A Phase 1/2 dose-escalation and expansion study of a conditionally active anti-AXL antibody drug conjugate (BA3011, CAB-AXL-ADC) in patients with advanced solid tumors

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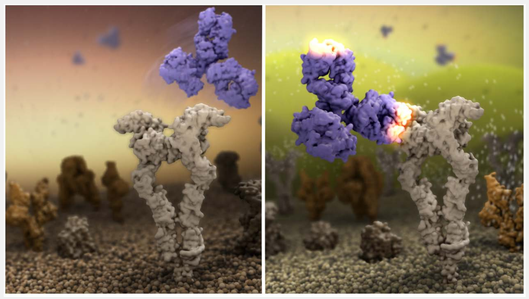
Background

- AXL is a TAM family receptor tyrosine kinase that has been implicated in the pathogenesis of many cancer types. The high level of expression on the cancer cell surface and increased expression in various settings such as PD-1 resistant tumors makes AXL a particularly attractive target for antibody therapeutics. However, AXL is expressed on many normal tissues and has been implicated in wide ranging requisite biological processes including response of endothelial cells to vascular injury, hematopoiesis, and regulation of immune responses. This normal tissue expression combined with the presence of soluble AXL may limit AXL as a target for antibody-drug-conjugates (ADC).
- The Conditionally Active Biologics (CAB) technology is a patented, proprietary platform that generates antibodies that reversibly bind to target antigen in the context of diseased tissues, but not normal tissues, by taking advantage of the unique cancer microenvironment that is produced largely as a result of the Warburg effect.
- Using our CAB technology, we have identified anti-AXL CAB Abs that reversibly bind to recombinant AXL and AXL expressing cells under conditions that are present in the tumor microenvironment, but not in normal tissues.

Figure 1. Condition specific binding of CABs

- Left panel- CAB Abs are selected to lack binding under normal conditions present in healthy tissue
- Right panel- Tumors have a unique microenvironment produced largely by Warburg effect (green). CAB Abs bind to target under conditions present in the tumor microenvironment



BA3011 (CAB-AXL-ADC)

- BA3011 binds to the AXL expressed on the tumor cell surface through the antibody portion, then BA3011 is internalized into the tumor cell where the peptide linker is cleaved by proteases to release the payload.
- The pharmacological properties of BA3011 were characterized in a number of in vitro and in vivo pharmacology studies. BA3011 binds selectively to human and cyno AXL in conditions reflective of the tumor microenvironment, but has reduced binding under normal tissue conditions.
- BA3011 demonstrated the ability to induce cytotoxicity of human tumor cell lines expressing AXL in vitro and inhibit tumor growth in LCLC-103H (lung), DU145 (prostate), and MIAPaCa-2 (pancreatic) human tumor xenografts and in selected gemcitabine resistant pancreatic cancer patient derived xenograft models in vivo.

Figure 2. Differential binding and cell killing capabilities of BA3011.

A) BA3011 binds to recombinant human (red) and cyno (orange) Axl ECD at pH 6 (solid) but not pH 7.4 (open) B) BA3011 binds to Axl protein under varying pH conditions C) BA3011 induces greater cell cytotoxicity of 293-huAXL expressing cells at pH6 (red solid) compared to pH 7.4 (red open) and compared to control ADCs (black)

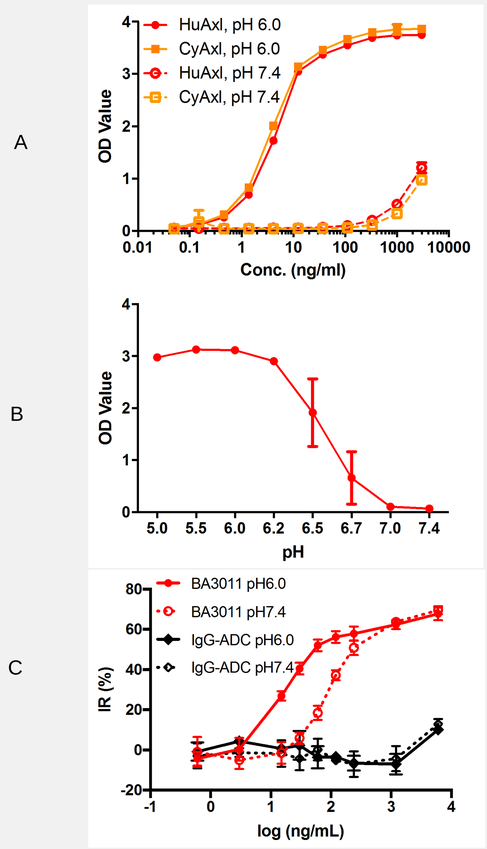
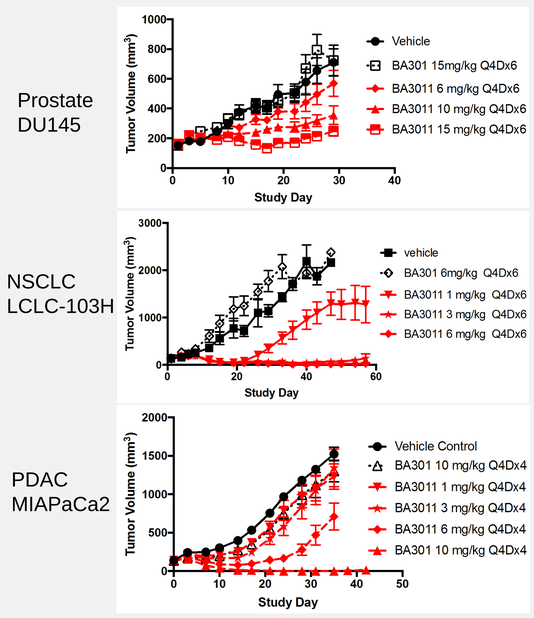


