Phase I Study of 2- or 3-Week Dosing of Telisotuzumab Vedotin, an Antibody–Drug Conjugate Targeting c-Met, Monotherapy in Patients with Advanced Non–Small Cell Lung Carcinoma

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ABSTRACT

Purpose: Telisotuzumab vedotin (Teliso-V) is an anti–c-Met–directed antibody–drug conjugate. Here, we present safety and efficacy data from a phase I/Ib study of Teliso-V monotherapy evaluated in once every 2 weeks/once every 3 weeks schedules in patients with non–small cell lung cancer (NSCLC).

Patients and Methods: During dose escalation, patients received Teliso-V monotherapy intravenously once every 3 weeks (0.15–3.3 mg/kg) or once every 2 weeks (1.6–2.2 mg/kg). The dose-expansion phase enrolled patients with NSCLC and c-Met *H*-score ≥150 (c-Met+) or *MET* amplification/exon 14 skipping mutations. Safety, pharmacokinetics, and efficacy were assessed. Herein, the analysis of patients receiving ≥1.6 mg/kg once every 2 weeks or ≥2.4 mg/kg once every 3 weeks Teliso-V is reported.

Results: Fifty-two patients with NSCLC were enrolled and received ≥1.6 mg/kg Teliso-V once every 2 weeks ($n = 28$) or ≥2.4 mg/kg Teliso-V once every 3 weeks ($n = 24$). The most common adverse events were fatigue (54%), peripheral neuropathy (42%), and nausea (38%). No dose-limiting toxicities were observed for Teliso-V once every 2 weeks and once every 3 weeks up to 2.2 and 2.7 mg/kg, respectively. The recommended phase II dose was established at 1.9 mg/kg once every 2 weeks and 2.7 mg/kg once every 3 weeks on the basis of overall safety and pharmacokinetics. Forty of 52 patients were c-Met+ (33 nonsquamous, 6 squamous, 1 mixed histology) and were included in the efficacy-evaluable population. Of those, 9 (23%) had objective responses with median duration of response of 8.7 months; median progression-free survival was 5.2 months.

Conclusions: Teliso-V monotherapy was tolerated and showed antitumor activity in c-Met+ NSCLC. On the basis of overall safety, pharmacokinetics, and efficacy outcomes, 1.9 mg/kg Teliso-V once every 2 weeks and 2.7 mg/kg once every 3 weeks schedules were selected for further clinical development.

Introduction

c-Met is a tyrosine kinase receptor expressed on the surface of epithelial and endothelial cells. Activation of c-Met by hepatocyte growth factor, its only known ligand, has been shown to control cell proliferation, angiogenesis, survival, and cellular motility (1, 2). Dysregulation of c-Met signaling via receptor overexpression has been implicated in the development of non–small cell lung cancer (NSCLC; refs. 3–5) and has been reported in other epithelial solid tumors, including breast (6), colorectal (7, 8), ovarian (9), and prostate cancers (10).

NSCLC represents 85% of all lung cancers and is the leading cause of cancer-related death worldwide (11, 12). Patients with NSCLC typically present with locally advanced or metastatic disease and have poor 5-year survival (13). Although chemotherapy generally provides a modest benefit in survival (14), the development of targeted agents in recent years has significantly improved prognosis for oncogene-related biomarker-selected subgroups (15–17). Aberrant c-Met signaling is common in NSCLC and believed to occur via multiple mechanisms, some of which introduce *MET* oncogene-addicted phenotypes, such as *MET* exon 14 skip mutations and high-level *MET* gene amplification. However, in many others, despite c-Met expression, oncogene addiction does not manifest. Deregulated c-Met signaling in general has been associated with poor prognosis (18–20), tumorigenesis, resistance to chemotherapy/radiotherapy (21), and acquired resistance to EGFR tyrosine kinase inhibitors (TKI; ref. 22). The presence of surface expression of c-Met protein in both *MET* oncogene-addicted and

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Translational Relevance

Non–small cell lung cancer (NSCLC) represents 85% of all lung cancers, and patients have poor 5-year survival. Many patients with NSCLC present with aberrant c-Met signaling. Telisotuzumab vedotin (Teliso-V) is an antibody–drug conjugate that links the anti–c-Met humanized monoclonal antibody ABT-700 with the potent antimicrotubule pharmacophore monomethyl auristatin E. Unlike unconjugated ABT-700, Teliso-V demonstrated promising antitumor activity in preclinical studies in cells overexpressing c-Met independent of *MET* amplification status. Herein, we report clinical results from an ongoing phase I/Ib study with Teliso-V monotherapy. Results showed that Teliso-V was tolerated at 1.9 mg/kg once every 2 weeks and 2.7 mg/kg once every 3 weeks dosing schedules, and it demonstrated encouraging preliminary efficacy in heavily pretreated patients with advanced c-Met–positive NSCLC. On the basis of these results, a 1.9 mg/kg once every 2 weeks dosing regimen was selected for further clinical development. Teliso-V is being investigated as monotherapy and in combination therapy in additional lung cancer studies.

nonaddicted forms may introduce a therapeutic sensitivity for a c-Met–directed antibody–drug conjugate (ADC) that utilizes c-Met as the means to preferentially deliver a cytotoxic payload to the cancer cells.

The first-in-class ADC telisotuzumab vedotin (Teliso-V) was created by linking the anti–c-Met humanized mAb ABT-700 to the potent antimicrotubule pharmacophore monomethyl auristatin E (MMAE) via a valine-citrulline linker. ABT-700 has been shown to specifically direct Teliso-V to c-Met–expressing tumor cells with high affinity (23–24). Binding of Teliso-V to c-Met results in the internalization of the ADC, cleavage of the linker, followed by the intracellular release of the MMAE payload (24). MMAE then inhibits cell division and other tumor cell functions by blocking tubulin polymerization, which results in cancer cell death. In a first-in-human phase I trial of unconjugated ABT-700, antitumor activity was observed in patients with *MET*-amplified advanced solid tumors but not in patients with c-Met–overexpressing tumors without *MET* amplification, consistent with c-Met expression alone not defining an oncogene-addicted state (25, 26). In contrast, Teliso-V, which in addition to disrupting c-Met signaling also delivers a toxic payload, has demonstrated promising antitumor activity in preclinical studies in cells overexpressing c-Met, independent of *MET* amplification status, potentially expanding the target population for this drug to patients whose tumors express c-Met, regardless of their addiction to the *MET* oncogene (24). This led to the design of a phase I/Ib dose-escalation and -expansion study in patients with solid tumors not initially preselected by c-Met protein expression. We previously reported the initial results from the dose-finding study of 48 patients with solid tumors receiving a range of 0.15 to 3.3 mg/kg doses of Teliso-V monotherapy once every 3 weeks (27). The initial recommended phase II dose (RP2D) of Teliso-V monotherapy (2.7 mg/kg once every 3 weeks) showed activity with a treatment-emergent adverse event (AE) profile that included fatigue, nausea, constipation, decreased appetite, vomiting, dyspnea, diarrhea, peripheral edema, and neuropathy. With regard to activity, Teliso-V monotherapy at doses ≥2.4 mg/kg once every 3 weeks showed promising efficacy in patients with c-Met–overexpressing NSCLC, with 3 (19%) patients achieving partial response (PR) and a median duration of response (DOR) of 4.8 months.

Herein, we report additional clinical results from this ongoing phase I/Ib study where Teliso-V monotherapy has been evaluated in both once every 2 weeks and once every 3 weeks administration schedules in a larger cohort of patients with NSCLC. The primary endpoints were the safety and pharmacokinetics (PK) of Teliso-V monotherapy once every 2 weeks and once every 3 weeks and the RP2D for the Teliso-V once every 2 weeks schedule. The secondary endpoint was evidence of antitumor activity of the once every 2 weeks and once every 3 weeks schedules in patients with c-Met–positive NSCLC. Exploratory analyses included evaluation of PK and pharmacodynamic modeling of the effects of dose and administration schedules on NSCLC tumor response and safety in patients who progressed after at least two prior lines of therapy.

