Research and Development
R&D Day

Down Town Association

New York, NY

October 12, 2017

Michael Tardugno

Chairman of the Board, President and Chief Executive Officer

R&D Day

Celsion

Safe Harbor Statement

Except for historical information, the statements made in this presentation are forward-looking statements involving significant risks and uncertainties.

These risks and uncertainties, including those related to the future financial position and business strategy of the Company, are detailed in the Company's filings with the Securities and Exchange Commission.

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Agenda and Speakers

ThermoDox - Targeted Chemotherapy

OPTIMA Study: Thesis and Design

Nicholas Borys, M.D., Senior Vice President and Chief Medical Officer, Celsion Corporation

Cases from The HEAT Study

Won Young Tak, M.D., Ph.D. Professor Internal Medicine, GI & Hepatology, Kyungpook National University Hospital Daegu, Republic of Korea

Clinical Experience with RFA + ThermoDox for HCC

Stephen N. Wong, M.D. Principal Investigator OPTIMA, Chinese General Hospital, Philippines

Options for Local-Ablative Treatment of Large HCC

Robert M. Eisele, M.D. Deputy Head of Department, Dept. of General, Visceral, Vascular and Pediatric Surgery, Medical Faculty University of Saarland, Homburg, Germany

Panel Discussion Q & A

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Agenda and Speakers

Gen-1: IL-12 DNA Immunotherapy

Science of TheraPlas and IL-12

Khursheed Anwer, Ph.D. Executive Vice President and Chief Scientific Officer, Celsion Corporation

OVATION Study: Design, Thesis and Clinical Results

Premal H. Thaker, M.D. Associate Professor in Gynecologic Oncology, Washington University School of Medicine

Translational Data & Novel Combination Immunotherapy Concepts

Richard C. Koya, M.D., Ph.D. Associate Professor of Oncology and Immunology, Director of the Vector Development & Production Facility, Associate Director of the Center for Immunotherapy, Roswell Park Cancer Institute, Center for Immunotherapy

Panel Discussion Q & A

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Today's Messages

- We are developing proprietary Drug Technologies that deliver known cancer treatments better and more effectively
- The Science behind our two clinical stage Drug Candidates is sound, if not incomparable. The evidence is clear: the mechanisms have been validated on the bench and in the clinic… our drugs work
- The Clinical Data supporting our studies is without question. Challenged, tested, and peer reviewed published, our findings suggest transformational potential for patients and the medical community
- Our Research targets specific cancers of high incidence, typically in first line, where treatment options are limited. Where the potential return – in terms of health and wealth -- is greatest

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Oncology Company

Two Clinical Stage Nanoparticle-Based Platforms

LTSL

Lysolipid Thermally
Sensitive Liposomes
Known Chemotherapeutics

TheraPlas

Synthetic Non-viral Vector
DNA Plasmids coded for
Therapeutic Proteins

ThermoDox®

Targeted Doxorubicin Delivery

- Phase III Study Enrolling in HCC
- Phase II Study in RCW Breast Cancer

GEN-1

Localized IL-12 Immunotherapy

- Neoadjuvant Study in 1st Line Ovarian
- Phase II Ready

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Pipeline of Targeting Therapeutics

Capital Efficient Drug Development

	INDICATION	PRODUCT CANDIDATE	PRE-CLINICAL	PHASE 1-2	PHASE 3
Clinical	Primary Liver Cancer	ThermoDox/OPTIMA Study			Phase III Enrolling
Clinical	Ovarian Cancer	GEN-1/OVATION Study		Phase I Complete	
Pre-Clinical	NMI Bladder Cancer	ThermoDox		Efficacy/Safety/Toxicology Complete	
Pre-Clinical	Glioblastoma	GEN-1		Efficacy/Safety/Toxicology Complete	

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Hepatocellular Carcinoma

Large and Deadly Global Cancer

- **5th most prevalent**
  - 850,000 global incidence growing 5% annually
  - By 2030, expected to be the #3 cancer
  - China has 50% of new cases; 75% in Asia
- **4th highest mortality**
  - 5-year survival rate less than 10%
  - Median survival from time of diagnosis is less than 3 years[1]
  - Curative surgery in less than 20% of patients
- **Local therapies include:**
  - RFA, TACE and radiation
  - RFA is the dominant treatment with local recurrence rates >50% for lesions >3 cm
  - ThermoDox + RFA addresses limitations of current standard of care by **"Expanding the Treatment Zone"**

Addressable Market Opportunity >200K Patients

[1] *Journal of Hepatology 2012 vol. 56 | 908-943*

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Ovarian Cancer

Global Cancer of High Unmet Need

- **8th most diagnosed cancer among women**
  - 225,000 annual incidence worldwide
  - 22,280 in US and 100,000 in developed countries
  - 14,240 deaths in 2015
- **5th highest mortality among women**
  - 5-year survival rate for all stages is >50%
  - Survival rate reduces dramatically if not localized cancer
  - 15% diagnosed with localized cancer, eligible for potentially curative surgery
- **Local therapies for ovarian cancer**
  - Ovarian cancer is not diagnosed early - spreads to regionally requiring combo regimens
  - Most common recurrence in abdomen–importance of intra-peritoneal administered therapy
  - GEN-1 administered IP; **ideal adjuvant to SoC** therapy

Addressable Market Opportunity >100K Patients

Sources: Cancer Statistics, American Cancer Society; Globocan; SEER database

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Nicholas Borys, M.D.

Senior Vice President and
Chief Medical Officer

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ThermoDox - Targeted Chemotherapy

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Randomized Clinical Trials *

Aimed to Change the Standard of Care In HCC Management

Indication	Randomized studies	2017 UPDATE
Adjuvant	1. Sorafenib *vs.* placebo	FAILED
Intermediate HCC	1. Chemoembolization ± sorafenib	HALTED
	2. Chemoembolization ± brivanib	FAILED
	3. Chemoembolization ± everolimus	N/A
Advanced HCC		
First line	1. Sorafenib ± erlotinib	FAILED
	2. Sorafenib *vs.* brivanib	FAILED
	3. Sorafenib *vs.* sunitinib*	FAILED
	4. Sorafenib *vs.* linifanib**	FAILED
	5. Sorafenib ± Yttrium-90	FAILED
	6. Sorafenib ± doxorubicin	HALTED
Second line	1. Brivanib *vs.* placebo**	FAILED
	2. Everolimus *vs.* placebo	FAILED
	3. Ramucirumab *vs.* placebo	FAILED

* Llovet JM, Ducreux M, Lencioni R, et al. J Hepatol 2012;56:908-943

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Only 8 of 68 Indications Show Survival QOL Benefit

thebmj

BMJ 2017;359:j4530 doi: 10.1136/bmj.j4530 (Published 2017 October 03)

RESEARCH

Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13

Courtney Davis *senior lecturer*[1], Huseyin Naci *assistant professor of health policy*[2], Evrim Gurpinar *MSc candidate in international health policy*[2], Elita Poplavska *assistant professor*[3], Ashlyn Pinto *MSc candidate in global health*[2], Ajay Aggarwal *academic clinical oncologist*[4 5]

[1]Department of Global Health and Social Medicine, King's College London, London WC2R 2LS, UK; [2]LSE Health, Department of Health Policy, London School of Economics and Political Science, London, UK; [3]Faculty of Pharmacy, Riga Stradins University, Riga, Latvia; [4]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK; [5]Institute of Cancer Policy, King's College

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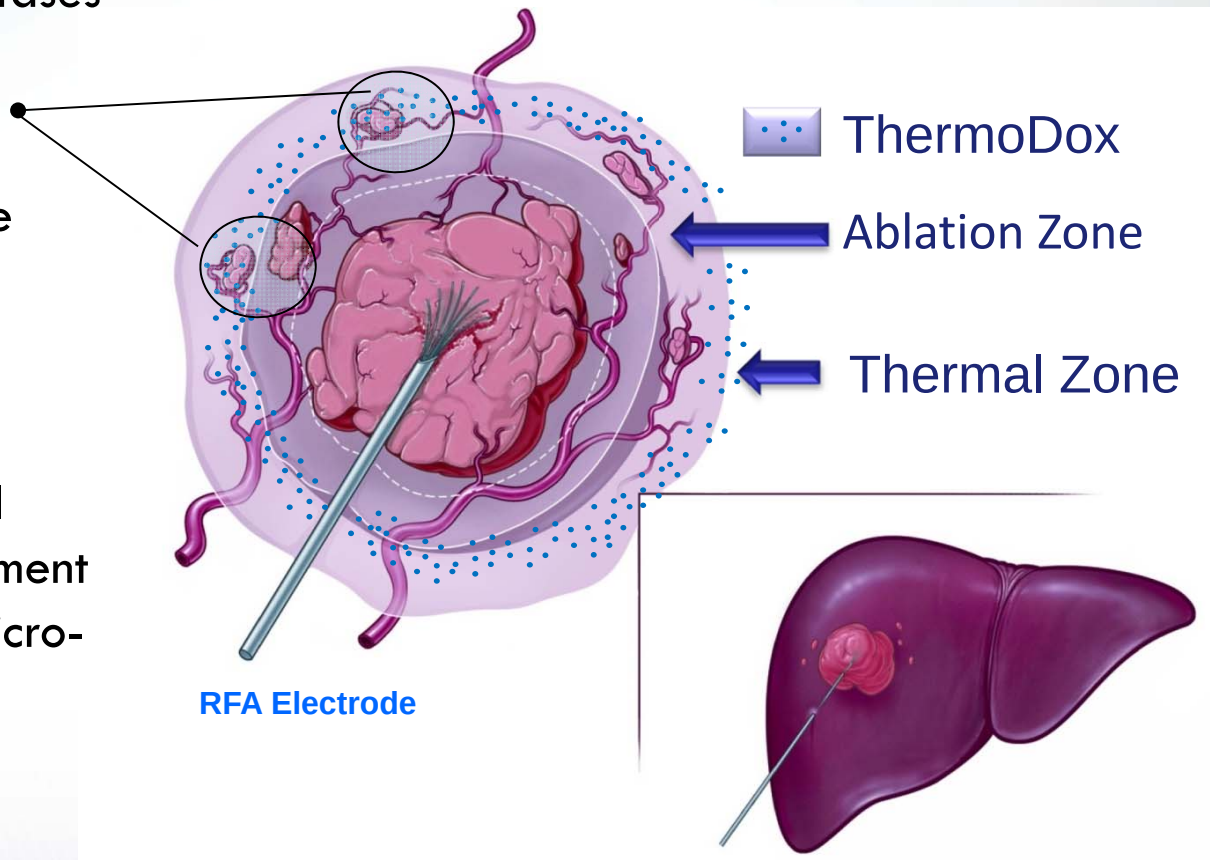
ThermoDox + Liver Ablation

- RFA misses micro-metastases outside ablation zone
- Drug concentrates in the "Thermal Zone"
- Ablation releases doxorubicin in "Thermal Zone" expanding treatment area and destroying micro-metastases



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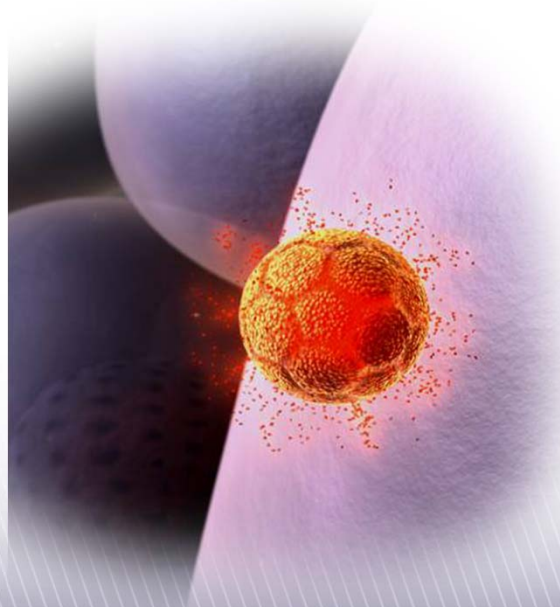
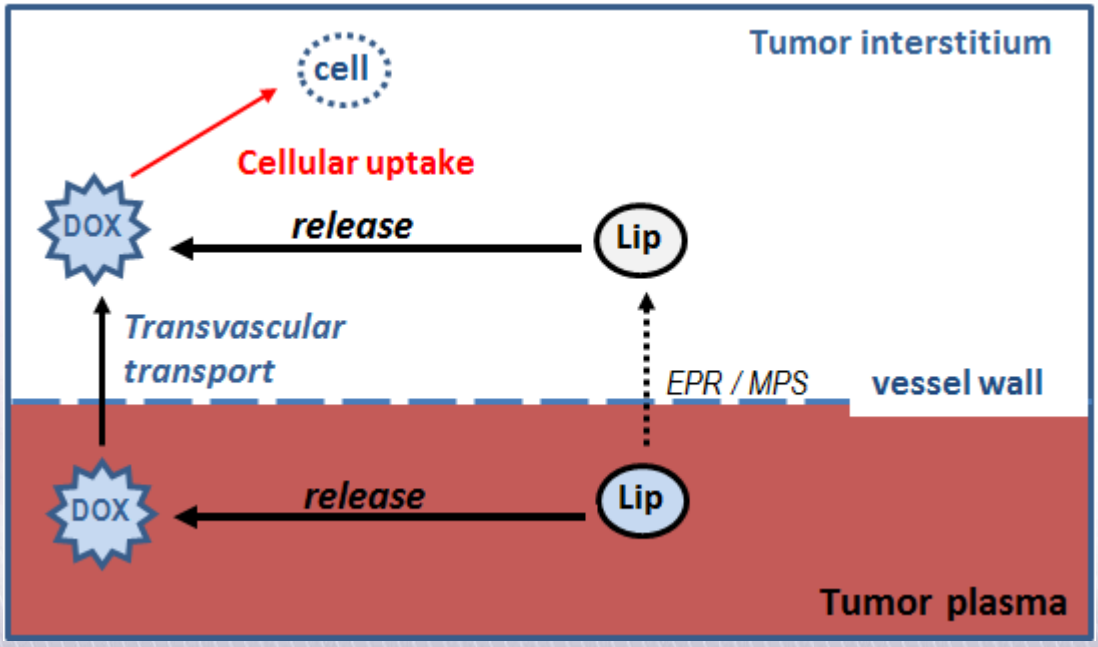
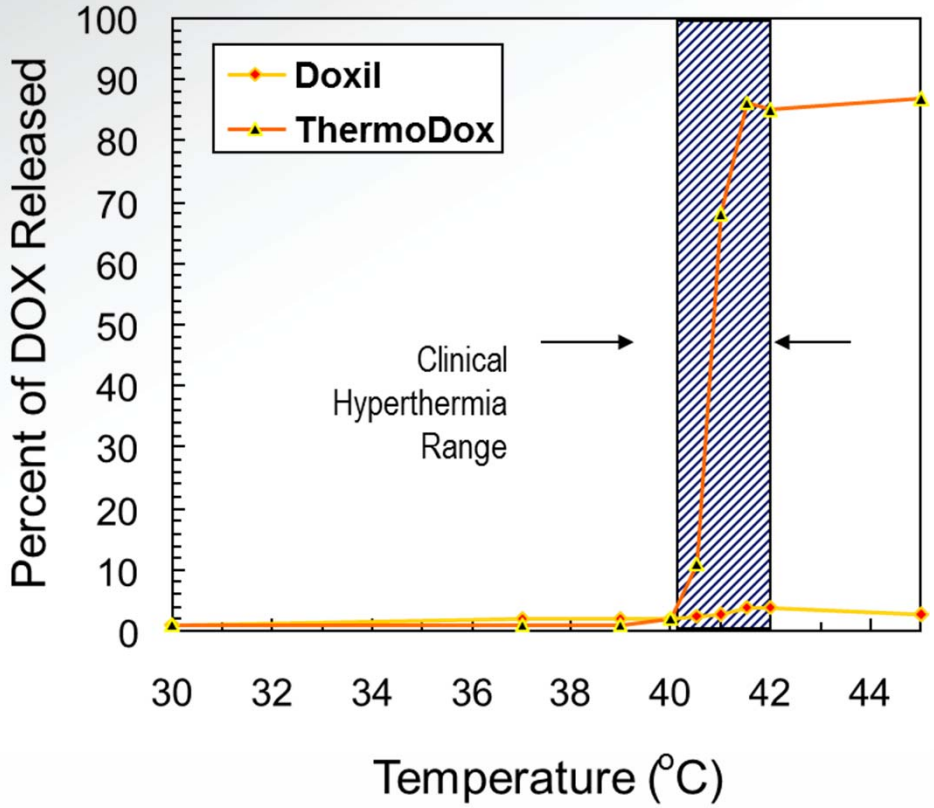
ThermoDox's Mechanism of Action

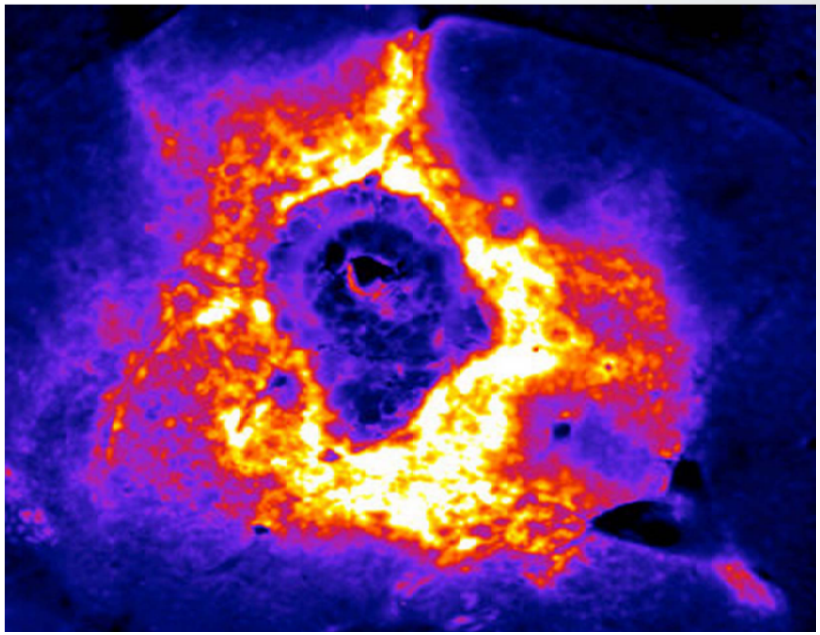
- Nanoparticle (100nm) which rapidly concentrates in the liver (MPS; Mononuclear Phagocytic System)
- Enhanced uptake by tumor due to EPR (Enhanced Permeability & Retention property of tumors)
- Rapid Diffusion of cytotoxic doxorubicin into local tissue follows from heating targeted area > 40°C





ThermoDox Design Principles In Action





Pig liver single ablation with ThermoDox
Courtesy D. Haemmerich

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Key Points

- Heat activated chemotherapy (ThermoDox) can improve the outcome of RFA
  - Focuses activity of cytotoxic activity at site of high recurrence
  - Combination activates immune response

- Can change standard of practice
  - Introduces a multimodality approach
  - Challenge surgery and palliative approaches

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HEAT Study Manuscript

Phase III HEAT Study Adding Lyso-Thermosensitive Liposomal Doxorubicin to Radiofrequency Ablation in Patients With Unresectable Hepatocellular Carcinoma Lesions

Won Young Tak*[1], Shi-Ming Lin[2], Yijun Wang[3], Jiancheng Zheng[4], Aldo Vecchione[5], Soo Young Park[1], Min Hua Chen[6], Stephen Wong[7], Huocai Xu[8], Cheng-Yuan Peng[9], Yi-You Chiou[10], Guan-Tarn Huang[11], Jianqiang Cai[12], Basri Johan Jeet Abdullah[13], June Sung Lee[14], Jae Young Lee[15], Jong-Young Choi[16], Julieta Lopez-Cervantes[17], Morris Sherman[18], Richard S. Finn[19], Masao Omata[20], Michael O'Neal[21], Lukas Makris[22], Nicholas Borys[23], Ronnie Poon[24], Riccardo Lencioni[25]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea.
[2]Chang Gung Memorial Hospital – Linkou, Taoyuan, Taiwan.
[3]Third Central Hospital of Tianjin, Tianjin, China.

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Key Points of HEAT Study Paper

- Large well controlled study in patients with intermediate size HCC (up to 4 lesions 3-7 cm)
  - Primary endpoint of PFS or OS was not met
  - Showed that RFA and adjuvant treatment is safe and feasible
  - Set a data standard: new role for RFA
- Subgroup analysis
  - Patients with solitary lesions and heated for ≥ 45 minutes showed OS benefit
  - Forms basis of OPTIMA Study

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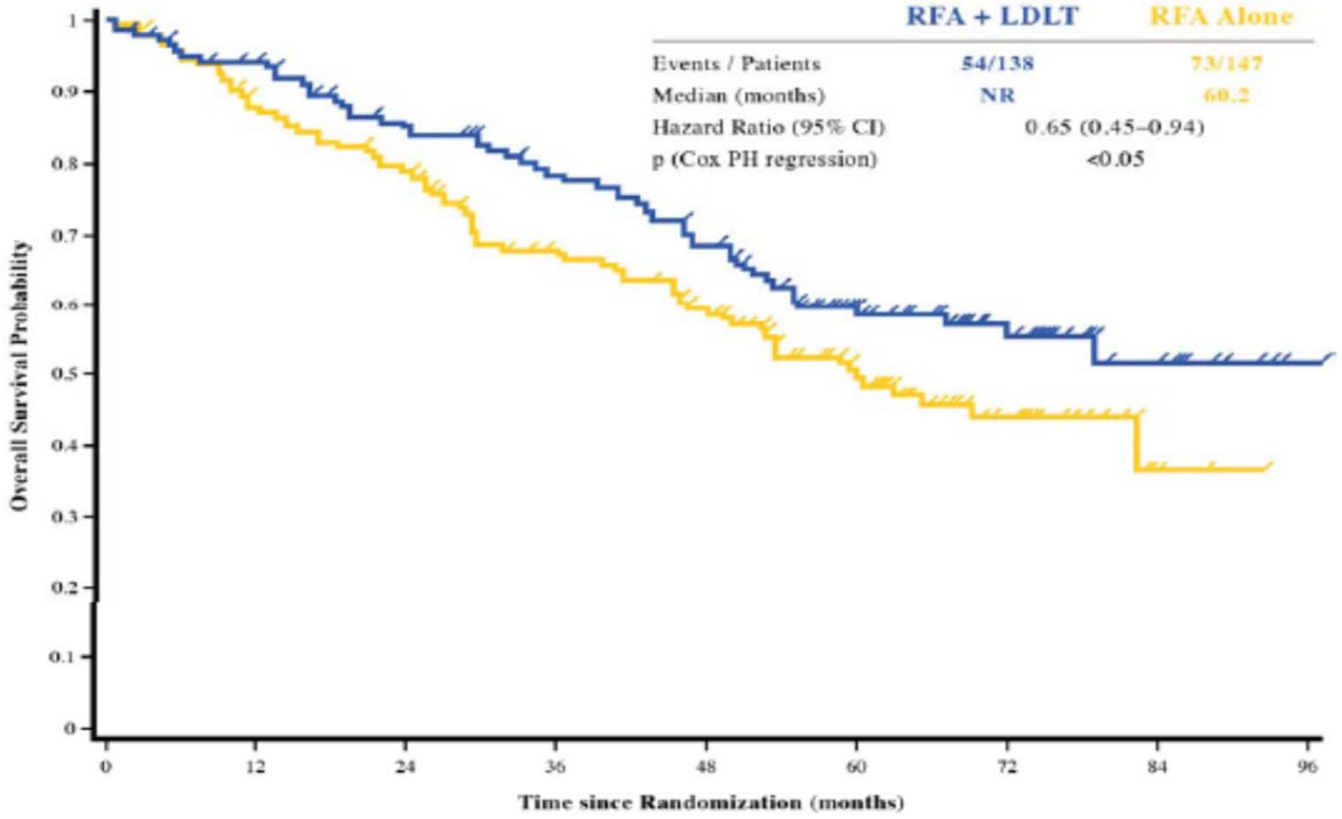
HEAT Subgroup KM

D. OS (Subset: Solitary lesion and RFA dwell time ≥45 min, n=285)



Number at Risk									
RFA Alone	147	127	113	90	76	48	19	3	0
RFA + LDLT	138	124	108	96	84	55	33	13	2

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ThermoDox + RFA vs TACE

Intermediate HCC

	Study	Lesion size	N	Median OS (mos.)	Year 1 (%)	Year 2 (%)	Year 3 (%)
	HEAT Study ITT Population	Overall: 2.7 - 7.5 cm Mean: 4.2 cm Median: 4 cm	701	53 mos.	85%	76%	64%
HEAT Study Subgroup	**ThermoDox + RFA ≥ 45 min.**	**Overall: 2.7 - 6.9 cm Mean: 4.3 cm Median: 4.2 cm**	**138**	**80+ mos.**	**94%**	**85%**	**77%**
HEAT Study Subgroup	RFA alone time ≥ 45 min.	Overall: 3 - 6.9 cm Mean: 4.2 cm Median: 3.9 cm	147	57 mos.	88%	79%	69%
	Ikeda et al (TACE) 2013	Median: 3.9; range 1-11	99	37 mos.	90%	75%	NR
		> 3.0	64	NR	NR	66%	NR
	Burrel (DEB TACE) 2012	BCLC A	41	54 mos.	90%	NR	68%
		BCLC B	63	48 mos.	88%	NR	64%

DEB TACE – Doxorubicin Eluding Beads

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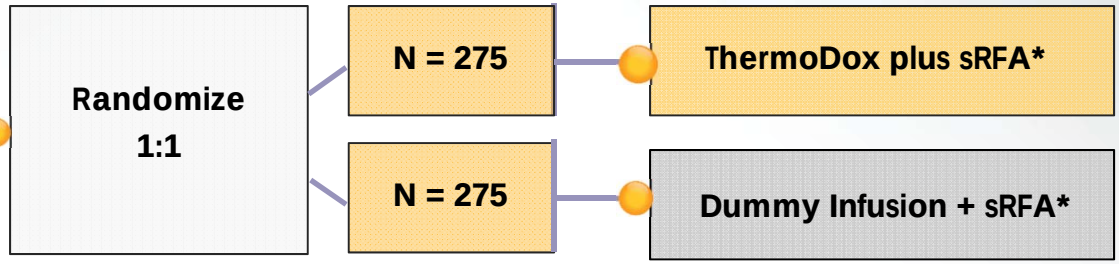
Phase III OPTIMA Study Design

General Eligibility

- Non-resectable HCC
- Single lesions
- Lesion > 3 cm but not > 7 cm
- Treatment naïve
- Child-Pugh A

Stratification

- Lesion size: 3-5 cm / 5-7 cm
- RFA Technique (Percutaneous, Laparoscopy, or Surgical)



Primary Endpoint	Overall Survival (OS)
Secondary Endpoints	Progression Free Survival; Safety
Interim Efficacy Analysis	118 OS Events / HR < 0.61 158 OS Events / HR < 0.70
Final Efficacy	197 OS Events / HR < 0.75

* sRFA45 Standardized Radiofrequency Ablation > 45 minutes

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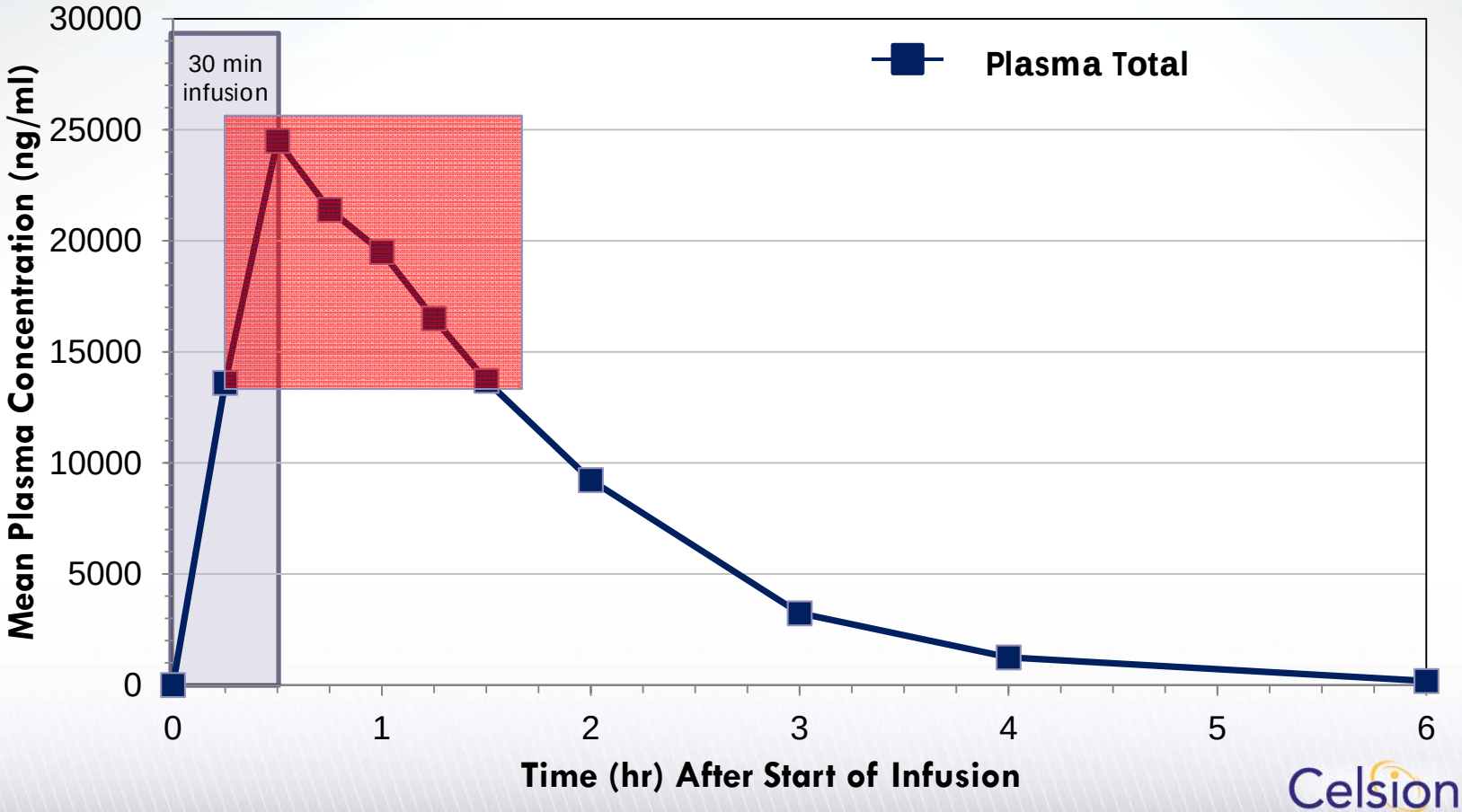
ThermoDox Human PK

Protocol 104-03-101: + Liver RFA @ 50 mg/m²
Mean Plasma Concentrations (n=6)



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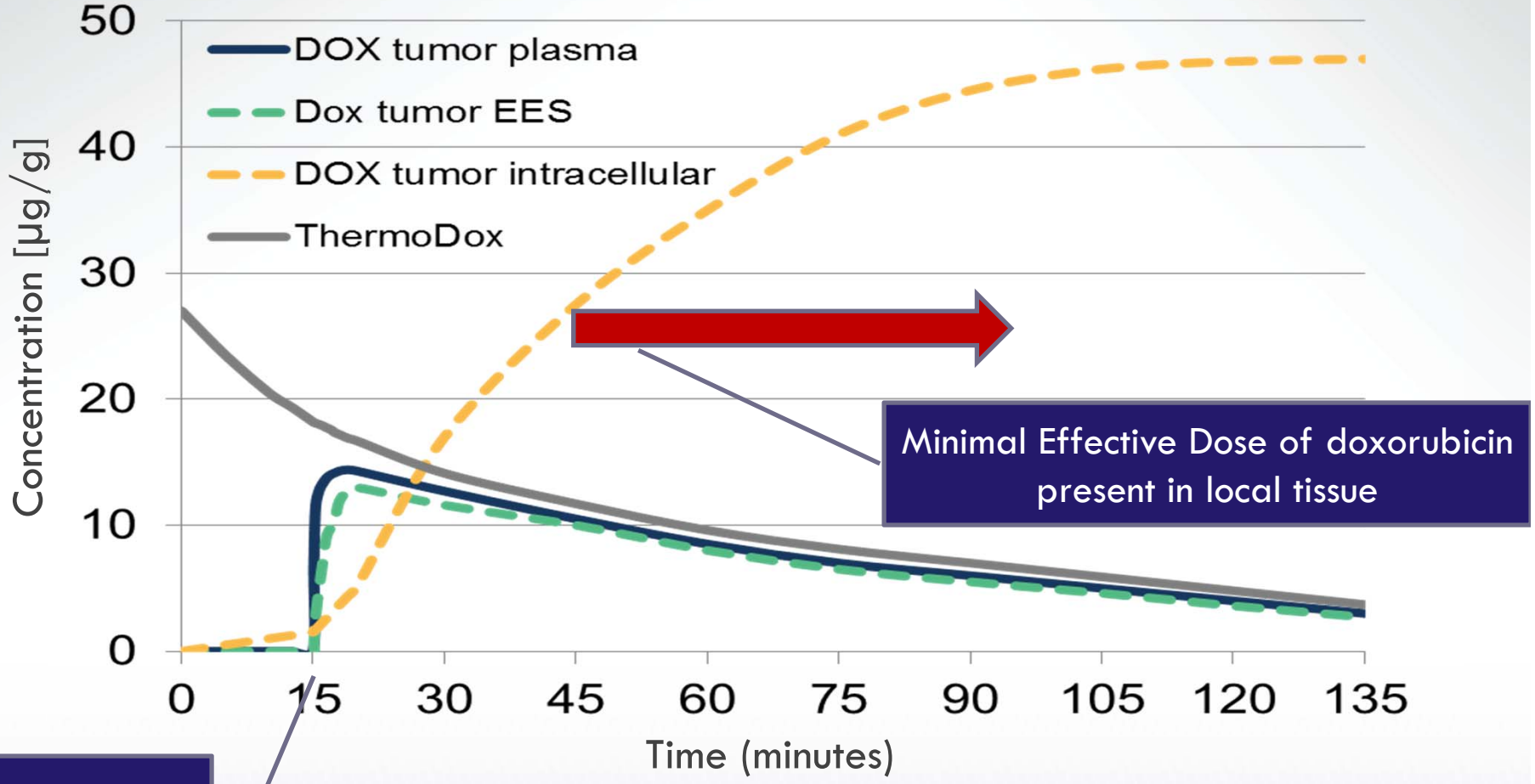
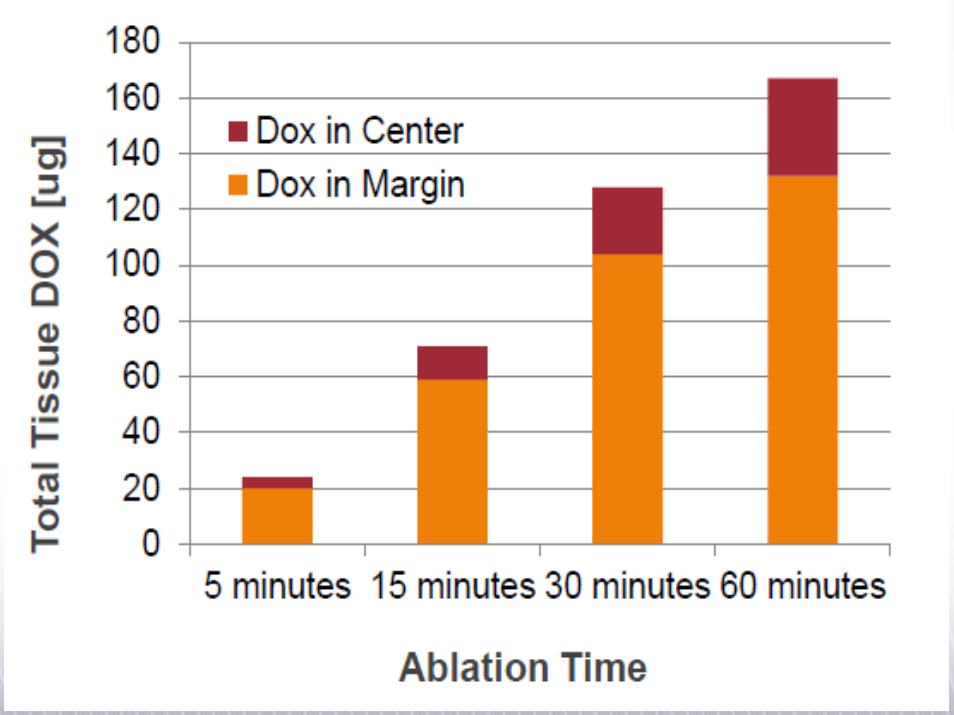
Impact of Mild Hyperthermia on Tissue Deposition



