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The Roaring 20s: A New Decade of Systemic Therapy for Renal Cell Carcinoma

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Abstract

Purpose of review—The genomic and immunologic profiling of renal cell carcinoma (RCC) has provided the impetus for advancements in systemic treatments using combination therapy – either with immune check point inhibitor (ICI) + ICI or with ICI + targeted therapy (TT). This approach has been examined in several landmark trials, treating both clear cell (ccRCC) and non-clear cell (nccRCC) histologies. In this review, we highlight systemic therapy advancements made in this new decade, the 2020s.

Recent Findings—Targeting the PD-1/PD-L1 pathway has created more tolerable and effective immunotherapy regimens, expanding the applications of ICIs. These new applications, paired with trial data, include ICI monotherapy in nccRCC and adjuvant pembrolizumab in resected, high-risk RCC. Additionally, ICI+ICI and ICI+TKI combination therapy have demonstrated oncologic efficacy in advanced ccRCC and sarcomatoid RCC.

Similar progress has been noted regarding new TTs. Along the HIF pathway, belzutifan has received FDA approval in VHL-associated RCC. Additionally, in papillary RCC, agents such as cabozantinib target the MET proto-oncogene pathway and have demonstrated impressive oncologic outcomes.

Summary—The 2020s utilize the molecular profiling of advanced RCC as a scaffold for recent trials in immunotherapy and TTs. Going forward, emphasizing patient-reported outcomes and careful clinical trial construction remain critical to improve systemic therapy in RCC.

Keywords

systemic therapy; immune checkpoint inhibitors; HIF inhibitor; clear cell RCC; non-clear cell RCC

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Introduction

Renal cell carcinoma (RCC), the most common kidney malignancy, is the 6th most common cancer in men and the 10th most common among women.[1] In the past several decades, the incidence of RCC has increased, likely due to increased axial imaging which detects renal incidentalomas. Despite stage migration towards incidentally detected small renal masses, up to 17% of patients may have distant metastasis at time of diagnosis.[2, 3] Furthermore, an additional 20%−40% patients initially treated with extirpative surgery may develop recurrent RCC.[2] Given the risk of advanced and metastatic RCC, defining effective systemic treatment regimens remains a burgeoning area of research and clinical development.

In the past two decades targeted therapies (TT) and immune checkpoint inhibitors (ICI) have become the new pillars of RCC systemic therapy, a departure from high-dose cytokines, such as IL-2 and IFN-α.[4, 5, 6], More specifically, inhibitors of angiogenesis with targets along the vascular endothelial grow factor (VEGF) / hypoxia inducible factor (HIF) pathway have offered encouraging response rates and outcomes in recent trials.[7, 8] Additionally, mutations in the *MET* proto-oncogene, which encodes for tyrosine kinases, often drive non-clear cell RCC (nccRCC) – particularly, papillary RCC (pRCC). Thus, trials investigating MET inhibitors have demonstrated encouraging response rates and oncologic outcomes.[9,10,11]

Regarding immunotherapy, prior work has described advanced RCC as immune sensitive. A particular interest has been paid to ICIs which revitalize T cells, inactivated by the tumor microenvironment. Here, tumor cells inactivate the cytotoxic T cells by engaging the programmed death receptor 1 (PD-1), allowing their escape of the immune system. Inhibitors of PD-1 and programmed death receptor ligands (PD-L1 and PD-L2) have demonstrated durable responses in metastatic RCC.[12, 13] Encouraging clinical trial results, perhaps most notably from the KEYNOTE-564 investigators, have provided the impetus for adjuvant PD-1 inhibitor (pembrolizumab) use after radical nephrectomy in high risk RCC, resulting in FDA approval in this setting.[14]

Investigation of systemic treatment in RCC is broadly divided into clear cell RCC (ccRCC) and non-clear cell RCC (nccRCC). Clear cell histology comprises 75% of diagnosed RCCs. Consequently, most clinical trials and studied therapeutics are first applied in ccRCC. Systemic treatment strategies for non-clear cell RCC (nccRCC) are thus typically adapted from treatment of ccRCC.[15] In this review article we aim to highlight the most recent advances in systemic treatment of advanced RCC.

