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Long-term follow-up of patients with human papillomavirus (HPV)–associated malignancies treated with bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1

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Declaration of interests

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HPV-associated malignancies

- HPV infections cause most cervical, anogenital, and oropharyngeal cancers[1]
- Approximately 690,000 new cases of HPV-related cancers are reported worldwide annually; 35,000 are reported in the USA[1,2]
- Over the last 16 years, the incidence of noncervical HPV-related cancers has increased significantly[3]

PD-(L)1 inhibitors

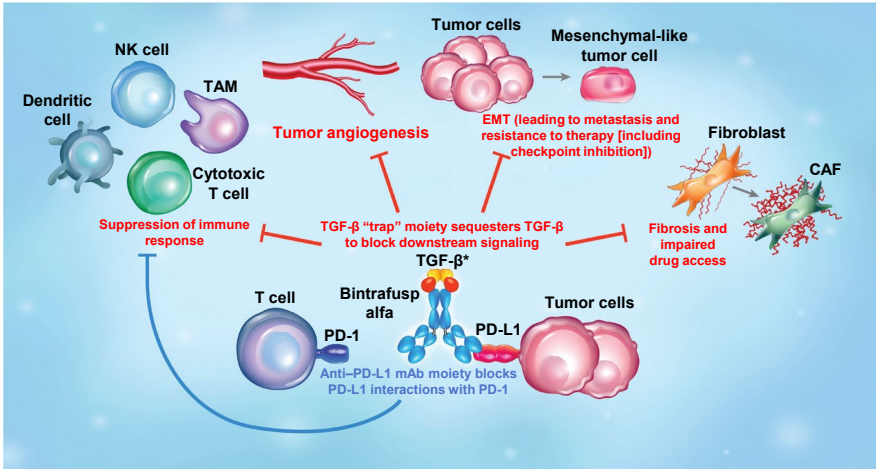
- PD-(L)1 expression has been positively associated with HPV infection in patients with HPV-related cancers[4,5]
- Anti–PD-(L)1 agents have shown activity in patients with recurrent or metastatic HPV-associated malignancies; however, median OS remains ≤12 months[6-10]

HPV, human papillomavirus; OS, overall survival. 1. De Martel C, et al. *Lancet Glob Health*. 2020;8(2):e180-90; 2. Senkomago V, et al. MMWR Morb Mortal Wkly Rep. 2019;68(33):724-8; 3. Liao C-I, et al. ASCO 2021:Abstract 107; 4. Yang W, et al. *J Obstet Gynaecol Res*. 2017;43:1602-12; 5. Ritprajak P and Azuma M. *Oral Oncol*. 2015;51:221-8; 6. Mehra R, et al. *Br J Cancer*. 2018;119(2):153-9; 7. Morris VK, et al. *Lancet Oncol*. 2017;18(4):446-53; 8. Chung HC, et al. SGO 2021:Abstract 10440; 9. Bauml J, et al. *J Clin Oncol*. 2017;35(14):1542-9; 10. Tewari KS, et al. ESMO Virtual Plenary May 2021:Abstract VP4-2021.

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

- HPV infection has been linked to upregulation of tumor TGF-β signaling[1]
- Inhibition of TGF-β activity while simultaneously blocking PD-L1 may be a novel and effective treatment option for patients with HPV-associated malignancies[2,3]
- Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the human TGF-βRII to function as a TGF-β "trap" fused to a human IgG1 antibody blocking PD-L1[2]

