HCC

What I need to know…

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Disclosures

Dr. Michael Chuong has no financial relationships to disclose relating to the subject matter of this presentation.

Brand names are included in this presentation for participant clarification purposes only. No product promotion should be inferred.

Proton Therapy for HCC

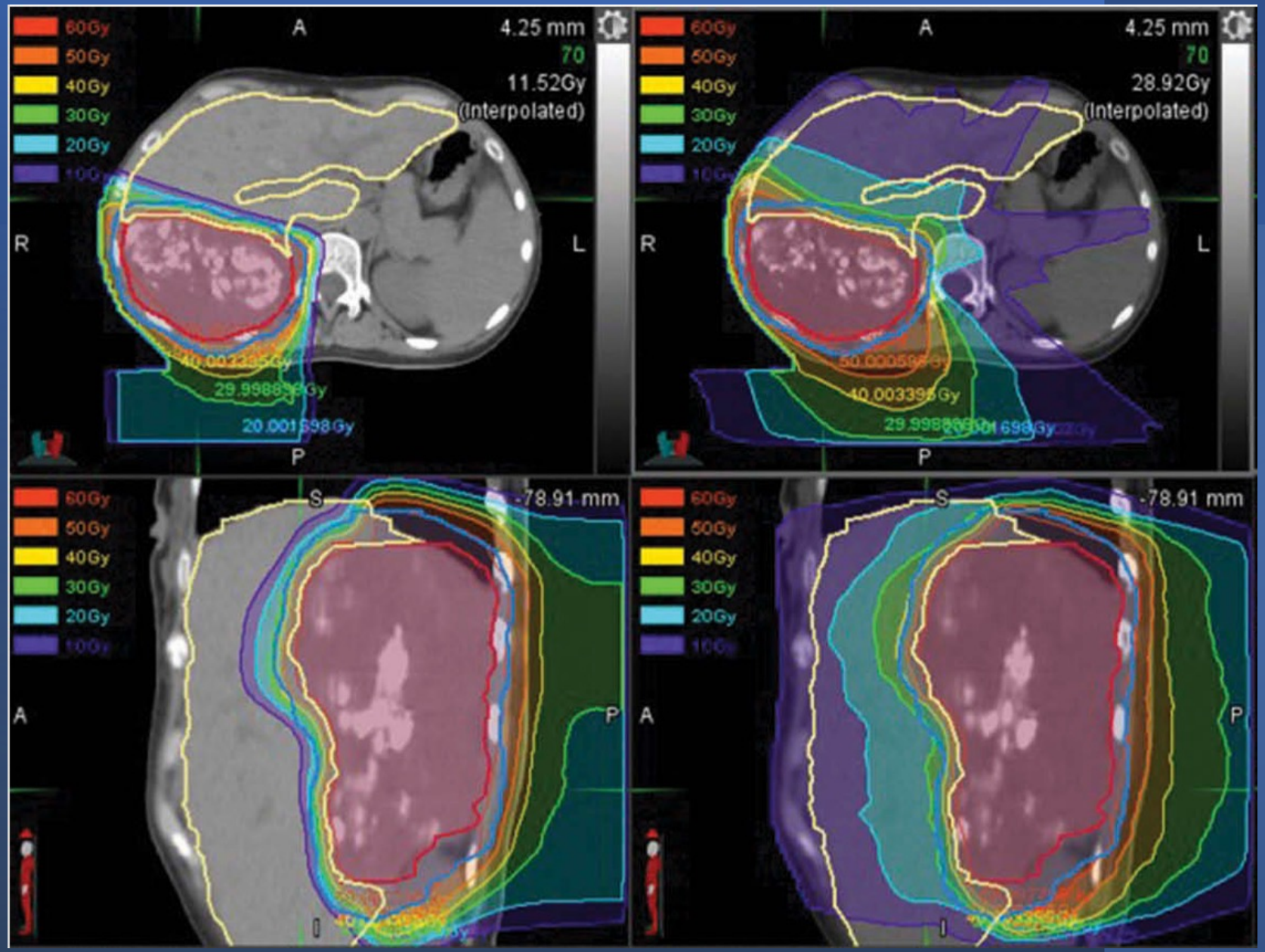
Proton therapy is not new!
First patient treated in 1954

Extensive prospective data of proton therapy for HCC published over several decades

As a result, HCC is in one of only a few cancers most strongly endorsed by ASTRO to receive proton therapy

PROTON

X-RAY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Research Article
Hepatic and Biliary Cancer

JOURNAL OF HEPATOLOGY

Proton beam radiotherapy *vs.* radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial

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- 144 patients (72 PBT, 72 RFA)
- All other the baseline characteristics were similar
- ~90% had tumors <2 cm in both arms
- ~97% were CP-A in both arms
- Primary endpoint: 2-yr local control w/ 15% non-inferiority margin

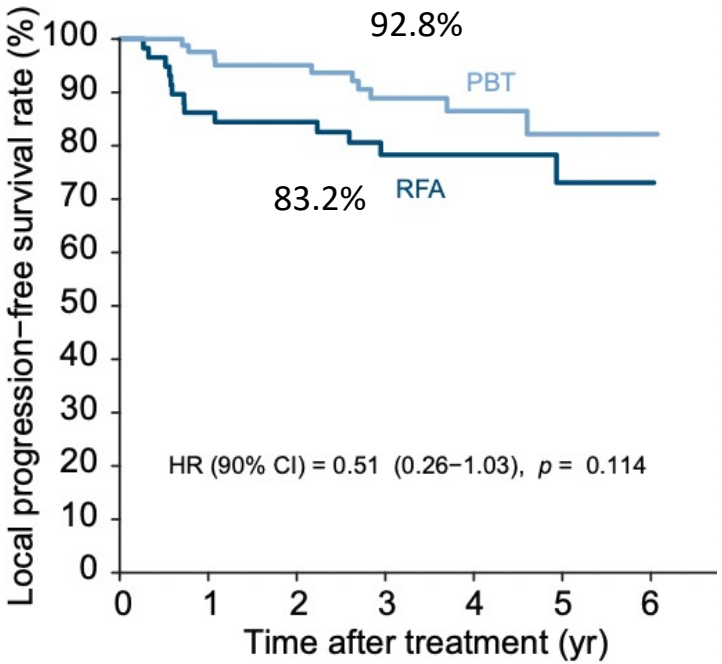


Table 3. Adverse events after proton beam radiotherapy and radiofrequency ablation.

