Phase II Evaluation of the Combination of PDS0101, M9241 and Bintrafusp Alfa in Patients with HPV 16+ Malignancies

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Background: More than 630,000 cases of HPV related cancer occur worldwide annually. About 15-20% of cases respond to PD-(L)1 inhibitors and about 30% respond to dual PD-L1/TGF-β blockade including 10% of checkpoint refractory pts, but for the majority of pts with checkpoint refractory disease there is no effective standard therapy. Preclinical studies show that the combination of PDS0101 (a therapeutic vaccine targeting HPV 16 E6/E7), M9241 (a tumor-targeting IL-12 immunocytokine), and bintrafusp alfa (BA, a bifunctional fusion protein targeting TGF-β and PD-L1), resulted in maximum T cell infiltration and tumor reduction compared to any 1 or 2 of these agents alone. Prior clinical data suggests that the combination is preferentially active in HPV 16+ disease.

Methods: 30 pts with advanced HPV 16+ cancer were treated with PDS0101, M9241 and BA (NCT04287868). Pts received BA at 1200 mg IV q2wks, M9241 at 16.8 mcg/kg SC q4wks or 8 mcg/kg SC q2wks, and PDS0101 as two 0.5 ml SC injections q4wks. Dose reductions or skipped doses for toxicities of BA and M9241 were allowed. 5 pts had surgical resection of tumor for disease control and were censored for PD but not survival.

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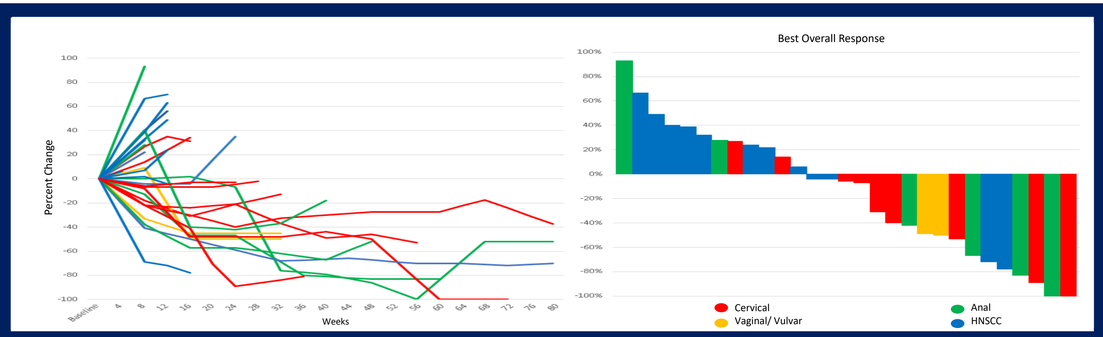
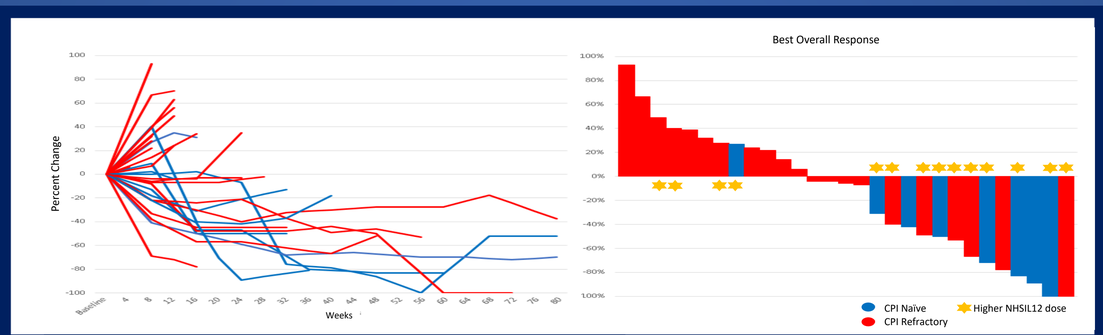
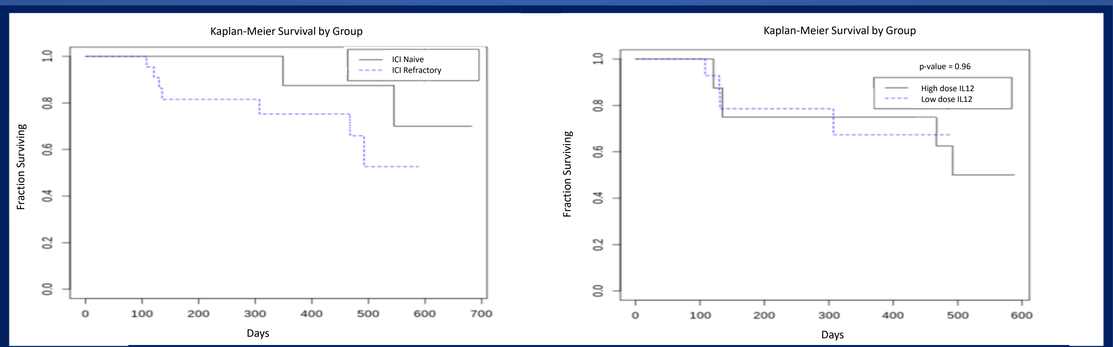


- **Responses have been durable**
- **Responses occurred irrespective of tumor type**



- **Overwhelming majority of CPI naïve pts had a response**
- **Nearly half of CPI refractory pts had some tumor reduction**
- **Higher NHSIL12 dose seemed to result in greater clinical activity**



- **Both ICI naïve & ICI refractory survival appear to be quite promising compared to historical controls**
- **ICI refractory survival curves are overlapping for high (16.8 mcg/kg) vs low (8 mcg/kg) dose NHSIL12**

Results: 30 pts (9 cervical, 2 vaginal/vulvar, 6 anal, 13 oropharyngeal) were treated. 13/30 had grade 3 treatment related AEs including grade 3 anemia in 9 pts associated with grade 3 hematuria in 3 pts and grade 3 GI bleeding in 3 pts. 2 pts had grade 3 AST/ALT elevation. Grade 3 flu like symptoms and grade 3 hemophagocytic lymphohistiocytosis were each seen in 1 pt. One pt had grade 3 lymphopenia/leukopenia plus grade 4 neutropenia and one pt had grade 4 AST/ALT elevation. There were no grade 5 treatment related AEs.

7/8 (88%) pts with checkpoint naïve disease had objective responses (OR) including 1 delayed response after initial PD with 4/7 (57%) responses ongoing (median 17 months follow up). For checkpoint refractory pts, M9241 dosing appeared to affect response rates. 5/8 (63%) pts receiving M9241 at 16.8 mcg/kg had an OR compared to 1/14 (7%) who received M9241 at 8 mcg/kg with an OR. In all, 10/22 (45%) with checkpoint refractory disease have had disease reduction including 6/22 (27%) with OR and 4/6 (67%) responses ongoing (median 12 months follow up). 6/8 (75%) pts with checkpoint naïve disease and 17/22 (77%) pts with checkpoint refractory disease are alive after a median of 17 and 12 months follow up respectively. While differences in response rates with higher vs lower M9241 dose were observed, survival outcomes in checkpoint refractory disease were similar irrespective of M9241 dose ($p = 0.96$ by Kaplan Meier analysis).

Conclusions: The combination of PDS0101, M9241 and BA appears to have a manageable safety profile along with early evidence of clinical activity for pts with checkpoint naïve and refractory advanced HPV 16+ cancer. Moreover, growing data suggest that all 3 drugs in the combination may contribute to the encouraging outcomes observed.