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The Emergence of Targeted Therapy for Patients with Metastatic Colorectal Cancer (mCRC) and BRAF V600E Tumor Mutations; HER2 and Other Potential Biomarkers

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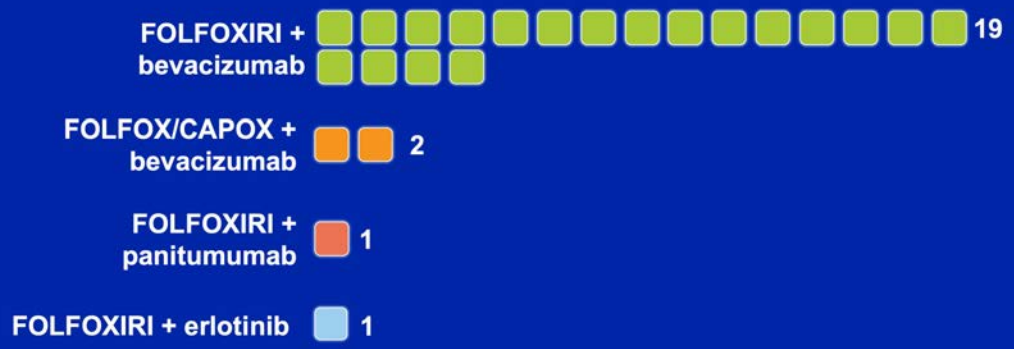
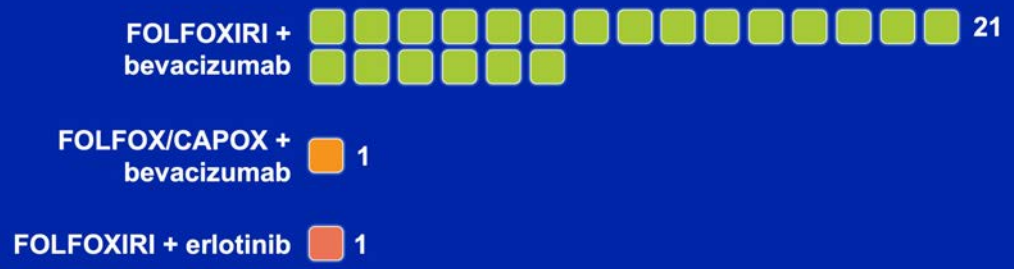
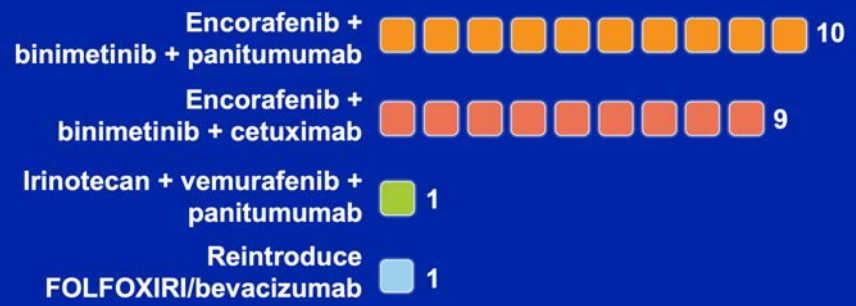
What is your usual first-line treatment for a 65-yo patient with left-sided, MSS, pan-RAS WT mCRC with a BRAF V600E mutation?



What is your usual first-line treatment for a 65-yo patient with right-sided, MSS, pan-RAS WT mCRC with a BRAF V600E mutation?



Reimbursement and regulatory issues aside, what would be your most likely treatment for a 65-yo patient with left-sided, MSS, pan-RAS WT mCRC and BRAF V600E mutation who received FOLFOXIRI/bev with progression 8 months later on bev/5-FU (PS 0)?

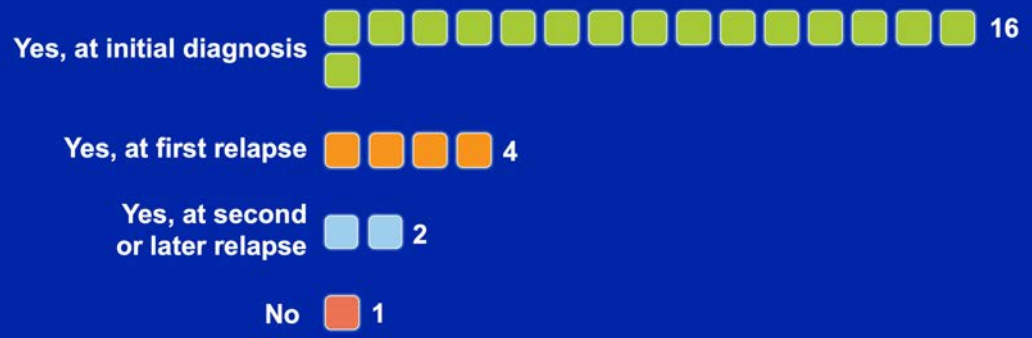


Chemotherapy + erlotinib (1)

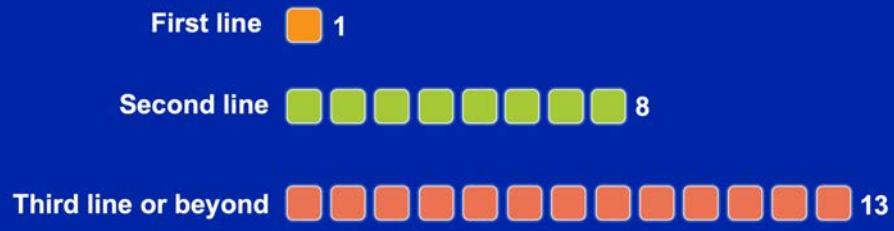
mCRC with BRAF V600E tumor mutations

- Sequencing of treatment
- Impact of tumor sidedness
- Optimal integration of targeted therapy: Efficacy/toxicity, selection of regimen

Do you generally assess HER2 status in patients with mCRC?



Reimbursement and regulatory issues aside, for a patient with pan-RAS WT mCRC and a HER2 mutation or amplification, when would you generally administer anti-HER2 therapy?



For a patient with HER2 mutated/amplified mCRC, regulatory and reimbursement issues aside, what would be your preferred HER2-targeted agent(s)?

Pertuzumab (1), Lapatinib (1)

mCRC with HER2 mutations/amplifications

- Testing
- Use and sequencing of anti-HER2 therapy

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Disclosures

Consulting Agreements	Amgen Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Chengdu Kanghong Pharmaceuticals Group Co Ltd, Exelixis Inc, Roche Laboratories Inc

Salient Facts

- BRAF MT
  - V600E accounts for 90% of mutations
  - Found in <10% of all mCRC patients
  - It is associated with a poor prognosis in non-MSI High patients.
  - Associated with right sided tumors, females and are more likely to have peritoneal disease.
  - Single agent BRAF inhibitors in mCRC have had negligible benefit of 5%.

