Locoregional Therapies for HCC. When Two Therapies May be Better than One:

Practical and Data Informed Approach

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Disclosures

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- American Cancer Society

Advisor:
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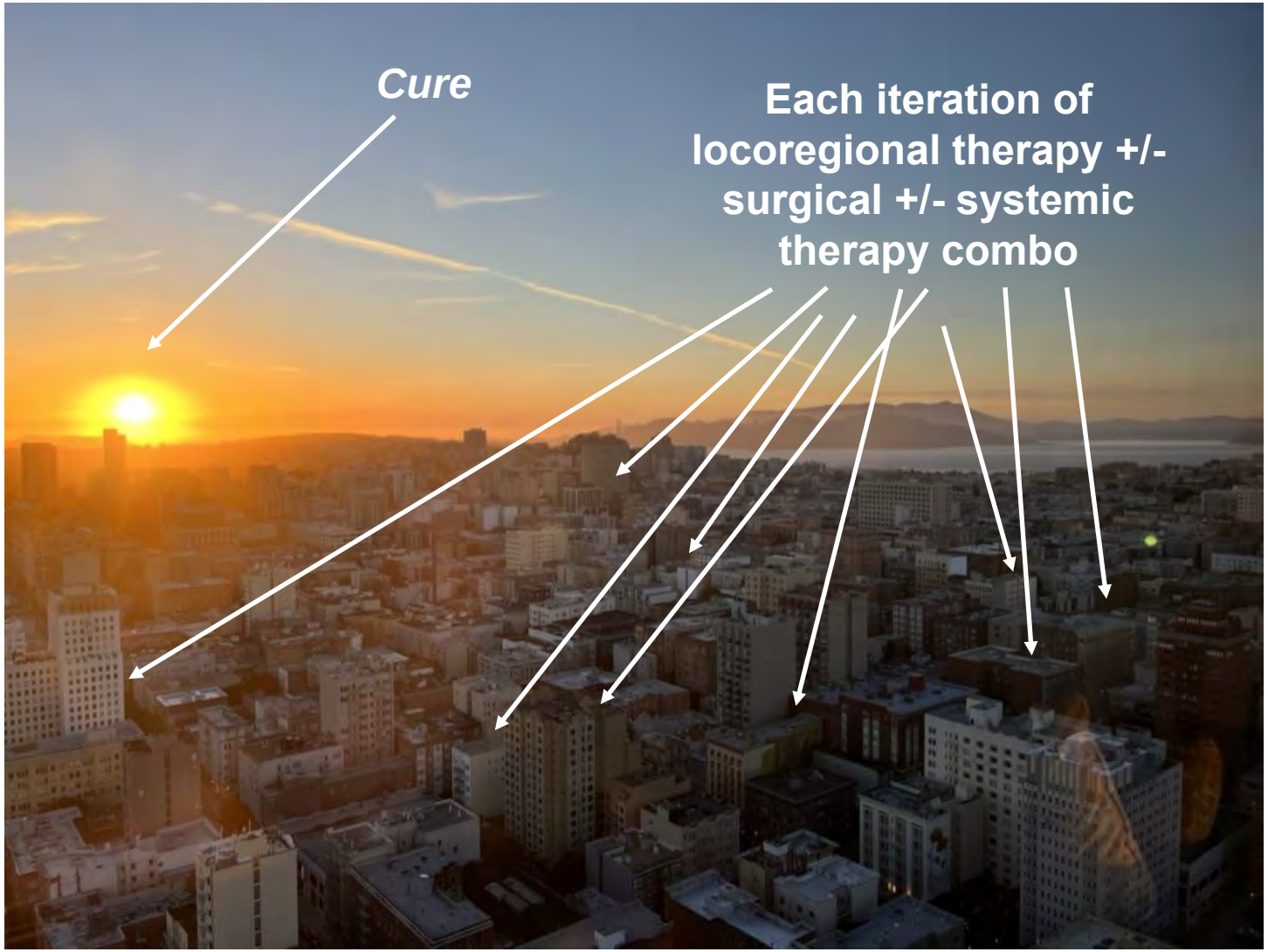
- AstraZeneca Pharmaceuticals LP
- Boston Scientific

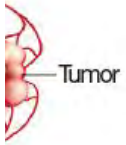
Industry Research support:
- Boston Scientific

Disclaimer


Cure
Each iteration of locoregional therapy +/- surgical +/- systemic therapy combo

Interventional Radiology and the Liver – Locoregional Therapy Toolkit

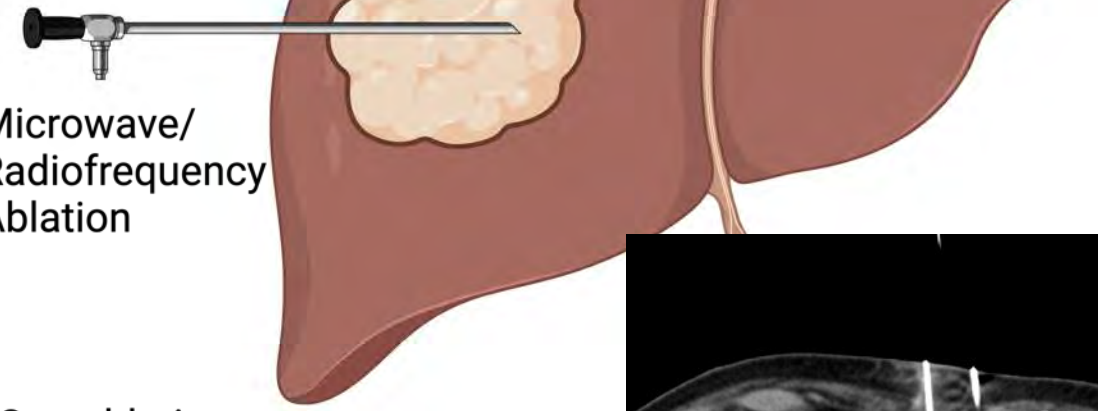
Percutaneous

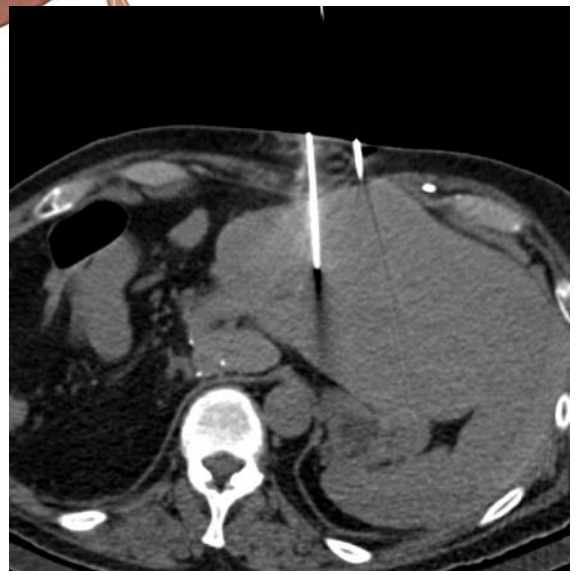


Microwave/
Radiofrequency
Ablation

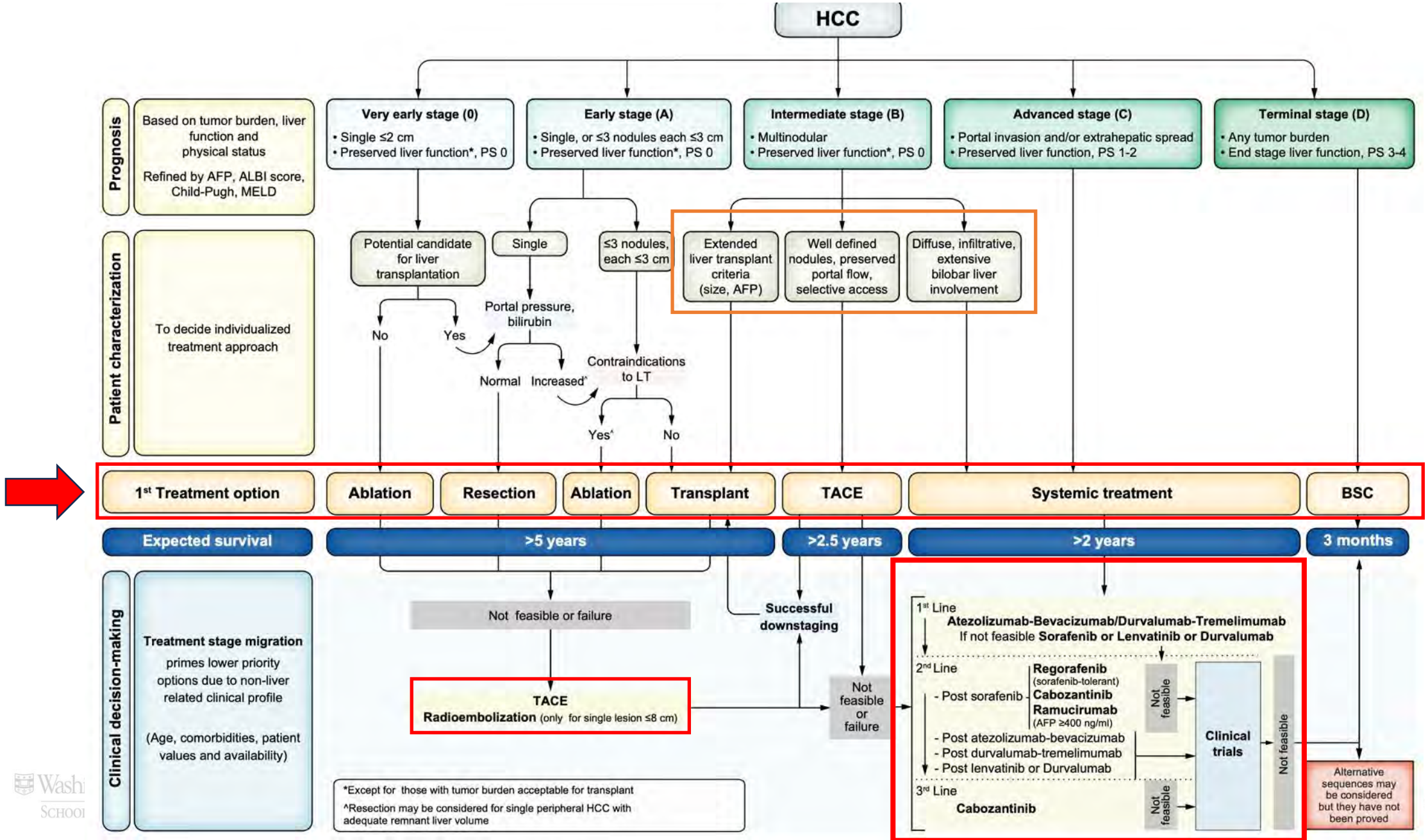
Cryoablation

Irreversible
Electroporation (IRE)

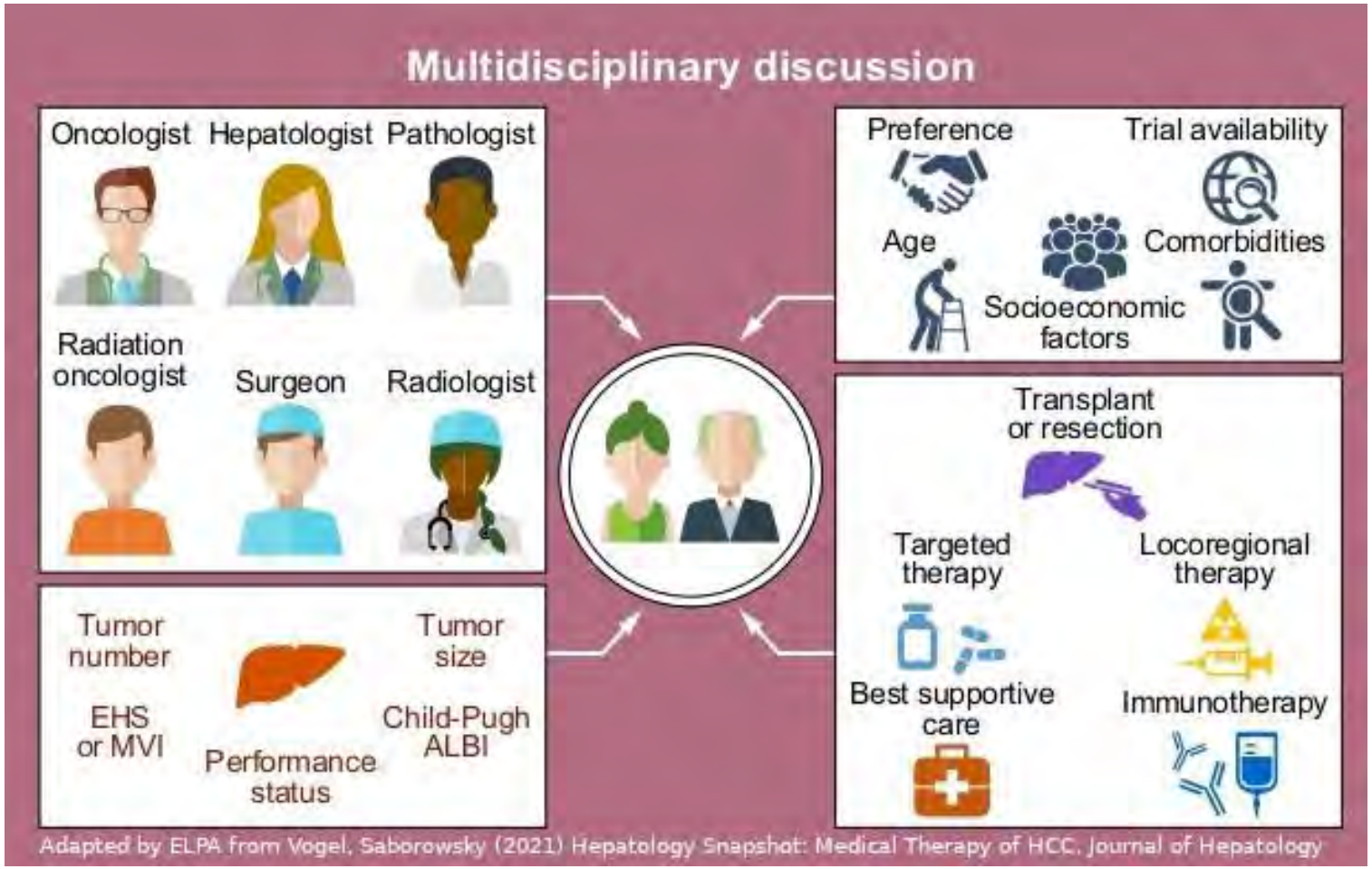




BCLC Staging and Treatment for HCC. What's new?



