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Original Study

A Randomized, Open-Label Phase II Study Evaluating Emibetuzumab Plus Erlotinib and Emibetuzumab Monotherapy in MET Immunohistochemistry Positive NSCLC Patients with Acquired Resistance to Erlotinib

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Abstract

This open-label Phase II study conducted prior to routine *EGFR* mutation testing, assessed whether acquired resistance to erlotinib in NSCLC patients with a given MET protein expression level enriched for *EGFR*mt could be overcome by emibetuzumab, an antibody against MET. Although some responses were seen, the trial did not meet its primary endpoint.

Introduction: The hepatocyte growth factor receptor MET represents a resistance mechanism to epidermal growth factor receptor *(EGFR)* inhibition in *EGFR* mutant (mt) non–small cell lung cancer (NSCLC). This Phase 2 study tested whether acquired resistance to erlotinib in MET protein positive NSCLC patients enriched for *EGFR*mt can be overcome by emibetuzumab plus erlotinib. **Patient and Methods:** Patients with Stage IV NSCLC with acquired resistance to erlotinib and MET diagnostic (+) (≥ 10% of cells expressing MET at ≥ 2+ IHC staining intensity at any time) were randomized (3:1) to receive emibetuzumab 750 mg every 2 weeks with or without erlotinib 150 mg once daily. The primary objective was to evaluate the overall response rate (ORR) relative to historic control, with a co-primary objective of ORR in patients with MET expression in ≥ 60% of cells ≥ 2+ (MET ≥ 60%). **Results:** One hundred and eleven MET+ patients received emibetuzumab plus erlotinib (N = 83) or emibetuzumab monotherapy (N = 28). 89 of 111 MET+ samples were post-erlotinib. ORR was 3.0% for emibetuzumab plus erlotinib (95% CI: 0.4, 10.5) and 4.3% for emibetuzumab (95% CI: 0.1, 21.9), in patients with post-erlotinib progression biopsies available (n = 89). Similar results were observed in patients with MET ≥ 60% expression (n = 74). Disease control rate and progression-free

Abbreviations: ADA, Antidrug antibodies; AE, Adverse events; CTCAE, Common Terminology Criteria for Adverse Events; CTS, Change in tumor size; DCR, Disease control rate; ECOG, Eastern Cooperative Oncology Group; EGFR, Epidermal growth factor receptor; ELISA, Enzyme-linked immunosorbent assay; HGF, Hepatocyte growth factor; IGTP, Institut Germans Trias i Pujol; ITT, Intent-to-treat; NSCLC, Non–small cell lung cancer; ORR, Overall response rate; OS, Overall survival; PFS, Progression-free survival; PR, Partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, Serious adverse event; SD, Stable disease; TKI, Tyrosine kinase inhibitors.

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survival were higher for emibetuzumab plus erlotinib (50%/3.3 months) than for emibetuzumab (26%/1.6 months). No unexpected safety signals emerged. Partial responses were observed in patients with and without *EGFR*mt or *MET* amplification. *EGFR* sensitizing mutations were identified retrospectively in 84.2% of those with available tissue (85/101). **Conclusion:** Acquired resistance to erlotinib in MET diagnostic (+) patients was not reversed by emibetuzumab plus erlotinib or emibetuzumab monotherapy, although a subset of patients obtained clinical benefit.

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Introduction

The epidermal growth factor receptor (*EGFR*) tyrosine kinase is mutated in up to 15% and 45% of Caucasian and east Asian non–small cell lung cancer (NSCLC) patients, respectively. EGFR mutations (*EGFR*mt) sensitizing to treatment with *EGFR* tyrosine kinase inhibitors (TKIs) include exon 19 deletions and L858R substitution in exon 21 which account for approximately 90% of all sensitizing *EGFR*mt.[1] Treatment of advanced *EGFR*mt NSCLC patients with first and second-generation *EGFR* TKIs such as erlotinib, gefitinib, and afatinib became the standard for first line *EGFR*mt NSCLC patients, following a series of positive studies comparing TKI to first line chemotherapy.[2-4] More recently, osimertinib, a third generation *EGFR* TKI, also received a first line license for the treatment of *EGFRmt* NSCLC.[5] However, virtually all patients ultimately develop resistance to *EGFR* TKIs, and progress on treatment with an *EGFR* TKI.[6]

Mechanisms considered to be responsible for this phenotype of "acquired resistance" to first and second-generation *EGFR* TKIs in *EGFR*mt NSCLC patients include the *EGFR* exon 20 T790M mutation detected in about 50% of all cases.[7] Activation of secondary signaling pathways as a mechanism for resistance to *EGFR* TKIs includes, among others, activation of the hepatocyte growth factor (HGF)/MET signaling pathway.[8-12] While the third generation *EGFR* TKIs are active against T790M, MET signaling remains a mechanism of acquired resistance to this class of drugs too.[13]

MET is a transmembrane receptor tyrosine kinase that is activated in cancers either by binding of its only known ligand HGF or ligand independently, predominantly through overexpression of MET due to *MET* gene amplification. In addition, MET can be transactivated following *EGFR* activation, in the absence of HGF, and simultaneous activation of MET and *EGFR* has been shown to be synergistic.[14] MET signaling results in scattering and motility of epithelial cells and promotes a more aggressive tumor phenotype associated with invasion and metastasis of tumor cells.[15-18] In *EGFR*mt NSCLC xenograft models, HGF elicits *EGFR* TKI resistance by induction of MET signaling.[9-11]