Final Study Design: BEACON

Results of Safety Lead-In led to the introduction of an additional primary endpoint of ORR and an interim OS analysis to allow for early assessment

Patients with *BRAF*^{V600E} mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

Safety Lead-in

ENCO + BINI + CETUX
N = 30

Encorafenib 300 mg PO daily
Binimetinib 45 mg PO bid
Cetuximab standard weekly dosing

A separate Safety Lead-in cohort of n=7 in Japan was enrolled subsequently. Results will be reported at a later time.

Phase 3

R 1:1:1

- **Triplet therapy**
  ENCO + BINI + CETUX
  n = 205
- **Doublet therapy**
  ENCO + CETUX
  n = 205
- **Control arm**
  FOLFIRI + CETUX, or irinotecan + CETUX
  n = 205

Overall Survival

Primary Endpoints:

Triplet vs Control

- **OS**
- **ORR**
  (Blinded Central Review)

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved).

Secondary Endpoints: Doublet vs Control OS & ORR, PFS, Safety

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Kopetz S et al. *N Engl J Med* 2019;381:1632-43.

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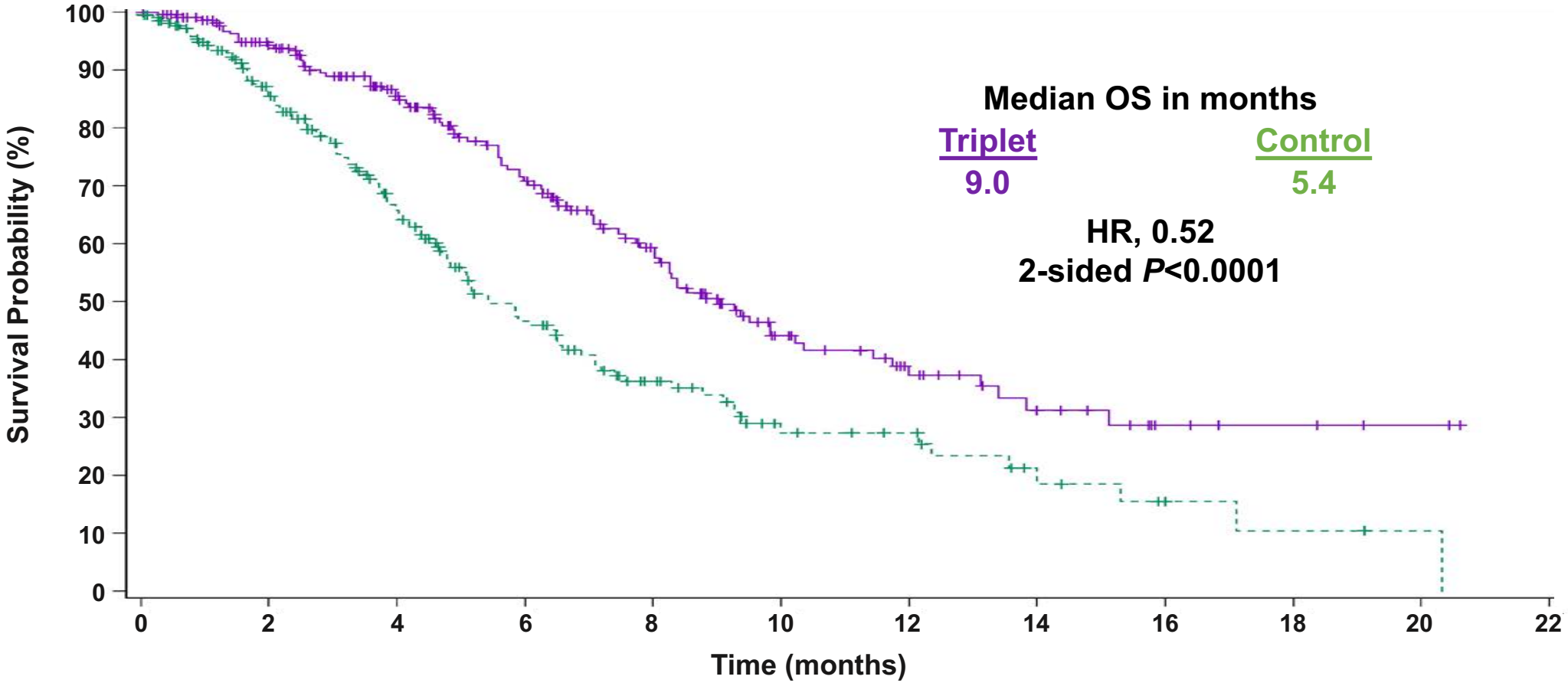
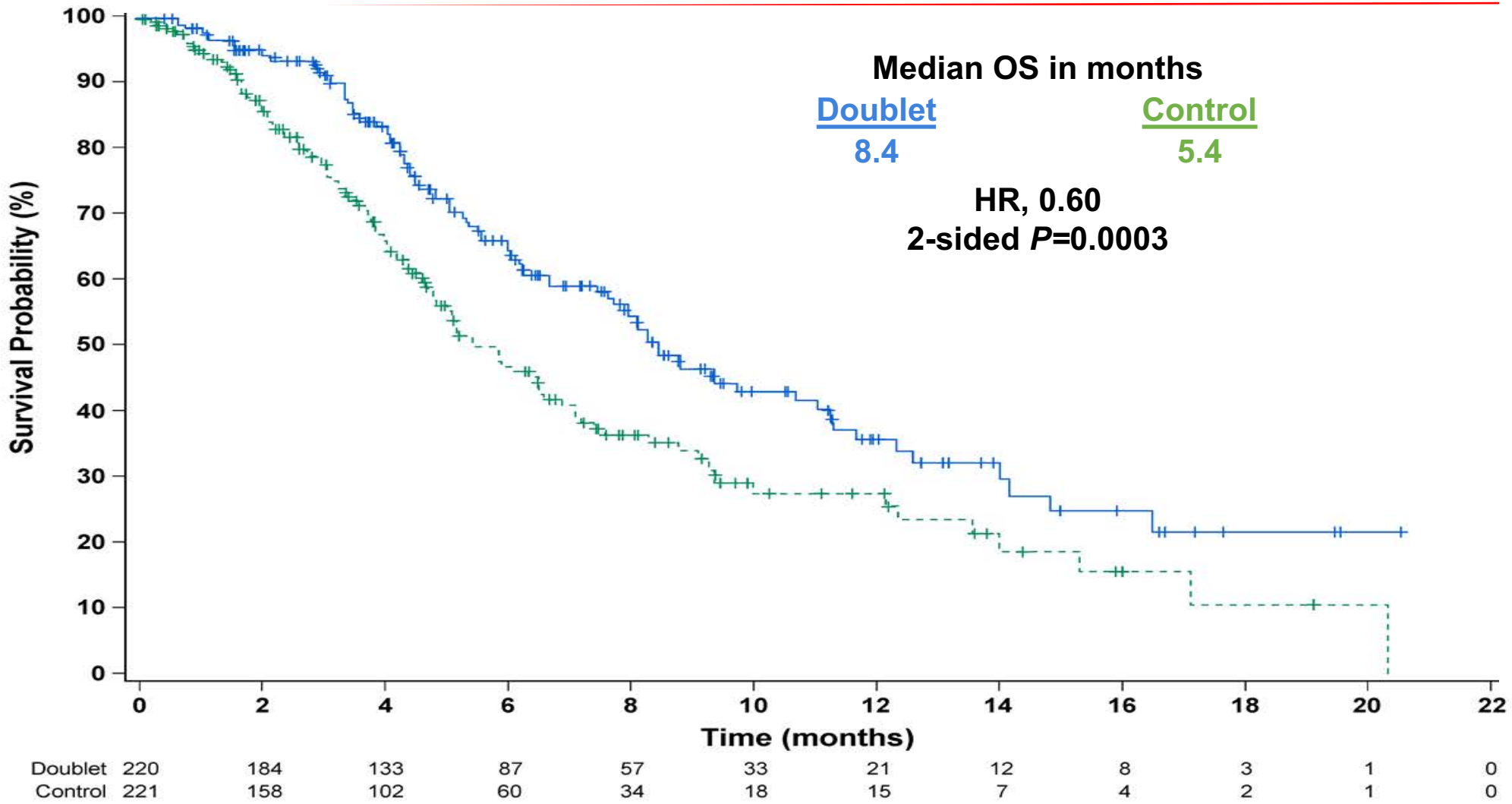
Primary Endpoint BEACON - Overall Survival: Triplet vs Control
(all randomized patients)



