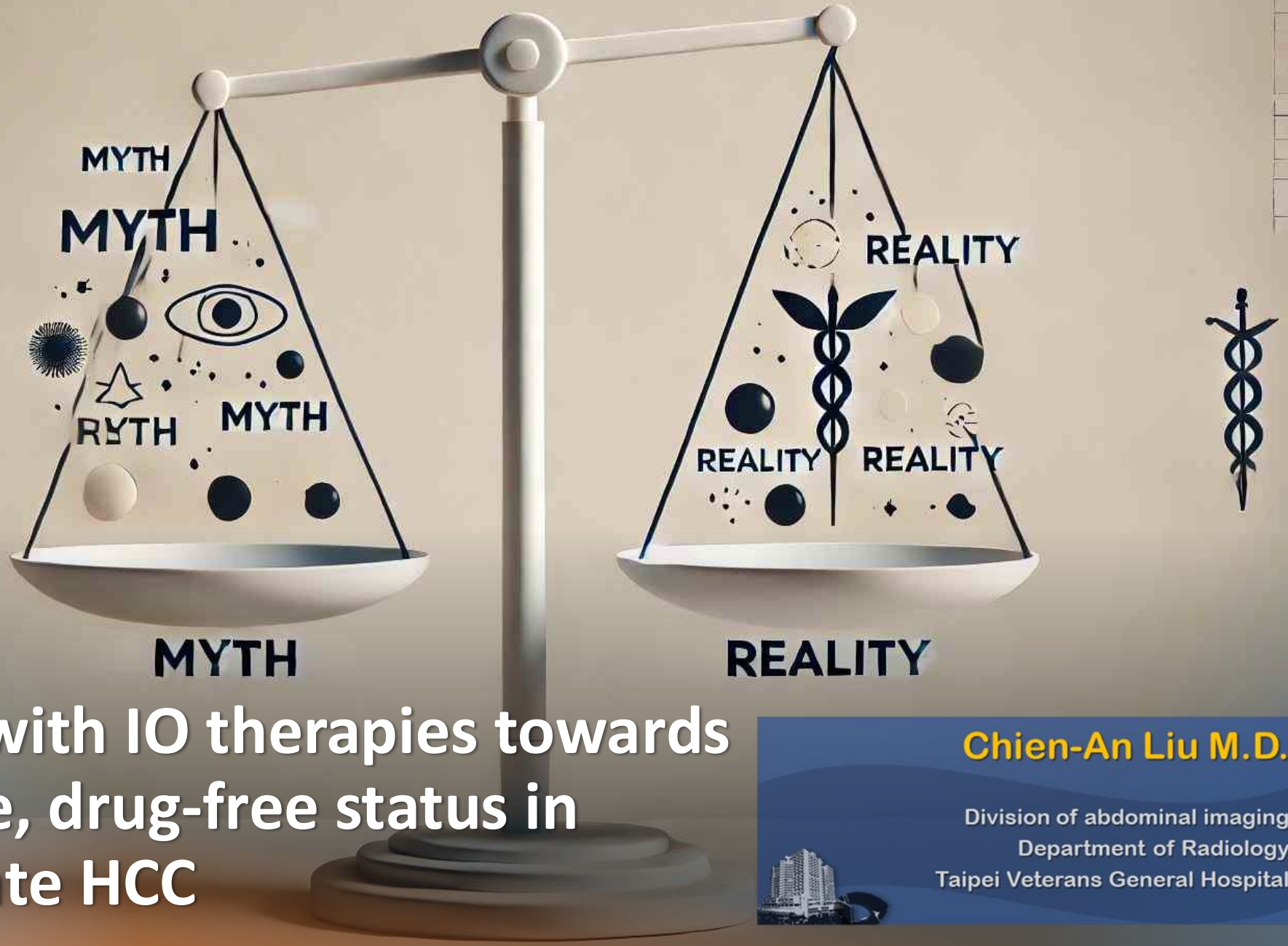


Synergies with IO therapies towards cancer-free, drug-free status in intermediate HCC

