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Clinical Trials Corner

Innovative New Studies in Kidney Cancer. A focus on Papillary cell renal cell carcinoma, a neglected sub group of patients in clinical trials research and an insight into new management strategies for localised RCC.

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 that are recruiting patients with papillary cell renal cell carcinoma (pRCC), an uncommon subtype often excluded from most RCC trials. Additionally, we highlight the ongoing PROSPER trial of Nivolumab as peri-operative therapy in localized RCC - led by Lauren Harshman - which is being conducted within the National Cancer Institute's National Clinical Trials Network (NCTN).

If you would like to inform us on a specific clinical trial, please do not hesitate to contact us: thomas.powles@bartshealth.nhs.uk and Laura.Morrison2@bartshealth.nhs.uk, or kca@iospress.com.

Sincerely,

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A Phase III, Open Label, Randomised, Controlled, Multi-Centre Study To Assess the Efficacy and Safety of Savolitinib Versus Sunitinib in Patients With MET-Driven, Unresectable and Locally Advanced, Or Metastatic Papillary Renal Cell Carcinoma (PRCC).

Status: Recruiting
Clinicaltrials.gov identifier: NCT03091192
Sponsor: AstraZeneca + Hutchinson MediPharma

Enrollment: 180

Study design: This is a phase III, open label, randomised, multicentre study investigating the efficacy and safety of savolitinib compared to sunitinib in patients with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma (pRCC). Patients can have had treatment previously (not sunitinib or MET inhibitors) or be treatment naïve.

Rationale: pRCC carries a poor prognosis and typically responds less well to standard therapies than clear cell RCC. It is frequently excluded from large scale clinical trials and as such there is little data on the use of specific therapies in this patient population. A single arm phase II study (NCT02127710) evaluating savolitinib, a new MET inhibitor, in pRCC showed an overall response rate of 7% with good tolerability. The response rate was better in those patients with MET-driven tumours irrespective of pathological classification.

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Endpoints: The primary endpoint for this study is progression free survival (PFS) defined as the time from randomisation to progression or death. There are several secondary endpoints in this study including overall survival (OS), defined as time from randomisation to death by any cause; objective response rate including all patients with complete or partial responses based on RECIST 1.1 criteria; the duration of any response achieved and the disease control rate (number of patients achieving complete or partial responses or stable disease according to RECIST 1.1).

Results: No results are currently available.

Comments: Papillary cell cancer is poorly represented in clinical trials and the inclusion of patients with papillary cell cancer in this trial provides an interesting option for a difficult to treat subtype of RCC. Standard therapies have typically performed poorly in pRCC and savolitinib may provide a more effective and well tolerated option for MET-driven pRCC.

MEDI4736 Combinations in Metastatic Renal Cell Carcinoma (CALYPSO).

Status: Recruiting
Clinicaltrials.gov identifier: NCT02819596
Sponsor: Queen Mary University of London

Enrolment: 195

Study Design: This study investigates both the safety and efficacy of the immunotherapy drug MEDI4736 (durvalumab) both alone and in combination with targeted therapy in patients with advanced or metastatic RCC. This phase is a randomised, multi-centre study recruiting across the UK and Spain. 195 patients with metastatic renal cell carcinoma will be enrolled. Patients with papillary cell cancer are automatically entered into a treatment arm (MEDI4736 + Savolitinib) while those with clear cell RCC are randomised to one of four treatment arms (a: tremelimumab + savolitinib, b: MEDI4736 alone, c: MEDI4736 + Savolitinib, d: Savolitinib alone).

Rationale: Patients with papillary cell cancer are often excluded from clinical trials. As such there is no prospective, randomised data on optimal treatment for this subgroup except that based on subgroup analysis within studies. MEDI14736, a monoclonal antibody which inhibits the PD-L1 checkpoint signal, has been shown to have some effectiveness in solid tumours inducing response rates of up to 20% in PD-L1 unselected patients. The response rate seems to be more marked in those with PD-L1 positive staining. Savolitinib, a selective c-Met kinase inhibitor, is currently under investigation in various studies and has shown some encouraging response rates in individuals with papillary type tumours in study D5081C00001. The potential of combining immune and targeted therapy is being increasingly explored in the domain of renal cell cancer and may lead to longer, durable responses, far superior to those currently seen.

