



Role of immunotherapy in metastatic renal cell cancer: past, present and future

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Introduction

It was only in the late 90s when the link between the immunology and oncology was known to scientists. Tumor shrinkage of sarcoma following injection of killed bacteria noted by Coley was one of the earlier observations which led to considering immunotherapy in cancer treatment (1). Although the initial studies on interferon gamma-1b failed to improve outcomes in metastatic renal cell carcinoma (mRCC) (2), cases of spontaneous regression of metastatic lung lesions perpetuated investigations to study the potential role of immunotherapy in mRCC (3).

RCC accounts for 2–3% of all malignancies, and it constitute >80% of primary renal neoplasm. Clear cell type is the commonest subtype of RCC (85%). Approximately, 1/3rd of cases diagnosed with RCC have metastasis at presentation, and another 1/3rd usually develop metastases at follow up (4). When localized, surgical excision can be curative. Unfortunately, prognosis and outcome of mRCC remains dismal.

Staging and risk assessment

Like in most of the solid tumors, TNM staging system is used in RCC to define the anatomic extent of cancer spread and to stratify to stage groups. The variable clinical course of patients in the same stage, however, forced researchers to think beyond the TNM staging to prognosticate outcomes.

Subsequently, various parameters such as disease extent, tumor size, tumor necrosis, nuclear grade histology, performance status, and presence of paraneoplastic syndromes (e.g., anemia, hypercalcemia, thrombocytosis, fever, weight loss) have been used to formulate an improved prognostic model (5-7). Most recent and frequently used models are the stage, size, grade and necrosis (SSIGN) score and the University of California Los Angeles Integrated Staging System (UISS) (8,9).

Predicting risk in advanced disease

In 1999, Motzer *et al.* published a multivariate analysis study on mRCC cases. They formulated a risk assessment scale of mRCC patients during pre-targeted therapy era (10). Parameters used in this model were low Karnofsky performance status, high serum lactate dehydrogenase, low hemoglobin, high “corrected” serum calcium, and absence of prior nephrectomy. Later in 2005, Makhail *et al.* validated Motzer’s model, and identified two additional independent prognostic factors: prior radiotherapy and sites of metastasis (11). While both models were helpful in prognosticating patients with mRCC, in the current era of targeted therapy, they are not frequently used.

Currently, most clinicians use the model proposed by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model for prognostication of survival

in patients with mRCC (12). The six parameters used in “IMDC score” are anemia, thrombocytosis, neutrophilia, hypercalcemia, Karnofsky performance status, and <1 year from diagnosis to first-line targeted therapy. IMDC model has since undergone external validation by several groups (12-14).

Cytokines in advanced RCC

Interleukins (IL) and interferons

IL-2 is a cytokine that primarily acts directly on T cells and plays a role in adequate functioning of the immune system. Similarly, interferon-alpha stimulates T cells to attack cancer cells. Both these agents were studied for their efficacy in several randomized controlled trials (15,16). However, both agents individually were found to be effective only in selected patients. More importantly, drug toxicity limited its use.

Many trials were embarked to explore the utility of adjunctive agents such as NG-monomethyl-L-arginine, superoxide dismutase, and others in reducing the toxicity of these cytokines without compromising the efficacy (17,18). However, with the shift to immunotherapeutic and targeted therapy, their role in the setting of more effective and better tolerated checkpoint inhibitors and anti-angiogenic agents is undefined but it still could be an option in selected patients.

Basics immune pathways

Programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) pathway

This pathway contains two proteins called PD-1, and PD-L1. There is a differential expression of these proteins on different cells. Cancer cells usually express PD-L1 and immune cells express PD-1. Interaction between PD-1 and PD-L1 forms an immune evading “shield” which protects tumor cells from being attacked by the immune system.

Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) Pathway

Similarly, in CTLA-4 pathway, CTLA-4 and cluster of differentiation 28 (CD28; a cell membrane protein), which are both expressed on T cells, compete with each other to bind to B7, a membrane protein present on activated antigen presenting cell (APC). The amount of CTLA-4:B7

binding compared to CD28:B7 binding determines if the T cells will be activated.

New ray of hope: combination therapies

Recently many studies have been conducted to study the efficacy of combination therapies. Various targets like PD-1, PD L-1, CTLA-4, VEGF, and mTOR have been studied and we will be discussing various trials and their outcome in following sections.