	PBT (n = 80), n (%)				RFA (n = 56), n (%)				
CTCAE grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	***p* value**
WBC increase	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0.412†
WBC decrease	18 (22.5)	1 (1.3)	0 (0.0)	0 (0.0)	9 (16.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.569†
PLT decrease	15 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	16 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	0.179*
ALT/AST increase	10 (12.5)	3 (3.8)	0 (0.0)	0 (0.0)	14 (25.0)	32 (57.1)	8 (14.3)	0 (0.0)	<0.001†
Albumin decrease	5 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	1.000†
Bilirubin increase	8 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.445*
Fever	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.9)	1 (1.8)	0 (0.0)	0 (0.0)	0.004†
Pain	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	10 (17.9)	7 (12.5)	0 (0.0)	0 (0.0)	<0.001†
Nausea	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	5 (8.9)	1 (1.8)	0 (0.0)	0 (0.0)	0.011†
Bleeding	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0.412†
Dermatitis	14 (17.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.001*
Radiation pneumonitis	26 (32.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001*
Ascites	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Upper gastrointestinal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
No. of patients with ≥ Grade 3 AEs	0 (0.0)				9 (16.1)				<0.001†
Change of Child-Pugh score	−1	0	+1	+2	−1	0	+1	+2	0.049†
	2 (2.5)	72 (90.0)	6 (7.5)	0 (0)	0 (0)	45 (80.4)	11 (19.6)	0 (0)	

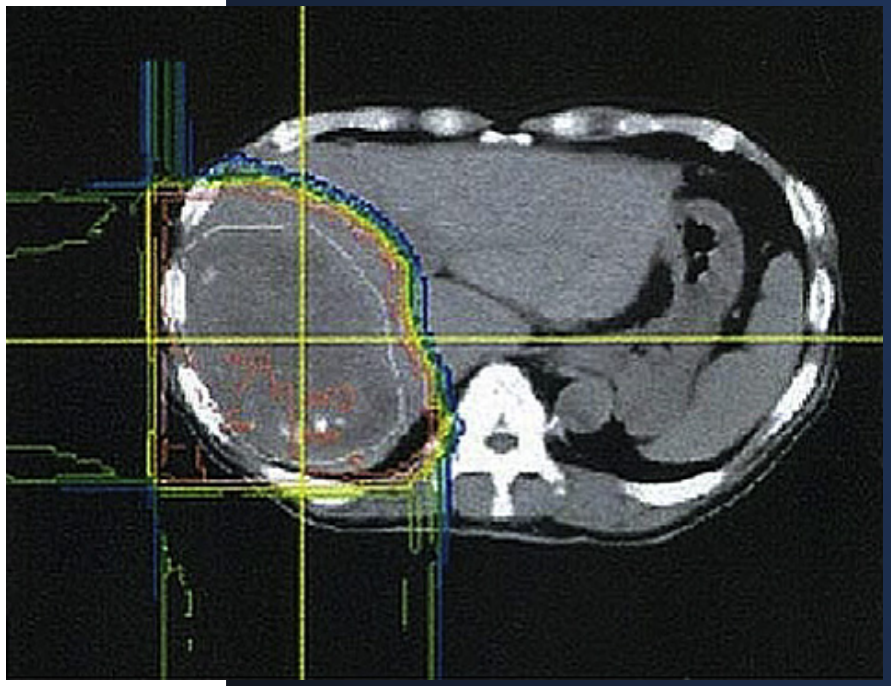
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBT, proton beam radiotherapy; PLT, platelet; RFA, radiofrequency ablation; WBC, white blood cell.
*Chi-square test.
†Fisher's exact test.

My Thoughts

RFA is clearly a standard of care for smaller HCC

Proton therapy has been proven highly effective and safe

- Most cost-effective for especially large tumors in challenging anatomic locations
- When proton therapy should be preferred over SBRT for HCC remains debated; currently being evaluated in the NRG GI-003 randomized trial
- Can be useful in combination with other liver-directed therapies



LEGACY Study

Edward Kim, MD FSIR
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Disclosure

- Advisory Board: BSC, Roche-Genentech, Merck-Eisai, SIRTeX

LEGACY: Local radioEmbolization using Glass Microspheres for the Assessment of Tumor Control with Y-90

Purpose: To examine outcomes when glass microspheres are used to treat early or advanced HCC

- Retrospective, single-arm, multi-center study conducted at 3 US sites
  - Northwestern Feinberg School of Medicine, Chicago
  - University of Washington, Seattle
  - Mount Sinai Health System, New York
- Consecutive patients treated with Y-90 glass microspheres at each site
  - Between January 2014 and December 2017
- Median follow-up of 29.9 months (95% CI: 24.7, 34.6)*

Primary Endpoint: To assess confirmed **local tumor control** (ORR (objective response rate)) and **Duration of Response** (DoR) following treatment with Y-90 glass microspheres in patients with unresectable solitary HCC lesions

Salem R et al. "Yttrium-90 Glass Microspheres in the Treatment of Hepatocellular Carcinoma: The LEGACY Study," Hepatology. 2021 Mar 19.

Baseline Characteristics

Patient Characteristics	Treated Population (N=162) N (%)
Median age (range), years	66 (21-90)
≥ 18 to < 65	69 (42.6)
≥ 65 to < 75	64 (39.5)
≥ 75	29 (17.9)
Gender, male	123 (75.9)
HCC Etiology	
HCV	112 (69.1)
Alcohol	48 (29.6)
NASH	23 (14.2)
HBV	15 (9.3)
Other/unknown	5 (3.1)
ECOG Status	
0	98 (60.5)
1	64 (39.5)
BCLC Status	
A	98 (60.5)
C	64 (39.5)
AFP ≥ 200 ng/mL	24 (14.8)

