Kidney Cancer 6 (2022) 53–68
DOI 10.3233/KCA-210005
IOS Press

Systematic Review

Systematic Review of Treatment of Metastatic Non-Clear Cell Renal Cell Carcinoma

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Received 7 September 2021
Accepted 18 January 2022
Pre-press 4 February 2022
Published 15 March 2022

Abstract.
BACKGROUND: Metastatic and unresectable non-clear cell renal cell carcinoma comprises more than a quarter of kidney cancers but does not have standardized treatment. Non-clear renal carcinoma consists of a variety of diverse histologic subtypes, including papillary, chromophobe, collecting duct, translocation, and medullary histologies, many of which carry a poor prognosis. Many prospective clinical trials exclude these kidney cancers, and for most clinical trials of non-clear cell renal cell carcinoma, only a small number of patients are enrolled.
OBJECTIVE: To perform a systematic review of recently published and currently enrolling prospective clinical trials for advanced non-clear cell renal cell carcinoma.
METHODS: A systematic search of Pubmed and MEDLINE (Ovid) was conducted as per PRISMA guidelines to identify recent prospective clinical trials in non-clear cell renal cell carcinoma. To ensure a thorough search, terms not only included non-clear cell renal carcinoma but also molecular subtypes. A review of currently enrolling clinical trials was conducted on Clinicaltrials.gov and the EU Clinical Trials Register as well.
RESULTS: A total of 33 prospective clinical trials with published results and 10 currently enrolling clinical trials were identified. About half (48.5%) of these studies were reported in 2020 or 2021, and 36.4% were in the first-line setting. Treatments investigated in these trials included mTOR inhibitors, *VEGF*- and *MET*-targeted tyrosine kinase inhibitors, immune checkpoint inhibitors, and combinatorial strategies. Outcomes from these data revealed a wide range of response rate and progression free survival, favoring TKIs and immune checkpoint inhibitors -based combination regimens.
CONCLUSIONS: Novel targeted therapies and immunotherapies have changed the landscape of treatment for advanced non-clear cell renal cell carcinoma. Combination regimens may provide even further clinical benefit and warrant further investigation in larger, randomized prospective clinical trials.

INTRODUCTION

Kidney cancer incidence is in the top ten among both men and women, with more than 75000 estimated cases in 2020 [1]. The most common pathology

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is clear cell renal cell carcinoma (ccRCC), which comprises at least 70 percent of renal cancers [2]. Many landmark trials for renal cell carcinoma (RCC) exclusively included clear cell carcinoma patients [3–5], making generalization to other types of RCC difficult.

Non-clear cell RCC (nccRCC), the remaining 25–30 percent of kidney cancers, comprises several different histologies. The World Health Organization (WHO) has classified thirteen different non-clear cell malignant renal cell histologies [2]. Of these, papillary is the most common, representing 10–15 percent of kidney cancer. Papillary RCC is further subclassified into two subtypes, type 1 and type 2, based on pathology [6]. Chromophobe RCC arises from the distal nephron and accounts for approximately 5 percent of kidney cancer and often carries a favorable prognosis [7]. Collecting duct RCCs, including medullary RCC, are rarer, comprising about 1 percent of all kidney cancers. These are aggressive tumors and carry a poor prognosis [8]. Another rare histologic variant that accounts for less than 1 percent of kidney cancer is Xp11 translocation RCC [9]. In addition to the aforementioned histologic subtypes of nccRCC, mixed histologies, such as papillary clear cell RCC (2–4 percent of kidney cancers), and unclassified RCC can be observed as well. Sarcomatoid and rhabdoid features, while not a separate histology, can be found in non-clear cell as well as clear cell histologies. Sarcomatoid features are present in 4 percent of kidney cancer but 20 percent of metastatic kidney cancer and carries a poor prognosis [10].

While many clinical trials have focused solely on the more common clear cell histology, the treatment landscape of metastatic nccRCC is rapidly evolving. Several recent published clinical trials have successfully reported treatment options for these less common kidney cancers. In this systematic review, we will discuss these recent advances as well as ongoing trials that will potentially shape the current management of advanced nccRCC.

METHODS

Search strategy

A systematic literature review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. A search was conducted on the EMBASE and MEDLINE (Ovid) databases by two co-authors (J.B. and P.B.) to identify relevant studies included through June 1, 2021. Keywords used for the searches include "Kidney Cancer" OR "Renal Cell Carcinoma" AND ("Non-clear cell" OR "Papillary" OR "Medullary" OR "Chromophobe" OR "Collecting Duct"). An additional search was conducted on the US National Library of Medicine database (clinicaltrials.gov) and European Union Clinical Trials Register (clinialtrialsregister.eu) using filters for currently enrolling phase II and phase III studies to incorporate ongoing clinical trials in advanced nccRCC.

The search was conducted by the two authors independently in three stages. In the first stage, duplicate references were removed. In the second stage, titles and abstracts from all unique references selected by the database were screened. In the final stage, a full-text reading of all remaining references was performed. A final search using Google Scholar and review of references from relevant articles was performed to ensure inclusion of all eligible studies.

Exclusion criteria

Only prospective clinical trials were considered for this review, so all abstracts, editorials, reviews, retrospective analyses, non-clinically focused studies, and non-English language articles were excluded. To narrow the scope of the review, phase I trials were excluded. Prospective trials that enrolled mostly ccRCC cases without planned nccRCC subset analyses were excluded as well. Repeated publications on the same cohort were excluded as well. To ensure only the most current data was included, the analysis was limited from January 1, 2011 to June 1, 2021.

Data extraction and synthesis

From all eligible studies with published results, the treatment intervention, number of enrolled patients, primary endpoint, objective response rate, and median progression free survival were extracted. For currently enrolling trials, the trial phase and planned treatment intervention were extracted. Outcomes between studies were compared but not combined due to heterogeneity between studies, especially regarding line of treatment and proportion between histologic subtypes included. All clinical trials were organized by category of treatment intervention, including *mTOR* inhibition, *VEGFR*-targeting tyrosine kinase inhibition, *MET*-targeting tyrosine kinase inhibition, immune checkpoint inhibition, and treatment combinations.

