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Clinical Trials Corner

Dear Readers,

This month's issue of the Clinical Trials Corner of the Bladder Cancer journal is devoted towards recently presented bladder cancer trials from this past ASCO 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 and/or cnsternberg@corasternberg.com.

Sincerely,

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Study Title: A Study of Atezolizumab in Patients With Locally Advanced or Metastatic Urothelial Bladder Cancer [IMvigor210]

Clinicaltrials.gov identifier: NCT02108652

Sponsor: Hoffmann-La Roche

Enrollment: 439

Study Design: Phase II, single arm multi-center trial of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer. Two cohorts were planned: Cohort 1 consisted of 119 treatment naïve patients who were cisplatin ineligible and Cohort 2 consisted of patients who had progressed during or following platinum therapy (see below). The results of cohort 1 were presented at the ASCO meeting for the first time (Balar AV et al).

The primary endpoint was objective response rate (ORR) and the secondary endpoints were duration of response, progression-free survival (PFS), overall survival (OS), and the incidence of adverse events.

Rationale: PD-L1 checkpoint blockade has recently received FDA approval for metastatic urothelial cancer refractory to standard chemotherapy and the results of Cohort 1 are exciting because this is the use of such therapy as upfront therapy for locally advanced or metastatic urothelial bladder cancer in patients who are ineligible for cisplatin-based chemotherapy.

Results: Most patients were ineligible due to renal impairment. Median follow-up for patients was 14.4 months with ORR of 24%, and responses we seen in all PDL-1 IC subgroups. Responders included patients with poor baseline prognostic factors. Median overall survival was 14.8 months. Severe adverse events were noted in 10–15% of patients including hypothyroidism, liver function abnormalities, rash, and diarrhea, with a low rate of Garde 3-4 side effects.

Comments: This is the first study to present atezolizumab as upfront therapy for urothelial cancer. The results are encouraging for the use of checkpoint blockade inhibitors as first line therapy, especially in patients unfit for cisplatin.

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Study Title: PDL-1 expression, the Cancer Genome Atlas (TCGA) Subtype and Mutational Load are independent predictors of response to atezolizumab in Metastatic Urothelial Carcinoma (mUC, IMvigor 210)

Clinicaltrials.gov identifier: NCT02108652

Sponsor: Hoffmann-La Roche

Enrollment: 310

Study Design: Cohort 2 was a phase II study of patients who had received > 1 platinum containing regimens. The results have been published (Rosenberg JE et al Lancet. 2016 May 7;387(10031):1909-20) leading to FDA approval of atezolizumab in metastatic urothelial cancer refractory to standard chemotherapy

Rationale: Immunologic correlates corresponding to the TCGA Subgroups were evaluated and updated at ASCO (Rosenberg JE et al).

Results: It was shown that PDL-1 status, TCGA subgroup (particularly the luminal subgroup) and mutational load were independently associated with response to atezolizumab. The luminal subgroup was associated with a more inflamed environment than the basal subtype. The luminal subtype was also found to have high Teff cells and low stromal gene expression. Assessment of these characteristics may define drivers of immune responses. Further work on the biology of immune response to checkpoint inhibits is clearly a priority.

Study Title: A Phase 1/2 Study to Evaluate MEDI4736

Clinicaltrials.gov identifier: NCT01693562

Sponsor: MedImmune LLC

Enrollment: 1014

Study Design: Phase I/II multicenter first in human study with standard 3+3 dose escalation in advanced solid tumors. The primary endpoint included safety and tolerability. The secondary endpoints include objective response rate, progression-free survival, overall survival, and PD-L1 expression on both tumor cells and tumor infiltrating immune cells.

Rationale: This is a first in human study of Medimmune's PD-L1 inhibitor durvalumab (MEDI4736) focused on dose expansion in a urothelial bladder cancer cohort (Massard C et al).

Results: 61 bladder cancer patients were enrolled. Drug-related adverse events occurred in 64% and only 3 patients had ≥ grade 3 adverse events**.** Objective response rate (ORR) was greater in patients with at least 25% or greater PD-L1 expression in either tumor cells or tumor infiltrating immune cells versus less than 25% expression in both (46% vs. 0%). ORR was 46% in the PDL-1 subgroup vs 0% in the PDL-1 negative group. For the whole population, the RR was 31%. Median duration of follow-up was 26 weeks.

