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REVIEW

A Profile of Avelumab Plus Axitinib in the Treatment of Renal Cell Carcinoma

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Abstract: Until recently, the approved first-line treatment for metastatic RCC (mRCC) consisted of tyrosine kinase inhibitors (TKI) targeting the vascular endothelial growth factor receptors (VEGFR) monotherapy. The landscape of first-line treatment has been transformed in the last few years with the advent of immune checkpoint inhibitors (ICI) or VEGFR TKI plus ICI combinations. This article focuses on the profile of one of these ICI plus VEGFR TKI combination, avelumab plus axitinib. We detail the characteristics of each drug separately, and then we explore the rationale for their association, its efficacy and the resulting toxicity. Finally, we examine the factors associated with avelumab plus axitinib outcomes, and their impact on therapeutic strategy.

Keywords: renal cell carcinoma, vascular endothelial growth factor, immune checkpoint inhibitor, axitinib, avelumab, pharmacology

Introduction

Renal cell carcinoma (RCC) is a frequent cancer representing 5% of the estimated new cases of cancer in males and 3% of the estimated new cases of cancer in females and is estimated to be responsible for 13,920 deaths in 2022 in the United States (US).[1] When diagnosed at a local stage, RCC can be treated with curative intent surgery. When diagnosed at an advanced or metastatic stage, active surveillance can be an option in the case of indolent growth of metastases, but disease will eventually progress in most cases requiring systemic therapy.[2,3] Until recently, the approved first-line treatment for metastatic RCC (mRCC) consisted of tyrosine kinase inhibitors (TKI) targeting the vascular endothelial growth factor receptors (VEGFR)[4,5] but the landscape of first-line treatment has been transformed in the last few years with the advent of immune checkpoint inhibitors (ICI) or VEGFR TKI plus ICI combinations.[6–10] This article focuses on one of these associations, avelumab plus axitinib, detailing each drug separately, then exploring the rationale for their association, its efficacy and the resulting toxicity, and finally examining the factors associated with avelumab plus axitinib outcomes and their impact on therapeutic strategy.

Axitinib

We previously reviewed the design, development, and place in therapy of axitinib monotherapy in the treatment of renal cell carcinoma,[11] but some aspects must be emphasized in the context of its association with ICI.

Pharmacodynamics

Axitinib (Inlyta®, Pfizer) is an indazole derivative produced by chemical synthesis, whose molecular weight is 386,47 Da. It is an oral second-generation TKI with an inhibitory concentration for the VEGF family receptors 10-fold lower than other TKI, but contrary to multiple TKIs, axitinib is weakly active in other receptors like KIT or PDGFR. Axitinib is therefore a potent and selective VEGFR inhibitor.[12]

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Pharmacokinetics

Orally taken, axitinib is rapidly absorbed and achieves maximal plasma concentration after 4 hours. There is no clinically significant difference between the fasted and fed states,[13] with a mean bioavailability of 58%.[14] Axitinib absorption is pH-dependent, with higher absorption at acidic pH, but anti-acid agents have a limited impact on axitinib area under the curve and therefore are not contraindicated during axitinib treatment. At therapeutic dose axitinib has a high protein-binding rate exceeding 99%, and preferentially binds to albumin. Particular attention must therefore be paid to patient with hypoalbuminemia. At steady state, axitinib pharmacokinetic is approximately linear over a dosing range of 1 to 20 mg.[15] Axitinib is mainly metabolized in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, 2C19 and UGT1A1, producing pharmacologically inactive metabolites. Attention should therefore be paid when axitinib is prescribed with known CYP3A4/5 inducer or inhibitor. However, axitinib is not considered as a cytochrome inducer or inhibitor but is a substrate for the efflux transporter P-glycoprotein (P-gp) and for the hepatic organic anion-transporting polypeptides (OATP1B1). Axitinib has been shown to inhibit the efflux transporter P-gp in vitro but not at therapeutic plasma concentration. Axitinib is mainly eliminated in feces due to hepatobiliary excretion, whereas axitinib renal excretion accounts for less than 20%. Unchanged axitinib is detected only in feces and not in urine.[16] A significant increase in axitinib plasma concentration has been observed in patients with moderate hepatic impairment (Child-Pugh B), but not for mild impairment (Child-Pugh A). Axitinib elimination remains constant during chronic dosing, without argument for auto-induction or auto-inhibition.[15] Axitinib half-life is shorter than other TKI and varies from 2.5 to 6.1 hours, justifying its twice daily schedule of prescription. Due to this short half-life, a steady state is expected in less than 3 days, and the plasma concentration quickly decreases after treatment interruption. Axitinib, as most TKI, shows an important pharmacokinetic variability. Inter-individual variability for AUC at the 5 mg bid standard dose is estimated around 80%. This inter-individual variability is quite the same after intravenous or oral administration, suggesting a greater role of metabolism than absorption.[15] Intra-individual variability is estimated around 20–22%.[14]

Pharmacokinetics-Pharmacodynamics Analysis (PK/PD)

An increase in blood pressure (BP) is a common on-target effect of VEGFR-TKIs. Thus, diastolic BP (dBP) as a biomarker of axitinib efficacy in solid tumors was investigated and increased dBP > 90 mm Hg was associated with axitinib efficacy.[17] A PK-PD model was later developed, showing that dBP increased with increasing drug exposure.[18] This relationship was not proportional, suggesting that an increase in dBP was not entirely explained by axitinib exposure, and thus that dBP should not be used exclusively to guide axitinib dosing. In a retrospective study, higher exposure and dBP were independently associated with longer PFS and overall survival (OS) and higher probability of partial response.[19] Another analysis reported that patients receiving axitinib dose titration for mRCC had an increased axitinib exposure and a significantly higher objective response rate (ORR) than those with placebo titration (54% versus 34%; $P = 0.019$).[20] Another study demonstrated that axitinib exposure could be increased with individual dose titration, leading to a greater response rate.[21] However, there was no improvement in PFS when axitinib plasma exposure increased, possibly due to toxicity from titration and the necessity of dose reduction after initial dose titration.

