Phase I Study of KN035, a novel fusion Anti-PD-L1 Antibody administered subcutaneously in Patients with Advanced Solid Tumors in the USA


Background

• KN035 is a novel fusion protein of anti-PD-L1 single domain antibody and Fc. As a recombinant fusion protein, KN035 consists of two distinct polypeptide chains linked via a pair of disulfide bonds. Each chain contains a human IgG1 Fc fragment and humanized single domain antibody.

Figure 1

• The single domain antibody (sAb) was obtained from a focused phage library, derived from phage display of human PD-L1 immunized random. The sAb was humanized hamstring. Due to two-point mutations, the Fc was fused into effector functions, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

The critical study suggested that the binding affinity of KN035 to PD-L1 was 1.46 times higher than that of durvalumab. The binding curve of KN035 and durvalumab with FcPD1 is shown in Figure 2.

• KN035 is formulated for subcutaneous (SC) injection.

• A phase 1 dose escalation study was performed in the USA to evaluate and characterize the safety and tolerability, MTD, PK/PD, and preliminary antitumor activity of single agent KN035 in patients with heavily advanced or metastatic solid tumors.

Objects and Study Population

• Primary Objectives: To evaluate and characterize the tolerability and safety profile of single agent KN035 in adult subjects with unresectable advanced cancer.

• Secondary Objectives Include: To characterize the PK profile, determine maximum tolerated dose (MTD) and to evaluate the antitumor activity of single agent of KN035.

• Study Population Induction/Exclusion Criteria

- Patients with histological or cytological confirmed advanced carcinoma, who had failed standard therapies, were intolerant to such therapy or considered ineligible for standard therapy.
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 1.
- Adequate hematologic and organ function.
- Active autoimmune disease, pneumonia were excluded.
- Subject will be enrolled if patient had prior treatment targeting PD-L1. Prior PD-L1 was defused following 4 weeks washout period.

Method

Study Design

A modified 3+3 dose-escalation design was adopted with the DLT evaluation period of 28 days.

Planned doses levels at 0.01, 0.03, 0.1, 0.5, 1.5, 2.5, and 5 mg/kg SC weekly.

Single-patient cohorts were placed at the doses levels of 0.01, 0.03, and 0.1 mg/kg/dose, whereas a 0.5 mg/kg dose was placed in the first 28-day cycle. Then 2 additional cohorts would be enrolled. Starting with 0.5 mg/kg, 3 or 6 subjects would be enrolled.

Seventy of adverse events was graded according to Common Terminology Criteria for Adverse Events CTCAE v4.0.

Responses were evaluated by RECIST 1.1 every 12 weeks.

Results

Baseline Characteristics and Disposition

- As of July 6, 2019, a total of 16 pts have been enrolled, median age 70.0 (range 53-79).

- Patient baseline characteristics and prior therapy exposure are summarized in Table 1.

- Median duration of exposure of KN035 was 9 weeks (range 3-32 weeks).

- At time of data cut-off, patients had discontinued treatment due to disease progression (n = 11) or adverse events (n = 1) or in the opinion of investigator (n = 1).

Treatment-Related adverse events (TRAEs)

- All patients experienced at least one TRAE (Table 2).

- Planned maximum dose of 10 mg/kg has been reached without DLT within the DLT evaluation window.

- TEAE Grade 3 ± attributed to KN035 were increased aspartate aminotransferase (n=2), alanine aminotransferase (n=2) and lymphopenia (n=2).

Conclusions

KN035 exhibits a favorable safety profile in patients with advanced malnourished and preliminary result demonstrates encouraging antitumor activity.

- Phase 2 study for MS144 solid tumors and a Phase 3 Study for BRAF wild-type melanoma are ongoing in China and a global Phase 3 study for hepatocellular carcinoma willinitiate soon.

Table 1 Baseline Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Median 70.0 (range 53-79)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 10, Female 6</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td>0 4, 1 12</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>Yes 14, No 2</td>
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</table>

Table 2 Summary of Best Responses

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
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<tbody>
<tr>
<td>Complete</td>
<td>1</td>
</tr>
<tr>
<td>Partial</td>
<td>2</td>
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</tbody>
</table>

Table 3 Summary of TEAEs regardless of attribution (occurring in ≥2 patients)

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Grade</th>
<th>n</th>
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<tbody>
<tr>
<td>Increased AST</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1

Figure 2

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9