Nivolumab plus ipilimumab vs. sunitinib

Amongst the initial landmark trials on immunotherapy for mRCC, the *Bristol-Myers Squibb* sponsored trial. Motzer *et al.* published the results of the phase 3 trial (Check Mate 214 trial, ClinicalTrials.gov number, NCT02231749). In this study, one arm received nivolumab plus ipilimumab (550 cases untreated mRCC) whereas other arm was given sunitinib (546 cases). They found that combination arm had significant overall survival (OS) and objective response rate (ORR) benefit compared to sunitinib alone. However, progression free survival (PFS) was similar in both the arms. Interestingly, within nivolumab plus ipilimumab arm, a greater response was noted in PD-L1 positive tumors when compared to PD-L1 negative ones (19,20). Cella *et al.* studied the same cohort and reported fewer adversities and better health-related quality of life (HRQoL) with the combination therapy (21).

Pembrolizumab plus axitinib vs. sunitinib

While Bristol-Myers Squibb was working on nivolumab plus ipilimumab combination regimen, Merck Sharp & Dohme Corp. initiated phase 1b trial (ClinicalTrials.gov, number NCT02133742) to assess the safety of treatment combination of pembrolizumab plus axitinib (22).

With the success of phase 1b, combination regimen entered phase 3 trial (KEYNOTE-426, ClinicalTrials.gov Identifier: NCT0285333). This phase 3 open-label study randomized 861 participants to either pembrolizumab plus axitinib (432 patients) or sunitinib alone (429 patients). At follow up, combination arm was superior to sunitinib alone with regards to OS [90% *vs.* 78% at 12 months, hazard Ratio (HR) 0.53, 95% CI, 0.38–0.74] and PFS (median 15.1 *vs.* 11.1 months, HR 0.69, 95% CI, 0.57–0.84), and ORR (59% *vs.* 36%, $P < 0.001$) (23).

Two differences to note between Check Mate 214 trial

Table 1 Landmark immunotherapy trials in treatment of RCC

Trial	Disease setting	Regimen	Total No. of patients	OS	PFS	HR	Others
Checkmate 214 (19)	Previously untreated advanced or metastatic clear cell RCC	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg vs. sunitinib 50 mg daily	1,096	Median not reached; 32.9 months	12.4 months; 12.3 months	0.68	Response much better if PD-L1 expression >1% and in intermediate and poor risk disease
Keynote 426 (23)	Previously untreated, advanced, clear cell RCC	Pembrolizumab plus axitinib vs. sunitinib	861	90%;78%	15.1 months; 11.1 months	0.69	No effect of PD-L1 expression and risk stratification
Checkmate 025 (24)	Advanced RCC treated with one or two antiangiogenic therapy	Nivolumab 3 mg/kg vs. everolimus 10 mg daily	821	25 months; 19.6 months	4.6 months; 4.4 months	0.73	Less toxicity and better quality of life
JAVELIN Renal 101 trial (25)	Previously untreated, advanced, clear cell RCC	Avelumab plus axitinib vs. sunitinib	886	11.6 months; 10.7 months	13.8 months; 8.4 months	0.69	No improvement in OS, PFS improved

RCC, renal cell carcinoma; OS, overall survival; PFS, progression free survival; HR, hazard ratio; PD-L1, programmed death ligand-1.

and KEYNOTE-426 trial are the treatment responses based on risk stratification (IMDC) and PD-L1 expression. While Check Mate 214 trial reported better outcome to combination regimen with intermediate- or poor-risk disease or with PD-L1-expressing tumors, the KEYNOTE-426 trial reported benefit irrespective of PD-L1 expression and risk classification. However, the response duration and off-treatment survival for the pembrolizumab plus axitinib therapy are still being tabulated, and the study is expected to be completed by January 27, 2020.

Based on results of the above two landmark trials, FDA has approved nivolumab plus ipilimumab combination and pembrolizumab plus axitinib on April 16, 2018 and on April 19, 2019, respectively.

Other major landmark trials for use of immunotherapy in RCC are highlighted in *Table 1*. Current ongoing clinical trials studying the use of immunotherapy in RCC are highlighted in *Table 2*.

