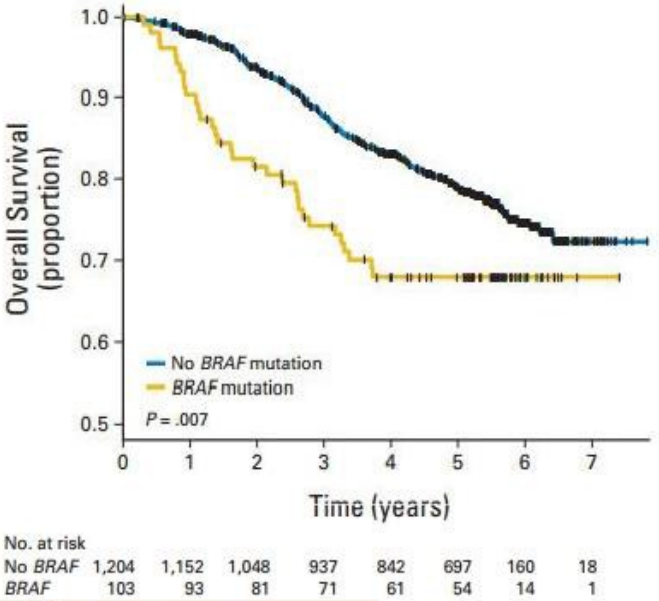
Yarden. *Nat Rev Mol Cell Biol*. 2001;2:127; Di Nicolantonio. *J Clin Oncol*. 2008;26:5705; Artale. *J Clin Oncol*. 2008;26:4217.

The Prognosis of Patients With *BRAF* V600E Mutations is Poor



No. at risk

No *BRAF*	1,204	1,091	940	862	786	660	99	9
BRAF	103	85	75	68	61	53	11	0



No. at risk

No *BRAF*	1,204	1,152	1,048	937	842	697	160	18
BRAF	103	93	81	71	61	54	14	1

Table 1. Association of the Mutation Status of the *BRAF* Oncogene with Progression-free Survival, Overall Survival, and Response Rate.*

Variable	Wild-Type *BRAF*	Mutated *BRAF*	P Value
No. of patients			
CB group	243	17	
CBC group	231	28	
Median progression-free survival (mo)			
CB group	12.2	5.9	0.003
CBC group	10.4	6.6	0.010
Median overall survival (mo)			
CB group	24.6	15.0	0.002
CBC group	21.5	15.2	0.001
Response rate (%)			
CB group	50	35	0.32
CBC group	48	39	0.43

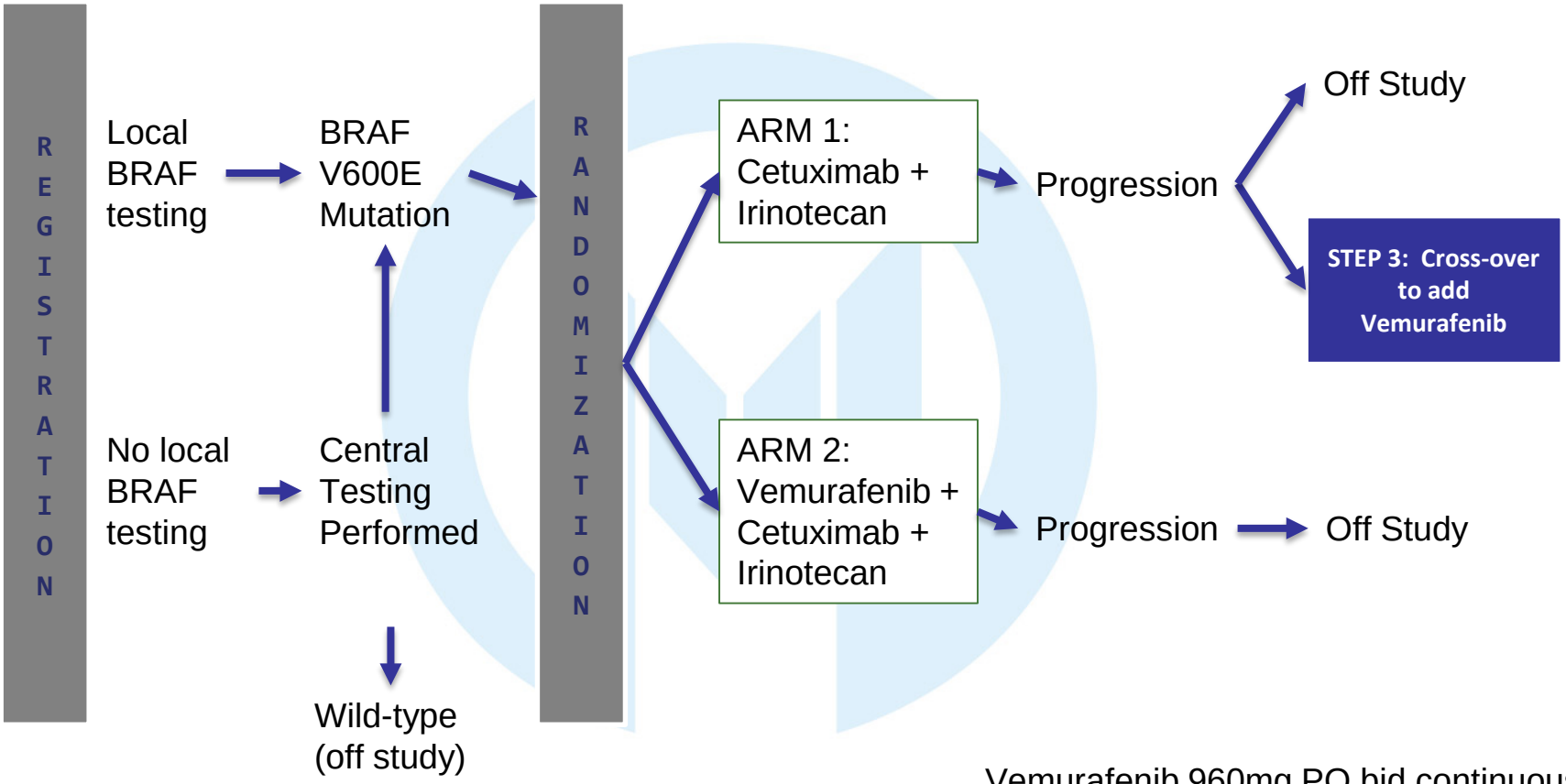
Roth AD, et al. *J Clin Oncol.* 2010;28(3):466-474. Tol J, et al. *N Engl J Med.* 2009;361(1):98-99.

Randomized trial of irinotecan and cetuximab with or without vemurafenib in *BRAF*-mutant metastatic colorectal cancer (SWOG S1406)

Scott Kopetz,[1] Shannon McDonough,[2] Heinz-Josef Lenz,[3] Anthony Magliocco,[4] Chloe Atreya,[5] Luis A. Diaz Jr.,[6] Carmen Allegra,[7] Kanwal Raghav,[1] Van Morris,[1] Stephen Wang,[8] Christopher Lieu,[9] Katherine A. Guthrie,[2] Howard S. Hochster[10]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Fred Hutchinson Cancer Research Center, Seattle, WA; [3]USC Norris Comprehensive Cancer Center, Los Angeles, CA; [4]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; [5]University of California, San Francisco, San Francisco, CA; [6]Memorial Sloan Kettering Cancer Center, NewYork, NY; [7]University of Florida, Gainesville, FL; [8]Kaiser Permanente, Sacramento, CA; [9]University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO; [10]Yale Cancer Center, New Haven, CT

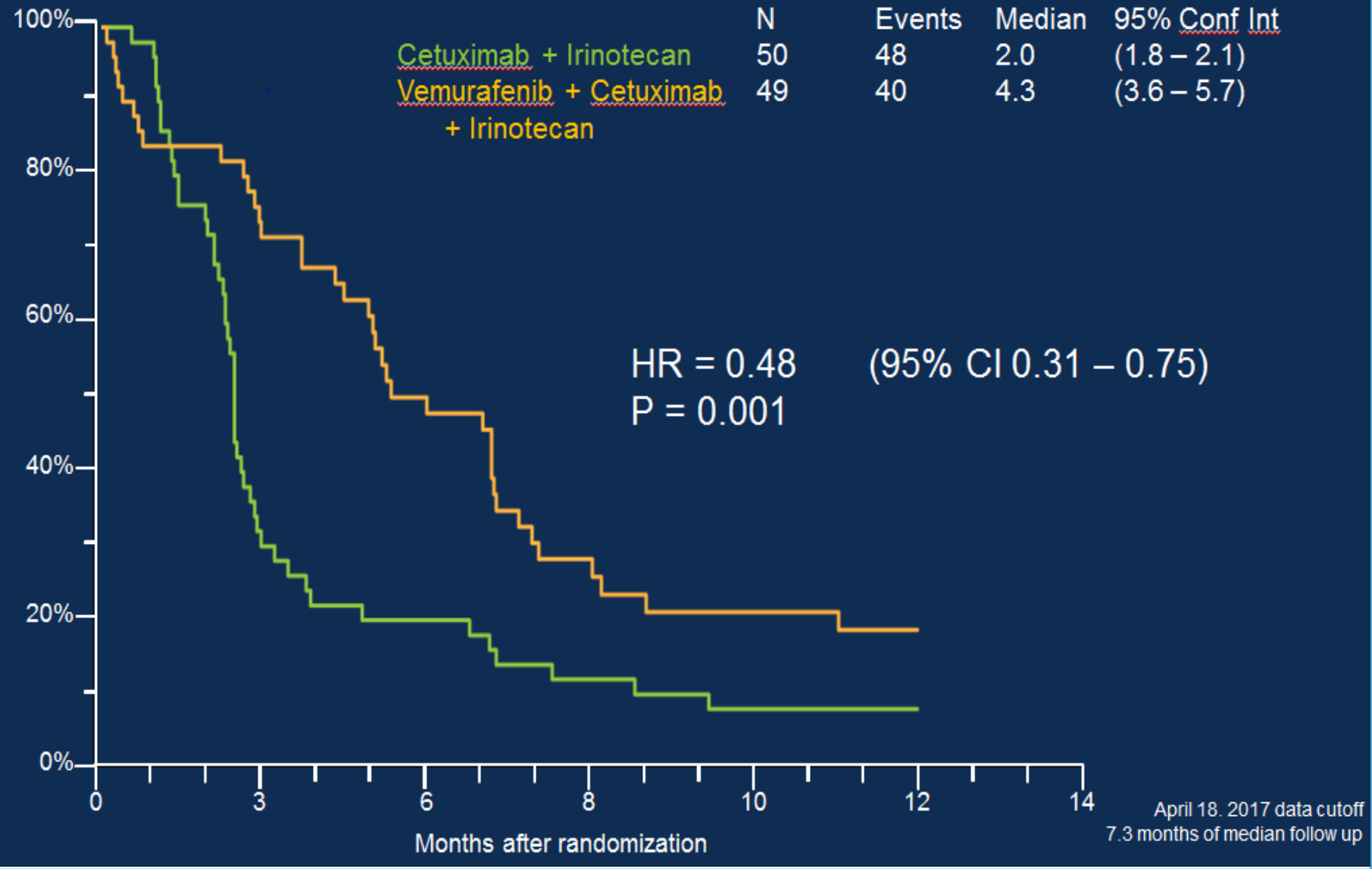
Study Design



Vemurafenib 960mg PO bid continuous
Cetuximab 500mg/m2 IV q2weeks
Irinotecan 180mg/m2 IV q2weeks

Presented by: Scott Kopetz, MD, PhD

Primary Endpoint: Progression-free survival



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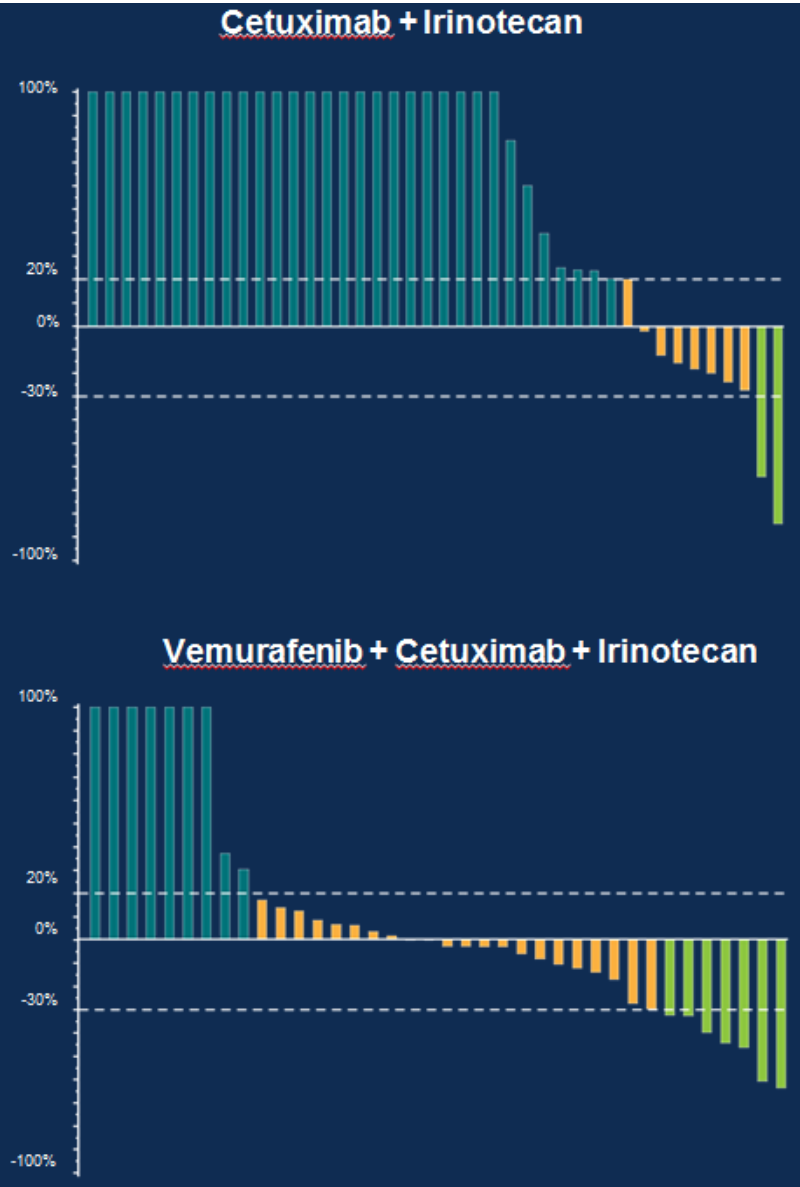
Response Rate

	Cetuximab + Irinotecan (n=47)[a]	Vemurafenib + Cetuximab + Irinotecan (n=44)[a]	P-value[c]
Partial response[b]	4%	16%	P=0.001
Stable disease	17%	50%	
Progression[c]	66%	18%	
Disease Control Rate	**22%**	**67%**	

