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ORIGINAL ARTICLE

Results from a phase Ib study of telisotuzumab vedotin in combination with osimertinib in patients with c-Met protein-overexpressing, *EGFR*-mutated locally advanced/metastatic non-small-cell lung cancer (NSCLC) after progression on prior osimertinib

H. Horinouchi[1], B. C. Cho[2], D. R. Camidge[3], K. Goto[4], P. Tomasini[5], Y. Li[6], A. Vasilopoulos[6], P. Brunsdon[6], D. Hoffman[6], W. Shi[6], E. Bolotin[6], V. Blot[6] & J. Goldman[7]*

[1]National Cancer Center Hospital, Tokyo, Japan; [2]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; [3]Department of Medicine, University of Colorado Cancer Center, Aurora, USA; [4]National Cancer Center Hospital East, Kashiwa, Japan; [5]Multidisciplinary Oncology and Therapeutic Innovations Department, Aix Marseille University, APHM, INSERM, CNRS, CRCM, Hôpital Nord, Marseille, France; [6]AbbVie Inc, North Chicago; [7]David Geffen School of Medicine at UCLA, Los Angeles, USA

Available online 11 January 2025

Background: Osimertinib is the standard first-line treatment for advanced epidermal growth factor receptor *(EGFR)*-mutated non-small-cell lung cancer (NSCLC). However, treatment resistance is inevitable and increased c-Met protein expression correlates with resistance. Telisotuzumab vedotin (Teliso-V) is an antibody—drug conjugate that targets c-Met protein overexpression. In this article, we report the results of a phase I/Ib trial evaluating Teliso-V plus osimertinib in patients with NSCLC after progression on osimertinib.

Patients and methods: This multicenter, open-label study (NCT02099058) enrolled patients with advanced *EGFR*-mutated, c-Met protein-overexpressing, non-squamous NSCLC that had progressed on prior osimertinib. Patients received Teliso-V (intravenously, every 2 weeks) plus osimertinib (orally, 80 mg once daily). Teliso-V was evaluated at 1.6 mg/kg in a safety lead-in phase and escalated to 1.9 mg/kg. Dose expansion included both doses. Endpoints included safety and tolerability, pharmacokinetics, objective response rate (ORR), duration of response (DOR), and progression-free survival (PFS).

Results: A total of 38 patients received Teliso-V (1.6 mg/kg, $n = 20$; 1.9 mg/kg, $n = 18$) plus osimertinib and were included in this analysis. No dose-limiting toxicities were observed. Most frequent any-grade treatment-emergent adverse events (TEAEs) were peripheral sensory neuropathy (50%), peripheral edema (32%), and nausea (24%). Most common grade 3/4 TEAEs were anemia (11%) and pulmonary embolism (8%). Five TEAEs led to death; none were reported as being related to Teliso-V or osimertinib. The pharmacokinetic profile of Teliso-V plus osimertinib was similar to Teliso-V monotherapy. After a median follow-up of 7.4 months, the ORR was 50.0% per independent central review (ICR) (DOR not reached), and median PFS per ICR was 7.4 months (95% confidence interval 5.4 months-not reached).

Conclusions: Teliso-V plus osimertinib had promising activity and a manageable safety profile in patients with c-Met protein-overexpressing, *EGFR*-mutated non-squamous NSCLC after progression on osimertinib. This combination has the potential to address an unmet medical need in this patient population.

Key words: advanced NSCLC, c-Met, antibody—drug conjugate, Teliso-V, osimertinib

INTRODUCTION

Patients with non-small-cell lung cancer (NSCLC) are often diagnosed with locally advanced or metastatic disease, with a 5-year survival rate of around 37% and 8%, respectively.[1] The development of treatments that target distinct characteristics, such as specific driver mutations or protein overexpression, has increased the number of therapeutic

**Correspondence to:* Dr Jonathan Goldman, Professor of Medicine, UCLA Hematology & Oncology Director of Clinical Trials in Thoracic Oncology, Associate Director of Drug Development, 2020 Santa Monica Blvd, Suite 600, Santa Monica, CA 90404, USA. Tel: +(310)-829-5471; Fax: +(310)-829-6192
E-mail: jwgoldman@mednet.ucla.edu (J. Goldman).

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options available for patients with advanced NSCLC who harbor certain molecular characteristics. Mutations in the epidermal growth factor receptor protein (*EGFR*) gene are found in ∼19% of patients[2]; notably, the incidence varies greatly by geographic region, with higher mutation rates in Asia (49%) versus other regions (12%-33%).[3] Osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), is the established first-line treatment for patients with *EGFR*-mutated NSCLC, after demonstrating superior efficacy to prior-generation EGFR TKIs in the landmark FLAURA trial.[4] Despite a median progression-free survival (PFS) of nearly 19 months, resistance to treatment is inevitable. c-Met protein (also known as MET protein) overexpression has been associated with resistance to EGFR TKI treatment.[5] c-Met is a transmembrane receptor tyrosine kinase that is encoded by the *MET* proto-oncogene and activated on binding to hepatocyte growth factor (HGF).[6-8] The c-Met/HGF axis is aberrantly activated in many cancers, including NSCLC, through various mechanisms including *MET* genomic amplification, c-Met protein overexpression, and HGF-dependent mechanisms. c-Met protein overexpression is found in ∼50% of *EGFR*-mutated NSCLC tumors after progression on EGFR TKIs, including osimertinib.[9] Patients with disease progression on osimertinib have limited treatment options, mostly chemotherapy and therapeutic antibodies, and currently there are no approved therapies specifically for patients with c-Met protein-overexpressing NSCLC.

