gpNMB Expression Patterns in Breast Cancer (BC): Retrospective Evaluation of Tumor Tissue from the Phase 2 EMERGE Study

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ABSTRACT #129

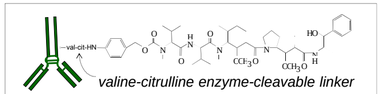
BACKGROUND

Glycoprotein NMB (gpNMB)

- An internalizable transmembrane glycoprotein over-expressed in 20% of breast cancers, 40% of triple-negative breast cancers (TNBC), plus melanoma, osteosarcoma, glioblastoma, head and neck cancer, and squamous cell lung cancer.
- Shorter metastasis-free and overall survival in patients with high gpNMB-expressing tumors (including breast,[1] small cell lung cancer,[2] and glioblastoma[3])

Glembatumumab Vedotin

- Novel antibody-drug conjugate that delivers the potent cellular toxin monomethylauristatin E (MMAE) to gpNMB-expressing tumor cells
- 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

Completed Phase II Study in Pts with Advanced Breast Cancer: "EMERGE"[4]

Study designed to examine whether anti-cancer activity of glembatumumab vedotin is dependent upon distribution/intensity of gpNMB expression

Treatment (2:1 randomization)

- Glembatumumab vedotin (GV) (1.88 mg/kg q3w IV)
- "Investigator's Choice" (IC) single-agent chemotherapy

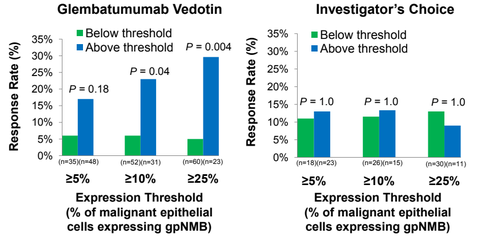
Population

- Advanced breast cancer, refractory/resistant to approved therapies
- gpNMB expression in ≥5% of tumor epithelial or stromal cells, by central IHC

gpNMB Expression Analysis

- 99% of screened pts met eligibility for gpNMB expression
- gpNMB overexpression (staining in ≥25% of tumor epithelial cells) detected in:
  - 21% of all screened pts
  - 40% of TNBC pts
- Activity of glembatumumab vedotin may be enhanced in patients with gpNMB-overexpressing tumors and/or TNBC

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



Activity in Subgroups of Interest

	High gpNMB Expression§		TNBC & High gpNMB§	
	GV (n=23)	IC (n=11)	GV (n=10)	IC (n=6)
Overall Response Rate (ORR)	7 (30%)	1 (9%)	4 (40%)	0 (0%)
Confirmed PR	3 (13%)	1 (9%)	1 (10%)	0 (0%)
Stable Disease or Better	15 (65%)	3 (27%)	9 (90%)	1 (17%)
Median PFS (months)	2.8 HR=0.63, p=0.18	1.5	3.5 HR=0.11, p=0.0017*	1.5
Median OS (months)	10.0 HR=0.67, p=0.31	5.7	10.0 HR=0.14, p=0.003*	5.5

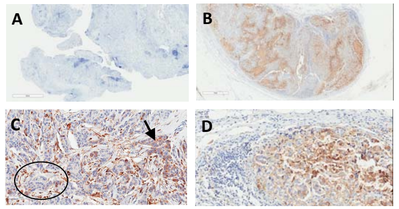
GV, Glembatumumab vedotin; IC, Investigator's Choice Therapy ; HR, Hazard Ratio
Intention To Treat (ITT) analysis of all randomized patients
§≥25% of tumor epithelial cells staining for gpNMB by IHC
* Statistically significant

1. *Rose, et al. CCR, 2010*
2. *Li, et al. APMIS 2013*
3. *Kuan, et al. CCR 2006*
4. *Yardley, et al. JCO, 2015*

Celldex therapeutics
www.Celldex.com

METHODS

- Retrospective analysis on the frequency of gpNMB overexpression (staining in ≥25% of tumor epithelial cells) by various baseline and disease characteristics
- Immunohistochemistry was performed on archival tumors in the primary or metastatic disease setting at a central lab (Clarient, Aliso Viejo, CA)
  - Deparaffinized slides were incubated overnight with goat polyclonal anti-gpNMB antibody (R&D Systems, Minneapolis, MN) at 1:500 dilution after heat-induced antigen retrieval in citrate buffer (pH 6.0)
  - Donkey anti-goat horseradish peroxidase polymer detection system was used for visualization (The Jackson Laboratory, Bar Harbor, ME); slides were counterstained with hematoxylin
  - Two pathologists scored percent of positive cells



IHC Staining of gpNMB Expression in EMERGE Tumor Samples
-Overexpression Defined as Staining in ≥25% of Tumor Epithelial Cells

A. Negative control sample, 1x magnification.
B. gpNMB expression in a lymph node metastasis, 2x magnification.
C. gpNMB expression, 20x magnification: axillary metastasis with ~30% positivity of tumor cells. A region of gpNMB+ stroma is delineated by the circle and a cluster of gpNMB+ tumor epithelial cells are marked by the arrow.
D. gpNMB expression, 20x magnification: lymph node metastasis with positive gpNMB staining in epithelial cells.

