ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.ijmio.com

International Journal of Molecular and Immuno Oncology

Editorial

Immune checkpoint inhibitor – antiangiogenic drugs combination in treatment-naïve metastatic clear cell renal cell carcinoma: Why should immunotherapy have all the fun!

H. S. Darling[1], Alok Gupta[2]

[1]Department of Medical Oncology and Hemato-oncology, Narayana Superspeciality Hospital, Gurugram, Haryana, [2]Department of Medical Oncology, Medanta, Lucknow, Uttar Pradesh, India.

***Corresponding author:**
Dr. H. S. Darling,
Department of Medical Oncology and Hematology-oncology, Narayana Superspeciality Hospital, Gurugram - 122 002, Haryana, India.

doc_iaf@yahoo.com

Received : 04 December 19
Accepted : 05 December 19
Published : 21 January 20

DOI
10.25259/IJMIO_23_2019

Quick Response Code:

ABSTRACT

Clear cell histology is the most common subtype of renal cell carcinoma (RCC). Immune dysregulation and angiogenic pathways are the main drivers of the pathophysiology of RCC. The prognosis of metastatic RCC has very steadily improved from the era of interferon-alpha to tyrosine kinase inhibitors (TKIs) and then with immune checkpoint inhibitors (IOs). The safety and efficacy of both TKIs and IOs as well as the dire unmet need of further improvement in survival has unfolded the feasibility of successful conduction of IO based combination therapy trials. This has led to the approval of IO-IO and IO-TKI combinations, altering the treatment algorithm altogether once again. In this review, we are trying to look at the robustness of IO–antiangiogenic drugs combination data in upfront setting and its real-life application.

Keywords: Anti-angiogenic drugs, Immune checkpoint inhibitors, Clear cell renal cell carcinoma, Tyrosine kinase inhibitors, Immune checkpoint inhibitor-antiangiogenic drug combination

INTRODUCTION

Renal cell carcinoma (RCC) constitutes various subtypes. Important ones include clear cell (cc), papillary, chromophobe, collecting duct, medullary carcinomas, as well as oncocytomas. The ambit of discussion of this article is resricted to ccRCC. Approximately 85% of renal epithelial cancers are ccRCCs.[1] ccRCC is a heterogeneous disease. The disease biology is highly variable, with the survival ranging from a few months to many years, depending on the clinicopathologic, laboratory, and imaging parameters of the disease, as well as the response to therapy. ccRCC is one of the very few cancers where chemotherapy has no active role. Mainstays of therapy are antiangiogenic drugs, mechanistic target of rapamycin (mTOR), and immune checkpoint inhibitors (IOs).

Quantum of the disease

A large proportion of RCC in India is metastatic at presentation as compared to the west. In a retrospective study from TMH India, 40% of patients were detected to have single or multiple

metastases at presentation.[2] A SEER database registry from the US revealed 16% of RCC patients presented with the metastatic disease between 2005 and 2011.[3] Many RCCs remain clinically silent initially, hence, are diagnosed at an unresectable or metastatic stage. Many cases recur after curative surgery.

PATHOPHYSIOLOGY AND TREATMENT TARGETS

Angiogenic pathways

The elucidation of pathogenesis of ccRCC has deciphered the major driver pathways in hereditary as well as more than three-fourth of the sporadic ccRCCs, deriving the discovery and successful testing of various molecularly targeted agents, laying down the therapeutic landscape. The VHL gene is implicated as the sole crucial factor in the molecular pathogenesis of ccRCC. Loss of heterozygosity at the VHL locus on chromosome 3p25, leads to overproduction of vascular endothelial growth factor (VEGF) and activation of its downstream pathways. Being a pro-angiogenic factor, it is a plausible therapeutic target. Another important pathway is phosphatidylinositol-3-kinase-Akt-mTOR signaling regulated by the phosphatase and tensin homolog tumor suppressor gene. Inhibition of this pathway leads to decreased protein translation and inhibition of both angiogenesis and tumor cell proliferation.