Telisotuzumab vedotin (Teliso-V) is a first-in-class antibody—drug conjugate (ADC) comprising the anti-c-Met monoclonal antibody telisotuzumab (ABT-700) and the potent microtubule inhibitor monomethyl auristatin E (MMAE).[10,11] In the phase II LUMINOSITY clinical trial (NCT03539536), Teliso-V monotherapy [1.9 mg/kg intravenously (i.v.) every 2 weeks (Q2W)] showed an encouraging overall response rate (ORR) of 28.6% with a median duration of response (DOR) of 8.3 months in patients with previously treated *EGFR* wild-type, c-Met protein-overexpressing non-squamous NSCLC.[12]

Previously, Teliso-V was combined with the first-generation EGFR TKI erlotinib in patients with *EGFR*-mutated, c-Met protein-overexpressing NSCLC in a phase Ib study (NCT02099058), and an encouraging ORR of 32.1% accompanied by an acceptable safety profile was observed.[13] In this article, we report the safety and efficacy of the arm E of this phase Ib study, evaluating Teliso-V combined with osimertinib in patients with *EGFR*-mutated, c-Met protein-overexpressing NSCLC whose disease had progressed on prior osimertinib.

PATIENTS AND METHODS

Study design and treatment

Arm E of the phase I/Ib multicenter, open-label study (NCT02099058) evaluated Teliso-V plus osimertinib in patients with advanced or metastatic *EGFR*-mutated, c-Met protein-overexpressing NSCLC after progression on prior osimertinib. At the data cut-off of 23 March 2023, 41 patients received Teliso-V (i.v., Q2W) plus osimertinib [orally, 80 mg once daily (QD)]. Teliso-V was evaluated at 1.6 mg/kg Q2W (safety lead-in cohort, $n = 7$), and after reviewing the safety data, escalated to 1.9 mg/kg Q2W (safety evaluation, $n = 3$). Dose-limiting toxicities (DLTs) were evaluated during the dose-escalation phase. In dose expansion, patients received Teliso-V at 1.6 mg/kg ($n = 16$) or 1.9 mg/kg ($n = 15$). Patients received study treatment until disease progression, unacceptable toxicity, or other discontinuation criteria were met. The study was conducted in accordance with the protocol, the International Conference on Harmonisation, Good Clinical Practice Guidelines, and the Declaration of Helsinki. All patients provided written informed consent; the study was approved by the local ethics committee/institutional review board.

Patient population

The study enrolled patients aged ≥18 years with metastatic/locally advanced c-Met protein-overexpressing, *EGFR*-mutated non-squamous NSCLC, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1.[14] Patients' disease must have progressed on prior osimertinib. In the dose-expansion cohorts, patients had received a maximum of two previous lines of therapy, one of which must have contained osimertinib, and no more than one may have contained chemotherapy. The study protocol was amended before expansion to restrict eligible *EGFR*-activating mutations to del19 or L858R mutations (per the osimertinib label), with or without T790 mutation, and no identified mutations conferring resistance to osimertinib. Tumors were assessed for c-Met protein overexpression by central laboratory testing using the immunohistochemistry (IHC) clinical trial assay (CTA) for MET (SP44) (Roche, Rotkreuz, Switzerland); the prespecified cut-off was ≥25% of tumor cells with strong (3+) membrane staining. Patients with *MET* amplification per local testing using an approved test were allowed to enroll before c-Met IHC results. Patients had Eastern Cooperative Oncology Group performance status of 0/1, and adequate bone marrow, renal, and hepatic function. Patients with brain metastases were eligible at least 2 weeks after definitive therapy to all known sites of central nervous system (CNS) disease.

Study assessments

Efficacy. Radiographic tumor assessments (via computed tomography or magnetic resonance imaging) were carried out within 28 days of treatment initiation and once every 8 weeks thereafter until documented disease progression, start of new anticancer therapy, death, or withdrawal of consent. Responses were assessed according to RECIST v1.1 by investigators and independent central review (ICR); efficacy endpoints included ORR, disease control rate (DCR), PFS, and DOR. ORR was defined as the proportion of patients with confirmed complete response (CR) or partial response (PR). DCR was defined as the proportion of patients with confirmed CR, PR, or stable disease (sustained for minimum 14 weeks). PFS was defined as the time from

the first dose of Teliso-V to the first objectively documented disease progression or death, whichever occurred first, or at the date of last disease assessment. DOR was defined as the time from the patient's initial objective response to the first objectively documented disease progression or death, whichever occurred first. The efficacy-assessable population included patients with c-Met protein-overexpressing or *MET*-amplified (by local test) tumors, who received at least one dose of Teliso-V.

Safety. DLTs were assessed during the safety evaluation phase with a monitoring period of 28 days. Adverse events (AEs) were assessed throughout the study and for 60 days following discontinuation of study treatment. AEs were reported by site using the Medical Dictionary for Regulatory Activities system organ class preferred terms as determined by the site investigators; multiple similar terms could be used to describe the same event in a single patient. AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. The safety population included all patients who received any amount of Teliso-V after study enrollment. Safety summaries are descriptive only.

Biomarker analysis. Patients were screened prospectively for c-Met protein expression level, preferably on recent tumor material (formalin-fixed paraffin-embedded) obtained after progression on prior osimertinib. If recent tumor material was not available, archival material was allowed. c-Met protein expression was measured by the IHC CTA for MET (SP44) (Roche). c-Met protein overexpression was defined as $\geq$25% of tumor cells with membrane staining at 3+ intensity (c-Met high, $\geq$50% of tumor cells with 3+ intensity; c-Met intermediate, $\geq$25%-$<$50% of tumor cells with 3+ intensity).

Pharmacokinetics. Serum concentrations of Teliso-V, total antibody, and plasma concentrations of MMAE were collected. Cycle 1 pharmacokinetic parameter values were tabulated for each patient.

