



HEAT Study

Hepatocellular
Carcinoma
Study of RFA and
ThermoDox[®]

KEY INCLUSION CRITERIA:

- Hepatocellular Carcinoma
- No more than 4 lesions
- At least 1 lesion \leq 3cm and none $>$ 7cm
- Child-Pugh A or B

KEY EXCLUSION CRITERIA:

- Resectable HCC
- Scheduled for transplant
- Previous treatment for HCC
- Extrahepatic metastasis
- Other malignancy
- Encephalopathy
- Ascites

PRIMARY STUDY OBJECTIVES:

To determine the efficacy of systemically delivered, heat-activated liposome encapsulated doxorubicin (ThermoDox) in combination with radiofrequency ablation (RFA) by comparison to RFA-alone in the treatment of hepatocellular carcinoma (HCC) as measured by progression free survival (PFS).

For more information on the HEAT Study:

www.Celsion.com • www.clinicaltrials.gov

Prohibited Medications

The parent compound of ThermoDox (Doxorubicin) is a substrate (major) of CYP2D6, 3A4. Inducers and inhibitors of CYP3A4 may alter the metabolism of ThermoDox. The following CYP3A4 inducers and inhibitors are prohibited from screening through after study treatment. Additionally, medications that modify gastric pH are included. Future updates to the list will be provided to the site as new information becomes available.

Drug Class	Agent	Wash-out ¹
CYP3A4 Inducers		
Antibiotics	all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)	14 days
Anticonvulsants	phenytoin, carbamazepine, barbiturates (e.g., phenobarbital)	
Antiretrovirals	efavirenz, nevirapine	
Glucocorticoids (oral)	cortisone (> 50 mg), hydrocortisone (> 40 mg), prednisone (> 10 mg), methylprednisolone (>8 mg), dexamethasone (> 1.5 mg) ²	
Other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
Antibiotics	clarithromycin, erythromycin, troleandomycin	7 days
Antifungals	itraconazole, ketoconazole, fluconazole (> 150 mg daily), voriconazole	
Antiretrovirals, Protease Inhibitors	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir	
Calcium channel blockers	verapamil, diltiazem	
Antidepressants	nefazodone, fluvoxamine	
GI Agents	cimetidine, aprepitant	
Other	grapefruit, grapefruit juice	
	amiodarone	6 months
Miscellaneous		
Antacids	Mylanta, Maalox, Tums, Rennie's	1 hour before and after dosing
Herbal or dietary supplements	Ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil	14 days

- At the time of screening, if a subject is receiving any of the above listed medications/substances, the medication or substance must be discontinued (if clinically appropriate) for the period of time specified prior to administration of the first dose of study treatment and throughout the period discussed above in order for the subject to be eligible to participate in the study.
- Glucocorticoid daily doses (oral) \leq 1.5 mg dexamethasone (or equivalent) are allowed. Glucocorticoid conversions are provided in parentheses.

Subjects may be randomized without a biopsy if they meet American Association for the Study of Liver Disease (AASLD) criteria for the diagnosis of HCC. These patients will be required to have a biopsy during the RFA procedure unless the biopsy is not possible or is contraindicated. Subjects not meeting AASLD criteria for HCC will need a biopsy for confirming HCC prior to randomization.

1. Diagnosed hepatocellular carcinoma (HCC).
2. No more than 4 HCC lesions with at least one ≤ 3.0 cm and none > 7.0 cm in maximum diameter, based on diagnosis at screening.
 - If a subject has a large lesion (5.0 - 7.0 cm), any other lesions must be less than 5.0 cm.
 - Anticipated ablation volume will be no larger than either removal of 3 hepatic segments or removal of more than 30% of total liver volume (as per maximum surgical limit).
 - If additional lesions are discovered during the laparoscopic or open treatment procedure, that were undetectable by CT at screening, the size and location of the lesion(s) will be recorded in the CRF and the lesions will be treated at the discretion of the physician and guided by the local standard of care. The subject will remain on study if all lesions are treated. If any lesions cannot be completely ablated within two treatment attempts the subject will be considered a treatment failure.
 - Study subjects being considered for re-treatment after disease progression may have more than 4 lesions.
3. Male or female 18 years of age or older.
4. Are willing to sign an informed consent form, indicating that they are aware of the investigational nature of this study that is in keeping with the policies of the institution.
5. Be an appropriate candidate for receiving RFA as a medically indicated treatment as evaluated by the following factors:
 - Number of lesions
 - Size of lesions
 - Overall health of liver
 - Not a candidate for surgical resection
6. Have an echocardiogram revealing a Left Ventricular Ejection Fraction (LVEF) $\geq 50\%$. Measurements with a multiple gated acquisition (MUGA) scan are allowed if an echocardiogram cannot be performed. The same method of measurement should be used to evaluate ejection fraction (EF) of the subject for the duration of the study.
7. Willing to return to the study site for their study visits.
8. Have life expectancy of ≥ 4 months.
9. Have Child-Pugh Class A or B liver disease without encephalopathy or/and ascites.

HEAT Study Exclusion Criteria

1. Have serious medical illnesses including, but not limited to, congestive heart failure, myocardial infarction or cerebral vascular accident within the last six months, or life threatening cardiac arrhythmias.
2. Is scheduled for liver transplantation.
3. Have previously received any treatment for HCC (except for study subjects being considered for completion of treatment or re-treatment).
4. Have previously received any doxorubicin (study subjects being considered for completion of treatment or re-treatment may have received ThermoDox previously).
5. Have extrahepatic metastasis.
6. Are pregnant or breast-feeding. In women of childbearing potential, a negative pregnancy test (serum) is required prior to study treatment.
7. Women of childbearing potential who are not practicing an acceptable form of birth control (i.e. diaphragm, cervical cap, condom, surgical sterility or birth control pills. Women whose partner has undergone a vasectomy must use a second form of birth control).
8. Have any known allergic reactions to any of the drugs or liposomal components or intravenous imaging agents to be used in this study.
9. Have portal or hepatic vein tumor invasion/thrombosis.
10. Have INR > 1.5 times the institution's upper normal limit (UNL), except in subjects who are therapeutically anticoagulated for medical conditions unrelated to HCC such as atrial fibrillation. Subjects may be re-screened after condition is treated or anticoagulant is withheld.
11. Have platelet count < 75,000/mm³, absolute neutrophil count < 1500/mm³, or Hgb < 10.0 g/dL (unless the hemoglobin value has been stable, the subject is cardiovascularly stable, asymptomatic and judged able to withstand the RFA procedure).
12. Have serum creatinine 2.5 mg/dL or calculated creatinine clearance (CrCl) 25.0 mL/min.
13. Have serum bilirubin > 3.0 mg/dL.
14. Have serum albumin < 2.8 g/dL.
15. Have body temperature >101°F (38.3°C) immediately prior to study treatment.
16. Have contraindications to receiving doxorubicin HCl.
17. Are being treated with other investigational agents.
18. Use of an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study medication (study subjects being considered for completion of treatment or re-treatment may have received ThermoDox previously).
19. Have other concurrent malignancy (subjects with treated squamous cell carcinoma of the skin or basal cell carcinoma of the skin may be included), evidence of extrahepatic cancer from their primary malignancy, or ongoing, medically significant active infection.
20. Documented HIV positive.
21. NYHA class III or IV functional classification for heart failure.
22. Evidence of hemochromatosis.
23. Have history of contrast-induced nephropathy.