FPN 361P

TUCATINIB PLUS TRASTUZUMAB IN PATIENTS (PTS) WITH HER2-POSITIVE METASTATIC COLORECTAL CANCER (mCRC): PATIENT-REPORTED OUTCOMES FROM PH 2 STUDY MOUNTAINEER

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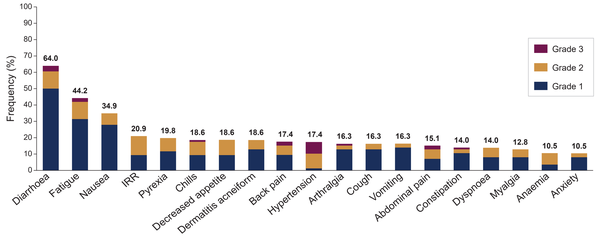
Background

- Current treatment strategies for mCRC focus on prolonging survival, delaying tumour progression, managing symptoms, and maintaining HRQoL[1,2]
- HER2 amplification/overexpression (HER2+) occurs in ~3%–5% of all patients with mCRC[3-8]
- Patients with HER2+ mCRC who progress on early lines of chemotherapy regimens receive limited clinical benefit from current standard-of-care treatments[3,4]
- The MOUNTAINEER trial (NCT03043313) is evaluating the efficacy and safety of the investigational combination of tucatinib with trastuzumab in patients with HER2+ *RAS* wild-type mCRC[9]
- Primary results from MOUNTAINEER showed that tucatinib plus trastuzumab was well tolerated with durable and clinically meaningful antitumour activity

Confirmed ORR per BICR, % (95% CI)[a]	Median DOR per BICR, months (95% CI)	Median PFS per BICR, months (95% CI)	Median OS per BICR, (95% CI)
38.1 (27.7, 49.3)	12.4 (8.5, 20.5)	8.2 (4.2, 10.3)	24.1 (20.3, 36.7)

a Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934)

Most Common TEAEs (≥10%)[10]

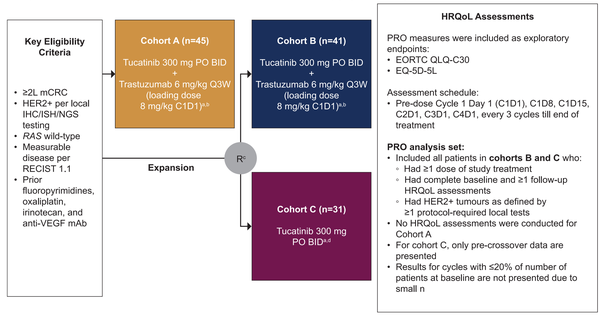


- Discontinuation due to AEs occurred in 5.8%
- Diarrhoea was predominantly low-grade and manageable
  - 50.0% were grade 1, 10.5% grade 2, and 3.5% grade 3; no grade 4 events
  - Antidiarrheal prophylaxis was not required
- No deaths resulted from AEs

Methods

MOUNTAINEER Trial Design[10]

- 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 plus trastuzumab (cohort B) or tucatinib monotherapy (cohort C)



HRQoL Assessments

PRO measures were included as exploratory endpoints:
- EORTC QLQ-C30
- EQ-5D-5L

Assessment schedule:
- Pre-dose Cycle 1 Day 1 (C1D1), C1D8, C1D15, C2D1, C3D1, C4D1, every 3 cycles till end of treatment

PRO analysis set:
- Included all patients in **cohorts B and C** who:
  - Had ≥1 dose of study treatment
  - Had complete baseline and ≥1 follow-up HRQoL assessments
  - Had HER2+ tumours as defined by ≥1 protocol-required local tests
- No HRQoL assessments were conducted for Cohort A
- For cohort C, only pre-crossover data are presented
- Results for cycles with ≤20% of number of patients at baseline are not presented due to small n

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 tumour 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

Methods (Cont'd)

