OPtimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC)

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BACKGROUND AND RATIONALE

- Standard first-line IO combinations for metastatic clear cell renal cell carcinoma (mccRCC) include an anti-PD-1 antibody plus either (1) an anti-CTLA-4 antibody (IO/IO), or (2) an anti-VEGF TKI (IO/TKI). Currently, there is no level-1 evidence to guide physician's choice between an IO/IO versus IO/TKI combination.
- Our group participated in a multi-omics evaluation of tumors from patients enrolled in the phase III IMmotion 151 trial of the IO/anti-angiogenesis combination of atezolizumab plus bevacizumab vs standard of care TKI sunitinib. This study identified seven RNAseq-defined tumor clusters (Fig. 1) with unique biology and differential response to treatment, including those driven predominantly by angiogenesis (clusters 1 and 2), others showing increased expression of inflammatory and/or proliferation pathways (clusters 4, 5 and 7), and a subgroup with high myeloid and low T-effector (Teff) gene expression patterns (clusters 3 and 6).
- Each IMDC category contained all 7 clusters (Fig. 2), suggesting this predictive biomarker is unique from IMDC criteria and will lead to therapeutic decisions that better target the underlying biology of individual patient's tumors.

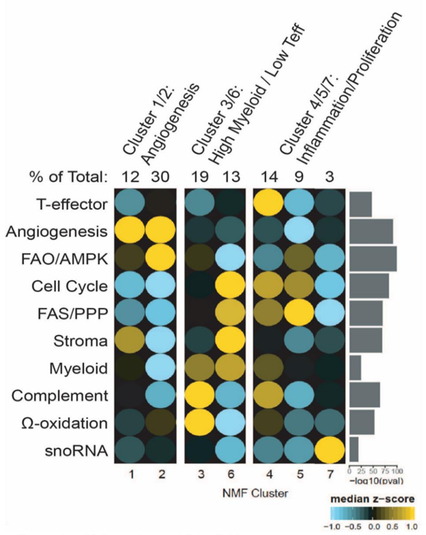


Fig. 1. IMmotion 151 RNAseq tumor clusters. RNAseq was performed on tumors from the IMmotion 151 trial. Cluster analysis identified seven groups. Relative gene expression for key pathways is shown.

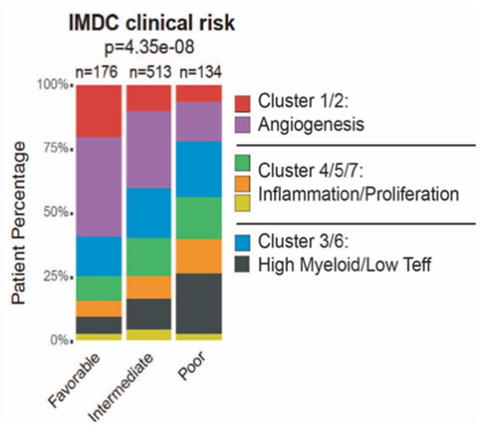


Fig. 2. IMmotion 151 clusters among IMDC risk groups. All seven clusters are represented in each IMDC risk group, suggesting diverse biologic drivers exist within each risk group. Adapted from Motzer et al., *Cancer Cell* 2020.

- When compared with the anti-VEGF TKI sunitinib, tumors with inflammatory and/or proliferative pathways (clusters 4, 5 and 7) had improved progression-free survival and overall survival when adding the IO-agent atezolizumab to the anti-VEGF antibody bevacizumab; no benefit was observed with the addition of atezolizumab in the angiogenic pathway enriched clusters (cluster 1 and 2).

