A Randomized Phase II Study of the Antibody-drug Conjugate CDX-011 in Advanced GPNMB Overexpressing Breast Cancer: The EMERGE study

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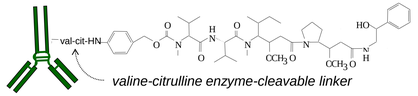
BACKGROUND

- GPNMB is an internalizable transmembrane glycoprotein over-expressed in ~40-75% of breast cancer as well as other tumor types.
- Promotes migration, invasion, and metastasis of breast cancer
- Expressed on epithelial tumor cells and supporting stromal cells
- Patients with high GPNMB-expressing tumors have significantly shorter metastasis-free and overall survival
- Tumor epithelial GPNMB expression is common in triple negative (ER/PR/HER2-) breast cancer and is associated with recurrence.

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

CDX-011 (CR011-vcMMAE; glembatumumab vedotin)



valine-citrulline enzyme-cleavable linker

CR011: fully-human IgG_2 specific to the extracellular domain of GPNMB

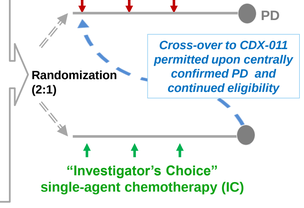
MMAE: dolastatin-like tubulin inhibitor

- CDX-011 antibody-drug conjugate delivers the potent cellular toxin monomethyl auristatin E (MMAE) to GPNMB-expressing tumor cells.
  - Same linker-MMAE technology as that used successfully in Adcetris™ (brentuximab vedotin; Seattle Genetics)
- Prior Phase I/II study in advanced, heavily pre-treated breast cancer (n=42)
  - Response rate (confirmed/unconfirmed) = ~20% and median PFS = ~18 weeks in patients with tumors overexpressing GPNMB and in patients with triple-negative breast cancer

RANDOMIZED PHASE II STUDY DESIGN

- Study designed to examine whether anti-cancer activity of CDX-011 is dependent upon distribution/intensity of GPNMB expression
  - Endpoints: overall response rate [primary], progression-free survival, duration of response, safety, PK/PD

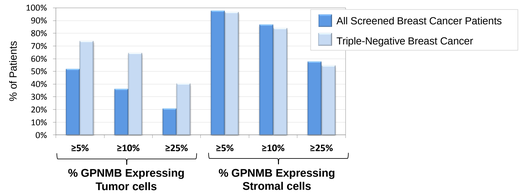
Planned sample size = 120
- **Locally advanced or metastatic, GPNMB+ breast cancer**
- **Refractory/resistant to approved therapies (taxane, anthracycline, capecitabine; and if HER2+, trastuzumab and lapatinib)**
- **2-7 prior lines of cytotoxic chemotherapy for advanced disease**
- **Progression within 6 months of last regimen**



TISSUE SCREENING FOR GPNMB EXPRESSION

- Validated, centralized IHC method on archived (primary or metastatic) tumor samples
- Eligibility required GPNMB expression in ≥5% of epithelial and/or stroma cells
  - 99% of 328 screened patients were potentially eligible for enrollment.
- High tumor GPNMB defined as GPNMB expression in ≥25% of epithelial cells
  - Consistent with conventional definitions for IHC positivity
  - Represents significant proportion of screened dataset
  - 15/16 patients with archival samples from different dates (up to 6.8 years) were consistently classified as high or low GPNMB expression using this cut-off