MET expression or amplification has been observed in up to 20% (depending on method and cut-point used) of patients with acquired resistance to *EGFR* TKIs.[9,10,13,19-23] High MET expression scores have been shown in NSCLC patient biopsies to be associated with MET receptor phosphorylation leading to activation of MET signaling as a potential resistance mechanism to *EGFR* inhibitors and may overlap with the occurrence of T790M mutations in *EGFR*mt NSCLC patients with acquired resistance to first- and second-generation *EGFR* TKIs.[9,24,25]

Emibetuzumab (LY2875358) is a humanized IgG4 monoclonal bivalent MET antibody blocking ligand-dependent and independent activation of MET.[26] In both HGF-dependent and HGF-independent tumor xenograft models, emibetuzumab showed strong antitumor activity.[26] In *EGFR*mt NSCLC xenograft models, additive activity was observed for combination treatments with emibetuzumab and *EGFR* TKIs including erlotinib and osimertinib. Emibetuzumab was shown to be well tolerated in a Phase I study of emibetuzumab monotherapy or in combination with erlotinib with no dose-limiting toxicities observed.[27] Of the 14 patients who received emibetuzumab plus erlotinib, 2 patients had a durable partial response (PR) to the combination treatment. Notably, these 2 patients both had tumoral MET expression and an activating *EGFR*mt, and had progressed on prior erlotinib therapy before coming on this study.[27] A different experimental anti–MET monoclonal antibody, onartuzumab, had also shown provocative progression-free survival (PFS) and overall survival (OS) improvements associated with the addition of onartuzumab to erlotinib in a MET protein positive subset of patients from a Phase II trial enrolled between March 2009 and August 2010 in the otherwise unselected 2nd or 3rd line setting.[28]

Based on these preclinical and clinical observations, the current study tested the hypothesis whether acquired resistance to erlotinib in NSCLC patients preselected for tumoral MET protein expression may be overcome by treatment with emibetuzumab plus erlotinib or emibetuzumab monotherapy. The study was conducted prior to the development of an *EGFR* mutation test approved by the FDA for prospective use. As such, clinical enrichment for *EGFR* mutations, based on the published "Jackman" criteria was used.[29] *EGFR* mutations and other MET-related biomarkers beyond MET protein expression were assessed retrospectively.

Patients and Methods

Study Design

This study was a multicenter, randomized, uncontrolled, open-label Phase 2 study of emibetuzumab plus erlotinib, and emibetuzumab monotherapy in MET Dx+ NSCLC patients with acquired resistance to erlotinib (clinicaltrials.gov: NCT01900652). Patients with acquired resistance to erlotinib and positive for MET tumor expression at $\geq$ 10% of cells expressing MET at $\geq$ 2+ IHC staining intensity (MET Dx+) were randomized in a 3:1 ratio to receive emibetuzumab plus erlotinib or emibetuzumab monotherapy. Randomization was stratified to minimize imbalance between treatment arms according to Eastern Cooperative Oncology Group

(ECOG) performance status (PS) (0 vs. 1 vs. 2) and the number of prior lines of cytotoxic chemotherapy (0 vs. 1 vs. ≥ 2).

To facilitate enrollment, any sample with MET positivity as defined by the studies MET diagnostic (+) criteria was sufficient for enrollment. However, recognizing that acquired resistance mechanisms could alter over time and with different drug exposures, the primary objective was to assess the overall response rate (ORR) of emibetuzumab plus erlotinib or emibetuzumab monotherapy in patients with MET diagnostic (+) NSCLC based on the post-erlotinib progression tumor sample taken after acquired resistance to erlotinib (primary analysis population). The study was conducted prior to the use of *EGFR* TKIs being restricted to those with an *EGFR* mutation in all lines of therapy and before an FDA approved test for prospective *EGFR* mutation selection existed, therefore, *EGFR* mutation status was enriched for by clinical criteria[29] and assessed retrospectively among those with available tissue. As a co-primary objective, the study evaluated the ORR in the subpopulation of patients with higher levels of MET expression, specifically MET expression in ≥ 60% of cells expressing MET at ≥ 2+ immunohistochemistry (IHC) staining intensity based on their post-erlotinib progression NSCLC tumor sample (co-primary population). Secondary objectives included PFS, disease control rate (DCR), change in tumor size (CTS), OS, safety, pharmacokinetics (PK), and immunogenicity. Exploratory objectives included evaluation of tumor tissue and blood for biomarkers related to MET and *EGFR* signaling pathways and to investigate any potential association between patient–clinical outcomes and level of MET tumor expression.

This study was sponsored by Eli Lilly and Company and conducted in accordance with the International Conference on Harmonization Good Clinical Practices E6 guidelines, and ethics guidelines that include the Declaration of Helsinki and Council for International Organizations of Medical Sciences. All patients provided written informed consent prior to any study-related procedures.

Patients

Eligible patients were ≥ 18 years of age with a confirmed diagnosis of metastatic Stage IV NSCLC.[30] Patients had to have acquired resistance to erlotinib as defined by Jackman et al.[29] A maximum erlotinib washout period of ≤ 28 days was allowed to minimize re-challenge effects from the erlotinib. Tumor biopsies (archival or fresh) prior to study had to be MET diagnostic (+) (defined as ≥ 10% of cells expressing MET at ≥ 2+ IHC staining intensity using the Dako MET 2 pharmDxTM kit (Agilent, Santa Clara, CA). The initial cut-point was selected based on the distribution of MET expression observed in a cohort of 81 Stage IV NSCLC tissues. In this population, 75% of the tumors were positive using the ≥ 10% cut-point, and 43% of tumors were positive at the ≥ 60% cut-off.

