DIGNITY Study

RCW study of ThermoDox® and microwave hYperthermia

Lyso-Thermosensitive Liposomal Doxorubicin shows efficacy with minimal adverse events in patients with breast cancer recurrence at the chest wall

H. Rugo, M.D.[1] , H. Pabbathi, M.D.[2], S. Shrestha, M.D.[3], S. Aithal, M.D.[4] Nicholas Borys, M.D.[5], L. Musso[5], I. Zoberi, M.D.[7]

UCSF Helen Diller Family Cancer Center, San Francisco, CA, 2. CTCA – Southeastern Regional Medical Center, Newnan, GA, 3. CTCA – Southwestern Regional Medical Center, Tulsa, OK, 4. CTCA – Eastern Regional Medical Center, Philadelphia, PA, 5.Celsion Corporation, Lawrenceville, NJ, 6. Washington University in St. Louis Medical Center, St. Louis, MO

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Introduction

- Local-regional recurrence after definitive treatment of breast cancer is reported in 5 – 40 % of patients depending risk factors and initial treatment. Chest wall recurrence is associated with poor quality of life and limited treatment options.
- Lyso-thermosensitive liposomal doxorubicin (LTLD, Thermodox®) is an intravenously administered agent designed to selectively release doxorubicin when exposed to temperatures ≥39.5° C at a targeted tumor.
- Mild hyperthermia, the elevation of tissue temperature in the range of 40° C to 44° C, causes direct cytotoxicity, enhances blood flow and oxygenation.
- We are reporting the interim findings of an ongoing Phase I/ & II Studies Evaluating the Maximum Tolerated Dose, Bioequivalence/Pharmacokinetics, Safety, and Efficacy of LTLD in Patients with Local-Regional Recurrent Breast Cancer.

Study Design

- During the Phase I trial, the DMC recommended a MTD for Phase II at 50 mg/m^2; however, due to local reactions experienced at the start of the Phase II portion of the trial a dose reduction to 40 mg/m^2 was implemented.
- LTLD was administered intravenously over 30 minutes.
- The hyperthermia dose goal in this study is to reach a temperature of 40-42° C for a total of 60 minutes duration in >90% of the temperature sensors monitoring the heat. For microwave and ultrasound hyperthermia, two independent hyperthermia fields can be treated for a total of 60 minutes per field for a total hyperthermia exposure of 120 minutes completed within 4 hours. The treatment fields should be treated in the same order at each cycle. Actual thermal dose delivered will be calculated in terms of CEM 43° C (Cumulative Equivalent Minutes at 43° C)
- Up to six cycles of LTLD/hyperthermia at 21 day intervals were permitted unless unacceptable toxicity, lifetime maximum of anthracycline was administered (600 mg/m^2), hyperthermia was no longer clinically indicated or progression of disease was seen.
- Response was assessed through clinical assessment, CT, and digital photos using Response Evaluation Criteria in Solid Tumors (RECIST).
- All subjects were assessed for safety.

Patient Population

- Patients with breast carcinoma on the chest wall with progression following radiation were eligible; prior chemotherapy and hormone therapy were allowed. Patients with prior free or liposomal doxorubicin exceeding > 450mg/m^2 were excluded from the trial.
- The Phase I & II trials treated a total of 28 subjects at 40 or 50 mg/m^2.

