Integrated PK/PD Modeling for Ulildlimab, an Anti-CD73 Monoclonal Antibody, in Non-Small Cell Lung Cancer Patients

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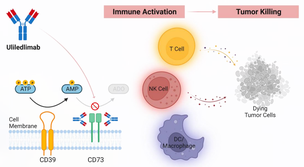
BACKGROUND

- Ulildlimab is a CD73 antagonistic monoclonal antibody designed to inhibit CD73 enzymatic activity leading to suppression of adenosine production.
- Adenosine has been shown to cause immunosuppression and PD-1/PD-L1 checkpoint inhibitor resistance.
- Complete inhibition of CD73 function across a wide range of expression and potentiation of PD-1/PD-L1 inhibitor activities *in vivo* supported Phase 1 clinical evaluation with combination therapies for non-small cell lung cancer (NSCLC) patients.

Figure 1. Mechanism of Action of Ulildlimab



METHODS

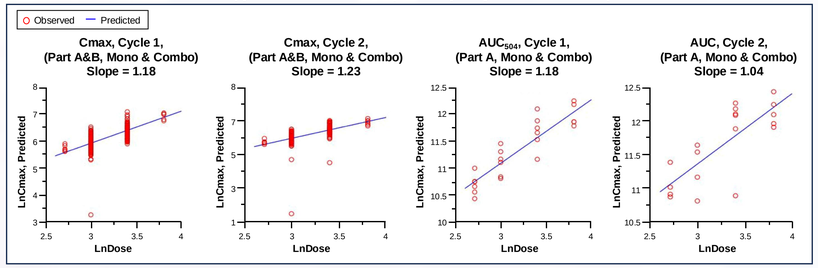
- To evaluate the impact of ulildlimab dosage after Phase 1 study, an integrated approach leveraging nonclinical and clinical results was applied, including target threshold estimation, PK/PD, population PK (popPK) modeling and simulation, and exposure-response (E-R) analyses.
- The target threshold in human serum was derived from functional activity inhibition and PK/PD analyses with consideration of tumor penetration rate.
- PK data from three previous clinical studies (4309ST101, TJ004309STM102 and TJ004309STM103) with ulildlimab monotherapy or in combination with atezolizumab or toripalimab were used to construct the popPK model.
- Study 4309ST101 is a Phase 1 open label, dose escalation study with patients received either ulildlimab alone or in combination with atezolizumab. Study TJ004309STM102 is a Phase 1/2 clinical study in Chinese patients with advanced solid tumors evaluating the safety, and efficacy of ulildlimab as a monotherapy or in combination with toripalimab (anti-PD-1 monoclonal antibody). Study TJ004309STM103 was an open label Phase 2 study evaluating safety and efficacy of ulildlimab in combination with atezolizumab in patients with advanced or metastatic solid tumors.
- The simulated exposure of ulildlimab in humans was used to evaluate trough concentrations against the target threshold of different dosing regimens.
- Serum exposure, overall response rate (ORR), and progression free survival (PFS) data from the patients with treatment-naïve metastatic NSCLC who received ulildlimab 20 and 30 mg/kg Q3W (in combination with toripalimab) were included in the E-R analyses.

RESULTS

Dose Proportionality

- Exposure of ulildlimab, both C_{max} and AUC, increased within 5 to 45 mg/kg in a dose-proportional manner, indicated linear PK at doses ≥ 5 mg/kg. Target-mediated drug disposition (TMDD) is apparent for the dose level of 2 mg/kg QW. Compared to the first dose, the exposure within the 3-week dosing interval increased during Cycle 2 (mean AUC accumulation ratio range 0.9-1.4) at 15-45 mg/kg Q3W.

Figure 2: Dose Proportionality (C_{max} and AUC) of ulildlimab at the dose levels between 15 to 45 mg/kg Q3W when administrated as monotherapy or combined with toripalimab (Study TJ004309STM102)

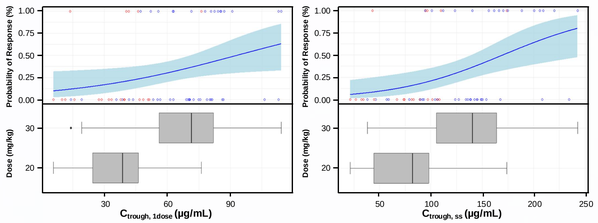


RESULTS

Exposure-Response Analysis

- Exposure-response (E-R) analysis was conducted in the first-line treatment metastatic NSCLC patients who were administered with toripalimab plus 20 or 30 mg/kg ulildlimab Q3W from TJ004309STM102 (n=67).
- A linear logistic model was used to explore the relationship between C_{trough} after the 1st dose or at steady state and ORR probability. Generally, higher trough concentrations after the 1st dose or at steady state, aligned with a higher exposure range observed at 30 mg/kg Q3W, indicating there is a higher probability of ORR with higher exposure achieved at 30 mg/kg than at 20 mg/kg

Figure 3: Logistic regression plot between ORR and C_{trough} after the 1st dose (left) and at steady state (right)

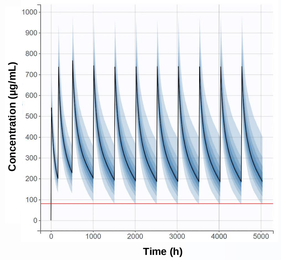


Note 1: 0 and 1 refer to if subjects experienced or did not experience objective response. Blue band represents the 5th to 95th percentile CI of a linear logistic regression fit. Horizontal boxplot below shows the exposure distribution for 20 and 30 mg/kg Q3W group.
Note 2: PD-L1 expression was not included in the E-R analysis

PK/PD Modeling and Simulation

- Ulildlimab exposure in human serum given once every 3 weeks (Q3W) was simulated based on the model parameters with estimated inter-individual variability.
- The 30 mg/kg dose with a single boost dose on C1D8 provided ulildlimab concentrations that achieved the target concentration of 80 μg/mL immediately post the first dose and maintain above the threshold afterwards.
- It was also observed that most of the simulated population (95%) could achieve the target threshold with the 30 mg/kg ulildlimab dose, but not for the 20 mg/kg dose.

