Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein–Overexpressing Advanced Nonsquamous *EGFR*-Wildtype Non–Small Cell Lung Cancer in the Phase II LUMINOSITY Trial

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DOI https://doi.org/10.1200/JCO.24.00720

ABSTRACT

PURPOSE Telisotuzumab vedotin (Teliso-V) is a c-Met–directed antibody-drug conjugate with a monomethyl auristatin E cytotoxic payload. The phase II LUMINOSITY trial (ClinicalTrials.gov identifier: NCT03539536) aimed to identify the optimal c-Met protein–overexpressing non–small cell lung cancer (NSCLC) population for treatment with Teliso-V (stage I) and expand the selected group for efficacy evaluation (stage II). Stage II enrolled patients with nonsquamous epidermal growth factor receptor (*EGFR*)-wildtype NSCLC.

METHODS Eligible patients had locally advanced/metastatic c-Met protein–overexpressing NSCLC and ≤2 previous lines of therapy (including ≤1 line of systemic chemotherapy). c-Met protein overexpression in nonsquamous *EGFR*-wildtype NSCLC was defined as ≥25% tumor cells with 3+ staining (high [≥50% 3+]; intermediate [≥25%–<50%]). Teliso-V was administered at 1.9 mg/kg once every 2 weeks. The primary end point was overall response rate (ORR) by independent central review.

RESULTS In total, 172 patients with nonsquamous *EGFR*-wildtype NSCLC received Teliso-V in stages I and II. ORR was 28.6% (95% CI, 21.7 to 36.2; c-Met high, 34.6% [95% CI, 24.2 to 46.2]; c-Met intermediate, 22.9% [95% CI, 14.4 to 33.4]). The median duration of response was 8.3 months (95% CI, 5.6 to 11.3; c-Met high, 9.0 [95% CI, 4.2 to 13.0]; c-Met intermediate: 7.2 [95% CI, 5.3 to 11.5]). The median overall survival was 14.5 months (95% CI, 9.9 to 16.6; c-Met high, 14.6 [95% CI, 9.2 to 25.6]; c-Met intermediate, 14.2 [95% CI, 9.6 to 16.6]). The median progression-free survival was 5.7 months (95% CI, 4.6 to 6.9; c-Met high, 5.5 [95% CI, 4.1 to 8.3]; c-Met intermediate: 6.0 [95% CI, 4.5 to 8.1]). Most common any-grade treatment-related adverse events (AEs) were peripheral sensory neuropathy (30%), peripheral edema (16%), and fatigue (14%); the most common grade ≥3 AE was peripheral sensory neuropathy (7%).

CONCLUSION Teliso-V was associated with durable responses in c-Met protein–overexpressing nonsquamous *EGFR*-wildtype NSCLC, especially in those with high c-Met. AEs were generally manageable.

ACCOMPANYING CONTENT

Appendix
Data Sharing Statement
Protocol

Accepted May 30, 2024
Published June 6, 2024

J Clin Oncol 42:3000-3011

View Online Article

INTRODUCTION

The *MET* proto-oncogene encodes the c-Met protein (also known as MET protein and hepatocyte growth factor receptor), a receptor tyrosine kinase that mediates cell proliferation, survival, and angiogenesis[1-3] and can be dysregulated in non–small cell lung cancer (NSCLC). Aside from any role in acquired resistance to targeted therapies, primary *MET* gene dysregulation can occur through amplification or mutation in approximately 5% and approximately 2%-4%

CONTEXT

Key Objective

To identify the c-Met protein–overexpressing non–small cell lung cancer (NSCLC) population best suited for telisotuzumab vedotin (Teliso-V) therapy in the second- or third-line setting and to further evaluate Teliso-V efficacy and safety in the selected population.

Knowledge Generated

Teliso-V was associated with durable responses in patients with c-Met protein–overexpressing nonsquamous epidermal growth factor receptor (*EGFR*)-wildtype NSCLC, especially in those with high c-Met protein expression. Adverse events were generally manageable.

Relevance *(T.E. Stinchcombe)*

The activity of Teliso-V in patients with nonsquamous EGFR-wildtype NSCLC with MET protein–overexpression informs an ongoing phase III trial of Teliso-V compared with docetaxel in this patient population. The squamous and nonsquamous EGFR mutant cohorts were closed based in the futility criteria.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

of patients with NSCLC, respectively.[4] c-Met tyrosine kinase inhibitors have been successfully developed for patients with *MET* exon 14 skipping mutations and are in development for *MET* amplification.[5,6] Approximately 25%-39% of patients with NSCLC have tumors that overexpress the c-Met protein, which may coexist with *MET* genomic alterations. Overexpression prevalence is approximately 25% in patients with nonsquamous epidermal growth factor receptor (*EGFR*)-wildtype NSCLC.[7,8] c-Met protein overexpression is a negative prognostic factor for survival in early and advanced NSCLC.[4,9-11] Although numerous clinical trials are evaluating targeted therapies against cancers with *MET* genomic alterations, there are currently no therapies available to specifically target c-Met protein overexpression.

Telisotuzumab vedotin (Teliso-V) is a first-in-class c-Met–directed antibody-drug conjugate comprising the monoclonal antibody telisotuzumab conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE) via a cleavable dipeptide linker.[12] Teliso-V uses c-Met protein overexpression as a biomarker to target the cytotoxic payload to tumor cells and has shown promising activity and an acceptable safety profile in patients with c-Met protein–overexpressing NSCLC in a phase I study.[12,13]

The phase II LUMINOSITY trial evaluated the efficacy and safety of Teliso-V in patients with c-Met protein–overexpressing locally advanced/metastatic NSCLC. The aim was to identify the population best suited for Teliso-V in the second or third line (stage I) and to further assess the efficacy and safety in the selected population (stage II). The c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC population was selected for further evaluation in stage II. Primary efficacy and safety analyses are reported.

METHODS

Trial Design

LUMINOSITY (ClinicalTrials.gov identifier: NCT03539536) is a phase II, multicenter, nonrandomized, two-stage study (Fig 1). Stage I enrolled patients into three cohorts defined by histology and *EGFR* mutation status: (1) c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC, (2) c-Met protein–overexpressing, nonsquamous *EGFR*-mutant NSCLC, and (3) c-Met protein–overexpressing squamous NSCLC. By design, stage II enrolled patients in specific group(s) meeting expansion criteria in stage I; patients with c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC were enrolled in stage II. c-Met protein overexpression was measured by immunohistochemistry (clinical trial assay for MET [SP44] [Roche]). For the nonsquamous cohorts, on the basis of correlative analysis of previous phase I efficacy data, overexpression was defined as ≥25% of tumor cells with membrane staining at 3+ intensity (c-Met high, ≥50% of tumor cells with 3+ intensity; c-Met intermediate, ≥25% to <50% of tumor cells with 3+ intensity). In the squamous cohort, where c-Met protein is expressed at a much lower level than in nonsquamous NSCLC, c-Met protein overexpression was defined as 75% of tumor cells with membrane staining at any intensity by immunohistochemistry to ensure approximately 25% of screened patients would be eligible. Prescreening for tumor c-Met protein overexpression on archival or postprogression tissue could occur before the initiation of the screening period. Teliso-V was dosed at 1.9 mg/kg intravenously once every 2 weeks in stages I and II. After completion of stage II global enrollment, a China extension cohort with Teliso-V dosed at 1.9 mg/kg once every 2 weeks was added to meet local regulatory requirements,

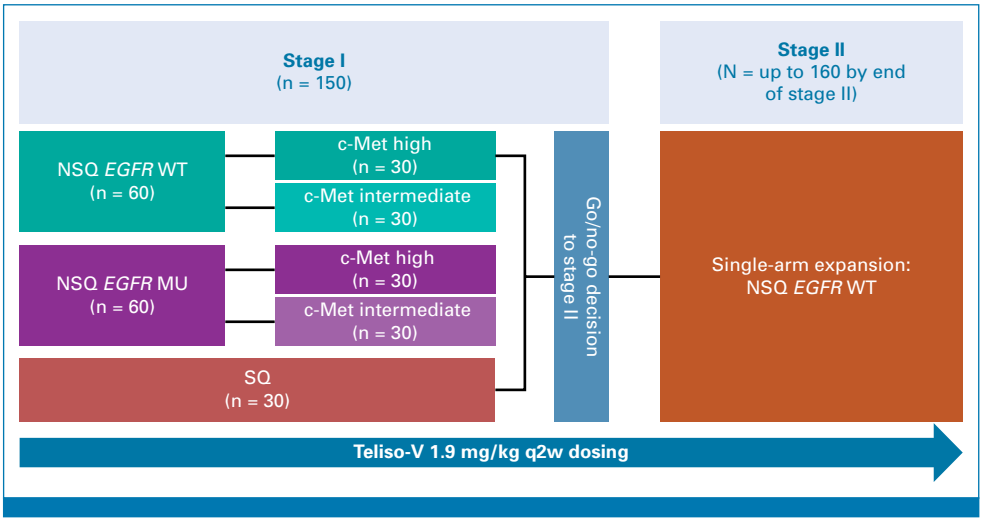

FIG 1. Study design. The nonsquamous *EGFR*-wildtype cohort was expanded in stage II. A stage II China extension cohort planned to enroll up to 12 patients was added after the global stage II enrollment was complete. In addition, a supplementary cohort evaluating Teliso-V at 1.6 mg/kg q2w in up to approximately 20 patients with nonsquamous *EGFR*-wildtype NSCLC was added after completion of stage II enrollment. *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; MU, mutant; OE, overexpressing; q2w, once every 2 weeks; SQ, squamous; Teliso-V, telisotuzumab vedotin; WT, wildtype.

and another supplementary cohort evaluating Teliso-V at 1.6 mg/kg once every 2 weeks was added, in accordance with the US Food and Drug Administration's Project Optimus initiative focused on dose optimization. Data from the 1.6-mg/kg once every 2 weeks cohort will be reported separately. All patients received Teliso-V until disease progression, intolerable toxicity, or other study discontinuation criteria were met.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonization and was approved by regulatory and independent ethics committees/institutional review boards at each site. All patients provided written informed consent before any study procedures were performed.

