Molecular correlates of response to capmatinib in advanced non-small-cell lung cancer: clinical and biomarker results from a phase I trial

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Background: Dysregulation of receptor tyrosine kinase MET by various mechanisms occurs in 3%—4% of non-small-cell lung cancer (NSCLC) and is associated with unfavorable prognosis. While MET is a validated drug target in lung cancer, the best biomarker strategy for the enrichment of a susceptible patient population still remains to be defined. Towards this end we analyze here primary data from a phase I dose expansion study of the MET inhibitor capmatinib in patients with advanced MET-dysregulated NSCLC.

Patients and methods: Eligible patients [$\geq$18 years; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2] with MET-dysregulated advanced NSCLC, defined as either (i) MET status by immunohistochemistry (MET IHC) 2+ or 3+ or H-score $\geq$150, or MET/centromere ratio $\geq$2.0 or gene copy number (GCN) $\geq$5, or (ii) epidermal growth factor receptor wild-type (EGFRwt) and centrally assessed MET IHC 3+, received capmatinib at the recommended dose of 400 mg (tablets) or 600 mg (capsules) b.i.d. The primary objective was to determine safety and tolerability; the key secondary objective was to explore antitumor activity. The exploratory end point was the correlation of clinical activity with different biomarker formats.

Results: Of 55 patients with advanced MET-dysregulated NSCLC, 40/55 (73%) had received two or more prior systemic therapies. All patients discontinued treatment, primarily due to disease progression (69.1%). The median treatment duration was 10.4 weeks. The overall response rate per RECIST was 20% (95% confidence interval, 10.4—33.0). In patients with *MET* GCN $\geq$6 (*n* = 15), the overall response rate by both the investigator and central assessments was 47%. The median progression-free survival per investigator for patients with *MET* GCN $\geq$6 was 9.3 months (95% confidence interval, 3.8—11.9). Tumor responses were observed in all four patients with *METex14*. The most common toxicities were nausea (42%), peripheral edema (33%), and vomiting (31%).

Conclusions: *MET* GCN $\geq$6 and/or *METex14* are suited to predict clinical activity of capmatinib in patients with NSCLC (NCT01324479).

Key words: capmatinib, MET amplification, MET exon 14, MET mutation, NSCLC

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INTRODUCTION

Aberrant signaling through the MET receptor tyrosine kinase is frequently encountered over a wide range of malignancies. Increased MET kinase activity triggers a highly diverse set of signaling cascades, resulting in pleiotropic effects on tumor cells, including survival, proliferation, metastasis, and drug resistance. Several mechanisms have

been identified by which the MET pathway becomes aberrantly activated in cancer. In epidermal growth factor receptor (*EGFR*) wild-type (wt) non-small-cell lung cancer (NSCLC), sporadic *MET* gene copy gain is detected in about 1%—4% of newly diagnosed cases.[1–3] *MET* amplification is also implicated in acquired resistance to EGFR tyrosine kinase inhibitors (TKIs), reported in 5%—26% of cases, regardless of the presence of the *T790M* mutation.[4–10] Genetic mutation is another way in which the MET pathway can be activated. Among them, mutations disrupting splice acceptor or donor sites leading to skipping of *MET* exon 14 that encodes the CBL binding site were identified in primary resected NSCLC. These genomic events result in a functionally activated MET receptor through stabilization and delayed internalization.[11,12] Such splice site alterations involving exon 14 (*METex14*) are detected in up to 3% of NSCLC.[13–18]

Capmatinib (INC280) is a highly potent MET inhibitor in biochemical (IC$_{50}$ 0.13 nM) and cellular assays across a range of tumor types, including NSCLC, that also causes regression of MET-dependent (amplified/autocrine) tumor models in animals at well-tolerated doses.[19] Capmatinib has been demonstrated to be highly selective versus other kinases in large panels of biochemical and binding assays.[19] In the completed dose-escalation part of this phase I study, the recommended phase II dose (RP2D) of capmatinib was established as 400 mg twice daily (b.i.d.) in tablet formulation or 600 mg b.i.d. in capsule formulation. The current established dose of capmatinib is 400 mg b.i.d. in tablet formulation. Efficacy was reported from expansion groups evaluating capmatinib in patients with advanced solid tumors.[20,21] We report here on the efficacy and safety of capmatinib, and the definition of clinically applicable predictive biomarkers in patients with advanced MET-dysregulated NSCLC treated at the RP2D in two dedicated expansion groups.

METHODS

Study design and treatment

In the expansion phase, patients with solid tumors, including an original NSCLC expansion group, were enrolled based on MET dysregulation. The initial expansion group enrolled patients with either local or central assessment of MET dysregulation, including MET overexpression and amplification, at the 600 mg b.i.d. capsule dose. An additional group of patients was added to enroll patients with *EGFR*wt NSCLC with high MET status by immunohistochemistry (MET IHC 3+) as determined by a central laboratory at the 400 mg b.i.d. tablet dose. Patient selection criteria by MET status were further refined by *post hoc* analyses of genomic aberrations [*MET* gene copy number (GCN) gain and amplification by FISH and *MET* mutation by next-generation sequencing (NGS)], where sufficient tumor sample was available. The primary objective of the study, completed in the dose-escalation part (part 1), was to determine the maximum tolerated dose (MTD)/RP2D of single-agent oral capmatinib [based on the incidence, frequency, and category of dose-limiting toxicities (in cycle 1) and adverse events (AEs)]. The key secondary end point was overall response rate (ORR) per RECIST (by investigator assessment). The key secondary objective in this second, expansion part (part 2) of the study reported here, was to explore the antitumor activity of capmatinib in patients with MET-dependent NSCLC. Additional information is provided in supplementary Appendix, available at *Annals of Oncology* online.

