

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

Denise A Yardley, MD^{1,2}, Michelle E Melisko, MD³, Andres Forero, MD⁴, Melinda Telli, MD⁵, Scott Cruickshank, PhD⁶, Jennifer Green⁷, Michael Yellin, MD⁷, Thomas Davis, MD⁷, Linda T Vahdat, MD⁸

San Antonio Breast Cancer Symposium
Cancer Therapy and Research
Center at UT Health Science Center
December 10-14, 2013

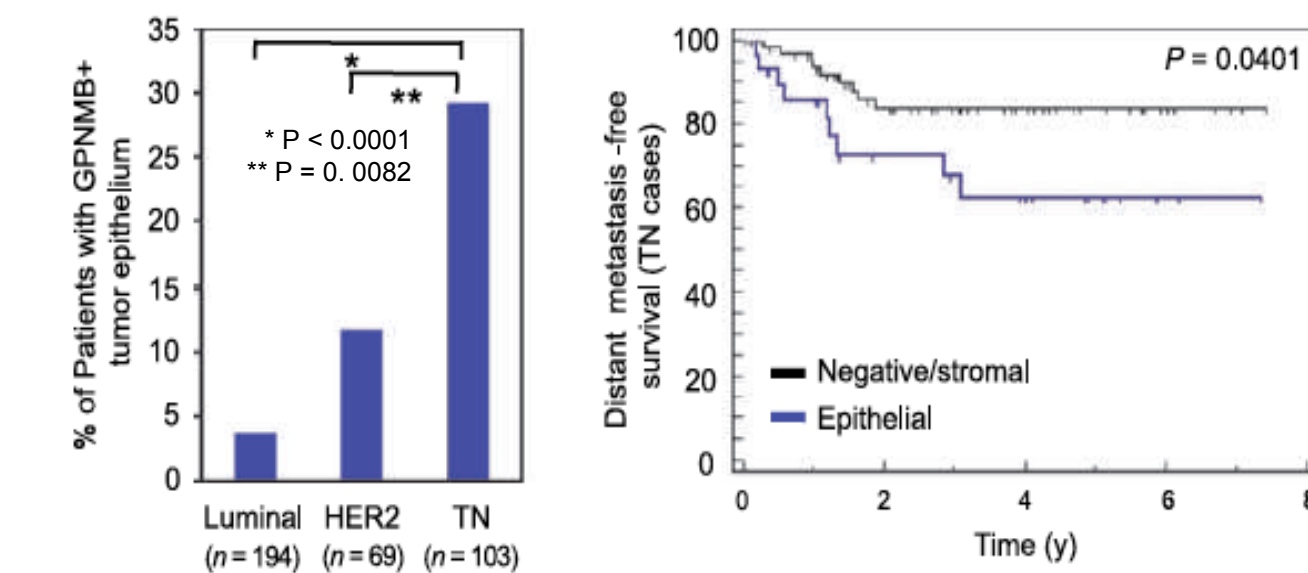
¹Sarah Cannon Research Institute, Nashville, TN, United States; ²Tennessee Oncology, PLLC, Nashville, TN, United States; ³University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, United States; ⁴University of Alabama, Birmingham, AL, United States; ⁵Stanford University School of Medicine, Stanford, CA, United States; ⁶Scott Cruickshank & Associates, Inc., Santa Barbara, CA, United States; ⁷Celldex Therapeutics, Inc., Needham, MA, United States; ⁸Weill Cornell Medical College, New York, NY, United States

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 glioblastoma³)

