

# The Clinical Activity of PD-1/PD-L1 Inhibitors in Metastatic Non-Clear Cell Renal Cell Carcinoma

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## Abstract

Programmed death 1 (PD-1) and PD ligand 1 (PD-L1) inhibitors have shown activity in metastatic clear cell renal cell carcinoma (ccRCC). Data on the activity of these agents in patients with non-clear cell RCC (nccRCC) or patients with sarcomatoid/rhabdoid differentiation are limited. In this multicenter analysis, we explored the efficacy of PD-1/PD-L1 inhibitors in patients with nccRCC or sarcomatoid/rhabdoid differentiation. Baseline and follow-up demographic, clinical, treatment, and radiographic data were collected. The primary endpoint was objective response rate. Secondary endpoints include time-to-treatment failure (TTF), overall survival (OS), and biomarker correlates. Forty-three patients were included: papillary ( $n = 14$ ; 33%), chromophobe ( $n = 10$ ; 23%), unclassified ( $n = 9$ ; 21%), translocation ( $n = 3$ ; 7%), and ccRCC with sarcomatoid differentiation ( $n = 7$ , 16%). Of those 43 patients,

11 patients (26%) had sarcomatoid and/or rhabdoid differentiation ( $n = 7$  with ccRCC;  $n = 4$  nccRCC). Overall, 8 patients (19%) objectively responded, including 4 patients (13%) who received PD-1/PD-L1 monotherapy. Responses were observed in patients with ccRCC with sarcomatoid and/or rhabdoid differentiation ( $n = 3/7$ , 43%), translocation RCC ( $n = 1/3$ , 33%), and papillary RCC ( $n = 4/14$ , 29%). The median TTF was 4.0 months [95% confidence interval (CI), 2.8–5.5] and median OS was 12.9 months (95% CI, 7.4–not reached). No specific genomic alteration was associated with clinical benefit. Modest antitumor activity for PD-1/PD-L1-blocking agents was observed in some patients with nccRCC. Further prospective studies are warranted to investigate the efficacy of PD-1/PD-L1 blockade in this heterogeneous patient population. *Cancer Immunol Res*; 6(7): 758–65. ©2018 AACR.

## Introduction

Metastatic non-clear cell renal cell carcinoma (nccRCC) comprises a heterogeneous group of diseases with distinct clinical and molecular features. Although clear cell renal cell carcinoma (ccRCC) accounts for the majority of renal cell carcinoma (RCC) cases, upward of 25% of patients have non-clear cell histology, including papillary (15%), chromophobe (5%), and multiple

other rare subtypes such as collecting duct carcinoma, medullary carcinoma, translocation, and unclassified RCC (1). Sarcomatoid or rhabdoid differentiation can be seen with any RCC subtype and is present in approximately 10% to 15% and 3% to 7% of RCC cases, respectively (2, 3). Sarcomatoid and/or rhabdoid differentiation is associated with poor outcomes (4, 5).

Unlike ccRCC, where the initiating oncogenic event has been attributed to *VHL* gene inactivation (6), driver mutation events of distinct nccRCC entities are heterogeneous (7–10). The diversity of this population and the small numbers in each subset have resulted in relatively few clinical trials informing patient management (11). The treatment paradigm for nccRCC has mirrored that of ccRCC (12). Targeted agents have improved outcomes in nccRCC; however, survival rates for nccRCC remain poor (13, 14).

One pathway responsible for mediating tumor-induced immune suppression is the programmed death-1 (PD-1) pathway. Interaction between PD-1, expressed on immune cells, and PD ligand 1 (PD-L1) and PD ligand 2 (PD-L2), expressed on immune and tumor cells, results in tolerance and inhibition of the cellular immune response (15). Therapies that target the PD-1 axis have demonstrated efficacy in a wide range of cancers including RCC. Treatment with nivolumab, a monoclonal antibody specific for PD-1, led to improved overall survival (OS) in a phase III metastatic ccRCC trial (16). Additionally, the combination of first-line nivolumab and ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4),

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**Note:** Supplementary data for this article are available at Cancer Immunology Research Online (<http://cancerimmunolres.aacrjournals.org/>).

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resulted in an improved objective response rate (ORR) and OS in intermediate and poor-risk ccRCC (17).

