Molecular profiling of metastatic renal cell carcinoma treated with ipilimumab-nivolumab

Tian Zhang[1,2], Landon Brown[1], Jennifer Tran[3], Rajan Gupta[1], Daniel J George[1], YongHee Lee[3], Sarabjot Pabla[4], Mary Nesline[4], Sean Glenn[4], Moshe Ornstein[3]

[1]Division of Medical Oncology, Dept. of Medicine, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC, USA
[2] Division of Hematology and Oncology, Dept of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA
[3] Taussig Cancer Center, Cleveland Clinic, Cleveland, OH, USA
[4] OmniSeq, Buffalo, NY, USA

BACKGROUND

- Molecular biomarkers are needed to predict for immunotherapy response in renal cell carcinoma.[1]
- Ipilimumab-nivolumab is now used for first-line treatment of metastatic renal cell carcinoma.[2]
- We previously found moderate cell proliferation to be somewhat predictive of nivolumab response; whereas poorly proliferative and PD-L1 negative tumors as well as low expression of a 5-gene panel are associated with nivolumab resistance.[3,4]
- We aimed to explore molecular alterations further in a cohort of patients with metastatic renal cell carcinoma treated with ipilimumab-nivolumab.

METHODS

- 62 archival tumor specimens were identified from patients treated with ipilimumab-nivolumab at Duke Cancer Institute and Cleveland Clinic.
- Performed genomic and transcriptomic sequencing using the CLIA-certified OmniSeq Immune Report Card®. IHC for PD-L1 and CTLA-4 were performed.
- Molecular features were correlated with clinical outcomes of objective response rates, progression free survival, and overall survival.
- Inflammation was characterized as strong/moderate/weak; cell proliferation as high/moderate/poor; and TMB high as top 20% (cutoff for top 20% = xxx).

Table 1. Baseline patient characteristics

Characteristic	Patients (%)
Gender: Male	16 (44%)
Median Age	59
IMDC risk:	
Favorable	15 (24%)
Intermediate	40 (65%)
Poor	7 (11%)
Line of treatment:	
First line	47 (76%)
Second line	10 (16%)
Third line or more	5 (8%)
Primary	42 (67%)
Metastatic	20 (32%)
Bone metastases	16 (26%)
Objective responses	
CR	4 (6.5%)
PR	21 (34%)
SD	18 (29%)
PD	19 (31%)

RESULTS

Figure 1. Inflammation score corresponding to clinical outcomes

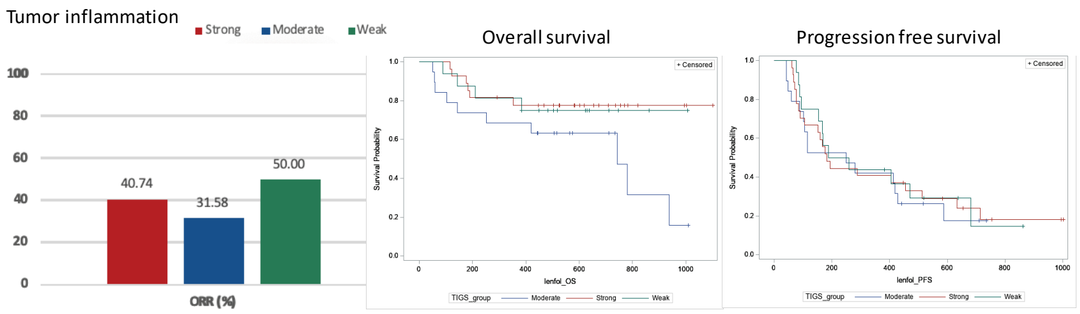


Figure 2. Cell proliferation score corresponding to clinical outcomes

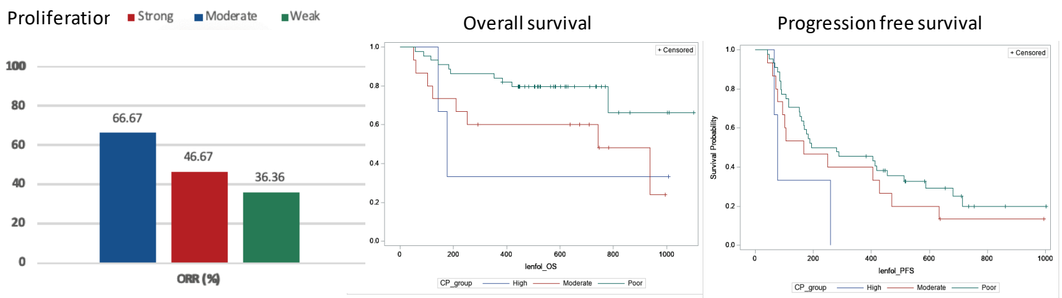


Table 2. Cell proliferation at high/moderate/poor with CTLA-4 high/low and PD-L1 high/low associated with clinical outcomes