Patients and Methods

Patient eligibility

Eligibility criteria for enrollment have been described previously (27). Briefly, patients with solid tumors and with measurable disease according to RECIST version 1.1 (28) that progressed on standard therapy, or for which no standard therapy was available, were enrolled in the dose-escalation phase. For the expansion phase, patients with NSCLC having c-Met membrane *H*-score ≥150 (c-Met+) via central lab assessment or local lab-reported *MET* amplification/*MET* exon 14 skipping mutation were enrolled. During the study, inclusion criteria were updated in response to a requirement from the FDA to require eligible patients to have received and progressed on or experienced failure of an immune checkpoint inhibitor prior to receiving Teliso-V monotherapy. Patients with grade ≥2 neuropathy were excluded. All patients provided written informed consent, and the study was approved by the local ethics committee or institutional review board. The study was conducted in accordance with International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. This study is registered with ClinicalTrials.gov (NCT02099058).

Study design

This was an open-label, multicenter, phase I/Ib study of Teliso-V monotherapy administered as an intravenous infusion once every 2 weeks in 4-week cycles or once every 3 weeks in 3-week cycles. The study was conducted in two parts, dose escalation and expansion. Part 1 enrolled patients with advanced solid tumors of multiple types, and dose escalation was performed following a standard 3+3 design to define the safety, MTD, and PK profile of Teliso-V once every 3 weeks and once every 2 weeks regimens. In once every 3 weeks cohorts, patients received Teliso-V at doses ranging from 0.15 to 3.3 mg/kg. In once every 2 weeks cohorts, initiated once the once every 3 weeks dose of 2.7 mg/kg was selected as potential RP2D, patients received Teliso-V at fixed doses of 1.6, 1.9, and 2.2 mg/kg; the starting dose was selected to approximate the dose intensity of 2.4 mg/kg once every 3 weeks. Dose-limiting toxicities (DLT) with the once every 2 weeks schedule were determined during the first 28-day cycle and are defined in the Supplementary Data. In the second phase of this study (dose expansion), the RP2Ds of Teliso-V once every 2 weeks and once every 3 weeks were further evaluated for safety, tolerability, and antitumor efficacy in biomarker-selected patients with c-Met+ NSCLC. Teliso-V was administered until disease progression or unacceptable toxicity.

During the study, the manufacturing process of Teliso-V was modified to specifically enrich conjugates with a stoichiometry of two to four MMAE molecules per antibody molecule to eliminate unconjugated antibody. Teliso-V produced through the new process was

evaluated during dose escalation and expansion in up to 50 patients dosed once every 2 weeks and once every 3 weeks. The newly processed Teliso-V conjugate showed comparable safety and tolerability to that of the antecedent ADC, and the protocol was amended to transition all ongoing patients to treatment with the newly processed Teliso-V at the same dose level and dosing schedule.

Safety

Safety was evaluated on the basis of reported treatment-emergent AEs, electrocardiograms, physical examination, vital signs, and laboratory test examinations. AEs were collected from the time of first dose of Teliso-V until 60 days after discontinuation or the start of a new anticancer treatment. The Medical Dictionary for Regulatory Activities was used to classify AEs by preferred term, and toxicity was graded using the NCI Common Terminology Criteria for Adverse Events version 4.03.

PK

For both Teliso-V once every 2 weeks and once every 3 weeks schedules, blood samples for PK evaluations were collected on: cycle 1 day 1 (predose and 30 minutes after infusion); during study visits on cycle 1 days 2, 4, 8, and 15; on cycle 2 day 1 and on day 1 of every subsequent cycle (predose and 30 minutes after infusion); and at the final visit. Serum concentrations of Teliso-V conjugate, total ABT-700 antibody, and plasma concentrations of MMAE molecule were examined using validated methods. PK parameters were estimated by noncompartmental analysis.

Antitumor activity

Tumor response was evaluated using contrast-enhanced CT (or MRI or noncontrast CT if contrast was not tolerated). Radiographic tumor assessments of the head, chest, abdomen, and pelvis were performed at baseline (within 28 days before cycle 1 day 1) and every 6 weeks after the start of Teliso-V treatment for patients in the once every 3 weeks dosing schedule, or every 8 weeks for patients in the once every 2 weeks dosing schedule, until disease progression or study termination, and at the final visit for patients without documented radiographic progression if clinically warranted. Changes in the size of target lesions were evaluated using RECIST version 1.1 (28) and the objective response rate (ORR), progression-free survival (PFS), and DOR were determined.

Biomarkers

Membrane c-Met expression was analyzed prospectively for the preselection of patients for dose expansion. c-Met expression was determined centrally by Flagship Biosciences via IHC using CONFIRM anti-Total c-Met SP44 antibody (Ventana Medical Systems) and ultraView Universal DAB Detection Kit (Ventana Medical Systems). Semiquantitative evaluation of the IHC staining was performed to determine the final *H*-score, ranging from 0 to 300. c-Met+ was defined by an *H*-score ≥150, the same *H*-score cutoff used previously (27). *MET* exon 14 skipping and *EGFR* mutations were reported on the basis of data provided by study sites. *MET* amplification status was determined by either site reporting of local FISH assay results, or central (Personal Genome Diagnostics) sequencing of plasma or tumor DNA from available samples. Additional details and biomarker methods can be found in the Supplementary Data.

Statistical analysis

The safety population included all patients who received one or more dose of Teliso-V. The efficacy-evaluable population included patients with NSCLC having c-Met *H*-score ≥150 who received one or more dose of Teliso-V with at least one postdose tumor assessment, or discontinued treatment before the first postdose assessment due to AEs, radiographic progressive disease (PD), clinical PD, or death. All safety and efficacy analyses were descriptive with no statistical inference drawn from the data. Definitions of efficacy variables can be found in the Supplementary Data. Efficacy data were analyzed by histology (squamous and nonsquamous NSCLC) and, for nonsquamous NSCLC patients, by dosing schedule. Because of the low numbers, data of patients with squamous NSCLC from once every 2 weeks and once every 3 weeks dosing cohorts were pooled for efficacy analyses.

Results

Patient demographics and baseline characteristics

From January 2015 to July 2018, 672 patients were screened for the full study (including several study arms) and 52 patients with NSCLC were enrolled in the Teliso-V monotherapy arms; 28 received Teliso-V monotherapy at ≥1.6 mg/kg doses once every 2 weeks and 24 received ≥2.4 mg/kg doses once every 3 weeks, constituting the safety population. The median age of the total population was 66 years (range, 30–86), and the majority of patients were male (n = 27, 52%). Patient demographic and baseline characteristics of the safety and efficacy-evaluable populations are summarized in **Table 1**. The median number of prior therapies was 3 (range, 0 to ≥7); 65% of patients received prior antimicrotubule agents. Further details on prior anticancer therapies are provided in Supplementary Table S1.

c-Met status

In total, 47 of 52 enrolled patients had c-Met expression tested by IHC; 12 (26%) patients had no intervening anticancer regimen between biopsy and Teliso-V (time range between biopsy and Teliso-V initiation 0.03–4.6 months), 33 (70%) had at least one intervening regimen (time range between biopsy and Teliso-V initiation 2.6–63.4 months), and for 2 (4%) patients biopsy dates were not known. In total, 44 enrolled patients had available c-Met expression results and 40 of these had a c-Met *H*-score ≥150 and were efficacy evaluable (c-Met+, 7 squamous, 33 nonsquamous; **Table 2**). In the efficacy-evaluable population, 18 patients received Teliso-V once every 2 weeks and 22 received Teliso-V once every 3 weeks; 2 patients had *MET* amplification, 1 had *MET* exon 14 skipping mutation, and 2 had canonical EGFR sensitizing mutations per site reporting. Among the 12 safety population patients who were not part of the efficacy population, 2 patients were *MET* amplified, 1 had *MET* exon 14 skipping mutation, and 1 had *EGFR* exon 20 insertion per site reporting.

Safety

At the time of data cutoff, all 52 safety-evaluable patients had discontinued treatment. In Teliso-V once every 2 weeks cohorts, no DLTs were reported at any tested dose level, and the MTD was not formally identified. The 1.9 mg/kg dose was selected for the expansion phase on the basis of overall safety and PK data. In cohorts receiving Teliso-V once every 3 weeks, the 2.7 mg/kg dose level was chosen for further evaluation on the basis of overall safety and tolerability (27). Patients received Teliso-V monotherapy for a median of 10.1 weeks (range, 0.1–60.1); median treatment duration was 19.6 weeks (range, 0.1–60.1) in once every 2 weeks cohorts and 6.1 weeks (0.1–57.1) in once every 3 weeks cohorts.

