



# First-in-Human Phase I, Dose-Escalation and -Expansion Study of Telisotuzumab Vedotin, an Antibody–Drug Conjugate Targeting c-Met, in Patients With Advanced Solid Tumors

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## A B S T R A C T

### Purpose

This first-in-human study evaluated telisotuzumab vedotin (Teliso-V), formerly called ABBV-399, an antibody–drug conjugate of the anti-c-Met monoclonal antibody ABT-700 and monomethyl auristatin E.

### Materials and Methods

For dose escalation, three to six patients with advanced solid tumors were enrolled in eight cohorts (0.15 to 3.3 mg/kg). The dose-expansion phase enrolled patients with non-small-cell lung cancer (NSCLC) with c-Met–overexpressing tumors (c-Met positive; immunohistochemistry membrane H-score  $\geq$  150). Patients received Teliso-V monotherapy intravenously on day 1 once every 3 weeks. Safety, tolerability, pharmacokinetics, and maximum tolerated dose were determined.

### Results

Forty-eight patients were enrolled (median age, 65 years; 35.4% NSCLC; median four prior therapies). One patient each in the 3.0-mg/kg (n = 9) and 3.3-mg/kg (n = 3) cohorts experienced dose-limiting toxicities. Although the maximum tolerated dose was not formally identified, the recommended phase II dose was defined as 2.7 mg/kg on the basis of overall safety and tolerability. The most frequent treatment-emergent adverse events (any grade) were fatigue (42%), nausea (27%), constipation (27%), decreased appetite (23%), vomiting (21%), dyspnea (21%), diarrhea (19%), peripheral edema (19%), and neuropathy (17%). The most frequent Teliso-V–related grade  $\geq$  3 adverse events were fatigue, anemia, neutropenia, and hypoalbuminemia (4% each). Teliso-V and total antibody pharmacokinetics were approximately dose proportional, with a mean harmonic half-life of 2 to 4 days each. Prospective screening identified 35 (60%) of 58 patients with c-Met–positive NSCLC. Of 16 patients with c-Met–positive NSCLC who were treated with Teliso-V 2.4 to 3.0 mg/kg, three (18.8%; 95% CI, 4.1% to 45.7%) achieved a partial response (median response duration, 4.8 months; median progression-free survival, 5.7 months; 95% CI, 1.2 months to 15.4 months). No other patients experienced a response.

### Conclusion

Teliso-V monotherapy demonstrated favorable safety and tolerability profiles, with encouraging evidence of antitumor activity in patients with c-Met–positive NSCLC.

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## INTRODUCTION

c-Met is a receptor tyrosine kinase expressed on the surface of epithelial and endothelial cells. Ligand-induced dimerization of c-Met leads to autophosphorylation, which results in cellular proliferation, survival, migration, and angiogenesis.<sup>1,2</sup> Aberrant c-Met pathway activation is frequently

found in various types of solid tumors, including non-small-cell lung cancer (NSCLC),<sup>3,4</sup> colorectal cancer,<sup>5,6</sup> breast cancer,<sup>7</sup> ovarian cancer,<sup>8</sup> advanced prostate cancer,<sup>9</sup> and others.<sup>10</sup> Abnormal c-Met signaling can occur as a result of transcriptional upregulation, receptor overexpression, *MET* amplification, *MET* activating mutations, or overexpression of its only known ligand, hepatocyte growth factor (HGF). c-Met signaling dysregulation

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is associated with oncogenic transformation<sup>11</sup> and resistance to chemotherapy and radiotherapy,<sup>12</sup> and it correlates with poor prognosis. Consequently, c-Met has emerged as a promising therapeutic target.<sup>13</sup>

Telisotuzumab vedotin (Teliso-V), formerly called ABBV-399, is a first-in-class antibody–drug conjugate (ADC) composed of the anti-c-Met humanized monoclonal antibody ABT-700 coupled to the cytotoxic monomethyl auristatin E (MMAE) through a valine–citrulline linker (ABT-700–vcMMAE). Teliso-V uses the same linker–drug payload as that of the US Food and Drug Administration–approved brentuximab vedotin.<sup>14</sup> Teliso-V targets c-Met–expressing tumor cells with specific and high-affinity binding, and it mediates the delivery of MMAE directly to tumor cells.<sup>15</sup> Engagement of c-Met by Teliso-V results in the internalization of the ADC and intracellular release of MMAE after proteolysis of the linker. MMAE then binds to tubulin, thereby inhibiting mitosis and causing tumor cell death. The unconjugated antibody, ABT-700, has shown significant antitumor activity in patients with *MET*-amplified advanced solid tumors but limited activity in patients with c-Met–overexpressing tumors that lack *MET* amplification.<sup>16,17</sup> However, preclinical studies have indicated that Teliso-V has antitumor activity in c-Met–expressing cells with and without *MET* gene amplification.<sup>15</sup>

Primary objectives of this phase I trial were to evaluate the safety and tolerability of Teliso-V monotherapy in patients with advanced solid tumors, to determine the pharmacokinetic (PK) profile, and to establish the maximum tolerated dose (MTD) and recommended phase II dose (RP2D). A dose-expansion phase at the RP2D assessed the preliminary antitumor efficacy of Teliso-V in patients with c-Met–overexpressing NSCLC.

