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A Phase I First-in-Human Study of ABBV-011, a Seizure-Related Homolog Protein 6–Targeting Antibody–Drug Conjugate, in Patients with Small Cell Lung Cancer

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ABSTRACT

Purpose: Seizure-related homolog protein 6 (SEZ6) is a novel target expressed in small cell lung cancer (SCLC). ABBV-011, a SEZ6-targeted antibody conjugated to calicheamicin, was evaluated in a phase I study (NCT03639194) in patients with relapsed/refractory SCLC. We report initial outcomes of ABBV-011 monotherapy.

Patients and Methods: ABBV-011 was administered intravenously once every 3 weeks during dose escalation (0.3–2 mg/kg) and expansion. Patients with SEZ6-positive tumors (≥25% of tumor cells with ≥1+ staining intensity by IHC) were preselected for expansion. Safety, tolerability, antitumor activity, and pharmacokinetics were evaluated.

Results: As of August 2022, 99 patients received ABBV-011 monotherapy [dose escalation, $n = 36$; Japanese dose evaluation, $n = 3$; dose expansion, $n = 60$ (1 mg/kg, $n = 40$)]; the median age was 63 years (range, 41–79 years). Also, 32%, 41%, and 26% of patients received 1, 2, and ≥3 prior therapies, respectively. The maximum tolerated dose was not reached through 2.0 mg/kg. The most common treatment-emergent adverse events were fatigue (50%), nausea (42%), and thrombocytopenia (41%). The most common hepatic treatment-emergent adverse events were increased aspartate aminotransferase (22%), increased γ-glutamyltransferase (21%), and hyperbilirubinemia (17%); two patients experienced veno-occlusive liver disease. The objective response rate was 19% (19/98). In the 1-mg/kg dose-expansion cohort ($n = 40$), the objective response rate was 25%; the median response duration was 4.2 months (95% confidence interval, 2.6–6.7); and the median progression-free survival was 3.5 months (95% confidence interval, 1.5–4.2).

Conclusions: ABBV-011 1.0 mg/kg every 3 weeks monotherapy was well tolerated and demonstrated encouraging antitumor activity in heavily pretreated patients with relapsed/refractory SCLC. SEZ6 is a promising novel SCLC target and warrants further investigation.

Introduction

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine tumor that accounts for approximately 15% of all lung cancers (1). It is characterized by rapid proliferation and a tendency to develop early widespread metastasis, with 75% to 80% of patients presenting with extensive-stage SCLC at diagnosis (2). The prognosis is poor, with a 5-year survival rate of 6.8% (3). The standard treatment for most patients with limited-stage disease is concurrent chemoradiotherapy, which is associated with a median progression-

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Translational Relevance

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine neoplasm with a dismal 5-year survival rate of 6.8%. There is a high unmet need for novel therapies. Seizure-related homolog protein 6 (SEZ6) is a cell surface protein expressed in SCLC, with normal tissue expression restricted to the brain and eye making it a rational therapeutic target. We report results from the phase I study of ABBV-011, a novel antibody–drug conjugate targeting SEZ6 linked to a calicheamicin payload. Our results demonstrate that SEZ6 protein is expressed in most SCLC tumors from patients. Additionally, the encouraging preliminary efficacy seen in heavily pretreated patients validates SEZ6 as a therapeutic target in SCLC. Lastly, the safety profile correlates with other calicheamicin-based antibody–drug conjugates, and no significant on-target ocular or neurologic toxicity was seen in this study. Our study sets the stage for next-generation SEZ6-targeting therapies with a potentially improved therapeutic index.

free survival (PFS) of 13.5 to 15.4 months (4, 5) and a 5-year PFS of 25% (5). For patients with extensive-stage disease, the standard first-line therapy is the combination of platinum with etoposide and an anti–PD-L1 antibody (6). In the second-line setting, topotecan and lurbinectedin are approved for patients whose disease progresses on or after platinum-based chemotherapy, and tarlatamab-dlle has recently been granted accelerated approval by the FDA in this patient population (7–9). Currently, there is no standard therapy for the third line and beyond. Despite the high response rates to first-line therapy, most patients experience relapse, with a median PFS of 5.1 months (10, 11). The benefit from treatment is even less pronounced in the second line, with a median PFS of 3.5 months following treatment with topotecan or lurbinectedin (7, 8). Hence, there remains a high unmet need for patients with SCLC.

Seizure-related homolog protein 6 (SEZ6) is a type I transmembrane protein involved in neuronal function and development (12–14). It is highly expressed in neuroendocrine tumors including SCLC, especially the ASCL1- and NEUROD1-positive subtypes (15). SEZ6 represents an attractive target in SCLC, as it is not expressed in most normal tissues, outside of neuronal tissues such as the brain, spinal cord, pituitary gland, and retina (15).

ABBV-011 is a novel antibody–drug conjugate (ADC) that targets SEZ6 (15). It comprises the SC17 anti–SEZ6 mAb, conjugated to the potent DNA-damaging N-acetyl-γ-calicheamicin payload via a novel noncleavable linker with a drug-to-antibody ratio of 2 (15). ABBV-011 is proposed to target SEZ6-expressing tumor cells with high affinity and release the calicheamicin payload intracellularly to induce cell death. Calicheamicin is also the payload in two approved ADC, gemtuzumab ozogamicin and inotuzumab ozogamicin (16, 17). The most relevant off-target toxicities with these ADC are cytopenia, hepatotoxicity [including veno-occlusive liver disease (VOD)], and infusion site reactions, which may limit their use (18, 19). Whereas the approved ADC contain an acid-labile linker, ABBV-011 uses a noncleavable linker; hence, off-target toxicity might be minimized. In preclinical studies, ABBV-011 had dose-dependent antitumor activity in patient-derived xenografts of SEZ6-expressing SCLC, and toxicities were consistent with those previously described for calicheamicin-based ADC (15).

