Phase 3, Randomized, Double-Blind, Dummy-Controlled, Trial Of Radiofrequency Ablation (RFA) + Lyso-Thermosensitive Liposomal Doxorubicin (LTLD, Thermodox®) For Hepatocellular Carcinoma (HCC) in Lesions 3-7 cm.

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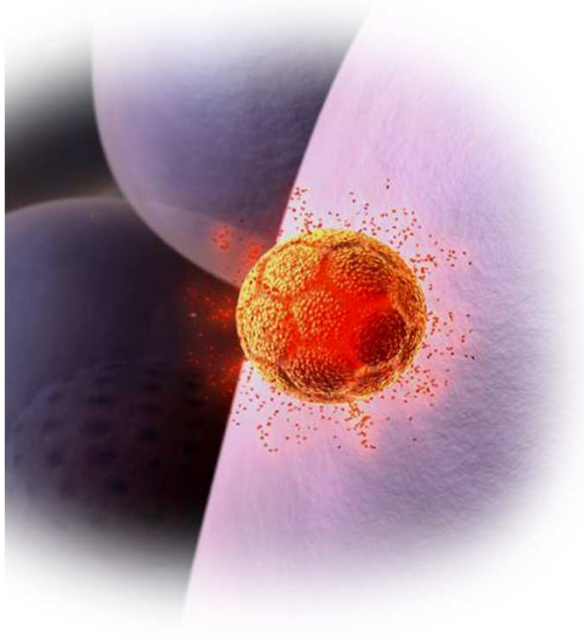
Intermediate Hepatocellular Carcinoma

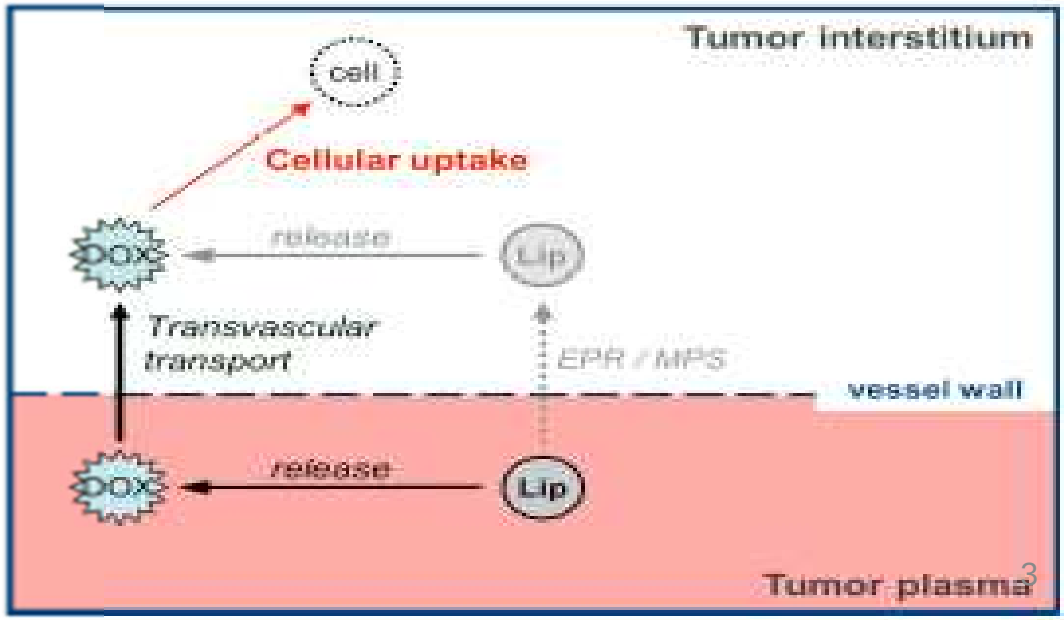
- HCC tumors > 3 cm are incurable
  - Difficult to obtain adequate margin around tumor
- Post-RFA local recurrence rate ≥ 40%
  - Efficacy of RFA influenced by tumor size
  - Large lesions cannot be treated within a single ablation zone
  - Viable tumor cells may be left in margins or clefts of overlapping ablation zones
- Multi-modality approach may be beneficial

Lyso-Thermosensitive Liposomal Doxorubicin (LTLD, ThermoDox®)

- LTLD is a 100 nm nanoparticle which rapidly concentrates in the liver (MPS; **M**ononuclear **P**hagocytic **S**ystem)
- Enhanced uptake by tumor due to EPR

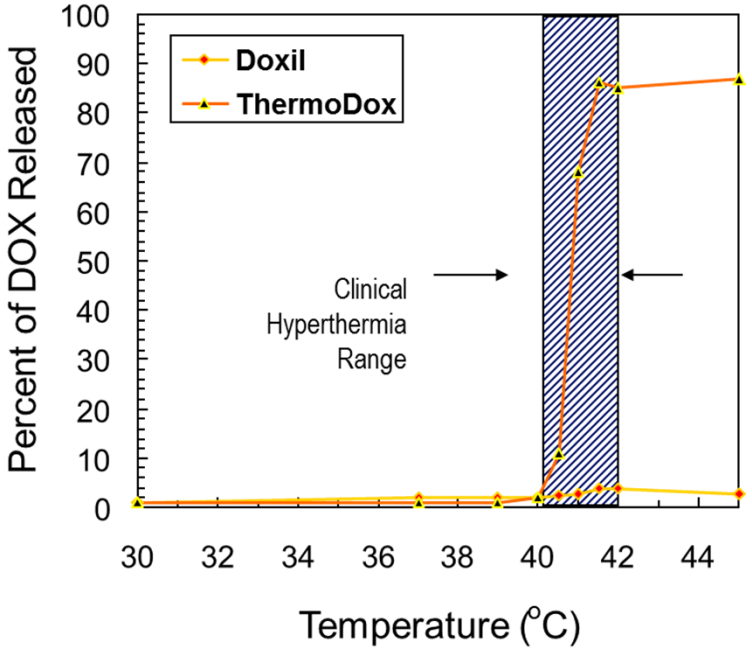
  (**E**nhanced **P**ermeability & **R**etention property of tumors)
- Primary delivery mechanism is attributed to heating > 39.5°C, driving rapid release of high concentrations of cytotoxic doxorubicin, followed by rapid diffusion into local tissue