Patients

Adults (age ≥18 years) with locally advanced/metastatic, c-Met protein–overexpressing, nonsquamous NSCLC with known *EGFR* status or squamous cell NSCLC were enrolled. c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC was required for stage II. Other key eligibility criteria included Eastern Cooperative Oncology Group performance status 0-1, measurable disease per RECIST v1.1, and ≤2 lines of previous systemic therapy in the locally advanced/metastatic setting, including cytotoxic chemotherapy (maximum one line), immunotherapy, and therapy targeting driver gene alterations (if eligible). Patients must not have received previous radiation therapy to the lungs within 6 months of the first dose of Teliso-V. Patients with brain metastases were eligible if the metastases received definitive treatment and were stable. Exclusion criteria included history of interstitial lung disease (ILD) or pneumonitis that required systemic steroid treatment (Appendix Table A1, online only).

Outcomes and Assessments

The primary end point was overall response rate (ORR) by independent central review (ICR) per RECIST v1.1.[14] Secondary end points were duration of response (DOR), disease control rate (DCR; per RECIST v1.1), progression-free survival (PFS), and overall survival (OS). Tumor assessments (computed tomography or magnetic resonance imaging) were performed at baseline and approximately every 6 weeks increasing to every 8 weeks after 1 year and every 12 weeks after 2 years. Safety and tolerability were assessed by evaluating adverse events (AEs) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. AEs were recorded and graded from initial drug administration until 30 days after last administration of Teliso-V. AE terms are as reported by the investigative site according to Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Cases of suspected ILD as reported by the investigative site were also reviewed retrospectively by an adjudication committee and classified as ILD or non-ILD; cases reviewed included investigative site-reported AEs of pneumonitis and ILD, among other related preferred terms.

Statistical Analysis

The planned sample size for stage I was up to 150 patients across the three cohorts and five groups defined by

histology, *EGFR* mutation status, and c-Met protein expression level (Fig 1), with up to 30 efficacy-evaluable patients with measurable disease per ICR per group. This sample size was to provide good operating characteristics for go/no-go decision making at stage I for each cohort and group on the basis of comprehensive evaluation via simulations under various scenarios. In stage I, efficacy was evaluated in interim analyses conducted after approximately every additional 30 c-Met protein–overexpressing, efficacy-evaluable patients were enrolled. The ORR (the proportion of patients with a confirmed complete response or a confirmed partial response) for each group was assessed using the Bayesian posterior probability of success, defined as the posterior probability of the ORR exceeding 25%; if this fell below 0.10, the group was considered futile; if this went above 0.70, the group was expanded.

The selected population from stage I was to be expanded to a planned sample size of up to 160 efficacy-evaluable patients enrolled globally by the end of stage II to provide approximately 84% power to rule out a 25% ORR by the lower limit of 95% CI of the estimated ORR at study end, assuming the true ORR for Teliso-V to be 36%. After completion of global enrollment, a stage II China extension cohort to enroll up to approximately 12 patients was opened. Primary analysis occurred 6 months after the first scheduled postbaseline tumor assessment for the last patient enrolled globally in stage II. All patients who received ≥1 dose of Teliso-V at 1.9 mg/kg once every 2 weeks were included in safety analyses. All dosed patients with c-Met protein overexpression enrolled globally in stage I and II or enrolled in the China extension cohort with ≥7.5 months of follow-up after first dose were included in the efficacy analyses.

The primary end point of ORR was summarized along with the two-sided 95% exact CI. Time-to-event end points, including DOR, PFS, and OS, were summarized by median time corresponding to the 50% event probability with two-sided 95% CIs estimated using the Brookmeyer and Crowley method.[15] Six-month PFS and 12-month OS were estimated using Kaplan-Meier methodology, along with 95% CI calculated with the SE derived from the Greenwood formula.[16] Patients without any postbaseline tumor assessments were considered nonresponders for ORR and DOR. For patients who are progression-free and alive, PFS was censored at the date of last tumor assessment. For patients without any postbaseline tumor assessments who did not die, PFS was censored at the day of the first dose. For patients with no reported death, OS was censored at the last date the patient was known to be alive.

RESULTS

Patients

Across all cohorts, 3,181 patients were prescreened/screened; of the 2,911 (91.5%) patients who did not enter the study, 2,531 did not meet eligibility criteria (79.6%), most commonly because of lack of c-Met protein overexpression. In total, 1,954 evaluable samples were submitted for eligibility prescreening of patients with nonsquamous *EGFR*-wildtype NSCLC (archival tissue, n = 1,628; postprogression tissue, n = 326); 23.6% were c-Met protein–overexpressing (≥25% 3+ by IHC; archival tissue, 22.1%; postprogression tissue, 31.6%) and 13.5% were c-Met high (≥50% 3+ by IHC; archival tissue, 12.5%; postprogression tissue, 18.1%). Among 28 patients with repeat biopsies available, >90% had the same or higher c-Met overexpression status on repeat biopsy (Appendix 1).

In total, 270 patients enrolled and received ≥1 dose of Teliso-V; 245 received Teliso-V at 1.9 mg/kg once every 2 weeks. There were 172 patients with nonsquamous *EGFR*-wildtype NSCLC dosed at 1.9 mg/kg once every 2 weeks (c-Met high, n = 84; c-Met intermediate, n = 84; c-Met negative, n = 4); 161 were evaluable for efficacy at the primary analysis (Fig 2). Baseline demographics and disease characteristics for patients with nonsquamous *EGFR*-wildtype NSCLC are shown in Table 1. Patients were predominantly male, White, and current/former tobacco users. The median number of previous therapies was 1 (range, 1-3); 98% of patients had previous platinum-based therapy, and 82% had received an immune checkpoint inhibitor. Appendix Table A2 summarizes the data for the nonsquamous *EGFR*-mutated NSCLC (n = 45) and squamous NSCLC (n = 28) cohorts that did not proceed to stage II.

At data cutoff (September 28, 2023), 159 (92.4%) of 172 patients with nonsquamous *EGFR*-wildtype NSCLC had discontinued study drug; the most common primary reasons were progressive disease per RECIST v1.1 (47.7%) and AEs (27.9%). The median duration of Teliso-V exposure was 19.7 weeks (range, 0.1-104), and 35 (20.3%) of 172 patients received ≥20 doses of Teliso-V. In total, 66 patients (41.0%) received ≥1 poststudy systemic therapy; most common were microtubule inhibitors (32 patients, 19.9%), targeted therapies (17 patients, 10.6%), and platinum-based chemotherapy (16 patients, 9.9%).

Efficacy

The nonsquamous *EGFR*-wildtype NSCLC cohort met protocol-specified criteria for expansion at Interim Analysis 3 (Appendix 1). The squamous and nonsquamous *EGFR*-mutant cohorts met protocol-specified criteria for futility at Interim Analyses 3 and 4, respectively (Appendix 1); ORRs for each cohort were 10.7% (95% CI, 2.3 to 28.2) and 11.4% (95% CI, 3.8 to 24.6), respectively. Detailed efficacy data for the squamous and nonsquamous *EGFR*-mutant cohorts are shown in Appendix Table A3 and Appendix Figs A1 and A2.

