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Denise A. Yardley

Robert Weaver

Michelle E. Melisko

Mansoor N. Saleh

Francis P. Arena

*See next page for additional authors*



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## Authors

Denise A. Yardley, Robert Weaver, Michelle E. Melisko, Mansoor N. Saleh, Francis P. Arena, Andres Forero, Tessa Cigler, Alison Stopeck, Dennis Citrin, Ira Oliff, Rebecca Bechhold, Randa Loutfi, Agustin A. Garcia, Scott Cruickshank, Elizabeth Crowley, Jennifer Green, Thomas Hawthorne, Michael J. Yellin, Thomas A. Davis, and Linda T. Vahdat

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ORIGINAL REPORT

# EMERGE: A Randomized Phase II Study of the Antibody-Drug Conjugate Glembatumumab Vedotin in Advanced Glycoprotein NMB–Expressing Breast Cancer

*Denise A. Yardley, Robert Weaver, Michelle E. Melisko, Mansoor N. Saleh, Francis P. Arena, Andres Forero, Tessa Cigler, Alison Stopeck, Dennis Citrin, Ira Oliff, Rebecca Bechhold, Randa Loutfi, Agustin A. Garcia, Scott Cruickshank, Elizabeth Crowley, Jennifer Green, Thomas Hawthorne, Michael J. Yellin, Thomas A. Davis, and Linda T. Vahdat*

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Author affiliations appear at the end of this article.

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Clinical trial information: NCT01156753.

Corresponding author: Linda T. Vahdat, MD, Weill Cornell Medical College, 425 East 61st St, 8th Floor, New York, NY 10065; e-mail: ltv2001@med.cornell.edu.



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## ABSTRACT

### Purpose
Glycoprotein NMB (gpNMB), a negative prognostic marker, is overexpressed in multiple tumor types. Glembatumumab vedotin is a gpNMB-specific monoclonal antibody conjugated to the potent cytotoxin monomethyl auristatin E. This phase II study investigated the activity of glembatumumab vedotin in advanced breast cancer by gpNMB expression.

### Patients and Methods
Patients (n = 124) with refractory breast cancer that expressed gpNMB in ≥ 5% of epithelial or stromal cells by central immunohistochemistry were stratified by gpNMB expression (tumor, low stromal intensity, high stromal intensity) and were randomly assigned 2:1 to glembatumumab vedotin (n = 83) or investigator's choice (IC) chemotherapy (n = 41). The study was powered to detect overall objective response rate (ORR) in the glembatumumab vedotin arm between 10% (null) and 22.5% (alternative hypothesis) with preplanned investigation of activity by gpNMB distribution and/or intensity (Stratum 1 to Stratum 3).

### Results
Glembatumumab vedotin was well tolerated as compared with IC chemotherapy (less hematologic toxicity; more rash, pruritus, neuropathy, and alopecia). ORR was 6% (five of 83) for glembatumumab vedotin versus 7% (three of 41) for IC, without significant intertreatment differences for predefined strata. Secondary end point revealed ORR of 12% (10 of 83) versus 12% (five of 41) overall, and 30% (seven of 23) versus 9% (one of 11) for gpNMB overexpression (≥ 25% of tumor cells). Unplanned analysis showed ORR of 18% (five of 28) versus 0% (0 of 11) in patients with triple-negative breast cancer (TNBC), and 40% (four of 10) versus 0% (zero of six) in gpNMB-overexpressing TNBC.

### Conclusion
Glembatumumab vedotin is well tolerated in heavily pretreated patients with breast cancer. Although the primary end point in advanced gpNMB-expressing breast cancer was not met for all enrolled patients (median tumor gpNMB expression, 5%), activity may be enhanced in patients with gpNMB-overexpressing tumors and/or TNBC. A pivotal phase II trial (METRIC [Metastatic Triple-Negative Breast Cancer]) is underway.

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## INTRODUCTION

Antibody-drug conjugates (ADCs) offer a novel therapeutic approach by virtue of their selective delivery of cytotoxic agents directly to the tumor. Glembatumumab vedotin (CDX-011 or CR011-vcMMAE) is an ADC that combines a fully human immunoglobulin 2 monoclonal antibody against the tumor-associated antigen glycoprotein NMB (gpNMB) and a potent microtubule inhibitor monomethyl auristatin E (MMAE). Glembatumumab vedotin is designed to bind to gpNMB, and, after internalization, release MMAE via cleavage of a protease-sensitive valine-citrulline peptide linker, resulting in tumor cell death by microtubule inhibition.

gpNMB, a type I transmembrane protein, is expressed at higher levels in several malignant human tissues than in normal tissue.[1-3] Overexpression of gpNMB promotes invasion and metastasis by several tumor types, decreases tumor cell apoptosis, and promotes angiogenesis in preclinical models.[2,4-7] gpNMB overexpression appears to be a negative prognostic marker in breast and small-cell lung cancer.[2,8]

Glembatumumab vedotin has been evaluated in phase I/II clinical studies of heavily pretreated patients with either advanced breast cancer or advanced melanoma.[9,10] In both studies, glembatumumab vedotin had an acceptable and manageable safety profile. The melanoma study, which evaluated various dosing levels and schedules, led to the recommended phase II dose of 1.88 mg/kg given intravenously once every 3 weeks. At this dose, a promising objective response rate (ORR) of 15% (five of 34) was observed. In the breast cancer study, this dose resulted in an ORR of 12% (four of 33) and median progression-free survival (PFS) of 2.1 months. In the subset of patients with triple-negative breast cancer (TNBC), defined by the lack of overexpression of estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2), ORR was 20% (two of 10), and median PFS was 4.1 months. For the small subset of patients with TNBC who also had gpNMB-expressing tumors ($\geq$ 5% of epithelial or stromal cells were positive), ORR was 25% (one of four), and median PFS was 5.1 months.

Given these encouraging results, the EMERGE (CDX011-03; A Study of Glembatumumab Vedotin in Patients With Advanced GPNMB-expressing Breast Cancer) study was initiated to test the hypotheses that glembatumumab vedotin treatment in patients with gpNMB-expressing advanced breast cancer would result in an ORR of more than 10% and that this activity would correlate with the gpNMB expression pattern.

## PATIENTS AND METHODS

The EMERGE study was a phase II, open-label, randomized study designed to evaluate glembatumumab vedotin activity in advanced gpNMB-expressing breast cancer. Approximately 120 patients were randomly assigned (2:1) to glembatumumab vedotin or to chemotherapy of the investigator's choice (IC).

The study was conducted at each of the participating institutions in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, after approval by a local human investigations committee and in accordance with an assurance filed with and approved by the Department of Health and Human Services, as appropriate. All patients signed written informed consent before undergoing any protocol-specific procedures.

### Patients

Eligible patients were age $\geq$ 18 years with locally advanced or metastatic carcinoma of the breast that was confirmed to express gpNMB via central immunohistochemistry on archived tumor tissue. Study eligibility included a low threshold for expression ($\geq$ 5% of malignant epithelial cells or tumor stromal cells expressing gpNMB at any intensity), and randomization was stratified by gpNMB expression pattern. Patients with gpNMB expression in $\geq$ 5% of malignant epithelial cells were preferentially included in Stratum 1, regardless of stromal expression. The remaining patients (with gpNMB expression in $\geq$ 5% of stromal cells) were allocated to either Stratum 2 (stromal intensity score of 1+ or 2+) or Stratum 3 (stromal intensity score of 3+). Enrollment to Stratum 2 was capped at 24 patients, because it was hypothesized that these patients were least likely to benefit from glembatumumab vedotin.

Patients must have received from two to seven prior chemotherapy-containing regimens for progressive, recurrent, or metastatic breast cancer, demonstrated disease progression during or within 6 months of the last anticancer regimen, and previously received approved agents for which the patient was a candidate, including a taxane, an anthracycline, capecitabine, ixabepilone and, if the patient was HER2-positive, trastuzumab and lapatinib. However, an amendment removed the requirement for prior ixabepilone to facilitate accrual. Additional eligibility requirements included measurable disease by RECIST (Response Evaluation Criteria in Solid Tumors) 1.1[11]; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; life expectancy $\geq$ 3 months; resolution of all chemotherapy or radiation-related toxicities to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) severity grade $\leq$ 1 (except for alopecia); and adequate bone marrow, renal, and liver functions. Ineligible patients included women who were pregnant or breast-feeding and those with neuropathy grade $\geq$ 2, active brain metastases, or significant cardiovascular disease.

### Treatment and On-Study Evaluation

Study treatment continued until disease progression or intolerance. Glembatumumab vedotin (1.88 mg/kg) was administered as a 90-minute intravenous infusion once every 3 weeks. Up to two dose-level reductions (to 1.34 or 1.0 mg/kg) were allowed for toxicity. IC consisted of single-agent chemotherapy, selected at the discretion of the investigator from the following drugs: eribulin, capecitabine, vinorelbine, gemcitabine, docetaxel, paclitaxel, albumin-bound paclitaxel, doxorubicin HCL, or liposomal doxorubicin. Treatment with ixabepilone was also permitted after a protocol amendment removed the eligibility requirement for prior ixabepilone exposure. Chemotherapy dosing and supportive care were managed per standard practice. After documented disease progression, IC-treated patients were permitted to receive glembatumumab vedotin in a cross-over treatment phase.

