CD166-DM4 Probody™ Drug Conjugate (CX-2009) Treatment of 198 Patient-derived Xenograft Models (PDX) in a Mouse Clinical Trial Format

Bob Y. Liu, Joel Shen, Matthias Will, Sreeni Yalamanchili, Judi Ford-Gordon, Mark Stroh, Jennifer Richardson, Annie Yang-Weaver, Luc R. Desnoyers, Marcia Belvin, W. Michael Kavanaugh, Siew Schleyer
CytomX Therapeutics, Inc., South San Francisco, CA

3948

ABSTRACT

Ideal targets for antibody drug conjugates (ADC) are highly and homogeneously expressed on tumor cells in a wide variety of tumor types and in a high proportion of patients. Such targets should also be efficient cellular internalizers and have limited expression on normal tissues. Unfortunately, targets that meet all these criteria are rare.

Probody™ drug conjugates (PDCs) are masked antibody prodrugs designed for activation by tumor-associated proteases. PDCs are designed to direct drug activity to the tumor microenvironment by exploiting the dysregulation of tumor protease activity that is the hallmark of most cancers. The Probody platform is designed to minimize interaction with healthy tissues, mitigate "on-target" toxicity regardless of expression outside of the tumor, and greatly expand the number of potential ADC targets.

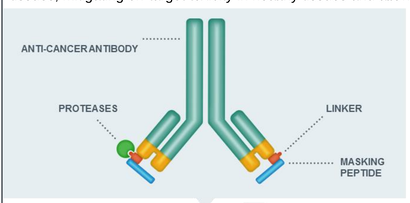
CD166 (ALCAM) is one such novel target. It is expressed at high levels in a high proportion of patients across multiple cancer types, but it is also on healthy tissues, including lung, gastro-intestinal tract, and liver. CX-2009, an investigational SPDB-DM4 PDC targeting CD166, is currently being evaluated in PROCLAIM CX-2009, a clinical phase I/II trial (NCT03149549). CX-2009 exhibited robust preclinical activity against cell-line derived xenograft (CDX) models across various solid tumor indications. Because the DM4 mechanism of action is similar to that of taxane-based chemotherapy, CX-2009 is being evaluated in the clinic for cancer types that respond to microtubule inhibitors and have prevalent CD166 expression.

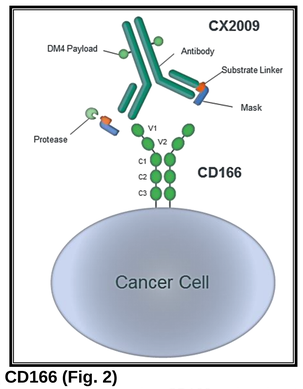
To help further inform patient selection for clinical studies, CX-2009 is being evaluated in 198 PDX models using a murine clinical trial format in collaboration with South Texas Accelerated Research Therapeutics (START). Each mouse is engrafted with a patient's resected tumor sample that has not been passaged *in vitro*, and when kept minimally passaged *in vivo*, may more faithfully recapitulate the tumor biology and response to therapeutics than CDX models. The PDX models are dosed with 5 mg/kg of CX-2009 every 2 weeks for 6 weeks via i.v. (q2wX3), and tumor volume is measured twice per week. Currently, we have dosed 66 breast, lung, and ovarian PDX models, obtaining an end-of-study response rate of 19% using clinically defined criteria, e.g. complete response (CR) plus partial response (PR), and a 22% disease-control rate (DCR). Relative to untreated controls, 48% of CX-2009-treated tumors yielded tumor growth inhibition (TGI) of greater than fifty percent. Because of the large cohort data set, this effort can potentially inform patient selection for clinical studies based on correlating efficacy with CD166 expression, tumor subtype, tumor growth rate (doubling time), and taxane sensitivity.

INTRODUCTION

Probody Drug Conjugates are Protease-Activated Antibody Prodrugs (Fig. 1)

PDCs are designed to direct drug activity to the tumor microenvironment by exploiting the dysregulation of tumor protease activity that is a common characteristic among cancers. The platform is intended to minimize drug exposure to healthy tissues, mitigating on-target toxicity in healthy tissues and allowing for expansion of potential ADC targets.