Endpoints: The primary endpoints are overall response in patients with metastatic papillary cell cancer as measured by RECIST 1.1 criteria as well as a biomarker enriched analysis in all (papillary and clear cell RCC) patients. The secondary endpoints included are OS and PFS as determined by time from onset of treatment to radiological progression by RECIST 1.1.

Results: No results are currently available.

Comments: Metastatic papillary cell cancer is associated with a poor prognosis due to a naturally more aggressive disease history. This trial provides these patients with an opportunity to receive a combination of immune and targeted therapy. This is an exciting opportunity in a somewhat neglected patient cohort at risk of rapid disease progression.

PROSPER: A phase III randomized study comparing perioperative nivolumab versus observation in patients with localized renal cell carcinoma (RCC) undergoing nephrectomy (ECOG-ACRIN 8143)

Status: Recruiting
Clinicaltrials.gov identifier: NCT03055013
Sponsor: National Cancer Institute/CTEP via the National Clinical Trials Network (Lead group: ECOG);

Enrolment: 766

Rationale: As of 2018, there remains no standard adjuvant systemic therapy that increases overall survival over nephrectomy alone for patients with non-metastatic RCC. Nivolumab is an antibody against PD-1 that can improve overall survival in metastatic RCC and is well tolerated. Moving this agent earlier in the disease course to improve clinical outcomes makes sense but requires a thoughtful approach. Within the primary tumor and its microenvironment, there is an ongoing but unsuccessful anti-tumor immune response. Work in murine models has shown that post-PD-1 blockade, anti-tumor CD8 T cells may preferentially expand in these areas and traffic to distant sites, developing into memory cells (Woo Cancer Research 2012). Nephrectomy may remove the majority of these effector cells and cytokines thereby inducing a less potent immune response. Mouse solid tumor models have revealed an overall survival benefit with a short course of neo-adjuvant PD-1 blockade compared to adjuvant therapy alone (Liu Cancer Discovery 2016). In humans, ongoing phase 2 studies of perioperative nivolumab in M0 RCC patients are showing preliminary feasibility and safety with no surgical delays or complications (NCT02575222; NCT02595918).

Study Design: PROSPER RCC (EA8143) is a global, un-blinded, phase 3 study which will examine if perioperative nivolumab in combination with radical or partial nephrectomy can improve clinical outcomes in patients with high risk localized and locally advanced RCC. 766 patients with clinical stage ≥T2 or node positive M0 RCC of any histology will be enrolled. T1 tumors are allowed if signs of clinical node positivity. Tumor biopsy prior to randomization is mandatory to ensure RCC but also permits unparalleled correlative science. Randomization is 1:1. Patients are stratified by clinical T stage, node positivity, and histology. Patients on the investigational arm receive two doses of nivolumab prior to surgery followed by adjuvant nivolumab for 9 months. The adjuvant dosing will be every 2 weeks for 3 months then transition to every 4 weeks x 6 months for enhanced quality of life. The control arm will receive standard of care surgical resection followed by observation. The primary endpoint is recurrence-free survival. The study is also powered to evaluate a significant increase in overall survival with the addition of perioperative PD-1 blockade. Safety, feasibility, and quality of life endpoints critical to adjuvant therapy considerations will be evaluated. PROSPER RCC exemplifies team science with a wealth of embedded correlative work aimed at investigating the impact of the baseline immune milieu, the changes induced by neoadjuvant anti-PD-1 priming, and how both correlate with clinical outcomes.

Comments: The success of PROSPER RCC requires a thoughtful disruption of the current practice of upfront surgery followed by consideration of adjuvant systemic therapy. Given the mechanism of action of nivolumab, it makes sense to engage the patient's immune system by priming with nivolumab prior to surgery when there is significant target (i.e., tumor antigen) in place. This change in practice has strong potential to increase cures, delay time to recurrence and improve overall survival in patients with high risk non-metastatic RCC.

For a more thorough review, please visit: http://content.iospress.com/articles/kidney-cancer/kca170010