THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Management of Newly Diagnosed CRC

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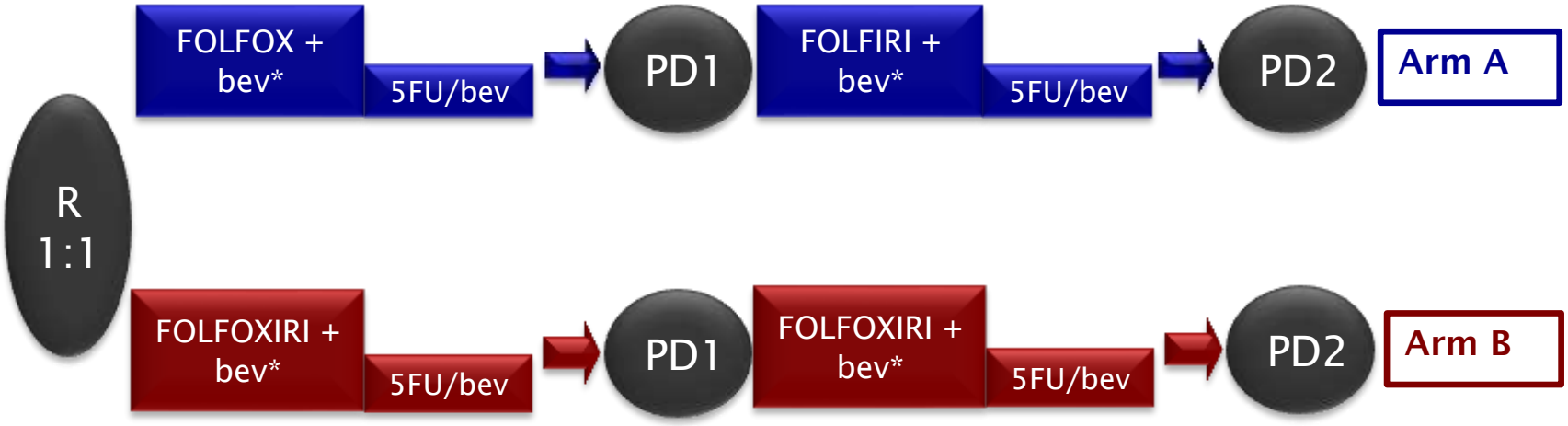
What are the alternatives and barriers to FOLFOX+B?

How are biomarkers being integrated into 1st line?

What are the implications of combination targeted + cytotoxic therapies?

TRIBE2: FOLFOXIRI+Bevacizumab vs FOLFOX+B>FOLFIRI+B



PRIMARY ENDPOINT: Progression Free Survival 2

* Up to 8 cycles

1st Progression Free Survival

2nd Progression Free Survival

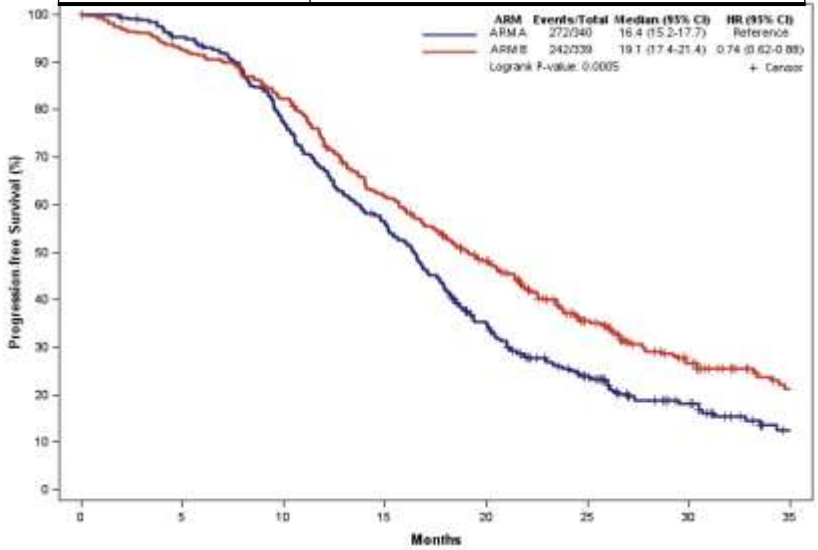
- Key secondary endpoint: Overall Survival
- 78% of patients had right sided primary or KRAS/NRAS mutation in the tumor

Cremolini et al Lancet Oncol '20

FOLFOXIRI+Bevacizumab Provides Survival Benefit

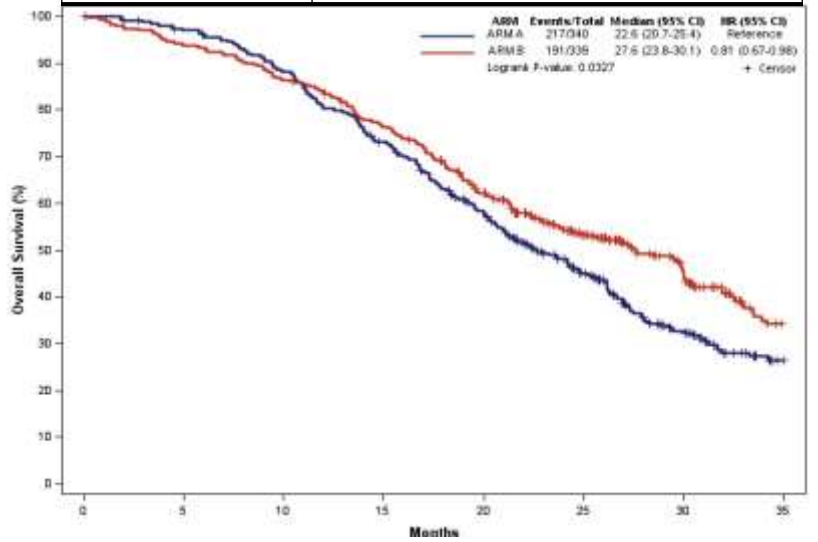
Progression Free Survival 2

Median follow up = 30.6 mos	Arm A N = 340	Arm B N = 339
Events, N (%)	272 (80%)	242 (71%)
Median PFS2, mos	**17.5**	**19.1**
	HR = 0.74 [95% CI: 0.62-0.88] p<0.001	



Overall Survival

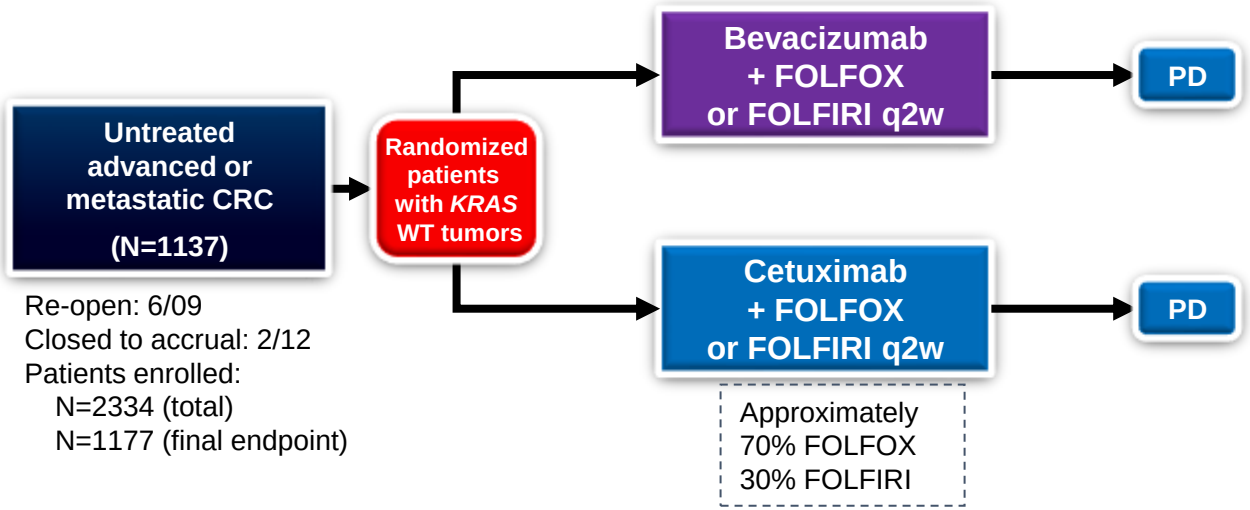
Median follow up = 30.6 mos	Arm A N = 340	Arm B N = 339
Events, N (%)	217 (64%)	191 (56%)
Median OS, mos	22.6	27.6
	HR = 0.81 [95%CI: 0.67-0.98] p=0.033	



Take away: Triplet cytotoxics can be used in selective patients, esp RAS mutated and/or Right sided tumors. But not a required approach.

