2024 16 PARIS HEPATOLOGY CONFERENCE

Hybrid PHC 2024
Institut Pasteur - Paris
18 - 19 March

HCC session 2: Management

Interventional Radiology

Prof. Laura Crocetti, MD, PhD, EBIR
Division of Interventional Radiology

IASIOS ACCREDITED CENTRE
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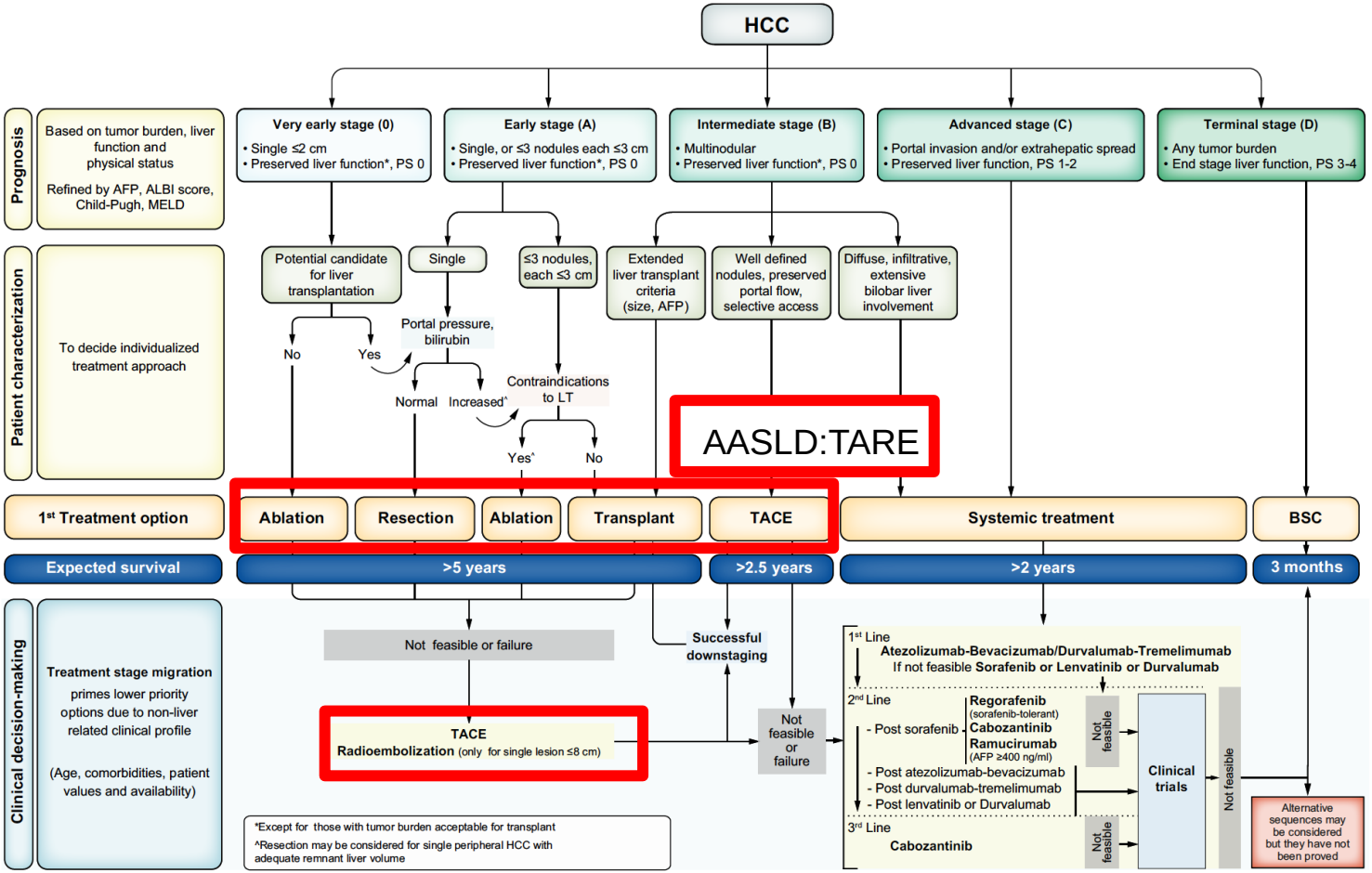
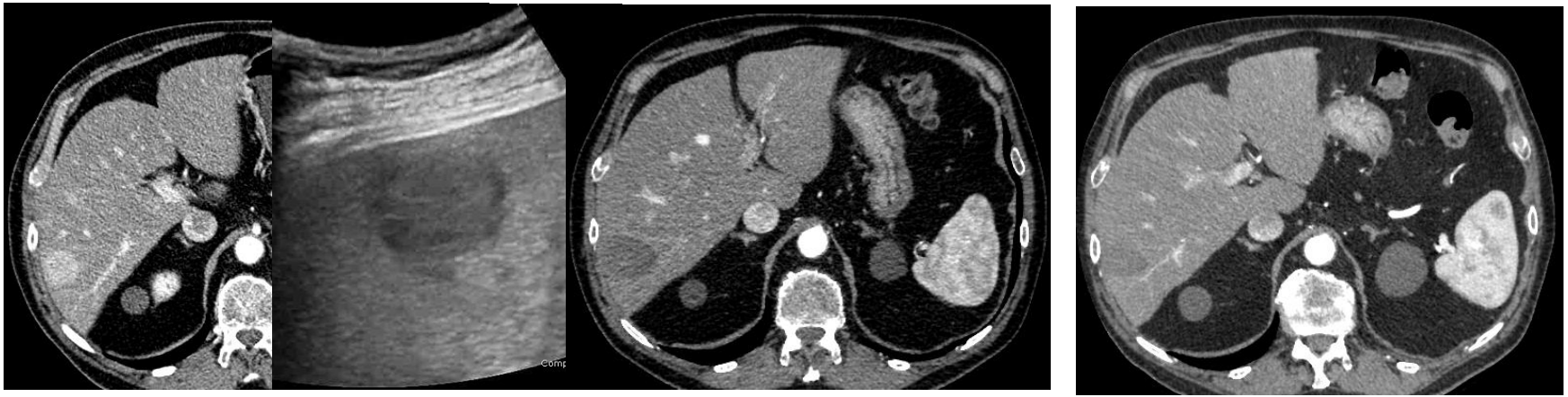


Journal of Hepatology DOI: (10.1016/j.jhep.2021.11.018)

♂, 83 years, HCV related cirrhosis

Pre-treatment **1 month** **3 years**



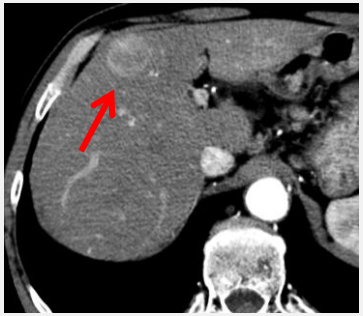
MW thermal ablation: single insertion of 14G probe with HS Amica™
Ablation time: 6 minutes
Power: 50W

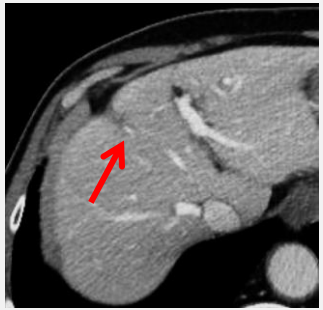
Recurrence of curative treatment of very early/early stage HCC

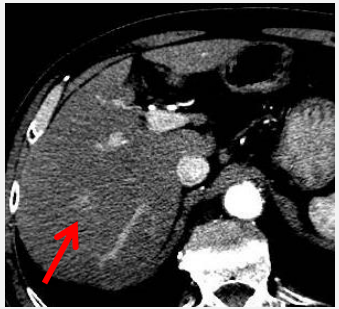
De-novo tumours

Intrahepatic metastases

Up to **80%** of people with eHCC experience disease recurrence **within 5 years** of receiving surgery or ablation with curative intent[1,2]