Herein, we report the initial results from the monotherapy part of the currently ongoing first-in-human phase I trial to investigate the safety, determine the MTD, and/or establish the recommended phase II dose (RP2D) and assess the preliminary antitumor efficacy of ABBV-011 in patients with relapsed or refractory (R/R) SCLC.

Patients and Methods

Study design

This is a first-in-human, multicenter, open-label phase I study of ABBV-011 administered as monotherapy or in combination with budigalimab, a programmed cell death 1 inhibitor, in patients with R/R SCLC. The first part of the study assessed ABBV-011 as monotherapy and consisted of a dose-escalation phase followed by a dose-expansion phase; a cohort evaluating the recommended ABBV-011 dose in Japanese patients [Japanese dose-evaluation cohort ($n = 3$)] was included, as per the Japanese Pharmaceuticals and Medical Devices Agency requirements (20). The second part of the study planned to evaluate ABBV-011 and budigalimab combination in dose-escalation and dose-expansion phases. Here, we present the initial results of ABBV-011 monotherapy. The primary objectives were to assess the safety and tolerability and determine the MTD and/or RP2D. The secondary objectives included pharmacokinetics (PK) and antitumor activity per RECIST v1.1.

There was no randomization or blinding for this study, and patients were assigned a unique identification number at the screening visit. All patients provided written informed consent before study entry. The study was approved by the relevant institutional review boards and/or independent ethics committees and was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The study is registered with ClinicalTrials.gov (NCT03639194).

Patient eligibility

Eligible patients included adults (≥18 years of age) with histologically or cytologically confirmed R/R SCLC who received ≤3 lines of prior therapy, including ≥1 prior platinum-containing chemotherapy, Eastern Cooperative Oncology Group performance status score of 0 or 1, measurable disease according to RECIST v1.1, and adequate hematologic, liver, and renal function. Prior anticancer therapy had to be completed ≥4 weeks before the first ABBV-011 dose. Patients with previously treated central nervous system metastases with stable or improved lesions for ≥2 weeks after therapy completion were eligible. There were no preselection criteria for enrollment of patients in dose escalation based on tumor SEZ6 expression. For dose expansion, patients with SEZ6-positive tumors (≥25% tumor cells with ≥1+ staining intensity by IHC) were preselected.

Dose-escalation and dose-expansion phases

In the dose-escalation phase, patients received ABBV-011 intravenously at dosages of 0.3, 0.6, 1.2, 1.6, and 2.0 mg/kg once every 3 weeks, on day 1 of each 21-day cycle, or at 0.5 mg/kg on days 1 and 8 of each 21-day cycle.

Dose escalation was guided by a Bayesian continual reassessment method, using a two-parameter Bayesian logistic regression model that incorporated the escalation with the overdose control principle for patient safety. The definitions of dose-limiting toxicities (DLT) are listed in the Supplementary Methods.

For dose evaluation in Japanese patients, ABBV-011 was administered at 1.0 mg/kg every 3 weeks. Three patients were enrolled

for DLT evaluation, and the evaluation was considered completed if no DLT were identified.

DLT were assessed in dose-escalation and Japanese dose-evaluation parts during the first 6 weeks of treatment; patients were considered DLT evaluable if they completed the DLT evaluation period or experienced a DLT.

In the dose-expansion phase, ABBV-011 was further evaluated for safety, tolerability, PK, and antitumor efficacy in patients with SEZ6-positive tumors. Initially, the highest dosage from dose escalation, 2 mg/kg every 3 weeks, was selected for dose expansion based on safety in dose escalation. In consultation with the safety monitoring committee and approved by the institutional review boards and/or independent ethics committees, the expansion dose was reduced to 1.6 mg/kg in cycle 1, followed by 1.2 mg/kg in subsequent cycles, and further to 1.0 mg/kg every 3 weeks on the basis of review of long-term safety, tolerability, PK, and efficacy data, as well as the risk for delayed hepatotoxicity. A 0.8-mg/kg every 3 weeks cohort was included to further explore the optimal ABBV-011 monotherapy dose. Patients received ABBV-011 until disease progression (PD) or other treatment discontinuation criteria were met.

Assessments

Safety parameters included physical examination, vital signs, laboratory tests, ECG, echocardiograms, and treatment-emergent adverse events (TEAE). TEAE were graded according to the NCI Common Terminology Criteria for Adverse Events, version 5.0. Serious adverse events (SAE) and non-SAE occurring from the time of consent until the first ABBV-011 dose were collected. Additionally, all TEAE and SAE from the time of ABBV-011 start until 60 days after the last dose were collected.

Blood samples for PK evaluation were collected on days 1 (preinfusion and 30 minutes and 2 hours postinfusion); on days 2, 4, 8, and 15 of cycles 1 and 3; and on day 1 (preinfusion and 30 minutes postinfusion) of cycles 2, 5, 7, and 9. Serum concentrations of ABBV-011 and plasma concentrations of the released catabolite of linker–drug (M8b) were determined using validated methods. PK parameters were estimated using noncompartmental analysis.

Tumor imaging response was evaluated every 6 weeks for the first 24 weeks of the study and then every 12 weeks for up to 4 years afterward until progression or treatment discontinuation. Clinical response was determined using RECIST v1.1 criteria by the investigator, including the objective response rate [ORR; included patients with confirmed complete response (CR) plus confirmed partial response] and clinical benefit rate (CBR; included patients with confirmed CR, confirmed partial response, and stable disease). Additionally, duration of response (DOR), duration of clinical benefit (DOCB), and PFS were determined.

