Recent Advances in First-Line Management of Metastatic Renal Cell Carcinoma

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Introduction

For the past 15 years, vascular endothelial growth factor tyrosine kinase inhibitors (VEGF TKIs; sunitinib and pazopanib) were standard first-line treatment in metastatic renal cell carcinoma (mRCC). A phase-III randomized controlled trial included 750 treatment-naive patients comparing sunitinib vs interferon alpha and showed higher objective response rate (ORR; 31 vs. 6%, $p < 0.001$) and higher progression-free survival (PFS) rate with sunitinib as compared with interferon alpha (11 vs. 5 months, hazard ratio [HR] = 0.42, 95% confidence interval [CI]: 0.32–0.54, $p < 0.001$). There was no complete response.[1]

Updated analysis of the study showed response rate of 47 versus 12% ($p < 0.001$), improved PFS (11 vs. 5 months, $p < 0.001$), and improved overall survival (OS; 26.4 vs. 21.8 months, HR = 0.821, 95% CI: 0.673–1.001, $p = 0.51$) of sunitinib as compared with interferon alpha.[2]

Another phase-III placebo-controlled trial randomized 435 treatment-naive or cytokine-pretreated patients into pazopanib versus placebo arm. ORR (30 vs. 3%, $p < 0.001$) and median PFS (9.2 vs. 4.2 months, HR = 0.46, 95% CI: 0.34–0.62, $p < 0.001$) were higher in the pazopanib as compared with placebo arm.[3]

Cabozantinib was compared with sunitinib in a phase-II randomized study including 157 intermediate- and poor-risk international mRCC database criteria (IMDC) patients.[4] ORR was 33% (95% CI: 23–44) for cabozantinib versus 12% (95% CI: 5.4–21) for sunitinib. Cabozantinib significantly improved the median PFS 8.2 versus 5.6 months as compared with sunitinib (HR = 0.66; 95% CI: 0.46–0.95; one-sided $p = 0.012$).

There were no studies of VEGF TKI combinations in first-line therapy of mRCC before the arrival of immunooncology (IO) drugs into the picture.

Nivolumab was the first immunotherapy drug approved in second-line therapy after failure of VEGF TKI. Five out of six IO drug combinations have been recently Food and Drug Administration (FDA) approved in first-line mRCC treatment. A summary of these six trials have been provided in ►**Table 1**.[5–10]

Out of the six first-line phase-III studies, four have shown OS advantage of IO over sunitinib. The study of ipilimumab–nivolumab, pembrolizumab–axitinib, and lenvatinib–pembrolizumab has shown OS advantage in intermediate- and poor-risk IMDC groups, cabozantinib–nivolumab has shown survival advantage across three IMDC groups. Programmed cell death ligand-1 (PDL1) testing has been done in various studies, but none of the studies have shown correlation of PDL1 status with survival.[5,6,9,10]

Ipilimumab–Nivolumab versus Sunitinib

A phase-III CheckMate 214 trial randomized 1,096 patients in 1:1 ratio into two arms, ipilimumab–nivolumab versus sunitinib.[5] A total of 423 patients were at intermediate risk and 416 had poor risk IMDC category. Ipilimumab–nivolumab was administered for four cycles every 3 weeks followed by nivolumab every 2 weeks. Sunitinib was given as 50-mg OD × 4 weeks followed by 2 weeks off (6-week cycle). The primary end points were OS, PFS, and ORR among patients with intermediate and poor risk. The 18-month OS rate was 75% (95% CI: 70–78) with IO and 60% with sunitinib (95% CI: 55–65; HR for death = 0.63; 99.8% CI: 0.44–0.89; $p < 0.001$). Median PFS, ORR, complete response (CR) rates, and median survival are mentioned in ►**Table 1**. Treatment-related adverse events occurred in 93% in IO and 97% in sunitinib arm. Grade 3 and 4 adverse events occurred in 46 and 63% patients, respectively. Latest update of the trial continues

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to show benefit of IO combination in ORR (42 vs. 26%), CR (10 vs. 1%), PFS (12 vs. 8.3 months), OS (48.1 vs. 26.6 months), and median duration of response (DOR; not reached vs. 19.7 months).[11] A 4-year OS was 50% with ipilimumab–nivolumab as compared with 35.8% with sunitinib.

