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ADDITIONAL ANALYSES OF MOUNTAINEER: A PHASE 2 STUDY OF TUCATINIB AND TRASTUZUMAB FOR HER2-POSITIVE MCRC

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Declaration of Interests

- Dr. Strickler reports grants paid to the institution by Amgen, Bayer, Erasca, Seagen, Daiichi-Sankyo, Gossamer Bio, AStar D3, Sanofi, Roche/Genentech, Curgenix, Nektar, AbbVie, and Silverback Therapeutics; receiving consulting fees from AbbVie, Takeda, AstraZeneca, Bayer, GSK, Inivata, Mereo Biopharma, Pfizer, Seagen, Silverback Therapeutics, and Viatris; receiving honoraria from Bayer, Natera, and Pfizer; receiving travel support from Seagen and Guardant Health; receiving other services from Guardant Health; and is a member of advisory boards for AbbVie and Pionyr Immunotherapeutics.

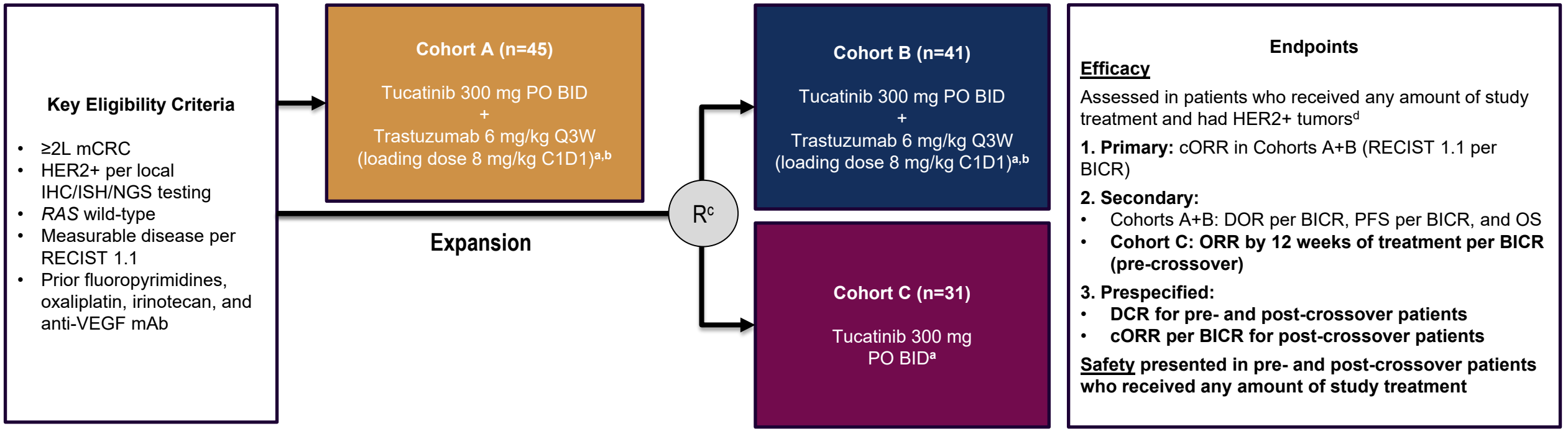
Background

- HER2 amplification/overexpression (HER2+) occurs in ~3%–5% of all patients with mCRC[1-6]
- Patients with HER2+ mCRC who were previously treated with chemotherapy receive limited clinical benefit from subsequent standard-of-care treatments[1]
- Tucatinib is a highly selective TKI for HER2[4]
  - Preclinical data demonstrated that the combination of tucatinib and trastuzumab led to greater antitumour activity compared with either agent alone in mCRC xenograft models
- Primary results from MOUNTAINEER showed that tucatinib in combination with trastuzumab was well tolerated with durable and clinically meaningful antitumour activity in patients with previously treated HER2+ RAS wild-type mCRC[7]
  - cORR per BICR of 38.1%, DOR of 12.4 months, median PFS of 8.2 months, and median OS of 24.1 months
  - Diarrhoea was predominantly low grade and manageable; no grade 5 AEs were reported

AE, adverse event; BICR, blinded independent central review; cORR, confirmed objective response rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; PFS, progression-free response; OS, overall survival; RAS, rat sarcoma virus; TKI, tyrosine kinase inhibitor.

