Correlation of GPNMB Expression with Outcome in Breast Cancer (BC) Patients Treated with the Antibody-Drug Conjugate (ADC), CDX-011 (CR011-vcMMAE)

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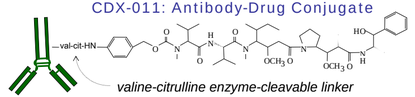
BACKGROUND

CDX-011 (glembatumumab vedotin) is designed to be stable in the bloodstream, but to release MMAE upon internalization into 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.

CDX-011: Antibody-Drug Conjugate

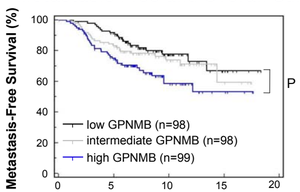


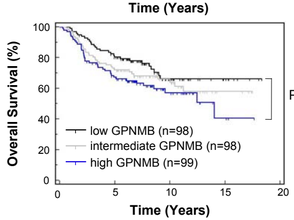
CR011: fully-human IgG_2 targeting GPNMB **MMAE:** dolastatin-like tubulin inhibitor

GPNMB:

- An internalizable glycoprotein expressed in more than 40% of breast cancers,[1] as well as other tumor types
- promotes the migration, invasion, and metastasis of breast cancer
- expressed within the tumor by epithelial tumor cells as well as stromal cells [1]
- highly expressed in triple-negative breast cancers and is associated with increased risk of recurrence within this subtype [1]

Patients with High GPNMB-Expressing Tumors Have Significantly Shorter Metastasis-Free and Overall Survival





1. Rose AA, et al. Clin Cancer Res 2010;16:2147-56.

In a Phase I/II study in patients with metastatic melanoma, CDX-011 has been shown to be active with observed objective responses. (Abstract #8525)

TRIAL DESIGN AND UPDATED RESULTS

Patient Population: 42 patients with heavily pre-treated, progressive, locally advanced or metastatic breast cancer were enrolled

Patient Characteristics (n=42)			
Median age *(range)*			58 (33-76)
ECOG Performance Status *(%)*			0=50%; 1=45%; 2=5%
Visceral metastases (liver and/or lung) *(n[%])*			34 (83%)
Triple-negative disease (ER-/PR-/HER-2/neu-) *(n[%])*			13 (32%) [a]
Median no. prior anticancer regimens *(range)*			7 (2-18)
Prior treatments received:			
Taxane	42 (100%)	Vinorelbine	23 (55%)
Capecitabine	41 (98%)	Epothilone	17 (40%)
Anthracycline	38 (90%)	Trastuzumab	14 (33%)
Hormonal therapy	30 (71%)	Lapatinib	8 (19%)
Gemcitabine	27 (64%)	Investigational agents	8 (19%)
Bevacizumab	24 (57%)		

[a] HER-2/neu status is unknown for one patient.

Treatment:

In each cohort, CDX-011 was administered as a 90 minute IV infusion, once every three weeks until intolerance or progression.

Study Design/Conduct:

Phase I (n=14): Standard 3+3 dose-escalation to evaluate tolerability and establish MTD

1.34 mg/kg n = 2 → 1.00 mg/kg n = 3 → 1.34 mg/kg n = 3 → 1.88 mg/kg n = 6

- Starting dose and maximum dose level were pre-defined, based on MTD of 1.88 mg/kg in the melanoma study.
- At the 1.34 mg/kg dose, 2/2 patients experienced DLT (worsening baseline neuropathy)
- Study was amended to exclude patients with baseline neuropathy ≥ Grade 2
- Dose-escalation resumed at 1.00 mg/kg, and completed through the pre-defined maximum dose of 1.88 mg/kg, with no further DLT

Phase II (n=28): Simon Two-Stage Design

1.88 mg/kg n = 28

Stage 1: Proceed to stage 2 if ≥ 2 patients without progression at 12 weeks (P_0 = ≤ 10%; P_1 = ≥ 30%)
Final study analysis: P_1 accepted if ≥ 5 out of 25 patients without progression at 12 weeks

Tolerability:

Patients received a mean of 3.5 (range: 1-8) cycles of treatment on study.

Treatment-Related Adverse Events	Total *(n [%])*	≥ Grade 3 *(n [%])*
Fatigue	21 (50%)	1 (2%)
Rash	20 (48%)	2 (5%)
Nausea	17 (40%)	2 (5%)
Neuropathy	16 (38%)	3 (7%)
Alopecia	14 (33%)	-
Neutropenia	13 (31%)	9 (21%)
Vomiting	13 (31%)	2 (5%)
Decreased appetite	11 (26%)	-
Asthenia	3 (7%)	2 (5%)

Table includes events potentially related to treatment, occurring in ≥ 20% of patients overall or ≥ Grade 3 severity in ≥ 5%. One event of Grade 4 neutropenia was reported; all other treatment related events were ≤ Grade 3.

Primary Efficacy Endpoint: Progression-Free Survival (PFS) at 12 Weeks

Statistical Plan: Study considered positive with ≥ 5 out of 25 patients without progression at 12 weeks

	Progression-free at 12 weeks
Primary Endpoint: Phase II population (1.88 mg/kg)	9/26 (35%)

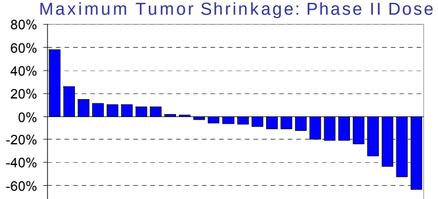
Phase II population includes the 28 patients enrolled in the Phase II study portion. Two patients are excluded due to study discontinuation in the absence of progression prior to 12 weeks.

