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Nearly 50% of patients with uveal melanoma (UM) will develop metastatic disease within 15 years from initial diagnosis. There is currently no effective therapy for advanced UM. A number of treatments have been evaluated, including systemic chemotherapy, immunotherapy, and targeted therapy, but response rates are generally less than 10%, and no therapy has been shown to improve overall survival. Novel treatment strategies for metastatic UM are desperately needed. Bromodomain and Extra-Terminal (BET) proteins are known epigenetic regulators of cancer growth, in part through activation of the Myc transcriptome. Preclinical studies from our institution support the efficacy of BET inhibition in UM, a disease characterized by activating mutations in GNAQ and GNA11 and amplification of MYC. Interestingly, the anti-tumor effects of BET inhibition do not appear to be mediated by c-Myc, as previously hypothesized, but by suppression of genes involved in apoptosis (Bcl-xL) and DNA damage response (Rad51).

PLX51107 is an oral small molecule BET inhibitor currently being investigated in a phase Ib dose escalation study in patients with advanced malignancies at our institution. There has been promising preliminary activity observed in UM patients. For Aim 1, we will assess the clinical efficacy of BET inhibition in a single-arm phase II study of PLX51107 in 35 patients with advanced UM, using the recommended phase 2 dose (RP2D) from the phase Ib study. The primary endpoint will be a target overall response rate of 20%. For Aim 2, we will confirm the preclinical findings that BET inhibition leads to suppression of Bcl-xL and Rad51 by analyzing target protein and gene expression in pre- and posttreatment biopsies. We will also correlate suppression of Bcl-xL and Rad51 with biological markers of response i.e. decreased proliferation and increased apoptosis. We hypothesize that PLX51107 will increase the response rate compared to what has been historically achieved with chemotherapy, and that anti-tumor effects will correlate with suppression of Bcl-xL and Rad51. This trial will evaluate a novel approach to the treatment of metastatic UM, as well as characterize the in vivo mechanism of action of BET inhibition. Results may ultimately lead to a more effective treatment option for patients with metastatic UM. An improved understanding of how PLX51107 exerts cytotoxicity will have significant implications for not only UM, but also other malignancies in which BET inhibition may prove active.