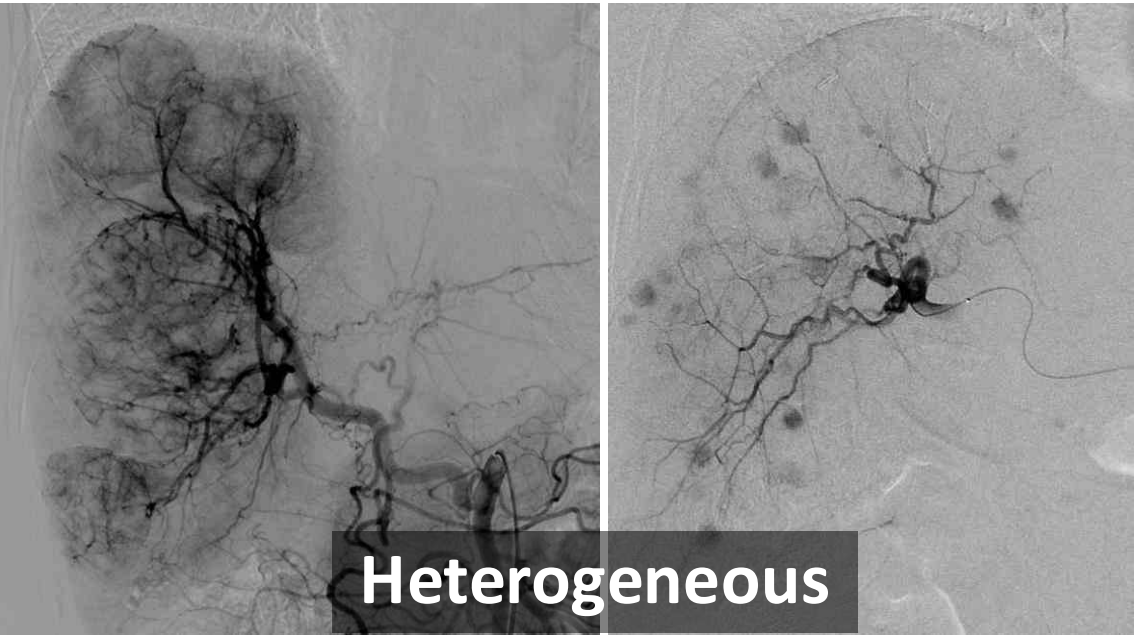
Chien-An Liu M.D.

Division of abdominal imaging
Department of Radiology
Taipei Veterans General Hospital

Outlines

- The unmet need of TACE
- TACE plus systemic treatments / recent evidences
- Synergistic effects of combining immunotherapies with Y90-TARE
- Possibility of “cancer-free, drug-free” status

Intermediate-stage HCC managements
Who is the best player ?



Intermediate-stage HCC managements
Who is the best player ?

Trans-arterial based Tx:
TACE (cTACE, dTACE),
Y90-TARE, HAIC

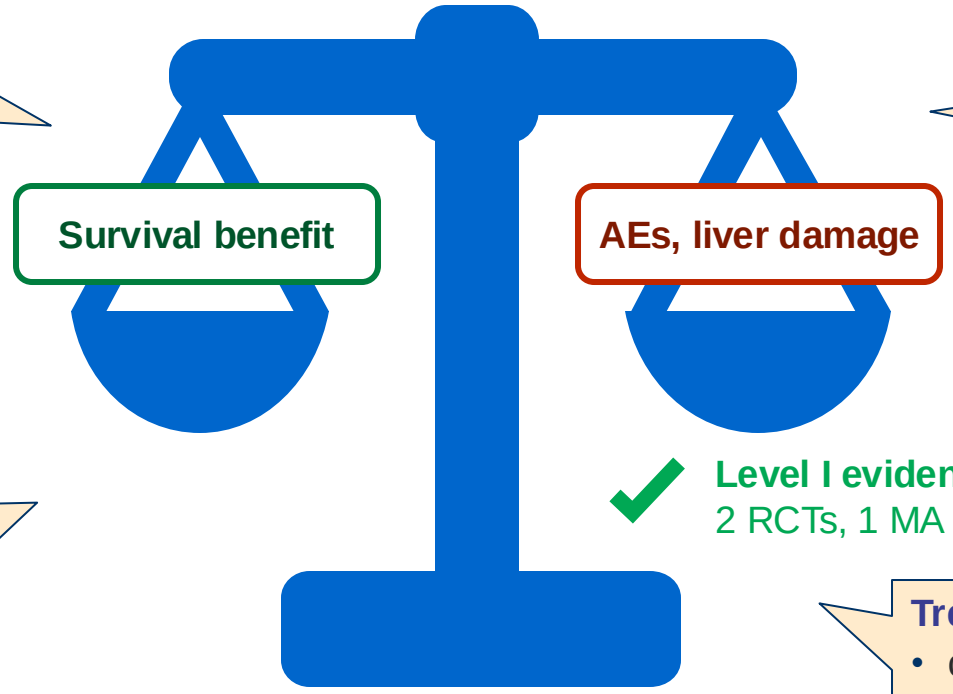
Systemic Therapy:
TKIs, Anti-VEGF,
ICIs, etc.