Gasselhuber et al, *Int J Hyperthermia*, 2012

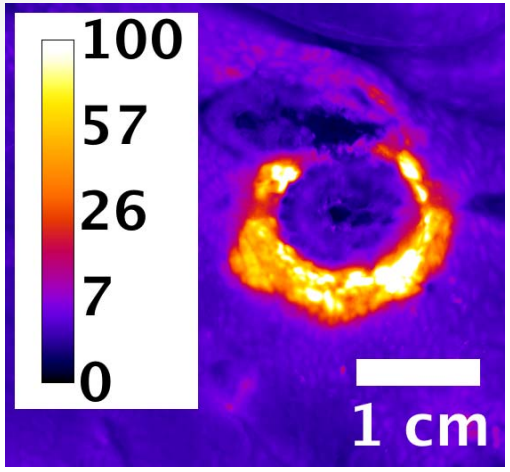
Post Hoc Analysis

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

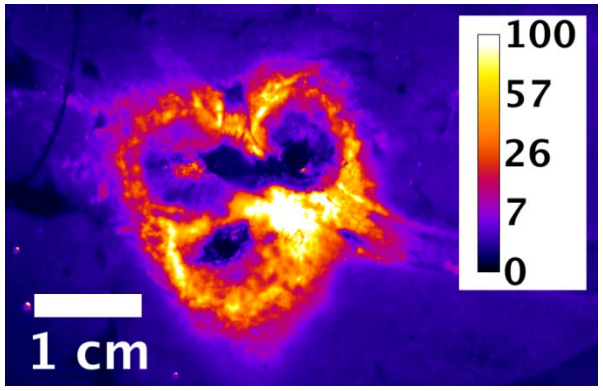


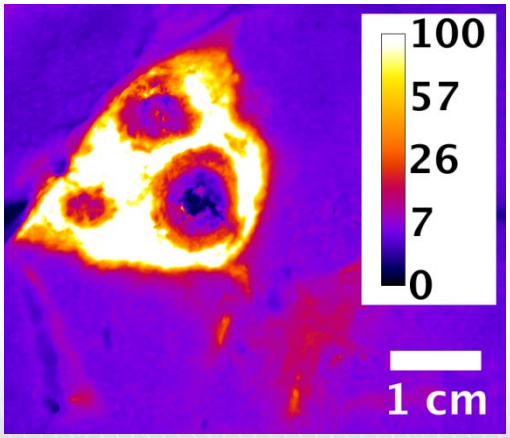
Fluorescence Mapping of Doxorubicin Distribution in pigs treated with ThermoDox

15 minute

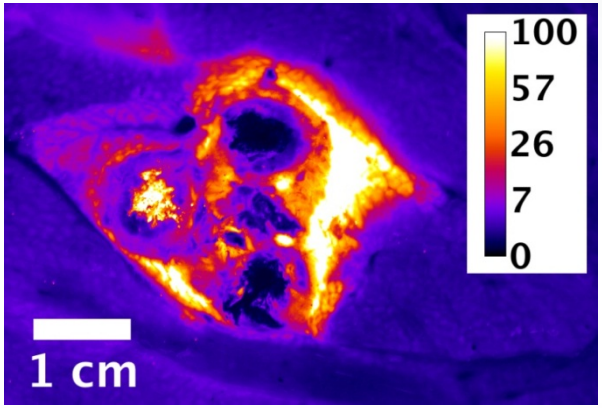


45 minute





90 minute



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Sub-Group Population Balanced for Risk Factors

Baseline Characteristics for Patients with Single HCC and RFA ≥ 45 min (N=285)

Parameter	RFA + LDLT (ThermoDox) (n = 138)	RFA (n = 147)
Male	99 (71.7%)	109 (74.1%)
Age > 65	56 (40.6%)	53 (36.0%)
Hepatitis B	89 (64.5%)	89 (60.5%)
Hepatitis C	26 (18.8%)	33 (22.4%)
Child Pugh A	138 (100%)	147 (100%)
Max. size 3-5 cm	111 (80.4%)	122 (83.0%)
Percutaneous route	123 (89.1%)	133 (90.5%)
Covidien Device	77 (55.8)	82 (55.8)

Celsion Corporation. Unpublished Data

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Multi-Variate Analysis

- A Multi-Variate Cox regression OS Analysis investigated the effect of 8 potential prognostic factors
  - RFA Dwell Time (< 45 minutes versus ≥ 45 minutes)
  - RFA Approach (Percutaneous, Laparoscopy, Open Surgical)
  - Age (< 65 years old versus > 65 years old)
  - Sex
  - Region
  - Disease Etiology (Hepatitis B versus other)
  - Number of Lesions (Solitary vs. Multiple)
  - Size of Lesions Maximum Diameter (3.0 to 5.0 cm and 5.1 to 7.0 cm)

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National Cancer Institute Review of the HEAT Study

The effect of burn time per tumor volume on PFS and OS was analyzed using multiple covariate Cox proportional hazard model.

PURPOSE

Does thermal dose have an effect on ThermoDox outcome?

Burn time per tumor volume (min/ml)

METHOD

Analyzed 437 HEAT subjects with single lesions

(RFA only n=210 vs. RFA + ThermoDox n=227)

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National Cancer Institute Review of the HEAT Study

Increase in the burn time per tumor volume improves survival in the RFA+ThermoDox subjects compared to RFA only patients.

RESULTS

Average burn time per volume for RFA+ThermoDox patients was 22.7% less than RFA-only patients

Cox multiple covariate analysis showed OS to be significant ($p=0.038$, $HR=0.85$)

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National Cancer Institute Review of the HEAT Study

RESULTS (cont.)

Analysis for effects of burn time per tumor volume:

For RFA + ThermoDox subjects:

One unit increase in RFA duration per tumor volume improved OS of RFA+ThermoDox subjects by 19.6%

(p=0.017, Hazard Ratio=0.836, n=227)

NOT TRUE FOR RFA-ONLY

Burn time per tumor volume did not have a significant effect

(p=0.57, Hazard Ratio=0.99, n=210)

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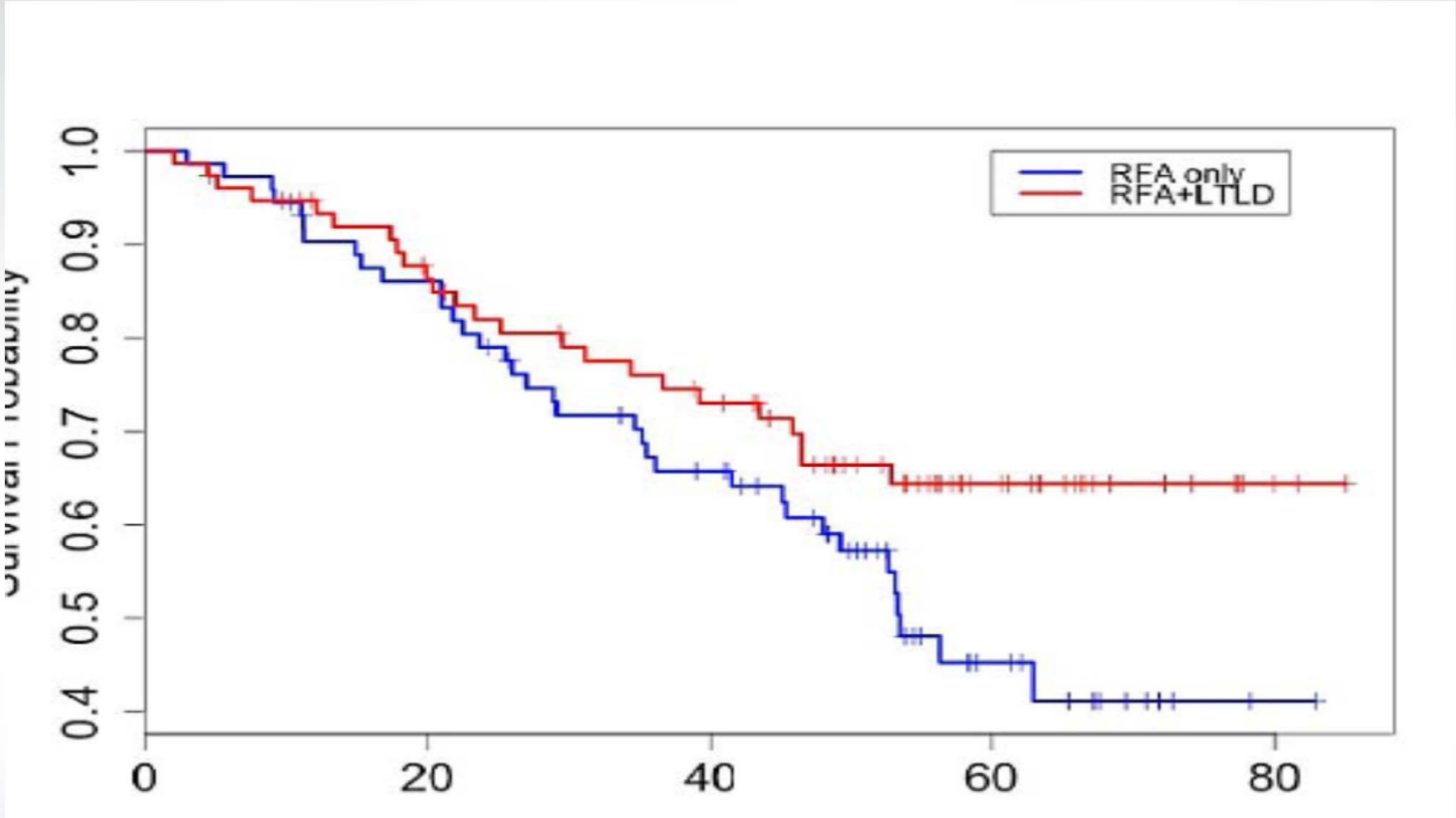
KM of Subjects with Burn Time > 2.5 min/ml



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National Cancer Institute Review of the HEAT Study

CONCLUSION

ThermoDox may improve overall survival as RFA duration per unit tumor volume increases

This study to be confirmed with OPTIMA

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Mechanism of Thermal Dose Effect

- Heat is Tumorcidal
- Higher Local Concentrations of Doxorubicin
- Doxorubicin may increase thermal sensitivity
- Immune Effect?

INTERNATIONAL JOURNAL OF HYPERTHERMIA, 2016
http://dx.doi.org/10.3109/02656736.2016.1164904

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Effect of thermal dose on heat shock protein expression after radio-frequency ablation with and without adjuvant nanoparticle chemotherapies

Marwan Moussa[a], S. Nahum Goldberg[a,b], Gaurav Kumar[a], Tatyana Levchenko[c], Vladimir Torchilin[c] and Muneeb Ahmed[a]

[a]Laboratory for Minimally Invasive Tumor Therapies, Department of Radiology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, Massachusetts, USA; [b]Division of Image-Guided Therapy and Interventional Oncology, Department of Radiology, Hadassah Hebrew University Medical Center, Jerusalem, Israel; [c]Department of Pharmaceutical Sciences and Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, Massachusetts, USA

- Longer Heating Times
  - > inflammation
  - >microvascular change
  - Maximizes volume of peri-ablational rim
- Therefore tailoring the ablation algorithm to increase the volume of tissue exposed to hyperthermia may be the key

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RFA in Intermediate Size Tumors

Thermal Dose

- Variation in tissue heating affects ablation zone size in liver
- Represented by Hsp70 expression
  - > lower temperature longer duration vs.
  - < higher temperature shorter duration

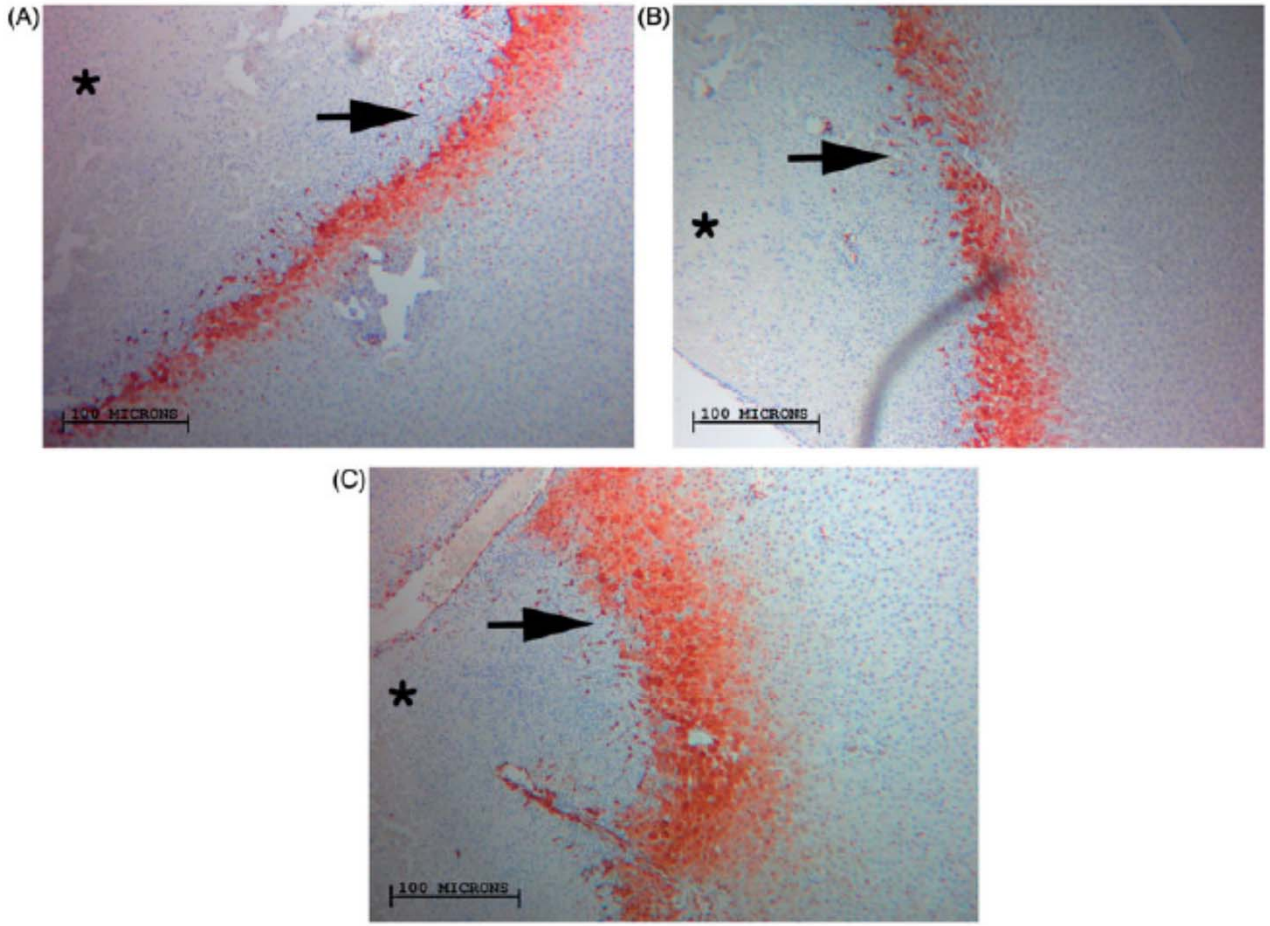

Figure 3. Comparison of RF-induced peri-ablational Hsp70 in normal rat liver for varied RF application. Magnified images (10×) of liver peri-ablational rims stained for Hsp70 expression after 2 min (A), 5 min, (B), and 10 min (C) for a standardised RF tip temperature (90 °C) demonstrates a significant increase in rim thickness when increasing duration of RF application ($p < 0.003$). By contrast, incremental increase of tip temperature at any constant application period did not result in significant increases in Hsp70 expression ($p < 0.4$).

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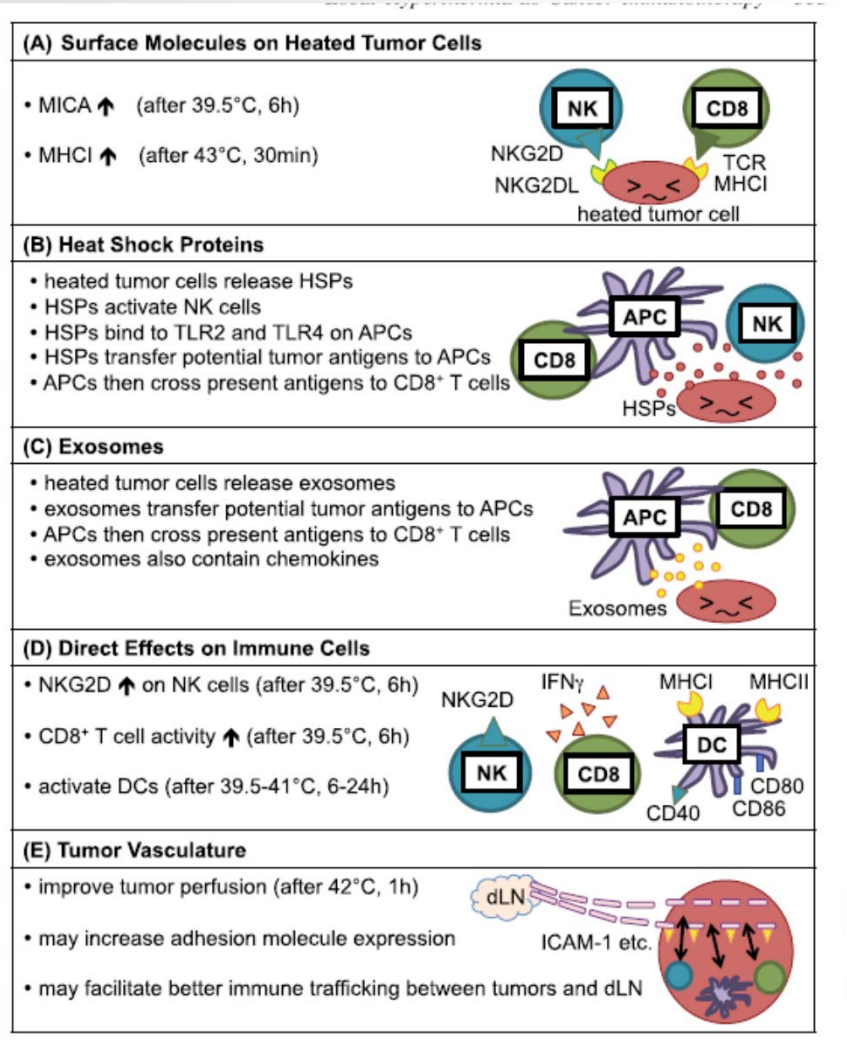
Findings

- Combined drug/ablation strategies can improve ablation efficacy

- For RF thermal ablation, longer heating, lower temperature protocols may permit greater zones of periablational inflammation compared to higher temperature, faster heating protocols.

- Such approaches may be tailored to maximize the peri-ablational effects of adjuvant nanodrugs…

Thermal Immune Activation



- Surface Molecule Targets
- Heat Shock Proteins
- NK cells
- Release exosomes transferring tumor antigens
- Increase in T-cell activity
- Activation of dendritic cells

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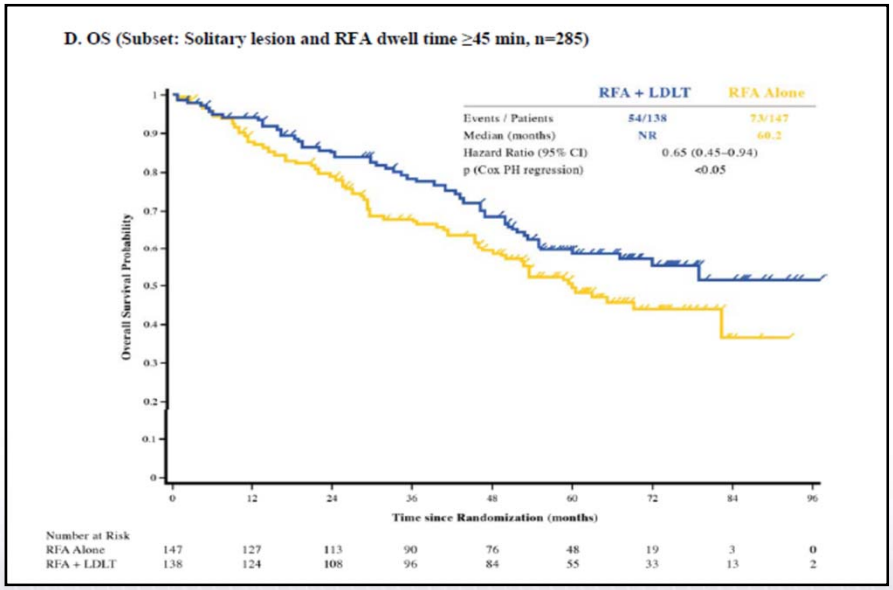
Conclusion

- Hepatocellular Carcinoma is an international unmet medical need
- Current single modality treatments are not sufficient
- ThermoDox offers multimodality approach
  - Adjunctive targeted concentrated cytotoxic
  - Immune response
  - Survival Benefit



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Won Young Tak, M.D., Ph.D.

Professor Internal Medicine, GI & Hepatology,
Kyungpook National University Hospital,
Daegu, Republic of Korea

R&D Day

ThermoDox - Targeted Chemotherapy

Cases of RFA ± ThermoDox for HCC -The HEAT Study

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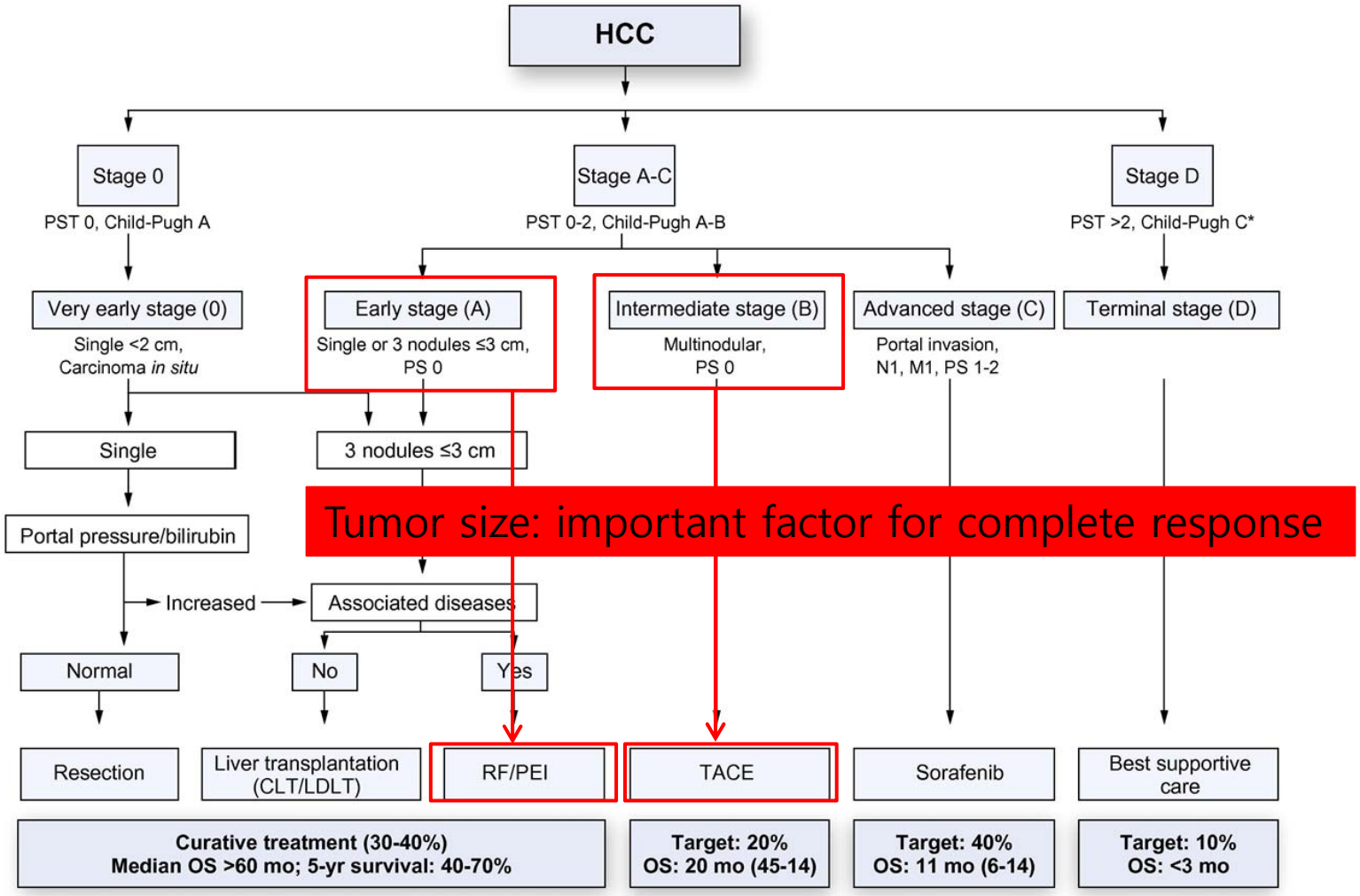
Cases of RFA ± Thermodox® for HCC (The HEAT Study)

Won Young Tak, M.D., Ph.D.

Kyungpook National University Hospital,
Daegu, South Korea

KNUH
경북대학교병원
KYUNGPOOK NATIONAL UNIVERSITY HOSPITAL

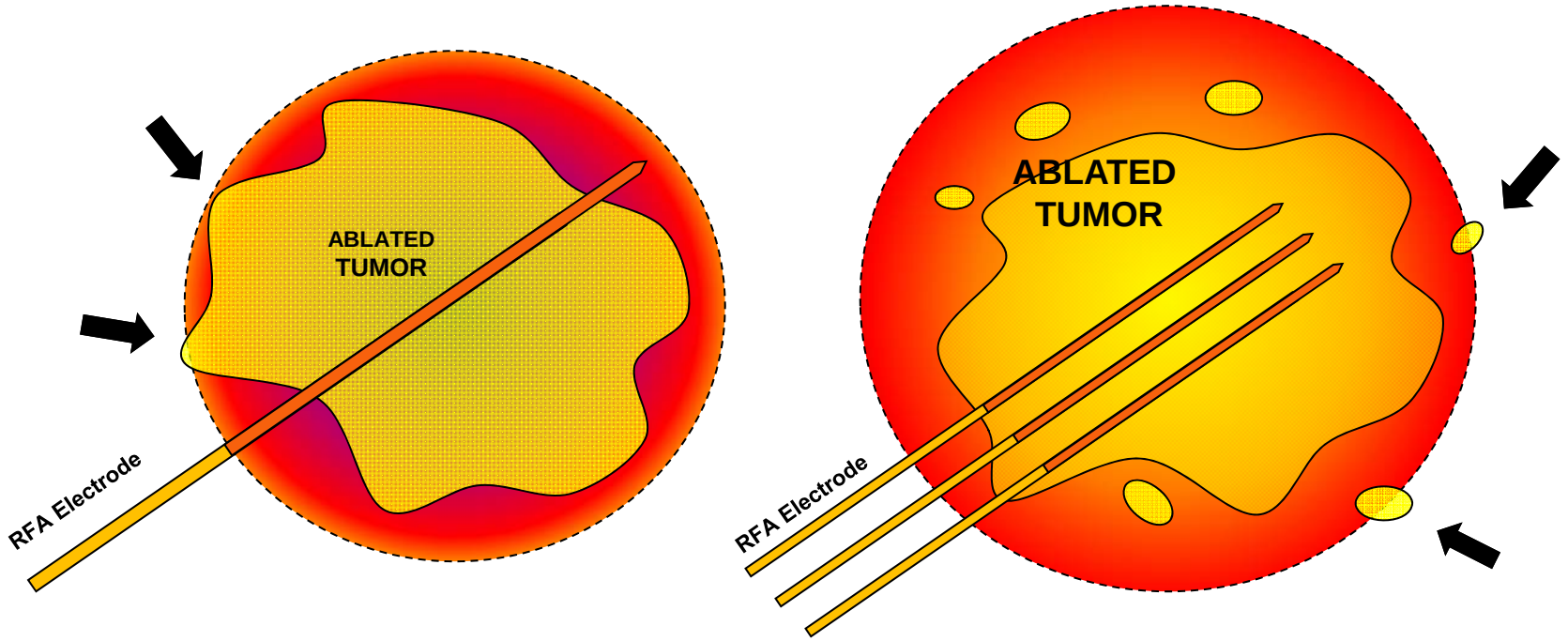
BCLC Classification



KNUH 경북대학교 KYUNGPOOK NATIONAL UNIVERSITY HOSPITAL

EASL-EORTC CPG management of HCC J Hepatol. 2012 56(4):908-43

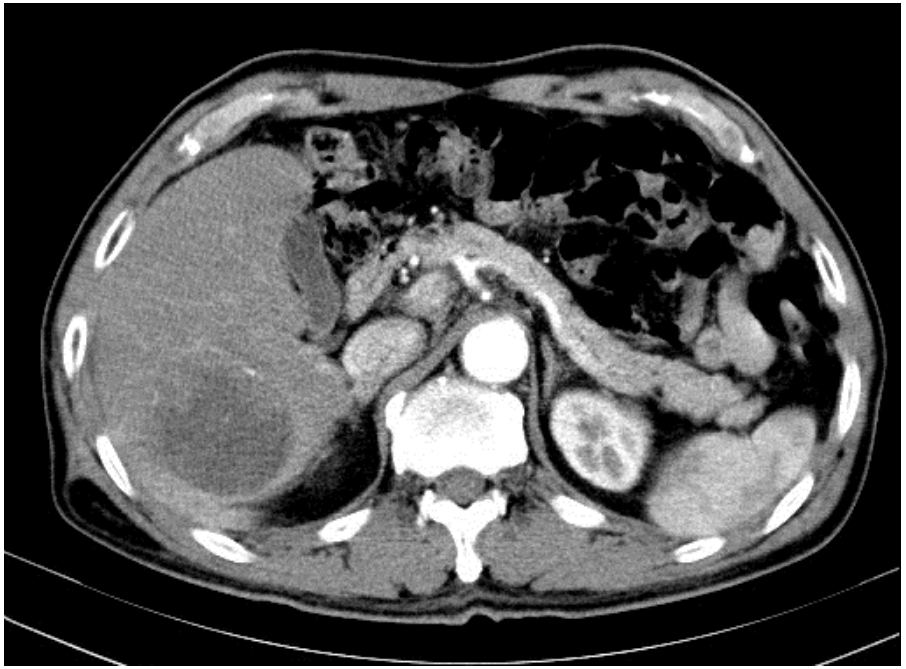
RFA: Limited Efficacy in Larger Tumors

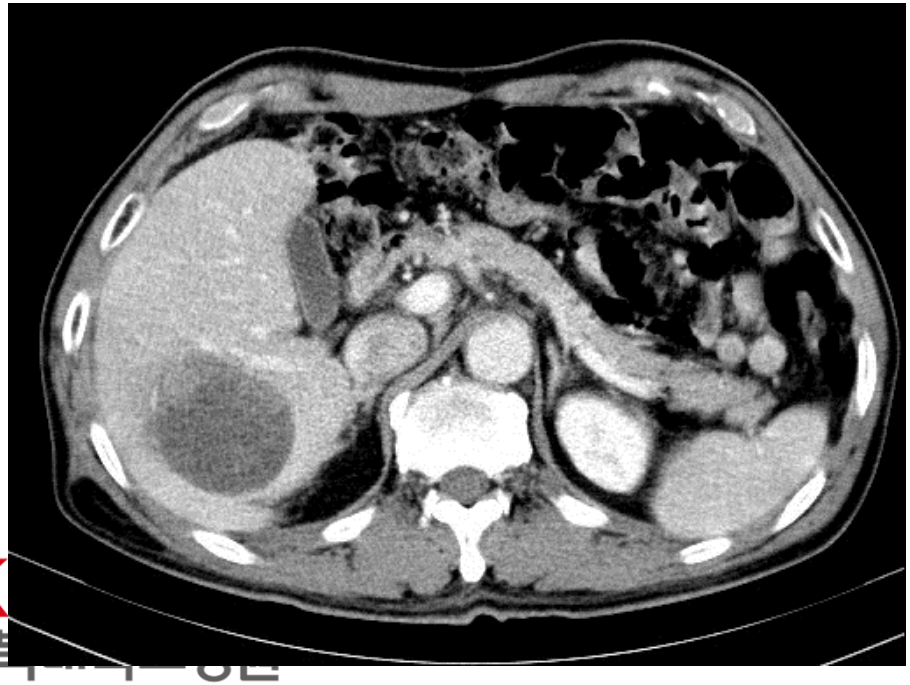


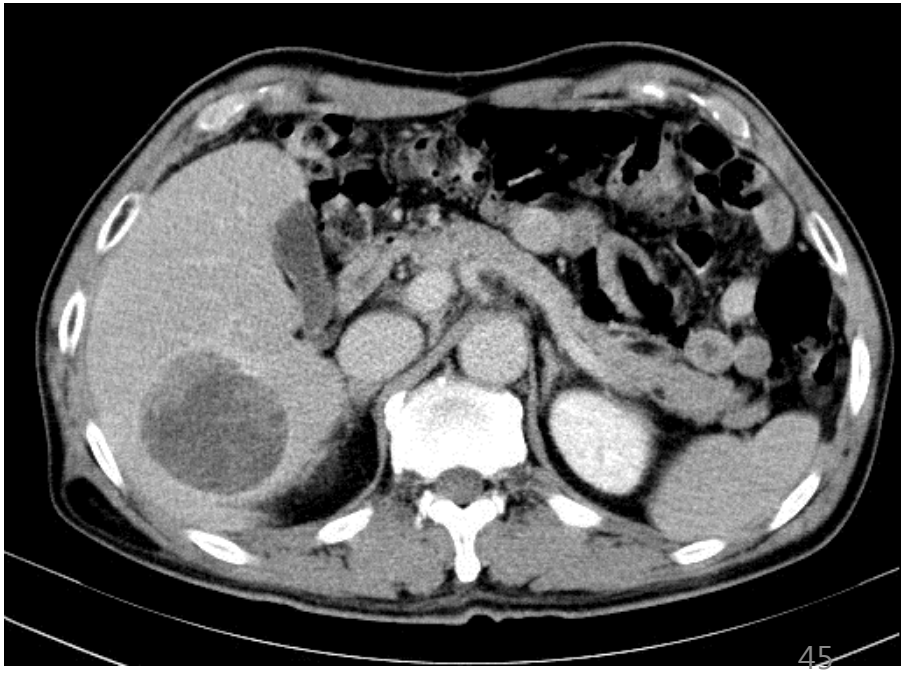
Viable tumors in margin or microsatellite nodules

