

A Phase I/II Study of CR011-vcMMAE, an Antibody-Drug Conjugate, in Patients with Unresectable Stage III or Stage IV Melanoma

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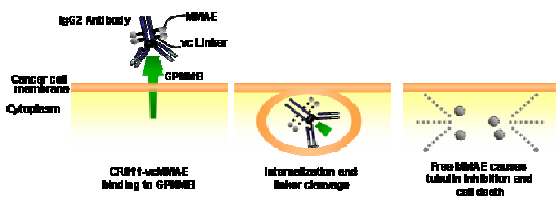
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BACKGROUND

Glycoprotein NMB (GPNMB) was identified by CuraGen as a novel therapeutic target for cancer. GPNMB is highly expressed in melanoma, breast cancer and glioma tissue. A fully-human monoclonal antibody (CR011) was raised against the extracellular domain of GPNMB and conjugated to the cytotoxic agent monomethyl auristatin E (MMAE) via a valine-citrulline dipeptide linker.

We conducted a Phase I study to evaluate the safety, maximum tolerated dose (MTD), and pharmacokinetics (PK) of CR011-vcMMAE in patients with metastatic melanoma. Preliminary results from an ongoing Phase II at the MTD are also presented.

Mechanism of Action of CR011-vcMMAE



STUDY DESIGN AND METHODS

Study Design

- Phase I dose-escalation study followed by Phase II at the MTD

Objectives

- Evaluate the dose-limiting toxicities (DLT) and determine the MTD of CR011-vcMMAE
- Assess the PK profile
- Explore anti-tumor activity in metastatic melanoma

Major Entry Criteria

- Measurable unresectable Stage III or Stage IV melanoma
- Progressive disease upon study entry
- Age \geq 18 years
- Karnofsky PS \geq 70%
- \leq 1 prior cytotoxic regimen
- Any number of prior cytokine, immune or vaccine therapies permitted
- Stable brain metastases allowed

Treatment

- CR011-vcMMAE administered as a 90 min IV infusion on day 1 of a 21-day cycle (IV Q3W)
- Treatment discontinued after 4 cycles unless tumor shrinkage demonstrated

Dose Escalation

- Sequential dose cohorts of 3-6 patients
- Doses escalated by 100% until Grade 2 or higher toxicity observed in 1 patient, after which doses escalated by 40% dose increments

Dose Limiting Toxicities

- DLTs defined as any of the following drug-related toxicities in Cycle 1:

- Grade 4 neutropenia $>$ 5 days or associated with a fever $>$ 100.5 °F
- Grade 4 thrombocytopenia
- Grade 3 or 4 non-hematologic toxicities not amenable to supportive care

- MTD defined as highest dose at which $<$ 2/6 patients had DLT

Assessments

- Safety assessments performed every cycle
- Plasma PK assessed during Cycles 1 and 2
- Tumor assessments every 2 cycles

DEMOGRAPHICS

Forty patients enrolled as of April 4, 2008

- 32 patients enrolled in Phase I dose-escalation portion
- 8 patients have enrolled in ongoing Phase II study

	Dose Escalation (N = 32)	Phase II (N = 8)
Gender		
Male : Female	18 : 14	5 : 3
Age (yrs)		
Median (range)	63 (47 - 81)	60 (45-69)
Race		
White : Non-white	28 : 4	8 : 0
Karnofsky PS		
100:90:80:70	9:16:4:1	7:1:0:0
Missing	2	0
Stage		
III : IV	6 : 26	0 : 8
M1a : M1b : M1c	3 : 11 : 12	3 : 0 : 5
Duration of Disease (mos.)		
Median (range)	23 (0 - 123)	21 (4 - 35)
Baseline LDH > ULN	7 (22%)	2 (25%)
Number Prior Regimens		
Median (range)	2 (0 - 6)	1.5 (1 - 2)
Prior Therapies^a		
Chemotherapy	17	4
Interleukin / Interferon	14	3
Investigational agent	11	0
Radiation	5	3
Limb Perfusion	5	0
Vaccine	4	3
Biochemotherapy	3	2

a. Patients may have received more than one prior therapy

DOSE ESCALATION TREATMENT SUMMARY

Cohort No.	Dose level mg/kg	No. Pts	Total Treatment Cycles	Range of Cycles per Patient	DLT
1	0.03	3	10	2-4	0
2	0.06	3	7	2-3	0
3	0.12	3	8	2-4	0
4	0.24	3	25+	2-19+	0
5	0.48	3	10	2-4	0
6	0.96	3	10	2-4	0
7	1.34	3	20	4-12	0
8	1.88	7	21+	2-6+	0
9	2.63	4	19	2-7	2
Total		32	130+	2-19+	