## MATERIALS AND METHODS

### Patient Eligibility

Patient enrollment began in April 2014, and as of September 2017, 48 patients have been treated. Patients who were enrolled had measurable disease—by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1<sup>18</sup>—that progressed despite standard therapy or because no standard therapy was available (the Data Supplement lists main eligibility criteria). All patients provided written informed consent and local ethics committee approval was obtained. This study was conducted in accordance with the International Conference on Harmonization, good clinical practice guidelines, and the Declaration of Helsinki.

### Study Design

This was a first-in-human, phase I, open-label, multicenter study in adult patients with advanced solid tumors conducted in two parts. Part one was a dose-escalation phase using a 3+3 design to determine the safety, MTD, and PK profile of Teliso-V. Teliso-V was administered by intravenous (IV) infusion to groups of three to six patients who were enrolled in eight-dose cohorts for dosing at 0.15 to 3.3 mg/kg on day 1, once every 21 days, or until disease progression or unacceptable toxicity. Dose-limiting toxicities (DLTs) were determined during the first cycle (the Data Supplement outlines DLT definition). Part two was a dose-expansion phase to further evaluate the RP2D of Teliso-V monotherapy for safety, tolerability, and antitumor efficacy only in patients with NSCLC—on the basis of preclinical data that show the sensitivity of NSCLC cell lines—and c-Met overexpression as determined by immunohistochemistry (IHC).

### Safety

Safety was evaluated on the basis of adverse events (AEs), vital signs, physical examination, electrocardiograms, and laboratory test assessments. The Data Supplement lists additional details.

### PKs

Blood samples for PK evaluation of Teliso-V, total ABT-700, and MMAE were collected on day 1 of cycle 1 (predose and 30 minutes postinfusion); during study visits on days 2, 4, 8, and 15 of cycle 1; on day 1 of cycle 2 (predose and 30 minutes postinfusion); day 1 of every subsequent cycle; and at the final visit. Serum concentrations of Teliso-V conjugate (ABT-700–vcMMAE), total ABT-700, and plasma concentrations of free MMAE were determined using validated methods. PK parameters were estimated using noncompartmental analysis.

### Antitumor Activity

Tumor response was assessed using contrast-enhanced computed tomography—or magnetic resonance imaging or noncontrast computed tomography if contrast was not tolerated—at baseline—within 28 days before the first dose—and every 6 weeks thereafter, and if clinically warranted at the final visit for patients without documented radiographic progression. Changes in measurable lesions were assessed by the investigator using RECIST version 1.1<sup>18</sup> to determine the objective response rate, progression-free survival (PFS), and duration of response.

### Biomarkers

Testing for c-Met expression was performed retrospectively on most patients in the dose-escalation cohort who had available archival tissue, and prospectively for patients in the dose-expansion cohort. c-Met expression in tumor samples was determined by IHC using the CONFIRM assay (Ventana Medical Systems, Tucson, AZ). Overexpression of c-Met (c-Met positive) was defined by an H-score of  $\geq 150$  of membrane staining. An H-score cut off of  $\geq 150$  was chosen by the sponsor (AbbVie, North Chicago, IL) to select patients who were most likely to benefit from Teliso-V, because it is known from preclinical studies that some level of c-Met expression is needed for the efficacy of Teliso-V in cell lines and animal models.<sup>15</sup> Additional details and exploratory biomarker methods using DNA from tumor tissue and/or circulating tumor DNA (ctDNA) using PlasmaSELECT-R 64 (Personal Genome Diagnostics, Baltimore, MD) are described in the Data Supplement.

### Statistical Analyses

The safety and efficacy-evaluable populations included all patients who received one or more dose of the study drug. All safety analyses were descriptive only. No formal statistical analysis was performed for efficacy variables, which were all exploratory in nature (efficacy variables are defined in the Data Supplement).

## RESULTS

### Patient Demographics and Baseline Characteristics

Forty-eight patients were enrolled and received one or more dose of Teliso-V (data cut off was September 21, 2017). Patient demographics and baseline characteristics are summarized in Table 1. Thirty-nine patients comprised the dose-escalation cohort and nine patients—all with c-Met–positive NSCLC—the dose-expansion cohort. Of 58 patients with NSCLC who were screened for membrane c-Met expression, 35 (60%) were identified as c-Met positive.