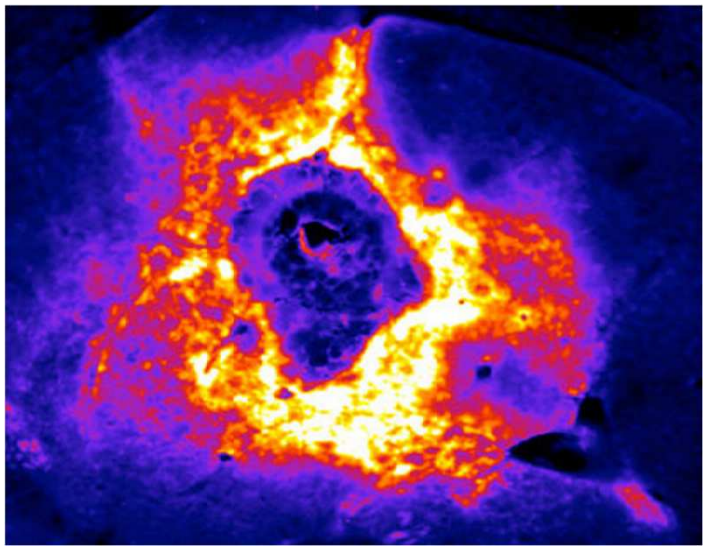




ThermoDox® Design Principles

- Near complete encapsulation of Doxorubicin HCl
- Release of the encapsulated Doxorubicin with mild thermal warming (> 39.5ºC)
- Optimized serum PK to allow the use of heat inducing medical devices to warm the target tumor - initiating a rapid drug release in the targeted tumor vasculature



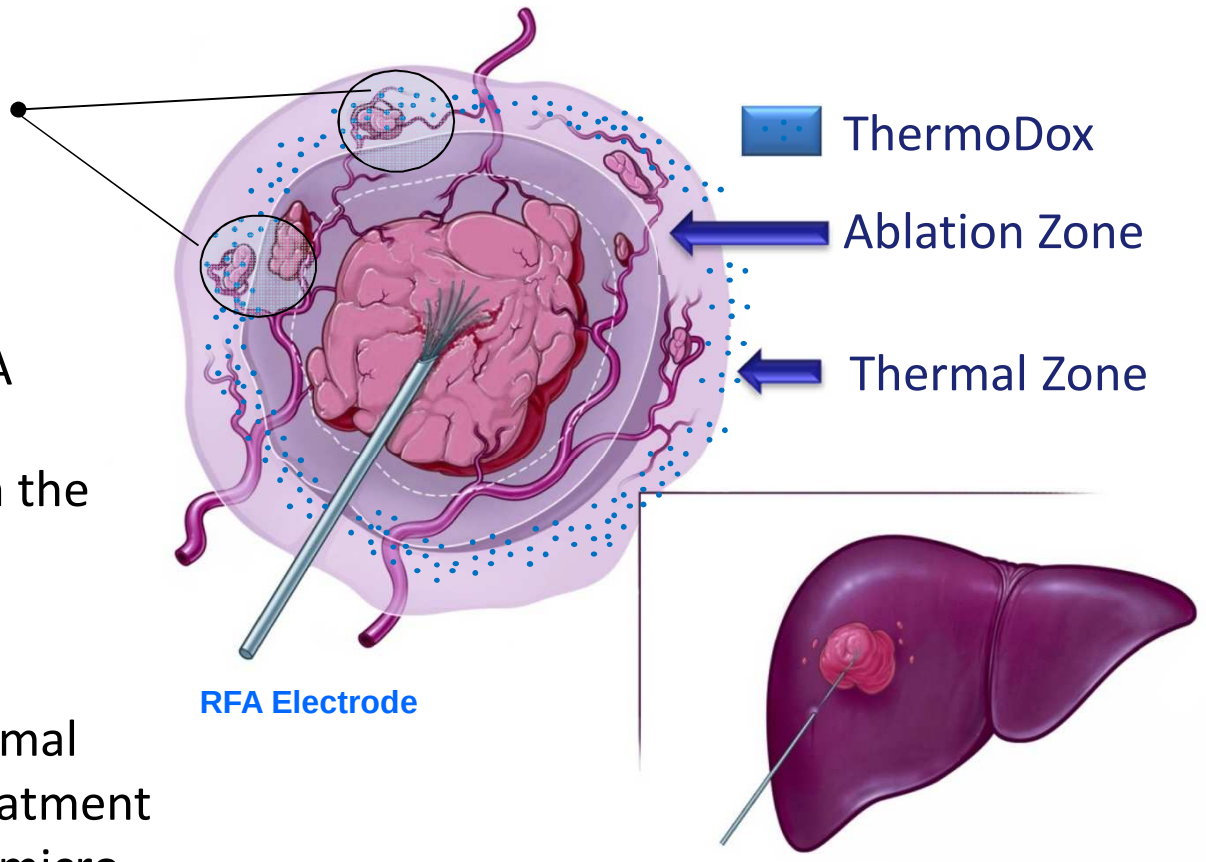


Pig liver single ablation with ThermoDox
Courtesy D. Haemmerich

RF Liver Ablation + ThermoDox

Expanding the Treatment Zone Addresses RFA Limitations

- RFA misses micro-metastases outside ablation zone
- RFA+Thermodox: Infuse Thermodox ~15 min. prior to RFA
- Drug concentrates in the "Thermal Zone"
- Ablation releases doxorubicin in "Thermal Zone" expanding treatment area and destroying micro-metastases



