Bladder Cancer 4 (2018) 133–136
DOI 10.3233/BLC-189028
IOS Press

Clinical Trials Corner

Dear Readers,

Cisplatin-based combination chemotherapy is the preferred first-line therapy for metastatic urothelial cancer and was the only treatment shown to improve survival in patients with previously untreated disease for years. Treatment of urothelial cancer has evolved, however, to include not only chemotherapy, but also immunotherapy with approvals of five PD-1 and PD-L1 checkpoint inhibitors, both in the first line setting for cisplatin ineligible patients and in second line for those who have failed platin-based chemotherapy. Immunotherapy has indelibly altered the treatment paradigm in bladder and urothelial cancer. This month's issue of the Clinical Trials Corner of the Bladder Cancer Journal is devoted towards first line phase III randomized trials evaluating the combination of chemotherapy and immunotherapy versus either one alone. 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 Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti−PD-L1 Antibody) as Monotherapy and in Combination with Platinum-Based Chemotherapy in Patients with Untreated Locally Advanced or Metastatic Urothelial Carcinoma (IMvigor130)

Clinicaltrials.gov identifier: NCT02807636

Sponsor: Hoffmann-La Roche

Enrollment: 1200

Rationale: With the approvals of checkpoint inhibitors for urothelial cancer it has become of interest to assess the PD-L1 checkpoint inhibitor, atezolizumab, versus the combination of platin-based chemotherapy and a checkpoint inhibitor versus chemotherapy alone in the front line setting in both cisplatin eligible and ineligible patients.

Study Design: This is a Phase III, 3-armed randomized clinical trial that includes both cisplatin eligible and ineligible patients with locally advanced or metastatic urothelial cancer and ECOG performance status < 2. The trial compares in a 1:1:1 randomization single agent atezolizumab alone to platinum-based combination chemotherapy with gemcitabine and cisplatin or carboplatin plus atezolizumab versus chemotherapy alone with gemcitabine and cisplatin or carboplatin and placebo.

Co-primary endpoints: PFS, OS and safety

Comments: This trial follows on the heels of the successful Phase II IMvigor 210 trial with atezolizumab in the first line setting in cisplatin ineligible patients (cohort 1) and IMvigor 210 (cohort 2) in patients who had failed

ISSN 2352-3727/18/€27.50/$35.00

prior platinum based chemotherapy (1-3). IMvigor 211, the phase III study in second line compared to chemotherapy did not meet its primary endpoint of an improvement in overall survival, in part due to the design of the study which relied heavily on PD-L1 status (4).

Study Start Date: June 30, 2016

Estimated Study Completion Date: June 30, 2020

Study Title: A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab with or without Platinum-Based Combination Chemotherapy Versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma (KEYNOTE 361)

Clinicaltrials.gov identifier: NCT02853305

Sponsor: Merck Sharp & Dohme Corp.

Enrollment: 990

Rationale: With the approvals of checkpoint inhibitors for urothelial cancer it has become of interest to assess the PD-1 checkpoint inhibitor, pembrolizumab, versus the combination of platin-based chemotherapy and a checkpoint inhibitor versus chemotherapy alone in the front line setting in both cisplatin eligible and ineligible patients. The primary hypotheses are that pembrolizumab plus chemotherapy is superior to chemotherapy alone with respect to Progression-free Survival (PFS) and Overall Survival (OS) in participants with programmed cell death ligand 1 (PD-L1) positive tumors (Combined Positive Score [CPS] ≥10%) and in all participants (includes those participants with PD-L1 positive tumors and those with PD-L1 negative tumors [CPS <10%]).

Study Design: Similar to the above trial, this is a Phase III, 3-armed randomized clinical trial that includes both cisplatin eligible and ineligible patients with first line unresectable or metastatic stage IV urothelial cancer. The trial compares in a 1:1:1 randomization single agent. Tumor PD-L1 status, with Immunohistochemical (IHC) assay confirmed by a reference laboratory, must be known prior to randomization.

Co-primary endpoints: PFS and OS

Comments: Pembrolizumab has approval in the first-line setting in patients with cisplatin-ineligible advanced/metastatic urothelial carcinoma based on the Phase 2 KEYNOTE 052 trial (5,6). In this study, durable responses were seen with objective responses in 106/370 (29%) patients, including complete responses in 25 (7%). The median duration of response was not reached after a median follow-up of 8 months. In the Phase 3 KEYNOTE-045 study, in the second-line setting, for patients with platinum-resistant/refractory disease, survival was superior to investigator's choice of chemotherapy at a median follow-up of 22.5 months (7).

Study Start Date: September 15, 2016

Estimated Study Completion Date: May 18, 2020

Study Title: A Phase III, Randomized, Open-Label, Controlled, Multi-Center, Global Study of First-Line MEDI4736 (Durvalumab) Monotherapy and MEDI4736 (Durvalumab) in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer

Clinicaltrials.gov identifier: NCT02516241

Sponsor: AstraZeneca

Enrollment: 1005

Rationale: Durvalumab is a fully human monoclonal antibody that blocks PDL-1 binding to its receptors PD-1 and CD80, resulting in enhanced T-cell responses against cancer cells. This is a randomized, open-label, controlled, multi-center, global Phase III study to determine the efficacy and safety of durvalumab (MEDI4736)

monotherapy and durvalumab in combination with tremelimumab, a CTLA-4 inhibitor versus gemcitabine and cisplatin or carboplatin as first-line chemotherapy in treatment-naïve patients with histologically or cytologically documented, unresectable, Stage IV transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder and urethra). As in the two prior studies, and to allow sufficient flexibility for Investigators and patients to select the agents that reflect their normal clinical practice and national guidelines, both cisplatin and carboplatin are permitted.

