A Phase I/II Study of CR011-vcMMAE, an Antibody-Drug Conjugate, in Patients with Locally Advanced or Metastatic Breast Cancer

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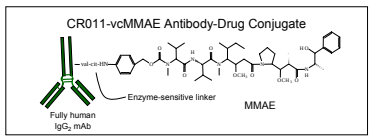
BACKGROUND

- GPNMB (osteoactivin) is a novel glycoprotein expressed in breast cancer, melanoma, and other tumors.
- Preclinical breast cancer models have demonstrated that GPNMB promotes the migration, invasion, and metastasis of breast cancer. GPNMB is expressed in 25 - 40% of human breast cancers and is an independent prognostic factor for recurrence of disease.
- GPNMB expression is observed in approximately one third of patients with triple negative (ER-, PR-, HER-2/neu-) disease, and is associated with a poor prognosis in that subset.

CR011-vcMMAE

- A fully-human monoclonal antibody (CR011) was raised against the extracellular domain of GPNMB
- CR011 is conjugated to the dolastatin-like tubulin inhibitor monomethylauristatin-E (MMAE) via a valine-citrulline enzyme-cleavable linker



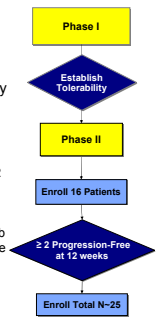
- In a Phase II study in patients with metastatic melanoma, CR011-vcMMAE (1.88 mg/kg IV q3w) has been shown to be active, leading to tumor shrinkage and PFS of 4.4 months.
- We are conducting a Phase I/II study to evaluate the safety and efficacy of CR011-vcMMAE in patients with heavily pre-treated advanced breast cancer.

METHODS

- Immunohistochemistry for GPNMB was performed on patient biopsy samples from this clinical study and 3 separately obtained tissue microarrays using a polyclonal goat anti-GPNMB antibody (R&D Systems) and a biotin-conjugated donkey anti-goat secondary antibody (Jackson ImmunoResearch Laboratories). Sections were developed with DAB and counterstained with hematoxylin.
- The tissue microarrays consisted of 517 undamaged cores representing 34 normal, 35 DCIS, 161 breast tumor and 47 lymph node metastasis samples independent of this clinical study. Patient samples were represented by multiple (2-4) cores on the array. Cores with ≥ 5% of the tissue expressing GPNMB were considered positive.

STUDY DESIGN

Eligibility
- Locally advanced or metastatic breast cancer
- Female, age ≥18
- Progressive disease on study entry
- ECOG Performance Status 0-2
- Received at least 2 prior chemotherapy regimens
  - Hormonal therapy and biologic therapy do not count as one of the 2 prior regimens
  - Prior regimens must include an anthracycline, a taxane, and capecitabine, as well as trastuzumab for HER-2/neu + disease, unless the patient was not a candidate for the agent
- No limit to the number of prior regimens



Study Design
- Phase I: Dose Escalation
  - Starting dose 1.34 mg/kg IV q3w (one dose level below MTD in melanoma study)
  - Sequential dose cohorts (n=3) enrolled based on tolerability
  - Cap at 1.88 mg/kg IV q3w (MTD in melanoma study)
- Phase II: Simon Two-Stage Design
  - Primary endpoint: Progression-free rate at 12 weeks
  - Statistical assumptions:
    - p_0=10%; p_1=30%; α=β= 0.10
    - First Stage: 16 patients
    - If ≥ 2 patients progression-free at 12 weeks, enroll total ~25

PT DISPOSITION

- Preliminary data from this ongoing study are presented
- Data cutoff: April 17, 2009
- Median Duration of Follow-up: 6 weeks

Patient Disposition	n
Treated	18
Ongoing	4
Discontinued	14
Reason for Discontinuation:	
Progressive Disease	12
Adverse Event	2
Neuropathy	1
Rash	1

DEMOGRAPHICS

Age		
Median	55 yrs	
Range	33 - 69	
ECOG Performance Status	n	%
0	11	61%
1	7	39%
2	0	0%
Liver and/or Lung Metastases		
Present	15	83%
Absent	3	7%
Estrogen Receptor		
Positive	9	50%
Negative	9	50%
Progesterone Receptor		
Positive	7	39%
Negative	11	61%
HER-2/neu		
Positive	3	17%
Negative	14	78%
Not reported	1	6%
ER negative/PR negative/HER-2 negative	8	44%

