Long-term follow-up of bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, in patients with advanced squamous cell carcinoma of the head and neck (SCCHN)

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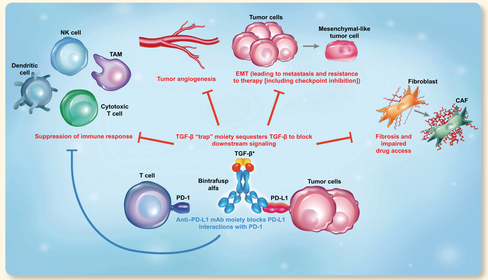
INTR@PID CLINICAL TRIALS™

BACKGROUND

SCCHN

- Patients with advanced or recurrent SCCHN have a poor prognosis:
  - Median OS is <12 months in the 1L setting, and even lower in the 2L and later settings, demonstrating the need for improved treatment options[1-4]
- ORRs of 13.3% and 16% have been reported with the PD-1 inhibitors nivolumab and pembrolizumab, respectively, in patients with SCCHN in the 2L setting, and of 15.9% and 16% in HPV-positive disease[1,5]
  - Nivolumab and pembrolizumab are approved for the treatment of patients with SCCHN who have disease progression on or after platinum-containing chemotherapy
- Given that HPV status is a prognostic biomarker in SCCHN, and that dysregulation of TGF-β signaling has been linked to the development of HPV-positive tumors, simultaneously inhibiting TGF-β and PD-L1 may provide a novel treatment approach for SCCHN[6-9]

Bintrafusp alfa



*Tumor cells are also a major source of TGF-β in the microenvironment.

- Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor to function as a TGF-β "trap" fused to a human IgG1 antibody blocking PD-L1[10,11]
- The bifunctional nature of bintrafusp alfa might allow for colocalized, simultaneous inhibition of two nonredundant immunosuppressive pathways, TGF-β and PD-L1, within the tumor microenvironment

Previously reported results from global phase 1 study (NCT02517398)

Database cutoff: Aug 24, 2018

Bintrafusp alfa 1200 mg Q2W demonstrated clinical efficacy and a manageable safety profile in patients with heavily pretreated advanced SCCHN[12]

Endpoint	Overall	HPV positive	HPV negative	TC PD-L1 ≥1%	TC PD-L1 <1%
ORR per IRC (95% CI), %	13 (4-29)	33 (8-70)	5 (0-23)	12 (3-31)	17 (0-64)

METHODS

INTR@PID 001 (NCT02517398): bintrafusp alfa in patients with advanced SCCHN

PHASE 1 | MONOTHERAPY | OPEN-LABEL | MULTICENTER

Primary endpoint
- BOR per RECIST 1.1

Key secondary endpoint
- Safety

Study population
- Patients with advanced SCCHN that progressed/ recurred after platinum therapy in the recurrent/ metastatic setting or <6 months after platinum therapy in the locally advanced setting

Exploratory endpoints
- DOR
- DCR
- PFS
- OS

Biomarker assessment
- Tumor cell PD-L1 expression was measured by IHC using antibody clone 73-10 (PD-L1 IHC 73-10 pharmDx; Dako, Carpinteria, CA, USA), as described previously[12]
- HPV status was determined by RNAseq

Objective

- To report efficacy and safety data for over 3 years of follow-up in this cohort of patients with heavily pretreated, advanced SCCHN receiving bintrafusp alfa

RESULTS (MAY 15, 2020, CUTOFF)

Baseline patient and disease characteristics

- The median follow-up to database cutoff of May 15, 2020, was 41.7 months (range, 39.8-43.5 months)
- The median duration of treatment was 2.8 months (range, 0.5-29.9 months); at database cutoff, no patient remained on treatment

ORR and DCR as assessed by IRC

Endpoint	Overall, N=32	HPV positive*, n=11	HPV negative*, n=20	TC PD-L1 ≥1%†, n=25	TC PD-L1 <1%†, n=6
ORR per IRC (95% CI), %	12.5 (3.5-29.0)	27.3 (6.0-61.0)	5.0 (0.1-24.9)	12.0 (2.5-31.2)	16.7 (0.4-64.1)
DCR per IRC (95% CI), %	34.4 (18.6-53.2)	36.4 (10.9-69.2)	35.0 (15.4-59.2)	32.0 (14.9-53.5)	50.0 (11.8-88.2)

ORR and DCR were comparable to prior database cutoff

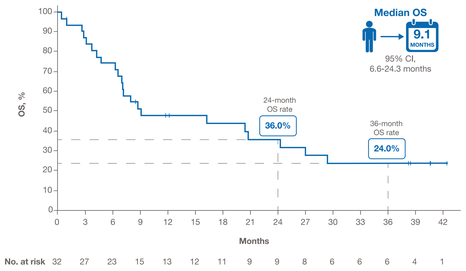
Clinical activity was greater in patients with detectable HPV

Responses were observed irrespective of PD-L1 expression

Investigator-assessed ORR and DCR were comparable to IRC assessments

*Patients with missing/non-evaluable HPV status at screening are not included in this analysis.
†Patients with non-evaluable TC PD-L1 expression are not included in this analysis.

