ORIGINAL ARTICLE

A Phase 1b Study of Telisotuzumab Vedotin in Combination With Nivolumab in Patients With NSCLC

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ABSTRACT

Introduction: Telisotuzumab vedotin (Teliso-V) is an anti-c-Met–directed antibody-drug conjugate that has exhibited antitumor activity as monotherapy in NSCLC. Its potential activity combined with programmed cell death protein-1 inhibitors has not been previously evaluated.

Methods: In a phase 1b study (NCT02099058), adult patients (≥18 y) with advanced NSCLC received combination therapy with Teliso-V (1.6, 1.9, or 2.2 mg/kg, every 2 wk) plus nivolumab (3 mg/kg, 240 mg, or per locally approved label). The primary objective was to assess safety and tolerability; secondary objectives included the evaluation of antitumor activity.

Results: As of January 2020, a total of 37 patients received treatment with Teliso-V (safety population) in combination with nivolumab; 27 patients (efficacy population) were c-Met immunohistochemistry–positive. Programmed death-ligand 1 (PD-L1) status was evaluated in the efficacy population (PD-L1–positive [PD-L1+]: n = 15; PD-L1–negative [PD-L1–]: n = 9; PD-L1–unknown: n = 3). The median age was 67 years and 74% (20 of 27) of patients were naive to immune checkpoint inhibitors. The most common any-grade treatment-related adverse events were fatigue (27%) and peripheral sensory neuropathy (19%). The pharmacokinetic profile of Teliso-V plus nivolumab was similar to Teliso-V monotherapy. The objective response rate was 7.4%, with two patients (PD-L1+, c-Met immunohistochemistry H-score 190, n = 1; PD-L1–, c-Met H-score 290, n = 1) having a confirmed partial response. Overall median progression-free survival was 7.2 months (PD-L1+: 7.2 mo; PD-L1–: 4.5 mo; PD-L1–unknown: not reached).

Conclusions: Combination therapy with Teliso-V plus nivolumab was well tolerated in patients with c-Met+ NSCLC with limited antitumor activity.

Keywords: c-Met; Antibody-drug conjugate; Non–small cell lung cancer; Telisotuzumab vedotin; Nivolumab

Introduction

Advances in novel treatment regimens that favor the use of molecularly targeted therapies or immunotherapy have led to improvements in overall survival (OS) for patients with NSCLC.[1,2] c-Met, a signaling tyrosine kinase receptor, is expressed on the surface of epithelial and endothelial cells. Activation of c-Met by hepatocyte growth factor has been found to control cell proliferation, angiogenesis, survival, and cellular motility.[3] Aberrant c-Met signaling is common in NSCLC and can occur through numerous mechanisms, including gene mutation, amplification, rearrangement, and protein overexpression.[4] Small-molecule inhibitors of c-Met, and some antibodies against c-Met, may exhibit activity in cancers addicted to the *MET* pathway. c-Met protein expression, which can occur together with or independent of *MET* pathway addiction, can be used as a target for antibody-drug conjugates (ADCs).

Nivolumab, a fully human programmed cell death protein-1 (PD-1) inhibitor antibody, is approved in the United States, Europe, and other countries for the treatment of advanced NSCLC with progression on or after platinum-based chemotherapy.[5,6] Pooled analysis from two phase 3 trials revealed continued improvement in OS (≥3 y of follow-up) with nivolumab monotherapy compared with docetaxel in patients with previously treated advanced squamous (CheckMate 017) and non-squamous (CheckMate 057) NSCLC; estimated 3-year OS rates: 17% versus 8%.[7]

Telisotuzumab vedotin (Teliso-V; ABBV-399) is an anti–c-Met ADC composed of the monoclonal antibody ABT-700 and the microtubule inhibitor monomethyl auristatin E (MMAE). Receptor-mediated internalization of Teliso-V by c-Met–expressing tumor cells leads to the

intracellular release of MMAE, inhibition of cell division, and subsequent cell death.[8] Clinical results from an ongoing first-in-human phase 1-1b study evaluating Teliso-V monotherapy in advanced NSCLC revealed a favorable safety profile and promising antitumor activity at the recommended phase 2 dose of 1.9 mg/kg once every 2 weeks (Q2W).[9]

There is evidence suggesting that ADCs, including those using vedotin as a payload, can potentiate antitumor response through immunogenic cell death, and can have additive efficacy with immuno-oncology agents.[10–12] These data provide the rationale to explore combination therapy with Teliso-V and nivolumab. Here, we report the findings of a phase 1b study that evaluated the safety and antitumor activity of Teliso-V in combination with nivolumab in patients with previously treated advanced NSCLC.

