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.

REFERENCES

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0427
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 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—patients with biopsy proven metastatic uveal melanoma, previously untreated with PD-1, CTLA-4 and/or LAG-3 inhibitors. LM22 was approved by the institutional review board at each participating 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.

As of the data cutoff (Mar 2, 2020), all 21 patients remained in response with improved OS observed in responders compared with non-responders. The study continues ongoing.

Conclusion At almost 5 years of follow-up, median PFS and OS were not reached for patients treated with the combination of TVEC 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 study continues ongoing.

Trial Registration NCT02263508

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

REFERENCE

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0429