OS in the overall population and by HPV* and PD-L1† status



HPV-positive (n=11) Median OS: 8.0 MONTHS; 95% CI, 2.9 months-NR; ≥24 months 45.5%; ≥36 months 34.1%

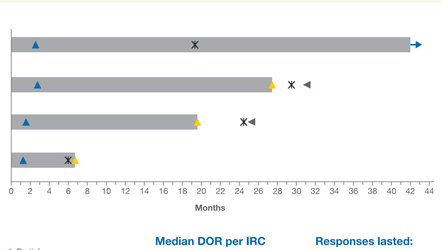
HPV-negative (n=20) Median OS: 9.1 MONTHS; 95% CI, 6.3-24.3 months; ≥24 months 30.7%; ≥36 months 18.4%

TC PD-L1 ≥1% (n=25) Median OS: 13.8 MONTHS; 95% CI, 3.2 months-NR; ≥24 months 33.9%; ≥36 months 22.6%

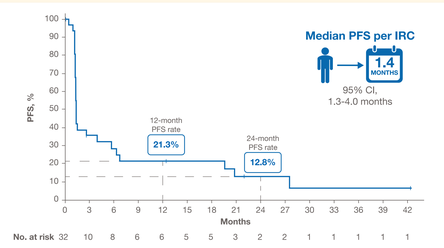
TC PD-L1 <1% (n=6) Median OS: 8.8 MONTHS; 95% CI, 6.3-27.0 months; ≥24 months 33.3%; ≥36 months 16.7%

*Patients with missing/non-evaluable HPV status at screening are not included in this analysis.
†Patients with non-evaluable TC PD-L1 expression are not included in this analysis.

DOR as assessed by IRC in the overall population



PFS as assessed by IRC in the overall population



Safety

- After a median follow-up of 41.7 months, there were no new grade ≥3 TRAEs and the overall safety profile was consistent with the previous report for this cohort[12]
  - Grade 3 TRAEs occurred in 11 patients (34.4%)
  - TRAEs led to treatment discontinuation in 2 patients (6.3%, autoimmune colitis [n=1], SCC of skin [n=1]); no new TRAEs that led to discontinuation of bintrafusp alfa were observed
  - No grade 4 TRAEs or treatment-related deaths occurred

CONCLUSIONS

- After 41.7 months of follow-up, bintrafusp alfa continued to show sustained clinical activity, with a median DOR of 21.4 months and 36-month OS rate of 24.0%, which compares favorably with historical data[13-15]
- Clinical activity was higher in patients with HPV-positive tumors than in those with HPV-negative tumors
  - ORR per IRC was 27.3% vs 5.0%
- While the median OS was similar in patients with HPV-positive and HPV-negative tumors (8.0 vs 9.1 months), the OS rate at 36 months was higher in patients with HPV-positive tumors (34.1% vs 18.4%)
- The safety profile was manageable and remained consistent with the earlier analysis, with no new safety signals or grade ≥3 TRAEs
- Further investigation of bintrafusp alfa in SCCHN and other HPV-associated cancers, including cervical cancer, is ongoing

Abbreviations

1L, first line; **2L**, second line; **BOR**, best overall response; **CAF**, cancer-associated fibroblast; **DCR**, disease control rate; **DOR**, duration of response; **EMT**, epithelial-mesenchymal transition; **HPV**, human papillomavirus; **IHC**, immunohistochemistry; **IRC**, independent review committee; **NK**, natural killer; **NR**, not reached; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **SCC**, squamous cell carcinoma; **SCCHN**, SCC of the head and neck; **TAM**, tumor-associated macrophage; **TC**, tumor cell; **TRAE**, treatment-related adverse event.

References

1. Ferris RL, et al. N Engl J Med. 2016;375(19):1856-67.
2. Chow LQM, et al. J Clin Oncol. 2016;34(32):3838-45.
3. Vermorken JB, et al. N Engl J Med. 2008;359(11):1116-27.
4. Cohen EEW, et al. Lancet. 2019;393(10167):156-67.
5. Bauml J, et al. J Clin Oncol. 2017;35(14):1542-9.
6. Guan X, et al. Clin Cancer Res. 2010;16(5):1416-22.
7. Tao Y, et al. Clin Cancer Res. 2018;24(9):2225-33.
8. Levovitz C, et al. Cancer Res. 2014;74(23):6833-44.
9. Bonner JA, et al. Oncologist. 2017;22(7):811-22.
10. Strauss J, et al. Clin Cancer Res. 2018;24:1287-95.
11. Lan Y, et al. Sci Transl Med. 2018;10(424):eaan5488.
12. Cho BC, et al. J Immunother Cancer. 2020;8(2):e000664.
13. Burtness B, et al. Lancet. 2019;394:1915-28.
14. Ferris RL, et al. Oral Oncol. 2018;81:45-51.
15. Colevas AD, et al. Ann Oncol. 2018;29:2247-53.

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Disclosures

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