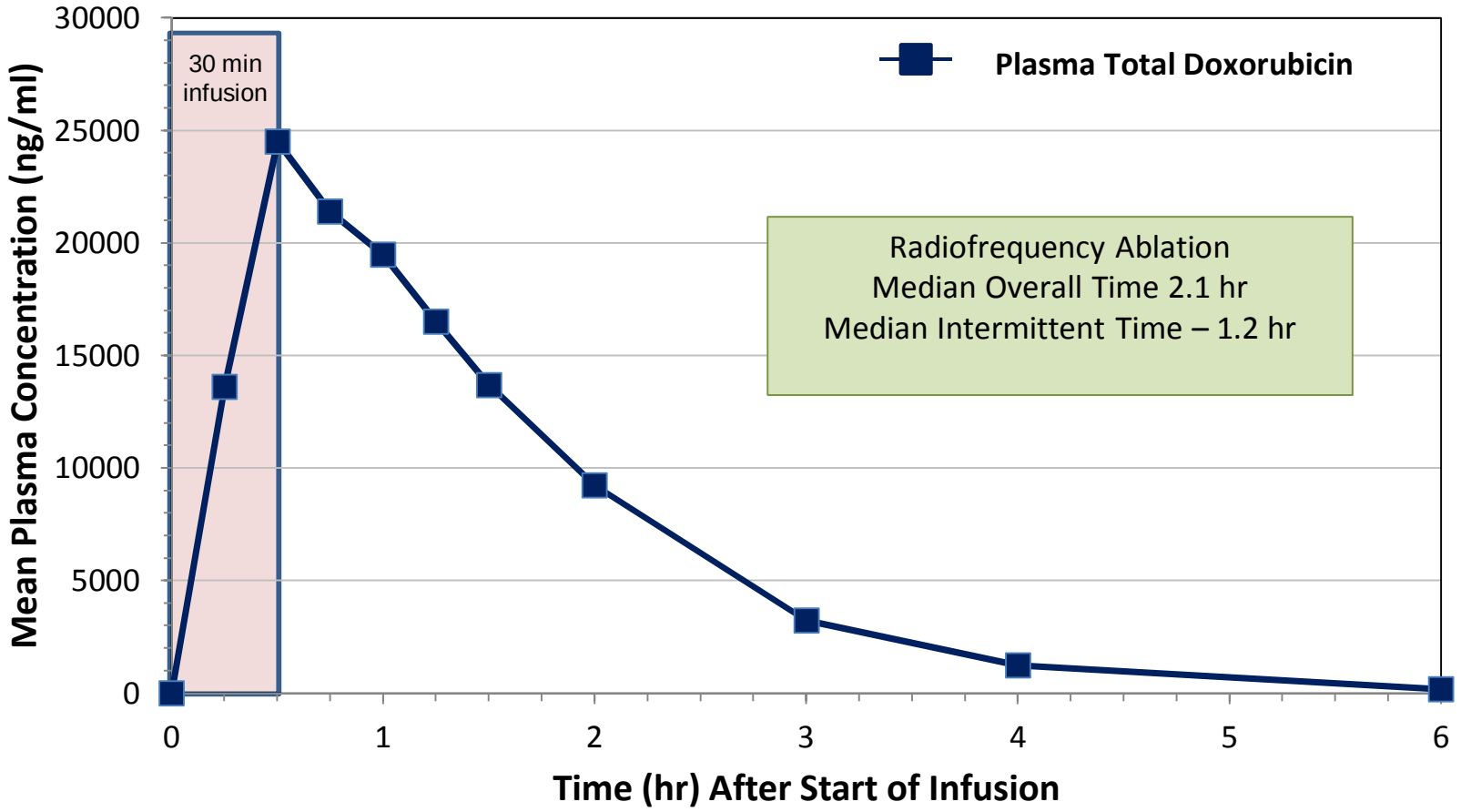
LTLD Previous Studies

- 50 mg/m^2 as MTD as a single dose administration
- Phase I studies demonstrated safety & activity in HCC and MLC (n=37)[1,2,3]
- Dose response relationship
- Safety profile similar to doxorubicin
  - Most important toxicity is neutropenia

[1.] Wood BJ, et al. J Vasc Interv Radiol 2012; 23:248-255
[2.] Poon RT, et al. Expert Opinion 2009;10(2):333-343
[3.] Ravikumar TS, et al. WCIO 2008

ThermoDox Human PK

Protocol 104-03-101: + Liver RFA @ 50 mg/m^2
Mean Plasma Concentrations (n=6)



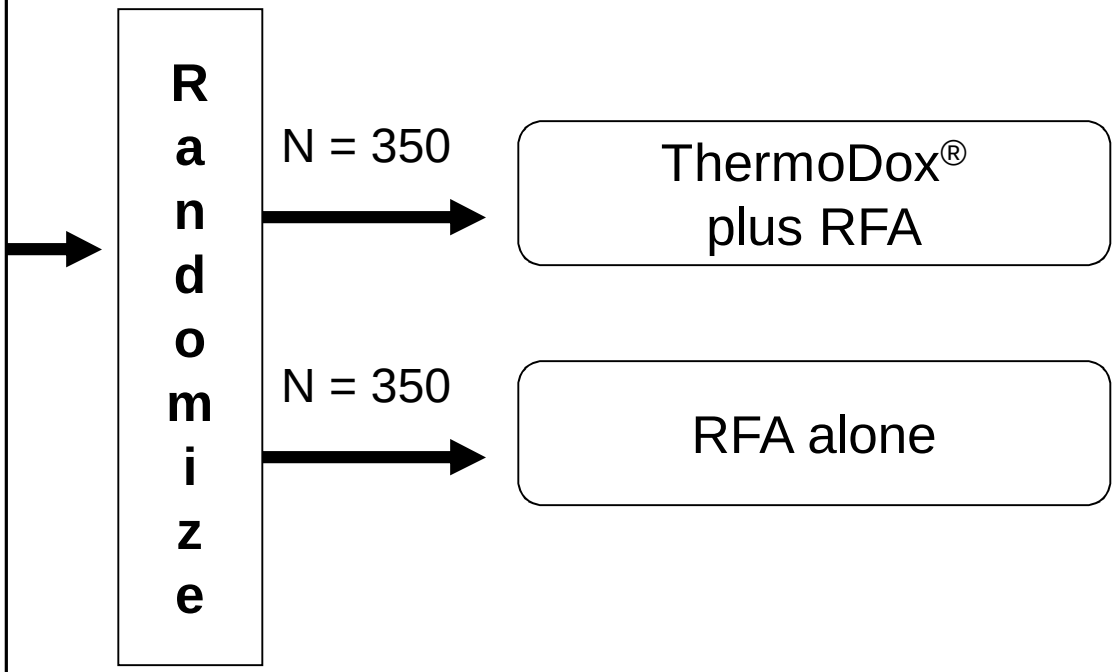
HEAT Study Design

General 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
- RFA technique:
  - open surgical
  - laparoscopic or
  - percutaneous