At the primary analysis, among patients with c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC, ORR per ICR was 34.6% (95% CI, 24.2 to 46.2) for c-Met high, 22.9% (95% CI, 14.4 to 33.4) for c-Met intermediate, and 28.6% (95% CI, 21.7 to 36.2) for c-Met overexpression total (Table 2). ORR per investigator assessment was similar (Appendix Table A4). Most patients exhibited reduction in tumor size (Fig 3A). The median time to onset of response per

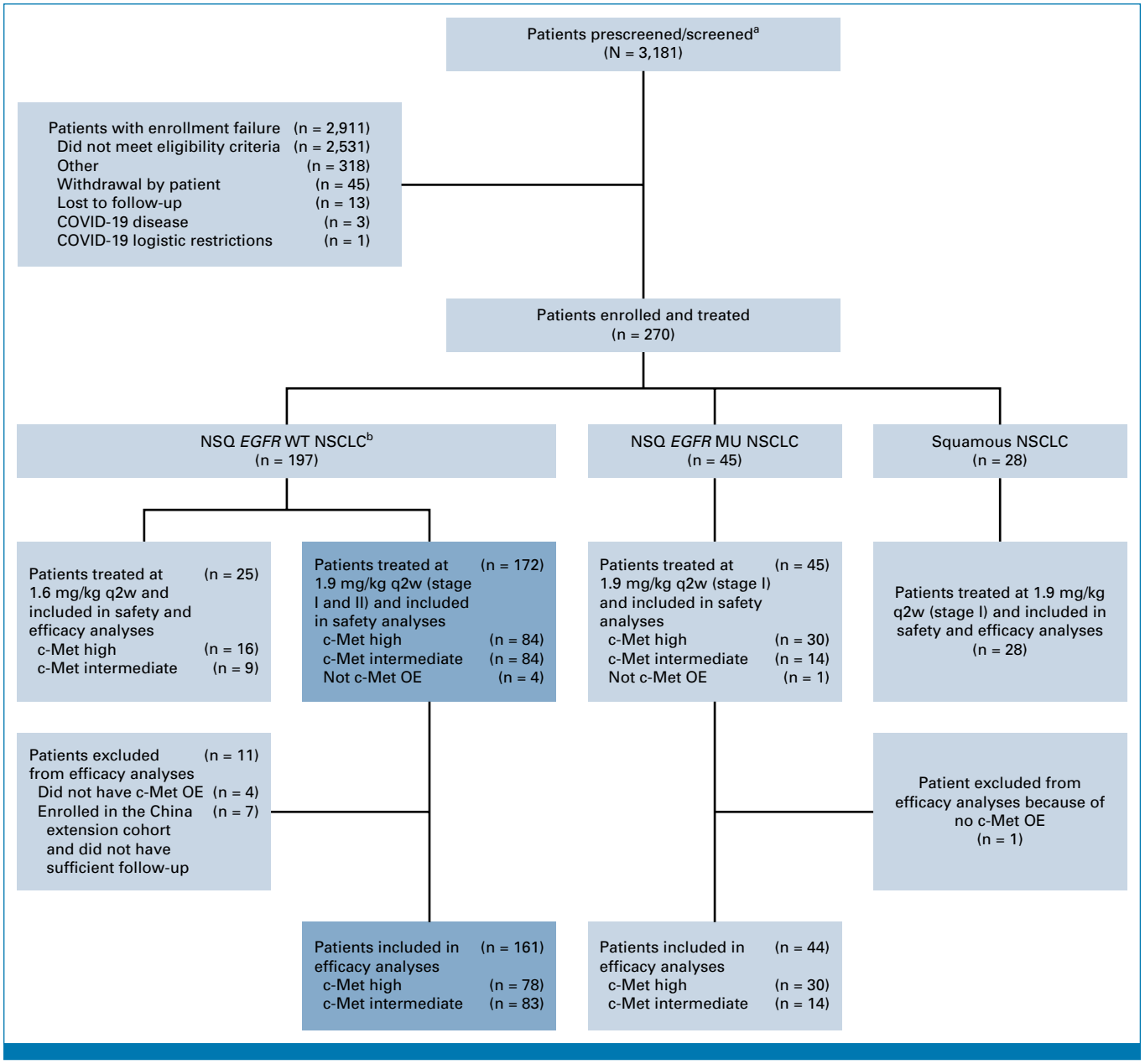

FIG 2. Among the 172 patients in the safety analysis set for NSQ *EGFR* WT NSCLC at 1.9 mg/kg q2w, eight were enrolled in the China extension cohort. [a]Among 1,954 evaluable submitted samples for prescreening patients for eligibility among those with nonsquamous *EGFR*-wildtype NSCLC, 23.6% were c-Met protein–overexpressing and 13.5% were c-Met high. [b]Of the 197 patients with nonsquamous *EGFR*-wildtype NSCLC, 53 patients were enrolled in stage I of the study. In total, 119 patients were enrolled in stage II: global enrollment, n = 111; China extension cohort, n = 8 (25 patients were enrolled in 1.6 mg/kg q2w cohort). *EGFR*, epidermal growth factor receptor; MU, mutated; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; OE, overexpression; q2w, once every 2 weeks; WT, wildtype.

ICR was 1.41 months (range, 1.0-7.4) for c-Met overexpression total. The median DOR was 9.0 months (95% CI, 4.2 to 13.0) for c-Met high, 7.2 months (95% CI, 5.3 to 11.5) for c-Met intermediate, and 8.3 months (95% CI, 5.6 to 11.3) for c-Met overexpression total; the proportion of responders with response ≥6 months was 63.0%, 47.4%, and 56.5%, respectively (Fig 3B). The median PFS per ICR was 5.5 months (95% CI, 4.1 to 8.3) for c-Met high, 6.0 months (95% CI, 4.5 to 8.1) for c-Met intermediate, and 5.7 months (95% CI, 4.6 to 6.9) for c-Met overexpression total (Fig 3C). The median follow-up time was 20.2 months for c-Met high, 18.9 months for c-Met intermediate, and 19.3 months for c-Met overexpression total; the median OS was 14.6 months (95% CI, 9.2 to 25.6), 14.2 months (95% CI, 9.6 to 16.6), and 14.5 months (95% CI, 9.9 to 16.6), respectively (Fig 3D).

Safety

Most patients with nonsquamous *EGFR*-wildtype NSCLC experienced a treatment-emergent AE (TEAE) of any grade

TABLE 1. Baseline Demographics and Disease Characteristics of Patients With c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC

Characteristic	c-Met High (n = 78)	c-Met Intermediate (n = 83)	c-Met OE Total (N = 161)[a]
Age, years, median (range)	64.0 (38-83)	66.0 (38-82)	64.0 (33-83)
Sex, No. (%)			
Male	58 (74.4)	53 (63.9)	111 (68.9)
Female	20 (25.6)	30 (36.1)	50 (31.1)
Race, No. (%)			
White	51 (65.4)	59 (71.1)	110 (68.3)
Black or African American	1 (1.3)	2 (2.4)	3 (1.9)
Asian	26 (33.3)	22 (26.5)	48 (29.8)
Region, No. (%)			
North America	9 (11.5)	19 (22.9)	28 (17.4)
Asia	25 (32.1)	19 (22.9)	44 (27.3)
Europe	29 (37.2)	22 (26.5)	51 (31.7)
Rest of world	15 (19.2)	23 (27.7)	38 (23.6)
Tobacco use, No. (%)			
Current	10 (12.8)	15 (18.1)	25 (15.5)
Former	54 (69.2)	47 (56.6)	101 (62.7)
Never	14 (17.9)	21 (25.3)	35 (21.7)
Stage IV at study entry, No. (%)	77 (98.7)	81 (97.6)	158 (98.1)
Brain metastasis, No. (%)	14 (17.9)	19 (22.9)	33 (20.5)
ECOG performance status, No. (%)			
0	20 (25.6)	27 (32.5)	47 (29.2)
1	57 (73.1)	56 (67.5)	113 (70.2)
2	1 (1.3)	0	1 (0.6)
No. of previous systemic cancer therapies, median (range)	1 (1-3)	1 (1-3)	1 (1-3)
Type of previous systemic cancer therapies, n (%)			
Platinum-based	75 (96.2)	82 (98.9)	157 (97.5)
Immune checkpoint inhibitor–based	66 (84.6)	66 (79.5)	132 (82.0)
Targeted therapy[b,c]	4 (5.1)	8 (9.6)	12 (7.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; OE, overexpressing.

[a]The efficacy analysis set excludes four patients who did not have c-Met protein overexpression and seven patients in the China extension cohort who did not have adequate follow-up time. The four patients who did not have c-Met protein overexpression were enrolled either on the basis of *MET* amplification, which was allowed in earlier versions of the protocol, or because of cohort assignment errors during stage I.

[b]The previous targeted therapies were crizotinib for four patients; alectinib, capmatinib, ceritinib, gefitinib, lapatinib + trastuzumab, lorlatinib, repotrectinib, sotorasib, tepotinib, trastuzumab deruxtecan, and glumetinib for one patient each.

[c]Alterations in genes other than *EGFR* were allowed, although available site-reported data on other alterations were limited and indicated alterations in a minority of patients.

(97.1%); 56.4% experienced a grade ≥3 TEAE. Any-grade treatment-related AEs (TRAEs) and grade ≥3 TRAEs occurred in 81.4% and 27.9% of patients, respectively. Most common any-grade TRAEs were peripheral sensory neuropathy (30.2%), peripheral edema (16.3%), fatigue (14.0%), decreased appetite (11.6%), increased ALT (11.0%), pneumonitis (10.5%), and hypoalbuminemia (10.5%; Table 3). These events were mostly grade 1/2. Any-grade treatment-related neutropenia occurred in two patients (1.2%); no patients experienced grade ≥3 neutropenia or any-grade febrile neutropenia. TRAEs for the nonsquamous *EGFR*-mutant and squamous NSCLC cohorts are shown in Appendix Table A5.

