Review

Molecular Cancer Therapeutics

Cabozantinib in Combination with Immunotherapy for Advanced Renal Cell Carcinoma and Urothelial Carcinoma: Rationale and Clinical Evidence

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Abstract

The treatment landscape for metastatic renal cell carcinoma (mRCC) and urothelial carcinoma (mUC) has evolved rapidly in recent years with the approval of several checkpoint inhibitors. Despite these advances, survival rates for metastatic disease remain poor, and additional strategies will be needed to improve the efficacy of checkpoint inhibitors. Combining anti-VEGF/VEGFR agents with checkpoint inhibitors has emerged as a potential strategy to advance the immunotherapy paradigm, because VEGF inhibitors have immunomodulatory potential. Cabozantinib is a tyrosine kinase inhibitor (TKI) whose targets include MET, AXL, and VEGFR2. Cabozantinib has a unique immunomodulatory profile and has demonstrated clinical efficacy as a monotherapy in mRCC and mUC, making it a potentially suitable partner for checkpoint inhibitor therapy. In this review, we summarize the current status of immunotherapy for mRCC and mUC and discuss the development of immunotherapy–TKI combinations, with a focus on cabozantinib. We discuss the rationale for such combinations based on our growing understanding of the tumor microenvironment, and we review in detail the preclinical and clinical studies supporting their use.

Introduction

According to data from 2008 to 2014, 5-year survival rates are approximately 93% for patients diagnosed with localized renal cancer, and 69% and 93% for patients diagnosed with *in situ* and localized and bladder cancers, respectively. However, these rates drop to 12% and 5%, for those diagnosed with metastatic renal and bladder cancers (1). Observational studies show improvements in renal cell carcinoma (RCC) survival since the arrival of targeted therapies. Nevertheless, 5-year survival for patients with metastatic disease remains poor, particularly for patients with poor prognostic factors (2). Novel therapies are therefore needed to improve outcomes for patients with advanced tumors.

Vascular endothelial growth factor (VEGF)-targeted therapies, including tyrosine kinase inhibitors (TKI), are established treatments for advanced or metastatic RCC (mRCC; ref. 3). Immunotherapy for mRCC has progressed from cytokines to checkpoint inhibitors, which target suppressive immune checkpoints including programmed cell death-1 (PD-1) receptor, programmed cell death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; ref. 4). Until recently, chemotherapy has been the standard of care for advanced or metastatic urothelial carcinoma (mUC). However, the treatment paradigm has evolved rapidly with the approval of several checkpoint inhibitor monotherapies in 2017, which have demonstrated clinically meaningful and durable responses (5, 6).

Despite the benefits of checkpoint inhibitors, there are important limitations to their use as monotherapies. In general, only a subset of patients achieve an objective response, some have a delayed response, and a significant number of patients experience no clinical benefit (7, 8). There are multiple hypotheses around the lack of efficacy with checkpoint inhibitor monotherapy in certain patients. Coexpression of multiple immune checkpoint molecules has been demonstrated in various solid tumors (9), with expression varying between patients and potentially changing upon treatment or progression (10, 11). The genetic makeup of the tumor and the cellular components of the tumor microenvironment influence the number, functionality, and location of immune effector cells and may also have a key role in response to checkpoint inhibitors (12). Therefore, targeting a single checkpoint alone may not lead to an optimal antitumor immune response.

Combinations of checkpoint inhibitor therapies have demonstrated significant improvements in overall survival (OS) compared with checkpoint inhibitor monotherapy in patients with melanoma (13). Prolonged progression-free survival (PFS) relative to chemotherapy was also observed in patients with lung cancer (14). This has encouraged studies of checkpoint inhibitor combinations for RCC and UC. The combination of the PD-1 inhibitor nivolumab with the CTLA-4 inhibitor ipilimumab has demonstrated efficacy in a phase III trial of RCC, and clinical activity has also been observed in UC (15, 16).

Combining anti-VEGF/VEGFR agents with checkpoint inhibitors has emerged as an alternative strategy to advance the immunotherapy paradigm. In addition to their effect on tumor vasculature, VEGF inhibitors have immunomodulatory potential, including the ability to promote infiltration and activation of