Immune mechanisms

The heterogeneous disease biology of ccRCC indicates the immune mechanisms of disease pathogenesis. Histopathological studies have shown diffuse tumor infiltration with T cells, natural killer cells, dendritic cells, and macrophages in RCC. Possibly, due to poor antigenicity of tumor cells, and camouflaging by the immune tolerance mechanisms, gradually tumors learn to evade the host defense mechanisms. As per Mapara and Sykes, the basic principles of immune tolerance include: Expression of death-inducing ligand (Fas) and secretion of immunosuppressive cytokines (Interleukin 10, transforming growth factor-beta), leading to direct deletion of immune effector cells, lack of expression of costimulatory molecules (CD 28 on T cells, B7 ligands on antigen-presenting cells) and overexpression of inhibitory molecules CTLA-4, programmed cell death-1 (PD-1), and PD-1 ligands causing inhibition of T cell activation or induction of anergy.[4]

Rationale of IO-antiangiogenic drug combos

Having seen the individual long-term safety and efficacy of tyrosine kinase inhibitors (TKIs) and IOs, with different mechanisms of action, thereby having no cross-resistance and negligible overlapping toxicities, it had been intriguing to add both of them in want of yielding better outcomes at the cost of minimally increased toxicities. This formed the rationale of IO-antiVEGF combination early phase trials. Tumor microenvironment (TME) is the complex interaction of milieu of cytokines present, phenotype of the immune cells, proteins expressed on the tumor cells, stromal components, and tumor microvasculature. VEGF inhibition is postulated to modulate the host TME by suppressing the immunogenicity through several mechanisms. High VEGF levels lead to an abnormal vasculature in the tumors with high interstitial pressures that can decrease the immune cell traffic, impacting the quantity and quality of the infiltrate. Hence, the level of pathological vascularity of TME can render the tumors "hot" or "cold" depending on the presence or absence of TILs, thereby, hot tumors being more responsive to IO. Exposing the mRCC to both modalities together may synergistically suppress the VEGF driven tumor proliferation as well as modulate the TME toward "hot" to regulate the immunologic action against tumor cells.[5] After the success of early trials, two-phase three trials have successfully demonstrated the feasibility and survival benefits. Likewise, a recent phase III trial of IO and antiVEGF monoclonal antibody combination has also been successful [Figure 1].

Recent studies

Two studies have parallely proved the progression-free survival (PFS) benefit of IO-TKI combos against the standard of care (SoC). KEYNOTE-426 is an open-label, phase three trial of 861 previously untreated advanced ccRCC patients who were randomized to receive 3 weekly pembrolizumab (200 mg) plus axitinib (5 mg) orally BD (432 patients) or sunitinib (50 mg) orally OD for the first 4 weeks of each 6-week cycle (429 patients). The primary endpoints were overall survival (OS) and PFS in the intention-to-treat (ITT) population. After a median follow-up of 12.8 months, the estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab–axitinib group and 78.3% in the sunitinib group (hazard ratio [HR] for death, 0.53; 95% confidence interval [CI], 0.38–0.74; $P < 0.0001$). Median PFS was 15.1 months in the pembrolizumab–axitinib group and 11.1 months in the sunitinib group (HR for disease progression or death, 0.69; 95% CI, 0.57–0.84; $P < 0.001$). The objective response rate (ORR) was 59.3% (95% CI, 54.5–63.9) in the pembrolizumab–axitinib group and 35.7% (95% CI, 31.1–40.4) in the sunitinib group ($P < 0.001$). The benefit of pembrolizumab plus axitinib was observed across the International Metastatic RCC Database Consortium (IMDC) risk groups, and regardless of programmed death ligand 1 (PDL1) expression, with stratified OS on subset analysis having consecutive HR of 0.64, 0.53, and 0.43 for favorable, intermediate, and poor risk groups. However, the stratified PFS benefit was more in intermediate and poor risk groups (i.e., favorable, intermediate, and poor risk, HR 0.81, 0.70, and

