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THE HEART OF MEDICAL EDUCATION

GI CONNECT

MEETING SUMMARY
LOWER GI CANCER HIGHLIGHTS
FROM ASCO GI 2023

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DEVELOPED BY GI CONNECT

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THIS PROGRAMME HAS BEEN DEVELOPED BY THE FOLLOWING EXPERTS

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CLINICAL TAKEAWAYS

- **SUNLIGHT trial[1]**
  - FTD/TPI plus bevacizumab improved OS and PFS in refractory CRC patients and should be considered a standard of care in the refractory treatment setting
- **Kinetics of postoperative cfDNA/ctDNA[2]**
  - Post operative ctDNA-positivity is significantly associated with shorter recurrence-free survival
  - Clinical data are insufficient at this stage to consider MRD testing as standard of care for patients with resectable CRC
- **Study of balstilimab plus botensilimab in MSS mCRC patients[3]**
  - Durable objective responses were observed in heavily pre-treated MSS CRC patients treated with balstilimab plus botensilimab. Further investigation is warranted
- **NRG-GI002[4]**
  - Neither veliparib or pembrolizumab significantly improved short-term outcomes in unselected patients when added to TNT
  - NRG-GI002 provides TNT outcome data for benchmarking in future LARC trials

CRC, colorectal cancer; cfDNA, cell-free DNA; ctDNA, circulating tumour DNA; FTD/TPI, trifluridine/tipiracil; LARC, locally advanced rectal cancer; MRD, molecular residual disease; MSS, microsatellite stable; OS, overall survival; PFS, progression free survival; TNT, total neoadjuvant therapy

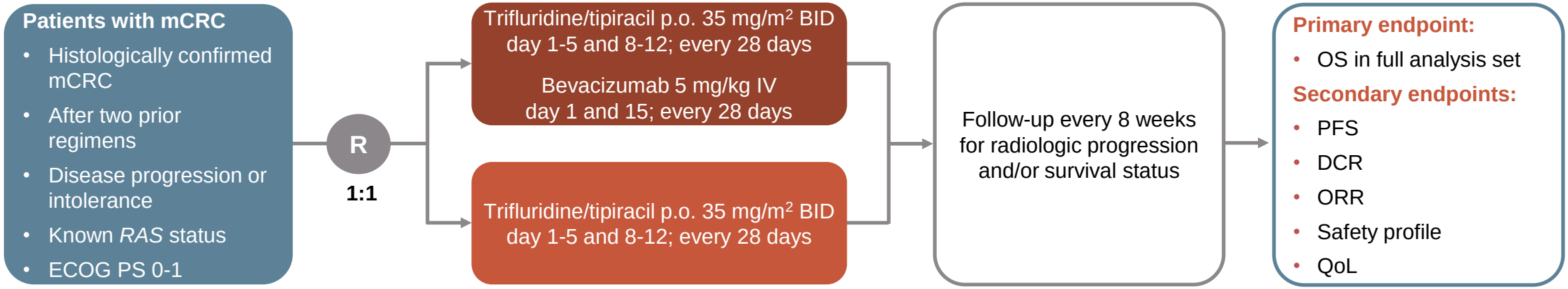
1. Tabernero J, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 4); 2. Cohen SA, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 5); 3. El-Khoueiry AB, et al. J Clin Oncol 41, 2023 (suppl 4; abstr LBA8); 4. George TJ, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 7)

TRIFLURIDINE/TIPIRACIL PLUS BEVACIZUMAB FOR THIRD-LINE TREATMENT OF REFRACTORY METASTATIC COLORECTAL CANCER: THE PHASE 3 RANDOMISED SUNLIGHT STUDY

Tabernero J, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 4)

SUNLIGHT: BACKGROUND AND STUDY DESIGN

- **Standard treatment options for refractory mCRC** (3rd/4th line) **include trifluridine/tipiracil and regorafenib** based on data from the RECOURSE and CORRECT trials[1,2]
- Recent data from the FRESCO-2 study suggests that **fruquintinib may also be a future treatment option** for these patients[3]
- **FTD/TPI plus bevacizumab improved OS and PFS** in a previous randomised phase 2 trial in heavily pre-treated mCRC patients[4]
- **SUNLIGHT** was designed to further **confirm the efficacy and safety of the combination treatment**[5]



BID, twice a day; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil; IV, intravenous; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; p.o., by mouth; QoL, quality of life; R, randomisation; RAS, RAS proto-oncogene GTPase