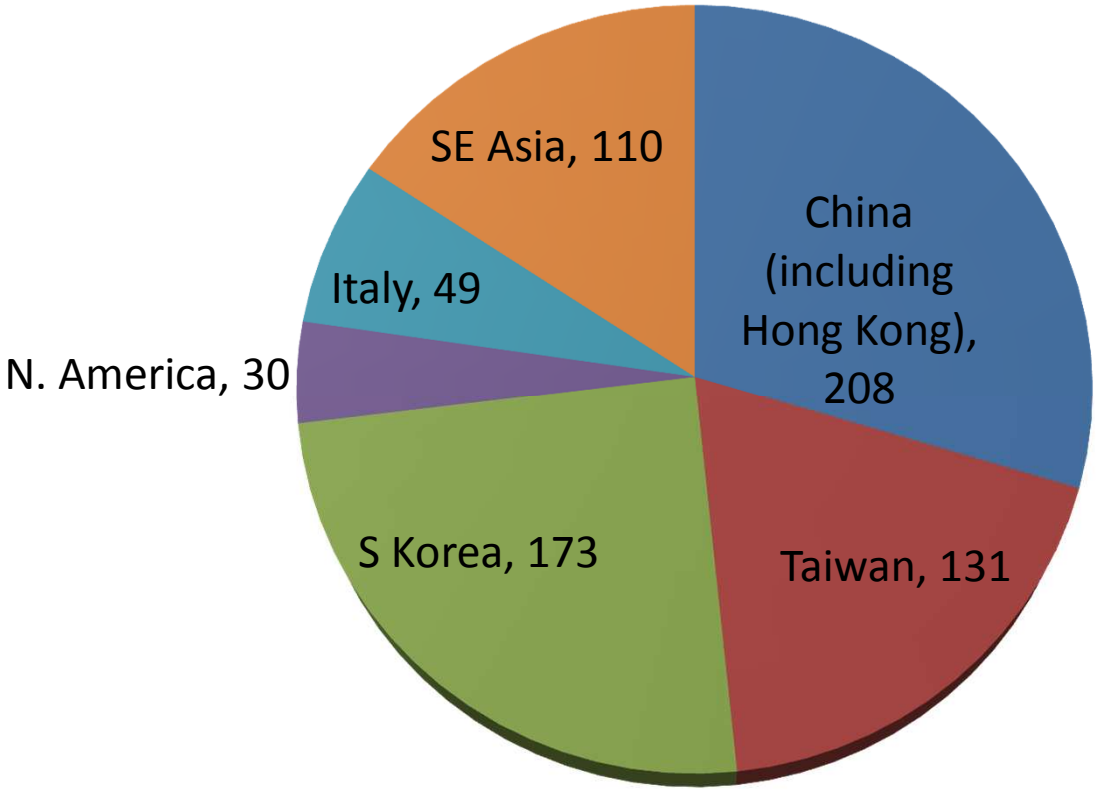


Endpoints

Primary: PFS (Progression Free Survival)
Secondary: OS (Overall Survival), TTLR (Time to Local Recurrence), Safety, PRO (Time to Definite Worsening)

Enrollment By Region

- FPI April, 2008 and LPO May, 2012 (n=701)



HEAT Study Methods

- 30-minute IV infusion of 50 mg/m^2 LTLD or dummy infusion of D5W
- RFA began 15 min. after starting the infusion and was completed within 3 hours
- A single retreatment was allowed for an incomplete initial ablation
- RFA was US FDA approved device and investigator must be experienced and follow general accepted practices of RFA operation
- No minimum ablation times or number of ablation spheres were prescribed in protocol

HEAT Study Endpoints

- Progression-free survival (PFS) was the primary endpoint
- Secondary
  - Time to local recurrence (TTLR)
  - Overall survival (OS) is ongoing
  - Time to definite worsening (PRO)
- Patients Analyzed

Subjects	RFA	RFA + LTLD	Total
Randomized (ITT)	347	354	701
As-Treated	334	343	677

Demographics

Parameter	RFA + LTLD	RFA	Total	p-value
Male	267 (75.4%)	263 (75.8%)	530 (75.6%)	0.9095
Female	87 (24.6%)	84 (24.2%)	171 (24.4%)	
Frequent Age: 60-65	65 (18.4%)	64 (18.4%)	129 (18.4%)	0.9293
Caucasian	42 (11.9%)	26 (7.5%)	68 (9.7%)	0.0505
Black	0	0	0	
Asian	312 (88.1%)	321 (92.5%)	633 (90.3%)	
Japanese	8 (2.3%)	11 (3.2%)	19 (2.7%)	
Korean	83 (23.4%)	91 (26.2%)	174 (24.8%)	
Taiwanese	66 (18.6%)	62 (17.9%)	128 (18.3%)	
Chinese	115 (32.5%)	125 (36.0%)	240 (34.2%)	
Other	40 (11.3%)	32 (9.2%)	72 (10.3%)	