Patients were seen at 3- to 4-week intervals throughout treatment. Safety assessments included physical examination, vital signs, hematology, blood chemistry, urinalysis, and electrocardiogram. Toxicity was graded according to NCI-CTCAE version 4.0. Radiographic assessments were performed within 4 weeks before treatment, every 6 weeks for 6 months, and every 3 months thereafter, until disease progression. Tumor response was assessed by the investigator per RECIST 1.1. Initially, survival follow-up continued until death. However, approximately 6 months before study completion, the protocol was amended to allow completion of follow-up on disease progression or initiation of alternative anticancer therapies.

### Correlative Studies

Serum samples for pharmacokinetic (PK) analysis (pre- and postdosing at cycles 1 to 3, end of treatment) were drawn for all patients. Additional samples were drawn during cycle 1 (through 5 hours postinfusion and on days 2 and 8) for 13 consenting patients. Intact ADC, total CR011 antibody (TA), free MMAE, and immunogenicity were measured as previously described.[10]

Immunohistochemistry for gpNMB expression in archived tumor sample was performed centrally (Clarient, Aliso Viejo, CA). Deparaffinized slides were incubated overnight with a goat polyclonal anti-gpNMB antibody (AF2550; R&D Systems, Minneapolis, MN) at a 1:500 dilution, after heat-induced antigen retrieval in citrate buffer (pH 6.0). Visualization was achieved with a donkey anti-goat horseradish peroxidase polymer detection system (The Jackson Laboratory, Bar Harbor, ME). Slides were counterstained with hematoxylin for 5 minutes, and scoring was performed manually by two pathologists who used a standard bright-field microscope. Staining intensity (0, negative; 1+, weak/translucent; 2+, moderate/opaque; 3+, strong/solid) and percentage of positive cells were reported for both epithelial and stromal compartments.

### Statistical Considerations

The sample size for the EMERGE study was not calculated to support direct comparisons between treatment arms. Rather, the primary objective of this study was to estimate ORR for the glembatumumab vedotin arm with a specified degree of precision and to determine whether the ORR exceeded a predefined minimum. The concurrent control arm was included for information purposes and to guide the design of future trials in this relatively unstudied population.

The highest priority secondary objective of the study was to evaluate any correlation between the antitumor response to glembatumumab vedotin and

  

the distribution or intensity of gpNMB expression. Therefore, the planned analyses were performed by gpNMB expression pattern and intensity to determine whether increased epithelial expression or bystander tumor cell killing through expression in stromal cells would have an impact on the outcome.

The sample size of 80 patients in the investigational arm allowed for the 95% CIs about the estimated ORR to extend to a maximum width of 22%. In addition, a one-sample exact binomial test with one-sided significance level of 2.5% would have 82% to 92% power to detect a difference between an ORR of 10% under the null hypothesis and an ORR of 22.5% to 25% under the alternative hypothesis. With a sample size of 40 patients in the control arm, the 95% CIs about the estimated ORR would extend to a maximum width of 31%.

Other activity end points included PFS, 12-week PFS rate, duration of response, and overall survival (OS). PFS and OS were calculated from the date of randomization and summarized descriptively by using the Kaplan-Meier method. Patients who discontinued the study, initiated alternative anticancer treatment, or missed two or more assessments before death or documented progression were censored for PFS analysis at the last evaluable tumor assessment.

The primary analyses were performed for the intention-to-treat population, which consisted of all randomly assigned patients. Supportive analyses used the per-protocol population, excluding patients with important deviations from the protocol and those without follow-up measurements relative to the analysis and including data for patients who received glembatumumab vedotin via crossover.

## RESULTS

### Patient Characteristics

One-hundred twenty-four patients were enrolled at 21 centers from September 2010 to December 2011. Patient screening, allocation to treatment, and disposition are shown in Figure 1. Pretreatment characteristics, including prior therapies, are summarized in Table 1.

### gpNMB Expression Analysis

Tumor samples were submitted for 328 patients, including 96 (29%) with TNBC. Approximately half were archival samples obtained from early-stage disease. For enrolled patients, submitted tumor samples were obtained from 2 weeks to 20 years (median, 3.3 years) before study entry.

Nearly all screened patients (99%) met the low threshold of gpNMB expression required for eligibility. More than half had significant gpNMB expression in stroma (staining in $\geq$ 25% of cells). The extent of stromal expression was similar for patients with TNBC relative to all others. However, significant epithelial expression (staining in $\geq$ 25% of cells) was seen in 40% of the TNBC samples compared with 21% of all others (Appendix Figs A1 and A2, online only).

Specimens from different time points were available for 16 screened patients (Appendix Fig A3, online only). In this small sample, gpNMB expression in malignant epithelial cells appeared relatively stable over time, with 94% (15 of 16) concordant with regard to the presence of significant expression (staining in $\geq$ 25% of cells). Greater variability was observed for stromal gpNMB expression.

### Study Treatments and Tolerability

Patients in both treatment arms received a median of two treatment cycles, with a range of one to 15 cycles in the glembatumumab vedotin arm and one to 14 cycles in the IC arm. IC therapies received were eribulin (n = 15), ixabepilone (n = 7), gemcitabine (n = 5), vinorelbine (n = 5), doxorubicin (n = 3), albumin-bound paclitaxel (n = 2), or other (n = 4).

Treatment-related toxicity (Table 2) mandated dose reduction for approximately one fourth of the patients in each arm and resulted in permanent discontinuation of study treatment for 8% of glembatumumab vedotin–treated and 5% of IC-treated patients. The most significant glembatumumab vedotin–related toxicities were rash, fatigue, neuropathy, and neutropenia. Neuropathy was predominantly sensory and was generally cumulative with continued dosing. Rashes, typically transient, ranged from mild erythema to more involved maculopapular dermatologic toxicity.

### PK and Immunogenicity

Serum concentrations of TA and ADC declined after glembatumumab vedotin infusion with terminal phase half-life of 36 and 34 hours, respectively. Mean time to maximum concentration of MMAE was approximately 5 days (Appendix Fig A4, online only). Volumes of distribution for TA and ADC approximated serum volume (Appendix Table A1, online only).

An antidrug antibody response was detected in 16 (17%) of the 93 glembatumumab vedotin-treated patients tested. Responses were confirmed to be specific against glembatumumab vedotin for six patients (6.5%), but only three (3.2%) were treatment emergent. The development of antibodies did not appear to have an impact on the PK profile or clinical outcome.

### Activity

ORR for the intention-to-treat population (confirmed response in all randomly assigned patients, that is, the primary study end point) was 6% (95% CI, 2% to 14%) for the glembatumumab vedotin arm and 7% (95% CI, 2% to 20%) for the IC arm (Table 3). Consistent with RECIST 1.1, which does not require confirmation of response in randomized trials, ORR inclusive of responses observed at a single time point was 12% (95% CI, 6% to 21%) for the glembatumumab vedotin arm and 12% (95% CI, 4% to 26%) for the IC arm (Table 3).

There were no clear indications that the activity of glembatumumab vedotin was enhanced for any of the three prespecified strata for gpNMB expression (Table 3). However, further analyses according to study objectives revealed that Stratum 1 patients whose tumors expressed higher levels of gpNMB in malignant epithelial cells (ie, using expression thresholds of $\geq$ 10% or $\geq$ 25% of malignant epithelial cells) had a significantly greater likelihood of tumor response compared with all other pooled Stratum 1, 2 and 3 patients (Fig 2). No such correlation was seen in the patients treated with IC therapy. By using a retrospectively defined threshold of $\geq$ 25% of malignant epithelial cells expressing gpNMB, ORR for patients with high tumor expression was 30% (seven of 23) for the glembatumumab arm and 9% (one of 11) for the IC arm (Table 4).

In an unplanned analysis, the ORR for patients with TNBC treated with glembatumumab vedotin was 18% (five of 28). No responses were observed in the 11 patients with TNBC treated with IC. For the patients with TNBC who also had high tumor gpNMB expression, ORR was 40% (four of 10) for the glembatumumab vedotin arm and 0% (zero of six) for the IC arm. In this small unplanned subgroup analysis, a possible improvement in PFS and OS was observed for the glembatumumab vedotin arm (Fig 3).

In the glembatumumab vedotin arm, development of rash in the first treatment cycle was associated with improved PFS (median, 3.4 *v*

