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Tyrosine kinase and immune checkpoints inhibitors in favorable risk metastatic renal cell carcinoma: Trick or treat?

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ABSTRACT

Over the past decade, the management of metastatic renal cell carcinoma (RCC) has undergone rapid evolution, culminating in a significant improvement in prognosis with frontline immunotherapy. RCC is a highly immunogenic and pro-angiogenic cancer, and mounting evidence has established the immunosuppressive effects of pro-angiogenic factors on the host's immune system. Anti-angiogenic agents such as tyrosine kinase inhibitors (TKIs) and bevacizumab, which obstruct the vascular endothelial growth factor pathway, have demonstrated the potential to enhance antitumor activity and improve the efficacy of immune checkpoint inhibitors (ICIs). Consequently, various combinations of TKIs and ICIs have been assessed and are currently considered the preferred regimens for all metastatic RCC patients, regardless of their prognostic risk score. Nevertheless, some inquiries have arisen within the medical community, as metastatic RCC patients with favorable risk scores who received ICIs and TKIs in combination showed no statistically significant advantage in overall survival compared to those treated with sunitinib alone. Considering these concerns, this review aims to elucidate the rationale behind TKI and ICI combination therapies, provide a summary of current first-line metastatic RCC combinations approved for use, with a focus on favorable-risk patients, and outline present challenges and future perspectives in this context.

Contents

Abbreviations: RCC, renal cell carcinoma; ITT, intention to treat population; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; AEs, adverse events; TRAEs, treatment-related adverse events; TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoints inhibitors; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International mRCC Database Consortium; MDSCs, myeloid-derived suppressor cells; OR, odd ratio; CR, complete response; DOR, duration of response; ccRCC, clear cell RCC; RCTs, randomized clinical trials; VEGF, vascular endothelial growth factor; IO, immuno-oncology; TMB, tumor mutational burden.

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1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 90–95% of kidney cancer and 3% of all adult cancers (Sung et al., 2021). Clear cell cancer histology represents 75% of all RCC subtypes, followed by papillary, chromophobe, and collecting ducts (Cheville, Lohse, Zincke, Weaver, & Blute, 2003). RCC typically occurs as a localized disease at diagnosis although about 25% of cases relapse after nephrectomy, while one-third of all patients have metastatic disease from the diagnosis (Dabestani et al., 2016). Since the cytokine era, metastatic RCC (mRCC) patients are classified into three prognostic categories, favorable, intermediate, and poor, according to clinical and laboratory features. Memorial Sloan Kettering Cancer Center (MSKCC) and International mRCC Database Consortium (IMDC), are still the main used prognostic models in clinical practice (Heng et al., 2009; Motzer, Bacik, Murphy, Russo, & Mazumdar, 2002). Despite the remarkable improvements in treatment with the advent of immunotherapy, patient stratification remains a crucial part of clinical and treatment decision-making for these patients. Combinations based on immune checkpoint inhibitors (ICIs) (*i.e.,* ICI/ICI or ICI/tyrosine kinase inhibitor [TKIs]) have replaced the use of TKI monotherapy at the forefront, even if the results are not uniform between RCC risk categories. Indeed, in patients with favorable risk, immunotherapy does not seem to improve overall survival (OS), so much so that different oncology guidelines still consider monotherapy with TKI as a valid alternative in this category of patients (Escudier et al., 2019; Motzer, Memorial Sloan Kettering Cancer Center, et al., 2023). This review aims to summarize the therapeutic combinations currently available for mRCC untreated patients, outline the challenges related to patients in the favorable risk group, and evaluate prospects.

2. Rational of tyrosine kinase and immune checkpoints inhibitors combination

The development of immunotherapy has deeply changed the treatment algorithm of several solid malignancies, including RCC (He, Li, Zhang, Tang, & Ren, 2020; Li et al., 2019; Marra, Viale, & Curigliano, 2019; Nishijima, Shachar, Nyrop, & Muss, 2017; Yun, Vincelette, Green, Wahner Hendrickson, & Abraham, 2016). Immune checkpoint inhibitors, commonly used in clinical practice include programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors. The efficacy of ICI monotherapy is limited in several tumors, and strategies of combination have been developed (Yang et al., 2020). It was shown that ICIs, combined with antiangiogenic drugs, can improve the prognosis of certain patients with tumors (Mennitto et al., 2020; Yi et al., 2019).

Tyrosine kinase inhibitors such as sunitinib, pazopanib, and cabozantinib have been the first-line standard of care for metastatic RCC for over a decade. This is due to the inactivation of the von Hippel-Lindau tumor suppressor gene in 45–80% of sporadic kidney cancers, leading to overexpression of vascular endothelial growth factor (VEGF) and subsequent alteration of the angiogenesis process (Rathmell & Chen, 2008). TKIs target the VEGF signaling pathway together with bevacizumab, a monoclonal antibody that blocks VEGF, promoting the normalization of blood vessels and facilitating the infiltration of lymphocytes into tumor tissues. Interestingly, VEGF also alters the tumor microenvironment (TME) up-regulating the number and function of immune suppressor cells such as regulatory T-lymphocytes (T*regs*), myeloid-derived suppressor cells (MDSCs), and M2 macrophages and disabling the activity of tumor-infiltrating lymphocytes (Gao & Yang, 2019). The interference of VEGF on monocyte differentiation inhibits the dendritic cells' maturation, essential for the activation of the host's immune system, and reduces the expression of PD-L1 in these cells (Chen & Hurwitz, 2018). Additionally, the action of VEGF is associated with a decrease in the expression of adhesion molecules on endothelial cells, reducing their ability to recognize tumor-killing T cells. VEGF also leads to a reduction in the expression of PD-1 and CTLA-4 on immune cells (Voron et al., 2015).

It appears evident that in RCC, the inhibition of VEGF by antiangiogenic drugs can potentiate the antitumor activity of the immune system through an additive or synergistic effect (Meder et al., 2018) (Fig. 1).

Specifically, sunitinib has been shown to reduce the expression of PD-1 in tumor-infiltrating T cells and to significantly increase the infiltration of CD8+ and CD4+ T cells into the tumor (Ko et al., 2009; Voron et al., 2015). It also reduced the amount and the suppressive function of T*reg* and MDSC (Ko et al., 2009; Voron et al., 2015). Similarly, cabozantinib was shown to reduce the number of T*regs* and MDSCs by significantly increasing the infiltration of CD4+ and CD8+ T cells (Kwilas, Ardiani, Donahue, Aftab, & Hodge, 2014). Antiangiogenic agents have been shown to reduce tumor solidity thereby relieving pressure on existing blood vessels (Farsaci et al., 2014; Farsaci, Higgins, & Hodge, 2012); this favors, despite the reduced vascularization, a better immune-cell infiltration into the tumor (Farsaci et al., 2014). To date, the effect of anti-PD-1/PD-L1 combined with anti-CTLA-4 or with TKI, hase notably improved the overall survival of mRCC patients.

