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

[1]Roy Herbst*, [2]Wei-Sen Lam, [3]Matthew Hellmann, [4]Matthew Gubens, [5]Charu Aggarwal, [6]Daniel Shao Weng Tan, [7]Enriqueta Felip, [8]Joanne 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, [4]Lawrence Fong, [16]Alexandra Snyder, [16]Jianda Yuan, [17]Martin Gutierrez. *[1]Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA; [2]Fiona Stanley Hospital and Western Australia Country Health Service, Perth, Australia; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [5]Perelman School of Medicine, University, Philadelphia, PA, USA; [6]National Cancer Centre Singapore, Singapore, Singapore; [7]Vall d'Hebron University Hospital, Vall, Barcelona, Spain; [8]University of Hong Kong, Queen Mary Hosp, Pok Fu Lam, Hong Kong; [9]Seoul National University Bundang Hospit, Seongnam, Republic of Korea; [10]National Taiwan University Hospital and, Taipei City, Taiwan; [11]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [12]IRCCS Humanitas Research Hospital, Milan, Italy; [13]Samsung Medical Center, Sungkyunkwan Uni, Seoul, Republic of Korea; [14]Leningrad Regional Clinical Hospital, Saint Petersburg, Russian Federation; [15]The Oncology Centre, KwaZulu-Natal, South Africa; [16]Merck and Co., Inc., Rahway, NJ, USA; [17]Hackensack University Medical Center, Hackensack, NJ, USA*

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.

Acknowledgements Medical writing and/or editorial assistance was provided by Mehak Aggarwal, PharmD, and Holly C. Cappelli, PhD, CMPP, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0635

J Immunother Cancer: first published as 10.1136/jitc-2022-SITC2022.0635 on 7 November 2022. Downloaded from http://jitc.bmj.com/ on April 27, 2024 by guest. Protected by copyright.