Cremolini et al Lancet Oncol '20

CALGB/SWOG 80405: Bevacizumab vs Cetuximab in First-line *KRAS* WT mCRC

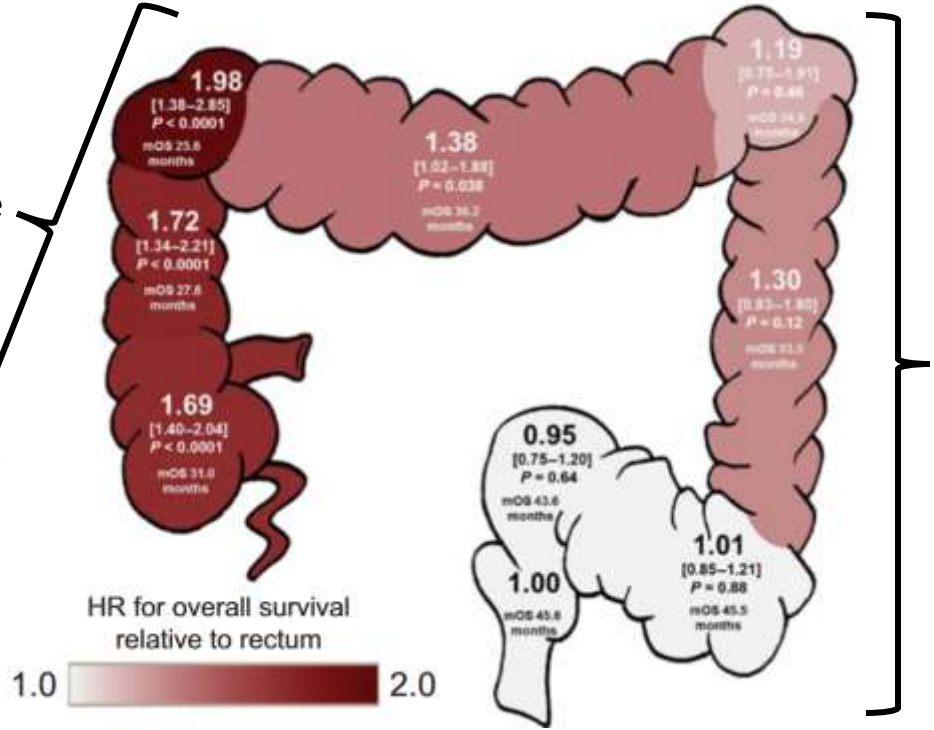


- **Primary endpoint: OS**
  - Superiority trial with 90% power to detect an OS HR of 1.25 (2-sided α=0.05)
- **Secondary endpoints: ORR, PFS, TTF, DOR, and safety**

H2H=head-to-head; TTF=time to treatment failure.
Venook et al, JAMA 2017. NCT identifier: NCT00265850.

Metastatic Colorectal Cancer: Tumor Location is Prognostic

NCCN defines right side as transverse to cecum

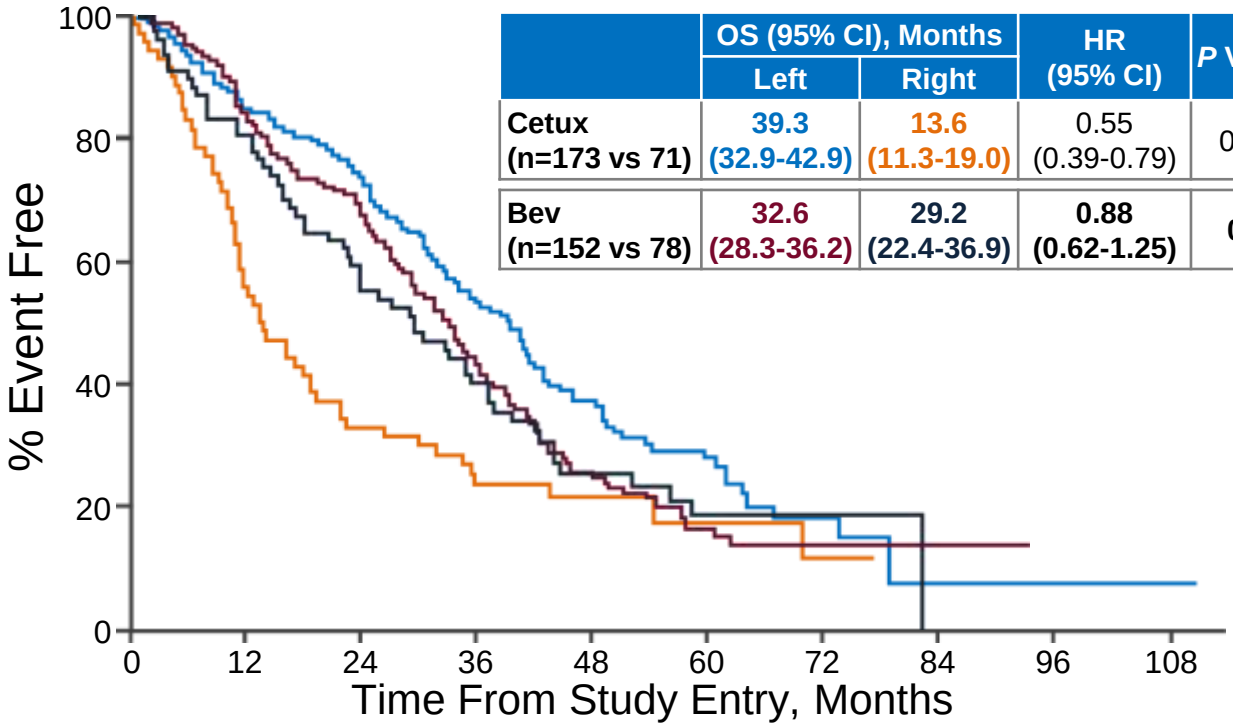


NCCN defines left sided as splenic flexure to rectum

… but also predictive for EGFR inhibition.

Loree, et al *CCR*, 2018

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

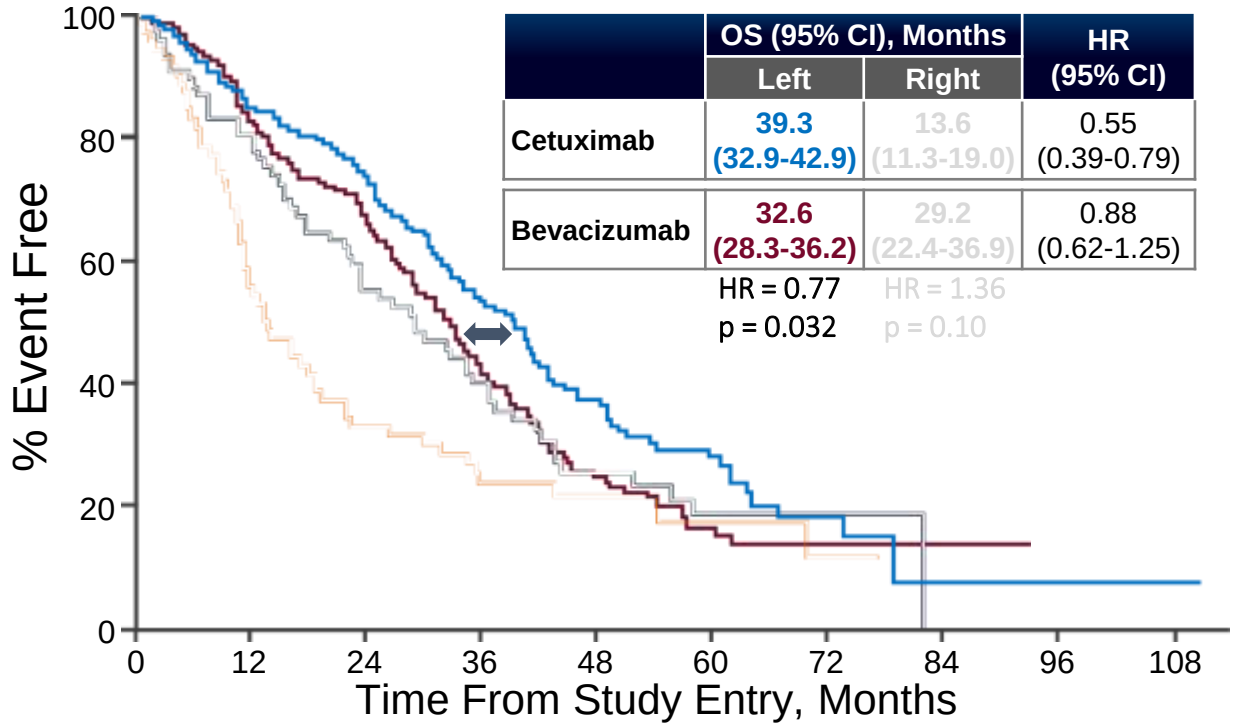


	OS (95% CI), Months		HR (95% CI)	*P* Value*
	Left	Right		
Cetux (n=173 vs 71)	39.3 (32.9-42.9)	13.6 (11.3-19.0)	0.55 (0.39-0.79)	0.001
Bev (n=152 vs 78)	**32.6 (28.3-36.2)**	**29.2 (22.4-36.9)**	**0.88 (0.62-1.25)**	**0.50**

*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.