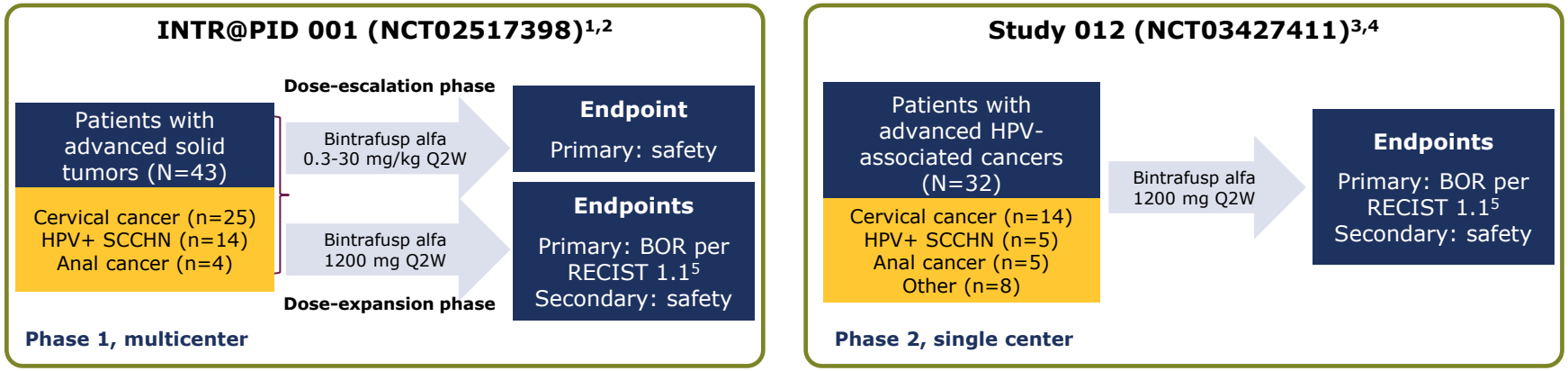
Proposed mechanism of action



CAF, cancer-associated fibroblast; EMT, epithelial-mesenchymal transition; HPV, human papillomavirus; IgG1, immunoglobulin G1; NK, natural killer; TAM, tumor-associated macrophage. *Tumor cells are also a major source of TGF-β in the microenvironment. 1. Torres-Poveda K, et al. *World J Clin Oncol*. 2014;5(4):753-63; 2. Lan Y, et al. *Sci Transl Med*. 2018;10:eaan5488; 3. Knudson KM, et al. *Oncoimmunology*. 2018;7:e1426519.

INTR@PID 001 and study 012: study designs

Patients with immune checkpoint inhibitor–naive, HPV-associated advanced malignancies who had exhausted standard-of-care treatment were included[1-4]



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

BOR, best overall response; HPV, human papillomavirus; Q2W, every 2 weeks; SCCHN, squamous cell carcinoma of the head and neck. 1. Strauss J, et al. *Clin Cancer Res*. 2018;24:1287-95; 2. ClinicalTrials.gov. Accessed July 20, 2021. https://clinicaltrials.gov/ct2/show/NCT02517398; 3. Strauss J, et al. *J Immunother Cancer*. 2020;8:e001395; 4. ClinicalTrials.gov. Accessed July 20, 2021. https://clinicaltrials.gov/ct2/show/NCT03427411; 5. Eisenhauer EA, et al. *Eur J Cancer*. 2009;45:228-47.

INTR@PID 001 and study 012

Previously reported pooled results:[1]

	Overall (n=59)
Confirmed ORR per RECIST 1.1 (95% CI), %	30.5 (19.2-43.9)
Median PFS (95% CI), months	2.8 (1.4-5.5)
Median OS (95% CI), months	NR (8.6-NR)
Any-grade TRAEs, %	83.1
Grade 3 TRAEs, %	27.1

Database cutoff: phase 1 (17 Apr 2019) and phase 2 (4 Oct 2019)

- Bintrafusp alfa 0.3-30 mg/kg Q2W or 1200 mg Q2W (RP2D) demonstrated clinical activity and manageable safety in patients with HPV-associated malignancies[1]

Objective of current analysis:

To report longer follow-up results using pooled data from these original patients and an additional 16 patients enrolled in study 012

Database cutoff: phase 1 (15 May 2020) and phase 2 (22 Dec 2020)

HPV, human papillomavirus; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event. 1. Strauss J, et al. *J Immunother Cancer*. 2020;8:e001395.

Baseline characteristics

	All patients (N=75)
Age, median (range), years	56.0 (30-84)
Sex, n (%)	
Male	20 (26.7)
Female	55 (73.3)
No. of prior anticancer therapies, n (%)	
1	26 (34.7)
2	22 (29.3)
≥3	27 (36.0)
ECOG performance status, n (%)	
0	38 (50.7)
1	35 (46.7)
Missing	2 (2.7)
Primary tumor type, n (%)	
Cervical cancer	39 (52.0)
SCCHN	19 (25.3)
Anal cancer	9 (12.0)
Other*	8 (10.7)
HPV status, n (%)†	
Positive	67 (89.3)
Negative	4 (5.3)
Missing	4 (5.3)

- As of 15 May 2020 (phase 1) and 22 December 2020 (phase 2), 75 patients had received bintrafusp alfa for a median duration of 3.2 months (range, 0.5-29.9 months)
- The median follow-up to data cutoff was 33.0 months (range, 6.5-51.6 months)
- At the time of this analysis, 3 patients remained on treatment
- 13 of 75 patients without progressive disease remained on study

ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PCR, polymerase chain reaction; SCCHN, squamous cell carcinoma of the head and neck. *Comprised of rectal cancer (n=3), vulvar cancer (n=2), neuroendocrine cervical cancer (n=1), penile cancer (n=1), and vaginal cancer (n=1). †In the dose-escalation cohort, HPV status was determined by PCR using the cobas 4800 HPV test. In the dose-expansion cohort, HPV status was determined by RNA sequencing or the investigators. In 012, HPV testing was an exploratory endpoint.

