Novel Treatment Paradigm: Colorectal Cancer

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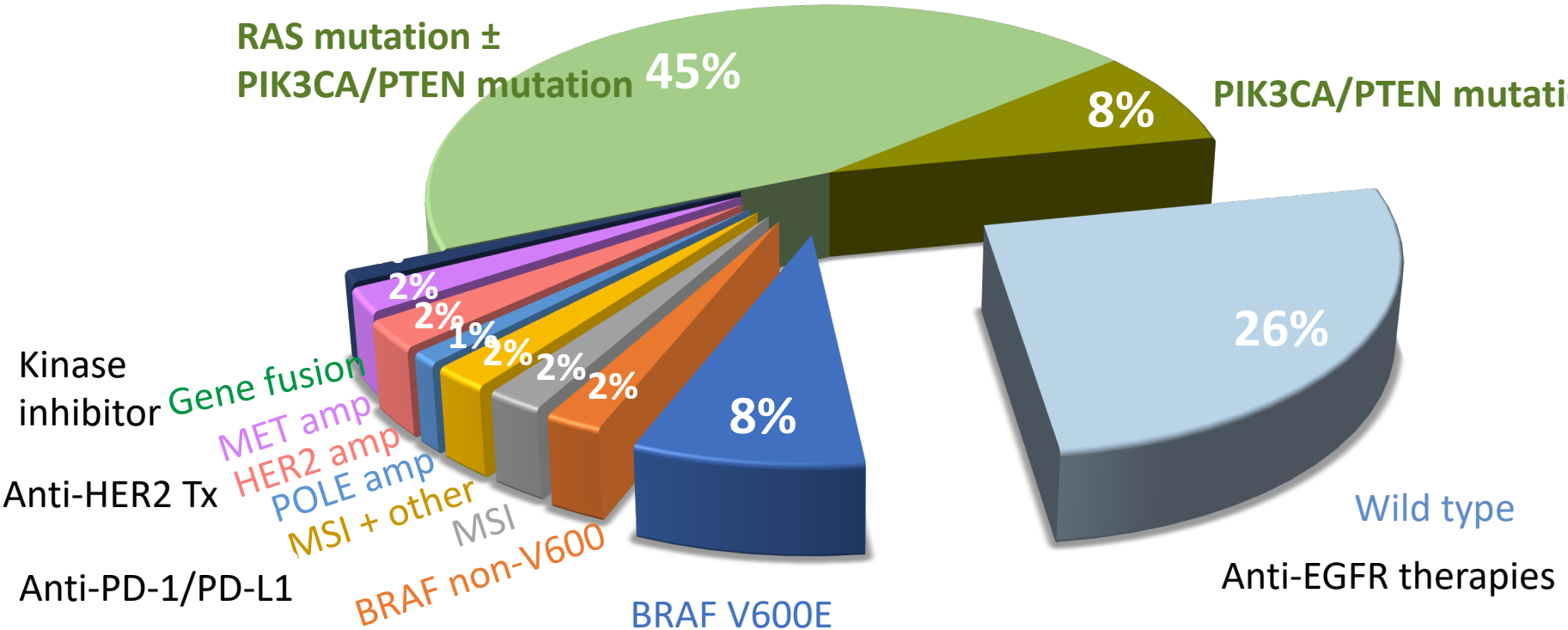
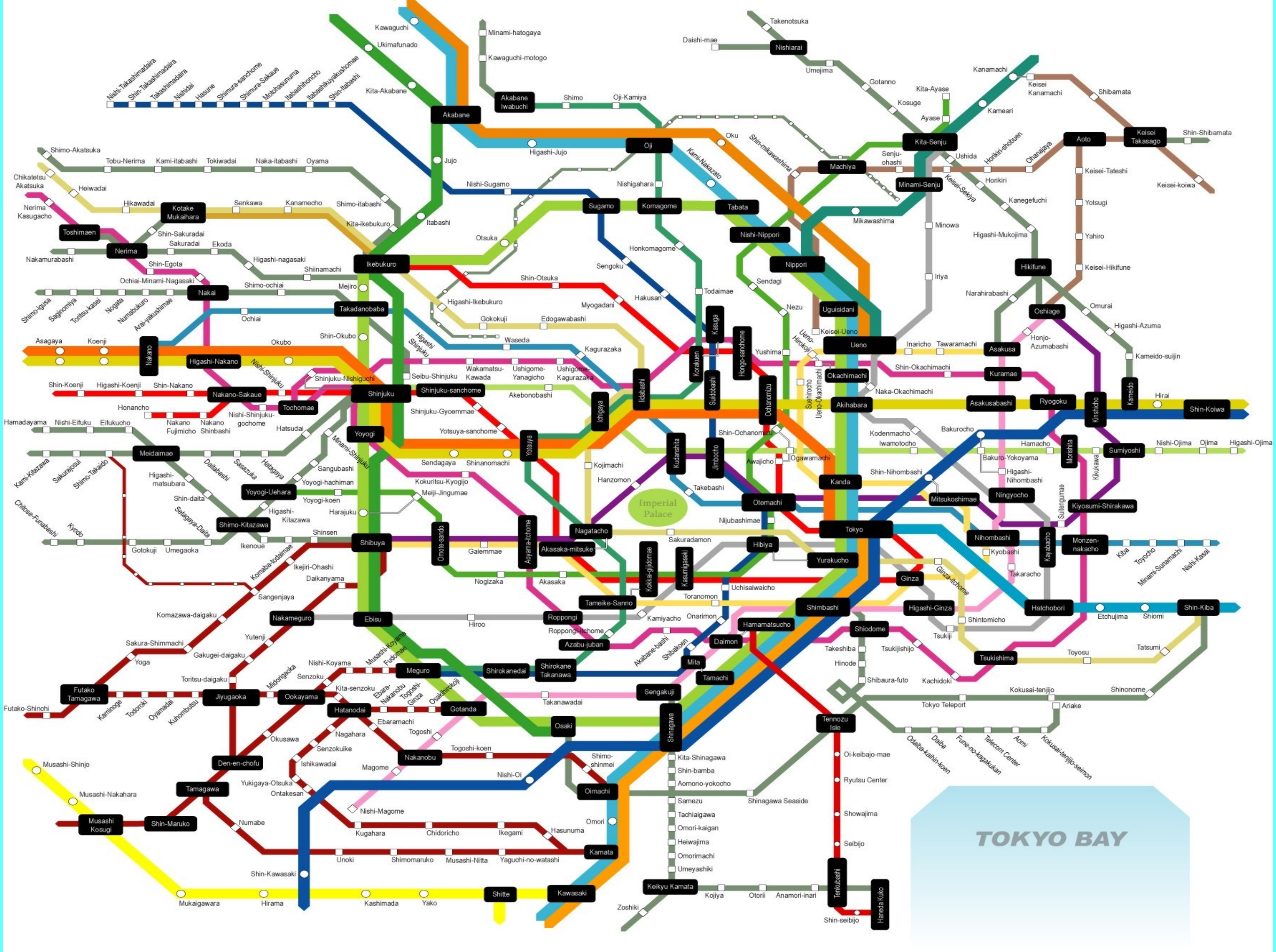
Genomic Markers in CRC



CRC = colorectal cancer.

