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# Thermally Sensitive Drug Carriers in Combination with Thermal Ablation

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# Disclosure

- Advisory Board member of Celsion Ltd.
- Asia-Pacific lead PI of Phase III Randomized Trial of Thermodox in Combination with RFA for HCC (HEAT study)

# Local Ablative Therapies for Liver Cancers

- Ethanol injection
- Cryotherapy
- Radiofrequency ablation
- Microwave
- High intensity focused ultrasound
- Electroporation

Thermal ablation

Indications for liver cancer:
< 5 cm tumor, </= 3 tumor nodules

# RFA for HCC < 5 cm
## Complete Ablation Rate

| Study | No. of patients | Route of RFA | Complete ablation |
|---|---|---|---|
| Curley 2000 | 110 | Percut (76)<br>Lap (31)<br>Open (3) | 100% |
| Giovannini 03 | 53 | Percut | 92.8% |
| Vivarelli 04 | 79 | Percut | 87% |
| Poon 04 | 86 | Percut (35)<br>Lap (3)<br>Open (48) | 93% |

# Local Recurrence after RFA for HCC

| Study | No. of patients | Median follow-up (months) | Local recurrence |
|---|---|---|---|
| Buscarini 01 | 88 | 34 | 14% |
| Giovannini 03 | 56 | 14 | 7% |
| Vivarelli 04 | 79 | 15.6 | 15% |
| Poon 04 | 86 | 11.5 | 6.2% |
| Lencioni 05 | 187 | 24 | 5.3% |
| Marchi 05 | 65 | 20 | 17% |
| Ng 08 | 207 | 26 | 14.5% |

# Local Recurrence after RFA for HCC

- Incomplete necrosis of tumor cells in ablated lesion
  - Complete necrosis only in 29 of 38 (83%) tumors ablated by RFA followed by liver transplantation based on histological examination of explants

*Lu et al. Radiology 2005*

- Untreated microsatellite nodules adjacent to tumor

# Risk Factors for Local Recurrence

Independent risk factors of local recurrence by meta-analysis of 5224 liver tumors treated by RFA from 95 series in the literature:

- tumor size > 3 cm ($p < 0.001$)
- percutaneous vs. surgical approach ($p < 0.001$)

*Mulier et al. Ann Surg 2005*

# Thermal Ablation for HCC 3-7 cm

102 patients with at least 1 tumor 3-7 cm ablated by RFA or microwave (89 patients 3-5 cm, 20 patients > 5 cm)

- Complete ablation rate 92%
- Local recurrence 22% (median time to recurrence 4.6 months), distant recurrence 53%
- 1-yr, 3-yr, 5-yr survival 75%, 31% and 15%
- Incomplete ablation, recurrent tumor and AFP > 200 ng/mL were independent prognostic factors of survival

*Yin et al. Cancer 2009*

# Potential Approaches to Reduce Recurrence after RFA for HCC > 3 cm

- Combination with transarterial chemoembolization
  - one more invasive procedure with potential serious complications

Peng et al. J Clin Oncol 2013

- Thermosensitive liposomes encapsulating cytotoxic drugs
  - a novel technology to deliver high concentrations of chemotherapy drugs to the tumor with lower systemic toxicity
  - simple intravenous injection prior to RFA procedure

# Thermal Sensitive Liposomal Drug Carriers

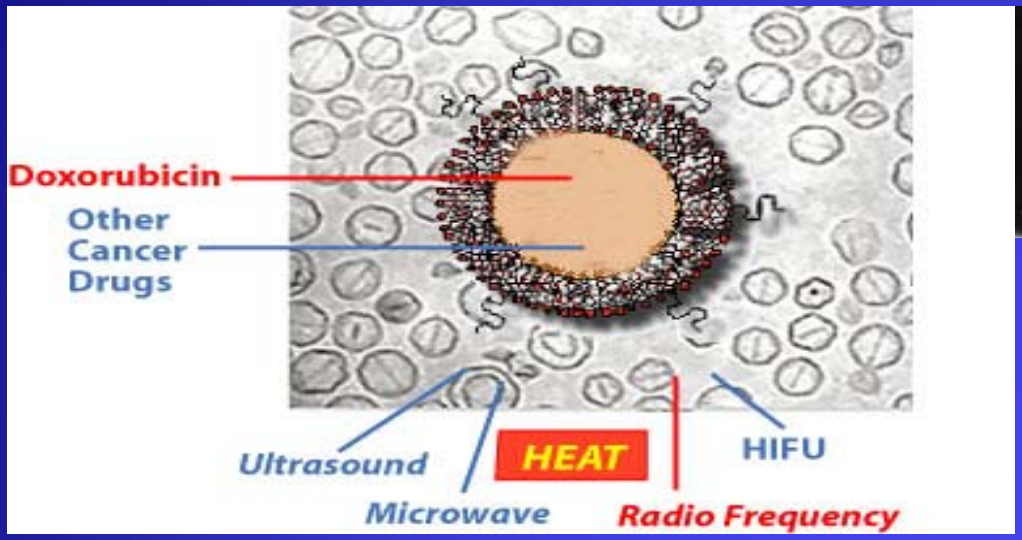
- Liposomal encapsulation can optimize and enhance the delivery of different cytotoxic agents with lower systemic toxicity and better drug cell internalization compared with free drugs

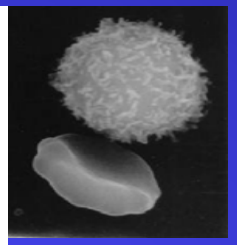
  (e.g. DOXIL - polyethylene glycolylated liposomes containing Doxorubicin)

- New generation of lyso-lipid heat-sensitive liposomes release drugs with hyperthermia and may further improve drug delivery to tumors

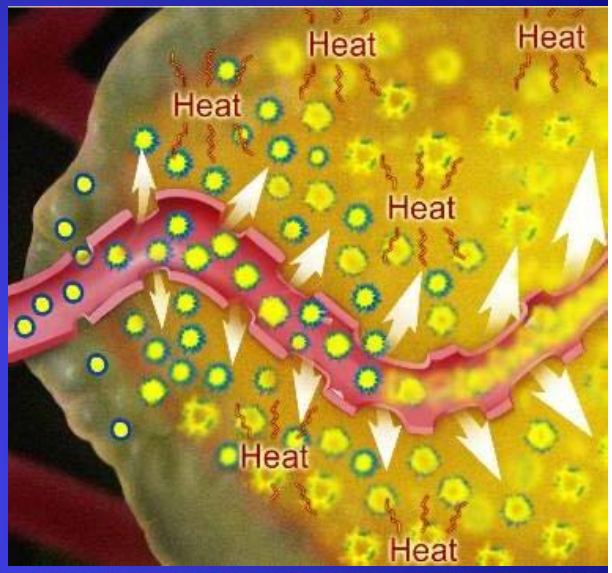
  (e.g. ThermoDox)

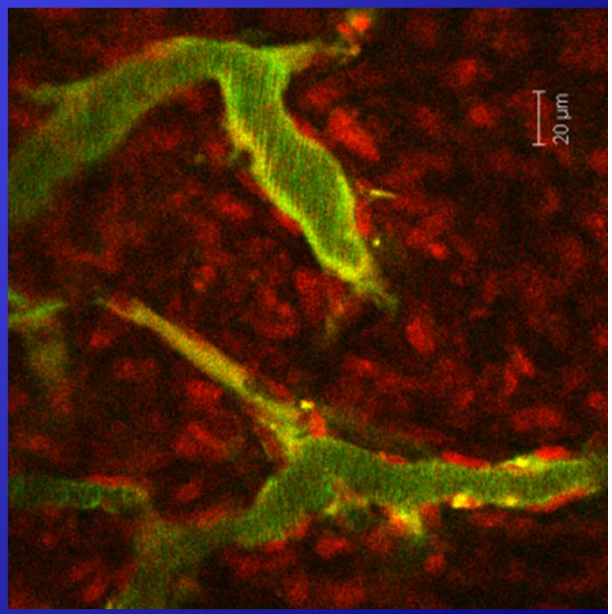
# Thermosensitive Liposomal Doxorubicin (ThermoDox)