Materials and Methods

Study Design and Patients

This phase 1-1b multicenter, open-label study (NCT02099058) evaluated Teliso-V as monotherapy or in combination with erlotinib or nivolumab in patients with advanced solid tumors.[8,13] The primary objective was to assess the safety and tolerability of Teliso-V as monotherapy or in combination; the evaluation of antitumor activity was as a secondary objective. The study design for phase 1-1b, details on patient eligibility criteria, and results of Teliso-V monotherapy in patients with advanced solid tumors[8] and Teliso-V in combination with erlotinib in patients with NSCLC[13] have been previously reported. Here, we report the phase 1b outcomes in patients with advanced NSCLC treated with Teliso-V plus nivolumab.

For phase 1b, patients with NSCLC were enrolled in a cohort receiving a combination of Teliso-V and nivolumab Q2W. Initially, patients with any level of c-Met expression were enrolled; criteria were subsequently modified to enroll only patients whose tumors were c-Met–positive (c-Met+) (membrane H-score 150). c-Met–negative (c-Met–) patients were included in the safety population but not in the efficacy population. Patients eligible for combination therapy satisfied the inclusion criteria for Teliso-V monotherapy described by Strickler et al.[8] and were not previously treated with nivolumab. An amendment to the protocol was made to exclude previous treatment with any other drug known to target PD-1 or programmed death-ligand 1 (PD-L1), approved or unapproved locally.

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 the International Conference on Harmonization, Good Clinical Practice Guidelines, and the Declaration of Helsinki.

Treatment

Patients received Teliso-V Q2W (1.6, 1.9, or 2.2 mg/kg, intravenous) with nivolumab (3 mg/kg, or 240 mg, or per locally approved label, intravenously). Patients with clinical benefit (complete response, partial response [PR], or stable disease) received the study treatment for up to 24 months as long as toxicities were manageable. Patients who discontinued nivolumab owing to safety issues unrelated to Teliso-V were allowed to continue on single-agent Teliso-V. Patients were followed up on the study until disease progression.

Safety

Safety evaluations were performed throughout the study and all adverse events (AEs) were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Additional details for safety evaluations, including criteria for dose-limiting toxicities, were published previously.[8]

Pharmacokinetics

Serial blood samples were collected at prespecified time points in cycle 1, before dosing, and 30 minutes after the completion of study drug infusion on the first day of each subsequent cycle. Samples were analyzed for concentrations of the Teliso-V conjugate. In addition, samples were analyzed for total ABT-700 and free MMAE drug levels (not presented for this analysis). Pharmacokinetics (PK) parameters such as the maximum observed plasma concentration (C_{max}), the time to C_{max}, and the area under the concentration-time curve for each of the Teliso-V analytes, when administered in combination with nivolumab, were estimated using noncompartmental methods.

Antitumor Activity

Baseline radiographic assessments using computed tomography or magnetic resonance imaging were obtained no more than 28 days before treatment initiation. Thereafter, tumor assessments were performed every 8 weeks until disease progression, the start of new anticancer therapy, death, or withdrawal of consent. Changes in measurable lesions were assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1[14] to evaluate objective response rate (ORR) and progression-free survival (PFS).