Despite the higher toxicity in sunitinib arm, treatment discontinuation was more common in IO arm, patient-reported outcomes suggested better tolerability of IO combination over sunitinib.[5]

Pembrolizumab–Axitinib versus Sunitinib

KEYNOTE 426 phase-III trial randomized 861 patients into two arms: pembrolizumab–axitinib versus sunitinib.[6] The study population included 30% favorable-risk, 56% intermediate-risk, and 13% poor-risk category patients. Primary end points were OS and PFS in intent to treat (ITT) population. Secondary end point was ORR. The updated result of this study shows better efficacy of pembrolizumab–axitinib combination over sunitinib. ORR was 60% versus 39.9%, CR was 8 versus 3%, and median survival was not reached in pembrolizumab-axitinib arm versus 36.7 months in sunitinib.[12] Median DOR was longer in pembrolizumab–axitinib versus sunitinib (23.5 vs. 15.9 months). No OS benefit was found in favorable risk patients. For IMDC intermediate- or poor-risk disease, PFS and OS were significantly better with pembrolizumab–axitinib with HR of 0.63 for OS and 0.69 for PFS. PFS was 8.3 months (95% CI: 6.7–10.1) with sunitinib versus 12.7 months (95% CI: 11.3–18.0) for pembrolizumab–axitinib combination. OS was 28.9 months (95% CI: 23.7–34.3) with sunitinib versus not reached in pembrolizumab–axitinib combination. A post hoc analysis found that achieving CR improved the chances of OS in both arms. An exploratory analysis of patients with sarcomatoid features showed that the risk of death was reduced by 42% with pembrolizumab–axitinib compared with sunitinib (HR = 0.58, 95% CI: 0.21–1.59). Grade 3 or higher adverse events occurred in 75.8 versus 70.6% of patients in pembrolizumab–axitinib and sunitinib, respectively.

Avelumab–Axitinib versus Sunitinib

Phase-III JAVELIN trial randomized 886 patients in 1:1 ratio into two arms: avelumab–axitinib versus sunitinib.[7] Dose of avelumab was 10 mg/kg in every 2 weeks along with axitinib 5 mg/day. Primary end points were PFS and OS in PDL1-positive patients. PFS was higher in overall, as well as PD L1-positive tumor, in avelumab–axitinib arm (►**Table 1**). PFS in overall population was 13.4 versus 8.4 months (HR = 0.69, 95% CI: 0.56–0.84; $p < 0.001$). Among PDL1-positive patients, PFS was 13.8 months with axitinib–avelumab versus 7.2 months with sunitinib (HR for disease progression or death = 0.61; 95% CI: 0.56–0.84; $p < 0.001$). ORR was higher with avelumab–axitinib PDL1-positive patients (55.2 vs. 25.5%). Updated analysis confirms the efficacy of avelumab–axitinib in prolonging the PFS in overall, as well as PDL1 population. OS data are immature. Grade 3 or higher adverse events occurred in 71.2 and 71.5% of patients, respectively.

Atezolizumab–Bevacizumab versus Sunitinib

IMmotion151 phase-III study randomized 915 patients into 1:1 ratio into two arms: atezolizumab (1,200 mg) + bevacizumab 15 mg/kg in every 3 weeks versus sunitinib 50-mg OD × 4 weeks (6-week cycle). A total of 40% patients were PDL1-positive. Primary end points were investigator-assessed PFS in PDL1-positive patients and OS in ITT population. This study showed that the median PFS was higher in atezolizumab + bevacizumab arm (11.2 months in the atezolizumab plus bevacizumab arm vs. 7.7 months in the sunitinib arm, HR of 0.74 [95% CI: 0.57–0.96]; $p = 0.0217$). In the ITT population, median OS had an HR of 0.93 (0.76–1.14). Also, 40 and 54% patients had grade 3 and 4 adverse events, respectively, and 5 and 8% patients had to discontinue treatment due to toxicity in atezolizumab–bevacizumab and sunitinib arm, respectively. Longer follow-up of the study is required.