There are no approved adjuvant therapies for eHCC to address this high recurrence risk and improve long-term outcomes in the curative-intent setting

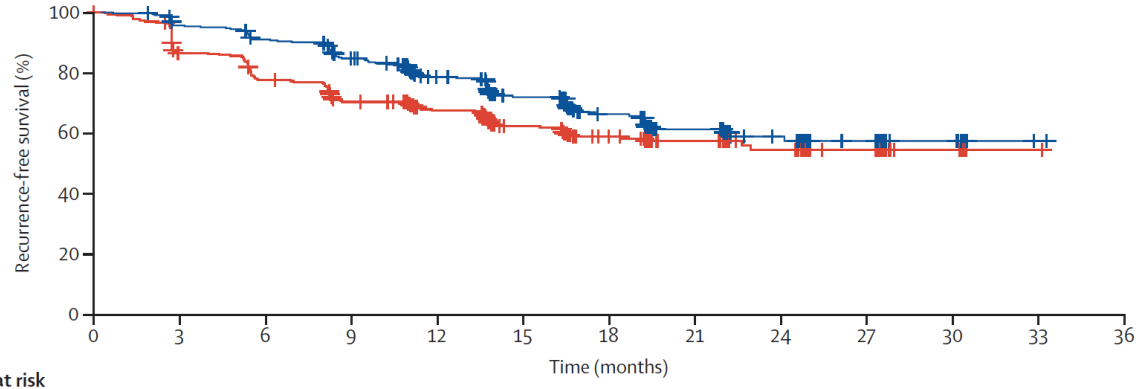
1. Shah SA, et al. Surgery 2007;141:330–339. 2. Hasegawa K, et al. J Hepatol 2013;58:724–729.

IMbrave050: adjuvant immunotherapy + VEGF inhibitor following resection or ablation

Pts at high risk of recurrence after surgery or ablation

Resection: 88% in treatment arm, 87% in active surveillance arm

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)	
Patients with events, n (%)	103 (31%)	128 (38%)	
Median RFS, months (95% CI)	NE (24·2–NE)	NE (22·7–NE)	
12-month INV-RFS event-free rate, % (95% CI)	79% (74–83)	68% (62–73)	
Stratified hazard ratio (95% CI)			0·70 (0·54–0·91)
p value (log rank)			0·007

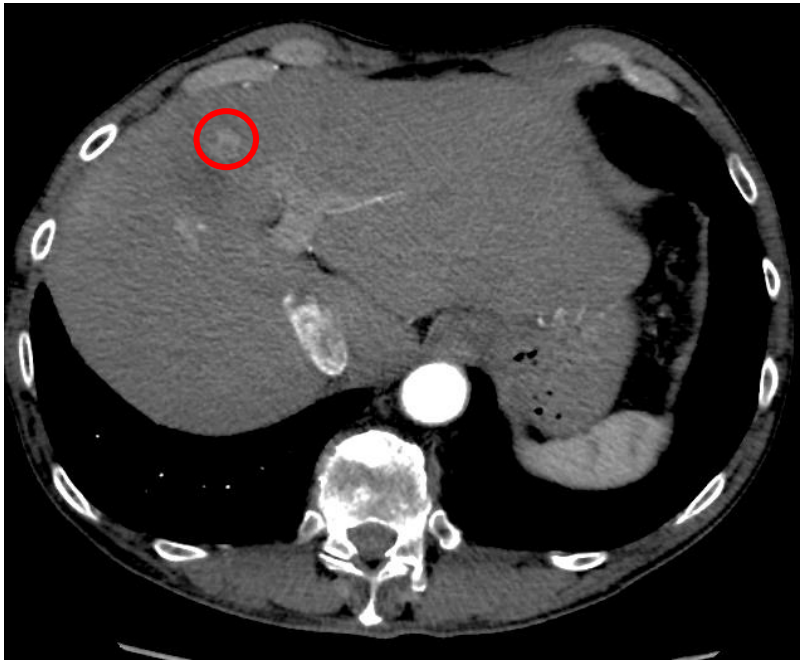


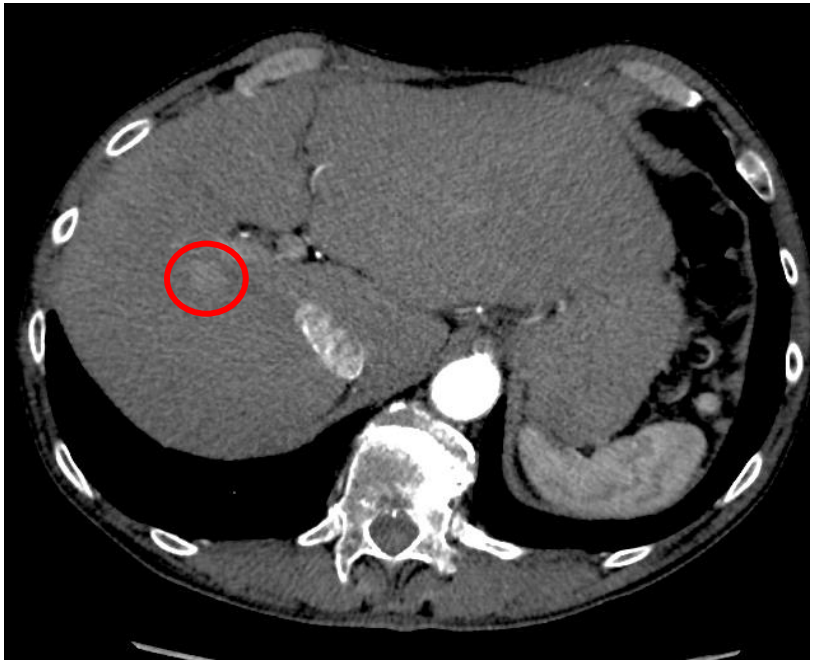
Number at risk (number censored)													
Atezolizumab plus bevacizumab	334 (0)	309 (11)	292 (13)	268 (17)	210 (57)	147 (104)	101 (140)	68 (166)	40 (192)	23 (208)	9 (222)	1 (230)	NE (NE)
Active surveillance	334 (0)	282 (9)	249 (12)	221 (17)	187 (43)	133 (84)	94 (116)	58 (150)	36 (170)	20 (186)	6 (200)	1 (205)	NE (NE)

Qin S et al. Lancet 2023; 402: 1835–47

Recurrence after ablation

3-year post MW ablation follow-up CT



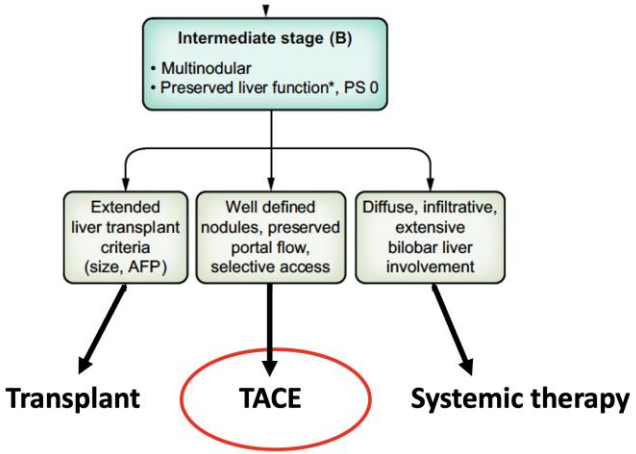


Local recurrence **+** **Distant recurrence**

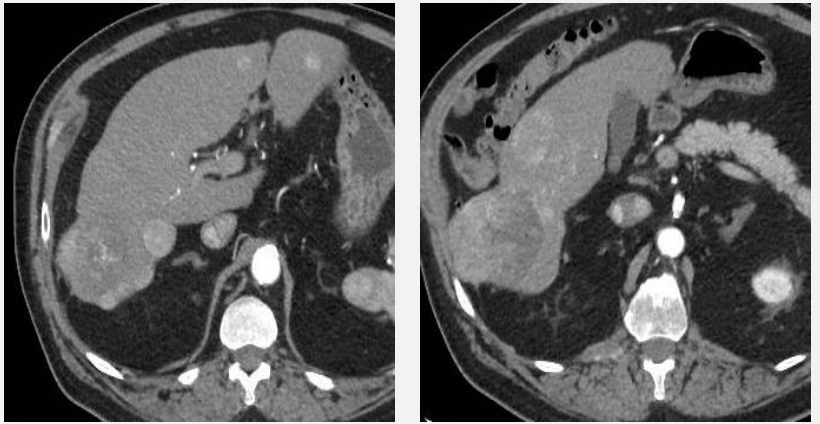
Ongoing trials in adjuvant setting after curative therapy