Table 1. Patient demographics, baseline clinical characteristics, and previous treatments—safety and efficacy populations.

	Safety population ($N = 52$)			Efficacy-evaluable population ($N = 40$)		
Characteristic	**Teliso-V Q2W ≥1.6 mg/kg NSCLC ($N = 28$)**	**Teliso-V Q3W ≥2.4 mg/kg NSCLC ($N = 24$)**	**Teliso-V Q2W and Q3W NSCLC ($N = 52$)**	**Teliso-V Q2W c-Met+ NSCLC ($N = 18$)**	**Teliso-V Q3W c-Met+ NSCLC ($N = 22$)**	**Teliso-V Q2W and Q3W c-Met+ NSCLC ($N = 40$)**
Age, median [range], years	67 [45.0–85.0]	65.0 [30.0–86.0]	66.0 [30.0–86.0]	68.5 [54.0–85.0]	65.0 [40.0–86.0]	66.0 [40.0–86.0]
Gender, *n* (%)						
Male	11 (39)	16 (75)	27 (52)	9 (50)	15 (68)	24 (60)
Female	17 (61)	8 (25)	25 (48)	9 (50)	7 (32)	16 (40)
ECOG performance status, *n* (%)						
0	6 (21)	3 (12.5)	9 (17)	4 (22)	3 (14)	7 (18)
≥1	22 (79)	21 (87.5)	43 (83)	14 (78)	19 (86)	33 (83)
Histology, n (%)						
Nonsquamous	22 (79)	19 (79)	41 (79)	16 (89)	17 (77)	33 (83)
Squamous	6 (21)	5 (21)	11 (21)	2 (11)	5 (23)	7 (18)
Smoking status, *n* (%)						
Former or current smoker	22 (79)	15 (62.5)	37 (71)	14 (78)	14 (64)	28 (70)
Never smoker	5 (18)	9 (37.5)	14 (27)	3 (17)	8 (36)	11 (28)
Unknown	1 (4)	0	1 (2)	1 (6)	0	1 (3)
Number of prior therapies, median [range]	3 [0–6]	3 [2 to ≥7]	3 [0 to ≥7]	3 [1–6]	2.5 [2 to ≥7]	3 [1 to ≥7]
Prior anticancer therapies, *n* (%)						
Platinum based	25 (89)	22 (92)	47 (90)	17 (94)	20 (91)	37 (93)
Immune checkpoint inhibitor based[a]	23 (82)	11 (46)	34 (65)	16 (89)	10 (45)	26 (65)
Docetaxel based	9 (32)	7 (29)	16 (31)	6 (33)	6 (27)	12 (30)
EGFR TKI based	6 (21)	6 (25)	12 (23)	5 (28)	5 (23)	10 (25)
c-Met inhibitor	4 (14)	2 (8)	6 (12)	2 (11)	2 (9)	4 (10)
Other	11 (39)	13 (54)	24 (46)	6 (33)	11 (50)	17 (43)
Time from initial diagnosis, median [range], days	780.5 [102.0–3,738.0]	1,072.0 [223.0–3,946.0]	816.0 [102.0–3,946.0]	780.5 [227.0–2,564.0]	1,072.0 [223.0–3,946.0]	816.0 [227.0–3,946.0]
Duration of last anticancer therapy line, median [range], months	2.9 [1.3–14.1]	4.2 [1.0–42.8]	3.3 [1.0–42.8]	3.0 [1.0–7.0]	3.0 [1.0–8.0]	3.0 [1.0–8.0]
Peripheral neuropathy at screening, *n* (%)	8 (29)	8 (33)	16 (31)	4 (22)	7 (32)	11 (28)
Previous treatment with neurotoxic agents, *n* (%)	18 (64)	20 (83)	38 (73)	11 (61)	18 (82)	29 (73)
Cisplatin	7 (25)	5 (21)	12 (23)	5 (28)	4 (18)	9 (23)
Previous treatment with microtubule inhibitors[b]	15 (54)	19 (79)	34 (65)	8 (44)	17 (73)	25 (63)

Abbreviations: c-Met+, c-Met overexpression; ECOG, Eastern Cooperative Oncology Group; Q2W, once every 2 weeks; Q3W, once every 3 weeks.

[a]The differences in the proportions of patients with prior immune checkpoint inhibitor treatment between Q2W and Q3W cohorts was the result of the change in eligibility required by the US Food and Drug Administration resulting in eligible patients being required to have received and progressed on or experienced failure of an immune checkpoint inhibitor prior to receiving Teliso-V monotherapy.

[b]Includes vinca alkaloids, paclitaxel, protein-bound paclitaxel, and docetaxel.

Table 2. c-Met status and *EGFR* mutations.

Characteristic	Efficacy-evaluable population ($N = 40$)		
	Teliso-V Q2W c-Met+ NSCLC ($N = 18$)	Teliso-V Q3W c-Met+ NSCLC ($N = 22$)	Teliso-V Q2W and Q3W c-Met+ NSCLC ($N = 40$)
c-Met *H*-score			
<150	0	0	0
150–224	11 (61)	14 (64)	25 (63)
≥225	7 (39)	8 (36)	15 (38)
Missing	0	0	0
MET amplification[a], *n* (%)	1 (6)	1 (5)	2 (5)
MET gain, *n* (%)	1 (6)	1 (5)	2 (5)
MET exon 14 skipping mutation, *n* (%)	0	1 (5)	1 (3)
EGFR mutation status, *n* (%)			
WT	17 (94)	19 (86)	36 (90)
Activating mutations (L858R or del19)	1 (6)	1 (5)	2 (5)
Rare mutations	0	0	0
Status unknown	0	2 (9)	2 (5)

Abbreviations: Q2W, once every 2 weeks; Q3W, once every 3 weeks; WT, wildtype.
[a]Defined as *MET* copy number fold amplification ≥2.

Fifty-one patients (98%) experienced at least one treatment-emergent AE, including all 28 (100%) patients in the Teliso-V once every 2 weeks cohorts and 23 of 24 (96%) in the once every 3 weeks cohorts, most of grade 1 or 2 severity. Treatment-emergent AEs of all grades experienced by ≥10% of patients with c-Met+ NSCLC are summarized in **Table 3**. The most common (≥30% of patients) treatment-emergent AEs were peripheral neuropathy (57%; all types), fatigue (50%), nausea (39%), and dizziness (32%) in Teliso-V once

Table 3. Summary of treatment-emergent adverse events of all grades occurring in ≥10% of patients during treatment with Teliso-V monotherapy—safety population.

