Phase 1b/2a clinical trial of the oral BET inhibitor PLX2853 as monotherapy for ARID1A mutated gynecologic cancers and in combination with carboplatin for platinum resistant ovarian cancer

EM Swisher1, LR Duska2, E Hamilton3, A Oza4, JG Fleming5, OO Yeku6, A Spira7, DL Richardson8, R Guo9, J Walling10, K Inokuchi10, D Zamarin9


• The aberrant regulation of epigenetic processes has emerged as a common feature underlying many malignancies, with epigenetic regulation of gene expression impacting both the initiation and maintenance of these malignancies.

• The Bromodomains and Extra-Terminal (BET) domain proteins facilitate the development of many types of human neoplasms by serving as the epigenetic regulators of genes essential for tumor growth and survival.

• It was recently shown that loss of ARID1A sensibly most ovarian cancer (OC) to BET inhibition, 30-60% of clear cell and endometrioid OC and epithelial ovarian cancers (EOC) have ARID1A mutations.

• PLX2853 is an orally active, small molecule inhibitor of BET bromodomain-mediated transcription that exhibits a high nanomolar potency in blocking 4 BET family members (BRD2, BRD3, BRD4, and BRD7).

• Driver Mutations Present

• These data provide rationale for further exploration of BET inhibitors in patients with ARID1A-mutated gynecologic malignancies, possibly in combination with agents targeting potential feedback mechanisms such as the PI3K pathway.

Conclusions

• Results did not meet the pre-specified response criteria for evidence of clinical activity

• The larger cohort of gynecologic cancer patients confirmed the safety profile of the agent and demonstrated the feasibility of combination with carboplatin at full monotherapy dosing of PLX2853 (80mg daily)

• These data provide rationale for further exploration of BET inhibitors in patients with ARID1A-mutated gynecologic malignancies, possibly in combination with agents targeting potential feedback mechanisms such as the PI3K pathway.