Metastatic Colorectal Cancer: State of the Art

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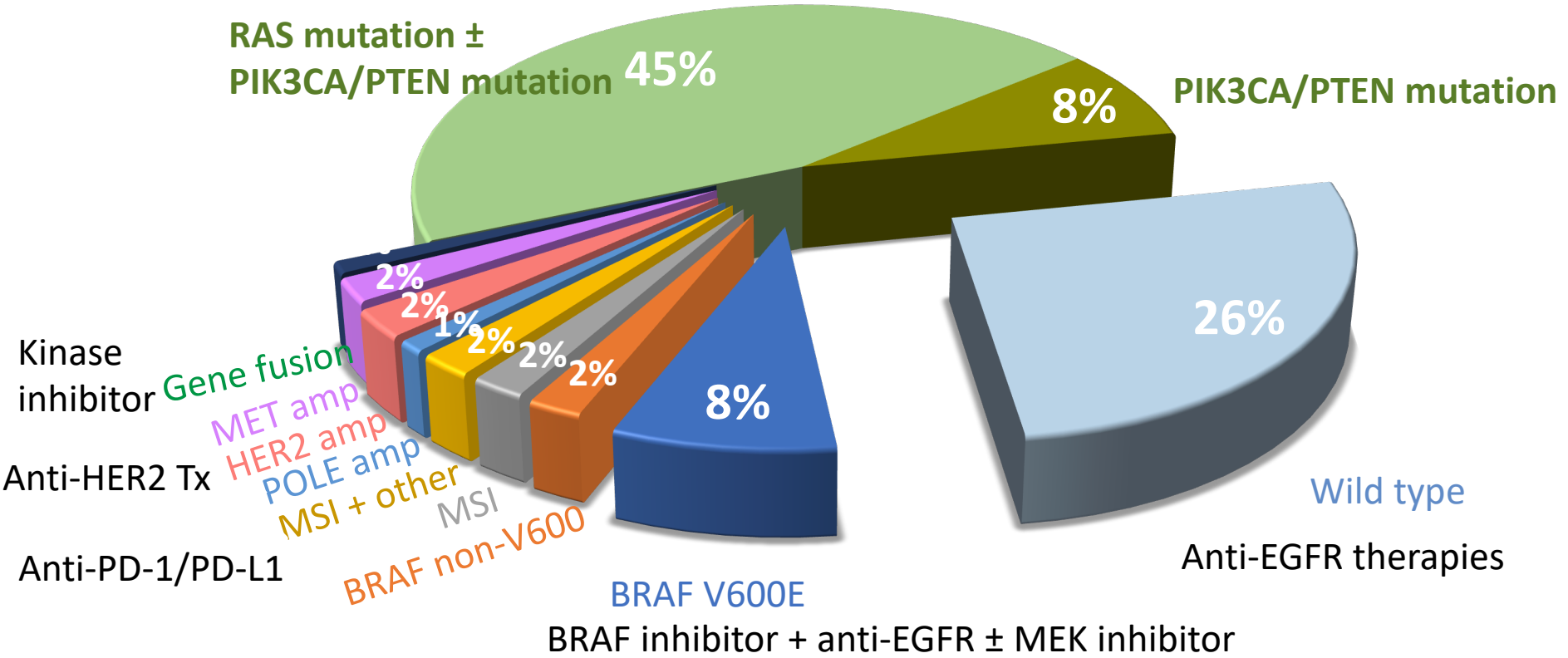
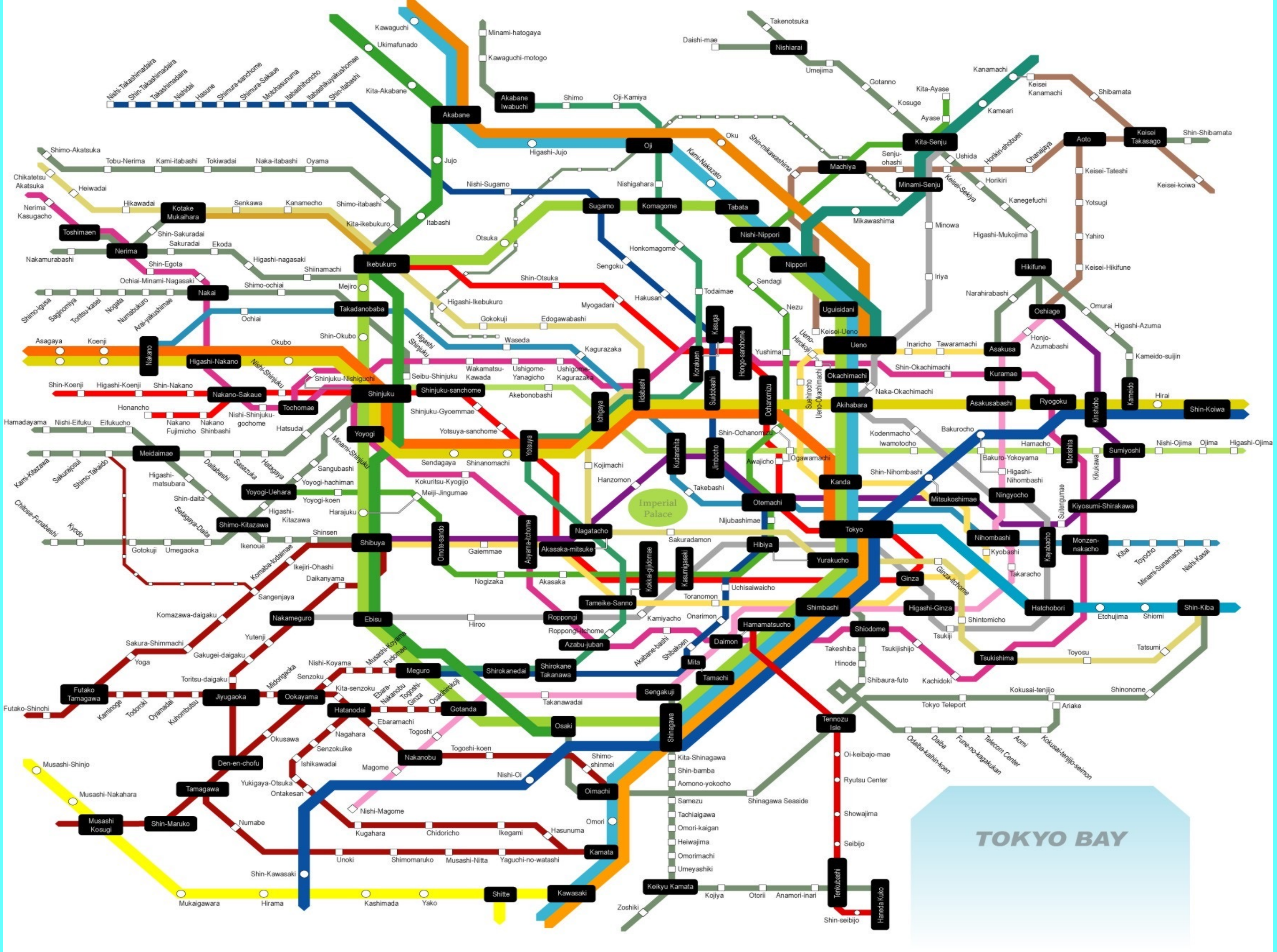
Genomic Markers in CRC



CRC = colorectal cancer.

Dienstmann R, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:231-238.

USC
NORRIS


TOKYO BAY
Imperial Palace
Kawaguchi
Ukimafunado
Minami-hatogaya
Kawaguchi-motogo
Takenotsuka
Daishi-mae
Nishiarai
Umejima
Gotanno
Kanamachi
Keisei Kanamachi
Shibamata
Kita-Ayase
Ayase
Kosuge
Kameari
Kita-Akabane
Akabane
Akabane Iwabuchi
Shimo
Oji-Kamiya
Oji
Oku
Kita-Senju
Keisei Takasago
Shin-Shibamata
Aoto
Keisei-Tateishi
Keisei-koiwa
Yotsugi
Yahiro
Keisei-Hikifune
Higashi-Jujo
Jujo
Nishi-Sugamo
Sugamo
Komagome
Tabata
Nishigahara
Machiya
Senju-ohashi
Minami-Senju
Ushida
Horikiri-shobuen
Horikiri
Ohanajaya
Kanegafuchi
Higashi-Mukojima
Hikifune
Minowa
Mikawashima
Nishi-Nippori
Nippori
Sendagi
Nezu
Uguisudani
Keisei-Ueno
Ueno
Inaricho
Tawaramachi
Asakusa
Honjo-Azumabashi
Oshiage
Omurai
Higashi-Azuma
Kameido-suijin
Kameido
Hirai
Shin-Koiwa
Iriya
Narahirabashi
Shimo-Akatsuka
Tobu-Nerima
Kami-itabashi
Tokiwadai
Naka-itabashi
Oyama
Chikatetsu Akatsuka
Heiwadai
Hikawadai
Kotake Mukaihara
Senkawa
Kanamecho
Shimo-itabashi
Kita-ikebukuro
Itabashi
Nerima Kasugacho
Toshimaen
Shin-Sakuradai
Sakuradai
Ekoda
Nerima
Nakamurabashi
Higashi-nagasaki
Shiinamachi
Ikebukuro
Otsuka
Honkomagome
Sengoku
Hakusan
Todaimae
Shin-Otsuka
Myogadani
Shin-Egota
Ochiai-Minami-Nagasaki
Nakai
Shimo-ochiai
Mejiro
Takadanobaba
Higashi-Ikebukuro
Gokokuji
Edogawabashi
Waseda
Kagurazaka
Ochiai
Shin-Okubo
Okubo
Asagaya
Koenji
Nakano
Higashi-Nakano
Higashi Shinjuku
Nishi-Shinjuku
Shinjuku-Nishiguchi
Shinjuku
Shinjuku-sanchome
Seibu-Shinjuku
Wakamatsu-Kawada
Ushigome-Yanagicho
Ushigome-Kagurazaka
Akebonobashi
Ichigaya
Iidabashi
Korakuen
Kasuga
Suidobashi
Hongo-sanchome
Ochanomizu
Yushima
Ueno-Hirokoji
Ueno-Okachimachi
Suehirocho
Okachimachi
Shin-Okachimachi
Naka-Okachimachi
Kuramae
Akihabara
Asakusabashi
Ryogoku
Kinshicho
Shin-Koenji
Higashi-Koenji
Shin-Nakano
Nakano-Sakaue
Tochomae
Honancho
Nakano Fujimicho
Nakano Shinbashi
Nishi-Shinjuku-gochome
Hatsudai
Shinjuku-Gyoemmae
Yotsuya-sanchome
Yotsuya
Yoyogi
Sendagaya
Shinanomachi
Kojimachi
Hanzomon
Kudanshita
Jimbocho
Shin-Ochanomizu
Awajicho
Ogawamachi
Kodenmacho
Iwamotocho
Bakurocho
Hamacho
Bakuro-Yokoyama
Higashi-Nihombashi
Morishita
Sumiyoshi
Nishi-Ojima
Ojima
Higashi-Ojima
Hamadayama
Nishi-Eifuku
Eifukucho
Meidaimae
Minami-Shinjuku
Sangubashi
Yoyogi-hachiman
Yoyogi-koen
Yoyogi-Uehara
Kokuritsu-Kyogijo
Meiji-Jingumae
Harajuku
Takebashi
Otemachi
Kanda
Shin-Nihombashi
Mitsukoshimae
Ningyocho
Kikukawa
Suitengumae
Kiyosumi-Shirakawa
Kami-Kitazawa
Sakurajosui
Shimo-Takaido
Higashi-matsubara
Daitabashi
Sasazuka
Hatagaya
Shin-daita
Higashi-Kitazawa
Shimo-Kitazawa
Setagaya-Daita
Chitose-Funabashi
Kyodo
Gotokuji
Umegaoka
Ikenoue
Shinsen
Shibuya
Omote-sando
Gaienmae
Aoyama-itchome
Nagatacho
Akasaka-mitsuke
Sakuradamon
Nijubashimae
Hibiya
Tokyo
Yurakucho
Nihombashi
Kyobashi
Kayabacho
Monzen-nakacho
Kiba
Toyocho
Minami-Sunamachi
Nishi-Kasai
Komaba-todaimae
Ikejiri-Ohashi
Sangenjaya
Nogizaka
Akasaka
Kokkai-gijidomae
Kasumigaseki
Uchisaiwaicho
Ginza
Ginza-itchome
Takaracho
Hatchobori
Etchujima
Shiomi
Shin-Kiba
Daikanyama
Komazawa-daigaku
Nakameguro
Ebisu
Hiroo
Roppongi
Roppongi-itchome
Tameike-Sanno
Toranomon
Kamiyacho
Onarimon
Shimbashi
Higashi-Ginza
Shintomicho
Tsukiji
Tsukishima
Toyosu
Tatsumi
Sakura-Shimmachi
Yutenji
Gakugei-daigaku
Yoga
Azabu-juban
Akabane-bashi
Shibakoen
Daimon
Hamamatsucho
Shiodome
Takeshiba
Hinode
Tsukijishijo
Kachidoki
Shibaura-futo
Futako Tamagawa
Futako-Shinchi
Toritsu-daigaku
Nishi-Koyama
Musashi-Koyama
Fudomae
Meguro
Shirokanedai
Shirokane Takanawa
Mita
Tamachi
Sengakuji
Takanawadai
Jiyugaoka
Midorigaoka
Senzoku
Ookayama
Kita-senzoku
Hatanodai
Ebara-Nakanobu
Togoshi-Ginza
Osakihirokoji
Gotanda
Osaki
Shinagawa
Kaminoge
Todoroki
Oyamadai
Kuhombutsu
Okusawa
Nagahara
Ebaramachi
Togoshi
Senzokuike
Nakanobu
Togoshi-koen
Den-en-chofu
Ishikawadai
Magome
Shimo-shinmei
Kita-Shinagawa
Shin-bamba
Aomono-yokocho
Tennozu Isle
Kokusai-tenjijo
Shinonome
Ariake
Tokyo Teleport
Odaiba-kaihin-koen
Daiba
Fune-no-kagakukan
Telecom Center
Aomi
Kokusai-tenjijo-seimon
Oi-keibajo-mae
Ryutsu Center
Showajima
Seibijo
Musashi-Shinjo
Musashi-Nakahara
Tamagawa
Yukigaya-Otsuka
Ontakesan
Nishi-Oi
Oimachi
Samezu
Shinagawa Seaside
Tachiaigawa
Omori-kaigan
Heiwajima
Omorimachi
Umeyashiki
Musashi Kosugi
Shin-Maruko
Numabe
Nishi-Magome
Omori
Kugahara
Chidoricho
Ikegami
Hasunuma
Kamata
Unoki
Shimomaruko
Musashi-Nitta
Yaguchi-no-watashi
Shin-Kawasaki
Keikyu Kamata
Kojiya
Otorii
Anamori-inari
Tenkubashi
Haneda Kuko
Shin-seibijo
Zoshiki
Mukaigawara
Hirama
Kashimada
Yako
Shitte
Kawasaki

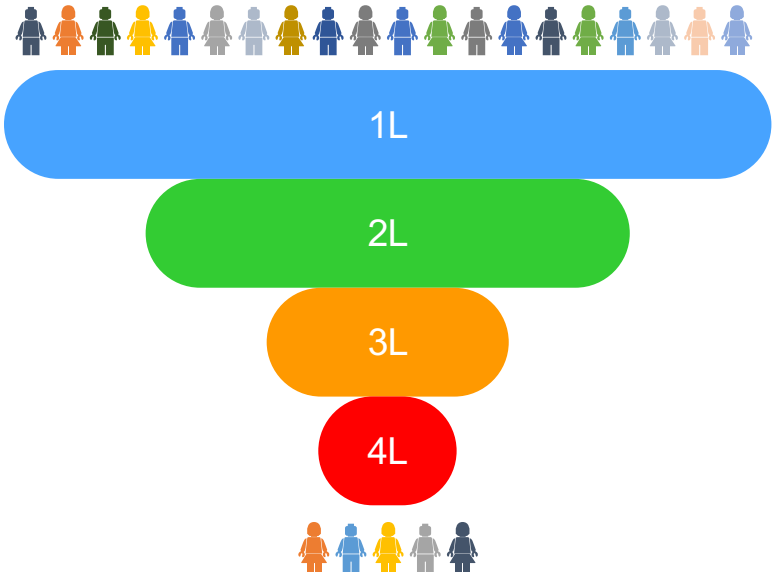
What influences treatment choices in mCRC?

