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Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study

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abstract

PURPOSE Small-cell lung cancer (SCLC) is an aggressive malignancy with limited treatments. Delta-like ligand 3 (DLL3) is aberrantly expressed in most SCLC. Tarlatamab (AMG 757), a bispecific T-cell engager molecule, binds both DLL3 and CD3 leading to T-cell–mediated tumor lysis. Herein, we report phase I results of tarlatamab in patients with SCLC.

PATIENTS AND METHODS This study evaluated tarlatamab in patients with relapsed/refractory SCLC. The primary end point was safety. Secondary end points included antitumor activity by modified RECIST 1.1, overall survival, and pharmacokinetics.

RESULTS By July 19, 2022, 107 patients received tarlatamab in dose exploration (0.003 to 100 mg; n = 73) and expansion (100 mg; n = 34) cohorts. Median prior lines of anticancer therapy were 2 (range, 1-6); 49.5% received antiprogrammed death-1/programmed death ligand-1 therapy. Any-grade treatment-related adverse events occurred in 97 patients (90.7%) and grade ≥ 3 in 33 patients (30.8%). One patient (1%) had grade 5 pneumonitis. Cytokine release syndrome was the most common treatment-related adverse event, occurring in 56 patients (52%) including grade 3 in one patient (1%). Maximum tolerated dose was not reached. Objective response rate was 23.4% (95% CI, 15.7 to 32.5) including two complete and 23 partial responses. The median duration of response was 12.3 months (95% CI, 6.6 to 14.9). The disease control rate was 51.4% (95% CI, 41.5 to 61.2). The median progression-free survival and overall survival were 3.7 months (95% CI, 2.1 to 5.4) and 13.2 months (95% CI, 10.5 to not reached), respectively. Exploratory analysis suggests that selecting for increased DLL3 expression can result in increased clinical benefit.

CONCLUSION In patients with heavily pretreated SCLC, tarlatamab demonstrated manageable safety with encouraging response durability. Further evaluation of this promising molecule is ongoing.

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ASSOCIATED CONTENT

See accompanying editorial on page 2877

Appendix

Data Supplement

Protocol

Video Abstract

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Small-cell lung cancer (SCLC) is an aggressive lung cancer subtype with neuroendocrine differentiation diagnosed in more than 150,000 people worldwide each year.[1,2] The 3-year survival rate for patients with extensive stage (ES) SCLC is 6%.[3] The addition of immune checkpoint inhibitors atezolizumab or durvalumab to platinum and etoposide chemotherapy followed by maintenance therapy with checkpoint inhibitor alone as first-line treatment for SCLC has led to approximately 30% reduction in the risk of death and durable but modest survival gains for a small subset of patients with ES-SCLC.[3,4] Available therapies are limited for the majority of patients with SCLC who relapse. Topotecan, the most widely used second-line agent globally, has limited efficacy and an unfavorable safety profile.[5,6] Lurbinectedin, in 2020 became the first drug approval by the US Food and Drug Administration in over 20 years for second line, was conditionally approved on the basis of an objective response rate (ORR) of 35%; however, a randomized study failed to demonstrate OS benefit.[7,8] No agent is specifically approved for third-line treatment of relapsed SCLC.

The notch signaling pathway is a regulator of neuroendocrine differentiation in SCLC.[9,10] The inhibitory notch ligand delta-like ligand 3 (DLL3) is aberrantly expressed on the surface of up to 85% of SCLC cells

CONTEXT

Key Objective

Tarlatamab, a half-life extended bispecific T-cell engager molecule targeting delta-like ligand 3, is the first agent in this new therapeutic class to be evaluated clinically in patients with small-cell lung cancer (SCLC). An analysis of data from the large phase I study of tarlatamab in patients with relapsed/refractory SCLC was performed to assess safety and efficacy.

Knowledge Generated

With more than 100 patients treated in the phase I study, tarlatamab has shown tolerability and remarkable antitumor activity over a wide range of target doses in patients with heavily pretreated SCLC. A promising response rate, high median duration of response, and encouraging median overall survival, along with a reasonable safety profile, observed in this study form the basis for planned and ongoing later-stage studies.

Relevance *(T.E. Stinchcombe)*

Tarlatamab has a novel mechanism of action, and the activity in previously treated SCLC, a patient population with few therapeutic options, is promising. The results of additional studies are eagerly awaited.*

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

and minimally expressed in normal tissues, making it a compelling therapeutic target.[11-14] In vitro SCLC models have indicated a role for DLL3 in promoting tumor growth, migration, and invasion.[15] The DLL3-targeted antibody-drug conjugate rovalpituzumab tesirine showed clinical antitumor activity in patients with SCLC.[16]

Tarlatamab, a half-life extended bispecific T-cell engager (HLE BiTE) molecule, binds both DLL3 on cancer cells and CD3 on T cells leading to T-cell–mediated tumor lysis. Tarlatamab promotes tumor regression in preclinical models of SCLC.[17] Tarlatamab is the first DLL3-targeted immune therapy to be evaluated clinically in SCLC.

In this phase I trial, we evaluated the safety, pharmacokinetics (PK), and preliminary efficacy of tarlatamab in patients with SCLC.

PATIENTS AND METHODS

Study Design and Participants

DeLLphi-300 (ClinicalTrials.gov identifier: NCT03319940) is a phase I, multicountry, open-label, dose-escalation study evaluating tarlatamab monotherapy and combination with antiprogrammed cell death protein one (PD-1) therapy in patients with SCLC. The results reported here are limited to the monotherapy regimen including dose escalation and expansion cohorts. Eligible patients were age 18 years or older with histologically or cytologically confirmed SCLC who had progressed or recurred after at least one previous platinum-based regimen and, if standard of care, a programmed cell death ligand 1 (PD-L1) inhibitor in addition to chemotherapy. Patients had an Eastern Cooperative Oncology Group performance status of two or less and at least two measurable lesions defined per modified response evaluation criteria in solid tumors (RECIST), version 1.1 and if present, brain metastases that were clinically and radiologically stable after treatment. Key exclusion criteria were untreated brain metastases and severe or recurrent immune-mediated adverse events (AEs) or infusion-related reactions while on prior immunotherapy. Full eligibility criteria are included in the study Protocol (online only).

