Phase I Dose-Escalation and -Expansion Study of Telisotuzumab (ABT-700), an Anti–c-Met Antibody, in Patients with Advanced Solid Tumors

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ABSTRACT

This first-in-human phase I study evaluated the pharmacokinetics, safety, and preliminary efficacy of telisotuzumab, formerly called ABT-700, an antagonistic antibody directed against c-Met. For dose escalation (3+3 design), 3 to 6 patients with advanced solid tumors were enrolled into four dose cohorts (5–25 mg/kg). In the dose-expansion phase, a subset of patients was prospectively selected for *MET* amplification (FISH screening). Patients received telisotuzumab intravenously on day 1 every 21 days. For dose expansion, 15 mg/kg was chosen as the dose on the basis of safety, pharmacokinetics, and other data from the escalation cohorts. Forty-five patients were enrolled and received at least one dose of telisotuzumab (dose escalation, $n = 15$; dose expansion, $n = 30$). Telisotuzumab showed a linear pharmacokinetics profile; peak plasma concentration was proportional to dose level. There were no acute infusion reactions and no dose-limiting toxicities were observed. The most common treatment-related adverse events included hypoalbuminemia ($n = 9$, 20.0%) and fatigue ($n = 5$, 11.1%). By Response Evaluation Criteria In Solid Tumors (RECIST), 4 of 10 (40.0%) patients with *MET*-amplified tumors had confirmed partial response in target lesions (one ovarian, two gastric, and one esophageal), two (20.0%) had stable disease, three (30.0%) had progressive disease; one patient was unable to be evaluated. Among patients with nonamplified tumors ($n = 35$), no objective responses were observed; however, 11 patients had stable disease per RECIST criteria. In conclusion, telisotuzumab has an acceptable safety profile with clinical activity observed in patients with *MET*-amplified advanced solid tumors.

Introduction

The *MET* oncogene encodes the tyrosine kinase receptor c-Met, a cell surface receptor that regulates tumor proliferation, migration, angiogenesis, invasion, and survival (1–3). Tumors with *MET* gene amplification are particularly dependent on c-Met signaling for growth and survival and have an aggressive phenotype (4, 5). In these *MET*-amplified tumors, inhibition of the Met receptor disrupts cellular growth and survival (6). *MET* amplification is rare, occurring in less than 5% of most advanced solid tumors at the time of initial diagnosis (7–9). On the other hand, *MET* amplification increases in the treatment-refractory setting, particularly under the selective pressure of EGFR inhibition therapy (10–12). Patients with *MET*-amplified advanced solid tumors dependent on signaling through the MET pathway for survival may be particularly likely to benefit from an anti–c-Met therapeutic strategy.

Telisotuzumab, formerly called ABT-700, is a humanized recombinant bivalent antibody that binds c-Met with high affinity and inhibits c-Met signaling. Telisotuzumab antagonizes c-Met activation by both hepatocyte growth factor–dependent and -independent mechanisms, and has potent antiproliferative activity against *MET*-amplified human tumor xenografts (13). In addition, *in vitro* studies indicate that the antitumor activity of telisotuzumab is enhanced by antibody-dependent cell-mediated cytotoxicity. In cynomolgus monkeys, telisotuzumab was well tolerated, even at the highest dose level (200 mg/kg; AbbVie, data on file). On the basis of these preclinical studies, we hypothesized that telisotuzumab would be well tolerated and would have single-agent clinical activity in patients with *MET*-amplified advanced solid tumors.

The primary objectives of the reported phase I, first-in-human study were to establish the pharmacokinetics, safety, tolerability, and recommended phase II dose (RP2D) of telisotuzumab. The secondary objective was to evaluate preliminary signals of efficacy. We also sought to explore the association between *MET* gene amplification and objective treatment response.

Patients and Methods

Patient eligibility

Patient enrollment began in October 2011. Eligible patients were at least 18 years old; had an Eastern Cooperative Oncology Group

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performance status of 2 or lower; had a histologically or cytologically confirmed solid tumor diagnosis; had measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1; ref. 14); had adequate hematologic, renal, and liver functions; and had disease that progressed despite standard therapy, or for which no standard therapy was available. Prior chemotherapy, radiotherapy, immunotherapy, biologic therapy, or investigational therapy had to be completed at least 21 days before first dose of telisotuzumab. Women who were pregnant or lactating were ineligible. Patients with known brain metastases were eligible provided the lesions were stable for at least 1 month after treatment. Patients who had severe or uncontrolled medical conditions were excluded. All patients provided written informed consent, and local ethics committee approval was obtained. This study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. This study is registered with ClinicalTrials.gov (NCT01472016).