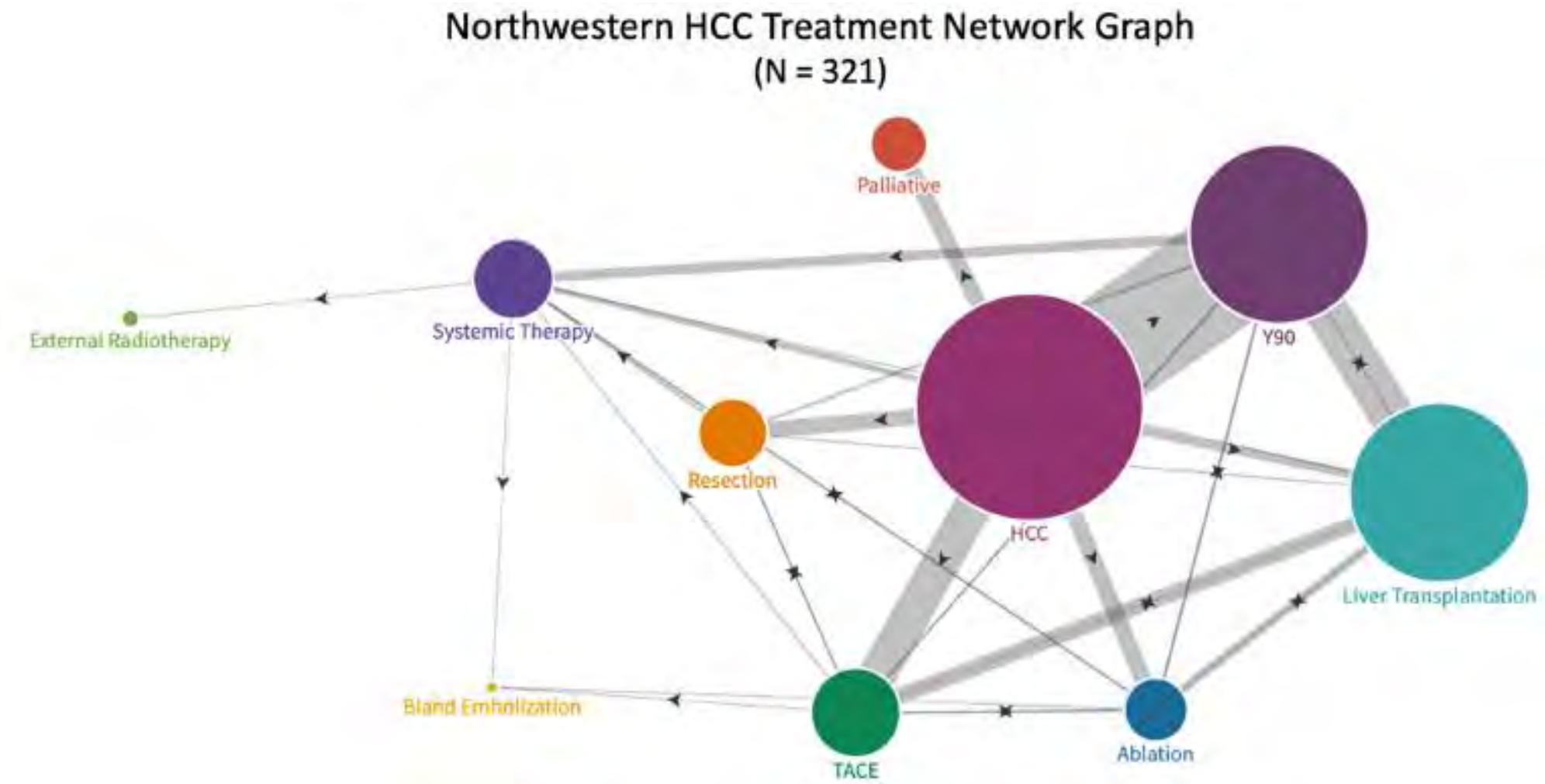
Not One Size Fits All



https://livercancermonth.eu/liver-cancer/

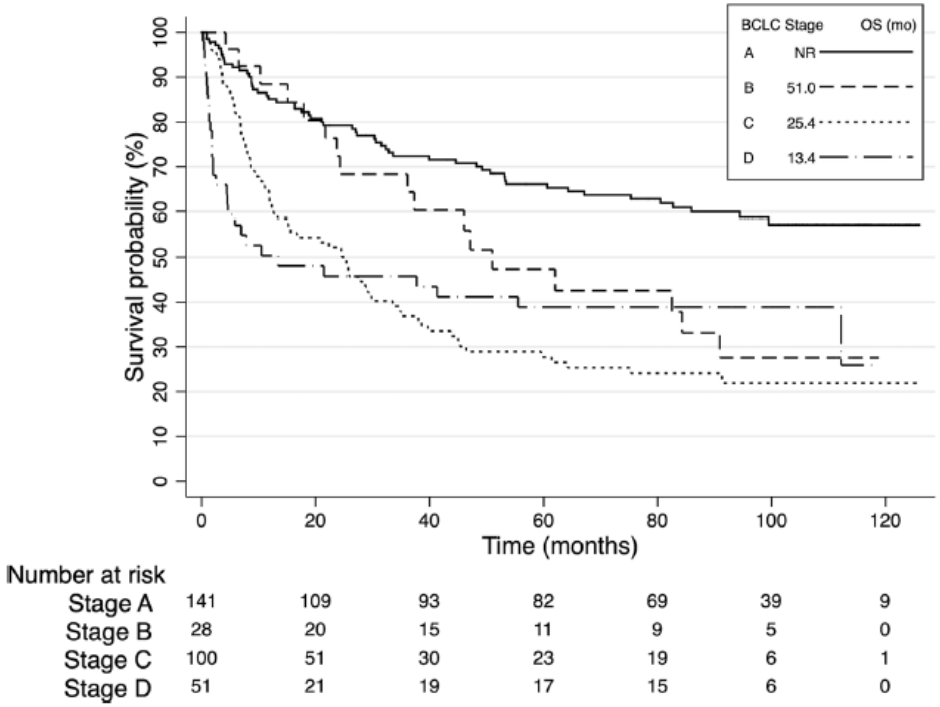
Multidisciplinary team approach, combination and sequencing of multiple therapies (liver function permitting), optimizes and increases chance of curative outcomes

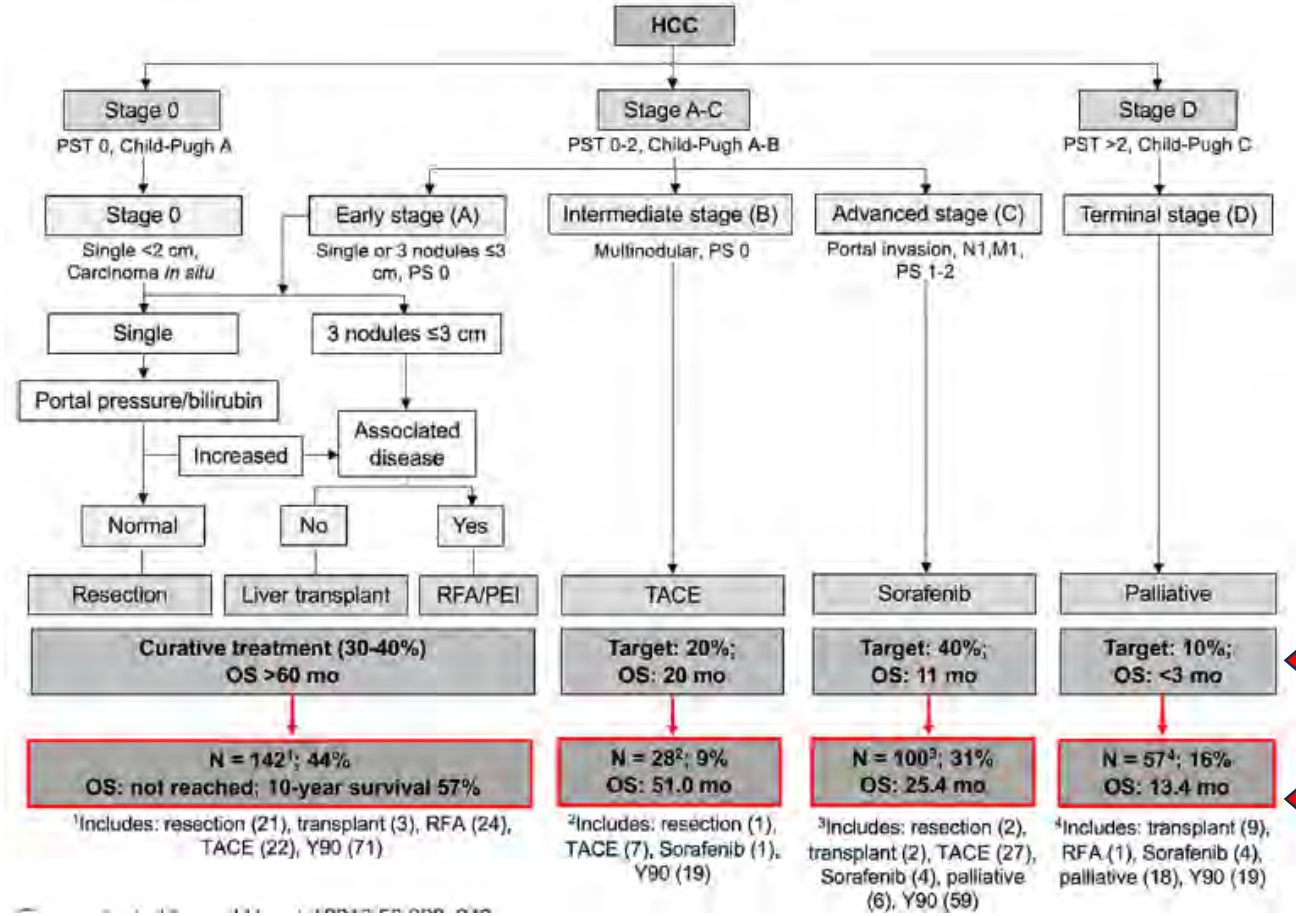
BCLC is Not Dogma



Cardiovasc Intervent Radiol (2021) 44:1070–1080

Personalized Approach





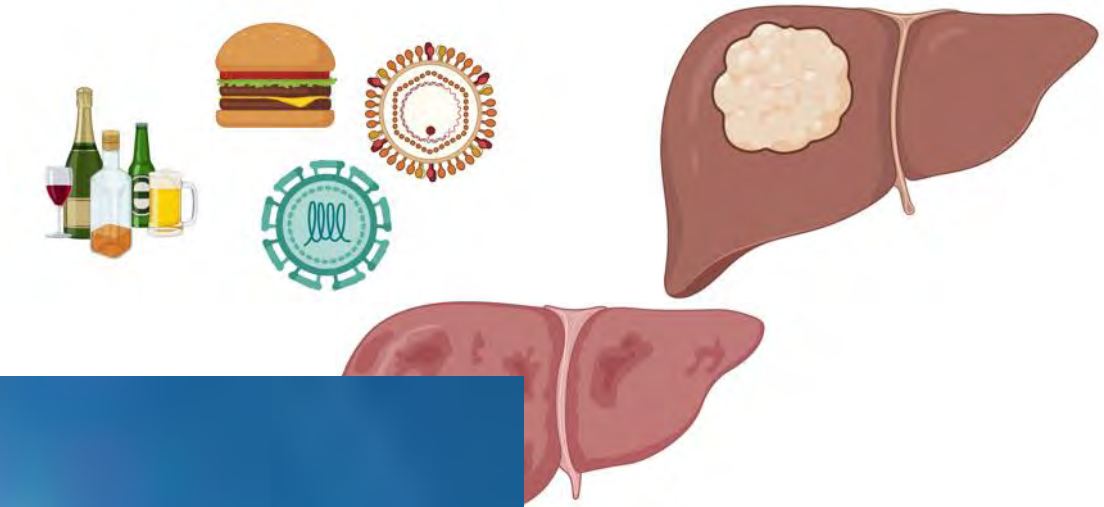
BCLC "Benchmark"

Achieved

Cardiovasc Intervent Radiol (2021) 44:1070–1080

What is the Patient's Destination?

Managing 2 Diseases!



Transplant?

A6-B7
ALBI 2

CP B8 +
ALBI 3

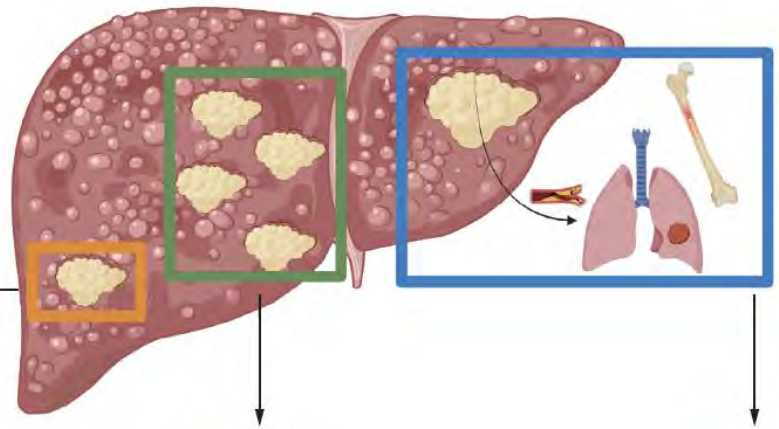
ALBI Score Often Outperforms Child Pugh, Especially in CP A

Review JHEP|Reports

ALBI grade: Evidence for an improved model for liver functional estimation in patients with hepatocellular carcinoma

Coskun O. Demirtas,[1,†] Antonio D'Alessio,[2,3,†] Lorenza Rimassa,[3,4] Rohini Sharma,[2] David J. Pinato[2,5,*]

JHep Reports 2022



BCLC 0-A

Resection	ALBI correlates with OS, PFS, post-surgical liver failure
Transplantation	ALBI correlates with survival, complications, late recurrences
Ablation	ALBI correlates with OS, PFS

BCLC B

TACE	ALBI correlates with OS, PFS, acute on chronic liver disease
TARE/ SIRT	ALBI correlates with survival, toxicity

BCLC C

Sorafenib	ALBI correlates with OS, PFS, ORR, toxicity, and selects candidates for second-line treatment
Lenvatinib	ALBI correlates with OS, PFS, ORR, toxicity, nutritional status, and liver reserve for further treatments
Cabozantinib	ALBI correlates with OS, PFS
Ramucirumab	ALBI correlates with OS, toxicity
Regorafenib	In CP-B, ALBI correlates with OS, ORR, toxicity
Immunotherapy	ALBI correlates with OS, post-immuno-therapy survival, 90-days mortality

Total Bilirubin and Albumin:

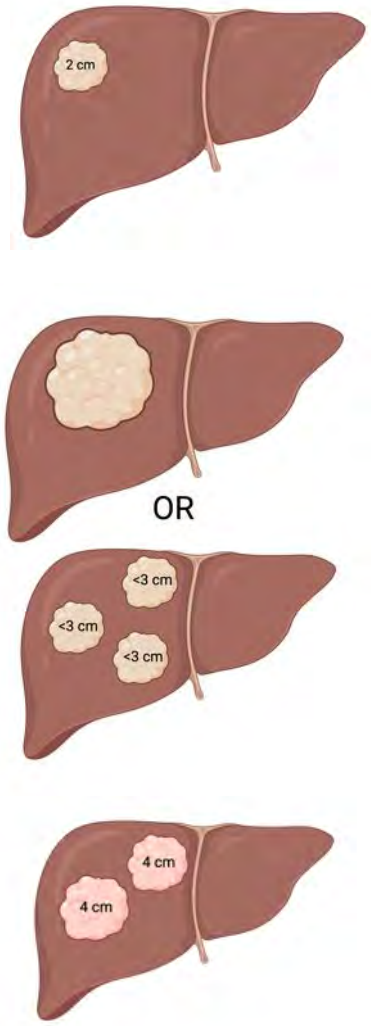
ALBI 1 👍

ALBI 2 👊

ALBI 3 👎

Very Early (BCLC 0) through UCSF Extended Transplant (BCLC B)

Focus on ***Curative*** Intent

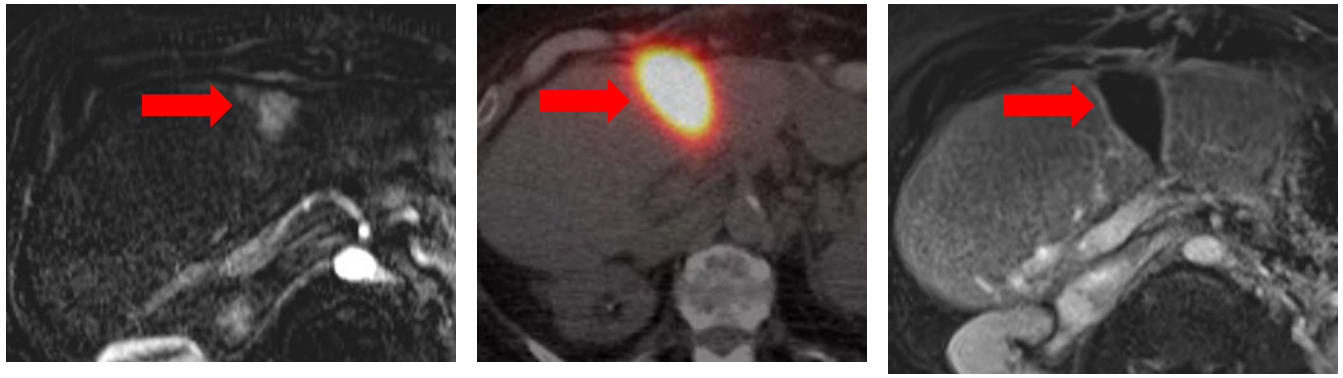


Locoregional Therapy as Monotherapy

Solitary tumor, no vascular invasion, no extrahepatic spread, Child Pugh A

Radiation Segmentectomy:
Potential Curative Therapy for Early Hepatocellular Carcinoma[1]

Radiology



Tumor No. and Size, Treatment Modality, and Clinical Study	No. of Patients	Survival (%) 1 y	3 y	5 y	Median Overall Survival (mo)
Solitary ≤3 cm					
Radiation segmentectomy					
Current study	45	100	82	75	Not reached
Surgical resection					
Pompili et al (34)	246	95	82	74*	Not reached
Huang et al (35)	45	100	96	82	Not reached
Radiofrequency ablation					
Pompili et al (34)	298	98	81	66*	Not reached
Huang et al (35)	57	87	77	55	Not reached
Solitary ≤5 cm					
Radiation segmentectomy					
Current study	70	98	66	57	80
Surgical resection					
Chen et al (36)	91	93	73	64*	Not reached
Radiofrequency ablation					
Lencioni et al (25)	145	100	89	61	65
Chen et al (36)	91	94	69	66*	Not reached

Lewandowski et al. Radiology 2018

Transplant Candidacy?