PRIOR THERAPY

Prior chemotherapy regimens in the metastatic setting		
Median	4	
Range	2 - 11	
Taxane	18	100%
Adjuvant / neoadjuvant setting	8	44%
Metastatic setting	17	94%
Anthracycline	15	83%
Adjuvant / neoadjuvant setting	11	61%
Metastatic setting	4	22%
Capecitabine		
Metastatic setting	18	100%
Other	18	100%
Gemcitabine	12	67%
Bevacizumab	10	56%
Vinorelbine	8	44%
Epothilone	4	22%
Trastuzumab	4	22%

TOXICITY

Treatment-Emergent Adverse Events, Regardless of Attribution

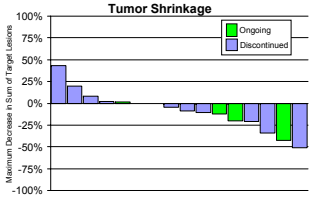
CTCAE Category/ Term	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Any Event	18 (100%)	10 (56%)	0 (0%)
Dermatology / Skin			
Rash	11 (61%)	1 (6%)	0 (0%)
Alopecia	9 (50%)	-	-
Pruritus	3 (17%)	0 (0%)	0 (0%)
Constitutional Symptoms			
Fatigue	9 (50%)	1 (6%)	0 (0%)
Fever	5 (28%)	0 (0%)	0 (0%)
Gastrointestinal			
Nausea	8 (44%)	1 (6%)	0 (0%)
Vomiting	7 (39%)	0 (0%)	0 (0%)
Constipation	6 (33%)	0 (0%)	0 (0%)
Diarrhea	5 (28%)	0 (0%)	0 (0%)
Anorexia	5 (28%)	0 (0%)	0 (0%)
Dysgeusia	4 (22%)	0 (0%)	0 (0%)
Neurology			
Neuropathy	7 (39%)	2 (11%)	0 (0%)
Dizziness	4 (22%)	0 (0%)	0 (0%)
Pain			
Pain-Gastrointestinal	6 (33%)	1 (6%)	0 (0%)
Pain-Musculoskeletal	5 (28%)	1 (6%)	0 (0%)
Pulmonary			
Cough	6 (33%)	1 (6%)	0 (0%)
Blood / Bone Marrow			
Neutropenia	5 (28%)	3 (17%)	0 (0%)

ACTIVITY

- Of 18 evaluable patients, 3 had partial response (one confirmed).
- Tumor shrinkage was observed in 9 patients (50%).

Best Response	n	%
Partial Response	3	17%
Confirmed PR	1	6%
Stable Disease	4	22%
Not evaluable	1	6%

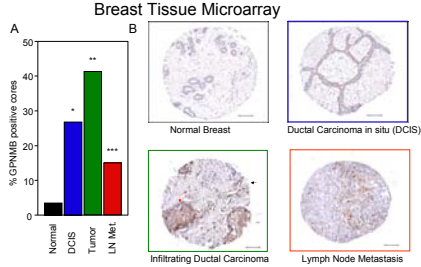
Tumor Shrinkage



Maximum percent decrease in the sum of the longest diameters of target lesions is plotted individually for each of the 16 patients with pre- and post-baseline tumor measurements

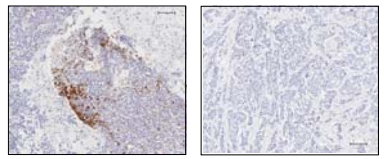
GPNMB EXPRESSION

Breast Tissue Microarray



(A) Cores with ≥ 5% of the tissue staining for GPNMB were considered positive. The indicated P values for each sample type relative to normal tissue (*; p = 0.001, **; p = 9.460x10-8, ***;p = 0.030) were obtained using Fisher's Exact Test.
(B) Representative images of normal, DCIS, breast tumor, and lymph node (LN) metastasis samples are shown. The red arrow indicates epithelial staining and the black arrow denotes stromal staining. Scale bar represents 100 µm.

