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Bintrafusp Alfa, a Bifunctional Fusion Protein Targeting TGF-β and PD-L1, in HPV–Associated Malignancies

SITC digital workshop "Global Access to Cancer Immunotherapy: Closing the Gaps"

December 10th, 2020

Claudia-N. Gann

Bintrafusp alfa

Designed to Simultaneously Inhibit TGF-β and PD-L1 Pathways

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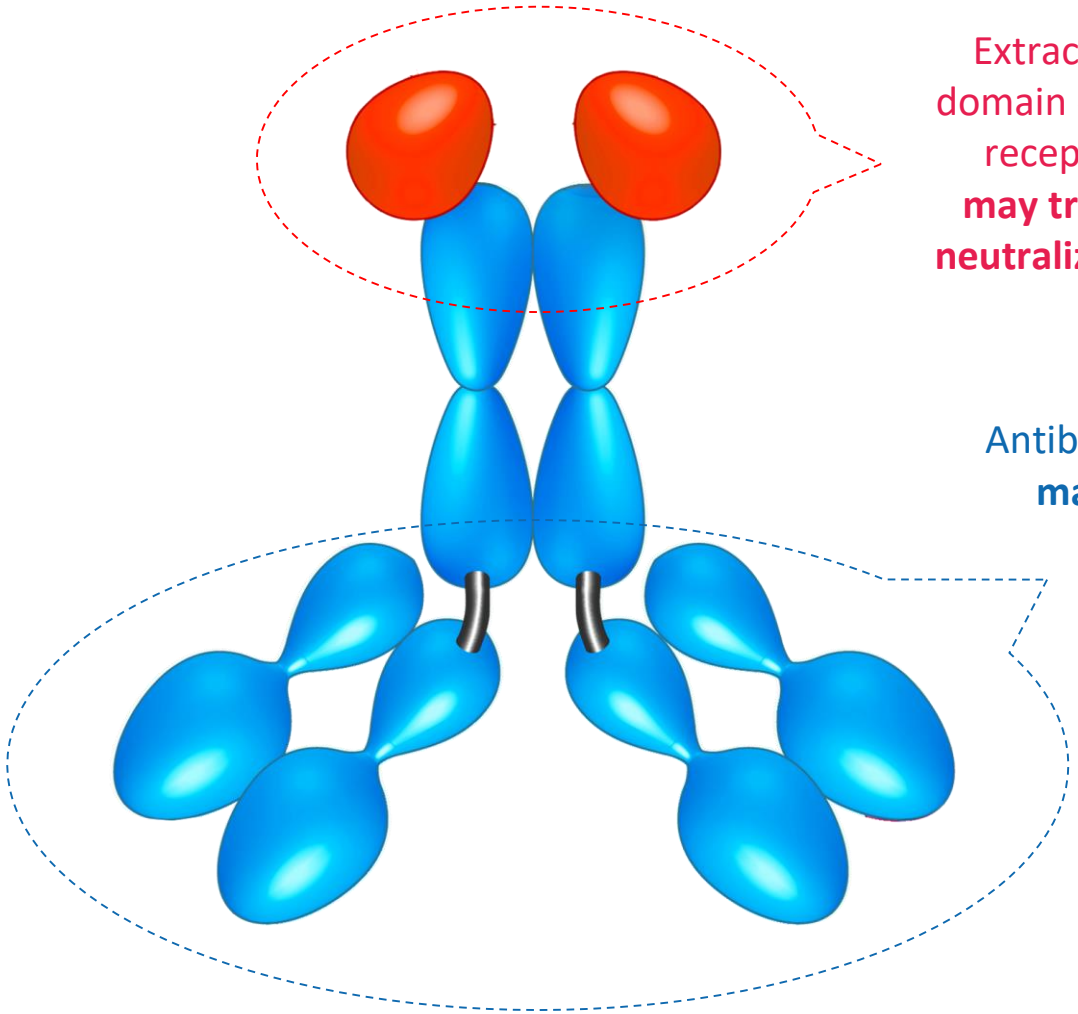
- **Bintrafusp alfa** is a **bifunctional fusion protein** composed of 2 extracellular domains of TGF-βRII to function as a TGF-β trap fused with a human IgG1 mAb against PD-L1
- Compared with 2 separate monotherapies, bintrafusp alfa is a bifunctional molecule which may achieve **localized and increased inhibition of TGF-β specifically in the TME, and inhibition of PD-L1**



As of March 2019, bintrafusp alfa is being jointly developed and commercialized in a **global alliance with GlaxoSmithKline**

Lan Y, et al. Sci Transl Med 2018;10(424):eaan5488

Bintrafusp alfa - Proposed mechanism of action based on preclinical studies

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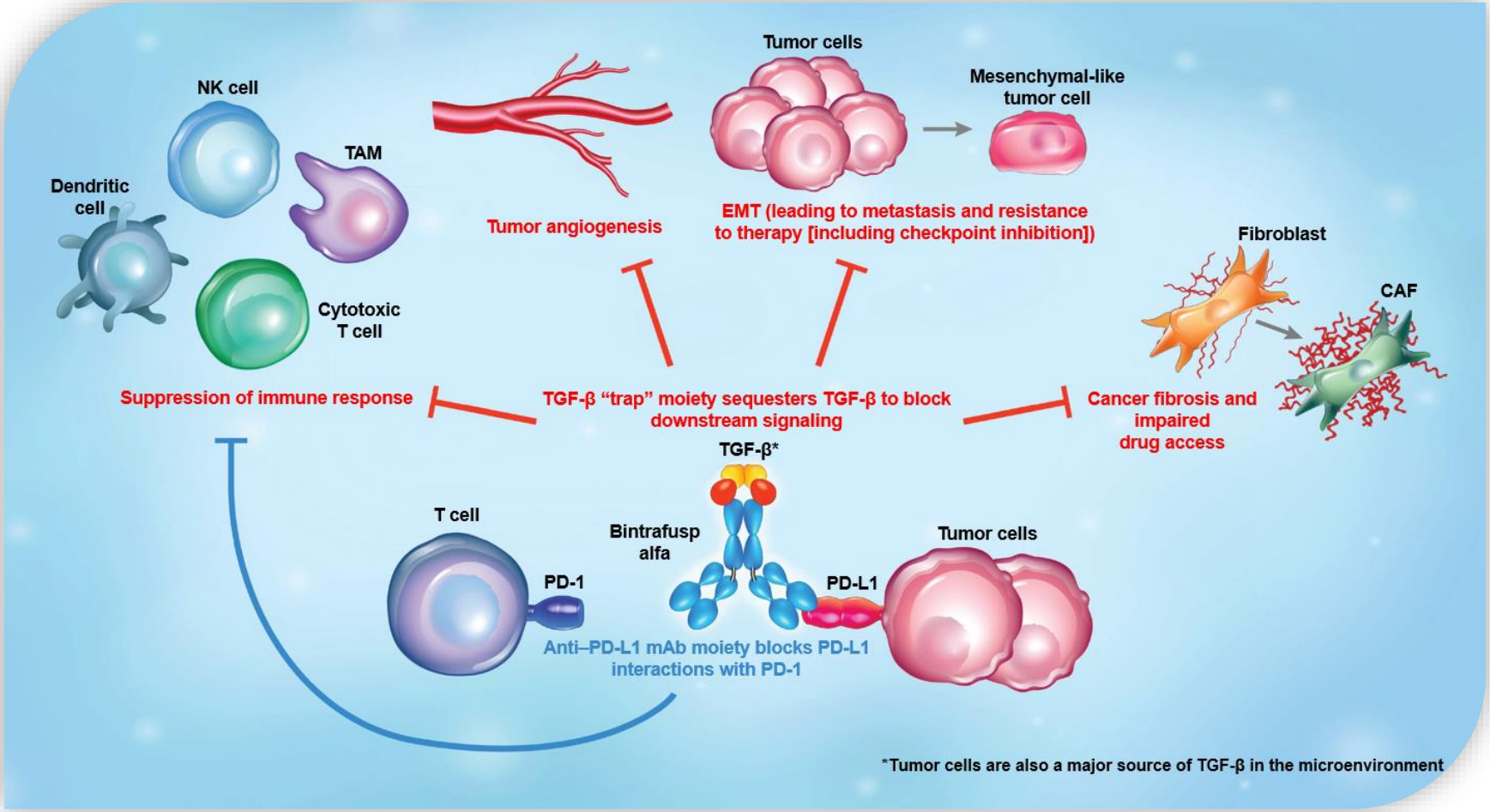
Potential for Enhanced Antitumor Effect through Simultaneous Blockade of PD-L1 and TGF-β Pathways



