First-in-human Phase I Study of the Bifunctional EGFR/TGFβ Fusion Protein BCA101 in Patients with EGFR-driven Advanced Solid Cancers

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Background and Rationale

BCA101X1101 (NCT04429542) is a phase 1/ib, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and anti-tumor activity of BCA101

- **Primary Objective:**
  - Characterize safety and tolerability of BCA101 with pembrolizumab in a phase I study

- **Secondary Objectives:**
  - Explore pharmacokinetic, pharmacodynamic and anti-tumor activity

- **Exploratory Objectives:**
  - Assess changes in circulating immune profiles pre- and post-BCA101 treatment

**Investigator Decision**

(n=11)

EGFR targeting Fab

EMT (metastasis and TGFβ signaling)

Fc functions retained

**Histologically or cytologically confirmed, EGFR-expressing tumors**

**Assessed for Eligibility**

(33 total evaluable patients)

**Race (n)**

White (28)

Asian (5)

**Sex (n)**

Male (30)

Female (2)

**ECOG Performance Status**

0 (28)

1 (2)

2 (2)

3 (1)

4 (1)

**Number of Prior Treatments**

1-2 (28)

≥3 (2)

**Number of Treatment HistoTypes**

Melanoma (19)

Colorectal cancer (15)

Glioblastoma (9)

Pancreatic cancer (6)

Ovarian cancer (3)

Anal cancer (2)

Head & Neck SCC (2)

Gastroesophageal adenocarcinoma (1)

Osteosarcoma (1)

**BCA101 dose escalation continues, currently at 500 mg dose level in combination with pembrolizumab**

**Data as of 1 April 2021**

**Adverse Events in > 1 Subject**

- Fatigue
- Pruritis
- Headache
- Epistaxis
- Aspartate aminotransferase increased
- Lipase Increase
- Hypophosphatemia
- Fever
- Dermatitis acneiform
- Rash papular (n=1)

**Pharmacokinetic Summary**

- **BCA101 single agent dose qw 600 mg**
  - Cmax=2185 ± 200 mg pembrolizumab
- **BCA101 (± 200 mg pembrolizumab)**
  - Cmax=500 ± 1000 mg pembrolizumab

**PK Parameters**

- Fmax in both groups
- AUC in both groups
- T91 in both groups

**Conclusions**

- The highest tested dose level of 1 April 2021 is 1000mg in single agent and continues to be well tolerated. Rash, is the most frequent TRAE. The maximum tolerated dose has not been reached.

- One partial response has been observed in combination with pembrolizumab in a PD-L1 naïve subject with cancer of the anal canal.

- BCA101 achieves dose-proportional PK and demonstrates target engagement based on pharmacodynamic biomarkers in both plasma and tissue

- BCA101 dose escalation continues, currently at the 1250mg dose level in single agent and 750mg dose level in combination with pembrolizumab.

**Adverse Events in > 1 Subject**

- Phospho-SMAD2 is a main downstream effector of the TGFβ pathway and, therefore, indicates the activation of this signaling axis in tumors

- We assessed the changes in SMAD2 activation in tumor tissues pre- and post-treatment with BCA101 using immunohistochemistry.

- Preliminary data suggest that treatment with BCA101 at higher doses reduces phospho-SMAD2 signal in tumors.

**We assessed changes in circulating immune cell profiles pre- and post-BCA101 treatment by flow cytometry.**

- BCA101 significantly increased the percentages of T cells and classical monocytes. Conversely, BCA101 significantly decreased the percentages of granulocytic MDCs.

- Blood immune phenotyping data suggest immunopotentiating responses to BCA101 treatment.

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