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Editorial

Immune Checkpoint Inhibitors in the Pre-operative Setting and Impact on the Primary Renal Tumor

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The treatment paradigm for metastatic renal cell cancer (RCC) has changed dramatically over the last decade with the United States Food and Drug Administration's (FDA) approval of various combination regimens with a backbone of immune checkpoint inhibitors (ICI) [1–5]. Despite the documented efficacy of ICIs in the metastatic setting, many patients either do not respond or become resistant after an initial response. Furthermore, even after curative surgery for early stage kidney cancer, up to 60% of the highest risk patients are predicted to relapse [6]. Recently, the ICI pembrolizumab was approved by the FDA for use in the adjuvant setting following the positive results of a phase III trial showing a modest improvement in disease-free survival in favor of pembrolizumab compared to placebo [7]. However, the results of subsequent phase III trials using other ICIs in the adjuvant setting did not improve outcomes [8–10].

There is therefore a need to constantly modify treatment algorithms for patients with RCC. Exposure of tumors to pre-operative ICIs, either before cytoreductive nephrectomy (CN) in the metastatic disease setting or before partial or radical nephrectomy as part of neoadjuvant therapy in the localized disease setting, is an area of focus in the paper presented in this issue of Kidney Cancer by Jones, et al.. These investigators report the results of a systematic review, concluding that it may be reasonable to consider an ICI-based regimen before CN in metastatic RCC based on a partial response of 35-56% and a pathological complete response reported in about 14% of patients. However, there remains paucity of data regarding the use of ICI-based strategies in the neoadjuvant setting for patients with localized disease. Several trials are ongoing to address these scenarios both in the metastatic and localized settings.

In patients with metastatic RCC, the role of upfront cytoreductive nephrectomy has been investigated in the SURTIME and CARMENA studies. In SURTIME, while no difference in PFS was seen, overall survival was better in patients with deferred nephrectomy [11]. In CARMENA, numerically worse overall survival was reported in patients with two or more IMDC risk factors when treated with upfront CN instead of systemic therapy with sunitinib [12]. From a review of the literature, it seems there is a paucity of data on the effect of ICI-based regimens on primary

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tumors despite several large phase-III clinical trials conducted for metastatic RCC. In the studies included in the systematic review by Jones et al, an encouraging partial response rate (>30% reduction in the size of the primary renal tumor) of 35-56% when using combinations of two ICIs or an ICI with a vascular endothelial growth factor- tyrosine kinase inhibitor (VEGF-TKI) before CN was observed. However, lower response rates were seen in the primary renal tumor with single-agent TKIs or single-agent nivolumab. It would thus appear that in selected patients with mRCC, CN would remain an important part of the algorithm; the choice of whether to precede this with systemic ICI-based therapy in combination with a VEGFR/TKI will need to be tailored to patients who are more likely to benefit. In the ICI era, this question is being investigated in the PROBE (NCT04510597) and NORDIC-SUN (NCT03977571) trials, which will provide prospective data from a large number of patients and should help establish meaningful conclusions. Importantly, recent interim data from 14 patients on the phase-2 CYTOKIK trial (using cabozantinib and nivolumab in the pre-operative setting prior to CN), did not report any treatment-related surgical complications [13]. Another phase II clinical trial (CYTOSHRINK-NCT04090710) [14] is investigating the efficacy of upfront cytoreductive stereotactic body radiation therapy (SBRT) in combination with systemic therapy (nivolumab plus ipilimumab) over the combination of nivolumab plus ipilimumab alone in patients with advanced RCC and IMDC intermediate/poor-risk disease who were not suitable for CN or had declined it. This study will provide information on the impact of radiation therapy, in addition to systemic therapy, on the primary renal mass.

For contextual comparison, many trials in other early-stage solid tumors such as bladder cancer, breast cancer, and non-small cell lung cancer have shown that the neoadjuvant setting is an important clinical space to develop "window-of-opportunity" studies. These trials offered a unique platform on which to acquire pre- and post-treatment tumor specimens which can then be analyzed to enhance our understanding of the biologic basis behind tumor response or resistance following systemic therapy. Based on the collective experience from neoadjuvant solid tumor trials, there is now renewed interest in exploring ICI-based regimens in the neoadjuvant RCC setting. Thus far, results from single-agent ICI studies in RCC described in the systematic review are discouraging in that no patients experienced any noteworthy shrinkage in their primary tumors, and no significant infiltration with immune cells was likewise seen. These observations were similar to those reported in a 1993 paper which showed that IL2 did not have any measurable effect on the primary tumor, while responses were seen at metastatic sites [15]. Two studies that have recently been reported in the neoadjuvant setting of early stage RCC: PROSPER (NCT03055013) and NeoAvAx (NCT03341845). In the PROSPER trial that employed both neoadjuvant and adjuvant nivolumab, only one dose of pre-operative nivolumab was used and hence may not have been sufficient to have any measurable impact on the primary tumor [9]. Correlative analysis from this study will provide important insights into the effect – if any - of an ICI on the primary renal tumor and its associated tumor microenvironment. NeoAvAx, on the other hand, utilized a combination of an ICI (avelumab) and a VEGFR-TKI (axitinib) for 12 weeks prior to nephrectomy [16]. Early data from this trial presented in abstract form showed an encouraging 30% partial response. Correlative analysis showed an upregulation of PD-L1 and CD8 between the pre-treatment biopsies and the subsequent nephrectomy specimen. Other ongoing trials in the neoadjuvant space are further highlighted in the systematic review by Jones, et al. Forthcoming data from these window-of-opportunity studies should include robust translational endpoints, which will help investigators understand mechanisms of action of and resistance to ICIs and will help in the design of future trials in this setting.