Testing for SEZ6 expression was performed by IHC in a central Clinical Laboratory Improvement Amendments–certified laboratory using archived tumor tissue or fresh tumor biopsy at screening in dose-escalation and Japanese dose-evaluation parts and at prescreening in dose expansion to select patients with SEZ6-positive tumors for the expansion phase. The study sponsor, AbbVie, Inc., in collaboration with CellCarta, developed a novel IHC assay with a pathologist-based algorithm and scoring method (CD166) to evaluate SEZ6 expression in patient tumor biopsies. The CD166 scoring method comprises a semiquantitative evaluation of the percentage of tumor cells with overall (membranous and cytoplasmic) staining at different intensities (0, 1+, 2+, and 3+) in tumor samples. The cutoff for SEZ6 positivity was based on correlative analysis of ABBV-011 *in vivo* efficacy and SEZ6 expression in patient-derived xenograft models of SCLC with variable SEZ6 expression levels.

Statistical analysis

The safety and efficacy populations included all patients who received ≥1 dose of ABBV-011. Patients without postbaseline tumor assessment were considered nonresponders; one patient at 0.8 mg/kg who received only one dose and had no postbaseline tumor assessment at the time of data cutoff was excluded from the response-evaluable analysis set. The PK population included patients with adequate blood sampling to estimate at least one PK parameter.

Safety analyses were performed using descriptive statistics. The two-sided 95% confidence intervals (CI) for ORR and CBR were calculated using the Clopper–Pearson (exact) method. Median PFS, DOR, and DOCB were estimated using the Kaplan–Meier method.

Data availability

AbbVie is committed to responsible data sharing with regard to the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis datasets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research and will be provided following review and approval of a research proposal, statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

Results

Patient demographics and baseline characteristics

Between November 2018 and August 2022, 99 patients were enrolled and received ≥1 dose of ABBV-011 [dose escalation, $n = 36$; Japanese dose evaluation, $n = 3$; dose expansion, $n = 60$ (1-mg/kg cohort: $n = 40$)]. Demographics and baseline disease characteristics are summarized in **Table 1**. Overall, the median age was 63 years (range, 41–79 years), 51% of patients were female, 88% were White, and 80% had an Eastern Cooperative Oncology Group performance status score of 1. The median number of prior lines of therapy was 2 (range, 1–4), which included a programmed cell death 1/PD-L1–targeted agent in 77% of patients. The median ABBV-011 treatment cycle received was 3 (range, 1–21). At data cutoff, 90 (91%) patients had discontinued treatment [PD (54%), AE (12%), consent withdrawal (4%), physician's decision (4%), and other (17%; mostly clinical progression)]. Seventy-five percent of patients were off study due to death (69%), consent withdrawal (2%), physician's decision (2%), loss to follow-up (1%), and other (1%). Patient disposition in the overall population and 1-mg/kg dose-expansion cohort is summarized in Supplementary Table S1. The representativeness of the study population to the real-world population is described in Supplementary Table S2.

Table 1. Patient demographics and baseline characteristics.

Characteristic	1-mg/kg expansion (*n* = 40)	All patients (*N* = 99)
Median age, years (range)	63 (46–79)	63 (41–79)
Female, *n* (%)	20 (50)	50 (51)
Race, *n* (%)		
White	34 (85)	87 (88)
Asian	2 (5)	5 (5)
Black or African American	3 (8)	5 (5)
Native Hawaiian or other Pacific Islander	1 (3)	1 (1)
American Indian or Alaska Native	0	1 (1)
Ethnicity, *n* (%)		
Hispanic or Latino	3 (8)	6 (6)
Not Hispanic or Latino	37 (93)	93 (94)
Tobacco user, *n* (%)		
Current	17 (43)	27 (27)
Former	22 (55)	69 (70)
Never	1 (3)	3 (3)
Median time since initial diagnosis, years (range)	1.2 (0.5–3.4)	1.2 (0.3–10.5)
VALG staging at diagnosis, *n* (%)[a]		
Limited disease	4 (10)	14 (14)
Extensive disease	34 (85)	72 (73)
Number of prior lines, *n* (%)		
1	12 (30)	32 (32)
2	22 (55)	41 (41)
3	6 (15)	23 (23)
>3	0	3 (3)
Prior anti–PD-1/PD-L1, *n* (%)	35 (88)	76 (77)
Chemotherapy-free interval, *n* (%)[b]		
<90 days	12 (30)	34 (34)
≥90 days	26 (65)	62 (63)
ECOG PS score, *n* (%)		
0	8 (20)	20 (20)
1	32 (80)	79 (80)
Brain metastases at baseline, *n* (%)	13 (33)	32 (32)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death 1; VALG, Veterans Administration Lung Study Group.
[a]Data missing: 1-mg/kg dose-expansion, $n = 2$ (5%); all patients, $n = 13$ (13%).
[b]Data missing: 1-mg/kg dose-expansion, $n = 2$ (5%); all patients, $n = 3$ (3%).

SEZ6 expression analysis

A total of 445 SCLC tumor tissue samples were analyzed for SEZ6 expression by IHC from patients on this study (prescreened, screened, and/or enrolled). The majority (86%) had ≥1% tumor cells with ≥1+ staining intensity, and 55% met the dose-expansion enrollment cutoff of ≥25% tumor cells with ≥1+ staining intensity. This selection cutoff in the dose-expansion cohorts was determined based on a preclinical efficacy study in which xenograft models derived from patients with SCLC with various levels of SEZ6 expression, as measured by SEZ6 IHC, were treated with ABBV-011. As shown in Supplementary Fig. S1, correlative analysis of SEZ6 expression IHC with efficacy in the patient-derived xenograft study indicated that significant antitumor activity was observed in the patient-derived xenograft models with SEZ6 expression on ≥25% of tumor cells with ≥1+ staining intensity.