Liver Transplant

- **<u>Most ideal</u>**: low recurrence rates ***and*** concurrent treatment of cirrhosis
- Transplant for HCC: those in Milan criteria achieve 5-year survival <u>≥</u>70%, ***similar to those without HCC***

Escartin A Transplant Proc. 2007
Mazzaferro V Liver Transplant. 2011
Mazzaferro V NEJM 1996

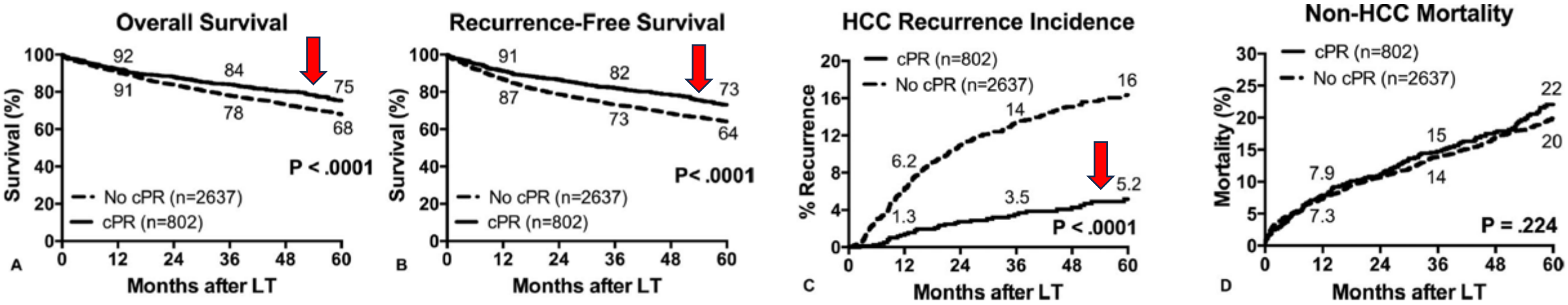
Locoregional Therapy for Bridging to Transplant

- Rationale to prevent dropouts, maintain patients within Milan
- Relevant in regions with long wait times
- Trends towards improved dropout rates with (L Kulik Hepatology 2018)

Pathologic Response to Pretransplant Locoregional Therapy is Predictive of Patient Outcome After Liver Transplantation for Hepatocellular Carcinoma

Analysis From the US Multicenter HCC Transplant Consortium

J DiNorcia Ann Surg 2020



Complete pathologic response to locoregional therapy confers better long term post transplant outcomes

Reduce chance of tumor under-staging on explant pathology (assoc w/ worse post transplant survival, Mehta JAMA Oncol 2017)

Downstaging for Transplant for those Beyond Milan Criteria

OPTN policy eligibility for the "downstaging" protocol **T3, ~ UCSF**	Downstaging Criteria: One lesion > 5 cm and < 8 cm; or 2–3 lesion with at least one > 3 cm and < 5 cm, and total combined diameter ≤ 8 cm; or 4–5 lesions each < 3 cm with total combined diameter ≤ 8 cm [70]
	If patient meeting the downstaging criteria are treated with locoregional therapy and are downstaged to T2 disease, they are automatically eligible to MELD tumor exception points

Abdominal Radiology (2021) 46:3528–3539

- Similar OS for T3 (UCSF) patients downstaged to T2 (Milan) compared to initial T2 patients (FY Yao Hepatology 2015), BUT had higher dropout rates
- Significant increase in 1 and 5 year post transplant OS for downstaged T3 patients vs those not downstaged (L Kulik, Hepatology 2018)

Potential Ceilings in Downstaging

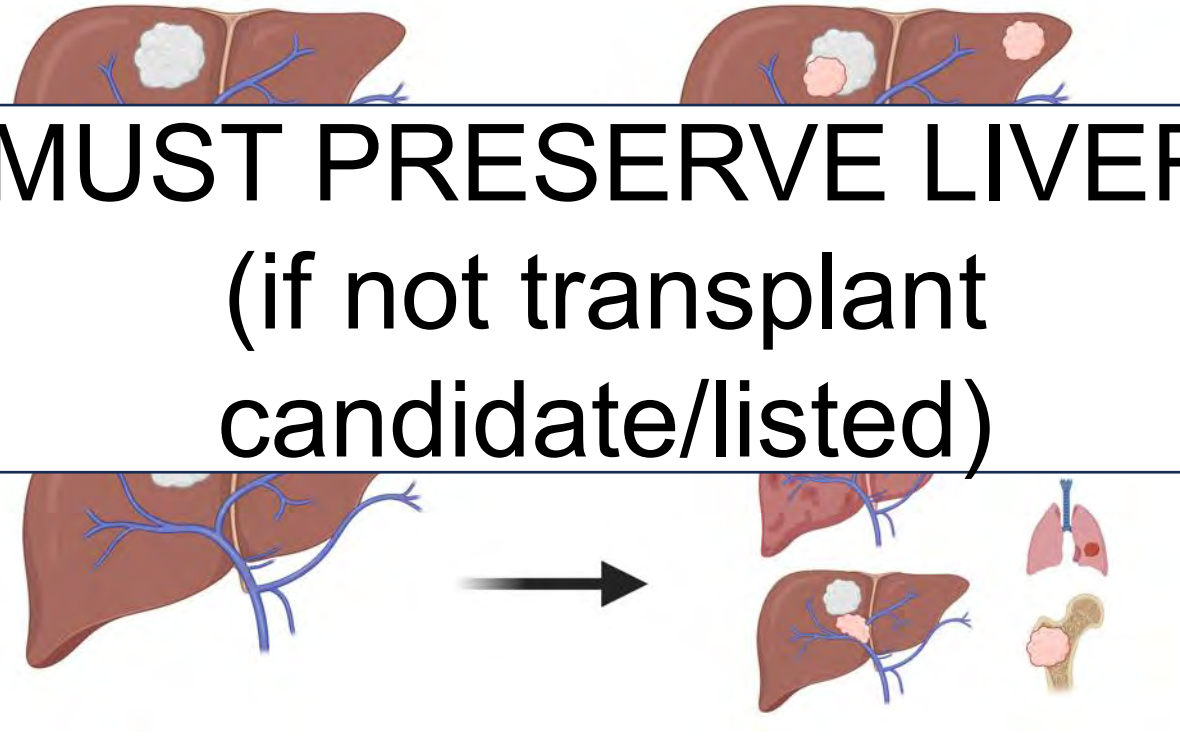
"All-comers" – exceed UNOS-DS criteria, with total tumor diameter > 8 cm without EHS or vascular invasion

- <50% downstaging to Milan if sum of largest lesion + # lesions > 12 (Sinha, Hepatology 2019)
- 67% successful downstaging in "All-comers" vs 83% in those meeting UNOS-DS criteria at 1 year
  - For every 1 unit increase in largest lesion size (cm) + # of lesions → probability of successful downstaging drops by 14% (Natarajan, AJT 2021)

AFP > 100 at transplant → higher risk of HCC recurrence and death (Mehta, Hepatology 2020)

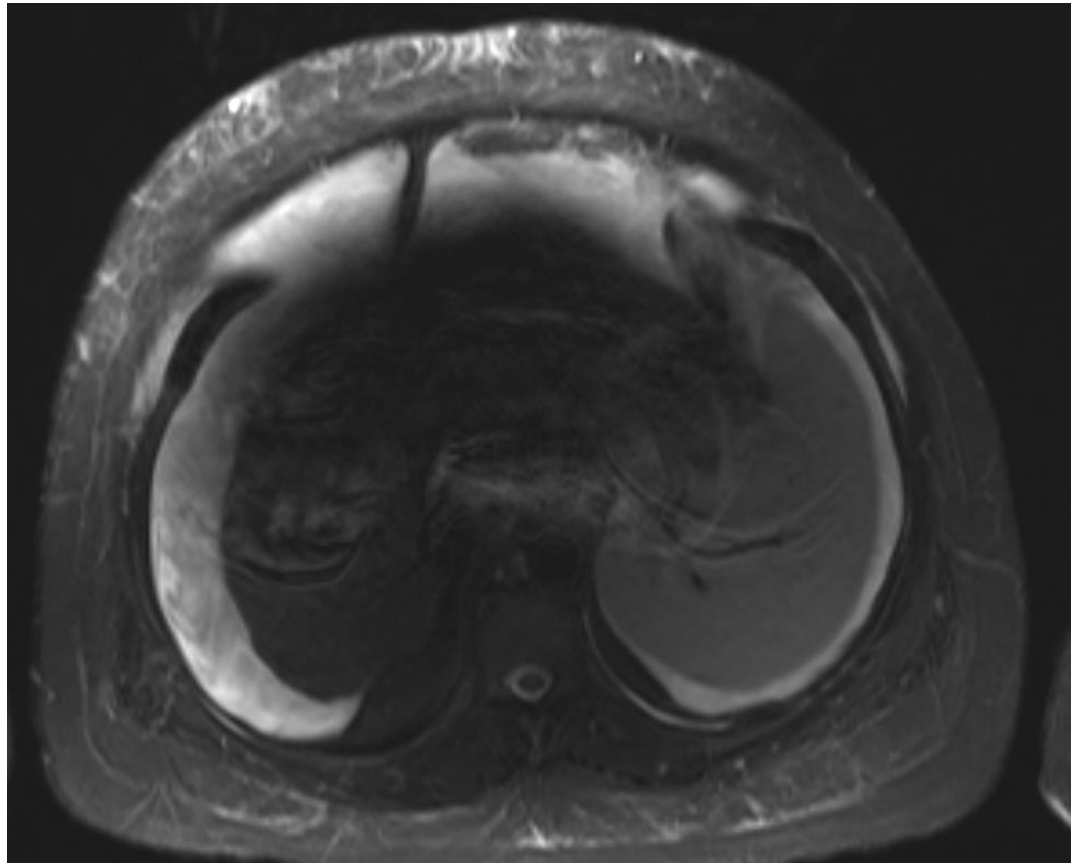
Don’t Burn Patients – Recognize Treatable vs Untreatable Progression

“Treatable” Progression: Potential for more LDT if maintained liver function



MUST PRESERVE LIVER (if not transplant candidate/listed)

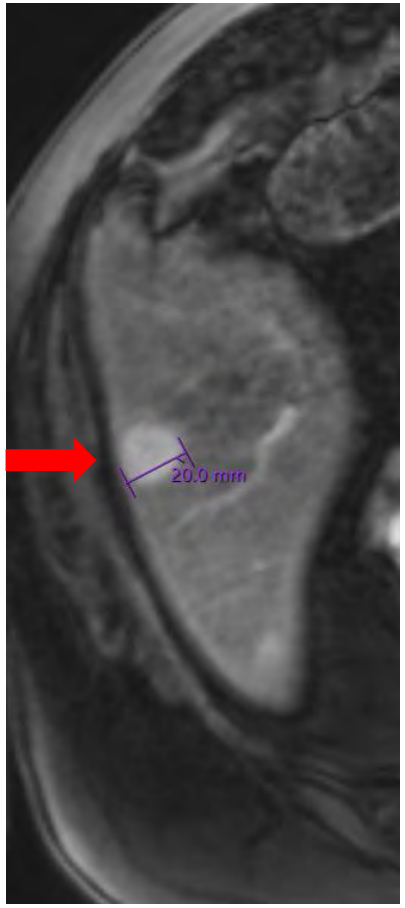
“Untreatable” Progression: liver function deterioration, new vascular invasion or mets



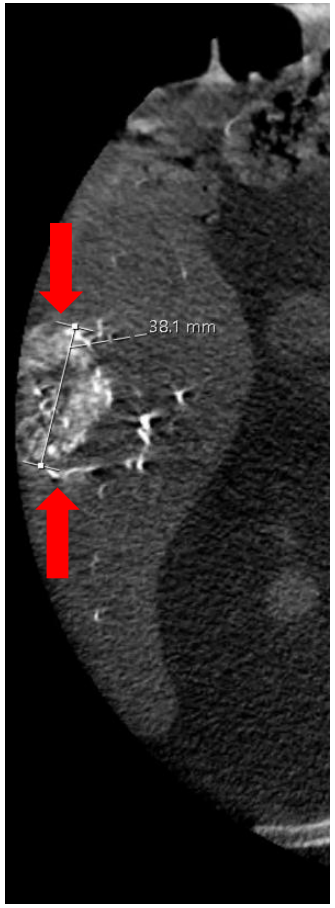
Limited systemic therapy options beyond CP B7

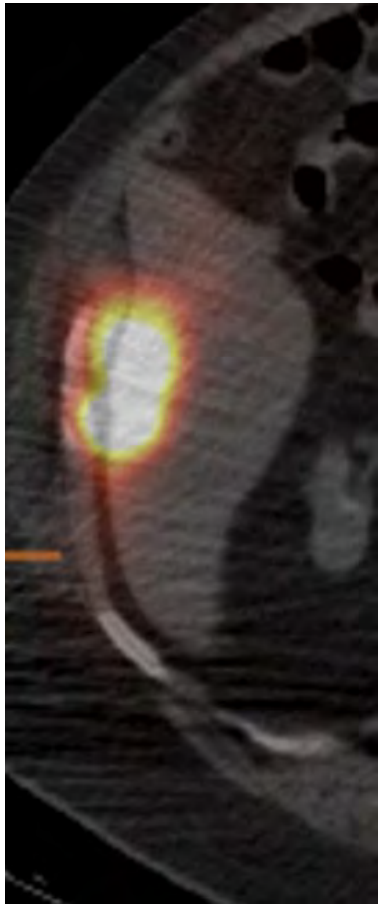
Reig et al Hepatology 2013

What about this patient?

