



# Editorial on the use of immunotherapy in renal-cell carcinoma—promising results in combination therapy with ipilimumab and nivolumab

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## Immunotherapy in cancer

During the last decades different immunotherapies have been used in the treatment of cancer without great success. However, stimulation of the immune system seems reasonable as there are immunogenic tumors such as melanoma and renal cell carcinoma which are known to rarely spontaneously regress when the immune system of the patient regains the ability to control the cancer (1). Multiple immune escape mechanisms are described which might be targeted by immunotherapies. The aim of all approaches is to enable the immune system to again recognize cancer antigens and eliminate the tumor cells (2). In contrast to chemotherapies and targeted therapies, immunotherapies thereby have the chance to lead to durable responses.

The breakthrough of immunotherapy came with introduction of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4)-inhibitor ipilimumab which showed revolutionary results in the treatment of metastatic melanoma as compared to standard therapies at that time (3,4). In a phase III study ipilimumab was the first systemic treatment to prolong overall survival (OS) of melanoma patients with a median OS of about 10 months, which was significantly superior to the results seen in patients treated with the peptide vaccine gp100 (4). Ipilimumab is an IgG1 monoclonal antibody directed against CTLA-4, a classical immune checkpoint. It is expressed on cytotoxic

T-lymphocytes and physiologically deactivates them to prevent autoimmune activity. The blockage of the CTLA-4 receptor finally prevents this “switch-off”-mechanism and allows T-cell immune response against the neoplastic cells. Further investigation of the interaction between immune and tumor cells resulted in the development of other immune checkpoint blockers with different molecular targets such as the programmed death-1 (PD-1)-inhibitors nivolumab and pembrolizumab which are meanwhile approved by the Food and Drug Administration (FDA) for the treatment of metastatic melanoma, lung cancer (5,6), renal-cell carcinoma, and others. PD-1 is a human immunoglobulin G4 antibody which blocks the interaction between the PD-1 receptor on activated T-cells and its ligand PD-L1/PD-L2 on tumor and dendritic cells. The overall response rates in studies with PD-1-inhibitors vary between different tumors. They were reported at a range of 30–40% and thereby superior to the prior results seen with ipilimumab treatment in patients with metastatic melanoma (7,8). Finally, metastatic melanoma is the first indication for which the combination of ipilimumab and nivolumab is approved. This combination led to even higher objective response rates (ORR) of up to almost 60% and a significant advantage in progression-free and OS could be seen compared to either agent alone (9). For metastatic melanoma, the approved doses in the combination treatment are 3 mg/kg ipilimumab and 1 mg/kg nivolumab 4 times in 3 weeks intervals followed by 3 mg/kg nivolumab

every other week for up to 2 years. In the phase 1 trial this dosage of the combination revealed the highest antitumor activity at first evaluation and was hence chosen for further investigation in the CheckMate 067 phase 3 trial (10).

However, the beneficial effects of an enhanced immune activity came at the cost of, partly severe (grade 3 or 4), immune-related adverse events (irAEs), especially treatment-induced hepatitis and enterocolitis which require immunosuppressive treatment (11). Even though the nature of the side effects is similar between the different immune checkpoint blockers, frequency differs greatly. PD-1 monotherapy leads to grade 3/4 treatment-related adverse events (AEs) in 15–20% of patients, ipilimumab in 20–30%, and the combination treatment in more than half of the patients with metastatic melanoma (12,13). Interestingly, even though toxicity is increased by ipilimumab in the combination treatment, grade 3/4 AEs did not differ much between the different tested dosages of the combination treatment in patients with metastatic melanoma in the phase 1 trial with about 66% of grade 3/4 AEs with 1 mg/kg nivolumab plus 3 mg/kg ipilimumab (N1I3; cohort 8) and 69% of grade 3/4 AEs with 3 mg/kg nivolumab plus 1 mg/kg ipilimumab (N3I1; cohort 2a) (10).

Meanwhile, the combination of ipilimumab and nivolumab is or has been tested in other tumor entities such as lung cancer, head and neck-, and renal-cell carcinoma.

### **First approaches with immune checkpoint blocker treatment in renal cell carcinoma**

Immunotherapies have been used in metastatic renal cell carcinoma similar to metastatic melanoma. Especially treatment with cytokines such as interferons and interleukin-2 has been applied with limited success. Standard first-line treatment to date is the application of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors such as sunitinib and pazopanib or the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab in combination with interferon. Further tyrosine kinase inhibitors such as axitinib, cabozantinib, and lenvatinib are approved for second or later lines (14–16). Concerning immune checkpoint blockers, ipilimumab induced partial responses in 8% of patients in a phase II study (17). A third of patients suffered from grade 3 or 4 AEs, mainly enteritis and endocrine deficiencies with a positive correlation between irAEs and tumor response, as it had been previously reported in