Study design and treatment

This multicenter, open-label study in adult patients with advanced solid tumors consisted of two parts: dose escalation and dose expansion. The dose escalation followed a standard 3+3 design to determine the safety, MTD, and pharmacokinetic profile of telisotuzumab. Telisotuzumab was administered by intravenous infusion to groups of 3 to 6 patients enrolled in four cohorts at 5, 10, 15, and 25 mg/kg on day 1 and once every 21 days (Q3W) until disease progression or unacceptable toxicity. Tumor assessments were performed every 6 weeks; response was evaluated using RECIST v1.1. The decision to escalate was based on safety data demonstrating lack of dose-limiting toxicities (DLT) as defined in the protocol. Dose expansion at the RP2D was performed to evaluate the safety, tolerability, and antitumor activity of telisotuzumab. *MET* gene amplification was identified in a subset of patients enrolled in the dose expansion through retrospective analysis and prospective screening (see below for definition). Fourteen patients were enrolled in combination therapy with telisotuzumab and either capecitabine-oxaliplatin (XELOX; $n = 5$), erlotinib ($n = 4$), or docetaxel ($n = 5$), 13 of whom were treated at dose levels of telisotuzumab that were below the dose chosen for the expansion cohort. The sponsor chose to terminate the study prior to completing enrollment in these cohorts. Therefore, there are insufficient data to derive meaningful conclusions. Only the results of telisotuzumab monotherapy (dose escalation and expansion) are formally reported.

Safety and efficacy assessments

Patients were assessed at multiple time points during cycle 1, and then Q3W thereafter. Efficacy was evaluated according to RECIST v1.1; disease assessment occurred every two cycles (6 weeks). Safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. DLT was defined as any grade 3 or higher study drug-related event occurring during the 21-day DLT window.

Pharmacokinetic/pharmacodynamic assessments

Blood samples for pharmacokinetic evaluation of telisotuzumab were collected on day 1 of cycle 1 (predose and 30 minutes postinfusion), during study visits on days 3 (for some patients), 8, and 15 of cycle 1, on day 1 (predose and 30 minutes postinfusion) of cycle 2, and day 1 of every subsequent cycle, and at the final visit. Standard pharmacokinetic parameters were computed by noncompartmental methods.

Plasma markers for pharmacodynamic evaluation of telisotuzumab were collected predose on day 1 cycle 1, during study visit on day 15 of cycle 1, on day 1 of cycles 2 and 3, and at the final visit.

MET gene amplification prospective screening and retrospective assessment

MET gene amplification was assessed in tumor tissue by FISH (Abbott Molecular Diagnostics). *MET* amplification identified by FISH was defined as a *MET/CEP7* ratio ≥2 in ≥20% of cells. *MET* amplification was also assessed in the circulating tumor DNA (ctDNA) using METDetect assay from Personal Genome Diagnostics. DNA was isolated from 1 mL of plasma and genomic libraries (containing ∼160 bp fragments) were generated. *MET* regions were captured using Agilent hybrid capture (Agilent) and sequenced (Illumina HiSeq next-generation sequencing) at 2,000× depth. All reads were matched back to normal reference genome. Tags were counted in all regions and compared with reference. Copy-number analysis was carried out using digital karyotyping. The amplification of *MET* gene was indicated as fold copy gain. *MET* amplification was also demonstrated by sequencing of tumor tissue in one sample (FoundationOne, Foundation Medicine).

Statistical analyses

The safety analysis population included all patients who received one or more dose of study drug. All safety analyses were descriptive only, with no statistical inference drawn from the data. The efficacy-evaluable population included all patients receiving one or more dose of study drug. No formal statistical analysis was done for efficacy variables, which were all exploratory in nature. Overall response rate (ORR) was defined as the proportion of patients with a confirmed partial response or complete response to treatment. Duration of response was defined as time from a patient's initial objective response to study drug until disease progression or death, whichever occurred first. Patients were followed until disease progression or up to 24 months if receiving study drug.

Results

Patient demographics and baseline characteristics

Forty-five patients were enrolled and received at least one dose of telisotuzumab (data cutoff September 27, 2018). Fifteen patients composed the dose-escalation cohort [5 mg/kg ($n = 3$); 10 mg/kg ($n = 3$); 15 mg/kg ($n = 3$); and 25 mg/kg ($n = 6$)], and 30 the dose-expansion cohort (15 mg/kg). Patient demographics were well balanced and evenly distributed across all treatment phases, with male and female patients enrolled at approximately equal percentages; median age of the dose-escalation cohort was 62.0 years (range, 49–80), and 59.0 years (range, 34–77) for the dose-expansion cohort. A summary of patient demographics and baseline characteristics is shown in **Table 1**.

Safety and determination of MTD/RP2D

The median duration of exposure was two cycles for both the dose-escalation (range, 1–12 cycles) and dose-expansion (range, 1–12 cycles) phase. The MTD was not reached during the study and no DLTs were observed. Although no formal MTD was identified, 15 mg/kg was chosen as the dose for the expansion cohort on the basis of safety, pharmacokinetics, and other data from the escalation cohorts.

One or more treatment-emergent adverse events (TEAE) were experienced by 42 (93.3%) patients, 14 (93.3%) in the dose-

Table 1. Patient demographics and baseline characteristics.