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

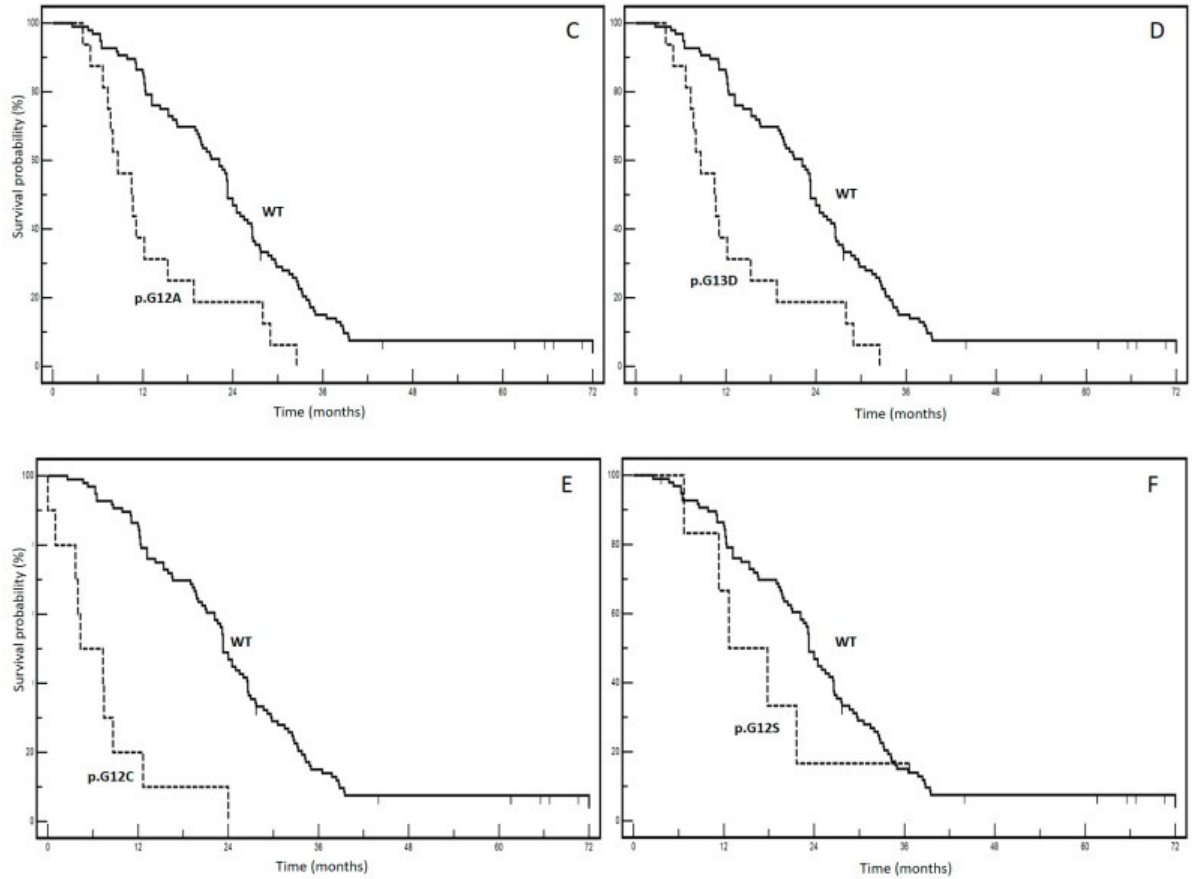

TOKYO BAY
Imperial Palace
Takenotsuka
Daishi-mae
Nishiarai
Umejima
Gotanno
Kosuge
Kita-Ayase
Ayase
Kanamachi
Keisei Kanamachi
Shibamata
Kameari
Kita-Senju
Ushida
Horikiri-shobuen
Ohanajaya
Aoto
Keisei Takasago
Shin-Shibamata
Keisei-koiwa
Keisei-Tateishi
Yotsugi
Yahiro
Keisei-Hikifune
Horikiri
Kanegafuchi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

Novel Approaches

1. RAS (G12C)

KRAS G12C Mutations Appear to Confer a Worse Prognosis

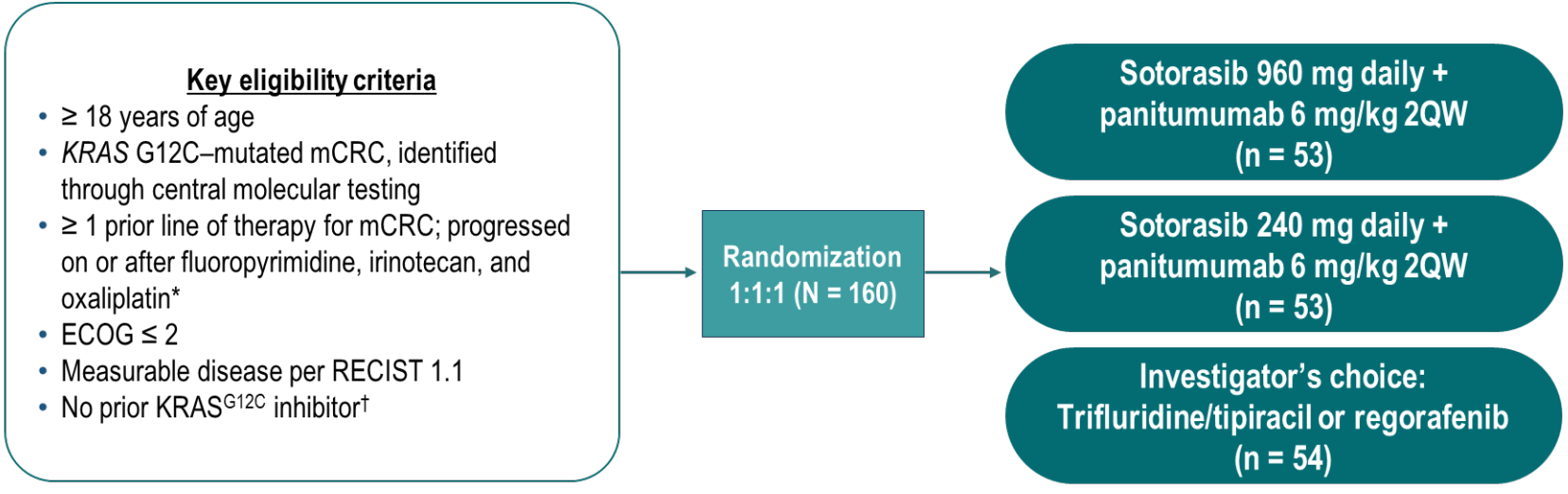
KRAS G12C



Ottaiano et al. *Cancers* 2023;15(14):3579.

CodeBreaK 300 Phase 3 Study Design

Global, randomized, open-label, active-controlled study of sotorasib + panitumumab in mCRC (NCT05198934)



Stratified by: prior anti-angiogenic therapy (yes / no), **time from diagnosis of mCRC** (≥18 mo / <18 mo), **ECOG status** (0 or 1 / 2)

Treat until disease progression, start of another anti-cancer treatment, withdrawal of consent , or intolerance of treatment

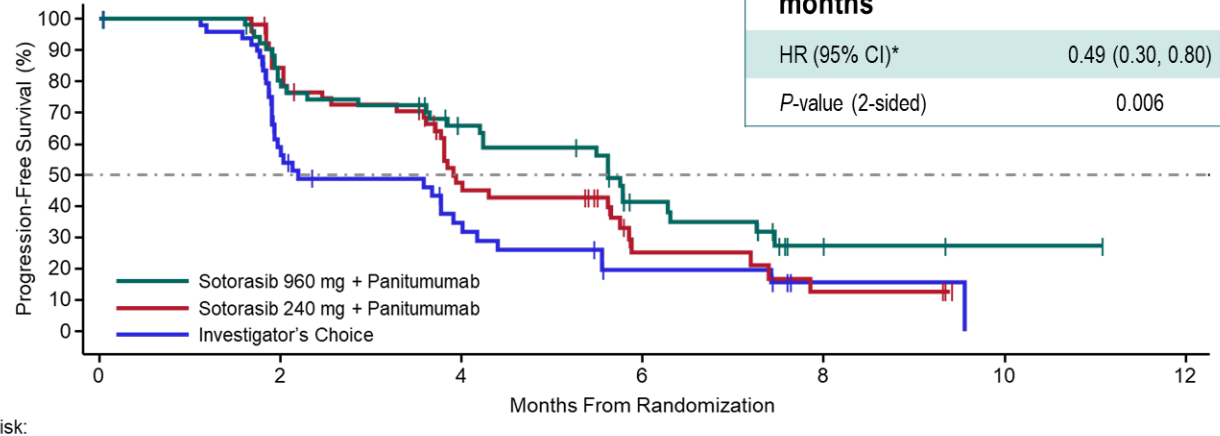
Primary endpoint: PFS by BICR (measured by CT / MRI and assessed by RECIST v1.1)
Key secondary endpoints: OS, ORR

*Patients deemed by the investigator not to be candidates for fluoropyrimidine, irinotecan, or oxaliplatin may still be eligible if ≥ 1 prior line of therapy was received for metastatic disease and trifluridine and tipiracil and/or regorafenib were deemed appropriate next line of therapy. †Patients with prior treatment with trifluridine and tipiracil and with regorafenib were excluded, where the investigator's choice would be these agents.

2QW, every 2 weeks; BICR, blinded independent central review; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Primary Endpoint: PFS in Intent-to-Treat Population

	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median PFS, months	**5.6**	**3.9**	**2.2**
HR (95% CI)*	0.49 (0.30, 0.80)	0.58 (0.36, 0.93)	–
P-value (2-sided)	0.006	0.030	–



Number of Patients at Risk:

Sotorasib 960 mg + Panitumumab	53	40	28	13	2	1	0
Sotorasib 240 mg + Panitumumab	53	43	20	6	3	0	
Investigator's Choice	54	24	12	5	1	0	

After a median follow-up of 7.8 months, sotorasib (240 mg and 960 mg) in combination with panitumumab significantly improved PFS by BICR versus investigator's choice

PFS was tested using stratified log-rank test. *HR is sotorasib 960 mg + panitumumab / investigator's choice therapy, or sotorasib 240 mg + panitumumab / investigator's choice therapy.
BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free survival.

