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Anti-Tumor Efficacy of BA3021 a Novel Conditionally Active Biologic (CAB) anti-ROR2-ADC

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ABSTRACT

ROR2 is a developmentally regulated member of the receptor tyrosine kinase orphan receptor (ROR) family and is a non-canonical receptor for selected Wnt family members. Many of the activities associated with ROR2 in development have also been implicated in cancer including cell migration and invasion. In many cancer types, expression of ROR2 correlates with advanced disease or poor prognosis. The high level of expression on the cancer cell surface has made it an attractive target for antibody-drug-conjugates (ADC). The Conditionally Active Biologics (CAB) technology is a patented, proprietary platform that selects 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-ROR2 selective Abs that reversibly bind to recombinant ROR2 and ROR2 expressing cells under conditions that are present in the tumor microenvironment, but not in normal tissues.

BA3021 is a CAB-ROR2-ADC. The pharmacological properties of BA3021 were characterized in a number of in vitro and in vivo pharmacology studies. BA3021 binds selectively to human and cyno ROR2 in conditions reflective of the tumor microenvironment, but has reduced binding under normal tissue conditions. BA3021 demonstrated ability to induce cytotoxicity of cell lines expressing ROR2 in vitro and inhibit tumor growth in LCLC-103H (lung), MDA-MB-436 (breast), HT1080 (sarcoma) and SK-MEL-5 (melanoma) human tumor xenografts and in selected sarcoma cancer patient derived xenograft models in vivo.

In conclusion, our data is consistent with our work on CAB-EGFR-ADC, CAB-AXL-ADC, CAB-PD-1 and other CAB programs and suggests that ADCs generated using the CAB technology provide biologics with increased therapeutic index. Specifically, the CAB-ROR2-ADC is an excellent candidate for evaluation as a treatment for human cancers that are ROR2 positive.

RATIONALE

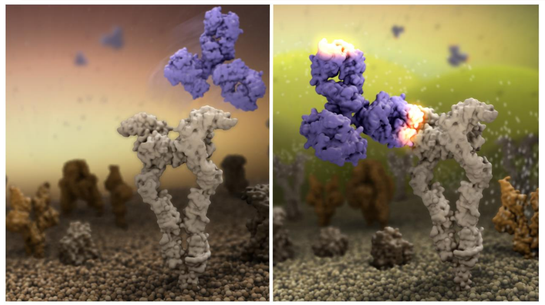

Figure 1. Condition specific binding of CABs
Left panel- CAB Abs are selected to lack binding under normal conditions present in healthy tissue
Right panel- Tumors have a unique microenvironment produced largely by Warburg effect (green). CAB Abs bind to target under conditions present in the tumor microenvironment

RESULTS

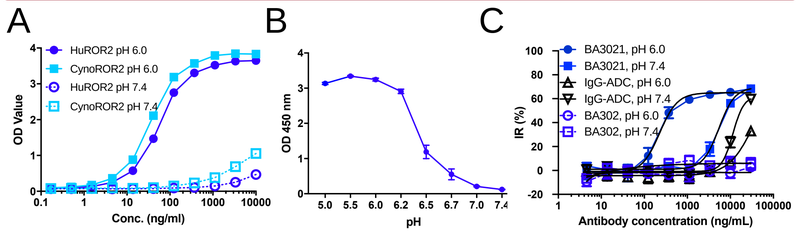

Figure 2. Differential binding and cell killing capabilities of BA3021. A) BA3021 binds to recombinant human (blue) and cyno (aqua) ROR2 ECD at pH 6 (solid) but not pH 7.4 (open) B) BA3021 binds to ROR2 protein under varying pH conditions C) BA3021 induces greater cell cytotoxicity of 293-huROR2 expressing cells at pH6 (blue solid circle) compared to pH 7.4 (blue solid square) and compared to control ADCs (black) and parental CAB-ROR2 Ab BA302 (blue open)