[a]93 patients had measurable disease; [b]Confirmed and unconfirmed; PR for patients previously treated with irinotecan was 0% and 18%, respectively; [c]Including symptomatic deterioration; [c] Chi-squared



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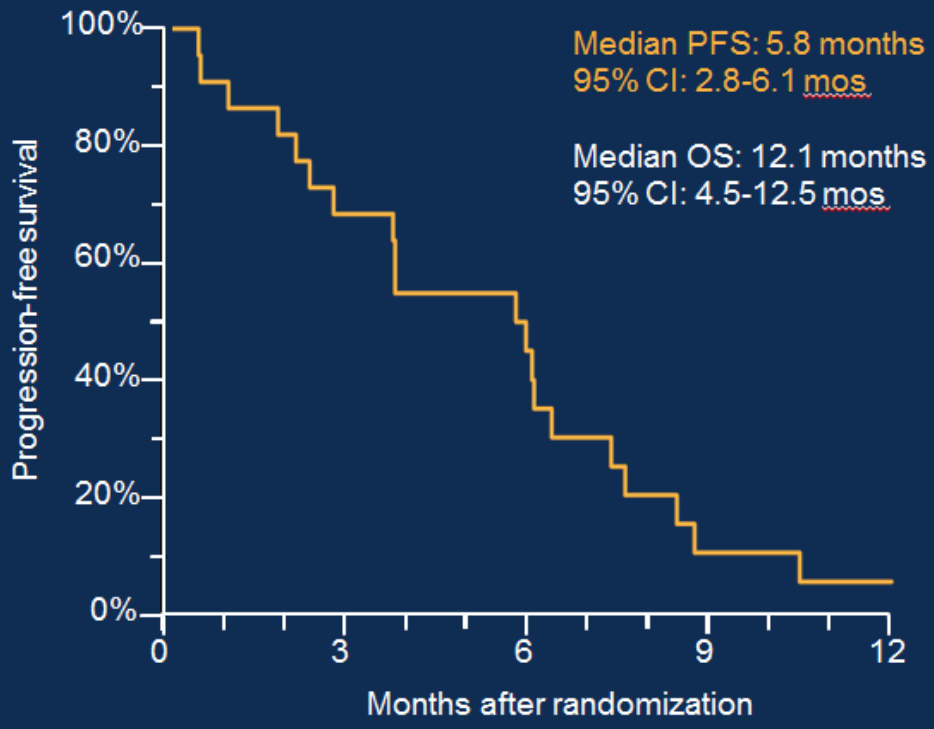
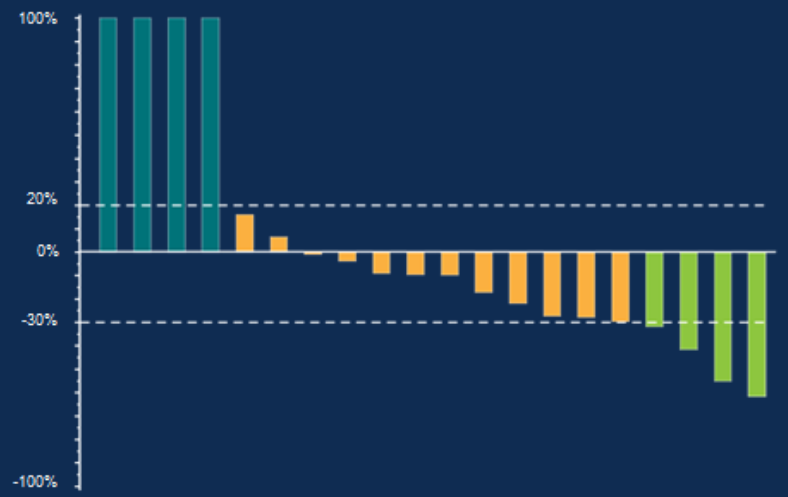
Crossover to VIC after progression

- Patients with radiographically documented progression on IC crossed over to receive VIC
- 48% of patients treated on IC arm crossed over





	Crossover (n=24)[a]
Partial response	17%
Stable disease	55%
Disease control rate	**72%**

[a]2 patients did not progress prior to crossover; 4 did not have measurable disease; these patients are excluded from response rates

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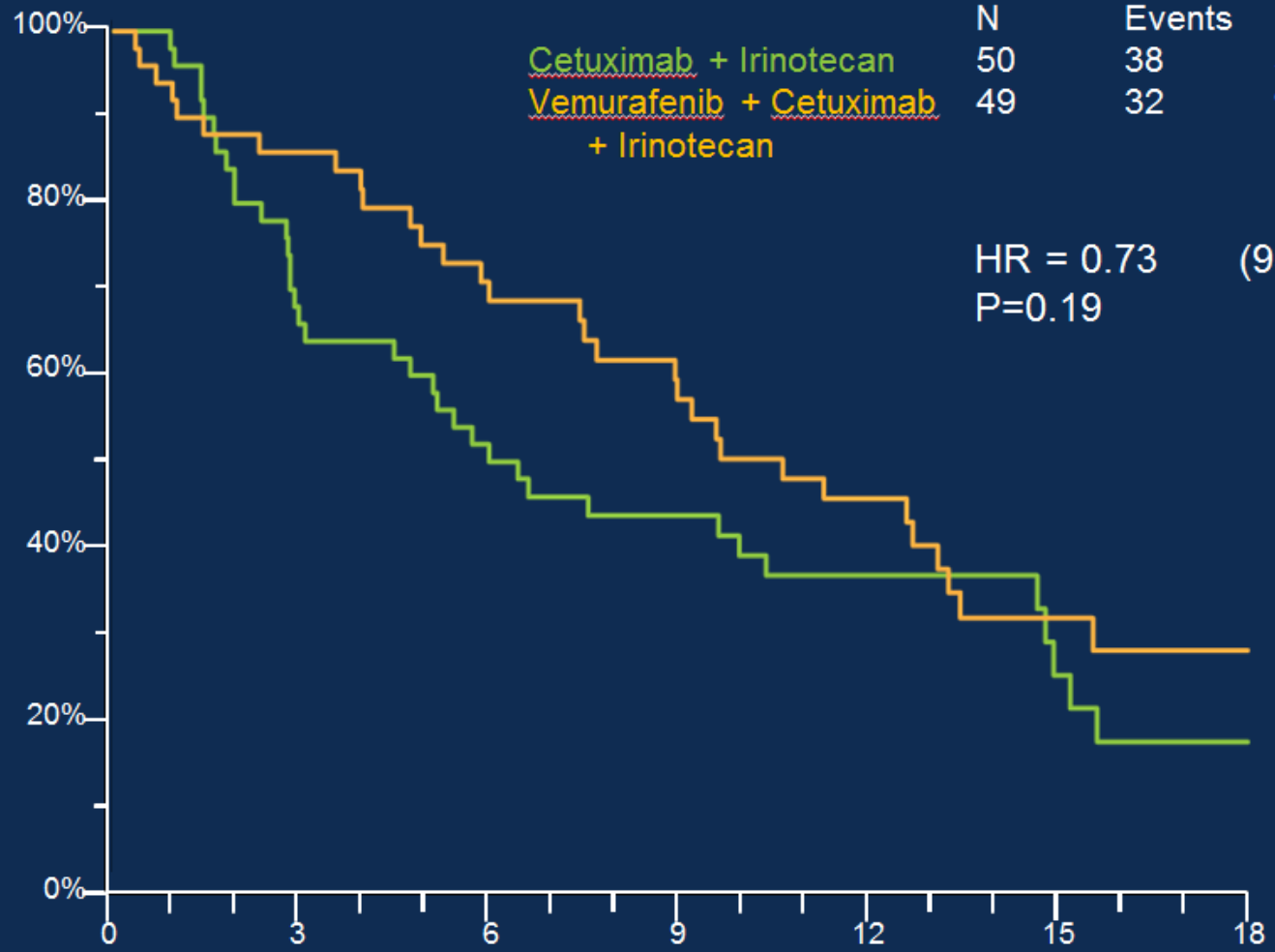
Secondary Endpoint: Overall Survival



	N	Events	Median	95% Conf Int
Cetuximab + Irinotecan	50	38	5.9	(3.0 – 9.9)
Vemurafenib + Cetuximab + Irinotecan	49	32	9.6	(7.5 – 13.1)

HR = 0.73 (95% CI 0.45 – 1.17)
P=0.19

April 18. 2017 data cutoff

Conclusions

- The combination of vemurafenib, cetuximab, and irinotecan (VIC) met its primary endpoint demonstrating improved progression-free survival in patients with $BRAF^{V600E}$ CRC
- Addition of Vemurafenib to IC showed activity even after progression on IC
- VIC represents a new treatment for metastatic $BRAF^{V600E}$ colorectal cancer

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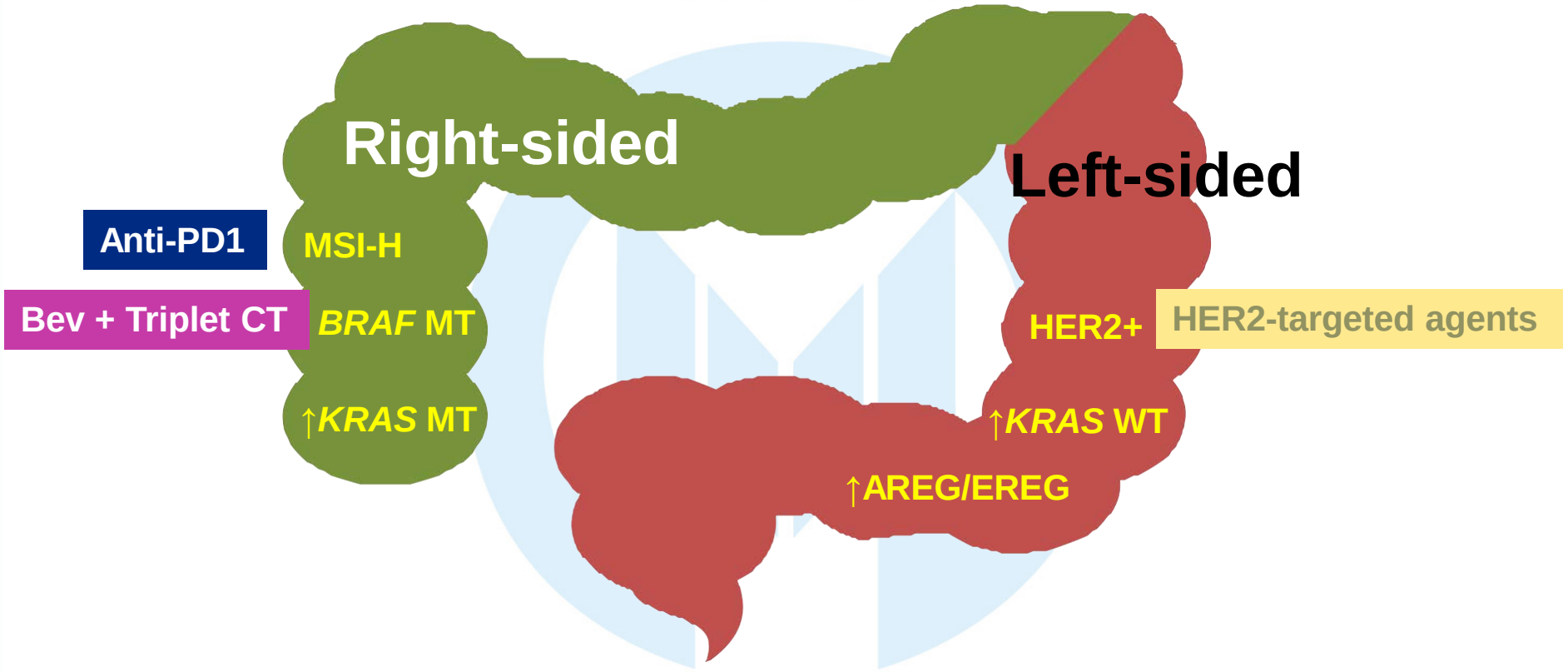
What is the impact of site of primary tumour?

Primary Tumor Location and Potential Treatments



: *KRAS* wt

1ST LINE
MET / ADVANCED
COLORECTAL

***KRAS* wt**
Codons 12 & 13

→

FOLFIRI
or
FOLFOX

MD choice

N = 1137

Chemo + Cetuximab
OS = 29.9 mos
PFS = 10.4 mos

: NO DIFFERENCE

Chemo + Bevacizumab
OS = 29.0 mos
PFS = 10.8 mos

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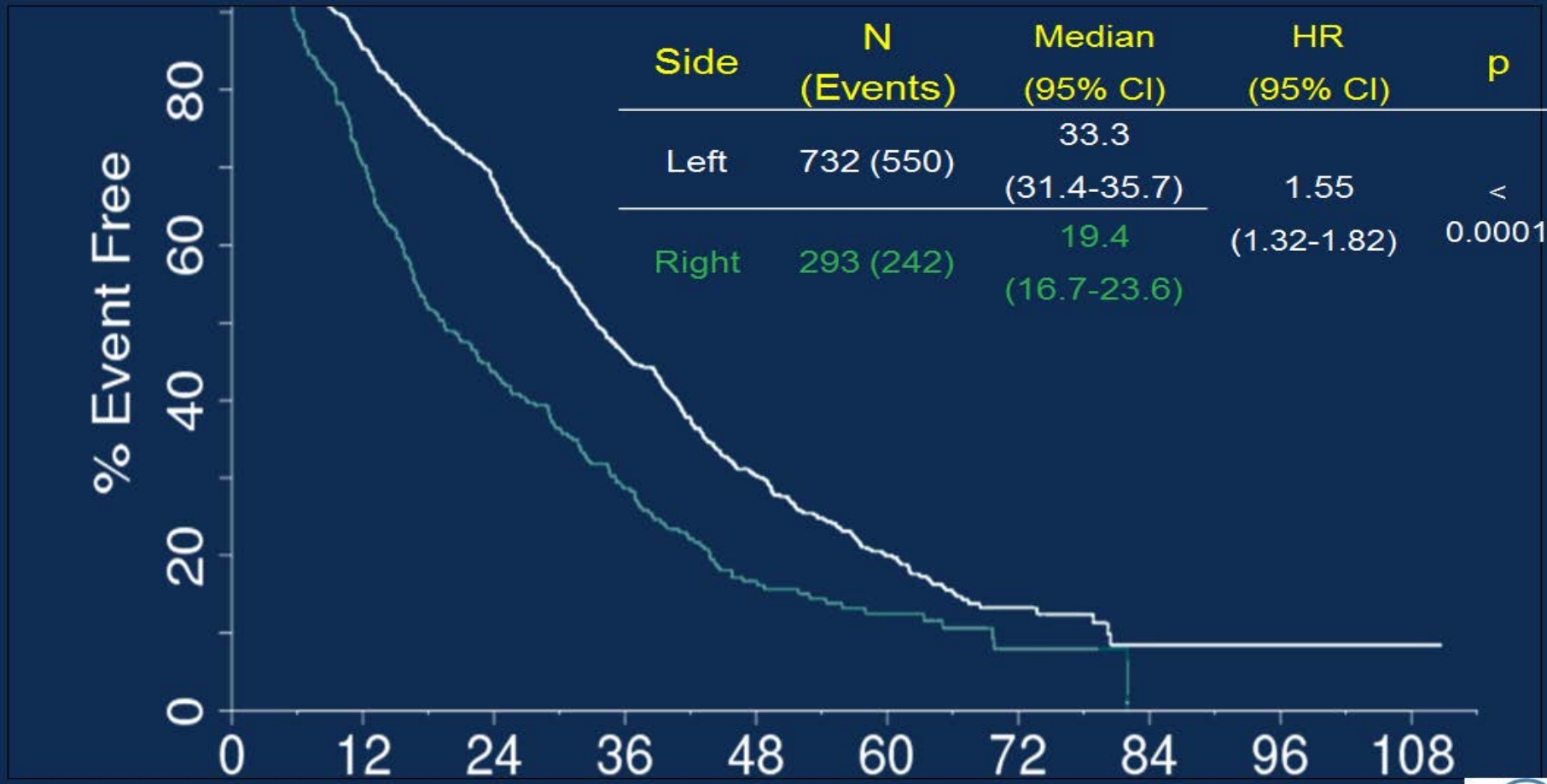
80405: (*KRAS* WT) Overall Survival by Sidedness