Striking a balance between anti-tumour efficacy and toxicity depends on many factors

- TACE has **dual ischaemic/cytotoxic** effects.
- Techniques are **operator-dependent** and delivered in a **heterogeneous** population

Tumour burden
- Size, n nodules, infiltrative spread
- Segmental portal vein involvement

Hepatic reserve
- Child-Pugh class/MELD score
- Ischaemic damage post-TACE



Level I evidence[1–3]
2 RCTs, 1 MA

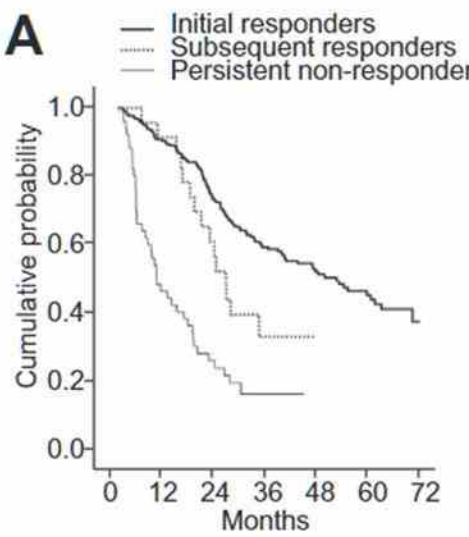
Patient factors
- Performance status
- Comorbidities
- Age

Treatment factors
- cTACE vs DEB-TACE
- Chosen drug (anthracyclines, platinum)
- Schedule

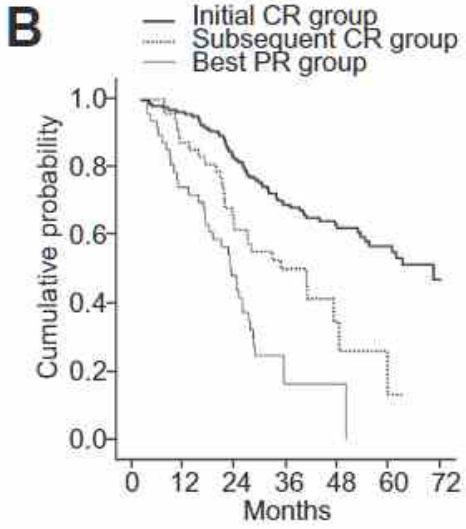
cTACE, conventional transarterial chemoembolisation
DEB-TACE, drug-eluting bead transarterial chemoembolisation; MA, meta-analysis
MELD, Model for End-Stage Liver Disease; RCT, randomised clinical trial

1. Llovet et al. Lancet 2002; 2. Lo et al. Hepatology 2002
3. Llovet et al. Hepatology 2003

Complete response at first chemoembolization is still the most robust predictor for favorable outcome in hepatocellular carcinoma



