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EVALUATION OF BINTRAFUSP ALFA, A BIFUNCTIONAL FUSION PROTEIN TARGETING TGF-β AND PD-L1, IN CERVICAL CANCER: DATA FROM PHASE 1 AND PHASE 2 STUDIES

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Introduction

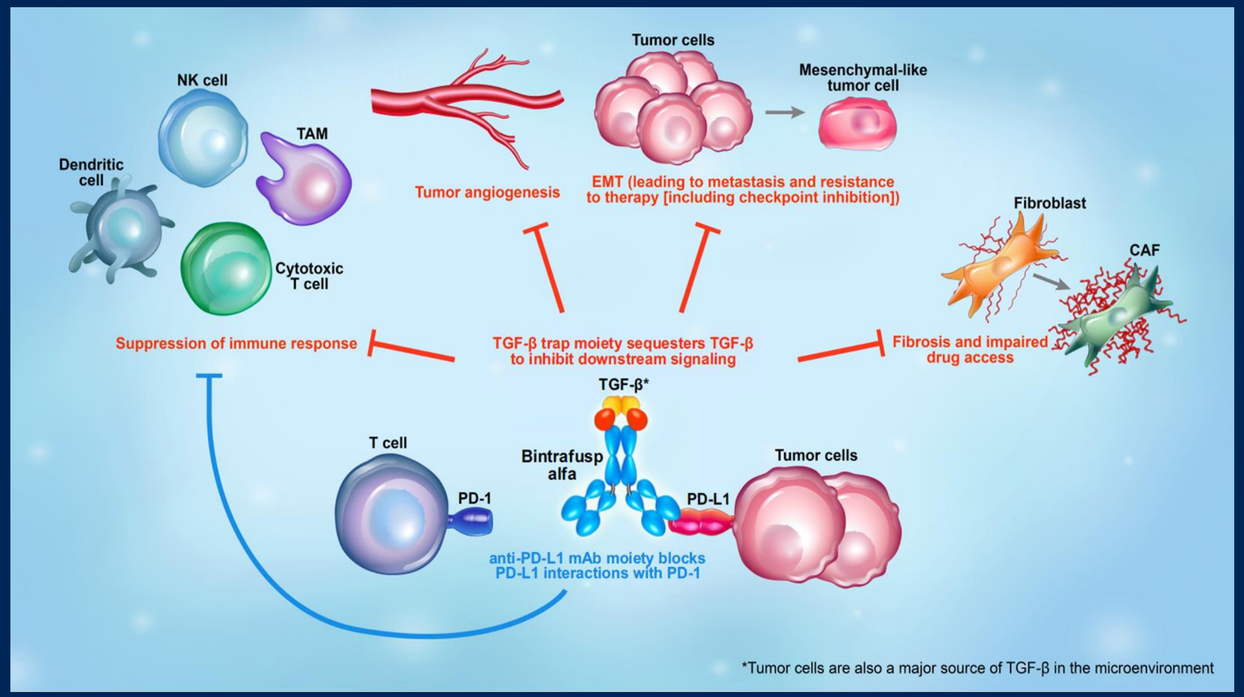
- HPV infection is implicated in 99% of cervical cancers; squamous cell carcinoma typically accounts for 70-80% of cervical cancers and adenocarcinoma for 20-25%[1]
- PD-(L)1 expression has been positively associated with HPV infection in patients with cervical cancer[2]
- Pembrolizumab, a PD-1 inhibitor, received accelerated FDA approval for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1; approval was based on an ORR of 14.3% in the KEYNOTE-158 study[3,4]
  - The ORR was 12.2% in the total population[3]
    - Among the 12 responders, only 1 had adenocarcinoma, and 2 had received prior bevacizumab,[3] which is considered the preferred first-line regimen for a majority of patients with cervical cancer[1]
  - In an updated analysis, the ORR was 17.1% in the PD-L1–positive cohort and was 14.3% in the total population[5]
- The limited response to pembrolizumab, including in the PD-L1–positive cohort, indicates a continued unmet need[3,5]
- HPV infection is also linked to upregulation of TGF-β signaling[6]
  - Genome-wide association studies showed that TGF-βR1 is significantly overexpressed in cervical cancer[7]

FDA, US Food and Drug Administration; HPV, human papillomavirus; ORR, objective response rate.

