Associations of ctDNA clearance and pathological response with neoadjuvant treatment in patients with resectable NSCLC from the phase III AEGEAN trial


1 Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany, 2 Oncology Cancer Biomarker Development, AstraZeneca, Cambridge, UK, 3 Department of Surgery, Duke University Medical Center, Durham, NC, USA, 4 Dermatology and Pathology, Bloomberg–Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Kimmel Cancer Center, Baltimore, MD, USA, 5 Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan, 6 Department of Respiratory and Critical Care Medicine, Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Klinik Floridsdorf, Vienna, Austria, 7 Internal Medicine II, Landeskrankenhaus Feldkirch, Feldkirch, Austria, 8 Oncology Bioinformatics, AstraZeneca, Gaithersburg, MD, USA, 9 Oncology Bioinformatics, AstraZeneca, Waltham, MA, USA, 10 Translational Medicine, AstraZeneca, Cambridge, UK, 11 Oncology Clinical Biomarker Development, AstraZeneca, Cambridge, UK, 12 Oncology R&D, AstraZeneca, Cambridge, UK, 13 Department of Thoracic/Head and Neck Medical Oncology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Background

In AEGEAN, perioperative durvalumab (D) + neoadj chemotherapy (CT) significantly improved pathological complete response (pCR), major pathological response (MPR), and event-free survival, vs neoadj CT alone among pts with resectable (R) NSCLC (modified ITT [mITT] population). We report exploratory analyses of ctDNA, including association of ctDNA clearance (CL) with pCR or MPR.

Methods

AEGEAN is a double-blind placebo (PBO)-controlled study (NCT03800134). Adults with Tx-naïve R-NSCLC (stage II–IIIB[N2]; AJCC 8th ed) were randomised (1:1) to receive neoadj CT + D or PBO IV (Q3W, 4 cycles) prior to surgery (Sx), followed by D or PBO IV (Q4W, 12 cycles), respectively, after Sx. Plasma samples were collected at protocol-specified timepoints, including prior to each neoadj Tx cycle and before Sx. Analysis was performed using patient-specific tumour-informed assays, following identification of mutations in diagnostic tissue by whole exome sequencing. ctDNA variant allele fractions (VAFs) and dynamics were assessed during neoadj Tx, including ctDNA CL and association with pCR or MPR.

Results

tDNA was evaluated in 831 samples from 186 mITT population pts (D arm, n=90; PBO arm, n=96) in the interim pCR analysis cohort. Baseline characteristics of ctDNA-evaluable pts were generally similar to those in the overall mITT population. In both Tx arms, decreases in median VAFs were observed as early as C2D1 (D arm, 97% decrease; PBO arm, 94% decrease) and, by C3D1, were significantly lower in pts with pCR/MPR vs pts with non-pCR/MPR (P≤0.003). After each cycle of neoadj Tx, higher ctDNA CL rates were observed in the D vs PBO arm (with 66% [95% CI, 54–77] vs 41% [95% CI, 30–52] at pre-Sx). Pts achieving ctDNA CL vs no CL at C2D1 had higher rates of pCR (D arm: 50.0% vs 15.1%; PBO arm: 14.3% vs 3.1%) and MPR (D arm: 66.7% vs 35.8%; PBO arm: 38.1% vs 12.5%). Among pts who were ctDNA+ at baseline, all pts achieving pCR and >90% achieving MPR had ctDNA CL by C4D1.

Conclusions

Neoadj Tx with D + CT resulted in greater ctDNA CL than PBO + CT. Earlier ctDNA CL was associated with higher likelihood of pCR and MPR, highlighting ctDNA CL as a potential early-response biomarker.

Clinical trial identification

NCT03800134 (release date: January 11, 2019).

Editorial acknowledgement

Medical writing support for the development of this abstract, under the direction of the authors, was provided by Andrew Gannon of Ashfield MedComms (New York, NY, USA), an Inizio company, and was funded by AstraZeneca.

Legal entity responsible for the study

AstraZeneca