Based upon preclinical studies. 1. Lan Y, et al. Sci Transl Med. 2018;10(424). 2. Knudson KM, et al. Oncoimmunology. 2018;7(5):e1426519. 3. Paz-Ares LG, et al. Ann Oncol. 2018;29(Suppl 8):Abstract No. 4393. 4. Bang Y-J, et al. Ann Oncol. 2018;29(Suppl 8):Abstract No. 4543.

Bintrafusp alfa showed greater antitumor activity vs anti–PD-L1 or anti–TGF-β treatment alone in preclinical mouse tumor models

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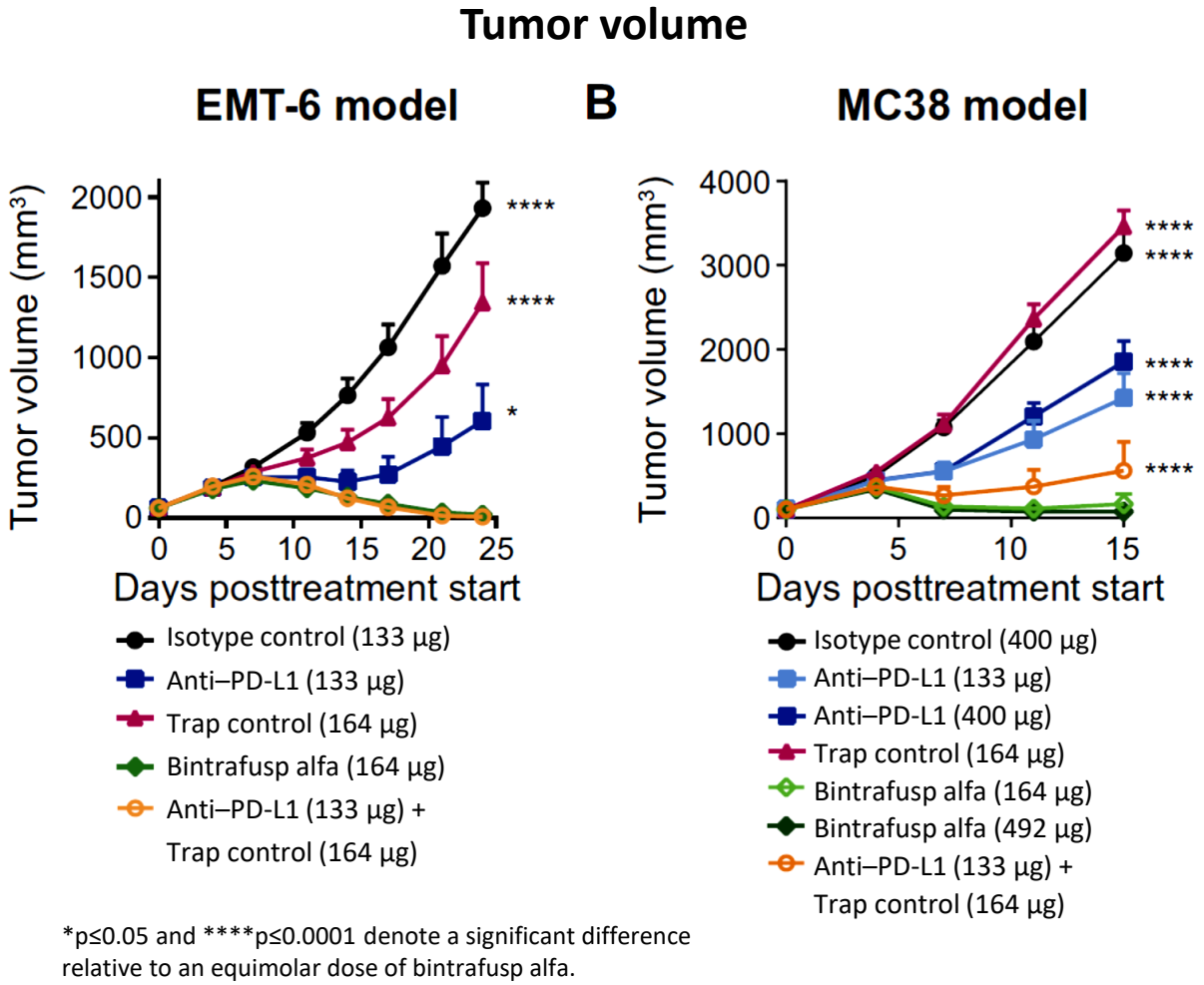
- Treatment with bintrafusp alfa resulted in superior tumor regression at day 24 compared with treatment with either anti–PD-L1 or the trap control (both of which also showed partial antitumor activity)
- The activity of bintrafusp alfa was comparable with combination therapy with anti–PD-L1 and the trap control in an EMT-6 orthotopic breast-tumor model
- Improved antitumor activity was also seen in mouse models of other solid tumors including colorectal cancer and subcutaneous tumors



*p≤0.05 and ****p≤0.0001 denote a significant difference relative to an equimolar dose of bintrafusp alfa.

Lan Y, et al. Sci Transl Med. 2018;10(424).