Cabozantinib–Nivolumab versus Sunitinib

Phase-III CheckMate 9ER study results have been recently presented in ESMO 2020 meeting.[9] The study included 651 patients in all IMDC risk categories (favorable, 22.7%; intermediate, 57.6%; and poor, 19.7%) and randomized patients into two groups: cabozantinib 40 mg/day + nivolumab 240 mg every 2 weeks versus sunitinib 50 mg/day × 4 weeks, every 6-week cycle. Primary end point was PFS, secondary end points were OS, ORR, BICR, and safety. Median PFS was 16.6 versus 8.3 months (HR = 0.51; 95% CI: 0.41–0.64, $p < 0.0001$). The OS, ORR, and median DOR were significantly improved with nivolumab + cabozantinib versus sunitinib. Median OS was not reached (HR = 0.60; 98.89% CI: 0.40–0.89; $p = 0.0010$), ORR was 55.7% (95% CI: 50.1–61.2) with the combination versus 27.1% (95% CI: 22.4–32.3) with sunitinib ($p < 0.0001$), the median DOR (DOR) was 20.2 versus 11.5 months, respectively. CR rate was 8% versus 4.6%. Treatment-related adverse events lead to discontinuation of nivolumab in 5.6% of patients, and of cabozantinib in 6.6% patients, whereas 3.1% of patients discontinued the combination (total 15.3%) and 8.8% of patients discontinued sunitinib.

Lenvatinib–Pembrolizumab versus Sunitinib

Recently published phase-III trial randomized 1,069 patients into three arms: lenvatinib + pembrolizumab, lenvatinib + everolimus, and sunitinib.[10] Primary end point was PFS assessed by independent review committee. Secondary end points were ORR, OS, safety, and PFS assessed by investigators. Also, 90% patients were either favorable- or intermediate-risk IMDC category. PFS was significantly longer in lenvatinib–pembrolizumab versus sunitinib (median = 23.9 vs. 9.2 months, 95% CI: 20.8–27.7), versus 9.2 months (95% CI: 6–11.0, HR for disease progression or death was 0.39; 95% CI: 0.32–0.49; $p < 0.001$, also significantly longer in lenvatinib–everolimus versus sunitinib (median = 14.7 months, 95% CI:

Table 1 The various studies comparing outcomes of Immunotherapy and VEGF TKIs in patients with mRCC

Study (ref.)	Intervention	No. Of patients	ORR	CR	mPFS (months)	OS (months)	Comment
CheckMate 214[5]	Ipilimumab–nivolumab Sunitinib	550 446	65% 50%	10% 1%	11.6 8.4 ($p = 0.02$)	48 26.6 (HR = 0.65, 95% CI: 0.54–0.78)	Study showed OS advantage in intermediate- and poor-risk patients (and not in favorable risk)
KEYNOTE 426[6]	Axitinib–pembrolizumab Sunitinib	432 429	59.3% (95% CI: 54.5–63.9) 35.7% (95% CI: 31.5–40.4), $p < 0.001$	5.5% 1.9%	15.1 (95% CI: 12.6–17.7) 11.1 (95% CI: 8.7–12.5)	Not reached Not reached	Updated result: at a minimum follow-up of 23 months, median OS is not reached with pembrolizumab–axitinib vs. 36.7 month with Sunitinib. No OS advantage was seen in favorable risk disease but there was PFS and ORR benefit. A post hoc analysis found that achieving CR improved the chances of overall survival in both arms
JAVELIN Renal 101[7]	Avelumab–axitinib Sunitinib	442 444	51.4%(95% CI: 46.6–56.1) 25.7% (95% CI: 27.1–30.0)	3.4% 1.8%	13.8 (95% CI: 11.1 to could not be estimated 8.4, HR = 0.69; 95% CI: 0.56 to 0.84; $p < 0.001$		PDL1 positive population, similar result as overall population
IMmotion 151[8]	Atezolizumab–bevacizumab Sunitinib	454 461			PFS in PDL1 positive population 11.2 7.7, HR = 0.74, 95% CI: 0.57–0.96, $p = 0.0217$		In ITT population median OS had a HR of 0.93 (0.76–1.14)
Check Mate9ER[9]	Cabozantinib–nivolumab Sunitinib	323 328	55.7% (95% CI: 50.1–61.2) 27.1% (95% CI: 22.4–32.3) ($p < 0.0001$	8% 4%	16.6 8.3 (HR = 0.51; 95% CI: 0.41–0.64], $p < 0.0001$).	Median OS was not reached (HR = 0.60; 98.89% CI: 0.40–0.89; $p = 0.0010$)	Results apply to all IMDC subgroups
CLEAR[10]	Lenvatinib–pembrolizumab Lenvatinib–everolimus Sunitinib	355 357 357	71% 53.5% 36.1% (95% CI: 1.69–2.29)	16.1% 9.8% 4.2%	23.9 (20.8–27.7) 14.7 (11.1–16.7) 9.2 (6.0–11), HR (lenvatinib–pembrolizumab vs. sunitinib) = 0.39, 95% CI: 0.32–0.49, $p < 0.001$	Not reached	Survival with lenvatinib–pembrolizumab significantly longer than sunitinib HR for death 0.66, 95% CI: 0.49–0.88; $p = 0.005$) OS benefit seen in all subgroups except favorable risk IMDC