Systemic Treatment Updates in Clear-Cell Renal Cell Carcinoma

ICI and TKI Combination Therapy in ccRCC

From the early 2000s onwards, the use of cytokine based systemic therapies – namely high-dose IL-2, declined. Much of this decline has been attributed to enthusiasm surrounding targeted therapies such as TKIs and their more manageable toxicity profile.[4] Small molecule TKIs such as sunitinib and pazopanib emerged as favored regimens. They subsequently gained FDA approval for metastatic RCC (Table 1). These single agent regimens, however,

had response rates between 10 – 40% and it was proposed that the VEGF / mTOR signaling pathways were incompletely blocked by monotherapy. Efforts to improve efficacy with combination TKI therapy were paired with significant toxicity. Doublet regimens such as sorafenib plus bevacizumab had significant rates of high-grade toxicity, often requiring dose attenuation or halting treatment.[16] In the 2010s, immunotherapy agents such as nivolumab, acting along the PD-1 / PD-L1 pathway emerged as alternatives to TKI-based therapies. To further balance efficacy and toxicity, newer investigations into ICI + TKI and ICI + ICI combination therapies have yielded promising results with more tolerable regimens (Table 1).[5, 17, 18]

Leading into the 2020s, three randomized controlled phase III trials were published in 2019 involving a combination of an ICI and an anti-VEGF agent. Javelin Renal 101 and IMmotion151 examined avelumab plus axitinib and atezolizumab plus bevacizumab, respectively. Neither demonstrated improvement in OS when compared to sunitinib monotherapy; however, they did show improvements in PFS regardless of PD-L1 expression.[19,20] KEYNOTE 426, the third trial, showed improved OS (HR 0.53, 95%CI 0.38–0.74), improved PFS (HR 0.69, 95%CI 0.57–0.84), and higher ORR (59.3% vs 35.7%) among patients receiving the axitinib plus pembrolizumab combination when compared to sunitnib monotherapy. In a subgroup analysis, however, overall survival benefit was not seen in patients with favorable risk disease.[21] In an extended follow-up study, continued survival benefits were noted in the intention to treat group in the combination immunotherapy arm (OS HR 0.68, 95%CI 0.55–0.85; PFS HR 0.71, 95%CI 0.60–0.84).[22]

Data from two additional clinical trials (CheckMate 9ER and CLEAR) were published in 2021, which continued to show favorable treatment efficacy for combination immunotherapy when compared to anti-VEGF TKI treatment alone. In CheckMate 9ER, patients receiving cabozantinib and nivolumab had longer OS (HR 0.60, 95%CI 0.40–0.89), longer PFS (HR 0.51, 95%CI 0.41–0.64), and higher ORR (55.7% vs 27.1%).[23] Similar results were seen in the CLEAR trial in regards to survival trends with the ICI plus TKI combination group (lenvatinib and pembrolizumab) showing an impressive complete response rate of 16.1% and an ORR of 71%.[24] The robust data from these trials have made ICI and TKI combination therapy the gold standard treatment for metastatic ccRCC (Table 2).

Adjuvant Therapy for ccRCC

Choueiri et al. published results from the KEYNOTE-564 trial, specifically examining adjuvant pembrolizumab after nephrectomy.[14] The trial examined 994 patients with confirmed locoregional ccRCC and with high risk of disease recurrence (T2 with nuclear grade 4 or sarcomatous features, T3, regional lymph node involvement, M1 with no evidence of disease after metastatectomy. Enrolled patients were randomized to receive either adjuvant pembrolizumab or placebo. With median follow up of 2 years, the authors noted improvements in disease-free survival (DFS) in the pembrolizumab arm (77.3%vs. 68.1%; HR 0.68, 95%CI 0.52–0.87).[14] The landmark trial has culminated in FDA approval for adjuvant pembrolizumab among ccRCC at high risk of recurrence after nephrectomy.