Many human solid tumors, including ccRCC, express PD-L1, which has been associated with worse prognosis in ccRCC (18). Our previous study of the expression patterns of PD-L1 in nccRCC included 101 patients and demonstrated differential PD-L1 expression based on histology and worse outcomes in patients with PD-L1 expression (19). Additionally, another study demonstrated that 50% of sarcomatoid RCCs coexpress PD-L1 on tumor cells and PD-1 on tumor-infiltrating lymphocytes (20). Although increased PD-L1 expression is associated with poorer survival (18), treatment with nivolumab was beneficial in ccRCC regardless of PD-L1 expression (16).

Patients with nccRCC as well as sarcomatoid and/or rhabdoid differentiation have poor survival and limited therapeutic options. Here, we evaluate the efficacy of PD-1/PD-L1-blocking agents in nccRCC. Additionally, we characterize the molecular genotype and PD-L1 expression status of a subset of patients to explore biomarkers that could predict response to PD-1/PD-L1 blockade.

## Materials and Methods

### Patients

We conducted a pooled analysis of patients treated at eight institutions: Dana-Farber Cancer Institute (Boston, MA, USA), Beneficiencia Portuguesa de Sao Paulo (São Paulo, Brazil), City of Hope (Duarte, CA, USA), Hospital Universitario 12 de Octubre (Madrid, Spain), Pontificia Universidade Católica do Rio Grande do Sul Sao Lucas Hospital (Porto Alegre, Brazil), Tom Baker Cancer Center (Calgary, Canada), University of Ulsan (Seoul, South Korea), and Memorial Sloan-Kettering Cancer Center (New York, NY, USA). Eligible patients were defined as those with metastatic nccRCC, as determined by pathology review at each participating institution. Additionally, patients with ccRCC with sarcomatoid and/or rhabdoid differentiation in >20% of the tumor specimen, as determined by pathology review at each participating institution, were eligible. Additionally, patients must have received treatment with either a PD-1- or PD-L1-targeting agent as monotherapy or in combination with another systemic agent at any time prior to July 2016. Demographic, clinical, treatment, and radiographic data were collected from the electronic medical record. Response was defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and was assessed by investigators at each participating institution. Patients were excluded if response data to therapy was not available. Institutional review board approval was obtained for data collection at participating institutions and individual patient consent obtained for use of archival tissue specimens.

### Next-generation sequencing analysis

Archival tissue from primary nephrectomy tissue was analyzed utilizing two next-generation genomic sequencing platforms in 19 patients with available tumor specimens. Eight patients underwent next-generation sequencing utilizing the Dana-Farber Cancer Institute Oncopanel test, a hybrid-capture and parallel sequencing assay that surveys exonic DNA of 400 cancer genes (21). An additional, 11 patients underwent testing via the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay, a clinical test for interro-

gating somatic alterations in 341 oncogenes and tumor suppressors in formalin-fixed, paraffin-embedded tumor specimens (22, 23). The assay utilizes hybridization capture for genomic sequencing of select genes. Additional information on the tests and mutation calling methods can be found in the references (21, 23). Genomic data were collected retrospectively.

### PD-L1 expression analysis

PD-L1 expression on tumor cell and tumor-infiltrating immune cells was assessed. Paraffin-embedded tissue sections (4  $\mu$ m thick) were baked in an Isotemp Oven at 60°C for 1 hour to melt excess paraffin. Immunohistochemistry double-staining for PD-L1 (1:100, 405. 9A11 mouse monoclonal antibody, Dr. Gordon Freeman lab, Dana-Farber Cancer Institute, Boston, MA) and CD45 (1:500, D9M81 XP Rabbit monoclonal antibody, CST) was performed by Dr. Signoretti's lab. Tumor sections were stained on Bond III Autostainer (Leica Biosystems) using the Bond Polymer Refine Detection Kit (DS9800; Leica Biosystems) and Bond Polymer Refine Red Detection Kit (DS9390, Leica Biosystems). Antigen retrieval was performed with Bond Epitope Retrieval Solution 2 (EDTA, pH = 9.0) for 30 minutes.