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; IMDC, international metastatic renal cell carcinoma (mRCC) database criteria; ITT, intent to treat; mPFS, median progression-free survival; ORR, overall response rate; OS, overall survival; PDL1, program cell death ligand-1; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.

11.1–16.7) versus 9.2 months (95% CI: 6–11.0, HR = 0.65; 95% CI: 0.53–0.80, $p < 0.001$). Median OS was not reached in any arm. Pembrolizumab–lenvatinib arm had longer OS as compared with sunitinib (HR for death = 0.66; 95% CI: 0.49–0.88; $p = 0.005$). OS benefit was seen across all subgroups except favorable risk IMDC. OS was 71.0, 53.5, and 36.1% with lenvatinib–pembrolizumab, lenvatinib–everolimus, and sunitinib arm, respectively. CR rate was 16.1, 9.8, and 4.2% in three arms, respectively. Grade 3 or higher adverse events occurred in 82.4, 83.1, and 71.8% of patients, respectively.

Single-Agent Immunotherapy as First Line Therapy

All patients may not be fit to receive combination therapy upfront. Recently, results of open-label, single–arm phase-II study of pembrolizumab monotherapy as first-line therapy in advanced clear cell RCC have been published.[13] A total of 110 patients were enrolled. Primary end point was ORR. ORR was 36.4%, CR was 3.6%, PR was 32.7%, and disease control rate was 58.2%. Median DOR was 18.9 months (range: 2.3–37.6 months). Median PFS was 7.1 months (95% CI: 5.6–11.0). Median OS was not reached. Durable responses were seen in all three IMDC subgroups. There is no phase-III study comparing single-agent IO versus IO–TKI combination. Single-agent IO may be a potential therapy option for patients who are not fit to receive IO combination upfront

How to Choose among Various Immunooncology Drugs

There is no head-to-head comparison among the six phase-III trials which have tested various IO or IO–TKI combinations. Cross-trial comparisons may not be appropriate. Choosing one treatment among the six combinations is difficult. There is no predictive marker to select treatment. There is no correlation of PDL1 status and survival. From whatever information we have, we have to choose the treatment based on response rate, survival, and toxicity profile. IMDC criteria should be factored in decision-making. Disease biology, patient characteristics, toxicity pattern, and cost are factors to be considered. If rapidity of response is desired (in high disease burden and symptomatic patient), IO with VEGF TKI combination is preferred over IO–IO combination. IO–TKI combinations have shown higher response rate and more tumor shrinkage. Among the six FDA approved combinations, lenvatinib–pembrolizumab combination has resulted in the highest PFS, and this combination has shown OS benefit in intermediate- and poor-risk IMDC group. Ipilimumab–Nivolumab and pembrolizumab–axitinib combinations have also shown OS benefit only in intermediate- and poor-risk IMDC group, and not in favorable risk. All three of these combinations should be used in intermediate- and poor-risk IMDC category. Cabozantinib–nivolumab has shown OS advantage in all three IMDC groups. The median follow-up of ipilimumab–nivolumab, pembrolizumab–axitinib, avelumab–axitinib, atezolizumab–bevacizumab, cabozantinib–nivolumab, and lenvatinib–pembrolizumab studies was 4 years, 30.6 months, 10.8 months, 24 months, 18.1 months, and 26.6 months, respectively. Longer follow-up of these studies will clarify which combination provides the best OS and which IMDC group benefits most. Immune-mediated side effects are more in IO–IO combinations. For atezolizumab–bevacizumab and avelumab–axitinib, mature results on OS are awaited.

