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 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]; nominal p=0.0200; mOS 10.4 vs 10.5 months). Various biomarkers of immune checkpoint inhibitor activity were 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.

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.

Acknowledgements Medical writing support for the development of this abstract, under the direction of the authors, was provided by Helen Kitchen of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by AstraZeneca.

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

Ethics Approval The study was done in accordance with applicable local regulations with approval from independent ethics committees or institutional review boards. CASPIAN was a large international, multicenter trial and there are too many ethics approvals to feasibly list these details for each site. All patients provided written informed consent for participation.