First-in-human pharmacokinetics and pharmacodynamics of oral small-molecule PD-L1 inhibitor AB-101 and correlation to preclinical models

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THU-254

Arbutus BIOPHARMA

BACKGROUND

Functional cure of chronic hepatitis B (CHB) requires suppression of viral replication, reduction of HBV antigens (particularly HBsAg), and induction of anti-HBV immune responses. The PD-1/PD-L1 immune checkpoint axis plays a key role in HBV immune tolerance, which is a critical driver of CHB persistence.

AB-101 is an oral small-molecule PD-L1 inhibitor with favorable liver distribution in preclinical species and the potential to enable tunable on-target engagement while reducing toxicities associated with systemic exposure[1].

AB-101 mediates reduction of PD-L1 expression via a mechanism distinct from antibody approaches; AB-101 interacts with PD-L1 on the cell surface, resulting in dimerization of the PD-L1 protein and its internalization into the cell and degradation (Figure 1).

Preliminary pharmacodynamic (PD) data from an ongoing Phase 1a/1b study of AB-101 (AB-101-001) in healthy subjects is presented. PD association with pharmacokinetic (PK) data is described and compared to PK-PD relationships observed in preclinical mouse efficacy models.

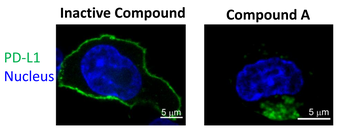


Figure 1. Confocal microscopy of CHO-K1 cells expressing human PD-L1 incubated with PD-L1 inhibitor or inactive compound at 1 µM[1].

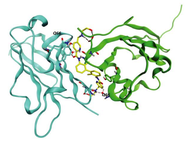


Figure 2. Co-crystal structure of representative small-molecule PD-L1 inhibitor (Compound A) and PD-L1 protein. Compound interaction with PD-L1 results in dimerization of two PD-L1 monomers (cyan and green, chains A and B)[1].

OBJECTIVES

- Assess association of clinical PD-L1 receptor occupancy following AB-101 dosing in healthy subjects with plasma AB-101 concentrations
- Compare clinical PK-PD association with PK-PD relationship observed in preclinical mouse efficacy models

MATERIALS AND METHODS

- PD-L1 receptor occupancy in healthy and chronic hepatitis B subjects in Parts 1, 2 and Cohort 3A of AB-101-001 was determined by a proprietary assay to quantitate levels of PD-L1 associated with peripheral blood cells
- PD-L1 receptor occupancy in humanized PD-L1/PD-1 mice bearing syngeneic subcutaneous MC38 tumors[1] or infected with adeno-associated virus expressing a 1.3× genome length of HBV genotype D[2] was measured by flow cytometry of tumor cells (median fluorescence intensity of $CD45^-$ human $PD\text{-}L1^+$ cells) or liver monocyte cells (median fluorescence intensity of $CD3^-$ $CD11b^+$ $CD11c^-$ $F4/80^-$ human $PD\text{-}L1^+$ cells)

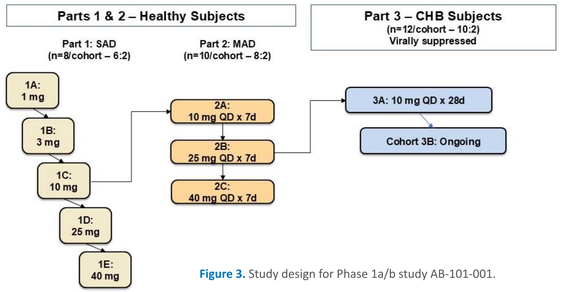


Figure 3. Study design for Phase 1a/b study AB-101-001.

RESULTS

AB-101 Mediates Dose Responsive Increases in Receptor Occupancy in Healthy Subjects

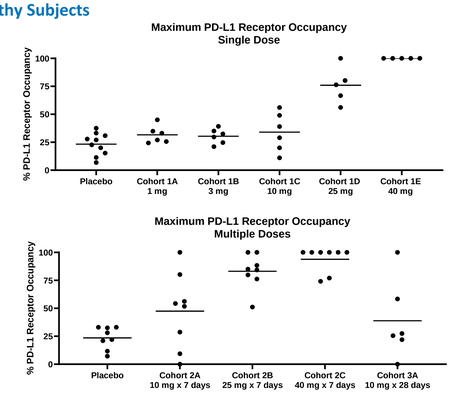


Figure 4. PD-L1 receptor occupancy in healthy and chronic hepatitis B subjects following single or multiple doses of AB-101. Placebo subjects in each cohort are shown grouped together. Shown are maximum % PD-L1 receptor occupancy for each individual subject through to 7 days post-last dose administration. Number of active subjects shown are N = 6 for SAD cohorts and N = 8 for MAD cohorts, except for Cohorts 1D and 1E (N = 5) and Cohort 3A (N = 6) where samples from 1 subject (Cohort 1D and 1E) and 3 subjects (Cohort 3A) had insufficient protein content to determine PD-L1 receptor occupancy. Data for 1 subject in Cohort 3A is pending.