Axitinib Monotherapy Prescription

Axitinib is available as 1, 3, 5 and 7 mg coated tablets. The recommended starting dose is 5 mg twice daily administered with continuous daily dosing. Dose adjustments are recommended based on individual tolerability. For patients with good tolerance after two weeks (no adverse event > grade 2, and no increase in BP > 150/90 mm Hg or introduction of antihypertensive treatment), the dose should be increased to 7 mg twice daily. With the same criteria, a good tolerance of axitinib 7 mg bid may lead to an increase in the dose to 10 mg twice daily. Conversely, adverse reaction could require treatment interruption and reintroduction after dose reduction. No dose adjustment is recommended based on race,[22] gender, weight,[15] renal function[23] or drug-metabolizing enzymes genotype.[24] Axitinib clearance decreases modestly in subjects older than 60 years but these changes are not considered clinically significant and no dose adjustment is recommended according to age.[15] No association has been identified between genetic polymorphisms in drug-metabolizing enzymes or transporters and axitinib pharmacokinetic variability.[24] As it has been described with the use of other VEGFR-TKI in mRCC patients, sarcopenia associated with a body mass index of less than 25 $kg.m^{-2}$ could help

identify patients at high risk of severe toxicity for whom particular attention may be needed at treatment initiation.[25,26] For patients with moderate hepatic impairment (Child-Pugh B), a two-fold higher axitinib exposure has been observed. A decrease of half the dose is recommended for these patients.[27] Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are not unusual in mRCC patients because of comorbidities and previous local treatments. However, there are few available data regarding the use of axitinib in patients with renal insufficiency, especially for patients with creatinine clearance of <15 mL/min. A population pharmacokinetic model found no difference according to basal renal function, in favor of no dose adjustment in patients with renal impairment.[23]

Drug Interaction

Acids suppressing agents have a slight effect on axitinib overall exposure and thus are not contraindicated during axitinib treatment.[16] CYP3A4/5 inhibitors[28] may increase axitinib plasma concentration[29] resulting in clinically significant effects.[30,31] If an alternative treatment is not possible, a dose decrease of axitinib is recommended (approximately half the dose). CYP3A4/5 inducers[28] may decrease axitinib exposure.[32] When CYP3A4/5 inducer cannot be discontinued, axitinib dose should be increased progressively with enhanced toxicity and therapeutic drug monitoring.

Clinical Development and Place in Therapy

Axitinib was approved by both American and European Agencies in 2012 for the treatment of advanced RCC after failure of one prior systemic therapy.[33] Table 1 summarizes the randomized Phase III clinical trials of axitinib alone or in combination with ICI in mRCC. The demonstration of clinical benefit for axitinib was based on a Phase III, randomized, open-label, multicenter study of axitinib compared with sorafenib in patients with advanced RCC after failure of a prior systemic first-line regimen.[34] In this study, 723 patients were assigned to receive axitinib (n = 361) or sorafenib (n = 362). The median PFS was 6.7 months with axitinib compared to 4.7 months with sorafenib (hazard ratio (HR) 0.665; 95% confidence interval (CI) 0.544–0.812; one-sided p < 0·0001). However, the updated median OS was 20.1 months (95% CI 16.7–23.4) with axitinib and 19.2 months (17.5–22.3) with sorafenib (HR 0.969, 95% CI 0.800–1.174; one-sided p = 0.3744). Importantly, axitinib dose increase to 7 mg and then to 10 mg, twice daily, was allowed for patients without hypertension or adverse reactions above grade 2 but dose increase was not allowed for patients receiving sorafenib. This difference could explain the difference in efficacy between axitinib and sorafenib.[35]

Table 1 Randomized Phase III Trials of Avelumab and/or Axitinib in Renal Cell Carcinoma

Clinical Trials Number	Purpose	Patients Included	Results	Year First Publicated
NCT00678392	Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma (AXIS)	723	Axitinib resulted in significantly longer progression-free survival compared with sorafenib.	2011
NCT00920816	Axitinib versus sorafenib as first-line therapy for advanced renal-cell carcinoma	288	Axitinib did not significantly increase progression-free survival compared to sorafenib.	2013
NCT01599754	Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma (ATLAS)	724	The trial was stopped due to futility. There was no significant difference in disease-free survival.	2018
NCT02684006	Avelumab plus axitinib versus sunitinib in advanced renal cell carcinoma (Javelin Renal 101)	886	Treatment with avelumab plus axitinib resulted in a statistically significant improvement in progression-free survival versus sunitinib.	2019
NCT02853331	Pembrolizumab plus axitinib versus sunitinib in advanced renal cell carcinoma (KEYNOTE-426)	861	Treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate, than treatment with sunitinib.	2019

Plasma monitoring can help identify disease progression linked to sorafenib underexposure and lead to dose optimization to restore efficacy.[36–39] Therefore sorafenib with plasma monitoring[40] may represent an alternative to axitinib.