53.2
27.0 months
13.3

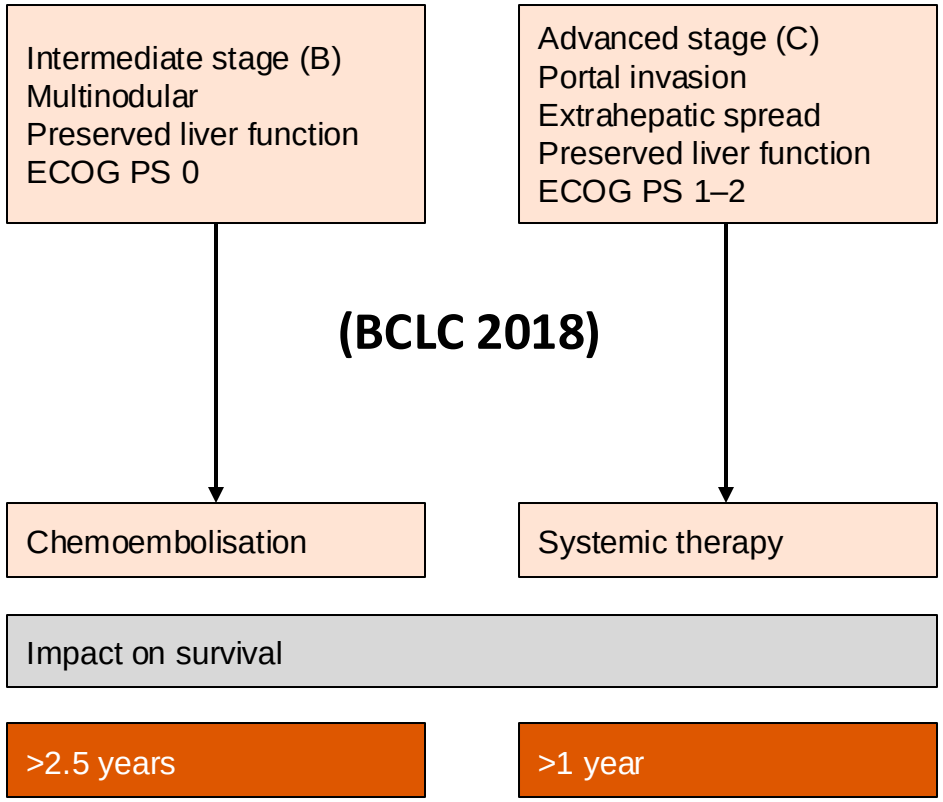


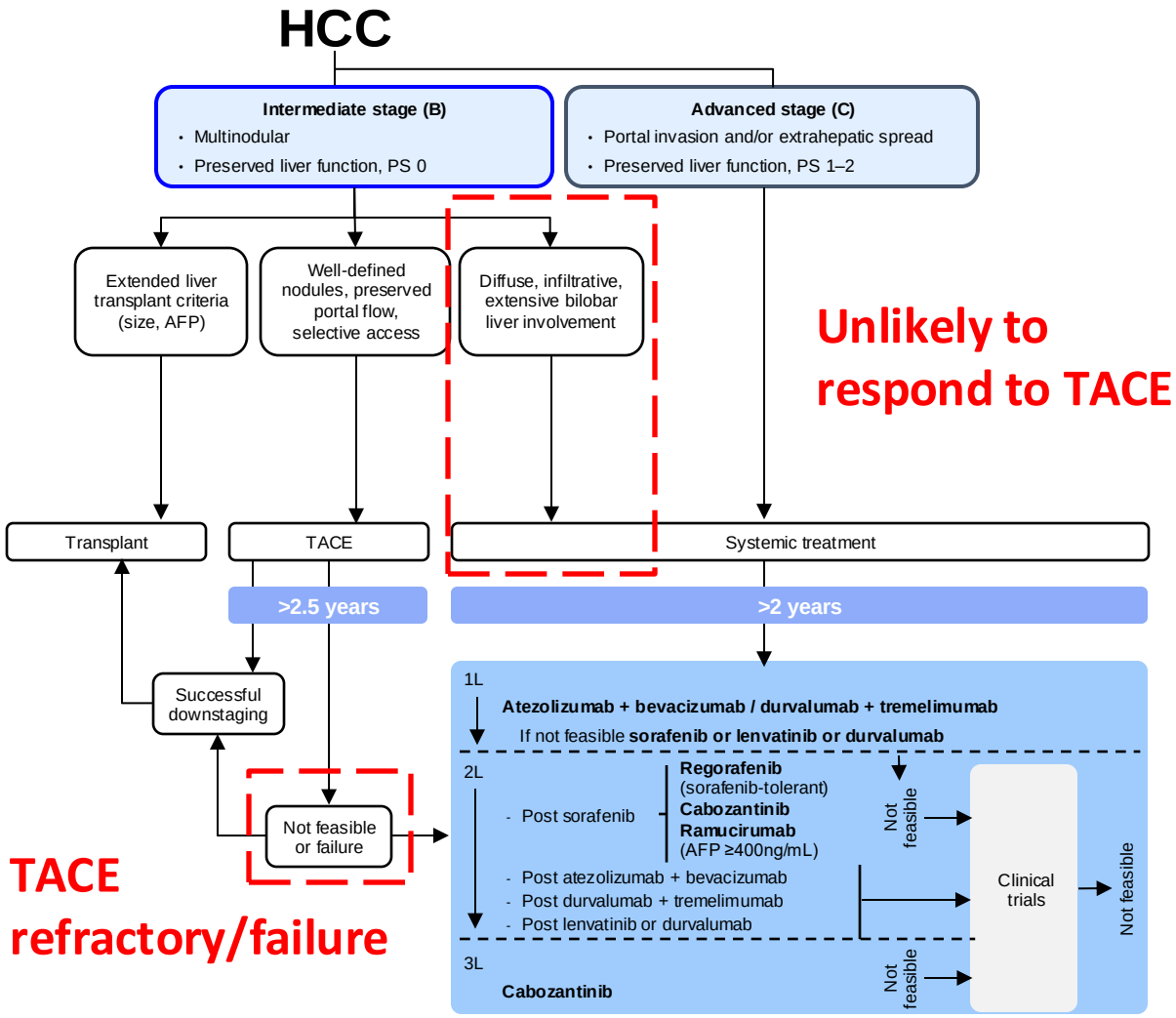
70.2
40.6 months
23.0

Variables	Univariate analysis	*Multivariate analysis (A)		*Multivariate analysis (B)	
	p value	*p* value	Adjusted HR (95% CI)	*p* value	Adjusted HR (95% CI)
Age	0.687				
Male gender	0.566				
Tumor size >5 cm	<0.001	0.025	1.487 (1.050-2.107)	0.014	1.535 (1.089-2.164)
Tumor number ≥4	<0.001	<0.001	2.320 (1.628-3.306)	<0.001	2.193 (1.529-3.145)
Baseline alpha-fetoprotein ≥200 ng/ml	0.015	n.s.	-	n.s.	-
Objective response as the initial response	<0.001	<0.001	0.410 (0.284-0.593)		
Objective response as the best response	<0.001			<0.001	0.335 (0.223-0.503)