Adverse event, *n* (%)	≥1.6 mg/kg Teliso-V Q2W ($n = 28$)			≥2.4 mg/kg Teliso-V Q3W ($n = 24$)			Total ($N = 52$)		
	Related or unrelated to Teliso-V		Related to Teliso-V	Related or unrelated to Teliso-V		Related to Teliso-V	Related or unrelated to Teliso-V		Related to Teliso-V
	Any grade	Grade ≥3	Grade ≥3	Any grade	Grade ≥3	Grade ≥3	Any grade	Grade ≥3	Grade ≥3
Fatigue	14 (50)	2 (7)	2 (7)	14 (58)	2 (8)	2 (8)	28 (54)	4 (8)	4 (8)
Nausea	11 (39)	0	0	9 (38)	0	0	20 (38)	0	0
Cough	8 (29)	0	0	6 (25)	0	0	14 (27)	0	0
Dizziness	9 (32)	0	0	5 (21)	0	0	14 (27)	0	0
Dyspnea	6 (21)	1 (4)	0	8 (33)	2 (8)	0	14 (27)	3 (6)	0
Diarrhea	7 (25)	0	0	6 (25)	1 (4)	0	13 (25)	1 (2)	0
Peripheral sensory neuropathy	8 (29)	2 (7)	2 (7)	5 (21)	1 (4)	1 (4)	13 (25)	3 (6)	3 (6)
Constipation	7 (25)	0	0	5 (21)	1 (4)	0	12 (23)	1 (2)	0
Peripheral edema	6 (21)	0	0	5 (21)	0	0	11 (21)	0	0
Hypoalbuminemia	7 (25)	1 (4)	1 (4)	4 (17)	1 (4)	0	11 (21)	2 (4)	1 (2)
Vomiting	7 (25)	1 (4)	0	4 (17)	0	0	11 (21)	1 (2)	0
Anemia	5 (18)	2 (7)	1 (4)	5 (21)	3 (13)	2 (8)	10 (19)	5 (10)	3 (6)
Decreased appetite	5 (18)	0	0	5 (21)	1 (4)	0	10 (19)	1 (2)	0
Hypotension	5 (18)	0	0	5 (21)	0	0	10 (19)	0	0
Peripheral neuropathy	8 (29)	0	0	1 (4)	0	0	9 (17)	0	0
Arthralgia	5 (18)	0	0	3 (13)	0	0	8 (15)	0	0
Hyponatremia	3 (11)	1 (4)	0	5 (21)	2 (8)	0	8 (15)	3 (6)	0
Musculoskeletal chest pain	7 (25)	2 (7)	0	1 (4)	0	0	8 (15)	2 (4)	0
Pneumonia	3 (11)	1 (4)	0	5 (21)	2 (8)	0	8 (15)	3 (6)	0
Back pain	6 (21)	1 (4)	0	1 (4)	0	0	7 (13)	1 (2)	0
Malignant neoplasm progression	6 (21)	6 (21)	0	1 (4)	1 (4)	0	7 (13)	7 (13)	0
Hypokalemia	3 (11)	2 (7)	1 (4)	3 (13)	1 (4)	0	6 (12))	3 (3)	1 (2)
Hypophosphatemia	4 (14)	1 (4)	1 (4)	2 (8)	1 (4)	0	6 (12)	2 (4)	1 (2)
Upper respiratory tract infection	5 (18)	0	0	1 (4)	0	0	6 (12)	0	0
Weight decreased	4 (14)	0	0	2 (8)	0	0	6 (12)	0	0
Abdominal pain	4 (14)	0	0	2 (8)	0	0	6 (12)	0	0
Muscle spasms	5 (18)	0	0	1 (4)	0	0	6 (12)	0	0
Pyrexia	5 (18)	0	0	1 (4)	0	0	6 (12)	0	0

Abbreviations: Q2W, once every 2 weeks; Q3W, once every 3 weeks.

every 2 weeks cohorts, and fatigue (58%), nausea (38%), and dyspnea (33%) in once every 3 weeks cohorts. Overall, 34 (65%) patients reported grade ≥3 treatment-emergent AEs, including 19 (68%) and 15 (63%) patients receiving Teliso-V once every 2 weeks and once every 3 weeks, respectively. Other than malignant neoplasm progression [progression of the disease under study during the treatment-emergent AE reporting period; 6 (21%) patients], grade ≥3 treatment-emergent AEs in 2 or more patients were fatigue, peripheral neuropathy, anemia, hypokalemia, increased gamma-glutamyltransferase, gait disturbance, and musculoskeletal chest pain [2 (7%) patients each] in once every 2 weeks cohorts, and anemia [3 (13%) patients], fatigue, dyspnea, chronic obstructive pulmonary disease exacerbation, pneumonia, and hyponatremia [2 (8%) patients each] in once every 3 weeks cohorts.

A total of 42 patients had at least one treatment-related AE of any grade, including 23 (82%) and 19 (79%) patients in once every 2 weeks and once every 3 weeks dosing cohorts, respectively. Most frequent treatment-related AEs (≥20% of patients) were fatigue (32%), nausea (29%), hypoalbuminemia (25%), peripheral neuropathy (25%), and peripheral sensory neuropathy (21%) in the once every 2 weeks schedule, and fatigue (38%) and nausea (33%) in once every 3 weeks cohorts. Grade ≥3 treatment-related AEs occurring in 2 or more patients included fatigue (2 patients in once every 2 weeks and once every 3 weeks cohorts, each), anemia (2 patients in once every 3 weeks cohorts), and peripheral sensory neuropathy (2 patients in once every 2 weeks cohorts and 1 patient in once every 3 weeks cohorts). Serious AEs were reported in 12 and 10 patients in once every 2 weeks and once every 3 weeks cohorts, respectively. No Teliso-V–related deaths were reported.

In Teliso-V once every 2 weeks cohorts, dose reduction or interruption due to an AE occurred in 7 (25%) and 15 (54%) patients, respectively. Six (21%) patients discontinued treatment due to AEs, 4 of whom (14%) discontinued due to Teliso-V–related AEs. Five (18%) patients discontinued Teliso-V due to peripheral neuropathy (1 patient each for grades 1 and 3 and 3 patients for grade 2), and 1 patient due to grade 3 gait disturbance.

In once every 3 weeks cohorts, Teliso-V dose reduction or interruption due to an AE was required in 3 (13%) and 9 (38%) patients, respectively. Of the 18 (35%) patients who discontinued treatment due to AEs, discontinuation due to Teliso-V–related AEs occurred in 8 (15%) patients: grade 2 pneumonitis ($n = 1$), grade 2 ($n = 3$) and grade 3 ($n = 2$) peripheral sensory neuropathy, grade 3 gait disturbance ($n = 1$), grade 1 peripheral neuropathy ($n = 1$), and grade 1 dizziness ($n = 1$). One event each of peripheral sensory neuropathy (grade 3) and gait disturbance was reported in the same patient.

In once every 2 weeks cohorts, any-grade peripheral neuropathy was observed in 16 (57%) patients, whereas in once every 3 weeks cohorts peripheral neuropathy was seen in 6 (25%) patients. The median time to onset of peripheral neuropathy was 3.3 months (range, 0.2–9.2) in once every 2 weeks cohorts and 3.5 months (range, 0.3–6.2) in once every 3 weeks cohorts (Supplementary Table S2). The median duration of peripheral neuropathy was slightly shorter in once every 2 weeks cohorts (2.8 months; range, 0.03–11.3) than in once every 3 weeks cohorts (5.4 months; range, 2.8–13.7). Grade ≥2 peripheral neuropathy was observed in 11 (39%) patients in once every 2 weeks cohorts and 6 (25%) patients in once every 3 weeks cohorts. The median time to onset of grade ≥2 peripheral neuropathy was 5.6 months (range, 0.7–9.2) and 4.2 months (range, 3.0–6.2) in once every 2 weeks and once every 3 weeks cohorts, respectively. The median duration of grade ≥2 peripheral neuropathy was 9.5 months (range, 0.2–25.2) in once every 2 weeks cohorts and 5.4 months (range, 2.8–54.8) in once every 3 weeks cohorts. In 4 patients in once every 2 weeks cohorts (14%) and 4 patients in once every 3 weeks cohorts (17%), Teliso-V dosing was interrupted due to peripheral neuropathy. Teliso-V dose was reduced as a response to peripheral neuropathy in 5 (18%) patients in once every 2 weeks cohorts and 1 (4%) patient in once every 3 weeks cohorts. The cumulative dose of Teliso-V correlated with neuropathy grade ($P < 0.001$).

PK and exposure response

The systemic exposure of Teliso-V conjugate after single-dose infusion was approximately dose proportional across 0.6 to 3.3 mg/kg doses once every 3 weeks (27) and 1.6 to 2.2 mg/kg doses once every 2 weeks. The mean concentration–time curves for Teliso-V conjugate, total antibody, and MMAE after single infusion of Teliso-V 2.7 mg/kg dose in the once every 3 weeks schedule, and of 1.9 mg/kg dose in the

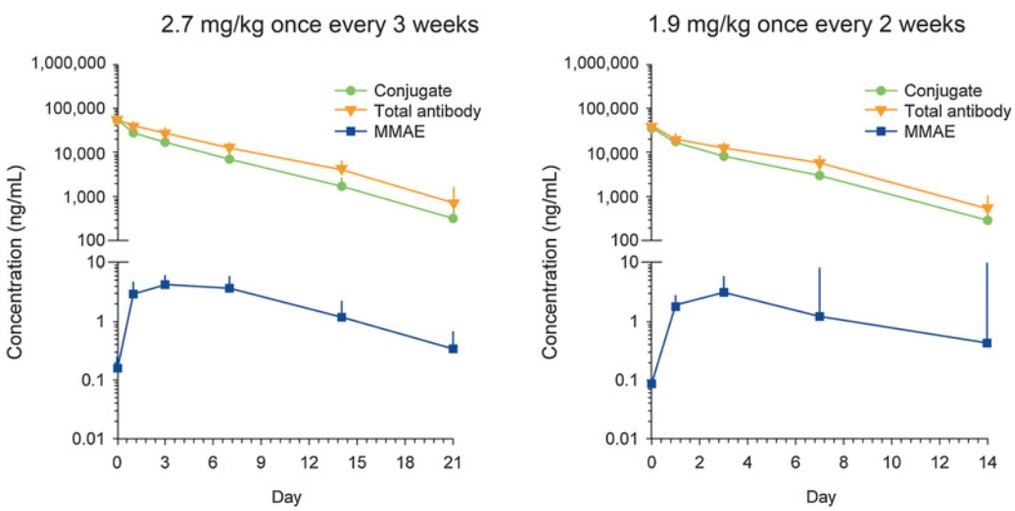

Figure 1.