The protocol and amendments were approved by the institutional review board or ethics committee at each participating site. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Procedures

The planned tarlatamab dose levels were 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, and 100 mg by intravenous (IV) infusion administered every 2 weeks. The first four dose levels were planned as single-patient cohorts as AEs were expected to be low. Tarlatamab administration was continued until disease progression, unacceptable side effects, or consent withdrawal.

Outcomes

The primary end point was safety including dose-limiting toxicities (DLTs; defined as tarlatamab-related toxicity within 28 days after the first dose and meeting protocol criteria), AEs during the treatment period (treatment-emergent AEs [TEAEs]), and TEAEs possibly related to tarlatamab per investigator review (treatment-related AEs). Secondary end points included PK, antitumor activity including objective response per modified RECIST 1.1[18-20] by investigator assessment, duration of response (DOR), time to response, progression-free survival (PFS), and overall survival (OS). Exploratory end points assessed included anti-tarlatamab antibody formation and relationship between baseline target protein expression and clinical benefit (Data Supplement [online only]).

Statistical Analysis

This analysis included patients enrolled in escalation and expansion cohorts. Data cutoff was July 19, 2022. Sample size was based on clinical considerations and standard dose-escalation design. A two-parameter Bayesian Logistic Regression Model guided dose exploration.[21] The Sponsor, in consultation with investigators, reviewed the Bayesian Logistic Regression Model recommended dose level and cumulative data by cohort before dose escalation decisions. AEs and DLTs were evaluated continually. On the basis of the overall benefit-risk profile of 100 mg, this dose was further evaluated as the expansion dose. Descriptive statistics are provided for selected demographics, safety, PK, pharmacodynamics, and biomarker data. Exploratory analysis was performed to evaluate the relationship between baseline expression of DLL3 and clinical benefit (Data Supplement). Kaplan-Meier methods were used to estimate the median and percentiles for time to event end points with 95% CI calculated using the Brookmeyer and Crowley[22] method.

RESULTS

Patients

Between December 26, 2017, and April 28, 2022, 107 patients received tarlatamab in dose escalation (0.003-100 mg; n = 73) and expansion (100 mg; n = 34) cohorts (Data Supplement). Step dosing was used starting with the 3-mg cohort (using 1 mg as the run-in dose, followed by target dose on day 8, day 15, and every 2 weeks thereafter) because of observed cytokine release syndrome (CRS) in prior cohorts.

Baseline characteristics are summarized in Table 1 (additional in Data Supplement). The median age was 63 years (range, 32-80). Eastern Cooperative Oncology Group performance status was 0-1 in 99% of patients. More than 70% of patients had ≥ 2 lines of prior therapy, 25% were platinum refractory, and 50% had prior PD-1/PD-L1 inhibitor.

The median follow-up was 8.7 months (range, 0.2-31.8). Treatment was discontinued in 92 patients (86%), most commonly for disease progression (n = 77 [72%]). At data cutoff, 47 patients (43.9%) had ended study because of death. The median number of treatment cycles started was 3 (interquartile range [IQR], 1-8), and the median number of tarlatamab doses received was 6 (IQR, 3-16).

Retrospective DLL3 immunohistochemistry analysis showed that DLL3 was expressed (≥ 1%) in 85 of 90 (94%) evaluable patients; the median H-score was 186 (range, 0-300), and the median tumor cell positivity was 95% (range, 0%-100%).

Safety and Tolerability

DLTs occurred in six patients including pneumonitis (n = 1 [last prior dose, 0.3 mg]), increased alanine aminotransferase (n = 1 [1 mg]), CRS (n = 1 [1 mg]), encephalopathy (n = 1 [10 mg]), chills, pyrexia, and

TABLE 1. Patient Demographics and Baseline Characteristics

Patient Characteristic	All Patients (N = 107)
Age, years, median (IQR)	63.0 (58.0-69.0)
Sex, No. (%)	
Male	61 (57)
Female	46 (43)
Race, No. (%)	
White	86 (80)
Asian	13 (12)
Black/African American	3 (3)
Other	5 (5)
Ethnicity, No. (%)	
Hispanic/Latino	2 (2)
Not Hispanic/Latino	105 (98)
Smoking history, No. (%)	
Never	10 (9)
Current	14 (13)
Former	81 (76)
Missing	2 (2)
ECOG performance status, No. (%)	
0	40 (37)
1	66 (62)
2	1 (1)
Prior lines of therapy	
Median (IQR)	2.0 (1.0-3.0)
1, No. (%)	30 (28)
2, No. (%)	45 (42)
≥ 3, No. (%)	32 (30)
Most recent line platinum-treated patients, No. (%)	
Platinum-sensitive	54 (50)
Platinum-resistant	22 (21)
Platinum-refractory	26 (24)
Not assessable/missing	4 (4)
Prior radiotherapy, No. (%)	
Yes	85 (79)
No	22 (21)
Prior anti–PD-1 or anti–PD-L1, No. (%)	
Yes	53 (50)
No	54 (50)
Metastatic at baseline, No. (%)	
Yes	100 (93)
Brain metastases	39 (36)
Liver metastases	54 (50)
No	7 (7)
ES disease, No. (%)[a]	100 (93)

(continued on following page)

TABLE 1. Patient Demographics and Baseline Characteristics (continued)

Patient Characteristic	All Patients (N = 107)
Sum of diameters of target lesions at baseline, mm	
Median (IQR)	75.0 (43.0-108.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ES, extensive stage; IQR, interquartile range; PD-1, programmed cell death protein one; PD-L1, programmed cell death ligand 1.

[a]Stage of disease unknown for one patient at baseline.

neutropenia (n = 1 each [100 mg]). A maximum tolerated dose was not reached; the highest protocol-planned dose (100 mg) was evaluated in the expansion cohort. Four patients (3.7%) discontinued tarlatamab because of treatment-related AEs of encephalopathy (n = 1), immune effector cell-associated neurotoxicity (ICANS; n = 1), and pneumonitis (n = 2). A single G5 pneumonitis event was recorded in a 70-year old man with a history of prior carboplatin/etoposide chemotherapy, chronic obstructive pulmonary disease, and radiation to the lung and pleural nodules. The event onset was cycle 1 day 18, 3 days after the second tarlatamab treatment (both doses 0.3 mg), and was confounded by clinically significant disease progression at the time of pneumonitis requiring urgent palliative radiation to the lung and to a soft tissue mass in the thoracic spine causing spinal cord compression. The cause of death was attributed by the investigator to disease progression and pneumonitis. An additional G3 and three additional G2 TEAEs of pneumonitis were observed (5 of 107 [4.7%] overall incidence of pneumonitis). Among patients with G2 pneumonitis, one patient ended treatment because of neurotoxicity (not pneumonitis), one patient had resolution of pneumonitis before discontinuation for PD, and one patient resumed treatment without dose change.

