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Efficacy and safety of capmatinib plus spartalizumab in treatment-naïve patients with advanced NSCLC harboring *MET* exon 14 skipping mutation

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CONCLUSIONS

- Capmatinib in combination with spartalizumab in advanced *MET*ex14 NSCLC patients, with no prior systemic therapy for advanced NSCLC, resulted in high rates of TRAEs leading to study treatment dose reduction and/or interruption and TRAEs leading to treatment discontinuation, compared to data from capmatinib monotherapy studies. This observation has led to the sponsor's decision to halt the study recruitment during the run-in phase of the study and to discontinue spartalizumab treatment in all ongoing patients.
- With limited sample size, modest ORR was seen with the combination. The ORR observed in this study was lower than the ORR of capmatinib monotherapy in first-line setting. Frequent dose reduction and/or interruption of study treatment due to TRAEs may be a contributing factor to ORR. Other efficacy endpoints including DOR and PFS, remain to mature to derive definitive conclusion on efficacy.
- Exploratory investigations to assess the relationship between selected baseline parameters, including PD-L1 expression, with clinical response are ongoing.
- Single-agent MET inhibitor remains the preferred therapeutic option for treatment-naive advanced NSCLC patients harboring *MET*ex14 skipping mutation.

This study is sponsored by Novartis.

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BACKGROUND

- *MET* exon 14 skipping mutation (*MET*ex14) is an established oncogenic driver for NSCLC, occurring in approximately 3% of non–small cell lung cancer (NSCLC) cases.[1-2] *MET*ex14 NSCLC is associated with poor prognosis and modest response to standard therapies, including immunotherapy.[3-5]
- Capmatinib is a small adenosine triphosphate competitive, orally bioavailable, potent, and selective inhibitor of the MET receptor tyrosine kinase. Capmatinib is approved as monotherapy for the treatment of patients with advanced NSCLC harboring *MET*ex14, based on the clinical data from an ongoing phase II GEOMETRY mono-1 study (NCT02414139).[6,7]
- Capmatinib monotherapy demonstrated an overall response rate (ORR) of 68.8% (95% CI: 50.0, 83.9) and median progression free survival (PFS) of 12.45 months (95% CI: 6.87, 20.50) in treatment-naive advanced NSCLC patients with *MET*ex14.[6,7]
- Preclinical studies suggested that MET signaling activation induces immunosuppression through diverse mechanisms. In syngeneic mouse models of several tumor types including lung cancer, combination of capmatinib and anti–programmed death protein-1 (PD-1) antibodies led to increased tumor T-cell infiltration and enhanced the immune-mediated antitumor activity compared to either single agent.[8-11]
- Spartalizumab, a humanized immunoglobulin G4 (IgG4) monoclonal antibody targeting PD-1, has demonstrated favorable safety profile and signals of antitumor activity in patients with advanced solid tumors.[12]
- We hypothesized that capmatinib plus spartalizumab combination may lead to enhanced and more durable antitumor response in advanced NSCLC with *MET*ex14 population.
- Here, we present the efficacy and safety outcomes from the run-in part of a Phase II study investigating capmatinib plus spartalizumab in treatment-naive patients with advanced *MET*ex14 NSCLC without *ALK* or *EGFR* alterations.

