Kidney Cancer 1 (2017) 89–91
DOI 10.3233/KCA-179002
IOS Press

Clinical Trials Corner

Dear Readers,

The Clinical Trials Corner of the newly launched *Kidney Cancer* journal aims to present results from recently published trials and draw attention to ongoing studies in the field of renal cell carcinoma.

We hope that this new section of the journal will help in the recruitment process of the trials and highlight new, possibly practice changing results. If you would like to inform us on a specific clinical trial, please do not hesitate to contact us on thomas.powles@bartshealth.nhs.uk or KCA@iospress.com.

Sincerely,

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A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC)

Clinicaltrials.gov identifier: NCT02853331
Sponsor: Merck Sharp & Dohme Corp.

Enrollment: 840

Study Design: KEYNOTE-426 is a phase III randomized, open-label, multicentre trial evaluating the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy in treatment-naive advanced or metastatic renal cell carcinoma (mRCC) subjects.

Status: recruiting

Rationale: The currently established first line treatment in mRCC are vascular endothelial growth factor (VEGF) pathway inhibitors or in rare cases interferon alpha and interleukin 2 therapy. A previous phase 1b study (NCT02133742) suggests that first-line pembrolizumab, an anti–programmed death 1 (PD-1) antibody, in combination with axitinib, exhibited substantial antitumor activity in mRCC patients. This study aims to evaluate efficacy and safety of the combination treatment pembrolizumab and axitinib versus sunitinib monotherapy.

Endpoints:
There are two primary endpoints: Progression-Free Survival (PFS) and overall survival (OS) as assessed by central imaging review per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in the combination arm of pembrolizumab plus axitinib versus sunitinib alone.

Secondary endpoints include the following: Objective Response Rate (ORR) and Disease Control Rate (DCR) as Per RECIST 1.1, safety and tolerability profiles in subjects treated with pembrolizumab plus axitinib versus sunitinib monotherapy.

Comments:
VEGF/VEGFR targeting anti-angiogenic agents, have made a substantial improvement in the outcome mRCC patients. However, most patients will progress following standard of care first-line treatment. Recent studies showed that nivolumab demonstrated statistically significant improvement in overall survival of treatment refractory patients.

ISSN 2468-4562/17/$35.00

This trial moves combination therapy with checkpoint inhibitors into the first line setting of treatment naïve mRCC subjects.

A Phase II, Randomized Study of Atezolizumab (Anti PD-L1 Antibody) Administered as Monotherapy or in Combination with Bevacizumab Versus Sunitinib in Participants with Untreated Advanced Renal Cell Carcinoma

Clinicaltrials.gov identifier: NCT01984242
Sponsor: Hoffmann-La Roche

Enrollment: 305

Study Design: This multicenter, randomized, open-label study evaluated the efficacy, safety and tolerability of atezolizumab as monotherapy or in combination with bevacizumab versus sunitinib in patients with histologically confirmed, previously untreated mRCC. After progression on atezolizumab or sunitinib, crossover to combination arm atezolizumab + bevacizumab was allowed.

Rationale: VEGF pathway inhibition has significantly improved the outcome of patients with advanced or metastatic renal cell carcinoma (mRCC), however most patients will develop resistance, often within 12 months. Therefore, new therapeutic strategies are needed to reach durable responses. Combination of immune checkpoint inhibitors with VEGF inhibitors may prevent the development of resistance.

Endpoints:
- Primary Endpoint: progression free survival (PFS) according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 measured in both Intent-to-Treat (ITT) Population and subjects who have detectable PD-L1 expression.
- Secondary Endpoints include overall response rate (ORR) per RECIST 1.1, duration of response (DoR), overall survival (OS) and safety profiles of the different treatment arms.

Results:
More than 50% of patients were PD-L1+. In the overall population, PFS was 11.7; 6.1 and 8.4 months in the combination atezolizumab + bevacizumab; atezolizumab monotherapy and sunitinib group respectively. In the PD –L1 + group, PFS reached 14.7 months (95% CI 8.2- 25.1, HR 0.64) with the combination therapy. Overall response rate was 32%, 25% and 29% in the combination arm, atezolizumab monotherapy and sunitinib group respectively. Upon progression in the monotherapy arms, 78% of the sunitinib and 60% of the atezolizumab patients subsequently crossed over to the combination arm with atezolizumab + bevacizumab and achieved ORRs of 28% and 24%, respectively. Safety data in all arms was comparable to the already known individual treatment profiles.

Comments:
PD-L1 inhibitor atezolizumab with bevacizumab showed promising antitumor activity in treatment naïve mRCC patients. Checkpoint inhibitors in combination with VEGF inhibitors may become a key component of the treatment options for mRCC.

A phase III study of first line atezolizumab in combination with bevacizumab versus sunitinib is currently ongoing (NCT02420821).

Nivolumab in Combination with Sunitinib, Pazopanib, or Ipilimumab in Subjects with Metastatic Renal Cell Carcinoma (mRCC) (CheckMate 016)

Clinicaltrials.gov identifier: NCT01472081.
Sponsor: Bristol-Myers Squibb

Enrollment: 175

Study Design: The purpose of this study was to determine the safety, efficacy and optimal dose of Nivolumab in combination with Sunitinib, Pazopanib, or Ipilimumab for the treatment of metastatic renal cell carcinoma

(mRCC). Patients in the immune combination arm were randomly assigned to one of three dosing options: nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3I1), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1I3), or nivolumab 3 mg/kg plus ipilimumab 3 mg/kg (N3I3).

Rationale:
This is an open-label, dose-escalation, phase I study that investigates for the first time, the efficacy and safety of immune combination therapy PD-1 inhibitor nivolumab and CTLA-4 inhibitor ipilimumab and nivolumab in combination with a tyrosine kinase inhibitor (TKI) in mRCC.

Endpoints:
- Primary Endpoints: Safety and tolerability of Nivolumab plus TKI or Nivolumab + Ipilimumab measured by the incidence of adverse events, serious adverse events and laboratory abnormalities.
- Secondary Outcome Measures: Efficacy of Nivolumab plus TKI, or Ipilimumab measured by Objective Response Rate and duration of response according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.

Results:
Safety and efficacy results from the immune combination nivolumab plus ipilimumab arms of the study were recently published (Hammers et al.). Patients in the N3I3 arm were censored due to dose-limiting toxicities. Forty-seven patients were treated in the remaining two immune combination arms. Almost 40% in the N3I1 arm and approximately 60% of the N1I3 arm patients presented grade 3 to 4, treatment-related adverse events. The objective response rate was 40%, with a 2-year overall survival of approximately 70% in both treatment arms.

Comments:
This study showed that immune combination treatments in mRCC are safe and present promsing efficacy with durable responses in patients. A Phase III study of Nivolumab combined with Ipilimumab versus Sunitinib monotherapy is currently (NCT02231749).