**Table 1.** Pretreatment Patient Characteristics

| Characteristic | GV (n = 83) | | IC (n = 41) | | All Patients (n = 124) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Age, years | | | | | | |
| Median | 57 | | 58 | | 57 | |
| Range | 34-77 | | 34-73 | | 34-77 | |
| ECOG performance status | | | | | | |
| 0 | 36 | 43 | 14 | 34 | 50 | 40 |
| 1 | 44 | 53 | 27 | 66 | 71 | 57 |
| 2 | 1 | 1 | 0 | | 1 | 1 |
| 3 | 1* | 1 | 0 | | 1 | 1 |
| Unknown | 1* | 1 | 0 | | 1 | 1 |
| Breast cancer stage | | | | | | |
| III | 2 | 2 | 0 | | 2 | 2 |
| IV | 81 | 98 | 41 | 100 | 122 | 98 |
| Visceral disease (liver or lung) | 70 | 84 | 34 | 83 | 104 | 84 |
| Duration of disease since initial diagnosis, years | | | | | | |
| Median | 6.7 | | 5.4 | | 5.9 | |
| Range | 1.1-30.8 | | 1.1-30.4 | | 1.1-30.8 | |
| Duration of metastatic or locally advanced disease, years | | | | | | |
| Median | 3.2 | | 2.6 | | 3.0 | |
| Range | 0.3-18.9 | | 0.5-19.5 | | 0.3-19.5 | |
| Receptor status | | | | | | |
| ER-positive | 50 | 60 | 26 | 63 | 76 | 61 |
| PR-positive | 31† | 37 | 19 | 46 | 50 | 40 |
| HER2-positive‡ | 9§ | 11 | 9§ | 22 | 18 | 15 |
| Triple negative (ER negative/PR negative/HER2 negative) | 28 | 34 | 11 | 27 | 39 | 31 |
| gpNMB expression by IHC‖ | | | | | | |
| Any tumor epithelial expression (Stratum 1) | 44 | 53 | 22 | 54 | 66 | 53 |
| Low to intermediate stromal expression (Stratum 2) | 18 | 22 | 8 | 20 | 26 | 21 |
| High stromal expression (Stratum 3) | 21 | 25 | 11 | 27 | 32 | 26 |
| No. of prior lines of anticancer therapy¶ | | | | | | |
| Median | 6 | | 5 | | 6 | |
| Range | 3-11 | | 3-11 | | 3-11 | |
| No. of prior lines of cytotoxic therapy for advanced/metastatic disease | | | | | | |
| Median | 4 | | 4 | | 4 | |
| Range | 2-7 | | 1-6 | | 1-7 | |
| Prior therapies received (in any setting) | | | | | | |
| Taxane | 83 | 100 | 41 | 100 | 124 | 100 |
| Anthracycline | 80 | 96 | 40 | 98 | 120 | 97 |
| Capecitabine | 81 | 98 | 40 | 98 | 121 | 98 |
| Ixabepilone | 35 | 42 | 15 | 37 | 50 | 40 |
| Eribulin | 11 | 13 | 7 | 17 | 18 | 15 |
| Gemcitabine | 47 | 57 | 20 | 49 | 67 | 54 |
| Bevacizumab | 36 | 43 | 15 | 37 | 51 | 41 |
| Vinorelbine | 31 | 37 | 14 | 34 | 45 | 36 |
| Hormonal therapy | 51 | 61 | 24 | 59 | 75 | 60 |
| Trastuzumab | 14 | 17 | 11 | 27 | 25 | 20 |
| Lapatinib | 11 | 13 | 10 | 24 | 21 | 17 |
| Investigational agents | 16 | 19 | 11 | 27 | 27 | 22 |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; gpNMB, glycoprotein NMB; GV, glembatumumab vedotin; HER2, human epidermal growth factor receptor 2; IC, investigator's choice (chemotherapy); IHC, immunohistochemistry; PR, progesterone receptor.

*Patients were randomized but did not receive glembatumumab vedotin.

†PR status is unknown for one patient.

‡Concomitant HER2-targeted therapies were not permitted during study treatment.

§HER2 status was unknown for two patients (one in each treatment arm).

‖Patients with gpNMB expression in ≥ 5% of malignant epithelial cells were preferentially included in Stratum 1, regardless of stromal expression. The remaining patients (with gpNMB expression in ≥ 5% of stromal cells) were assigned to Stratum 2 if stromal intensity scores were 1+ or 2+ and to Stratum 3 if stromal intensity score was 3+.

¶Including hormonal therapies.

  

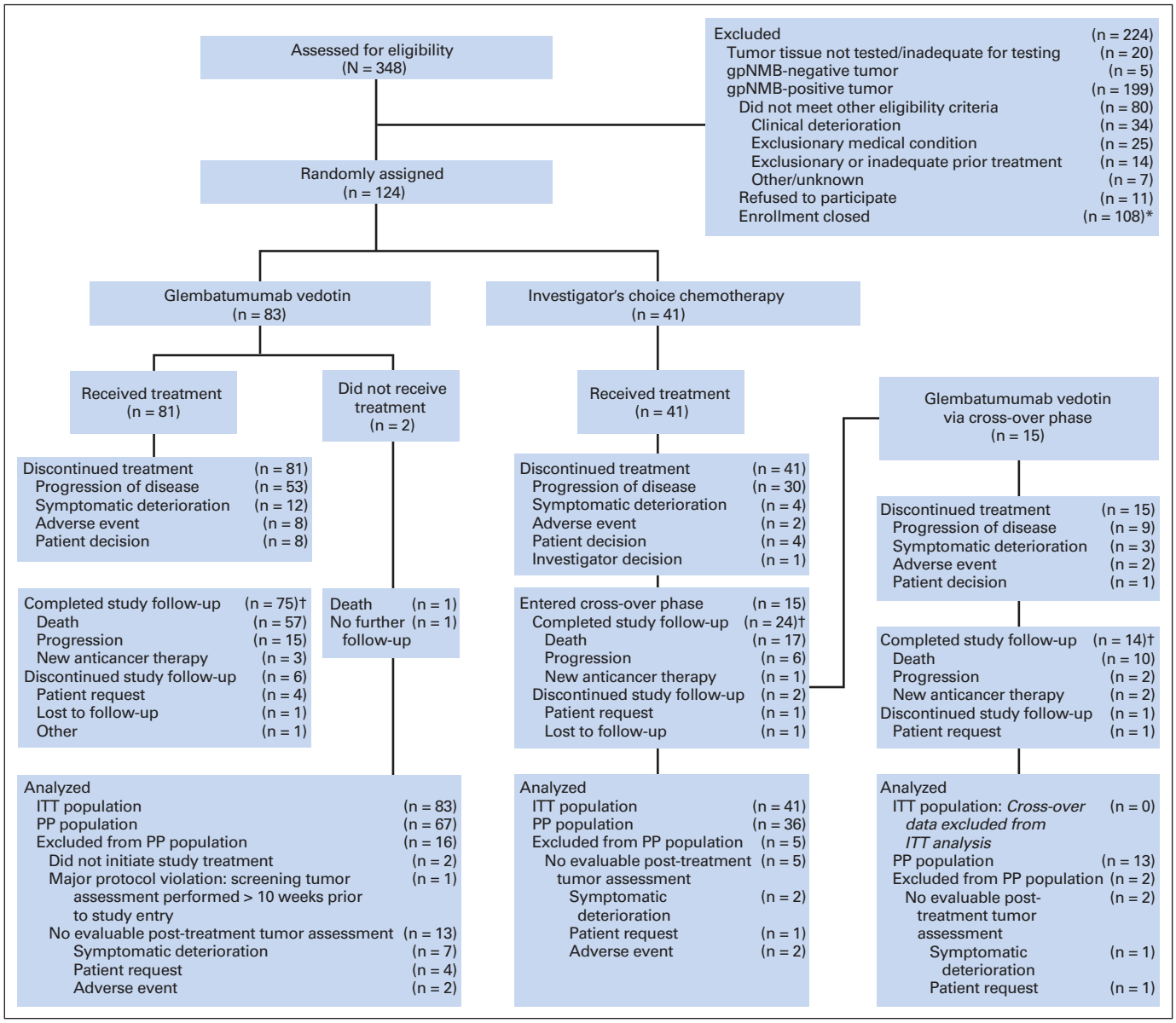


**Fig 1.** CONSORT diagram. (*) Includes patients who had agreed to tumor tissue screening for glycoprotein NMB (gpNMB) expression in advance of disease progression on current anticancer therapy. (†) Approximately 6 months before study completion, the protocol was amended such that post-treatment follow-up was completed on progression of disease as per RECIST 1.1 or initiation of alternative anticancer therapies rather than death. ITT, intention-to-treat population (all randomly assigned patients); PP, per-protocol population (excludes data for patients with important deviations from the protocol and those without an evaluable postbaseline radiographic assessment).

1.5 months) and OS (median, 8.8 *v* 5.3 months) (Appendix Fig A5, online only). However, ORR was similar for the glembatumumab vedotin-treated patients who developed rash in cycle 1 (14%; five of 37) compared with those who did not (11%; five of 46).

## DISCUSSION

The phase II EMERGE study was conducted in patients with gpNMB-expressing breast cancer to evaluate whether the activity of glembatumumab vedotin was dependent on gpNMB expression. The primary efficacy end point, demonstration of ORR of more than 10% for all enrolled patients, was not met. Overall study results are perhaps not surprising, given that 99% of screened patients met the low gpNMB expression threshold for eligibility. Outcomes were similar for glembatumumab vedotin and standard chemotherapy and were consistent with the prior phase I/II single-arm trial of glembatumumab vedotin in advanced breast cancer (CR011-CLN-20; A Phase I/II Study of Glembatumumab Vedotin in Patients with Locally Advanced or Metastatic Breast Cancer), which did not select patients on the basis of gpNMB expression status.[9]

Additional analyses performed to evaluate activity by gpNMB expression pattern revealed noteworthy outcomes in subsets of patients, specifically those with TNBC and/or higher levels of tumor