NCT number	Study phase	Investigational arm(s)	Curative therapy given	Patient enrolment, N	Status	Primary endpoint(s)
IMbrave050 NCT04102098	**3**	• Arm A: atezolizumab + bevacizumab • Arm B: active surveillance	Resection or ablation	668 (actual)	Active, not recruiting	• RFS (IRF)
EMERALD-2 NCT03847428	**3**	• Arm A: durvalumab + bevacizumab • Arm B: durvalumab + bevacizumab placebo • Arm C: durvalumab placebo + bevacizumab placebo	Resection or ablation	908 (actual)	Active, not recruiting	• RFS for Arm A vs Arm C
CheckMate 9DX NCT03383458	**3**	• Nivolumab • Placebo	Resection or ablation	545 (actual)	Active, not recruiting	• RFS
NCT04639180	**3**	• Camrelizumab + rivoceranib (apatinib) • Active surveillance	Resection or ablation	687 (actual)	Active, not recruiting	• RFS (BICR)
PREVENT-2 NCT05910970	**3**	• Tislelizumab + lenvatinib • Tislelizumab	Resection or ablation	200 (estimated)	Not yet recruiting	• RFS
KEYNOTE-937 NCT03867084	**3**	• Pembrolizumab • Placebo	Resection or ablation	950 (estimated)	Active, not recruiting	• RFS (BICR*) • OS
NCT02725996	**2**	• Curative therapy + NK cells • Curative therapy	Resection or ablation	140 (estimated)	Unknown	• RFS • OS
NCT05367687	**2**	• Camrelizumab + rivoceranib (apatinib) • Camrelizumab	Resection or ablation	251 (actual)	Active, not recruiting	• RFS (investigator)

Is TACE a treatment option for all intermediate-stage HCC patients?

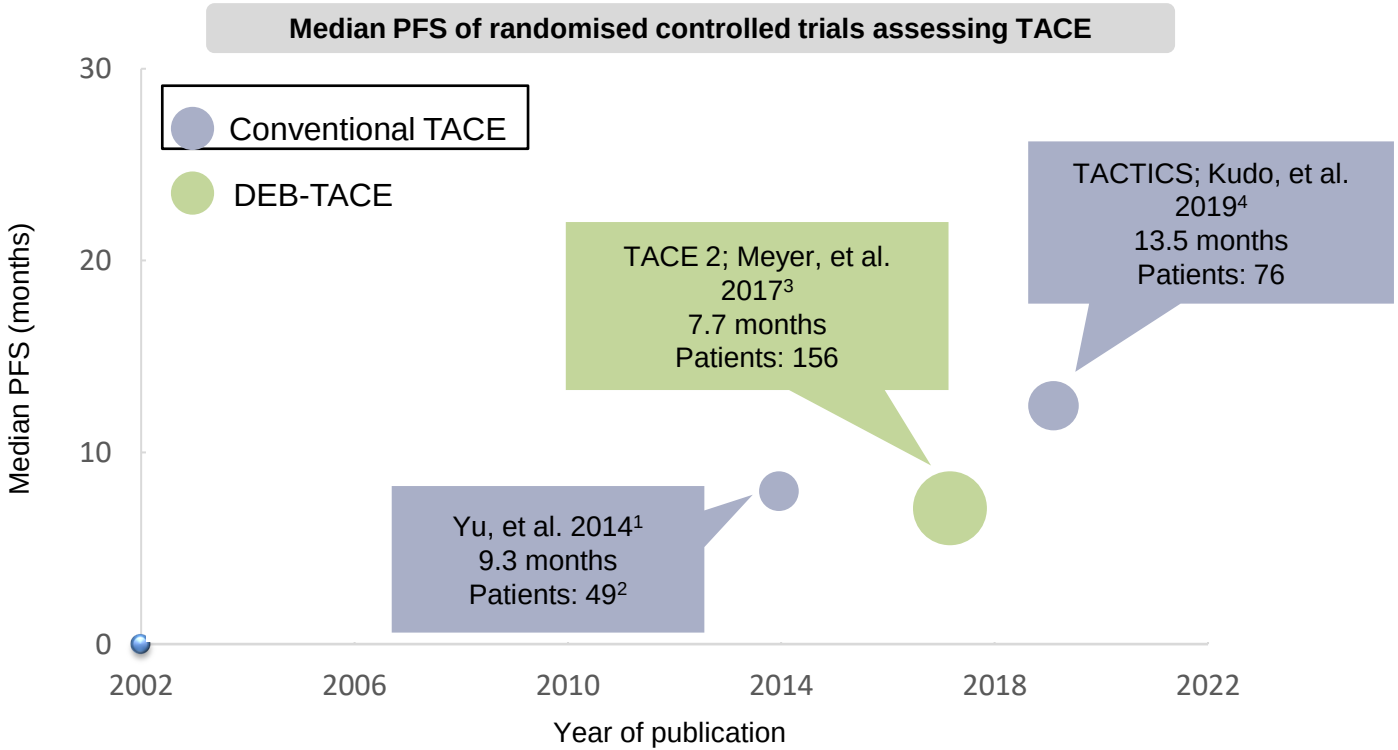


Journal of Hepatology DOI: (10.1016/j.jhep.2021.11.018)



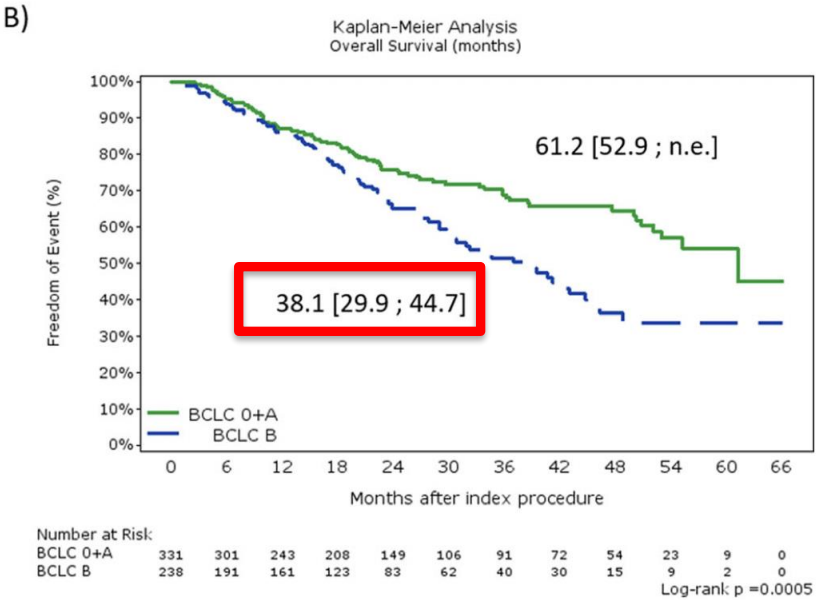
- Only selected patients with intermediate disease are optimal candidates for TACE
- Efficacy of TACE is affected by tumour burden
- Repeat cycles of TACE can compromise liver function