Characteristic	Dose-escalation cohort ($N = 15$) Dose level				Dose-expansion cohort (15 mg/kg) ($N = 30$)	All patients ($N = 45$)
	5 mg/kg ($n = 3$)	10 mg/kg ($n = 3$)	15 mg/kg ($n = 3$)	25 mg/kg ($n = 6$)		
Age, median (range), years	63.0 (59–69)	61.0 (60–71)	55.0 (49–67)	62.5 (53–80)	59 (34–77)	60 (34–80)
Gender, *n* (%)						
Male	3 (100)	2 (66.7)	0	3 (50.0)	15 (50.0)	23 (51.1)
Female	0	1 (33.3)	3 (100)	3 (50.0)	15 (50.0)	22 (48.9)
ECOG PS at baseline						
0	0	1 (33.3)	0	0	12 (40.0)	13 (28.9)
1	3 (100.0)	2 (66.7)	3 (100.0)	4 (66.7)	16 (53.3)	28 (62.2)
2	0	0	0	2 (33.3)	2 (6.7)	4 (8.9)
Primary tumor type, *n* (%)						
Adenocarcinoma of gallbladder	0	1 (33.3)	0	0	0	1 (2.2)
Colon	1 (33.3)	0	1 (33.3)	3 (50.0)	8 (26.7)	13 (28.9)
Esophageal	0	0	0	0	2 (6.7)	2 (4.4)
Gastric	0	0	0	0	3 (10.0)	3 (6.7)
Head and neck	1 (33.3)	0	0	0	0	1 (2.2)
Lung cancer	0	0	0	0	1 (3.3)	1 (2.2)
Metastatic SCC	0	0	0	1 (16.7)	0	1 (2.2)
NET	0	0	0	0	1 (3.3)	1 (2.2)
Non-small cell lung	0	0	0	1 (16.7)	5 (16.7)	6 (11.3)
Ovarian	0	0	2 (66.7)	0	5 (16.7)	7 (15.6)
Rectal	0	1 (33.3)	0	0	3 (10.0)	4 (8.9)
Renal	1 (33.3)	1 (33.3)	0	0	1 (3.3)	3 (6.7)
Thyroid	0	0	0	1 (16.7)	0	1 (2.2)
Uterine	0	0	0	0	1 (3.3)	1 (2.2)
Median number of prior therapies (range)	4 (2–7)	3 (2–4)	5 (2–7)	4 (1–6)	3 (1–9)	4 (1–9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NET, neuroendocrine tumor; PS, performance status; SCC, small-cell carcinoma.

Table 2. Summary of TEAEs with telisotuzumab occurring in ≥10% of patients, and telisotuzumab TRAEs occurring in ≥5% of patients.

Adverse event	TEAEs Telisotuzumab				TRAEs Telisotuzumab			
	Any grade *n* (%)		Grade ≥3 *n* (%)		Any grade *n* (%)		Grade ≥3 *n* (%)	
	All doses ($N = 45$)	Expansion cohort ($N = 30$)	All doses ($N = 45$)	Expansion cohort ($N = 30$)	All doses ($N = 45$)	Expansion cohort ($N = 30$)	All doses ($N = 45$)	Expansion cohort ($N = 30$)
Any TEAE	42 (93.3)	28 (93.3)	20 (1.7)	13 (43.3)	22 (48.9)	12 (40.0)	3 (6.7)	0
Constipation	13 (28.9)	8 (26.7)	1 (2.2)	1 (3.3)	0	0	0	0
Fatigue	12 (26.7)	8 (26.7)	0	0	5 (11.1)	3 (10.0)	0	0
Decreased appetite	9 (20.0)	7 (23.3)	0	0	3 (6.7)	2 (6.7)	0	0
Hypoalbuminemia	12 (26.7)	6 (20.0)	4 (8.9)	1 (3.3)	9 (20.0)	4 (13.3)	2 (4.4)	0
Peripheral edema	12 (26.7)	5 (16.7)	0	0	4 (8.9)	1 (3.3)	0	0
Hypokalemia	10 (22.2)	5 (16.7)	1 (2.2)	1 (3.3)	1 (2.2)	0	0	0
Nausea	10 (22.2)	5 (16.7)	2 (4.4)	1 (3.3)	2 (4.4)	2 (6.7)	0	0
Vomiting	9 (20.0)	5 (16.7)	1 (2.2)	1 (3.3)	1 (2.2)	1 (3.3)	0	0
Anemia	7 (15.6)	5 (16.7)	2 (4.4)	1 (3.3)	2 (4.4)	1 (3.3)	0	0
Abdominal pain	6 (13.3)	5 (16.7)	0	0	0	0	0	0
Back pain	6 (13.3)	4 (13.3)	0	0	0	0	0	0
Dyspnea	6 (13.3)	4 (13.3)	1 (2.2)	1 (3.3)	0	0	0	0
Abdominal distension	5 (11.1)	4 (13.3)	0	0	1 (2.2)	1 (3.3)	0	0
Diarrhea	5 (11.1)	4 (13.3)	0	0	2 (4.4)	2 (6.7)	0	0
Ascites	6 (13.3)	3 (10.0)	1 (2.2)	1 (3.3)	0	0	0	0
Pruritus	5 (11.1)	3 (10.0)	0	0	1 (2.2)	0	0	0

Abbreviations: TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

escalation and 28 (93.3%) in the dose-expansion phase. The most common TEAEs were constipation ($n = 13$; 28.9%), fatigue, hypoalbuminemia, and peripheral edema ($n = 12$; 26.7%, each). Twenty patients (44.4%) reported grade ≥3 TEAEs, the most frequently reported being hypoalbuminemia ($n = 4$; 8.9%). TEAEs occurring in ≥10% of patients and the most common grade ≥3 TEAEs are summarized in **Table 2**.

