Development of a first in class APRIL Fully Blocking Antibody BION-1301 for the Treatment of Multiple Myeloma

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INTRODUCTION

APRIL (Tumor Necrosis Factor[Ligand] Antibody, TNSF13F), is a ligand for the receptors BCMA and TACI, APRIL, serum levels are elevated in patients diagnosed with multiple myeloma (MM), Chronic Lymphocytic Leukemia (CLL), and Cerebral Carcinoma correlated with poor prognosis. Our and APRIL, hAPRIL.01A, a monoclonal antibody (mAb) designed to block APRIL interactions with BCMA (B) and TACI as a single agent or in combination with lenalidomide or other standard-of-care drugs. Blocking potency (IC50) was 1.61 ± 0.78 nM for APRIL and blocking of APRIL to BCMA or TACI.

Fig. 1 Unique epitope mapped to receptor binding sites, no other fully anti-APRIL blocking antibodies known.

Fig. 2 Binding of BION-1301 to APRIL and blocking of APRIL to BCMA or TACI.

Fig. 3 Complete blockade of APRIL-induced cytotoxicity of BCMA-Fas and TACI-Fas Jurkat transfectants by BION-1301.

CONCLUSION

We generated and functionally characterized a novel humanized APRIL, neutralizing antibody, designated BION-1301. The mechanism of action and anti-tumor activity described for the parental antibody hAPRIL.01A in vitro and in vivo strongly support the development of BION-1301 as a single agent or in combination with lenalidomide or bortezomib, and suggest a rationale for combination with checkpoint inhibitors. BION-1301 is expected to enter clinical development in 2017.

REFERENCES


BION-1301 blocks APRIL enhanced TGFβ IL-10 and PD-L1 expression. A)

H929 or MM1S MM cells were incubated overnight with or without APRIL in the presence or absence of MM cell lines. Human APRIL transgenic mice developed a CLL-like microenvironment. Blood. 2016 Jun 23;127(25):3225-36

H2228 or MM1S MM cells were incubated overnight with or without APRIL in the presence or absence of MM cell lines. Human APRIL transgenic mice developed a CLL-like microenvironment. Blood. 2016 Jun 23;127(25):3225-36

Mouse B-cells were cultured with recombinant FLAG-APRIL, proliferation and IgA secretion was determined after 6 days of incubation. The mouse parental anti-APRIL antibody NAPRIL.01A inhibits APRIL-mediated B-cell proliferation (A) and IgA production (B). Human APRIL transgenic (Tg) or wild type (WT) mice were immunized with NP-Ficoll and humoral immune response was determined by detection of IgG, IgG2a and IgA antibody titers against NP-Ficoll antigen (C). Mice were treated with PBS, NAPRIL.01A (hA.01A), NAPRIL.03A (hA0.03A) or mouse IgG1 isotype-matched control. ***= p<0.001, **= p<0.01, *= p<0.05.

Mouse B-cells were cultured with recombinant FLAG-APRIL and blocking of APRIL to BCMA or TACI. BION-1301 as a single agent or in combination with lenalidomide or other standard-of-care drugs. Blocking potency (IC50) was 1.61 ± 0.78 nM for APRIL and blocking of APRIL to BCMA or TACI.