The higher, co-primary endpoint scoring level was in part suggested by the level retrospectively associated with benefit in the onartuzumab studies (≥ 50% of tumor cells with moderate or higher staining using the Ventana SP44 anti–MET antibody).[28] Additional key inclusion criteria included availability or willingness to undergo collection of a post-erlotinib progression tumor biopsy, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1,[31] ECOG PS ≤ 2, adequate bone marrow, and organ functions. Key exclusion criteria were untreated symptomatic central nervous system metastasis and previous treatment with a MET targeting experimental therapeutic.

Study Treatment and Assessments

All patients received emibetuzumab administered as a 750-mg flat dose 1.5-hour infusion on Days 1 and 15 of a 28-day cycle. Patients in the combination arm received in addition erlotinib 150 mg once daily on a 28-day cycle. Treatment continued until progressive disease, unacceptable toxicity, or any other discontinuation criteria were met. Tumor assessments were performed by CT scans or magnetic resonance imaging according to RECIST 1.1 every 6 weeks. Safety and tolerability were assessed through clinical and laboratory evaluations and adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v.4.0).

Pharmacokinetics and Immunogenicity

Serum and plasma samples were analyzed for emibetuzumab and erlotinib using a validated enzyme-linked immunosorbent assay and liquid chromatography-tandem mass spectrometry method, respectively. Sparse sampling, including pre- and post-infusion samples, was conducted for analysis of emibetuzumab PK for all patients. Mean serum concentrations over time were calculated and summarized by post-dose sampling times over the first 2 dosing intervals, and concentrations following first dose were subjected to standard noncompartmental methods using Phoenix WinNonlin version 6.4 (Certara L.P.) in a subset of patients who participated in the PK protocol addendum.

Patient samples for immunogenicity assessment were analyzed for the presence of antidrug antibodies (ADAs) using a validated enzyme-linked immunosorbent assay (ELISA), following a 4-tier approach.[32] The ADA screening assay was validated in accordance with the Food and Drug Administration Guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins.[33]

Biomarker Assessments

Tumor biopsies were tested for MET expression by IHC using the Dako MET 2 pharmDxTM kit, an exploratory kit employing the A2H2-3 MET antibody clone.[34] A composite scoring system was devised to determine the status of MET by IHC, enumerating the percentage of tumor cells with immunoreactivity of 0, 1+, 2+, or 3+ staining intensity in the cell membrane as described previously.[34] The analysis was performed by a trained pathologist in a blinded fashion. Sites were allowed to submit an archival tumor biopsy for pre-screening MET tumor expression for eligibility.

EGFR mutation status was centrally tested on all samples available, retrospectively, using the FDA approved therascreen *EGFR* RGQ PCR Kit. Testing for *MET* gene amplification was performed on tissue samples available by FISH and next generation sequencing (Foundation Medicine, Cambridge, MA; Personal Genome Diagnostics, Baltimore, MD), respectively. Locally generated data for additional molecular alterations of patient tumor samples were collected as existing.

Table 1a Baseline Characteristics

Characteristics	Emibetuzumab + Erlotinib (n = 83)	Emibetuzumab (n = 28)	TOTAL (N = 111)
Age (y), median (range)	64 (41 - 86)	63 (41 - 80)	63 (41 - 86)
Weight (kg), median (range)	65.0 (34.3 - 108.8)	70.1 (50.8 - 109.0)	65.8 (34.3 - 109.0)
Gender, n (%)			
Female	55 (66.3)	20 (71.4)	75 (67.6)
Race, n (%)			
White	64 (77.1)	23 (82.1)	87 (78.4)
Asian	10 (12)	3 (10.7)	13 (11.7)
Black	4 (4.8)	0 (0.0)	4 (3.6)
Multiple	1 (1.2)	0 (0.0)	1 (0.9)
Missing	4 (4.8)	2 (7.1)	6 (5.4)
ECOG, n (%)			
PS 0	18 (21.7)	9 (32.1)	27 (24.3)
PS 1	60 (72.3)	17 (60.7)	77 (69.4)
PS 2	5 (6.0)	2 (7.1)	7 (6.3)
Prior anti–cancer therapies, n (%)			
Radiotherapy	35 (42.2)	14 (50.0)	49 (44.1)
Surgery	30 (36.1)	9 (32.1)	39 (35.1)
Number of prior lines of systemic anticancer, median agents, median (range)	2 (1 - 9)	2 (1 - 6)	2 (1 - 9)

Abbreviations: Dx = diagnostic; ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Statistical Analysis

All efficacy analyzes were conducted for the primary analysis population (defined as patients with ≥ 10% of cells expressing MET at ≥ 2+ IHC staining intensity in the post-erlotinib progression tumor biopsy), the co-primary analysis population (MET in ≥ 60% of cells at ≥ 2+ IHC staining intensity in the post-erlotinib progression biopsy), and the intent-to-treat population (ITT). The primary objective of confirmed ORR was measured according to RECIST 1.1 relative to baseline tumor measurements. A true ORR of ≥ 20% relative to a historic ORR of 10% for single-agent chemotherapy[35] was considered worthy of further development. The study planned to randomize 100 MET diagnostic (+) patients with a 3:1 randomization ratio. Assuming a type I error of 0.05 with a 1-sided χ^2 test, the experimental arm had approximately 82% power to detect an ORR difference between 10% and 20%. For the co-primary objective, it was anticipated that approximately 60 patients (in a 3:1 ratio) with MET high expression status based on their post-erlotinib progression NSCLC tumor sample were to be included. Assuming a type I error of 0.05 with a 1-sided χ^2 test, the experimental arm provided approximately 88% power to detect the ORR difference between 10%, and 25%. Median PFS and OS were measured from randomization and estimated using the Kaplan-Meier method and 95% confidence limits were reported for each treatment arm. The statistical analyses were performed using SAS and R.