Statistical analysis. ORR was assessed using the two-sided 95% confidence intervals (CIs) provided by the Clopper—Pearson (exact) method. DOR and PFS were summarized by the Kaplan—Meier estimates and median DOR and PFS were calculated with two-sided 95% CIs. Safety and tolerability were assessed by evaluating AEs, physical examinations, and changes in laboratory data and vital signs, as well as drug discontinuation or dosing modification due to AEs, for the entire study duration.

RESULTS

At the data cut-off of 23 March 2023, 41 patients were treated with Teliso-V plus osimertinib. Three patients were over-enrolled and not evaluated due to insufficient follow-up. Efficacy and safety results are based on 38 patients treated with Teliso-V 1.6 mg/kg (n = 20) or 1.9 mg/kg (n = 18) Q2W plus osimertinib 80 mg QD. Patients were allocated to specific dose-level cohorts as they opened.

Patient characteristics

Demographics and baseline clinical characteristics are presented in Table 1; 66% (n = 25) of patients were female, 53% (n = 20) were Asian, and 61% (n = 23) were never smokers. Median age was 60 years (range 40-79 years). Seven patients had CNS metastases at baseline (n = 6 in the 1.9-mg/kg dose cohort; n = 1 in the 1.6-mg/kg dose cohort). High c-Met protein overexpression was reported in 64% (21/33) of patients and intermediate c-Met protein

Table 1. Demographics and baseline clinical characteristics (efficacy-assessable population)

	Teliso-V		Total (N = 38)
	1.6 mg/kg Q2W plus osimertinib (n = 20)	1.9 mg/kg Q2W plus osimertinib (n = 18)	
Median age, years (range)	60 (40-79)	59 (41-79)	60 (40-79)
Sex, *n* (%)			
Female	12 (60)	13 (72)	25 (66)
Race, *n* (%)			
Non-Asian	9 (45)	9 (50)	18 (47)
Asian	11 (55)	9 (50)	20 (53)
Tobacco use, *n* (%)			
Former	9 (45)	6 (33)	15 (39)
Never	11 (55)	12 (67)	23 (61)
ECOG performance status, *n* (%)			
0	9 (45)	7 (39)	16 (42)
1	10 (50)	11 (61)	21 (55)
2	1 (5)	0	1 (3)
Brain metastases at baseline			
Yes	1 (5)	6 (33)	7 (18)
No	19 (95)	12 (67)	31 (82)
EGFR mutations, *n* (%)			
Exon 19 deletions	12 (60)	7 (39)	19 (50)
L858R	7 (35)	11 (61)	18 (47)
Other[a]	1 (5)	0	1 (3)
c-Met protein overexpression level, *n* (%)			
Intermediate: 25%-49% 3+	4 (25)	8 (47)	12 (36)
High: 50%-100% 3+	12 (75)	9 (53)	21 (64)
Missing	4	1	5[b]
Prior lines in metastatic setting, *n* (%)			
1	8 (40)	7 (39)	15 (40)
2	6 (30)	10 (56)	16 (42)
$>$2[c]	6 (30)	1 (6)	7 (18)
Prior platinum-based regimen in metastatic setting, *n* (%)			
Yes	11 (55)	7 (39)	18 (47)
No	9 (45)	11 (61)	20 (53)

Note: Percentages calculated on non-missing values.
ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; Q2W, every 2 weeks; Teliso-V, telisotuzumab vedotin.
[a]One patient enrolled with an *EGFR* G719S mutation before the protocol amendment restricting enrollment of mutation (i.e. L858R and del19) per the osimertinib label.
[b]Five of the patients who enrolled on the basis of local *MET* amp testing had later IHC failed or showing $<$25% 3+.
[c]Patients enrolled in the dose escalation were permitted to have received more than two prior lines of therapy.

https://doi.org/10.1016/j.annonc.2025.01.001

overexpression in 36% (12/33) of patients. Five patients enrolled on the basis of local *MET* amplification results had either c-Met IHC missing or <25% 3+. Forty percent, 42%, and 18% of patients had one, two, and more than two prior lines of therapy in the metastatic setting, respectively.

Twenty-seven patients discontinued Teliso-V, 26 patients discontinued osimertinib, and 25 discontinued the study, mostly due to progressive disease ($n = 18/27$; 67%). Total median exposure to Teliso-V was 155 days (range 1.0-981.0± days); the median number of 28-day cycles of Teliso-V was 6.0 (range 1.0-30.0±).

Safety

No treatment-emergent AE (TEAE) met the DLT criteria. All patients experienced one or more TEAE (Table 2); 37 patients (97%) experienced one or more TEAE considered possibly related to Teliso-V. Grade 3/4 TEAEs were experienced by 19 (50%) patients and serious TEAEs by 11 (29%) patients; 12 (32%) and 3 (8%) were considered possibly related to Teliso-V, respectively. TEAEs leading to Teliso-V discontinuation, dose interruption, or dose reduction occurred in 9 (24%) patients [6 (16%) possibly related to Teliso-V], 22 (58%) patients, and 14 (37%) patients, respectively. Of the six patients with Teliso-V-related AEs leading to discontinuation, five experienced peripheral sensory neuropathy with a range of onset of 91-270 days and one patient had an event of hypoalbuminemia on day 15.

