A Phase 1b Trial of Cirmtuzumab and Paclitaxel in Locally Advanced /Unresectable or Metastatic Her2 Negative Breast Cancer

Rebecca A. Shatsky, MD[1], Catriona H. M. Jamison, MD, PhD[1], Ruifeng Chen[1], James Breitmeyer, MD, PhD[2], Teresa Helsten, MD[1], Cristal M. Martinez[1], Emily I. Pittman PhD[1], Richard B Schwab, MD[1], Alfredo Molinolo, MD PhD[1], Rupa Subramanian MD[1], Elizabeth Weihe MD[1], George Widhopf, PhD[1], Thomas J. Kipps, MD, PhD[1], Barbara A. Parker, MD[1]

[1]University of California San Diego School of Medicine Moores Cancer Center, La Jolla, CA

[2]Oncternal Therapeutics, Inc., San Diego, CA

Funding for this trial was provided by CIRM UC San Diego Alpha Stem Cell Clinic and Stanford Stem Cell Clinical Center, Oncternal Therapeutics Inc., UC San Diego Moores Cancer Center Padres Pedal the Cause and Gonick Breast Cancer Research Funds

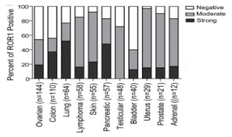
BACKGROUND

Cirmtuzumab is a humanized monoclonal antibody that targets the receptor tyrosine kinase like orphan receptor 1 (ROR1). ROR1 is an oncoembryonic protein that functions in embryonic skeletal, cardio-respiratory and neurological development. It is detected in embryonic tissue but not in normal adult tissues. ROR1 is expressed by malignant cells in many cancers including breast cancer, ovarian cancer, other solid tumors, CLL and mantle cell lymphoma. As such, it is an ideal drug target for cancer therapy.

ROR1 is a receptor of Wnt5a, which can induce activation of Rac1, RhoA, HS1, and other downstream targets to enhance cell proliferation, migration, and "stemness."

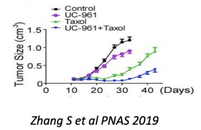
ROR1 expression correlates with aggressive breast cancer and early relapse. ROR1 expression correlates with "stemness" features in breast cancer tissues. Silencing ROR1 inhibits tumor growth and metastases. In patients treated with neoadjuvant chemotherapy ROR1 expression is increased at the time of surgery. A PDX breast cancer model shows at least additive anti-tumor activity of cirmtuzumab in combination with paclitaxel.

A recently completed Phase 1 trial of Cirmtuzumab in CLL showed the antibody to be both safe and effective in inhibiting tumor cell ROR1 signaling in CLL.



Zhang, S. et al. Am J. Pathol. 2012

Choi M et al, Cell Stem Cell 2018



Zhang S et al PNAS 2019

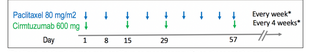
METHODS

The primary aim of this trial was to determine the safety of cirmtuzumab and weekly paclitaxel in patients with advanced Her2 negative breast cancer based upon dose limiting toxicities (DLTs) in the first cycle of treatment. Secondary endpoints were clinical activity, pharmacokinetics and correlative biomarkers on tumor specimens. Eligible patients were those with locally advanced, unresectable or metastatic Her2 negative breast cancer who had not received paclitaxel in the metastatic setting, had not developed metastatic disease within 6 months of (neo)adjuvant paclitaxel, had ECOG performance status of 0-2, and had adequate laboratory parameters.

Trial Design

Study Endpoints	Eligibility
Primary: Safety **Secondary:** Clinical effects **Exploratory:** Biologic effects *Duration of therapy until progression*	•Metastatic or locally advanced Her2 negative •No prior Taxane for mets •Any line of prior therapy

Trial Schema



*Paclitaxel or cirmtuzumab may continue as monotherapy if the other agent stopped due to toxicity

Any number of prior lines of therapy were allowed. Study treatment included fixed dose 600mg cirmtuzumab given days 1 and 15 of cycle 1 and then day 1 of each subsequent 28 day cycle. Paclitaxel was given weekly at a dose of 80mg/m2. Patients were evaluated in dose cohorts of 5 for DLTs with a target of 15 evaluable patients.