3. Current approval of immunotherapy in advanced RCC

Similar to other malignancies, the use of immunotherapy in RCC initially began with the second line of treatment, following the FDA approval of nivolumab in 2015 (FDA, 2021). In this phase III study, CheckMate 025, nivolumab showed to significantly prolonger OS compared with everolimus (25 *vs.* 19.6 months, Hazard Ratio [HR] 0.73; 98.5% CI, 0.57–0.93; $p = 0.002$). The objective response rate (ORR) was 25% in the nivolumab group and 5% in everolimus group (Odd Ratio [OR] 5.98, 95% CI, 3.68–9.72; $p < 0.001$), whereas no difference on progression-free survival (PFS) was recorded (4.6 *vs.* 4.4 months, HR 0.88; 95% CI, 0.75–1.03; $p = 0.11$) (Motzer et al., 2015). Successively, several ICI-based combinations are extensively explored in treatment-naïve advanced RCC patients (Choueiri et al., 2021; Motzer et al., 2021; Motzer et al., 2018a, 2018b, 2019; Rini et al., 2019; Rini et al., 2019a, 2019b) (Table 1). The first ICI-based combination approval in untreated mRCC patients took place in 2018 based on the phase III trial, CheckMate 214 (Motzer et al., 2018b). In this randomized trial, 1096 patients were randomized 1:1 to receive nivolumab and ipilimumab combination therapy *versus* sunitinib monotherapy. OS, PFS, and ORR in intermediate- and poor-risk patients and in intention-to-treat (ITT) populations were the primary and secondary endpoints, respectively. Intermediate- and poor-risk patients receiving nivolumab plus ipilimumab combination had significantly longer PFS than those receiving sunitinib (11.6 *vs.* 8.4 months, HR 0.82; 99.1% CI, 0.64–1.05; $p = 0.03$). The ORR was 42% with nivolumab plus ipilimumab *vs.* 27% with sunitinib ($p < 0.001$), with 9 and 1% of complete responses (CR), respectively. Contrariwise, in the favorable risk subgroup, the median PFS was 15.3 nivolumab plus ipilimumab 25.1 months with sunitinib (HR 2.18; 99.1% CI, 1.29–3.68; $p < 0.001$), and ORR was 29% *vs.* 52% ($p < 0.001$) with CR in 11% and 6%, respectively. Moreover, PFS was significantly longer in patients with PD-L1 > 1% receiving immunotherapy *vs.* sunitinib, whereas no difference emerged in patients with PD-L1 < 1%. Patients with intermediate/poor risk achieved significantly longer OS when treated with nivolumab plus ipilimumab compared to sunitinib (median OS not reached [NR] *vs.* 26 months). In the favorable risk, instead, the median OS was not reached in both groups. In patients with PD-L1 > 1% expression, the median OS was NR and 19.6 months (95% CI, 14.8-not estimable) with nivolumab plus ipilimumab and sunitinib, respectively. At a median follow-up of 67.7 months, OS benefits were confirmed in both intermediate-risk patients (HR, 0.74), poor-risk patients (HR, 0.58), and in ITT patients regardless of tumor programmed death ligand 1 (PD-L1) expression status (Motzer et al., 2022). Contrarywise, in favorable-risk patients, the median OS was 74.1 months with nivolumab plus ipilimumab *vs.* 68.4 months with

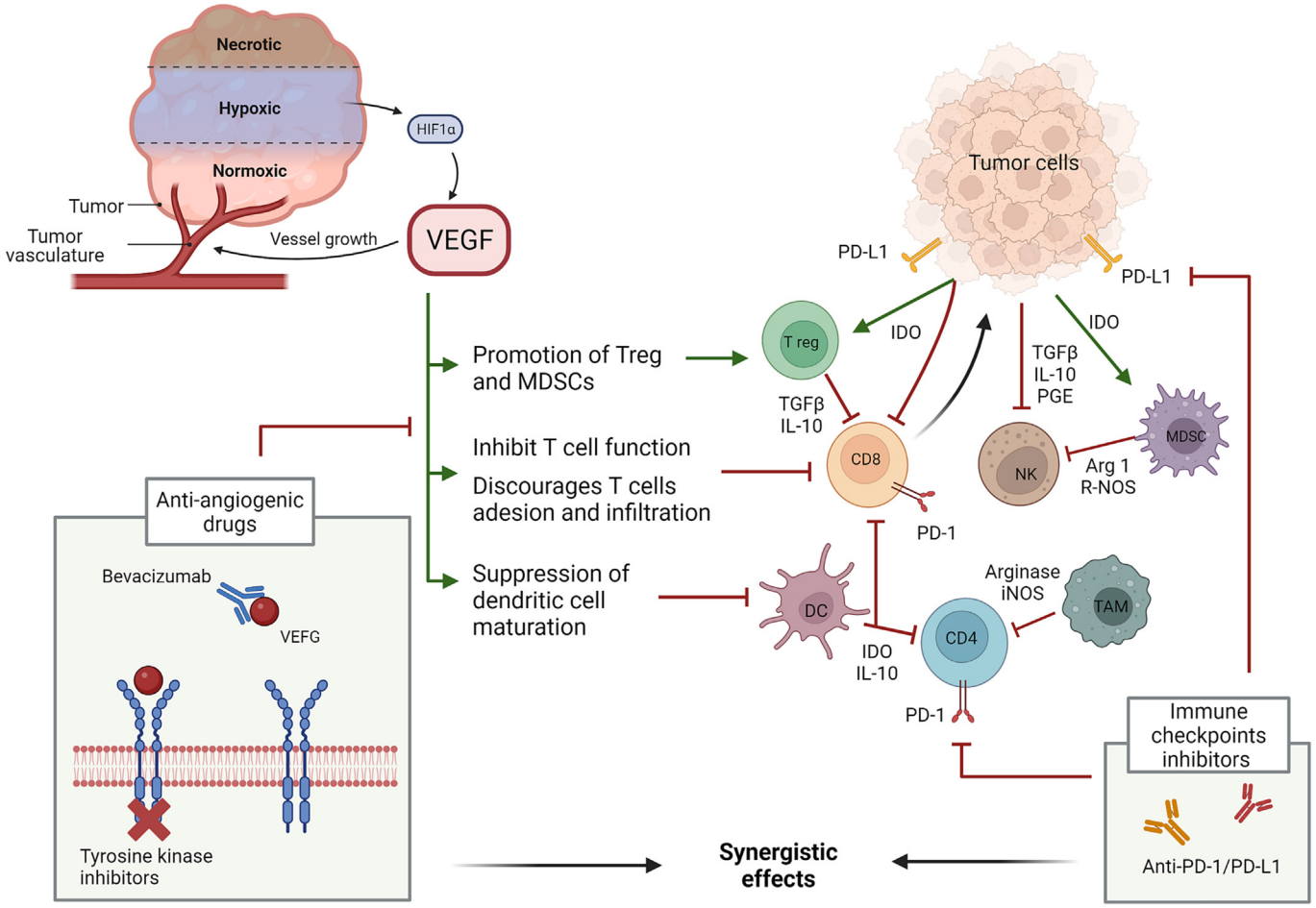

Fig. 1. Synergistic effect of anti-VEGF and immune checkpoint inhibitors. Tumor growth induces a hypoxic environment that activates hypoxia-inducible factor and vascular endothelial growth factor (VEGF). VEGF can suppress the host's immune response by interfering with monocyte differentiation into mature dendritic cells, increasing the number of myeloid-suppressing cells in tumor infiltrates, inhibiting differentiation of progenitor cells into CD4+ and CD8+ cells, and modifying the expression of proteins on endothelial cells, which blocks immune cell infiltration into the tumor. The use of drugs that block VEGF can enhance the antitumor activity of the immune system, thereby improving the efficacy of immune checkpoint inhibitors. Created with *BioRender.com*.

sunitinib with an HR for OS of 0.94 (95% CI, 0.65–1.37). HR for PFS was HR 0.86 (0.73–1.01) in the ITT population ($p = 0.0628$), and 1.60 (1.13–2.26) in favorable risk. In the intermediate- and poor-risk groups grade 3–4 adverse events (AEs) have been reported in 46% of patients treated with nivolumab plus ipilimumab and 63% treated with sunitinib (Motzer et al., 2018b). At the 5 years update, the overall incidence of treatment-related AEs remained consistent with previous reports, and no new safety signals emerged (Motzer et al., 2022).