Triplet	224	186	141	103	69	37	24	14	6	4	2	0
Control	221	158	102	60	34	18	15	7	4	2	1	0

Kopetz S et al. *N Engl J Med* 2019;381:1632-43.

Overall Survival: Doublet vs Control (all randomized patients)



Kopetz S et al. *N Engl J Med* 2019;381:1632-43.

BEACON: Efficacy Summary

Efficacy	Triplet Regimen	Doublet Regimen	Control
Median OS (n = 224, 220, 221)	**9.0 mo**	**8.4 mo**	**5.4 mo**
	HR = 0.52, p<0.001	HR = 0.60,p <0.001	Reference
Median PFS (n = 224, 220, 221)	**4.3 mo**	**4.2 mo**	**1.5 mo**
	HR = 0.38, p<0.001	HR = 0.40, p<0.001	Reference
ORR (n = 111, 113, 107)	**29%**	**23%**	**2%**
	p<0.001	p<0.001	Reference

Kopetz S et al. *N Engl J Med* 2019;381:1632-43.

BEACON: Safety Summary

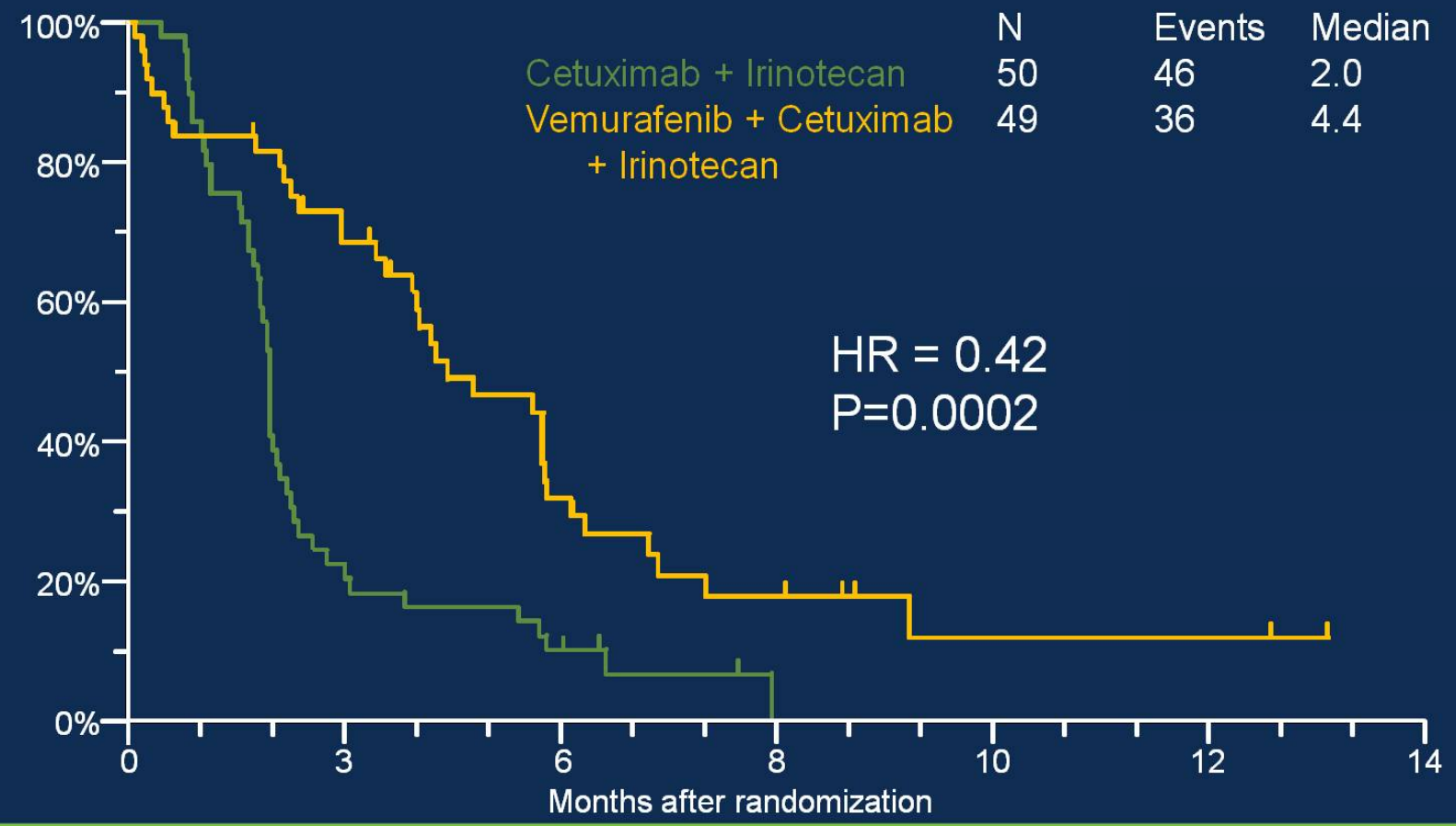
Safety	Triplet Regimen (N = 222)	Doublet Regimen (N = 216	Control (N = 193)
Grade ≥3 AEs	58%	50%	61%
Diarrhea (Grade ≥3)	10%	2%	10%
Acneiform dermatitis (Grade ≥3)	2%	<1%	3%
Nausea (Grade ≥3)	5%	<1%	1%
Fatigue (Grade ≥3)	2%	4%	4%
Treatment discontinuation	7%	8%	11%
Median duration of exposure to trial treatment	21 weeks	19 weeks	7 weeks

- Relative dose intensities were similar in the triplet-therapy group and the doublet-therapy group.
- Adverse events were as anticipated based on prior trials with each combination.

Kopetz S et al. *N Engl J Med* 2019;381:1632-43.