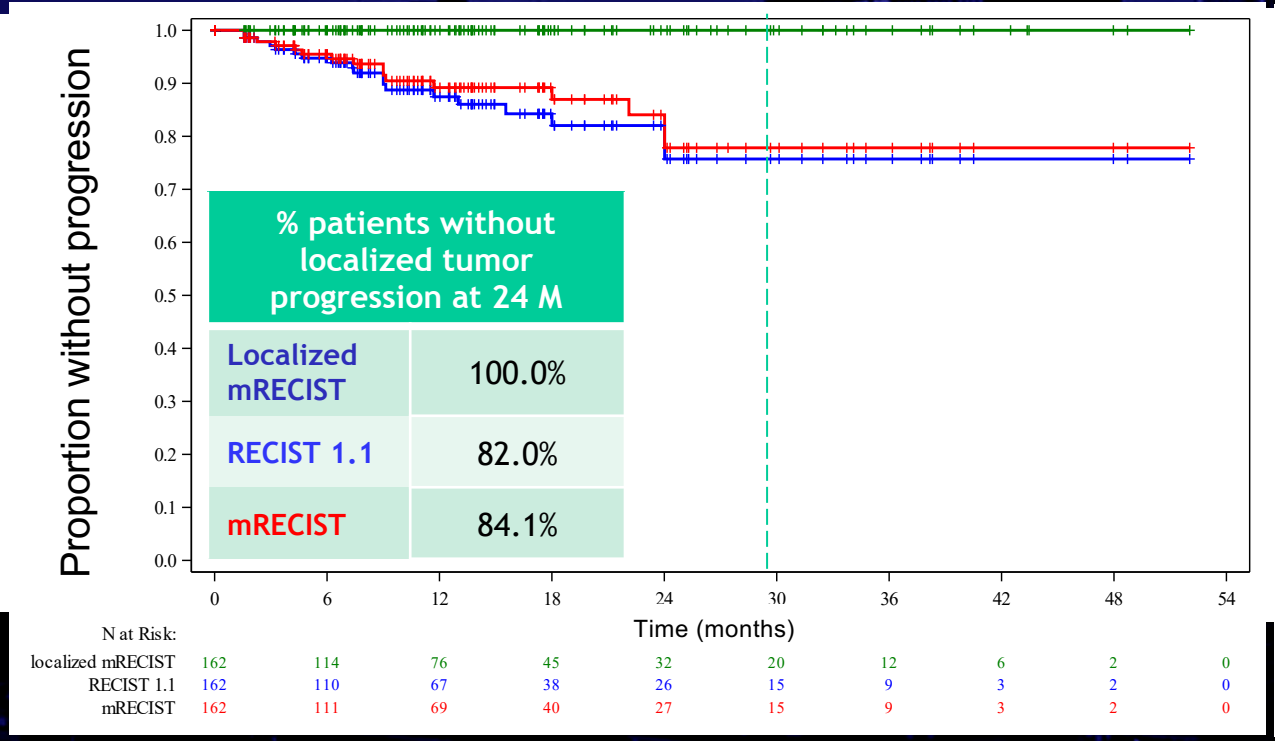
Treatment Characteristics	Treated Population (N=162) N (%)
Median Tumor Size (range), cm	2.6 (0.9-8.1)
Initial Y-90 Treatment Goal	
Radiation segmentectomy	104 (64.2)
Radiation lobectomy	8 (5.0)
Bridge to liver transplantation	36 (22.2)
Other	1 (0.6)
Unknown	13 (8.0)
Type of Infusion	
Selective	155 (95.7)
Lobar	3 (1.9)
Mixed	4 (2.5)
Absorbed dose to perfused liver volume (Gy), median, (IQR)	410.1 (199.7, 797.7)
Number of TheraSphere Treatments	
1	130 (80.2)
≥2	32 (19.8)

Salem R et al. "Yttrium-90 Glass Microspheres in the Treatment of Hepatocellular Carcinoma: The LEGACY Study," Hepatology. 2021 Mar 19.

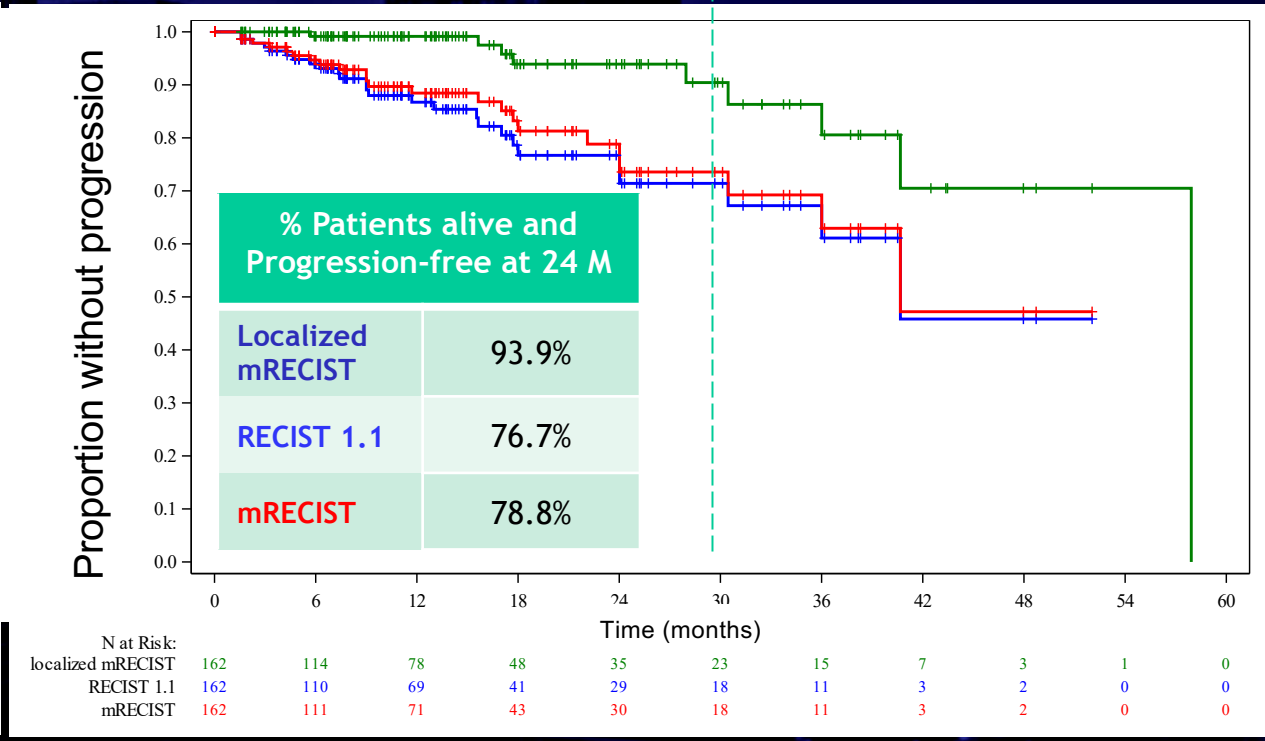
Time to Event Outcomes (Treated Population)