Patients

This study enrolled adult patients (aged ≥18 years) with advanced (stage IIIB or IV, any histology) NSCLC refractory to currently available therapies or for which no effective treatment is available. Molecular biomarker status criteria in the original NSCLC dose expansion group were MET H-score ≥150 or a ratio of *MET*/centromere ≥2.0, or *MET* GCN ≥5, or ≥50% of tumor cells with IHC score 2+ or 3+ determined either locally or centrally. In the additional NSCLC expansion group, molecular biomarker status criteria were MET IHC 3+ expression in ≥50% of tumor cells determined centrally and documented *EGFR*wt status. MET expression levels were determined by anti-total c-MET (SP44) rabbit monoclonal antibody (Ventana Medical Systems, Tuscon, AZ, #790-4430). Retrospective central analyses were carried out to determine *MET* gene copy gain or amplification (FISH) and mutation (NGS) in all patients with available tumor samples. NGS analysis, carried out using the Foundation Medicine®, Cambridge, MA T7 panel, interrogated 395 genes as well as introns of 31 genes involved in rearrangements. No more than three lines of prior therapy were allowed in the *EGFR*wt MET IHC 3+ NSCLC expansion group (unless accepted following discussion with the study sponsor). Other key inclusion criteria were one or more measurable lesions per RECIST v1.1 in the *EGFR*wt MET IHC 3+ NSCLC expansion group and Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Exclusion criteria are included in the supplementary Appendix, available at *Annals of Oncology* online.

Clinical assessments

Tumor lesions were assessed (investigator-confirmed) using computed tomography unless contraindicated, in which case magnetic resonance imaging with contrast was carried out. Additional information is provided in supplementary Appendix, available at *Annals of Oncology* online.

Statistical analysis

The data cut-off date for this report was 17 July 2017, when all patients had discontinued. No formal statistical hypothesis was tested. Additional information is provided in supplementary Appendix, available at *Annals of Oncology* online.

RESULTS

Patient characteristics and disposition

At the primary analysis cut-off date of 17 July 2017, a total of 55 patients with NSCLC were enrolled: 26 patients were

from the original dose expansion group and 29 patients from the *EGFR*wt MET IHC 3+ group (supplementary Figure S1, available at *Annals of Oncology* online). All of the 26 patients in the original expansion group received capsules, and of these, seven patients subsequently switched to tablets. In the *EGFR*wt MET IHC 3+ group, all patients received tablets.

Baseline demographics and disease characteristics are presented in Table 1. The majority of patients were white (73%), had stage IV disease (76%) at initial diagnosis, adenocarcinoma histology (89%), and an ECOG performance status of ≤1 (96%). Overall, 52 patients (95%) had received one or more prior antineoplastic regimens, with 20 patients (36%) receiving three or more regimens. In total, 21 patients (38%) presented with controlled brain metastases at study entry.

At the data cut-off date, all patients had discontinued treatment, with disease progression [38 patients (69%)] being the primary reason, followed by AEs [11 patients (20%)], withdrawal of consent [four patients (7%)], lost to follow-up [one patient (2%)], and because of transfer to rollover study [one patient (2%)].

Efficacy

Overall, a complete response (CR) by RECIST was reported in 1/55 assessable patients and partial responses (PRs) were observed in 10/55 assessable patients (ORR 20%) per investigator assessment (Table 2); the ORR by investigator assessment in the original expansion group was 19% [95% confidence interval (CI) 6.6—39.4] with five PRs. The ORR was 21% (95% CI 8—39.7) with one CR and five PRs in the *EGFR*wt MET IHC 3+ NSCLC patient group. Overall 38/55 patients experienced some reduction in tumor size as best response, and 6/55 patients had a percentage change in target lesion contradicted by overall lesion response equivalent to progressive disease (Figure 1). The median duration of response for responders is shown in Figure 2.

Combined analysis of all assessable patients (*n* = 37) with MET IHC 3+ NSCLC revealed one CR and eight PRs (ORR 24%; Table 2, Figure 1) per investigator assessment. Assessable patients (*n* = 15) with *MET* GCN ≥6 (24% also had MET IHC 3+ expression) reported one CR and six PRs (ORR 47%; Table 2, Figure 1) per investigator assessment.

There were 41 NSCLC patients with available *MET/CEP7* ratios; of these, nine were reported to have *MET/CEP7* ratio of ≥2.0 and the other 32 patients had *MET/CEP7* ratio <2.0. In the nine patients with *MET/CEP7* ratio of ≥2.0, one CR and two PRs were reported per investigator assessment. Of the 46 NSCLC patients with available H-score, 17 patients had reported H-score equal to 300, 25 patients had H-score ≥150 to <300, and the remaining four patients had H-score <150. Based on investigator assessment, 4/17 patients with H-score of 300 had a best overall response of CR or PR (one CR and three PRs); 4/25 patients with H-score of ≥150 and <300 had a best overall response of PR (Table 2). Response

Table 1. Patient demographics and disease characteristics			
Characteristic/demographic	NSCLC original expansion group *N* = 26	NSCLC *EGFR*wt MET IHC3+ expansion group *N* = 29	All NSCLC patients in both expansion groups *N* = 55
Age, years, median (range)	60 (29—81)	61 (44—84)	60 (29—84)
Sex, male, *n* (%)	13 (50)	20 (69)	33 (60)
Race, *n* (%)			
White	20 (77)	20 (69)	40 (73)
Asian	6 (23)	9 (31)	15 (27)
ECOG PS, *n* (%)			
0	15 (58)	4 (14)	19 (35)
1	10 (38)	24 (83)	34 (62)
2	1 (4)	1 (3)	2 (3)
Prior systemic therapy, *n* (%)	25 (96)	27 (93)	52 (95)
0	1 (4)	2 (7)	3 (5)
1	5 (19)	15 (52)	12 (22)
2	6 (23)	6 (21)	20 (36)
≥3	14 (54)	6 (21)	20 (36)
Histology, *n* (%)			
Adenocarcinoma	21 (81)	28 (97)	49 (89)
Large-cell carcinoma	1 (4)	0	1 (2)
Mucinous adenocarcinoma	1 (4)	0	1 (2)
Squamous cell carcinoma	2 (8)	0	2 (4)
EGFR, *n* (%)			
Wild-type	20 (77)	29 (100)	49 (89)
Mutant	1 (4)	0	1 (2)
Unknown	5 (19)	0	5 (9)
ALK, *n* (%)			
Negative	22 (85)	29 (100)	51 (93)
Unknown	4 (15)	0	4 (7)
Brain metastases at baseline, *n* (%)	11 (42)	10 (35)	21 (38)

ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*wt, epidermal growth factor receptor wild-type; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer.

Table 2. Best overall response by MET status treatment group per investigator and BIRC assessment

Investigator assessment	MET IHC N = 54			MET GCN N = 44			MET/CEP7 ratio N = 41		MET H-score N = 46			METex14 N = 4	All patients N = 55
	0/1+ (n = 3)	2+ (n = 14)	3+ (n = 37)	<4 (n = 17)	≥4 and <6 (n = 12)	≥6 (n = 15)	≥2 (n = 9)	<2 (n = 32)	<150 (n = 4)	≥150 and <300 (n = 25)	=300 (n = 17)		
Complete response	0	0	1	0	0	1	1	0	0	1	0	1	1
Partial response	0	2	8	0	2	6	2	5	1	3	4	2	10
Stable disease	2	1	14	8	4	5	3	13	2	8	7	1	17
Progressive disease	0	8	8	5	3	2	2	7	0	8	4	0	17
Unknown	1	3	6	4	3	1	1	7	1	5	2	0	10
Overall response rate, n (%) (95% CI)	0 (0.0—70.8)	2 (14) (1.8—42.8)	9 (24) (11.8—41.2)	0 (0.0—19.5)	2 (17) (2.1—48.4)	7 (47) (21.3—73.4)	3 (33) (7.5—70.1)	5 (16) (5.3—32.8)	1 (25) (0.6—80.6)	4 (16) (4.5—36.1)	4 (24) (6.8—49.9)	3 (75) (19.4—99.4)	11 (20) (10.4—33.0)
Disease control rate, n (%) (95% CI)	2 (67) (9.4—99.2)	3 (21) (4.7—50.8)	23 (62) (44.8—77.5)	8 (47) (23.0—72.2)	6 (50) (21.1—78.9)	12 (80) (51.9—95.7)	6 (67) (29.9—92.5)	18 (56) (37.7—73.6)	3 (75) (19.4—99.4)	12 (48) (27.8—68.7)	11 (65) (38.3—85.8)	4 (100.0) (39.8—100.0)	28 (51) (37.1—64.6)

BIRC assessment	MET IHC N = 54			MET GCN N = 44			MET/CEP7 ratio N = 41		MET H-score N = 46			METex14 N = 4	All patients N = 55
	0/1+ (n = 3)	2+ (n = 14)	3+ (n = 37)	<4 (n = 17)	≥4 and <6 (n = 12)	≥6 (n = 15)	≥2 (n = 9)	<2 (n = 32)	<150 (n = 4)	≥150 and <300 (n = 25)	=300 (n = 17)		
Complete response	0	0	1	0	0	1	1	0	0	1	0	1	1
Partial response	0	2	9	1	3	6	3	7	0	3	7	2	11
Stable disease	1	2	13	7	2	5	2	10	2	7	4	1	16
Progressive disease	1	6	7	5	3	2	2	7	1	8	2	0	15
Unknown	1	4	7	4	4	1	1	8	1	6	4	0	12
Overall response rate, n (%) (95% CI)	0 (0.0—70.8)	2 (14) (1.8—42.8)	10 (27) (13.8—44.1)	1 (6) (0.1—28.7)	3 (25) (5.5—57.2)	7 (47) (21.3—73.4)	4 (44) (13.7—78.8)	7 (22) (9.3—40.0)	0 (0.0—60.2)	4 (16) (4.5—36.1)	7 (41) (18.4—67.1)	3 (75) (19.4—99.4)	12 (22) (11.8—35.0)
Disease control rate, n (%) (95% CI)	1 (33) (0.8—90.6)	4 (29) (8.4—58.1)	23 (62) (44.8—77.5)	8 (47) (23.0—72.2)	5 (42) (15.2—72.3)	12 (80) (51.9—95.7)	6 (67) (29.9—92.5)	17 (53) (34.7—70.9)	2 (50) (6.8—93.2)	11 (44) (24.4—65.1)	11 (65) (38.3—85.8)	4 (100.0) (39.8—100.0)	28 (51) (37.1—64.6)