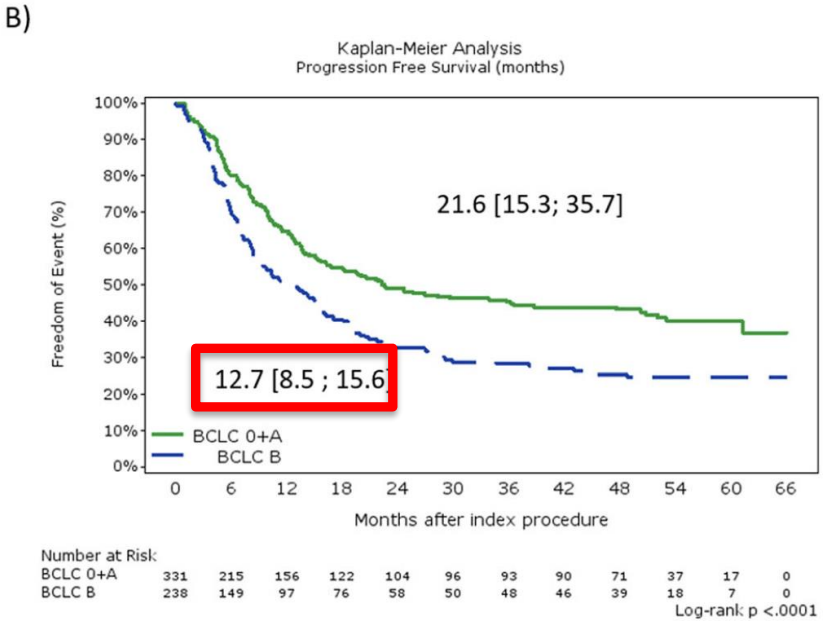
Progression free survival (PFS) after TACE



1. Yu SCH, et al. *Radiology* 2014;270:607–620. 2. Llovet JM, et al. *Nat Rev Gastroenterol Hepatol*. 2021:293-313. 3. Meyer T, et al. *Lancet Gastroenterol Hepatol* 2017;2:5657–575. 4. Kudo M, et al. *Gut* 2020;69:1492–1501.

Overall survival (OS) and progression free survival (PFS) after TACE





Stage B: 238 patients, mean number of tumors 1.4 ± 1.6, sum of tumor diameters 69.9± 36.5 mm

Veloso Gomes F, et al. CVIR 2023;46:436-446

TACE + Immune checkpoint inhibitors (ICI): Early phase studies

The open-label, single-arm, Phase 2 IMMUTACE study investigated the safety and efficacy of TACE + nivolumab in HCC amenable to embolisation[1]

Summary of clinical outcomes (median follow-up of 20 months)[1]

	TACE + nivolumab N=49
ORR (95% CI), %	71.4 (56.8–83.4)
Median (95% CI) PFS, months	7.2 (5.3–11.2)
Median (95% CI) time to failure of strategy, months	11.2 (7.2–13.5)
Median (95% CI) time to subsequent systemic therapy, months	24.9 (12.2–NE)
Median (95% CI) OS, months	**28.3 (20.0–NE)**

A pilot study evaluated the combination of tremelimumab + TACE, RFA or chemoablation in patients with advanced HCC[2]

Summary of efficacy with tremelimumab + TACE

	Tremelimumab + TACE N=11
6-month PFS (95% CI), %	63.6 (29.7–84.5)
12-month PFS (95% CI), %	29.1 (5.4–59.3)
Median (95% CI) OS, months	**13.6 (7.5–NE)**
12-month OS (95% CI), %	80.8 (42.4–94.9)

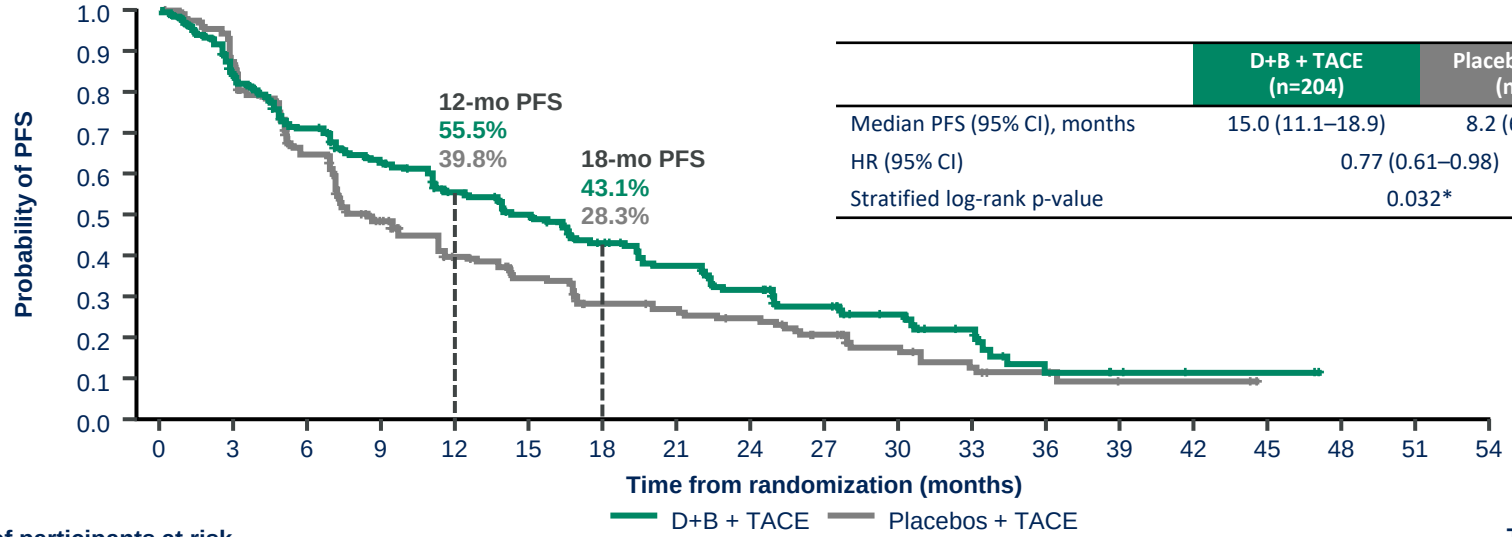
Early-phase studies suggest TACE + ICI may be efficacious in advanced / unresectable HCC and HCC amenable to embolisation

1. Saborowski A, et al. Presented at: ASCO; 3–7 June 2022; Chicago, IL, USA. Abs 4116. 2.Duffy AG, et al. *J Hepatol* 2017;66:545–551.