Comments: Durvalumab had a reasonable safety profile and ORR was greater in the PD-L1+ group versus the PD-L1 negative group. Of note, each trial has used different definitions for PD-1/PD-L1 expression. Expression does appear to correlate with response with some tests but absolute numbers are variable across different agents and different studies. Phase III trials are ongoing with this agent in bladder cancer.

Study Title: Limited versus extended pelvic lymphadenectomy in patients with bladder cancer undergoing radical cystectomy: Survival results from a prospective randomized trial (LEA AUO AB 25/02).

Clinicaltrials.gov identifier: NCT01215071

Sponsor: Association of Urogenital Oncology (AUO)

Enrollment: 400 (to detect an improvement in 5-year recurrence-free survival from 50% to 65% with 90% power)

Study Design: This is the first randomized surgical study in bladder cancer randomizing patients with pT2 or greater disease and without neoadjuvant chemotherapy to either a limited lymph node dissection or an extended lymph node dissection. The limited node dissection consisted of external iliac, internal iliac, and obturator lymph nodes while the extended lymph node dissection included these areas in addition to the deep obturator, presacral, interaortocaval, paracaval, and periaortic lymph nodes up to the inferior mesenteric artery. Patients with organ-confined disease and negative nodes were observed whereas patients with non-organ-confined disease and/or positive lymph nodes were offered adjuvant chemotherapy. The primary endpoint was 5-year recurrence-free survival (RFS). Secondary endpoints include complication rate, influence of adjuvant chemotherapy, disease-specific survival, overall survival, and local recurrences and distant metastases.

Rationale: The proximal extent of a lymph node dissection (LND) at the time of radical cystectomy has always been an issue of controversy. Some reports suggest that a dissection to the common iliac bifurcation or to the ureter crossing over the iliac vessels is adequate whereas others suggest that more proximal dissection to the inferior mesenteric artery may affect survival. Furthermore, removal of the presacral lymph nodes and the deep obturator lymph nodes are not routinely done by all surgeons.

Results: Ultimately 437 patients were randomized but 64 patients dropped out due to inclusion/exclusion violations leaving 190 patients in the limited LND group and 183 in the extended LND group by an intention to treat analysis. Median follow-up was about 33 months. The lymph node positive rate was 27.4% for the limited LND group and 20.2% for the extended LND group. Overall, the positive node rate was 23.9% among patients and approximately 14% of patients received adjuvant chemotherapy. The median lymph node removal was 19 for limited LND and 31 for extended LND, $p < 0.01$. The 5-year RFS was 61.5% for the limited LND and 67% for the extended LND, $p = 0.34$. Secondary endpoints were also not statistically significant including 5-year disease-specific survival, 5-year OS, and complication rate. On post-hoc analysis of organ-confined tumors (pT2), there was a survival benefit in 5-year RFS (62.5% vs. 85%, $p = 0.01$) and 5-year OS (59.1% vs. 79.8%, $p = 0.04$) favoring the extended LND group. In 89 patients with positive lymph nodes, adjuvant chemotherapy improved median RFS (35.9 months vs. 8.8 months, $p = 0.0002$).

Comments: Although there was a trend towards improved survival in the extended LND group, there was not a statistically significant difference. There are two factors likely for this as 1) the limited LND was still extensive in these patients as evidenced by a median lymph node removal count of 19 and 2) the magnitude of benefit was probably overestimated from an extended LND and the rate of recurrence in the limited LND was also overestimated. The benefit was seen in the organ-confined group on post-hoc analysis, however, no patients with neoadjuvant chemotherapy were included and perhaps this difference would have disappeared with the addition of neoadjuvant chemotherapy? However, adjuvant chemotherapy appeared have a statistically significant benefit even though its use was limited. It will be interesting to see the conclusions reached by the ongoing SWOG 1011 trial but this study failed to show a benefit based on its design.