original reports

Phase Ib Study of Telisotuzumab Vedotin in Combination With Erlotinib in Patients With c-Met Protein–Expressing Non–Small-Cell Lung Cancer

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abstract

PURPOSE Overexpression of c-Met protein and epidermal growth factor receptor (*EGFR*) mutations can co-occur in non–small-cell lung cancer (NSCLC), providing strong rationale for dual targeting. Telisotuzumab vedotin (Teliso-V), a first-in-class antibody-drug conjugate targeting c-Met, has shown a tolerable safety profile and antitumor activity as monotherapy. Herein, we report the results of a phase Ib study (ClinicalTrials.gov identifier: NCT02099058) evaluating Teliso-V plus erlotinib, an EGFR tyrosine kinase inhibitor (TKI), in patients with c-Met–positive (+) NSCLC.

PATIENTS AND METHODS This study evaluated Teliso-V (2.7 mg/kg once every 21 days) plus erlotinib (150 mg once daily) in adult patients (age ≥ 18 years) with c-Met+ NSCLC. Later enrollment required presence of an *EGFR*-activating mutation (*EGFR*-M+) and progression on a prior EGFR TKI. End points included safety, pharmacokinetics, objective response rate (ORR), and progression-free survival (PFS). The efficacy-evaluable population consisted of c-Met+ patients (confirmed histology [H]-score ≥ 150) who had at least one post-baseline scan; c-Met+ patients with H-scores ≥ 225 were classified as c-Met high.

RESULTS As of January 2020, 42 patients were enrolled (N = 36 efficacy-evaluable). Neuropathies were the most common any-grade adverse events reported, with 24 of 42 patients (57%) experiencing at least one event. The pharmacokinetic profile of Teliso-V plus erlotinib was similar to Teliso-V monotherapy. Median PFS for all efficacy-evaluable patients was 5.9 months (95% CI, 2.8 to not reached). ORR for *EGFR*-M+ patients (n = 28) was 32.1%. Of *EGFR*-M+ patients, those who were c-Met high (n = 15) had an ORR of 52.6%. Median PFS was 6.8 months for non-T790M+ and for those whose T790M status was unknown, versus 3.7 months for T790M+.

CONCLUSION Teliso-V plus erlotinib showed encouraging antitumor activity and acceptable toxicity in EGFR TKI-pretreated patients with *EGFR*-M+, c-Met+ NSCLC.

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INTRODUCTION

Non–small-cell lung cancer (NSCLC) represents approximately 85% of all lung cancers and is the leading cause of cancer-related deaths worldwide.[1] Unfortunately, most patients diagnosed with NSCLC are affected by advanced-stage disease, conferring a 5-year survival rate as low as 7%.[2]

c-Met is a transmembrane receptor tyrosine kinase that is encoded by the *MET* proto-oncogene and activated upon binding to the hepatocyte growth factor.[3,4] Dysregulation of c-Met is observed in several types of cancer, including overexpression in approximately 50% of NSCLC.[5-8] *MET*-based primary driver alterations include *MET* amplification,[9] *MET* exon 14 skipping mutations,[10,11] and *MET* fusions.[12] *MET* amplification can also act as a potential second driver in the setting of acquired resistance to epidermal growth factor receptor (EGFR) inhibitors.[13,14] Overexpression of c-Met overlaps with these genetic *MET* driver and codriver states, but can also exist independently and may provide a target for therapy regardless of the *MET*-signaling addiction of the tumor.[5,6]

Telisotuzumab vedotin (ABBV-399; Teliso-V) is a first-in-class antibody-drug conjugate (ADC) that uses a cleavable linker to combine a recombinant c-Met–targeting humanized monoclonal antibody (ABT-700) and monomethyl auristatin E (MMAE), a potent inhibitor of microtubule polymerization.[15] The first-in-human study, to our knowledge, evaluating Teliso-V as monotherapy showed a favorable safety profile and promising antitumor activity in patients

CONTEXT

Key Objective

Patients diagnosed with advanced non–small-cell lung cancer (NSCLC) have a poor prognosis. Acquired resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is common because of the potential acquisition of resistance mutations and/or the aberrant activation of c-Met, a protein that promotes tumor development and progression. This study examined the safety, pharmacokinetics, and preliminary efficacy in patients with c-Met–positive (+) NSCLC treated with the c-Met–targeting drug telisotuzumab vedotin (Teliso-V) in combination with the EGFR TKI erlotinib.

Knowledge Generated

Teliso-V plus erlotinib showed encouraging antitumor activity and an acceptable safety profile in EGFR TKI-pretreated patients with *EGFR* mutation (M)+, c-Met+ NSCLC.

Relevance

This early-phase trial provides preliminary data on the adverse events and efficacy of an antibody-drug conjugate targeting c-Met, Teliso-V, in combination with erlotinib. The subsets of greatest clinical interest are the patients with *EGFR*-M+ NSCLC who progressed on a prior EGFR TKI, and with high c-Met H-scores by immunohistochemistry. Antibody-drug conjugates are potentially a novel mechanism of targeting *MET* resistance in *EGFR*-M+ NSCLC. Ongoing studies will evaluate the combination of Teliso-V with osimertinib.

with c-Met–overexpressing (c-Met+) NSCLC, and established 2.7 mg/kg dosed once every 21 days (once every 3 weeks; equivalent to one treatment cycle) as the recommended phase two dose (RP2D) and schedule.[16]

Originally approved as salvage therapy in unselected patients with NSCLC, the use of EGFR tyrosine kinase inhibitors (TKIs) shifted following the discovery of *EGFR* mutations and their heightened sensitivity to EGFR TKIs.[17] Common *EGFR*-activating mutations are exon 19 deletions (del19) and the exon 21 point mutation L858R. Erlotinib, gefitinib, afatinib, and osimertinib are all licensed for first-line treatment of tumors harboring these common mutations.[18-23] Afatinib is also licensed to treat uncommon *EGFR* mutations such as S768I, L861Q, and G719.[20]

Acquired resistance to first- and second-generation EGFR TKIs most frequently occurs via acquisition of the T790M *EGFR* mutation,[13,14,24] but can also occur through aberrant c-Met activation, with the frequency varying by whether resistance emerges on a first-/second- versus a third-generation EGFR TKI.[24-28]

Herein, we report on a phase Ib study evaluating dual targeting of c-Met and EGFR via combination therapy with Teliso-V plus erlotinib in patients with c-Met+ NSCLC, focusing primarily on the *EGFR* mutation-positive (*EGFR*-M+) post-EGFR TKI–treated population.