The most frequent any-grade TEAEs were peripheral sensory neuropathy ($n = 19$; 50%), peripheral edema ($n = 12$; 32%), nausea ($n = 9$; 24%), anemia ($n = 8$; 21%), and fatigue ($n = 8$; 21%). The most common grade 3/4 TEAEs were anemia in four (11%) patients and pulmonary

Table 2. TEAEs

	Teliso-V		Total ($N = 38$) *n* (%)
	1.6 mg/kg Q2W plus osimertinib ($n = 20$) *n* (%)	1.9 mg/kg Q2W plus osimertinib ($n = 18$) *n* (%)	
Any TEAE	20 (100)	18 (100)	38 (100)
TEAE with reasonable possibility of being related to Teliso-V	20 (100)	17 (94)	37 (97)
Grade 3/4 TEAE	7 (35)	12 (67)	19 (50)
Grade 3/4 TEAE with reasonable possibility of being related to Teliso-V	6 (30)	6 (33)	12 (32)
Treatment-emergent serious AE	3 (15)	8 (44)	11 (29)
Treatment-emergent serious AE with a reasonable possibility of being related to Teliso-V	1 (5)	2 (11)	3 (8)
TEAE meeting DLT criteria	0	0	0

Continued

Table 2. Continued

	Teliso-V		Total ($N = 38$) *n* (%)
	1.6 mg/kg Q2W plus osimertinib ($n = 20$) *n* (%)	1.9 mg/kg Q2W plus osimertinib ($n = 18$) *n* (%)	
TEAE			
Peripheral sensory neuropathy	11 (55)	8 (44)	19 (50)
Peripheral edema	7 (35)	5 (28)	12 (32)
Nausea	2 (10)	7 (39)	9 (24)
Anemia	4 (20)	4 (22)	8 (21)
Fatigue	5 (25)	3 (17)	8 (21)
Hypoalbuminemia	5 (25)	2 (11)	7 (18)
Muscle spasms	4 (20)	3 (17)	7 (18)
Paronychia	5 (25)	2 (11)	7 (18)
Vision blurred	3 (15)	4 (22)	7 (18)
Decreased appetite	4 (20)	2 (11)	6 (16)
Myalgia	2 (10)	4 (22)	6 (16)
Alopecia	3 (15)	2 (11)	5 (13)
Diarrhea	2 (10)	3 (17)	5 (13)
Dizziness	1 (5)	4 (22)	5 (13)
Paresthesia	2 (10)	3 (17)	5 (13)
Back pain	2 (10)	2 (11)	4 (11)
Constipation	1 (5)	3 (17)	4 (11)
Cough	2 (10)	2 (11)	4 (11)
Dry eye	1 (5)	3 (17)	4 (11)
Dyspnea	1 (5)	3 (17)	4 (11)
Hemoptysis	2 (10)	2 (11)	4 (11)
Malignant neoplasm progression	1 (5)	3 (17)	4 (11)
Edema	2 (10)	2 (11)	4 (11)
Peripheral motor neuropathy	2 (10)	2 (11)	4 (11)
Rash	2 (10)	2 (11)	4 (11)
Grade 3/4 TEAE			
Any	7 (35)	12 (67)	19 (50)
Anemia	2 (10)	2 (11)	4 (11)
Pulmonary embolism	0	3 (17)	3 (8)
Deep vein thrombosis	0	2 (11)	2 (5)
Hemoptysis	1 (5)	1 (6)	2 (5)
Hypoalbuminemia	2 (10)	0	2 (5)
Malignant neoplasm progression	0	2 (11)	2 (5)
Peripheral motor neuropathy	1 (5)	1 (6)	2 (5)
Peripheral sensory neuropathy	1 (5)	1 (6)	2 (5)
Pneumonia	1 (5)	1 (6)	2 (5)
Serious TEAE			
Any AE	3 (15)	8 (44)	11 (29)
Malignant neoplasm progression	0	3 (17)	3 (8)
Hemoptysis	1 (5)	1 (6)	2 (5)
Pneumonia	1 (5)	1 (6)	2 (5)
Acute respiratory failure	1 (5)	0	1 (3)
Deep vein thrombosis	0	1 (6)	1 (3)
Diarrhea	1 (5)	0	1 (3)
Hepatic failure	1 (5)	0	1 (3)
Hydrocephalus	0	1 (6)	1 (3)
Peripheral sensorimotor neuropathy	0	1 (6)	1 (3)
Pneumothorax	0	1 (6)	1 (3)
Pulmonary embolism	0	1 (6)	1 (3)
Pulmonary hemorrhage	0	1 (6)	1 (3)

A TEAE is defined as an event that occurs or worsens on or after the first dose of Teliso-V through 60 days after the last dose or to the start of another anticancer therapy.

AE, adverse event; DLT, dose-limiting toxicity; Q2W, every 2 weeks; TEAE, treatment-emergent AE; Teliso-V, telisotuzumab vedotin.

embolism in three (8%) patients (Table 2). Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.01.001, presents the most common any-grade TEAEs possibly related to Teliso-V and serious TEAEs. Grade 3/4 TEAEs possibly related to Teliso-V were anemia ($n = 4$; 11%), peripheral motor neuropathy ($n = 2$; 5%), and peripheral sensory neuropathy ($n = 2$; 5%). There were five TEAEs leading to death: hepatic failure due to progression of disease ($n = 1$), pneumonia ($n = 1$), and tumor progression ($n = 3$). No deaths were reported as being related to Teliso-V or osimertinib. TEAEs and serious TEAEs possibly related to osimertinib are presented in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.01.001.

Incidence and median time to onset of select TEAEs. Using the peripheral neuropathy standard MedDRA Queries (SMQ), 61% of patients reported one or more event, with no difference between the 1.6-mg/kg and 1.9-mg/kg doses. Most events were low grade; five (13%) patients reported grade 3/4 events considered possibly related to Teliso-V. Peripheral neuropathy led to Teliso-V discontinuation, interruption, or dose reduction in 13%, 31.6%, and 28.9% of patients, respectively. The most reported term in the peripheral neuropathy SMQ was peripheral sensory neuropathy (45%). Median time to onset for the first event of peripheral neuropathy was 99 days (range 22-253 days).

Using the interstitial lung disease (ILD) SMQ with broad search terms, three patients (8%) reported events; two events (5.3%) of pneumonitis (deemed possibly related to Teliso-V) occurred in the 1.6-mg/kg cohort, and one event of radiation pneumonitis, not related to study drugs, occurred in the 1.9-mg/kg cohort. These events were low grade and led to Teliso-V interruption or dose reduction in two (5%) and one (3%) patients, respectively. No events in the ILD SMQ with broad terms led to Teliso-V discontinuation or were considered serious. The median time to onset for ILD events was 54 days (range 49-225 days).

