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/malignantly 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 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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