PATIENTS AND METHODS

Study Design and Treatment

This was a phase I/Ib multicenter, open-label study (ClinicalTrials.gov identifier: NCT02099058) evaluating Teliso-V plus erlotinib (150 mg orally once daily) in patients with advanced c-Met+ NSCLC. All enrolled patients received the RP2D of 2.7 mg/kg Teliso-V intravenously once every 3 weeks.[29] A subset of patients (n = 3) was enrolled in a safety lead-in cohort (2.4 mg/kg Teliso-V once every 3 weeks) to assess the safety of this drug combination before escalating to the RP2D; these patients were included in the safety assessment.

Patients could receive study treatment until disease progression, death, or withdrawal of consent. Patients who discontinued erlotinib because of toxicity unrelated to Teliso-V could continue Teliso-V monotherapy. Detailed dose-modification guidelines are provided in the study Protocol (online only). Briefly, protocol-mandated dose interruptions were required for grade 3 neuropathies, or grades 3/4 neutropenia, until the adverse event (AE) improved to grade ≤ 2. Study discontinuation criteria were met after three dose reductions or a dose interruption of > 21 days (or > 42 days for neuropathy).

The study was conducted in accordance with the protocol, the International Conference on Harmonization, 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

This study enrolled adult patients (age ≥ 18 years) with advanced NSCLC (measurable per Response Evaluation Criteria in Solid Tumors v1.1) not amenable to resection or other approved therapies. Patients were required to have archival tumor tissue available for biomarker analysis and confirmation of c-Met overexpression, *MET* exon 14 skipping mutations, or *MET* amplification, as determined by a central/local site laboratory. Samples could have been

TABLE 1. Demographics and Baseline Clinical Characteristics (Efficacy-Evaluable Population)

	Teliso-V Plus Erlotinib			
Characteristic	**c-Met+ *EGFR*-M+ (n = 28)**	**c-Met+ *EGFR*-WT (n = 5)**	**c-Met+ *EGFR*-Rare/Unknown (n = 3)**	**Total (N = 36)**
Age, years, median (range)	65 (34-80)	67 (41-77)	66 (63-74)	65 (34-80)
Sex, No. (%)				
Female	19 (68)	0	2 (67)	21 (58)
Male	9 (32)	5 (100)	1 (33)	15 (42)
ECOG performance status, No. (%)				
0	8 (29)	1 (20)	1 (33)	10 (28)
1	20 (71)	4 (80)	2 (67)	26 (72)
NSCLC histology, No. (%)				
Nonsquamous	27 (96)	5 (100)	3 (100)	35 (97)
Squamous	1 (4)	0	0	1 (3)
Confirmed *EGFR* mutation, No. (%)				
Del19	16 (57)	0	0	16 (44)
L858R	12 (43)	0	0	12 (33)
Rare (L861R, L861Q)	0	0	2 (66)	2 (6)
c-Met H-score,[a] No. (%)				
150-224	13 (46)	2 (40)	2 (67)	17 (47)
T790M+	7 (54)	0	0	7 (19)
Met amp	0	0	1 (50)	2 (6)
≥ 225	15 (54)	3 (60)	1 (33)	19 (53)
T790M+	6 (40)	0	0	6 (17)
Met amp	4 (27)	1 (33)	0	6 (17)
MET amplification status, No. (%)				
Amplified	4 (14)	1 (20)	1 (33)	6 (17)
Polysomy	1 (4)	1 (20)	0	2 (6)
No, or not reported	23 (82)	3 (60)	2 (67)	28 (78)
Prior anticancer regimens, No. (%)				
EGFR TKI	27 (96)	1 (20)	3 (100)	31 (86)
Platinum-based	19 (68)	5 (100)	1 (33)	25 (69)
Other	7 (25)	3 (60)	1 (33)	11 (31)
Immune checkpoint inhibitors	7 (25)	3 (60)	1 (33)	11 (31)
c-Met inhibitor	2 (7)	2 (40)	1 (33)	5 (14)
Docetaxel-based	1 (4)	4 (80)	1 (33)	6 (17)
No. of lines of prior therapy (%)				
1	3 (11)	1 (20)	1 (33)	5 (14)
2	6 (21)	0	0	6 (17)
3	9 (32)	0	1 (33)	10 (28)
≥ 4	10 (36)	4 (80)	1 (33)	15 (42)
No. of lines of prior EGFR TKI (%)				
1	5 (18)	0	1 (33)	6 (17)
2	7 (25)	1 (20)	0	8 (22)
3	9 (32)	0	1 (33)	10 (28)
≥ 4	6 (21)	0	1 (33)	7 (19)

(continued on following page)

TABLE 1. Demographics and Baseline Clinical Characteristics (Efficacy-Evaluable Population) (continued)

Characteristic	Teliso-V Plus Erlotinib			
	c-Met+ *EGFR*-M+ (n = 28)	c-Met+ *EGFR*-WT (n = 5)	c-Met+ *EGFR*-Rare/Unknown (n = 3)	Total (N = 36)
Types of EGFR TKI received across all lines, No. (%)				
First/second generation	26 (93)	1 (20)	3 (100)	30 (83)
Third generation	16 (57)	0	0	16 (44)

Abbreviations: c-Met+, c-Met–overexpressing; Del19, exon 19 deletion mutation; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; *EGFR*-M+, *EGFR* mutation-positive; *EGFR*-WT, *EGFR* wild-type; NSCLC, non–small-cell lung cancer; Teliso-V, telisotuzumab vedotin; TKI, tyrosine kinase inhibitor.

