Phase 2 Dose Optimization Results From MOUNTAINEER-02: A Study of Tucatinib, Trastuzumab, Ramucirumab, and Paclitaxel for HER2+ Gastroesophageal Cancer (GEC)

Mustapha Tehfe,[1] Jeeyun Lee,[2] Sun Young Rha,[3] Yoshiaki Nakamura,[4] Josep Tabernero,[5] Kohei Shitara,[4] Do-Youn Oh,[6] Jennifer Eads,[7] John Marshall,[8] Zev Wainberg,[9] Keun-Wook Lee,[10] Yoon-Koo Kang,[11] Chih-Yi Liao,[12] Sung Yong Oh,[13] Kun-Huei Yeh,[14] Donald Richards,[15] Michelle Ubowski,[16] Kechen Zhao,[16] Sucharita Bhaumik,[17] John Strickler[18]

[1]Centre Hospitalier de l'Université de Montréal, Quebec, Canada; [2]Samsung Medical Center, Seoul, South Korea; [3]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; [4]National Cancer Center of Hospital East, Chiba, Japan; [5]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Seoul National University Hospital, Seoul, South Korea; [7]University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA, USA; [8]Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC, USA; [9]University of California, Los Angeles Department of Medicine, Hematology and Oncology, Los Angeles, CA, USA; [10]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; [11]Asan Medical Center, Seoul, Korea; [12]University of Chicago Medical Center, Chicago, IL, USA; [13]Dong-A University Hospital, Busan, South Korea; [14]National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei City, Taiwan; [15]Texas Oncology, Northeast Texas Cancer and Research Institute, Tyler, TX, USA; [16]Seagen Inc., Bothell, WA, USA; [17]Merck & Co., Inc., Rahway, NJ, USA; [18]Duke University Medical Center, Durham, NC, USA

Objectives

- To determine the recommended dose of paclitaxel when administered in combination with tucatinib, trastuzumab, and ramucirumab
- To evaluate the safety and preliminary activity of tucatinib in combination with trastuzumab, ramucirumab, and paclitaxel in patients with previously treated locally-advanced unresectable or metastatic HER2+ GEC
- To evaluate the PK of paclitaxel and its metabolites in the presence and absence of tucatinib

Conclusions

The safety of the regimen was consistent with the known safety profiles of each individual component

Coadministration of tucatinib with paclitaxel did not impact the plasma concentrations of paclitaxel

Based on the preliminary data from MOUNTAINEER-02, the combination of tucatinib, trastuzumab, paclitaxel and ramucirumab with dose modifications per protocol was tolerable with encouraging antitumor activity in patients with previously treated HER2+ GEC

Abbreviations

2L, second line; AE, adverse event; AUC_{last}, area under the plasma concentration-time profile until the last time point; BID, twice daily; BTC, biliary tract cancer; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; CR, complete response; cORR, confirmed objective response rate; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEC, gastroesophageal cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth receptor 2; HER2+, HER2 positive; IHC, immunohistochemistry; ISH, in situ hybridization; ISO, International Organization for Standardization; M, median; MBC, metastatic breast cancer; mCRC, metastatic colorectal cancer; NGS, next generation sequencing; ORR, objective response rate; PD, progressive disease; PK, pharmacokinetic, PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SMC, Safety Monitoring Committee; SD, stable disease; TEAE, treatment emergent adverse event; TESAE, treatment emergent serious adverse event; TKI, tyrosine kinase inhibition

Acknowledgements

This study was sponsored by Seagen Inc., Bothell, WA, USA in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, US and Lilly, Indianapolis, IN, USA. The authors thank Kim Nolte, PhD of MMS Holdings, Pretoria, RSA, and Irene Park, PhD, of Seagen Inc., supported by Seagen Inc. for providing medical writing and editorial support in accordance with Good Publication Practice guidelines.