EORTC QLQ-C30

- 30-item questionnaire consisting of functional, symptom, and global health status/QoL (each question is scored 0-100)
  - For global health status/QoL and functional domain scores, higher scores represent better QoL and functioning
  - For symptom scales, higher scores represent worsening of symptoms
- Mean change from baseline graphs for key domains that are relevant for mCRC disease and treatment are presented (ie, global health status/QoL, physical functioning, fatigue, pain, nausea & vomiting, and diarrhoea)[11,12]
  - The absolute change from baseline of 10 points in QLQ-C30 scale score is generally considered to be clinically meaningful[13]

EQ-5D-5L

- A standardized questionnaire that measures health outcomes, comprising five health state dimensions and VAS
  - The VAS records the patient's self-rated health status on a graduated scale from 0 (worst health) to 100 (best health)

Results

Key Patient Baseline Characteristics

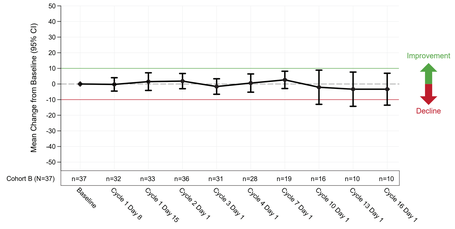
- Characteristics between patients in cohorts A+B and cohort B were similar

Characteristics		Tucatinib + Trastuzumab Cohort A+B (N=84)[a,b]	Tucatinib + Trastuzumab Cohort B PRO set (N=37)[b]	Tucatinib monotherapy Cohort C PRO set (N=28)[b]
Median age, years (range)		55.0 (24, 77)	59.0 (31, 77)	59.0 (29, 75)
Sex, n (%)	Male	51 (60.7)	24 (64.9)	13 (46.4)
	Female	33 (39.3)	13 (35.1)	15 (53.6)
ECOG Performance Status, n (%)	0	50 (59.5)	25 (67.6)	17 (60.7)
	1	31 (36.9)	10 (27.0)	11 (39.3)
	2	3 (3.6)	2 (5.4)	0
Primary tumour site, n (%)	Left colon and rectum	71 (84.5)	36 (97.3)	25 (89.3)
	All other primaries	13 (15.5)	1 (2.7)	3 (10.7)
	Transverse colon	7 (8.3)	1 (2.7)	0
	Right colon	5 (6.0)	0	3 (10.7)
	Multiple/overlapping sites	1 (1.2)	0	0
Patients with liver metastases at study entry, n (%)		54 (64.3)	27 (73.0)	14 (50.0)
Patients with lung metastases at study entry, n (%)		59 (70.2)	23 (62.2)	19 (67.9)
Prior lines of systemic therapy in metastatic or recurrent setting, n (%)	1 line	19 (22.6)	7 (18.9)	5 (17.9)
	2 lines	32 (38.1)	19 (51.4)	14 (50.0)
	3+ lines	33 (39.3)	11 (29.7)	9 (32.1)

a Two patients did not have HER2+ disease as specified per protocol and were excluded
b Included all patients who had ≥1 dose of study treatment, had complete baseline and ≥1 follow-up HRQoL assessments, and had HER2+ tumours as defined by ≥1 protocol-required local tests

EORTC QLQ-C30 Global Health Status/QoL (Cohort B)

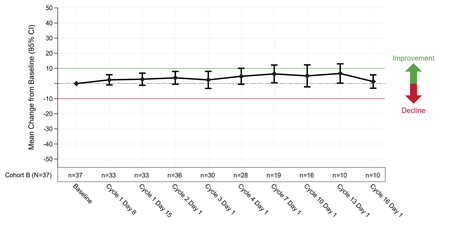
- The mean changes from baseline during the treatment period were small in magnitude



Results (Cont'd)

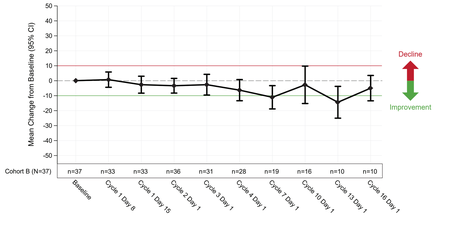
EORTC QLQ-C30 Functional Domains- Physical Functioning (Cohort B)

- The mean changes from baseline during the treatment period were small in magnitude



