IMMUNOTHERAPY IN ADVANCED OR METASTATIC RENAL CELL CARCINOMA EXCERPT OF A NEEDS ASSESSMENT

Rationale for the use of immunotherapies in RCC

Renal cell carcinomas were shown to be sensitive to immunotherapy as evidenced by spontaneous tumor regression, high infiltration with T-cells, and a high response to interleukin (IL-2) and interferon treatment *(Choueiri and Motzer, 2017b; Mazza et al, 2017)*.

Recent evidence about the interaction of the immune system with the programmed cell death protein-1 (PD-1)/PDL-1 pathway pointed to a checkpoint mechanism that negatively regulates anti-tumor response*(Choueiri and Motzer, 2017b)*.

The PD-1 receptor is located on CD4+ and CD8+ natural killer(NK) cells, and most renal cell carcinomas express the PD1 receptor ligand (PDL1) on tumor cell membranes and on tumor-infiltrating mononuclear cells. Binding of (PD-1) receptor to PDL-1 blunts the cytotoxic response of anti-tumor T-cells. Approximately 50% of RCCs' tumor infiltrating lymphocytes express PDL-1 and are associated with distant relapses and poor survival*(Thompson et al, 2006)*.

Together, these facts suggest that further studies investigating immune checkpoint inhibitors are warranted.

PD-1/PD-L1 checkpoint inhibitors

Immunotherapy agents in mRCC are directed at two main pathways: the cytokine T-lymphocyte associated antigen 4 (CTLA-4) and the (PD-1) receptor. Both receptors inhibit immune functions when activated and block T cell stimulation.

The rationale of immune checkpoint inhibitors, therefore, is to reduce these inhibitory responses and restore the ability of T-cell and natural killer cells to attack antigen presenting tumors.

The advent of immune checkpoint inhibitors has quickly shifted the paradigm of treatment in advanced RCC.

Nivolumab is the first humanized immunoglobulin G4 PD-1 inhibitor antibody that selectively targets PDL-1 and PDL-2, and blocks receptor activation (Zarrabi et al, 2017). It is FDA approved in the treatment of metastatic melanoma, squamous and non-squamous non-small cell lung cancer, Hodgkin's disease and recently, mRCC.

CTLA-4 checkpoint inhibitors Ipilimumab is a CTLA-4 antibody that blocks the inhibitory interaction of CTLA-4,- present on activated T-cells-, with its ligand CD80/CD86, expressed on immune cells.

Immune checkpoint inhibitors: A paradigm shift in treatment

• *Nivolumab approved in monotherapy in 2nd line advanced or mRCC in patients previously treated with angiogenic therapy*

Nivolumab was approved in 2015 for the treatment of patients with advanced RCC who have failed prior antiangiogenic therapy and in 2017, received approval in combination with ipilimumab for the 1st line treatment of advanced renal cell carcinoma (RCC) in immediate and poor risk patients.

In the phaseIb CheckMate 016 dose escalation trial, nivolumab plus ipilimumab has shown efficacy in pretreated and in treatment naïve patients with advanced renal cell carcinoma, with a 40% ORR, a durable response and an acceptable toxicity profile *(Zarrabi et al, 2017)*.

The landmark CheckMate025 trial established nivolumab as the preferential monotherapy in the 2nd line treatment of patients who have progressed on VEGFR therapies *(Zarrabi et al, 2017)*. In that phase III trial, Nivolumab resulted in a significantly higher median OS than everolimus in patients with pretreated advanced or metastatic clear cell RCC (median, 25.0 vs 19.6 months, hazard ratio (HR) 0.73, 95% CI 0.57-0.93), and the study was stopped early because of improved efficacy*(Escudier et al, 2017)*.

Nivolumab was better tolerated than everolimus, and a subset analysis showed that patients who received nivolumab had a higher QOL than everolimus.

Continued treatment with nivolumab post disease progression showed tumor regression in patients who disease had progressed on nivolumab, and 13% of those treated patients achieved >30% reduction in tumor burden *(Escudier et al, 2017; Zarrabi et al, 2017)(NCT016687874)*.

Checkpoint inhibitors in combination with angiogenic therapies

• *Nivolumab and ipilimumab in 1st line treatment of advanced or mRCC*

In the phase IIIb CheckMate 214 trial, the combination of nivolumab and ipilimumab was superior to sunitinib in treatment-naïve patients with advanced or metastatic clear cell RCC. A significantly higher OS and ORR was achieved with nivolumab-ipilimumab in the intermediate to poor risk patients. This combination also had fewer grade 3 or 4 adverse events compared to sunitinib*(Motzer et al, 2018b)*.

A total of 1096 patients were randomized 1:1 to receive nivolumab 3mg/kg plus ipilimumab intravenously 1mg/kg every 3 weeks for four doses followed by nivolumab 3mg/kg every 2 weeks or sunitinib 50mg orally once a day for 4 weeks in 6-week cycles.

At the 25.2 months follow up, the 18 month OS in intermediate to poor risk patients was 75% in the combination group (95% CI, 70-78) versus 60% (95% CI, 55 to 65) with sunitinib.

The overall response rate (ORR) was 42% in the nivolumab-ipilimumab group versus 27% (P<0.001), and the complete response (CR) rate was 9% versus 1% (Motzer et al, 2018b). Patients with PDL-1>1% expression had a significantly longer PFS (22.9 vs 5.9 months; HR, 0.48; P = .0003). ORR results favored sunitinib treatment in the favorable risk group.
This combination also had fewer grade 3 or 4 adverse events compared to sunitinib*(Broderick, 2018a)*.

Based on these results, nivolumab in combination with ipilimumab was FDA approved in 1st line therapy in intermediate to poor risk patients with advanced or mRCC and is listed by the NCCN as category 1, preferred treatment for these patients *(NCCN, 2018)*. Results from the phase I CheckMate 016 trial suggested the use of this combination in all risk groups including the favorable risk profile, but further confirmation is needed.

• *Pembrolizumab and lenvatinib in the treatment of advanced or mRCC* ¬
In January 2018, the combination of lenvatinib and the PD-1 inhibitor pembrolizumab was granted breakthrough therapy designation by the FDA for the treatment of advanced and/or mRCC, based on the results of the phase Ib/II study 111 *(Broderick, 2018b; PR Newswire, 2017)*.

The 24-week ORR, the primary endpoint of the study, was 63% (95% CI, 43-80) in all treatment naïve and pretreated patients; all responses were partial. The secondary endpoint, disease control rate (DCR) (complete response [CR] + partial response PR + stable disease [SD]) was 96%*(Broderick, 2018b; PR Newswire, 2017)*.

In treatment naïve patients, the ORR was 83%, and the median duration of response was not reached, further establishing the efficacy of the combination in mRCC*(Broderick, 2018b; PR Newswire, 2017)*.
The phase 3 CLEAR trial will investigate lenvatinib with everolimus or pembrolizumab versus sunitinib alone in the first-line treatment of mRCC.