Twenty-five patients (55.6%) experienced a treatment-related AE (TRAE) of any grade related to telisotuzumab; the most common were hypoalbuminemia ($n = 9$; 20.0%) and fatigue ($n = 5$; 11.1%). Three patients (6.7%) experienced a grade ≥3 TRAE, with hypoalbuminemia ($n = 2$; 4.4%) as the most common. Any-grade TRAEs that occurred in ≥5% of patients are summarized in **Table 2** (additional details on TEAEs and TRAEs for all doses in the escalation cohort are provided in Supplementary Table S1).

Overall, 7 patients experienced a TEAE that led to study drug discontinuation, 4 (26.7%) in the dose-escalation, and 3 (10.0%) in the dose-expansion phase. Eleven patients (24.4%) died during the study, all as a result of disease progression. No deaths were considered related to telisotuzumab.

Pharmacokinetic assessment

Telisotuzumab pharmacokinetic/pharmacodynamic data were available for 15 patients enrolled in dose-escalation and are presented in **Fig. 1**. The mean cycle 1 day 1 30-minute postdose plasma concentrations ranged from 114 to 659 μg/mL for the doses ranging from 5 mg/kg to 25 mg/kg. Mean plasma concentration–time profiles are shown in **Fig. 1** for escalation cohorts. Telisotuzumab had linear pharmacokinetics, and the peak plasma concentration is proportional to dose level. Mean plasma concentration–time profiles and pharmacokinetic parameters for the 15-mg/kg dose are similar between the expansion cohort and the escalation cohort. At the RP2D level of 15 mg/kg, the half-life was 14.1 days.

Antitumor activity and correlation with *MET* amplification

Forty-five patients were enrolled and treated with telisotuzumab and of those 10 had tumors with *MET* gene amplification (identified through retrospective analysis and prospective screening): 3 were retrospectively identified by FISH, 5 were prospectively identified by FISH and 2 were identified by site/investigator (1 FISH and 1 NGS). For prospective screening, 211 patient tumor samples (consisting of non–small cell lung cancer, gastroesophageal, ovarian, and colorectal cancers mainly from primary tumors) were prospectively screened by FISH. Seventeen samples were determined to be *MET* amplified (8.1%) and of those 5 (29.4% of the *MET*-amplified or 2.4% of screened patients) were enrolled on the expansion cohort.

Thirty-six patients had one or more postbaseline tumor assessments. The best percentage change from baseline in size of target lesions for all patients is shown in **Fig. 2A** and for *MET*-amplified patients in **Fig. 2B** [$n = 10$; two in dose escalation (5 and 15 mg/kg) and 8 in dose expansion; tumor-specific details for *MET*-amplified patients are shown in Supplementary Table S2). Four partial responses were seen among all patients enrolled (8.9%; **Table 3**).

Among patients with *MET*-amplified tumors (including lung, gastric, esophageal, ovarian, and colorectal cancer), 4 of 10 patients had confirmed partial response (40%), two had stable disease, while the remainder had disease progression; one patient did not have a postbaseline tumor assessment and was unevaluable. Four of the *MET*-amplified patients had gastroesophageal cancer, with initial primary tumor samples that were negative for amplification, demonstrating that a gain of *MET* amplification occurred during the course of treatment (**Fig. 3**). Among these patients, three achieved a partial response and one had progressive disease as best response (ORR = 75%). The duration of disease control in responders ranged from 18 to 27 weeks and the median duration of response was 16.1 weeks. The median progression-free survival in *MET*-amplified patients was 17.9 weeks (Supplementary Fig. S1); overall survival was not determined in this study. One of the responders who received telisotuzumab 15 mg/kg Q3W demonstrated a rapid response with tumor shrinkage (45% decrease in tumor size at week 6) and rapid reduction in carcinoembryonic antigen levels corresponding with the patient's clinical report of symptomatic improvement. The carcinoembryonic antigen reached its nadir at day 42 and slowly increased thereafter, correlating with acquired resistance and eventual progressive disease in nontarget lesions (Supplementary Fig. S2).

