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Review

A Review of Papillary Renal Cell Carcinoma and MET Inhibitors

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Abstract. Papillary renal cell carcinoma (PRCC) is a subtype of renal cell carcinoma (RCC) accounting for approximately 15–20% of cases and further divided into Type 1 and Type 2. Type 1 PRCC tends to have more alterations in the MET tyrosine kinase receptor than Type 2 PRCC. Treatment for RCC patients is based on studies with minimal participation from patients with PRCC; consequently, conventional therapies tend to be less effective for RCC patients with a subtype other than ccRCC (non-ccRCC). Since MET is a known alteration in PRCC, it is potential target for directed therapy. There have been many attempts to develop MET inhibitors for use in solid tumors including PRCC. The following review will discuss the current research regarding MET-targeted therapy, MET inhibitors in clinical trials, and future directions for MET inhibitors in PRCC.

Keywords: Papillary renal carcinoma, kidney cancer, renal cell cancer, molecularly targeted therapies, immune-checkpoint inhibitor, non-clear cell renal cell carcinoma, MET

INTRODUCTION

Renal cell carcinoma (RCC) is the sixth most commonly diagnosed cancer in men and the tenth in women with approximately 140,000 deaths yearly, ranking RCC as the 13th most common cause of cancer death worldwide [1–4]. The lifetime risk for developing RCC in Europe and North America is 1.3%–1.8%. In the United States, there are 15.9 cases per 100,000 each year with a 0.6% increase each year in new cases of kidney and renal pelvis cancer over the last decade [5]. Papillary renal cell carcinoma (PRCC) is the second most common type of RCC, following clear cell carcinoma (ccRCC), comprising 15–20% of RCC cases. PRCC is further subdivided into type 1 and type 2 based on histology. Although similar mutations are found within the two types of PRCC, each type has characteristic common mutations. Type 1 PRCC is more associated with MET alterations, either genetic mutations or gain of chromosome 7 where the MET gene is found. Type 2 PRCC tends to have mutations in CDKN2A, SETD2, BAP1, PBRM1, TERT, NF2, FH, and NRF2-ARE pathway genes. Type 2 is also associated with a CpG island methylator phenotype (CIMP) (Table 1) [6–8].

MET mutations in PRCC were first identified in hereditary PRCC as an autosomal dominant mutation in the MET gene on chromosome 7q31 [9, 10]. Since then, additional somatic mutations and chromosome duplications have been identified in sporadic renal carcinoma [8]. MET mutations are also found in other malignancies, such as hepatocellular carcinomas (HCC), lung cancer, breast cancer, colorectal cancer (CRC), head and neck squamous cell cancers (HNSCC), gastric carcinomas (GC), and cancers of

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Table 1
Common Mutations in PRCC

Type 1 PRCC	Type 2 PRCC
MET mutations	CDKN2A
Gain of chromosome 7	SETD2
	BAP1
	PBRM1
	CpG island methylation
	NRF2-ARE pathway genes (*NFE2L2*, *CUL3*, *KEAP1*, and *SIRT1*)

unknown primary origin [7]. Increased expression of MET can occur via overexpression, gene amplification, activating point mutations, gene fusions, increased chromosome 7 copy number, paracrine signaling, autocrine loop formation, receptor mutations, and splice variants [10–13]. Although MET alterations are more common in type 1 PRCC, one study found a larger percentage of type 2 PRCC with MET mutation than previously identified, with 46% of type 2 and 81% of type 1 PRCC cases positive for MET mutation [14].

THE MET PATHWAY

MET is a tyrosine kinase receptor of hepatocyte growth factor/scatter factor (HGF/SF). This pathway is involved in a variety of normal functions, including: liver regeneration, wound healing, organ morphogenesis, and embryo development [11]. In normal tissues, HGF and MET are upregulated after renal injury as a mechanism of tissue repair and regeneration. In oncogenesis, MET is involved in invasion, anti-apoptosis, angiogenesis, and metastasis (Fig. 1)

There is also influence from other growth factors, such as epidermal growth factor receptor (EGFR) activation of c-MET after stimulation of cells with the EGFR ligands EGF or transforming growth factor (TGF-α) (Fig. 1) [13]. This interaction is further evidenced in non-small cell lung carcinomas (NSCLC) with acquired resistance to EGFR inhibitors due to amplifications in MET.