Bintrafusp alfa - Study 001 in solid tumors [NCT02517398][1-14]

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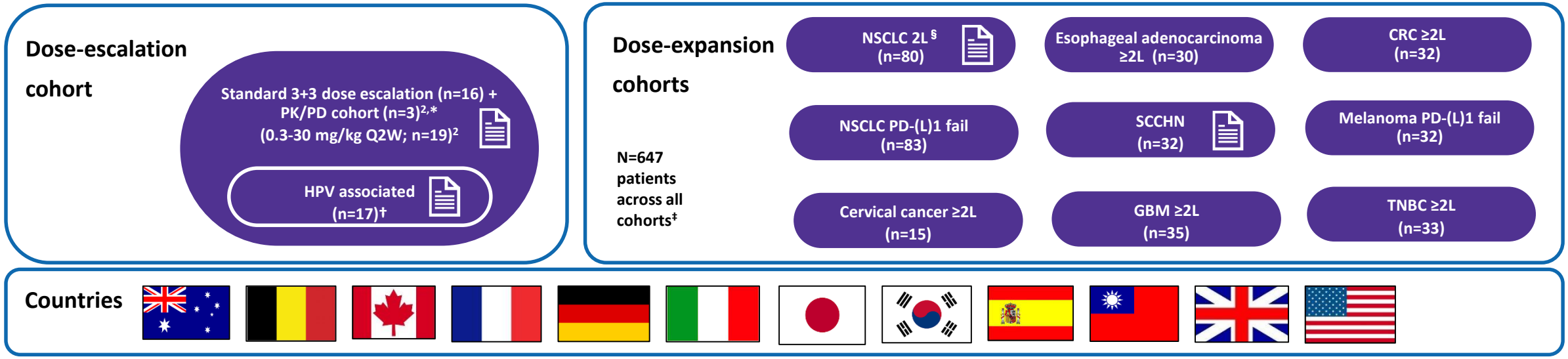
A phase 1, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, and biological and clinical activity of bintrafusp alfa in metastatic or locally advanced solid tumors and expansion to selected indications



*A cohort of 3 patients received an initial dose at 0.3 mg/kg to establish a PK/PD relationship at low-dose levels where no full-PD effect is present, followed by 10-mg/kg dosing thereafter.
†Retrospective analysis; included patients with SCCHN, anal, and cervical cancers.
‡Patient numbers based on the clinical trial protocol, unless other reference cited.
§ Included 500-mg Q2W and 1200-mg Q2W arms.

1. Clinical study protocol EMR200647-001. Version 6.0. February 22, 2017.
2. Strauss J, et al. Clin Cancer Res 2018;24(6):1287-95.
3. Paz-Ares L, et al. J Thorac Oncol. 2020;15:1210-22.
4. Barlesi F, et al. SITC 2017:Abstract No. O14.
5. Kopetz S, et al. J Clin Oncol. 2018;36(Suppl 4):Abstract No. 764.
6. Strauss J, et al. AACR 2019:Abstract No. 7829.
7. Allan S, et al. ESGO 2019:Abstract No. 418.
8. Cho BC, et al. J Immunother Cancer. 2020;8:e000664.
9. Tan B, et al. Ann Oncol. 2018;29(Suppl 8):Abstract No. 4622.
10. Khasraw M, et al. SNO 2018:Abstract No. 499390.
11. Spira A, et al., SABCS 2019:Abstract No. 477.
12. Locke G, et al. SITC 2019: Poster P346.
13. Locke G, et al., SABCS 2019:Abstract No. 1132.
14. https://clinicaltrials.gov/ct2/show/NCT02517398. Accessed October 27, 2020.

Study 001: trial design[1,2]

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Dose-escalation

Patients with advanced solid tumors

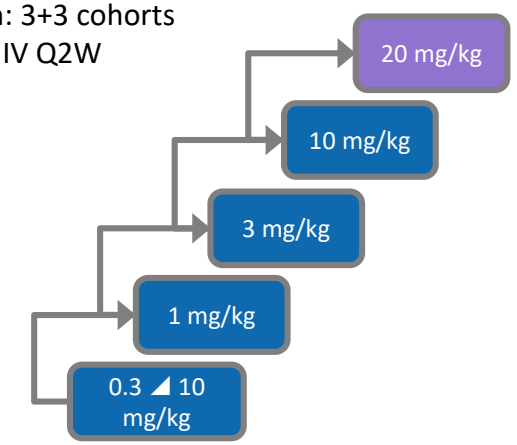
Bintrafusp alfa dose: 3+3 dose escalation

Endpoints
Primary
- Safety and tolerability

Key secondary
- BOR per RECIST 1.1

Treatment until confirmed progression, unacceptable toxicity, or any criteria for withdrawal

Part A: Bintrafusp alfa Monotherapy
- Dose escalation: 3+3 cohorts
- **Bintrafusp alfa** IV Q2W
- Total N = 19



Dose-expansion

Patients with advanced solid tumors specified in the planned cohort (NSCLC, CRC, SCCHN, GBM, esophageal cancers)

Bintrafusp alfa dose based on dose-escalation study

Endpoints
Primary
- BOR per RECIST 1.1

Key secondary
- Safety and tolerability

Part B: Expansion
- Disease-specific expansion cohorts
- **Bintrafusp alfa** 1200 mg IV Q2W

1. Clinical study protocol EMR200647-001. Version 6.0. February 22, 2017.
2. Strauss J, et al. Clin Cancer Res. 2018;24(6):1287-95.

Study 001: escalation part

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- Confirmed metastatic or locally advanced solid tumors, n=19
- Bintrafusp alfa appeared to have a safety profile in line with findings from previous studies
- AEs, serious AEs, and treatment-related serious AEs were reported in 100%, 58%, and 26% of patients respectively
- Grade ≥3 treatment-related AEs occurred in 4 patients
  - Grade 2 bullous pemphigoid followed by grade 3 superimposed skin infection
  - Grade 3 asymptomatic lipase increase
  - Colitis
  - Grade 4 hypokalemia/grade 3 gastroparesis
  - 3 patients discontinued bintrafusp alfa treatment due to treatment-related AEs described above (bullous pemphigoid, colitis, and gastroparesis)
- The MTD was NR at the highest dose level in this study, 20 mg/kg
- No AEs led to death
- Evidence of clinical activity with bintrafusp alfa was observed across all evaluated dose levels, including:

  1 ongoing confirmed CR (cervical cancer)

  2 durable confirmed PRs (pancreatic cancer; anal cancer)

  1 near-PR (cervical cancer)

  2 cases of prolonged stable disease in patients with growing disease at study entry (pancreatic cancer; carcinoid)

TRAEs

(n=19)	Any Grade	Grade ≥3
Patients with any event, n (%)	9 (47.4)	4 (21.1)
Anemia	1 (5.3)	1 (5.3)
Appetite decrease	1 (5.3)	
Bullous pemphigoid	1 (5.3)	
Colitis	1 (5.3)	1 (5.3)
Dermatitis acneiform	1 (5.3)	
Dyspnea	1 (5.3)	
Gastroparesis	1 (5.3)	1 (5.3)
Hyperthyroidism	2 (10.5)	
Hypokalemia*	1 (5.3)	1 (5.3)
Hypothyroidism	3 (15.8)	
Infusion-related reaction	1 (5.3)	
Keratoacanthoma	2 (10.5)	
Lipase increase	1 (5.3)	1 (5.3)
Nausea	2 (10.5)	
Pruritus	1 (5.3)	
Rash maculopapular	3 (15.8)	
Skin infection	1 (5.3)	1 (5.3)
Skin papilloma	1 (5.3)	
Vomiting	2 (10.5)	
Weight decrease	1 (5.3)	

Strauss J, et al. Clin Cancer Res. 2018;24(6):1287–95.