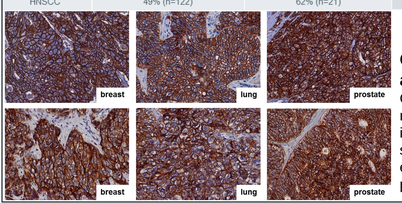




CX-2009, an investigational SPDB-DM4 PDC targeting CD166 (Fig. 2)

CX-2009 is a novel recombinant PDC derived from a humanized monoclonal antibody against CD166 and conjugated to N-succinimidyl 4-(2-pyridyldithio) butanoate-N2'-deacetyl-N2'-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (SPDB-DM4), a potent microtubule inhibitor. Linker-Payload and Conjugation Technology licensed from ImmunoGen.

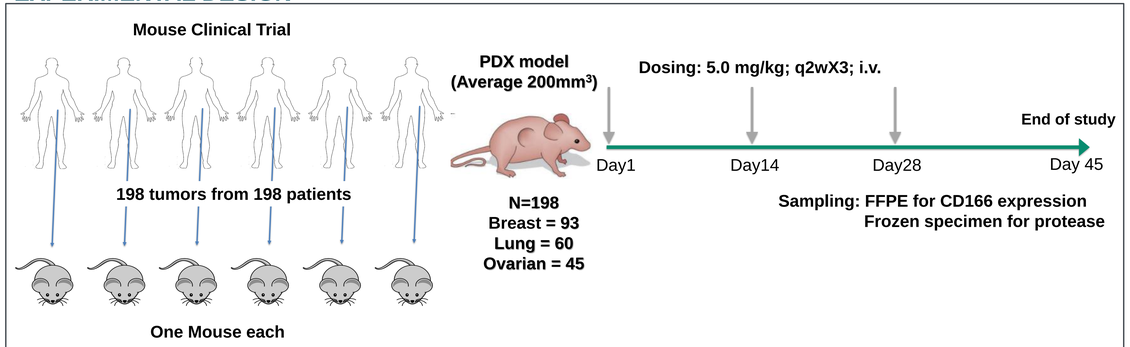
	CANCERS		NORMAL TISSUES			
	Commercial Samples	PROCLAIM CX-2009 Samples	CD166 Expression by IHC			
	% Patients with highest CD166 expression (IHC 3+)					
Prostate	89% (n=119)	0% (n=2)	Breast	2+	Pancreas	2+
Breast	70% (n=533)	79% (n=95)	Colon	2+	Prostate	3+
NSCLC	60% (n=465)	64% (n=22)	Liver	2+	Small Intestine	2+
Endometrial	57% (n=315)	67% (n=3)	Lung	1+	Stomach	3+
Ovarian	52% (n=129)	59% (n=107)	Ovary	1+	Uterus	2+
HNSCC	49% (n=122)	62% (n=21)				



CD166 (ALCAM) is homogenously expressed across a number of cancers (Fig. 3)

CD166 (also known as activated leukocyte cell adhesion molecule) is highly expressed in multiple cancers and also in healthy tissue. Tables summarize IHC scoring of CD166 staining in cancer and normal tissues. The panels are examples of CD166 IHC staining in breast, lung, and prostate cancers.

EXPERIMENTAL DESIGN



Enrollment of the mouse clinical trial (MCT) (Fig. 4)

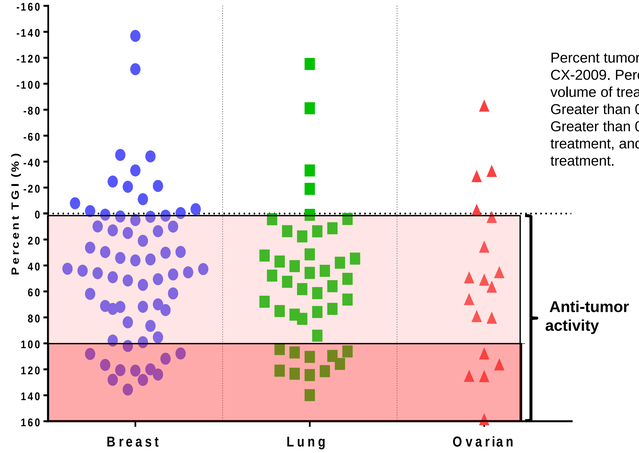
Each mouse harbored one unique tumor derived from one patient tumor, and the mouse was treated with CX-2009. Tumors were not pre-selected for high CD166 expression. The untreated control group consisted of N greater than 3.

CX-2009 dosing schedule (Fig. 5)

198 PDX models were dosed at 5 mg/kg every two weeks for 6 weeks (q2wX3). Unlike patients, mice were not treated at the highest tolerated dose to progression. Dosing commenced when tumor volume was 150-200mm3, and 93 breast, 60 lung, and 45 ovarian PDX are being enrolled. At the end of the study, 45 days, FFPE and frozen tumor samples were collected for CD166 expression and protease analysis.