Study Design: This is a Phase III, 3-armed randomized clinical trial that includes both cisplatin eligible and ineligible patients with first line metastatic urothelial cancer. The trial compares in a 1:1:1 randomization of single agent durvalumab to the combination of durvalumab and tremilumumab to platinum-based chemotherapy alone with gemcitabine in combination with either cisplatin or carboplatin. Patients will be treated with durvalumab or durvalumab with tremelimumab or treated with chemotherapy until progressive disease is confirmed, unacceptable toxicity occurs, withdrawal of consent, or another discontinuation criterion is met. Patients will be followed for up to 2 years.

Co-primary endpoints: OS of the combination of durvalumab with tremelimumab compared to standard of care chemotherapy and to assess the efficacy of durvalumab monotherapy versus standard of care chemotherapy in terms of OS in patients with unresectable Stage IV PD-L1- High urothelial cancer.

Comments: An ongoing phase 1/2 open-label study of 191 adult patients with histologically or cytologically confirmed locally advanced/metastatic urothelial cancer whose disease had progressed on, were ineligible for, or refused prior chemotherapy was used to establish the clinical benefit of durvalumab as second-line therapy for locally advanced or metastatic urothelial carcinoma, resulting in its US FDA approval. As of October 24, 2016 (90-day update), the median follow-up was 5.78 months (range, 0.4-25.9 months). All patients had stage 4 disease, and 190 (99.5%) had prior anticancer therapy (182 [95.3%] post platinum). The ORR was 17.8% (34 of 191; 95% CI, 12.7%-24.0%), including 7 complete responses. Responses were seen early with a median time to response of 1.41 months, durable (median duration of response not reached), and observed irrespective of PD-L1 expression. Durvalumab, given every 2 weeks, demonstrates favorable clinical activity and an encouraging and manageable safety profile (7). The combination of durvalumab with tremelimumab have been evaluated in other tumor types.

Study Start Date: November 2, 2015

Estimated Study Completion Date: September 23, 2019

Study Title: A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab, or with Standard of Care Chemotherapy, Versus Standard of Care Chemotherapy in Participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer (Checkmate-901)

Clinicaltrials.gov identifier: NCT03036098

Sponsor: Bristol-Myers Squibb + Ono Pharmaceutical Co. Ltd

Enrollment: 897

Rationale: The purpose of this study is to determine whether immunotherapy with a PD-1 inhibitor, Nivolumab, in combination with ipilimumab, a CTLA-4 inhibitor, or in combination with standard of care chemotherapy is more effective than standard of care chemotherapy alone in treating patients with previously untreated inoperable or metastatic urothelial cancer.

Study Design: This is a Phase III, 4-armed randomized parallel assessment clinical trial with experimental and comparator arms that includes both cisplatin eligible and ineligible patients with first line unresectable or metastatic urothelial cancer. The trial compares the combination of nivolumab and ipilumimab to nivolumab plus cisplatin and gemcitabine followed by nivolumab only versus gemcitabine and cisplatin or gemcitabine and carboplatin.

Co-primary endpoints: PFS and OS

Comments: Nivolumab has been evaluated in metastatic urothelial carcinoma after platinum therapy in the CheckMate 275 trial. This was a multicenter, single-arm, phase 2 trial in which 270 patients received nivolumab and 265 were evaluated for activity. Median follow-up for overall survival was 7 months. Confirmed objective response was achieved in 52 (19.6%) of 265 patients. Confirmed objective response was observed in 23 (28.4%) of 81 patients with PD-L1 expression > 5%, 29 (23.8%) of 122 patients with PD-L1 expression > 1%, and 23 (16.1%) of 143 patients with PD-L1 expression <1% PD-L1 expression. In this study, nivolumab monotherapy provided meaningful clinical benefit, irrespective of PD-L1 expression, and was associated with an acceptable safety profile in previously treated patients with metastatic or surgically unresectable urothelial carcinoma. The CTLA-4 inhibitor ipilimumab has clinical activity in melanoma as a single agent or in combination with the nivolumab, establishing the paradigm for exploring the combination in urothelial carcinoma (9). Additionally, some evidence has suggested that ipilimumab has biologic activity in urothelial cancer (10).

Study Start Date: March 24, 2017.

Estimated Study Completion Date: December 23, 2022.

REFERENCES

[1] Balar AV et al. Lancet 2017;389(10064):67-76.
[2] Hoffman-Censits JH et al. J Clin Oncol 2016;34(suppl 2S; abstr 355).
[3] Rosenberg JE et al. Lancet 2016;387(10031):1909-20
[4] Powles T et al. EAS Congress 2017: abstr.
[5] Balar A et al. Lancet Oncol 2017 Sep 26, S1470-2045(17)30616-2.
[6] O' Donnell PH et al. ASCO 2017, abstr 4502.
[7] Powles T et al. JAMA Oncol 2017;3(9); Epub 2017 Sep 14.
[8] Sharma P et al. Lancet Oncol 2017;18(3):312-322.
[9] Wolchok JD et al. N Engl J Med 2017 Oct 5;377(14):1345-1356.
[10] Callahan MK et al. J Clin Oncol 2017;35(suppl 6S; abstract 384).