Study 001: expansion cohort of a phase 1 trial in 2nd line NSCLC

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- Adults with recurrent NSCLC who progressed following 1L systemic treatment (chemotherapy or targeted therapy) and had no prior immune checkpoint inhibitor therapy
- The primary endpoint was BOR assessed by IRC; secondary endpoints included dose exploration at two dose levels and safety/tolerability:
  - 500 mg Q2W, n=40
  - 1200 mg Q2W (RP2D), n=40
- Bintrafusp alfa monotherapy showed clinical activity across PD-L1 subgroups
- At the RP2D of 1200 mg, the confirmed IRC-adjudicated ORR was 37.0% in PD-L1–positive patients and 85.7% in PD-L1–high patients
- The IRC-adjudicated median PFS in the 1200-mg cohort was 9.5 months in PD-L1–positive patients and 15.2 months in PD-L1–high patients
- The IRC-adjudicated median DOR was 14.1 months in the cohort that received 500 mg and NR in the 1200-mg cohort

Table 2. IRC-Adjudicated Efficacy According to RECIST 1.1

Parameter	500 mg (n = 40)	1200 mg (n = 40)	Overall (N = 80)
BOR, n (%)			
Complete response	0	0	0
Partial response	7 (17.5)	10 (25.0)	17 (21.3)
Stable disease	5 (12.5)	8 (20.0)	13 (16.3)
Non-complete response or non-progressive disease[a]	1 (2.5)	1 (2.5)	2 (2.5)
Progressive disease	22 (55.0)	17 (42.5)	39 (48.8)
Not evaluable	5 (12.5)	4 (10.0)	9 (11.3)
ORR, n (%)	7 (17.5)	10 (25.0)	17 (21.3)
DCR, n (%)[b]	13 (32.5)	19 (47.5)	32 (40)
ORR in PD-L1-evaluable patients, n of N (%)			
All	7 of 38 (18.4)	10 of 37 (27.0)	17 of 75 (22.7)
PD-L1 negative[c]	1 of 7 (14.3)	0 of 10 (0)	1 of 17 (5.9)
PD-L1 positive[d]	6 of 31 (19.4)	10 of 27 (37.0)	16 of 58 (27.6)
Low[e]	4 of 25 (16.0)	4 of 20 (20.0)	8 of 45 (17.8)
High[f]	2 of 6 (33.3)	6 of 7 (85.7)	8 of 13 (61.5)
Median PFS (95% CI), mo			
All	1.4 (1.3-4.2)	4.0 (1.3-9.5)	2.6 (1.3-4.2)
PD-L1 negative[c]	1.4 (0.3-10.9)	1.3 (0.9-4.0)	1.3 (1.3-4.0)
PD-L1 positive[d]	1.4 (1.2-4.2)	9.5 (2.6-15.2)	2.7 (1.4-9.6)
Low[e]	1.4 (1.2-4.2)	5.5 (1.3-11.0)	2.6 (1.3-9.5)
High[f]	1.3 (0.2-NR)	15.2 (1.3-NR)	15.2 (1.0-NR)
Median DOR (95% CI), mo	14.1 (7.0-NR)	NR (4.2-NR)	14.1 (7.0-NR)

[a]Persistence of one or more nontarget lesions or maintenance of tumor marker level above the normal limits.
[b]DCR included those patients who achieved a complete response, partial response, or stable disease (including non-complete response or non-progressive disease).
[c]PD-L1 expression on less than 1% of tumor cells.
[d]PD-L1 expression on greater than or equal to 1% of tumor cells.
[e]PD-L1 expression on 1% to less than 80% of tumor cells.
[f]PD-L1 expression on greater than or equal to 80% of tumor cells.
BOR, best overall response; CI, confidence interval; DCR, disease control rate; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

PD-L1 positivity was defined by PD-L1 expression in ≥1% of tumor cells detected by IHC using a proprietary assay (PD-L1 IHC 73-10 pharmDx; Dako, Carpinteria, CA, USA).
73-10 and 22C3 PD-L1 IHC assays were similar at a cut-off of 80% and 50%, respectively

Paz-Ares L, et al. J Thorac Oncol. 2020;15:1210-22

Study 001: expansion cohort of a phase 1 trial in 2nd line NSCLC - safety

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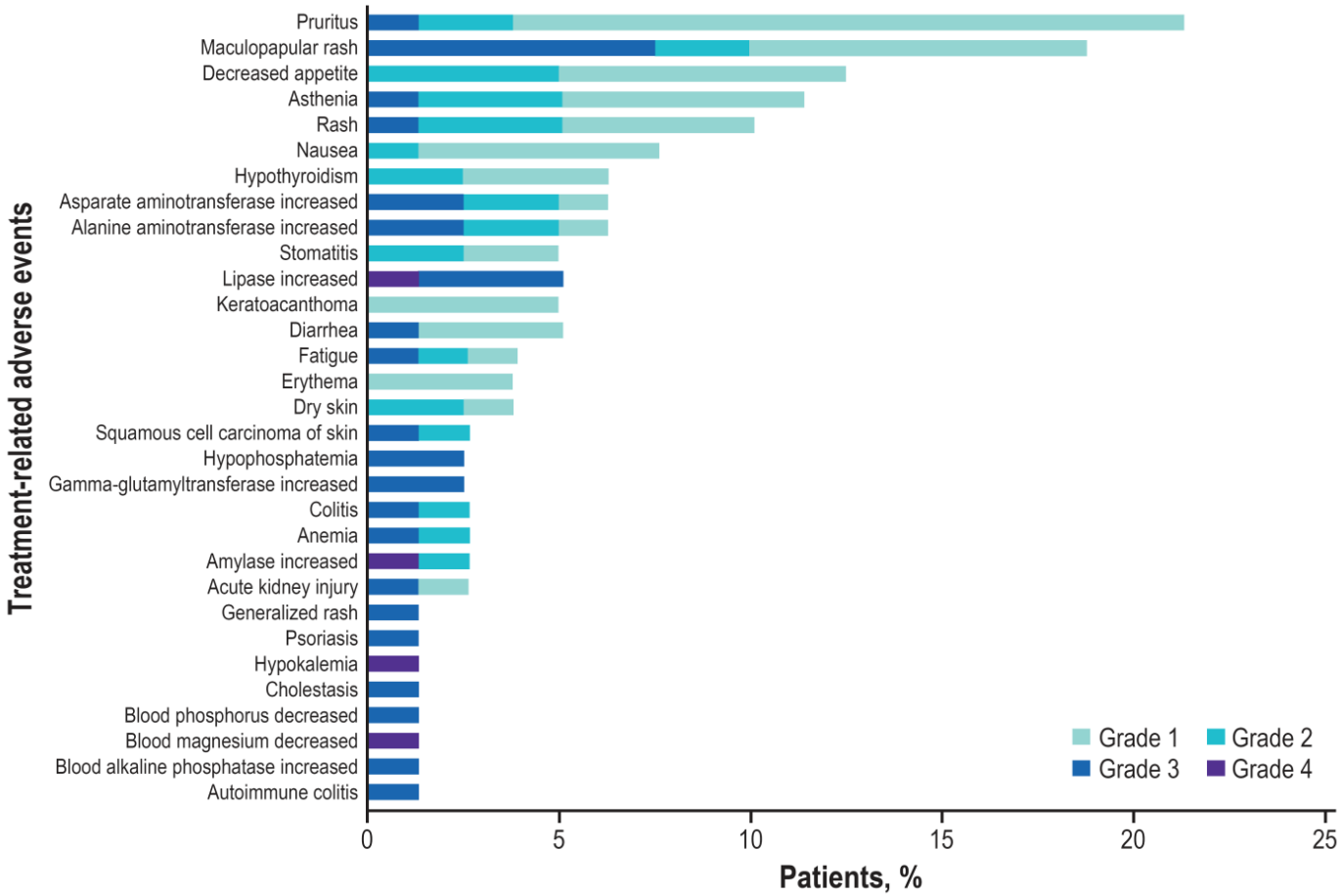
- The safety profile of bintrafusp alfa was similar to that seen for other established immune checkpoint inhibitors, except for skin TRAEs (keratoacanthomas, hyperkeratosis, and SCC), which are anticipated AEs with TGF-β inhibition[2,3]
- TRAEs occurred in 28.8% of patients
  - The most common TRAEs were pruritus (21.3%), maculopapular rash (18.8%), decreased appetite (12.5%), asthenia (11.3%), and rash (10.0%)
- Potentially TGF-β–related skin lesions occurred in 7 patients (8.8%)
  - These TRAEs were well managed with simple surgical excision and did not require any patient to discontinue treatment
- Grade 4 TRAEs occurred in 2 patients (2.5%) and were asymptomatic laboratory abnormalities that did not lead to treatment discontinuation
- No treatment-related deaths occurred
- TRAEs led to discontinuations in 8 patients (500 mg Q2W, n=2; 1200 mg Q2W, n=6)