J Hepatol. 2015 Jun;62(6):1304-10.

The evolution of treatment strategy in BCLC 2022 – systemic therapies are recommended in certain types of BCLC B HCC





TACE is current standard of care in intermediate-stage BUT improving outcomes remains a huge unmet need

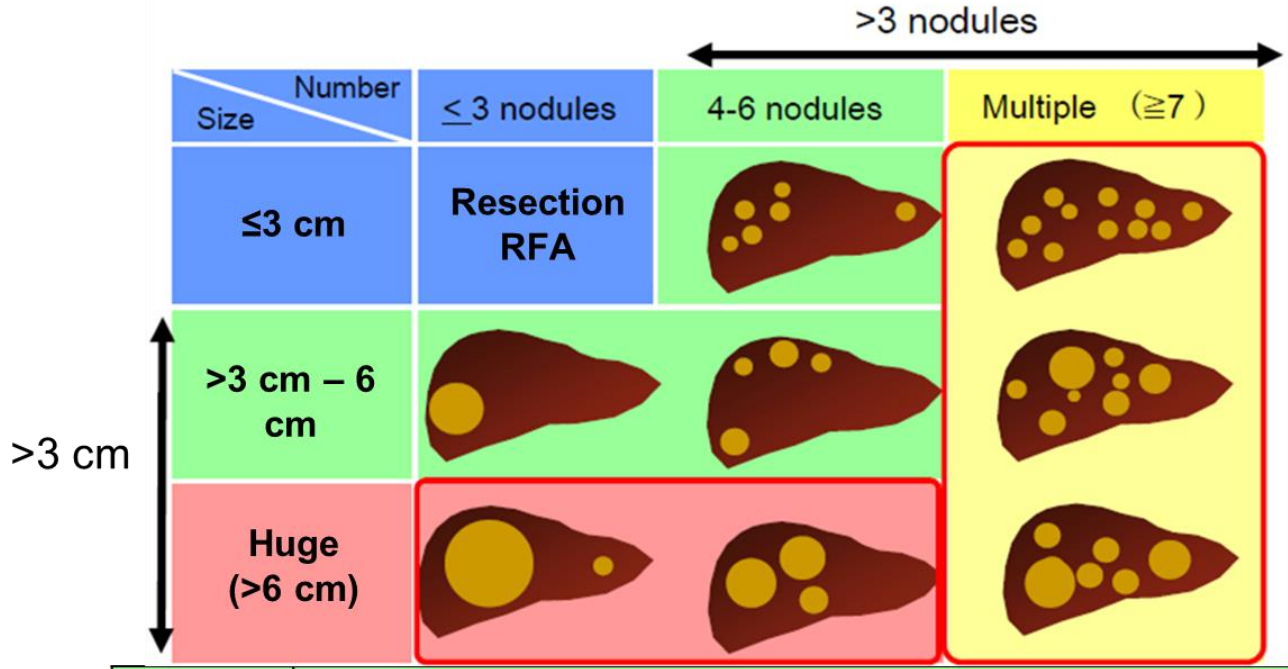
A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: Asia-Pacific primary liver expert consensus statements

Masatoshi Kudo, Kwang-Hyub Han, Sheng-Long Ye, Jian Zhou, Yi-Hsiang Huang, Shi-Ming Lin, Chung-Kwe Wang, Masafumi Ikeda, Stephen Lam Chan, Su Pin Choo, Shiro Miyayama, Ann Lii Cheng; on behalf of the APPLE Association

APPLE 2020 consensus

CQ.9: What is TACE-unsuitable?