BIRC, blinded independent review committee; CI, confidence interval; GCN, gene copy number; IHC, immunohistochemistry.
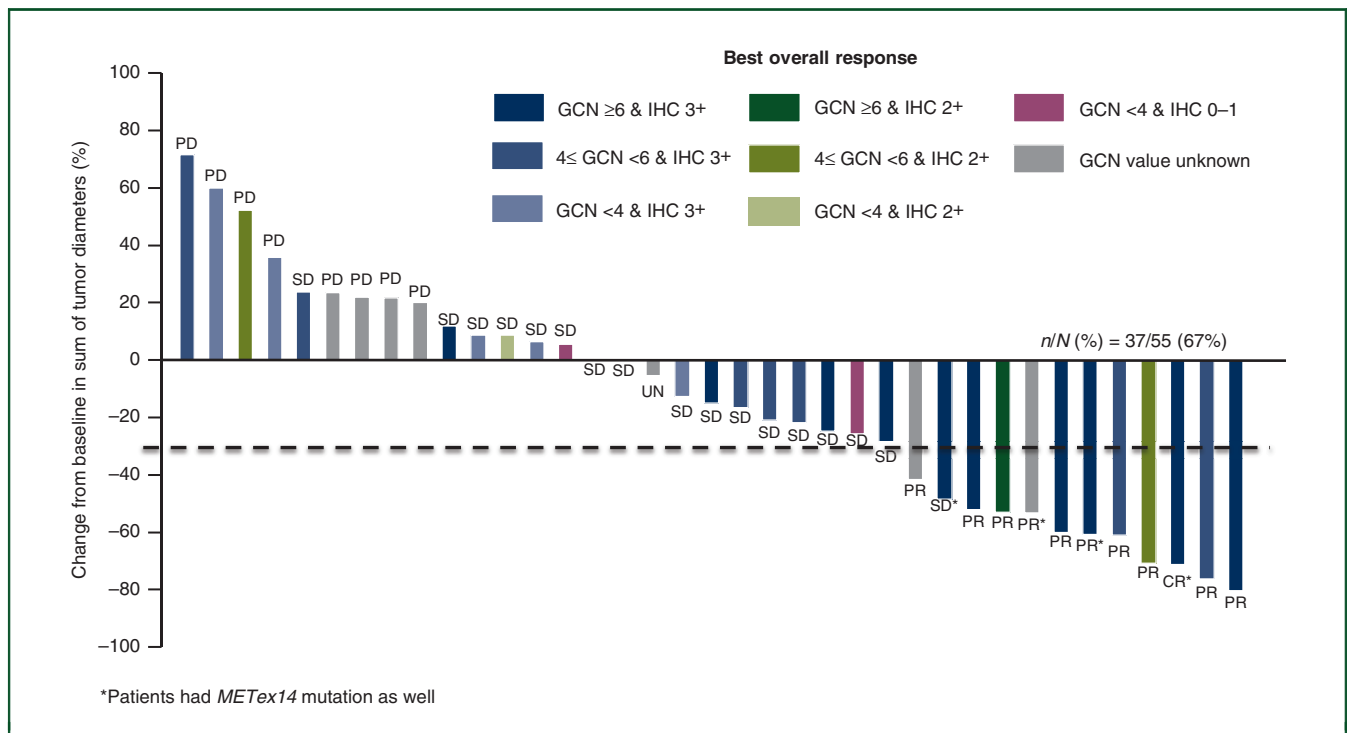
Figure 1. Best percentage change from baseline in sum of longest diameters in all NSCLC patients from both expansion groups.
MET IHC scores and MET GCN status are shown using different colors in the waterfall plot (investigator assessment, full analysis set; data cut-off 17 July 2017). A total of 17 patients had no evaluable responses due to lack of post-baseline tumor assessment or percentage change in target lesion contradicted by overall lesion response at the time of data cut-off. n is the total number of events included in the analysis; N is the total number of patients included in the analysis.
CR, complete response; GCN, gene copy number; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; UN, unknown.

rates were consistent between the investigator assessment and blinded independent review committee (BIRC) assessment (Table 2 and supplementary Table S1, available at *Annals of Oncology* online).

The median progression-free survival (PFS) for all patients (*n* = 55) with NSCLC in both expansion groups was 3.7 months (95% CI 1.8—7.3, 80% PFS events) per investigator assessment (RECISTv1.1) and 3.7 months (95% CI 1.9—7.4,
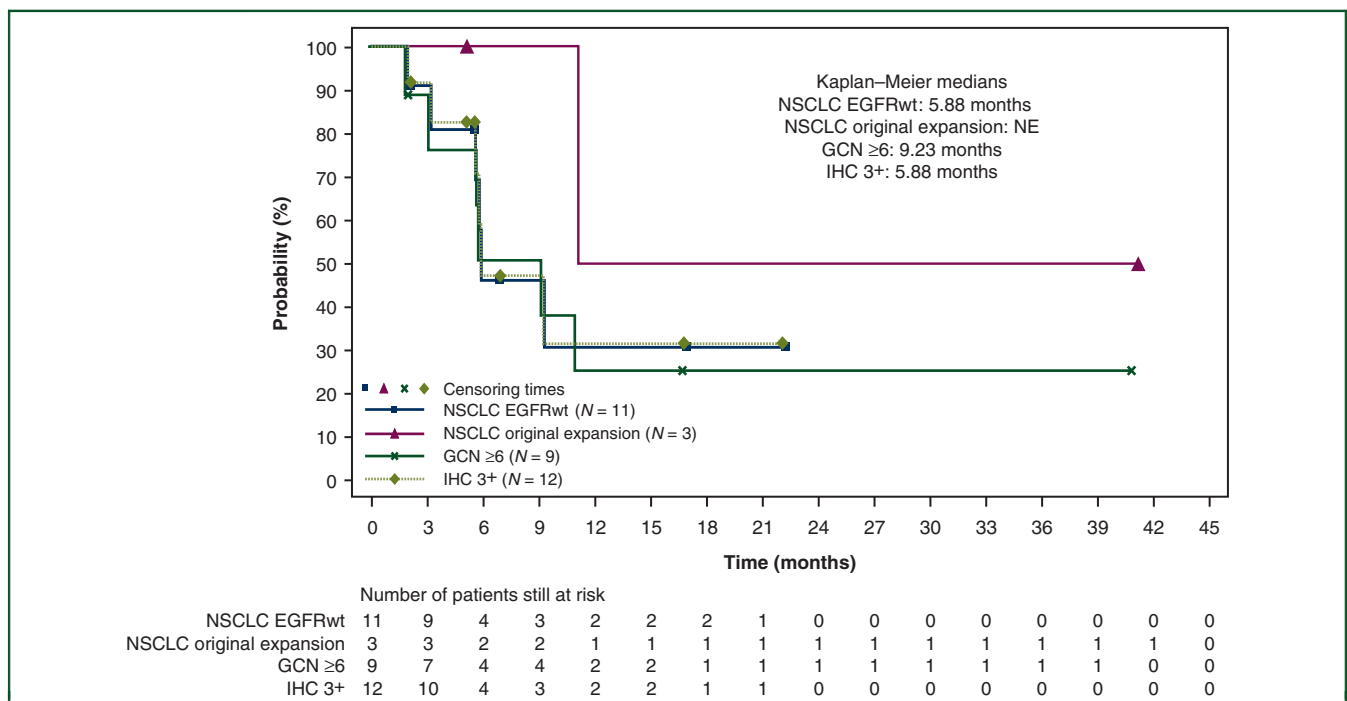