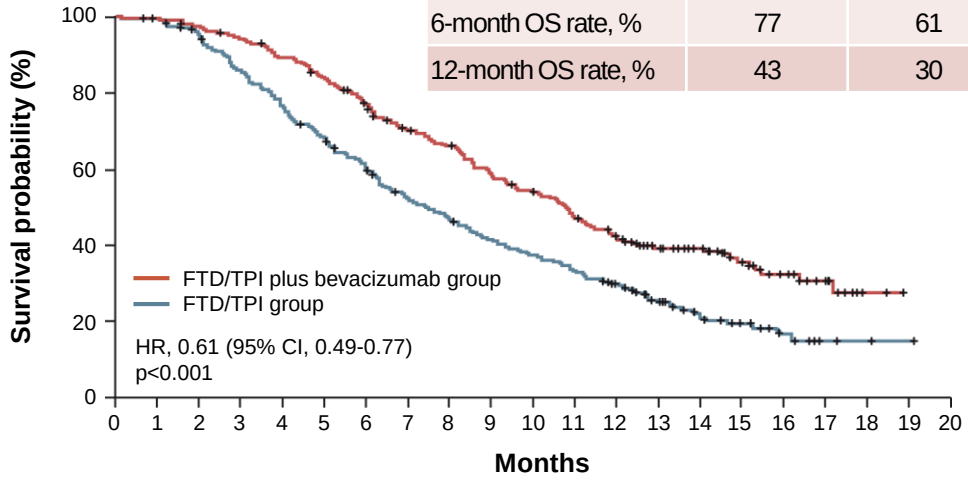
1. Mayer RJ, et al. N Engl J Med. 2015;372:1909-19; 2. Grothey A, et al. Lancet. 2013;381:303-12; 3. Dasari NA, et al. Ann Oncol. 2022; 33 (suppl_7): S808-S869 (ESMO 2022 presentation); 4. Van Custem E, et al. Ann Oncol 2020; 31 (9): 1160-1168; 5. Tabernero J, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 4) (ASCO GI 2023, oral presentation)

SUNLIGHT: EFFICACY RESULTS (FULL ANALYSIS SET)

- FTD/TPI plus bevacizumab improved OS and PFS in refractory CRC patients

OVERALL SURVIVAL (PRIMARY ENDPOINT)

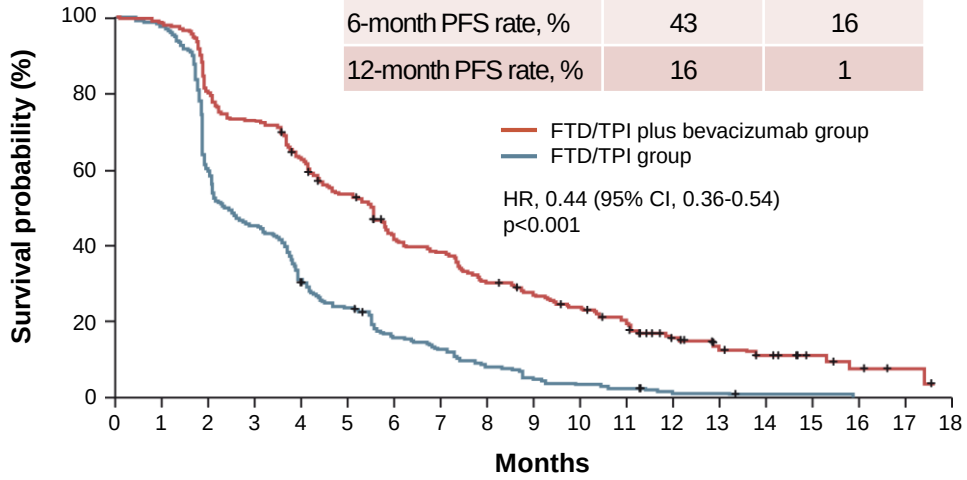
	FTD/TPI plus bevacizumab (N=246)	FTD/TPI (N=246)
Median OS, months	10.8	7.5
6-month OS rate, %	77	61
12-month OS rate, %	43	30



No. at risk																				
FTD/TPI plus bevacizumab group	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
FTD/TPI group	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

PROGRESSION-FREE SURVIVAL

	FTD/TPI plus bevacizumab (N=246)	FTD/TPI (N=246)
Median PFS, months	5.6	2.4
6-month PFS rate, %	43	16
12-month PFS rate, %	16	1



No. at risk																				
FTD/TPI plus bevacizumab group	246	242	198	179	153	128	99	89	70	61	52	43	25	18	13	7	4	2	0
FTD/TPI group	246	236	147	109	74	56	36	29	19	12	8	6	2	2	1	1	0	0	0

CI, confidence interval; CRC, colorectal cancer; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival; PFS, progression free survival

Tabernero J, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 4) (ASCO GI 2023, oral presentation)

SUNLIGHT: SAFETY RESULTS

OVERALL SAFETY

Event (any cause), n (%)	FTD/TPI plus bevacizumab (N=246)	FTD/TPI (N=246)
Overall AEs	241 (98)	241 (98)
FTD/TPI-related AEs	221 (90)	200 (81)
Bevacizumab-related AEs	119 (48)	NA
Severe (grade ≥3) AEs	178 (72)	171 (70)
Serious AEs	61 (25)	77 (31)
Treatment-related deaths	0	0
AEs leading to withdrawal from the study	31 (13)	31 (13)