METHODS

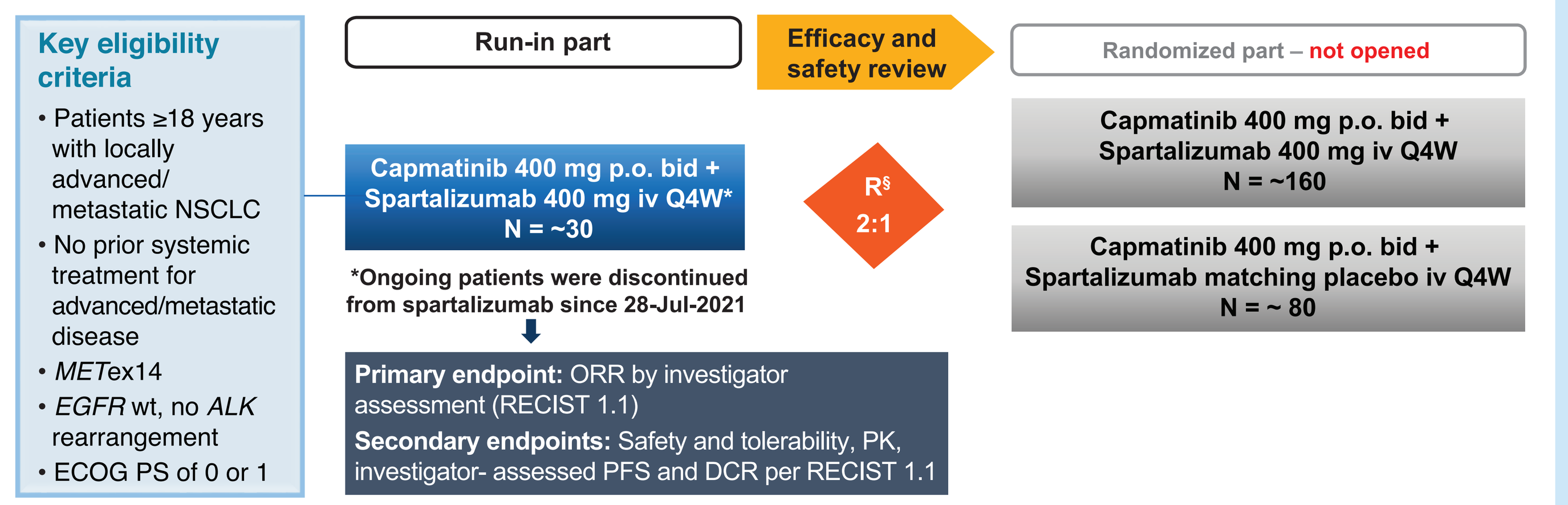
Study Design[13]

- This Phase II study (NCT04323436) consisted of 2 parts: open-label, single-arm run-in part, where patients received capmatinib 400 mg orally bid + spartalizumab 400 mg iv Q4W. This was to be followed by a randomized, double-blind, placebo-controlled part to evaluate the efficacy and safety of capmatinib + spartalizumab vs capmatinib + placebo (**Figure 1**).
- The primary endpoint of the run-in part of the study was investigator-assessed ORR as per RECIST v1.1. Secondary endpoints included safety and tolerability, pharmacokinetics (PK), investigator-assessed PFS and disease control rate (DCR) (**Figure 1**).

Statistical analysis

- In the run-in part, ORR as per investigator assessment was calculated based on full analysis set and the corresponding 95% CI based on the Clopper-Pearson exact binomial distribution was presented. Best overall response took into account all available efficacy assessments up to the data cut-off date (DCO). Evaluable patients must have had at least one post-baseline tumor assessment at DCO.

Figure 1. Study design



§Randomization is stratified by presence or absence of brain metastasis at baseline and PD-L1 expression (<1%, 1%-49%, ≥50%). *ALK*, anaplastic lymphoma kinase; bid, twice a day; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; iv, intravenous; *MET*, mesenchymal–epithelial transition factor; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non–small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; p.o., orally; Q4W, monthly; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; wt, wild type.

RESULTS

Patient disposition

- Based on the review of available data and in agreement with the study independent steering committee, the study enrollment was halted on July 28, 2021, during the run-in part, due to high rates of adverse events (AEs) leading to dose interruption and/or reduction and AEs leading to study treatment discontinuation observed with the combination (refer to **Table 4**). All ongoing patients were discontinued from spartalizumab and were allowed to continue with capmatinib alone.
- At the time of enrollment halt, the enrollment to the run-in part had been completed with a total of 31 patients (28 patients were treated with the combination and 3 patients, who were in screening at the time the enrollment halt was announced, received only capmatinib as study treatment from the start). The randomized part of the study was not opened.
- At data cut-off (DCO) of February 1, 2022, 16/31 (51.6%) patients had discontinued study treatment; 15 patients continued to receive capmatinib monotherapy in the study.
- The reasons for treatment discontinuation were AEs (n=6, 19.4%), progressive disease (n=5, 16.1%), patient decision (n=3, 9.7%), physician decision (n=1, 3.2%), and death (n=1, 3.2%). The death event was due to deterioration of the patient's general condition, considered as not related to the study treatment.
- Baseline characteristics of patients are described in **Table 1.**