Localized mRECIST
RECIST 1.1
mRECIST

Time to Progression



Progression-Free Survival



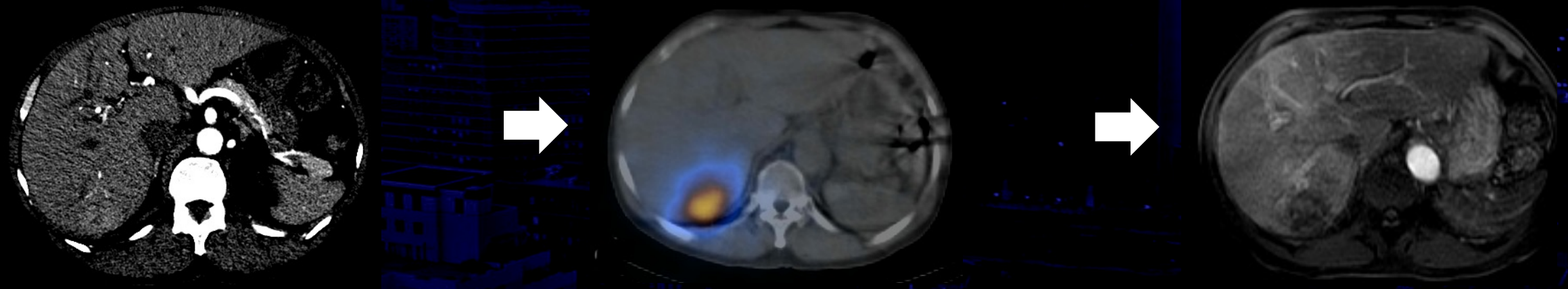
Local recurrence rate of 5.6% (9/162)

ORR: Objective Response Rate; DoR: Duration of Response; TTP: Time to Progression; PFS: Progression-Free Survival; CI: Confidence Interval; RECIST: Response Evaluation Criteria in Solid Tumors; mRECIST: modified Response Evaluation Criteria in Solid Tumors

Results of LEGACY

Parameter	Localized mRECIST
ORR (best response)	88.3% (95% CI: 82.4,92.4)
CR/PR/SD/PD, n	136/7/0/0
DoR ≥ 6M**	76.1% (95% CI: 67.6, 82.9)

	Treated Population (N=162) N (%)		
	6 Months	12 Months	24 Months
Maintenance or improvement from baseline ECOG status	69/77 (**89.6%**)	41/47 (**87.2%**)	14/17 (**82.4%**)
Attain and/or Maintain Milan criteria	116/122 (**95.1%**)	77/86 (**89.5%**)	29/34 (**85.3%**)



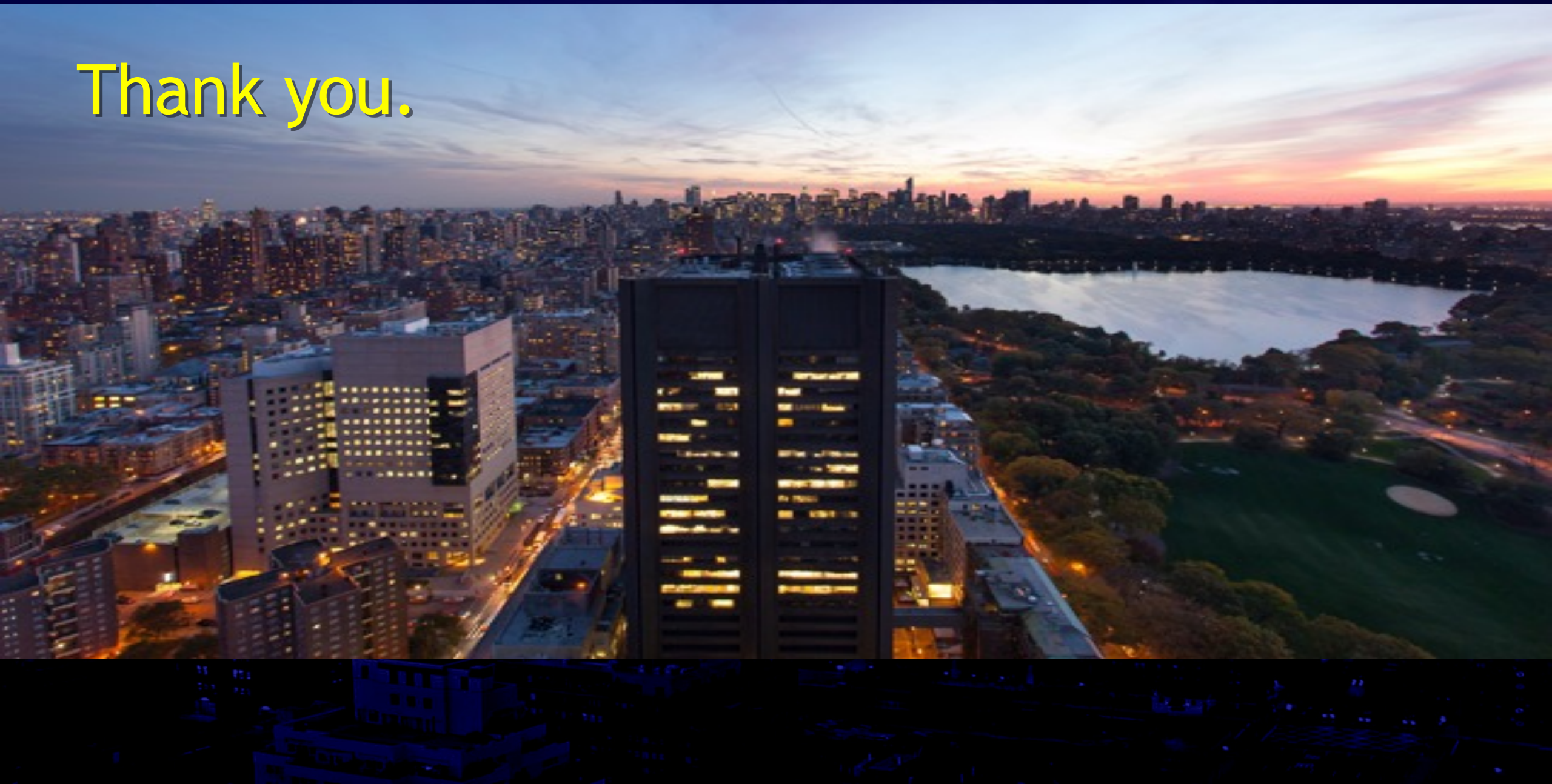
LEGACY

The multicenter LEGACY study demonstrated use of Y-90 as neoadjuvant to:

Transplant, Resection, or as a Stand-alone treatment (Curative Intent/Palliative)

and

Supports the use of a perfused volume absorbed dose of > 400 Gy, which may lead to higher rates of CPN.


Thank you.

What Else Happened in HCC

Nadine Abi-Jaoudeh MD FSIR CCRP

Disclosures

- Research Collaborative Agreement with Philips Medical Systems
- Research Collaboration with Teclison Limited
- Research collaboration, Guerbet SA
- Sponsored research by Sillajen Inc, Sirtex Medical Ltd, Instylla HES, Blackswan vascular Inc,
- Intellectual property and part owner in Bruin Biosciences Inc
- Advisory board for Genentech F. Hoffmann-La Roche Ltd, QED Therapeutics Inc, Eisai, Pfizer, Johnson and Johnson, Medtronic Inc

Journal of Hepatocellular Carcinoma

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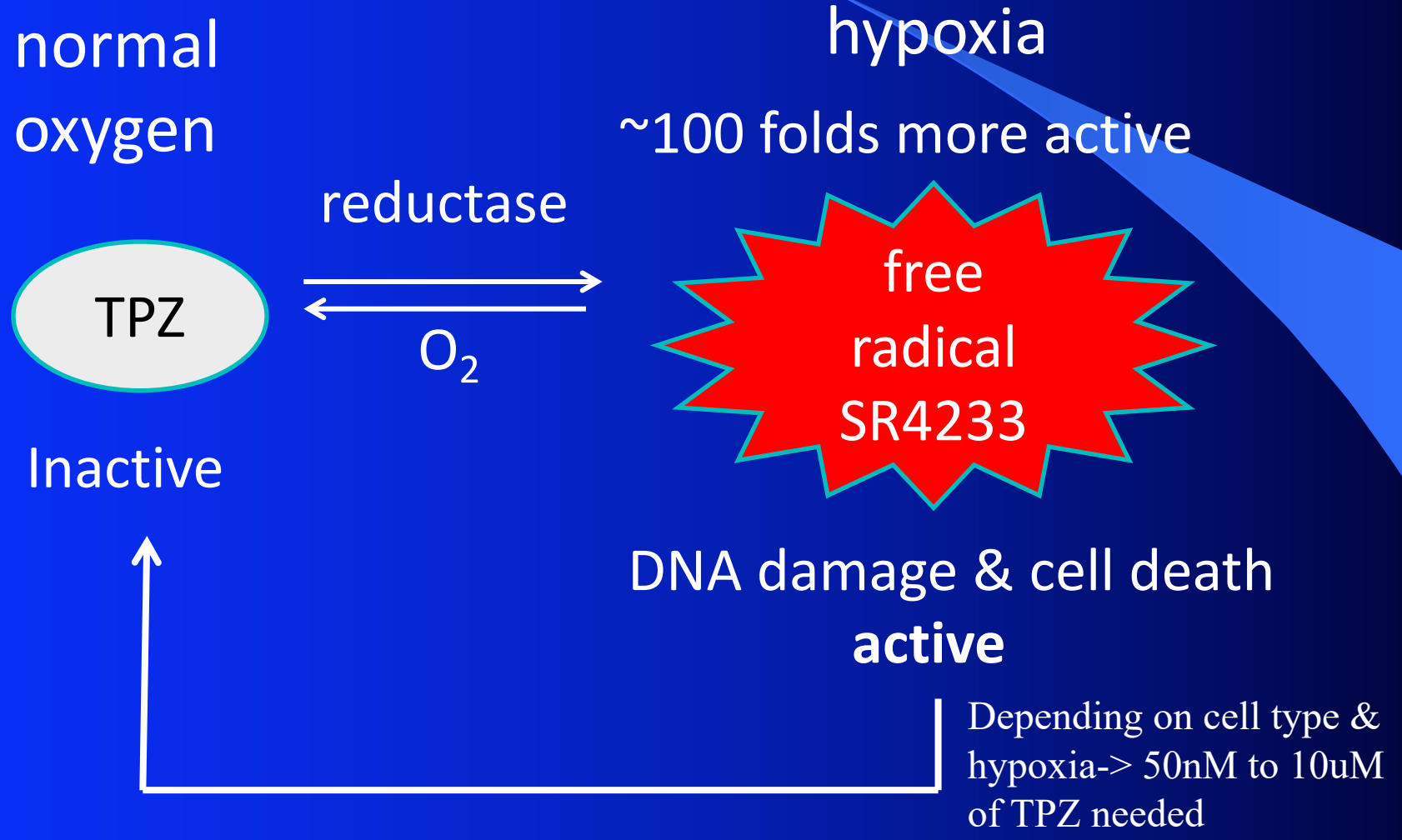
CLINICAL TRIAL REPORT

Phase I Trial on Arterial Embolization with Hypoxia Activated Tirapazamine for Unresectable Hepatocellular Carcinoma

Nadine Abi-Jaoudeh[1]
Farshid Dayyani[2]
Pei Jer Chen[3]
Dayantha Fernando[1]
Nicholas Fidelman[4]
Hanna Javan[1]
Po-Chin Liang[5]
Jen-I Hwang[6]
David K Imagawa[7]

Replacing standard chemo in TACE w/ TPZ, activated by hypoxia



Methods

- Phase 1 multicenter, open-label, non-randomized trial with a classic 3+3 dose escalation + an expansion cohort in patients with unresectable HCC, Child Pugh A, ECOG 0 or 1.
- Primary objective:
- evaluate the safety of combining TPZ + TAE in patients with unresectable HCC,
- determine optimal dose for Phase II

