Liver metastases are associated with a unique tumor microenvironment and impaired treatment outcomes in urothelial bladder cancer patients treated with tislelizumab

Authors: Linlin Xu[1], Mo Liu[2], Ruiqi Huang[3], Xiaopeng Ma[2], Xikun Wu[3], Vanitha Ramakrishnan[1], Lilin Zhang[4], Yun Zhang[5]

Affiliations:

1. Clinical biomarkers, BeiGene USA, Inc, San Mateo, USA
2. Bioinformatics, BeiGene (Beijing) Co., Ltd., Beijing, China
3. Biostatistics, BeiGene (Shanghai) Co., Ltd., Shanghai, China
4. Clinical development, BeiGene (Shanghai) Co., Ltd., Shanghai, China
5. Clinical biomarkers, BeiGene (Beijing) Co., Ltd., Beijing, China

Background: Tislelizumab, a humanized monoclonal antibody that targets programmed cell death protein 1 (PD-1), has shown promising activity in the treatment of advanced urothelial bladder cancer (UBC). Recent studies suggest that liver metastases (LM) are associated with reduced effectiveness of PD-1/PD-L1 therapies (Yu, et al. *Nat Med.* 2021;27[1]:152-164). We evaluated how LM correlate with survival outcomes and the tumor immune microenvironment in UBC patients treated with tislelizumab in the BGB-A317-204 trial (NCT04004221).

Methods: Cox regression was used to evaluate the effect of LM on overall survival (OS). Other key baseline characteristics were further included as covariates in the model to investigate the adjusted effect of LM and the interactions of LM with them. Gene expression profiling and multiplex immunohistochemistry (mIHC) analysis were performed on baseline tumor samples. Gene expression differences between LM positive (LM+) and LM negative (LM–) patients were compared by Wilcoxon rank-sum test for continuous biomarkers, and Fisher's exact test for categorical biomarkers. All *P*-values reported in this post-hoc exploratory analysis were descriptive, without multiplicity adjustment. A result of $P<0.05$ was considered statistically significant.

Results: A total of 113 patients were included in the analysis. LM were present in 27/113 (23.9%) of them. Cox regression analysis showed the presence of LM was a negative prognostic factor for overall survival (OS) in UBC patients treated with tislelizumab, OS (hazard ratio (HR), 3.7; 95% CI, 2.3-6.2; $P<0.001$). The LM negative prognostic value remained unaffected after adjustment for other baseline covariates. Next, we investigated immune cell infiltration and gene expression as potential indicators of impaired response in LM+ patients included in this analysis. Significantly fewer circulating lymphocytes at baseline were found in LM+ compared to LM– patients ($P<0.05$), while no differences were observed in other immune cell types. Reduced expression of gene signatures of CD4 Th1 ($P<0.05$), CD8+T cells ($P<0.05$) and NK cells functions ($P<0.05$) within tumor tissues was observed in samples from LM+ patients. Reduced CD8+ T-cell infiltration within the tumor and the intra-tumor stroma was also observed in LM+ patients based on mIHC analysis. No significant differences were observed in tumor mutational burden level between LM+ and LM– patients.

Conclusion: LM were associated with worse outcomes of UBC patients treated with tislelizumab in the A317-204 study. Diminished number and impaired function of CD8+ T cells and NK cells in the tumor microenvironment of LM+ patients may have contributed to the worse survival observed in this subset of patients.