TRAEs leading to treatment discontinuation were reported in 21.5% of patients with nonsquamous *EGFR*-wildtype NSCLC; most common were pneumonitis (7.6%), peripheral sensory neuropathy (7.0%), peripheral sensorimotor neuropathy (2.3%), and ILD (1.2%). The median time to onset was 170 days (range 1-519). The median time to onset of ILD (*Standardised MedDRA Queries* [SMQ]; broad) events resulting in treatment discontinuation was 48 days (range, 7-344); the median time to onset of peripheral neuropathy (SMQ narrow) events leading to discontinuation was 222.5 days (range, 57-519). Ocular toxicities (eg, keratitis and vision blurred) did not lead to discontinuation in any patient. Two patients (1.2%) had

TABLE 2. Efficacy Summary in Patients With c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC

Outcome	c-Met High (n = 78)	c-Met Intermediate (n = 83)	c-Met OE Total (N = 161)
ORR,[a] % (95% CI)	34.6 (24.2 to 46.2)	22.9 (14.4 to 33.4)	28.6 (21.7 to 36.2)
DCR,[a] % (95% CI)	60.3 (48.5 to 71.2)	57.8 (46.5 to 68.6)	59.0 (51.0 to 66.7)
DOR,[a] months, median (95% CI)	9.0 (4.2 to 13.0)	7.2 (5.3 to 11.5)	8.3 (5.6 to 11.3)
DOR ≥6 months,[a] n/no. of responders (%)	17/27 (63.0)	9/19 (47.4)	26/46 (56.5)
PFS,[a] median, months (95% CI)	5.5 (4.1 to 8.3)	6.0 (4.5 to 8.1)	5.7 (4.6 to 6.9)
6-month PFS,[a,b] % (95% CI)	45.8 (33.8 to 57.1)	50.1 (37.9 to 61.1)	48.0 (39.5 to 56.1)
OS, months, median (95% CI)	14.6 (9.2 to 25.6)	14.2 (9.6 to 16.6)	14.5 (9.9 to 16.6)
12-month OS,[b] % (95% CI)	57.0 (45.0 to 67.4)	55.0 (43.5 to 65.2)	56.0 (47.7 to 63.4)

Abbreviations: DCR, disease control rate; DOR, duration of response; *EGFR*, epidermal growth factor receptor; NE, not estimable; NSCLC, non–small cell lung cancer; OE, overexpressing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[a]Per independent central review.
[b]Estimated using the Kaplan-Meier method.

grade 5 AEs that were considered possibly related to Teliso-V; these were ILD and respiratory failure.

Adjudicated events of ILD occurred in 17 patients (9.9%; grade 1, n = 3 [1.7%]; grade 2, n = 5 [2.9%]; grade 3, n = 5 [2.9%]; grade 4, n = 1 [0.6%]; grade 5, n = 3 [1.7%]). Of the three grade 5 events, one death was considered related to ILD per the investigator (two were considered related to progressive disease per the investigator).

DISCUSSION

The phase II LUMINOSITY study aimed to determine which c-Met protein–overexpressing NSCLC patient population would most benefit from treatment with Teliso-V and to further evaluate the efficacy within those patients. The nonsquamous *EGFR*-wildtype NSCLC cohort met criteria for expansion, whereas the squamous and nonsquamous *EGFR*-mutant cohorts met protocol-specified criteria for futility. Lower efficacy may be observed in the squamous cohort because of the lower cutoff used for c-Met overexpression versus the nonsquamous cohort. For patients with nonsquamous *EGFR*-mutant NSCLC, it is notable that higher response rates have been reported in a comparable population of patients treated with Teliso-V plus osimertinib, and preclinical data suggest an interaction between the mechanisms of action for Teliso-V and osimertinib may improve response to the combination.[17]

The highest ORR was observed among patients with c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC, and ORR was enriched among patients with c-Met high overexpressing tumors. The observed trend toward higher ORR with higher level of c-Met protein overexpression contrasts with studies evaluating ADCs targeting trophoblast antigen 2 (TROP2) in NSCLC, where TROP2 expression was not predictive of response.[18,19] Although ORR was increased in the c-Met high population, DCR, PFS, and OS were comparable between c-Met high, c-Met intermediate, and c-Met total overexpression, consistent with the reduction in tumor burden observed in most patients and indicating Teliso-V was efficacious in patients with c-Met protein–overexpressing tumors regardless of the level of expression.

The ORRs in patients with c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC observed with Teliso-V compare favorably with those for standard of care in the second-line-and-beyond setting, which are generally limited to single-agent chemotherapy, such as docetaxel with or without an antiangiogenic agent. The phase III REVEL trial evaluating docetaxel with or without ramucirumab enrolled patients with NSCLC who had disease progression on platinum-based therapy. In a subgroup analysis in patients with nonsquamous disease, ORRs per investigator were 21.9% (95% CI, 18.3 to 26.0) for docetaxel plus ramucirumab and 14.5% (95% CI, 11.4 to 18.2) for docetaxel plus placebo.[20] The phase III LUME-Lung 1 study evaluated docetaxel with or without nintedanib in patients whose NSCLC progressed after first-line chemotherapy. In those patients with adenocarcinoma, ORR per ICR was 4.7% for docetaxel plus nintedanib and 3.6% for docetaxel plus placebo.[21] In LUMINOSITY, Teliso-V was evaluated in a similar population of patients, with a median of one previous treatment line, and 98% of patients having received previous platinum.

The REVEL and LUME-Lung 1 studies did not report median DOR. However, other published data indicate that the observed median DOR in patients with c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC treated with Teliso-V exceeds that reported for docetaxel in other phase III studies. The phase III CheckMate 057 study included a docetaxel treatment arm and enrolled patients with advanced/metastatic nonsquamous NSCLC who received previous platinum therapy, comparable with the nonsquamous, predominantly metastatic, and previous platinum-treated NSCLC population in our study. In contrast to the LUMINOSITY study, patients in CheckMate 057 were naïve to immune checkpoint inhibitors, and 13% of those in the docetaxel arm had *EGFR* mutations. The reported median

