

A Phase I/II Study of CR011-vcMMAE, an Antibody-Drug Conjugate Targeting GPNMB in Patients with Advanced Melanoma

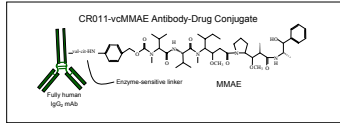
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BACKGROUND

- Antibody drug conjugates allow targeted delivery of drug to tumors
 - Increase therapeutic index
 - Induce tumor cell death and release novel antigens
- CR011, an IgG₂ antibody, targets the extracellular domain of GPNMB, a glycoprotein expressed in melanoma and other cancers.
- CR011 is conjugated to the dolastatin-like tubulin inhibitor monomethylauristatin-E (MMAE) via a valine-citrulline enzyme-cleavable linker



GPNMB is expressed in 80% of melanomas



STUDY DESIGN

Study Design

- Phase I dose-escalation study followed by Phase II at the maximum tolerated dose (MTD)

Major Entry Criteria

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

Treatment

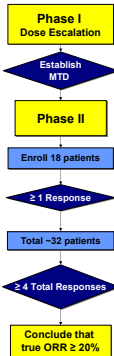
- Phase I starting dose: 0.03 mg/kg IV q3w
- Sequential escalating dose cohorts of 3-6 patients until MTD reached
- Phase II dose: 1.88 mg/kg IV q3w

Assessments

- Safety assessments performed every cycle
- Tumor assessments every 2 cycles (q 6 weeks)
- Response measured by RECIST

Phase II Statistical Design

- Primary Endpoint: Objective Response Rate
- Simon Two-Stage Minimax Design:
 - $\alpha=5\%$, $\beta=20\%$, $\alpha\beta=0.10$
 - First Stage: 18 patients
 - If ≥ 1 response observed, enroll total ~32 patients
 - If ≥ 4 responses observed, conclude true ORR ≥ 20%
- PFS and 6-month PFS rate calculated using the Kaplan-Meier method



PHASE I RESULTS

Phase I Dose Escalation

- 32 patients treated for a total of 132 cycles
- Cohorts treated at escalating doses from 0.03 to 2.63 mg/kg IV q3w

Phase I Doses (mg/kg)	n	DLT
0.03	3	0
0.06	3	0
0.12	3	0
0.24	3	0
0.48	3	0
0.96	3	0
1.34	3	0
1.88	7	0
2.63	4	2

- Generally well-tolerated
- Most common toxicity was rash
- Two patients with dose limiting toxicities (rash/desquamation) at 2.63 mg/kg
- One confirmed partial response observed in Phase I

➔ 1.88 mg/kg IV q 3 wk dose selected for Phase II

PHASE II RESULTS

Patient Status as of April 30, 2009

Patient Disposition	n
Treated	36
Ongoing	2
Discontinued	34

Reason for Discontinuation:

Progressive Disease	27
Withdraw Consent	4
Adverse Event	2
Stable Disease	1

PH II: DEMOGRAPHICS

Demographics	n (%)
Gender	
Male	24 (67%)
Female	12 (33%)
Age (yrs)	
Median (range)	62 (37 - 79)
Race	
Caucasian	36 (100%)
Karnofsky PS	
≥90	33 (92%)
Disease Characteristics	
Stage	
III	2 (6%)
IV	34 (94%)
M1a	7 (21%)
M1b	4 (12%)
M1c	23 (68%)
Baseline LDH > ULN	13 (36%)
Duration of Metastatic Disease (yrs)	1.2 (0.1 - 6.7)
Prior Regimens for Metastatic Disease	
Median (range)	1 (0 - 3)
Prior Therapies	
Chemotherapy	17 (47%)
Immunotherapy	14 (39%)
Biochemotherapy	5 (14%)
CTLA-4 inhibitors	7 (19%)
Other investigational agents	9 (25%)
Vaccine	4 (11%)