Patient characteristics

- Comorbidities
- Prior adjuvant treatment
- Age
- Performance status

Tumor characteristics

- Tumor burden
- Resectability
- Tumor location



Molecular characteristics

- RAS
- BRAF
- MSI-high
- HER2

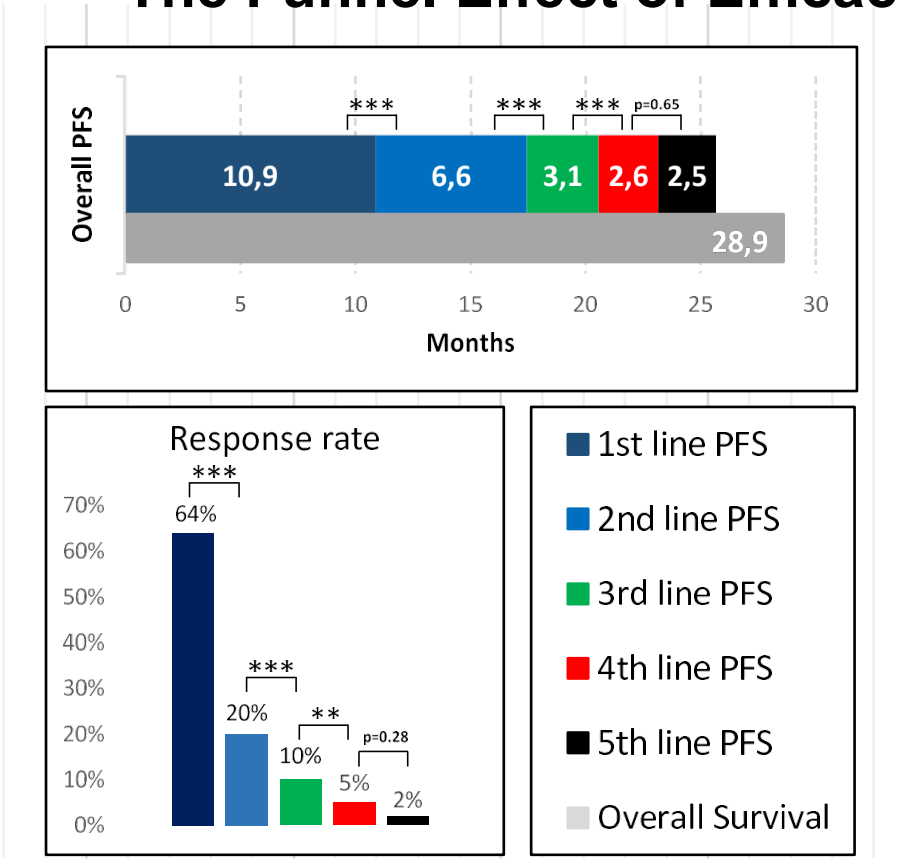
Patient preference

- Quality of life
- Toxicity profile

Goals of care

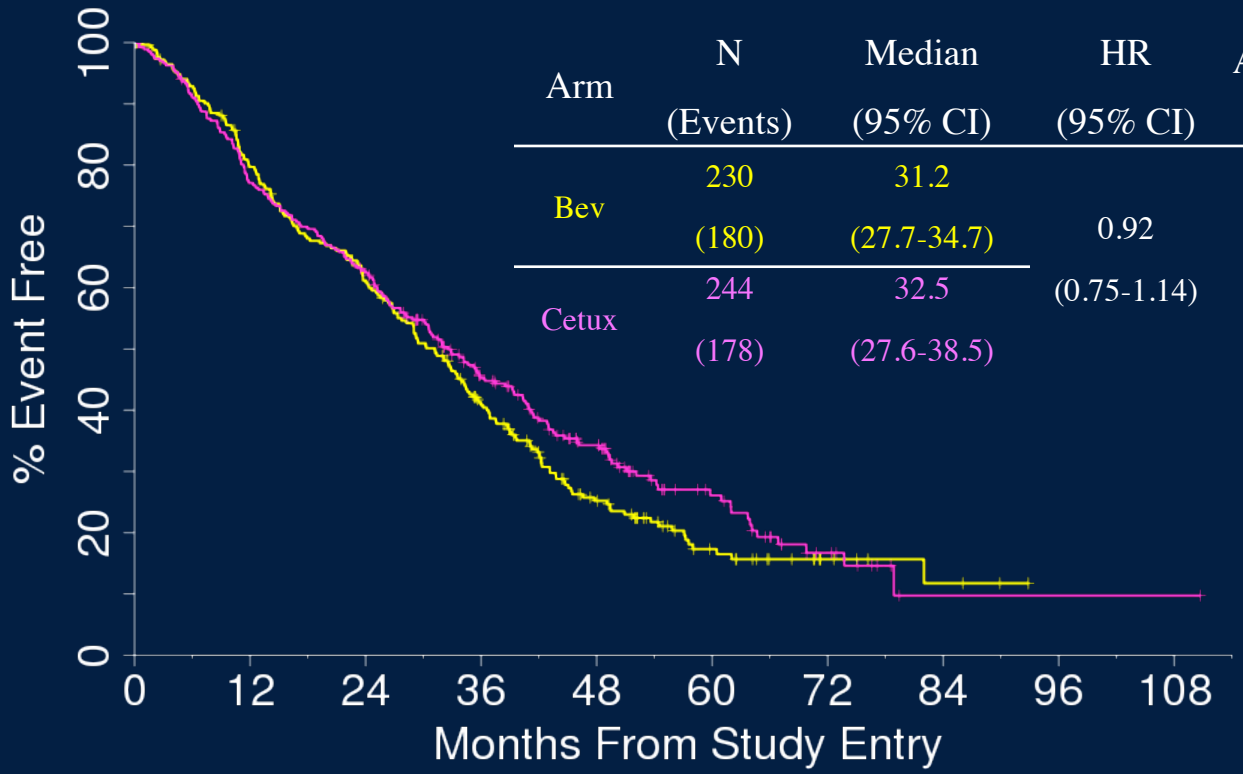
Therapy tailored according to individual patient needs

mCRC - Starting Point #2: The Funnel Effect of Efficacy



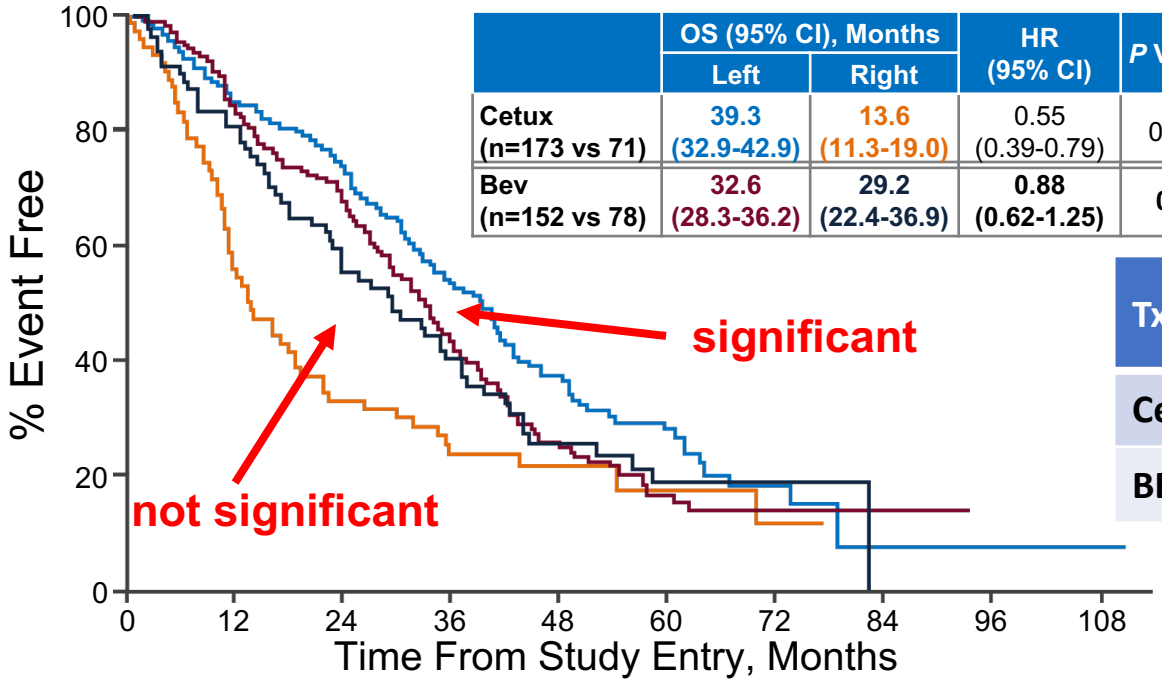
Rossini D, et al. *Eur J Cancer*. 2022;170:64-72.

Overall Survival by Biologic, All *RAS* wt



Arm	N (Events)	Median (95% CI)	HR (95% CI)	Adjusted P
Bev	230 (180)	31.2 (27.7-34.7)	0.92 (0.75-1.14)	0.48
Cetux	244 (178)	32.5 (27.6-38.5)		

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

Tx	ΔR vs L (mos)
Cetux	25.7
BEV	3.4

*Adjusted for biologic, protocol CT, prior adjuvant therapy, prior RT, age, sex, synchronous disease, in place primary, liver metastases.

Venook A, Lenz HJ et al. Presented at: ESMO. 2016.

Doublets Plus anti-EGFR in RAS Wt Left-sided mCRC

	mPFS (mos)	mOS (mos)	ORR (%)
TRIPLETE** [mFOLFOX6/pan] n=191	13.6	NA	75.9
PARADIGM [mFOLFOX6/pan] n=312	13.7	37.9	80.2
FIRE-3 [FOLFIRI/cet] n=157	10.7	38.3	68.8
CALGB80405 [chemo doublet*/cet] N=173	12.7	39.3	69.4
PEAK [mFOLFOX6/pan] n=53	14.6	43.4	64.1

*FOLFOX or FOLFIRI at investigator choice; **_RAS_ and _BRAF_ wt

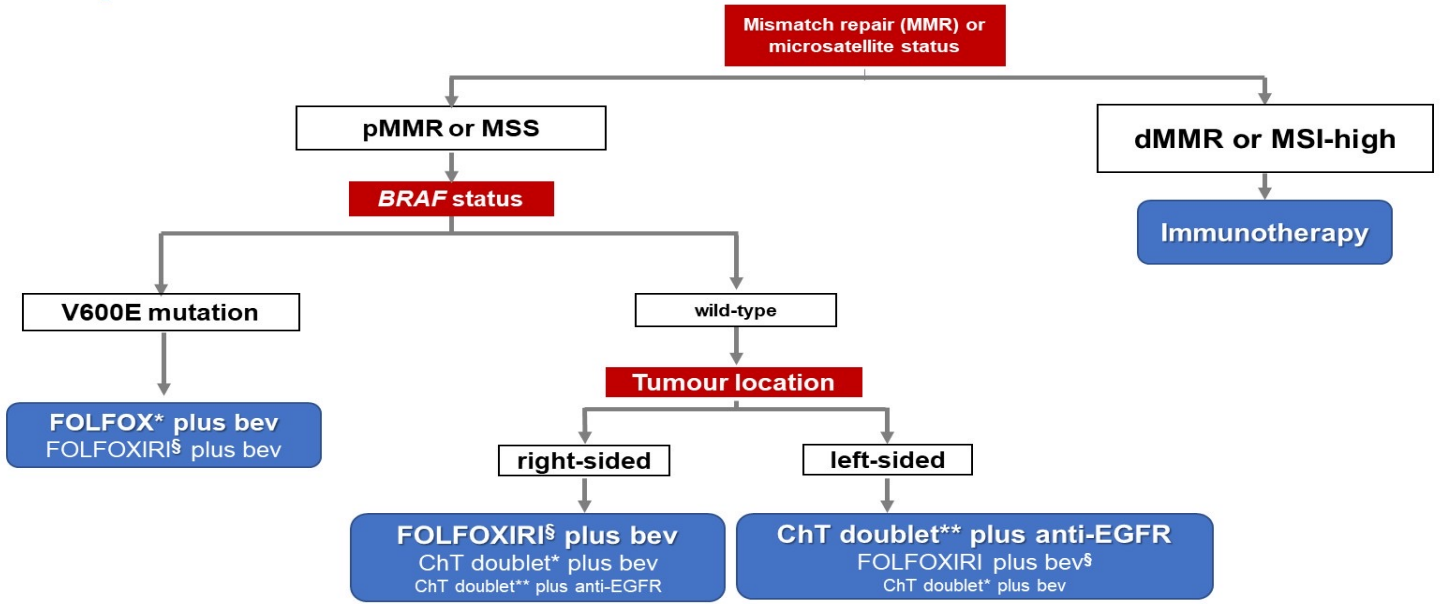
Arnold D, et al. *Ann Oncol*. 2017;28(8):1713-1729. Holch JW, et al. *Eur J Cancer*. 2017;70:87-98. Yoshino T, et al. Presented at: ASCO;2022. Rossini D, et al. *J Clin Oncol*. 2022;40(25):2878-2888.

Sequence Matters

Choice of Line of Therapies Will Change in Future

1. Most effective therapy (location, mutational status)
2. FOLFOXIRI long OS as well as doublets with targeted agents
3. Second line therapies limited efficacies (response/survival)
    a. Liquid Biopsies will impact
4. Immunotherapies for MSI in 1L
5. Tucantinib/trastzumab and Encorafenib/cetux moving into 1L

Treatment algorithm for the choice of the upfront therapy for *RAS* wt mCRC patients



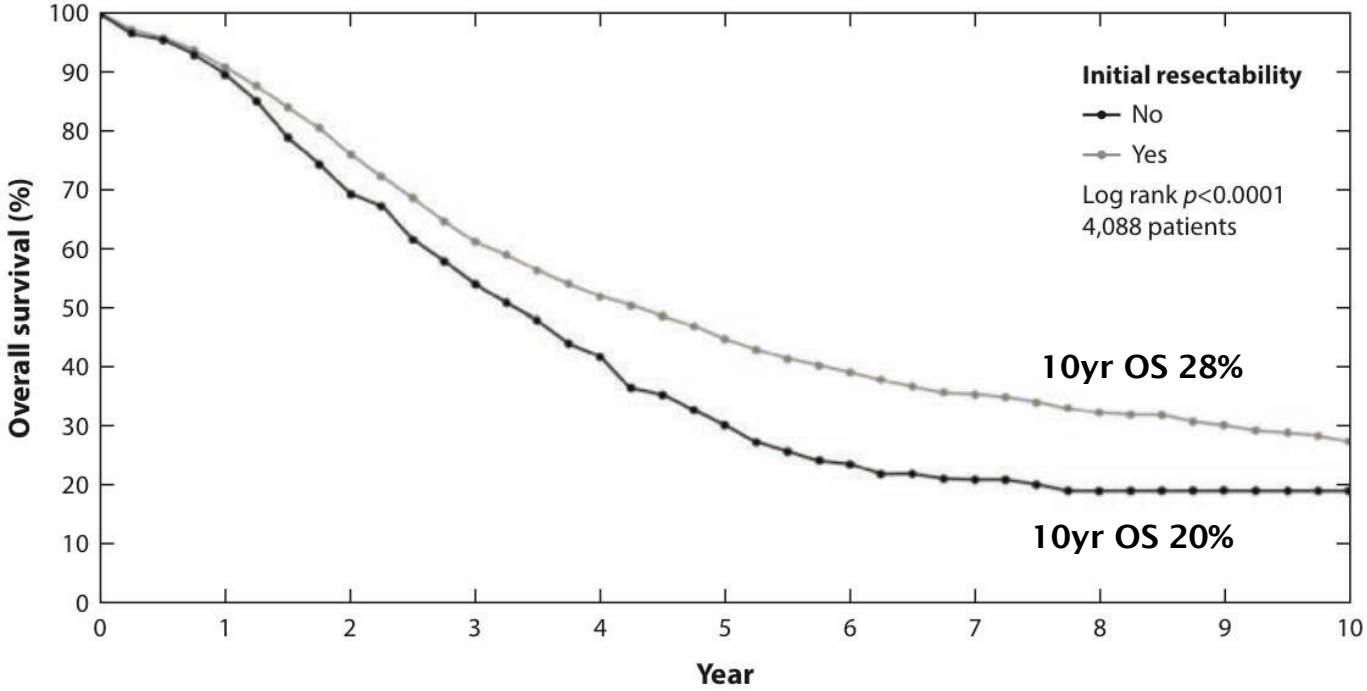
Bev: bevacizumab; ChT: chemotherapy.

* Fluoropyrimidine monotherapy if not fit for doublet chemotherapy
** 5-fluorouracil/leucovorin if not fit for doublet chemotherapy;
§ only if <75 years old (71-75 years old with ECOG Performance Status 0)

Cremolini C, et al. Presented at: ASCO;2022.

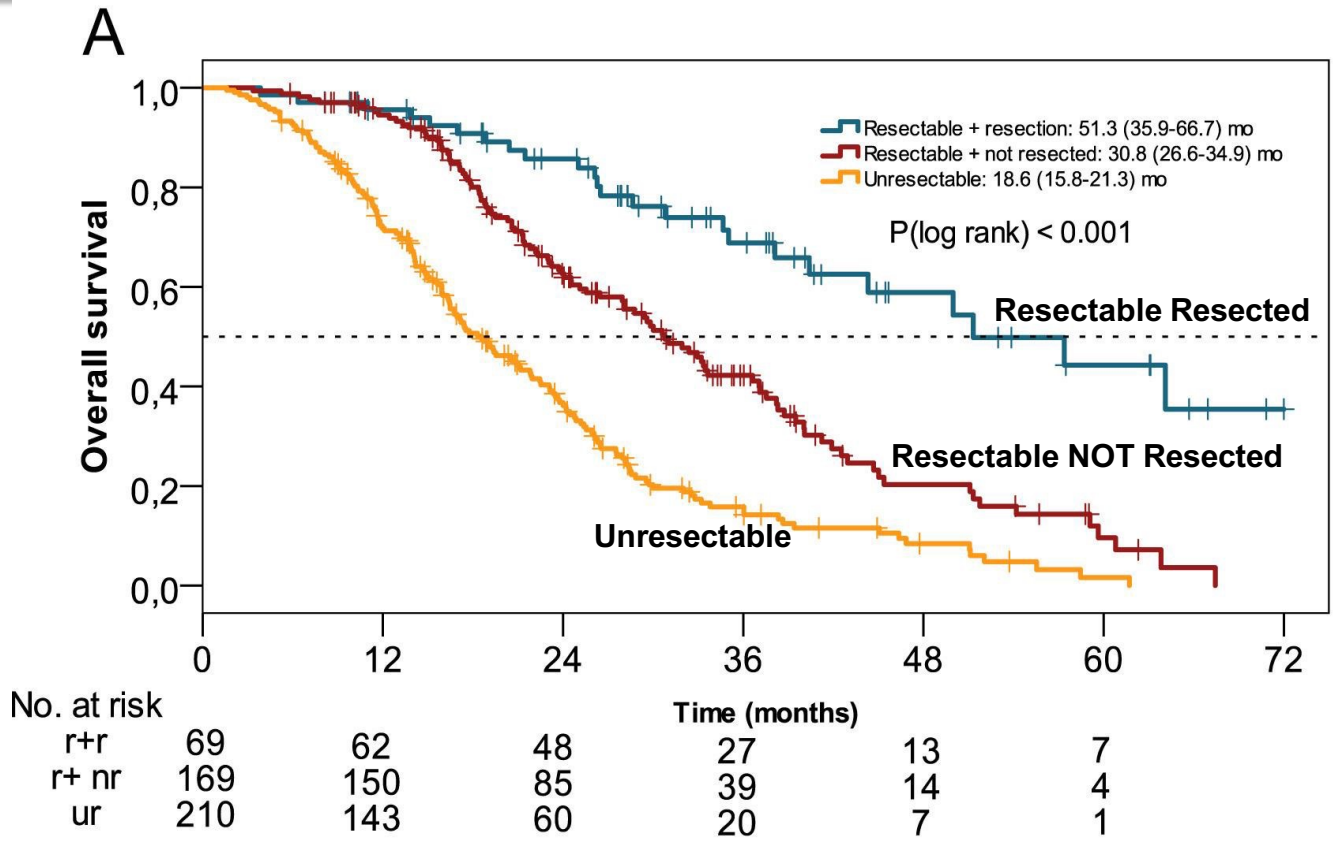
To cure? …Yes, WE CAN!