References

1. Tanner M. Ann Oncol. 2005;16(2):273-8.
2. Yan B. J Clin Pathol. 2010;63(9):839-42.
3. Chua TC. Int J Cancer. 2012;130(12):2845-56.
4. Gomez-Martin C. J Clin Pathol. 2012;65(8):751-7.
5. Janjigian YY. Ann Oncol. 2012;23(10):2659-62.
6. Kunz PL. Appl Immunohistochem Mol Morphol. 2012;20(1):13-24.
7. Lopez A. Ann Transl Med. 2018;6(4):78.
8. Kulukian A. Mol Cancer Ther. 2020;976-87.
9. TUKYSA. Prescribing information. Seagen Inc., Jan 2023. Accessed Apr 10, 2023.
10. Peterson. Ann Oncol. 2017;28(Suppl 5):576.
11. Murthy R. N Engl J Med. 2020;382(7):597-609.
12. Curigliano G. Ann Oncol. 2022;33:321-9.
13. Strickler JH. Lancet Oncol. 2023;24:496-508.
14. Nakamura Y. J Clin Oncol.JCO2300606.
15. Clinicaltrials.gov. https://www.clinicaltrials.gov/study/NCT04499924. Accessed Aug 3, 2023.

European Society for Medical Oncology; Madrid, Spain
October 20-24, 2023; Abstract No. 1523P

Background

- Approximately 12%-23% of patients with GEC overexpress HER2[1-6]
- Ramucirumab in combination with paclitaxel are commonly used in the 2L setting for GEC; however, overall response and survival rates remain low[7]
- Tucatinib is a highly selective, HER2-directed TKI[8] currently approved to treat adult patients with[9]:
  - HER2+ MBC (in combination with trastuzumab and capecitabine), including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting
  - RAS WT HER2+ mCRC (in combination with trastuzumab) that has progressed after fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy
- Preclinical data have shown that the combination of tucatinib and trastuzumab in various HER2+ tumor types results in superior antitumor activity compared with either agent alone[8,10]
- In clinical settings, the combination of tucatinib and trastuzumab has proven efficacy and tolerability in HER2+ MBC (when given with capecitabine), HER2+ mCRC, and HER2+ metastatic BTC[10-14]
- Here, safety and efficacy results from the dose optimization phase of MOUNTAINEER-02 (NCT04499924), a trial evaluating tucatinib in combination with trastuzumab, paclitaxel, and ramucirumab[15], are presented
- Countries where patients were enrolled included Australia, Canada, South Korea, Taiwan, UK, and US

Methods

Key eligibility criteria

- Locally advanced unresectable or metastatic HER2+ gastric or GEJ adenocarcinoma
- HER2 amplification in a blood-based NGS assay performed at a central laboratory or HER2 overexpression/amplification by IHC/ISH (IHC3+ or IHC2+/ISH+) processed in a CLIA- or ISO-accredited laboratory
- Prior treatment with a HER2-directed antibody
- Cannot have received >1 line of prior systemic therapy for locally advanced unresectable or metastatic disease
- Measurable disease per RECIST v1.1

Paclitaxel dose optimization

Paclitaxel 60 mg/m² + tucatinib + trastuzumab + ramucirumab[a] → Safety assessment[b] → Paclitaxel 80 mg/m² + tucatinib + trastuzumab + ramucirumab[a]

Outcomes

- Primary
  - Safety/tolerability
- Secondary:
  - Antitumor activity (ORR, cORR, DOR, DCR, and PFS per investigator assessment)
  - PK

Study enrollment closed following completion of dose optimization
a Tucatinib 300 mg BID, trastuzumab (6 mg/kg loading dose then 4 mg/kg D1 and 15), paclitaxel (D1, 8, and 15) and ramucirumab (8 mg/kg D1 and 15) every 28 days.
b SMC assessment following completion of paclitaxel 60 mg/m² cohort to confirm safety/tolerability prior to initating paclitaxel 80 mg/m² cohort.

Results

Patient Disposition

Patient Disposition		Paclitaxel 60 mg/m² (n = 8)	Paclitaxel 80 mg/m² (n = 9)	Total (N = 17)
Patients who received at least one dose of study treatment, n (%)		8 (100)	9 (100)	17 (100)
Patients on treatment, n (%)		0	2 (22.2)	2 (11.8)
Patients off treatment, n (%)		8 (100)	7 (77.8)	15 (88.2)
Duration of treatment, months (range)	Paclitaxel	5.2 (1.1-16.8)	9.7 (2.1-15.7)	7.8 (1.1-16.8)
	Tucatinib	5.1 (0.8-18.2)	10.7 (3.1-15.7)	8.8 (0.8-18.2)
	Trastuzumab	5.3 (1.1-17.9)	11.5 (6.4-15.7)	8.8 (1.1-17.9)
	Ramucirumab	5.3 (1.1-17.9)	9.9 (6.4-14.7)	9.4 (1.1-17.9)
Reason for treatment discontinuation, n (%)	Progressive disease	6 (75.0)	6 (66.7)	12 (70.6)
	AE	1 (12.5)	0	1 (5.9)
	Investigator decision	1 (12.5)	0	1 (5.9)
	Patient decision	0	1 (11.1)	1 (5.9)