1. **Unlikely to respond to TACE:**
   Confluent multinodular type, massive or infiltrative type, simple nodular type with extra-nodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules, or sarcomatous changes after TACE
2. **Likely to develop TACE failure/refractoriness:**
   Up-to-7 criteria out nodules
3. **Likely to become Child-Pugh B or C after TACE:**
   Up-to-7 criteria out nodules (especially, bilobar multifocal HCC), mALBI grade 2b



Green	Good response to cTACE subgroup (within up-to-7 criteria)
Pink	Poor response to cTACE subgroup (beyond up-to-7 criteria)
Yellow	Poor response to cTACE subgroup (beyond up-to-7 criteria, bilobar multifocal tumors)

Kudo M, et al. Liver Cancer, A Changing Paradigm for the Treatment of Intermediate-Stage Hepatocellular Carcinoma: Asia-Pacific Primary Liver Cancer Expert Consensus Statements, Volume 1, Issue 3.

TACE is current standard of care in intermediate-stage BUT improving outcomes remains a huge unmet need

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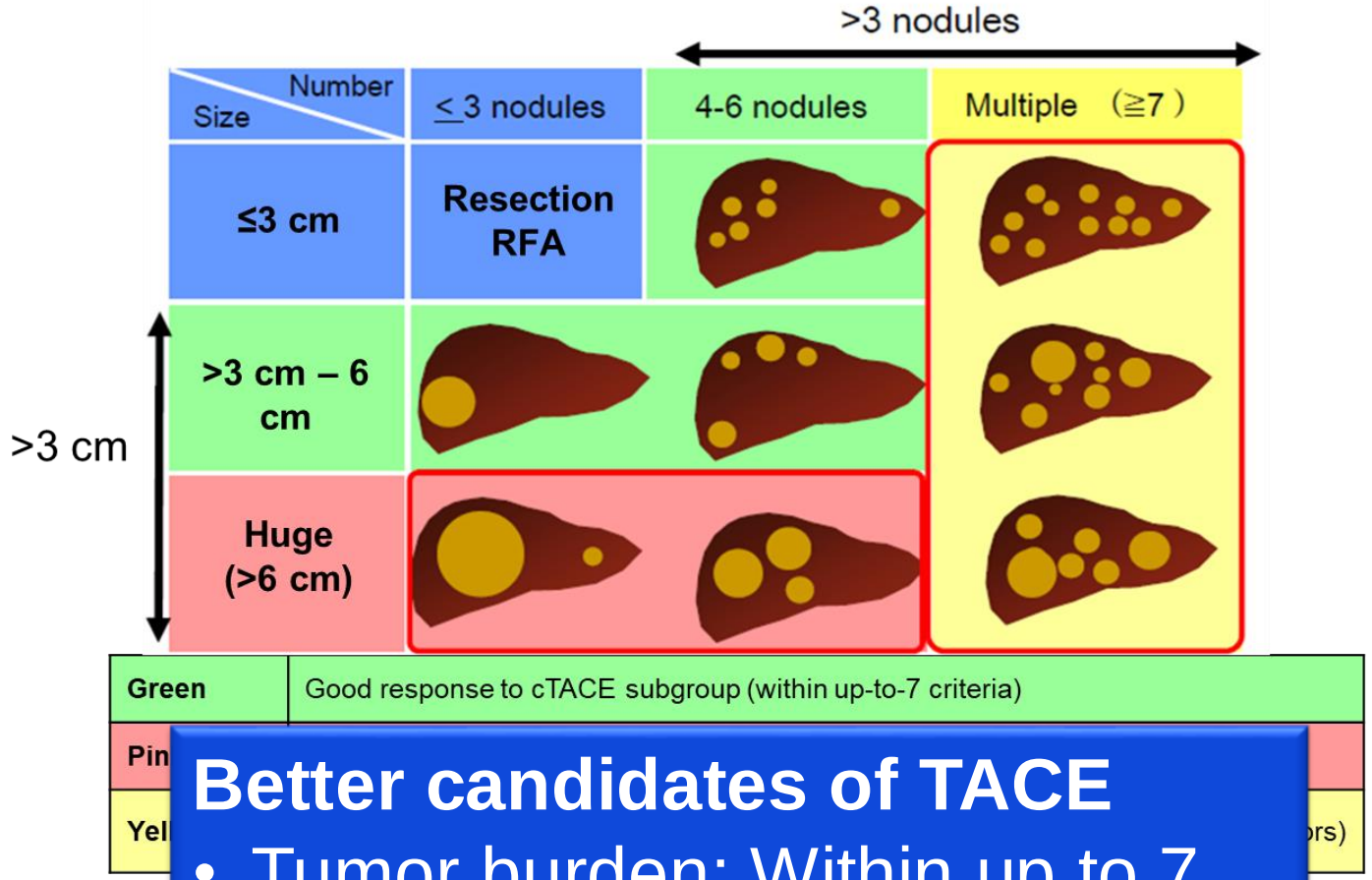