Table 1. Demographic and Clinical Characteristics for 27 Efficacy-Assessable Patients

	Teliso-V ≥1.6 mg/kg Plus Nivolumab Q2W			
Characteristics	PD-L1+ n = 15	PD-L1- n = 9	PD-L1-unk n = 3	Total N = 27
Age, median [range]	67 [45-89]	63 [51-78]	73 [61-76]	67 [45-89]
Gender, n (%)				
Female	11 (73)	5 (56)	2 (67)	18 (67)
Male	4 (27)	4 (44)	1 (33)	9 (33)
ECOG performance status, n (%)				
0	4 (27)	1 (11)	1 (33)	6 (22)
1	10 (67)	8 (89)	1 (33)	19 (70)
2	1 (7)	0	1 (33)	2 (7)
NSCLC, n (%)				
Nonsquamous	13 (87)	8 (89)	3 (100)	24 (89)
Squamous	1 (7)	1 (11)	0	2 (7)
None or not reported	1 (7)	0	0	1 (4)
c-MET H-score				
150-224	12 (80)	1 (11)	2 (67)	15 (56)
≥225	3 (20)	8 (89)	1 (33)	12 (44)
Tobacco use (cigarettes)				
Current	3 (20)	0	0	3 (11)
Former	6 (40)	7 (78)	2 (67)	15 (56)
Never	6 (40)	2 (22)	1 (33)	9 (33)
Lines of previous anticancer therapy, n (%)				
1	7 (47)	3 (33)	0	10 (37)
2	3 (20)	2 (22)	1 (33)	6 (22)
3	2 (13)	2 (22)	1 (33)	5 (19)
≥4	2 (13)	2 (22)	1 (33)	5 (19)
Missing	1 (7)	0	0	1 (4)
Type of previous anticancer therapy, n (%)				
EGFR tyrosine kinase inhibitor	2 (13)	2 (22)	1 (33)	5 (19)
Platinum-based therapies	12 (80)	8 (89)	2 (67)	22 (81)
Immune checkpoint inhibitors	4 (27)	3 (33)	0	7 (26)
Docetaxel	1 (7)	1 (11)	0	2 (7)
c-Met inhibitor	1 (7)	2 (22)	2 (67)	5 (19)
Other	5 (33)	3 (33)	2 (67)	10 (37)
Time from initial diagnosis to study entry, mo, median [range]	35.9 [6.8-122.7]	27.4 [9.8-95.7]	28.0 [15.8-30.6]	28.0 [6.8-122.7]
Duration of last line of prior anticancer therapy, mo, median [range]	9.2 [2.1-48.2]	4.5 [1.4-19.0]	10.3 [3.1-14.3]	9.0 [1.4-48.2]

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death receptor ligand-1; PD-L1+, PD-L1-positive; PD-L1-, PD-L1-negative; PD-L1-unk, PD-L1-unknown; Q2W, every 2 weeks; Teliso-V, telisotuzumab vedotin.

Biomarkers

Archived or fresh formalin-fixed paraffin-embedded tumor tissue was analyzed for c-Met and PD-L1 expression levels by immunohistochemistry (IHC). c-Met IHC was determined in a central laboratory (Flagship Biosciences Inc., Westminster, CO) using the SP44 antibody (Ventana; Tucson, AZ) and the UltraView Universal DAB Detection Kit (Ventana). Each cell in a fixed field was assigned a score on the basis of the staining intensity for c-Met (0, no staining; 1+, weak; 2+, moderate; 3+, strong). The final H-score (range: 0–300) was calculated as (1 × [% cells 1+] + 2 × [% cells 2+] + 3 × [% cells 3+]). c-Met+ was defined by an H-score greater than or equal to 150 of membrane staining. An H-score cutoff of greater than or equal to 150 was chosen by the sponsor (AbbVie, North Chicago, IL) to identify patients who were most likely to benefit from Teliso-V therapy. An in vitro diagnostic-companion diagnostic kit from Agilent was used for PD-L1 (rabbit clone 28-8) with DAB and IHC was performed in accordance with the instructions provided. Additional details for PD-L1 staining can be found in the Supplementary Data. Clinical sites reported *MET* amplification, if available. If tumor tissue remained after c-Met IHC, additional biomarker testing using whole-exome analysis was performed to deduce *MET* amplification by

Table 2. Treatment-Emergent Adverse Events by Preferred Term Occurring in Greater Than or Equal to 15% (Any Grade), Greater Than or Equal to 5% (Grade ≥3), or One or More Patients (Serious) Treated With Teliso-V