Simultaneously, several TKI and ICIs combinations have been tested in the first-line setting of patients with mRCC. In the randomized phase III clinical trial Keynote-426, patients with untreated metastatic RCC have been enrolled to receive 1:1 pembrolizumab plus axitinib or sunitinib (Rini, Plimack, et al., 2019). OS and PFS in the ITT population were the primary endpoints. In the pembrolizumab plus axitinib group one-year OS was 89.9% *vs.* 78.3% in the sunitinib group (HR 0.53; $p < 0.0001$); PFS was 15.1 *vs.* 11.1 months in the two arms, respectively (HR 0.69; $p < 0.0001$). The ORR, the secondary endpoint, was 59.3% in the experimental arm and 37.5% in the control group. Advantage has been reported across all subgroups analyzed regardless of the PD-L1 expression or IMDC risk score. Based on these results, pembrolizumab plus axitinib has been approved by FDA in the 2019, in all mRCC regardless of IMDC risk classification (FDA approves pembrolizumab plus axitinib for advanced renal cell carcinoma, 2019).

At the updated follow up (median of 67.2 months), longer OS (47.2 *vs.* 40.8 months; HR 0.84) and PFS (15.7 *vs.* 11.1 months; HR 0.69) were confirmed with pembrolizumab plus axitinib *versus* sunitinib, respectively. In the experimental arm, ORR, DCR, and median duration of response (DOR) were 60.6%, 83.3%, and 23.6 months compared to 39.6%, 75.3%; and 15.3 months in the control arm. The primary refractory rate was 17.0% with pembrolizumab plus axitinib *versus* 11.6% with TKI alone (Rini et al., 2023). A rate of 75.85% of grade ≥ 3 treatment-related adverse events (TRAEs) has been recorded in the pembrolizumab plus axitinib group compared to 70.65% in the sunitinib group, without new safety signals at the latest follow-up. To date, Keynote-426 is the combination study with a longer follow-up in untreated mRCC patients. It confirms the advantage in OS, PFS, and ORR of ICI plus TKI *versus* sunitinib alone in the ITT population, while, in patients with favorable risk, no advantage in OS is recorded. Notably, a substantial proportion of patients that completed 35 cycles of pembrolizumab showed a significant deflection of PFS and OS curves, prompting reflection on the importance of continuing immunotherapy until disease progression.

In the same year, another FDA approval resulted from the phase III trial JAVELIN Renal 101, which evaluated avelumab plus axitinib *versus* sunitinib in treatment-naïve patients with metastatic cell clear (cc)RCC (FDA approves pembrolizumab plus axitinib for advanced renal cell carcinoma, 2019). PFS and OS in PD-L1-positive patients were the co-primary endpoints. PFS was 13.8 months in the avelumab plus axitinib group compared with 7.2 months in patients treated with sunitinib (HR 0.61; $p < 0.0001$). ORR in the PD-L1 positive patients was 55.2% in the experimental arm and 25.5% in the control arm. Data for OS are

Table 1
Results of phase III clinical trials combining TKI and ICIs at forefront in mRCC.

Study [ref]	Experimental *vs* control arm	No. patients	mFU (mo.)	mPFS (mo.)	mOS (mo.)	ORR (%)	CR (%)	mFU latest update(mo.) [ref]	Update Efficacy	AEs (Grade ≥ 3)
Checkmate 214 (Motzer et al., 2018a, 2018b)	Nivolumab + Ipilimumab *vs* Sunitinib	1096	25.2	ITT: 12.4 *vs.* 12.3 (HR 0.98; $p = 0.85$) I/P: 1.6 *vs* 8.4 (HR 0.82; $p = 0.03$) PD-L1 > 1%:22.8 *vs.* 5.9 (HR 0.46)	ITT: NR *vs.* 32.9 (HR 0.68; $p < 0.001$) I/P: NR *vs.* 26.6 (HR 0.63; $p < 0.001$) PD-L1 > 1%: NR *vs.* 19.6 (HR 0.45)	ITT: 42 *vs.* 27 I/P: risk: 41.1 *vs.* 26.5	ITT: 12 I/P: 11	67.7 (Motzer et al., 2022)	ITT: OS: 55.7 *vs.* 38.4 mo. (HR 0.72; $p < 0.001$) ITT: PFS: 12.3 *vs.* 13.3 mo. (HR 0.86; $p = 0.062$) ITT: ORR 39 *vs.* 32%; I/P: 42 *vs.* 27%	93 *vs.* 97% (46% *vs.* 63%)
Keynote 426 (Rini, Plimack, et al., 2019)	Pembrolizumab + Axitinib *vs* Sunitinib	861	12.8	ITT 15.1 *vs* 11.1 (HR 0.69; $p < 0.001$)	ITT: NR (HR 0.53; $p < 0.0001$)	ITT: 59.3 *vs.* 35.7	ITT: 10	67.2 (Rini et al., 2023)	OS ITT: 47.2 *vs.* 40.8 mo. (HR 0.84) PFS ITT: 15.7 *vs.* 11.1 mo. (HR 0.69) ORR: 60.6% *vs* 39.6	98.4 *vs.* 99.5% (75.8% *vs.* 70.6%)
Javelin Renal 101 (Motzer et al., 2019)	Avelumab + Axitinib *vs* Sunitinib	560	13	ITT: 13.3 *vs* 8.4 (HR 0.69; $p < 0.001$) PD-L1+: 13.8 *vs* 7.2 (HR 0.1; $p < 0.001$)	ITT: NR (HR 0.80; $p = 0.0392$) PD-L1+: NR (HR 0.83; $p = 0.1301$)	ITT: 52.5 *vs.* 27.3 PD-L1+: 55.9 *vs.* 27.3	ITT: 3.8	19.3 (Choueiri, Motzer, et al., 2020)	PFS ITT: 13.3 *vs* 8 mo. (HR 0.69; $p < 0.0001$) PFS PD-L1+: 13.8 *vs* 7 mo. (HR 0.62, $p < 0.0001$) OS PD-L1+: HR 0.828; $p = 0.1301$ OS ITT: HR 0.796; $p = 0.0392$	99.5 *vs* 99.3% (71.2 *vs* 71.5%)
Checkmate 9ER (Choueiri et al., 2021)	Nivolumab + Cabozantinib *vs* Sunitinib	651	18.1	ITT: 16.6 *vs.* 8.3 (HR 0.51; $p < 0.001$)	ITT: NR *vs.* NR (HR 0.60; $p < 0.001$)	ITT: 55.7 *vs.* 27.1	ITT: 12.4	44 (Burotto et al., 2023)	PFS ITT: 16.6 *vs* 8.4 mo. (HR 0.58; $p < 0.0001$) OS ITT: 49.5 *vs* 35.5 mo. (HR 0.70; $p = 0.0043$) ORR ITT: 55.7*vs.* 28.4%	99.7 *vs* 99.1% (75.3 *vs* 70.6%)
Clear/Keynote 581(Motzer et al., 2021)	Pembrolizumab + Lenvatinib *vs* Everolimus + Lenvatinib *vs* Sunitinib	1069	26.6	ITT: 23.9 *vs.* 9.2 (HR 0.39; $p < 0.001$) ITT: 14.7 *vs.* 9.2 (HR 0.65; $p < 0.001$)	ITT: NR *vs.* NR (HR 0.66; $p = 0.005$) ITT: NR *vs.* NR (HR 1.15; $p = 0.30$)	ITT: 71% *vs.* 53.5% *vs.* 36.1	ITT: 16.1	49 (Motzer, Porta, et al., 2023)	PFS ITT: 23.9 *vs.* 9.2 mo. (HR 0.47; p < 0.0001) OS ITT: 53.7 *vs.* 54.3(HR 0.79; $p = 0.042$) ORR: 71.3 *vs.* 36.7%	99.7 *vs* 99.7 *vs* 98.5% (82.4 *vs* 83.1 *vs* 71.8%)
IMmotion 151 (Rini, Powles, et al., 2019a)	Atezolizumab+ bevacizumab *vs* Sunitinib	915	15	ITT: 11.2 *vs.* 8.4 (HR 0.83; $p = 0.021$) PD-L1+: 11.2 *vs.* 7.7 (HR 0.74; $p = 0.021$)	ITT: 34.0 *vs.* 32.7 (HR 0.93; $p = 0.475$) PD-L1+: 33.6 *vs.* 34.9 (HR 0.84; $p = 0.285$)	ITT: 37 *vs.* 33 PD-L1+: 43 *vs.* 35	NA	Final survival analysis (Motzer et al., 2022)	ITT: 36.1 *vs.* 35.3 mo. (HR 0.91; $p = 0.27$) PD-L1+: 38.7 *vs.* 31.6 mo. (HR 0.85; $p = 0.26$)	91.0 *vs.* 96.0% (40.0 *vs.* 54.0%)
COSMIC-313 (Choueiri et al., ESMO 2022)	Nivolumab + ipilimumab + cabozantinib *vs.* nivolumab + ipilimumab	855	14.9	ITT: NR *vs.* 11.3 (HR 0.73; $p = 0.013$) I: NR *vs.* 11.4 (HR 0.63, 0.47–0.85) P: 37 *vs.* 30 (HR 1.04, 0.65–1.69)	NA	I/P: 43 *vs.* 36 I: 45 *vs.* 35 P: 37 *vs.* 38	I/P: 3 I: 3 P: 2	20.2 (Powles et al., 2023)	PFS ITT: 16.9 *vs.* 11.3 (HR 0.74) PFS I: 17.9 *vs.* 11.3 (HR 0.68) PFS P: 9.5 *vs.* 11.2 (HR 0.93) ORR ITT: 43 *vs.* 36% ORR I: 45 *vs.* 36% ORR P: 36 *vs.* 38%	(73 *vs.* 41%)