Results

Patients

In order to prescreen for MET tumor expression, tumor tissue samples from a total of 263 patients were submitted to the central lab for MET expression analysis. Out of these, 233 (88.6%) were diagnosed as MET diagnostic (+) by using the Dako MET 2 pharmDx kit. Twenty-seven patients (10.3%) were determined MET diagnostic (-) and 3 patients (1.1%) were indeterminable. Out of the MET diagnostic (+) patients, 111 patients were eligible and randomized between August 2013 and September 2014 at a 3:1 ratio to receive emibetuzumab plus erlotinib (N = 83) or emibetuzumab monotherapy (N = 28) at 51 participating investigative sites in 10 countries (patient disposition shown in Supplementary Figure S1). Of the total cohort (n = 111), only 88% of patients (n = 98) received erlotinib as last line before enrollment, due to protocol deviations.

Of these patients, 89 had MET IHC analysis conducted on the post-erlotinib progression sample (primary analysis population). All patients randomized received at least 1 dose of study treatment. Baseline characteristics were similar between the 2 treatment arms (Table 1a). The majority of patients had an ECOG PS ≤ 1 with a median of 2 prior systemic therapies including erlotinib. Of the 101 patients with tissue evaluable from any time for central testing of *EGFR*mt status, *EGFR* sensitizing mutations were identified in 84.2% (n = 85, Table 1b). Thirteen patients (12.9%) were found to be *EGFR* wildtype and samples from 3 patients were not evaluable. A total of 85 patients had evaluable post-*EGFR* TKI progression samples. *EGFR* T790M mutations were observed in 29.7% of those patients (30 patients), whereas none was detected in biopsies collected prior to *EGFR* TKI progression. Post-progression tumor samples for MET testing were successfully obtained from 104 patients enrolled in the trial, of whom 89 patients (85.6%) were MET diagnostic (+) (primary analysis population; combination arm: n = 66; monotherapy arm: n = 23). Eleven patients from this group did not have a valid MET IHC result on their post-progressions sample and 4 were MET negative on these samples after previously being reported as MET positive on a prior biopsy

Table 1b Baseline Biomarker Characteristics

Central Laboratory Results	Emibetuzumab + Erlotinib(n = 83)	Emibetuzumab(n = 28)	TOTAL(n = 111)
MET Dx + anytime biopsy (ITT Population), n (%)			
MET High	66 (79.5)	23 (82.1)	89 (80.2)
Patients with post-erlotinib biopsy available, n (%)	78 (94.0)	26 (92.9)	104 (93.7)
MET Dx+ (Primary Analysis Population)	66 (84.6)	23 (88.5)	89 (85.6)
MET High (Co-Primary Analysis Population)	53 (68.0)	21 (80.8)	74 (71.2)
MET Dx	4 (5.1)	0 (0.0)	4 (3.8)
MET not evaluable	8 (10.3)	3 (11.5)	11 (10.6)
EGFR status,[a] n (%)	76 (91.6)	25 (89.3)	101 (91.0)
EGFR sensitizing mutations	63 (82.9)	22 (88.0)	85 (84.2)
With T790M post-erlotinib progression	18 (28.6)	10 (45.5)	28 (32.9)
Without T790M	45 (71.4)	12 (54.5)	57 (67.1)
WT EGFR	11 (14.5)	2 (8.0)	13 (12.9)
Other EGFR mutations	2 (2.6)	1 (4.0)	3 (3.0)
T790M only	1 (1.3)	0 (0.0)	1 (1.0)
Ex 20 insertion only	1 (1.3)	0 (0.0)	1 (1.0)
L861Q + T790M	0 (0.0)	1 (4.0)	1 (1.0)

Abbreviations: WT = wild type[a]EGFR results were obtained from evaluable samples collected either anytime or post-progression.

(possibly due to tumor heterogeneity and/or temporal effects). This included 74 patients (71.2%) in the co-primary analysis population with MET ≥ 2+ in ≥ 60% of tumors cells (combination arm: n = 53; monotherapy arm: n = 21).

At the time of primary database lock, in the overall population 103 patients (92.8%) had discontinued from treatment including 78 patients (94.0%) in the emibetuzumab plus erlotinib combination arm and 25 patients (89.3%) in the emibetuzumab monotherapy arm. The primary reason for discontinuing from study drug(s) was progressive disease (combination arm: n = 58 [69.9%]; monotherapy arm: n = 20 [71.4%]). Patients randomized to emibetuzumab plus erlotinib received a median of 3 treatment cycles (range, 1-16) relative to 2 cycles (range, 1-13) for patients in the emibetuzumab monotherapy arm.

Efficacy

The study did not meet its primary endpoint of ORR ≥ 20% in patients with MET diagnostic (+) patients. The observed confirmed ORRs were similar in both study arms: for the primary analysis population of MET diagnostic (+) patients based on their post-erlotinib progression tumor sample (n = 89), the ORR in the emibetuzumab plus erlotinib combination arm was 3.0% (n = 2, 95% confidence interval [CI]: 0.4, 10.5) and 4.3% (n = 1, 95% CI: 0.1, 21.9) in the emibetuzumab monotherapy arm (Table 2). All of those responses were observed in the co-primary analysis subpopulation for patients with MET expression in ≥ 60% of cells at ≥ 2+ MET intensity (n = 74) for an ORR of 3.8% (n = 2, 95% CI: 0.5, 13.0) and 4.8% (n = 1, 95% CI: 0.1, 23.8) for the combination and the monotherapy arm, respectively. One additional confirmed PR in the combination arm was observed in the ITT population (ORR: 3.6%, n = 3) in a patient with no post-erlotinib progression sample available. Confirmed PRs lasted up to 11 months (88, 113, and 349 days, respectively, for the 3 responders in the combination arm and 125 days for the 1 responder in the monotherapy arm). There were no complete responses in this study.