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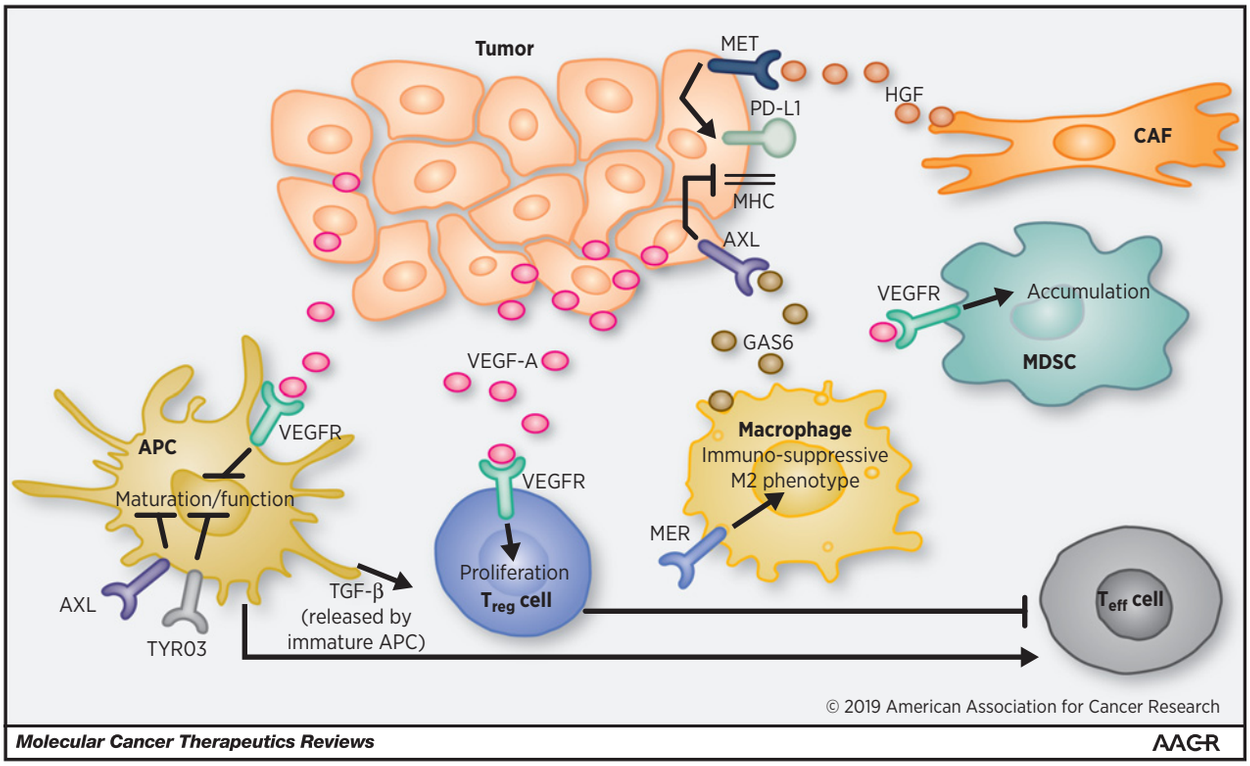

Figure 1.

Immune-modifying behavior of the cabozantinib-targeting receptor tyrosine kinases VEGFR, MET, AXL, MER, and TYRO3. VEGF is released by tumor cells, which increases the number MDSCs and regulatory T cells. VEGF also inhibits the maturation of DCs into mature APCs and reduces lymphocyte infiltration (17, 48). CAFs release HGF, which binds to MET (76), and MET activation drives PD-L1 expression (44). Tumor-associated macrophages release GAS6 which binds to AXL and to a lesser degree, MER and TYRO3 (77). AXL suppresses MHC class 1 expression (59), and both AXL and MER signaling pathways dampen APC function. MER signaling also polarizes macrophages into an immunosuppressive M2 phenotype (62). Abbreviations: APC, antigen-presenting cell; CAF, cancer-associated fibroblast; T_{eff}, effector T cell; Treg, regulatory T cell.

effector cells and inhibit suppressive immune cells (17). Studies are assessing checkpoint inhibitors with several VEGF/VEGFR-targeted therapies. Early studies with nivolumab plus sunitinib and nivolumab plus pazopanib showed clinical activity but were not pursued further owing to excessive hepatic and gastrointestinal toxicity (18). However, alternative combinations are proving to be tolerable and active (19–22).

Cabozantinib, a multitargeting TKI and new standard of care for mRCC, has emerged as a potential partner for checkpoint inhibitor therapy. Cabozantinib has demonstrated significant clinical benefit as a single agent and is approved for use in all patients with mRCC, based on results from the pivotal phase III METEOR study in the second-line setting, and the phase II CABOSUN study in the first-line setting. In METEOR, patients with mRCC had significantly improved PFS, OS, and objective response rate (ORR) when treated with cabozantinib versus everolimus (23). CABOSUN, a randomized phase II trial in intermediate- and poor-risk treatment-naïve patients with mRCC, demonstrated ORR and PFS benefits with cabozantinib over sunitinib (24). Cabozantinib has also demonstrated clinical activity as a single agent in patients with relapsed/refractory mUC (25).

In addition to inhibiting VEGF signaling, cabozantinib targets MET and the TAM family of receptor kinases (TYRO-3, AXL, and MER), which are implicated in tumor growth, metastasis, and therapeutic resistance; MET and AXL are also associated with resistance to VEGF inhibition (26, 27). Targets of cabozantinib also help to promote a tumor-permissive immune environment (Fig. 1). Owing to the unique immunomodulatory and antitumor properties of cabozantinib (28), there is a strong rationale for combining cabozantinib and immune checkpoint inhibitors, and preliminary clinical results of such combinations suggest tolerability and efficacy (19). In this review, we consider the combination of immunotherapy with TKIs in mRCC and mUC, with a focus on cabozantinib.