Months (mo.); number (No.); versus (vs); intention to treat population (ITT); median follow up (mFU); hazard ratio (HR); programmed death-ligand 1 (PD-L1); not reached (NR); overall survival (OS); progression free survival (PFS); objective response rate (ORR); adverse events (AEs); intermediate/poor (I/P).

still pending (Choueiri et al., 2020). PFS in the ITT population, the secondary endpoint, was 13.8 *vs.* 8.4 months for the avelumab plus axitinib group and sunitinib, respectively (HR 0.69; $p < 0.0001$). 71.2% of patients treated with the combination therapy and 71.5% of patients treated with TKI alone reported grade 3 or higher AEs (Motzer et al., 2019). At a follow-up of 13 months, PFS was confirmed longer for the patients receiving avelumab plus axitinib *vs.* sunitinib in both PD-L1 positive (13.8 *vs.*7 months, HR 0.62; $p < 0.0001$) and ITT populations (13.3 *vs.* 8 months, HR 0.69; $p < 0.0001$) regardless of the IMDC score prognostic group.

Most recently, the phase III trial CheckMate 9ER, investigated nivolumab in combination with cabozantinib *versus* sunitinib in treatment-

naïve patients with mRCC, regardless of the PD-L1 expression or IMDC prognostic score (Choueiri et al., 2021). PFS, the primary endpoint resulted significantly longer in the experimental arm compared with sunitinib (16.6 *vs.* 8.3 months, HR 0.51; 95% CI, 0.41–0.64; $p < 0.001$), as well as OS, the secondary endpoint, although the median value was NR in both arms. ORR was 55.7 *vs.* 27.1% for patients receiving nivolumab plus cabozantinib and sunitinib, respectively ($p < 0.001$). Survival benefits have been recorded in all patient subgroups analyzed (Choueiri et al., 2020). This combination received FDA approval in January 2021, for the first-line treatment of patients with mRCC regardless of risk score (Administration, 2021). The recent update confirmed the superiority of nivolumab plus cabozantinib *versus* sunitinib for PFS (16.6 *vs.* 8.4 months, HR 0.58) and OS (49.5 *vs.* 35.3 months, HR 0.70) in the ITT population (Burotto et al., 2023). Contrariwise, in the favorable risk subgroup, PFS was 21.4 *vs.* 13.9 months (HR 0.75) and OS was NR *vs.* 47.6 months (HR 1.07). An ORR of 66% and CR of 14% were recorded in the favorable risk patients who received nivolumab plus cabozantinib compared to 44% and 11% (Burotto et al., 2023). Overall, nivolumab plus cabozantinib has been confirmed as a viable first-line option for RCC patients, demonstrating a sustained response rate, an improved likelihood of achieving a complete response, and notably, a low proportion of patients who do not respond to treatment, irrespective of their IMDC risk class.

The three-arms phase III clinical trial CLEAR/Keynote 581 evaluated pembrolizumab plus lenvatinib *vs.* everolimus plus lenvatinib *vs.* sunitinib in patients with previously untreated metastatic ccRCC (Motzer et al., 2021). The primary endpoint, PFS, was 23.9 months in the group of patients receiving pembrolizumab plus lenvatinib *vs.* 9.2 months in those treated with sunitinib (HR 0.39; $p < 0.0001$); while, in patients treated with everolimus plus lenvatinib *vs.* sunitinib, PFS was 14.7 and 9.2 months, respectively (HR 0.65; $p < 0.0001$). In patients treated with pembrolizumab plus lenvatinib, OS was longer than with sunitinib (HR 0.66; $p = 0.005$) although, the median OS was NR. No significant difference in OS has been recorded between patients receiving everolimus plus lenvatinib and sunitinib (HR 1.15; $p = 0.30$). An ORR of 71%, 53.5%, and 36.1%, and a median DOR of 25.8, 16.6, and 14.6 months, have been recorded in the pembrolizumab plus lenvatinib, everolimus plus lenvatinib and sunitinib arm, respectively. Grade ≥ 3 TRAEs were observed in 82.4%, 83.1% and 71.8% of the patients treated with pembrolizumab plus lenvatinib, everolimus plus lenvatinib, and sunitinib, respectively (Motzer et al., 2021). Based on these results, this combination was approved in August 2021 for the first-line treatment of metastatic ccRCC patients regardless of risk score subgroups (FDA approves lenvatinib plus pembrolizumab for advanced renal cell carcinoma | FDA, 2023). At the final prespecified overall survival (OS) analysis (4-year follow-up), lenvatinib plus pembrolizumab maintained a statistically significant advantage in OS compared to sunitinib alone, with an HR of 0.79 (0.63–0.99), despite similar median OS of 53.7 *vs.* 54.3 months, respectively. No OS benefit was observed in patients with a good prognosis (Motzer et al., 2023). Therefore, despite the superiority of this combination in terms of PFS, ORR, and DOR, the survival data, while statistically significant, may not have significant clinical relevance. It remains to be determined what factors may have influenced these results.