[a]Samples, either archival or fresh, could have been collected at any point in the patient's prior treatment journey and not specifically after the most recent EGFR TKI therapy, and type of sample (blood *v* tissue) was not captured.

collected at any point in the patient's prior treatment journey. Although not initially required, later study protocol amendments required the patient's tumor to have a del19 or L858R *EGFR*-activating mutation and to have previously progressed on an EGFR TKI. Patients must have had an Eastern Cooperative Oncology Group performance status of 0-2 and adequate bone marrow, renal, and hepatic function. Main exclusion criteria included any prior anticancer therapy, uncontrolled central nervous system metastases, or any medical condition that would put the patient at an unacceptably high risk for toxicity.

Assessments

Pharmacokinetics. Detailed methodology on pharmacokinetic analysis can be found in the Data Supplement (online only).

Safety. AEs were assessed throughout the study and for 60 days following discontinuation of study treatment. AEs were reported by site using Medical Dictionary for Regulatory Activities system organ class preferred terms as determined by the site investigator; multiple similar terms could be used to describe the same event in a single patient. AE severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.

The safety analysis population included all patients who received any amount of study drug. Safety summaries were descriptive only, and no statistical inference was performed.

Efficacy. Radiographic tumor assessments (via computed tomography or magnetic resonance imaging) were performed within 28 days of treatment initiation and once every 6 weeks thereafter until documented disease progression, start of new anticancer therapy, death, or withdrawal of consent. Responses were assessed according to Response Evaluation Criteria in Solid Tumors v1.1. Efficacy end points included objective response rate (ORR) and progression-free survival (PFS).

ORR was defined as the proportion of patients with confirmed complete response (CR) or partial response (PR). Disease control rate (DCR) was defined as the proportion of patients with confirmed CR, PR, or stable disease (SD; sustained for a minimum 6 weeks). PFS was defined as the time from the first dose of study drug to either the first date of documented disease progression, or death, whichever occurred first, or at the date of last disease assessment. Patients with no tissue available for H-score assessment, or those with H-score < 150, were not included in the efficacy analysis.

Biomarker analysis. Detailed methodology on biomarker analysis can be found in the Data Supplement. Briefly, archived or newly acquired tumor tissue was analyzed for c-Met protein expression by immunohistochemistry. c-Met–overexpressing tumors were defined as H-score ≥ 150 (c-Met+); this threshold was chosen by the sponsor (AbbVie, North Chicago, IL) to enrich for patients most likely to benefit from Teliso-V, as preclinical studies have shown that some level of c-Met expression is needed for Teliso-V efficacy.[15] Tumors with H-score ≥ 225 were defined as c-Met high, as previous clinical studies noted that this higher threshold of expression enriched for antitumor responses.[29]

Statistical analysis. A sample size of 40 patients with c-Met+ NSCLC was estimated to provide 80% power to detect an absolute improvement in ORR from 10% to 25%, with a 10% two-sided significance level.

ORR was assessed using the two-sided 95% CIs provided by the Clopper-Pearson (exact) method. PFS was summarized by Kaplan-Meier estimates, and median PFS was calculated with two-sided 95% CIs.

RESULTS

Patient Characteristics

Between April 2015 and January 2020, 42 patients were enrolled in the cohort evaluating the combination of Teliso-V plus erlotinib. Patients who either did not have tumor tissue available for H-score assessment or had H-score < 150 (n = 6) were not included in the efficacy set (N = 36). A subset of patients (n = 8) was enrolled before the amendment restricting enrollment to *EGFR* L858R or

TABLE 2. Adverse Events

Adverse Event	Teliso-V Plus Erlotinib (N = 42), No. (%)	
	Any Grade (≥ 10% of Patients)	Grade ≥ 3 (≥ 5% of Patients)
Any adverse event	42 (100)	27 (64)
Peripheral sensory neuropathy	18 (43)	3 (7)
Dermatitis acneiform	16 (38)	2 (5)
Diarrhea	14 (33)	3 (7)
Hypoalbuminemia	14 (33)	0
Fatigue	13 (31)	2 (5)
Dyspnea	12 (29)	2 (5)
Decreased appetite	10 (24)	1 (2)
Nausea	10 (24)	0
Asthenia	9 (21)	2 (5)
Vomiting	9 (21)	0
Cough	8 (19)	0
Peripheral neuropathy	8 (19)	1 (2)
Alopecia	6 (14)	0
Anemia	6 (14)	2 (5)
Decreased weight	6 (14)	0
Hypomagnesemia	6 (14)	0
Increased aspartate aminotransferase	6 (14)	0
Keratitis	6 (14)	0
Muscle spasms	6 (14)	0
Pulmonary embolism	6 (14)	6 (14)
Arthralgia	5 (12)	0
Constipation	5 (12)	0
Dry skin	5 (12)	0
Hypokalemia	5 (12)	4 (10)
Hypophosphatemia	5 (12)	3 (7)
Peripheral edema	5 (12)	0
Pneumonia	5 (12)	2 (5)
Dehydration	4 (10)	1 (2)
Fall	4 (10)	0
Hypocalcemia	4 (10)	0
Increased alanine aminotransferase	4 (10)	0
Increased blood alkaline phosphatase	4 (10)	0
Increased gamma-glutamyltransferase	4 (10)	0
Paronychia	4 (10)	0
Pruritus	4 (10)	1 (3)
Upper respiratory tract infection	4 (10)	0
Malignant neoplasm progression	3 (7)	3 (7)