S1406: VIC (Vemurafenib, Cetuximab and Irinotecan)

Primary Endpoint: Progression-free survival



PRESENTED AT: 2017 Gastrointestinal Cancers Symposium | #GI17

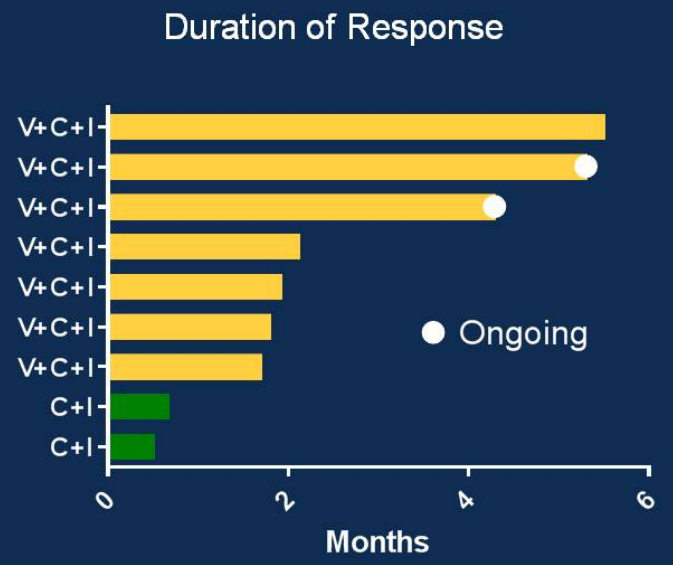
Presented by: Scott Kopetz, MD, PhD

S1406: VIC (Vemurafenib, Cetuximab and Irinotecan)

Response Rate

	Cetuximab + Irinotecan (n=45)[a]	Vemurafenib + Cetuximab + Irinotecan (n=43)[a]	P-value[c]
Partial response	4%	16%	P=0.001
Stable disease	17%	48%	
Progression[b]	56%	12%	
Disease Control Rate	22%	67%	

[a]93 patients had measurable disease; 5 patients did not have restaging results at time of data cutoff (10/11/16); [b] Including symptomatic deterioration; [c] Chi-squared

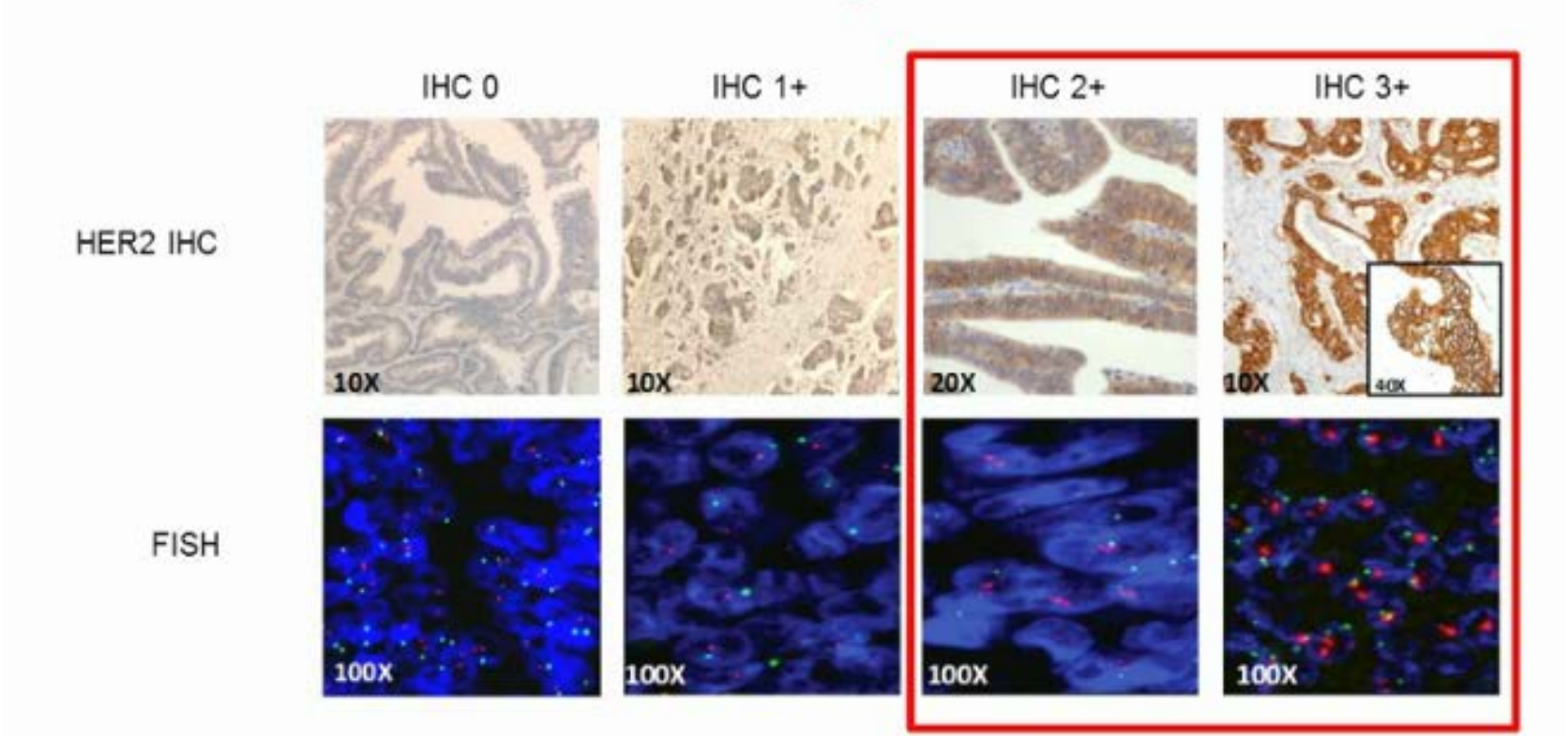


Presented by: Scott Kopetz, MD, PhD

Comparison of RR and PFS for *BRAF-V600E* Mutated 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
Dabrafenib + trametinib	12%	3.5 months	Corcoran, ASCO ’14
Doublet with EGFR			
Vemurafenib + panitumumab	13%	3.2 months	Yeager et al, CCR ’14
Vemurafenib + cetuximab	20%	3.2 months	Tabernero et al, ASCO ’14
Encorafenib + cetuximab [R]	23%	4.2 months	Tabernero et al, ESMO ’19
Dabrafenib + panitumumab	10%	3.4 months	Atreya, ASCO ’15
Triplet with EGFR			
Vemurafenib + cetuximab + irinotecan [R]	35%	4.2 months	Kopetz, ASCO ‘17
Encorafenib + binimetinib + cetuximab [R]	26%	4.3 months	Tabernero, ESMO ‘19
Dabrafenib + trametinib + panitumumab	26%	4.1 months	Atreya, ASCO ’15
Encorafenib + cetuximab + alpelisib	32%	4.4 months	Tabernero et al, ESMO ’14

HER2 Amplification: 4% of CRC Tumors



- Mutually exclusive with RAS/BRAF mutations
- Prevalence of 7-8% of RAS/BRAF wild type tumors eligible for EGFR inhibitors

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Valtorta E, et al. *Mod Pathol.* 2015;28(11):1481-1491.