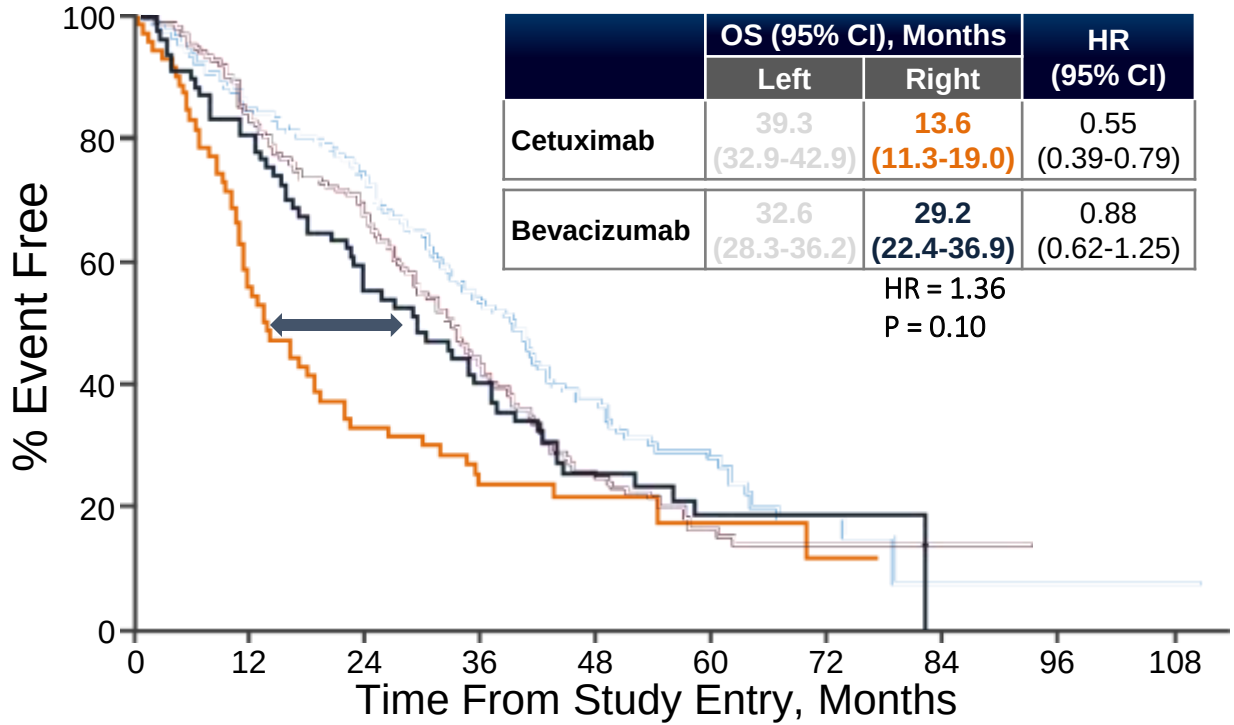
CALGB/SWOG 80405: OS by Tumor Location (*RAS* WT)



	OS (95% CI), Months		HR (95% CI)
	Left	Right	
Cetuximab	39.3 (32.9-42.9)	13.6 (11.3-19.0)	0.55 (0.39-0.79)
Bevacizumab	32.6 (28.3-36.2)	29.2 (22.4-36.9)	0.88 (0.62-1.25)
	HR = 0.77 p = 0.032	HR = 1.36 p = 0.10	

Take Away: Left sided tumors have better prognosis and benefit from cetuximab more than bevacizumab

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



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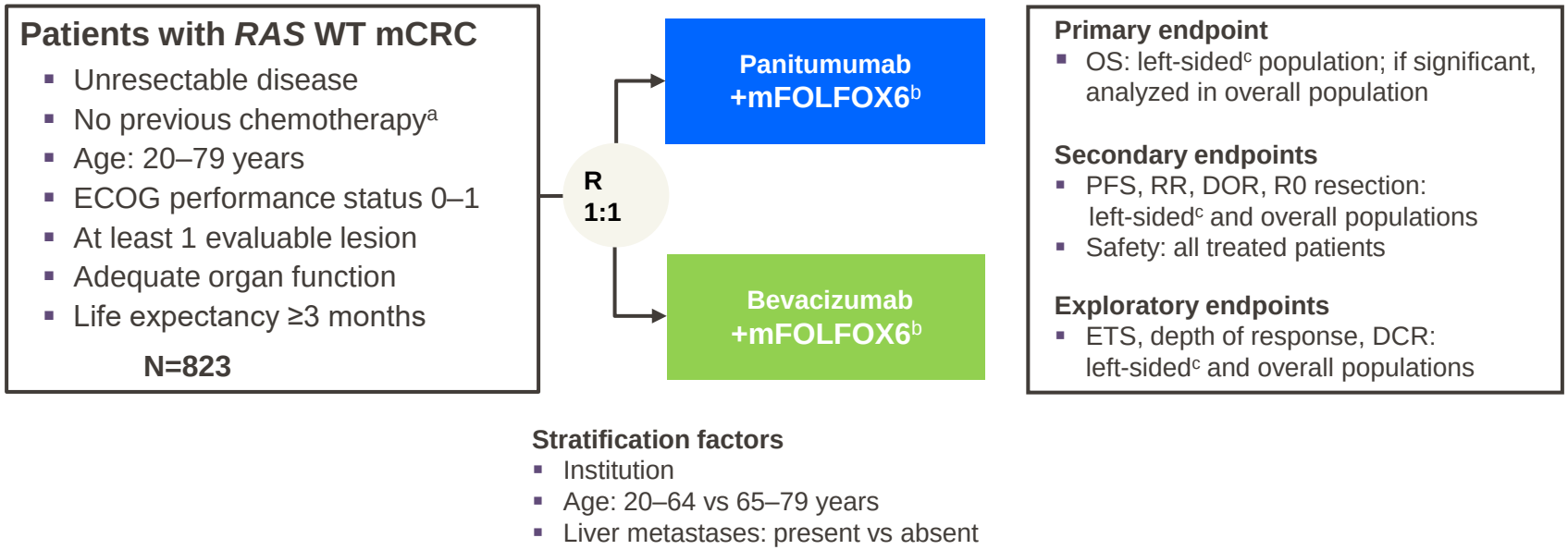
HR = 1.36
P = 0.10

Take Away: Right sided tumors have better prognosis and benefit from bevacizumab

PARADIGM TRIAL DESIGN

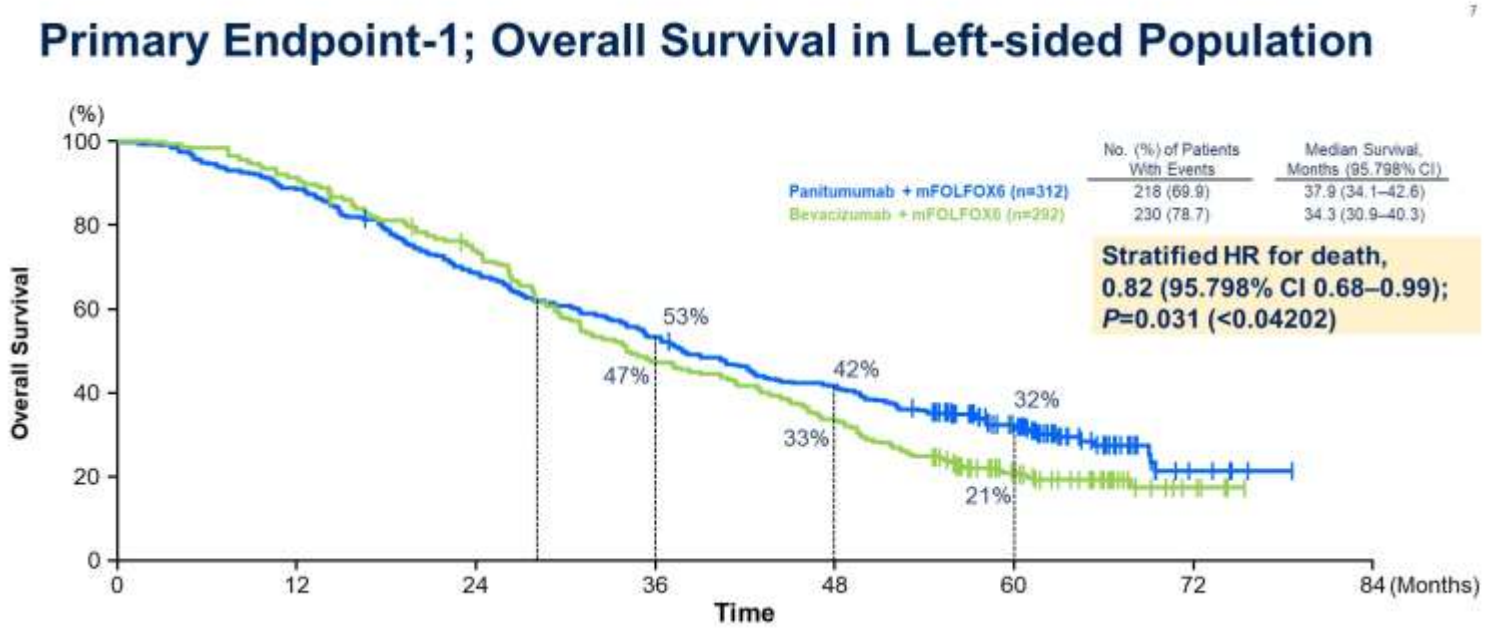
Phase 3, randomized, open-label, multicenter study (NCT02394795)



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.