Avelumab

Pharmacodynamics

Avelumab (Bavencio®, Merck) is a fully human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors removing the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells, resulting in the restoration of anti-tumor T-cell responses. Avelumab has also been shown to induce natural killer (NK) cell-mediated direct tumor cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC).[41]

Pharmacokinetics

Avelumab is expected to be distributed in the systemic circulation and to a lesser extent in the extracellular space. Consistent with a limited extravascular distribution, the volume of distribution of avelumab at steady state is small. As expected for an antibody, avelumab does not bind to plasma proteins in a specific manner.[41]

Steady-state concentrations of avelumab were reached after approximately 4 to 6 weeks of repeated dosing at 10 mg/kg every 2 weeks, and systemic accumulation was approximately 1.25-fold. The elimination half-life at the recommended dose is 6.1 days based on the population PK analysis.[41]

The exposure of avelumab increased dose-proportionally in the dose range from 10 mg/kg to 20 mg/kg every 2 weeks. The avelumab dose of 10 mg/kg every 2 weeks was selected based on adequate safety and tolerability, as well as PK and target occupancy data.[42] No maximal tolerated dose was reached with doses up to 20 mg/kg. The mean target occupancy was 90% or higher at doses of 3 and 10 mg/kg. However, several patients treated at 3 mg/kg (but none treated at 10 mg/kg) had trough levels below 1 μg/mL, which in vitro studies suggested was the serum level required to ensure 90% target occupancy.[43] Population PK, exposure-efficacy, and exposure-safety models and simulations in Merckel cell carcinoma and urothelial carcinoma[44,45] patient populations provided the basis for the subsequent approval of an avelumab 800-mg flat dose every two weeks.

A population PK analysis suggested no difference in the total systemic clearance of avelumab based on age, gender, race, PD-L1 status, tumour burden, renal impairment and mild or moderate hepatic impairment.[41]

Pharmacokinetics-Pharmacodynamics Analysis

Logistic regression analysis of data from 88 patients with Merkel cell carcinoma treated with avelumab 10 mg/kg every 2 weeks identified an apparent relationship between trough concentration at steady state and best objective response, with higher exposure associated with improved response contrasting with findings concerning other PD-(L)1 inhibitors.[43] Concerning exposure–safety relationship there was a weak association between increased exposure and increased incidence of immune-related adverse events, but none with the risk of treatment emergent adverse events or infusion-related reactions.[43]

Avelumab Prescription

Avelumab was developed with infusions of 10 mg/kg every two weeks but was later modified to a flat dose of 800 mg infusions every two weeks.

No clinically important difference in the clearance of avelumab was found between patients with mild (glomerular filtration rate (GFR) 60 to 89 mL/min, Cockcroft-Gault Creatinine Clearance (CrCL); n = 623), moderate (GFR 30 to 59 mL/min, n = 320) and patients with normal (GFR ≥ 90 mL/min, n = 671) renal function.[41]

No clinically important difference in the clearance of avelumab was found between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin between 1 and 1.5 times ULN, n = 217) and normal hepatic function (bilirubin and AST ≤ ULN, n = 1388) in a population PK analysis.[41]

Drug Interaction

No formal drug–drug interaction studies were conducted for avelumab. However, because monoclonal antibodies are large molecules that are not commonly metabolized by CYP450 enzymes, the potential for co-administered small-molecule drugs (most of which are metabolized by CYP450) to alter the exposure of monoclonal antibodies by the route of metabolism and transport is low.[43] In particular, avelumab did not induce cytokines in humans at concentrations needed to affect either transporters involved in the distribution or CYP450 metabolism of small-molecule drugs.[43]

Complementary Mechanisms of Action of Immune Checkpoint Inhibitors and Vascular Endothelial Growth Factor Pathway Inhibitors

The combination of ICI plus VEGFR inhibitor is a new first-line option for patients with advanced RCC.[46] This combination downregulates two major hallmarks of cancer: avoiding immune destruction and inducing angiogenesis.[47] The rationale for this combination relies on the interplay between the immune and angiogenic systems (Figure 1). Avelumab plus axitinib could have a synergistic effect similar to the other ICI plus VEGFR inhibitor combinations. Avelumab inhibits interactions between PD-L1 and programmed cell death protein (PD-1), leading to immunosuppression signal elimination and the restoration of anti-tumor T-cell functions in the tumor microenvironment. It is important to note that avelumab could also mediate antibody-dependent cell-mediated cytotoxicity (ADCC) lysis of tumor cells, which could be an additional method of action compared to other anti-PD-(L)1 antibody.[42,48] Axitinib was selected for the association with avelumab because of a lower incidence of hepatic toxic effects compared to other VEGFR inhibitors previously tested.[49] The hypothesis of synergy over additive effects is based on two main concepts: the immunomodulatory roles of VEGF pathway inhibitors and the vascular-remodeling of immunotherapy.