+ indicates ongoing

ONGOING PHASE II TREATMENT SUMMARY

- As of April 4, 2008, 8 patients treated at 1.88 mg/kg for a total of 13 cycles (range 1 - 3 cycles per patient)
- Enrollment and treatment in Phase II are ongoing

TREATMENT EMERGENT ADVERSE EVENTS REPORTED IN \geq 10% OF PATIENTS (N=40)

Dose Cohort	\leq 0.96 mg/kg (n=18)				1.34 mg/kg (n=3)				1.88 mg/kg (n=15)				2.63 mg/kg (n=4)								
	Grade	1	2	3	4	Grade	1	2	3	4	Grade	1	2	3	4	Grade	1	2	3	4	
Blood and Bone Marrow																					
Neutropenia	-	-	-	-	-	-	-	-	1	-	-	1	-	-	2	1					
Constitutional																					
Fatigue	4	2	-	-	1	1	-	-	7	3	-	-	1	2	1	-					
Fever	1	-	-	-	1	1	-	-	5	-	-	-	-	-	-	-					
Insomnia	1	-	-	-	-	-	-	-	4	-	-	-	-	-	-	-					
Chills	-	-	-	-	-	-	-	-	1	1	-	-	1	1	-	-					
Dermatology																					
Rash	3	-	-	-	1	2	-	-	5	3	1	-	2	2	-						
Pruritus	1	-	-	-	2	1	-	-	6	1	-	-	1	2	1	-					
Alopecia	-	-	-	-	-	-	-	-	5	2	-	-	1	2	-	-					
Dry skin	1	-	-	-	-	-	-	-	2	-	-	-	1	1	-	-					
Gastrointestinal																					
Diarrhea	5	1	-	-	3	-	-	-	7	1	-	-	2	1	-	-					
Nausea	4	2	-	-	2	-	-	-	7	1	-	-	2	-	-	-					
Anorexia	1	2	-	-	3	-	-	-	6	1	-	-	2	1	-	-					
Constipation	2	-	-	-	-	-	-	-	5	2	-	-	3	-	-	-					
Dysgeusia	-	-	-	-	-	-	-	-	5	-	-	-	2	-	-	-					
Mucositis	2	-	-	-	-	-	-	-	2	-	-	-	1	1	1	-					
Vomiting	-	2	-	-	2	-	-	-	2	-	-	-	1	-	-	-					
Lymphatics																					
Edema: limb	2	1	-	-	-	-	-	-	2	1	-	-	2	-	-	-					
Nervous System																					
Neuropathy	4	-	-	-	-	-	-	-	4	-	-	-	2	-	-	-					
Pain																					
Musculoskeletal	5	1	-	-	1	-	-	-	1	2	1	-	1	2	1	-					
GI: abdominal	1	2	-	-	1	-	-	-	1	-	-	-	1	-	-	-					
Neurology: headache	4	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-					
Pulmonary: chest	-	1	-	-	1	-	-	-	2	-	-	-	-	-	-	-					
Pulmonary																					
Cough	3	-	-	-	1	-	-	-	2	-	-	-	1	-	-	-					

RASH ASSOCIATED WITH CR011-vcMMAE



GRADE 2, 3 & 4 HEMATOLOGIC LABORATORY (N=40)

Laboratory	\leq 0.96 mg/kg (n=18)				1.34 mg/kg (n=3)				1.88 mg/kg (n=15)				2.63 mg/kg (n=4)			
	Grade	2	3	4	Grade	2	3	4	Grade	2	3	4	Grade	2	3	4
Hemoglobin	1	-	-	-	1	1	-	-	3	-	-	-	1	-	-	-
White Blood Cells	-	-	-	-	-	1	-	-	7	1	-	-	1	1	-	-
Absolute Neutrophil Count	-	-	-	-	-	1	-	-	5	2	2	-	1	1	-	-
Platelets	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-

DOSE LIMITING TOXICITIES OBSERVED AT 2.63 MG/KG IV Q3W

- 70-year old man with Stage IV melanoma treated at 2.63 mg/kg. Six days after Cycle 2 was hospitalized for Grade 2 erythema multiforme consisting of exfoliative, erythematous rash over trunk and extremities with blistering in the groin and desquamation over the palms and soles. Rash improved 1 week later; patient discontinued from study.
- 66-year old woman with Stage IV melanoma treated at 2.63 mg/kg hospitalized for Grade 3 pruritic, erythematous rash 4 days after Cycle 1. Rash involved ~85% BSA with blistering in intertriginous regions; event resolved within 5 days. Dose was reduced to 1.88 mg/kg. She developed limited erythematous rash without blistering and continued on study at the reduced dose.

