Bladder Cancer 4 (2018) 447–449
DOI 10.3233/BLC-189040
IOS Press

Clinical Trials Corner

Dear Readers,

The European Society for Medical Oncology just completed its annual meeting in Munich this month and we would like to highlight several trials presented during this meeting. In the previous issue, we previously discussed the antibody-drug conjugate enfortumab vedotin and the pan FGFR inhibitor INCB054828. 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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Received 24 October 2018
Accepted 25 October 2018

Study Title: A Phase I/II Study of IMMU-132 (hRS7-SN38 Antibody Drug Conjugate) in Patients With Epithelial Cancers

Clinicaltrials.gov identifier: NCT01631552

Sponsor: Immunomedics, Inc.

Enrollment: 250

Rationale: Patients with advanced epithelial cancers, including metastatic urothelial cancer (mUC), have a poor prognosis and this phase I/II trial looks at the safety and efficacy of a novel antibody-drug conjugate, IMMU-132 (hRS7-SN38), also known as Sacituzumab Govitecan. The antibody, hRS7, is a humanized anti-Trop-2 monoclonal antibody attached to SN38 which is the active metabolite of irinotecan (CPT-11). The drug targets Trop-2 which is overexpressed in aggressive epithelial cancers including up to 83% of urothelial tumors and the conjugate binds to Trop-2 and delivers the active metabolite of a topoisomerase I inhibitor.

Study Design: The Phase I/II trial included an expansion cohort of 41 patients with metastatic urothelial cancer that progressed after one or more prior systemic therapies. Patients were treated until progression or unacceptable toxicity.

Endpoints: The primary endpoint was safety and antitumor efficacy was the secondary endpoint.

Results: This was a heavily pre-treated cohort as patients received a median of 3 prior therapies including prior platinum chemotherapy in up to 93% of patients. Furthermore, 34% of patients had received a checkpoint inhibitor (CPI). Overall, the treatment was highly tolerable with grade 3-4 neutropenia being the most commonly seen adverse event (AE) in 39%. The overall response rate (ORR) was 34% with 2 complete responses. The response rate was 29% in patients who had received a previous checkpoint inhibitor. The median overall survival was 16.1 months.

ISSN 2352-3727/18/€27.50/$35.00

Ongoing Trials: TROPHY-U-01 (NCT03547973) is a single-arm, open-label, global phase 2 trial evaluating the antitumor activity and safety of Sacituzumab Govitecan (IMMU-132) in 140 patients with advanced urothelial cancer after progression on platinum-based chemotherapy or anti-PD-1/PD-L1 checkpoint inhibitor therapy. The primary cohort (progression after platinum chemotherapy and CPI) will enroll 100 pts in a Simon 2-stage design with >90% power accounting for dropouts to exclude the null hypothesis or ORR <12%. A second cohort (40 pts) will comprise cisplatin-ineligible pts who received prior CPI. The primary objective is ORR assessed by central review per RECIST 1.1. Secondary objectives include response duration, PFS, OS, and safety/tolerability. Enrollment began in August 2018.

Comments: Similar to data presented at ASCO 2018 for another antibody-drug conjugate, enfortumab vedotin, this trial demonstrates that IMMU-132 (hRS7-SN38), Sacituzumab Govitecan, also has good activity in patients who have not only failed prior platinum chemotherapy but also in patients who have failed prior checkpoint inhibitor therapy. The ongoing trial will further establish its activity.

Study Title: Nivolumab Alone or in Combination With Ipilimumab in Patients With Platinum-Pretreated Metastatic Urothelial Carcinoma, Including the Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Expansion From CheckMate 032

Clinicaltrials.gov identifier: NCT01928394

Sponsor: Bristol-Myers Squibb

Enrollment: This was a multi-cohort randomized non-comparative phase II study in which urothelial carcinoma was one of 6 tumor types evaluated. In the first part of the study patients were randomized between nivolumab 3 mg/kg (n=78) and the combination of nivolumab 3 mg/kg and ipilimimab 1 mg/kg IV Q3W for 4 cycles followed by nivolumab (n=104). The third part of the study was presented at the ESMO meeting by Dr. Jonathan Rosenberg. Patients were allocated to receive nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV Q3W (NIVO1IPI3) for 4 cycles followed by nivolumab (n = 92).

Rationale: Immunotherapy has become the recommended treatment for patients with previously treated metastatic urothelial cancer. Preclinical and clinical data indicate that the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) can improve antitumor activity in advanced melanoma, NSCLC, and mRCC.

Study Design: Open-label, multicenter, phase 1/2 study

Endpoints: Primary endpoints were investigator-assessed confirmed ORR by RECIST v1.1 and duration of response. Secondary endpoints included PFS, OS and safety. Exploratory endpoint was ORR by PD-L1 expression status.