Current Status of Immunotherapy for RCC and UC

Immunotherapy for RCC

Checkpoint inhibitors are approved in the United States for the treatment of several tumor types. Nivolumab is the only checkpoint inhibitor approved as a monotherapy for the treatment of mRCC, based on the pivotal phase III study CheckMate 025 (8). In CheckMate 025, nivolumab demonstrated a significant OS benefit compared with everolimus in pretreated patients [HR, 0.73; 98.5% confidence interval (CI), 0.57–0.93], and a significant improvement in ORR (25% vs. 5%, $P < 0.001$). However, no PFS benefit was observed; 35% of patients treated with nivolumab experienced progressive disease as best response. For OS,

everolimus was favored for the subgroup of patients ages 75 years or older (8). Atezolizumab (PD-L1 inhibitor) monotherapy was investigated as part of the IMmotion 150 study in treatment-naïve patients with mRCC; however, there was no benefit relative to sunitinib for PFS or ORR, and OS data are pending (22).

Immunotherapy for UC

Five checkpoint inhibitors have been approved in the United States for the treatment of mUC since 2017, including accelerated approval of pembrolizumab (PD-1 inhibitor) and atezolizumab (PD-L1 inhibitor) as first-line treatments for patients ineligible for platinum-based chemotherapy (subsequent to second-line approvals), and avelumab (PD-L1 inhibitor), durvalumab (PD-L1 inhibitor), and nivolumab (PD-1 inhibitor) in the second-line setting, based on phase I/II trials (5, 6). However, preliminary data from two ongoing phase III trials of pembrolizumab and atezolizumab in first-line mUC suggested inferiority of these agents as monotherapy in patients with low PD-L1 expression. These data prompted label updates requiring an FDA-approved test for measurement of PD-L1 expression, and both trials have ceased enrollment of patients with low PD-L1 into the monotherapy treatment arms (29). KEYNOTE-045, the phase III study evaluating pembrolizumab in pretreated patients with advanced UC, reported improved OS and ORR without a PFS benefit compared with chemotherapy; ORR was 21% with pembrolizumab, but almost 50% of patients experienced progressive disease as best response (7). Recent results from the phase III IMvigor211 study showed that atezolizumab failed to reach its primary endpoint of improved OS relative to chemotherapy in pretreated patients with locally advanced or mUC with PD-L1 expression on $\geq$5% of tumor-infiltrating immune cells (30).

Immunotherapy combinations

To improve efficacy, checkpoint inhibitors are being investigated as combination therapies in mRCC and mUC. Recently, the combination of nivolumab and ipilimumab demonstrated a survival benefit compared with sunitinib as first-line therapy for patients with mRCC in the phase III CheckMate 214 study. Patients with intermediate- and poor-risk scores [according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)] were the population of primary clinical interest. These patients had significantly longer OS (HR, 0.63; 99.8% CI, 0.44–0.89) and improved ORR with the combination versus sunitinib (42% vs. 27%, $P < 0.001$), with a modest improvement in PFS (HR, 0.82; 99.1% CI, 0.64–1.05). However, older patients showed less of a survival benefit with the combination, and an exploratory analysis of favorable-risk patients reported inferior outcomes with the combination relative to sunitinib (15). It is worth noting that the IMDC model was developed in patients receiving first-line VEGF-targeting therapies (31); no risk model for RCC has been validated in the first-line immunotherapy setting to date. In mUC, nivolumab is also being combined with CTLA-4 inhibitors. A phase III study (CheckMate 901, NCT03036098) of nivolumab combined with ipilimumab is ongoing, as is a phase III trial of durvalumab in combination with the CTLA-4 inhibitor tremelimumab (DANUBE, NCT02516241).

Safety is a concern with checkpoint inhibitor combinations because toxicity appears greater versus monotherapy (32). Although clinical trials in patients with mRCC and mUC did not compare checkpoint inhibitor combination therapy with monotherapy, high rates of adverse events (AE) were observed with the combination in mRCC patients (data are not yet available for mUC). In Checkmate 214, 22% of mRCC patients in the nivolumab plus ipilimumab arm discontinued owing to toxicity, exceeding the rate of discontinuation with sunitinib (12%) for the same reason. Furthermore, aggressive interventions to manage immune-related AEs were needed for patients receiving the combination—35% required high-dose glucocorticoids (15).

To further develop immunotherapies, it will be important to achieve durable responses in a broad patient population, while mitigating immune-related toxicities. Additional strategies will be needed to improve the efficacy of checkpoint inhibitors through our understanding of the tumor-immune microenvironment. This understanding can help identify new therapeutic targets and provide support for rational combination strategies that overcome barriers to response.