Safety

In dose escalation, one of nine patients in the 2-mg/kg dose cohort experienced a DLT of grade 3 fatigue. No MTD was identified, and the 2-mg/kg dosage every 3 weeks was initially selected for the expansion phase based on overall safety during the DLT evaluation period. However, the occurrence of delayed-onset hepatotoxicity [5/14 (36%; median time to onset: 65 days; range, 37–176) in patients with a γ-glutamyltransferase (GGT) increase and 4/14 (29%; median time to onset: 53.5 days; range, 37–65) in patients with a bilirubin increase in the 1.6- and 2-mg/kg dose cohorts combined] led to the reduction of the recommended dose for the expansion phase to 1.6 mg/kg in cycle 1 and 1.2 mg/kg in subsequent cycles. Continued findings of hepatotoxicity at that dose with 9/13 (69%; median time to onset: 50 days; range, 8–127) and 2/13 (15%; median time to onset: 64.5 days; range, 44–85) patients with GGT and bilirubin increase, respectively, led to another reduction of the recommended dose to 1 mg/kg, with 93% of patients receiving ≥80% relative dose intensity at this dose. The time to onset of the first hepatotoxicity events is listed in Supplementary Table S3. TEAE leading to treatment discontinuation, dose interruption, and dose reduction occurred, respectively, in 19%, 34%, and 8% of patients in the overall population and in 13%, 35%, and 15% in the 1-mg/kg dose-expansion cohort.

TEAE in the overall population ($N = 99$) and the 1-mg/kg dose-expansion cohort ($n = 40$) are summarized in **Table 2**. Overall, 96 (97%) of 99 patients experienced at least one TEAE. The most common TEAE (all grades) were fatigue (50%), nausea (42%), thrombocytopenia (41%), decreased appetite (40%), and vomiting (31%). Grade ≥3 TEAE occurred in 63 (64%) patients. Fatigue and thrombocytopenia (9% each) and increased GGT and pneumonia (7% each) were the most frequent. Treatment-related AE were reported in 76 (77%) patients and were grade ≥3 in 34 (34%; **Table 2**) patients; the most frequent treatment-related AE are summarized in

Table 2. Summary of TEAE.

TEAE, *n* (%)	1-mg/kg expansion (*n* = 40)		All patients[a] (*N* = 99)	
Any TEAE	39 (98)		96 (97)	
Any TRAE	31 (78)		76 (77)	
Grade ≥3 TEAE	26 (65)		63 (64)	
Grade ≥3 TRAE	15 (38)		34 (34)	
Serious TEAE	18 (45)		41 (41)	
Serious TRAE	3 (8)		6 (6)	
DLT	0		1 (1)[b]	
TEAE leading to treatment discontinuation	5 (13)		19 (19)	
TRAE leading to treatment discontinuation	3 (8)		13 (13)	
TEAE leading to dose interruption	14 (35)		34 (34)	
TRAE leading to dose interruption	12 (30)		29 (29)	
TEAE leading to dose reduction	6 (15)		8 (8)	
TRAE leading to dose reduction	6 (15)		8 (8)	
TEAE leading to death	7 (18)		19 (19)	
TRAE leading to death	0		0	
TEAE (any grade) in ≥15% of total patients, *n* (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Fatigue	19 (48)	4 (10)	49 (50)	9 (9)
Nausea	18 (45)	1 (3)	42 (42)	1 (1)
Thrombocytopenia[c]	16 (40)	4 (10)	41 (41)	9 (9)
Decreased appetite	15 (38)	0	40 (40)	1 (1)
Vomiting	14 (35)	1 (3)	31 (31)	1 (1)
AST increased	6 (15)	0	22 (22)	1 (1)
Constipation	11 (28)	0	21 (21)	0
GGT increased	5 (13)	2 (5)	21 (21)	7 (7)
Weight decreased	8 (20)	0	18 (18)	0
Hyperbilirubinemia[d]	7 (18)	1 (3)	17 (17)	2 (2)
Anemia	6 (15)	3 (8)	16 (16)	6 (6)
Hypokalemia	8 (20)	3 (8)	16 (16)	6 (6)
Diarrhea	7 (18)	0	15 (15)	0
Hepatotoxic TEAE,[e] *n* (%)	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Any TEAE	14 (35)	5 (13)	42 (42)	12 (12)
AST increased	6 (15)	0	22 (22)	1 (1)
GGT increased	5 (13)	2 (5)	21 (21)	7 (7)
Hyperbilirubinemia[d]	7 (18)	1 (3)	17 (17)	2 (2)
Ascites	4 (10)	0	7 (7)	1 (1)
ALT increased	0	0	7 (7)	1 (1)
INR increased	2 (5)	2 (5)	3 (3)	2 (2)
VOD	1 (3)	1 (3)	2 (2)	2 (2)
Hepatic pain	0	0	1 (1)	0
LFT increased	0	0	1 (1)	1 (1)
Portal hypertension	1 (3)	1 (3)	1 (1)	1 (1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; LFT, liver function test; TRAE, treatment-related adverse event.

[a]Safety population defined as patients who received ≥1 dose of ABBV-011.

[b]One event of fatigue grade 3 at 2 mg/kg.

[c]Includes platelet count decreased and thrombocytopenia preferred terms.

[d]Includes hyperbilirubinemia and blood bilirubin increased preferred terms.

[e]Hepatotoxicity was identified using the two preferred terms of "veno-occlusive disease" or "veno-occlusive liver disease" and the Narrow "Drug-Related Hepatic Disorders–comprehensive search" Standardized MedDRA query (SMQ 20000006).

Supplementary Table S4. Notably, no grade >2 neurologic events and no eye toxicities of any grade related to ABBV-011 treatment were reported.

A summary of hepatic TEAE is shown in **Table 2**. Hepatic TEAE were observed in 42 (42%) patients in the overall population; the most common TEAE were increased aspartate aminotransferase (22%), increased GGT (21%), and hyperbilirubinemia (17%). In the 1-mg/kg dose-expansion cohort, 14 (35%) patients reported hepatic TEAE, including hyperbilirubinemia (18%), increased aspartate aminotransferase (15%), increased GGT (13%), ascites (10%), VOD (3%), and portal hypertension (3%). Hepatic TEAE grade ≥3 occurred in 12 (12%) patients in the overall population and five (13%) patients in the 1-mg/kg dose-expansion cohort. Two patients experienced grade 3 VOD that was resolved with appropriate management. The first patient developed VOD after one 1.6-mg/kg dose of

ABBV-011 and was treated with ursodiol and diuretics. The second patient developed VOD after three 1-mg/kg doses of ABBV-011 and was treated with defibrotide and ursodiol.