KNUH
경북대학교병원
KYUNGPOOK NATIONAL UNIVERSITY HOSPITAL

- M, 62Y
- Chronic hepatitis B
- Longest diameter: 6.0 cm
- RFA only
- RFA dwell time 84 minutes







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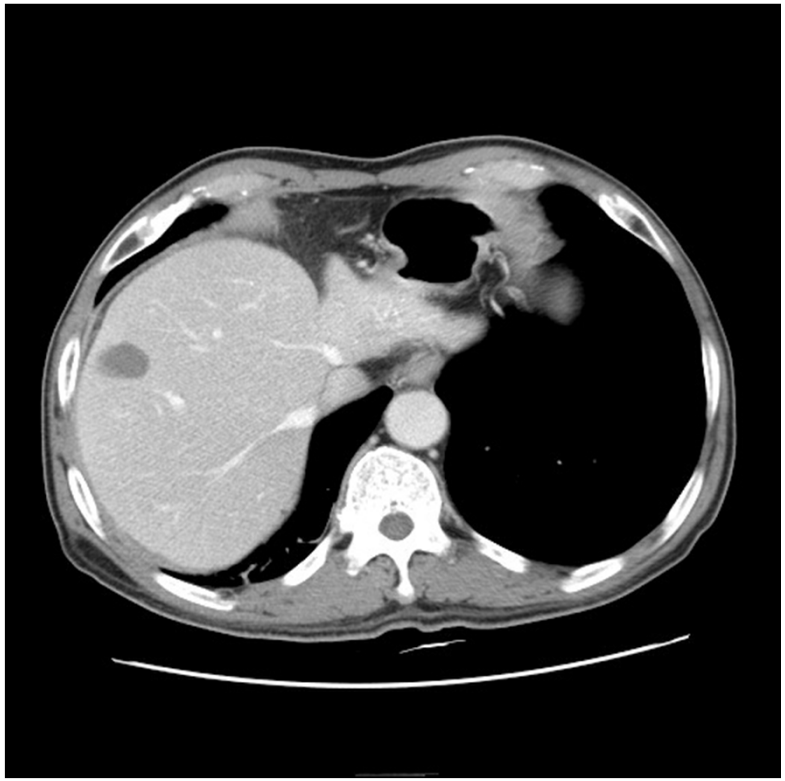
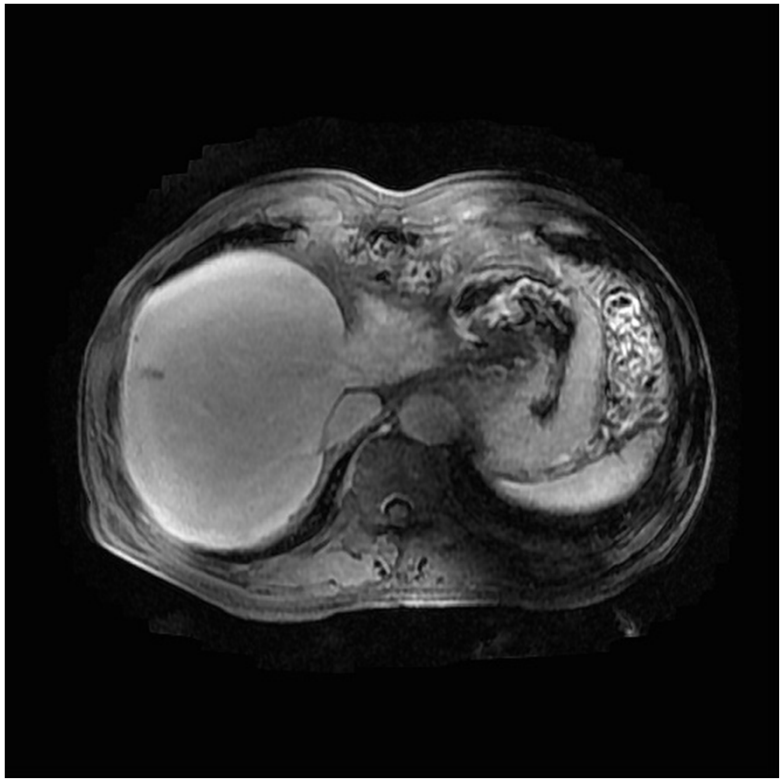
Post RFA - 1 month



Post RFA - 1 year



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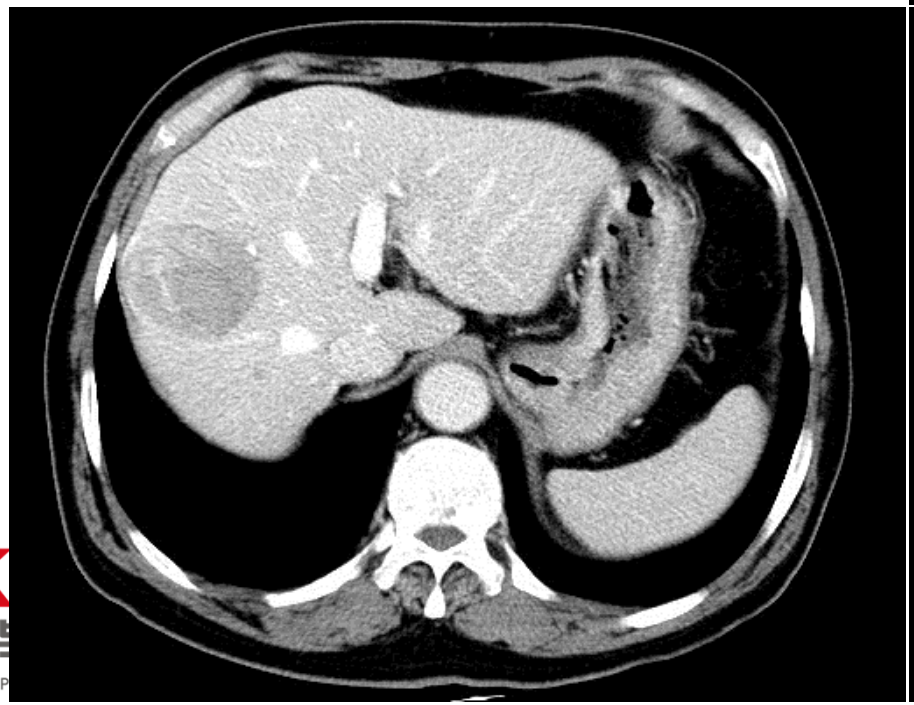
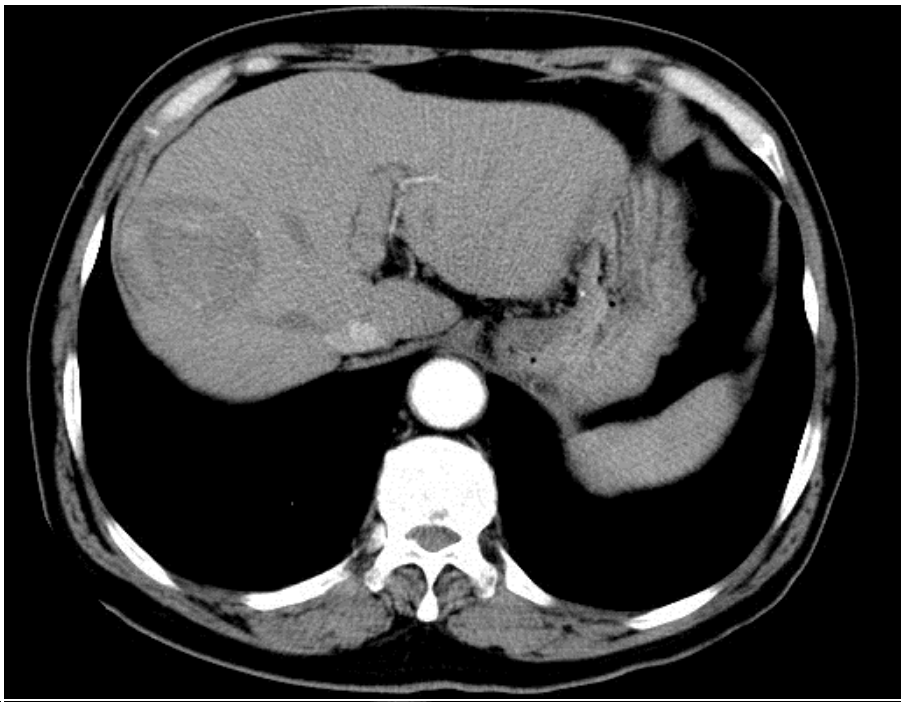
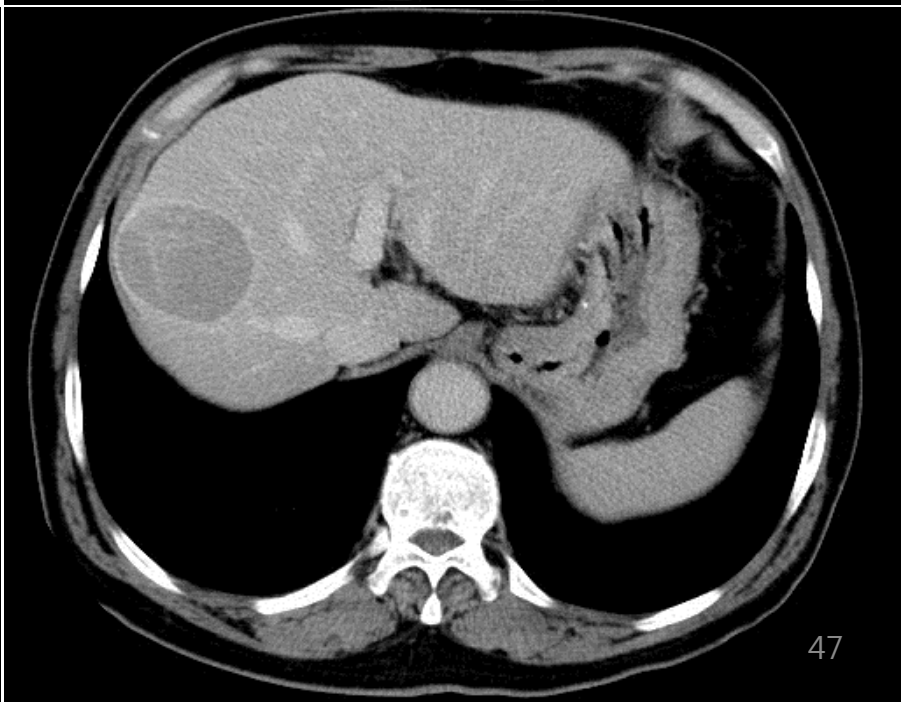
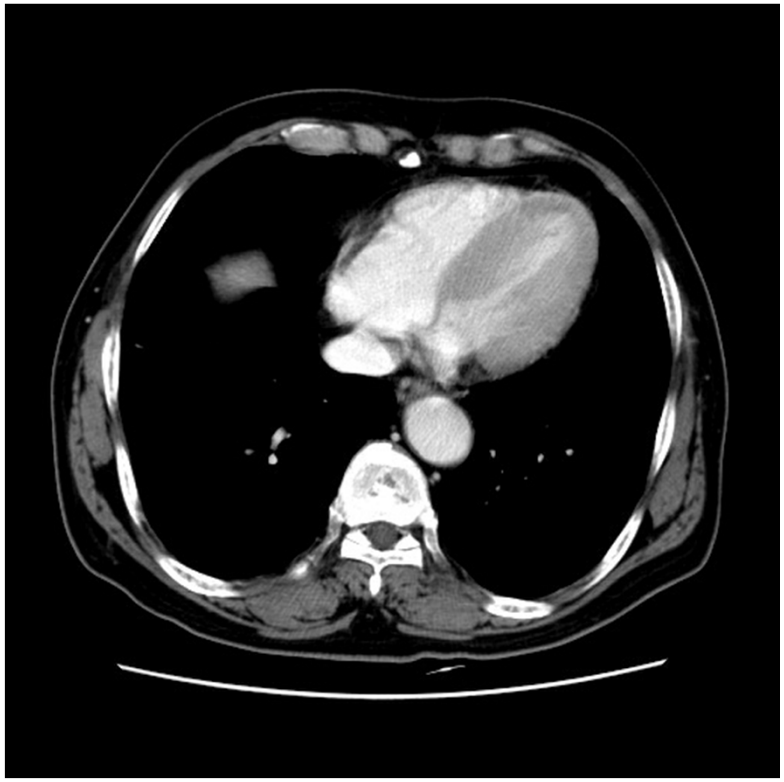
- M, 66Y
- Chronic hepatitis B
- Longest diameter: 5.6 cm
- RFA + Thermodox®
- RFA dwell time 72 minutes



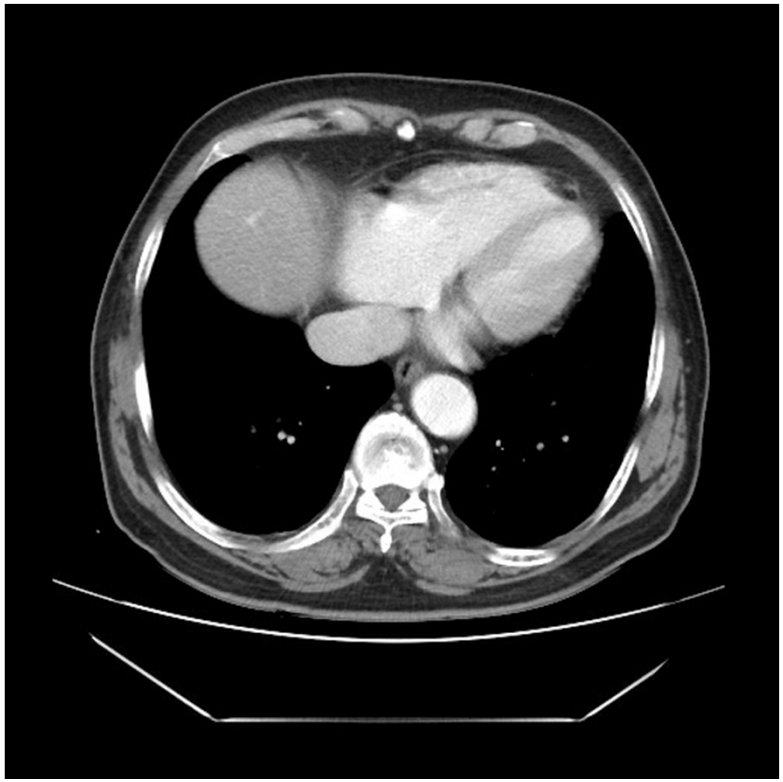




Post RFA - 1 month



Post RFA - 7 years



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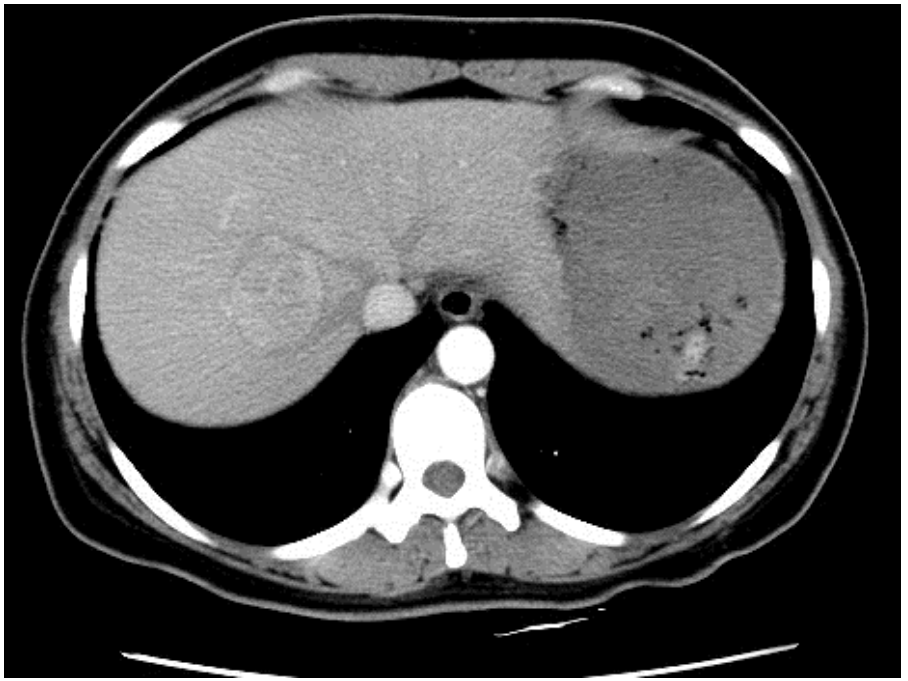
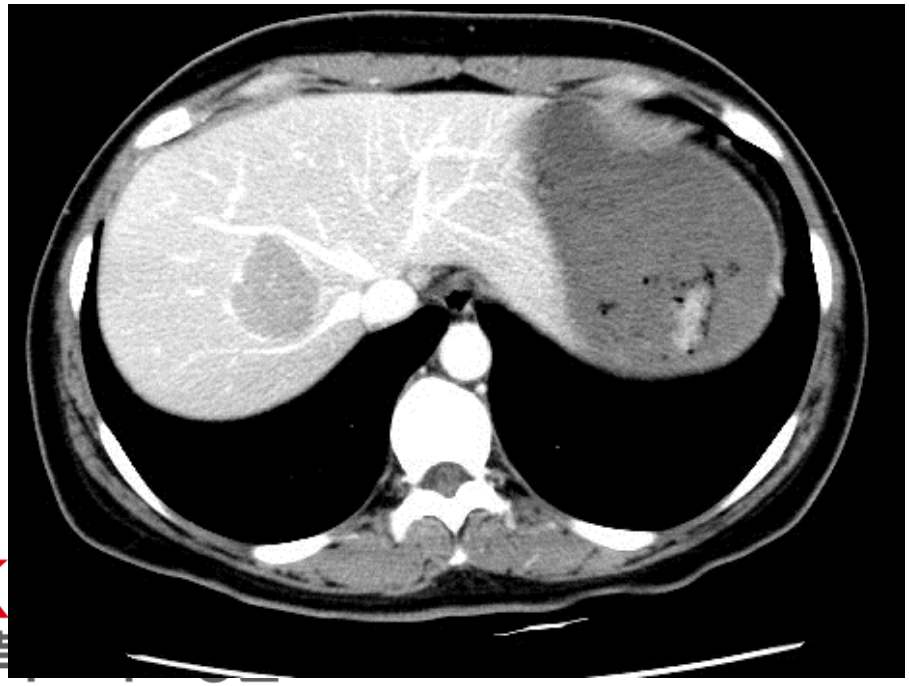
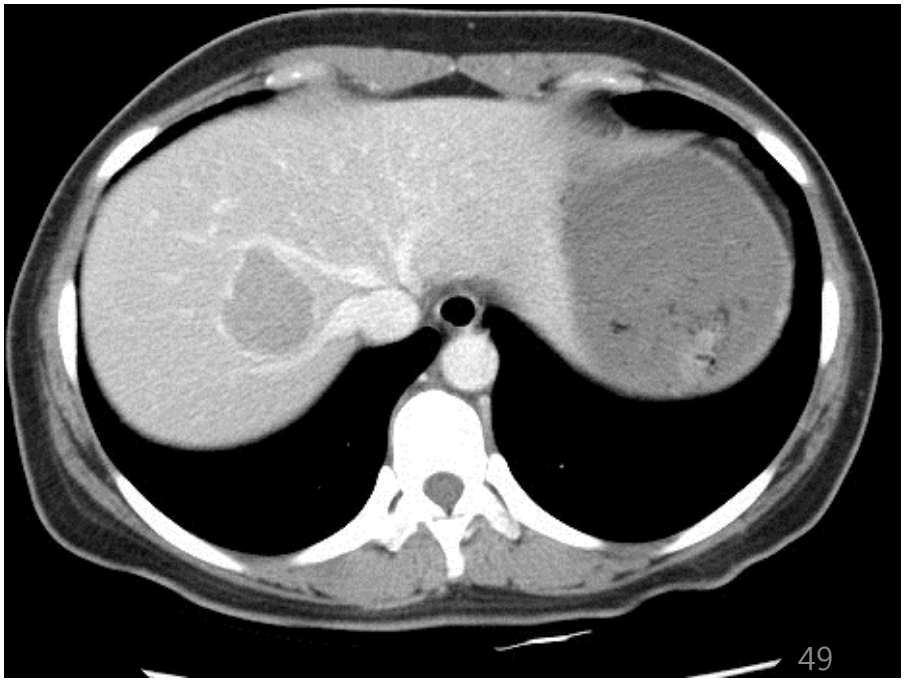
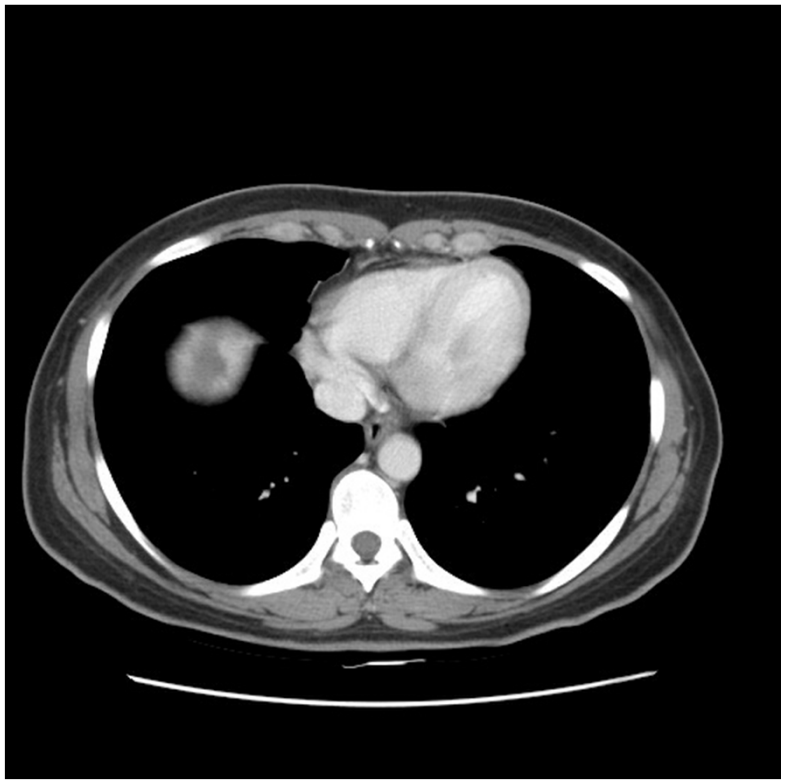
- F, 38Y
- Chronic hepatitis B
- Longest diameter: 4.0 cm
- RFA + Thermodox®
- RFA dwell time 49 minutes



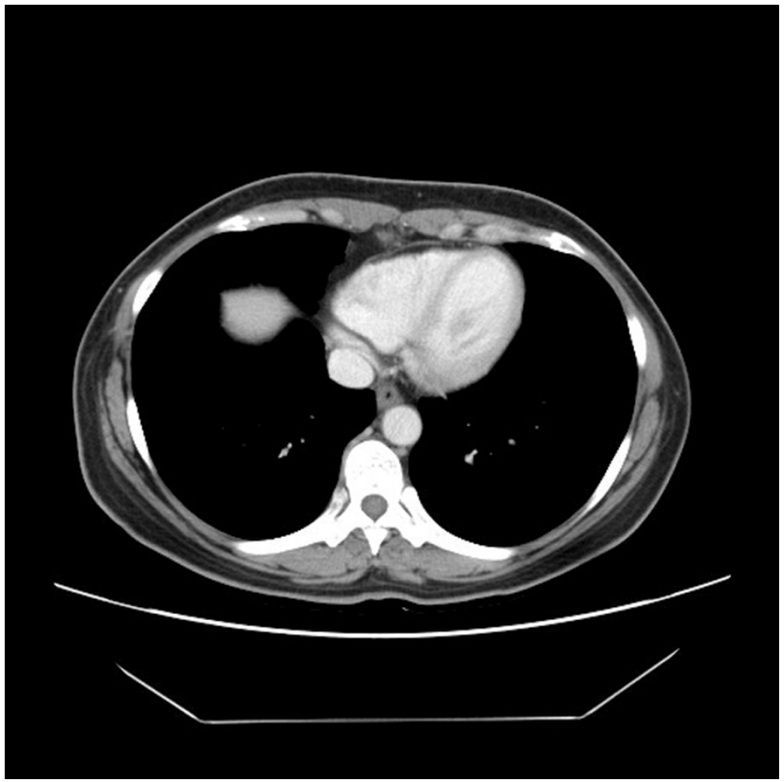




Post RFA - 1 month



Post RFA - 5 years



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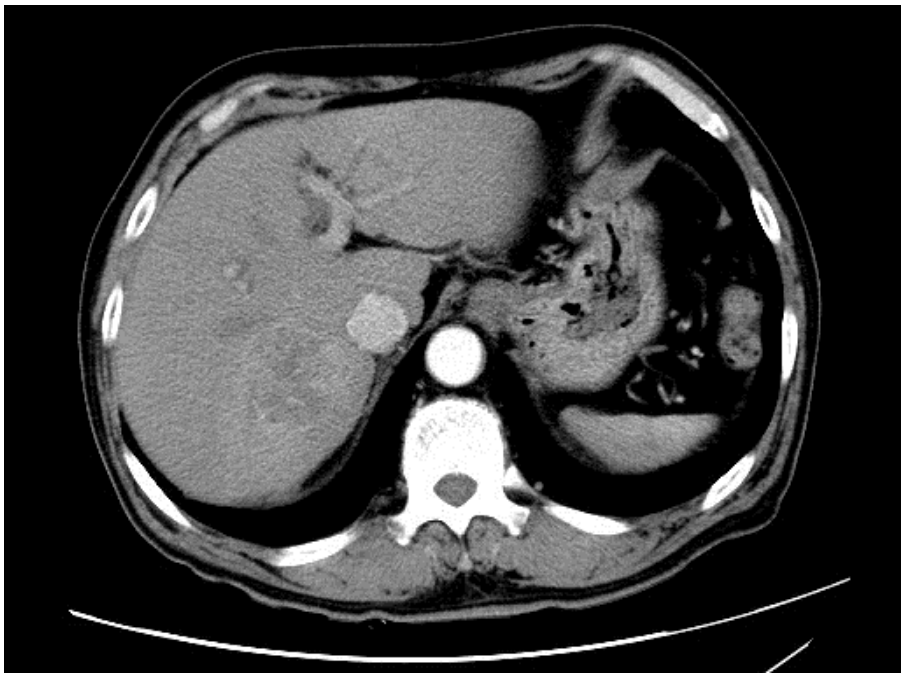
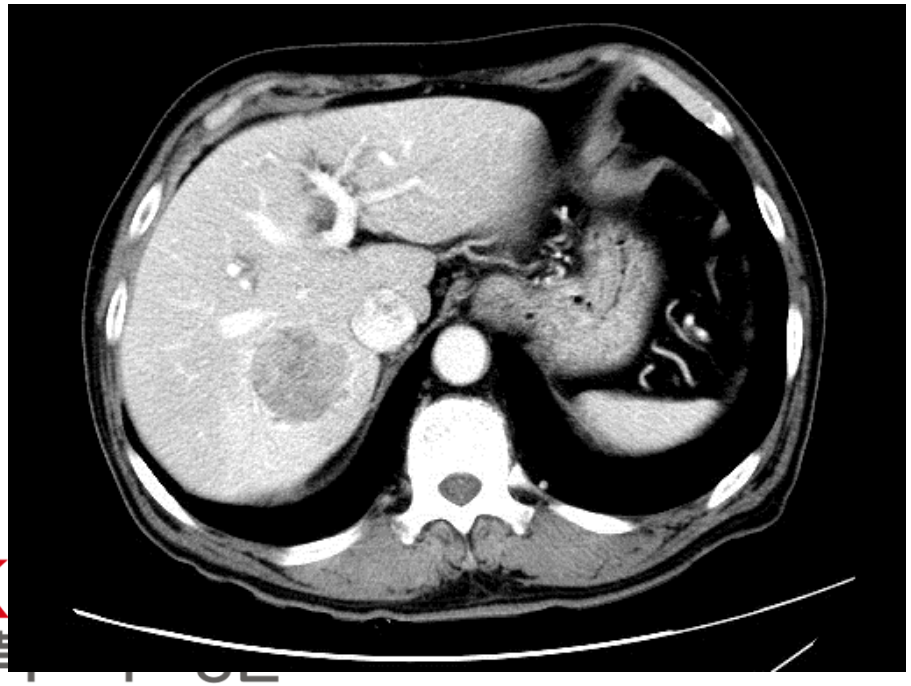
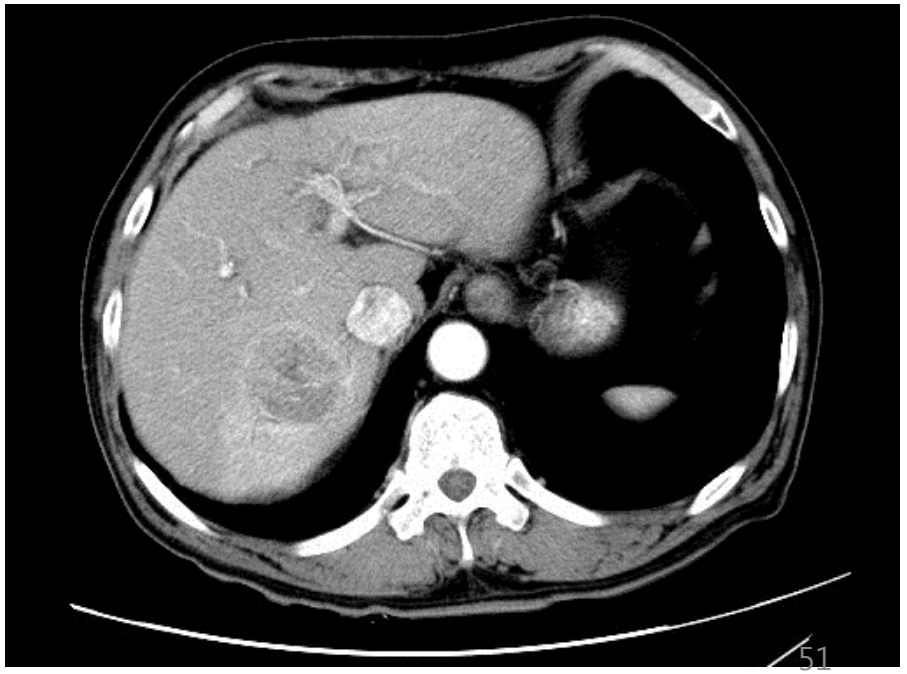
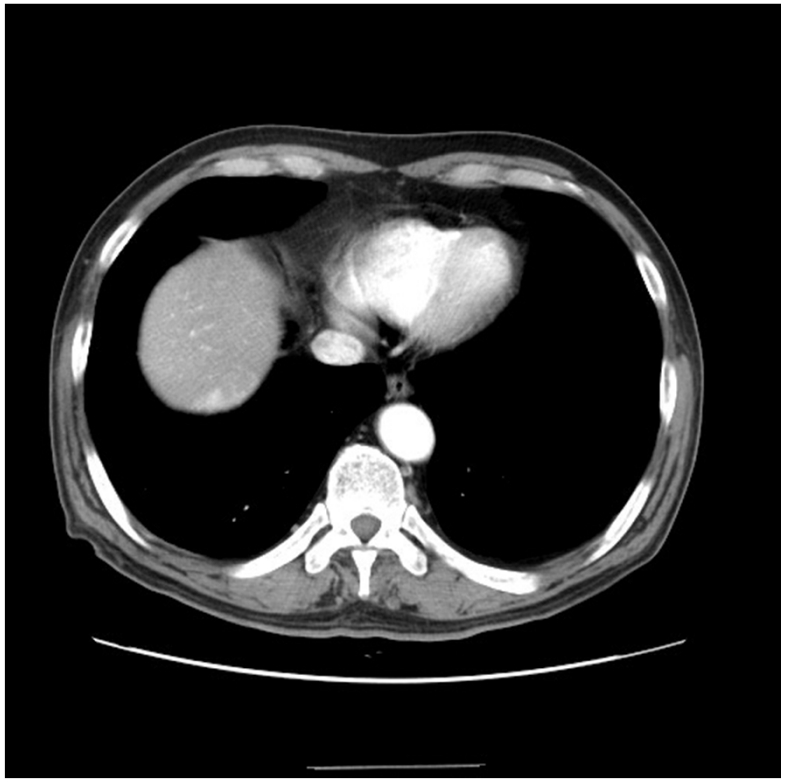
- M, 67Y
- Chronic hepatitis C
- Longest diameter: 4.3 cm
- RFA + Thermodox®
- RFA dwell time 72 minutes



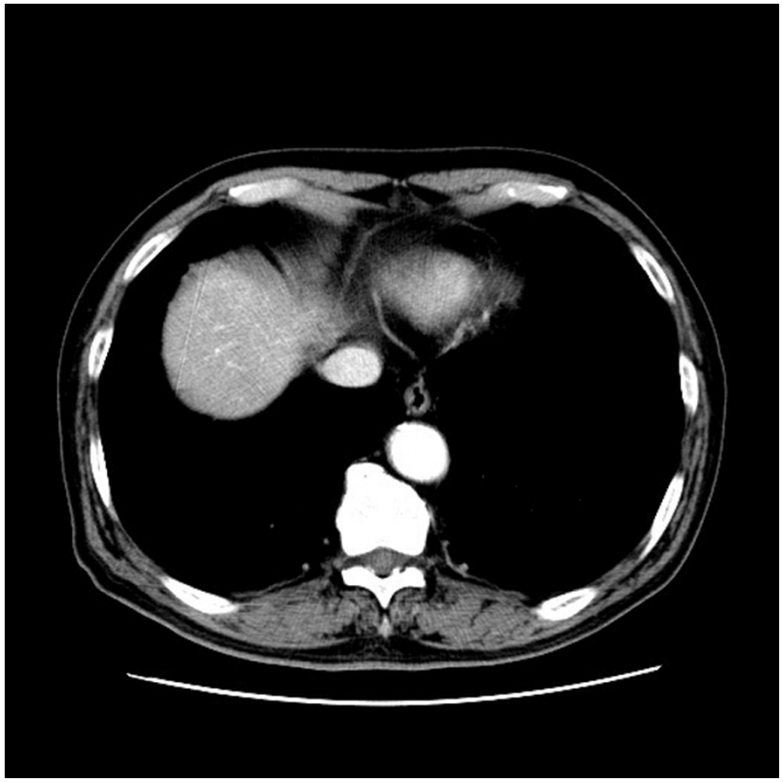




Post RFA - 1 month



Post RFA - 9 year



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Summary

- Possibility of microinvasion in HCC greater than 3cm in diameter is major limitation of RFA.
- Extensive ablation with RFA does not guarantee complete response in HCC greater than 3cm.
- We have many cured HCC patients from HEAT study and we expect successful data from OPTIMA study.