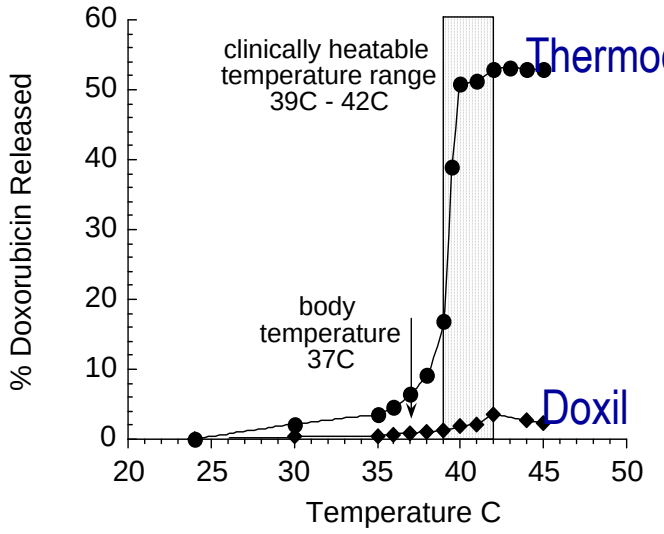



ThermoDox is 100 nm, a Fraction of RBC



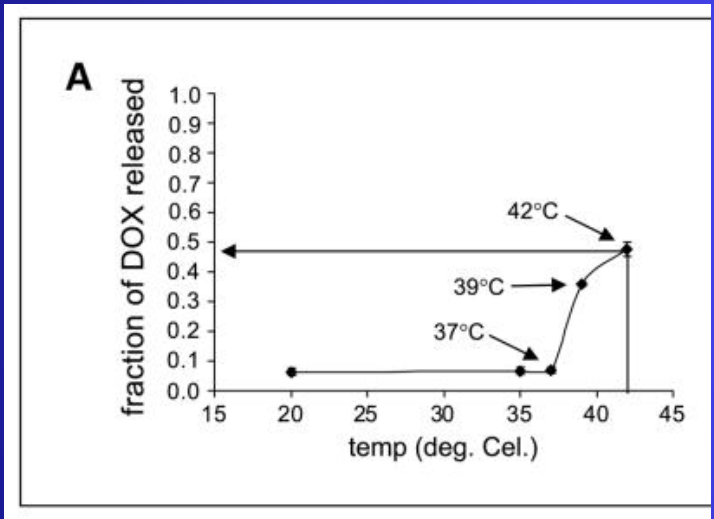




In vitro

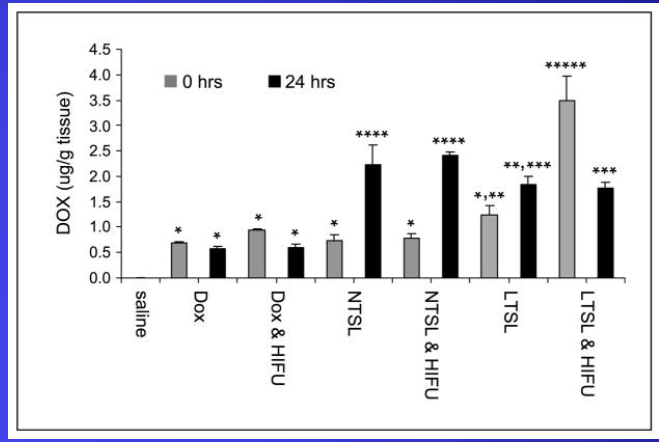


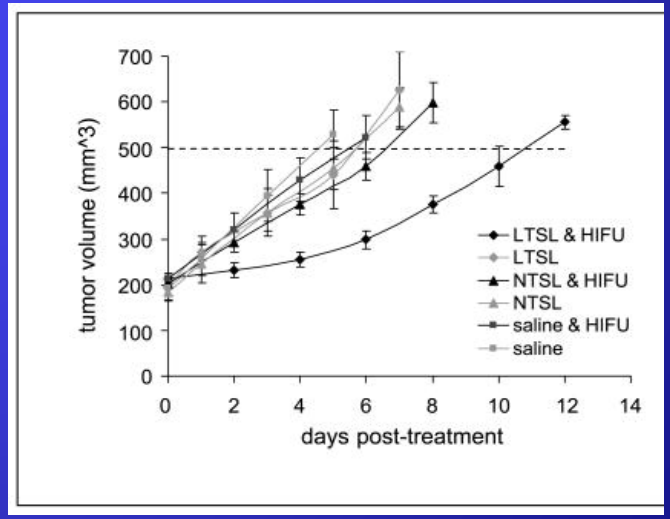
# ThermoDox in Mice Tumor Study

Combining Thermodox with pulsed HIFU enhanced its delivery to tumor and its anti-tumor effects compared with Doxil




Thermodox started releasing doxorubicin at a temperature of 39°C. At a temperature of 42°C, release of doxorubicin at 2 min was ~ 50% and nearly 100% by 12 min