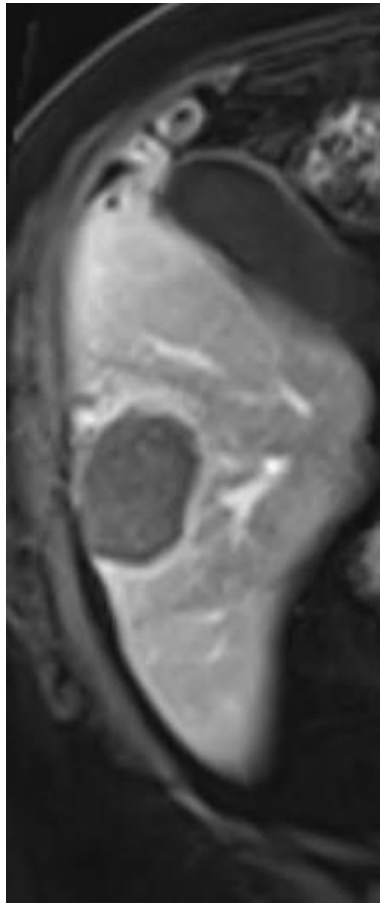


Solitary 2.0 cm
AFP 283
ALBI 1

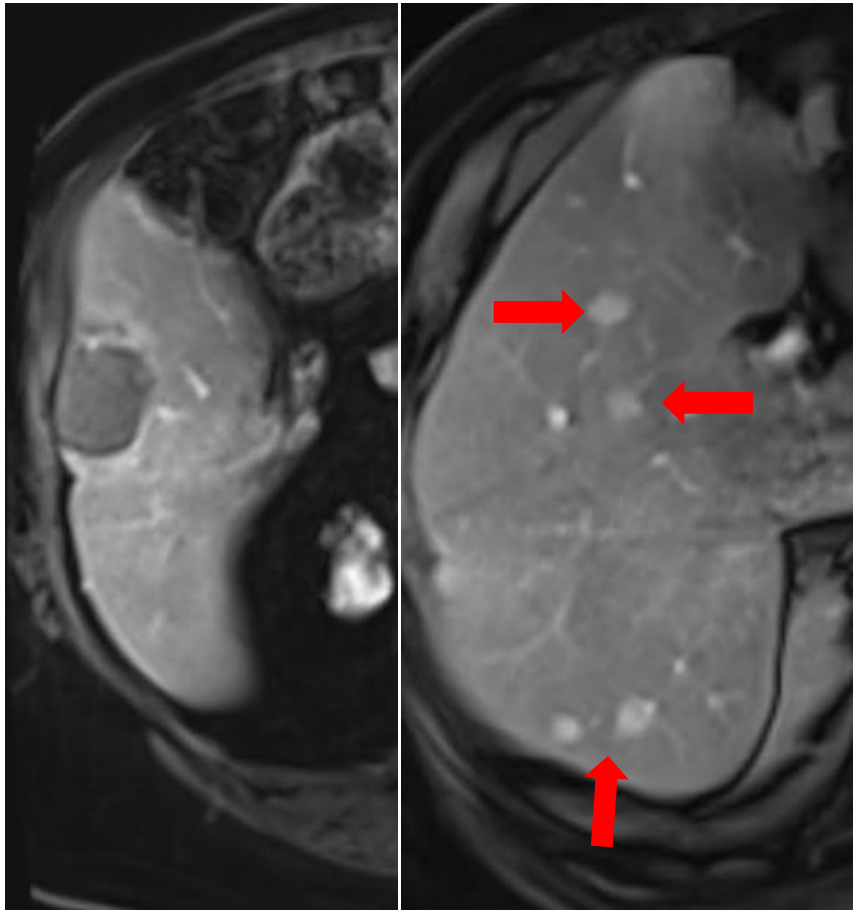




Now 3.8 cm
AFP 7368

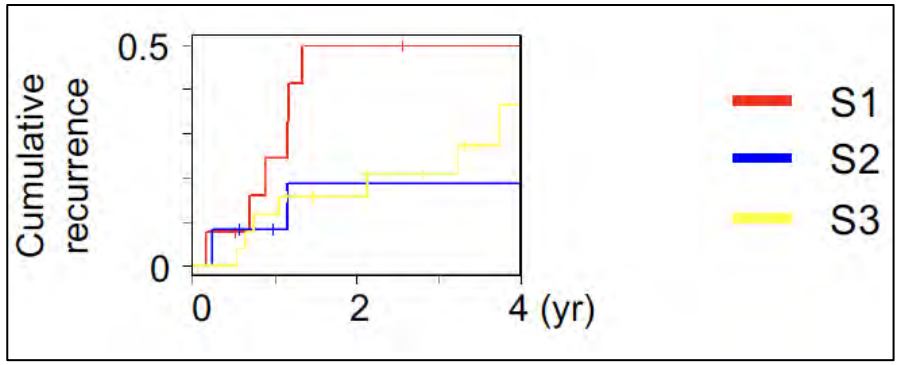


AFP 281



AFP 2228

Early Out of Field Progression (OFP) is Relevant



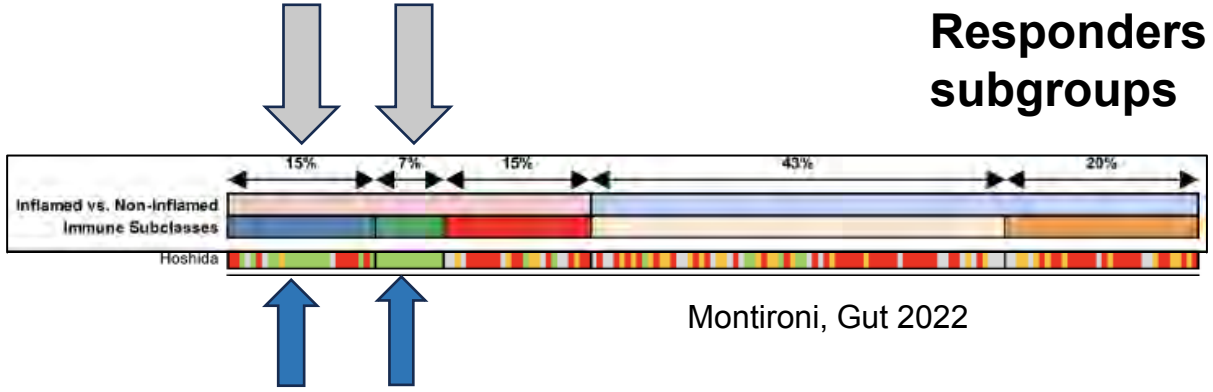
Hoshida Cancer Res 2009

Hoshida S1 gene expression subclass associated with **<u>early recurrence</u>** after surgical resection. Parallel with early OFP after locoregional therapy

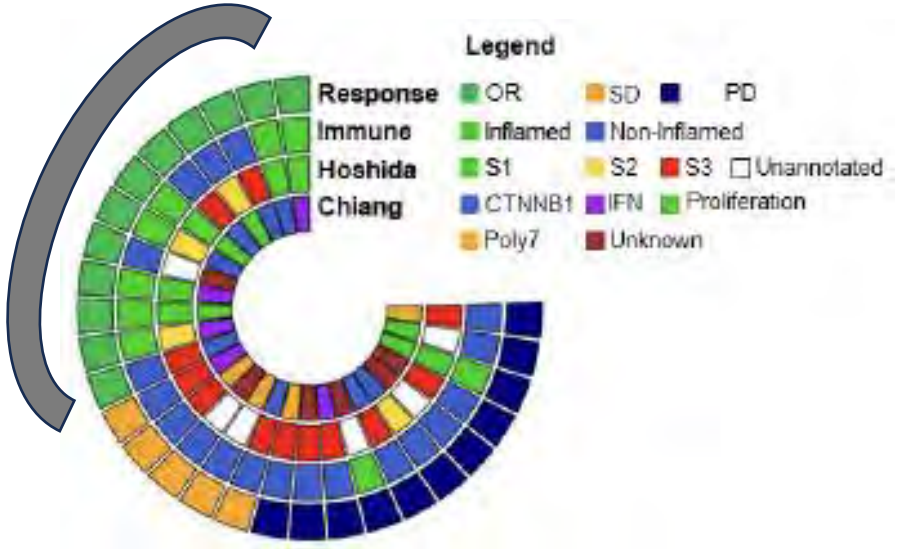
Potential marker of treatment resistance, dissemination of primary tumor.

Inflamed (Immune Active and Exhausted) TIME's enriched with S1 tumor subclass

Responders to ICI's more likely to be S1 subclass and Inflamed subgroups

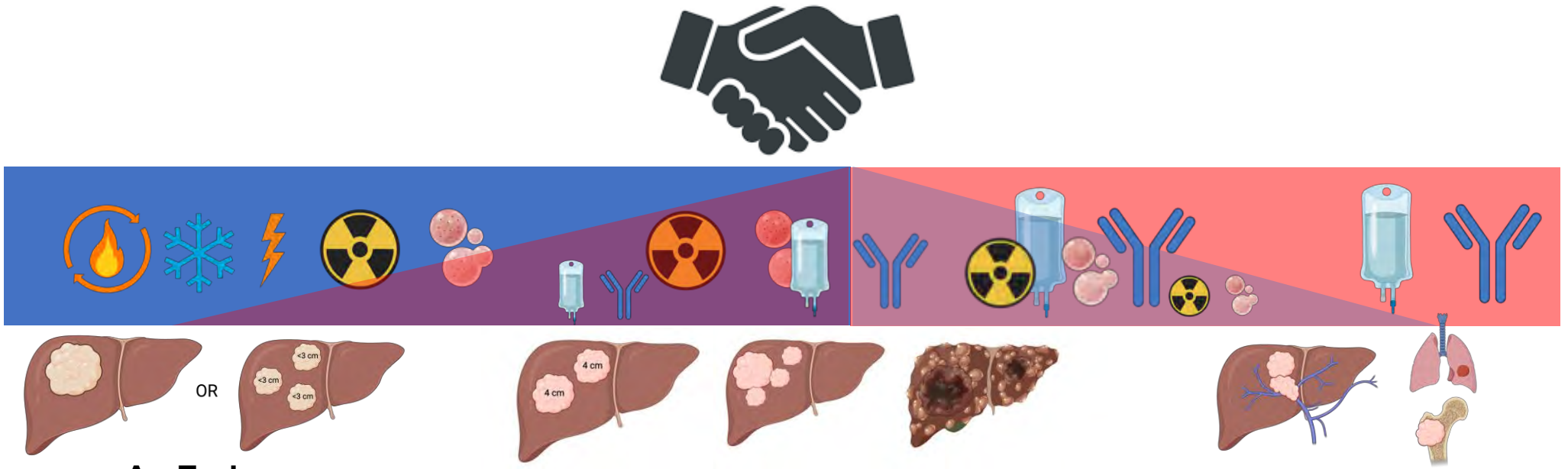


Montironi, Gut 2022



Haber, Gastroenterology 2023

Combination LDT and Systemic (Immuno) Therapies: Current and Future Potentials



A - Early
Solitary
3 up to 3cm

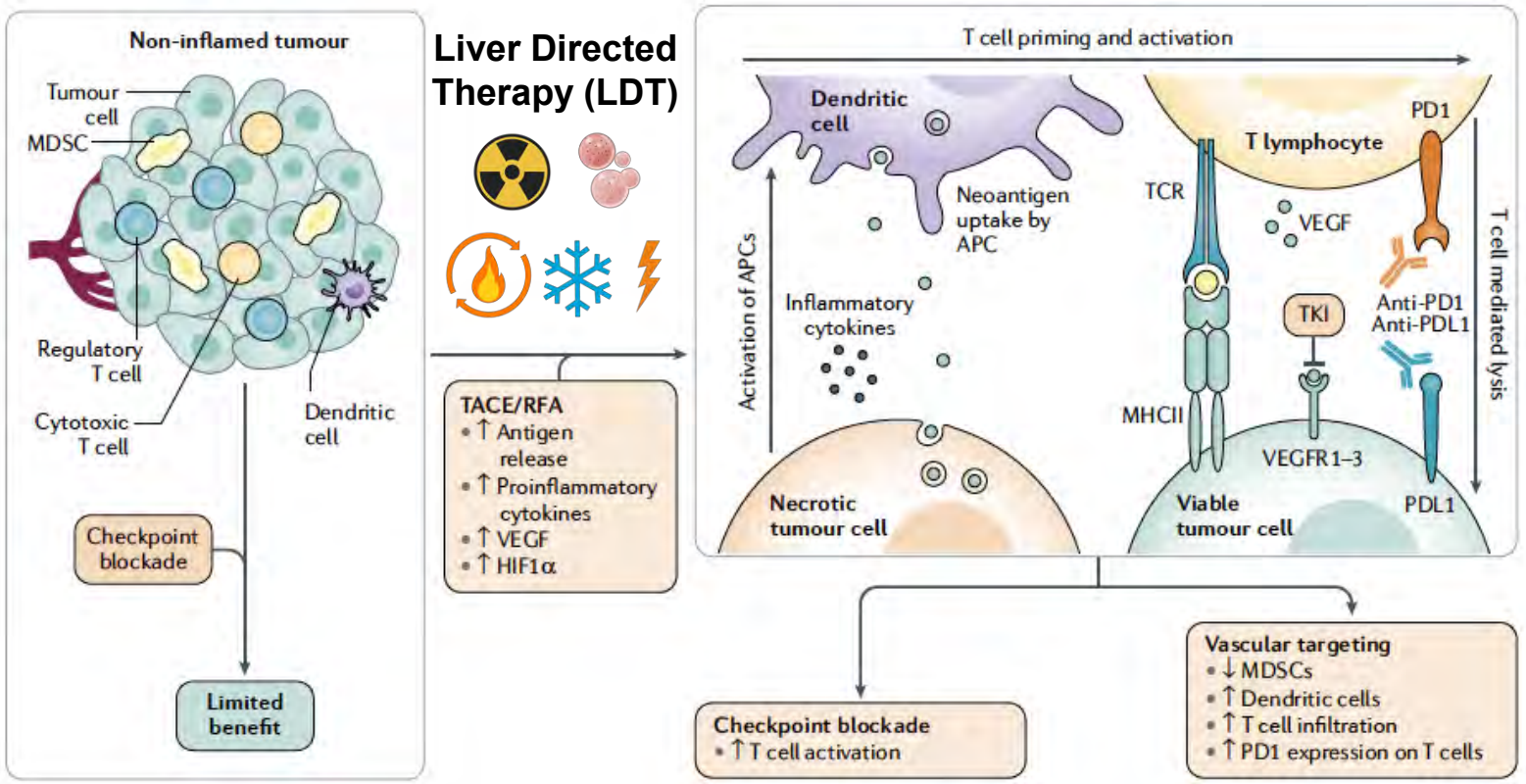
B - Intermediate
Extended Transplant
Well defined tumors
Infiltrative, bilobar

C - Advanced
Vascular Invasion
Extrahepatic

Limitations potentially addressed

- Out of field progression
- Out of field progression Watershed regions
- Complete tumor coverage
- Occult microsatellite disease
- Low response rates (<30%)
- Tolerability and candidacy of ideal regimens
- Immunologically cold tumors and microenvironments
- Narrow Therapeutic Index

Overarching Rationale for Combination Therapy



Llovet. Nat Rev Gastroenterol Hepatol. 2021

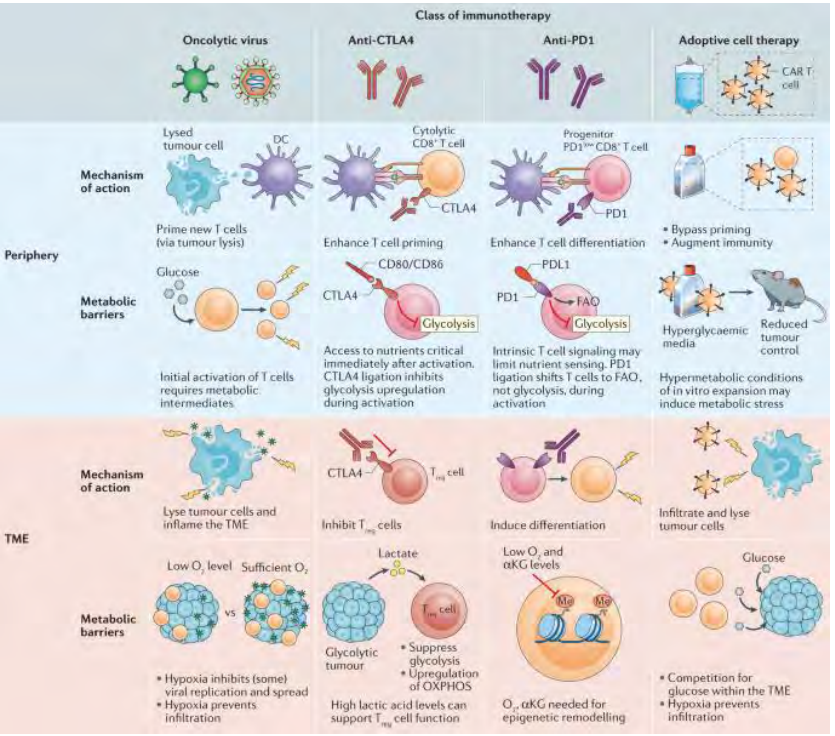
Convert cold tumors to hot/inflamed?

