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Clinical Trials Corner

Dear Readers,

The Clinical Trials Corner of the *Bladder Cancer* Journal is a new section devoted towards highlighting ongoing trials or recently completed trials in urothelial cancer. Our hope is to encourage accrual for ongoing trials and to educate readers on the results of completed trials. If you feel that you would like to draw attention to a specific trial, please feel free to email us at: piyush.agarwal@nih.gov and/or cnsternberg@corasternberg.com.

Cisplatin-based combination chemotherapy regimens are the standard of care for metastatic bladder cancer. Patients with metastatic urothelial carcinoma who progress after first-line chemotherapy have limited treatment options. This issue will highlight a few trials of second line therapy.

Sincerely,

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Second Line Immunotherapy Trials

Recently Closed to Accrual

Study Title: A Study of Nivolumab in Participants With Metastatic or Unresectable Bladder Cancer

Clinicaltrials.gov identifier: NCT02387996

Sponsor: Bristol-Myers Squibb

Participating Centers: United States (several centers), Australia, Belgium, Czech Republic, Finland, Germany, Italy, Japan, Poland, Spain, Sweden

Accrual: 242

Study Design: Phase II, single arm trial of nivolumab in patients with metastatic or unresectable urothelial cancer who have progressed or recurred after platinum-based chemotherapy

Rationale: Nivolumab is a monoclonal antibody against PD-1 and is being evaluated in a Phase I/II in combination with ipilimumab in advanced or metastatic solid tumors including patients with urothelial cancer. It has demonstrated activity in melanoma, lung cancer, and renal cancer. This trial aims to look at the efficacy of nivolumab as a second line therapy in platinum-recurrent or -resistant urothelial tumors.

Comments: Patients were stratified in this trial based on their PD-L1 expression. Nivolumab has been approved by the FDA for patients with lung cancer and more recently for second line renal cell cancer after a comparison with everolimus revealed a clear improvement in overall survival (Checkmate 025 Phase III trial; Motzer RJ, et al. N Engl J Med. 2015: 373; 1803-13).

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Study Title: A Study of Atezolizumab Compared With Chemotherapy in Patients With Locally Advanced or Metastatic Urothelial Bladder Cancer [IMvigor211]

Clinicaltrials.gov identifier: NCT02302807

Sponsor: Roche/Genentech

Participating centers: United States (several centers), Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Japan, Korea, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Serbia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom

Accrual: expected 767

Study Design: Phase III, randomized trial comparing atezolizumab (anti-PD-L1 antibody) with chemotherapy in locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy

Rationale: Powles et al. reported a 26% overall response rate with atezolizumab in patients with metastatic urothelial cancer in a Phase I study. Recently, more data in heavily pretreated patients from the IMvigor210 study have been presented by Rosenberg et al. at the European Cancer Congress (Vienna, September 2015) meeting and at the Genitourinary Cancers Symposium (GUCS) in January 2016. IMvigor 210 enrolled an all-comer population independent of PD-L1 immunohistochemistry (IC) status (n=311). There was a 27% response rate in patients with IC2/3 status, 10% with IC1 and 9% with IC0. Therefore, the IMvigor211 trial is trying to establish the merits of using atezolizumab in the second-line setting after failing platinum-based chemotherapy.

Comments: It will be interesting to see how the responses and more importantly overall survival of second-line chemotherapy will compare with second-line immunotherapy, that has been shown to improve OS in other tumor types.

Study Title: A Study of Ramucirumab (LY3009806) Plus Docetaxel in Participants With Urothelial Cancer (RANGE)

Clinicaltrials.gov identifier: NCT02426125

Sponsor: Eli Lilly and Company

Participating centers: 123 locations: United States (several centers), Australia, Belgium, Canada, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Japan, South Korea, Netherlands, Poland, Romania, Russia, Spain, Taiwan, Turkey, United Kingdom

Accrual: expected 524

Study Design: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Ramucirumab Plus Docetaxel Versus Placebo Plus Docetaxel in Patients With Locally Advanced or Unresectable or Metastatic Urothelial Carcinoma Who Progressed on or After Platinum-Based Therapy. Patient must have had disease progression while on a platinum containing regimen in the first-line setting or within 14 months after completing the first-line platinum regimen. Participants who received treatment with one immune checkpoint inhibitor regimen are eligible (for example PD-1, PDL1, or CTLA4) and may have a longer interval since prior platinum-containing therapy (≤24 months). Patients are excluded who have received prior systemic taxane therapy.

Rationale: Ramucirumab is a monoclonal antibody that acts to inhibit vascular endothelial growth factor (VEGF); ramucirumab acts on VEGF-2. Adding this new antiangiogenic agent ramucirumab to docetaxel chemotherapy has shown promising results as a second-line therapy in advanced or metastatic urothelial carcinoma. At the Genitourinary Cancers Symposium (GUCS) in 2015.

Petrylak et al. presented a planned interim analysis of a phase 2 randomized trial that showed that the combination regimen significantly increased progression-free survival (22 weeks) as compared with docetaxel alone (10.4 weeks).

The ramucirumab plus docetaxel combination conferred a statistically significant progression-free survival improvement of greater than 11.5 weeks and reduced the risk of disease progression by 61%. Results were

consistent across pre-specified subgroups and it showed an acceptable safety profile. Ramucirumab has been approved for use in gastric cancer and non–small cell lung cancer after it was shown to prolong overall survival in phase 3 second-line studies.

Recruiting

Study Title: An Efficacy and Safety Study of JNJ-42756493 in Participants With Urothelial Cancer

Clinicaltrials.gov identifier: NCT02365597

Sponsor: Janssen Research & Development, LLC

Participating Centers: United States (several centers), France, United Kingdom, Belgium, Germany, Italy, Korea, Russia, Spain, Taiwan, Germany, Austria, Romania, Moldova

Accrual: estimated 165

Study Design: A Phase 2, Two-arm Multicenter, Open-Label Study to Determine the Efficacy and the Safety of Two Different Dose Regimens of a Pan-FGFR Tyrosine Kinase Inhibitor JNJ-42756493 in Subjects With Metastatic or Surgically Unresectable Urothelial Cancer With FGFR Genomic Alterations. Patients who have failed first line chemotherapy for metastatic disease or unresectable urothelial cancer or patients who are ineligible for cisplatin based chemotherapy (GFR < 60 mL/min) will be included.

Rationale: JNJ-42756493 is a selective and potent orally administered pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor with demonstrated activity in patients with solid tumors with alterations in the FGFR pathway including urothelial carcinoma (Tabernero J et al., ASCO 2015), indicating the potential to be a new therapeutic option for these patients. Thus far no molecularly targeted agents have been approved for the treatment of this disease. However, recent advances in genomic profiling of urothelial carcinomas have identified potential therapeutic molecular targets in 69% of tumors (The Cancer Genome Atlas Project Nature 2014). Of the molecular alterations identified, FGFR signaling in particular is altered in a high proportion of bladder tumors in both muscle invasive (15–20%) and non-invasive tumors (70–80%).