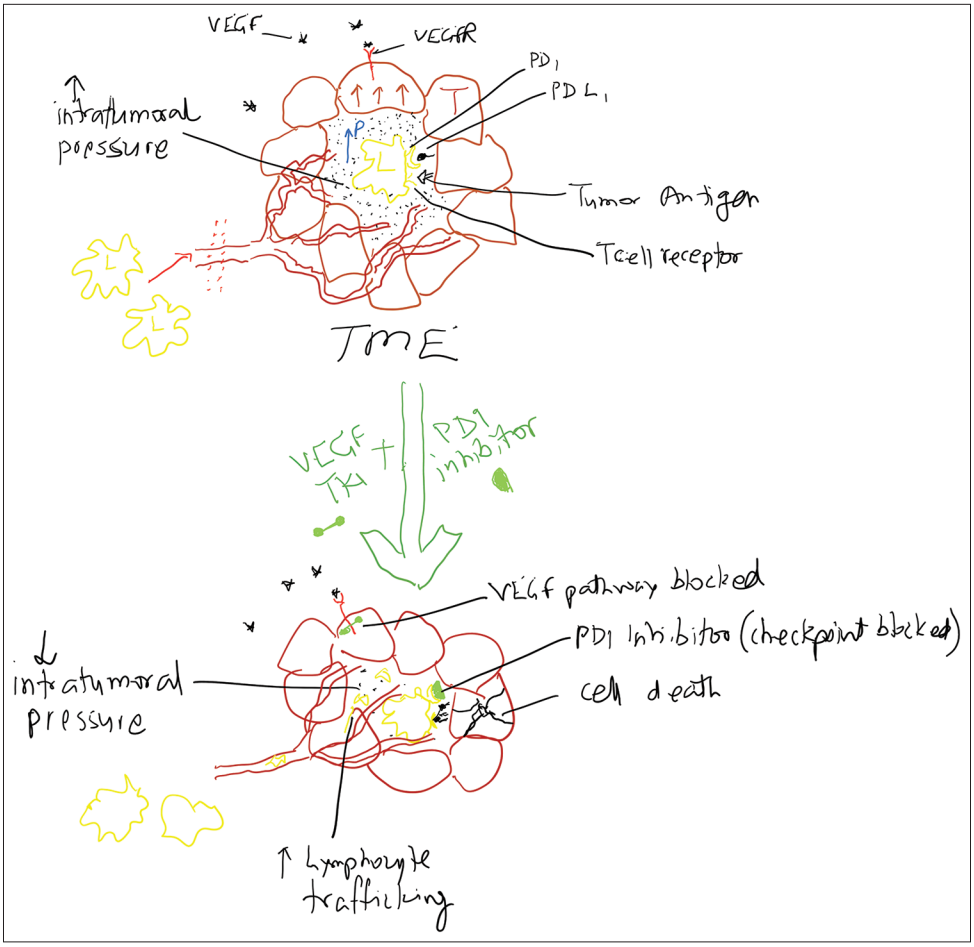

Figure 1: Pathophysiology of immune checkpoint inhibitors-antiangiogenic drug combos. IO can be Anti PD1/PDL1/CTLA4 mab. Antiangiogenic drug can be TKI or antVEGF mab.

0.58, respectively). Grade 3 or higher adverse events of any cause occurred in 75.8% of patients in the pembrolizumab–axitinib group and in 70.6% in the sunitinib group.[6]

In Javelin Renal 101, randomization was of 886 patients in a 1:1 ratio to 2 weekly avelumab (10 mg/kg of body weight) plus axitinib (5 mg) orally BD or sunitinib (50 mg) orally OD for 4 weeks (6-week cycle). The two independent primary endpoints were PFS and OS among patients with PDL1 positive (≥1% of immune cells staining positive within the tumor area, by Ventana SP263) tumors. Among the 560 patients with PDL1 positive tumors (63.2%), the median PFS (mPFS) was 13.8 months with avelumab plus axitinib, as compared with 7.2 months with sunitinib (HR for disease progression or death, 0.61; 95% CI, 0.47–0.79; $P < 0.001$); in the overall population, the mPFS was 13.8 months, as compared with 8.4 months (HR, 0.69; 95% CI, 0.56–0.84; $P < 0.001$). The stratified PFS benefit in overall population was equivalent in all risk groups (HR 0.50, 0.64, 0.53 in favorable, intermediate and poor risk groups, respectively). Among the patients with PDL1 positive tumors, the ORR was 55.2% with avelumab plus axitinib and 25.5% with sunitinib, and at a median follow-up for OS of 11.6 months and 10.7 months in the two groups, 37 patients and 44 patients had died, respectively (stratified HR for death, 0.82).[7]

