A Phase I Trial of the Bifunctional EGFR/TGFβ Fusion Protein BCA101 alone and in combination with pembrolizumab in Patients with Advanced Solid Cancers

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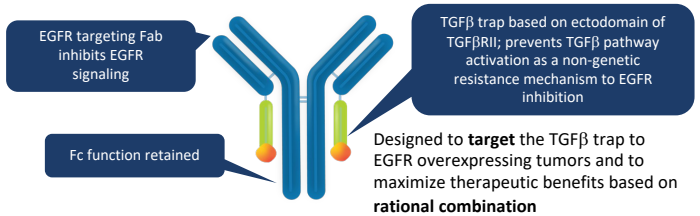
BCA101X1101 (NCT04429542)

Background and Rationale

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



Designed to **target** the TGFβ trap to EGFR overexpressing tumors and to maximize therapeutic benefits based on **rational combination**

Proposed mechanisms of action of BCA101 include inhibiting epithelial-mesenchymal transition (EMT), reducing the activity of protumorigenic cancer-associated fibroblasts, activation of immune effector mechanisms and reducing immune suppression in the tumor microenvironment.

Trial Design and Objectives

In a parallel 3+3 design, 60 subjects with advanced solid tumors refractory to standard of care therapy received escalating doses of BCA101 as single agent (n=45) or in combination with pembrolizumab (n=15) ranging from 64 mg to 1500 mg qw.

Primary Objective:

- Safety and tolerability of single-agent (SA) BCA101 and BCA101 in combination with pembrolizumab and to establish MTD and/or RD

Secondary Objectives:

- Characterize PK profile and evaluate immunogenicity in single agent BCA101 and combination with pembrolizumab
- Evaluate preliminary anti-tumor activity

Exploratory Objectives:

- Explore pharmacodynamic and biomarkers

Table 1: Demographics of treated subjects in dose escalation

		BCA101 SA (n=45)	BCA101 + pembrolizumab (n=15)
Age (y)	Mean (Range)	61.0 (43-82)	65.0 (42-81)
Sex (n)	Male / Female	22/23	10/5
Race (n)	White	36	10
	Asian	3	1
	Black	3	0
	Not reported	3	4
# prior antineoplastic therapies	Mean (Range)	4 (1-7)	3 (1-8)
Performance status	ECOG 0/1	13/32	4/11

Acknowledgements: The authors would like to thank the patients, their families and all investigators and study personnel involved in this study.

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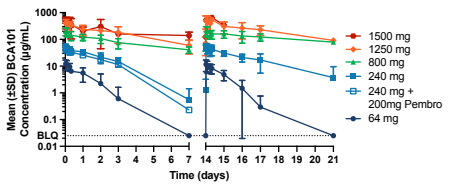
Results

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

	BCA101 Single Agent (n=45)				BCA101 + pembrolizumab (n=15)			
Most common TRAEs (≥10% of subjects)	**Grade 1**	**Grade 2**	**Grade 3**	**Total [%]**	**Grade 1**	**Grade 2**	**Grade 3**	**Total [%]**
Dermatitis acneiform	16	4	0	20 (44)	6	3	0	9 (60)
Fatigue	6	2	0	8 (18)	6	1	0	7 (47)
Headache	5	1	0	6 (13)	0	0	0	0 (0)
Rash	2	4	0	6 (13)	0	0	0	0 (0)
Rash maculo-papular	5	1	0	6 (13)	4	1	0	5 (33)
Nausea	5	0	0	5 (11)	2	0	0	2 (13)
Stomatitis	5	0	0	5 (11)	1	0	2	3 (20)
Hypomagnesemia	3	2	0	5 (11)	0	0	0	0 (0)
Epistaxis	5	0	0	5 (11)	5	0	0	5 (33)
Pruritus	4	1	0	5 (11)	2	3	0	5 (33)
Anemia	0	0	3	3 (7)	0	0	2	2 (13)
Hypophosphatemia	0	3	0	3 (7)	0	1	1	2 (13)
Diarrhea	2	0	0	2 (4)	2	0	0	2 (13)
Infusion related reaction	0	1	0	1 (2)	0	2	0	2 (13)

BCA101 is well tolerated as single agent and in combination with pembrolizumab. Most common AEs, suspected to be related to BCA101, included dermatologic events, as expected for the anti-EGFR backbone of the bifunctional protein, but there was no G3 rash. One DLT was reported at the 1250 mg qw dose level (G3 Anemia/G3 Hematuria). There were no G4/5 events related to study drug. The MTD was not reached.

Figure 2: PK concentration-time data and PK parameters. BCA101 achieves dose-proportional exposure.



