#1633 ABL501 (PD-L1 x LAG-3), a bispecific antibody promotes enhanced human T cell activation through targeting simultaneously two immune checkpoint inhibitors, LAG-3 and PD-L1.

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ABSTRACT

PD-(L)1 blockade has demonstrated the remarkable success for cancer treatment, but significant unmet needs remain to fully achieve clinical benefit for PD-(L)1 resistant/refractory patients. Recent studies suggest that expression of Lymphocyte Activation Gene 3 (LAG-3) on exhausted T cells may be a key factor responsible for resistance to therapies targeting PD-(L)1. LAG-3 is mainly expressed on the activated T cells where it also functions as a negative regulator of T cell function. Despite enhanced antitumor efficacy in preclinical studies, combinational effect of anti-LAG-3 and PD-(L)1-targeted therapeutics has been modest unless patients were stratified with LAG-3 high group.

To overcome limitations of current LAG-3-targeting antibodies, ABL501, a LAG-3/PD-L1 bispecific antibody, is generated by the genetic fusion of scFv-PD-L1 to the LAG-3 with an engineered IgG4 isotype so that PD-1/PD-L1 blockade can be made more often in the LAG-3 high tumor microenvironment. Functional evaluation data by using various cell-based assays and patient-derived lung cancer organoids indicate that ABL501 retains full checkpoint blockade activity of both PD-1/PD-L1 and LAG-3/MHCII signaling axis. Furthermore, ABL501 shows a co-blockade of PD-(L)1 and LAG-3 leading to a synergistic increase of T cell activation higher than the enhancements induced by combination of anti-PD-L1 and LAG-3. Antitumor effects of ABL501 were demonstrated in studies with humanized Balb/c-hPD-1/hLAG-3 mice subcutaneously inoculated with CT26-hPD-L1 tumor cells. In a preclinical study using a humanized mouse model, ABL501 shows dose-dependent tumor growth inhibition with maximum effect at 10 mg/kg which was superior to anti-PD-L1 alone.

The safety of ABL501 in a pivotal GLP study was evaluated in cynomolgus monkeys by dosing twice weekly for a total of 8 administrations over a 28-day period. Reversibility of the findings was evaluated following a 56-day recovery period. The toxicokinetics (TK) and immunology of ABL501 were also determined. ABL501 was well-tolerated and the no observed adverse effect level (NOAEL) was considered to be 200 mg/kg/dose.

Together with safety profile in the toxicology study, the preclinical studies support that ABL501 effectively suppressed tumor growth through activation of immune cells by releasing immune suppressive environments. This alternative therapeutic strategy may have a potential to overcome limitations of the current immune-oncology therapy for further clinical evaluation.

Background and Mode of Action

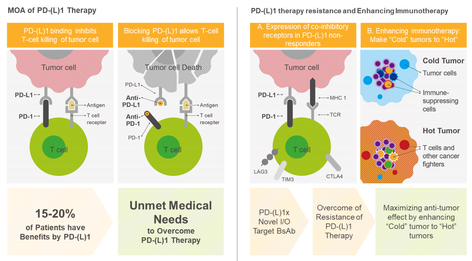

Figure 1. Next Generation of PD-(L)1 based BsAb to Overcome Resistance of PD-(L)1 for More Effective Therapy.

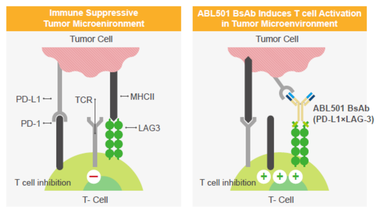

Figure 2. Proposed mode of action of ABL501
ABL501 is an bispecific antibody composed of a mAb against PD-L1 and LAG-3, designed to simultaneously block the two immunosuppressive signaling pathways commonly used by cancer microenvironment.

RESULT

Grabody I Platform: Dual Immune Checkpoint blockade, ABL501 (PDxL1-LAG-3 BsAb)

Antigen	Ka (1/Ms)	Kd (1/s)	KD (M)
PD-L1	(1.9±0.1) x 10^4	(2.9±0.3)x10^{-4}	(1.6±0.2)x10^{-8}
LAG-3	(1.4±0.2) x 10^5	(2.8±0.7)x10^{-4}	(2.0±0.4)x10^{-9}

Figure 3. ABL's Grabody™ I platform is a bispecific antibody platform. PD-L1 based dual immune checkpoint blockade, ABL501 is generated using Grabody™ I platform and simultaneously targeting dual immune checkpoint inhibitor PD-L1 and LAG-3. Binding affinity of ABL501 was measured by surface plasmon resonance (SPR).