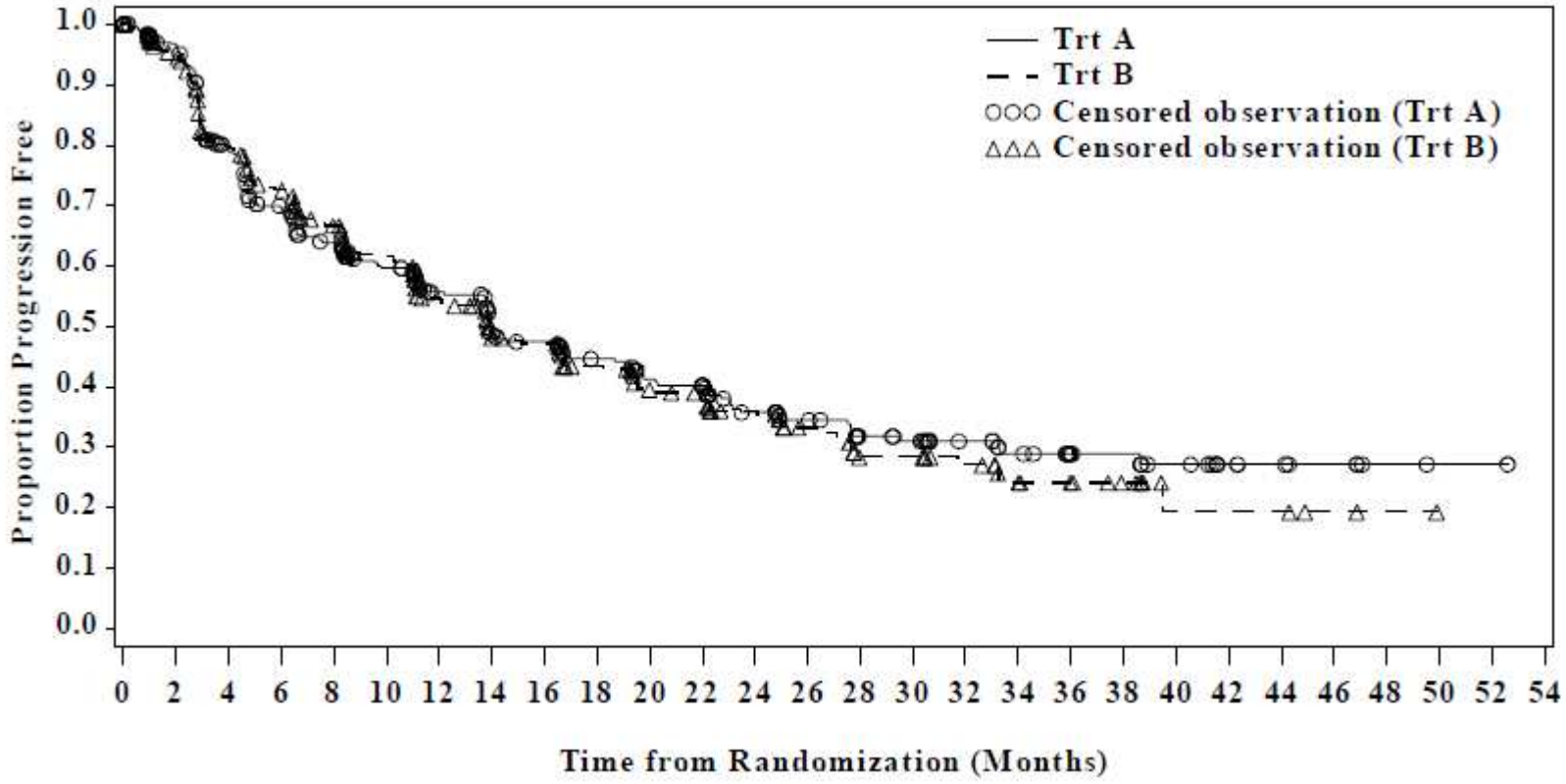
Lesion Characteristics

Parameter	RFA + LTLD	RFA	Total	P-value
Largest Lesion Stratification Level				
3.0 - 5.0 cm	109 (85.2%)	111 (88.8%)	220 (87.0%)	0.3896
>5.0 - 7.0 cm	19 (14.8%)	14 (11.2%)	33 (13.0%)	
Number of Target Lesions at Initial Treatment				
1	83 (64.8%)	79 (63.2%)	162 (64.0%)	0.4927
2	29 (22.7%)	28 (22.4%)	57 (22.5%)	
3	8 (6.3%)	14 (11.2%)	22 (8.7%)	
4	2 (1.6%)	4 (3.2%)	6 (2.4%)	
5	1 (0.8%)	0	1 (0.4%)	
Missing	5 (3.9%)	0	5 (2.0%)	