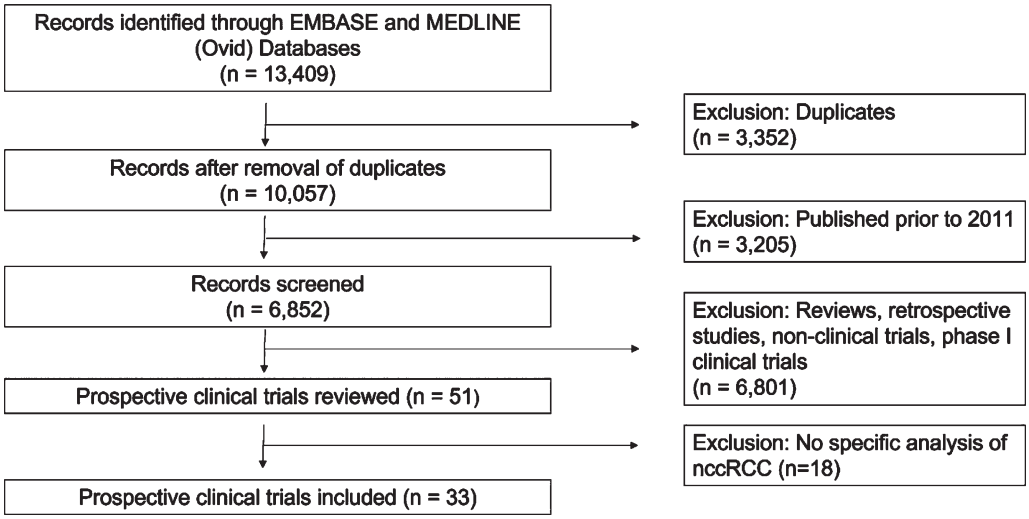

Fig. 1. Inclusion and exclusion criteria for systematic review of phase II and phase III prospective clinical trials for advanced non-clear cell renal cell carcinoma.

Table 1
Results of recent prospective studies of mTor inhibitors in treatment of advanced non-clear cell renal cell carcinoma

Study/Reference	Report Date	Phase	Enrollment (n)	Intervention	Disease Setting	Histology	Primary Endpoint	ORR (%)	Median PFS (months)
Koh et-al. [15]	2013	II	49	Everolimus	Multiple lines	Multiple subtypes	Median PFS	10.2	5.2
Escudier et-al. (RAPTOR) [22]	2016	II	88	Everolimus	First-line	Papillary	6-months PFS	1 (0–5)	4.1 (3.6–5.5)
Voss et-al. [16]	2016	II	35	Everolimus+ Bevacizumab	First-line	Multiple subtypes	6-months PFS	29	11.0 (3.8–19.3)
Feldman et-al. [17]	2020	II	39	Everolimus+ Bevacizumab	First-line	Papillary variant	6-months PFS	35	13.7 (10.8–16.4)
Hutson et-al. [18]	2021	II	31	Everolimus+ Lenvatinib	First-line	Multiple subtypes	ORR	26 (12–45)	9.2 (5.5-NE)
Mahoney et-al. [21]	2016	II	13	Temsirolimus+ Bevacizumab	VEGFR-TKI refractory	Multiple subtypes	4-months PFS	7.7	5.6 (3.4–13.7)

RESULTS

This systematic review yielded 13,409 records through the EMBASE and MEDLINE databases (Fig. 1). Of these, 3351 were duplicates and subsequently removed for a total of 10,058 unique sources. After sources published prior to 2011 were eliminated, 6,852 records remained. Ultimately, 33 prospective phase II and phase III clinical trials that focused on treatment of advanced nccRCC were identified, which are summarized in Tables 1–3. Out of the 33 prospective studies identified, 16 (48.5%) were reported in 2020 or 2021. Five of these clinical trials (15.2%) were randomized, whereas the remainder were single arm studies. Most trials were phase II (93.9%), with one reported phase III and one phase III/IV trial. 12 trials (36.4%) exclusively enrolled papillary RCC patients, whereas the remainder included multiple histologic subtypes. Twelve trials (36.4%) treated patients in the first-line setting, while two trials were exclusively for patients refractory to prior treatments.

An additional 121 trials were identified on clinicaltrials.gov, of which 27 were actively enrolling patients, and 10 fit the criteria of being prospective interventional studies that exclusively enrolled patients with non-clear cell renal cell carcinoma (Table 4). A similar search on the EU clinical trials registry yielded 10 results, of which 3 fit the prespecified criteria. All three trials were duplicates of currently enrolling trials identified on clinicaltrials.gov.

Studies will be presented according to mechanism of action of therapeutic agents, which generally fit

Table 2
Results of recent prospective studies of tyrosine kinase inhibitors advanced non-clear cell renal cell carcinoma

Study/ Reference	Report Date	Phase	Enrollment (n)	Intervention	Disease Setting	Histology	Primary Endpoint	ORR (%)	Median PFS (months)
Molina et-al. [29]	2012	II	23	Sunitinib	Multiple lines	Multiple subtypes	ORR	4.5	5.5 (2.5–7.1)
Tannir et-al. [30]	2012	II	55	Sunitinib	≤2 prior systemic therapies	Multiple subtypes	ORR and PFS	5	2.7 (1.4–5.4)
Lee et-al. [31]	2012	II	31	Sunitinib	Any line	Multiple subtypes	ORR	36 (19–52)	6.4 (4.2–8.6)
Ravaud et-al. [52] (SUPAP)	2015	II	61	Sunitinib	First-line	Papillary	ORR	11.7	6.6 (2.8–14.8) (type 1 pRCC) 5.5 (3.8–7.1) (type 2 pRCC)
Tannir et-al. [25] (ESPN)	2016	II	68	Sunitinib vs. Everolimus	First-line	Multiple subtypes	PFS	9 vs. 3	6.1 (4.2–9.4) vs. 4.1 (2.7–10.5) (not significant)
Armstrong et-al. [26] (ASPEN)	2016	II	109	Sunitinib vs. Everolimus	First-line	Multiple subtypes	PFS	18 vs. 9	8.3 (5.8 – 11.4) vs. 5.6 (5.5– 6.0) (significant)
Bergmann et-al. [28]	2020	II	22	Sunitinib vs. Temsirolimus	First-line	Multiple subtypes	PFS	30 vs. 16.7	13.2 vs. 9.3 (not significant)
Jung et-al. [34]	2018	II	29	Pazopanib	Multiple lines, no prior TKI	Papillary, chromophobe, unclassified	ORR	28 (12–44)	16.5 (10.9–22.1)
Costello et-al. [35] (PINCR)	2020	II	35	Pazopanib	≤1 prior systemic therapies	Multiple subtypes	12-months OS	11	7.5 (5.0–11.0)
Park et-al. [36]	2018	II	40	Axitinib	Temsirolimus-refractory	Multiple subtypes	PFS	37.5	7.4 (5.2–9.5)
Negrier et-al. [53] (AXIPAP)	2020	II	44	Axitinib	First-line	Papillary	24-week PFS	28.6 (15.7–44.6)	6.6 (5.5–9.2)
Choueiri et-al. [44]	2012	II	74	Foretinib	≤1 prior systemic therapies	Papillary	ORR	13.5 (6.7–23.5)	9.3 (6.9–12.9)
Choueiri et-al. [47]	2017	II	111	Savolitinib	Multiple lines	Papillary	ORR	7	MET-driven: 6.2 (4.1–7.0) MET-independent: 1.4 (1.4–2.7)
Schoffski et-al. [48] (CREATE)	2017	II	23	Crizotinib	Multiple lines	Type 1 Papillary	ORR	17.4 (4.9–38.8)	5.8 (2.6–30.5)
Twardowski et-al. [49]	2017	II	50	Tivatinib+/- Erlotinib	≤1 prior systemic therapies	Papillary	ORR	0	Single agent: 2.0 (1.8–3.0) Combination: 3.9 (1.8–7.3)
Srinivasan et-al. [50]	2020	II	83	Erlotinib+ Bevacizumab	≤2 prior *VEGF*-TKI therapies	HLRCC or sporadic papillary	ORR	51 (40–61)	21.1 (15.6–26.6)
Leger et-al. [51]	2020	II	20	Capmatinib	≤4 prior systemic therapies	Type 1 Papillary	ORR	15	TBD
Procopio et-al. [41] (BONSAI)	2021	II	25	Cabozantinib	First-line	Collecting duct	ORR	35	6
Choueiri et-al. [45] (SAVIOR)	2020	III	60	Savolitinib vs. Sunitinib	Multiple lines	*MET*-driven Papillary	PFS	27 (13.3–45.5) vs. 7 (0.9–24.3)	7.0 (2.8-NE) vs. 5.6 (4.1–6.9) (not significant)
Pal et-al. [38] (PAPMET)	2021	II	147	Cabozantinib vs. Sunitinib (and Savolitinib, Crizotinib)	≤1 prior systemic therapies	Papillary	Median PFS	23 vs. 4	9.0 (5.6–12.4) vs. 5.6 (2.9–6.7) (significant)

