MAYO CLINIC

Advances and Updates in the Management of Metastatic Colorectal Cancer

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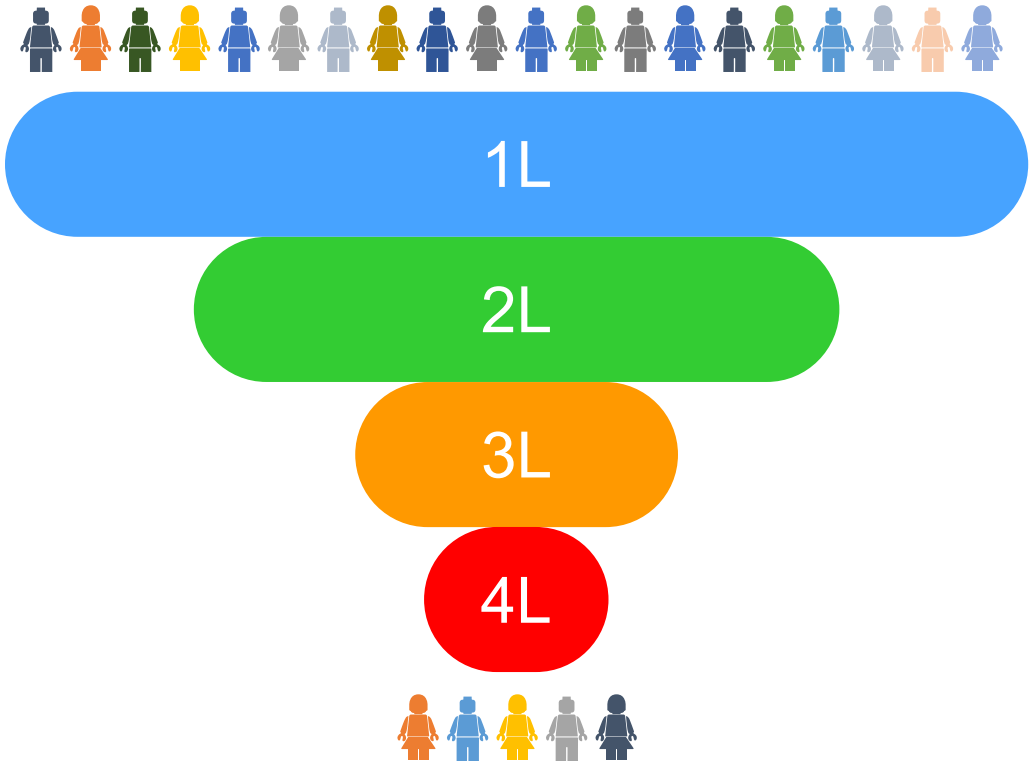
What Influences Treatment Choices in mCRC?

Patient characteristics

- Comorbidities
- Prior adjuvant treatment
- Age
- Performance status

Tumor characteristics

- Tumor burden
- Resectability
- Tumor location



Molecular characteristics

- RAS
- BRAF
- MSI-high
- HER2

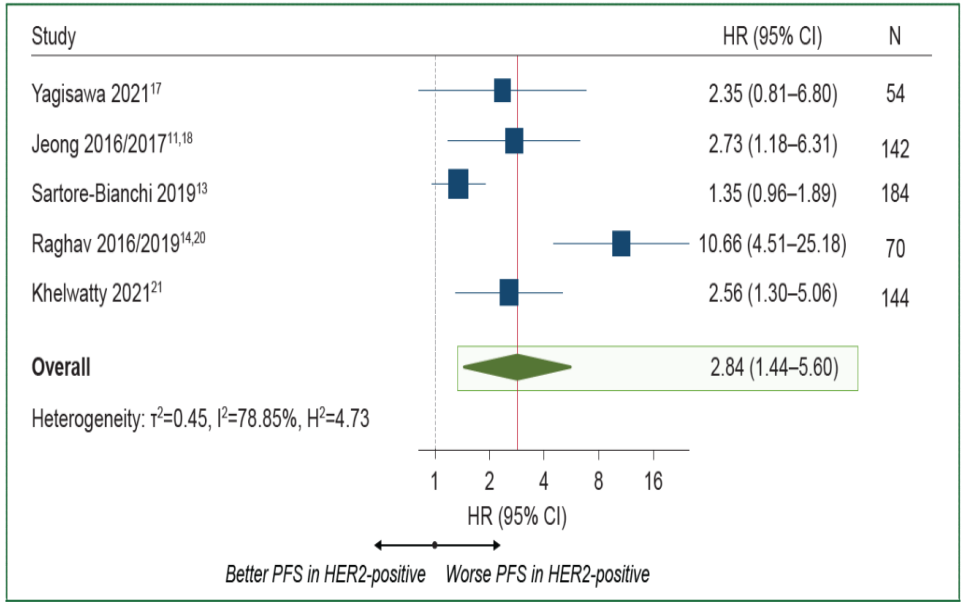
Patient preference

- Quality of life
- Toxicity profile

Therapy tailored according to individual patient needs

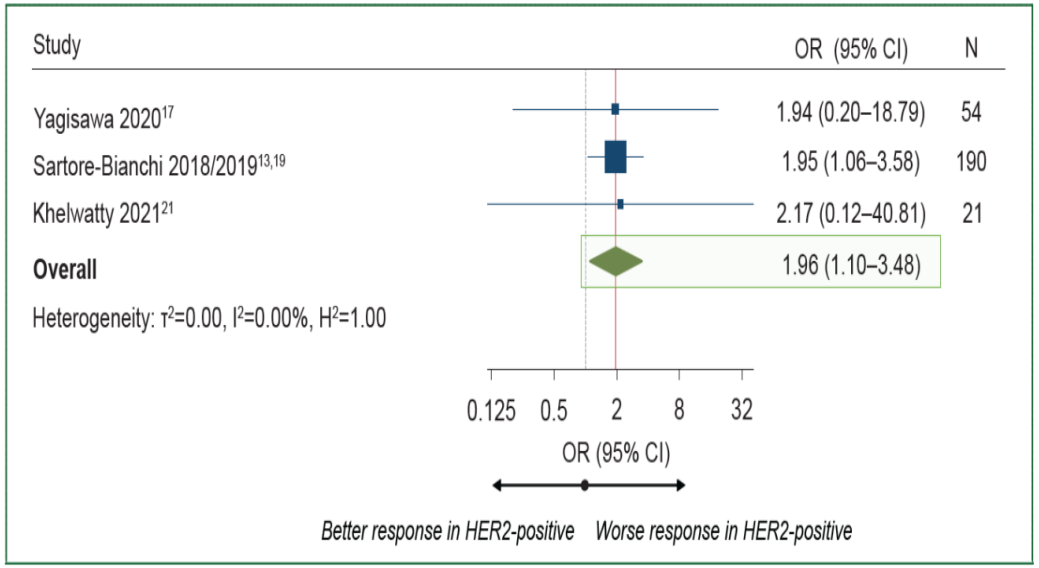
Impact of Anti-EGFR Therapies on HER2-Positive Metastatic Colorectal Cancer: A Systematic Literature Review and Meta-Analysis of Clinical Outcomes

Figure 1. Meta-analysis of PFS with anti-EGFR treatment in patients with RAS WT mCRC who were HER2-positive compared with patients with mCRC who were HER2-negative



Notes: HR=1 signifies no statistically significant differences between the HER2-positive and HER2-negative groups in the risk of death or progression on anti-EGFR treatment (represented by the gray vertical dashed line); HR >1 signifies higher risk of death or progression on anti-EGFR treatment in the HER2-positive group compared with the HER2-negative group; HR <1 signifies higher risk of death or progression on anti-EGFR treatment in the HER2-negative group compared with the HER2-positive group. The exact effect size of the ORR for the meta-analysis is represented by the vertical red line. CI, confidence interval; HR, hazard ratio; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; PFS, progression-free survival; WT, wild-type.

Figure 3. Meta-analysis of ORR to anti-EGFR treatment in patients with RAS WT mCRC who were HER2-positive compared with patients with mCRC who were HER2-negative

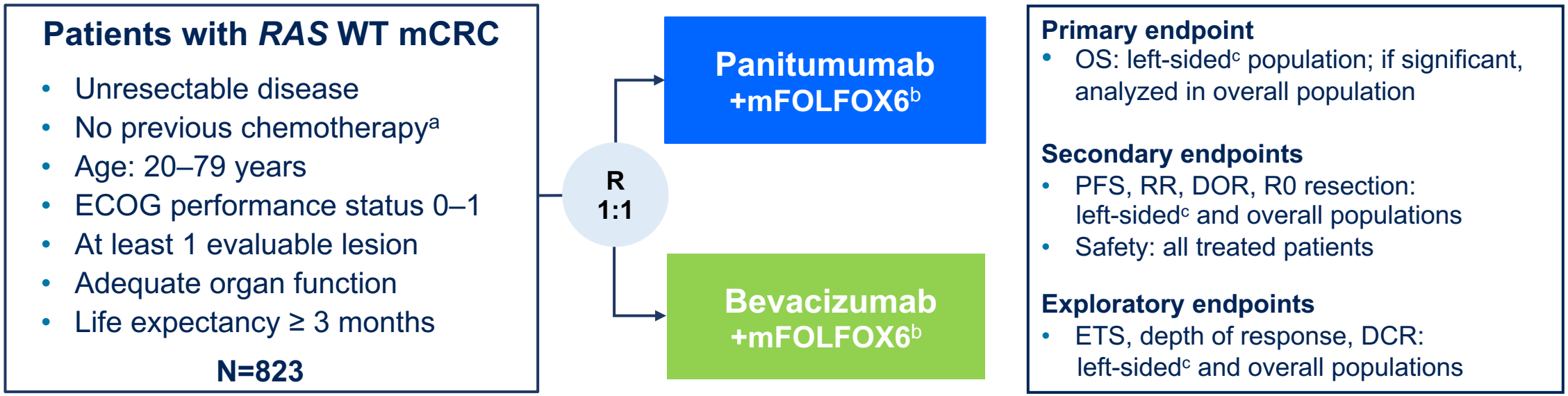


Notes: OR=1 signifies no statistically significant differences between the HER2-positive and the HER2-negative groups in response to anti-EGFR treatment (represented by the gray vertical dash line); OR <1 signifies higher odds of response to anti-EGFR treatment in the HER2-positive group compared with the HER2-negative group; OR >1 signifies higher odds of response to anti-EGFR treatment in the HER2-negative group compared with the HER2-positive group. The exact effect size of ORR for the meta-analysis is represented by the vertical red line. CI, confidence interval; HR, hazard ratio; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; OR, odds ratio; ORR, overall response rate; WT, wild-type.

Bekaii-Saab T el al . ESMO 2022

PARADIGM Trial Design

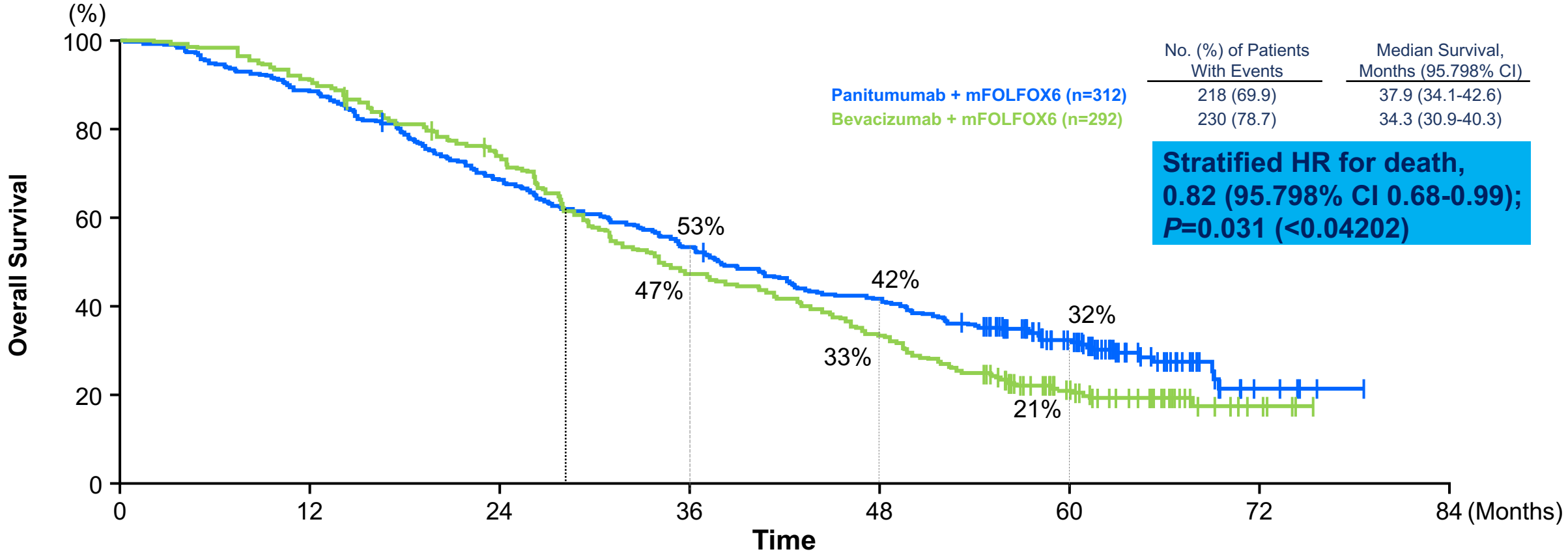
Phase 3, randomized, open-label, multicenter study (NCT02394795)



Stratification factors
- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

mCRC, metastatic colorectal cancer; WT, wild type; Mono, monotherapy; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression free survival; RR, response rate; DOR; duration of response; R0, curative resection; ETS, early tumor shrinkage; DCR, disease control rate.
[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection.
[c]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