Mean (+Standard Deviation) Teliso-V, total antibody, and MMAE concentration–time profiles after a single intravenous infusion of Teliso-V 2.7 mg/kg on a once every 3 weeks schedule (left) or 1.9 mg/kg on a once every 2 weeks schedule (right).

once every 2 weeks schedule are represented in **Fig. 1**. The mean harmonic half-life was 2 to 4 days for Teliso-V conjugate and total antibody, and approximately 5 days for free MMAE.

The median predicted trough plasma concentration (C_{min}) using population PK modeling (29) was higher for the 1.9 mg/kg once every 2 weeks (0.96 μg/mL) than the 2.7 mg/kg once every 3 weeks (0.25 μg/mL) dosing schedule (Supplementary Table S3). Exposure-response analyses predicted a higher probability of achieving objective responses (31% vs. 20%) and of grade ≥2 peripheral neuropathy occurrence (33% vs. 17%) for the 1.9 mg/kg once every 2 weeks regimen compared with the 2.7 mg/kg once every 3 weeks regimen.

The 1.9 mg/kg once every 2 weeks schedule resulted in approximately 3.8-fold higher predicted C_{min}, as compared with the 2.7 mg/kg once every 3 weeks RP2D schedule, with an overall similar total weekly dose. Although no DLTs were observed with either the 1.9 mg/kg or the highest tested 2.2 mg/kg once every 2 weeks doses, the clinical efficacy and safety data, the rate of late-onset peripheral neuropathy (which may be associated with cumulative dose), similarity of total weekly dose to once every 3 weeks RP2D, and considerations related to the balance between achievable duration of dosing and dose intensity led to the nomination of 1.9 mg/kg as RP2D for the once every 2 weeks schedule.

Efficacy

Among the 40 patients included in the efficacy-evaluable population, efficacy data were analyzed by dosing schedule cohorts and by NSCLC histology.

Overall, 9 of 40 [23%; 95% confidence interval (CI), 10.8–38.5] patients achieved confirmed objective response (**Table 4**), including 1 (3%) patient with CR (once every 2 weeks cohort) and 8 (20%) patients with PR; ORR was 28% (95% CI, 9.7–53.5; 5 of 18 patients) in once every 2 weeks and 18% (95% CI, 5.2–40.3; 4 of 22 patients) in once every 3 weeks cohorts. Median DOR was 8.7 months (95% CI, 5.5–10.6) and the disease control rate was 70% (95% CI, 53.5–83.4). Two (5%) patients (1 each in once every 2 weeks and once every 3 weeks cohorts) had unconfirmed PRs, 19 (48%) patients (9 in once every 2 weeks and 10 in once every 3 weeks cohorts) had stable disease (SD), and 10 (25%) patients (3 in once every 2 weeks and 7 in once every 3 weeks cohorts) had PD as best response. Percentage change to nadir in the sum of diameters of target lesions in the 38 patients with one or more postdose tumor assessment are represented in **Fig. 2A**. The PFS curves are shown in **Fig. 2B**.

Among 33 patients with nonsquamous NSCLC, 6 (18%) had confirmed objective responses (**Table 4**). In once every 2 weeks cohorts, the ORR was 31% (95% CI, 11.0–58.7; 5 of 16 patients) and in once every 3 weeks cohorts, the ORR was 6% (95% CI, 0.1–28.7; 1 of 17 patients). For patients with squamous NSCLC ($n = 7$) the ORR was 43% (95% CI, 9.9–81.6; 3 of 7 patients); all responses were in the once every 3 weeks cohort.

Fifteen (37.5%) patients in the efficacy-evaluable population had high c-Met *H*-scores of 225 or above, and this population was included in an exploratory efficacy analysis. All these patients had nonsquamous NSCLC (45.5% of all evaluable nonsquamous NSCLC), 7 in once every 2 weeks and 8 in once every 3 weeks Teliso-V cohorts. Four objective responses (ORR = 26.7%; 95% CI, 7.8–55.1) were observed in this subgroup, 3 in once every 2 weeks (ORR = 43%; 95% CI, 9.9–81.6), and 1 in once every 3 weeks (ORR = 13%; 95% CI, 0.3–52.7) Teliso-V cohorts. Five of 25 patients with an *H*-score of 150 to 224 had an objective response (ORR = 20%; 95% CI, 6.8–40.7). The median PFS in once every 2 weeks cohorts was 8.0 months (range, 1.2–9.1) and the median treatment duration was 19.6 weeks (range, 0.1–60.1). For patients in once every 3 weeks cohorts, the median PFS was not reached (1.2–not estimable) and median treatment duration was 6.1 weeks (range, 0.1–57.1).

Five patients (3 in once every 2 weeks, 2 in once every 3 weeks cohorts) had *MET* amplification identified based either on site reporting or on centrally performed circulating tumor DNA analysis. Two patients with *MET* amplification were included in the efficacy-evaluable cohort: 1 had an objective response and 1 had SD. The patient with a *MET* exon 14 skipping mutation was a nonresponder whose best response was PD (c-Met *H*-score 190). In addition, 2 patients with sensitizing *EGFR* mutations (L858R or del19) were included in the efficacy-evaluable population, and these were both nonresponders (PD; c-Met *H*-scores 245 and 170).

Discussion

The c-Met pathway is commonly dysregulated in solid tumors, at times as a major oncogenic driver event and at times as a passenger or paraneoplastic event. Several new agents that block this pathway have been developed over the past years, including small molecules that inhibit c-Met tyrosine kinase activity and downstream signaling, as well as antibodies against c-Met or hepatocyte growth factor. c-Met TKIs have shown meaningful antitumor activity in patients with *MET* oncogene-addicted tumors harboring *MET* exon 14 skip mutations, and, to a lesser extent, *MET* amplification (17, 30–32). The c-Met TKIs tepotinib and capmatinib have recently received regulatory approvals in NSCLC with *MET* exon 14 skip mutations (33, 34). However, efficacy of agents targeting c-Met signaling in patients with c-Met–overexpressing tumors that lack *MET* exon 14 skipping mutations or amplification has been disappointing (26, 35–38). Although *MET* genomic alterations compatible with *MET* oncogene addiction are only present in approximately 4% of patients with NSCLC, as many as 30% to 50% of patients with NSCLC have tumors that overexpress c-Met (19, 20, 39).

Teliso-V is an ADC targeted to c-Met that is tolerated with a manageable safety profile when administered as monotherapy at the defined RP2D of 2.7 mg/kg once every 3 weeks dosing schedule (27). In addition, ≥2.4 mg/kg doses of Teliso-V once every 3 weeks showed preliminary antitumor activity in patients with c-Met–overexpressing NSCLC, including those who had tumors lacking *MET* amplification or *MET* exon 14 mutations (27). However, 2.7 mg/kg doses of Teliso-V once every 3 weeks failed to meet prespecified response criteria in patients with c-Met–positive squamous cell NSCLC in the Lung-MAP S1400K clinical trial (40). During this trial, there were also three grade 5 events: two cases of pneumonitis in patients who were immune checkpoint inhibitor refractory, and one case of bronchopulmonary hemorrhage in an immune checkpoint inhibitor–naive patient. Although the Lung-MAP S1400K trial was terminated, Teliso-V 1.9 mg/kg once every 2 weeks is being investigated in both squamous and nonsquamous NSCLC in an ongoing phase II study (NCT03539536).