TACE/TAE + ICI: Ongoing trials

	Phase	Investigational arm(s)	Control arm	Patient enrollment (N)	Primary endpoint(s)
EMERALD-1 NCT03778957	**3**	Arm A: TACE + durvalumab Arm B: TACE + durvalumab + bevacizumab	TACE + placebo (Arm C)	724 (actual)	PFS (Arm B vs Arm C; BICR)
EMERALD-3 NCT05301842	**3**	Arm A: TACE + STRIDE + lenvatinib Arm B: TACE + STRIDE	TACE (Arm C)	725 (estimated)	PFS (Arm A vs Arm C; RECIST 1.1 by BICR)
LEAP-012 NCT04246177	**3**	TACE + pembrolizumab + lenvatinib	TACE + placebo	450 (estimated)	PFS (RECIST 1.1 by BICR) OS
TACE-3 NCT04268888	**2 / 3**	TACE / TAE + nivolumab	TACE / TAE	522 (estimated)	OS (Phase 3) TTTP (Phase 2)
TALENTACE NCT04712643	**3**	TACE + atezolizumab + bevacizumab	TACE	342 (actual)	TACE PFS (investigator assessed) OS
DEMAND NCT04224636	2	Up-front atezolizumab + bevacizumab, then TACE	atezolizumab + bevacizumab + TACE (combined)	106 (estimated)	24-months survival rate

EMERALD-1: PFS with durvalumab + bevacizumab + TACE versus placebo + TACE

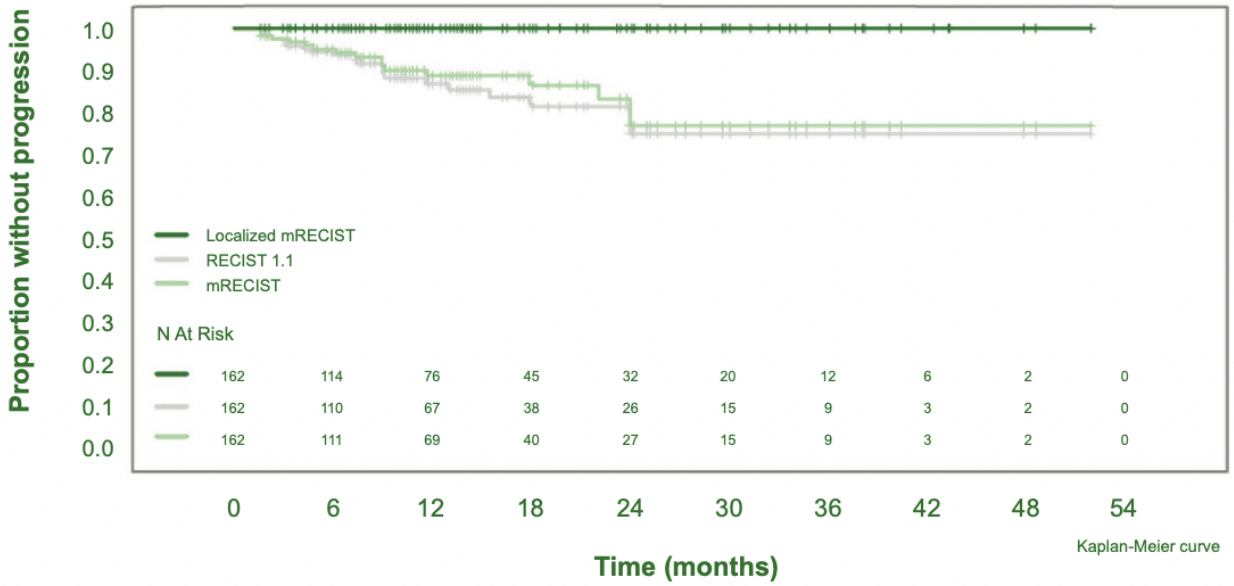


	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

No. of participants at risk																				Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

Lencioni R, et al. Presented at: ASCO GI; 18-20 January 2024; San Francisco, CA, USA. Abs LBA432.

TARE for solitary HCC: the LEGACY study



- Retrospective, multicenter, **162** pts
- Solitary HCC **< 8 cm** (median 2.7 cm)

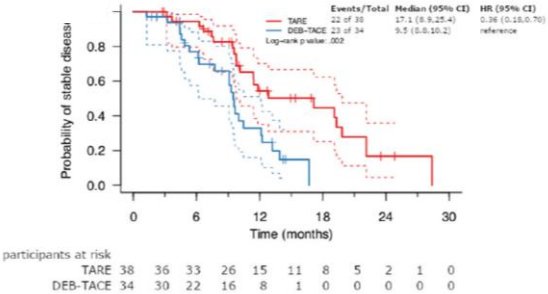
- Best ORR **88.3%**
- Median DoR for confirmed response 11.8 months
- Three-year overall survival was **86.6%**

Salem R, et al. Hepatology 2021;74(5):2342-2352.

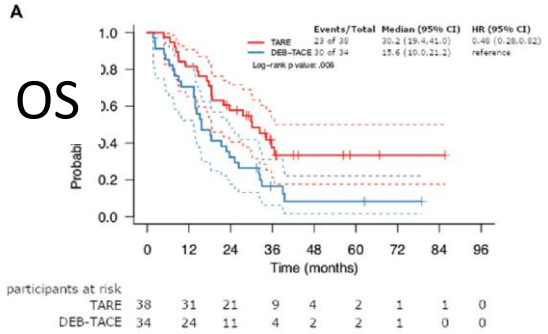
Phase II RCT comparing TACE and TARE: TRACE study

	TARE	TACE	HR	P
TTP (months)	17.1	9.5	0.36 (0.18, 0.70)	0.002
ORR treated liver (%)	94	100		
ORR liver (%)	88	87		
n. transplanted	10	4		
PFS (months)	11.8	9.1	0.40 (0.24, 0.67)	<0.001
OS (months)	30.2	15.6	0.48 (0.28, 0.82)	0.006
OS censored for LTx (months)	27.6	15.6	0.49 (0.28, 0.87)	0.01

PFS



OS



Dhondt E, et al. *Radiology* 2022;303:699–710.

The immunological impact of Y90 TARE

Design

Time-of-flight mass cytometry and next generation sequencing were used to examine the immune landscapes of TILs, tumour tissues and PBMCs at various interval points prior to and following Y90-RE

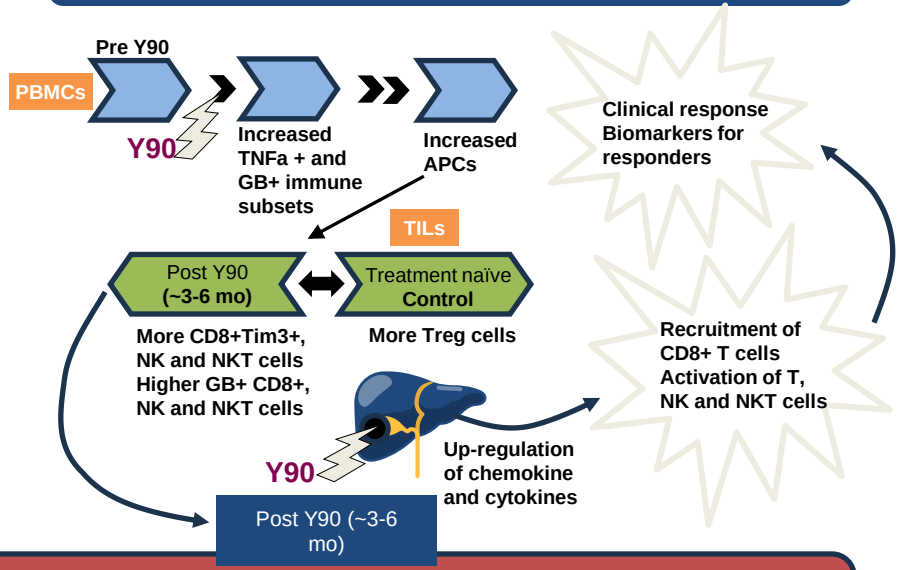
Results

Local and systemic immune activation that corresponded to the sustained response to Y90-RE was identified

Conclusions

Potential biomarkers associated with a positive clinical response were identified and a prediction model was built to identify sustained responders prior to treatment

Model showing a series of immune responses induced by Y90-RE in TILs and PBMCs



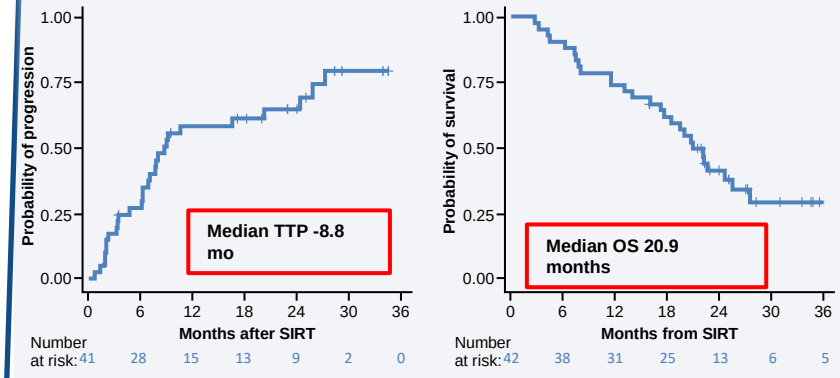
Deep immunophenotyping and transcriptomic analysis showed significant immune activation locally both within the tumour microenvironment and in the peripheral blood of patients with HCC, who exhibited a sustained response to Y90-RE

Chew V, et al. Gut 2019;68:335–346.