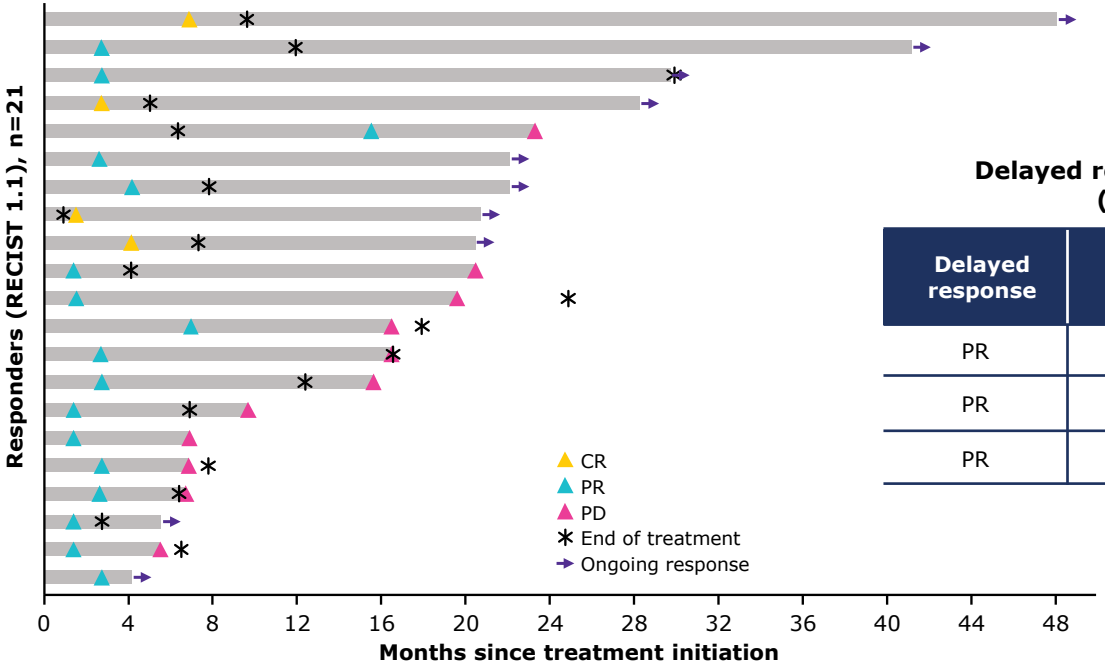
Bintrafusp alfa showed long-term efficacy at 33 months

	All patients (N=75)
BOR, n (%)	
CR	4 (5.3)
PR	17 (22.7)
SD	11 (14.7)
PD	36 (48.0)
NE	7 (9.3)
Delayed PR	3 (4.0)
Confirmed ORR (CR + PR), n (%)	21 (28.0)
95% CI	(18.2-39.6)
DCR (CR + PR + SD), n (%)	32 (42.7)
Total clinical response rate (ORR + delayed PR), n (%)	24 (32.0)
DOR, median (range), months	17.3 (1.4-41.2)
Durable response ≥6 months, n/n (%)	15/21 (71.4)
Durable response ≥12 months, n/n (%)	12/21 (57.1)
Ongoing response, n/n (%)	10/21 (47.6)

- The updated confirmed ORR was 28.0% in patients with HPV-associated malignancies
- An additional 3 patients had a PR after initial disease progression

BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; HPV, human papillomavirus; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Responses to bintrafusp alfa were durable