Table 3
Results of recent prospective studies of immune checkpoint inhibition in advanced non-clear cell renal cell carcinoma

Study/ Reference (months)	Report Date	Phase	Enrollment (n)	Intervention	Disease Setting	Histology	Primary Endpoint	ORR (%)	Median PFS
Vogelzang et-al. [54] (CHECK-MATE374)	2020	III/IV	44	Nivolumab	≤3 prior systemic therapies	Multiple subtypes	High grade immune AEs	13.6 (5.2–27.4)	2.2 (1.8–5.4)
Gedye et-al. [55] (UNISON)	2021	II	83	Niviolumab	Multiple lines	Multiple subtypes	ORR	17	4.0 (3.6–7.4)
Atkins et-al. [56] (HCRN G16-260)	2021	II	35	Nivolumab → Ipilimumab + Nivolumab	First-line	Papillary, chromophobe, unclassified	1-year PFS	14.3 6.3	4.0 (2.7–4.3) Not reported
Mcdermott et-al. [57] (KEYNOTE427-Cohort B)	2021	II	165	Pembrolizumab	First-line	Papillary, chromophobe, unclassified	ORR	26.7 (20.1–34.1)	4.2 (2.9–5.6)
McGregor et-al. [58]	2019	II	65	Atezolizumab + Bevacizumab	Multiple lines	Multiple subtypes	ORR	26	8.3
Powles et-al. [64] (CALYPSO)	2020	II	42	Savolitinib + Durvalumab	Multiple lines	Papillary	ORR	27	4.9 (2.5–12.0)
Lee et-al. [67] (CA209-9KU)	2021	II	47	Nivolumab + Cabozantinib	≤1 prior systemic therapies	Multiple subtypes	ORR	48 (31.5–63.9)	12.5 (6.3–16.4)

Table 4
Ongoing prospective clinical trials in non clear-cell renal cell carcinoma

Study	Launch Date	Phase	Intervention	Disease Setting	Histology	Reference
NCT03541902 (CABOSUN Ii)	2018	II	Cabozantinib vs. Sunitinib	Multiple lines	Multiple subtypes	[42]
NCT03685448 (UNICAB)	2019	II	Cabozantinib	Refractory	Multiple subtypes	[43]
NCT03075423 (SUNIFORECAST)	2017	II	Ipilimumab + Nivolumab	First-line	Multiple subtypes	[62]
NCT03274258	2017	II	Ipilimumab + Nivolumab	Multiple lines	Medullary	[63]
NCT05043090 (SAMETA)	2021	III	Savolitinib + Durvalumab vs. Sunitib vs. Durvalumab	First-line	*MET*-driven papillary	[66]
NCT04267120 (LENKYN)	2020	II	Pembrolizumab + Lenvatinib	First-line	Multiple subtypes	[68]
NCT04704219 (KEYNOTE-B61)	2021	II	Pembrolizumab + Lenvatinib	First-line	Multiple subtypes	[69]
NCT04413123	2020	II	Ipilimumab + Nivolumab + Cabozantinib	Multiple lines	Multiple subtypes	[70]
NCT04068831	2019	II	Avelumab + Talazoparib	Second-Line or later	*FH*- and *SDH*-Deficient	[71]
NCT04644432	2020	II	Based on DNA and RNA signatures	First-Line	Multiple subtypes	[93]

into four categories. The first category is mTOR inhibitors that target this signaling pathway, including everolimus and temsirolimus. Four single arm clinical trials and multiple arm trials used mTOR inhibitors. A second category is tyrosine kinase inhibitors (TKI) that target molecular alterations implicated in RCC carcinogenesis, notably *VEGFR*, and *MET*. 14 completed single arm trials and 2 cur-

rently enrolling studies exclusively treated patients with TKIs. All 5 multi-arm studies compared TKIs to other TKIs or mTOR inhibitors. Another category of treatment for nccRCC is immune checkpoint inhibition, targeting the PD-1/PD-L1 axis. Seven clinical trials, including two of which are currently enrolling patients, treated patients with immune checkpoint inhibitors. The final category that is being explored is combination between immunotherapy and TKIs, which included two trials with reported results and four currently enrolling trials.

mTOR inhibitors

The PI3K/Akt/mTOR signaling pathway was one of the first targeted by direct inhibition in kidney cancer. This pathway has been found to be dysregulated in RCC, resulting in aggressive tumors and overall poor prognosis [12, 13]. Everolimus and temsirolimus were both mTOR inhibitors previously approved for RCC treatment, however early studies primarily focused on the clear cell subtype. One of these early studies was REACT, which was an expanded access trial that provided everolimus to metastatic RCC patients refractory to *VEGF*-targeted therapy. Although this study primarily enrolled ccRCC patients, a subgroup analysis considered 75 patients with nccRCC and demonstrated 1.3% ORR and median PFS of 12.4 weeks [14]. Later prospective trials evaluated everolimus in management of advanced nccRCC. One such multicenter phase II trial enrolled 49 patients, who were treated with everolimus. In this trial, reported median PFS, the primary endpoint, was 5.2 months, which was significantly highest in chromophobe RCC ($p = 0.084$). Secondary endpoints included ORR, which was 10.2%, and median OS, which was 14.0 months [15].