Table 1. Baseline characteristics

Variable	Capmatinib + Spartalizumab N = 31
Age, years, median (min-max)	73.0 (52.0 to 89.0)
Age category, n (%)	
18 to <65	6 (19.4)
65 to <85	24 (77.4)
≥85 years	1 (3.2)
Female/Male, n (%)	16 (51.6) / 15 (48.4)
Race, n (%)	
Caucasian	23 (74.2)
African American	1 (3.2)
Asian	6 (19.4)
Unknown	1 (3.2)
Smoking history, n (%)	
Current	2 (6.5)
Former	17 (54.8)
Never	12 (38.7)
ECOG PS, n (%)	
0	12 (38.7)
1	19 (61.3)
Histology, n (%)	
Adenocarcinoma	29 (93.6)
Large Cell Carcinoma	1 (3.2)
Other	1 (3.2)
Disease stage at study entry, n (%)	
Stage IVA/ IVB	31 (100)
Prior antineoplastic agents	
Yes	1 (3.2)*
No	30 (96.8)
Prior radiotherapy	
Yes	6 (19.3)
No	25 (80.7)
Presence of brain metastasis, n (%)	9 (29.0)

*One patient received 4 cycles of adjuvant cisplatin plus gemcitabine with curative intent. The treatment was completed 9 years prior to study entry. ECOG PS, Eastern Cooperative Oncology Group performance status .

- The median age was 73 years and 51.6% were female. The majority of patients were Caucasian; were former smokers; had predominant tumor histology of adenocarcinoma; had stage IV disease at study entry; and had ECOG PS of 1. Nine patients (29%) had brain metastases at baseline.

Efficacy

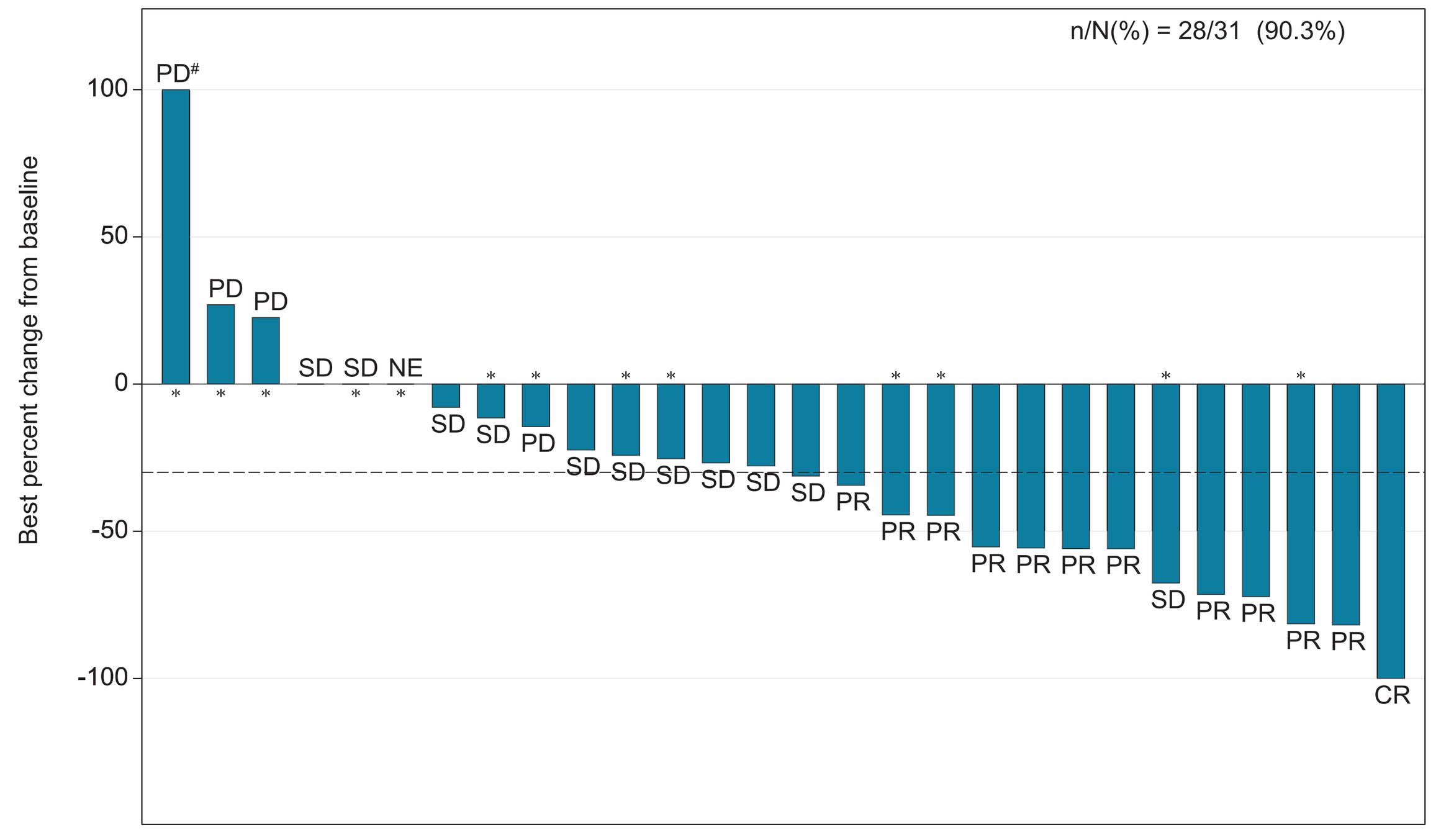
- The ORR was 38.7% (95% CI: 21.8, 57.8) and DCR was 77.4% (95% CI: 58.9, 90.4; **Table 2 and Figure 2).** Individual treatment durations and periodic efficacy assessments are shown in **Figure 3**.
- Median duration of response (DOR) was not reached; median PFS was 13.3 months (95% CI: 9.3, NA)