Of 16 patients with c-Met–positive NSCLC, one had increased *MET* gene copy number and one had a mutation in *MET* exon 14

**Table 1.** Patient Demographics and Baseline Characteristics

Demographic or Characteristic	Dose-Escalation Cohort (n = 39), Dose Level, mg/kg										Dose-Expansion Cohort (2.7 mg/kg; n = 9)		All Patients (N = 48)	
	0.15 (n = 3)	0.3 (n = 3)	0.6 (n = 3)	1.2 (n = 3)	1.8 (n = 4)	2.4 (n = 6)	2.7 (n = 5)	3.0 (n = 9)	3.3 (n = 3)	69 (59-75)	65 (51-86)	3 (100)		0 (0)
Age, years, median (range)	69 (40-75)	59 (55-72)	73 (66-79)	66 (66-70)	56 (44-75)	57 (47-83)	63 (56-86)	58 (49-77)	69 (59-77)	69 (59-75)	65 (51-86)	3 (100)	0 (0)	65 (40-86)
Gender, No. (%)														
Male	1 (33.3)	2 (66.7)	1 (33.3)	1 (33.3)	2 (50.0)	1 (16.7)	4 (80.0)	5 (55.6)	3 (33.3)	3 (100)	5 (55.6)	3 (100)	0 (0)	25 (52.1)
Female	2 (66.7)	1 (33.3)	2 (66.7)	2 (66.7)	2 (50.0)	5 (83.3)	1 (20.0)	4 (44.4)	0 (0)	0 (0)	4 (44.4)	0 (0)	0 (0)	23 (47.9)
ECOG at baseline, No. (%)														
Grade 0	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)	1 (25.0)	2 (33.3)	1 (20.0)	3 (33.3)	1 (33.3)	1 (33.3)	2 (22.2)	1 (33.3)	0 (0)	13 (27.1)
Grade 1	2 (66.7)	2 (66.7)	2 (66.7)	3 (100)	3 (75.0)	3 (50.0)	4 (80.0)	6 (66.7)	2 (66.7)	2 (66.7)	7 (77.8)	2 (66.7)	0 (0)	34 (70.8)
Grade 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.1)
Primary tumor type, No. (%)														
Non-small-cell lung cancer	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)	1 (16.7)	4 (80.0)	2 (22.2)	0 (0)	0 (0)	9 (100)	0 (0)	0 (0)	17 (35.4)
Nonsquamous	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	3 (75.0)	2 (100)	0 (0)	0 (0)	5 (55.6)	0 (0)	0 (0)	12 (25.0)
Squamous	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25.0)	0 (0)	0 (0)	0 (0)	4 (44.4)	0 (0)	0 (0)	5 (10.4)
Breast cancer	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	2 (33.3)	0 (0)	1 (11.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (8.3)
Colon/rectal cancer	0 (0)	1 (33.3)	2 (66.7)	0 (0)	2 (50.0)	1 (16.7)	0 (0)	2 (22.2)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	9 (18.8)
Endometrial cancer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (20.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.2)
Ovarian cancer	0 (0)	0 (0)	1 (33.3)	2 (66.7)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (8.3)
Other	3 (100)	1 (33.3)	0 (0)	1 (33.3)	1 (25.0)	0 (0)	0 (0)	4 (44.4)	2 (66.7)	2 (66.7)	0 (0)	0 (0)	0 (0)	12 (25.0)
Median No. of prior therapies (range)	5 (4-8)	6 (3-8)	5 (3-7)	5 (2-10)	3 (2-8)	7 (2-15)	5 (2-7)	4 (2-10)	2 (1-3)	2 (1-3)	3 (1-6)	2 (1-3)	0 (0)	4 (1-15)
c-Met positive by IHC, No. positive/No. with tissue available for testing	0/3	1/3	1/3	0/3	0/1	2/4	5/5	5/5	0/0	0/0	9/9	0/0	0/0	23/36

Abbreviations: c-Met positive, c-Met overexpressing; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry.

(Data Supplement). Tumor samples from a subset of patients with NSCLC were analyzed by RNA sequencing (11 of 16) and whole-exome sequencing (five of 16; Data Supplement). In general, there was good correlation between protein—H-score by IHC—and RNA expression.

### Safety

At the time of data cut off, all 39 patients in the dose-escalation cohort had discontinued treatment (four as a result of AEs, 28 as a result of progressive disease [PD], three as a result of consent withdrawal, and four for other reasons), and eight of nine patients in the dose-expansion cohort had discontinued treatment (three as a result of AEs and five as a result of PD). In the dose-escalation cohort, multiple DLTs were observed in two patients—one in the 3-mg/kg dose-level group (febrile neutropenia, glucose intolerance, and hypophosphatemia) and one in the 3.3-mg/kg (septic shock, edema, and hypoalbuminemia) dose-level group, which enrolled nine and three patients per cohort, respectively. In addition, at the 3.3-mg/kg dose level, one patient developed an elevation in total bilirubin (2.5 mg/dL; normal levels  $\leq$  1.2 mg/dL), and another had a decrease in albumin that delayed the next scheduled dose (albumin 2.2 g/dL; normal levels  $>$  3.5 g/dL). Therefore, enrollment at 3.3 mg/kg was halted and the lower dose of 2.7 mg/kg was further evaluated for safety and tolerability. Although no formal MTD was identified,

after five patients received treatment at 2.7 mg/kg without DLTs, the dose for the expansion phase was defined as 2.7 mg/kg every 21 days on the basis of overall safety and tolerability profiles (Table 2).