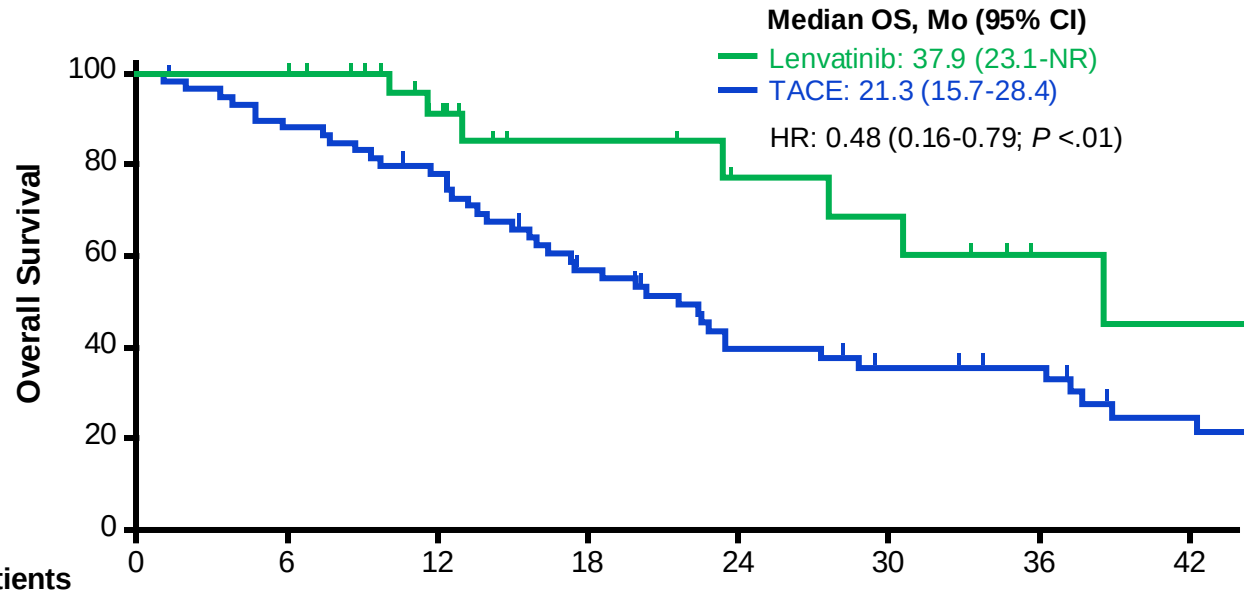
Better candidates of TACE

- Tumor burden: Within up to 7
- Absence of vascular invasion
- Preserved hepatic function

Kudo M, et al. Liver Cancer, A Changing Paradigm for the Treatment of Intermediate-Stage Hepatocellular Carcinoma: Asia-Pacific Primary Liver Cancer Expert Consensus Statements, Volume 1, Issue 3.

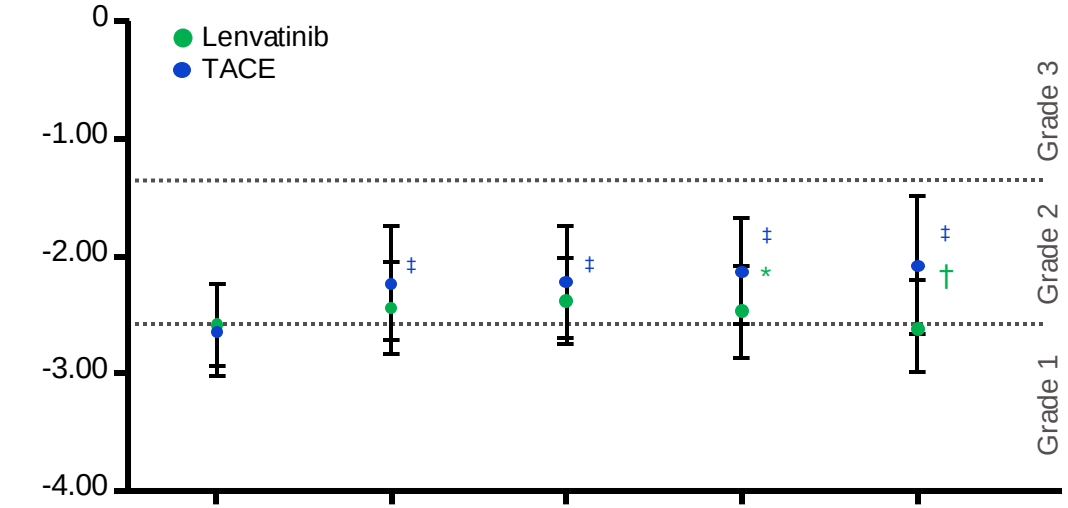
Systemic Therapy May Be Preferred in Patients With "TACE unsuitable" Intermediate-Stage HCC

