457 KEYNOTE-495/KEYIMPACT: INTERIM ANALYSIS OF A RANDOMIZED, BIOMARKER-DIRECTED, PHASE 2 TRIAL OF PEMBROLIZUMAB-BASED COMBINATION THERAPY FOR NON–SMALL CELL LUNG CANCER (NSCLC)

[1]Martin Gutierrez*, [2]Wei-Sen Lam, [3]Matthew Hellmann, [4]Matthew Gubens, [5]Charu Aggarwal, [6]Daniel Shao Weng Tan, [7]Enriqueta Felip, [8]Joanne WY Chiu, [9]Jong-Seok Lee, [10]James Chih-Hsin Yang, [11]Edward Garon, [12]Giovanna Finocchiaro, [13]Myung-Ju Ahn, [14]Alexander Luft, [15]Gregory Landers, [16]Andrea Basso, [16]Hua Ma, [16]Julie Kobie, [16]John Palcza, [16]Razvan Cristescu, [17]Lawrence Fong, [16]Alexandra Snyder, [16]Jianda Yuan, [18]Roy Herbst. *[1]Hackensack University Medical Center, Hackensack, NJ, USA; [2]Fiona Stanley Hospital and Western Australia Country Health Service, Perth, Australia; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]University of California, San Francisco, San Francisco, CA, USA; [5]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [6]SingHealth Duke NUS Academic Medical, Singapore, Singapore; [7]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [8]University of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong; [9]Seoul National University, Bundang Hospital, Seongnam, Korea, Republic of; [10]National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei City, Taiwan, Province of China; [11]David Geffen School of Medicine at UCLA, Santa Monica, USA; [12]IRCCS Humanitas Research Hospital, Milan, Italy; [13]Samsung Medical Center, Sungkyunkwan University of Medicine, Seoul, Korea, Republic of; [14]Leningrad Regional Clinical Hospital, St. Petersburg, Russian Federation; [15]The Oncology Centre, KwaZulu-Natal, South Africa; [16]Merck and Co., Inc., Kenilworth, NJ, USA; [17]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [18]Comprehensive Cancer Center Yale School, New Haven, CT, USA*

Background T-cell–inflamed gene expression profile ($Tcell_{inf}$GEP) and tumor mutational burden (TMB) are clinically validated biomarkers that independently predict pembrolizumab response. This study investigated prospective $Tcell_{inf}$GEP 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-1308), or LAG-3 inhibitor favezelimab (MK-4280) in patients with advanced NSCLC. DNA and RNA were extracted from tumor tissue to determine $Tcell_{inf}$GEP and TMB; patients were assigned to one of four biomarker-defined subgroups ($Tcell_{inf}GEP^{low}TMB^{low}$, $Tcell_{inf}GEP^{low}TMB^{high}$, $Tcell_{inf}GEP^{high}TMB^{low}$, $Tcell_{inf}GEP^{high}TMB^{high}$) and randomly assigned 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] Q3W; 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 clinical signal is observed. The first interim analysis for each combination therapy 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 $Tcell_{inf}$GEP and TMB was 94%. In patients treated with pembrolizumab+lenvatinib, pembrolizumab+quavonlimab, or pembrolizumab+favezelimab, ORRs were generally highest in the $Tcell_{inf}GEP^{high}TMB^{high}$ subgroup (table 1); response rates were similar across combinations within this subgroup. ORR was low across combinations within the $Tcell_{inf}GEP^{low}TMB^{low}$ 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).

Abstract 457 Table 1 Confirmed ORR by Therapy and Biomarker Status

Arm, % (95% CI) [n/N]	$Tcell_{inf}GEP^{low}$ TMB^{low}	$Tcell_{inf}GEP^{low}$ TMB^{high}	$Tcell_{inf}GEP^{high}$ TMB^{low}	$Tcell_{inf}GEP^{high}$ TMB^{high}	Total
Pembro + lenvatinib	12 (3-31) [3/25]	22 (3-60) [2/9]	30 (12-54) [6/20]	39 (17-64) [7/18]	25 (16-37) [18/72]
Pembro + quavonlimab	12 (2-30) [3/26]	33 (8-70) [3/9]	9 (1-29) [2/22]	40 (16-68) [6/15]	19 (11-30) [14/72]
Pembro + favezelimab 200 mg	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]
Pembro + favezelimab 800 mg	N/A[a]	50 (7-93) [2/4]	11 (1-35) [2/18]	42 (15-72) [5/12]	26 (13-44) [9/34]

[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.

Conclusions These data demonstrate the feasibility and clinical usefulness of prospective $Tcell_{inf}$GEP 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 $Tcell_{inf}GEP^{high}TMB^{high}$ 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.

Acknowledgements Jeanne Fahey, PhD, of Merck & Co., Inc., Kenilworth, New Jersey, USA, provided critical review of the abstract. Elisha Dettman PhD, Mark Ayers MS, and Andrey Loboda PhD of Merck & Co., Inc., Kenilworth, New Jersey, USA, provided critical review of study translational data. Medical writing and/or editorial assistance was provided by Shane Walton, PhD, and Lei Bai, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.457