**Table 2.** Treatment-Related AEs

| AE | GV (n = 96)* | | | | IC (n = 41) | | | |
|---|---|---|---|---|---|---|---|---|
| | All Grades | | Grade 3 to 4 | | All Grades | | Grade 3 to 4 | |
| | No. | % | No. | % | No. | % | No. | % |
| Any treatment-related AE | 87 | 91 | 39 | 40 | 37 | 90 | 16 | 36 |
| Hematologic | | | | | | | | |
| Neutropenia | 28 | 29 | 21 | 22 | 18 | 44 | 12 | 29 |
| Leukopenia | 10 | 10 | 4 | 4 | 11 | 27 | 6 | 15 |
| Thrombocytopenia | 4 | 4 | 1 | 1 | 6 | 15 | 1 | 2 |
| Nonhematologic | | | | | | | | |
| Constipation | 13 | 14 | 0 | | 9 | 22 | 0 | |
| Nausea | 31 | 32 | 2 | 2 | 14 | 34 | 0 | |
| Vomiting | 17 | 18 | 0 | | 4 | 10 | 0 | |
| Stomatitis | 15 | 16 | 2 | 2 | 7 | 17 | 1 | 2 |
| Fatigue | 36 | 38 | 7 | 7 | 19 | 46 | 2 | 5 |
| Decreased appetite | 18 | 19 | 1 | 1 | 6 | 15 | 0 | |
| Dehydration | 10 | 10 | 3 | 3 | 3 | 7 | 1 | 2 |
| Peripheral neuropathy | 22 | 23 | 3 | 3 | 5 | 12 | 1 | 2 |
| Alopecia | 24 | 25 | 0 | | 6 | 15 | 0 | |
| Rash | 45 | 47 | 4 | 4 | 1 | 2 | 0 | |
| Pruritus | 20 | 21 | 1 | 1 | 1 | 2 | 0 | |
| Discontinuation of study treatment as a result of treatment-related AE | 8 | 8 | 5 | 5 | 2 | 5 | 1 | 2 |
| Hematologic | | | | | | | | |
| Neutropenia | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 |
| Nonhematologic | | | | | | | | |
| Diarrhea | 0 | | 0 | | 1 | 2 | 0 | |
| Stomatitis | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 2 |
| Decreased appetite | 1 | 1 | 1 | 1 | 1 | 2 | 0 | |
| Dehydration | 1 | 1 | 1 | 1 | 0 | | 0 | |
| Malnutrition | 1 | 1 | 1 | 1 | 0 | | 0 | |
| Neuropathy | 4 | 4 | 2 | 4 | 0 | | 0 | |
| Rash | 1 | 1 | 0 | | 0 | | 0 | |
| Skin hyperpigmentation | 1 | 1 | 0 | | 0 | | 0 | |
| Dose reduction as a result of treatment-related AE | 22 | 23 | 14 | 15 | 9 | 22 | 5 | 12 |
| Hematologic | | | | | | | | |
| Leukopenia | 0 | | 0 | | 3 | 7 | 1 | 2 |
| Neutropenia | 7 | 7 | 6 | 6 | 4 | 10 | 2 | 5 |
| Thrombocytopenia | 1 | 1 | 1 | 1 | 2 | 5 | 1 | 2 |
| Nonhematologic | | | | | | | | |
| Nausea | 2 | 2 | 2 | 2 | 1 | 2 | 0 | |
| Fatigue | 5 | 5 | 4 | 4 | 1 | 2 | 1 | 2 |
| Performance status decreased | 1 | 1 | 1 | 1 | 0 | | 0 | |
| Pyrexia | 0 | | 0 | | 2 | 5 | 0 | |
| Neuropathy | 5 | 5 | 0 | | 1 | 2 | 1 | 2 |
| Headache | 0 | | 0 | | 1 | 2 | 0 | |
| Palmar-plantar erythrodysesthesia syndrome | 0 | | 0 | | 1 | 2 | 1 | 2 |
| Pruritus | 0 | | 0 | | 1 | 2 | 0 | |
| Rash | 3 | 3 | 3 | 3 | 0 | | 0 | |
| Skin toxicity (burning/peeling) | 1 | 1 | 0 | | 0 | | 0 | |

NOTE. Table presents treatment-related AEs with incidence > 15% overall or ≥ 3% at grade 3 to 4 severity in either study arm. No grade 5 treatment-related AEs were reported.
Abbreviations: AE, adverse event; GV, glembatumumab vedotin; IC, investigator's choice (chemotherapy).
*Includes data for the 15 patients who crossed over to receive glembatumumab vedotin after progression on investigator's choice chemotherapy.

gpNMB expression. Stratum 1 (patients with gpNMB expression in ≥ 5% of tumor cells) was included to evaluate whether epithelial expression of gpNMB, a negative prognostic indicator for breast cancer recurrence,[2] has an impact on the outcome with glembatumumab vedotin. Increased ORR was seen for glembatumumab vedotin-treated, but not IC-treated, Stratum 1 patients with greater tumor gpNMB expression compared with all others, whether defined by thresholds of ≥ 10% or ≥ 25%. Specifically, ORR was 30% for patients with ≥ 25% of tumor cells expressing gpNMB.

The contribution of stroma to survival and metastatic potential of cancer cells is well documented.[12] Because data from the CR011-CLN-20 study suggested that gpNMB expression in breast cancer stroma may be associated with response to glembatumumab vedotin, the study included Stratum 2 (low to intermediate stromal intensity)

  

**Table 3.** Antitumor Activity by Predefined Strata for gpNMB Expression

| | All Patients | | | | | | Stratum 1* | | | | | | Stratum 2* | | | | | | Stratum 3* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GV | | | IC | | | GV | | | IC | | | GV | | | IC | | | GV | | | IC | | |
| Response | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI |
| ITT population† | | (n = 83) | | | (n = 41) | | | (n = 44) | | | (n = 22) | | | (n = 18) | | | (n = 8) | | | (n = 21) | | | (n = 11) | |
| ORR‡ | 10 | 12 | 6 to 21 | 5 | 12 | 4 to 26 | 8 | 18 | 8 to 33 | 3 | 14 | 3 to 35 | 1 | 6 | 0 to 27 | 2 | 25 | 3 to 65 | 1 | 5 | 0 to 24 | 0 | | 0 to 28 |
| Confirmed PR | 5 | 6 | 2 to 14 | 3 | 7 | 2 to 20 | 3 | 7 | 1 to 19 | 2 | 9 | 1 to 29 | 1 | 6 | 0 to 27 | 1 | 13 | 0 to 53 | 1 | 5 | 0 to 24 | 0 | | 0 to 28 |
| DOR, weeks | 34.0 | | | 30.1 | | | 12.3 | | | 30.1 | | | 23.1 | | | 18.0 | | | 34.0 | | | NA | | |
| | 23.1 | | | 20.3 | | | 12.0 | | | 20.3 | | | | | | | | | | | | | | |
| | 12.3 | | | 18.0 | | | 10.4 | | | | | | | | | | | | | | | | | |
| | 12.0 | | | | | | | | | | | | | | | | | | | | | | | |
| | 10.4 | | | | | | | | | | | | | | | | | | | | | | | |
| SD or better | 41 | 49 | | 19 | 46 | | 22 | 50 | | 10 | 45 | | 4 | 22 | | 5 | 63 | | 15 | 71 | | 4 | 36 | |
| PFS | | | | | | | | | | | | | | | | | | | | | | | | |
| 12-week rate, % | | 40 | 35 to 45 | | 39 | 33 to 45 | | 38 | 32 to 44 | | 40 | 32 to 48 | | 25 | 20 to 30 | | 50 | 33 to 67 | | 56 | 44 to 69 | | 20 | 15 to 25 |
| Median, months | 2.3 | | 1.6 to 3.0 | 2.0 | | 1.4 to 2.9 | 2.0 | | 1.6 to 3.3 | 2.0 | | 1.4 to 3.5 | 1.4 | | 1.4 to 2.8 | 3.4 | | 1.4 to 7.0 | 3.0 | | 2.1 to 5.4 | 1.7 | | 1.0 to 2.9 |
| OS | | | | | | | | | | | | | | | | | | | | | | | | |
| Median, months | 7.5 | | 5.6 to 8.8 | 7.4 | | 5.4 to 13.9 | 7.6 | | 5.3 to 10.2 | 6.9 | | 5.2 to 12.5 | 5.4§ | | 2.6 to NE | 15.6§ | | 3.4 to NE | 7.7 | | 5.2 to 13.3 | 4.8 | | 2.0 to NE |
| PP population‖ | | (n = 80) | | | (n = 36) | | | (n = 45) | | | (n = 20) | | | (n = 16) | | | (n = 8) | | | (n = 19) | | | (n = 8) | |
| ORR‡ | 13 | 16 | 5 to 30 | 5 | 14 | 5 to 29 | 9 | 20 | 10 to 35 | 3 | 15 | 3 to 38 | 3 | 19 | 4 to 46 | 2 | 25 | 3 to 65 | 1 | 5 | 0 to 26 | 0 | | 0 to 37 |
| Confirmed PR | 8 | 10 | 4 to 19 | 3 | 8 | 2 to 22 | 4 | 9 | 2 to 21 | 2 | 10 | 1 to 32 | 3 | 19 | 4 to 46 | 1 | 13 | 0 to 53 | 1 | 5 | 0 to 26 | 0 | | 0 to 37 |
| DOR, weeks | 34.0 | | | 30.1 | | | 18.3¶ | | | 30.1 | | | 23.1 | | | 18.0 | | | 34.0 | | | NA | | |
| | 23.1 | | | 20.3 | | | 12.3 | | | 20.3 | | | 15.3¶ | | | | | | | | | | | |
| | 18.3¶ | | | 18.0 | | | 12.0 | | | | | | 12.1 | | | | | | | | | | | |
| | 15.3¶ | | | | | | 10.4 | | | | | | | | | | | | | | | | | |
| | 12.3 | | | | | | | | | | | | | | | | | | | | | | | |
| | 12.1 | | | | | | | | | | | | | | | | | | | | | | | |
| | 12.0 | | | | | | | | | | | | | | | | | | | | | | | |
| | 10.4 | | | | | | | | | | | | | | | | | | | | | | | |
| SD or better | 46 | 58 | | 19 | 53 | | 25 | 56 | | 10 | 50 | | 5 | 31 | | 5 | 63 | | 16 | 84 | | 4 | 50 | |

Abbreviations: DOR, duration of response; gpNMB, glycoprotein NMB; GV, glembatumumab vedotin; IC, investigator's choice (chemotherapy); ITT, intention-to-treat; NA, not applicable; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PP, per-protocol population; PR, partial response; SD, stable disease.