1. Marth C, et al. Ann Oncol. 2017;28:iv72-83; 2. Yang W, et al. J Obstet Gynaecol Res. 2017;43:1602-12; 3. Chung HC, et al. J Clin Oncol. 2019;37:1470-8; 4. Keytruda (pembrolizumab). Prescribing information. Merck & Co, Inc; 2021; 5. Chung HC, et al. SGO 2021: Abstract 10440; 6. Torres-Poveda K, et al. World J Clin Oncol. 2014;5:753-63; 7. Levovitz C, et al. Cancer Res. 2014;74:6833-44.

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

Proposed mechanism of action[1,2]



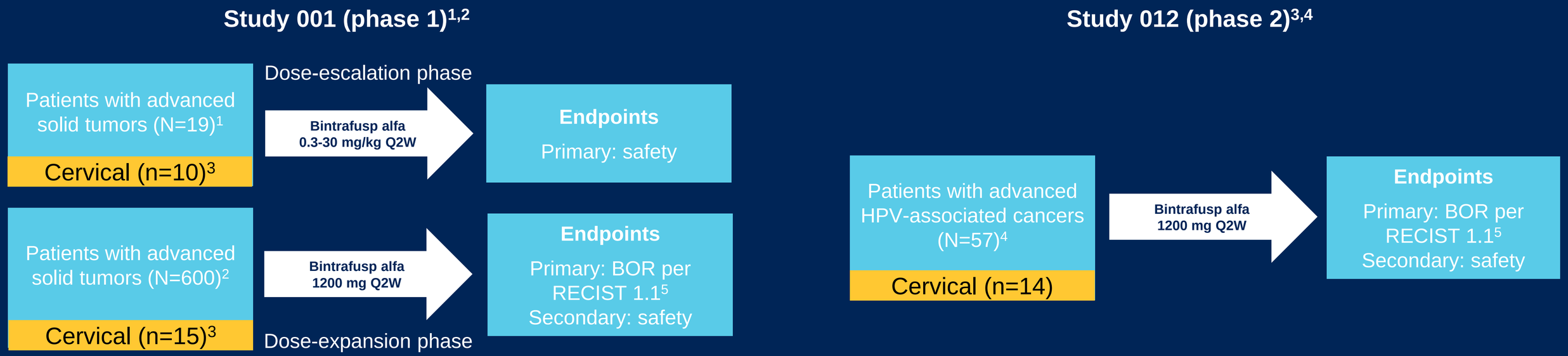
- Inhibition of TGF-β activity while simultaneously blocking an additional immunosuppressive cellular mechanism, e.g. the PD-L1 pathway, may provide a novel treatment approach[2,3]
- Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 monoclonal antibody blocking PD-L1[2]
- Colocalized, simultaneous inhibition of two nonredundant immunosuppressive pathways in the tumor microenvironment might enhance the anticancer effect observed with independent blockade of either pathway alone or in combination[2]

CAF, cancer-associated fibroblast; EMT, epithelial-mesenchymal transition; NK, natural killer; TAM, tumor-associated macrophage.

1. Birrer MJ, et al. ESMO 2018: Abstract 879TiP; 2. Lan Y, et al. Sci Transl Med. 2018;10:eaan5488; 3. Knudson KM, et al. Oncoimmunology. 2018;7:e1426519.

Study Design

- In this post hoc pooled analysis, we report safety and efficacy from phase 1 (INTR@PID 001; NCT02517398) and phase 2 (study 012; NCT03427411) studies in patients with immune checkpoint inhibitor-naive, recurrent or metastatic cervical cancer treated with bintrafusp alfa monotherapy[1-4]



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

BOR, best overall response; Q2W, every 2 weeks.