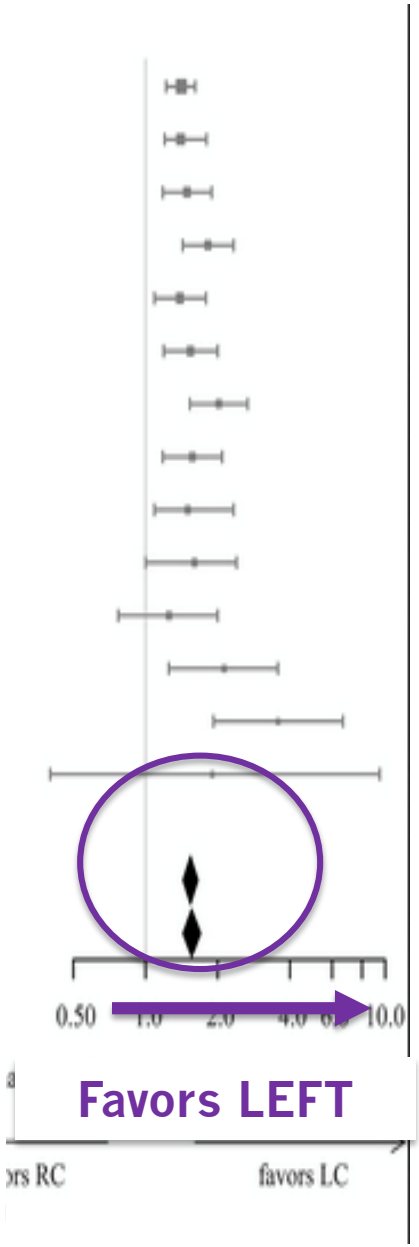


Side	N (Events)	Median (95% CI)	HR (95% CI)	p
Left	732 (550)	33.3 (31.4-35.7)	1.55 (1.32-1.82)	< 0.0001
Right	293 (242)	19.4 (16.7-23.6)		

Federally Funded Research

Meta-analysis: Sidedness in MCRC

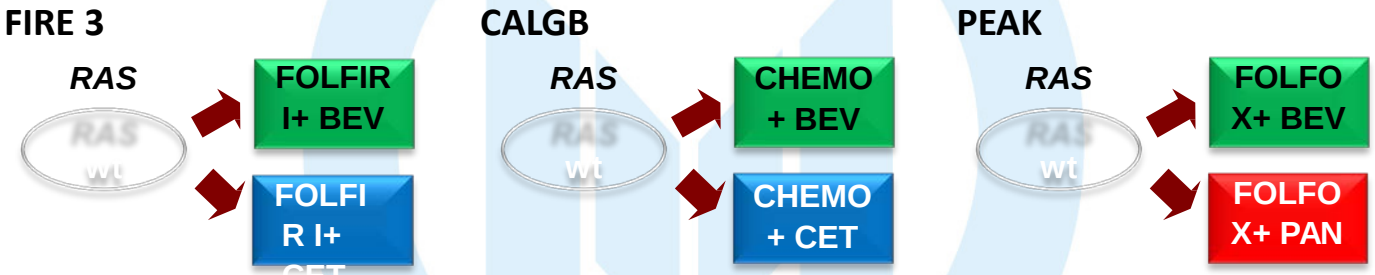
Study	n
NO16966	1268
FOCUS	1390
AGITG MAX	440
AVF2107g	559
CALGB80405	474
FIRE-1	423
FIRE-3	394
CRYSTAL	364
FIRE-2	95
PRIME	416
MAVERICC	376
PROVETTA	200
JACCRO-CC 05/06	110
PEAK	143



Holch et al, Eur J Cancer, 2017

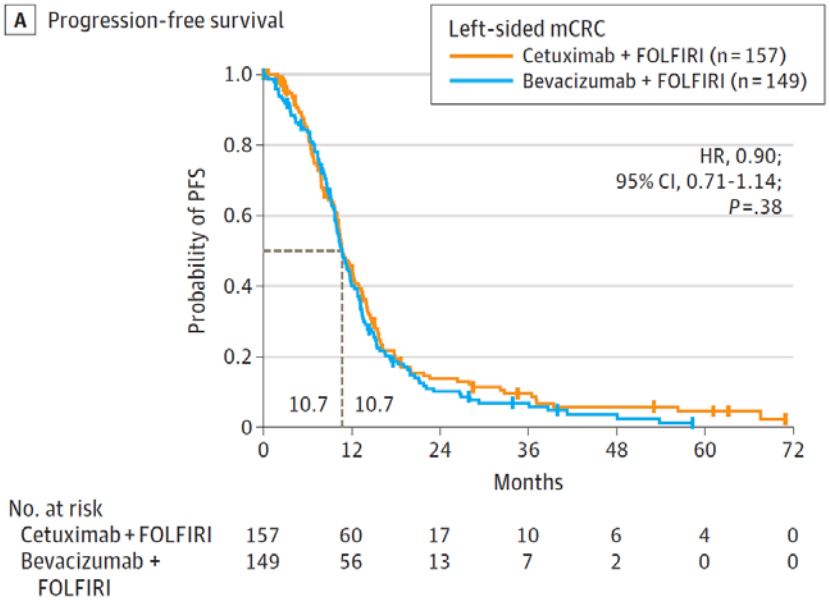
Predictive impact – bev versus anti-EGFRs

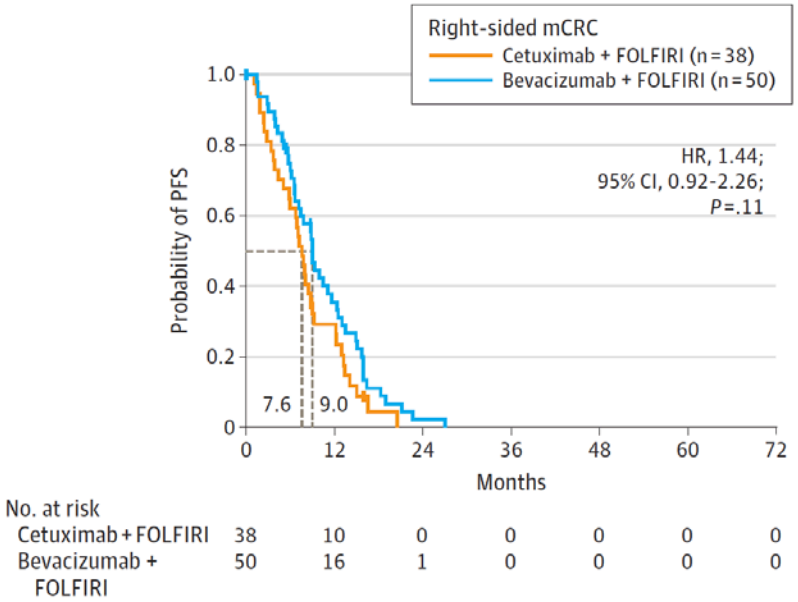
Chemo+anti-EGFR vs Chemo+Bev

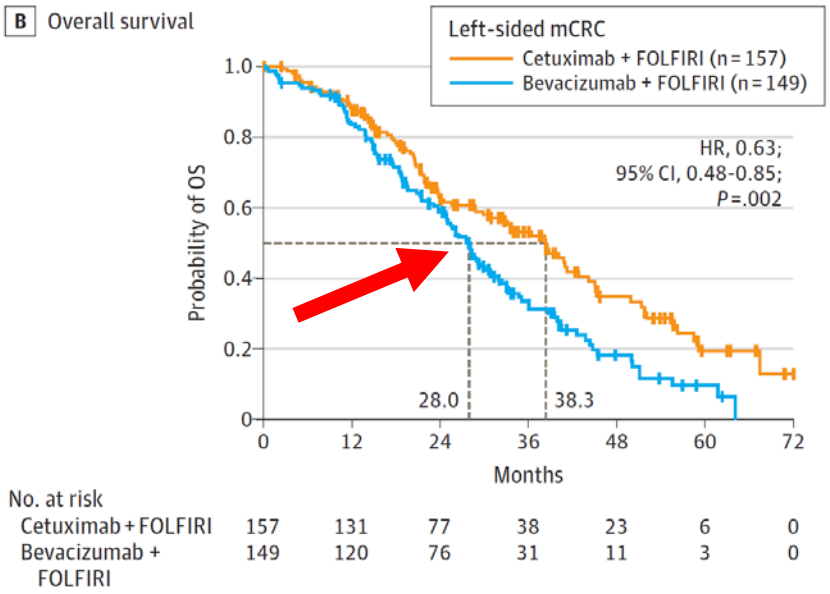


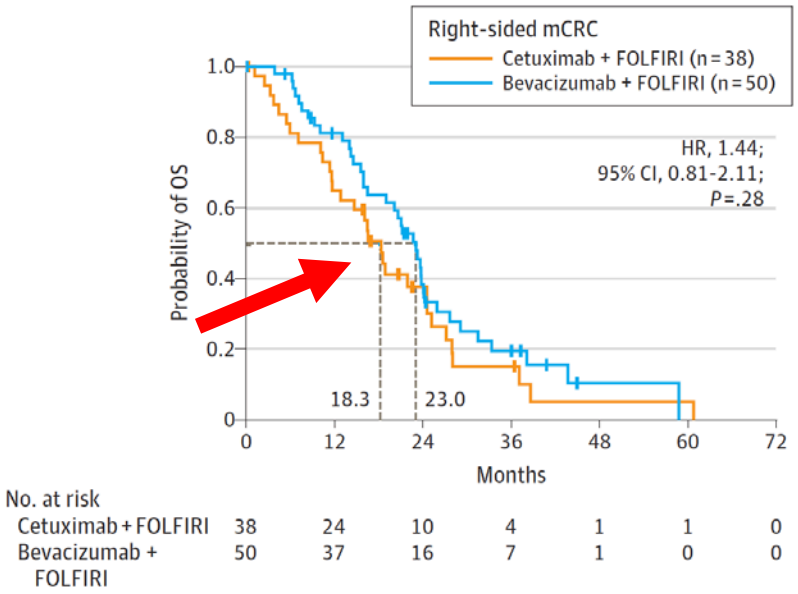
FIRE-3

Tejpar et al., JAMA Oncol 2016

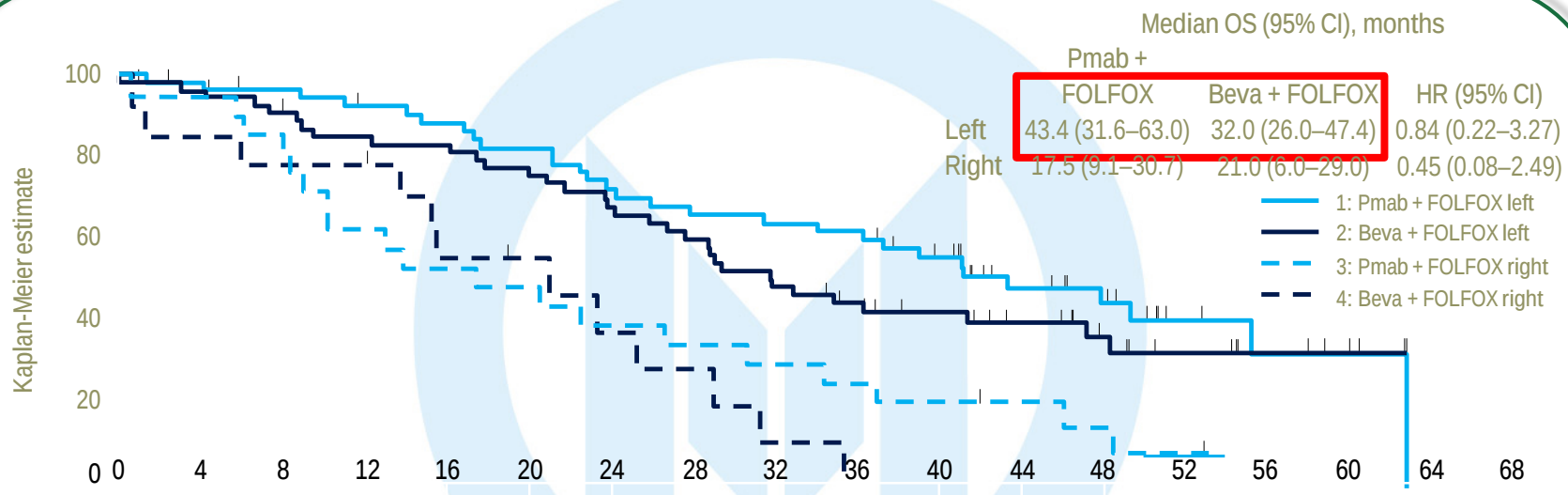








Right versus Left: PEAK – OS



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

Boeckx ESMO 2016; Peeters et al. Ann Oncol 2017. Apr 25. Epub ahead of print.

Right versus Left: CALGB80405 study - OS

31%

Lenz et al. ESMO Congress 2016.