However, despite its impressive results when examining DFS, the trial does not have enough data maturity to draw conclusions regarding OS. Without defined OS benefits, clinicians

must weigh the risk of administering therapy that does not yet measurably improve survival while adding to treatment-related toxicity and costs. Similar concerns have been raised regarding adjuvant sunitinib, which offers similar DFS improvements, but no significant gains in OS.[25] Additionally, administering single agent ICI after nephrectomy may not adequately treat patients with occult metastases after surgery given that ICI + TKI and ICI + ICI are current standards of care in the metastatic setting.[26] Thus, in addition to overtreating some patients whose RCC may never recur, a certain percentage of patients with occult metastatic disease may be undertreated. Furthermore, the efficacy of any subsequent ICI-based combination therapy for recurrent disease after receiving adjuvant pembrolizumab monotherapy is not well understood. Until the OS data matures, careful consideration should be given before the broad adoption of adjuvant pembrolizumab.[27]

Further exploring the role of adjuvant immune checkpoint blockade, the PROSPER RCC (NCT03288532) trial has recently completed accrual. This phase III trial assesses the role of ICI in high-risk locoregional or oligometastatic RCC of any histology. Patients are randomized to receive either perioperative nivolumab, before and after nephrectomy, or assigned to observation only. The PROSPER RCC trial further represents efforts to use patients' immune system (i.e., 'prime' the immune system pre-nephrectomy) to impact treatment outcomes in aggressive renal masses. Like urothelial or high-risk breast cancers, RCC is another malignancy which may benefit from neoadjuvant PD-1 blockade. This may further amplify the T cell response induced by a renal tumor, thus improving oncologic outcomes.[28]

HIF2α Inhibitors in ccRCC

Belzutifan (MK6482), a second-generation HIF2α antagonist has shown encouraging results in several recent trials. In one study, 55 previously treated patients with mRCC (81% and 92% of whom previously received PD-1/PD-L1 inhibitors and VEGF inhibitors, respectively) had an ORR of 25% and PFS of 14.5 months.[29] In two separate phase II studies, when combined with cabozantinib or lenvatinib, belzutifan showed objective response rates of 25% and 22%, respectively, in heavily pretreated patients with metastatic disease.[30,31] There are currently multiple phase 3 trials involving belzutifan in metastatic ccRCC, including a triple therapy-based trial of pembrolizumab, lenvatinib and belzutifan evaluating tolerability and efficacy.[32,33,34]

In patients with von Hippel-Lindau (VHL) disease, belzutifan represents a new FDA-approved treatment for non-metastatic RCC. Patients with germline VHL mutations have their renal tumors managed with surgical resection, ideally partial nephrectomy, particularly when they grow >3cm.[35] Often this requires patients to undergo multiple renal surgeries over their lifetime.[36] In VHL patients, VHL is inactivated resulting in overactive HIF2α. Jonasch et al. studied if belzutifan could reduce tumor growth in such patients, thus potentially sparing them multiple surgeries. Eligible patients had VHL germline mutations and had at least one tumor >1 cm, but none >3 cm, requiring prompt intervention. With 61 patients enrolled, 30 patients demonstrated objective response (49%). Among patients showing response, median linear growth rate (of the longest tumor diameter) on treatment was −5.6 mm/year vs. 4.1 mm/year off treatment at time of trial entry.

Results also demonstrated encouraging results in extra-renal tumors associated with VHL (i.e., pancreatic neuroendocrine tumors and brain/spine hemangioblastomas, among other potential lesions).[37]

Systemic Treatment Updates in Non-clear Cell RCC

While nccRCC histology accounts for approximately a quarter of RCC cases, there is limited prospective evidence to inform treatment selection for advanced nccRCC. Multiple histologic subtypes – papillary, clear cell papillary, chromophobe, medullary, collecting duct, translocation, and unclassified – comprise nccRCC.[38] Due to distinct pathologic and molecular features, systemic treatments generally are less effective in advanced nccRCC patients compared to their clear cell counterparts. Furthermore, systemic therapy regimens for nccRCC are often adapted from ccRCC, and are less effective.[39, 40] Additionally, neoplasm heterogeneity has made trial construction challenging.[16] As a result, this space has been primed for clinical trials to guide systemic therapy in nccRCC. To better target nccRCC, there have been many recent efforts to characterize the genomic landscape, even for rarer tumors such as clear cell papillary RCC.[41, 42, 43] Most recently, we have seen significant advancements using therapies targeting HIF and MET pathways as well as ICIs (Table 3) in the past two years.