Forty-six (96%) of 48 patients experienced one or more treatment-emergent AEs (TEAEs; Table 3). The most common TEAEs included fatigue (42%), constipation (27%), nausea (27%), decreased appetite (23%), dyspnea (21%), vomiting (21%), diarrhea (19%), peripheral edema (19%), and neuropathy (17%; Table 2). Twenty-three patients (48%) reported grade  $\geq$  3 TEAEs, the most frequently reported being anemia and pneumonia (10% each), hyponatremia (8%), and decreased appetite, dyspnea, hypoalbuminemia, hypophosphatemia, and neutropenia (6% each). The most frequent TEAEs and Teliso-V–related TEAEs (TRAEs) for all dose cohorts and at the RP2D of 2.7 mg/kg are summarized in Table 2.

Thirty-four patients (71%) experienced a TRAE of any grade (Table 3). The most common any-grade TRAEs were fatigue (25%), nausea (23%), neuropathy (15%), decreased appetite (13%), vomiting (13%), and diarrhea (10%; Table 2). Eight patients (17%) experienced a grade  $\geq$  3 TRAE. The most common grade  $\geq$  3 TRAEs were fatigue, hypoalbuminemia, anemia, and neutropenia, each of which occurred in two patients (4%). No treatment-related deaths were reported.

**Table 2.** Summary of TEAEs With Teliso-V Monotherapy Occurring in  $\geq$  10% of Patients, and TEAEs Considered to Be Related to Teliso-V Treatment Occurring in  $\geq$  5% of Patients

TEAE	Related or Unrelated to Teliso-V				Related to Teliso-V			
	Any Grade		Grade $\geq$ 3		Any Grade		Grade $\geq$ 3	
	All Doses (N = 48)	2.7 mg/kg (n = 14)	All Doses (N = 48)	2.7 mg/kg (n = 14)	All Doses (N = 48)	2.7 mg/kg (n = 14)	All Doses (N = 48)	2.7 mg/kg (n = 14)
Fatigue	20 (41.7)	9 (64.3)	2 (4.2)	2 (14.3)	12 (25.0)	6 (42.9)	2 (4.2)	2 (14.3)
Constipation	13 (27.1)	3 (21.4)	0	0	3 (6.3)	2 (14.3)	0	0
Nausea	13 (27.1)	6 (42.9)	0	0	11 (22.9)	6 (42.9)	0	0
Decreased appetite	11 (22.9)	2 (14.3)	3 (6.3)	1 (7.1)	6 (12.5)	1 (7.1)	1 (2.1)	0
Dyspnea	10 (20.8)	6 (42.9)	3 (6.3)	2 (14.3)	0	0	0	0
Vomiting	10 (20.8)	3 (21.4)	0	0	6 (12.5)	3 (21.4)	0	0
Diarrhea	9 (18.8)	3 (21.4)	1 (2.1)	0	5 (10.4)	2 (14.3)	0	0
Peripheral edema	9 (18.8)	4 (28.6)	1 (2.1)	0	1 (2.1)	0	1 (2.1)	0
Neuropathy	8 (16.7)	4 (28.6)	1 (2.1)	0	7 (14.6)	3 (21.4)	1 (2.1)	0
Anemia	7 (14.6)	3 (21.4)	5 (10.4)	2 (14.3)	3 (6.3)	1 (7.1)	2 (4.2)	1 (7.1)
Hypoalbuminemia	7 (14.6)	1 (7.1)	3 (6.3)	1 (7.1)	4 (8.3)	0	2 (4.2)	0
Hypophosphatemia	7 (14.6)	3 (21.4)	3 (6.3)	1 (7.1)	1 (2.1)	0	1 (2.1)	0
Abdominal pain	6 (12.5)	1 (7.1)	0	0	0	0	0	0
Anxiety	6 (12.5)	3 (21.4)	0	0	0	0	0	0
Arthralgia	6 (12.5)	1 (7.1)	0	0	3 (6.3)	1 (7.1)	0	0
Hypomagnesemia	6 (12.5)	1 (7.1)	0	0	2 (4.2)	0	0	0
Hyponatremia	6 (12.5)	3 (21.4)	4 (8.3)	2 (14.3)	1 (2.1)	0	1 (2.1)	0
Insomnia	6 (12.5)	0	1 (2.1)	0	1 (2.1)	0	0	0
Pneumonia	6 (12.5)	4 (28.6)	5 (10.4)	3 (21.4)	0	0	0	0
Cough	5 (10.4)	2 (14.3)	0	0	0	0	0	0
Dizziness	5 (10.4)	2 (14.3)	0	0	1 (2.1)	1 (7.1)	0	0
Fall	5 (10.4)	2 (14.3)	1 (2.1)	1 (7.1)	1 (2.1)	0	0	0
Hypokalemia	5 (10.4)	1 (7.1)	0	0	1 (2.1)	0	0	0
Hypotension	5 (10.4)	4 (28.6)	0	0	0	0	0	0
Asthenia	4 (8.3)	2 (14.3)	0	0	3 (6.3)	1 (7.1)	0	0
Dysgeusia	3 (6.3)	1 (7.1)	0	0	3 (6.3)	1 (7.1)	0	0
Neutropenia	4 (8.3)	1 (7.1)	3 (6.3)	1 (7.1)	3 (6.3)	1 (7.1)	2 (4.2)	1 (7.1)

NOTE. Data are given as No. (%).

