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Letter to the Editor

Reply to Michael Staehler, Dena Battle, Axel Bex, Hans Hammers, and Daniel George's Letter to the Editor re: Arnaud Méjean, Alain Ravaud, Simon Thezenas, et al. Sunitinib Alone or After Nephrectomy in Metastatic Renal-cell Carcinoma. Eur Urol 2018;74:842–3

Lymphocyte Phenotype and Timing of Radical Nephrectomy in Patients Treated with Immunocheckpoint Inhibitors for Renal Cell Carcinoma

We read with great interest the letter by Staehler et al. [1] focused on the CARMENA trial, a practice-changing phase III study aimed at clarifying the role of radical nephrectomy in the era of targeted agents for metastatic renal cell carcinoma (mRCC). In this study, Méjean et al. [2] reported that sunitinib alone at standard schedule was not inferior to nephrectomy followed by sunitinib in patients with Memorial Sloan Kettering Cancer Center intermediate- or poor-risk renal cell carcinoma (RCC). Indeed, median overall survival (OS) was longer with sunitinib alone (18.4 vs 13.9 mo, hazard ratio 0.89, 95% confidence interval 0.71–1.10).

In their letter [1], Staehler and colleagues underlined three main topics: (1) the median tumor size of patients included in the CARMENA study [2], which was higher than that in previous clinical trials and, as a consequence, indicative of a high-risk population; (2) the necessity of a universal multidisciplinary approach to patients with mRCC in order to identify those who will benefit from upfront systemic therapy or radical nephrectomy; and (3) the importance of the communication with patients in relation to the risk and benefits of performing upfront surgery or systemic therapy.

These findings give rise to a series of questions. In particular, we agree with the authors that understanding patients' preferences will be fundamental in this setting. In this view, the results of the CheckMate 214 trial [3] showing an advantage in terms of OS and drug tolerability for the combination of anti–programmed death (anti-PD)-1 agent nivolumab and anti-cytotoxic T-lymphocyte antigen (CTLA)-4 ipilimumab compared with sunitinib will, again, turn the cards on the table.

The incorporation of nivolumab/ipilimumab as first-line therapy will open the discussion on the timing of nephrectomy in these patients. Indeed, it is correct to generalize the results obtained by sunitinib in the CARMENA study sustaining that this can also be true for other systemic therapies, including nivolumab and ipilimumab (Fig. 1). In our opinion, results of the CARMENA trial cannot step into the shoes of immunotherapy without careful consideration. This is based on a series of findings including the (1) evidence that in situ RCC may serve as a continuous source of tumor antigens that contribute to T-cell recruitment and activation, (2) results in RCC patient cohorts with postimmunotherapy nephrectomy with interleukin (IL)-2 [4] and interferon (IFN)-α [5], and (3) immunosuppressive effect of radical nephrectomy, characterized by decreased expression of T-cell activation antigens (such as CD25 and CD71) and reduced production of cytokines including IL-2 and IFN-γ [6].

The first confirmation that immunotherapy will also not be inferior to upfront surgery may come from the results of ongoing neoadjuvant trials on nivolumab. At present, two different phase I studies are investigating the use of preoperative nivolumab administered at 3 mg/kg every 2 wk for three (NCT02575222) or four cycles (NCT02595918). Similarly, two other phase II studies are exploring the role of nivolumab administered before surgery at 3 mg/kg every 2 wk for four cycles and prolonged after nephrectomy until no further clinical benefit (NCT02446860, ADAPTeR study) or administered for two preoperative cycles followed by six postoperative administrations (ECOG-ACRIN 8143, PROSPER RCC).

In the same view, we have to focus on the enthusiastic results recently obtained by the combination of immunocheckpoint inhibitors with antivascular endothelial growth factor monoclonal antibodies [7] or tyrosine kinase inhibitors [8–10], which will absolutely merit further investigations also in the preoperative setting (Fig. 1).

