Background The group sequential, adaptively randomized, open-label, phase 2 KEYNOTE-495/KeyImPaCT trial (NCT03516981) demonstrated the feasibility of using prospective T-cell-inflamed gene expression profile (TcellinfGEP) and tumor mutation burden (TMB) dual biomarker status to assess the clinical activity of first-line pembrolizumab-based combination therapies in advanced non–small-cell lung cancer (NSCLC). Here, we present updated efficacy data relative to prespecified biomarker-defined subgroups for each treatment arm.

Methods Patients with previously untreated stage IV NSCLC were categorized by TcellinfGEP and TMB dual biomarker status (TcellinfGEPlowTMBnon-high, TcellinfGEPlowTMBhigh, TcellinfGEPnon-lowTMBhigh, TcellinfGEPnon-lowTMBlow), then randomly assigned 1:1:1 to receive pembrolizumab (200 mg IV Q3W) plus the multitargeted kinase inhibitor (targeting VEGFRs 1-3, FGFRs 1-4, PDGFRα, RET, and KIT) lenvatinib (20 mg oral QD), CTLA-4 inhibitor quavonlimab (75 mg IV Q6W), or LAG-3 inhibitor favezelimab (initially 200 mg and then 800 mg IV Q3W). Adaptive randomization based on objective response rate (ORR) was employed, and frequent interim analyses were performed to quantify efficacy and assess for futility. The primary end point of investigator-assessed ORR per RECIST v1.1 was assessed using prespecified efficacy thresholds for each biomarker-defined subgroup: an ORR of >5% within the TcellinfGEPlowTMBhigh subgroup, >20% within the TcellinfGEP TMB high subgroup and TcellinfGEPnon-lowTMBhigh subgroup, and >45% within the TcellinfGEPnon-lowTMBlow subgroup evaluated using a Bayesian posterior probability. Secondary end points included progression-free survival (PFS) per RECIST v1.1, overall survival (OS), and safety.

Results At data cutoff (March 21, 2022), 243 patients had been treated (pembrolizumab+ lenvatinib, n = 80; pembrolizumab+quavonlimab, n = 82; pembrolizumab+favezelimab 200 mg, n = 30; pembrolizumab+favezelimab 800 mg, n = 51). Efficacy data are presented in table 1. ORR with pembrolizumab + lenvatinib in the TcellinfGEPnon-lowTMBhigh subgroup met the prespecified efficacy threshold. The safety profile of each treatment arm was consistent with the known safety profile of each combination.

Conclusions Pembrolizumab-based combination therapy continued to show promising antitumor activity and durable response in the TcellinfGEPnon-lowTMBhigh subgroup across all combinations. Response in the TcellinfGEPnon-lowTMBhigh subgroup treated with pembrolizumab+lenvatinib met the prespecified efficacy threshold. Although response in the pembrolizumab+favezelimab arm did not reach the efficacy bar, there was a trend toward improved ORR in the TcellinfGEPnon-lowTMBlow subgroup versus the other 3 biomarker-defined subgroups; median PFS and OS were also numerically longer in the TcellinfGEPnon-lowTMBlow subgroup compared with the other 3 biomarker-defined subgroups. Prospective assessment of dual biomarkers, as performed in this study, may help identify patients with NSCLC most likely to respond to pembrolizumab-based combination therapies.

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Consent The study protocol and all amendments were approved by the institutional review board or ethics committee at each institution. All patients provided written informed consent.