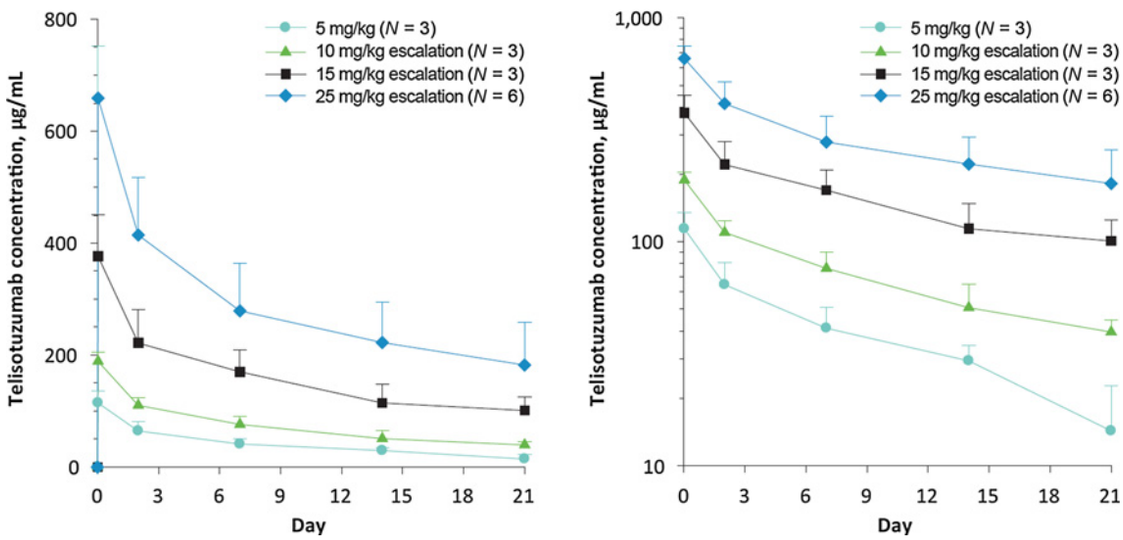

Figure 1.
Mean + SD of intensive telisotuzumab plasma concentration collected postcycle 1 in linear and log-linear scales.

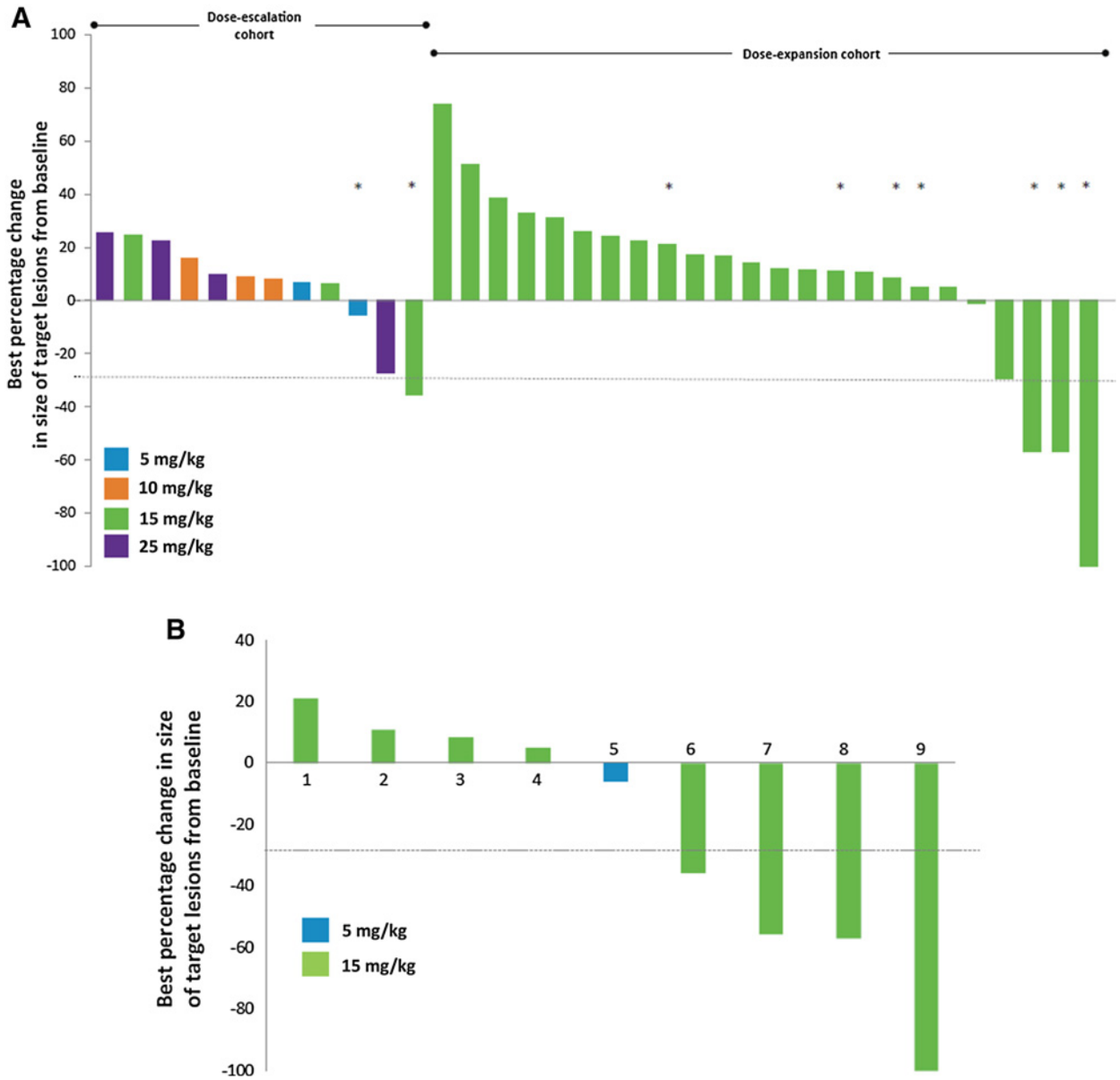

Figure 2.