Dose modification, n (%)	FTD/TPI plus bevacizumab (N=246)	FTD/TPI (N=246)
Dose reductions	40 (16)	30 (12)
Dose delays	171 (70)	131 (53)

TEAEs IN ≥20% OF ALL PATIENTS

TEAE, n (%)	FTD/TPI plus bevacizumab (N=246)		FTD/TPI (N=246)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	153 (62)	106 (43)	126 (51)	79 (32)
Nausea	91 (37)	4 (2)	67 (27)	4 (2)
Anemia	71 (29)	15 (6)	78 (32)	27 (11)
Asthenia	60 (24)	10 (4)	55 (22)	10 (4)
Fatigue	53 (22)	3 (1)	40 (16)	9 (4)
Diarrhea	51 (21)	2 (1)	46 (19)	6 (2)
Decreased appetite	50 (20)	2 (1)	38 (15)	3 (1)

- Hypertension (10% vs 2%), nausea and neutropenia occurred more frequently in the combination group
  - One case of febrile neutropenia with FTD/TPI plus bevacizumab versus six with FTD/TPI

AE, adverse event; FTD/TPI, trifluridine/tipiracil; TEAE, treatment emergent AE

Tabernero J, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 4) (ASCO GI 2023, oral presentation)

SUNLIGHT: SUMMARY

- FTD/TPI plus bevacizumab improved OS and PFS in refractory CRC patients
- Improvements in survival occurred in all clinically relevant subgroups
- The safety profile was manageable and consistent with the individual safety profiles of FTD/TPI and bevacizumab

Clinical Takeaway

- **SUNLIGHT results indicate that FTD/TPI plus bevacizumab should be considered a standard of care in the refractory treatment setting**
- **There was a modest increase in toxicities and financial cost, but this comes with significant improvements in mPFS and mOS**

CRC, colorectal cancer; FTD/TPI, trifluridine/tipiracil; (m)OS, median overall survival; (m)PFS, median progression-free survival

Tabernero J, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 4) (ASCO GI 2023, oral presentation); Deming D, Discussant of abstract 4 (ASCO GI 2023)

KINETICS OF POSTOPERATIVE CIRCULATING CELL-FREE DNA AND IMPACT ON MRD DETECTION RATES IN PATIENTS WITH RESECTED STAGE I-III CRC

Cohen SA, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 5)

CRC, colorectal cancer; MRD, minimal residual detection

BACKGROUND AND STUDY DESIGN

BACKGROUND

- **Circulating tumour DNA** (ctDNA) has emerged as **a useful biomarker for detecting molecular residual disease (MRD) in colorectal cancer (CRC)**[1,2]
- **High levels of cell-free DNA** (cfDNA) from normal tissue **may limit the detection of tumour-derived ctDNA** in certain clinical scenarios (immediately after surgery or during adjuvant therapy)[3]
- The optimal timing of blood collection for reliable MRD detection after surgery or adjuvant therapy needs to be determined