Anti-tumor Activity: Phase II Dose (1.88 mg/kg)

	All Patients (n=34) [a]	Triple-negative disease (n=10)
Best Response (RECIST)		
Partial Response (PR)	4/33 (12%)	2/10 (20%)
Confirmed PR	2/33 (6%)	1/10 (10%)
Stable Disease (SD) or better	19/33 (58%)	8/10 (80%)
Any tumor shrinkage	16/26 (62%) [b]	7/9 (78%) [c]
Stable disease > 12 weeks	13/33 (39%)	7/10 (70%)
Median PFS (weeks)	9.1	17.9

[a] Patients treated at the Phase II dose (1.88 mg/kg; n=34), including dose-escalation (n=6) and Phase II (n=28). One patient is excluded due to study discontinuation prior to post-baseline tumor assessment.
[b] Excludes an additional seven patients without post-baseline imaging of measurable lesions.
[c] One patient without post-baseline imaging of measurable lesions is excluded.

Maximum Tumor Shrinkage: Phase II Dose



Maximum percent decrease in the sum of longest diameters of target lesions is plotted individually for all patients treated at the Phase II dose (1.88 mg/kg), including dose-escalation (n=6) and Phase II (n=28). Excludes eight patients without post-baseline imaging of measurable lesions.

GPNMB EXPRESSION ANALYSIS

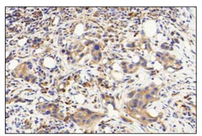
Tumor samples from this completed Phase I/II study were analyzed for GPNMB using a newly developed, validated, centralized assay intended for use in Phase II studies of CDX-011.

- Tumor tissue submission was optional; samples were tested for a subset of patients across all dose groups
- Collected samples were generally historical samples from prior resections (sample age up to 13 years).

Outcomes were examined for patients with significant stromal and tumor cell expression of GPNMB:

	Median PFS (weeks)	12-week PFS rate	Objective response rate
Significant (≥2+) stromal expression (n=6)	16.6	4/6 (67%)	2/6 (33%)
Significant (≥60%, ≥1-2+) tumor cell expression (n=5)	17.3	3/5 (60%)	1/5 (20%)
Significant GPNMB expression in either compartment (n=9)	17.3	6/9 (67%)	2/9 (22%)

Table presents data for evaluable patients treated at the Phase II dose (1.88 mg/kg) with GPNMB expression analysis performed (n=14).



Patient 5009
- **Triple-negative disease**
- **Significant tumor cell and stromal expression of GPNMB**
- **Received CDX-011 at 1.88 mg/kg**
- **Partial Response (53% shrinkage); continues to receive CDX-011 at 54+ weeks**

GPNMB DETECTION METHODS

- Following heat-induced epitope retrieval on the Leica Bond™ platform, GPNMB was detected in sections with rabbit polyclonal anti-GPNMB (Sigma-Aldrich prod. AV44499), and visualized with poly-HRP anti-rabbit IgG secondary antibody, followed by DAB. Intensity and proportion of positively staining cells were characterized in both epithelial (tumor cell) and stromal compartments.
- Immunohistochemistry (IHC) for the detection of GPNMB in paraffin embedded tissue was optimized using known positive and negative control cell lines (MCF-7 breast cancer and TK-10 renal cell, resp.) and validated using 60 whole mount breast cancer tissue sections at Clarient Diagnostic Services (Aliso Viejo, CA).

Validation Results – Whole Mount Breast Cancer Sections

Criteria	n (%)
Significant (≥2+) stromal expression	18 (30%)
Significant (≥60%, ≥1-2+) tumor cell expression	16 (28%)
Significant GPNMB expression in either compartment	33 (57%)

SUMMARY / CONCLUSIONS

This is a positive Phase II study of CDX-011 in a population of advanced breast cancer patients who were heavily pretreated (median of seven prior regimens).

- **The primary efficacy endpoint has been met, with 35% of treated patients progression-free at 12 weeks.**
- **Encouraging evidence of activity is seen in the subset of patients with triple-negative disease where treatment options are limited.**

These new data, using the GPNMB detection assay intended for Phase II, suggest that patients with significant expression of GPNMB on tumor cells or stroma may receive greatest benefit from CDX-011.

- **The activity of CDX-011 in patients with significant stromal expression of GPNMB may be due to both a "bystander effect", in which MMAE is released from the GPNMB-expressing stromal cells, killing neighboring tumor cell populations, as well as direct depletion of supporting stromal cells.[2]**
- **Both patients with tumor tissue assessed by IHC who achieved objective, confirmed Partial Responses showed significant tumor cell and/or stromal expression of GPNMB, and continued on treatment from 27 to 54+ weeks.**
- **These data, from a relatively small subset of patients, should be verified in a larger Phase II trial.**

2. Okeley NM, et al. Clin Cancer Res 2010;16:888-97.

FUTURE DIRECTIONS

A Phase II trial in heavily pre-treated, advanced breast cancer patients who are refractory/ resistant to all approved therapies is planned.

- **Patients will be selected for significant GPNMB expression in historical tissue samples or current biopsies.**
- **120 patients will be randomized (2:1) to receive CDX-011 or "Investigator's Choice" single-agent chemotherapy.**
- **Endpoints will include overall response rate, duration of response, PFS, overall survival, and PK/PD.**