PRCC OUTCOMES WITH CONVENTIONAL THERAPY

PRCC tends to have a less robust response to conventional therapy used in RCC compared with clear cell carcinoma (ccRCC) given that ccRCC is associated with distinct mutations not typically found in PRCC, such as VHL and PBRM1 [15–20]. Multiple large studies have found significantly lower response rates with shorter median progression-free survival (PFS) and overall survival (OS) in patients with non-ccRCC variants, such as PRCC, when compared to ccRCC. One large study of 5474 patients with metastatic RCC showed better OS, PFS, and objective

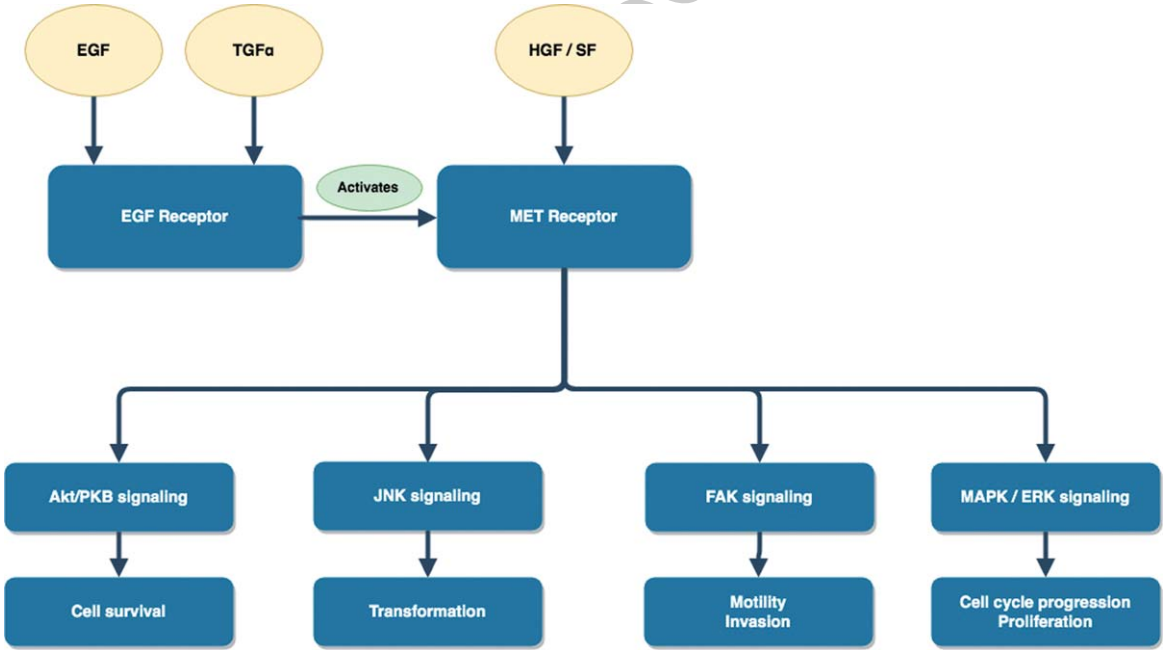

Fig. 1. MET molecular pathway.

response rate (ORR) for ccRCC compared to non-ccRCC with an OS 8 months longer for ccRCC [17]. Another large systematic review and meta-analysis evaluated 49 studies composed of 7771 patients and found that non-ccRCC had significantly lower response rates compared with ccRCC, with a 10.5% overall response rate in non-ccRCC. Among patients with non-ccRCC, median PFS and OS were 7.4 and 13.4 months, respectively. For patients with ccRCC, these clinical outcomes were significantly higher with a PFS and OS of 10.5 months and 15.7 months, respectively [16]. Therapeutic interventions (including bevacizumab, sorafenib, sunitinib, temsirolimus, and sunitinib) were less effective for patients with non-ccRCC with a response rate of 9.2% compared to 14.8% in ccRCC [16].