Activity Outcomes

Response by BICR	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
ORR, % (95% CI)*†	26 (15.3–40.3)	6 (1.2–15.7)	0 (0–6.6)
Complete response, n (%)	1 (2)	0	0
Partial response, n (%)	13 (25)	3 (6)	0
Stable disease, n (%)	24 (45)	33 (62)	25 (46)
Progressive disease, n (%)	12 (23)	13 (25)	17 (31)
Not evaluable / not done, n (%)	3 (6)	2 (4)	11 (20)
DCR, % (95% CI)*	72 (57.7–83.2)	68 (53.7–80.1)	46 (32.6–60.4)

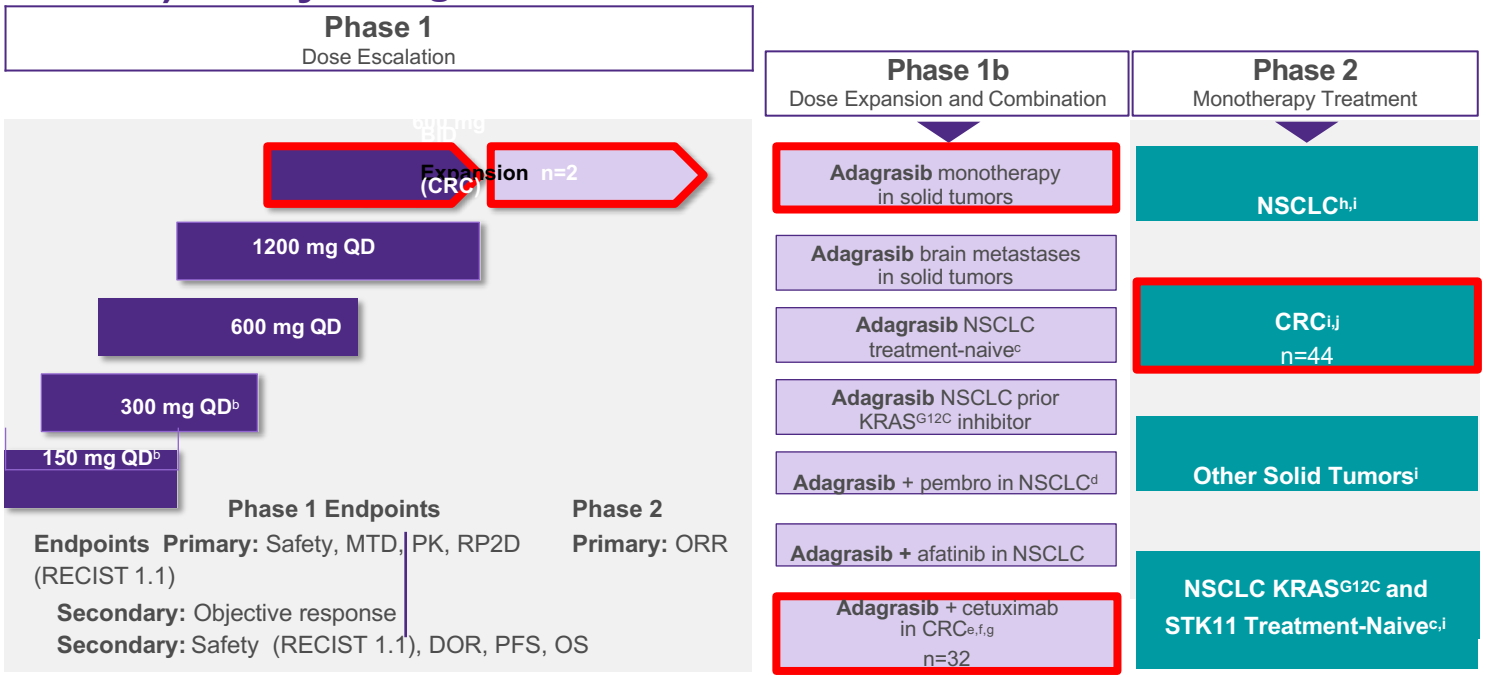
ORR and DCR by BICR were higher with sotorasib (960 mg and 240 mg) + panitumumab versus investigator's choice

The intention-to-treat analysis set included all patients who underwent randomization.
*95% CIs were estimated using the Clopper-Pearson method. BICR, blinded independent central review; DCR, disease control rate; ORR, objective response rate
†Two patients (4%) in the 240 mg arm and 1 patient (2%) in the investigator's choice arm had non-complete response/non-progressive disease; these patients had BICR assessed non-target disease only

KRYSTAL-1 (849-001) Study Design

Key Eligibility Criteria (Up to n=565)

- Solid tumor with a KRAS^{G12C} mutation[a]
- Unresectable or metastatic disease
- No available treatment with curative intent or available standard of care



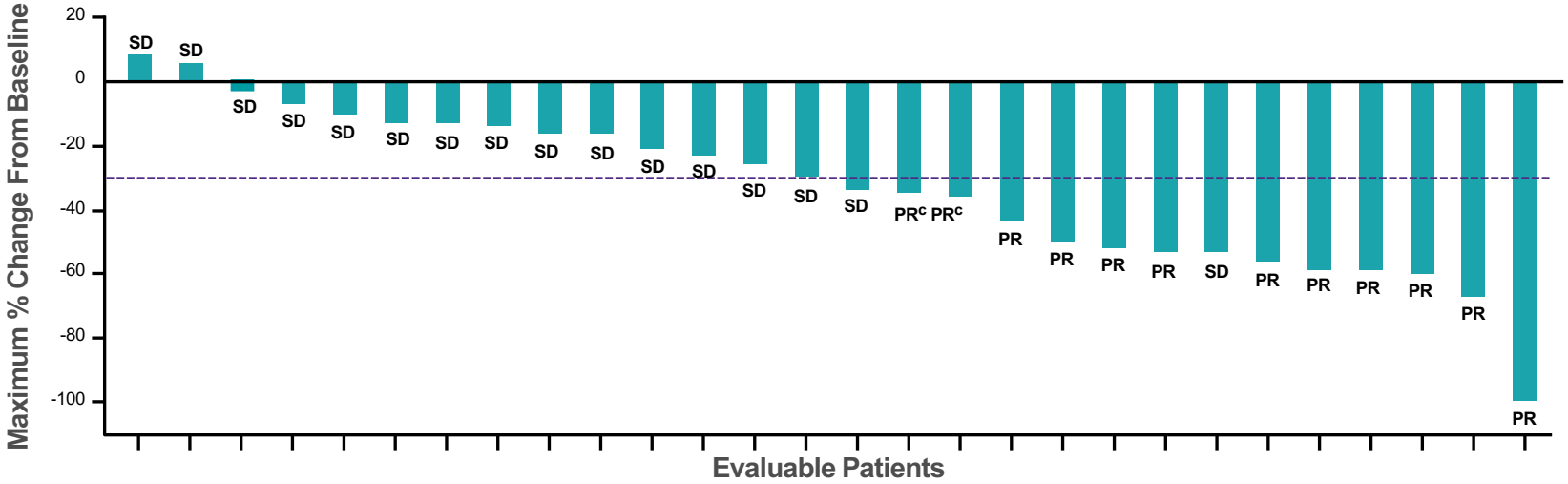
- Previously reported data demonstrated the clinical activity of adagrasib in patients with pretreated CRC with a KRAS^{G12C} mutation[9]
- Here we report preliminary data for adagrasib 600 mg BID as monotherapy (n=2 in Phase 1/1b and n=44 in Phase 2; median follow-up: 8.9 months) and in combination with cetuximab (n=32; median follow-up: 7 months) in patients with pretreated CRC with a KRAS^{G12C} mutation
- Data as of 25 May 2021 (monotherapy), 9 July 2021 (cetuximab combination)

[a]Tissue test and/or ctDNA allowed for Phase 1/1b eligibility. [b]Patients subsequently dose escalated up to 600 mg BID. [c]Patients must have declined 1L systemic therapy. [d]Subjects receiving prior treatment with a KRAS^{G12C} inhibitor not eligible. [e]Subjects receiving prior treatment with a KRAS^{G12C} inhibitor eligible for the Phase 1b adagrasib + cetuximab cohort. [f]Patients who received cetuximab who experienced clinical benefit had the option to continue on adagrasib alone. [g]Cetuximab was administered IV at a dose of 400 mg/m^2 followed by 250 mg/m^2 QW, or 500 mg/m^2 Q2W (Phase 1b). [h]Trial is registrational. [i]KRAS^{G12C} mutation detected in tumor tissue and/or blood. [j]Patients who have stable disease compared to baseline measurements at week 13 or later during treatment with single agent adagrasib are eligible to cross over to adagrasib + cetuximab combination cohort. ClinicalTrials.gov. NCT03785249.

