Poster 9020

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Capmatinib in *MET* exon 14-mutated, advanced NSCLC: updated results from the GEOMETRY mono-1 study

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KEY FINDINGS & CONCLUSIONS

- The preliminary efficacy results of expansion Cohort 7 (65.6% ORR) are comparable to those previously reported for Cohort 5b (67.9% ORR)[6], both in treatment-naive patients with *MET*ex14 NSCLC
- In pretreated patients, the ORR was 51.6% in 2L (Cohort 6) and 40.6% in 2/3L (Cohort 4)
- Clinically meaningful median OS of 20.8 months and 13.6 months were observed in treatment-naive (Cohort 5b) and pretreated patients (Cohort 4), respectively, demonstrating a long-term survival benefit of capmatinib in these patient populations
- The manageable safety profile of capmatinib remains unchanged based on the updated safety results from the GEOMETRY mono-1 study
- The updated results further confirm *MET*ex14 as a targetable oncogenic driver in NSCLC and strengthen the evidence for capmatinib as a valuable targeted treatment option for patients with *MET*ex14 NSCLC

This study is sponsored by Novartis Pharmaceuticals Corporation
Poster presented at ASCO 2021 held virtually on Friday, 4 June 2021

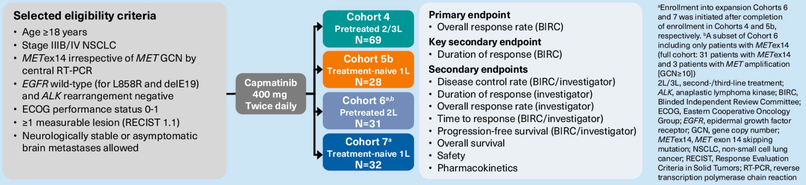
INTRODUCTION

- Capmatinib, an orally bioavailable, highly potent and selective MET inhibitor, is approved in the US and in Hong Kong for adult patients with metastatic non-small cell lung cancer (NSCLC) and *MET* exon 14 skipping mutation (*MET*ex14), and in Japan for patients with advanced and/or recurrent unresectable NSCLC and *MET*ex14[1-5]
- Previously published data from the open-label, multicohort GEOMETRY mono-1 Phase II study (NCT02414139) showed a clinically meaningful efficacy and manageable safety profile in patients with *MET*ex14 NSCLC who were either treatment-naive (Cohort 5b) or pretreated (Cohort 4 and expansion Cohort 6)[6]
- Here, we report the analysis of preliminary data from the *MET*ex14 expansion Cohort 7 in treatment-naive patients, along with updated efficacy data for the other *MET*ex14 cohorts, and safety data from all patients enrolled in the study

METHODS

- Adult patients with stage IIIB/IV NSCLC (any histology) and *MET*ex14 or *MET* amplification were enrolled and stratified into several cohorts based on previous lines of therapy and *MET* status[6]
- This analysis (data cutoff: Sep 18, 2020) includes patients with *MET*ex14 NSCLC who were treatment-naive (Cohorts 5b and 7) and those who had previously received 1 or 2 lines of therapy (Cohorts 4 and 6) (**Figure 1**)
- Patients were treated with capmatinib 400 mg twice daily, administered under fasting conditions in Cohorts 4 and 5b, and without fasting restrictions in the expansion Cohorts 6 and 7
- Efficacy outcomes were assessed by investigators and by a Blinded Independent Review Committee (BIRC) using RECIST 1.1, but only the BIRC-assessed results are presented here

Figure 1. GEOMETRY mono-1 study design: *MET*ex14 cohorts



[a]Enrollment into expansion Cohorts 6 and 7 was initiated after completion of enrollment in Cohorts 4 and 5b, respectively. [b]A subset of Cohort 6 including only patients with *MET*ex14 (full cohort: 31 patients with *MET*ex14 and 3 patients with *MET* amplification [GCN≥10])
2L/3L, second-/third-line treatment; *ALK*, anaplastic lymphoma kinase; BIRC, Blinded Independent Review Committee; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; GCN, gene copy number; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors; RT-PCR, reverse transcription polymerase chain reaction

