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Kidney ccRCC immune classification (KIC) enhances the predictive value of T effector (Teff) and angiogenesis (Angio) signatures in response to nivolumab (N)

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Background

The NIVOREN GETUG-AFU 26 study reported safety and efficacy of N in metastatic (m-) ccRCC patients (pts) in a "real world setting". A translational research program including gene expression signatures was launched to identify biomarkers for outcome to N.

Methods

Among the 324 pts included in the NIVOREN translational cohort, RNA-sequencing was performed on 79 FFPE primary ccRCCs. We first evaluated the impact of Teff and Angio signatures on the outcome, based on median mRNA expression values, as described in the IMmotion 150 RCC trial. To better characterize the tumor microenvironment, we performed an unsupervised analysis using MCP-Counter to classify tumors according to their infiltration by 8 immune (I) and 2 stromal (S) (fibroblasts and endothelial) cell populations. Outcomes were the response rate (RR, best response determined by complete or partial response) and PFS.

Results

Angio– and Teff signatures were not predictive of outcomes on N when applied separately. However, combination of these two signatures revealed that the most aggressive tumors Teff-high/Angio-low and Teff-low/Angio-low were significantly associated with RR and PFS (Table).Unsupervised classification identified 5 KIC subtypes (A to E). CD8-high/S-low (KIC C+E) tumors were associated with higher RR and longer PFS compared to I-low/S-low (KIC A), I-low/S-high (KIC B) and I-high/S-high (KIC D) tumors (Table). Principal component analysis showed a similar contribution of KIC stromal cells and the Angio signatures in worst outcome tumors. The KIC classification identified tumor microenvironments linked to good outcomes on N and unraveled the deleterious clinical impact of the potential immunosuppression exerted by neutrophils, fibroblasts and endothelial cells.Table: 700O

	RR	P-value Fisher exact	Median PFS [CI95%] (mo)	P-value Log rank
Teff-high/Angio-low	8/17 (47%)		10.1 [2.7; NE]	
Teff-high/Angio-high	4/22 (18%)		4.1 [2.6;5.6]	
Teff-low/Angio-high	5/16 (31%)	0.01	3.2 [2.4;NE]	0.0005
Teff-low/Angio-low	1/21 (5%)		2.6 [2.1;2.8]	
KIC C-E	10/21 (48%)		11.4 [2.4;NE]	
KIC A-B-D	8/55 (15%)	0.005	2.8 [2.7;4.2]	0.03

Conclusions

We report for the first time from a prospective trial that Immune high/angiogenesis and stromal low signatures likely predict nivolumab efficacy in m-ccRCC patients.

Clinical trial identification

NCT03013335.

Legal entity responsible for the study

Unicancer.

Funding

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Disclosure

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