Primary analysis of MOUNTAINEER: A phase 2 study of tucatinib and trastuzumab for HER2-positive mCRC

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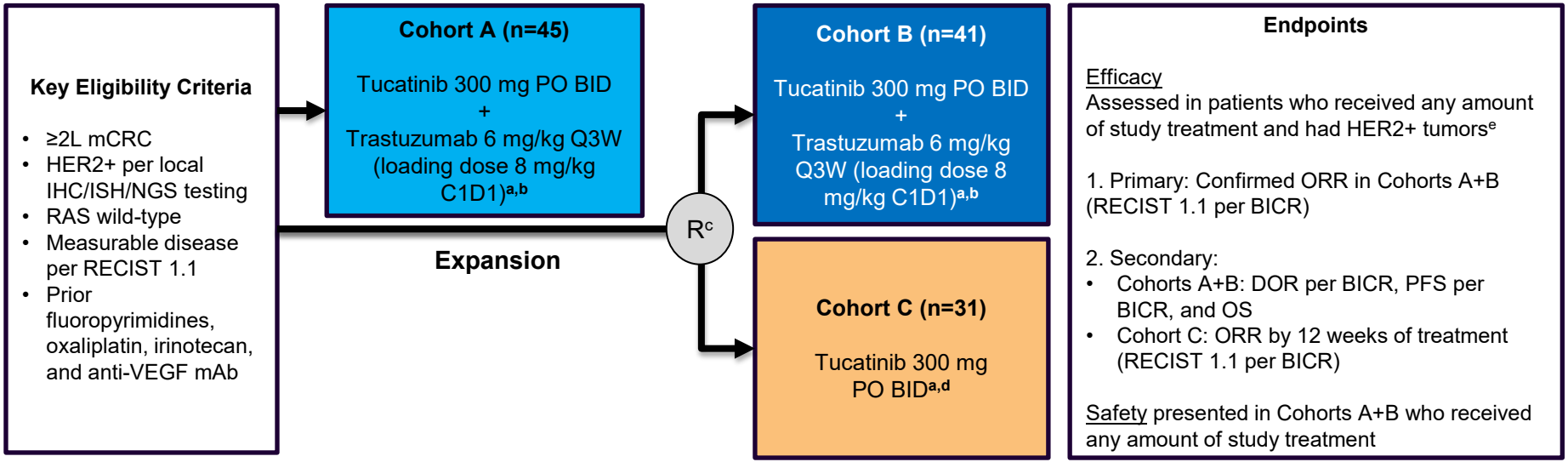
Background

- HER2 amplification/overexpression (HER2+) occurs in ~3%–5% of all patients with mCRC and ~10% of patients with RAS/BRAF wild-type mCRC[1-5]
- Patients with HER2+ mCRC who progress on early lines of chemotherapy regimens receive limited clinical benefit from current standard-of-care treatments[1]
- Tucatinib is a highly selective TKI for HER2 with minimal inhibitory effect on EGFR[3]
  - In patient-derived xenograft models of HER2+ mCRC, tucatinib + trastuzumab showed significantly greater antitumor activity compared with either agent alone
- The MOUNTAINEER trial (NCT03043313) evaluates the efficacy and safety of the investigational combination of tucatinib with trastuzumab in patients with HER2+ and RAS wild-type mCRC[6]

BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; RAS, rat sarcoma virus; TKI, tyrosine kinase inhibitor.

1. Benson et al. J Natl Compr Canc Netw. 2021;19(3):329. 2. Kang et al. J Manag Care Spec Pharm. 2021;S20. 3. Kulukian et al. Mol Cancer Ther. 2020;19:976. 4. Patel et al. J Pers Med. 2019;9. 5. Sartore-Bianchi et al. Oncologist. 2019;24:1395. 6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03043313. Accessed Jun 1, 2022.

