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A First-in-Human Phase I Study of a Bivalent MET Antibody, Emibetuzumab (LY2875358), as Monotherapy and in Combination with Erlotinib in Advanced Cancer

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Abstract

Purpose: The MET/HGF pathway regulates cell proliferation and survival and is dysregulated in multiple tumors. Emibetuzumab (LY2875358) is a bivalent antibody that inhibits HGF-dependent and HGF-independent MET signaling. Here, we report dose escalation results from the first-in-human phase I trial of emibetuzumab.

Experimental Design: The study comprised a 3+3 dose escalation for emibetuzumab monotherapy (Part A) and in combination with erlotinib (Part A2). Emibetuzumab was administered i.v. every 2 weeks (Q2W) using a flat dosing scheme. The primary objective was to determine a recommended phase II dose (RPTD) range; secondary endpoints included tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity.

Results: Twenty-three patients with solid tumors received emibetuzumab monotherapy at 20, 70, 210, 700, 1,400, and 2,000 mg and 14 non–small cell lung cancer (NSCLC) patients at 700, 1,400, and 2,000 mg in combination with erlotinib 150 mg daily. No dose-limiting toxicities and related serious or $\geq$ grade 3 adverse events were observed. The most common emibetuzumab-related adverse events included mild diarrhea, nausea, and vomiting, and mild to moderate fatigue, anorexia, and hypocalcemia in combination with erlotinib. Emibetuzumab showed linear PK at doses >210 mg. Three durable partial responses were observed, one for emibetuzumab (700 mg) and two for emibetuzumab + erlotinib (700 mg and 2,000 mg). Both of the responders to emibetuzumab + erlotinib had progressed to prior erlotinib and were positive for MET protein tumor expression.

Conclusions: Based on tolerability, PK/PD analysis, and preliminary clinical activity, the RPTD range for emibetuzumab single agent and in combination with erlotinib is 700 to 2,000 mg i.v. Q2W. *Clin Cancer Res; 23(8); 1910–9. ©2016 AACR.*

Introduction

The MET/HGF signaling pathway is involved in formation of metastasis and an invasive tumor phenotype through increased cell proliferation, motility, invasion, angiogenesis, and suppression of apoptotic cell death (1–3). The *MET* proto-oncogene is encoding a cell surface tyrosine kinase receptor composed of extracellular and intracellular domains. Upon binding of HGF as its only known ligand, MET forms a homodimer that triggers the activation of its intracellular kinase domain. Besides this ligand-dependent activation, MET signaling can also be induced by ligand-independent mechanisms such as MET gene amplification, mutation, or receptor heterodimerization (4). Increased expression of MET protein has been reported in various types of human cancers, including gastric, colorectal, breast, pancreatic, lung, and hepatocellular carcinoma (1, 5). In these tumors, high MET expression is correlated with poor prognosis (1, 2). MET and HGF upregulation has collectively been identified as a mechanism of acquired resistance to tyrosine kinase inhibitors of the EGFR, including erlotinib and gefitinib (6–8). Clinical studies with MET/HGF pathway inhibitors in combination with erlotinib have demonstrated clinical efficacy in phase II trials (9, 10).

Emibetuzumab is a humanized IgG4 bivalent mAb that binds to the extracellular domain of MET, preventing HGF from binding to MET and thereby inhibiting ligand-dependent activation of MET. Moreover, emibetuzumab triggers MET receptor internalization and downregulation of total membrane MET expression, leading to inhibition of ligand-independent activation of MET signaling, as well (11).

In preclinical models, emibetuzumab inhibited growth of tumors that are dependent on MET, including tumors that exhibit HGF-dependent and HGF-independent biology. Administration of a single dose of emibetuzumab resulted in continuous reduction of MET protein expression for 14 days in

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Translational Relevance

The MET/HGF pathway is involved in oncogenic processes, such as cell proliferation, survival, invasion, motility, and metastasis, and its activation is associated with poor patient outcomes. This first-in-human dose phase I study demonstrates a favorable safety profile for emibetuzumab—a humanized, bivalent monoclonal antibody. Emibetuzumab blocks HGF-dependent signaling by binding to MET, and also blocks independent signaling of the MET receptor by subsequent internalization and degradation. Pharmacokinetic/pharmacodynamic modeling and simulation suggest that emibetuzumab exposures achieved by 700 mg every 2 weeks (Q2W) or higher are expected to prevent MET signaling, reduce expression of MET, and inhibit MET-driven growth of tumors based on preclinical studies (11). Three patients treated in the biologically efficacious dose range of 700 to 2,000 mg emibetuzumab 700 mg Q2W or greater demonstrated partial response according to Response Evaluation Criteria in Solid Tumors. An additional 9 patients achieved stable disease. Based on these data, further clinical evaluation of emibetuzumab is warranted.

mouse xenografts. Emibetuzumab demonstrated dose-dependent, single-agent activity in various MET-expressing tumor models, and additive effects were observed in combination with erlotinib for reducing tumor volume in lung cancer mouse xenograft models (11).

Herein, we report results from the first-in-human dose (FHD) phase I dose-escalation trial of emibetuzumab as monotherapy (Part A) or combination with erlotinib (Part A2) in patients with advanced or metastatic cancer. The primary objective of this study was to identify a recommended phase 2 dose range for emibetuzumab, when administered as monotherapy or in combination with erlotinib to patients with advanced cancer.

Patients and Methods

Study design

This study was a multicenter, nonrandomized, open-label, FHD phase I, dose-escalation study of emibetuzumab given as monotherapy or as a combination treatment with erlotinib (NCT01287546). Emibetuzumab was administered by intravenous infusion on days 1 and 15 of a 28-day cycle as monotherapy (Part A) or in combination with erlotinib at the FDA-approved dose of 150 mg once daily (QD; Part A2). Dose escalations of emibetuzumab were performed following a standard 3+3 design.