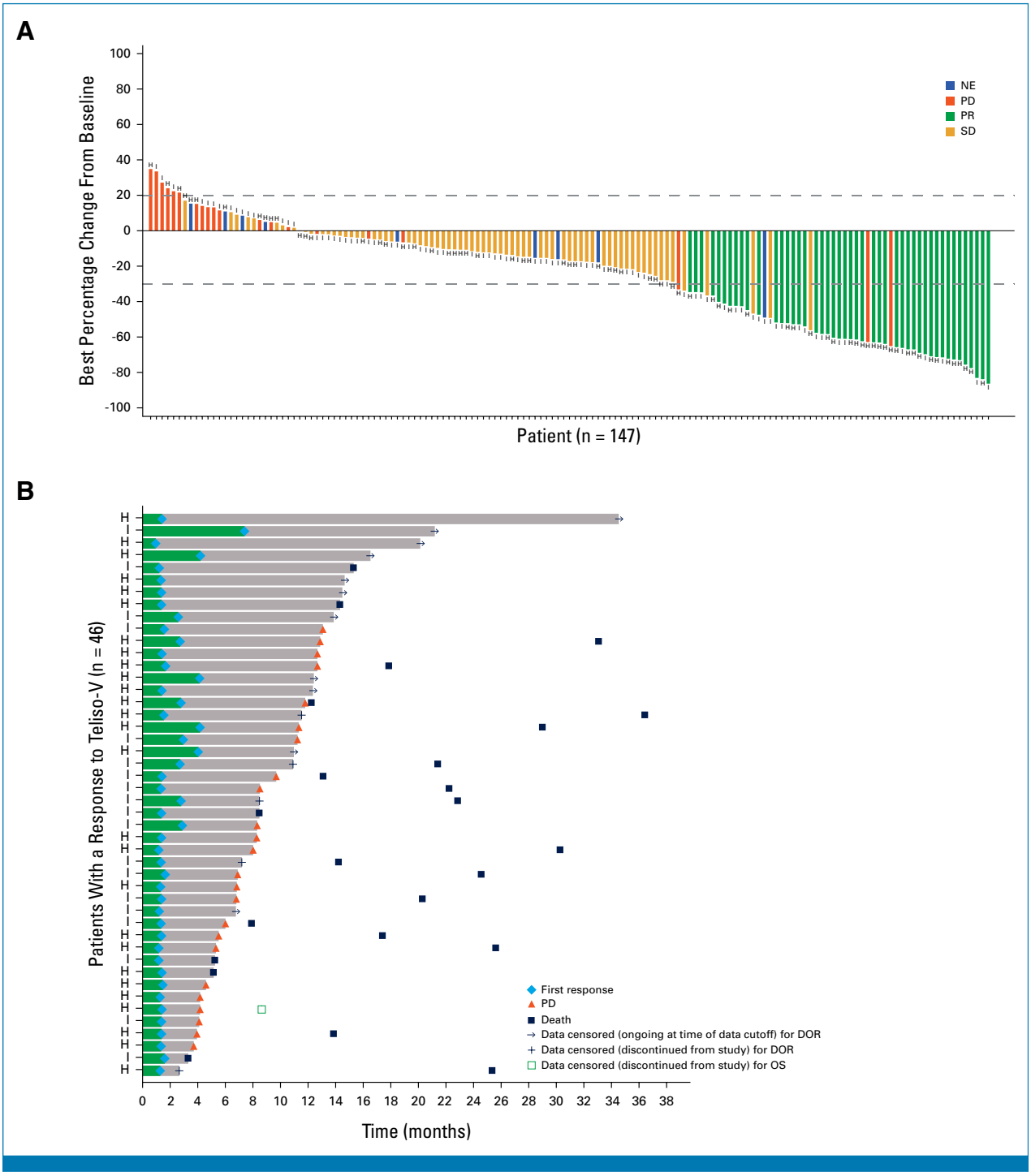

FIG 3. (A) Waterfall plot showing best reductions in target lesions[a]; (B) time to response and duration of response for patients with a confirmed response; and (C) PFS and (D) OS for patients with c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC receiving 1.9 mg/kg Teliso-V. [a]Only patients who had measurable disease at baseline and who had at least one measurable postbaseline assessment were included in the plot. DOR, duration of response; *EGFR*, epidermal growth factor receptor; H, c-Met high; I, c-Met intermediate; NE, not evaluable; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; Teliso-V, telisotuzumab vedotin; WT, wildtype. (continued on following page)

ORR with docetaxel was 12% (95% CI, 9 to 17) and the median DOR was 5.6 months (95% CI, 4.4 to 6.9).[22,23] Given c-Met expression is associated with worse outcomes in NSCLC,[11] whether these historical data are directly comparable with the patient population in LUMINOSITY remains to be determined within a randomized trial.

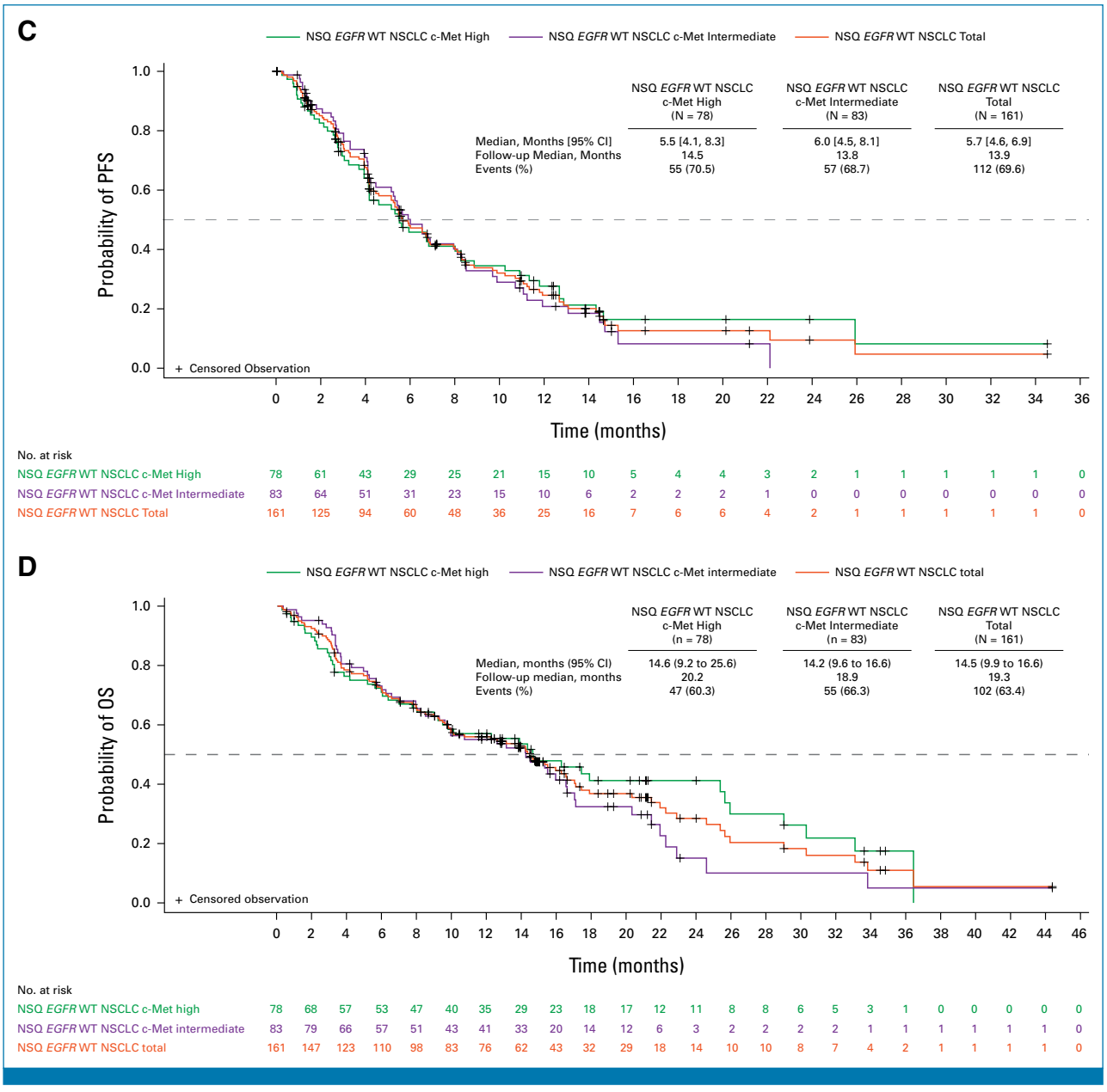

FIG 3. (Continued).

The AE profile among patients with nonsquamous *EGFR*-wildtype NSCLC observed with Teliso-V was generally consistent with reports of MMAE ADCs and MET-targeting agents. Peripheral sensory neuropathy was the most common AE and has been associated with MMAE ADCs.[24] These events were predominantly low grade, and patients were generally able to continue treatment after onset by dose reductions and interruptions. Ocular toxicities have also been reported with MMAE ADCs,[24] and events including keratitis and blurred vision were reported with Teliso-V. These were rarely grade ≥3, and no events of keratitis or blurred vision led to discontinuation. Peripheral edema and hypoalbuminemia are frequently reported with MET inhibitors.[7,8] These events were also observed with Teliso-V, although any-grade TRAEs occurred in a minority of the patients (peripheral edema, 16.3%; hypoalbuminemia, 10.5%) and were predominantly low grade. ILD cases, including grade 5 events, were also observed. Most patients with nonsquamous *EGFR*-wildtype NSCLC in the current study received previous immune checkpoint inhibitor, and a previous report has suggested that patients with previous immune checkpoint inhibitor have a greater likelihood of ILD during subsequent therapy.[25] ILD, including fatal cases, has been reported with other NSCLC agents, including ADCs trastuzumab deruxtecan[26] and datopotamab deruxtecan.[27] Hematologic toxicity has also been reported for MMAE

TABLE 3. The Most Common Any-Grade and Grade ≥3 TRAEs Experienced by Patients in the c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC Cohort

	c-Met High (n = 84), No. (%)		c-Met Intermediate (n = 84), No. (%)		c-Met OE Total (N = 172), No. (%)	
Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAE	83 (98.8)	50 (59.5)	80 (95.2)	45 (53.6)	167 (97.1)	97 (56.4)
TRAE	68 (81.0)	25 (29.8)	69 (82.1)	23 (27.4)	140 (81.4)	48 (27.9)
TRAEs occurring in >5% of patients in the NSQ *EGFR* WT NSCLC population						
Peripheral sensory neuropathy	24 (28.6)	5 (6.0)	27 (32.1)	7 (8.3)	52 (30.2)	12 (7.0)
Peripheral edema	17 (20.2)	2 (2.4)	11 (13.1)	1 (1.2)	28 (16.3)	3 (1.7)
Fatigue	11 (13.1)	3 (3.6)	12 (14.3)	1 (1.2)	24 (14.0)	4 (2.3)
Decreased appetite	7 (8.3)	0	13 (15.5)	1 (1.2)	20 (11.6)	1 (0.6)
Increased alanine aminotransferase	8 (9.5)	2 (2.4)	11 (13.1)	4 (4.8)	19 (11.0)	6 (3.5)
Pneumonitis[a]	11 (13.1)	3 (3.6)	7 (8.3)	2 (2.4)	18 (10.5)	5 (2.9)
Hypoalbuminemia	10 (11.9)	0	8 (9.5)	0	18 (10.5)	0
Nausea	6 (7.1)	0	11 (13.1)	0	17 (9.9)	0
Vision blurred	11 (13.1)	1 (1.2)	5 (6.0)	1 (1.2)	16 (9.3)	2 (1.2)
Increased aspartate aminotransferase	7 (8.3)	0	9 (10.7)	0	16 (9.3)	0
Asthenia	4 (4.8)	1 (1.2)	9 (10.7)	0	13 (7.6)	1 (0.6)
Anemia	7 (8.3)	1 (1.2)	2 (2.4)	0	10 (5.8)	1 (0.6)
Increased gamma-glutamyltransferase	5 (6.0)	1 (1.2)	5 (6.0)	0	10 (5.8)	1 (0.6)
Keratitis	5 (6.0)	0	5 (6.0)	0	10 (5.8)	0
Peripheral neuropathy	6 (7.1)	1 (1.2)	3 (3.6)	0	9 (5.2)	1 (0.6)
Decreased weight	4 (4.8)	0	4 (4.8)	0	9 (5.2)	0

NOTE. Considered possibly related to study drug by the investigator. TRAEs are shown by the MedDRA Preferred Term according to investigative site reporting.