STUDY DESIGN

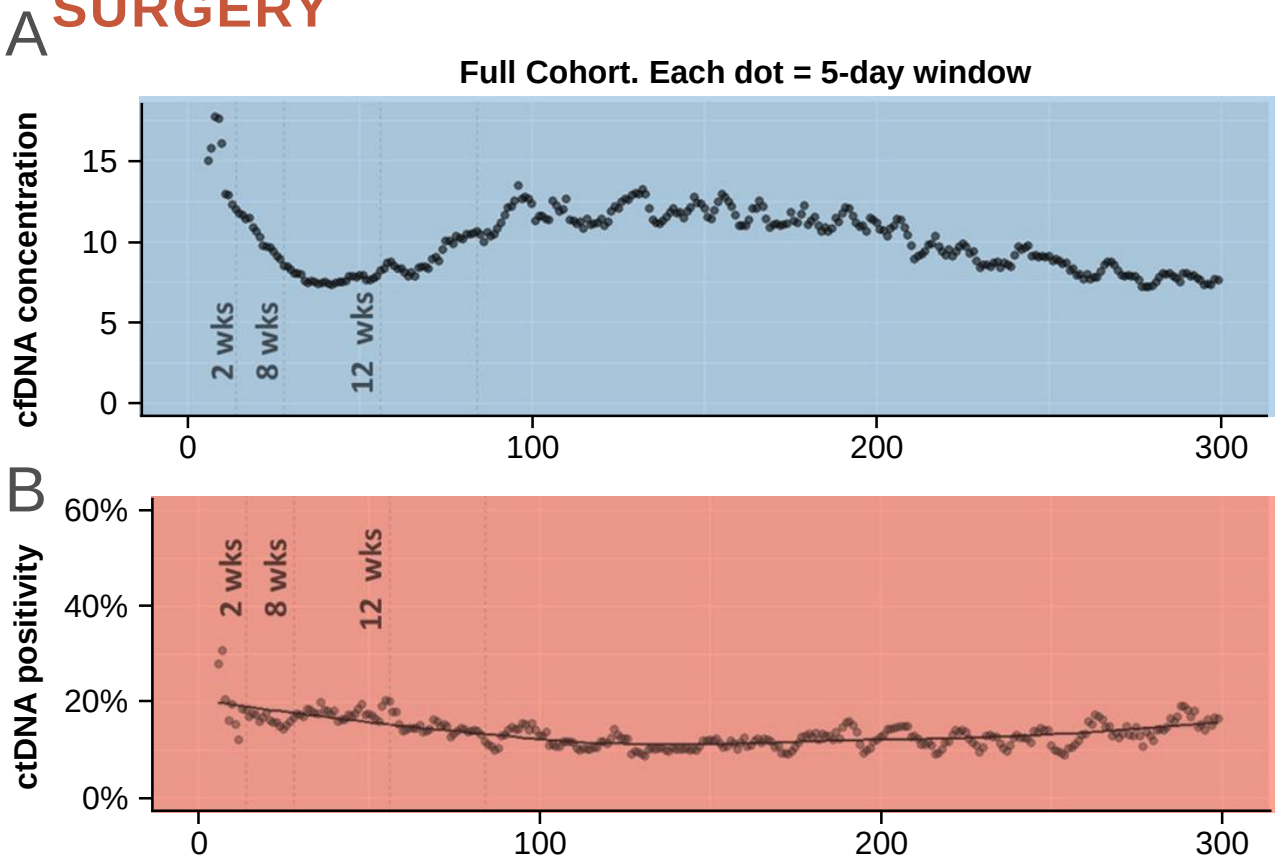
- A **retrospective, US-based, multi-institutional study** where data from commercial ctDNA testing in 16,347 patients with stage I-III CRC were analysed
  - Complete clinical data were available for 417 patients with 2,538 plasma samples collected between 6/2019 and 4/2022
  - Median follow-up for relapsed and non-relapsed patients was 730 and 615 days, respectively
  - A NGS assay (Signatera) was used to quantify ctDNA prior to surgery and postoperatively
  - **The kinetics of total cfDNA was analysed and compared with the ctDNA MRD positivity rates** at various time points after surgery

NGS, next generation sequencing; US, United States

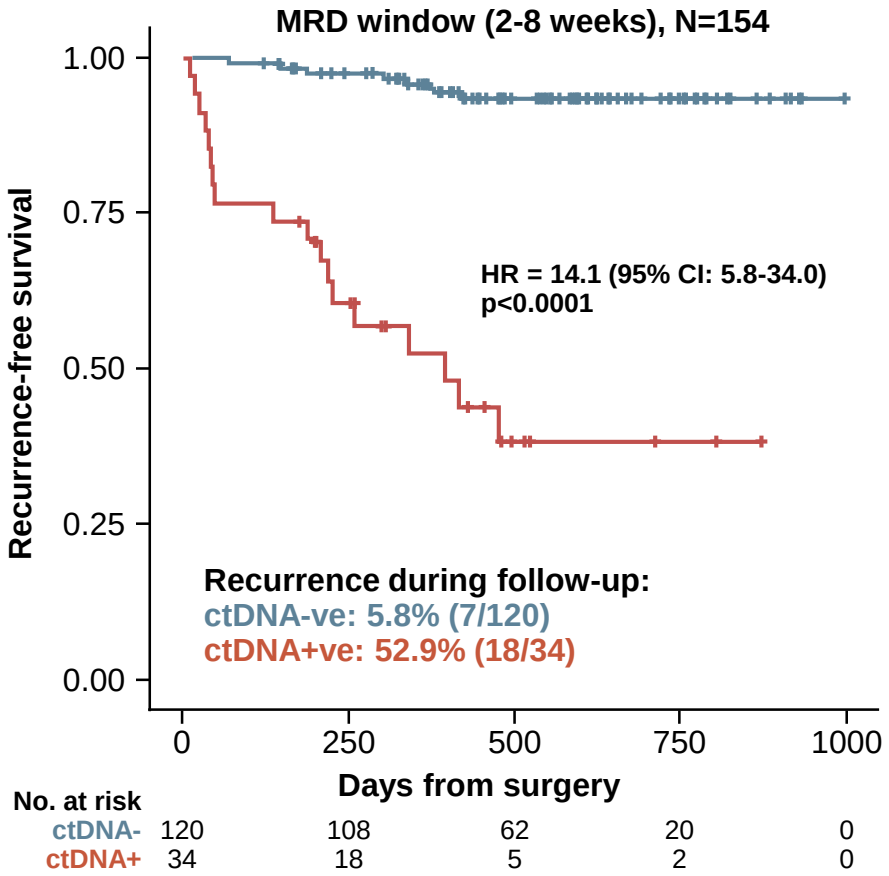
1. Kotani D, et al. Nature Med. 2023;29:127-34; 2. Malla M, et al. J Clin Oncol. 2022;40:2846-57; 3. Henriksen TV, et al. Mol Oncol. 2020;14:1670-9; 4. Cohen SA, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 5) (ASCO GI 2023, oral presentation)

