A PHASE 1B/2 STUDY OF CABOZANTINIB IN COMBINATION WITH PEMBROLIZUMAB IN ADVANCED MELANOMA

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Background: In the United States, melanoma is the fifth leading cancer in men and the seventh in women. Immunotherapy has improved antitumor activity and survival. Overall response rate (ORR) with single agent PD-1 inhibitor is 35%, and 55% with the combination of PD-1/CTLA-4 inhibitors but with significant grade 3–4 toxicity. Cabozantinib inhibits multiple receptor tyrosine kinases, including c-MET and vascular endothelial growth factor receptor 2 (VEGFR2), and has been shown to have immunomodulatory effects in vitro and in murine models. In addition, c-Met has been found to induce overexpression of PD-L1. We hypothesize that combination treatment with these two drugs has the potential to improve response rate in metastatic or recurrent melanoma, without significant regimen-limiting toxicities.

Methods: This trial in progress is an open-label, single center Phase 1b/2 study of the combination of cabozantinib and pembrolizumab in patients with advanced melanoma. Eligible patients have stage IV or recurrent/medically inoperable melanoma, treatment naïve for immunotherapy. Prior BRAF and MEK inhibitor is allowed in metastatic setting. Exclusion criteria includes those with ocular or mucosal melanoma or uncontrolled CNS metastases. The trial is currently recruiting. The phase 1b study is based on a 3+3 design with a fixed dose of pembrolizumab (200 mg IV every 3 weeks) and three dose levels of cabozantinib (40, 20 and 60 mg), administered orally daily. The primary endpoint of the phase 1b study is safety of the combination in metastatic melanoma patients. The phase 2 study will be conducted in two stages to evaluate the preliminary efficacy of combination cabozantinib and pembrolizumab, with up to a total of 44 subjects. The study will be terminated early if five or fewer subjects respond in the first stage; otherwise, additional subjects will be accrued. The primary endpoint is best ORR. The secondary endpoints are disease control rate (DCR), duration of DCR, time to response, progression-free survival and overall survival. Exploratory endpoints include assessing biomarkers as a measure of clinical efficacy.

Results: N/A

Conclusions: N/A

Trial Registration: NCT03957551

Ethics Approval: The study was approved by The University of Iowa’s Institutional Review Board, approval number 201904712.

REFERENCES:

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INTERIM ANALYSIS OF PHASE 2 RESULTS FOR CEMIPLIMAB IN PATIENTS WITH METASTATIC BASAL CELL CARCINOMA (mBCC) WHO PROGRESS ON OR ARE INTOLERANT TO HEDGEHOG INHIBITORS (HHIs)

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Background: HHIs, vismodegib and sonidegib, are approved for treatment of patients with mBCC or locally advanced BCC who are not candidates for surgery or radiation. There is no approved option for patients who progress on or are intolerant to HHIs. Cemiplimab is an anti-programmed cell death-1 monoclonal antibody approved for treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Here we present the prespecified interim analysis of the mBCC cohort from the pivotal Phase 2, non-randomized, multi-center study of cemiplimab in patients with advanced BCC who discontinued HHI therapy due to disease progression, intolerance, or no better than stable disease after 9 months (NCT03132636).

Methods: Patients with mBCC (nodal and/or distant) received cemiplimab 350 mg intravenously every 3 weeks; interim analysis included patients with the opportunity to be followed for approximately 57 weeks. The primary endpoint was objective response rate (ORR) per independent central review (ICR). Secondary objectives included assessment of safety and tolerability, estimation of duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Results: In this interim efficacy analysis of 28 patients, 82.1% were males and median age was 65.5 years (range 38–90). Six patients had a partial response, per ICR, for an ORR of 21.4% (95% CI, 8.3, 41.0). ORR per investigator assessment was 28.6% (95% CI, 13.2, 48.7). Among responders, observed DOR was 9–23 months. Median time to response per ICR was 3.2 months (range, 2.1–10.5). Median Kaplan-Meier (KM) estimation of PFS was 8.3 months. Median DOR had not been reached and median KM estimation of OS was 25.7 months. All six responses had observed durations of at least 8 months. The disease control rate was 67.9% (95% CI, 47.6, 84.1). The most common treatment emergent adverse events (TEAEs) regardless of attribution were fatigue (50.0%), diarrhea (35.7%), pruritus (25.0%), and constipation (25.0%). Hypertension (n=2) was the only emergent adverse event (TEAE) regardless of attribution occurring in ≥2 patients. TEAEs leading to death occurred in one (3.6%) patient who died from staphylococcal pneumonia, considered unrelated to study treatment.

Conclusions: This interim analysis demonstrates that cemiplimab is the first agent to provide clinically meaningful anti-