Everolimus has also been studied in combination with other treatments. A single-institution trial evaluated the combination of everolimus and bevacizumab for front-line treatment. 35 patients were treated, 23 of whom had unclassified RCC. The primary endpoint was PFS at 6 months, which was 53%, and this significantly associated with histology ($p < 0.001$). Highest PFS rate was seen in chromophobe RCC, papillary RCC, or unclassified RCC with papillary features [16]. This cohort was subsequently expanded to include a total of 39 patients with papillary features, including 20 from the original cohort. By enrolling patients with this subtype with a more favorable response, 6-month PFS, the primary endpoint improved from 53% to 78% and ORR improved slightly from 29% to 35%. Median PFS was 13.7 months (95% CI 10.8–16.4), and median OS was 33.9 months (95% CI 23.3–71.9). No significant differences were seen between papillary RCC and unclassified RCC with papillary features [17].

Another phase II trial of 31 patients investigated the combination of everolimus and lenvatinib, a multikinase inhibitor, for first-line treatment of advanced nccRCC. ORR, the primary endpoint, was reported as 26% (95% CI 12–45). ORR amongst papillary RCC was 15% (95% CI 3–38) and for chromophobe RCC was 44% (95% CI 14–79). Median PFS by investigator assessment was 9.2 months (95% CI 5.5-NE) and median OS was 15.6 months (95% CI 9.2-NE). This combination met its prespecified endpoint and demonstrated promising efficacy compared to single agent everolimus or TKIs [18].

Temsirolimus is another mTOR inhibitor that is administered intravenously. The ARCC study was a multicenter phase III trial that compared temsirolimus to interferon-alpha in advanced RCC [19]. In a subsequent exploratory analysis of 73 patients exhibiting non-clear cell histology (18% of the entire cohort), median OS with temsirolimus was 11.6 months (95% CI 8.9–14.5) compared to the interferon arm 4.3 months (95% CI 3.2–7.3). Median PFS for the termsirolimus arm was 7.0 months (95% CI 3.9–8.9) and for the interferon arm was 1.8 months (95% CI 1.6–2.1). Reported OS hazard ratio was 0.49 (95% CI 0.29–0.85) and PFS hazard ratio was 0.38 (95% CI 0.23–0.62), indicating significantly improved survival with temsirolimus in the subset of patients with nccRCC [20]. Temsirolimus was also evaluated in combination with bevacizumab in a phase II trial of patients who were refractory to VEGF-based tyrosine kinase inhibition. In the subset of 13 patients with nccRCC, ORR was 7.7% and clinical benefit rate was 76.9%. Median PFS was 5.6 months (95% CI 3.4–13.7), and median OS was 13.1 months (95% CI 5.0–24.6), neither of which were statistically different from the simultaneously treated ccRCC cohort [21].

Studies also evaluated mTOR inhibitors in specific histologic subtypes. RAPTOR, a phase II multicenter prospective trial analyzed the efficacy of everolimus in metastatic papillary RCC. Primary endpoint was 6-months PFS in the 46-patient per protocol population. This was reported as 34% (80% CI 25–45), whereas 6-month PFS in the 88-patient intent-to-treat population at final analysis was 33% (80% CI 26–40). In the intent-to-treat population, median PFS was 4.1 months (95% CI 3.6–5.5), and median OS

was 21.4 months (95% CI 15.4 – 28.4) [22]. For metastatic chromophobe RCC, a separate retrospective study compared treatment with mTOR inhibitors and antiangiogenic agents but found no significant differences in OS, ORR, or time to treatment failure [23].

Tyrosine kinase inhibitors

Sunitinib, a multikinase inhibitor that targets *VEGFR*, *PDGFR*, and *c-kit*, is active in patients with localized and metastatic RCC. This agent became one of the first TKIs to be used in nccRCC after demonstrating improved progression-free survival compared to sorafenib, another *VEGFR*-targeting TKI [24]. Two prospective randomized trials, ESPN and ASPEN, directly compared sunitinib to everolimus in metastatic nccRCC. In the ESPN trial, 68 patients were treated prior to planned interim analysis. This was a negative trial, as there was no significant difference between PFS amongst the two arms, as median PFS was 6.1 months (95% CI 4.2–9.4) in the sunitinib arm and 4.1 months (95% CI 2.7–10.5) in the everolimus arm ($p = 0.6$). At final analysis, there was no significant difference in overall survival, 16.2 months (95% CI 14.2-NA) in the sunitinib arm and 14.9 months (95% CI 8.0–23.4) in the everolimus arm ($p = 0.18$) [25]. The ASPEN trial enrolled 108 patients and met its prespecified level of significance for primary endpoint, PFS. Median PFS in the sunitinib arm was 8.3 months (80% CI 5.8–11.4) compared to 5.6 months (80% CI 5.8–11.4) in the everolimus arm (HR 1.41, 80% CI 1.03–1.92, $p = 0.16$). In subgroup analysis, PFS was improved in the sunitinb arm for papillary and unclassified RCC and improved in the everolimus arm for chromophobe RCC. There was no significant difference in median OS between sunitinib, 31.5 months (95 % CI 14.8-NR) and everolimus, 13.2 months (95% CI 9.7–37.9) with reported HR 1.12 (95% CI 0.7–2.1, $p = 0.6$). ORR was 18% (95% CI 7–28) in the sunitinib arm and 9% (95% CI 1–16) in the everolimus arm [26]. Further biomarker analysis from this trial evaluated twenty-three plasma-based angiokines. OPN, HGF, and VCAM-1 were found to be prognostic for worse OS, however no angiokines were found to predict comparative outcomes with sunitinib and everolimus [27].

Similarly, in the phase II study sponsored by CESAR, sunitinib was compared to temsirolimus in 22 patients with advanced RCC. This trial did not achieve its prespecified endpoint, as the difference in median PFS between sunitinib and temsirolimus, 13.2 vs 9.3 months, was not statistically significant. There was also no significant difference in median OS, 19.8 vs. 19.4 months [28].

Despite low response rates in many single-arm trials, sunitinib remains a treatment option for advanced nccRCC. Three initial prospective single-arm phase II clinical trials addressed the efficacy of sunitinib in treatment of either first-line or refractory metastatic nccRCC. One single-institution trial enrolled 23 patients with metastatic nccRCC. Only one evaluable patient (4.5%) achieved partial response, however 65% of patients had a best response of stable disease. Median PFS was 5.5 months (95% CI 2.5–7.1) and was 5.6 months (95% CI 1.4–7.1) for patients with papillary histology [29]. In another trial with 55 evaluable patients, overall response rate (ORR) was 5%, however disease control rate, which included stable disease, was 58%. These rates were relatively higher with chromophobe pathology, 40% and 100%, respectively and lower with papillary pathology, 0% and 48%, respectively. Median progression-free survival (PFS) was 2.7 months (95% CI 1.4–5.4) [30]. Another phase II study enrolled 31 patients and demonstrated higher ORR at 36% with an additional 55% of patients having stable disease. Median PFS in this trial was also better at 6.4 months (95% CI 4.2–8.4) and expected median overall survival (OS) was 25.6 months [31]. Distribution of histologic subtypes was similar between the three trials, with the main difference being a higher proportion of collecting duct RCC in the trial with lowest progression free survival [30].