RESULTS

cfDNA (A) CONCENTRATION AND ctDNA POSITIVITY (B) OVER TIME POST-SURGERY



RECURRENCE-FREE SURVIVAL BY ctDNA STATUS



cfDNA, cell-free DNA, CI, confidence interval; ctDNA, circulating tumour DNA; HR, hazard ratio; MRD, molecular residual disease

Cohen SA, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 5) (ASCO GI 2023, oral presentation)

SUMMARY

- cfDNA concentration is significantly increased in first 2 weeks post surgery
- Higher cfDNA levels did not impact ctDNA detection
- High ctDNA positivity in the first week after surgery
- Standard MRD testing windows could start as early as 2 weeks after surgery (Day 15+)
- Testing for MRD between weeks 2-4 showed similar sensitivity as weeks 4-8
- Post operative ctDNA-positivity is significantly associated with shorter recurrence-free survival

cfDNA, cell-free DNA; CRC, colorectal cancer; ctDNA, circulating tumour DNA; MRD, minimal residual disease

Cohen SA, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 5) (ASCO GI 2023, oral presentation)

SUMMARY

CLINICAL TAKEAWAY

- Levels of cfDNA in plasma do not significantly affect ctDNA detection
- Standard testing window for MRD could start as early as 15 days postoperatively
- MRD testing via ctDNA is not standard of care for CRC
- The study provides the first stage III data and builds on the DYNAMIC trial results which demonstrated that a ctDNA-guided approach to the treatment of stage II colon cancer reduced adjuvant chemotherapy use without compromising recurrence-free survival
- At this stage, ctDNA is an interesting biomarker but further studies required before it can be used to guide treatment decisions

cfDNA, cell-free DNA; CRC, colorectal cancer; ctDNA, circulating tumour DNA; MRD, minimal residual disease

Cohen SA, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 5) (ASCO GI 2023, oral presentation); Deming D. Discussant of abstract 5 (ASCO GI 2023); Tie J, et al. N Engl J Med 2022; 386: 2261-2272

RESULTS FROM A PHASE 1A/1B STUDY OF BOT, A NOVEL INNATE/ADAPTIVE IMMUNE ACTIVATOR, PLUS BAL (ANTI-PD-1 ANTIBODY) IN METASTATIC HEAVILY PRE-TREATED MSS CRC

El-Khoueiry AB, et al. J Clin Oncol 41, 2023 (suppl 4; abstr LBA8)

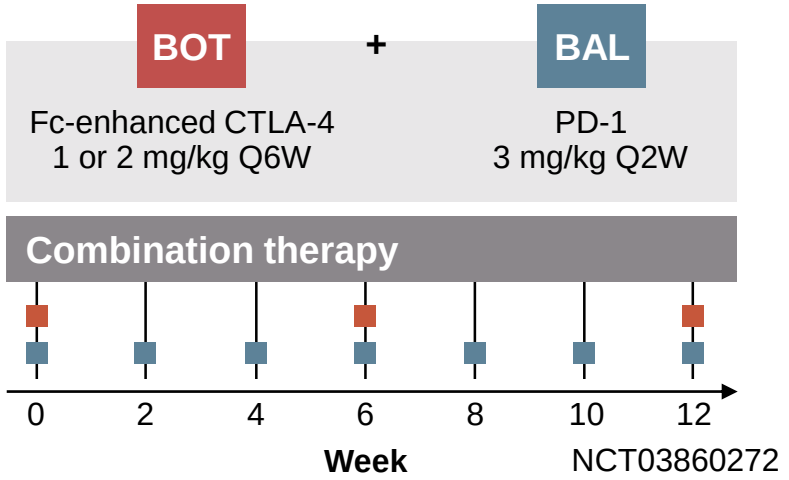
BAL, balstilimab; BOT, botensilimab; CRC, colorectal cancer; MSS, microsatellite stable; PD-1; programmed cell death protein 1

BACKGROUND AND STUDY DESIGN

- Botensilimab is an Fc-enhanced CTLA-4 inhibitor which is active in 'cold' and IO refractory tumours[1,2]
- Balstilimab is a PD-1 inhibitor with safety and efficacy analogous to approved anti-PD-1 mAbs[3,4]
- Results are presented for an expanded phase 1a/1b study of BOT plus BAL in MSS CRC patients[5]

Key eligibility for CRC:
- Refractory metastatic CRC
- MSS by local assessment
- Prior IO allowed
- Tbili ≤1.5 × IULN
- AST/ALT ≤2.5 × IULN

Evaluable population:
Treated with 1 or 2 mg/kg bot + bal as of 29 August 2022 with ≥1 Q6W imaging assessment



ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAL, balstilimab; BOT, botensilimab; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IO, immuno-oncology; IULN, institutional upper limit of normal; mAbs, monoclonal antibodies; MSS, microsatellite stable; PD-1; programmed cell death protein 1; Q'X'W, every 'X' weeks; Tbili, bilirubin test