Slides were scanned at 200 $\times$  magnification and analyzed by Indica Lab HALO platform algorithm. CD45 was used as a mask to differentiate immune cells from tumor cells. The algorithm calculated percent PD-L1-positive cells in both tumor and immune cells, and semi-quantified the PD-L1 expression on tumor cell membrane on a scale of 0+ to 3+ based staining intensity. Positivity was defined as detection of PD-L1 expression on >1% of cells.

### Statistical analysis

Clinical and disease characteristics were summarized as median and range for continuous variables, and as number and percentage for categorical variables. The primary endpoint was to assess the ORR as defined by RECIST version 1.1. ORR was summarized in the total cohort, by histology and line of therapy, with 90% exact binomial confidence interval (CI). Secondary endpoints included time-to-treatment failure (TTF) and OS. TTF was defined as the interval between the date of initiation of anti-PD-1/PD-L1 therapy and the date of radiographic progression, drug cessation, or death, whichever occurred first, or censored at the last follow-up date. OS was calculated from the date of initiation of anti-PD-1/PD-L1 therapy to the date of death or censored at the most recent follow-up. Median TTF and OS for the overall cohort were calculated using the Kaplan-Meier method. Additionally, TTF was calculated in the monotherapy cohort and by histology and International Metastatic RCC Database Consortium (IMDC) risk group and compared among IMDC risk groups using the log-rank test.

## Results

### Baseline characteristics

Baseline patient and disease characteristics were captured for the 43 patients (Supplementary Table S1). The median age at PD-1/PD-L1 therapy initiation was 57 years (range, 24–75 years). The majority of patients were male ( $n = 26$ , 61%), with good performance status (Eastern Cooperative Oncology Group performance status 0/1:  $n = 40$ , 93%), and intermediate-risk disease by IMDC criteria ( $n = 25$ , 58%). The most common histology was papillary

(*n* = 14; 33%), and 26% (*n* = 11) of patients had sarcomatoid and/or rhabdoid differentiation >20%. Nearly all patients had undergone a prior nephrectomy (*n* = 41, 95%) and most were previously treated with systemic therapy (*n* = 30, 70%). Bone and liver metastases were present in approximately one-third of patients (*n* = 16, 37% for bone metastases; *n* = 14, 33% for liver metastases).

**Treatment exposure**

Most patients (29 of 30) received PD-1–targeted monotherapy, 1 patient received PD-L1–targeted therapy, and 13 of 30 received either one in combination with ipilimumab (*n* = 4), or vascular endothelial growth factor (VEGF)–targeted therapy (*n* = 9; Supplementary Table S1).

**Summary of best overall response**

The ORR for the total cohort was 19% (*n* = 8; 90% CI, 10%–31%; Table 1). Stable disease was observed in 33% (*n* = 14) of the overall population. Of the patients with a response to therapy, three remained on therapy at last follow-up (time on therapy 21, 18, and 12 months). The ORR rate was different based on underlying histology. Patients with ccRCC with sarcomatoid and/or rhabdoid differentiation >20% (*n* = 3/7, 43%; 90% CI, 13%–77%) and papillary RCC (*n* = 4/14, 29%; 90% CI, 10%–54%) experienced a higher ORR. One patient with translocation RCC (*n* = 1/3, 33%; 90% CI, 2%–86%) achieved an objective response. No patient with chromophobe RCC (*n* = 0/10, 0%) or unclassified RCC (*n* = 0/9, 0%) responded. The ORR rate was different based on prior treatment status. Treatment-naïve patients had a higher ORR (*n* = 4/13, 31%; 90% CI, 11%–57%) compared with previously treated patients (*n* = 4/30, 13%; 90% CI, 5%–28%).

In patients receiving PD-1/PD-L1 monotherapy, the ORR was 13% (*n* = 4/30). By specific histology, ORR were 18% (*n* = 2/11;

90% CI, 3%–47%), 50% (*n* = 1/2, 90% CI, 3%–97%), and 33% (*n* = 1/3, 90% CI, 2%–86%) for patients with papillary, ccRCC with sarcomatoid and/or rhabdoid differentiation >20%, and translocation RCC, respectively. Twenty-eight patients (93%) were previously treated and ORR was 14% (*n* = 4/28; 90% CI, 5%–30%) in this population.