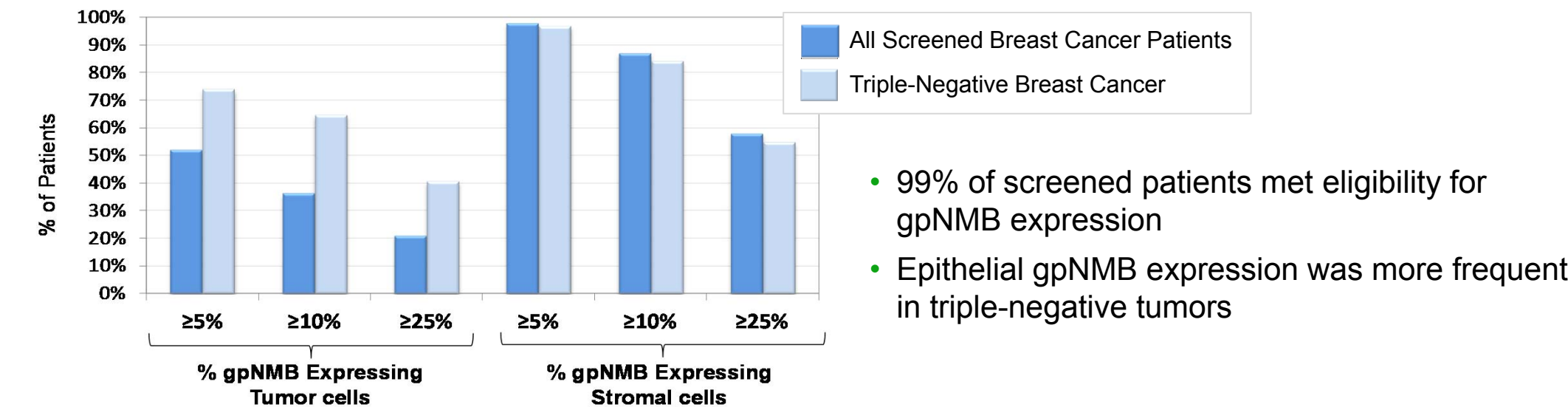
Tumor Epithelial gpNMB Expression is Common in Triple Negative Breast Cancer (ER-/PR-/HER2-) and is Associated with Recurrence¹



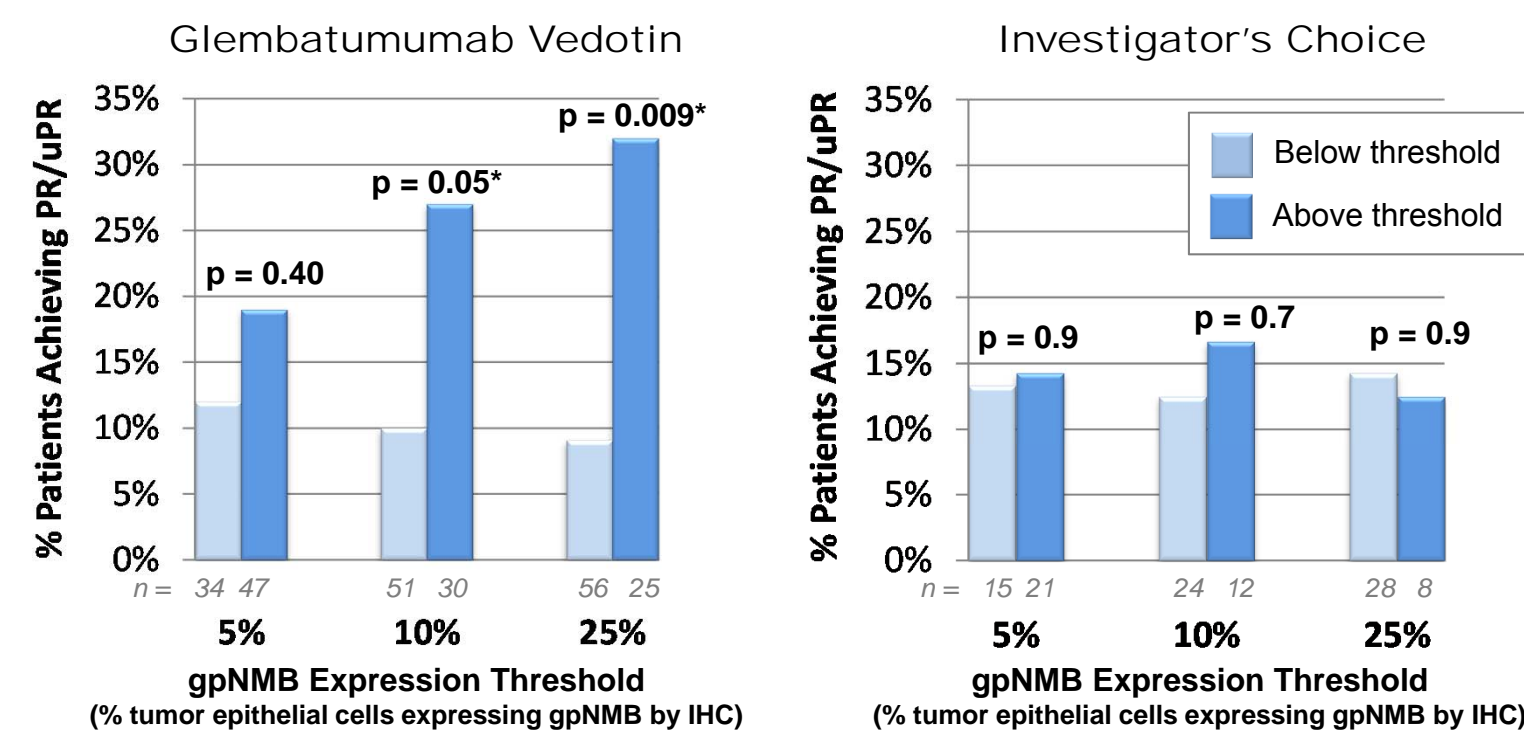
Completed Phase II Study in Patients with Advanced Breast Cancer: "EMERGE"