TARE + immune checkpoint inhibitors (ICI): Early phase studies

NASIR-HCC, a phase 2, single-arm study investigated the safety and efficacy of nivolumab + for the treatment of patients with HCC that are candidates for LRTs[1]

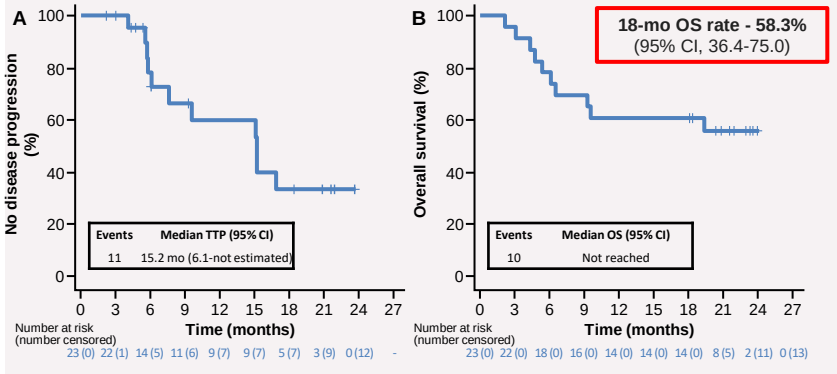
KM plots of TTP per investigator assessment and OS



AEs and SAEs grade 3–4 were observed in 19% and 26% of patients, respectively

A phase 2 /3a pilot trial investigated the efficacy and safety of Y-90 RE + durvalumab for locally advanced uHCC[2]

KM estimates of median TTP and OS



While up to 50% of patients experienced any-grade TRAEs during the study, **0%** developed any TRSAEs

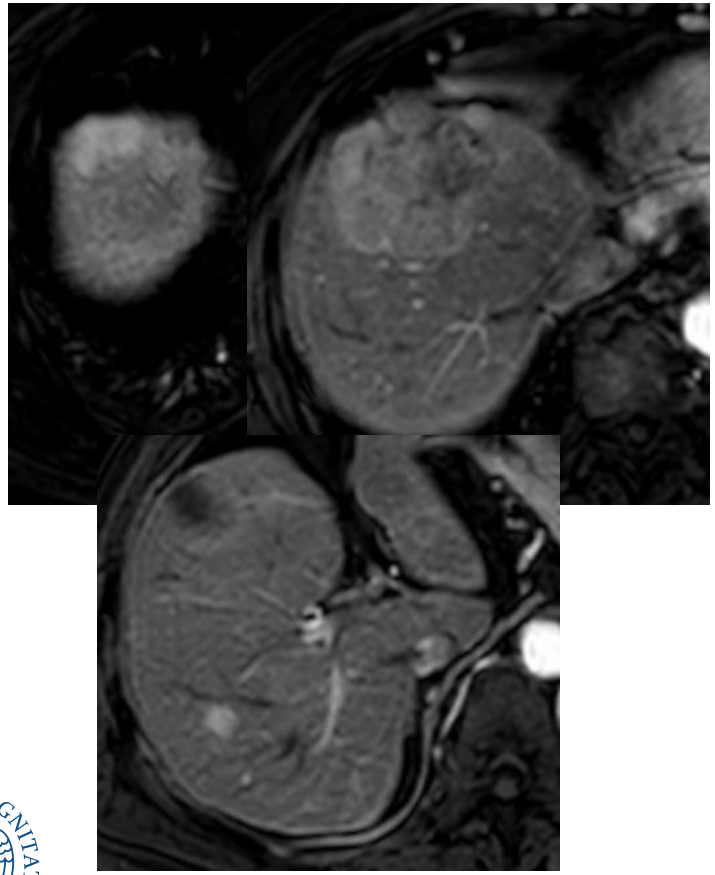
In patients with HCC that are candidates for LRT, the combination of Y90-RE and immunotherapy may be effective and tolerable, warranting further evaluation in large-scale controlled trials[1,2]

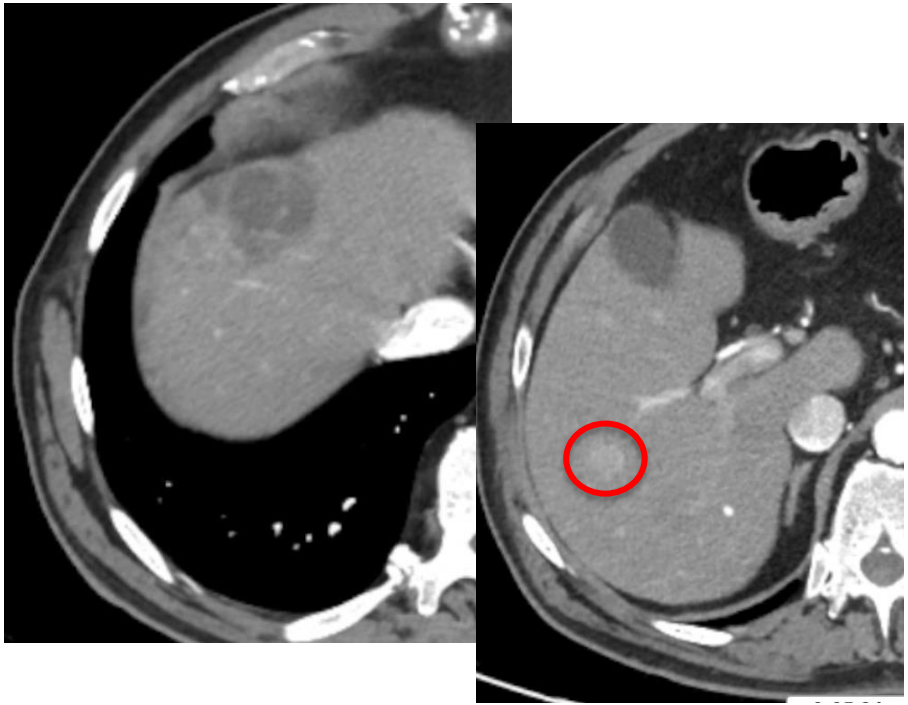
1. de la Torre-Aláez M, et al. *J Immunother Cancer* 2022;10(11):e005457. 2. Lee YB, et al. *Clin Cancer Res* 2023;29(18):3650-3658.