Table 1: Patient Demographics

ID	Age at enrollment	Prior Lines of Chemo in met setting	ER IHC	HER2	ROR1 IHC	NGS Type (tissue vs. ctDNA)	NGS Profile
BROR-001	54	3	2+ (60%)	neg	3+ (4%) 2+ (67%) 1+ (27%)	Tissue	*PIK3CA E542K, DNMTA3 loss, FAT1 K1488fs*1, TP53 splice site 375+1G>A*
BROR-002	59	0	0%	neg			
BROR-005	41	3	0%	neg	3+ (0%) 2+ (0%) 1+ (48%) 0+ (52%)	Tissue	*TP53 R248Q*
BROR-007	42	3	1+ (<5%)	neg	3+ (0%) 2+ (0%) 1+(48%) 0+ (52%)	Tissue	*PTEN T319*, KMT2D S4456, TP53 R175H, KEAP1 C518Ys*8, ADGRA2 amp, FGFR1 amp, EBF1 del, ZNF703 amp*
BROR-008	59	2	1+ (40%)	neg		ctDNA	*PTEN T319fs, TP53 P278R*
BROR-009	30	0	0%	neg		Tissue	*TP53 H179R, BRCA1 (NM_007294)-PMEPA1(NM_020182) fusion, PIK3R1 splice site 1300-140_1425+39del305, RB1 loss,*
BROR-011	72	0	1+ (5%)	neg		Tissue	*TP53 splice site exon 5, FGFR2 N549K, MAP3K1 T457Nfs*4, CASP8 L665Fs*10, DNMT3A R736H,*
BROR-012	54	0	0%	neg	3+ (2%) 2+ (38%) 1+(60%)	ctDNA	*TP53 R175H, TP53 R213**

* 1/8 patients identified as Hispanic or Latino and more than one race. All other patients identified as not Hispanic/not Latino and white.
* ctDNA = circulating tumor DNA
* NGS = next generation sequencing

Tables 2 & 3: Safety Data

Table 2: Most Common Adverse Events (all paclitaxel related)

Adverse Event	# of Events	# of Patients	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	10	8	10	0	0	0
Nausea	6	6	6	0	0	0
Peripheral motor neuropathy	6	6	6	0	0	0
Flu-like symptoms	4	2	3	0	1	0
Neutrophil count decrease	4	2	0	1	3	0

Table 3: ≥ Grade 3 Adverse Events

Patient ID	Adverse Event Type	Adverse Event Name	Severity/Grade	Taxol Attribution	Cirmtuzumab Attribution	Treatment Attribution
BROR-001	Adverse Event	Hyperglycemia	3	Definite	Not related	Definite
BROR-001	Adverse Event	Neutrophil count decreased	3	Definite	Possible	Definite
BROR-001	Adverse Event	Neutrophil count decreased	3	Definite	Possible	Definite
BROR-008	Adverse Event	Neutrophil count decreased	3	Definite	Unlikely	Definite
BROR-011	Serious Adverse Event	Flu like symptoms	3	Probable	Unlikely	Probable
BROR-008	Adverse Event	Back pain	3	Not related	Not related	Not related
BROR-008	Serious Adverse Event	Back pain	3	Not related	Not related	Not related
BROR-002	Adverse Event	Pain	3	Not related	Not related	Not related
BROR-002	Adverse Event	Dysphagia	3	Not related	Not related	Not related
BROR-002	Adverse Event	Anemia	3	Not related	Not related	Not related
BROR-002	Adverse Event	Anemia	3	Not related	Not related	Not related
BROR-002	Serious Adverse Event	Joint range of motion decreased cervical spine	3	Not related	Not related	Not related