- Study designed to examine whether anti-cancer activity of glematumumab vedotin is dependent upon distribution/intensity of gpNMB expression
- Treatments (2:1 randomization):
 - Glematumumab vedotin (1.88 mg/kg q3w)
 - "Investigator's Choice" (IC) single-agent chemotherapy
 - Cross-over from IC to glematumumab 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



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



Safety

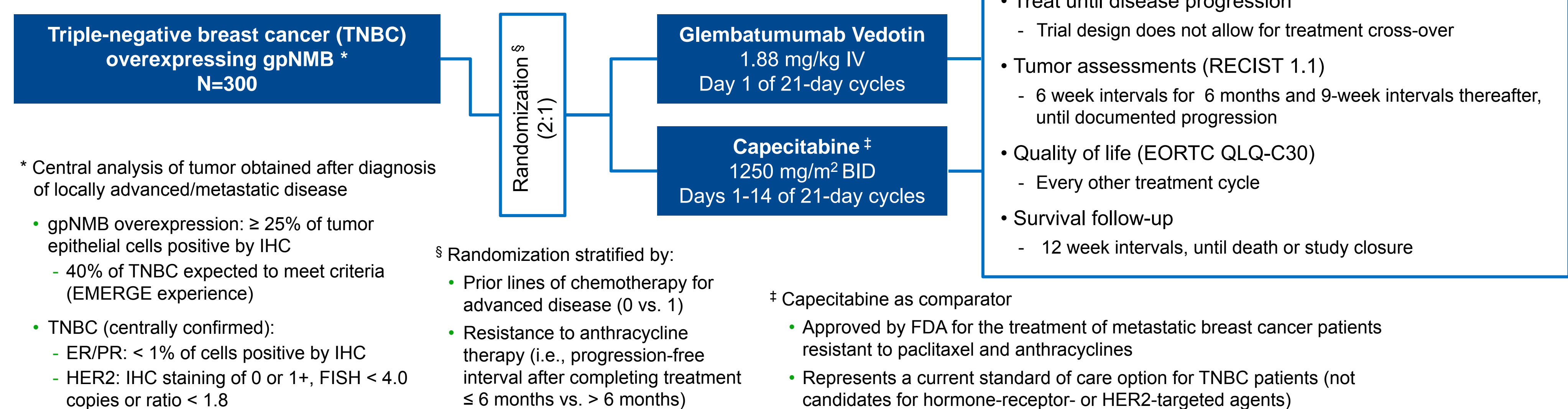
- Glematumumab vedotin well-tolerated
- Treatment-related toxicity: Rash, neutropenia, fatigue, nausea, vomiting, alopecia, decreased appetite and peripheral neuropathy
- Less hematologic toxicity than Investigator's Choice

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, Glematumumab 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 glematumumab 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



* 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)

- 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

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

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

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 glematumumab vedotin
 - α = 0.01, 80% power
- ORR:
 - H₀ = 15% vs. H_A = 30%
 - α = 0.04, 80% power