The primary objective of this study was to determine a recommended phase II dose (RPTD) range of emibetuzumab that could be safely administered to patients as monotherapy or in combination with erlotinib. Secondary objectives included safety and toxicity assessments, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity. The protocol was approved by Institutional Review Boards before patient recruitment, and each patient provided written informed consent before enrollment. The study was conducted in accordance with the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice.

Patient population

Eligible patients were $\geq$18 years of age with advanced and/or metastatic cancer after failure of standard-of-care therapy(s), or for whom there was no standard therapy. Additional key eligibility criteria included adequate hematologic, renal and hepatic function, and an Eastern Cooperative Oncology Group performance status of $\leq$2. For patients receiving combination therapy of LY2875358 and erlotinib, a confirmed diagnosis of squamous or nonsquamous non–small cell lung cancer (NSCLC; Stage IIIB with malignant pleural effusion or Stage IV per American Joint Committee on Cancer Staging Criteria, 6th Edition) and measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) were required (12).

Patients were excluded if they had received any cancer therapy within 21 days or 5 half-lives prior to study enrollment (whichever was shorter), had not recovered from the acute effects of treatment-related toxicities, had liver cirrhosis with a Child–Pugh Stage of B or C, or had a second primary malignancy that may affect the interpretation of results. Patients were excluded from Part A2 if they had a symptomatic central nervous system malignancy or metastasis, prior MET targeting therapy, or if they had been previously intolerant of erlotinib therapy.

Study treatments

Patients in Part A received emibetuzumab at doses of 20, 70, 210, 700, 1,400, or 2,000 mg using a flat dosing scheme every 14 days (Q2W). The starting dose and the dose range were selected based on toxicology results and modeling of PK and PD data from nonclinical studies (11). Emibetuzumab was administered intravenously over 90 minutes at the 20- to 700-mg dose levels and over 150 minutes at the 1,400- and 2,000-mg dose levels. No

Table 1. Patient and disease characteristics

Parameter	Emibetuzumab monotherapy (Part A)	Emibetuzumab + erlotinib (Part A2)
Number of patients	*N* = 23	*N* = 14
Age, mean (SD)	61.6 (10.6)	68.3 (9.6)
Sex, *n* (%)		
Female	10 (43.5)	8 (57.1)
Male	13 (56.5)	6 (42.9)
Race		
Caucasian	20 (87.0)	13 (92.9)
African descent	3 (13.0)	1 (7.1)
Weight (kg), mean (SD)	73.1 (18.8)	72.0 (17.1)
ECOG performance status, *n* (%)		
0	6 (26.1)	0 (0.0)
1	17 (73.9)	12 (85.7)
2	0 (0.0)	2 (14.3)
Type of cancer, *n* (%)		
Colorectal	9 (39.1)	0 (0.0)
NSCLC	4 (17.4)	14 (100.0)
Ovarian	2 (8.7)	0 (0.0)
Other[a]	8 (34.8)	0 (0.0)
Prior therapies, *n* (%)		
Prior systemic therapy*	23 (100)	14 (100)
Prior radiotherapy	11 (47.8)	9 (64.3)
No prior therapy reported	0 (0)	0 (0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; *N*, population size; *n*, number of patients in group.

[a]Cancer types included adrenal cortical adenocarcinoma, breast, gastric, head and neck, hepatocellular, malignant mesothelioma, papillary cell carcinoma, and papillary urothelial (each *n* = 1).

*Patients had a wide range of treatments.

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intrapatient dose escalations were allowed. In Part A2, patients with advanced NSCLC were treated with emibetuzumab at escalating flat doses of 700, 1,400, and 2,000 mg in combination with erlotinib administered at the dose of 150 mg QD. Part A2 was initiated at a dose level of 700-mg emibetuzumab after the 1,400-mg emibetuzumab monotherapy dose in Part A was judged to be safe and tolerable.

Safety

Safety and tolerability were assessed through clinical and laboratory evaluations at weekly intervals for the first two cycles and Q2W thereafter. Adverse events (AE) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v.4.0) and were recorded for all patients who received at least one dose of emibetuzumab. Dose-limiting toxicities (DLT) were defined as possibly drug-related AEs during cycle 1 if they met the following criteria: $\geq$ Grade 3 nonhematologic toxicity (except for Grade 3 nausea, vomiting, diarrhea, constipation, fatigue, or anorexia for <2 days), Grade 4 hematologic toxicity of >5 days duration, febrile neutropenia, or any toxicity that required the withdrawal of the patient from the study.

Pharmacokinetics

Serial samples from all patients were taken prior to emibetuzumab infusion, at mid-infusion, at the end of the infusion, and at 2, 4, 24, 72 to 120, 144 to 192, and 336 hours after the end of the infusion. Serum concentrations of emibetuzumab were determined using a validated sandwich ELISA. The lower limit of quantification was 20 ng/mL, and the upper limit of quantification was 800 ng/mL. Samples above the limit of quantification were diluted to yield results within the calibrated range.

A noncompartmental analysis following single (first) doses of emibetuzumab was conducted using Phoenix WinNonlin (version 6.3, Certara L.P.). Area under the concentration–time curve (AUC), time of maximum observed serum concentration (C_{max}), and elimination half-life ($t_{1/2}$) were summarized as geometric mean and percent coefficient of variation (%CV). In addition, a population PK analysis was conducted using NONMEM version 7.2 to fit a target-mediated drug disposition (TMDD) model to emibetuzumab concentration–time data to facilitate simulation of phase 2 dosing scenarios (13).

Pharmacodynamics and immunogenicity

For PD analysis, blood serum was collected prior to each dose of emibetuzumab throughout the study and assessed for total (free + emibetuzumab-bound) circulating extracellular domain of MET (MET-ECD) by ELISA (Midwest BioResearch). The validated quantification range of this assay was 0.08 to 5.00 ng/mL.