Another phase III trial, IMmotion 151, evaluated the association of atezolizumab and bevacizumab *versus* sunitinib in treatment-naïve mRCC patients, including patients with sarcomatoid tumor features (Rini, Powles, et al., 2019a). Patients have been enrolled according to the MSKCC score, PD-L1 expression (<1% *vs* >1%), and the presence of liver metastases. PFS in the PD-L1 positive patients and OS in the ITT population were the co-primary endpoints. PFS was 11.2 months in the experimental arm and 7.7 months in the control arm (HR 0.74; 95% CI, 0.57–0.96; $p = 0.021$). No significant differences in OS have been recorded (HR 0.93; 95% CI, 0.76–1.14; $p = 0.475$). In the ITT population PFS, the secondary endpoint was 11.2 months in patients receiving atezolizumab plus bevacizumab *vs.* 8.4 months in the sunitinib group (HR 0.83; $p = 0.021$). The ORR in the experimental arm *vs.* control arm was 43% *vs.* 35%, in the PD-L1 > 1% population, and 37% *vs.* 33%, in the ITT population, respectively (Rini, Powles, et al., 2019a). No differences in survival have been recorded after 24 months of follow-up in the ITT population (HR 0.93) (Atezolizumab/Bevacizumab vs Sunitinib in Previously Untreated Patients With Metastatic RCC Final Overall Survival Analysis of IMmotion151 - The ASCO Post, 2023).

Based on these results, a sub-analysis according to the molecular profile of tumor tissue was performed (Rini, 2023). Enrolled patients were classified into three groups defined: “angio-high”, “T effector-high” and “myeloid-high”. Results showed that patients with angio-high had a greater benefit with TKI and belonged to the favorable prognostic group. Conversely, patients with T effector-high benefited more from immunotherapy and belonged to the intermediate and poor prognosis groups. Furthermore, patients with *BRCA-1* Associated Protein-1 (*BAP1*) mutations had a worse prognosis and shorter PFS when treated with sunitinib, while patients with *PBRM1* mutations had a worse prognosis with the use of immunotherapy (Rini, 2023).

For the first time in the phase III COSMIC 313 trial, an ICI-based combination (nivolumab plus ipilimumab) represented the control arm of the triplet therapy including nivolumab, ipilimumab and cabozantinib (Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRC… | OncologyPRO), 2023). Based on the Checkmate 214 results, this study enrolled only previously untreated patients with IMDC intermediate or poor risk clear cell RCC. At the first analysis, median PFS was NR (95% CI, 14.0-not estimable) for triplet *vs.* 11.3 months (95% CI, 7.7–18.2) for doublet therapy, and ORR was 43% (95% CI, 37.2–49.2) *vs.* 36% (95% CI, 30.1–41.8), respectively. Median DOR was NR in either treatment group. 73% of patients in the experimental arm and 41% in the control arm developed grade 3/4 TRAEs (Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRC… | OncologyPRO), 2023). At the recent update analysis (additional follow-up of ~5 months), the PFS benefit with the triplet regimen was maintained in the overall population (HR: 0.74), as well as in intermediate-risk patients (HR: 0.68). Data of OS are yet immature. TRAEs led to treatment discontinuation more frequently in the intermediate-risk group compared with the poor-risk group for the triplet regimen (Powles et al., 2023).

Other TKI and ICIs combinations are currently under evaluation (Pal et al., 2021; Powles et al., 2019). In the phase Ib trial, Cosmic-021, the combination between atezolizumab and cabozantinib is being tested in different solid tumors, including metastatic ccRCC. In this cohort, patients receive cabozantinib 40 mg ($N = 34$, ccRCC and non-ccRCC) or 60 mg ($N = 36$, only ccRCC) plus atezolizumab. All three prognostic subgroups according to IMDC score were included in the trial, with a prevalence of those with intermediate prognostic risk. The ORR was 53% *vs* 58% in patients receiving cabozantinib 40 and 60 mg, whit a median PFS of 19.5 and 15.1 months, respectively. Unexpectedly, a higher rate of grade ≥ 3 TRAEs was reported in patients who received cabozantinib 40 mg than in cabozantinib 60 mg (71 *vs* 67%) with hypertension, hypophosphatemia, diarrhea, and elevation of liver enzymes the most common (Pal et al., 2021).

Finally, in the phase Ib/II trial, Calypso evaluated the combination of durvalumab and savolitinib in patients with untreated papillary metastatic non-ccRCC as well as previously treated. All IMDC score prognostic groups were included with a predominance of intermediate prognostic group (63%). In the ITT population, the ORR and PFS were 27% and 3.3 months, respectively, whereas in treatment- naïve patients were 27% and 12.2 months, respectively. Grade 3–4 AEs affected 35.7% of patients (Powles et al., 2019) (Table 2). Table 2 summarizes ongoing clinical trials in untreated RCC patients.

Table 2
Results of updated phase III clinical trials combining TKI and ICIs at forefront in IMDC favorable risk population.

Trial (updated results)	ITT population* (n)	Favorable-risk (n, %*)	mFU update (mo.)	mPFS (mo.)	mOS (mo.)	ORR (%)	CR (%)	Primary refractory (%)	DOR (mo.)
Checkmate 214 (Motzer et al., 2022)	Nivolumab + ipilimumab (550) *vs.* sunitinib (546)	Nivolumab + ipilimumab (125, 22.72) *vs.* sunitinib (124, 22.71)	67.7	12.4 *vs.* 28.9 HR 1.60 (1.13–2.26)	74.1 *vs.* 68.6 HR 0.94 (0.65–1.37)	30 *vs.* 52	13 *vs.* 6	18 *vs.* 14	61.5 *vs.* 33.2
Checkmate 9ER (Burotto et al., 2023)	Nivolumab + cabozantinib (323) *vs.* sunitinib (328)	Nivolumab + cabozantinib (74, 22.91) *vs.* sunitinib (72, 0.95)	44	21.4 *vs.* 13.9 HR 0.75 (0.50–1.13)	NR *vs.* 47.6 HR 1.07 (0.63–1.79)	66.2 *vs.* 44.4	13.5 *vs.* 11	6 *vs.* 14	NA
Keynote 426 (Rini et al., 2021) (Rini et al., 2023)	Pembrolizumab + axitinib (432) *vs.* sunitinib (429)	Pembrolizumab + axitinib (138, 32.62) *vs.* sunitinib (131, 30.53)	42.8 67.2	20.7 *vs.* 17.8 HR 0.76 (0.56–1.03) HR 0.76 (95% CI 0.57–1.02)	42 mo. rates (%): 72.3 *vs.* 73 HR 1.17 (0.76–1.80) HR 1.10 (95% CI 0.79–1.54)	68.8 *vs.* 50.4 68.8 *vs.* 50.4	17 *vs.* 6.1	11 *vs.* 17	NA
Clear (Porta et al., ESMO 2022) (Motzer, Porta, et al., 2023)	Pembrolizumab + axitinib (355) *vs.* sunitinib (357)	Pembrolizumab + lenvatinib (110, 30.98) *vs.* sunitinib (124, 34.73)	33.7 49	HR 0.47 (0.32–0.69) HR 0.50 (0.35–0.71)	HR 1.22 (0.66–2.26) NR *vs.* 59.9 HR 0.94 (0.58–1.52)	NA	NA	5 *vs.* 14	26 *vs.* 14.7

Intention to treat population (ITT); number (n); months (mo); median follow-up (mFU); median progression free survival (mPFS); median overall survival (mOS); Objective response rate (ORR); complete repnse (CR); duration of response (DOR); not available (NA); not reached (NR); hazard ratio (HR). *Percentage referred to ITT population.

