427 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.[1 2] 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.[3] In addition, c-Met has been found to induce overexpression of PD-L1.[4] 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.

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428 INTERIM ANALYSIS OF PHASE 2 RESULTS FOR CEMIPLIMAB IN PATIENTS WITH METASTATIC BASAL CELL CARCINOMA (MBCC) WHO PROGRESSED 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 Grade ≥3 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-

tumor activity, including durable responses, in patients with mBCC after progression or intolerance on HHI therapy.

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Ethics Approval The study protocols and all amendments were approved by the institutional review board at each participating study site. The study was conducted in accordance with the principles of the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients provided written informed consent before enrollment.

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429 LONG-TERM ANALYSIS OF MASTERKEY-265 PHASE 1B TRIAL OF TALIMOGENE LAHERPAREPVEC (T-VEC) PLUS PEMBROLIZUMAB IN PATIENTS WITH UNRESECTABLE STAGE IIIB-IVM1C MELANOMA

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Background Previous findings from the MASTERKEY-265 phase 1b study showed that the combination of T-VEC and pembrolizumab was well tolerated and produced a high complete response (CR) rate of 43% in patients with advanced melanoma.[1] The 3-year progression-free survival (PFS) and overall survival (OS) rates at that time were 53.6% and 71%, respectively. Here, we report the results of the long-term follow-up efficacy analyses.

Methods The MASTERKEY-265 phase 1b trial (NCT02263508) was an open-label, single-arm study that enrolled patients who had unresectable, stage IIIB-IVM1c melanoma with injectable, measurable lesions and no prior systemic treatment. T-VEC was administered intralesionally at the approved dosing starting day 1 of week 1. Pembrolizumab (200 mg) was administered intravenously Q2W beginning on day 1 of week 6. The maximum treatment period was 2 years. The primary endpoint was dose-limiting toxicities; key secondary endpoints included objective response rate and PFS per modified irRC, OS, and safety.

Results As of the data cutoff (Mar 2, 2020), all 21 patients enrolled were off treatment; 6 died and 15 are in long-term follow-up. The median follow-up time was 58.6 months (range: 1.4–61.6). The CR rate remained 43% (9/21 patients). Twelve of the 13 responders (92.3%) are still in response, including all 9 patients with a CR. Median duration of response was not reached (range: 2.8+–54.3+ months). Median PFS and OS were not reached at the data cutoff. KM estimates of 4-year PFS and OS rates were 55.9% and 71.4%, respectively, which have held stable since the 3-year analysis. Patients who achieved a CR or partial response had better OS (p=0.0056) compared to those who did not respond. Median OS for non-responders was 24.4 months and was not reached for responders. No additional safety signals were detected.

Conclusions At almost 5 years of follow-up, median PFS and OS were not reached for patients treated with the combination of T-VEC and pembrolizumab in this phase 1b study of unresectable metastatic melanoma. 92% of responders remained in response with improved OS observed in responders compared with non-responders. The corresponding randomized phase 3 trial has completed enrollment and is currently ongoing.

Trial Registration NCT02263508

Ethics Approval The study was approved by the Ethics Board of each institution involved in this study and can be produced upon request.

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430 A PHASE II STUDY OF NIVOLUMAB + BMS-986016 (RELATLIMAB) IN PATIENTS WITH METASTATIC UVEAL MELANOMA(UM) (CA224–094)

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Background Fifty percent of patients with uveal melanoma (UM) develop metastatic disease, surviving 6–12 months from metastatic diagnosis. Liver-directed therapies, immunotherapy, targeted therapy and chemotherapy have limited activity. Lymphocyte activation gene 3(LAG-3) is an immune checkpoint receptor associated with decreased T-cell effector function and tumor escape. Preclinical models have shown that dual inhibition of LAG-3 and PD-1 blockade generates synergistic anti-tumor activity.[1] In uveal melanoma, CD8+ T cells express the checkpoint receptor LAG3 to a greater extent than PD1 or CTLA4.[2 3] This recent discovery nominates LAG3 as a potential candidate for checkpoint inhibitor immunotherapy in UM.

Methods This is an open-label, single arm, single site investigator-initiated phase II study. Based on Simon two-stage minimax design, 13 patients will be enrolled in Stage 1. If at least one response is noted, the study will proceed to Stage 2 and enroll additional 14 patients. The null hypothesis will be rejected if 4 or more responses are observed among 27 patients. This design achieves 5% type I error and 80% power when the true ORR is 20%.Main eligibility criteria includes patients with biopsy proven metastatic uveal melanoma, previously untreated with PD-1, CTLA-4 and/or LAG-3 blocking antibodies and in good performance status.Enrolled patients will be treated in the outpatient setting. Nivolumab 480 mg will be mixed in the same bag with relatlimab 160 mg and administered intravenously over 60 minutes every 4 weeks until disease progression or intolerable toxicity for up to 24 months.The primary endpoint is best objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression-free survival (PFS), overall survival (OS), median duration of response (mDOR), and adverse events