VEGF pathway inhibitors regulate immune cells and their interaction with tumor microenvironment in two different ways: direct effects on immune cells and indirect effects through endothelial cells and hypoxia. Proangiogenic factors such as VEGF-A can have direct immunosuppressive effects on innate and adaptative immune cells. VEGF-A/VEGFR-1 and VEGF-A/VEGFR-2 signaling downregulate dendritic cells maturation and differentiation, respectively.[50] Mature dendritic cells play a critical role for the antigenic presentation and the induction of anti-tumor T-cell functions. Proangiogenic factors recruit tumor-associated macrophages, which can contribute to tumor immunosuppression.[51] VEGF signaling also impacts adaptative immune cells, such as anti-tumor effector T cells and pro-tumor regulatory T cells. VEGF-A reduces proliferation and function and promotes exhaustion of anti-tumor effector T cells.[52,53] Conversely, VEGF-A can favor regulatory T cells tumor infiltration and accumulation.[54] VEGF pathway inhibitors, including axitinib, could reverse direct immunosuppressive effects of VEGF. VEGF pathway inhibitors reduce tumor immunosuppressive cells, such as myeloid-derived suppressor cells (MDSC) and regulatory T cells and promote mature dendritic cells and effector T cells.[55] Some studies focused particularly on axitinib effects. In murine RCC xenografts model, axitinib treatment decreases MDSC in the spleens and tumor beds of animals and promotes anti-tumor CD8+

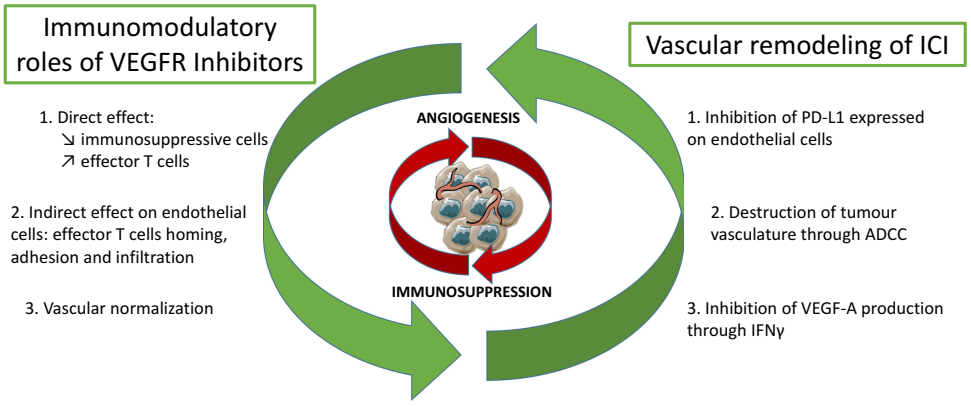

Figure 1 Complementary mechanisms of action of immune checkpoint inhibitors and Vascular endothelial growth factor pathway inhibitors.
Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; ICI, Immune checkpoint inhibitor; VEGFR, Vascular endothelial growth factor receptor.

T-cell functions.[56] Axitinib treatment also promotes natural killer cell recognition and degranulation in RCC cell lines model.[57] Natural killer cells play an important role in anti-tumor innate response and their degranulation triggers tumor cells destruction. In murine models, axitinib treatment reduces the number of immune-suppressive cells such as tumor-associated macrophages and improves T cell response.[58] VEGF pathway inhibitors also reverse immunosuppressive tumor microenvironment through an indirect effect on endothelial cells. VEGF pathway inhibitors can increase anti-tumor effector lymphocytes infiltration through normalization of vascularization.[59]

Tumor angiogenesis favors immunosuppression through tumor endothelial cells and hypoxia. Proangiogenic factors affect several steps involved in tumor infiltration by circulating immune cells: homing of cells, adhesion to endothelium, and extravasation through endothelial intercellular junctions.[55] For example, VEGF-A in association with interleukin 10 and prostaglandin E2 induces Fas ligand expression on endothelial cells, which acquire the capacity to kill effector lymphocytes T cells, but not regulatory T cells.[60] Anarchic proliferation of abnormal tumor vessel can lead to hypoxic areas creation and disrupted immune cell infiltration. Hypoxia promotes pro-tumor macrophages, which exhibit proangiogenic activity and could suppress effector lymphocytes T cells proliferation.[61] Tumor hypoxia also promotes the recruitment of regulatory T cell via the expression of the chemokine CC-chemokine ligand 28.[62] VEGF pathway inhibitors could modulate tumor immunosuppression mediated by indirect effects through endothelial cells and hypoxia. Sunitinib, a VEGFR TKI such as axitinib, increases anti-tumor lymphocytes T cells infiltration through endothelial activation and up-regulation of T lymphocyte-attracting chemokines, CXCL10 and CXCL11.[63] Normalization of tumor vasculature related to VEGF pathway inhibitor effects can also promote immune-cell infiltration into tumors, but more studies should be conducted to determine the optimal window of tumor vascular normalization.[63] Indeed, VEGF pathway inhibitors can also damage tumor vessel and reduce immune cells and therapeutics infiltration in some cases. The dosing of antiangiogenic seems particularly important for the tumor vascular normalization and immune cells infiltration. For example, lower doses of anti-VEGFR2 antibody seems superior to the high doses in polarizing tumor macrophage from pro- toward anti-tumor phenotype and promoting infiltration of effector T cells.[64] Overall, VEGF pathway inhibitors, including axitinib, help to reverse the immunosuppressive tumor microenvironment, increase antitumor immunity and are thus good candidates for combination with ICI.