- Dose responsive increases in PD-L1 receptor occupancy (RO) in blood observed with increasing AB-101 dose
- Saturation of PD-L1 RO in blood observed after dosing with 40 mg AB-101
- Safety, tolerability and subject demographics described in Poster THU-248

PD-L1 Receptor Occupancy is Dose Responsive in Humanized PD-L1 Mouse Models

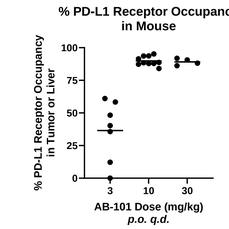


Figure 5. Data are % PD-L1 receptor occupancy in tumor cells or liver $CD14^+$ monocyte cells in an individual animal at pre-defined study termination, after AB-101 dosing for 20 or 28 days, respectively. %PD-L1 receptor occupancy calculated as 100-(PD-L1 median fluorescence intensity of cell type in individual treated animal/mean of PD-L1 median fluorescence intensity of cell type in vehicle group)*100.
N = 7 for 3 mg/kg group, N = 10 for 10 mg/kg group, N = 4 for 30 mg/kg group.

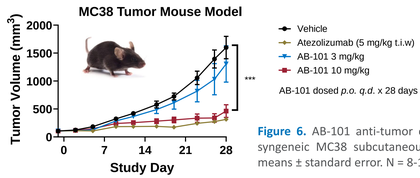
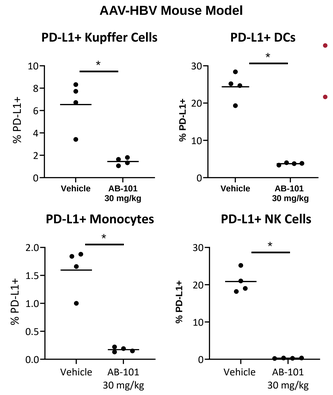


Figure 6. AB-101 anti-tumor efficacy in humanized PD-L1/PD-1 syngeneic MC38 subcutaneous mouse model. Data are group means ± standard error. N = 8-16 mice per group.

***p<0.0001 by Dunnett's T3 multiple comparisons test



- Liver target engagement confirmed
- PD-L1 reduced in liver immune cells

Animals were terminated at 24 h post-last dose of AB-101 and frequencies of PD-L1+ immune cells in liver were assessed by flow cytometry.
Kupffer cells = $CD3^-$ $CD11b^+$ $CD11c^-$ $F4/80^+$
Pan Dendritic cells = $CD3^-$ $CD11b^+$ $CD11c^+$
Monocytes = $CD3^-$ $CD11b^+$ $CD11c^-$ $F4/80^-$
NK cells = $CD3^-$ $CD11b^-$ $NK1.1^+$

*P<0.05 by unpaired t-test with Welch's correction

Figure 7. Frequency of $PD\text{-}L1^+$ immune cells in livers of AAV-HBV humanized PD-L1/PD-1 mice treated with AB-101 at 30 mg/kg for 20 days. Each symbol is an individual animal. N = 4 mice per group.

- Dose responsive increase in PD-L1 RO observed with increasing dose in humanized PD-L1/PD-1 tumor and AAV-HBV mouse models
- Increase in PD-L1 RO associated with increased anti-tumor efficacy and PD-L1 reduction in liver immune cells