Abbreviation: Teliso-V, telisotuzumab vedotin.

del19 was added. Five of these eight patients had an unaltered *EGFR* gene (*EGFR*-wild-type [WT]), and three had either rare (L861Q or L861R) or unknown *EGFR* mutations. Baseline demographics of the c-Met+ efficacy-evaluable population are summarized in Table 1. Importantly, 53% were c-Met high (H-score ≥ 225). *MET* amplification was found in six patients (17%): four *EGFR*-M+, one *EGFR*-WT, and one rare/unknown *EGFR*. Of the six *MET*-amplified patients, five were c-Met high. Patients with confirmed T790M mutations (n = 13) were split evenly between c-Met high (n = 6) and lower c-Met expression (n = 7).

Twenty-five of 36 efficacy-evaluable patients (69%) had received three or more prior lines of therapy. Thirty of 36 patients (83%) received a first-/second-generation EGFR TKI across all lines, and 16 patients (44%) received a third-generation EGFR TKI. In 33%, a third-generation EGFR TKI was their last prior therapy.

Safety

All patients experienced one or more AE (Table 2). The most common any-grade AEs were peripheral sensory neuropathy (43%), dermatitis acneiform (38%), diarrhea (33%), and hypoalbuminemia (33%). Grade ≥ 3 AEs occurred in 27 patients (64%); most common were pulmonary embolism (PE) (14%), hypokalemia (10%), and diarrhea, malignant neoplasm progression, peripheral sensory neuropathy, and hypophosphatemia (7% each). Any-grade AEs deemed possibly related to Teliso-V (treatment-related AEs) were observed in 37 patients (88%), the most common being peripheral sensory neuropathy (36%) and peripheral neuropathy (19%; Data Supplement).

Grade ≥ 3 treatment-related AEs occurred in 13 patients (31%); the most frequently occurring were hypophosphatemia and peripheral sensory neuropathy (7% each; Data Supplement). Serious AEs (≥ 5% of patients) were malignant neoplasm progression (7%), and pneumonia, dehydration, and PE (5% each; Data Supplement). Three of 42 patients (7%) reported ≥ 1 serious AE deemed possibly related to Teliso-V: decreased appetite, dehydration, hemoptysis, peripheral neuropathy, and pneumonia (2% each).

Twenty-four of 42 patients (57%) reported at least one event falling into the peripheral neuropathy Standardized Medical Dictionary for Regulatory Activities Queries. There were 32 any-grade neuropathy-type events reported in these 24 patients, with peripheral sensory neuropathy the most common (18/32). These events were mostly low grade, with five events of grade ≥ 3 (three peripheral sensory neuropathy, one peripheral sensorimotor neuropathy, and one peripheral neuropathy). Median time to first onset of any event from the peripheral neuropathy Standardized Medical Dictionary for Regulatory Activities Queries was 72.5 days (range, 5-197 days). The most common AE leading to study drug reductions, interruptions,

TABLE 3. Efficacy Summary

Response	Teliso-V Plus Erlotinib			
	c-Met+ *EGFR*-M+ (n = 28), No./n (%)	c-Met+ *EGFR*-WT (n = 5), No./n (%)	c-Met+ *EGFR*-Rare/Unknown (n = 3), No./n (%)	Total (N = 36), No./N (%)
Best overall response[a]				
Complete response	1/28 (4)	0/5	0/3	1/36 (3)
Partial response	8/28 (29)	2/5 (40)	0/3	10/36 (28)
Stable disease	15/28 (54)	2/5 (40)	3/3 (100)	20/36 (56)
Progressive disease	4/28 (14)	1/5 (20)	0/3	5/36 (14)
Objective response rate[b] [95% CI]	9/28 (32.1) [15.9 to 52.4]	2/5 (40.0) [5.3 to 85.3]	0 [0.0 to 70.8]	11/36 (30.6) [16.3 to 48.1]
Disease control rate[c] [95% CI]	24/28 (85.7) [67.3 to 96.0]	4/5 (80.0) [28.4 to 99.5]	3/3 (100) [29.2 to 100]	31/36 (86.1) [70.5 to 95.3]
Progression-free survival				
Median, months [95% CI]	5.9 [2.8 to NR]	6.0 [1.2 to NR]	4.0 [1.6 to NR]	5.9 [2.8 to NR]

Abbreviations: c-Met+, c-Met–overexpressing; *EGFR*, epidermal growth factor receptor; *EGFR*-M+, *EGFR* mutation-positive; *EGFR*-WT, *EGFR* wild-type; NR, not reached; Teliso-V, telisotuzumab vedotin.

[a]Median duration of response was NR at the time of data cutoff.

[b]Objective response rate is the proportion of patients with a confirmed complete response or partial response.

[c]Disease control rate is the proportion of patients with a confirmed complete response, partial response, or stable disease.

or discontinuations was peripheral sensory neuropathy (10%, 21%, and 21%, respectively; Data Supplement). Death due to AEs occurred in three patients (7%), resulting from one case of hemoptysis (2%) that was deemed possibly related to Teliso-V, and two cases (5%) of malignant neoplasm progression (Data Supplement).

Pharmacokinetics

The preliminary pharmacokinetic parameters for Teliso-V conjugate in the patients who received Teliso-V plus erlotinib at 2.7 mg/kg once every 3 weeks are summarized in the Data Supplement. The estimated half-life was approximately 3 days. Teliso-V concentrations peaked immediately post-infusion (time to C_{max} [maximum observed plasma concentration]; ≈ 1 hour), with geometric mean (%CV) C_{max} of 57.0 μg/mL (21%) and area under the concentration-time curve from time zero to infinity (%CV) of 4,048 μg h/mL (17%).

