Preliminary Results from a First-in-Human Phase 1 Study of a Dual-Conditionally Binding CAB-EpCAM x CAB-CD3 Bispecific T-cell Engager, BA3182, in Patients with Treatment Refractory Metastatic Adenocarcinoma

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Background

EpCAM (epithelial cell adhesion molecule): transmembrane glycoprotein expressed in virtually all epithelia-containing tissues

- Robust expression of EpCAM among adenocarcinomas of the colon, stomach, pancreas, biliary tract, lung, breast, prostate, and thyroid makes it a compelling bispecific T-cell engager (TCE) target when reliably restricting antibody binding-to the tumor microenvironment (TME).[1,2]
- The development of a non-conditionally binding EpCAM TCE, solitomab, was discontinued due to on-target injury to normal hepatic, biliary, and gastrointestinal tissues.[3]

BA3182: dual-conditionally active biologic (CAB)-bispecific TCE antibody targeting EpCAM and CD3 (Figure 1)

- Both CAB-EpCAM and CAB-CD3 binding domains of BA3182 have been designed to bind to their target proteins specifically and reversibly in the acidic TME and have markedly reduced binding outside the TME under normal physiological conditions, thus widening the therapeutic window.[4]
- CABs are not masked or caged prodrugs and do not require enzymatic cleavage for activation.[4] **(Figure 2)**
- Selective T-cell engagement by BA3182 in the TME has the potential to reduce local T-cell exhaustion and lead to sustained tumor cell killing.[4]
- Preclinical studies using dual CAB BA3182 demonstrated potent antitumor activity in a human CRC xenograft model with a >100-fold improvement in the therapeutic index compared to non-CAB EpCAM x CD3 variants.[1,4] **(Figure 4)**

Figure 1. Structure of BA3182

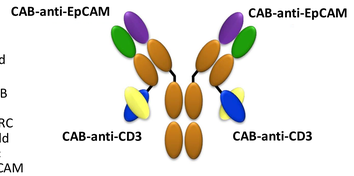


Figure 2. Proposed mechanism of action of dual-CAB EpCAM x CD3 bispecific T-cell engager BA3182

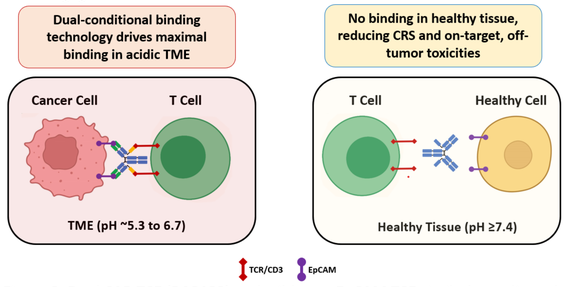
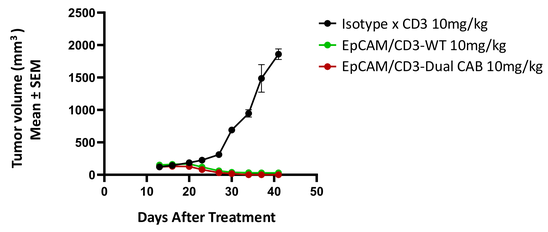


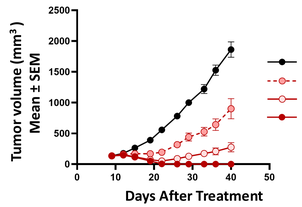
Figure 3. Dual CAB TCE (BA3182) and wild-type EpCAM TCE similarly eradicated established tumors *in vivo* in a HCT116 cell line-derived xenograft humanized mouse model of human colorectal cancer



Clinical Trial Identifier

A Phase 1 Multi-center, Open-label, Study Of BA3182 (a Bispecific Epithelial Cell Adhesion Molecule (EpCAM)/CD3 Antibody) in Patients With Advanced Adenocarcinoma.
Clinical Trial Registry Number: NCT05808634

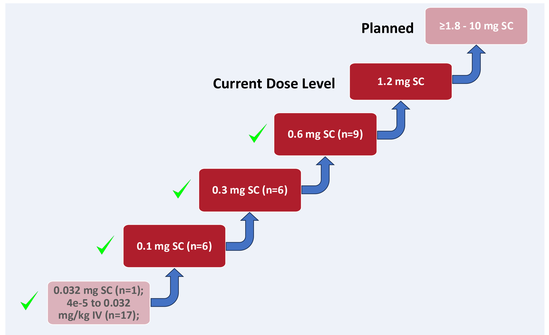
Figure 4. *In vivo* efficacy and dose response of BA3182 against HCT116 Cell-Line Derived Xenograft model of human colorectal cancer in humanized immunodeficient mice



