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 progression of the 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 naive 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 cabozantinib (60 mg 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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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. 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 intradermally at the approved dosing starting day 1 of week 1. Pembrolizumab (200 mg) was administered intravenously over 60 minutes every 4 weeks beginning on day 1 of week 6. The maximum treatment period was 2 years. The primary endpoint was dose-limiting toxicity; 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. The CR rate remained 43% (9/21 patients). Twelve of the 13 responders (92.3%) are still in follow-up. The median follow-up time was 58.6 months. Median PFS and OS were not reached at the data cutoff (range: 2.8+–48.0+ months). Median PFS and OS were not reached at the data cutoff (range: 2.8+–48.0+ 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.

REFERENCE

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