ICI efficacy relies mainly on the restoration of anti-tumor T-cell functions in the tumor microenvironment, but more and more studies show that immunotherapy might also improve the efficacy of VEGF pathway inhibitors through changes to the tumor vasculature. Interferon-γ activated endothelial cells can inhibit lymphocytes T cells activation via the expression of immune checkpoint molecules, such as PD-L1 or PD-L2.[65] Treatment with anti-PDL-1 inhibits immune checkpoint expressed on endothelial cell and promotes lymphocytes T cells activation but could also directly destroy tumor vasculature through ADCC, particularly in the case of avelumab.[48] Effector T cells activated by ICI secrete interferon-γ which has direct and indirect anti-vascular effects. Interferon-γ inhibits the expression of delta-like protein 4 on endothelial cells, which is necessary to Notch signaling and tumor angiogenesis.[66] Furthermore, interferon-γ down-regulates the mRNA of VEGF-A production.[66] Overall, synergy of ICI plus VEGF pathway inhibitor combination could be based on an immunostimulatory vascular-modulating cycle.[67] An important study illustrated this mutual regulation and showed an impact of vascular normalization disruption on effector T lymphocytes infiltration and an impact of T lymphocytes depletion on vascular normalization in tumor microenvironment.[68] Avelumab plus axitinib falls within the framework of this win–win relation.

Avelumab Plus Axitinib Combination in mRCC: The JAVELIN 101 Trial

In the phase III trial comparing avelumab plus axitinib to sunitinib in 886 advanced, treatment naïve, RCC patients, after a minimum follow-up of 13 months, PFS was significantly longer in the avelumab plus axitinib arm than in the sunitinib arm (PD-L1+ population: hazard ratio (HR) 0.62 [95% confidence interval (CI) 0.490–0.777]; one-sided $P < 0.0001$; median 13.8 (95% CI 10.1–20.7) versus 7.0 months (95% CI 5.7–9.6); overall population: HR 0.69 (95% CI 0.574–0.825); one-sided $P < 0.0001$; median 13.3 (95% CI 11.1–15.3) versus 8.0 months (95% CI 6.7–9.8)) but no overall survival benefit was demonstrated at the last data cut off, possibly reflecting immature data.[10,69] In this phase III trial, avelumab 10 mg/kg was administered in combination with axitinib 5 mg and the respective exposures of avelumab and axitinib were unchanged compared to the single agents. There was no evidence to suggest a clinically relevant change in

avelumab clearance over time in patients with advanced RCC.[41] Furthermore, analyses using PK and E-R modeling and simulation provide support for the labeling of an 800-mg flat dose of avelumab in combination with axitinib in patients with treatment-naive RCC.[70] In the setting of the treatment combination, no titration of axitinib is recommended in the current label.

These results lead to the approval of axitinib plus avelumab by the FDA in the US. However, in the absence of a demonstrated benefit to overall survival, the combination is not currently recommended in the main international guidelines. Its place is all the more compromised as such approval was also obtained for the alternative combinations that were all compared to sunitinib: ipilimumab plus nivolumab, pembrolizumab plus axitinib, pembrolizumab plus lenvatinib and nivolumab plus cabozantinib (Table 2). To date, only indirect comparison in meta-analyses exists between the different treatment combinations.[71–73] These meta-analyses, which vary in their methodology, tend to report better efficacy outcomes with nivolumab plus cabozantinib or pembrolizumab plus lenvatinib. Ipilimumab plus nivolumab is consistently associated with the highest likelihood of complete responses. Finally, in one of these reports, avelumab plus axitinib had the highest likelihood of an OS benefit for patients with favorable risk of advanced RCC.[71]

Toxicity Profile of Avelumab Axitinib Combination

The frequency and severity of adverse events observed with the combination of avelumab plus axitinib seem consistent with the known safety profiles of avelumab and axitinib when used as monotherapy.

Table 2 Randomized Phase III Trials of First-Line Immune Checkpoint Inhibitors and Vascular Endothelial Growth Factor Inhibitors Combinations in Advanced Renal Cell Carcinoma

Clinical Trials Number	Purpose	Patients Included	Results	Year First Publicated
NCT02231749	Nivolumab plus Ipilimumab versus sunitinib in patients with previously untreated advanced renal-cell carcinoma (CheckMate 214)	1096	Overall survival and objective response rates were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients.	2018
NCT02420821	Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated advanced renal-cell carcinoma (IMmotion151)	915	Atezolizumab plus bevacizumab prolonged progression-free survival versus sunitinib, although no improvement in overall survival was observed with atezolizumab plus bevacizumab at the final analysis.	2019
NCT02684006	Avelumab plus axitinib versus sunitinib in patients with previously untreated advanced renal-cell carcinoma (Javelin Renal 101)	886	Treatment with avelumab plus axitinib resulted in a statistically significant improvement in progression-free survival versus sunitinib.	2019
NCT02853331	Pembrolizumab plus axitinib versus sunitinib in patients with previously untreated advanced renal-cell carcinoma (KEYNOTE-426)	861	Treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate, than treatment with sunitinib.	2019
NCT03141177	Nivolumab plus cabozantinib versus sunitinib in patients with previously untreated advanced renal-cell carcinoma (CheckMate 9ER)	651	Nivolumab plus cabozantinib had significant benefits over sunitinib with respect to progression-free survival, overall survival, and likelihood of response.	2021
NCT02811861	Lenvatinib plus pembrolizumab or everolimus in patients with previously untreated advanced renal-cell carcinoma (CLEAR)	1069	Lenvatinib plus pembrolizumab was associated with significantly longer progression-free survival and overall survival than sunitinib.	2021