Blood samples for anti–emibetuzumab-binding antibodies were collected throughout the study from all enrolled patients, and the formation of anti-drug antibodies (ADA) was assessed by

Table 2. Emibetuzumab-related treatment emergent AEs

Emibetuzumab monotherapy (Part A)							
CTCAE term	**20 mg *n* = 6**	**70 mg *n* = 3**	**210 mg *n* = 3**	**700 mg *n* = 5**	**1,400 mg *n* = 3**	**2,000 mg *n* = 3**	**Total *N* = 23, *n* (%)**
Patients with at least 1 drug-related AE	0	2	1	2	0	1	6 (26.1)
Diarrhea	0	1	1	0	0	0	2 (8.7)
Nausea	0	0	0	1	0	1	2 (8.7)
Vomiting	0	0	0	2	0	0	2 (8.7)
Abdominal pain	0	0	0	1	0	0	1 (4.3)
Anorexia	0	1	0	0	0	0	1 (4.3)
Chills	0	1	0	0	0	0	1 (4.3)
Fatigue	0	0	0	0	0	1	1 (4.3)
General disorders and administrations site conditions, other, specify	0	1	0	0	0	0	1 (4.3)
Emibetuzumab + erlotinib (Part A2)							
CTCAE term	**700 mg *n* = 5**		**1,400 mg *n* = 3**		**2,000 mg *n* = 6**		**Total *N* = 14 (%)**
Patients with at least 1 drug-related AE	2		2		5		9 (64.3)
Fatigue	0		1		2		3 (21.4)
Anorexia	0		1		1		2 (14.3)
Creatinine increased	0		0		1		1 (1.7)
Diarrhea	0		1		0		1 (7.1)
Dry skin	0		0		1		1 (7.1)
Endocrine disorders, other, specify	0		0		1		1 (1.7)
General disorders and administrations site conditions, other specify	0		0		1		1 (1.7)
Hypocalcemia	0		0		1		1 (7.1)
Hypotension	0		0		1		1 (7.1.)
Investigations, other, specify	0		0		1		1 (7.1)
Nausea	0		0		1		1 (7.1)
Pain in extremity	0		0		1		1 (7.1)
Peripheral sensory neuropathy	0		1		0		1 (7.1)
Pruritus	0		1		0		1 (7.1)
Rash, acneiform	1		0		0		1 (7.1)
Rash, maculopapular	1		0		0		1 (7.1)
Vomiting	0		0		1		1 (7.1)
Weight loss	1		0		0		1 (7.1)

Abbreviations: *N*, total number of patients; *n*, number of patients in the specified category.

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ELISA. This ADA screening assay was validated in accordance with the FDA Guidance for Industry "Assay Development for Immunogenicity Testing of Therapeutic Proteins" (FDA 2009).

Biomarker assessments

Tumor samples from the optional tissue collection were evaluated for MET protein expression and *MET* amplification. For MET protein expression, the CONFIRM anti-total c-Met (SP44) rabbit monoclonal primary antibody (Ventana Medical Systems, Inc.; Catalog No. 790-4430) was used (14). Antigen recovery was conducted under standard conditions with CC1 buffer (VMSI; Catalog No. 950-120), and anti-MET antibodies were detected using the ultraViewdetection Kit (VMSI; Catalog No. 760-500). A composite scoring system was devised to determine the status of MET by immunohistochemistry. Tumor samples with $\geq$50% of cells stained 2+ or 3+ for MET expression were considered as MET diagnostic positive.

Amplification of *MET* was assessed by FISH by Molecular Pathology Laboratory Network, Inc. (MPLN). A board-certified pathologist reviewed each hematoxylin and eosin slide to determine the target area to be evaluated by FISH, and the signal patterns present were recorded. MPLN analyzed 200 cells (if available) from the marked tumor area on each slide. Tumor samples were considered to be *MET* amplified if the *MET*/*CEP7* ratio cutoff of $\geq$2.

Antitumor activity

Patients' tumors were measured by CT scan, magnetic resonance imaging, and/or chest x-ray. Assessments of antitumor activity were performed according to RECIST 1.1 (15) at baseline, in cycles 2 and 4, and every 2 to 4 cycles thereafter as clinically indicated.

Statistical methods

The statistical analyses for this study were descriptive. Data summaries, including demographic and baseline characteristics, safety, PK, and preliminary efficacy were reported by study part and dose groups as appropriate. For continuous variables, summary statistics included number of patients, mean, and SD. Categorical endpoints were summarized using number of patients, frequency, and percentages. No formal sample size calculation or hypothesis testing was performed.

Results

Patient disposition and demographics

A total of 37 patients were enrolled and received at least 1 dose of emibetuzumab (Table 1). Twenty-three patients with solid tumors were enrolled in the emibetuzumab monotherapy part (Part A) and were treated at one of the six emibetuzumab dose levels: 20 mg ($n = 6$), 70 mg ($n = 3$), 210 mg ($n = 3$), 700 mg ($n = 5$), 1,400 mg ($n = 3$), or 2,000 mg ($n = 3$) emibetuzumab as a flat dose every 2 weeks. Fourteen patients with NSCLC received emibetuzumab at one of three dose levels: 700 mg ($n = 5$), 1,400 mg ($n = 3$), and 2,000 mg ($n = 6$) as flat doses every 2 weeks in combination with erlotinib 150 mg QD. All patients had undergone prior anticancer treatment. Baseline patient and disease characteristics are summarized in Table 1.

Safety and tolerability

There were no DLTs or study drug-related serious adverse events (SAE) reported up to the maximum studied dose level of 2,000 mg emibetuzumab in either part of the study. The overall occurrence of related treatment-emergent adverse events (TEAE) was low at all dose levels (Table 2) for monotherapy and in combination with erlotinib (TEAEs regardless of causality are presented in Supplementary Table S1).