Table 4 Detailed Responses for Target Lesions and Overall Lesions Including Overall Response Rate and Disease Control Rate (by mRECIST and RECIST Criteria)

Response Rate (%)	mRECIST Evaluation		RECIST Evaluation	
	Target Lesion	Overall Response	Target Lesion	Overall Response
CR (95% CI)	60.0% (38.7–78.9)	56.0% (34.9–75.6)	4.0% (0.1–20.4)	0.0% (0–9.5)
PR (95% CI)	24.0% (9.4–45.1)	24.0% (9.4–45.1)	68.0% (46.5–85.1)	68.0% (46.5–85.1)
SD (95% CI)	12.0% (2.5–31.2)	12.0% (2.5–31.2)	24.0% (12.1–49.4)	24.0% (12.1–49.4)
PD (95% CI)	4.0% (0.1–20.4)	8.0% (1.0–26.0)	4.0% (0.1–20.4)	8.0% (1.0–26.0)
ORR (CR+PR)	84.0% (63.9–95.5)	80.0% (59.3–93.2)	72.0% (50.2–88.2)	68.0% (46.5–85.1)
DCR (CR+PR+SD)	96.0%	92.0%	96.0%	92.0%

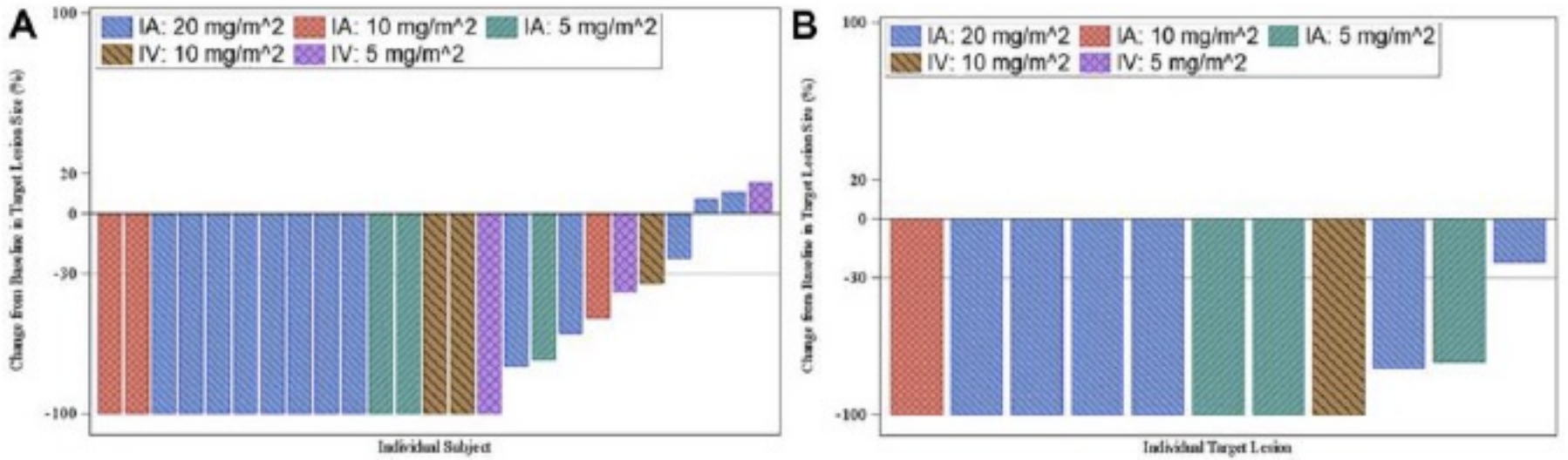


Figure 2 (A) Waterfall plot of best target lesion response. (B) Waterfall plot for best target lesion response for tumors greater than 5 cm. The results are shown per mRECIST criteria and color-coded by dose cohort.

- Phase II is prospective randomized trial

Accuracy and Safety of Scout Dose Y90 for Personalized Selective Internal Radiation Therapy Planning

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10/22/2021

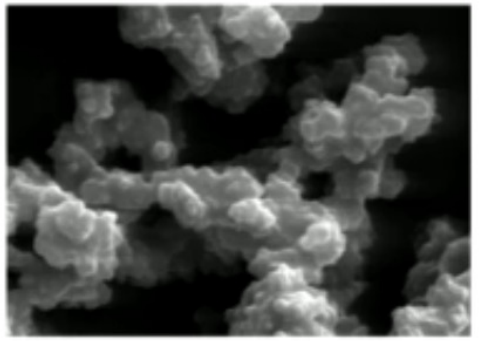
Disclosure

- N. K. conducts research partially sponsored by Sirtex Medical Ltd.
- N.K. has an educational grant from Boston Scientific.
- N. K. is a consultant for Sirtex Medical Ltd.
- Present study was partially sponsored by Sirtex Medical Ltd.

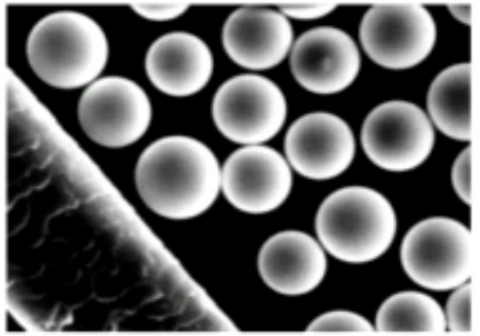
Background

- Tc99-m MAA
  - Imperfect/flawed surrogate for **Y90 biodistribution**

- **Overestimates lung shunt fraction (LSF)** up to **100%**[1-2]
  - Free pertechnetate primarily absorbed by lungs
  - Heterogenous size of MAA << microspheres
    - both glass and resin
- Imperfect in **predicting Y90 liver biodistribution**[3-5]
  - **Overestimates TNR** (linear correlation)
  - Accurate estimation for NTL



95% 5-40 um, up to 150 um



90% 30-35 um

1. Ho CL et al. *EJNMMI.* 2018.
2. Kao YH et al. *EJNMMI Research.* 2013.
3. Song YS et al. Medicine (United States). 2015.
4. Kokabi N et al. *JVIR.* 2014.
5. Villalobos A et al. *JVIR.* 2021.