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021

Adagrasib + Cetuximab in Patients With Advanced CRC: Best Overall Response

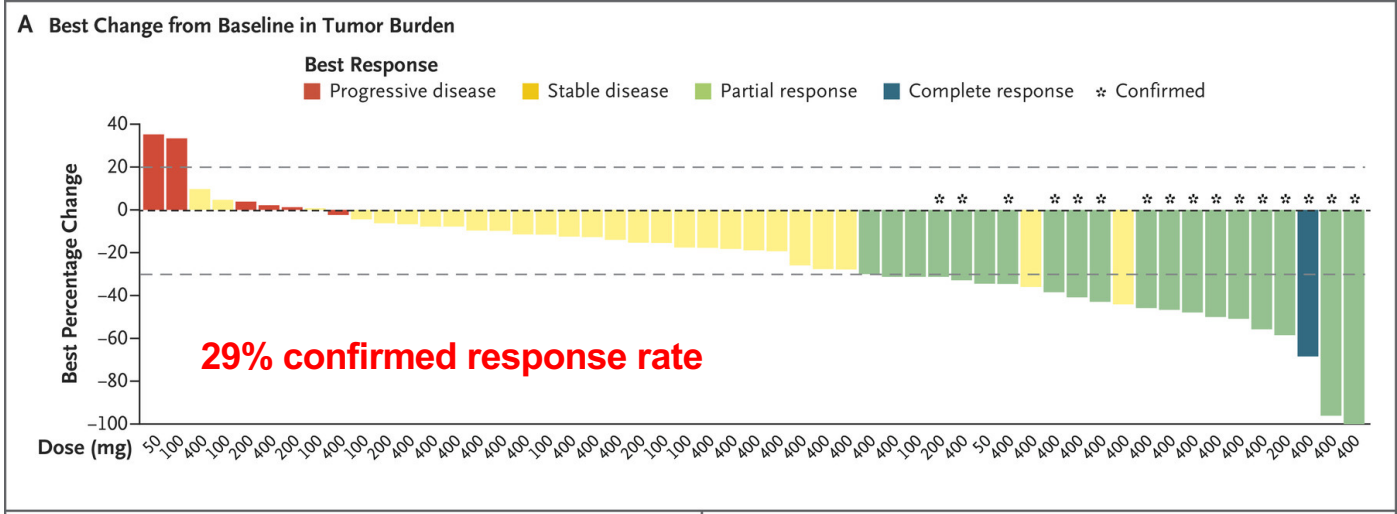
Best Tumor Change From Baseline (n=28)[a,b]

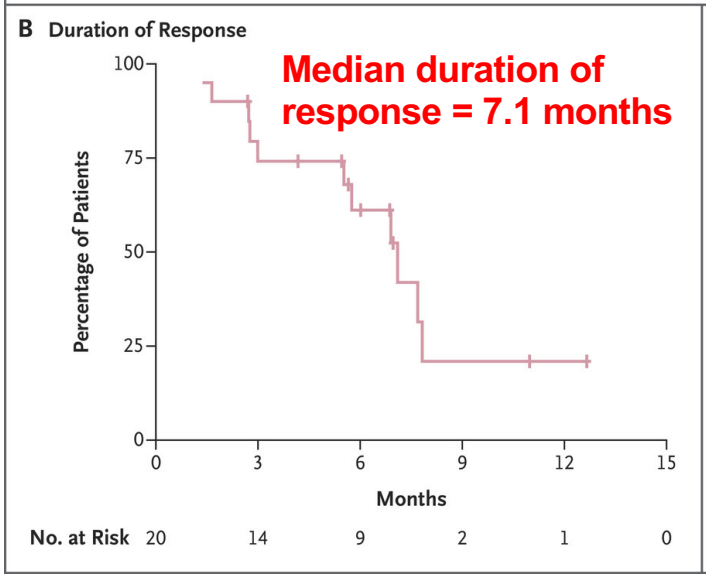


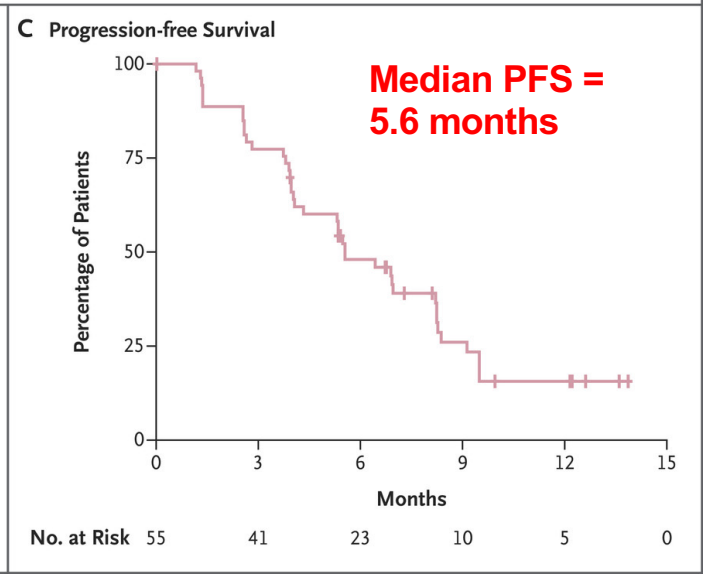
- Response rate was 43% (12/28), including 2 unconfirmed PRs
- SD was observed in 57% (16/28) of patients
- Clinical benefit (DCR) was observed in 100% (28/28) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

[a]All results are based on investigator assessments. [b] Evaluable population (n=28) excludes 4 patients who withdrew consent prior to the first scan. [c]At the time of the 9 July 2021 data cutoff, 2 patients had uPRs.
[e]Molecular status (BRAF V600E mutation, MSI-H or dMMR, EGFR amplification, TP53 mutation, PIK3CA mutation) includes patients with conclusively evaluable test results.
Data as of 9 July 2021 (median follow-up: 7 months).

Divarasib in metastatic KRAS G12C mCRC *(n = 55)*

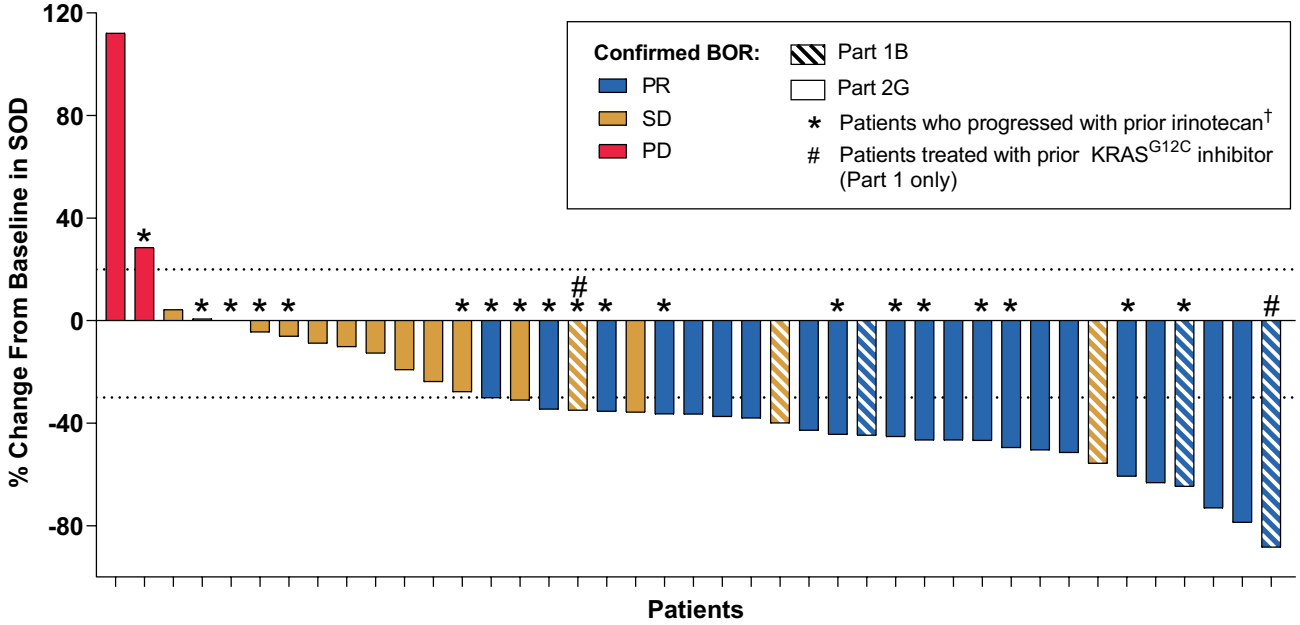






Sacher et al. *N Engl J Med* 2023.