4. Controversial role in favorable risk RCC

Although the therapy combinations have clearly improved the survival of patients with mRCC, there are still some points that need to be clarified, especially regarding the efficacy outcome for the favorable risk group (Table 3). Since 2020 several meta-analyses have been performed to evaluate the efficacy and safety of ICIs and anti-VEGF combination therapy *versus* TKI monotherapy for previously untreated metastatic RCC.

The first network analysis to compare systemic treatments in the first-line setting for advanced or metastatic RCC separately by risk group has been performed in 2020 by Cao et al. and included 15 randomized clinical trials (RCTs) for a total of 8995 patients (Cao et al., 2020a). They concluded affirming that avelumab plus axitinib might be the optimum treatment for favorable risk advanced or metastatic RCC and pembrolizumab plus axitinib for intermediate and poor-risk patients (Cao et al., 2020b).

In the same year, Liu et al. analyzed 5 RCTs, reporting that avelumab plus axitinib and pembrolizumab plus axitinib were the best treatment options in terms of PFS (Liu et al., 2021). In the subgroup analysis regarding IMDC risk subgroups, they found a better PFS in the favorable and intermediate IMDC risk score groups receiving avelumab plus axitinib (HR 0.50; 95% CI 0.26–0.95 for the favorable group and HR 0.64; 95% CI 0.47–0.87 for the intermediate group), and in a poor IMDC risk score group patients receiving atezolizumab plus bevacizumab (HR 0.52; 95% CI 0.22–1.2) (Liu et al., 2021).

Table 3
Ongoing trials in untreated advanced renal cell carcinoma.

Study	Treatment	Status	Patients	Phase	Primary endpoint	Estimated enrollment
NCT04518046	Sitravatinib +nivolumab + ipilimumab	Active, not recruiting	ccRCC	I	AEs	92
NCT04540705 (PIVOT IO 011)	Bempegaldesleukin + nivolumab and TKI *vs.* nivolumab and TKI alone	Active, not recruiting	Advanced or mRCC	I	AEs, DLT	30
NCT05808608	AK104 + axitinib	Not yet recruiting	ccRCC and nccRCC	I/II	ORR 12-month PFS rate	33
NCT04300140	AVB-S6–500 (Batiraxcept) + cabozantinib or ± nivolumab or monotherapy	Active, not recruiting	ccRCC	I/II	AEs RP2D ORR	80
NCT04698213	Avelumab + intermittent axitinib	Recruiting	mRCC	II	ORR PFS	75
NCT05256472	Cadonilimab (AK104) + axitinib	Not yet recruiting	mRCC	II	ORR	40
NCT05805501	Axitinib + RO7247669/tiragolumab/pembrolizumab	Recruiting	ccRCC	II	PFS	210
NCT05522231	Fruquintinib + sintilimab *vs.* axitinib or everolimus	Not yet recruiting	Advanced RCC	II/III	PFS ORR	264
NCT04394975	Toripalimab + axitinib *vs.* sunitinib	Active, not recruiting	Unresectable or mRCC	III	ORR	286
NCT03793166 (PDIGREE)	Nivolumab + ipilimumab followed by nivolumab or nivolumab + cabozantinib	Recruiting	mccRCC	III	OS	1046
NCT05219318	Treatment pause *vs.* treatment continuation	Recruiting	IMDC good or intermediate risk RCC with only 1 adverse prognostic factor and an OR at 12 months with ICIs+TKI	III	PFS	372
NCT03260894 (KEYNOTE-679/ ECHO-302)	Pembrolizumab + epacadostat *vs.* SoC	Active, not recruiting	RCC	III	ORR PFS OS	129

(n) ccRCC, (non) clear cell renal cell carcinoma; m, metastatic; ORR, objective response rate; PFS, progression free survival; AEs, adverse events; IMDC, International mRCC Database Consortium; Soc, standard of care; RP2D, recommended Phase 2 dose; ICI, immune checkpoint inhibitor; TKI, Tyrosine Kinase Inhibitors.

In March 2021 Kartolo et al. analyze through seven phase II/III RCTs the impact of first-line dual therapy involving ICIs on survival outcomes in mRCC patients with IMDC favorable risk (Kartolo, Holstead, Duran, Robinson, & Vera-Badillo, 2021a). No OS benefit shown comparing dual therapy *versus* sunitinib monotherapy in mRCC favorable-risk group. Authors indicated that a longer follow-up was needed to definitively detect potential OS benefits, suggesting however an alternative management option in advanced RCC with a favorable prognosis (Kartolo, Holstead, Duran, Robinson, & Vera-Badillo, 2021b).

Simultaneously, Quhal et al. in their network meta-analysis including six RCTs suggest that ICIs-TKIs provide superior PFS, ORR, and OS to ICI-ICI combinations, regardless of the IMDC risk group and that ICI-ICI combination could be the optimal treatment for tumors with PD-L1 expression. In the favorable-risk subgroup avelumab plus axitinib had the highest likelihood of providing the maximal OS ($p = 0.5660$), whereas lenvatinib plus pembrolizumab the maximal PFS ($p = 0.9211$) (Quhal et al., 2021).

In September 2021 Cattrini et al. provide evidence regarding the likely preferred first-line treatment option for mRCC patients. All combinations with anti-PD-1 (pembrolizumab or nivolumab) showed an OS benefit in the ITT population but less evident in patients treated with anti-PD-L1 (atezolizumab or avelumab). Conversely, in the favorable-risk population, the analysis showed unclear benefit in OS with combined therapy compared with sunitinib, in favor of a significantly lower OR of grade 3–4 AEs in the TKI monotherapy (Cattrini et al., 2021).

Tao et al. in their meta-analysis including six RCTs showed that ICIs combined with anti-VEGF improved the prognosis in patients with RCC although for IMDC-favorable risk patients failed to prove a better OS (RR 0.90; 95% CI 0.55–1.46) (Tao et al., 2021).

Regarding PD-L1 expression, the analysis of PFS and OS, showed that patients with PD-L1 > 1% could receive more PFS benefits from combination therapy (HR 0.59; 95% CI 0.50–0.70; $p < 0.00001$) compared to PD-L1-negative subgroup (HR 0.73; 95% CI 0.51–1.03; $p = 0.07$). However, data on the role of PD-L1 expression are contrasting (Cattrini et al., 2021) and although some authors supported the conclusion that patients with PD-L1-positive expression might benefit more from combination therapy (Buti et al., 2020; Sun et al., 2020), further studies are needed to define the real impact on survival. Moreover, the ICI combination recorded an increased incidence of specific AEs compared with monotherapy in this analysis (Tao et al., 2021).

In addition, Riaz et al. carried out a living, interactive systematic review, and network meta-analysis for first-line treatment of mRCC comparing current treatment options with single-agent TKI. Results show cabozantinib plus nivolumab as the best combination for all efficacy outcomes although causes more AEs, whereas nivolumab plus ipilimumab is correlated with more CR. Among patients with favorable risk, PFS was significantly better with avelumab plus axitinib (HR 0.63; 95% CI 0.40–0.90) and significantly worse with nivolumab plus ipilimumab (HR 1.62; 95% CI 1.14–2.31) compared to sunitinib monotherapy. No significant differences in OS were observed across comparisons for patients with favorable risk (Riaz et al., 2021).