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Thanks for your attention!

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Stephen Ng Wong, M.D., FPCP, FPSG, FPSDE
Gastroenterology and Hepatology,
Chinese General Hospital, Philippines

R&D Day

ThermoDox - Targeted Chemotherapy

Clinical Experience with RFA + ThermoDox for HCC 3-7 cm in Size

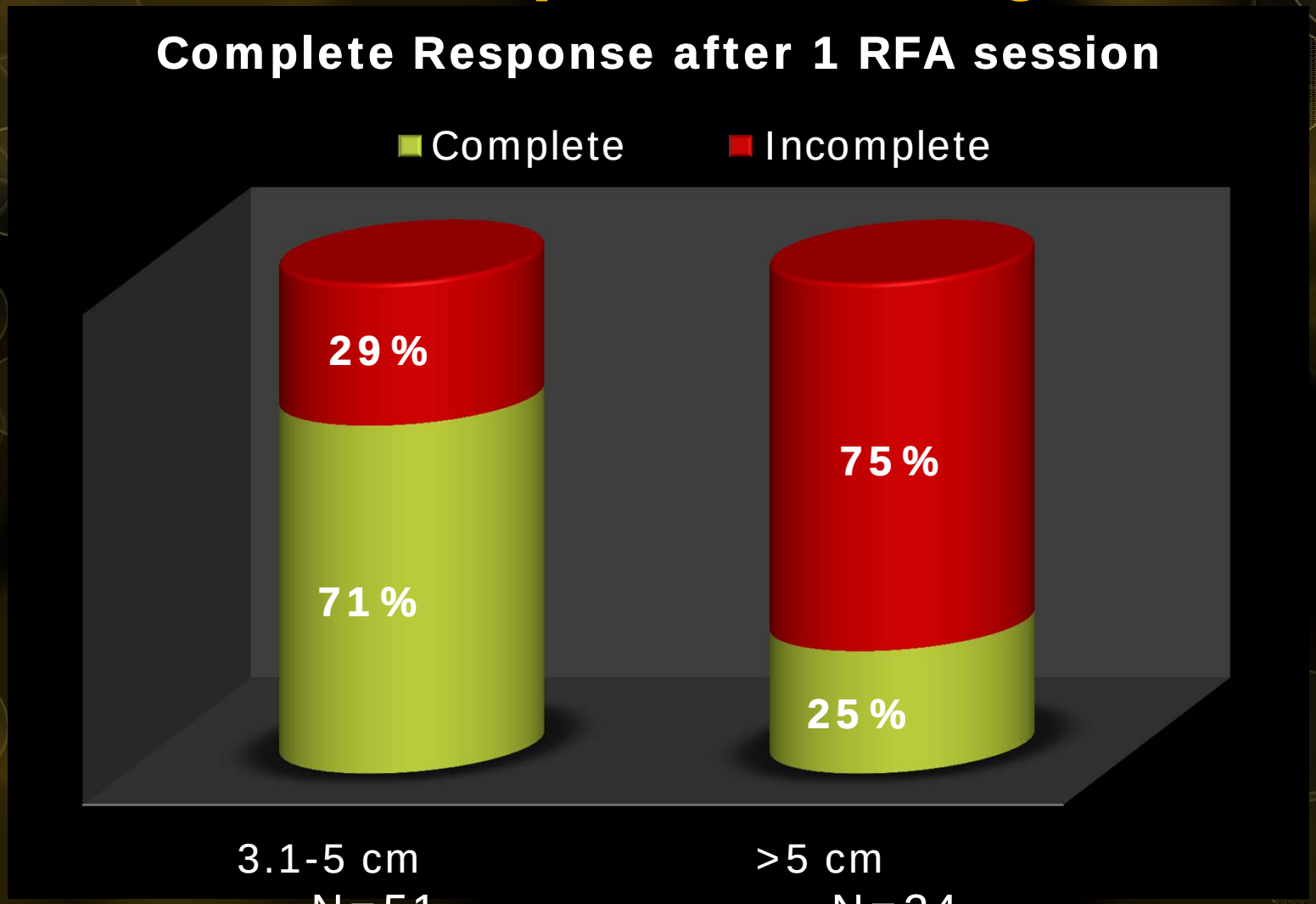
Celsion

RFA + Thermodox for HCC 3-7 cm in Size

Stephen N. Wong, MD

snwong@ust.edu.ph

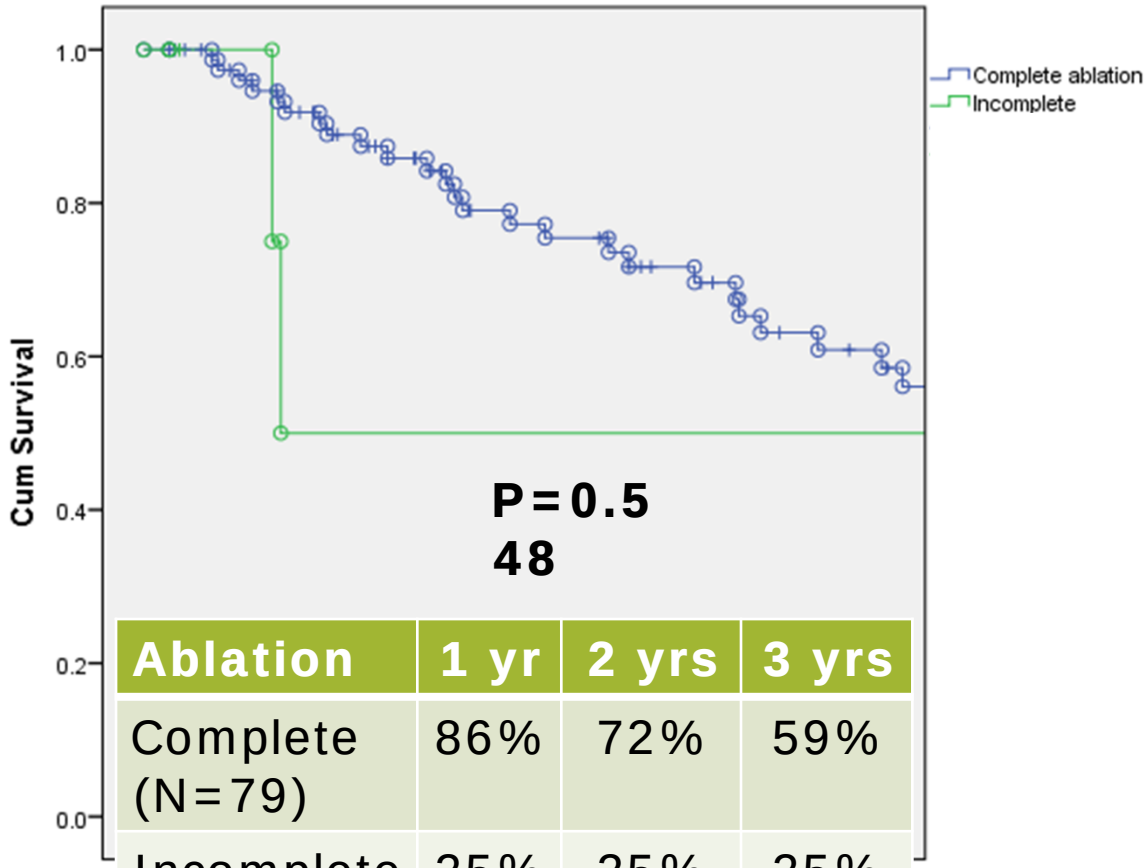
In Older Studies, Complete Response is Less Frequent in Larger HCC



Livraghi, et al. Radiology 2000

snwong@ust.edu.ph

Complete Response is a Factor in Survival After RFA

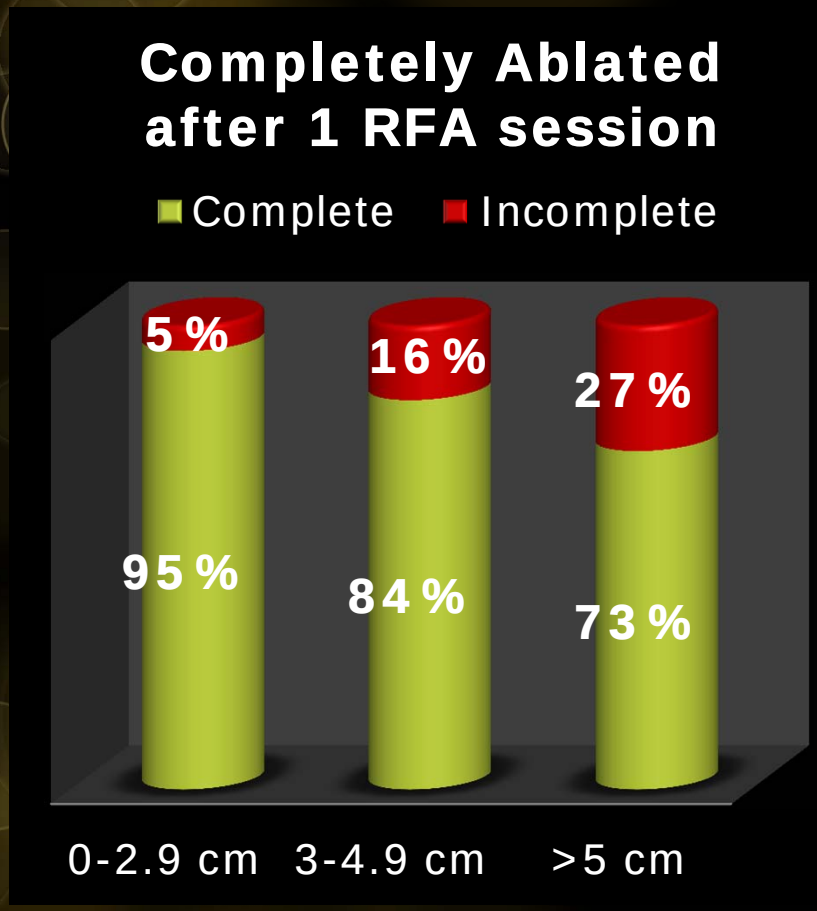


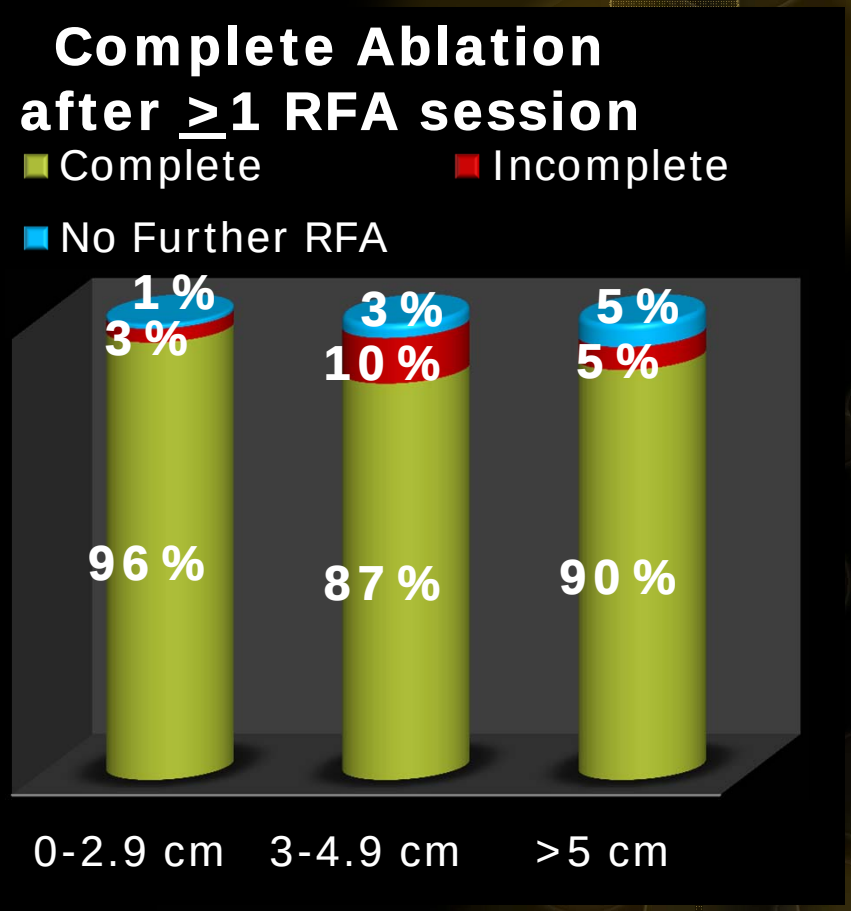
Ablation	1 yr	2 yrs	3 yrs
Complete (N=79)	86%	72%	59%
Incomplete (N=5)	25%	25%	25%

S. Wong. Unpublished data Feb 2007-Feb 2015

snwong@ust.edu.ph

Complete Ablation is High in HCC > 5 cm





N=147 N=62 N=41

S. Wong. Unpublished data Feb 2007-Feb 2015

snwong@ust.edu.ph

On 7.1 years follow-up – no recurrence and doing well

HEAT STUDY:
RFA + Thermodox
49 y/o Male: 5.2 cm
60 minutes dwell time

snwong@ust.edu.ph

Had recurrence after 20 months

↓

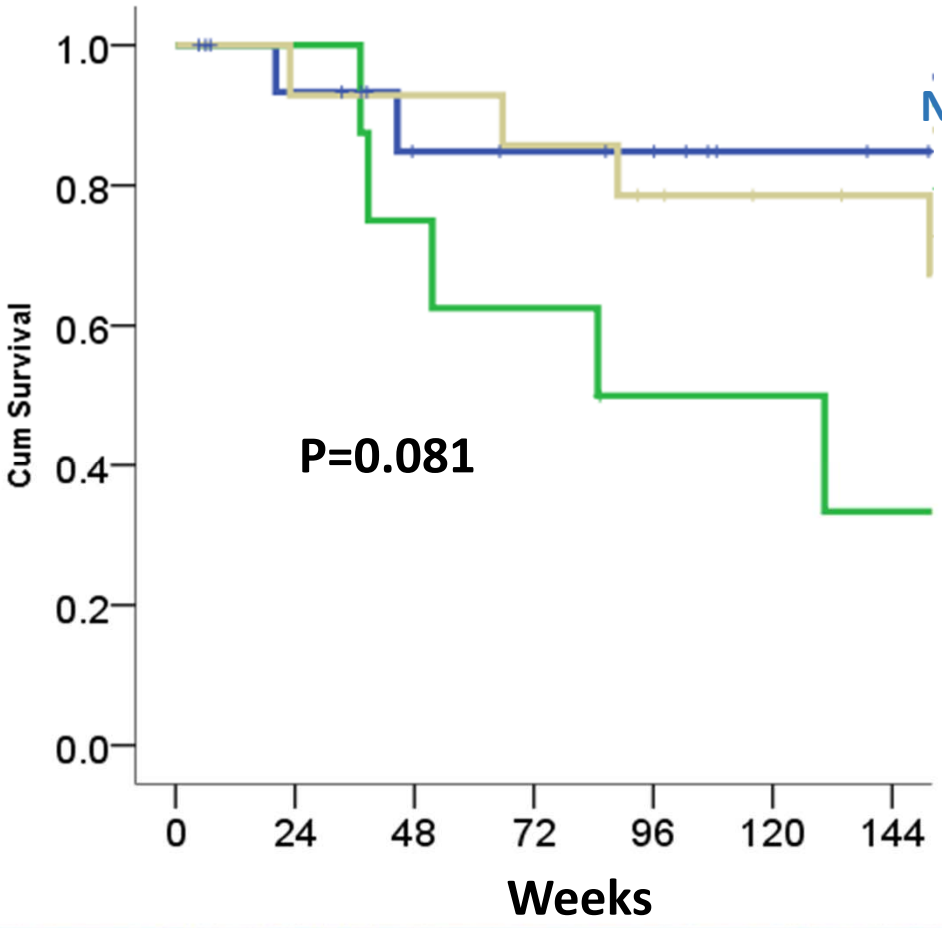
Repeat RFA done with complete response

Died 3 years 5 months after RFA from liver failure

HEAT STUDY:
RFA + Thermodox
63 y/o Male: 5.2 cm
62 minutes dwell time

snwong@ust.edu.ph

Repeat RFA Improves Survival After Recurrence



No recurrence (n=18)

Rpt. RFA after recur (n=14)

No rpt. RFA (n=8)

3 years survival:

82%

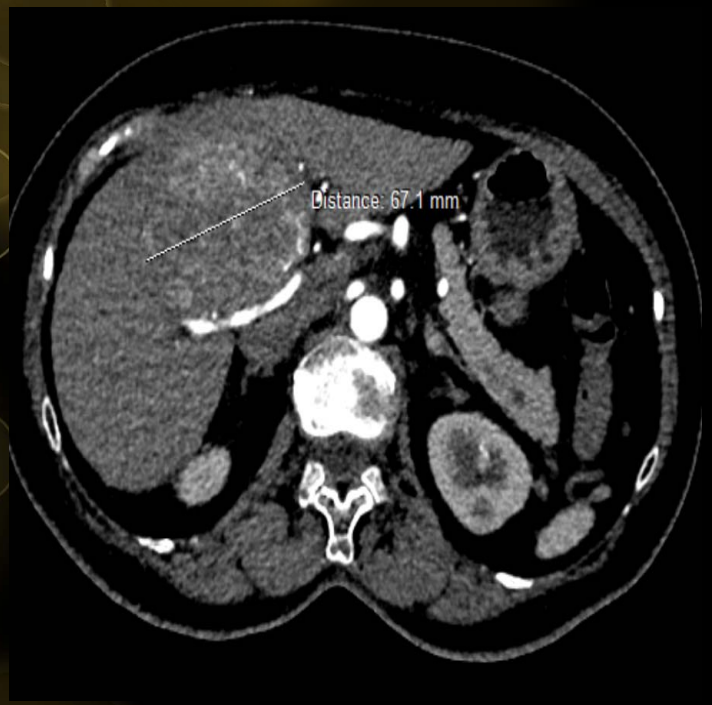
78%

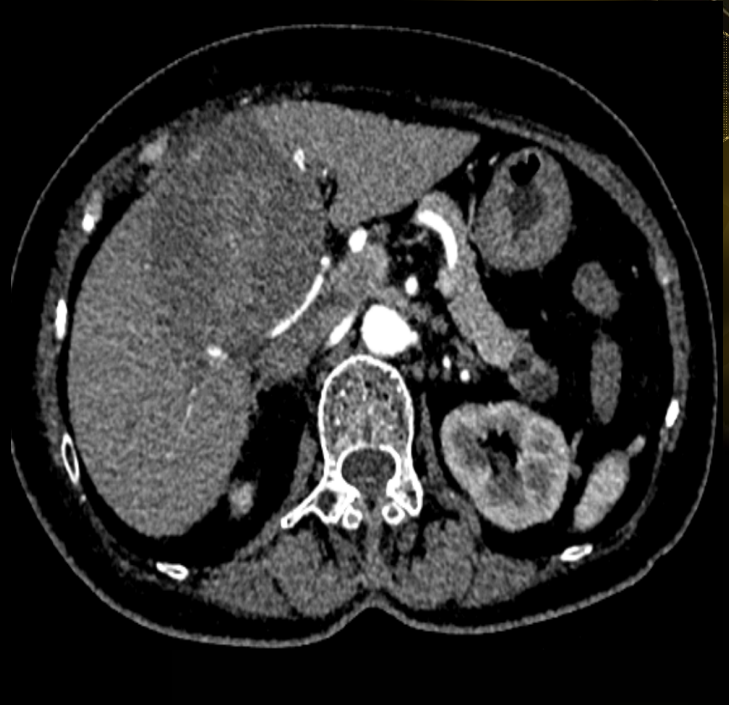
35%

swongliver@yahoo.com

Lim M & Wong S. APASL 2013

62





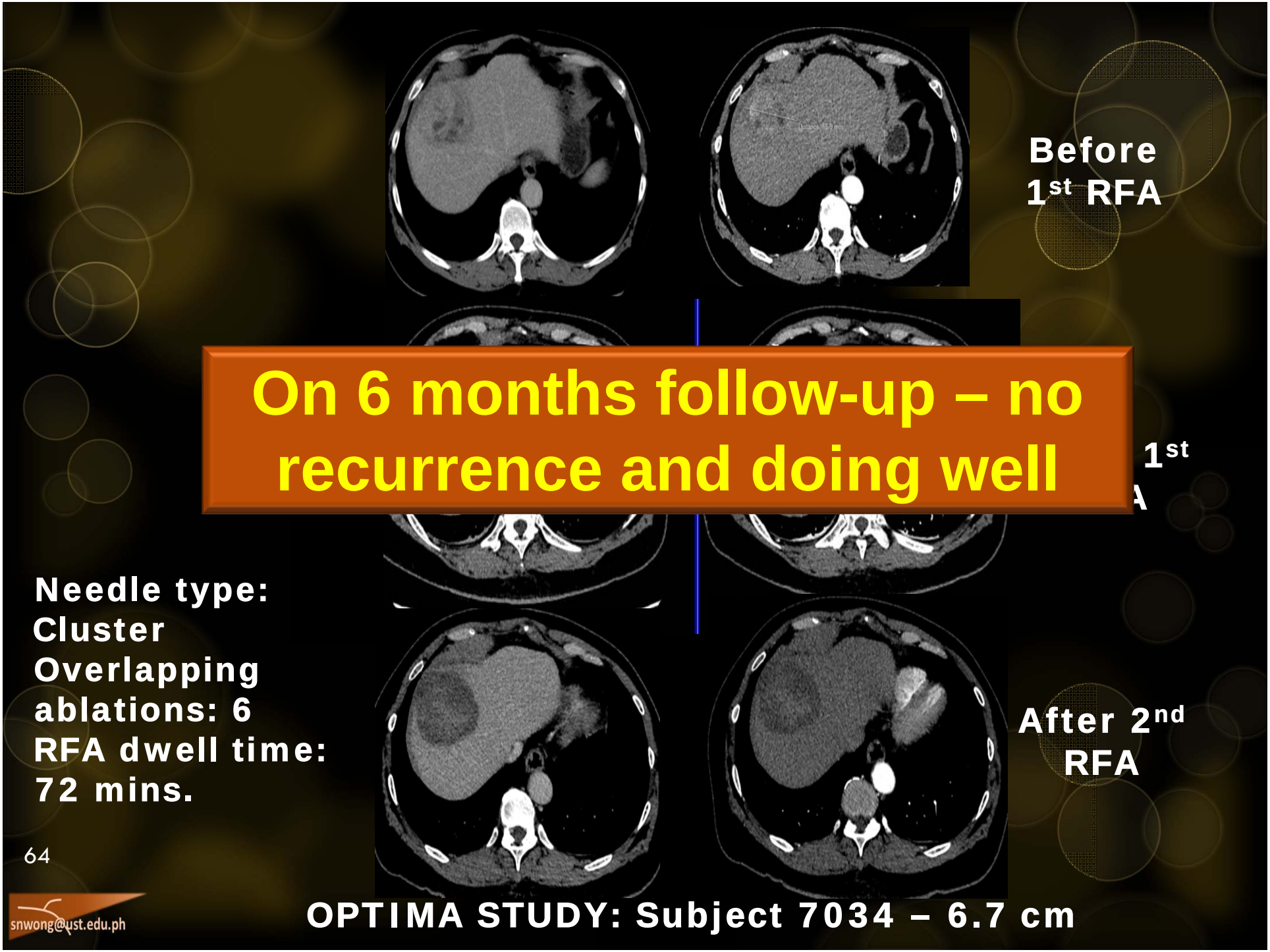
Before RFA

After RFA

OPTIMA STUDY:
Subject 7037 – 6.7 cm

Needle type: Cluster
Overlapping ablations: 10
RFA dwell time: 102 mins.

snwong@ust.edu.ph



OPTIMA STUDY: Subject 7034 – 6.7 cm

snwong@ust.edu.ph

SUMMARY

- Complete response is achieved for HCC 3-7 cm with RFA
- Complete response to RFA increases survival
- Recurrence can be re-treated with RFA with survival approaching those patients with no recurrence after RFA

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Thank You for your attention!

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Medical Faculty of University of Saarland,
Homburg, Germany

R&D Day

ThermoDox - Targeted Chemotherapy

Options for Local-Ablative Treatment of Large Hepatocellular Carcinoma

Celsion

UKS
Saarland University
Medical Center

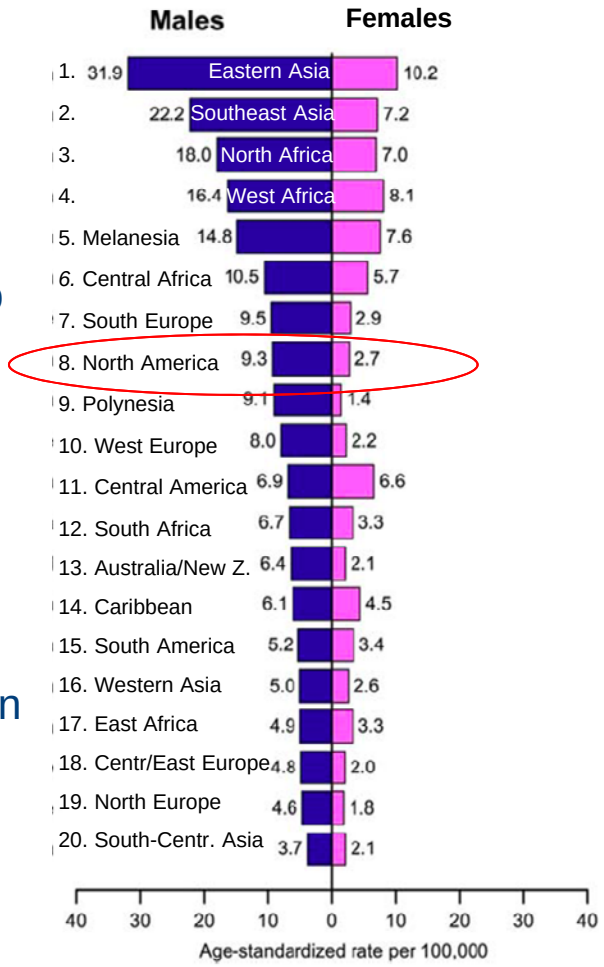
Options for local-ablative treatment of large hepatocellular carcinoma

Agenda

1. 3 facts, 3 tasks
2. 8 options to achieve the goals
3. OPTIMA
4. summary and outlook

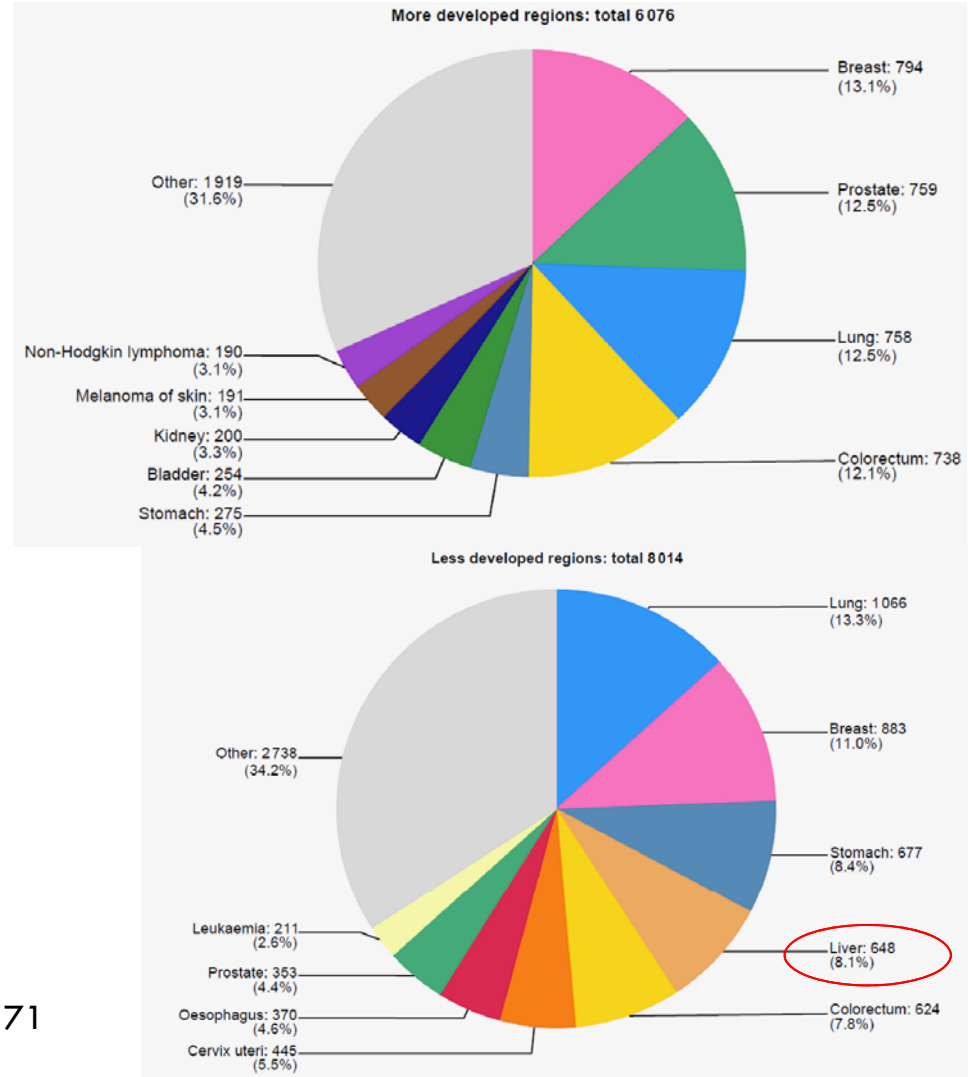
HCC: a worldwide problem

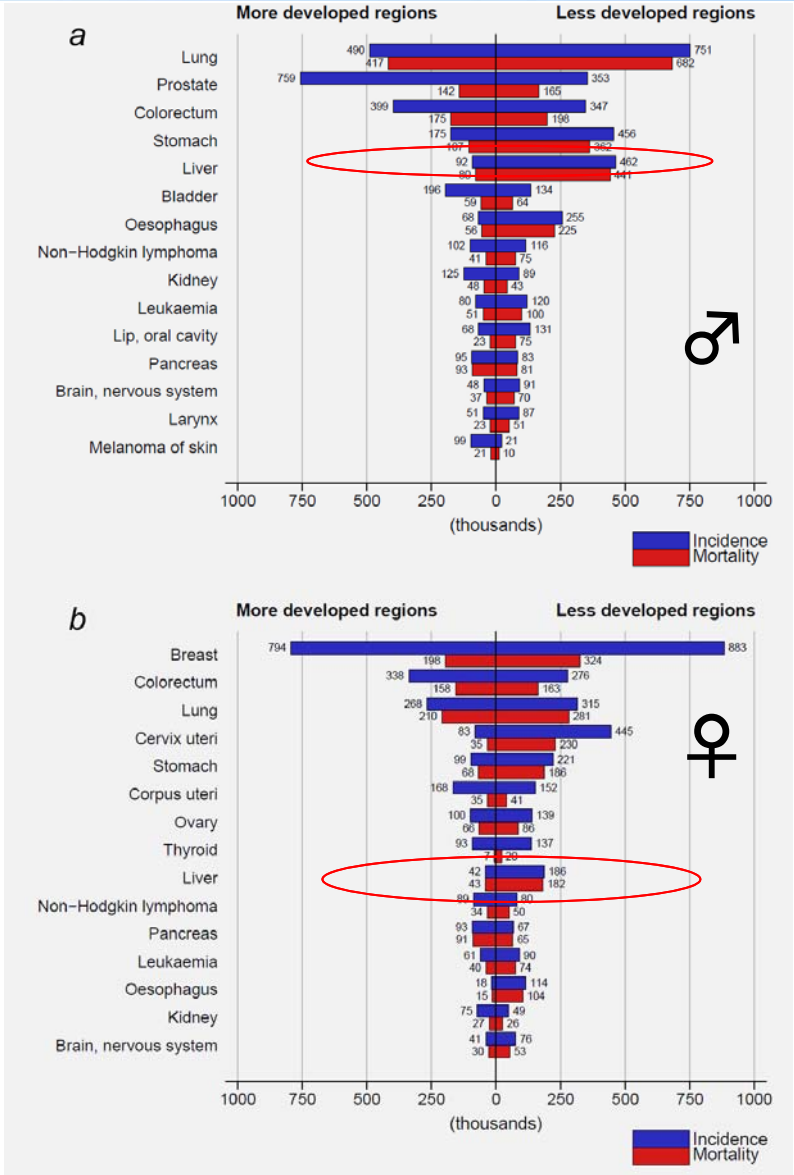
- Worldwide 782.500 cases of **new HCC diagnoses** in 2012
- Worldwide 745.500 **deaths** due to HCC in 2012
- North America in 8th place of the worldwide hit list; HCC is most common in Eastern/ South Eastern Asia