Avelumab and Axitinib Monotherapy Safety Profile

Avelumab is generally well tolerated and demonstrates a manageable safety profile in a large population of patients with advanced solid tumors. Among 1738 patients in the phase IB Javelin solid tumor trial,[74] the incidence of grade 3 treatment related adverse events (TRAEs) or immune related adverse events (IRAEs) of any grade was low. The most common TRAEs reported with avelumab monotherapy were fatigue, pruritus, nausea, diarrhea, and increased serum biomarkers. Infusion-related reactions (IRRs) and related symptoms occurred in 439 patients (25.3%) and mostly at first infusion. IRAEs occurred mainly during the first 2 infusions and were generally of low grade, easily manageable, and reversible. Most common were thyroid disorders and immune-related rashes.[75] Treatment discontinuation was rarely required. This is consistent with TRAEs reported in other trials of anti–PD-L1/PD-1 antibodies, although avelumab might appear with most favorable safety profile according to some meta-analyses.[76,77] It has been suggested that this might be linked to avelumab shorter half-life, its ADCC activity or its specificity towards PD-L1, leaving PD-L2/PD-1 interaction free.[77–79] Axitinib-related toxicity is globally similar to that reported with other VEGFR inhibitors. Dose limiting toxicities occurring in first in human study of axitinib were hypertension and stomatitis.[16] In Phase 3 trials, the most common grade 3 TRAES reported with axitinib were hypertension, diarrhea, decreased appetite, dysphonia and hypothyroidism.[19,80,81] These have been reported with other VEGFR inhibitors, but other AEs often reported with currently approved VEGFR inhibitors are less commonly seen with axitinib: palmar-plantar erythrodysesthesia (PPE) syndrome, cutaneous toxicities, and myelosuppression. This might constitute a potential advantage of using more specific VEGFR inhibitors.

Toxicity Profile of Avelumab Plus Axitinib Combination

The combination of avelumab plus axitinib was initially evaluated in the phase Ib JAVELIN Renal 100 trial.[82] In the dose-finding stage, patients received axitinib monotherapy twice daily for 1 week, followed by intravenous avelumab every 2 weeks plus axitinib twice daily. Only grade 3 proteinuria was dose-limiting. The maximum tolerated dose was defined as avelumab 10 mg/kg every 2 weeks and axitinib 5 mg twice daily. In the dose-expansion stage, 58% of grade 3–5 treatment-related adverse events were reported, the most frequent being hypertension, increased alanine aminotransferase, amylase, and lipase, and PPE syndrome. In the phase 3 JAVELIN 101 study,[10] TRAEs occurred in 95.4% of patients who received avelumab plus axitinib versus 96.4% receiving sunitinib. Adverse events of grade 3 or higher occurred in 309 patients (56.7%) in the combination group versus 314 patients (55.4%) in the sunitinib group. Overall, 183 (42.2%) had at least one dose reduction of axitinib in the combination group compared to 187 (42.6%) in the sunitinib group. TRAEs leading to discontinuation of both avelumab and axitinib occurred in 33 patients (7.6%), which was lower than in the sunitinib group (13.4%). In both groups, the most frequent TRAEs were diarrhea, hypertension, PPE syndrome, and alanine aminotransferase increase. Adverse events categorized as IRAEs occurred in 166 out of 434 patients (38.2%), 9% of which were grade 3 or higher. The most frequent was immune-related thyroid disorders (24.7%). High-dose glucocorticoids were administered to 48 patients (11.1%). The JAVELIN 101 safety results were consistent with those of other phase 3 studies comparing TKI plus ICI combination strategies to sunitinib, in which TRAEs were similar between the study arms for all grade adverse events, grade 3 TRAEs being hypertension, diarrhea, PPE syndrome and ALT increase.[7–9]

Toxicity Management, a New Issue: Managing Overlapping Toxicities

A particular concern when combining VEGFR TKI plus ICI is overlapping toxicities. As with other approved combinations of VEGFR inhibitors plus ICI, axitinib plus ICI therapies have shown toxicity, likely due to overlapping toxicities, including fatigue, diarrhea, and hepatic toxicity.[83,84] Therefore, a new issue to be addressed is the early identification of the underlying etiology of the toxicity: axitinib or immune related, which is crucial to set up appropriate management strategies. IRAEs are related to a non-specific activation of the immune system that can impact multiple organs. ICI-related toxicity management relies on the administration of immunosuppressors such as systemic corticosteroids.[85–87] Conversely, antiangiogenic agents related to toxicity result from various underlying mechanisms due to on-target effects and are mainly managed by dose reductions and treatment interruption. The use of ICI plus TKI combination thus leads

to a more complex management and recognition of treatment-related toxicity, as there is an overlap between some ICI related and VEGFR TKI related adverse events.

As the number of patients treated with axitinib–based combination has increased, it appears necessary to get new guidance on how to distinguish IRAEs from axitinib-related adverse events and how to manage them specifically. An evidence and expert-based class IV consensus recommendation for treatment optimization and management of related adverse events in the management of axitinib plus ICI combination was published in 2020.[88] In this international consensus, a systematic review of the literature with avelumab plus axitinib and pembrolizumab plus axitinib combinations was performed, and adverse events associated with each combination were compared with the monotherapy treatments in similar indication. The most common (>10%) treatment-related adverse events associated with each combination that may be immune-related or associated with axitinib monotherapy included endocrinopathies, dermatologic, gastrointestinal, and musculoskeletal disorders. TRAEs that required additional guidance based on overlapping toxicities were identified, and recommendations were set up focusing on adverse events requiring differential diagnosis of etiology, for which no published guidelines were yet available.[84,85,87,89,90] These events were identified as diarrhea, hepatitis, cardiovascular events, and fatigue and lead to specific recommendations.[88]

As a general rule for low-grade adverse events, it is recommended to first assess the absence of severity symptoms that would require immediate intervention. In the absence of severe clinical signs of immune-related toxicity, the recommended first step is the interruption of axitinib and observation for resolution or improvement. In case of quick improvement or resolution, the adverse event is most likely due to axitinib, and intermittent treatment or dose reduction is recommended. If persistence, immune-related etiology must be considered and may require treatment with steroids.