Best percentage change in size of target lesions from baseline in all patients with one or more postbaseline tumor assessment ($n = 36$; **A**), and *MET*-amplified patients with one or more postbaseline tumor assessment ($n = 9$; **B**); additional information in Supplementary Table S2. **MET* amplification determined by FISH as amplified (*MET/CEP7* ratio ≥2 in ≥20% of cells).

FISH analysis or ctDNA analysis for *MET* amplification was done for 29 and 25 of the 45 enrolled patients, respectively (Supplementary Table S3). ctDNA correlated with tumor tissue FISH only when percentage of *MET/CEP7* cells ≥2 was relatively high (≥63%) and sufficient tumor mass was present. Three of 4 patients with *MET*-amplified gastroesophageal cancer were positive both by tissue FISH and ctDNA; the patient with discordant tissue FISH and ctDNA results had *MET*-amplified tumor resected prior to study entry. The small number of patients precludes further analysis to correlate tissue-based FISH assay with blood assay for *MET* amplification. Retrospective ctDNA analysis of FISH-negative patients (based on analysis of primary tumors) did not reveal any who were positive by ctDNA (Supplementary Table S3).

Discussion

In this first-in-human phase I study, we demonstrated that telisotuzumab, a highly selective bivalent anti–c-Met antibody, is well tolerated at all dose levels, including the highest dose level (25 mg/kg Q3W). Telisotuzumab was well tolerated at the RP2D of 15 mg/kg

Table 3. Best overall response.

Parameter	All patients ($N = 45$)[a]	*MET*-amplified patients ($N = 10$)
Best overall response, *n* (%)[b]		
Complete response (CR)	0	0
Partial response (PR)	4 (8.9)	4 (40)
Objective response rate (CR + PR)	4 (8.9)	4 (40)
Stable disease	13 (28.9)	2 (20)
Progressive disease	18 (40.0)	3 (30)
No postbaseline scan	9 (20.0)	1 (10)

[a]One patient not evaluable.
[b]On the basis of RECIST Version 1.1 (14).

Q3W with a toxicity profile similar to that observed with other agents targeting the c-Met pathway (15). Consistent with other c-Met inhibitors (both biologic and small molecule), the most common TRAEs included hypoalbuminemia. Of the serious AEs reported in this phase I trial, only one event (fatigue) was considered possibly related to telisotuzumab by the treating physician. Even though no DLTs were observed at higher dose levels, the 15-mg/kg dose was chosen on the basis of a number of observations: (i) in preclinical models this dose fully saturated the target receptor and provided exposure within the predicted efficacious range; (ii) dose was well tolerated; and (iii) dose had single-agent antitumor activity during dose escalation (albeit in one *MET*-amplified patient treated during the dose escalation at that dose level). However, it is possible that an even higher dose (e.g., 25 mg/kg Q3W) might be more efficacious.

Single-agent clinical antitumor activity was observed only in patients with *MET*-amplified advanced solid tumors, consistent with preclinical models of antitumor activity observed in MET-dependent tumors (16–18). In the 45 patients treated with telisotuzumab, the clinical activity of single-agent telisotuzumab was exclusively demonstrated in patients with *MET*-amplified tumors (ORR 40% in 10 patients with *MET*-amplified tumors versus 0% in 35 patients with nonamplified tumors). Among the four patients with *MET*-amplified tumors who had an objective response, subjective clinical benefit (increased energy level, decreased pain, decreased lymphadenopathy) was generally noted early after starting treatment. Although disease progression occurred in all patients with *MET*-amplified tumors, progression typically occurred in nontarget lesions. Interestingly, among the 4 patients who had an objective response, 3 patients had *MET*-amplified gastroesophageal cancer.

This study illustrated several important findings regarding gastroesophageal cancer and *MET* amplification. The first is that each of the responding patients with gastroesophageal cancer had what could be considered "high-level" *MET* amplification, defined as 78%–100% *MET*-amplified cells and a *MET/CEP7* ratio mean of 3.95–6.91. It