Efficacy

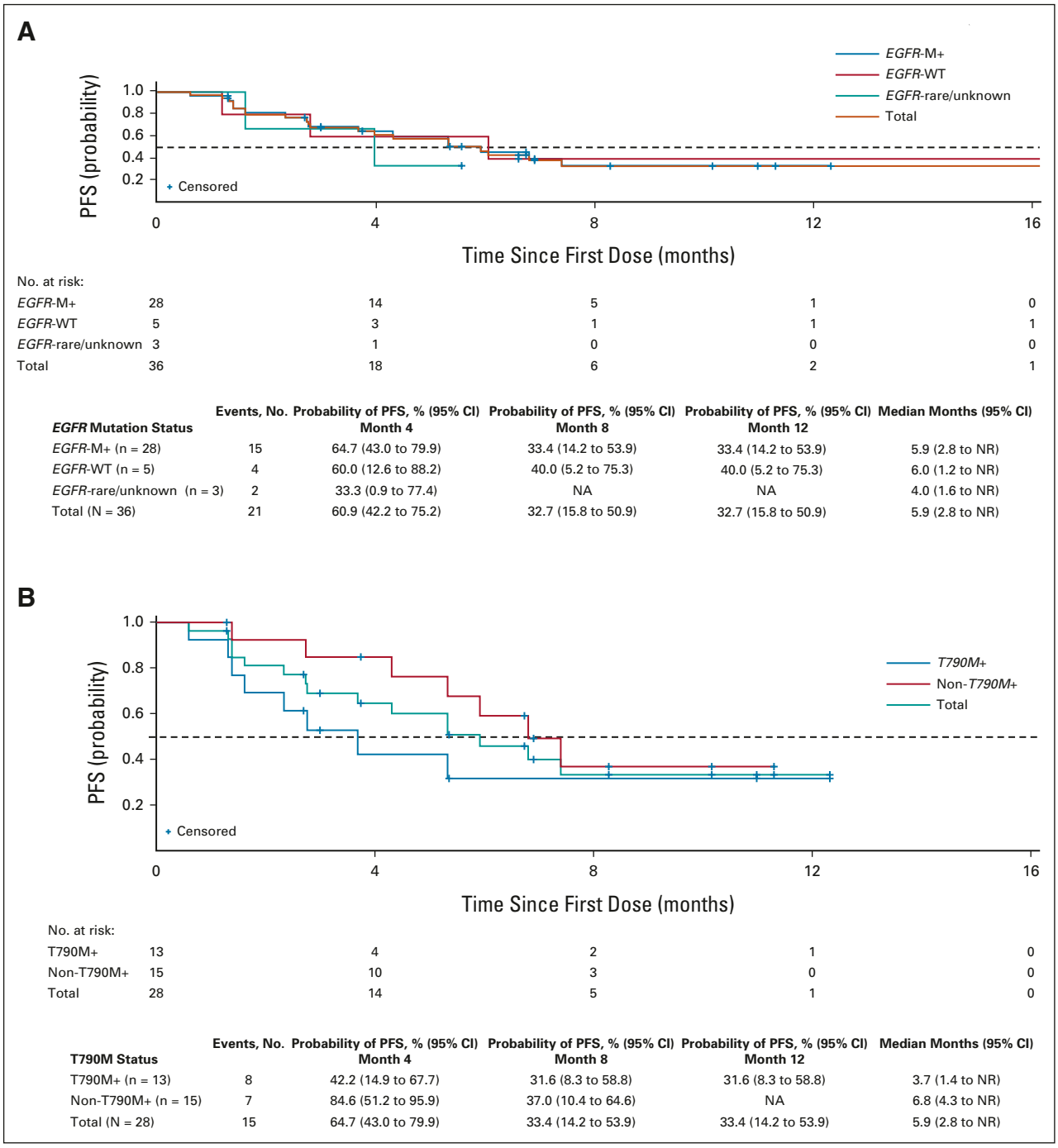
Median duration of exposure to Teliso-V was 18.1 weeks (range, 3.1-99.1 weeks), and patients received a median seven treatment cycles (range, 2.0-34.0 cycles). Median duration of exposure to erlotinib was 20.3 weeks (range, 3.1-110.4 weeks), with patients receiving a median five-and-a-half treatment cycles (range, 2.0-33.0 cycles).

Efficacy results are summarized in Table 3. ORR for all efficacy-evaluable patients was 30.6% (11/36; 95% CI, 16.3 to 48.1), and DCR was 86.1% (31/36; 95% CI, 70.5 to 95.3). Median PFS for all efficacy-evaluable patients was 5.9 months (95% CI, 2.8 to not reached [NR]). Duration of response was NR at the time of data cutoff.

For *EGFR*-M+ patients (n = 28), ORR was 32.1% (9/28; 95% CI, 15.9 to 52.4), with one CR (3.6%) and eight PR (28.6%). DCR was 85.7% (24/28; 95% CI, 67.3 to 96.0) and median PFS was 5.9 months (95% CI, 2.8 to NR; Table 3, Fig 1A). In an exploratory ad hoc subgroup analysis of *EGFR*-M+ patients by T790M status (n = 13 T790M+ *v* n = 15 non-T790M+), ORR and DCR were 31% and 77%, respectively, in T790M+, and 33% and 93%, respectively, in non-T790M+ patients (Table 4). Median PFS was 3.7 months (95% CI, 1.4 to NR) for T790M+ patients, compared with 6.8 months (95% CI, 4.3 to NR) for non-T790M+ patients (Fig 1B).

