ABSTRACT

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 hemopoiesis, 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. BA3011 is a CAB-AXL-ADC. 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 MIA PaCa-2 (pancreatic) human tumor xenografts and in selected gemcitabine resistant pancreatic cancer patient derived xenograft models in vivo. In conclusion, our data is consistent with our work on CAB-EGFR-ADC, CAB-ROR2-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-AXL-ADC is an excellent candidate for evaluation as a treatment for human cancers that are AXL 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 the 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 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 over 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 immuno-deficient mice. Tumor bearing animals were randomized to treatment groups when the tumor volume reached approximately 150 mm3. Following randomization, animals were dosed with vehicle control or BA3011 at 6 mg/kg Q4Dx6. A representative tumor volume curve for model CTG-0851. B) Tumor Growth Inhibition (TGI) relative to vehicle control for the indicated models

Figure 4. In vivo efficacy of BA3011 gemcitabine resistant pancreatic patient derived xenograft (PDX) models. The indicated models were implanted in immuno-deficient mice. Tumor bearing animals were randomized to treatment groups when the tumor volume reached approximately 150 mm3. Following randomization, animals were dosed with vehicle control or BA3011 at 6 mg/kg Q4Dx6. A) Tumor volume curve for model CTG-0851. B) TGI relative to vehicle control for the indicated models

CONCLUSIONS

BA3011 selectively binds to AXL under tumor, but not normal conditions
BA3011 is cytotoxic to AXL expressing cells under tumor, but not normal conditions
BA3011 is efficacious in cell line derived and patient derived xenograft models
BA3011 is currently under 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. NCT03425279