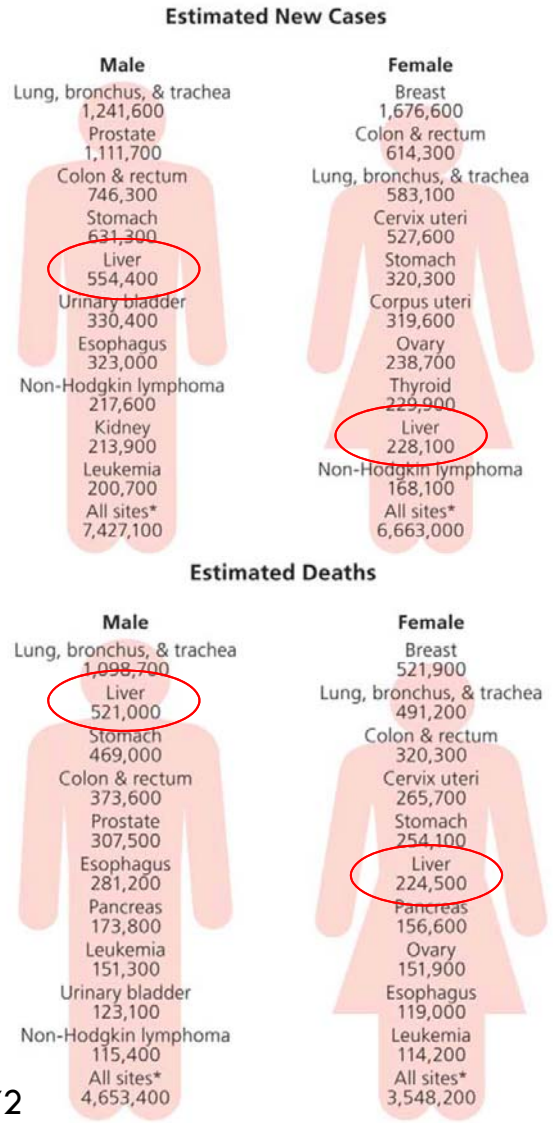


Torre et al., *CA Cancer J Clin* **2015,** 65: 87-108

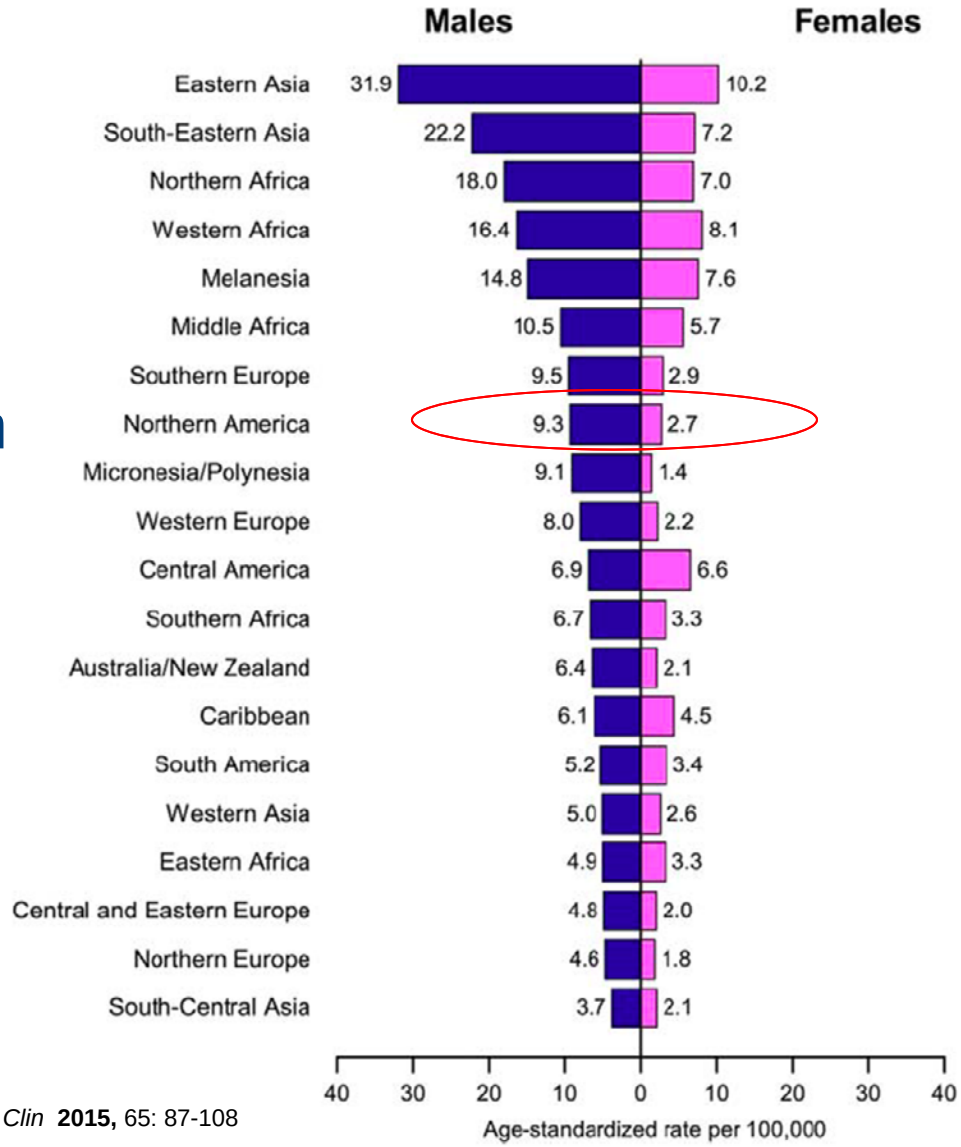
HCC: a developmental problem







HCC: a gender specific problem



Torre et al., *CA Cancer J Clin* **2015,** 65: 87-108

First facts:

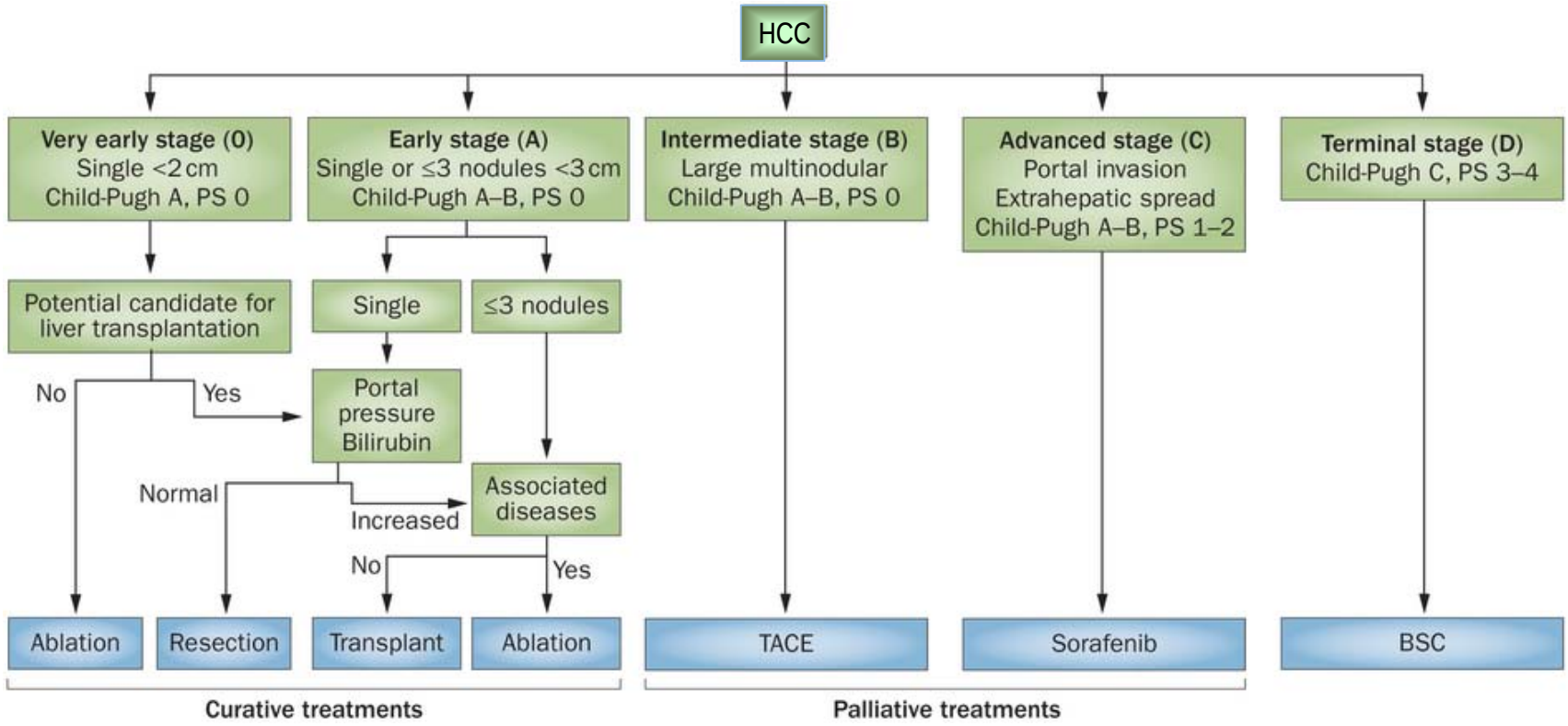
1. The worldwide incidence of HCC is high and still rising
2. HCC is not equally distributed over the planet
3. HCC is more common in males and in less developed countries

First task:

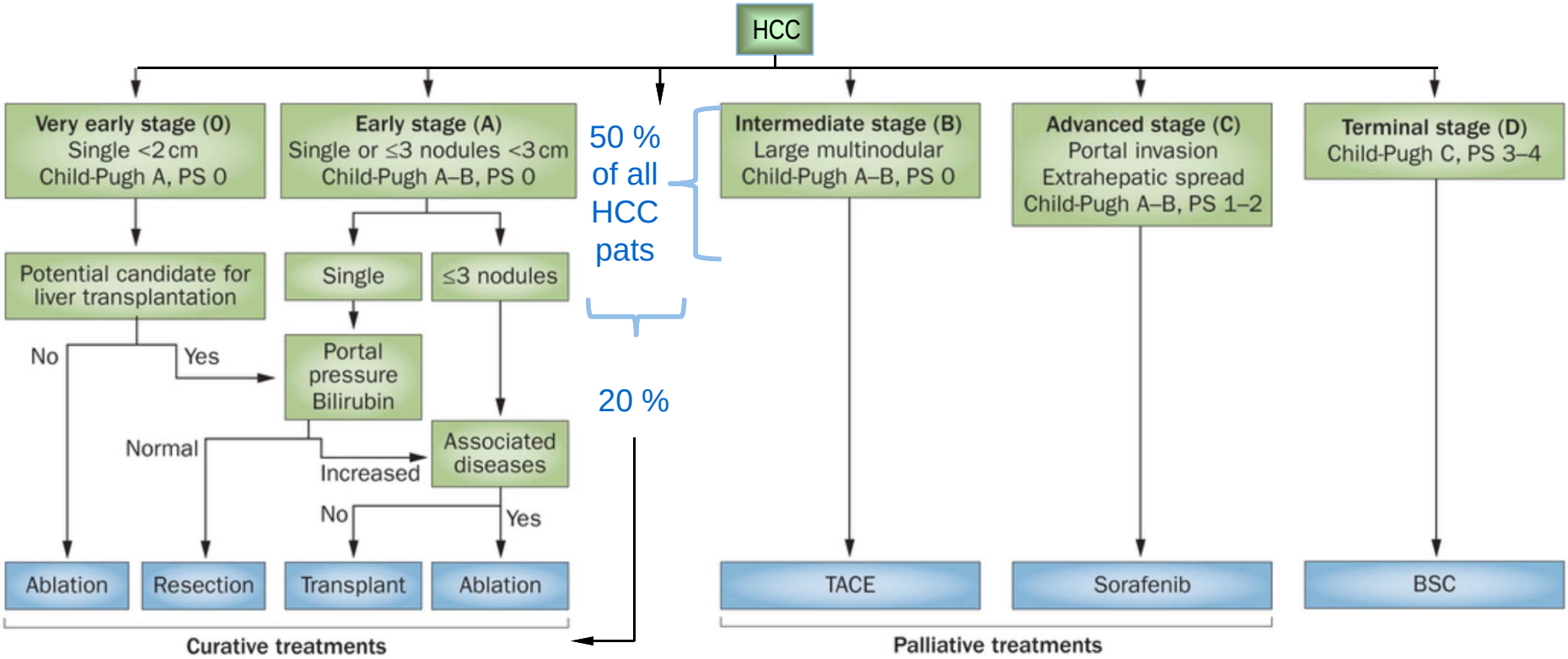
Tailored treatment strategies should be

made available also to regions

outside Europe and North America!



The Barcelona Clinic Liver Cancer staging system classifies large HCC into the Intermediate stage B.



Han et al., *World J Gastroenterol* **2015,** 21: 103277-35

Kayaalp et al., *Hepatoma Res* **2015,** 1: 165-70

Second fact:

The vast majority of all HCC patients are assigned to BCLC stage B.

Only 20 % of them are amenable to potentially curative treatment strategies.

Second task:

Increasing the rate of patients which are potentially amenable to a curative treatment option!

Risk stratification in liver surgery

Treatment of large HCC using RFA

	n	Def.	Mean size	Range	Follow-up	Technology	Technique	Local control
Buscarini 1999	14	> 3.5 cm	5.2 cm	3.8 – 6.8 cm	13 (6-23)	TACE => RFA [3 days]	single abl. intended	78 %
Livraghi 2000	114	> 3.0 cm	5.4 cm	3.1 – 9.5 cm	6	simple RFA	< 4 cm single abl. intended, > 4 cm multiple overlapping (2-4)	52 %
Chen 2004	68	> 3.5 cm	4.8 cm	3.6 – 7.0 cm	11 (3-26)	simple RFA	multiple overlapping (geometrical model)	81 %
Miyamoto 2004	3	> 4.0 cm	5.2 cm	4.4 – 5.7 cm	n.a.	simult. TAE+RFA+HVBO	single abl. intended	66 %
Sakr 2005	40	> 5.0 cm	7.3 cm	5.5 – 9.7 cm	12	RFA => PEI [2-3 weeks]	multiple overlapping (3 [< 7 cm], or 4 [> 7 cm])	80 %
Vallone 2006	40	> 4.0 cm	4.7 cm	4.1 – 7.0 cm	35 (7-69)	simult. RFA+PEI	single/double abl. intended	95 %
Kurokohchi 2006	1	-	7.0 cm	-	short	TACE => simult. RFA+PEI [7 days]	double abl.	100 %
Zangos 2007	32	> 5.0 cm	n.a.	5.0 – 8.0 cm	36	3-5x TACE => LITT [4-6 weeks]	multiple overlapping (3 [2-5])	63 %
Seror 2008	26	> 5.0 cm	5.7 cm	5.0 – 9.0 cm	14 (3-34)	simple RFA	single or double abl. intended (multipolar)	69 %
Tarantino 2009	29	> 3.0 cm	5.5 cm	3.0 – 7.5 cm	8 (2-15)	simple RFA	single abl. intended	72 %
Hirooka 2010	20	< 15.0 cm	5.7 cm	+/- 2.1 cm	31 (24-36)	RFA => HAI [9 days (5-14)]	single abl. intended	30 %
Iezzi 2015	40	> 3.0 cm	4.7 cm	3.2 – 7.5 cm	24 +/- 17	simultaneous RFA+DEB-TACE	single abl. intended	63 %

Third fact:

The efficacy of local ablation of large HCC is limited and insufficient.

Third task:

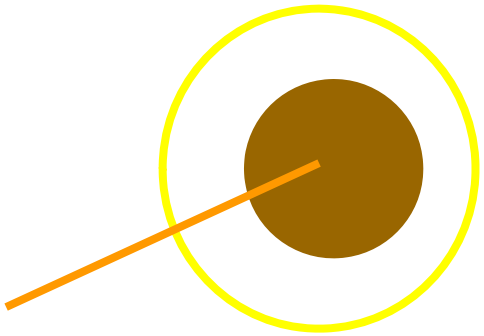
Increasing the local control rate in patients with

large HCC undergoing thermoablation!

8 options to increase the efficacy of local ablation for HCC

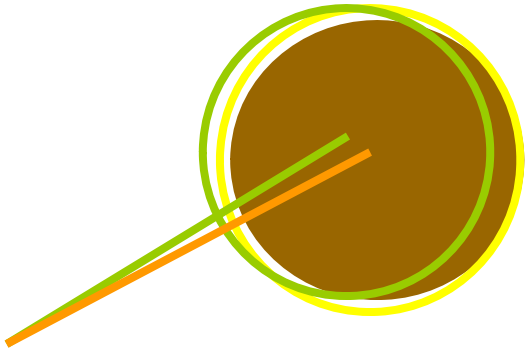
- Abate the safety margin
- Change the technology
- Change the access route
- Reduce the tissue perfusion
- Combine with TACE
- Going multipolar
- Create compound lesions
- Use thermosensitizer

First option: Reducing the safety margin



"meaningful margin"

Risk factor for local recurrence	No. of patients included	*p*
Tumor size >3/>5 cm	1817	<0.001
Entity metastasis (vs. HCC)	4605	<0.001
Proximity to major vessel	375	<0.001
Superficial tumor site	70	<0.001
Percutaneous approach	4424	<0.001
Safety margin ≤5 mm (vs. 10 mm)	5224	<0.001
No pringle maneuvre performed	4690	<0.05
Local anesthesia/sedation	2491	<0.001
Modality of image guidance	4341	n.s.
Unexperienced interventionalist	4495	<0.001
Early years of intervention	5224	n.s.



Influence of safety margin upon local recurrence

Mulier et al., *Ann Surg* **2005,** 242: 158-71

First option: Reducing the safety margin

NO OPTION

EXPERIENCE WITH MICROWAVE COAGULATION THERAPY IN THE TREATMENT OF LARGE HEPATOCELLULAR CARCINOMA

AUTHOR/YEAR	ACCESS	N	DEF.	MEAN SIZE (RANGE)	FOLLOW-UP (MON.)	TECHNOLOGY	TECHNIQUE	LOCAL CONTROL RATE
Yu Z et al. 2009	percutaneous	4	> 5 cm	9.0 cm (6.1-13.8)	13 (3-19)	Simple MCT	Double, triple or multiple overlapping	75%
Liu FY et al. 2010	percutaneous	39	> 4 cm	4.2 cm (4.0-4.8)	9 (6-24)	Simple MCT	Double/triple + 2nd abl. if appropriate	60%
Liu Y et al. 2013	percutaneous	80	> 3 cm	4.6 cm (3.1-8.0)	32 (2-95)	Simple MCT	Multiple overlapping (2-9)	68%
Liang PC et al. 2014	laparoscopic/ open surgical	10	> 4 cm	5.7 cm (4.0-7.0)	17 (> 12)	Simple MCT	Multiple overlapping (1-4)	70%
Sun AX et al. 2015	percutaneous	182	> 3 cm	3.7 cm (3.0-5.0)	18 (3-37)	Simple MCT	Multiple overlapping (number not reported)	73%
Abdelaziz AO et al. 2015	percutaneous	32	> 5 cm	5.7 cm (5.0-7.0)	22 (not reported)	Simple MCT	Not reported	59%
Liang PC et al. 2015	percutaneous/ laparoscopic/ open surgical	14	> 5 cm	5.8 cm (5.0-7.0)	16 (13-19)	Simple MCT	Multiple overlapping (1-4)	75%

Second option: Use of MCT instead of RFA
Comparative trials

Ref.	Method	Guidance	Patients	Lesions	Mean age	Time	Size in cm	Complete ablation (%)	Local recurrence (%)	Overall survival					
										1 yr (%)	2 yr (%)	3 yr (%)	4 yr (%)	5 yr (%)	Median (mo)
Shibata *et al*[50]	MWA	Percutaneous	36	46	62.5	-	< 4	89	17.4	-	-	-	-	-	-
	RFA	Percutaneous	36	48	63.6	-	< 4	96	8.3	-	-	-	-	-	-
Xu *et al*[84]	MWA	Percutaneous	54	112	53.4	-	2.5 ± 1.1	94.6	7.1	-	-	-	-	-	-
	RFA	Percutaneous	43	78	53.4	-	2.6 ± 1.4	89.7	12.8	-	-	-	-	-	-
Simo *et al*[85]	MWA	Laparoscopic, US	13	15	59	8-10 min	2.31	-	-	-	-	-	-	-	7
	RFA	Laparoscopic, US	22	27	59	10-12 min	2.53	-	-	-	-	-	-	-	19
Lu *et al*[78]	MWA	Percutaneous, US	49	98	50.1	5 min	3 (25/49)	94.9	11.8	81.6	61.2	50.5	36.8	-	32.5
	RFA	Percutaneous, US	53	72	54.5	10 min	3 (32/53)	93.1	20.9	71.7	47.2	37.6	24.2		27.1
Qian *et al*[63]	MWA	Percutaneous, US	22	22	52	-	4.8	95.5	18	-	-	-	-	-	-
	RFA	Percutaneous, US	20	20	56	-	3.5	95	15	-	-	-	-	-	-
Zhang *et al*[86]	MWA	Percutaneous, US	77	105	54	8 min	< 3 (36), 3.1 to 5 (41)	86.7	10.5	92.2	-	51.7	-	38.5	-
	RFA	Percutaneous, US	78	97	54	6-20 min	< 3 (47), 3.1 to 5 (31)	83.4	11.8	91	-	64.1	-	41.3	-
Abdelaziz *et al*[79]	MWA	Percutaneous	66	-	53.5	-	2.9 ± 0.97	96.1	3.9	96.4	62	-	-	-	-
	RFA	Percutaneous	45	-	56.8	-	2.95 ± 1.03	94.2	13.5	67.6	47.4	-	-	-	-
Ding *et al*[81]	MWA	Percutaneous	85	98	59	10	< 3	98.5	10.9	98.7	92.3	82.7	77.8	-	45.34
	RFA	Percutaneous	113	131	58.6	12	< 3	99	5.2	98	90.7	77.6	77.6	-	52.99
Ohmoto *et al*[80]	MWA	Percutaneous	49	56	64		< 2		19	89	70	49	39	-	-
	RFA	Percutaneous	34	37	67		< 2		9	100	83	70	70	-	-

Green: favouring MCT

Red: favouring RFA
(be aware of larger tumor sizes treated with MCT!)

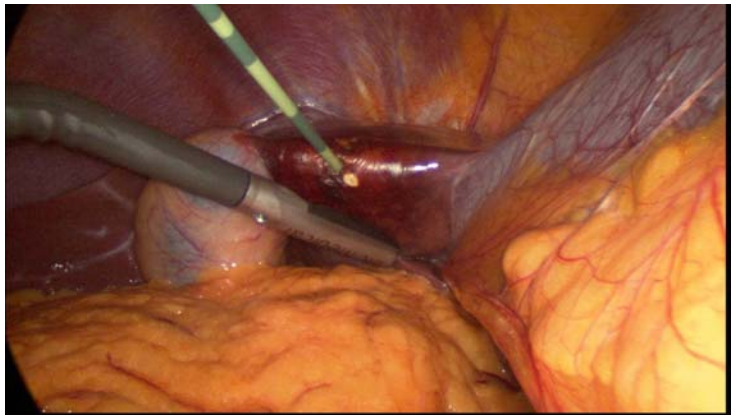
Poulou et al., *World J Hepatol* **2015,** 7: 1054-63

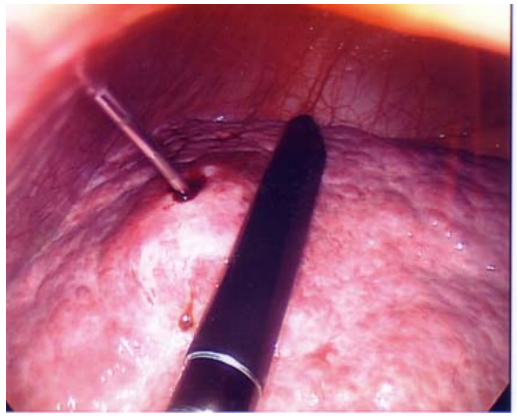
Second option: Change the technology

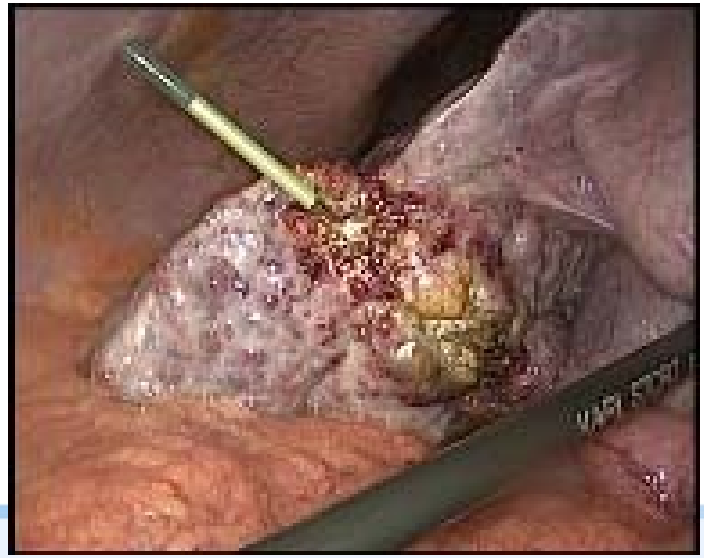
NO EVIDENCE

Third option: Surgical access to ablation

- Minimally invasive
- Low risk procedure
- Superficial tumor site
- High frequency ultrasound
- Precise needle placement
- Pringle maneuvre appliable
- Effect of pneumoperitoneum







Clinical results of MCT

	Total	Laparoscopic	Percutaneous	Statistics
Age (years)	64.5	65	64	p=0.29 (t-test)
Gender (♂/♀)	15/36	7/13	8/23	p=0.34 (χ2-test)
Tumor size (mm)	25.5	26	25	p=0.12 (t-test)
Follow-up (Months)	20	20	19	p=0.59 (t-test)
Recurrence	39%	19%	52%	p=0,011(χ2-test)
Local recurrence	**12%**	**4%**	17%	p=0.032 (χ2-test)

Eisele et al., *Zentralbl Chir* **2014,** 139: 235-43

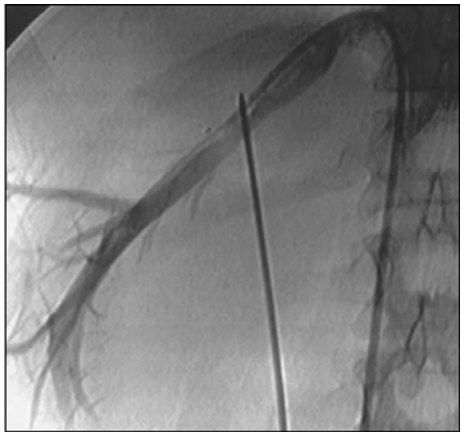
Third option: Surgical access to ablation

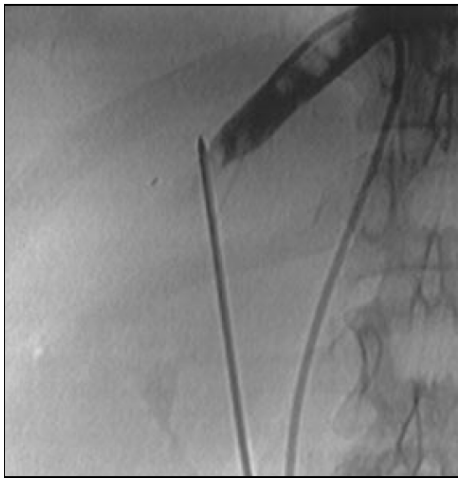
ABSOLUTELY AN OPTION

Third option: Surgical access to ablation

ABSOLUTELY AN OPTION

Fourth option: Reducing tissue perfusion





Seminal work:

- 10 patients, 2 HCCs
- Average tumor size 34 mm

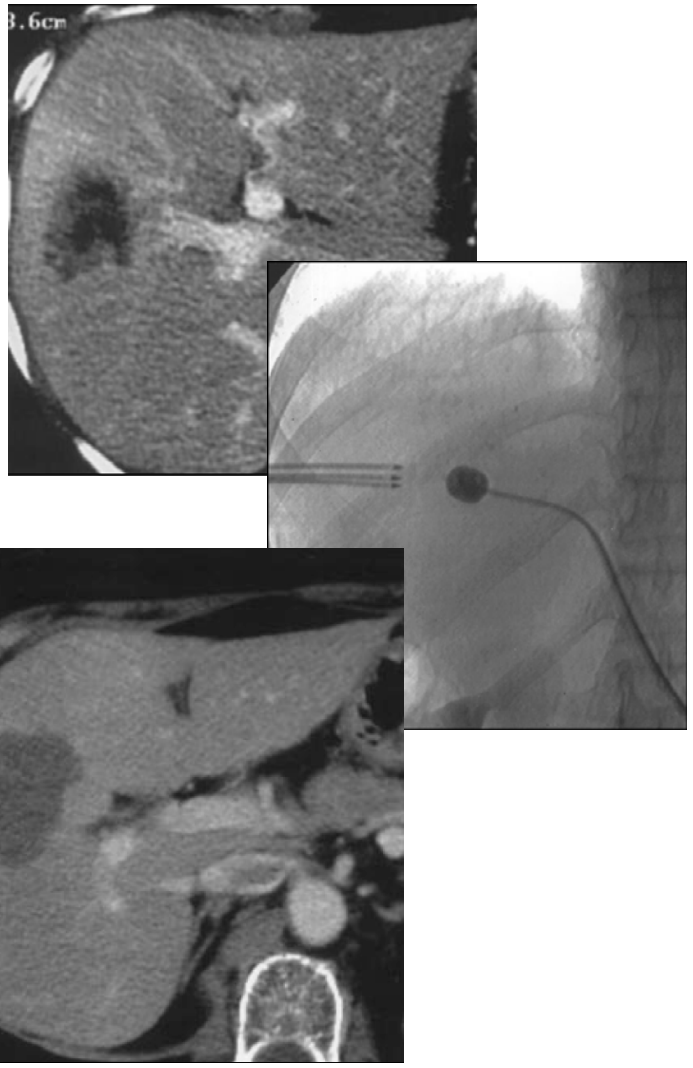
Matched to 18 other pats.

Ablation area (mm):
51 +/- 10 x
48 +/- 7

vs.

33 +/- 6 x
27 +/- 7

p< 0.0003



de Baere et al., *Am J Roentgenol* **2002,** 178: 53-9

Fourth option: Reducing tissue perfusion

USEFUL OPTION

- Pneumoperitoneum
- Pringle maneuvre
- Balloon occlusion

Fifth option: Combination with TACE

Two meta-analyses

Tumor size	Survival			
	1 yr	3 yr	5 yr	
< 3 cm	*p = 0.06*	*p = 0.40*		
> 3 cm	*p = 0.01*	*p = 0.0003*	*p < 0.0001*	
> 5 cm	*p = 0.0004*	*p < 0.00001*		

Ni et al., *World J Gastroenterol* **2013,** 19: 3872-82

				Morbidity
< 3 cm	*p = 0.46*	*p = 0.49*		*p = 0.96*
> 3 cm	*p = 0.0004*	*p = 0.0002*	*p = 0.0001*	*p = 0.55*

Lu et al., *Eur J Gastroenterol Hepatol* **2013,** 25: 187-94

Fifth option: combination with TACE

EVIDENCE BASED, GOOD OPTION

Sixth option: Bipolar RFA

Number of patients	Access		
74	58 laparoscopic	14 open surgical	2 percutaneous

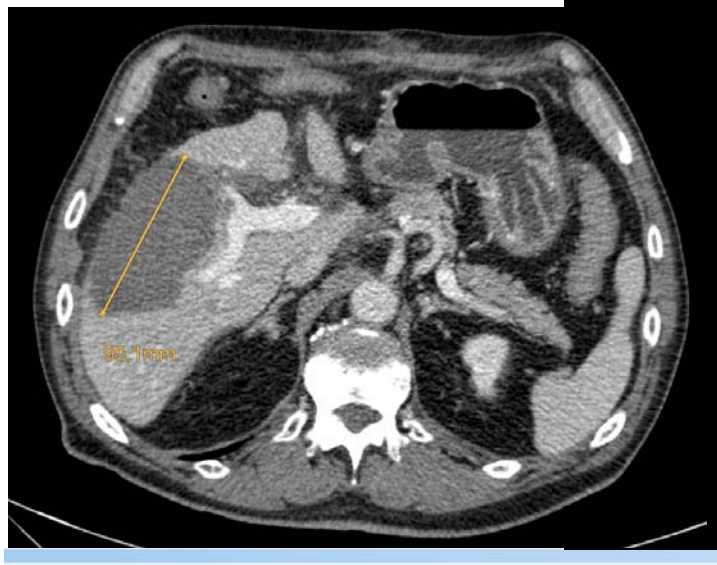
Indications:

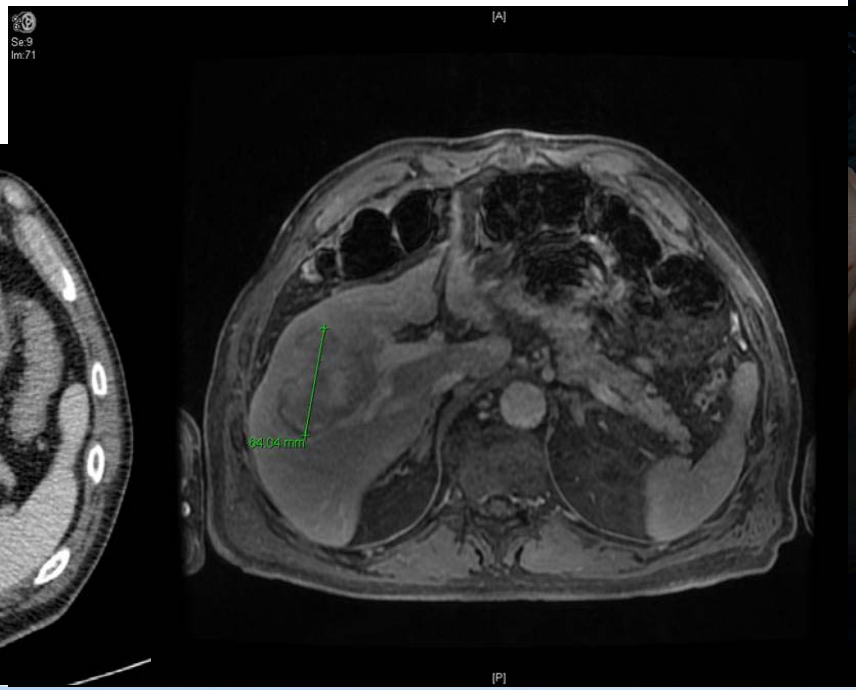
39 metastases | 31 primary liver malignancies | 4 benign tumors

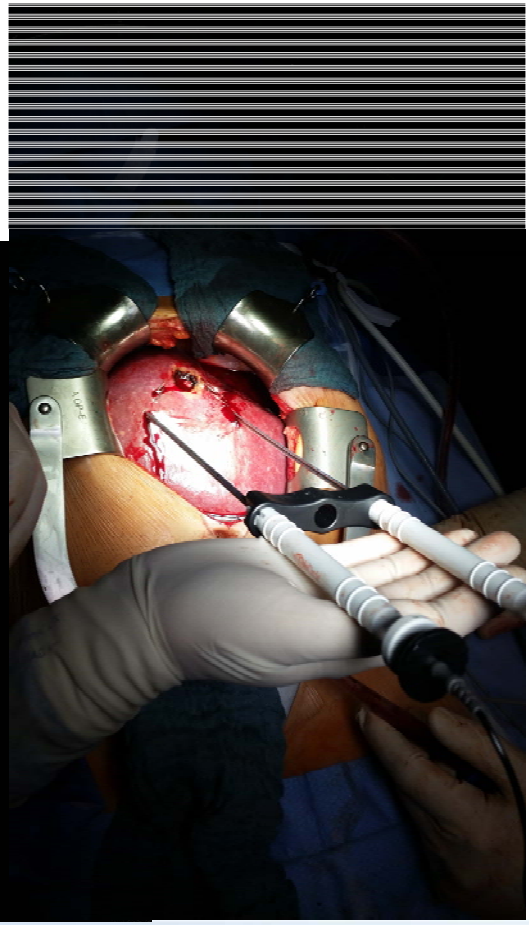
Average tumor size: appr. 5 cm !