Table 2. Best overall response by investigator assessment (RECIST v1.1)

Variable	Capmatinib + Spartalizumab N =31
Best overall response, n (%)	
CR	1 (3.2)
PR	11 (35.5)
SD	12 (38.7)
PD	4 (12.9)
NE*	3 (9.7)
ORR (CR + PR), n (%) [95% CI]	**12 (38.7%)** [21.8%; 57.8%]
DCR (CR + PR + SD), n (%) [95% CI]	**24 (77.4%)** [58.9%; 90.4%]

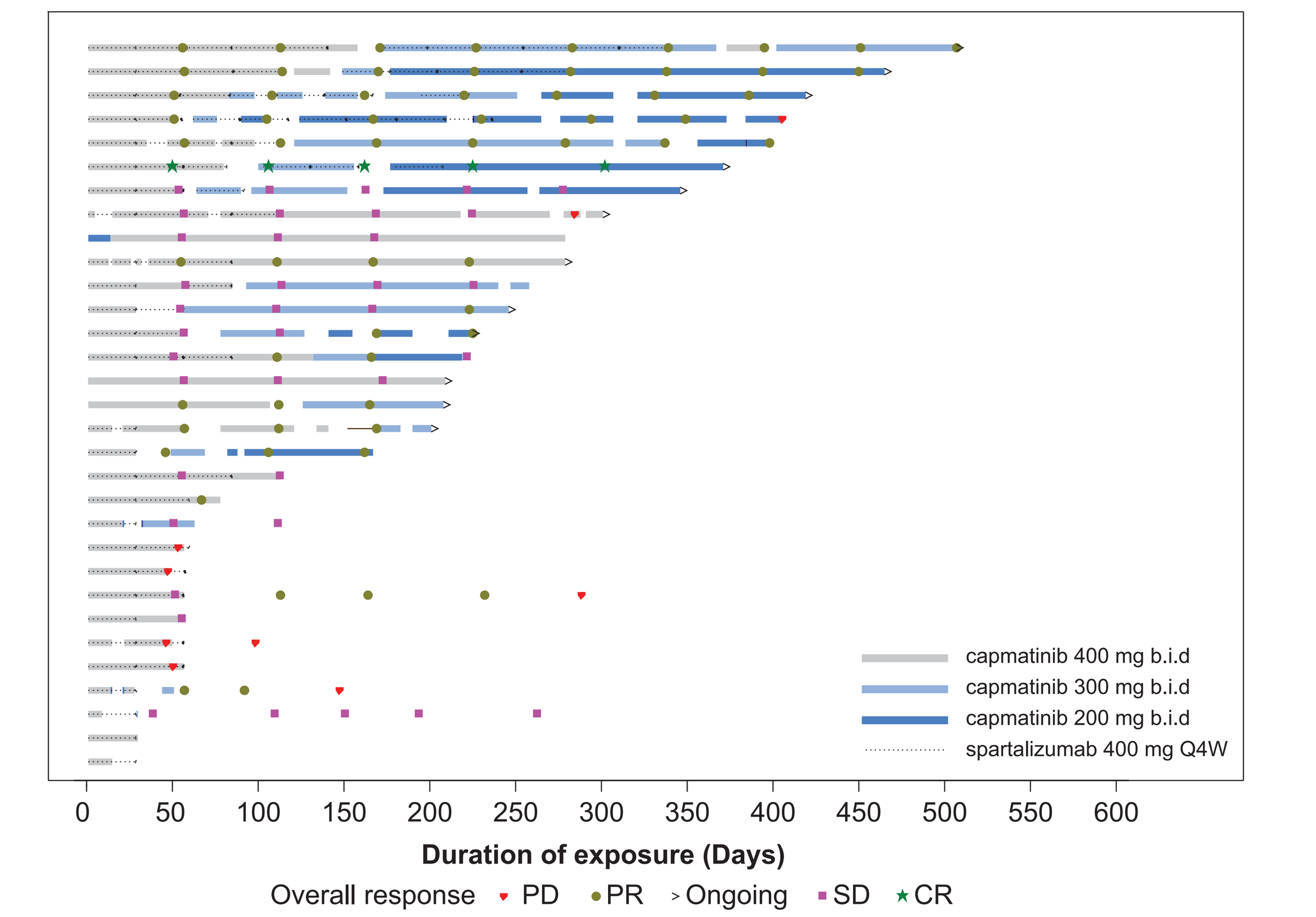
Full analysis set. *Patients with no available post-baseline efficacy assessments at DCO. CI, confidence interval; CR, complete response; DCR, disease control rate; n, number of patients who are at the corresponding category; N, total number of patients in the treatment group; NE, not evaluable; ORR, overall response rate; PR, partial response; PD, progressive disease; SD, stable disease.

Figure 2. Best percentage change from baseline in target lesions



Full analysis set. PD# indicates that the % change from baseline exceeds 100%. *Patient was ongoing at the data cut-off. CR, complete response; n, number of patients with a baseline and ≥ one post-baseline assessment of target lesions based on investigator's assessment; N, total number of patients in the treatment group; NE, not evaluable; PR, partial response; PD, progressive disease; SD, stable disease.

Figure 3. Duration of capmatinib plus spartalizumab treatment and overall response



Full analysis set. b.i.d, twice a day; CR, complete response; PR, partial response; PD, progressive disease; Q4W, monthly; SD, stable disease.

PK analysis

- With limited sample size, the preliminary PK results of both drugs showed consistency with prior monotherapy studies.[7,12]

Table 3. Preliminary PK analysis of capmatinib and spartalizumab

Capmatinib (n = 5)	AUC_{last} (hr*ng/mL)	AUC_{tau} (hr*ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
Geo-mean	12600	16800	3710	—
Geo-CV%	42.3	35.3	49.1	—
Median (min; max)	11200 (9260; 25500)	14700 (11900; 29200)	3250 (2490; 8310)	1.75 (1.00; 3.92)