Retrospective studies examining ICIs in nccRCC, particularly nivolumab and ipilimumab, have noted encouraging response rates (20% – 33%), informing the development of recently resulted prospective trials.[44,45,46] Specifically, KEYNOTE 427 and CheckMate 374, evaluated pembrolizumab monotherapy and nivolumab monotherapy, respectively.[47,48]

KEYNOTE 427, a single-armed phase II trial, prospectively assessed the efficacy and safety profile of pembrolizumab in advanced nccRCC. Key inclusion criteria included newly diagnosed or recurrent stage IV nccRCC – with histologic status determined by a central pathology review. Additionally, while neoadjuvant and/or adjuvant therapy was permitted (if administered >12 months from trial enrollment), systemic treatment for metastatic disease was not allowed. Of 165 enrolled patients, 72% had pRCC, 13% had chromophobe RCC (chRCC); 23% of these patients had sarcomatous features as well. Additionally, 61.8% of patients had PD-L1 expression (CPS≥1). The objective response rate (ORR) of pembrolizumab was 26.7% (44/165) (95%CI: 20.1%–34.1%) with 6.7% demonstrating complete response. Median progression-free survival (PFS) and overall survival (OS) were 4.2 months and 28.9 months, respectively. Regarding toxicity, nearly 70% of patients reported treatment-related side effects – most commonly pruritus (20.0%) and hypothyroidism (14.5%).[47]

CheckMate 374, a prospective phase IIIb/IV study examined nivolumab monotherapy in advanced RCC. Among those enrolled, 44 had nccRCC and 97 had predominantly ccRCC histology; the analysis described by Vogelzang pertains to the nccRCC cohort only. 55% (24/44) of patients had pRCC, with 9% having sarcomatous features. Additionally, 34.2% of patients were noted to have positive PD-L1 expression. ORR in the nccRCC cohort was 13.6% (95%CI: 5.2%−27.4%). With median follow up of 11 months, median PFS was

2.2 months and OS 16.3 months. Three quarters of patients (33/44) experienced treatment related adverse events, especially nausea (20.5%) and fatigue (15.9%).[48]

Among non-clear cell histologies, interest in targeting the *MET* proto-oncogene pathway has resulted in significant advancements in the treatment of advanced pRCC. Alterations in this pathway have been observed in roughly 80% of type 1 pRCC and nearly 50% of type 2 pRCC.[49,50,51] Given these alterations and a multicenter retrospective study, enthusiasm for MET pathway inhibitors entered the clinical trial space.[52] In 2020, the SAVOIR Phase 3 clinical trial, a randomized control trial, examined patients with metastatic pRCC (type 1 or 2). Specifically, the study was restricted to those with MET-driven disease with gains in chromosome 7, MET kinase mutations, or HGF alterations.[53] Hypothesizing that a MET inhibitor, savolitinib, would yield favorable outcomes compared to sunitinib, often the reference agent for nccRCC trials, 60 patients were randomized into the two treatment arms. After accrual of 60 patients, interim analysis demonstrated significantly improved response rates in patients receiving savolitinib (27%) vs. sunitnib (7%). However, a concurrent retrospective study of patients with MET-driven pRCC treated with sunitinib demonstrated that MET status did not predict poor outcomes in sunitinib-treated pRCC – a core assumption for the SAVOIR trial. Understanding that it would be difficult to detect meaningful survival differences in the treatment arms, the trial was halted. Consequently, due to short follow-up data and small sample size, inferences regarding long term efficacy and safety are challenging.[51, 53]

Most recently, Pal et al. completed a four-armed trial, PAPMET, enrolling 147 patients with advanced / metastatic pRCC. It compared cabozantinib (N=44), savolitinib (N=29), crizotinib (N=28), and sunitinib (N=46). However, interim analysis showed poor response rates in the crizotinib (ORR=0%) and savolitinib (3%) arms; thus, these two treatment groups were stopped. When comparing cabozantinib to sunitinib – previously the standard of care in nccRCC – the authors noted improved ORR (cabozantinib 23% vs. sunitinib 4%, p=0.010) and PFS (HR 0.60, 95%CI 0.37–0.97; p=0.019).[51] The trial's elegant design, directly comparing several therapeutics of interest to the historical sunitinib standard, allow for extension to clinical practice, especially considering the encouraging results of cabozantinib. The authors do note some key limitations, such as a discordance between central and local histology review and relatively small sample size. Furthermore, patients were not restricted by MET pathway alteration status, which may explain poor response rates of crizotinib and savolitnib.[51]

Systemic Therapy Updates in Sarcomatoid Renal Cell Carcinoma

Patients with sarcomatoid features, representing roughly 5% of RCCs, have historically had poor outcomes and poor response to tyrosine kinase inhibitors. Most recently, genomic profiling has demonstrated increased expression of PD-1 and PD-L1.[54] Consequently, ICIs and combination therapy have demonstrated more encouraging results. Several recent trials have delineated subsets within their cohorts with sarcomatoid RCC (sRCC), and some have also incorporated a *post hoc* analysis of these sarcomatoid tumors (Table 4).