TEAE leading to death occurred because of PD ($n = 16$) and stroke, cardiac failure, and respiratory distress ($n = 1$ each). No treatment-related deaths were reported.

PK

Following ABBV-011 intravenous infusion in cycle 1, preliminary systemic exposures of the ADC were approximately dose proportional across 0.3- to 2.0-mg/kg doses. The harmonic mean elimination half-life of the ADC was 4.6 days ($n = 87$) across doses. ABBV-011 ADC serum concentration–time profiles and estimated PK parameters are shown in Supplementary Fig. S2 and Supplementary Table S5, respectively. Preliminary plasma concentrations of the catabolite of linker–drug M8b were generally low across doses. At 1.0 mg/kg every 3 weeks, M8b concentrations were quantifiable only at 24 hours postinfusion in some patients, with a geometric mean of approximately 0.2 ng/mL, slightly above the lower limit of quantitation of 0.15 ng/mL.

Antitumor activity

The best percentage changes from baseline in target lesions for the overall population and the 1-mg/kg dose-expansion cohort are shown in **Fig. 1**.

Confirmed responses were observed at doses ≥0.6 mg/kg. The ORR in the 98 evaluable patients was 19%, including CR in one (1%) patient. The CBR was 69%, and the CBR lasting >12 weeks was 37% (**Table 3**).

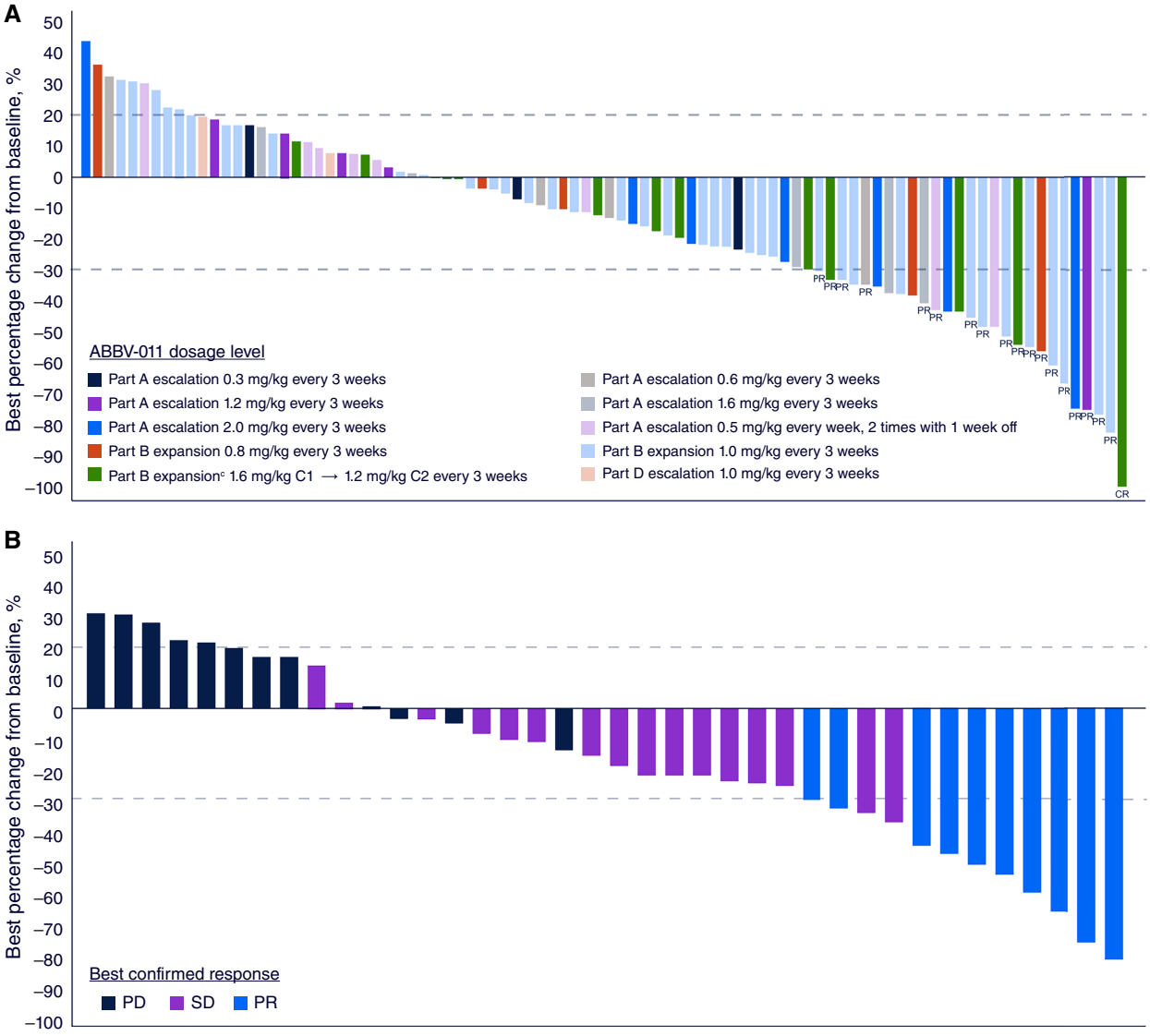

Figure 1.

Best percentage change in target lesions from baseline in (**A**) the overall population ($n = 90$)[a] and (**B**) 1-mg/kg dose-expansion cohort ($n = 38$).[b] C, cycle; PR, partial response; SD, stable disease. [a]Nine patients not included: seven patients who were off treatment before postbaseline disease assessment, one patient with PD due to a new lesion, and one patient on treatment without postbaseline disease assessments (not response evaluable). [b]The two patients not included were off treatment before postbaseline disease assessment. [c]One patient received the first dose at 2 and 1.2 mg/kg subsequently.