1. Strauss J, et al. Clin Cancer Res. 2018;24:1287-95; 2. ClinicalTrials.gov. Accessed April 1, 2021. https://clinicaltrials.gov/ct2/show/NCT02517398; 3. Strauss J, et al. J Immunother Cancer. 2020;8:e001395; 4. ClinicalTrials.gov. Accessed April 1, 2021. https://clinicaltrials.gov/ct2/show/NCT03427411; 5. Eisenhauer EA, et al. Eur J Cancer. 2009;45:228-47.

Results

	All patients N=39
Age, median (range), years	55 (30-79)
ECOG performance status, n (%)	
0	17 (43.6)
1	21 (53.8)
Missing	1 (2.6)
Histology, n (%)	
Squamous cell carcinoma	25 (64.1)
Adenocarcinoma	12 (30.8)
Adenosquamous carcinoma	1 (2.6)
Neuroendocrine	1 (2.6)
No. of prior anticancer therapies, n (%)	
1	13 (33.3)
2	10 (25.6)
≥3	16 (41.0)
Prior platinum therapy, n (%)	39 (100)
Prior platinum doublet therapy, n (%)	34 (87.2)
Prior bevacizumab use, n (%)	25 (64.1)
Prior radiotherapy, n (%)	32 (82.1)
HPV status, n (%)	
Positive	32 (82.1)
Negative	3 (7.7)
Missing	4 (10.3)
Tumor cell PD-L1 expression, n (%)*	
≥1%	12 (30.8)
<1%	2 (5.1)
Missing/not done	25 (64.1)

Key baseline patient and disease characteristics

- As of May 15, 2020 (phase 1) and December 22, 2020 (phase 2), 39 patients had received bintrafusp alfa for a median duration of 2.8 months (range, 0.5-19.3)
  - The median follow-up to data cutoff was 35.0 months and 24.1 months for the phase 1 and phase 2 studies, respectively

*Detected by IHC staining of tumor tissue using an anti–PD-L1 clone 73-10 (Dako PD-L1 IHC 73-10 pharmDx)[1]. PD-L1 status was not captured in Study 001 dose-escalation cohort and Study 012.
IHC, immunohistochemistry.
1. Strauss J, et al. J Immunother Cancer. 2020;8:e001395.

Results

	All patients N=39
	Any grade*
Any TRAEs	33 (84.6)
Any TRAEs leading to discontinuation	5 (12.8)
Any treatment-related serious AEs	6 (15.4)
Any skin lesions†	5 (12.8)
Any TRAEs in ≥10% of patients	
Dermatitis acneiform	8 (20.5)
Anemia	7 (17.9)
Epistaxis	7 (17.9)
Maculopapular rash	6 (15.4)
Pruritus	6 (15.4)
Hypothyroidism	5 (12.8)
Diarrhea	4 (10.3)
Fatigue	4 (10.3)

Safety summary

- Grade ≥3 TRAEs occurred in 8 (20.5%) patients (anemia, colitis, gastroparesis, upper gastrointestinal hemorrhage, keratoacanthoma, cystitis noninfective, hematuria, pneumonitis, rash macular [n=1 each])
- Skin lesions were hyperkeratotic in nature
- A patient in the dose-escalation cohort (10 mg/kg) had grade 3 gastroparesis and developed asymptomatic grade 3 hypokalemia, which worsened to grade 4 and led to permanent treatment discontinuation
- No treatment-related deaths occurred

*Medical Dictionary for Regulatory Activities V23.0 was used for Study 001 and V20.0 for Study 012; †Defined as squamous cell carcinoma of skin (1 event observed), keratoacanthoma (4 events), hyperkeratosis, basal cell carcinoma (2 events), actinic keratosis (1 event), Bowen disease, and squamous cell carcinoma of the lip. One patient had keratoacanthoma, basal cell carcinoma, and actinic keratosis; another patient had keratoacanthoma and squamous cell carcinoma of skin.
TRAE, treatment-related adverse event.

