UPDATES IN THE TREATMENT OF ADVANCED/METASTATIC COLON CANCER

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July 21, 2023

DISCLOSURE

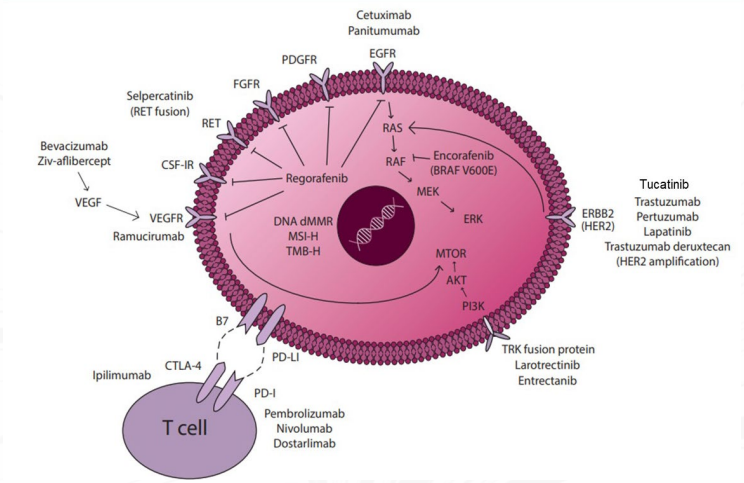
Research funding: Taiho Oncology, Ipsen Pharmaceuticals, GSK, Bristol Myers Squibb, PCI Biotech AS, ASCO, Calithera Biosciences, Inc., SynCore Biotechnology Co. Ltd., Suzhou Transcenta Therapeutics Co., Ltd, Corcept Therapeutics Inc., Hutchison MediPharma, Boehringer Ingelheim, Xencor Inc., Cue Biopharma, Inc., Merck, Syros Pharmaceuticals Inc., Inhibitex Inc, Arcus Biosciences Inc., ImmunoGen

Consulting/Advisory Role: Ipsen Pharmaceuticals, Aadi Bioscience, Taiho, Pfizer, Seagen Inc., Bristol Myers Squibb, AstraZeneca, Exelixis, Takeda

LEARNING OBJECTIVES

- Review novel treatment strategies for advanced/metastatic colorectal cancer (CRC)
  - Targeted therapies
  - Chemotherapy
- Winship clinical trials

MOLECULAR TARGETS IN CRC



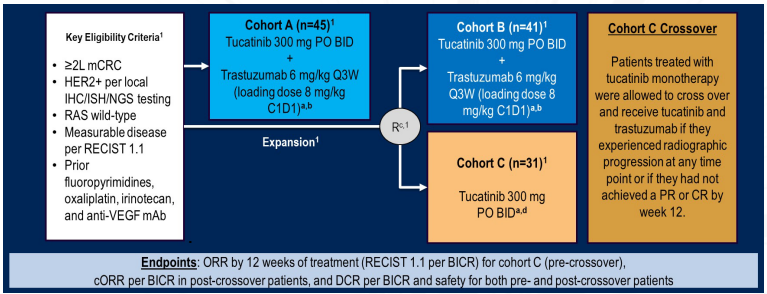
Targets	Drug
EGFR (RAS/RAF wild-type)	• Cetuximab • Panitumumab
VEGF	• Bevacizumab • Ziv-aflibercept • Ramucirumab • Regorafenib
PDL-1 (dMMR or MSI-H)	• Pembrolizumab • Nivolumab +/- ipilumumab • Dostarlimab
BRAF V600E mutation	• Encorafenib + anti-EGFR
ERBB2 (HER2) overexpression (+RAS/RAF wild-type)	• Trastuzumab + Tucatinib Pertuzumab Lapatinib • Trastuzumab deruxtecan
TRK fusion	• Larotrectinib • Entrectanib
RET fusion	• Selpercatinib

Alese OB, et al. Am Soc Clin Oncol Educ Book. 2023 May;43:e389574.

MOUNTAINEER

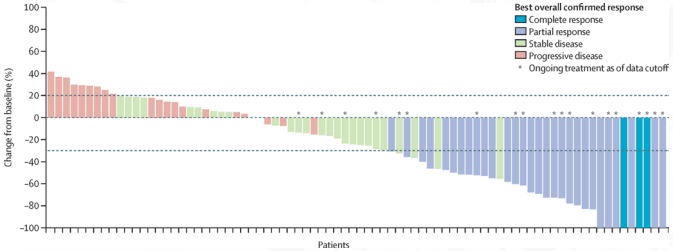
Tucatinib plus trastuzumab for chemotherapy-refractory, HER2-positive, *RAS* wild-type unresectable or metastatic colorectal cancer (MOUNTAINEER): a multicentre, open-label, phase 2 study

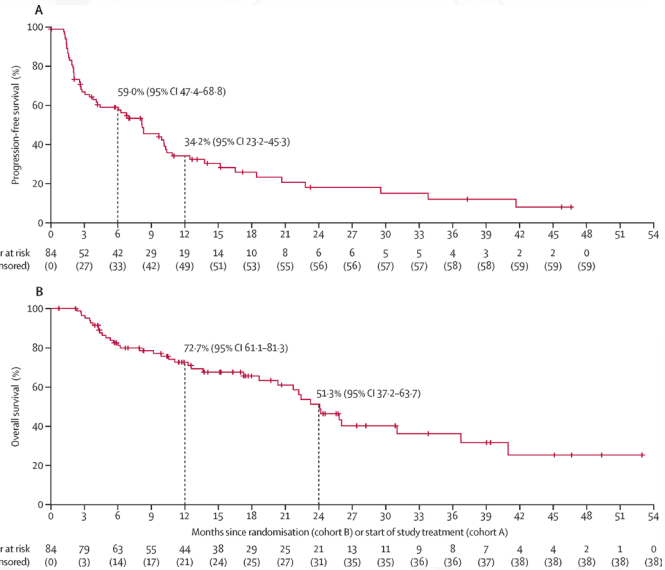
*John H Strickler, Andrea Cercek, Salvatore Siena, Thierry André, Kimmie Ng, Eric Van Cutsem, Christina Wu, Andrew S Paulson, Joleen M Hubbard, Andrew L Coveler, Christos Fountzilas, Adel Kardosh, Pashtoon M Kasi, Heinz-Josef Lenz, Kristen K Ciombor, Elena Elez, David L Bajor, Chiara Cremolini, Federico Sanchez, Michael Stecher, Wentao Feng, Tanios S Bekaii-Saab, on behalf of the MOUNTAINEER investigators**