Minimal difference between bev and cetux in left sided tumors

	Median OS (95% CI)	Log-rank	Adjusted HR
Population	L-sided R-sided	p-value	(95%, CI)
80405 (N = 728)	32.9 (30.7, 35.3) 19.6 (7.0, 23.6)	< 0.0001	1.39 (1.03, 1.88)
All *RAS* /*BRAF* wt (N = 225)			
BV (N = 91)	38.7 (34.3, 42.3) 34.4 (23.6, 82.0)	0.918	0.62 (0.32, 1.23)
Cet (N = 96)	40.3 (34.0, 48.3) 18.4 (14.2, 30.1)	0.003	1.68 (0.85, 3.34)
BRAF mut (N = 48)			
BV (N = 23)	12.0 (4.8, 14.5) 23.7 (7.9, 36.9)	0.035	
Cet (N = 16)	9.6 (8.6, NE) 5.8 (1.9, 11.7)	0.508	

Venook A, ASCO 2017; abstract 3503

Take Home Points

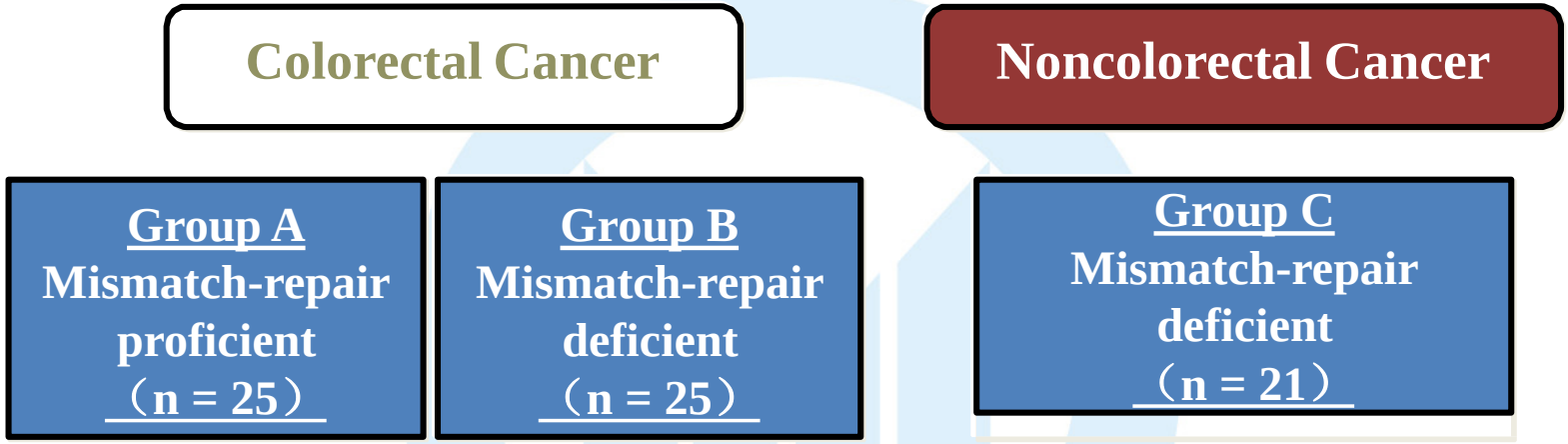
- Left sided primary colorectal cancers have better prognosis than right sided colon cancers
- Right sided colorectal cancers do not benefit from anti-EGFR therapy but do benefit from bevacizumab
- Left sided tumors benefit from both bevacizumab and anti-EGFR therapy

MSI-high CRC and Immune Checkpoint Blockade

Background

- In non selected colorectal cancer patients PD-1 blockade seems to be ineffective.
- Average tumor has dozens of somatic mutations.
- Mismatch repair deficient tumors harbor thousands of mutations
- Somatic mutations have the potential to generate neo-antigiens which can be recognized by immune system.

Clinical Trial Design: Basket Trial

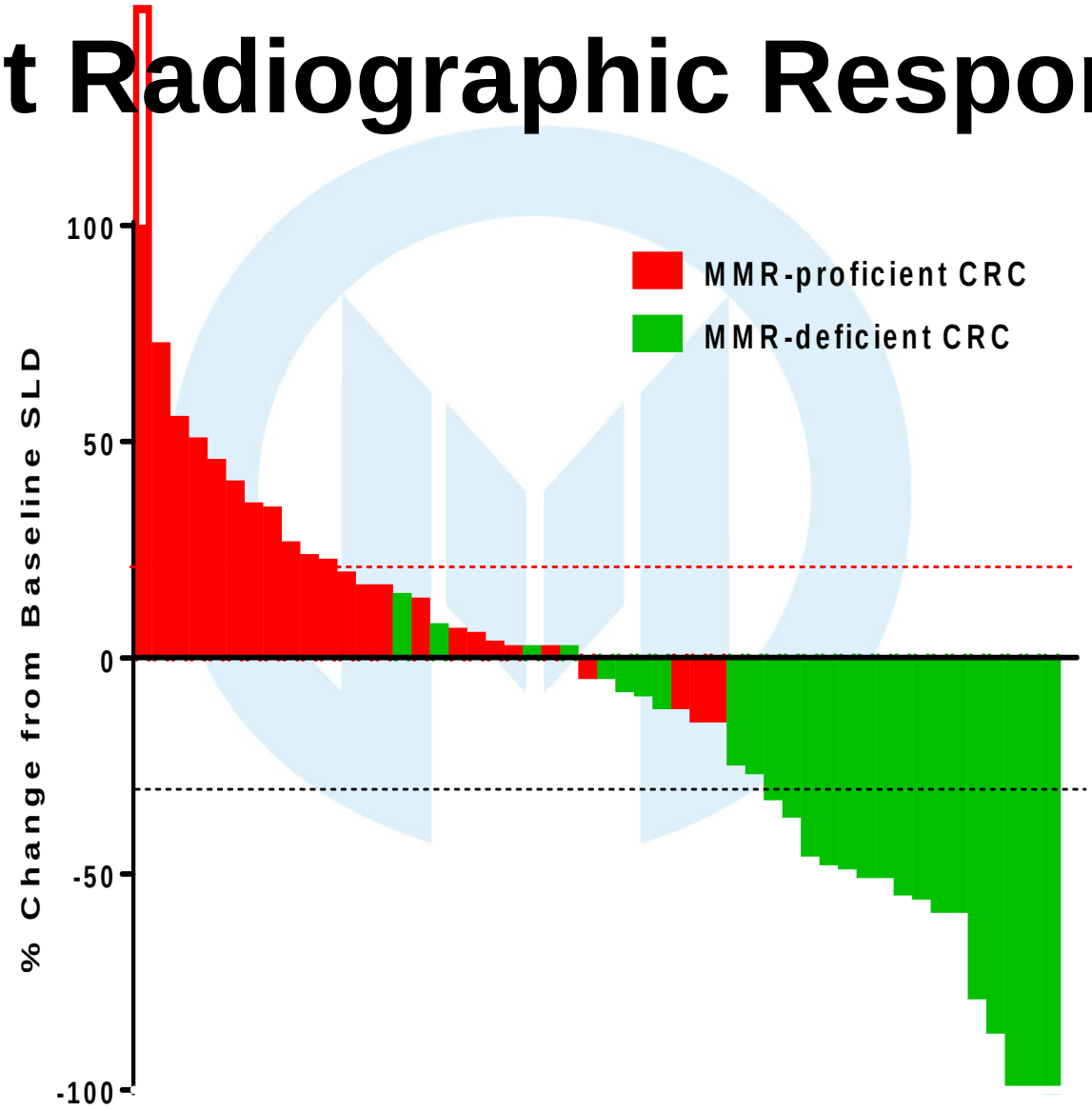


- **Anti–PD-1 antibody (Pembrolizumab): 10 mg/kg q 2 week**
- **Primary endpoint: Immune-related ORR and the 20-week immune-related PFS rate**
- **Mismatch-repair status was assessed in tumors with the use of the MSI Analysis System**

MSI, Microsatellite Instability Analysis System

Le DT, et al. *N Engl J Med*. 2015;372(26):2509-2520.

Best Radiographic Response



Objective Responses According to RECIST Criteria

Table 2. Objective Responses According to RECIST Criteria.

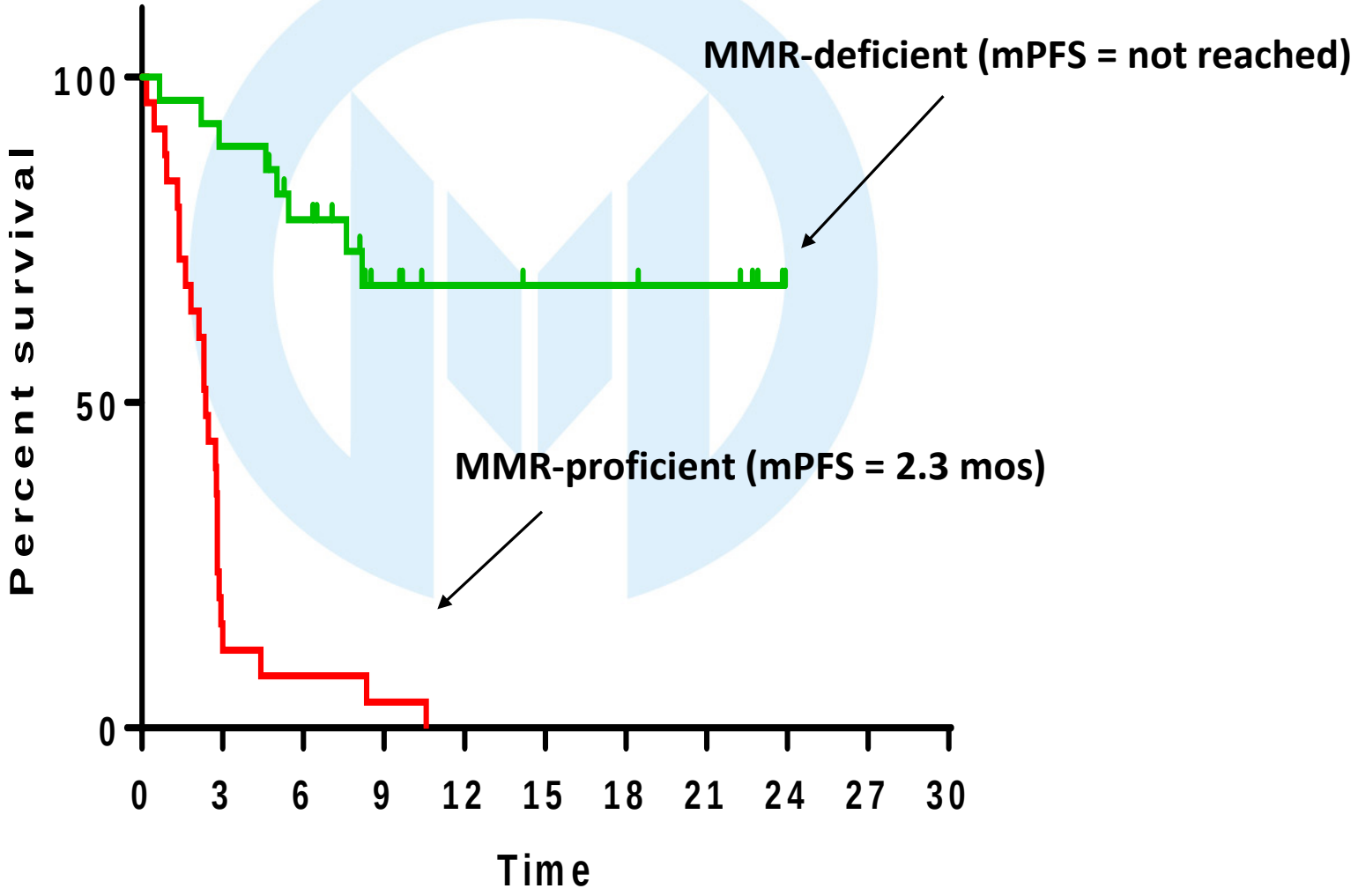
Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.
† One patient had a partial response at 12 weeks.
‡ Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.
§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.
¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.

RECIST, Response Evaluation Criteria in Solid Tumors

Le DT, et al. *N Engl J Med.* 2015;372(26):2509-2520.

Progression-free Survival



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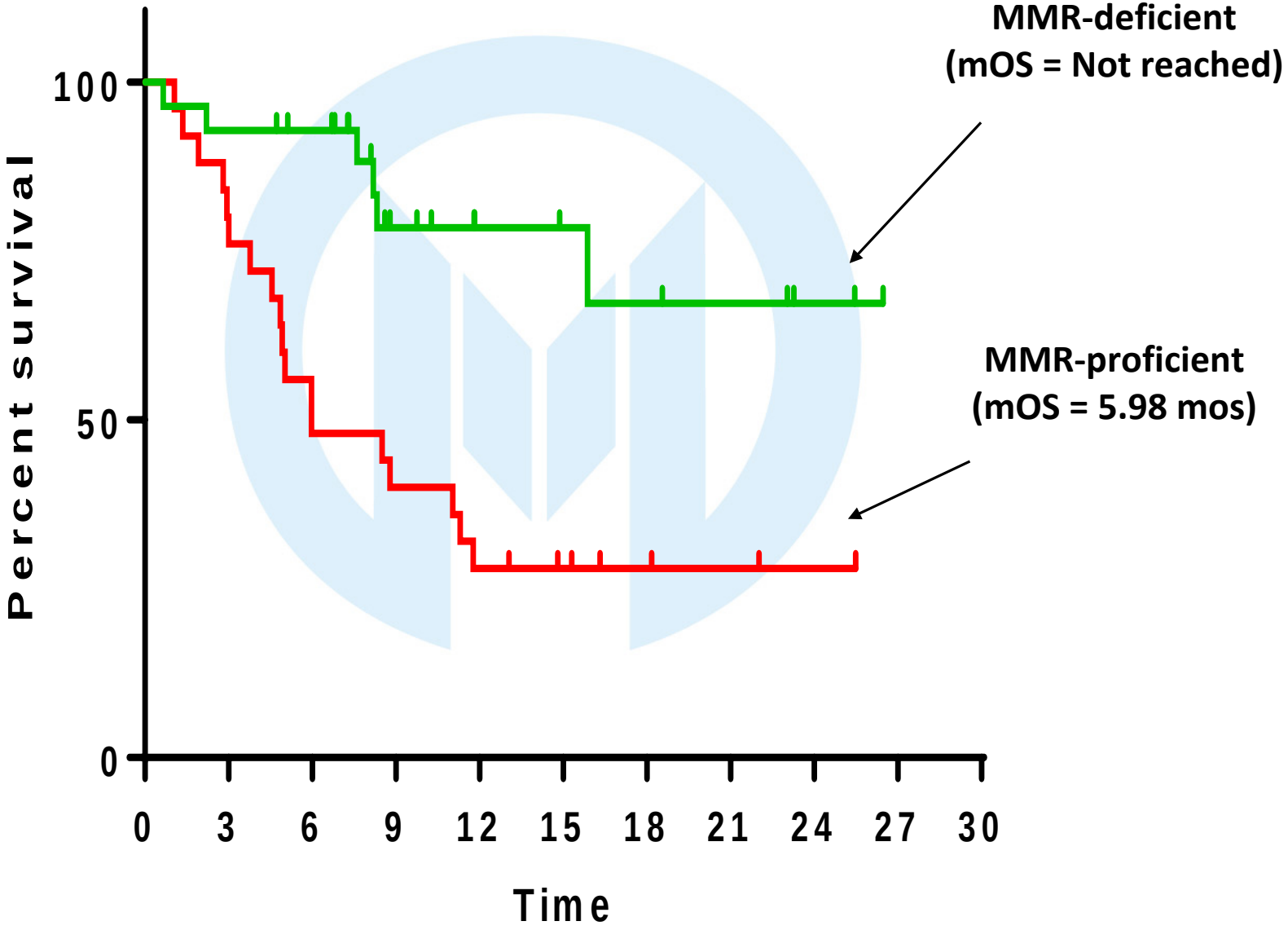
Overall Survival



