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

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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
- Dual targeting of PD-L1 and CD73 enhances anti-tumor activity in preclinical and clinical studies

Uliledlimab is a differentiated CD73 antibody that can achieve complete inhibition of CD73 expression and clinical studies have demonstrated a strong correlation between baseline tumor CD73 expression and clinical response.

METHODS

- This is a dose expansion part of a phase 2 study evaluating uliledlimab in combination with toripalimab in patients with treatment-naive 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

RESULTS

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients n=70 (n=68 evaluable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median (Min-Max) 63 (18-90)</td>
</tr>
<tr>
<td>Race</td>
<td>Asian                      52 (74.3%)</td>
</tr>
<tr>
<td>ECOG Status</td>
<td>Not Applicable            78 (108%)</td>
</tr>
<tr>
<td>Smoking History</td>
<td>No                             80 (112%)</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-Squamous               28 (40.4%)</td>
</tr>
<tr>
<td>PD-L1 expression</td>
<td>TP5&lt;1%                  25 (35.7%)</td>
</tr>
<tr>
<td></td>
<td>TP5%                       20 (28.6%)</td>
</tr>
<tr>
<td></td>
<td>TP5%≥1%                  24 (33.3%)</td>
</tr>
</tbody>
</table>

- Safety:
  - Most treatment-related AEs (TRAEs) were Gr1 or Gr2 with 18.6% Gr3, 1.4% Gr4, 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>
<thead>
<tr>
<th>Term</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Total</th>
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<tbody>
<tr>
<td>Treatment-related AEs</td>
<td>29 (41.2%)</td>
<td>20 (28.6%)</td>
<td>8 (11.4%)</td>
<td>2 (2.8%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>59 (84.3%)</td>
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<td>Chills</td>
<td>8 (11.4%)</td>
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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

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CONCLUSION

- Uliledlimab is safe and well tolerated up to 30mg/kg Q3W in combination with toripalimab in patients with treatment-naive 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 TP5≥1%, demonstrating the potential role of CD73 as a predictive biomarker for this combination
- A biomarker-guided pivotal trial is being planned

Biomarker analysis:

- Baseline PD-L1 and CD73 expression was determined in tumor samples
- A preliminary cutoff score for CD73 expression was determined as >40% of tumor or ≥1% determined in tumor microenvironment
- Among all the patients, ORR was higher in patients with CD73 expression (53%, 10/19) as compared to those with CD73<0.5% (18%, 8/45)

In patients with CD73≥0.5% and PD-L1 TP5≥1%, ORR further increased to 63% (10/16)

Key eligibility criteria:
- Age ≥18 years
- Histologically or cytologically confirmed unmistakable or metastatic NSCLC with no prior systemic therapy
- Driver mutation (EGFR/ALK) negative
- Ineligible for or refusing 1L SOC treatment
- Adequate organ function
- Tumor tissue required for CD73 and PD-L1 expression testing

Uliledlimab 20mg/kg or 30mg/kg Toripalimab 240mg Q2W

Tumor assessment every 4 weeks
- Treatment until disease progression, unacceptable toxicity, death or withdrawal of consent

Table 2. Summary of TRAEs ≥10%

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Figure 1. Mechanism of Action of Uliledlimab

Figure 2. Study scheme

Figure 3. Best percentage change in target lesions

Figure 4. Duration of treatment

Figure 5. ROC analysis in patients with PD-L1 TP5<1%

Figure 6. Overall response in PD-L1 TP5≥1%

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