Frequent Dosing and GPNMB Expression with CDX-011 (CR011-vcMMAE), an Antibody-Drug Conjugate (ADC), in Patients with Advanced Melanoma

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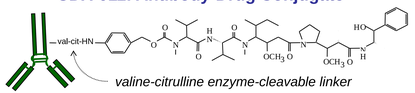
BACKGROUND

CDX-011 (glembatumumab vedotin) is designed to be stable in the bloodstream, but to release MMAE upon internalization into GPNMB-expressing tumor cells, resulting in a targeted cell-killing effect.

- Linker-MMAE technology, as used in brentuximab vedotin (SGN-35), licensed from Seattle Genetics.

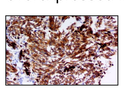
CDX-011: Antibody-Drug Conjugate



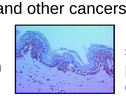
CR011: fully-human IgG_2 targeting GPNMB

MMAE: dolastatin-like tubulin inhibitor

GPNMB identified by high throughput genomic screening; overexpressed in melanoma and other cancers



GPNMB expressed in 80% of human melanoma specimens



IHC shows some staining of pigmented epithelium in normal human skin

ERK Pathway Inhibitors and Imatinib Upregulate GPNMB and Sensitize Melanoma Cells Lines to CDX-011[1]

- ERK inhibitors and imatinib upregulate GPNMB expression on melanoma cell lines in vitro
- Effect of ERK inhibitors was dependent on cell lines harboring NRAS or BRAF mutations
- Pre-treatment with ERK pathway inhibitors augmented tumor growth inhibition by CDX-011 in vitro
- Potential for synergistic activity in the clinic

[1] Qian, et. al., Mol Oncology, 2:91:2008

In a Phase I/II study in patients with heavily pre-treated, advanced breast cancer (abstract #1095), CDX-011 has been shown to be active with observed objective responses. The current Phase I/II study evaluates the safety and efficacy of CDX-011 in metastatic melanoma.

GPNMB DETECTION

- Tumor tissue was analyzed for GPNMB expression at a centralized laboratory via IHC, using a biotinylated CR011 monoclonal antibody.
- Tumor tissue for 33 of 42 (79%) patients analyzed to date are positive for GPNMB expression.

STUDY DESIGN AND CONDUCT

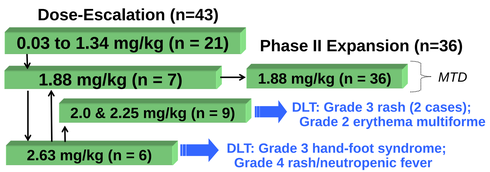
Patient Population

- Unresectable Stage III or Stage IV melanoma
- Progressive disease at entry
- Karnofsky PS ≥70%
- ≤ 1 prior cytotoxic regimen
- Any number of cytokine, immune or vaccine therapies

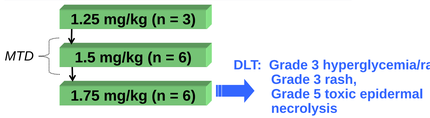
Study Design

- Multicenter, Open-label, Phase I/II Trial
- CDX-011: 90 minute IV infusion
- Every three week (q3w) dosing schedule:
  - Sequential dose-escalation cohorts (n=3-6 patients)
  - Phase II expansion at MTD
    - ♦ Primary activity endpoint: Objective Response Rate (p_0=5%; p_1=20%; α=β=0.10)
- Subsequent evaluation of more frequent dosing schedules:
  - Once weekly for 2 of 3 weeks (q2/3w) and weekly (qw)
  - Sequential dose-escalation cohorts (n=3-6 patients)
  - Option to expand (n=15) at MTDs