Tumor-Immune Microenvironment: Rationale for Combination Therapy

In the tumor-immune microenvironment, there is a balance between the eradication of cancer cells and prevention of autoimmunity. The immune system can often suppress early tumor growth and development. However, to prevent damage to healthy cells, the immune response shuts down over time, T cells become "exhausted" following prolonged exposure to tumor-associated antigens, and tumor cells escape immune control leading to disease progression (12). Sustained PD-1 expression is a characteristic of tumor-infiltrating lymphocytes (TILs) possessing an exhausted phenotype. PD-1 binding to its ligands PD-L1 and PD-L2 results in a strong immune inhibitory signal, forming the basis for PD-1/PD-L1 checkpoint inhibitor therapy (33). Studies indicate that a variety of factors, in addition to checkpoint molecule expression, determine whether a response to checkpoint inhibitor monotherapy occurs. These factors include tumor and germline genetics and epigenetics, the microbiome, and components of host immunity. Collectively, these factors determine the characteristics of the tumor-immune phenotype, which may be classed as immune-inflamed or noninflamed (immune-excluded or immune-desert; ref. 12).

Clinical responses to PD-1/PD-L1 therapy occur most often in patients with inflamed tumors, characterized by the presence of PD-L1–positive TILs, high mutational burden, and high density of $CD4^+$ and $CD8^+$ T cells within both tumor and stroma. Tumor cells may also express PD-L1, and proinflammatory and effector cytokines may be present. This inflamed profile suggests a preexisting immune response that was arrested. In contrast, tumors with an immune-excluded phenotype contain abundant immune cells in the stroma, but not within the tumor itself. This profile suggests a preexisting immune response that was ineffective owing to a blockade of T-cell infiltration. After checkpoint inhibitor therapy, T cells show evidence of activation but not infiltration, and clinical responses are uncommon; therefore, T-cell infiltration may be the critical response-limiting factor. Tumors with an immune-desert phenotype are characterized by very low numbers of effector T cells and may be more genomically stable. They contain cell types associated with immunosuppression, including regulatory T cells, myeloid-derived suppressor cells (MDSC), and tumor-associated macrophages. This phenotype reflects an absence of preexisting immunity, and such tumors are unlikely to respond to checkpoint inhibitors (12).

Table 1. Immune cell markers in patients with solid tumors and their correlation with improved response to checkpoint inhibitor or TKI therapy

Tumor	Therapy	Immune cell markers associated with improved response to therapy
mRCC (72)	Atezolizumab	• Increased baseline effector T-cell to regulatory T-cell gene expression ratio
mRCC (73)	Nivolumab	• Low baseline inflammatory index defined as platelets × neutrophils/lymphocytes
mRCC (22)	Atezolizumab + Bevacizumab	• High effector T-cell signature gene expression
mRCC (74)	Sunitinib	• High tumor score for T-cell gene expression signatures (including $CD8^+$ T cell, Th1 cell, Th2 cell, T_{reg} cell, and stromal cell)
mRCC (22)	Sunitinib	• High expression of angiogenesis gene signature
mUC (75)	Nivolumab	• High CD8 expression • High CD8 combined with low epithelial–mesenchymal transition-associated gene expression
mUC (64)	Cabozantinib	• Low levels of T_{reg}s at baseline • Changes in T_{reg} PD-1 expression

Abbreviations: Th, T helper cell; T_{reg}, regulatory T cell.

To use checkpoint inhibitors more effectively, it will be necessary to identify which patients are likely to respond, what are the mechanisms of response and resistance, and how can patients with a noninflamed, resistant tumor phenotype be converted to responders. PD-L1 expression on tumor cells and immune cells is a common feature of RCC (8, 15, 22) and UC (7, 30), although its role as a predictive biomarker is unclear. In the CheckMate 214 study of untreated intermediate-/poor-risk mRCC patients, PFS favored the combination of nivolumab plus ipilimumab over sunitinib for patients with $\geq$1% tumor PD-L1 expression and showed no benefit for PD-L1–negative patients. However, OS and ORR favored the combination regardless of PD-L1 status, although the magnitude of benefit was greater for the PD-L1–positive group (15). The CheckMate 025 trial of second-line nivolumab showed a benefit regardless of tumor PD-L1 status and did not support PD-L1 as a marker of response (8). With atezolizumab plus bevacizumab, preliminary analyses from IMmotion 151 showed no evidence that PD-L1 expression on TILs correlated with response (22).

Elements of the genomic landscape contribute to an inflamed tumor microenvironment and may predict response to checkpoint inhibitors. These include defects in DNA damage repair mechanisms and the resulting mutational load and tumor-specific neoepitope expression (12). UC is characterized by a relatively high tumor mutation burden (TMB) compared with other solid tumors (34), and subgroup analyses of the CheckMate 275 and IMvigor 210 studies suggest that high TMB may predict response to checkpoint inhibitors (35, 36). One study also identified an 18-gene expression signature that included components of the IFNγ signaling pathway to predict response to pembrolizumab in patients with several tumor types, including UC (37).

The RCC microenvironment is characterized by a high degree of T-cell infiltration, indicating a strong preexisting immune response (38). A balance of immune cells that promotes antitumor immunity has been associated with a higher response rate to checkpoint inhibitor monotherapy. Predictive baseline immune-related biomarker signatures that include macrophages, dendritic cells (DC), natural killer cells, B cells, and T cells (the latter in the context of MHC class I) have been proposed for RCC, UC, and other solid tumors (Table 1).