Data cutoff: Aug 7, 2023

Demographics and Baseline Characteristics

- All 17 patients had histological or cytologically confirmed diagnosis of HER2+ gastric or GEJ adenocarcinoma
- The most common sites of disease were GI tract (76.5% [13/17]), lymph node(s) (70.6% [12/17]), liver (64.7% [11/17]), abdomen/abdominal cavity (23.5% [4/17]), bone (23.5% [4/17]), lung(s) (23.5% [4/17]), and CNS (17% [3/17])

Patient Characteristics		Paclitaxel 60 mg/m² (n = 8)	Paclitaxel 80 mg/m² (n = 9)	Total (N = 17)
Median age, years (range)		50.5 (38-66)	60.0 (42-68)	59.0 (38-68)
Male, sex, n (%)		8 (100)	8 (88.9)	16 (94.1)
Race	Asian	5 (62.5)	4 (44.4)	9 (52.9)
	White	3 (37.5)	5 (55.6)	8 (47.1)
ECOG PS score, n (%)	0	2 (25.5)	3 (33.3)	5 (29.4)
	1	6 (75.0)	6 (66.7)	12 (70.6)
Primary diagnosis, n (%)	Gastric adenocarcinoma	3 (37.5)	4 (44.4)	7 (41.2)
	Gastroesophageal junction adenocarcinoma	5 (62.5)	5 (55.6)	10 (58.8)
Histological subtype, n (%)	Diffuse	2 (25.5)	2 (22.2)	4 (23.5)
	Intestinal	4 (50.0)	5 (55.6)	9 (52.9)
	Other	2 (25.0)	2 (22.2)	4 (23.5)
Has a history of unresectable locally advanced disease, n (%)		0	1 (11.1)	1 (5.9)
Has a history of metastatic disease, n (%)		8 (100)	8 (88.9)	16 (94.1)

Data cutoff: Aug 7, 2023

Safety

- No DLTs were observed in 7 DLT-evaluable patients treated with paclitaxel 60 mg/m²
  - One patient in the paclitaxel 60 mg/m² cohort did not receive at least 75% of the planned administration of each study drug during the DLT period and therefore was excluded from the DLT analysis
- 9 patients were enrolled in the paclitaxel 80 mg/m² cohort and evaluable for DLTs
  - 2 patients experienced DLTs (1 patient with grade 2 mucositis and 1 patient with grade 2 fatigue and diarrhea resulting in dose holds during the DLT period)
- Paclitaxel dose was reduced in 3 patients (37.5%) in the 60 mg/m² cohort vs 8 patients (88.9%) in the 80 mg/m² cohort
- No deaths resulted from TEAEs

Safety Summary

Events, n (%)	Paclitaxel 60 mg/m² (n = 8)	Paclitaxel 80 mg/m² (n = 9)	Total (N = 17)
Any TEAEs	8 (100)	9 (100)	17 (100)
Treatment-related	8 (100)	9 (100)	17 (100)
Grade ≥3 TEAEs	6 (75.0)	9 (100)	15 (88.2)
Treatment-related	5 (62.5)	9 (100)	14 (82.4)
Any TESAEs	4 (50.0)	5 (55.6)	9 (52.9)
Treatment-related	1 (12.5)	2 (22.2)	3 (17.9)
Patients who discontinued any study treatment due to TEAEs	2 (25.0)[a]	4 (44.4)[b]	6 (35.3)

a One patient discontinued tucatinib, and one patient discontinued trastuzumab and paclitaxel.
b One patient discontinued tucatinib, one patient discontinued paclitaxel, one patient discontinued ramucirumab, and one patient discontinued paclitaxel and ramucirumab.
Data cutoff: Aug 7, 2023

Most Common TEAEs (≥30% in the Total Population)

