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Commentary

Evaluating the Optimal Duration of Immunotherapy in Kidney Cancer

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Immune checkpoint inhibitor (ICI) therapy has rapidly altered the landscape of treatment of metastatic renal cell carcinoma (mRCC), resulting in significant improvements in outcomes for patients with this disease. Nivolumab, an antibody inhibiting the programmed death-1 (PD-1) receptor, was first approved for treatment of refractory mRCC, on the basis of the Phase III CheckMate 025 study comparing nivolumab to everolimus; in this study, patients were treated with nivolumab until development of progression or unacceptable toxicity [1]. More recently, several Phase III randomized controlled trials have established the benefit of incorporating ICI therapy to the first-line treatment of patients with mRCC, conferring durable responses in a subset of patients [2–5]. For patients who do have durable responses to ICI therapy, we are often faced with a quandary of how long to continue treatment. We may be at a point now to examine this clinical question in a prospective fashion.

Similar to the CheckMate 025 study, the CheckMate 214 study evaluating nivolumab plus ipilimumab in comparison to sunitinib in patients with treatment-naïve mRCC continued treatment with nivolumab indefinitely until disease progression or toxicity [2]. On the other hand, the KEYNOTE-426 study, which evaluated the combination of pembrolizumab plus axitinib in comparison to sunitinib in patients with untreated mRCC, clearly delineated a prescribed duration of pembrolizumab therapy [3]. Patients in that study were treated with pembrolizumab for up to 35 cycles (or 2 years) of treatment. Similarly, more recent studies, like the CLEAR study evaluating the combination of lenvatinib plus pembrolizumab and the CheckMate-9ER study evaluating the combination of nivolumab plus cabozanitib, have also capped the length of ICI treatment to 2 years [4, 5].

Long-term follow-up data are available from the CheckMate 025, CheckMate 214 and KEYNOTE-426 studies, which shed some light on patients who have durable responses on ICI therapy. The first of those studies, CheckMate 025, has reported data from a median follow-up of 72 months [1]. Of the patients treated with nivolumab, the median duration of treatment was 23.6 months; of the 94 patients in the study on nivolumab with an objective response, 8 remained on treatment at the time of last database lock. Notably, 29% of the responding patients who were no longer on treatment for any reason did not require subsequent therapy. In general, patients who did respond to nivolumab and discontinued therapy had a median treatment-free interval of 12.7 months on this study. In the CheckMate 214 study, 547 patients were treated with nivolumab plus ipilimumab. At 42 months after randomization, 31% of patients were free of subse-

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quent therapy, while 14% remained on nivolumab [6]. There was an 18% probability of remaining treatment-free at 42 months in the nivolumab plus ipilimumab arm. With a further median follow-up of 55 months, 10% ($n = 53$) of patients remained on treatment with nivolumab [7]. Interestingly, of the 59 patients who experienced a complete response with nivolumab plus ipilimumab, 32.2% ($n = 19$) of patients remained on therapy, but 45.8% ($n = 27$) discontinued therapy with no need for further systemic therapy. In the 156 patients experiencing a partial response, 17.9% ($n = 28$) remained on treatment with nivolumab, while 42.9% ($n = 67$) discontinued treatment without requiring further systemic therapy. These data in summary indicate that a subset of patients receiving ICI therapy have sustained responses that maintain after treatment discontinuation.

The results of long-term follow-up from the KEYNOTE-426 study offer some additional insights. For this study, median duration of follow-up of 30.6 months has thus far been reported, therefore there are more limited data regarding responders compared to the aforementioned studies [8]. Furthermore, discontinuation of therapy was more difficult to characterize, since this study combined the anti-PD-1 antibody pembrolizumab in combination with axitinib, a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF TKI). In this study, 19 patients completed the protocol-indicated 2 years of pembrolizumab. Of the 312 patients who discontinued treatment on this arm of the study, 181 discontinued due to progressive disease, 18 due to clinical progression, and 78 discontinued treatment due to adverse events; 92 patients discontinued pembrolizumab due to adverse events. At the time of data cut-off, 98 patients remained on treatment, though it is not clear if these patients were on pembrolizumab plus axitinib or axitinib alone. While more follow-up, especially delineating continued responses in those patients discontinuing pembrolizumab therapy, would likely provide more insight, this study does demonstrate that survival does remain superior to sunitinib, even with a finite treatment of pembrolizumab.

The other data we may examine for the potential to discontinue ICI therapy comes from retrospective data regarding immune-related adverse events (irAEs) requiring discontinuation of therapy. The first study evaluated 19 patients with mRCC who experienced an initial clinical response to ICI therapy but required discontinuation of all systemic therapy due to an irAE [9]. Durable clinical benefit, consisting of a response lasting at least 6 months, was observed in 68% ($n = 13$) of patients. A larger, systematic review of prospective studies reporting individual outcomes after ICI discontinuation in patients with mRCC encompassed 16 cohorts comprising of 1833 patients treated with ICIs [10]. Of the 572 patients who had responses to treatment and had available data, 327 patients stopped ICI therapy, with 86 (26%) continuing to respond off-treatment. Treatment-free survival (TFS) in this analysis was considerable: in patients treated with dual ICI therapy, the 6-month and 12-month mean rates were 57% and 50% respectively. Those treated with an ICI + VEGF-directed therapy has 6-month and 12-month mean TFS rates of 20% and 5%, respectively. These data collectively indicate that patients who discontinue ICI therapy may enjoy a sustained response to therapy.

Though the rate of irAEs does not appear to increase with longer duration of therapy, risk of development of irAEs remains while patients continue on treatment. In addition, continuous ICI treatment should be considered in the context of its impact on the overall burden of cancer care costs. Yet, the prospect of discontinuing ICI therapy after a patient achieves a response can be anxiety-provoking for both the patient and the physician. While an Alliance clinical trial is evaluating this question in patients with metastatic urothelial carcinoma who have achieved a response to treatment with ICI (NCT04637594), no prospective studies have yet evaluated this question in mRCC.

Perhaps the first step towards addressing the optimal duration of ICI therapy should involve a more sophisticated approach. To that end, a recent study collected 457 blood samples from two cohorts of patients with mRCC: the Phase II OMNIVORE study and a prospective institutional cohort from the University of Wisconsin [11]. Circulating tumor cell (CTC) enumeration and fluorescence were evaluated, as well as the interplay between HLA I and PD-L1 relative to CTC abundance, as well as the HLA I to PD-L1 (HP) ratio. Patients who had radiographic responses to therapy had much lower CTC abundance. Furthermore, HP ratio trajectories that were highest correlated to the shortest overall survival. With further advancements in CTC enumeration and other biomarkers, we may be able to establish a way to characterize 'minimal residual disease' or a manner to identify patients likely to maintain a response to ICI therapy after discontinuation. Pilot prospective studies focused in this area may then enable the

design of a larger, prospective study that may spare selected patients from unnecessary or prolonged ICI treatment.

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AUTHOR CONTRIBUTIONS

MP and PNL contributed to the conception of the work and interpretation of data.

CONFLICT OF INTEREST

PNL is an Editor-in-Chief and MP is an Associate Editor of this journal, but they were not involved in the review process of this paper, nor had access to any information regarding its review.

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