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Clinical Trials Corner

Dear Readers,

The American Society of Clinical Oncology (ASCO) just completed its annual meeting in Chicago this year and early clinical trial data were presented with new mechanisms of action. In addition, we are presenting ongoing trials other than immunotherapy trials against metastatic disease. Some of the trials have data and other advanced urothelial cancer trials are ongoing. We will also highlight the results for the English POUT trial in upper tract tumors, presented at the ASCO GU, EAU, and AUA annual meetings. 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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Study Title: A Study of Escalating Doses of ASG-22CE Given as Monotherapy in Subjects With Metastatic Urothelial Cancer and Other Malignant Solid Tumors That Express Nectin-4

Clinicaltrials.gov identifier: NCT02091999

Sponsor: Astellas Pharma Global Development, Inc.

Enrollment: 215

Rationale: Patients with metastatic urothelial cancer (mUC) have a poor prognosis despite the approval of several immunotherapy agents. Therefore, this trial evaluates the use of a novel antibody-drug conjugate, ASG-22CE also known as enfortumab vedotin, in mUC patients. The drug targets Nectin-4 which is overexpressed in urothelial tumors and the conjugate binds to Nectin-4 and delivers a microtubule disrupting toxin.

Study Design: This is a Phase I, single arm clinical trial of patients with mUC treated with 1 or more prior chemotherapy regimens or who were cisplatin-ineligible. In this analysis, patients with mUC treated at the recommended phase 2 dose (RP2D) were analyzed.

Primary endpoints: The primary endpoint was tolerability and antitumor efficacy was the secondary endpoint.

Results: Data as of January 2018 was presented at this year's ASCO meeting (Abstract #4504), 155 mUC patients accrued of whom 112 received ASG-22CE at the RP2D. This was a heavily pre-treated cohort with aggressive disease evidenced by the following: 81% of patients received prior platinum chemotherapy, 60% received two or more prior therapies for metastatic disease, and 29% of patients had liver metastases. Furthermore, 84 patients (75%) had received a checkpoint inhibitor. Overall, the treatment was highly tolerable with grade ≤2 fatigue being the most commonly seen adverse event (AE) in 50%. Four patients however did experience a fatal treatment-related AE including respiratory failure, urinary tract obstruction, diabetic

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ketoacidosis, and multi-organ failure. The overall response rate (ORR) was 33% with 3 complete responses and 34 partial responses. Response rates were 32% in patients previously treated with checkpoint inhibitor vs. 37% in checkpoint inhibitor-naïve patients. The median overall survival was 12.5 months.

Comments: This trial presents a unique and novel therapy for mUC patients who have not only failed prior platinum chemotherapy but also has activity in patients who have failed prior checkpoint inhibitor therapy and even have liver metastases. The data are still not yet mature but the preliminary data presented at ASCO 2018 are intriguing.

Study Title: A Phase 2, Open-Label, Single-Agent, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Metastatic or Surgically Unresectable Urothelial Carcinoma Harboring FGF/FGFR Alterations

Protocol Number: NCT02872714

Sponsor: Incyte

Rationale: This is an open-label monotherapy study of INCB054828, a selective FGFR 1, 2, and 3 inhibitor, in subjects with metastatic or surgically unresectable urothelial carcinoma harboring FGF/FGFR alterations. Subjects will receive INCB054828 at a once-daily (QD) starting dose of 13.5 mg on a 2-weeks-on-therapy and 1-week-off-therapy schedule.

Study Design: Subjects must have a known FGF/FGFR alteration and have either: (a) failed at least 1 previous treatment for their metastatic or surgically unresectable urothelial carcinoma (ie, chemotherapy, immunotherapy), or (b) have not received chemotherapy for metastatic or surgically unresectable urothelial carcinoma due to poor ECOG performance or have insufficient renal function (ie, creatinine clearance < 60 mL/min or local guidelines).

Primary endpoints: Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results (Cohort A). Response will be based on review of scans by a centralized radiological review committee.

Secondary Endpoints: Objective response rate in all subjects with FGFR3 mutations or fusions and all other FGF/FGFR alterations (Cohorts A and B combined). Objective response rate in subjects with all other FGF/FGFR alterations (Cohort B). Progression-free survival (both cohorts). Duration of response (both cohorts). Overall survival (both cohorts). Safety.

Enrollment: Approximately 140 patients

Study Title: A Phase 2, Two-arm Multicenter, Open-Label Study to Determine the Efficacy and the Safety of Two Different Dose Regimens of a pan-FGFR Tyrosine Kinase Inhibitor JNJ-42756493 in Subjects with Metastatic or Surgically Unresectable Urothelial Cancer with FGFR Genomic Alterations

Protocol Number: NCT02365597

Sponsor: Janssen Research & Development, LLC

Rationale: JNJ-42756493 (Erdafitinib) is a selective and potent orally administered pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor with activity in patients with solid tumors with alterations in the FGFR pathway including urothelial carcinoma, indicating the potential to be a new therapeutic option for these patients. Recent advances in genomic profiling of urothelial carcinomas have identified potential therapeutic molecular targets in 69% of tumors (The Cancer Genome Atlas Project Nature 2014). Of the molecular alterations identified, FGFR signaling in particular is altered in a high proportion of bladder tumors in both muscle invasive (15–20%) and non-invasive tumors (70–80%).

