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PHASE II EVALUATION OF THE TRIPLE COMBINATION OF PDS0101, M9241, AND BINTRAFUSP ALFA IN PATIENTS WITH HPV 16 POSITIVE MALIGNANCIES

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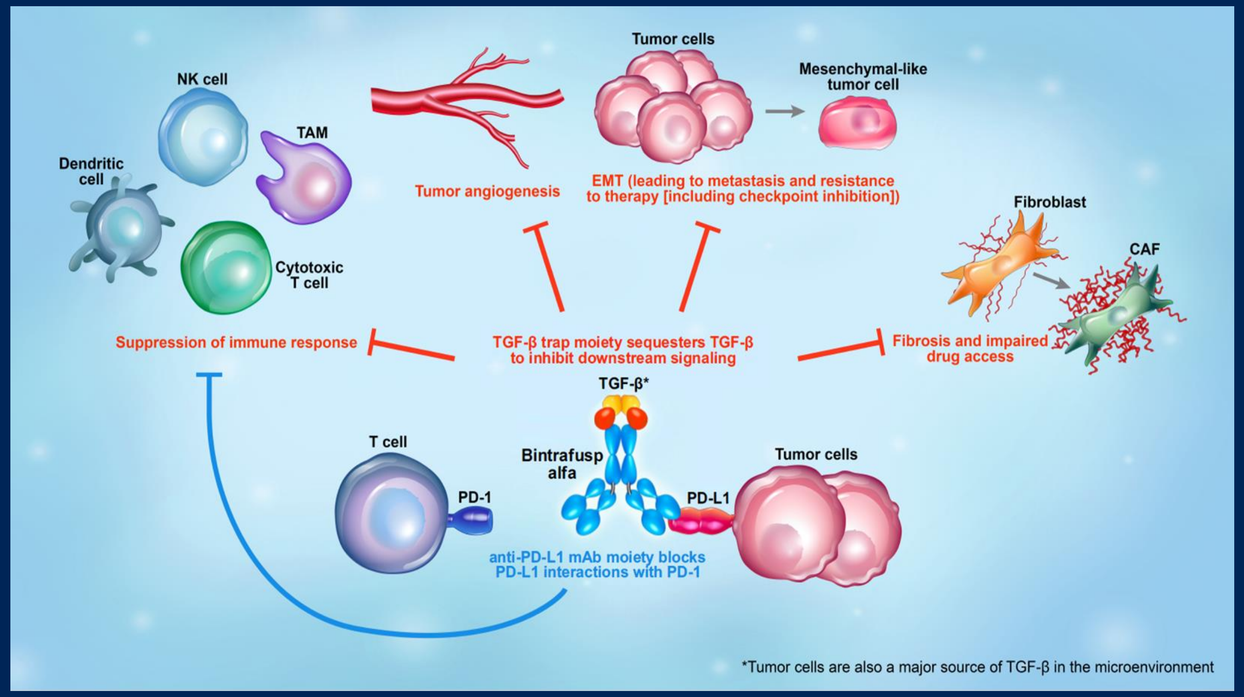
Introduction

- >630,000 new cases of HPV-related cancer (e.g. cervical, oropharyngeal, anal) reported worldwide annually[1]
- PD-1 inhibitors have been evaluated in these tumor types and ORRs have ranged from 13–24%[2-8]
- Nivolumab & pembrolizumab are FDA approved for HNSCC; pembrolizumab is approved for PD-L1+ cervical cancer
- Unfortunately, the majority of patients who receive these anti PD-1 inhibitors will progress
- For these patients with checkpoint refractory disease there is no clear effective standard of care therapy
- HPV infection is also linked to upregulation of TGF-β signaling[9]
  - Genome-wide association studies showed that TGF-βR1 is significantly overexpressed in HPV-related cancer[10]

1. de Martel C, et al. *Int J Cancer.* 2017;141:664–70; 2. Viens LJ, et al. *MMWR Morb Mortal Wkly Rep*.; 2. Bauml J, et al. *J Clin Oncol* 2017;35:1542–49; 3. Ott PA, et al. *Ann Oncol.* 2017;28:1036–41; 4. Hollebecque A, et al. *J Clin Oncol*. 2017;35(Suppl):Abstract 5504; 5. Chung HC, et al. *J Clin Oncol*. 2018;36(Suppl):Abstract 5522; 6. Ferris RL, et al. *N Engl J Med*. 2016;375:1856–67; 7 Mehra R, et al. *Br J Cancer.* 2018;119:153–59; 8 Morris VK, et al. *Lancet Oncol*. 2017;18:446–53. 2016;65:661–66; 9. Torres-Poveda K, et al. *World J Clin Oncol.* 2014;5:753-63; 10. Levovitz C, et al. *Cancer Res.* 2014;74:6833-44.