	Tucatinib plus trastuzumab (n=84)	Tucatinib monotherapy (n=30)
Age, years		
Median (IQR)	55·0 (44·5–62·0)	59·5 (52·0–66·0)
<65 years	72 (86%)	19 (63%)
≥65 years	12 (14%)	11 (37%)
Sex		
Male	51 (61%)	15 (50%)
Female	33 (39%)	15 (50%)
Ethnicity		
Hispanic, Latino/a, or of Spanish origin	3 (4%)	1 (3%)
Not Hispanic, Latino/a, or of Spanish origin	64 (76%)	25 (83%)
Not available*	17 (20%)	4 (13%)
Race		
American Indian or Alaska Native	1 (1%)	0
Asian	3 (4%)	0
Black or African American	3 (4%)	3 (10%)
White	65 (77%)	23 (77%)
Multiple	1 (1%)	0
Not available*	11 (13%)	4 (13%)
Geographical region		
North America	69 (82%)	16 (53%)
Europe	15 (18%)	14 (47%)
ECOG performance status score†		
0	50 (60%)	17 (57%)
1	31 (37%)	13 (43%)
2	3 (4%)	0
Site of primary tumour		
Left colon and rectum‡	71 (85%)	27 (90%)
Transverse colon	7 (8%)	0
Right colon§	5 (6%)	3 (10%)
Multiple or overlapping sites	1 (1%)	0
RAS wild-type status¶	84 (100%)	30 (100%)

MOUNTAINEER





MOUNTAINEER

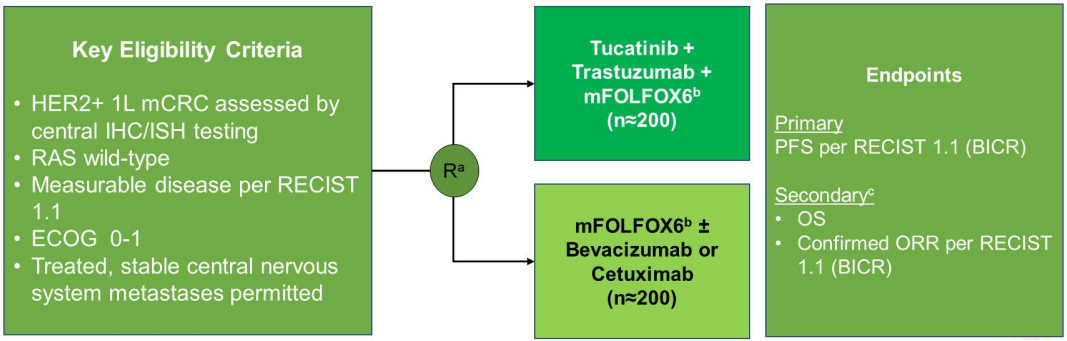
- Dual HER2 blockade with Tucatinib plus trastuzumab had clinically meaningful anti-tumor activity and favorable tolerability
- First FDA-approved anti-HER2 regimen for metastatic colorectal cancer

Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (4%)	0	0
	PR	29 (35%)	1 (3.3)	5 (17.9)
	SD[b]	28 (33%)	23 (76.7)	18 (64.3)
	PD	22 (26%)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2%)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		38 (27.7-49.3)[f]	3 (0.1-17.2)[g]	18 (6.1-36.9)[f]
DCR[e] per BICR, n (%)		60 (71.4)	24 (80.0)	23 (82.1)

	Grade 1–2	Grade 3	Grade 4
Any adverse event	49 (57%)	27 (31%)	6 (7%)
Diarrhoea	52 (60%)	3 (3%)	0
Fatigue	36 (42%)	2 (2%)	0
Nausea	30 (35%)	0	0
Infusion-related reaction	18 (21%)	0	0
Pyrexia	17 (20%)	0	0
Decreased appetite	16 (19%)	0	0
Dermatitis acneiform	16 (19%)	0	0
Chills	15 (17%)	1 (1%)	0
Cough	14 (16%)	0	0
Vomiting	14 (16%)	0	0
Back pain	13 (15%)	2 (2%)	0
Arthralgia	13 (15%)	1 (1%)	0
Dyspnoea	12 (14%)	0	0
Abdominal pain	11 (13%)	2 (2%)	0
Constipation	11 (13%)	1 (1%)	0
Myalgia	11 (13%)	0	0
Anaemia	9 (10%)	0	0
Anxiety	9 (10%)	0	0
Hypertension	9 (10%)	6 (7%)	0
Pain in extremity	7 (8%)	1 (1%)	0
Nephrolithiasis	3 (3%)	1 (1%)	0
Flank pain	3 (3%)	2 (2%)	0
Aspartate aminotransferase increase	3 (3%)	0	2 (2%)
Alanine aminotransferase increase	2 (2%)	1 (1%)	2 (2%)