Watanabe J et al. JAMA 2023

First Prospective Phase III of L-sided RAS WT mCRC:
FOLFOX + bevacizumab or panitumumab (PARADIGM)



Take Away: Prospective confirmation that EGFRi is better than VEGFi for left-sided, RAS wt pts.

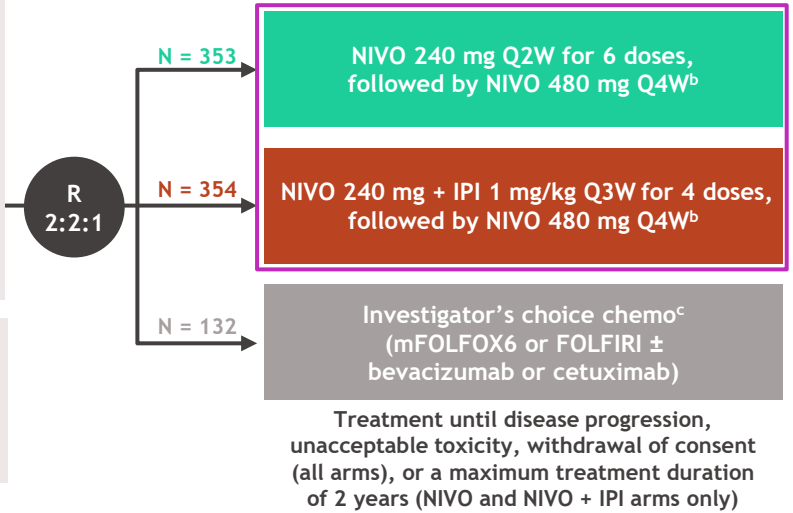
Watanabe et al JAMA ‘23

Microsatellite Instability High: PD1 + CTLA4 Blockade

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- Immunotherapy-naive
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

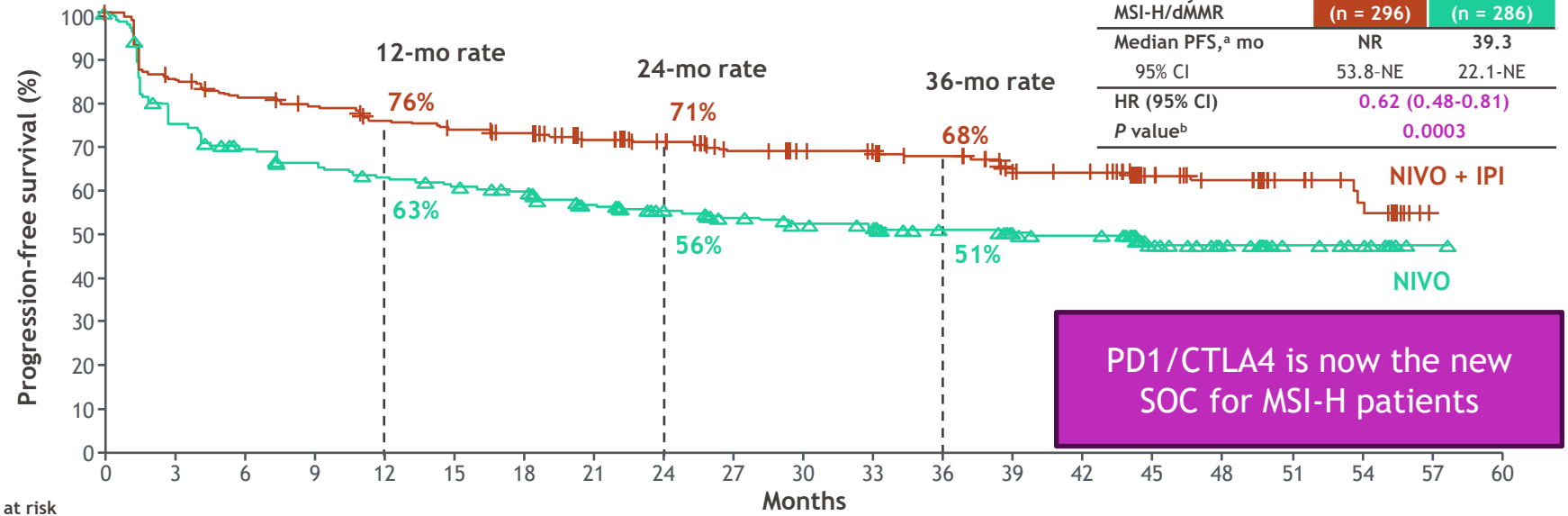
Other select endpoints:
- Safety
- ORR by BICR[e] (NIVO + IPI vs NIVO across all lines)
- HRQoL
- OS

- At data cutoff (August 28, 2024), the median follow-up[f] was 47.0 months (range, 16.7–60.5)

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either IHC and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and data cutoff among all randomized patients across all 3 treatment arms.

Andre et al GI ASCO '25 Abstract number LBA143; Andre TA, et al. Lancet. 2025;405:383-395.

Progression-free survival favors the doublet of PD1/CTLA4



Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS,[a] mo	NR	39.3
95% CI	53.8-NE	22.1-NE
HR (95% CI)	0.62 (0.48-0.81)	
P value[b]	0.0003	

PD1/CTLA4 is now the new SOC for MSI-H patients

No. at risk																					
NIVO + IPI	296	248	234	225	214	207	200	180	164	146	136	134	121	102	100	61	54	29	23	0	0
NIVO	286	210	191	179	169	164	158	141	124	109	98	95	81	72	69	39	31	15	12	1	0

- NIVO + IPI demonstrated statistically significant and clinically meaningful PFS benefit vs NIVO in patients with centrally confirmed MSI-H/dMMR mCRC across all lines of therapy
  - PFS benefit with NIVO + IPI vs NIVO was consistent in all randomized patients (median PFS: 54.1 vs 18.4 months; HR, 0.64 [95% CI, 0.52-0.79])

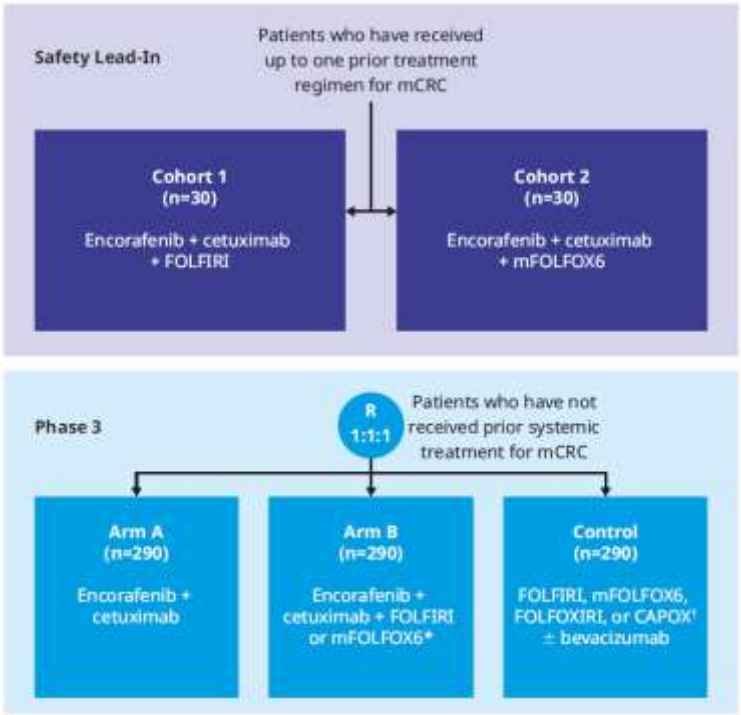
[a]Per BICR. [b]Boundary for statistical significance, p < 0.0095.

Andre et al GI ASCO '25 Abstract number LBA143; Andre TA, et al. Lancet. 2025;405:383-395.