**Summary of time-to-treatment failure and overall survival**

The median follow-up was 11.4 months (range, 1.2–21.1). Eight patients (19%) remained on therapy at last follow-up, three of whom had an objective response. Overall, 35 patients (81%) experienced a treatment failure event and median TTF was 4.0 months (95% CI, 2.8–5.5; Table 2, Fig. 1A–C). Median TTF among the eight responders was 10.4 months (range, 2.8–21 months). When stratified by histology, median TTF was 4.8 months (95% CI, 1.9–8.8) for papillary, 4.3 months (95% CI, 0.7–6.7) for chromophobe, and 4.0 months (95% CI, 1.0–not reached) for ccRCC with sarcomatoid and/or rhabdoid differentiation >20% (Table 2; Fig. 1A). In the overall cohort, patients with IMDC favorable risk disease had the longest TTF (6.0 months; 95% CI, 0.7–not reached), whereas the TTF for patients with intermediate- and poor-risk disease was 4.0 months (95% CI, 2.8–6.7) and 1.9 months (95% CI, 0.5–4.0), respectively (log-rank *P* = 0.15; Table 2, Fig. 1B). TTF was similar by line of systemic therapy (untreated vs. previously treated). The median TTF for patients receiving PD-1/PD-L1 monotherapy was 4.6 months (*n* = 30; 95% CI, 2.8–6.0) for the overall population and 4.0 months (*n* = 7; 95% CI, 0.9–7.2) for patients with papillary histology, 6.0 months (*n* = 7; 95% CI, 2.1–8.1) for patients with chromophobe histology, 2.8 months for patients with unclassified histology (*n* = 7; 95% CI, 0.5–not reached), and 2.5 months (*n* = 2; 95% CI, 1.0–4.0) for patients with ccRCC with sarcomatoid and/or rhabdoid differentiation >20%.

**Table 1.** Summary of best overall response

	Total N	CR		PR		SD		PD	
		N	%	N	%	N	%	N	%
All	43	1	2	7	16	14	33	21	49
Histology									
Papillary	14	1	7	3	21	4	29	6	43
Chromophobe	10	—	—	—	—	4	40	6	60
Unclassified	9	—	—	—	—	3	33	6	67
Clear cell with sarcomatoid and/or rhabdoid differentiation >20%	7	—	—	3	43	2	29	2	29
Translocation	3	—	—	1	33	1	33	1	33
Sarcomatoid and/or rhabdoid differentiation									
No	32	1	3	4	13	11	34	16	50
Yes <sup>a</sup>	11	—	—	3	27	3	27	5	45
IMDC risk group									
Favorable	9	—	—	1	11	5	56	3	33
Intermediate	25	—	—	5	20	8	32	12	48
Poor	9	1	11	1	11	1	11	6	67
Line of systemic therapy									
1	13	1	8	3	23	4	31	5	38
2	18	—	—	2	11	6	33	10	56
≥3	12	—	—	2	17	4	33	6	50
Type of checkpoint blockade									
Monotherapy	30	—	—	4	13	11	37	15	50
Combination therapy	13	1	8	3	23	3	23	4	46
PD-1/PD-L1 + CTLA-4 inhibitor	4	1	25	1	25	1	25	1	25
PD-1/PD-L1 + VEGF-targeted therapy	9	—	—	2	22	2	22	5	56

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; IMDC, International Metastatic RCC Database Consortium. <sup>a</sup>Clear cell (*n* = 7), chromophobe (*n* = 3), and unclassified (*n* = 1).

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**Table 2.** Summary of time-to-treatment failure