Bintrafusp alfa: a TGF-β and PD-L1 Inhibitor

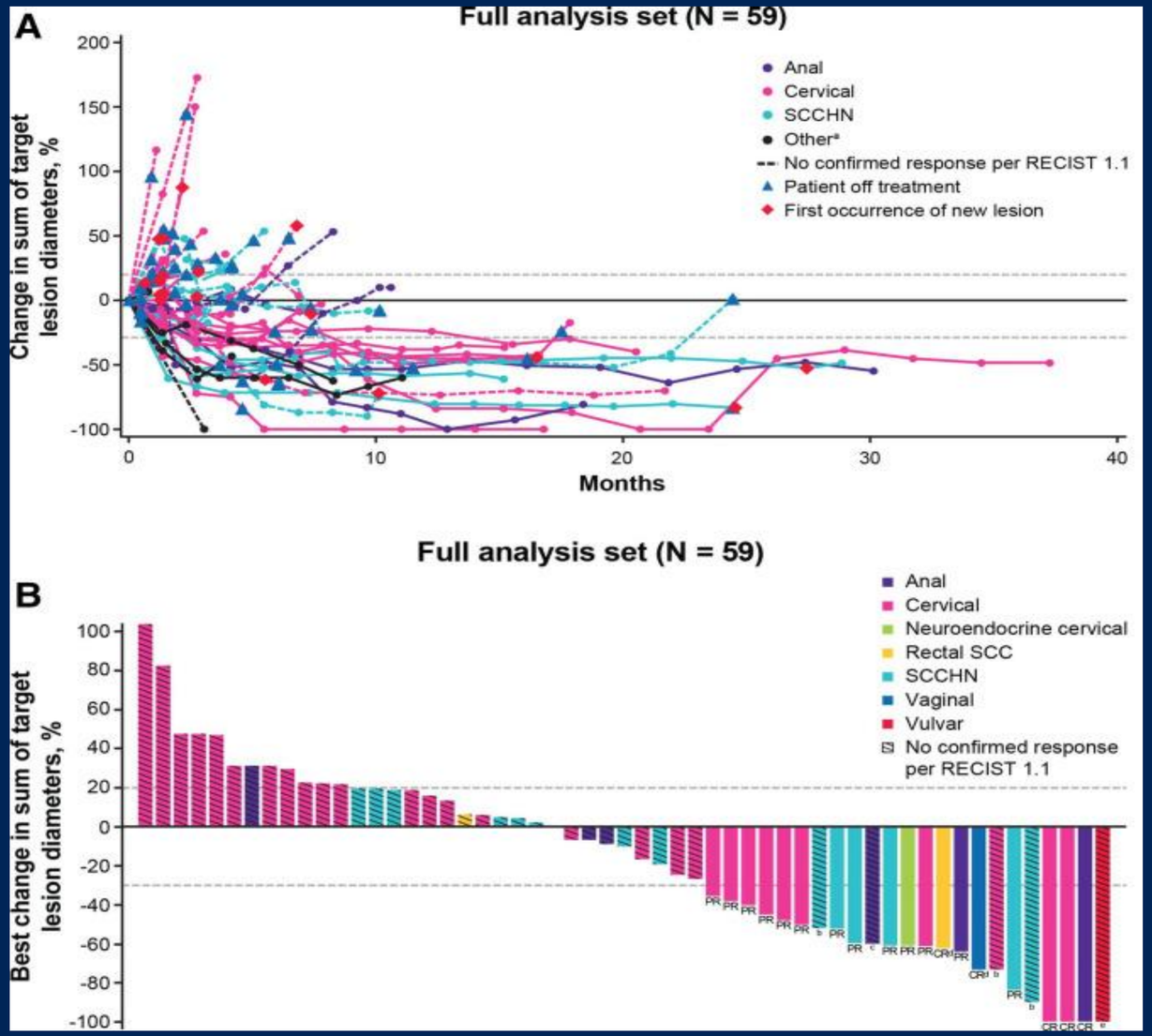


- **Bintrafusp alfa is an innovative first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1**

- **In a phase 1 study, bintrafusp alfa was well tolerated and produced durable responses in several solid tumor types [1-3]**

1.Strauss J, et al. *Clin Cancer Res.* 2018;24:1287–95; 2. Paz-Ares L, et al. *J Clin Oncol.* 2018;36(Suppl):Abstract 9017; 3. Cho BC, et al. *Ann Oncol.* 2018;29(Suppl):Abstract 1048O..