Tumor Response with Sotorasib and FOLFIRI



Data cutoff, April 13, 2023.

†Patients whose disease progressed on prior irinotecan include those with clinical or radiographic progression.

‡42 patients enrolled at least 7 weeks before analysis cutoff were included for response summary; 1 patient with no post-baseline scan is not shown in figure but is included in the denominator.

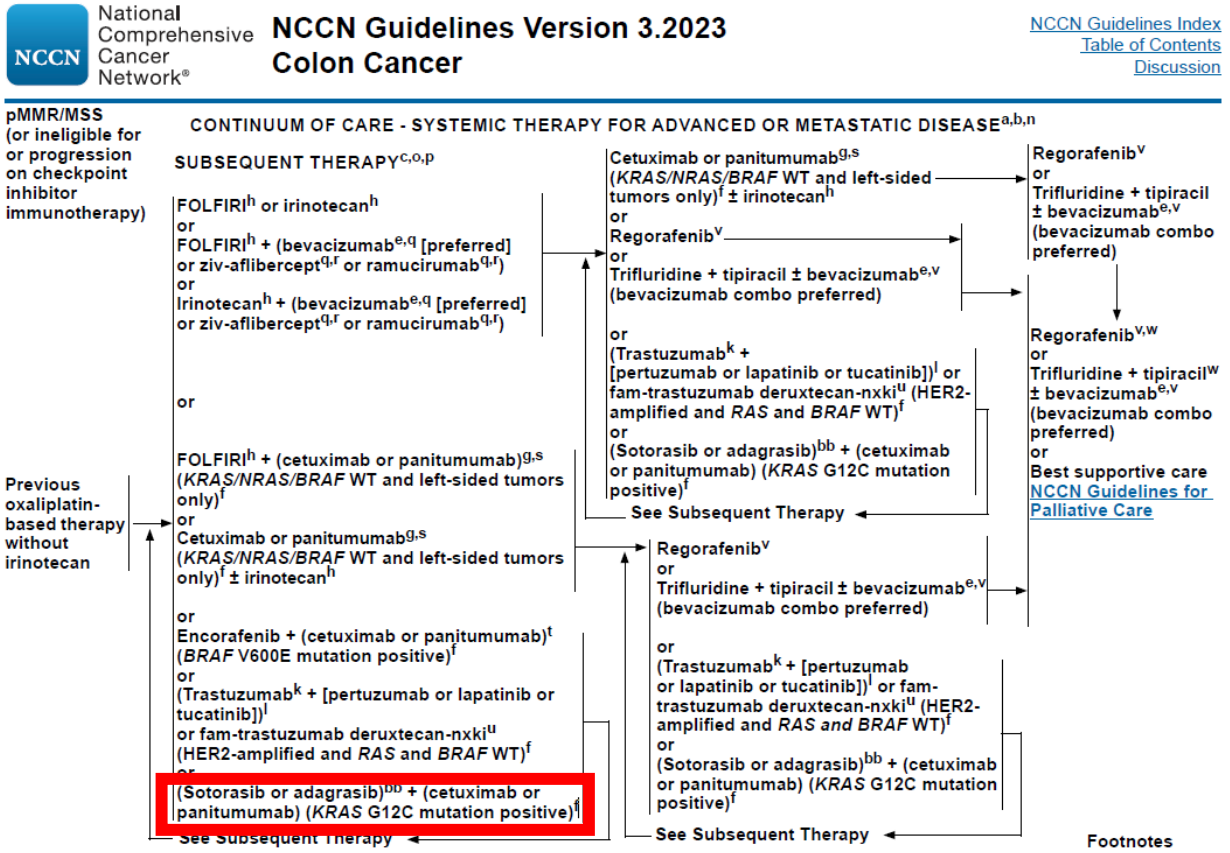
- **Reduction in RECIST target lesions was observed in 86% of patients‡**

Hong DS, et al. Poster presented at: American Society of Clinical Oncology; June 2-6, 2023; Chicago, IL. Abstract #3513

Take Home Points:

- KRAS G12C is present in approximately 3% of all patients with mCRC
- Emerging data with G12C inhibitors + anti EGFR antibodies show significant response rates and promising progression-free survival
- Promising results seen with pan ras inhibitors, and the field is becoming increasingly crowded
- Combinations are well-tolerated, but dermatologic toxicity is seen in over half the patients treated
- Early data with chemotherapy (FOLFIRI) show impressive response rates

NCCN Colon Cancer Update 2023



NCCN Guidelines Colon Cancer v3.2023

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

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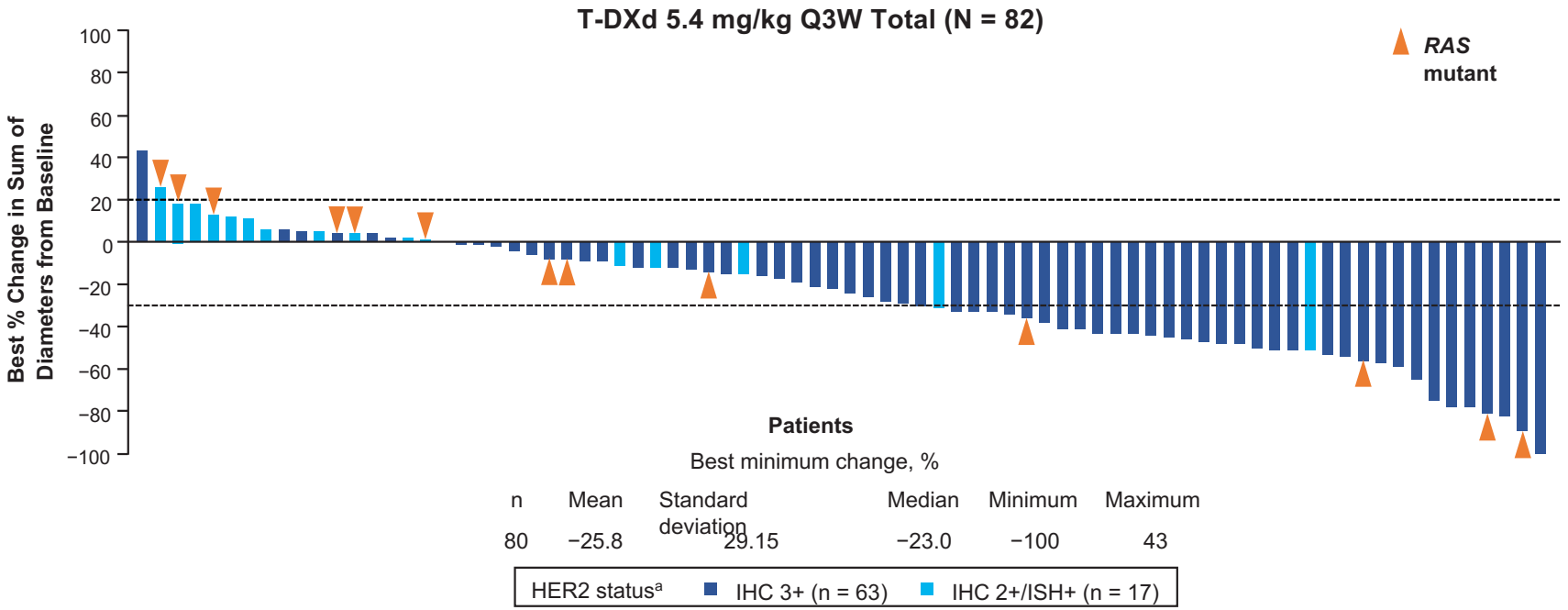
June 4, 2023

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.

