Title: BET inhibition sensitizes preclinical models of bladder cancer to DDR inhibitors

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Abstract:

Bladder cancer (BC) remains a common and deadly malignancy, with a projected 83,190 new diagnoses and 16,840 deaths in the U.S. in 2024. According to the MSK/TCGA BC dataset, mutations in DNA damage response (DDR) genes that are part of the homologous recombination (HR) pathway occurred in up to 55% of patients, representing a potential therapeutic target in BC. Previously, we used UNC's EpiG Diamond compound library to show that inhibition of the methyl-lysine reader bromodomain and extra-terminal domain (BET) proteins potently abrogates BC cell line viability. We discovered that simultaneous inhibition of BET and PARP was the most synergetic amongst several compounds tested. In an effort to elucidate the mechanisms of BETi potency and perfect a synergetic approach, we evaluated the effects of OTX-015 and olaparib combination treatments on cell cycle phase synchronized J82 and 5637 BC cell lines. We found that synchronous and asynchronous BC cells displayed comparable gene expression changes to RAD51, RBBP8 and POLQ after combined PARP+BET inhibition, suggesting a lack of cell-cycle specific effect. BET inhibition significantly reduced TMEJ in both 5637 and J82 BC cells but did not significantly impact HR or NHEJ. Despite this, BET inhibition did significantly reduce gene expression of HR pathway members RAD51 and RBBP8 in a time-dependent manner. Asynchronous BC cells treated with combined OTX-015 and olaparib showed significant reduction in gene expression of RAD51 and RBBP8. Next steps include further

categorizing the effects of combination treatment by evaluating protein expression and in vivo models.