Abbreviations: TEAE, treatment-emergent adverse event; Teliso-V, telisotuzumab vedotin.

**Table 3.** TEAEs (safety analysis data set)

TEAE	Dose-Escalation Cohort (n = 39)	Dose-Expansion Cohort (n = 9)	All Patients (N = 48)
Any AE	38 (97.4)	8 (88.9)	46 (95.8)
Any AE related to study drug	27 (69.2)	7 (77.8)	34 (70.8)
NCI CTCAE grade 3 or 4	18 (46.2)	5 (55.6)	23 (47.9)
NCI CTCAE grade 3 or 4 related to study drug	5 (12.8)	3 (33.3)	8 (16.7)
Any serious AE	12 (30.8)	3 (33.3)	15 (31.3)
Any serious AE related to study drug	2 (5.1)	0 (0)	2 (4.2)
AE leading to study drug discontinuation	8 (20.5)	3 (33.3)	11 (22.9)
Death			
As a result of AE	4 (10.3)	0 (0)	4 (8.3)
As a result of AE related to study drug	0 (0)	0 (0)	0 (0)

NOTE. Data are given as No. (%).  
Abbreviations: AE, adverse event; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; TEAE, treatment-emergent adverse event.

### PKs

The preliminary Teliso-V conjugate PK parameters were estimated for 48 patients who received at least one dose of the study drug and are summarized in the Data Supplement. After a single-dose IV infusion of Teliso-V, preliminary systemic exposures of Teliso-V conjugate (Fig 1) were approximately dose proportional across 0.6- to 3.3-mg/kg doses. The mean harmonic half-life of Teliso-V conjugate and total antibody was 2 to 4 days.

### Antitumor Activity

Forty-three patients had one or more postbaseline tumor assessments and were included in the preliminary efficacy analysis (Fig 2A). Postbaseline tumor assessments were missing for five patients as a result of clinical progression (n = 3), withdrawal of consent (n = 1), and death as a result of pneumonia (unrelated to study drug; n = 1). These patients were considered as non-responders and were included in the efficacy-evaluable population (n = 48). The best overall response to Teliso-V monotherapy at any

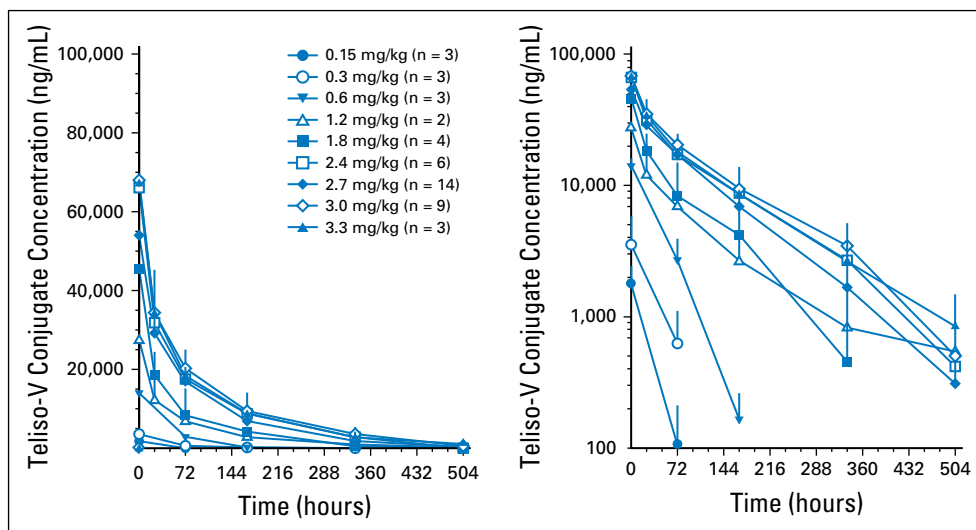
dose level (Table 4) was partial response (PR) in three patients (all with c-Met–positive squamous NSCLC). c-Met H-scores and best responses per patient are provided in the Data Supplement.