Real world data has mirrored findings from prospective clinical trials of sunitinib. An expanded access study of sunitinib in metastatic RCC analyzed responses in patients with nccRCC, which comprised 532 patients, or 12% of the overall study. Amongst this subset, objective response was 8%, compared with 16% in the overall cohort. Clinical benefit rate, including patients with stable disease was 51% in the non-clear cell subset, compared with 61% for all RCC patients in the study [32].

Pazopanib is another multikinase inhibitor that targets *VEGFR*, *PDGFR*, *c-kit*, and *FGFR*. First-line pazopanib for metastatic nccRCC was evaluated by the retrospective PANORAMA study. This study showed a 27% response rate and 81% disease control rate. Median PFS was 15.9 months (95% CI 5.9–25.8) and median OS was 17.3 months (95% CI 11.5–23.0) [33]. A single-arm phase II trial evaluated pazopanib for locally advanced and metastatic

nccRCC. Results were similar with 28% response rate and 89% disease control rate. Median PFS was 16.5 months (95% CI 10.9–22.1), and median OS was not met at the time of publication, however 69% survival was reported within one year of follow-up [34]. Another single-arm phase II trial evaluated pazopanib in 35 patients with metastatic nccRCC. Primary endpoint was 12-months OS, reported at 65.7% (90% CI 50.5–78.9). ORR was 11% and disease control rate 71%, which was slightly lower than the other prospective pazopanib trial. Median PFS was 7.5 months (90% CI 5.0–11.0) and median OS was 18.9 months (90% CI 13.0-NE) [35].

Another multikinase inhibitor used to treat RCC is axitinib, which targets *VEGFR1-3*, *PDGFR*, and *c-kit*. Prospective clinical trials have evaluated its efficacy in treating non-clear cell histologies. A multi-center phase II trial that enrolled forty patients previously treated with temsirolimus demonstrated 37.5% response rate and 67.5% disease control rate. Median PFS in this study was 7.4 months (95% CI 5.2–9.5), meeting the prespecified primary endpoint, and median OS was 12.1 months (95% CI 6.4–17.7) [36].

Tyrosine kinase inhibitors in specific RCC histologies

The *HGF*/*MET* kinase signaling pathway has been implicated in tumorigenesis, metastasis, and invasiveness in renal cell carcinoma. In papillary RCC samples, *MET* alterations are prevalent. One study identified copy number alterations in 81% of type I papillary RCC and 46% of type II papillary RCC samples, and somatic mutations in *MET* were identified in 21.6% of type I papillary RCC [37]. Given the prevalence of *MET* alterations in RCC, this is an intriguing potential therapeutic target. Cabozantinib, a TKI that targets *c-MET* and *VEGFR2* was compared to cabozantinib, crizotinib and savolitinib in the phase II SWOG 1500 PAPMET study. In this clinical trial, 90 patients were treated with either sunitinib or cabozantinib. Median PFS, primary endpoint of this trial, was 9.0 months (95% CI 5.6–12.4) for cabozantinib and 5.6 months (95% CI 2.9–6.7) for sunitinib, with significantly improved HR for PFS of 0.60 (95% CI 0.37–0.97; $p = 0.019$). ORR was also significantly higher in the cabozantinib arm (23% vs. 4%, $p = 0.010$), with 5% of patients demonstrating complete response. There was no significant difference in overall survival between the four treatment groups, with reported median OS of 20.0 months (95% CI 11.3-NR) in the cabozantinib arm and 16.4 months (95% CI 12.8–21.6) in the sunitinib arm [38]. In addition to comparing cabozantinib and sunitinib, the SWOG 1500 PAPMET trial enrolled an additional 57 patients to crizotinib and savolitinib arms. Both arms were closed due to hazard ratio for PFS greater than 1 at prespecified interim analysis. Retrospective studies had similarly previously reported activity of cabozantinib in nccRCC, including histologies other than papillary, with similar response rate and PFS to that found in the PAPMET trial [39, 40].

The BONSAI trial evaluated cabozantinib as first-line treatment for metastatic collecting duct RCC. 25 patients were enrolled, and reported ORR was 35%, with one patient achieving complete response. Reported median PFS was 6 months [41]. Similar to PAPMET, the ongoing phase II CABOSUN Ii trial will also compare cabozantinib to sunitinib, however this study includes all histologic subtypes of metastatic nccRCC [42]. Another currently enrolling clinical trial, UNICAB, is enrolling advanced nccRCC patients who progressed on immunotherapy. Unlike PAPMET and CABOSUN Ii, UNICAB is a single arm study [43].

Foretinib is a dual *MET*/*VEGFR2* inhibitor. In a phase II study that enrolled 74 patients with locally advanced, bilateral multifocal, or metastatic papillary RCC, ORR, the primary endpoint, was 13.5% (95% CI 6.7–23.5). Median duration of response in this trial was 18.5 months. Reported PFS was 9.3 months (95% CI 6.9–12.9), which was slightly higher with intermittent dosing compared to continuous dosing (11.6 vs. 9.1 months). Median OS was not yet reached, but 1-year OS was 70% overall. In retrospective biomarker analysis, germline *MET* mutation predicted response, however somatic *MET* mutations, amplifications, or gain of chromosome 7 did not correlate with drug response [44].

Savolitinib is a selective *MET* inhibitor that was also investigated in advanced papillary RCC. This was compared to sunitinib for treatment of *MET*-driven unresectable, locally advanced, or metastatic papillary RCC in the SAVIOR trial. This trial was prematurely closed due to a concurrent retrospective molecular epidemiologic study that determined *MET-driven* status did not negatively predict outcomes for treatment with sunitinib, and therefore only 60 patients were treated rather than the planned enrollment of 180 patients [45, 46]. In terms of the primary endpoint, PFS, there was not a statistically significance between the arms (HR 0.71, 95% CI 0.4–1.4, $p = 0.31$). Median PFS was 7.0 months (95% CI 2.8-

not calculated) in the savolitinib arm and 5.6 months (95% CI 4.1–6.9) in the sunitinib arm. There was also not a significant difference in terms of OS (HR 0.51, 95% CI 11.9-not calculated, $p = 0.11$) [45].

Selective *MET*-inhibition has also been studied in single-arm multicenter trials. One phase II trial enrolled 111 patients, 40% of whom had a *MET*-driven papillary RCC. The primary endpoint, ORR was 7%, although this was increased to 18% where *MET* alterations were present, compared to 0% for patients with *MET*-independent tumors ($p = 0.002$). Stable disease was also comparatively higher in the *MET*-driven papillary RCC (50% vs. 24%). Median PFS was also significantly longer in the subset of patients with *MET*-driven tumor, 6.2 months (95% CI 4.1–7.0) compared to 1.4 months (95% CI 1.4–2.7) in the *MET*-independent subset, and hazard ratio between these subsets was 0.33 (95% CI 0.20–0.52, $p = 0.001$) [47].