Local recurrence rate: 11 % !

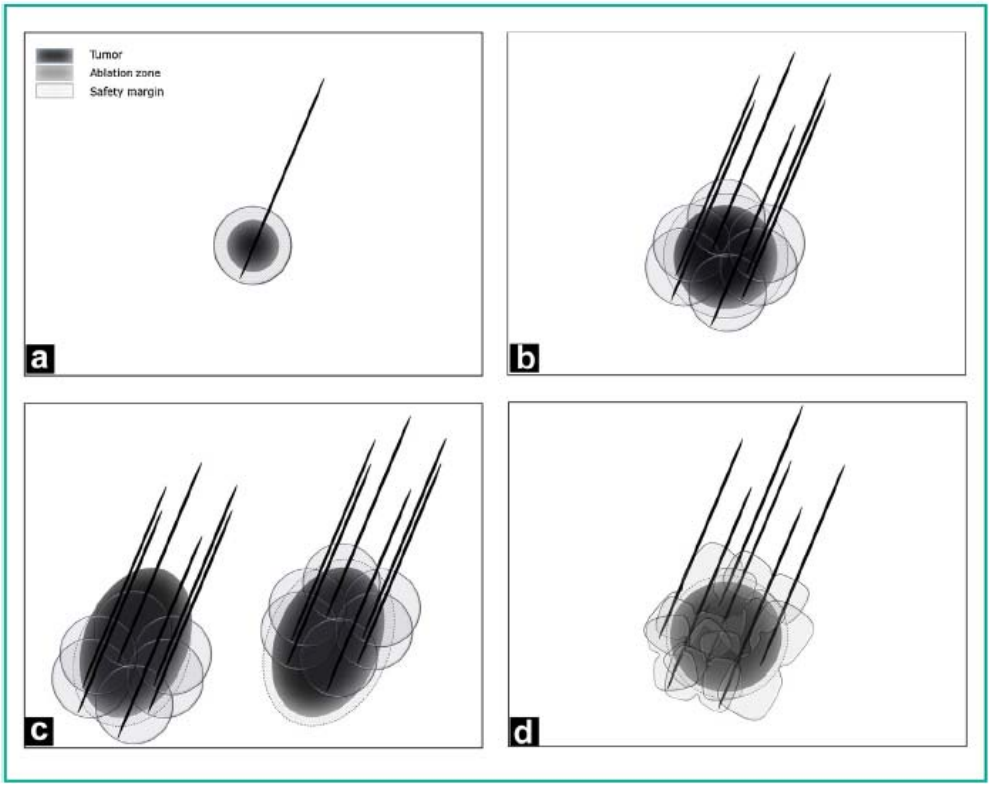
Morbidity appr. 16 % !







Multiple bipolar RFA



Seror O, *Diagn Interv Imaging* **2015**, 96: 617-24

Large (≥5.0-cm) HCCs: Multipolar RF Ablation with Three Internally Cooled Bipolar Electrodes—Initial Experience in 26 Patients[1]

Characteristics of Tumors and Treatments in 27 HCCs 5.0 cm or Larger according to Early Response to Multipolar RF Ablation

Parameter	Complete Ablation ($n = 22$)	Incomplete Ablation ($n = 5$)
Tumor characteristic		
Diameter (cm)*	5.9 ± 0.9 (5.0–8.0)	6.2 ± 1.7 (5.0–8.5)

Characteristics of Tumors and Treatments in 22 of 27 HCCs 5.0 cm or Larger That Were Completely Ablated with Multipolar RF Ablation according to the Occurrence of Local Tumor Progression during Follow-up

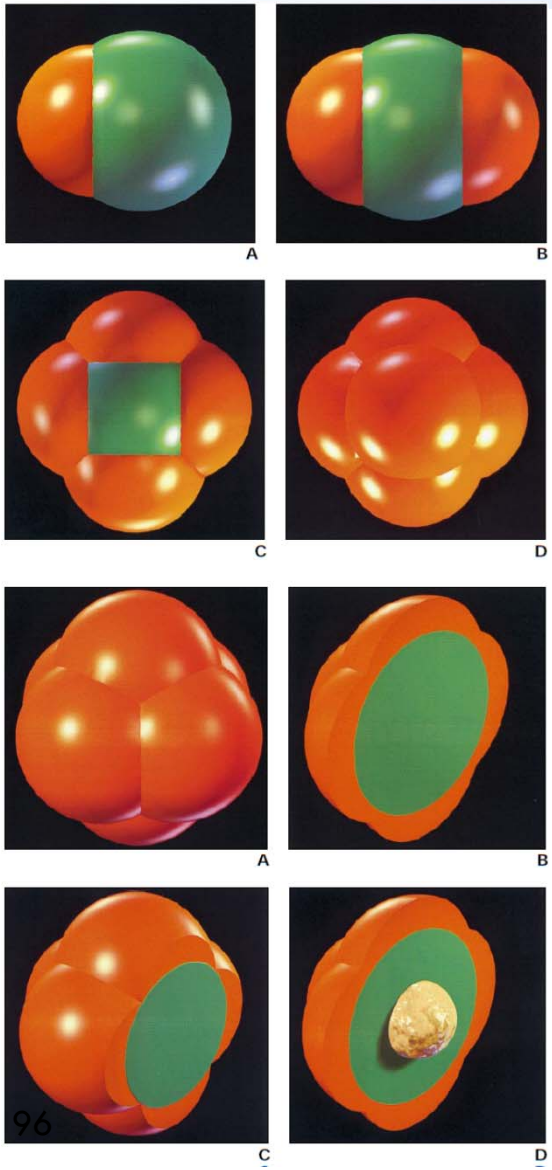
Parameter	No Local Tumor Progression ($n = 19$)	Local Tumor Progression ($n = 3$)
Tumor characteristic		
Diameter (cm)*	5.8 ± 0.7 (5.0–7.5)	6.5 ± 1.5 (5.0–8.0)

Seror et al., *Radiology* **2008**, 248: 288-96

Sixth option: Bi-, Multipolar RFA

DEFINITELY AN OPTION

Seventh option: Compound lesions



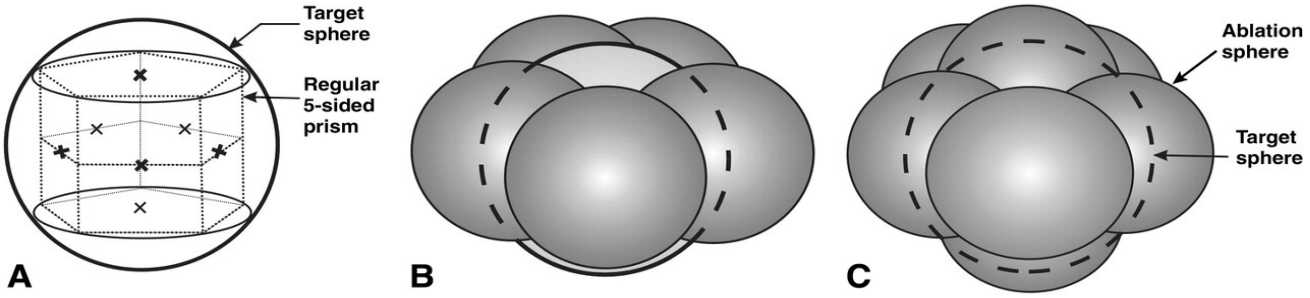


Figure 2. Computer representations of a regular five-sided prism model. *A,* Transillumination view of the model: A regular five-sided prism is inscribed in a target sphere. The ablation model is constructed by performing five ablations on the five lateral sides, one ablation on the upper side, and another ablation on the lower side, for a total of seven ablations. *B,* Anterosuperior view of the model: Five ablations are performed on lateral sides of the regular prism. *C,* Two additional spheres are used to cover the upper and lower sides. The drawing depicts the ablation volume encompassing the target sphere—that is, the tumor plus at least 0.5 cm of tumor-free margin. × indicates the target site of each ablation—that is, the ablation sphere center.

Chen et al., *Radiology* **2004,** 232: 260-71

A-D, Six-sphere ablation model is constructed by performing four ablations in the *x–y* plane (**A–C** sequentially) and two along the *z*-axis (**D**). Green sphere represents total volume of tissue requiring ablation (tumor plus 1-cm tumor-free margin), and red spheres represent individual thermal ablation spheres that are being overlapped. Largest composite ablation sphere is created when all spheres are overlapped by approximately 23% of diameter.

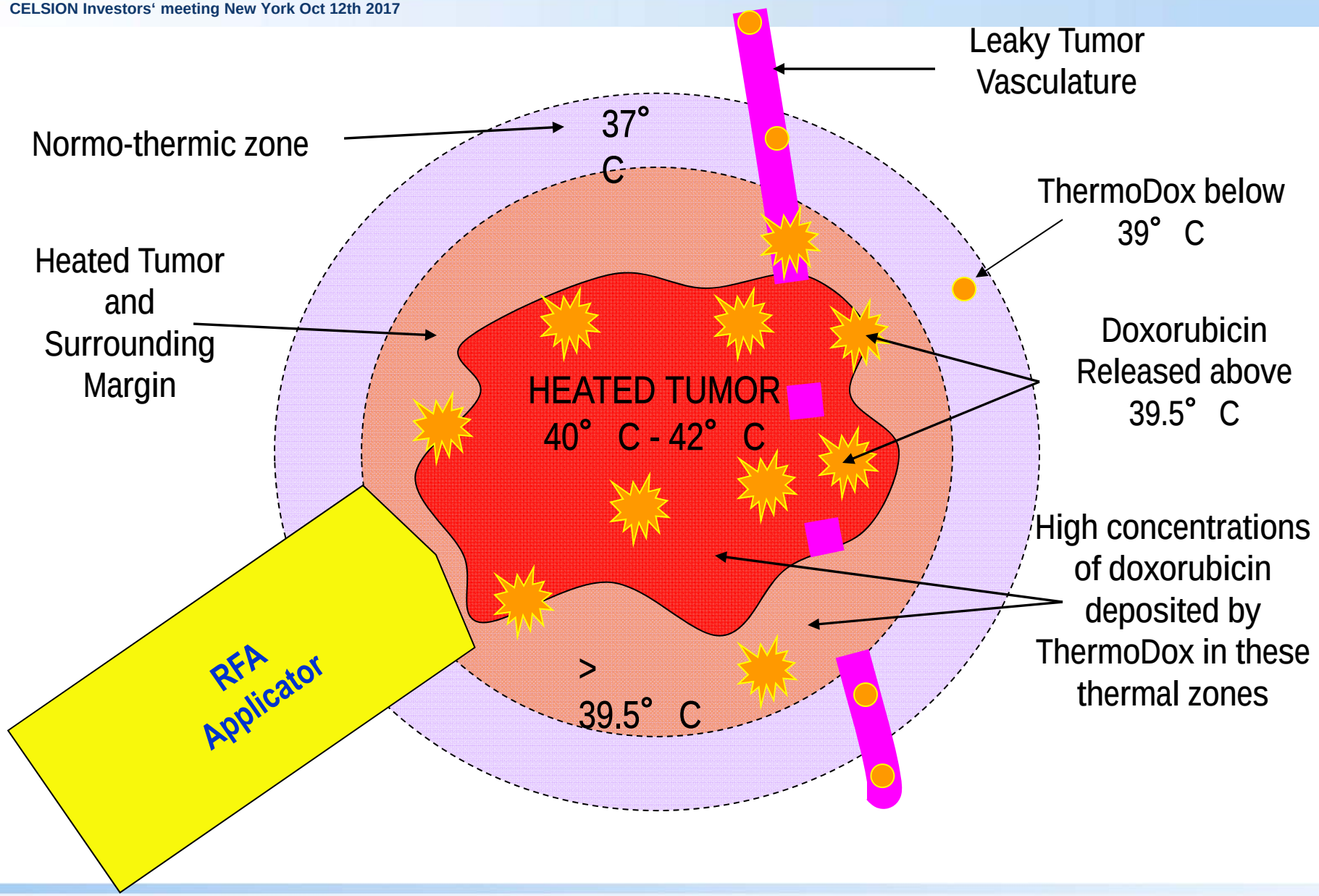
Dodd et al., *AJR* **2001,** 177: 777-81

Seventh option: Overlapping ablation areas

TECHNICALLY
DIFFICULT OPTION

Eighth option: A thermosensitizer

- Exclusive effect on tumor cells
- No systemic toxicity
- Temperature dependant
- Max. intratumoral concentration
- Ideally enhancing radiological visibility


Leaky Tumor
Vasculature
Normo-thermic zone
37°
C
ThermoDox below
39° C
Heated Tumor
and
Surrounding
Margin
HEATED TUMOR
40° C - 42° C
Doxorubicin
Released above
39.5° C
High concentrations
of doxorubicin
deposited by
ThermoDox in these
thermal zones
RFA
Applicator
>
39.5° C

OPTIMA Trial:

Celsion Protocol 104-13-302

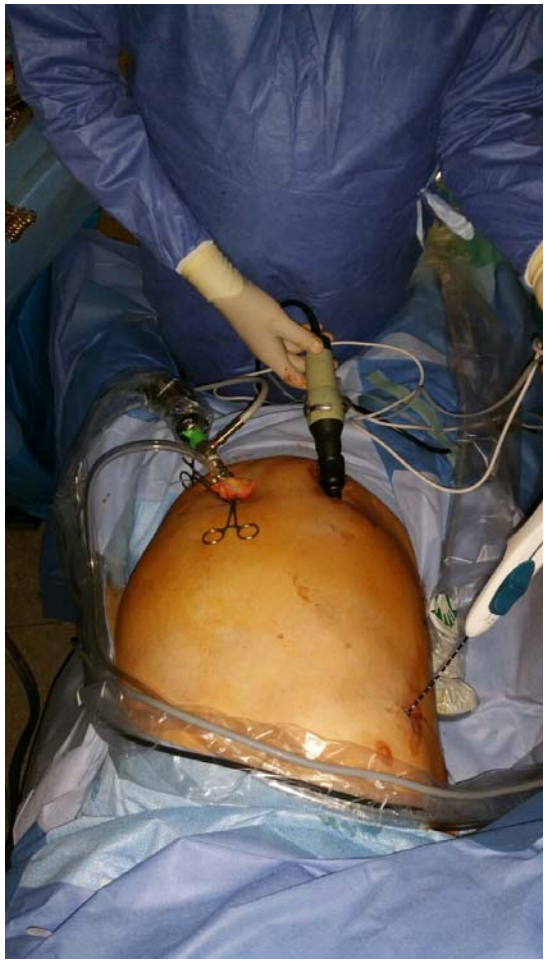
A Phase III, Randomized, Double Blind, Dummy-Controlled Study of ThermoDox® (Lyso-Thermosensitive Liposomal Doxorubicin-LTLD) in Hepatocellular Carcinoma (HCC) using standardized Radiofrequency Ablation (RFA) treatment time ≥ 45 minutes for solitary lesions ≥ 3 cm to ≤ 7 cm.

Celsion

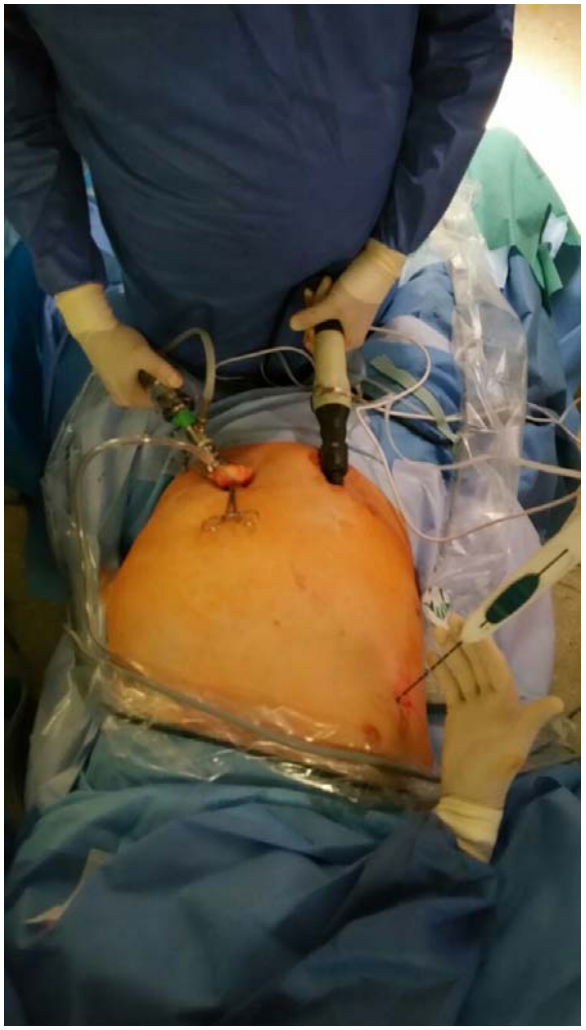
OPTIMA – preliminary experience

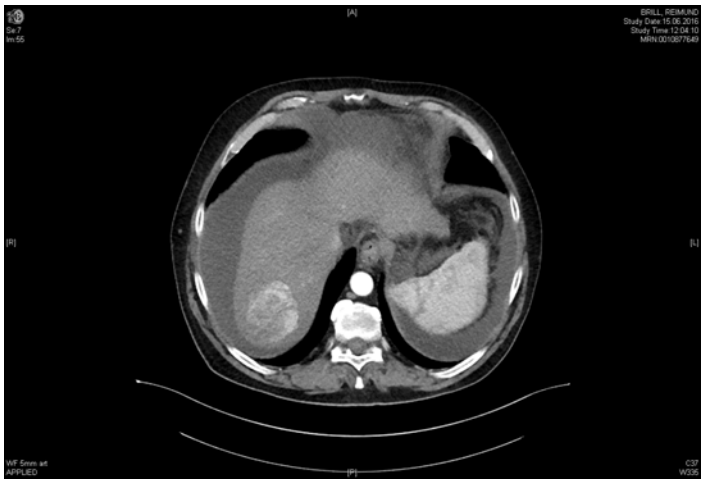
Pat.	Age	Size	min.	days	Seg.	access	f-u
1	78	4.7	170	15	IVa	Open	655
2	78	6.5	71	7	VIII	CT	604
3	77	4.0	93	4	VII	Sono	563
4	59	6.4	155	8	VII	Lap.	452
5	81	6.0	95	3	VIII	CT	381
6	80	4.4	95	2	V/VIII	Sono	136
7							

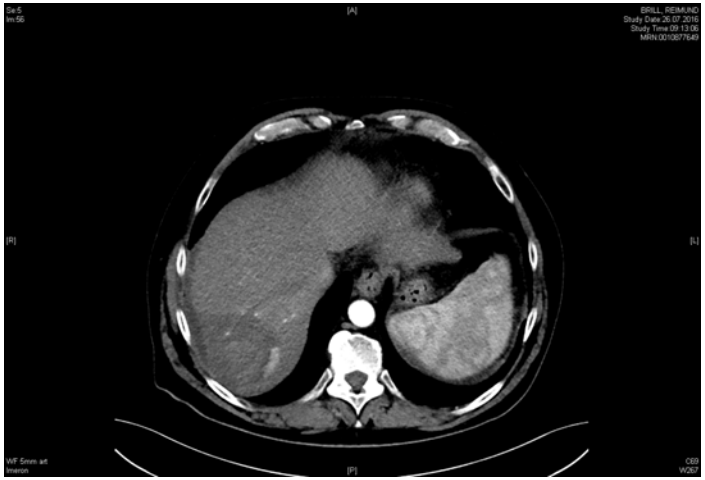
Pat.	f-u	access	initial success	f-u treatm.	LTR	rec.	Status
1	655	Open	complete	0	0	CR	alive
2	604	CT	complete	SIRT	113	PD	alive
3	563	Sono	complete	0	0	CR	alive
4	452	Lap.	incomplete	redo, MCT	0	CR	alive
5	381	CT	complete	0	0	CR	alive
6	136	Sono	complete	0	0	CR	alive
7							



OPTIMA – laparoscopic case







ThermoDox toxicity data

- Toxicity profile is similar to intravenous infusions of Adriamycin
  - Bone marrow suppression (nadir ~ 10-14 days post-infusion)
    - Bone marrow recovers by ~21 days
  - Mild to moderate alopecia
  - Nausea and Vomiting
  - Delayed cardiotoxicity cumulative dose (months/years)

Pat.	adverse side effects	suggestion
1	Stomatitis aphthosa, leucopenia, portal vein thrombosis (partial)	Verum
2	Urinary tract infection, leucopenia, alopecia	Verum
3	Pain, leucopenia, alopecia	Verum
4	None	Placebo
5	Elevated inflammation markers in clinical chemistry	?
6	None	Placebo
7		

Eighth option: ThermoDox

A PROMISING OPTION !

Summary

- ~~Abate the safety margin~~
- Change the technology ?
- Change the access route ✓
- Reduce the tissue perfusion ✓
- Combine with TACE ?
- Going multipolar ✓
- Create compound lesions ?
- Use thermosensitizer ✓

Thank you very much for your patience!

DEUTSCHE GESELLSCHAFT FÜR ALLGEMEIN- UND VISZERALCHIRURGIE
DGAV
CHIRURGISCHE ARBEITSGEMEINSCHAFT LEBER GALLE PANKREAS
DGAV · CALGP
Kompetenzzentrum
Chirurgische Erkrankungen der Leber

Khursheed Anwer, Ph.D.

Executive Vice President and
Chief Science Officer

R&D Day

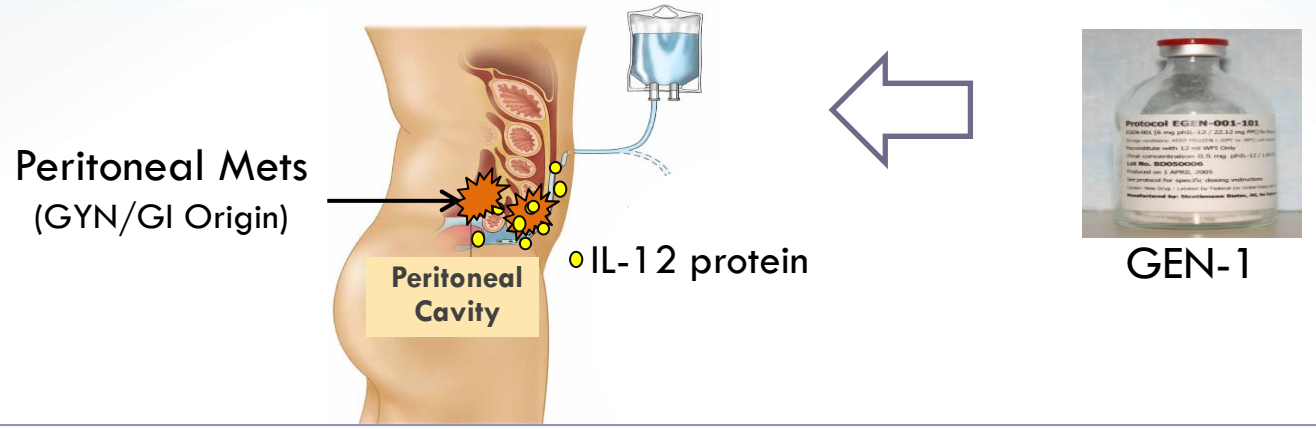
The Science of GEN-1

A DNA-based Immunotherapeutic

Celsion

GEN-1 Design Objectives

- To modulate the tumor microenvironment (TME) favoring immune stimulation through delivery of a potent immune agent IL-12 into peritoneal cavity in a local and persistent manner



Design Rationale

- TME modulation to shift the environment from immune suppression to immune activation is key to immunotherapy success
- Persistent immunotherapy levels at TME offer better safety/activity profile
- IL-12 is a naturally produced immune cytokine with multi-action immune profile

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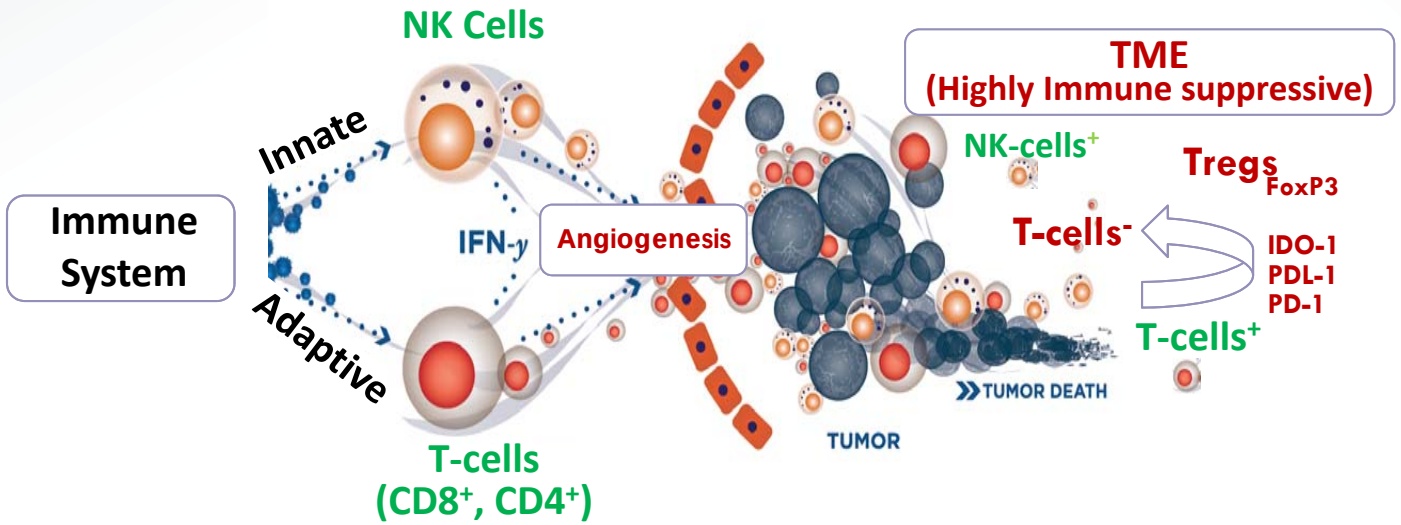
TME Modulation is Important for Effective and Durable Treatment of Cancer

TME is a Battleground b/w Immune Activation & Immune Suppression Factors

Red Font: Immune suppressive factors
Green Font: Immune activation factors



For an Effective & Durable Treatment the TME must be shifted from Immune Suppression to Immune Activation

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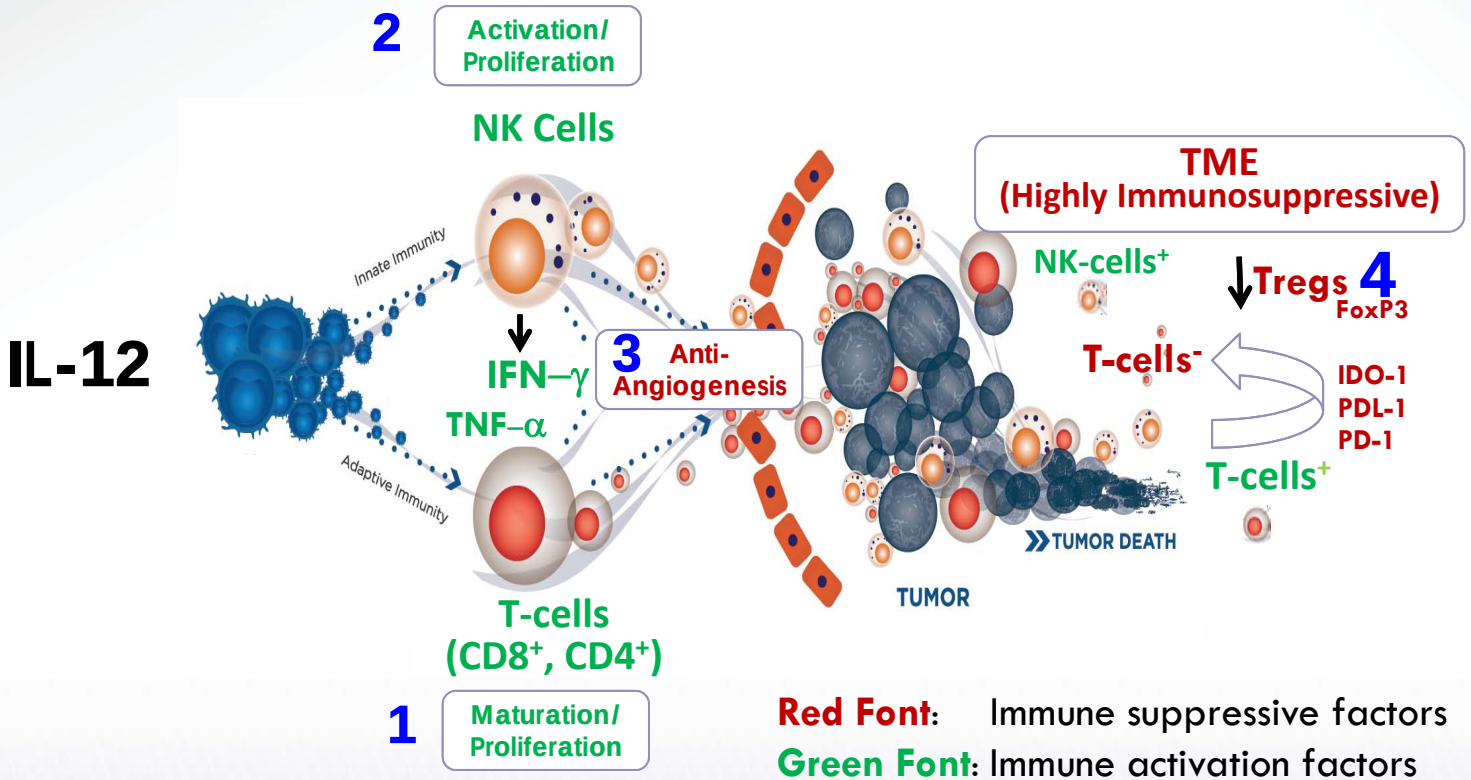
IL-12 is a Multifunctional Immune Modulating Agent Against Cancer

At least Four Distinct Mechanisms of Immune Modulation by IL-12

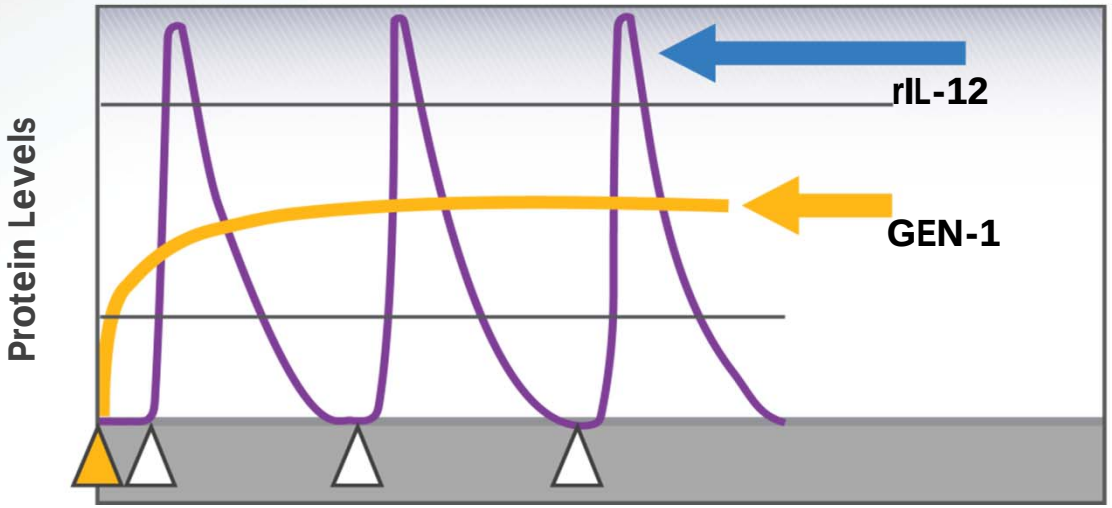


Red Font: Immune suppressive factors

Green Font: Immune activation factors

Celsion

Despite Clinical Benefits in Multiple Cancer Types Poor PK of rIL-12 Limits its Clinical Use

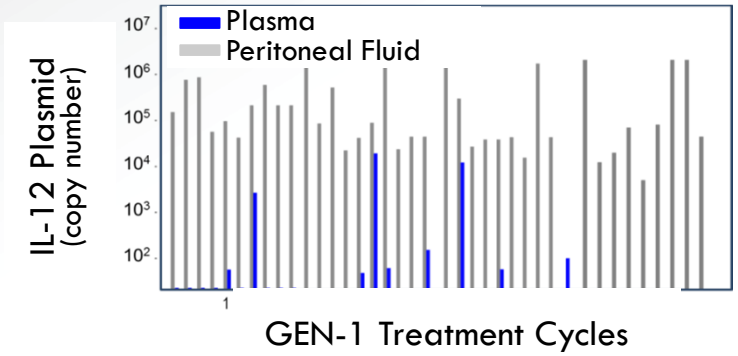


- Frequent bolus dosing, resulting in high systemic IL-12, serious toxicity, and desensitization undermines IL-12 pluripotency
- Celsion's GEN-1 approach addresses the above limitations of rIL-12 and provides a unique pharmacokinetic profile

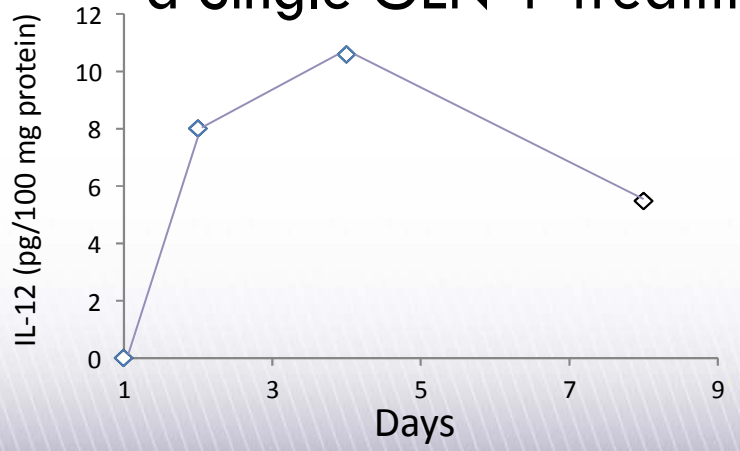
Celsion

Evidence of Local Delivery & Durability of IL-12 by GEN-1 IP in Ovarian Cancer

Peritoneal Localization of GEN-1 Plasmid



Durable IL-12 Production after a Single GEN-1 Treatment



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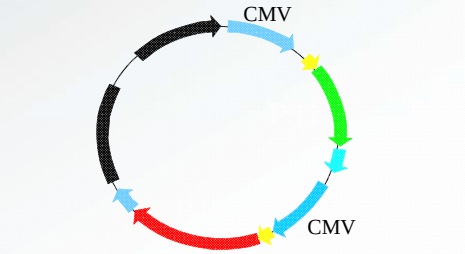
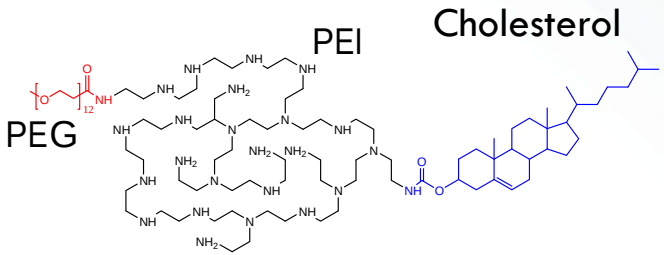
GEN-1 Composition is Key to its Functional Properties

IL-12 plasmid Vector



Carries IL-12 gene & elements for gene expression

Delivery system (PPC)



Protects DNA degradation & facilitates uptake and trafficking

Nanoparticles (~150nm)

Lyophilized Product

Persistent Local Delivery of IL-12 into Peritoneal Cavity

Celsion

GEN-1 Ovation Trial in Ovarian Cancer

The OVATION Study

(newly diagnosed ovarian cancer)

- **Review of the Clinical Data**

  Dr. Premal Thaker, M.D., Associate Professor, Obstetrics and Gynecology, Washington University School of Medicine in St. Louis

- **Review of the Translational Data & Novel GEN-1 Combination Strategies**

  Dr. Richard Koya, M.D., Ph.D.; Associate Professor of Oncology and Immunology, Director of the Vector Development & Production Facility, Associate Director of the Center for Immunotherapy, Roswell Park Cancer Institute Center for Immunotherapy

Celsion

Premal Thaker, M.D., M.Sc.

