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Dose expansion results of the bifunctional EGFR/TGFβ inhibitor BCA101 with pembrolizumab in patients with recurrent, metastatic head and neck squamous cell carcinoma

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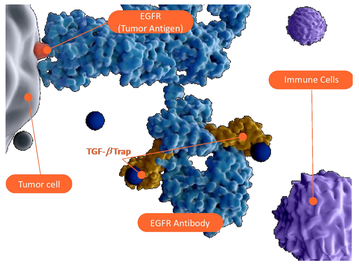
Background and Rationale

Figure 1: BCA101, a bispecific antibody targeting EGFR and TGFβ



Proposed mechanisms of action of BCA101:

- Localizes TGFβ inhibition to the TME through an EGFR-directed approach
- Aims to increase anti-tumor activity via enhanced ADCC and increased NK cell activation
- TGFβ inhibition prevents a mesenchymal phenotype to allow EGFR inhibition to continue to work and prevent resistance

Trial Design and Objectives

In a Simon-2-stage design 39 (stage 1 n=18 + stage 2 n=21) evaluable subjects with PD-L1-positive (CPS≥1) recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), who had not received any prior therapy in the R/M setting, received BCA101 (anti-EGFR/TGFβ-trap) 1500mg qw in combination with pembrolizumab 200mg q3w.

Primary Objective:

- Safety and tolerability

Key Secondary Objective:

- Evaluate preliminary anti-tumor activity

Key Inclusion Criteria:

- **HNSCC**, **metastatic** or **unresectable, recurrent** with a Combined Positive Score **(CPS) ≥1**.
- Primary tumor locations of **oropharynx**, **oral cavity**, **hypopharynx**, or **larynx**.
- **No prior systemic therapy** administered in the **R/M setting** (exception: completed >6 months prior if given as part of multimodal treatment for locally advanced disease).
- **No prior immune checkpoint inhibitors** (exception: neoadjuvant therapy (>6 months prior).
- **No prior** history of **anti-EGFR** antibodies (exception: radiosensitizing agents and multimodal treatment for locally advanced disease).
- HPV testing by **p16 IHC testing for subjects with oropharyngeal** cancer.

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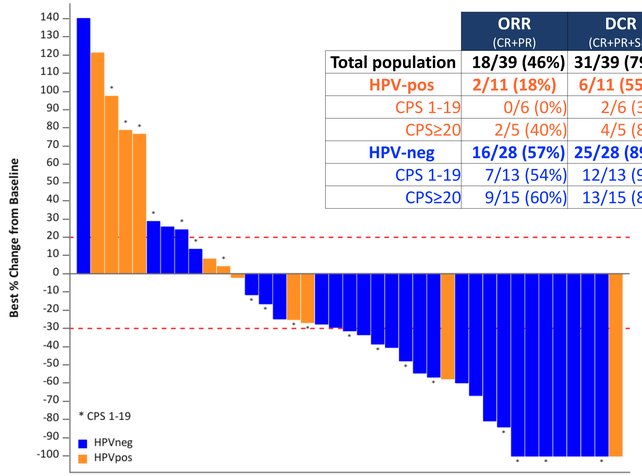
Baseline Characteristics

Table 1		N = 42 (100%)
Age	Median (range)	63 (31-84)
Sex – n (%)	Male/Female	30/12 (71% vs. 29%)
HNSCC Primary site of disease	Oropharynx	20 (48%)
	HPV-pos	12 (60% of Oropharynx)
	HPV-neg	8 (40% of Oropharynx)
	Oral Cavity	13 (31%)
	Hypopharynx	3 (7%)
	Larynx	4 (10%)
	Hypopharynx + Larynx	1 (2%)
	Maxillary Sinus	1 (2%)
CPS - n (%)	≥20	22 (52%)
	1-19	20 (48%)
Distant metastasis – n (%)		33 (79%)
ECOG Performance Status – 0 vs.1 (%)		19 vs. 23 (45% vs. 55%)

Preliminary Efficacy

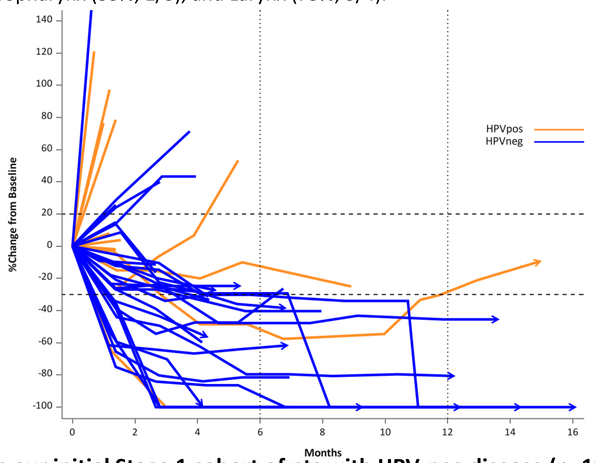
Figure 2: Preliminary anti-tumor activity of BCA101 in combination with pembrolizumab