Other *MET*-targeting TKIs studied in advanced nccRCC include crizotinib, tivatinib, and capmatinib. The EORTC 90101 CREATE trial was a prospective phase II trial that treated 23 patients with locally advanced and metastatic type I papillary RCC, of which 4 had mutations in *MET*, with crizotinib. ORR, the primary endpoint, in the *MET*+ subset was 50% (95% CI 6.8–93.2), which was higher than 6.3% (95% CI 0.2–30.2) in the *MET*– subset. 1-year PFS was also higher in the *MET*+ patient subset at 75% (95% CI 12.8–96.1) vs. 27.3% (95% CI 8.5–50.4), and median PFS for the overall cohort was 5.8 months (95% CI 2.6–30.5). 1-year OS was similar between both subsets at 75.0% (95% CI 12.8–96.1) vs. 71.8% (95% CI 41.1–88.4), with median OS overall of 30.5 months (95% CI: 12.3-not reached) [48]. A phase II study evaluated tivatinib as a single agent and in combination with erlotinib, an EGFR-targeting TKI that has potential efficacy in FH-deficient RCC, with 25 patients enrolled on each arm. Primary endpoint was ORR, which was 0% in both arms. Median PFS was 2.0 months (95% CI 1.8–3.0) in the single-agent arm and 3.9 months (95% CI 1.8–7.3) in the combination arm. Median OS was 10.3 months (95% CI 7.3–15.7) in the former arm and 21.9 months (95% CI 6.7–21.9) in the latter arm [49]. Erlotinib as a single agent was also evaluated in combination with bevacizumab in a phase II trial that enrolled 42 patients with HLRCC and 41 patients with sporadic papillary RCC. Efficacy was much higher than in the tivatinib study, as reported primary endpoint, ORR was 51% (95% CI 40–61) overall. Median PFS was 14.2 months (95% CI 11.4–18.6). For both ORR and median PFS, better response was seen in the HLRCC subset than the sporadic papillary RCC cohort with 64% ORR (95% CI 49–77) and 21.1 months median PFS (95% CI 15.6–26.6) reported in patients with HLRCC. In the sporadic papillary RCC subset, ORR was 37% (95% CI 24–52) and median PFS was 8.7 months (95% CI 6.4–12.6) [50]. Another phase II study is evaluating capmatinib, a selective *MET* inhibitor in advanced papillary RCC and reported a 15% ORR with 35% of patients attaining stable disease, however survival data has not yet been reported [51].

In the first-line setting of treatment for advanced nccRCC, sunitinib has been studied in papillary RCC. SUPAP, a prospective stage II single-arm study, investigated sunitinib as first-line treatment for metastatic or locally advanced papillary RCC. ORR was 11.7% with an additional 58.3% achieving stable disease. Stable disease rate was higher in the patients with type 1 papillary RCC. Median progression free survival was 6.6 months (95% CI 2.8–14.8) for type 1 and 5.5 months (95% CI 3.8–7.1) for type 2. Median overall survival was 17.8 months (95% CI 5.7–26.1) for type 1 and 12.4 months (95% CI 8.2–16) for type 2 [52].

Another phase II single-arm prospective trial treated 44 patients with papillary RCC with axitinib. Primary endpoint of this study was progression free rate at 24 weeks, which was 45.2% (95% CI 32.6-$+\infty$). ORR was 28% (95% CI 15.7–44.6), and disease control rate was 90.5%. Response rate was higher in the type 2 papillary subset (35.7%) compared to type 1 papillary RCC (7.7%). Median PFS was 6.6 months (95% CI 5.5–9.2), which was similar between type 1 and type 2. Median OS was 18.9 months (95% CI 12.8 – NR) [53].

Immunotherapy

Immune checkpoint inhibition has demonstrated promise for treatment of advanced nccRCC. Prospective trials of immune checkpoint inhibitors, including nivolumab, pembrolizumab, and atezolizumab have demonstrated efficacy in advanced nccRCC. CHECKMATE-374 was a phase III/IV trial that investigated nivolumab in refractory advanced nccRCC. This trial enrolled forty-four patients, and primary endpoint was number of high-grade immune-mediated adverse events, of which there were none. In terms of secondary efficacy endpoints, ORR was 13.6% (95% CI 5.2–27.4) with 2.3% of patients exhibiting complete response and 36.4% of patients with stable disease. Median PFS was 2.2 months

(95% CI 1.8–5.4), and 14.0% (95% CI 5.4–26.5) of patients exhibited PFS after 12 months. Median OS was 16.3 months (95% CI 9.2-NE), and 52.8% (95% CI 36.2–67.0) of patients survived beyond 12 months. Median OS was higher (16.3 months vs. 11.8 months) in patients with tumor PD-L1 expression $\geq 1\%$ [54]. The UNISON trial (ANZUP 1602) treated 83 patients with advanced nccRCC with nivolumab. Reported ORR with nivolumab monotherapy was 17%, with 3.6% of patients achieving complete response and another 49% with stable disease. Median PFS was 4.0 months (95% CI 3.6–7.4) and PFS was 30% (95% CI 21–40%) at one year [55]. Another phase II trial of patients with advanced nccRCC, HCRN G16-260-Cohort B, treated 35 patients with nivolumab. Reported ORR was 14.3% (95% CI 4.8–30.3), and ORR was 25% for patients with PD-L1 greater than 20%. Median PFS was 4.0 months (95% CI 2.7–4.3) [56].

Pembrolizumab, another PD-1 targeting drug, was investigated for first-line management of advanced nccRCC in the phase II KEYNOTE-427 trial – cohort B. This single-arm trial enrolled 165 treatment naïve patients with different nccRCC histologies, of which the majority (72%) were papillary. ORR was 26.7% (95% CI 20.1–34.1), with 6.7% of patients achieving complete response. Median PFS was 4.2 months (95% CI 2.9–5.6), and median OS was 28.9 months (95% CI 24.3-NR). For patients with higher PD-L1 expression, measured as CPS ≥ 1, higher ORR, median PFS, and median OS were observed. Higher ORR was observed with papillary (28.8%) and unclassified (30.8%) histology than with chromophobe histology (9.5%) [57].

A phase II study evaluated the combination of atezolizumab, an anti-PD-L1 antibody, and bevacizumab in 42 patients with metastatic nccRCC. ORR, primary endpoint of the study, was 26%. ORR was significantly higher in PD-L1 positive (67%) than in PD-L1 negative (14%) patients ($p = 0.02$). Median PFS, which included patients with sarcomatoid features, was 8.3 months (95% CI 5.7–10.9) [58]. These studies have demonstrated promise for immunotherapy in treatment in advanced nccRCC.