Overall, 16 patients with c-Met–positive NSCLC (five with squamous and 11 with nonsquamous histology) received Teliso-V and comprised the population included in the c-Met–positive NSCLC efficacy-subset analysis. Available biomarker data at baseline are shown in the Data Supplement. All patients were refractory to standard therapies and had received a median of three (range, one to six) prior therapies for metastatic disease. Post-baseline tumor assessments were not performed for two patients in the 2.7-mg/kg dose-escalation cohort (one patient withdrew consent and one died of pneumonia after one dose of drug). Changes in the size of target lesions in the 15 patients with one or more postbaseline tumor assessment, including one c-Met–negative patient who was treated with 1.8 mg/kg Teliso-V, are shown in Figure 2B. In the three patients with PR—confirmed on at least one subsequent scan—the duration of response was 3.1, 4.8, and 11.1 months, and PFS was 5.7, 6, and 15.4 months, respectively. The disease control rate (PR plus stable disease at first tumor assessment) was 56% (nine of 16; 95% CI, [3.0% to 80.2%]), with three with PR (19%) and six with stable disease (38%; Table 4 and Fig 2B). Median PFS for the 16 patients with c-Met–positive NSCLC was 5.7 months (95% CI, 1.2 months to 15.4 months). No mutations in *KRAS* or *EGFR* were detected in patients who experienced disease response (Data Supplement).

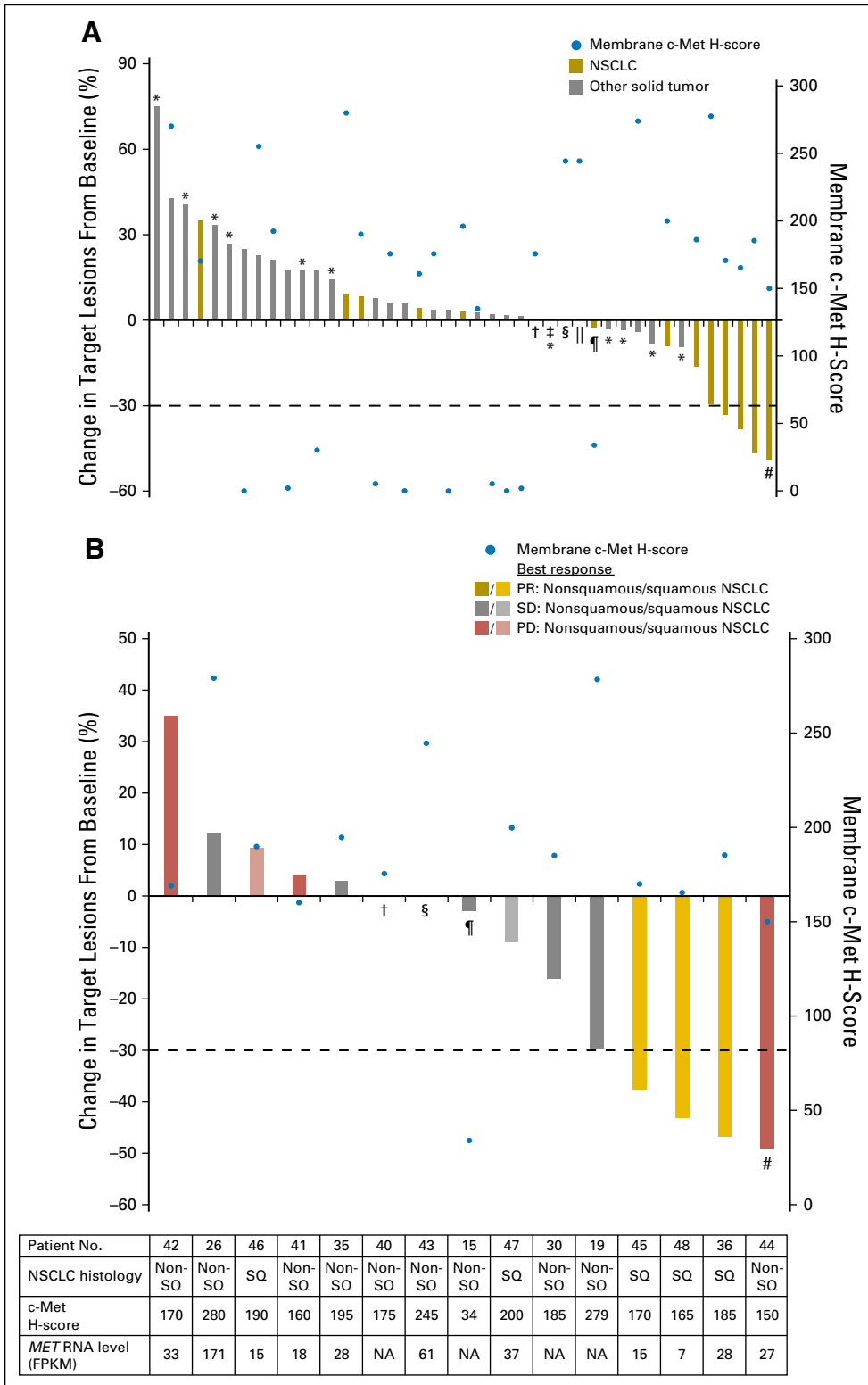
Reductions in the size of target lesions from baseline were observed in seven patients (44%), including four patients with squamous NSCLC. Of note, two patients with adenocarcinoma had significant tumor shrinkage, although neither met RECIST PR criteria.