1. Benson et al. J Natl Compr Canc Netw. 2021;19(3):329. 2. Benson et al. J Natl Compr Canc Netw. 2020; 18(7):806; 3. Kang et al. J Manag Care Spec Pharm. 2021;S20. 4. Kulukian et al. Mol Cancer Ther. 2020;19:976. 5. Patel et al. J Pers Med. 2019;9. 6. Sartore-Bianchi et al. Oncologist. 2019;24:1395. 7. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

MOUNTAINEER: Global, Open-label, Phase 2 Trial[1]



Patients treated with tucatinib monotherapy 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

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 tumour primary vs other; d 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; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2+, human epidermal growth receptor 2-positive; IHC, immunohistochemistry; ISH, in situ hybridisation; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumours; VEGF, vascular endothelial growth factor.
Data cutoff: 28 March 2022
1. Adapted from Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

Key Baseline Patient Characteristics[1]

Characteristics		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, n (%)	Male	51 (60.7)	15 (50.0)
	Female	33 (39.3)	15 (50.0)
ECOG Performance Status, n (%)	0	50 (59.5)	17 (56.7)
	1	31 (36.9)	13 (43.3)
	2	3 (3.6)	0
Primary tumor site, n (%)	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
Patients with liver metastases at study entry, n (%)		54 (64.3)	15 (50.0)
Patients with lung metastases at study entry, n (%)		59 (70.2)	20 (66.7)
Prior lines of systemic therapy in any setting, median (range)[c]		3.0 (1, 6)	2.0 (1, 5)

a Two patients did not have HER2+ disease as specified per protocol and were excluded; b One patient discontinued before receiving treatment; c Treatments used in adjuvant/neoadjuvant setting are counted as 1 line
ECOG, Eastern Cooperative Oncology Group.
Data cutoff: 28 Mar 2022
1. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

Efficacy Outcomes

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 (3.6)	0	0
	PR	29 (34.5)	1 (3.3)	5 (17.9)
	SD[b]	28 (33.3)	23 (76.7)	18 (64.3)
	PD	22 (26.2)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2.4)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		**38.1 (27.7-49.3)[e]**	**3.3 (0.1-17.2)[f]**	**17.9 (6.1-36.9)[e]**
DCR[g] per BICR, n (%)		**60 (71.4)**	**24 (80.0)**	**23 (82.1)**

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 cORR; f ORR by 12 weeks of treatment; g 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; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.
Data cutoff: 28 Mar 2022
1. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

Safety Summary

- Safety profiles for tucatinib monotherapy pre- and post-crossover groups are consistent with the known tucatinib safety profile

TEAEs, n (%)		Tucatinib + Trastuzumab Cohorts A+B n=86[1]	Tucatinib Monotherapy Cohort C[a] n=30	Tucatinib + Trastuzumab Post-Crossover[b] n=28
Any grade AEs		82 (95.3)	28 (93.3)	23 (82.1)
Grade ≥3 AEs		33 (38.4)	8 (26.7)	6 (21.4)
SAEs		19 (22.1)	3 (10.0)	2 (7.1)
AEs leading to tucatinib discontinuation		5 (5.8)[c]	0	2 (7.1)[d]
Deaths due to AEs		0	0	0
Most common AEs[e]	Diarrhoea	55 (64.0)	10 (33.3)	10 (35.7)
	Abdominal pain	13 (15.1)	6 (20.0)	3 (10.7)
	Fatigue	38 (44.2)	6 (20.0)	3 (10.7)

a AEs pre-crossover are defined as AEs that are newly onset or worsened on or after receiving the first dose of tucatinib and up to 30 days after last dose of tucatinib for patients who didn't crossover, or the day before crossover for patients who crossed over; b AEs post-crossover are defined as AEs that are newly onset or worsened on or after crossover (date of first dose of tucatinib or trastuzumab, whichever came first, in the first cycle of trastuzumab) and up to 30 days after the last dose of study treatment (tucatinib or trastuzumab); c Three patients discontinued trastuzumab; d One patient discontinued tucatinib due to ALT increase, and one patient discontinued tucatinib due to AST increase. One patient discontinued trastuzumab; e AEs reported in ≥20% of patients in patients treated with tucatinib monotherapy (pre-crossover).
AE, adverse event; ALT; alanine transaminase; AST, aspartate transaminase; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Data cutoff: 28 Mar 2022
1. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

Author's Conclusions

- Overall, data from MOUNTAINEER support concurrent initiation of dual-HER2 blockade with tucatinib plus trastuzumab to achieve optimal clinical benefit
- Modest antitumour activity and disease stabilisation was observed for most patients with tucatinib monotherapy
  - Radiographic response rates increased after crossover
- Tucatinib monotherapy and tucatinib plus trastuzumab after crossover were well tolerated, consistent with the known tucatinib safety profile[1]
- HER2-targeted therapy with tucatinib plus trastuzumab in mCRC is being further investigated in MOUNTAINEER-03 (NCT05253651), an ongoing, randomised, global phase 3 trial
  - Trial evaluates the efficacy of tucatinib, trastuzumab, and mFOLFOX6 compared with standard of care in first-line HER2+ mCRC

HER2, human epidermal growth receptor 2; HER2+, human epidermal growth receptor 2-positive; mCRC, metastatic colorectal cancer; mFOLFOX6, 5-fluorouracil, leucovorin, and oxaliplatin.

1. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

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