	<b>N</b>	<b>Number of failure events</b>	<b>Median month (95% CI)</b>
All	43	35	4.0 (2.8-5.5)
Histology			
Papillary	14	11	4.8 (1.9-8.8)
Chromophobe	10	10	4.3 (0.7-6.7)
Unclassified	9	7	2.8 (0.5-4.6)
Clear cell with sarcomatoid and/or rhabdoid differentiation >20%	7	5	4.0 (1.0-NR)
Translocation	3	2	<sup>a</sup>
Sarcomatoid and/or rhabdoid differentiation			
No	32	26	4.6 (2.4-6.7)
Yes <sup>b</sup>	11	9	4.0 (1.0-4.6)
IMDC risk group			
Favorable	9	6	6.0 (0.7-NR)
Intermediate	25	21	4.0 (2.8-6.7)
Poor	9	8	1.9 (0.5-4.0)
Line of systemic therapy			
1	13	10	3.7 (1.2-12.5)
2	18	14	4.6 (2.4-6.7)
≥3	12	11	4.0 (1.0-8.1)
Type of checkpoint blockade			
Monotherapy	30	25	4.6 (2.8-6.7)
Combination therapy	13	10	3.6 (1.4-12.5)
PD-1/PD-L1 + CTLA-4 inhibitor	4	3	8.1 (2.5-NR)
PD-1/PD-L1 + VEGF-targeted therapy	9	7	2.8 (0.7-NR)

Abbreviations: NR, not reached; IMDC, International Metastatic RCC Database Consortium.

<sup>a</sup>TTF is 1.1, 6.5+, 8.3 months in the 3 patients with translocation histology.

<sup>b</sup>Clear cell (*n* = 7), chromophobe (*n* = 3), and unclassified (*n* = 1).

Overall, there were 15 deaths (35%) in the total cohort. Median OS was 12.9 months (95% CI, 7.4 months–not reached; Supplementary Fig. S1). The 6-month OS rate was 77% (95% CI, 60%–88%) and 12-month OS rate was 64% (95% CI, 45%–77%).

**Next-generation sequencing analysis**

Nineteen (44.2%) patients had genomic data available (Fig. 2). We identified recurrent mutations in *BAP1* (*n* = 5, 23.3%) and *SETD2* (*n* = 3, 15.8%) in our cohort. Additionally, aberrations in DNA repair genes, including *BRCA2* (*n* = 1), *ATM* (*n* = 1), *FANCA* (*n* = 1), *FANCG* (*n* = 1), and *POLQ* (*n* = 1), were identified in 4 patients (21.1%). Median tumor mutation burden was 2.44 mutations/megabase (range, 0–4.92 mutations/megabase; Supplementary Table S2).

Patients were stratified based on response to PD-1/PD-L1 therapy. Seven of the 19 patients (36.8%) experienced either an objective response (*n* = 2) or stable disease (*n* = 5) from PD-1/PD-L1 therapy. In this limited dataset, no specific gene mutations differed between patients with an objective response or stable disease compared with those with progressive disease as best response. In the 2 patients who experienced an objective response, tumor mutation burden was low at 1.09 and 3.45 mutations/megabase.

**PD-L1 expression analysis**

PD-L1 expression analysis was performed on 8 patient samples (Supplementary Table S3; Supplementary Fig. S2). All 3 patients (37.5%) who had PD-L1–positive tumor cells experienced clinical benefit with one partial response and 2 patients with stable disease. Three patients (37.5%) had positive PD-L1 expression on immune cells, of whom two had stable disease and one had progressive disease. No patient with progressive disease (*n* = 3/8) had PD-L1 expression in tumor cells.

