A Phase I/II Study of CR011-vcMMAE (CDX-011), an Antibody-Drug Conjugate, in Patients with Locally Advanced or Metastatic Breast Cancer

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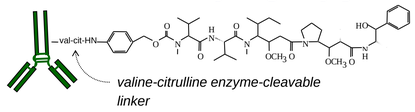
BACKGROUND

- GPNMB (osteoactivin):
  - a novel glycoprotein expressed in 25 - 40% of breast cancers, as well as other tumor types
  - promotes the migration, invasion, and metastasis of breast cancer and is an independent prognostic factor for recurrence of disease
- CDX-011 (CR011-vcMMAE; glembatumumab vedotin) consists of a fully-human monoclonal antibody targeting the extracellular domain of GPNMB (CR011), conjugated via an enzyme-sensitive linker to the potent chemotherapeutic, MMAE (Seattle Genetics).
  - CDX-011 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.
  - In a Phase II study in patients with metastatic melanoma, CDX-011 (1.88 mg/kg IV q3w) has been shown to be active with observed objective responses.
- The current Phase I/II study evaluates the safety and efficacy of CDX-011 in patients with heavily pre-treated, advanced breast cancer.

CDX-011: Antibody-Drug Conjugate



CR011
fully-human IgG_2 targeting GPNMB

MMAE
dolastatin-like tubulin inhibitor

STUDY DESIGN AND CONDUCT

Patient Population
- Progressive locally advanced or metastatic breast cancer
- At least 2 prior chemotherapy regimens
- Prior treatments must include, when clinically appropriate, an anthracycline, taxane, capecitabine and trastuzumab.
- No limit to number of prior treatments.

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

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 (based on 12-week PFS)

Stage 1 1.88 mg/kg n = 16 → Stage 2 1.88 mg/kg n = 12

Stage 1: Proceed to stage 2 if ≥ 2 patients without progression at 12 weeks (P_0 = ≤ 10%; P_1 = ≥ 30%)
- **Criteria for further Phase II expansion met.**

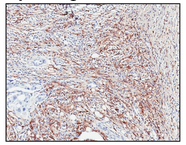
Final study analysis: P_1 accepted if ≥ 5 out of 25 patients without progression at 12 weeks
- **Primary efficacy endpoint met (to date, 9/26 without progression at 12 weeks)**
- Three patients continue on treatment.

GPNMB EXPRESSION

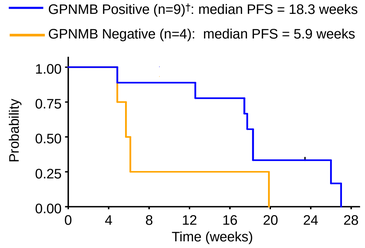
Immunohistochemistry for GPNMB was performed on biopsy samples for a subset of patients using a polyclonal goat anti-GPNMB antibody (R&D Systems) and a biotin-conjugated donkey anti-goat secondary antibody (Jackson ImmunoResearch Laboratories). Sections were developed with DAB and counterstained with hematoxylin. Samples with ≥ 5% of cells expressing GPNMB were considered positive.

All Doses	Analyzed n	Positive n (%)
Overall	14	10 (71%)
Triple-negative (ER-/PR-/HER-2/neu-)	7	5 (71%)
Partial Response (PR)	3	3 (100%)
Stable Disease (SD) or better	9	8 (89%)
Progression-free at 12 weeks	8	7 (88%)

Patient 5009: Strongly positive stromal expression of GPNMB at study entry and Partial Response (53% shrinkage) maintained for 23+ weeks in this patient with triple-negative disease.



Progression-free Survival by GPNMB Expression Status (All Doses)



† One patient without a post-baseline tumor assessment or clinical progression is excluded.

ACTIVITY

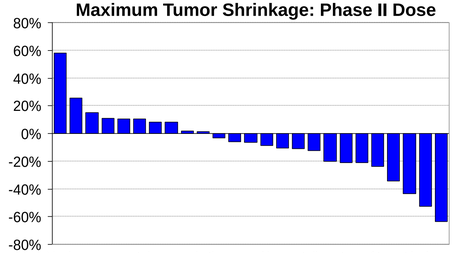
Primary Efficacy Endpoint: Progression-Free Survival (PFS) at 12 Weeks

Statistical Plan: **Study considered positive with ≥ 5 out of 25 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 are excluded due to pending data or study discontinuation without progression prior to 12 weeks.