Change in tumor size with a decrease in sum of target lesions relative to baseline was observed in approximately one-third of the ITT population (combination arm: 34.8%; monotherapy arm: 30.4%; Figure 1). Similar to the primary analysis population, the fraction of patients showing an overall tumor reduction was comparable in both treatment arms in the co-primary analysis subpopulation (Figure 2). Besides the 4 confirmed responders, there was 1 additional unconfirmed responder in the co-primary population whereas no patients with < 60% of cells at ≥ 2+ MET intensity had any tumor response according to RECIST 1.1.

The DCR in the primary analysis population was higher in the emibetuzumab plus erlotinib combination arm (DCR: 50% [95% CI: 37.4, 62.6]) relative to the monotherapy arm (DCR: 26.1% [95% CI: 10.2, 48.4]). For the co-primary analysis population, DCRs were similar as in the primary analysis population with 47.2% and 28.6% in the combination and monotherapy arms, respectively (Table 2).

At the time of primary analysis, a total of 81 PFS events were observed between both treatment arms (combination arm: n = 59; monotherapy arm: n = 22). Similar median PFS were observed for the primary and co-primary analysis populations (combination arm: 3.3 and 2.9 months; monotherapy arm: 1.6 and 1.6 months, respectively) as summarized in Supplementary Table S1 for both treatment arms. The median PFS in the emibetuzumab plus erlotinib combination arm was 2.9 months (95% CI: 2.7, 4.1) and for the emibetuzumab monotherapy arm was 1.6 months (95% CI: 1.4, 3.1) in the ITT population. Supplementary Figure S2 shows the Kaplan-Meier curve for PFS in the primary analysis population.

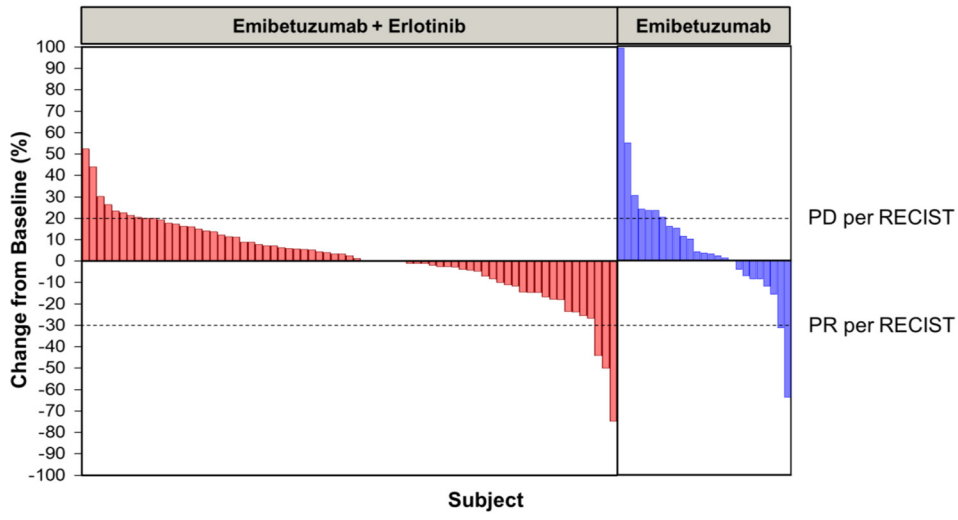
The final OS analysis was based on 79 OS events reported across both arms (28.8% censoring). In the primary and co-primary analy-

Table 2 Summary of Response

	Primary analysis population (MET Dx+ post-progression) (n = 89)		Co-primary population (MET High post-progression) (n = 74)		ITT population (MET Dx+ anytime) (N = 111)	
	Emibetuzumab + Erlotinib (n = 66)	Emibetuzumab (n = 23)	Emibetuzumab + Erlotinib (n = 53)	Emibetuzumab (n = 21)	Emibetuzumab + Erlotinib (n = 83)	Emibetuzumab (n = 28)
BOR, n (%)						
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	2 (3.0)	1 (4.3)	2 (3.8)	1 (4.8)	3 (3.6)[a]	1 (3.6)
SD	31 (47.0)	5 (21.7)	23 (43.4)	5 (23.8)	40 (48.2)	8 (28.6)
PD	21 (31.8)	13 (56.5)	18 (34.0)	11 (52.4)	27 (32.5)	15 (53.6)
Unknown	2 (3.0)	0 (0.0)	2 (3.8)	0 (0.0)	2 (2.4)	0 (0.0)
Not done	7 (10.6)	3 (13.0)	5 (9.4)	3 (14.3)	8 (9.6)	3 (10.7)
Not evaluable	3 (4.5)	1 (4.3)	3 (5.7)	1 (4.8)	3 (3.6)	1 (3.6)
ORR (CR + PR), n (%)	2 (3.0)	1 (4.3)	2 (3.8)	1 (4.8)	3 (3.6)	1 (3.6)
95% CI	0.4 - 10.5	0.1 - 21.9	0.5 - 13.0	0.1 - 23.8	0.8 - 10.2	0.1 - 18.3
DCR (CR+ PR + SD), n (%)	33 (50.0)	6 (26.1)	25 (47.2)	6 (28.6)	43 (51.8)	9 (32.1)
95% CI	37.4 - 62.6	10.2 - 48.4	33.3 - 61.4	11.3 - 52.2	40.6 - 62.9	15.9 - 52.4

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; Dx = diagnostic; ITT = intent-to-treat; N = total population size; n = number of patients; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.
[a] MET Dx+ status was determined on post-progression biopsy for 2 patients, and on anytime biopsy for 1 patient.

