Novel Targeted Therapy for Breast Cancer Chest Wall Recurrence: Low Temperature Liposomal Doxorubicin and Mild Local Hyperthermia

H. Rugo M.D.[1], Timothy Zagar, M.D.[2], Silvia Formenti, M.D.[3], Zeljko Vujaskovic, M.D.[4], Franco Muggia, M.D.[5], Brigid O'Connor, M.D., PhD.[6], Robert Myerson, M.D., PhD.[7], I-Chow Hsu, M.D.[1], Nicholas Borys, M.D.[7], Kimberly Blackwell, M.D.[8] and Mark Dewhirst, D.V.M, PhD.[8]

[1] UCSF Helen Diller Family Cancer Center [2] University of North Carolina, Chapel Hill, NC [3] NYU Langone Medical Center [4] University of Maryland Medical Center, Baltimore, MD
[5] Commonwealth Hematology/Oncology PC. [6] Washington University in St. Louis Medical Center [7] Celsion Corporation [8] Duke University Medical Center

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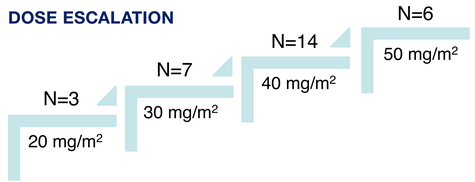
DIGNITY Study
RCW study of ThermoDox® and microwave hYperthermia

INTRODUCTION

- An investigator-initiated trial conducted at Duke University (Trial A) and a multicenter trial- DIGNITY trial (Trial B) are reporting combined data of 2 similarly designed Phase I studies for Unresectable Chest Wall Recurrence of Breast Cancer using ThermoDox (Lyso-thermosensitive liposomal doxorubicin LTLD) plus Mild Local Hyperthermia (MLH).
- ThermoDox is a novel liposomal heat activated formulation of doxorubicin. It is being studied for its potential use in cancer cell killing in conjunction with thermal treatments of solid tumors.
- ThermoDox is engineered to release high concentrations of doxorubicin when exposed to temperatures ≥ 39.5° C to 42° C. The elevated temperature lyses the liposomes and within seconds releases the doxorubicin where it is localized in tumors due to their leaky vasculature.
- Recurrent Chest Wall (RCW) patients can suffer from disfiguring tumors and clinical symptoms including pain, reduced ranges of motion, and skin ulceration with bleeding and potential necrotic, infected, foul-smelling wounds.
- Unresectable breast cancer chest wall recurrence (RCW) is very difficult to treat and often responds poorly to radiation and systemic chemotherapy.
- We hypothesize that thermally enhanced drug delivery using low temperature liposomal doxorubicin (ThermoDox®) given with mild local hyperthermia (MLH) would be a safe and effective targeted therapy.

STUDY DESIGN

- Both trials employed an open label 3+3 dose escalation study design.
- Eligible patients have RCW tumors < 3 cm in depth and have progressed on standard therapy including chemotherapy, radiotherapy and hormone therapy.
- Subjects were eligible to receive 6 cycles of LTLD followed immediately by chest wall MLH for 1 hour at 40-42 C every 21-35 days.
- FDA Approved microwave or ultrasound hyperthermia devices were permitted.



PATIENT POPULATION

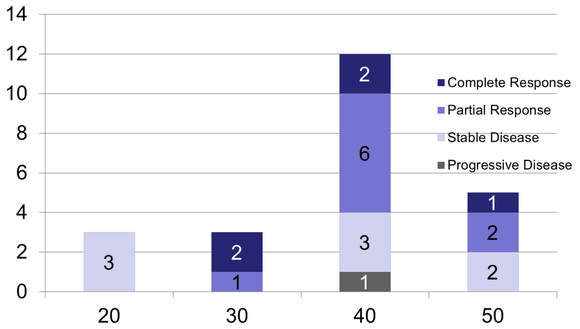
- Trial A treated 18 subjects at 20, 30, or 40 mg/m².
- Trial B treated 11 subjects at 40 or 50 mg/m².