*Patients with gpNMB expression in ≥ 5% of malignant epithelial cells by central immunohistochemistry were preferentially included in Stratum 1, regardless of stromal expression. The remaining patients with gpNMB expression in ≥ 5% of stromal cells were allocated by intensity of stromal gpNMB expression. Patients with stromal intensity scores of 1+ or 2+ were assigned to Stratum 2. Patients with stromal intensity score of 3+ were assigned to Stratum 3.

†ITT population includes all randomly assigned patients and uses gpNMB expression group assigned by the investigative site at the time of randomization.

‡ORR per RECIST 1.1, inclusive of response observed at a single time point. DOR shown only for responses that were confirmed at a subsequent time point.

§Statistically significant comparison $P = .015$.

‖PP population excludes data for patients with important deviations from the protocol and for those without an evaluable postbaseline radiographic assessment and includes data for patients who received GV via crossover. In addition, for this supportive analysis, three patients who were assigned to an incorrect stratum at random assignment were reassigned to the appropriate gpNMB expression group.

¶Patients were censored for duration of response.

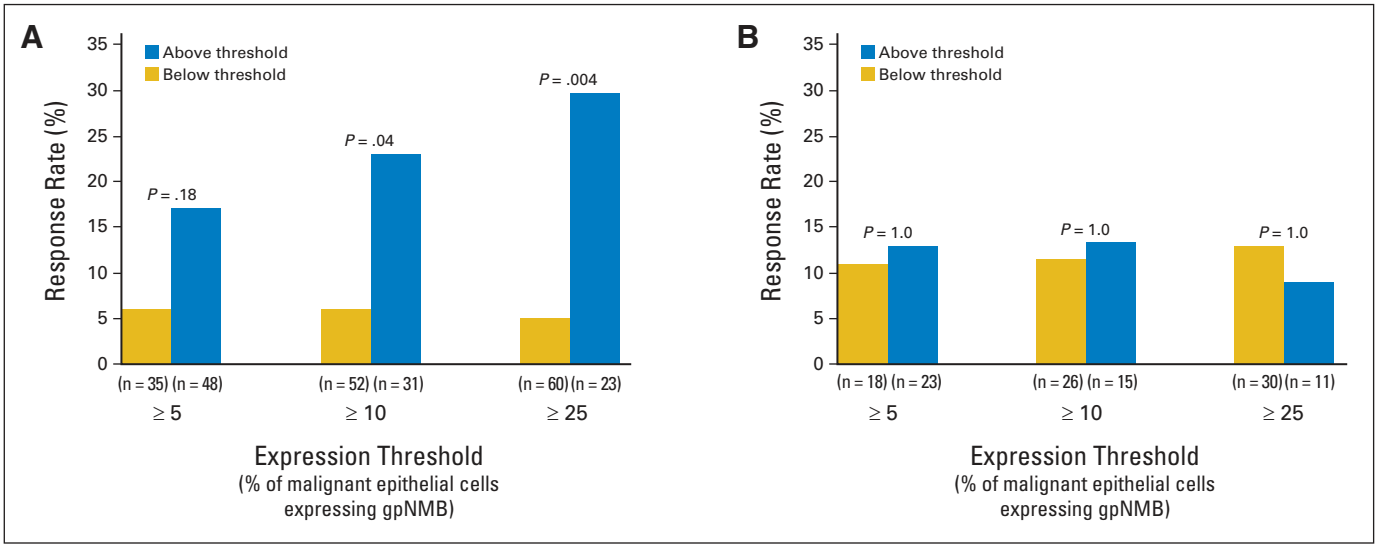


**Fig 2.** Correlation of tumor response and glycoprotein NMB (gpNMB) expression in malignant epithelial cells within (A) the glembatumumab vedotin arm, and (B) the investigator's choice chemotherapy arm. Objective response rate is shown for subgroups of patients with gpNMB expression in archived tumor falling below or above different thresholds. Analysis based on intention-to-treat population.

and Stratum 3 (high stromal intensity). Consistent with the study hypotheses, Stratum 2 patients appeared to derive limited benefit from glembatumumab vedotin, with decreased survival relative to IC-treated patients. However, nonsignificant trends toward increased PFS and OS were observed in Stratum 3, and a small number of patients with predominantly stromal cell expression experienced tumor response. In light of the observed variability of stromal cell expression in tumor specimens over time, one might speculate a possible role for glembatumumab vedotin relative to gpNMB expression on infiltrating immune response cells, or a bystander effect in which free MMAE is released during apoptosis of gpNMB-positive stromal cells.[13,14]

TNBC, which is categorized by a lack of proven therapeutic targets, represents a disease with substantial molecular heterogeneity.[15] Responses to standard chemotherapy are usually brief and are associated with progressive resistance and short survival.[16] Thus, there

**Table 4.** Retrospective Analysis of Antitumor Activity for Subgroups of Interest

| | TNBC | | | | | | High gpNMB Expression* | | | | | | TNBC and High gpNMB Expression* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | GV | | | IC | | | GV | | | IC | | | GV | | | IC | | |
| Group | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI | No. | % | 95% CI |
| ITT population† | (n = 28) | | | (n = 11) | | | (n = 23) | | | (n = 11) | | | (n = 10) | | | (n = 6) | | |
| ORR‡ | 5 | 18 | 6 to 37 | 0 | 0 | 0 to 28 | 7 | 30 | 13 to 53 | 1 | 9 | 0 to 41 | 4 | 40 | 12 to 74 | 0 | 0 | 0 to 46 |
| Confirmed PR | 2 | 7 | 1 to 24 | 0 | 0 | 0 to 28 | 3 | 13 | 3 to 34 | 1 | 9 | 0 to 41 | 1 | 10 | 0 to 45 | 0 | 0 | 0 to 46 |
| DOR, weeks | 34.0 | | | NA | | | 12.3 | | | 30.1 | | | 10.4 | | | NA | | |
| | 10.4 | | | | | | 12.0 | | | | | | | | | | | |
| | | | | | | | 10.4 | | | | | | | | | | | |
| SD or better | 17 | 61 | | 3 | 27 | | 15 | 65 | | 3 | 27 | | 9 | 90 | | 1 | 17 | |
| PP population§ | (n = 27) | | | (n = 9) | | | (n = 25) | | | (n = 8) | | | (n = 12) | | | (n = 4) | | |
| ORR‡ | 5 | 19 | 6 to 38 | 0 | 0 | 0 to 34 | 8 | 32 | 15 to 54 | 1 | 13 | 0 to 53 | 4 | 33 | 10 to 65 | 0 | 0 | 0 to 60 |
| Confirmed PR | 2 | 7 | 1 to 24 | 0 | 0 | 0 to 34 | 4 | 16 | 5 to 36 | 1 | 13 | 0 to 53 | 1 | 8 | 0 to 38 | 0 | 0 | 0 to 60 |
| DOR, weeks | 34.0 | | | NA | | | 18.3‖ | | | 30.1 | | | 10.4 | | | NA | | |
| | 10.4 | | | | | | 12.3 | | | | | | | | | | | |
| | | | | | | | 12.0 | | | | | | | | | | | |
| | | | | | | | 10.4 | | | | | | | | | | | |
| SD or better | 18 | 67 | | 3 | 33 | | 16 | 64 | | 3 | 38 | | 9 | 75 | | 1 | 25 | |

Abbreviations: DOR, duration of response; gpNMB, glycoprotein NMB; GV, glembatumumab vedotin; IC, investigator's choice (chemotherapy); ITT, intention-to-treat; NA, not applicable; PP, per-protocol population; PR, partial response; ORR, overall response rate; SD, stable disease; TNBC, triple-negative breast cancer.
*Defined as ≥ 25% of tumor epithelial cells expressing gpNMB by immunohistochemistry.
†ITT population includes all randomly assigned patients.
‡ORR per RECIST 1.1, inclusive of response observed at a single time point. DOR shown only for responses that were confirmed at a subsequent time point.
§PP population excludes data for patients with important deviations from the protocol and those without an evaluable postbaseline radiographic assessment and includes data for patients who received glembatumumab vedotin via crossover.
‖Patients were censored for duration of response.