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

Patient Disposition

Disposition, n (%)		Tucatinib + Trastuzumab Cohorts A+B n=86	Tucatinib Monotherapy Cohort C n=31
Patients enrolled or randomised[a]		86 (100)	31 (100)
Patients who received at least one dose of study treatment		86 (100)	30 (96.8)
Patients on treatment		19 (22.1)	11[b] (35.5)
Patients off treatment		67 (77.9)	19 (61.3)
Reason for treatment discontinuation	Progressive disease	59 (68.6)	18 (58.1)
	AE	3 (3.5)	1 (3.2)
	Investigator decision	1 (1.2)	0
	Patient decision, non-AE	4 (4.7)	0

Data cutoff: 28 Mar 2022
Median overall study follow-up (IQR): 16.3 months (10.8, 28.2)

a Includes enrolled patients from Cohort A and randomised patients from Cohort B and Cohort C; b All 11 patients in Cohort C who remain on treatment at the time of data cut off have crossed over to receive tucatinib + trastuzumab
AE, adverse event; IQR, interquartile range.

Key Baseline Patient Characteristics

Characteristics, n (%)		Tucatinib + Trastuzumab Cohorts A+B n=84[a]	Tucatinib Monotherapy Cohort C n=30[b]
Median age, years (range)		55.0 (24, 77)	59.5 (29, 75)
Sex	Male	51 (60.7)	15 (50.0)
	Female	33 (39.3)	15 (50.0)
ECOG Performance Status	0	50 (59.5)	17 (56.7)
	1	31 (36.9)	13 (43.3)
	2	3 (3.6)	0
Primary tumor site	Left colon and rectum	71 (84.5)	27 (90.0)
	All other primaries	13 (15.5)	3 (10.0)
	Transverse colon	7 (8.3)	0
	Right colon	5 (6.0)	3 (10.0)
	Multiple/overlapping sites	1 (1.2)	0
Stage IV at initial diagnosis		50 (59.5)	19 (63.3)
Patients with liver metastases at study entry		54 (64.3)	15 (50.0)
Patients with lung metastases at study entry		59 (70.2)	20 (66.7)

a Two patients did not have HER2+ disease as specified per protocol and were excluded; b One patient discontinued before receiving treatment

ECOG, Eastern Cooperative Oncology Group.

Summary of Prior Systemic Anticancer Therapies

Prior Systemic Therapies		Tucatinib + Trastuzumab Cohorts A+B n=84	Tucatinib Monotherapy Cohort C n=30
Prior lines of systemic therapy in any setting, median (range)[a]		3.0 (1, 6)	2.0 (1, 5)
Prior lines of systemic therapy in metastatic or recurrent setting, n (%)	1 line	19 (22.6)	5 (16.7)
	2 lines	32 (38.1)	16 (53.3)
	3+ lines	33 (39.3)	9 (30.0)
Prior systemic therapies in any setting, n (%)	Fluoropyrimidine	84 (100)	30 (100)
	Oxaliplatin	84 (100)	30 (100)
	Irinotecan	83 (98.8)	30 (100)
	Anti-VEGF antibody	72 (85.7)	26 (86.7)
	EGFR antibody	44 (52.4)	17 (56.7)
	Trifluridine and tipiracil	7 (8.3)	1 (3.3)
	Other[b]	6 (7.1)	4 (13.3)
	Regorafenib	1 (1.2)	1 (3.3)

a Lines used in adjuvant/neoadjuvant setting are counted as 1 line; b Includes anti-PD-(L)1 antibody, anti-CTLA-4 antibody, and investigational drugs

CTLA-4, cytotoxic T-lymphocyte associated protein 4; EGFR, epidermal growth factor receptor; PD-(L)1, programmed cell death-1/programmed death ligand-1; VEGF, vascular endothelial growth factor.