Most recently, in their meta-analysis focusing on favorable-risk mRCC Manneh et al., showed that combination therapy improves PFS, ORR, and CR, and failed to demonstrate any advantage in terms of OS (Manneh et al., 2022). Indeed, in a sensitivity analysis including only ICI-TKI trials, a benefit in PFS for the combination arms compared to sunitinib alone (HR 0.60; 95% CI 0.45–0.81) has been observed, whereas no difference between treatments in terms of OS emerged (Manneh et al., 2022).

While further confirmation is still required, hypotheses regarding the lack of OS benefits with combination therapy compared to TKI monotherapy in favorable-risk patients can be proposed. One of the primary hypotheses is the indolent biology of the favorable risk tumor and the short follow-up period to which patients were subjected, which reduces the number of events. Another hypothesis is an increased sensitivity to antiangiogenic drugs in patients with favorable risk, suggested by molecular profiling enriched with angiogenic clusters and increased expression of the VEGF pathway (Manneh et al., 2022). Finally, the lower baseline PD-L1 expression highlighted in favorable risk patients compare with other prognostic groups, could explain the lack of success of ICI combination to sunitinib monotherapy in these patients (Motzer et al., 2018b).

Current guidelines recommend ICI-TKI combinations as the preferred option for IMDC favorable-risk patients, however, a cautious approach to treatment selection should be taken in light of this evidence (Escudier et al., 2019; Motzer, Memorial Sloan Kettering Cancer Center, et al., 2023). Indeed, updated results of Keynote-426 and CLEAR trials recently presented at the American Society of Clinical Oncology 2023, confirmed the absence of an OS advantage for the combination treatment in patients with favorable risk., In these patients, treatment selection should involve careful evaluation of various factors including toxicity profile, impact on quality of life, drug availability, and economic considerations, as monotherapy with VEGFR-TKI can still represent a valid option. As previously reported sunitinib showed a significantly lower rate of grade ≥ 3 TRAEs than most of the ICI-based combinations. In their meta-analysis Rizzo et al. reported a similar relative risk between patients receiving ICI-TKI combinations *versus* sunitinib monotherapy (Rizzo et al., 2022); however, the use of ICI-TKI combinations was associated with a higher risk of all grade and grade ≥ 3 diarrhea, aspartate and alanine transaminase increase, all grade hypothyroidism and grade ≥ 3 decreased appetite. This suggests that the risks of TRAEs should be carefully considered when choosing ICI-TKI combinations in metastatic RCC patients.

Hence, for the favorable risk subgroup, TKI monotherapy could be prioritized, while combination therapy may be considered for specific cases such as those with high tumor burden, hepatic involvement, or rapidly progressive disease, particularly in younger patients. Additionally, given the lack of OS benefit in this subgroup, a sequential approach with first-line TKI monotherapy followed by second-line ICI could be the optimal treatment strategy, particularly for older patients, those with an indolent disease, or those with comorbidities.

Interestingly, a recent clinical study compared the OS in favorable risk mRCC patients who received immediate medical treatment (started <3 months after metastatic diagnosis) *versus* delayed medical treatment. The study found that the median OS was 59.3 months and 75.9 months in the two groups, respectively ($p = 0.028$) (Cyrielle et al., 2022). Building on previous research findings, these new data suggest that some patients may not require immediate systemic therapy and could potentially benefit from local treatment of metastases. Fig. 2 presents a more personalized therapy selection model for patients with metastatic renal cancer and a favorable prognosis. Nevertheless, there is still a need for prospective clinical trials that are specifically designed to evaluate the effectiveness of combination therapy in the favorable-risk patient subgroup and determine the optimal treatment sequence.

5. Predictive biomarkers to better select patients

Unfortunately, the identification of potential biomarkers capable of predicting response in RCC, such as PD-L1 expression or tumor mutational burden (TMB), has been unsuccessful, and IMDC remains the only validated prognostic score for metastatic RCC (IMDC | International mRCC Database Consortium, 2023).

PD-L1 is a validated biomarker predictive of response to immunotherapy most used in clinical practice (Doroshow et al., 2021). In patients with RCC, elevated PD-L1 expression has been correlated with a worse prognosis, regardless of the treatment received, nivolumab *vs.* everolimus (Albiges et al., 2020; Motzer et al., 2015). Conversely, in the Checkmate 214 study, low- and intermediate-risk patients with PD-L1 expression had longer PFS when treated with nivolumab/ipilimumab compared to sunitinib. No differences were found in the

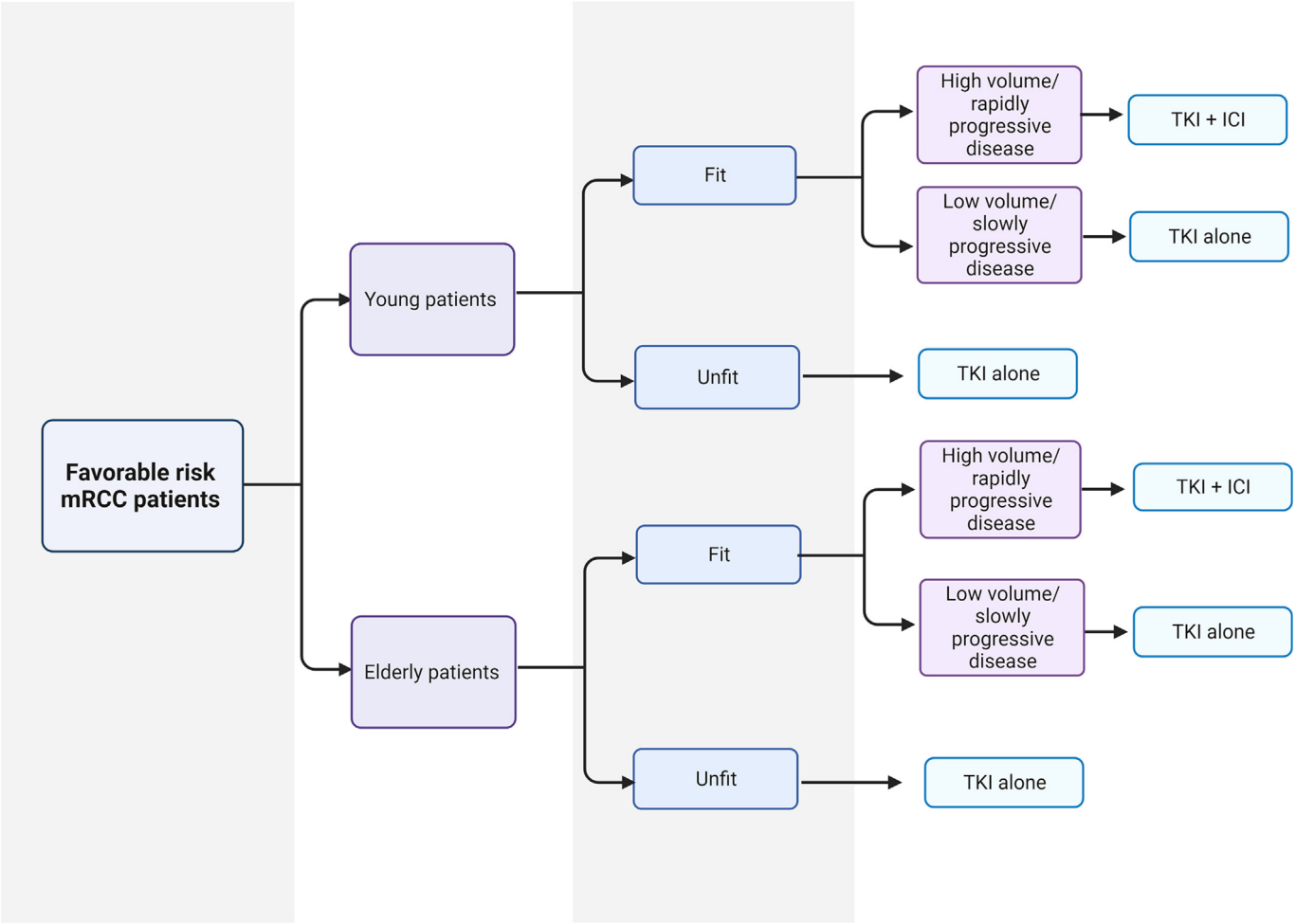

Fig. 2. Proposed management of immune checkpoint inhibitor and/or tyrosine kinase inhibitor in favorable risk mRCC patients. Created with *BioRender.com*.

