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Clinical Trials Corner

Dear Readers,

The Clinical Trials Corner of *Bladder Cancer* 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

Sincerely,

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Ongoing Trials that are Recruiting Patients

Study Title: A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects With Advanced/Unresectable or Metastatic Urothelial Cancer (MK-3475-052/KEYNOTE-52)
Clinicaltrials.gov identifier: NCT02335424

Sponsor: Merck Sharp & Dohme Corp

Participating centers: United States (several centers), Australia, Canada, Denmark, Guatemala, Hungary, Ireland, Israel, Italy, Korea, Malaysia, Puerto Rico, Singapore, Spain, Taiwan, United Kingdom

Accrual: 350

Study Design: Phase II, single arm interventional trial using pembrolizumab in cisplatin-ineligible, chemotherapy-naïve patients with inoperable and/or metastatic urothelial cancer

Rationale: In a recently reported multi-cohort Phase 1b Trial, pembrolizumab (PD-1 inhibitor) demonstrated ~15% grade 3-5 adverse events and 28% overall response rate in advanced urothelial cancer failing 2 or more systemic therapies. Therefore, pembrolizumab is being evaluated in a previously untreated population (except neoadjuvant chemotherapy >12 months prior) with aggressive disease.

Comments: At least two trials now demonstrate the safety and efficacy of checkpoint blockade inhibitors (both PD-1 and PD-L1 inhibition) in urothelial cancer. This new trial will evaluate the impact of PD-1 inhibition in patients with aggressive urothelial cancer who have not been pre-treated. A possible concern with this trial is that PD-1 expression in tumors and tumor infiltrating immune cells may be limited as PD-1 expression increases in response to IFN-γ which can be released from prior treatments. In the absence of prior treatments, up regulation of PD-1 may not be as robust.

Study Title: A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Versus Observation as Adjuvant Therapy in Patients With PD-L1-Selected, High-Risk Muscle-Invasive Bladder Cancer After Cystectomy
Clinicaltrials.gov identifier: NCT02450331

ISSN 2352-3727/15/€27.50/$35.00

Sponsor: Hoffman-La Roche

Participating centers: United States (several centers), Australia, Belarus, Belgium, Canada, Czech Republic, Finland, France, Denmark, Germany, Greece, Israel, Italy, Korea, Netherlands, Poland, Russian Federation, Serbia, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom

Accrual: 440

Study Design: Phase III, randomized trial comparing adjuvant atezolizumab versus observation in patients with PD-L1 positive muscle invasive bladder cancer (urothelial histology) status post cystectomy. On the study patients may have had no neo-adjuvant chemotherapy or may have had neo-adjuvant chemotherapy and then after cystectomy are pT2-T4a or N+. No prior adjuvant RT or chemotherapy is allowed.

Rationale: In a recently reported Phase I trial with update at ASCO 2015 Annual Meeting, Powles et al reported 26% overall response rate with MPDL3280A (atezolizumab) in patients with metastatic urothelial cancer. Results are impressive considering that at least 72% of patients failed 2 or more prior regimens. Therefore, PD-L1 inhibition is being evaluated in patients in an earlier stage of disease in this current trial.

Comments: Emerging literature demonstrates that immunotherapies are more effective in patients with limited tumor burden. Given the impressive efficacy from the Phase I trial (as high as 43% in patients with strong PD-L1 expression), this trial optimizes atezolizumab therapy for patients with low tumor burden and PD-L1 expression.

Recently Closed to Accrual

Study Title: A Study of Pembrolizumab (MK-3475) Versus Paclitaxel, Docetaxel, or Vinflunine for Participants With Advanced Urothelial Cancer (MK-3475-045/KEYNOTE-045)

Clinicaltrials.gov identifier: NCT02256436

Sponsor: Merck Sharp & Dohme Corp

Participating Centers: United States (several centers), Australia, Austria, Belgium, Canada, Chile, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Korea, Netherlands, Norway, New Zealand, Peru, Poland, Portugal, Puerto Rico, Romania, Singapore, Spain, Sweden, Taiwan, Turkey, United Kingdom

Accrual: 450

Rationale: In a recently reported multi-cohort Phase 1b Trial, pembrolizumab (PD-1 inhibitor) demonstrated ~15% grade 3-5 adverse events and 28% overall response rate in advanced urothelial cancer failing 2 or more systemic therapies. Therefore, pembrolizumab is being evaluated in a previously treated population.

Participants with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy will be randomly assigned to receive pembrolizumab or investigator's choice of paclitaxel, docetaxel, or vinflunine. The primary study hypotheses are that pembrolizumab will prolong OS and PFS.

Comments: Checkpoint blockade inhibitors (both PD-1 and PD-L1 inhibition) appear to be active in urothelial cancer. In the USA there is no standard second line therapy for patients who have failed first line cisplatin based chemotherapy. In Europe, vinflunine is approved in this setting. For this reason patients will be randomized between pembrolizumab and the investigator's choice of chemotherapy.

Recently Completed Trials

Study Title: Randomized Phase III Trial Comparing Immediate Versus Deferred Chemotherapy After Radical Cystectomy in Patients With pT3-pT4, and/or N+M0 Transitional Cell Carcinoma (TCC) of the Bladder

Clinicaltrials.gov identifier: NCT00028756

Publication: Sternberg CN et al, Lancet Oncol. 2015 Jan;16(1):76-86.

Sponsor: EORTC with collaboration from GETUG, NCRI, NCIC and AUO

PI: Cora N. Sternberg, MD

Accrual: 284

Study Design: Patients at least 90 days out of cystectomy with pT3-T4 and/or node positive urothelial cancer of the bladder were randomized to either immediate chemotherapy or deferred chemotherapy (latter being given at clinical relapse of disease)

Rationale: Adjuvant chemotherapy has been evaluated in small single center studies and the trials have never been powered adequately to demonstrate a benefit with adjuvant chemotherapy. This large, multi-center trial was designed through the EORTC to try to evaluate adjuvant chemotherapy more rigorously

Results: This is the largest randomized trial ever reported of adjuvant chemotherapy in patients with muscle invasive bladder cancer.

Immediate adjuvant cisplatin based combination chemotherapy after radical cystectomy led to a statistically significant improvement in PFS**.** 5 yr PFS was 47.6% vs 31.8% on the deferred arm. The median PFS was 3.11 years vs 0.99 years on the deferred arm (HR =0.54 p = 0.54 (95% CI : 0.40 – 0.73) P < 0.0001). A non-significant reduction of 22.2% in the risk of death was also observed.

Comments: Unfortunately, the trial was closed early due to difficulties with accrual. One can only speculate that the trend in OS may have become significant if more paitents had been enrolled. A meta analysis of the literature suggests a benefit of adjuvant chemotherapy but is limited by severe between trial heterogeneity.

An updated individual patient data meta-analysis and biomarker research are needed to further elucidate the potential for survival in subgroups of patients. Although immediate chemotherapy after radical cystectomy led to a significant improvement in PFS, overall survival was not improved. However, immediate chemotherapy might extend survival in patients without lymph-node involvement.