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

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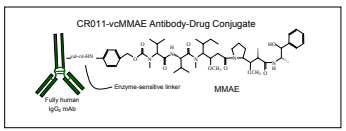
BACKGROUND

- Antibody drug conjugates allow targeted delivery of drug to tumors
  - Increase therapeutic index
  - Induce tumor cell death and release novel antigens
- CR011, an IgG_2 antibody, targets the extracellular domain of GPNMB, a glycoprotein expressed in melanoma and other cancers.

GPNMB is expressed in 80% of melanomas

- CR011 is conjugated to the dolastatin-like tubulin inhibitor monomethylauristatin-E (MMAE) via a valine-citrulline enzyme-cleavable linker



STUDY DESIGN

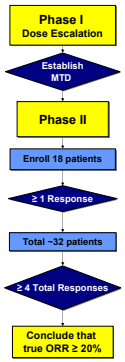
Study Design
- Phase I dose-escalation study followed by Phase II at the maximum tolerated dose (MTD)

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:
  p_0=5%; p_1=20%; α=β= 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
Withdrew 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)	
Median (range)	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%)	-	-
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%)

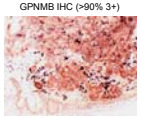
PH II: GPNMB EXPRESSION

- 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 (1-100%, 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).

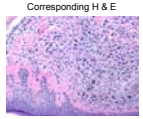
Summary of IHC for GPNMB in Phase II Patients (n=13)

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

GPNMB IHC (>90% 3+)



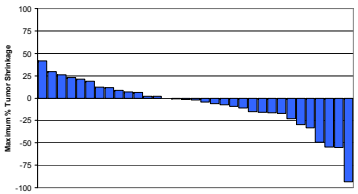
Corresponding H & E



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



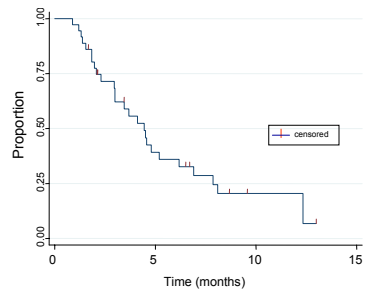
Maximum percent decrease in the sum of the longest diameters of target lesions is plotted individually for each of the 33 patients with pre-and post-baseline tumor measurements. **Tumor shrinkage observed in 19 (58%) patients.**

Prognostic Factors
- Prognostic factors for PFS were assessed using proportional hazards modeling.
- Baseline LDH and gender were statistically significant predictors of PFS.
- Other factors including age (above and below 60 years), presence of visceral disease, prior cytotoxic chemotherapy, and prior immunotherapy were not statistically significant predictors of PFS in this study population.

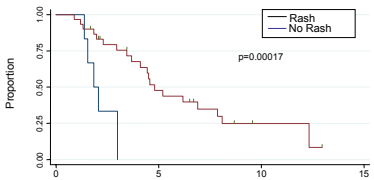
Variable	n	HR	95% Confidence Interval
LDH			
WNL	23	1.00	
>ULN	13	5.42	1.33 - 21.95
Gender			
Female	12	1.00	
Male	24	0.17	0.05 - 0.56

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%

Kaplan-Meier Estimate of Progression-Free Survival



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.