A recent multicenter, open-label Phase III randomized controlled trial (IMmotion 151) compared atezolizumab 1200 mg plus bevacizumab 15 mg/kg q3 weekly with sunitinib 50 mg PO OD for first 4 weeks every 6 weekly. This is a combination trial of a total of 915 patients randomized in 1:1 fashion (454:461) in the comparator arms. Coprimary endpoints were investigator assessed PFS in the PDL1 positive (≥1% of tumour-infiltrating immune cells expressing PD-L1 SP142 by Ventana IHC) population and OS in ITT population. The preliminary results have shown a mPFS benefit of 3.5 months (11.2 vs. 7.7 months) in the PDL1 positive population (HR 0.74). mOS benefit did not cross the significant boundary in the ITT population at the interim analysis (HR 0.93). Forty percent patients in the atezolizumab-bevacizumab arm and 54% in the sunitinib arm suffered Grade 3–4 treatment related adverse effects.[8]

CURRENT TREATMENT LANDSCAPE

The choice of treatment in advanced RCC is governed by prognostic risk factors. The IMDC prognostic model integrates six adverse factors, namely Karnofsky Performance Status <80%, time from diagnosis to treatment <1 year, hemoglobin concentration <lower limit of normal, serum calcium >upper limit of normal, neutrophil count >upper limit of normal, and platelet count >upper limit of normal. Patients with none of these risk factors are considered good risk, those with one or two are considered intermediate risk, and those with three or more risk factors are considered poor risk. Options of systemic therapy for such patients include (anti-VEGF Mabs, TKIs, immunotherapy, and mTOR inhibitors) [Table 1].

In recent times, there has been a mammoth change in the diagnostic and therapeutic algorithms in oncology. mRCC is no exception. Various newer treatment paradigms have been postulated and tested. Simultaneous blocking of various targets has emerged as an exciting avenue. Chemo-IO combos are already approved in lung cancer. IO-IO combination was earlier approved in RCC. Of late, IO-TKI combos have been tested in RCC and have been proved to be of PFS benefit and got Food and Drug Administration (FDA) approval in quick succession. IO-bevacizumab has also proven its worth in the first line, although it is not yet FDA approved. Other newer molecules are also being tested. The FDA approved first-line drugs in metastatic ccRCC are cabozantinib, sunitinib, pazopanib, nivolumab-ipilimumab, pembrolizumab-axitinib, and avelumab-axitinib combinations. Nivolumab-ipilimumab is FDA approved only for intermediate/poor risk advanced ccRCC. Nevertheless, National Comprehensive Cancer Network (NCCN) lists nivolumab-ipilimumab (Cat 1), pembrolizumab-axitinib (Cat 1), and cabozantinib (Cat 2a) for intermediate/poor risk patients, and pembrolizumab-axitinib, sunitinib and pazopanib (all Cat 2a) for favorable risk group patients as preferred first-line regimens. For asymptomatic disease with a limited tumor burden, close active surveillance is also an option.

Unmet needs in Indian context

1. Despite significant advancements in various systemic agents, the ideal sequencing of agents is not known
2. Agents with better central nervous system potency are not clear
3. Some drugs are not available in India, namely, cabozantinib, avelumab and ipilimumab
4. Indian patients are relatively of poorer PS due to detection in advanced stages
5. Cost further doubles the trouble as significant number of patients are on self-payment mode.

MAJOR ONGOING STUDIES

A lot of trials are further attempting such combinations and hopefully, we will have a range of such combination approvals in the near future [Table 2].

DISCUSSION

Anticancer therapies have seen the transition from blunder burst therapies like cytotoxic chemotherapies to personalized targeted therapies followed by the apparently more physiological immunotherapy over past 20 years or so. This paradigm shift has occurred with the constant endeavors of developing more effective and less toxic therapies. Researching new molecular targets and developing newer drugs is a time and cost consuming venture. Meanwhile, it is practical and wise to derive maximum benefit from the available molecules and modalities. This entails trying various drug and mechanism combinations, and this has seen success in various diseases.