	Paclitaxel 60 mg/m² (n = 8)		Paclitaxel 80 mg/m² (n = 9)		Total (N = 17)	
TEAEs, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any event	8 (100)	6 (75.0)	9 (100)	9 (100)	17 (100)	15 (88.2)
Diarrhea	4 (50.0)	2 (25.0)	8 (88.9)	1 (11.1)	12 (70.6)	3 (17.6)
Fatigue	2 (25.0)	0	7 (77.8)	3 (33.3)	9 (52.9)	3 (17.6)
Nausea	2 (25.0)	0	7 (77.8)	0	9 (52.9)	0
Epistaxis	2 (25.0)	0	6 (66.7)	0	8 (47.1)	0
Peripheral sensory neuropathy	1 (12.5)	0	7 (77.8)	2 (22.2)	8 (47.1)	2 (11.8)
Constipation	3 (37.5)	0	4 (44.4)	0	7 (41.2)	0
Stomatitis	2 (25.0)	0	5 (55.6)	1 (11.1)	7 (41.2)	1 (5.9)
Hypertension	2 (25.0)	1 (12.5)	4 (44.4)	3 (33.3)	6 (35.3)	4 (23.5)
Neutropenia	1 (12.5)	1 (12.5)	5 (55.6)	4 (44.4)	6 (35.3)	5 (29.4)
Weight decreased	2 (25.0)	1 (12.5)	4 (44.4)	1 (11.1)	6 (35.3)	2 (11.8)

Data cutoff: Aug 7, 2023

Hepatotoxicity

- Two of 8 patients (25%) in the paclitaxel 60 mg/m² cohort experienced grade 3 LFT elevations, while none were reported in the paclitaxel 80 mg/m² cohort
  - No grade 4 LFT elevations occurred on study
- No events met Hy's law criteria at either dose level

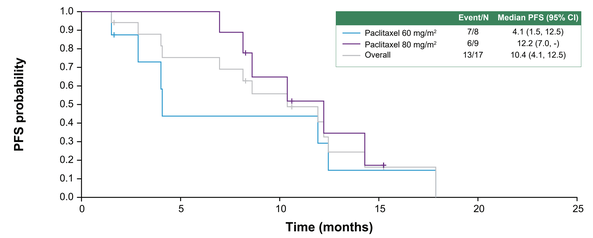
Summary of Responses

		Paclitaxel 60 mg/m² (n = 8)	Paclitaxel 80 mg/m² (n = 9)	Total (N=17)
Best overall response[a], n (%)	CR	0	1 (11.1)	1 (5.9)
	PR	4 (50.0)	8 (88.9)	12 (70.6)
	SD	3 (37.5)	0	3 (17.6)
	PD	1 (12.5)	0	1 (5.9)
ORR, % (95% CI)		50.0 (15.7-84.3)	100.0 (66.4-100.0)	76.5 (50.1-93.2)
cORR[b], % (95% CI)		37.5 (8.5-75.5)	100.0 (66.4-100.0)	70.6 (44.0-89.7)
DCR, % (95% CI)		87.5 (47.3-99.7)	100.0 (66.4-100.0)	94.1 (71.3-99.9)
mDOR, months[c] (95% CI)		10.6 (2.8-inestimable)	11.0 (2.9-inestimable)	10.6 (2.9-12.9)

a Best overall response assessed per RECIST v1.1.
b Excludes 1 patient with uncomfirmed PR.
c As estimated using Kaplan-Meier methods.
Data cutoff: Aug 7, 2023

Progression-free Survival

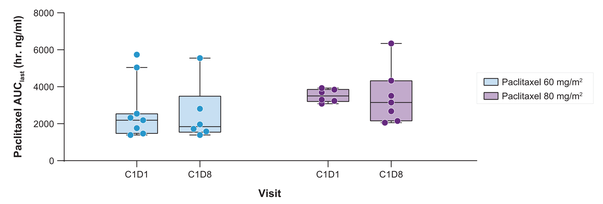
- Median PFS was 10.4 months (4.1-12.5) for the overall population after 13 PFS events



Data cutoff: Aug 7, 2023

Pharmacokinetics

- Paclitaxel plasma concentrations did not increase in presence of tucatinib



C1D1: in absence of tucatinib; C1D8: in presence of steady-state tucatinib.
Data cutoff: Aug 7, 2023