Liver Metastasis Is Associated With a Unique Tumor Microenvironment and Impaired Treatment Outcomes in Urothelial Bladder Cancer Patients Treated With Tislelizumab

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Conclusions

LM was associated with worse survival outcomes of PD-L1+ UBC patients treated with tislelizumab in the A317-204 study, consistent with previous findings

The diminished number of CD8+ T cells and antitumor-related immune cell signatures in the tumor microenvironment of LM+ patients may contribute to the worse survival outcomes observed in this population

Background

Urothelial bladder cancer (UBC) accounts for more than half a million new diagnoses and 212,536 deaths annually.[1]

Tislelizumab, a humanized monoclonal antibody that targets programmed cell death protein 1 (PD-1), has shown encouraging activity in the treatment of advanced UBC.[2]

Recent studies suggest liver metastasis (LM) is associated with reduced effectiveness of immunotherapy.[3–7]

In this study, we evaluated the effects of LM on UBC patients treated with tislelizumab in the BGB-A317-204 trial (NCT04004221).[2] We further explored LM+ and LM– populations for possible mechanisms associated with survival.

Methods

- Previously treated patients with PD-L1+ locally advanced or metastatic UBC who had received tislelizumab monotherapy and had tissue samples available for biomarker evaluation were eligible for this retrospective analysis (**Table 1**)
- Available baseline tumor tissues were evaluated by either gene expression profiling (HTG EdgeSeq Precision Immuno-Oncology Panel) and/or multiplex-immunohistochemistry (mIHC) (Opal automation Multiplex IHC kit, panels CD8, CD68, PD-L1, panCK, CD64, DAPI) and/or tumor mutational burden (TMB) analysis. Gene signature scores were calculated using the gene set variation analysis method. TMB scores were evaluated in baseline tumor samples by OncoScreen Plus®. Peripheral blood cell counts were obtained by local investigators
- Cox regression analysis 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. Differences between LM+ and LM– patients were compared by Wilcoxon rank-sum test for continuous biomarkers and Fisher's exact test for categorical biomarkers. All *P*-values reported were descriptive and without multiplicity adjustment in this post hoc exploratory study. A result with $P<0.05$ was considered as statistically significant

Results

Baseline characteristics

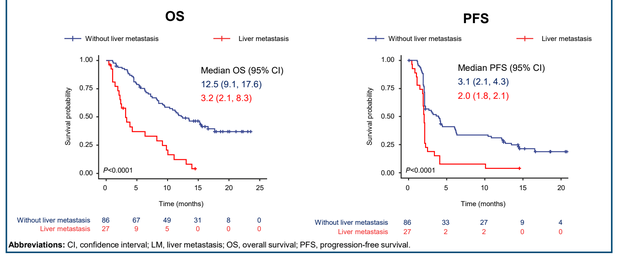
- Of the 113 patients enrolled in this study, 27/113 (24%) had LM (**Table 1**)
- One hundred patients had evaluable gene expression profiles (87 from primary and 13 from metastatic tumor); 25 patients had evaluable tumor CD8 density as detected by mIHC (21 from primary and 4 from metastatic tumor); 54 patients had evaluable TMB (49 from primary and 5 from metastatic tumor), and all patients had peripheral blood cell counts

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Patients (N=113)
Age, y	
Median (range)	63 (36, 81)
Sex, n (%)	
Male/female	84 (74)/29 (26)
Smoking status, n (%)	
Never/current/former	60 (53)/13 (12)/40 (35)
ECOG performance status at baseline, n (%)	
0/1	53 (47)/60 (53)
Site of primary tumor, n (%)	
Urinary bladder	50 (44)
Renal pelvis	31 (27)
Ureter	24 (21)
Urethra	3 (3)
Other	5 (4)
Known metastasis at baseline, n (%)	
Liver	27 (24)
Lung	43 (38)
Bone	26 (23)
Lymph node only	27 (24)
Number of prior regimens of anticancer therapies, n (%)	
1/2/≥3	69 (61)/37 (33)/7 (6)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Figure 1. Patients With LM Had Shorter OS and PFS Compared to Patients Without LM



Abbreviations: CI, confidence interval; LM, liver metastasis; OS, overall survival; PFS, progression-free survival.

