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ABBV-706, a seizure-related homolog protein 6 (SEZ6)-targeting antibody-drug conjugate (ADC), in patients (pts) with relapsed/refractory (R/R) small cell lung cancer (SCLC): Circulating biomarker and molecular response analyses

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Background

SEZ6 is a transmembrane protein expressed in SCLC. ABBV-706 is a first-in-class ADC composed of a potent topoisomerase 1 inhibitor attached via a stable linker to a SEZ6-directed monoclonal antibody, delivering the cytotoxic payload specifically to SEZ6-expressing tumor cells. Preliminary results from the ongoing phase I study of ABBV-706 (NCT05599984) showed antitumor activity and manageable safety in pts with advanced solid tumors, including SCLC. We report the circulating biomarker and molecular response analyses of ABBV-706 monotherapy in pts with R/R SCLC.

Methods

This phase I, open-label, multicenter trial enrolled pts (≥18 years) with R/R SCLC (≥1 prior platinum-containing chemotherapy). ABBV-706 was administered IV (Q3W; 21-day cycles) at 1.8 or 2.5 mg/kg. Circulating tumor cells (CTCs) were longitudinally enumerated. Circulating tumor DNA (ctDNA) was assessed longitudinally with Guardant INFINITY™ (Guardant Health).

Results

Molecular response monitoring indicated that ABBV-706 treatment resulted in rapid ctDNA (Table) and CTC clearance by cycle (C)2 day (D)1, and early *γH2AX* induction (C1D3). Faster and deeper ctDNA clearance was observed with 2.5 mg/kg. Pts with 100% ctDNA clearance (n=23) at C3D1 had significantly higher progression-free survival (PFS; HR 1.7, *P*=0.039) and overall survival (OS; HR 4.2, *P*=0.002) vs pts without ctDNA clearance (n=19) and significantly higher OS (HR 3.7, *P*=0.006) vs pts with ≥50% but <100% ctDNA reduction (n=16). Baseline ctDNA revealed genomic variations that may associate with resistance mechanisms related to prior immunotherapy and chemotherapy.

Conclusions

ABBV-706 treatment in pts with R/R SCLC triggered rapid CTC and ctDNA clearance; early ctDNA clearance is associated with significantly improved PFS and OS, highlighting the potential of ctDNA as a molecular response marker in R/R SCLC. Table: 2778P

ctDNA methylation-based molecular response

Analysis set,* % (n)		RECIST responders, % (n)	
Methyl cTF reduction from baseline		Methyl cTF reduction from baseline	
50%	100%	50%	100%
1.8 mg/kg 92 (22/24)	50 (12/24)	100 (14/14)	71 (10/14)
2.5 mg/kg 94 (17/18)	61 (11/18)	100 (13/13)	69 (9/13)

* Pts with ctDNA at relevant time point C3D1, from 3 January 2025 data cutoff were included in this analysis. cTF, circulating tumor fraction.

Clinical trial identification

NCT05599984.

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Legal entity responsible for the study

AbbVie, Inc.

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Disclosure

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