Primary Endpoint-1; Overall Survival in Left-sided Population



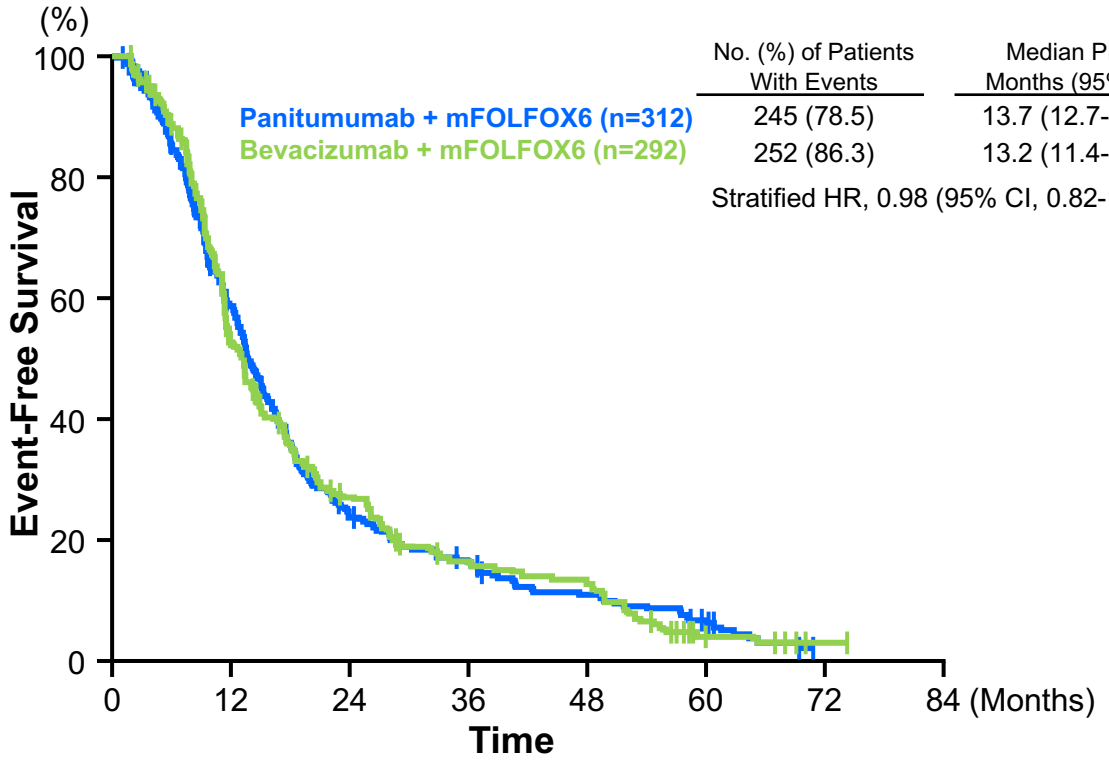
	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1-42.6)
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9-40.3)

Stratified HR for death, 0.82 (95.798% CI 0.68-0.99); *P*=0.031 (<0.04202)

No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

Progression-free Survival*

Left-sided Population

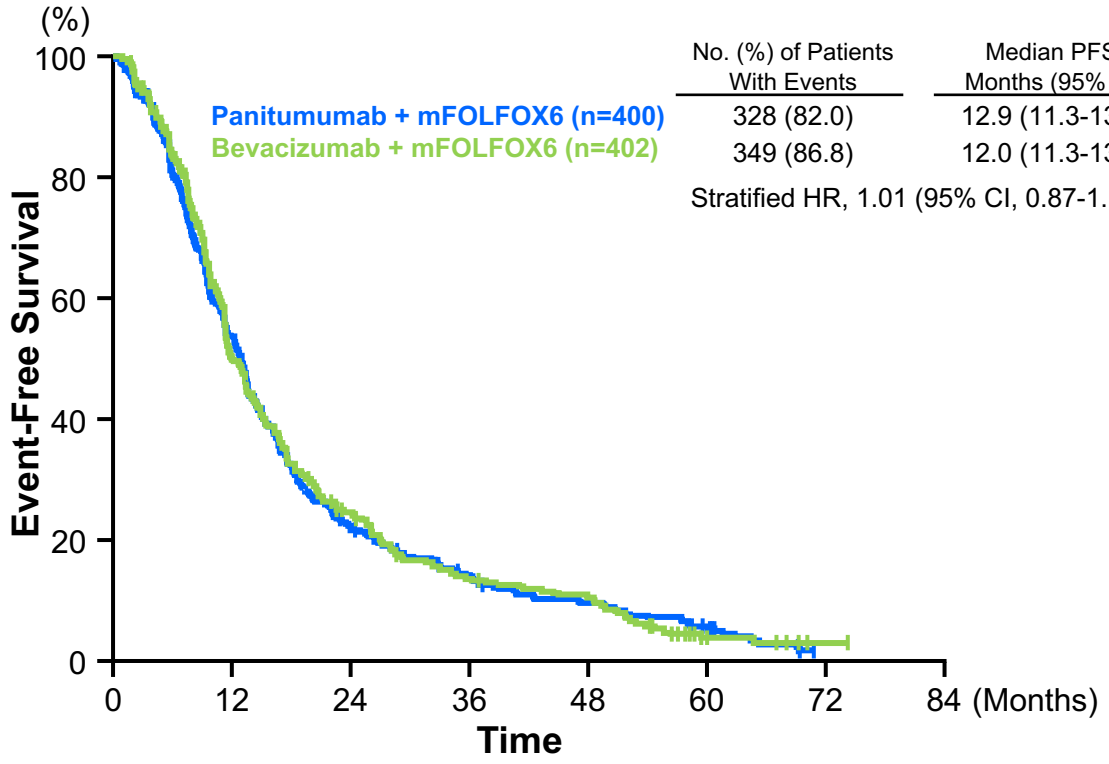


	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=312)	245 (78.5)	13.7 (12.7-15.3)
Bevacizumab + mFOLFOX6 (n=292)	252 (86.3)	13.2 (11.4-14.5)

Stratified HR, 0.98 (95% CI, 0.82-1.17)

No. at risk								
Panitumumab	312	149	59	38	24	13	0	0
Bevacizumab	292	139	67	40	31	5	1	0

Overall Population



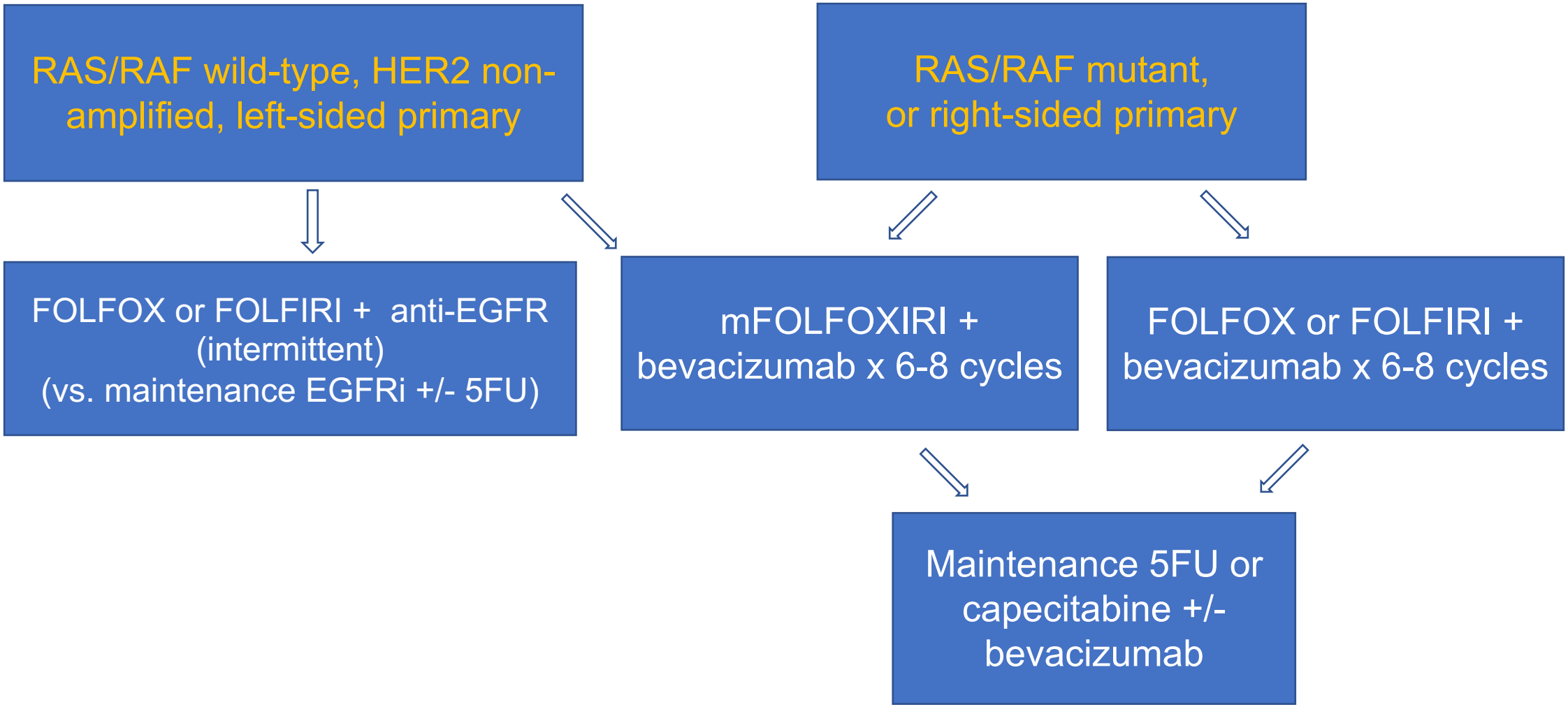
	No. (%) of Patients With Events	Median PFS, Months (95% CI)
Panitumumab + mFOLFOX6 (n=400)	328 (82.0)	12.9 (11.3-13.6)
Bevacizumab + mFOLFOX6 (n=402)	349 (86.8)	12.0 (11.3-13.5)

Stratified HR, 1.01 (95% CI, 0.87-1.18)

No. at risk								
Panitumumab	400	179	71	43	28	15	0	0
Bevacizumab	402	182	83	45	35	6	1	0

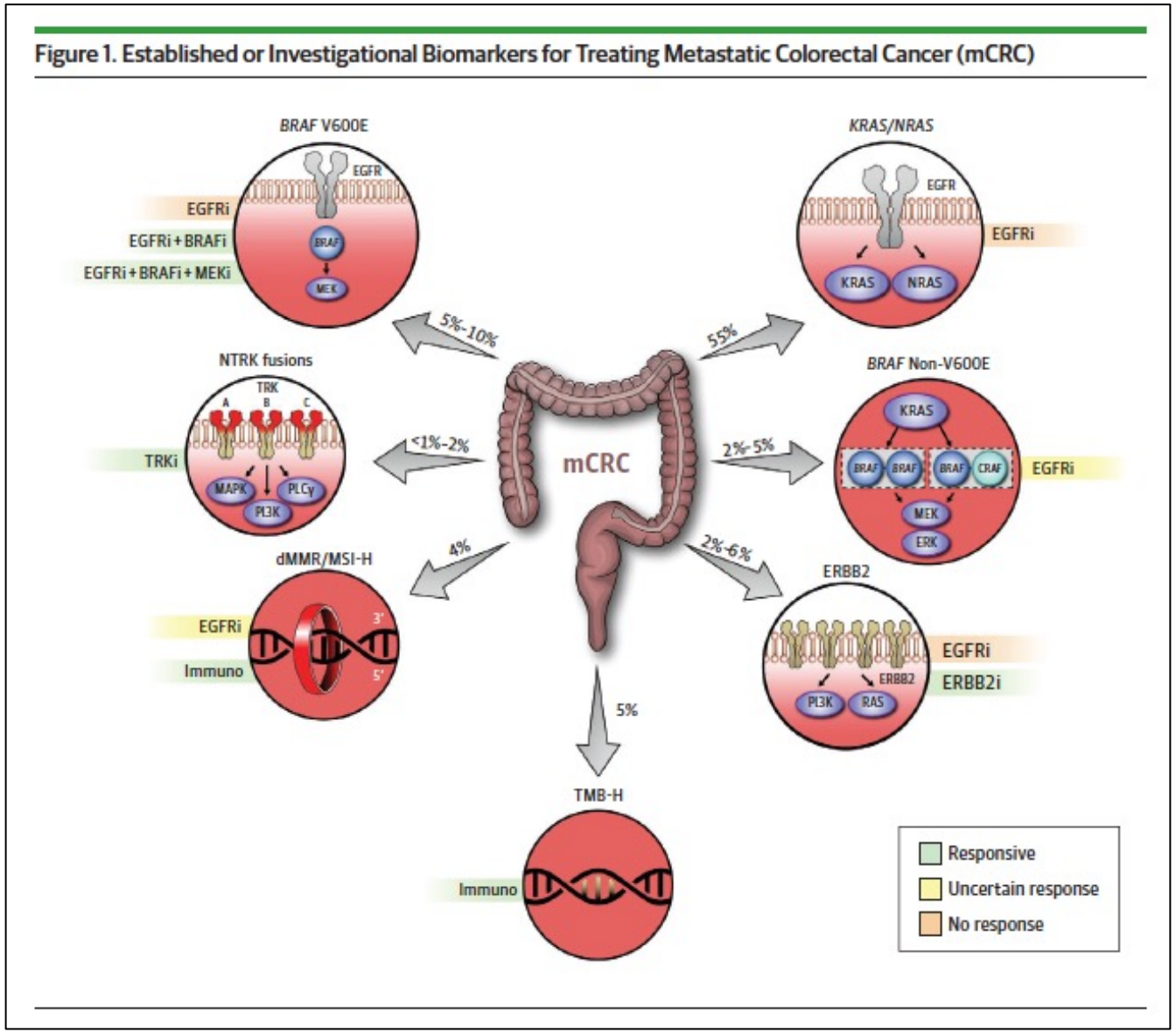
*Patients who underwent curative intent resection were censored at the last tumor evaluable assessment date before the resection.

1st line therapy for MSS metastatic colorectal cancer patients



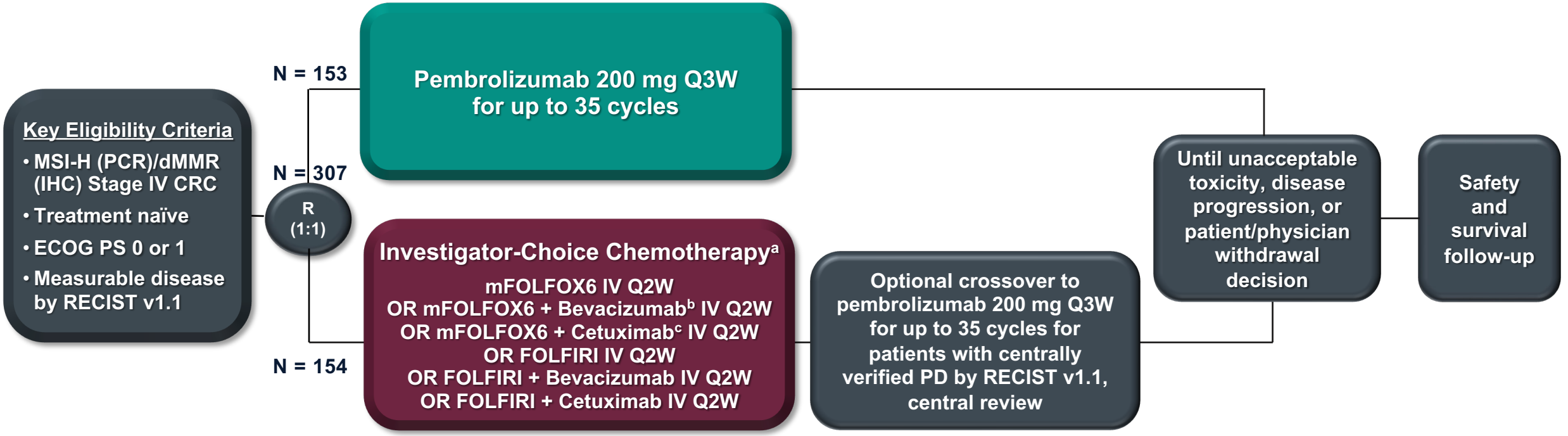
Courtesy/Adapted : Christina Wu, MD from ASCO 2022

Relevant Targets in mCRC



Strickler J , Bekaii-Saab T et al JAMA Onc 2022.