Pharmacokinetics

The administration of osimertinib in combination with Teliso-V (1.6 and 1.9 mg/kg Q2W) resulted in Teliso-V conjugate and MMAE exposures comparable to monotherapy. Preliminary pharmacokinetic parameters for Teliso-V conjugate in patients who received Teliso-V 1.6 or 1.9 mg/kg plus osimertinib Q2W are summarized in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.01.001. The estimated half-life of Teliso-V was ∼3 days; concentrations peaked immediately post-infusion [time to maximum observed plasma concentration (C_{max}), 1 h] for both dose levels, with geometric means [coefficient of variation (%CV)] C_{max} of 23.1 μg/ml (31%) and 29.6 (30%) μg/ml and area under the concentration-time curves from time zero to infinity (%CV) of 1510 μg h/ml (31%) and 1950 (33%) μg h/ml for the 1.6-mg/kg and 1.9-mg/kg doses, respectively.

Efficacy

Efficacy outcomes are summarized in Table 3. After a median follow-up of 7.4 months, the ORR was 50.0% (95% CI 33.4% to 66.6%) per ICR and 52.6% (95% CI 35.8% to 69.0%) per investigator assessment, and generally comparable between 1.6-mg/kg and 1.9-mg/kg Teliso-V doses; all responses were confirmed partial responses. The DCR was 76.3% (ICR) and 71.1% (investigator). Per ICR, most patients had a reduction in target lesion size across doses (Figure 1) that was sustained over time (Figure 2); investigator-assessed results are shown in Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.annonc.2025.01.001. Median DOR was not reached (NR) per ICR

Table 3. Efficacy outcomes

	ICR			Inv		
	Teliso-V		Total ($N = 38$)	Teliso-V		Total ($N = 38$)
	1.6 mg/kg Q2W plus osimertinib ($n = 20$)	1.9 mg/kg Q2W plus osimertinib ($n = 18$)		1.6 mg/kg Q2W plus osimertinib ($n = 20$)	1.9 mg/kg Q2W plus osimertinib ($n = 18$)	
Response						
ORR, *n* (%)	10 (50.0)	9 (50.0)	19 (50.0)	11 (55.0)	9 (50.0)	20 (52.6)
(95% CI)	(27.2-72.8)	(26.0-74.0)	(33.4-66.6)	(31.5-76.9)	(26.0-74.0)	(35.8-69.0)
Confirmed PR	10 (50.0)	9 (50.0)	19 (50.0)	11 (55.0)	9 (50.0)	20 (52.6)
DCR, *n* (%)	15 (75.0)	14 (77.8)	29 (76.3)	13 (65.0)	14 (77.8)	27 (71.1)
(95% CI)	(50.9-91.3)	(52.4-93.6)	(59.8-88.6)	(40.8-84.6)	(52.4-93.6)	(54.1-84.6)
DOR						
Patients with events, *n* (%)	—	3 (33.3)	3 (15.8)	3 (27.3)	6 (66.7)	9 (45.0)
Patients censored, *n* (%)	10 (100)	6 (66.7)	16 (84.2)	8 (72.7)	3 (33.3)	11 (55.0)
Median DOR, months (95% CI)	—	11.0 (3.7, NR)	— (5.6, NR)	27.7 (3.7, NR)	7.4 (3.7-12.9)	8.0 (5.6, NR)
PFS						
Patients with events, *n* (%)	7 (35.0)	10 (55.6)	17 (44.7)	11 (55.0)	13 (72.2)	24 (63.2)
Patients censored, *n* (%)	13 (65.0)	8 (44.4)	21 (55.3)	9 (45.0)	5 (27.8)	14 (36.8)
Median PFS, months (95% CI)	31.1 (1.9, NR)	6.8 (4.7, NR)	7.4 (5.4, NR)	7.4 (3.5, NR)	5.6 (5.3-9.2)	6.8 (5.3, 9.2)

CI, confidence interval; DCR, disease control rate; DOR, duration of response; ICR, independent central review; Inv, investigator assessment; NR, not reached; ORR, objective response rate; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; Teliso-V, telisotuzumab vedotin.