Avelumab plus axitinib vs. sunitinib

After the successful outcome of KEYNOTE-426 and Check Mate 214 trials, many other pharmaceutical companies have started studying other PD1/PD-L1 inhibitors. A phase 3, multinational, randomized study compared avelumab (a PD-L1 inhibitor) plus axitinib with sunitinib alone in

advanced RCC (JAVELIN Renal 101 trial, ClinicalTrials.gov number, NCT02684006). They found significant longer median PFS in general (13.8 *vs.* 8.4 months, HR 0.69) and among those with PD-L1 positive expressing tumors (13.8 *vs.* 7.2 months, HR 0.61) (25). However, there was no benefit in OS among the two groups. Also, both groups had similar grade ≥ 3 toxicities.

Based on this study, the FDA, on May 14, 2019, approved avelumab plus axitinib as first-line treatment of mRCC.

Atezolizumab plus bevacizumab vs. sunitinib

Results of phase 2 study (funded by F Hoffmann-La Roche Ltd. and Genentech Inc.) which confirmed efficacy and safety of combination regimen of atezolizumab plus bevacizumab (IMmotion150 trial, ClinicalTrials.gov number, NCT01984242) was shared at the ASCO meeting in 2017.

Following this, a multicenter, open-labelled, phase 3 trial was conducted involving 915 patients with previously untreated mRCC (IMmotion151 trial, ClinicalTrials.gov, number NCT02420821). One arm received atezolizumab plus bevacizumab (454 patients) and other arm received sunitinib alone (461 patients) (26).

The combination arm had improved PFS as compared to sunitinib alone arm in the PD-L1 positive population (HR 0.74; 95% CI, 0.57–0.96; P=0.0217). Based on the available

Table 2 Current trials of immunotherapy in RCC

Trial	Regimen	No of patients	Primary outcome	Phase
NCT02420821	Atezolizumab + bevacizumab vs. sunitinib	900	PFS, OS	3
NCT02996110	Nivolumab + ipilimumab vs. nivolumab + bms-986016	650	ORR, PFSR, DOR	2
NCT02811861	Lenvatinib + everolimus vs. lenvatinib + pembrolizumab	735	PFS	3
NCT03141177	Nivolumab vs. sunitinib or pazopanib	244	OS	2
NCT03987698	PD-1 inhibitor combination with autologous cell immunotherapy	90	PFS	2
NCT03873402	Nivolumab plus ipilimumab vs. nivolumab	418	PFS, OS	3
NCT03065179	SBRT in combination with nivolumab/ipilimumab	25	AE, RR	2

RCC, renal cell carcinoma; PFS, progression free survival; ORR, objective response rate; OS, overall survival; PFSR, progression free survival rate; DOR, duration of response; AE, adverse events; RR, response rate.

data on interim analysis, no significant difference in the median OS in the intent-to-treat population was noted amongst the two groups (26).

Sunitinib or pazopanib plus nivolumab

CheckMate 016 trial (Clinicaltrials.gov identifier, NCT01472081) was a phase 1 study which involved studying combination of sunitinib with nivolumab or Pazopanib with nivolumab. Unfortunately, both these combinations resulted in high-grade toxicities leading to premature closure of study. All patients in both the arms (100%) suffered treatment-related adverse events (AEs). 82% in sunitinib plus nivolumab arm and 70% in Pazopanib plus nivolumab arm had grade 3/4 treatment-related AEs (27).

Pazopanib and pembrolizumab

Similar to CheckMate 016 trial, another phase I/II study (Novartis sponsored) was discontinued prematurely due to liver toxicity (Pazopanib and pembrolizumab) (28).

Immune-check inhibitor as a monotherapy

As mentioned above, most of the trials initially focused on PD-1/PD L-1 inhibitor-based combination therapy. With encouraging results of combination therapy, PD-1 inhibitor monotherapy as a first line agent was studied in KEYNOTE-427 trial.

This trial studied pembrolizumab monotherapy as first-line therapy in aRCC (ClinicalTrials.gov Identifier: NCT02853344) and found promising efficacy and acceptable tolerability (27). Best response was noted amongst patient with intermediate-risk/poor-risk disease and with expression of PD-L1 of ≥ 1 percent (29).

Other ongoing trials

There is an ongoing phase III trial on combination therapy including lenvatinib comparing with sunitinib alone (NCT02811861). Another study is comparing nivolumab plus cabozantinib vs. sunitinib (NCT03141177). Results of these trials might add more immunotherapeutic options in the treatment of RCC (Table 2).

Current data of immunotherapy as second line agent (study on nivolumab vs. everolimus)

It is clear that immunotherapeutic agents targeting PD1/PD-L1 and CTLA 4 have proven their benefit as a first-line agent in mRCC.