Figure 1 Waterfall Plot ITT Population. Abbreviations: ITT = intent-to-treat; PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumors.



sis populations, the median OS in the combination and monotherapy arms were similar (combination arm: 9.2 and 9.8 months; monotherapy arm: 8.2 and 8.2 months, respectively) (Supplementary Table S1). The median OS in the ITT population was 9.9 months (95% CI: 7.0, 12.9) for the combination arm and 9.0 months (95% CI: 4.0, 12.9) in the monotherapy arm.

Safety

The safety population included patients who received at least 1 dose of emibetuzumab (N = 111). The frequency of patients experiencing at least 1 possibly drug-related AE of any grade was higher in the combination arm (80.7%; n = 67 patients) compared to the emibetuzumab monotherapy arm (57.1%; n = 16;

Figure 2 Waterfall Plot by MET IHC Status. Abbreviations: BOR = best overall response; IHC = immunohistochemistry; PD = progressive disease; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = stable disease; UN = unknown.

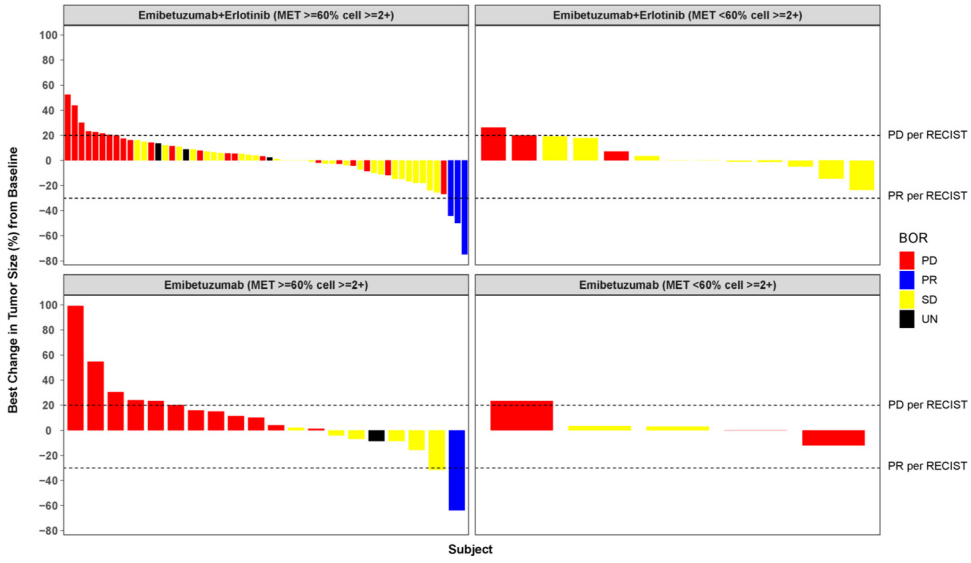


Table 3 Summary of Adverse Events

Preferred Term	Emibetuzumab + Erlotinib(n = 83)		Emibetuzumab(n = 28)		Total(N = 111)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥3
Patients with ≥ 1 TEAE,[a] n (%)	67 (80.7)	20 (24.1)	16 (57.1)	1 (3.6)	83 (74.8)	21 (18.9)
Fatigue	24 (28.9)	2 (2.4)	4 (14.3)	1 (3.6)	28 (25.2)	3 (2.7)
Diarrhea	21 (25.3)	1 (1.2)	4 (14.3)	0 (0.0)	25 (22.5)	1 (0.9)
Nausea	19 (22.9)	0 (0.0)	3 (10.7)	0 (0.0)	22 (19.8)	0 (0.0)
Edema peripheral	14 (16.9)	0 (0.0)	3 (10.7)	0 (0.0)	17 (15.3)	0 (0.0)
Dermatitis acneiform	15 (18.1)	5 (6.0)	0 (0.0)	0 (0.0)	15 (13.5)	5 (4.5)
Decreased appetite	11 (13.3)	0 (0.0)	2 (7.1)	0 (0.0)	13 (11.7)	0 (0.0)
Vomiting	9 (10.8)	0 (0.0)	3 (10.7)	0 (0.0)	12 (10.8)	0 (0.0)
Hypoalbuminemia	8 (9.6)	3 (3.6)	0 (0.0)	0 (0.0)	8 (7.2)	3 (2.7)
Rash	8 (9.6)	1 (1.2)	0 (0.0)	0 (0.0)	8 (7.2)	1 (0.9)
Dry skin	6 (7.2)	0 (0.0)	1 (3.6)	0 (0.0)	7 (6.3)	0 (0.0)
Paronychia	7 (8.4)	0 (0.0)	0 (0.0)	0 (0.0)	7 (6.3)	0 (0.0)
Aspartate aminotransferase increased	4 (4.8)	0 (0.0)	2 (7.1)	0 (0.0)	6 (5.4)	0 (0.0)
Asthenia	5 (6.0)	0 (0.0)	1 (3.6)	0 (0.0)	6 (5.4)	0 (0.0)
Constipation	3 (3.6)	0 (0.0)	3 (10.7)	0 (0.0)	6 (5.4)	0 (0.0)
Leukopenia	6 (7.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.4)	0 (0.0)
Stomatitis	5 (6.0)	0 (0.0)	1 (3.6)	0 (0.0)	6 (5.4)	0 (0.0)

Abbreviations: TEAE = treatment-emergent adverse event.
[a] Treatment-emergent adverse events considered possibly related to at least one of the study drugs and occurring in ≥ 5% of patients, and who received at least 1 dose of emibetuzumab.