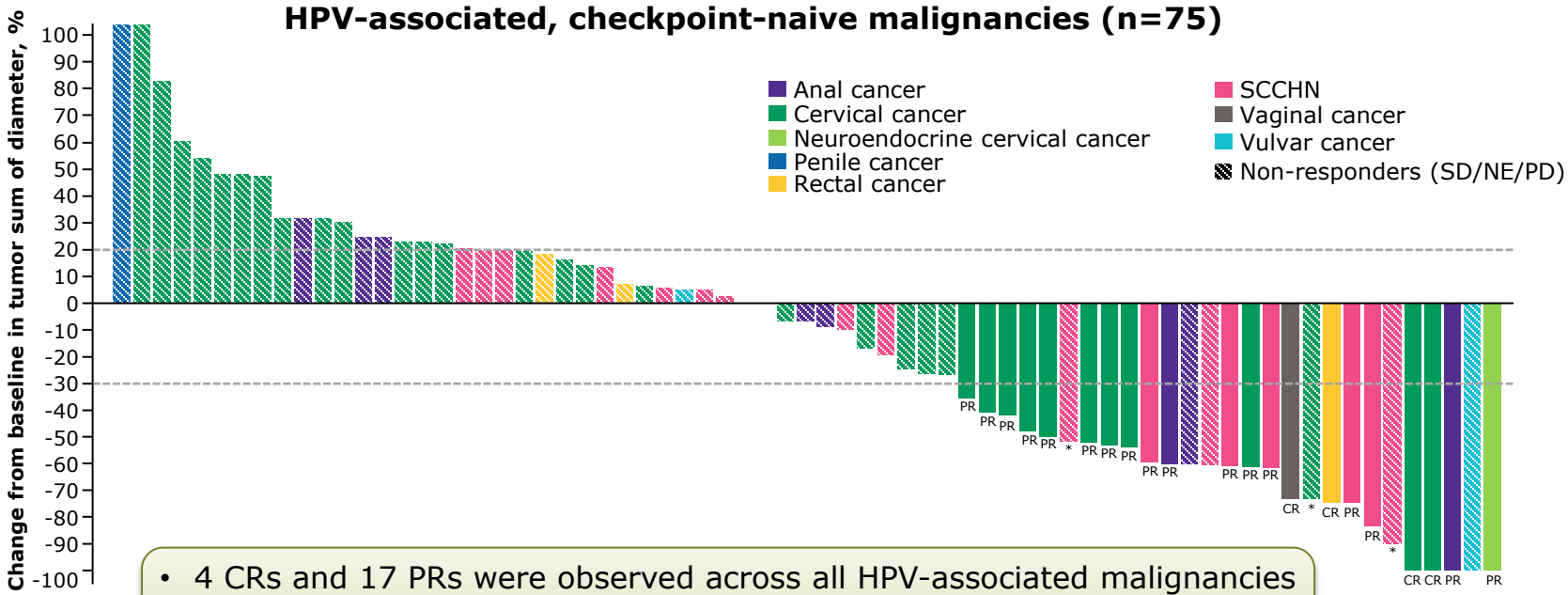
Delayed responders after initial PD (by investigator)

Delayed response	Time to delayed response, months	Duration of response, months
PR	7.1	23.7
PR	4.1	6.1
PR	8.5	15.9

At the time of this analysis, all patients were alive and 10 of 21 responses (47.6%) were ongoing

CR, complete response; PD, progressive disease; PR, partial response.

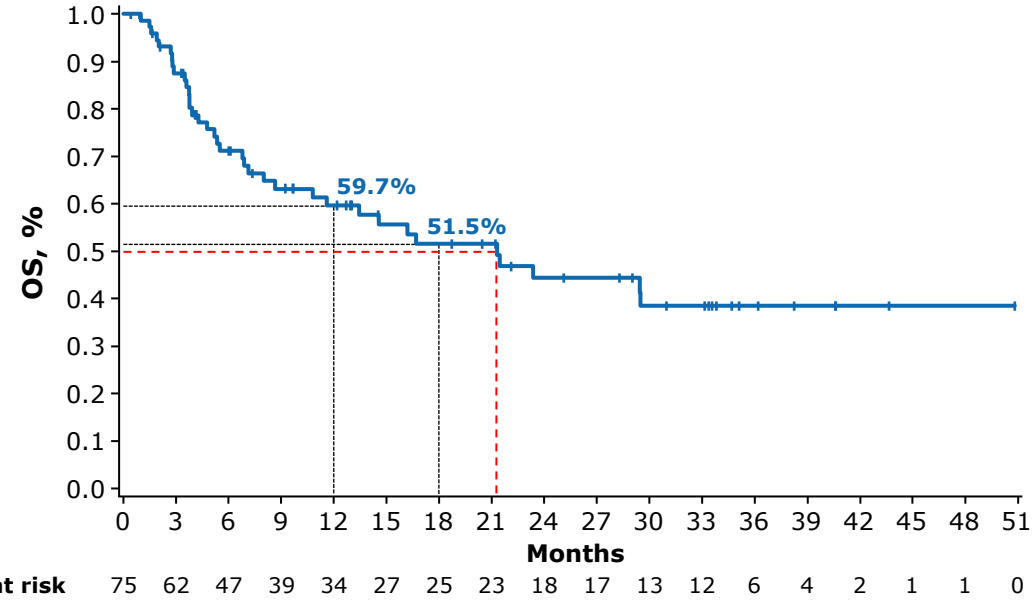
Responses occurred across HPV-associated malignancies