In the emibetuzumab monotherapy cohort, the most frequently reported AEs that were possibly study drug related included diarrhea, nausea, and vomiting (8.7% each). All were considered to be of mild intensity (i.e., CTCAE grade 1). No trend between dose level and AEs was observed in this small patient sample. The MTD for emibetuzumab monotherapy was not determined as no DLT was observed up to the maximum protocol prespecified dose

Table 3. Emibetuzumab PK for cycle 1 day 1 by dose

Emibetuzumab monotherapy						
Dose	**20 mg**	**70 mg**	**210 mg**	**700 mg**	**1,400 mg**	**2,000 mg**
N	**6**	**3**	**3**	**5**	**3**	**3**
t_{max}[a] (h)	3.52 (1.50–3.62)	1.58 (1.55–3.50)	5.33 (5.25–5.47)	3.60 (3.25–5.25)	6.25 (4.50–6.50)	4.53 (2.58–6.25)
C_{max} (ng/mL)	7,280 (83)	20,700 (30)	65,000 (18)	185,000 (28)	283,000 (42)	892,000 (10)
AUC(0–t_{last}) (μg•h/mL)	146 (25)	1,250 (37)	8,020 (15)	29,400 (35)	44,200 (50)	113,000 (21)
AUC(0–∞) (μg•h/mL)	162 (16)	1,320 (32)	9,380 (17)	46,400 (42)	74,400 (53)	223,000 (9)
$t_{1/2}$ (h)	18.0 (17)	45.4 (9)	122 (11)	246 (36)	255 (16)	342 (49)
CL (L/hr)	0.123 (16)	0.0529 (32)	0.0224 (17)	0.0151 (42)	0.0188 (53)	0.00895 (9)
V_{ss} (L)	3.31 (16)	3.72 (25)	3.80 (16)	5.24 (36)	6.86 (48)	4.23 (39)
Emibetuzumab in combination with erlotinib 150-mg QD						
Dose		**700 mg**		**1,400 mg**		**2,000 mg**
N		**5**		**3**		**6**
t_{max}[a] (h)		5.5 (1.53–7.50)		7.93 (2.50–8.50)		2.57 (2.50–4.75)
C_{max} (ng/mL)		205,000 (17)		621,000 (27)		646,000 (14)
AUC(0–t_{last}) (μg•h/mL)		28,900 (29)		87,800 (13)		103,000 (19)
AUC(0–∞) (μg•h/mL)		48,900 (21)		120,000 (12)		157,000 (20)
$t_{1/2}$ (h)		224 (19)		173 (16)		226 (27)
CL (L/hr)		0.0143 (21)		0.0117 (12)		0.0128 (20)
V_{ss} (L)		4.62 (14)		2.92 (19)		4.09 (28)

NOTE: Values are reported as geometric mean (%CV).

Abbreviations: AUC(0–∞), area under the concentration–time curve from time of dose to infinity; AUC(0–t_{last}), area under the concentration–time curve from time of dose to the last quantifiable concentration measurement; CL, systemic clearance; Cmax, maximum observed serum concentration; CV, coefficient of variation; min, minimum; max, maximum; t1/2, half-life; tmax, time to Cmax; Vss, volume of distribution at steady state.

[a]Median (Min - Max).

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level of 2,000 mg. Although no dose reductions or omissions were allowed by protocol, 3 patients had an emibetuzumab dosing delay. The mean average dose intensity, defined as ratio of delivered dose to planned dose, was 98.0%.

In the erlotinib combination portion of the study (Part A2), 14 patients received at least 1 dose of emibetuzumab. Across the three emibetuzumab dose levels studied, there were a total of 9 patients with possibly emibetuzumab-related AEs reported, all of which were either CTCAE Grade 1 or 2. The most frequent emibetuzumab-related AEs included fatigue (21.4%) and anorexia (14.3%; Table 2). The only four Grade 2 AEs possibly related to emibetuzumab comprised one case each of hypocalcemia,