Spartalizumab (n = 5)	AUC_{last} (hr*µg/mL)	AUC_{tau} (hr*µg/mL)	C_{max} (µg/mL)	T_{max} (hr)
Geo-mean	50800	55200	140	—
Geo-CV%	33.6	36.0	31.8	—
Median (min; max)	43200 (38200; 76900)	66900 (36600; 78800)	152 (95.3; 204)	1.0 (1.00; 97.1)

AUC, area under the curve; AUC_{last}, AUC from time zero to the last quantifiable concentration point; AUC_{tau}, AUC calculated to the end of the dosing interval; C_{max}, maximum serum concentration; CV, coefficient of variation; Geo, geometric; hr, hour; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration; n, number of patients with corresponding evaluable PK parameters.

Safety

- Median relative dose intensity was 80.9% (range: 30.2%–100%) and 100% (range: 66.7%–100%) for capmatinib and spartalizumab, respectively.
- Treatment-related SAE occurred in 11 patients (35.5%), all were grade [GR] ≥3. Twenty-five patients (80.6%) had dose reduction/interruption, and 11 patients (35.5%) discontinued study treatment due to AEs (any GR), all considered as treatment-related (**Table 4**).
- The most common TRAEs (any GR ≥30%) were peripheral edema (71.0%), elevated blood creatinine (45.2%), elevated ALT and AST (35.5% each) (**Table 5**).
- The most common TRAEs (any GR ≥5%) leading to treatment discontinuation were elevated ALT (22.6%) and elevated AST (9.7%); and TRAEs (any GR ≥10%) leading to dose reduction or interruption were peripheral edema (32.3%), elevated ALT and AST levels (25.8% each), and elevated blood creatinine (12.9%). There was no GR 3/4 interstitial lung disease and no fatal AEs were reported.

Table 4. Overall summary of AEs

Variable	Capmatinib + Spartalizumab N=31	
	Any GR, n (%)	**GR 3/4, n (%)**
All AEs	31 (100)	26 (83.9)
Treatment-related AEs	30 (96.8)	21 (67.7)
All SAEs	17 (54.8)	17 (54.8)
Treatment-related SAEs	11 (35.5)	11 (35.5)
All AEs leading to treatment discontinuation	11 (35.5)	10 (32.3)
Treatment-related AEs leading to treatment discontinuation	11 (35.5)	10 (32.3)
All AEs leading to dose reduction*/interruption#	25 (80.6)	23 (74.2)
Treatment-related AEs leading to dose reduction/interruption	25 (80.6)	21 (67.7)

Safety analysis set. n, represents counts of patients. A patient with multiple severity grades for an AE is only counted under the maximum grade. *represents dose reduction of capmatinib. #represents dose interruption of capmatinib and/or spartalizumab. MedDRA version 24, CTCAE version 5. AEs, adverse events; CTCAE, common terminology criteria for AEs; GR, grade; MedDRA, medical dictionary for regulatory activities; SAEs, serious adverse events.

Table 5. AEs suspected to be treatment-related (≥10%, any GR)

Preferred term	Capmatinib + Spartalizumab N = 31 n (%)	
	Any GR	**GR ≥3**
Peripheral edema	22 (71.0)	9 (29.0)
Elevated blood creatinine	14 (45.2)	0
Elevated ALT	11 (35.5)	8 (25.8)
Elevated AST	11 (35.5)	4 (12.9)
Nausea	9 (29.0)	0
Decreased appetite	6 (19.4)	0
Fatigue	6 (19.4)	0
Elevated blood bilirubin	5 (16.1)	0
Constipation	5 (16.1)	0
Hypoalbuminemia	5 (16.1)	0
Elevated lipase	5 (16.1)	3 (9.7)
Rash maculo-papular	5 (16.1)	1 (3.2)
Elevated amylase	4 (12.9)	1 (3.2)
Dyspnea	4 (12.9)	2 (6.5)
Thrombocytopenia	4 (12.9)	0
Increased weight	4 (12.9)	0

Safety analysis set. A patient with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 24.0, CTCAE version 5. All data are n (%). Numbers (n) represent counts of patients. AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for AEs; GR, grade; MedDRA, medical dictionary for regulatory activities.

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Presenting Author Disclosures

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