Table 3). Common drug-related AEs (occurring in ≥ 15% of patients) in the combination arm included fatigue (28.9%), diarrhea (25.3%), nausea (22.9%), dermatitis acneiform (18.1%), and peripheral edema (16.9%). Most of these events were graded to be of either mild or moderate intensity. Twenty patients (24.1%) experienced a possibly related ≥ Grade 3 AE including dermatitis acneiform as the only event reported for more than 3 patients (n = 5 [6.0%]). No possibly related AEs in the emibetuzumab monotherapy arm were reported in more than 15% of patients. AEs that were more frequently observed in the combination arm

compared to monotherapy, with at least 10 percentage points difference, included fatigue (28.9 vs. 14.3%), diarrhea (25.3 vs. 14.3%), nausea (22.9 vs. 10.7%), and dermatitis acneiform (18.1 vs. 0%).

A total of 34 patients (41.0%) in the combination arm and 11 patients (39.3%) in the monotherapy arm experienced at least 1 serious adverse event (SAE). Eight of these SAEs (9.6%) were reported as possibly related to study drugs and all reported for patients enrolled in the combination arm. The only SAEs that were observed in more than 1 patient were diarrhea and pulmonary embolism (for both n = 2).

There were 3 on treatment deaths due to AEs across the study, all in the combination arm. This included 2 cases of lung embolism and 1 case of massive pleural effusion. None of these fatal events was considered related to study drugs by the investigators. Of the AEs leading to discontinuation, 3 in the combination arm were considered possibly related to study drug (1 case each of cardiac disorder, pneumonitis, and dermatitis acneiform) and none in the monotherapy arm.

Pharmacokinetics and Immunogenicity

Noncompartmental analysis of plasma samples from 19 patients included in a PK addendum with frequent serial sampling following the first 2 infusions of emibetuzumab showed PK results similar to those previously reported for emibetuzumab in Phase I.[27] Mean concentrations of emibetuzumab are summarized in Supplementary Table S2.

Immunogenicity samples available for evaluation of ADA were analyzed for the presence of anti–emibetuzumab antibodies from all patients. None of the patients developed treatment-emergent ADA against emibetuzumab. Two patients (3.3%) had detectable ADA against emibetuzumab detected prior to first dosing and 3 patients (4.9%) at any time while on treatment. For those patients with ADAs detected while on treatment, titers did not reach the prespecified criteria for treatment-emergent ADA.

Exploratory Biomarker Analysis

While the study did not meet its primary endpoint, there was a subset of patients deriving clinical benefit in both treatment arms. Confirmed and unconfirmed PRs across both arms were only observed in patients with ≥ 60% of cells ≥ 2+ MET intensity in their post-progression or, in 2 cases, where a post-progression sample was not available, in their archival tissue sample (Supplementary Table S3). In addition, while there were no patients with disease control in the monotherapy arm with tumors showing < 60% of cells at ≥ 2+ MET intensity, DCR was 28.6% in patients with tumors above this MET expression cut-off. Further biomarker and MET cut-offs explored for any association with confirmed and unconfirmed PRs (n = 5) are shown in Supplementary Table S3. All patients with confirmed PRs (n = 4) had ≥ 80% of cells ≥ 2+ MET intensity in 1 of their tumor biopsies. However, while high levels may be necessary, they are not sufficient to ensure tumor shrinkage. Employing this post-hoc MET expression cut-off did not significantly enrich further for patients receiving a confirmed PR (combination: 3 of 56 patients [5.4%]; monotherapy: 1 of 20 patients [5.0%]). Confirmed responses were seen in 2 patients without activating *EGFR*mts, both in the combination arm. Such a result could suggest either a primary MET-driven state (due to, for example, a *MET* exon 14 skip mutation or high-level *MET* amplification), or a missed *EGFR*mt. Certainly, in 1 case with a documented *EGFR* exon 19 deletion on archival tissue and an unconfirmed PR on the study arm, no *EGFR* mutation was detected in the post-progression biopsy consistent with the possibility of false negative *EGFR*mt cases existing. None of the patients with a confirmed or unconfirmed PR was identified to have *MET* exon 14 skipping mutation based on exploratory analysis of plasma ctDNA. Only 1 patient with a PR had *MET* amplification based on the post-progression tumor sample as reported by local testing in the presence of a co-existing L858R *EGFR*mt in the combination arm (Supplementary Table S3). Among 76 patients (68.5%) for whom central lab *MET* FISH testing results were available, no patient was found to have a *MET* focal amplification event (defined as MET/CEP7 ratio of ≥ 2.0), including the patient for whom the event was reported based on local lab testing. Two patients harboring a T790M mutation in a post-progression sample had responses, 1 in each arm (Supplementary Table S3). In summary, exploratory biomarker analysis suggested high MET expression may be necessary but not sufficient for benefit, and did not identify any biomarker consistently associated with response to either emibetuzumab plus erlotinib combination or emibetuzumab monotherapy.

Discussion

This randomized, biomarker-driven Phase 2 study examined the combination of emibetuzumab plus erlotinib and emibetuzumab monotherapy in MET diagnostic (+) NSCLC patients with acquired resistance to erlotinib. The primary or co-primary endpoints of ORR in patients with MET diagnostic (+) or MET tumor expression ≥ 60% of cells at ≥ 2+ MET intensity based on post-progression samples were not met in this study. These data demonstrate that acquired resistance to erlotinib in MET positive selected patients at the cut-offs studied was not reversed by the emibetuzumab plus erlotinib combination or emibetuzumab monotherapy at the given dose and schedule. Even though the study was not designed to compare activity between the 2 experimental treatment arms, no obvious difference in ORR or the percentage of patients with numerical tumor regression was observed between treatment arms. The interpretation of the monotherapy efficacy data was limited by the small sample size. With a 3:1 randomization ratio, only approximately 1/4 of the ITT population were randomly assigned to the monotherapy arm and thus the efficacy analyses for this arm were exploratory in nature.