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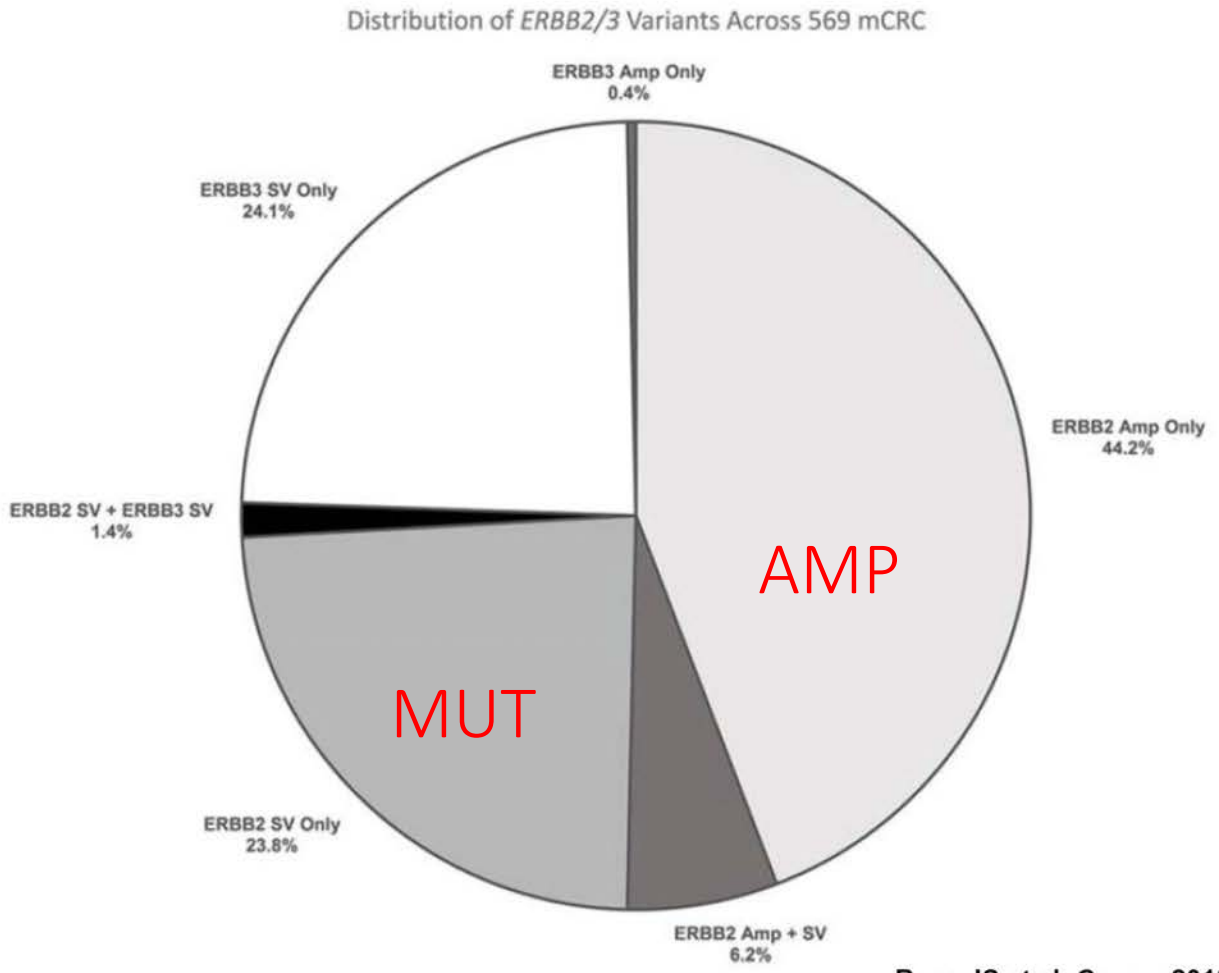
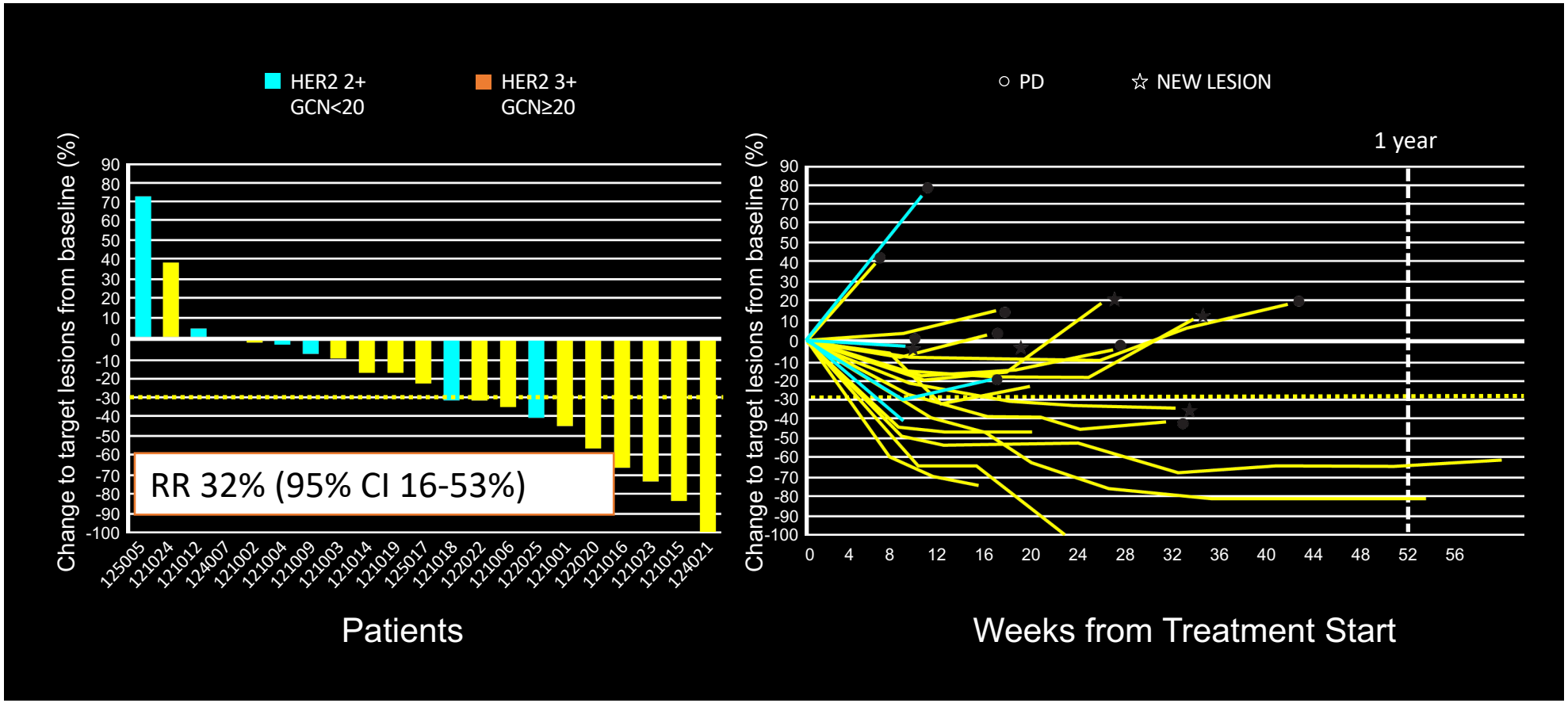
HER2 Amplification and Mutations