Single agent VEGF TKI

As per NCCN, cabozantinib, sunitinib, and pazopanib are approved for the first line [Table 1]. Sunitinib had been the SoC for past many years for all risk groups. It got approval after showing better survival in good and intermediate risk ccRCC, in a randomized comparison with interferon alpha, the SoC at that time. COMPARZ trial showed non-inferiority and better tolerability of pazopanib as compared to sunitinib. In the latter, there was no stratification as per risk. Cabozantinib was compared with sunitinib in CABOSUN trial in first line treatment of intermediate and poor risk patients, where it showed better PFS (8.6 vs. 5.3 m) and better OS (26.6 vs. 21.2 m) with similar safety profile. No study has directly prospectively compared axitinib with any of these in first line. A retrospective multicenter analysis has shown prolonged cancer specific survival and OS and better safety profile of axitinib versus sunitinib as first-line therapy.[9]

Single agent IO

There is no IO approved as single agent in the first-line setting. Nivolumab is approved as single agent in second line. Pembrolizumab is not approved as a single agent in ccRCC. However, it is being studied as a single agent in first line in KEYNOTE-427 trial where preliminary results have shown a PFS of 8.7 m and a higher response in IM/poor risk disease as compared to favorite risk dis (42 vs. 32%).[10]

Combo

With the advent and experience of molecularly targeted safer drugs, the research is focusing on various combinations,

Table 1: Comparison of all first-line drugs.

Parameter/Drugs	Ipi-nivo versus Sunitib		Pem-Axi versus Sunitib	Ave-Axi versus Sun		Pazo versus Sunitib	Caboz versus Sunitib	Ate/Bev* versus Sun	
Study (Phase)	CM 214 (3)		KN 426 (3)	Javelin renal 101 (3)		COMPARZ (3)	CABOSUN (2)	IMmotion 151 (3)	
Subgroups	IM and poor risk	ITT		Overall popu	PDL1+			ITT	PDL1+
n	847 (425/422)	1096 (550/546)	861 (432/429)	886 (442/444)	560 (270/290)	1110 (557/553)	157 (79/78)	915 (456/461)	362 (178/184)
IMDC									
Fav	0	23 versus 23%	31.9 versus 30.5%	21.7 versus 22.5%	19.3 versus 20.3			20 versus 20%	17 versus 17%
Intermed	79 versus 79%	61 versus 61%	55.1 versus 57.3%	64 versus 66%	64.1 versus 65.9		81 versus 80.8	69 versus 69%	72 versus 72%
Poor	21 versus 21%	17 versus 16%	13 versus 12.1%	11.5 versus 10.1%	16.3 versus 13.4		19 versus 19.2	12 versus 12%	11 versus 11%
PDL1 ≥1%	26 versus 29%	23 versus 25%	59.3 versus 61.7%	61 versus 65.3%	100 versus 100			39 versus 40%	100 versus 100%
mPFS (m)	11.6 versus 8.4#	12.4 versus 12.3 m	15.1 versus 11.1#	13.8 versus 8.4	13.8 versus 7.2#	8.4 versus 9.5#	8.2 versus 5.6#	11.2 versus 8.4	11.2 versus 7.7#
OS/HR	NR versus 26 m/0.63#	NR versus 32.9 m	0.53#		0.82#	28.4 versus 29.3 m	30.3 versus 21.8 m	33.6 versus 34.9#	34 versus 32.7
Objective RR	42 versus 27%#	39 versus 32%	59.3 versus 35.7	51.4 versus 25.7%	55.2 versus 25.5	31 versus 25%	46 versus 18%	37 versus 33	43 versus 35
CR	9 versus 1%		5.8 versus 1.9	3.4 versus 1.8%	4.4 versus 2.1	1 versus 3 pts	1.3 versus 1.3%	5 versus 2	9 versus 4
AEs		93 versus 97%	98.4 versus 99.5%	99.5 versus 99.3%				91 versus 96	
SAEs		46 versus 63%	75.8 versus 70.6%	71.2 versus 71.5%				40 versus 54	
Subseqant cancer Rx		39 versus 54%	50 versus 60.7%	20.8 versus 39.2			52 versus 58%		

*Not FDA approved yet, #primary endpoint. ITT: Intention-to-treat, PDL1: Programmed death ligand 1, mPFS: Median progression-free survival, OS: Overall survival, HR: Hazard ratio, RR: Risk ratio, AE: Adverse events, SAE: Serious adverse events, IMDC: International Metastatic RCC Database Consortium, RCC: Renal cell carcinoma

Table 2: Major ongoing clinical studies.