Baseline Disease	Combined N = 29	Trial A N = 18	Trial B N = 11	P-Value
Age (Years)	Years	Years	Years	0.1042[1]
Mean	57.8	59.1	55.6	
Standard Deviation	8.2	9.7	4.7	
Estrogen Receptor (ER) Status	N %	N %	N %	1.0000[2]
Negative	19 65.5%	12 66.7%	7 63.6%	
Positive	9 31.0%	5 27.8%	4 36.4%	
Not Assessed/Unknown	1 3.4%	1 5.6%	0 0.0%	
Progesterone Receptor (PR)	N %	N %	N %	0.6525[2]
Negative	22 75.9%	14 77.8%	8 72.7%	
Positive	6 20.7%	3 16.7%	3 27.3%	
Not Assessed/Unknown	1 3.4%	1 5.6%	0 0.0%	
HER2 Status	N %	N %	N %	0.1535[2]
Negative	21 72.4%	15 83.3%	6 54.5%	
Positive	6 20.7%	2 11.1%	4 36.4%	
Not Assessed/Unknown	2 6.9%	1 5.6%	1 9.1%	
Triple Neg. (ER, PR, and HER2)	N %	N %	N %	0.1212[2]
No	12 41.4%	5 27.8%	7 63.6%	
Yes	16 55.2%	12 66.7%	4 36.4%	
Not Assessed/Unknown	1 3.4%	1 5.6%	0 0.0%	
Distant Metastases at Baseline	N %	N %	N %	0.2490[2]
No	16 55.2%	8 44.4%	8 72.7%	
Yes	13 44.8%	10 55.6%	3 27.3%	
Time from Initial Diagnosis to Chest Wall Recurrence (Years)	Years	Years	Years	0.2515[1]
Mean	4.1	3.8	4.6	
Standard Deviation	3.7	4.2	3.1	
Prior Anthracycline Exposure (mg/m²)				0.7233[1]
Mean	304.1	307.1[4]	299.2[3]	
Standard Deviation	115.4	101.5[4]	140.7[3]	
Prior Radiation Exposure (cGy)				0.7913[1]
Mean	6,449	6,100	7,021	
Standard Deviation	2,455	812.2	3,895	

[1] Exact Wilcoxon-Mann-Whitney test, two-tailed
[2] Fisher's exact test, two-tailed
[3] Excludes one subject who reportedly received a single anthracycline treatment of unknown dose.
[4] Excludes one subject each whose prior anthracycline dose was reported as unknown and as not assessed.

EFFICACY

- Subjects were evaluated for efficacy prior to treatment Cycle 3, Cycle 5 and End of Treatment
- Local Response was evaluated by superficial lesion measurement upon clinical examination with digital imaging to support outcome.
- Local Response Rate 48.3% (14/29; 95% CI: 30.1% - 66.5%)
- 23 of 29 Subjects were eligible for evaluation of efficacy, however efficacy is reported using the intent to treat population.
- Best local response by dose is reported below.



ADVERSE EVENTS

Adverse Event Term	Combined * N=29	Trial A N=18		Trial B N=11	
	Combined Percent	Grade 3	Grade 4	Grade 3	Grade 4
Neutrophil Count Decrease/Neutropenia**	51.7%	6	2	5	3
WBC decrease/Leukopenia**	24.1%	3	0	4	0
Thermal Injury/Wound	3.4%	0	0	1	0
Cellulitis (Chest Wall)	3.4%	0	0	1	0
Dehydration	3.4%	1	0	0	0
Hypokalemia	3.4%	0	0	1	0

* Combined is total events with subjects counted 1 time at most severe grade.
**Combined reporting of myelosuppression events – Trial A coded terms as Neutrophil Count decrease and WBC count decrease
Trial B coded terms as Neutropenia and Leukopenia.

DIGITAL IMAGING

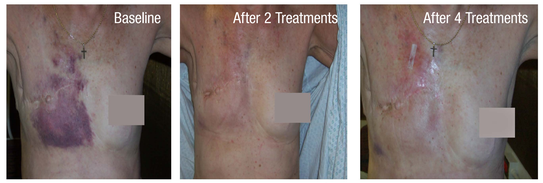


Figure 1 Trial A – Complete Response (CR) at 30 mg/m²

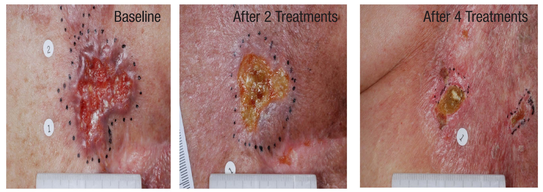


Figure 2 Trial B – Local Lesion Partial Response (PR) at 50 mg/m²

CONCLUSIONS

SAFETY RESULTS

- DMC recommended a Phase II dose at 50 mg/m²
- Reversible myelosuppression was most frequently observed toxicity
- Local toxicities of significance included a single thermal burn in patient with breast implants (Grade 3) and possible radiation recall (Grade 2)

EFFICACY

- ThermoDox and mild hyperthermia therapy appears to be active in heavily pre-treated patients with recurrent breast cancer and prior exposure to doxorubicin or other anthracyclines
- Target lesion response rate of 48%; 5 complete local responses

ONGOING DEVELOPMENT PROGRAM

- Future trials should test LTLD delivery in a less advanced, less heavily pre-treated population
- A multicenter Phase II trial is ongoing

CONTACT INFORMATION

Hope Rugo, M.D. *UCSF CA/USA,* hrugo@medicine.ucsf.edu

Nicholas Borys, M.D. *Celsion Corporation, NJ,* nborys@celsion.com

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