	Teliso-V ≥1.6 mg/kg Plus Nivolumab Q2W (N = 37)					
	Regardless of Relationship to Teliso-V			Reasonable Possibility of Relationship to Teliso-V		
Adverse Event, n (%)	Any Grade	Grade ≥3	Serious	Any Grade	Grade ≥3	Serious
Any adverse event	36 (97)	23 (62)	15 (41)	29 (78)	12 (32)	6 (16)
Fatigue	17 (46)	2 (5)	0	10 (27)	2 (5)	0
Decreased appetite	11 (30)	1 (3)	0	6 (16)	0	0
Cough	10 (27)	0	0	0	0	0
Hypoalbuminemia	10 (27)	1 (3)	0	6 (16)	0	0
Nausea	8 (22)	0	0	5 (14)	0	0
Peripheral edema	8 (22)	0	0	5 (14)	0	0
Peripheral sensory neuropathy	8 (22)	0	0	7 (19)	0	0
Decreased weight	8 (22)	0	0	2 (5)	0	0
Constipation	6 (16)	0	0	0	0	0
Diarrhea	6 (16)	1 (3)	1 (3)	2 (5)	1 (3)	1 (3)
Dyspnea	6 (16)	0	0	1 (3)	0	0
Hypotension	6 (16)	1 (3)	1 (3)	3 (8)	1 (3)	1 (3)
Hypertension	4 (11)	2 (5)	0	0	0	0
Peripheral neuropathy	4 (11)	2 (5)	1 (3)	4 (11)	2 (5)	1 (3)
Malignant neoplasm progression	3 (8)	3 (8)	3 (8)	0	0	0
Peripheral sensorimotor neuropathy	3 (8)	2 (5)	1 (3)	3 (8)	2 (5)	1 (3)
Pulmonary embolism	3 (8)	3 (8)	2 (5)	0	0	0
Colitis	2 (5)	2 (5)	2 (5)	0	0	0
Immune-related adverse events						
Rash	5 (14)	0	0	1 (3)	0	0
Upper respiratory tract infection	3 (8)	0	0	0	0	0
Pruritus	2 (5)	0	0	2 (5)	0	0
Urinary tract infection	2 (5)	0	0	0	0	0
Bronchitis	1 (3)	1 (3)	1 (3)	0	0	0
Genital herpes simplex	1 (3)	0	0	1 (3)	0	0
Herpes simplex	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)
Hypothyroidism	1 (3)	0	0	0	0	0
Pneumonia	1 (3)	1 (3)	1 (3)	0	0	0
Rash maculopapular	1 (3)	0	0	0	0	0
Sepsis	1 (3)	1 (3)	1 (3)	0	0	0
Staphylococcal infection	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)
Staphylococcal skin infection	1 (3)	0	0	0	0	0
Viral infection	1 (3)	0	0	0	0	0

Q2W, every 2 weeks; Teliso-V, telisotuzumab vedotin.

copy number variation analysis. In addition, plasma was tested for circulating tumor DNA (ctDNA) using PlasmaSELECT-R 64 (Personal Genome Diagnostics, Baltimore, MD). Additional details on methods are provided in the Supplementary Data.

Statistical Analysis

A sample size of 40 patients for enrollment was calculated to provide approximately 80% power using the two-stage minimax design to detect an absolute improvement in ORR from 20% to 40% with a 5% two-sided significance level. The safety analysis population included all patients who received one or more doses of the study drug. Safety summaries were descriptive, and no statistical inference was performed. Efficacy-assessable patients were c-Met+ per designated IHC assay, received one or more doses of study drug, and had at least one postdose tumor assessment or discontinued treatment owing to AEs, progressive disease, clinical progression, or died before the first postbaseline tumor assessment. Patients who withdrew consent for reasons other than AE before the first scan were not included in the efficacy population. The two-sided 95% confidence intervals (CIs) of ORR and complete response and PR rates were provided on the basis of the Clopper-Pearson (exact) method. PFS was summarized by Kaplan-Meier estimates and median PFS was calculated with two-sided 95% CIs.

