Preliminary Safety, Tolerability and Efficacy Results of KN046 (an anti-PD-L1/CTLA-4 Bispecific Antibody) in combination with Nab-paclitaxel in Metastatic Triple-negative Breast Cancer (mTNBC)

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Background

mTNBC:• Triple-negative breast cancer (TNBC) is the term used to describe breast cancers that lack ER and PR expression and do not overexpress HER2. Patients with TNBC have poor clinical outcomes.
• In patients with TNBC, the expression of PD-L1 occurs mainly on tumor-infiltrating immune cells rather than on tumor cells and can inhibit antitumor immune responses. The inhibition of PD-1 and PD-L1 has been proved to be a useful treatment strategy.

KN046: Bispecific PD-L1 and CTLA-4 Antibody

• KN046 is a recombinant humanized PD-L1-CTLA-4 domain antibody Fc fusion protein.
• KN046 can block CTLA-4 with B7 and PD-L1 with PD-1 and CD80 simultaneously.
• Limited peripheral distribution of KN046 reduces treatment-associated off-target immunotoxicity.
• KN046 reserves IgG1 Fc domain, which allows for half-life extension.

Study Design

• Eligible patients were 15 years of age or older and received nab-paclitaxel plus KN046 at two dose levels (4 mg/kg Q2W or 5 mg/kg Q2W).
• Tumor response was evaluated by RECIST 1.1.
• Primary endpoint was ORR and key secondary endpoints were PFS and OS.
• Patients had a representative tumor specimen that could be evaluated for PD-L1 expression on immune cells (SP142 PD-L1 immunohistochemical assay).

Results

Disposition and Exposure:

Table 1. Patient disposition and treatment duration (as of 8-Mar-2021)

<table>
<thead>
<tr>
<th>Grade</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Not evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>2 (8.0%)</td>
<td>6 (45.5%)</td>
<td>6 (45.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>1 (9.1%)</td>
<td>8 (53.3%)</td>
<td>7 (45.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>8 (29.6%)</td>
<td>1 (3.6%)</td>
<td>14.1 (2.0, 56.0)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2</td>
<td>7 (25.9%)</td>
<td>3 (11.1%)</td>
<td>21.3%, 73.4%</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>8 (29.6%)</td>
<td>17 (48.1%)</td>
<td>14 (56.0%)</td>
<td>5</td>
</tr>
</tbody>
</table>

Median PFS in pts with PD

Figure 2. Waterfall plot (as of 8-Mar-2021)

Efficacy:

Table 2. Summary of best responses (as of 8-Mar-2021)

<table>
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Median PFS in pts with PD

Figure 3a. Kaplan-Meier plot of ORR (as of 8-Mar-2021)

Conclusion

• We report here the primary results from a phase 2 trial of KN046 in patients with mTNBC. Administered as first-line treatment, the combination of KN046 with nab-paclitaxel was well tolerated and showed favorable clinical efficacy in PD-L1 positive patients. Preliminary overall survival data is encouraging.
• Combination therapy with KN046 plus nab-paclitaxel had a safety profile that was consistent with the known toxic effects of each agent. Consent with observations from other trials of KN046, no new adverse event signals were observed. Majority of 2 Grade 3 TRAEs were hepatotoxicity and hematotoxicity, which were reversible after symptomatic treatment.

Clinical trial information: NCT03872791

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Key eligibility criteria:

• Metastatic or inoperable locally advanced TNBC
• Histologically documented
• No prior therapy for advanced TNBC
• Prior chemo in the curative setting, including taxanes allowed if TFI ≤ 12 mmoles/l
• ECOG PS 0-1

• From Jun. 2019 through Mar. 2021, 27 patients (all female) were enrolled.
• At the time of data cutoff, 5 patients had died and 4 patients were lost to follow-up. The median OS was not reached.
• Of 27 evaluable TNBC pts, the objective response rate was 40.0% and disease control rate was 96.0%.

• Of 25 evaluable TNBC pts, the objective response rate was 40.0% and disease control rate was 96.0%.
• Median PFS in pts with PD-L1 positive (IC-PD-L1>12%) was 13.8 months and 15-month OS rate was 77.1%.
• The frequency of grade 3 or 4 AEs (related to KN046) was 48.1%. KN046 related SAEs occurred in 4 patients (14.8%).
• Immune related adverse events (irAEs) occurred in 40.7% of patients. Only 3 patients experienced grade 3 irAEs.