When evaluating specific agents used in RCC, the efficacy is diminished for non-ccRCC compared to ccRCC. One example is everolimus. A shorter PFS was confirmed for non-ccRCC patients compared to ccRCC patients in the ASPEN, RECORD-3, and ESPN trials [18–21]. Other examples include VEGF inhibitors, such as sunitinib, which has a shorter PFS specifically in metastatic PRCC, ranging from 1.6–6.6 months, compared to 9–12 months in ccRCC [20, 22–26]. Data from meta-analyses support the use of sunitinib over everolimus and temsirolimus for metastatic non-ccRCCs in first-line treatment, but the difference in PFS is not statistically significant [27]. Based on this data, guidelines from the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) both recommend sunitinib as first line therapy in metastatic non-ccRCC [28, 29].

Immunotherapy also has a role in treating RCC. Nivolumab, a PD-L1 inhibitor, is approved for metastatic RCC, but this was based on studies excluding patients with non-ccRCC [30, 31]. For ccRCC, nivolumab improves OS, with patients surviving 25 months with nivolumab versus 19.6 months with everolimus [30]. For non-ccRCC, a few case reports describe responses of patients with PRCC to nivolumab [32–34]. In 2018, a study from Koshkin et al. evaluated nivolumab in non-ccRCC with 16 of 41 patients having PRCC. The study found clinical response to nivolumab seen as an ORR of 20% and stable disease (SD) in 29% of all patients in the study. Results specific to the 16 patients with PRCC, included PR of 14% and SD in 21% [35].

Given the limited response of PRCC to conventional therapies used in all RCC, MET-targeted therapy alone or combination with other agents could provide better outcomes for these patients. Several agents targeted to MET have been tested in RCC with varying outcomes, including tyrosine kinase inhibitors (TKI) and monoclonal antibodies (Table 2).

TKIS TARGETING MET

Crizotinib

Crizotinib is a TKI that targets MET in addition to ALK and ROS1 [34]. Currently, crizotinib is approved in NSCLC; however, there is evidence to support its use in PRCC. A phase II study, the CREATE trial, evaluated crizotinib in 23 patients with PRCC [36]. Four patients had confirmed MET alterations with two achieving partial response (PR) and a 1-year OS of 75.0% [36]. Additional evidence to support the use of crizotinib in patients with MET mutations was a small study of NSCLC patients showing PR more often with high level MET genomic amplification [35]. Currently, there are phase II trials evaluating the use of crizotinib in RCC, NSCLC, and anaplastic large cell lymphoma (Table 3) [38, 39]. Recently, the crizotinib arm in the SWOG 1500 trial (NCT02761057) was closed for accrual.

Savolitinib

Savolitinib is a small molecule inhibitor of MET that was initially found to induce tumor regression in PRCC xenograft models *in vivo* [40]. A later study of savolitinib in PRCC patients found a PR in 18% of participants with MET-driven disease and none with MET-independent disease (P = 002) [41]. Savolitinib was part of a phase II trial, SWOG 1500, evaluating MET inhibitors in PRCC, but this arm was recently closed for accrual (NCT02761057) [39]. Phase III trials are underway investigating savolitinib compared to sunitinib for MET alteration-driven PRCC (NCT03091192) (Table 3) [41, 42].

Cabozantinib

Cabozantinib is another TKI that targets multiple receptors, including c-MET, VEGF, RET, KIT, AXL, TIE2, and FLT3 [43]. Data from phase I study from Choueiri et al. demonstrated safety and tolerability in RCC [44]. The phase 3 trial, METEOR, found significant improvement in OS for advanced ccRCC patients who received cabozantinib compared to everolimus (OS 21.4 months vs 17.1 months) [44].