**Discussion**

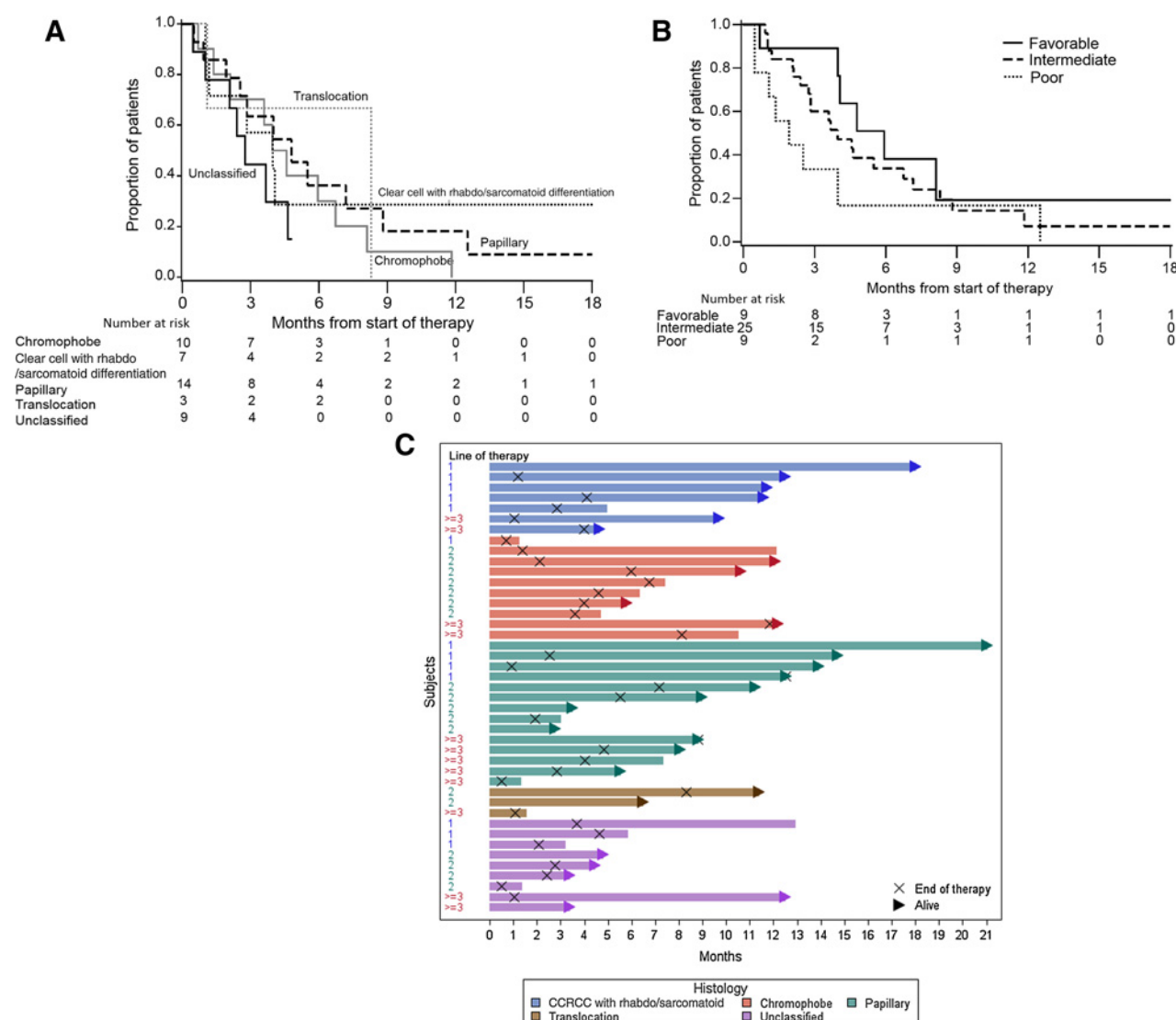
nccRCC and RCC with sarcomatoid and/or rhabdoid differentiation represent a heterogeneous group of malignancies that are associated with poor prognosis. These patients are underrepresented in clinical trials and their treatment outcomes need improvement. PD-L1 is expressed on tumors of nccRCC and sarcomatoid RCC; however, it is not clear if this is predictive of response (19). Here, we studied the collective outcomes of patients with nccRCC or sarcomatoid/rhabdoid RCC treated with PD-1/PD-L1–targeted therapy. Although our sample size is small, when stratified by histology, our data support future investigation of treatments that block the PD-1/PD-L1 pathway.

The overall ORR was 19%, with a 13% ORR in the monotherapy subgroup. This rate is lower than the antitumor activity of PD-1–targeted checkpoint immunotherapy in ccRCC (25% ORR; refs. 16, 24, 25). In our study, the ORR was 31% in treatment naïve patients, which is higher than the ORR reported in two randomized phase II studies evaluating the efficacy of sunitinib compared with everolimus in treatment-naïve patients with nccRCC (ORRs ranging from 9% to 18% for sunitinib-treated patients; refs. 24, 25).

In our cohort, the ORR rates differed by histology. Responses were the most pronounced in patients with ccRCC with sarcomatoid and/or rhabdoid differentiation and papillary RCC, whereas no responses were observed in patients with chromophobe or unclassified RCC. Prior studies have demonstrated that PD-L1 expression on tumor cell membrane is only observed in 5.6% of patients with chromophobe RCC (19).