KEYNOTE 427, described above, was a single arm study of pembrolizumab in advanced nccRCC. 23% (38/165) patients had sarcomatoid differentiation and the ORR in this cohort was 42.1% (95%CI 26.3–59.2); the overall cohort had an ORR of 26.7% (95%CI 20.1–34.1). Additionally, these patients had median PFS and OS of 6.9 months and 25.5 months, respectively. Similar to the prior data that sarcomatoid differentiation may portend response to ICI in ccRCC, KEYNOTE 427 suggests that nccRCC may also respond to ICI therapy.[47]

KEYNOTE 426, CheckMate 9ER, and CheckMate 214 examined several ICI combination regimens in advanced ccRCC with reference to sunitinib, a historical standard of care for sRCC. Since publication of the original trial results, post-hoc analyses specifying patients with sarcomatous features have been described. KEYNOTE 426 included 105 sRCC (18.2%), comparing axitinib-pembrolizumab combination therapy versus sunitinib. With median follow up of 12 months, in patients receiving axitinib-pembrolizumab, the authors noted improved PFS (HR 0.54, 95%CI 0.29–1.00) and ORR (58.8% vs. 31.5%), consistent with improvements noted in the overall cohort.[55] CheckMate 9ER also evaluated the role of ICIs and TT combination therapy, specifically nivolumab-cabozantinib vs. sunitinib. Of 651 patients in the trial, 75 (11.5%) had sarcomatous features. The investigators found improved PFS (HR 0.39, 95%CI 0.22–0.70) and ORR (55.9% vs. 22.0%) among the sRCC patients in the nivolumab-cabozantinib trial arm.[56] CheckMate 214 (N=112) similarly found improved PFS (HR 0.61, 95%CI 0.38–0.97) and ORR (56.7% vs. 19.2%) in those receiving nivolumab-ipilimumab.[57]

Choueiri et al. published a post hoc analysis of the Javelin 101 trial, avelumab-axitinib vs. sunitinib, specific to sRCC. Considering the enhanced expression of immune checkpoint proteins in sRCC, VEGFR TKIs may have a synergy with ICIs. The TKIs improve immune cell response to tumor cells and reduce immunosuppressive effects. In their analysis of 108 sRCC patients, the authors noted improved ORR (46.8% vs. 21.3%) and PFS (HR 0.57, 95%CI 0.325–1.003) among those receiving avelumab-axinitib.[58]

Lastly, two recent studies have studied atezolizumab and bevacizumab for sRCC. The two monoclonal antibodies continue to build on the synergy between the ICIs and the VEGF pathway targeted by the various TKIs. The first trial (NCT02724878) examined the atezolizumab-bevacizumab combination in a single arm study of 60 patients with advanced variant histology RCC, including ccRCC with ≥20% sarcomatoid features. In the entire cohort, ORR was 33.3% and 46.2% among sRCC.[59] Additionally, a prespecified analysis of the IMmotion 151 trial (N=142 with sRCC) assessed atezolizumab-bevacizumab vs. sunitinib in the advanced sRCC subset, noting similar results. The atezolizumab-bevacizumab doublet resulted in improved response rates (ORR 49% vs. 14%) and PFS (HR 0.46, 95%CI 0.28–0.78).[60]

Conclusion:

The 2020s to date have been marked by considerable progress in the treatment of advanced RCC. Leaps in immunotherapy have targeted the PD-1/PD-L1 pathways to create more tolerable and efficacious doublet treatment regimens. Importantly, these pathways have opened the possibility of adjuvant immune check point blockade in high risk