Survival following hepatectomy for colorectal liver metastases



Jones and Poston, Annu Rev Med 2017

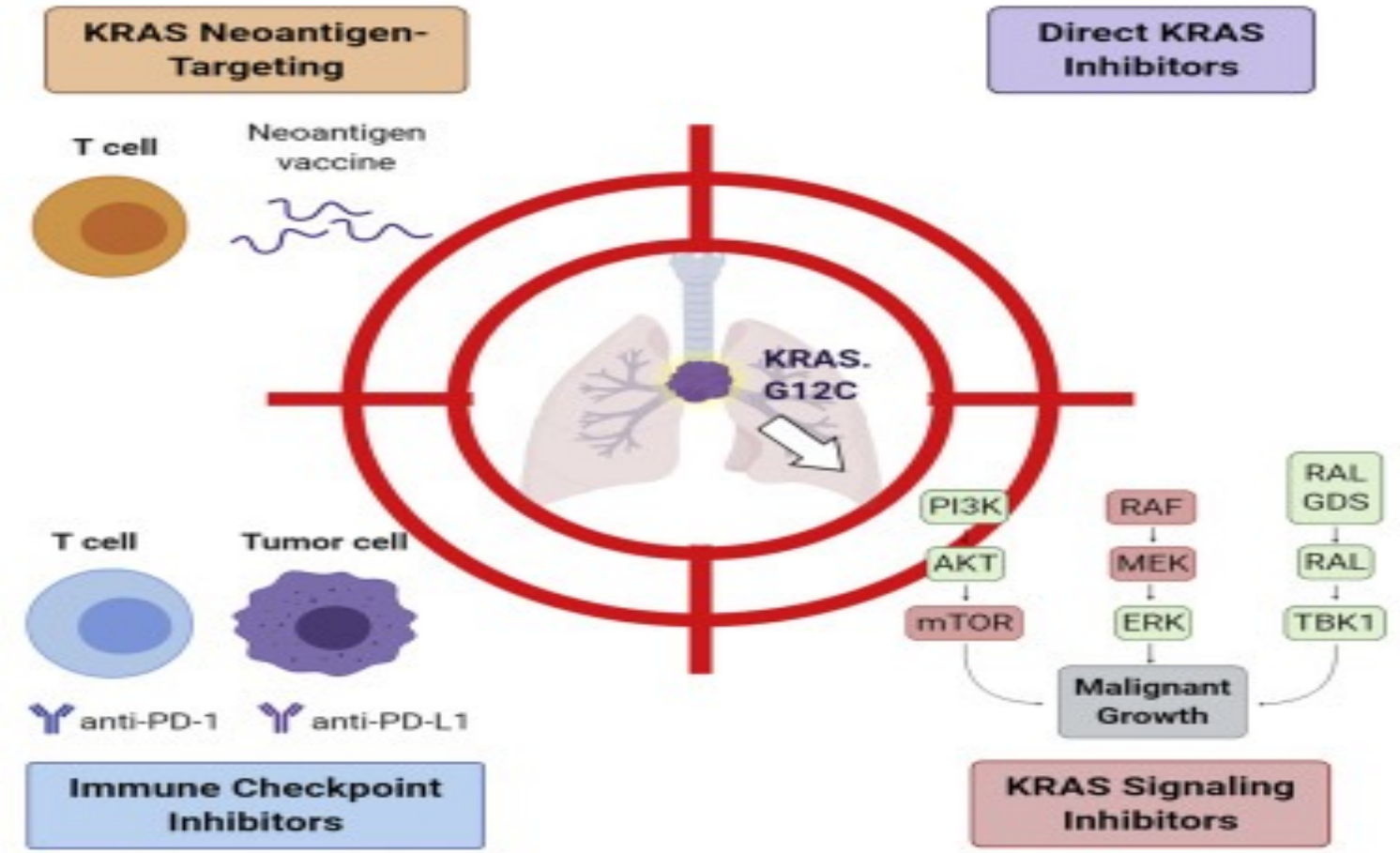
Overall survival according to surgical treatment in FIRE-3



Modest, EJC 2017

Novel Approaches

1. RAS/RAF (G12C, G12D, G12V)
2. Pan Inhibitor



Salgia R, et al. *Cell Rep Med*. 2021;2(1):100186.

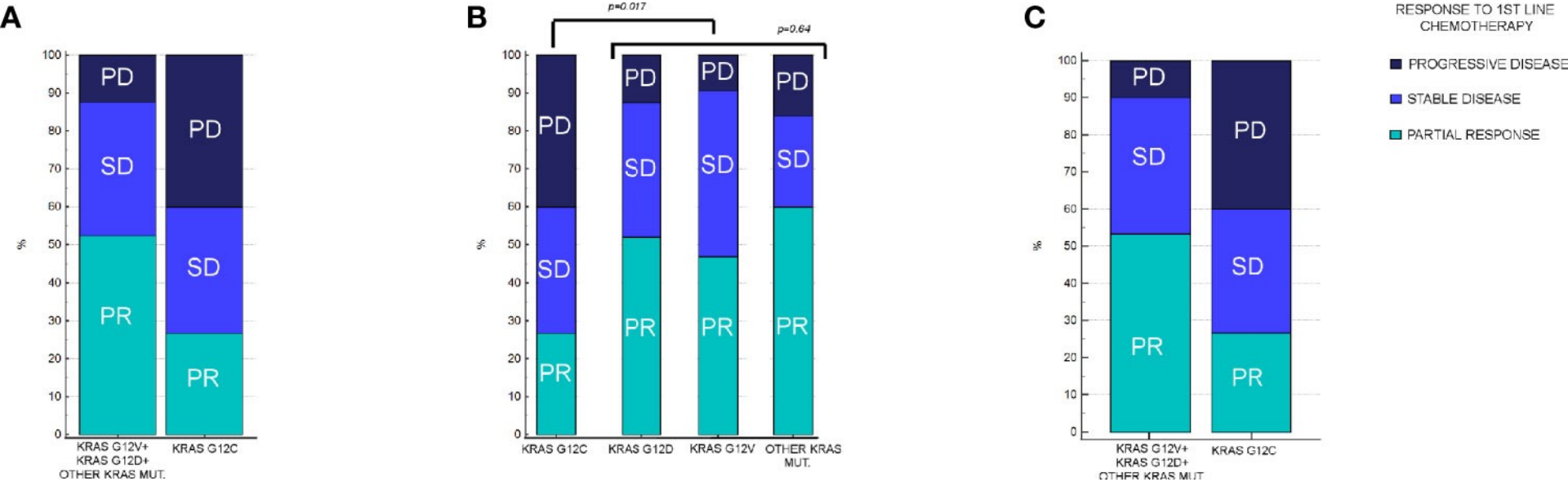
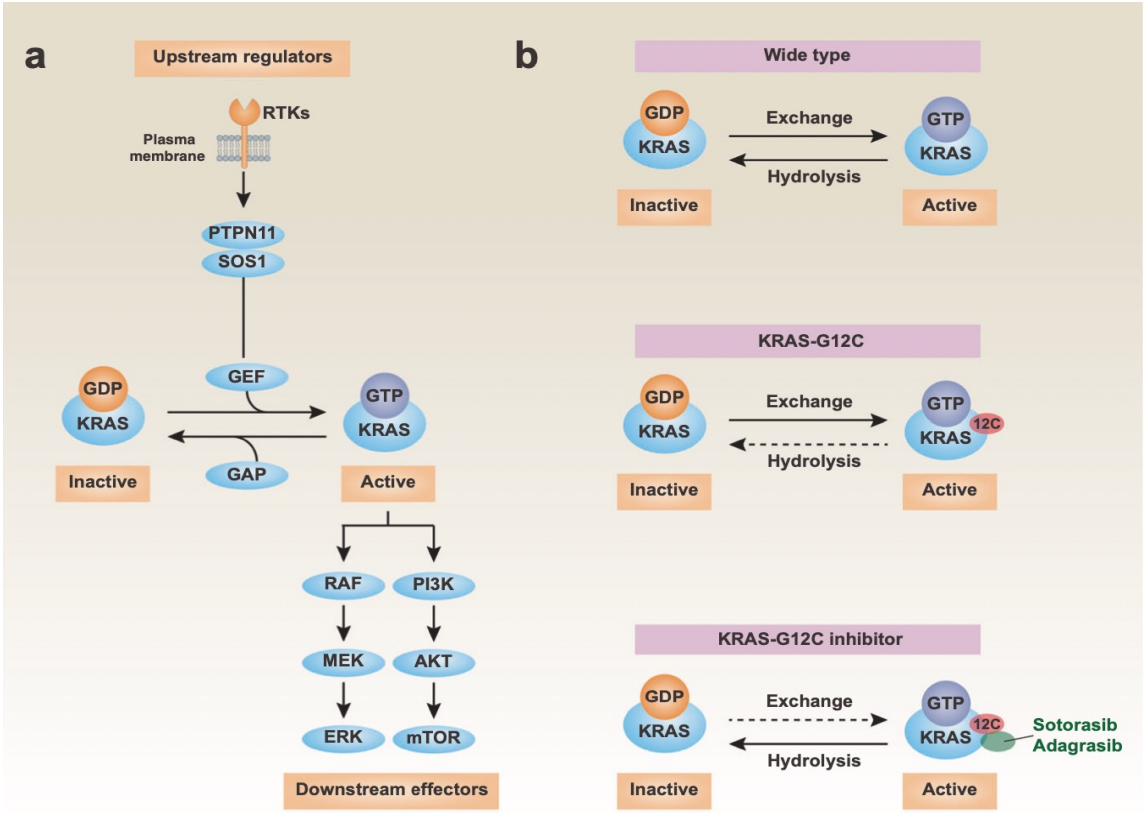
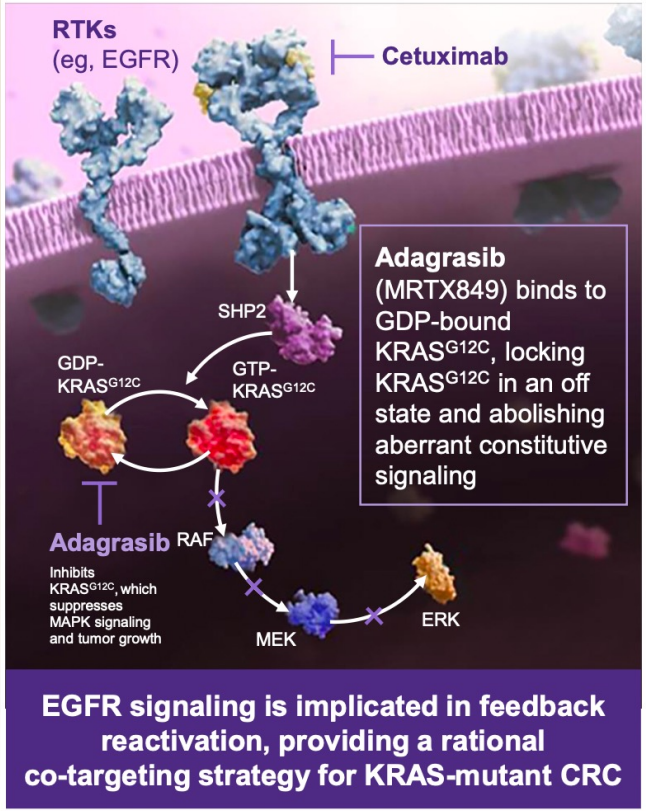


Figure 2 Response rates in patients enrolled in the analysis, stratified by KRAS mutation. (A) Response rates in KRAS G12C vs all other KRAS mutations combined. In KRAS G12C, PR: 27%, SD: 40%, and PD: 33%. In other KRAS mutations combined, PR: 52%, SD: 35%, and PD: 12% (p = 0.017). (B) Response rates between KRAS G12C vs G12D, G12V, and other KRAS mutations different from G12C, G12D, or G12V. In KRAS G12D, PR: 52%, SD: 35%, and PD: 13%. In KRAS G12V, PR: 47%, SD: 44%, and PD: 9%. In remaining KRAS mutations cohort, PR: 60%, SD: 24%, and PD: 16%. Difference in RR among KRAS G12V, G12D, and remaining mutations was not statistically significant (p = 0.64). (C) Response rates between KRAS G12C vs all other KRAS mutations combined after matching procedures. In other KRAS mutation cohort, PR: 56%, SD: 37%, and PD: 7% (p = 0.016).

Giamperi R, et al. *Front Oncol*. 2021;11:736104.

KRAS G12C Inhibitors (3-4% of mCRC)





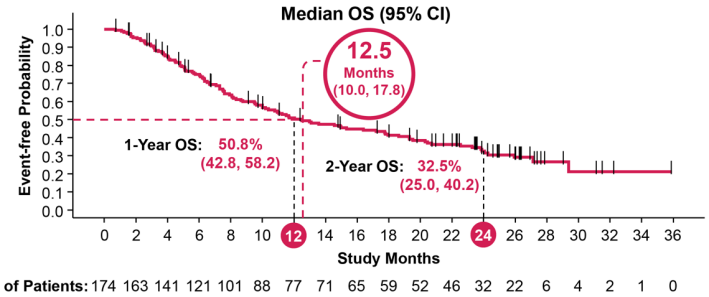
Liu J, et al. Accessed June 28, 2023. https://www.nature.com/articles/s41417-021-00383-9.

Codebreak

- Sotorasib, a selective KRAS^{G12C} inhibitor, is approved in Europe, the US, and other countries for patients with previously treated *KRAS* p.G12C-mutated NSCLC[1–4]
- In Phase 1/2 of the CodeBreaK 100 study,[5,6] sotorasib monotherapy demonstrated:

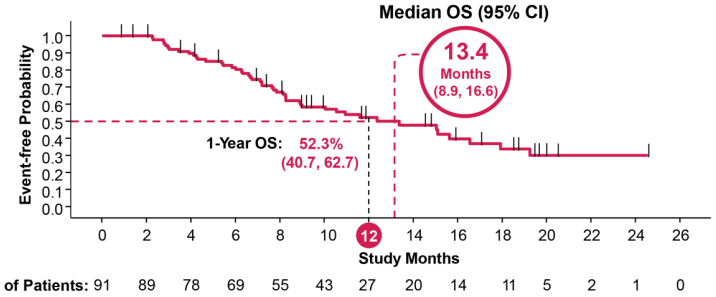
NSCLC

- **ORR: 41%**
- Median PFS: 6.3 months
- DCR: 84%



CRC

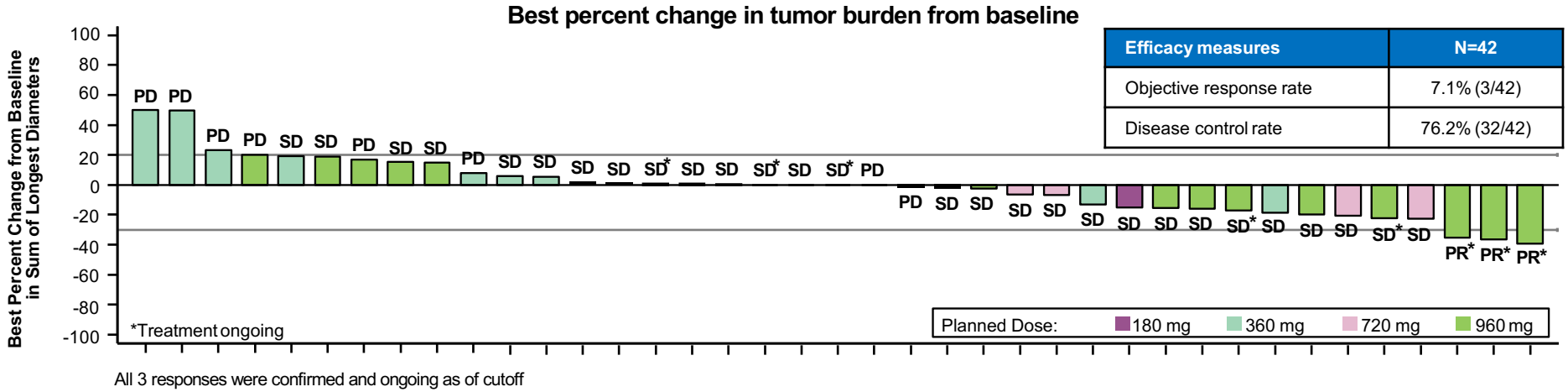
- **ORR: 12%**
- Median PFS: 4.2 months
- DCR: 82%



We describe putative mechanisms of acquired resistance to sotorasib in patients with CRC from the CodeBreaK 100 study

1. Canon J, et al. *Nature.* 2019;575:217-23; 2. FDA. Accessed June 28, 2023. chrome extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf. 3. NCT03600883. Accessed June 28, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT03600883. 4. Dy GK, et al. Presented at: AACR; April 8-13 2022, New Orleans, Lousiana. Abstract CT008.