Gene expression data from The Cancer Genome Atlas indicate that a considerable proportion of noninflamed tumors exist within RCC and UC (39). It was found that noninflamed tumors constituted 3% (18/525) of clear cell renal carcinomas, 20% (52/257) of renal papillary cell carcinomas, 53% (35/66) of renal chromophobe carcinomas, and 40% (139/344) of urothelial carcinomas (S. Spranger; personal communication). Strategies to induce T-cell infiltration may improve response to checkpoint inhibitor therapy in patients with this noninflamed phenotype. VEGF/VEGFR-targeting agents such as bevacizumab and sunitinib have been shown to increase effector T-cell infiltration and functionality, while decreasing the number and proportion of inhibitory cell subsets such as regulatory T cells and MDSCs (40). Given these immunomodulatory properties of VEGF-targeting TKIs, combining them with checkpoint inhibitors would be expected to promote an effective immune response in previously noninflamed tumors.

The success of checkpoint inhibitor–TKI combination strategies depends on the specific immunomodulatory activity of each inhibitor, as well as intrinsic properties of the tumor-immune microenvironment. Cabozantinib may be a suitable partner for checkpoint inhibitors as it inhibits multiple receptor tyrosine kinases in addition to VEGF [a number of which play a role in immunosuppression (28, 41, 42)] and has demonstrated clinical efficacy as a monotherapy in mRCC and mUC (23–25).

Combining Checkpoint Inhibitors with Cabozantinib: Preclinical Studies

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases including VEGFR, MET, the TAM kinases, KIT, FLT3, TRKB, and TIE2 (43). In addition to their roles in angiogenesis, tumor growth, and metastasis, several targets of cabozantinib play a role in immunosuppression, particularly VEGFR, MET, and the TAM kinases (17, 44–46). Inhibition of these signaling molecules likely contributes to the antitumor immunomodulatory effect of cabozantinib (Fig. 1; refs. 26, 28). Clear cell RCC (ccRCC) is a highly angiogenic tumor owing to prevalent loss of von Hippel–Lindau (VHL) function leading to VEGF overexpression (47). Increased levels of local and circulating VEGF have immunosuppressive effects. VEGF inhibits differentiation of monocytes into DCs and DC maturation and promotes the accumulation and proliferation of immunosuppressive cell types such as MDSCs and regulatory T cells (17, 48). These effects can be reversed by inhibition of the VEGF pathway (48), and this is clinically evidenced by the reduction in regulatory T cells and MDSCs observed in mRCC patients following treatment with bevacizumab or sunitinib (49, 50).

The loss of VHL may partly explain the prominent overexpression of MET in ccRCC (51), via upregulation of the HIF transcription factor (52). MET overexpression is also evident in mUC (53), but is not thought to result from specific genetic alterations. MET signaling promotes tumor cell survival, invasion,

and metastasis, and drives expression of PD-L1 in RCC tumor cells (44). MET is also implicated in immune suppression and is expressed on several immune cell subsets (54, 55). In a mouse melanoma model, checkpoint blockade resulted in MET-dependent recruitment of an immune-suppressive subset of neutrophils that blunted T-cell antitumor activity. This neutrophil-mediated suppression was blocked by MET inhibition with a concomitant increase in tumor response to checkpoint inhibition (54).

The TAM kinases play an important role in maintaining immune homeostasis and are expressed on innate immune cells such as DCs, macrophages, monocytes, and natural killer cells (45, 46). TAM receptor triple-knockout mice develop multi-organ autoimmune disease, reflecting the normal physiologic role of these kinases in limiting immune responses. Tumor expression of TAM kinases has been reported and is associated with resistance to chemotherapy and TKIs (56). Increased expression of TAM kinases has been associated with poor prognosis in mUC and mRCC (57, 58).

AXL is the most widely studied TAM kinase family member, and its expression has been implicated in resistance to checkpoint inhibitors due to T-cell exclusion. In preclinical models, AXL expression on tumor cells suppressed MHC class 1 expression and secretion of myeloid-promoting cytokines, and reduced levels of immune cell infiltrate (59). In patients with melanoma, increased AXL mRNA expression levels correlated with resistance to anti–PD-1 therapy (60). Both AXL and MER may promote an immunosuppressive phenotype in tumor-associated immune cells; for example, AXL activation inhibits the activity of DCs (61), whereas MER activation on tumor-associated macrophages promotes polarization to an M2 immunosuppressive phenotype (62). Perhaps as a consequence, in an MER-knockout mouse tumor model, tumors grew poorly; concentrations of tumor-associated macrophages and $CD8^+$ T cells were increased, along with IL12 cytokine levels (63).

Several studies have highlighted the antitumor immunomodulatory effects of cabozantinib, both indirectly via tumor-associated immune cells and directly via tumor cells. In general, the effects reported are consistent with the target inhibition profile of cabozantinib and the roles of the individual targets on tumor and immune cells discussed above. The net effect of cabozantinib in preclinical tumor models is promotion of a more immune-permissive environment and enhancement of the activity of immune-directed therapies. *In vitro*, treatment of tumor cells with cabozantinib induces MHC class 1 expression, rendering the cells more susceptible to T-cell–mediated killing (28). AXL suppresses antigen presentation through MHC class 1 (59); therefore, it is possible that inhibition of AXL plays a role in this outcome. Cabozantinib also reversed the MET-dependent increase in PD-L1 expression observed in RCC tumor cells treated with the MET ligand hepatocyte growth factor (HGF) (44).