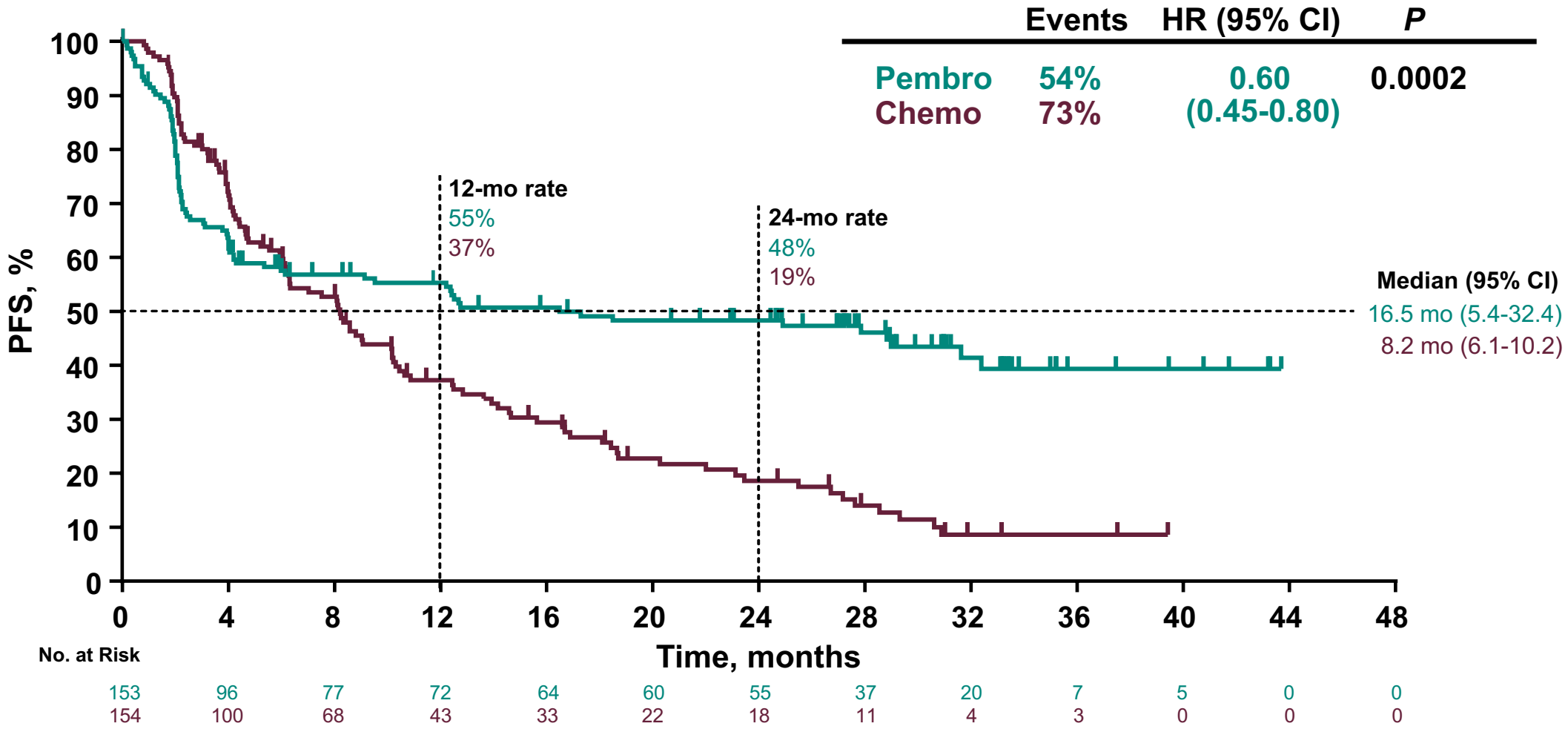
KEYNOTE-177 : 1L in MSI-H mCRC



- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

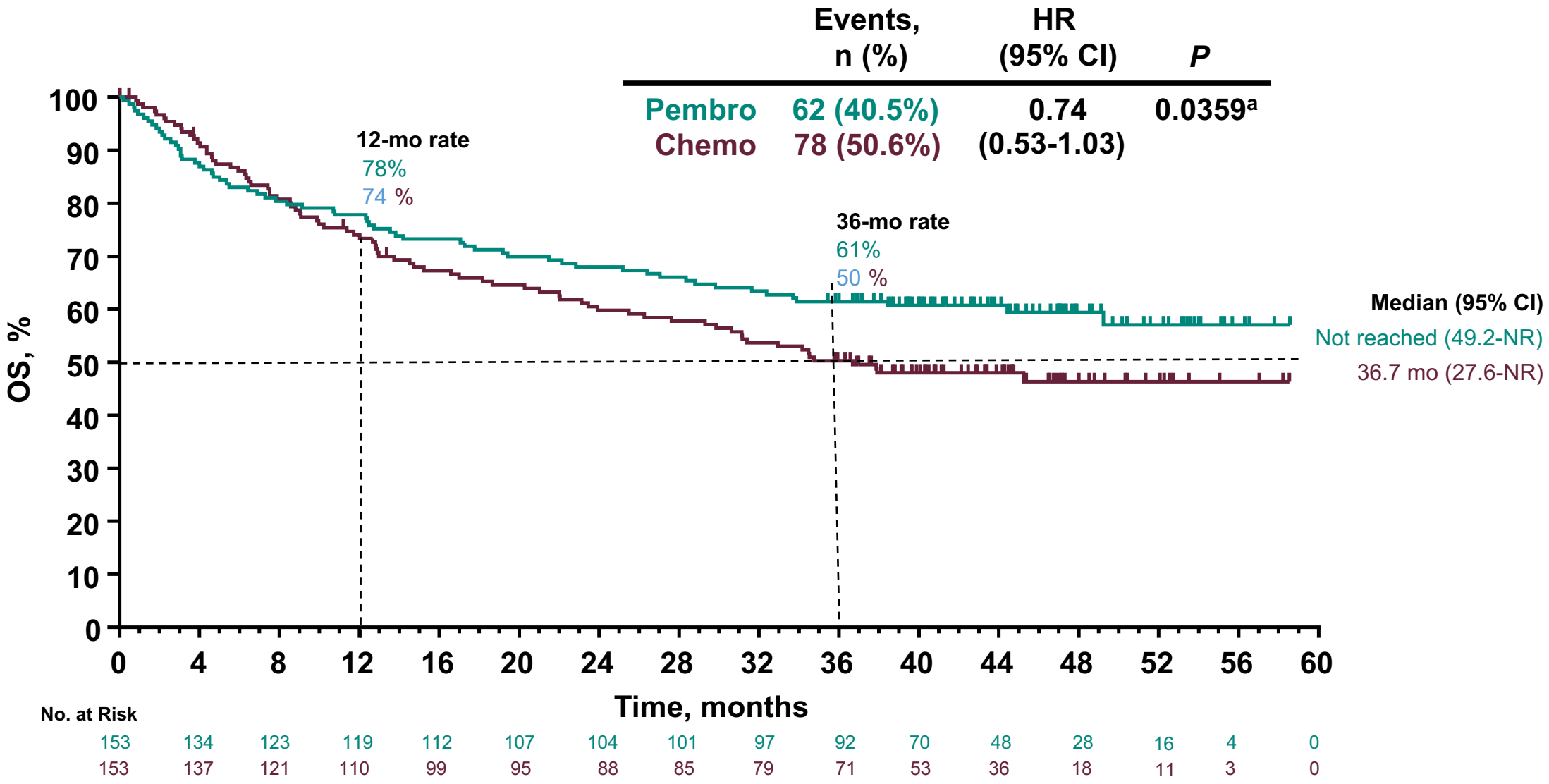
[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Progression-Free Survival



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR; Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

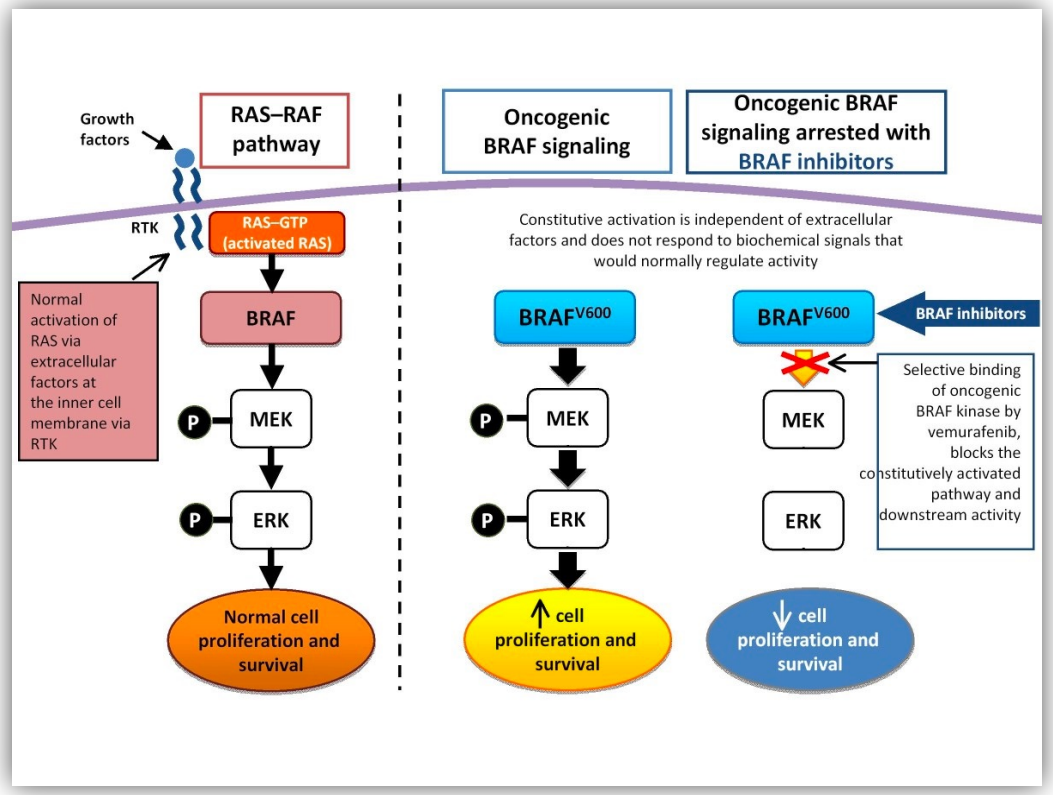
Overall Survival



[a]**Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38).** Data cut-off: 19Feb2021.

BRAF V600E Mutations: Not so much of a "MATCH" without tissue specific approaches!

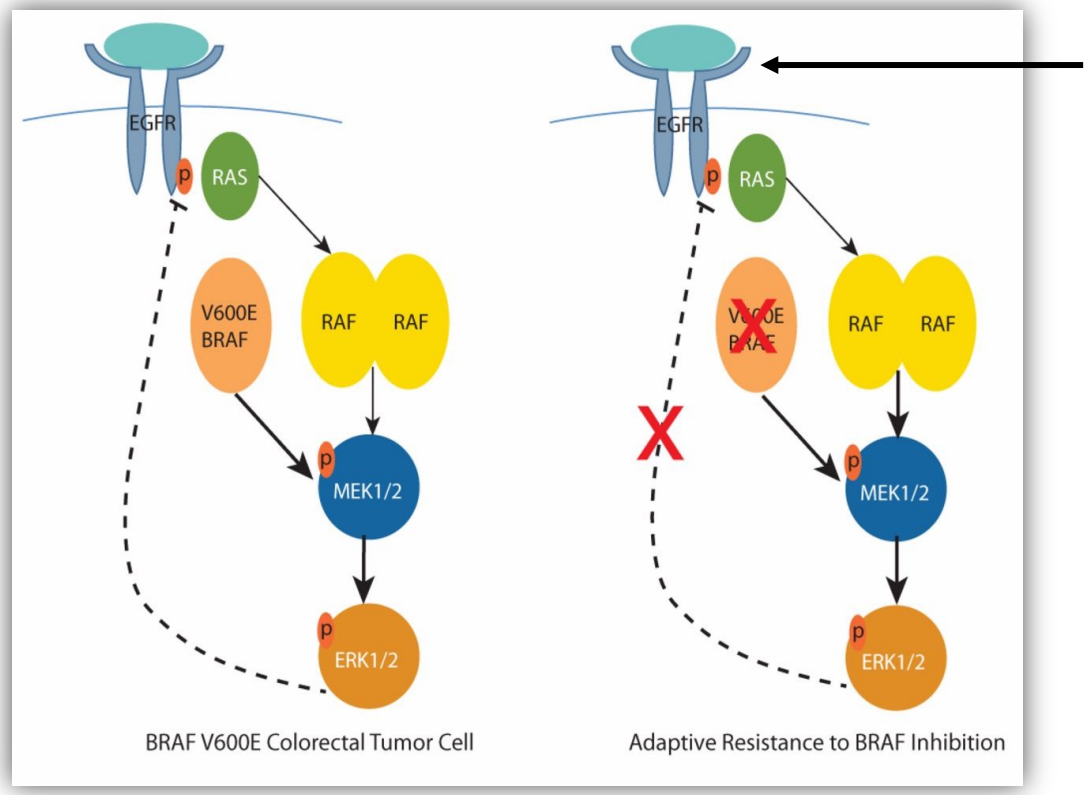
BRAF V600E and Melanoma



ORR with single-agent vemurafenib ~50%

Chapman PB et al. *N Engl J Med*. 2011;364:2507-2516.