Finally, as is always the case in oncology, it is important to remember that these drugs can lead to adverse events and sometimes cause long-term damage to end-organs requiring immunosuppressants, among other interventions. These considerations are obviously of critical importance in the pre-operative setting since they may have an influence on operative complications and outcomes. Even though surgical complications were not reported in many of the reported studies, one study did reveal that 11% of patients developed Clavien-Dindo Grade 3b surgical complications after nivolumab. In the NeoAvAx study, Clavien-Dindo Grade 3 or higher surgical complications were reported in 5/40 patients after 12 weeks of avelumab and axitinib [16]. As noted by Jones and colleagues, there is a need for multi-dimensional clinical and molecular biomarkers that will select those patients most suited for pre-operative therapy and/or exclude those who are least likely to benefit.

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SG and PNL wrote and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

PNL is Co-Editor of this journal and SG is an Editorial Board Member of this journal, but they were not involved in the peer-review process of this paper, nor had access to any information regarding its peer-review.

REFERENCES

[1] Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019;20(10):1370-1385. doi:10.1016/S1470-2045(19)30413-9

[2] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1116-1127. doi:10.1056/NEJMoa1816714

[3] Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. Ann Oncol. 2020;31(8):1030-1039. doi:10.1016/j.annonc.2020.04.010

[4] Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2021;384(9):829-841. doi:10.1056/NEJMoa2026982

[5] Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med. 2021;384(14):1289-1300. doi:10.1056/NEJMoa2035716

[6] Westerman ME, Shapiro DD, Wood CG, Karam JA. Neoadjuvant Therapy for Locally Advanced Renal Cell Carcinoma. Urol Clin North Am. 2020;47(3):329-343. doi:10.1016/j.ucl.2020.04.010

[7] Choueiri TK, Tomczak P, Park SH, et al. Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N Engl J Med. 2021;385(8):683-694. doi:10.1056/NEJMoa2106391

[8] Motzer RJ, Russo P, Gruenwald V, et al. LBA4 Adjuvant nivolumab plus ipilimumab (NIVO+IPI) vs placebo (PBO) for localized renal cell carcinoma (RCC) at high risk of relapse after nephrectomy: Results from the randomized, phase III CheckMate 914 trial. Ann Oncol. 2022;33:S1430. doi:10.1016/j.annonc.2022.08.069

[9] Allaf M, Kim SE, Harshman LC, et al. LBA67 Phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial. Ann Oncol. 2022;33:S1432-S1433. doi:10.1016/j.annonc.2022.08.072

[10] Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. The Lancet. 2022;400(10358):1103-1116. doi:10.1016/S0140-6736(22)01658-0

[11] Bex A, Mulders P, Jewett M, et al. Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA Oncol. 2019;5(2):164-170. doi:10.1001/jamaoncol.2018.5543

[12] Mejean A, Thezenas S, Chevreau C, et al. Cytoreductive nephrectomy (CN) in metastatic renal cancer (mRCC): Update on Carmena trial with focus on intermediate IMDC-risk population. J Clin Oncol. 2019;37(15_suppl):4508-4508. doi:10.1200/JCO.2019.37.15_suppl.4508

[13] Runcie K, Ornstein M, Saraiya B, Krishnamurthi V, Lee B. Assessment of Clavien- Dindo Classification in patients with metastatic Clear Cell RCC who received Perioperative Cabozantinib and Nivolumab on the Cyto-KIK Clinical Trial. Published online 2022:12.

[14] Lalani AKA, Swaminath A, Pond GR, et al. Phase II trial of cytoreductive stereotactic hypofractionated radiotherapy with combination ipilimumab/nivolumab for metastatic kidney cancer (CYTOSHRINK). J Clin Oncol. 2022;40(6_suppl):TPS398-TPS398. doi:10.1200/JCO.2022.40.6_suppl.TPS398

[15] Haas GP, Redman BG, Rao VK, Dybal E, Pontes JE, Hillman GG. Immunotherapy for Metastatic Renal Cell Cancer: Effect on the Primary Tumor. J Immunother. 1993;13(2):130-135.

[16] Bex A, Abu-Ghanem Y, Van Thienen JV, et al. Efficacy, safety, and biomarker analysis of neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). J Clin Oncol. 2022;40(6_suppl):289-289. doi:10.1200/JCO.2022.40.6_suppl.289