The effects of cabozantinib on immune cells *in vivo* have been studied in several preclinical models. In a murine colon cancer model, cabozantinib increased tumor $CD8^+$ T-cell infiltration and decreased the number of tumor-associated macrophages and MDSCs, effects that were enhanced when cabozantinib was combined with a cancer vaccine (28). In a murine castrate-resistant prostate cancer (CRPC) model, cabozantinib induced tumor clearance that was associated with increased release of neutrophil chemotactic factors from tumor cells, and robust neutrophil infiltration (42). In another CRPC model, cabozantinib reduced the number and activity of MDSCs, impairing their ability to suppress proliferation of effector T cells. Quantities of key cytokines necessary for MDSC recruitment and function, such as CCL5, CCL12, CD40, and HGF, were also reduced. In this model, cabozantinib monotherapy or combined anti–CTLA-4/anti–PD-1 checkpoint inhibitor therapy both had moderate effects on tumor growth. However, cabozantinib synergized with dual checkpoint inhibitor therapy when combined, with profound effects on tumor growth and metastasis (41).

Although limited, available clinical data on the immunomodulatory impact of cabozantinib are consistent with the preclinical data. In a phase I trial of patients with mUC treated with cabozantinib, a reduction in peripheral regulatory T cells was observed (64). In a phase II trial of cabozantinib in patients with triple-negative breast cancer, a sustained increase in $CD8^+$ T cells and a reduction in peripheral MDSCs were reported (65).

Together, these studies demonstrate an impact of cabozantinib on cells of both the adaptive and innate immune system that results in synergistic antitumor immune activation when combined with either checkpoint inhibition or a cancer vaccine. These data provide a rationale for the ongoing clinical trials combining cabozantinib with checkpoint inhibitors discussed below.

Clinical Studies

Checkpoint inhibitors with VEGF-targeting agents in RCC

Numerous clinical studies are investigating VEGF-targeted agents in combination with checkpoint inhibitors in mRCC. Bevacizumab, a VEGF-targeting monoclonal antibody, combined with atezolizumab, has yielded encouraging PFS compared with sunitinib in the phase II IMotion150 study (22), particularly in patients with mRCC who have PD-L1 expression on $\geq$1% of TILs. Based on these findings, the phase III IMmotion151 study evaluated the combination relative to sunitinib in treatment-naïve patients with mRCC. The study met its first primary endpoint; investigator-assessed PFS favored bevacizumab/atezolizumab over sunitinib in patients with PD-L1 $\geq$1% (median PFS 11.2 vs. 7.7 months; HR, 0.74; 95% CI, 0.57–0.96), and the benefit was maintained in the intention-to-treat population. However, PFS assessed by independent review committee (IRC) showed no difference between the treatment arms (median 8.9 vs. 7.2 months; HR, 0.93; 95% CI, 0.72–1.21), and OS data are pending (22).

Axitinib primarily targets VEGFR1–3 and is approved for use in mRCC in the second-line setting. Axitinib has shown efficacy in combination with pembrolizumab or avelumab in treatment-naïve patients with mRCC (20, 21). In the phase III KEYNOTE-426 study, axitinib plus pembrolizumab improved OS (HR, 0.53; 95% CI, 0.38–0.74) and PFS (per IRC; HR, 0.69; 95% CI, 0.57–0.84) relative to sunitinib. The ORR was 59% in the axitinib plus pembrolizumab group and 36% in the sunitinib group. The frequency of grade 3 or higher AEs was similar between treatment arms (76% vs. 71%); in the combination arm, 8% of patients discontinued both axitinib and pembrolizumab due to an AE, and 10% discontinued sunitinib (21). Recent results from the phase III trial (JAVELIN renal 101) of axitinib plus avelumab in treatment-naïve mRCC patients showed longer PFS (per IRC) with the combination relative to sunitinib (20). For patients with PD-L1–positive tumors (expression on $\geq$1% of immune cells), median PFS was 13.8 months in the combination arm and 7.2 months in the sunitinib arm (HR, 0.61; 95% CI, 0.47–0.79),

and ORR was 55% and 26%, respectively. The frequency of grade 3 or higher AEs was similar between treatment arms (71% and 72%), with AEs leading to discontinuation in 8% of the combination arm and 13% of the sunitinib arm. Results for the overall population were similar, and mature OS data are pending. The majority of patients enrolled in this study were classified as intermediate risk (by Memorial Sloan Kettering Cancer Center criteria), which was also the case for the phase III IMmotion151 study of bevacizumab plus atezolizumab (22). As more data from these and other phase III trials of immunotherapy with VEGF-targeting agents emerge, it will be important to determine efficacy across the different risk groups.