NCT	Study name	Phase	Description
NCT03937219	COSMIC-313	3	Study of cabozantinib in combination with nivolumab and ipilimumab in patients with previously untreated advanced or metastatic renal cell carcinoma
NCT 02811861	CLEAR	3	Multicenter, open-label study comparing lenvatinib plus pembrolizumab or lenvatinib plus everolimus versus sunitinib in treatment-naive patients with advanced RCC is underway
NCT 03141177	CheckMate9ER	3	A Phase III study assessing the combination of nivolumab plus cabozantinib versus Sunitinib in treatment-naïve patients with advanced RCC is underway. Enrollment began in August 2017, and is ongoing
NCT02853344	KEYNOTE-427	2	Pembrolizumab as a single agent in first line

RCC: Renal cell carcinoma

using "vertical" or "horizontal" blockade' strategies. The FDA approved combination of lenvatinib+ everolimus in ccRCC in subsequent setting is an example of vertical blockade.[11] The discussion at hand of IO-TKI combo in upfront setting will be incomplete without knowing the added advantage of using both drugs together versus sequentially. In addition, survival benefits of individual drugs of the combination are needed to be known beforehand. Unfortunately, we do not yet have concrete data of such a head to head comparison. The IO-IO combo of ipilimumab-nivolumab versus sunitinib was first attempt of such kind in first-line Phase III CM 214 trail, where it showed better OS as compared to sunitinib (HR 0.68) although the PFS was not different in the ITT population. Interestingly, in this trial, in the subset of PDL1 positive (>1%), intermediate, and poor risk patients; the mPFS was 22.8 versus 5.9 m, with a CR of 16%. With IO-IO combo, Grade 3 or 4 events occurred in 46% and 63%, respectively. Treatment-related adverse events resulting in therapy discontinuation occurred in 22% and 12% of the patients in the respective groups.[12] On the basis of OS benefit, FDA approved this combo for first-line treatment of intermediate and poor risk patients. The IO-TKI combo is principally a synergistic phenomenon, where the expected benefits may be exponential, rather than being just additive. The available data look promising and complete OS data are eagerly awaited. In the KEYNOTE-426 trial, PFS (15.1 vs. 11.1 m) and OS (HR 0.53) both show improvement, and the maximum benefit was received by poor risk patients (poor>intermediate>fav) in both PFS and OS. The IO-TKI combo has yielded statistically significant improvement in OS as per the HR although median has not yet been reached. The benefit was seen in all the risk groups. Javelin study failed to show any OS benefit at data cutoff, however, it also showed a PFS benefit of 13.8 versus 8.4 m. As the mechanisms of drug action are different, and there are no overlapping toxicities, the adverse events profiles are not much different between the two arms in both the trials. The severe adverse events are slightly higher in the IO-TKI combination arms as compared to single agent TKI. However, the severe adverse events in Atezolizumab-Bevacizumab combination were much lower than sunitinib single agent.

There are some unignorable controversies in IO-antiangiogenic trials. First, going by the simple logic, comparator arm in IO-TKI trials should have been axitinib or the combo should have been IO plus sunitinib. Although the reason given by proponents of this trial design is that sutent in combination with IO was more toxic in earlier phase trials, nevertheless, the patent expiry of sutent earlier than inlyta (expiry 2025) is a food for thought. Second, all the five drugs in the comparator arms of IO-antiangiogenic drugs (pembrolizumab, avelumab, axitinib, bevacizumab, and atezolizumab) have never been prospectively tested in metastatic ccRCC as single agents in the first line. How much benefit IO has actually added to antiangiogenic drug, if the latter was used alone remains an unanswered question. Third, patients with untreated or symptomatic CNS metastases were excluded from all three trials, as is done in most of the other trials. Fourth, PDL1 assessment methodology was not same in all the three studies. Finally, sunitinib required a dose reduction in 42%. Do we face such high toxicity practically in real life where we have patients with much poorer PS and many comorbidities?