BRAF V600E and mCRC



ORR with single-agent vemurafenib < 5%

Yeager R et al. *J Natl Compr Cancer Netw*. 2012;10(11):1456-1458.

BEACON: Phase 3 in 2nd/ 3rd Line BRAF V600E mut mCRC

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

ENCORAFENIB + BINIMETINIB + CETUXIMAB
N = 30

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

R 1:1:1

Triplet therapy
ENCORAFENIB + BINIMETINIB + CETUXIMAB
n = 205

Doublet therapy
ENCORAFENIB + CETUXIMAB
n = 205

Control arm
FOLFIRI + CETUXIMAB, or irinotecan + CETUXIMAB
n = 205

Primary Endpoints:

Triplet vs Control

OS
(All randomized Pts)

ORR – Blinded Central Review
(1st 331 randomized Pts)

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

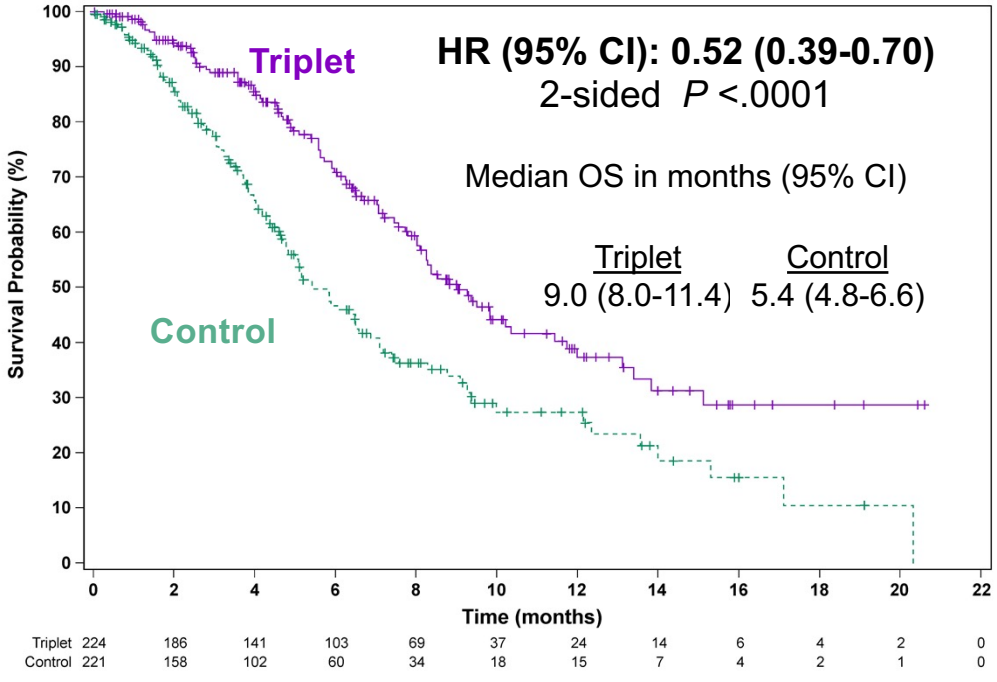
Secondary Endpoints: Doublet vs Control and Triplet vs Doublet - OS & ORR, PFS, Safety

QOL Assessments: EORTC QOL Questionnaire (QLQ C30), Functional Assessment of Cancer Therapy Colon Cancer, EuroQol 5D5L, and Patient Global Impression of Change).

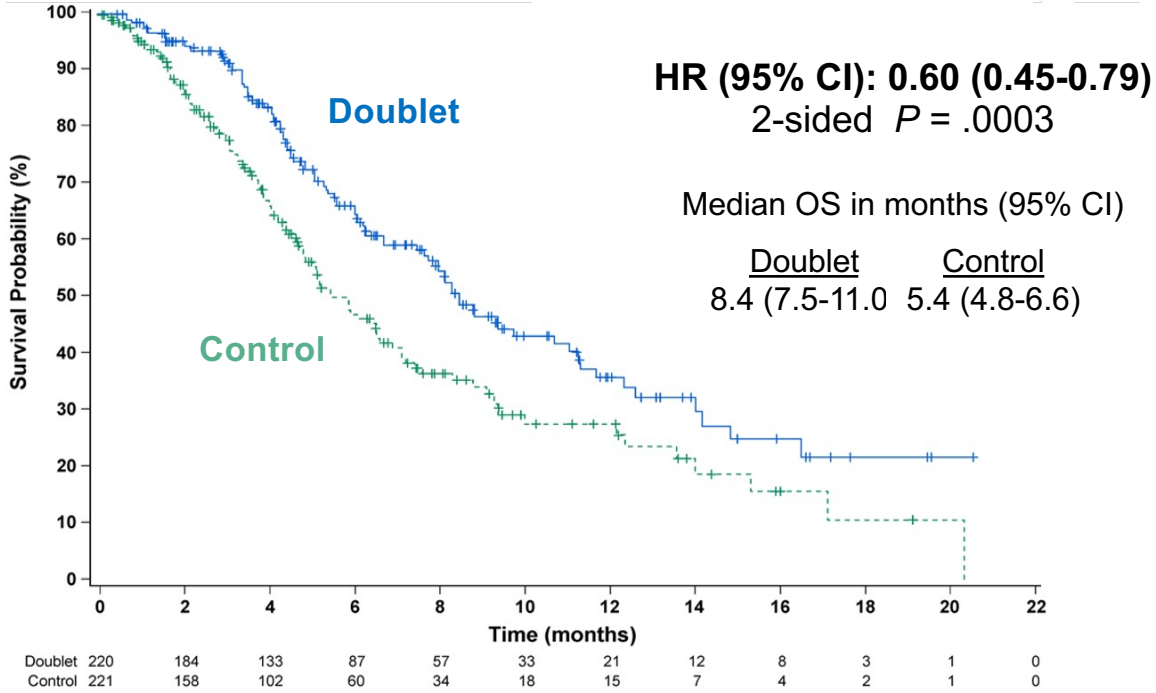
Kopetz et al., NEJM 2019

BEACON: Overall Survival and Objective Response Rate

Triplet vs Control



Doublet vs Control



Objective Response Rate (first 331 randomized patients)

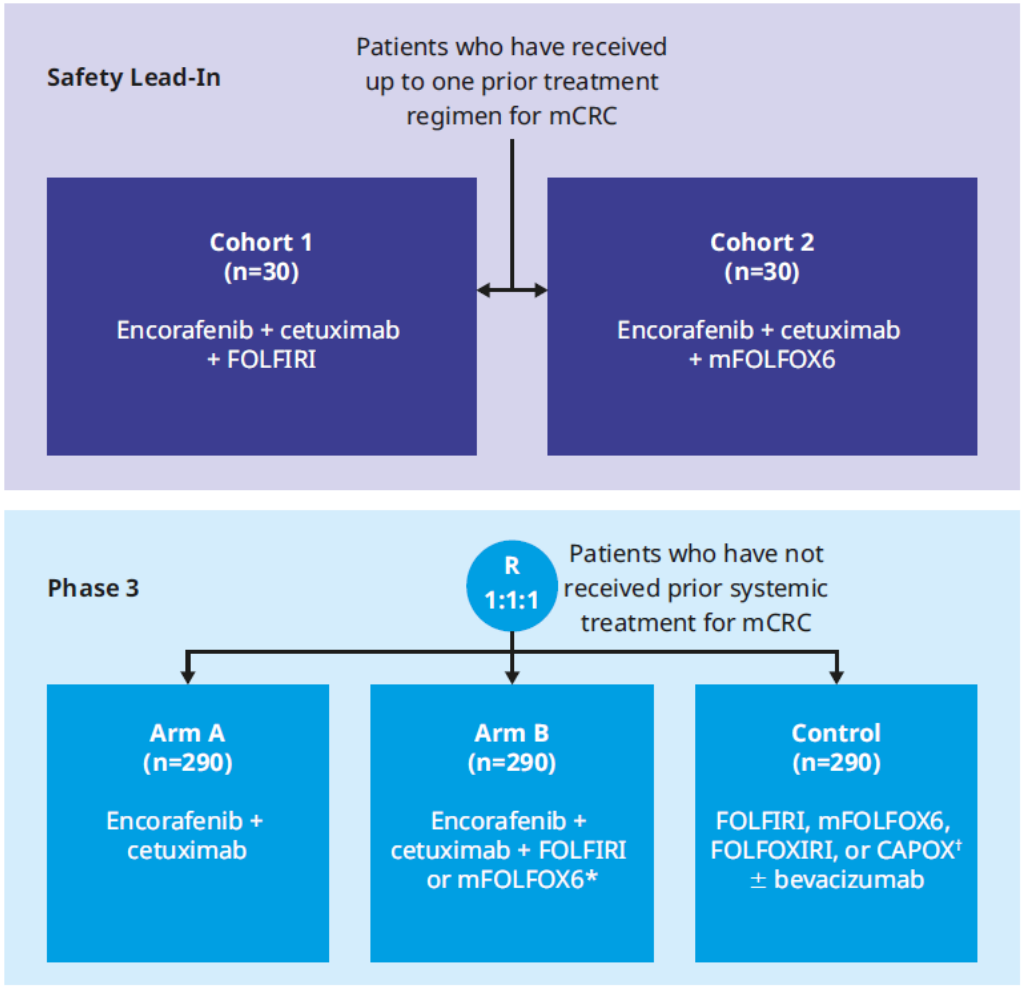
Confirmed Response by BICR	Triplet N = 111	Doublet N = 113	Control N = 107
Objective response rate	**26%**	**20%**	**2%**
(95% CI)	(18–35)	(13–29)	(<1–7)
P value vs control	<.0001	<.0001	

Tabernero J, Grothey A, et al. JCO 2021; Kopetz S, Grothey A, et al. *N Engl J Med*. 2019;381:1632-1643.

BREAKWATER: First-line Encorafenib + Cetuximab ± Chemotherapy Versus SOC in Patients With *BRAF* V600E–Mutant mCRC

Key Eligibility Criteria (N=930)

- Patients aged ≥16 (phase 3)
- Measurable, histologically or cytologically confirmed CRC adenocarcinoma (phase 3)
- Presence of metastatic disease
- *BRAF* V600E mutation present in tumor tissue or blood
- No dMMR/MSI-H disease
- Participants who received ≤1 (safety lead-in) or no (phase 3) prior systemic regimens for metastatic disease; No previous treatment with BRAFi or EGFRi
- ECOG PS of 0 or 1



Primary Endpoints

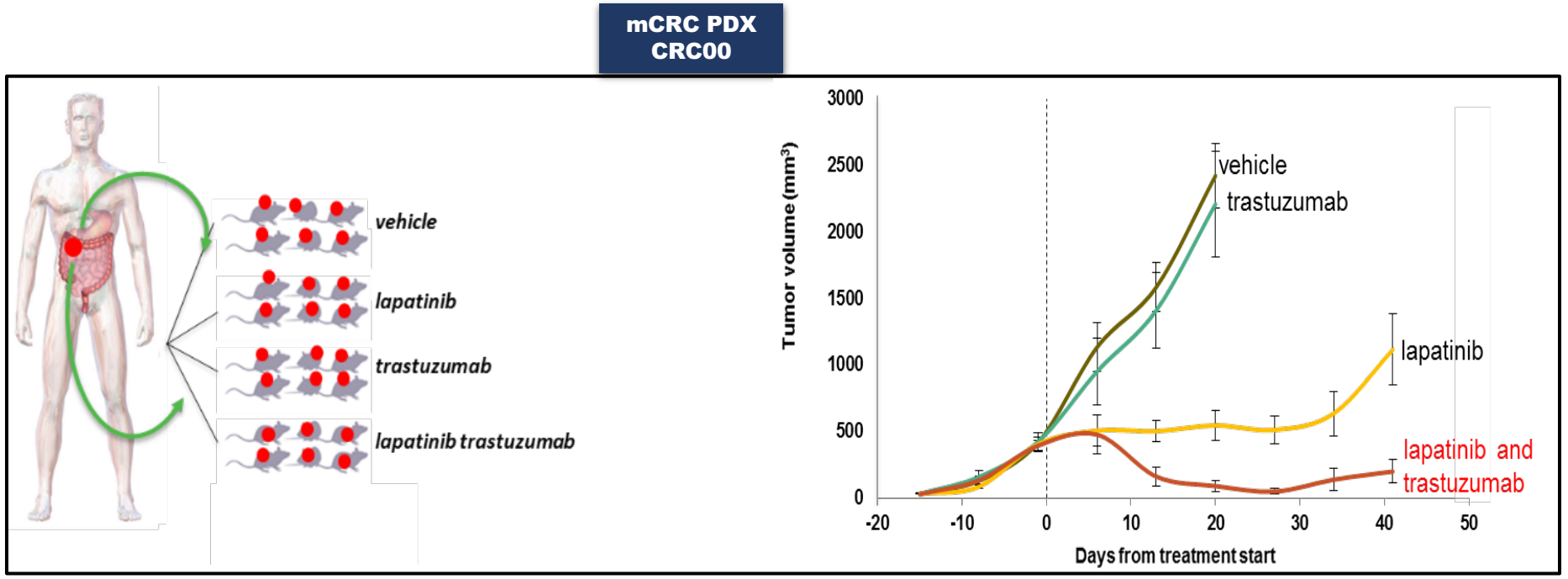
- Safety lead-in: Incidence of dose-limiting toxicities
- Phase 3: PFS by BICR of Arm A vs Arm C and Arm B vs Arm C

NCT04607421

A multicenter, open-label, randomized, interventional study to determine the safety, tolerability, and efficacy of encorafenib + cetuximab with or without chemotherapy versus standard of care chemotherapy in patients with previously untreated *BRAF* V600E-mutant mCRC. Prior to the phase 3 portion, a safety lead-in will be conducted to evaluate the safety/tolerability and PK of encorafenib + cetuximab in combination with either mFOLFOX6 or FOLFIRI

1. ClinicalTrials.gov https://www.clinicaltrials.gov/ct2/show/NCT04607421. Accessed October 29, 2020..

Anti-HER2 PreclinicalHER2+ mCRC PDXs



Bertotti A et al. *Cancer Discov*. 2011;1(6):508-523; Trusolino L. Unpublished data;

PARIS 2022 ESMO congress

Additional analyses of MOUNTAINEER: A phase 2 study of tucatinib and trastuzumab for HER2-positive mCRC

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Duke University Medical Center, Durham, NC, USA

Coauthors: Andrea Cercek, Salvatore Siena, Thierry Andre, Kimmie Ng, Eric Van Cutsem, Christina Wu, Andrew Scott Paulson, Joleen M. Hubbard, Andrew L. Coveler, Christos Fountzilas, Adel Kardosh, Pashtoon Murtaza Kasi, Heinz-Josef Lenz, Kristen Ciombor, Elena Elez, David L. Bajor, Michael Stecher, Wentao Feng, Tanios S. Bekaii-Saab

MOUNTAINEER: Global, Open-label, Phase 2 Trial[1]

Key Eligibility Criteria

- ≥2L mCRC
- HER2+ per local IHC/ISH/NGS testing
- *RAS* wild-type
- Measurable disease per RECIST 1.1
- Prior fluoropyrimidines, oxaliplatin, irinotecan, and anti-VEGF mAb

Cohort A (n=45)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)[a,b]

Expansion

R[c]

Cohort B (n=41)

Tucatinib 300 mg PO BID
+
Trastuzumab 6 mg/kg Q3W (loading dose 8 mg/kg C1D1)[a,b]

Cohort C (n=31)

Tucatinib 300 mg PO BID[a]

Endpoints

Efficacy

Assessed in patients who received any amount of study treatment and had HER2+ tumors[d]

1. **Primary:** cORR in Cohorts A+B (RECIST 1.1 per BICR)
2. **Secondary:**
   - Cohorts A+B: DOR per BICR, PFS per BICR, and OS
   - **Cohort C: ORR by 12 weeks of treatment per BICR (pre-crossover)**
3. **Prespecified:**
   - **DCR for pre- and post-crossover patients**
   - **cORR per BICR for post-crossover patients**

Safety presented in pre- and post-crossover patients who received any amount of study treatment

Patients treated with tucatinib monotherapy were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12

a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumour primary vs other; d Patients had HER2+ tumors as defined by one or more protocol required local tests: IHC 3+ (n=46), amplification by ISH (n=36), or amplification by NGS (n=69)

≥2L, second line and later; BICR, blinded independent central review; BID, twice a day; C1D1, cycle 1 day 1; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2+, human epidermal growth receptor 2-positive; IHC, immunohistochemistry; ISH, in situ hybridisation; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumours; VEGF, vascular endothelial growth factor.