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

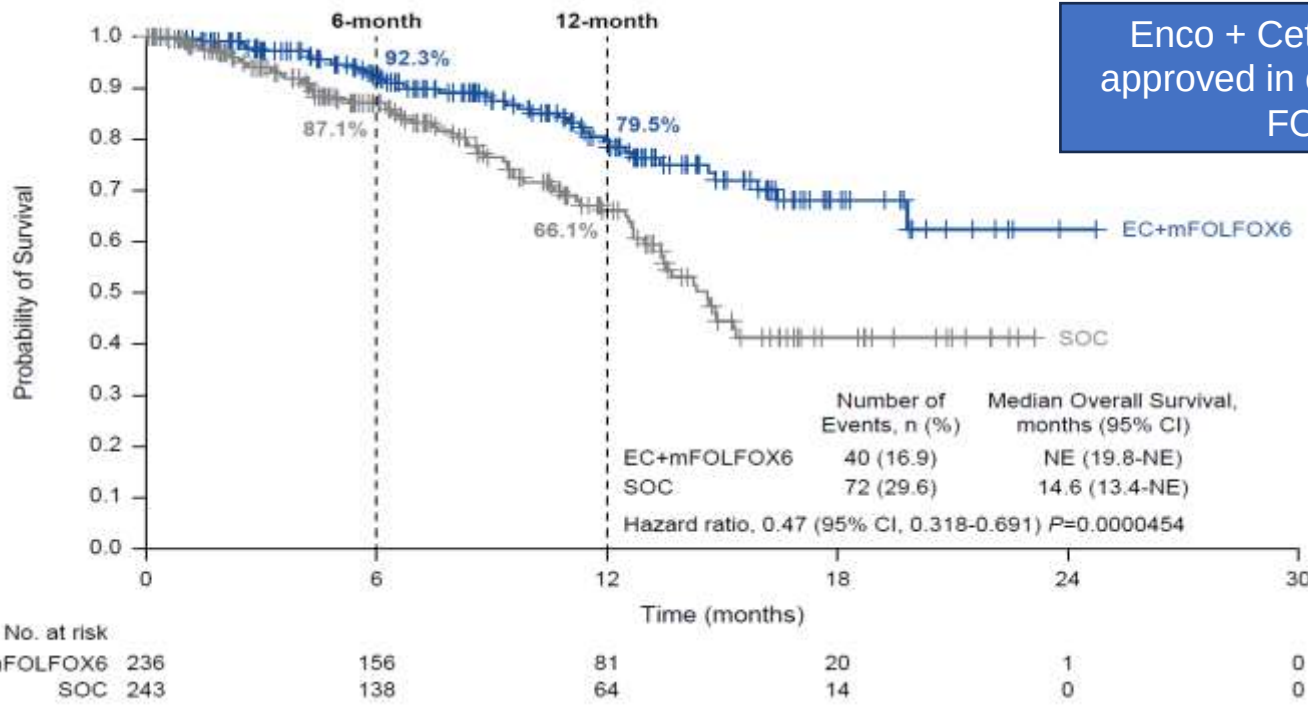
NCT04607421

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..

Overall Survival EC+FOLFOX vs SOC

Enco + Cetux is now FDA approved in combination with FOLFOX

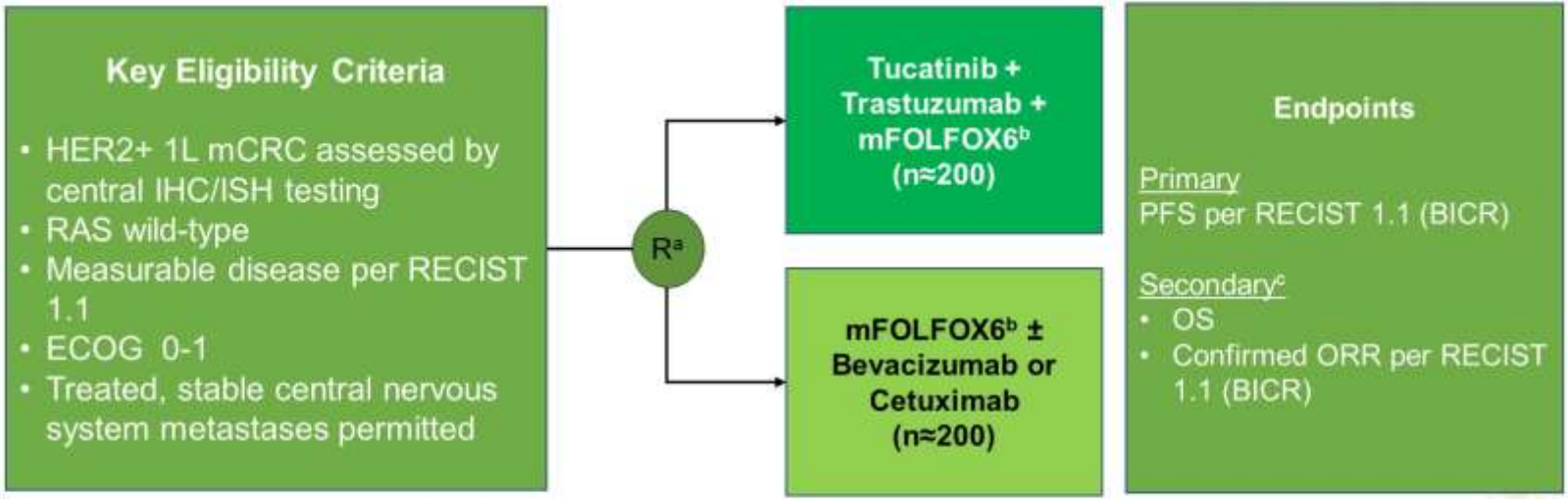


Data cutoff: December 22, 2023.

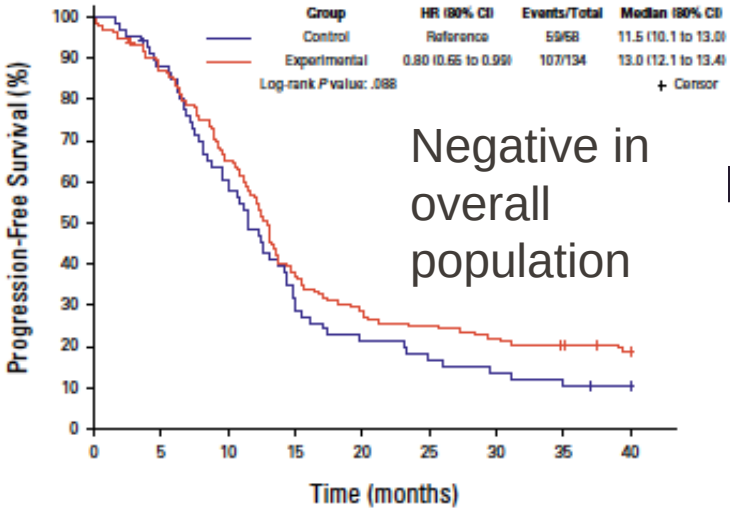
[a]OS was tested following the prespecified plan with one-sided alpha of 0.000000083, calculated as a portion of the nominal one-sided alpha of 0.001. Statistical significance was not achieved at this time.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care.

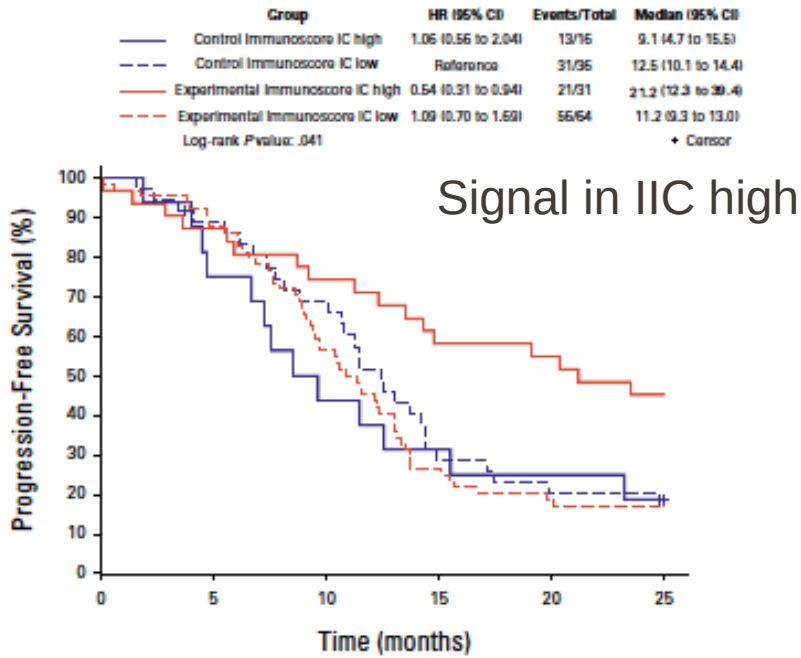
MOUNTAINEER-03:
Global, Randomised, Open-Label, Phase 3 Trial



AtezoTRIBE study in 1st line MSS mCRC



Negative in overall population



Signal in IIC high

Subgroup analysis based on Immunoscore Immune-Checkpoint (IIC) status (high [IIC-low: low density and proximity of CD8 and PD-L1 cells] vs low)

Immunoscore IIC: PD-L1 expression + CD8 cell densities + proximity analysis

Ghiringhelli F et al. EBioMedicine 2023
Antoniotti C et al. J Clin Oncol 2024

Barriers to uptake of alternatives to FOLFOX + B

Molecular testing is not routinely available in the US in a timely manner

- Medical oncology services are administered in a different health care system than diagnostic tissue collection in 70% of US patients

Toxicity vs benefit discussions differ in US and ROW

- Skin rash tolerance and perception of FOLFOXIRI risks

Applicability of non-US studies are also raised as practice drivers (?)