Trial Design

Evaluating safety, tolerability, PK, immunogenicity, and antitumor activity of BA3182 in patients with advanced adenocarcinomas

Figure 5. First-in-human, multicenter, open-label, Phase 1, dose escalation study



Treatment notes:
Prophylactic acetaminophen and diphenhydramine delivered prior to all doses; starting at 0.00018 mg/kg dose level prophylactic tocilizumab (Q2W x 3 doses) given at day 1 full dose; Evaluating no tocilizumab prophylaxis with 0.3 mg dose level.
0, 1, or 2 smaller priming doses (0.00012 mg/kg, 0.0001 mg, 0.003 mg, 0.1 mg, or 0.3 mg) delivered 4-7 days prior to weekly larger treatment doses
Ongoing weekly treatment dosing continues after DLT observation interval concludes
IV = Intravenous (weight-based dosing), **SC** = Subcutaneous (flat dosing).

Key Eligibility Criteria

Age ≥ 18 years, ECOG 0 or 1, unresectable or metastatic adenocarcinoma, standard of care therapy has failed, or no curative therapy is available, or are not eligible, or intolerant to standard therapy.

Study Objectives

Primary:

Assess dose-limiting toxicity (DLT), determine the maximum tolerated dose (MTD) and/or pharmacologically active dose (PAD), and evaluate other safety parameters.

Secondary:

Evaluate preliminary antitumor activity; characterize pharmacokinetics (PK); evaluate immunogenicity.

Preliminary Results

Patient characteristics, disposition, and PK

- 39 pts were dosed per protocol in cohorts ranging from 0.0026 to 0.6 mg BA3182 QW, with 0, 1, or 2 priming doses 4 to 7 days prior to treatment dosing.
- Patients received a mean of 10 doses IV and 6 doses SC.
- Compared with IV dosing, plasma BA3182 levels associated with SC dosing showed a delayed and lower maximum concentration (Cmax) and similar trough concentrations.
- All data employ a June 20, 2025 cutoff.

Preliminary Results

Table 1. Patient characteristics

Patient Characteristic	IV N=17	SC N=22	Total N=39
Age, mean (SD), y	55 (10)	58 (10)	57 (10)
Male (n, %)	6 (35)	13 (59)	19 (49)
Female (n, %)	11 (65)	9 (41)	20 (51)
ECOG performance status			
0 (n, %)	9 (53)	15 (59)	24 (62)
1 (n, %)	8 (47)	7 (41)	15 (38)
Median lines of prior therapy	4	3	3

Table 2. Tumor histology

Tumor	IV N=17	SC N=22	Total N=39
Adenoid Cystic Carcinoma	0	1 (5)	1 (3)
Breast	2 (12)	0	2 (5)
Cholangiocarcinoma	1 (6)	1 (5)	2 (5)
Colorectal	10 (59)	12 (60)	22 (56)
Esophagus	1 (6)	0	1 (3)
Gallbladder	0	1 (5)	1 (3)
Lung	1 (6)	0	1 (3)
Ovarian	0	1 (5)	1 (3)
Pancreas	2 (12)	6 (27)	9 (23)

Safety (Table 3 & Figure 6)

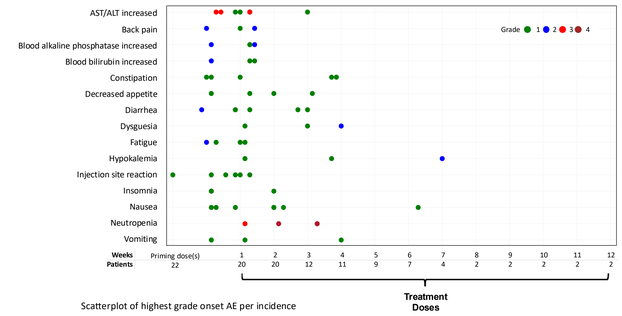
- Cytokine Release Syndrome that readily resolved was only observed with IV dosing prior to implementation of prophylactic tocilizumab for first treatment dose: G1 (n=2) and G2 (n=1).
- Early, transient, asymptomatic G1 to G3 hepatic transaminase elevations resolved without delaying next weekly treatment dose (IV and SC, n=8 total).
- Early, non-febrile neutropenia was temporally associated with combined BA3182 and tocilizumab dosing.
- Related SAEs: incidental atrial fibrillation with G2 hypotension, resolved with hydration; G2 enteritis, resolved <24 hours; and G3 acute kidney injury in setting of PD, resolved after steroid treatment.
- MTD has not yet been defined and AEs meeting criteria for DLT were observed in 2 pts.
  - Transient G3 diarrhea at the 0.0001875 mg/kg IV QW dose level, resolved; measured PK exposure was notably higher than the exposure measured from all other patients in cohort and did not align with predicted PK exposure from subsequent higher doses.
  - Transient, asymptomatic G4 non-febrile neutropenia at the 0.3 mg SC dose level; prophylactic tocilizumab was a confounding factor; neutrophil counts improved with filgrastim and BA3182 treatment resumed at 0.1 mg SC QW without neutropenia recurrence.