PD-L1 Receptor Occupancy Increases as AB-101 Plasma Concentration Increases

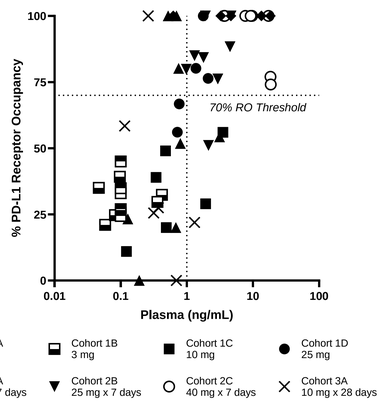


Figure 8. PD-L1 receptor occupancy (RO) is associated with AB-101 plasma concentrations in healthy and chronic hepatitis B subjects following single or multiple doses of AB-101. Shown are maximum % PD-L1 receptor occupancy for each individual subject through to 7 days post-last dose administration with that subject's maximum AB-101 plasma concentration. Number of active subjects shown are N = 6 for SAD cohorts and N = 8 for MAD cohorts, except for Cohorts 1D and 1E (N = 5) and Cohort 3A (N = 6) where samples from 1 subject (Cohort 1D and 1E) and 3 subjects (Cohort 3A) had insufficient protein content to determine PD-L1 receptor occupancy. RO and PK data for one subject in Cohort 3A is pending; data for that subject is not included in this dataset. 70% RO threshold considered maximum receptor occupancy.

- Dose responsive increase in PD-L1 receptor occupancy observed with increasing AB-101 plasma concentrations
- Saturation in receptor occupancy mostly observed at AB-101 plasma concentrations > 1 ng/mL

High Liver Concentrations and High Target Engagement Evident with Corresponding Low Plasma Concentrations

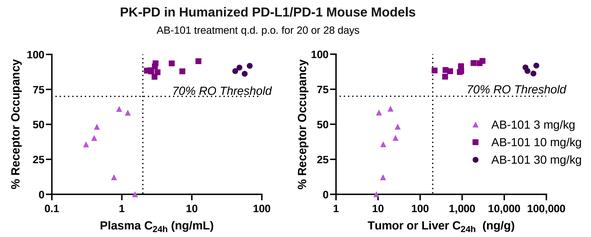


Figure 9. PD-L1 receptor occupancy is associated with low AB-101 plasma concentrations but high tumor or liver concentrations in humanized PD-L1/PD-1 mouse models following multiple doses of AB-101. Shown are % PD-L1 receptor occupancy for each individual animal at 24 h after completion of AB-101 dosing. N = 7 for 3 mg/kg group, N = 10 for 10 mg/kg group, N = 4 for 30 mg/kg group. 70% RO threshold considered maximum receptor occupancy.

No Increases in ALT with AB-101 Repeat Dosing

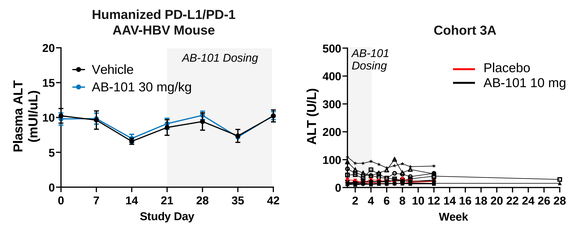


Figure 10. Plasma ALT levels in humanized PD-L1/PD-1 AAV-HBV mouse at 30 mg/kg q.d. p.o. for 20 days and in chronic hepatitis B subjects in Cohort 3A at 10 mg q.d. p.o. for 28 days.

CONCLUSIONS

- AB-101 mediates dose responsive increases in PD-L1 receptor occupancy (RO) in blood of healthy subjects and in preclinical humanized PD-L1/PD-1 mouse models
- Increases in PD-L1 RO were observed with increasing AB-101 plasma concentrations in healthy and chronic hepatitis B subjects, with saturation of RO associated with AB-101 plasma concentrations > 1 ng/mL
- Saturation of PD-L1 RO was also observed in preclinical humanized PD-L1/PD-1 mouse models at low AB-101 plasma concentrations, this was associated with high AB-101 concentrations in mouse tumor and liver
  - Given the predicted high liver:plasma ratio of AB-101 in humans, the preliminary data suggests high concentrations of AB-101 may be present in human liver; however, liver biopsies would be needed to confirm
- No increases in ALT were observed in preclinical mouse models or in chronic hepatitis B subjects administered AB-101 for 20 or 28 days
- Assessment of the relationship between RO, antiviral activity and AB-101 exposures in chronic hepatitis B subjects in Cohort 3B is ongoing

REFERENCES / ACKNOWLEDGEMENTS

1. EP Thi, et al., Poster SAT-391 at EASL Congress, London, England, 22-26 June, 2022
2. EP Thi, et al., Poster 1221 at AASLD The Liver Meeting, Washington, D.C., 04-08 Nov, 2022
3. E. Gane, et al., Poster THU-248 at EASL Congress, Amsterdam, Netherlands, 7-10 May, 2025

CONTACT

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