Tumor (Epithelial) GPNMB Expression is More Frequent in Triple-Negative Tumors



BASELINE CHARACTERISTICS

	CDX-011 (N=81)	Investigator's Choice (N=41)	Cross Over† (n=15)
Age, years [Median (range)]	57 (34-77)	58 (34-73)	51 (36-65)
Female [n (%)]	81 (100%)	41 (100%)	15 (100%)
ECOG Performance Status			
0	36 (44%)	14 (34%)	7 (47%)
1	44 (54%)	27 (66%)	8 (53%)
2	1 (1%)	0	0
Breast Cancer Stage [n (%)]			
III	2 (2%)	0	0
IV	79 (98%)	41 (100%)	15 (100%)
Visceral disease (Liver or Lung) [n (%)]	68 (84%)	33 (80%)	12 (80%)
Duration of Disease, years [Median (range)]			
Overall	6.7 (1.1-30.8)	5.4 (1.1-30.4)	4.7 (2.0-16.5)
Locally advanced or Metastatic	3.2 (0.3-18.9)	2.4 (0.5-19.5)	3.3 (0.8-5.5)
Receptor Status [n (%)]			
PR+	31 (38%)*	19 (46%)	8 (53%)
ER+	48 (59%)	26 (63%)	10 (67%)
HER2 +	8 (10%)**	9 (22%)**	5 (33%)
Triple Negative (ER-/PR-/HER2-)	28 (35%)	11 (27%)	3 (20%)
Prior lines of anticancer therapy [Median (Range)]	6 (3-11)	5 (3-11)	6 (4-9)
Prior lines of cytotoxic therapy for advanced/ metastatic disease [Median (Range)]	4 (2-9)	4 (1-6)	4 (2-7)
Prior Therapies Received [n (%)]			
Taxane	81 (100%)	41 (100%)	15 (100%)
Anthracycline	79 (98%)	40 (98%)	15 (100%)
Capecitabine	79 (98%)	40 (98%)	15 (100%)
Ixabepilone	35 (43%)	15 (37%)	8 (53%)
Eribulin	10 (12%)	7 (17%)	7 (47%)
Gemcitabine	45 (56%)	20 (49%)	7 (47%)
Bevacizumab	35 (43%)	15 (37%)	5 (33%)
Vinorelbine	29 (36%)	14 (34%)	6 (40%)
Hormonal therapy	49 (60%)	24 (59%)	11 (73%)
Trastuzumab	13 (16%)	11 (27%)	7 (47%)
Lapatinib	10 (12%)	10 (24%)	6 (40%)
Investigational agents	15 (19%)	11 (27%)	5 (33%)

† Status at cross-over is displayed for the 15 IC patients who received CDX-011 after progression .
** PR status is unknown for 1 patient. ** HER2 status is unknown for 2 pts (1 in each arm).*

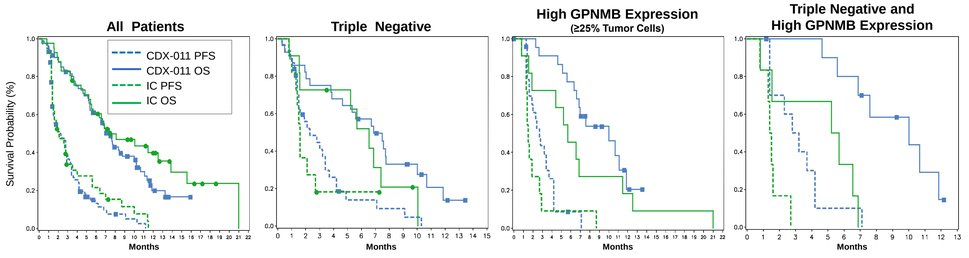
ACTIVITY DATA

Tumor Response

	All Patients		Triple Negative		High GPNMB Expression (≥25% Tumor Cells)		Triple Negative and High GPNMB Expression	
	CDX-011 (n=81)	IC (n=36)	CDX-011 (n=27)	IC (n=9)	CDX-011 (n=25)	IC (n=8)	CDX-011 (n=12)	IC (n=4)
Partial Response (PR)	13 (16%)	5 (14%)	5 (19%)	0 (0%)	8 (32%)	1 (13%)	4 (33%)	0 (0%)
Confirmed PR	8 (10%)	3 (8%)	2 (7%)	0 (0%)	4 (16%)	1 (13%)	1 (8%)	0 (0%)
Stable Disease or Better	46 (57%)	19 (53%)	18 (67%)	3 (33%)	16 (64%)	3 (38%)	9 (75%)	1 (25%)

Responses per RECIST 1.1; CDX-011 arm includes 15 patients who crossed over to receive CDX-011 treatment after progression on IC. Analysis of best response excludes patients who discontinued from study without evaluable post-baseline radiographic imaging (n=15 for CDX-011 arm; n=5 for IC arm).

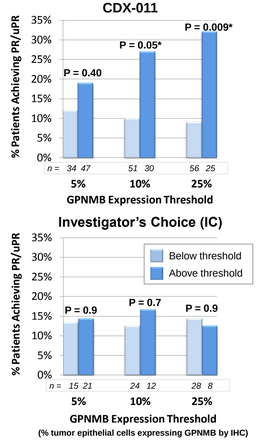
Progression-Free Survival (PFS) and Overall Survival (OS)