TRAEs of any grade occurring in ≥3% of patients or of grade ≥3 in any patient



1. Paz-Ares L, et al. J Thorac Oncol. 2020;15:1210-22.
2. Rose AM, et al. Cell Cycle. 2017; 16: 386–7.
3. Gibney GT, et al. Nat Rev Clin Oncol. 2013;10 390-9.

Ongoing Studies with Bintrafusp alfa in NSCLC

INTR@PID CLINICAL TRIALS

gsk Merck KGaA
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INTR@PID LUNG 037

STAGE IV | PHASE 3 RANDOMIZED | MONOTHERAPY

An adaptive phase 3, randomized, open-label, controlled study evaluating bintrafusp alfa versus pembrolizumab in the first-line treatment of patients with stage IV non-small cell lung cancer (NSCLC) that has high expression of PD-L1.*

ClinicalTrials.gov: NCT03631706

INTR@PID LUNG 005

STAGE III | PHASE 2 RANDOMIZED | COMBINATION THERAPY

A phase 2, randomized, controlled study evaluating bintrafusp alfa with concurrent chemoradiation (cCRT) followed by bintrafusp alfa versus placebo with cCRT followed by durvalumab for the treatment of patients with unresectable stage III non-small cell lung cancer (NSCLC).

ClinicalTrials.gov: NCT03840902

INTR@PID LUNG 024

STAGE IV | PHASE 1/2 | COMBINATION THERAPY

A phase 1b/2, open-label study evaluating bintrafusp alfa with chemotherapy for the treatment of patients with stage IV non-small cell lung cancer (NSCLC).

ClinicalTrials.gov: NCT03840915

Study 008: Bintrafusp alfa in solid tumors in Asia [1-6]

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A phase 1, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, and biological and clinical activity of bintrafusp alfa in metastatic or locally advanced solid tumors with expansion to selected indications in Asian patients

Dose-escalation cohort

Standard 3+3 dose escalation
(1, 3, 10, and 20 mg/kg Q2W; n≤18)*

Dose-expansion cohorts

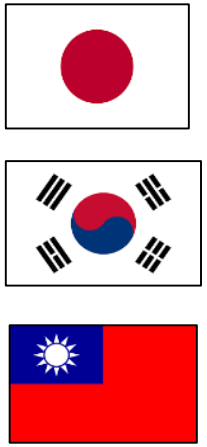
Biliary tract
(n=30)

Gastric
(n=31)

Esophageal squamous cell
(n=30)

N≤99 patients across all cohorts

Countries



*Patient numbers based on the clinical trial protocol.

1. Clinical study protocol MS200647-0008. Version 3.0. April 29, 2016.
2. Doi T, et al. Oncologist. 2020;25:e1292-e1302.
3. Kang YK, et al. Clin Cancer Res. 2020;26:3202-10.
4. Yoo C, et al. J Immunother Cancer. 2020;8:e000564.
5. Lin CC, et al. Ann Oncol. 2018;29(Suppl 8):Abstract No. 3721.
6. https://clinicaltrials.gov/ct2/show/NCT02699515. Accessed October 28, 2020.

Study 008: expansion cohort of a phase 1 trial in 2nd line BTC [1]

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- The analysis included 30 Asian patients with pretreated biliary tract cancer for which standard first-line chemotherapy has failed
- Clinical activity was observed across BTC subtypes and irrespective of PD-L1 expression level
- At the August 24, 2018 data cut off 63.3% of patients experienced TRAEs
  - 11 patients (36.7%) experienced grade ≥3 TRAEs
  - 2 patients experienced grade 4 events (increased amylase, aspartate aminotransferase, and lipase levels)

  3 treatment-emergent deaths occurred
  - Septic shock (n=1) due to bacteremia of unknown etiology 249 days after the first dose and 14 days after the last dose
  - Interstitial lung disease (reported term, interstitial pneumonitis) in 2 patients
- After 28 months of follow-up, no additional deaths or safety signals were observed; 1 new grade ≥3 TRAE (grade 3 keratoacanthoma) was observed [2]

Efficacy according to RECIST 1.1

	By investigator (N=30)	By IRC (N=30)
BOR, n (%)		
CR	1 (3)	2 (7)
PR	6 (20)	4 (13)
SD	4 (13)	6 (20)
PD	17 (57)	16 (53)
NE	2 (7)	2 (7)
Objective response, n (%; 95% CI)	7 (23; 10-42)	6 (20; 8-39)
Objective response by BTC subtype, n/N (%)		
Ampullary cancer	0/1 (0)	0/1 (0)
Extrahepatic cholangiocarcinoma	1/7 (14)	0/7 (0)
Gallbladder cancer	2/12 (17)*	3/12 (25)
Intrahepatic cholangiocarcinoma	4/10 (40)	3/10 (30)
Disease control, n (%; 95% CI)	11 (37; 20-56)	12 (40; 23-59)
DOR, median (range), mo	9.7 (2.8-12.5)	NE (8.3-14.5)
PFS, median (95% CI), mo	2.5 (1.3-4.0)	2.5 (1.3-5.6)
OS, median (95% CI), mo	12.7 (6.7-15.7)	

*One patient with gallbladder cancer had a partial response per IRC and initial pseudoprogression on the first evaluation visit, followed by a partial response as assessed by the investigator (investigator-assessed best overall response, progressive disease).