*Dromi et al. Clin Cancer Res 2007*

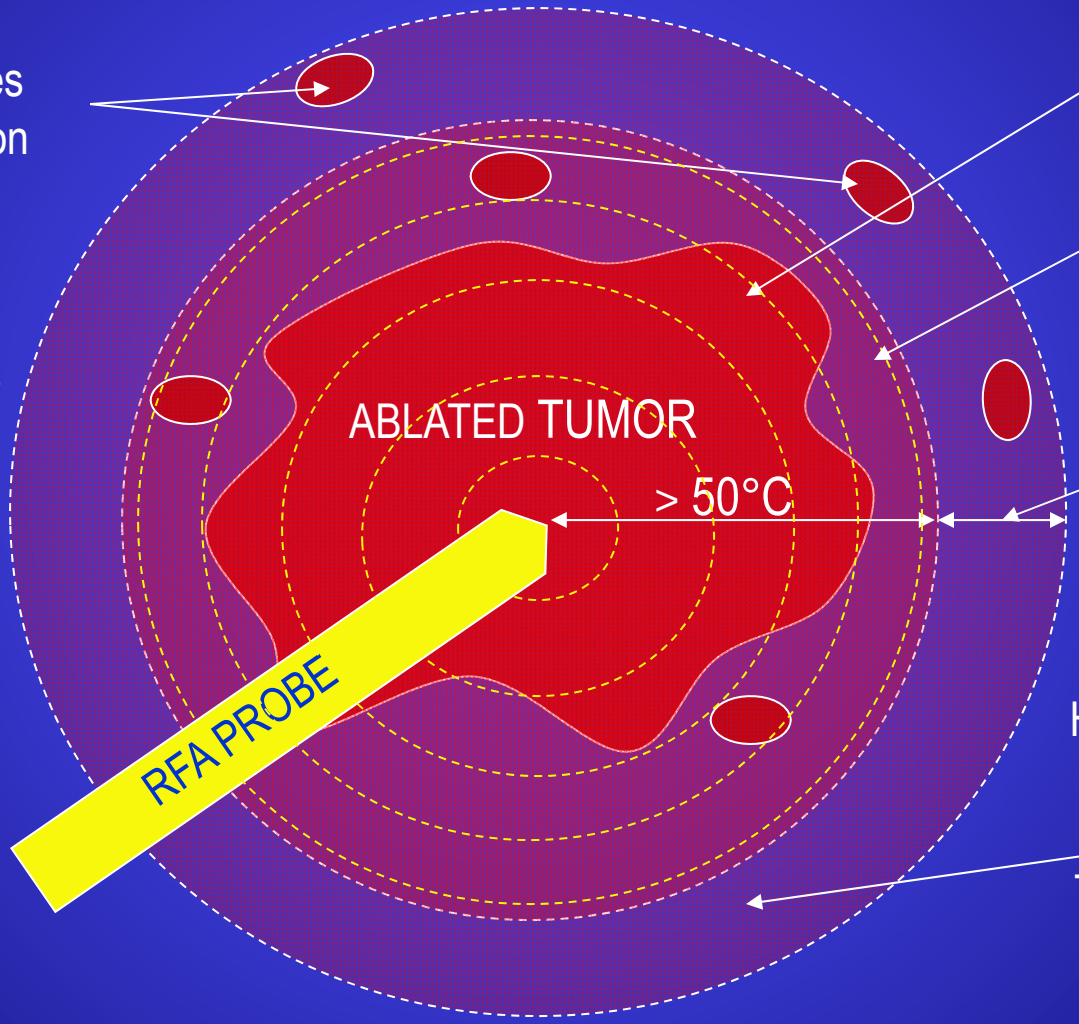
# Mode of Action for ThermoDox

- Local tissue concentration ~ 10x that of standard free doxorubicin, achieving higher cancer cytotoxicity and reduced systemic toxicity
- Direct toxicity to tumor vasculature

Synergistic effects:

- Cytotoxic effect of doxorubicin enhanced by heat (doxorubicin binding to tumor DNA)
- Doxorubicin reduces ablation threshold temperature – enhanced lesion size

# RF Ablation / ThermoDox Combination




Micro - metastases outside the ablation zone "kill" area. These are a potential site of recurrence if not treated

Ablated Tumor and 1 cm "Tumor-Free" Margin

<50°C >39°C

High concentration of doxorubicin deposited by ThermoDox in this thermal zone

# Phase I Study at NCI (USA) and QMH (HK)

- Phase I, single dose, dose escalation study to evaluate tolerability of Thermodox in patients with liver tumors undergoing RFA
- Patients with primary or secondary liver cancer, 4 or fewer tumor nodules up to 7 cm, were enrolled following the dose escalation design
- Six ThermoDox dose levels were planned:

  20, 30, 40, 50, 60 and 70 $mg/m^2$
- Patients received a single dose of 30-min. IV infusion of ThermoDox starting 15 min. before percutaneous or surgical RFA
- Patients were monitored for safety up to 3 months, and contrast CT scan was performed at day 28 to assess treatment efficacy

*Wood, et al. J Vasc Interv Radiol. 2012*

# Tumor Characteristics

- A total of 24 patients were treated (3, 6, 6, 6, 3 patients at doses of 20, 30, 40, 50 and 60 mg/m$^2$, respectively)

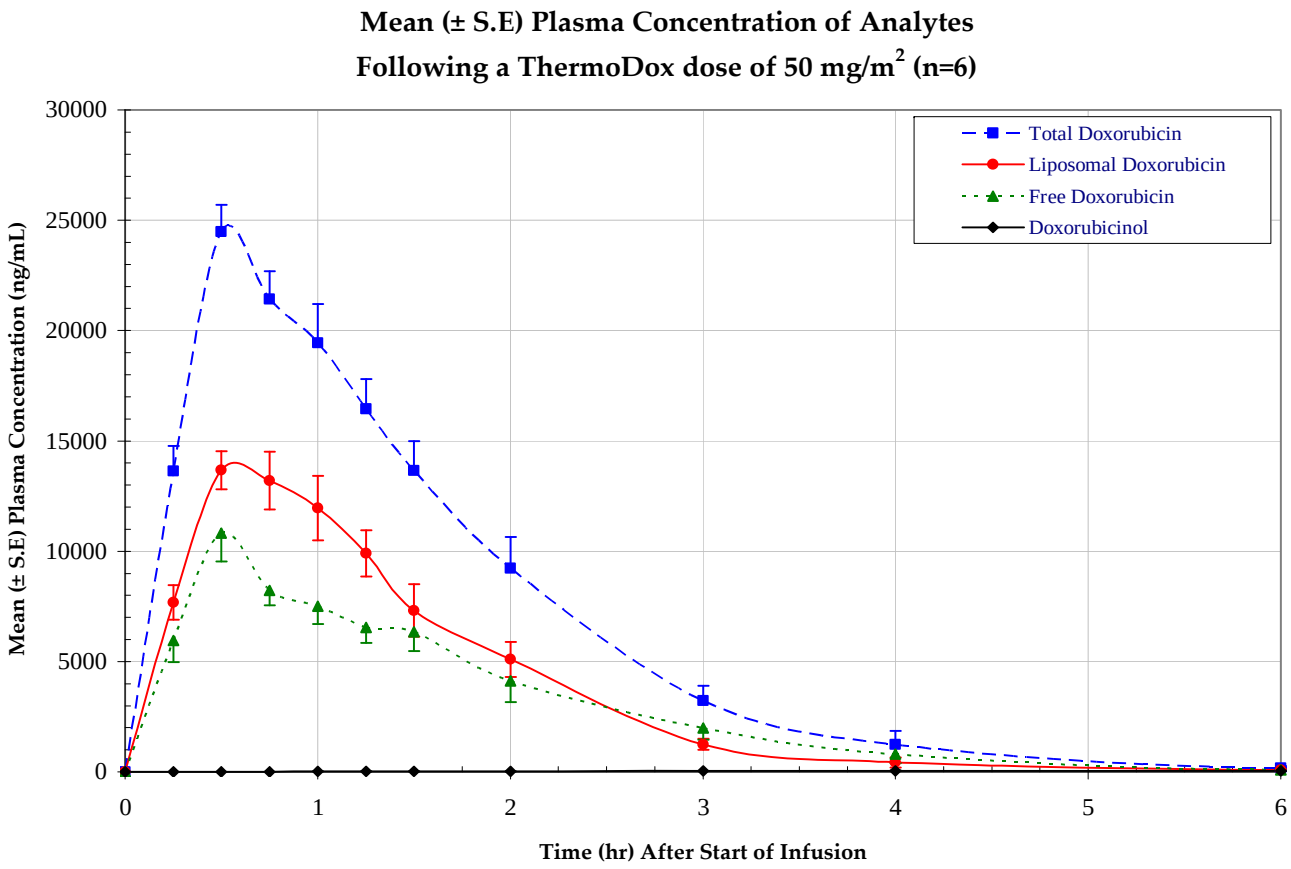
- Median tumor size 3.7 cm (range 1.7-6.5 cm), and totally 28 tumors treated

- Pathology:

  Hepatocellular carcinoma n = 9

  Metastatic carcinoma n = 15 (Primary sites: adrenal, colorectal, esophageal, breast, cervix uteri, kidney, pancreas)

# Pharmacokinetics




- The concentration of doxorubicin peaked at 30 minutes and then decreased as doxorubicin is cleared (initial half-life 0.92 hr.)
- A simple approach of initiating RFA halfway into a 30 minute IV infusion of Thermodox captured 51% of the $AUC_0$-∞ with RFA current on and 90% of the $AUC_0$-∞ with the overall RFA time.

