## 635 KEYNOTE-495/KEYIMPACT: UPDATED ANALYSIS OF A BIOMARKER-DIRECTED, RANDOMIZED, PHASE 2 TRIAL OF PEMBROLIZUMAB-BASED COMBINATION THERAPY FOR NON-SMALL CELL LUNG CANCER

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**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 ($Tcell_{inf}GEP$) 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 $Tcell_{inf}GEP$ and TMB dual biomarker status ($Tcell_{inf}GEP^{low}TMB^{non\text{-}high}$, $Tcell_{inf}GEP^{low}TMB^{high}$, $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$, $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$) then randomly assigned 1:1:1 to receive pembrolizumab (200 mg IV Q3W) plus the multikinase 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 $Tcell_{inf}GEP^{low}TMB^{non\text{-}high}$ subgroup, >20% within the $Tcell_{inf}GEP^{low}TMB^{high}$ subgroup and $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$ subgroup, and >45% within the $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$ 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 $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$ 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 $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$ subgroup across all combinations. Response in the $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$ 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 $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$ subgroup versus the other 3 biomarker-defined subgroups; median PFS and OS were also numerically longer in the $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$ 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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**Trial Registration** NCT03516981

**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

**Abstract 635 Table 1** Efficacy by treatment and dual biomarker status

| Arm | End point | $Tcell_{inf}GEP^{low}TMB^{non\text{-}high}$ | $Tcell_{inf}GEP^{low}TMB^{high}$ | $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$ | $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$ | Total |
|---|---|---|---|---|---|---|
| Pembrolizumab+ lenvatinib | ORR, % (95% CI) [n/N] | 12 (2-31) [3/25] | 33 (10-65) [4/12] | 41 (21-64) [9/22] | 57 (34-78) [12/21] | 35 (25-46) [28/80] |
| | Median PFS, months (95% CI) | 5 (2-9) | 14 (1-NR) | 8 (4-21) | 18 (6-22) | 8 (6-12) |
| | Median OS, months (95% CI) | 16 (5-20) | 19 (4-NR) | 21 (12-NR) | 23 (17-NR) | 19 (16-23) |
| Pembrolizumab+ quavonlimab | ORR, % (95% CI) [n/N] | 12 (2-30) [3/26] | 31 (9-61) [4/13] | 14 (3-35) [3/22] | 52 (30-74) [11/21] | 26 (17-36) [21/82] |
| | Median PFS, months (95% CI) | 3 (2-6) | 3 (1-17) | 6 (2-13) | 17(10-NR) | 6 (3-10) |
| | Median OS, months (95% CI) | 12 (8-20) | 24 (8-NR) | 19 (8-NR) | 28 (17-NR) | 20 (14-26) |
| Pembrolizumab+ favezelimab 200 mg | ORR, % (95% CI) [n/N] | 0 (0-28) [0/11] | 33 (4-78) [2/6] | 25 (3-65) [2/8] | 60 (15-95) [3/5] | 23 (10-42) [7/30] |
| | Median PFS, months (95% CI) | 2 (2-2) | 8 (2-NR) | 2 (1-6) | 6 (0-NR) | 2 (2-6) |
| | Median OS, months (95% CI) | 9 (4-NR) | 21 (2-NR) | 13 (1-NR) | NR (13-NR) | 15 (8-25) |
| Pembrolizumab+ favezelimab 800 mg | ORR, % (95% CI) [n/N] | N/A[a] | 27 (6-61) [3/11] | 14 (3-35) [3/22] | 50 (26-74) [9/18] | 29 (17-44) [15/51] |
| | Median PFS, months (95% CI) | | 4 (2-12) | 3 (2-8) | 13 (4-NR) | 6 (3-8) |
| | Median OS, months (95% CI) | | 24 (3-NR) | 11 (5-16) | NR (13-NR) | 16 (12-NR) |

[a]Not applicable; this group did not proceed because of the lack of clinical activity in this subgroup observed at the 200-mg dose of favezelimab.
NR, not reached.

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