RESULTS

- 37 patients assessable for tumor response as of May 15, 2008

Evaluable for Tumor Response	Dose Escalation		Phase II 1.88 mg/kg
	\leq 0.96 mg/kg	\geq 1.34 mg/kg	
PR	0	1	1 ^a
SD	10	6	3
Median Length of SD (range)	12 wks (11 - 48+)	17 wks (12 - 36)	10+ wks (8+ - 11+)
PD	8	6	2

a. Confirmation pending
PR, partial response; SD, stable disease; PD, progressive disease; + indicates ongoing

- Of evaluable patients treated at doses \geq 1.34 mg/kg

- 50% had tumor shrinkage
- 64% were progression-free at 12 weeks

Patient 02-139

57 year old man with metastases to right common iliac lymph node previously treated with high dose interferon and biochemotherapy. Pt. treated with CR011-vcMMAE 1.88 mg/kg. Partial response after Cycle 2. Confirmatory scan is pending.

Patient 03-127

54 year old woman with metastases to right inguinal lymph node and lung. Pt. received prior biochemotherapy, sorafenib and temozolamide. Pt. treated with CR011-vcMMAE 2.63 mg/kg and developed Gr 4 neutropenia and Gr 3 rash. Dose reduced to 1.88 mg/kg in cycles 2 - 4, and further reduced to 1.34 mg/kg in Cycles 6 - 7. Partial response after Cycle 2 was maintained until the pt. discontinued study after Cycle 7.

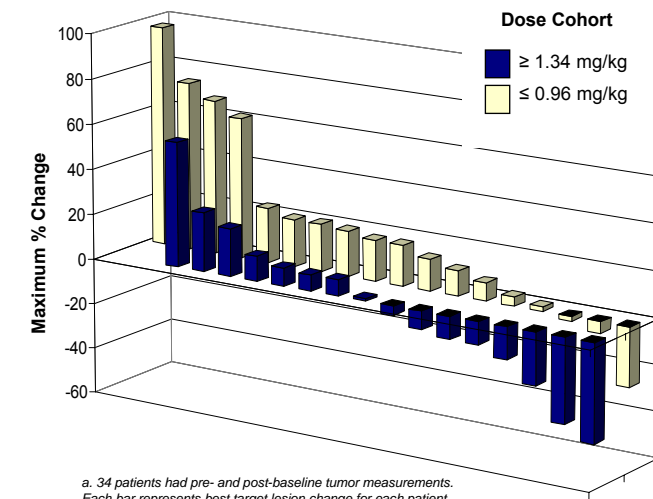
Patient 03-128

67 year old woman with metastases to the lung, liver and spleen. Pt. received prior biochemotherapy and anti-CTLA-4. Pt. treated with CR011-vcMMAE 2.63 mg/kg and developed Gr 2 rash. Dose reduced to 1.88 mg/kg in cycles 5 - 6. Pt. had SD for 18 weeks including reductions in liver (not shown) and splenic metastases.

Patient 04-134

46 year old woman with metastases to the scalp and lymph nodes previously treated with dacarbazine. Pt. treated with CR011-vcMMAE 1.88 mg/kg. Pt. has marked improvement in cutaneous scalp lesions and is ongoing after Cycle 4 with SD.

MAXIMUM PERCENT TUMOR SHRINKAGE (n = 34)^a

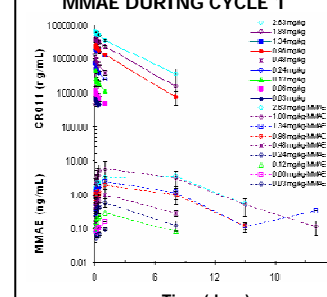


a. 34 patients had pre- and post-baseline tumor measurements. Each bar represents best target lesion change for each patient.

PHARMACOKINETICS

- Exposure of total measurable CR011-vcMMAE antibody and free MMAE are dose-proportional
- Terminal half-life of CR011-vcMMAE at the MTD is approximately 37.5 hours
- Maximum levels of free MMAE were ~ 0.6% of maximum levels of total antibody

SERUM CONCENTRATIONS OF TOTAL ANTIBODY AND FREE MMAE DURING CYCLE 1



Dose (mg/kg)	n	T _{1/2} (hr)	C _{max} (ug/mL)	AUC _{inf} (hr*ug/mL)
0.03	3	16.7	0.7	15
0.06	3	16.0	1.2	23
0.12	3	27.6	4.7	85
0.24	3	20.6	5.4	159
0.48	3	24.5	10.0	296
0.96	3	38.1	24.8	1838
1.34	3	32.2	22.7	994
1.88	9 ^a	37.5	41.2	2614
2.63	4	49.5	67.9	4644

a. Includes two patients from Phase II.
T_{1/2} =