  

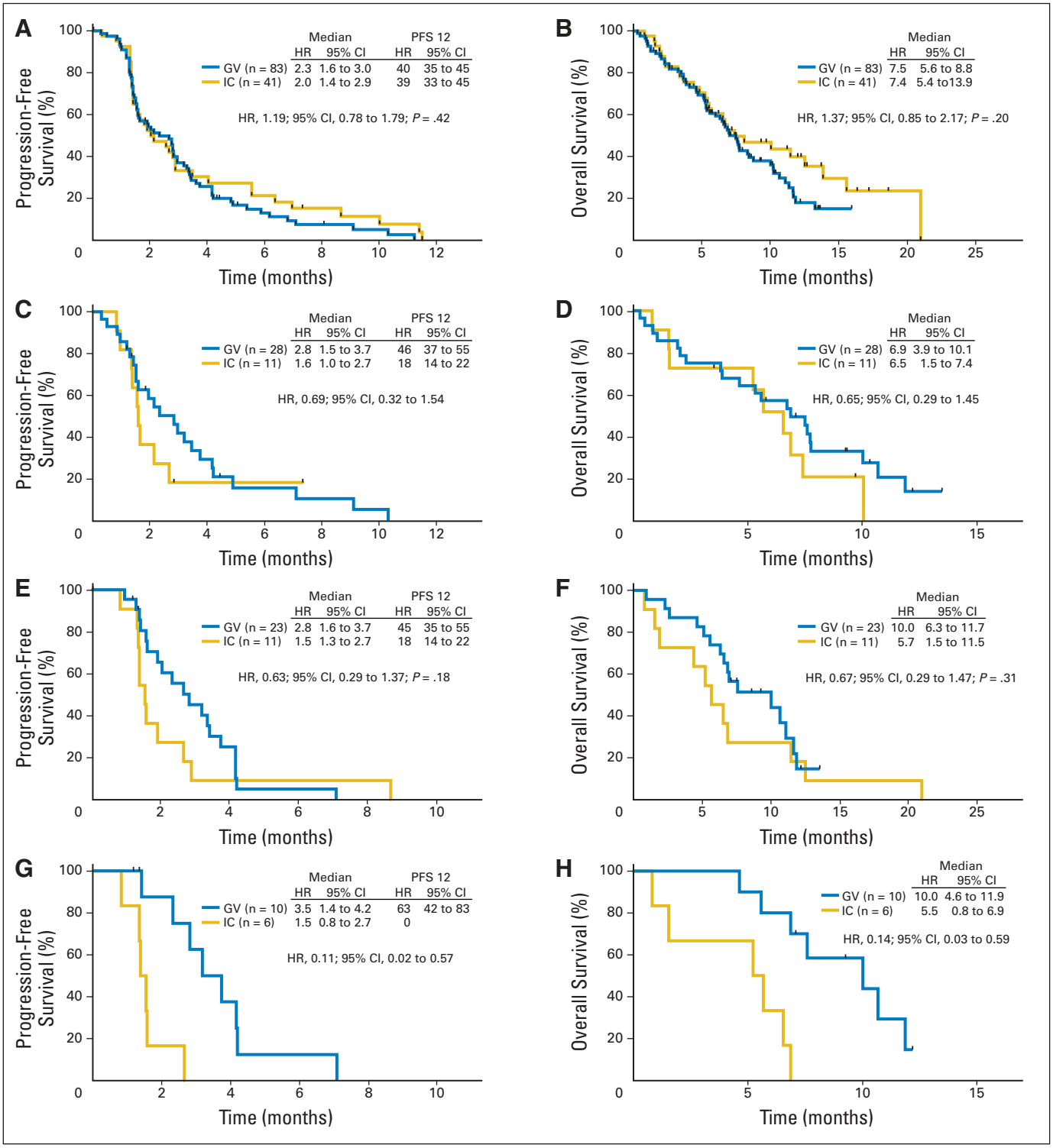


**Fig 3.** (A, C, E, G) Progression-free survival (PFS) and (B, D, F, H) overall survival for subgroups of interest. Data are shown for (A, B) all enrolled patients, (C, D) patients with triple-negative breast cancer, (E, F) patients with high glycoprotein NMB (gpNMB) –expressing tumors, and (G, H) patients with breast cancer that is both triple negative and gpNMB expressing. gpNMB expression is defined by staining in ≥ 25% of malignant epithelial cells in archived tumor specimen. Analysis based on intention-to-treat population. Patients who received investigator's choice (IC) of chemotherapy treatment but crossed over to receive glembatumumab vedotin (GV) are included in the IC group only. Median shown as months (95% CI), 12-week PFS rate (PFS 12) shown as percentage (95% CI) and tick marks represent censored data. HR, hazard ratio.

is great interest in identifying molecular markers that can be targeted for therapeutic interventions. gpNMB is highly expressed in TNBC, in which it has been shown to correlate with the metastatic phenotype.[2] Consistent with study CR011-CLN-20, noteworthy activity was observed for glembatumumab vedotin-treated patients with TNBC, with a possible improvement in PFS and OS observed for the albeit small subset of patients with gpNMB-overexpressing TNBC.

Toxicity with glembatumumab vedotin was generally manageable and consistent with prior studies. Hematologic toxicity was less frequent, but drug-related rash, peripheral neuropathy, and alopecia were more frequent in the glembatumumab vedotin arm compared with IC. In the melanoma study, development of rash correlated with improved ORR and PFS in glembatumumab vedotin–treated patients.[10] A similar association was observed in EMERGE, in which PFS and OS (but not ORR) were prolonged for patients who developed a rash in cycle 1 compared with those who did not. Although the mechanism by which these observations are linked is unknown, early development of a rash may prove to be an important biomarker for response in patients treated with glembatumumab vedotin.

The half-life (mean ± standard deviation) was 34 ± 9.9 hours for ADC and 36.4 ± 9.8 hours for TA. However, the presence of free MMAE for up to 3 weeks suggests that the ADC may be in circulation for at least that duration, albeit below the level of assay sensitivity. PK results similar to those previously observed in melanoma[10] suggest that PK of glembatumumab vedotin are not sex or tumor specific.

In conclusion, the EMERGE study suggests that patients with TNBC and tumor gpNMB overexpression may potentially derive the greatest benefit from glembatumumab vedotin. The identified threshold for gpNMB expression (≥ 25% of malignant epithelial cells) captures a significant proportion (41%) of the screened patients with TNBC. In addition, epithelial gpNMB expression with regard to this cutoff appears to be relatively stable over time, supporting the use of archival samples for determination of eligibility. However, the EMERGE analyses were subject to a number of limitations, including small sample sizes for subgroups of interest and the exploratory/unplanned nature of the analyses inherent in the study design. A pivotal trial (METRIC) has been initiated to confirm these findings. METRIC will randomly assign 300 women with metastatic gpNMB-overexpressing TNBC to receive glembatumumab vedotin or capecitabine in a 2:1 ratio. The primary analysis end point is PFS, and secondary end points include ORR, duration of response, OS, quality of life, and safety. Studies in other gpNMB-positive cancers, including cutaneous and uveal melanomas, pediatric osteosarcoma, and squamous cell lung cancer, are also planned.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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## AUTHOR CONTRIBUTIONS

**Conception and design:** Scott Cruickshank, Elizabeth Crowley, Jennifer Green, Thomas Hawthorne, Michael J. Yellin, Thomas A. Davis, Linda T. Vahdat
**Provision of study materials or patients:** Denise A. Yardley, Ira Oliff, Rebecca Bechhold
**Collection and assembly of data:** Denise A. Yardley, Robert Weaver, Michelle E. Melisko, Mansoor N. Saleh, Francis P. Arena, Andres Forero, Tessa Cigler, Alison Stopeck, Dennis Citrin, Ira Oliff, Rebecca Bechhold, Randa Loutfi, Agustin A. Garcia, Elizabeth Crowley, Jennifer Green, Thomas Hawthorne, Michael J. Yellin, Thomas A. Davis, Linda T. Vahdat
**Data analysis and interpretation:** Denise A. Yardley, Michelle E. Melisko, Andres Forero, Scott Cruickshank, Elizabeth Crowley, Jennifer Green, Thomas Hawthorne, Michael J. Yellin, Thomas A. Davis, Linda T. Vahdat
**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

## REFERENCES


1. Tse KF, Jeffers M, Pollack VA, et al: CR011, a fully human monoclonal antibody-auristatin E conjugate, for the treatment of melanoma. Clin Cancer Res 12:1373-1382, 2006
2. Rose AA, Grosset AA, Dong Z, et al: Glycoprotein nonmetastatic B is an independent prognostic indicator of recurrence and a novel therapeutic target in breast cancer. Clin Cancer Res 16:2147-2156, 2010
3. Kuan CT, Wakiya K, Dowell JM, et al: Glycoprotein nonmetastatic melanoma protein B, a potential molecular therapeutic target in patients with glioblastoma multiforme. Clin Cancer Res 12:1970-1982, 2006
4. Rose AA, Pepin F, Russo C, et al: Osteoactivin promotes breast cancer metastasis to bone. Mol Cancer Res 5:1001-1014, 2007
5. Rich JN, Shi Q, Hjelmeland M, et al: Bone-related genes expressed in advanced malignancies induce invasion and metastasis in a genetically defined human cancer model. J Biol Chem 278:15951-15957, 2003
6. Onaga M, Ido A, Hasuike S, et al: Osteoactivin expressed during cirrhosis development in rats fed a choline-deficient, L-amino acid-defined diet, accelerates motility of hepatoma cells. J Hepatol 39:779-785, 2003
7. Rose AA, Annis MG, Dong Z, et al: ADAM10 releases a soluble form of the GPNMB/Osteoactivin extracellular domain with angiogenic properties. PLoS One 5:e12093, 2010
8. Li YN, Zhang L, Li XL, et al: Glycoprotein nonmetastatic B as a prognostic indicator in small cell lung cancer. APMIS 122:140-146, 2014
9. Bendell J, Saleh M, Rose AA, et al: Phase I/II study of the antibody-drug conjugate glembatumumab vedotin in patients with locally advanced or metastatic breast cancer. J Clin Oncol 32:3619-3625, 2014
10. Ott PA, Hamid O, Pavlick AC, et al: Phase I/II study of the antibody-drug conjugate glembatumumab vedotin in patients with advanced melanoma. J Clin Oncol 32:3659-3666, 2014
11. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009
12. Guise TA: Breast cancer bone metastases: It's all about the neighborhood. Cell 154:957-959, 2013
13. Kovtun YV, Audette CA, Ye Y, et al: Antibody-drug conjugates designed to eradicate tumors with homogeneous and heterogeneous expression of the target antigen. Cancer Res 66:3214-3221, 2006