1. El-Khoueiry AB. SITC 2021 Annual meeting. Poster #479; 2. Wilky B, SITC 2022 Annual Meeting. Oral #778; 3. O'Malley et al. Gynecol. Oncol. 2021;163:274-80; 4. O'Malley et al. J Clin Oncol 2022;40(7):762-71; 5. El-Khoueiry AB, et al. J Clin Oncol 41, 2023 (suppl 4; abstr LBA8) (ASCO GI 2023, oral presentation)

RESULTS

BASELINE DATA

- Median age: 57 years (25–83), 57% female
- Median prior lines of therapy: 4
- 31% had received prior immunotherapy

EFFICACY

Efficacy	N=70
ORR, % (95% CI)	23 (14-34)
BOR, n (%)	
CR	1 (1)
PR	15 (21)
SD	37 (53)
DCR (CR + PR + SD), % (95% CI)	76 (64-85)
Median OS, months (95% CI)	NR (10.3-NR)
Median PFS, months (95% CI)	4.1 (2.8-5.5)
Median F/U, months (min, max)	7 (2, 31)

ANY GRADE TRAEs IN ≥15% OF ALL PATIENTS

N (%)	All Grade	Grade 3	Grade 4
Any TRAE	64 (91)	28 (40)	2 (3)
Gastrointestinal			
IM diarrhea/colitis[a]	30 (43)	14 (20)	1 (1)
Nausea	16 (23)	1 (1)	0
Constitutional			
Fatigue	24 (34)	3 (4)	0
Decreased appetite	19 (27)	0	0
Chills	15 (21)	0	0
Pyrexia	16 (23)	3 (4)	0

N (%)	All Grade	Grade 3	Grade 4
Skin			
Rash	19 (27)	0	0
Pruritus	12 (17)	0	0
Endocrine			
Hypo/hyperthyroidism	11 (16)	0	0

[a]immune-mediated diarrhoea/colitis defined as patients who received steroids or infliximab

BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; F/U, follow-up; NR, not reached; ORR, objective response rate; PFS, progression free survival; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event

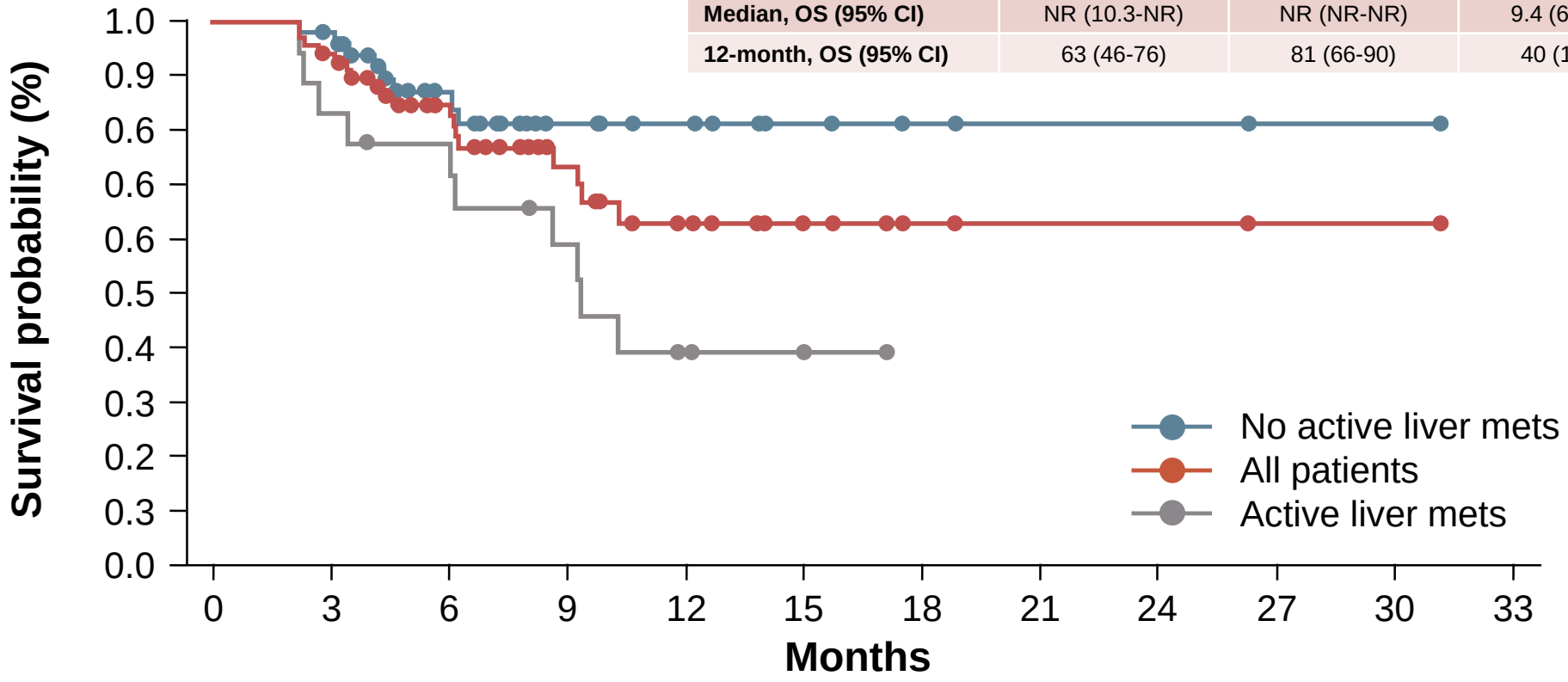
El-Khoueiry AB, et al. J Clin Oncol 41, 2023 (suppl 4; abstr LBA8) (ASCO GI 2023, oral presentation)

