Uliledlimab and toripalimab combination therapy in treatment-naïve advanced NSCLC: Phase 1b/2 clinical trial results using CD73 as a potential predictive biomarker

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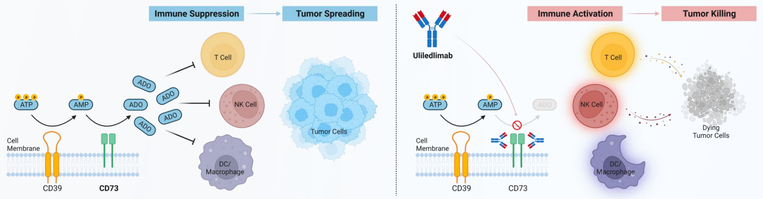
Abstract 2570

INTRODUCTION

- CD73 is the rate-limiting enzyme in the adenosine pathway which mediates immune suppression in the tumor microenvironment
- High CD73 expression correlates with poor prognosis of various cancers and is recently reported to associate with worse clinical outcome of PD-L1 therapy in patients with NSCLC[1]
- Dual targeting of PD-(L)1 and CD73 enhances anti-tumor activity in preclinical and clinical studies[2]
- Uliledlimab is a differentiated CD73 antibody that can achieve complete inhibition of CD73 activity with no hook effect
- Here we report safety and efficacy of uliledlimab in combination with toripalimab, a PD-1 antibody, in patients with treatment-naïve advanced NSCLC and explore the potential value of CD73 expression as a predictive biomarker

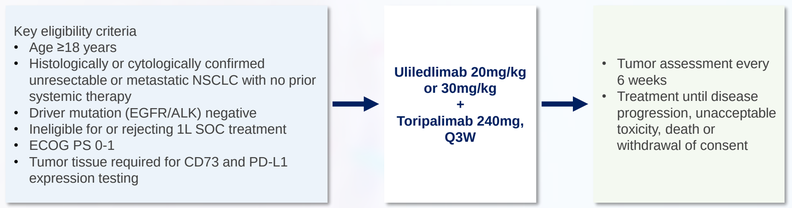
Figure 1. Mechanism of Action of Uliledlimab



METHODS

- This is a dose expansion part of a ph1b/2 study evaluating uliledlimab combined with toripalimab in patients with treatment-naïve advanced NSCLC
- The primary endpoint is safety and secondary endpoints include ORR, DCR, PFS and OS
- The correlation between baseline tumor CD73 expression and clinical response is investigated

Figure 2. Study scheme



RESULTS

Patient Demographics

- As of 4/14/2023, 70 patients with treatment-naïve unresectable or metastatic NSCLC were enrolled and received at least one dose of study treatment

Table 1. Baseline characteristics

Characteristics		All patients n=70 n (%)
Age at consent(years)		
	Median (Min, Max)	63.5 (42, 80)
Sex		
	Female	12 (17.1%)
	Male	58 (82.9%)
Race		
	Asian	70 (100.0%)
ECOG		
	0	27 (38.6%)
	1	41 (58.6%)
	Miss	2 (2.9%)
Smoking		
	No	18 (25.7%)
	Yes	52 (74.3%)
Histology		
	Non-Squamous	29 (41.4%)
	Squamous	41 (58.6%)
PD-L1 expression		
	TPS <1%	25 (35.7%)
	TPS 1-49%	24 (34.3%)
	TPS ≥50%	18 (25.7%)
	Unknown	3 (4.3%)

Safety

- Most treatment-related AEs (TRAEs) were Gr1 or Gr2 with 18.6% Gr3, 1.4% Gr4, no Gr5, and frequently reported TRAEs were chills, pyrexia, vomiting, diarrhea following initial infusion which were well managed (Table 2)
- Serious adverse reactions were 14.3% among which the most reported was pneumonia in 2 patients
- Only 2 patients discontinued treatment due to TRAE (2.9%)