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Adverse Events

Event-no. (%)	All Grades N=53	Grade 3 or 4 N=53
Generalized Symptoms		
Fatigue	5 (9)	0 (0)
Arthralgias	8 (15)	0 (0)
Gastrointestinal		
Nausea/vomiting	4 (8)	0 (0)
Diarrhea/colitis	6 (11)	1 (2)
Endocrine Disorders		
Thyroiditis/hypothyroidism	6 (11)	0 (0)
Hepatobilliary		
Pancreatitis	4 (8)	2 (4)
hyperbilirubinemia	2 (4)	0 (0)
Rash/pruritus	13 (25)	1 (2)
Respiratory		
Pneumonitis	2 (4)	0 (0)
Other		
Anemia	2 (4)	1 (2)
Flu-like symptoms	2 (4)	0 (0)
Leukopenia	2 (4)	1 (2)
Thrombocytopenia	3 (6)	1 (2)

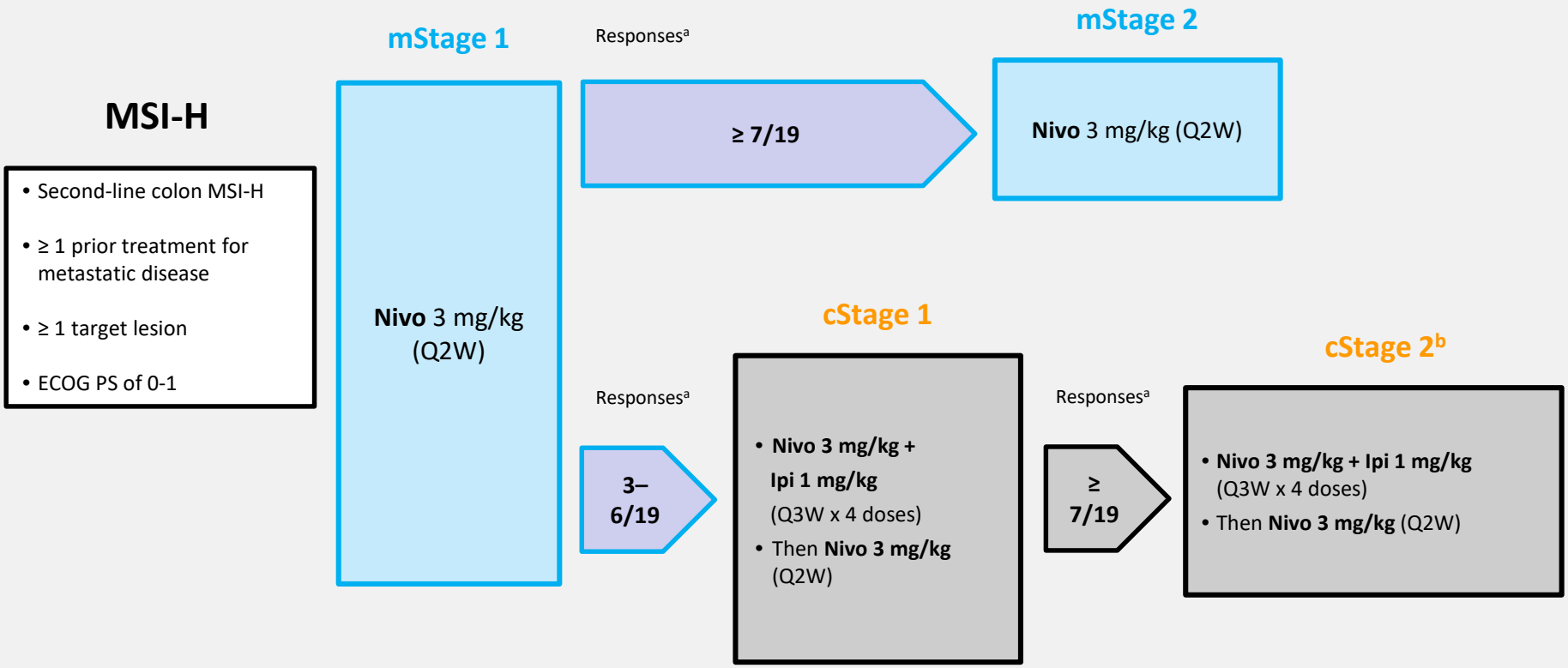
Nivolumab ± Ipilimumab in Treatment of Patients With Metastatic Colorectal Cancer With and Without High Microsatellite Instability: CheckMate 142 Interim Results

Michael Overman,[1] Scott Kopetz,[1] Ray McDermott,[2] Joseph Leach,[3] Sara Lonardi,[4] Heinz-Josef Lenz,[5] Michael Morse,[6] Jayesh Desai,[7] Andrew Hill,[8] Michael Axelson,[9] Rebecca A. Moss,[9] Chen-Sheng Lin,[9] Monica Goldberg,[9] Thierry Andre[10]

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]St Vincent's University Hospital, Dublin, Ireland; [3]Allina Health System, Minneapolis, MN, USA; [4]Istituto Oncologico Veneto IOV-IRCSS, Padova, Italy; [5]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [6]Duke University Office of Research Administration, Durham, NC, USA; [7]Royal Melbourne Hospital, Victoria, Australia; [8]Tasman Oncology Research Pty Ltd, Southport, Queensland, Australia; [9]Bristol-Myers Squibb, Princeton, NJ, USA; [10]Hopital Saint Antoine, Paris, France

PRESENTED AT: ASCO ANNUAL MEETING '16

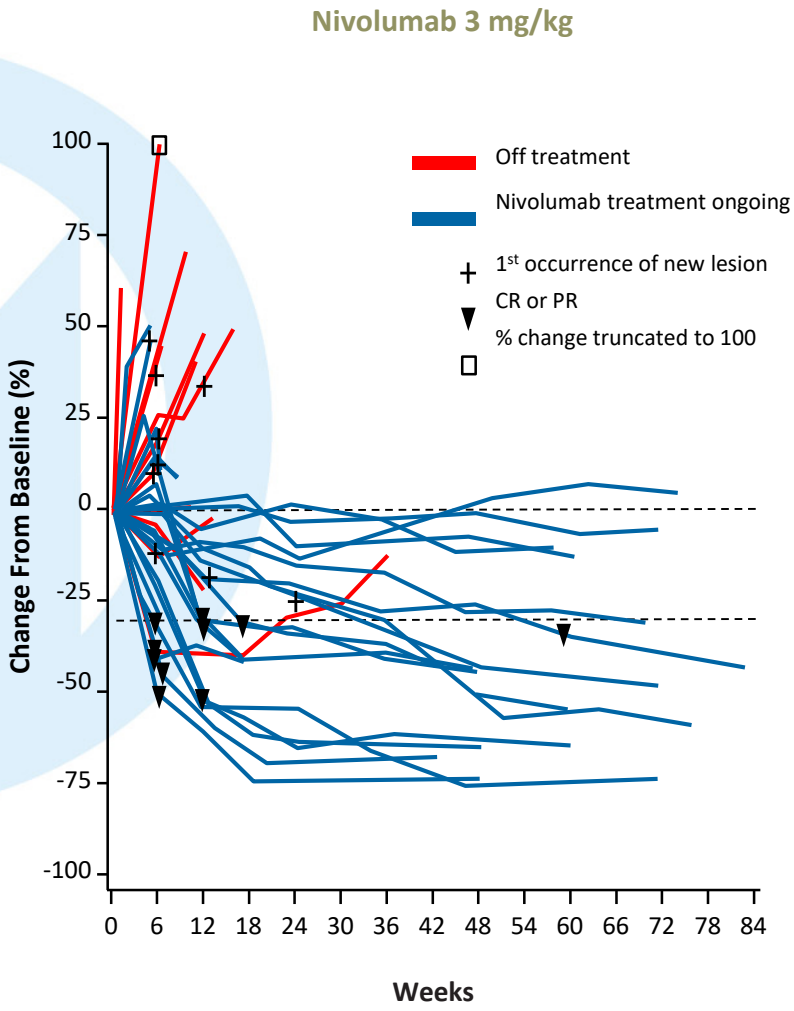
Phase 2 CheckMate 142 Study Design: MSI-H Cohort



[a]In patients with centrally confirmed MSI-H status
[b]Currently enrolling
cStage 1 = combination therapy stage 1; cStage 2 = combination therapy stage 2; Ipi = ipilimumab; mStage 1 = monotherapy stage 1; mStage 2 = monotherapy stage 2; Nivo = nivolumab; Q2W = every 2 weeks; Q3W = every 3 weeks

Investigator-Assessed Best Overall Response in Patients With MSI-H Receiving Nivolumab Monotherapy

	Nivolumab 3 mg/kg (n = 47)[a]
ORR, n (%) (95% exact CI)	12 (25.5) (15.4, 38.1)
Complete response	0
Partial response	12 (25.5)
Stable disease	14 (29.8)
Progressive disease	17 (36.2)
Unable to determine	4 (8.5)
Median time to response, mo (range)	2.12 (1.3–13.6)
Median duration of response, mo (range)	NE (0.0[b]–15.2[b])



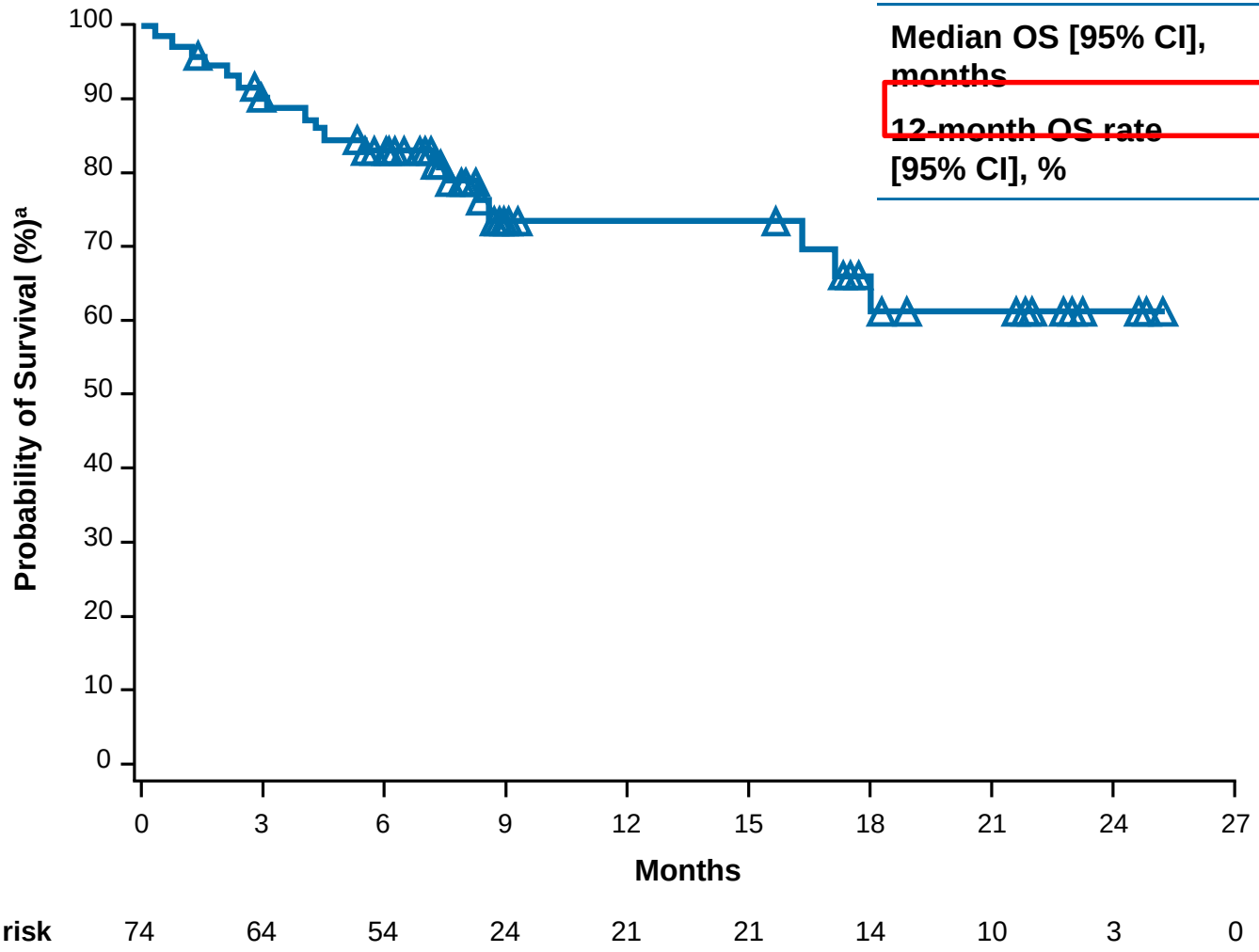
Horizontal reference line indicates 30% reduction

Response and Disease Control

	dMMR/MSI-H per Local Laboratory (N = 74)		dMMR/MSI-H per Central Laboratory (n = 53)	
	Investigator	BICR	Investigator	BICR
ORR, n (%) 95% CI	23 (31.1) 20.8, 42.9	20 (27.0) 17.4, 38.6	19 (35.8) 23.1, 50.2	17 (32.1) 19.9, 46.3
Best overall response, n (%) CR PR SD PD Unable to determine	 0 23 (31.1) 29 (39.2) 18 (24.3) 4 (5.4)	 2 (2.7) 18 (24.3) 28 (37.8) 20 (27.0) 6 (11.1)	 0 19 (35.8) 21 (39.6) 10 (18.9) 3 (5.7)	 1 (1.9) 16 (30.2) 21 (39.6) 12 (22.6) 3 (5.7)
Disease control for ≥ 12 weeks, n (%)[a]	51 (68.9)	46 (62.2)	39 (73.6)	37 (69.8)

BICR, blinded independent central review.
[a] Patients with CR, PR, or SD for ≥ 12 weeks.