Abbreviations: *EGFR*, epidermal growth factor receptor; ILD, interstitial lung disease; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; OE, overexpressing; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WT, wildtype.

[a]Pneumonitis events shown are those with a MedDRA preferred term of pneumonitis according to the investigative site reporting. In addition, TRAEs with a preferred term of ILD according to investigative site reporting were noted in 4 (2.3%) patients with c-Met OE total (c-Met high, n = 2 [2.4%]; c-Met intermediate, n = 2 [2.4%]). Investigative site-reported events of potential ILD, including the terms of pneumonitis and ILD, were also adjudicated as ILD or not ILD by an independent committee. Adjudicated events of ILD occurred in 17 patients (9.9%); nine had events adjudicated as grade ≥3 (5.2%), of which three were grade 5.

ADCs[24] but was generally uncommon with Teliso-V, with related grade ≥3 anemia reported in one patient, no grade ≥3 related neutropenia, and no febrile neutropenia reported for the nonsquamous *EGFR*-wildtype NSCLC population.

The frequency of TRAEs leading to discontinuation was 21.5%. The TRAEs leading to discontinuation were most commonly peripheral neuropathy or ILD/pneumonitis. Per protocol, drug discontinuation was recommended for pneumonitis events of grade ≥2. Peripheral neuropathy is a known cumulative toxicity associated with MMAE ADCs.[28] The median time to onset of a TRAE leading to discontinuation was 170 days and the median time to onset of peripheral neuropathy TRAEs leading to discontinuation was 222.5 days, suggesting many discontinuations were among patients who remained on drug for an extended time. Teliso-V was administered for ≥20 cycles in 20.3% of patients, indicating tolerability of the treatment.

This phase II trial is limited by the lack of a comparator arm. The ongoing global, randomized phase III study TeliMET NSCLC-01 (ClinicalTrials.gov identifier: NCT04928846) compares Teliso-V monotherapy with docetaxel in patients with previously treated locally advanced/metastatic, c-Met protein–overexpressing, nonsquamous *EGFR*-wildtype NSCLC. Given the potential overlap of some genomic markers of *MET* activation with c-Met protein overexpression, retrospective analyses of the current study data on available tissue or blood for these markers will be of interest.

Currently, no therapies specifically for patients with c-Met protein–overexpressing NSCLC are available. In LUMINOSITY, Teliso-V was associated with durable responses in c-Met protein–overexpressing nonsquamous *EGFR*-wildtype NSCLC, with ORRs enriched in patients with high c-Met expression.

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PRIOR PRESENTATION

Presented in part at the ASCO Annual Meeting, Chicago, IL, May 31-June 3, 2024; the ASCO Annual Meeting, Chicago, IL, June 3-7, 2022; and the American Association for Cancer Research Annual Meeting, virtual, April 10-15 and May 17-21, 2021.

CLINICAL TRIAL INFORMATION

NCT03539536 (LUMINOSITY)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.24.00720.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at https://doi.org/10.1200/JCO.24.00720.
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ACKNOWLEDGMENT

AbbVie funded this 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.
AbbVie and the authors thank all the trial investigators and the patients who participated in this clinical trial. Medical writing support was provided by Joanne Franklin, PhD, CMPP, from Aptitude Health, The Hague, the Netherlands, and funded by AbbVie.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met Protein–Overexpressing Advanced Nonsquamous *EGFR*-Wildtype Non–Small Cell Lung Cancer in the Phase II LUMINOSITY Trial

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No other potential conflicts of interest were reported.

APPENDIX: SUPPLEMENTARY METHODS AND RESULTS

Prespecified Criteria for Futility Analysis

The decision to stop the enrollment of a group for futility in stage I or move a group to the expansion cohort in stage II was based on the estimated posterior probabilities of success by comparing it with the lower and upper decision thresholds. The posterior probability of success was defined as the posterior probability of the overall response rate exceeding 25%. The lower decision threshold was defined as 10% and the upper decision threshold was defined as 70%. The above analysis was also performed at the cohort level. For each interim analysis, decision making started when at least 10 efficacy-evaluable patients were enrolled under one group or at least 15 efficacy-evaluable patients were enrolled in one cohort (ie, nonsquamous *EGFR*-wildtype; nonsquamous *EGFR*-mutated). When the posterior probability of success for a specific group exceeding 25% fell below 0.10, the group was considered futile. Conversely, if the same posterior probability estimate was high (exceeded 0.70), then that group was graduated to the stage II expansion.

Interim Analysis Decision-Making Results

At Interim Analysis 3, the *EGFR*-wildtype nonsquamous cohort was determined to advance to stage II on the basis of the posterior probability of success of 91% and the squamous cohort was stopped for futility on the basis of the posterior probability of success of 9.3%. The *EGFR*-mutant nonsquamous cohort continued enrolling until Interim Analysis 4 when the futility criteria were met (posterior probability of success of 1.6% for the *EGFR*-mutant nonsquamous cohort and 2.9% for the *EGFR*-mutant nonsquamous c-Met intermediate group; the *EGFR*-mutant nonsquamous c-Met high group met the enrollment cap of 30 patients with a posterior probability of success of 14.5%).

Changes in MET Over Time

In the *EGFR*-wildtype nonsquamous non–small cell lung cancer cohort, 28 paired tissues were available. Of these, 21 (75%) had the same *MET* status, 2 (7%) changed from positive to negative, and 5 (18%) changed from negative to positive. Collectively then, over 90% of the time, c-Met protein overexpression status was the same or higher in repeat biopsy.