Strickler JH, et al. Lancet Oncol. 2023 May;24(5):496-508

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



HER2 INHIBITION IN ADVANCED CRC

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

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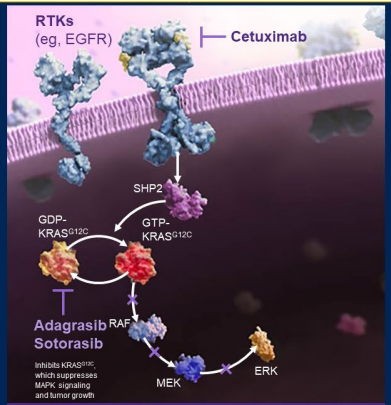
Pertuzumab and T-DM1	HERACLES-B (n=31) – 2020	9.7%	4.1m	Not reported	Thrombocytopenia 7%
Trastuzumab deruxtecan	DESTINY-CRC01 (N=78; 53 HER2+) – 2021	45.3%	6.9m	15.5m	Neutropenia 15% Anemia 13%
Trastuzumab + tucatinib	MOUNTAINEER (n=117) - 2022	38.1%	8.2m	24.1m	Hypertension 7% Diarrhea 3.5%

KRAS G12C

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



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

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

KRYSTAL-1 PHASE 1B/2 CRC COHORT STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated *KRAS* G12C

Rona Yaeger, M.D., Jared Weiss, M.D., Meredith S. Pelster, M.D., Alexander I. Spira, M.D., Ph.D., Minal Barve, M.D., Sai-Hong I. Ou, M.D., Ph.D., Ticiana A. Leal, M.D., Tanios S. Bekaii-Saab, M.D., Cloud P. Paweletz, Ph.D., Grace A. Heavey, B.A., James G. Christensen, Ph.D., Karen Velastegui, B.Sc., Thian Kheoh, Ph.D., Hirak Der-Torossian, M.D., and Samuel J. Klempner, M.D.

Phase 1b CRC Combination	Phase 2 CRC Monotherapy
Adagrasib 600 mg BID + cetuximab (n=32)	Adagrasib 600 mg BID (n=44)

CODEBREAK 101 SUBPROTOCOL H STUDY

Part 1: Cohort B dose exploration† (N = 6)

Dose Level 1:
Sotorasib: 960 mg PO daily
+
Panitumumab: 6 mg/kg IV Q2W
+
FOLFIRI IV Q2W

→ No DLTs were observed, and Dose Level 1 was declared the RP2D‡ →

Part 2: Cohort G dose expansion† (N = 40)

Sotorasib: 960 mg PO daily
+
Panitumumab: 6 mg/kg IV Q2W
+
FOLFIRI IV Q2W

Primary Endpoint: Safety and tolerability
Secondary Endpoints: Anti-tumor efficacy (ORR, DCR, DOR, TTR, PFS per RECIST v1.1, and OS) and PK

Yaeger R, et al. N Engl J Med. 2023 Jan 5;388(1):44-54;
Hong DS, et al. Journal of Clinical Oncology 2023 41:16_suppl, 3513-3513

KRYSTAL-1

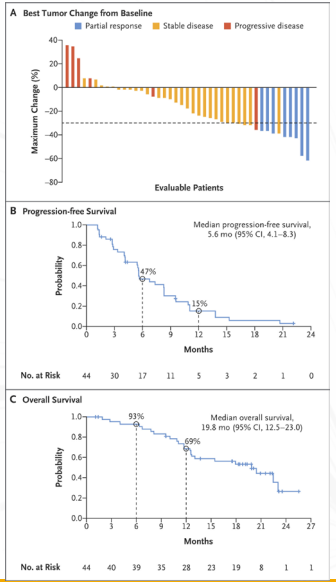
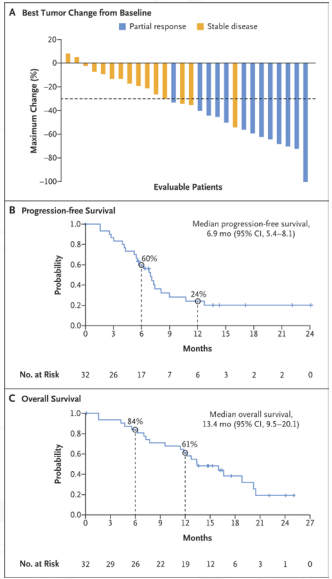
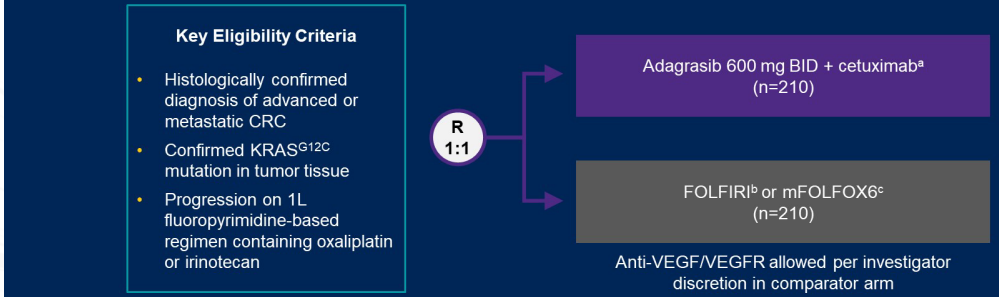


Table 2. **Overall Summary of Clinical Activity.***

Variable	Adagrasib Monotherapy (N=43)†	Adagrasib plus Cetuximab (N=28)‡
Objective response§		
Per blinded independent central review — no. of patients	10	13
% (95% CI)	23 (12–39)	46 (28–66)
As confirmed by investigator — no. of patients	8	13
% (95% CI)	19 (8–33)	46 (28–66)
Best overall response — no. (%)		
Complete response	0	0
Partial response	8 (19)	13 (46)
Stable disease	29 (67)	15 (54)
Progressive disease	6 (14)	0
Not evaluable	0	0
Median duration of response — mo	4.3	7.6
95% CI	2.3–8.3	5.7–NE
Median progression-free survival — mo¶	5.6	6.9
95% CI	4.1–8.3	5.4–8.1
Median overall survival — mo¶	19.8	13.4
95% CI	12.5–23.0	9.5–20.1