- **8887 CRC** (colonic 85.5% and rectal 14.5%) evaluated by comprehensive genomic profiling for genomic alterations in 315 cancer-related genes,
- **569 mCRCs were positive for ERBB2 (429 cases; 4.8%)** and/or ERBB3 (148 cases; 1.7%) and featured **ERBB amplification, short variant alterations, or a combination of the 2**.
- In the HERACLES-A study, **48/914 (5%)** patients with *KRAS* ex2 WT harbored ampl/overexpression



Both

HERACLES: Trastuzumab + Lapatinib in HER2 2+/3+



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

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Siena S, et al. *J Clin Oncol.* 2015;33(suppl):Abstract 3508.

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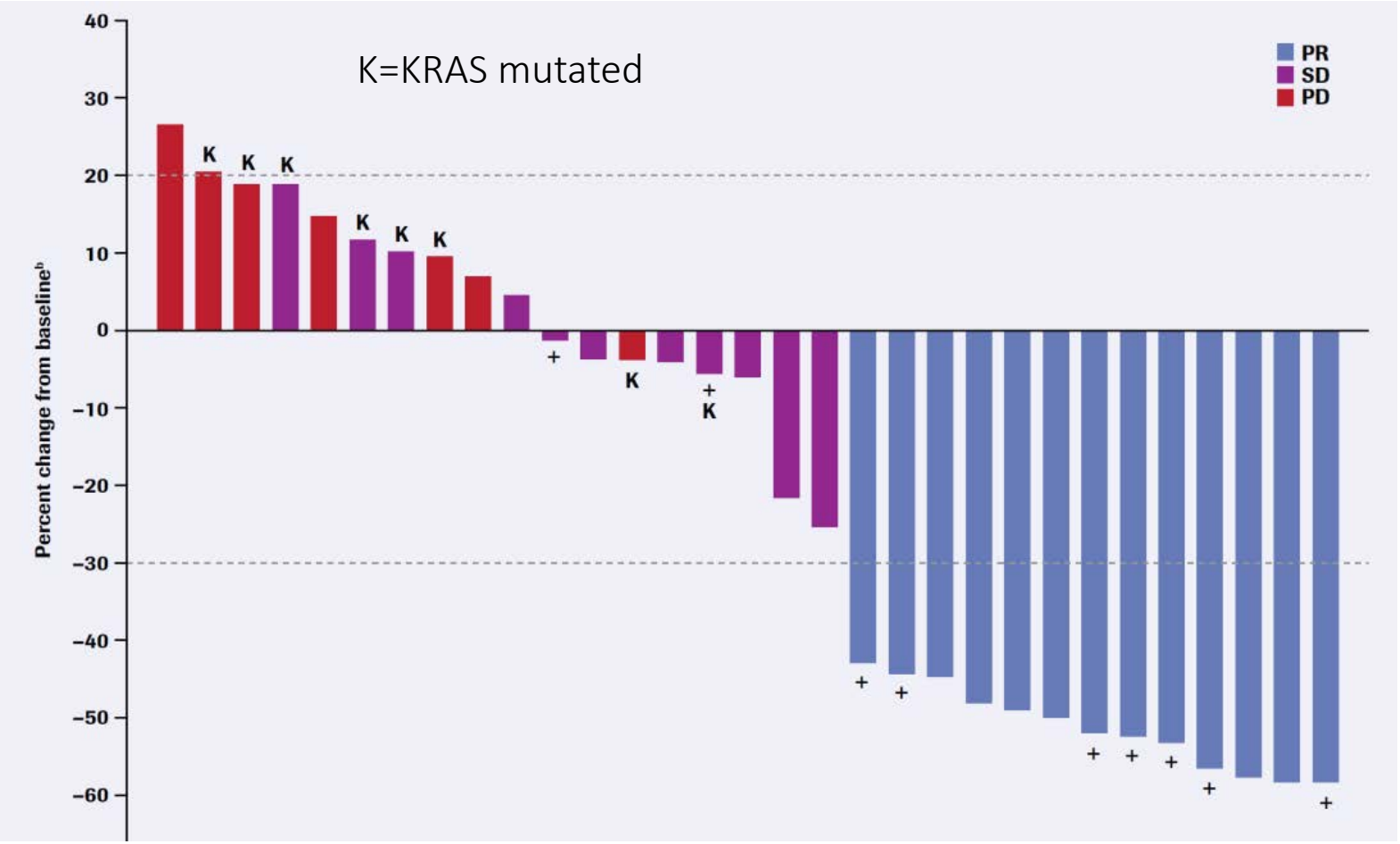
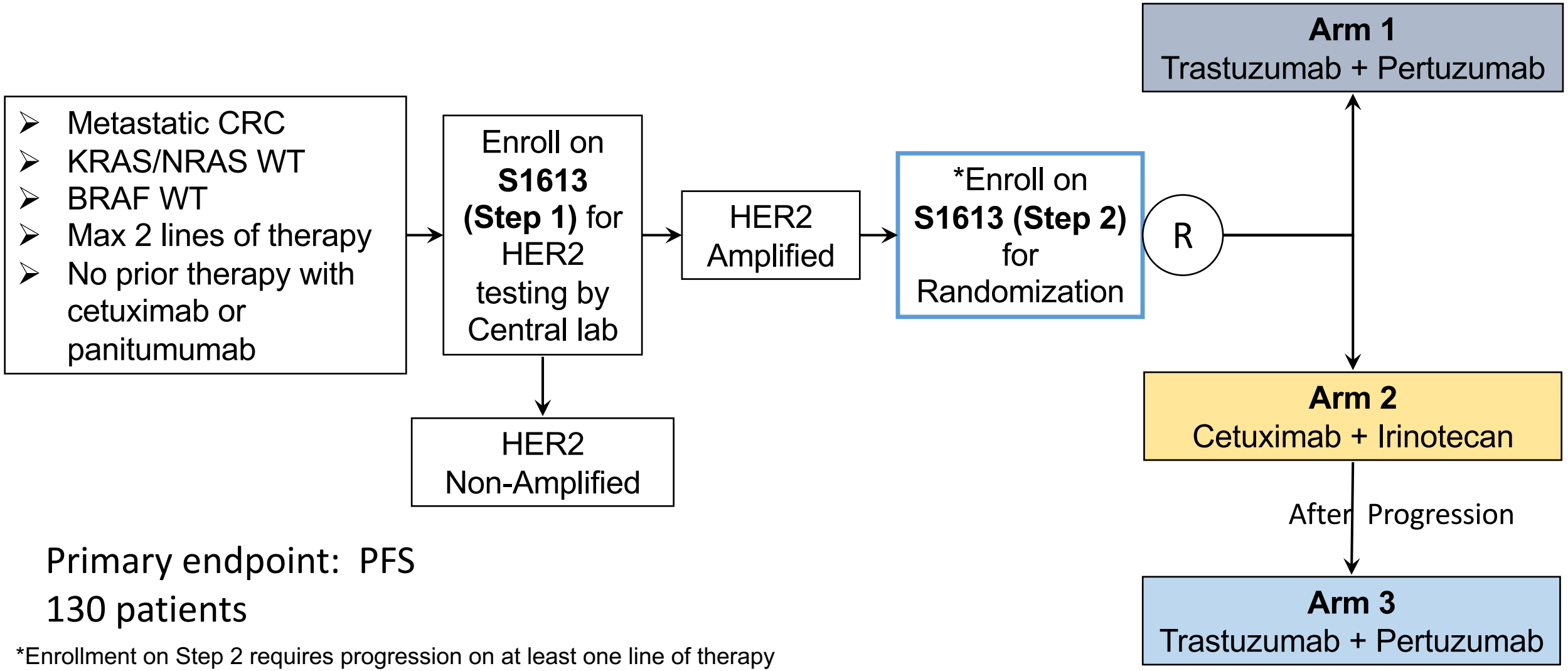
MyPathway: Trastuzumab + Pertuzumab in HER2 Amp