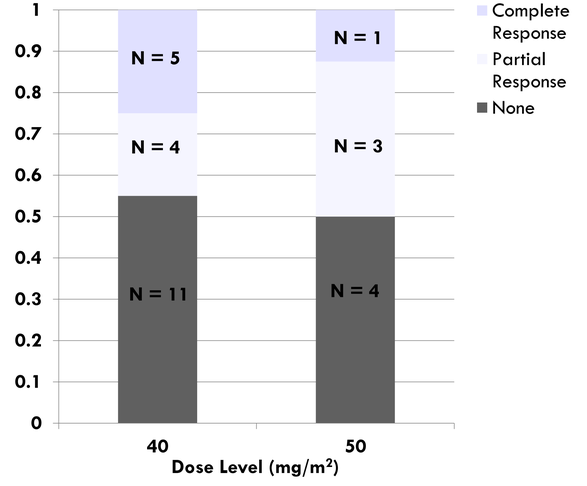
Characteristic	Phase I Trial (N = 11)	Phase II Trial (N = 17)
Age (Years)		
Minimum	49	27
Median	55	58
Maximum	67	72
Estrogen Receptor (ER) Status (n, %)		
Negative	7, 64%	7, 41%
Positive	4, 36%	10, 59%
Progesterone Receptor (PR) Status (n, %)		
Negative	8, 73%	9, 53%
Positive	3, 27%	7, 41%
Not Assessed/Unknown	0, 0%	1, 6%
HER2 Status (n, %)		
Negative	6, 54%	13, 76%
Positive	4, 36%	2, 12%
Not Assessed/Unknown	1, 9%	2, 12%
Triple Negative for ER, PR, and HER2 (n, %)		
No	7, 64%	12, 71%
Yes	4, 36%	5, 29%
Distant Metastases at Baseline (n, %)		
No	8, 73%	9, 53%
Yes	3, 27%	8, 47%

Safety

Combined Phase I/II Safety Data	40 mg/m^2 (N = 20)	50 mg/m^2 (N = 8)
Any Adverse Event (n, %)	19, 95%	8, 100%
Grade 3+ Adverse Event (n, %)	13, 65%	6, 75%
Serious AE (n, %)	6, 30%	4, 50%
Hematological AE (n, %)	11, 55%	7, 88%
Deaths due to AE (n, %)	0, 0%	0, 0%

Efficacy

- In the Phase I/II trials, subjects were evaluated for efficacy prior to treatment Cycle 3, Cycle 5 and End of Treatment.
- Local Response was evaluated by superficial lesion measurement, clinical examination and digital imaging by local investigator.
- A combined local response rate 46.4% (13/28). All efficacy data is investigator reported.
- A total of 5 patients experienced a durable local response lasting ≥ 3 months (4 CRs and 1 PR). 80% of the durable responses were from patients dosed at 40 mg/m^2.



The preliminary data included within the abstract was compiled in July 2015 and the data presented in this poster is from November 2015. A patient dosed at 40mg/m^2 went from an initial PR response to Not Evaluable as the target lesion measurements could not be confirmed at the time of the final evaluation.

Digital Imaging

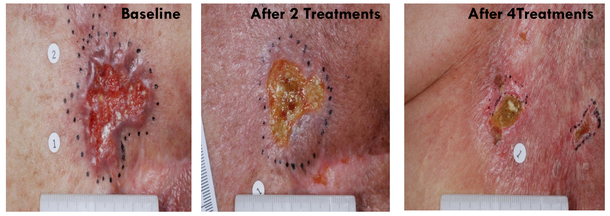


Figure 1 Phase I Trial – Local Lesion Partial Response (PR) at 50 mg/m^2

Conclusions

Safety & Efficacy

- The most commonly reported adverse events are hematologic in nature including reversible neutropenia managed with ASCO g-CSF treatment recommendations.
- At 50 mg/m^2 dose levels, up to 2 patients treated with LTLD demonstrated a localized reaction to the treatment area of erythema, woody induration, and pain. When the dose was adjusted to 40 mg/m^2, the reaction did not recur at subsequent treatments.
- Local response rate was 46.4% and a total of 5 patients experienced a durable local response lasting ≥ 3 months.
- We conclude that LTLD at a dose of 40 mg/m^2 combined with superficial hyperthermia offers a promising and well tolerated treatment option for patients with recurrent chest wall disease from breast cancer.

Ongoing Development Program

- The Phase II DIGNITY trial will be completed this year.
- A Phase II trial will be initiated throughout Europe and Israel in a less advanced, less heavily pretreated population

Contact Information

Hope Rugo, M.D.- UCSF CA/USA Hope.Rugo@ucsf.edu
Nicholas Borys, M.D. Celsion Corporation, NJ - nborys@celsion.com

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