TEAEs of any cause/grade occurred in 107 patients (100%; Table 2 and Data Supplement). The most common were CRS (56 patients [52.3%]), pyrexia (43 [40.2%]), and constipation (33 [30.8%]). Grade ≥ 3 AEs occurred in 61 patients (57.0%) with the most common being neutropenia (8.4%; Data Supplement). Serious AEs occurred in 55 patients (51.4%; Data Supplement). TEAEs led to dose reductions in nine patients (8.4%) with 4 (3.7%) having CRS-related reductions (Data Supplement). Dose interruption occurred in 20 patients (18.7%; Data Supplement). Any-grade and grade ≥ 3 treatment-related AEs occurred in 97 (90.7%) and 33 (30.8%) patients, respectively (Data Supplement).

CRS, neutropenia, and neurologic events were monitored as events of interest on the basis of preclinical, clinical, and mechanistic data with tarlatamab, other BiTE molecules, and other T-cell–associated therapies. Amgen MedDRA Query narrow searches were performed to supplement standard system organ class single preferred term safety reporting (defined in Data Supplement and summarized in Table 2). Measures to ameliorate the potential for CRS included prophylactic corticosteroids (cycle 1 only) and IV hydration. Grade ≥ 2 treatment-emergent CRS was reported in 15 patients (14.0%) and grade 3 CRS in one patient (0.9%); no grade 4 or 5 CRS has been reported. In patients where time of onset of CRS as well as date of onset of CRS was recorded (n = 47), the median time to onset of CRS after the last dose was 17.5 hours. CRS was transient (median duration, 3 days [IQR, 2-4 days]) and resolved in all cases. Eight patients (7.5%) received tocilizumab for CRS. CRS was largely confined to cycle 1. A total of five patients (4.7%) had CRS in cycle 2 or later; four had prior CRS in cycle 1 while one first experienced CRS in cycle 2. Treatment-emergent neurologic AEs of any grade occurred in 75 patients (70.1%) and were mostly grade 1: dysgeusia (29.0%), headache (19.6%), and dizziness (10.3%) were most common. Grade ≥ 3 treatment-emergent neurologic events occurred in 12 patients (11.2%) including confusional state (4.7%), delirium (1.9%), and encephalopathy (1.9%). One patient had a grade 4 neurologic event (confusion), and none had grade 5. All grade ≥ 3 neurologic AEs resolved, with one patient discontinuing tarlatamab because of G3 encephalopathy and two other patients continuing treatment at reduced doses. G2 ICANS was the other neurologic cause leading to discontinuation in one patient. First onset of any grade neurological event was mostly within the first 30 days of treatment (median, 9 days [IQR, 2-29 days]) with a median duration of 5 days (IQR, 2-15 days). Grade ≥ 3 neutropenia occurred in 11 patients (10.3%). Any-grade neutropenia first onset occurred at a median of 30 days (IQR, 21-31 days) after first tarlatamab administration, and the median duration was 7 days (IQR, 4-13); overall, 10 patients (9.3%) received G-CSF. Febrile neutropenia occurred in one patient and was not considered treatment related.

Efficacy

Confirmed ORR was 23.4% (95% CI, 15.7 to 32.5) including two complete and 23 partial responses by modified RECIST 1.1 per investigator assessment (Table 3). Figure 1A illustrates best percentage change from baseline in sum of diameters for patients with evaluable postbaseline assessments (n = 94). The disease control rate was 51.4% (95% CI, 41.5 to 61.2). Responses were seen starting with the 0.3 mg dose and generally higher rates of response were observed at doses of 3 mg and above. At least 30% tumor shrinkage in target lesions at postbaseline assessment was observed in 39 patients (36.4%). Among confirmed responders, the median time to response was 1.8 months (range, 1.2-7.4) and the median DOR was 12.3 months (95% CI, 6.6 to 14.9; Fig 1B). The longest DOR was 14.9 months, and 11 patients (44% of responders) had ongoing response at data cutoff. The median PFS was 3.7 months (95% CI, 2.1 to 5.4), and the

TABLE 2. AEs (preferred term and AMQ for selected terms)

AE	All Patients (N = 107)				
	Any Grade, No. (%)	Grade 1-2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)	Grade 5, No. (%)
AEs of any cause that occurred during treatment[a]					
Any	107 (100)	46 (43)	48 (45)	12 (11)	1 (1)
Serious	55 (51)	25 (23)	23 (21)	6 (6)	1 (1)
Resulting in discontinuation	4 (4)	1 (1)	3 (3)	0 (0)	0 (0)
Treatment-related AEs	97 (91)	64 (60)	23 (21)	9 (8)	1 (1)
Treatment-related AEs occurring in > 10% of patients or grade ≥ 3 in > 1%)[a]					
CRS	56 (52)	55 (51)	1 (1)	0	0
Pyrexia	40 (37)	38 (36)	2 (2)	0	0
Dysgeusia	24 (22)	24 (22)	0	0	0
Fatigue	23 (22)	20 (19)	3 (3)	0	0
Nausea	21 (20)	21 (20)	0	0	0
Decreased appetite	14 (13)	14 (13)	0	0	0
Vomiting	13 (12)	13 (12)	0	0	0
Anemia	12 (11)	11 (10)	1 (1)	0	0
Asthenia	12 (11)	10 (9)	2 (2)	0	0
Neutropenia	12 (11)	4 (4)	5 (5)	3 (3)	0
Headache	11 (10)	11 (10)	0	0	0
Decreased white blood cell count	9 (8)	4 (4)	4 (4)	1 (1)	0
Decreased lymphocyte count	8 (8)	3 (3)	2 (2)	3 (3)	0
Confusional state	6 (6)	1 (1)	4 (4)	1 (1)	0
Decreased neutrophil count	6 (6)	3 (3)	2 (2)	1 (1)	0
Hyponatremia	6 (6)	4 (4)	2 (2)	0	0
Maculopapular rash	6 (6)	4 (4)	2 (2)	0	0
Pneumonitis	4 (4)	2 (2)	1 (1)	0	1 (1)
Lymphopenia	3 (3)	1 (1)	1 (1)	1 (1)	0
Encephalopathy	3 (3)	1 (1)	2 (2)	0	0
Hypertension	3 (3)	1 (1)	2 (2)	0	0
AEs of interest[b]					
CRS					
Any cause	56 (52)	55 (51)	1 (1)	0	0
Related	56 (52)	55 (51)	1 (1)	0	0
Neurologic events					
Any cause	75 (70)	63 (59)	11 (10)	1 (1)	0
Related	53 (50)	46 (43)	6 (6)	1 (1)	0
Neutropenia					
Any cause	17 (16)	6 (6)	7 (7)	4 (4)	0
Related	17 (16)	7 (7)	6 (6)	4 (4)	0