Patients with ccRCC with sarcomatoid and/or rhabdoid differentiation had an ORR of 43% in our study. This ORR is

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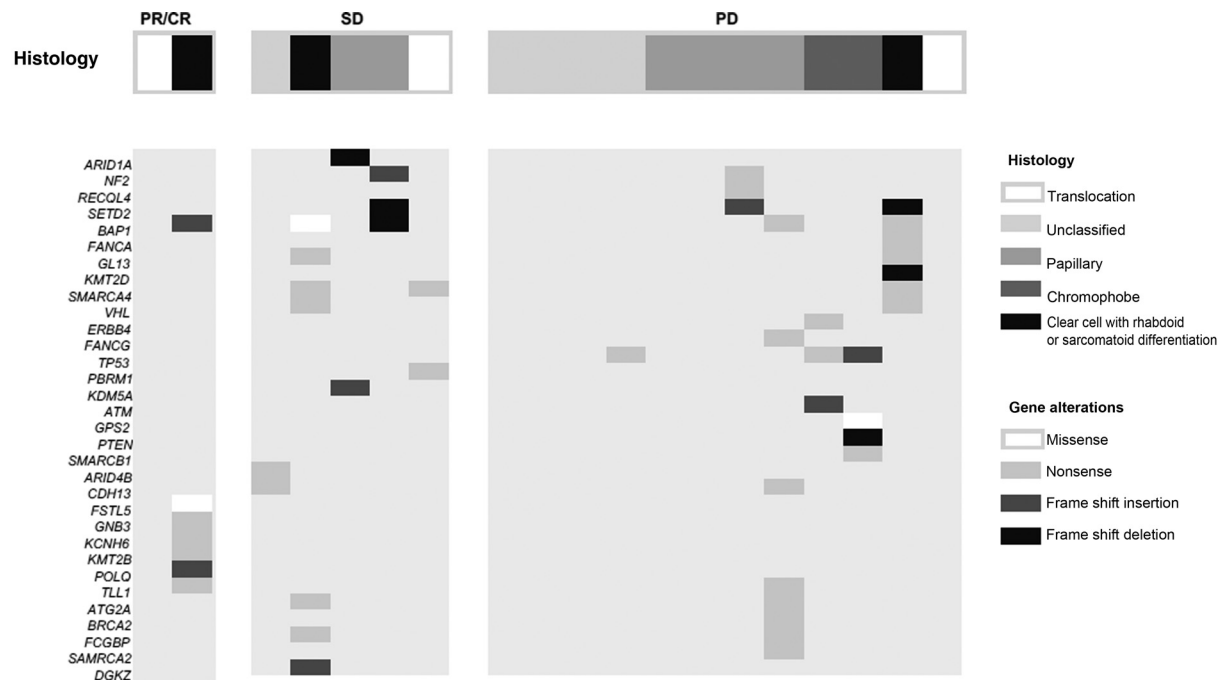


**Figure 1.** Patient outcomes. Time-to-treatment failure (A) by histology and (B) by the IMDC risk group. Time-to-treatment failure did not differ by histology. Time-to-treatment failure was more prolonged in favorable risk group patients. C, Swimmer plot of all patients stratified by histology and line of prior therapy. Each bar represents an individual patient. X, Time that treatment with PD-1/PD-L1 therapy was discontinued. ►, Patients who are still alive at the time of last follow-up.

higher than responses observed with targeted therapies in sarcomatoid RCC (ORR, 10%–20% with targeted therapies; ref. 26) and is consistent with data from the phase I study of atezolizumab, in which tumors with sarcomatoid features had an ORR of 33% ( $n = 2/6$ ; ref. 27) and another phase II trial in which treatment with atezolizumab and bevacizumab appeared to favor those with sarcomatoid differentiation (28). A higher proportion of patients with RCC with sarcomatoid differentiation may express PD-1/PD-L1 than RCC without sarcomatoid differentiation (20), so these patients may be particularly sensitive to PD-1/PD-L1–blocking agents (20). Additionally, an integrative analysis using whole-exome sequencing, RNA sequencing, and DNA methylation profiling identified a cluster of ccRCC with sarcomatoid differentiation enriched for aberrations in genes regu-

lating T-cell receptor signaling and adaptive immunity, suggesting potential sensitivity to immune checkpoint inhibitors (29).