  

**14.** Okeley NM, Miyamoto JB, Zhang X, et al: Intracellular activation of SGN-35, a potent anti-CD30 antibody-drug conjugate. Clin Cancer Res 16:888-897, 2010

**15.** Cancer Genome Atlas Network: Comprehensive molecular portraits of human breast tumours. Nature 490:61-70, 2012

**16.** Crown J, O'Shaughnessy J, Gullo G: Emerging targeted therapies in triple-negative breast cancer. Ann Oncol 23:vi56-vi65, 2012

***Affiliations***

Denise A. Yardley, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; Robert Weaver, Florida Cancer Specialists, Tampa, FL; Michelle E. Melisko, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco; Scott Cruickshank, Scott Cruickshank & Associates, Santa Barbara; Agustin A. Garcia, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA; Mansoor N. Saleh, Georgia Cancer Specialists, Sandy Springs, GA; Francis P. Arena, New York University Langons Arena Oncology, Lake Success; Tessa Cigler and Linda T. Vahdat, Weill Cornell Medical College, New York, NY; Andres Forero, University of Alabama, Birmingham, AL; Alison Stopeck, University of Arizona Cancer Center, Tucson, AZ; Dennis Citrin, Cancer Treatment Centers of America/Midwestern Regional Medical Center, Zion; Ira Oliff, Orchard Healthcare Research, Skokie, IL; Rebecca Bechhold, Oncology Hematology Care, Cincinnati, OH; Randa Loutfi, Henry Ford Health System, Detroit, MI; and Elizabeth Crowley, Jennifer Green, Thomas Hawthorne, Michael J. Yellin, and Thomas A. Davis, Celldex Therapeutics, Hampton, NJ.

## GLOSSARY TERMS

**angiogenesis:** the process involved in the generation of new blood vessels. Although this is a normal process that naturally occurs and is controlled by so-called on and off switches, blocking tumor angiogenesis (antiangiogenesis) disrupts the blood supply to tumors, thereby preventing tumor growth.

**antibody-drug conjugate:** an antibody chemically linked to a therapeutic cytotoxic agent providing targeted delivery of the cytotoxic agent preferentially to cancer cells expressing the antigen recognized by the antibody.

**apoptosis:** also called programmed cell death. Apoptosis is a signaling pathway that leads to cellular suicide in an organized manner. Several factors and receptors are specific to the apoptotic pathway. The net result is that cells shrink and develop blebs on their surface, and their DNA undergoes fragmentation.

**HER2/neu (human epidermal growth factor receptor 2):** also called ErbB2. HER2/neu belongs to the epidermal growth factor receptor (EGFR) family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the human epidermal growth factor family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any members of the family. It is typically overexpressed in several epithelial tumors.

**monoclonal antibody:** an antibody that is secreted from a single clone of an antibody-forming cell. Large quantities of monoclonal antibodies are produced from hybridomas, which are produced by fusing single antibody-forming cells to tumor cells. The process is initiated with initial immunization against a particular antigen, stimulating the production of antibodies targeted to different epitopes of the antigen. Antibody-forming cells are subsequently isolated from the spleen. By fusing each antibody-forming cell to tumor cells, hybridomas can each be generated with a different specificity and targeted against a different epitope of the antigen.

**prognostic marker:** a marker that predicts the prognosis of a patient (eg, the likelihood of relapse, progression, and/or death) independent of future treatment effects. A factor can be both prognostic and predictive.

**RECIST (Response Evaluation Criteria in Solid Tumors):** a model proposed by the Response Evaluation Criteria Group by which a combined assessment of all existing lesions, characterized by target lesions (to be measured) and nontarget lesions, is used to extrapolate an overall response to treatment.

**stromal cells:** the noncancer cells in tumors. The stroma is distinct from the parenchyma, which consists of the key functional elements of an organ.

**triple-negative breast cancer:** breast tumors that are negative for estrogen and progesterone receptor expression and that also underexpress HER-neu.



 

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## Appendix

**Table A1.** Noncompartmental Pharmacokinetic Parameters

| | Dose (mg/kg) | Half-Life (hours) | | $T_{max}$ (hours) | | $C_{max}$ ($\mu$g/mL) | | $T_{last}$ (hours) | | $AUC_{all}$ (hours × $\mu$g/mL) | | $AUC_{\infty}$ (hours × $\mu$g/mL) | | $V_z$ (mL/kg) | | Cl (mL/h/kg) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| TA | > 1.88 | 36.4 | 9.8 | 4.0 | 6.7 | 63.9 | 12.3 | 113 | 78 | 3,450 | 2,399 | 3,909 | 2,143 | 30 | 10 | 0.7 | 0.4 |
| ADC | 1.88 | 34.0 | 9.9 | 2.3 | 1.2 | 44.8 | 13.4 | 136 | 68 | 2,373 | 1,245 | 2,501 | 1,191 | 43 | 15 | 1.1 | 0.9 |
| | | | | | | $C_{max}$ (ng/mL) | | | | | | | | $V_z$/F | | Cl/F | |
| | | | | | | Mean | SD | | | | | | | Mean | SD | Mean | SD |
| MMAE | 0.04 equivalents | 76.1 | 14.5 | 121.2 | 71.2 | 5.4 | 3.7 | 402 | 169 | 1.404 | 0.938 | 1.886 | 0.837 | 2,667 | 843 | 26 | 11 |

NOTE. Noncompartmental pharmacokinetic parameters (mean ± standard deviation) are presented from 12 patients consenting to dense sampling. One patient with missing 12-hour time point data was excluded. Sampling time points were pre-dose, at the end of the 90-minute infusion, and at 3 hours, 5 hours, 24 hours, 1 week, and 3 weeks after initiation of the infusion. Total CR011 antibody (TA) and antibody-drug conjugate (ADC) concentrations were analyzed by using model 202 constant infusion, and free monomethyl auristatin E (MMAE) concentrations were analyzed with model 200 extravascular input in WinNonlin v 5.3 (Pharsight, Montain View, CA). Dosing of free MMAE equivalents was estimated on the basis of the theoretical concentration of total MMAE in drug product and the nominal drug-to-antibody ratio at a dose of 1.88 mg/kg glembatumumab vedotin. Area under the curve was estimated with the linear trapezoidal method with linear interpolation and uniform weighting. Terminal-phase parameters of the TA and ADC were estimated from the last three quantifiable points, which were extended earlier if possible by monitoring goodness of fit. Terminal-phase parameters of free MMAE were calculated from two points.

Abbreviations: $AUC_{all}$, area under the concentration-time curve from the time of dosing to the time of the last observation; $AUC_{\infty}$, area under the concentration-time curve extrapolated to infinity; Cl, clearance; Cl/F, apparent clearance; $C_{max}$, maximum concentration; $T_{last}$, time of the last point with quantifiable concentration; $T_{max}$, time to maximum concentration; $V_z$, volume of distribution; $V_z$/F, apparent volume of distribution.

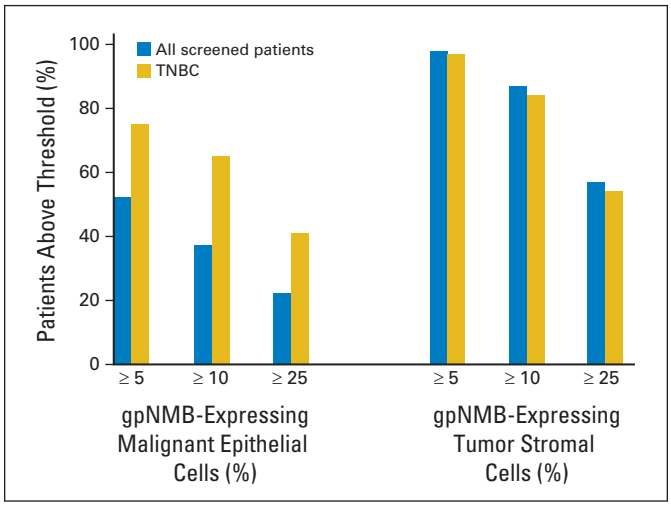


**Fig A1.** Glycoprotein NMB (gpNMB) expression analysis. Graph shows the proportion of patients with tumors expressing gpNMB in malignant epithelial cells and tumor stromal cells, according to different expression thresholds. Blue bars represent results for all screened patients with breast cancer (n = 328); gold bars represent results for screened patients with triple-negative breast cancer (TNBC; n = 96).