Tucatinib + Trastuzumab: Efficacy Outcomes

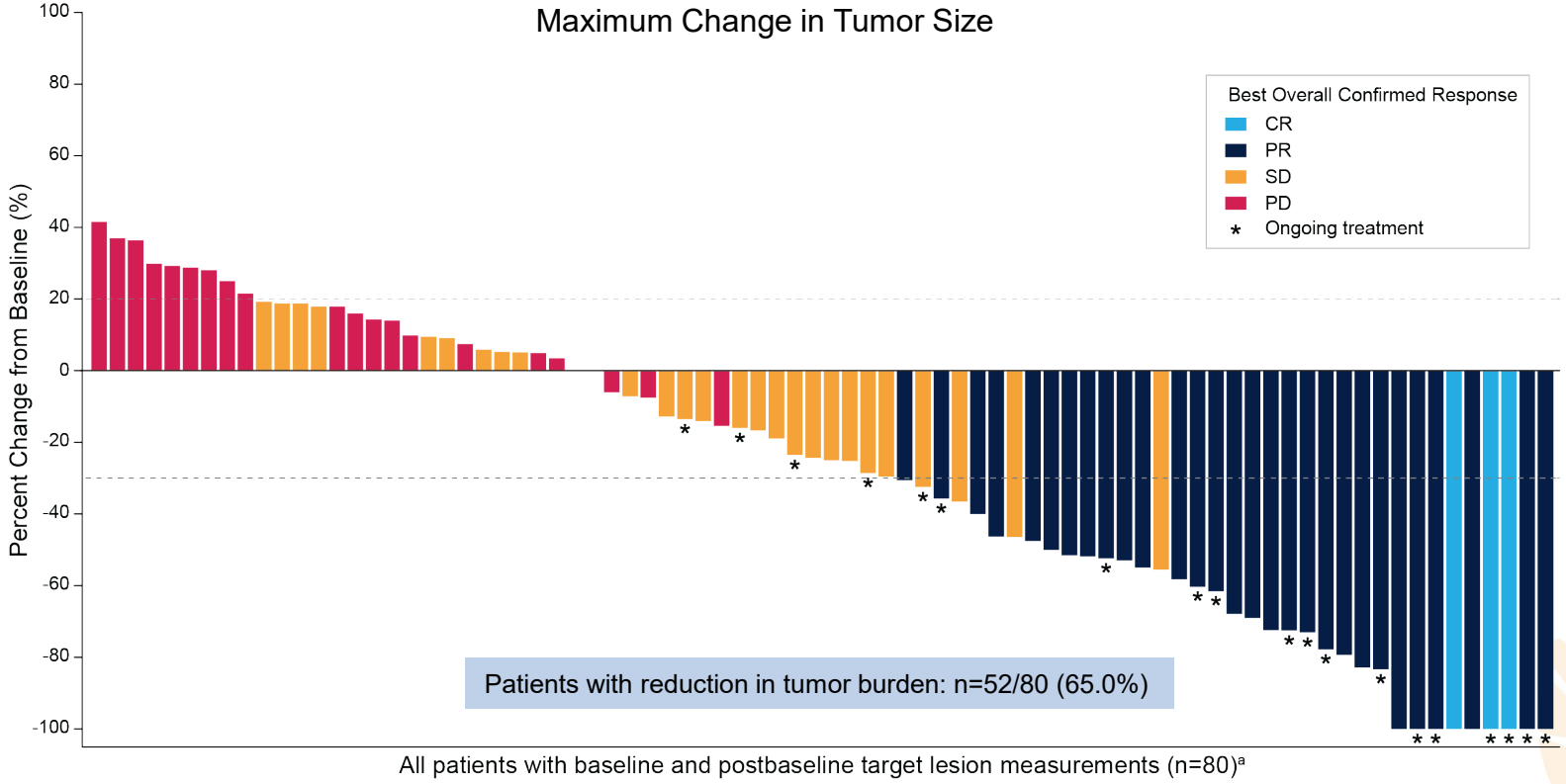
Responses	Tucatinib + Trastuzumab Cohorts A+B n=84
Best overall response per BICR[a], n (%)	
CR	3 (3.6)
PR	29 (34.5)
SD[b]	28 (33.3)
PD	22 (26.2)
Not available[c]	2 (2.4)
cORR per BICR, % (95% CI)[d]	**38.1 (27.7, 49.3)**
cORR per Investigator, % (95% CI)[d]	42.9 (32.1, 54.1)
Median time to objective response per BICR[e], months (range)	2.1 (1.2, 9.8)
DCR[f] per BICR, n (%)	60 (71.4)
Median DOR per BICR, months (95% CI)	**12.4 (8.5, 20.5)**