Although PD-L1 expression has been associated with poor prognosis, the predictive ability of this biomarker in RCC is still being explored. In our study, PD-L1 expression on either tumor cells or immune cells was observed in 50% of patients ( $n = 4/8$ ), of whom 1 patient experience a partial response. In the phase III study of nivolumab in RCC, the benefit of nivolumab was observed irrespective of PD-L1 expression (16). The combination of atezolizumab and bevacizumab resulted in encouraging results compared with sunitinib in patients with PD-L1<sup>+</sup> immune cells (median PFS, 14.7 months compared with 7.8 months; HR, 0.064; 95% CI, 0.38–1.08; ref. 28). The combination is currently being investigated in a phase II single-arm trial in patients with



**Figure 2.** Genomic sequencing. Genomic mutations detected by deep-sequencing analysis from archival tumor specimens from 19 patients. Columns represent individual subjects. Rows represent selected genes of interest examined for each sample.

nccRCC or sarcomatoid differentiation (NCT02724878). Additional studies are investigating nivolumab (NCT02596035) and pembrolizumab (NCT02853344), a humanized monoclonal antibody to PD-1, in nccRCC patients.

Our next-generation sequencing analysis revealed that 1 patient in the objective response cohort had a POLQ nonsense mutation in the DNA-binding domain, which could affect microhomology-mediated end-joining (MMEJ). However, this did not correspond to an increased mutational burden. Although the DNA-damage repair genes had additional mutations (26%), none of these correlated with response to treatment. Although only 19 patients had next-generation DNA sequence data, our results support the conclusion that tumor mutation burden in RCC, including nccRCC, is not associated with a response to treatment.

The limitations of this study include its retrospective nature, heterogeneous patient population, and a wide spectrum of nccRCC histologies represented. Additionally, we included patients receiving different PD-1/PD-L1-blocking agents either alone or in combination. We also used the metric TTF rather than progression-free survival. TTF reflects actual clinical practice patterns, as the determination to discontinue treatment is based on the physician's clinical judgment. Additionally, ORR did not appear to correlate with TTF, which is consistent with results from the large phase III study evaluating the efficacy of nivolumab compared with everolimus in ccRCC (16). Specifically, that study noted differences in ORR and OS between nivolumab and everolimus, although PFS did not differ between arms. In our study, PD-L1 expression analysis was limited to 8 patients. Next-generation sequencing was

only available for a subset of our patients and two sequencing platforms were used. Finally, although drugs targeting the PD-1/PD-L1 axis show promise for treatment of many tumors, the opportunity to target known potential drivers such as c-MET in clinical trials should be considered. Currently, two randomized studies compare sunitinib to selective or non-selective MET inhibitors in patients with advanced papillary RCC, where MET is known to be altered (NCT02761057 and NCT03091192).

In summary, this multicenter pooled analysis provides insight into the clinical management of patients with nccRCC and sarcomatoid/rhabdoid RCC, highlighting the differential activity of PD-1/PD-L1-blocking agents in patients with varying RCC histologies. The efficacy of PD-1/PD-L1 blockade in this heterogeneous population needs further investigation, which may support the design of future clinical and correlative studies investigating both standard-of-care and novel approaches to improve the outcomes in this understudied population.

**Disclosure of Potential Conflicts of Interest**

R.R. McKay reports receiving commercial research support from Pfizer and Bayer and is a consultant/advisory board member for Novartis and Janssen. E.M. Van Allen is a consultant/advisory board member for Genome Medical, Tango Therapeutics, and Invitae. G. De Velasco is a consultant/advisory board member for Bristol-Myers Squibb. D.Y.C. Heng is a consultant/advisory board member for Bristol-Myers Squibb, Pfizer, and Roche. A. P. Fay is a consultant/advisory board member for Pfizer, Bristol-Myers Squibb, AstraZeneca, Roche, and Novartis. F.A. Schutz has received speakers bureau honoraria from Bristol-Myers Squibb, Pfizer, Roche, Novartis, and MSD and is a consultant/advisory board member for Bristol-Myers Squibb, MSD, Pfizer, and Ipsen. S.K. Pal has received speakers bureau honoraria from

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