- **RR 38% ; PFS: 4.6 m**
- **5.7 months vs 1.4 months for concurrent KRAS WT vs MUT**

Hurwitz H, et al. Presented at ASCO GI 2017:Abstract 676.

Dual Inhibition: SWOG 1613 Study Schema



Primary endpoint: PFS

130 patients

*Enrollment on Step 2 requires progression on at least one line of therapy

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www.clinicaltrials.gov (NCT03365882)

NCI National Clinical Trials Network

PI's: Kanwal Raghav
Marwan Fakih

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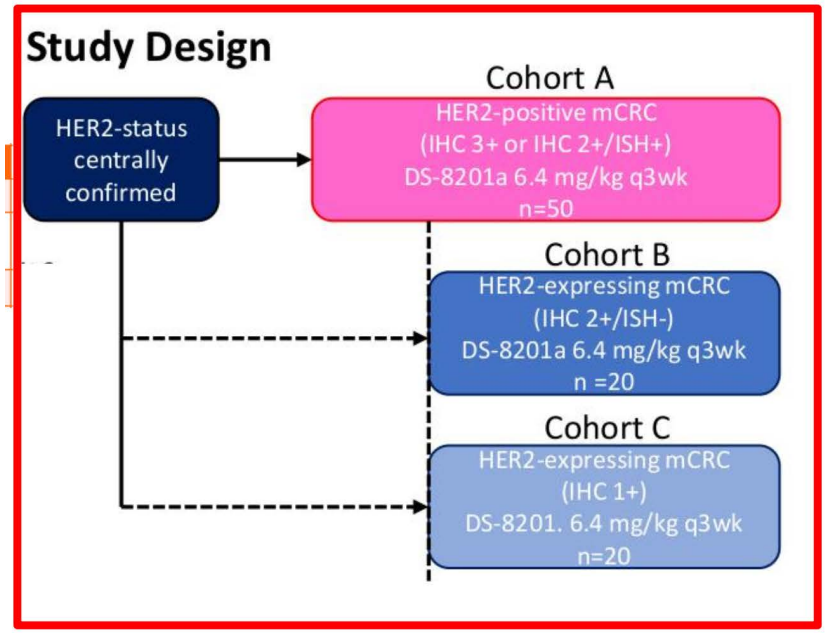
Mechanisms of Action of Novel HER2-Targeted Agents

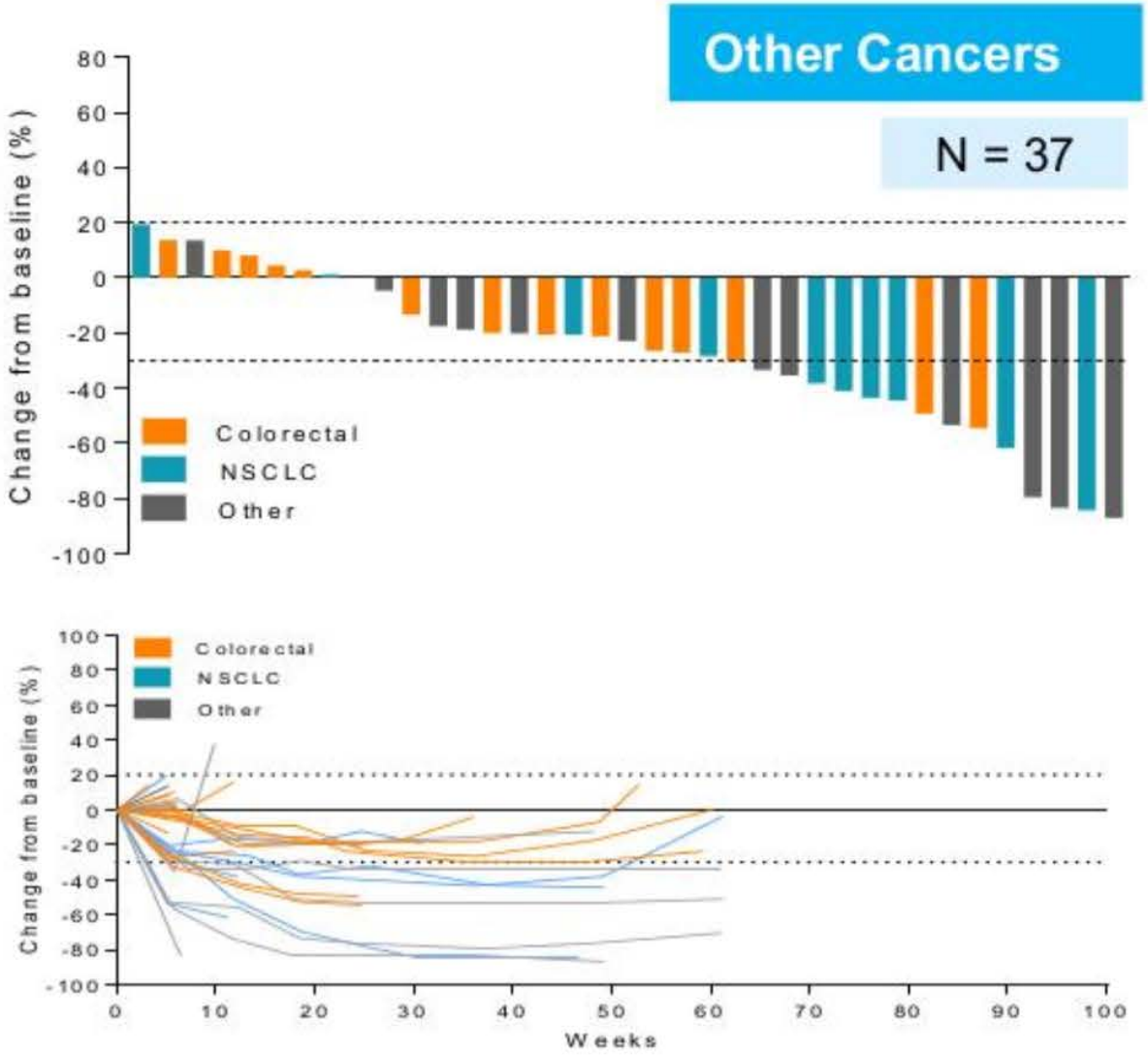
Agent	Mechanism of action	Defining features
Tucatinib[1]	Selective small molecular tyrosine kinase inhibitor	Potent selective inhibitor of HER2 but not EGFR, resulting in decreased potential for EGFR-related toxicities
Margetuximab[2]	Chimeric monoclonal antibody	Binds Fab region of HER2 but also Fc-engineered to activate and enhance immune responses compared to trastuzumab (binds Fab only)
Trastuzumab deruxtecan[3]	Antibody-drug conjugate	Humanized HER2 antibody with cleavable peptide-based linker and potent topoisomerase I inhibitor (exatecan derivative) payload