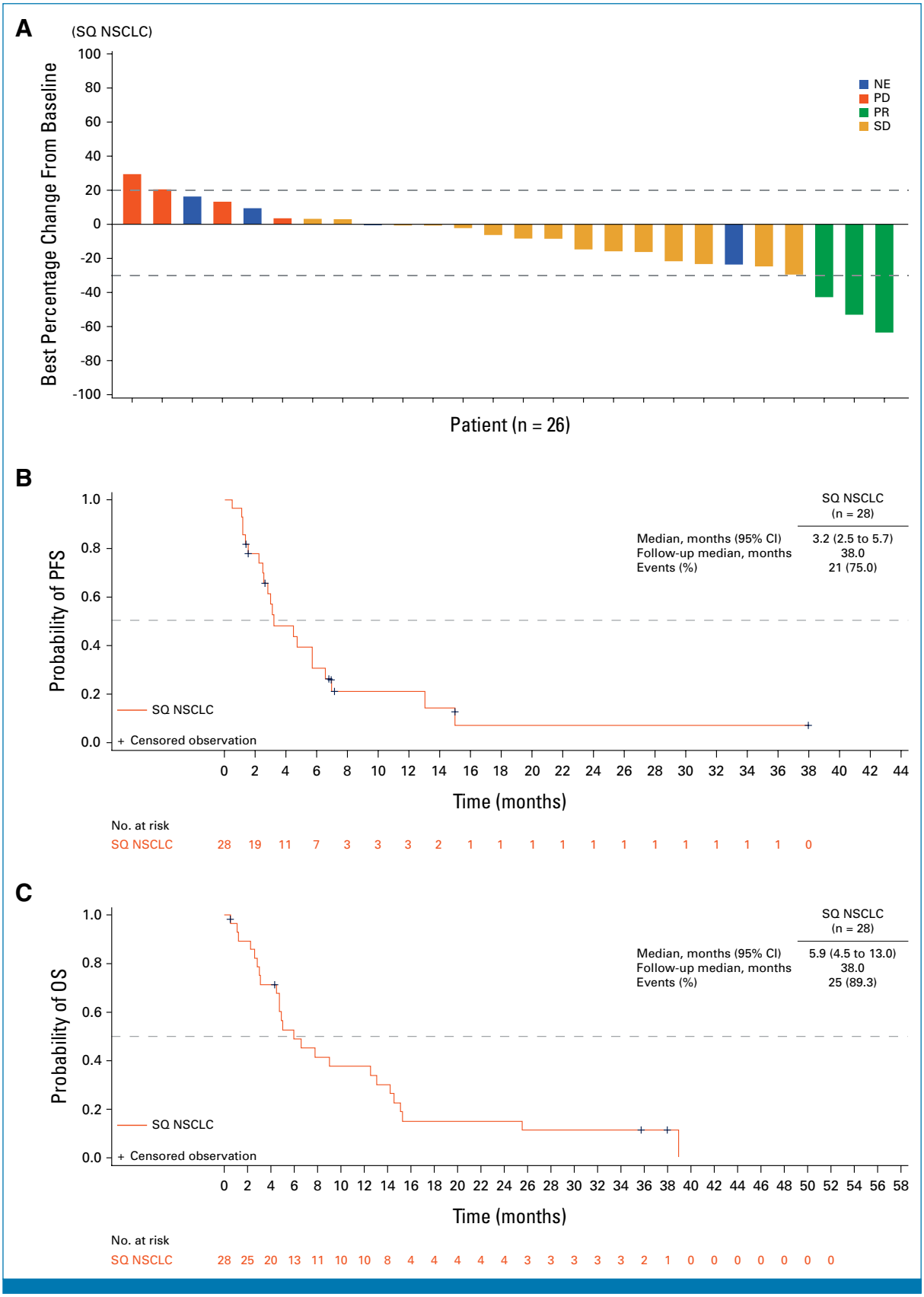

FIG A1. (A) Waterfall plot showing best reductions in target lesions for patients with c-Met protein–overexpressing, squamous NSCLC receiving 1.9 mg/kg Teliso-V[a]; (B) progression-free survival for patients with c-Met protein–overexpressing, squamous NSCLC receiving 1.9 mg/kg Teliso-V; (C) OS for patients with c-Met (continued on following page)

FIG A1. (Continued). protein–overexpressing, squamous NSCLC receiving 1.9 mg/kg Teliso-V. [a]Only patients who had measurable disease at baseline and who had at least one measurable postbaseline assessment were included in this analysis. NSCLC, non–small cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SQ, squamous; Teliso-V, telisotuzumab vedotin.

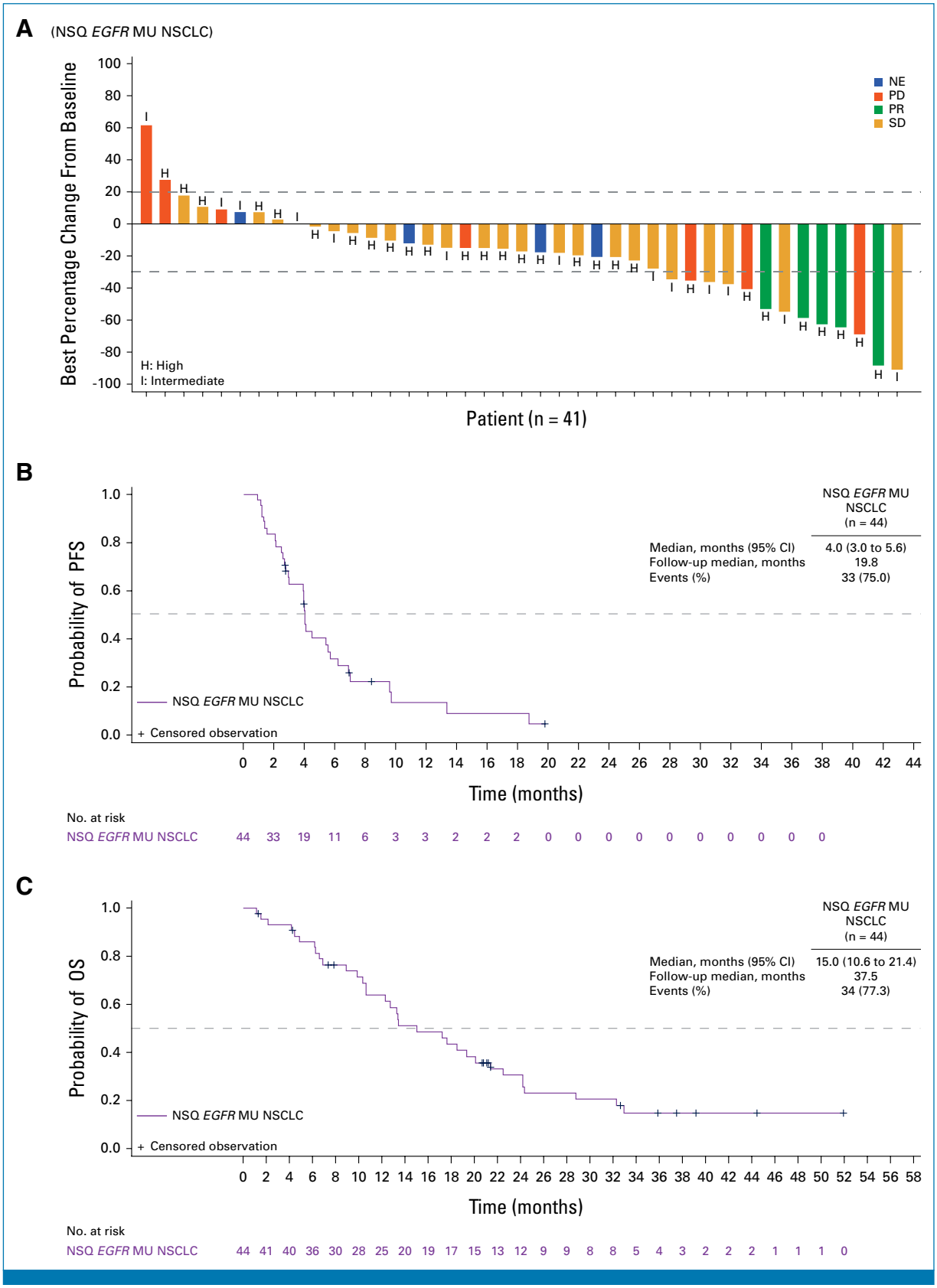

FIG A2. (A) Waterfall plot showing best reductions in target lesions[a] for patients with c-Met protein–overexpressing, nonsquamous *EGFR*-mutant NSCLC receiving 1.9 mg/kg Teliso-V; (B) progression-free survival for (continued on following page)

FIG A2. (Continued). patients with c-Met protein–overexpressing, nonsquamous *EGFR*-mutant NSCLC receiving 1.9 mg/kg Teliso-V; (C) OS for patients with c-Met protein–overexpressing, nonsquamous *EGFR*-mutant NSCLC receiving 1.9 mg/kg Teliso-V. [a]Only patients who had measurable disease at baseline and who had at least one measurable postbaseline assessment were included in this analysis. *EGFR*, epidermal growth factor receptor; H, c-Met high; I, c-Met intermediate; MU, mutant; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; Teliso-V, telisotuzumab vedotin.

TABLE A1. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Adults age ≥18 years	Adenosquamous histology
c-Met protein overexpression as assessed by sponsor-designated IHC criteria	Received previous c-Met–targeted therapies
Adequate bone marrow, renal, and hepatic function	History of other malignancies except Malignancy treated with curative intent and with no known active disease present for ≥2 years before the first dose of Teliso-V and considered low risk for recurrence by investigator Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease Adequately treated carcinoma in situ without current evidence of disease
Histologically documented nonsquamous NSCLC with known *EGFR* mutation (wildtype or mutant) or histologically documented squamous cell NSCLC	History of ILD or pneumonitis that required treatment with systemic steroids
Locally advanced/metastatic NSCLC	Evidence of pulmonary fibrosis on screening imaging assessment or any history of pneumonitis or ILD within 3 months of the planned first dose of Teliso-V
ECOG performance status 0 or 1	Unresolved clinically significant adverse events grade ≥2 from previous anticancer therapy, except for alopecia or anemia
Measurable disease per RECIST v1.1	Major surgery within 21 days before the first dose of Teliso-V
Received no more than two lines of previous systemic therapy, including no more than one line of systemic cytotoxic chemotherapy; multiple lines of TKIs targeting the same tyrosine kinase count as one line of therapy	Received radiation therapy to the lung <6 months before the first dose of Teliso-V
Progression on systemic cytotoxic chemotherapy (or are ineligible for systemic cytotoxic chemotherapy) and an immune checkpoint inhibitor (as monotherapy or in combination with systemic cytotoxic chemotherapy, or ineligible for an immune checkpoint inhibitor), and previous anticancer therapies targeting driver gene alterations (if applicable)	A clinically significant condition(s) including, but not limited to, the following: Grade ≥2 edema or lymphedema Grade ≥2 ascites or pleural effusion Grade ≥2 or history of grade ≥3 peripheral neuropathy Active uncontrolled bacterial or viral infection New York Heart Association Class ≥III congestive heart failure Unstable angina pectoris or cardiac arrhythmia
Patients with CNS metastasis if they have received definitive therapy and There is no evidence of progression ≥2 weeks after definitive therapy They are asymptomatic and off systemic steroids and anticonvulsants for at least 2 weeks before the first dose of Teliso-V	History of major immunologic reaction to any immunoglobulin (IgG)-containing agent
Negative serum pregnancy test and no breastfeeding	Known active severe COVID-19 disease
Male and female patients must be using birth control methods	Received any live vaccine within 30 days of first dose of Teliso-V
	Received any of the following in the noted time intervals: Within 1 week (7 days): strong cytochrome P450 3A4 (CYP3A4) inhibitors Within 2 weeks (14 days): radiation not involving the thoracic cavity Within 4 weeks (28 days): systemic cytotoxic chemotherapy; small-molecule targeted; monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or T-cell or other cell-based therapies

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; NSCLC, non–small cell lung cancer; Teliso-V, telisotuzumab vedotin; TKI, tyrosine kinase inhibitor.