	ORR (CR+PR)	DCR (CR+PR+SD)
Total population	**18/39 (46%)**	**31/39 (79%)**
HPV-pos	**2/11 (18%)**	**6/11 (55%)**
CPS 1-19	0/6 (0%)	2/6 (33%)
CPS≥20	2/5 (40%)	4/5 (80%)
HPV-neg	**16/28 (57%)**	**25/28 (89%)**
CPS 1-19	7/13 (54%)	12/13 (92%)
CPS≥20	9/15 (60%)	13/15 (87%)

Among HPV-neg pts:

- Similar ORR in CPS 1-19 (54%, 7/13) and CPS≥20 (60%, 9/15), as well as in pts with distant metastasis (55%, 12/22) and locoregional disease (67%, 4/6).
- Responses across mucosal subsites: Oral cavity (58%, 7/12), Oropharynx (63%, 5/8), Hypopharynx (33%, 1/3), and Larynx (75%, 3/4).



In our initial Stage 1 cohort of pts with HPV-neg disease (n=12) the mPFS has not been reached but has extended past 10 mos

Preliminary Safety

Table 2: Incidence of treatment-related adverse events (AEs)

	Safety Set (N=42)				
Most common TRAEs (≥10% of subjects*)	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Total n [%]**
Unique subjects with TRAEs**	39 (93)	35 (83)	17 (40)	1 (2)	39 (93)
Dermatitis acneiform	16 (38)	12 (29)	3 (7)	0	31 (74)
Fatigue	14 (33)	4 (10)	1 (2)	0	19 (45)
Hypophosphatemia	9 (21)	6 (14)	0	0	15 (36)
Pruritus	9 (21)	4 (10)	1 (2)	0	14 (33)
Anemia	5 (12)	4 (10)	5 (12)	0	14 (33)
Hypomagnesemia	12 (29)	1 (2)	0	0	13 (31)
Dry skin	8 (19)	3 (7)	0	0	11 (26)
Stomatitis	6 (14)	4 (10)	1 (2)	0	11 (26)
Infusion related reaction	2 (5)	5 (12)	1 (2)	0	8 (19)
AST increased	5 (12)	1 (2)	1 (2)	0	7 (17)
Blood TSH increased	7 (17)	0	0	0	7 (17)
Nausea	6 (14)	1 (2)	0	0	7 (17)
Proteinuria	6 (14)	1 (2)	0	0	7 (17)
Amylase increased	2 (5)	3 (7)	1 (2)	0	6 (14)
Decreased appetite	3 (7)	2 (5)	1 (2)	0	6 (14)
Hyponatremia	6 (14)	0	0	0	6 (14)
Rash maculo-papular	3 (7)	2 (5)	1 (2)	0	6 (14)
Diarrhea	2 (5)	2 (5)	1 (2)	0	5 (12)
Epistaxis	5 (12)	0	0	0	5 (12)
Gingival bleeding	5 (12)	0	0	0	5 (12)
Lipase increased	1 (2)	4 (10)	0	0	5 (12)
Colitis	0	2 (5)	2 (5)	0	4 (10)
Eosinophilia	3 (7)	0 (0)	1 (2)	0	4 (10)
Headache	2 (5)	1 (2)	1 (2)	0	4 (10)
ALT increased	1 (2)	0	2 (5)	0	3 (7)
Blood ALP increased	2 (5)	0	1 (2)	0	3 (7)
Lymphocyte count decreased	0	1 (2)	1 (2)	0	2 (5)
Tracheal hemorrhage	0	1 (2)	1 (2)	0	2 (5)
Encephalitis	0	0	1 (2)	0	1 (2)
Failure to thrive	0	0	1 (2)	0	1 (2)
Pericarditis	0	0	0	1 (2%)	1 (2)

AEs of Interest:

- **Skin toxicity**
  - Acneiform rash in 74% (7% G3)
- **Mucosal bleeding**
  - Generally low-grade without need for dose interruptions
  - 1xG3 related tracheal hemorrhage

Treatment-related AEs leading to:

- **Dose interruption: 15/42 (36%)**
  - Most common: 4x anemia, 3x acneiform rash, 3x colitis
- **Dose reduction: 3/42 (7%)**
  - G2 acneiform rash, G3 blood alkaline phosphatase/AST/ALT increased, G3 maculo-papular rash
- **Permanent discontinuation: 6/42 (14%)**
  - 2xG3 colitis, G3 blood alk.phos./AST/ALT increased, G3 diarrhea, G3 tracheal hemorrhage, G4 pericarditis

*Events <10% included if Grade 3/4
**Patients with any related AE

Data from open database, as of 27-Aug-2023

Conclusions

- **BCA101 + pembrolizumab** has demonstrated a **manageable safety profile.**
- **Overall response rate** of 46% in the total population, **57% in HPV-negative patients.**
- Among HPV-negative patients, **responses** were observed **across** all **mucosal subsites** and **CPS subgroups (CPS 1-19 and ≥20),** and in **both distant metastatic and locoregional** disease.
- **mPFS for stage 1 in HPV-neg patients not reached, but extended past 10 mos.**
- Data warrants further evaluation of BCA101 in combination with anti-PD1 therapy in HPV-negative patients in a randomized study.

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