In this study, the 2.7 mg/kg Teliso-V once every 3 weeks dosing regimen was further evaluated and the manageable safety profile was confirmed in a larger cohort of patients with c-Met+ NSCLC. In addition, an alternative Teliso-V monotherapy once every 2 weeks schedule was assessed at 1.6, 1.9, and 2.2 mg/kg doses in patients with c-Met+ NSCLC, and the Teliso-V 1.9 mg/kg dose was selected for the once every 2 weeks dose-expansion phase on the basis of its safety and PK profile. Teliso-V 1.9 mg/kg once every 2 weeks and 2.7 mg/kg once every 3 weeks yielded approximately dose-proportional systemic exposures, with total antibody and conjugate exposures being highly

Table 4. Efficacy summary in c-Met+ NSCLC patients treated with Teliso-V monotherapy Q2W and Q3W and by histology[a].

	NSQ			SQ			NSQ and SQ			NSQ and SQ	
	Total NSQ (*n* = 33)	**Q2W (*n* = 16)**	**Q3W (*n* = 17)**	**Total SQ (*n* = 7)**	**Q2W (*n* = 2)**	**Q3W (*n* = 5)**	**Total NSQ and SQ (*n* = 40)**	**Q2W (*n* = 18)**	**Q3W (*n* = 22)**	**c-Met *H*-score 150–224 (*n* = 25)**	**c-Met *H*-score ≥225 (*n* = 15)**
ORR, *n* (%) [95% CI]	6 (18.2) [7.0–35.5]	5 (31.3) [11.0–58.7]	1 (5.9) [0.1–28.7]	3 (42.9) [9.9–81.6]	0	3 (60.0) [14.7–94.7]	9 (22.5) [10.8–38.5]	5 (27.8) [9.7–53.5]	4 (18.2) [5.2–40.3]	5 (20) [6.8–40.7]	4 (26.7) [7.8–55.1]
Best overall response, *n* (%)											
CR	1 (3)	1 (6.3)	0	0	0	0	1 (2.5)	1 (5.6)	0	0	1 (6.7)
PR	5 (15.2)	4 (25)	1 (5.9)	3 (42.9)	0	3 (60)	8 (20)	4 (22.2)	4 (18.2)	5 (20)	3 (20)
SD	16 (48.5)	7 (43.8)	9 (52.9)	3 (42.9)	2 (100)	1 (20)	19 (47.5)	9 (50)	10 (45.5)	13 (52)	6 (40)
PD	9 (27.3)	3 (18.8)	6 (35.3)	1 (14.3)	0	1 (20)	10 (25)	3 (16.7)	7 (31.8)	5 (20)	5 (33.3)
DCR, *n* (%) [95% CI]	22 (66.7) [48.2–82.0]	12 (75.0) [47.6–92.7]	10 (58.8) [32.9–81.6]	6 (85.7) [42.1–99.6]	2 (100) [15.8–100]	4 (80.0) [28.4–99.5]	28 (70.0) [53.5–83.4]	14 (77.8) [52.4–93.6]	14 (63.6) [40.7–82.8]	18 (72.0) [50.6–87.9]	10 (66.7) [38.4–88.2]
PFS, median (95% CI), months	3.8 (1.6–8.8)	5.2 (1.7–8.8)	2.7 (1.2–NE)	6.2 (1.2–14.3)	8.7 (6.4–11.0)	6.0 (1.2–14.3)	5.2 (2.5–8.8)	5.2 (2.7–9.0)	5.7 (1.3–NE)	5.2 (1.7–6.4)	8.0 (1.3–NE)
Duration of response, median (95% CI), months	10.6 (6.2–NE)	9.0 (6.2–NE)	NR (NE–NE)	4.8 (3.1–10.0)	NA	4.8 (3.1–10.0)	8.7 (5.5–10.6)	9.0 (6.2–NE)	7.4 (3.1–NE)	7.4 (3.1–NE)	NR (6.2–NE)
Treatment duration, median [range], weeks	8.9 [0.1–60.1]	14.9 [0.1–60.1]	3.4 [0.1–47.7]	22.4 [3.1–57.1]	34.4 [22.3–46.4]	22.4 [3.1–57.1]	10.1 [0.1–60.1]	19.6 [0.1–60.1]	6.1 [0.1–57.1]	10.1 [0.1–60.1]	10.1 [0.1–59.9]

Abbreviations: NE, not estimable; NR, not reached; NSQ, nonsquamous; PD, progressive disease; Q2W, once every 2 weeks; Q3W, once every 3 weeks; SQ, squamous.

[a]Postbaseline tumor assessments were not available for 2 patients, 1 in the Q2W dose cohort due progressive disease leading to death, and 1 in the Q3W dose cohort due to death by pneumonia. These patients were included in the efficacy-evaluable population and considered nonresponders.

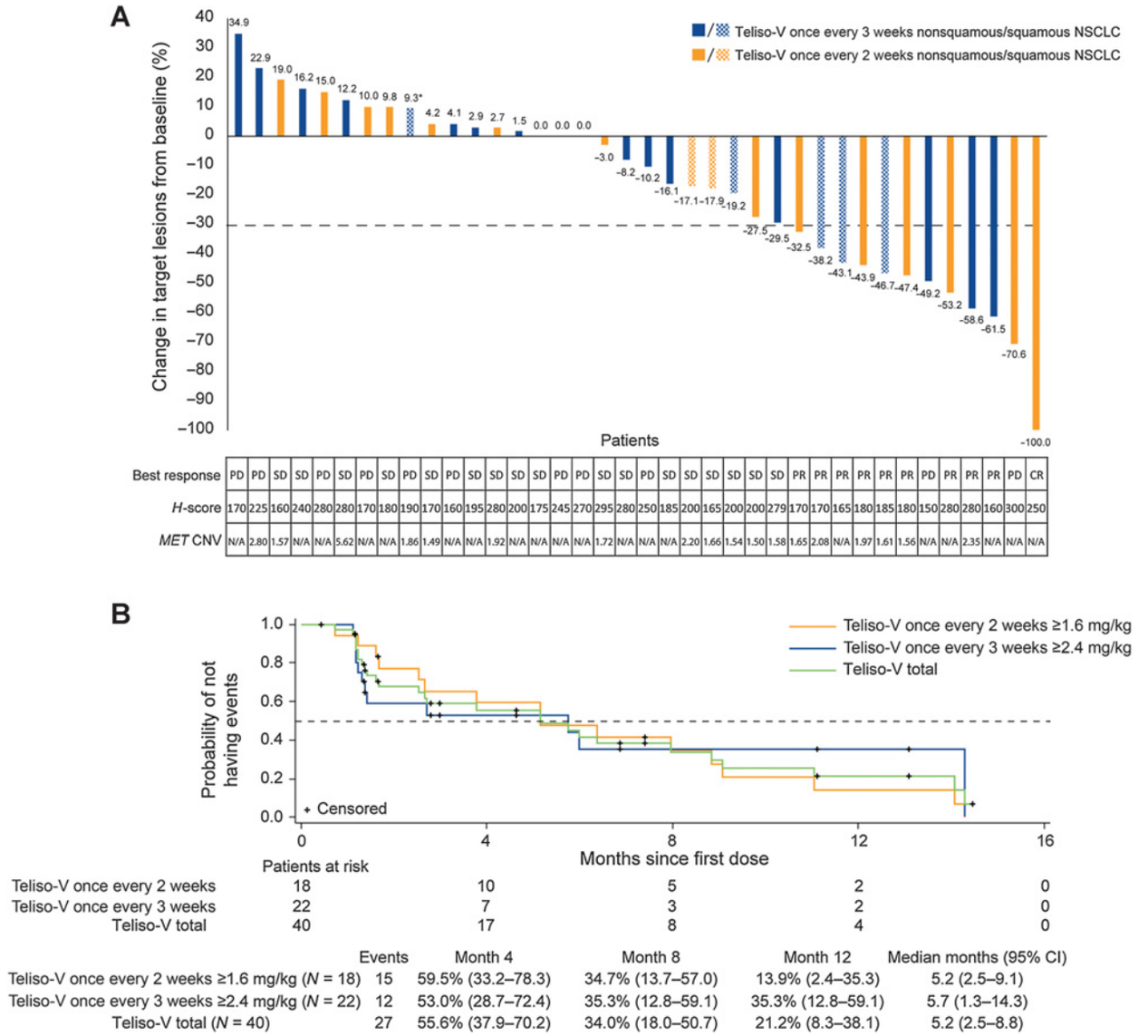

Figure 2.