- 4 CRs and 17 PRs were observed across all HPV-associated malignancies
- Responses were observed across tumor types: anal, cervical, neuroendocrine cervical, rectal, vaginal, and SCCHN

CR, complete response; HPV, human papillomavirus; NE, not evaluable; PD, progressive disease; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.
*Delayed PR. Due to an objective response of PD before onset of response, these patients did not meet response criteria by RECIST 1.1.

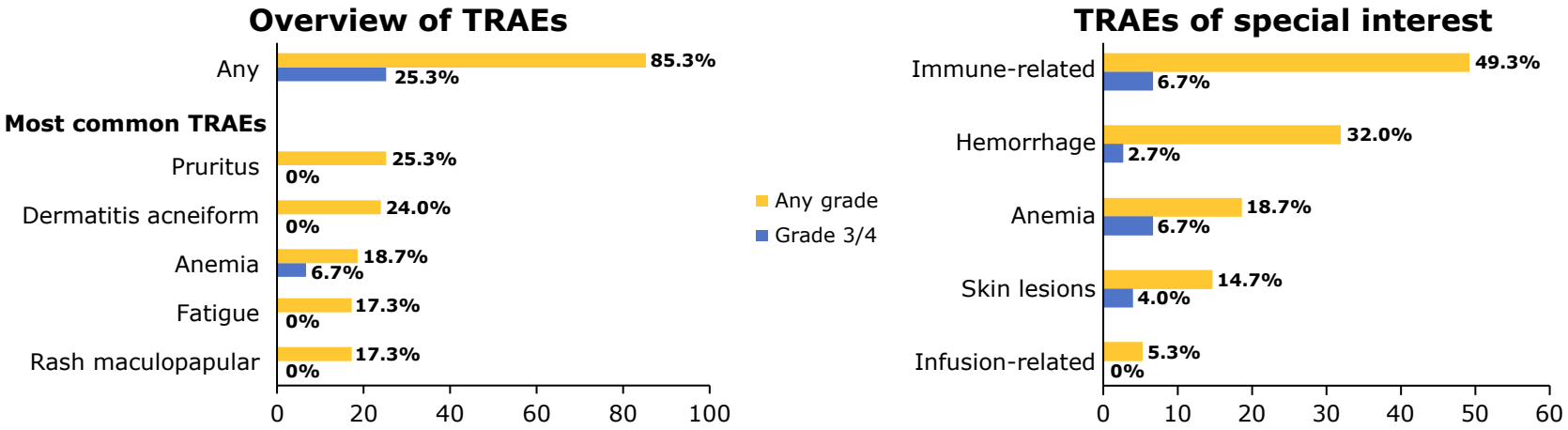
Median OS was 21.3 months



- Median OS was 21.3 months (95% CI, 10.8-NR); OS rate was 59.7% at 12 months and 51.5% at 18 months
- Median PFS was 2.8 months (95% CI, 1.4-4.1); PFS rate was 23.7% at 12 months and 18.6% at 18 months

NR, not reached; OS, overall survival; PFS, progression-free survival.

Bintrafusp alfa had a manageable safety profile



- No treatment-related deaths were reported
- TRAEs led to discontinuation in 9 patients (12.0%)
- Grade 4 TRAEs occurred in 2 patients (2.7%); hypokalemia and blood creatine phosphokinase increase (n=1 each)

TRAE, treatment-related adverse event.

Summary and conclusions

Bintrafusp alfa showed long-term efficacy and a manageable safety profile in patients with pretreated, immune checkpoint inhibitor–naive, HPV-associated malignancies

ORR

Median OS

21.3 MONTHS

Median DOR

17.3 MONTHS

Grade 3/4 TRAEs

- **The need for effective treatment options in patients with HPV-associated malignancies is high; therefore, these results showing efficacy of bintrafusp alfa across different HPV-related tumor types are of interest**
- **Clinical trials of bintrafusp alfa in HPV-associated malignancies are ongoing**

DOR, duration of response; HPV, human papillomavirus; ORR, objective response rate; OS, overall survival; TRAE, treatment-related adverse event.

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