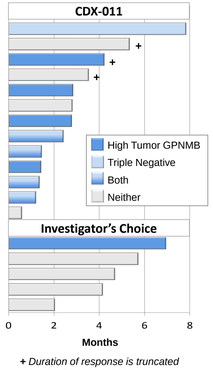
	All Patients			Triple-Negative			High GPNMB Expression (≥25% Tumor Cells)			Triple Negative and High GPNMB Expression		
	CDX-011	IC		CDX-011	IC		CDX-011	IC		CDX-011	IC	
Median PFS (months)	**2.1** (n=96)	**2.0** (n=41)	*P=0.38*	**2.3** (n=31)	**1.6** (n=11)	*P=0.43*	**2.7** (n=27)	**1.5** (n=11)	*P=0.14*	**3.0** (n=12)	**1.5** (n=6)	*P=0.008**
Median OS (months)	**7.5** (n=81)	**7.4** (n=41)	*P=0.24*	**6.9** (n=28)	**6.5** (n=11)	*P=0.30*	**10.0** (n=22)	**5.7** (n=11)	*P=0.18*	**10.0** (n=10)	**5.5** (n=6)	*P=0.003**

*Analyses include all treated patients. Patients who initially received Investigator's Choice and subsequently crossed over to receive CDX-011 (n=15) are included in the PFS analysis for each treatment . These patients, with a median OS of 12.5 months, are assigned to the Investigator's Choice arm only for OS analysis. Median OS for the remaining IC patients who did not cross over is 5.4 months. * Statistically significant*

High Tumor GPNMB Expression Correlates Significantly with Response to CDX-011



Duration of Response



+ Duration of response is truncated at last disease assessment (discontinued treatment without radiographic progression).

TREATMENT EXPOSURE AND TOLERABILITY

Treatment Parameter	CDX-011 (n=96)	IC (n=41)
Treatment cycles *(median [range])*	2 (1-15)	2 (1-14)
Dose modification (delay or decrease) for toxicity *(n [%])*	35 (36%)	16 (39%)
Discontinued treatment *(n [%])*	96 (100%)	41 (100%)
Treatment-Related Toxicity	8 (8%)	2 (5%)
Progressive Disease	65 (65%)	30 (73%)
Symptomatic Deterioration	15 (16%)	4 (10%)
Other	11 (11%)	5 (12%)
Investigator's Choice Therapy *(n [%])*		
Eribulin		15 (37%)
Ixabepilone		7 (17%)
Gemcitabine		5 (12%)
Vinorelbine		5 (12%)
Doxorubicin HCL		3 (7%)
Albumin-bound Paclitaxel		2 (5%)
Other		4 (10%)

Treatment-Related Adverse Events	CDX-011 (n=96) All Grades	CDX-011 (n=96) Grade 3	CDX-011 (n=96) Grade 4	IC (n=41) All Grades	IC (n=41) Grade 3	IC (n=41) Grade 4
Hematologic						
Neutropenia	29%	16%	6%	44%	22%	7%
Leukopenia	10%	3%	1%	27%	15%	0%
Thrombocytopenia	4%	0%	1%	15%	2%	0%
Non-hematologic						
Rash	47%	4%	0%	2%	0%	0%
Fatigue	38%	7%	0%	46%	5%	0%
Nausea	32%	2%	0%	34%	0%	0%
Alopecia	25%	0%	0%	15%	0%	0%
Decreased appetite	19%	1%	0%	15%	0%	0%
Pruritus	21%	1%	0%	2%	0%	0%
Peripheral neuropathy	23%	3%	0%	12%	2%	0%
Vomiting	18%	0%	0%	10%	0%	0%
Constipation	14%	0%	0%	22%	0%	0%
Stomatitis	16%	2%	0%	17%	2%	0%
Dehydration	10%	3%	0%	7%	2%	0%

Table presents treatment-related adverse events with incidence >15% overall, or ≥3% at Grade 3-4 severity, in either study arm. No Grade 5 treatment-related adverse events were reported. Growth factors were permitted.

CONCLUSIONS

EMERGE results consistent with previous study in similar population

- CDX-011 well-tolerated
  - Less hematologic toxicity but more rash and neuropathy than Investigator's Choice (IC)
- Promising activity in triple-negative breast cancer (TNBC), where treatment options are limited
  - CDX-011 response rate of 19% in TNBC compared to 0% for IC
- Significant tumor expression of GPNMB associated with greater activity
  - CDX-011 response rate of 32% compared to 13% for IC
  - Stromal expression of GPNMB did not appear to correlate with outcome.
  - High GPNMB expression in 41% of patients with TNBC
    - CDX-011 response rate of 33% and doubling of PFS (p=0.008) and OS (p=0.003)
- A registrational study is being planned.