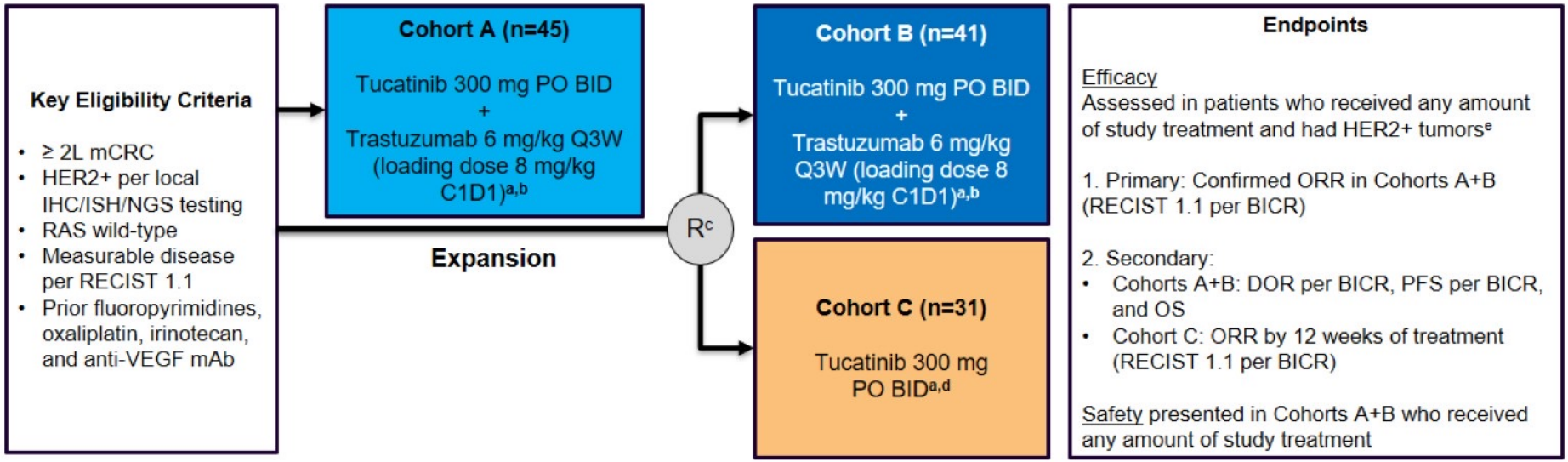
Best Percentage Change in Sum of Diameters by BICR for T-DXd 5.4 mg/kg



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.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial

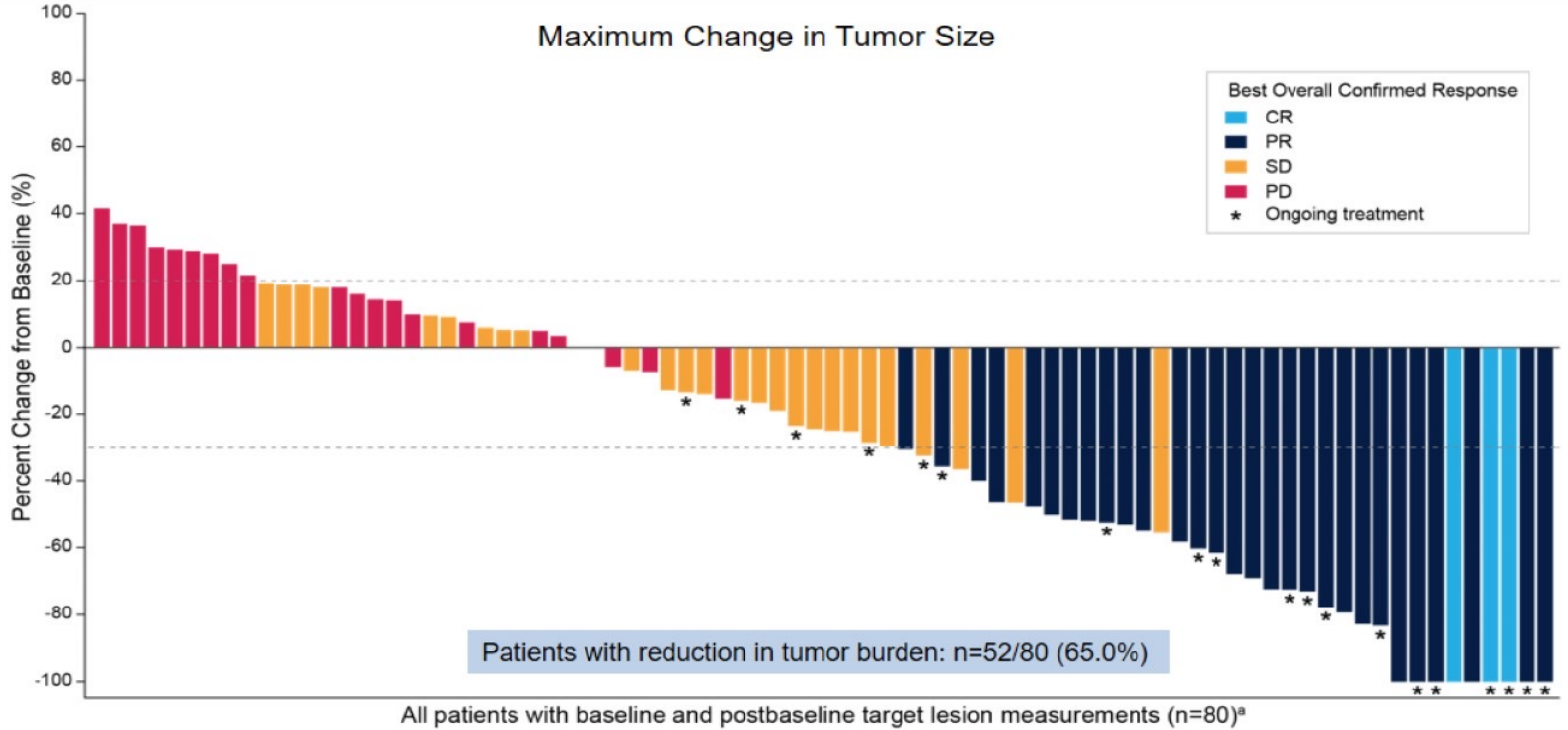


MOUNTAINEER began as a US Investigator-Sponsored Trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomised to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

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



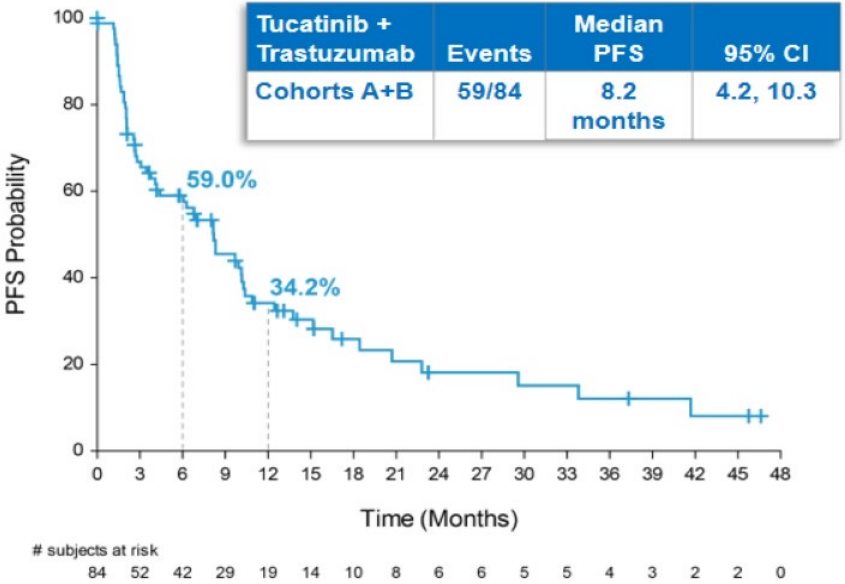
a Four patients who did not have baseline and/or post-baseline target lesion measurements are excluded
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
Data cutoff: 28 Mar 2022

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

Tucatinib + Trastuzumab: PFS and OS

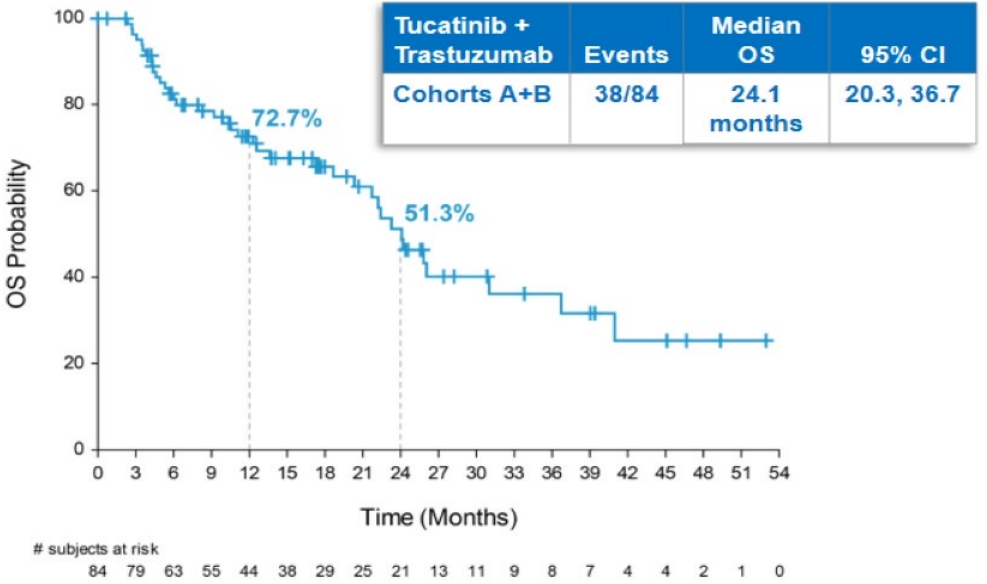
Progression-free Survival per BICR

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

Nivo/Ipi in first line

2024 ASCO ANNUAL MEETING

Nivolumab plus ipilimumab vs chemotherapy as first-line treatment for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: expanded efficacy analysis from CheckMate 8HW