Sotorasib Single Agent - Efficacy in CRC

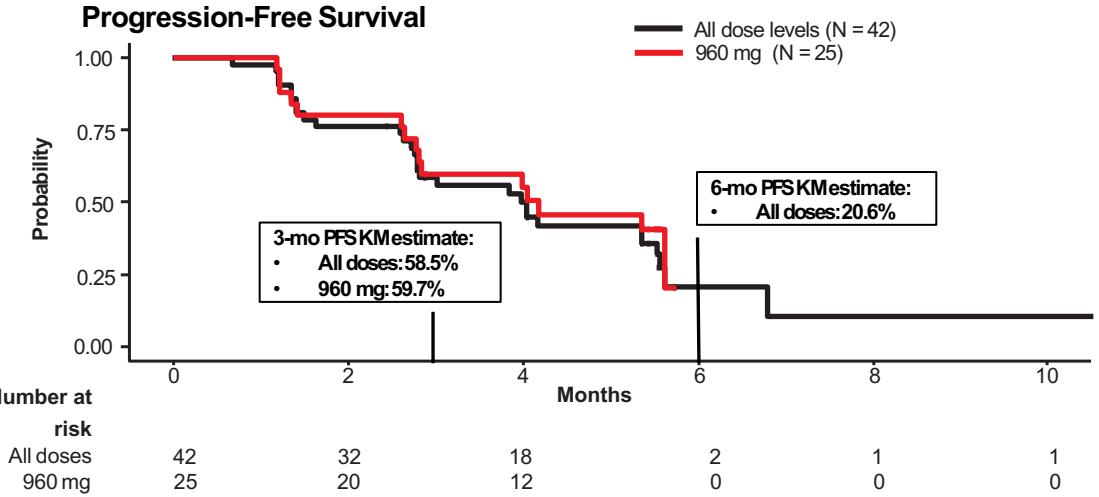


Efficacy measures	N=42
Objective response rate	7.1% (3/42)
Disease control rate	76.2% (32/42)

All 3 responses were confirmed and ongoing as of cutoff

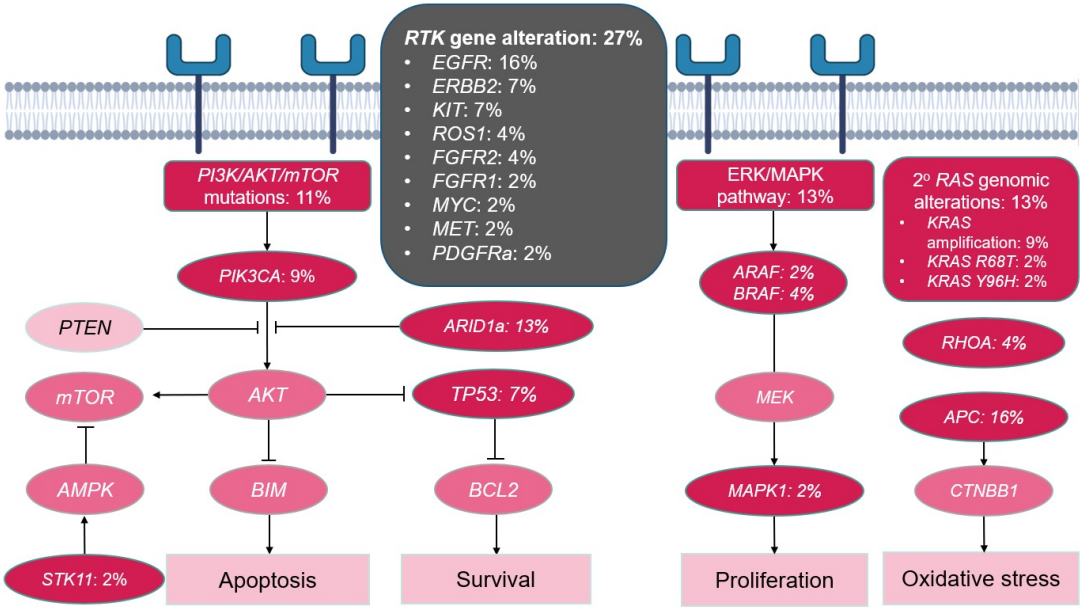
PFS, month	Median (min, max)
All doses	4.0 (0.7, 11.0)
960 mg	4.2 (1.2, 5.7+)

+: censored value.



Strickler JH, et al. Presented at: ESMO;2020.

Putative Acquired Resistance Mechanisms After Sotorasib[a]



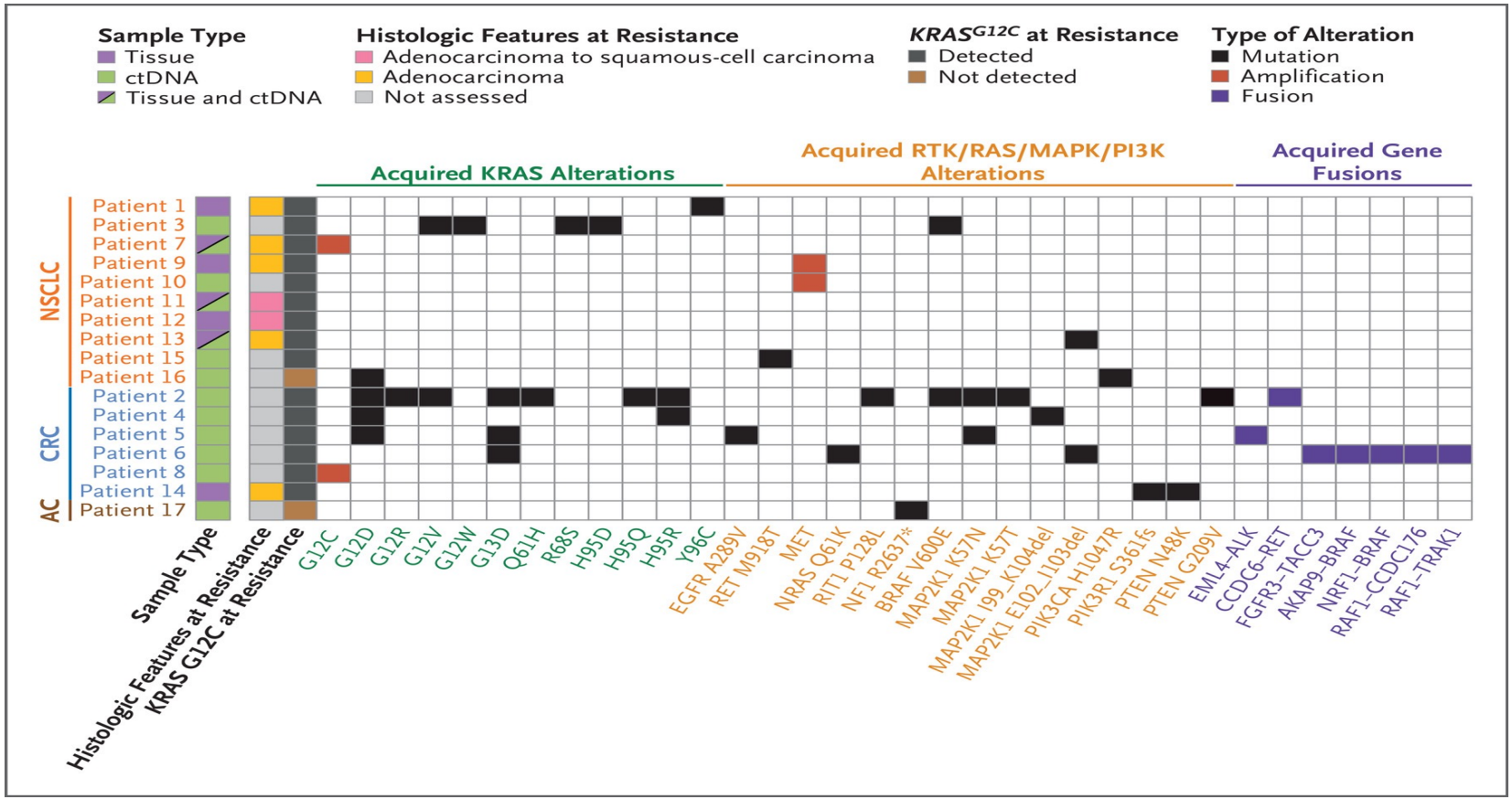
OncoKB[1]

- 16/100 alterations were potentially targetable[b]
- Higher incidence of secondary *RAS* variants in CRC versus NSCLC

***RTK* gene alterations were the most prevalent acquired genomic alteration in patients with CRC (12/45; 27%)**

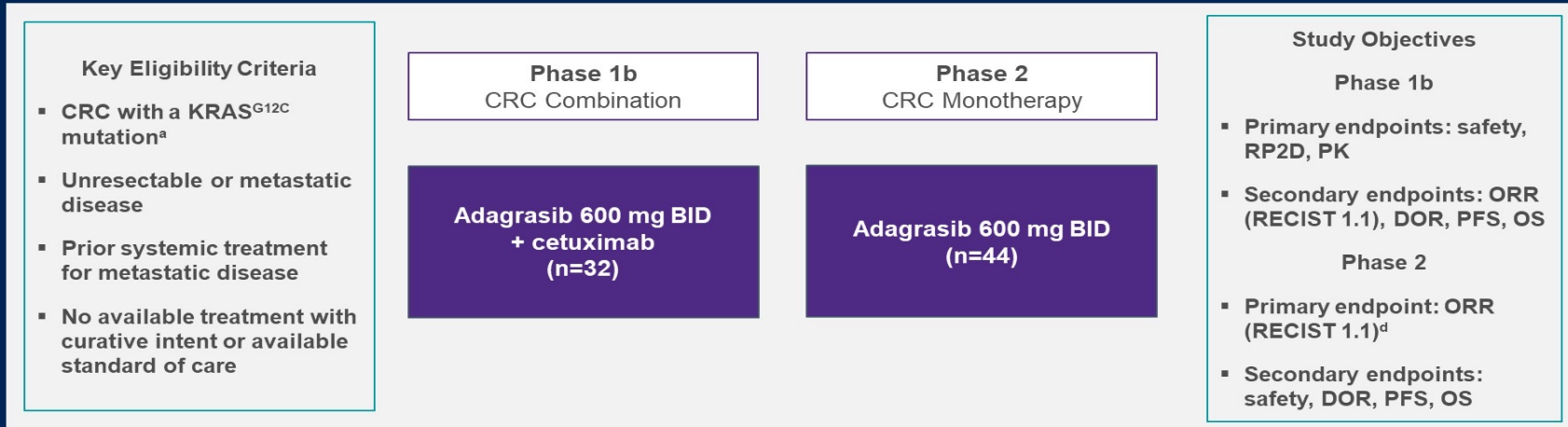
[a]Mutation rate presented based on 45 evaluable patients with CRC; [b]Actionability levels defined in full at https://www.oncokb.org/levels. Actionable variants: Level 1; *BRCA1* E352* (n = 1), *BRCA2* S196R (n = 1), *CDK12* G909* (n = 1), *PIK3CA* E542K (n = 2). Level 2; *PIK3CA* R38C (n = 1). Level 4; *ARID1A* Q1402* (n = 1), *ARID1A* R1721* (n = 1), *ARID1A* single nucleotide variant (n = 1), *CDKN2A* truncating mutation (n = 1), *EGFR* copy number variant (n = 6); *Termination or stop codon.

Chakravarty D, et al. *JCO Precis Oncol*. 2017:PO.17.0001 [Epub ahead of print].



Awad MM, et al. *N Engl J Med.* 2021;384(25):2382-2393.

KRYSTAL-1 Phase 1b/2 CRC cohort Study Design



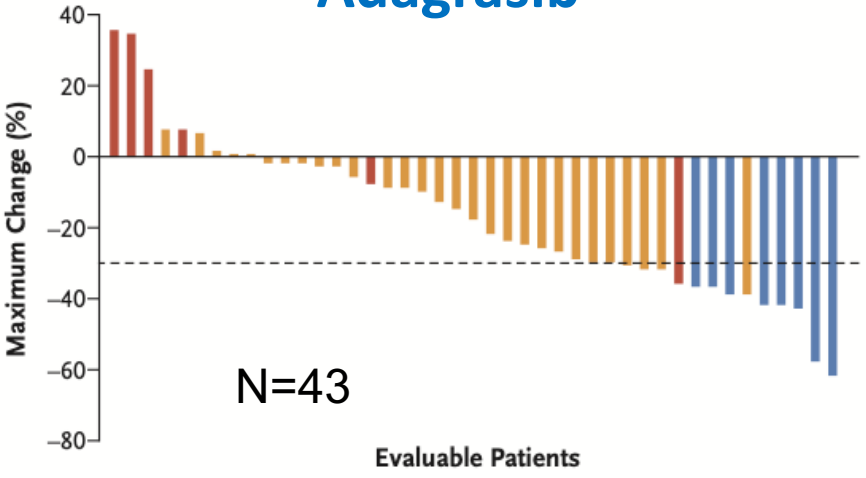
- Previously reported data demonstrated clinical activity of adagrasib monotherapy and adagrasib + cetuximab in patients with previously treated KRASG12C-mutated CRC[10,e]
- Here we report updated data for adagrasib 600 mg BID as monotherapy (Phase 2; median follow-up: 20.1 months) and in combination with cetuximab (Phase 1b; median follow-up: 17.5 months) in patients with previously treated KRASG12C-mutated CRC

[a]KRASG12C mutation detected in tumor tissue and/or ctDNA per protocol. [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]

Wu C, et al. Presented at: ASCO;2023.

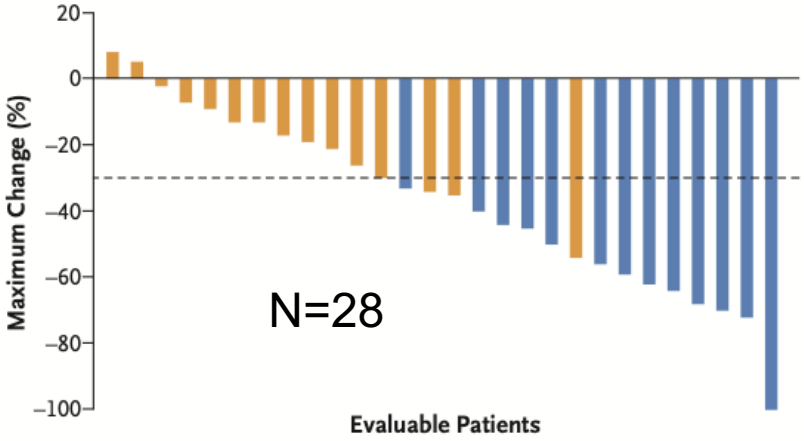
KRYSTAL-1:

Adagrasib



RR: 23%
DOR: 4.3 mos
PFS: 5.6 mos
OS: 19.8 mos

Adagrasib + Cetuximab

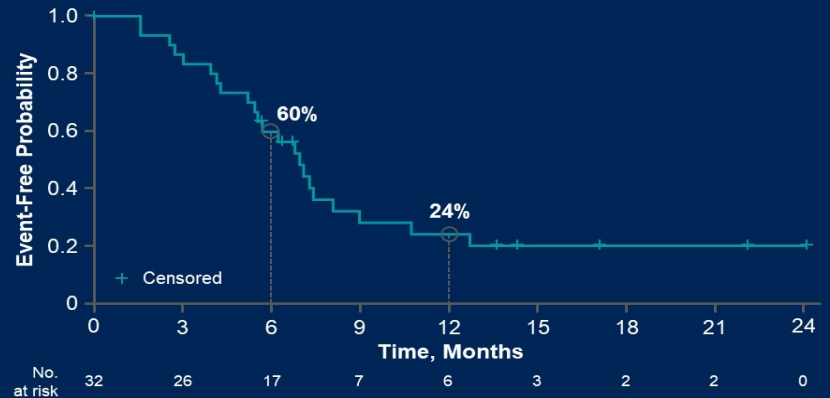


RR: 46%
DOR: 7.6 mos
PFS: 6.9 mos
OS: 13.4 mos

Yaeger R, et al. *N Engl J Med*. 2023;388(1):44-54.

