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Review article

Nivolumab treatment for advanced renal cell carcinoma: Considerations for clinical practice

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Abstract

Background: Nivolumab is an important new therapy option for patients with advanced renal cell carcinoma, and has a different mechanism of action compared with vascular endothelial growth factor -targeted therapies. It is a programmed death 1 immune checkpoint inhibitor antibody with response patterns, efficacy, and safety profiles that differ from those of conventional antiangiogenic or mammalian target of rapamycin inhibition therapy.

Methods and Purpose: This commentary discusses and evaluates the clinical experience with nivolumab from the available literature and presents practical considerations for the use of nivolumab immunotherapy in aRCC to optimize clinical management.

Keywords: Advanced renal cell carcinoma; Immune checkpoint inhibitor; Immunotherapy agents; Nivolumab; Second-line therapy; PD-1 inhibitor

1. Introduction

Nivolumab, a programmed death 1 (PD-1) checkpoint inhibitor, was recently approved by the US Food and Drug Administration and the European Commission to treat patients with advanced renal cell carcinoma (aRCC) who have received prior antiangiogenic therapy [1,2]. Approval as second-line therapy was based on superior overall survival (OS) of nivolumab in a large, international, open-label, phase III study (CheckMate 025; NCT01668784) that randomized patients with advanced clear cell RCC to 3 mg/kg nivolumab intravenously every 2 weeks (n = 410) or 10 mg everolimus orally once daily (n = 411) [3].

Nivolumab provides an important novel therapy option for patients with aRCC, with a different mechanism of action from other targeted therapies. It is a fully human IgG4 anti-PD-1 antibody that selectively blocks interaction between PD-1, which is expressed on activated T cells, and its ligands PD-L1 and PD-L2, which are expressed on immune cells and tumor cells (Fig.) [4–6].

In contrast, targeted agents used in the treatment of aRCC, for example, tyrosine kinase inhibitors, inhibit vascular endothelial growth factor (VEGF)/VEGF receptors or mammalian target of rapamycin (mTOR)-mediated pathways to suppress angiogenesis [6,8]. Although tyrosine kinase inhibitors and agents targeting mTOR have produced robust clinical effects in aRCC, some patients are resistant to these approaches and most, if not all, acquire resistance over time, limiting the overall clinical benefit of these treatments [9]. This underlines the need for therapies with a different mechanism of action.

With their unique mechanism of action, PD-1–targeted immunotherapy agents have response patterns, efficacy, and safety profiles that differ from conventional antiangiogenic or mTOR inhibition therapy. This editorial discusses practical considerations with use of PD-1–targeted immunotherapy, with specific reference to nivolumab in aRCC, to optimize clinical management.

2. OS with nivolumab vs. other second-line therapies

Despite significant improvements in progression-free survival (PFS) with antiangiogenic therapies, significant OS benefit in aRCC in the second-line setting is just emerging with new drug therapies (Table 1) [3,10–15].