Events in Progression Free Survival

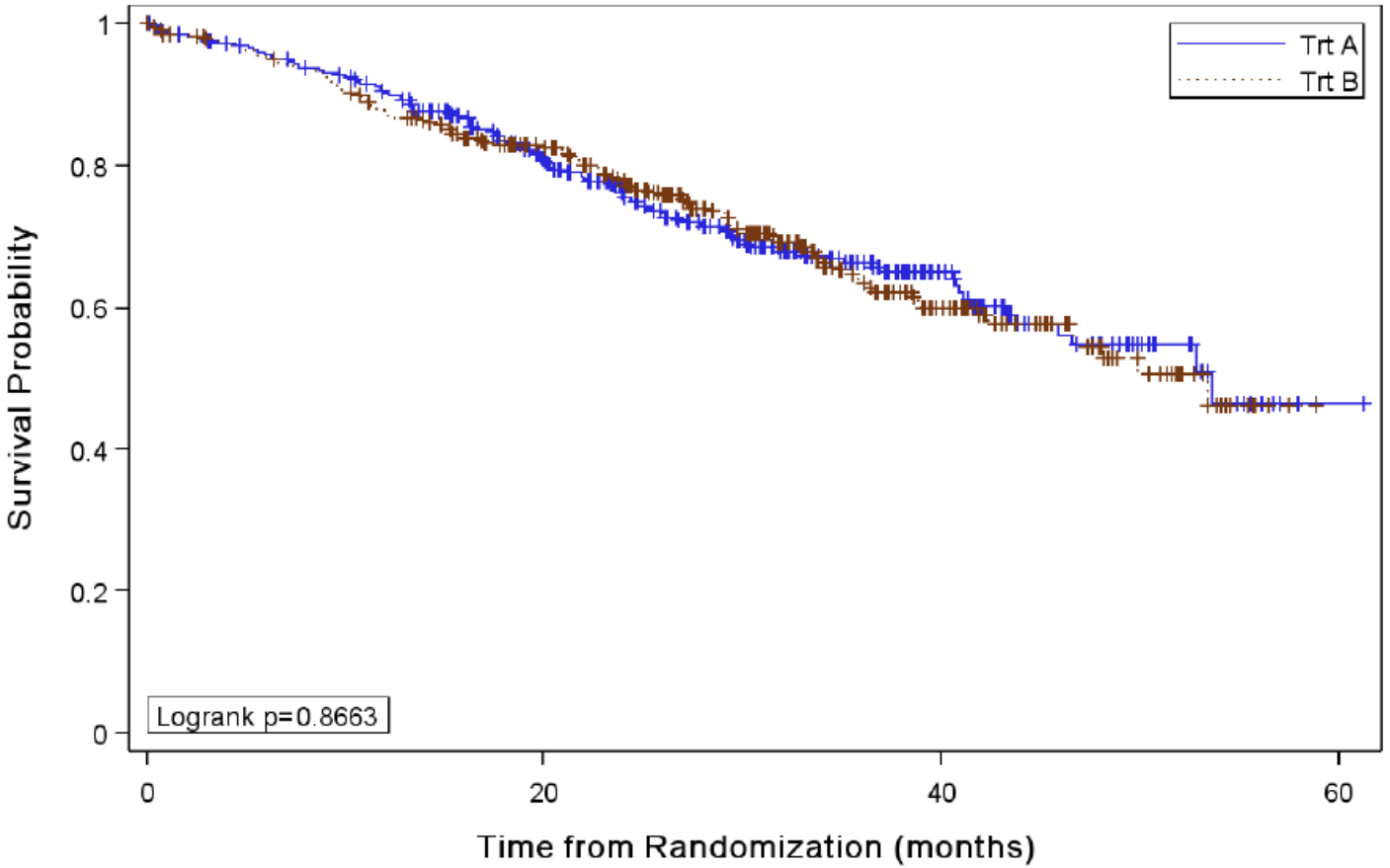
Type of Progression (Events)	RFA + TDox (n=185)	RFA (n=186)	Total (n=371)
Local Recurrence	41 (22.2%)	37 (19.9%)	78 (21%)
Distal Intrahepatic	78 (42.2%)	95 (51.1%)	173 (46.6%)
Extrahepatic	13 (7.0%)	10 (5.4%)	23 (6.2%)
Combination	7 (3.8%)	8 (4.3%)	15 (4.0%)
Death	17 (9.2%)	17 (9.1%)	34 (9.2%)
Treatment Failure	29 (15.7%)	19 (10.2%)	48 (12.9%)

Progression Free Survival



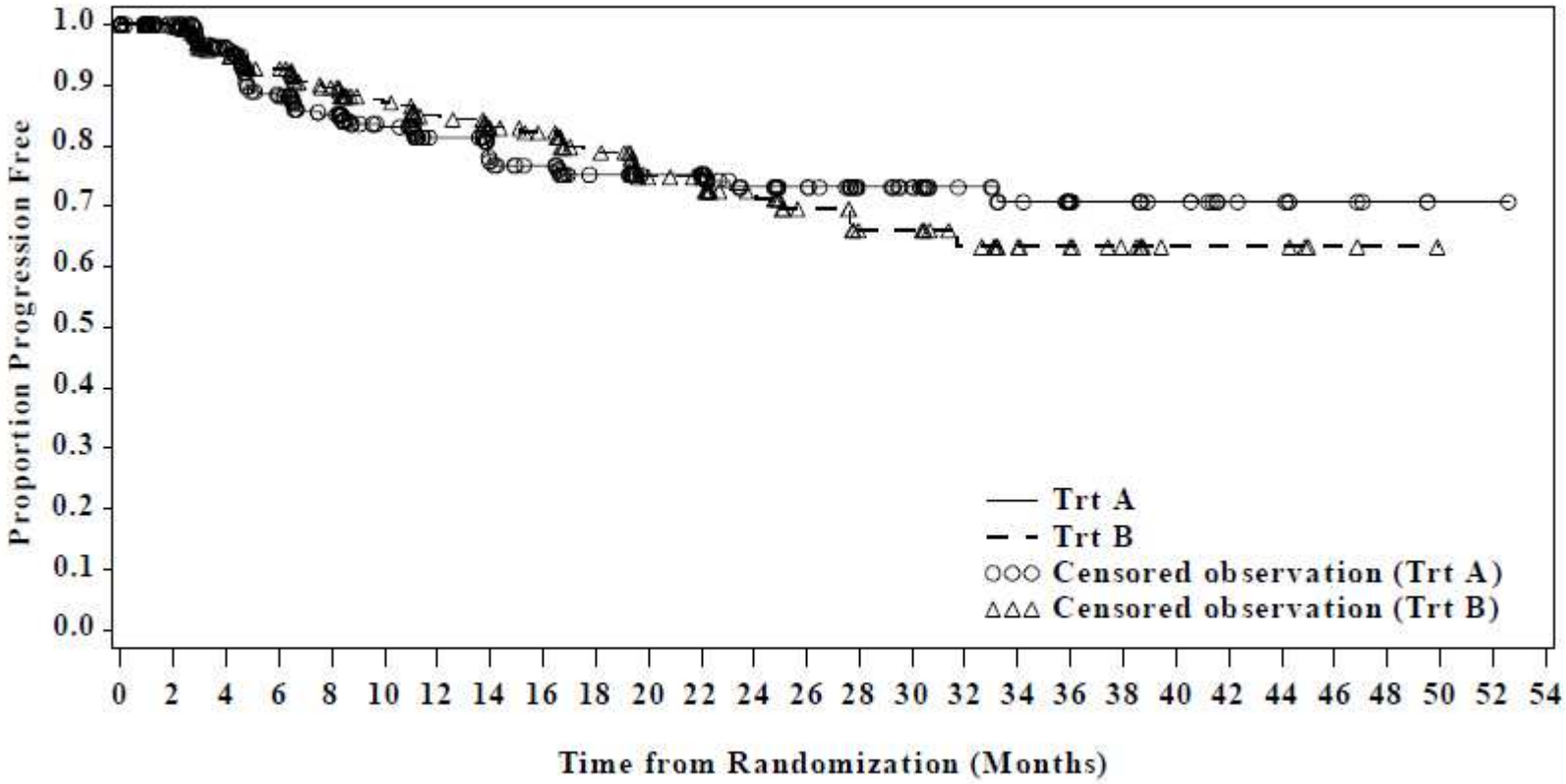
Median Time to Progression RFA + TDox:	13.97 mos.
RFA Alone:	13.87 mos.
Hazard Ratio (Trt A/Trt B):	0.957 (CI 0.780, 1.170)

