A Phase 2 Study of Glembatumumab Vedotin, an Antibody Drug Conjugate Targeting gpNMB, in Advanced Melanoma

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Glycoprotein NMB (gpNMB)

- Internalizable transmembrane glycoprotein overexpressed in multiple tumor types
- High tumor gpNMB expression associated with worse prognosis\(^1-3\)
- BRAF/MEK inhibition upregulates expression of gpNMB\(^4\)

Glembatumumab Vedotin

- Antibody-drug conjugate containing a fully human IgG\(_2\) antibody against gpNMB linked to the potent cellular toxin MMAE*\(^\)
- Delivers MMAE to gpNMB-expressing tumor cells

*Seattle Genetics

1. Rose et al. CCR 2010
2. Li et al. APMIS 2013
3. Kuan et al. CCR 2006
4. Rose et al. CCR 2016
Prior Clinical Experience with Glembatumumab Vedotin

Three completed clinical studies in melanoma and breast cancer\textsuperscript{1-3}

- Promising overall response rate = 13\% in Phase 1/2 melanoma study
  - Unresectable Stage III or IV melanoma
  - Prior to availability of checkpoint inhibitors
  - Eligibility criteria included $\leq 1$ prior chemotherapy

- Rash, neutropenia, and neuropathy most significant treatment-related toxicities

\begin{center}
\begin{tikzpicture}
\begin{axis}[
    width=\textwidth,
    height=0.5\textwidth,
    xtick={0,5,10,15},
    xticklabels={0,5,10,15},
    ytick={0,50,100},
    yticklabels={0,50,100},
    xmin=0, xmax=15,
    ymin=0, ymax=100,
    xlabel=Time (months),
    ylabel=Progression-Free Survival (\%),
    legend style={at={(0.5,0.95)},anchor=north west},
    \]

\addplot[blue,mark=square] coordinates {
    (0,100)
    (5,75)
    (10,50)
    (15,25)
};
\addplot[red,mark=x] coordinates {
    (0,100)
    (5,95)
    (10,90)
    (15,85)
};
\legend{Rash in Cycle 1 ($n=46$), No Rash in Cycle 1 ($n=19$)}
\end{axis}
\end{tikzpicture}
\end{center}

Development of Rash Associated with Greater PFS and ORR\textsuperscript{1}

\begin{itemize}
\item Rash, neutropenia, and neuropathy most significant treatment-related toxicities
\end{itemize}

CDX011-05 Phase 2 Study Design

• Unresectable Stage III/IV melanoma
  – Measurable disease
• Received checkpoint inhibitor
  – Anti-CTLA-4, -PD-1, or -PD-L1
• Received BRAF/MEK inhibitor if BRAF$^{V600}$ mutation
• ≤1 prior cytotoxic regimen

Single Arm

• Glembatumumab vedotin (1.9 mg/kg every 3 weeks, 90-minute IV infusion)
• Tumor assessments every 6 weeks for 6 months, then every 9 weeks

Open Label

Primary Endpoint
• Overall Response Rate (RECIST 1.1)
  – Threshold for positive study: >6 responses in 52 pts
  – Type I error rate ($\alpha$): 0.05 (1-sided exact binomial); Power 80%

Secondary Endpoints
• Progression Free Survival
• Duration of Response
• Overall Survival
• Safety
• gpNMB expression vs. outcome
## Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Enrolled Patients (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male (n [%])</strong></td>
<td>34 (55)</td>
</tr>
<tr>
<td><strong>Age, years (median [min, max])</strong></td>
<td>67 (37-86)</td>
</tr>
<tr>
<td><strong>Stage IV (n [%])</strong></td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>62 (100)</td>
</tr>
<tr>
<td></td>
<td>55 (89)</td>
</tr>
<tr>
<td><strong>Duration of Advanced and/or Metastatic Disease, Months (median [min, max])</strong></td>
<td>25.3 (3.1 - 318.8)</td>
</tr>
<tr>
<td><strong>Any BRAF&lt;sup&gt;V600&lt;/sup&gt; Mutation (n [%])</strong></td>
<td>12 (19)</td>
</tr>
<tr>
<td><strong>&gt; 4 Disease Sites (n [%])</strong></td>
<td>27 (44)</td>
</tr>
<tr>
<td><strong>No. of Prior Regimens (median [min, max])</strong></td>
<td>3 (1, 8)</td>
</tr>
<tr>
<td><strong>Prior Therapies (n [%])</strong></td>
<td></td>
</tr>
<tr>
<td>Checkpoint Inhibitor</td>
<td>62 (100)</td>
</tr>
<tr>
<td>Anti-CTLA-4</td>
<td>58 (94)</td>
</tr>
<tr>
<td>Anti-PD-1/PD-L1</td>
<td>58 (94)</td>
</tr>
<tr>
<td>BRAF or BRAF/MEK Inhibitor</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Cytokines</td>
<td>23 (37)</td>
</tr>
</tbody>
</table>
Safety