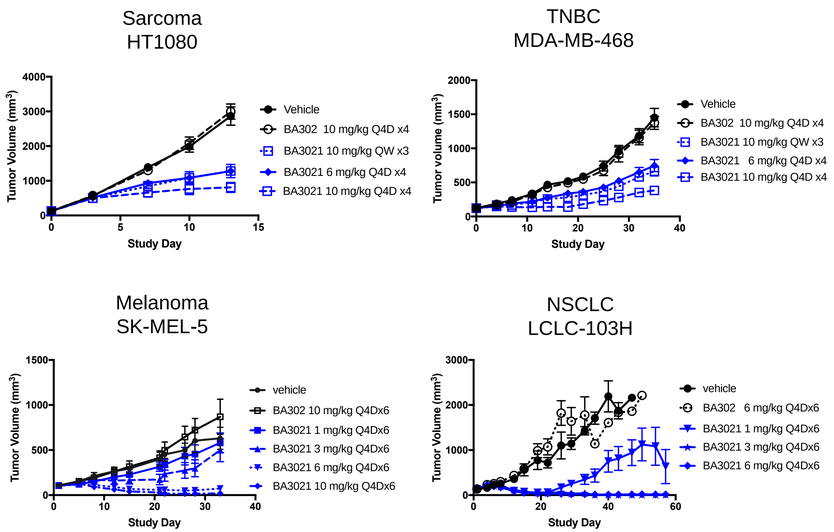

Figure 3. In vivo efficacy of BA3021 in cell line derived xenograft models The indicated cell line models were implanted in immunodeficient mice. Tumor bearing animals were randomized to treatment groups when the tumor volume reached approximately 150 mm^3. Following randomization, animals were dosed with the indicated test article at the indicated schedule. BA3021 is indicated in blue. BA302 is the parental Ab for BA3021 (black open symbols)

RESULTS

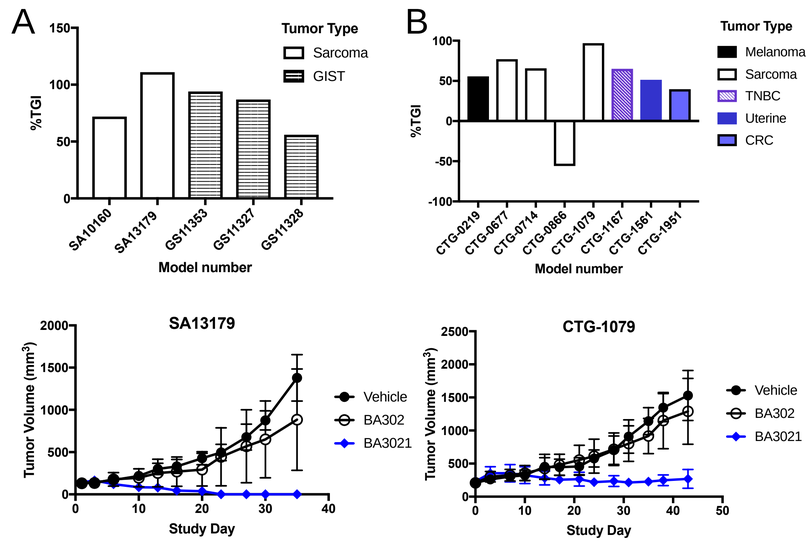

Figure 4. In vivo efficacy of BA3021 in patient derived xenograft (PDX) models. The indicated models were implanted in immunodeficient mice. Tumor bearing animals were randomized to treatment groups when the tumor volume reached approximately 150 mm^3. Following randomization, animals were dosed with vehicle control or BA3021 at 6 mg/kg Q4Dx4. % Tumor Growth Inhibition (TGI) relative to vehicle control for the indicated models Bottom panels show individual model data

CONCLUSIONS

BA3021 selectively binds to ROR2 under tumor, but not normal conditions

BA3021 is cytotoxic to ROR2 expressing cells under tumor, but not normal conditions

BA3021 is efficacious in cell line derived and patient derived xenograft models

BA3021 is planned for investigation in a multi-center, open-label Ph1/2 study to evaluate the safety, tolerability, PK, immunogenicity, and anti-tumor activity in advanced solid tumors

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