RCC, demonstrated by the FDA's recent approval of adjuvant pembrolizumab. Similarly, along the HIF pathway, belzutifan has also received FDA approval in VHL-associated RCC. In ccRCC, trials examining combination therapy have noted improved response rates and promising survival outcomes, including in patients with sarcomatoid RCC. In advanced nccRCC, trials investigating immunotherapy regimens – notably pembrolizumab and nivolumab – have produced encouraging results. In pRCC, agents targeting the MET proto-oncogene pathway, such as cabozantinib, have demonstrated practice-changing results. These advancements in the current decade represent careful efforts to characterize the genomic landscape for immune checkpoint and target therapies.[61, 62] This has provided a crucial scaffold to provide patients with advanced RCC more efficacious and tolerable systemic treatments. Continued attention to survival as well as patient-reported outcomes, and an unwavering commitment to clinical trial accrual, will ensure that the '20s continue to roar.[63, 64]

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Key Points

- In the 2020s, recent trials have demonstrated the efficacy of immune check point inhibitors in ccRCC – particularly as part of combination regimens and as adjuvant therapy – and for nccRCC.
- New targeted therapies along the HIF pathway in VHL-associated ccRCC and the MET proto-oncogene pathway in papillary RCC have provided practice-changing treatment options.
- Future trials examining combination therapies and new genomic targets comprise a promising future for the systemic treatment of advanced RCC.

Table 1:

Treatment of Metastatic Clear Cell RCC by FDA Approval Date

Therapy	FDA Approval	Mechanism of Action	Treatment Line	Risk Groups	Comparison Arm	Endpoint	Route
Interleukin-2	May 1992	Cytokine immunotherapy	First-line	Favorable	Phase II - None	ORR	IV
Sorafenib	Dec 2005	VEGFR, PDGFR, KIT inhibitor	Cytokine failure	Favorable Intermediate	Placebo	OS	PO
Sunitinib	Jan 2006	VEGFR, PDGFR inhibitor	First-line	Favorable Intermediate	IFN-α	PFS	PO
Temsirolimus	May 2007	mTOR inhibitor	First-line	Intermediate Poor	IFN-α	OS	IV
Everolimus	Mar 2009	mTOR inhibitor	VEGFR failure	All groups	Placebo	PFS	PO
Bevacizumab + IFN-α	Jul 2009	Anti-VEGF monoclonal antibody	First-line	Favorable Intermediate	IFN-α ± Placebo	OS	IV + SC
Pazopanib	Oct 2009	VEGFR, PDGFR, KIT inhibitor	First-line or Cytokine failure	Favorable Intermediate	Placebo	PFS	PO
Axitinib	Jan 2012	VEGFR inhibitor	Second-line		Sorafenib	PFS	PO
Nivolumab	Nov 2015	Anti-PD1 monoclonal antibody	Second-line	All groups	Everolimus	OS	IV
Cabozantinib	Apr 2016	VEGFR, MET, AXL inhibitor	Second-line	All groups	Everolimus	PFS	PO
Lenvantinib + Everolimus	May 2016	VEGFR, PDGFR, KIT, FGFR, RET inhibitor mTOR inhibitor	Second-line	All groups	Everolimus or Levantinib	PFS	PO
Cabozantinib	Dec 2017	VEGFR, MET, AXL inhibitor	First-line	Intermediate Poor	Sunitinib	PFS	PO
Nivolumab + Ipilimumab	Apr 2018	Anti-PD1 monoclonal antibody Anti-CTLA-4 monoclonal antibody	First-line	Intermediate Poor	Sunitinib	OS ORR PFS	IV + IV
Pembrolizumab + Axitinib	Apr 2019	Anti-PD1 monoclonal antibody VEGFR inhibitor	First-line	All groups	Sunitinib	OS PFS	IV + PO
Avelumab + Axitinib	May 2019	Anti-PD-L1 monoclonal antibody VEGFR inhibitor	First-line	All groups PD-L1+ tumor	Sunitinib	OS PFS	IV + PO
Nivolumab + Cabozantinib	Jan 2021	Anti-PD1 monoclonal antibody VEGFR, MET, AXL inhibitor	First-line	All groups	Sunitinib	PFS OS ORR	IV + PO
Tivozanib	Mar 2021	VEGFR inhibitor	Third-line	All groups	Sorafenib	PFS OS ORR	PO
Lenvatinib + Pembrolizumab	Aug 2021	VEGFR, PDGFR, KIT, FGFR, RET inhibitor Anti-PD1 monoclonal antibody	First-line	All groups	Sunitinib	PFS OS ORR	PO + IV
Pembrolizumab (adjuvant)	Nov 2021	Anti-PD1 monoclonal antibody	Adjuvant	High risk locoregional	Placebo	DFS OS	IV