Subsequently, trials studied their role as a second-line agent in previously treated aRCC (24,30). One of them was Bristol-Myers Squibb sponsored Check Mate 025 trial which included 803 patients who underwent randomization to nivolumab (406 patients) or everolimus (397 patients). There was a median OS benefit of 5.4 months with nivolumab as compared to everolimus (25.0 vs. 19.6 months). Similarly, nivolumab arm had a better ORR and PFS as

compared to everolimus. Importantly, nivolumab arm had better hazard ratio for death (from any cause) as compared to everolimus (HR 0.73; 98.5% CI, 0.57–0.93; $P=0.002$). When compared for grade 3 or more AEs, nivolumab was found to be better than everolimus (19% *vs.* 37%) (24).

Escudier *et al.* also studied the same cohort of patients for any difference in OS and ORR with nivolumab compared with everolimus based on multiple prognostic factors. They found nivolumab to be superior to everolimus across all the risk groups, age groups, and consistently better irrespective to the number and sites of metastases, and type and duration of prior therapy. Also, both PD L1 positive and negative population had similar response to nivolumab (30).

Cella *et al.* studied the HRQoL differences in patients receiving nivolumab *vs.* everolimus (31). HRQoL was assessed based on Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) and European Quality of Life (EuroQol)-5 Dimensions (EQ-5D) questionnaires. HRQoL improvement was noted to be significantly higher with nivolumab compared to everolimus (95% CI, 1.4–1.9; $P<0.0001$).

Role of immunotherapy as adjuvant therapy

Currently, there is no benefit of using targeted therapy or immunotherapy as adjuvant therapy after definitive surgical resection, as these approaches have shown no OS benefit and, instead, have led to increased toxicity.

Personalized, patient-specific immunotherapeutic approach

Autologous dendritic cell (DC)-based immunotherapy (AGS-003 product)

A single-arm, open-label phase 2 trial (sponsored by Argos Therapeutics, ClinicalTrials.gov Identifier, NCT00678119), studied the effectiveness of autologous DC therapy *vs.* sunitinib in aRCC patients with unfavorable risk factors (32). The concept behind this study was to use genetic engineering technique and follow an autologous immunotherapy approach. They generated AGS-003 product which was an *ex vivo* prepared concentrate of DCs co-electroporated with the patient's amplified tumor RNA and synthetic CD40L RNA. Subsequently, this patient-tailored, RNA-loaded mature DCs concentrate is injected

intradermal in to an axillary lymph node. These DCs were designed to efficiently present tumor antigens to both CD4+ and CD8+ T cells and thereby heightening the anti-tumor response of the patient's immune system. Study population involved 21 intermediate and poor-risk mRCC patients who received serial intradermal injections of AGS-003 following debulking nephrectomy and sunitinib until disease progression. This combination therapy showed median PFS of 11.2 months (95% CI, 6.0–19.4 months) and a median OS of 30.2 months (95% CI, 9.4–57.1 months) (32).

Unfortunately, a phase III trial that compared the combination therapy to standard therapy failed to show any benefit, which led to premature termination of the study (ADAPT trial, NCT01582672) (33).

Cancer vaccine IMA901

Another phase 3 trial sponsored by Immatics Biotechnologies GmbH (IMPRINT trial, ClinicalTrials.gov Identifier: NCT01265901), investigated the clinical effect of adding IMA901, a multi-peptide cancer vaccine (TUMAP), to sunitinib (33). 339 HLA-A*02-positive, newly diagnosed and untreated aRCC patients were randomly assigned to either sunitinib plus serial intradermal vaccinations of IMA901 (204 patients) or sunitinib alone (135 patients). Unfortunately, median OS did not differ significantly between the groups (HR 1.34; 95% CI, 0.96–1.86; $P=0.087$) (34).

Conclusions

Immune-checkpoint inhibitors (ICI) have revolutionized the treatment of many cancer types, including RCC. Specific checkpoint inhibition has already become a primary treatment modality in the management of advanced disease. There are several ongoing trials to better elucidate the ideal, personalized strategy, and it is expected that treatment of RCC would witness the addition of newer immunotherapeutic drugs. As usage of these newer molecules are increasing, reports of the AEs are also on rising trend (35,36). The challenge is to develop therapies which would be more impactful than the existing ones with minimal AEs.

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Footnote

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