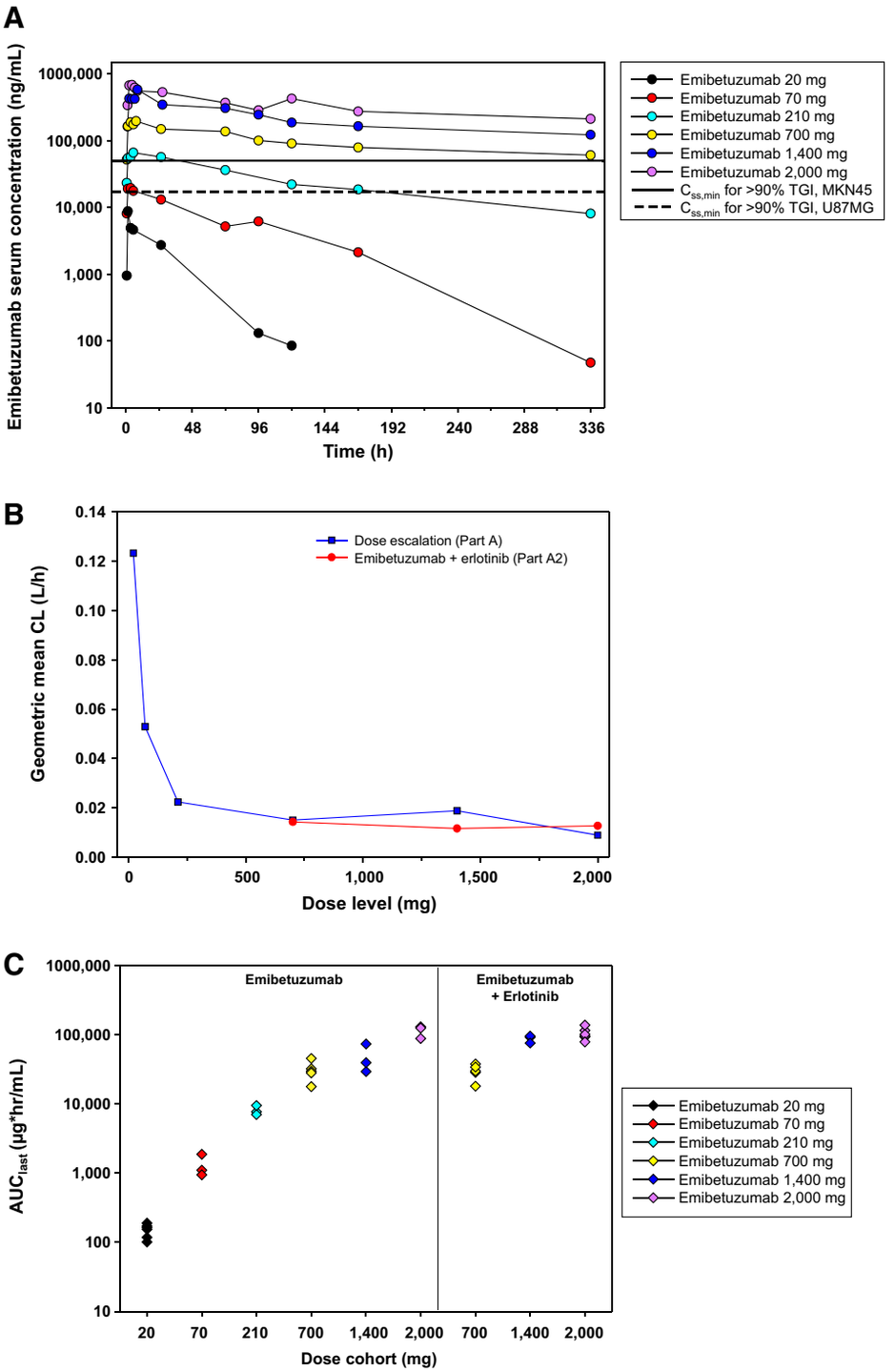

Figure 1.
PK and PD profiles. **A,** Emibetuzumab mean concentration–time profiles. **B,** Emibetuzumab geometric mean clearance by dose level. **C,** Emibetuzumab exposure by dose level. (*Continued on the following page.*)

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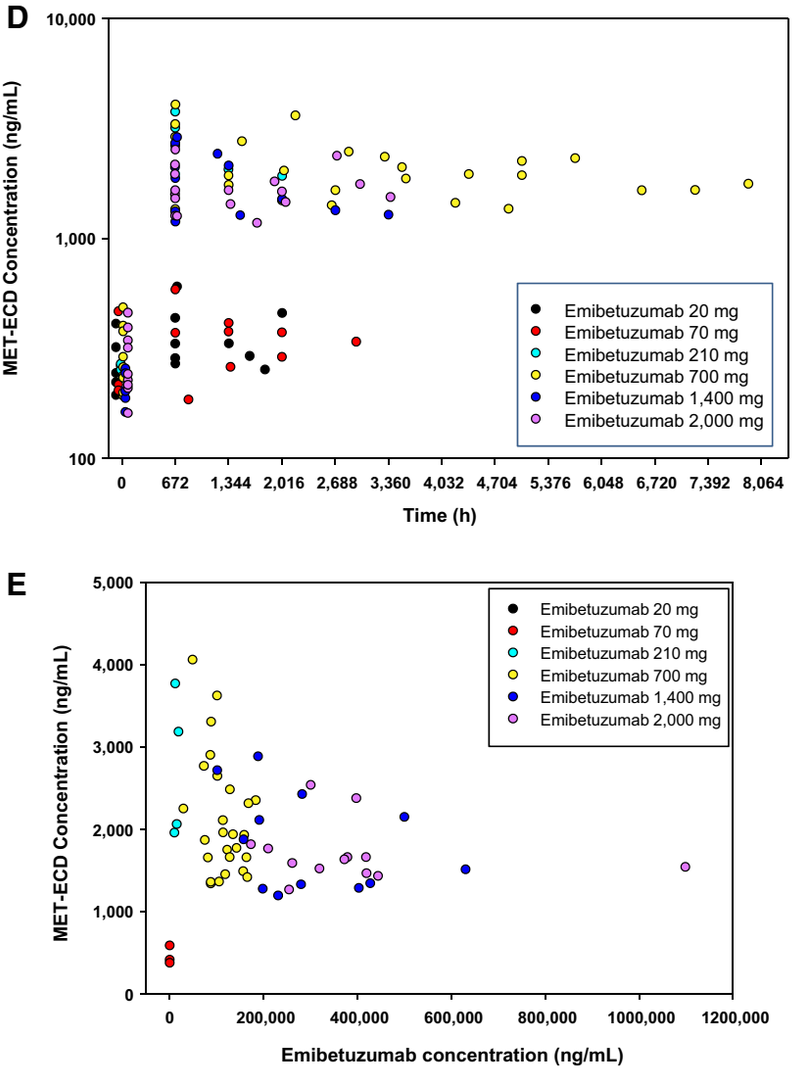

Figure 1.
(*Continued.*) **D,** Emibetuzumab treatment resulted in approximately a 10-fold MET-ECD increase at 4 weeks relative to baseline. **E,** MET-ECD concentrations generally decreased with increasing emibetuzumab plasma concentrations.

fatigue, nausea, and papulopustular rash. Three patients had a dosing delay of emibetuzumab in the combination arm for a mean average dose intensity for emibetuzumab of 98.9%. There were 7 patients with erlotinib-omitted doses. Of these dose omissions, 3 patients missed doses due to AEs [2 patients due to rash (grade 2) and 1 patient due to diarrhea (grade 1)]. The mean average dose intensity of erlotinib in combination with emibetuzumab was 81.2%.

Progressive disease was the primary reason for study treatment discontinuation from either Part A or Part A2 of the study (73.9% and 64.3%, respectively). Further reasons for discontinuation of study treatment are presented in Supplementary Table S3. No patient discontinued study treatment due to a LY3023414-related AE. One patient in Part A2 (700 mg dose level) discontinued study treatment due to an AE of acneiform rash during cycle 6 considered by the investigator related to erlotinib but not related to emibetuzumab. There were three discontinuations of study treatment due to death including 2 cases resulting from study disease and one due to an AE unrelated to emibetuzumab (myocardial infarction in a patient with 30-pack per year history of smoking enrolled at the 20 mg dose level in Part A). No emibetuzumab infusion–related reactions were reported in either part of the study. In the absence of any DLT observations, a MTD of emibetuzumab could not be determined for monotherapy or in combination with erlotinib.

