Background T-cell-inflamed gene expression profile (TcellinfGE) and tumor mutational burden (TMB) are clinically validated biomarkers that independently predict pembrolizumab response. This study investigated prospective TcellinfGE and TMB assessment in evaluating first-line pembrolizumab-based combination therapies; the different treatment combinations evaluated may provide insight into the unique biology of each combination therapy.

Methods KEYNOTE-495/KEYImpaCT is a group-sequential, adaptively randomized, multisite, open-label phase 2 study investigating first-line pembrolizumab plus the VEGF/FGFR inhibitor lenvatinib, CTLA-4 inhibitor ivavzelimab (MK-1308), or LAG-3 inhibitor favezelimab (MK-4280) in patients with advanced NSCLC. DNA and RNA were extracted from tumor tissue to determine TcellinfGE and TMB; patients were assigned to one of four biomarker-defined subgroups (TcellinfGE<sub>low</sub>TMB<sub>low</sub>, TcellinfGE<sub>low</sub>TMB<sub>high</sub>, TcellinfGE<sub>high</sub>TMB<sub>low</sub>, TcellinfGE<sub>high</sub>TMB<sub>high</sub>) and randomly assigned 1:1:1:1 to receive pembrolizumab (200mg IV Q3W)+lenvatinib (20mg oral QD), pembrolizumab+quavonlimab (75mg IV Q6W), or pembrolizumab+favezelimab (200mg n=30) or 800mg n=34) QD; the initial prespecified dose was 200mg but changed to 800mg based on emerging data). The primary end point was investigator-assessed ORR per RECIST v1.1. Multiple interim analyses will be performed until the prespecified number of patients is reached; further validation is needed to determine additional signals and may be addressed as more mature data become available.

Conclusions These data demonstrate the feasibility and clinical usefulness of prospective TcellinfGE and TMB assessment to study the clinical activity of three first-line pembrolizumab-based combination therapies in patients with advanced NSCLC. Although sample sizes were small, the TcellinfGE<sub>low</sub>TMB<sub>high</sub> subgroup demonstrated the best response among the biomarker subgroups for all three combination therapies; further validation is needed to determine additional signals and may be addressed as more mature data become available.