Overall Survival



Median Time to OS event RFA + TDox:	**53.66 mos.**
RFA Alone:	**53.40 mos.**
Hazard Ratio (Trt A/Trt B):	**1.011 (CI 0.761, 1.286)**

Time to Local Recurrence



Summary

Patients Still Being Followed for OS

	RFA	RFA + LTLD	p-Value
Number Randomized	347	354	
As-Treated Population	334	343	
Safety			
Subjects AE ≥ Gr 3			
- Any (n,%)	101, 30.2	224, 65.3	0.00
- Neutropenia (n,%)	7, 2.1	161, 46.9	0.00
- Thrombocytopenia (n,%)	7, 2.1	18, 5.2	0.04
- Anemia (n,%)	2, 0.6	6, 1.7	0.28
- CHF (n,%)	1, 0.3	0, 0.0	0.49
Efficacy			
- Median PFS (95% CI) [mos]	13.9 (11.1-16.7)	14.0 (11.5-19.3)	0.68

Patient Disposition & Treatment

Reason For Discontinuation	RFA + TDox (n=354)	RFA (n=347)	Total (n=701)
Disease Progression	167 (47%)	192 (55%)	359 (51%)
Death prior to progression	15 (4.2%)	13 (3.7%)	28 (4.0%)
Withdrawn Consent	21 (5.9%)	8 (2.3%)	29 (4.1%)
AE or Medical Condition	12 (3.4%)	10 (2.9%)	22 (3.1%)
Prohibited Medications	11 (3.1%)	3 (0.9%)	14 (2.0%)
Liver Transplant or Resection	1 (0.3%)	2 (0.6%)	3 (0.4%)
Failure to Comply with Protocol	11 (3.1%)	11 (3.2%)	22 (3.1%)
Treatment Failure	6 (1.7%)	6 (1.7%)	12 (1.7%)

Subsequent Non-Study Treatment

	RFA + TDox (n=354)	RFA (n=347)	Total (n=701)
TACE	51 (14.4%)	76 (21.9%)	127 (18.1%)
RFA	83 (23.4%)	82 (23.6%)	165 (23.5%)
Surgery	5 (1.4%)	6 (1.7%)	11 (1.6%)
Liver Transplant	1 (0.3%)	4 (1.2%)	5 (0.7%)
Other Procedure	17 (4.8%)	8 (2.3%)	25 (3.6%)
Systemic Therapies	7 (2.0%)	11 (3.2%)	18 (2.6%)
TOTAL:	152 (42.9%)	173 (49.9%)	325 (46.4%)

Adverse Event Summary

	RFA/TDox (n=343)			RFA (n=334)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
All AE's	327	87	129	301	85	10
GI	164	10	2	170	11	3
- abd pain	97	1	0	108	3	0
- nausea	54	0	0	43	0	0
- vomiting	35	0	0	28	0	0
General	106	4	0	133	4	1
- pyrexia	57	1	0	100	2	0
Blood	191	42	111	27	6	3
- neutropen	143	34	95	6	2	1
- leukopenia	92	38	24	5	1	0
- thrombocy	18	8	1	2	0	0

Adverse Event Summary (cont)

	RFA/Tdox (n=343)			RFA (n=334)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
All AE's	327	87	129	301	85	10
Procedural	80	5	2	88	4	0
- pain	29	2	0	40	1	0
- wound cm	34	2	0	34	1	0
Skin	183	13	0	18	0	0
- alopecia	173	13	0	2	0	0

Treatment-Emergent AE Resulting in Deaths

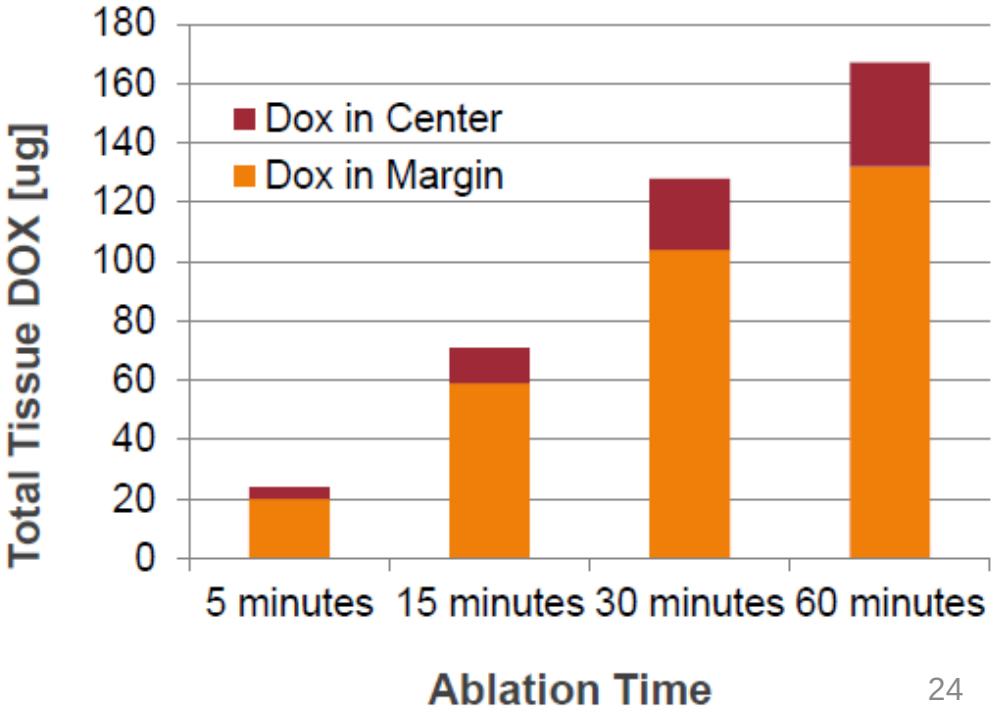
	RFA/TDox (n=343)	RFA (n=334)
All Treatment Deaths*	8	6
- Abdominal Haemorrhage	3	2
- Haematemesis	1	
- Portal Hypertensive Gastropathy		1
- Multi-Organ Failure		1
- Chronic Obstructive Pulmonary Dis		1
- Aspiration		1
- Septic Shock	1	1
- Abdominal Infection		1
- Liver Failure	2	1
- Cerebral Ischemia		1
- Myocardial Infarction	1	