# Adverse Events and MTD

- Common drug-related adverse events included:
  - alopecia (grade 1 or 2 only, 66.7%)
  - reversible grade 3/4 neutropenia (50%, dose-dependent)

- No treatment death

- No renal toxicity, congestive heart failure, reduced ventricular ejection fraction or hand-foot reaction

- The maximum tolerated dose (MTD) was determined as 50 mg/m$^2$ based on two dose-limiting toxicities (a grade 3 alanine aminotransferase increase and a grade 4 neutropenia) occurring at 60 mg/m$^2$ dose

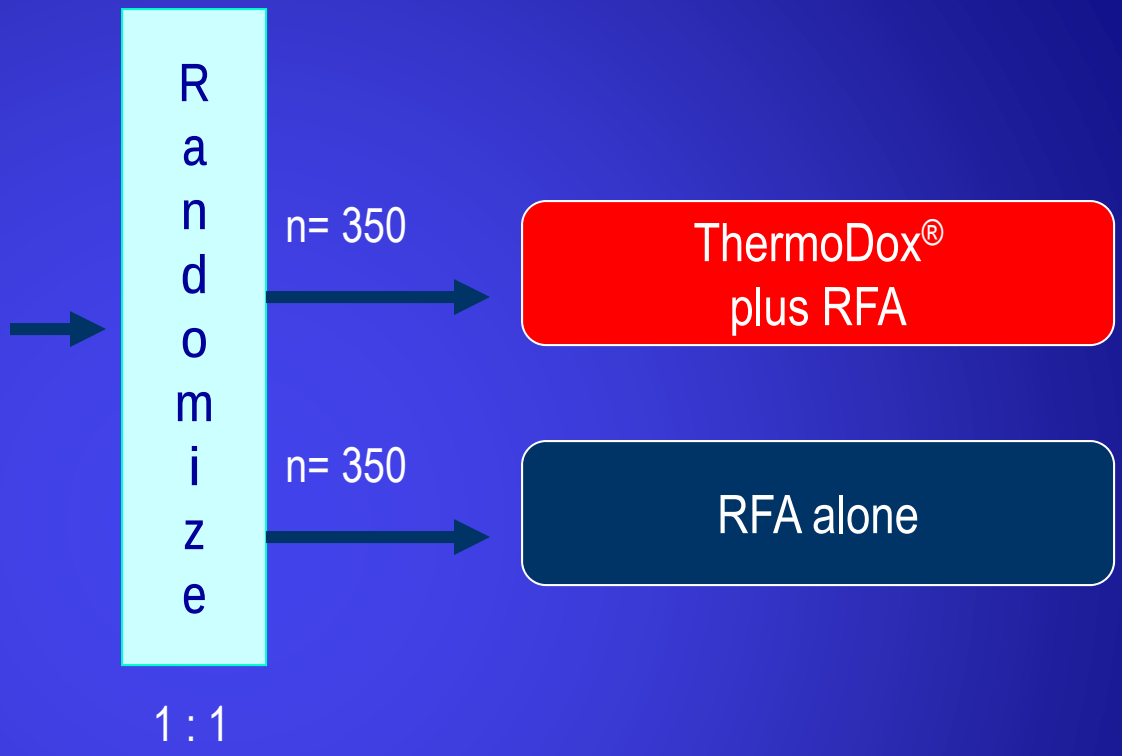
# Tumor Control

- Totally 28 tumors were treated
- Three patients had local failure detected at 28 days post-treatment (12.5%)
- There was a statistically significant ThermoDox dose-response relationship in time to tumor progression (P = 0.011)

# Phase III Double-blind Randomized Trial

Eligibility:
- non-resectable HCC
- no more than 4 lesions
- at least 1 lesion ≥ 3cm and none > 7cm
- no previous treatment
- Child-Pugh A or B

Stratification
- lesion size: 3-5 vs >5-7 cm and RFA technique:
  - open surgical
  - laparoscopic or
  - percutaneous




End Points:

Primary: PFS (Progression Free Survival)

designed to show a 33% improvement in PFS with 80% power and a p-value = 0.05

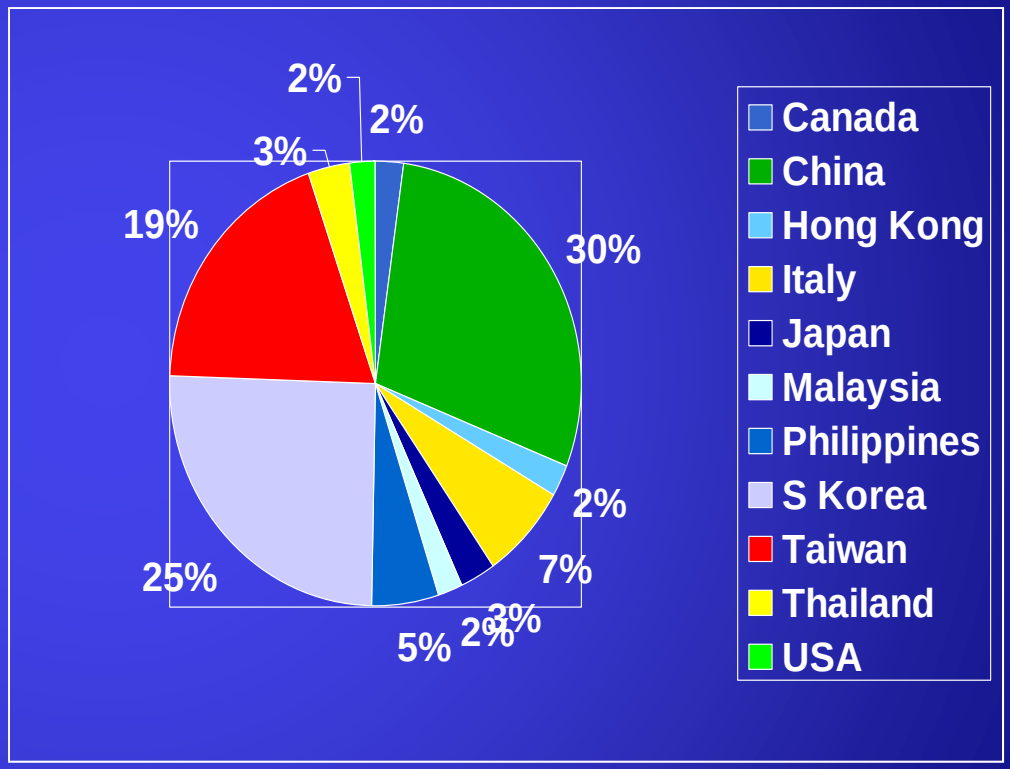
Secondary: OS (Overall Survival), TTLR (time to local recurrence), Safety

HEAT Study

Hepatocellular Carcinoma Study of RFA and ThermoDox®

# Phase III HEAT Study

- conducted under a Special Protocol Assessment agreed to with the U.S. Food and Drug Administration (FDA)
- 76 clinical sites in 11 countries/regions
- Completed enrollment of 701 by June, 2012
  (49 from Italy
  30 from USA/Canada
  622 from Asia)






HEAT Study
Hepatocellular Carcinoma Study of RFA and ThermoDox®

# Topline Results of HEAT Study

- ThermoDox® in combination with RFA did not meet the primary endpoint of the Phase III HEAT Study in patients with HCC

- In the trial, ThermoDox® was well-tolerated with no unexpected serious adverse events

  (most important AE: neutropenia)