A, Best percentage change in the size of target lesions in all patients with one or more postbaseline tumor assessment ($n = 38$). **B,** PFS for all efficacy-evaluable patients ($n = 40$) by NSCLC histology and by dosing schedule. CNV, copy-number variation; N/A, not available. *, *MET* exon 14 skipping mutation.

correlated after single-dose infusion (**Fig. 1**). The most frequent AEs (in >30% of patients) were peripheral neuropathy (57%; all types), fatigue (50%), nausea (39%), and dizziness (32%) in once every 2 weeks dosing cohorts, and fatigue (58%), nausea (38%), and dyspnea (33%) in once every 3 weeks cohorts.

Peripheral neuropathy is an expected class toxicity of antimicrotubule agents, frequently observed following treatment with MMAE-based ADCs in patients with hematologic and solid tumors (41). Moreover, in this study, a large proportion of patients either presented with baseline neuropathy (31%) or had received previous treatment with antimicrotubule agents (65%) and/or other neurotoxic chemotherapy (73%; **Table 1**), which are well-known risk factors for neuropathy. Despite this, exposure-safety analyses did not identify prior history of peripheral neuropathy or prior therapy with neurotoxic agents as significant covariates; the small patient sample size may impact the results. However, a trend to higher rate of peripheral neuropathy was observed in patients who had received a prior therapy with microtubule inhibitors (Supplementary Table S2). Peripheral neuropathy associated with Teliso-V was mostly sensory and generally mild or moderate in severity. Grade 3 peripheral neuropathy occurred in only 3 patients, 2 in the once every 2 weeks cohort and 1 in the once every 3 weeks cohort.

The main difference in the toxicity profile between the two schedules was the higher incidence of peripheral neuropathy (all types) observed in the ≥1.6 mg/kg Teliso-V once every 2 weeks cohorts compared with ≥2.4 mg/kg once every 3 weeks (57% vs. 25%). Significantly, median Teliso-V treatment duration was approximately three-fold longer in once every 2 weeks (19.6 weeks) than in once every

3 weeks (6.1 weeks) cohorts, which may have contributed to the higher incidence of peripheral neuropathy observed in patients following the Teliso-V once every 2 weeks regimen. Peripheral neuropathy was considered related to Teliso-V in 13 of 16 cases in once every 2 weeks cohorts and 5 of 6 cases in once every 3 weeks cohorts. The median time to onset of neuropathy was similar in both dosing regimens, whereas its median duration appeared to be slightly longer for patients in once every 3 weeks cohorts (3 vs. 5 months; Supplementary Table S2). A greater incidence of peripheral neuropathy has also been observed with other MMAE-containing ADCs when they are administered at a higher frequency, such as brentuximab vedotin, an FDA-approved ADC that uses MMAE payload (42, 43), or glembatumumab vedotin (44). In line with this observation, the higher minimum trough concentration reached with the 1.9 mg/kg once every 2 weeks dosing regimen compared with 2.7 mg/kg once every 3 weeks was identified in exposure-safety analyses as a potential reason for the greater probability for grade ≥2 peripheral neuropathy with Teliso-V 1.9 mg/kg once every 2 weeks (Supplementary Table S3).

Overall antitumor objective responses were observed in 9 of 40 patients (23%), which is notable in this highly pretreated (median three prior therapies) population with advanced disease characterized by a large baseline size of target lesions (>100 mm in 32% of patients). Responses were achieved in 3 of 7 (43%) patients with squamous and in 6 of 33 (18%) with nonsquamous NSCLC. Responses were of significant duration (median DOR 4.8 and 10.6 months, respectively). Neither NSCLC histology nor c-Met *H*-scores were found to be significant covariates in exposure-efficacy analyses. Although response rates appeared to be higher for patients who had c-Met *H*-scores of 225 or above than for patients with c-Met *H*-scores of 150 to 224, no clear conclusions can be drawn from this observation due to the limited number of patients analyzed. All 3 responders (3 PR) with squamous NSCLC were enrolled in once every 3 weeks cohorts, and among the 6 responders with nonsquamous NSCLC, 5 received Teliso-V once every 2 weeks (1 CR and 4 PR) and 1 Teliso-V once every 3 weeks (PR). Predictions from the exposure-efficacy analyses are in line with the higher efficacy of Teliso-V 1.9 mg/kg once every 2 weeks dosing regimen in patients with nonsquamous NSCLC (Supplementary Table S3). Notably, the majority of responses (8 of 9) occurred in patients without known *MET* amplification or *MET* exon 14 skip mutations. Other studies are further evaluating c-Met protein expression as a potential predictive marker.

Study limitations include predefining c-Met+ as an *H*-score of ≥150 on the basis of results from preclinical studies and incomplete data on *MET* amplification and *MET* exon 14 skip mutation status (not all patients were tested due to tissue availability limitations). The use of c-Met expression levels as a biomarker has been hampered, in part, by the heterogeneous c-Met expression levels within tumors and the availability in most cases of only archival tissue obtained at the time of diagnosis for analyses. Consequently, a standardized method to quantify c-Met levels is still lacking and the c-Met expression threshold required for anticancer activity has not been validated. The semiquantitative method used here to define c-Met+ shows correlation between membrane c-Met receptor intensity by IHC and *MET* mRNA levels (27). The ORR of 22% observed in the population of patients with a c-Met *H*-score ≥150 combined with lack of correlation between the level of c-Met expression and antitumor activity within this preselected population suggests that although the ≥150 *H*-score cutoff could represent a valid c-Met expression threshold for Teliso-V efficacy, additional resistance mechanisms independent of c-Met expression may limit antitumor responses.

In conclusion, Teliso-V monotherapy was tolerated at both the 1.9 mg/kg once every 2 weeks and 2.7 mg/kg once every 3 weeks dosing schedules in patients with NSCLC. In addition, Teliso-V monotherapy demonstrated encouraging preliminary efficacy in heavily pretreated patients with advanced c-Met–expressing NSCLC. On the basis of the higher ORR in patients with nonsquamous NSCLC in Teliso-V once every 2 weeks cohorts, the higher C_{min} reached with the once every 2 weeks schedule, and the similar tolerability of both schedules, the 1.9 mg/kg once every 2 weeks dosing regimen was selected as the Teliso-V monotherapy RP2D for further clinical development. Additional studies with Teliso-V as monotherapy and in combination therapy in patients with lung cancer are ongoing.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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References