Results: 35 patients responded for a 38% RR with 6 CR and 29 PR. The overall response rate by the investigator in patients with baseline PD-L1 ≥1% status was 58.1% and 54.8% by independent review. PFS assessed by the investigator was 4.9 (2.7–6.6) months. Median OS was 15.3 (10.1–27.6) months. ORR was numerically higher in patients with ≥1% tumor PD-L1 treated with NIVO1IPI3 (58%), and efficacy was observed across PD-L1 expression levels in all treatment arms.

Ongoing Trials: These results support the ongoing phase 3 trial of NIVO1IPI3 versus chemotherapy in previously untreated mUC (CheckMate 901; NCT03036098)

Comments: CheckMate 032 is a multicenter, phase 1/2 study and not a randomized trial and one cannot compare across studies. The study reproduces previously presented preliminary results. Selected toxicities were higher but do not preclude treatment. A 38% RR is encouraging. Follow up is not mature but long-term outcomes (tail on curve) may be important. PD-L1 positive tumors may benefit the most (58%). It is still uncertain whether PD-L1 is a good predictive biomarker, as it has been problematic. More detailed interrogation of tumors beyond just PD-L1 would be ideal. A phase III trial is needed and ongoing (CheckMate 901; NCT03036098)

Study Title: Keynote 57: 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

Protocol Number: NCT02625961

Sponsor: Merck Sharp & Dohme Corp.

Enrollment: 260 patients

Rationale: High-risk (HR) non-muscle invasive bladder cancer (NMIBC) is defined as carcinoma in situ (CIS), T1 tumor and/or high grade Ta tumor. The CR rate from TURBT and intravesical BCG is approximately 70%, however, a significant percentage of patients with high risk disease experience a recurrence and progression risk is 30-40% over a 10-year period. This is a single arm open-label Phase II study of pembrolizumab (MK-3475) 200mg IV every 3 weeks in patients unresponsive to BCG who refuse or are ineligible for cystectomy. Due to some of the remarkable long lasting responses and rapid approval of PD-1/PD-L1 inhibitors in metastatic urothelial cancer, several trials are ongoing to evaluate the impact of these drugs in patients with BCG unresponsive high risk NMIBC. In the absence of novel therapy, these patients ultimately are treated with radical cystectomy which is a potentially morbid operation. Therefore, this trial is the first of many that are ongoing to look at the potential impact of checkpoint inhibitors in localized high-risk urothelial cancer.

Study Design: Eligible patients had high-risk NMIBC unresponsive to BCG who refuse or are ineligible for cystectomy. Patients with papillary disease were fully resected prior to therapy. There were two cohorts: A) carcinoma in situ (CIS) with or without high grade papillary disease and B) high grade papillary disease without CIS. Subjects received pembrolizumab every 3 weeks and had standard cystoscopy, cytology, and if indicated, biopsy every 12 weeks for 2 years followed by every 24 weeks for 2 years.

Primary Endpoints: In Cohort A, complete response (defined as the absence of high risk NMIBC) up to 3 years is the primary endpoint. In Cohort B, disease-free survival up to 3 years is the primary endpoint.

Secondary Endpoints: The duration of response in Cohort A (absence of any disease either high-risk or low-risk NMIBC) along with overall safety/tolerability.

Results: At ESMO 2018, Dr. De Wit and colleagues presented a 38.8% complete response (CR) rate in 40/103 patients in Cohort A (CIS containing BCG unresponsive high risk NMIBC) at 3 months among 103 patients. The median time to CR was 12.4 weeks and 80% had a CR duration of greater than or equal to 6 months. However, 25% of patients experienced recurrent NMIBC after CR. No patient developed muscle-invasive or metastatic bladder cancer.

Future Trials: A Phase III randomized study to evaluate efficacy and safety of pembrolizumab in combination with BCG in patients with HR NMIBC that is persistent following BCG induction will be initiated (Keynote -676).

Comments: In this trial there was a very low risk of "missing the window of opportunity" for radical cystectomy as no patients progressed to muscle invasive disease and the complications of radical cystectomy were not increased. Although this preliminary data is exciting and establishes safety and efficacy, it may fall short of the bar set by expert consensus suggesting that novel therapies with activity in CIS BCG unresponsive NMIBC should result in an initial 40-50% CR rate at 6 months with a more durable CR of 30% at 12 months. Furthermore, this finding raises several important questions in patients who achieve a CR such as how long should therapy be continued and can the cost be justified especially if treatment continues beyond 12 months? This interim analysis is of interest, but 12-month data are needed.

CONFLICTS OF INTEREST

Conflicts of interest can be found under Board Disclosures on the website: https://www.bladdercancerjournal.com.