RESULTS

Baseline characteristics and patient disposition

- At the data cutoff date, 160 patients with *MET*ex14 were enrolled in the 4 cohorts: 60 treatment-naive and 100 pretreated patients
  - Nineteen (31.7%) treatment-naive and 14 (14.0%) pretreated patients were still receiving treatment
  - Disease progression was the main reason for discontinuation: 22 (36.7%) treatment-naive and 58 (58.0%) pretreated patients
- Median age of patients in Cohort 7 was 73 years, 71.9% were female, and 62.5% never smokers. Most patients were diagnosed with adenocarcinomas (90.6%), and 18.8% of patients had brain metastases at baseline (**Table 1**)

Table 1. Baseline characteristics of 160 *MET*ex14 patients

Characteristic	Treatment-naive		Pretreated		All *MET*ex14 patients
	Cohort 5b N=28	Cohort 7 N=32	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	N=160
Median age, years (range)	71 (57-86)	73 (48-86)	71 (49-90)	69 (49-81)	71 (48-90)
Female patients, n (%)	18 (64.3)	23 (71.9)	40 (58.0)	16 (51.6)	97 (60.6)
Race, n (%)					
Caucasian	24 (85.7)	26 (81.3)	49 (71.0)	24 (77.4)	123 (76.9)
Asian	4 (14.3)	3 (9.4)	19 (27.5)	5 (16.1)	31 (19.4)
Other[a]	0	3 (9.4)	1 (1.4)	2 (6.5)	6 (3.8)
ECOG PS, n (%)					
0	7 (25.0)	7 (21.9)	16 (23.2)	10 (32.3)	40 (25.0)
≥1	21 (75.0)	25 (78.1)	53 (76.8)	21 (67.7)	120 (75.0)
Smoking history, n (%)					
Never smoked	18 (64.3)	20 (62.5)	40 (58.0)	19 (61.3)	97 (60.6)
Former smoker	9 (32.1)	11 (34.4)	27 (39.1)	10 (32.3)	57 (35.6)
Current smoker	1 (3.6)	1 (3.1)	2 (2.9)	2 (6.5)	6 (3.8)
Patients with brain metastases, n (%)	3 (10.7)	6 (18.8)	10 (14.5)	7 (22.6)	26 (16.3)
Histology, n (%)					
Adenocarcinoma	25 (89.3)	29 (90.6)	53 (76.8)	25 (80.6)	132 (82.5)
Squamous cell carcinoma	2 (7.1)	1 (3.1)	6 (8.7)	4 (12.9)	13 (8.1)
Large cell carcinoma	0	1 (3.1)	1 (1.4)	1 (3.2)	3 (1.9)
Others	1 (3.6)	1 (3.1)	9 (13.0)	1 (3.2)	12 (7.5)

[a]Others: Black, Native American, other, unknown
2/3L, second-/third-line treatment; ECOG, Eastern Cooperative Oncology Group; *MET*ex14, *MET* exon 14 skipping mutation; PS, performance status

Efficacy

- In the preliminary analysis of treatment-naive patients in Cohort 7, the overall response rate (ORR) was 65.6% (21 partial responses) which was in line with the previously reported ORR of 67.9% for Cohort 5b (**Table 2**)[6]
- In pretreated patients, ORR was 51.6% in second-line treatment (2L) and 40.6% in second- or third-line treatment (2/3L) (**Table 2**)
- Tumor size reduction was documented for treatment-naive and pretreated patients in expansion Cohorts 7 and 6, respectively (**Figure 2**)
- The onset of responses occurred early, within 2 months, for most patients in all cohorts: 68.4%, 66.7%, 82.1%, and 62.5% for Cohorts 5b, 7, 4, and 6, respectively
- Median progression-free survival (PFS) for Cohorts 5b, 4, and 6 has been reported previously.[6] Although not mature at the data cutoff date, the median PFS for treatment-naive patients in Cohort 7 was 10.8 months (**Table 2**)
- Median overall survival (OS) for treatment-naive patients from Cohort 5b was 20.8 months (95% confidence interval [CI], 12.4-NE; **Figure 3A**) and 13.6 months (95% CI, 8.6-22.2; **Figure 3B**) for pretreated patients in Cohort 4. Median OS for Cohorts 6 and 7 is not yet mature

