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Markers of inflammation are associated with clinical outcomes in patients with metastatic renal cell carcinoma treated with nivolumab

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Background

In previously treated patients with metastatic renal cell carcinoma (mRCC), the programmed death-1 (PD-1) inhibitor antibody nivolumab demonstrated objective response rates of 20%–22% and median overall survival (OS) of 18.2– 25.5 months[1]. An exploratory biomarker analysis of baseline and on-therapy changes was conducted to investigate the relationship between the clinical and immunomodulatory activity of nivolumab.

Methods

Patients with 1–3 prior therapies for mRCC received nivolumab 0.3, 2, or 10 mg/kg IV every 3 weeks (Q3W); treatment-naïve patients received 10 mg/kg IV Q3W. Biopsies and peripheral blood mononuclear cells were obtained at baseline and cycle 2 day 8. Tumor burden reduction was defined as a ≥20% decrease. Gene expression data were obtained on Affymetrix U219. OS parameters were estimated by the Kaplan-Meier method or by Cox proportional hazards regression. PD-1 ligand 1 (PD-L1) expression was measured by tumor membrane immunohistochemical staining (28-8 antibody; Dako) in baseline biopsies. Serum-soluble factors were quantified using a Luminex multiplex panel (Myriad Rules-Based Medicine). T cell receptor sequencing was conducted with the immunoSEQ assay (Adaptive Biotechnologies).

Results

91 patients were treated. 59 baseline and 55 on-therapy biopsies were evaluable for gene expression, with 42 matched samples. Patients with tumor burden reduction had differential expression (>1.3-fold, $P < 0.01$, q-value < 0.16) of 311 genes at baseline (n = 13) and 779 genes on-therapy (n = 11) compared with patients without tumor burden reduction, including higher expression of transcripts associated with cell-mediated immunity. CTLA-4, TIGIT, and PD-L2 transcripts were present at higher levels on-therapy in patients with tumor burden reduction. Table 1 summarizes OS and OS by PD-L1 expression. 18/56 biopsies (32%) had ≥5% PD-L1 expression. Among serum-soluble factors, recognized prognostic markers (VEGF, ICAM1, VCAM1, TIMP1) were associated with OS. Based on T cell sequencing, increased tumor T cell counts and decreased blood T cell clonality at baseline were associated with longer OS.

Conclusions

Immune markers at baseline and on-therapy suggest pre-existing adaptive immunity is associated with nivolumab-induced tumor regression. Upregulation of immune checkpoint molecules provides rationale for study of nivolumab and ipilimumab combination in mRCC. A minimal difference in OS by PD-L1 expression was observed for up to 2 years.

Trial registration

ClinicalTrials.gov identifier NCT01358721.

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Table 1

	Median OS, mo (95% CI)	OS rate, % (95% CI)	
		1-yr	2-yr
Treatment group			
0.3 mg/kg (n=22)	16.4 (10.1-NR)	71 (47-86)	44 (22-64)
2.0 mg/kg (n=22)	NR	72 (48-86)	61 (36-78)
10 mg/kg (n=23)	25.2 (12.0-NR)	74 (48-88)	51 (27-71)
10 mg/kg (naïve) (n=24)	NR	81 (57-92)	76 (51-89)
PD-L1 expression			
≥5% (n=18)	NR	71 (44-87)	64 (37-82)
<5% mg/kg (n=38)	23.4 (13.1-33.3)	71 (52-83)	48 (30-64)

NR = not reached

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