PK Parameters					
Dose (mg)	AUC_{inf} (hr*µg/mL)	C_{max} (µg/mL)	$T_{1/2}$ (hr)	CL (L/hr)	V_z (L)
64	340	12.1	14	0.242	4.2
240	2870	52.8	31	0.087	3.8
240 combo	2180	50.5	27	0.131	5.5
800	19300	216	91	0.045	5.9
1250	38000	479	84	0.034	4.2
1500	78450	500	171	0.033	5.2

Figure 3: TGFβ concentration in plasma. BCA101 fully neutralizes TGFβ1 and partially neutralizes TGFβ2.

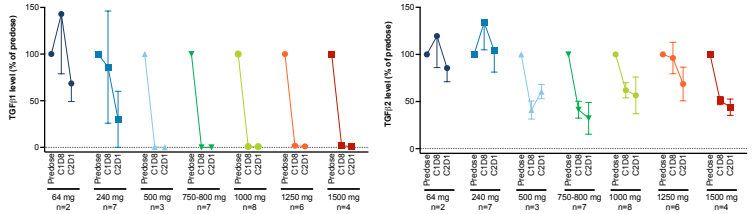


Figure 4: pSMAD2 levels in tumor tissue. BCA101 demonstrates target engagement at the tumor site, as shown by pSMAD2 reduction of up to 62% in subjects treated at higher dose levels.

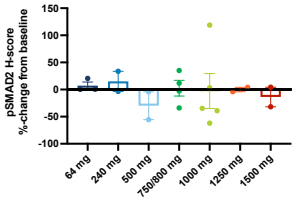


Figure 5: Preliminary anti-tumor activity of **BCA101 single agent** in dose escalation. Of 40 evaluable subjects treated at different doses, 14 had stable disease and one, with squamous cell carcinoma of the lung, had a PR

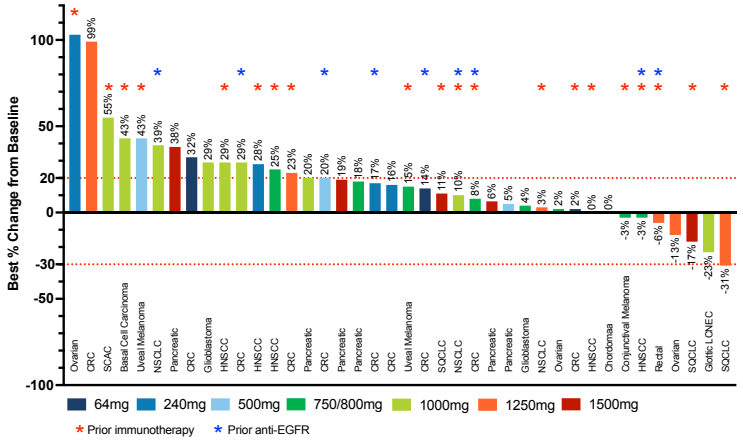
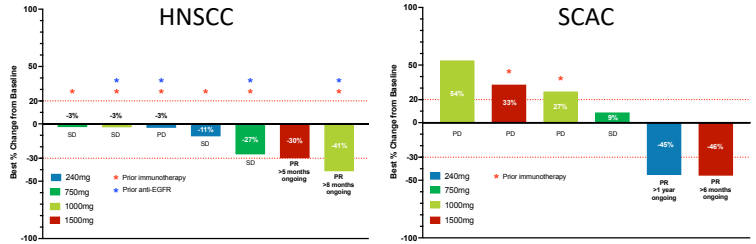


Figure 6: Preliminary anti-tumor activity of **BCA101 in combination with pembrolizumab** in dose escalation. Partial Responses were achieved in 4/13 evaluable subjects.



Efficacy data from open database, as of 09-May-2022

Conclusions

- BCA101 was safe at all tested dose levels as single agent and in combination with pembrolizumab. The MTD was not reached.
- BCA101 achieves dose-proportional PK and demonstrates target engagement in both plasma and tissue.
- The recommended dose (RD) was declared at 1500 mg qw for BCA101 as single agent and in combination with pembrolizumab.
- In this heavily pretreated and advanced cancer population, durable responses were achieved with the combination in two subjects with SCAC (one >one year) and in two subjects with HNSCC (one refractory to cetuximab, PD1 and chemo). In single agent, one subject with SQCLC (refractory to chemo and PD1) achieved PR and continues in the study.
- **Dose expansion for BCA101 + pembrolizumab in HNSCC and SCAC, as well as BCA101 single agent in cutaneous squamous cell carcinoma is ongoing.**