Background In the Phase 3 CASPIAN study, first-line D+EP significantly improved overall survival (OS) vs EP in patients with ES-SCLC, and OS benefit was sustained at >3 years of median follow-up (HR 0.71 [95% CI 0.60–0.86]; nominal p=0.0003; median OS [mOS] 12.9 vs 10.5 months). Although not statistically significant, a numerical improvement in OS was observed with D+T+EP vs EP, which continued at >3 years of median follow-up (HR 0.81 [95% CI 0.67–0.97]; nominal p=0.0200; mOS 10.4 vs 10.5 months). Various biomarkers of immune checkpoint inhibitor activity have been identified previously, including CD8A, CD4, CTLA-4, and FOXP3 (a regulatory T-cell marker), although such biomarkers are not well characterized in SCLC. In this exploratory analysis using RNA sequencing (RNAseq) data from CASPIAN, we explored the association of these canonical biomarkers with OS in patients with ES-SCLC.

Methods In CASPIAN, treatment-naïve patients with ES-SCLC received 4 cycles of D+EP or D+T+EP followed by maintenance D; or up to 6 cycles of EP. RNAseq data were generated from FFPE tumor samples collected at screening. Data cutoff: Mar 22, 2021.

Results 57/268 (21.3%) patients in the D+EP arm, 60/268 (22.4%) patients in the D+T+EP arm, and 47/269 (17.5%) patients in the EP arm had RNAseq data (biomarker-evaluable population; BEP). In the BEP, mOS was 11.8 months in the D+EP arm, 11.9 months in the D+T+EP arm, and 9.1 months in the EP arm (HR for D+EP vs EP: 0.61 [95% CI 0.40–0.92]; HR for D+T+EP vs EP: 0.53 [95% CI 0.35–0.81]). In both the D+EP and D+T+EP arms, mOS was higher in the CD8A-high vs -low expression group (table 1). In the D+T+EP arm only, mOS was higher in the CD4, CTLA-4, or FOXP3-high vs -low expression groups (table 1).

Conclusions These exploratory data on the association of CD8A, CD4, CTLA-4, and FOXP3 with outcomes in CASPIAN provide insights into the mechanism and biology of IO in ES-SCLC and support their further exploration as biomarkers in this setting. Pre-existing cytotoxic T cells may be an important factor for durvalumab to extend anti-tumor activity, and tremelimumab may enhance T-cell activation by overcoming sequestration of CD28 ligands by regulatory T cells. The RNAseq BEP was ~20% of the CASPIAN intention-to-treat population, so these findings should be regarded as hypothesis generating.

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Trial Registration Clinicaltrials.gov, NCT03043872 (Release date February 6, 2017)

Ethics Approval The study was done in accordance with applicable local regulations with permission to display the preprint. All rights reserved. No reuse allowed without permission.