Bladder Cancer 3 (2017) 315–317
DOI 10.3233/BLC-179024
IOS Press

Clinical Trials Corner

Dear Readers,

The use of immunotherapies in the treatment of urothelial cancer was a major theme at this year's European Society for Medical Oncology (ESMO) conference in Madrid in September 2017. This month's issue of the Clinical Trials Corner of the Bladder Cancer Journal is devoted towards some trials highlighted at this meeting. 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,

Piyush K. Agarwal, MD
Associate Editor, Bladder Cancer
Head, Bladder Cancer Section
Urologic Oncology Branch
National Cancer Institute
Bethesda, MD, USA

Cora N. Sternberg, MD, FACP
Associate Editor, Bladder Cancer
Chair, Department of Medical Oncology
San Camillo Forlanini Hospital
Rome, Italy

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

Enrollment: 542

Rationale: Until recently, there were limited options for patients with locally advanced/unresectable urothelial cancer (UC) that has recurred or progressed after combination platinum-based chemotherapy. Given the activity of PD-1/PD-L1 inhibitors in the metastatic setting, this randomized trial aims to compare the impact of pembrolizumab on overall survival (OS) and progression-free survival (PFS) compared to chemotherapy (investigator's choice of paclitaxel, docetaxel, or vinflunine). Previous Phase III results demonstrated longer OS in the pembrolizumab group and the updated results were presented at ESMO.

Study Design: This is a Phase III, randomized clinical trial comparing pembrolizumab for up to 2 years to chemotherapy in terms of OS and PFS. The chemotherapy regimen consists of either paclitaxel, docetaxel, or vinflunine and in a recent amendment, patients are able to crossover to receive pembrolizumab if they experience disease progression with chemotherapy. Eligibility is limited to patients with histologically confirmed UC with measurable disease after previous platinum therapy.

Results: With median follow-up of 22.5 months for both treatment arms, median OS was significantly longer in the pembrolizumab arm in all patients (10.3 vs. 7.4 months; HR 0.70, $p = 0.0003$) which was an improvement over the earlier analysis with HR of 0.73. In patients with PD-L1 combined positive score (CPS; % of PD-L1 expressing tumor and inflammatory cells) $\geq 10\%$, median OS was also improved with pembrolizumab vs. chemotherapy (8.0 vs. 5.2 months; HR 0.58, $p=0.003$). The overall response rate was greater with pembrolizumab (21.1% vs. 11.0%) and treatment-related AEs of any grade were fewer (62.0% vs. 90.6%). However, PFS was not statistically different between the groups.

ISSN 2352-3727/17/$35.00

Comments: Additional follow-up confirms superior OS of pembrolizumab immunotherapy over chemotherapy as second-line treatment after cisplatin based combination chemotherapy.

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

Clinicaltrials.gov identifier: NCT02426125

Sponsor: Eli Lilly and Company

Enrollment: 530

Rationale: Again, given the limited options for platinum-refractory advanced or metastatic UC, this phase III trial evaluates the addition of ramucirumab (RAM) to docetaxel in these patients. Ramucirumab is a monoclonal antibody directed against VEGFR-2. In a previous phase II trial, the combination significantly improved median PFS over docetaxel alone.

Study Design: This is a Phase III, randomized double-blind, clinical trial comparing docetaxel to docetaxel and RAM in patients with progressive advanced or metastatic UC after platinum-based chemotherapy with the primary endpoint being PFS. Secondary endpoints included OS and objective response rate (ORR). Of note, patients were allowed to have received previous immune checkpoint inhibitor treatment.

Results: Median PFS was slightly prolonged in the combination group compared to docetaxel plus placebo (4.1 vs. 2.8 months; HR 0.76, p=0.0118). The data were immature for OS determination but ORR was higher in the combination arm (24.5% vs. 14.0%). Finally, grade ≥3 adverse events were similar between the arms.

Comments: This trial demonstrated the first statistically significant improvement in PFS in patients that have received previous platinum-based chemotherapy and possibly a previous immune-checkpoint inhibitor.

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

Clinicaltrials.gov identifier: NCT02387996

Sponsor: Bristol-Myers Squibb

Rationale: The abstract presented at ESMO evaluated the impact of tumor mutation burden (TMB) on nivolumab's efficacy (PD-1 inhibitor) from the previously conducted Checkmate 275 study.

Study Design: In the single-arm phase II Checkmate 275 study, patients with metastatic or surgically unresectable UC were treated with nivolumab. Of the 270 patients, 139 (51%) had evaluable TMB ascertained from tumor DNA from pre-treatment archival tumor tissue and matched whole blood samples. TMB was defined by the total number of missense somatic mutations per tumor. In this abstract, the association between TMB and PFS, ORR, and OS was investigated.

Results: TMB demonstrated a statistically significant positive association with PFS (p=0.005) and ORR (p=0.002) but a statistically insignificant association with OS (p=0.067) even when adjusted for baseline tumor PD-L1 expression. In fact, patients with TMB had high ORR even with low (<1%) PD-L1 expression.

Comments: This study suggests that TMB might enrich for responses to nivolumab that may be independent of PD-L1 expression.

Study Title: A Study of Atezolizumab in Participants with Locally Advanced or Metastatic Urothelial Bladder Cancer (Cohort 2)

Clinicaltrials.gov identifier: NCT02108652

Sponsor: Hoffman-La Roche

Rationale: The abstract presented at ESMO evaluated the outcomes of post-progressive disease (PD) in patients treated on the phase II IMvigor210 study.

Study Design: The IMvigor210 study demonstrated safety and efficacy of atezolizumab in metastatic UC patients. This study looked at the outcomes of 220 patients (out of 310 total in cohort 2 of the study) who developed PD after therapy. Interestingly, 137 of these patients continued on atezolizumab post-PD compared with 83 patients who either received no systemic therapy (64 patients) or other systemic therapy (19 patients).

Results: The duration of pre-PD therapy was similar in both groups of patients and the patients continuing atezolizumab after PD had higher pre-PD ORR compared to the other patients. Interestingly, median OS was better in the group that continued atezolizumb after PD versus the patients that did not (12.8 months vs. 3.6 months). Furthermore, 45 patients in the atezolizumab continuation group experienced decreases in the sum of their target lesion diameters.

Comments: This study suggests that patients may continue to derive benefit from atezolizumab even in the setting of progressive disease. Unfortunately, only 19 patients received alternate therapies after PD and so it would be difficult from this study to ascertain if other therapies might be more effective in the post-PD setting.