Time to Treatment Resolution

Considering this, the time to resolution (TTR) of VEGFR TKI toxicity might be helpful in clinical practice. A shorter toxicity resolution decreases the risk of cumulative toxicity, and in combination regimens, TTR may help in determining the etiology of the toxicity. In a post hoc analysis of data from 5 studies of axitinib monotherapy or in combination with immunotherapy, Rini et al described the TTR of axitinib-related toxicity. Data from this analysis[91] suggested that TTR for axitinib-related adverse events seems shorter after treatment interruption for axitinib monotherapy than for other VEGFR inhibitors. This was the same for axitinib monotherapy compared with combined axitinib and immunotherapy. In addition to fatigue, the majority of TTRs associated with combined axitinib plus ICI were longer than for axitinib monotherapy. The most common grade 3 events were fatigue, nausea, hypertension, and diarrhea. In the axitinib monotherapy cohort, the median TTR was 3 days for diarrhea, 8 days for fatigue, 2 days for hypertension, 4 days for nausea, and 3 days for PPE. In the axitinib plus ICI cohort, the median TTR was 4 to 11 days for all TRAEs. Although fully descriptive and extracted from clinical trials and not real-world data, these data suggest that axitinib-based combination toxicity may be easier to manage and the etiology easier to determine than with other combination regimens. The fast resolution of the adverse events (1–3 days except for fatigue) for axitinib monotherapy is likely related to its half-life (2.5 to 6.1 hours) which is notably shorter than that of other VEGFR TKI (approximately 28 hours for lenvatinib, 99 hours for cabozantinib, 50 hours for sunitinib). This may advantage axitinib in the management of TKI plus ICI combination toxicity and particularly in determining the underlying etiology.

Real Life Data

Phase 3 trials reporting the efficacy of ICI plus TKI, or ICI plus ICI combination have dramatically changed the standard of care for front-line therapy in mRCC. Physicians are now faced with larger therapeutic options with different toxicity profiles, but real-world evidence is lacking to accurately describe TKI plus ICI combination toxicity profile in non-trial selected populations, and to help better address patient selection. In a review, Allison et al reported their real-world experience of axitinib plus avelumab in 44 patients.[92] The combination was well tolerated and the rate of grade 3 or higher adverse events was 36%, most common being hypertension (11%) and hepatitis (11%). Overall, 22% of patients had limiting toxicity and 20% of the patients received corticosteroids for suspicion of IRAEs, which was higher than data shown in the JAVELIN 101. As physicians are facing a growing number of patients eligible for this combination, more real-life data will be needed in the future to assess its true toxicity profile and set up optimal management strategies.

Factors Associated with Avelumab – Axitinib Outcomes and Their Impact on Therapeutic Strategy

Avelumab plus axitinib significantly improves PFS among treatment-naïve mRCC patients.[69] However, data suggest that almost half of patients will not benefit from this regimen. Thus, identifying factors associated with response remains a major challenge.

Tumor-Related Factors

The effectiveness of a treatment depends on its sufficient delivery to the tumor site, and the bone and brain are two potential sanctuaries for mRCC therapies. In the Phase II trial NIVOREN, nivolumab monotherapy failed to demonstrate efficacy in brain metastases from mRCC.[93] However, nivolumab plus ipilimumab combination showed encouraging results in this same situation, with a 32% to 44% ORR.[94,95] Among the VEGFR TKIs, cabozantinib has shown significant activity in brain and bone metastases, while data concerning axitinib and other TKIs in the same setting lacks.[96] Therefore, sites of cancer extension are key factors in the treatment decision process, and avelumab plus axitinib may not be the preferred regimen for brain and bone involvement. Of all pathological subtypes, sarcomatoïd mRCC have the poorest prognosis.[97] VEGFR TKIs have shown limited efficacy in this population, whereas nivolumab plus ipilimumab combination has become a standard.[98,99] Interestingly, in a subgroup analysis of the sarcomatoïd mRCC population of JAVELIN 101 trial, the objective response rate was twice as high with avelumab plus axitinib combination as with sunitinib.[100] Thus, this combination could be considered as an eligible option for these patients. As RCC patients represent a heterogeneous cancer population, IMDC risk criteria are critical in determining patient prognosis and can help predict patient response to systemic therapies. In the CHECKMATE 214 trial, nivolumab plus ipilimumab combination has shown limited benefit in favorable IMDC risk group in comparison to sunitinib monotherapy. Progression-free survival and objective response rates were even higher with sunitinib in this population (25.1 months [20.9 – NE] vs 15.3 months [9.7–20.3] HR: 0.45 [0.27–0.78], $p < 0.001$; 52% vs 29%, $p < 0.001$), suggesting pathological and molecular features associated with immune-resistance or VEGFR TKI high sensibility in this subgroup.[6] Similarly, the benefit of pembrolizumab plus axitinib and nivolumab plus cabozantinib combinations in the favorable-risk subpopulations of KEYNOTE-426 and CHECKMATE-9ER trials failed to reach significance.[7,8] However, in the JAVELIN 101 trial, avelumab plus axitinib showed consistent efficacy in all IMDC risk groups. This questions the impact of PD-L1 tumor expression, as the population is enriched in PD-L1-positive tumors. PD-L1 expression by tumor cells or tumor microenvironment has been widely investigated as a predictive biomarker for ICI[69](p1),[101](p1). In lung cancer, the tumor PD-L1 expression determines the choice of treatment for first line of therapy.[102] In RCC, this biomarker seems to be associated with a poor prognosis,[103] but to this day its predictive value remains controversial[104,105] and the interpretation of the predictive value of PD-L1 tumor expression in mRCC is all the more complex in the era of ICI plus TKI association. Recently, Damotte et al have demonstrated that an 18-gene expression assay measuring the level of tumor microenvironment inflammation (TIS score) is independently predictive of tumor response to anti-PD1 therapies in a cohort of 58 solid cancer patients including 10 RCC.[106] Given the limited sample size, further trials are warranted to implement these results in clinical practice. Other biomarkers such as tumor mutational burden, soluble biomarkers and molecular characterization have shown encouraging yet preliminary results.[107–112]