Table 2
Current Data on MET inhibitors in PRCC

Drug	Molecular Targets	Current Data in PRCC	FDA Approval	References
Crizotinib	MET ALK ROS1	*Schöffski P, et al.* – phase II trial, CREATE – 23 patientswith PRCC – ORR = 50% (2/4 patients with MET alterations with a PR) – 1-year OS = 75%	NSCLC with mutations in: ROS-1, ALK, or MET	36, 37
Savolitinib	MET	*Choueiri TK, et al.* – phase II trial – 109 patients with PRCC, 44 with MET-driven disease – PR = 18% in MET-driven disease	None	40, 41
Cabozantinib	MET, VEGF, RET, KIT, AXL, TIE2, FLT3	*Campbell MT, et al.* – Retrospective – 30 patients with non-ccRCC, 57% with PRCC – ORR of 14.3% *Chanza NM, et al.* – Retrospective – 80 patients with non-ccRCC, 59% with PRCC – ORR of 27.3%	RCC	43–48
Foretinib	MET, VEGFR2, RON, AXL, TIE-2	*Choueiri TK, et al.* – phase II trial – 74 patients with PRCC – PFS 9.3 mon – PR: 50% for germline MET mutations (5 of 10 patients), 20% for somatic MET mutation (1 of 5 patients), 9% without a MET mutation (5 of 57 patients), 5% with a gain of chromosome 7 (1 of 18 patients), and none in patients with MET amplification (2 patients)	None	50–54
Tivantinib	MET	*Twardowski PW, et al.* – phase II trial (SWOG 1107) – 50 patients, 48% with confirmed PRCC – no clinical activity with either tivantinib alone or in combination with erlotinib	None	54, 55
Rilotumumab	Fully human IgG2 mAb directed against HGF	*Schöffski P, et al.* – phase II trial – 61 patients with RCC – no objective responses	None	58, 59
ARGX-111	Antibody that blocks HGF/MET	*Aftimos PG, et al.* – phase 1b trial – 16 patients with multiple solid tumors, 3 with RCC – demonstrated safety	None	60–62
LY3164530	Antibody to EGFR/MET	*Patanik A, et al.* – phase I trial – 36 patients with various solid tumors, including PRCC – progressive disease in PRCC – significant toxicities and no predictive biomarker	None	64, 65

Table 3
Ongoing Trials for PRCC

Drug	Targets	NCT ID	Trial Details
Crizotinib	MET ALK ROS1	NCT02761057 [39]	– Phase II trial (SWOG 1500): Evaluating cabozantinib, crizotinib, savolitinib,or sunitinib in PRCC
Savolitinib	MET	NCT03091192 [42]	– Phase III trial: Evaluating savolitinib vs sunitinib in MET driven PRCC
		NCT02761057 [39]	– Phase II trial (SWOG 1500): Evaluating cabozantinib, crizotinib, savolitinib,or sunitinib in PRCC.
Cabozantinib	MET, VEGF, RET, KIT, AXL, TIE2, FLT3	NCT02761057 [39]	– Phase II trial (SWOG 1500): Evaluating cabozantinib, crizotinib, savolitinib,or sunitinib in PRCC
Capmatinib	MET	NCT02019693 [82]	– Phase II trial: Evaluating capmatinib in PRCC
Nivolumab+/- ipilimumab	anti-PD-1 + anti-CTLA-4 mAb	NCT03177239 [72]	– Phase II trial: sequential treatment of nivolumab followed by nivolumab+ipilimumab if single agent treatment is not effective in PRCC
Savolitinib or Tremelimumab with Durvalumab	MET TKI or anti-CTLA-4 with anti-PD-L1	NCT02819596 [71]	– Phase and II trial: evaluating savolitinib, tremelimumab, durvalumab alone or in combination in PRCC and ccRCC

A Phase II study, CABOSUN, looking at cabozantinib compared to sunitinib in metastatic intermediate/poor risk ccRCC patients found prolonged PFS in the cabozantinib arm (8.6 months vs 5.3 months) [45]. As a result, cabozantinib has been approved for use in RCC as first or second line in this population (46). Retrospective studies have reported clinical response with cabozantinib specifically in PRCC patients [47, 48]. One study composed of 57% PRCC (total of 30 non-ccRCC patients) found a median PFS of 8.6 months and OS of 25.4 months. SD was achieved in 64.2% patients with an ORR of 14.3% [47]. Another study showed cabozantinib is safe and active in PRCC with 27.3% ORR, median OS of 11 months and a time to treatment failure of 6.9 months [48]. Currently, a phase II trial is evaluating cabozantinib and other MET targeted therapies specifically in PRCC (NCT02761057) (Table 3) [39].