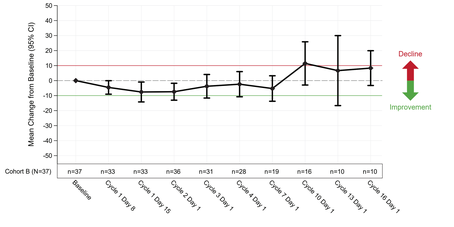
EORTC QLQ-C30 Symptom- Fatigue (Cohort B)

- The mean changes from baseline decreased, reaching the clinical meaningful threshold at one or more cycles up to cycle 16



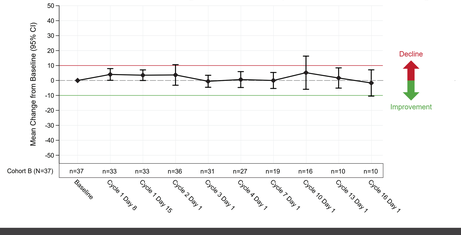
EORTC QLQ-C30 Symptom- Pain (Cohort B)

- There was no worsening of the mean changes from baseline until cycle 10



EORTC QLQ-C30 Symptom- Nausea & Vomiting (Cohort B)

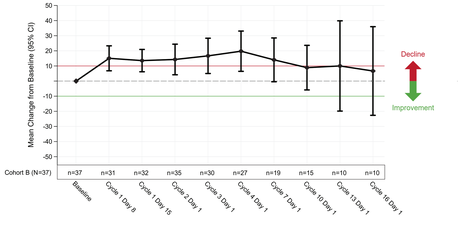
- The mean changes from baseline during the treatment period were small in magnitude



Results (Cont'd)

EORTC QLQ-C30 Symptom- Diarrhoea (Cohort B)

- There was an increase of the mean changes from baseline, reaching the clinical meaningful threshold at one or more cycles up to cycle 16



EORTC QLQ-C30 Remaining Domains

- Overall, the majority of mean changes from baseline for remaining scales was stable over time, although fluctuations in individual domains were observed
  - Dyspnoea and insomnia demonstrated mean changes greater than ±10 points

EQ-5D-5L VAS (Cohort B)

- VAS scores remained stable with a trend of improvement throughout the study period

Cycle numbers	Mean VAS scores (STD)
Baseline (N=37)	75.5 (18.2)
Cycle 4 (n=28)	78.1 (16.4)
Cycle 7 (n=19)	79.3 (15.0)
Cycle 10 (n=16)	79.8 (17.1)
Cycle 16 (n=10)	81.0 (18.1)

EORTC QLQ-C30 and EQ-5D-5L VAS (Cohort C)

- In cohort C, the observed mean score changes from baseline in EORTC QLQ-C30 global health status and functioning domains were small in magnitude
- Mean changes from baseline for symptom domains generally remained stable over time, although some fluctuations in individual domains were observed
  - Mean changes for fatigue, nausea and vomiting, and pain remained stable
  - Mean changes for diarrhoea increased
- Mean EQ-5D-5L VAS scores remained stable over time

Conclusions

- In chemotherapy-refractory patients with HER2+ mCRC, tucatinib plus trastuzumab was well tolerated with durable and clinically meaningful antitumour activity
- Patients treated with tucatinib plus trastuzumab generally maintained HRQoL throughout the treatment period
  - Consistent trends were observed for patients treated with tucatinib monotherapy
- These results further support the overall tolerability profile of this regimen and suggest tucatinib plus trastuzumab has the potential to be an important treatment option for patients with HER2+ mCRC

Abbreviations

2L, second line; AE, adverse event; BICR, blinded independent central review; BID, twice a day; BRAF, v-raf murine sarcoma viral oncogene homolog B1; C, cycle; CR, complete response; D, day; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire: EQ-5D-5L, European Quality of Life 5 Dimension 5 Level; HER2, human epidermal growth receptor 2; HRQoL, health-related quality of life; IHC, immunohistochemistry; IRR, infusion-related reaction; 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; PR, partial response; PRO, patient-reported outcome; pts, patients; Q3W, every 3 weeks; QoL, quality of life; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumours; STD, standard deviation; US, United States; VAS, visual analog scale; VEGF, vascular endothelial growth factor.

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