- The presence of LM was an important factor that is associated with inferior OS and progression-free survival (PFS) in patients treated with tislelizumab (**Figure 1**)
- LM was a negative prognostic factor for both OS and PFS in univariate analysis (**Table 2**). Negative prognostic value of LM remained when other baseline covariates were included in the Cox model
- Patients with LM had significantly fewer circulating lymphocytes at baseline (**Figure 2**). No differences in monocytes, basophils, eosinophils, or neutrophils were observed between patients with or without LM
- LM+ patients showed lower gene signature expressions for prespecified T-cell ($P<0.05$), NK cell ($P<0.05$), and CD8+ T-cell ($P<0.05$) function within tumor tissues (**Figure 3**). No differences were observed for immune suppressive cell signatures including Treg and myeloid-derived suppressor cells
- Patients with LM had lower CD8+ T-cell densities in the tumor (**Figure 4,** only four samples were available for analysis for LM+ patients). No significant differences were observed in TMB levels between LM+ and LM– patients (**Figure 5**)

Table 2. Effect of Baseline Metastasis and LDH Levels on OS and PFS Assessed by Cox Regression Analysis

Characteristic	Patients (N)	HR for OS	*P*-value*	HR for PFS	*P*-value
Liver metastasis			<0.0010		<0.0010
Y	27	3.74		2.56	
N	86	Reference			
Lung metastasis			0.0016		0.0002
Y	43	2.10		2.28	
N	70	Reference			
Bone metastasis			0.0075		0.0519
Y	26	2.01		1.60	
N	87	Reference			
LDH level			0.0412		0.0705
Elevated (≥280 U/L)	95	1.87		1.67	
Normal	18	Reference			

*Only showing Cox regression analysis results with *P*<0.1. Other characteristics analyzed included age, sex, ECOG PS (0, 1), PD-L1 expression (≥50%, <50%). **Abbreviations:** ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

Figure 2. Lymphocyte Count

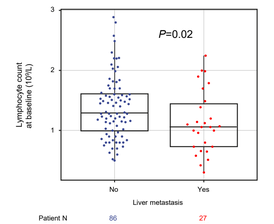
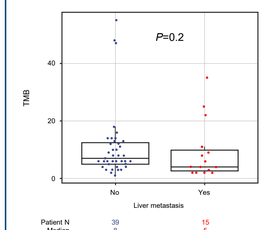
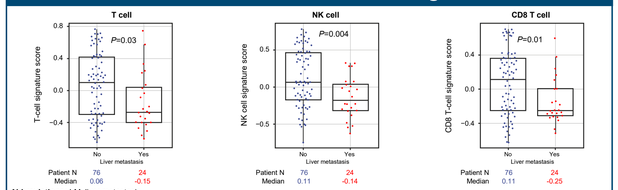


Figure 5. LM and TMB



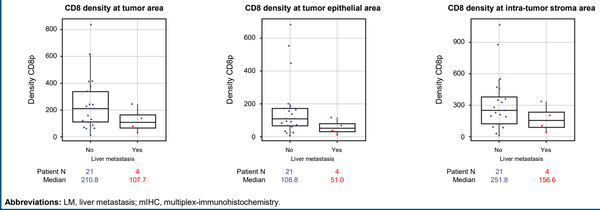
Abbreviations: LM, liver metastasis; TMB, tumor mutational burden.

Figure 3. LM+ Patients Had Significantly Lower Antitumor-Related Immune Cell Signatures



Abbreviations: LM, liver metastasis.

Figure 4. mIHC Showed That Patients With LM Had Lower CD8 T-Cell Densities in Different Tumor Areas



Abbreviations: LM, liver metastasis; mIHC, multiplex-immunohistochemistry.

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Disclosures

LX, ML, RH, XM, XW, VR, LZ, and YZ are all employees of BeiGene. LX, RH, VR, and YZ own stocks or shares in BeiGene. VR owns stocks or shares in Takeda.

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