Foretinib

Foretinib is a TKI against MET, VEGFR2, RON, AXL, and TIE-2 [49]. The dual targeting of MET and VEGF resulted in a median PFS of 9.3 months in non-ccRCC, which is comparable to responses seen in ccRCC patients treated with VEGF inhibitors. Germline MET mutations tended to correlate best with patient response to the drug with 50% (five of ten patients) achieving a PR. PR was seen in 20% of patients with a somatic MET mutation (one of five patients), 9% without a MET mutation (five of 57 patients), 5% with a gain of chromosome 7 (one of 18 patients), and none in patients with MET amplification (zero of two patients) [49]. Most recent studies of foretinib have involved breast cancer and NSCLC patients [50–52].

Tivantinib

Tivantinib is a selective non-competitive c-MET inhibitor that was initially found in phase I studies to induce disease stabilization in three of five patients with non-ccRCC [53, 54]. However, later phase 2 evaluation in the SWOG S1107 cohort found no clinical activity in patients with advanced PRCC with either tivantinib alone or in combination with erlotinib, an EGFR inhibitor. However, these results reflect a patient population predominately composed of type 2 PRCC (42%). Notably, only 6% of patients had type 1 PRCC and only 1 of 16 tissue samples sequenced had a MET alteration; therefore, it is difficult to draw definitive conclusions about the use of tivantinib in PRCC patients with identified MET mutations [55]. Ultimately, the study was terminated due to increased incidence of interstitial lung disease and projected futility during analysis.

Amuvatinib

Amuvatinib is a TKI that inhibits MET in addition to c-kit, Flt3, AXL, and PDGFR alpha. Initial phase 2 studies were conducted in small cell lung cancer (SCLC) and did not meet clinical primary endpoint, so further clinical development of this agent was discontinued [56, 57].

MONOCLONAL ANTIBODIES TARGETING MET

Rilotumumab

Rilotumumab (AMG 102), a fully human IgG2 mAb directed against HGF, was initially evaluated as a targeted therapy in renal cancers and glioblastomas to inhibit MET-mediated signal transduction leading to apoptosis in c-MET expressing cells [58]. However, studies of the drug were stopped early due to poor outcomes. A phase II study evaluating activity of rilotumumab in mRCC including PRCC showed no ORR [59].

ARGX-111

ARGX-111, is an antagonistic anti-MET antibody that blocks HGF/MET and kills MET-overexpressing cells via antibody-dependent cellular cytotoxicity [58]. The drug competes with HGF for MET binding, inhibits ligand-dependent MET activity, downregulates cell surface expression of MET, decreases HGF-independent MET activity, and engages natural killer cells to kill MET-expressing cancer cells [60]. Phase Ib trials have demonstrated safety in patients with multiple solid tumors, including RCC, NSCLC, GC, pancreatic cancer, and cervical cancer [60–62].

Onartuzumab

Onartuzumab, a MET targeting antibody, elicited responses in patients with MET-amplified NSCLC and gastric cancer in early studies. A later phase III study of onartuzumab plus erlotinib in patients with MET-positive advanced NSCLC did not find an improvement in clinical outcomes. Median OS was 6.8 months for the onartuzumab plus erlotinib arm and 9.1 months for the erlotinib plus placebo arm; therefore, further development of onartuzumab has been halted [63].

LY3164530

LY3164530 is an anti-EGFR/MET bispecific antibody created by fusing a cetuximab variable fragment to an emibetuzumab heavy chain [64]. Phase I trials indicate future development is limited since patients experienced significant toxicities, especially renal toxicity from insoluble metabolites [65]. Additionally, the patients in this study with PRCC experienced progressive disease [64, 65].