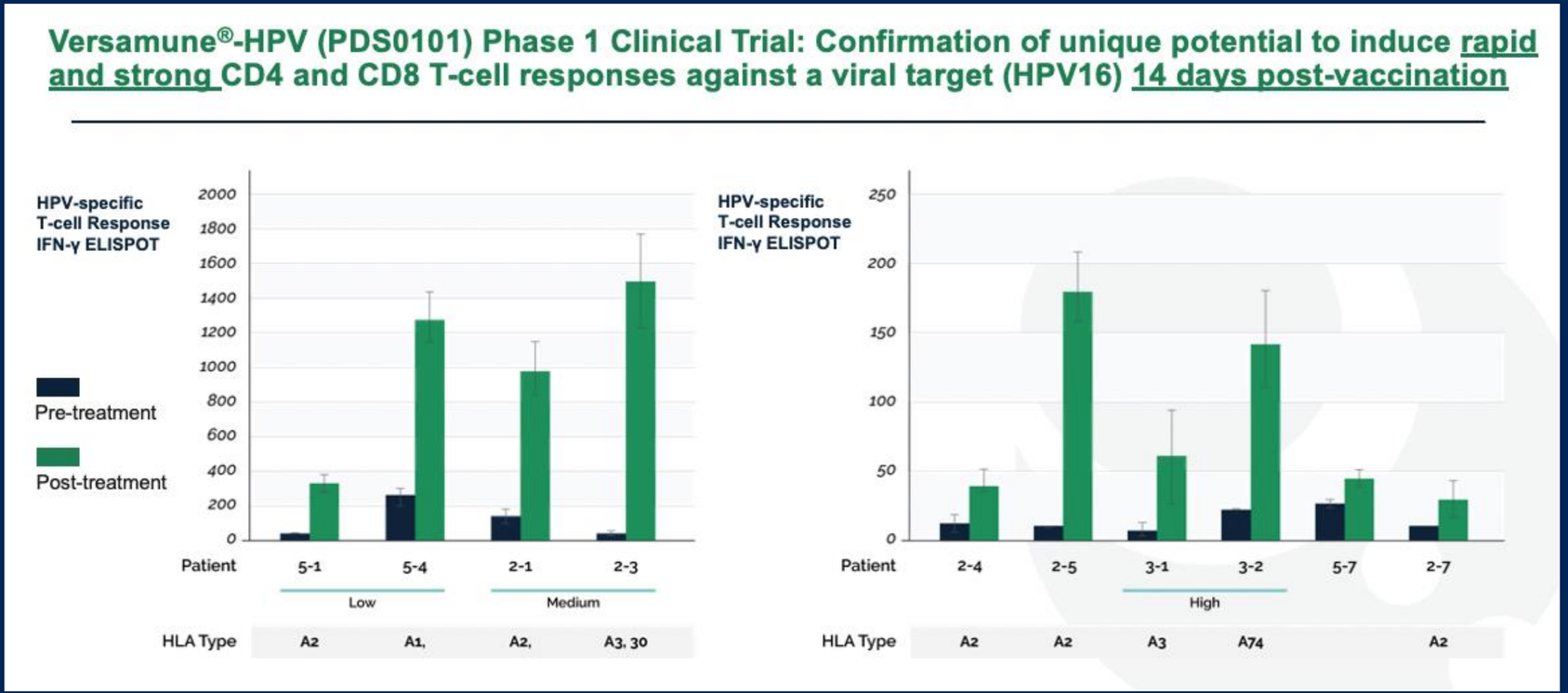
Bintrafusp alfa in HPV-Related Cancers



- 79 patients with advanced HPV-associated cancers (59 checkpoint naïve and 20 checkpoint refractory) received bintrafusp alfa IV every 2 weeks until disease progression or intolerance[1]
- Side effect profile similar to standard anti-PD(L)1 inhibitors with the addition of keratoacanthomas & mucosal bleeding
- ORR was 30.5% in checkpoint naïve disease
- ORR was 10% in checkpoint refractory disease

1.Strauss J, et al. J Immunother Cancer. 2020 Dec;8(2):e001395.

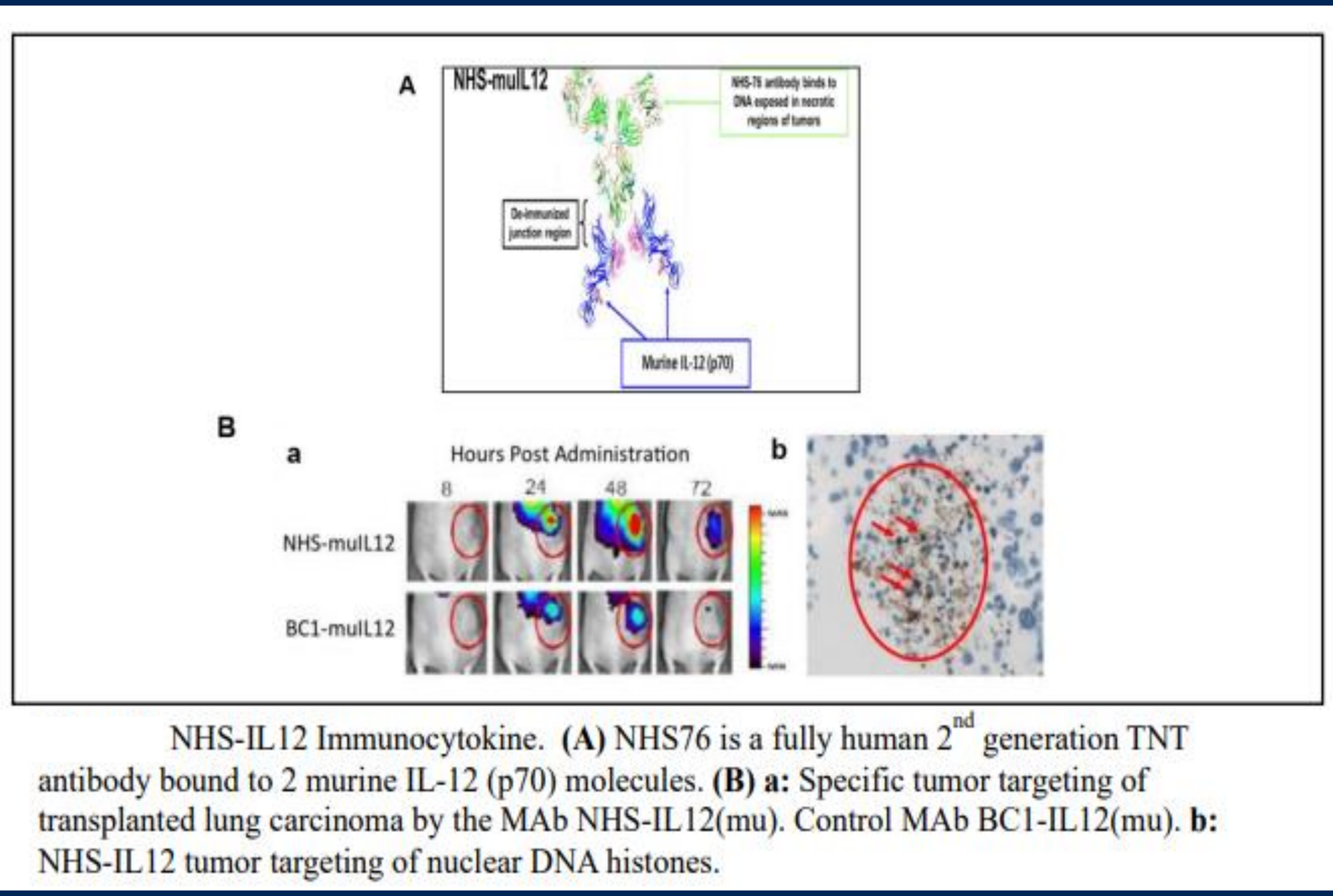
PDS0101: Versamune®-based HPV 16 cancer vaccine



