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Clinical Trials Corner

Innovative Approaches to Immune Checkpoint Inhibition in Kidney Cancer

Dear Readers,

The Clinical Trials Corner of *Kidney Cancer* highlights planned or ongoing high-impact studies in renal cell carcinoma (RCC). In this issue, we discuss two current clinical trials evaluating the use of immune checkpoint inhibitor therapy in the adjuvant setting in localized renal cell carcinoma (RCC). We also highlight a novel study evaluating a finite duration of nivolumab monotherapy in RCC that also seeks to determine if addition of ipilimumab can convert nivolumab-refractory patients to responders.

In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at mbparikh@ucdavis.edu or kca@iospress.com.

Sincerely,

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A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (KEYNOTE-564).

Status: Recruiting
Clinicaltrials.gov identifier: NCT03142334
Sponsor: Merck Sharp & Dohme Corp.

Enrollment: 950

Rationale: While strides have been made in the treatment of metastatic RCC, there remains no standard adjuvant systemic therapy that has demonstrated an overall survival benefit in the non-metastatic setting. Most patients with intermediate- to high-risk advanced RCC will progress within 3 years following nephrectomy. Pembrolizumab, an anti-PD-1 antibody, has demonstrated benefit in treating metastatic RCC. It is thought that there may be benefit to immune checkpoint inhibitor therapy after resection of localized disease, the hypothesis being that such therapy may allow for eradication of micrometastatic disease and thus translate to improvements in disease-free (DFS) and overall survival (OS).

Study Design: This is a phase III, randomized, double-blind, multicenter trial (KEYNOTTE-564) evaluating the efficacy of pembrolizumab compared to placebo in improving survival in patients who have undergone a partial nephroprotective or radical complete nephrectomy with intermediate- to high-risk clear-cell RCC, as defined as pT2N0M0 disease of Fuhrman Grade 4 or with sarcomatoid features, pT3N0M0 disease of any grade, pT4N0M0 disease of any grade, or any pT stage with N+, M0 disease. Patients with M1 disease who have completely resectable disease in a synchronous or metachronous fashion are also eligible. Those with residual thrombus post-nephrectomy in the renal vein or vena cava are excluded. Surgery must have been performed within 12 weeks prior to randomization. Patients will be randomized 1:1 to receive either placebo or pembrolizumab every 3 weeks for up to 17 cycles unless there is disease recurrence or unacceptable toxicity. Patients will be stratified by metastasis stage.

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Endpoints: The primary outcome of the trial is DFS by investigator assessment, with OS as a secondary endpoint. OS will also be assessed by PD-L1 expression status.

Comments: see below.

A Phase III, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of Atezolizumab (Anti-PD-L1 Antibody) as Adjuvant Therapy in Patients with Renal Cell Carcinoma at High Risk of Developing Metastasis Following Nephrectomy

Status: Recruiting
Clinicaltrials.gov identifier: NCT03024996
Sponsor: Hoffmann-La Roche

Enrolment: 664

Rationale: Much as the aforementioned study, this study seeks to evaluate the role of immune checkpoint inhibitor therapy in the adjuvant setting. Atezolizumab, an anti-PD-L1 antibody, has demonstrated activity in the metastatic setting in RCC, in particular in combination with bevacizumab in the IMmotion150 and IMmotion151 trials.

Study Design: This phase III, randomized, double-blind, multicenter trial (IMmotion010) is enrolling patients with clear cell or sarcomatoid RCC at high risk for RCC recurrence after radical or partial nephrectomy, with lymphadenectomy allowed in select patients, high risk defined as T2N0M0 Fuhrman Grade 4, T3aN0M0 Fuhrman Grade 4 or higher, T3b/c & T4 with any Fuhrman grade, or any T stage or Fuhrman grade with lymph node positive disease. Similar to the KEYNOTE-564 trial, complete resection of limited synchronous or metachronous metastases is permitted. Patients are randomized 1:1 to receive either atezolizumab or placebo every 3 weeks for 16 cycles or 1 year unless there is unacceptable toxicity or disease progression. Patients will be stratified by stage and PD-L1 status.