Abbreviations: AE, adverse event; AMQ, Amgen MedDRA Query; CRS, cytokine release syndrome.

[a]Based on single preferred term incidence. Coded using MedDRA, version: 25.0. AEs graded using CTCAE, version 4.0 and CRS events graded using Lee et al[33] criteria.

[b]CRS based on AMQ narrow search, which includes cytokine abnormal, CRS, cytokine storm, cytokine test. Neutropenia based on AMQ narrow search. Neurologic events on the basis of central neuropsychiatric events due to direct neurotoxicities AMQ narrow search. Coded using MedDRA, version: 25.0. CRS events graded using Lee et al[33] criteria. Neutropenia and neurologic events graded using CTCAE, version 4.0.

TABLE 3. Tumor Response to Tarlatamab According to Investigator Assessment

Response	Interim Efficacy Analysis Set[a] (N = 107)
ORR, % (95% CI)	
Confirmed	23 (15.7 to 32.5)
Confirmed and unconfirmed	25 (17.3 to 34.6)
Disease control rate, % (95% CI)	51 (41.5 to 61.2)
Best overall response, No. (%)	
Confirmed complete response	2 (2)
Confirmed partial response	23 (22)
Stable disease	30 (28)
Progressive disease	9 (8)
Could not be evaluated[b]	34 (32)
No assessment[c]	9 (8)
TTR, months, median (IQR)	1.81 (1.68-1.91)
Duration of objective response months, median (95% CI)	12.3 (6.6 to 14.9)

Abbreviations: IQR, interquartile range; ORR, objective response rate; PD, progressive disease; RECIST 1.1, response evaluation criteria in solid tumors, 1.1; TTR, time to response.

[a]The Interim efficacy analysis set is a subset of the safety analysis set. The Interim efficacy analysis set include patients whose data cut-off date is at least 9 weeks after the first dose date.

[b]This includes 32 patients who had PD, in the post-baseline scan however without further confirmation scan (unconfirmed PD, per modified RECIST 1.1).

[c]Reasons for no imaging assessment included consent withdrawn (n = 4), death (n = 2), clinical PD (n = 1), and starting new anticancer therapy (n = 1). An additional patient (n = 1) did not have the scan entered at the time of data snapshot.

median OS was 13.2 months (95% CI, 10.5 to NE; Fig 2), respectively. Of 77 progressive disease events, eight were in the brain (10.4%). Twenty-eight patients (26.2%) received subsequent anticancer therapies after tarlatamab. Representative computed tomography scans from patients receiving tarlatamab are provided (Data Supplement). An exploratory post hoc analysis demonstrates the sensitivity and specificity of enriching for responders (using confirmed OR) when total DLL3 expression is retrospectively considered for patient selection (Fig 3). Clinical benefit is observed across a range of thresholds.

Clinical PK

As of April 15, 2022, preliminary pharmacokinetic data from dose escalation and expansion cohorts were available for 101 patients. Briefly, tarlatamab exhibited approximate dose proportional increase in serum exposures. Approximate steady state in serum tarlatamab exposures were achieved within 4 weeks of every other week target regimen initiation, with minimal accumulation. The mean (± standard deviation) terminal elimination half-life estimated at steady state across the evaluated target dose range was approximately 5.7 (± 2.2) days, which is consistent with the intended half-life extension of the HLE platform relative to non-HLE BiTEs.[23]

Immunogenicity

Among patients with available samples, 10 of 97 (10.3%) developed anti-tarlatamab antibodies after tarlatamab administration. Two of 99 patients (2.0%) had preexisting antibodies at baseline. There is no apparent antidrug antibody impact on tarlatamab exposures or the safety profile in these patients.

Pharmacodynamics

The pharmacodynamic response after first dose of tarlatamab infusion was characterized by initial T-cell redistribution (Data Supplement [Figs 3A and 3B, online only]), T-cell activation (Data Supplement [Fig 3C]), and transient IFN-gamma elevation (Data Supplement [Fig 3D]). For step-dose cohorts, pharmacodynamic responses were greatest after initial administration of 1-mg step dose and not exceeded with target dose administration.

DISCUSSION

Tarlatamab demonstrated a manageable safety profile across a wide dose range through the expansion dose of 100 mg and was associated with encouraging response rates in a heavily pretreated population of patients with SCLC. Confirmed responses were durable, and OS seems promising. Across all doses (N = 107), tarlatamab was discontinued in only 4 (3.7%) patients. A maximum tolerated dose was not reached; the highest dose (100 mg) was further evaluated in dose expansion.

CRS is expected based on the mechanism of action of tarlatamab. CRS was the most frequent TEAE observed (56%) but was generally low-grade, transient, and typically occurred in the first cycle. CRS was reversible and generally managed with antipyretics, IV fluids, and steroids; tocilizumab was used to treat CRS in eight of 107 patients (7.5%). Neutropenia was a risk associated with tarlatamab observed in this study and was unexpected based on preclinical data; the mechanism is not understood. The study protocol was updated accordingly for specific monitoring and management. Further evaluation of neutropenia will be relevant to trials of tarlatamab use in combination with other marrow-suppressing therapies. Neurologic evaluation was conducted as part of frequent clinical evaluation to assess study patients for CRS and/or neurologic AEs due to the known association with immune effector cell therapies. Most neurologic AEs were mild and self-limiting without need for treatment discontinuation or dose reduction, though 12 patients (11.2%) had grade ≥ 3 neurologic AEs. Neurologic AEs led to tarlatamab discontinuation in two patients (encephalopathy, ICANS). Careful evaluation of neurologic AEs is ongoing to better characterize these events and identify risk factors or interventions that might specifically improve management.