Immunotherapy has been especially promising in sarcomatoid variant RCC, which can be observed in both clear cell or nonclear cell histologies. IMMotion 151 was a phase III study that compared atezolizumab and bevacizumab to sunitinib for first-line treatment for inoperable RCC. A planned subgroup analysis examined 142 patients with sarcomatoid features, 19% of whom exhibited nonclear cell histology. Median PFS was reported at 8.3 months (95% CI 5.4–12.9) in the immunotherapy arm compared to 5.3 months (95% CI 3.3–6.7) in the sunitinib arm, and hazard ratio was 0.52 (95% CI 0.34–0.79). This effect was even more pronounced in patients with PD-L1 positive tumor, where hazard ratio for PFS was 0.45 (0.26–0.77). Median OS in the immunotherapy arm was 21.7 months (95% CI 15.3-NE) compared to 15.4 months (10.4–19.5) in the sunitinib arm, and reported hazard ratio was 0.64 (95% CI 0.41–1.01) [59]. In KEYNOTE-427, a subset of 38 patients exhibited sarcomatoid differentiation. ORR was 42.1% (95% CI 26.3–59.2), median PFS was 6.9 months (95% CI 2.8–15.4), and median OS was 25.5 months (95% CI 13.1–30.0), all of which were higher than the overall cohort [57]. A phase II trial of atezolizumab and bevacizumab included patients with sarcomatoid features, including 8 with nccRCC. ORR for these patients was 38%, which was higher than ORR for overall nonclear cell histology (26%) but lower than clear cell histology with sarcomatoid features (50%) [58]. This finding is in line with a retrospective analysis that compared patients with sarcomatoid ccRCC to nccRCC. In this analysis ORR was 14.3% (95% CI 0.4–57.9) in nccRCC compared to 35.4% (95% CI 23.4–49.6). Median PFS (HR 0.25, 95%CI 0.08–0.78, $p = 0.0145$) and median OS (HR 0.13, 95% CI 0.04–0.44, $p = 0.0009$) were both significantly improved in sarcomatoid ccRCC compared to nccRCC with sarcomatoid features [60]. Therefore, while immunotherapy has demonstrated benefit for sarcomatoid RCC, further studies are necessary to determine the utility of this treatment for nccRCC with sarcomatoid features.

Immunotherapy combinations

While single-agent immunotherapy drugs have demonstrated promise in treatment of advanced nccRCC, there may even be greater benefit in combinations with other immune checkpoint inhibitors or targeted small molecule inhibitors. A phase II study, HCRN GU-16-260-Cohort B, treated 16 patients with combination ipilimumab and nivolumab following progression prior to or stable disease at 48 weeks on single-agent nivolumab. This study found 6% ORR to the combination with PFS of 2.8 month (95% CI 2.7-NE) [56]. Similarly, the second part of the phase II UNISON trial, is currently enrolling patients with metastatic or unresectable nccRCC who progressed on single agent nivolumab for treatment with

combination nivolumab and ipilimumab [55]. A retrospective study evaluated 18 patients with metastatic nccRCC treated with ipilimumab plus nivolumab. ORR was 33.3% with another 16.7% of patients with stable disease. Median progression-free survival was 7.1 months, however 61% of patients had treatment related adverse events requiring high doses of glucocorticoids [61]. A phase II clinical trial, SUNIFORECAST, will compare ipilimumab plus nivolumab to sunitinib for patients with advanced nccRCC, and is currently enrolling patients [62]. Another phase II study is currently investigating ipilimumab and nivolumab in advanced medullary RCC [63].

Combined treatment between immunotherapy and TKIs is being explored as well. The phase I/II CALYPSO trial evaluated savolitinib, a MET inhibitor, plus durvalumab, a PD-L1 inhibitor, in 41 patients with metastatic papillary RCC. ORR, the primary endpoint, was 27%. Median PFS was 4.9 months (95% CI 2.5–12), and median OS was 12.3 months (95% CI 5.8–21.3) [64, 65]. Of note, PD-L1 and MET expression were not associated with improved response or survival [65]. In the ongoing phase III SAMETA trial, the combination of savolitinib and durvalumab will be compared to both sunitinib and durvalumab monotherapy in *MET*-driven advanced papillary RCC [66].

CA209-9KU, a phase II trial of 47 patients treated with nivolumab plus cabozantinib in advanced nccRCC demonstrated ORR of 48% (95% CI 31.5–63.9) in patients with papillary, unclassified, or translocation-associated RCC and no responses among patients with chromophobe histology. Median PFS among the former group was 12.5 months (95% CI 29–65) and median OS was 28 months (95% CI 16.3-NE) [67]. Other clinical trials currently enrolling advanced non clear-cell RCC patients for treatment with immunotherapy/TKI combinations include LENKYN [68] and KEYNOTE-B61 [69] with pembrolizumab plus lenvatinib and a phase II study with nivolumab plus ipilimumab plus cabozantinib [70]. A planned PAPMET-2 study will also evaluate the combination of cabozantinib with immunotherapy.

Poly adenosine diphosphate-ribose polymerase (PARP) inhibitors are also being studied in combination with immune checkpoint inhibitors in nccRCC. One ongoing study is enrolling patients with FH- and SDH-deficient RCC to receive the combination of talazoparib, a PARP inhibitor, and avelumab, an immune checkpoint inhibitor [71].

Next generation sequencing, predictive biomarkers, and potential future therapeutic targets

Molecular analysis of nccRCC has revealed a unique characterization for these subtypes as well as potential therapeutic targets. Molecular characterization of papillary RCC has revealed *MET* alterations in both pathologic subtypes, though more commonly in type 1, including autosomal dominant germline mutations in hereditary papillary renal carcinoma. Other genetic alterations commonly observed in papillary RCC include *TERT*, *CDKN2A/B*, *SETD2, KDM6A, SMARCB1, NF2*, and *FH* [72, 73]. A molecular subtype of papillary RCC characterized by CpG island methylation demonstrated worse prognosis. This subtype also exhibited an increased Th2 immune signature, potentially despite correlating with worse survival could indicate response to immunotherapy [74]. Chromophobe histology is associated with germline *FLCN* and *PTEN* in Burt-Hogg-Dubé syndrome and Cowden syndrome, respectively. Unique somatic alterations include rearrangements in the *TERT* promoter region and mutations in mitochondrial DNA [75]. Although chromophobe RCC typically portends a good prognosis, poor prognosis was found in a subset of chromophobe tumors with altered expression of metabolically associated genes including low expression of Krebs cycle, AMPK pathway, and electron transport chain genes [76]. Mutations in *NF2*, *SETD2*, *SMARCB1*, and *CDKN2A* have been observed in collecting duct RCC [77]. *CDKN2A* mutations also associate with poorer prognosis [76]. Medullary RCC, which is associated with sickle trait, is commonly characterized by loss of *SMARCB1/INI1* [78–80]. Xp11 translocation RCC is characterized by *TFE3* gene fusions [9].