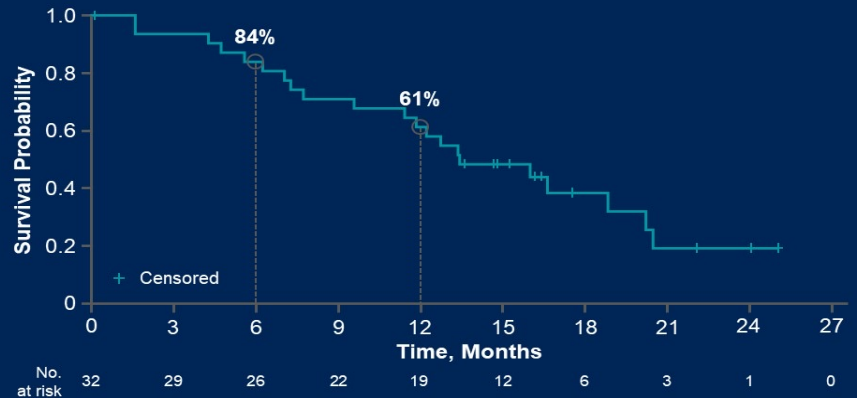
Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: PFS and OS

Progression-Free Survival



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

Overall Survival



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

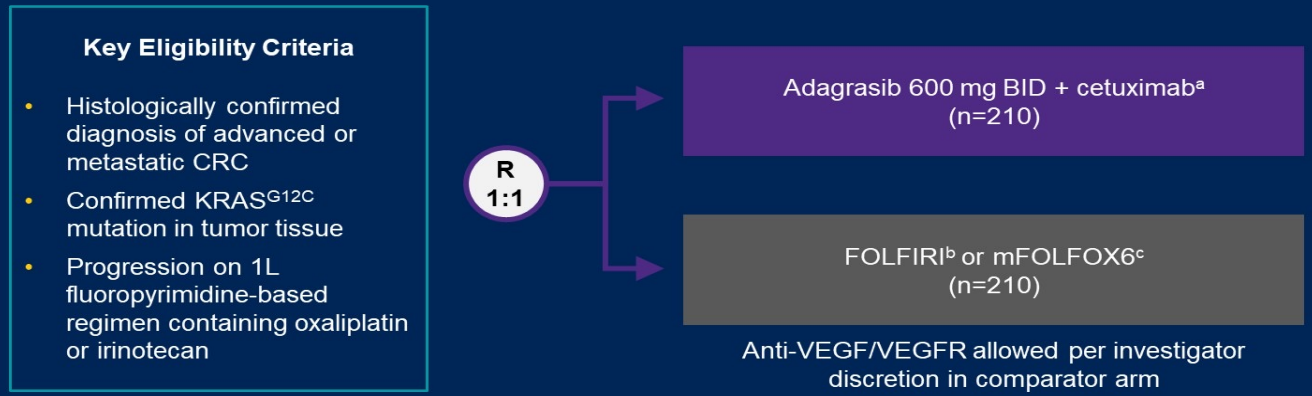
PFS per investigator assessment (n=32)

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

R Yaeger et al. N Engl Med 2023;388:44-54

Wu C, et al. Presented at: ASCO;2023.

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



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.

Wu C, et al. Presented at: ASCO;2023.

TABLE. Clinical Development of *KRAS* Mutant–Specific Inhibitors

Drug (sponsor/collaborator)	Description	Phase Clinical trial name/ Clinicaltrials.gov identifier
KRAS G12C inhibitors		
Sotorasib (AMG 510) (Amgen)	Vs docetaxel in previously treated locally advanced and unresectable or metastatic *KRAS* G12C–mutant NSCLC	Phase 3 CodeBreak 200/ NCT04303780
	In *KRAS* G12C–mutant advanced nonsquamous NSCLC	Phase 2 Lung-MAP cohort/NCT04625647[a]
	+/- a PD-1/PD-L1 inhibitor in *KRAS* G12C–mutant advanced solid tumors	Phase 1/2 CodeBreak 100/NCT03600883
	+/- various different drugs in *KRAS* G12C–mutant advanced solid tumors	Phase 1 CodeBreak 101/NCT04185883
Adagrasib (MRTX849) (Mirati Therapeutics, Inc)	+ pembrolizumab in *KRAS* G12C–mutant advanced NSCLC	Phase 2 KRYSTAL-7/NCT04613596
	+/- cetuximab, afatinib, or pembrolizumab in *KRAS* G12C–mutant advanced solid tumors	Phase 1/2 KRYSTAL-1/NCT03785249
	+ TNO155 (SHP2 inhibitor) in *KRAS* G12C–mutant advanced solid tumors	Phase1/2 KRYSTAL-2/NCT04330664
GDC-6036 (Genentech, Inc)	+/- atezolizumab, cetuximab, bevacizumab, or erlotinib in *KRAS* G12C–mutant advanced or metastatic solid tumors	Phase 1 GO42144/NCT04449874
Exosomes engineered to deliver siRNA targeting *KRAS* G12D		
iExosomes (The University of Texas MD Anderson Cancer Center)	In *KRAS* G12D–mutant metastatic pancreatic cancer	Phase 1 2018-0126/NCT03608631[a]
mRNA vaccine targeting *KRAS* G12C, G12D, G12V, and G13D		
mRNA-5671 (Moderna Therapeutics/Merck)	+/- pembrolizumab in *KRAS* G12C–, G12D–, G12V–, or G13D–mutant advanced/ metastatic NSCLC, CRC, or pancreatic adenocarcinoma with specific HLA subtypes	Phase 1 V941-001/NCT03948763
T cells transduced with *KRAS* G12V–specific TCRs		
KRAS TILs (Changhai Hospital/Providence Cancer Center, Earle A. Chiles Research Institute)	In *KRAS* G12V–mutant advanced pancreatic cancer with a specific HLA subtype	Phase 1/2 ChanghaiH-PP06/NCT04146298

CRC, colorectal cancer; HLA, human leukocyte antigen; NSCLC, non–small cell lung cancer siRNA, small interfering RNA; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

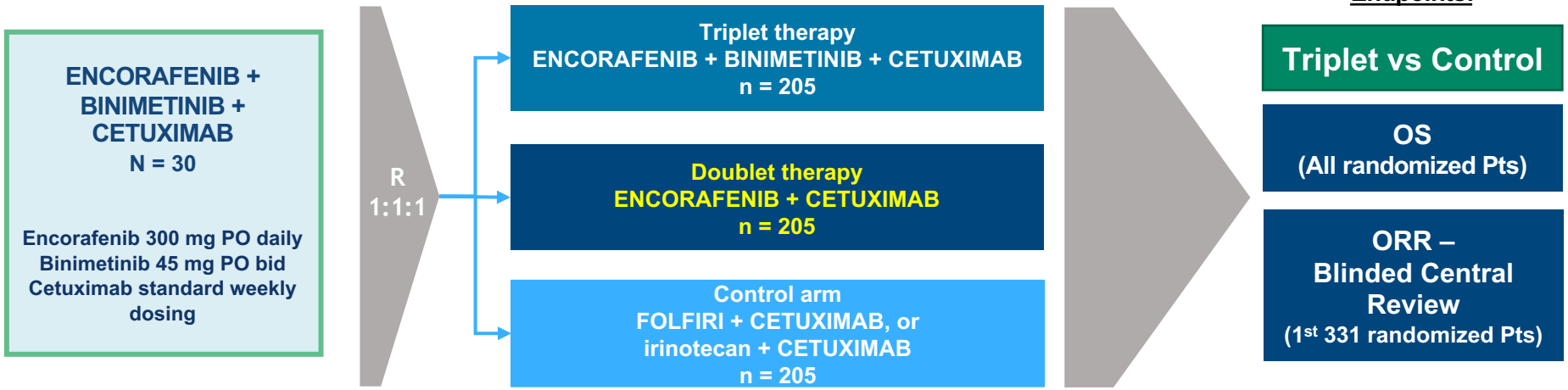
[a]Trial is not yet recruiting participants.

Novel Approaches

1. BRAF V600E

BEACON: Phase 3 in Second-/Third-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



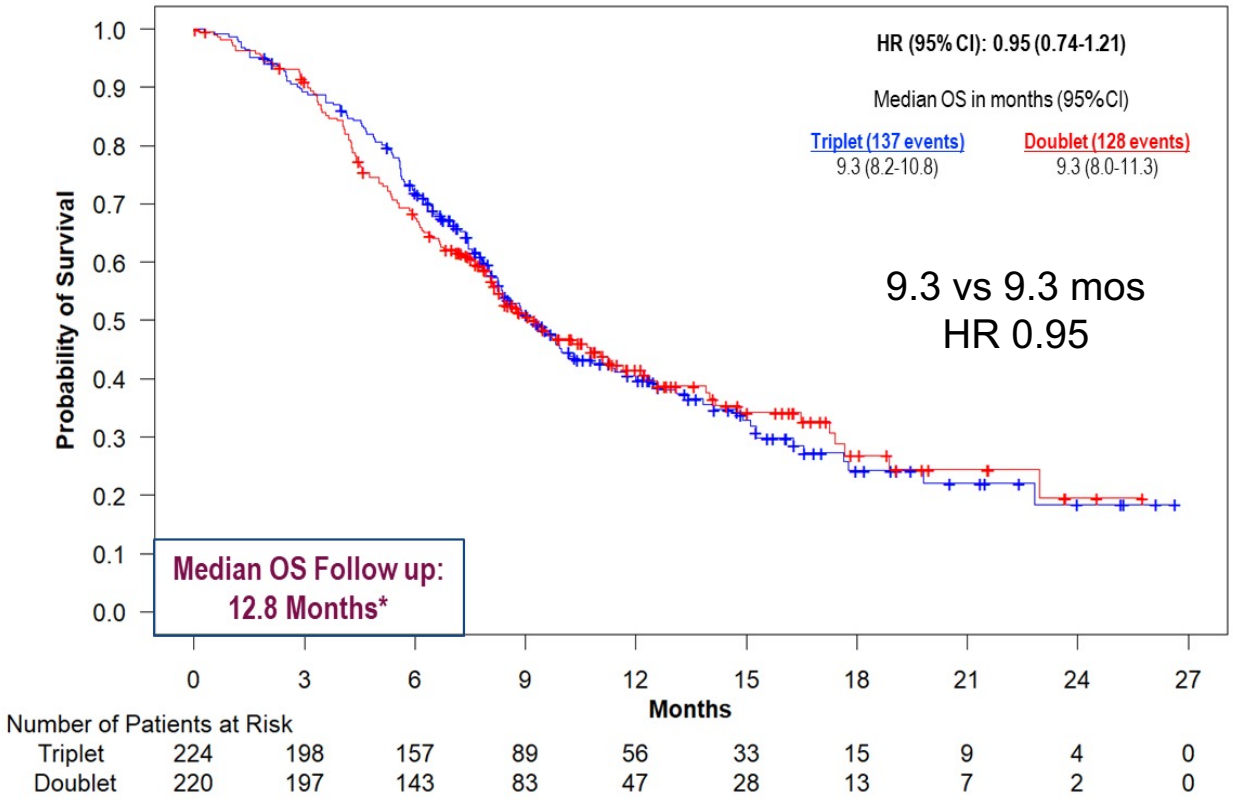
Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

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 S, et al. *N Engl J Med*. 2019;381(17):1632-1643.

BEACON CRC: Updated Analysis Triplet vs Doublet



Tabernero J, et al. *J Clin Oncol*. 2021;39(4):273-284.

ANCHOR CRC, Phase 2 Study in First-line BRAF^{V600E} mCRC

2-STAGE DESIGN[1]

Patient population
N=90

- mCRC
- With BRAF^{V600E} mutation
- Untreated in metastatic setting
- No prior treatment with any RAF inhibitor, MEK inhibitor, or anti-EGFR inhibitor
- ECOG PS 0 or 1

Stage 1
N=40#

Encorafenib + binimetinib + cetuximab

Stage 2*
N=50

Encorafenib + binimetinib + cetuximab

Treatment until:

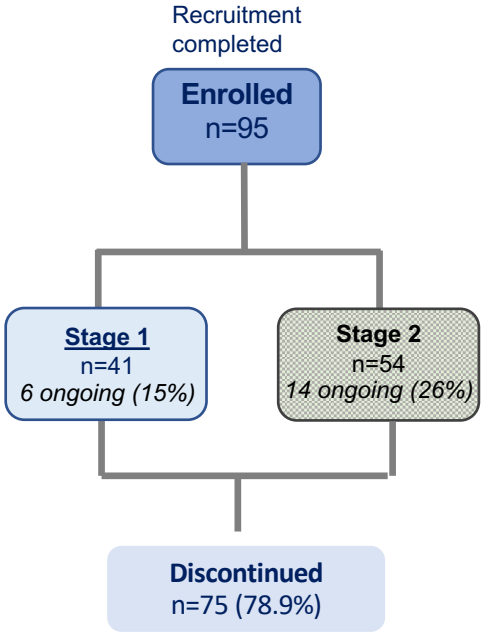
- Disease progression
- Unacceptable toxicity
- Consent withdrawal

Continued follow up for survival every 3 months

Main analysis on 90 pts

Primary objective & endpoint: cORR (investigator assessed)

Secondary endpoints: PFS, OS, Safety, QoL, PK



- Progressive disease 48 (64%)
- Adverse events 16 (21%)
- Physician decision 6 (8%)
- Protocol deviation 2 (2.7%)
- Death 1 (1.3%)
- Patient withdrawal 1 (1.3%)
- Drug non-compliance 1 (1.3%)

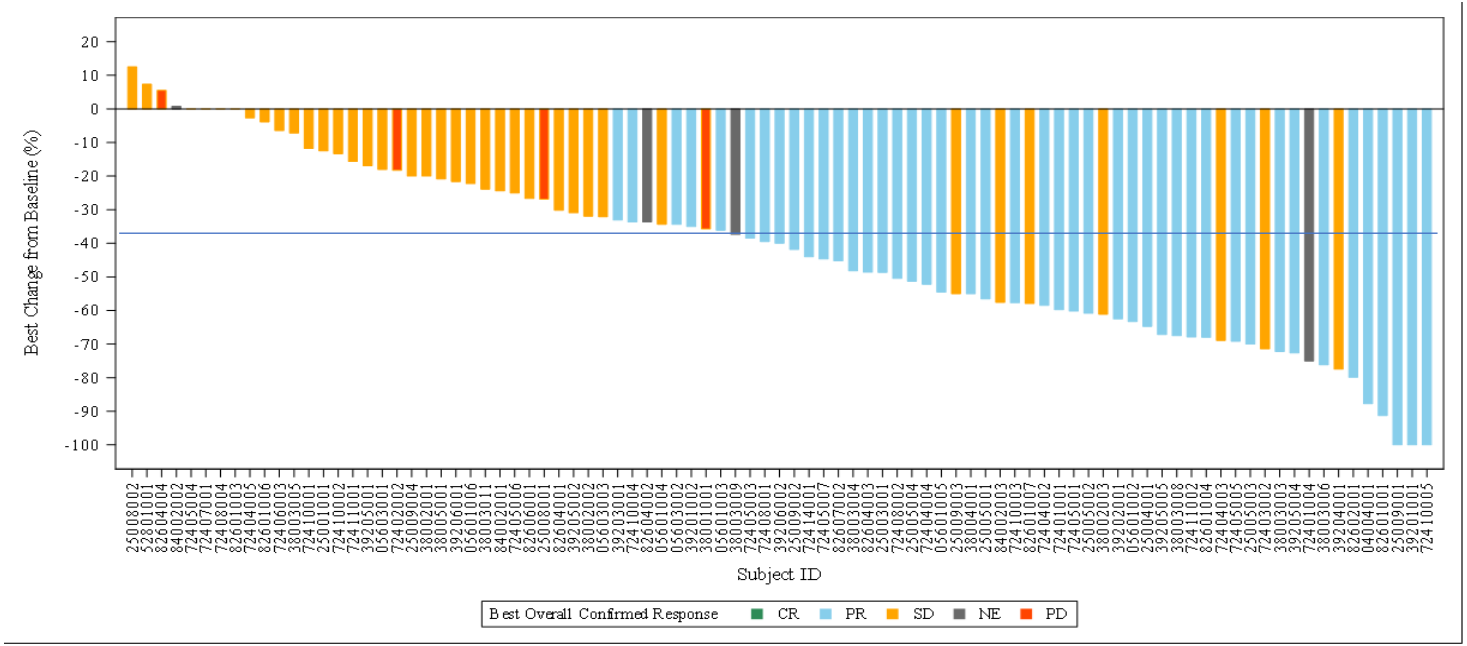
1. Grothey A, et al. *Annals Oncol*. 2019;30(suppl 4):P-400
#Futility analysis
*Stage 2 enrolment only after ≥ 12 responses observed in stage 1
cORR=confirmed objective response rate, OS=overall survival, PK=pharmacokinetics, PFS=progression free survival, QoL=quality of life

Cut-off date: 29-June-20

Van Cutsem E, et al. Presented at: ASCO;2021. NCT03693170. Accessed June 29, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT03693170.

ANCHOR CRC, Phase 2 Study in First-line BRAF^{V600E} mCRC

Investigator's assessment, patients evaluable for efficacy (N=92)



RR 48%
DCR 88%
PFS 5.8 mos
OS 18.3 mos

3 patients have been excluded from the efficacy analysis as the BRAF mutation was not confirmed/indeterminate by central lab
The 4 subjects with the best percentage change from baseline equal to 0% have their Best Overall Confirmed Response equal to Stable Disease (SD).
Two subjects (38003012 and 72406001) with BOCR equal to NE are not presented in the plot because they don't have post-baseline tumor diameters.
One subject (72402001) with BOCR equal to PD is not presented in the plot because 1 target lesion was not evaluable and sum of longest diameters cannot be calculated at the unique post-baseline evaluation.

NCT03693170. Accessed June 29, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT03693170.
Van Custem E, et al. *J Clin Oncol*. 2023;41(14):2628-2637.

New Updates on Targeting Her2

1. Tucanitib (new kid on the block)

Key Clinical Trials in *HER2*+ mCRC

Trial	Regimen	N	ORR, %	Median PFS, mo	Median OS, mo
HERACLES-A[1]	Trastuzumab + lapatinib[a]	27	30 (14-50)	4.8 (3.7-7.4)	10.6 (7.6-15.6)
MyPathway (*KRAS*wt subgroup)[2]	Trastuzumab + pertuzumab[a]	43	40 (25-56)	5.3 (2.7-6.1)	14 (8-NE)
TRIUMPH[3]	Trastuzumab + pertuzumab[a]	17 (tissue)	35 (14-62)	4 (1.4-5.6)	—
TAPUR[4] **(no *RAS* data)**	Trastuzumab + pertuzumab[a]	28	25 (11-45)	4 (2.6-6.3)	25 (6-NE)
MOUNTAINEER[5] **(Cohorts A + B)**	**Trastuzumab + tucatinib**	**86**	**38 (28-39)**	**8.2 (4.2-10.3)**	**24.1 (20.3-36.7)**
DESTINY-CRC01[6,b] **(Cohort A)**	**T-DXd**	**54**	**45 (32-60)**	**6.9 (4.1-8.7)**	**15.5 (8.8-20.8)**
HERACLES-B[7,c]	T-DM1 + pertuzumab	30	10 (0-28)	4.8 (3.6-5.8)	—

[a] In NCCN guidelines. [b] ORR in subgroup with prior HER2 rx 43.8% (19.8-70.1); without prior HER2 rx 45.9% (29.5-63.1). [c] Did not meet primary endpoint. T-DM1 had 0% response rate in MATCH Arm Q[8] and MSKCC Basket Trial.[9]

1. Sartore-Bianchi A et al. *Lancet Oncol*. 2016;17:738-746. 2. Meric-Bernstam F, et al. *Lancet Oncol*. 2019;20:518-530. 3. Nakamura Y, et al. ESMO 2019. Abstract 1057. 4. Gupta R, et al. ASCO GI 2020. Abstract 132. 5. Strickler J, et al. ESMO GI 2022. Abstract LBA 2. 6. Yoshino T, et al. Nat Com 2023 in press.
7. Sartore-Bianchi A. ESMO 2019. Abstract 3857. 8. Jhaveri KL, et al. *Ann Oncol*. 2019;30:1821-1830. 9. Li BT, et al. *J Clin Oncol*. 2018;36:2532-2537.