Patient Tumor Biopsies



Immunohistochemistry for GPNMB has been performed in 5 patient tumor samples to date. One sample was positive (pt 2001, above left), 1 had a small area of focal positivity (not shown), and 3 were negative (representative image above right). Scale bar represents 100 µm.

DOSE ESCALATION

Dose Escalation
- The first two patients enrolled at 1.34 mg/kg had dose limiting worsening of peripheral sensory neuropathy. Both patients had baseline neuropathy.
- Subsequently, patients with baseline grade 2 or higher neuropathy were excluded.
- Dose escalation was re-started at 1.00 mg/kg IV q3w.
- 1.88 mg/kg IV q3w was tolerated and selected for expansion in Phase II.
- Phase II dosing is ongoing.

	Dose (mg/kg q3w)	n	DLT
Phase I (completed)	1.34	2	2
	1.00	3	0
	1.34	3	0
	1.88	6	0
Phase II (ongoing)	1.88	4	-

Activity in Individual Patients
- Pt 3008 is a 56 year old woman with ER+/PR+/HER2+ breast cancer, with metastatic disease in 2000. The patient received hormonal therapies and 11 prior chemotherapy regimens in the metastatic setting, including various combinations of paclitaxel, docetaxel, cyclophosphamide, adriamycin, capecitabine, trastuzumab, vinorelbine, gemcitabine, carboplatin, and two investigational agents. She had soft tissue and bony metastases on study entry. CT scans demonstrated partial response after two cycles of CR011-vcMMAE and confirmed 6 weeks later. As of the data cutoff, the patient has been on study for over 5 months with maximum tumor reduction of 42%.
- Pt 2001 is a 39 year old woman with ER+/PR+/HER2- breast cancer, with metastatic disease since February 2007. Previous regimens in the metastatic setting were paclitaxel/bevacizumab, capecitabine, and tamoxifen. She had liver, lung and bone metastases at study entry. Tumor biopsy was positive for GPNMB expression. CT scans demonstrated partial response (51% reduction in target lesions) after two cycles of CR011-vcMMAE. The patient was discontinued from study 6 weeks later after restaging revealed tumor growth.
- Pt 2002 is a 69 year old woman with triple negative (ER-/PR-/HER2-) breast cancer, with metastatic disease since 2006. Prior therapy included combinations of paclitaxel, bevacizumab, capecitabine, cisplatin, gemcitabine, Abraxane, and ixabepilone. She had hepatic metastases and a pleural effusion at study entry. CT scans demonstrated partial response (34% reduction in target lesions) after four cycles of CR011-vcMMAE. Approximately 9 weeks later, the patient was hospitalized with cough and dyspnea and was discontinued after 23 weeks on study.
- Pt 2003 is a 41 year old woman with triple negative (ER-/PR-/HER2-) breast cancer with metastatic disease since April 2006. Prior regimens included bevacizumab, Abraxane, gemcitabine, capecitabine, and tamoxifen. At study entry, she presented with disease in the liver and bone including skull metastases associated with paresis of the mental nerve and pain requiring narcotic analgesics. Following two cycles of CR011-vcMMAE, the patient had marked clinical improvement with resolution of mental nerve paresis and discontinuation of analgesics. CT scan showed mixed results with some regression in hepatic lesions and two new small lesions, thought to be "inflammatory". Bone scan and MRI were unchanged. The patient continued to receive treatment with CR011-vcMMAE for a total of 17 weeks.

CONCLUSIONS

- CR011-vcMMAE 1.88 mg/kg IV q3w is well-tolerated in patients with advanced breast cancer.
  - Peripheral sensory neuropathy was dose-limiting in 2 patients with neuropathy at baseline.
- Tumor shrinkage, including partial responses, palliation of bone pain, and stable disease have been observed in heavily-pretreated patients, including some with triple-negative disease.
- Toxicity in patients with breast cancer is similar to that observed in patients with melanoma. Rash is the most common adverse event reported in patients treated with CR011-vcMMAE.
- GPNMB, the target of CR011-vcMMAE, is specifically expressed in breast cancer tissue as observed in a microarray comprising over 500 core samples.
- Immunohistochemical staining of patient tumor samples for GPNMB expression is ongoing.
- The Phase II portion of the study is currently ongoing and has enrolled 12 patients to date.