Celsion Corporation 31 Jan 2013

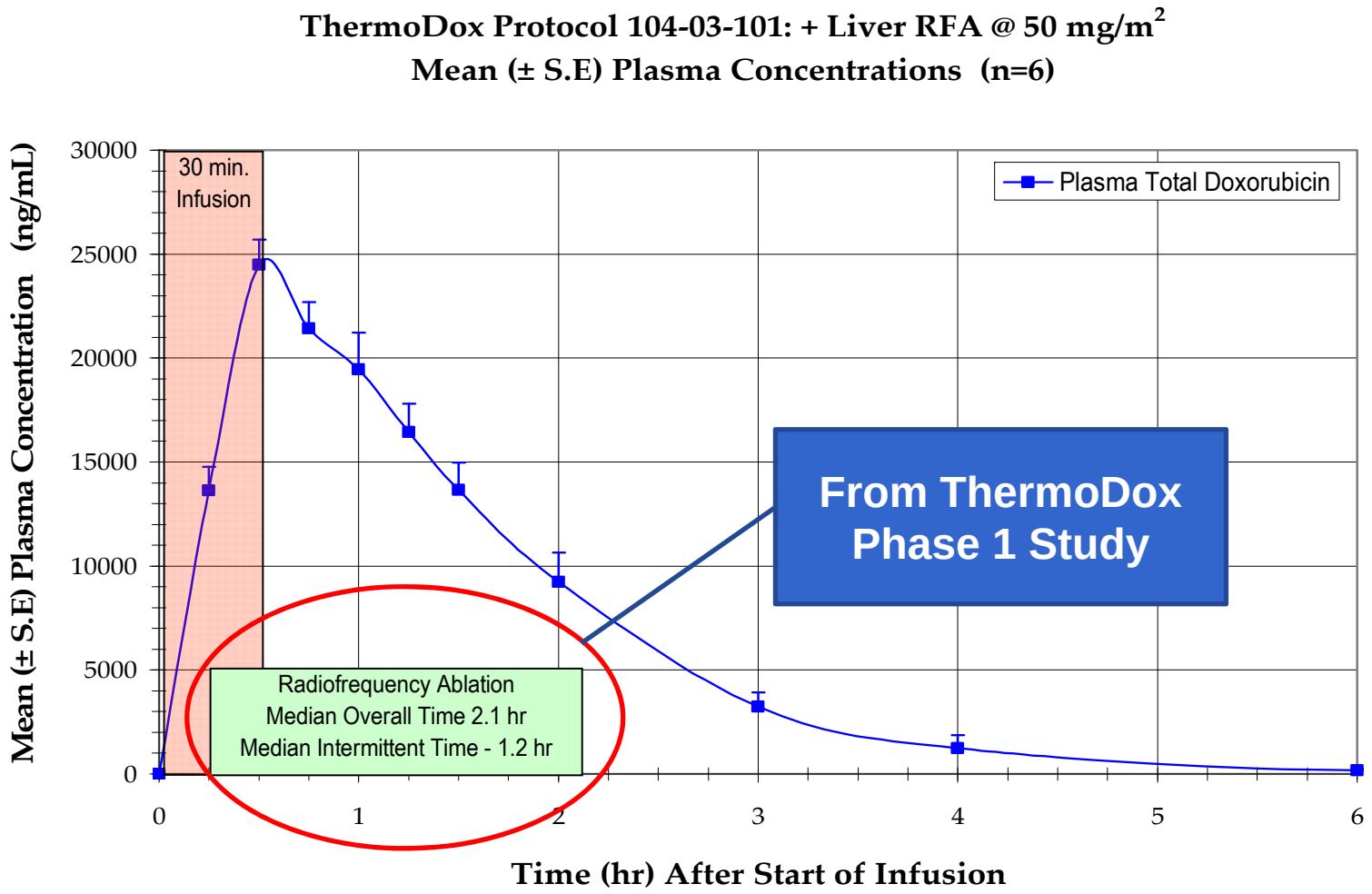
# Topline Results of HEAT Study

- PFS of Thermodox vs. Control: 13.97 vs. 13.87 months (HR 0.96)
- Patients with smaller lesions (< 5 cm, n=575) showed potential benefit with Thermodox

  PFS: 16.6 vs. 13.9 months (HR 0.90)

  [5-7 cm: 6.6 vs. 9.6 months, HR 1.16]
- Greatest benefit in patients that had RFA > 45 mins
  - Single lesion patients (65% of population)
  - Consistent in both PFS & OS analysis

