

Clinical Trials Corner Issue 8(2)

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Dear Readers,

In this issue, we highlight a recently published clinical trial evaluating a fixed dose of durvalumab and a biomarker analysis of the landmark KEYNOTE clinical trials. 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: An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab in Advanced Solid Malignancies (STRONG Study).

Clinicaltrials.gov identifier: NCT03084471

Sponsor: AstraZeneca

Enrollment: 867

Rationale: Checkpoint inhibition has demonstrable activity in patients with locally advanced or metastatic urothelial carcinoma refractory to platinum chemotherapy. Durvalumab has previously demonstrated safety and efficacy in patients at 10 mg/kg dosed every 2 weeks. This trial evaluates a fixed dose of 1500 mg given every 4 weeks, a more convenient dosing schedule. Furthermore, it does so in a “real-world” clinical setting as patients could have non-urothelial histology and could have progressed or not responded to platinum or non-platinum chemotherapy.

Study Design: 867 patients with urothelial or non-urothelial urinary tract carcinoma (UTC) who progressed during or after one platinum or non-platinum chemotherapy regimen were treated with fixed dose durvalumab (1500 mg every four weeks) to progressive disease. Thirteen percent of patients had an ECOG performance status (PS) of 2, but most had an ECOG PS of 0-1.

Endpoints: The primary end-point was the incidence of adverse events of special interest (AESIs), including immune-mediated AEs (imAEs). Secondary end-points included overall survival (OS), objective response rate (ORR), and disease control rate (at six and 12 months) (DCR).

Results: Median treatment duration was 12.1 weeks and 31% were alive and being followed for survival. The median follow-up for patients was 13.8 months. AEs of any grade occurred in 787 patients (91%) with the most common being asthenia (27%), constipation (20%), and anemia (21%). AESIs of any grade occurred in 51% of patients (8% grade \geq 3). The incidence of imAEs was 11% (2% grade \geq 3). The median OS was 7.0 months (95% confidence interval [CI]: 6.4–8.2) and ORR was 18% (95% CI: 14.8–20.6), with complete responses in 5% of patients and a disease control rate at six months of 19% (95% CI: 16.1–22.1).

Comments: Durvalumab at a fixed dose was well tolerated. Of note, PD-L1 expression was available in 577 patients and tumor expression of PD-L1 was high in 239 (41%). Despite this finding, median OS was only 7 months in this fixed dose study compared to a previous study of durvalumab (study 1108) showing a median OS of 11 months. This is felt to be due to the “all-comers” status of this current trial with 13% of patients having ECOG PS of 2 and patients with nonurothelial histology. Although Durvalumab had attained Accelerated Approval by the FDA in urothelial cancer, failure of the DANUBE study in the first line setting, caused the company to voluntarily withdraw durvalumab from the US market. The data is nonetheless encouraging in the STRONG study that revealed durable clinical activity in previously chemotherapy-treated patients with advanced urothelial or nonurothelial urinary tract carcinoma.

Reference: Sonpavde GP, Sternberg CN, Loriot Y, Marabelle A, Lee JL, Fléchon A, Roubaud G, Pouessel D, Zagonel V, Calabro F, Banna GL, Shin SJ, Vera-Badillo FE, Powles T, Hellmis E, Miranda PAP, Lima AR, Emeribe U, Oh SM, Hotte SJ.

Primary results of STRONG: An open-label, multicenter, phase 3b study of fixed-dose durvalumab monotherapy in previously treated patients with urinary tract carcinoma.
.Eur J Cancer. 2022 Mar;163:55-65. doi: 10.1016/j.ejca.2021.12.012. Epub 2022 Jan 15. PMID: 35042068

Study Title: Putative Biomarkers of Clinical Benefit With Pembrolizumab in Advanced Urothelial Cancer: Results From the KEYNOTE-045 and KEYNOTE-052 Landmark Trials

Clinicaltrials.gov identifier: NCT02335424 and NCT02256436

Sponsor: N/A (Merck sponsored KEYNOTE studies but not this current analysis of biomarkers)

Rationale: This publication is an exploratory analysis performed retrospectively on the cohorts for both of these clinical trials to determine any association of putative biomarkers (PD-L1, tumor mutational burden (TMB), T-cell inflamed gene expression profile (Tcell_{inf}GEP), and stromal signature with outcomes of patients treated with pembrolizumab monotherapy in locally advanced or metastatic urothelial cancer.

Study Design: Patients with biomarker data were identified from each trial and the majority of patients had PD-L1 data but only 50-55% of patients had stromal signature data. The association of these biomarkers with clinical outcomes such as overall survival (OS) and overall response rate (ORR) was analyzed. Of note, KEYNOTE-045 included patients with urothelial cancer and progressive disease after platinum-based chemotherapy while KEYNOTE-052 included patients with unresectable or metastatic urothelial cancer who were ineligible for systemic chemotherapy. The KEYNOTE-045 patients received pembrolizumab salvage therapy while KEYNOTE-052 patients received first-line pembrolizumab therapy.

Endpoints: The primary endpoint was to test if the biomarkers (tested as continuous variables) were associated with clinical outcomes (OS, ORR, progression-free survival (PFS)).

Results: In KEYNOTE-052, PD-L1, TMB, Tcell_{inf}GEP were associated with improved clinical outcomes while higher stromal signature was associated with worse outcomes. In KEYNOTE-045, TMB and Tcell_{inf}GEP were

significantly associated with improved clinical outcomes. Of note, PD-L1 was not significantly associated with improved outcomes. Furthermore, stromal signature was not associated with worse outcomes.

Comments: It appears increasingly evident that biomarkers other than PD-L1 may be important to understanding potential outcomes with immunotherapy. PDL-1 was not important in the second line setting in the randomized KEYNOTE-045 trial, but maintained importance in untreated patients in KEYNOTE-052 and possibly also in other larger randomized trials, where the FDA and EMA stopped accrual in first line setting of patients who were PDL-1 negative. There is clearly much more to learn from evaluating these and other biomarkers.

Reference: Bellmunt J, de Wit R, Fradet Y, Climent MA, Petrylak DP, Lee JL, Fong L, Necchi A, Sternberg CN, O'Donnell PH, Powles T, Plimack ER, Bajorin DF, Balar AV, Castellano D, Choueiri TK, Culine S, Gerritsen W, Gurney H, Quinn DI, Vuky J, Vogelzang NJ, Cristescu R, Lunceford J, Saadatpour A, Loboda A, Ma J, Rajasagi M, Godwin JL, Homet Moreno B, Grivas P. Putative Biomarkers of Clinical Benefit With Pembrolizumab in Advanced Urothelial Cancer: Results From the KEYNOTE-045 and KEYNOTE-052 Landmark Trials. *Clin Cancer Res.* 2022 Mar 3;clincanres.3089.2021. doi: 10.1158/1078-0432.CCR-21-3089. Online ahead of print. PMID: 35247908

DISCLOSURES

Cora N. Sternberg

Consultant: Pfizer, Merck Ga, MSD, AstraZeneca, Astellas Pharma, Sanofi-Genzyme, Roche/Genentech, Immunomedics now Gilead, Clovis Oncology, Bayer, Bristol Myers Squibb, Impact Therapeutics, Foundation Medicine, UroToday, Medscape

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