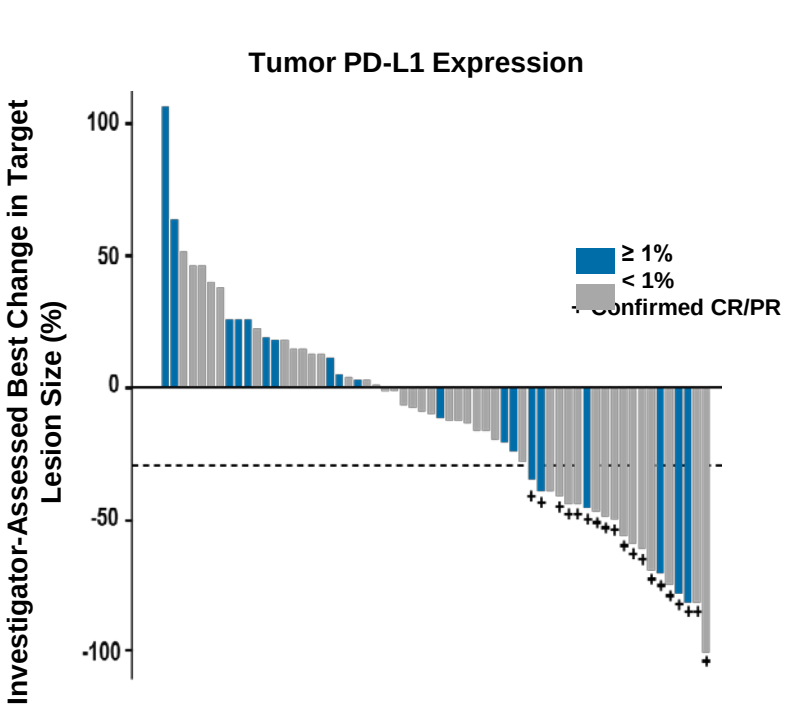
Overall Survival

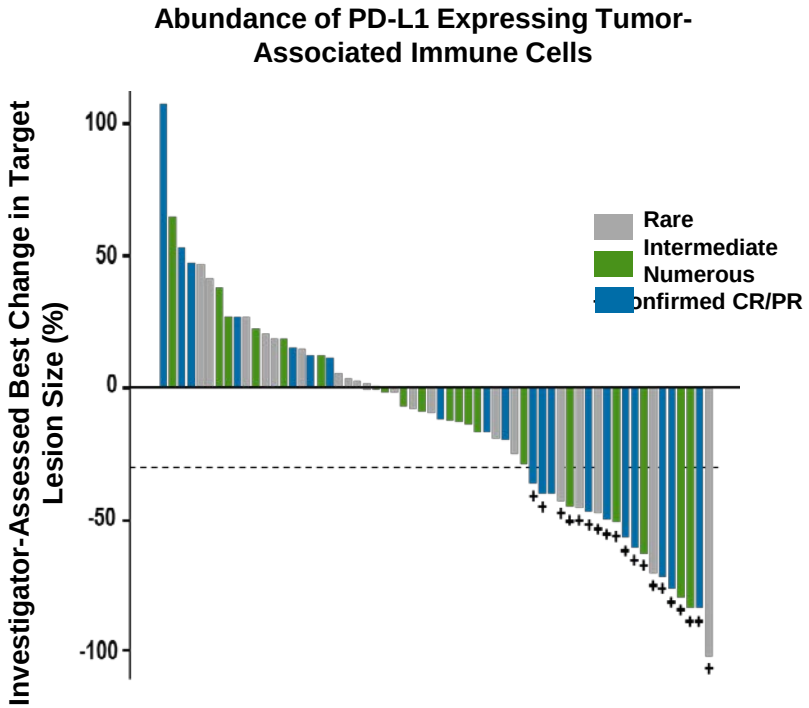


Median OS [95% CI], months	NR [17.1, NE]
12-month OS rate [95% CI], %	73.8 [59.8, 83.5]

NR, not reached. [a] Patients evaluated as dMMR/MSI-H by local laboratory.

Reduction in Target Lesion Size Regardless of PD-L1 Expression

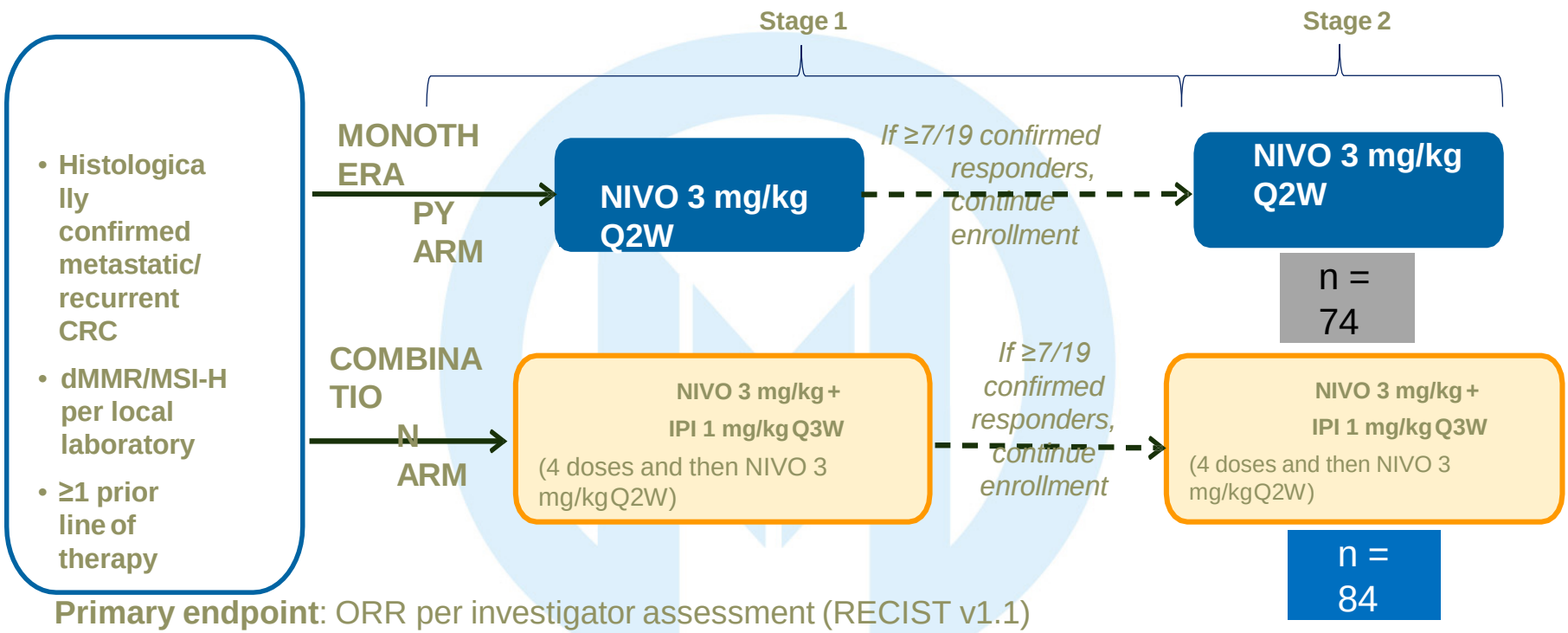




ORR, n/N (%)	Investigator	BICR
Tumor PD-L1 expression		
≥ 1%	6/21 (28.6)	7/20 (35.0)
< 1%	13/45 (28.9)	11/45 (24.4)

ORR, n/N (%)	Investigator	BICR
Abundance of PD-L1 expressing immune cells		
Rare	5/23 (21.7)	4/22 (18.2)
Intermediate	5/20 (25.0)	4/20 (20.0)
Numerous	9/23 (39.1)	10/23 (43.5)

Study Design



Primary endpoint: ORR per investigator assessment (RECIST v1.1)

Other key endpoints: ORR per blinded independent central review (BICR), PFS, OS, and safety

- Current analysis included all patients (n = 84) who received their first dose ≥6 months prior to the data cut-off
  - Median (range) time from first dose to data cut-off: 8.6 (6.3-19.4) months

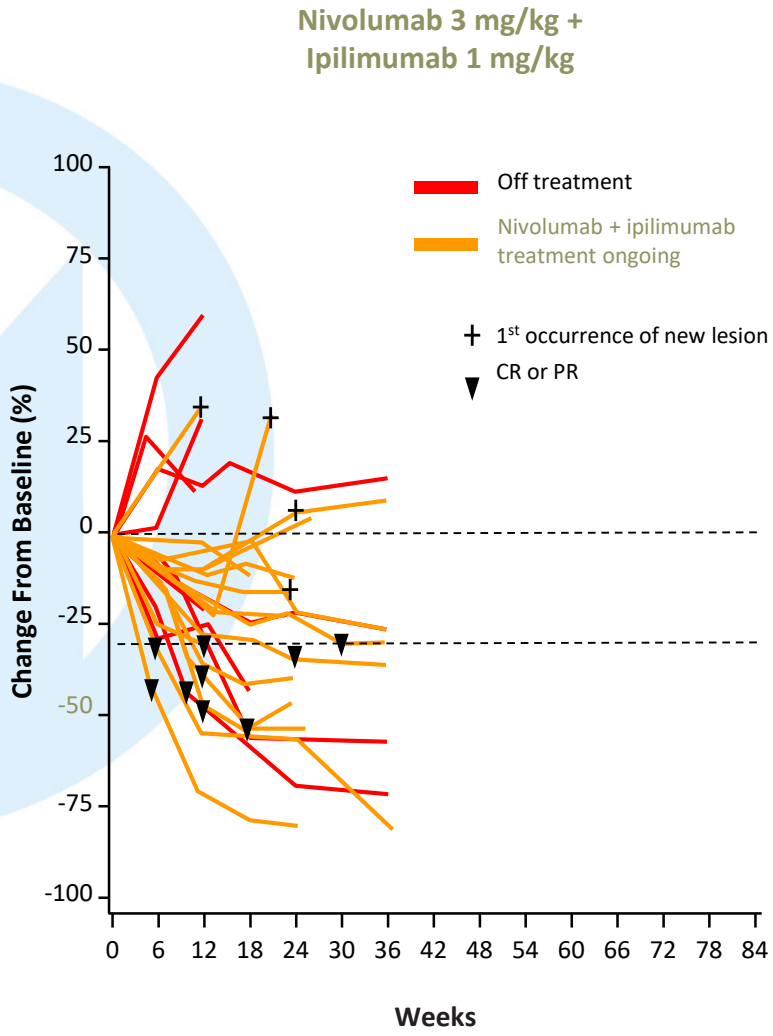
ORR, overall response; OS, overall survival; PFS, progression-free survival

Andre T, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 3531.

Investigator-Assessed Best Overall Response in Patients With MSI-H Receiving Nivolumab + Ipilimumab

	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 27)[a]
ORR, n (%) (95% exact CI)	11 (41.3) (18.6, 50.9)
Complete response	1
Partial response	10(37)
Stable disease	14 (51.9)
Progressive disease	2(7)
Unable to determine	0
Median time to response, mo (range)	2.73 (1.2–6.9)
Median duration of response, mo (range)	NE (NE–NE)

[a]Patients with ≥ 12 weeks of follow-up
[b]Includes censored observations
CR = complete response; NE = not estimable; PR = partial response



Horizontal reference line indicates 30% reduction

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Overall Response and Disease Control

	NIVO + IPI (n = 84)	NIVO Monotherapy[1] (n = 74)
	Investigator-Assessed	Investigator-Assessed
ORR, n (%) [95% CI]	46 (55) [43.5, 65.7]	23 (31) [20.8, 42.9]
Best overall response, n (%)	2 (2)	0
CR	44 (52)	23 (31)
PR	26 (31)	29 (39)
SD	9 (11)	18 (24)
PD	3 (4)	4 (5)
Not determined/reported		
Disease control for ≥12 weeks, n (%)[a]	66 (79)	51 (69)

[a]Patients with CR, PR, or SD for ≥12 weeks

1. Overman M, et al. *J Clin Oncol.* 2017;35(suppl 4 8): Abstract 518.

Andre T, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 3531.

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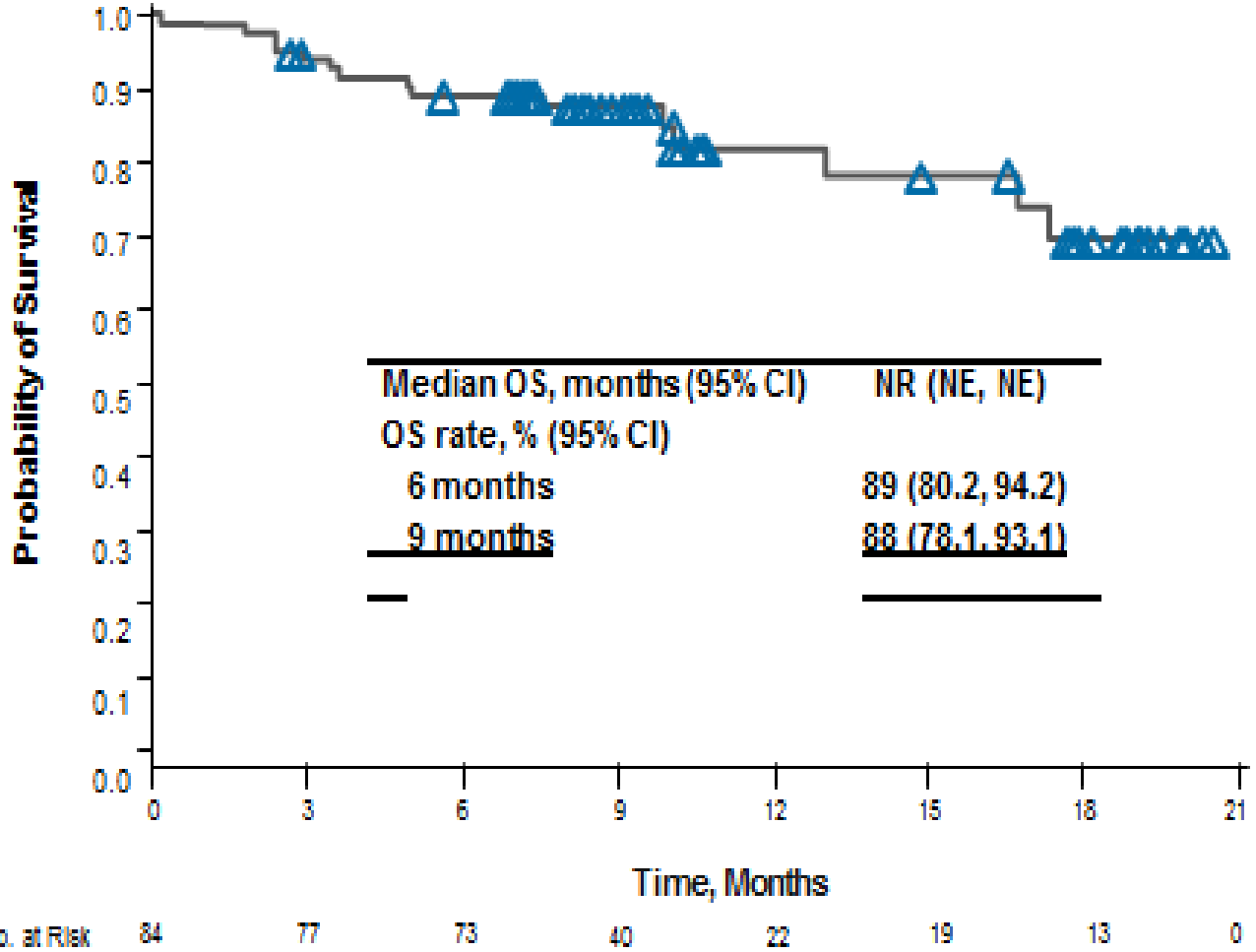
Overall Survival



Andre T, et al. *J Clin Oncol.* 2017;35(suppl): Abstract 3531.