Table 3. Overview of antitumor response to treatment.

Efficacy outcome	1-mg/kg expansion (n = 40)	All patients[a] (n = 98)
Response rate,[b] n (%)		
ORR	10 (25)	19 (19)
(95% CI)	(13–41)	(12–29)
CBR	26 (65)	68 (69)
(95% CI)	(48–79)	(59–78)
CBR lasting >12 weeks	17 (43)	36 (37)
(95% CI)	(27–59)	(27–47)
Confirmed best overall response,[c] n (%)		
CR	0	1 (1)
PR	10 (25)	18 (18)
Stable disease	16 (40)	49 (50)
PD	12 (30)	23 (24)
Median DOR,[d] months (95% CI)	4.2 (2.6–6.7)	3.5 (2.8–4.7)
Median DOCB,[e] months (95% CI)	5.8 (4.1–7.6)	5.6 (4.6–6.7)

	1-mg/kg expansion		
PFS	1 prior line (n = 12)	≥2 prior lines (n = 28)	Total (n = 40)
Median PFS, months (95% CI)	5.4 (1.4–8.3)	2.7 (1.4–4.1)	3.5 (1.5–4.2)
PFS estimate, %			
At 3 months (95% CI)	73.3 (37.9–90.6)	46.2 (27.2–63.2)	54.0 (37.3–68.1)
At 6 months (95% CI)	41.9 (13.3–68.8)	11.5 (2.9–26.7)	19.5 (8.5–33.9)

Abbreviation: PR, partial response.
[a]One ongoing patient without postbaseline assessments is excluded.
[b]Assessment on the basis of RECIST v1.1. CR or PR confirmed in an assessment at least 4 weeks later.
[c]Seven patients had no postbaseline assessments due to early death (n = 5), clinical progression (n = 1), and other reason (n = 1).
[d]DOR is calculated from the time of first response.
[e]DOCB is calculated from the time of first dose.

For the 1-mg/kg dose-expansion cohort, the ORR (n = 40) was 25%, CBR was 65%, and CBR lasting >12 weeks was 43% (**Table 3**). The median treatment duration was 12 weeks (range, 2–63), the median DOR was 4.2 months (95% CI, 2.6–6.7), and the median DOCB was 5.8 months (95% CI, 4.1–7.6). The evolution of response over time for each patient is shown in **Fig. 2**. In patients who had received 1 (n = 12) and ≥2 prior lines (n = 28) of therapy, the ORR was 25% and 25%, CBR was 75% and 61%, and CBR lasting >12 weeks was 58% and 36%, respectively (Supplementary Table S6). In patients who had a chemotherapy-free interval <90 (n = 12) and ≥90 days (n = 26) following a first-line platinum-based therapy, the ORR was 25% and 27%, CBR 58% and 69%, and CBR lasting >12 weeks 33% and 50%, respectively (Supplementary Table S6).

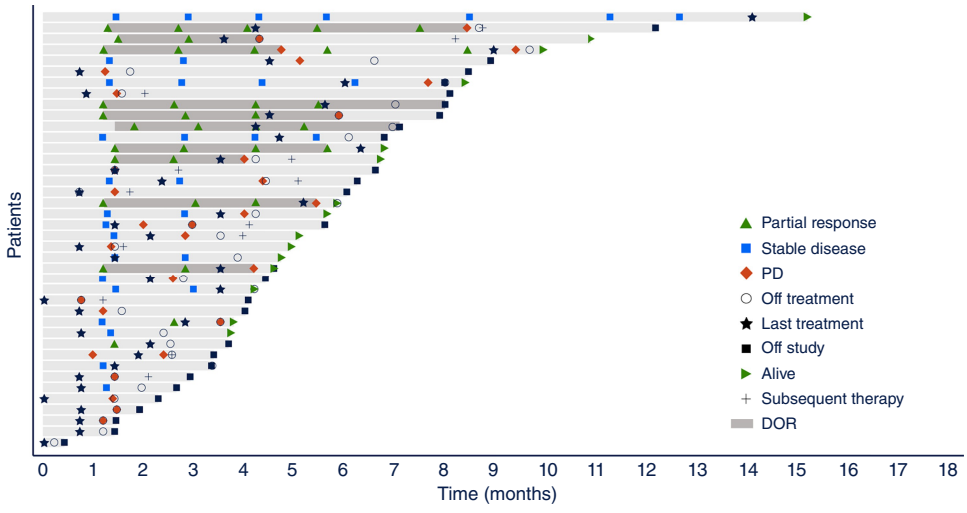

Figure 2.
Change in antitumor response over time in the 1-mg/kg dose-expansion cohort (n = 40).

The median PFS was 3.5 months (95% CI, 1.5–4.2) in the 1-mg/kg dose-expansion cohort ($n = 40$), 5.4 months (95% CI, 1.4–8.3) for patients who had received one prior line of therapy, and 2.7 months (95% CI, 1.4–4.1) for patients who had received ≥2 prior lines (**Fig. 3**; Supplementary Table S6). The median PFS was 3.0 months (95% CI, 1.2–3.9) and 4.1 months (95% CI, 1.5–5.8) for patients with a chemotherapy-free interval <90 and ≥90 days, respectively (Supplementary Table S6).

Discussion

In this first-in-human phase I study, ABBV-011 at 1 mg/kg every 3 weeks showed promising efficacy in SEZ6-positive R/R SCLC with an ORR of 25% and a median DOR of 4.2 months. The median PFS was 3.5 months (95% CI, 1.5–4.2) for all patients and 5.4 months (95% CI, 1.4–8.3) for patients receiving ABBV-011 as second-line therapy, which compares favorably with that observed in previous studies with second-line topotecan (3.5 months; 95% CI, 2.9–4.2) and lurbinectedin (3.5 months; 95% CI, 2.6–4.3; refs. 7, 8).

