375 **Poster Session**

Association between biomarkers and clinical outcomes of lenvatinib + pembrolizumab in advanced renal cell carcinoma (RCC): Results from Study 111/KEYNOTE-146.

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Background: In the Study 111/KEYNOTE-146 trial (NCT02501096; N=147), lenvatinib (lenva) + pembrolizumab (pembro) showed encouraging antitumor activity and a manageable safety profile in treatment-naive (n=23) or previously treated metastatic RCC (n=105, previously treated with immune checkpoint inhibitor [ICI]; n=19, previously treated ICI naive); 145 had clear cell RCC and 2 had non-clear cell RCC. In this exploratory analysis, we evaluated the association between clinical outcomes and gene expression signatures and DNA variants for individual RCC-specific driver genes of interest based on published reports. **Methods:** Patients (pts) with metastatic RCC were treated with lenva 20 mg orally once daily + pembro 200 mg intravenously once every 3 weeks. The analysis population included pts with treatment-naive (n=10) and ICI pretreated (n=70) disease with evaluable RNA-sequencing data for the 18-gene T-cell–inflamed gene expression profile ($Tcell_{inf}GEP$) and for 11 other signatures (angiogenesis; glycolysis; gMDSC; hypoxia; mMDSC; MVD; MYC; proliferation; RAS; stroma/EMT/TGFβ; WNT) and whole exome sequencing (WES) data for DNA variants for individual genes (*VHL*, *PBRM1*, *BAP1,* and *SETD2*). Specimens were collected prior to the start of treatment. The associations between each signature score and ORR and PFS per immune-related RECIST were evaluated using logistic regression and Cox proportional hazards, respectively. One-sided *P* values for $Tcell_{inf}GEP$ (hypothesized positive association) and two-sided *P* values for all other signatures (no hypothesized association) were adjusted for multiplicity using the Hochberg step-up procedure; significance was prespecified at α=0.05. The association between DNA variants for individual genes and ORR was evaluated descriptively. Clinical data cutoff was August 18, 2020. **Results:** Of 147 treated pts, RNA sequencing and WES data were available for 80 (54%) and 60 (41%), respectively. $Tcell_{inf}GEP$ was not associated with ORR (*P*=0.827) or PFS (*P*=0.741), nor were the other 11 signatures before or after adjustment for $Tcell_{inf}GEP$. ORR for DNA variants reported in the table. **Conclusions:** In this exploratory analysis of pts with metastatic RCC enrolled in Study 111/KEYNOTE-146 treated with lenva + pembro, responses were observed regardless of biomarker status. There were no statistically significant associations between gene signatures and clinical outcomes. Clinical benefit was observed regardless of *VHL*, *PBRM1*, *BAP1,* or *SETD2* mutation status. Analyses in larger randomized datasets will provide additional information on the role of biomarkers in RCC. Clinical trial information: NCT02501096. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and Eisai Inc., Woodcliff Lake, NJ, USA.

	VHL – mut	*VHL* – no mut	*PBRM1* – mut	*PBRM1* – no mut	*BAP1* – mut	*BAP1* – no mut	*SETD2* – mut	*SETD2* – no mut
Responders/ pts	24/35	8/14	16/23	16/26	7/10	25/39	9/15	23/34
ORR, % (95% CI)	69 (51-83)	57 (29-82)	70 (47-87)	62 (41-80)	70 (35-93)	64 (47-79)	60 (32-84)	68 (50-83)