1. Yoo C, et al. J Immunother Cancer. 2020;8:e000564. 2. Yoo C, et al. Ann Oncol. 2020;31(Suppl 4):Abstract No. 1418.

Ongoing Studies with Bintrafusp alfa in BTC

INTRePID CLINICAL TRIALS

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INTRePID BTC 047

ADVANCED | PHASE 2 | MONOTHERAPY

A phase 2, single-arm study evaluating bintrafusp alfa in the second-line treatment of patients with locally advanced or metastatic biliary tract cancer (BTC) who have failed or are intolerant to first-line platinum-based chemotherapy.

ClinicalTrials.gov: NCT03833661

Location: *Global*

Status: Active, Not Recruiting

INTRePID BTC 055

ADVANCED | PHASE 2/3 RANDOMIZED | COMBINATION THERAPY

A safety run-in followed by a phase 2/3, randomized, placebo-controlled study evaluating bintrafusp alfa with gemcitabine plus cisplatin in the first-line treatment of patients with locally advanced or metastatic biliary tract cancer (BTC).

ClinicalTrials.gov: NCT04066491

Location: *Global*

Status: **Now Enrolling**

Study 001: expansion cohort of a phase 1 trial in ≥ 2nd line cervical cancer

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- The cervical cancer expansion cohort from the 001 study was heavily pretreated, with 72.0% of patients receiving ≥2 prior anticancer therapies (n=25)
- The Moore criteria identified 18 patients (76.0%) as having a mid- or high-risk disease prognosis
- Most patients (72.0%) had confirmation of HPV-positive disease
- Treatment showed clinical activity (ORR, 24.0%; DCR, 32.0%) that was independent of PD-L1 expression on tumor cells
- Responses were long lasting, ranging from 4.2 to 30.4 months (median DOR ne)
- Safety:
  - 6 patients experienced grade 3 TRAEs (24.0%); 1 of these patients had a grade 4 TRAE (asymptomatic hypokalemia) related to a grade 3 gastroparesis
  - There were no treatment-related deaths
  - 6 patients (24.0%) discontinued treatment due to TRAEs
  - Immune-related TRAEs occurred in 5 patients (20.0%), including rash macular (n=2 [8.0%]) and pneumonitis, pruritus, rash, and rash maculopapular (n=1 each [4.0%]); both rash macular and pruritus occurred in 1 patient
  - Treatment-related skin lesions, potentially related to TGF-β inhibition, were reported in 4 patients (16.0%), including KA (n=3 [12.0%]) and actinic keratosis and basal cell carcinoma (n=1 each [4.0%]); 1 patient experienced both KA and actinic keratosis

Investigator-assessed efficacy according to RECIST 1.1

Outcome	Overall (N=25)
BOR, n (%)	
CR	2 (8.0)
PR	4 (16.0)
SD	2 (8.0)
PD	12 (48.0)
Delayed PR*	1 (4.0)
NE	4 (16.0)
Objective response, n (%)	6 (24.0)
95% CI	9.4-45.1
Disease control, n (%)	8 (32.0)
95% CI	15.0-53.5
Total clinical response, n (%)†	7 (28.0)
95% CI	12.1-49.4
Objective response by tumor cell PD-L1 expression, n/n (%)‡	
Positive (n=12)	3/12 (25.0)
Negative (n=2)	1/2 (50.0)
NE (n=1)	0/1 (0)
Not available (n=10)	2/10 (20.0)

Allan S, et al. ESGO 2019:Abstract No. 418.

Study 001: expansion cohort of a phase 1 trial in advanced SCCHN

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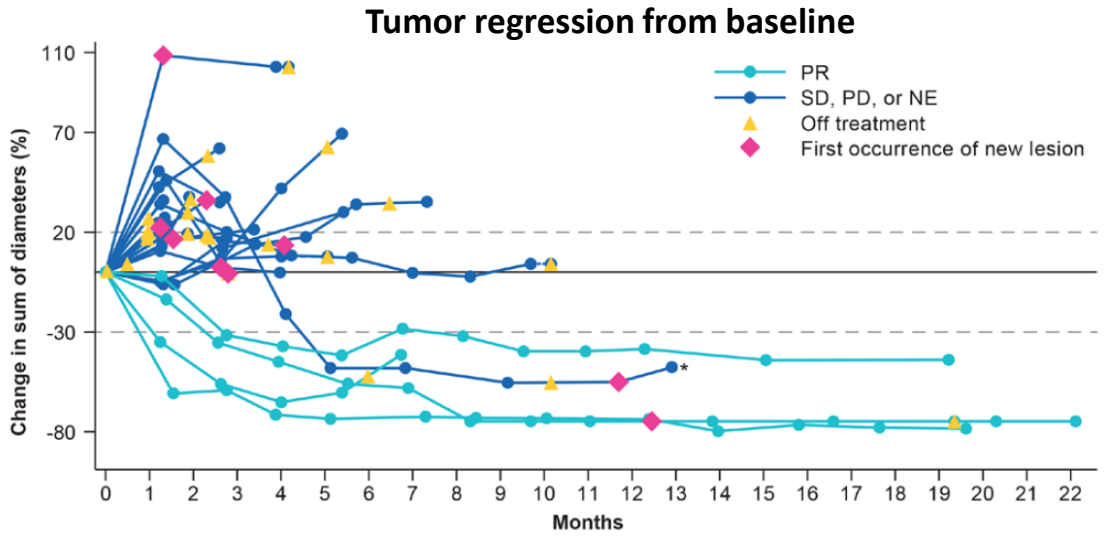
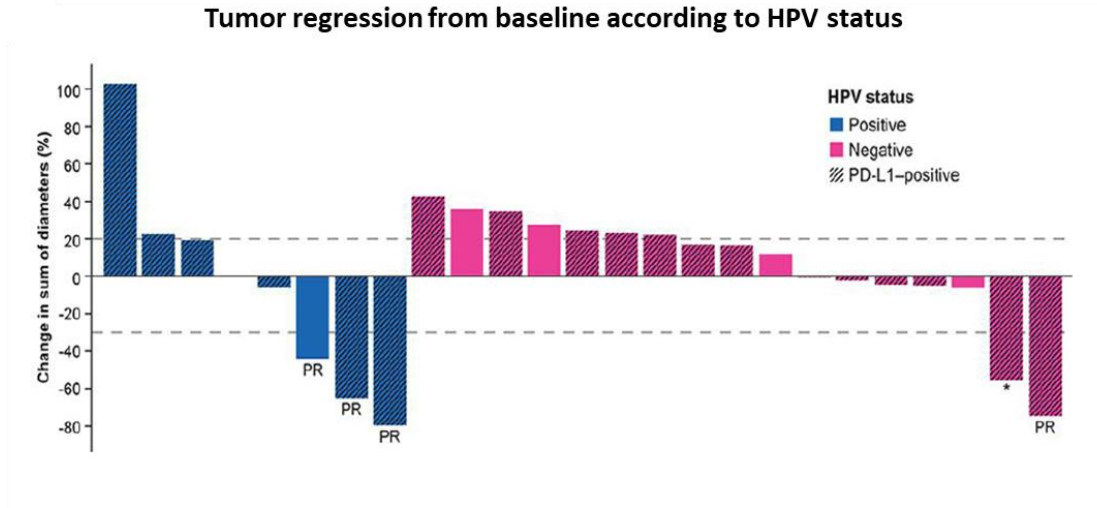
- Adults (n= 32) with SCCHN tumors unselected for PD-L1 and HPV status that were either metastatic or not amenable to local therapy with curative intent, and that progressed or recurred <6 months since the last platinum dose
- Tumor HPV status was available for 31 of 32 patients
  9 (28%) were positive and 22 (69%) were negative
- 4 PRs per IRC were observed (13%) and an additional 4 patients had SD, resulting in a DCR of 34%
- Median DOR was 18.1 months (range, 6-20+ months)
- The ORR in patients with HPV-positive tumors was 33% (95% CI, 5-70%)
- Safety:
  - 22 patients (69%) experienced TRAEs of any grade
  - 11 patients (34%) experienced grade 3 TRAEs
  - No grade 4 or 5 TRAEs occurred
  - No study discontinuations due to TRAEs occurred
- Bintrafusp alfa showed clinical activity across subgroups of PD-L1 expression and in HPV-positive tumors and had a manageable safety profile in patients with heavily pretreated advanced SCCHN. Activity in HPV-positive tumors is favorable compared with historical data