# Phase I Results: ThermoDox Human PK



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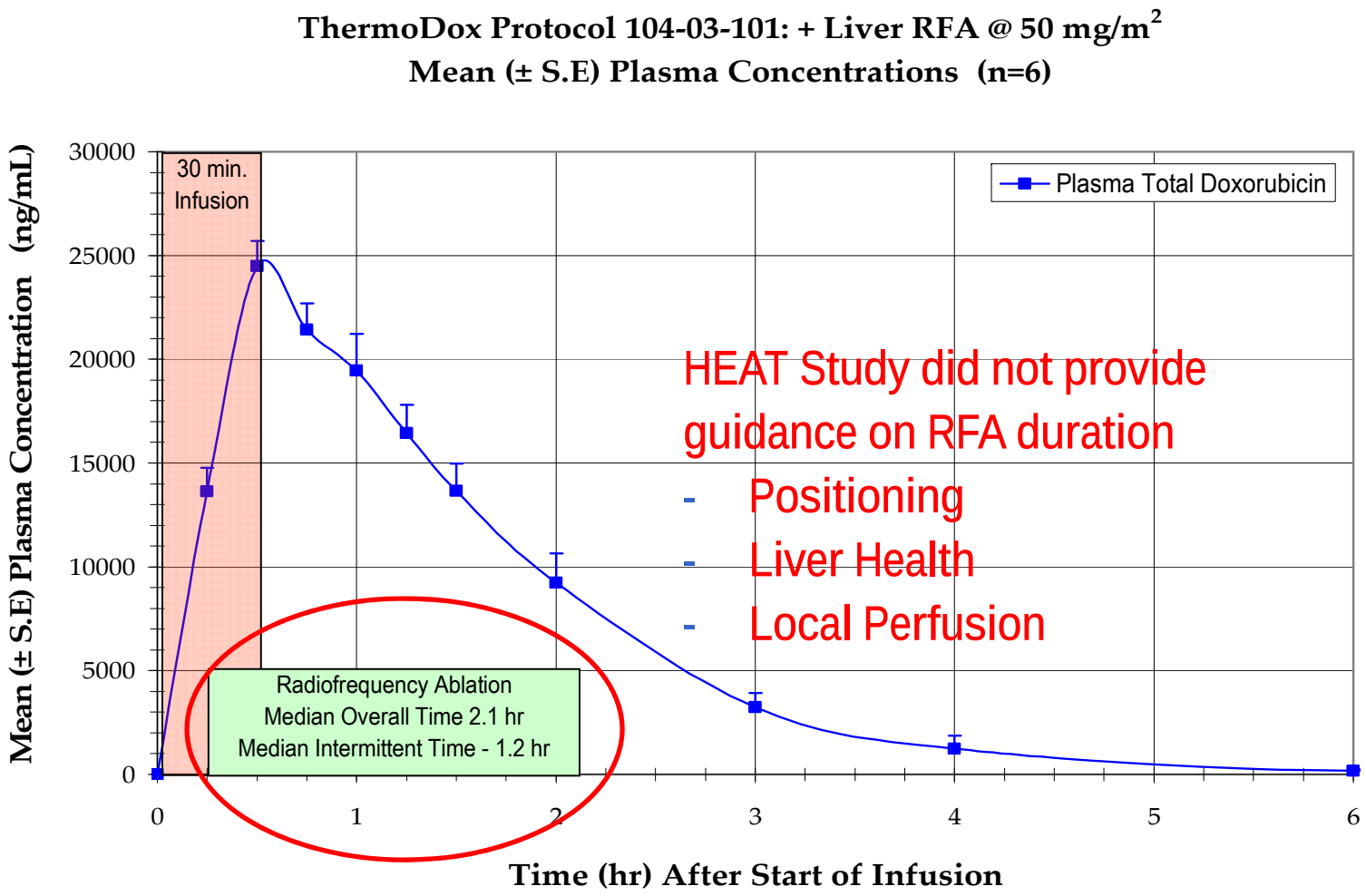
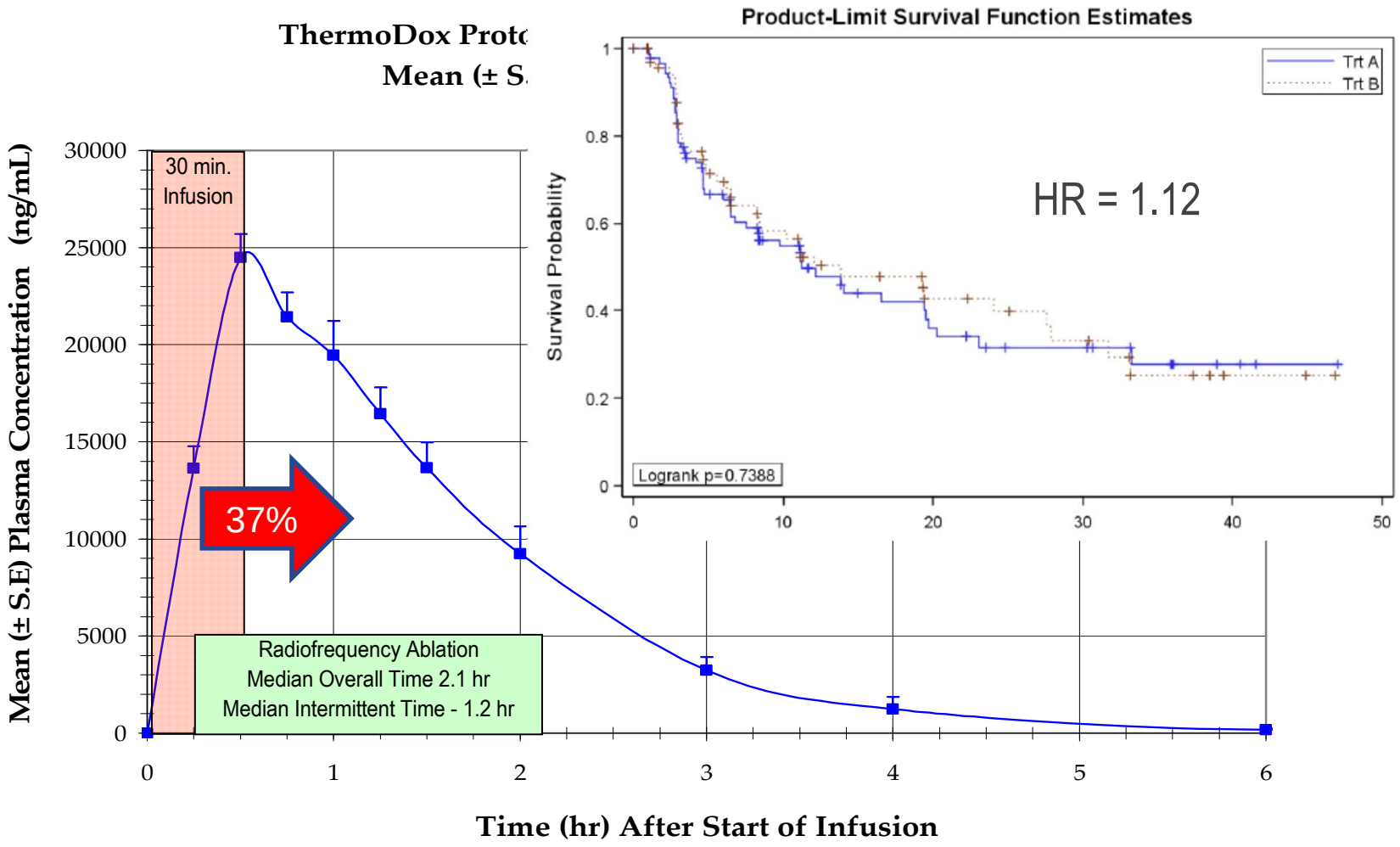
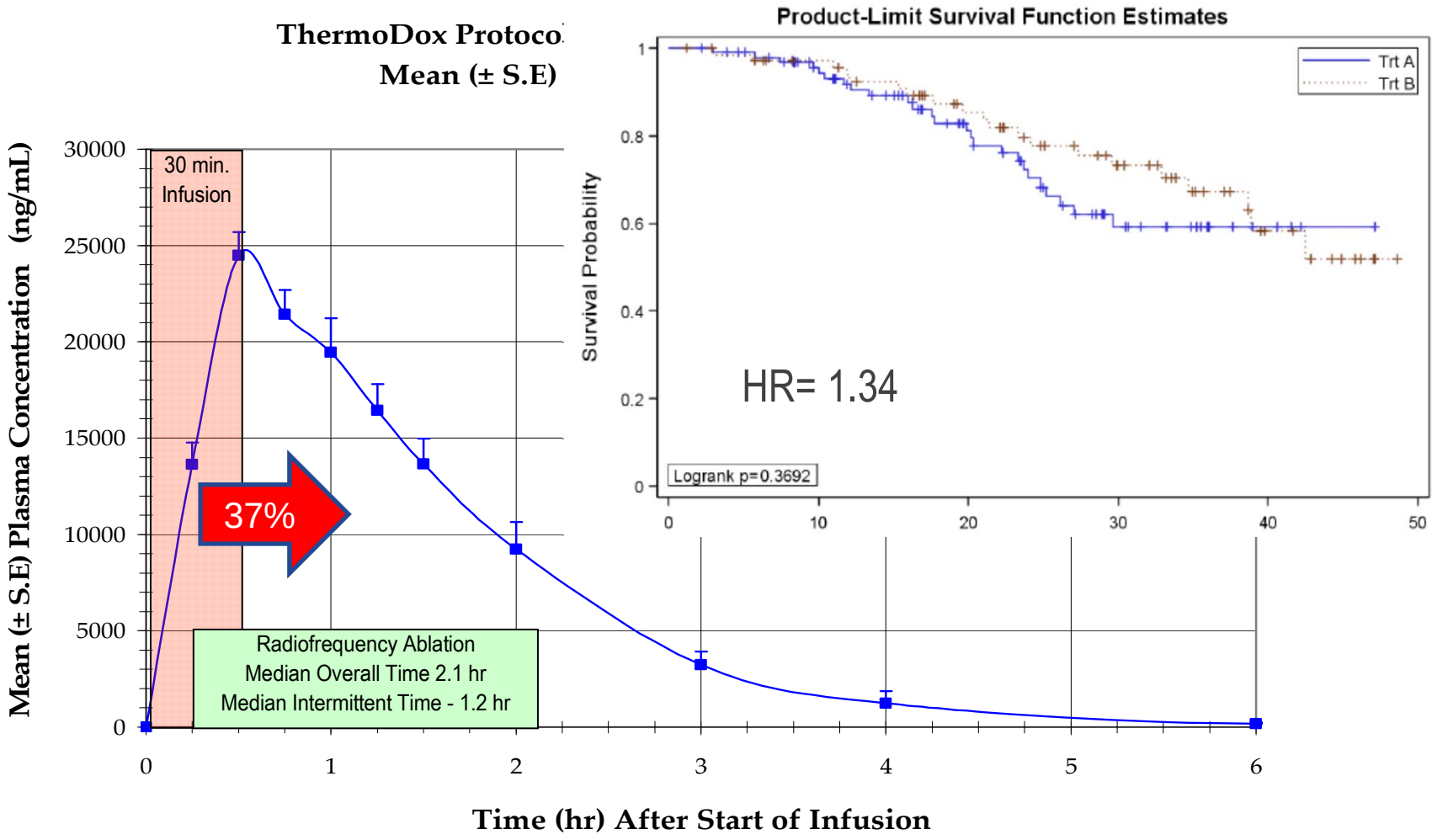