ORR in *EGFR*-M+ patients who had previously received the third-generation EGFR TKI osimertinib (n = 15) was 27% (4/15). ORR was 39% (5/13) in *EGFR*-M+ patients who had never received osimertinib. DCR was 100% (13/13) for those with no prior exposure to osimertinib compared with 73.3% (11/15) for those who had prior exposure (Table 4). ORR in *EGFR*-WT patients (n = 5) was 40% (2/5; two PR) and DCR was 80% (4/5; two PR and two SD). All three patients with rare/unknown *EGFR* mutations achieved SD.

Figure 2 shows best percentage change from baseline in target lesions. Among patients with c-Met–high scores (n = 19), one achieved a CR (1/19; 5.3%; *EGFR*-M+), nine achieved a PR (9/19; 47.4%; six *EGFR*-M+ and three *EGFR*-WT), five had SD (5/19; 26.3%; *EGFR*-M+), and four experienced progressive disease (4/19; 21.1%; three *EGFR*-M+ and one rare/unknown *EGFR*), indicating an ORR of 52.6% and DCR of 78.9%. No patients with lower c-Met scores achieved a CR; two of 16 had a PR (12.5%), 12 had SD (75%), and two had progressive disease (12.5%), indicating an ORR of 12.5% and DCR of 87.5%. Of note, five of six *MET*-amplified patients were also c-Met high. Of these, three of five achieved a PR (60%) and two had SD (50%), indicating a DCR of 100%. The one *MET*-amplified patient with a lower c-Met score achieved SD.



EGFR Mutation Status	Events, No.	Probability of PFS, % (95% CI) Month 4	Probability of PFS, % (95% CI) Month 8	Probability of PFS, % (95% CI) Month 12	Median Months (95% CI)
EGFR-M+ (n = 28)	15	64.7 (43.0 to 79.9)	33.4 (14.2 to 53.9)	33.4 (14.2 to 53.9)	5.9 (2.8 to NR)
EGFR-WT (n = 5)	4	60.0 (12.6 to 88.2)	40.0 (5.2 to 75.3)	40.0 (5.2 to 75.3)	6.0 (1.2 to NR)
EGFR-rare/unknown (n = 3)	2	33.3 (0.9 to 77.4)	NA	NA	4.0 (1.6 to NR)
Total (N = 36)	21	60.9 (42.2 to 75.2)	32.7 (15.8 to 50.9)	32.7 (15.8 to 50.9)	5.9 (2.8 to NR)

T790M Status	Events, No.	Probability of PFS, % (95% CI) Month 4	Probability of PFS, % (95% CI) Month 8	Probability of PFS, % (95% CI) Month 12	Median Months (95% CI)
T790M+ (n = 13)	8	42.2 (14.9 to 67.7)	31.6 (8.3 to 58.8)	31.6 (8.3 to 58.8)	3.7 (1.4 to NR)
Non-T790M+ (n = 15)	7	84.6 (51.2 to 95.9)	37.0 (10.4 to 64.6)	NA	6.8 (4.3 to NR)
Total (N = 28)	15	64.7 (43.0 to 79.9)	33.4 (14.2 to 53.9)	33.4 (14.2 to 53.9)	5.9 (2.8 to NR)

FIG 1. Kaplan-Meier estimates of progression-free survival in (A) the efficacy-evaluable population stratified by *EGFR* mutation status and (B) the subset of patients classified as *EGFR*-M+ with confirmed T790M resistance status. EGFR, epidermal growth factor receptor; *EGFR*-M+, *EGFR* mutation-positive (del19, L858R); *EGFR*-WT, *EGFR* mutation wild-type; NR, not reached; PFS, progression-free survival.

Most responses were achieved by the first post-treatment scan (Data Supplement).

DISCUSSION

Teliso-V plus erlotinib had an acceptable safety profile in patients with c-Met+ NSCLC. Importantly, the addition of erlotinib to Teliso-V produced no unexpected safety signals, and the pharmacokinetic profile was similar to that observed with Teliso-V monotherapy.[16] This combination also showed promising efficacy, especially in c-Met–high *EGFR*-M+ patients, in agreement with each drug's mechanism of action.

The most frequent AE observed in this study was neuropathy (any kind; 57%; Table 2), a known side effect of MMAE-containing drugs.[30] Although 11 patients (26%)

TABLE 4. Exploratory Subgroup Analysis

Response	Teliso-V Plus Erlotinib c-Met+ *EGFR*-M+ (n = 28)
Objective response rate,[a] No./n (%)	
T790M+	4/13 (31)
Non-T790M+	5/15 (33)
Previously treated with osimertinib	
Yes	4/15 (27)
No	5/13 (39)
Disease control rate,[b] No./n (%)	
T790M+	10/13 (77)
Non-T790M+	14/15 (93)
Previously treated with osimertinib	
Yes	11/15 (73)
No	13/13 (100)
Progression-free survival[c]	
T790M+, median months	3.7
Non-T790M+, median months	6.8

Abbreviations: c-Met+, c-Met–overexpressing; *EGFR*, epidermal growth factor receptor; *EGFR*-M+, *EGFR* mutation-positive; Teliso-V, telisotuzumab vedotin.

[a]Objective response rate is the proportion of patients with a confirmed complete response or partial response.

[b]Disease control rate is the proportion of patients with a confirmed complete response, partial response, or stable disease.

[c]Median duration of response was NR at the time of data cutoff.

required dose interruption or discontinuation of Teliso-V because of neuropathy, most of these events were mild-to-moderate (only 12% grade ≥ 3). The rate of peripheral sensory neuropathy in this study (43%) was similar to that observed with other approved MMAE ADC-containing drugs.[31-34] Of note, 86% of patients in this study had received prior chemotherapy and several had prior history of neuropathy, both of which are risk factors for development of subsequent neuropathy.[35]

Ocular toxicities affecting the cornea are also associated with the use of MMAE ADCs and erlotinib,[17,18,36,37] with incidence rates as high as 46%-77% for some approved drugs.[32,38] Grade 1-2 keratitis was reported in 14% of patients in this study (Table 2); however, no patients experienced grade ≥ 3 keratitis. Incidence rates of all other ocular toxicities were ≤ 5% for patients treated with Teliso-V plus erlotinib, well below the rates reported for other approved MMAE ADC-containing drugs.