On this scenario, preoperative immunotherapy with immunocheckpoint inhibitors alone or combined with targeted agents seems to have all the characteristics to become the future standard of care for patients with mRCC. This needs to be carefully evaluated into randomized clinical

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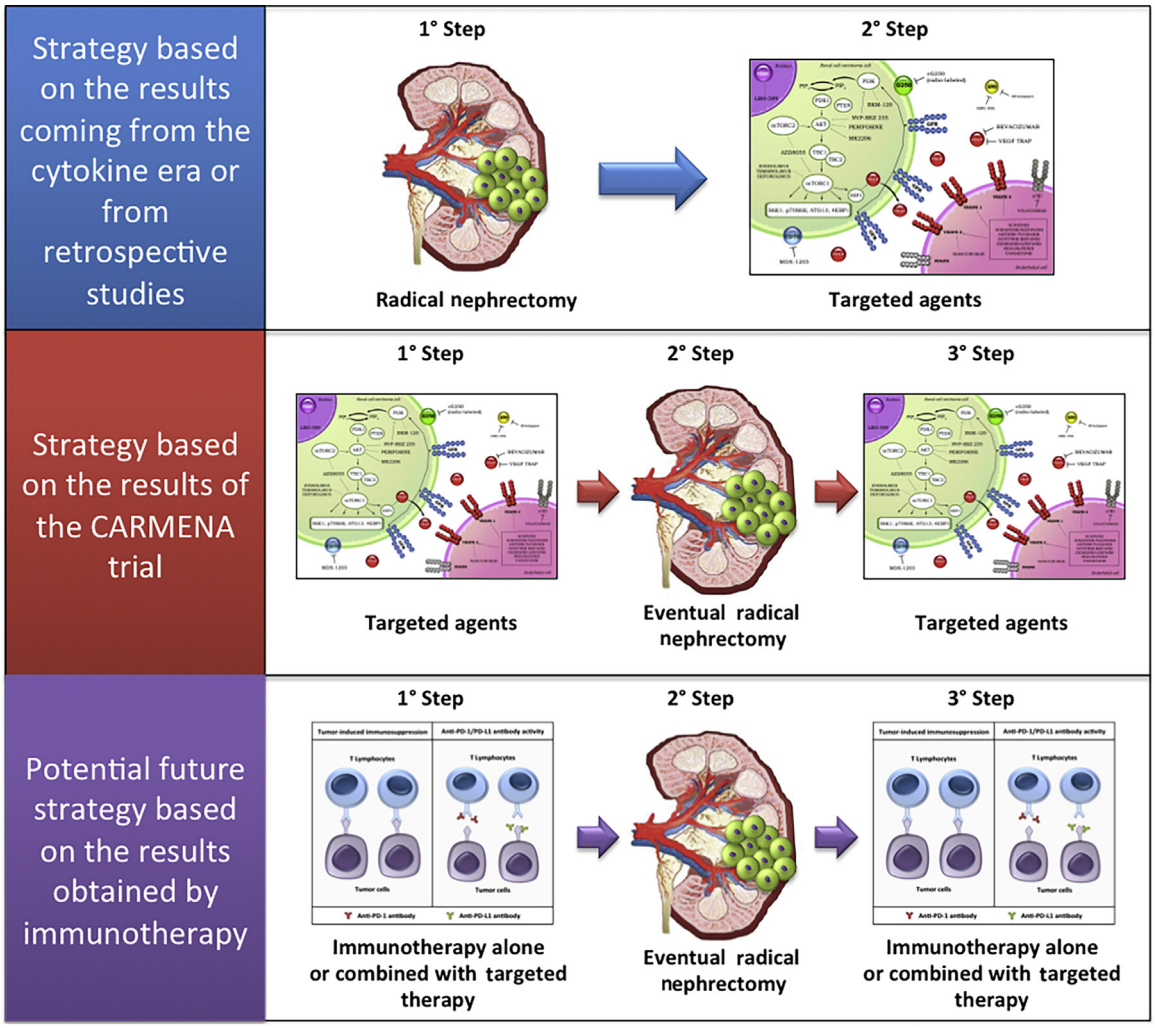

Fig. 1 – Past, present, and future of surgery and systemic therapy for metastatic renal cell carcinoma.

studies in order to make another substantial step forward on the route to precision medicine for mRCC.

Conflicts of interest: The authors have nothing to disclose.

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