Brief Correspondence

Primary Renal Tumour Response in Patients Treated with Nivolumab and Ipilimumab for Metastatic Renal Cell Carcinoma: Real-world Data Assessment

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Abstract

Following CARMENA and SURTIME, patients with metastatic renal cell carcinoma (mRCC) and International Metastatic RCC Database Consortium (IMDC) intermediate and poor risk receive systemic therapy with the primary tumour (primary) in place, with the option of deferred cytoreductive nephrectomy (CN) in responding patients. We retrospectively analysed the safety and efficacy of first-line nivolumab/ipilimumab in 71 primary mRCC patients (42.3% IMDC poor risk; 43.6% with more than three metastatic sites). The baseline mean primary diameter was 9.3 cm and median follow-up was 11.5 mo. Of 69 patients with at least one follow-up computed tomography scan, 23 (33.3 %) had a partial response (PR) of the primary after a median of 4.8 mo, which was associated with a 91.3% overall response rate at metastatic sites (MSs) and absence of progressive disease, irrespective of the IMDC risk. The complete response (CR) rate at MSs (n = 7 [10.1%]) is similar to the CR rate in CheckMate 214. Thirteen deferred CNs were performed (18.8%) after a median of 13 mo, rendering four patients disease free. Only 4.3% of primaries progressed; grade 3–4 immune-related adverse events occurred in 31.9%. Irrespective of the IMDC risk, patients with a PR in the primary had a 1-yr overall survival rate of 89% versus 67% in those without (p = 0.012).

Patient summary: Patients with metastatic kidney cancer receiving immunotherapy with nivolumab and ipilimumab had superior response at metastatic sites and better survival irrespective of International Metastatic RCC Database Consortium (IMDC) risk.

Based on the results of CARMENA and SURTIME [1,2], European guidelines recommen...
Meanwhile, immune checkpoint inhibitor (ICI)-based combination therapy has become the standard first-line treatment for International Metastatic RCC Database Consortium (IMDC) intermediate- and poor-risk patients [5]. Consequently, the recent evidence and recommendations from CARMENA and SURTIME have been superseded, and up to 30% of metastatic renal cell carcinoma (mRCC) patients were treated with their primary in place in the pivotal ICI combination therapy trials [6]. With up to 16% of complete response (CR) rates at metastatic sites [7], patients are increasingly being offered deferred CN to achieve surgical complete remissions. In a retrospective analysis involving 20 patients who underwent deferred CN following ICI therapy, 10% had a complete pathological response in the primary [8], and currently two randomised controlled trials investigate the role of deferred CN in this setting [6]. We retrospectively analysed, within the context of a clinical audit, safety and oncological outcome data from three European referral centres of patients with treatment-naïve mRCC who received first-line nivolumab and ipilimumab with the primary in place (Supplementary material).

Of 71 patients treated between April 2019 and April 2021 (Table 1), 69 had at least one follow-up cross-sectional imaging result available for response assessment by radiology review at each centre. The median follow-up was 11.5 (interquartile range [IQR] 6.9–15.8) mo. Adverse events (AEs) were similar to those previously reported, with 31.9% grade 3–4 immune-related AEs (Supplementary Table 1). Five patients (7%) developed macroscopic haematuria, requiring embolisation in two (2.8%). The overall response rate (ORR) was 33.3% (23/69; 95% confidence...
Fig. 2 – Overall survival (A) for patients with a partial response in the primary tumour (PR) and those without (SD/PD) and (B) for IMDC intermediate- and poor-risk patients. CR = complete response; Cum = cumulative; IMDC = International Metastatic RCC Database Consortium; Int = intermediate PD = progressive disease; PR = partial response; RCC = renal cell carcinoma; SD = stable disease.
whereas 10.1% (7/69) patients had a CR at metastatic sites, none of whom developed local symptoms. A PR in the primary occurred in 34.5% after a median time to surgery of 13 (IQR 10–14.9) mo, of 56.8% (24/42) had PD as the best response. A total of 69.6% (32/46) progressed during follow-up and 30.4% (14/46) died of disease (Supplementary Table 2). A response in the primary tumour discriminated responders better than median tumour downsizing (Supplementary Table 3). Time to response in the primary was not associated with the outcome (Supplementary Table 4 and Supplementary Fig. 2).

Overall, only 4.4% (3/69) patients had RECIST 1.1 PD of the primary, none of whom developed local symptoms, whereas 10.1% (7/69) patients had a CR at metastatic sites (Fig. 1).

Irrespective of the IMDC risk, patients with a PR in the primary had a 1-yr overall survival (OS) rate of 89% versus 67% in patients without (<p = 0.012; Fig. 2A). The median OS has been reached for IMDC poor-risk patients (14.7 mo [95% CI 10–19.4]; Fig. 2B) who overall had a poorer outcome (Supplementary Table 5 and Supplementary Fig. 3). The median progression-free survival (PFS) was 10.1 mo (95% CI 4.84–15.4; Supplementary Fig. 4).

A total of 13/69 (18.8%) deferred CNs were performed after a median time to surgery of 13 (IQR 10–14.9) mo, the majority (62%) being in IMDC intermediate-risk patients (Supplementary Table 5). The predominant reason for deferred CN was a response at metastatic sites (n = 12; four CRs and eight PRs). In three patients, deferred CN was performed to control haematuria. In the majority (62%) being in IMDC intermediate-risk patients (Supplementary Table 5). The predominant reason for deferred CN was a response at metastatic sites (n = 12; four CRs and eight PRs). In three patients, deferred CN was performed to control haematuria. The fact that these patients had previous lines of therapy, this suggests that combination therapies may be more effective in downsizing the primary.

In summary, these real-world data demonstrate that, similar to the tyrosine kinase inhibitor era, irrespective of the IMDC risk, patients with a RECIST response in their primary have better outcome in terms of progression and disease-related death. In addition, deferred CN leads to NED in those with a CR at metastatic sites. As a legacy of CARMENA and SURTIME [4], two phase 3 randomised controlled trials are investigating deferred CN versus no CN after ICI combination therapy (NORDIC SUNCH [NCT03977571] and PROBE trial [NCT04510597]) [6]. Finally, treatment with the primary tumour in place seems to be safe. Only two patients required embolisation to control haematuria.

Limitations include retrospective design, a small number of patients, and multi-institutional inclusion.

**Author contributions:** Axel Bex had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Bex, Meerveld-Eggink, Graafland, Haanen, Powles.

**Acquisition of data:** Bex, Graafland, Meerveld-Eggink, Wilgenhof, Van Thienen, Szabados, Boleti, Grant.

**Analysis and interpretation of data:** Lalezari, Bex, Blank, Powles, Graafland.

**Statistical analysis:** Meerveld-Eggink, Bex, Abu-Ghanem.

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Appendix A. Supplementary data

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