Background More than 630,000 cases of HPV related cancer (e.g. cervical, oropharyngeal, anal) occur worldwide annually. Unfortunately, only about 15-20% of cases respond to PD-L1 inhibitors alone. Recent data with the triple combination of PDS0101 (a therapeutic vaccine targeting HPV 16 E6/E7), M9241 (a tumor-targeting IL-12 immunocytokine), and bintrafusp alfa (a bifunctional fusion protein targeting TGF-β and PD-L1) have shown early clinical activity in advanced checkpoint refractory HPV related cancers, with 45% of patients having disease reduction, including 27% with objective responses.1 In addition, preclinical studies have shown that the triple combination of entinostat (histone deacetylase inhibitor), M9241, and bintrafusp alfa may also have promising anti-tumor activity in checkpoint refractory disease.

Methods 7 patients with advanced checkpoint refractory HPV positive cancers who had been previously treated with PDS0101, M9241 and bintrafusp alfa (NCT04287868) and progressed went on to be treated with the combination of entinostat, M9241, and bintrafusp alfa (NCT04708470). These patients received bintrafusp alfa at 300 mg IV q 2 weeks, entinostat 3 mg po weekly including a 1 week lead in of entinostat alone, and M9241 at either 4 mcg/kg SC q 2 weeks or 8 mcg/kg SC q 4 weeks (based on dose escalation cohort). Pts receiving M9241 at 8 mcg/kg did not receive entinostat on the week of M9241 treatment but did on all other weeks.

Results 7 patients with advanced checkpoint refractory HPV positive cancers (5 oropharyngeal, 1 anal, 1 neuroendocrine rectal) who had progressed on PDS0101, M9241 and bintrafusp alfa went on to receive entinostat, M9241, and bintrafusp alfa. After switching to the entinostat based triple combination, 2/7 patients had grade 3 treatment related AEs including grade 3 anemia in one patient and grade 3 leukopenia/lymphopenia in another. Otherwise, there were no grade 3 or greater treatment related AEs observed in patients switching to the entinostat based triple combination. 3/7 (43%) patients (2 oropharyngeal, 1 anal) have had tumor reduction of 28.8%, 38.3% and 42.6% by RECIST after switching to the entinostat based triple combination.

Conclusions Escalating doses of the triple combination of entinostat, M9241 and bintrafusp alfa continue to be evaluated in an ongoing phase I/II trial (NCT04708470). To date the triple combination appears to have a manageable safety profile along with encouraging clinical activity in patients with advanced checkpoint refractory HPV related cancers including in pts who have previously progressed on PD(L)1 inhibitor then on PDS0101, M9241 and bintrafusp alfa.

Trial Registration NCT04708470

REFERENCE

Ethics Approval Ethics approval for NCT04708470 was obtained from the National Institutes of Health IRB (Ref # 551458). Participants gave informed consent prior to participating.