Data cutoff: 28 March 2022

1. Adapted from Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

Efficacy Outcomes

Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (3.6)	0	0
	PR	29 (34.5)	1 (3.3)	5 (17.9)
	SD[b]	28 (33.3)	23 (76.7)	18 (64.3)
	PD	22 (26.2)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2.4)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		**38.1 (27.7-49.3)[e]**	**3.3 (0.1-17.2)[f]**	**17.9 (6.1-36.9)[e]**
DCR[g] per BICR, n (%)		**60 (71.4)**	**24 (80.0)**	**23 (82.1)**

a Confirmed best overall response assessed per RECIST 1.1; b Includes SD and non-CR/non-PD; c Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable; d Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); e cORR; f ORR by 12 weeks of treatment; g Defined as sum of CR, PR, and SD.

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Data cutoff: 28 Mar 2022

1. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

Safety Summary

- Safety profiles for tucatinib monotherapy pre- and post-crossover groups are consistent with the known tucatinib safety profile

TEAEs, n (%)		Tucatinib + Trastuzumab Cohorts A+B n=86[1]	Tucatinib Monotherapy Cohort C[a] n=30	Tucatinib + Trastuzumab Post-Crossover[b] n=28
Any grade AEs		82 (95.3)	28 (93.3)	23 (82.1)
Grade ≥3 AEs		33 (38.4)	8 (26.7)	6 (21.4)
SAEs		19 (22.1)	3 (10.0)	2 (7.1)
AEs leading to tucatinib discontinuation		5 (5.8)[c]	0	2 (7.1)[d]
Deaths due to AEs		0	0	0
Most common AEs[e]	Diarrhoea	55 (64.0)	10 (33.3)	10 (35.7)
	Abdominal pain	13 (15.1)	6 (20.0)	3 (10.7)
	Fatigue	38 (44.2)	6 (20.0)	3 (10.7)

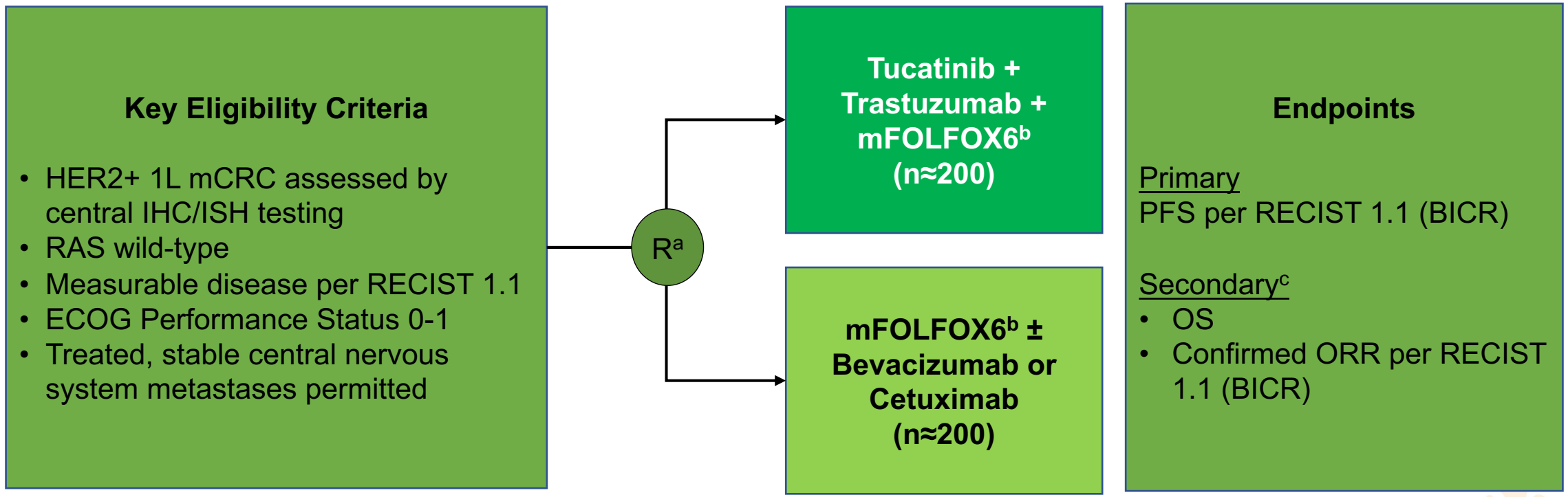
a AEs pre-crossover are defined as AEs that are newly onset or worsened on or after receiving the first dose of tucatinib and up to 30 days after last dose of tucatinib for patients who didn't crossover, or the day before crossover for patients who crossed over; b AEs post-crossover are defined as AEs that are newly onset or worsened on or after crossover (date of first dose of tucatinib or trastuzumab, whichever came first, in the first cycle of trastuzumab) and up to 30 days after the last dose of study treatment (tucatinib or trastuzumab); c Three patients discontinued trastuzumab; d One patient discontinued tucatinib due to ALT increase, and one patient discontinued tucatinib due to AST increase. One patient discontinued trastuzumab; e AEs reported in ≥20% of patients in patients treated with tucatinib monotherapy (pre-crossover).

AE, adverse event; ALT; alanine transaminase; AST, aspartate transaminase; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Data cutoff: 28 Mar 2022

1. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

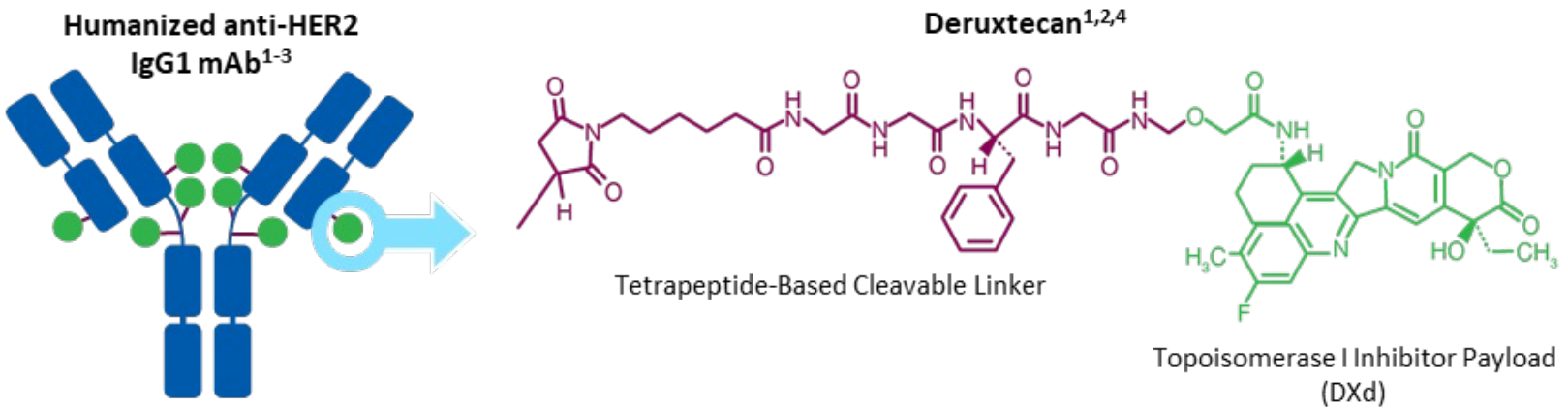
MOUNTAINEER-03:
Global, Randomised, Open-Label, Phase 3 Trial



T-DXd is a Novel ADC Designed to Deliver an Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

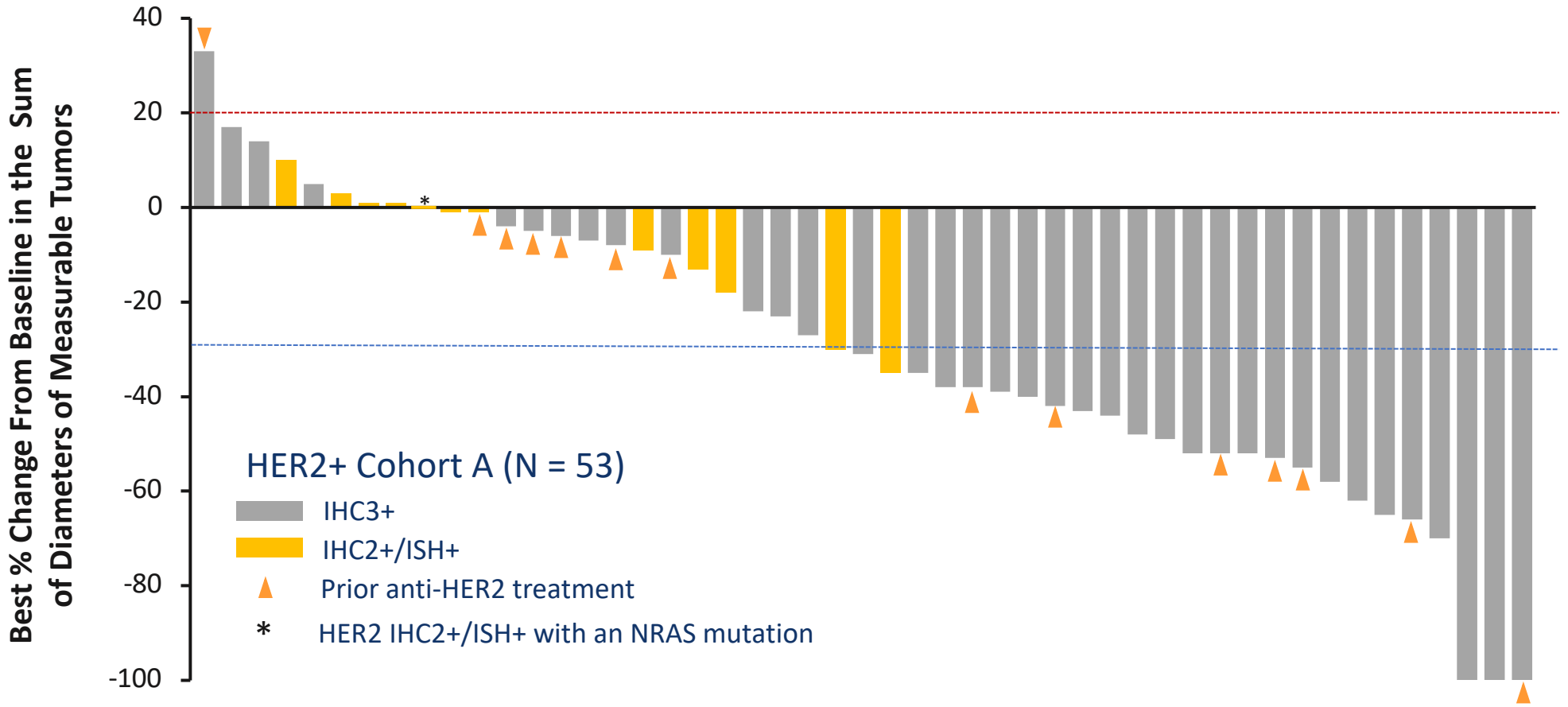


- Payload mechanism of action: topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio ≈ 8
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.

1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

DESTINY-CRC01: Single Arm PII WF Plot



AEs of Special Interest: Interstitial Lung Disease

	All Patients (N = 78)					
Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial Lung Disease	0	2 (2.6)	1 (1.3)	0	2 (2.6)	5 (6.4)

Among the 5 total events:

- Median time to investigator-reported onset was 80 days (range, 22-132)
- 5 of 5 patients with grade ≥ 2 ILD received corticosteroids
- 2 patients recovered, 1 did not recover (later died due to disease progression), and 2 died
- In the 2 fatal cases, onset was from 40-126 days, both received steroids as part of treatment, and death occurred 6-18 days after diagnosis

Protocol recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

Drug related; ILD was determined by an Independent ILD Adjudication Committee based on 44 preferred terms.
One additional grade 5 ILD case in Cohort B was reported after the data cutoff. This case was adjudicated after data cutoff as drug-related ILD.

