An immune-related gene expression profile to predict the efficacy of adding atezolizumab to first-line FOLFOXIRI plus bevacizumab in metastatic colorectal cancer: a translational analysis of the phase II randomized AtezoTRIBE study.

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Background

- The phase II randomized AtezoTRIBE study demonstrated that the addition of atezolizumab (atezo) to first-line FOLFOXIRI/bevacizumab (bev) prolongs PFS in metastatic colorectal cancer (mCRC) patients, unselected for mismatch repair (MMR) status. Limited benefit was observed among patients with proficient MMR (pMMR) tumours.

Antoniotti, Lancet Oncol 2022 (in press)

- DetermaIO™ is an immune-related gene expression signature, reflecting the presence of infiltrating inflammatory cells *versus* a differentiated stromal microenvironment. It has never been investigated whether this gene signature may predict benefit from ICI-based therapeutic strategies in mCRC.

Iwase, Cancers 2021; Nielsen, Heliyon 2021; Seitz, J Clin Oncol 2021; Ranganath BMC Cancer 2022.

Objective

We performed a mRNA gene expression analysis of tumour samples from patients randomized in the AtezoTRIBE study to investigate the relative benefit from the addition of atezo to first-line FOLFOXIRI/bev according to the DetermaIO™ status.

Methods

- AtezoTRIBE was a phase II comparative trial in which 218 mCRC patients, unselected for MMR status, were randomized 1:2 to receive first-line FOLFOXIRI/bev (control arm) or FOLFOXIRI/bev/atezo (experimental arm).

- RNA was obtained from FFPE blocks of pre-treatment tumour specimens from 142 (65%) out of 218 enrolled patients. RT-qPCR was performed using DetermaIO™, to assess mRNA expression of a 27-gene targeted panel. In each sample the IO score was calculated according to the established pan-cancer IO algorithm. The predefined IO cut-point (0.09) was applied to dichotomize tumours as IO+ or IO-.

Results

- IO score was successfully determined in 122 (86%) cases, and 33 tumours were defined as IO+ (27%).
- No differences in terms of baseline clinical and molecular features were observed between IO+ and IO- tumours (**Table 1**).

Results – IO signature and baseline characteristics

Table 1. Baseline key characteristics according to IO status.

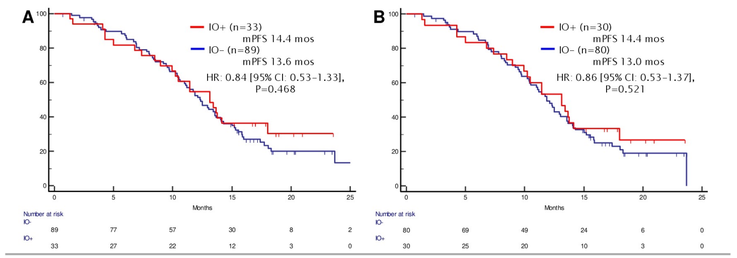
Characteristic, % patients	IO- (n= 89)	IO+ (n= 33)	*P*
Age, years, median (IQR)	59 (52–67)	61 (52–67)	0.910
Gender			
Male / Female	65 / 35	64 / 36	1.000
ECOG Performance Status			
0 / 1	87 / 13	94 / 6	0.347
Time to Metastases			
≤ / > 3 months	84 / 16	76 / 24	0.296
Primary Tumour Site			
Right / Left or rectum	45 / 55	48 / 52	0.838
Liver-Only Disease			
Yes / No	26 / 74	36 / 64	0.267
Primary Tumour Resected			
Yes / No	64 / 36	58 / 42	0.534
***RAS* and *BRAF* status**			
All wild-type / *RAS* mut / *BRAF* mut	20 / 68 / 12	9 / 82 / 9	0.330
Missing data	-	1	
MMR status			
pMMR / dMMR	92 / 8	91 / 9	1.000
Missing data	2	-	
TMB status			
Low / High	92 / 8	82 / 18	0.165
Missing data	14	5	
Arm			
Control / Experimental	40 / 60	30 / 70	0.404

Data are median (IQR) or number (%). ECOG, Eastern Cooperative Oncology Group; MMR, mismatch repair; TMB, tumour mutational burden.

Results – IO signature and prognosis

Patients with IO+ and IO- tumours showed similar PFS in both the overall population (n=122; median PFS: 14.4 vs 13.6; HR 0.84 [95%CI: 0.53-1.33], p=0.468) (**Figure 1, panel A**) and in the subgroup of patients with pMMR tumours (n=110; median PFS: 14.4 vs 13.0; HR 0.86 [95% CI: 0.53 – 1.37], p=0.521 (**Figure 1, panel B**).

Figure 1. PFS according to IO status in the overall population (N=122) (A) and in pMMR subgroup (N=110) (B).



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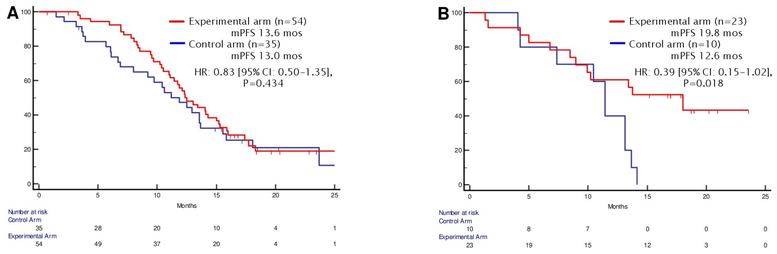
Results – IO signature and treatment outcome

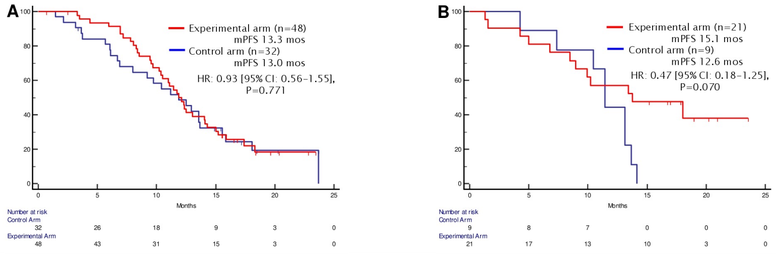
An interaction effect between IO status and treatment arm was reported (p for interaction=0.066), with higher PFS benefit in favor of the experimental arm among patients with IO+ (HR 0.39 [95% CI:0.15-1.02]) than among those with IO- tumours (HR 0.83 [95% CI 0.50-1.35]) (**Figure 2, panel A and B**).

Figure 2. PFS according to treatment arm among patients with IO- (N=89) (A) and IO+ (N=33) tumours (B).



Similar results were reported in the pMMR subgroup (p for interaction=0.139) (**Figure 3, panel A and B**).

Figure 3. PFS according to treatment arm among patients with pMMR IO- (N=80) (A) and pMMR IO+ (N=30) tumours (B).



Conclusions

- The DetermaIO™ signature may be helpful to predict benefit from the addition of atezo to first-line FOLFOXIRI/bev in mCRC patients, also in the cohort of pMMR tumours.
- Our results support the hypothesis that a deeper characterization of tumour immune microenvironment may help identifying mCRC patients more likely to benefit from ICI-based therapeutic strategies.
- These findings are worthy of further investigation in independent cohorts.

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