Results: The Phase 2 study BLC2001 presented at the 2018 ASCO Genitourinary Cancers Symposium showed an overall response rate of 42 percent in 59 patients with relapsed/refractory metastatic urothelial cancer whose tumors harbored actionable FGFR mutations (ASCO-GU abstract #411, ASCO abstract #4503)

A Breakthrough Therapy Designation in March 2018 was granted by the US FDA based on data from this multicenter, open-label Phase 2 clinical trial evaluating the efficacy and safety of erdafitinib in the treatment of adult patients with locally advanced or metastatic urothelial cancer, whose tumors have certain fibroblast growth factor receptor (FGFR) genetic alterations.

Study Title: A Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Participants With Advanced Urothelial Cancer and Selected Fibroblast Growth Factor Receptor (FGFR) Gene Aberrations

Protocol Number: NCT03390504

Sponsor: Janssen Research & Development, LLC

Rationale: This trial will evaluate erdafitinib compared with chemotherapy or immunotherapy in patients with advanced urothelial cancer and FGFR gene aberrations. This is evaluating erdafitinib in the first line setting.

Study Design: Participants will be screened based on Fibroblast Growth Factor Receptor Inhibitor Clinical Trial Assay (FGFRi CTA) to determine molecular eligibility and participants who meet molecular eligibility criteria will be enrolled.

Cohort 1: Erdafitinib vs Vinflunine or Docetaxel
Cohort 2: Erdafitinib vs. Pembrolizumab

Primary Endpoint: Overall Survival (OS)

Secondary Endpoints: Time Frame: Approximately up to 3 years ; Progression-free Survival (PFS), Overall Response Rate (ORR), Patient-Reported Health Status, Patient-Global Impression of Severity (PGIS) Score, the Visual Analog Scale (VAS) of the EQ-5D-5L, Utility Scale of the EQ-5D-5L, Duration of Response (DOR), Safety, Oral Clearance (CL/F) of Erdafitinib, AUC of Erdafitinib

Enrollment: 631

Study Title: Study of Rogaratinib (BAY1163877) vs Chemotherapy in Patients With FGFR (Fibroblast Growth Factor Receptor)-Positive Locally Advanced or Metastatic Urothelial Carcinoma (FORT-1)

Protocol Number: NCT03410693

Sponsor: Bayer

Rationale: To compare rogaratinib (BAY1163877) with chemotherapy (docetaxel, paclitaxel or vinflunine) in terms of prolonging the Overall survival (OS) of patients with FGFR positive urothelial carcinoma.

At randomization, patients will have locally advanced or metastatic urothelial carcinoma and have received at least one prior platinum-containing chemotherapy regimen. Only patients with FGFR1 or 3 positive tumors can be randomized into the study. Archival tumor tissue is adequate for testing of FGFR1 and 3 mRNA expressions, which will be determined centrally using an RNA in situ hybridization (RNA-ISH) test. Approximately 42 % of UC patients with locally advanced or metastatic UC are identified as FGFR-positive by the RNA-ISH cut-off applied.

Primary Endpoint: Overall Survival

Secondary Endpoints: Time Frame: Up to 45 months; Progression-free survival (PFS), Objective response rate (ORR,) Disease-control rate (DCR), Duration of response (DOR), safety and tolerability

Enrollment: 400 participants

Comments: The FGFR inhibitor trials are all being conducted in patients with FGFR alterations and locally advanced UC and the preliminary data presented at ASCO in at least one inhibitor is very encouraging. It will be interesting to see how an FGFR inhibitor performs in the first line setting in patients with an alteration when compared to standard chemotherapy or immunotherapy.

Upper tract urothelial cancer (UTUC)

Study Title: Pout: A phase III randomized trial of perioperative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC)

Protocol Number: NCT01993979

Rationale: The role of post nephro-ureterectomy (NU) treatment for UTUC is unclear. POUT (CRUK/11/027) addresses whether adjuvant chemotherapy improves disease free survival (DFS) for pts with histologically confirmed pT2-T4 N0-3 M0 UTUC.

Study Design: Patients with UTUC ≤90 days post NU were randomized (1:1) to 4 cycles of gemcitabine-cisplatin (gemcitabine-carboplatin if GFR 30-49ml/min) or surveillance with subsequent chemotherapy if required. Pts had 6 monthly cross sectional imaging and cystoscopy for the first 2 years, then annually to 5 years. Toxicity was assessed by CTCAE v4.

Primary endpoint: DFS

Results: The results were presented at ASCO GU, J Clin Oncol; abstract 407 in February 2018. Between May 2012 & Sept 2017, 248 pts were recruited (123 surveillance; 125 chemotherapy) at 57 UK centers. In Oct 2017, the independent trial oversight committees recommended POUT close to recruitment as data collected thus far (as of 05/09/2017) met the early stopping rule for efficacy. At the time of interim analysis, median follow-up was 17.6 months (IQR 7.5-33.6). Patients had median age 69 years (range 36-88), 30% pT2, 65% pT3; 91% pN0; Grade ≥3 toxicities were reported in 60% chemotherapy pts & 24% surveillance pts. 47/123 (surveillance) & 29/125 (chemotherapy) DFS events were reported; unadjusted HR = 0.47 (95% CI: 0.29, 0.74) in favor of chemotherapy (log-rank p = 0.0009). Two year DFS was 51% for surveillance (95% CI: 39, 61) and 70% for chemotherapy (95% CI: 58, 79). PFS favored chemotherapy: HR = 0.49 (95% CI: 0.30, 0.79, p = 0.003).

Conclusions: Adjuvant chemotherapy improved PFS in UTUC. POUT is the largest randomized trial in this patient population. The trial was terminated early because of efficacy favoring the chemotherapy arm. Follow up for OS continues, this may be considered a new standard of care in these patients, although many physicians dislike the use of carboplatin in the peri-operative setting.