Table 3. IV and SC dosing cohort summary of related adverse events (AE)

Characteristic	IV N=17	SC N=22
Any AE (n, %)	16 (94)	20 (91)
Grade 3 (n, %)	8 (47)	6 (32)
Grade 3 (n, %) excluding transient asymptomatic hepatic transaminase elevations	2 (12)	3 (14)
Grade 4 (n, %)	0	1 (5)*
Serious AE (n, %)	0	3 (14)
AE leading to death	0	0
AE leading to treatment discontinuation	0	0

IV G3 related: diarrhea, blood bilirubin Increased, fatigue, ALT increased, AST increased, white blood cell count decreased
SC G3+ related: ALT increased, AST increased, acute kidney injury, neutrophil count decreased (the only related G4 AE)
*possibly related to tocilizumab

Figure 6. Temporal occurrence of ALL (related and unrelated) treatment emergent AEs occurring in >10% among patients who received SC dosing (n=22)

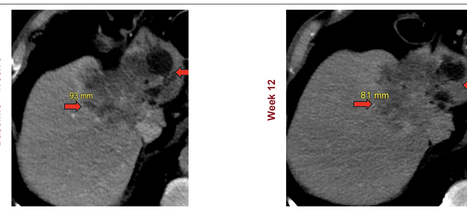


Scatterplot of highest grade onset AE per incidence

Preliminary assessment of anti-tumor activity among those with available scans

- Five patients achieved objective tumor size reductions: CRC (-8%, 10%), breast (-11%), cholangiocarcinoma (-13%) and NSCLC (-25%).
- Prolonged progression-free intervals observed in 2 CRC pts: 11 mo and 16 mo.
- Over 50% (n=12) of SC patients are pending first scan.

Figure 7. 13% tumor reduction in intrahepatic cholangiocarcinoma from BA3182 at 0.1 mg SC QW without progression for 13 weeks, ongoing



71-year-old male with stage IV cholangiocarcinoma previously treated on clinical trial with gemcitabine, cisplatin, durvalumab, and investigational agent. Since being on study, patient has experienced measured tumor reduction and symptom improvement with resolution of pain and resumption of activities of daily living. Patient dose-escalated to 0.3 mg for 15th weekly treatment dose.

Conclusions

- **BA3182 is designed to conditionally bind EpCAM and CD3 targets at low pH thus restricting beneficial cytolytic immune synapses to the TME while avoiding damage to normal EpCAM-expressing tissues**
- **Related adverse events were generally low-grade, transient, and readily manageable, suggesting the therapeutic window targeting EpCAM may be meaningfully widened**
- **Preliminary evidence of prolonged tumor control and tumor reductions have been achieved with BA3182 among heavily pretreated pts**
- **Dose escalation presently continues at 1.2 mg SC QW**

Abbreviations

AE = Adverse Event, **ALT** = Alanine Aminotransferase, **AST** = Aspartate Aminotransferase, **CAB** = Conditionally Active Biologic, **CD3** = cluster of differentiation (3), **CRC** = colorectal cancer, **Cmax** = maximum concentration, **CRS** = cytokine release syndrome, **DLT** = dose-limiting toxicity, **ECOG** = Eastern Cooperative Oncology Group, **EpCAM** = Epithelial Cell Adhesion Molecule, **FIH** = first-in-human, **IHC** = Immunohistochemistry, **IV** = intravenous (weight-based dosing), **MTD** = maximum tolerated dose, **NSCLC** = Non-Small Cell Lung Cancer, **PAD** = pharmacologically active dose, **PD** = pharmacodynamics, **PK** = pharmacokinetics, **SAE** = serious adverse event, **SC** = subcutaneous, **TCE** = T-cell engager, **TCR** = T-cell receptor, **TME** = tumor microenvironment, **WT** = wild type.

References

1. Frey G., et al. mAbs. 2024;16(1):2322562. doi: 10.1080/19420862.2024.2322562. 2. Went P., et al. *Hum Pathol.* 2004;35(1):122-8. 3. Kebenko M., et al., *Oncoimmunology.* 2018;7(8):e1450710. doi: 10.1080/2162402X.2018.1450710. 4. Chang HW., et al. *Proc Natl Acad Sci USA.* 2021;118(9):e2020606118. doi:10.1073/pnas.2020606118.

Disclosures

AS: Nothing to disclose.

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