RESULTS

OVERALL SURVIVAL

Efficacy evaluable population, N=70

	Overall	No active liver mets	Active liver mets
Median, OS (95% CI)	NR (10.3-NR)	NR (NR-NR)	9.4 (6.1-NR)
12-month, OS (95% CI)	63 (46-76)	81 (66-90)	40 (17-62)



CI, confidence interval; NR, not reached; OS, overall survival

El-Khoueiry AB, et al. J Clin Oncol 41, 2023 (suppl 4; abstr LBA8) (ASCO GI 2023, oral presentation)

SUMMARY

- Durable objective responses were observed in heavily pre-treated MSS CRC patients treated with BOT plus BAL
- The combination treatment was well tolerated with no new immune-mediated safety signals
- All objective responses and a better overall survival were observed to patients w/o active liver metastases
- A global phase 2 trial is ongoing investigating BOT as monotherapy and in combination with BAL or standard of care in patients with MSS CRC (NCT05608044)

Clinical Takeaway

- **Interesting early data for the first human trial of botensilimab plus balstilimab in patients with advanced MSS CRC. Further investigation is warranted.**

BAL, balstilimab; BOT, botensilimab; CRC, colorectal cancer; MSS, microsatellite stable; w/o, without

El-Khoueiry AB, et al. J Clin Oncol 41, 2023 (suppl 4; abstr LBA8) (ASCO GI 2023, oral presentation)

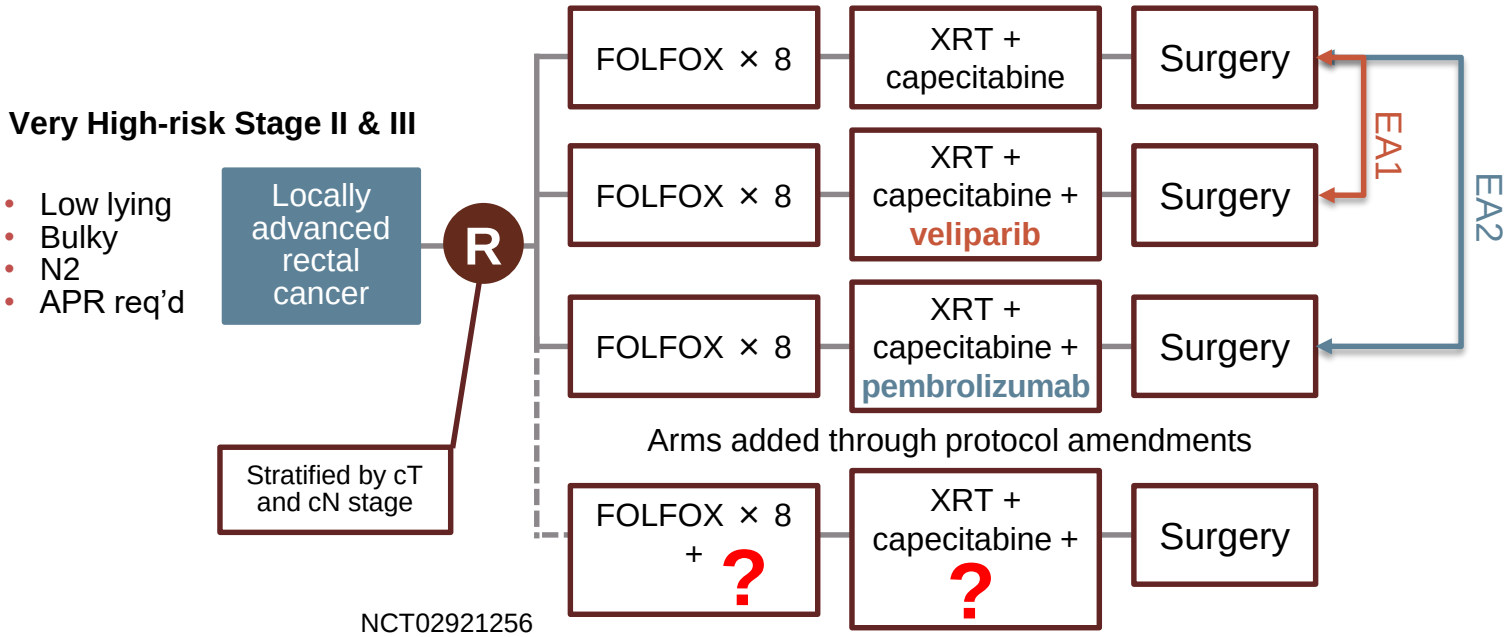
LONG-TERM RESULTS FROM NRG-GI002: A PHASE 2 CLINICAL TRIAL PLATFORM USING TNT IN LARC