- Micellar multi-peptide based therapeutic vaccine targeting HPV 16 E6/ E7 (HPV 16 is the genotype responsible for majority of HPV-related cancers worldwide)
- Versamune® nanoparticles contain the cationic lipid R-DOTAP which upregulates type I IFNs and promotes antigen cross-presentation
- In a phase I trial patients with cervical intraepithelial neoplasia developed strong HPV-specific CD4+ and CD8+ T cell immune responses[1]
- Was well tolerated with mild transient site reactions and minimal systemic toxicity

1.Wood LV, et al., SITC 2019, (O19) Abstract ID 12533

M9241 (NHSIL12)

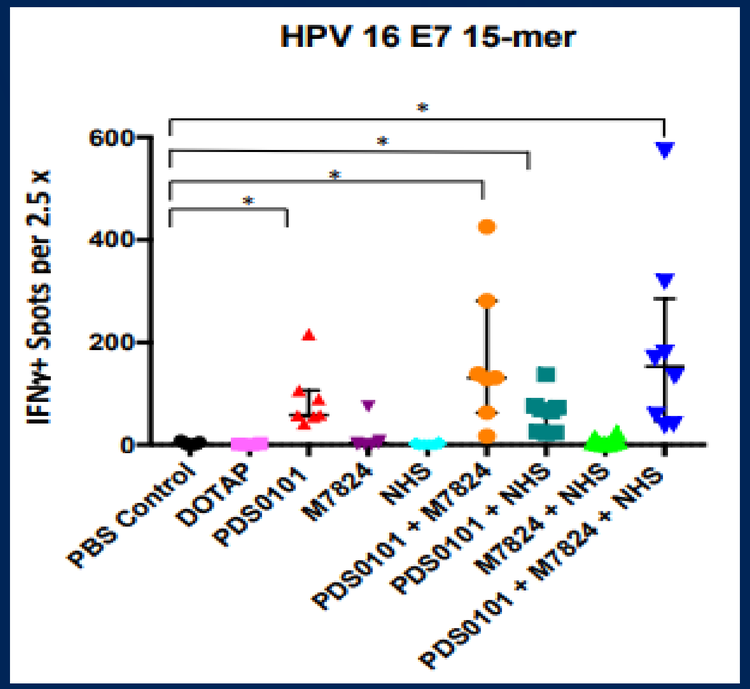


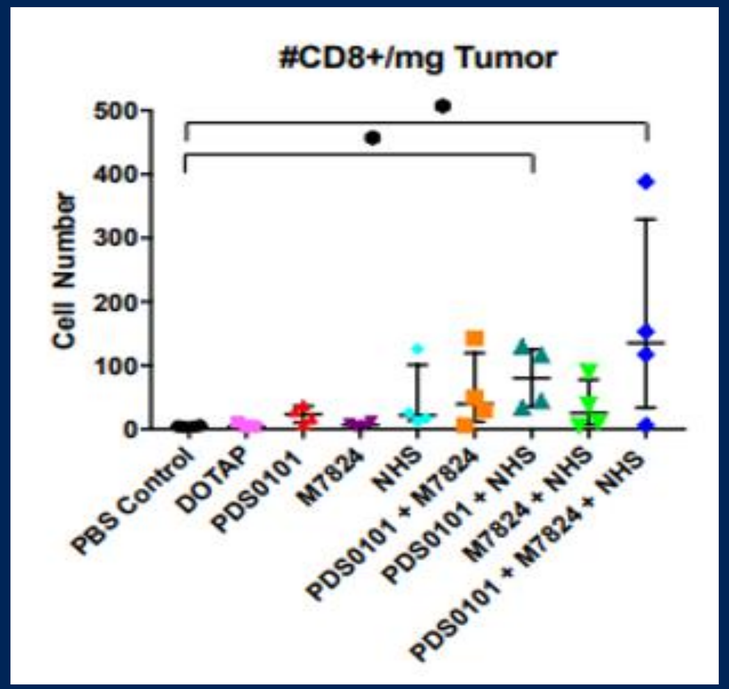
NHS-IL12 Immunocytokine. **(A)** NHS76 is a fully human 2nd generation TNT antibody bound to 2 murine IL-12 (p70) molecules. **(B) a:** Specific tumor targeting of transplanted lung carcinoma by the MAb NHS-IL12(mu). Control MAb BC1-IL12(mu). **b:** NHS-IL12 tumor targeting of nuclear DNA histones.