Results

	All patients N=39
BOR, n (%)	
CR	2 (5.1)
PR	9 (23.1)
SD	3 (7.7)
PD	20 (51.3)
Not evaluable	5 (12.8)
Delayed PR	1 (2.6)
Confirmed ORR (CR + PR), n (%)	11 (28.2)
95% CI	15.0-44.9
DCR (CR + PR + SD), n (%)	14 (35.9)
Total clinical response rate (ORR + delayed PR), n (%)	12 (30.8)
Duration of response (confirmed ORR), median (range), months	11.7 (1.4-41.2)
Durable response ≥6 months, n/n (%)	8/11 (72.7)
Durable response ≥12 months, n/n (%)	5/11 (45.5)
Ongoing response, n/n (%)	5/11 (45.5)
Duration of ongoing response (range), months	1.4-41.2

CR, complete response rate; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.

Response and duration of response in all patients

- One patient had a delayed PR after initial disease progression and did not meet response criteria by RECIST 1.1
  - Duration of response was 23.7 months
- In patients who received at least 1 line of prior platinum doublet therapy (n=34), the ORR was 26.5% and the DCR was 32.4%

Results

	Tumor histology		Prior bevacizumab use	
	Squamous cell carcinoma n=24	Adenocarcinoma n=12	Yes n=25	No n=14
BOR, n (%)				
CR	1 (4.2)	1 (8.3)	2 (8.0)	0
PR	5 (20.8)	4 (33.3)	4 (16.0)	5 (35.7)
SD	3 (12.5)	0	2 (8.0)	1 (7.1)
PD	11 (45.8)	7 (58.3)	14 (56.0)	6 (42.9)
Not evaluable	4 (16.7)	0	3 (12.0)	2 (14.3)
Delayed PR*	1 (4.2)	0	1 (4.0)	0
Confirmed ORR (CR + PR), n (%)	6 (25.0)	5 (41.7)	6 (24.0)	5 (35.7)
95% CI	9.8-46.7	15.2-72.3	9.4-45.1	12.8-64.9

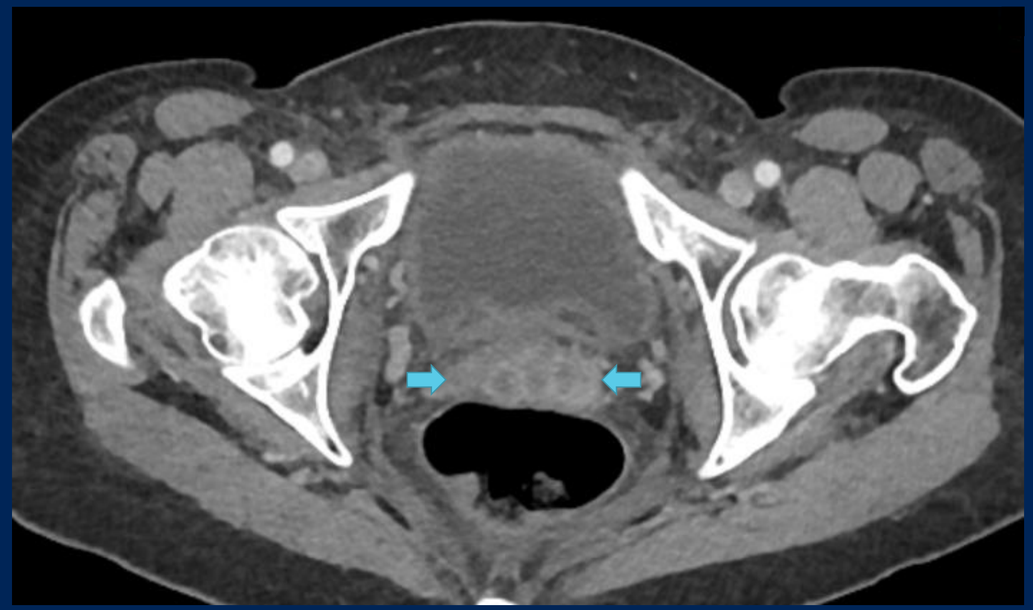
- Responses occurred irrespective of tumor histology or prior bevacizumab use

*Patient had a delayed PR after initial disease progression and did not meet response criteria by RECIST 1.1.