Sequential use

OS is the most desired study end-point. The most pertinent question at this stage is whether combined use of these IO-TKI will yield superior survival than sequential use of the same agents. No one has answer to this question. Moreover, we do not yet have complete OS data for this combo itself. If sequential use is going to give same or superior survival, then there is no point in exposing the patients to dual toxicity. In addition, we might be inviting dual resistance together and earlier, whereas on sequential use we retain the option of drug rechallenge.

CONCLUSIONS

Having six options in frontline setting gives the clinician a leeway to choose as per the situation but more important will be to know the best sequence to yield maximum survival benefit. Cross trial comparisons can be highly misleading,

and we do not have the independent efficacy data of drugs used in combos. Nevertheless, the IO-TKI combos look quite promising. As the OS benefit with combo was seen in all the risk groups as per the HRs, and Ipilimumab/Cabozantinib being not yet available in India, it makes a case to use Pembrolizumab-Axitinib combo in first line in all patients. OS being the best yard stick, we will need to wait for the OS data to mature before we draw a final conclusion. Furthermore, keeping in mind the expected toxicities (including financial toxicity) of combo, we recommend TKI alone for favorable risk patients. For intermediate and poor risk patients, whereever feasible. We recommend using IO-TKI or IO-IO combination. Future trials should compare sequential versus combo. More robust biomarkers are needed.

Declaration of patient consent

Not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Patard JJ, Leray E, Rioux-Leclercq N, Cindolo L, Ficarra V, Zisman A, *et al*. Prognostic value of histologic subtypes in renal cell carcinoma: A multicenter experience. J Clin Oncol 2005;23:2763-71.
2. Joshi A, Anand A, Prabhash K, Noronha V, Shrirangwar S, Bakshi G, *et al*. Kidney cancer demographics and outcome data from 2013 at a tertiary cancer hospital in India. Indian J Cancer 2017;54:601-4.
3. SEER Stat Fact Sheets: Kidney and Renal Pelvis. Available from: http://www.seer.cancer.gov/statfacts/html/kidrp.html. [Last accessed on 2019 Dec 13]
4. Raman R, Vaena D. Immunotherapy in metastatic renal cell carcinoma: A comprehensive review. Biomed Res Int 2015;2015:367354.
5. Amin A, Hammers H. The evolving landscape of immunotherapy-based combinations for frontline treatment of advanced renal cell carcinoma. Front Immunol 2019;9:3120.
6. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, *et al*. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N E J Med 2019;380:1116-27.
7. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, *et al*. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N E J Med 2019;380:1103-15.
8. Rini BI, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, *et al*. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): A multicentre, open-label, phase 3, randomised controlled trial. Lancet 2019;393:2404-15.
9. Hatakeyama S, Tanaka T, Ikehata Y, Fujita N, Masumori N, Kitamura H, *et al*. Axitinib versus sunitinib as first-line therapies for metastatic renal cell carcinoma: A multicenter retrospective analysis. J Clin Oncol. Available from: https://www.ascopubs.org/doi/abs/10.1200/JCO.2019.37.7_suppl.555?af=R. [Last accessed on 2019 Dec 02].
10. Pembrolizumab Monotherapy as First-Line Therapy in Advanced Clear Cell Renal Cell Carcinoma (ccRCC) Cohort A KEYNOTE-427. Oncology PRO. Available from: https://www.oncologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress/KEYNOTE-427-Cohort-A-Pembrolizumab-Monotherapy-as-First-Line-Therapy-in-Advanced-Clear-Cell-Renal-Cell-Carcinoma-ccRCC. [Last accessed on 2019 Dec 02].
11. The ASCO Post. FDA Approves Lenvatinib in Combination with Everolimus in Advanced Renal Cell Carcinoma. Available from: https://www.ascopost.com/issues/may-25-2016/fda-approves-lenvatinib-in-combination-with-everolimus-in-advanced-renal-cell-carcinoma. [Last accessed on 2019 Dec 02].
12. Motzer RJ, Tannir NM, McDermott DF, Frontera OA, Melichar B, Choueiri TK, *et al*. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N E J Med 2018;378:1277-90.

How to cite this article: Darling HS, Gupta A. Immune checkpoint inhibitor – anti-angiogenic drugs combination in treatment-naïve metastatic clear cell renal cell carcinoma: Why should immunotherapy have all the fun! Int J Mol Immuno Oncol 2020;5(1):1-7.