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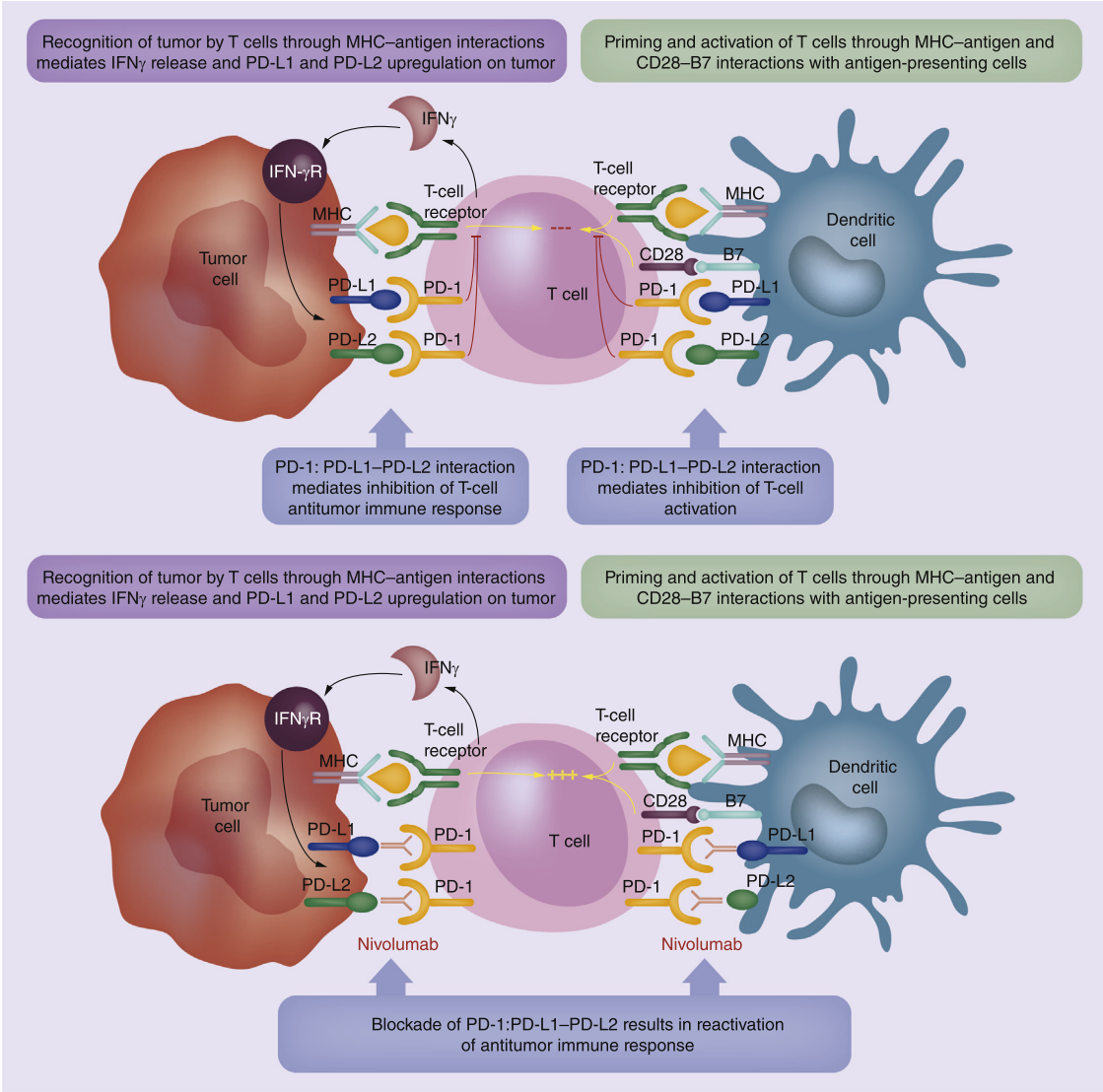

Fig. Mechanism of action of nivolumab [7]. Interaction between PD-1 and PD-L1 or PD-L2 normally results in inhibition of the cellular immune response, and tumors with increased PD-L1 expression are associated with poor prognosis in renal cell carcinoma [4,5]. By disrupting PD-1/PD-L1–mediated signaling, nivolumab is thought to restore the immune response and antitumor immunity [6]. IFN = interferon; MHC = major histocompatibility complex. (Republished with permission of Future Medicine Ltd, from Brahmer et al. [7]; permission conveyed through Copyright Clearance Center, Inc.) (Color version of figure is available online).

Nivolumab is the first approved immunotherapy to show a significant OS benefit in second-line aRCC treatment, with a median OS of 25.0 months (95% CI: 21.8–not reached [NR]) with nivolumab vs. 19.6 months (95% CI: 17.6–23.1) with everolimus. The hazard ratio for death with nivolumab vs. everolimus was 0.73 (98.5% CI: 0.57–0.93, $P = 0.002$) [3]. In long-term follow-up studies of nivolumab in aRCC, approximately one-third of patients are alive at 5 years in the phase I study and 3 years in the phase II study [16].

3. Subgroup analysis of OS data to identify patients who may benefit from nivolumab treatment

Nivolumab showed benefit over everolimus across patient subgroups based on baseline factors in CheckMate 025, including Heng risk group, Karnofsky performance status, prior sunitinib or pazopanib therapy, and number of prior antiangiogenic therapies (Table 2) [3,17,18].

Tumor PD-L1 expression $\geq/<1\%$ was not found to be a marker of nivolumab treatment OS benefit in aRCC (Table 2) [3]. Similar results were observed among patients with PD-L1 expression $\geq/<5\%$ [3].

Although associations between tumor PD-L1 expression and improved outcomes have been observed with nivolumab treatment in other tumors (metastatic melanoma and non–small cell lung cancer [19]), the predictive role of PD-L1 status on treatment outcomes remains to be determined [20,21]. There is currently a lack of identified biomarkers that reliably predict treatment benefit with immune PD-1 checkpoint inhibitors. This is an important area of ongoing investigation [8].