Cho BC, et al. J Immunother Cancer. 2020;8:e000664.

Study 001 & 012 (NCI): pooled analyses in Patients With Human Papillomavirus–Associated Malignancies [1]

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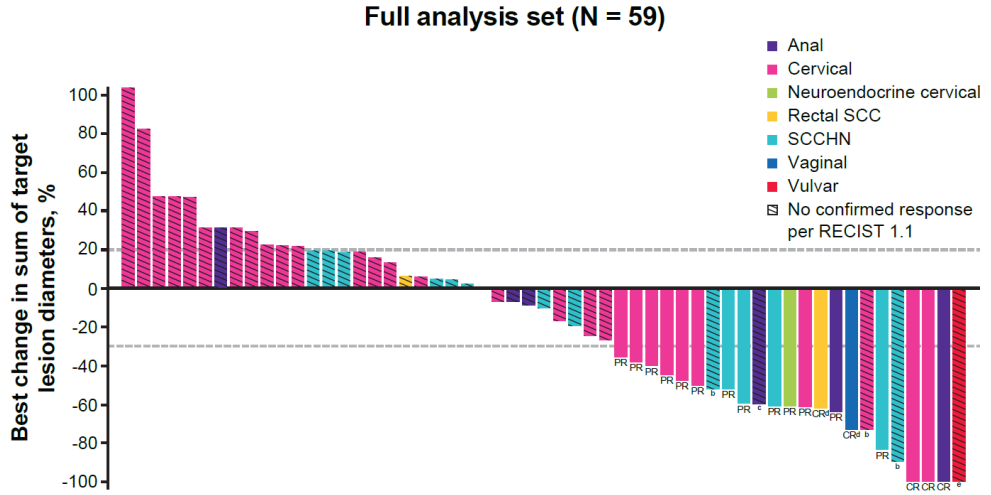
- 59 patients, including 43 from the phase 1 trial and 16 from the phase 2 trial, with checkpoint inhibitor-naive disease were included in this post hoc analysis
- 52 patients (88.1%) had confirmed HPV-positive tumors, 3 patients (5.1%, all with cervical cancer) had HPV-negative disease by RNAseq, and HPV status was missing or not available for 4 patients (7%, all with cervical cancer)
- Confirmed CRs occurred in
  - cervical (n = 2)
  - anal (n = 1)
  - vaginal (n = 1)
  - and rectal SCC (n = 1) cancers
- Confirmed PRs occurred in
  - SCCHN (n = 4),
  - cervical cancer (n = 8; including 1 neuroendocrine cervical cancer)
  - anal cancer (n = 1)
- Response durations ranged from 2.8+ to 30.4 months (median, 19.1 months [95% CI, 9.6-27.4 months])
- Treatment responses occurred irrespective of PD-L1 expression in the phase 1 study

Summary of tumor response and survival data

	Study 001 (n=43)	Study 012 (n=16)	Full analysis set (N=59)
Confirmed BOR, n (%)			
CR	3 (7.0)	2 (12.5)	5 (8.5)
PR	9 (20.9)	4 (25.0)	13 (22.0)
SD	6 (14.0)	2 (12.5)	8 (13.6)
PD	20 (46.5)	7 (43.8)	27 (45.8)
Not evaluable	5 (11.6)	1 (6.3)	6 (10.2)
Delayed PR*	3 (7.0)	0	3 (5.1)
Confirmed objective response, n (%; 95% CI)	12 (27.9; 15.3-43.7)	6 (37.5; 15.2-64.6)	18 (30.5; 19.2-43.9)
Disease control, n (%; 95% CI)†	18 (41.9; 27.0-57.9)	8 (50.0; 24.7-75.3)	26 (44.1; 31.2-57.6)
Total clinical response, n (%; 95% CI)‡	15 (34.9; 21.0-50.9)	6 (37.5; 15.2-64.6)	21 (35.6; 23.6-49.1)§
Duration of response (95% CI), months	19.1 (4.2-27.4)	NR (4.2 to NR)	19.1 (9.6-27.4)
KM-estimated PFS (95% CI), months	2.8 (1.4-4.6)	3.3 (1.4 to NR)	2.8 (1.4-5.5)



1. Strauss J, et al. J Immunother Cancer. 2020; forthcoming. & Strauss et al. AACR 2019 CT075

Study 001 & 012 (NCI): pooled analyses in Patients With Human Papillomavirus–Associated Malignancies – safety [1]

Merck KGaA
Darmstadt, Germany

- TRAEs occurred in 83.1% (49/59) patients
- The most common TRAE was pruritus, which occurred in 15 patients (25.4%)
- Grade 3 TRAEs occurred in 16 patients (27.1%); the most common was anemia, which occurred in 4 patients (6.8%)
- No treatment-related deaths occurred
- Treatment-related infusion-related reactions occurred in 3 patients (5.1%)