FOLFIRI has advantages; due to historic reasons, have had little change in use

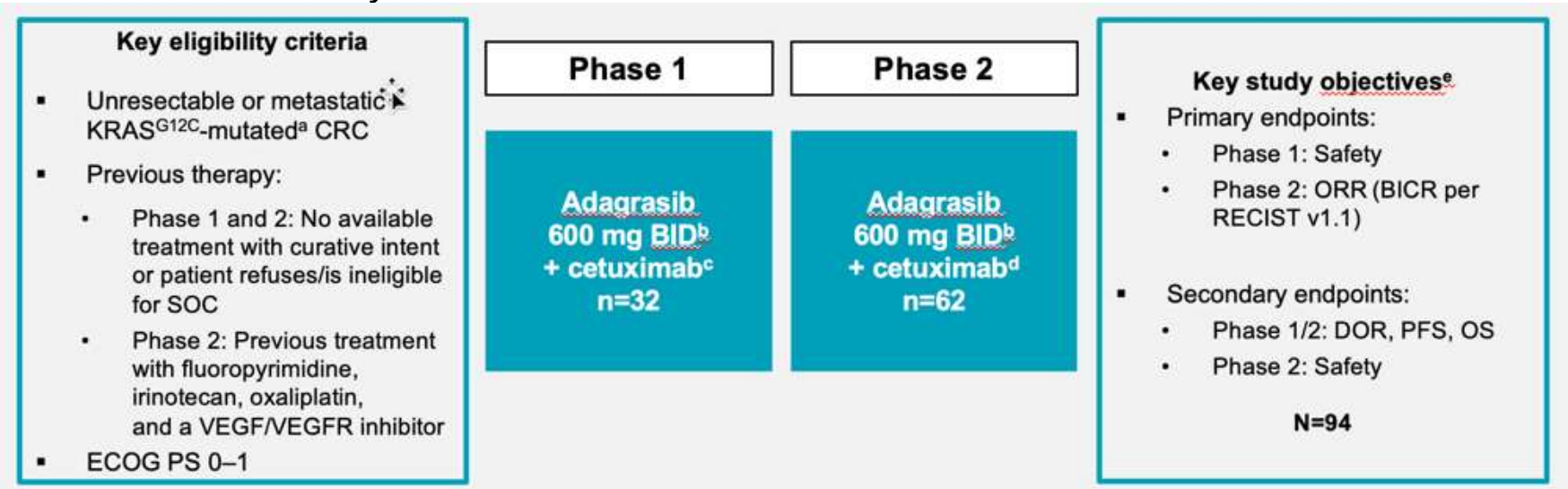
Practice change in this space remains a challenge but data supports it

What are key treatment options to review for later line therapy?

- Molecularly defined subsets of KRAS, HER2
- All-comer therapies

Adagrasib + Cetuximab for KRAS^{G12C} CRC

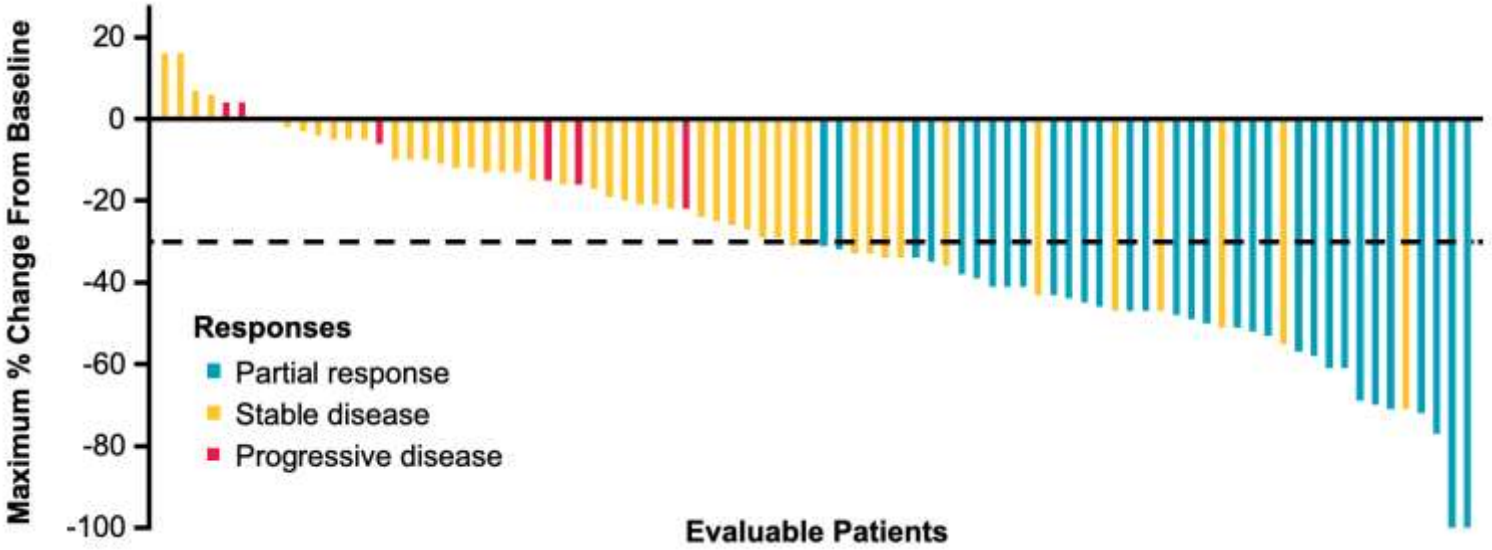
KRYSTAL-1 Study



Take Away: Rationale for EGRFi + KRASi is the same as for BRAF tumors…. Adaptive resistance.

Kopetz et al AACR ’24, Yaeger et al Can Disc ‘24

Adagrasib + Cetuximab: Accelerated Approval



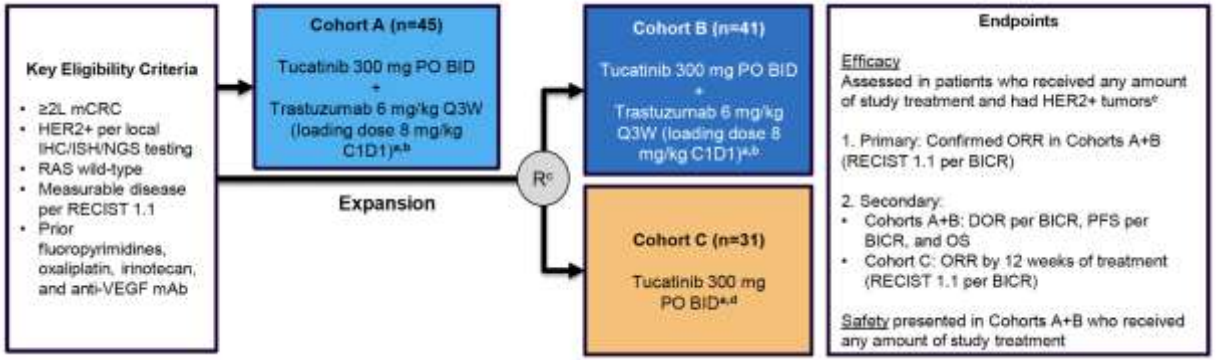
- **Confirmed objective response rate was 34.0%[a]**
- **Disease control was observed in 80/94 patients (85.1%)**