ABL501 effectively enhances T cell activation by blocking PD-1/PD-L1 and LAG-3/MHCII In Vitro

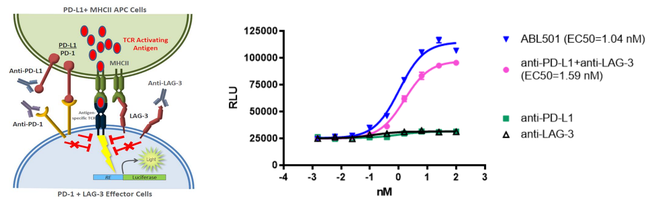

Figure 4. ABL501 shows superior activity in vitro over combination or anti-PD-L1
PD-1 and MHCII co-expressing effector cells suppressed luciferase activity when co-cultured with PD-L1 and LAG-3 expressing target cells. Suppressed luciferase activity was recovered by simultaneous release of PD-1/PD-L1 and LAG-3/MHCII blockage by ABL501

A)

Study	Mixed Lymphocyte Reaction Assay
Model	Co-culture of Allo DC+T cells from healthy donor PBMC
Measurement	IFN-gamma
Process	3 days incubation with antibodies

B)

Study	Autologous Organoid Assay
Model	Cancer organoid from lung cancer patient co-cultured with autologous PBMC
Measurement	Tumor killing
Process	3 days incubation with antibodies

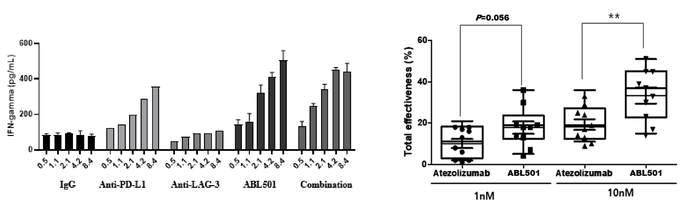

Figure 5. ABL501 shows superior activity. A) Enhanced IFN-g production of human CD3+T cells stimulated with allogeneic human dendritic cells in the presence of varied concentration of ABL501 as indicated. The concentration of IFN-g was measured with ELISA assay. A humanized IgG4 was used as a negative control. B) The efficacy of bispecific antibody ABL501 was evaluated using an Autologous organoid-based Discovery for Immuno-Oncology drug (ADIO™) platform from ORGANOIDSCIENCE. The ADIO™ platform is a co-culture system for cancer organoids and immune cells from a same patient, allowing a specific interaction between MHC and TCR to create a tumor microenvironment. The activity of ABL501 was assessed in 11 lung patient samples with the ADIO™ platform. Atezolizumab: in-house produced Genentech's anti-PD-L1 antibody

RESULT

ABL501 effectively enhances T cell activation In Vivo

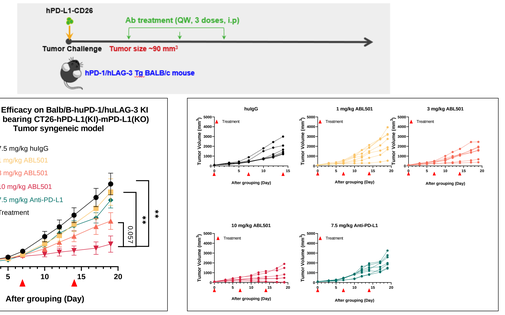

Figure 5. ABL501 shows potent anti-tumor activity in vivo
HuPD-1 and huLAG-3 double knock-in mice were inoculated with CT26 expressing hPD-L1 (hPD-L1-CT26) and treated QW total 3 doses (n=7 mice/group).

ABL501 shows good safety profile

GLP Toxicity Study

Group	Dose (mg/kg/day)	Number of Animals (M + F)	
		Dosing Phase	Recovery Phase
1	0	3 + 3	2+2
2	20	3 + 3	2+2
3	60	3 + 3	2+2
4	200	3 + 3	2+2

- ✓ All animals were well tolerated with at all dose levels
- ✓ No treatment-related adverse changes were observed
- ✓ Minor reversible decreased platelet counts and increased fibrinogen and C-reactive protein were observed at 200 mg/kg/dose in both sexes
- ✓ No treatment-related changes in in-life evaluation, safety pharmacology, immunophenotyping, and cytokines were observed

Summary

- **Molecular Information**
  - ABL501 is a bivalent bispecific antibody (bsAb) composed of a mAb against LAG-3 and scFv binders against PD-L1
  - IgG-scFv format: 200kDa
  - IgG4 S228P mutation
- **MOA & Efficacy**
  - ABL501 is a bispecific antibody composed with clinically proven dual immune modulators
  - ABL501 shows better biological activity than combination in vitro & in vivo
  - No cytokine release
- **CMC Development**
  - ABL501 was successfully produced in 1000 L scale bioreactor (GMP production)
  - DS/DP was achieved at 50 mg/ml
- **Preclinical Development**
  - GLP toxicology study was completed (well tolerated at 200 mg/kg)
  - IND submission planned in 2021 2Q
- **Business Opportunity**
  - Patent: PCT/CN2019/101747
  - Right: ABL Bio owns the global right to ABL501, except for Greater China which is owned by I-Mab Biopharma

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