Editorial Commentary

Immune-checkpoint inhibitors in brain metastases from renal cell carcinoma: a battle was lost but not the war

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Immune-checkpoint inhibitors have recently changed the landscape treatment for metastatic clear cell renal-cell carcinoma (ccRCC) since they showed to be effective in disease control and survival improving. In particular, the programmed death 1 (PD-1) checkpoint inhibitor nivolumab demonstrated efficacy in two phase 3 studies analyzing patients with both alone and in association with ipilimumab (1,2). However, patients with brain involvement were not enrolled and this clinical setting represents a treatment challenge for physicians.

We congratulate the authors of the NIVOREN study (3) because it represents the first prospective study assessing nivolumab activity in patients with brain metastases from ccRCC. Indeed, about 10% of patients with metastatic ccRCC develop brain metastases and this event is usually associated with poor prognosis (4). The role of systemic treatment for this setting of patients remains challenging: a few data are available from sunitinib (5) and sorafenib (6) expanded access programmes with median progression-free survival (PFS) between 5 to 7 months and from single cases or retrospective series on cabozantinib (7,8) and pazopanib (9). Farther, the role of immunotherapy needs to be clarified for these patients.

Flippot *et al.* (3) prospectively analyzed patients enrolled in the Nivoren trial, a multicenter phase II study evaluating the activity and safety of nivolumab in patients with metastatic ccRCC, asymptomatic and with measurable brain metastases, who failed at least one prior treatment of antiangiogenic therapy.

The primary endpoint of this study was the best intracranial response in patients with brain metastases that were not locally treated with surgery or radiation therapy. Assessment of intracranial response was performed every 12–15 weeks with mRECIST criteria by contrast-enhanced magnetic resonance imaging or computed tomography scan. Intracranial response was assessed in 34 patients and objective intracranial response was limited to 4 cases (12%); stable disease was observed in 13 (38%) of patients. Moreover, median intracranial PFS was 2.7 months. These data demonstrated the poor activity of nivolumab against untreated brain metastases in patients with ccRCC. Noteworthy, the overall extracranial response rate was about twice that of the overall intracranial response (21.2% *vs.* 11.8%), although no complete response was reported among extracranial disease. The reasons for this are unclear; indeed, studies analyzing immune-checkpoint inhibitor activity in other types of tumors, such as melanoma and non-small cell lung cancer (NSCLC), reported a strong concordance between central nervous system and systemic response. Yet, the intracranial response was much lower in ccRCC compared to the other tumors (10,11). Likely, brain metastases from ccRCC can develop different tumor

microenvironments and molecular characteristics compared to primary tumor, which could lead to the improvement of their immunosuppressive activity (12).

There is a growing interest in combining radiotherapy and immunotherapy, especially immune-checkpoint inhibitors. Emerging evidence supports their synergistic effect; in particular, radiotherapy can cause inflammation and upregulate the inflammatory cytokines which improve immunogenicity of tumors and therefore the efficacy of immunotherapy itself (13) against both irradiated brain metastases and unirradiated lesions, by abscopal immune effect (14). However, small studies evaluating the impact of the radiotherapy plus immunotherapy combination on outcome in terms of overall survival and PFS in patients with brain metastases reported discordant results (15-18). Recently, Theelen *et al.* (19) in a randomized phase 2 study (PEMBRO-RT trial) in which 76 patients with metastatic NSCLC received pembrolizumab with or without stereotactic ablative radiotherapy performed within 7 days before immunotherapy, found no statistically significant difference of overall response rate at 12 weeks between the two arms of patients, although a doubling of overall response rate was observed in patients receiving radiotherapy compared to patients treated with pembrolizumab alone (36% *vs.* 18%, respectively; P=0.07); interestingly, a positive result was obtained with combination treatment in the subgroup of patients with tumors expressing less than 1% PD-L1 (HR =0.49, P=0.03).