## DISCUSSION

The c-Met pathway is involved in tumorigenesis and treatment resistance and represents a potential target for cancer therapy.<sup>2,13</sup> Many c-Met–targeted agents, such as kinase inhibitors, have demonstrated antitumor activity in tumors with *MET* amplification or *MET* exon 14 mutations—presumably dependent on or



**Fig 1.** Mean (+ standard deviation) preliminary telisotuzumab vedotin (Teliso-V) conjugate concentration–time profiles after a single intravenous infusion (0.15 to 3.3 mg/kg) on a dosage schedule of every 21 days. Linear (left) and log-linear (right) scales.



**Fig 2.** (A and B) Best percentage change in the size of target lesions from baseline in (A) all patients with one or more postbaseline tumor assessment (n = 43) and (B) patients with non-small-cell lung cancer (NSCLC) with one or more postbaseline tumor assessment (n = 15). (\*) c-Met status not available. (†) Patient with nonsquamous NSCLC and a c-Met H-score of 175. (‡) Patient with other solid tumor and c-Met status not available. (§) Patient with nonsquamous NSCLC and a c-Met H-score of 245. (||) Patient with other solid tumor and a c-Met H-score of 245. (¶) Patient with nonsquamous NSCLC and a c-Met H-score of 34 received Teliso-V 1.8 mg/kg during dose escalation. (#) Patient with > 30% tumor shrinkage in target lesions experienced PD as a result of new lesion. FPKM, fragments per kb million; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease; SQ, squamous.

addicted to the c-Met pathway—but these same c-Met inhibitors are not active for tumors that overexpress c-Met through other mechanisms. In this first-in-human, phase I study, we demonstrated that Teliso-V, a highly selective anti-c-Met ADC, was well tolerated at the RP2D of 2.7 mg/kg. In addition, Teliso-V had

single-agent antitumor activity at doses  $\geq 2.4$  mg/kg in patients with NSCLC who had c-Met overexpression but not increased *MET* gene copy number or an *MET* exon 14 mutation.

Recently, several molecules that target the c-Met pathway have been in clinical development. These agents can be classified as

**Table 4.** Best Overall Response

Parameter	All Patients (N = 48)*	Patients With c-Met-Positive NSCLC (n = 16)*
Best overall response, No. (%)†		
Complete response	0	0
PR	3 (6.3)	3 (18.8)
SD	22 (45.8)	6 (37.5)
Disease control rate (PR + SD)	25 (52.1)	9 (56.3)
Progressive disease	20 (41.7)	5 (31.3)

Abbreviations: c-Met positive, c-Met overexpressing; NSCLC, non-small-cell lung cancer; PR, partial response; SD, stable disease.  
\*Patients treated at all dose levels.  
†On the basis of RECIST version 1.1.<sup>18</sup>

monoclonal antibodies that inhibit HGF binding or receptor dimerization, or small molecules that inhibit c-Met tyrosine kinase activity and block downstream pathway activation. Several c-Met antagonists have shown substantial antitumor activity in *MET*-amplified tumors—generally defined as a greater than two-fold increase in the *MET/CEP7* ratio—including kinase inhibitors, such as crizotinib<sup>19-21</sup> and the antibody ABT-700.<sup>16,17</sup> In the first-in-human, phase I trial evaluating ABT-700, clinical benefit was observed only in patients with *MET*-amplified tumors. In eight patients with *MET*-amplified tumors, four RECIST responses were observed, all in patients with high levels of *MET* gene amplification.<sup>16,17</sup> Comparable response rates were observed in patients who were treated with the selective c-Met inhibitors AMG-337 and SAR125844 and the nonselective inhibitor crizotinib<sup>19,20,22,23</sup>; however, in patients with nonamplified, c-Met-overexpressing tumors, c-Met inhibitors have had limited clinical activity. A phase III trial of onartuzumab, which blocks HGF binding to c-Met, was discontinued because of the lack of clinically significant benefit of the onartuzumab-erlotinib combination compared with erlotinib alone.<sup>24</sup> Although the reasons for the failure of onartuzumab and an anti-HGF antibody (rilutimumab)<sup>25</sup> are unknown, inhibition of the c-Met receptor and its downstream signaling pathways may be insufficient to generate clinical benefit in tumors that are not entirely dependent on c-Met signaling.

Although *MET* amplification is a therapeutically actionable target, it generally occurs in < 1% to 5% of de novo cancers.<sup>4,21,26-28</sup> c-Met overexpression is more common, occurring in up to 50% of many advanced solid tumors.<sup>4-10</sup> To broadly target c-Met-expressing tumors, we are developing Teliso-V, an anti-c-Met antibody (ABT-700) conjugated to MMAE. The use of an ADC that targets c-Met-positive tumors represents a novel therapeutic strategy with which to induce tumor cell killing independently of c-Met signaling pathway inhibition because it involves the delivery of the potent cytotoxin MMAE directly to c-Met-positive tumor cells. We hypothesize that Teliso-V will have antitumor activity not only in tumors with increased *MET* gene copy number, but also in tumors without increased *MET* gene copy number that overexpress c-Met. Preclinical studies have demonstrated the antitumor activity of Teliso-V in *MET*-amplified and nonamplified tumor xenografts, including those refractory to ABT-700 treatment.<sup>15</sup> An additional advantage of ADCs is that the delivery of a potent cell death-inducing cytotoxin directly to the tumor may limit systemic toxicity.