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



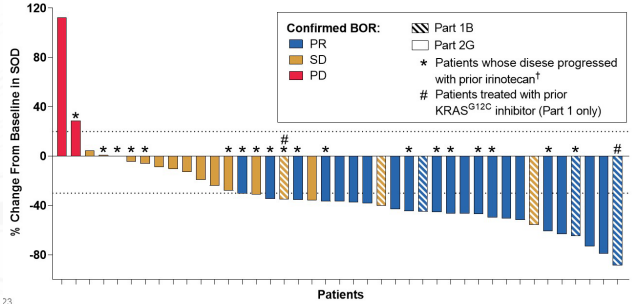
Outcome Measures

Primary: PFS, OS

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

CODEBREAK 101

Response by investigator assessment*	Part 1 Sotorasib + Panitumumab + FOLFIRI (n = 6)	Part 2 Sotorasib + Panitumumab + FOLFIRI (n = 36)	Total (N = 42*)
ORR confirmed, n (%) (95% CI)	3 (50) (11.8, 88.2)	20 (56) (38.1, 72.1)	**23 (55)** (38.7, 70.2)
CR	0	0	0
PR	3 (50)	20 (56)†	23 (55)†
SD, n (%)	3 (50)	13 (36)	16 (38)
PD, n (%)	0	2 (6)	2 (5)
Unavailable, n (%)	0	1 (3)	1 (2)
DCR, n (%) (95% CI)	6 (100) (54.1, 100.0)	33 (92) (77.5, 98.3)	**39 (93)** (80.5, 98.5)

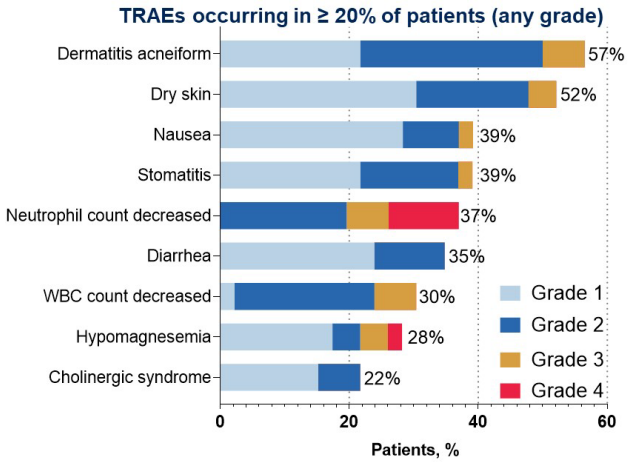


Hong DS, et al. Journal of Clinical Oncology 2023 41:16_suppl, 3513-3513

Safety

TRAE	N = 46 n (%)
TRAE, any grade	44 (96)
Grade 3	13 (28)
Grade 4*	7 (15)
Serious	2 (4)
Fatal	0
TRAE leading to ≥ 1 dose interruption/reductions	34 (74)
Attributed to sotorasib	6 (13)
Attributed to panitumumab	20 (43)
Attributed to FOLFIRI (any component)	30 (65)
TRAE leading to discontinuation of ≥ 1 agent	12 (26)
Sotorasib†	1 (2)
Panitumumab	2 (4)
FOLFIRI (any component)‡	11 (24)
TRAE leading to discontinuation of all agents	1 (2)

Data cutoff, April 13, 2023.



PARIS 2022 ESMO congress

FRESCO-2: A global phase 3 multiregional clinical trial evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer

Arvind Dasari[1], Sara Lonardi[2], Rocio Garcia-Carbonero[3], Elena Elez[4], Takayuki Yoshino[5], Alberto Sobrero[6], James Yao[1], Pilar Garcia-Alfonso[7], Judit Kocsis[8], Antonio Cubillo Gracian[9], Andrea Sartore-Bianchi[10], Taroh Satoh[11], Violaine Randrian[12], Jiri Tomasek[13], Geoff Chong[14], Zhao Yang[15]; William Schelman[15]; Marek Kania[15], Josep Tabernero[4], and Cathy Eng[16]

Patient Eligibility

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

R 2:1

N=687

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

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

Treatment until progression or unacceptable toxicity

Objectives

- **Primary: Overall Survival**
- Key Secondary: PFS
- Other Secondary: ORR, DCR, Safety

Patient and Disease Characteristics

ITT Population
Enrollment: Sep 2020 to Dec 2021
Data Cutoff: 24 June 2022

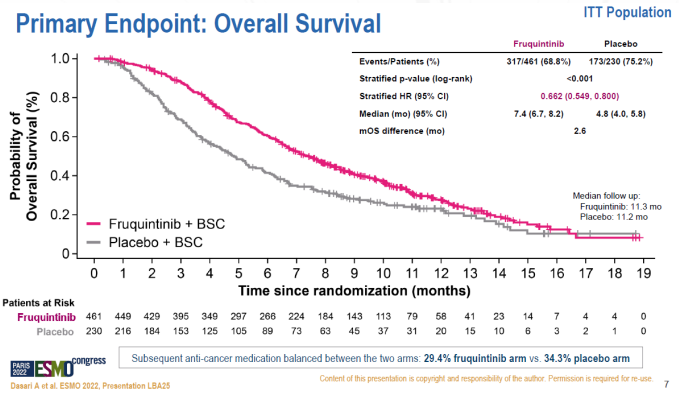
Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Age, y	Median (range)	64 (25, 82)	64 (30, 86)
	≥ 65	214 (46.4)	111 (48.3)
Sex	Female	216 (46.9)	90 (39.1)
	Male	245 (53.1)	140 (60.9)
Region	North America	82 (17.8)	42 (18.3)
	Europe	329 (71.4)	166 (72.2)
	Asia Pacific	50 (10.8)	22 (9.6)
ECOG PS	0	196 (42.5)	102 (44.3)
	1	265 (57.5)	128 (55.7)
Primary site at 1st diagnosis	Colon left	192 (41.6)	92 (40.0)
	Colon right	97 (21.0)	53 (23.0)
	Colon left and right	4 (0.9)	2 (0.9)
	Colon unknown	25 (5.4)	13 (5.7)
	Rectum only	143 (31.0)	70 (30.4)
Liver metastases	Yes	339 (73.5)	156 (67.8)

Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Duration of metastatic disease	≤ 18 mo	37 (8.0)	13 (5.7)
	> 18 mo	424 (92.0)	217 (94.3)
RAS status	WT	170 (36.9)	85 (37.0)
	Mutant	291 (63.1)	145 (63.0)
BRAF V600E mutation	No	401 (87.0)	198 (86.1)
	Yes	7 (1.5)	10 (4.3)
	Other/Unknown	5 (11.5)	22 (9.6)
Number of prior treatment lines in metastatic disease	Median (range)	5 (2, 16)	5 (2, 12)
	≤ 3	125 (27.1)	64 (27.8)
	> 3	336 (72.9)	166 (72.2)
Prior therapies	VEGF inhibitor	445 (96.5)	221 (96.1)
	EGFR inhibitor	180 (39.0)	88 (38.3)
Prior TAS-102 and/or regorafenib	TAS-102	240 (52.1)	121 (52.6)
	Regorafenib	40 (8.7)	18 (7.8)
	Both	181 (39.3)	91 (39.6)

PARIS 2022 ESMO congress

Dasari A et al. ESMO 2022, Presentation LBA25

FRESCO-2



Well tolerated with a safety profile consistent with the previously established monotherapy profile

- Met key secondary endpoint of PFS; improvement of 1.9 months (3.7 m vs 1.8 m; HR=0.32;*p*< 0.001)
- PFS improvement was consistent across all pre-specified subgroups

Category, n (%)	Fruquintinib (N=456)	Placebo (N=230)
Any TEAE	**451 (98.9)**	**213 (92.6)**
Grade ≥ 3	286 (62.7)	116 (50.4)
Treatment-related Grade ≥ 3	164 (36.0)	26 (11.3)
Leading to Death	48 (10.5)	45 (19.6)
Any Serious TEAE	**171 (37.5)**	**88 (38.3)**
Grade ≥ 3	162 (35.5)	85 (37.0)
TEAEs leading to dose modifications		
Dose interruption	247 (54.2)	70 (30.4)
Dose reduction	110 (24.1)[a]	9 (3.9)
Dose discontinuation	93 (20.4)[b]	49 (21.3)

PARADIGM

Research

JAMA | Original Investigation

Panitumumab vs Bevacizumab Added to Standard First-line Chemotherapy and Overall Survival Among Patients With *RAS* Wild-type, Left-Sided Metastatic Colorectal Cancer

A Randomized Clinical Trial

Jun Watanabe, MD, PhD; Kei Muro, MD, PhD; Kohei Shitara, MD, PhD; Kentaro Yamazaki, MD, PhD; Manabu Shiozawa, MD, PhD; Hisatsugu Ohori, MD, PhD; Atsuo Takashima, MD, PhD; Mitsuru Yokota, MD, PhD; Akitaka Makiyama, MD, PhD; Naoya Akazawa, MD; Hitoshi Ojima, MD, PhD; Yasuhiro Yuasa, MD, PhD; Keisuke Miwa, MD, PhD; Hirofumi Yasui, MD, PhD; Eiji Oki, MD, PhD; Takeo Sato, MD, PhD; Takeshi Naitoh, MD, PhD; Yoshito Komatsu, MD, PhD; Takeshi Kato, MD, PhD; Masamitsu Hihara, MS; Junpei Soeda, MD, PhD; Toshihiro Misumi, PhD; Kouji Yamamoto, PhD; Kiwamu Akagi, MD, PhD; Atsushi Ochiai, MD, PhD; Hiroyuki Uetake, MD, PhD; Katsuya Tsuchihara, MD, PhD; Takayuki Yoshino, MD, PhD

- Advanced RAS WT CRC; no prior chemotherapy
- Adjuvant or neoadjuvant Oxaliplatin was excluded
- Age 20 to 79 years

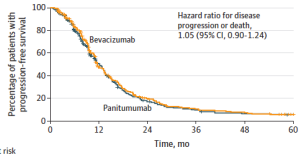
Table 1. Baseline Participant Characteristics