TRAEs occurring at any grade in ≥5% of patients or grade ≥3 in any patient and any AESI from the full analysis set

n (%)	Study 001 (n=43)		Study 012 (n=16)		Full analysis set (N=59)	
	Any grade	Grade 3	Any grade	Grade 3	Any grade	Grade 3
Patients with any TRAE	**35 (81.4)**	**11 (25.6)**	**14 (87.5)**	**5 (31.3)**	**49 (83.1)**	**16 (27.1)**
Pruritus	10 (23.3)	0	5 (31.3)	0	15 (25.4)	0
Dermatitis acneiform	7 (16.3)	0	5 (31.3)	0	12 (20.3)	0
Keratoacanthoma	9 (20.9)	2 (4.7)	0	0	9 (15.3)	2 (3.4)
Hypothyroidism	7 (16.3)	1 (2.3)	2 (12.5)	0	9 (15.3)	1 (1.7)
Rash maculopapular	6 (14.0)	0	3 (18.8)	0	9 (15.3)	0
Anemia	4 (9.3)	1 (2.3)	5 (31.3)	3 (18.8)	9 (15.3)	4 (6.8)
Fatigue	2 (4.7)	0	5 (31.3)	1 (6.3)	7 (11.9)	1 (1.7)
Stomatitis	3 (7.0)	0	2 (12.5)	0	5 (8.5)	0
Rash macular	3 (7.0)	1 (2.3)	0	0	3 (5.1)	1 (1.7)
ALT increased	2 (4.7)	0	1 (6.3)	0	3 (5.1)	0
AST increased	2 (4.7)	0	1 (6.3)	0	3 (5.1)	0
Asthenia	3 (7.0)	0	0	0	3 (5.1)	0
Diarrhea	2 (4.7)	0	1 (6.3)	0	3 (5.1)	0
Epistaxis	2 (4.7)	0	1 (6.3)	0	3 (5.1)	0
Decreased appetite	3 (7.0)	0	0	0	3 (5.1)	0
Influenza-like illness	1 (2.3)	0	2 (12.5)	0	3 (5.1)	0
Infusion-related reaction	2 (4.7)	0	1 (6.3)	0	3 (5.1)	0
Mouth hemorrhage	0	0	3 (18.8)	0	3 (5.1)	0
Nausea	3 (7.0)	0	0	0	3 (5.1)	0
Colitis	1 (2.3)	1 (2.3)	1 (6.3)	0	2 (3.4)	1 (1.7)

1. Strauss J, et al. J Immunother Cancer. 2020; forthcoming. & Strauss et al. AACR 2019 CT075

Ongoing Studies with Bintrafusp alfa in cervical cancer

INTR@PID CLINICAL TRIALS

Merck KGaA
Darmstadt, Germany

INTR@PID CERVICAL 017

ADVANCED | PHASE 2 | MONOTHERAPY

A phase 2, single-arm study evaluating bintrafusp alfa for the treatment of patients with advanced, unresectable cervical cancer that progressed during or after platinum-containing chemotherapy.*

ClinicalTrials.gov: NCT04246489

Location: *Global*

Status: **Now Enrolling**

INTR@PID CERVICAL 046

ADVANCED | PHASE 1 | COMBINATION THERAPY

Ph 1 study is to evaluate the safety and tolerability of bintrafusp alfa in combination with other anti-cancer therapies in participants with locally advanced or advanced cervical cancer.

ClinicalTrials.gov: NCT04551950

Merck KGaA
Darmstadt, Germany

Thank you!

INTR@PID CLINICAL TRIALS IN CERVICAL CANCER

INTR@PID CERVICAL 017 (NCT04246489)[1]

Merck KGaA
Darmstadt, Germany

Open-label, single-arm trial design
Phase 2

Advanced unresectable/metastatic cervical cancer*

N=135

→

Bintrafusp alfa†
1200 mg IV Q2W

Key endpoints:

ORR, DOR, DRR, safety, PFS, OS, pharmacokinetics, clinical efficacy according to PD-L1 expression

Key inclusion criteria
• Age ≥18 years with histologically documented advanced unresectable and/or metastatic cervical cancer
• Disease progression during or after prior platinum-containing chemotherapy*
• Availability of archival tumor tissue sample or newly obtained (preferred) biopsy of tumor lesion
• ECOG PS of 0 or 1
• Adequate organ and coagulation function and a life expectancy ≥12 weeks
Key exclusion criteria
• Prior cancer immunotherapy or treatment targeting T-cell costimulation, checkpoint pathways, or immune-suppressive pathways (such as TGF-β)
• Active central nervous system metastases causing clinical symptoms or requiring therapeutic intervention

*Participants must have experienced disease progression with platinum-containing chemotherapy that was given as a systemic treatment for advanced unresectable, recurrent, persistent, or metastatic disease or in the adjuvant or neoadjuvant setting, with disease progression or recurrence within 6 months of completion of platinum-containing chemotherapy. Participants who previously only received platinum as a radiosensitizer are not eligible. †Until confirmed disease progression, death, unacceptable toxicity, or study withdrawal.

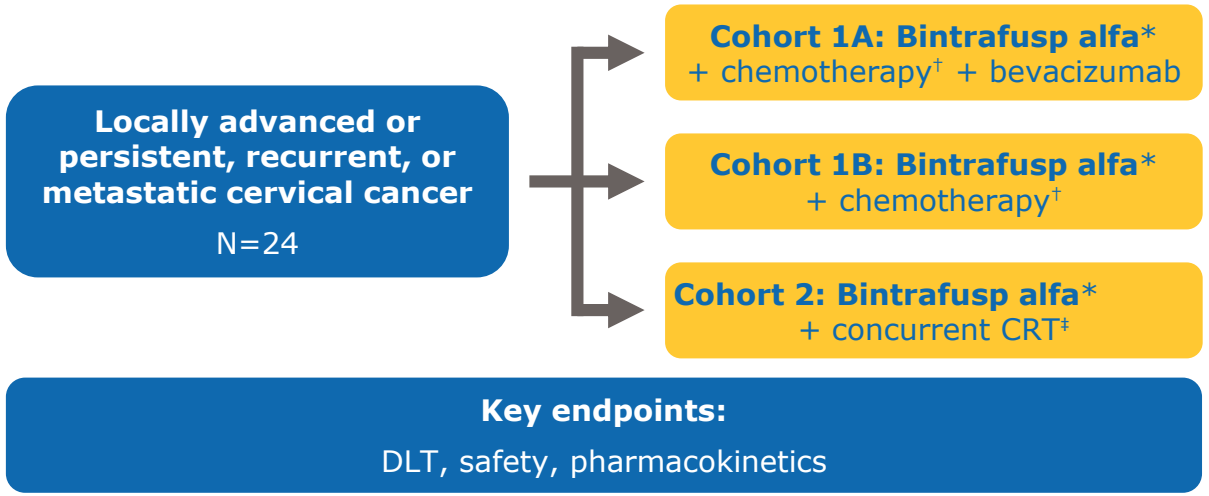
1. Birrer MJ, et al. ESMO 2020. Poster 879 TiP.

INTR@PID CLINICAL TRIALS IN CERVICAL CANCER

INTR@PID CERVICAL 046 (NCT04551950)[1]

Merck KGaA
Darmstadt, Germany

Open-label, parallel-assignment trial design
Phase 1



Key inclusion criteria

- Participants in cohort 1 must have persistent, recurrent, or metastatic cervical cancer and not have received prior systemic chemotherapy that was not given as part of concurrent chemoradiation
- Participants in cohort 2 must have FIGO 2018 stage IB2 to IVA cervical cancer and must not have received prior chemotherapy or radiation therapy for cervical cancer
- ECOG PS of 0 or 1

Key exclusion criteria

- Prior cancer treatment with any immunotherapy, checkpoint inhibitor, or immune-modulating monoclonal antibody

*For 2 years or until confirmed disease progression, death, unacceptable toxicity, or study withdrawal. †Chemotherapy consists of cisplatin/carboplatin + paclitaxel. ‡Concurrent chemoradiation consists of radiation therapy + cisplatin.

1. https://clinicaltrials.gov/ct2/show/NCT04551950. Accessed October 18, 2020.