RESULTS

CX-2009 induces tumor growth inhibition in majority of PDX models tested to date (Fig. 6)



Percent tumor growth inhibition (TGI) is plotted for 129 PDX models treated with CX-2009. Percent TGI is determined by 100 x [1-(final tumor volume – initial tumor volume of treated) / (final tumor volume – initial tumor volume of untreated)]. Greater than 0% and 100% TGI is marked by dotted and solid line respectively. Greater than 0%TGI indicates evidence of anti-tumor activity relative to control treatment, and greater than 100% TGI is associated with tumor shrinkage post treatment.

	Overall	Breast	Lung	Ovarian
> 0% TGI	106 (82%)	53 (79%)	39 (89%)	14 (78%)
>100% TGI	28 (22%)	12 (18%)	11 (25%)	5 (28%)
N	129	67	44	18

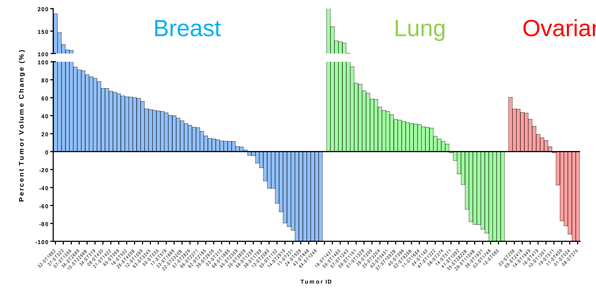
Table 1: Summary of percent TGI
Percentage of TGI greater than 0% and 100% is shown. Data analysis is up to 2/26/2019, which represents 129/198 (65%) of the study.

SAMPLE BREAKDOWN

Breast Subtypes	%	Lung subtypes	%	Ovarian subtypes	%
ER+	18	NSCLC-Adeno	55	Serous carcinoma	83
PR+	17	NSCLC-SCC	14	Clear cell carcinoma	3
Her2+	49	SLCL	9	Endometrioid	1
TNBC	36			Granulosa	1
		EGFR positive	34	Mucinous	1
		EGFR negative	15	Neuroendocrine	1
				Mixed type	1
				High grade	83
				Intermediate grade	9
				Low grade	3

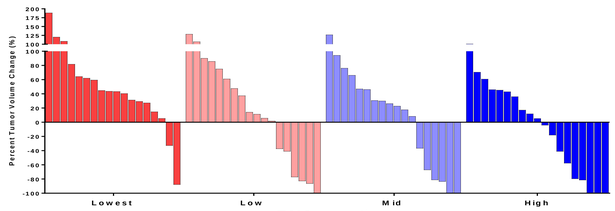
Table 2: Cancer subtype distributions of PDX models for breast, lung, and ovarian indications.
The collection of PDX subtypes that are being treated with CX-2009 at START.

CX-2009 induced tumor shrinkage in unselected PDX models in multiple indications (Fig. 7)



Percent tumor volume change is plotted for 129 PDX models treated with CX-2009. Percent tumor volume change is determined from the best tumor shrinkage relative to the tumor volume prior to drug dosing.

CX-2009 anti-tumor activity is associated with high CD166 mRNA expression (Fig. 8)



Tumor volume change is plotted against relative mRNA levels in tumor samples, and P value is determined by one-way ANOVA analysis. RNA levels were determined based on mRNA sequencing of the archival tumor samples. The four level mRNA quartiles were derived by equal distribution of the 73 samples. Data analysis is up to 2/26/2019.

SUMMARY/CONCLUSIONS

1) CX-2009 is a Probody drug conjugate targeting a novel target, ALCAM (CD166), which is highly expressed on variety of different cancers.
2) CX-2009 anti-tumor activity is being evaluated in 198 PDX tumor models using a mouse clinical trial format and 5 mg/kg q2wX3 dosing.129 models (65%) have been dosed to date.
3) CX-2009 is broadly active in unselected PDX models using this short-term and limited dosing regimen.
4) CD166 mRNA level was associated with antitumor activity, with tumor shrinkage in 9/19 (47%) high CD166 models. These data suggest high CD166 expression may identify patients most likely to respond to CX-2009. Analysis of CD166 expression in these models by IHC is ongoing.

ACKNOWLEDGEMENTS

PDX models using a murine clinical trial format is performed in collaboration with South Texas Accelerated Research Therapeutics (START)