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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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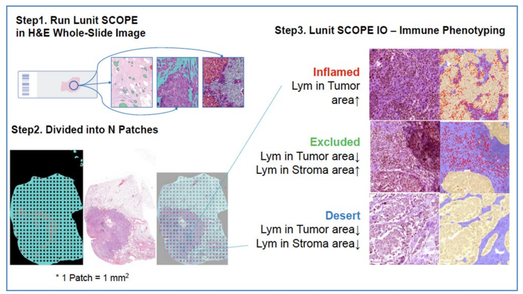
BACKGROUND

- Pembrolizumab has been approved for its use in microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC), but microsatellite stable (MSS) CRC represents a high unmet need since there are currently no approved immunotherapy options.
- MP-VAC-204 (NCT03724851) is a phase I/II clinical trial to assess safety and efficacy of vactosertib (anti-TGFßR1) in combination with pembrolizumab (anti-PD1) in patients with previously heavily treated MSS mCRC, which showed overall response rate of the combination was 16% by RECIST v1.1 and 20% by iRECIST in preliminary analysis (N=50).[1]
- Artificial intelligence (AI)-powered spatial tumor infiltrating lymphocyte (TIL) analysis using H&E image showed inflamed TIL infiltration was significantly related to favorable outcome of immune checkpoint inhibitors in multiple cancer types.[2]
- In the current study, we hypothesized that comprehensive analysis of AI-powered analysis of H&E images or multiplex IHC stained images for immune cell deconvolution would predict the responder of vactosertib + pembrolizumab (vac+pem) in previously heavily treated MSS CRC.

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 AI-powered H&E analyzer, named Lunit SCOPE IO, which automatically detects TIL, tumor and stroma. It calculates the proportion of immune phenotype which consists of inflamed, as high TIL density inside tumor area, or immune-excluded, as high TIL density in stroma in whole-slide images (Figure 1).[3]
- Additionally, PD-L1 and CD8 were stained using multiplex immunohistochemistry to validate immune phenotype assessed by Lunit SCOPE IO.

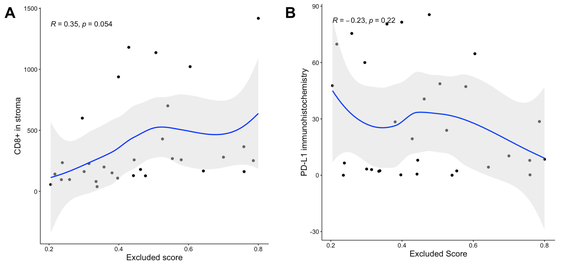
Figure 1. Lunit SCOPE IO inference on H&E slide images



RESULTS

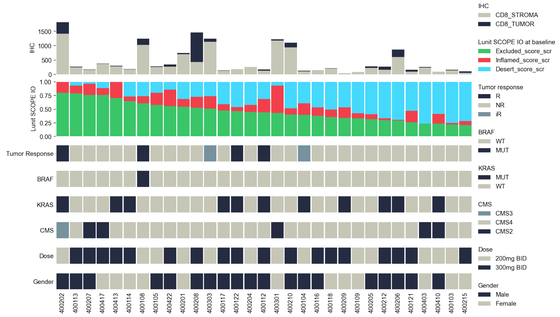
- At baseline, the proportion of immune-excluded area (immune-excluded score, IES) was positively correlated with the density of CD8-positive cells in stroma area measured by mIHC (coefficient = 0.349), but it was not related to the density of PD-L1-positive cells evaluated by tumor proportion score (TPS) (coefficient = -0.226) (Figure 2).

Figure 2. Correlation between IES and CD-8 positive cells in stroma (A) and IES and PD-L1 positive cells (B)



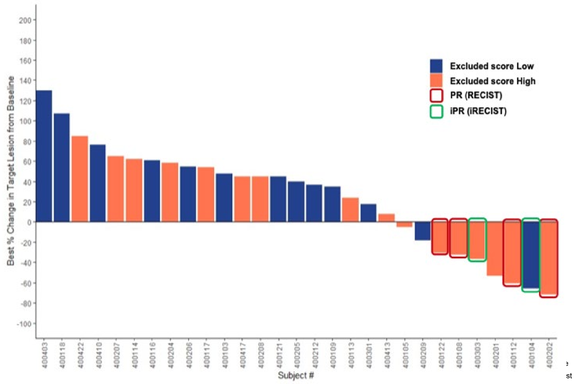
- Area under receiver operating characteristics to predict the responder as partial response by RECIST v1.1 by IES, CD8-positive cells in stroma and PD-L1 were 0.741, 0.657 and 0.528, respectively.
- According to the median value of IES (43%), the patient group was divided into high IES (>43%) or low IES. The red line in figure 3 indicates the cutoff. There were no significant differences between the two groups in gene expression (BRAF, KRAS, and CMS), drug dose, and gender.

Figure 3. Distribution of IHC, IES, and clinical information of 31 patients



- The overall response rate of vac+pem in patients with high IES > 43% was 25% (4 out of 16), while no response was observed in those with low IES (0 out of 15) (Figure 4).

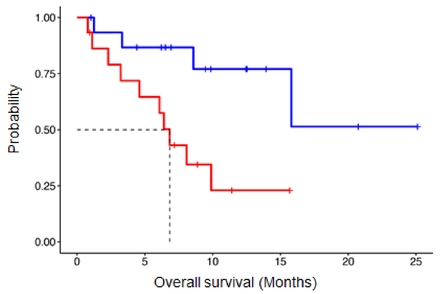
Figure 4. The overall response and Lunit SCOPE IO immune-excluded score in the patients having RECIST



- Overall survival (OS) of vac+pem was significantly prolonged in those with high IES > 43% compared to low IES (median OS: not reached versus 6.8 months, P = 0.001) (Figure 5).

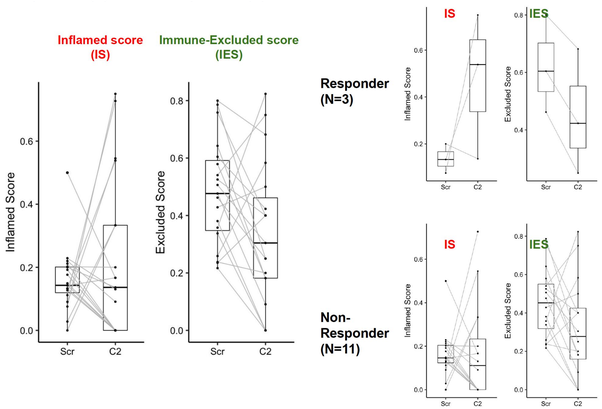
Figure 5. OS in high/low IES group (HR; hazard ratio, CI; confidence interval, NR; not reached)

Group	N	Median OS (95% CI)	HR (95% CI)	P value
IES High	16	NR (15.8-NR)	Ref	Ref
IES Low	15	6.8 (4.6-NR)	4.7 (1.3-17.3)	0.001



- After treatment of vac+pem, 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) (Figure 6).

Figure 6. Change of inflamed score (IS) and IES before and after vac+pem treatment (A) in responders (B) and non-responders (C)



SUMMARY and CONCLUSIONS

- Pathologic assessment of TIL with its spatial relation with stroma is a promising biomarker to predict the overcoming the resistance to pembrolizumab, by vactosertib.
- IES 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.

REFERENCE

1) *J Clin Oncol* 2021;39(S15):3573.
2) *J Clin Oncol* 2021;39(S15):2607.
3) *Cancer Res* 2021;81(S13):1908.

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