As immune checkpoint inhibitors that target the PD-1/PD-L1 pathway are being increasingly used in the treatment of metastatic nccRCC, expression of these potential targets has been extensively studied. In a study of 101 patients with nccRCC, immunohistochemical staining for PD-L1 demonstrated positive tumor cell membrane staining, defined by $\geq 5\%$ tumor cell membrane staining in 10.9% of patients. PD-L1 positive was associated with higher stage ($p = 0.01$) and Fuhrman grade ($p = 0.03$) but not with histologic subtype. Tumor infiltrating mononuclear cells demonstrated positive staining in 56.4% of patients, which was significantly associated with increased risk of death (HR 6.41, 95% CI 2.17–18.88, $p < 0.001$) [81]. A similar study of

immunohistochemical staining for PD-1 and PD-L1 in tumor specimens from 64 patients with nccRCC found 19% of patients with PD-1 positive tumor infiltrating mononuclear cells and 46.4% of patients with intratumoral PD-L1 expression. Neither positive PD-1 expression ($p = 0.88$) or PD-L1 expression ($p = 0.08$) significantly correlated with cancer-specific survival [82]. Another study used a less stringent threshold for PD-L1 positivity, $\geq 1\%$ staining by immunohistochemistry. This study analyzed tissue from 45 patients with nccRCC. In this study, 20% of tumors demonstrated PD-L1 positivity, which was associated with higher Fuhrman grade ($p = 0.048$) and perineural invasion ($p = 0.043$), but not significantly with higher stage. PD-L1 positivity was not prognostic with no significant correlation with progression-free survival ($p = 0.58$) or cancer-specific survival ($p = 0.47$) [83]. A multicenter study analyzed PD-1 and PD-L1 expression in papillary RCC specimens from 301 patients. Threshold for positivity was $\geq 1\%$ for PD-1 in tumor infiltrating mononuclear cells and $> 5\%$ for tumoral PD-L1. PD-1 expression was positive in 4.9% of type 1 papillary RCC and 2.4% of type 2 papillary RCC, and PD-L1 expression was positive in 7.2% of type 1 papillary RCC and 6.2% of type 2 papillary RCC. Neither PD-1 nor PD-L1 positivity was significantly associated with 5-year overall survival in either subtype of papillary RCC [84]. This was consistent with findings from prior studies that demonstrated no correlation between PD-L1 positivity and PFS or OS in papillary RCC [85, 86], although PD-L1 expression significantly correlated with worse PFS in ccRCC [85]. In another retrospective study, Xp11 translocation RCC correlated with worse response to TKIs and improved response to immune checkpoint inhibition, and they had greater density of CD8 positive infiltrating T cells. T cell immunophenotype was $CD8^+PD1^+TIM3^-LAG3^+$ in this population, compared to a more prevalent $CD8^+PD1^+TIM3^+LAG3^-$ immunophenotype in ccRCC [87, 88].

A greater understanding of the molecular composition of nccRCC will lead to further therapeutic options. One case report detailed excellent response to palbociclib, a CDK4/6 inhibitor in a patient with metastatic collecting duct RCC with *CDKN2A* loss [89]. A pre-clinical study in renal medullary carcinoma examined the effects of *SMARCB1* loss on *MYC* expression and replicative stress *in vitro* and *in vivo*. This study found that potential therapies that affect the DNA damage pathway, such as PARP inhibitors, including olaparib and niraparib, ATR inhibitors, and WEE1 inhibitors could all present promising therapies for this nccRCC subtype [90]. Single-cell transcriptomics has also identified potential therapeutic targets in medullary RCC, including novel targetable immune checkpoint receptors TIGIT and CD96, contrasting with low PD1 and CTLA4 expression [91]. Another study evaluated somatic and germline mutations from 116 patients with metastatic nccRCC. For somatic mutations, including *ALK* translocations, *MET* amplifications, *PI3KCA* mutations, and *TSC1/2* mutations, 13% of patients had a potentially clinically actionable mutation. An additional 24% of patients who underwent germline testing had potentially clinically actionable mutations, most commonly in *FH* [92]. The INDIGO trial, which is currently enrolling patients, determines treatment based on DNA and RNA analysis for first-line treatment of advanced nccRCC. Treatment options in this clinical trial for metastatic nccRCC include targeted therapies for specific DNA mutations, sunitinib for patients who exhibit an angiogen profile, or Nivolumab patients who have an immune profile or do not qualify for other targeted treatments [93].

There are inherent limitations to this systematic review. Included studies that enrolled multiple histologic subtypes of nccRCC comprised varying proportions between these histological subtypes and therefore cannot be directly compared. Studies also had differing primary endpoints, and therefore some are not sufficiently powered for survival analysis, which is reported in this systematic review. Additionally, eighteen studies initially reviewed that did not have a nccRCC subgroup analysis were unable to be included in the final analysis.

CONCLUSIONS

Treatment of advanced nccRCC remains challenging, and response rates to most therapies remains low. Although most RCC trials focus on the more common ccRCC, trials have detailed outcomes with mTOR inhibitors, tyrosine kinase inhibitors, and immune checkpoint inhibitors. These trials are imperfect, however, with low patient accrual and heterogeneity between histologic subtypes that could limit their overall applicability. At this time, the most data supports using tyrosine kinase inhibitors, such as sunitinib, or cabozantinib in papillary RCC, especially after results of the PAPMET study. Immune checkpoint inhibition is emerging as a viable alternative and is preferred in nccRCC with sarcomatoid fea-

tures. With growing data and ongoing studies involving combination strategies with immunotherapy and TKIs, this may ultimately emerge as the preferred therapy for nccRCC. Molecular characterization of advanced nccRCC will increase the arsenal of potential treatments, especially in rarer subtypes such as medullary RCC, and will hopefully improve prognosis.

ACKNOWLEDGMENTS

The authors have no acknowledgments.

FUNDING

The authors report no funding.

AUTHOR CONTRIBUTIONS

J.B. and P.B. were involved in literature review and composition of the manuscript. A.C., E.C., and J.G. helped review the manuscript and offered suggestions for improvement.

CONFLICT OF INTEREST

J.G. received institutional research funding from Astellas, Pfizer, Merck, Serono, Janssen, Genentech, and Clovis. He has also served in a consulting or CME speaking role for Bristol-Myers Squibb, Merck, Clovis, AAA, Sanofi, Bayer, Targeted Oncology, and Amgen. He is also an Oncology Drug Advisory (ODAC) committee member for the FDA.

P.B. receives institutional research funding from AstraZeneca, BlueEarth Diagnostics, Merck, and Seattle Genetics/Astellas. He also served in a consulting role for Astellas, Bayer, Bristol-Myers Squibb, Caris, Clovis, Eisai, EMD Serono, Dendreon, and Pfizer, Inc.

J.G. is an Editorial Board Member of this journal, but was not involved in the peer-review process of this paper, nor had access to any information regarding its peer-review.

J.B., A.C. and E.C. have no conflicts of interest to declare.

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