George TJ, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 7)

LARC, locally advanced rectal cancer; TNT, total neoadjuvant therapy

NRG-GI002: BACKGROUND AND STUDY DESIGN

- Total neoadjuvant therapy (TNT) is a therapeutic strategy that incorporates chemotherapy with chemoradiotherapy antecedent to surgery
- The NRG-GI002 nested, randomised, phase 2 study was designed to rapidly seek activity signals for new agents in TNT
- Long-term outcomes of all patients enrolled in the NRG-GI002 study are presented



- ***EA1 hypothesis:*** PARPi can enhance RT-induced synthetic lethality
- ***EA2 hypothesis:*** RT can enhance anti-tumour immunogenicity via release of neoantigens and immunogenic cell surface marker upregulation

Primary endpoint:

- Neoadjuvant rectal score (NAR)

Key secondary endpoints:

- pCR
- cCR rates
- OS
- DFS
- Toxicity

APR, Abdominoperineal resection; cCR, clinical complete response; cT, clinical T stage; DFS, disease-free survival; EA, experimental arms; FOLFOX, folinic acid, fluorouracil and oxaliplatin; N, evaluation of regional lymph nodes; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; pCR, pathological complete response; RT, radiation; XRT, radiotherapy

George TJ, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 7) (ASCO GI 2023, oral presentation)

NRG-GI002: RESULTS

PATIENT TUMOUR CHARACTERISTICS

Patient tumour characteristics, %	EA1	EA2
Distal	65	72
Bulky	58	62
N2	43	39
Not SSS candidate	50	46
T4	29	22

EFFICACY RESULTS

First comparison (EA1) – Median follow-up: EA1 = 3.5 yrs

Outcome	Control (N=88)	Veliparib (N=90)	Stat	p value (*Log rank)
NAR score	Mean 12.5 95% CI (9.7, 15.2)	Mean 13.3 95% CI (10.1, 16.5)	Mean diff -0.8 (95% CI (-5.0, 3.3)	0.81
3 yr DFS	67% 29 events	60% 38 events	HR=1.36 95% CI (0.83, 2.25)	0.23*
3 yr OS	92% 7 deaths	85% 14 deaths	HR=2.13 95% CI (0.86, 5.29)	0.10*

Addition secondary endpoints (control vs veliparib)
pCR: 21.6 vs 33.8%
cCR: 28.2 vs 33.3%
SSS: 52.5 vs 59.3%

Second comparison (EA2) – Median follow-up: EA2 = 3.15 yrs

Outcome	Control (N=95)	Pembrolizumab (N=90)	Stat	p value (*Log rank)
NAR score	Mean 14.4 95% CI (11.1, 17.7)	Mean 11.5 95% CI (8.5, 14.5)	Mean diff 2.9 95% CI (-1.6, 7.3)	0.21
3 yr DFS	64% 33 events	64% 31 events	HR=0.95 95% CI (0.58, 1.55)	0.82*
3 yr OS	87% 13 deaths	95% 6 deaths	HR=0.35 95% CI (0.12, 1.00)	0.04*

Addition secondary endpoints (control vs veliparib)
pCR: 29.4 vs 31.9%
cCR: 13.6 vs 13.9%
SSS: 71.0 vs 59.4%

cCR, clinical complete response; CI, confidence interval; DFS, disease free survival; EA1/2, experimental arm 1/2; HR, hazard ratio; N, evaluation of regional lymph nodes; NAR, neoadjuvant rectal; OS, overall survival; pCR, pathological complete response; SSS, sphincter-sparing surgery; T, T stage; TNT, total neoadjuvant therapy; yr/s, year/s

George TJ, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 7) (ASCO GI 2023, oral presentation)

NRG-GI002: SUMMARY

- Neither veliparib or pembrolizumab significantly improved short-term outcomes in unselected patients when added to TNT
- Pembrolizumab improved 3-year OS despite no significant improvement in NAR score or DFS

Clinical Takeaway

- **The NRG-GI002 provides TNT outcome data for benchmarking in future LARC trials**
- **Further work is ongoing to identify subgroups that might benefit from these targeted treatments**

DFS, disease-free survival; LARC, locally advanced rectal cancer; NAR, neoadjuvant rectal; OS, overall survival; TNT, total neoadjuvant therapy

George TJ, et al. J Clin Oncol 41, 2023 (suppl 4; abstr 7) (ASCO GI 2023, oral presentation)

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