Results

Patient Characteristics

As of January 2020, a total of 37 patients with NSCLC received treatment with Teliso-V (safety population; 1.6 mg/kg, n = 9; 1.9 mg/kg, n = 24; 2.2 mg/kg, n = 4) in combination with nivolumab. A total of 27 patients were c-Met+ (efficacy population; PD-L1+: n = 15; PD-L1–: n = 9; PD-L1 unknown [PD-L1–unk]: n = 3). Of the 27 patients from whom c-Met IHC scores were derived, 20 patients had archival tissue (1.9–82 mo from biopsy to start of treatment with Teliso-V plus nivolumab), and seven were fresh tissues (0–1.7 mo from biopsy to start of treatment with Teliso-V plus nivolumab; no intervening treatments between biopsy and combination treatment start). Demographics and clinical characteristics of c-Met+ patients are summarized in Table 1. The median age was 67 years (range: 45–89). Overall, 89% (n = 24) of patients had nonsquamous NSCLC and 74% (n = 20) had not received previous treatment with immune checkpoint inhibitors (ICIs). A total of 33% of patients were never-smokers. Although central genetic testing for oncogene status was not conducted, 19% of patients had received an EGFR tyrosine kinase inhibitor previously, and 19% had received a MET tyrosine kinase inhibitor previously. A total of 59% of patients (16 of 27) had received two or more previous lines of anticancer therapy. Clinical sites provided *MET* amplification status as positive for three patients; however, none of the three patients had tumor tissue to verify the *MET* amplification by whole-exome sequencing. Circulating tumor DNA analysis did not also detect *MET* amplification status in these patients. The *MET* H-scores in these cases were 280, 270, and 260.

Safety

The most common treatment-emergent AEs (TEAEs) (any grade ≥15%; grade ≥3, ≥5%) reported during the study are reported in Table 2. Most patients (97%, n = 36) experienced one or more TEAE, with 23 (62%) reporting TEAEs grades 3 or higher. The most common TEAEs of any grade (≥25%) were fatigue (46%), decreased appetite (30%), cough, and hypoalbuminemia (27% each). Grade greater than or equal to 3 TEAEs occurring in greater than or equal to 5% of patients were malignant neoplasm progression, pulmonary embolism (8% each), colitis, fatigue, hypertension, peripheral neuropathy, and peripheral sensorimotor neuropathy (5% each). Immune-related AEs (IRAEs) of any grade reported in more than one patient included rash (14%, n = 5), upper respiratory tract infection (8%, n = 3), urinary tract infection, and pruritus (5%, n = 2 each); no events were grade greater than or equal to 3.

TEAEs considered possibly related to Teliso-V were reported in 78% (n = 29) of patients; 32% (n = 12) were grade greater than or equal to 3 (Table 2). The most common TEAEs of any grade (≥15%) and grade greater than or equal to 3 (≥5%) considered related to Teliso-V were fatigue (27%, 5%), peripheral sensory neuropathy (19%, 0%), decreased appetite (16%, 0%), hypoalbuminemia (16%, 0%), peripheral neuropathy (11%, 5%), and peripheral sensorimotor neuropathy (8%, 5%). Rash and pruritus were the only IRAEs considered related to Teliso-V reported in greater than one patient; no events were grade greater than or equal to 3.

Serious AEs occurring in greater than or equal to 5% of patients were malignant neoplasm progression (8%), colitis, and pulmonary embolism (5% each); none were related to Teliso-V (Table 2). Five patients (14%) died as a consequence of a TEAE (pericardial effusion [n = 1], sepsis [n = 1], malignant neoplasm progression [n = 3]); none of the deaths were related to Teliso-V.