Lenvatinib, an inhibitor of VEGFR1–3, FGFR1–4, PDGFRα, KIT, and RET (66), is being partnered with pembrolizumab. In a phase Ib/II trial, ORR was 67% (20/30) for the combination. Median PFS (per IRC) was 18 months (95% CI, 9.6—undefined), and median duration of response was 16.6 months (95% CI, 8.9—undefined). Grade 3/4 AEs were reported in 73% of patients, and discontinuation of lenvatinib and pembrolizumab due to AEs occurred in 20% and 27% of patients, respectively (67).

Checkpoint inhibitors with cabozantinib in RCC and UC

Cabozantinib is being evaluated in combination with a number of checkpoint inhibitors in ongoing trials (Table 2). Encouraging data have been observed in patients with mUC, mRCC, and other genitourinary tumors in a recent phase I study with expansion cohorts (NCT02496208). In patients with previously treated metastatic genitourinary tumors ($N = 78$), including patients who received prior checkpoint inhibitor therapy ($N = 6$), the combination of cabozantinib and nivolumab (CaboNivo) with or without ipilimumab (CaboNivoIpi) was tolerated and active. ORR was 36% (23/64, including 20 partial responses and 3 complete responses) for all evaluable patients, 42% (8/19, including 6 partial responses and 2 complete responses) for the mUC cohort, and 54% (7/13, all partial responses) for the RCC cohort. In the UC cohort, ORR for patients who received CaboNivo was 50% (6/12), compared with 29% (2/7) for CaboNivoIpi. Median PFS was 12.8 months (95% CI, 1.8–undefined) for the UC cohort and 18.4 months (95% CI, 6.4–18.4) for the RCC cohort. Median duration of response was 24.1 months (95% CI, 14.7–undefined); and at the time of data cutoff, 70% of responses were ongoing (19).

Both CaboNivo and CaboNivoIpi demonstrated acceptable toxicity profiles. Approximately 57% and 72% of patients in the CaboNivo and CaboNivoIpi arms, respectively, experienced grade 3/4 AEs. Of these, fatigue (12% and 11%) and hypertension (8% and 17%) were the most common (19). This is consistent with the AE profile of cabozantinib in patients with mRCC. In the METEOR phase III trial, 71% of patients with mRCC receiving cabozantinib experienced grade 3/4 AEs, the most common being hypertension (15%), diarrhea (13%), and fatigue (11%; ref. 23). Tolerability was also consistent with that of nivolumab monotherapy (8). Increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were common in the combination arms, but were predominantly low-grade. In the CaboNivo and CaboNivoIpi treatment arms, 55% and 37% of patients had increased AST; 59% and 41% had increased ALT (any grade). Grade 3/4 immune-related AEs were uncommon (19). CheckMate 9ER, an ongoing phase III study, will now evaluate CaboNivo compared with sunitinib as first-line therapy in mRCC (NCT03141177).

Table 2. Studies investigating cabozantinib–IO combinations in mRCC and mUC

Study	Combinations	Study design	Key efficacy results	Key safety results
NCT02496208 (19)	Cabozantinib + nivolumab, ± ipilimumab	• Phase I (mUC, RCC, and other GU tumors) • $N = 78$ • ± prior therapy	• UC cohort: ORR 42% (8/19), 2 CR, 6 PR; median PFS: 12.8 mo (95% CI, 1.8–UN) • RCC cohort: ORR 54% (7/13), all PR; median PFS 18.4 mo (95% CI, 6.4–18.4) • All patients: Median DOR: 24.1 mo (95% CI, 14.7–UN)	• Acceptable toxicity profile • Most common AEs: fatigue, diarrhea, and skin disorders • Immune-related AEs uncommon
CheckMate 9ER (NCT03141177)	Cabozantinib + nivolumab vs. sunitinib	• Phase III (mRCC) • Treatment-naïve patients • $N = 630$ (estimate)	Fully enrolled; data expected in Q1 2020	
NCT03170960	Cabozantinib + Atezolizumab	• Phase I/II (mUC, mRCC, and others) • $N = 360$ (estimate) • ± prior therapy	Ongoing	
NCT03149822	Cabozantinib + Pembrolizumab	• Phase I/II (mRCC) • $N = 55$ (estimate) • ± prior VEGF therapy	Ongoing	
NCT03200587	Cabozantinib + Avelumab	• Phase I (mRCC) • $N = 20$ (estimate) • Patients who are candidates for CN	Ongoing	

Abbreviations: CN, cytoreductive nephrectomy; CR, complete response; DOR, duration of response; GU, genitourinary; IO, immuno-oncology; PR, partial response; Q1, first quarter; UN, undefined.

An ongoing phase Ib study (NCT03170960) will evaluate safety and efficacy of cabozantinib combined with atezolizumab in patients with solid tumors. Preliminary results of the dose-escalation stage show encouraging antitumor activity in patients with previously treated or treatment-naïve advanced RCC, treated with a standard dose of atezolizumab in combination with 40 or 60 mg cabozantinib (68). The ORR for 12 patients with RCC was 67%, with 80% (8/10) of ccRCC patients achieving a confirmed objective response (1 complete response and 7 partial responses).