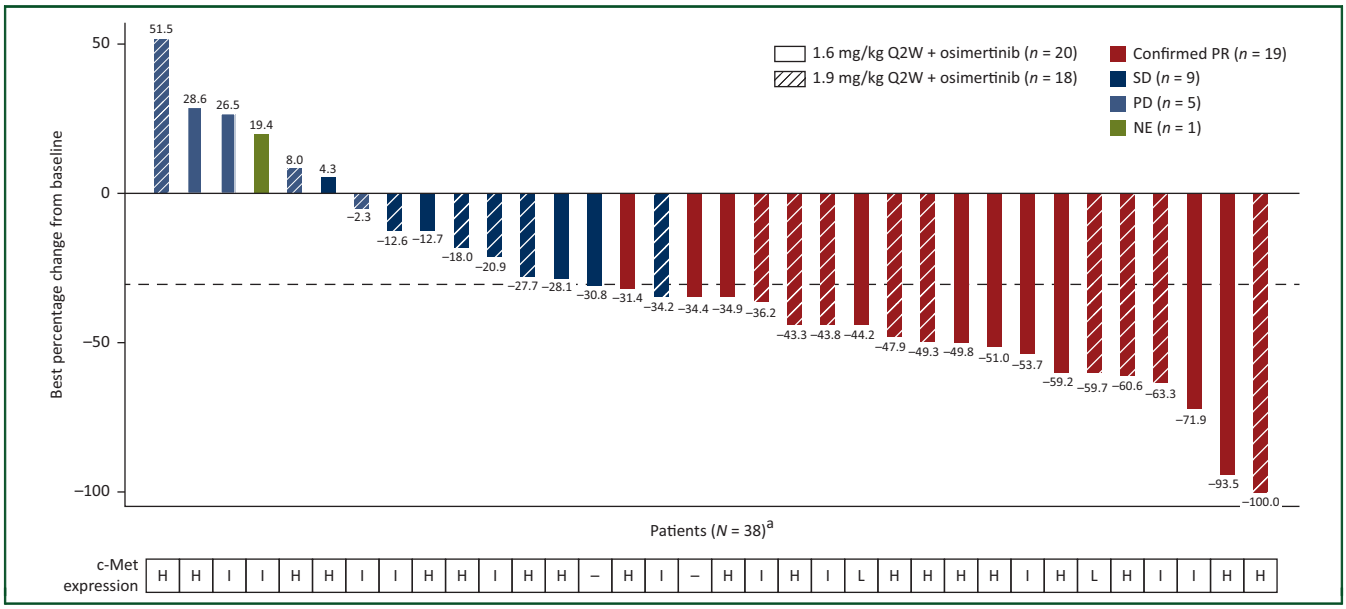

Figure 1. Best percentage change in target lesion size from baseline per ICR.
H, high; I, intermediate; ICR, independent central review; L, low; NE, not evaluable; PD, progressive disease; PR, partial response; Q2W, every 2 weeks; SD, stable disease.
[a]Data missing for four patients: one patient without post-baseline tumor assessment, and ICR did not confirm the presence of target lesion at baseline for three patients.
H = IHC staining ≥50%, 3+; I = IHC staining ≥25%-<50%, 3+; L = <25%, 3+.

and 8.0 months (95% CI 5.6 months-NR) per investigator assessment (Table 3). Median PFS was 7.4 months (95% CI 5.4 months-NR) and 6.8 months (95% CI 5.3-9.2 months) per ICR and investigator, respectively.

ORRs and DCRs were generally comparable between patients with high versus intermediate c-Met protein overexpression, and for patients whose tumors harbored *EGFR* L858R or del19 (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.01.001). ORRs and DCRs were also generally similar in patients who had received one, two, or more than two lines of prior anticancer therapy, and in patients who had received prior platinum therapy in the metastatic setting versus platinum-naive patients (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.01.001). ORR and DCR were generally similar between groups of patients whose first prior regimen containing osimertinib lasted 0-6 months, 6-12 months, or >12 months (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.01.001). Some patients entered the study and started receiving Teliso-V plus osimertinib at the time of progression on their prior osimertinib treatment, while others had an osimertinib treatment interruption, often while receiving a different therapy such as platinum-based chemotherapy. The ORR/DCR per ICR reported for patients who entered the study <1 month after their prior

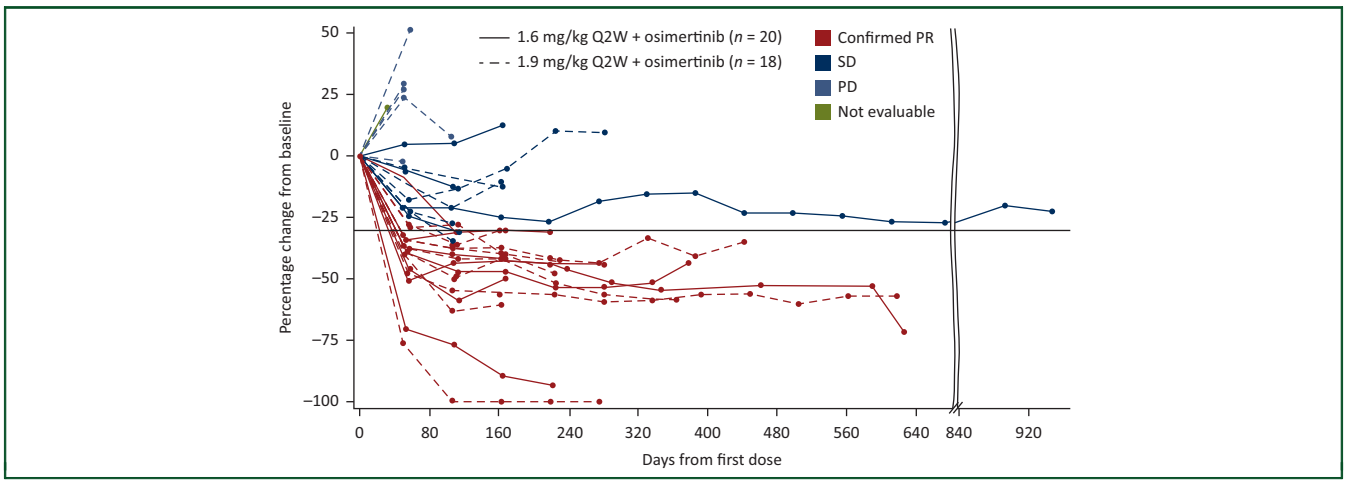

Figure 2. Change in target lesion size over time per ICR.[a]
ICR, independent central review; PD, progressive disease; PR, partial response; Q2W, every 2 weeks; SD, stable disease.
[a]Data missing for four patients: one patient without post-baseline tumor assessment, and ICR did not confirm the presence of target lesion at baseline for three patients.