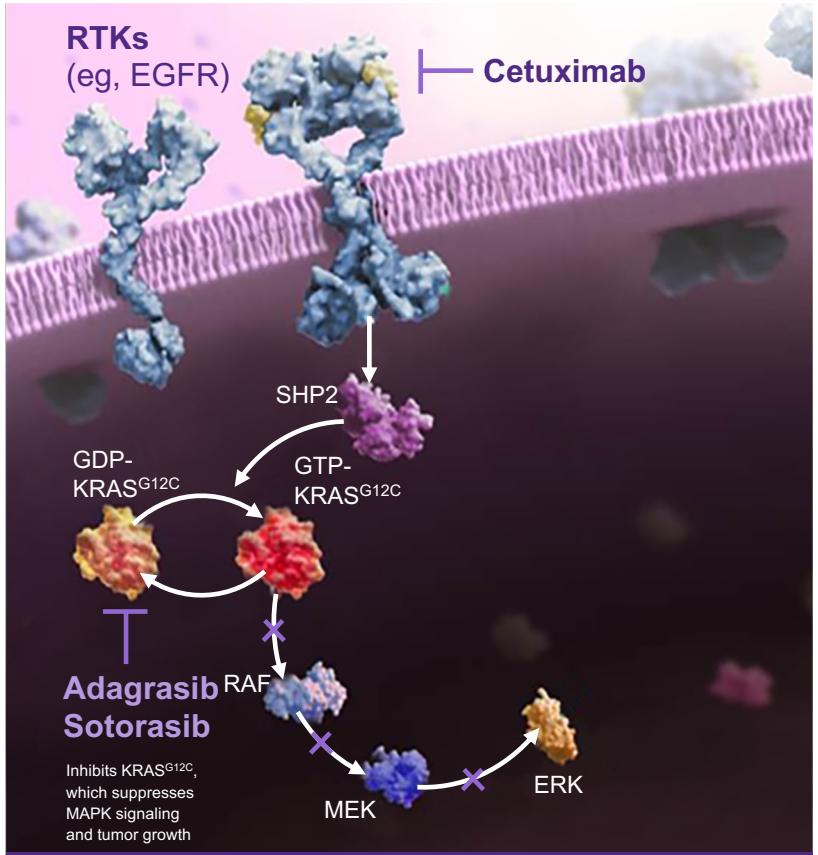
Recent data of HER2-targeted therapies in patients with advanced or metastatic colorectal cancer

Regimen	Trial (n) – year	ORR	PFS	OS	Most common Grade 3+ AEs
Trastuzumab + lapatinib	HERACLES-A (n=32) – 2016	28%	4.7m	10m	Fatigue 16% Decreased LVEF 6%
Trastuzumab + pertuzumab	MyPathway (n=84; 57 evaluable) – 2019	32%	2.9m	11.5m	Hypokalemia 5% Abdominal pain 5%
Pertuzumab and T-DM1	HERACLES-B (n=31) – 2020	9.7%	4.1m	Not reported	Thrombocytopenia 7%
Trastuzumab deruxtecan	DESTINY-CRC01 (N=78; 53 HER2+) – 2021	45.3%	6.9m	15.5m	Neutropenia 15% Anemia 13%
Tucatinib + trastuzumab	MOUNTAINEER (n=117) - 2022	38.1%	8.2m	24.1m	Hypertension 7% Diarrhea 3.5%

Tosi F, Sartore-Bianchi A, et al. Long-term Clinical Outcome of Trastuzumab and Lapatinib for HER2-positive Metastatic Colorectal Cancer. Clin Colorectal Cancer. 2020 Dec;19(4):256-262.e2. doi: 10.1016/j.clcc.2020.06.009. Epub 2020 Jun 27. PMID: 32919890.
Meric-Bernstam F, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2019 Apr;20(4):518-530. doi: 10.1016/S1470-2045(18)30904-5. Epub 2019 Mar 8. PMID: 30857956; PMCID: PMC6781620.
Sartore-Bianchi A, et al. Pertuzumab and trastuzumab emtansine in patients with HER2-amplified metastatic colorectal cancer: the phase II HERACLES-B trial. ESMO Open. 2020 Sep;5(5):e000911. doi: 10.1136/esmoopen-2020-000911. PMID: 32988996; PMCID: PMC7523198.
Siena S, et al; DESTINY-CRC01 investigators. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2021 Jun;22(6):779-789. doi: 10.1016/S1470-2045(21)00086-3. Epub 2021 May 4. PMID: 33961795.
https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.3004
https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.4_suppl.119

KRAS G12C Mutations in CRC : Background

- $KRAS^{G12C}$ mutations occur in approximately 3–4% of CRC, act as oncogenic drivers, and are a negative predictor of cetuximab efficacy[1–4]
- The KRAS protein cycles between guanosine triphosphate (GTP)-on and guanosine diphosphate (GDP)-off states and has a protein resynthesis half-life of ~24 hours[5,6]
- In patients with chemotherapy refractory KRAS mutant CRC, current standard therapies have a response rate of ~1% and a median progression-free survival (PFS) of approximately 2 months
- Adagrasib, a covalent inhibitor of $KRAS^{G12C}$, irreversibly and selectively binds $KRAS^{G12C}$ in its inactive, GDP-bound state and was optimized for desired properties, including[7]:
- Sotorasib is another first-in-class, irreversible inhibitor of the KRASG12C protein[8]
- Combining KRAS G12C inhibitors with an epidermal growth factor receptor (EGFR) inhibitor, may enhance inhibition of KRAS-dependent signaling or overcome adaptive feedback to improve outcomes[9]



EGFR signaling is implicated in feedback reactivation, providing a rational co-targeting strategy for KRAS-mutant colorectal cancer (CRC)

1. Zehir A, et al. *Nat Med*. 2017;23(6):703-713; 2. Schirripa M, et al. *Clin Colorectal Cancer*. 2020;S1533-0028(20)30067-0; 3. NIH TCGA: *The Cancer Genome Atlas*. February 11, 2021; https://www.cbioportal.org; 4. Modest DP, et al. *Oncology*. 2012;83:241-247; 5. Bos JL, et al. *Cell*. 2007;129:865-877; 6. Shukla S, et al. *Neoplasia*. 2014;16(2):115-128; . Hallin J, et al. *Cancer Discov*. 2020;10(1):54-71;8. Lanman BA, et al. J Med Chem. 2020;63:52-65. 9. Tabernero J, et al. Presented at ESMO 23rd World Congress on Gastrointestinal Cancer; June 30-July 3, 2021; virtual.

PARIS 2022 ESMO congress

KRYSTAL-1: Updated Efficacy and Safety of Adagrasib (MRTX849) With or Without Cetuximab in Patients With Advanced Colorectal Cancer (CRC) Harboring a KRAS^{G12C} Mutation

Samuel J. Klempner[1], Jared Weiss[2], Meredith S. Pelster[3], Alexander I. Spira[4], Minal Barve[5], Sai-Hong Ignatius Ou[6], Ticiana A. Leal[7], Tanios S. Bekaii-Saab[8], James G. Christensen[9], Thian Kheoh[9], Karen Velastegui[9], Hirak Der-Torossian[9], Rona Yaeger[10]

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KRYSTAL-1 (849-001) Phase 1b/2 CRC Cohorts Study Design

Key Eligibility Criteria

- CRC with a $KRAS^{G12C}$ mutation[a]
- Unresectable or metastatic disease
- Prior systemic treatment for metastatic disease
- No available treatment with curative intent or available standard of care

Phase 1b
CRC Combination

Adagrasib 600 mg BID[b] + cetuximab[c] (n=32)

Phase 2
CRC Monotherapy

Adagrasib 600 mg BID[b] (n=44)

Study Objectives

Phase 1b

- Primary endpoints: safety, RP2D, PK
- Secondary endpoints: ORR (RECIST 1.1), DOR, PFS, OS

Phase 2

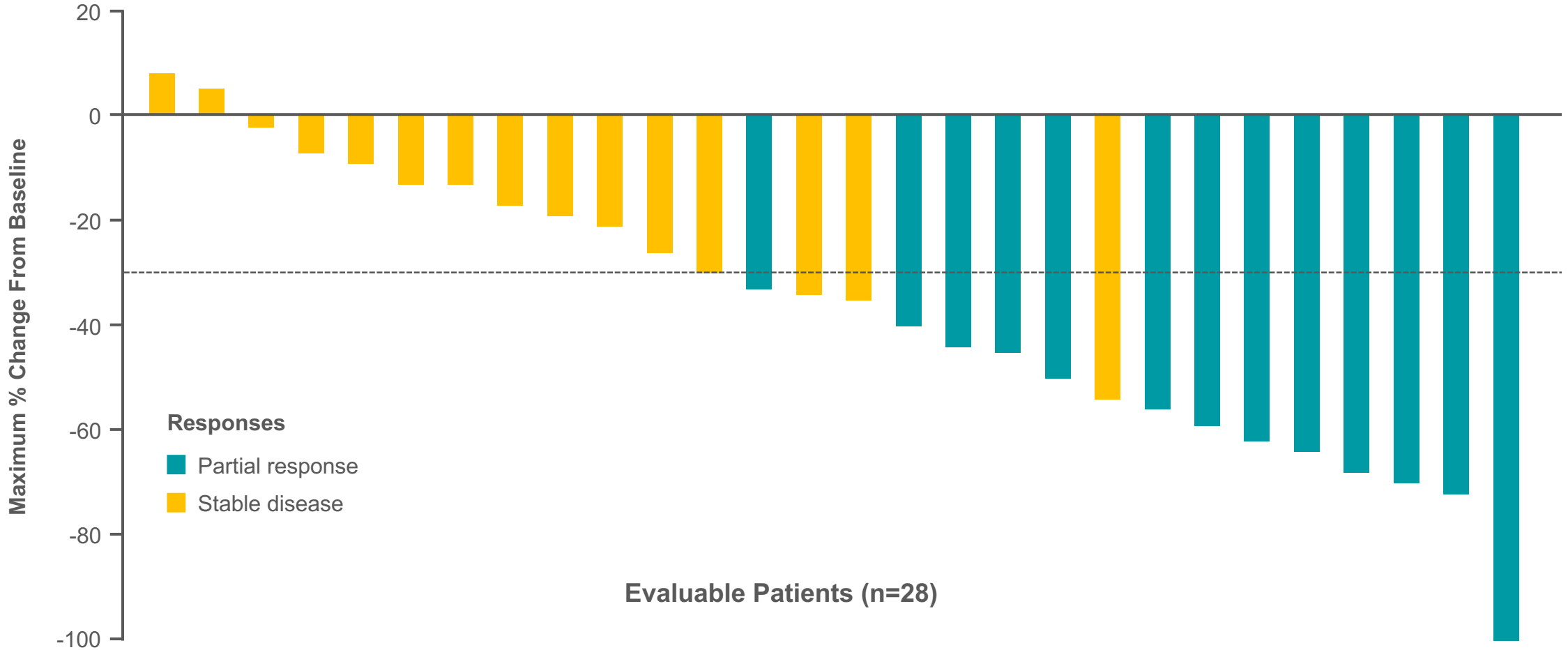
- Primary endpoint: ORR (RECIST 1.1)[d]
- Secondary endpoints: safety, DOR, PFS, OS

- Previously reported data demonstrated clinical activity of adagrasib monotherapy and adagrasib + cetuximab in patients with previously treated $KRAS^{G12C}$-mutated CRC[10,e]
- Here we report updated data for adagrasib 600 mg BID as monotherapy (Phase 2; median follow-up: 20.1 months) and in combination with cetuximab (Phase 1b; median follow-up: 17.5 months) in patients with previously treated $KRAS^{G12C}$-mutated CRC

[a]$KRAS^{G12C}$ mutation detected in tumor tissue and/or ctDNA per protocol. [b]Capsule, fasted. [c]Cetuximab dosing, 400 mg/m^2 followed by 250 mg/m^2 QW, or 500 mg/m^2 Q2W. [d]Response was analysed in the clinically evaluable population with local radiology review. [e]Previous data were reported for 46 patients (n=2 in Phase 1/1b and n=44 in Phase 2) receiving adagrasib monotherapy (median follow-up: 8.9 months) and 32 patients receiving adagrasib + cetuximab (median follow-up: 7 months)[10]

ClinicalTrials.gov. NCT03785249

Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Best Tumor Change From Baseline

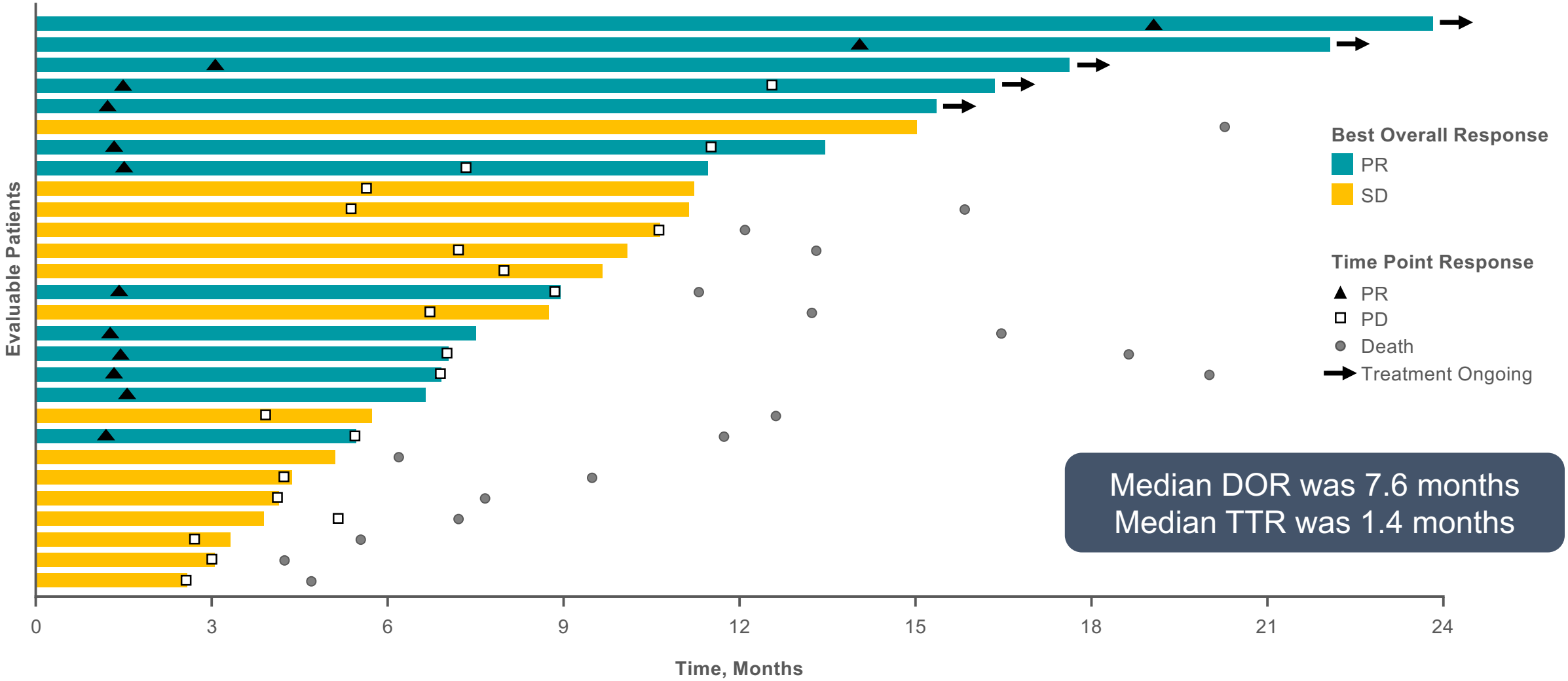


- Confirmed objective responses[a] were observed in 46% (13/28[b]); DCR was 100% (28/28)
- Tumor shrinkage of any magnitude occurred in 93% of patients