Enable ICI efficacy?

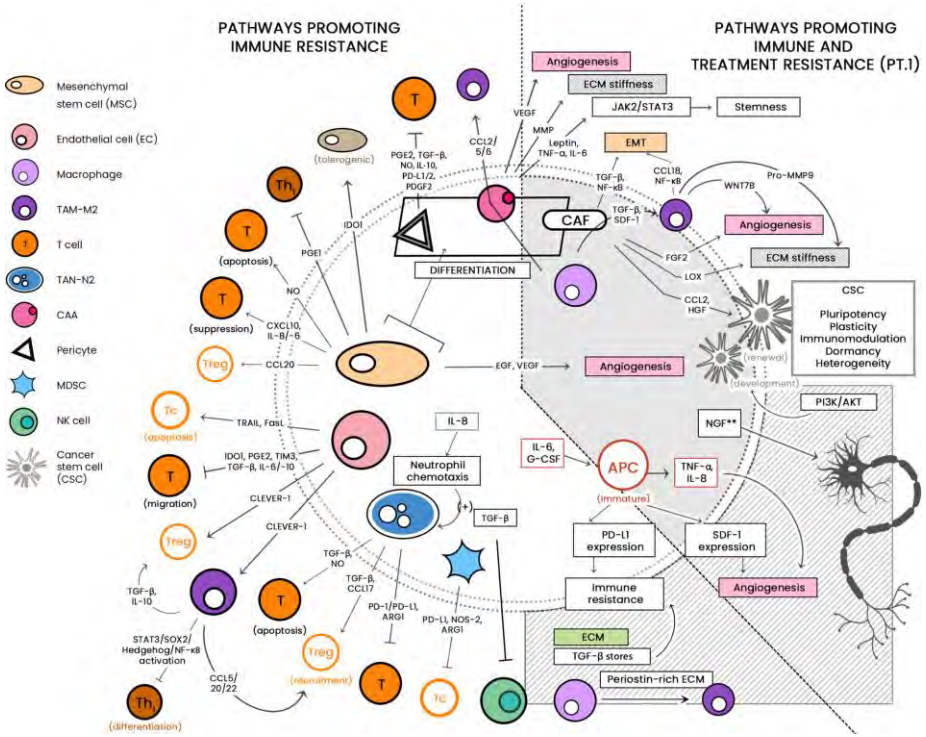
Abscopal effect?

Does this really happen? Is it this simple?

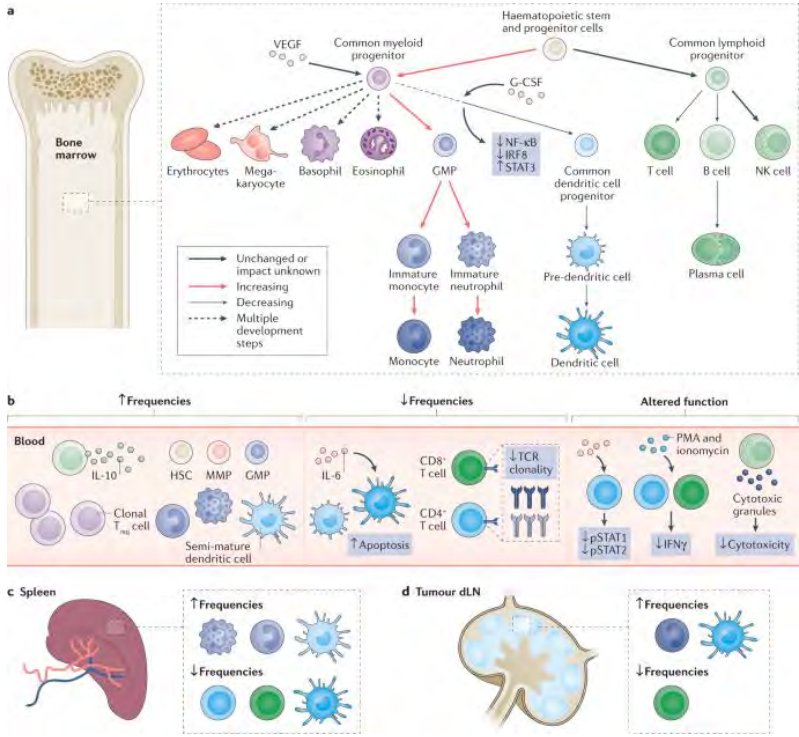
Cancer Immunology is **Complicated**



Nat Rev Immunol. 2021

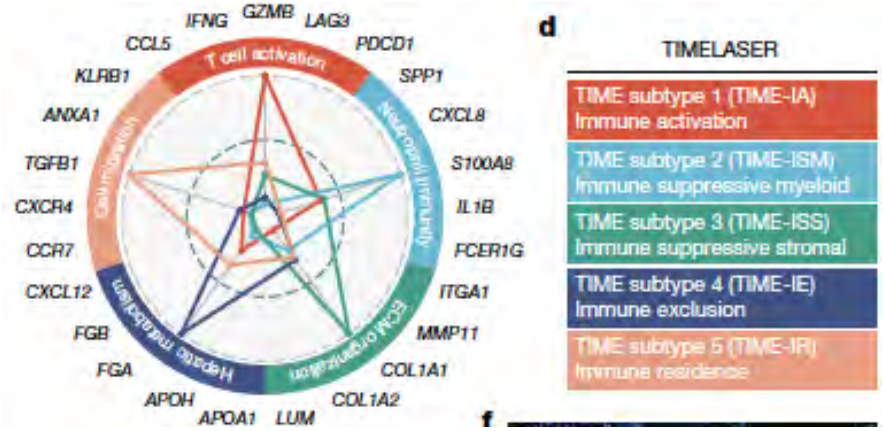


Front. Immunol. 2021

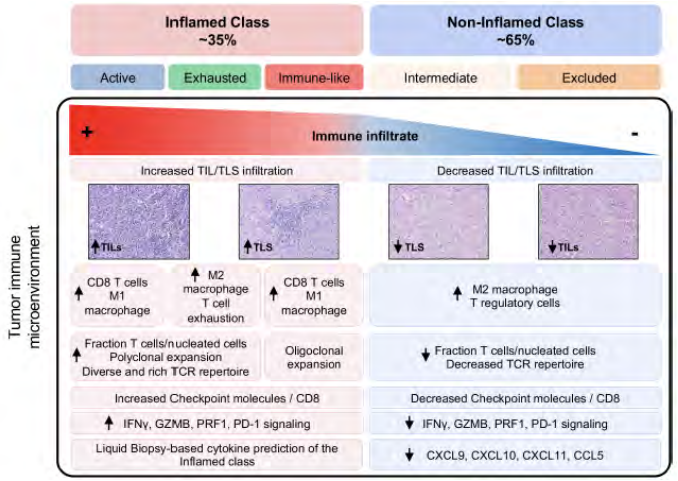


Nat Rev Cancer. 2021

HCC Tumor Immune Microenvironment is **Diverse**, Impacts Overall Prognosis and Response to ICI

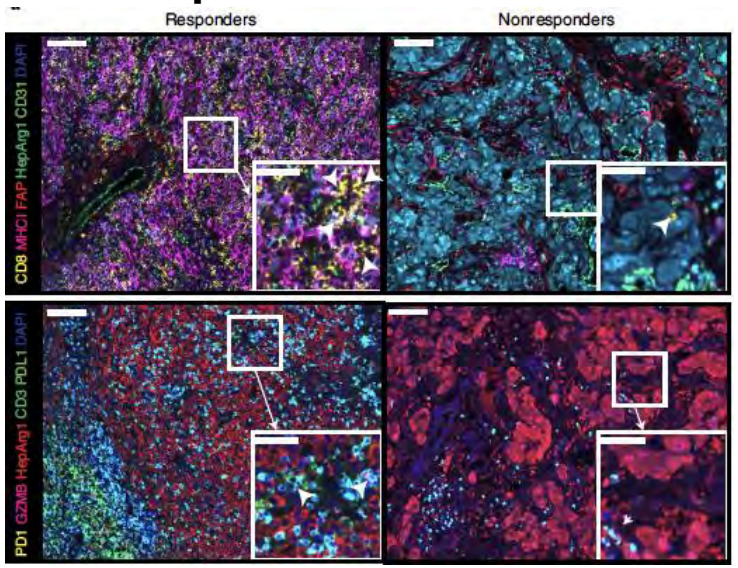


Xue et al. Nature 2022

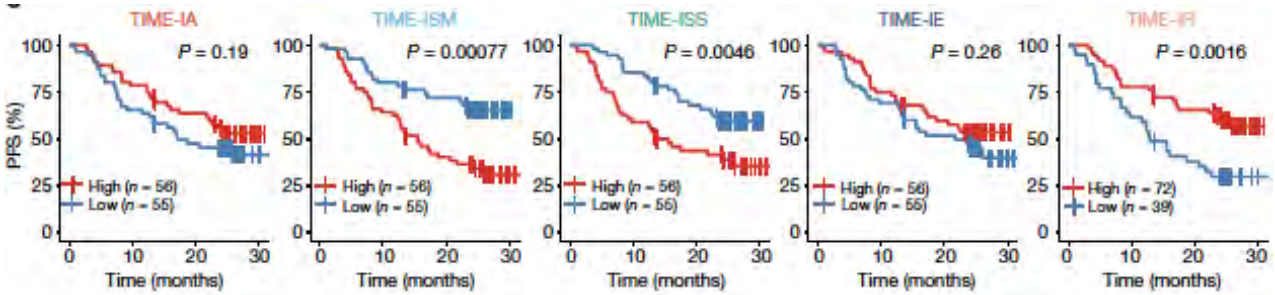


Montironi et al. Gut 2022

Response to Atezo/Bev



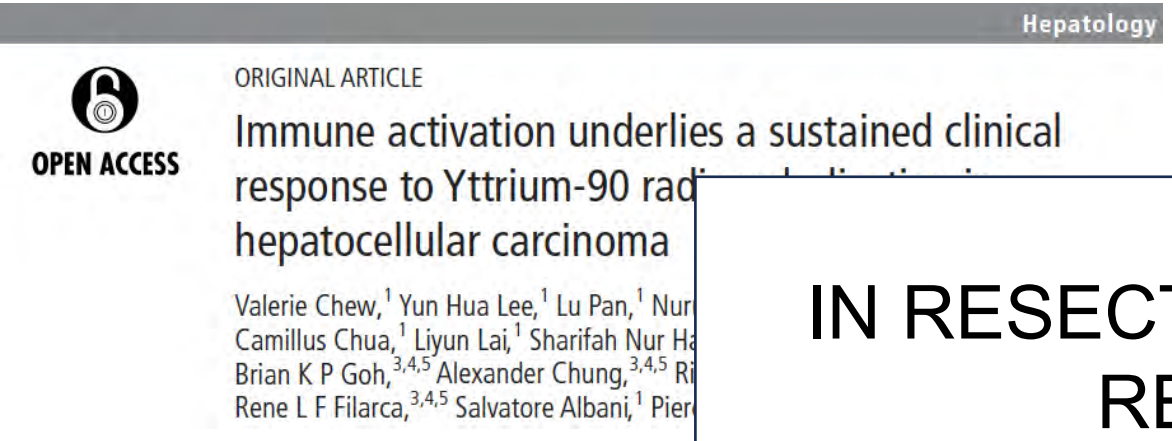
Zhu et al. Nature Medicine 2022



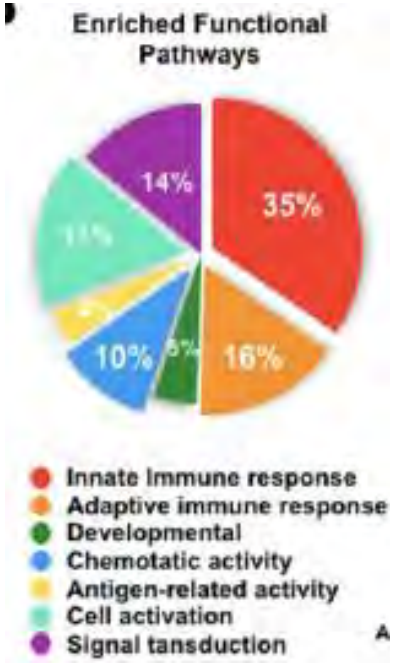
Xue et al. Nature 2022

Contemporary advances in characterizing baseline HCC TIME have been <u>agnostic to locoregional therapies</u>

Early Biological Evidence that Y-90 may Augment Anti-tumor Immune Response



IN RESECTED TUMORS THAT RESPONDED



Enrichment of **granzyme B + CD8+ T cells**, **innate** and **adaptive** immune responses

Y-90-RE induced **chemotaxis of CD8$^+$ T cells** to TME

Lower Foxp3$^+$CD152$^+$CD4$^+$ **T_{reg} cells**

Early Signal with Y-90

ARTICLE: LIVER

Immunotherapy and Transarterial Radioembolization Combination Treatment for Advanced Hepatocellular Carcinoma

Yeo, Yee Hui MD[1,2,*]; Liang, Jeff MD[1,*]; Lauzon, Marie MS[3]; Luu, Michael MPH[3]; Noureddin, Mazen MD[2]; Ayoub, Walid MD[2]; Kuo, Alexander MD[2]; Sankar, Kamya MD[4]; Gong, Jun MD[4]; Hendifar, Andrew MD[4]; Osipov, Arsen MD[4]; Friedman, Marc L MD[5]; Lipshutz, H Gabriel MD[5]; Steinberger, Jonathan MD[5]; Kosari, Kambiz MD[4,6,7]; Nissen, Nicholas MD[4,6,7]; Abou-Alfa, Ghassan K MD[8]; Singal, Amit G. MD[9,10]; Yang, Ju Dong MD[2,4,6,a]