Few approved therapies exist for SCLC after first line. A phase II study of lurbinectedin in second-line SCLC found an ORR of 35% and a median DOR of 5.3 months.[7] In a

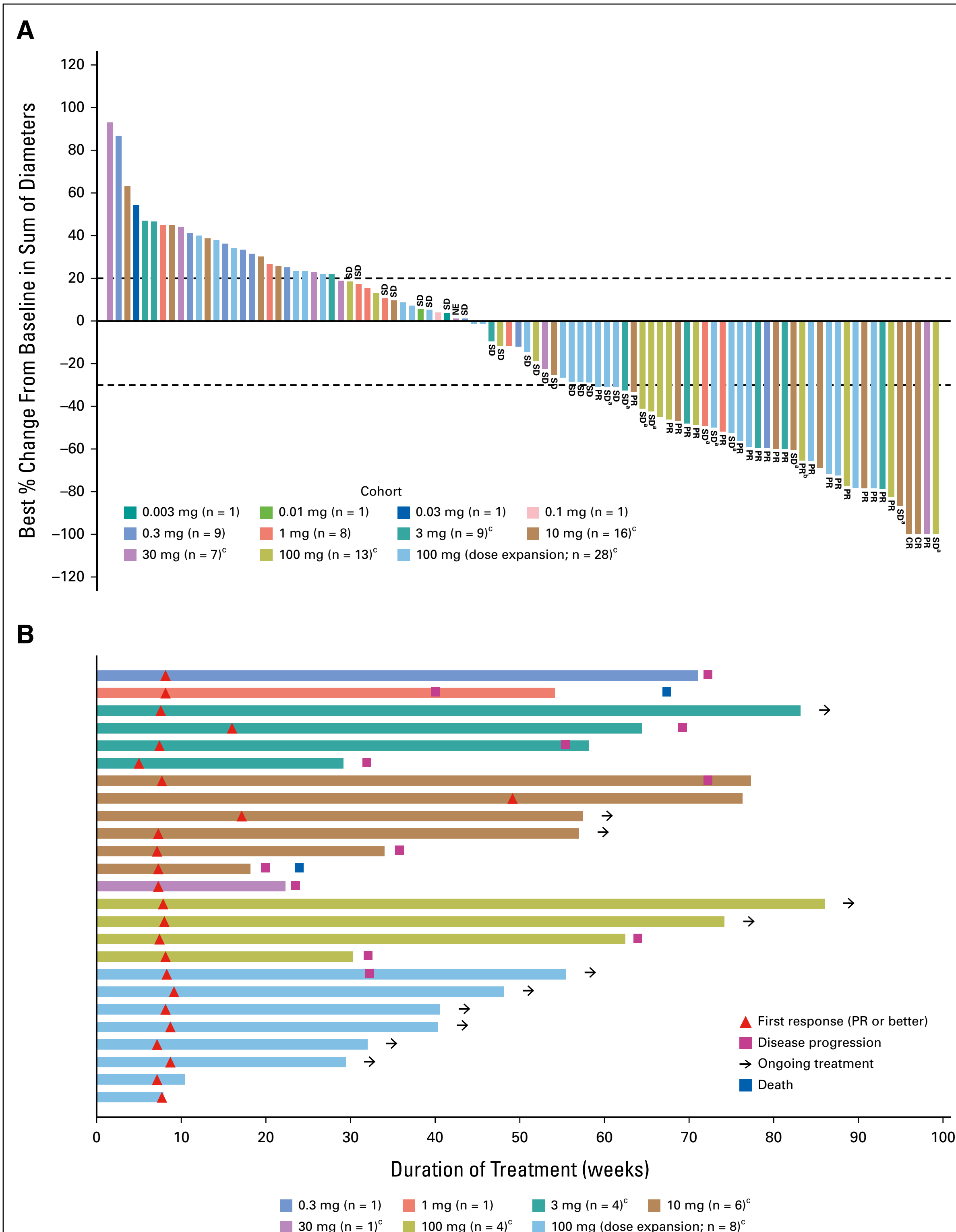

FIG 1. Response to tarlatamab. (A) Best percent change from baseline in tumor burden (defined by the sum of the longest diameters of all target lesions) in 94 patients whose data cutoff date is at least 9 weeks after the first dose date and for whom postbaseline tumor data were available. [a]SD, patients had an initial response but did not have confirmation of response on the subsequent scan and [b]PR, patients had an initial PR and still have potential for future confirmative scans. One confirmed patient in the 100 mg expansion cohort had missing sum of diameters for lesion measurement and was not included in the plot. [c]Step dosing (ie, 1 mg run-in dose) was used in these cohorts. (B) TTR, the duration of treatment, and patient status as of the data cutoff date according to dose of tarlatamab for all patients with confirmed response (n = 25). CR, complete response; NE, not evaluable; PR, partial response; SD, stable disease; TTR, time to response.

