Frequent Dosing and GPNMB Expression with CDX-011 (CR011-vcMMAE), an Antibody-Drug Conjugate (ADC), in Patients with Advanced Melanoma

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BACKGROUND
CDX-011 (glembatumumab vedotin) is designed to be stable in the bloodstream, but releasable in GPNMB-positive melanoma cells. GPNMB expressing tumor cells, resulting in a targeted cell-killing effect.

- Linker/MMAE technology, as used in brentuximab vedotin (SGN-35), licensed from Seattle Genetics.

STUDY DESIGN AND CONDUCT

Patient Population
Unresectable Stage III or Stage IV melanoma
Progressive disease at entry
Karnofsky PS ≤ 70
≤ 1 prior cytotoxic regimen
Any number of cytotoxic, immune, or targeted therapies

Study Design
- Multicenter, Open-label, Phase III Trial
- CDX-011: 90 minute IV infusion
- Extended dosing schedule
- Sequential dose-escalation cohort (n=35 patients)
- Phase II expansion at MTD
- Primary activity endpoint: Objective Response Rate (ORR) (p≤0.05, p≤0.05, p≤0.05, p≤0.05)
- Subsequent evaluation of more frequent dosing
- Do 2 weeks of 3 weeks q2/3w schedule
- Sequential dose-escalation cohort (n=6 patients)
- Expand to option (expansion testing) at n=15 MTDs

PMI CHARACTERISTICS, TOLERABILITY AND TREATMENT EXPOSURE

Demographic Characteristics (n=117)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Age (years) (median [range])</td>
<td>75 (40-92)</td>
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<tr>
<td>Karnofsky PS (n=117)</td>
<td>82 (43-100)</td>
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<tr>
<td>Stage (n=117)</td>
<td>11 (13%)</td>
</tr>
<tr>
<td>II</td>
<td>104 (95%)</td>
</tr>
<tr>
<td>III</td>
<td>59 (50%)</td>
</tr>
<tr>
<td>Baseline IUL (n=117)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>Grade of melanoma disease (n=117)</td>
<td>1.0 (0.1-1.0)</td>
</tr>
<tr>
<td>Duration of metastatic disease (n=117)</td>
<td>0.4 (0.1-1.0)</td>
</tr>
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GPNMB DETECTION

- Tumor tissue was analyzed for GPNMB expression at a central laboratory via IHC, using a polyclonal CR011 monoclonal antibody.
- Tissue for 33 of 42 (79%) patients analyzed to date is positive for GPNMB expression.

PHARMOCINETICS

- For the q2/3w schedule, the half-life of antibody-drug conjugate (ADC) and total toxin (TA) increased with dose (ranges: 16-82 hours and 15-120 hours, respectively). The cumulative AUC for the q3w schedule was 4.2-169 hours.
- Across all dose levels and schedules, maximum exposure to TA is higher than the 1:1 (CR011) suggested toxicity for the q2/3w schedule.
- ORR for patients with strong GPNMB expression and M1c disease = 2/5 (40%).
- One patient continues on treatment.

CONCLUSIONS

- CDX-011, dosed either q3w, q2/3w or qw, is active in advanced melanoma.
- The primary activity endpoint has been met.
- Overall Response Rate (ORR) of 21% is promising.
- There is evidence of increased activity with the q2/3w and qw schedules over the q3w schedule but this is accompanied by increased toxicity.
- Strong GPNMB expression on the development of rash, which may be related to the presence of GPNMB in the skin, are associated with greater progression-free survival.

Further evaluation of CDX-011 in melanoma will include patients with strong GPNMB expression and combination therapy intended to upregulate GPNMB.