Pharmacokinetics

PK data were available from 37 patients who received at least one dose of emibetuzumab. The PK parameters from a non-compartmental analysis of cycle 1 dose 1 are summarized in Table 3. After the end of an intravenous infusion, emibetuzumab serum concentrations peaked at approximately 1.5 to 6.5 hours, and appeared to decline in a biphasic manner at doses above 210 mg (Fig. 1A). Emibetuzumab clearance decreases with increasing doses from 20 mg to 210 mg, and remains constant at doses of 700 mg to 2,000 mg (Table 3 and Fig. 1B), with total systemic clearance approximately 10 times lower at the 2,000-mg dose compared with the 20-mg dose. Exposure by criterion of AUC increases with dose level (Fig. 1C), and at a dose of 2,000 mg, the mean terminal elimination t1/2 is 259 hours (approximately 11 days), with

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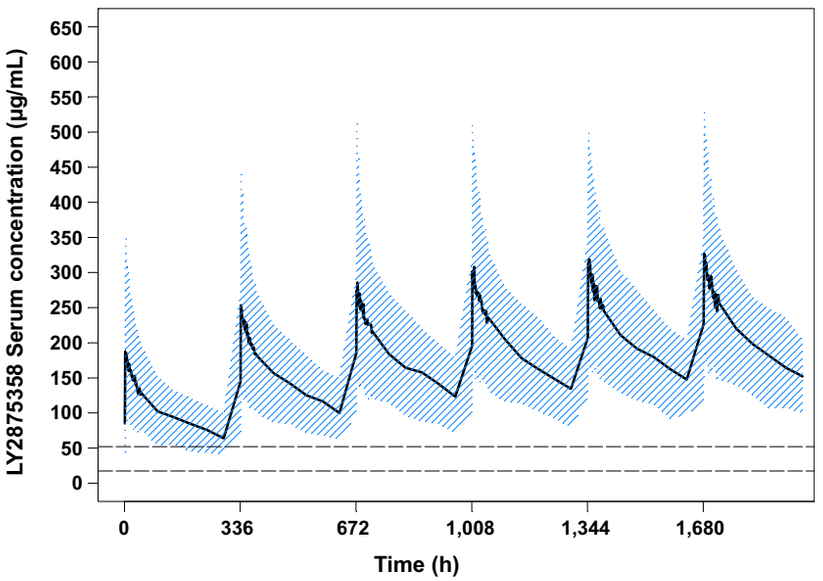

Figure 2.
Model-predicted emibetuzumab plasma concentrations for 750-mg Q2W. The hashed areas represent the 90% prediction interval, and the solid black line represents the median population prediction. The horizontal dashed lines represent the $C_{min,ss}$ associated with ≥90% tumor growth inhibition for U87MG (bottom) and MKN45 (top) xenograft models (Eli Lilly and Company, data on file).

a range of 170 to 572 hours (approximately 7 to 24 days). The mean volume of distribution at steady state (Vss) is approximately 4 to 5 L. For doses greater than or equal to 210 mg Q2W, accumulation in serum is observed, with an accumulation ratio of approximately 2 in the 2,000 mg Q2W regimen. Emibetuzumab PKs were similar in the monotherapy and erlotinib combination groups (Table 3; Fig. 1C).These nonlinear changes in clearance with dose level are consistent with TMDD, wherein rapid, receptor-mediated clearance predominates at lower doses (20 mg to 210 mg) and slower, non–receptor-mediated clearance predominates at higher doses (700 to 2,000 mg). A TMDD population model adequately fit the human PK data from the monotherapy group, and was used to simulate several dosing regimens (13), which ultimately led to the RPTD range of 700 to 2,000 mg Q2W. Based on simulations of emibetuzumab concentration–time profiles from this model, 100% of the population is predicted to have a minimum concentration at steady state ($C_{min,ss}$) above 50 µg/mL, which is the $C_{min,ss}$ of emibetuzumab associated with ≥90% tumor growth inhibition *in vivo* (Fig. 2; ref. 11). In the dose range of 700 to 2,000 mg Q2W, non–receptor-mediated clearance predominates, suggesting that the nonlinear (receptor-mediated) clearance pathway is saturated. Therefore, emibetuzumab exposures achieved by 700 mg Q2W or higher are expected to be sufficient to prevent HGF binding and signaling, reduce expression of MET, and inhibit MET-driven tumor growth in cancer patients (Fig. 2).

Pharmacodynamic biomarker

The extracellular domain of MET (MET-ECD) in the circulation has been suggested to correlate with the MET receptor target occupancy *in vivo* and as a PD biomarker of target engagement (16). As shown in Fig. 1D, emibetuzumab treatment resulted in an about 10-fold MET-ECD increase at 4 weeks relative to baseline in patients receiving emibetuzumab at doses of 210 mg Q2W or higher, but not at lower dose levels. These elevated MET-ECD levels were maintained over time by continued emibetuzumab treatment, but no further dose dependency was observed at dose levels higher than 210 mg, indicating saturation of MET receptors at these dose levels. MET-ECD concentrations generally decreased with increasing emibetuzumab plasma concentrations (Fig. 1E).

All patients enrolled were evaluated for ADAs before, during, and after completion of study treatment. No samples from any of the patients tested positive for ADAs.

Antitumor activity

Of the 23 patients receiving emibetuzumab monotherapy (Part A), 19 patients had postbaseline radiological tumor assessment allowing assessment based on RECIST criteria. There was 1 confirmed PR according to RECIST observed in a transitional cell cancer patient receiving 700 mg emibetuzumab which lasted for seven cycles for an objective response rate (ORR) of 4.3% in this part of the study (Fig. 3A; Supplementary Table S2). Another patient with colon cancer achieved 30% reduction in target lesions, although failed to achieve partial response due to the appearance of a new lesion. Four patients treated at emibetuzumab doses of 700 mg or higher demonstrated a decrease in the sum of target lesions relative to baseline. Five patients (21.7%) demonstrated SD as their best response to therapy for a disease control rate (DCR) of 26.1%. Patients treated with emibetuzumab monotherapy completed a median of 2 cycles of therapy (range, 1–7; Supplementary Fig. S1A).