Regarding the impact of RT + immunotherapy on brain metastases from ccRCC in the NIVOREN trial, patients with untreated brain metastases (cohort A) were compared to patients with brain metastases who had undergone prior local therapy (cohort B) before nivolumab (85% stereotactic radiation therapy, 12% whole brain RT, 3% stereotactic plus whole brain RT). Median duration of treatment was very similar between the two groups: 4.9 months in cohort A and 4.5 in cohort B. Although, the difference in intracranial progression free-survival between untreated and pretreated brain lesions was not the primary endpoint of the NIVOREN trial, the authors reported a better result in patients receiving prior radiation therapy: median intracranial PFS was 4.8 months (95% CI, 3.0–8.0 months) in cohort B and 2.7 months (95% CI, 2.3–4.6 months) in cohort A; the 6-month intracranial PFS rate was 23.8% (95% CI, 11.1–39.2%) and 49.4% (95% CI, 31.7–64.8%) in cohort A and B, respectively. Noteworthy, patients in cohort B reported a better outcome despite the presence of more negative prognostic factors than in group A; indeed, most patients with an excellent performance status (27% *vs.* 9% in group A and B, respectively), with a favorable IMDC risk disease (24% *vs.* 18% in group A and B, respectively), with a single brain metastasis (67% in group A and 59% in group B), with smaller brain lesions (11 *vs.* 17 mm in group A and B, respectively) and with a tumor grade ≤2 (36% in group A and 22% in group B) were in cohort A.

Moreover, on multivariate analysis adjusted for baseline characteristics (prior focal brain therapy, ECOG PS, number of brain lesions, Fuhrman grade, number of previous systemic therapies, international metastatic renal cell risk group), prior radiotherapy (cohort B) decreased the risk of intracranial progression with an HR of 0.49 (95% CI, 0.26–0.92). However, this impressive result could be due to sample bias; first, the number of patients was not calculated for the analysis of the efficacy of combination treatment *vs.* nivolumab alone, so we could have a false positive result; therefore, a larger randomized and prospective study should be performed to confirm the real role of radiotherapy when associated with immunotherapy in patients with brain metastases from ccRCC. Secondly, the paper did not report the timing between previous RT and administration of nivolumab; could radiotherapy lose its synergistic effect if it was performed long before immunotherapy? How long should this time be? What is the optimal dosage and fractionation of radiation therapy in this setting of patients? This should be one focus of future clinical trials. Third, despite increased inflammation due to irradiation, patients in cohort B showed a lower use of steroids during immunotherapy: could these patients have a better prognosis compared to patients in cohort A? Could steroids have decreased effectiveness of immunotherapy in cohort A patients?

Another topic for further consideration is the possible impact of the lesion size on immunotherapy efficacy; indeed, cases with complete intracranial response were seen only in patients with small single brain metastases (<10 mm) and all of these were untreated brain metastases; moreover, patients with bigger lesions (≥10 mm) reported progressive disease as best response during nivolumab therapy compared to cases with smaller lesions (58% *vs.* 40%). Intriguingly, the median sum of diameters of brain target lesions was higher in cohort B patients, who had a better outcome compared to patients of group A. Could radiotherapy increase tumor immunogenicity, especially in larger lesions?

Lastly, Flippot *et al.*, in their study, did not analyze possible molecular factors as predictors of immunotherapy benefit; biopsy of brain lesions should be mandatory in

these patients to obtain molecular information such as tumor mutational burden, mismatch repair system status, PD-L1 expression rate and density of tumor-infiltrating CD8 + T cells. Indeed, activity of immunotherapy on brain lesions could correlate with these molecular characteristics (20).

In conclusion, the use of immune-checkpoint inhibitors against brain metastases from ccRCC showed limited results; the association with radiation therapy may improve their efficacy but a larger prospective study needs to be performed. However, in order to improve effectiveness, the combination of radiotherapy, checkpoint inhibitors and antiangiogenic drugs, such as bevacizumab, sunitinib or cabozantinib, should be analyzed in patients with brain lesions from ccRCC; preclinical studies have demonstrated that antiangiogenic treatment can promote antitumor immunity and increase the efficacy of immune checkpoint blockade (21). Moreover, expression of MET was shown to be higher in metastatic lesions from ccRCC, in particular in brain disease when matched with primary tumors (22), and cabozantinib, a MET inhibitor, was shown to have a possible role against ccRCC brain lesions (7,8). Besides, the combination of nivolumab and ipilimumab was found to be effective as first line therapy for metastatic RCC patients with intermediate or poor risk disease (IMDC) (1) without brain disease; the same combination treatment had showed more efficacy than nivolumab alone in melanoma brain metastases (10). Therefore, it is necessary to evaluate this therapy, possibly associated with irradiation, in patients with brain metastases from renal cell carcinoma.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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