Author Information

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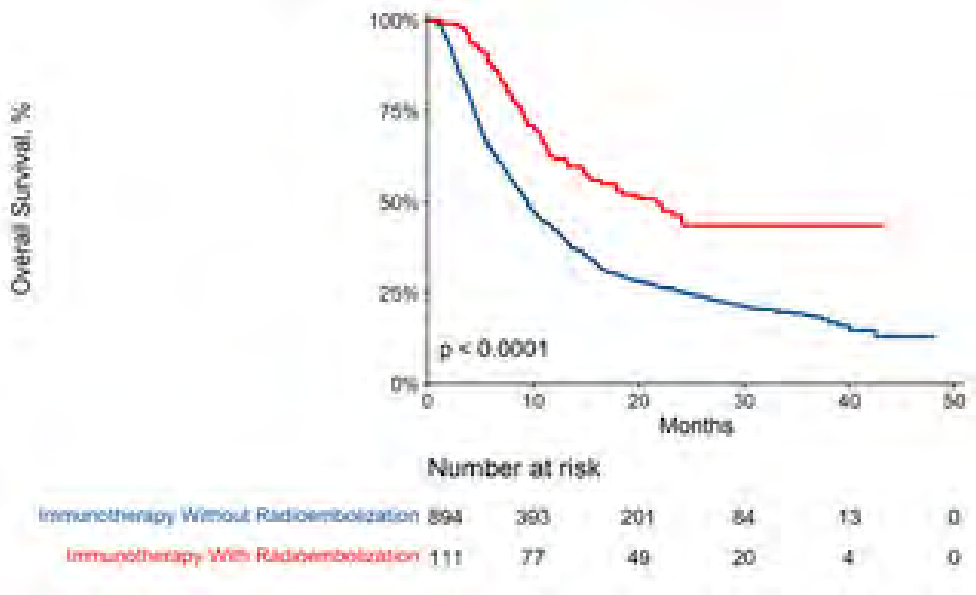
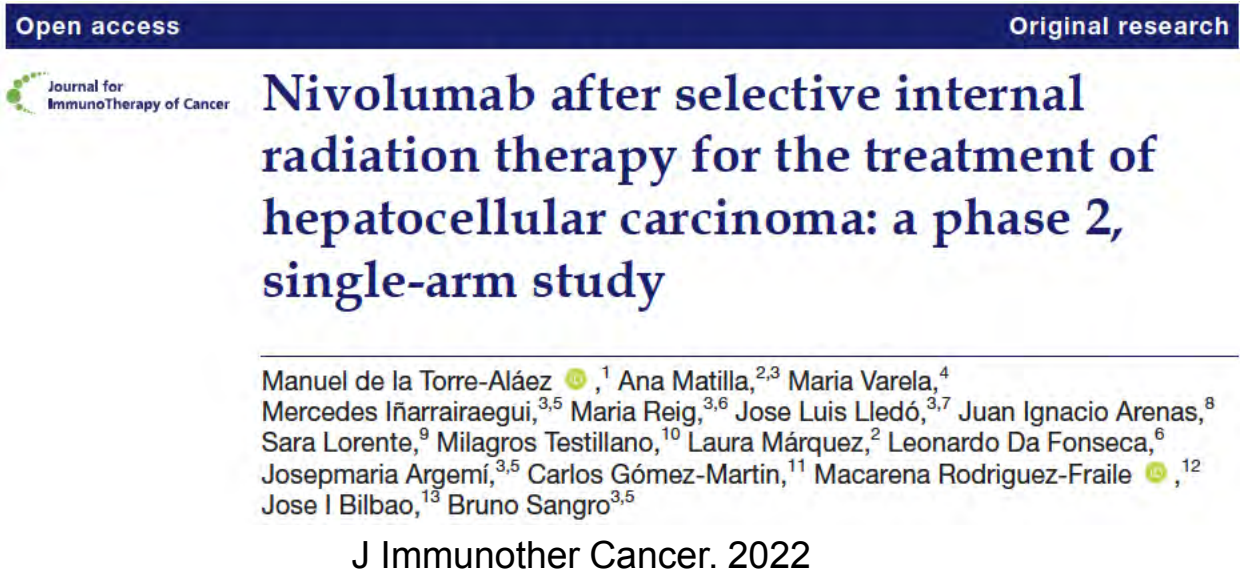


- National Cancer Database analysis 2017-2019
- TNM Stages 3 and 4 (BCLC B and C). IO vs combined Y-90/IO as first treatments
- Median OS higher in combined Y-90/IO group (19.8 vs 9.5 months)
- Multivariate analysis: combination Y-90/IO associated w/ reduced mortality (HR 0.50, 95%CI: 0.36-0.68, p<0.001

Early Prospective Readouts – Y-90 + ICI



Open access Original research

Journal for ImmunoTherapy of Cancer

Nivolumab after selective internal radiation therapy for the treatment of hepatocellular carcinoma: a phase 2, single-arm study

Manuel de la Torre-Aláez ,[1] Ana Matilla,[2,3] Maria Varela,[4] Mercedes Iñarrairaegui,[3,5] Maria Reig,[3,6] Jose Luis Lledó,[3,7] Juan Ignacio Arenas,[8] Sara Lorente,[9] Milagros Testillano,[10] Laura Márquez,[2] Leonardo Da Fonseca,[6] Josepmaria Argemí,[3,5] Carlos Gómez-Martin,[11] Macarena Rodriguez-Fraile ,[12] Jose I Bilbao,[13] Bruno Sangro[3,5]

J Immunother Cancer. 2022

- Prospective single arm, BCLC B/C (up to lobar PVT)
- Y-90 followed by Nivo 3 weeks later
- **Safety primary endpoint**

- Treatment related G3/4 AE's in 5/41 patients (12%)
- ORR 41.5%. 4 patients downstaged to hepatectomy
- Median TTP 8.8 mo, median OS 20.9 months

Early Prospective Readouts – Y-90 + ICI

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

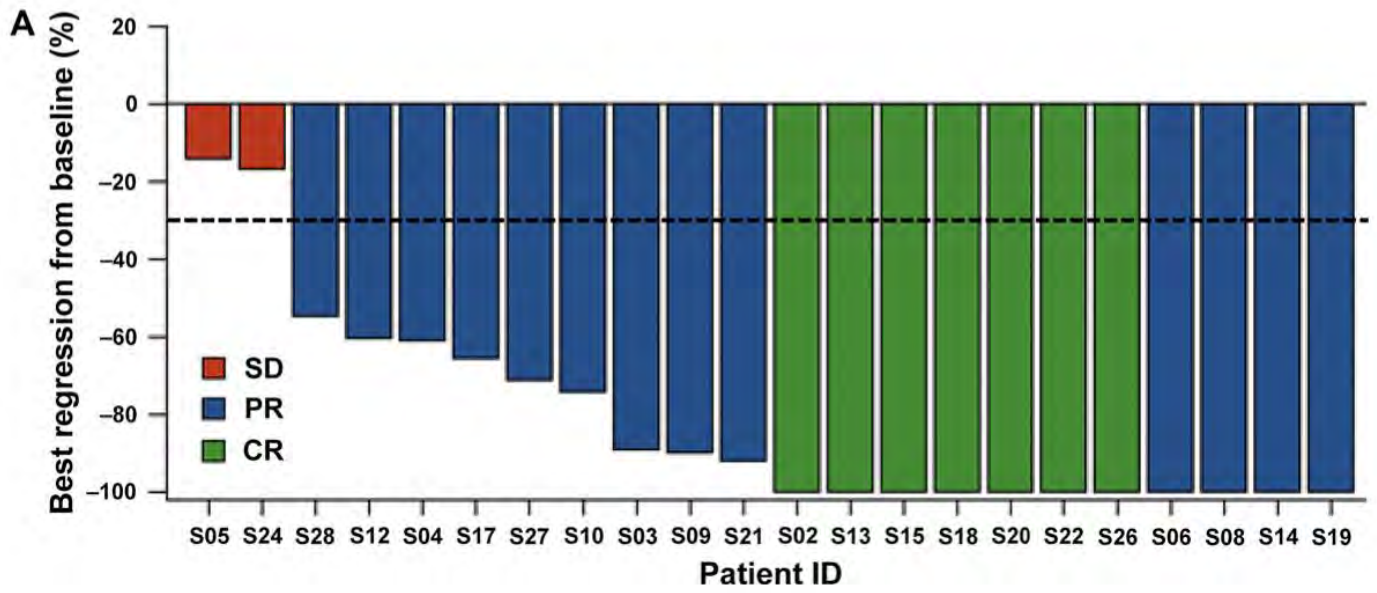
A Phase I/IIa Trial of Yttrium-90 Radioembolization in Combination with Durvalumab for Locally Advanced Unresectable Hepatocellular Carcinoma

Yun Bin Lee[1], Joon Yeul Nam[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Hyo-Cheol Kim[2], Jin Chul Paeng[3], Jung-Hwan Yoon[1], and Yoon Jun Kim[1]

Clin Cancer Res. 2023

- Phase I/2a, **safety and efficacy** of Y-90 combined with Durva in 24 locally advanced (BCLC B/C) HCC patients

- Median TTP 15.2 mo
- Median OS not reached
- 18 mo OS 58.3%
- 2 G3 AE's (fever, neutropenia)



Early Prospective Readouts – Y-90 + ICI

The Oncologist, 2024, **XX**, 1–14
https://doi.org/10.1093/oncolo/oyad331
Advance access publication 7 February 2024
Clinical Trial Results

OXFORD

A Pilot Study of Pembrolizumab in Combination With Y90 Radioembolization in Subjects With Poor Prognosis Hepatocellular Carcinoma

Shawn Yu[1,†], Menggang Yu[2,†], Barry Keane[1], David M. Mauro[1], Paul R. Helft[3], William P. Harris[4], Hanna K. Sanoff[1], Matthew S. Johnson[5], Bert O'Neil[6], Autumn Jackson McRee[7], Ashwin Somasundaram[*,‡,1]

- Prospective, multicenter trial evaluating safety and efficacy of Y-90 + Pembro in 29 patients w/ **poor prognosis** HCC (multifocal, diffuse, or macrovascular invasion HCC, BCLC B/C).
- ORR 30.8% (RECIST 1.1)
- Median PFS 9.95 mo
- Median OS 27.3 mo

Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial

*Andrew X Zhu, Richard S Finn, Julien Edeline, Stephane Cattan, Sadahisa Ogasawara, Daniel Palmer, Chris Verslype, Vittorina Zagonel, Laetitia Fartoux, Arndt Vogel, Debashis Sarker, Gontran Verset, Stephen L Chan, Jennifer Knox, Bruno Daniele, Andrea L Webber, Scot W Ebbinghaus, Junshui Ma, Abby B Siegel, Ann-Lii Cheng, Masatoshi Kudo, for the KEYNOTE-224 investigators**

Lancet Oncology 2018

- ORR 18%
- Median PFS 4.9 mo
- Median OS 12.9 mo

HEPATOBILIARY CANCER

LBA432

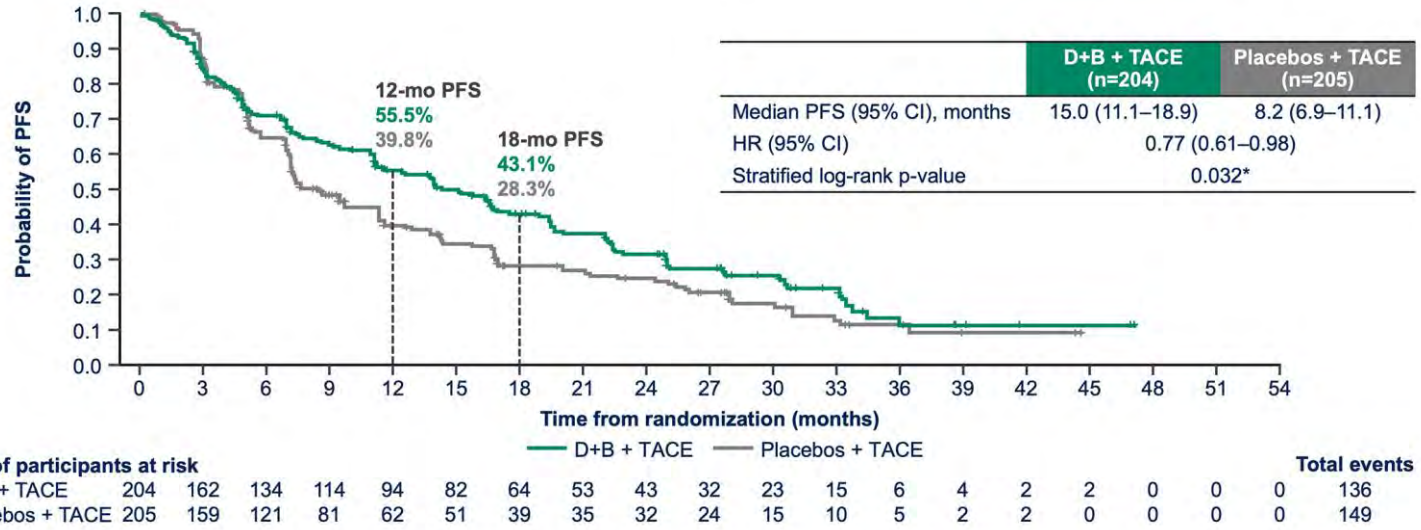
Oral Abstract Session

EMERALD-1: A phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization.

Riccardo Lencioni, Masatoshi Kudo, Joseph Erinjeri, Shukui Qin, Zhenggang Ren, Stephen Chan, Yasuaki Arai, Jeong Heo, Ahn Mai, Jose Escobar,

ASCO GI 2024

- Multicenter phase 3 RCT unresectable, TACE-eligible HCC
  - Majority intermediate stage, BCLC B (57.3%)
- TACE + Durva + Bev vs TACE + Durva vs TACE alone
- PFS primary endpoint



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

Met primary endpoint: significantly improved PFS in D+B+TACE vs TACE alone
Significantly longer TTP in D+B+TACE vs TACE alone
No new safety signals

As Adjuvant?

Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial

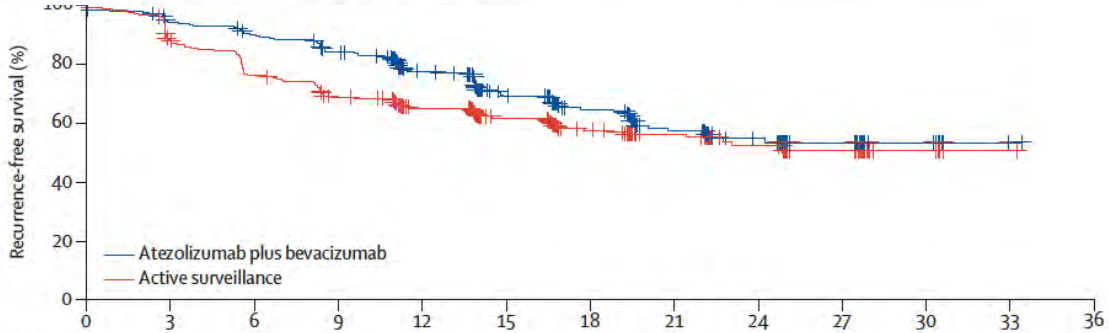
Shukui Qin, Minshan Chen*, Ann-Lii Cheng*, Ahmed O Kaseb*, Masatoshi Kudo*, Han Chu Lee*, Adam C Yopp*, Jian Zhou, Lu Wang, Xiaoyu Wen, Jeong Heo, Won Young Tak, Shinichiro Nakamura, Kazushi Numata, Thomas Uguen, David Hsiehchen, Edward Cha, Stephen P Hack, Qinshu Lian, Ning Ma, Jessica H Spahn, Yulei Wang, Chun Wu, Pierce K H Chow*, for the IMbrave050 investigators†*

Summary

Background

included overall survival (OS) and safety.

The primary endpoint of RFS was met at the first interim analysis in early 2023. As of a clinical cut-off date of 3 May 2024, updated analysis data shows that the RFS benefit seen at the first interim analysis is not sustained with longer follow-up. Of note, OS data remain immature and continue to not show a benefit. The overall safety profile remains consistent with the first interim analysis. The data from this analysis will be presented at an upcoming medical congress.



Number at risk (number censored)													
Atezolizumab plus bevacizumab	334 (0)	305 (10)	290 (12)	268 (15)	211 (53)	139 (105)	97 (139)	63 (164)	37 (188)	22 (202)	9 (215)	1 (223)	NE (NE)
Active surveillance	334 (0)	283 (12)	245 (12)	214 (20)	179 (44)	131 (84)	93 (114)	57 (148)	36 (166)	20 (181)	6 (195)	1 (200)	NE (NE)

Genentech
A Member of the Roche Group

IMPORTANT DRUG WARNING

August 2024

Subject:
Tecentriq (atezolizumab) in combination with Avastin (bevacizumab) is NOT approved as adjuvant therapy in patients with hepatocellular carcinoma at high risk of recurrence after surgical resection or ablation and should not be used in this setting

Dear Healthcare Provider:

The purpose of this letter is to inform you of important new information that impacts the benefit-risk of off-label use of Tecentriq and Avastin in hepatocellular carcinoma (HCC) patients in the adjuvant setting, following curative resection or ablation.