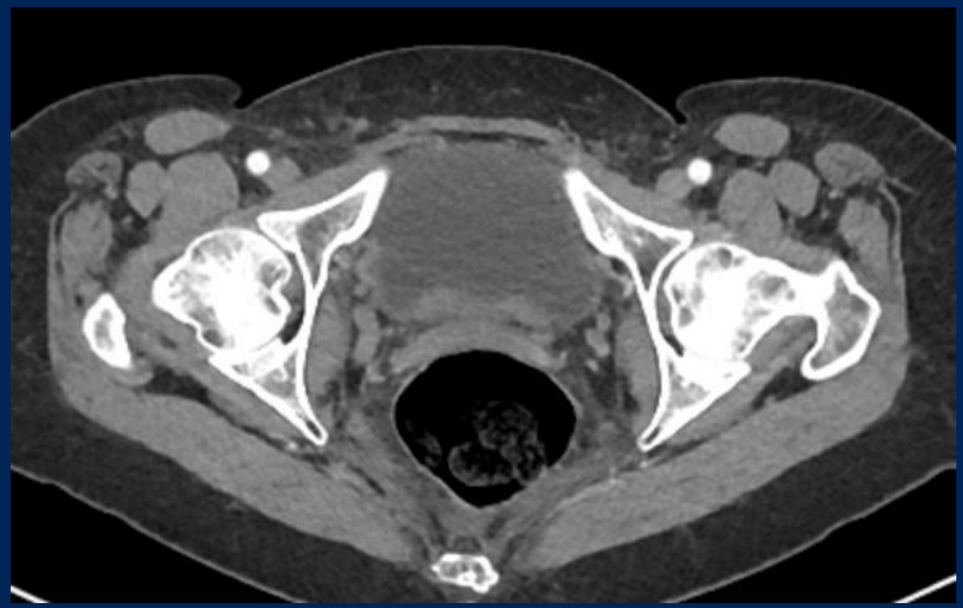
Results

Tumor reduction in target lesions in previously irradiated regions

- 4 patients had target lesions in previously irradiated regions; tumor reduction was observed in 3 different patients (2 in the cervix and 1 in the iliac node)