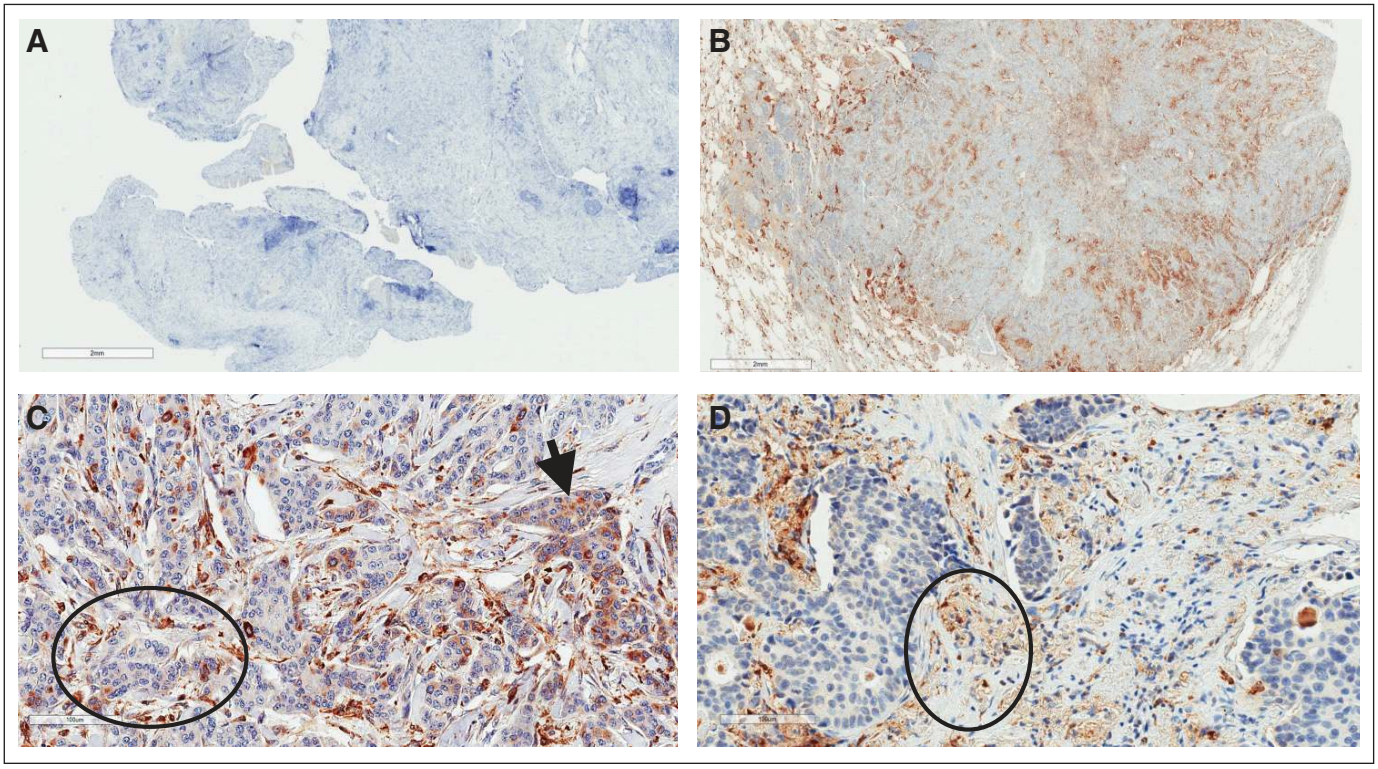


**Fig A2.** Glycoprotein NMB (gpNMB) expression in malignant breast cancer epithelial cells and stroma. The expression pattern of gpNMB in malignant breast cancer tissue samples was assessed by immunohistochemical analysis. (A) A representative image of the negative control sample is shown at low magnification. (B, C, D) gpNMB expression at (B) low and (C, D) high magnification. (C) Tissue sample was chosen to reflect mean staining intensity (approximately 2.0) and percent positivity of tumor cells (approximately 30%), as determined from the database of all samples screened. (C, D) Images are representative of stratification groups 1 and 3, respectively. (C) A region of gpNMB-positive stroma is delineated by the oval, and a cluster of gpNMB-positive tumor epithelial cells is indicated by the arrow. (D) Tumor epithelial cells are uniformly negative compared with a region of gpNMB-positive stroma (oval).

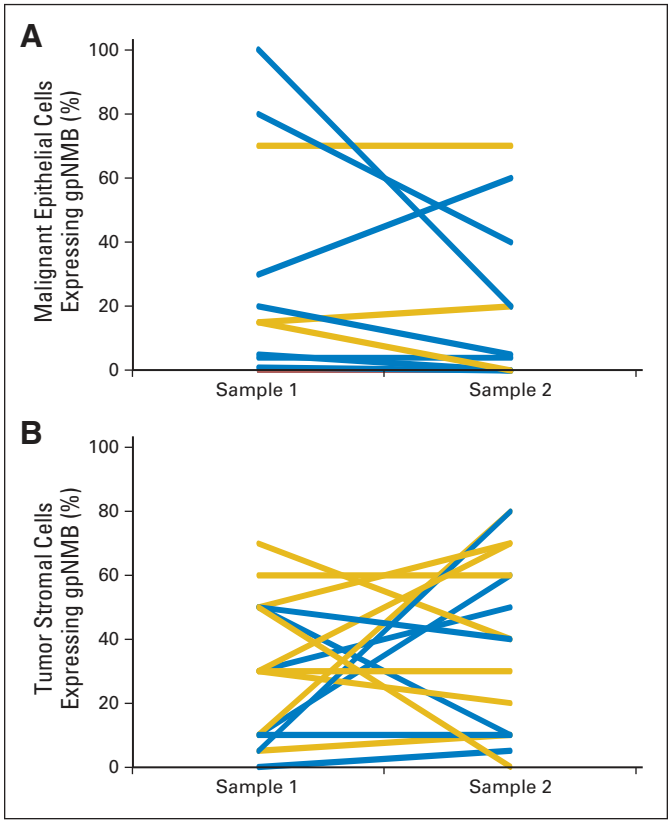


**Fig A3.** Consistency of glycoprotein NMB (gpNMB) expression over time. gpNMB expression in (A) malignant epithelial cells and (B) tumor stromal cells is shown for 16 screened patients who provided tumor specimens from different surgical procedures, ranging from 1.3 to 81.5 months apart. Seven patients (blue lines) provided samples taken from the same site, and the remaining nine patients (gold lines) provided samples from different sites, including at least one sample from a metastatic site.

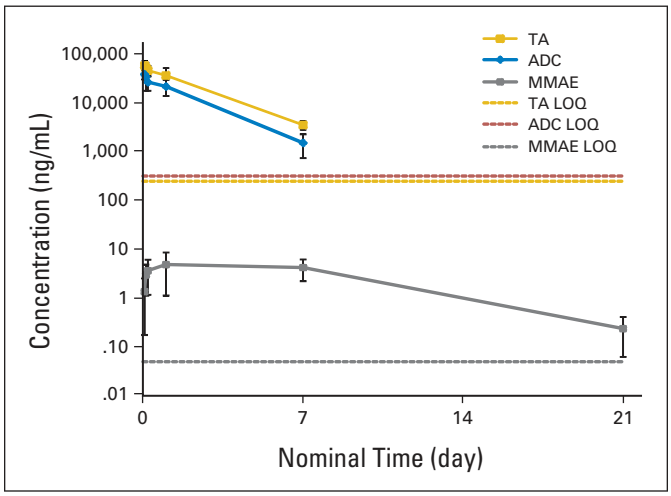


**Fig A4.** Concentration-time curves for CR011 antibody (TA), glembatumumab vedotin antibody-drug conjugate (ADC), and free monomethyl auristatin E (MMAE). Serum concentrations are shown as mean ± standard deviation for 13 patients who received glembatumumab vedotin (1.88 mg/kg once every 3 weeks). Sampling time points were predose, at the end of the 90-minute infusion, and at 3 hours, 5 hours, 24 hours, 1 week, and 3 weeks after initiation of the infusion. Dotted lines represent limits of quantitation (LOQ) for TA (250 ng/mL), ADC (320 ng/mL), and MMAE (0.05 ng/mL).

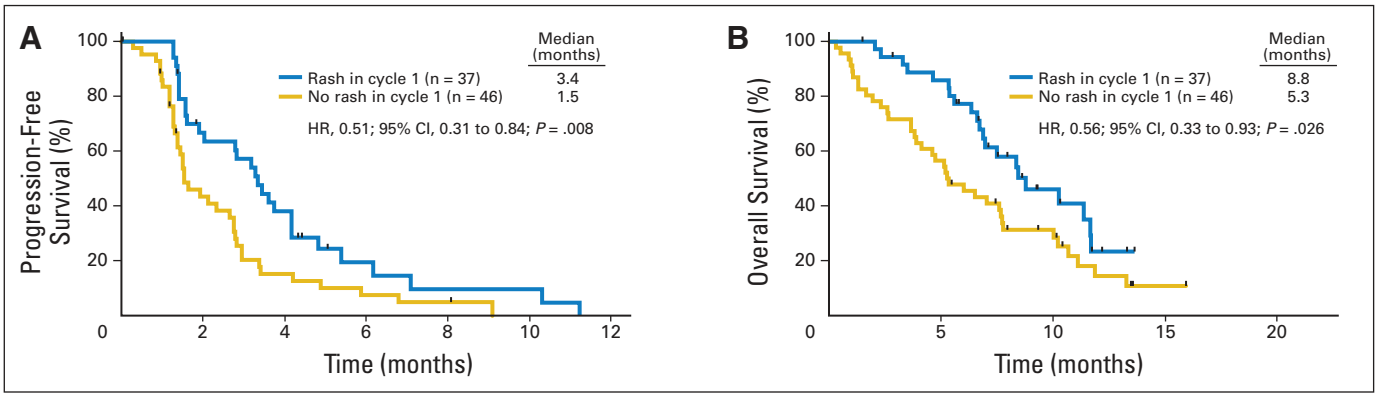


**Fig A5.** Development of rash in cycle 1 is associated with greater (A) progression-free and (B) overall survival following treatment with glembatumumab vedotin. Retrospective analysis based on intention-to-treat population. Tick marks represent censored data. HR, hazard ratio.