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HCP) is

- There is no impact on the approved indication of unresectable or metastatic HCC, where the combination of Tecentriq and Avastin remains a standard of care treatment option.

Background on the recent benefit-risk data

IMbrave050 is a Phase 3, multicenter, randomized, open-label study of Tecentriq + Avastin vs active surveillance as adjuvant therapy in patients with HCC at high risk of recurrence after surgical resection or ablation.

The primary endpoint was independent review facility (IRF)-assessed RFS[1]. Select secondary endpoints included overall survival (OS) and safety.

The primary endpoint of RFS was met at the first interim analysis in early 2023. As of a clinical cut-off date of 3 May 2024, updated analysis data shows that the RFS benefit seen at the first interim analysis is not sustained with longer follow-up. Of note, OS data remain immature and continue to not show a benefit. The overall safety profile remains consistent with the first interim analysis. The data from this analysis will be presented at an upcoming medical congress.

Based on this data, the benefit-risk profile does not support the use of Tecentriq plus Avastin as an adjuvant therapy for HCC.

Adding Liver Directed Therapy in Advanced Stage?

original reports

Lenvatinib Combined With Transarterial Chemoembolization as First-Line Treatment for Advanced Hepatocellular Carcinoma: A Phase III, Randomized Clinical Trial (LAUNCH)

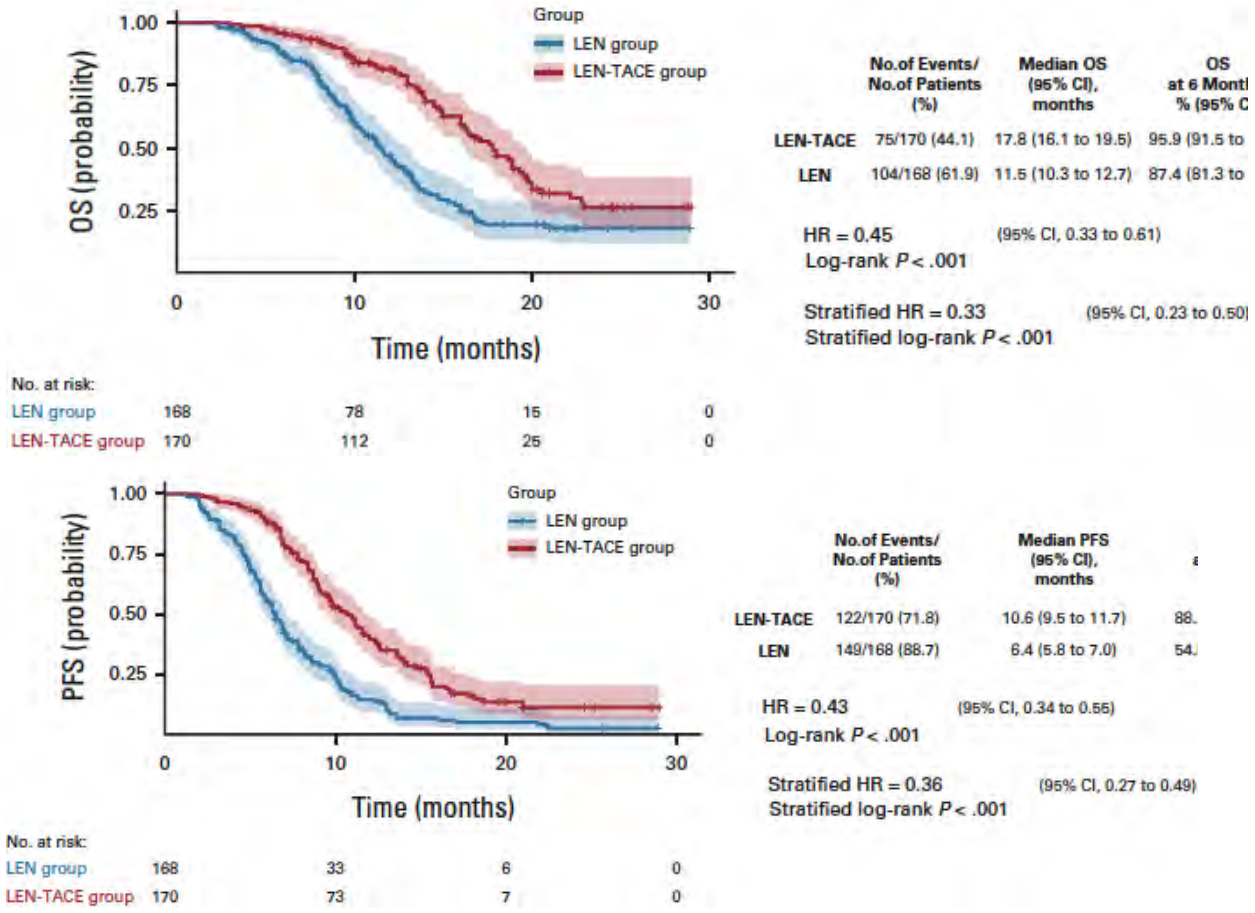
Zhenwei Peng, MD, PhD[1,2]; Wenzhe Fan, MD[3]; Bowen Zhu, MSc[3]; Guoying Wang, MD[4]; Junhui Sun, MD[5]; Chengjiang Xiao, MSc[6]; Fuxi Huang, MSc[7]; Rong Tang, MSc[8]; Yu Cheng, MSc[9]; Zhen Huang, MSc[10]; Yuchuang Liang, MSc[11]; Huishuang Fan, MSc[12]; Liangliang Qiao, MSc[13]; Fuliang Li, MSc[14]; Wenquan Zhuang, MD[15]; Baogang Peng, MD[16]; Jiping Wang, MD, PhD[17]; Jiaping Li, MD[3]; and Ming Kuang, MD, PhD[1,16]

JCO 2022

Locally advanced, phase 3 RCT:
Lenvatinib vs
Lenvatinib + TACE (on demand)

TABLE 1. Baseline Characteristics of Patients in the Two Groups

Characteristic	LEN-TACE Group (n = 170)	LEN Group (n = 168)
ALBI grade, No. (%)		
Grade 1	41 (24.10)	53 (31.50)
Grade 2	129 (75.90)	115 (68.50)
Intrahepatic tumors, No. (%)		
Single	30 (17.60)	38 (22.60)
Multiple	140 (82.40)	130 (77.40)
Main tumor size, cm, median (IQR)	8.4 (4.5-9.5)	7.4 (4.1-9.7)
< 5, No. (%)	47 (27.60)	58 (34.50)
≥ 5, No. (%)	123 (72.40)	110 (65.50)
Primary tumor, No. (%)		
Yes	157 (92.40)	142 (84.50)
No	13 (7.60)	26 (15.50)
Macroscopic portal vein invasion, No. (%)		
Yes	122 (71.80)	117 (69.60)
No	48 (28.20)	51 (30.40)
Extrahepatic spread, No. (%)		
Yes	94 (55.30)	95 (56.50)
No	76 (44.70)	73 (43.50)



Ongoing for HCC (not exhaustive)

EMERALD-Y90

ROWAN

NCT Number	Study Title	Interventions
NCT06040099	A US Study to Evaluate Transarterial Radioembolization (TARE) in Combination With Durvalumab and Bevacizumab Therapy in People With Unresectable Hepatocellular Carcinoma Amenable to TARE	DRUG: Durvalumab|DRUG: Bevacizumab|PROCEDURE: Transarterial Radioembolization (TARE)
NCT05992584	Lenvatinib, Sintilimab Plus SIRT for Unresectable HCC	DRUG: Lenvatinib, sintilimab plus SIRT
NCT05809869	Immunotherapy and Radioembolisation for Metastatic Hepatocellular Carcinoma	DRUG: Durvalumab|DRUG: Tremelimumab|RADIATION: Yttrium-90 radioembolisation
NCT05705791	Clinical Investigation Evaluating Safety and Efficacy of Selective Intra-arterial 166Holmium Radiation Therapy in Combination With Atezolizumab and Bevacizumab for Non Resectable Hepatocellular Carcinoma	DEVICE: QuiremSpheres
NCT05701488	SIRT With Tremelimumab and Durvalumab for Resectable HCC	DRUG: Durvalumab|DRUG: Tremelimumab|DEVICE: SIRT
NCT05620771	Therasphere¬Æ and Systemic Therapy for Patients With Hepatocellular Carcinoma That is High-risk	DRUG: Atezolizumab and Bevacizumab|DRUG: Y90 + TKI
NCT05377034	Multinational Phase II Trial to Compare Safety and Efficacy of SIRT (Y-90 Resin Microspheres) Followed by Atezolizumab Plus Bevacizumab, vs SIRT (SIRT-Y90) Followed by Placebo in Locally Advanced HCC Patients	COMBINATION_PRODUCT: SIRT-Y90 with Atezolizumab + Bevacizumab|COMBINATION_PRODUCT: SIRT-Y90 with Placebo (IV)
NCT05063565	TheraSphere With Durvalumab and Tremelimumab for HCC	DEVICE: TheraSphere Y-90 glass microsphere therapy|DRUG: Durvalumab (Imfinzi) immunotherapy|DRUG: Tremelimumab immunotherapy
NCT04541173	Study of Atezolizumab and Bevacizumab With Y-90 TARE in Patients With Unresectable Hepatocellular Carcinoma (HCC)	OTHER: Y-90 TARE|DRUG: Atezolizumab|DRUG: Bevacizumab
NCT04522544	Durvalumab and Tremelimumab in Combination With Either Y-90 SIRT or DEB-TACE for Intermediate Stage HCC	DRUG: Tremelimumab|DRUG: Durvalumab|PROCEDURE: Y-90 SIRT|PROCEDURE: DEB-TACE
NCT03033446	Study of Y90-Radioembolization With Nivolumab in Asians With Hepatocellular Carcinoma	RADIATION: Y-90 Radioembolization|DRUG: Nivolumab

ClinicalTrials.gov (accessed Feb 2024)

TABLE 2 Selected Phase 2/3 studies combining systemic therapy and liver-directed therapy for intermediate-stage (BCLC B) HCC

Systemic ICI therapy arms	Liver-directed therapy	Design	Sample size	Primary end points	NCT/Trial ID
Durvalumab + bevacizumab, durvalumab monotherapy, or placebo	TACE	3-arm RP3	600	PFS	NCT03778957 (EMERALD-1)
Nivolumab + Ipilimumab, nivolumab monotherapy, or placebo	TACE	3-arm RP3	765	TTP, OS	NCT04340193 (CheckMate-74W)
Nivolumab	TACE	2-arm RP2/3	522	OS, TTP	NCT04268888 (TACE-3)
Lenvatinib + pembrolizumab or placebo (PO + IV)	TACE	2-arm RP3	950	PFS, OS	NCT04246177 (LEAP-012)
Camrelizumab + rivoceranib	TACE	RP3	360	PFS	NCT05320692

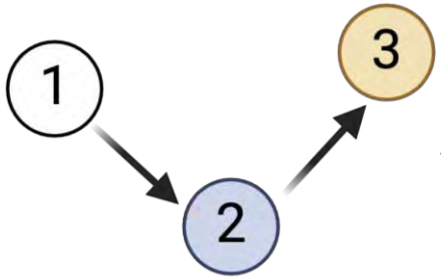
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ICI, immune checkpoint inhibitors; OS, overall survival; PFS, progression free survival; TACE, trans-arterial chemo-embolization; TTP, time to tumor progression.

Mehta Hepatology 2024

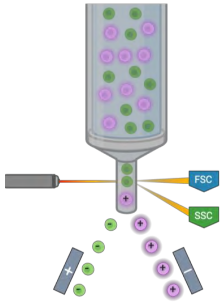
Key unanswered questions. Field in its **Infancy**.

Patient Selection

Timing

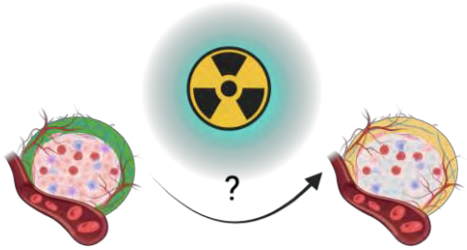


Sequencing

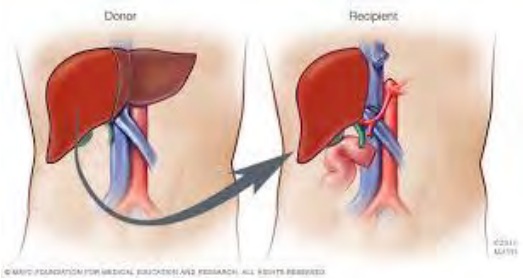


Feasible Biomarkers

Dose



How does each HCC TIME adapt/respond to various locoregional therapies and dosing heterogeneities/profiles?



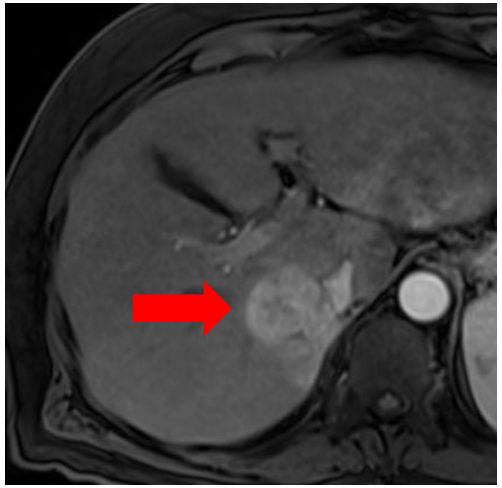
Peri-transplant setting

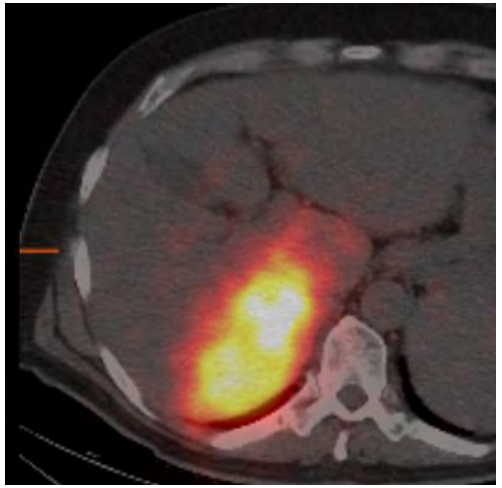
Patient Selection: Which Early and Intermediate Stage (BCLC A, B) HCC's Would Most Benefit from ICI + Locoregional?