a Confirmed best overall response assessed per RECIST 1.1; b Includes SD and non-CR/non-PD; c Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable; d Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); e Time from the start of study treatment (Cohort A) or date of randomisation (Cohort B) to the first documentation of objective response (CR or PR that is subsequently confirmed); f Defined as sum of CR, PR, and SD

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Data cutoff: 28 Mar 2022

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

Tucatinib + Trastuzumab: cORR per BICR in Prespecified Subgroups

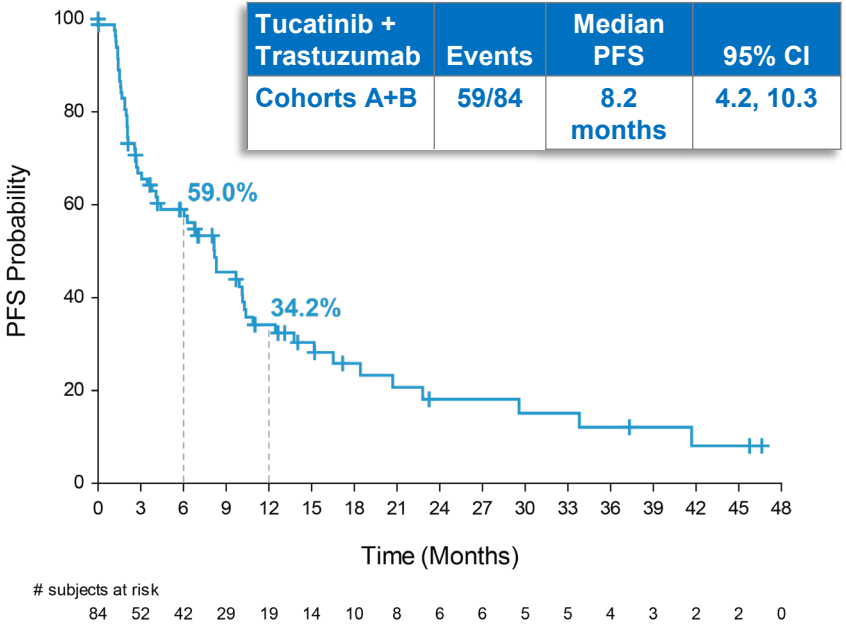
Subgroups	cORR, %	[95% CI]
Overall (n=84)	**38.1**	**[27.7, 49.3]**
Age		
<65 years (n=72)	36.1	[25.1, 48.3]
≥65 years (n=12)	50.0	[21.1, 78.9]
ECOG performance score at baseline		
0 (n=50)	44.0	[30.0, 58.7]
1–2 (n=34)	29.4	[15.1, 47.5]
Primary site of disease		
Left sided primary (n=71)	42.3	[30.6, 54.6]
All other primaries (n=13)	15.4	[1.9, 45.4]
Geographic region		
North America (n=69)	39.1	[27.6, 51.6]
Europe (n=15)	33.3	[11.8, 61.6]

BICR, blinded independent central review; cORR, confirmed objective response rate; ECOG, Eastern Cooperative Oncology Group.
Data cutoff: 28 Mar 2022