Table 2. Key efficacy outcomes by BIRC in 160 *MET*ex14 patients

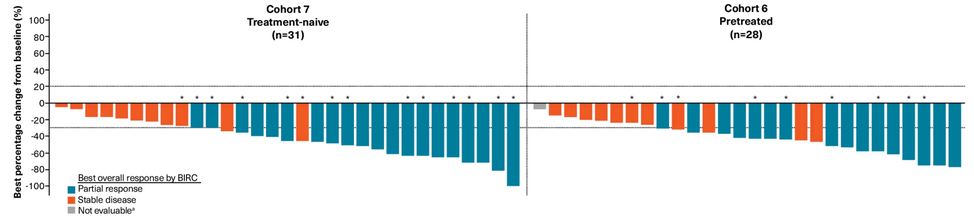
	Treatment-naive			Pretreated		
	Cohort 5b N=28	Cohort 7 N=32	All patients N=60	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All patients N=100
Best overall response, n (%)						
Complete response	1 (3.6)	0	1 (1.7)	0	0	0
Partial response	18 (64.3)	21 (65.6)	39 (65.0)	28 (40.6)	16 (51.6)	44 (44.0)
Stable disease	7 (25.0)	11 (34.4)	18 (30.0)	25 (36.2)	11 (35.5)	36 (36.0)
Non-complete response/ non-progressive disease	1 (3.6)	0	1 (1.7)	1 (1.4)	1 (3.2)	2 (2.0)
Progressive disease	1 (3.6)	0	1 (1.7)	6 (8.7)	0	6 (6.0)
Not evaluable[a]	0	0	0	9 (13.0)	3 (9.7)	12 (12.0)
ORR,[b] % (95% CI)	67.9 (47.6-84.1)	65.6 (46.8-81.4)	66.7 (53.3-78.3)	40.6 (28.9-53.1)	51.6 (33.1-69.8)	44.0 (34.1-54.3)
DCR,[c] % (95% CI)	96.4 (81.7-99.9)	100.0 (89.1-100.0)	98.3 (91.1-100.0)	78.3 (66.7-87.3)	90.3 (74.2-98.0)	82.0 (73.1-89.0)
DOR events,[d] n (%)	12 (63.2)	5 (23.8)	17 (42.5)	23 (82.1)	11 (68.8)	34 (77.3)
Median DOR, months (95% CI)	12.6 (5.6-NE)	NE (5.5-NE)	12.6 (8.4-NE)	9.7 (5.6-13.0)	8.4 (4.2-NE)	9.7 (5.6-13.0)
PFS events, n (%)	18 (64.3)	14 (43.8)	32 (53.3)	60 (87.0)	22 (71.0)	82 (82.0)
Median PFS, months (95% CI)	12.4 (8.2-23.4)	10.8 (6.9-NE)	12.3 (8.2-21.6)	5.4 (4.2-7.00)	6.9 (4.2-13.3)	5.5 (4.2-8.1)

[a]Unknown as per RECIST 1.1, ie, not qualified for confirmed complete response or partial response and without stable disease after more than 6 weeks or progression within the first 12 weeks. [b]ORR: Patients who achieved complete or partial response. [c]DCR: Patients who achieved complete response, partial response, stable disease or non-complete response/non-progressive disease. [d]For DOR calculations, the total number of responders (patients with confirmed complete or partial responses) as assessed by BIRC was used for percentage calculation: 19 responders in Cohort 5b, 21 responders in Cohort 7, 28 responders in Cohort 4, and 16 responders in Cohort 6
2/3L, second-/third-line treatment; BIRC, Blinded Independent Review Committee; CI, confidence interval; DCR, disease control rate; DOR, duration of response; *MET*ex14, *MET* exon 14 skipping mutation; NE, not estimated; ORR, overall response rate; PFS, progression-free survival