Toxicity of the cabozantinib/atezolizumab combination was manageable; no dose-limiting toxicities were reported. Grade 3 AEs were experienced by 92% of patients, the most common being hypertension (42%), diarrhea (17%), and hypophosphatemia (17%). Grade 3 immune-related AEs were reported in 25% of patients; there were no grade 4 or 5 AEs. Toxicity was managed with dose reductions and/or dose holds, and all patients remained on therapy as of data cutoff. Based on these results, the 40 mg cabozantinib dose has been selected for expansion cohorts, and recruitment is ongoing (68). In addition to safety and efficacy outcomes, this study will investigate tumor and plasma biomarkers including tumor PD-L1, MET, and AXL expression, circulating VEGF, and mutational load and immune cell infiltrates. Phase I/II studies are also underway to evaluate cabozantinib with pembrolizumab and cabozantinib with avelumab in patients with mRCC (Table 2).

Summary and Future Directions

As we have outlined, the strategy of combining TKIs with checkpoint inhibitors has a strong biological rationale. It is possible that patients with immunotherapy-resistant, noninflamed tumors may be susceptible to TKI–checkpoint inhibitor combinations; the immunomodulatory properties of agents such as cabozantinib may induce an inflamed phenotype, rendering these tumors more responsive to checkpoint inhibitors. Although strategies of dual checkpoint inhibition are emerging, existing regimens (e.g., nivolumab/ipilimumab) are hampered by toxicity issues—severe immune-related AEs are more common with these approaches and may warrant extended use of high-dose steroids (15). Furthermore, combinations of checkpoint inhibitors with novel immunotherapy agents (e.g., pembrolizumab with the IDO inhibitor epacadostat) have thus far failed to improve on response rates achieved with monotherapy (69).

In addition to enhancing efficacy, combinations of TKIs with checkpoint inhibitors may mitigate concerns over immune-related AEs associated with dual checkpoint inhibition, given their largely nonoverlapping toxicity profiles. Any potentially overlapping toxicities, such as diarrhea and transaminitis, should be distinguishable by their time course of onset (rapid for targeted therapy and delayed for immunotherapy). In this manner, appropriate supportive care measures can be employed, and dose intensity can be preserved.

Various immune-cell markers have been proposed as biomarkers of improved response to TKIs or immunotherapies (Table 1), although it is unclear whether these will translate to combination therapies. Genetic markers of response are also under investigation; a composite genetic biomarker signature including TP53 mutation, wild-type VHL, and FLT1 C/C variant was recently found to correlate with response to first-line VEGF therapy in mRCC (70). MET expression correlates with poor prognosis (71), and may correlate with response to cabozantinib (24). Circulating plasma markers offer the benefit of noninvasive testing. Circulating VEGF-A and acute-phase proteins have been suggested as on-treatment markers of response to atezolizumab in mRCC (72). The role of PD-L1 as a predictive biomarker in mRCC and mUC is unclear; cross-study comparisons are confounded by differences in testing platforms and cutoff values for positivity. Further studies will be needed to define the predictive value of PD-L1 expression on tumor cells versus TILs. Because PD-L1 expression is one of several characteristics of an inflamed tumor, it is possible that composite biomarker signatures which identify an inflamed versus noninflamed tumor microenvironment may identify patients likely to respond to checkpoint inhibitor monotherapy, and those likely to benefit from additional targeted therapy.

There are limited data regarding biomarkers with combined TKI and checkpoint inhibitor therapy. Exploratory analyses of the phase II IMmotion 150 trial showed that RCC patients with a high effector T-cell gene expression signature had an improved response to atezolizumab plus bevacizumab, relative to patients with a low effector T-cell expression score. Patients with this high effector T-cell signature also had a higher response rate to the combination treatment relative to sunitinib (22). Ongoing biomarker studies may provide additional insight (e.g., exploratory endpoints of the phase I study with cabozantinib plus atezolizumab; NCT03170960). Neoadjuvant trials are also emerging, exploring regimens such as axitinib with avelumab (NCT03341845). Studies such as these may provide an opportunity to correlate changes in the tumor and microenvironment with response.

Conclusions

An increasing body of preclinical and clinical evidence supports the immunomodulatory role of VEGFR-targeted therapies which may synergistically enhance the activity of checkpoint inhibitors when administered concurrently. Additional targets of cabozantinib are implicated in VEGF pathway inhibitor resistance and immunosuppression, thereby differentiating cabozantinib from other VEGF-targeting agents and providing a strong rationale for partnering cabozantinib with checkpoint inhibitors. Early clinical evidence shows that this combination is active in mRCC and mUC, with durable responses and acceptable tolerability. Ongoing clinical studies will evaluate cabozantinib in combination with nivolumab, as well as atezolizumab, pembrolizumab, and avelumab in mUC and mRCC.

Disclosure of Potential Conflicts of Interest

P. Lamb and E. Wang are employees of Exelixis, Inc. S. Pal has received honoraria from Astellas Pharma, Medivation, and Novartis; and fees for a consulting or advisory role from Aveo, Bristol-Myers Squibb, Exelixis, Genentech, Myriad Pharmaceuticals, Novartis, and Pfizer. P. Bergerot has nothing to disclose.

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