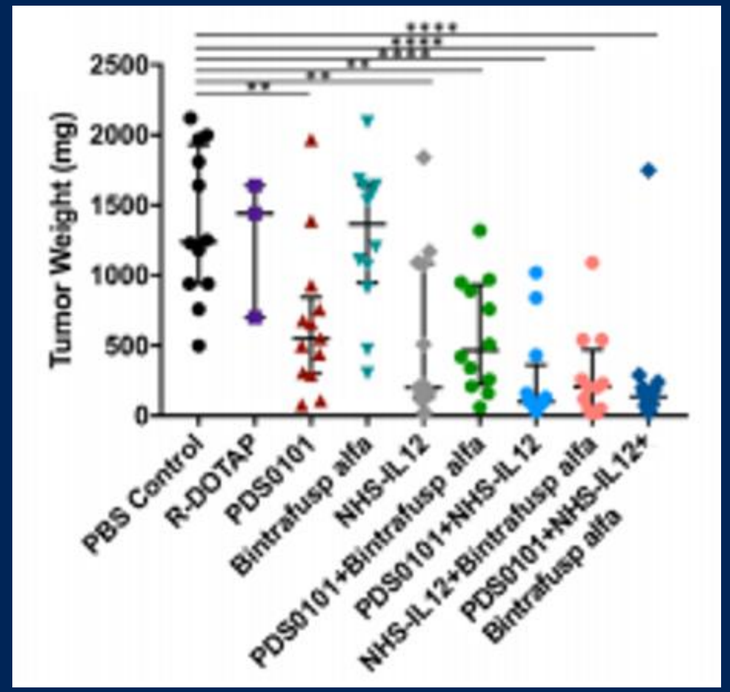
- Tumor targeting IL12 immunocytokine
- Composed of two IL12 heterodimers fused to NHS76 antibody which binds to histones on free DNA fragments found in areas of tumor necrosis
- In phase 1 trial in patients with advanced solid tumors the most frequently observed AEs included flu like symptoms and asymptomatic lab abnormalities (e.g. mild cytopenias and liver enzyme elevations) [1]
- M9241 treatment resulted in increased T cell infiltration in the TME

1.Strauss J, et al. Clin Cancer Res. 2019 Jan 1;25(1):99-109

Preclinical Combo of PDS0101, M9241 & Bintrafusp alfa







- Single, double and triple combinations were evaluated in a TC-1 HPV16+ tumor model
- Triple combination generated the maximum HPV-specific immune response, T cell infiltration in the TME and tumor reduction[1]

1.Rumfield C, J Immunother Cancer. 2020 Jun;8(1):e000612

Study Design

- Patients with advanced HPV-related cancers received the combination of bintrafusp alfa at 1200 mg flat dose i.v. q 2wks, M9241 at 16.8 mcg/kg s.c. q 4 wks and PDS0101 given as two separate 0.5 ml s.c. injections q 4 wks [NCT04287868]
- Dose reductions of M9241 to 8 mcg/kg were allowed as well as skipped doses of agent(s) for toxicities
- HPV genotyping was done with PCR based assays (BD Onclarity or Molecular MD) if testing not already done

Population

- Cervical
- Anal
- P16+ oropharyngeal
- Other HPV-associated

Endpoints

Primary: ORR
Secondary: safety

Treatment until confirmed progression, unacceptable toxicity, or any criteria for withdrawal; treatment past progression was allowed

Results

	All patients N=25
Age, median (range), years	50 (37-80)
Female, n (%)	17 (68)
Tumor type, n (%)	
Cervical	10 (40)
Anal	6 (24)
Head & Neck SCC	6 (24)
Vulvar/ Vaginal	3 (12)
Number of prior anticancer therapies, n (%)	
1	5 (20)
2	11 (44)
≥3	9 (36)
Prior chemotherapy, n (%)	25 (100)
Prior radiotherapy, n (%)	24 (96)
Prior PD-(L)1 inhibitor therapy, n (%)	14 (56)
HPV status, n (%)	
HPV 16	18 (72)
HPV type other than 16	6 (24)
Negative	1 (4)

Key baseline patient and disease characteristics

- As of 01 MAR 2021, 25 patients had received the triple combination of PDS0101, M9241 & bintrafusp alfa
  - The median follow-up is 8 months

Results

	All patients N=25
	Grade ≥2
Treatment-related adverse events (TRAEs)	23 (92)
TRAEs leading to discontinuation of ≥ 1 drug(s)	5 (20)
Treatment-related serious AEs	7 (28)
TRAEs in ≥5% of patients	
Anemia	12 (48)
Lymphocyte decrease	7 (28)
Flu like symptoms	6 (24)
Injection site reactions	5 (20)
Hematuria	4 (16)
AST/ ALT/ Alk phos elevation	4 (16)
Keratoacanthomas	4 (16)
Leukocyte decrease	3 (12)
Maculopapular rash	3 (12)
Pruritis	3 (12)
Nausea/ vomiting	3 (12)
Mucositis	3 (12)
Hypothyroidism	3 (12)
Peripheral motor neuropathy	2 (8)
Fatigue	2 (8)

1. **Hemophagocytic lymphohistiocytosis**

Safety summary

- Grade 3 TRAEs occurred in 10 (40%) patients
  - anemia due to hematuria (n=4), AST/ALT elevation (n=2); flu like symptoms (n=1), nausea/ vomiting (n=1), leukopenia (n=1), lymphopenia (n=2), HLH[1] (n=1)
- All four patients with grade 3 hematuria had cervical ca with prior pelvic RT + brachytherapy
- One patient with transient grade 3 leukopenia and lymphopenia also had transient grade 4 neutropenia
- 4 patients who originally had grade 3 toxicities with the triple combo including M9241 at 16.8 mcg/kg tolerated the triple combo with M9241 at 8 mcg/kg w/o any further grade ≥3 toxicities
- No treatment-related deaths occurred