PHASE II RESULTS: TOXICITY

Treatment-Emergent Adverse Events, Regardless of Attribution

CTCAE Category/Term	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Any Event	36 (100%)	22 (61%)	2 (6%)
Dermatology / Skin			
Rash	31 (86%)	12 (33%)	0 (0%)
Alopecia	26 (72%)	0 (0%)	-
Pruritus	25 (69%)	0 (0%)	0 (0%)
Dry Skin	7 (19%)	0 (0%)	0 (0%)
Flushing	5 (14%)	0 (0%)	0 (0%)
Constitutional Symptoms			
Fatigue	29 (81%)	2 (6%)	0 (0%)
Fever	6 (17%)	0 (0%)	0 (0%)
Insomnia	6 (17%)	0 (0%)	0 (0%)
Gastrointestinal			
Diarrhea	20 (56%)	1 (3%)	0 (0%)
Anorexia	17 (47%)	0 (0%)	0 (0%)
Nausea	17 (47%)	0 (0%)	0 (0%)
Constipation	14 (39%)	0 (0%)	0 (0%)
Dysgeusia	10 (28%)	0 (0%)	0 (0%)
Mucositis	7 (19%)	0 (0%)	0 (0%)
Vomiting	5 (14%)	0 (0%)	0 (0%)
Dyspepsia	4 (11%)	0 (0%)	0 (0%)
Blood / Bone Marrow			
Neutropenia	7 (19%)	3 (8%)	2 (6%)
Neurology			
Neuropathy	12 (33%)	2 (6%)	0 (0%)
Dizziness	10 (28%)	0 (0%)	0 (0%)
Anxiety	4 (11%)	0 (0%)	0 (0%)
Pain			
Pain-Musculoskeletal	19 (53%)	2 (6%)	0 (0%)
Pain-Gastrointestinal	5 (14%)	0 (0%)	0 (0%)
Lymphatics			
Edema	8 (22%)	0 (0%)	0 (0%)
Pulmonary			
Cough	6 (17%)	0 (0%)	0 (0%)

PH II: GPNMB EXPRESSION

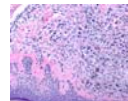
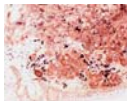
- Paraffin-embedded tissues from 13 patients (36%) were evaluated immunohistochemically for expression of GPNMB using biotinylated CR011 antibody.
- Samples were scored based on percentage of tumor cells staining positive and on intensity of staining (1+ to 3+).
- In the 2 patients (15%) with GPNMB negative tumors, PFS was 2.1 and 2.9 months, respectively.
- In patients with any positive staining for GPNMB (1+ to 3+, n=11), median PFS was 4.5 months, equivalent to the median PFS for the overall study population.
- Patients with the highest degree of positivity (> 90%, 3+; n=4) had a median PFS of 5.5 months (range 4.1-7.9 months) (representative image below).

Summary of IHC for GPNMB in Phase II Patients (n=13)

% Tumor Cells Positive	Staining Intensity			
	0	1+	2+	3+
0	2	-	-	-
1% to <90%	-	1	3	2
>90%	-	1	0	4

GPNMB IHC (>90% 3+)

Corresponding H & E

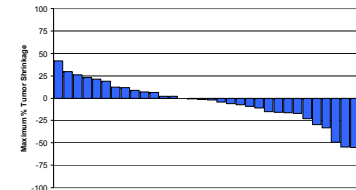


PHASE II RESULTS: ACTIVITY

Primary efficacy endpoint has been met

- 34 patients evaluable for response
 - 2 patients withdrew consent prior to efficacy evaluation
- Median duration of follow-up: 3.4 months
- 5 responses observed (1 unconfirmed)
 - Median duration 5.3 months
- 20 patients had RECIST-defined stable disease
 - Median duration 4.8 months

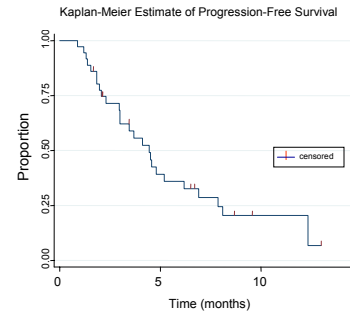
Tumor Shrinkage



Maximum percent decrease in the sum of the longest diameters of target lesions plotted individually for each of the 33 patients with pre- and post-baseline tumor measurements. Tumor shrinkage observed in 19 (58%) patients.

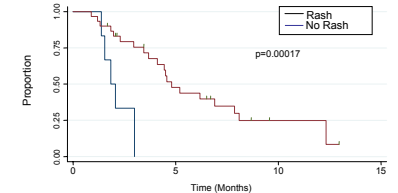
Progression-Free Survival

- Kaplan-Meier estimate of PFS was performed based on 27 events and 9 censored observations
- Overall Median PFS: 4.4 Months
- 6-month PFS rate: 36%



Skin rash in the first cycle predicts activity

- 30 patients had skin rash reported in Cycle 1
- Univariate analysis of skin rash and PFS was performed
- Lack of skin rash in Cycle 1 was associated with decreased progression-free survival



CONCLUSIONS

- This Phase II study of CR011-vcMMAE in patients with advanced melanoma has met its primary endpoint and observed objective response rate is 15%.
- Elevated LDH and male gender were negative prognostic factors in this study population, as expected based on historical data and meta-analyses.
- Progression-free survival of 4.4 months and 6-month PFS rate of 36% is favorable compared with benchmark data in patients with melanoma.
- The most common toxicity associated with CR011-vcMMAE was rash, which may be associated with the presence of GPNMB in the skin. Absence of skin rash in the first cycle was associated with shorter PFS.
- High levels of tumor expression of GPNMB may be predictive of favorable response to CR011-vcMMAE therapy. Further evaluation of GPNMB expression in patient biopsies is warranted.
- More frequent dosing schedules and other indications are being explored.
- Rational combinations with other agents may be important in future studies.