[1] Tolaney S. ASCO 2018. Metastatic Breast Cancer Poster Discussion Session Discussant;
[2] Rugo H et al. ASCO 2019;Abstract 1000; [3] Modi S et al. ASCO 2019;Abstract TPS1102.

DS-8201a: Trastuzumab deruxtecan

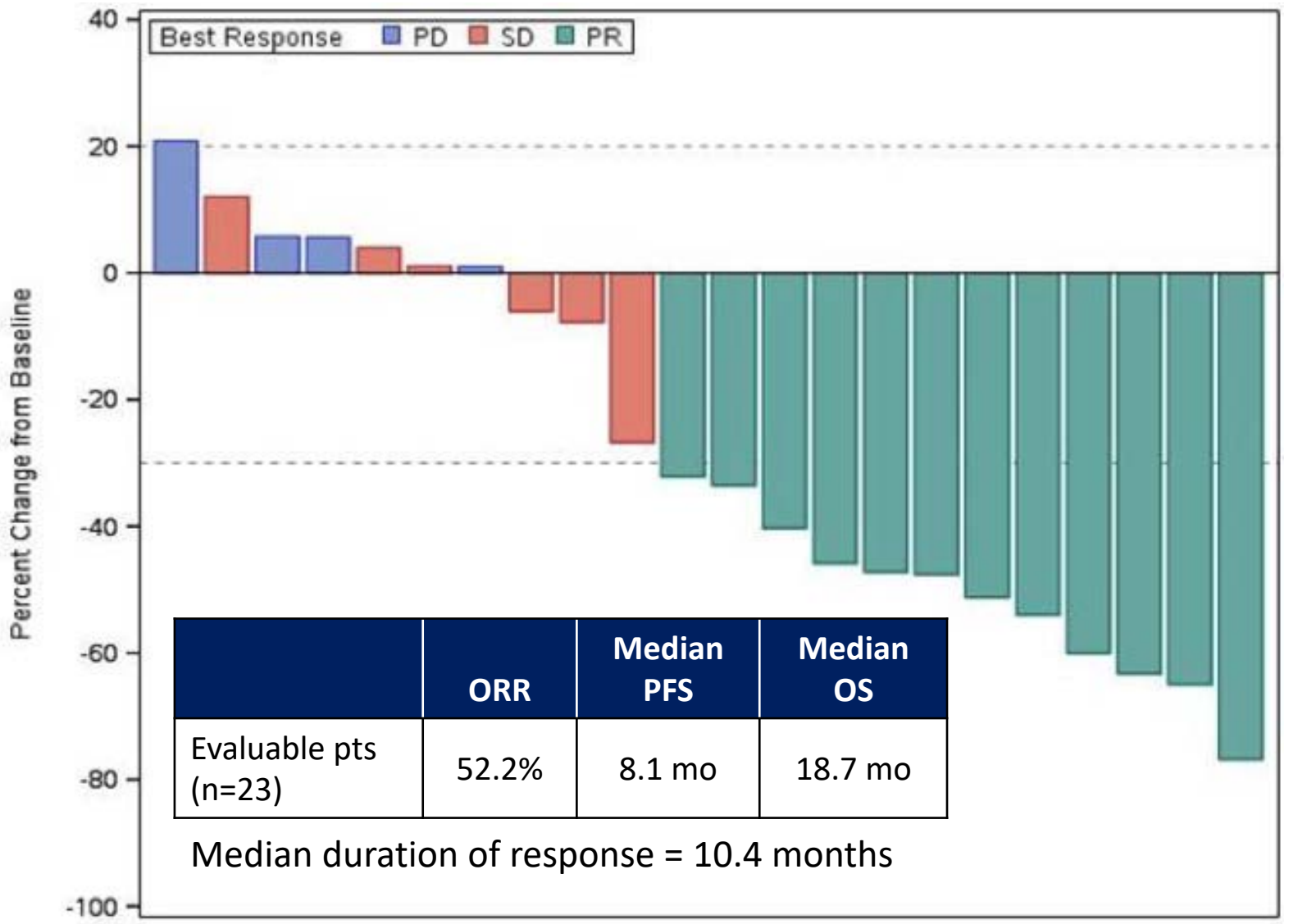


Primary Endpoint	Secondary Efficacy Endpoints
• ORR (proportion who achieved a best overall response of CR or PR) assessed by the independent radiologic facility review based on RECIST version 1.1 in Cohort A	• OS • PFS • DCR • DoR • ORR based on RECIST version 1.1 in Cohorts B and C • ORR assessed by the investigator based on RECIST version 1.1



Yoshino T et al. ESMO GI 2018;Abstract P-295.

MOUNTAINEER: Trastuzumab and Tucatinib for HER2-Amplified mCRC



	ORR	Median PFS	Median OS
Evaluable pts (n=23)	52.2%	8.1 mo	18.7 mo

Median duration of response = 10.4 months

Strickler JH et al. *Proc ESMO* 2019;Abstract 527PD.

Conclusions:

- BRAF V600E is a poor prognostic indicator for OS = BAD
  - Reduced median OS with standard chemotherapy (FOLFOX/FOLFIRI) = 12-14 mos, but improved to 17-19 mos with FOLFOXIRI-bev as 1L therapy
- TARGETED THERAPY EFFECTIVE = GOOD
  - BEACON = triplet and doublet NON-CHEMO were superior for OS vs. control (irinotecan/FOLFIRI + cetuximab) in 2L/3L
  - Superiority of triplet regimen vs. doublet regimen cannot be determined and was not so powered
  - VIC regimen (Vemurafenib, irinotecan, Cetux) appears equally effective
  - S1406 and BEACON demonstrate poor PFS with standard chemo of $\leq$ 2M in the refractory setting
  - It is **premature** to adopt the BEACON triplet regimen for treatment-naïve patients
- HER2 amplification is a negative predictive factor = BAD
  - HER2 directed therapy appears promising and effective; S1613 enrolling