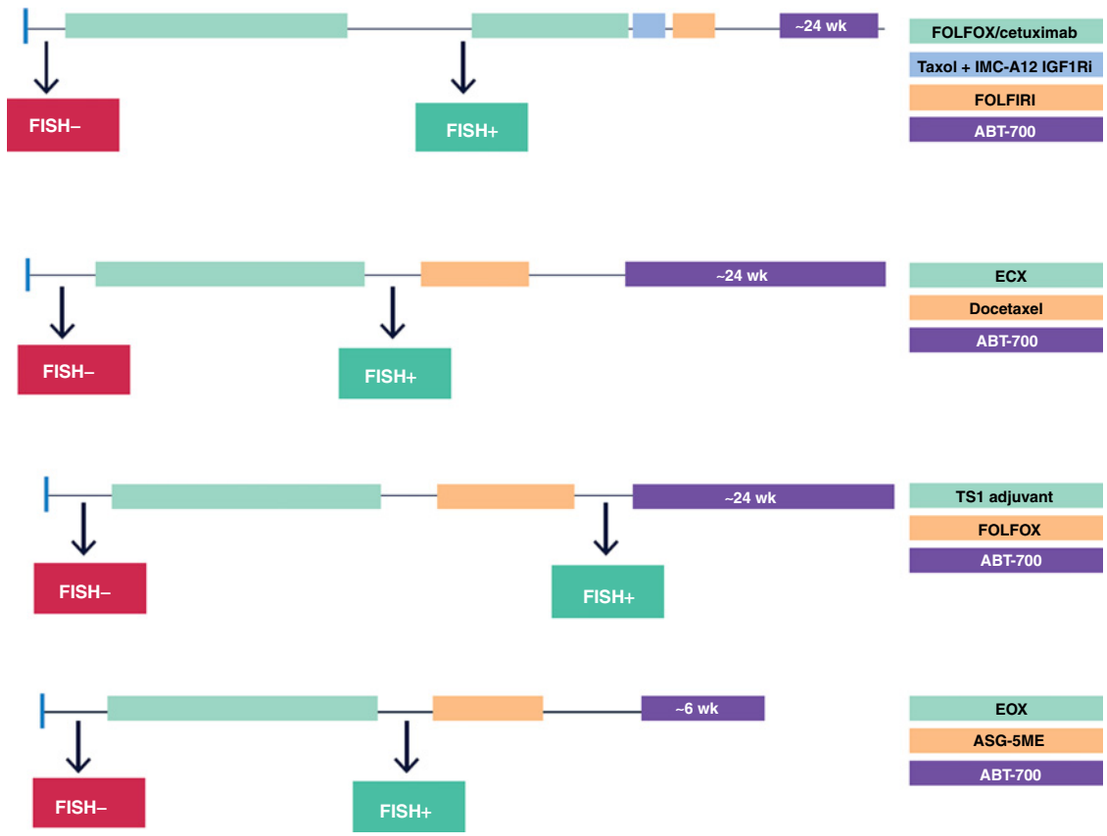

Figure 3.
Conversion from *MET* FISH-negative ($FISH^-$) primary tumor to *MET* FISH–positive ($FISH^+$) metastatic lesion after therapy. 5-FU, 5-fluorouracil; ECX, epirubicin–cisplatin–capecitabine; EOX, epirubicin–oxaliplatin–capecitabine; FOLFIRI, folinic acid–5-FU–irinotecan; FOLFOX, folinic acid–5-FU–oxaliplatin; IGF1Ri, insulin-like growth factor 1 receptor inhibitor; IMC-A12, cetuximab; NGS, next-generation sequencing; TS1, tegafur-gimeracil-oteracil; wk, weeks.

should be noted that there is no standard definition for *MET* amplification and it is possible that high-level *MET* amplification is required for the clinical activity of telisotuzumab as it appears to be for crizotinib in non–small cell lung cancer (19). Second, *MET* amplification was found to occur only in the metastatic lesions of patients with gastroesophageal cancer and was not detectable in the primary tumor. It is likely that *MET* amplification was pre-existing in the tumor either at levels below detection with the assays utilized or not detected because of tumor heterogeneity. The low frequency of *MET* amplification in primary tumors has been confirmed in other studies, and was also noted in our prospective screening using FISH and a prespecified cutoff of *MET/CEP7* ratio ≥2 in ≥20% of cells; 17 of 211 (8.1%) primary tumor samples were positive. However, when a potentially more biologically meaningful cutoff was used (*MET/CEP7* ratio ≥2 in >50% of cells), the number of positive primary tumor samples decreased to only three of 211 (1.4%). Although most *MET*-amplified patients identified on this study did not respond, the findings suggest that a more stringent cutoff for *MET* amplification will likely result in higher response rates.

Given the low frequency of *MET* amplification in primary tumors and the observation that *MET* amplification can be acquired, screening metastatic tumor tissue will likely generate a higher yield of *MET* amplification. However, tissue biopsies of metastatic lesions are not always feasible. Thus, newer methodologies for detecting *MET* amplification, such as use of ctDNA, are undergoing further evaluation. While FISH and ctDNA for *MET* amplification were not always concordant, this study did suggest that ctDNA could potentially be used for screening purposes. It is worthwhile to note that ctDNA will not identify all cases of *MET* amplification, because detection is influenced by timing of the blood draw relative to treatment, absolute tumor burden, shedding of ctDNA from tumor, and *MET* amplification level; therefore, additional and complementary modes of detection should be explored.

Among patients with *MET*-amplified tumors who responded and then progressed or did not respond, the mechanisms of telisotuzumab resistance are not known. It is possible that non–*MET*-amplified clones emerged under the selective pressure of anti–c-MET therapy. In prior studies, molecular heterogeneity was observed both between metastatic lesions, and within metastatic lesions (20, 21). Alternatively, it is possible that concomitant mutations and/or coamplifications within *MET*-amplified cells rescued neoplastic cells from *MET* inhibition. For example, a patient on this study with *KRAS/NRAS/BRAF* wild-type metastatic colorectal cancer had coamplification of the *TOP1, CCND3, MYCL1, ZNF217, ARFRP1, MYST3*, and *SRC* genes. After treatment and progression on anti-EGFR therapy, the patient developed *MET* amplification. Despite high levels of *MET* amplification by FISH (*MET/CEP7* = 6.41; 92% of cells), the tumor was capable of growth, independent of c-Met blockade with telisotuzumab. Finally, it is possible that, in at least one case, the dose of telisotuzumab was below the minimum efficacious range. A patient with *MET*-amplified metastatic papillary renal cancer was treated at 5 mg/kg intravenously Q3W. This patient experienced stable disease as best response (–6% in RECIST target lesions). The patterns of treatment sensitivity and resistance observed in this trial illustrate the complexity of single-agent target inhibition in patients with treatment-refractory advanced solid tumors.