Table 2. Summary of TRAEs ≥10%

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)
Chills	20 (28.6%)	9 (12.9%)	0	0	0	29 (41.4%)
Pyrexia	19 (27.1%)	5 (7.1%)	0	0	0	24 (34.3%)
Vomiting	16 (22.9%)	3 (4.3%)	1 (1.4%)	0	0	20 (28.6%)
Rash	9 (12.9%)	6 (8.6%)	0	0	0	15 (21.4%)
Diarrhoea	12 (17.1%)	0	1 (1.4%)	0	0	13 (18.6%)
Anaemia	8 (11.4%)	3 (4.3%)	1 (1.4%)	0	0	12 (17.1%)
Pruritus	11 (15.7%)	1 (1.4%)	0	0	0	12 (17.1%)
Hyponatraemia	6 (8.6%)	0	1 (1.4%)	0	0	7 (10.0%)
Hypothyroidism	2 (2.9%)	5 (7.1%)	0	0	0	7 (10.0%)

Efficacy

- The ORR was 31.3% in the overall population regardless of PD-L1 and CD73 expression (Table 3)
- With 10.4m median follow up time as of the data cut-off, 18 out of 21 responders remain on treatment, and median DOR was not reached
- PFS and OS are to be analyzed upon data maturing

Table 3. Summary of tumor response

Variables	All patients n=67† n (%)
Best overall response	
Partial response*	21 (31.3%)
Stable disease	35 (52.2%)
Progression disease	11 (16.4%)
Objective response rate*	21 (31.3%)
Disease control rate	56 (83.6%)

*Include one unconfirmed PR
†67 patients received at least one post baseline tumor assessment per iRECIST criteria

Figure 3. Best percentage change in target lesions

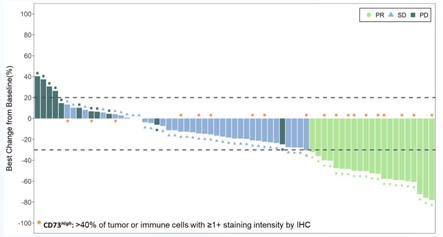
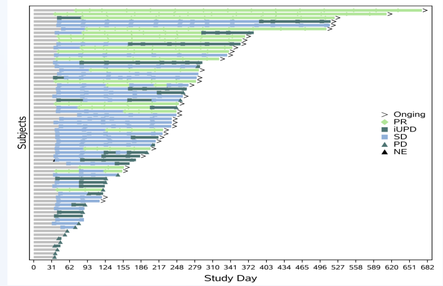


Figure 4. Duration of treatment



Biomarker analysis

- Baseline PD-L1 and CD73 expression was determined in tumor samples from 64 patients
- A preliminary cutoff score for CD73^{High} was determined as >40% of tumor or immune cells with ≥1+ staining intensity by IHC based on the receiver operating characteristic (ROC) analysis
- Among all the patients, ORR was higher in patients with CD73^{High} (53%, 10/19) as compared to those with CD73^{Low} (18%, 8/45)
- In patients with CD73^{High} and PD-L1 TPS≥1%, ORR further increased to 63% (10/16)

Figure 5. ROC analysis in patients with PD-L1 TPS≥1%

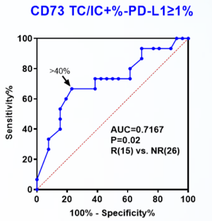


Figure 6. Overall response in PD-L1≥1%

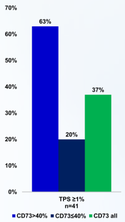


Table 4. Overall response by PD-L1 and CD73 expression

N ORR%	PD-L1 All (n=64)	PD-L1 <1% (n=23)	PD-L1 1-49% (n=24)	PD-L1 ≥50% (n=17)	PD-L1 ≥1% (n=41)
CD73 >40%	10/19 (53%)	0/3 (0%)	3/6 (50%)	7/10 (70%)	10/16 (63%)
CD73 ≤40%	8/45 (18%)	3/20 (15%)	2/18 (11%)	3/7 (43%)	5/25 (20%)
CD73 All	18/64 (28%)	3/23 (13%)	5/24 (21%)	10/17 (59%)	15/41 (37%)

CONCLUSION

- Uliledlimab is safe and well tolerated up to 30mg/kg Q3W in combination with toripalimab in patients with treatment-naïve advanced NSCLC
- Encouraging clinical response is observed by the combination therapy of uliledlimab and toripalimab
- High CD73 expression in tumor correlates with better response, particularly in those patients with PD-L1 TPS≥1%, demonstrating the potential role of CD73 as a predictive biomarker for this combination
- A biomarker-guided pivotal trial is being planned

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Reference
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2. Herbst RS, et al. J Clin Oncol 2022;40(29):3383-3393.

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