T-DXd in Patients with HER2-Overexpressing/Amplified (HER2+) Metastatic Colorectal Cancer (mCRC): Primary Results from the Multicenter, Randomized, Phase 2 DESTINY-CRC02 Study

Kanwal Raghav

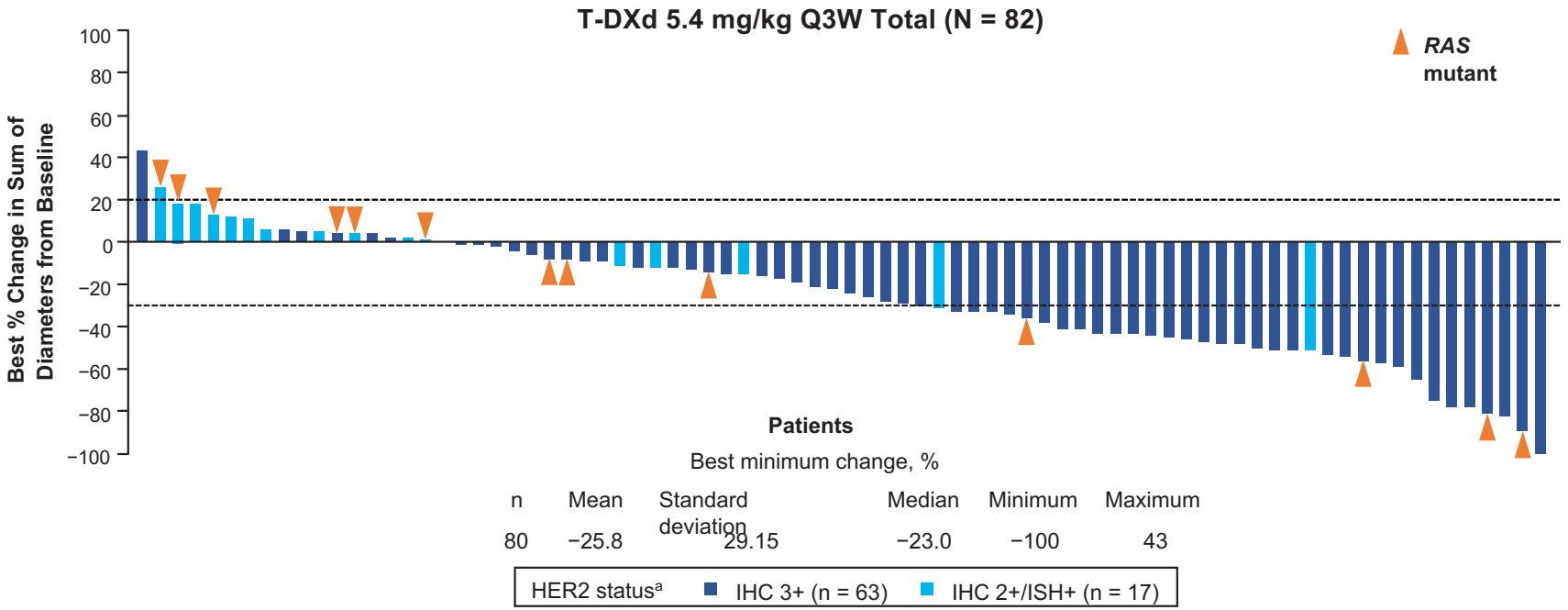
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 4, 2023

Additional authors: Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Christina Gravalos Castro, John Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino

Raghav K, et al. Presented at: ASCO;2023.

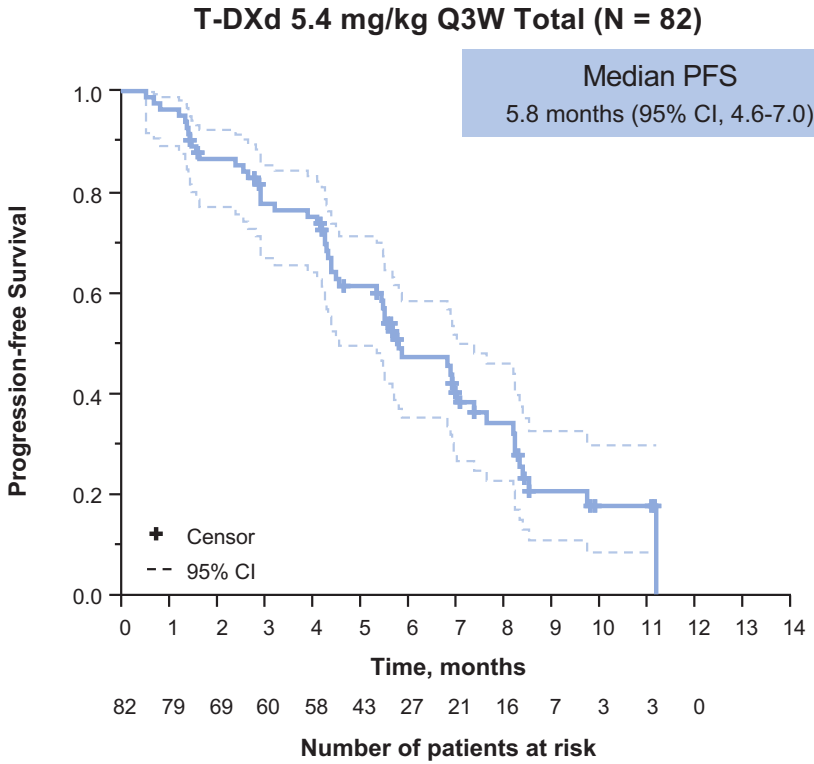
Best Percentage Change in Sum of Diameters by BICR for T-DXd 5.4 mg/kg

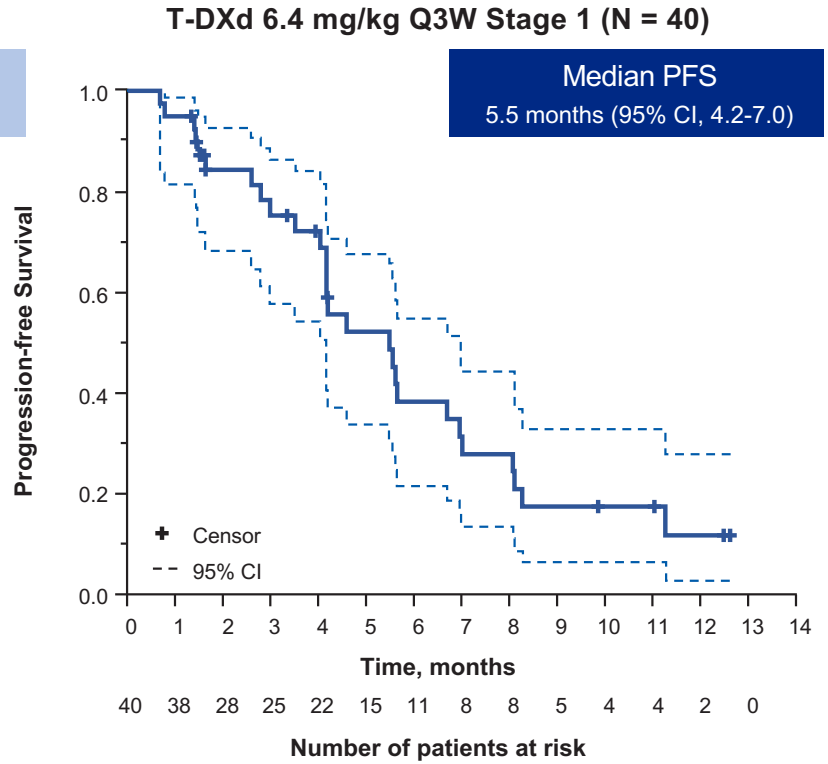


BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

Raghav K, et al. Presented at: ASCO;2023.

Median Progression-Free Survival by BICR

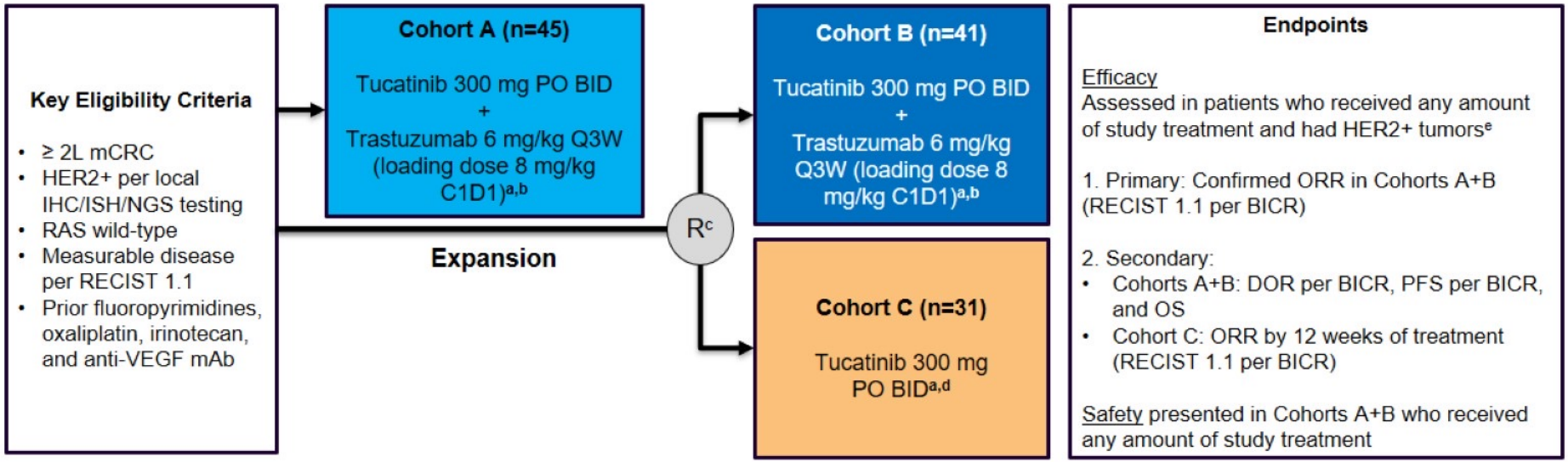




BICR, blinded independent central review; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Raghav K, et al. Presented at: ASCO;2023.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial

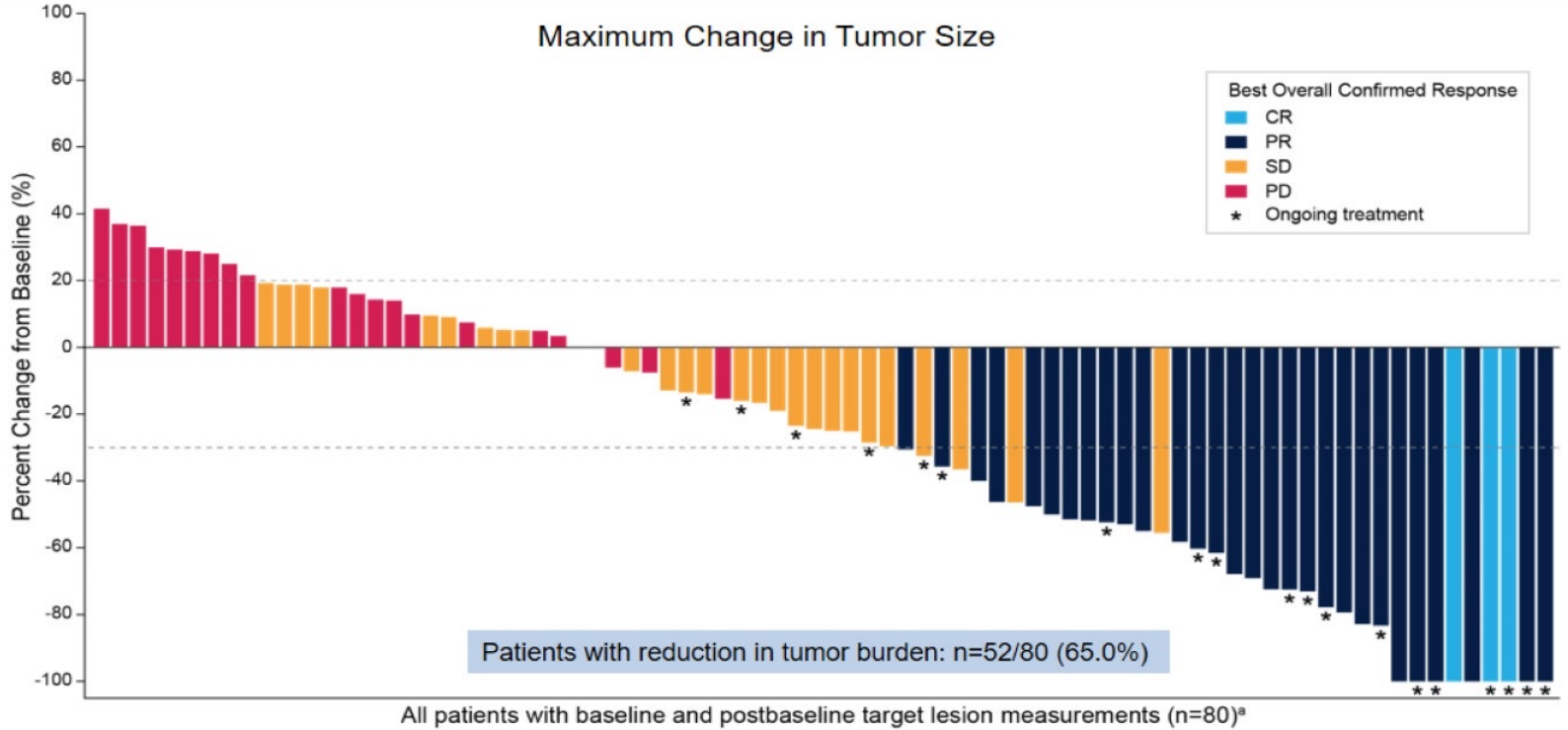


MOUNTAINEER began as a US Investigator-Sponsored Trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomised to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

Data cut-off for current analysis, March 28, 2022
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 tumor primary vs other; d Patients 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; e 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; CR, complete response; DOR, duration of response; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States; VEGF, vascular endothelial growth factor.
https://clinicaltrials.gov/ct2/show/NCT03043313

Stricker J, et al. Presented at: ESMO-WCGI;202.

Tucatinib + Trastuzumab: Change in Tumor Size



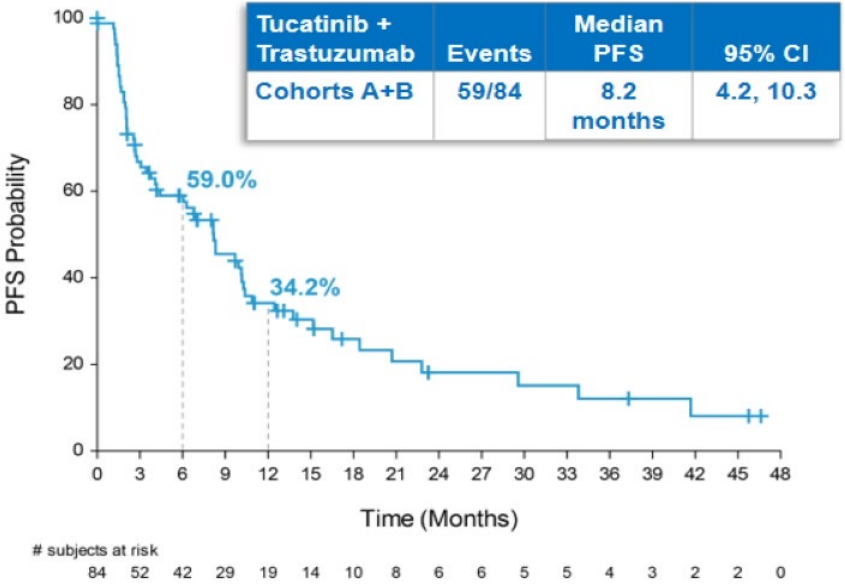
a Four patients who did not have baseline and/or post-baseline target lesion measurements are excluded
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Data cutoff: 28 Mar 2022

Raghav K, et al. Presented at: ASCO;2023.