Among the 14 NSCLC patients treated with emibetuzumab in combination with erlotinib (Part A2), 12 patients had postbaseline radiological tumor assessment allowing assessment based on RECIST criteria. Clinical activity observed in these 12 patients included confirmed durable PRs in 2 patients (one each at 700 mg and 2,000 mg emibetuzumab) for an ORR of 14.3% (Fig. 3B; Supplementary Table S2). Four patients (28.6%) had SD as best response to treatment for a DCR of 42.9% in Part A2. Pretreatment tumor biopsy material (optional collection) obtained from the 2 patients with partial response to emibetuzumab + erlotinib were MET diagnostic positive by IHC (H-scores of 149 and 280). None of these patients or any other patient's tumor samples available for testing displayed evidence of *MET* gene amplification. Patients treated with emibetuzumab in

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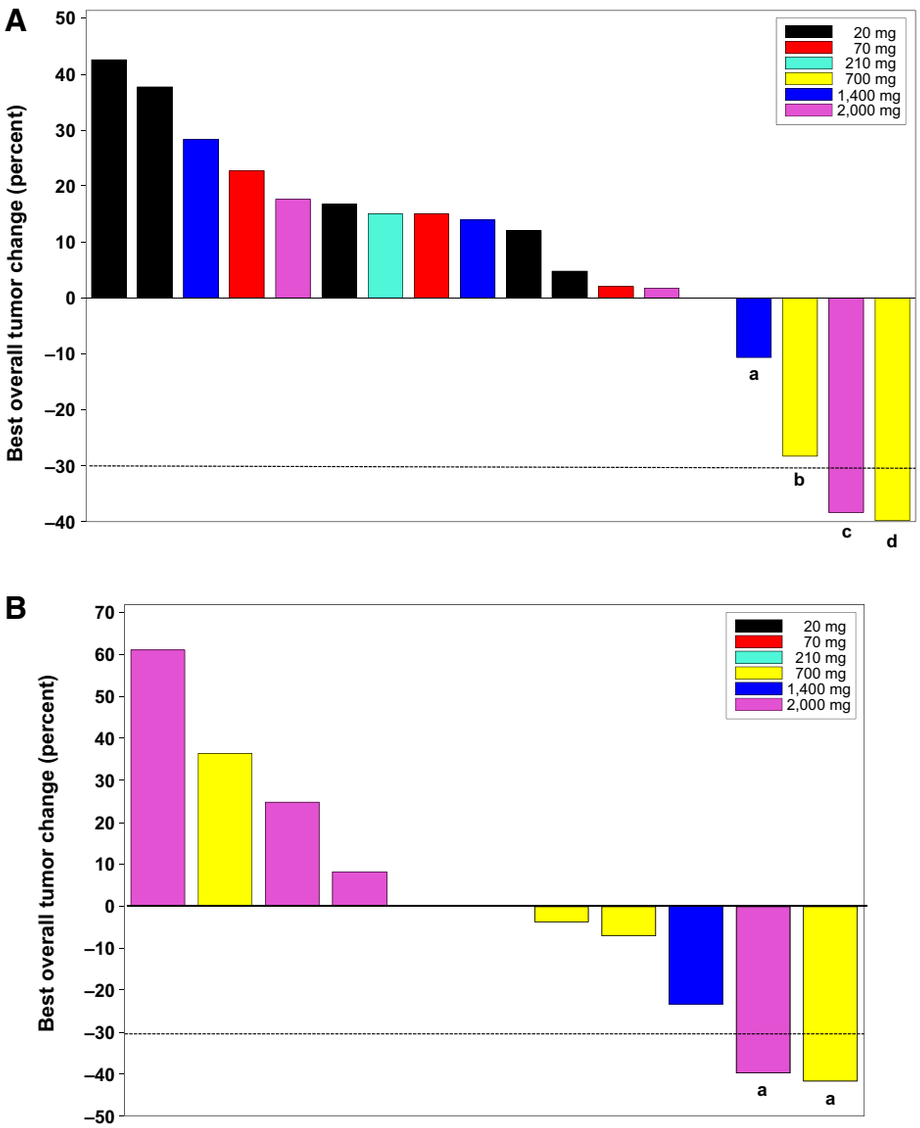

Figure 3.

Waterfall plot for best response and treatment duration. **A,** Waterfall plot of maximum percent change in sum of target lesions relative to baseline for emibetuzumab monotherapy. [a]The patient had colorectal cancer. [b]The patient had ovarian cancer. [c]The patient had adenocarcinoma of colon. Progressive disease due to appearance of new lesions. [d]The patient had transitional cell carcinoma. **B,** Waterfall plot of maximum percent change in sum of target lesions relative to baseline for emibetuzumab + erlotinib. [a]Both patients were enrolled to this study immediately following progression on erlotinib monotherapy, having only recorded stable disease during this prior erlotinib treatment. Immunohistochemical analysis of available tumor tissue samples from both patients was positive for MET expression.

combination with erlotinib completed a median of 2 cycles of therapy (range, 0–36; Supplementary Fig. S1B). One of the 2 patients with PR was still ongoing at cycle 28 at the time of data cutoff (March 25, 2014).

Discussion

In this FHD dose-escalation study in patients with advanced cancer emibetuzumab, a bivalent MET mAb blocking ligand-dependent and -independent MET signaling was safe and well tolerated as a single agent and in combination with erlotinib without any DLTs or drug-related SAEs. The RPTD range for emibetuzumab monotherapy and in combination with erlotinib was determined to be 700 to 2,000 mg i.v. Q2W based on tolerability, PK/PD analysis, and preliminary clinical activity.