OBJECTIVE AND HYPOTHESIS

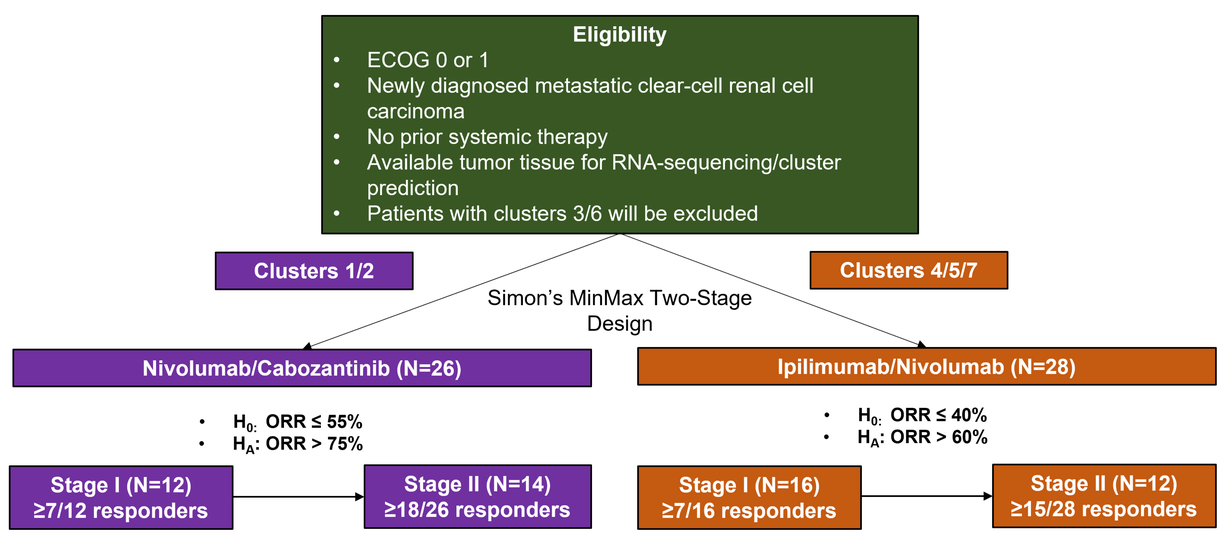
- To improve clinical efficacy of ipilimumab/nivolumab and nivolumab/cabozantinib in mccRCC by prospectively assigning treatment according to a patient's biologic cluster as defined by an RNA-based gene expression profile.
- We hypothesize that use of gene expression clusters which characterize individual tumor biology to select front-line therapy using either an immuno-oncology (IO)/IO (ipilimumab/nivolumab) or IO/TKI (nivolumab/cabozantinib) regimen will lead to improved efficacy compared to unselected historical data for patients with advanced RCC.

TRIAL ENDPOINTS

- **Primary Endpoint**: Objective response rate (ORR) per RECIST 1.1 criteria
- **Secondary Endpoints**: Progression free survival (PFS), depth of response >80% at 6 months.

SCHEMA

Phase II, open-label, parallel single-arm study using tumor RNAseq cluster to assign protocol treatment



STATISTICAL CONSIDERATIONS

- For the Nivolumab/Cabozantinib arm, we will power the study to detect a 20% improvement in ORR (55% historical control from CheckMate 9ER to 75%). For the Ipilimumab/Nivolumab arm, we will power the study to detect a 20% improvement in ORR (40% historical control from CheckMate 214 trial to 60%).
- Both arms will adopt Simon's MinMax two-stage design to provide 80% statistical power with a one-sided significance level of 10% (type I error).
- For the nivolumab/cabozantinib arm, primary endpoint will be reached if there are ≥18 responders among 26 patients at the end of stage II; for the ipilimumab/nivolumab arm, primary endpoint will be reached if there are ≥15 responders among 28 patients at the end of stage II.

REFERENCES

- Motzer et al, Cancer Cell 2020 Dec 2020 Dec 14;38(6):803-817
- Motzer et al, N Engl J Med. 2018 Apr 5;378(14):1277-1290
- Choueiri et al, N Engl J Med. 2021 Mar 4;384(9):829-841

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