[a]ORR defined as the proportion of patients documented to have a confirmed CR or PR according to RECIST 1.1 as the best response. Patients who could not be assessed for response were counted as not evaluable. [b]Response per investigator assessment (n=28; four patients are not included due to no post-baseline assessment of target lesions)

Data as of June 16, 2022 (median follow-up, 17.5 months)

Adagrasib + Cetuximab in Previously Treated Patients with $KRAS^{G12C}$-Mutated CRC: Duration of Treatment

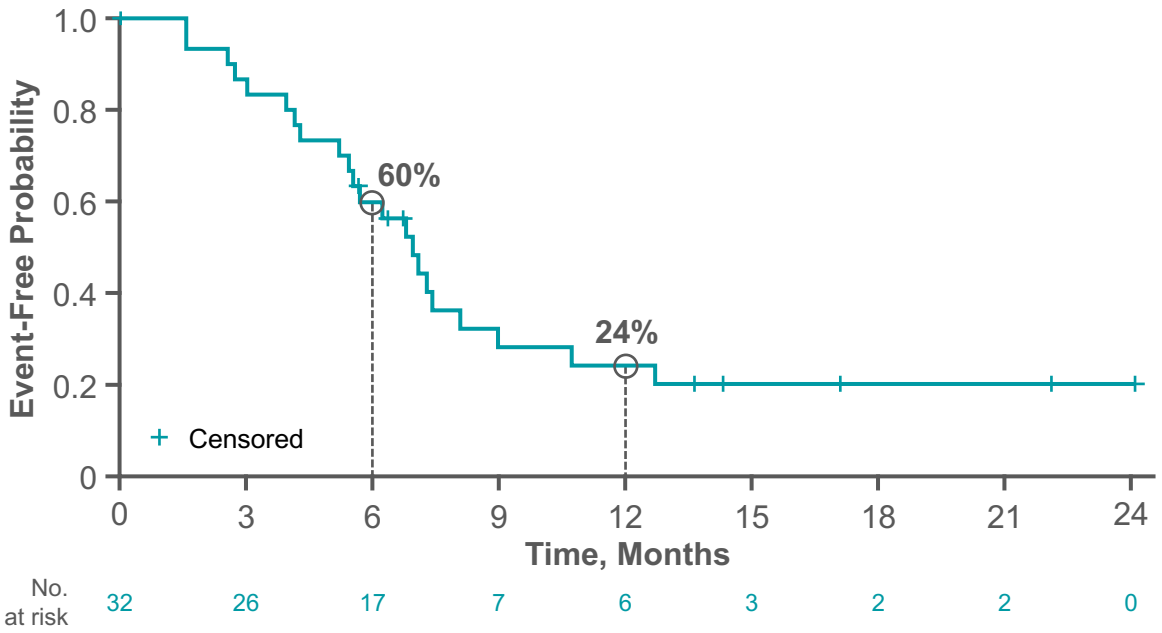


Response outcomes per investigator assessment (n=28; four patients are not included due to no post-baseline assessment of target lesions)

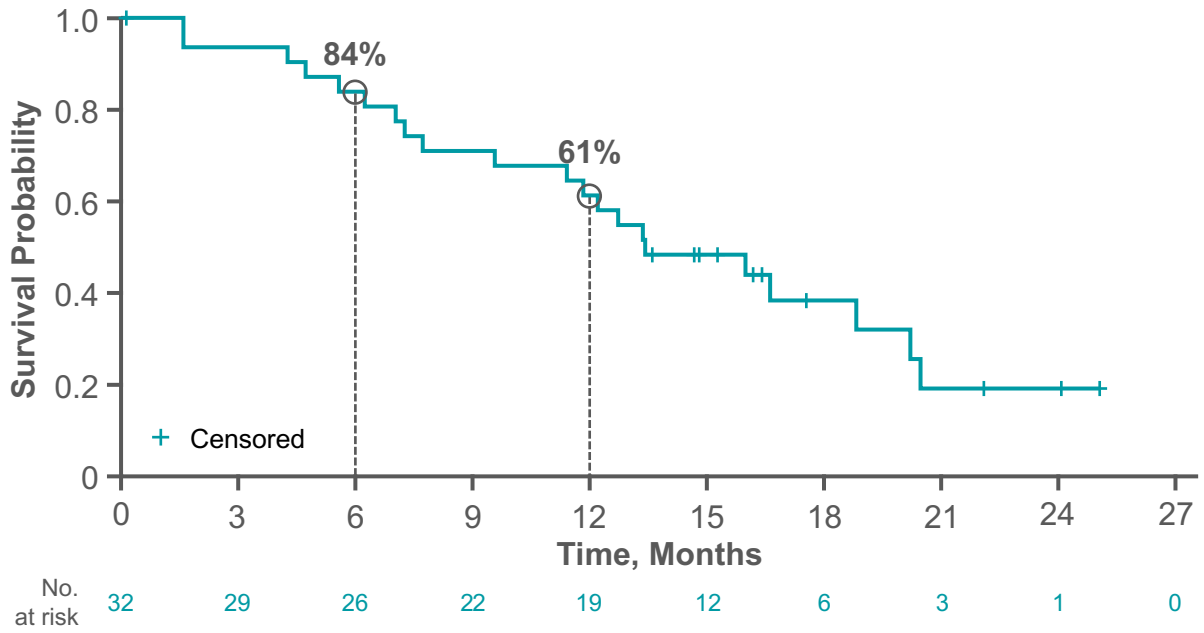
Data as of June 16, 2022 (median follow-up, 17.5 months)

Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: PFS and OS

Progression-Free Survival



Overall Survival



Median PFS was 6.9 months (95% CI, 5.4–8.1)

Median OS was 13.4 months (95% CI, 9.5–20.1)

PFS per investigator assessment (n=32)

Data as of June 16, 2022 (median follow-up, 17.5 months)

Adagrasib + Cetuximab in Previously Treated Patients with $KRAS^{G12C}$-Mutated CRC: Treatment-Related Adverse Events

Most Frequent TRAEs	Adagrasib + Cetuximab (n=32)			
TRAEs, %	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**
Any TRAEs[a]	100%	16%	69%	9%
Most frequent TRAEs[b], %				
Nausea	63%	41%	22%	0
Diarrhea	56%	34%	19%	3%
Vomiting	53%	41%	13%	0
Dermatitis acneiform	47%	34%	9%	3%
Fatigue	47%	25%	22%	0
Dry skin	41%	34%	6%	0
Headache	31%	22%	9%	0
Dizziness	25%	13%	13%	0
Rash maculopapular	25%	22%	3%	0
Stomatitis	22%	16%	3%	3%

- 2 Grade 4 TRAEs (cetuximab-related infusion-related reaction, n=1; hyperkalemia, n=1); no Grade 5 TRAEs
- 16% (5/32) of TRAEs led to discontinuation of cetuximab[c]. No TRAEs led to discontinuation of adagrasib
- TRAEs led to adagrasib dose reduction in 31% (10/32) and to adagrasib interruption in 44% (14/32)

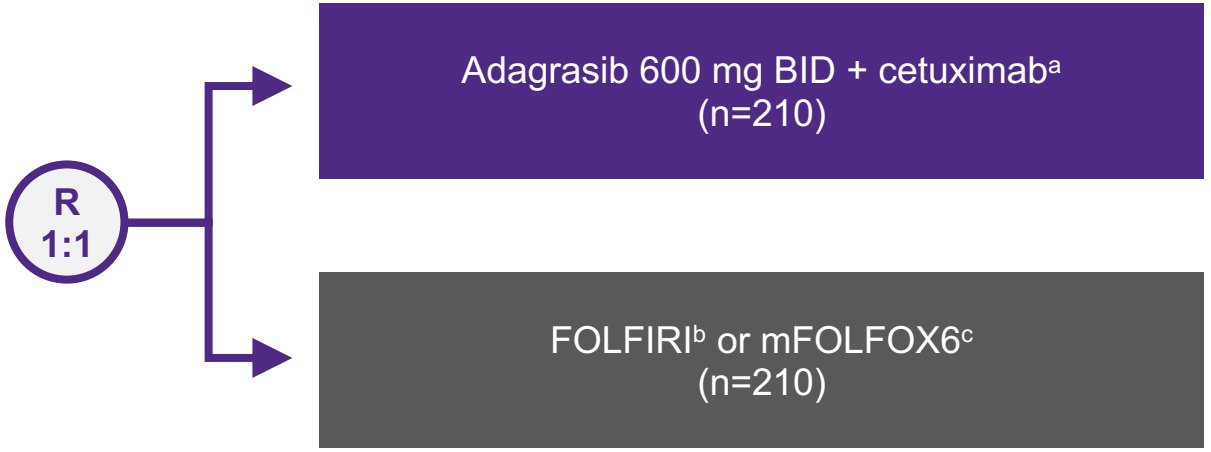
[a]By maximum grade. [b]Occurring in >20% of patients (any grade). [c]TRAEs leading to cetuximab discontinuation were treatment-related cetuximab-related infusion-related reaction (n=3), malaise (n=1) and vascular flushing (n=1)

Data as of June 16, 2022 (median follow-up, 17.5 months)

KRYSTAL-10 (849-010): Phase 3 Randomized, Open-Label Trial of 2L Adagrasib + Cetuximab vs Chemotherapy in metastatic CRC With KRAS^{G12C} Mutation

Key Eligibility Criteria

- Histologically confirmed diagnosis of advanced or metastatic CRC
- Confirmed KRAS^{G12C} mutation in tumor tissue
- Progression on 1L fluoropyrimidine-based regimen containing oxaliplatin or irinotecan



Anti-VEGF/VEGFR allowed per investigator discretion in comparator arm

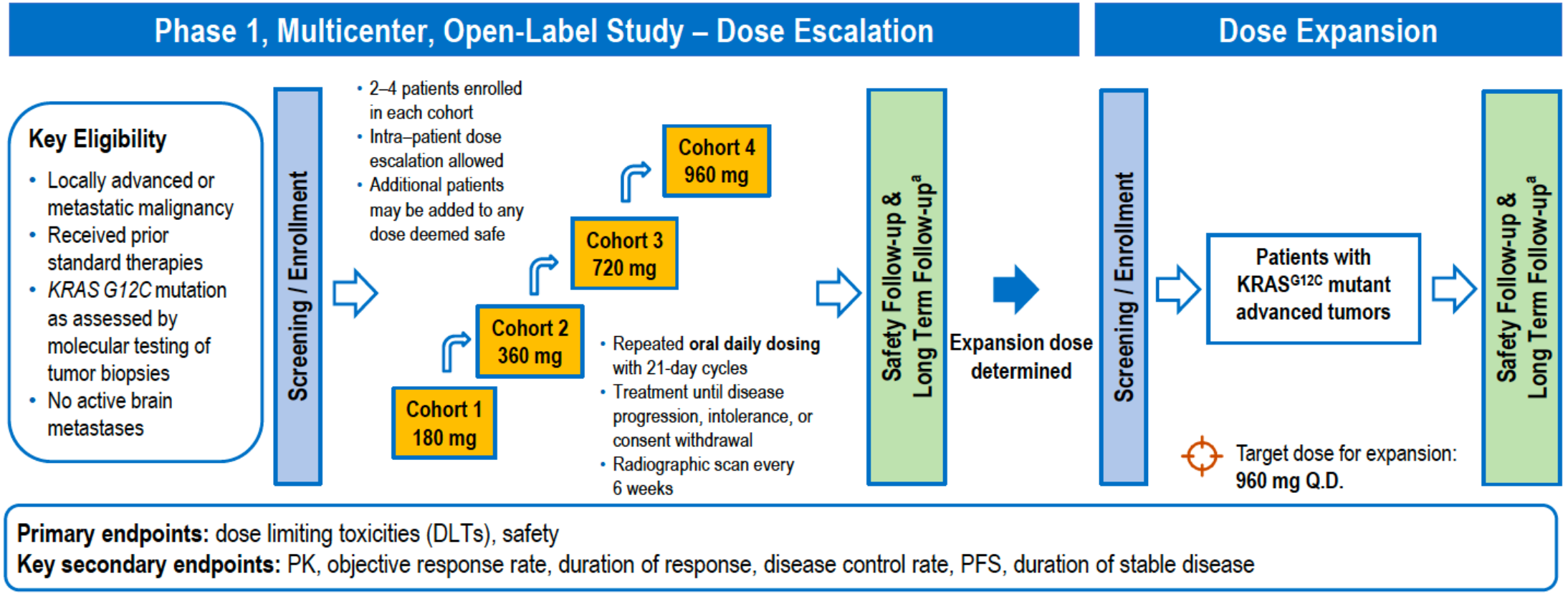
Outcome Measures

Primary: PFS, OS

Secondary: Safety, ORR (RECIST 1.1), 1-year OS, DOR, PK, PROs

[a]Dosing: cetuximab, 500 mg/m^2 Q2W. [b]FOLFIRI Q2W (irinotecan, 180 mg/m^2, 5-FU/LV with fluorouracil given as a 400 mg/m^2 IV bolus followed by a 2400 mg/m^2 dose given as a continuous infusion over 46–48 hours). [c]mFOLFOX6 Q2W (oxaliplatin, 85 mg/m^2, 5-FU/LV, with fluorouracil given as a 400 mg/m^2 IV bolus followed by a 2400 mg/m^2 dose given as continuous infusion over 46–48 hours). ClinicalTrials.gov NCT04793958.

CodeBreak 100 : Sotorasib +/- Panitumumab in mCRC



[a]30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long term follow-up. PK: pharmacokinetics; PFS: progression-free survival.

