(PF725) ABS CATA-001: A NOVEL CD38/AL BISPECIFIC FOR TREATING MULTIPLE MYELOMA

Topic: 13. Myeloma and other monoclonal gammopathies - Biology & translational research

Chengcheng Fu*[1], Yue Liu[2], Yun Xu[3], Saroja Putrevu[2], Allison Titong[2], Nicholas Spadoni[2], Bo Wang[2], Matt Hoag[2], Nathan Fay[2], Jianbo Dong[2], Jiazi Zhou[1]

[1]First Affiliated Hospital of Soochow University, Hematology, Suzhou, China;[2]Ab Studio Inc., Hayward, United States of America; [3]The First Affiliated Hospital of Soochow University, Suzhou, China;

Background

In multiple myeloma cases, approximately 15-20% suffer from light chain multiple myeloma (LCMM). Beyond that, clonal plasma cells abnormally secrete free light chain which can evolve to AL amyloidosis leading to amyloid deposition in organs. The treatment goal for LCMM is to control **plasma cell proliferation** and to rapidly reduce **free light chains (FLC)** to prevent or reverse **renal damage** . Current first-line therapy involves a proteasome Inhibitor -based triplet or quadruplet treatment, consisting of a PI +IMiD+ anti-CD38 mAb.

Aims

LCMM is frequently associated with **higher tumor burden, faster renal decline,** and **poorer prognosis** making disease control challenging. These clinical features expose the unmet needs for novel therapeutic strategies that specifically are designed to address both the malignant cancer cells and the pathogenic free light chains driving renal injury. ABS CATA-001 is a bispecific antibody targeting CD38 and free light chain (CD38/AL BsAb), representing a first-in-class approach with dual functionality of MM cell depletion with the unique catalytic capacity to bind and clear circulating free light chain aggregates. This dual mechanism positions ABS CATA-001 as a promising next-gen therapeutic candidate for effective treatment of LCMM.

Methods

ABS CATA-001was designed with a structurally symmetric bispecific antibody. The CD38 binding arm is a humanized VHH antibody discovered from panning from a computer designed pre-humanized llama VHH library. The anti-AL arm was selected from a preexisting mAb targeting aggregated light chain (2A4). The bispecific antibody was further developed using computer-aided design rationale: detuned CD38 binding to enable better safety; effective CD38 binding to lead to MM cell depletion; built-in catalytic function (computationally optimized) to enable clearance of AL aggregates by both ADPC and catalytic function MOAs. Manufacturability also was optimized by computer-aided design to increase clinical potential backed by on bench validation and clinical POCs.

Results

We selected a CD38 binding arm with a unique epitope that does not compete with Daratumumab. In order to balance safety and efficacy of CD38 affinity, we detuned the CD38 binding arm to retain MM cell depletion function, without affecting NK cells and activated T cells. Functionally, *in vitro* ADPC studies show that ABS CATA-001 can deplete H929 cancer cells in the presence of human PBMCs of a healthy donor. Furthermore, *in vivo* studies showed that ABS CATA-001 can effectively and safely deplete and inhibit MM cells without affecting body weight in a human PBMC reconstituted, and H929 engrafted NDG mouse model. Additionally, the computer designed AL binding arm showed significantly improved catalytic function, implicating therapeutic efficacy against protein aggregates. The *in vitro* assessments studies show that ABS CATA-001 significantly reduces aggregated human serum amyloid A1 (hSAA1). LCMM patient serum treated with ABS CATA-001 showed better reduction of serum light chain aggregates in all five LCMM patient donors when compared to Birtamimab. Computer-aided manufacturability optimization of ABS CATA-001 validated on bench, demonstrated high purity based on SEC-HPLC data and low aggregation potential based on DLS data.

Summary/Conclusion

These findings demonstrate that ABS CATA-001 may serve as a next generation therapy for patients with LCMM