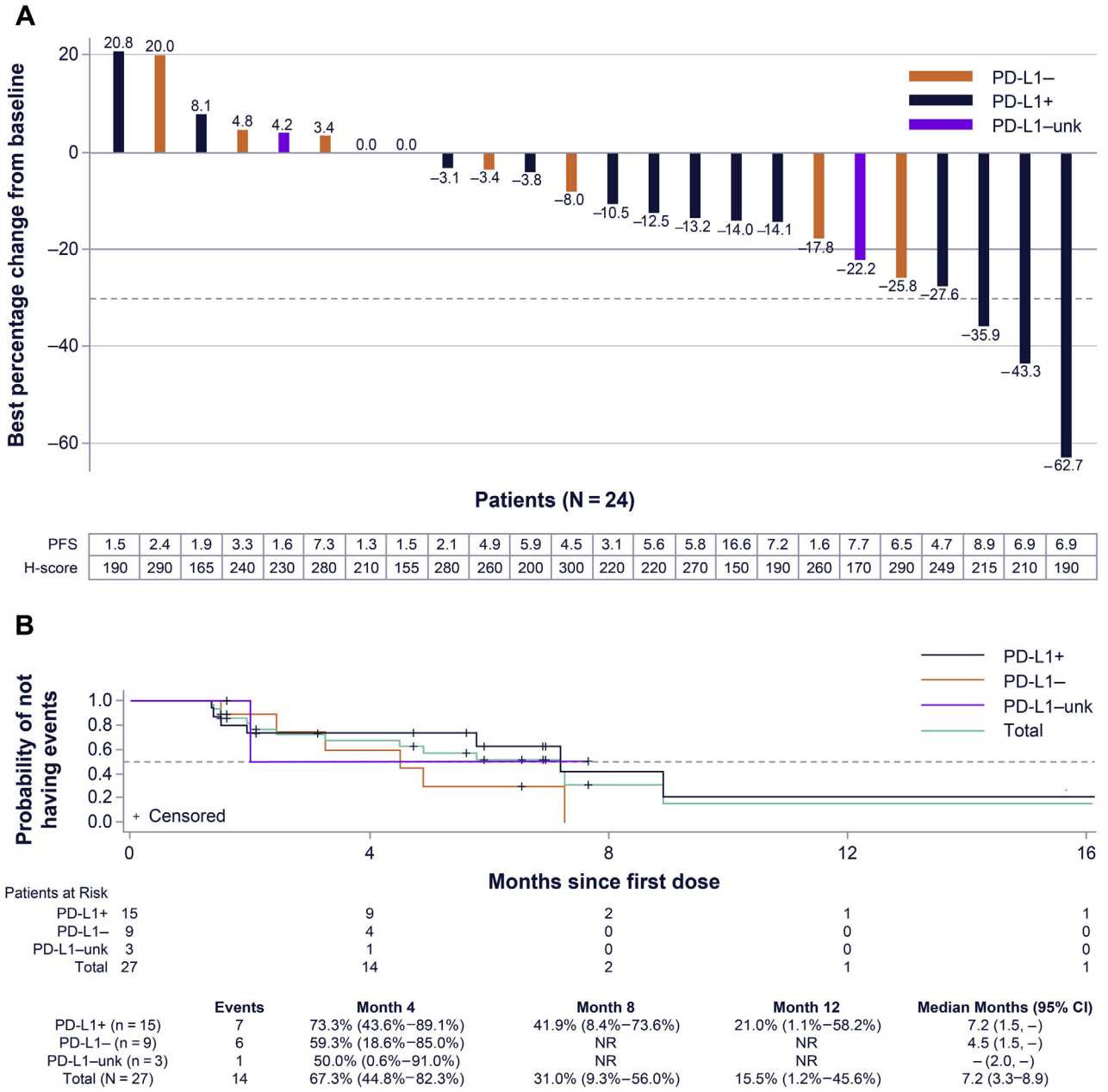
Teliso-V was discontinued by all patients in the efficacy population owing to either progressive disease (radiographic: 37%, n = 10; clinical: 15%, n = 4), AEs (33%, n = 9), or other reasons (15%, n = 4). Peripheral sensory neuropathy was the most common cause for Teliso-V dose reductions (8%, n = 3), and peripheral neuropathy was the most common cause for dose interruptions and discontinuation (8% each, n = 3). One dose-limiting toxicity of hepatic steatosis (grade ≥3) occurred at the 1.9-mg/kg Teliso-V combination dose with nivolumab.

Pharmacokinetics

Teliso-V preliminary PK were characterized after 1.6-, 1.9-, and 2.2-mg/kg Q2W doses (N = 10) in combination with nivolumab. Teliso-V conjugate concentrations in combination with nivolumab peaked after the end of infusion (~1 hour) and declined with a half-life of 2 to 3 days. The geometric mean (%CV) C_{max} and area under the concentration-time curve of Teliso-V in combination with nivolumab ranged from approximately 28.0 (20)–35.7 (27) μg/mL and 1849 (15)–2876 μg/mL × hr, respectively, across the doses of 1.6–2.2 mg/kg Q2W. The Teliso-V conjugate clinical PK profiles and parameters in combination with nivolumab were consistent with those previously reported for Teliso-V monotherapy.[15]