TABLE A2. Baseline Demographics and Disease Characteristics of Patients With Nonsquamous *EGFR*-Mutated NSCLC and Squamous NSCLC

Characteristic	NSQ *EGFR* MU[a] NSCLC (n = 44)[b, c]	SQ NSCLC (n = 28)	Total Study Population (N = 233)
Age, years, median (range)	62 (36-81)	66 (45-76)	64 (33-83)
Sex, No. (%)			
Male	19 (43.2)	17 (60.7)	147 (63.1)
Female	25 (56.8)	11 (39.3)	86 (36.9)
Race, No. (%)			
White	17 (38.6)	26 (29.9)	153 (65.7)
Black or African American	0	0	3 (1.3)
Asian	27 (61.4)	2 (7.1)	77 (33.0)
Region, No. (%)			
North America	8 (18.2)	6 (21.4)	42 (18.0)
Asia	22 (50.0)	2 (7.1)	68 (29.2)
Europe	10 (22.7)	6 (21.4)	67 (28.8)
Rest of world	4 (9.1)	14 (50.0)	56 (24.0)
Tobacco use, No. (%)			
Current	0	6 (21.4)	31 (13.3)
Former	17 (38.6)	20 (71.4)	138 (59.2)
Never	27 (61.4)	2 (7.1)	64 (27.5)
Stage IV at study entry, No. (%)	43 (97.7)	20 (71.4)	221 (94.8)
Brain metastasis, No. (%)	13 (29.5)	1 (3.6)	47 (20.2)
ECOG performance status, No. (%)			
0	15 (34.1)	4 (14.3)	66 (28.3)
1	29 (65.9)	24 (85.7)	166 (71.2)
2	0	0	1 (0.4)
No. of previous systemic cancer therapies, median (range)	2 (1-4)	1 (1-4)	1 (1-4)
Type of previous systemic cancer therapies, No. (%)			
Platinum-based	40 (90.9)	28 (100)	225 (96.6)
Immune checkpoint inhibitor–based	8 (18.2)	26 (92.9)	166 (71.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; MU, mutated; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; SQ, squamous; TKI, tyrosine kinase inhibitor.
[a]Data on mutations were site-reported. The most common mutations were DEL 19 (n = 22), L858R (n = 17), and T790M (n = 12).
[b]One patient in the NSQ *EGFR* MU NSCLC cohort did not overexpress c-Met.
[c]Forty-three patients (97.7%) in the NSQ *EGFR* MU NSCLC cohort had previous EGFR TKI (first/second generation, 39 [88.6%]; third generation, 16 [36.4%]).

TABLE A3. Efficacy Summary of Patients With c-Met Protein–Overexpressing Nonsquamous *EGFR*-Mutant NSCLC and Squamous Cell NSCLC

	NSQ *EGFR* MU NSCLC			
Outcome	c-Met High (n = 30)	c-Met Int (n = 14)	c-Met OE Total (N = 44)	SQ NSCLC (N = 28)
ORR,[a] % [95% CI]	5 (16.7) [5.6 to 34.7]	0 [0.0 to 23.2]	5 (11.4) [3.8 to 24.6]	3 (10.7) [2.3 to 28.2]
DCR,[a] % [95% CI]	46.7 [28.3 to 65.7]	28.6 [8.4 to 58.1]	40.9 [26.3 to 56.8]	35.7 [18.6 to 55.9]
Median DOR,[a] months [95% CI]	17.4 [3.0 to NE]	NE [NE to NE]	17.4 [3.0 to NE]	4.4 [3.0 to NE]
DOR ≥6 months,[a] n/no. of responders (%)	2/5 (40)	0	2/5 (40)	0
PFS,[a] months, median [95% CI]	4.1 [2.8 to 5.7]	4.0 [2.1 to 6.2]	4.0 [3.0 to 5.6]	3.2 [2.5 to 5.7]
6-month PFS[a,b], % [95% CI]	31.7 [15.2 to 49.6]	31.3 [8.1 to 58.5]	31.5 [17.4 to 46.7]	30.6 [13.8 to 49.2]
OS, months, median [95% CI]	13.4 [8.9 to 19.3]	21.4 [9.9 to 32.3]	15.0 [10.6 to 21.4]	5.9 [4.5 to 13.0]
12-month OS[b], % [95% CI]	61.1 [40.8 to 76.3]	68.6 [35.9 to 87.0]	63.7 [47.1 to 76.3]	37.6 [20.0 to 55.2]

Abbreviations: DOR, duration of response; *EGFR*, epidermal growth factor receptor; MU, mutated; NE, not evaluable; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; OE, overexpressing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SQ, squamous.
[a]Per independent central review.
[b]Estimated by Kaplan-Meier method.

TABLE A4. Investigator-Assessed Overall Response Rates of Patients With c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC

Response Rate	c-Met High (n = 78)	c-Met Intermediate (n = 83)	NSQ *EGFR* WT NSCLC Total (N = 161)
ORR (CR + PR) [95% CI]	29 (37.2) [26.5 to 48.9]	18 (21.7) [13.4 to 32.1]	47 (29.2) [22.3 to 36.9]

Abbreviations: CR, complete response; *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; ORR, overall response rate; PR, partial response; WT, wildtype.

TABLE A5. Most Common Any-Grade and Grade ≥3 TRAEs Experienced by Patients in All Study Cohorts

	NSQ *EGFR* WT NSCLC Total (n = 172), No. (%)		NSQ *EGFR* MU NSCLC Total (n = 45), No. (%)		SQ NSCLC Total (n = 28), No. (%)		Overall Total (N = 245), No. (%)	
Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAE	167 (97.1)	97 (56.4)	45 (100)	21 (46.7)	28 (100)	18 (64.3)	240 (98.0)	136 (55.5)
TRAE	140 (81.4)	48 (27.9)	41 (91.1)	11 (24.4)	19 (67.9)	9 (32.1)	200 (81.6)	68 (27.8)
TRAEs occurring in >5% of patients in the NSQ *EGFR* WT NSCLC								
Peripheral sensory neuropathy	52 (30.2)	12 (7.0)	11 (24.4)	1 (2.2)	2 (7.1)	1 (3.6)	65 (26.5)	14 (5.7)
Edema peripheral	28 (16.3)	3 (1.7)	8 (17.8)	0	2 (7.1)	0	38 (15.5)	3 (1.2)
Fatigue	24 (14.0)	4 (2.3)	4 (8.9)	0	4 (14.3)	3 (10.7)	32 (13.1)	7 (2.9)
Decreased appetite	20 (11.6)	1 (0.6)	8 (17.8)	0	1 (3.6)	0	29 (11.8)	1 (0.4)
Increased ALT	19 (11.0)	6 (3.5)	4 (8.9)	1 (2.2)	2 (7.1)	0	25 (10.2)	7 (2.9)
Pneumonitis	18 (10.5)	5 (2.9)	1 (2.2)	1 (2.2)	2 (7.1)	1 (3.6)	21 (8.6)	7 (2.9)
Hypoalbuminemia	18 (10.5)	0	5 (11.1)	1 (2.2)	5 (17.9)	0	28 (11.4)	1 (0.4)
Nausea	17 (9.9)	0	10 (22.2)	0	3 (10.7)	0	30 (12.2)	0
Blurred vision	16 (9.3)	2 (1.2)	9 (20.0)	0	2 (7.1)	0	27 (11.0)	2 (0.8)
Increased AST	16 (9.3)	0	5 (11.1)	0	1 (3.6)	0	22 (9.0)	0
Asthenia	13 (7.6)	1 (0.6)	6 (13.3)	1 (2.2)	1 (3.6)	1 (3.6)	20 (8.2)	3 (1.2)
Anemia	10 (5.8)	1 (0.6)	4 (8.9)	1 (2.2)	3 (10.7)	0	17 (6.9)	2 (0.8)
Increased gamma-glutamyltransferase	10 (5.8)	1 (0.6)	3 (6.7)	0	3 (10.7)	1 (3.6)	16 (6.5)	2 (0.8)
Keratitis	10 (5.8)	0	8 (17.8)	0	2 (7.1)	0	20 (8.2)	0
Peripheral neuropathy	9 (5.2)	1 (0.6)	1 (2.2)	0	0	0	10 (4.1)	1 (0.4)
Decreased weight	9 (5.2)	0	0	0	1 (3.6)	0	10 (4.1)	0

Abbreviations: *EGFR*, epidermal growth factor receptor; MU, mutated; NSCLC, non–small cell lung cancer; NSQ, nonsquamous; SQ, squamous; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WT, wildtype.