Characteristics	Participants with left-sided tumors[a]		Overall population		Participants with right-sided tumors[b]	
	Panitumumab plus mFOLFOX6	Bevacizumab plus mFOLFOX6	Panitumumab plus mFOLFOX6	Bevacizumab plus mFOLFOX6	Panitumumab plus mFOLFOX6	Bevacizumab plus mFOLFOX6
No. of patients[c]	312	292	400	402	84	103
Age, y						
Median (range)	65.5 (35-79)	65.5 (28-79)	66.0 (32-79)	66.0 (28-79)	68.0 (32-79)	67.0 (39-79)
No. (%)						
20-64	138 (44.2)	127 (43.5)	164 (41.0)	168 (41.8)	26 (31.0)	39 (37.9)
65-79	174 (55.8)	165 (56.5)	236 (59.0)	234 (58.2)	58 (69.0)	64 (62.1)
Sex, No. (%)						
Female	104 (33.3)	91 (31.2)	148 (37.0)	134 (33.3)	43 (51.2)	42 (40.8)
Male	208 (66.7)	201 (68.8)	252 (63.0)	268 (66.7)	41 (48.8)	61 (59.2)
ECOG performance status score, No. (%)[d]						
0 (Fully active with no performance restriction)	261 (83.7)	231 (79.1)	328 (82.0)	319 (79.4)	65 (77.4)	82 (79.6)
1 (Ambulatory but strenuous physical activity restricted)	51 (16.3)	61 (20.9)	71 (17.8)	83 (20.6)	18 (21.4)	21 (20.4)
2 (Capable of self-care but unable to carry out work activities)	0	0	1 (0.3)	0	1 (1.2)	0
Primary tumor location, No. (%)						
Left side	312 (100.0)	292 (100.0)	312 (78.0)	292 (72.6)	0	0
Right side	0	0	84 (21.0)	103 (25.6)	84 (100.0)	103 (100.0)
Both sides	0	0	4 (1.0)	7 (1.7)	0	0
No. of organs with metastasis, No. (%)						
1	155 (49.7)	147 (50.3)	196 (49.0)	194 (48.3)	40 (47.6)	44 (42.7)
≥2	157 (50.3)	145 (49.7)	204 (51.0)	208 (51.7)	44 (52.4)	59 (57.3)
Metastasis site, No. (%)						
Liver	225 (72.1)	206 (70.5)	275 (68.8)	278 (69.2)	49 (58.3)	66 (64.1)
Liver as only site of metastasis	90 (28.8)	89 (30.5)	105 (26.3)	113 (28.1)	14 (16.7)	21 (20.4)
Prior treatment, No. (%)						
Primary tumor resection	185 (59.3)	193 (66.1)	239 (59.8)	272 (67.7)	51 (60.7)	73 (70.9)
Radiotherapy	2 (0.6)	2 (0.7)	2 (0.5)	3 (0.7)	0	0
Adjuvant chemotherapy[e]	17 (5.4)	16 (5.5)	22 (5.5)	20 (5.0)	5 (6.0)	3 (2.9)

PARADIGM

Overall study population

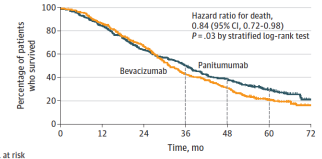
	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 400)	294 (73.5)	12.2 (10.8-13.2)
Bevacizumab plus mFOLFOX6 (n = 402)	316 (78.6)	11.4 (11.2-13.2)



No. at risk						
Panitumumab	400	147	46	23	14	9
Bevacizumab	402	153	56	27	19	6

Overall study population

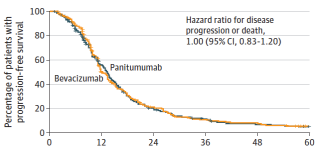
	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 400)	291 (72.8)	36.2 (32.0-39.0)
Bevacizumab plus mFOLFOX6 (n = 402)	322 (80.1)	31.3 (29.3-34.1)



No. at risk							
Panitumumab	400	338	253	199	150	80	6
Bevacizumab	402	348	265	166	119	54	5

Participants with left-sided tumors

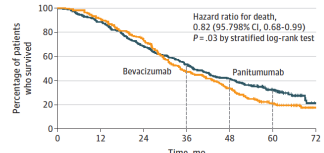
	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 312)	217 (69.6)	13.1 (11.6-14.5)
Bevacizumab plus mFOLFOX6 (n = 292)	224 (76.7)	11.9 (11.3-13.5)



No. at risk						
Panitumumab	312	123	40	21	12	7
Bevacizumab	292	115	43	22	15	5

Participants with left-sided tumors

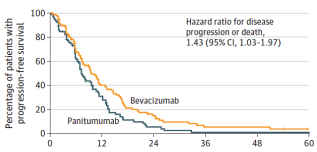
	No. (%) of patients with events	Median survival, mo (95.798% CI)
Panitumumab plus mFOLFOX6 (n = 312)	218 (69.9)	37.9 (34.1-42.6)
Bevacizumab plus mFOLFOX6 (n = 292)	230 (78.7)	34.3 (30.9-40.3)



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

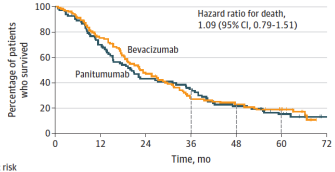
Participants with right-sided tumors

	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 84)	73 (86.9)	7.2 (6.6-9.9)
Bevacizumab plus mFOLFOX6 (n = 103)	85 (82.5)	9.4 (7.6-13.0)



No. at risk						
Panitumumab	84	21	4	1	1	1
Bevacizumab	103	35	12	4	4	1

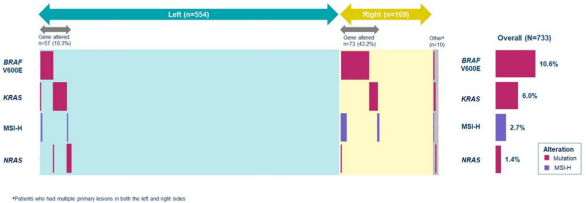
	No. (%) of patients with events	Median survival, mo (95% CI)
Panitumumab plus mFOLFOX6 (n = 84)	71 (84.5)	20.2 (15.2-32.0)
Bevacizumab plus mFOLFOX6 (n = 103)	85 (82.5)	23.2 (18.5-29.1)



lo. at risk							
Panitumumab	84	58	36	29	18	11	1
Bevacizumab	103	77	49	28	23	14	0

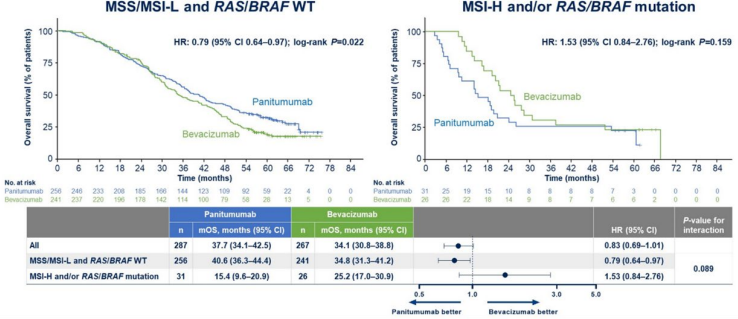
Co-occurring gene alterations by tumor sidedness

