Phase 1b/2 trial of Ipilimumab, Nivolumab, and Ciforadenant (INC) (adenosine A2a receptor antagonist) in first-line advanced renal cell carcinoma

Dr. Kathryn Beckermann MD, PhD\textsuperscript{1}, Dr. Brian Rini MD\textsuperscript{1}, Dr Naomi Haas MD\textsuperscript{2}, Dr Daniel George MD\textsuperscript{3}, Dr Eric Jonasch MD\textsuperscript{4}

\textsuperscript{1}Vanderbilt University Medical Center. \textsuperscript{2}University of Pennsylvania. \textsuperscript{3}Duke University Medical Center. \textsuperscript{4}MD Anderson

**Background:** Ciforadenant is an investigational immunotherapeutic small molecule that selectively and reversibly binds adenosine2A receptors (A2ARs) on T lymphocytes and other cells of the immune system. RCC metabolism is known to be highly glycolytic, with a need to export adenosine triphosphate (ATP) to allow for continued proliferation of cancer cells. In the tumor microenvironment (TME) ATP is hydrolyzed to adenosine by CD39/CD73. Adenosine has immune suppressive effects on the TME through the A2 adenosine receptor (A2AR) including decreased T cell activation and proliferation (Ohta et al., 2009). Blocking A2AR on tumor associated myeloid cells such as macrophages, dendritic cells, and myeloid derived suppressor cells in preclinical mouse models have shown enhanced tumor killing (Cekic et al. 2014). Preclinical studies show that the addition of ciforadenant to CTLA4 and PD1 blockade shows enhanced efficacy and in some cases elimination of the established tumors (Willingham et al., 2018). Recently, in a first in human study, the A2AR antagonist ciforadenant was found to be safe and showed activity as monotherapy in RCC patients with refractory disease following multiple lines of therapy showing a median progression free survival (mPFS) of 4.1 months (Fong et al., 2019). In the same study, the addition of ciforadenant to PD-L1 blockade with atezolizumab was shown to be safe and demonstrate activity with mPFS of 5.8 months and OS probability at 25 months of 90%. We hypothesize that the addition of the A2aR antagonist, ciforadenant, to the combination of ipilimumab and nivolumab will favorably modulate metabolic adenosine signaling and the myeloid compartment to enhance patient response by reducing immunosuppression.

**Methods:** INC is a Phase 1b/2 single-arm, multicenter study to assess safety and efficacy of the combination of ipilimumab, nivolumab, and ciforadenant in the frontline treatment of patients with advanced clear cell renal cell carcinoma. This study is being conducted through the Kidney Cancer Clinical Trial Consortium. Eligibility criteria include untreated advanced clear cell RCC, ECOG PS 0 or 1, measurable disease by RECIST 1.1 and adequate organ function and excludes patients who have previously received immunotherapy. The study will include a lead-in safety phase 1b portion with enrollment of four to eight patients treated with ciforadenant 100 mg BID, nivolumab 3 mg/kg and ipilimumab 1 mg/kg (IV) q3 weeks. If the rate of patients with a dose limiting toxicity is more than 45% another four patients will be enrolled at reduced dose of ciforadenant 50 mg BID, nivolumab 3 mg/kg and ipilimumab 1 mg/kg IV q3 weeks. If continuing on trial, patients will receive nivolumab 480 mg infusion and ciforadenant beginning Cycle 2, Day 1 q4 weeks. In the Phase 2 dose-expansion portion of the study, 42 additional patients (total 50) patients consisting of untreated advanced clear cell renal cell carcinoma will be treated at the RCD determined in the Phase 1b portion of the study.

The primary objective is to determine the safety and tolerability and to assess the depth of response (>50% by RECIST 1.1 Eisenhaur, 2009) based on a Bayesian design in patients with advanced RCC treated with ipilimumab, nivolumab, and ciforadenant. Secondary objectives will estimate the objective response rate (ORR), duration of response (DOR) progression free survival (PFS), progressive disease (PD) rate, and irAE rate of ipilimumab, nivolumab, and ciforadenant combination in untreated advanced RCC. Exploratory objectives include assessing gene expression signatures and pharmacodynamic parameters with outcome.

This study is open to enrollment with six patients on trial anticipating lead-in safety analysis to be completed shortly for identification of randomized phase 2 dosing and opening the expansion cohorts. The trial will be open through the Kidney Cancer Research Consortium at
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