Emibetuzumab was well tolerated with or without erlotinib and no new safety signals were observed. AEs reported in more than 15% of patients in the emibetuzumab plus erlotinib combination arm such as fatigue, diarrhea, nausea, and dermatitis acneiform were largely consistent with the safety profile reported for erlotinib monotherapy. This notion is supported by the observation that none of these AEs was reported for patients in the emibetuzumab monotherapy arm at a rate of 15% or higher. Peripheral edema as a known class effect of HGF/MET pathway-directed therapies[36,37] was observed in approximately 15% of patients across both arms

suggesting on target activity was achieved, although edema events were mild to moderate only. Notably, no infusion related reactions were reported in this study underscoring the low immunogenic potential of emibetuzumab administered without any premedication.

PK exposure of emibetuzumab was comparable to historic data and no emergence of anti–emibetuzumab antibody was detected. Dosing of emibetuzumab 750 mg every 2 weeks yielded first-infusion serum exposures that exceeded the preclinical threshold associated with activity, and the observed elimination half-life of approximately 2 weeks supports the proposed dosing interval of 14 days.

Enrolling MET diagnostic (+) patients defined as having MET expression at a rather low MET expression cut-off of ≥ 10% of cells expressing MET at ≥ 2+ IHC staining intensity, which was fulfilled by 88.6% of all patients tested, might be not a stringent enough selection criterion. While the MET IHC kit in this study performed as expected from an analytical perspective, assessing MET expression at a higher cut-off might be a more promising strategy to enrich NSCLC patients sensitive to MET targeting agents.

While the study did not meet its primary endpoint, there was a subset of patients deriving meaningful clinical benefit in both treatment arms including PRs lasting for up to 11 months (Supplementary Table S3). These confirmed PRs observed in both arms were only reported in patients with ≥ 80% cells expressing MET at ≥ 2+ IHC staining intensity and, as they occurred in both arms, appeared to be independent of co-administration of erlotinib in some cases. However, while these levels may be necessary, even this post-hoc MET expression criterion was not sufficient to enrich significantly for patients receiving clinical benefit. Further exploratory biomarker analyzes did not identify any biomarker or combinations consistently associated with response. Other MET targeting agents have been recently reported to have activity mostly in patients with *MET* amplification as defined by various techniques and cut-offs after progression on erlotinib or Osimertinib.[38,39,40] However, the frequency of these molecular alterations seems to be low in NSCLC[39,40] as illustrated by having identified a single patient with a *MET* amplification in our study who had a confirmed PR with a 75% reduction in target lesions.

Whether the prolonged stable disease (SD) and responses seen reflect a true MET-driven or co-driven subset—enriched for but not identified conclusively by MET protein expression—has to be considered. As our biomarker analyzes were undertaken retrospectively, the true negative predictive value of reported wildtype MET and *EGFR* diagnostics (given that *EGFR* mutations were noted and not-noted in the same patient over time in some cases in Supplementary Table S3) also has to be interpreted with caution considering the limited sample size of this study.

Recently, while a first line study of emibetuzumab added to erlotinib in the treatment naive *EGFR*mt NSCLC setting also failed to demonstrate benefit in the overall population, comparable retrospective analyzes did suggest a PFS benefit among the 20% of patients with the highest MET expression levels.[41] Consequently, MET signaling likely remains a valid target within *EGFR*mt NSCLC, albeit with ongoing challenges related to the accurate detection of those patients whose tumors harbor a true MET-driven/co-driven state.

Conclusion

Acquired resistance to erlotinib in MET diagnostic (+) patients as defined in the current study was not reversed by emibetuzumab plus erlotinib or emibetuzumab monotherapy. Emibetuzumab was well tolerated, and a limited subset of patients obtained clinically meaningful benefit from emibetuzumab treatment in the combination or potentially independent of co-administration of erlotinib in some cases, supporting the need for improved predictive biomarkers for such agents in the future.

Clinical Practice Points

Although MET remains a target being actively explored as a mechanism of acquired resistance to EGFR TKIs in subsets of EGFRmt NSCLC, immunohistochemistry for MET protein expression appears to be an inadequate mechanism for identifying these patients.

- The hepatocyte growth factor (HGF) receptor MET represents one mechanism of resistance to epidermal growth factor receptor (EGFR) inhibition in EGFR mutant (mt) non–small cell lung cancer (NSCLC). This open-label Phase 2 study conducted prior to routine EGFR mutation testing, assessed whether acquired resistance to erlotinib in NSCLC patients with a given MET protein expression level enriched for EGFRmt could be overcome by emibetuzumab treatment, a bivalent MET antibody blocking ligand dependent, and independent HGF/MET signaling, as a monotherapy or in combination with erlotinib.
- In this study, acquired resistance to erlotinib in MET diagnostic (+) patients (defined as ≥ 10% of tumor cells expressing MET at ≥ 2+ IHC staining intensity) was not reversed in the overall population by emibetuzumab monotherapy or emibetuzumab plus erlotinib. Emibetuzumab was well tolerated and a subset of patients in both arms obtained clinical benefit, particularly those with MET tumor expression in ≥ 60% of cells expressing MET at ≥ 2+ staining intensity.
- The findings from this trial are important and will be of interest to readers of *Clinical Lung Cancer*, as we provide insights on trial design, and drug efficacy which may be crucial for further research in this field.

Disclosure

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Conflict of Interest

All other authors have no conflicts of interest to disclose.

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Supplementary materials

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