Gene alteration status, n (%)	Left-sided mCRC (n=554)	Right-sided mCRC (n=169)	Other* (n=10)	Overall (n=733)
MSI-H or *RAS*/*BRAF* mutation	57 (10.3)	73 (43.2)	5 (50%)	135 (18.4)
MSS/MSI-L and *RAS*/*BRAF* WT	497 (89.7)	96 (56.8)	5 (50%)	598 (81.6)



*Patients who had multiple primary lesions in both the left and right sides

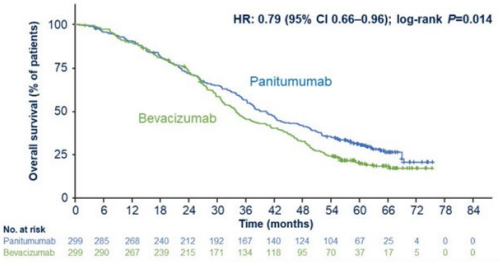
Overall survival by MSS/MSI and *RAS/BRAF* status in left-sided mCRC



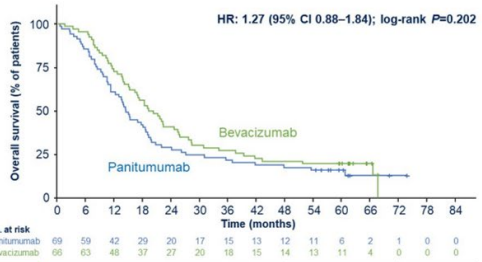
	Panitumumab		Bevacizumab			*P*-value for interaction
	n	mOS, months (95% CI)	n	mOS, months (95% CI)	HR (95% CI)	
All	287	37.7 (34.1–42.5)	267	34.1 (30.8–38.8)	0.83 (0.69–1.01)	
MSS/MSI-L and *RAS*/*BRAF* WT	256	40.6 (36.3–44.4)	241	34.8 (31.3–41.2)	0.79 (0.64–0.97)	0.089
MSI-H and/or *RAS*/*BRAF* mutation	31	15.4 (9.6–20.9)	26	25.2 (17.0–30.9)	1.53 (0.84–2.76)	

Overall survival by MSS/MSI and *RAS/BRAF* status in the overall population

MSS/MSI-L and *RAS/BRAF* WT



MSI-H and/or *RAS/BRAF* mutation

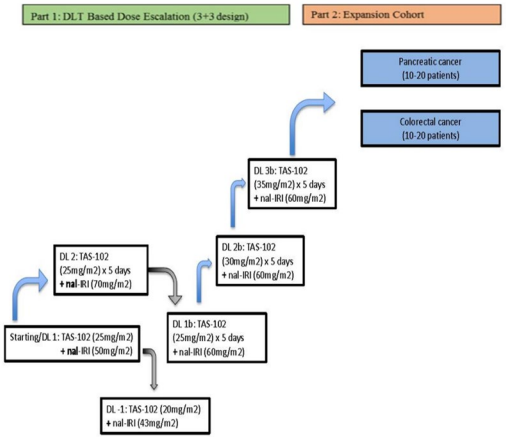


	Panitumumab		Bevacizumab		HR (95% CI)	*P*-value for interaction
	n	mOS, months (95% CI)	n	mOS, months (95% CI)		
All	368	35.6 (31.1–38.9)	365	31.6 (29.3–34.5)	0.87 (0.73–1.02)	
MSS/MSI-L and *RAS/BRAF* WT	299	39.0 (36.3–43.3)	299	34.1 (31.1–37.6)	0.79 (0.66–0.96)	0.027
MSI-H and/or *RAS/BRAF* mutation	69	14.6 (11.3–18.8)	66	19.8 (15.3–25.5)	1.27 (0.88–1.84)	

WINSHIP 4146: ONILON

Phase I/II Study of Trifluridine/Tipiracil (TAS102) + Nanoliposomal Irinotecan (NAL-IRI) in Advanced GI Cancers

- Stage IV or locally advanced unresectable GI adenocarcinomas (Gastric, Esophageal [EA], Pancreatic [PDAC], biliary tract cancer [BTC], CRC)
- Progression of disease after at least 1 prior line of therapy (including Irinotecan).
- Exclusion criteria included patients homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) or heterozygotes for UGT1A1*28 (UGT1A11 7/6 genotype)
- Trial design - standard 3+3



Drug	Frequency	Route	Treatment Period
NAL-IRI	Day 1	IV infusion	Cycle is 14-days
TAS-102	BID, Days 1-5	Oral	

Clinical trial information: NCT03368963

Sponsors: Taiho Oncology, Ipsen Biopharmaceuticals

Primary objective - RP2D of the combination therapy

WINSHIP 4146: ONILON

Table 1: Descriptive Statistics

Variable	Level	N (%) = 22
Gender	F	11 (50)
	M	11 (50)
Race	Asian	1 (4.8)
	African American	8 (38.1)
	White	12 (57.1)
	Unknown	1
Age	Median	58.5 (IQR – 18)
Median lines of prior therapy		1 (Range 1-4)
Concurrent Bevacizumab		10 (47.6)
Prior Irinotecan		3 (13.6)
Overall response rate (ORR)		15% (3 PR)
Disease Control Rate (DCR)		75%
Median PFS		9.7 months (95% CI:5.6, 14.2)
Median OS		10.1 months (95% CI: 7.3, 15.9)
6-month OS Rate		83.6% (95% CI: 57.3%, 94.4%)
12-month OS Rate		39.5% (95% CI: 15.2%, 63.3%)
Duration of progression free (for patients with SD)		7.6 months (95% CI: 5.5, NA)