Figure 1: % Tumor Volume Reduction by Week of Therapy

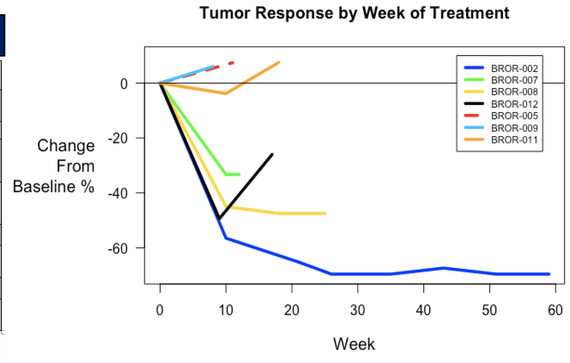


Figure 2: Best Tumor Response by Patient and % Tumor Volume Reduction

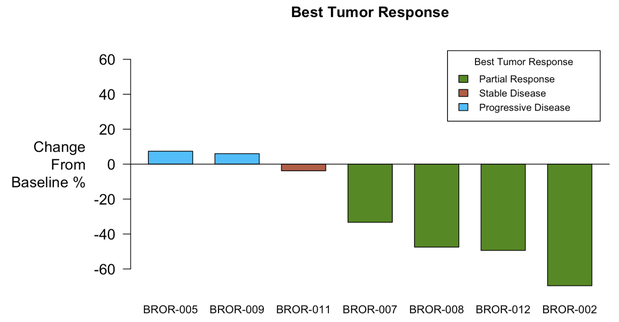


Figure 3: BROR2 Response Scans at Start of Therapy and at Cycle 6

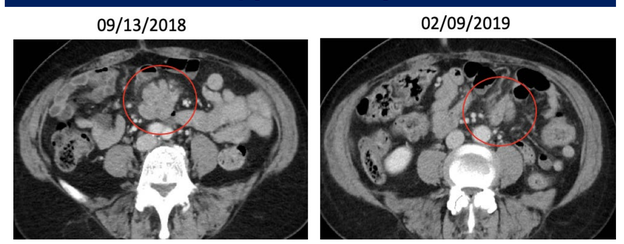


Figure 4: Pretreatment ROR1 IHC

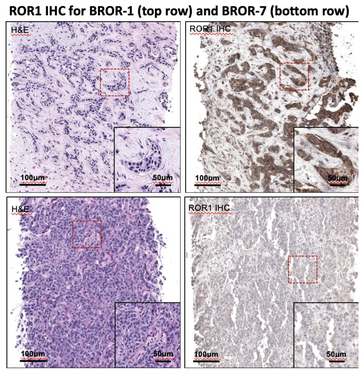


Figure 4: Pretreatment ROR1 IHC: Top panel ROR1 high expressor with 99% of the cells highly positive (3+= 5%; 2+ =67%; 1+ =27%; 0+ =1%). Bottom panel ROR1 low expressor; 48% of the cells weakly positive (3+= 0%; 2+ =0.2%; 1+ =48%; 0+ =52% The stained FFPE sections were scanned and quantified using a Leica-Aperio T2 scanner. The dotted red squares in are the areas magnified in the insets.

Figure 5: Pharmacokinetic Data

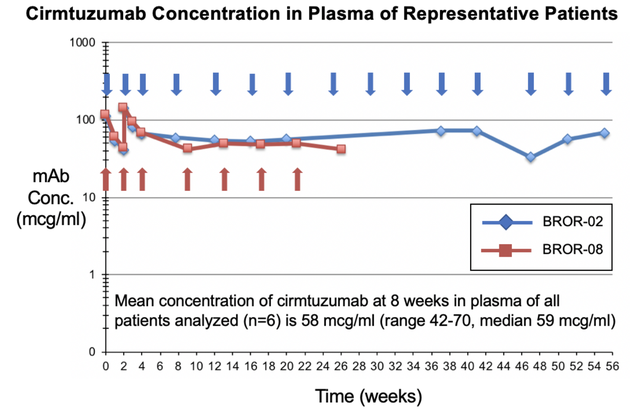


Figure 5: Cirmtuzumab concentration in plasma of representative patients. Cirmtuzumab concentration (mcg/mL) is indicated on the y axis, and time (weeks) is indicated on the x axis. Arrows indicate days of infusion of cirmtuzumab. Values indicated were determined by interpolation using a four-parameter logistic nonlinear regression model compared to a standard curve generated by serial dilutions of a known concentration of cirmtuzumab mAb.

RESULTS

To date, 8 patients evaluable for safety and 7 patients evaluable for DLTs were treated. Age range is 30 to 59 years. Four of 8 safety-evaluable patients had triple negative breast cancer at study enrollment. Prior lines of chemotherapy in the metastatic setting ranged from 0-3. No discontinuations for toxicity and no DLTs have been observed to date. Adverse events (AEs) have been consistent with the known safety profile of paclitaxel. Partial responses have been observed in 4/7 patients with one patient response that continued on cimtuzumab alone for 30 weeks after stopping paclitaxel. Pharmacokinetic analysis of serial plasma samples for free unbound antibody from two patients provided results similar to those observed in CLL patients treated with cirmtuzumab with a projected half-life of 30 days. No decline in antibody concentration over time was observed consistent with the absence of neutralizing antibodies.

CONCLUSIONS

- Preliminary results indicate that the combination of fixed dose cirmtuzumab and paclitaxel is safe and well tolerated in patients with locally advanced or metastatic breast cancer.
- Adverse event assessment indicates no new safety signals of the combination compared to that of paclitaxel alone.
- Responses to therapy have been observed (4/7 partial responses).
- Preliminary pharmacokinetic results are consistent with sustained potentially therapeutic levels of cirmtuzumab.
- One patient was maintained on cirmtuzumab monotherapy with stable disease for 30 weeks after discontinuation of paclitaxel.