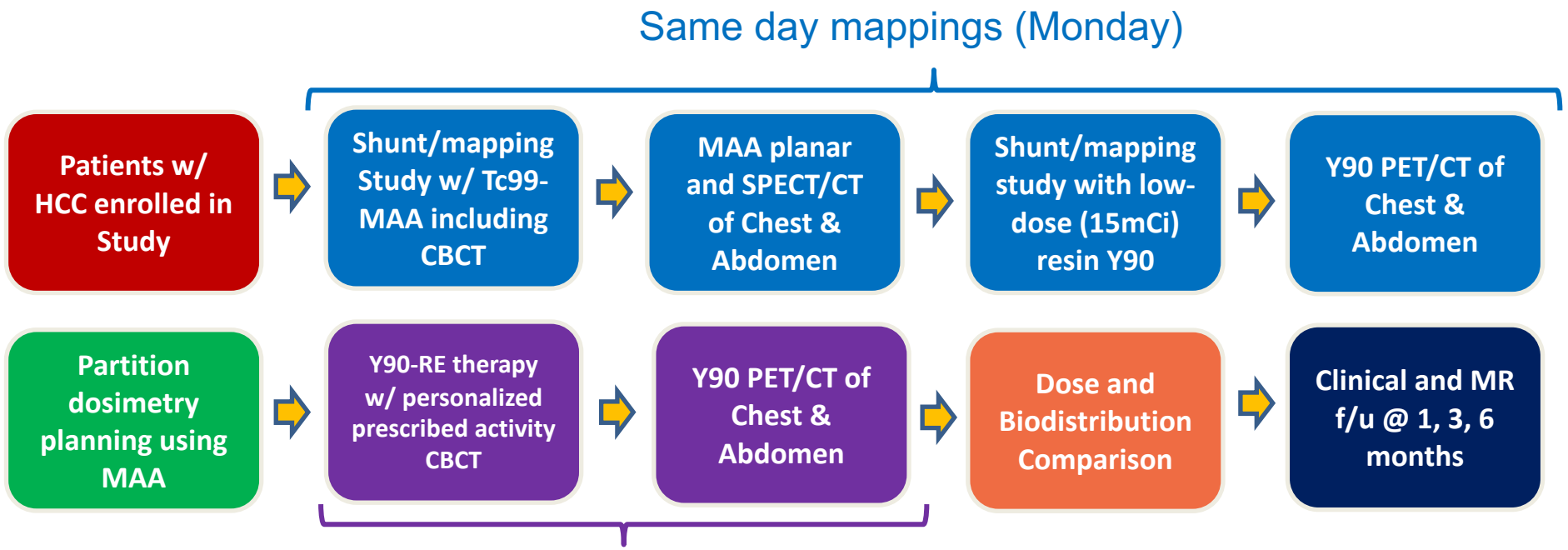
Objectives

- **Scout dose Y90 resin microspheres vs. Tc99m-MAA**
- **Accuracy: liver and lung biodistribution**
- **Safety:**
  - **? Non-target embolization**
  - **Degree of embolic effect of the scout dose Y90**

Study Design

- Prospective
- Single Arm
- Single Center (Emory)
- **N=30 Treatment naive HCC patients**
- ClincialTrials.gov ID: NCT04172714

Study Flow Chart



Therapy Activity= Prescribed Activity - 15 mCi

Results (Mean TNR)

TNR	Mean	STD
MAA	2.67	1.61
Scout Dose Y90 **PET**	2.75	1.20
High Dose Y90 **PET**	2.71	1.31

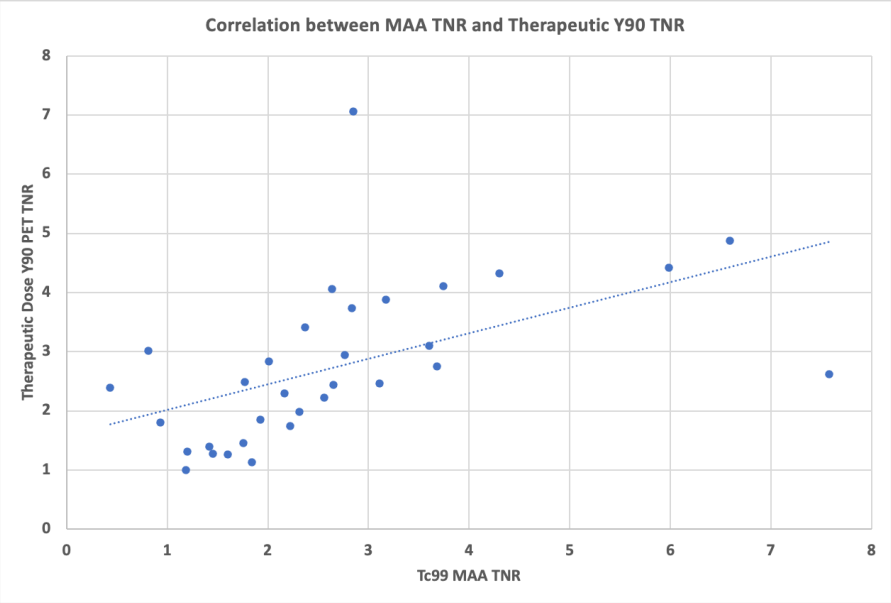
TNR	P-value
MAA vs. **High Dose** Y90 **PET**	**0.635**
Scout Dose Y90 PET vs. **High Dose** Y90 **PET**	**0.893**