Results

	All patients N=25	HPV 16+ N=18	HPV 16+ CPI Naïve N=6	HPV 16+ CPI Refractory N=12
BOR, n (%)				
Complete response (CR)	2 (8)	2 (11.1)	1 (16.7)	1 (8.3)
Partial response (PR)	8 (32)	8 (44.4)	4 (66.7)	4 (33.3)
ORR (CR+PR), n (%)	10 (40)	10 (55.6)	5 (83.3)	5 (41.7)
Disease Reduction, n (%)	13 (52)	12 (66.7)	5 (83.3)	7 (58.3)
Ongoing response, n/n (%)	8/10 (80)	8/10 (80%)	4/5 (80%)	4/5 (80%)
Overall Survival, n/n (%)*	20/25 (80)	16/18 (88.9)	6/6 (100)	10/12 (83.3)

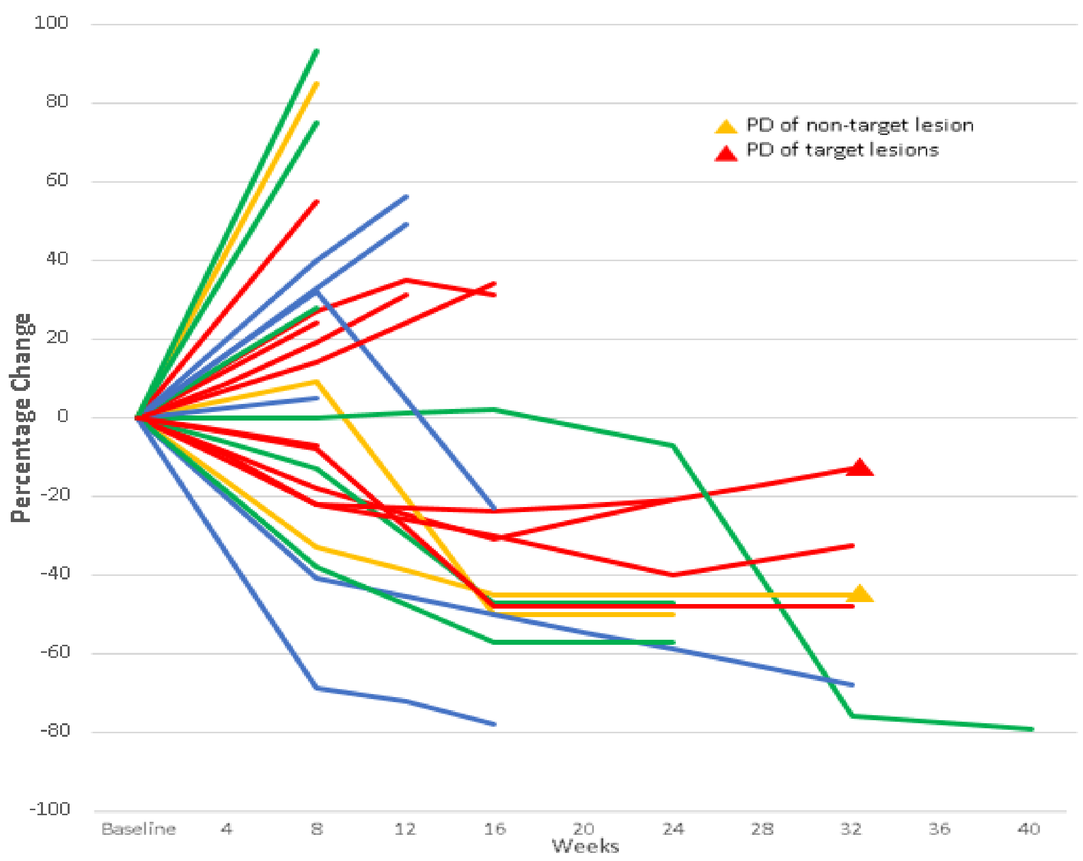
* Median 8 months of follow up

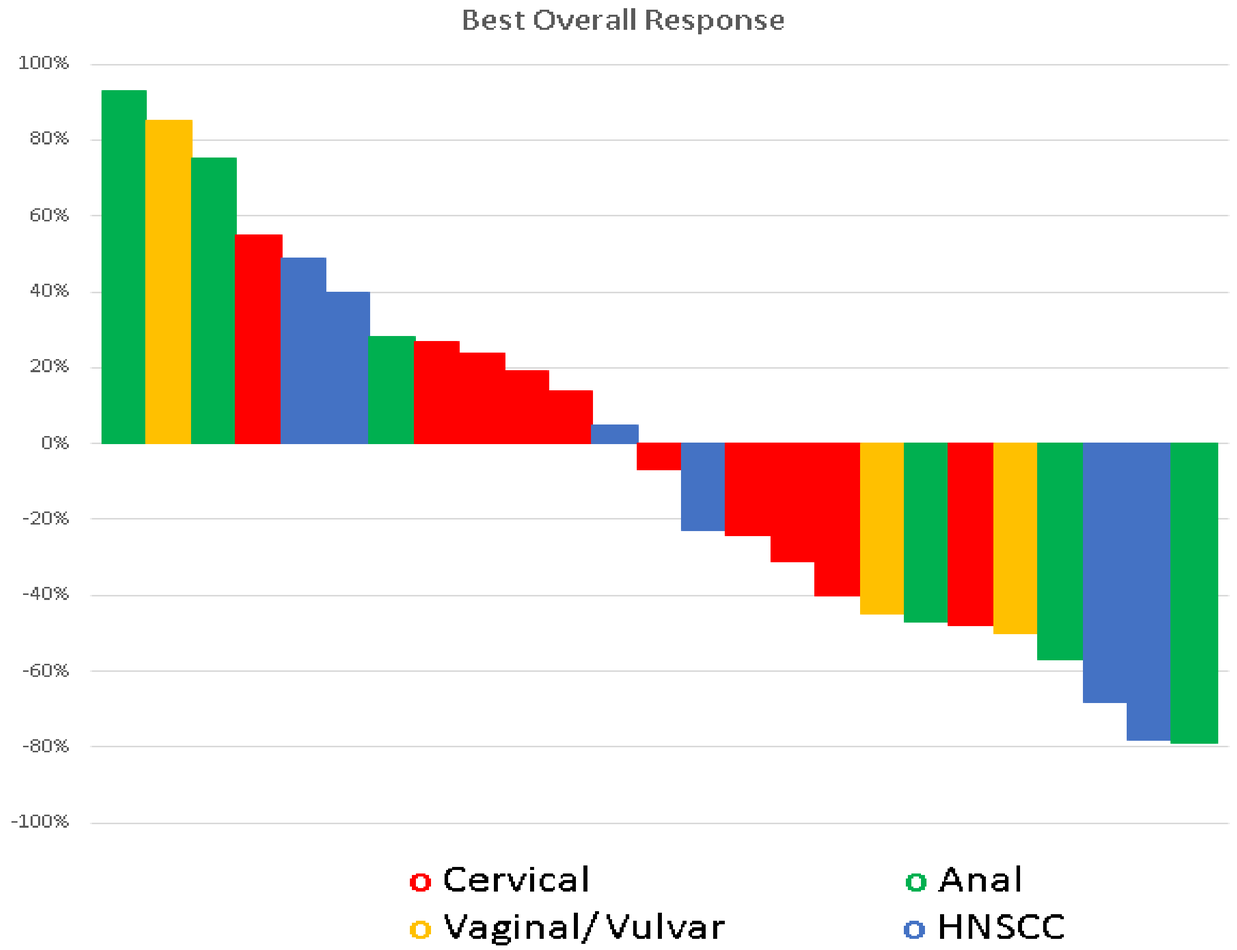
Patient Outcomes

- ORR 55.6% (tumor reduction 66.7%) in HPV 16+ disease
- ORR 83.3% in CPI *naïve* HPV 16+ disease
- ORR 41.7% (tumor reduction 58.3%) in CPI *refractory* HPV 16+ disease
- After a median 8 months of follow up:
  - 80% of responses are ongoing
  - 6/6 (100%) pts with HPV 16+ CPI naïve disease remain alive (historical median OS is 7-11 mo)[1-6]
  - 10/12 (83.3%) pts with HPV 16+ CPI refractory disease remain alive (historical median OS is 3-4 mo) [7]

1. Bauml J, et al. *J Clin Oncol* 2017;35:1542–49; 2. Ott PA, et al. *Ann Oncol.* 2017;28:1036–41; 3. Mehra R, et al. *Br J Cancer.* 2018;119:153–59; 4. Ferris RL, et al. *N Engl J Med*. 2016;375:1856–67;
5. Morris VK, et al. *Lancet Oncol*. 2017;18:446–53; 6. Chung HC, et al. *J Clin Oncol* 2019;37: 1470-8; 7. Strauss J, et al. J Immunother Cancer. 2020 Dec;8(2):e001395