Figure 3. In vivo efficacy of BA3011 in cell line derived xenograft models

The indicated cell line models were implanted in immunodeficient mice. Tumor bearing animals were randomized to treatment groups when the tumor volume reached approximately 150 mm^3. Following randomization, animals were dosed with the indicated test article at the indicated schedule. BA3011 is indicated in red. BA301 is the parental Ab for BA3011 (black open symbols)



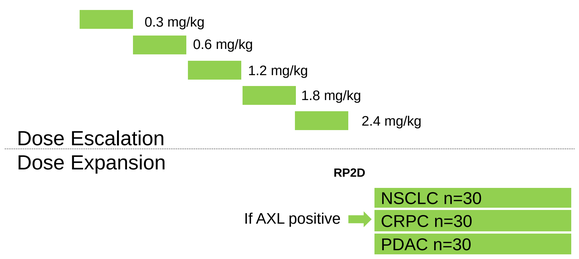
Study Objective

- A multi-center, open-label, Phase 1/2 study will evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of BA3011 in patients with advanced solid tumors.

Study Design and Dosing Regimen

- This is a Phase 1/2, open-label, multicenter study (**Figure 4**)
- The study consists of a dose escalation phase and a dose expansion phase .
- BA3011 will be administered every 3 weeks (q3w) via intravenous infusion

Figure 4. Study Design



Patient Population

- For the dose escalation phase: Patients with histologically or cytologically confirmed locally advanced or metastatic solid tumor and have failed available standard of care (SoC) therapy and for whom no curative therapy is available or who are not eligible, intolerant to or refuse standard therapy
- For the dose expansion phase: Patients with locally advanced unresectable or metastatic, non-small cell lung cancer (NSCLC), castration-resistant prostate cancer (CRPC) and pancreatic ductal adenocarcinoma (PDAC)
- Key inclusion and exclusion criteria are summarized in **Table 1**

Table 1. Key Eligibility Criteria

Key Inclusion Criteria
For the dose escalation phase: Patients with histologically or cytologically confirmed locally advanced or metastatic solid tumor and have failed available standard of care (SoC) therapy and for whom no curative therapy is available or who are not eligible, intolerant to or refuse standard therapy.
Patients must have measurable disease.
For the dose expansion phase: Patients with locally advanced unresectable or metastatic, non-small cell lung cancer (NSCLC), castration-resistant prostate cancer (CRPC) and pancreatic ductal adenocarcinoma (PDAC)
Age ≥ 18 years.
Adequate renal function
Adequate liver function
Adequate hematological function
Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
Life expectancy of at least three months.

Key Exclusion Criteria

Patients must not have clinically significant cardiac disease.
Patients must not have known non-controlled CNS metastasis.
Patients must not have received granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor support 3 weeks prior to first BA3011 administration.
Patients must not have had prior therapy with a conjugated or unconjugated auristatin derivative/vinca-binding site targeting payload.
Patients must not have Grade 2 or higher peripheral neuropathy.
Patients must not have known human immunodeficiency virus (HIV) infection, active hepatitis B and/or hepatitis C.
Patients must not be women who are pregnant or breast feeding.

Study Endpoints

Primary Endpoints

- Safety: DLTs, MTD (Phase 1 Dose-Escalation phase only), adverse events (AEs), serious adverse events (SAEs), and changes from baseline in laboratory parameters and vital signs.
- Efficacy (Phase 2 Dose-Expansion Phase only): objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.

Secondary Endpoints

- Efficacy (Phase 2 Dose-Expansion Phase only): objective response (OR), disease control, time-to-response, duration of response (DOR), progression-free survival (PFS), OS, and change from baseline in tumor size, according to RECIST Version 1.1, prostate-specific antigen (PSA) Response ≥ 50% (CRPC only)
- Pharmacokinetics of BA3011: plasma concentrations of antibody, ADC and MMAE, and PK parameters, including Cmax and AUC.
- Immunogenicity of BA3011: the number and percentage of patients who develop detectable anti-drug antibodies.

Study Status

- The study is currently recruiting patients
- Further information is available at www.clinicaltrials.gov (identifier: NCT03425279)

References

1. Schoumacher M, Burbridge M. Key Roles of AXL and MER Receptor Tyrosine Kinases in Resistance to Multiple Anticancer Therapies. Curr Oncol Rep. 2017;19(3):19.
2. Hugo W, Zaretsky JM, Sun L, et al. Genomic and transcriptomic features of response to Anti-PD 1 therapy in metastatic melanoma. Cell 2016;165(1):35–44.
3. Sharp L.L., et al. Anti-Tumor Efficacy of BA3011 a Novel Conditionally Active Biologic (CAB) anti-AXL-ADC, AACR Abstract # 827

Disclaimer

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