ABBV-011 was well tolerated at the dosage of 1 mg/kg every 3 weeks; the most common TEAE were fatigue, nausea, thrombocytopenia, and decreased appetite. Notably, no on-target neurologic or ocular toxicities were reported. Hepatotoxicity, including VOD, is a class effect of calicheamicin-based ADC, such as gemtuzumab ozogamicin (14, 18, 21) and inotuzumab ozogamicin (15, 19), and the cumulative dosing of ABBV-011 led to GGT and bilirubin increases along with cases of VOD. Two patients experienced ABBV-011–related grade 3 VOD that was resolved with medical management. Efforts to further refine the optimal dosing of ABBV-011 are ongoing, and the RP2D will be confirmed once the results from the 0.8-mg/kg dose cohort become available.

Study limitations include the modest number of patients enrolled at the preliminary RP2D of 1 mg/kg every 3 weeks and the lack of a control treatment arm. Additionally, patients enrolled in the dose-expansion group were preselected for SEZ6, although it is currently unknown if SEZ6 expression in tumor cells is associated with a favorable prognosis. These limitations preclude drawing definitive conclusions on efficacy outcomes, such as DOR and PFS, indicating the need for larger, confirmatory randomized studies.

Insights on the predictive value of SEZ6 will come from the ongoing correlative analysis of SEZ6 expression levels and response to ABBV-011. Preliminary data did not show a correlation between objective response and SEZ6 expression levels in the dose-expansion cohort. However, this observation remains inconclusive because of the small number of patients and the heterogeneity in prior treatments among the patient population (data not shown). It is also important to note that in addition to SEZ6 expression, other molecular features including, but not limited to, innate sensitivity to the payload and disease molecular subtypes may confer differential therapeutic vulnerabilities to ABBV-011. One potential limitation that may confound the analysis of the predictive value of SEZ6 expression is that SEZ6 expression was mainly analyzed in archival tissue collected before any anticancer treatment, as the majority of samples received were from the original diagnosis, and it is unclear whether SEZ6 expression levels changed after exposure to chemotherapy and/or immunotherapy. This topic and the aforementioned molecular features are being investigated in the ongoing correlative analysis of ABBV-011's efficacy.

Current outcomes for patients with R/R SCLC are poor, and there is a clear need for more effective treatment options beyond chemotherapy. Although SCLC is characterized by a high mutational burden, immune checkpoint inhibitors failed to show a survival benefit compared with chemotherapy in patients with R/R disease (22). Previous attempts with agents against potential targets have failed consistently, and there are still no approved targeted therapies for SCLC (23–25). Recent studies have identified novel potential targets including PARP, WEE1, EZH2, and delta-like ligand 3 (DLL3; refs. 26–30). Of these, two DLL3-targeting agents, rovalpituzumab tesirine and tarlatamab-dlle have reached phase III trials. Rovalpituzumab tesirine development has been discontinued due to a lack of efficacy and the presence of significant toxicity (29, 30). Tarlatamab-dlle, a DLL3–CD3 bispecific T-cell engager, was recently granted accelerated approval by the FDA on the basis of promising efficacy in a phase II study in patients with R/R extensive-stage SCLC (9) and is currently under investigation in a phase III study in relapsed SCLC (NCT05740566; ref. 31). Thus, identifying novel targeted therapies remains a key focus of SCLC research. Our study results suggest that SEZ6 is broadly expressed in SCLC, and ABBV-011 had encouraging efficacy in patients with R/R disease, establishing SEZ6 as a valid therapeutic target. As a follow-up to this study, a different SEZ6-targeted ADC, using a topoisomerase 1 inhibitor payload (ABBV-706), is currently being evaluated in a first-in-human phase I study (NCT05599984). Preliminary results show that ABBV-706 has a manageable safety profile in patients with SCLC, neuroendocrine neoplasms, and central nervous system tumors, as well as promising preliminary efficacy in R/R SCLC and neuroendocrine neoplasms (32).

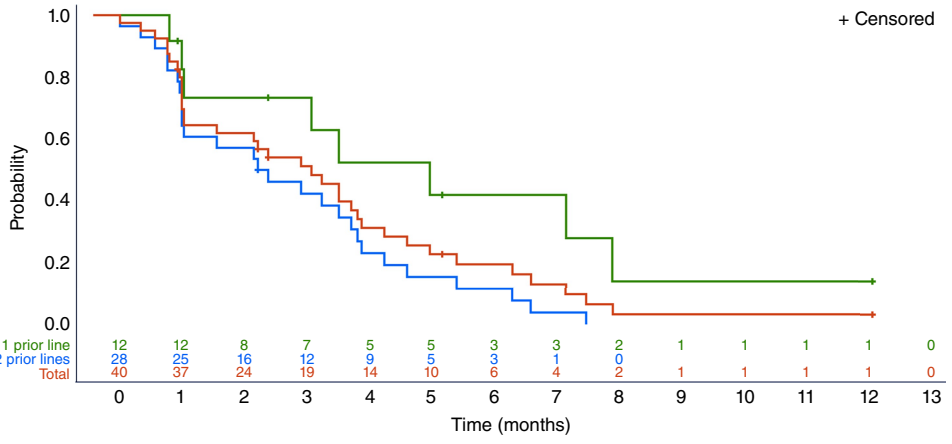

Figure 3.
PFS in the 1-mg/kg dose-expansion cohort ($n = 40$).

