METRIC: A Randomized International Study of the Antibody-Drug Conjugate Glembatumumab Vedotin (GV or CDX-011) in Patients (pts) with Metastatic gpNMB-Overexpressing Triple-Negative Breast Cancer (TNBC)

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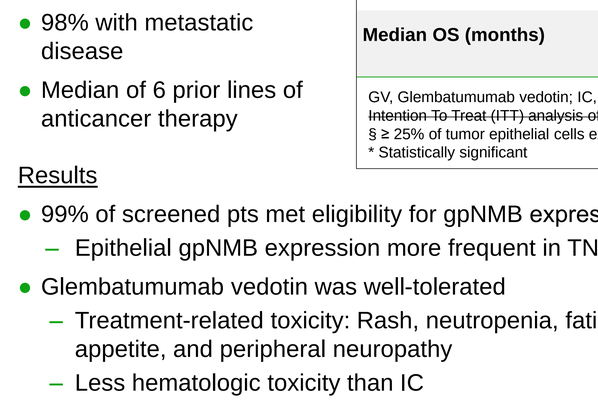
Abstract #TPS1110

BACKGROUND

Glycoprotein NMB (gpNMB)

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

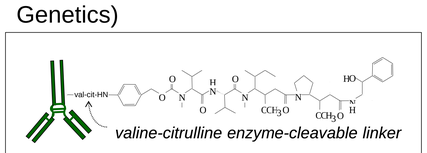
Tumor Epithelial gpNMB Expression is Common in Triple Negative Breast Cancer (ER-/PR-/HER2-)* and is Associated with Recurrence[1]



*ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2

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)



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
  - Clinical benefit appears greatest in pts with TNBC and/or gpNMB+ tumors

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

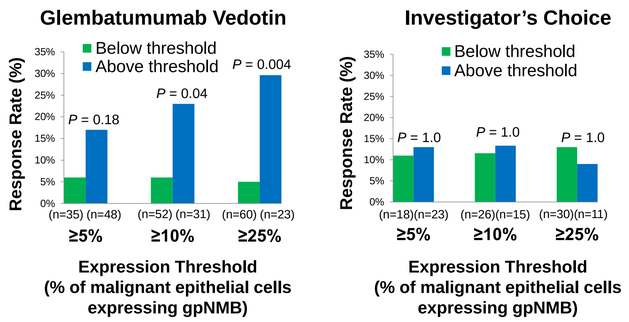
<u>Treatment</u>

- 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

<u>Population</u>

- gpNMB+ breast cancer
- Refractory/resistant to approved therapies
- Progression within 6 months of last regimen
- 98% with metastatic disease
- Median of 6 prior lines of anticancer therapy

High Tumor gpNMB Expression Correlates Significantly with Response to Glemabatumumab 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	1.5	3.5	1.5
	HR=0.63, p=0.18		HR=0.11, p=0.0017*	
Median OS (months)	10.0	5.7	10.0	5.5
	HR=0.67, p=0.31		HR=0.14, p=0.003*	

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 expressing gpNMB by IHC
* Statistically significant

<u>Results</u>

- 99% of screened pts met eligibility for gpNMB expression (≥5% of epithelial or stromal cells positive)
  - Epithelial gpNMB expression more frequent in TNBC
- Glembatumumab vedotin was well-tolerated
  - Treatment-related toxicity: Rash, neutropenia, fatigue, nausea, vomiting, alopecia, decreased appetite, and peripheral neuropathy
  - Less hematologic toxicity than IC
- Activity of glembatumumab vedotin may be enhanced in patients with gpNMB-overexpressing tumors and/or TNBC

Celldex therapeutics
www.Celldex.com

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

THE "METRIC" STUDY DESIGN

Metastatic 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
  - No treatment cross-over
- Tumor assessments (Response Evaluation Criteria In Solid Tumors (RECIST) 1.1)
  - 6-week intervals for 6 months and 9-week intervals thereafter, until documented progression
- Quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30))
  - Every other treatment cycle
- Survival follow-up
  - 12 week intervals, until death or study closure

Capecitabine as comparator

- FDA-approved for metastatic breast cancer resistant to paclitaxel and anthracyclines
- Represents a current standard of care option for TNBC patients (not candidates for endocrine or HER2-targeted agents)

Objectives

Primary:

- Progression-free survival (PFS) per independent, blinded central review committee (RECIST 1.1)

Secondary:

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

Exploratory:

- Quality of life and/or cancer-related pain

Statistical Design

- Type I error rate (α): 0.05 (2-sided)
- Power: 85%
- Hypothesized PFS Hazard Ratio: 0.64
- Hypothesized median PFS for two arms:
  - Capecitabine: 4.0 months
  - Glembatumumab vedotin: 6.25 months
- Targeted PFS events = 203

Eligibility Criteria

- Tumor obtained in the advanced disease setting must show:
  - gpNMB overexpression (≥25% of tumor epithelial cells positive by central IHC)
    - 40% of TNBC expected to meet criteria (EMERGE experience)
  - 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
- No untreated brain metastases. Pts must be asymptomatic and stable for ≥2 months.
- Measurable disease (RECIST 1.1)
- ECOG 0 or 1
- Peripheral neuropathy Grade ≤ 1
- No investigational therapy within 4 weeks of study treatment
- Resolution of all chemotherapy or radiation-related toxicities to Grade ≤ 1 severity, except for alopecia

Study Status

- Study being conducted at approximately 100 sites in US, Canada, and Australia
- For an updated listing of open sites or further details, please visit:
  - www.clinicaltrials.gov, NCT#01997333
  - www.triplenegativebc.com
  - www.facebook.com/metricstudy

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