Background  T-cell–inflamed gene expression profile (TcellinfGEP) and tumor mutational burden (TMB) are clinically validated biomarkers that independently predict pembrolizumab response. This study investigated prospective TcellinfGEP 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 biomarker subgroup.

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 quavonlimab (MK-4280) in patients with advanced NSCLC. DNA and RNA were extracted from tumor tissue to determine TcellinfGEP and TMB; patients were assigned to one of four biomarker-defined subgroups (TcellinfGEPlowTMBlow, TcellinfGEPloothTMBhigh, TcellinfGEPhighTMBlow, TcellinfGEPhighTMBhigh) and randomly assigned 1:1:1:1 to receive pembrolizumab (200 mg I.V. Q3W)+lenvatinib (20mg oral QD), pembrolizumab+quavonlimab (75mg I.V. Q6W), or pembrolizumab+favezelimab (200mg [n=30] or 800mg [n=34]) as initial dose, respectively. The initial prespecified dose was 200mg but changed to 800mg based on early data. The primary end point was investigator-assessed ORR per RECIST v1.1. Multiple interim analyses will be performed until the prespecified clinical signal is observed. The first interim analysis occurred after ≥10 patients had ≥12 weeks of follow-up.

Results  At the data cutoff (January 11, 2021), 208 patients were treated (pembrolizumab+lenvatinib, n=72; pembrolizumab+quavonlimab, n=72; pembrolizumab+favezelimab 200mg, n=30; pembrolizumab+favezelimab 800mg, n=34). The overall assay success rate for testing and determining TcellinfGEP and TMB was 94%. In patients treated with pembrolizumab+lenvatinib, pembrolizumab+quavonlimab, or pembrolizumab+favezelimab, ORRs were generally highest in the TcellinfGEPhighTMBhigh subgroup (table 1); response rates were similar across combinations within this subgroup. ORR was low across combinations within the TcellinfGEPhighTMBlow subgroup. Treatment-related adverse events (TRAEs) occurred in 88%, 65%, 57%, and 59% of patients in the pembrolizumab+lenvatinib, pembrolizumab+quavonlimab, pembrolizumab+favezelimab 200mg and pembrolizumab+favezelimab 800mg arms, respectively. Consistent with the known TRAEs of these agents, most TRAEs were grade 1 or 2 in severity except in the pembrolizumab+lenvatinib arm (grade 3–5, 63%). Three deaths from TRAEs occurred (pembrolizumab+lenvatinib [n=2], brain hemorrhage and myocardial infarction; pembrolizumab+favezelimab 800 mg [n=1], pneumonitis).

Conclusions  These data demonstrate the feasibility and clinical usefulness of prospective TcellinfGEP 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 TcellinfGEPhighTMBhigh 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.

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Trial Registration  ClinicalTrials.gov, NCT03516981

Ethics Approval  The study protocol and all amendments were approved by the relevant institutional review board or ethics committee at each study site. All patients provided written informed consent to participate in the clinical trial.

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