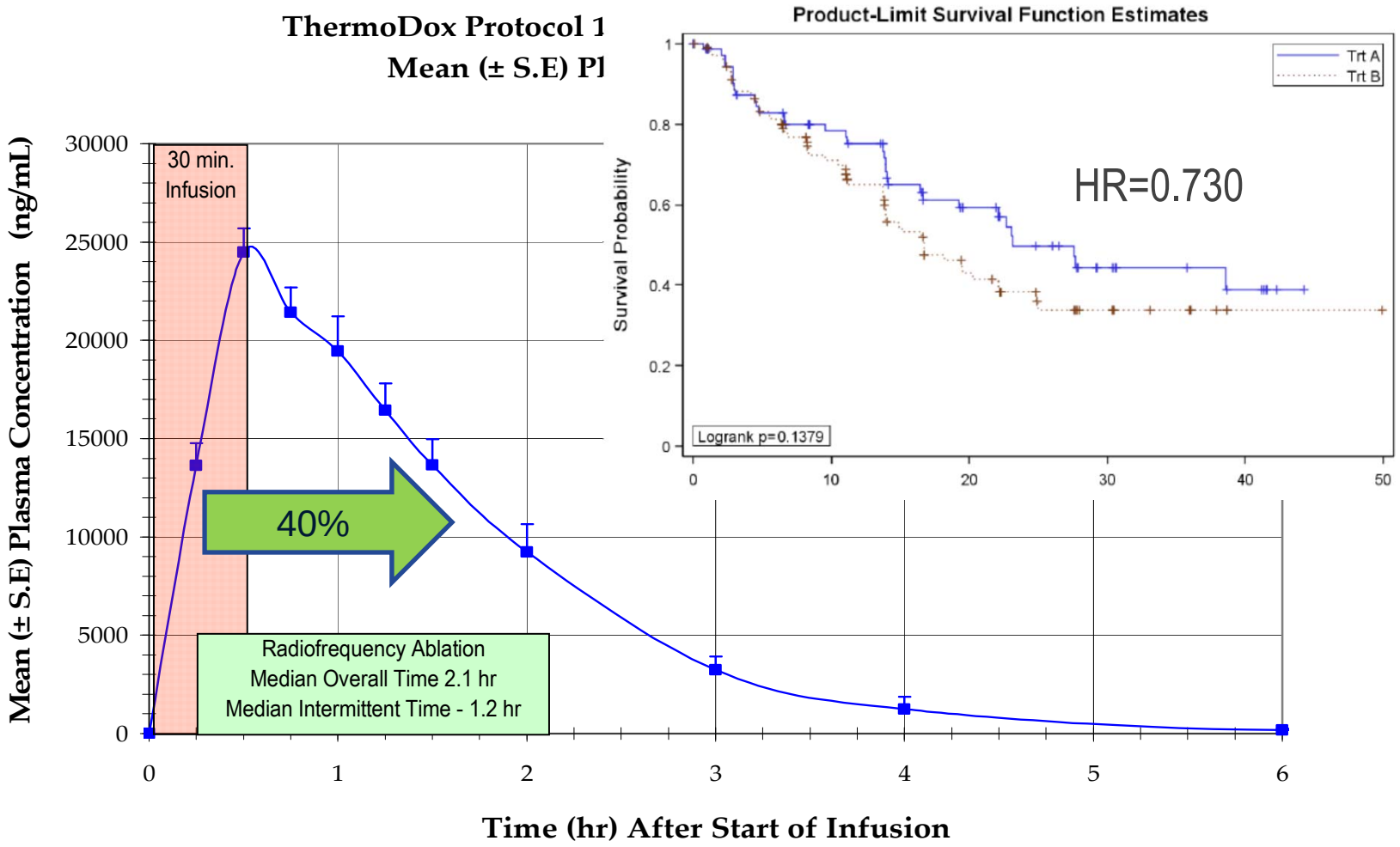
# PFS of Patients who had RFA < 45 mins (n=166)



# OS of Patients who had RFA < 45 mins (n=166)



# PFS of Patients had RFA 45-90 mins (n=181)



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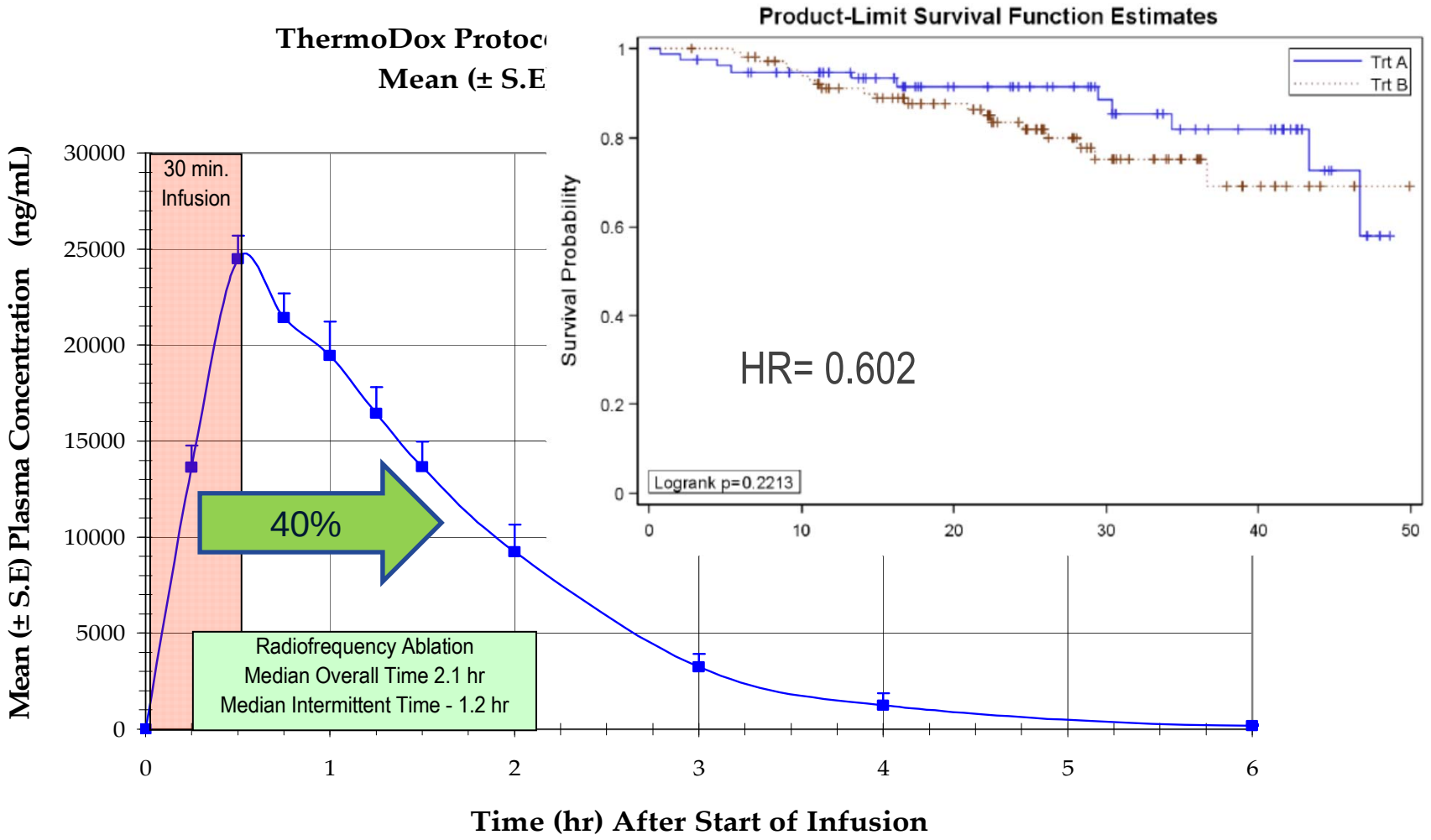
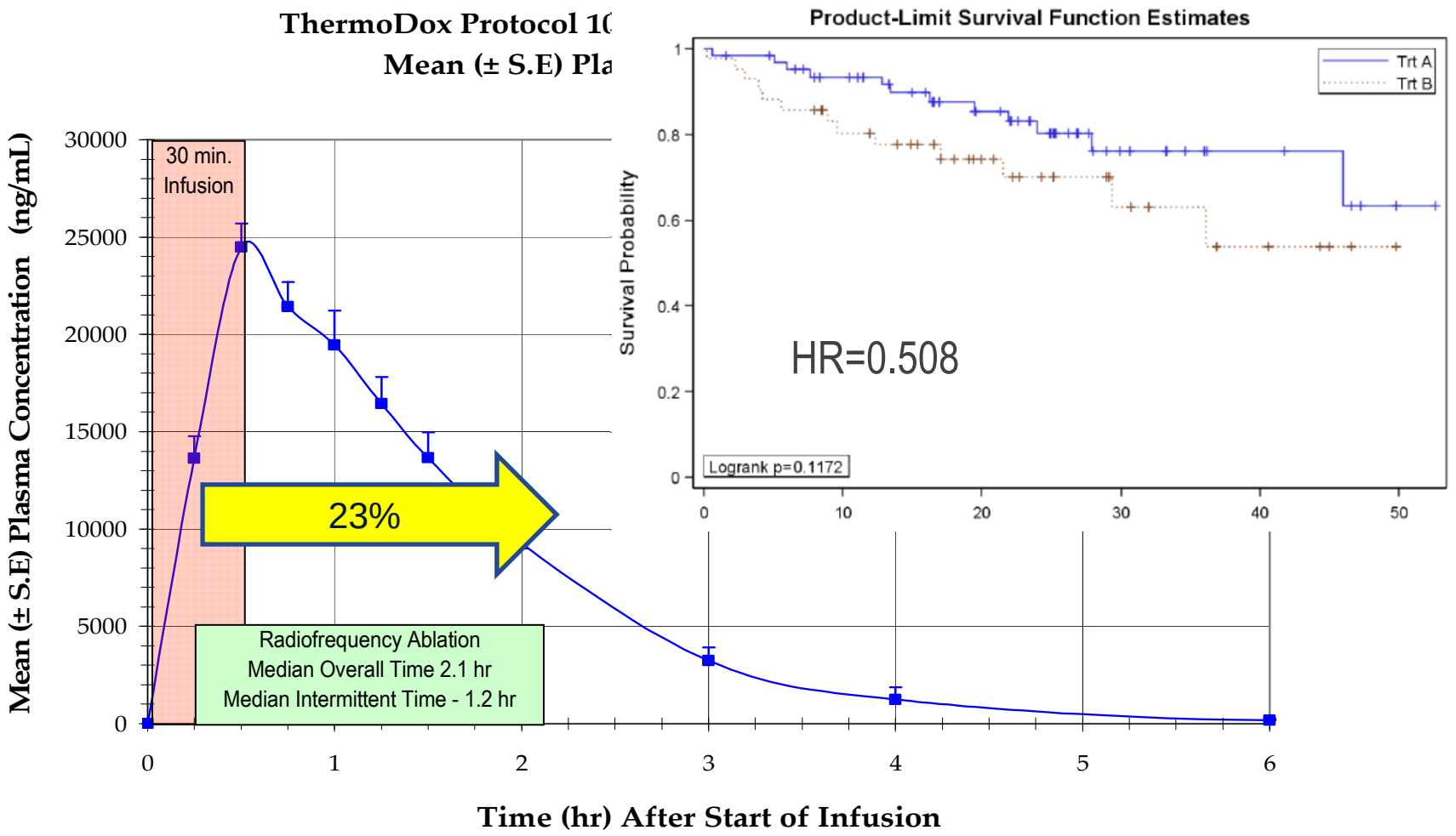


