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SPATIAL ANALYSIS OF TUMOR-INFILTRATING LYMPHOCYTES CORRELATES WITH THE RESPONSE OF METASTATIC COLORECTAL CANCER PATIENTS TREATED WITH VACTOSERTIB IN COMBINATION WITH PEMBROLIZUMAB

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Background Previously, we presented a promising anti-tumor efficacy (ORR: 16%, mOS: 15.8 months, RECIST) of the combination of vactosertib, a potent and selective TGF- β receptor I, and pembrolizumab (vac+pem) in patients with microsatellite stable metastatic colorectal cancer (MSS mCRC, MP-VAC-204 study). Recent reports showed immune-excluded TIL located in stroma would be closely related to TGF- β signature, which may harbor the primary resistance of pembrolizumab. In this study, we performed an exploratory biomarker analysis of TIL resided in either intra-tumoral or stromal area in pathology slides, and we hypothesized that spatial features of TIL would correlate with the response of vac+pem.

Methods Pathology slides stained with H&E were obtained from 31 patients at baseline and 14 patients at cycle 2 in MSS mCRC patients in MP-VAC-204 study. For spatial TIL analysis, we applied an artificial intelligence -powered H&E analyzer, named Lunit SCOPE IO, which automatically detects TIL, tumor and stroma. It calculates the proportion of immune phenotype consists of inflamed, as high TIL density inside tumor area, or immune-excluded, as high TIL density in stroma in whole-slide images. Additionally, PD-L1 and CD8 were stained using multiplex immunohistochemistry to validate immune phenotype assessed by Lunit SCOPE IO.

Results At baseline, the proportion of immune-excluded area (immune-excluded score, IES) was positively correlated with the density of CD8-positive cells in stroma area measured by mIHC (coefficient = 0.349), but it was not related to the density of PD-L1-positive cells (coefficient = -0.226). Area under receiver operating characteristics to predict the responder as partial response by RECIST v1.1 by IES and PD-L1 were 0.741 and 0.528. The overall response rate of vac+pem in the patients with high IES > 42.3% was 25% (4 out of 16), while no response was observed in those with low IES (0 out of 15). Overall survival (OS) of vac+pem was significantly prolonged in those with high IES > 42.3% compared to low IES (median OS: not reached versus 6.8 months, $P = 0.0097$), but it was not different according to PD-L1 level. After treatment of vac+pem, while IES was decreased regardless of treatment response, the proportion of inflamed area was increased in the responders ($N=3$) but decreased in the non-responders ($N=11$).

Conclusions Immune-excluded score which reflects TGF- β -driven TIL exclusion into stroma is correlated with anti-tumor response of vac+pem in MSS mCRC. Further investigation on spatial TIL analysis as a potential biomarker should be warranted. (Clinical trial information: NCT03724851)

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