		NIVO OS				IPI + NIVO OS				IPI + NIVO PFS			
Predictor		Hazard Ratio	CI Low	CI High	P Value	Hazard Ratio	CI Low	CI High	P Value	Hazard Ratio	CI Low	CI High	P Value
CP_Group	High vs Poor at CTLA4=High, PDL1_IHC=High	14.243	2.567	79.038	0.002	1.61E+10	0	I	1.00	89.00	1.00	7945.90	0.05
	High vs Poor at CTLA4=Not High, PDL1_IHC=High	14.243	2.567	79.038	0.002	307.20	7.87	11991.90	0.00	9.42	0.70	126.80	0.09
	Moderate vs Poor at CTLA4=High, PDL1_IHC=High	130.700	7.772	2197.100	0.001	1.44E-08	0	I	0.99	0.69	0.07	6.54	0.75
	Moderate vs Poor at CTLA4=Not High, PDL1_IHC=High	0.028	0.001	0.690	0.029	20.82	2.13	203.30	0.01	8.58	1.86	39.62	0.01
	High vs Moderate at CTLA4=High, PDL1_IHC=High	0.109	0.005	2.237	0.151	1.12E+18	0	I	0.99	128.80	0.91	18206.30	0.05
	High vs Moderate at CTLA4=Not High, PDL1_IHC=High	512.400	10.464	25091	0.002	14.75	0.67	327.00	0.09	1.10	0.08	15.33	0.94

CONCLUSIONS

- In a multicenter cohort of 62 patients with metastatic renal cell carcinoma treated with ipilimumab-nivolumab, tumors were profiled using the OmniSeq Immune Report Card. Moderate tumor inflammation was prognostic but not predictive, CTLA-4 expression was associated with objective responses, and the 5-gene panel did not predict for treatment response or resistance.
- Predictive markers remain elusive for metastatic renal cell carcinoma.
- Gene expression profiles that predict for response may vary by immunotherapy treatment regimen.
- Prospective studies are needed to further validate transcriptomic biomarkers for treatment selection in first-line renal cell carcinoma.

Figure 3. CTLA-4 and PD-L1 status corresponding to clinical outcomes

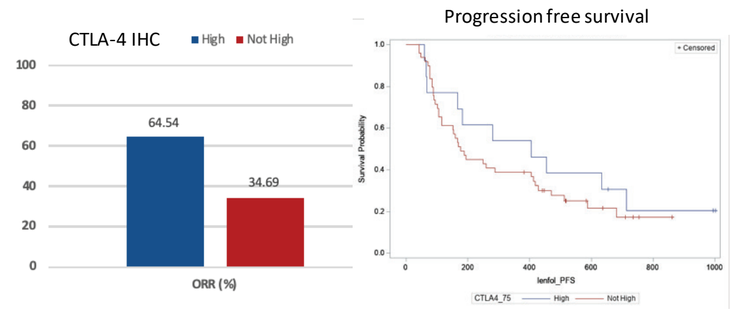


Figure 4. 5-gene panel (FOXP3, CCR4, KLRK1, ITK, TIGIT) not associated with disease control and progression free survival

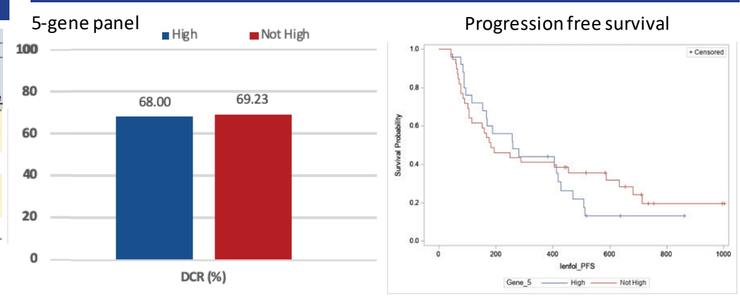
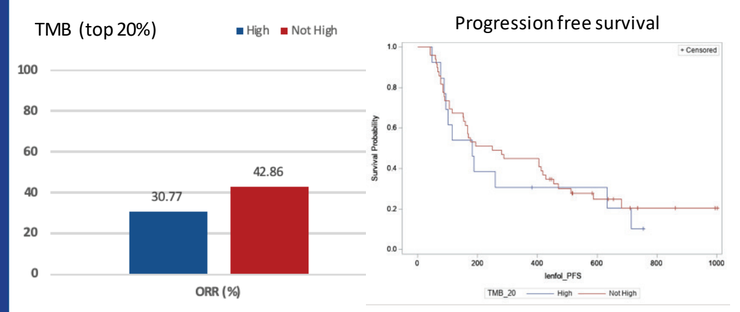


Figure 5. Tumor mutational burden not associated with objective response and progression free survival



REFERENCES

1. Bakouny Z et al, Eur Urol Focus, 2020.
2. Albiges L et al, ESMO Open, 2020.
3. Zhang T et al, Oncoimmunology, 2020.
4. Zhu J et al, GU ASCO, 2020.

Correspondence:
tian.zhang@utsouthwestern.edu

Acknowledgments: Study supported by Kidney Cancer Association Young Investigator Award.
We appreciate patients and investigators at Duke, Cleveland Clinic, and OmniSeq who contributed.

Presented at IKCS 2021 | November 5-6, 2021