AEs possibly related to emibetuzumab monotherapy were reported at low frequencies (less than 10% of patients) and were all considered to be of mild intensity, with diarrhea, nausea, and vomiting as the most common. Although sample size was limited, no relationship was observed between dose and emibetuzumab-related AEs. Peripheral edema has been suggested as a potential on-target class effect for therapies targeting the MET/HGF pathway (17). Ryan and colleagues (18) noted peripheral edema by treatment with rilotumumab (a fully human mAb against HGF), and Salgia and colleagues reported peripheral edema following treatment with onartuzumab (a monovalent MET Ab) at doses $\geq$10 mg/kg (17). In the current study, non–emibetuzumab-related peripheral edema was reported for monotherapy in 2 patients at the lowest dose level, and 1 patient each at the 700-mg and 1,400-mg dose levels. In combination with erlotinib, treatment-related AEs were more common than for emibetuzumab monotherapy. However, the higher incidence and type of non–emibetuzumab-related AEs observed for the combination with erlotinib relative to emibetuzumab alone were consistent with the expected safety profile for erlotinib (e.g., rash, diarrhea, nausea). Infusion-related reactions are known dose-independent AEs commonly associated with antibody treatment. Although no premedication with corticosteroids or antihistamines was required in the current

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study, no emibetuzumab infusion–related reaction was reported in any of the 37 patients enrolled. In addition, no antitherapeutic antibodies against emibetuzumab were detected in patient blood samples. These data underline the favorable safety profile of emibetuzumab as a humanized IgG4 mAb targeting the MET receptor with low immunogenic potential.

Because no DLTs have been reported in this study, no MTD was established. Therefore, the RPTD range of 700 to 2,000 mg Q2W was determined primarily based on the PK profile observed and supported by PK/PD modeling guided by preclinical *in vivo* efficacy studies. The observed decrease of emibetuzumab plasma clearance at higher doses, plateauing at doses from 210 to 2,000 mg emibetuzumab Q2W, indicates saturation of target-mediated clearance. The increase of shed MET-ECD in patient samples as a measure for target engagement and receptor occupancy following emibetuzumab exposure at dose levels $\geq$210 mg further supports this notion. Rapid, receptor-mediated clearance appears to predominate at lower doses, and slower, non–receptor-mediated clearance at higher doses, resulting in an approximately linear increase of exposure at doses from 210 to 2,000 mg Q2W. Based on PK simulations at doses of $\geq$700 mg emibetuzumab Q2W, 100% of the population is predicted to have a minimum plasma concentration at steady state ($C_{min,ss}$) $\geq$50 μg/mL, which is the $C_{min,ss}$ associated with $\geq$90% tumor growth inhibition in the ligand-independent xenograft model MKN45. Furthermore, based on *in vivo* target inhibition studies (11), MET inhibition at the level of the tumor would be maximized at exposures achieved by doses $\geq$700 mg Q2W.

The RPTD range of 700- to 2,000-mg emibetuzumab Q2W as a biologically active dose range in humans is supported by the preliminary clinical activity results observed in this dose escalation study. For emibetuzumab monotherapy, only patients treated at a dose level of at least 700 mg emibetuzumab or higher demonstrated tumor size reduction of target lesions consistent with the RPTD for emibetuzumab. This included 1 patient with a transitional cell tumor who had a confirmed partial response by RECIST lasting for 7 months.

Due to optional tissue collection for all enrolled patients, there is no information available about the tumor MET expression level for most patients enrolled in this study. The patient experiencing a PR emibetuzumab monotherapy underwent an on treatment rebiopsy, but the tissue obtained was not assessable for MET expression due to necrosis.

In the emibetuzumab plus erlotinib combination portion of this study, 2 of 14 patients had a durable partial response. Of note, both PR patients had an EGFRmt (exon 19 deletion) based on local testing and had received prior treatment with erlotinib as a single agent for approximately 9 months with a best overall response of stable disease. Upon progression on this erlotinib monotherapy, both patients were enrolled into Study JTBA and displayed a partial response to the combination treatment with emibetuzumab and erlotinib. Available pretreatment tumor samples from these 2 patients were evaluated as MET diagnostic-positive by IHC, but no *MET* amplification was observed as assessed by FISH. These anecdotal data are consistent with a role of MET as resistance mechanism to erlotinib treatment in EGFRmt patients (19) which might be overcome by simultaneously blocking the MET and the EGFR pathway. In order to test this hypothesis, there are currently two phase II studies for emibetuzumab plus erlotinib ongoing, one for patients with NSCLC with acquired resistance to erlotinib (NCT01900652) and one for first-line treatment in patients with EGFRmt NSCLC (NCT01897480). Relative to previous failed studies with MET targeting antibodies (20), the dual mechanism of action of emibetuzumab of blocking ligand-dependent and ligand-independent MET signaling in conjunction with focusing on EGFR-mutant NSCLC patients might be a more promising strategy for targeting MET in NSCLC.

In summary, the MET antibody emibetuzumab has a favorable safety profile with no observed DLTs and with demonstrable preliminary clinical activity as monotherapy and in combination with erlotinib. The RPTD range of emibetuzumab is 700 to 2,000 mg Q2W administered as monotherapy or in combination with erlotinib. Emibetuzumab is being administered in flat doses of 750 mg Q2W in combination with erlotinib in ongoing phase II trials for patients with NSCLC.

Disclosure of Potential Conflicts of Interest

L.S. Rosen reports receiving commercial research support from Eli Lilly. J.W. Goldman is a consultant/advisory board member for Genentech, and reports receiving commercial research grants from AbbVie, Eli Lilly, and Genentech/Roche. A.P. Algazi reports receiving commercial research support from AstraZeneca, Bristol-Myers Squibb, Merck, and OncoSec. P.K. Turner, B. Moser, T. Hu, X.A. Wang, V. Wacheck, and J.E. Woolridge have ownership interest (including patents) in Eli Lilly. No potential conflicts of interest were disclosed by the other authors.

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