To overcome potential resistance mechanisms to monotherapy telisotuzumab, it would be possible to combine telisotuzumab with standard-of-care drugs. Indeed, 14 patients were enrolled in combination therapy with telisotuzumab. Unfortunately, the study was terminated by the sponsor in favor of developing an antibody–drug conjugate based on telisotuzumab. From the limited safety information available for the combination arms (treatment-emergent AEs are shown in Supplementary Table S4), no unexpected safety signals were noted beyond those expected for the combination of telisotuzumab and the standard-of-care therapy. Regarding efficacy, the best observed response in each combination cohort was the following: XELOX, five stable disease (none known to be *MET* amplified); erlotinib, two partial responses (one *MET* amplified, one EGFR-mutant previously treated with erlotinib) and two progressive disease; docetaxel, two partial responses, two stable disease, and one progressive disease (none known to be *MET* amplified). With the small numbers of patients treated, no meaningful conclusions can be drawn from the combination therapy data other than to generally consider the combinations displaying expected safety characteristics and the potential for efficacy similar to the combination partner.

Although telisotuzumab has not demonstrated antitumor activity as a monotherapy in patients with c-Met–expressing tumors lacking *MET* amplification, it has shown promise when used as a component of an antibody–drug conjugate. Telisotuzumab vedotin (ABBV-399) is a first-in-class antibody–drug conjugate composed of telisotuzumab coupled to the cytotoxic monomethyl auristatin E through a valine-citrulline linker. Preclinical studies with telisotuzumab vedotin have shown antitumor activity in c-Met–expressing cells lacking *MET* gene amplification (22). Telisotuzumab vedotin has also demonstrated encouraging evidence of antitumor activity in patients with c-Met–overexpressing NSCLC (23). The antitumor activities of telisotuzumab in *MET*-amplified tumors and that of telisotuzumab vedotin in c-Met–expressed tumors suggest that there is a fundamental biologic difference in the tumors that respond to these treatments. It appears that telisotuzumab exhibits antitumor activity only in tumors that are addicted to the *MET* oncogene and depend on c-Met signal for survival. In contrast, the antibody–drug conjugate does not require the tumors to be addicted to the oncogene, but rather requires sufficient c-Met protein on the cell surface for binding and delivery of the cytotoxin. As a result, telisotuzumab vedotin may be active in both subjects with *MET*-amplified tumors and those overexpressing c-Met through other mechanisms. However, as with other targeted agents (including antibody–drug conjugates), the antitumor activity of telisotuzumab vedotin may be limited by the heterogeneity of target (antigen) expression in tumor cells.

In conclusion, we have demonstrated that telisotuzumab is safe and well tolerated. Although interpretations regarding efficacy in patients with *MET*-amplified tumors are limited by small patient numbers, the single-agent activity of telisotuzumab in patients with *MET*-amplified advanced solid tumors is consistent with results from other *MET*-targeting agents (15–18). At the RP2D, telisotuzumab has clinical antitumor activity in some patients with *MET*-amplified advanced solid tumors.

Disclosure of Potential Conflicts of Interest

J.H. Strickler is a consultant at Seattle Genetics, Roche/Genentech, Amgen, reports receiving a commercial research grant from Seattle Genetics, Exelixis, AbbVie, Roche/Genentech, and Amgen. P.M. LoRusso is a consultant/advisory board member at AbbVie, Agios, Cybrexa, Agenus, Tyme, IQVIA, TRIGR, Pfizer, I-MAB, ImmunoMet, Black Diamond, GlaxoSmithKline, Five Prime, QED Therapeutics, AstraZeneca, EMD Serono, Shattuck, Astellas, Salarius, Silverback, MacroGenics, GenMab, Halozyme, Roche-Genentech, Genentech, CytomX, Takeda, and SOTIO. Y.-K. Kang is a consultant at Ono, BMS, ALX Oncology, Zymeworks, Amgen, Novartis, and Daehwa. C.-C. Lin is a consultant at Novartis, Boehringer-Ingelheim, Daiichi-Sankyo, has received speakers' bureau honoraria from Novartis, Roche. P. Ansell is a senior principal research scientist at AbbVie. M. Motwani is a research fellow at AbbVie. S. Wong is a director of clinical

pharmacology at AbbVie. H. Yue is a statistician and has ownership interest (including patents) at AbbVie. L. Wang is a study project manager II at AbbVie Inc. E.B. Reilly is a distinguished research fellow at AbbVie. D.E.H. Afar is an employee and has ownership interest (including patents) at AbbVie. L. Naumovski is a group medical director at AbbVie, Inc. No potential conflicts of interest were disclosed by the other authors.

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