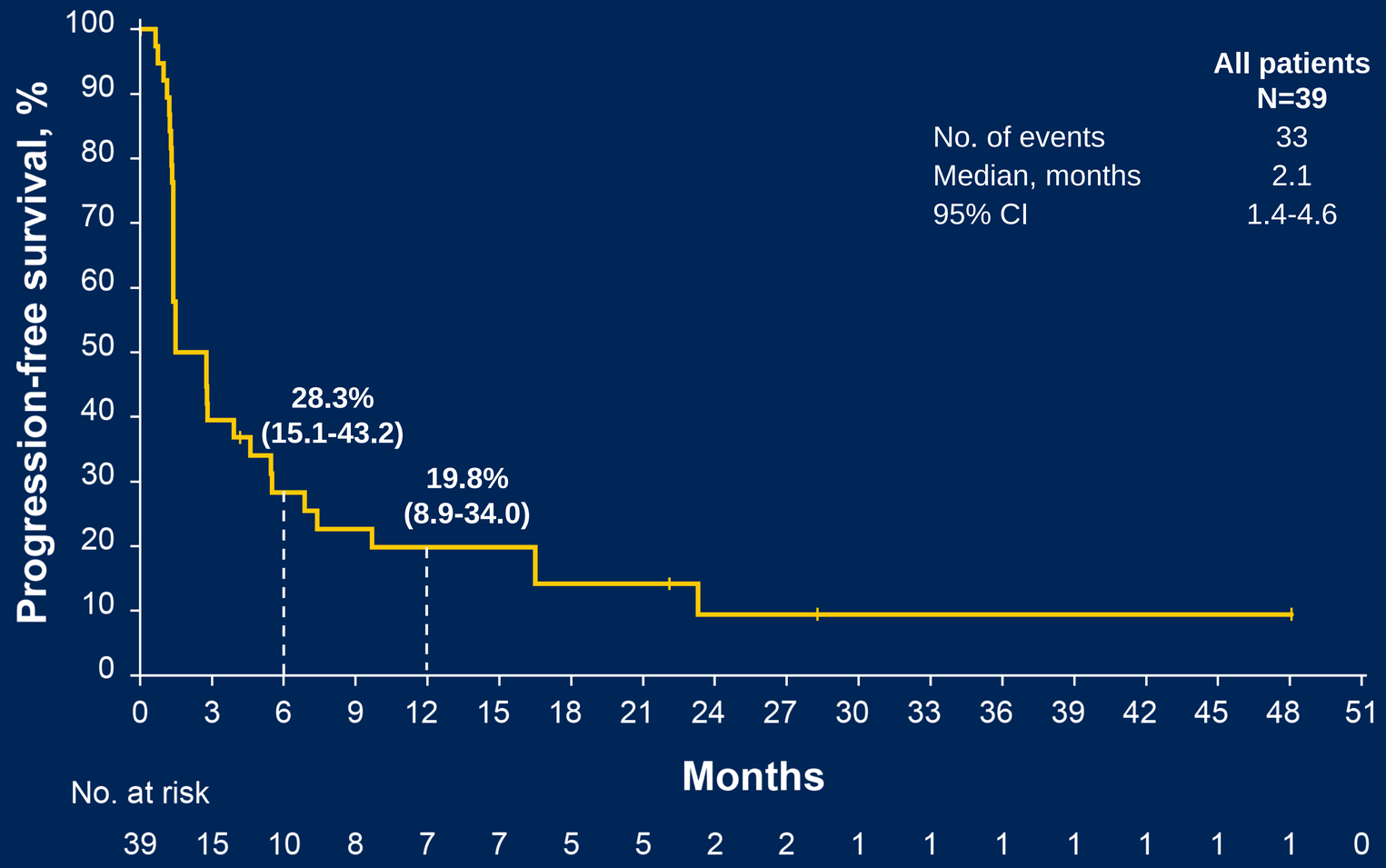


Baseline



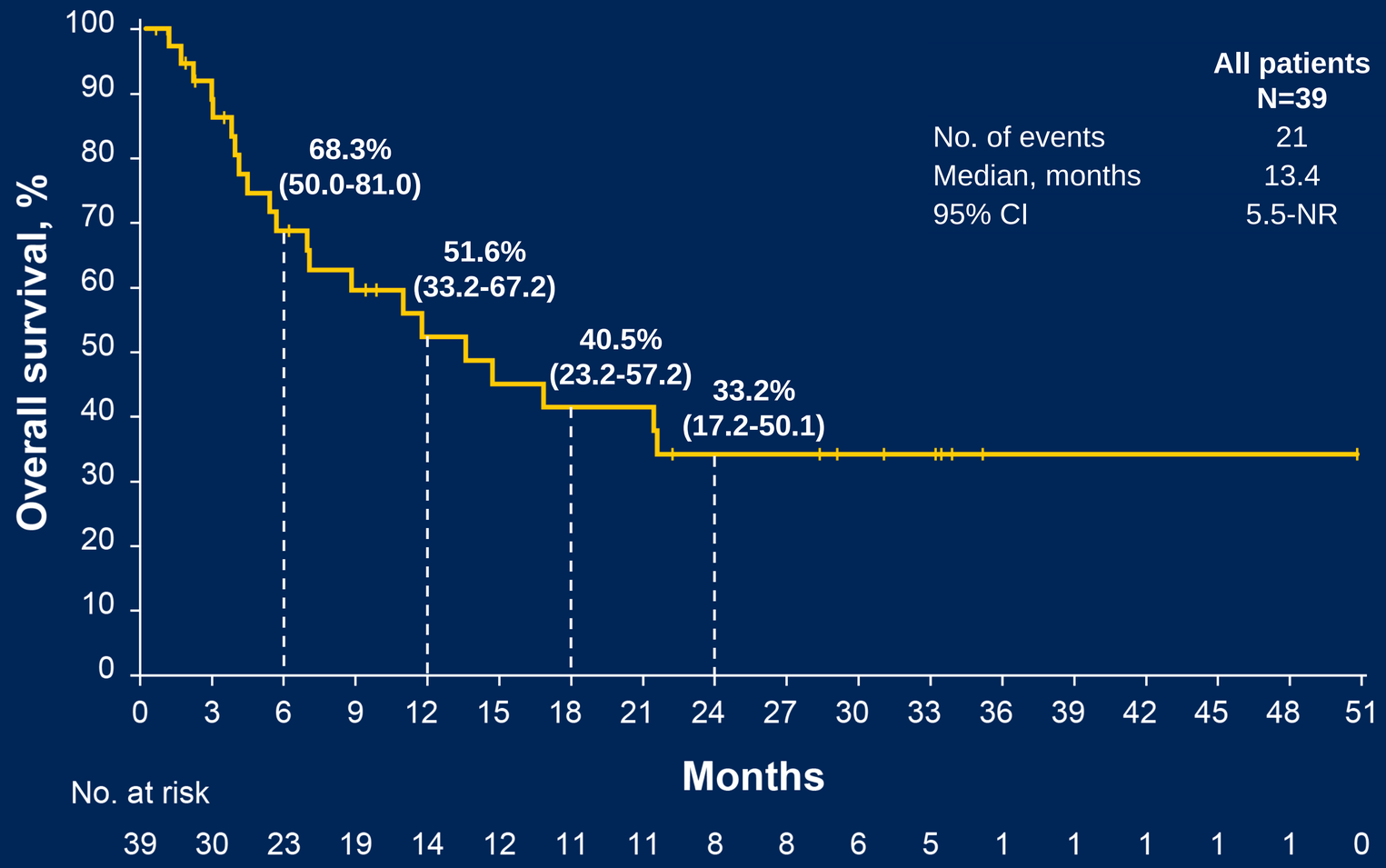
Post treatment

Progression-free Survival



	All patients N=39
No. of events	33
Median, months	2.1
95% CI	1.4-4.6

Overall Survival



Conclusions

- In this pooled analysis of patients from INTR@PID 001 and Study 012, responses to bintrafusp alfa were observed in patients with heavily pretreated, immune checkpoint inhibitor-naive cervical cancer, irrespective of tumor histology or prior bevacizumab treatment
  - Confirmed ORR was 28.2% in all patients, and 26.5% in patients who received at least a single line of platinum doublet therapy in a non-curative setting
  - Tumor reduction was observed in target lesions in previously irradiated regions
- Treatment with bintrafusp alfa showed median overall survival of 13.4 months in this patient population
- Overall, bintrafusp alfa showed promising clinical activity and manageable safety in patients with recurrent or metastatic cervical cancer, indicating that simultaneous inhibition of TGF-β and PD-L1 pathways warrants further investigation
- Additional trials assessing bintrafusp alfa in recurrent or metastatic cervical cancer are currently ongoing (INTR@PID 017 [NCT04246489] and INTR@PID 046 [NCT04551950])[1,2]

1. ClinicalTrials.gov. Accessed April 30, 2021. https://clinicaltrials.gov/ct2/show/NCT04246489; 2. ClinicalTrials.gov. Accessed April 30, 2021. https://clinicaltrials.gov/ct2/show/NCT04551950.

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