Tucatinib + Trastuzumab: PFS and OS

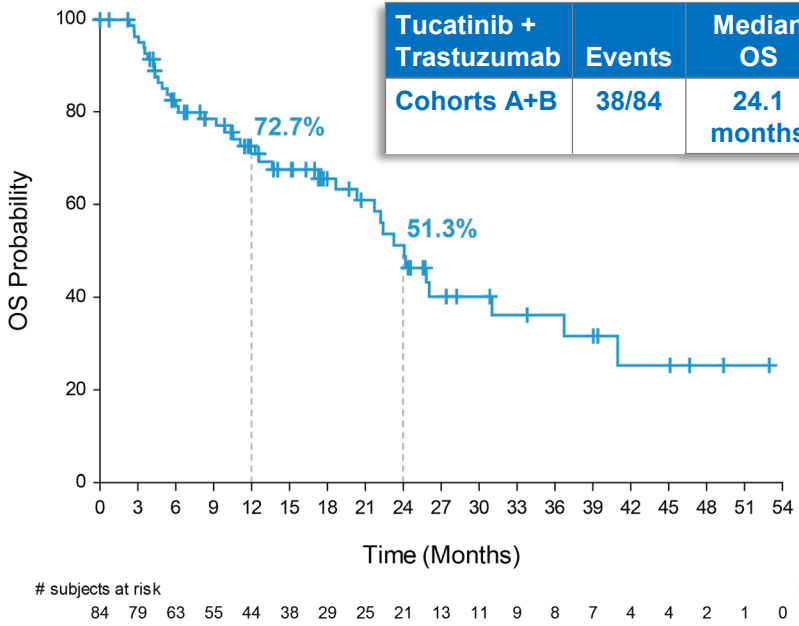
Progression-free Survival per BICR

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

Tucatinib Monotherapy: ORR by 12 Weeks of Treatment

Responses	Tucatinib Monotherapy Cohort C (n=30)
Best Overall Response per BICR[a], n (%)	
CR	0
PR	1 (3.3)
SD	23 (76.7)
PD	4 (13.3)
Not available[b]	2 (6.7)
ORR per BICR, % (95% CI)[c]	**3.3 (0.1, 17.2)**
ORR per Investigator, % (95% CI)[c]	3.3 (0.1, 17.2)
DCR[d] per BICR	24 (80.0)

a Best overall response assessed per RECIST 1.1 by 12 weeks of treatment or before start of cross-over if the patient crosses over earlier than 12 weeks. No confirmation needed; b Includes patients with no post-baseline response assessment and patients whose disease assessment are not evaluable; c Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); d Defined as sum of CR, PR, and SD