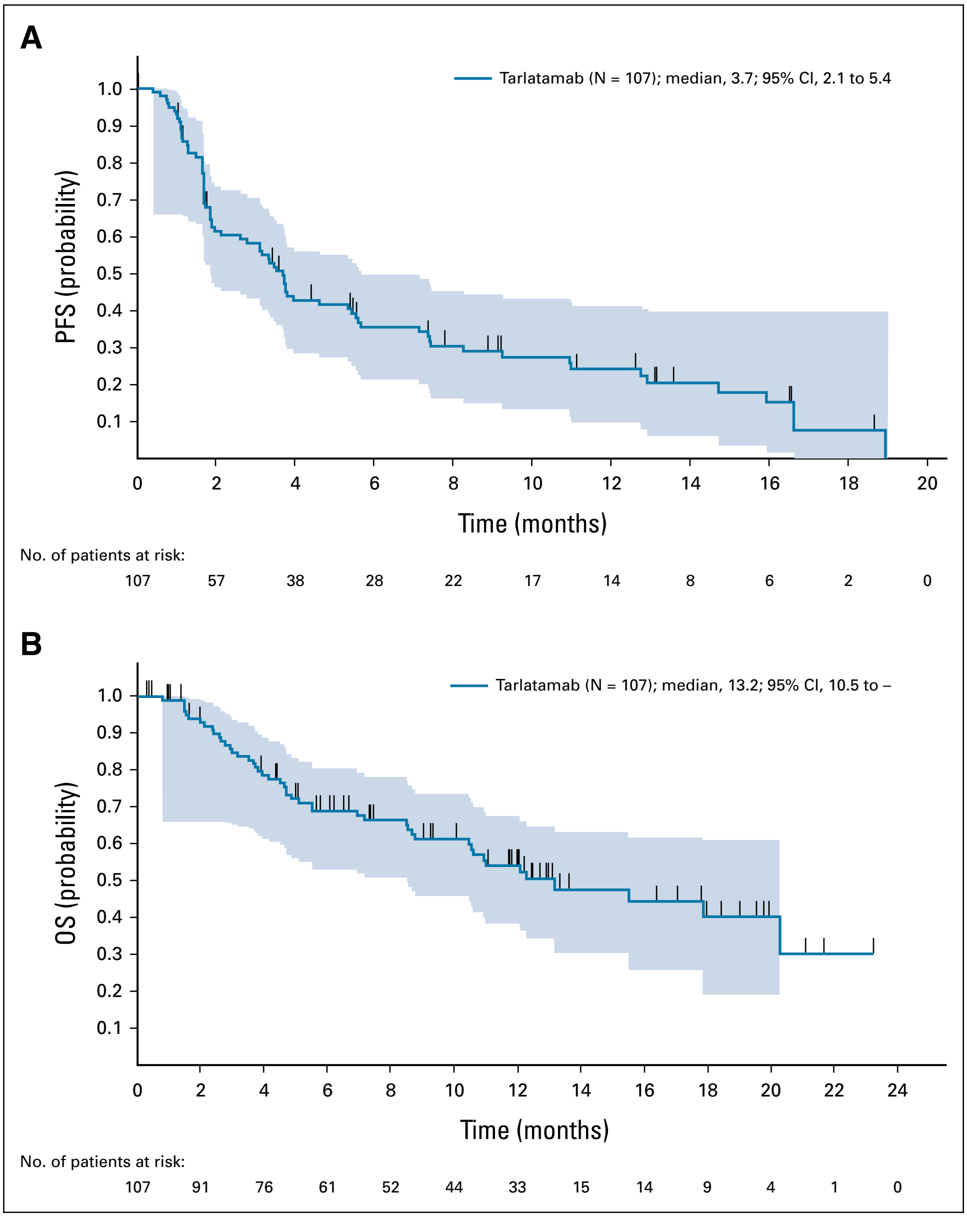

FIG 2. Efficacy of tarlatamab in patients with SCLC. (A) Kaplan-Meier curve of PFS for patients whose data cutoff date is at least 9 weeks after the first dose date (N = 107). (B) Kaplan-Meier curve of OS for patients whose data cutoff date is at least 9 weeks after the first dose date (N = 107). OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung cancer.

randomized study of topotecan versus combination chemotherapy in recurrent SCLC, topotecan ORR was 24% and the median DOR was 3.3 months.[5] The prior conditional approval by US Food and Drug Administration of nivolumab and pembrolizumab for third-line or later SCLC was based on response rates of 12% and 19%, respectively, with durable responses seen at ≥ 12 months in > 60% of responding patients.[24] These approvals were subsequently withdrawn as survival benefit was not demonstrated.[25] The ORR of 23% and median DOR of 12.3 months for tarlatamab compares well with other therapies, especially considering that more than 70% of patients had at least two prior lines of therapy. Fifty percent of patients in this study had received prior PD-1/PD-L1 therapy, representative of current practice in first-line SCLC. Despite the relatively short median PFS (3.7 months) seen with tarlatamab, the median OS (13.2 months) is relatively high and compares favorably with 9.3-month median OS reported previously with lurbinectedin or approximately 6-month OS with topotecan, although the value of comparisons is limited by differences in study design and patient populations.[5,7] The promising OS benefit may reflect the long durability of response seen thus far in those who respond to tarlatamab but further follow up

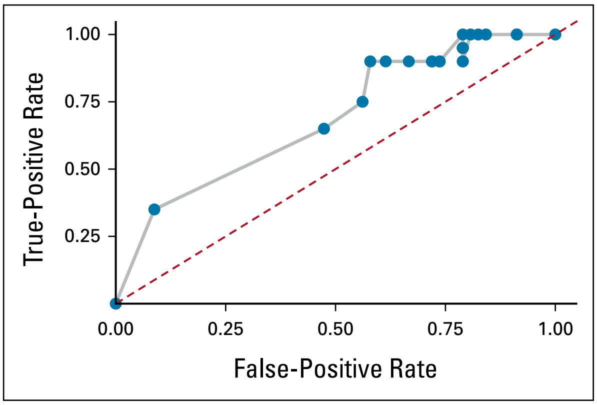

FIG 3. ROC curve of objective response enrichment by DLL3 expression. ROC curve reflecting true-positive rate and false-positive rate of enrichment of objective response when FIH patients (1-100 mg cohorts) are retrospectively examined for selection using DLL3 expression assessed with the Ventana SP347 assay. ROC analysis included 77 patients enrolled in the 1-100 mg cohorts for whom pretreatment DLL3 expression readouts were available. DLL3, delta-like ligand 3; FIH, first-in-human; ROC, receiver operating characteristic.

is needed in larger randomized studies. Another explanation could be that OS benefit derived from post-tarlatamab treatment, although this is less likely a major factor because only 26.2% of patients received such treatment in this heavily pretreated cohort. Identifying factors predictive of response and/or toxicity (eg, prior therapies) is an ongoing effort. An exploratory analysis suggests that increased DLL3 expression trends with higher magnitude of clinical benefit.

Limitations of this study include moderate median follow-up time (8.7 months) and selected patient population required for a first-in-human trial. Interpretation of preliminary efficacy is limited in a single-arm, dose-ranging study. Efficacy data from several different dose levels was pooled for some analyses; enrollment to the expansion cohort is ongoing.

