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# Clinical Trials Corner

Dear Readers,

The American Association for Cancer Research (AACR) just completed its annual meeting in Chicago this year and two novel trials of immunotherapy in urothelial cancer were presented. These trials position immunotherapy, not only in the metastatic setting, but also potentially in earlier stages of locally advanced disease. Therefore, we are highlighting these two trials in this issue. In the future, 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 or cnsternberg@corasternberg.com and/or at BLC@iospress.com.

Sincerely,

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**Study Title:** An Open Label, Single-arm, Phase 2 Study of Neoadjuvant Pembrolizumab (MK-3475) Before Cystectomy for Patients with Muscle-invasive Urothelial Bladder Cancer.

**Clinicaltrials.gov identifier:** NCT02736266

**Sponsor:** Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

**Enrollment:** 90

**Rationale:** Patients with muscle-invasive bladder cancer (MIBC) are at risk for relapse and poor overall survival due to understaging of disease and micrometastatic disease. Due to poor adoption of neoadjuvant chemotherapy and the lack of an effective non-cisplatin based regimen, this group from Italy sought to investigate the use of neoadjuvant pembrolizumab prior to radical cystectomy for MIBC.

**Study Design:** This is a Phase II, single arm clinical trial of patients with histologically confirmed MIBC (T2-T3bN0), predominant urothelial histology (≥50%), and residual disease after transurethral resection of bladder tumor. Although patients had to have GFR ≥20 mL/min, researchers were agnostic to cisplatin eligibility and patients were not offered cisplatin. Patients were treated with 3 treatments of 3 weekly treatments of pembrolizumab and then underwent radical cystectomy. Cystectomy specimens underwent genomic sequencing with the Foundation One Assay.

**Primary endpoints:** In this interim analysis, the primary endpoint was pathologic complete response (pT0) rate and responses ≥25% were considered significant. Thirty-six patients were evaluated. The final trial will look at the 2-year overall survival rate in all planned 90 patients.

**Results:** Interim efficacy and an interim biomarker analysis was presented at the AACR meeting. The pT0 rate was 38.9% in all patients (47.4% in those with high PD-L1 expression defined as a combined positive score ≥23% which measures expression in tumor cells, lymphocytes, and macrophages). The pT0 rate was 60% in those with DNA Damage Repair (DDR) mutations and 100% in those with DDR mutations AND high PD-L1

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expression. Mutational analysis demonstrated that Rb1 mutations were associated with pT0 response whereas FGFR3 mutations were associated with a non-pT0 response. Interestingly the median time from the end of pembrolizumab to radical cystectomy was 22 days and only 14 days in the last ten patients. Any grade adverse events were experienced in 47% patients but only 5.6% patients experienced grade 3-4 toxicity.

**Comments:** Overall, the results are very exciting and suggest that neoadjuvant pembrolizumab has activity in this setting and potential biomarkers associated with pT0 responses were identified. Although pT0 rates as high as almost 40% have been associated with neoadjuvant chemotherapy, a meta-analysis of 10 trials suggests that the pT0 rate from chemotherapy is closer to 27.8%.[1] Also this trial required residual disease after transurethral resection of the bladder tumor and so the pT0 rate is even more impressive with pembrolizumab. Finally, the association of improved pT0 rates with DDR mutations, PD-L1 expression, and Rb1 mutations foretells a future where we may be able to more intelligently select patients for neoadjuvant therapies.

However, there are some concerns with the trial. Four patients on the trial suffered unique complications such as ileal anastomosis dehiscence/fistula or ureteral anastomosis dehiscence. This raises a concern about the nature of potential surgical complications if completing immunotherapy 2-3 weeks before surgery. Nevertheless, this is a novel trial and will probably open the door for a randomized neoadjuvant trial of immunotherapy versus chemotherapy prior to radical cystectomy.

**Study Title:** A Phase I Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination with Tremelimumab (Anti-CTLA-4 Antibody) in Subjects with Advanced Solid Tumors

**Clinicaltrials.gov identifier:** NCT02261220

**Sponsor:** Medimmune LLC

**Enrollment:** 380

**Rationale:** Anti-PD-(L)-1 antibody therapy has activity and approval as a post-platinum therapy for locally advanced and metastatic urothelial cancer. Anti-CTLA-4 agents are approved as second line therapy for urothelial cancers and may have synergistic activity with anti-PD-(L)-1 antibodies. This trial explores the safety and efficacy of the combination of durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4) in the metastatic urothelial cancer cohort of the dose-expansion phase for this phase I study of patients with advanced solid tumors.

**Study Design:** This is a phase I combination study of durvalumab and tremelimumab for patients with metastatic urothelial cancer that has progressed after 1-2 prior treatments (including cisplatinum). Patients were treated with 4 cycles of concurrent durvalumab and tremelimumab and then treated with durvalumab alone for the remainder of the year.

**Primary endpoints:** Overall response rate, progression-free survival, overall survival

**Results:** A total of 168 patients were analyzed. Overall treatment related adverse events were seen in 75.6% of patients. Pruritus, fatigue, diarrhea, and rash were the most common. However, grade 3 and 4 events were only seen in 28.6% and 0.6% suffered a grade 5 event. The overall response rate (complete and partial responses) was 20.8% for all patients. The response was 29.4% in patients with at least 25% or greater PD-L1 expression in tumor cells and immune cells. The median time to response was 1.8 months and median progression-free survival was 1.9 months. Median overall survival was 9.5 months in all patients. For patients who again had ≥25% PD-L1 expression, median survival was 18.9 months.

**Comments:** This trial demonstrates that combination therapy has manageable toxicity. Although efficacy was observed in all patients, it was better in those with ≥25% PD-L1 expression. Surprisingly, the addition of tremelimumab did not achieve response rates significantly higher than those seen in single agent anti-PD-(L)-1 trials begging the question, "do we really need to add an anti-CTLA4 antibody?"

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[1]Zhu et al. Oncotarget 2017.