Treatment-Related Adverse Events in ≥ 15% of Patients With MSI-H

Event, n (%)	Nivolumab 3 mg/kg (n = 70)		Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg (n = 30)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any event	41 (58.6)[a]	10 (14.3)	25 (83.3)	8 (26.7)
Fatigue	13 (18.6)	1 (1.4)	6 (20.0)	0
Diarrhea	10 (14.3)	1 (1.4)	13 (43.3)	0
Pruritus	8 (11.4)	0	5 (16.7)	1 (3.3)
Nausea	5 (7.1)	0	6 (20.0)	0
Pyrexia	3 (4.3)	0	7 (23.3)	0
Any event leading to discontinuation	4 (5.7)	2 (2.9)	4 (13.3)	4 (13.3)

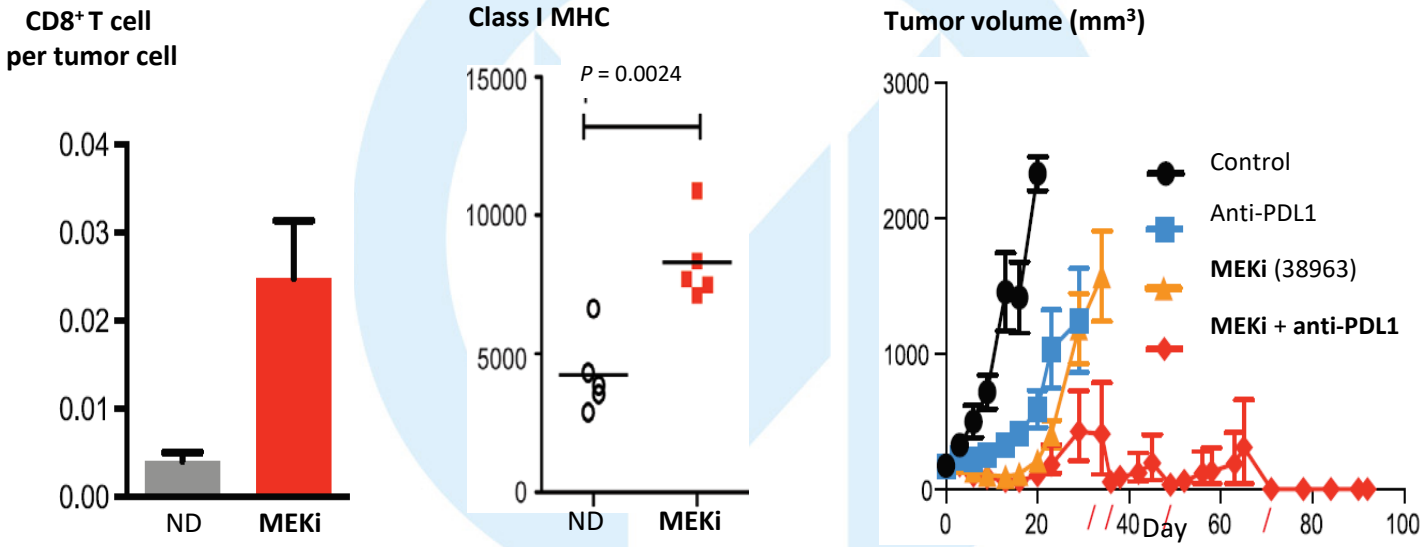
[a]One Grade 5 event of sudden death

Question??

- Can we convert non-immunogenic tumor into immunogenic tumor?

PD-L1 and MEK Inhibition: A Rational Combination

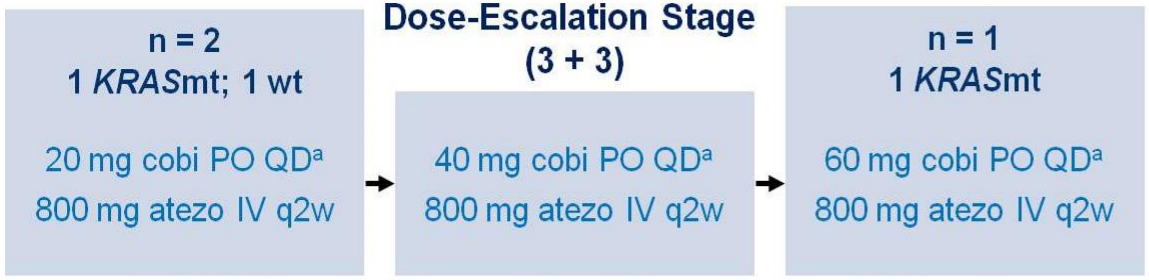
- MEK inhibition alone can result in **intratumoral T-cell accumulation** and **MHC I upregulation**, and synergizes with an anti-PDL1 agent to promote **durable tumor regression**[1]

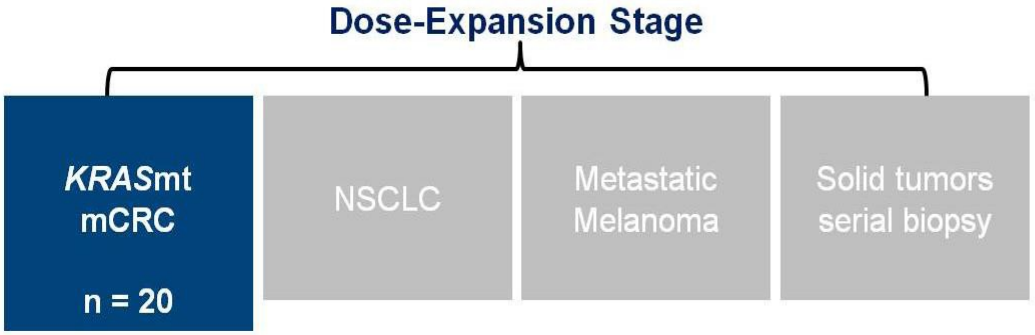


- To examine the possible benefits of MEK inhibition with an anti-PDL1 agent, we evaluated cobimetinib + atezolizumab in patients with advanced solid tumors

MHC, major histocompatibility complex; ND, no drug (vehicle alone).
CT26 (KRASmt) CRC models. 1. Ebert et al. *Immunity* 2016.

Cobimetinib + Atezolizumab in CRC:
Phase Ib Dose Escalation and Cohort Expansion Study





Key eligibility Criteria

- ECOG PS of 0 or 1
- Measurable disease per RECIST v1.1

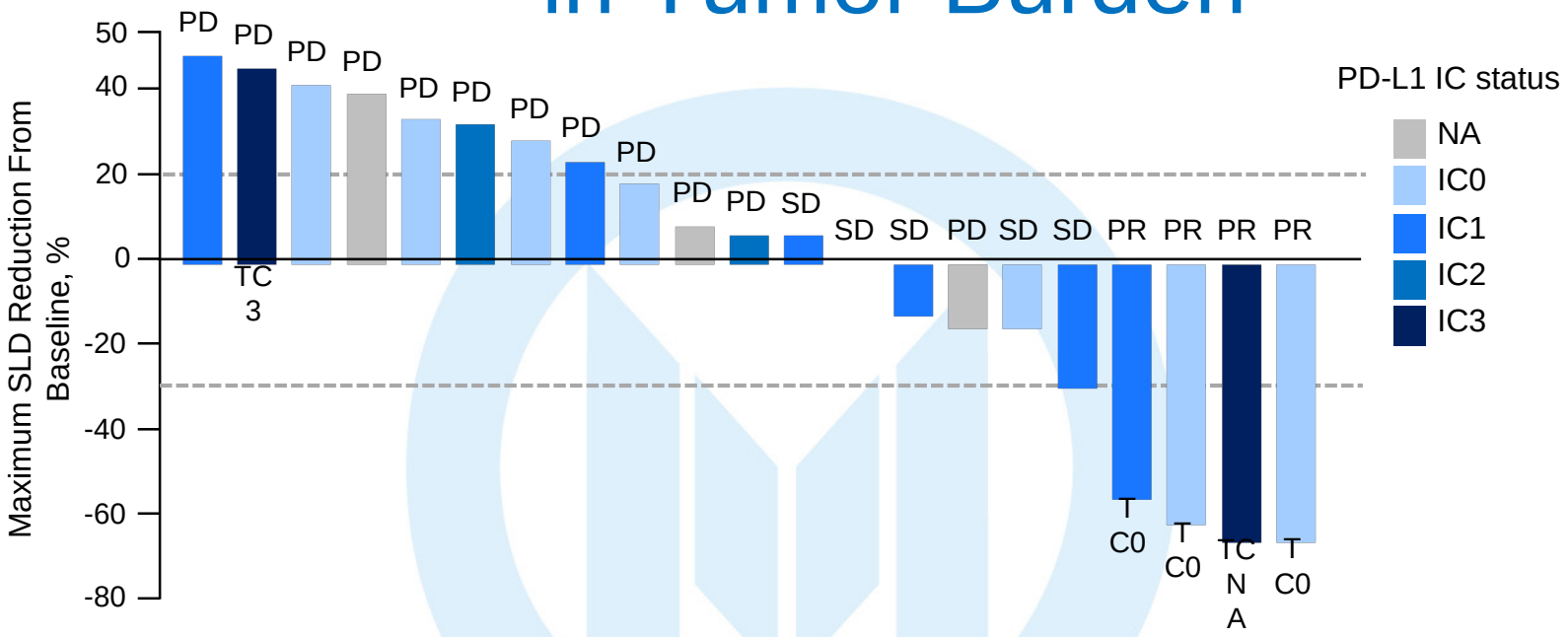
Primary Objectives

- Safety and clinical activity of cobimetinib + atezolizumab

[a]Cobimetinib was administered on 21 days on/7 days off dosing schedule.
Atezo, atezolizumab; cobi, cobimetinib; DLT, drug limited toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*mt, *KRAS* mutant; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer

Bendell J, et al. *J Clin Oncol*. 2016;34(suppl): Abstract 3502.

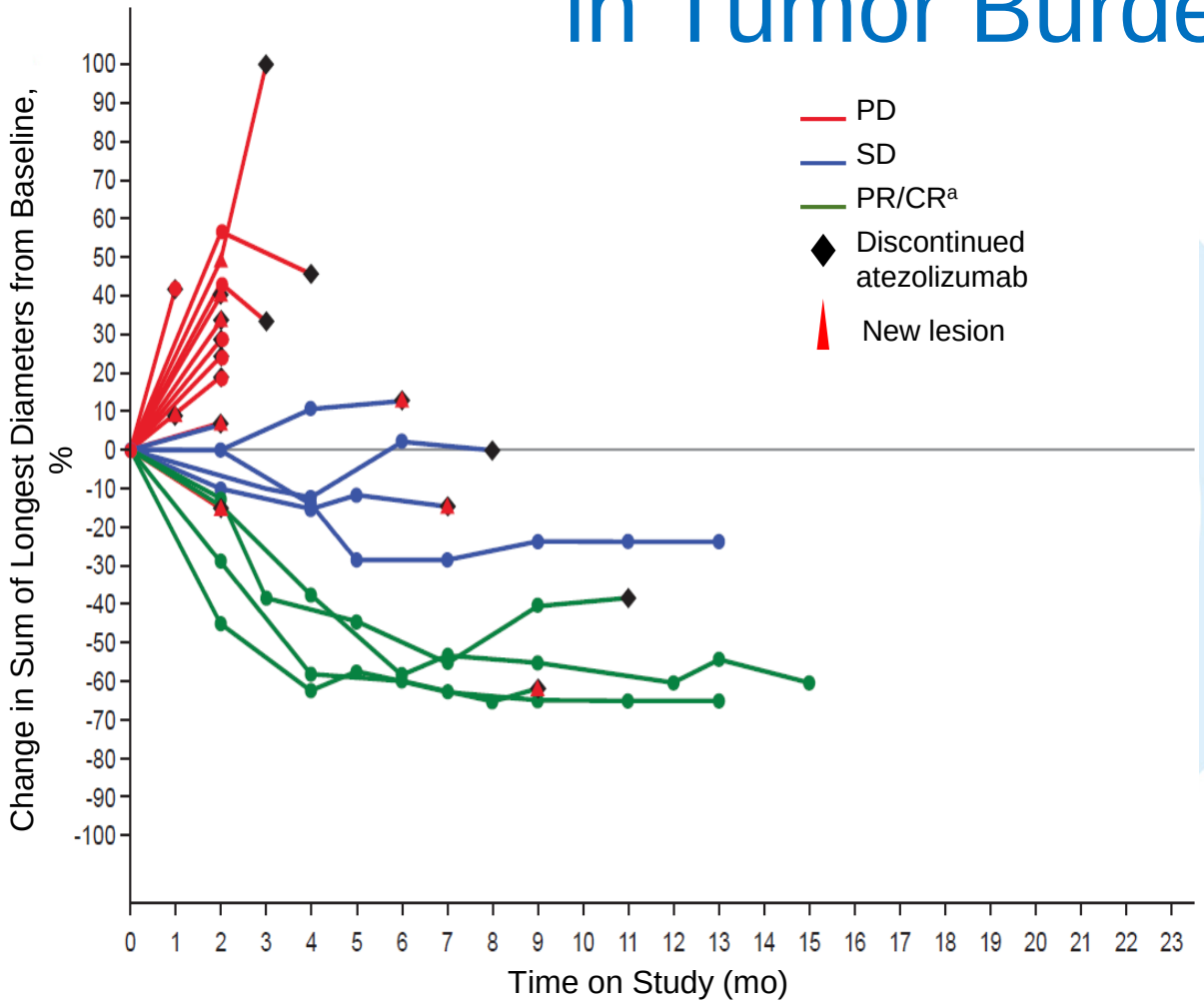
Efficacy: Change in Tumor Burden



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

PD-L1 IHC status on tumor cells (TC) and tumor-infiltrating immune cells (IC) defined as: TC3 = TC ≥ 50% PD-L1+ cells; IC3 = IC ≥ 10% PD-L1+ cells; TC2 = TC ≥ 5% and < 50% PD-L1+ cells; IC2 = IC ≥ 5% and < 10% PD-L1+ cells; TC1 = TC ≥ 1% and < 5% PD-L1+ cells; IC1 = IC ≥ 1% and < 5% PD-L1+ cells; TC0 = TC < 1% PD-L1+ cells; IC0 = IC < 1% PD-L1+ cells.
NA, not available; NGS, next generation sequencing. Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016.