Additionally, patients in this study displayed some toxicities associated with targeting c-Met,[39,40] including peripheral edema (12%) and hypoalbuminemia (33%). However, similar to Teliso-V monotherapy, no patients experienced grade ≥ 3 peripheral edema or hypoalbuminemia.[16] Altogether, this suggests that the addition of erlotinib did not exacerbate the safety profile of Teliso-V.

AEs associated with use of erlotinib, most notably skin toxicities, have been previously reported.[18,41,42] Skin-related AEs were also reported in our study, including dermatitis

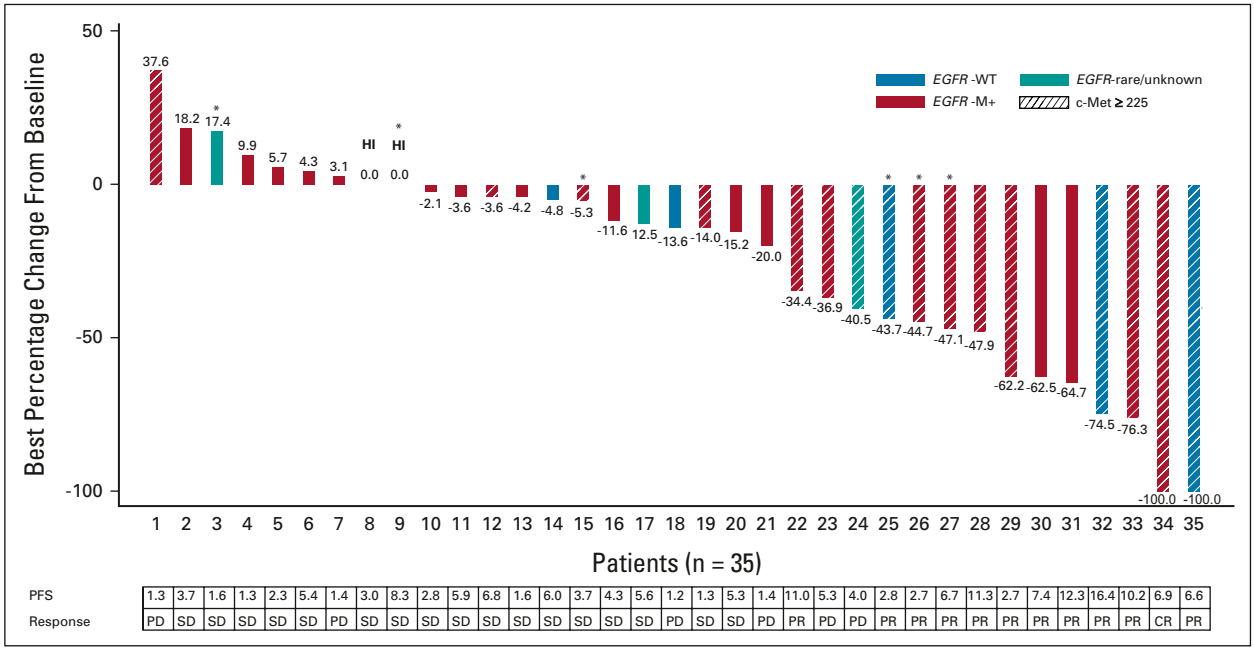


FIG 2. Best percentage reduction in target lesions from baseline in patients receiving Teliso-V plus erlotinib. Asterisks indicate *MET*-amplified patients (n = 6). HI indicates c-Met high (≥ 225; n = 19). CR, complete response; EGFR, epidermal growth factor receptor; *EGFR*-M+, *EGFR* mutation-positive; *EGFR*-WT, *EGFR* mutation wild-type; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

acneiform (38%). Although our sample is small, this rate is higher than that reported for erlotinib monotherapy. Importantly, most AEs of dermatitis acneiform in this study were low grade (2 grade ≥ 3). Notably, more than half of the patients enrolled in this study had received three or more prior lines of EGFR TKI therapy, and consequently may have become hypersensitized to EGFR TKI-mediated skin toxicity.

There were six events of PE in our study, all of which were grade ≥ 3. However, none of these events were deemed by investigators as related to Teliso-V. It is important to note that the patients in this study were in generally poor health with heavily pretreated metastatic lung cancer, thus putting them at increased risk for high-grade pulmonary events. Previous clinical studies of Teliso-V monotherapy[16,29] reported fewer PE AEs, and it cannot be excluded that the observations made here are related to the combination of Teliso-V plus erlotinib. Further studies with larger data sets are needed to understand this potential relationship.

Promising antitumor activity was observed with Teliso-V plus erlotinib in this heavily pretreated population, including almost 50% who had previously received three or more lines of EGFR TKI treatment. Despite these demographics, the ORR and DCR were 30.6% and 86.1%, respectively, in the overall efficacy set, demonstrating an improvement over Teliso-V monotherapy (ORR, 18.8%; DCR, 56.3%),[16] and 32.1% and 85.7%, respectively, for the *EGFR*-M+ group.

We cannot rule out the possibility that the antitumor activity reported in our study is driven by Teliso-V alone, as most *EGFR*-M+ patients had received one or more prior line of TKI therapy, which often leads to acquired resistance to subsequent EGFR-targeted therapies.[13,14,24] Indeed, 46% of *EGFR*-M+ patients in our study were T790M+, a known acquired mutation conferring resistance to first-/second-generation EGFR TKIs. Here, we report that median PFS for non-T790M+ patients was higher (6.8 months) compared with T790M+ patients (3.7 months), suggesting that non-T790M+ patients derived greater benefit from the combination of Teliso-V plus erlotinib.