The first DLL3-targeted agent to enter the clinic was the antibody-drug conjugate rovalpituzumab tesirine (Rova-T).[11] During development, data showed strong enrichment in clinical benefit in patients with relatively high DLL3 expression; however, despite implementing DLL3 expression as an eligibility or stratification factor in later phase studies, Rova-T failed to show a survival benefit versus standard of care in two phase III studies and was discontinued.[16,26,27] Rova-T toxicity in preclinical and especially clinical studies turned out to be a significant problem with this construct and was more consistent with general effects of the pyrrolobenzodiazepine payload rather than the DLL3 target.[16,26,28] In contrast, tarlatamab has exhibited tolerability and efficacy over a broad range of doses in a heavily pretreated population confirming the value of this target. Other DLL3-specific therapies undergoing clinical evaluation include the T-cell engaging molecules HPN328 and BI 764532 and the chimeric antigen receptor T-cell therapy AMG 119.[29-32]

These results demonstrate promising activity in patients with high unmet medical need and have led to ongoing investigations of tarlatamab as monotherapy in SCLC and other neuroendocrine cancers (phase II study in patients with third-line SCLC [NCT05060016]; phase Ib study in neuroendocrine prostate cancer [NCT04702737]) and in combination in earlier lines of therapy (phase I study of first-line ES-SCLC tarlatamab in combination with carboplatin, etoposide, and PD-L1 inhibitor [NCT05361395]).

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This study was designed by the sponsor (Amgen, Inc) and study investigators. Data were collected by the investigators and their site personnel. The authors and sponsor did data analyses and data interpretation. The sponsor managed the study database, supplied the study drug, and provided editorial assistance.

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DATA SHARING STATEMENT

There is a plan to share data. This may include deidentified individual patient data for variables necessary to address the specific research question in an approved data sharing request, also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report.

Data sharing requests relating to data in this manuscript will be considered after the publication date and (1) this product and indication (or other new use) have been granted marketing authorization in both the United States and Europe, or (2) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data.

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Further details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request.

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Research Funding: AstraZeneca (Inst), Boehringer Ingelheim (Inst), Novartis (Inst), Amgen (Inst), Pfizer (Inst), Bristol Myers Squibb Foundation (Inst), AbbVie (Inst), Blueprint Medicines, Celgene, PharmaMar (Inst), Merck (Inst), Mirati Therapeutics (Inst)
Travel, Accommodations, Expenses: Boehringer Ingelheim

Afshin Dowlati
Consulting or Advisory Role: AbbVie/Stemcentrx, AstraZeneca, Bristol Myers Squibb, Ipsen, Merck
Research Funding: Lilly/ImClone (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Tesaro (Inst), Takeda (Inst), Mirati Therapeutics (Inst), AbbVie/Stemcentrx (Inst), Bayer (Inst), Seattle Genetics (Inst), Ipsen (Inst), Pionyr (Inst), Coordination Pharmaceuticals (Inst), Astellas Pharma (Inst), Bicycle Therapeutics (Inst), Gilead Sciences (Inst)

Noemi Reguart
Consulting or Advisory Role: Pfizer, MSD Oncology, BMS, Boehringer Ingelheim, AstraZeneca, Roche, Takeda, Amgen, Lilly, Sanofi, Janssen
Speakers' Bureau: AstraZeneca, Roche, Roche Molecular Diagnostics, MSD, Boehringer Ingelheim, Amgen, Novartis, Merck Serono, Takeda, Sanofi
Research Funding: Pfizer, Novartis
Travel, Accommodations, Expenses: MSD, Roche

Tatsuya Yoshida
Honoraria: AstraZeneca, MSD Oncology, Ono Pharmaceutical, Chugai/Roche, Lilly Japan, Nippon Boehringer Ingelheim, Bristol Myers Squibb Japan, Novartis, Archer, Takeda, Pfizer
Consulting or Advisory Role: Lilly Japan, Chugai/Roche, Novartis, Boehringer Ingelheim, AstraZeneca
Research Funding: Chugai/Roche (Inst), AstraZeneca (Inst), AbbVie (Inst), Amgen (Inst), MSD (Inst), Bristol Myers Squibb (Inst), Ono Pharmaceutical (Inst), Takeda (Inst), Daiichi Sankyo (Inst), Chugai/Roche (Inst), Novartis (Inst)

Kai He
Consulting or Advisory Role: Perthera, Mirati Therapeutics, Bristol Myers Squibb, Iovance Biotherapeutics, Geneplus, Lyell Immunopharma, AstraZeneca
Research Funding: Bristol Myers Squibb (Inst), Mirati Therapeutics (Inst), Adaptimmune (Inst), Genentech/Roche (Inst), GlaxoSmithKline (Inst), Amgen (Inst), Iovance Biotherapeutics (Inst), AbbVie (Inst), Oncoc4 (Inst)

Shirish M. Gadgeel
Honoraria: Merck
Consulting or Advisory Role: Genentech/Roche, AstraZeneca, Bristol Myers Squibb, Takeda, Daichii-Sanyko, Novartis, Blueprint Medicines, Lilly, Pfizer, Janssen Oncology, Mirati Therapeutics, Merck, Esai Pharma, Gilead Sciences, GlaxoSmithKline
Research Funding: Merck, Genentech/Roche (Inst), Merck (Inst), Blueprint Medicines (Inst), Astellas Pharma (Inst), Daiichi Sankyo (Inst), I-Mab (Inst), Nektar (Inst), AstraZeneca (Inst), Pfizer (Inst), Amgen (Inst), Turning Point Therapeutics (Inst), Regeneron (Inst), Mirati Therapeutics (Inst), Nektar (Inst), Janssen Oncology (Inst), BioMed Valley Discoveries (Inst), Ymabs Therapeutics Inc (Inst), Calithera Biosciences (Inst), InventisBio (Inst), Daichii Sanyko (Inst), Dragonfly Therapeutics (Inst), eFFECTOR Therapeutics (Inst), Elevation Oncology (Inst), Erasca, Inc (Inst), Helsinn Therapeutics (Inst), Incyte (Inst), Numab (Inst), Verastem (Inst), Regeneron (Inst)
Travel, Accommodations, Expenses: Mirati Therapeutics
Other Relationship: AstraZeneca