Tucatinib + Trastuzumab: PFS and OS

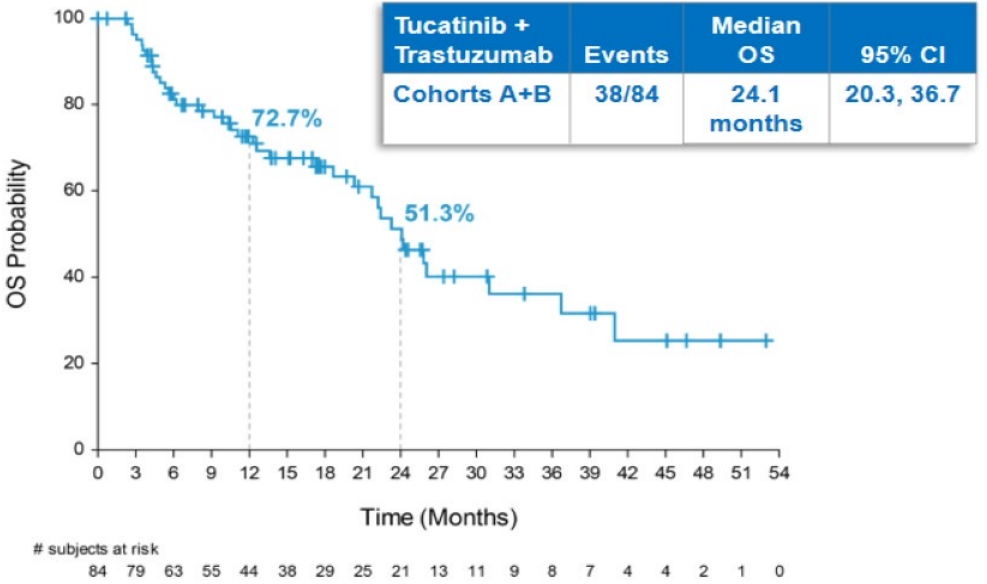
Progression-free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



Overall Survival

Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	24.1 months	20.3, 36.7



Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

BICR, blinded independent central review; IQR, interquartile range; OS, overall survival; PFS, progressive-free survival.
Data cutoff: 28 Mar 2022

Raghav K, et al. Presented at: ASCO;2023.

Take Home Messages : HER2+ mCRC

- Confirmed ORR in IHC2+/ISH+ is lower than IHC3+ but remained clinically relevant for TT (= Her2 Dependency), but not as much with TDxd (= Her2 expression).
- May exclude EGFRi
- Trastuzumab and Tucatanib (TT ; FDA approved) initial line following chemotherapy line(s)
  - RAS WT and IHC2+/ISH+ or IHC 3+
- T-DXd @ 5.4 mg/Kg as subsequent line of therapy to TT
  - RAS MT/WT and IHC 3+
  - Data supports activity post prior anti-Her2 Rx
  - Toxicities remain concerning
  - ? Retesting for Her2 ?

cORR: confirmed objective response rate; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization

Raghav K, et al. Presented at: ASCO;2023.

IO in MSI H

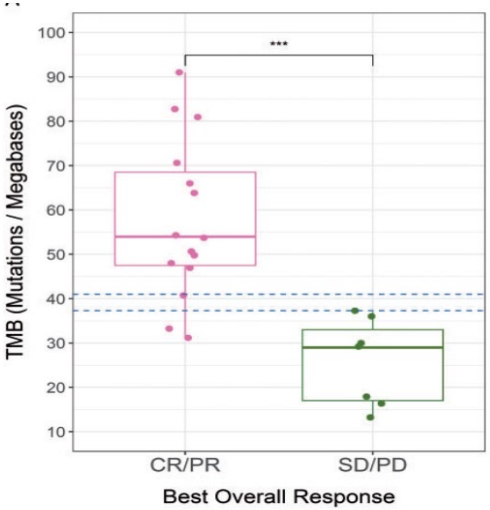
1. Not all MSI H are equal
2. Role of TMB
3. Role of CTLA
4. Novel Immune therapies for MSS CRC

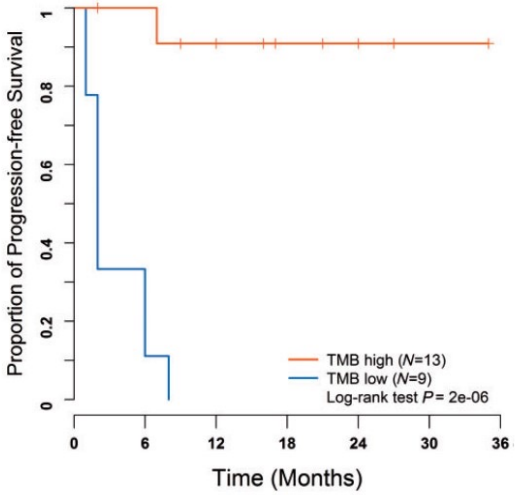
Not all MSI-High/dMMR tumors are created equal

Salem ME, et al. Presented at: ASCO;2022.

TMB as an IO Response Predictor in MSI-H

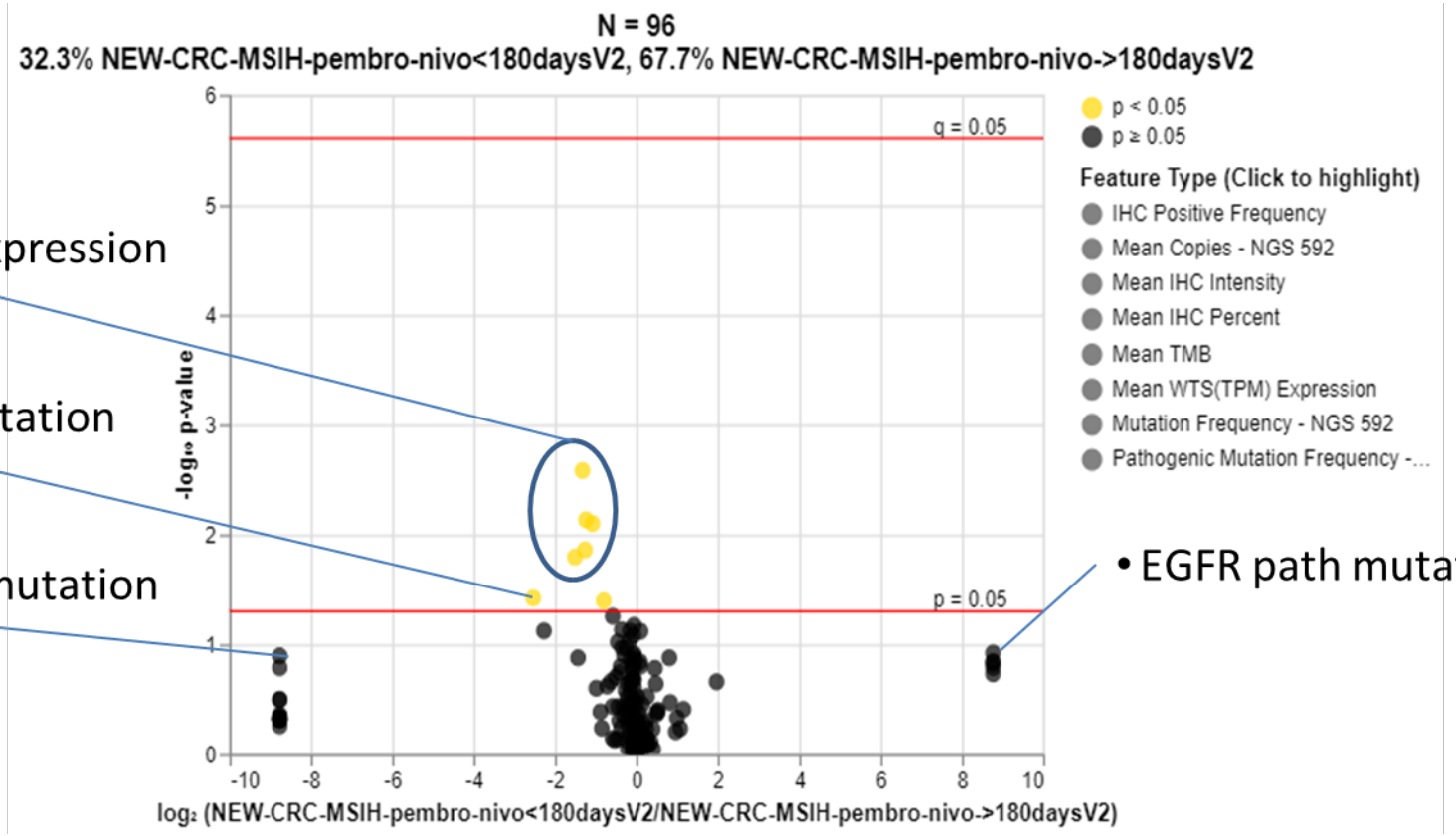
- 22 pts treated with PD-1 based therapy
- Optimal TMB cut-off point: 37-41 mut/Mb
  - PR/CR vs. SD/PD p = 0.0003 (p = 0.088 for MSI score)
- (foundation medicine 37.4 mut/Mb = 35th percentile)





Schrock et la. Ann Oncol. 2019

TMB = tumor mutation burden; IO = immunotherapy.
Salem ME, et al. Presented at: ASCO;2022.



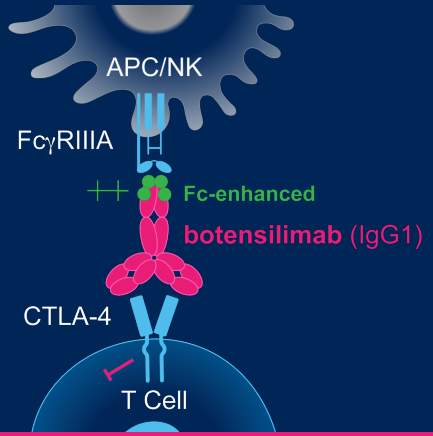
- HLA gene expression
- PDGFRA mutation
- HER2 path mutation
- EGFR path mutation

Lenz H-J, et al. *J Clin Oncol*. .2023;41(4_suppl):202.

Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor

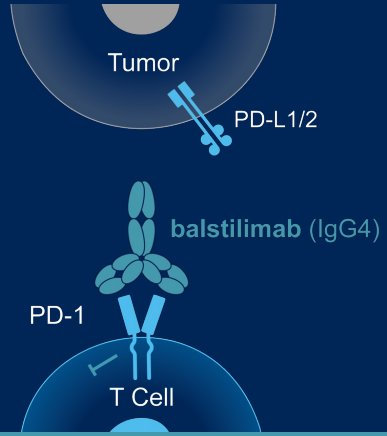


Active in cold and IO refractory tumors[1,2]:

- ↑ T cell priming, expansion, memory[3,4]
- ↑ Frequency of activated DCs
- ↑ Treg depletion
- ↓ Complement mediated toxicity

balstilimab

PD-1 Inhibitor

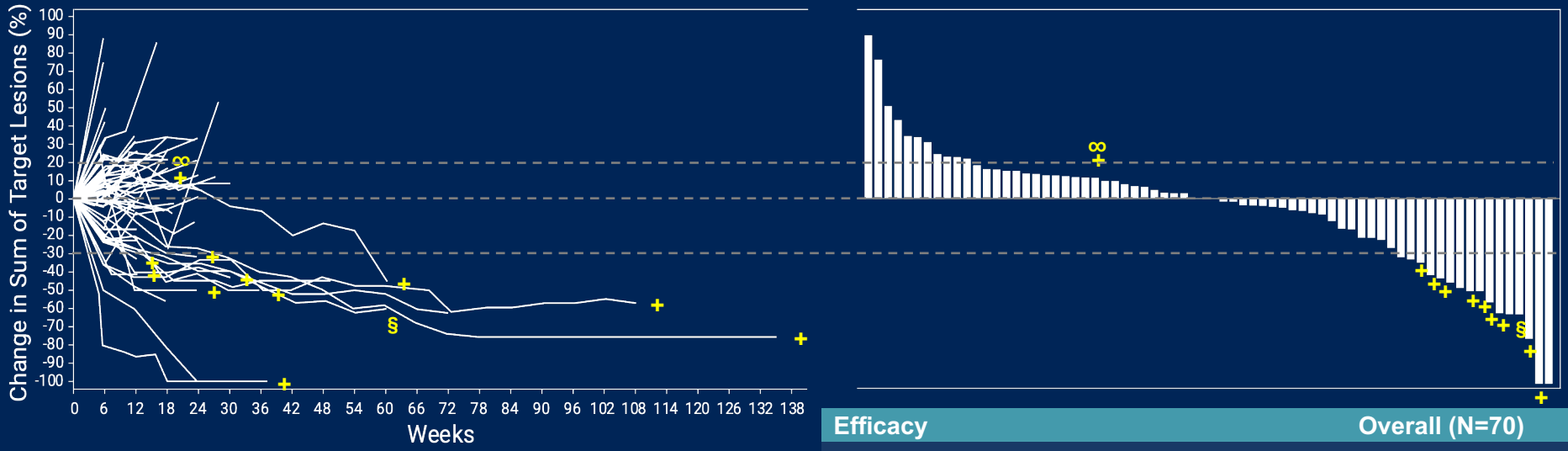


Safety and efficacy analogous to approved anti-PD-1 mAbs[5,6]

- > 750 patients treated; 10 ongoing trials / 2 completed
- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function

El-Khoueiry AB, et al. Presented at: ASCO;2023. El-Khoueiry AB, et al. Presented at: SITC;2021. Poster 479. Wilky B, et al. SITC;2022. Abstract 778. Waight JD, et al. *Cancer Cell*. 2018;33(6):1033-1047. NCT03860272. Accessed July 1, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT03860272. O'Malley DM, et al. *Gynecol Oncol*. 2021;163(2):274-280. O'Malley DM, et al. *J Clin Oncol*. 2022; 40(7):762-771.

Efficacy: Durable Objective Responses



Efficacy	Overall (N=70)
ORR*, % (95% CI)	**23** (xx-xx)
BOR, n (%)	
CR	1 (1)
PR	15 (21)
SD	37 (53)

Efficacy	Overall (N=70)
DCR (CR + PR + SD), % (95% CI)	76 (64-85)
Median DOR, months (95% CI)	10 (3-NR)
Median PFS, months (95% CI)	**4.1 (2.8-5.5)**
Median F/U, months (Min, Max)	6 (2, 31)

Responder Characteristics (n=16)

- 3 with prior I-O (all refractory)
- 1/13 TMB >10 mut/Mb
- 1/8 PD-L1 positive (≥1%)
- 11 RAS mutant

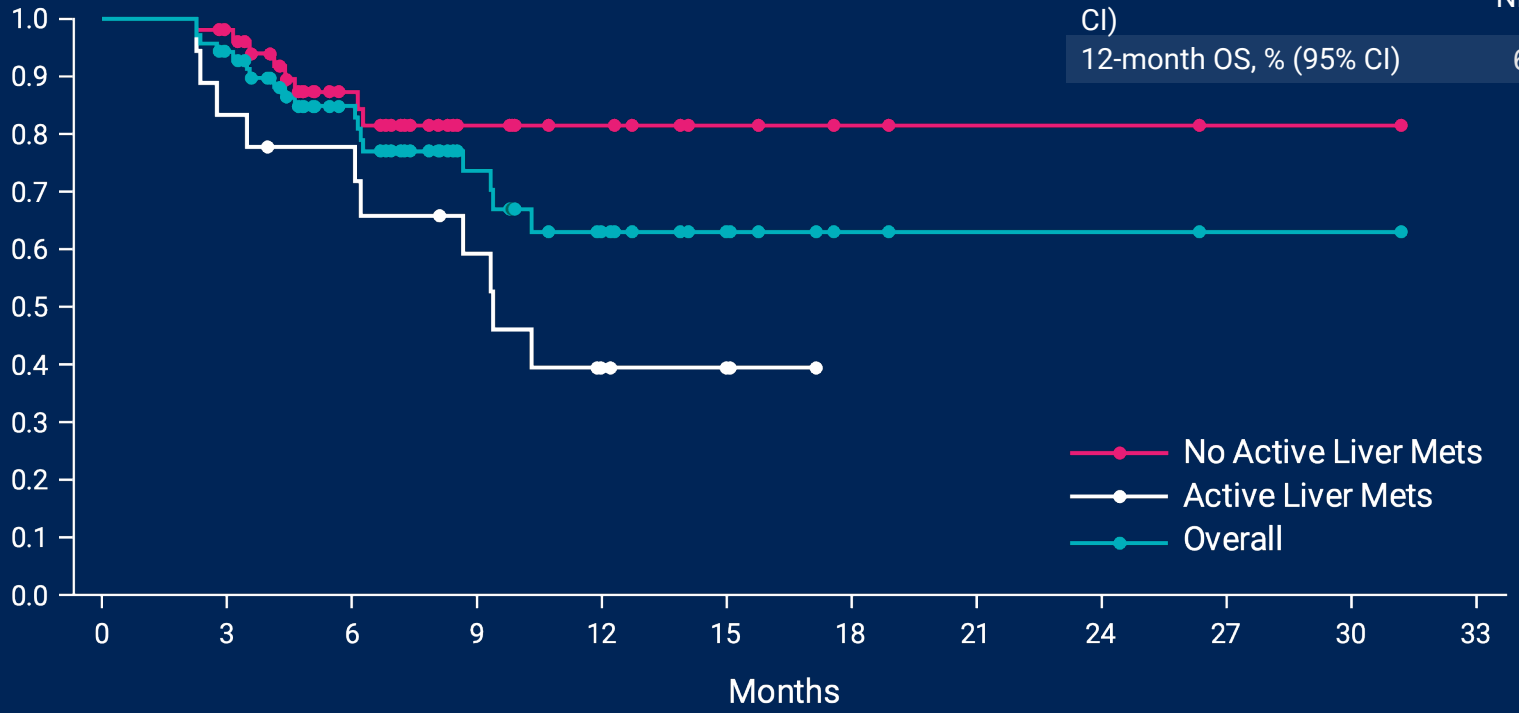
*Includes unconfirmed responses. + Ongoing responses (n=11/16). ∞ Resected target lesions showed complete pathologic response. § Response by iRECIST.

El-Khoueiry AB, et al. Presented at: ASCO;2023.

