A Pivotal, Multicenter, Randomized Study Evaluating the Novel Antibody-Drug Conjugate Glembatumumab Vedotin (CDX-011; CR011-vcMMAE) in Patients with Metastatic, Triple-negative, gpNMB Over-expressing Breast Cancer

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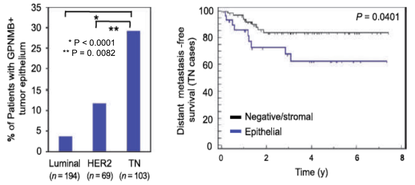
BACKGROUND

Glycoprotein NMB (gpNMB)

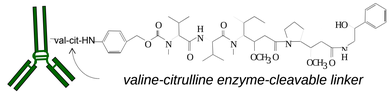
- An internalizable transmembrane glycoprotein over-expressed in ~40-60% of breast cancers as well as other tumors
  - Expressed on epithelial tumor cells and supporting stromal cells
  - Promotes migration, invasion, and metastases
- Shorter metastasis-free and overall survival have been noted in patients with high gpNMB-expressing tumors (including breast,[1] small cell lung cancer,[2] and glioblastoma[3])

Tumor Epithelial gpNMB Expression is Common in Triple Negative Breast Cancer (ER-/PR-/HER2-) and is Associated with Recurrence[1]



Glembatumumab Vedotin

- Novel antibody-drug conjugate that delivers the potent cellular toxin monomethylauristatin E (MMAE) to gpNMB-expressing tumor cells
  - Fully human gpNMB-specific monoclonal antibody (CR-011) conjugated to MMAE via a protease-sensitive peptide linker, designed to cleave upon cellular internalization
  - Same linker-MMAE technology as that used successfully in Adcetris™ (brentuximab vedotin; Seattle Genetics)



valine-citrulline enzyme-cleavable linker

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

MMAE: dolastatin-like tubulin inhibitor

- Three completed clinical studies in melanoma and breast cancer
  - MTD (Phase II dose) established as 1.88 mg/kg q3w
  - Favorable ORR and PFS in heavily-pretreated populations
  - Clinical benefit appears greatest in patients with triple-negative tumors and/or tumors expressing higher levels of gpNMB

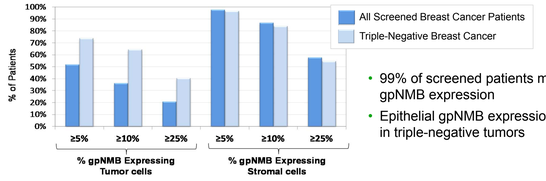
Celldex therapeutics
www.Celldex.com

1. Rose, et al. CCR, 2010
2. Li, et al. APMIS 2013
3. Kuan, et al. CCR 2006

Completed Phase II Study in Patients with Advanced Breast Cancer: "EMERGE"

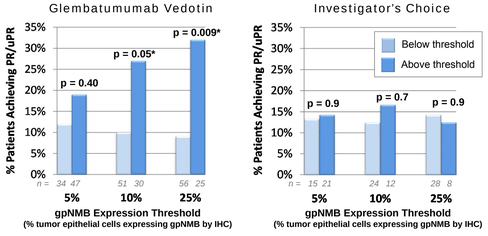
- Study designed to examine whether anti-cancer activity of glembatumumab vedotin is dependent upon distribution/intensity of gpNMB expression
- Treatments (2:1 randomization):
  - Glembatumumab vedotin (1.88 mg/kg q3w)
  - "Investigator's Choice" (IC) single-agent chemotherapy
  - Cross-over from IC to glembatumumab vedotin permitted at progression
- Population:
  - gpNMB+ breast cancer (≥5% of epithelial or stroma cells positive by centralized IHC)
  - Refractory/resistant to approved therapies (taxane, anthracycline, capecitabine; and if HER2+, trastuzumab and lapatinib)
  - Progression within 6 months of last regimen
  - 98% with metastatic disease
  - Median of 6 prior lines of anticancer therapy (4 lines of cytotoxic therapy for advanced disease)

Tissue Screening for gpNMB Expression



- 99% of screened patients met eligibility for gpNMB expression
- Epithelial gpNMB expression was more frequent in triple-negative tumors

High Tumor gpNMB Expression Correlates Significantly with Response to Glemabatumumab Vedotin, but not to IC



Safety

- Glembatumumab vedotin well-tolerated
- Treatment-related toxicity: Rash, neutropenia, fatigue, nausea, vomiting, alopecia, decreased appetite and peripheral neuropathy
- Less hematologic toxicity than Investigator's Choice

Activity: Tumor Response, Progression-Free Survival (PFS) and Overall Survival (OS)

	All Patients		Triple-Negative		High gpNMB Expression§		Triple Negative & High gpNMB§	
	GV (n=96)	IC (n=41)	GV (n=31)	IC (n=11)	GV (n=27)	IC (n=11)	GV (n=12)	IC (n=6)
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%)
Median PFS (months)	2.1	2.0	2.3	1.6	2.7	1.5	3.0	1.5
	p=0.38		*p=0.43*		*p=0.14*		*p=0.008**	
Median OS (months)	7.5	7.4	6.9	6.5	10.0	5.7	10.0	5.5
	p=0.24		*p=0.30*		*p=0.18*		*p=0.003**	