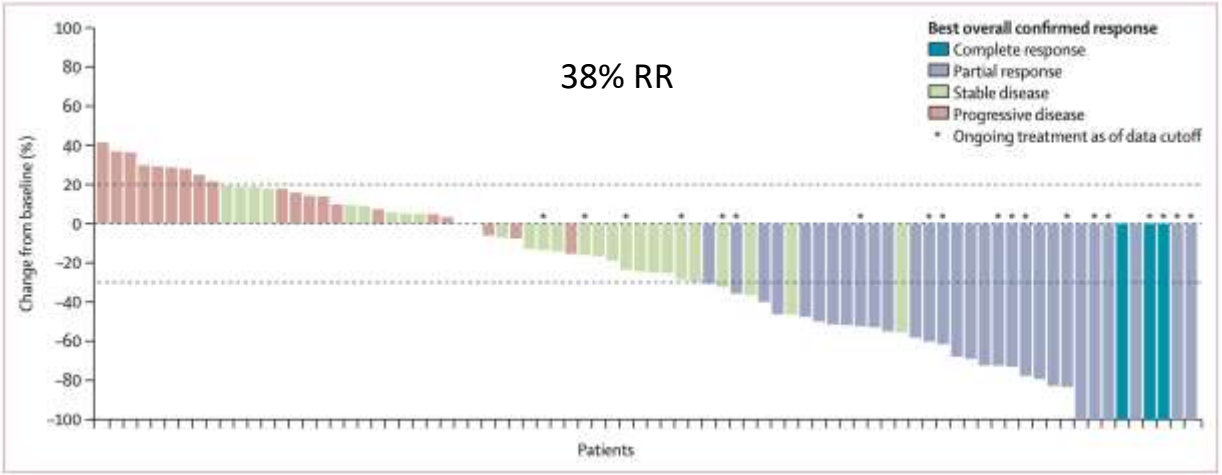
Median PFS was 6.9 months
(95% CI, 5.7–7.4)

Take Away: Adagrasib + Cetuximab is FDA approved for 2nd or 3rd line mCRC with KRAS G12C
Similar data supported more recent approval for sotorasib + panitumumab

Kopetz et al AACR ’24, Yaeger et al Can Disc ‘24

Trastuzumab + Tucatinib – HER2:

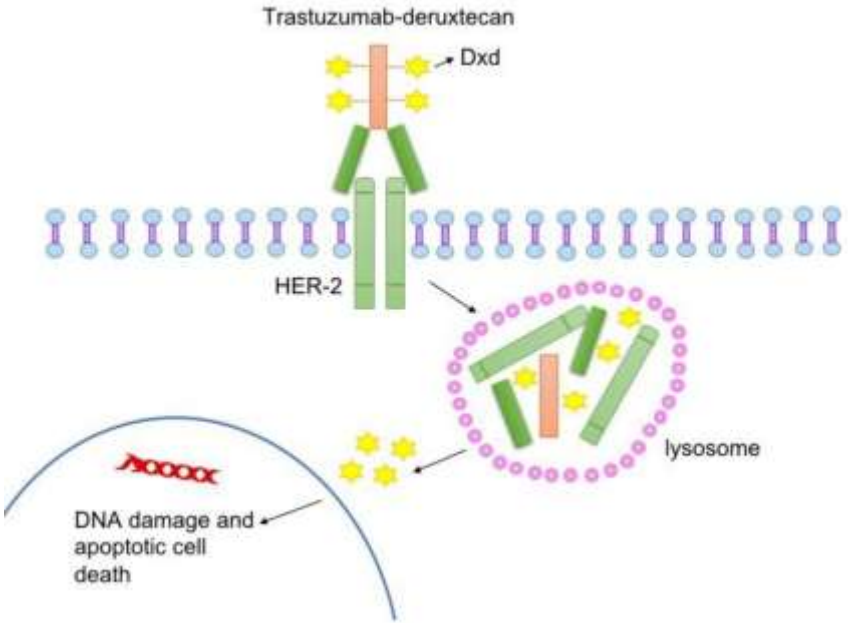




Take Away: T+T is FDA approved for RAS wild type, HER2 amplified patients

Stickler et al. Lancet Oncology 2023

Trastuzumab deruxtecan (T-dx): Topoisomerase payload with HER2 antibody



DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)

Patients

- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- *RAS/BRAF*^{V600E} wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

6.4 mg/kg dose of T-DXd administered Q3W (all cohorts)

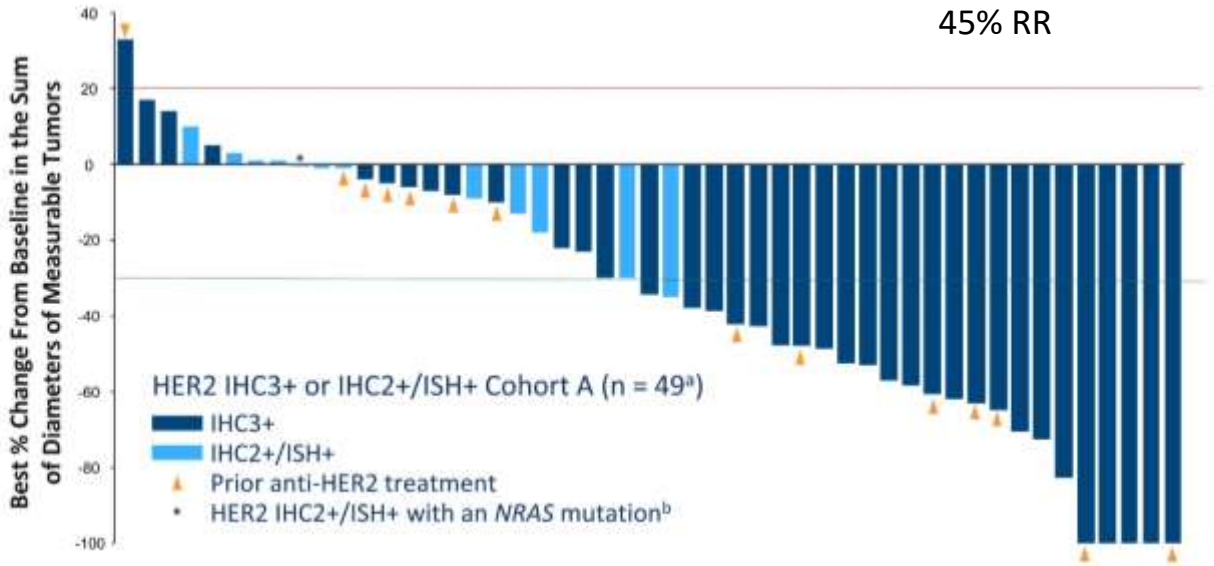
Cohort A: HER2 Positive (IHC3+ or IHC2+/ISH+) n = 53

Cohort B[a]: HER2 IHC2+/ISH− n = 15

Cohort C[a]: HER2 IHC1+ n = 18

Yoshino et al Lancet Oncology ‘21

Trastuzumab deruxtecan (T-DXd) in HER2 3+, or 2+ with ISH amplification



Take Away: Approved for all HER2 amplified solid tumors (including CRC)

Yoshino et al Lancet Onc 2021

AEs of Special Interest: Interstitial Lung Disease

All Patients (N=86)	n (%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)[a]
Any Grade/Total	8 (9.3)[b,c]

Adjudicated drug-related ILDs:

- Median time to adjudicated onset was 61.0 days (range, 9-165 days)
- 8 of 8 patients received corticosteroids
- 4 patients with grade 2 recovered and 1 patient with grade 3 did not recover (later died due to disease progression)
- Median time from adjudicated onset date to initiation of steroid treatment in the 8 ILD cases was 3.5 days, (range 0-50)

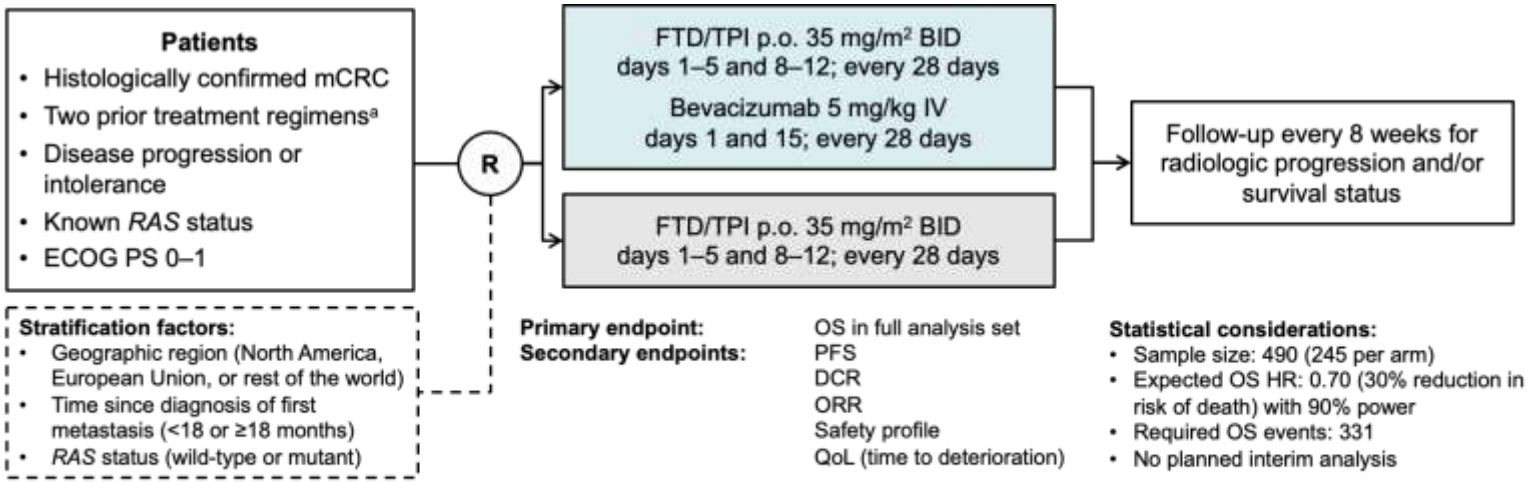
Grade 5 ILDs:

- In the 3 fatal cases adjudicated as drug-related ILD, onset was from 9 days to 120 days (median: 22 days); and death occurred 6-19 days after diagnosis (median: 6 days)

Updated ILD/pneumonitis guidelines recommend to monitor for symptoms, interrupt or discontinue T-DXd, conduct imaging (as clinically indicated), and start steroids as soon as ILD is suspected.