Host-Related Factors

The factors associated with immune response appear to be in a large part host-related and independent of the tumor. The ELY study investigated the measured resting energy expenditure (REE) as a predictive clinical marker for 6-month progression-free survival among 110 metastatic non-small cell lung cancer patients treated with ICI.[113] Hypermetabolism, defined as a measured/theoretical REE ratio of 110% or above, was associated with a 35% decrease of 6-months PFS rates (22% versus 55%; odds ratio: 4.76; IC95 [1.87–12.89], $p < 0.001$). Hypermetabolism is also correlated with sarcopenia and cancer cachexia and is associated with a shorter survival in metastatic cancer patients.[114] A previous study has also highlighted sarcopenia as a predictive factor for anti-PD1 toxicity.[115] Taken together, these results point to hypermetabolism not only as a major prognostic marker but also as a potential target for improving ICI response. The gut microbiota is another host-related marker, which may reflect the immune system efficiency. The impact

of antibiotic consumption on ICI efficacy is now thoroughly documented.[116,117] Its deleterious effect results from excessive bacterial depletion, as specific commensal germs such as *Akkermansia muciniphila, Alistipes indistinctus* and *Enterococcus hirae* seem to be critical for T-cell activation.[118,119] Among the various corrective strategies under investigation, such as probiotic use or antibiotic sparing, fecal microbiota transplantation (FMT) is one of the most promising. A preliminary clinical study has investigated FMT obtained from long-responding melanoma patient as a therapy for anti-PD1 refractory melanoma patients and demonstrated that a single transplantation could help overcome resistance in a subset of patients.[120] A very recent Phase 1 trial showed that a bifidogenic live bacterial product appears to enhance the clinical outcome in patients with mRCC treated with nivolumab-ipilimumab.[121] Interestingly, although diarrhea is a common adverse event of anti-VEGF therapies, very few studies have investigated the clinical impact of TKI-induced dysbiosis. In 2015, Pal et al have conducted stool bacteriomic profiling of patients with mRCC receiving VEGF TKIs, and found that high rates of *Bacteroides spp*. and low rates of *Prevotella spp*. were associated with higher risks of diarrhea.[122] These findings are supported by recent studies suggesting that microbioma modulating therapies such as probiotics and FMT from healthy donors may also be effective treatments for VEGFR TKIs induced diarrhea in mRCC patients.[123,124] In summary, the understanding of the host, its metabolism and its immunity could ultimately lead to therapeutic strategies based on the optimization of the immune response and limit the stakes of the choice of combination.

Treatment-Related Factors

Therapeutic drug monitoring is a powerful instrument for dose adjustment of targeted therapies.[125,126] A strong PK/PD relationship has been demonstrated for cabozantinib and sunitinib.[127,128] However, the mechanism of inter-individual variability in exposure remains unclear. For axitinib, several data suggest that dose titration is insufficient to overcome underexposure.[21,129] Various factors, such as body composition, drug–drug interactions and self-medication, are likely to influence exposure as well.[130] Conversely, there is no demonstrated exposure–response relationship with anti-PD(L)1 therapies, which confirms that addressing host-related factors associated with response is crucial to derive the highest benefit of these therapies.[44,131] Therefore, a tailored pre-therapeutic pharmacological risk assessment, taking into account individual patient characteristics at the same level as the plasma concentration of the drug, should be the first step into decision-making.

Conclusion

Avelumab plus axitinib combination was developed in times of dramatically increasing therapeutic opportunities for mRCC patients. Although ICI plus TKI and ICI plus ICI combinations are standard of care, the added value of each combination in comparison to the others is debatable Axitinib has some advantages over other TKIs for a combination with ICI: it displays few risks of drug–drug interaction, its dose can be easily optimized with up-titration based on hypertension (a non-overlapping toxicity), and it has a short half-life with therefore a short time to toxicity resolution. For avelumab, the induced ADCC and a favorable safety profile may be advantageous over other ICI. Nevertheless, better understanding of the complex interaction between immunomodulation and angiogenesis and improving our ability to restore the immune system may be more discriminating than the choice of systemic combination.

Disclosure

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