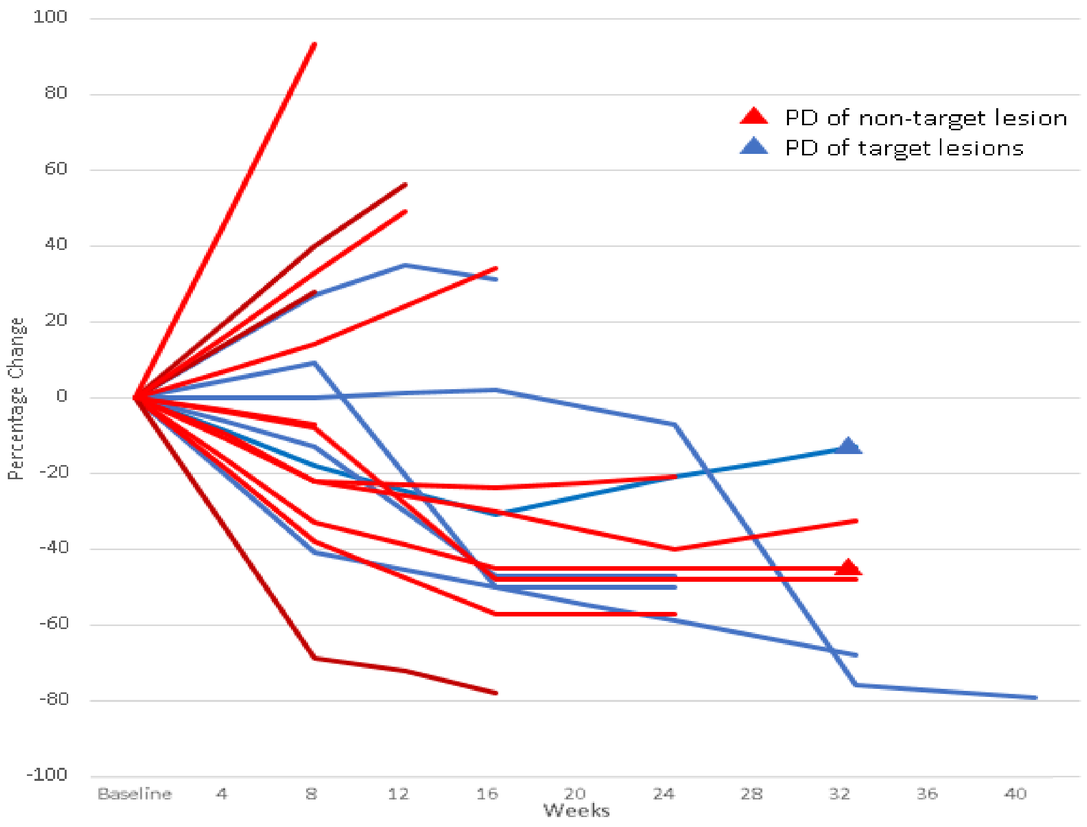
Results

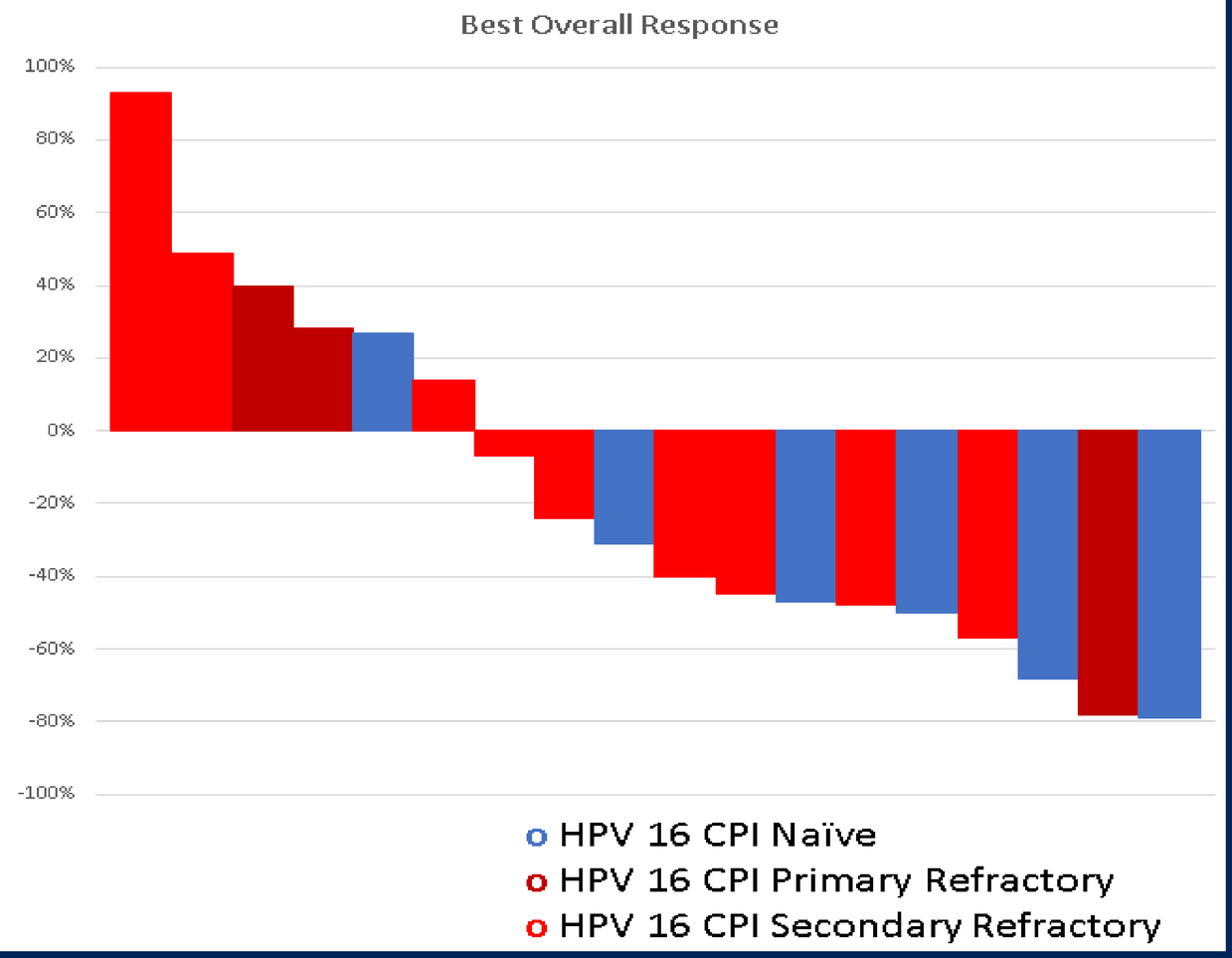




- Responses in HPV 16+ disease occurred irrespective of tumor type

Results





- Overwhelming majority of HPV 16+ CPI naive pts had a response
- Majority of HPV 16+ CPI refractory pts had tumor shrinkage

Primary Refractory: Prior PD or SD < 6 months
Secondary Refractory: Prior PR or SD > 6 months

Conclusions

- Triple combination of PDS0101, M9241 and bintrafusp alfa appears to have a manageable safety profile along with early evidence of notable clinical activity for pts with advanced HPV 16+ malignancies

- Clinical activity noted irrespective of tumor type or CPI status
- ORR was 55.6% (tumor reduction 66.7%) in all pts with advanced HPV 16+ disease
- ORR was 83.3% in patients with CPI *naive* HPV 16+ disease
- ORR was 41.7% (tumor reduction 58.3%) in patients with CPI *refractory* HPV 16+ disease

- After a median 8 months of follow up:
  - 80% of responses are ongoing
  - 6/6 (100%) pts with HPV 16+ CPI naïve disease remain alive
  - 10/12 (83.3%) pts with HPV 16+ CPI refractory disease remain alive

- Accrual is ongoing to the triple combination [NCT04287868]

Acknowledgments

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Disclosures

Will be added by ASCO