PD-L1-negative population (Motzer et al., 2018b). While, the JAVELIN Renal 101 and Keynote-426 studies, showed significantly longer PFS regardless of prognostic group or PD-L1 expression (Bedke et al., 2022; Choueiri, Motzer, et al., 2020).

TMB, which refers to the number of mutations per megabase present in tumor cells, is a biomarker that has been extensively studied for its potential to predict response to immunotherapy. In certain types of cancer, such as lung cancer and melanoma, TMB is a predictive marker for a positive response to immunotherapy treatment (Strickler, Hanks, & Khasraw, 2021). However, despite the high response rate of RCC to immunotherapy, the prognostic/predictive value of TBM in this tumor is still inconclusive (Bedke et al., 2022; Samstein et al., 2019).

A retrospective analysis of RCC patients showed that there is no correlation between TMB values, PD-L1 expression, and survival as well as response to treatment (Labriola et al., 2020; Rini, Powles, et al., 2019a).

Other studies have shown that tumors infiltrated with CD8+ cells and M1 macrophages are associated with a better prognosis and response to immunotherapy, while infiltrates rich in regulatory T cells and M2 macrophages are associated with a poor prognosis (Kawashima, Uemura, & Nonomura, 2019; Şenbabaoğlu et al., 2016; Wallin et al., 2016; Yao et al., 2018; Zhang et al., 2019; Zhu et al., 2019). Contrariwise other authors showed no correlation between TMB, neoantigen load, and CD8+ T cell infiltration and response to anti-PD-1 therapy in ccRCC (Braun et al., 2020). One potential explanation is that CD8+ T cell-infiltrated tumors that are associated with improved survival with anti-PD-1 therapy are relatively depleted for *PBRM1* mutations and enriched for chromosomal losses of 9p21.3, which is associated with resistance to PD-1 blockade in infiltrated tumors (Braun et al., 2019; Miao et al., 2018). However, the exact mechanism by which *PBRM1* mutations could alter the response to PD-1 blockade remains largely undefined, and further investigations are needed to evaluate this correlation.

Hope is pinned on molecular classification as a tool to identify patients who may benefit from combination therapy or TKI alone.

In the above-mentioned IMmotion 151 phase III study, a comprehensive molecular analysis of 823 tumors from advanced RCC patients treated with atezolizumab plus bevacizumab or sunitinib was performed. Unsupervised transcriptomic analysis revealed seven molecular subsets (angiogenesis, immune, cell cycle, metabolism, and stromal programs) that were validated in a previous study which also enrolled patients with untreated advanced RCC (IMmotion 150) (Powles et al., 2021; Rini, Powles, et al., 2019b).

Patients who were categorized in the angiogenesis-enriched clusters 1 and 2 demonstrated a more favorable prognosis when treated with atezolizumab plus bevacizumab or sunitinib, with no significant differences observed in PFS between the two treatment groups. This similarity could be attributed to the presence of an angiogenesis inhibitor in both treatment options. On the other hand, in the angiogenesis-poor, but immune-rich, and cell cycle enriched clusters 4 and 5, sunitinib showed worse clinical outcomes, whereas atezolizumab + bevacizumab significantly improved ORR and PFS compared to sunitinib. This is consistent with the inclusion of an immunotherapeutic agent in the combination therapy. The study revealed that tumors from favorable risk patients were enriched in the angiogenic/stromal and angiogenic

clusters, which exhibited higher expression of genes associated with the VEGF pathway. These findings offer a molecular basis for the better clinical outcomes of combined immune checkpoint inhibitors plus VEGF inhibition compared to ICI monotherapy across clinical risk categories and suggest that favorable risk patients should be treated with therapeutic regimens that include VEGF pathway inhibitors.

In the recent non-comparative phase II trial, BIONIKK evaluated patient selection based on tumor molecular phenotype for choosing the best treatment (Vano et al., 2022). The BIONIKK trial investigated the response to immunotherapy and TKI therapy based on the molecular tumor profile, using a 35-gene expression profile. Patients were categorized into four subgroups: group 1 (immune-low), group 2 (angio-high), group 3 (normal-like), and group 4 (immune-high), and were randomized to receive nivolumab or nivolumab plus ipilimumab in groups 1 and 4, and sunitinib or nivolumab plus ipilimumab in groups 2 and 3. The primary endpoint, ORR, was 33.3% and 20.7% in group 1 for patients treated with nivolumab plus ipilimumab or nivolumab, respectively, and 42.9% *vs.* 41.2% in group 4, respectively. In group 2, the ORR was 58.3% *vs.* 34.5% in patients receiving sunitinib *vs.* nivolumab plus ipilimumab, respectively. Group 3, which included a very small number of patients, only showed responses in patients treated with the immunotherapy combination (Vano et al., 2022). The findings of the studies mentioned above demonstrate the potential for using molecular profiling of tumors to select the most effective first-line therapy for metastatic ccRCC patients. If validated prospectively, treating patients based on transcriptomic profiling of tumors, regardless of IMDC risk categorization, could lead to a more personalized and biology-based approach to treatment selection.

The microbiome and its bidirectional interaction with ICIs have been extensively studied, and the results suggest that greater diversity in the microbiome profile of mRCC patients treated with ICI is associated with better therapeutic efficacy (Deluce, Maleki Vareki, & Fernandes, 2022). On the other hand, the administration of antibiotics just before or soon after the initiation of ICI has been linked to reduced efficacy (Lalani et al., 2020; Salgia et al., 2020). Furthermore, in patients treated with TKIs, a microbiota rich in *Bacteroides* has been associated with gastrointestinal toxicity, that reduced drug tolerance and required dose reduction (Hahn et al., 2018). In these patients, the use of antibiotics, targeting *Bacteroides,* improved PFS (Hahn et al., 2018). These results require further attention in the choice of treatment in patients with favorable risk, to ensure that concomitant drugs do not interfere with or may favor the efficacy of oncological treatments.

6. Conclusion

The superiority of ICI-based therapy over sunitinib alone as the first-line treatment for advanced or metastatic RCC patients is well-established and has become the new standard of care (Vano et al., 2021). However, despite being the preferred regimen, ICI-based combinations have not shown any advantage in terms of OS for favorable-risk patients. In the era of precision medicine, it is essential to identify patients who can truly benefit from the ICI-TKI combination. Therefore, when choosing treatment for patients in the favorable-risk group, several factors must be considered, including drug profile, patient preference, and affordability.

The clinicopathological characteristics such as tumor burden, site of metastases, and patient age may also influence the choice of therapy, towards a more or less aggressive regimen (Grimm, Leucht, & Foller, 2021).

These findings help optimize available resources, avoid overtreatment, and prevent unnecessary toxicities. Finally, identifying biomarkers that can predict the response to immunotherapy could improve the selection of patients for the best possible first-line therapy.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

None.

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