Bladder Cancer 6 (2020) 93–95
DOI 10.3233/BLC-200002
IOS Press

Clinical Trials Corner

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Received 4 March 2020
Accepted 7 March 2020

Dear Readers,

In this issue, we highlight two recent and pivotal developments in the treatment of urothelial cancer with immunotherapy. First, is the recent FDA approval of pembrolizumab for the treatment of non-muscle-invasive bladder cancer (NMIBC) following the heels of a favorable FDA Oncologic Drugs Advisory Committee (ODAC) meeting. This is based on the results of the KEYNOTE-057 Trial highlighted below. Second, is the negative results from the adjuvant atezolizumab trial in locally advanced bladder tumors after radical cystectomy. In the future, please reach out to us directly in order to highlight any specific clinical trials at pkagarwal@uchicago.edu or cns9006@med.cornell.edu and/or at BLC@iospress.com.

Sincerely,

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Study Title: A Phase II Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Subjects With High Risk Non-muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG) Therapy

Clinicaltrials.gov identifier: NCT02625961

Sponsor: Merck Sharp & Dohme Corp

Enrollment: 260

Rationale: PD-L1 and PD-1 inhibitors are now established treatments both for 1st line treatment of patients with locally advanced or metastatic bladder cancer that are cisplatin-ineligible or experiencing disease progression after platinum-based chemotherapy. Recently, data from 2 small phase II trials suggest their potential efficacy when given as neoadjuvant therapy prior to radical cystectomy. Several ongoing trials have also evaluated this immunotherapy in the treatment of BCG-unresponsive NMIBC. This trial by Merck Sharp & Dohme specifically evaluated the safety and efficacy of its PD-1 inhibitor, pembrolizumab, in the treatment of patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) given the already encouraging results in other disease states of urothelial cancer (neoadjuvant prior to cystectomy and metastatic).

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ISSN 2352-3727/20/$35.00

Study Design: This is a phase II, multicenter trial for patients with high risk NMIBC (T1, CIS, and/or high-grade Ta) who are deemed BCG-unresponsive after adequate BCG therapy who are either unfit or refuse radical cystectomy. This was a single-arm study in which all patients were treated with intravenous pembrolizumab, 200 mg, every 3 weeks until recurrence of high-risk disease or unacceptable toxicity for up to 24 months. Assessment of tumor status was performed by cystoscopy and cytology and for cause biopsies every 3 months.

Endpoints: Primary outcomes were complete response rate and disease-free survival rate. Complete response rate (CR) was defined by a negative cystoscopy or bladder biopsies performed for an abnormal cystoscopy, negative urine cytology, and normal CT urogram. Secondary outcome was duration of response.

Results: At the time of analysis, the trial enrolled 148 patients of whom 96 patients had BCG-unresponsive CIS either with or without papillary tumors. The 3-month CR rate in the 96 patients with CIS was 41% (95% CI: 31-51) and the median duration of response was 16.2 months (range 0-30.4 months). Among the 39 patients with a CR, 18 (46%) and 19% among all patients with CIS maintained a CR of at least 12 months after starting treatment [Reference: fda.gov 1/8/2020]. The safety profile was in line with other PD-1 inhibitor studies, however, 99 patients experienced 1 or more adverse events (AEs) and treatment-related AEs were seen in up to 65.7% of patients. Although grade 3-5 AEs were only seen in 29.4% of patients, two patients died while on therapy during the course of the trial, but only one of these deaths was deemed to be immune-related.

Comments: This trial led to the approval of pembrolizumab in patients with BCG-unresponsive CIS. Although this is a valuable advance in the treatment of NMIBC, it does raise several potential concerns. Will this be used as first line therapy for patients with BCG unresponsive disease or will urologists choose alternative intravesical therapies such as gemcitabine/docetaxel. Two other intravesical therapies, vicinium and adenoviral mediated interferon mediated gene therapy, are currently under review by the FDA. The cost of immunotherapy will raise the cost of bladder cancer care astronomically imploring us to evaluate whether such treatment justifies the cost. This is especially sobering when one considers that on follow-up, only 19% of the entire cohort of CIS-treated patients continued with a CR of at least one year begging the question whether this is an appropriate benchmark for new therapies in the BCG-unresponsive disease state.

Study Title: A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) Versus Observation as Adjuvant Therapy in Patients With High-Risk Muscle-Invasive Urothelial Carcinoma After Surgical Resection.

Clinicaltrials.gov identifier: NCT02450331

Sponsor: Hoffmann-La Roche

Enrollment: 809

Rationale: Patients with high-risk muscle invasive urothelial cancer after surgical resection have limited options for treatment. Historically, they have been observed only to later develop local or systemic recurrences and to eventually succumb to urothelial cancer. However, with the absence of a proven benefit of adjuvant therapy and dearth of treatments except for chemotherapy, there has been little progress in this disease space of urothelial cancer. This trial, also known as the IMvigor010 trial, aimed to evaluate the impact of adjuvant atezolizumab, a PD-L1 inhibitor, in patients randomized to receiving such therapy after radical cystectomy with high risk features seen on pathology.

Study Design: This is a phase III, multicenter open-label trial that randomly assigned patients with muscle-invasive urothelial cancer after surgical resection with high risk features for recurrence to either observation or adjuvant atezolizumab treatment in a 1:1 fashion. Patients randomized to intravenous atezolizumab received therapy with 1200 mg every 3 weeks for up to 16 cycles. Patients with pT2-T4 disease after neoadjuvant chemotherapy, or pT3-4 disease without neoadjuvant chemotherapy, or any node positive disease after radical cystectomy were considered high risk for recurrence and eligible for the trial. Assessment of tumor status was performed by radiographic imaging prior to initiation of treatment.

Endpoints: Primary outcome was disease-free survival (DFS) from the time of randomization and included pelvic (local) recurrence, extravesical urinary tract recurrence, distant metastases, or death from any cause. Secondary outcomes included overall survival, disease-specific survival, disease metastasis-free survival, and non-urinary tract recurrence-free survival.

Results: In this trial, Atezolizumab failed to meet the primary end point, disease-free survival (DFS), as adjuvant monotherapy in patients with muscle-invasive urothelial cancer (MIUC) compared with observation in the phase III IMvigor010 clinical trial, according to a press release from Roche, developer of the drug on January 24, 2020 (https://bit.ly/38zdRoE)

Comments: This trial unfortunately did not demonstrate a difference in DFS with the use of adjuvant atezolizumab. One of the criticisms is that this trial may have excluded patients likely to benefit and included patients unlikely to benefit with atezolizumab. Patients with positive surgical margins are most likely to recur with local (pelvic) recurrence and may benefit most from adjuvant therapy but were excluded from this trial. Another potential issue is potentially that there may be a difference in efficacy between PD-1 and PD-L1 inhibitors as PD-1 inhibitors have demonstrated slightly better survival results in some studies although no studies have directly compared these two different types of inhibitors.

CONFLICT OF INTEREST

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Renal
Honoraria: Pfizer, IPSEN
Consultant: Eisai, Pfizer, IPSEN, BMS, Roche, Bayer, MSD, Novartis

Bladder
Consultant: Merck, Clovis, BMS, Incyte, AstraZeneca
Honoraria: Lilly
Institutional Funding: Janssen

Prostate
Consultant: Sanofi, Bayer, Pfizer
Honoraria: Clovis, Janssen, AstraZeneca, Sanofi, Astellas
Institutional Funding: Roche-Genentech, Bayer, Sanofi , Janssen, Medivation, Exelixis, Sanofi Genzyme

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