Washington University School of Medicine,
Associate Professor of Obstetrics and Gynecology,
Division of Gynecologic Oncology

R&D Day

OVATION Study

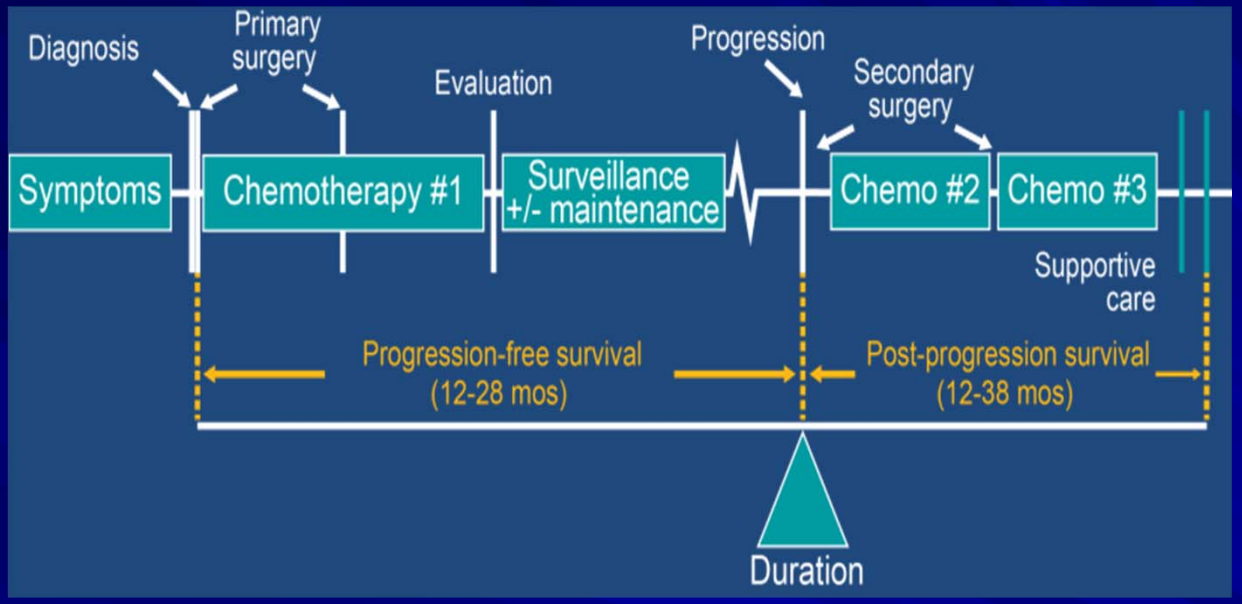
Review of Clinical Data

Celsion

Ovation Trial: Clinical Results

Premal H. Thaker
Associate Professor
Gynecologic Oncology
Washington University School of Medicine

Treatment Landscape Overview for Advanced Ovarian Cancer



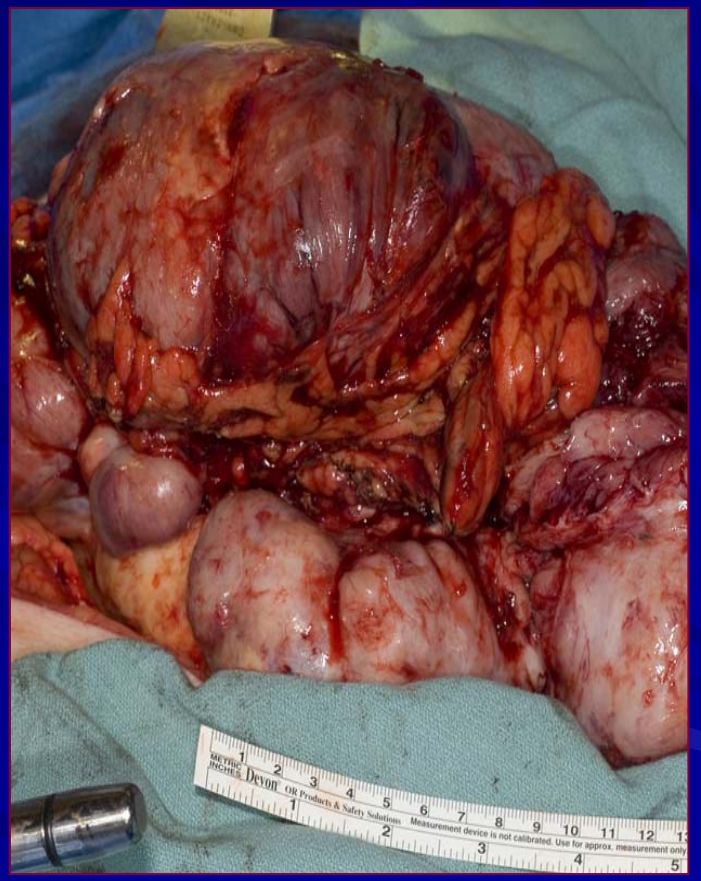
- Surgical goal is complete cytoreduction of all macroscopic visible disease[1]
- Standard adjuvant chemotherapy is an IV or IP taxane/platinum combination[1]
- Despite optimal upfront surgery and adjuvant chemotherapy, approximately 80% of patients will relapse[2]
- Unknowns: maintenance therapy, antiangiogenic therapy, role of IP therapy, and dose-dense schedule

EOC, epithelial ovarian cancer; IV, intravenous; IP, intraperitoneal.
Image curtesy of Dr. Robert Coleman

1. Ledermann et al. Ann Oncol. 2013;24 Suppl 6:vi24-32.
2. du Bois. Cancer. 2009;115(6):1234-44.

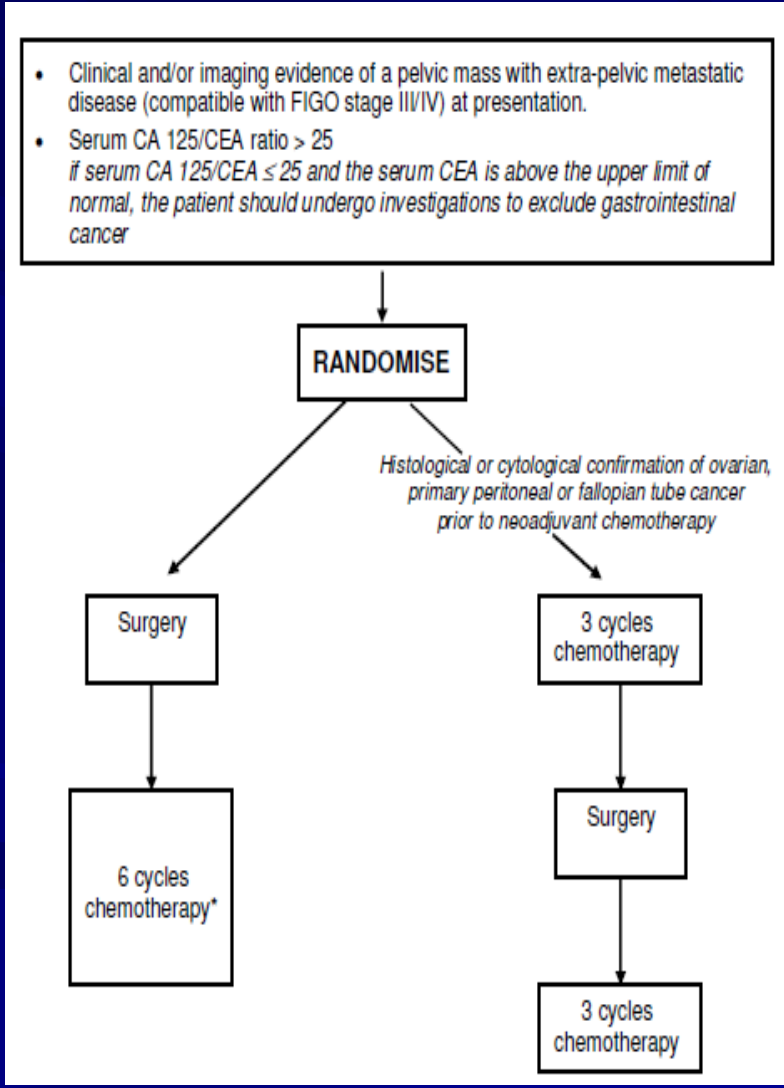
Rationale for Neoadjuvant Chemotherapy

- Theoretical:
  - Primary surgical benefit is largely in those with R0 resection
    - 25-40% of patients
  - Biology driving disease distribution is more important to survivorship than surgical effort
- Practical:
  - Easier surgery
  - Higher rates of R0
  - Decreased surgical morbidity
  - Test of chemosensitivity



Kehoe Lancet Oncol 2015

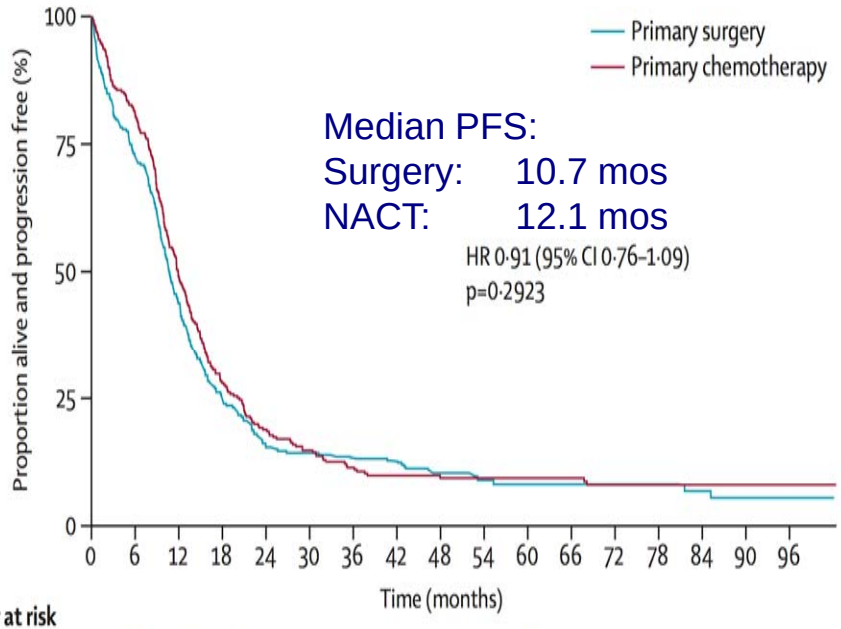
CHORUS: Chemo or Upfront Surgery



	Primary surgery (n=276)	Primary chemotherapy (n=274)	Total (n=550)
Median age (years)	66 (26–87, 57–72)	65 (34–88, 59–71)	65 (26–88, 58–72)
Median tumour size (cm)	8 (0·7–30, 5–12)	8 (0·9–28, 5–12)	8 (0·7–30, 5–12)
≤2 cm	13 (5%)	13 (5%)	26 (5%)
≤5 cm	59 (21%)	60 (22%)	119 (22%)
≤10 cm	111 (40%)	110 (40%)	221 (40%)
≤20 cm	79 (29%)	79 (29%)	158 (29%)
>20 cm	7 (3%)	7 (3%)	14 (3%)
Unmeasurable disease	7 (3%)	5 (2%)	12 (2%)
Clinical FIGO stage			
III	206 (75%)	206 (75%)	412 (75%)
IV	70 (25%)	68 (25%)	138 (25%)
CA125/CEA ratio			
>25	272 (99%)	268 (98%)	540 (98%)
≤25	4 (1%)	6 (2%)	10 (2%)
WHO performance status			
0	83 (30%)	88 (32%)	171 (31%)
1	138 (50%)	133 (49%)	271 (49%)
2	53 (19%)	49 (18%)	102 (19%)
3	1 (<1%)	4 (1%)	5 (1%)
Missing data	1	0	1
Prespecified chemotherapy regimen			
Single agent carboplatin	66 (24%)	63 (23%)	129 (23%)
Carboplatin plus paclitaxel	207 (75%)	210 (77%)	417 (76%)
Carboplatin plus other chemotherapy agent	3 (1%)	1 (<1%)	4 (1%)

Data are median (range, IQR) or n (%; percentages calculated for patients with non-missing data). FIGO=International Federation of Gynaecology and Obstetrics. CA125=cancer antigen 125. CEA=carcinoembryonic antigen.

PFS

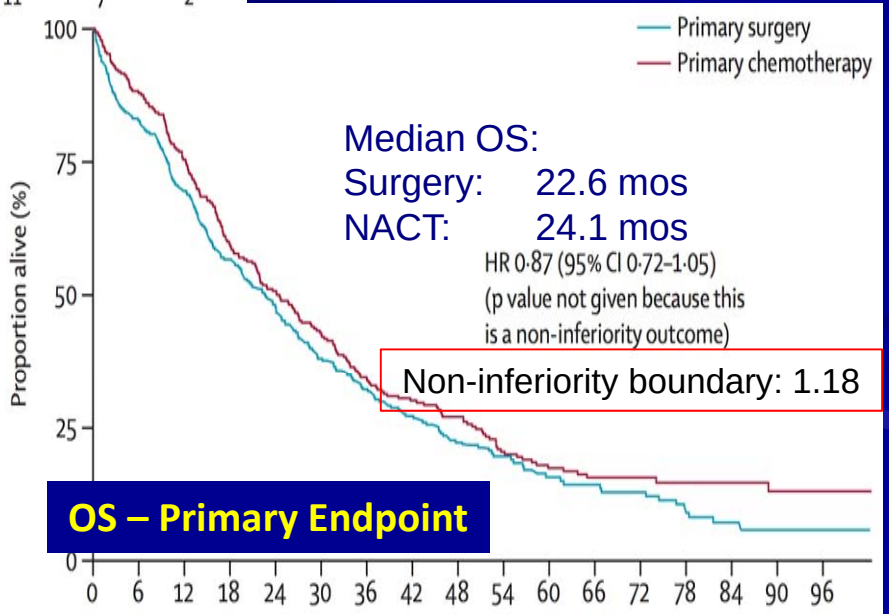


Median PFS:
Surgery: 10.7 mos
NACT: 12.1 mos

HR 0·91 (95% CI 0·76–1·09)
p=0·2923

Number at risk

Primary surgery	276	198	119	68	41	35	23	10	9	5	3
Primary chemotherapy	274	221	133	76	51	30	19	17	11	7	2



Median OS:
Surgery: 22.6 mos
NACT: 24.1 mos

HR 0·87 (95% CI 0·72–1·05)
(p value not given because this is a non-inferiority outcome)

Non-inferiority boundary: 1.18

OS – Primary Endpoint

Number at risk

Primary surgery	276	225	189	153	128	83	51	22	17	6	3
Primary chemotherapy	274	239	205	161	137	88	59	31	21	14	3

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NACT Trends

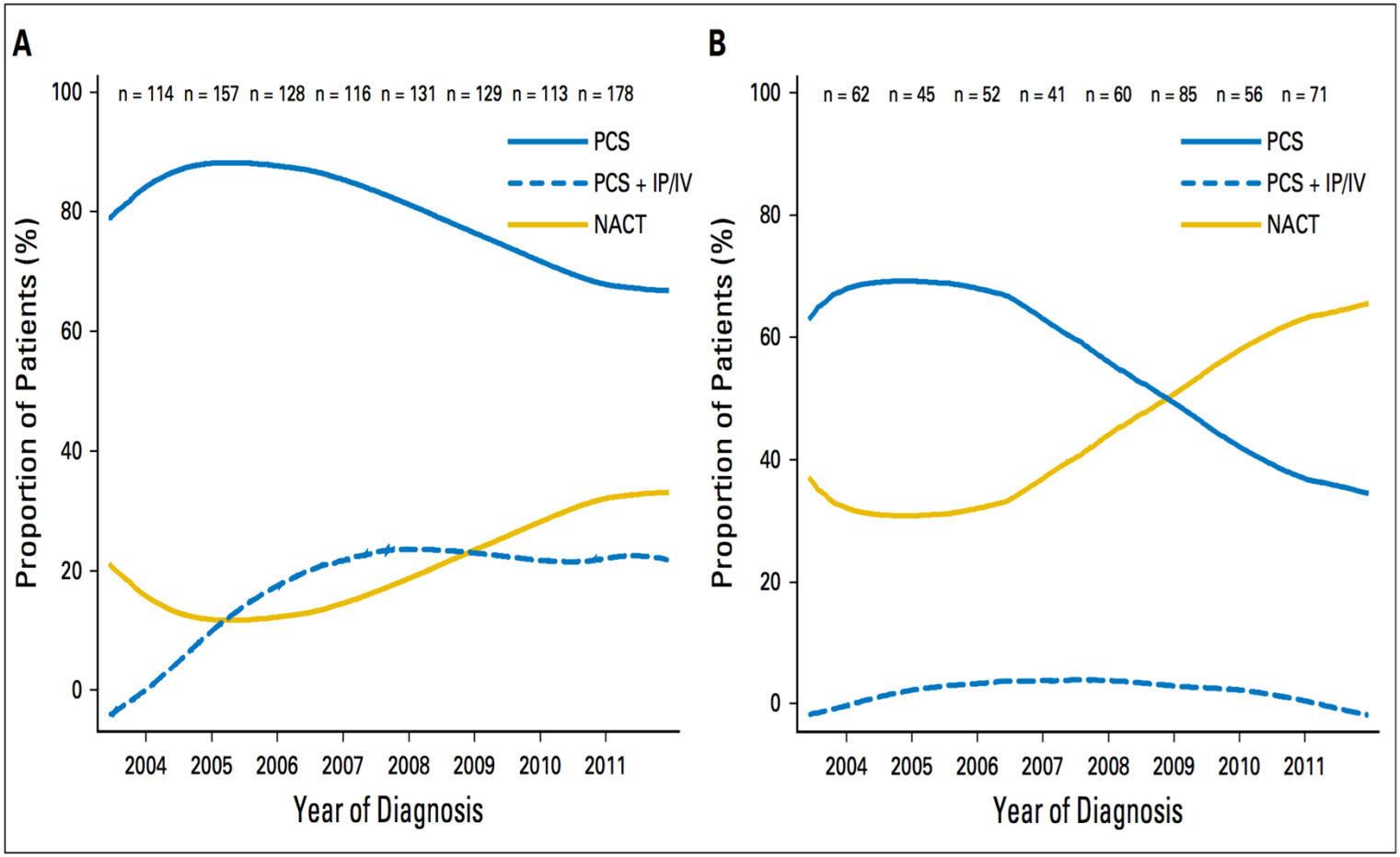
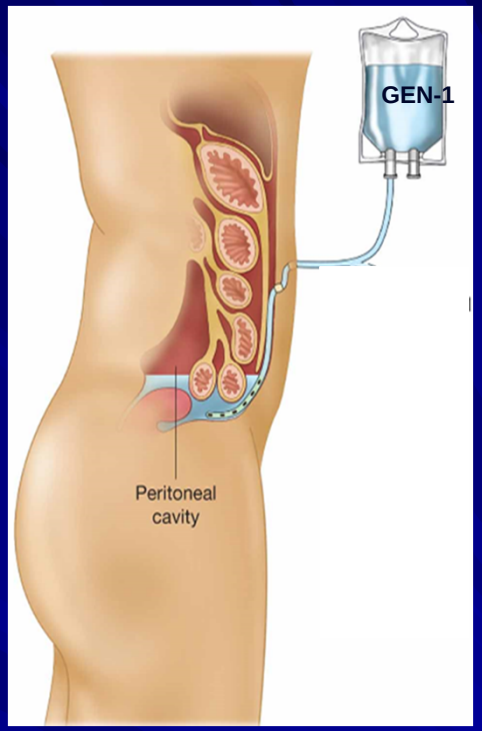


Fig 1. (A) Stage IIIC disease. (B) Stage IV disease. Use of neoadjuvant chemotherapy (NACT) increased significantly over time ($P_{trend} < .001$ for both groups). Intraperitoneal and intravenous (IP/IV) chemotherapy is shown for comparison. Three patients with stage IIIC disease and one with stage IV who were diagnosed in 2003 are included in the estimate for 2004. Twenty-three patients with stage IIIC disease and seven with stage IV who were diagnosed in 2012 are included in the estimate for 2011. PCS, primary cytoreductive surgery.



GEN-1 CLINICAL EXPERIENCE

GEN-1 Prior Clinical Studies

Study	N	Platinum Sensitivity	IP Dose (mg/m2)	Dosing Schedule
EGEN-001-101	13	Resistant	.6, 3.0, 12, 24	Weekly x4
EGEN-001-201	13	Sensitive	12, 18, 24	Weekly x8
GOG-170Q	20	Resistant	24	Weekly until toxicity/progression
GOG-9928	16	Resistant	24, 36	Weekly until toxicity/progression
201-14-101	18	First Line (Neoadjuvant)	36, 47, 61, 79	Weekly x8
Total Subjects	80			

PT

Phase I Trial of GEN-1 + Neoadjuvant Chemo in Newly Diagnosed Ovarian Cancer Patients (The "OVATION" Trial)

Primary Objective: Safety, tolerability, MTD

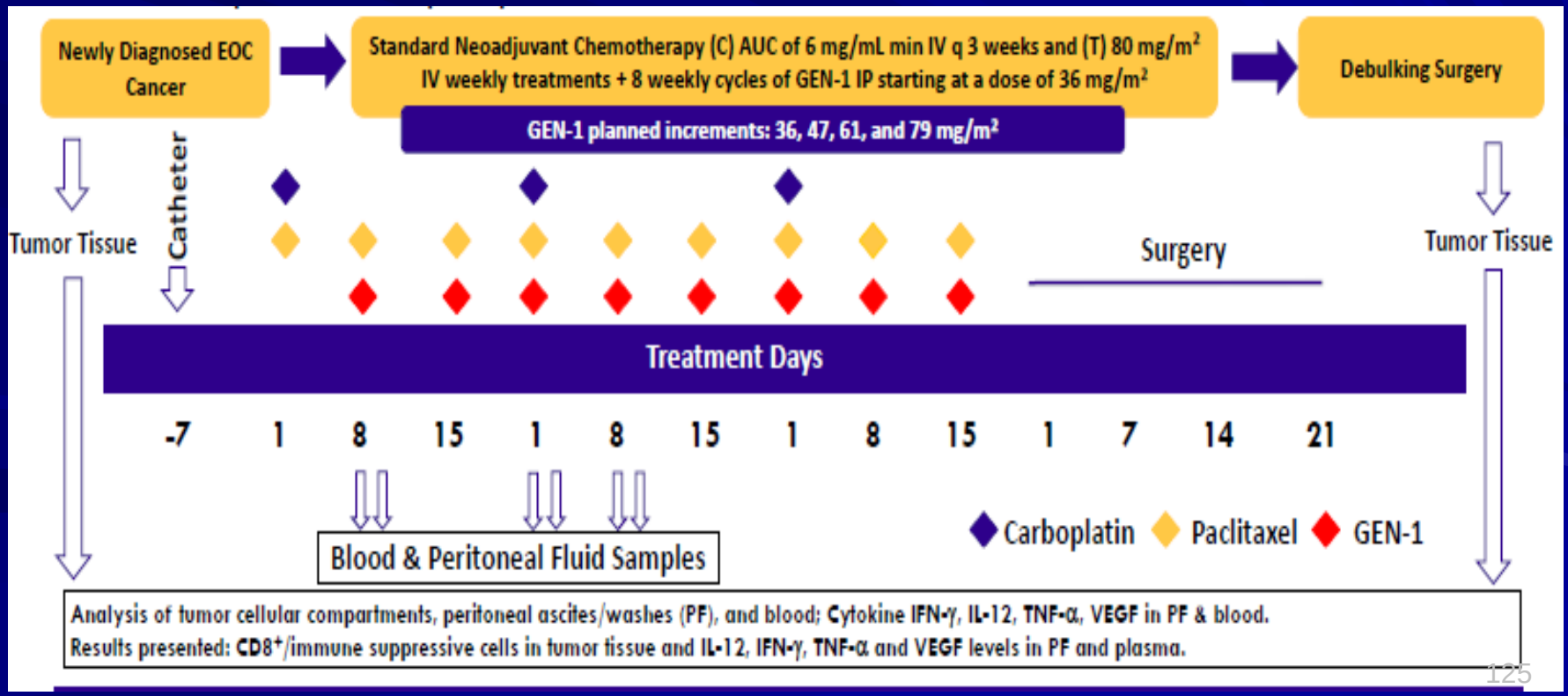
Secondary Objective: Objective Tumor Response Rate, pCR, PFS, OS

Translational Research

Newly Diagnosed Ovarian Cancer				
Cohort	Number of Subjects	GEN-1 (mg/m^2)	Carboplatin (AUC)	Paclitaxel (mg/m^2)
1	3-6	36	6	80
2	3-6	47	6	80
3	3-6	61	6	80
4	3-6	79	6	80

OVATION (Protocol 201-14-101) Phase 1
Study Design and Methods

- Standard 3+3 design with approximate 30% dose increments between successive cohorts of patients. Dose levels of GEN-1 in conjunction with standard carboplatin (C) and paclitaxel (T)
- Tolerated dose is confirmed when 3-6 patients are treated at a dose level and <2 patients experience dose-limiting toxicities (DLTs)



OVATION (Protocol 201-14-101)
Study Population

- Patients newly diagnosed with EOC were eligible; patients who received prior radiotherapy or chemotherapy to any portion of the abdominal cavity and/or pelvis were excluded.
- Candidates for neoadjuvant chemotherapy
- A majority of the patients were Stage IIIC (10, 63%), followed by Stage IV (5, 31%) and one patient was Stage IIIB (1, 6%).
- All but one patient had high grade serous adenocarcinoma (15, 94%); the exception being clear cell adenocarcinoma (1, 6%).
- The median baseline CA-125 reported was 683 (78 – 4348) across all 4 cohorts.

OVATION (Protocol 201-14-101)
Safety Results

- The safety evaluation period is based on the first 4 doses of GEN-1 administered to each patient. The DSMB has reviewed data from the first 4 cohorts of patients. To date, 15 patients have been evaluated for safety and no DLTs have been identified.
- Most common adverse events reported, regardless of causality, in descending order are nausea, constipation, fatigue, abdominal pain and cramping, neutropenia, anemia, anorexia, and vomiting.
- Most common toxicities reported, which can be attributed to GEN-1, in descending order include nausea, abdominal pain and cramping, fatigue, vomiting, neutropenia and diarrhea.
- A total of 5 patients discontinued GEN-1 treatments due to adverse events. Only one was GEN-1 related (altered taste).

OVATION (Protocol 201-14-101)

Efficacy Results

RECIST Response	Cohort 1 (n=3)	Cohort 2 (n=3)	Cohort 3 (n=3)	Cohort 4 (n=5)	Total (n=14)
Complete Response	1, 33.3%	0, 0%	0, 0%	1, 20%	2, 14%
Partial Response	0, 0%	3, 100%	3, 100%	4, 80%	10, 72%
Stable Disease	2, 66.6%	0, 0%	0, 0%	0, 0%	2, 14%
Interval Debulking Status	Cohort 1 (n=3)	Cohort 2 (n=3)	Cohort 3 (n=3)	Cohort 4 (n=5)	Total (n=14)
R0	2, 66.6%	0, 0%	2, 66.6%	5, 100%	9, 64.3%
R1	1, 33.3%	2, 66.6%	0, 0%	0, 0%	3, 21.4%
R2	0, 0%	1, 33.3%	1, 33.3%	0, 0%	2, 14.3%
Pathological Response	Cohort 1 (n=3)	Cohort 2 (n=3)	Cohort 3 (n=3)	Cohort 4 (n=5)	Total (n=14)
cPR	1, 33.3%	0, 0%	0, 0%	0, 0%	1, 7%
micoPR	1, 33.3%	2, 66.6%	1, 33.3%	3, 60%	7, 50%
macroPR	1, 33.3%	1, 33.3%	2, 66.6%	2, 40%	6, 43%

OVATION Study

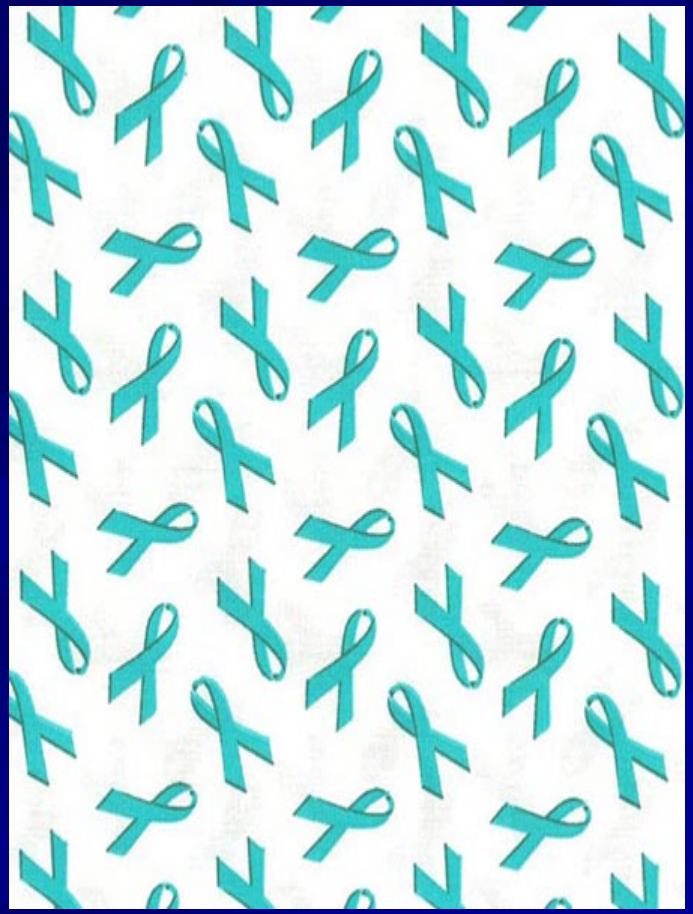
Summary of Progression Data: As Treated

- **Current PFS Median – 14.0 months**
  - *Assumes all ongoing patients censored 3 October 2017*
  - *Only patients treated according to protocol requirements*

Cohort	Patient ID	First Dose of Chemo	Date of Progression or Date of Last Update	Time from Chemo (days)	Time from Chemo (months)
4	OV01-06(17)	2/15/2017	10/3/2017	230	7.67
4	OV04-07(16)	12/14/2016	10/3/2017	293	9.77
1	*OV01-01(01)*	*10/5/2015*	*9/19/2016*	*350*	*11.67*
4	OV03-02(14)	10/10/2016	10/3/2017	358	11.93
4	OV04-06(15)	10/4/2016	10/3/2017	364	12.13
4	OV04-05(13)	9/28/2016	10/3/2017	370	12.33
3	OV02-02(12)	8/9/2016	10/3/2017	420	14.00
3	*OV04-04(10)*	*6/21/2016*	*8/16/2017*	*421*	*14.03*
3	OV01-05(11)	7/6/2016	10/3/2017	454	15.13
2	OV03-01(09)	4/13/2016	10/3/2017	538	17.93
2	OV04-02(07)	3/30/2016	10/3/2017	552	18.40
1	OV01-04(05)	2/8/2016	10/3/2017	603	20.10
1	OV01-02(02)	10/6/2015	10/3/2017	728	24.27

Grey Row = Progression

Thank You!



Washington University in St. Louis
School of Medicine

Richard Koya, M.D., Ph.D.