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References

1. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. Adv Exp Med Biol 2016;893:1–19.
2. Kahnert K, Kauffmann-Guerrero D, Huber RM. SCLC-state of the art and what does the future have in store? Clin Lung Cancer 2016;17:325–33.
3. Cittolin-Santos GF, Knapp B, Ganesh B, Gao F, Waqar S, Stinchcombe TE, et al. The changing landscape of small cell lung cancer. Cancer 2024;130:2453–61.
4. Faivre-Finn C, Snee M, Ashcroft L, Appel W, Barlesi F, Bhatnagar A, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017;18:1116–25.
5. Bogart J, Wang X, Masters G, Gao J, Komaki R, Gaspar LE, et al. High-dose once-daily thoracic radiotherapy in limited-stage small-cell lung cancer: CALGB 30610 (Alliance)/RTOG 0538. J Clin Oncol 2023;41:2394–402.
6. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Small Cell Lung Cancer Version 3. 2023 [cited 2024 Feb 5]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf.
7. von Pawel J, Jotte R, Spigel DR, O'Brien MER, Socinski MA, Mezger J, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. J Clin Oncol 2014;32:4012–9.
8. Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol 2020;21:645–54.
9. U.S. Food and Drug Administration. FDA grants accelerated approval to tarlatamab-dlle for extensive stage small cell lung cancer. 2024 [cited 2024 Jul 5]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tarlatamab-dlle-extensive-stage-small-cell-lung-cancer.
10. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2021;22:51–65.
11. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220–9.
12. Shimizu-Nishikawa K, Kajiwara K, Sugaya E. Cloning and characterization of seizure-related gene, SEZ-6. Biochem Biophys Res Commun 1995;216:382–9.
13. Gunnersen JM, Kim MH, Fuller SJ, De Silva M, Britto JM, Hammond VE, et al. Sez-6 proteins affect dendritic arborization patterns and excitability of cortical pyramidal neurons. Neuron 2007;56:621–39.
14. Nash A, Aumann TD, Pigoni M, Lichtenthaler SF, Takeshima H, Munro KM, et al. Lack of Sez6 family proteins impairs motor functions, short-term memory, and cognitive flexibility and alters dendritic spine properties. Cereb Cortex 2020;30:2167–84.
15. Wiedemeyer WR, Gavrilyuk J, Schammel A, Zhao X, Sarvaiya H, Pysz M, et al. ABBV-011, a novel, calicheamicin-based antibody-drug conjugate, targets SEZ6 to eradicate small cell lung cancer tumors. Mol Cancer Ther 2022;21:986–98.
16. Amadori S, Suciu S, Selleslag D, Aversa F, Gaidano G, Musso M, et al. Gemtuzumab ozogamicin versus best supportive care in older patients with newly diagnosed acute myeloid leukemia unsuitable for intensive chemotherapy: results of the randomized phase III EORTC-GIMEMA AML-19 trial. J Clin Oncol 2016;34:972–9.
17. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016;375:740–53.
18. Mylotarg (gemtuzumab ozogamicin) for injection [prescribing information]. Philadelphia (PA): Pfizer Inc; 2021.
19. Besponsa (inotuzumab ozogamicin) for injection [prescribing information]. Philadelphia (PA): Pfizer Inc; 2018.
20. Asano K, Komuro Y, Nitta A, Uyama Y. New guidance for promoting global drug development–basic principles for conducting phase I trials in the Japanese population prior to global clinical trials. Reg Sci Med Prod 2015;5:167–72.
21. Swaminathan M, Cortes JE. Update on the role of gemtuzumab-ozogamicin in the treatment of acute myeloid leukemia. Ther Adv Hematol 2023;14:20406207231154708.
22. Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331. Ann Oncol 2021;32:631–41.
23. Langer CJ, Albert I, Ross HJ, Kovacs P, Blakely LJ, Pajkos G, et al. Randomized phase II study of carboplatin and etoposide with or without obatoclax mesylate in extensive-stage small cell lung cancer. Lung Cancer 2014;85:420–8.

24. Cani M, Napoli VM, Garbo E, Ferrari G, Del Rio B, Novello S, et al. Targeted therapies in small cell lung cancer: from old failures to novel therapeutic strategies. Int J Mol Sci 2023;24:8883.
25. Waqar SN, Morgensztern D. Treatment advances in small cell lung cancer (SCLC). Pharmacol Ther 2017;180:16–23.
26. Byers LA, Wang J, Nilsson MB, Fujimoto J, Saintigny P, Yordy J, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2012;2:798–811.
27. Sen T, Tong P, Diao L, Li L, Fan Y, Hoff J, et al. Targeting AXL and mTOR pathway overcomes primary and acquired resistance to WEE1 inhibition in small-cell lung cancer. Clin Cancer Res 2017;23:6239–53.
28. Poirier JT, Gardner EE, Connis N, Moreira AL, de Stanchina E, Hann CL, et al. DNA methylation in small cell lung cancer defines distinct disease subtypes and correlates with high expression of EZH2. Oncogene 2015;34:5869–78.
29. Rudin CM, Reck M, Johnson ML, Blackhall F, Hann CL, Yang JC-H, et al. Emerging therapies targeting the delta-like ligand 3 (DLL3) in small cell lung cancer. J Hematol Oncol 2023;16:66.
30. Blackhall F, Jao K, Greillier L, Cho BC, Penkov K, Reguart N, et al. Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC: results from the phase 3 TAHOE study. J Thorac Oncol 2021;16:1547–58.
31. Paz-Ares LG, Felip E, Ahn M-J, Blackhall FH, Borghaei H, Cho BC, et al. Randomized phase 3 study of tarlatamab, a DLL3-targeting bispecific T-cell engager (BiTE), compared to standard of care in patients with relapsed small cell lung cancer (DeLLphi-304). J Clin Oncol 2023;41:TPS8611.
32. Chandana SR, Choudhury NJ, Dowlati A, Chiang AC, Garmezy B, Kim J-H, et al. First-in-human study of ABBV-706, a seizure-related homolog protein 6 (SEZ6)–targeting antibody-drug conjugate (ADC), in patients (pts) with advanced solid tumors. J Clin Oncol 2024;42:3001.