Treatment-Related Adverse Events (>20%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Overall N (%)</th>
<th>Grade ≥ 3 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Treatment-Related Event</td>
<td>55 (89)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>30 (48)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>29 (47)</td>
<td>N/A</td>
</tr>
<tr>
<td>Rash</td>
<td>27 (44)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (39)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (36)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>17 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>17 (27)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (21)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

- Most frequent grade ≥ 3 toxicity was neutropenia
- 2 patients discontinued due to grade 2 sensory neuropathy
  - No other discontinuations due to a treatment-related toxicity
- 1 patient with grade 5 pneumonia possibly treatment-related
Clinical Efficacy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint: Confirmed Responses (ORR); P=0.035*</td>
<td>7/62 (11%; 95% CI: 4.7, 21.9)</td>
</tr>
<tr>
<td>* 1-sided exact test comparing to ORR of 5%</td>
<td></td>
</tr>
<tr>
<td>Any Response Including Those Not Confirmed at Subsequent Assessment</td>
<td>10/62 (16%; 95% CI: 8.0, 27.7)</td>
</tr>
<tr>
<td>Stable Disease ≥ 6 weeks</td>
<td>33/62 (53%; 95% CI: 40.1, 66.0)</td>
</tr>
<tr>
<td>Disease Control Rate (SD or better ≥ 3 months)</td>
<td>32/62 (52%; 95% CI: 38.6, 64.5)</td>
</tr>
<tr>
<td>Median Duration of Response, months</td>
<td>6.0 (95% CI: 4.1 to not reached)</td>
</tr>
</tbody>
</table>

### Duration of Tumor Responses

- **Pt 1**: First response date, Complete Response (CR), Partial Response (PR), Continues on treatment
- **Pt 2**: First response date, Complete Response (CR), Partial Response (PR)
- **Pt 3**: First response date, Complete Response (CR), Partial Response (PR)
- **Pt 4**: First response date, Complete Response (CR), Partial Response (PR), Progressive Disease
- **Pt 5**: First response date, Complete Response (CR), Partial Response (PR)
- **Pt 6**: First response date, Complete Response (CR), Partial Response (PR)
- **Pt 7**: First response date, Complete Response (CR), Partial Response (PR)
Clinical Efficacy

Maximal Change in Tumor Size from Baseline

- Best Overall Response
  - Progressive Disease
  - Stable Disease
  - Partial Response
  - Complete Response
  - On Treatment

*Single time-point PR; *Single time-point CR
Example of Objective Response

Baseline

Week 35

- 68 year old female with retroperitoneal lymph node and bone metastases
- Progressed on pembrolizumab prior to study enrollment
- Additional prior therapies included an autologous tumor vaccine and ipilimumab
- 73% tumor reduction after 11 doses glembatumumab vedotin
- Remains on treatment as of 19 months
Progression Free Survival and Overall Survival

**Progression Free Survival**

- Median PFS (months [95% CI]) = 4.4 (2.6, 5.5)

**Overall Survival**

- Median OS (months [95% CI]) = 9.0 (6.1, 13.0)
Early Development of Rash Associated with Improved Outcome

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>Median PFS (months [95% CI])</th>
<th>Median OS (months [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash in Cycle 1</td>
<td>4/19 (21%)</td>
<td>5.5 (2.9, 7.6)</td>
<td>15.8 (6.7, Not reached)</td>
</tr>
<tr>
<td>No Rash in Cycle 1</td>
<td>3/43 (7%)</td>
<td>4.0 (1.4, 4.4)</td>
<td>6.6 (4.6, 11.5)</td>
</tr>
</tbody>
</table>

Progression Free Survival

HR = 0.39 (0.20, 0.78)
P = 0.006

Overall Survival

HR = 0.44 (0.21, 0.92)
P = 0.026
Assessment of Tumor gpNMB Expression

- Pre-treatment tumor tissues analyzed by immunohistochemistry at a centralized laboratory
- Tumors were gpNMB+ for all 59 pts with available tissue, and 78% had tumors with 100% epithelial cells gpNMB+
- No clear correlation of gpNMB expression and outcome
- Consistent expression (95-100% gpNMB+) between primary and metastatic tumor for 10 patients with available matched tissues
Conclusions

• Encouraging antitumor activity in poor-prognosis patients with checkpoint inhibitor-refractory melanoma
  – Primary study endpoint of ORR was met: promising ORR / duration of response
  – Majority of patients experienced disease control

• Tolerable safety profile consistent with prior studies

• High gpNMB expression in this population with no clear correlation of gpNMB expression and outcome

• Treatment-related rash in cycle 1 may be a predictive marker of response, consistent with previous experience
Future Directions

- Additional cohorts evaluating glembatumumab vedotin in combination with the CD27 agonist antibody, varlilumab, or with PD-1 inhibitors are ongoing
  - Microtubule-depolymerizing cytotoxic agents such as MMAE convert tumor-resident tolerogenic dendritic cells into active antigen-presenting cells\(^1,2\)
  - Synergistic antitumor activity between ADC-MMAE with checkpoint inhibitors in preclinical studies\(^1\)

1. Muller et al. STM 2015
2. Muller et al. CIR 2014
Acknowledgements

Thank you to the study patients and their families

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  - Florida Cancer Specialists
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