Heinz-Josef Lenz,[1] Sara Lonardi,[2] Elena Elez Fernandez,[3] Eric Van Cutsem,[4] Lars Henrik Jensen,[5] Jaafar Bennouna,[6] Guillermo Ariel Mendez,[7] Michael Schenker,[8] Christelle de la Fouchardiere,[9] Maria Luisa Limon Miron,[10] Takayuki Yoshino,[11] Jin Li,[12] José Luis Manzano Mozo,[13] Giampaolo Tortora,[14] Rocio Garcia-Carbonero,[15] Rohit Joshi,[16] Elvis Cela,[17] Tian Chen,[17] Lixian Jin,[17] Thierry Andre[18]

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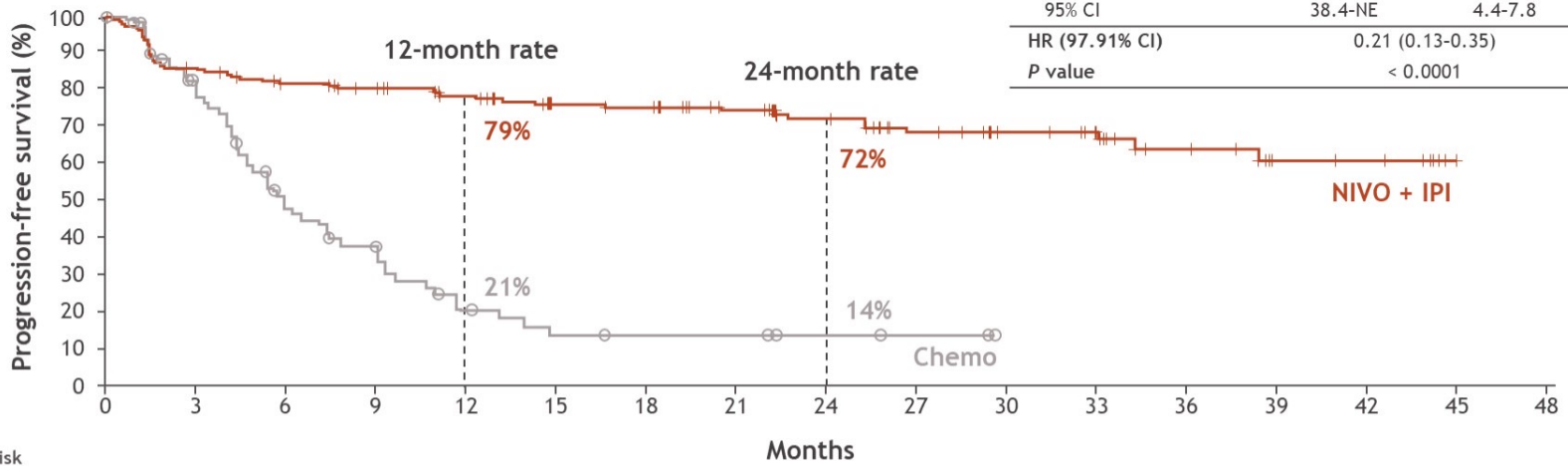
Abstract number 3503

Progression-free survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



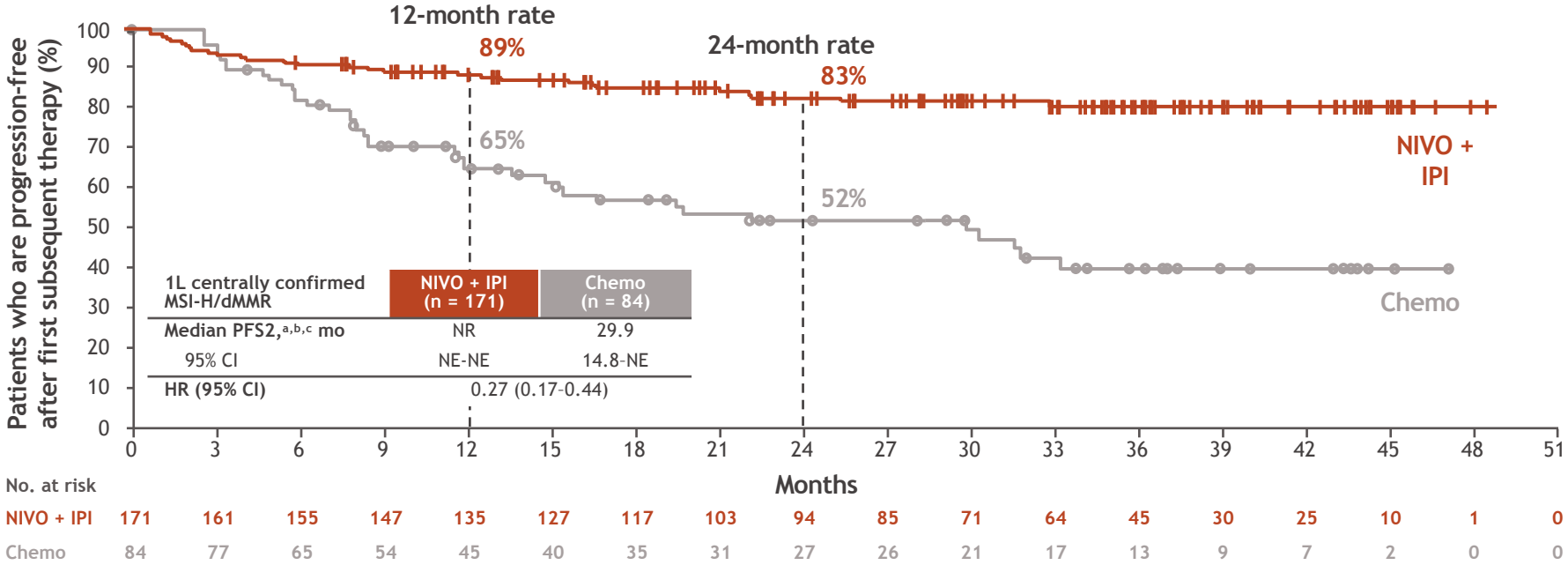
No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

Lenz et al ASCO 2024

[a]Per BICR. [b]Median follow-up, 24.3 months.

PFS2: progression-free survival after subsequent therapy



- PFS2[a] favored NIVO + IPI vs chemo with a 73% reduction in the risk of death or disease progression after first subsequent therapy

Lenz et al ASCO 2024

[a]Defined as time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death. [b]Per investigator. [c]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

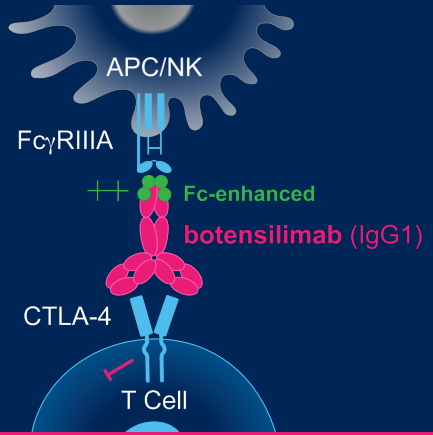
IO in MSS

1. Role of CTLA
2. Novel Immune therapies for MSS CRC
3. Role of liver metastases

Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor

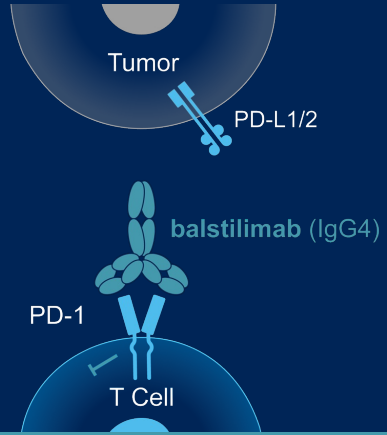


Active in cold and IO refractory tumors[1,2]:

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

balstilimab

PD-1 Inhibitor

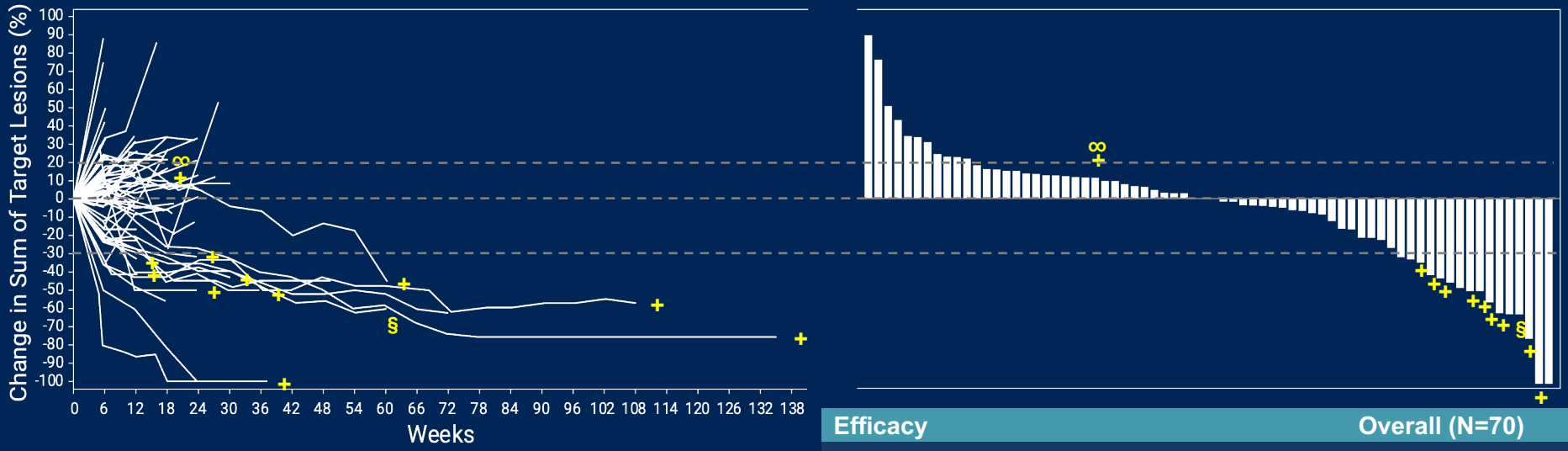


Safety and efficacy analogous to approved anti-PD-1 mAbs[5,6]

- > 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

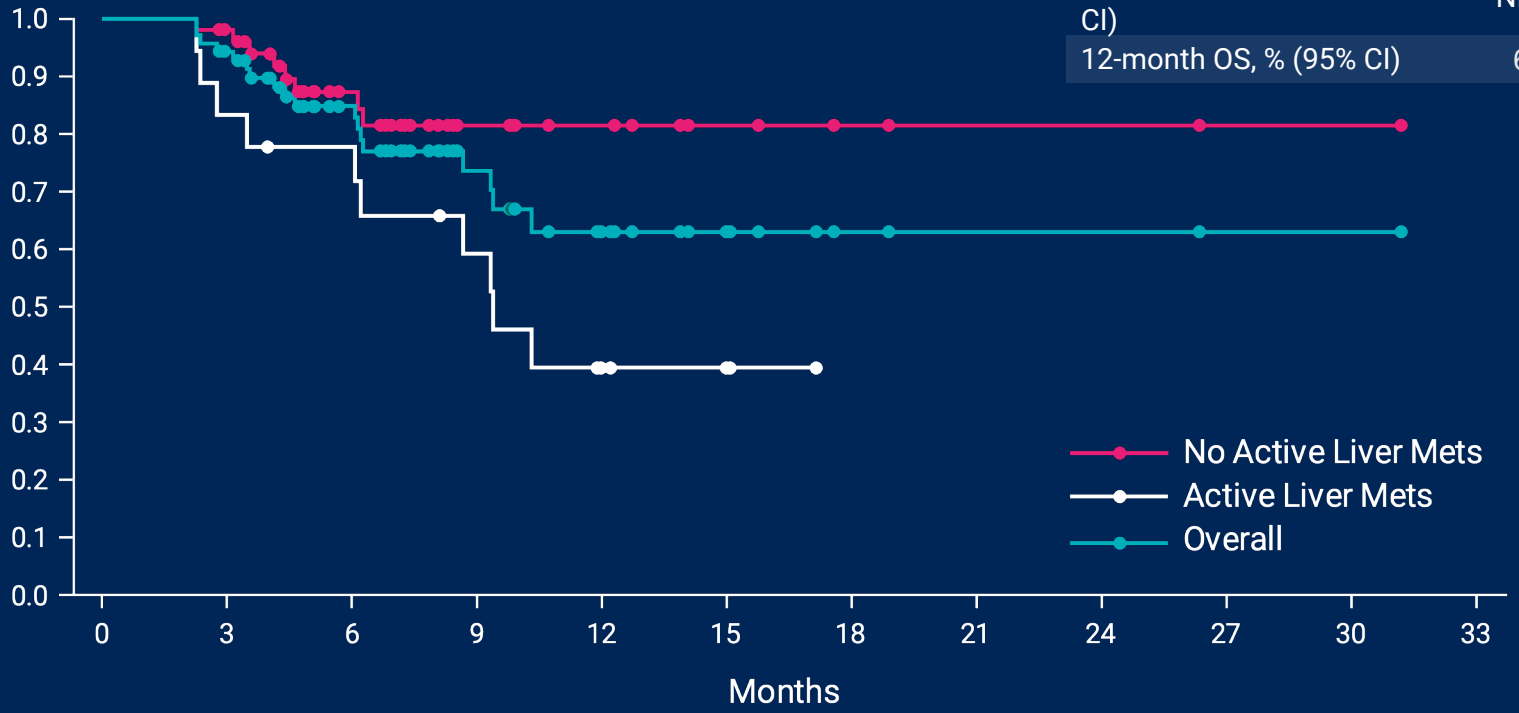
*Includes unconfirmed responses. + Ongoing responses (n=11/16). ∞ Resected target lesions showed complete pathologic response. § Response by iRECIST.

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

Overall Survival by Liver Involvement

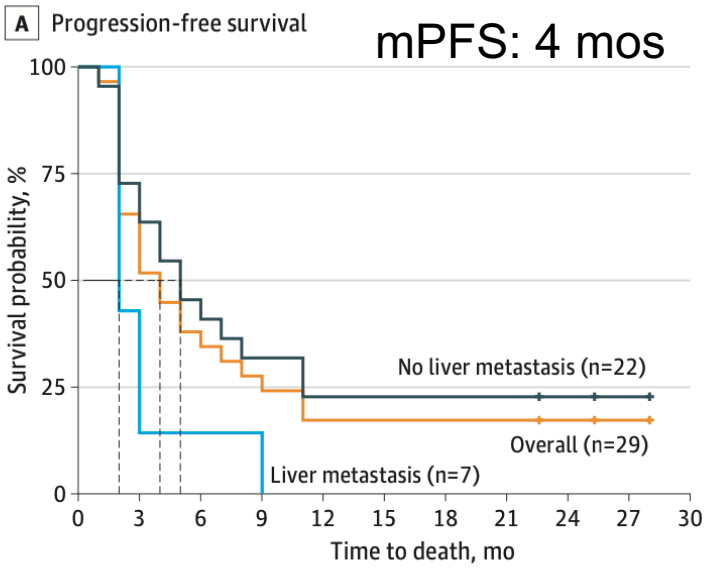
Efficacy evaluable population, N=70

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

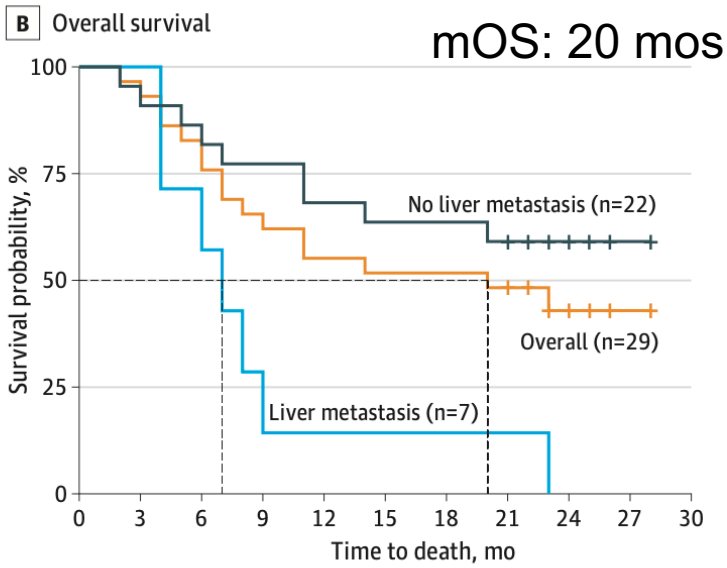


El-Khoueiry AB, et al. Presented at: ASCO;2023.

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.

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