Patients in the efficacy-evaluable cohort of this study were all c-Met+ as defined by H-score ≥ 150. However, levels of c-Met overexpression within the tumor varied among patients, and response rates were higher in tumors with higher H-scores. This observation is in line with the proposed mechanism of action of Teliso-V, whereby internalization of Teliso-V bound to c-Met allows for the intracellular release of the MMAE toxin. Other studies have proposed targeting both EGFR and c-Met using TKIs against both receptors.[40,43,44] One key difference with our study is that to respond to a c-Met TKI, tumors must be addicted to c-Met signaling, which requires a genetic alteration such as *MET*-amplification or a *MET* exon14 skipping mutation.[5,6] Here, we were able to target both *MET*-amplified (17%) as well as c-Met+ but nonamplified tumors (78%), possibly expanding the patient population that could benefit from this combination compared with a combination of TKIs. Interestingly, the *MET*-amplified patient subset responded particularly well to Teliso-V plus erlotinib, with an ORR of 62.5% and a DCR of 100%. Of the five patients who were c-Met high and *MET*-amplified, the ORR was 60% (three PR) and the DCR was 100% (three PR and two SD). These results could indicate that *MET*-amplified tumors have higher levels of c-Met protein expression, that Teliso-V also exercises a c-Met signaling inhibition effect in addition to its direct cell killing effect, or both.

Predefining c-Met+ as H-score ≥ 150 is a limitation of this study, as this threshold was determined on the basis of preclinical data and may not represent the most appropriate threshold.[9] Additionally, assessment of c-Met expression was determined on the basis of tissue obtained at any time before enrollment, including archival tissue, and c-Met levels could have changed during the period between tissue collection and study enrollment. The use of archival tissue also hampered assessment of *MET* amplification and *MET* exon 14 skipping mutation status, as not all patients had sufficient tissue available for testing.

Additionally, several *EGFR*-WT patients were enrolled, and some activity was seen in these patients (ORR, 40%; DCR, 80%). This activity could be due to Teliso-V alone, as patients with *EGFR*-WT tumors are unlikely to benefit from erlotinib therapy. The antitumor activity of Teliso-V monotherapy in *EGFR*-WT patients is currently being explored in the LUMINOSITY clinical trial (ClinicalTrials.gov identifier: NCT03539536).

Osimertinib has now displaced prior-generation agents as first-line treatment because of the improvements in overall survival and PFS observed in the phase III FLAURA study (ClinicalTrials.gov identifier: NCT02296125),[27,28] as well as its activity against T790M+ tumors (reviewed in Gao et al[45]). As such, the combination of Teliso-V plus osimertinib is now being explored in a phase I study (ClinicalTrials.gov identifier: NCT02099058).[9]

In conclusion, the combination of Teliso-V plus erlotinib showed an acceptable safety profile and encouraging antitumor activity in heavily pretreated patients, especially in *EGFR*-M+ c-Met+ NSCLC in which previous EGFR TKIs failed. Although exploratory, targeting c-Met and *EGFR* showed promising results in this underserved patient population and is worthy of further evaluation in larger studies. Our data also support additional prospective investigations of Teliso-V in combination with osimertinib in selected patient populations.

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DATA SHARING STATEMENT

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

Phase Ib Study of Telisotuzumab Vedotin in Combination With Erlotinib in Patients With c-Met Protein–Expressing Non–Small-Cell Lung Cancer

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Research Funding: EMD Serono (Inst), Genentech (Inst), AbbVie (Inst), Regeneron (Inst), Astellas Pharma (Inst), Tizona Therapeutics, Inc (Inst), Lilly (Inst), Novartis (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Five Prime Therapeutics (Inst), Jounce Therapeutics (Inst)
Patents, Royalties, Other Intellectual Property: Author Royalties for UpToDate, an evidence based, peer reviewed information resource, available via the web, desktop, and PDA

Daniel Morgensztern
Stock and Other Ownership Interests: Bristol Myers Squibb/Medarex, Abbott Laboratories
Consulting or Advisory Role: Bristol Myers Squibb, AbbVie, G1 Therapeutics, Lilly Medical, Mirati Therapeutics, Arcus Biosciences
Research Funding: Heat Biologics (Inst), Merck (Inst), Celgene (Inst), AstraZeneca (Inst), Baxter (Inst), Incyte (Inst), AbbVie (Inst), Bristol Myers Squibb (Inst), EpicentRx (Inst), Pfizer (Inst), Roche (Inst), Lilly (Inst), Altum Pharmaceuticals (Inst), Array BioPharma (Inst), Surface Oncology (Inst), Arcus Biosciences (Inst), Boehringer Ingelheim (Inst), Y-mAbs Therapeutics (Inst)

Monica Motwani
Employment: AbbVie, Gilead Sciences, GlaxoSmithKline
Stock and Other Ownership Interests: Gilead Sciences, AbbVie
Patents, Royalties, Other Intellectual Property: A patent on the DR4/5 and KRAS relationship. Patent filed by AbbVie and I am listed as a coinventor. No royalties are received
Travel, Accommodations, Expenses: Gilead Sciences, AbbVie

Everett Vokes
Stock and Other Ownership Interests: Coordination Pharmaceuticals, McKesson
Honoraria: Takeda, Ascendis Pharma
Consulting or Advisory Role: Takeda, Ascendis Pharma, Bristol Myers Squibb/Sanofi, EMD Serono
Research Funding: AbbVie, Bristol Myers Squibb, Celgene, Novartis, Lilly (Inst)
Open Payments Link: https://openpaymentsdata.cms.gov/physician/930740

Apurvasena Parikh
Employment: AbbVie
Stock and Other Ownership Interests: AbbVie

No other potential conflicts of interest were reported.