JNJ-61186372

JNJ-61186372, is an EGFR/MET antibody with activity against NSCLC based on *in vitro* and *in vivo* studies [66]. Currently, phase I trials are underway and expected to be completed in 2020 [67].

IMMUNE CHECKPOINT INHIBITORS AND COMBINATION WITH MET INHIBITORS

There are recent studies indicating the role of immune checkpoint inhibitors specifically in non-cc RCC. A phase II study of pembrolizumab in non-ccRCC with 72% of participating having PRCC, found an overall ORR of 24.8% and an ORR for PRCC of 25.4% [68]. A recent phase II study evaluating atezolizumab and bevacizumab in participants with non-ccRCC or sarcomatoid variant RCC (sscRCC) with 38.9% of participants having PRCC, found an overall ORR of 31% and an ORR for non-ccRCC of 26% [69]. Stable disease (SD) was seen in 44% in overall population and 50% in non-ccRCC. A study of combination therapy with durvalumab and savolitinib in metastatic PRCC was recently presented and showed an ORR of 27%, SD in 39%, and a PFS of 3.3 months. For MET positive patients, ORR was 20% [70]. There are also other ongoing combination trials for PRCC. One study, MEDI4736 Combinations in Metastatic RCC (CALYPSO), investigates the use of durvalumab, savolitinib, tremelimumab alone or in combination in PRCC (NCT02819596) [71]. Another phase II study, ANZUP1602 (UNISON) looks at sequential treatment of single agent nivolumab followed by nivolumab with ipilimumab if single agent treatment is not effective in PRCC (NCT03177239) (Table 3) [72].

OTHER AGENTS

In addition to the TKIs and mAbs described, several additional MET inhibitors are at an early stage of investigation in pre-clinical studies or are undergoing testing in other malignancies that may have potential role in treatment of PRCC in the near future. Glesatinib, golvatinib, and AMG208 are MET TKIs shown to have activity and tolerability in phase I trials in malignancies other than PRCC [73–80]. Capmatinib is another MET TKI with *in vitro* activity against cells harboring METex14 alterations [81]. Although prior studies have focused on NSCLC, there is a phase II trial of capmatinib in PRCC that is ongoing [82]. There is also several mAbs targeting c-MET that are in early developmental stages have largely been tested in other malignances as well. These agents include emibetuzumab and DN30 [83–91]. SAIT301 is a humanized mAb that promotes MET degradation that has shown activity and tolerability in MET positive patients; however, the study focused mostly on colorectal cancer [92–94]. Another drug under investigation, ABT-700, is a humanized bivalent monoclonal antibody that inhibits MET dimerization and activation with activity in cancer cell lines [91, 95]. In 2017, a phase I study was completed of ABT-700 alone and in combination with docetaxel, 5-fluorouracil, folinic acid, irinotecan and cetuximab (FOLFIRI/cetuximab) or erlotinib in patients with advanced solid tumors, with some patients harboring MET amplification or overexpression [96]. Additionally, a phase I study of telisotuzumab vedotin (Teliso-V), anantibody-drug conjugate of ABT-700 and monomethyl auristatin E, in NSCLC patients who carried a MET alteration found a PFS of 5.7 months in three of 16 patients with c-MET-positive NSCLC [97]. Phase II studies are underway [98].

CONCLUSION

MET is an appealing drug target given its prevalence in PRCC and developing effective MET targeted therapies is needed since outcomes are typically worse for PRCC when treated with conventional therapies. Therapeutic interventions targeted to the MET pathway in PRCC are still under active investigation, such as, MET TKIs and MET-directed antibodies. There is a need for continued research into MET-targeted therapy and more studies to include patients with PRCC. Additionally, recent studies indicate that there may be a role for immune checkpoint inhibitors alone or combination with MET inhibitors in treatment of PRCC. Going forward, PRCC patients may benefit from targeting multiple components of the MET pathway, targeting pathways that are known to interact with the MET pathway, and incorporating immune checkpoint inhibitors.

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CONFLICTS OF INTEREST

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