* Patient may have experienced more than one event

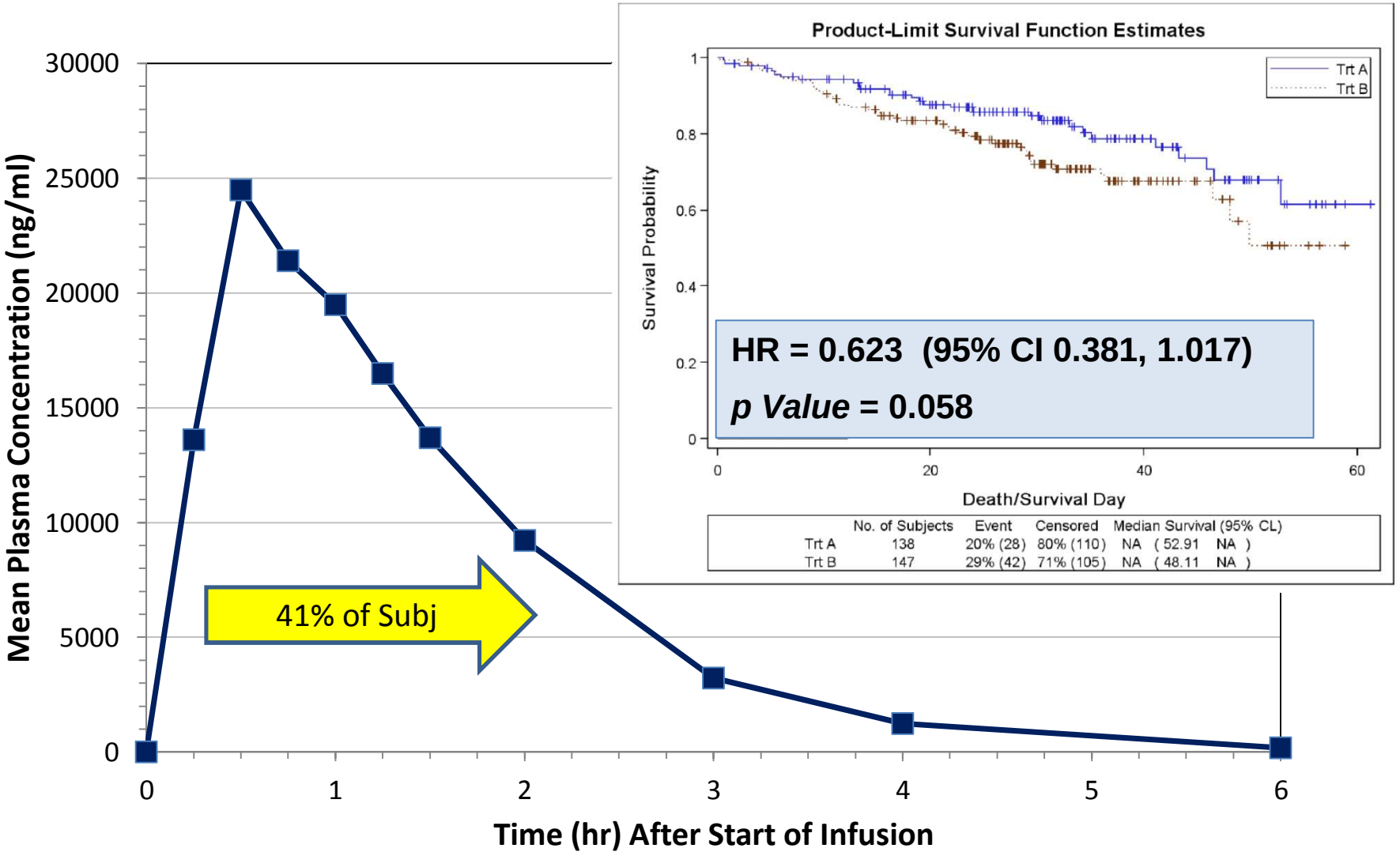
Post Hoc Analysis

- Ablation time or strategy was not mandated in HEAT Study
  - High degree of variability exists with ablation cycles (burns) and treatment time by lesion size

- Recent simulation studies show that prolonged heating is required in order to achieve optimal tissue concentrations of doxorubicin



OS of Patients with RFA ≥ 45 mins (n=285)



Duration of RFA May Have Marked Effect on Clinical Outcome with ThermoDox

		# of Pts	Deaths		HR	
< 45 mins	RFA + TDox	96	29	30%		
	RFA Only	71	27	38%		
		167	56		1.139	
> 45 mins						
< 90 mins	RFA + TDox	76	14	18%		
	RFA Only	105	27	26%		
		181	41		0.585	
> 90 mins	RFA + TDox	62	14	23%		
	RFA Only	42	15	36%		
		104	29		0.584	
> 45 mins	RFA + TDox	138	28	20%		
	RFA Only	147	42	29%		
		285	70		0.623	p = 0.058

Conclusion

- RFA with ThermoDox is safe, with reversible myelotoxicity
  - Safety profile similar to doxorubicin
- The HEAT Study did not show a benefit in the primary endpoint of PFS
  - OS data, a secondary endpoint has not matured
- Post hoc analysis suggests patients showed improvement when RFA treatment time ≥ 45 mins
- Additional prospective studies are being planned
  - Patients with single lesions with optimized RFA may be best target

HEAT Investigators

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Appreciation

Dedicated to the 701 patients and their families who selflessly volunteered for the HEAT Study during a most difficult period in their lives.