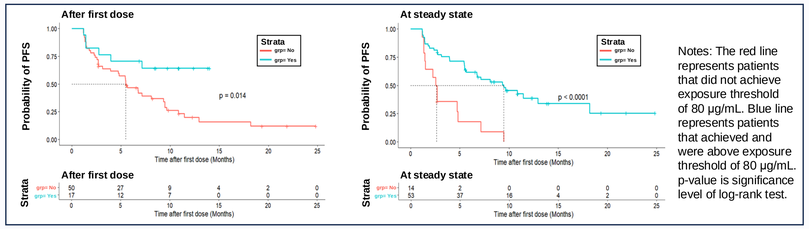
Figure 4: Simulated ulildlimab concentration-time profiles in human at 30 mg/kg with a single boost dose Q3W



Progression Free Survival (PFS) based on Exposure

- The PFS Kaplan-Meier curves stratified by a trough level of 80 μg/mL after the 1st dose and at steady state and displays a clear separation of the PFS for patients who did and did not achieve exposure equal or above 80 μg/mL.
- These PFS analyses by C_{trough} further support that the target threshold of 80 μg/mL may be clinically meaningful.

Figure 5: PFS Kaplan-Meier Plots for C_{trough} metrics by target concentration (80 μg/mL) attainment at 1st dose (left) and steady state (right)

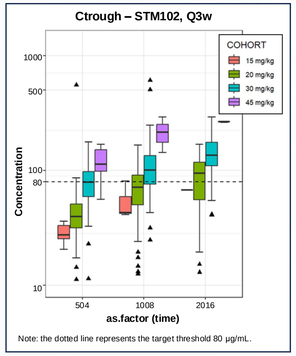


Notes: The red line represents patients that did not achieve exposure threshold of 80 μg/mL. Blue line represents patients that achieved and were above exposure threshold of 80 μg/mL. p-value is significance level of log-rank test.

Integrated PK/PD Modeling

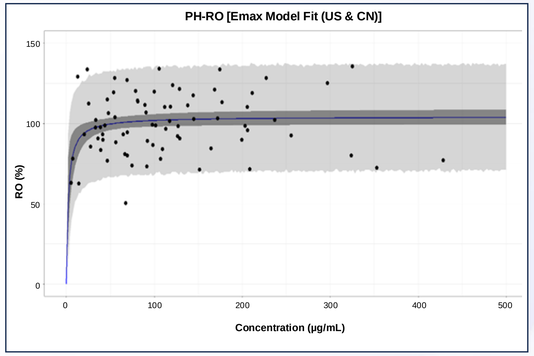
- The integrated PK/PD modeling and pharmacometric analyses indicate a positive relationship between the ulildlimab trough concentration and the probability of overall response rate. A serum level 80 μg/mL in humans was selected to be the target threshold based on the functional enzymatic inhibition (IC_{80}) and the assumption of 10% tumor penetration rate. The exposure-response showed a clear separation of the PFS probability-time curves between target threshold (80 μg/mL) stratified exposure.
- The PK simulation shows that a dose level of 30 mg/kg with a boost dose on C1D8 could achieve the target threshold immediately post the first dose and maintain above throughout treatment period.
- The observed trough concentration of ulildlimab following the first, second and the third dose. Trough concentrations continue to increase with the doses from 15 to 45 mg/kg. Combined with the findings from the ER analysis, wherein patients had an improved odds of clinical response with greater exposure, the increased exposure from 45 mg/kg dose level may potentially provide a greater clinical benefit.
- Combined PK/PD analyses illustrated that after the first dose of ulildlimab at the dose levels of 15, 20, and 30 mg/kg Q3W, CD73 receptor occupancy (RO) in peripheral B cells achieved 90% or above and maintained at high levels until end of treatment. The Emax model fit the observed results, the observed mean Ctrough at steady state indicates that the complete RO can be achieved for most patients at the dose levels ≥ 20 mg/kg

Figure 6: Observed trough concentration after administration of ulildlimab Q3W at different dose levels (Study TJ004309STM102)



Note: the dotted line represents the target threshold 80 μg/mL.

Figure 7: Peripheral B cell CD73 receptor occupancy over serum ulildlimab concentration (Study 4309ST101 and TJ004309STM102)



CONCLUSION

- A population PK model was established, and the integrated PK/PD analyses were performed.
- The E-R analysis showed a positive relationship between ulildlimab concentration and the probability of ORR in patients with NSCLC.
- A C_{trough} target threshold of 80 μg/mL may be associated with PFS benefit and is achievable by a 30 mg/kg dose with a boost dose on C1D8.
- A clinical study at the optimal dose of ulildlimab in combination with checkpoint inhibitors and chemotherapy in patients with NSCLC is planned.

Presenting author disclosures: employee of I-Mab Biopharma. WCLC travel, accommodations, and expenses from I-Mab.
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References:
Qing Zhou et al. *Journal of Clinical Oncology* 2023;41:2570.
Qing Zhou et al. *Journal of Clinical Oncology* 2023;40:e21123.