Figure 2. Duration of response per BIRC assessed by RECIST v1.1 by group, GCN status ≥6 and IHC 3+ for NSCLC patients using Kaplan—Meier method.
BIRC, blinded independent review committee; EGFRwt, epidermal growth factor receptor wild-type; GCN, gene copy number; IHC, immunohistochemistry; NE, not estimable; NSCLC, non-small-cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.
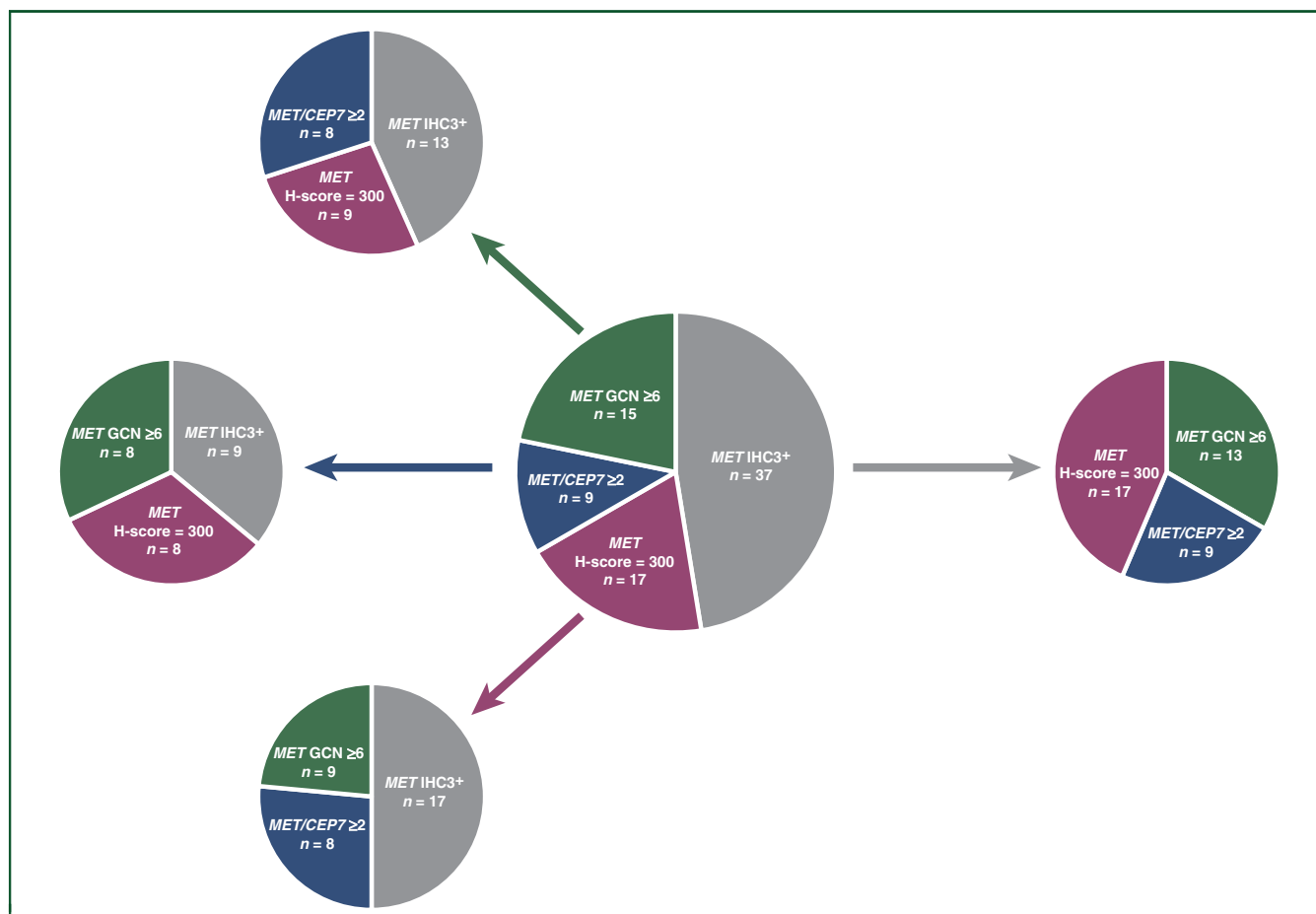
Figure 3. Venn diagram showing overlap of MET IHC 3+, GCN ≥6, H-score = 300, and *MET/CEP7* ≥2.
GCN, gene copy number; IHC, immunohistochemistry.