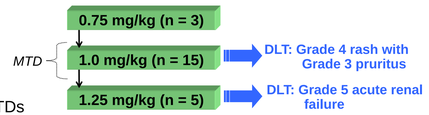
Every Three Week (q3w) Dosing Schedule



Two of Three Week (q2/3w) Dosing Schedule



Weekly (qw) Dosing Schedule



ACTIVITY

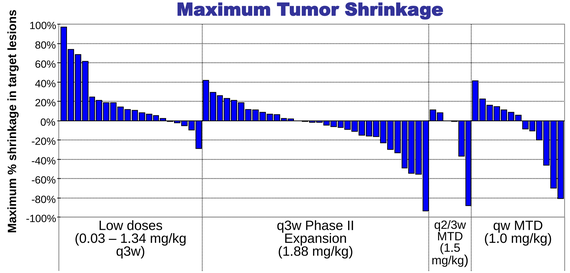
Primary Activity Endpoint: Objective Response Rate (ORR) for the Phase II Expansion Cohort (q3w Schedule)

Statistical Plan: Study considered positive if ≥ 4 responses in 32 patients

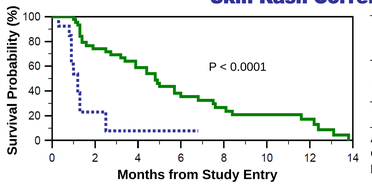
	ORR
Primary Endpoint: Phase II population (1.88 mg/kg) [a]	5/34 (15%)

[a] Phase II population includes the 36 patients enrolled in the Phase II study portion. Two patients are excluded due to withdrawal of consent prior to post-treatment tumor assessment.

Maximum Tumor Shrinkage



Skin Rash Correlates with Outcome



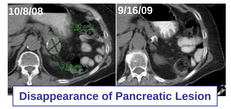
	Median PFS (months)	ORR
— Rash (n=44)	4.8	10/44 (23%)
.... No rash (n=13)	1.2	0%

Analyses include pooled patients from the q3w Phase II MTD expansion, q2/3w MTD and qw MTD. For 41/44 (93%) of patients who experienced rash, onset was within the first cycle.

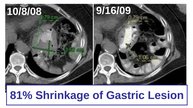
Examples of Responses in GPNMB-Expressing Patients

Pt 4191: Strong GPNMB expression

- Treated at 1.5 mg/kg q2/3w
- Partial Response (88% shrinkage)
- PFS = 11.7 months (discontinued treatment due to neuropathy)



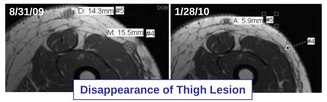
Disappearance of Pancreatic Lesion



81% Shrinkage of Gastric Lesion

Pt 2219: Strong GPNMB expression

- Treated at 1.0 mg/kg qw
- Partial Response (81% shrinkage), with disappearance of multiple thigh lesions
- PFS = 4.9 months



Disappearance of Thigh Lesion

Activity Parameters by Dosing Schedule and GPNMB Expression

	q3w Phase II MTD expansion (1.88 mg/kg)	q2/3w MTD (1.5 mg/kg)	qw MTD (1.0 mg/kg)	Strong (3+, 90%) GPNMB expression [a]
M1c Disease	18/34 (53%)	4/6 (67%)	12/15 (80%)	5/7 (71%)
Any tumor shrinkage	18/32 (56%) [b]	3/6 (50%)	6/15 (40%)	6/7 (86%)
Overall response rate (ORR)	5/34 (15%) [c]	2/6 (33%)	3/15 (20%)	2/7 (29%) [d]
PR or SD ≥ 12 weeks	20/34 (59%)	3/6 (50%)	5/15 (33%)	6/7 (86%)
Median PFS (months)	3.9	3.0	1.4 [e]	4.9

[a] Includes pooled patients from the q3w Phase II MTD expansion, q2/3w MTD and qw MTD.
[b] Excludes two additional patients without post-baseline assessment of measurable lesions.
[c] Including 1 unconfirmed PR (93% tumor shrinkage).
[d] ORR for patients with strong GPNMB expression and M1c disease = 2/5 (40%).
[e] One patient continues on treatment.