Antitumor Activity

The efficacy population consisted of 27 c-Met+ patients (PD-L1+: n = 15; PD-L1–: n = 9; PD-L1–unk: n = 3). Seven patients (26%) had received a previous treatment with ICI (PD-L1+: n = 4, 27%; PD-L1–: n = 3,



	Events	Month 4	Month 8	Month 12	Median Months (95% CI)
PD-L1+ (n = 15)	7	73.3% (43.6%−89.1%)	41.9% (8.4%−73.6%)	21.0% (1.1%−58.2%)	7.2 (1.5, –)
PD-L1− (n = 9)	6	59.3% (18.6%−85.0%)	NR	NR	4.5 (1.5, –)
PD-L1−unk (n = 3)	1	50.0% (0.6%−91.0%)	NR	NR	– (2.0, –)
Total (N = 27)	14	67.3% (44.8%−82.3%)	31.0% (9.3%−56.0%)	15.5% (1.2%−45.6%)	7.2 (3.3−8.9)

Figure 1. Best percentage reduction in (*A*) target lesions and (*B*) Kaplan-Meier estimates of PFS. (*A*) Responses were reported at the same visit as the best percentage change from the baseline assessment. *(B)* Three efficacy-assessable patients did not have a postbaseline scan owing to the withdrawal of consent (n = 1) and discontinuation owing to AE (n = 2). AE, adverse event; CI, confidence interval; NR, not reached; PD-L1, programmed death-ligand 1; PD-L1+, PD-L1-positive; PD-L1-, PD-L1-negative; PD-L1-unk, PD-L1-unknown; PFS, progression-free survival.

33%). The ORR was 7.4% (95% CI: 0.9–24.3), with two patients (PD-L1+, n = 1; PD-L1–, n = 1) having a confirmed PR; no response was reported in patients with PD-L1–unk status. Stable and progressive disease was reported for 19 (70.4%; PD-L1+: n = 10; PD-L1–: n = 7; PD-L1–unk: n = 2) and four (14.8%; PD-L1+: n = 3; PD-L1–unk: n = 1) patients, respectively. One additional patient (PD-L1+) had an unconfirmed PR with greater than 30% reduction in target lesions from baseline. Three efficacy-assessable patients did not have post-baseline tumor assessments owing to consent withdrawal (n = 1) or discontinuation owing to AE (n = 2). (Fig. 1*A*). Overall, 67% of patients (16 of 24) had evidence of tumor size reduction; three (13%) reported a greater than 30% reduction in target lesion. The median treatment duration of Teliso-V was 4.6 months (range: 0.7–15.7), 1.9 months (0.4–7.1), and 5.1 months (1.6–6.9) for PD-L1+, PD-L1–, and PD-L1–unk patients,

respectively. The median treatment duration of nivolumab was 3.7 months (range: 0.6–15.7), 1.9 months (0.4–7.1), and 1.6 months (0.5–5.1) for PD-L1+, PD-L1–, and PD-L1–unk patients, respectively. The overall median PFS (95% CI) was 7.2 months (3.3–8.9); 7.2 months (1.5–not reached [NR]) for PD-L1+ patients, 4.5 months (1.5–NR) for PD-L1– patients, and NR (2.0–NR) for PD-L1–unk patients (Fig. 1*B*).

Three patients assessable for response had *MET*-amplified tumors (H-scores: 260, 270, 280); all were *EGFR* wild-type. None of the *MET*-amplified patients had a clinical response (ORR = 0%). The two responders (ORR = 7.4%) had *MET* IHC H-scores of 190 (PD-L1+) and 290 (PD-L1–) (Fig. 1*A*).