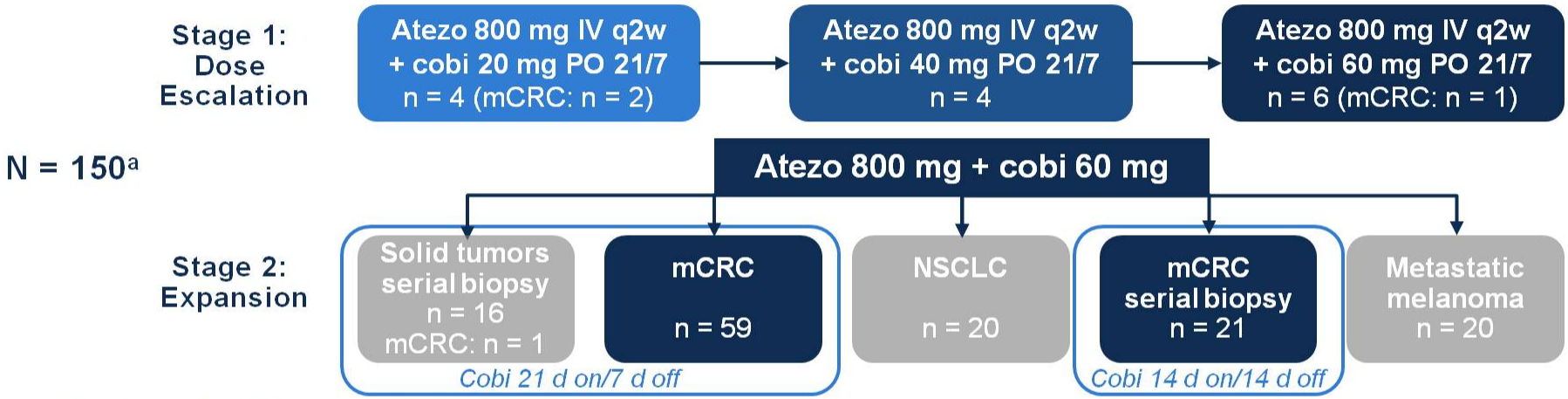
Efficacy: Change in Tumor Burden Over Time



- Median duration of response was not reached (range: 5.4 to 11.1+ mo)
- Responses are ongoing in 2 of 4 responding patients

[a]Confirmed per RECIST v1.1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Efficacy-evaluable patients. 2 patients missing or unevaluable are not included. Data cut-off February 12, 2016.

Phase Ib Dose Escalation and Cohort Expansion Study (NCT01988896)

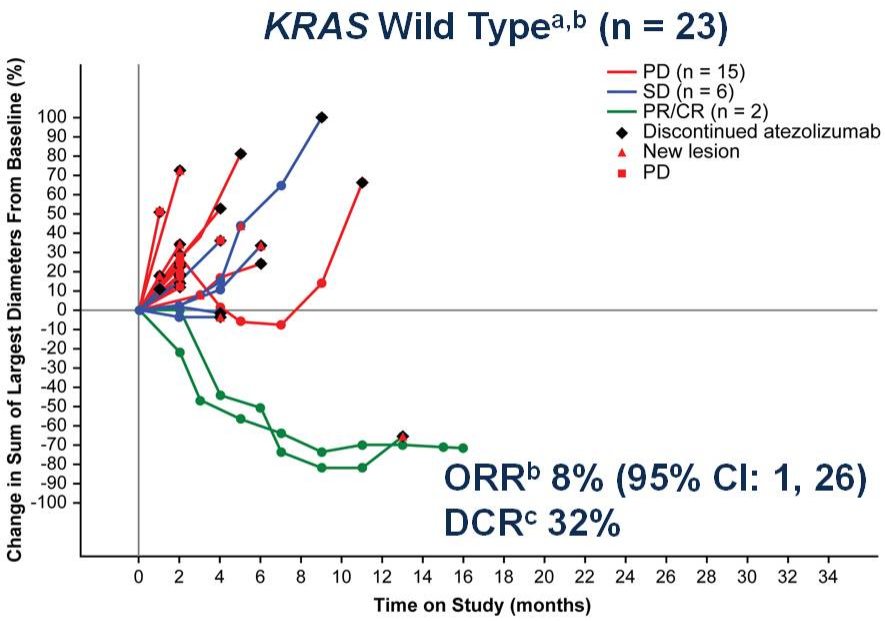


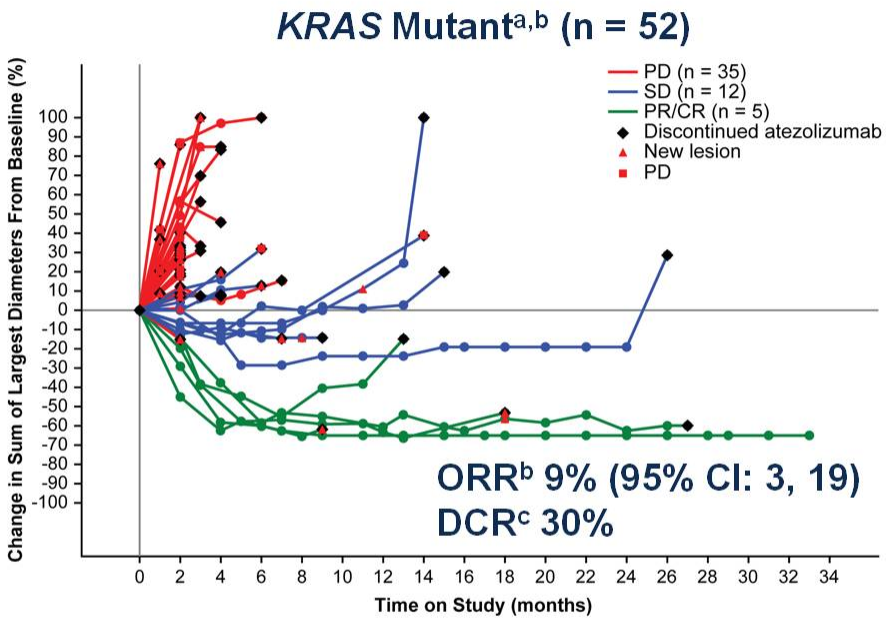
- **Endpoints:** Primary – Safety and tolerability
  Secondary – Investigator-assessed ORR and PFS by RECIST v1.1, and OS
- **Patients:** PD-L1 unselected
  MSI status was locally reported and centrally confirmed by NGS-based scoring

Atezo, atezolizumab; cobi, cobimetinib; IV, intravenously; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; q2w, every 2 weeks.

[a] Safety-evaluable population consisting of patients who received at least 1 dose of atezolizumab.

Duration of Response

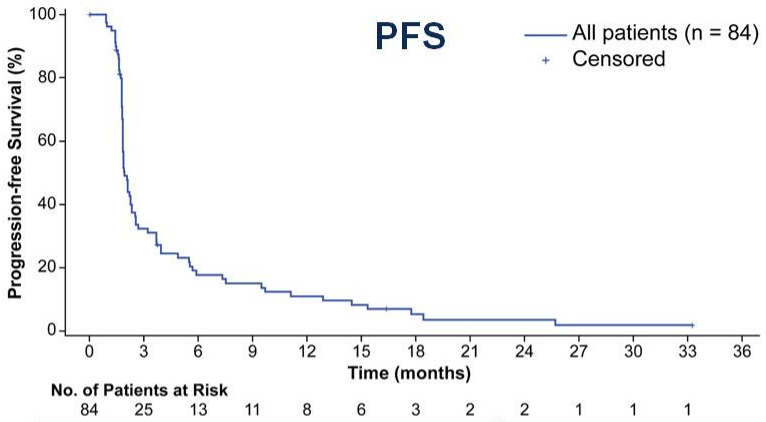


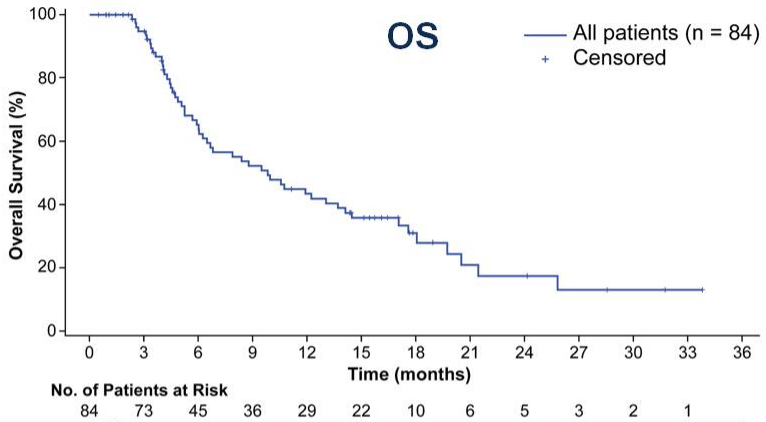


- The median duration of response was 14.3 months (95% CI: 6.0, NE)

NE, not estimable.
Data cutoff: September 4, 2017.
[a] 2 patients had unknown *KRAS* mutation status and are not included in these graphs. [b] BOR was missing or unevaluable for 2 KRAS wild type and 5 KRAS mutant patients.
[c] DCR defined as PR or SD ≥ 6 weeks.

Progression-Free Survival and Overall Survival



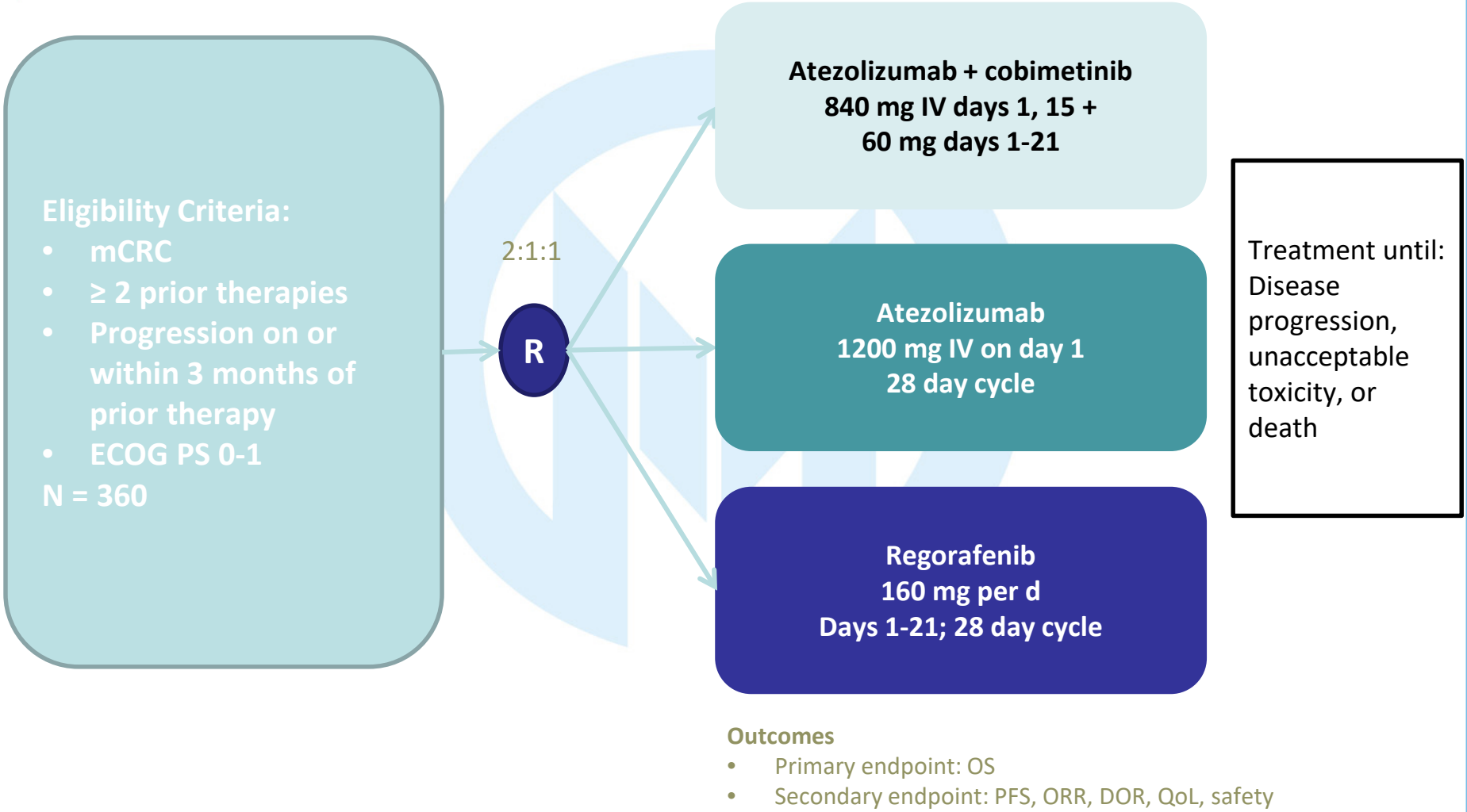


Patients	PFS		OS		
	Median (95% CI)	6-mo	Median (95% CI)	6-mo	12-mo
All (n = 84)	1.9 mo (1.8, 2.3)	18%	9.8 mo (6.2, 14.1)	65%	43%
MSS (n = 42)[a]	2.5 mo (1.8, 3.7)	27%	13.0 mo (6.0, 25.8)	71%	51%
KRAS mutant (n = 57)[b]	2.0 mo (1.8, 2.3)	22%	9.5 mo (6.0, 17.6)	67%	44%
KRAS wild type (n = 25)[b]	1.8 mo (1.8, 2.6)	9%	10.0 mo (4.9, 17.1)	65%	43%

Data cutoff: September 4, 2017.

[a] Of the remaining 42 non-MSS patients, 32 patients had unknown MSI status, 9 patients were MSI-low and 1 patient was MSI-high. [b] 2 patients had unknown *KRAS* mutation status.

COTEZO IMblaze-370: Phase 3 Trial
Atezolizumab With and Without Cobimetinib vs Regorafenib



Outcomes
- Primary endpoint: OS
- Secondary endpoint: PFS, ORR, DOR, QoL, safety

1, https://clinicaltrials.gov/ct2/show/NCT02788279

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Summary

- VEGF and EGFR mAbs competing for first-line patients in RAS wt CRC
- For anti-EGFR treatment, all *RAS* tests are required
- Primary tumor location is related to effect of cetuximab
- Bevacizumab, *Ramucirumab* and Aflibercept competing for second-line patients with each other, and with EGFR mAbs in KRAS wt CRC

Summary

- Best sequence of therapies (VEGFi vs EGFRi) still to be established
- Regorafenib and TAS 102 as salvage therapy option
- Checkpoint inhibitors are highly active in select molecular subsets
- Rationale combination maybe able to covert “cold” tumor to “hot” tumor

Thank you !

GI oncology questions
Richard.kim@moffitt.org