Enriqueta Felip
Consulting or Advisory Role: Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Lilly, GlaxoSmithKline, Janssen, Merck Serono, Novartis, Pfizer, Sanofi, Takeda, Peptomyc, Daiichi Sankyo Europe GmbH, F. Hoffmann LaRoche, Merck Sharp & Dohme
Speakers' Bureau: AstraZeneca, Bristol Myers Squibb, Lilly, Medscape, Merck Sharp & Dohme, PeerVoice, Pfizer, Takeda, Amgen, F. Hoffmann LaRoche, Janssen, Medical Trends, Merck Serono, Sanofi, TouchONCOLOGY
Research Funding: Merck (Inst), Merck KGaA (Inst)
Other Relationship: GRIFOLS

Yiran Zhang
Employment: Gilead Sciences, Amgen
Stock and Other Ownership Interests: Amgen

Amrita Pati
Employment: Amgen
Stock and Other Ownership Interests: Amgen, Roche Sequencing Solutions, AbbVie, Regeneron, Gilead Sciences, BioNTech SE
Patents, Royalties, Other Intellectual Property: ClaMS—A computational application that classified Metagenome sequences. Receive royalty for above application SW through Lawrence Berkeley National Labs

Mukul Minocha
Employment: Amgen
Stock and Other Ownership Interests: Amgen

Sujoy Mukherjee
Employment: Amgen
Stock and Other Ownership Interests: Amgen

Amanda Goldrick
Employment: Amgen
Stock and Other Ownership Interests: Amgen

Dirk Nagorsen
Employment: Amgen
Leadership: Amgen
Stock and Other Ownership Interests: Amgen
Patents, Royalties, Other Intellectual Property: Inventor on patents related to the use of CD3 bispecifics

Nooshin Hashemi Sadraei
Employment: Amgen
Stock and Other Ownership Interests: Amgen
Travel, Accommodations, Expenses: Amgen

Taofeek K. Owonikoko
Stock and Other Ownership Interests: CAMBIUM MEDICAL TECHNOLOGIES, Taobob LLC, GenCart, Coherus Biosciences
Consulting or Advisory Role: Novartis, Celgene, AbbVie, Eisai, G1 Therapeutics, Takeda, Bristol Myers Squibb, MedImmune, BerGenBio, Lilly, Amgen, AstraZeneca, PharmaMar, Boehringer Ingelheim, EMD Serono, Xcovery, Bayer, Merck, Jazz Pharmaceuticals, Zentalis, Wells Fargo, Ipsen, Eisai, Roche/Genentech, Janssen, Exelixis, BeiGene, Triptych Health Partners, Daichi, Xcovery, Coherus Biosciences
Speakers' Bureau: AbbVie
Research Funding: Novartis (Inst), Astellas Pharma (Inst), Bayer (Inst), Regeneron (Inst), AstraZeneca/MedImmune (Inst), AbbVie (Inst), G1 Therapeutics (Inst), Bristol Myers Squibb (Inst), Corvus Pharmaceuticals, United Therapeutics (Inst), Amgen (Inst), Loxo/Lilly (Inst), Fujifilm (Inst), Pfizer (Inst), Aeglea Biotherapeutics (Inst), Incyte (Inst), Merck (Inst), Oncorus (Inst), Ipsen (Inst), GlaxoSmithKline (Inst), Calithera Biosciences (Inst), Eisai (Inst), WindMIL (Inst), Turning Point Therapeutics (Inst), Roche/Genentech (Inst), Mersana (Inst), Meryx Pharmaceuticals (Inst), Boehringer Ingelheim (Inst)
Patents, Royalties, Other Intellectual Property: OVERCOMING ACQUIRED RESISTANCE TO CHEMOTHERAPY TREATMENTS THROUGH SUPPRESSION OF STAT3 (Inst), SELECTIVE CHEMOTHERAPY TREATMENTS AND DIAGNOSTIC METHODS RELATED THERETO (Inst), DR4 Modulation and its Implications in EGFR-Target Cancer Therapy Ref:18089 PROV (CSP) United States Patent Application No. 62/670210 June 26, 2018 (Co-Inventor; Inst), Soluble FAS ligand as a biomarker of recurrence in thyroid cancer; provisional patent 61/727519 (Inventor; Inst)
Other Relationship: Roche/Genentech, EMD Serono, Novartis
Uncompensated Relationships: Reflexion Medical
Open Payments Link: https://openpaymentsdata.cms.gov/physician/253457

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Study Sites and Primary Investigators

Study Site	Primary Investigator
Chris O'Brien Lifehouse	Michael Boyer
National Cancer Center Hospital East	Hiroki Izumi
National Cancer Center Hospital	Tatsuya Yoshida
Wakayama Medical University Hospital	Hiroaki Akamatsu
Gustave Roussy	Stephane Champiat
Comprehensive Cancer Center Mainfranken	Horst-Dieter Hummel
Netherlands Cancer Institute	Neeltje Steeghs
Maastricht Universitair Medisch Centrum	Judith Vos de-Geelen
Hospital Universitario 12 de Octubre	Luis Paz-Ares
Hospital Clinic I Provincial de Barcelona	Noemi Reguart
Hospital Universitari Vall Hebron	Enriqueta Felip
Hospital Universitario La Paz	Francisco Javier de Castro
Hospital Universitario Ramon y Cajal	Maria Eugenia Olmedo
Christie Hospital	Fiona Blackhall
Centre Hospitalier Universitaire Vaudois	Solange Peters
Kantonsspital St Gallen	Martin Frueh
Universitaetsklinikum Salzburg	Richard Greil
Klinische Abteilung für Onkologie	Angelika Terbuch
Fox Chase Medical Center	Hossein Borghaei
Winship Cancer Institute of Emory University	Taofeek K. Owonikoko[a]/Jennifer Carlisle
Sarah Cannon Research Institute	Melissa L. Johnson
University Hospitals Cleveland Medical Center	Afshin Dowlati
Washington University of St Louis	Ramaswamy Govindan
MSKCC	Wei-Chu Victoria Lai
University of Chicago	Everett Vokes
John Hopkins	Christine Hann
Yale	Anne Chiang
Moffitt Cancer Center	Alberto Chiappori
Ohio State University	Kai He
Henry Ford Cancer Institute	Shirish M. Gadgeel

[a]Previously primary investigator for this site before leaving site in 2020.