Therapy	FDA Approval	Mechanism of Action	Treatment Line	Risk Groups	Comparison Arm	Endpoint	Route
				Full resected M1			

Table 2:

Recent Trials Involving Combination Immunotherapy in Metastatic Clear Cell RCC

Study	Treatment Agent	N	ORR
CheckMate 214	Nivolumab + Ipilimumab	1096	Nivolumab + Ipilimumab 42%, Sunitnib 27%
CheckMate 9ER	Nivolumab + Cabozantinib	651	Nivolumab + Cabozantinib 55.7%, Sunitinib 27.1%
CLEAR	Pembrolizumab + Lenvatinib	1069	Pembrolizumab + Lenvatinib 71%, Everolimus + Lenvatinib 53.5%, Sunitinib 36.1%
IMotion151	Atezolizumab + Bevazicumab	915	Atezolizumab + Bevazicumab 37%, Sunitinib 33%
Javelin Renal 101	Avelumab + Axitinib	886	Avelumab + Axitinib 51.4%, Sunitinib 25.7%
KeyNote 426	Pembrolizumab + Axitinib	861	Pembrolizumab + Axitinib 59.3%, Sunitinib 35.7%

ORR = objective response rate

Table 3:

Notable Recent Trials in Non-Clear Cell Renal Cell Carcinoma

Immune Checkpoint Inhibitors							
			Histology				
Study	**Treatment Agent**	**N**	**Papillary**	**Chromophobe**	**Other**	**Sarcomatoid***	**ORR**
KEYNOTE 427	Pembrolizumab	165	72%	13%	16%	23%	27%
CheckMate 374	Nivolumab	44	55%	16%	30%	9%	14%
MET Pathway Inhibitors							
			Histology				
Study	**Treatment Agent**	**N**	**Papillary**	**Chromophobe**	**Other**	**Sarcomatoid***	**ORR**
PAPMET (SWOG 1500)	Cabozantinib, Crizotinib, Savolitnib vs. Sunitinib	152	100%	0%	0%	0%	Cabozantinib 23%, Crizotinib 0%, Savolitinib 3%, Sunitinib 4%
SAVIOUR	Savolinitinib vs. Sunitinib	60	100%	0%	0%	0%	Savolinitib 27%, Sunitinib 7%

ORR = objective response rate;

*Sarcomatoid features can be found in any histologic subtype and are described distinctly from other histologic subtypes

Table 4:

Recent Trials Addressing Sarcomatoid Features in Advanced RCC

			Histology					
Study	**Treatment Agent**	**N**	**Clear Cell**	**Papillary**	**Chromophobe**	**Other**	**Sarcomatoid***	**ORR****
KEYNOTE 427	Pembrolizumab	165	0%	72%	13%	16%	23%	42%
KEYNOTE 426	Pembrolizumab + Axitinib	861	100%	0%	0%	0%	12%	Pembrolizumab + Axitinib 59%, Sunitinib 32%
CheckMate 9ER	Nivolumab + Cabozantinib vs. Sunitinib	651	100%	0%	0%	0%	12%	Nivolumab + Cabozantinib 56%, Sunitinib 22%
Immotion 151	Atezolizumab + Bevacizumab vs. Sunitinib	915	92%	0%	0%	0%	16%	Atezolizumab + Bevacizumab 49%, Sunitinib 14%
CheckMate 214	Nivolumab + Ipilimumab	1096	100%	0%	0%	0%	13%	Nivolumab + Ipilimumab 57%, Sunitinib 19%
Javelin 101	Avelumab + Axitinib vs. Sunitinib	886	100%	0	0	0	12%	Avelumab + Axitinib 47%, Sunitinib 21%
NCT02724878	Atezolizumab + Bevacizumab	60	30%	20%	17%	33%	42%	46%

ORR = objective response rate;

*Sarcomatoid features can be found in any histologic subtype and are described distinctly from other histologic subtypes;

**Reported response rates specific to sarcomatoid histology