Strickler J et al . ESMO GI 2020

CodeBreak101 : Sotorasib + Panitumumab

- As of March 25, 2022, 40 pts (75% female, median age 57.5 years) were enrolled and received oral Soto 960 mg daily and Pmab 6 mg/kg IV every 2 weeks.
- Median prior lines of therapy was 2.
- Grade 3 TRAEs occurred in 9 (22.5%) pts; related to Soto and Pmab in 6 (15%) and 8 (20%) pts, respectively.
- Confirmed ORR was 30% (95% CI: 16.6, 46.5).
  - Disease control rate was 90% (95% CI: 76.3, 97.2).

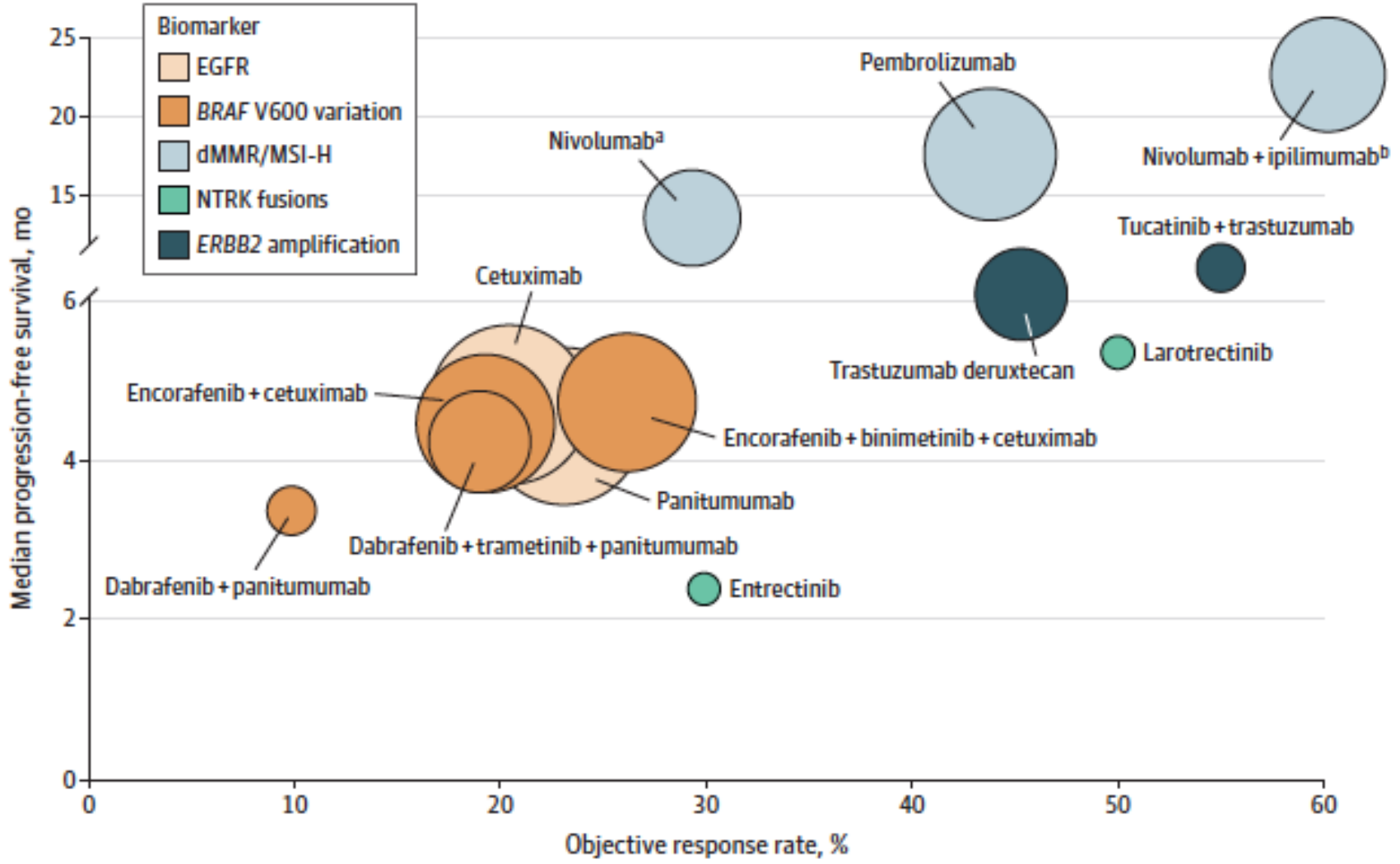
Kuboki Y et al . ESMO 2022

Sotorasib and Panitumumab Versus Investigator's Choice for Participants With KRAS p.G12C Mutation (CodeBreak 300)

A Phase 3 Multicenter, Randomized, Open-label, Active-controlled Study of Sotorasib and Panitumumab **Versus Investigator's Choice (Trifluridine and Tipiracil, or Regorafenib)** for the Treatment of Previously Treated Metastatic Colorectal Cancer Subjects With Kirsten Rat Sarcoma (KRAS) p.G12C Mutation

ClinicalTrials.gov Identifier: NCT05198934

Figure 2. Studies of Biomarker-Driven Therapies in Metastatic Colorectal Cancer (mCRC)



Strickler J , Bekaii-Saab T et al JAMA Onc 2022

FRESCO-2 Study Design

Patient Eligibility

- Prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if *RAS* wild type, an anti-EGFR therapy
- Progression on, or intolerance to, TAS-102 and/or regorafenib
- Prior treatment with an immune checkpoint inhibitor or BRAF inhibitor if indicated

R 2:1

N=687

Fruquintinib 5 mg PO, QD (3 weeks on, 1 week off) + BSC (N=458)

Placebo 5 mg PO, QD (3 weeks on, 1 week off) + BSC (N=229)

Treatment until progression or unacceptable toxicity

Stratification Factors

- Prior therapy (TAS-102 vs regorafenib vs TAS-102 and regorafenib)
- *RAS* mutational status (wild-type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months)

Note: To ensure the patient population is reflective of clinical practice, the number of patients treated with prior regorafenib was limited to 344 patients (50%)

BSC, best supportive care.
NCT04322539.

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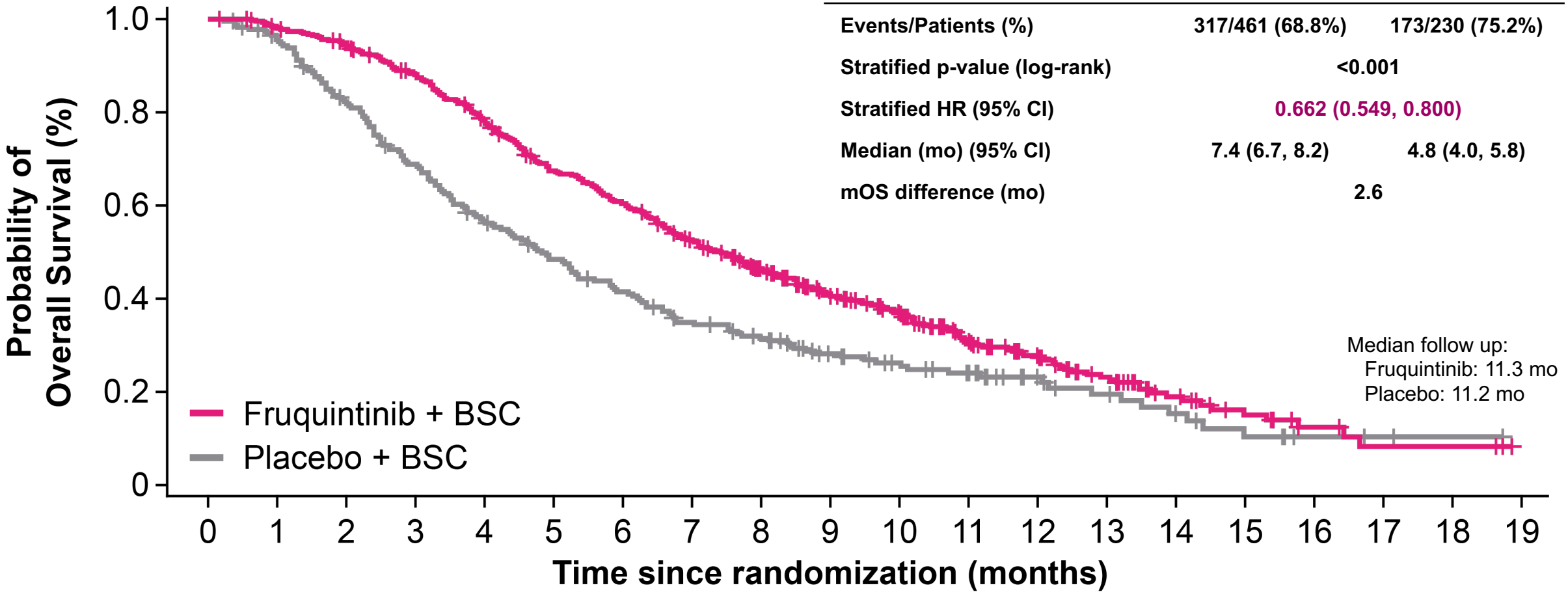
Dasari A et al. ESMO 2022, Presentation LBA25

Primary Endpoint: Overall Survival

ITT Population

	Fruquintinib	Placebo
Events/Patients (%)	317/461 (68.8%)	173/230 (75.2%)
Stratified p-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.662 (0.549, 0.800)	
Median (mo) (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
mOS difference (mo)	2.6	



Patients at Risk

Fruquintinib	461	449	429	395	349	297	266	224	184	143	113	79	58	41	23	14	7	4	4	0
Placebo	230	216	184	153	125	105	89	73	63	45	37	31	20	15	10	6	3	2	1	0

Subsequent anti-cancer medication balanced between the two arms: **29.4% fruquintinib arm** vs. **34.3% placebo arm**

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Most Common TEAEs
(Any Grade ≥ 15% in Either Arm)

TEAE, n (%)	Fruquintinib (N=456)		Placebo (N=230)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients with ≥1 TEAE	451 (98.9)	286 (62.7)	213 (92.6)	116 (50.4)
Hypertension	**168 (36.8)**	**62 (13.6)**	**20 (8.7)**	**2 (0.9)**
Asthenia	155 (34.0)	35 (7.7)	52 (22.6)	9 (3.9)
Decreased appetite	124 (27.2)	11 (2.4)	40 (17.4)	3 (1.3)
Diarrhea	110 (24.1)	16 (3.5)	24 (10.4)	0
Hypothyroidism	94 (20.6)	2 (0.4)	1 (0.4)	0
Fatigue	91 (20.0)	18 (3.9)	37 (16.1)	2 (0.9)
Hand-foot syndrome	**88 (19.3)**	**29 (6.4)**	**6 (2.6)**	**0**
Abdominal pain	83 (18.2)	14 (3.1)	37 (16.1)	7 (3.0)
Nausea	79 (17.3)	3 (0.7)	42 (18.3)	2 (0.9)
Proteinuria	79 (17.3)	8 (1.8)	12 (5.2)	2 (0.9)
Constipation	78 (17.1)	2 (0.4)	22 (9.6)	0
Dysphonia	74 (16.2)	0	12 (5.2)	0

Dasari A et al. ESMO 2022, Presentation LBA25

CROSS-TRIAL COMPARISONS

	Regorafenib				TAS-102		Fruquintinib	
Study	CORRECT		CONCUR		RECOURSE		FRESCO-2	
Prior biologics	100% BEV 100% EGFR mAbs		60%		100% BEV 100% EGFR mAbs 18% Rego		96% BEV 40% EGFR mAbs 52% TAS, 8% Rego 40% both TAS & Rego	
	Rego	**BSC**	**Rego**	**BSC**	**TAS-102**	**BSC**	**Fruq**	**Plac**
N pts	505	255	136	68	534	266	461	230
mOS (mos)	6.4	5.0	8.8	6.3	7.1	5.3	7.7	4.8
	HR 0.77 p=0.0052		**HR 0.55** p=0.0002		**HR 0.68** p<0.0001		**HR 0.662** p<0.001	
mPFS (mos)	1.9	1.7	3.2	1.7	2.0	1.7	3.7	1.8
	HR 0.49 p<0.0001		HR 0.31 p<0.0001		HR 0.48 p<0.0001		HR 0.32 p<0.001	
RR (%)	1.0	0.4	4.4	0	1.6	0.4	3.7	1.8
Main AEs	HFSR				Neutropenia		Hypertension	

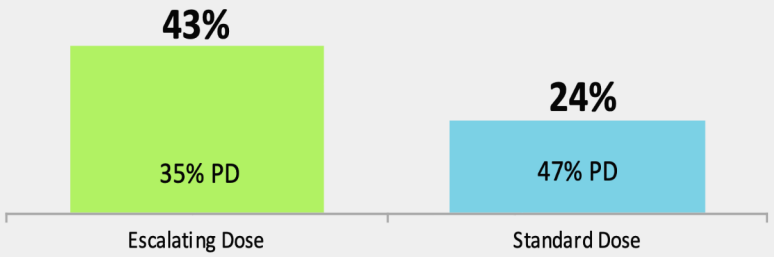
ReDOS : Improving Tolerability while Optimizing Outcome

ReDOS[1] Dose Escalation Schedule

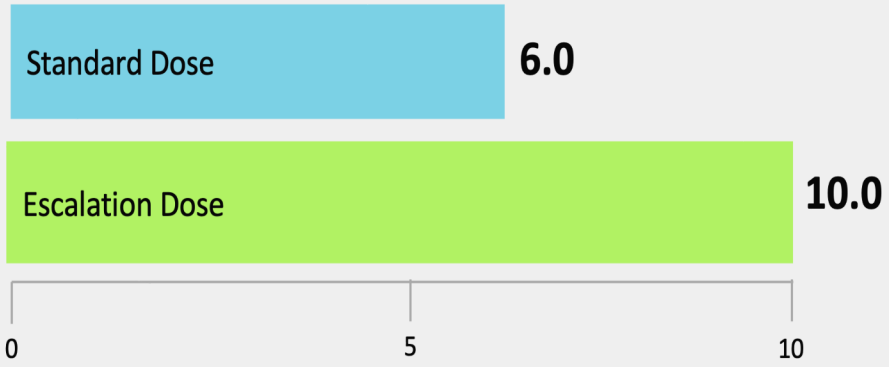
	Cycle 1				Cycle 2
Week	1	2	3	4	1
Once-daily dose	80 mg	120 mg	160 mg	Dosing-free interval	Last dose from cycle 1

ReDOS Dose Optimization Study[1] Results

Percentage Patients Starting Treatment at Cycle 3
(primary endpoint)
P = .0281



Median OS (months)



1 Bekaii-Saab TS, et al. Lancet Oncology , 2019

CRC: Rx PARADIGM 2022