metastatic melanoma (18). The PD-1 inhibitor nivolumab is already approved for second-line treatment of renal cell cancer. It was investigated in a phase 3 study in which 821 patients with clear-cell renal cell carcinoma received therapy with either nivolumab or everolimus, a mammalian target of rapamycin (mTOR)-inhibitor widely used as a second-line agent in renal cell carcinoma (19). In this study, nivolumab showed a favorable side effect profile and improved quality of life compared to everolimus and a superior efficacy with an ORR of 25% and significantly longer median OS (25 *vs.* 19.6 months, respectively). Whereas in melanoma patients PD-L1 expression of tumors was associated with better response to PD-1 inhibitors, no significant differences in response could be detected in advanced renal-cell carcinoma (19,20).

Thus, efficacy of immune checkpoint blockers in renal cell carcinoma had been demonstrated. Yet, responses to ipilimumab and nivolumab monotherapy did not reach as high results as seen for advanced melanoma with response rates of 12% and 40%, respectively (9).

### **The CheckMate 016 study—newest advances in renal cell carcinoma**

The encouraging results for metastatic melanoma on the combination treatment of ipilimumab and nivolumab led to several similar clinical trials for other tumor entities. In patients with metastatic renal cell carcinoma a phase I study with the combination treatment of nivolumab and ipilimumab, the CheckMate 016 study, was installed and recently published (21). Five treatment arms existed, three of which consisted of the combination therapy of nivolumab and ipilimumab [nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3), and nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (N3I3)], and two consisted of the combination of nivolumab with a tyrosine kinase inhibitor for which results have not yet been released. Regardless of dosage, the combined treatments of nivolumab and ipilimumab were administered intravenously every 3 weeks for up to four doses (induction phase) after which the regimen was switched to nivolumab monotherapy 3 mg/kg every other week until disease progression or intolerable toxicity. The primary objective of this study was to determine a recommended phase II dose regarding safety and tolerability. Forty-seven patients were assigned to each the N3I1 and N1I3 arm. In the N3I3 arm all 6

included patients had to be censored early because of disease progression (3 patients), treatment-related toxicity (2 patients), or withdrawal of consent (1 patient). Because of this high censoring percentage, no confirmed responses were found in this treatment arm, and efficacy hence could not to be evaluated. In both remaining treatment arms ORR was 40.4% with more complete responses (CR) in the N3I1 arm compared to the N1I3 arm (10.6% *vs.* 0% of patients). In the N3I1 arm 42.1% of responses were ongoing compared to 36.8% in the N1I3 arm. Median PFS was 7.7 months for the N3I1 arm, and 9.4 months for the N1I3 arm, respectively. At 12 and 24 months, OS was 81% and 67% in the N3I1 arm and 85% and 70% in the N1I3 arm, respectively. Hence, preliminary data did not show leading differences in treatment efficacy.

In contrast, toxicity was lower in the N3I1 arm with only 38.3% of patients developing grade 3/4 AEs compared to 61.7% in the N1I3 arm. Colitis and hepatitis were again the most common treatment-related AEs requiring short-term systemic glucocorticoids, confirming the experiences that had been gathered in the melanoma studies. However, in the phase 1 trial in metastatic melanoma, grade 3/4 toxicity did not differ much between N1I3 and N3I1 (10). Hence, side effects of immune checkpoint blockers seem to vary in patients with different tumor entities. Another example is the higher rate of pneumonitis in patients with lung cancer (12).

Similar to the melanoma studies, the combination of ipilimumab and nivolumab showed promising efficacy with acceptable toxicity in renal cell carcinoma. The synergistic effects of PD-1- and CTLA4-inhibition again seem to lead to a more effective T-cell-mediated anti-tumor response compared to the respective monotherapies. ORR and OS were similar in both dosage groups of this phase 1 study described by Hammers *et al.* Yet, the safety profile with significantly less cases of grade 3 and 4 AEs favors the N3I1 dosage of the combination therapy for further clinical development (CheckMate 214; NCT02231749). Further studies investigating the combination of VEGF-targeted therapy with immune checkpoint inhibitors have already shown promising results in early phases and phase 3 data of first-line trials are expected to be presented soon (IMmotion 151, NCT02420821; Javelin renal 101, NCT02684006; Keynote-426, NCT02853331).

## Conclusions

In summary, comparable to the results in metastatic

melanoma, treatment of renal cell carcinoma with combined ipilimumab and nivolumab leads to promising responses and improved survival of patients. Side effects are well-known in the meantime and can be safely managed based on our experience in other tumor entities, such as melanoma. How the combination treatment performs first-line compared to sunitinib is under investigation in a phase 3 trial. Further ongoing strategies explore the efficacy of a combinatorial approach of VEGF-targeted and immune checkpoint blockade.

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