Table 4. Efficacy by end of osimertinib treatment

	ICR		Inv	
	Time since end of last prior osimertinib treatment to first dose		Time since end of last prior osimertinib treatment to first dose	
	<1 month ($n = 19$)	≥1 month ($n = 16$)	<1 month ($n = 19$)	≥1 month ($n = 16$)
ORR, *n* (%)	9 (47.4)	9 (56.3)	7 (36.8)	12 (75)
(95% CI)	(24.4-71.1)	(29.9-80.2)	(16.3-61.6)	(47.6-92.7)
DCR, *n* (%)	14 (73.7)	14 (87.5)	12 (63.2)	14 (87.5)
(95% CI)	(48.8-90.9)	(61.7-98.4)	(38.4-83.7)	(61.7-98.4)

CI, confidence interval; DCR, disease control rate; ICR, independent central review; Inv, investigator assessment; ORR, objective response rate.

osimertinib treatment was 47.4%/73.7% and 56.3%/87.5% for patients with an osimertinib treatment interruption (time since end of last osimertinib treatment to first dose of study drugs >1 month) (Table 4). When the investigator assessed, the ORR/DCR values were 36.8%/63.2% for those who entered the study <1 month after their prior osimertinib treatment and 75.0%/87.5% for patients with an osimertinib treatment interruption.

In patients with no brain metastases at baseline, the ORR was 61.3% (ICR and investigator); in the seven patients with baseline brain metastases, the ORR was 0% per ICR or 14.3% per investigator (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.01.001). The DCR was 83.9% (ICR) and 74.2% (investigator) for patients without baseline brain metastases and 42.9% (ICR) and 57.1% (investigator) for those with baseline brain metastases.

DISCUSSION

Osimertinib is the first-line standard of care for patients with identified L858R or del19 *EGFR*-mutated non-squamous advanced NSCLC.[4,15] It has demonstrated good efficacy with high intracranial activity,[16,17] and is well tolerated. However, tumors invariably progress due to the emergence of EGFR-dependent or -independent resistance mechanisms.[18] Therapeutic options post-osimertinib progression are currently mostly limited to chemotherapy, with a platinum-based doublet in the second line and docetaxel in the third line. Recently reported trials suggest a potential role for amivantamab[19] and for ADCs such as patritumab.[20] c-Met protein overexpression (≥25% of tumor cells with 3+ c-Met staining) is found in ∼50% of patients whose disease progresses on EGFR TKIs. In this phase Ib study, we evaluated the dual targeting of c-Met and *EGFR* in patients whose tumors have *EGFR* mutations and c-Met protein overexpression after progression on osimertinib, using Teliso-V combined with osimertinib. The targeted dose of Teliso-V was 1.9 mg/kg Q2W, in line with the recommended phase II monotherapy dose. An additional expansion at 1.6 mg/kg was later added for dose optimization exploration. As previously reported, Teliso-V monotherapy in the *EGFR*-mutation-positive population demonstrated an ORR of 11.6%.[21] The heterogeneous nature of progressive disease suggests that osimertinib-sensitive clones may remain; thus, continuing osimertinib beyond progression may provide benefit. Furthermore, mutated *EGFR* signaling results in the disruption of cellular microtubule networks and lysosomal trafficking, which were restored by EGFR TKI.[22,23] Teliso-V's cytotoxic activity depends on functional microtubule networks to internalize and traffic the ADC to the lysosomes and release the microtubule inhibitor payload. Further preclinical research is ongoing to help elucidate the mechanism of action of the combination.

The tolerability of the combination was acceptable, with no new safety concerns compared with Teliso-V or osimertinib monotherapy, and patients received a median of six 28-day treatment cycles (maximum of 30 cycles at the time of the database lock). AEs were typically associated with the MMAE payload, such as peripheral neuropathy or ocular symptoms [particularly blurred vision (18%) or dry eye (11%)], or associated with c-Met targeting, such as peripheral edema or hypoalbuminemia. Notably, the median time to onset of peripheral neuropathy was 99 days, longer than that reported for chemotherapy-associated peripheral neuropathy.[24] AEs were primarily managed through interruptions and dose reductions and led to Teliso-V discontinuation in nine (24%) patients [Teliso-V-related AE in six (16%) patients], and osimertinib discontinuation in 16% of the patients. Two patients reported cases of pneumonitis possibly related to Teliso-V and one patient reported a case of radiation pneumonitis not related to study drug. These events were low grade and non-serious. Overall, the safety profile of the combination was comparable for Teliso-V at 1.6 and 1.9 mg/kg Q2W.

The pharmacokinetic profile of Teliso-V in the combination was similar to that of Teliso-V monotherapy for both the 1.6-mg/kg and 1.9-mg/kg doses.

Teliso-V plus osimertinib showed promising efficacy with a robust response rate that was sustained over time in most patients. Compared with responses using standard-of-care platinum-based chemotherapy in this setting, Teliso-V plus osimertinib elicited an ORR of 50% (by ICR) or 52.6% (by investigator), whereas a platinum-based doublet demonstrated ORR between 31%[25] and 25%.[26] The median DOR of 8 months per investigator (NR per ICR) and the median PFS of 7.4 months per ICR and 6.8 months per investigator are also very encouraging, especially compared with the standard-of-care platinum-based chemotherapy in this setting.[26] Efficacy was comparable between the two doses of Teliso-V. Recent reports of second-line amivantamab and chemotherapy demonstrated a response rate of 64% and a median PFS of 6.3 months, suggesting there may be a future role for both amivantamab and Teliso-V in refractory *EGFR*-mutated NSCLC.[19]

These data suggest that an osimertinib rechallenge effect is unlikely to be the sole explanation for the efficacy of the combination. Indeed, patients who entered this combination trial <1 month after the end of their prior osimertinib treatment had a similar response to patients who entered the trial >1 month after the end of their prior osimertinib (47.4% versus 56.3%). Responses were also comparable

between patients who received prior osimertinib treatment that lasted >12 months (47.6%), 6-12 months (66.7%), or <6 months (50%), indicating the combination is effective even in patients whose disease could be considered refractory to first-line osimertinib treatment. Altogether, these results suggest that Teliso-V and osimertinib therapy may result in more than additive activity.