Endpoints: The primary endpoint of IMmotion010 will be DFS as assessed by independent review facility (IRF). The secondary endpoints will be overall survival, and investigator-assessed DFS. IRF-assessed and investigatory-assessed DFS will also be evaluated based on tumor-infiltrating immune cell (IC) levels.

Comments: The KEYNOTE-564 and IMmotion010 trials will evaluate the role of immune checkpoint inhibitor therapy after definitive surgical intervention, but the results of these trials will be of particular interest to contrast to the ongoing PROSPER trial which was discussed in the last issue of *Kidney Cancer*. PROSPER is based on the hypothesis that the primary tumor and its microenvironment is critical to the effectiveness of immune checkpoint inhibitor therapy; thus, that trial is administering nivolumab, an anti-PD-1 antibody, for two cycles prior to proceeding to nephrectomy. All three trials are evaluating DFS as a primary endpoint, though all will report OS as a secondary endpoint. The results of these trials may be revealing in terms of the interplay between the tumor microenvironment and immunotherapy, with potential to optimally treat localized RCC and reduce the risk of recurrence and mortality from the disease.

Phase II Study of Optimized Management of Nivolumab Based on Response in Patients with Advanced Renal Cell Carcinoma (OMNIVORE Study)

Status: Recruiting
Clinicaltrials.gov identifier: NCT03203473
Sponsor: Dana-Farber Cancer Institute

Enrolment: 58

Rationale: Nivolumab is an established therapy for treatment of advanced RCC (aRCC) after progression on antiangiogenic therapy after the findings of the CheckMate-025 study. The CheckMate-214 trial established the efficacy of nivolumab combined with ipilimumab in intermediate- to poor-risk metastatic RCC but with the tradeoff of increased toxicity as compared to single agent immune checkpoint inhibition. There are also no

studies which have addressed the optimal duration of this type of therapy in mRCC, and it is not known if the benefit of combining nivolumab with ipilimumab is derived from combined treatment upfront, if these drugs can be sequenced, or if ipilimumab can convert a non-responder to nivolumab to a responder.

Study Design: This Phase II, open-label study enrolls patients with treatment-naïve or previously treated aRCC with either clear cell or non-clear cell disease. Prior immune checkpoint inhibitor therapy is not permitted. All patients enrolled receive nivolumab every 2 weeks initially, with subsequent management outlined based on RECIST response within the first 6 months of nivolumab. If patients have a confirmed partial response (PR) or complete response (CR), nivolumab will be discontinued and patients will be observed. At the time of progression, these patients will be treated again with nivolumab, and if there is further progression, 2 treatments with ipilimumab every 3 weeks will be given in addition to nivolumab (which will be given every 3 weeks when combined with ipilimumab). These patients will be considered part of 'Arm A.' If, instead, patients are found to have stable disease (SD) or progression (PD) after initial nivolumab treatment, 2 treatments with ipilimumab every 3 weeks will be given while continuing nivolumab, with these patients constituting 'Arm B.'

Endpoints: There are co-primary endpoints in this trial – the proportion of patients with durable CR/PR at 1 year after nivolumab discontinuation in Arm A and proportion of patients with SD or PD who convert to CR/PR at 1-year after addition of ipilimumab to nivolumab (Arm B). Progression-free survival (PFS), OS, salvage therapy-free interval, safety and immune related objective response rate (irORR) will also be determined as secondary endpoints.

Comments: The findings of this Phase II study will help to guide the design of future trials evaluating immune checkpoint inhibitor therapy. For example, if Arm A indicates that a favorable proportion of patients have a durable CR/PR after discontinuation of nivolumab, this would warrant a more robust trial to determine the optimal duration of nivolumab. If Arm B of this trial finds that a promising proportion of patients convert to CR/PR after the addition of ipilimumab, this could indicate that we may be able to spare some patients from the toxicity of combined immunotherapy without sacrificing efficacy.