Overall Survival by Liver Involvement

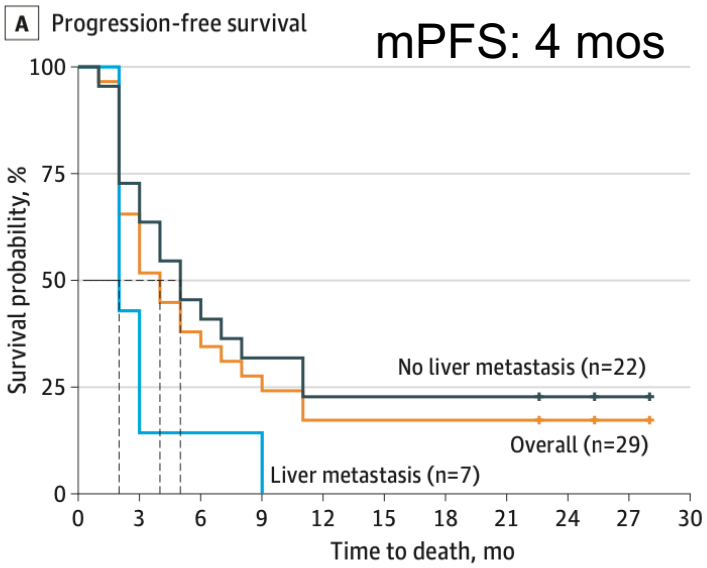
Efficacy evaluable population, N=70

Efficacy	Overall
Median OS, months (95% CI)	NR (10.3-NR)
12-month OS, % (95% CI)	63 (46-76)

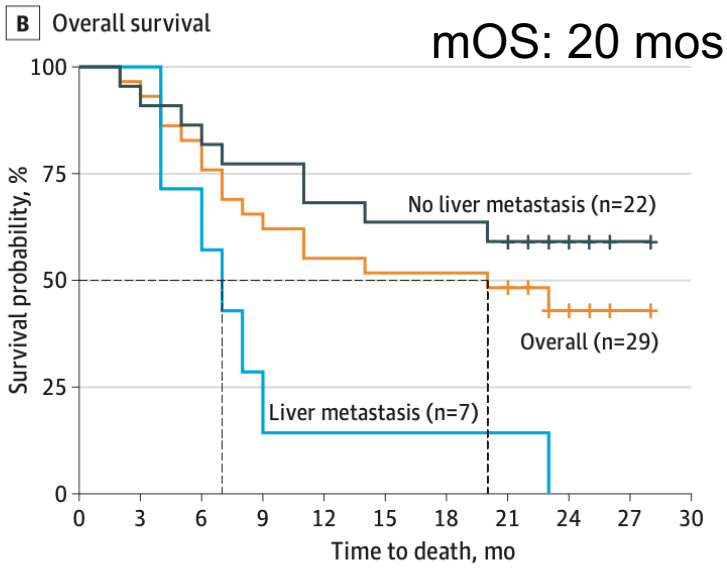


El-Khoueiry AB, et al. Presented at: ASCO;2023.

Phase 1 Study Rego/Nivo/Ipi in MSS mCRC



No. at risk											
Overall	29	19	11	8	5	5	5	5	2	1	0
Liver metastasis	7	3	1	1	0	0	0	0	0	0	0
No liver metastasis	22	16	10	7	5	5	5	5	2	1	0



No. at risk											
Overall	29	28	24	19	16	15	15	14	7	1	0
Liver metastasis	7	7	5	2	1	1	1	1	0	0	0
No liver metastasis	22	21	19	17	15	14	14	13	7	1	0

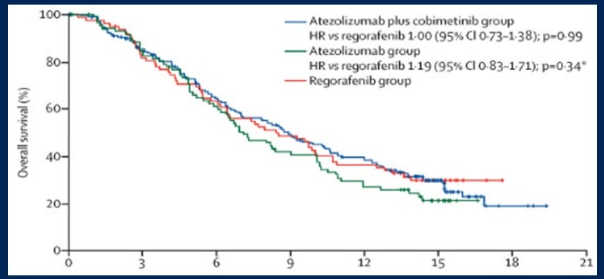
RR: No liver mets (22): 36%, Liver mets (7): 0%

Fakih M, et al. *JAMA Oncol*. 2023;9(5):627-634.

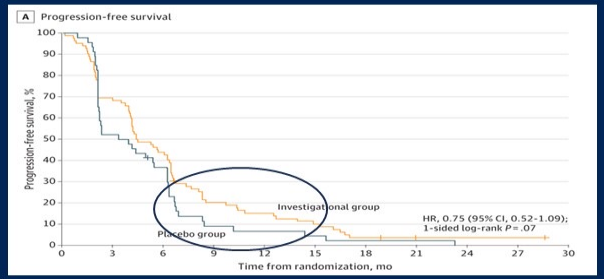
Knowledge Prior to ASCO 2023

Randomized PII/III studies with IO+ for MSS mCRC: From Negative to Borderline Positive

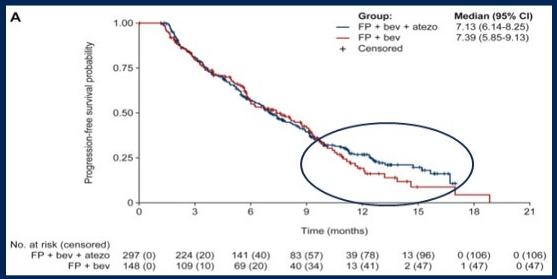
Imblaze 370 : Ref L Atezo +/- cobi vs. Rego



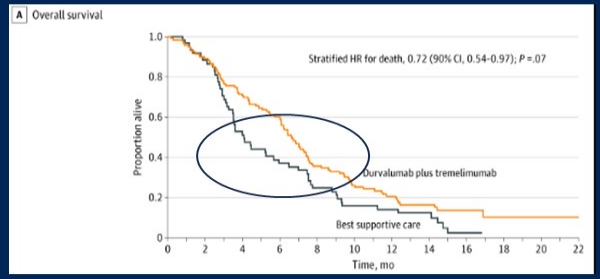
BACCI : Ref L Cape/Bev +/- Atezo/PBO



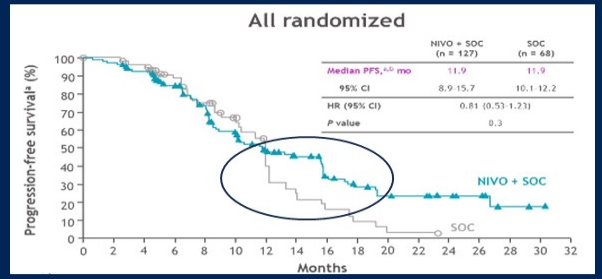
MODUL : Maint FP/Bev +/- Atezo



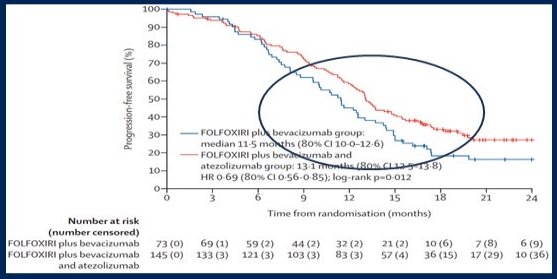
CO.26 : Ref L Tremi/Durva vs. BSC



CM 9X8: 1L mFOLFOX6 + Bev +/- Nivo



AtezoTRIBE: 1L FOLFOXIRI/Bev +/- Atezo



Eng C et al . *Lancet Oncol* 2019; Mettu N et al . *JAMA NO*, 2022; Tabernero J et al . *ESMO Open* 2022; Chen E et al , *JAMA Oncol*, 2020; Lenz HJ. ASCO GI 2022; Antoniotti C et al . *Lancet Oncol* 2022

Bekaii-Saab T, et al. Presented at: ASCO;2023.

FOLFOXIRI Plus Bevacizumab and Atezolizumab as upfront Treatment of Unresectable mCRC Patients: Updated and Overall Survival Results of the Phase II Randomized AtezoTRIBE Study

Carlotta Antoniotti, Daniele Rossini, Filippo Pietrantonio, Lisa Salvatore, Federica Marmorino, Margherita Ambrosini, Sara Lonardi, Maria Bensi, Roberto Moretto, Stefano Tamberi, Ilaria Toma, Alessandro Passardi, Maria Caterina De Grandis, Veronica Conca, Federica Palermo, Alessandro Cappetta, Aurelie Catteau, Luca Boni, Jérôme Galon, Chiara Cremolini

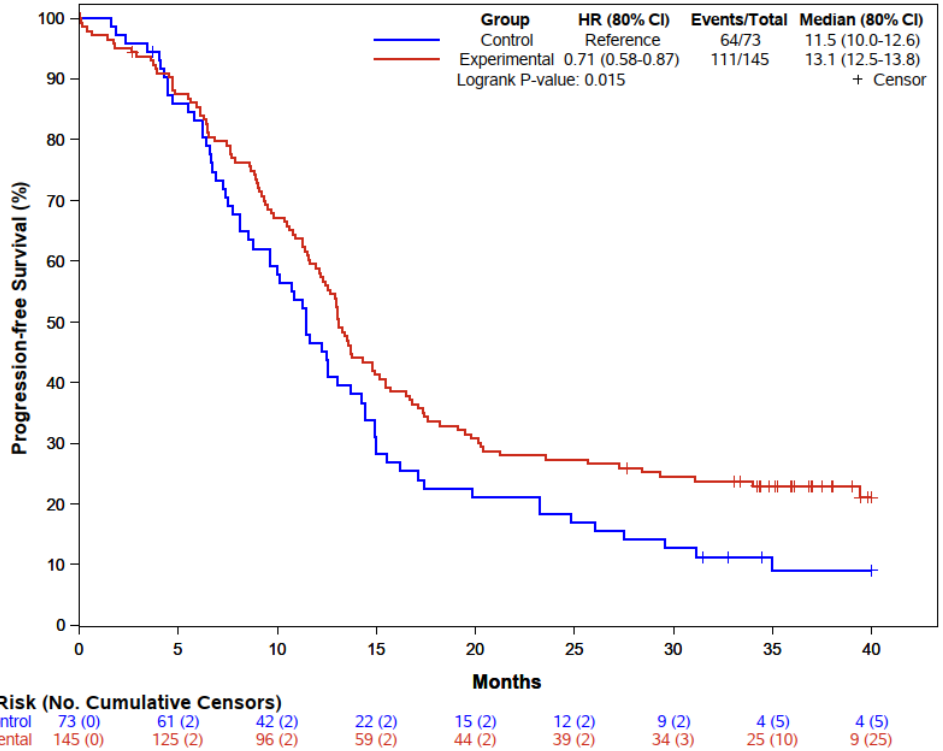
On behalf of GONO Foundation investigators

Carlotta Antoniotti, MD PhD

University Hospital of Pisa, Italy

Carlotta Antoniotti C, et al. Presented at: ASCO;2023.

Updated PFS – ITT population

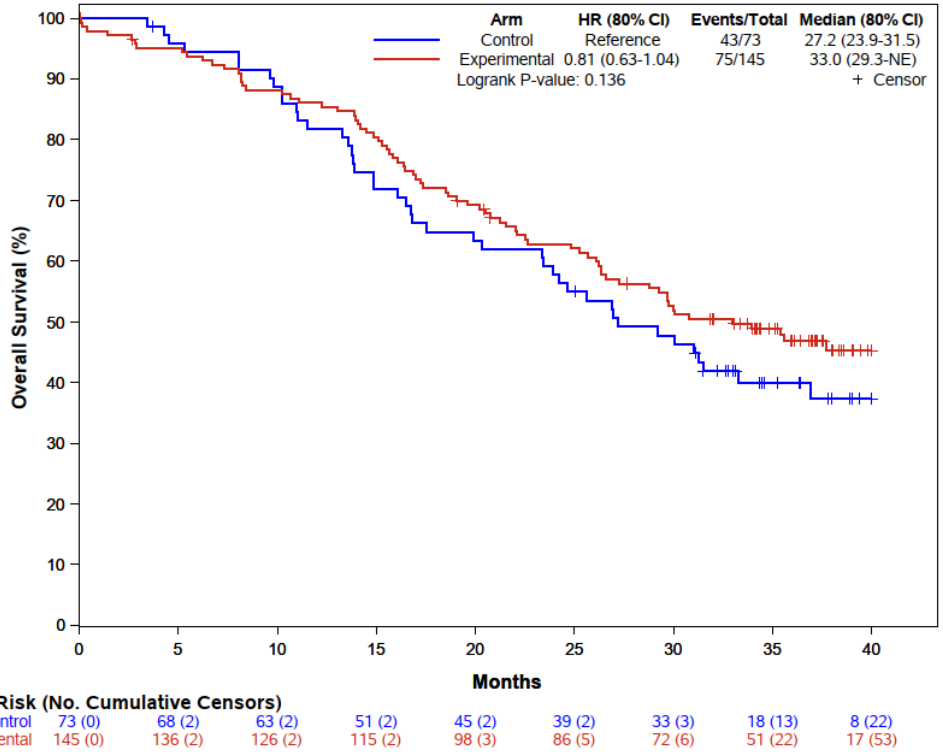


Cut-off date: January 23rd, 2023. At median follow-up: 37.0 months (IQR: 34.3-40.5)

ITT = intention to treat.

Carlotta Antoniotti C, et al. Presented at: ASCO;2023.

Overall Survival – ITT population

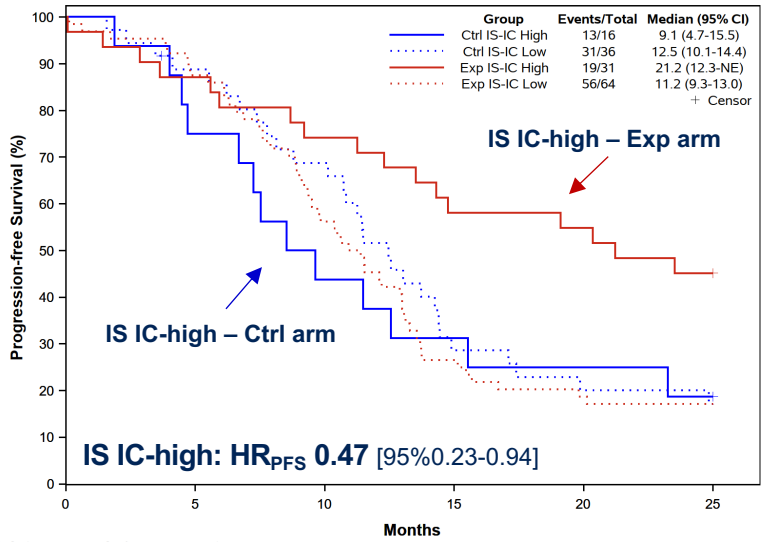


Cut-off date: January 23rd, 2023. At median follow-up: 37.0 months (IQR: 34.3-40.5)

Carlotta Antoniotti C, et al. Presented at: ASCO;2023.

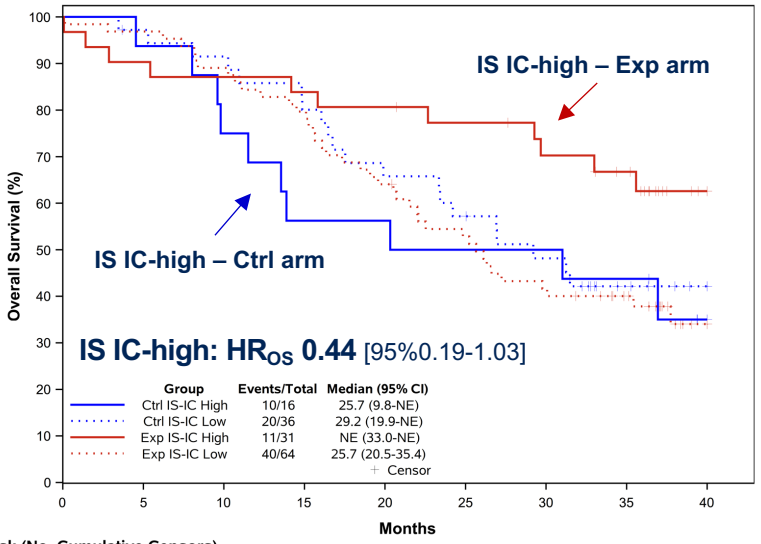
Outcomes According to Immunoscore IC and Arm – pMMR Cohort

Progression-Free Survival



No. at Risk (No. Cumulative Censors)						
Ctrl IS-IC High	16 (0)	12 (0)	7 (0)	5 (0)	4 (0)	3 (0)
Ctrl IS-IC Low	36 (0)	31 (1)	24 (1)	10 (1)	7 (1)	6 (1)
Exp IS-IC High	31 (0)	27 (0)	23 (0)	18 (0)	17 (0)	14 (0)
Exp IS-IC Low	64 (0)	56 (0)	36 (0)	17 (0)	12 (0)	11 (0)

Overall Survival



No. at Risk (No. Cumulative Censors)									
Ctrl IS-IC High	16 (0)	15 (0)	12 (0)	9 (0)	9 (0)	8 (0)	8 (0)	6 (1)	2 (4)
Ctrl IS-IC Low	36 (0)	34 (1)	32 (1)	28 (1)	23 (1)	20 (1)	16 (2)	8 (8)	4 (12)
Exp IS-IC High	31 (0)	28 (0)	27 (0)	26 (0)	25 (0)	23 (1)	20 (2)	17 (4)	5 (15)
Exp IS-IC Low	64 (0)	62 (0)	57 (0)	51 (0)	41 (0)	33 (1)	26 (1)	19 (7)	4 (20)

Carlotta Antoniotti C, et al. Presented at: ASCO;2023.

Our Goal: Right Treatment, Right Time

- Genetic testing of tumor at time of diagnosis and if repeat at time of progression
- Germline testing of patients if evidence of predisposition
- Active monitoring with liquid biopsies
- Accelerating access to clinical trials
- Identification of druggable novel targets
- Multi-omics approach in the future (ai)

Immanuel Kant (Photo from a steel engraving)

The one who knows more, may decide better