GV, Glembatumumab vedotin; IC, Investigator's Choice Therapy. § ≥ 25% of tumor epithelial cells expressing gpNMB by IHC * *Statistically significant*
Patients who received Investigator's Choice and subsequently crossed over to receive glembatumumab vedotin (n=15) are included in the tumor response and PFS analyses for each treatment received, but are assigned to the Investigator's Choice arm only for OS analysis. Analysis of best response (RECIST 1.1) excludes patients who discontinued from study without evaluable post-baseline radiographic imaging (n=15 for GV arm; n=5 for IC arm).

THE "METRIC" STUDY DESIGN

Triple-negative breast cancer (TNBC) overexpressing gpNMB * N=300

Randomization § (2:1)

Glembatumumab Vedotin 1.88 mg/kg IV Day 1 of 21-day cycles

Capecitabine ‡ 1250 mg/m² BID Days 1-14 of 21-day cycles

- Treat until disease progression
  - Trial design does not allow for treatment cross-over
- Tumor assessments (RECIST 1.1)
  - 6 week intervals for 6 months and 9-week intervals thereafter, until documented progression
- Quality of life (EORTC QLQ-C30)
  - Every other treatment cycle
- Survival follow-up
  - 12 week intervals, until death or study closure

* Central analysis of tumor obtained after diagnosis of locally advanced/metastatic disease

- gpNMB overexpression: ≥ 25% of tumor epithelial cells positive by IHC
  - 40% of TNBC expected to meet criteria (EMERGE experience)
- TNBC (centrally confirmed):
  - ER/PR: < 1% of cells positive by IHC
  - HER2: IHC staining of 0 or 1+, FISH < 4.0 copies or ratio < 1.8

§ Randomization stratified by:

- Prior lines of chemotherapy for advanced disease (0 vs. 1)
- Resistance to anthracycline therapy (i.e., progression-free interval after completing treatment ≤ 6 months vs. > 6 months)

‡ Capecitabine as comparator

- Approved by FDA for the treatment of metastatic breast cancer patients resistant to paclitaxel and anthracyclines
- Represents a current standard of care option for TNBC patients (not candidates for hormone-receptor- or HER2-targeted agents)

Additional Eligibility Criteria

- 0 or 1 chemotherapy-containing regimen for advanced breast cancer
- Progression/recurrence-free interval > 6 months after completion of neoadjuvant or adjuvant chemotherapy
- Resistant to taxane therapy
  - If progression-free interval >12 months from neo- or adjuvant taxane, must receive taxane for advanced disease
  - If taxane administered for advanced disease, must demonstrate progression during or within 6 months of completing therapy
- Receipt of anthracycline-containing chemotherapy in any setting, with no further anthracycline therapy indicated
  - i.e., contraindicating cardiac conditions, prior intolerance, or cumulative dose ≥ 240 mg/m² doxorubicin or equivalent
- Measurable disease by RECIST 1.1 criteria
- ECOG Performance Status 0 or 1
- Neuropathy Grade ≤ 1
- No investigational therapy within 4 weeks of study treatment

Objectives

- Primary:
  - Overall response rate (ORR) and duration of progression-free survival (PFS)
  - Per independent central review committee (RECIST 1.1)
  - Co-primary endpoints designed to allow for filing for accelerated approval if either endpoint is met
- Secondary:
  - Duration of response (DOR)
  - Overall survival (OS)
  - Safety
  - Pharmacokinetics
- Exploratory: Quality of life and/or reduction in cancer-related pain

Statistical Design

- Type I error rate (α) of 0.05 allocated between the co-primary endpoints
- PFS:
  - Hypothesized HR = 0.64
  - Hypothesized median PFS:
    - 4 months for capecitabine
    - 6.25 months for glembatumumab vedotin
  - α = 0.01, 80% power
- ORR:
  - H_0 = 15% vs. H_A = 30%
  - α = 0.04, 80% power

Study Status

- Study to be conducted at approximately 100 sites in US, Canada, and Australia
- 7 sites are currently open to screening; with additional sites to be initiated shortly.
  - Mark Taylor, MD, Summit Cancer Care PC, Savannah, GA
  - Clyde Jones, MD, Jones Clinic PC, Germantown, TN
  - Milton Seiler, MD, Crescent City Research Consortium, LLC, Marrero, LA
  - David Ellison, MD, Charleston Hematology Oncology, Charleston, SC
  - Ira Oliff, MD, Orchard Research, Skokie, IL
  - Troy Guthrie, MD, Baptist Cancer Institute, Jacksonville, FL
  - Marc Citron, MD, ProHealth Care Associates LLP, Lake Success, NY
- For an updated listing of open sites, please visit www.clinicaltrials.gov, NCT# NCT01997333.
- Accrual anticipated to be completed in 15-18 months

metric
A Clinical Trial of CDX-011 in Metastatic Triple-Negative Breast Cancer