67% PFS events) per BIRC, assessed by RECISTv1.1. The median PFS in the original NSCLC expansion group ($N = 26$) was 2.0 months (95% CI 1.6—7.4, 73% PFS events) versus 5.1 months (95% CI 1.9—7.9, 62% PFS events) in the *EGFR*wt MET IHC 3+ group ($N = 29$), assessed by BIRC. Across both expansion groups ($N = 55$), the median PFS for patients with MET IHC 3+ tumors was 7.3 months (95% CI 3.0—8.2, 76% PFS events) per investigator assessment and 7.3 months (95% CI 3.5—8.1, 62% PFS events) per BIRC. The median PFS for patients with *MET* GCN ≥6 ($n = 15$) was 9.3 months (95% CI 3.8—11.9, 73% PFS events) per investigator and 7.9 months (95% CI 3.6—12.8, 67% PFS events) per BIRC. In patients with *MET/CEP7* ratio of ≥2.0, median PFS was 5.6 months (95% CI 1.0—11.0) per investigator assessment. Among the patients with H-score of ≥150 to <300 and 300, the median PFS by investigator assessment was 3.0 months (95% CI 1.7—7.4) and 7.3 months (95% CI 1.8—9.2), respectively.

Supplementary Table S2, available at *Annals of Oncology* online, depicts the biomarker profile by GCN and IHC status. Overall, 13/55 patients (24%) had a GCN status ≥6 and IHC status 3+. Among 15 patients with GCN status ≥6, there were eight patients who reported *MET/CEP7* ratio of ≥2, of which responses were observed in three patients. Furthermore, there were eight patients who had H-score of 300

and GCN status ≥6. All patients with *MET/CEP7* ratio of ≥2.0 also had IHC status 3+. Overlaps between MET IHC, GCN, *MET/CEP7*, and H-score are available in Figure 3.

There were 39 patients eligible for retrospective central NGS panel analysis interrogating 395 cancer-related genes as well as introns of 31 cancer-related genes, of which eight patients had failed results. Among the 31 evaluable specimens, four patients had *METex14* (two each in the original expansion group and *EGFR*wt MET IHC 3+ NSCLC patients group) mutated NSCLC, all of whom showed tumor shrinkage ranging from 14% to 83% (one CR, two PRs, one stable disease) (Table 2; details of individual patients provided in supplementary Table S3, available at *Annals of Oncology* online). Specific genomic alterations of four patients with *METex14* were as follows: patient 1—missense D1010H, *MET/CEP7* ratio was not recorded; patient 2—splice site 3028+1G>T, FISH *MET/CEP7* ratio was 2.32, FISH *MET* GCN was 13.8; patient 3—splice site 2888_19/ 2888_3del17, FISH *MET/CEP7* ratio was 4.7, FISH *MET* GCN was 13.6; and patient 4—missense D1010N, FISH *MET/CEP7* ratio was 4.40, FISH *MET* GCN was 11.2.

Safety

The median duration of exposure with capmatinib b.i.d. dosing was 2.4 months (range, 0.03—43.01); 73% of the

Table 3. Adverse events, regardless of causality (any grade occurring in ≥10% of patients and corresponding grades 3/4)

Preferred term	All patients N = 55	
	All grades n (%)	Grades 3/4 n (%)
Nausea	28 (60)	2 (4)
Peripheral edema	25 (46)	2 (4)
Vomiting	22 (40)	2 (4)
Decreased appetite	17 (31)	2 (4)
Fatigue	15 (27)	2 (4)
Dyspnea	14 (26)	2 (4)
Blood creatinine increased	13 (24)	0
Asthenia	11 (20)	2 (4)
Diarrhea	11 (20)	2 (4)
Back pain	10 (18)	1 (2)
Hypoalbuminemia	9 (16)	3 (6)
Alanine aminotransferase increase	8 (15)	3 (6)
Cough	8 (15)	0
Hypokalemia	8 (15)	3 (6)
Musculoskeletal pain	8 (15)	0
Pyrexia	8 (15)	0
Abdominal pain	7 (13)	2 (4)
Amylase increase	7 (13)	4 (7)
Headache	7 (13)	0
Pneumonia	7 (13)	4 (7)
Arthralgia	6 (11)	0
Aspartate aminotransferase increase	6 (11)	2 (4)
Constipation	6 (11)	1 (2)
Dizziness	6 (11)	0
Pruritus	6 (11)	0
Stomatitis	6 (11)	0

patients received >90% of the planned dose of capmatinib. AEs requiring dose adjustment or interruption were reported in 34/55 patients (62%), and 19 patients (35%) required more than one dose reduction. AEs leading to study drug discontinuation were reported in 11 patients (20%). Treatment discontinuation due to suspected AEs occurred in nine patients (16%).

All patients had one or more AEs during the study. The most frequent AEs, regardless of causality and those suspected as drug-related, are presented in Tables 3 and supplementary Table S4, available at *Annals of Oncology* online. The most frequent (occurring in >20% of patients) study drug-related AEs that occurred at any grade were nausea (42%), peripheral edema (33%), and vomiting (31%) (Table 3). Grade 3/4 AEs, regardless of causality, occurred in <10% of patients (Tables 3 and supplementary Table S4, available at *Annals of Oncology* online). The most frequent drug-related grade 3 or 4 AEs were nausea, peripheral edema, and fatigue (all 4%; supplementary Table S3, available at *Annals of Oncology* online). Serious AEs, regardless of study drug relationship, occurred in 30 patients (55%); those with an incidence of ≥2% were pneumonia (7%), pulmonary embolism (6%), pericardial effusion, abdominal pain, nausea, vomiting, general physical health deterioration, increased blood creatinine, malignant pleural effusion, tumor pain, and pleural effusion (4% each). Drug-related serious AEs each occurred in eight patients (15%); pericardial effusion, nausea, vomiting, malaise, hypersensitivity, increased amylase, increased blood creatinine, cerebral

venous thrombosis, and headache (2%). Fourteen deaths (26%) were reported in the expansion groups of NSCLC patients. Six of these deaths were observed during survival follow-up.