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 nine patients without post-baseline imaging of measurable lesions.

Additional Measures of Anti-tumor Activity: Phase II Dose

	Phase II dose 1.88 mg/kg	Triple-negative disease	Expressing GPNMB
Best Response (RECIST criteria)			
Partial Response (PR)	4/32 (13%) †	2/10 (20%)	2/7 (29%) **
Confirmed PR	2/32 (6%)	1/10 (10%)	2/7 (29%)
Stable Disease (SD) or better	18/32 (56%) †	8/10 (80%)	7/7 (100%) **
Any tumor shrinkage	15/25 (60%) †,‡	7/9 (78%) *	5/7 (71%) **
Median PFS (weeks)	9.1	17.9	18.3

† Patients treated at the Phase II dose (1.88 mg/kg), including dose-escalation (n=6) and Phase II (n=28). Two patients without a post-baseline tumor assessment or clinical progression are excluded.
‡ Excludes an additional seven patients without post-baseline imaging of measurable lesions.
* Ten triple-negative patients were treated at the Phase II dose. One patient without post-baseline imaging of measurable lesions is excluded.
** Eight GPNMB-expressing patients were treated at the Phase II dose. Of these, one without post-baseline tumor assessment or clinical progression is excluded.

PATIENT CHARACTERISTICS & PRIOR THERAPIES

Characteristic		All Patients (n = 42)
Cancer Stage (n [%])	III	2 (5%)
	IV	40 (95%)
Age (median [range])		58 (33-76)
ECOG Performance Status (n [%])	0	21 (50%)
	1	19 (45%)
	2	2 (5%)
Metastatic to liver and/or lung (n [%])		34 (83%)
Receptor status (n [%])	ER+	24 (57%)
	PR+	15 (36%)
	HER-2/neu+	11 (27%)†
	Triple-negative (ER-/PR-/HER-2/neu-)	13 (32%) †

† HER-2/neu status is unknown for one patient.

Prior Therapies	All Patients (n = 42)
Prior chemotherapy regimens (median [range])	7 (2-18)
Taxane	42 (100%)
Capecitabine	41 (98%)
Anthracycline	38 (90%)
Hormonal Therapy	30 (71%)
Gemcitabine	27 (64%)
Bevacizumab	24 (57%)
Vinorelbine	23 (55%)
Epothilone	17 (40%)
Trastuzumab	14 (33%)
Lapatinib	8 (19%)
Investigational agents	8 (19%)

TOLERABILITY

- Treated patients (n=42) received a mean of 3.5 (range 1-8) cycles of treatment on study.
- Four patients discontinued treatment due to adverse events (neuropathy, rash, dermatologic bullae and acute renal failure).
- Dose-escalation DLTs were limited to two cases of neuropathy (at the 1.34 mg/kg dose). After revision of the protocol to exclude pre-existing neuropathy ≥ Grade 2, no further DLT occurred.
- Serious adverse events potentially related to CDX-011 (all single cases at the Phase II dose):
  - intractable vomiting/nausea
  - dermatologic bullae
  - acute renal failure

Adverse events potentially related to CDX-011	All Patients (n=42) Total n (%)	Grade 3 n (%)
Fatigue	20 (48%)	2 (5%)
Rash	19 (45%)	2 (5%)
Nausea	19 (45%)	2 (5%)
Alopecia	14 (33%)	-
Neutropenia	12 (29%)	8 (19%)
Vomiting	12 (29%)	1 (2%)
Neuropathy	10 (24%)	1 (2%)
Anemia	10 (24%)	-
Asthenia	3 (7%)	2 (5%)

Table includes events potentially related to treatment, occurring in ≥ 20% of patients overall or at Grade 3 severity in ≥ 5%. There were no Grade 4/5 treatment-related events.

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.**

The target GPNMB was frequently expressed in this patient population (71%) and expression of GPNMB was associated with improved outcomes following treatment with CDX-011.

- **All activity parameters appear to be improved for CDX-011-treated patients expressing GPNMB.**
- **Both patients who achieved an objective, confirmed Partial Responses expressed GPNMB, with response durations of 23+ to 27 weeks.**

Encouraging evidence of activity is seen in the subset of patients with triple-negative disease where treatment options are relatively limited.