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Data cutoff: 28 Mar 2022

Tucatinib + Trastuzumab: Safety Summary

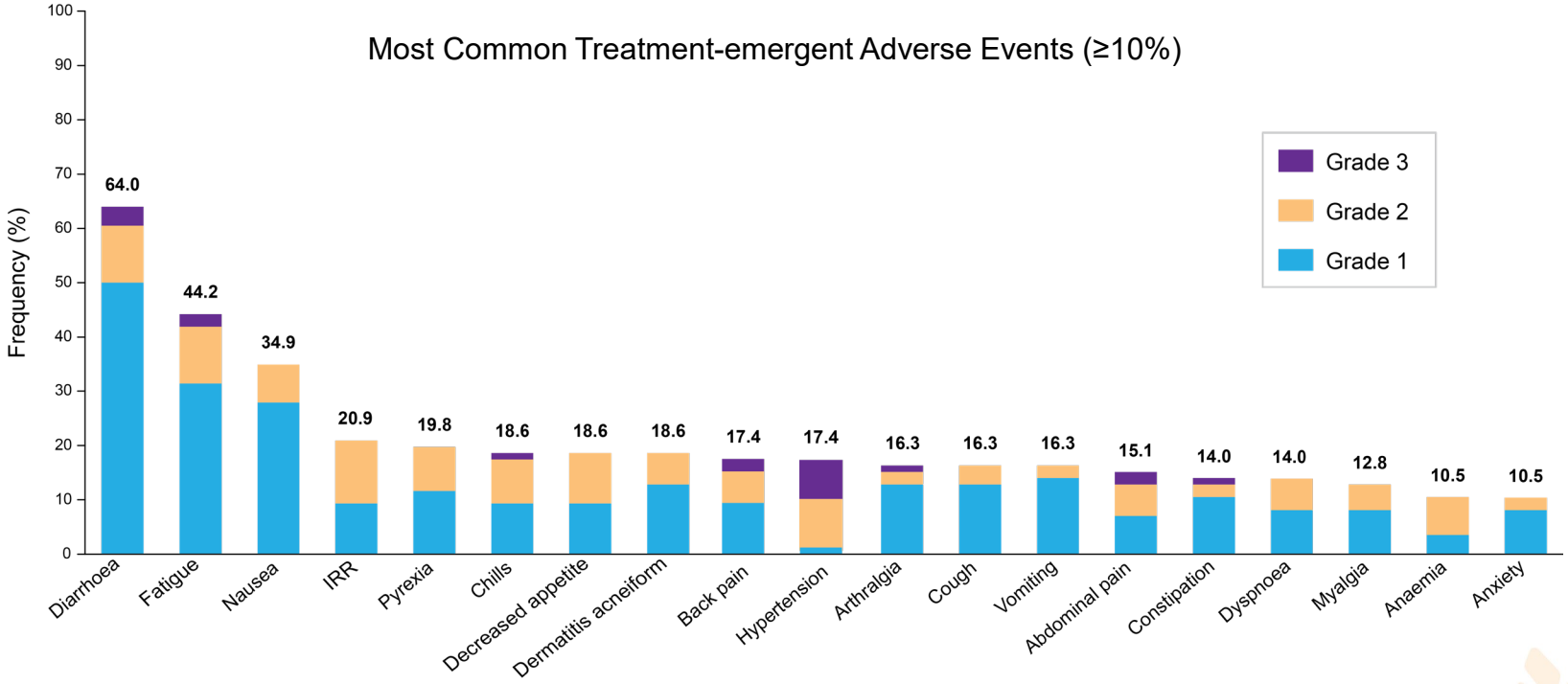
TEAEs, n (%)	Tucatinib + Trastuzumab Cohorts A+B (n=86)
Any grade AEs	82 (95.3)
Tucatinib-related	63 (73.3)
Trastuzumab-related	58 (67.4)
Grade ≥3 AEs	33 (38.4)
Tucatinib-related	8 (9.3)
Trastuzumab-related	6 (7.0)
SAEs	19 (22.1)
Tucatinib-related	3 (3.5)
Trastuzumab-related	2 (2.3)
AEs leading to study treatment discontinuation[a,b]	5 (5.8)
AEs leading to tucatinib dose modification	22 (25.6)
Deaths due to AEs	0

a TEAEs leading to discontinuation of tucatinib included alanine aminotransferase increase (2.3%), COVID-19 pneumonia (1.2%), cholangitis (1.2%), and fatigue (1.2%); b TEAEs leading to discontinuation of trastuzumab included alanine aminotransferase increase (2.3%) and COVID-19 pneumonia (1.2%)

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Data cutoff: 28 Mar 2022

Most Common TEAEs (≥10%) for Tucatinib + Trastuzumab



- Most common tucatinib-related AEs (≥10%): diarrhoea (52.3%), fatigue (29.1%), nausea (18.6%), and dermatitis acneiform (17.4%)
  - Grade ≥3 tucatinib-related AEs (≥2%): alanine aminotransferase increase (2.3%) and diarrhoea (2.3%)

AE, adverse event; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.
Data cutoff: 28 Mar 2022

Adverse Events of Special Interest for Tucatinib + Trastuzumab

- Diarrhoea
  - Most common TEAE: Grade 1, 50.0%; Grade 2, 10.5%; Grade 3, 3.5%
    - No treatment discontinuations due to diarrhoea
    - Tucatinib dose modifications for diarrhoea: dose reduction, 2.3%; dose hold, 3.5%
  - Antidiarrheal prophylaxis was not mandated

- Hepatotoxicity
  - Grade ≥3: increased ALT (3.5%), increased AST (2.3%), and hypertransaminasemia (1.2%)
  - Hepatotoxicity leading to tucatinib modification or discontinuation occurred in 5.8%
  - No Hy's Law cases identified

- Cardiotoxicity
  - Asymptomatic LVEF decrease leading to dose modification or discontinuation occurred in 3.5%

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction; TEAE, treatment-emergent adverse event.