TARE and ICI ongoing clinical trials

Study	Phase	Intervention arms	Patient enrollment (N)	Primary outcomes
EMERALD-Y90 NCT06040099	2	• TARE+ durvalumab +bevacizumab	100 (estimated)	PFS
IMMUWIN NCT04522544	2	• Y-90 SIRT + tremelimumab + durvalumab • DEB-TACE + tremelimumab + durvalumab	55 (estimated)	ORR at 6 months
ROWAN NCT05063565	2	• TARE + tremelimumab + durvalumab	100 (estimated)	ORR
ZUGSPITZE 2020-003925-42	2	• Personalised-SIRT + tremelimumab + durvalumab • Standard-dose SIRT + tremelimumab + durvalumab • Immunotherapy followed by on-demand SIRT	84 (planned)	ORR

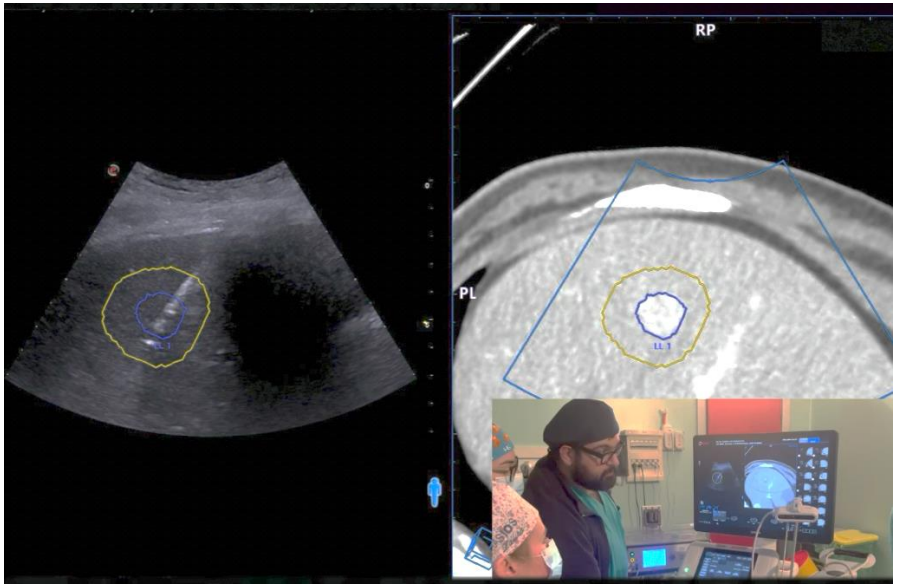
June 2023, ♂, 78 years, biopsy-proven HCC, no chronic liver disease



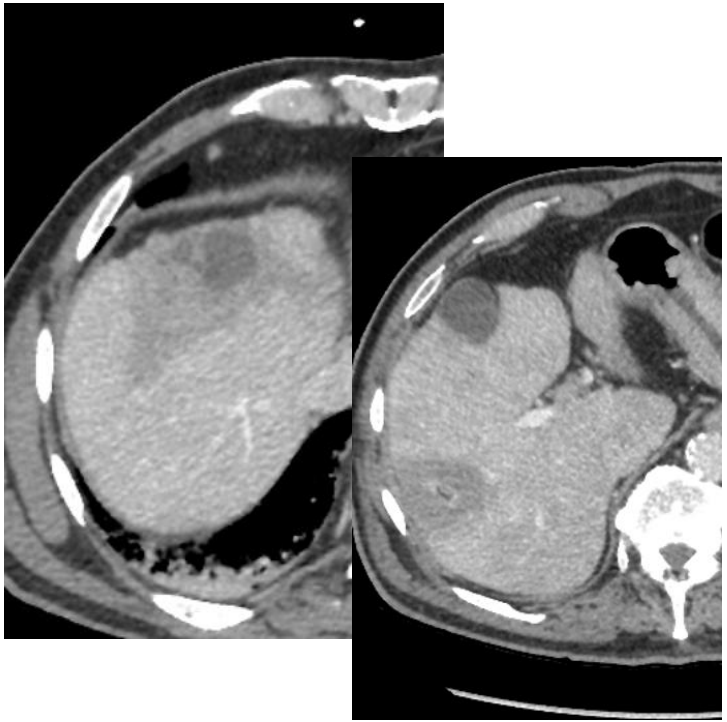


60 days after TARE + 5 months after Atezo-Bev

June 2023, ♂, 78 years, biopsy-proven HCC, no chronic liver disease



US/CT fusion-guided MW ablation



Immediate post-procedural CT

Comparing Real World, Personalized, MDT Recommendations with BCLC Algorithm: 321-Patient Analysis

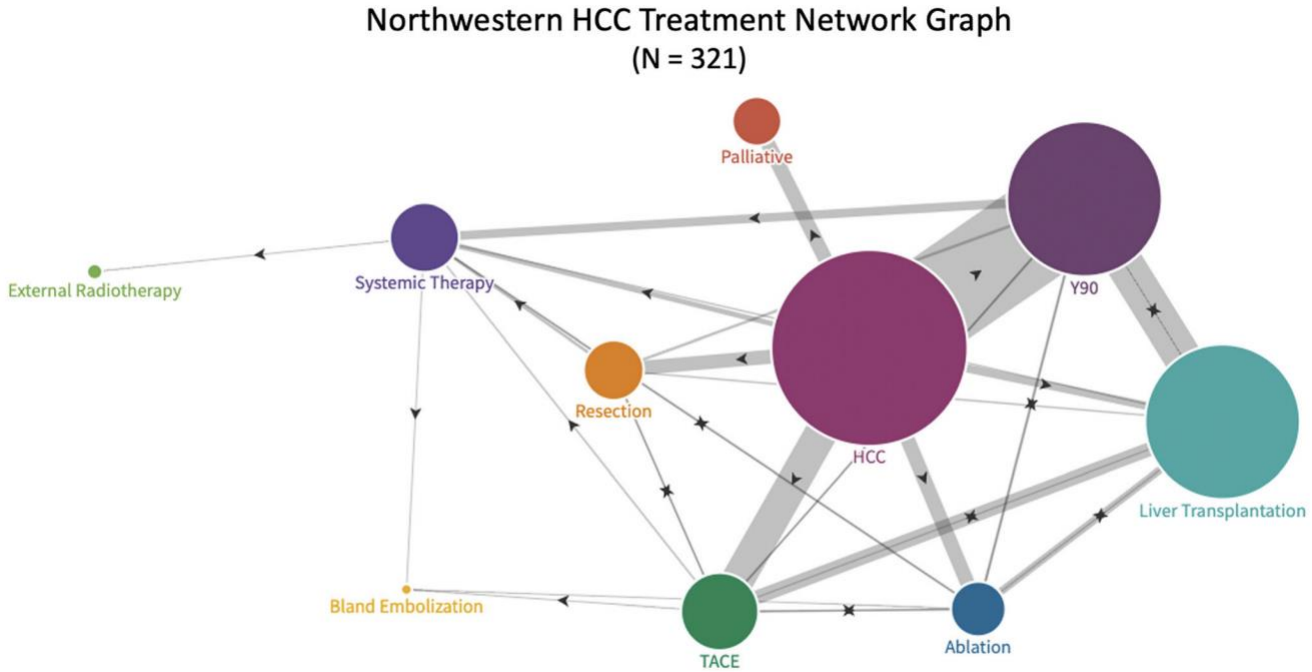
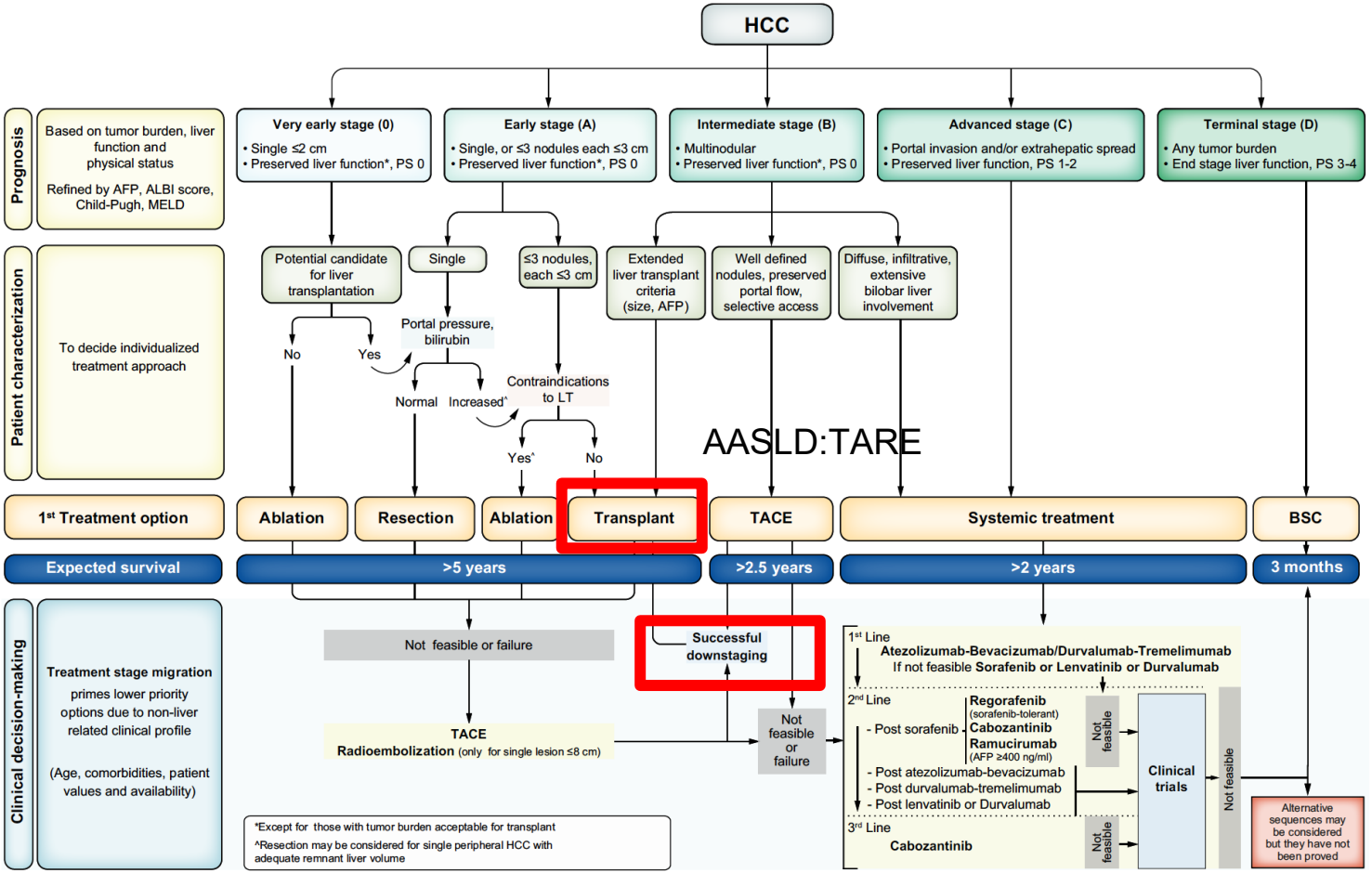