Teliso-V was well tolerated at the RP2D of 2.7 mg/kg every 21 days. The toxicity profile of Teliso-V was similar to that previously observed in another ADC using MMAE, brentuximab vedotin, in patients with CD30<sup>+</sup> hematologic malignancies.<sup>29,30</sup> The acute toxicity that defines the DLT is often bone marrow suppression—that is, neutropenia—whereas the chronic toxicity is related to the MMAE microtubule-inhibitor function.<sup>31</sup> Hypoalbuminemia and peripheral edema were noted with Teliso-V at the highest doses tested. This finding may be a class effect or on-target toxicity of c-Met inhibition, which has also been noted with other c-Met inhibitors, including ABT-700.<sup>16</sup> The 2.7-mg/kg dose was selected for the expansion phase on the basis of the overall safety and tolerability observed in the dose-escalation cohorts. Patients who were administered MMAE ADCs may have both acute and chronic toxicity, such as neuropathy, and we attempted to balance efficacy with safety to minimize neuropathy in patients who received multiple doses of drug. This was also considered an efficacious dose, showing antitumor activity in the dose-escalation cohort.

In our exploratory efficacy analysis, only patients with c-Met-positive NSCLC experienced responses to Teliso-V monotherapy, as indicated by three patients with PR and two other patients with a significant reduction in target lesions. Remarkably, all patients with PR had squamous NSCLC histology. Of the five patients with squamous NSCLC, three experienced PR. The reason for the high observed response rate in squamous NSCLC is currently unknown. The two patients who demonstrated significant tumor reduction, both with adenocarcinoma NSCLC, did not meet RECIST PR criteria—one had extensive cavitation of tumor lesions, with a 29.5% tumor reduction, but discontinued the study at 2.8 months without PD as a result of the recurrence of preexisting pneumonitis, and the other had a > 30% reduction of target lesions, but experienced PD as a result of a new lesion. The finding of PR only in patients with squamous histology is limited by low patient numbers. Indeed, data that emerged after the completion of this portion of the study demonstrated objective responses in Teliso-V-treated patients with c-Met-positive adenocarcinoma (data not shown). Herein, we found that, unlike other c-Met-targeting agents, Teliso-V has antitumor activity in tumors that lack genomic alterations in *MET*. Retrospective biomarker analysis demonstrated that none of the responding patients had tumors with increased *MET* gene copy number or exon 14 mutations.

Limitations of the current study include its exploratory nature and the small number of patients analyzed, which limited the accurate quantification of Teliso-V antitumor efficacy. In addition, c-Met expression was mainly analyzed in archival tissue that was obtained before any therapy, and c-Met expression levels may have changed after exposure to cytotoxic therapy or immunotherapy. In an attempt to detect potential increases in *MET* gene copy number acquired in the interval between the archival biopsy and Teliso-V treatment, we evaluated ctDNA. Neither of the two responding patients who were tested showed evidence of increased *MET* gene copy number; however, additional reasons, including tumor heterogeneity, low ctDNA shedding, and low tumor volume, may explain a negative test result. Another limitation of this study is that the optimal threshold to define c-Met overexpression is unknown. The selection of patients with a c-Met H-score of  $\geq 150$  was based on preclinical evidence that suggested that c-Met expression is necessary for antitumor activity. On the basis of the lack of

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [jco.org](http://jco.org).

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response in most patients with high H-scores, c-Met overexpression is apparently not sufficient for response, which suggests that some tumors harbor intrinsic resistance mechanisms. No responses were observed in patients with other tumor types enrolled in the dose-escalation cohort, irrespective of c-Met expression levels. NSCLC may be more sensitive to Teliso-V than other tumor types; however, additional studies are needed.

In conclusion, Teliso-V was well tolerated at a dose of 2.7 mg/kg IV every 21 days in patients with advanced solid tumors. Furthermore, Teliso-V demonstrated antitumor activity in patients with c-Met–positive NSCLC. Retrospective biomarker evaluation of samples from patients with c-Met–positive NSCLC may provide additional insight into Teliso-V clinical activity. Additional studies evaluating Teliso-V as a single agent as part of the Lung Master Protocol<sup>32</sup> clinical trial and in combination therapy are ongoing.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**First-in-Human Phase I, Dose-Escalation and -Expansion Study of Telisotuzumab Vedotin, an Antibody–Drug Conjugate Targeting c-Met, in Patients With Advanced Solid Tumors**

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