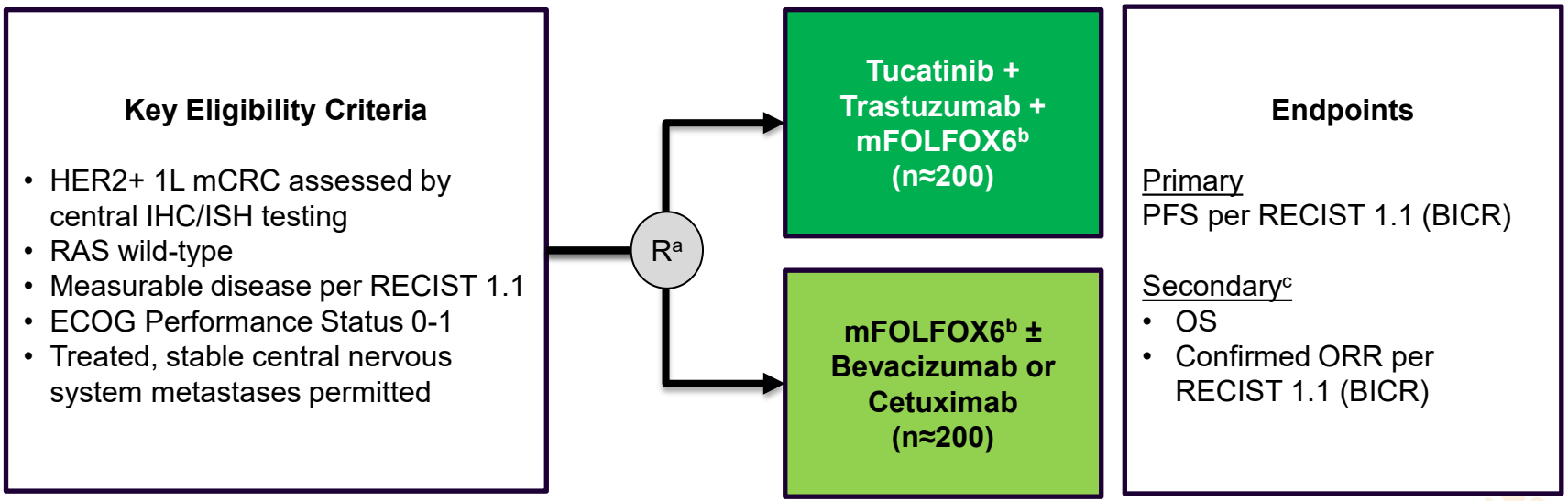
Data cutoff: 28 Mar 2022

Conclusions

- In chemotherapy-refractory patients with HER2+ mCRC, tucatinib in combination with trastuzumab demonstrated durable and clinically meaningful antitumor activity
  - Confirmed ORR of 38.1%, DOR of 12.4 months, median PFS of 8.2 months, and median OS of 24.1 months
- Tucatinib + trastuzumab was well tolerated and had low discontinuation rate
  - Diarrhoea was predominately low grade and manageable; no Grade 4 events
  - No deaths resulted from AEs
- Tucatinib in combination with trastuzumab has the potential to become a new standard of care for patients with HER2+ mCRC
- Ongoing phase 3 MOUNTAINEER-03 trial (NCT05253651) will compare tucatinib + trastuzumab + mFOLFOX6 with standard of care

AE, adverse event; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LFT, liver function test; mCRC, metastatic colorectal cancer; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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



a Stratification: Primary tumor sidedness, liver metastases; b Levoleucovorin may be given in place of leucovorin; c Alpha-controlled

1L, first line; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors.

https://clinicaltrials.gov/ct2/show/NCT05253651

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