The efficacy of Teliso-V plus osimertinib was similar across *EGFR* mutations, levels of c-Met protein overexpression, number of prior lines of therapy, or use of prior systemic platinum-based chemotherapy, suggesting that this regimen could be utilized in a wide range of patients across different line settings after progression on osimertinib. Among a small study population, patients with baseline brain metastases who were eligible after definitive therapy did not respond as well as patients with no CNS disease. There was no discernible pattern in the site of progression, whether in the CNS or other sites. This lack of observed response may indicate that these patients have different, more aggressive disease; alternatively, this may simply reflect the small sample size.

Other strategies targeting the MET pathway in *EGFR*-mutated NSCLC after progression on osimertinib are being explored.[27] Recent results from the phase Ib TATTON trial (NCT02143466) studying the combination of the MET TKI savolitinib in combination with osimertinib showed encouraging results.[28] The phase II Lung-MAP trial (NCT05642572) is studying the activity of osimertinib with the MET TKI capmatinib. Unlike Teliso-V, which shows activity in c-Met-protein-overexpressing tumors regardless of underlying *MET* gene alterations,[29] MET TKIs' antitumor activity is mainly restricted to tumors with *MET* gene alterations, particularly METex14 or *MET* gene amplification.[30,31] In the *EGFR*-mutated NSCLC population experiencing progression on osimertinib, c-Met protein overexpression is seen in 50%, compared with *MET* amplification seen in 15%-20% of patients,[32] suggesting that Teliso-V plus osimertinib could be an option for a larger number of patients.

In conclusion, Teliso-V and osimertinib therapy demonstrated response rates, DOR, and median PFS exceeding those observed with current standard-of-care therapies. The combination has the potential to address an unmet medical need for patients with advanced or metastatic c-Met protein-overexpressing, *EGFR*-mutated non-squamous NSCLC after progression on osimertinib.

ACKNOWLEDGEMENTS

AbbVie and the authors thank all the trial investigators and the patients who participated in this clinical trial. We would also like to thank Shawn Jeffries, PhD, for his leadership and support of this study and the Teliso-V program, and his commitment to bringing new therapies to patients with lung cancer. Medical writing support was provided by Delyth Eickermann, PhD, from Aptitude Health, The Hague, The Netherlands, and funded by AbbVie.

FUNDING

This work was supported by AbbVie, Inc. (no grant number), which funded the study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the manuscript. All authors had access to relevant data and participated in the drafting, review, and approval of this manuscript. No honoraria or payments were made for authorship.

DISCLOSURE

HH: research funding: AbbVie, MSD, Chugai/Roche, Daiichi Sankyo, Janssen, Genomic Health; honoraria: AstraZeneca, MSD, Lilly, BMS, Ono, Janssen, Kyowa Kirin, Nihonkayaku. BCC: royalties: Champions Oncology, Crown Bioscience, Imagen; research funding: MOGAM Institute, LG Chem, Oscotec, Interpark Bio Convergence Corp., GI Innovation, GI Cell, Abion, AbbVie, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Champions Oncology, CJ Bioscience, CJ Blossom Park, Cyrus, Dizal Pharma, Genexine, Janssen, Lilly, MSD, Novartis, Nuvalent, Oncternal, Ono, Regeneron, Dong-A ST, Bridge Biotherapeutics, Yuhan, ImmuneOncia, Illumina, Kanaph Therapeutics, Therapex, J INTS BIO, Hanmi, CHA Bundang Medical Center; consulting: Abion, BeiGene, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, BMS, CJ, CureLogen, Cyrus Therapeutics, Ono, Onegene Biotechnology, Yuhan, Pfizer, Eli Lilly, GI Cell, Guardant, HK Inno-N, Imnewrun Biosciences Inc., Janssen, Takeda, MSD, Janssen, MedPacto, Blueprint Medicines, Rand Bioscience, Hanmi; employment: Yonsei University Health System; advisory boards: Kanaph Therapeutics Inc., Bridgebio Therapeutics, Cyrus Therapeutics, Guardant Health, Oscotec Inc.; speaker: ASCO, AstraZeneca, Guardant, Roche, ESMO, IASLC, Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, MSD, The Chinese Thoracic Oncology Society, Pfizer; stocks/shares: TherCanVac Inc., Gencurix Inc., Bridgebio Therapeutics, Kanaph Therapeutics Inc., Cyrus Therapeutics, Interpark Bio Convergence Corp., J INTS BIO; founder of DAAN Biotherapeutics; member of the board of directors: Interpark Bio Convergence Corp., J INTS BIO. DRC: consulting or advisory role: AbbVie, Apollomics, AstraZeneca, Daiichi Sankyo, Elevation, Kestrel, Nuvalent, Seattle Genetics, Takeda, Turning Point, Amgen, Anchiano, BioThera, BMS, Eisai, EMD Serono, Eli Lilly, GSK, Helsinn, Janssen, OnKure, Mersana, Pfizer, Qilu, Roche, Sanofi, CBT Pharmaceuticals, G1 Therapeutics, Blueprint, Achilles, BeyondSpring, Archer, Medtronic, Ribon; research funding: Inivata; other relationships (company-sponsored trials at institution): AbbVie, AstraZeneca, Dizal, Inhibrx, Karyopharm, Pfizer, Phosplatin, PsiOxus, Rain, Roche/Genentech, Seattle Genetics, Takeda, Turning Point. PT: research funding: Roche, Janssen; expert testimony: AstraZeneca, Roche, BMS, AbbVie, Johnson & Johnson, Takeda. JG: research funding: AbbVie, AstraZeneca; honoraria: AbbVie,

AstraZeneca. VB, WS, DH, PB, AV, EB, YL: employment by AbbVie and may own stocks or options. KG has declared no conflicts of interest.

DATA SHARING

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis datasets), as well as other information (e.g. protocols, clinical study reports, or analysis plans), 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, statistical analysis plan (SAP), and execution of a data-sharing agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. 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.abbvieclinicaltrials.com/hcp/data-sharing/.

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