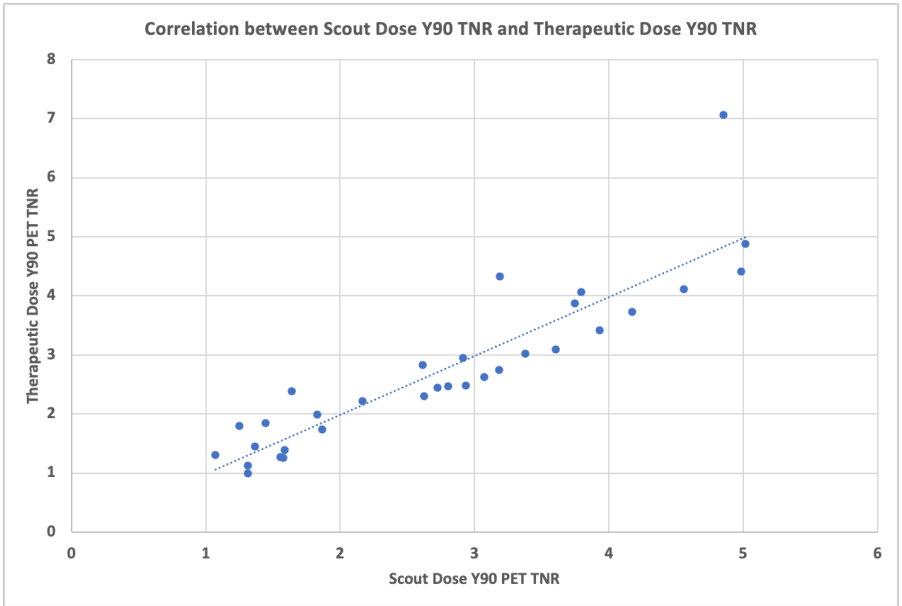
Results (Mean LSF)

TNR	Mean	STD
MAA	6%	3%
Scout Dose Y90 **PET**	6%	3%
High Dose Y90 **PET**	5%	2%

LSF	P-value
MAA vs. **High Dose** Y90 **PET**	**0.429**
Scout Dose Y90 PET vs. **High Dose** Y90 **PET**	**0.239**

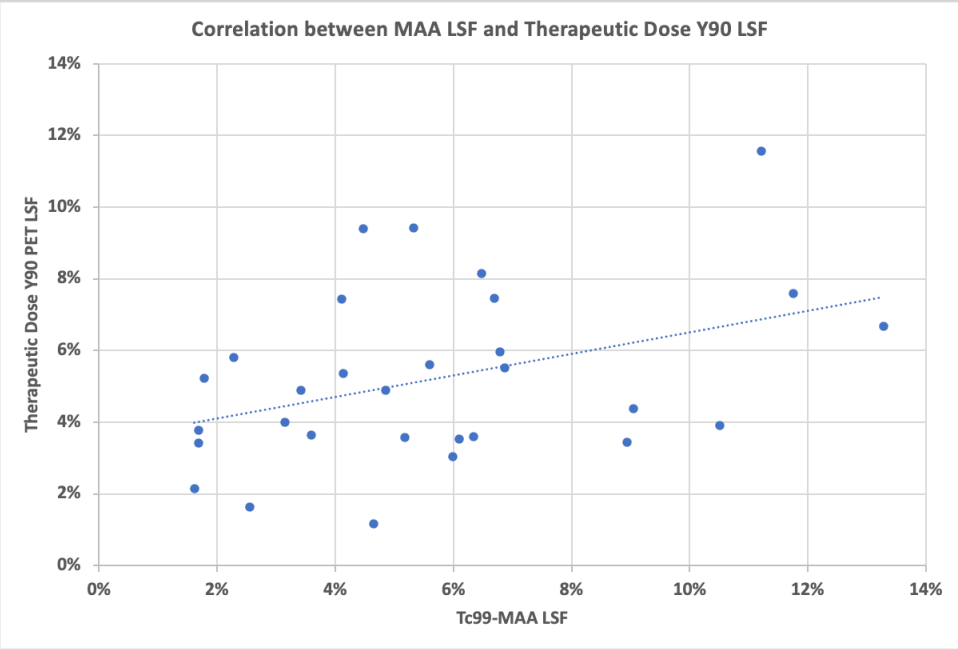
Pearson Linear Correlations: TNR

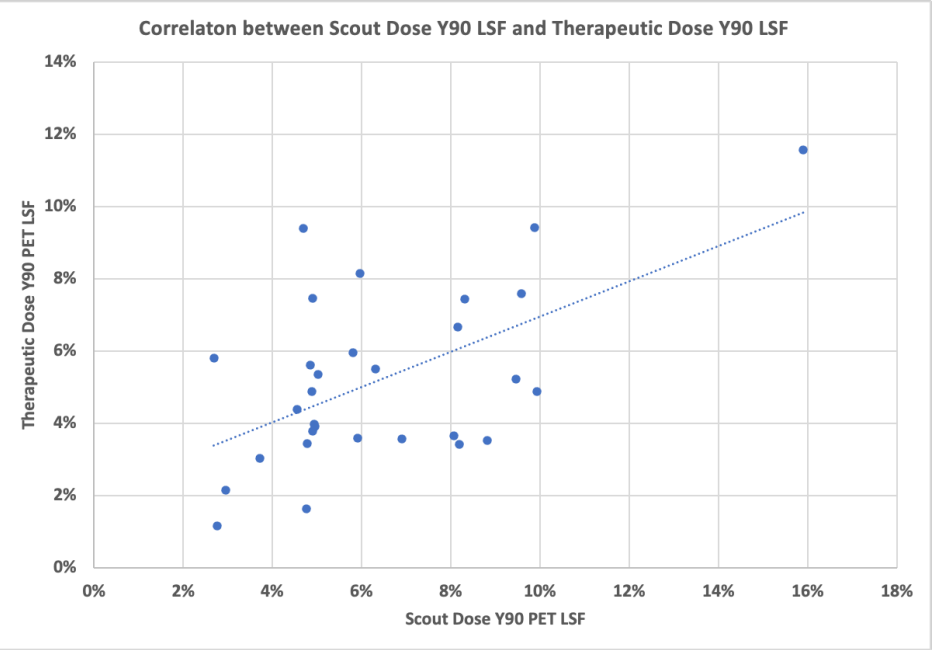




TNR	r	p-value	Correlation
MAA vs. **High Dose** Y90 **PET**	0.531	**0.001**	Moderate
Scout Dose Y90 **PET** vs. **High Dose** Y90 **PET**	0.816	**<0.001**	High

Pearson Linear Correlations: LSF





LSF	r	p-value	Correlation
MAA vs. **High Dose** Y90 **PET**	0.394	**0.031**	**Low**
Scout Dose Y90 **PET** vs. **High Dose** Y90 **PET**	0.562	**0.001**	**Moderate**

Conclusions

- **Scout dose Y90** is more accurate than **MAA** for prospective dosimetry planning

- **15 mCi 3-day pre-calibrated resin microsphres** is safe and effective
  - No non-target embolization
  - Not grossly embolic
  - Decreased enhancement post scout dose can treatment related (3 day lag)

Thank You

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