Associate Professor of Oncology and Immunology,
Director of the Vector Development & Production Facility,
Associate Director of the Center for Immunotherapy,
Roswell Park Cancer Institute Center for Immunotherapy

R&D Day

OVATION Study

Review of Translational Data & Novel Combination Immunotherapy Concepts

ROSWELL PARK CANCER INSTITUTE

TACTIVA Celsion

Key Objectives of the Ovation TR Studies:

Determine the evidence of molecular signaling

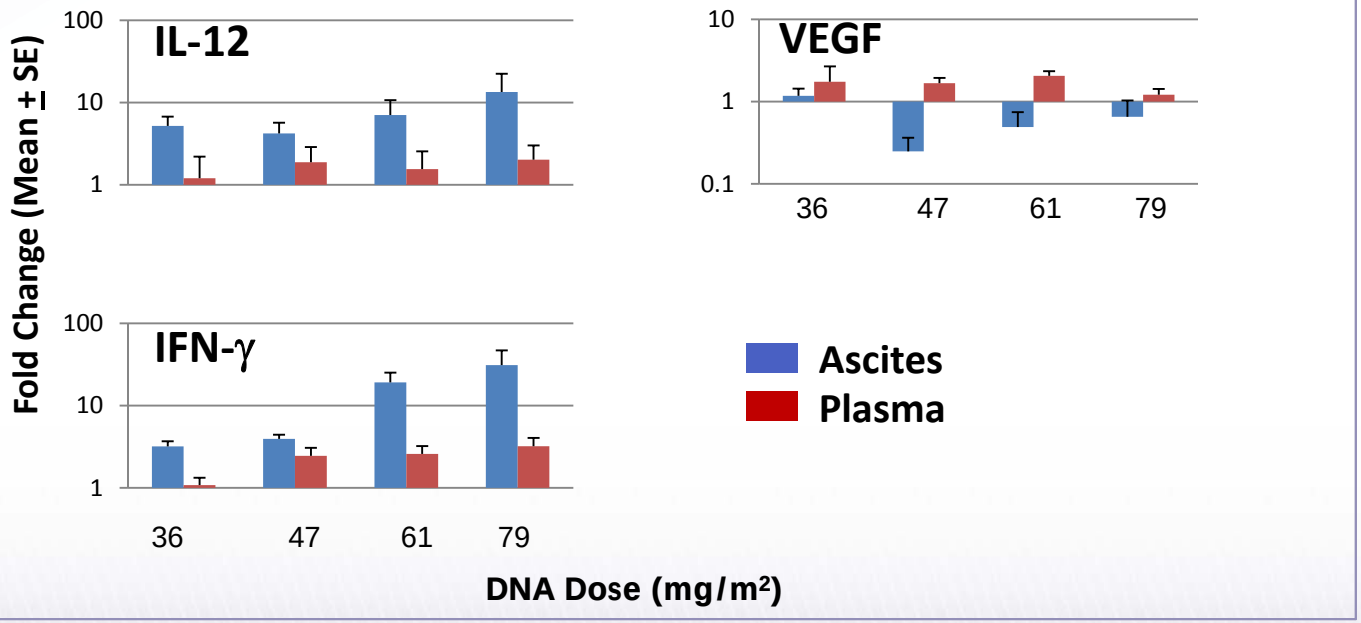
- Changes in IL-12 (gene transfer), IFN-g (immune activation) and VEGF (anti-angiogenesis) levels in biological fluid

Determine the evidence of cellular signaling at tumor site

- Changes in specific immune cells populations
- Balance b/w activating and suppressive immune cells populations

Evidence of Molecular Signaling

- Rise in IL-12 levels shows evidence of IL-12 gene transfer
- Rise in IFN-g shows activation of the downstream IL-12 signaling
- Inhibition of VEGF shows anti-angiogenic response
- Molecular response follows a dose trend
- Molecular changes primarily local than systemic



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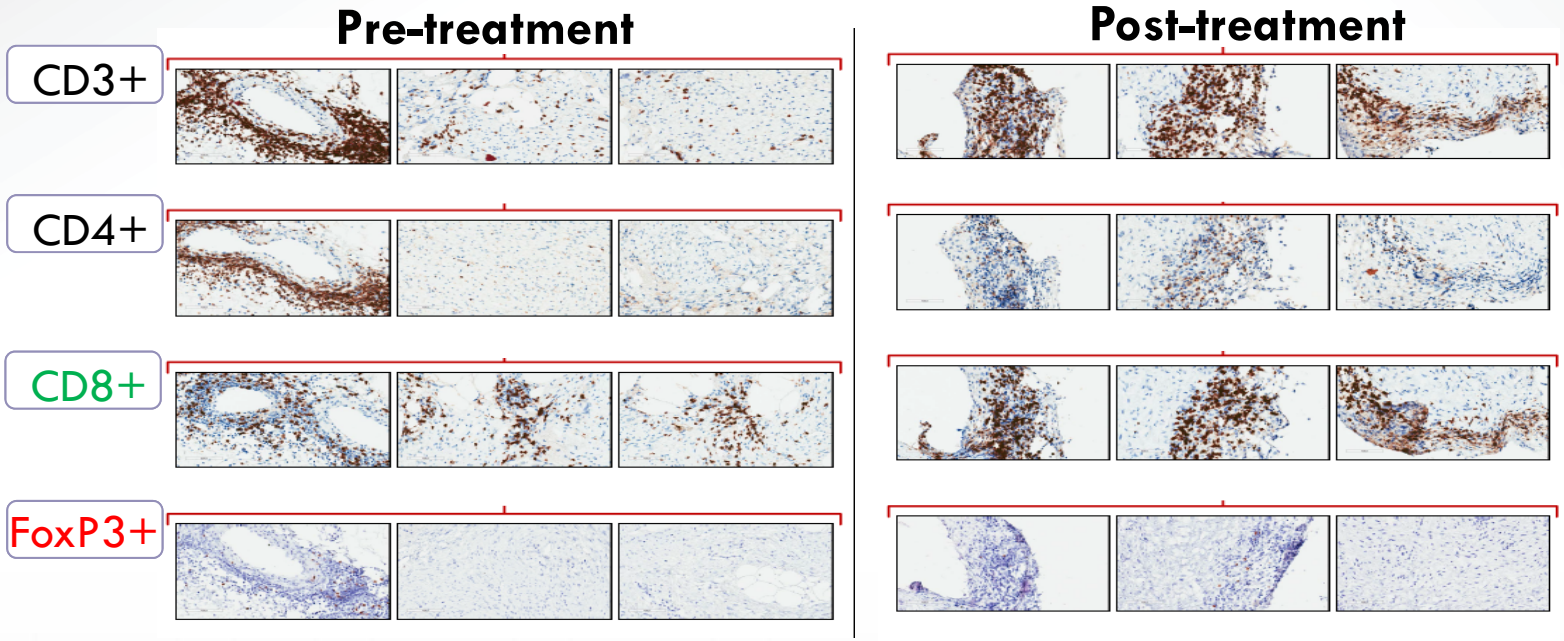
Evidence of Cellular Signaling

- Higher Infiltration of T-cells into Tumor Tissue Following Treatment

IHC: Subject OV01-02(02)



Brown stain represents T- cells

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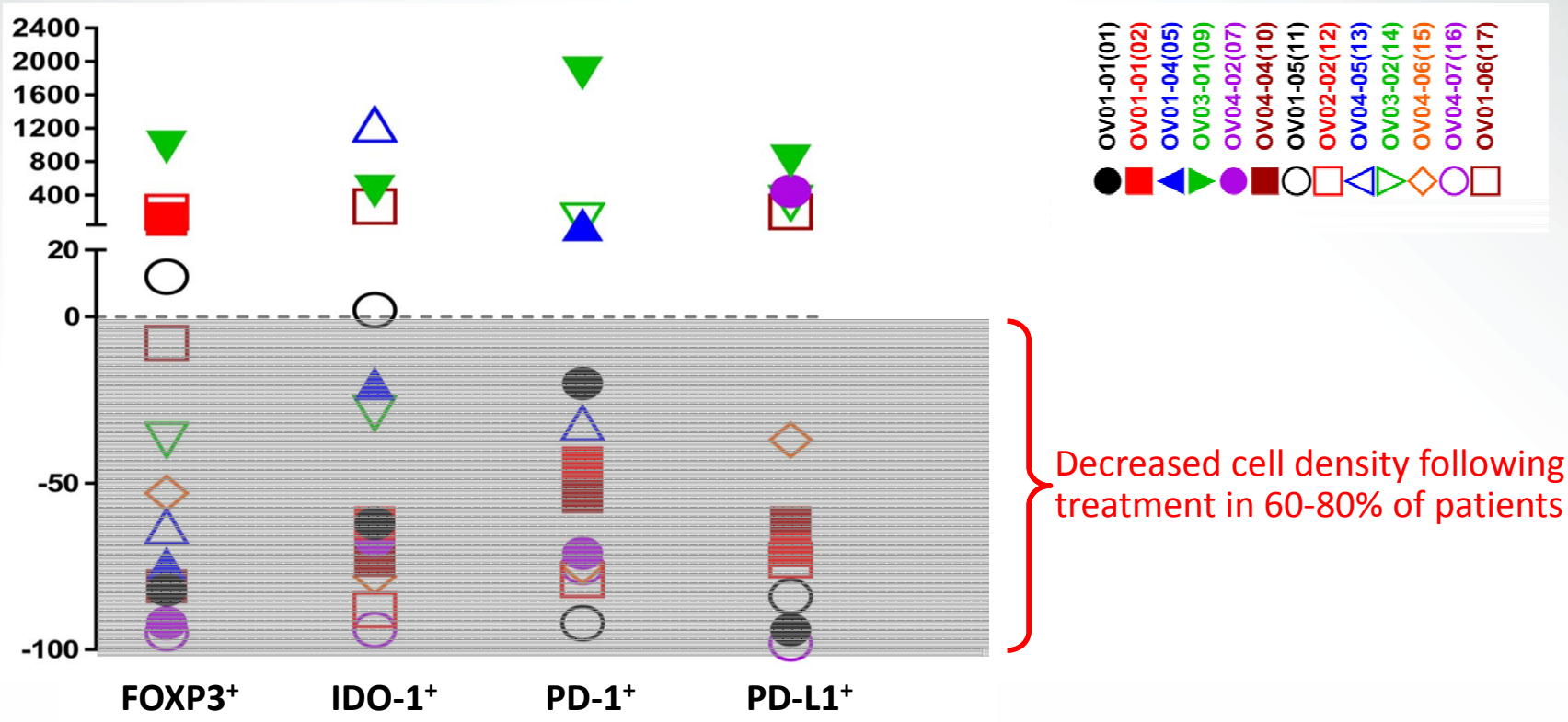
Reduction in the Immune Suppressive Markers in TME of a Majority of Patients



- T-cell expressing FoxP3, IDO-1, PD-1 or PD-L1 in tumor sections counted
- % change b/w pre & post-treatment counts plotted

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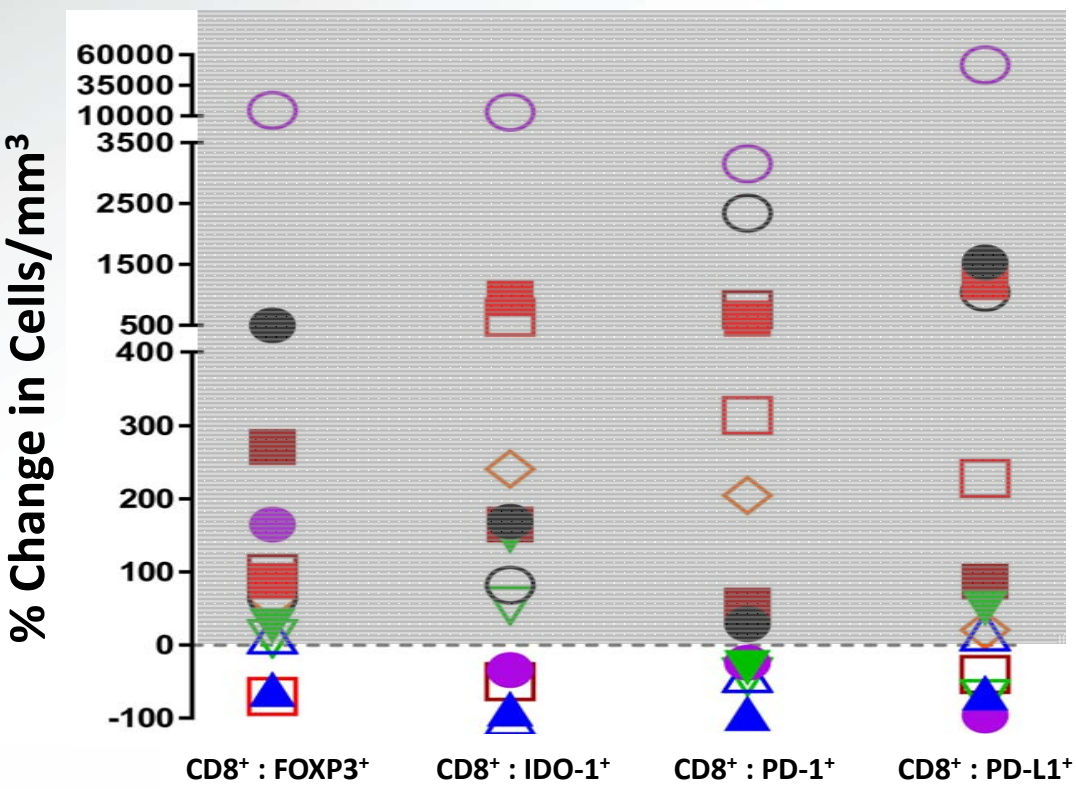
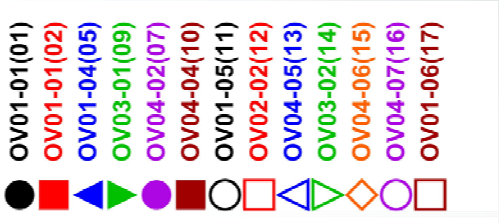
Shift from Immune Suppressive to Immune Favoring TME in a Majority of Patients





Increased ratio of CD8⁺ to suppressive markers following treatment in 60-80% of patients

- Ratio of CD8 cells to FoxP3, IDO-1, PD-1 or PD-L1 T-cells in tumor sections counted
- % change in the ratio b/w pre & post-treatment plotted

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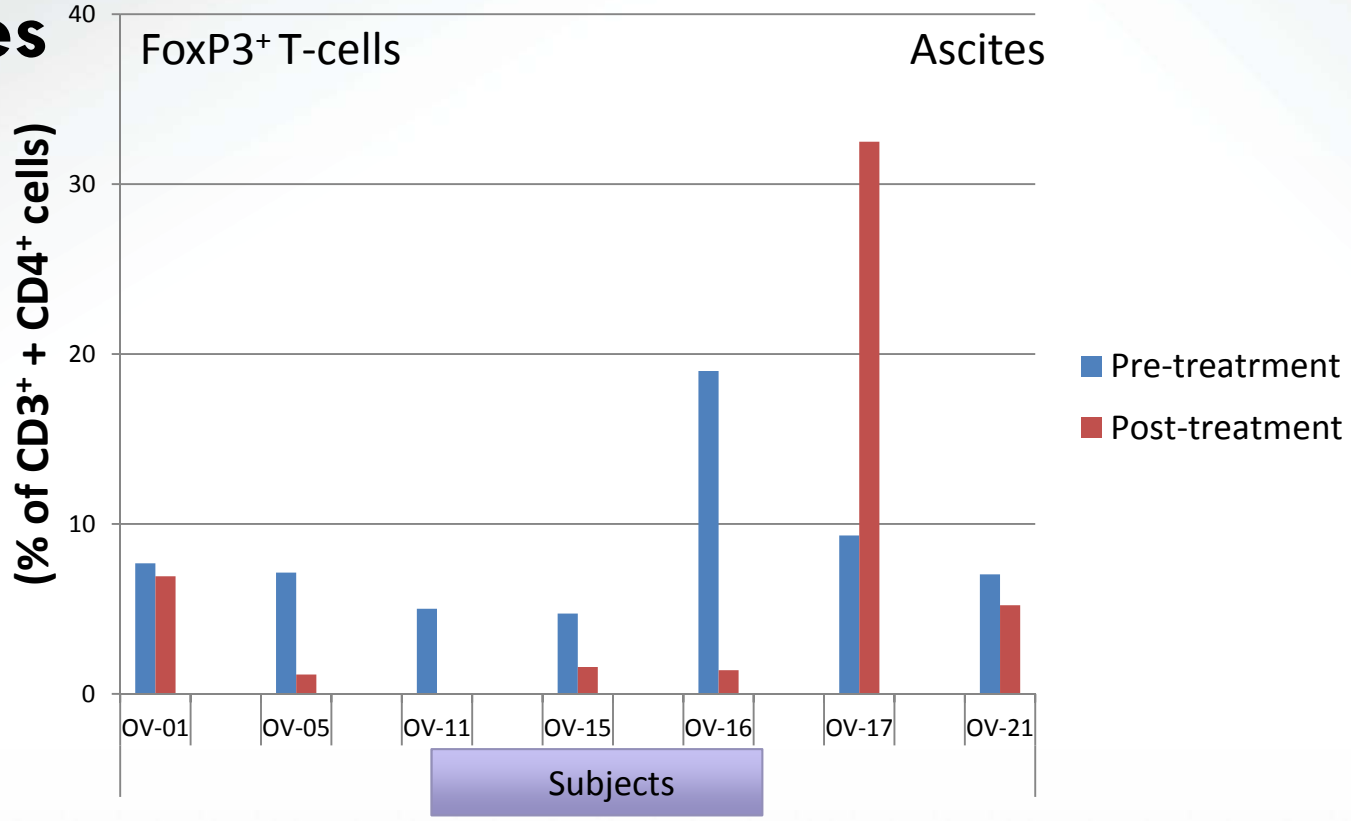
Reduction in the Immunosuppressive Mechanisms in TME also Observed in Tumor Ascites



- Treg cells in ascites samples were counted by FACS before and after treatment
- The $CD8^+$ cell count is expressed as % of $CD3^+$ gated cells

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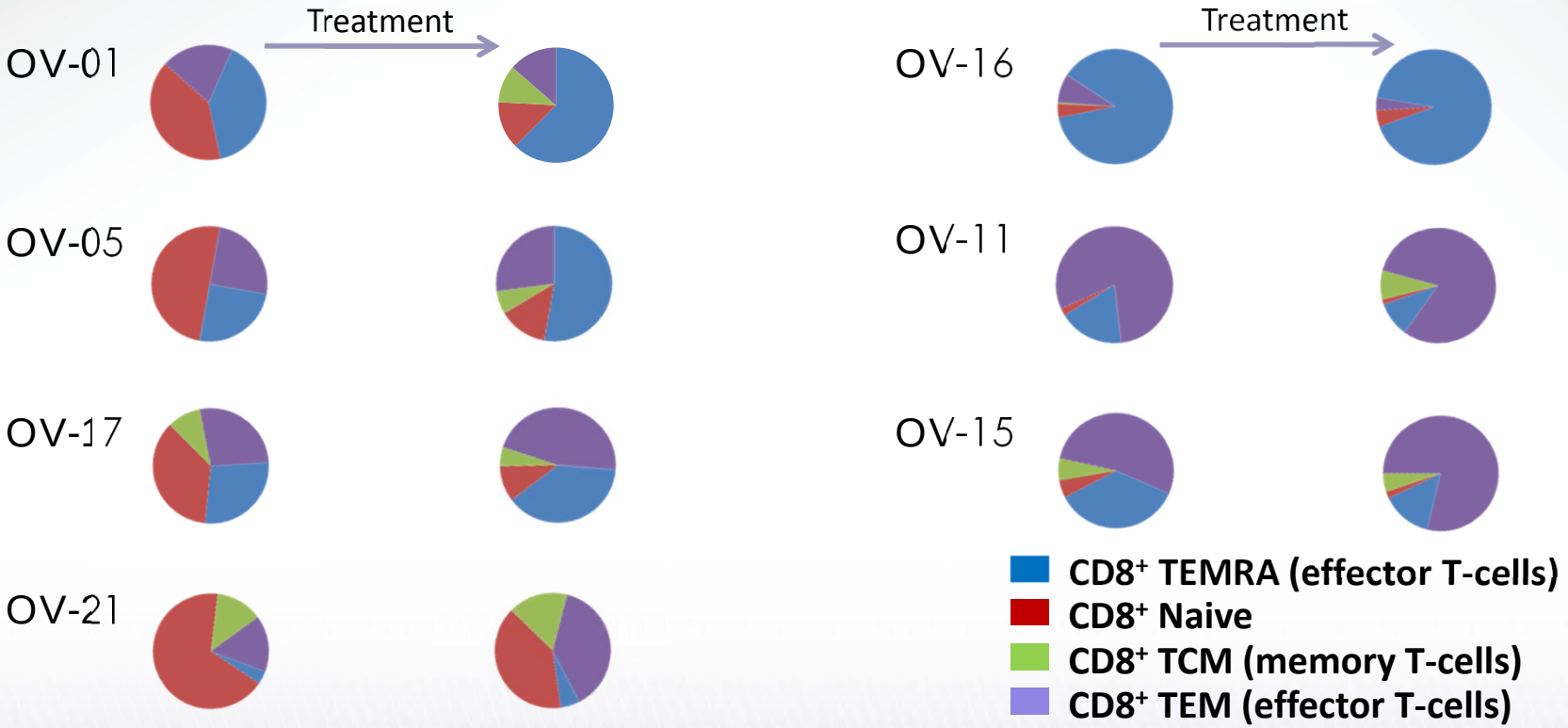
Increased Tumor-Killing Function of CD8+ T- Cells in Ascites

A phenotypic shift from high naïve T-cell subset to cytotoxic effector subset



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Novel Immunotherapy Combination Approaches with GEN-1

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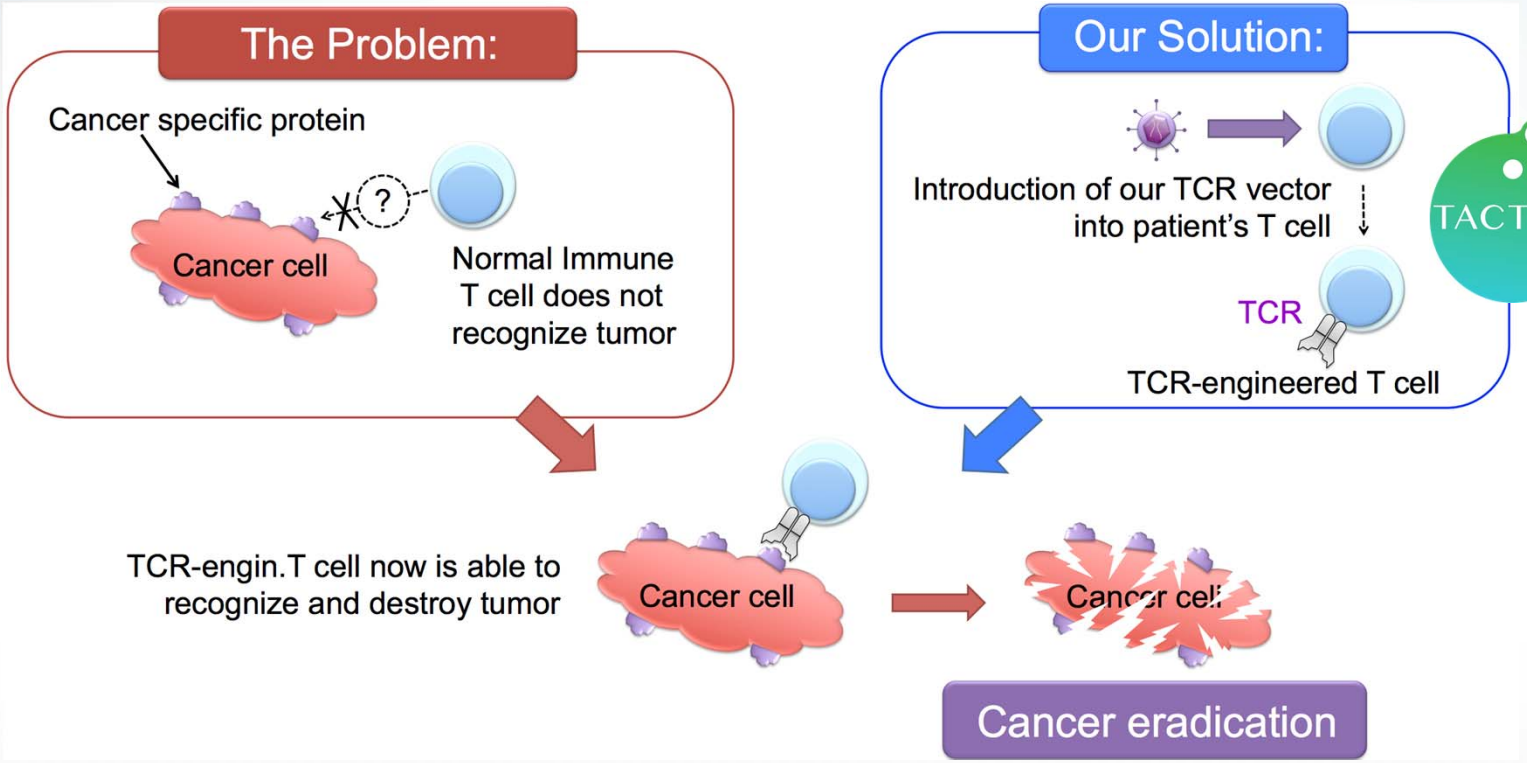
Adoptive T-Cell Therapy

Potential GEN-1 Combination Partner

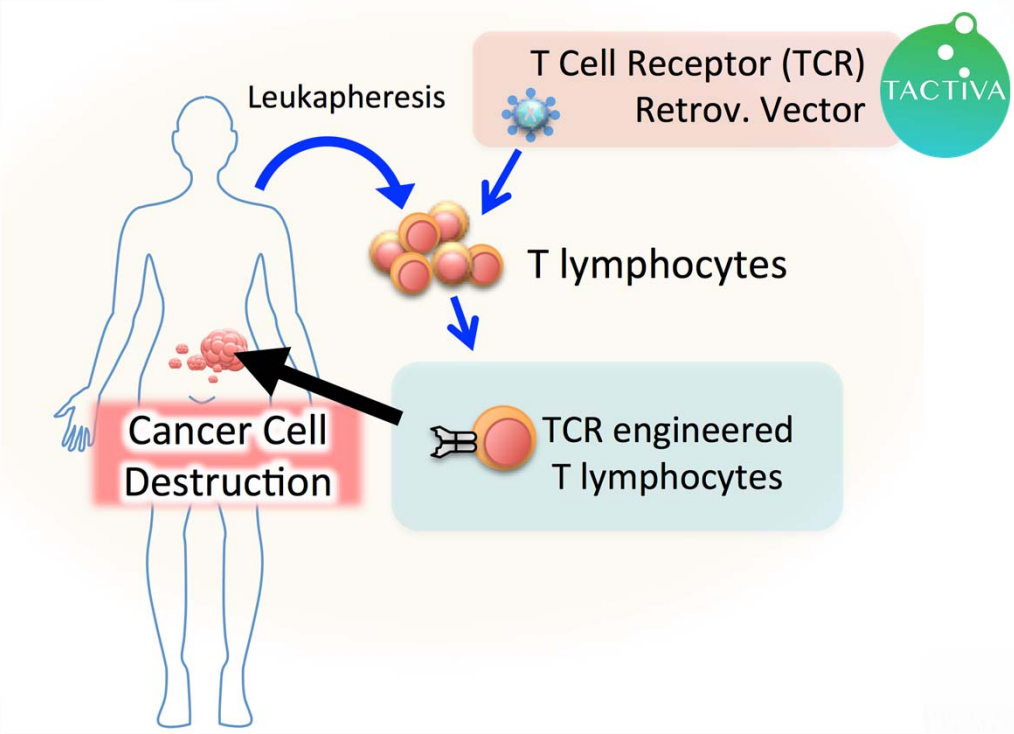
Adoptive T-Cell Therapy (ACT)



Adoptive T-Cell Therapy

Potential GEN-1 Combination Partner

Adoptive T-Cell Therapy (ACT)



Adoptive T-Cell Therapy

Potential GEN-1 Combination Partner

Adoptive T-Cell Therapy (ACT)

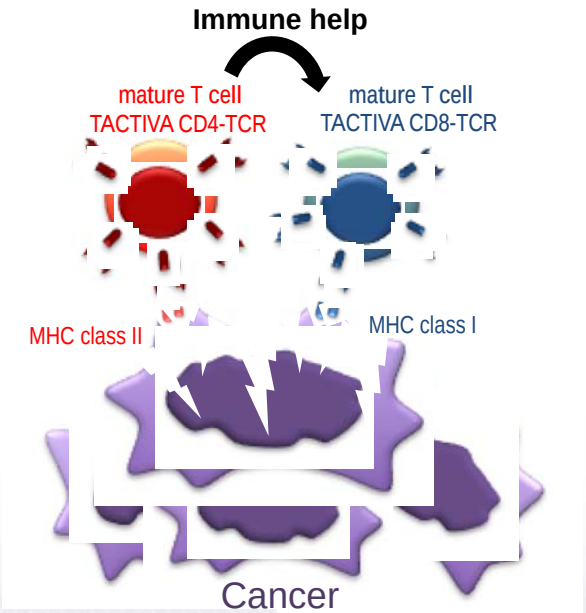
- Gaining Momentum as a Novel Cancer Treatment Approach
  - First product approval in Aug 2017; additional approvals in the pipeline
  - Gilead acquisition of Kite Pharma (Adoptive T Cell Therapy) for $11.9 Billion in Aug 2017
- Technology
  - Patients' T-cells isolated
  - Engineered to provide anti-tumor specificity and killing; improve T-cell survival and immune function; re-administered into patient
- Key Limitations/Challenges
  - Poor ATCs persistence and function due to highly immunosuppressive tumor environment; may work better in a pro-immune tumor environment
  - Serious systemic toxicity from hyper immune stimulation

Tactiva's Adoptive T-Cell Therapy

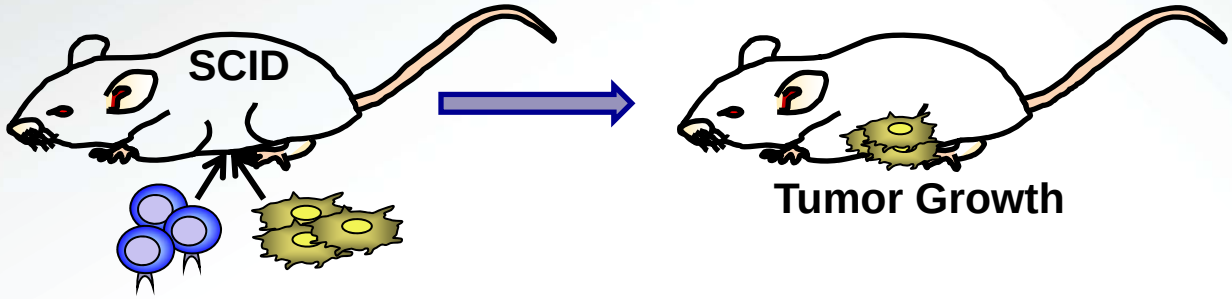
Advantages Over Conventional T-Cell Therapies

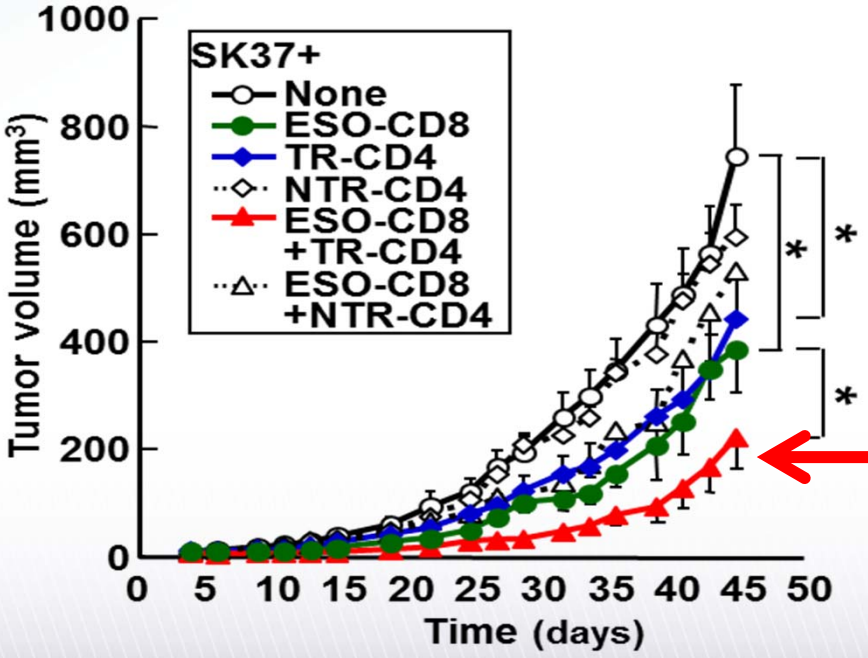
TACTIVA DEACT (Dual Enhanced ACT) Technology

- Developing Novel Adoptive T-cell Therapies for Cancer:
  - DEACT Technology: better than conventional ACTs; $CD8^+$ & $CD4^+$ combination
    - Increases persistence
  - Dual Adoptive Cell Therapy
    - Increases potency
    - Increases specificity

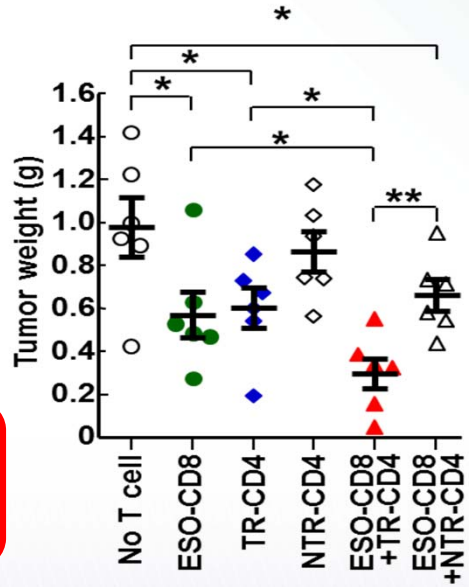


DEACT Technology





TACTIVA DEACT



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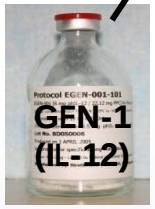
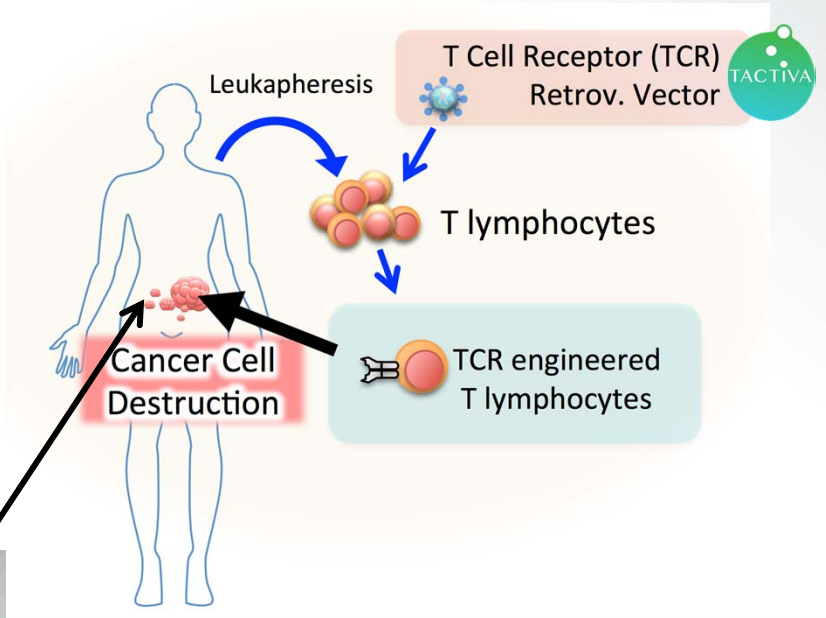
TACTIVA Adoptive T-Cell Therapy

Potential GEN-1 Combination Partner

DEACT + GEN-1 Combination Concept

- GEN-1 pre-treatment: relieves tumor immune suppression and improves immune environment for T Cell function
- DEACT treatment: Better ATC function under less harsh tumor environment
- Low risk of combination systemic toxicity: GEN-1 immune effects more local than systemic





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Celsion-Tactiva
Proposed Collaborative Study

Objective: Demonstrate benefit of GEN-1 + Tactiva DEACT TCR (NY-ESO-1) in a mouse ovarian cancer model

- Animal Model
  - Tg (HLA-A2.1)1EngeC57Bl6 mouse with peritoneally disseminated ovarian cancer (developed at Roswell Park)
- Reagents
  - GEN-1 and Tactiva's DEACT TCR (NY-ESO-1) immunotherapies
- Study Readouts
  - Tumor growth and animal survival
  - Immune parameters (T-cell function, cytokines, etc.)

Today's Messages

- We are developing proprietary Drug Technologies that deliver known cancer treatments better and more effectively
- The Science behind our two clinical stage Drug Candidates is sound, if not incomparable. The evidence is clear: the mechanisms have been validated on the bench and in the clinic… our drugs work.
- The Clinical Data supporting our studies is without question. Challenged, tested, and peer reviewed published, our findings suggest transformational potential for patients and the medical community
- Our Research targets specific cancers of high incidence, typically in first line, where treatment options are limited. Where the potential return – in terms of health and wealth -- is greatest

Thank you for attending Celsion's R&D Day

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