Fig. 5 Dynamic network graph demonstrating the interaction of all HCC treatments. The size of the node is commensurate with the number of patients (HCC N = 321). The thickness of the link is commensaurate with the frequency of the interaction

M.M. Matsumoto, et al CVIR 2021;44:1070-1080.



Journal of Hepatology DOI: (10.1016/j.jhep.2021.11.018)

ESOT | Transplant International

GUIDELINES
published: 14 September 2023
doi: 10.3389/ti.2023.11648

European Society of Organ Transplantation (ESOT) Consensus Report on Downstaging, Bridging and Immunotherapy in Liver Transplantation for Hepatocellular Carcinoma

Marco Petrus Adrianus Wilhelmus Claasen[1,2], Dimitri Sneiders[1†], Yannick Sebastiaan Rakké[1†], René Adam[3], Sherrie Bhoori[4], Umberto Cillo[5], Constantino Fondevila[6], Maria Reig[7], Gonzalo Sapisochin[2], Parissa Tabrizian[8] and Christian Toso[9] on behalf of the ESOT Guidelines Taskforce*

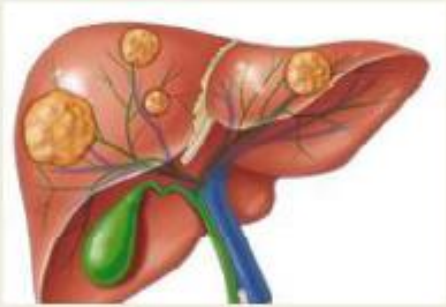
Recommendation 1.1: *All HCC patients achieving a successful downstaging to pre-defined transplantable criteria should be considered for liver transplantation as the benefit in terms of both recurrence-free survival and overall survival of this approach is significantly higher than any other non transplant strategy*

1. Should all eligible patients be transplanted after successful downstaging?

Quality of Evidence: High **Strenght of Recommendation: Strong for**

Downstaging Outcomes for Hepatocellular Carcinoma: Results From the Multicenter Evaluation of Reduction in Tumor Size before Liver Transplantation (MERITS-LT) Consortium

HCC meeting UNOS-DS criteria*



UNOS-DS inclusion criteria*

1 lesion > 5 cm and ≤ 8 cm
2 or 3 lesions ≤ 5 cm w/ total diameter ≤ 8 cm
4 or 5 lesions ≤ 3 cm w/ total diameter ≤ 8 cm
No vascular invasion or extrahepatic spread

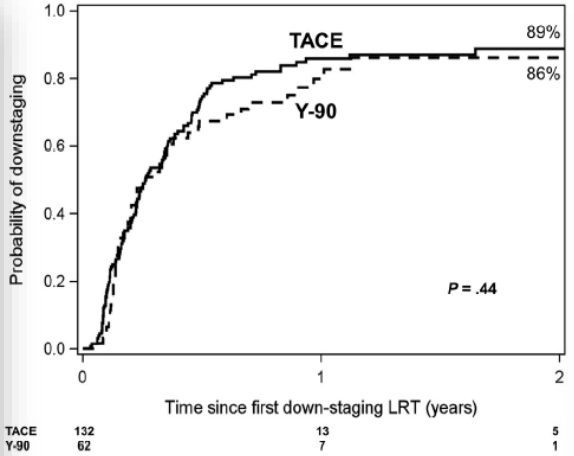


Figure 2. Kaplan–Meier probability of successful down-staging by the type of the first LRT with TACE vs Y-90.

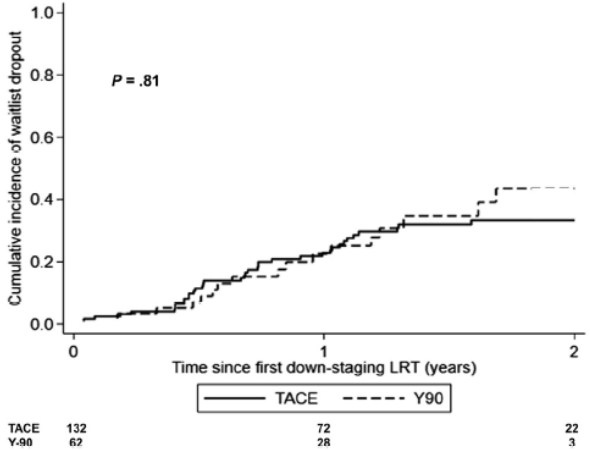


Figure 3. Kaplan–Meier probability of protocol dropout from the date of the first downstaging treatment.

TARE patients had a higher proportion of completely necrotic tumor(s) (31% vs 21%) and a lower proportion of both tumor beyond Milan criteria (23% vs 43%) and microvascular invasion (8% vs 21%)

Mehta N et al. Gastroenterology 2021;161(5):1502-1512

IR for management of HCC

Ablation is an established effective treatment for very early/early stage HCC

The risk of recurrence following surgery or ablation may be reduced by the addition of adjuvant immunotherapy; specifities of ablation should be investigated

Initial clinical experience confirms the feasibility and safety of combined embolisation (TACE / TARE) + immunotherapy regimens

Phase 3 clinical trials results are promising and support the evolution of immunotherapy-based combination from unresectable advanced HCC intermediate stage HCC

The results of further trials are highly anticipated

Thank you!!

SEE YOU THERE!

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