Safety

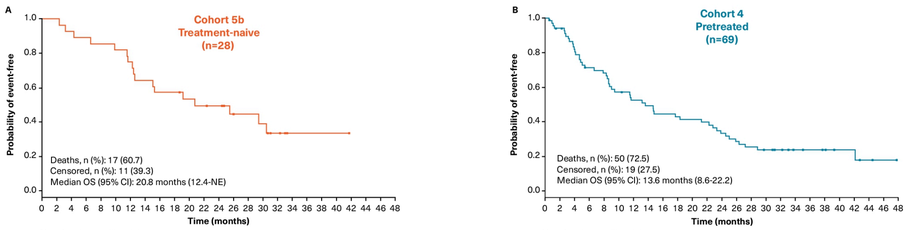
- Overall, capmatinib demonstrated a manageable safety profile and there were no new safety signals or unexpected safety findings. Out of 373 patients across all cohorts, including patients with *MET*ex14 and *MET* amplification, 367 (98.4%) experienced an adverse event (AE) of any grade irrespective of study-drug relationship
- The most common AEs (≥20%, all grades) regardless of causality were peripheral edema (54.2%), nausea (45.0%), vomiting (28.2%), increased blood creatinine (26.5%), dyspnea (23.3%), fatigue (22.3%), and decreased appetite (21.2%) (**Table 3**)
  - Treatment-related AEs were reported in 86.9% of patients, and the most frequent (≥20%, all grades) were peripheral edema (46.1%) and nausea (34.3%)
- Serious AEs (SAEs) of any grade and irrespective of study-drug relationship were reported in 190 (50.9%) patients; 13.1% were suspected to be treatment-related
- AEs irrespective of study-drug relationship leading to discontinuations occurred in 60 (16.1%) patients. There were 4 (1.1%) treatment-related fatal SAEs: cardiac arrest, hepatitis, organizing pneumonia, and pneumonitis, with 1 (0.3%) patient each

Figure 2. BIRC-determined change in tumor size from baseline for treatment-naive (Cohort 7) and pretreated (Cohort 6) patients with *MET*ex14 NSCLC



n (number of patients with measurable disease at baseline and at least one valid postbaseline assessment) was used for calculation of percentages.
[a]Patients still on-treatment. [a]Unknown as per RECIST 1.1, ie, not qualified for confirmed complete response or partial response and without stable disease after more than 6 weeks or progression within the first 12 weeks
BIRC, Blinded Independent Review Committee; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease; UNK, unknown

Figure 3. (A) Overall survival for treatment-naive patients with *MET*ex14 NSCLC in Cohort 5b. (B) Overall survival for pretreated (2/3L) patients with *MET*ex14 NSCLC in Cohort 4



1L/2L/3L, first-/second-/third-line treatment; CI, confidence interval; *MET*ex14, *MET* exon 14 skipping mutation; NE, not estimated; NSCLC, non-small cell lung cancer

Table 3. Most common adverse events regardless of causality (≥20%, all grades)

	Treatment-naive				Pretreated				All patients[a]	
	Cohort 5b N=28		Cohort 7 N=32		Cohort 4 (2/3L) N=69		Cohort 6 (2L) N=31		N=373	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any event, n (%)	28 (100)	21 (75.0)	31 (96.9)	20 (62.5)	68 (98.6)	52 (75.4)	31 (100)	18 (58.1)	367 (98.4)	256 (68.6)
Most common events, n (%)										
Peripheral edema	21 (75.0)	3 (10.7)	23 (71.9)	4 (12.5)	37 (53.6)	10 (14.5)	22 (71.0)	4 (12.9)	202 (54.2)	36 (9.7)
Nausea	13 (46.4)	0	14 (43.8)	0	32 (46.4)	0	10 (32.3)	1 (3.2)	168 (45.0)	9 (2.4)
Vomiting	7 (25.0)	0	5 (15.6)	1 (3.1)	19 (27.5)	0	8 (25.8)	0	105 (28.2)	9 (2.4)
Increased blood creatinine	10 (35.7)	0	10 (31.3)	0	23 (33.3)	0	9 (29.0)	0	99 (26.5)	0
Dyspnea	6 (21.4)	2 (7.1)	2 (6.3)	1 (3.1)	19 (27.5)	7 (10.1)	3 (9.7)	0	87 (23.3)	25 (6.7)
Fatigue	4 (14.3)	1 (3.6)	6 (18.8)	0	18 (26.1)	6 (8.7)	9 (29.0)	0	83 (22.3)	16 (4.3)
Decreased appetite	8 (28.6)	0	5 (15.6)	1 (3.1)	15 (21.7)	1 (1.4)	5 (16.1)	0	79 (21.2)	4 (1.1)

[a]All patients with *MET*-dysregulated advanced NSCLC in the trial (includes *MET*ex14 and *MET* amplification)
2/3L, second-/third-line treatment; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer

Acknowledgements

The authors would like to thank our patients, their families and caregivers, the participating clinical sites and teams. Capmatinib was originally developed by Incyte Corporation, and was in-licensed by Novartis as of November 24, 2009. This study was sponsored by Novartis Pharmaceuticals Corporation. The authors thank Sara Henriques, of Chameleon Communications, London, UK, for providing medical writing assistance, which was funded by Novartis, East Hanover, NJ, USA, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3)

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