Recent systemic review and network meta-analysis including six trials and 5,121 patients has been published.[14] It concludes that the nivolumab–cabozantinib has the highest likelihood of providing maximum OS, lenvatinib–pembrolizumab has the highest likelihood of PFS and ORR. CR were more likely with ipilimumab–nivolumab. The highest likelihood of adverse event-related treatment discontinuation was associated with ipilimumab–nivolumab and lenvatinib–pembrolizumab.

A study from the United States on clinical and economic outcome of treatment sequences in intermediate- and poor-risk mRCC patients favors cost effectiveness of IO combination followed by TKI versus the reverse sequence [15]. Another study from the United States evaluating the cost effectiveness of pembrolizumab–axitinib and ipilimumab–nivolumab in first-line mRCC suggests that pembrolizumab–axitinib treatment is associated with greater quality-adjusted life years (QALYs) compared with ipilimumab–nivolumab treatment in patients with advanced RCC but may not be cost effective.[16]

Sequencing of Therapy

As more patients will be receiving first-line IO combinations in mRCC, it is critical to choose the second-line therapy, but presently we do not have published prospective studies to guide the second-line therapy. Retrospective studies are presently the guide to base our treatment decision. Dudani and colleagues[17] analyzed 188 patients of which 113 were treated with first-line IO–TKI and the rest were treated with ipilimumab–nivolumab combination. Response to subsequent therapy was higher in patients who received first-line ipilimumab–nivolumab than those who received first-line IO–TKI (45 vs. 15%, $p = 0.040$). Efficacy of cabozantinib post-IO therapy has been retrospectively analyzed and shows a disease control rate of 82% in patients treated with prior IO and 75% in patients treated with IO–TKI.[18] PDIGREE is an ongoing phase-III clinical trial (NCT03793166) where patients will be treated with first-line ipilimumab–nivolumab combination. Patients who achieve CR will receive single-agent nivolumab, patients who have progressive disease will receive cabozantinib, and patients who do not achieve CR and do not have PD are randomized to nivolumab maintenance or cabozantinib–nivolumab. Results of the trial are awaited. Axitinib has been studied in a phase-II study by Ornstein and colleagues[19] in patients treated with IO in first line. This study showed a PFS of 8.8 months, ORR of 20%, and stable disease of 50%

Nonclear Cell Histology

Patients with nonclear histology were poorly represented in VEGF TKI studies. Pembrolizumab–axitinib study included patients with sarcomatoid histology (17.9% in pembrolizumab–axitinib arm and 18.4% in sunitinib arm), lenvatinib–pembrolizumab study had 7.9 and 6.6% patients with sarcomatoid features in IO versus sunitinib arm, and cabozantinib–nivolumab study had 10.9 and 12.9% patients with sarcomatoid features in the two arms, respectively. A meta-analysis of

four randomized controlled trials provided data on 467 patients with sarcomatoid RCC. This study showed IO drugs to be associated with higher ORR (>50 vs. 20% with sunitinib), higher PFS, higher chance of achieving CR, and higher OS.[20]

The number of patients with sarcomatoid histologies in IO studies is small, and firm conclusion cannot be drawn regarding efficacy of IO in this variety of RCC. However, IO appears to be the better treatment option for sarcomatoid RCC as compared with VEGF TKI.

Toxicity of Immunooncology Combinations

►**Table 2** shows the adverse events, dose reduction, and discontinuation of therapy due to toxicity.