Figure 1: KM curve on progression free survival

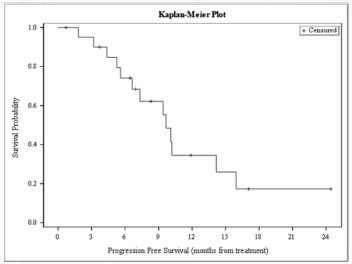
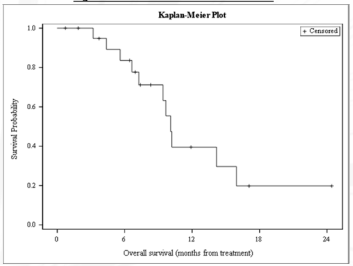
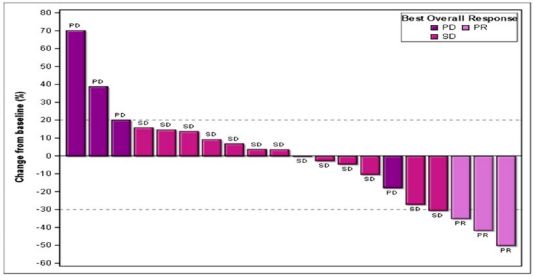


Figure 2: KM curve on overall survival





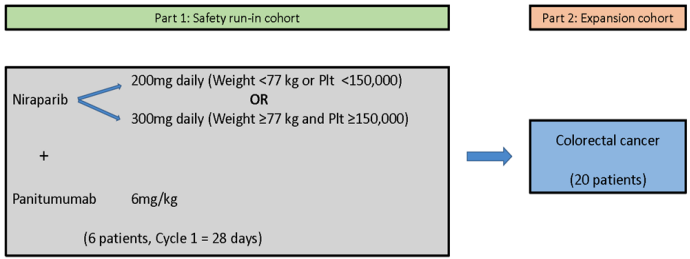
*Patients with missing response or percent tumor size change were excluded. (N= 20)

- Combination of TAS-102 and nal-IRI had an acceptable safety profile, and showed antitumor activity in patients with advanced CRC.
- Additional biomarker analyses such as survival correlation with UGT1A1 phenotype and RAS mutational status are ongoing.
- A dose expansion phase II study of this combination is currently enrolling patients with PDAC

WINSHIP 4517: NIPAVECT

Abstract ID #3579: Phase II Study of Niraparib + Panitumumab in Patients with Advanced Colorectal Cancer

- Advanced, metastatic RAS WT CRC after at least one line of systemic therapy.
- No prior therapy with PARP inhibitors or with EGFR inhibitors approved for the treatment of colorectal cancer (Cetuximab or Panitumumab)
- Measurable disease based on RECIST 1.1
- ECOG 0 or 1
- Adequate organ function



- Primary endpoint – CBR = CR +PR + SD

Secondary end points:

- Toxicity profile of the combination of Panitumumab and Niraparib.
- Efficacy endpoints: ORR, DoR, OS and PFS

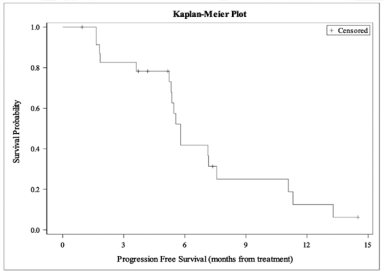
Sponsor: Winship Cancer Institute of Emory University
Registration: clinical-trials.gov: NCT03983993

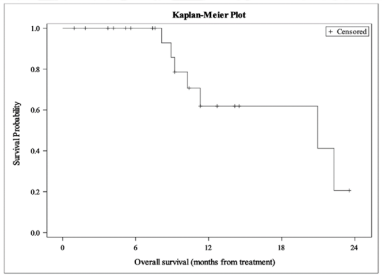
Alese OB, Diab M, Gbolahan O, et al. Journal of Clinical Oncology 41 (16_suppl), 3579-3579

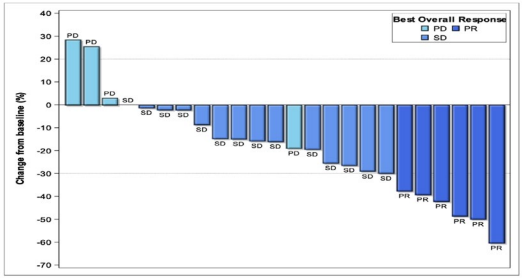
WINSHIP 4517: NIPAVECT

Table 1: Descriptive Statistics

Variable	Level	N (%) = 24
Gender	F	12 (50)
	M	12 (50)
Race	Asian	3 (13)
	African American	5 (21.7)
	White	15 (65.2)
	Unknown	1
Age	Median	58.5 (IQR – 12)
Median lines of prior therapy		2 (Range 1-4)
Tumor sidedness (Left)		22 (92)
Overall response rate (ORR)		25% (6 PR)
Clinical benefit rate (CBR)		83.3%
Median PFS		5.6months (95% CI: 3.7, 6.9)
Median OS		20.9months (95% CI: 9.2, NR)







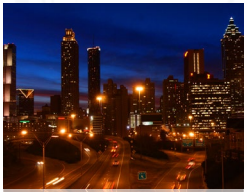
*Patients with missing response or percent tumor size change were excluded. (N= 24)

- Panitumumab + Niraparib had an acceptable safety profile, with considerable antitumor activity compared to historical rates.
- "Chemotherapy free" treatment option and a therapy platform for further drug development.
- Additional biomarker analyses such as survival correlation with Homologous recombination repair (HRR), immune cell infiltration in paired skin biopsies and HER2/BRAF mutational status are ongoing.

Alese OB, Diab M, Gbolahan O, et al. Journal of Clinical Oncology 41 (16_suppl), 3579-3579

CONCLUSION

- Advanced/Metastatic CRC represents an area of immense need for more effective treatment options
- Current efforts at targeted treatments are promising, and could improve the current treatment landscape



THANK YOU