Discussion

Immune synergy refers to drugs that work better in combination than as monotherapy (or in sequence) through their individual mechanisms of action to enhance, or prime, the host immune response to cancer.[16] ADCs containing MMAE have been hypothesized to induce immunogenic cell death, activation of the immune system against cancer in an immunocompetent setting, and may act synergistically when combined with immuno-oncology drugs.[16] Data supporting this concept were recently reported in the EV-103 phase 1 trial evaluating pembrolizumab (PD-1 inhibitor) in combination with enfortumab vedotin (nectin-4–targeted ADC conjugated to MMAE) in patients with locally advanced or metastatic urothelial carcinoma. Responses were seen regardless of PD-L1 expression assessed by combined positive score.[17]

To our knowledge, this is the first report of a c-Met–targeted MMAE-containing ADC combined with nivolumab in patients with previously treated advanced NSCLC. The combination of Teliso-V (1.6–2.2 mg/kg intravenous Q2W) and nivolumab was generally well tolerated with manageable neuropathy and PK comparable with Teliso-V monotherapy. In the reported study, patients reported TEAEs of peripheral sensory neuropathy (n = 7, 19%), peripheral neuropathy (n = 4, 11%), and peripheral sensorimotor neuropathy (n = 3, 8%); zero (0%), two (5%), and two (5%) patients reported AEs of at least grade 3, respectively. Although neuropathy is a class-effect toxicity of ADCs conjugated to MMAE,[18] it is noteworthy that most patients were heavily pretreated, and 14 patients (38%) had baseline neuropathy (grade 1) before study enrollment. Neuropathy developed while on the study in 10 of the 23 patients without baseline neuropathy. A limited number of patients discontinued treatment with Teliso-V owing to TEAEs of neuropathy: peripheral neuropathy (n = 3, 8%), peripheral sensory neuropathy (n = 2, 5%), and peripheral sensorimotor neuropathy (n = 2, 5%). In addition, no grade greater than or equal to 3 IRAEs were reported in more than one patient. These data support the manageability of neuropathy-related TEAEs, and thus, the overall combination of Teliso-V and checkpoint inhibitors.

The ORR of the combination in this trial was disappointing, given the previous results reported in nivolumab and Teliso-V monotherapy studies. An ORR of 19% was reported in the CheckMate 057 study with nivolumab monotherapy in patients with nonsquamous NSCLC that had progressed during or after platinum-based doublet chemotherapy.[19] The response rate to Teliso-V monotherapy in NSCLC with c-MET H-scores greater than or equal to 150 was 23%.[9]

Most patients in our study were ICI-naive, but nearly a third of patients were never-smokers and 19% were previously treated with either an EGFR or MET tyrosine kinase inhibitor. These characteristics suggest that a substantial proportion of patients may have had an underlying driver oncogene—two groups associated with lower benefit from ICIs. Despite no difference being observed in the ORR between PD-L1+ and PD-L1– subpopulations (PR, n = 1 each), duration of treatment (PD-L1+: 4.6 mo versus PD-L1–: 1.9 mo), and PFS (PD-L1+: 7.2 mo versus PD-L1–: 4.5 mo) seemed to trend longer for the PD-L1+ subpopulation, suggesting additional benefit for this group of patients. Notably, 81% of patients who received combination therapy with Teliso-V and nivolumab had received previous treatment with platinum-based therapies.

In the reported study, one of two patients who reported a confirmed response was PD-L1+ and did not receive a previous ICI. PD-L1 selection was not a criterion for this phase 1b study, and 12 patients had PD-L1– or PD-L1–unk status. In addition, a fresh biopsy was not a requirement for study enrollment and most PD-L1 scoring was done on archival tissue. PD-L1 levels can change over time and might not reflect actual levels at study entry. In addition, before an amendment to the study protocol, seven patients (26%) who received ICI were enrolled. c-Met protein levels were also assessed on archival or fresh tissue; most patients had the archival tissue submitted.

Taken together, these data suggest that, while tolerable, any further evaluation of combination therapy with Teliso-V and ICI would require a stronger a priori hypothesis to select a subgroup with an increased likelihood of benefit from either or both agents.

CRediT Authorship Contribution Statement

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Rybkin, Minal Barve, Todd M. Bauer, Angelo Delmonte, Karen Kelly: Investigation, Writing - review & editing.

Martin Dunbar, Monica Motwani, Apurvasena Parikh, Elysa Noon, Jun Wu: Formal analysis, Data curation, Writing – review & editing.

Vincent Blot: Supervision, Writing - original draft preparation, Writing – review & editing.

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), and 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 after review and approval of a research proposal and statistical analysis plan and execution of a data-sharing agreement. 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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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100262.

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