Yoshino et al Lancet Onc 2021

SUNLIGHT study of TAS102 +/- Bevacizumab

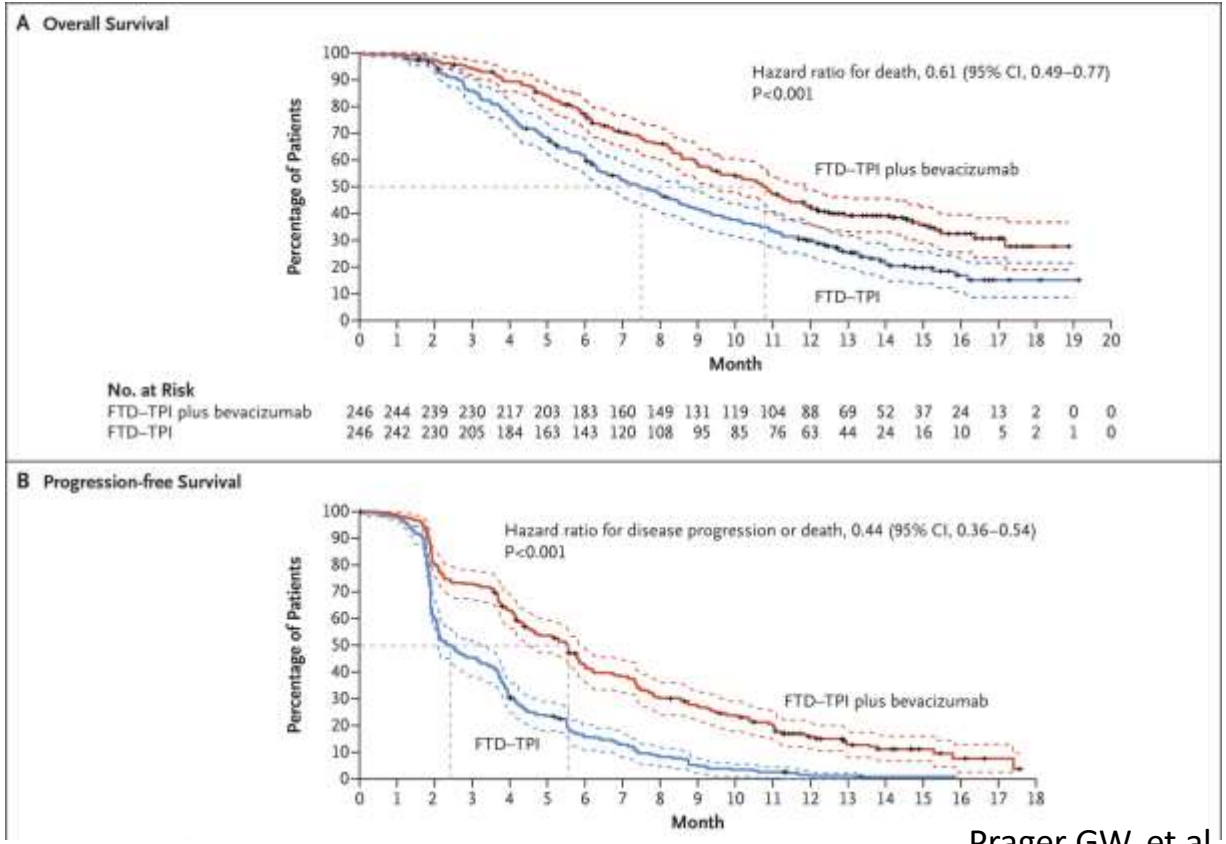


[a] Prior treatment must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (not necessarily bevacizumab), and/or an anti-EGFR monoclonal antibody for patients with *RAS* wild-type and could have included (neo)adjuvant chemotherapy if disease had recurred during treatment or within 6 months of the last administration of (neo)adjuvant therapy. BID, twice daily; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EFGR, epidermal growth factor receptor; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; IV, intravenous; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; p.o., orally; QoL, quality of life; R, randomization; VEGF, vascular endothelial growth factor.

Prager et al NEJM ‘23

Take Away: Bevacizumab beyond progression works in 2nd **and** 3rd line

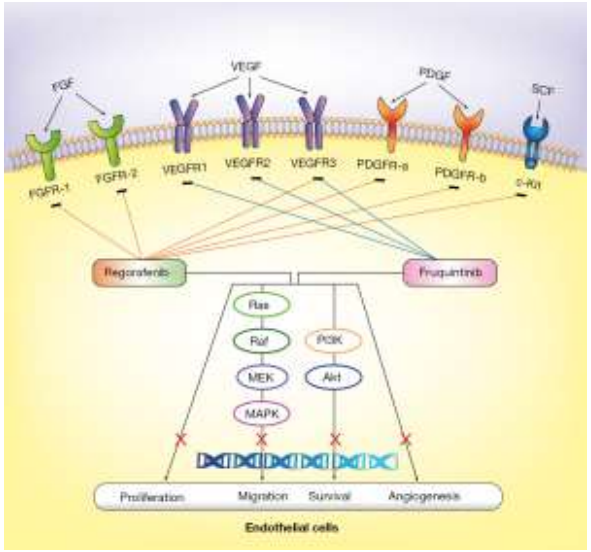
SUNLIGHT Study: TAS102 + Bev

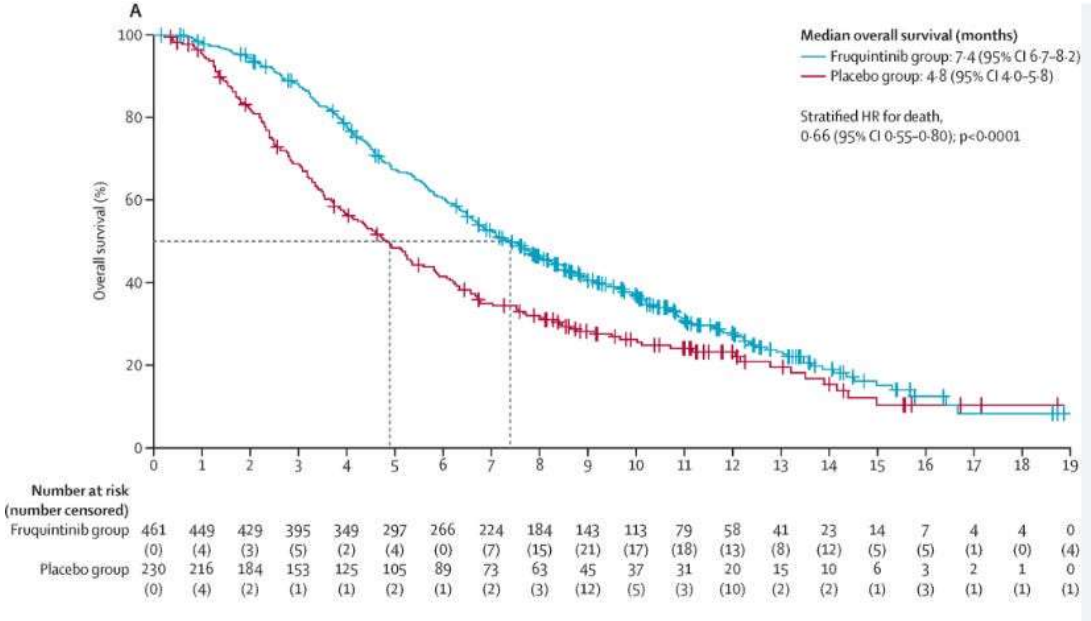


Take Away: Bevacizumab + TAS102 meaningfully improved PFS and OS and is considered the preferred regimen

Prager GW, et al. N Engl J Med. 2023;388:1657-1667.

Fruquitinib, VEGFR TKI, improves OS





Take Away: Fruquitinib is FDA approved for 3+ line patients

Dasari A, et al. Lancet. 2023;402:41-53.

Conclusions: Therapy for advanced mCRC

- Multiple treatment options available, with heterogeneous treatment patterns
- Biomarkers being integrated, with logistic difficulties
- Active area of development for clinical development
- Rationale exists for combination therapy to constrain mechanisms of resistance – More to come on this!

Thank You!