PATIENT CHARACTERISTICS, TOLERABILITY AND TREATMENT EXPOSURE

Demographic Characteristics (n=117)	
Male *(n [%])*	75 (64%)
Age *(years; median [range])*	62 (36-82)
Karnofsky PFS ≥ 90% *(n [%])*	102 (87%)
Disease Characteristics (n=117)	
Stage *(n [%])*	
III	13 (11%)
IV	104 (89%)
M1c	59 (50%)
Baseline LDH > ULN *(n [%])*	49 (42%)
Duration of metastatic disease *(years; median [range])*	1.4 (0.05-10)
Prior anticancer regimens for metastatic disease *(median [range])*	1 (0-8)
Prior Therapies *(n [%])*	
Chemotherapy	61 (52%)
Immunotherapy	44 (38%)
Biochemotherapy	12 (10%)
CTLA-4 inhibitors	25 (21%)
Other investigational agents	26 (22%)
Kinase Inhibitors	16 (14%)
Vaccines	12 (10%)

Toxicity	Occurring at any severity				≥ Grade 3 Severity (CTCAE)			
	q3w MTD (n=43)	q2/3w MTD (n=6)	qw MTD (n=15)	All (n=117)	q3w MTD (n=43)	q2/3w MTD (n=6)	qw MTD (n=15)	All (n=117)
Rash	70%	50%	60%	57%	26%	-	33%	20%
Fatigue	65%	67%	53%	56%	7%	17%	13%	8%
Pruritus	63%	33%	47%	49%	-	-	7%	3%
Alopecia	63%	33%	33%	40%	-	-	-	-
Diarrhea	47%	67%	20%	35%	2%	-	-	3%
Nausea	37%	50%	7%	29%	-	-	-	-
Anorexia	42%	33%	13%	26%	-	-	-	-
Neuropathy	35%	33%	60%	34%	5%	17%	27%	7%
Dysgeusia	33%	33%	13%	21%	-	-	-	-
Constipation	28%	33%	20%	19%	-	-	-	-
Neutropenia	26%	33%	13%	21%	14%	17%	13%	15%
Myalgia	12%	-	27%	13%	-	-	13%	3%
Arthralgia	7%	17%	7%	9%	-	-	7%	3%

- Table presents treatment-related adverse events occurring at any severity in >20%, or ≥ Grade 3 severity in >2% of patients. (Data cut-off as of May 7, 2010)
- Treatment-related deaths: Pneumococcal Sepsis (2.25 mg/kg q3w), Acute Renal Failure (1.25 mg/kg qw), and Toxic Epidermal Necrolysis (1.75 mg/kg q2/3w).

Treatment Parameter	q3w MTD (n=43)	q2/3w MTD (n=6)	qw MTD (n=15)
Duration of treatment (weeks) *(median [range])*	11 (0.1-58)	4 (1-49)	7 (0.1-38)
Cumulative dosing (mg/kg) *(median [range])*	7.5 (1.8-33)	6.1 (3.0-37)	6.0 (1.0-32)
Discontinued treatment for toxicity *(n [%])*	1 (2%)	2 (33%)	4 (27%)

PHARMACOKINETICS

- For the q3w schedule, half-life of antibody-drug conjugate (ADC) and total antibody (TA) increased with dose (ranges: 16-38 hours and 15-43 hours, respectively). Maximum MMAE and Tmax were dose proportional (ranges: 0.1-7.1 ng/mL and 20-169 hours, respectively).
- At doses of 1.88 mg/kg and higher in the q3w schedule, we observed correlations between severe rash and dose normalized exposure in cycle 1 to ADC (p=0.010) and TA (p=0.0129) but not MMAE (p=0.180).
- Across all dose levels and schedules, dose normalized exposure to TA in cycle 1 (AUCinf/dose) differed significantly for best response of PD, PR and SD (Kruskal-Wallis; p=0.0167) and correlated directly with objective response (Dunn's post test of PD vs. PR; p<0.05).

CONCLUSIONS

- **CDX-011, dosed either q3w, q2/3w or qw, is active in advanced melanoma.**
  - **The primary activity endpoint has been met.**
  - **Overall Response Rate (ORR) of ≥15% is promising.**
  - **There is evidence of increased activity with the q2/3w and qw schedules over the q3w schedule but this is accompanied by increased toxicity.**
- **Strong GPNMB expression and the development of rash, which may be related to the presence of GPNMB in the skin, are associated with greater progression-free survival.**
- **Further evaluation of CDX-011 in melanoma will include patients with strong GPNMB expression and combination therapy intended to upregulate GPNMB.**