DISCUSSION

In this dose-expansion part dedicated to NSCLC, capmatinib demonstrated antitumor activity in pretreated patients with advanced NSCLC with putative MET dependency. Prior studies of MET targeting agents have suffered from ambiguous biomarker criteria to select patients with high likelihood of clinical benefit. Published data of different biomarker prevalences in surgical series and samples from patients with stage IV NSCLC have indicated that IHC-measured expression of MET does not always correlate with activated p-MET, and therefore, overexpression of MET may not precisely reflect increased MET receptor activation.[22,23] The phase II trial of onartuzumab plus erlotinib showed promising results in patients with MET-positive NSCLC, where MET status was determined using IHC scoring (IHC 3+, 2+, 1+, or 0; patients with 2+ or 3+ score were considered MET-positive). However, onartuzumab plus erlotinib was less effective than erlotinib plus placebo in locally advanced or metastatic NSCLC, determined to be MET-positive by IHC.[24,25]

Against this background, we made use of this uniformly treated study population to systematically compare different biomarkers and cut-off levels to inform the design of pivotal studies of capmatinib in *MET*-positive NSCLC. These included MET protein expression determined by IHC (H-score and IHC status), *MET* GCN and gene amplification assessed by FISH, and *MET* mutations detected by NGS. The strongest association with capmatinib benefit was found in patients with *MET* GCN ≥6, which was present in 13/55 patients (24%). Almost half of these patients experienced an objective response per RECIST with a median PFS of 9.3 months. Patient subgroups defined by MET IHC (H-score or IHC status) and *MET/CEP7* ratio exhibited much lower ORRs and PFS times. Hence, despite considerable overlap between these different biomarker definitions, *MET* GCN ≥6 clearly emerged as clinically the most useful biomarker for selection of NSCLC patients with high likelihood of benefit from capmatinib. According to recent work by Guo et al.,[26] MET IHC appears not to be predictive for *METex14* mutations or *MET*-amplification.

During the conduct of our study, *METex14* mutations emerged as novel recurrent genomic aberrations leading to oncogenic MET receptor signaling. The resulting mutant MET is stabilized through defective ubiquitination and internalization, which adds another layer of activity over the pure increase in genomic material. In a *post hoc* analysis, we analyzed surplus tumor tissue from 39 study patients (31 assessable) by NGS for a panel of cancer-related genes. We identified four cases with *METex14* mutations, of which three showed confirmed PR to capmatinib. These findings confirm that *METex14* mutations serve as another biomarker in addition to *MET* GCN ≥6 for patient selection in

capmatinib studies in NSCLC. In a prospective study of 860 patients with recurrent or metastatic lung adenocarcinoma analyzed by Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay, *MET* splicing and amplification was observed in 3% and 1.4% of patients, respectively. Clinical benefit with matched treatment was observed in 13/17 patients (76.5%) with *METex14* alterations and one of two patients (50%) with *MET* amplification.[17] Crizotinib is an anaplastic lymphoma kinase/ROS1/MET multi-targeted receptor TKI, which first demonstrated antitumor activity (ORR of 32%) in patients with advanced *METex14* NSCLC.[14] In the same study, responses (ORR of 40%) to crizotinib were also observed in patients with high *MET* amplification.[27] Our data of capmatinib from this study clinically validate specific *MET* aberrations as a targetable oncogenic dependency. Further evaluation of the predictive value of different mechanisms of MET dysregulation, including *MET* GCN gain and *METex14* mutation, in patients with advanced NSCLC is being explored prospectively in an ongoing phase II, seven-cohort study with capmatinib, including treatment-naive patients (GEOMETRY *mono-1*, NCT02414139), and promising efficacy data in *METex14*-mutated NSCLC have been recently presented.[28] Based on the current knowledge, *METex14* is considered as a strong molecular driver while evidence for *MET* is less strong. Therefore, the contributory role of high amplification to the efficacy of capmatinib in such cases cannot be fully elucidated. However, based on the GEOMETRY mono-1 data, the efficacy in *METex14* seems to be independent from the level of *MET* amplification. More specifically, in the GEOMETRY mono-1 study, the duration of response was noted to be independent of *MET* amplification (GCN <6 or ≥6) determined by FISH, in the *MET*-mutated patients, with a P value of 0.85 showing that the difference of duration of response between *MET*-amplified (GCN ≥6) and non-amplified (GCN <6) is not statistically different (data on file). The findings of our study clearly argue for an independent contribution of *MET* amplification (GCN ≥6) to capmatinib activity in heavily pretreated NSCLC patients.

Capmatinib was well tolerated with an acceptable safety profile in patients with advanced NSCLC. The most common ($\geq25\%$) AEs, regardless of causality, were low-grade nausea, peripheral edema, vomiting, decreased appetite, fatigue, and dyspnea. Suspected drug-related peripheral edema occurred in 33% of patients (majority were grade 1 or 2); this adverse effect has been reported for other MET inhibitors,[29,30] and may therefore be a potential drug class effect not specific to capmatinib. Overall, capmatinib has an acceptable safety profile. Even when combined with other TKIs (gefitinib and nazartinib), it was well tolerated which nominates capmatinib for further clinical exploration in rationally designed combination therapies.[31,32]

In summary, capmatinib showed a clinically meaningful rate of antitumor activity and acceptable safety profile in pretreated advanced NSCLC patients with either *MET* GCN ≥6 and/or *METex14* mutation. Overexpression alone cannot be considered as a reliable biomarker to predict the efficacy of capmatinib.