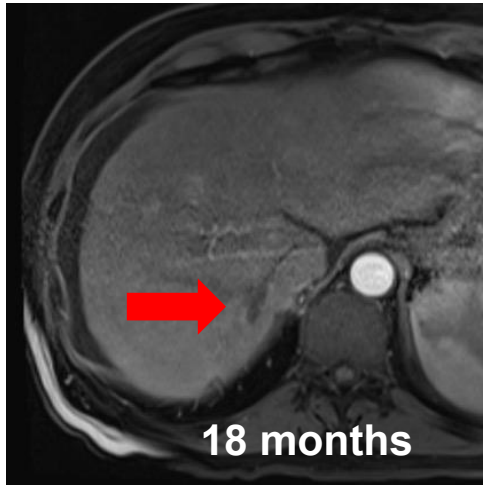
- Outside of Advanced stage (BCLC C), combination strategies with ICI still done **empirically**
  - Limitations in peri-transplant setting
  - Not all Early and Intermediate stage patients will benefit from combination therapy (plus new AE profile)
  - Many have long-durable responses to ablative therapies **alone**

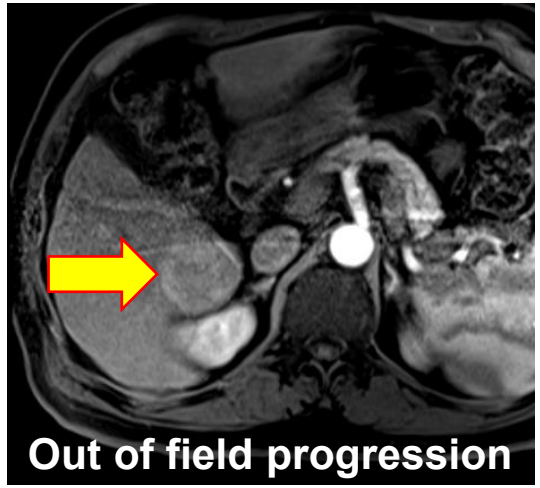
Conversely, who are late Advanced stage (EHS, Vp4) patients who would benefit from locoregional as adjuvant?

Immunotherapy (ICI) can make Locoregional Therapy look better and **vice versa**









ICI as Adjuvant?

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

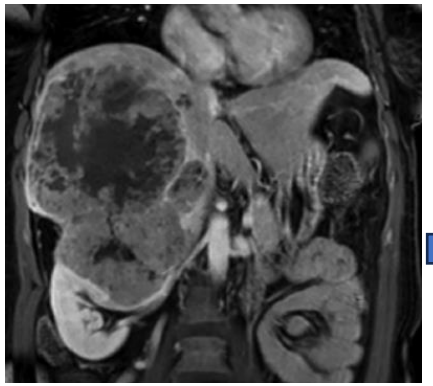
RCR RADIOLOGY CASE REPORTS

ELSEVIER

Case Report

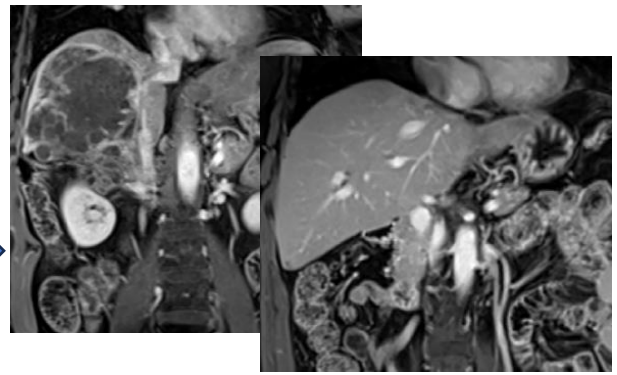
Ipilimumab and nivolumab plus radioembolization as salvage therapy for atezolizumab and bevacizumab refractory hepatocellular carcinoma resulting in complete pathologic response ☆

Claudia R. Silver, BS[a], Cynthia De la Garza-Ramos, MD[b,], John A. Stauffer, MD[c], Umair Majeed, MBBS, MD[d], Jianfeng Wang, MD[e], Beau B. Toskich, MD[b]*



Extrahepatic and IVC invasion, ***progressed on Atezo/bev***

Y-90 plus Ipi + Nivo



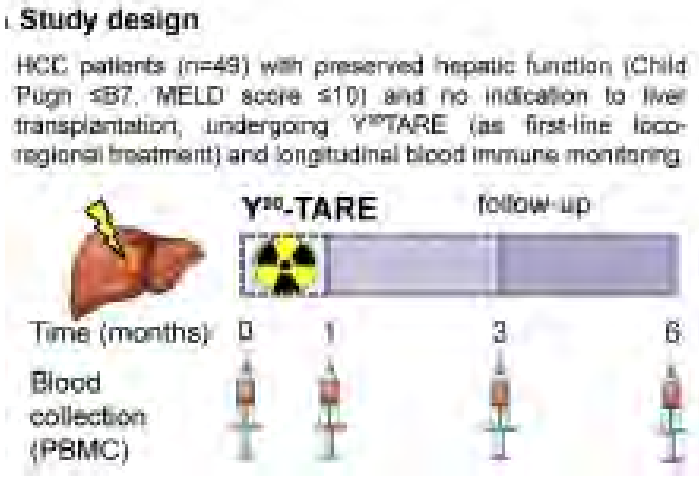
Hepatectomy with ***complete path response***

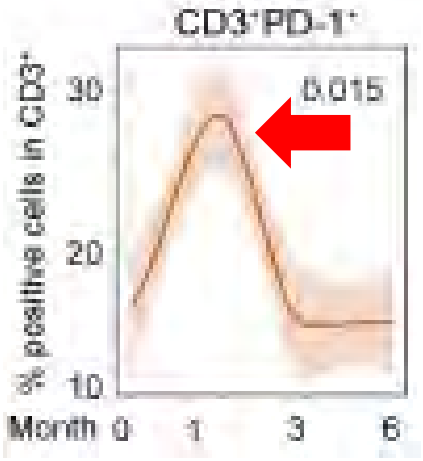
Y90 as Adjuvant?

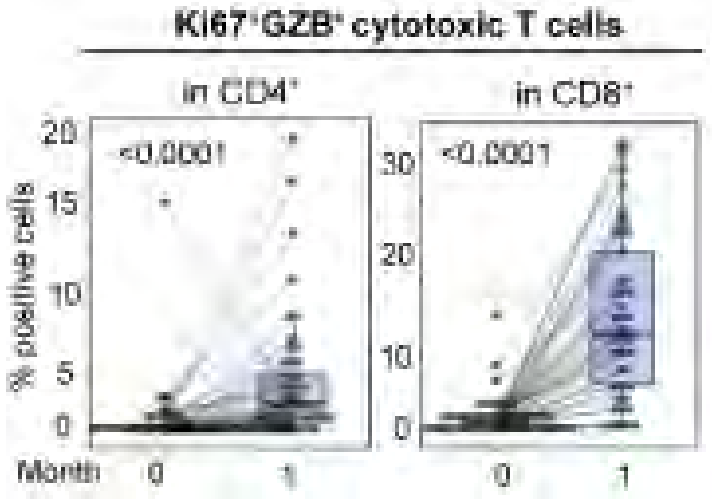
Timing: ICI within 1 month?

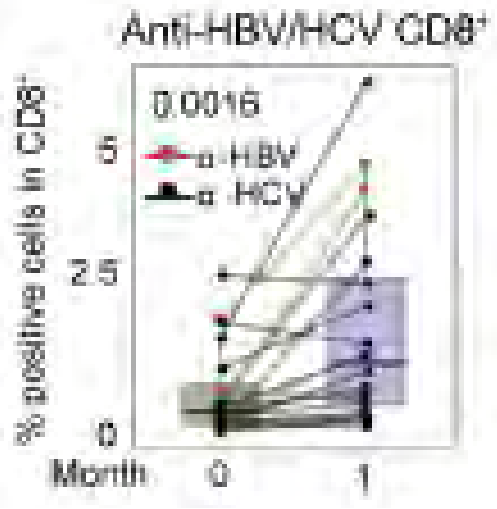
Y^{90}-radioembolisation in hepatocellular carcinoma induces immune responses calling for early treatment with multiple checkpoint blockers

Rivoltini et al Gut 2022









Actual Synergy is **Elusive**. Seeking Safe Additivity More Realistic

nature cancer

Analysis

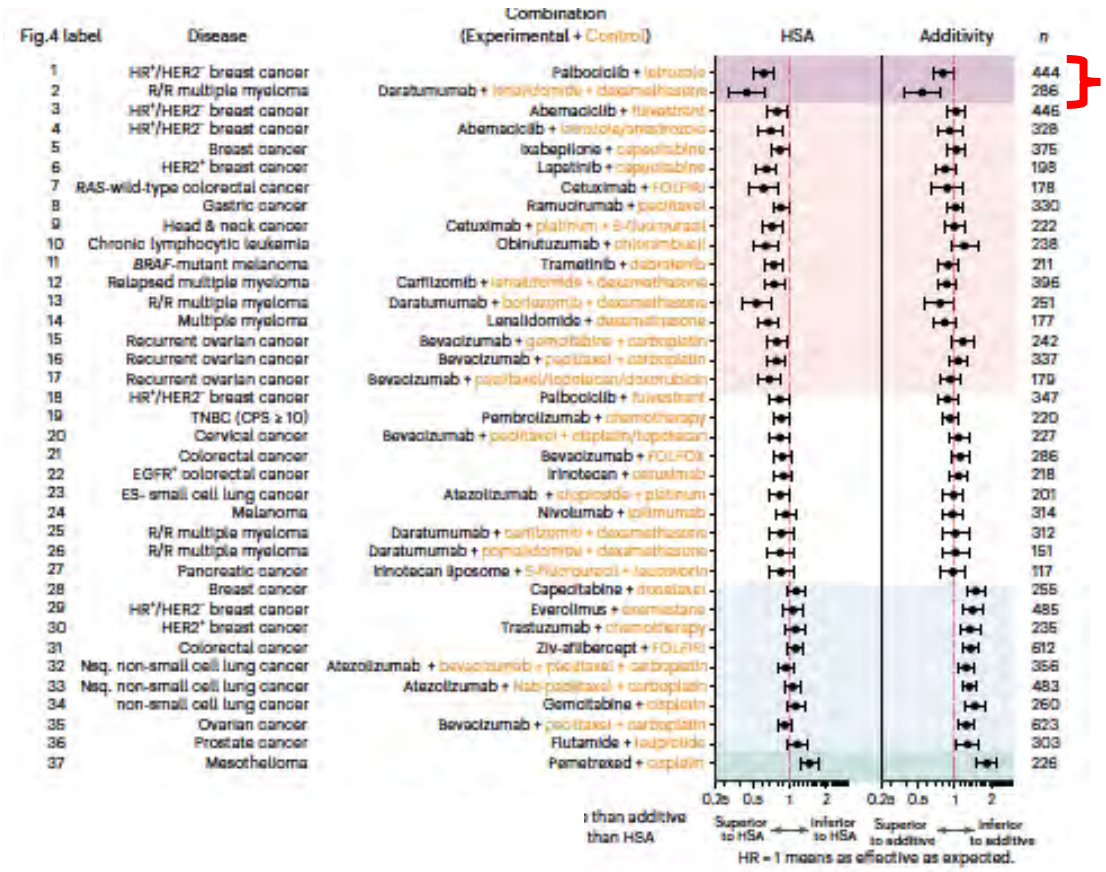
https://doi.org/10.1038/s43018-023-00667-z

Additivity predicts the efficacy of most approved combination therapies for advanced cancer

Received: 12 April 2023

Accepted: 11 October 2023

Haeun Hwangbo[1,2], Sarah C. Patterson[1], Andy Dai[3], Deborah Plana[4] & Adam C. Palmer[1]



Only 2 trials w/ potential "synergy"

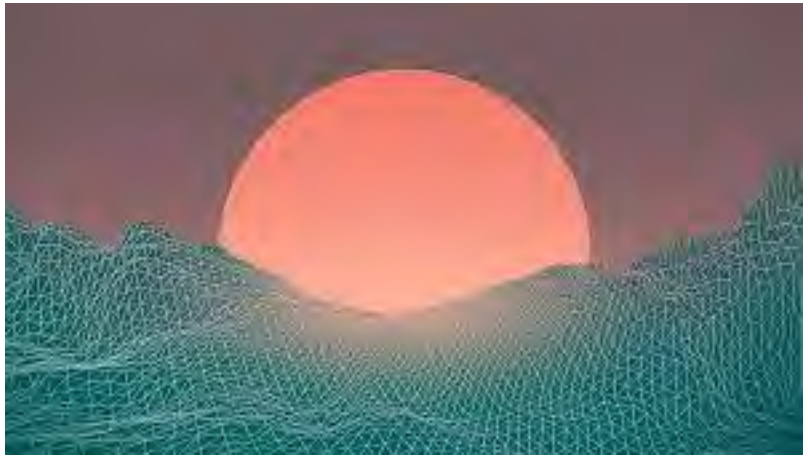
2 + 2 = 3-4 more likely than 2 + 2 = 5

Don't want 2 + 2 < 2

"Synergy is neither a necessa ffective drug combinations."

is the JUICE worth the SQUEEZE?

What about in the Peri-Transplant Setting?



Still many unknowns

UNOS – receipt of ICI should not exclude patients from undergoing transplant, but consider ~ 12 week washout period

Opportunities to extend curative outcomes to those with residual viable disease or not downstaged by LRT alone

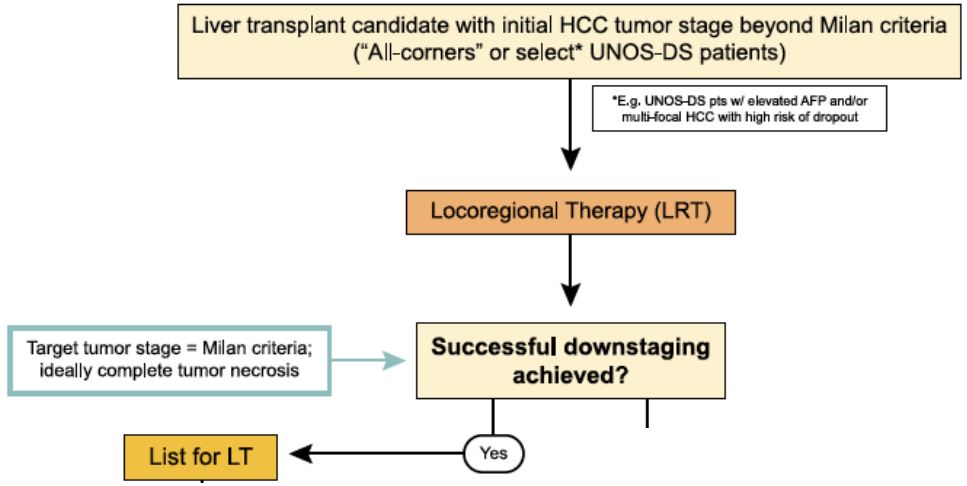
What about in the Peri-Transplant Setting?

REVIEW

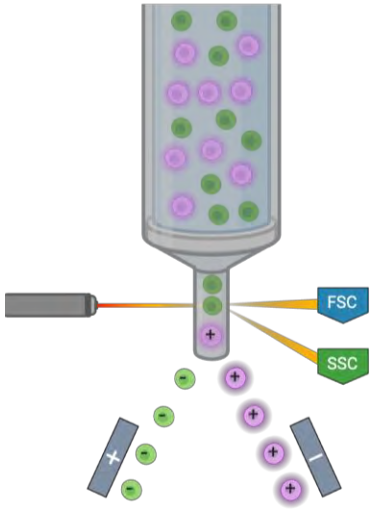
Refining the approach to down-staging transplantation: Patient selection, loco and systemic therapies

Neil Mehta[1] | R. Katie Kelley[2] | Francis Y. Yao[1,3]

Mehta Hepatology 2024



Feasible Biomarkers



We need ***better biomarkers*** to select patients
- HCC is ***diverse***
- Currently mostly based on disease “tempo”

Development of noninvasive imaging and liquid biopsy (ctDNA, extracellular vessicles, etc…) biomarkers will require **primary tissue sampling**
- Limited with current diagnostic approach. We don’t usually have tissue on these patients.

Conclusions

- HCC treatment paradigm is increasingly ***complex***
- Getting patients to ***curative*** outcomes should be our north star
- Advancements in **both** locoregional (Y-90 personalized dosimetry, ablation modalities, etc…) and systemic therapies are tipping more BCLC B and C stage patients towards ***durable and curative*** outcomes
- Critical need to better understand **biology trajectory** at earlier stages to better inform combination approaches
- With rationale combination approaches that minimize toxicity, can push envelope even further to cure the previously uncurable

Thank you