A phase 3, randomized, placebo-controlled trial of nivolumab plus ipilimumab in patients with localized renal-cell carcinoma at high risk of relapse after radical or partial nephrectomy (CheckMate 914)

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Introduction

• Current standard treatment for early-stage nonmetastatic (stage I–III) renal cell carcinoma (RCC) is radical or partial nephrectomy.1–3
• Although the post-nephrectomy prognosis of patients with stage I tumors is good, many patients with stage II and III tumors have a high risk of relapse and represent a patient population with a high unmet medical need.4–6
• In clinical trials of adjuvant therapy for patients with high-risk nonmetastatic RCC, where tumors were predominantly stage II or III, 5-year disease-free survival (DFS) rates ranged from approximately 51%–56% among the placebo.7–9
• Reducing the risk of recurrence through adjuvant therapy is an important goal in patients with high-risk nonmetastatic RCC.10
• Several trials have assessed the efficacy of approved RCC agents in the adjuvant setting, including sunitinib,11 sorafenib,3 pazopanib,12 and everolimus.13
• To date, only adjuvant sunitinib treatment has extended the duration of DFS after nephrectomy in a phase 3 trial, with a median DFS of 4.8 years versus 3.6 years in the placebo arm.14
• Adjuvant sunitinib, however, did not improve overall survival (OS), and was associated with a high incidence of treatment-related adverse events (all grades, 91% vs 56%; grade 3–4, 51% vs 31%) and decreased patient quality of life.15
• Moreover, a recent pooled analysis of the phase 3 trials of sunitinib, sorafenib, and pazopanib did not reveal a statistically significant effect of adjuvant VEGFR-targeted therapy in terms of improved DFS or OS in patients with resected localized RCC, but treatment was associated with potentially significant side effects.16
• Dual immune checkpoint inhibition with nivolumab plus ipilimumab (NIVO+IPI) has demonstrated statistically significant and clinically meaningful long-term improvements versus sunitinib in treatment-naïve patients with advanced RCC,17,18 leading to the hypothesis that the NIVO+IPI combination might also provide benefits as an adjuvant treatment for RCC.
• On this basis, the CheckMate 914 trial was initiated to study clinical outcomes with NIVO+IPI in the adjuvant setting of surgically resected early-stage RCC (NCT03138312).
• However, the treatment landscape for RCC continues to evolve and recent evidence has indicated efficacy of programmed death-1 (PD-1) programmed death ligand 1 (PD-L1) inhibitor monotherapy in treatment-naïve patients with advanced RCC,19–21 suggesting the potential for clinical activity with an adjuvant VEGFR/anti-PD-1 combination.
• As such, the study design of CheckMate 914 has been amended to incorporate a NIVO monotherapy arm, allowing the evaluation of both adjuvant NIVO monotherapy and adjuvant NIVO+IPI in patients with localized RCC with high risk of relapse after radical or partial nephrectomy.

Study design

Figure 1. CheckMate 914 study design

Part A

Adult patients with localized RCC at high risk of relapse after radical or partial nephrectomy

• Randomization: 4 weeks and 12 weeks after surgery
• Stratified by TNM stage and type of nephrectomy

Part B

Adult patients with localized RCC at high risk of relapse after radical or partial nephrectomy

Primary endpoint

• DFS for NIVO+IPI vs placebo

Secondary endpoints

• OS (including 5-year OS rates) for NIVO+IPI vs placebo

Safety and tolerability of NIVO

Primary endpoint

• DFS for NIVO vs placebo

Secondary endpoints

• OS (including 5-year OS rates) for NIVO vs placebo

Safety and tolerability of NIVO

Recruitment

• Recruitment is ongoing with a target enrollment of approximately 1600 randomized patients across approximately 20 countries.12

Figure 2. Active study sites (as of October 2020)

References


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• The statistical analysis staff
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• All authors contributed to and approved the presentation; writing and editorial assistance were provided by Richard Daniel, PhD, of Parexel, Waltham, Massachusetts, USA.
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• This is a phase 3, randomized, double-blind, multicenter, 2-part study (Figure 1).
• Key inclusion and exclusion criteria are shown in Table 1.

Table 1. Key eligibility criteria

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<tr>
<th>Inclusion criteria</th>
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<tr>
<td>Age ≥ 18 years</td>
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<td>Radical or partial nephrectomy with negative surgical margins (randomization must occur in 4 and 12 weeks after surgery)</td>
<td>Active, brown, or suspected autoimmune disease</td>
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<td>Predominantly clear cell histology, including patients with sarcomatoid features</td>
<td>Conditions requiring systemic corticosteroids or other immunosuppressive medications ≤ 30 days before first dose of study treatment</td>
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<td>No clinical/radiological evidence of macroscopic residual disease or distant metastases after nephrectomy</td>
<td>Uncontrolled adrenal insufficiency</td>
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<td>Tumor tissue obtained ≥ 3 months pre-enrollment</td>
<td>Prior active malignancies within 3 years, except for locoregional cancers that have been apparently cured</td>
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