Role of Cytoreductive Nephrectomy in Immunooncology Era

From Cancer du Rein Metastatique nephrectomie et Antiangiogeniques and Surgical safety of cytoreductive nephrectomy following Sunitinib trials, both of which were done with VEGF TKI to define the role and timing of CN, we can conclude that most patients with intermediate- and poor-risk IMDC do not benefit from cytoreductive nephrectomy (CN).[21,22] But again, role of CN in era of IO drugs is uncertain. IO studies mostly include patients who had a prior nephrectomy. CLEAR, CheckMate 9ER, JAVELIN, KEYNOTE 426, CheckMate 214 studies included 73, 68.7, 79.6, 82, and 82% patients, respectively, who

Table 2 Toxicity and treatment discontinuation

	Pembrolizumab–axitinib	Sunitinib	
Adverse event of any cause Grade 3 or higher adverse event attributable to trial drug Discontinuation of either drug Discontinuation of both drugs Interruption of treatment Dose reduction Treatment-related death	98.4% 62.9% 30.5% 10.7% 69.(% (interruption of either drug) 20.3% (axitinib) 0.9%	99.5% 58.1% 13.9% 49.9% 30.1% 1.6%	
	Ipilimumab–nivolumab	Sunitinib	
Treatment-related adverse events of any grade Grade 3 or 4 adverse event Treatment-related adverse events leading to discontinuation of treatment Death	93% 46% 22% 1.4%	97% 63% 12% 0.74%	35% patients received high dose glucocorticoids for immune-mediated adverse events
	Atezolizumab–bevacizumab	Sunitinib	
Grade 3 or higher adverse events Discontinuation of treatment	40% 5%	54% 8%	
	Avelumab–axitinib	Sunitinib	
Adverse grade of any grade Grade 3 or higher adverse event At least one dose reduction Discontinuation of treatment Death	99.5% 71.2% 42.2% (axitinib) 7.6% (both drugs) 0.7%	99.3% 71.5% 42.6% 13.4% 0.2%	High-dose glucocorticosteroids required by 11.1% patients who had immune mediated adverse event due to avelumab
	Lenvatinib–pembrolizumab	Sunitinib	
Adverse events of any cause Grade 3 or higher adverse events of any cause Discontinuation due to adverse event Dose reduction Interruption of treatment	99.7% 82.4% Lenvatinib 25.6%, pembrolizumab 28.7%, both 13.4%) 68.8% (lenvatinib) 78.4%	98.5% 71.8% 14.4% 50.3% 53.8%	
	Nivolumab–cabozantinib	Sunitinib	
Adverse events of any cause Treatment-related adverse events Grade 3 or higher treatment related adverse event Adverse events leading to discontinuation of treatment Treatment-related death	99.7% 96.6% 60.6% 19.7% (6% nivolumab only, 7.5% cabozantinib only, 5.6% discontinued both) 1 patient (1/323)	99.1% 93.1% 50.9% 16.9% 2 patients (2/328)	19.1% patients in nivolumab arm received high-dose glucocorticoids to manage immune-mediated adverse events

had prior nephrectomy. It requires further studies to identify which patient will benefit and how can CN be incorporated and timed with immunotherapy.

Conclusion

There have been significant changes in management of mRCC in last few years. Immunotherapy/VEGF TKI combinations are replacing VEGF TKI alone as a first-line treatment. Response rates and PFS of IO–IO or combinations of IO + TKI is higher than sunitinib. CR was rare with VEGF TKI. Immunotherapy drugs produced higher CR rates. It has to be seen whether CR leads to long-term survival. OS with IO is higher as compared with sunitinib in intermediate- and poor-risk categories with pembrolizumab–axitinib, and ipilimumab–nivolumab, and lenvatinib–pembrolizumab. Cabozantinib–nivolumab and lenvatinib has shown OS advantage in all IMDC groups. Few IO studies included patients with sarcomatoid histologies and some of these studies show higher ORR, PFS, and OS with IO drugs, but number of patients included is small, thus firm conclusion cannot be drawn about the efficacy of IO in sarcomatoid histology. However, among the available options, IO appears to be better than VEGF TKI. There are no predictive biomarkers to choose among various therapies. Single-agent IO may be an option for patients who are not fit to receive combination IO therapy. Long-term follow-up of various studies will confirm which subgroup benefits most with IO combination and help us in choosing the best strategy and best drug for individual patient. Role of CN needs to be defined. Cost of treatment is the bigger issue in countries where patients have to spend out of pocket. The actual benefit of IO therapy will not pass on to the patients unless cost of therapy is affordable for them.

Conflict of Interest
None declared.

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