# OS of Patients had RFA > 90 mins (n=105)

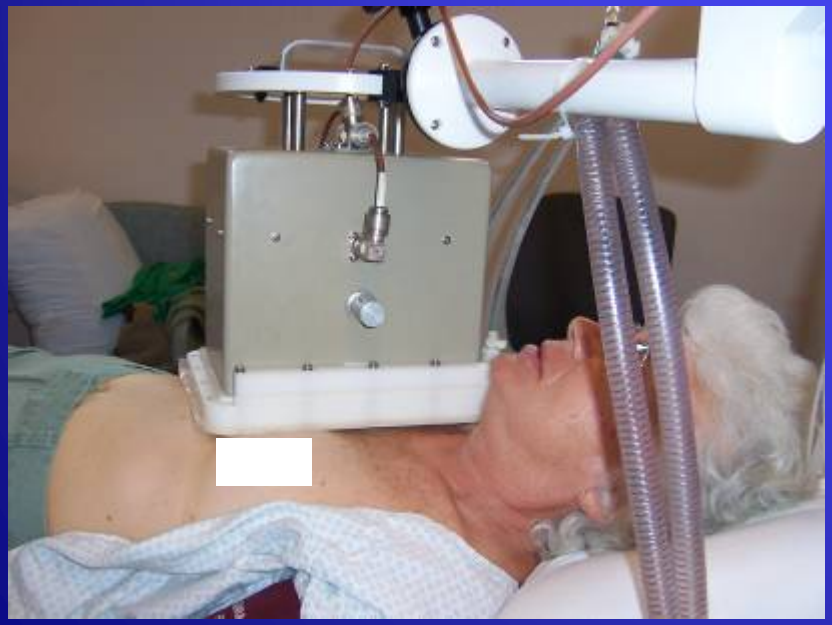


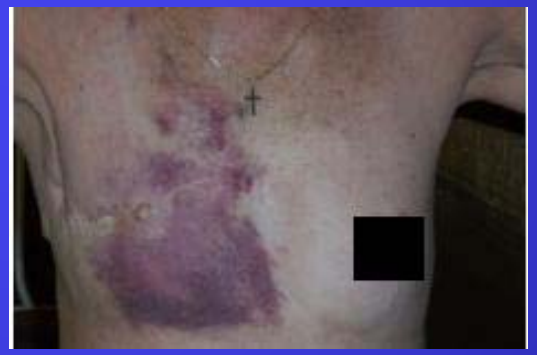
# Next Step – Further Trial?

- Duration of RFA has marked effect on clinical outcome
  - PFS data is supported by OS data
  - Mechanism of ThermoDox is consistent with findings
- ? Design another randomized trial with RFA > 45 mins. in 3-5 cm HCC

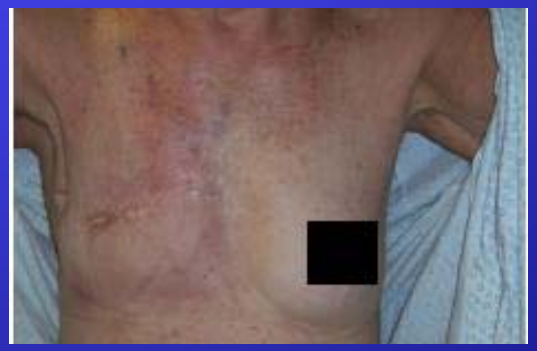
# Other On-going Trials of ThermoDox

- Phase II Study of ThermoDox in colorectal MLC patients
  - 2 arm, randomized, RFA +/- ThermoDox; 88 patients
- Phase II trial of combination of Thermodox with HIFU for HCC
- Phase I/II trial for chest wall recurrence of breast cancer
- Potential use in other cancers e.g. pancreatic cancer, bone cancer





Pre-treatment



Post-treatment

# Conclusions

- Thermosensitive liposome is a novel technology of heat-activated delivery of high concentration of cancer drugs to tumor sites, with potential benefit in combination with thermal therapy
- Topline results of phase 3 trial on Thermodox in combination with RFA did not meet primary endpoint, however, post-hoc data analysis suggest potential benefit of Thermodox in HCC 3 -5 cm with RFA time > 45 min, supporting a new trial to further clarify
- Potential use in other cancers with other encapsulated drugs in combination with heat