1. Ma PC, Maulik G, Christensen J, Salgia R. c-Met: structure, functions and potential for therapeutic inhibition. Cancer Metastasis Rev 2003;22:309–25.
2. Gherardi E, Birchmeier W, Birchmeier C, Vande Woude G. Targeting MET in cancer: rationale and progress. Nat Rev Cancer 2012;12:89–103.
3. Ma PC, Jagadeeswaran R, Jagadeesh S, Tretiakova MS, Nallasura V, Fox EA, et al. Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non-small cell lung cancer. Cancer Res 2005;65:1479–88.
4. Spigel DR, Ervin TJ, Ramlau RA, Daniel DB, Goldschmidt JH Jr, Blumenschein GR Jr, et al. Randomized phase II trial of onartuzumab in combination with erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol 2013;31:4105–144.
5. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511:543–54.
6. Lengyel E, Prechtel D, Resau JH, Gauger K, Welk A, Lindemann K, et al. C-Met overexpression in node-positive breast cancer identifies patients with poor clinical outcome independent of Her2/neu. Int J Cancer 2005; 113:678–82.
7. Fujita S, Sugano K. Expression of c-met proto-oncogene in primary colorectal cancer and liver metastases. Jpn J Clin Oncol 1997;27:378–83.
8. Resnick MB, Routhier J, Konkin T, Sabo E, Pricolo VE. Epidermal growth factor receptor, c-MET, beta-catenin, and p53 expression as prognostic indicators in stage II colon cancer: a tissue microarray study. Clin Cancer Res 2004;10: 3069–75.
9. Sawada K, Radjabi AR, Shinomiya N, Kistner E, Kenny H, Becker AR, et al. c-Met overexpression is a prognostic factor in ovarian cancer and an effective target for inhibition of peritoneal dissemination and invasion. Cancer Res 2007;67:1670–91.
10. Verhoef EI, Kolijn K, De Herdt MJ, van der Steen B, Hoogland AM, Sleddens HFBM, et al. MET expression during prostate cancer progression. Oncotarget 2016;7:31029–36.
11. International Agency for Research on Cancer. World Health Organization. Cancer Fact Sheets. World. [cited 2021 Feb 3]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf.
12. American Cancer Society. About lung cancer. [cited 2021 Feb 2]. Available from: https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html.
13. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83: 584–94.
14. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008;26:4617–25.
15. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239–46.
16. Lin JJ, Cardarella S, Lydon CA, Dahlberg SE, Jackman DM, Jänne PA, et al. Five-year survival in EGFR-mutant metastatic lung adenocarcinoma treated with EGFR-TKIs. J Thorac Oncol 2016;11:556–65.
17. Awad MM, Leonardi GC, Kravets S, Dahlberg SE, Drilon AE, Noonan S, et al. Impact of MET inhibitors on survival among patients (pts) with *MET* exon 14 mutant (*MET*del14) non-small cell lung cancer (NSCLC). J Clin Oncol 2017;35: abstract8511.
18. Cappuzzo F, Marchetti A, Skokan M, Rossi E, Gajapathy S, Felicioni L, et al. Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. J Clin Oncol 2009;27:1667–741.
19. Vuong HG, Ho ATN, Altibi AMA, Nakazawa T, Katoh R, Kondo T. Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer: a systematic review and meta-analysis. Lung Cancer 2018;123: 76–82.
20. Tong JH, Yeung SF, Chan AWH, Chung LY, Chau SL, Lung RWM, et al. MET amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. Clin Cancer Res 2016;22:3048–56.
21. Gu FF, Zhang Y, Liu YY, Hong XH, Liang JY, Tong F, et al. Lung adenocarcinoma harboring concomitant SPTBN1-ALK fusion, c-Met overexpression, and HER-2 amplification with inherent resistance to crizotinib, chemotherapy, and radiotherapy. J Hematol Oncol 2016;9:66.
22. Turke AB, Zejnullahu K, Wu YL, Song Y, Dias-Santagata D, Lifshits E, et al. Preexistence and clonal selection of MET amplification in EGFR mutant NSCLC. Cancer Cell 2010;17:77–88.
23. Wang J, Goetsch L, Tucker L, Zhang Q, Gonzalez A, Vaidya KS, et al. Anti-c-Met monoclonal antibody ABT-700 breaks oncogene addiction in tumors with MET amplification. BMC Cancer 2016;16:105.
24. Wang J, Anderson MG, Oleksijew A, Vaidya KS, Boghaert ER, Tucker L, et al. ABBV-399, a c-Met antibody-drug conjugate that targets both *MET*-amplified and c-Met-overexpressing tumors, irrespective of *MET* pathway dependence. Clin Cancer Res 2017;23:992–1000.
25. Strickler JH, LoRusso P, Salgia R, Kang YK, Yen CJ, Lin CC, et al. Phase I dose-escalation and -expansion study of telisotuzumab (ABT-700), an anti-c-Met antibody, in patients with advanced solid tumors. Mol Cancer Ther 2020;19: 1210–7.
26. Kang YK, LoRusso P, Salgia R, Yen CJ, Lin CC, Ramanathan RK, et al. Phase I study of ABT-700, an anti-c-Met antibody, in patients (pts) with advanced gastric or esophageal cancer (GEC). J Clin Oncol 2015;33: abstract167.
27. Strickler JH, Weekes CD, Nemunaitis J, Ramanathan RK, Heist RS, Morgensztern D, et al. 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. J Clin Oncol 2018;6:3298–306.

28. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
29. Parikh A, Menon R, Afar D, Naumovski L, Friedel A, Kasichayanula S, et al. Pharmacokinetics (PK) and exposure-response (ER) analyses of telisotuzumab vedotin (Teliso-V) in patients with advanced solid tumors: preliminary phase 1 results. Clin Pharmacol Ther 2019;105: abstractPII–085.
30. Caparica R, Yen CT, Coudry R, Ou SHI, Varella-Garcia M, Camidge DR, et al. Responses to crizotinib can occur in high-level MET-amplified non-small cell lung cancer independent of MET exon 14 alterations. J Thorac Oncol 2017;12: 141.
31. Camidge DR, Otterson GA, Clark JW, Ou SHI, Weiss J, Ades S, et al. Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): Updated safety and efficacy findings from a phase 1 trial. J Clin Oncol 2018; 36: abstract9062.
32. Drilon AE, Camidge DR, Ou SHI, Clark JW, Socinski MA, Weiss J, et al. Efficacy and safety of crizotinib in patients (pts) with advanced *MET* exon 14-altered non-small cell lung cancer (NSCLC). J Clin Oncol 2016;34: abstract108.
33. Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, et al. Tepotinib in non-small-cell lung cancer with *MET* exon 14 skipping mutations. N Engl J Med 2020;383:931–43.
34. Wolf J, Seto T, Han JY, Reguart N, Garon EB, Groen HJM, et al. Capmatinib in *MET* exon 14-mutated or *MET*-amplified non-small-cell lung cancer. N Engl J Med 2020;383:944–57.
35. Spiegel DR, Edelman MJ, O'Byrne K, Paz-Ares L, Mocci S, Phan S, et al. Results from the phase III randomized trial of onartuzumab plus erlotinib versus erlotinib in previously treated stage IIIB or IV non-small-cell lung cancer: METLung. J Clin Oncol 2017;35:412–20.
36. Strickler JH, LoRusso P, Yen CJ, Lin CC, Kang YK, Kaminker P, et al. Phase 1, open-label, dose-escalation, and expansion study of ABT-700, an anti-C-met antibody, in patients (pts) with advanced solid tumors. J Clin Oncol 2014;32: abstract2507.
37. Angevin E, Spitaleri G, Rodon J, Dotti K, Isambert N, Salvagni S, et al. A first-in-human phase I study of SAR125844, a selective MET tyrosine kinase inhibitor, in patients with advanced solid tumours with MET amplification. Eur J Cancer 2017;87:131–9.
38. Hong DS, LoRusso PM, Hamid O, Janku F, Kittaneh M, Catenacci DVT, et al. Phase 1 study of AMG 337, a highly selective small-molecule MET inhibitor, in patients with advanced solid tumors. Clin Cancer Res 2019;25:2403–13.
39. Scagliotti G, von Pawel J, Novello S, Ramlau R, Favaretto A, Barlesi F, et al. Phase III multinational, randomized, double-blind, placebo-controlled study of tivantinib (ARQ 197) plus erlotinib versus erlotinib alone in previously treated patients with locally advanced or metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol 2015;33:2667–74.
40. Waqar SN, Redman MW, Arnold SM, Hirsch FR, Mack PC, Schwartz LH, et al. A phase II study of telisotuzumab vedotin in patients with c-MET-positive stage IV or recurrent squamous cell lung cancer (LUNG-MAP sub-study S1400K, NCT03574753). Clin Lung Cancer 2020;14:S1525–7304.
41. Masters JC, Nickens DJ, Xuan D, Shazer RL, Amantea M. Clinical toxicity of antibody drug conjugates: a meta-analysis of payloads. Invest New Drugs 2018; 36:121–35.
42. Younes A, Bartlett NL, Leonard JP, Kennedy DA, Lynch CM, Sievers EL, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 2010;363:1812–21.
43. Fanale MA, Forero-Torres A, Rosenblatt JD, Advani RH, Franklin AR, Kennedy DA, et al. A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. Clin Cancer Res 2012;18:248–55.
44. Ott PA, Hamid O, Pavlick AC, Kluger H, Kim KB, Boasberg PD, et al. Phase I/II study of the antibody-drug conjugate glembatumumab vedotin in patients with advanced melanoma. J Clin Oncol 2014;32:3659–66.