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DATA AVAILABILITY STATEMENT

Novartis will not provide access to patient-level data if there is a reasonable likelihood that individual patients could be re-identified. Phase 1 studies, by their nature, present a high risk of patient re-identification; therefore, patient individual results for phase 1 studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may preclude granting access under these provisions. Where co-development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

REFERENCES

1. Cappuzzo F, Marchetti A, Skokan M, et al. Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. *J Clin Oncol*. 2009;27(10):1667—1674.
2. Kawakami H, Okamoto I, Okamoto W, et al. Targeting MET amplification as a new oncogenic driver. *Cancers (Basel)*. 2014;6(3):1540—1552.
3. Schildhaus H-U, Schultheis AM, Rüschoff J, et al. MET amplification status in therapy-naïve adeno- and squamous cell carcinomas of the lung. *Clin Cancer Res*. 2015;21(4):907—915.
4. Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Natl Acad Sci U S A*. 2007;104(52):20932—20937.
5. Sadiq AA, Salgia R. MET as a possible target for non-small-cell lung cancer. *J Clin Oncol*. 2013;31(8):1089—1096.
6. Chen HJ, Mok TS, Chen ZH, et al. Clinicopathologic and molecular features of epidermal growth factor receptor T790M mutation and c-MET amplification in tyrosine kinase inhibitor-resistant Chinese non-small cell lung cancer. *Pathol Oncol Res*. 2009;15(4):651—658.
7. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*. 2007;316(5827):1039—1043.
8. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3(75):75ra26.
9. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19(8):2240—2247.
10. Minari R, Bordi P, Tiseo M. Third-generation epidermal growth factor receptor-tyrosine kinase inhibitors in T790M-positive non-small cell lung cancer: review on emerged mechanisms of resistance. *Transl Lung Cancer Res*. 2016;5(6):695—708.
11. Onozato R, Kosaka T, Kuwano H, et al. Activation of MET by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers. *J Thorac Oncol*. 2009;4(1):5—11.
12. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. *Cancer Res*. 2006;66(1):283—289.
13. Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov*. 2015;5(8):850—859.
14. Drilon AE, Clark J, Weiss J, et al. Updated antitumor activity of crizotinib in patients with met exon 14-altered advanced non-small cell lung cancer. *J Thorac Oncol*. 2018;13(10):S348.

15. Schrock AB, Frampton GM, Suh J, et al. Characterization of 298 patients with lung cancer harboring MET exon 14 skipping alterations. *J Thorac Oncol*. 2016;11(9):1493—1502.
16. Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non—small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met over-expression. *J Clin Oncol*. 2016;34(7):721—730.
17. Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov*. 2017;7(6):596—609.
18. Reis H, Metzenmacher M, Goetz M, et al. MET expression in advanced non-small-cell lung cancer: effect on clinical outcomes of chemotherapy, targeted therapy, and immunotherapy. *Clin Lung Cancer*. 2018;19(4):e441—e463.
19. Liu X, Wang Q, Yang G, et al. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. *Clin Cancer Res*. 2011;17(22):7127—7138.
20. Bang Y-J, Su W-C, Nam D-H, et al. Phase I study of the safety and efficacy of INC280 in patients with advanced MET-dependent solid tumors. *J Clin Oncol*. 2014;32(15_suppl):2520.
21. Bang Y-J, Su W-C, Schuler M, et al. Phase 1 study of capmatinib in MET-positive solid tumor patients: dose escalation and expansion of selected cohorts. *Cancer Sci*. 2019;00:1—12.
22. Tsuta K, Kozu Y, Mimae T, et al. c-MET/phospho-MET protein expression and MET gene copy number in non-small cell lung carcinomas. *J Thorac Oncol*. 2012;7(2):331—339.
23. Onitsuka T, Uramoto H, Ono K, et al. Comprehensive molecular analyses of lung adenocarcinoma with regard to the epidermal growth factor receptor, K-ras, MET, and hepatocyte growth factor status. *J Thorac Oncol*. 2010;5(5):591—596.
24. Spigel DR, Ervin TJ, Ramlau RA, et al. Randomized phase II trial of onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31(32):4105—4114.
25. Spigel DR, Edelman MJ, O'Byrne K, et al. Results from the phase III randomized trial of onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIB or IV non-small-cell lung cancer: METLung. *J Clin Oncol*. 2017;35(4):412—420.
26. Guo R, Berry LD, Aisner DL, et al. MET IHC is a poor screen for MET amplification or MET exon 14 mutations in lung adenocarcinomas: data from a tri-institutional cohort of the lung cancer mutation consortium. *J Thorac Oncol*. 2019;14(9):1666—1671.
27. Camidge DR, Otterson GA, Clark JW, et al. Crizotinib in patients (pts) with MET-amplified non small cell lung cancer (NSCLC): updated safety and efficacy findings from a phase 1 trial. *J Clin Oncol*. 2018;36(15_suppl):9062.
28. Wolf J, Seto T, Han J-Y, et al. Capmatinib (INC280) in METΔex14-mutated advanced non-small cell lung cancer (NSCLC): efficacy data from the phase II GEOMETRY mono-1 study. *J Clin Oncol*. 2019;37(15_suppl):9004.
29. Felip E, Horn L, Patel JD, et al. Tepotinib in patients with advanced non-small cell lung cancer (NSCLC) harboring MET exon 14-skipping mutations: phase II trial. *J Clin Oncol*. 2018;36(15_suppl):9016.
30. Salgia R, Patel P, Bothos J, et al. Phase I dose-escalation study of onartuzumab as a single agent and in combination with bevacizumab in patients with advanced solid malignancies. *Clin Cancer Res*. 2014;20(6):1666—1675.
31. Wu YL, Zhang L, Kim DW, et al. Phase Ib/II study of capmatinib (INC280) plus gefitinib after failure of endothelial growth factor receptor (EGFR) inhibitor therapy in patients with EGFR-mutated, MET factor-dysregulated non-small-cell lung cancer. *J Clin Oncol*. 2018;36(31):3101—3109.
32. Tan DSW, Lee DH, Soo R, et al. P3.02b-117 phase Ib results from a study of capmatinib (INC280) + EGF816 in patients with EGFR-mutant non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2017;12(1_suppl):S1264—S1265.