RESULTS

gpNMB Over-Expression Rate

	All Screened Patients (n=327*)	TNBC Patients (n=96)
Age (years)		
<50	31/146 (21%)	17/43 (40%)
≥50	37/181 (20%)	21/53 (40%)
Race		
American Indian/Alaskan Native	2/2 (100%)	1/1 (100%)
White/Caucasian	54/261 (21%)	31/68 (46%)
Black/African American	9/42 (21%)	5/19 (26%)
Asian	2/14 (14%)	0/6 (0%)
Other	1/8 (13%)	1/2 (50%)
Disease Setting§		
Early	32/161 (20%)	19/51 (37%)
Advanced	36/164 (22%)	19/44 (43%)

gpNMB Over-Expression Rate

	All Screened Patients (n=327*)	TNBC Patients (n=96)
Tumor Site#		
Lung	3/7 (43%)	2/2 (100%)
Lymph Node	12/39 (31%)	4/11 (36%)
Chest Wall	3/13 (23%)	1/2 (50%)
Breast	44/209 (21%)	30/73 (41%)
Liver	3/24 (13%)	1/3 (33%)
Bone	1/8 (13%)	0/1 (0%)
Histopathologic Classification‡		
Carcinoma NOS	11/37 (30%)	6/10 (60%)
Ductal	57/270 (21%)	32/84 (38%)
Lobular	0/17 (0%)	0/2 (0%)
Receptor Status		
Estrogen Receptor (ER) Positive	22/190 (12%)	-
Progesterone Receptor (PR) Positive	17/127 (13%)	-
HER2 Positive	8/54 (15%)	-
Triple (ER/PR/HER2) Negative	-	38/96 (40%)

* Specimens for 328 patients were screened for gpNMB expression analysis; however, data tabulations exclude data for one patient without available clinical data.
§ Disease setting at time of tissue procurement is unknown for 2 patients (1 with TNBC).
# Tumor site was unknown for 4 samples.
‡ Histopathologic classification is unknown for 3 samples.

gpNMB expression by prior treatment is not presented, due to insufficient number of patients who received therapies within a one-week window prior to tissue procurement.

View Poster

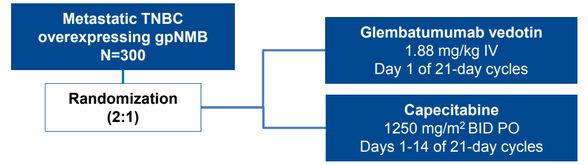
CONCLUSIONS

- gpNMB overexpression in breast cancer, including in TNBC, appears consistent regardless of disease setting (early or advanced) or age
  - Observed across disease sites, including lung, lymph node, chest wall, breast, liver and bone
  - Detected in 40% of TNBC tumors, as well as 12-15% of tumors expressing progesterone, estrogen, or HER2+ receptors
- Promising results obtained in the EMERGE study supported initiation of the "METRIC" study in patients with gpNMB overexpressing TNBC

FUTURE DIRECTIONS

- Ongoing study in metastatic TNBC overexpressing gpNMB: The "METRIC" Study (Protocol CDX011-04)
- Ongoing study in advanced melanoma (Protocol CDX011-05)
- Additional studies are planned in osteosarcoma, uveal melanoma, and squamous cell lung cancer

THE "METRIC" STUDY DESIGN



MAJOR ELIGIBILITY CRITERIA

- Tumor obtained in the advanced disease setting must show:
  - gpNMB overexpression (staining in ≥25% of tumor epithelial cells by central IHC)
  - TNBC status:
    - ER/PR: <10% of cells positive by IHC
    - HER2: IHC staining of 0 or 1+, FISH < 4.0 copies or ratio < 2.0
- 0 to 2 prior chemotherapy-containing regimens for advanced breast cancer
- Prior taxane chemotherapy in any setting
- Prior anthracycline chemotherapy in any setting, unless contraindicated

OBJECTIVES/STATISTICS

Primary:

- Progression-free survival (PFS) per independent, blinded central review committee (RECIST 1.1)
  - Type I error rate (α): 0.05 (2-sided)
  - Power: 85%
  - Hypothesized PFS Hazard Ratio: 0.64

Secondary:

- Objective response rate (ORR), Duration of response (DOR), Overall survival (OS)
- Safety
- Pharmacokinetics

Exploratory:

- Quality of life and/or cancer-related pain

STUDY STATUS

Study being conducted at approximately 100 sites in US, Canada, and Australia with expansion planned into Europe

For an updated listing of open sites or further details, please visit:

www.clinicaltrials.gov,
NCT#01997333

www.triplenegativebc.com

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