Overall Survival



Patients at Risk, n								
Lenvatinib	30	30	19	12	9	8	4	3
TACE	60	52	44	31	20	16	13	7

Albumin–Bilirubin Score Over Time



	Baseline	1 mo	2 mo	3 mo	End of treatment
Lenvatinib	-2.61	-2.45	-2.40	-2.49	-2.61
TACE	-2.66	-2.25	-2.24	-2.15	-2.09

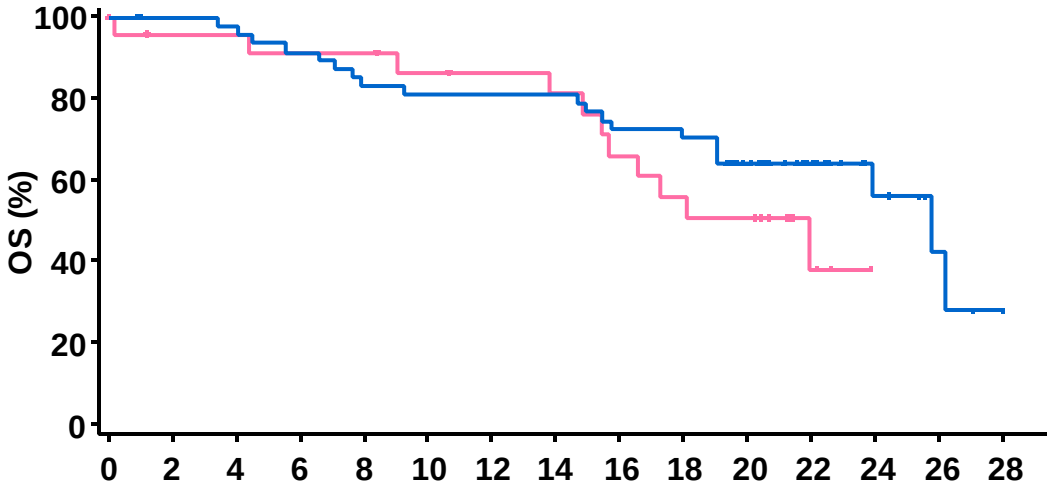
*P <.05 (lenvatinib vs TACE)
†P <.01 (lenvatinib vs TACE)
‡P <.01 (vs TACE at baseline)

Kudo. Cancers (Basel). 2019;11:1084.

IMbrave150: Exploratory analysis of patients with BCLC stage B disease

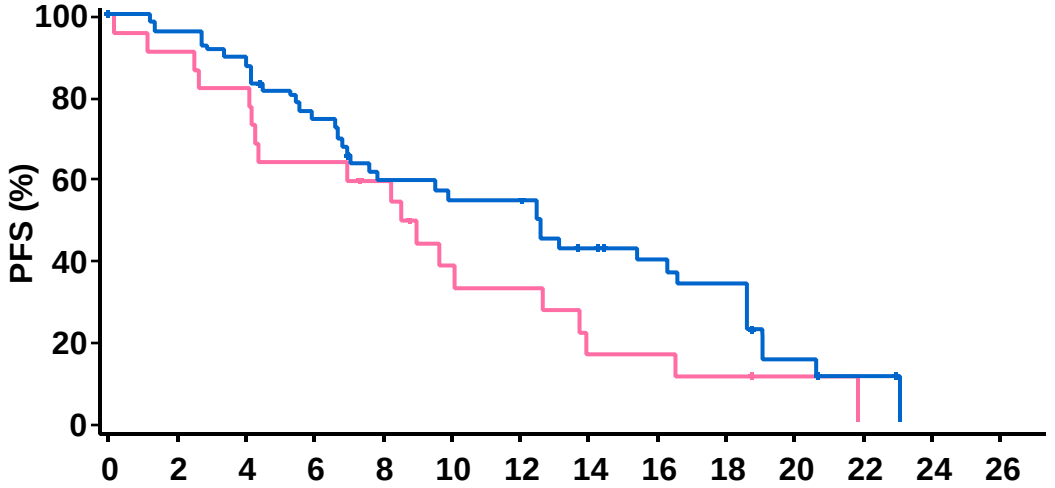
OS

	Atezolizumab + bevacizumab (n=49)	Sorafenib (n=24)
Median OS, months	25.8	21.9
HR (95% CI)	0.63 (0.29–1.34)	



PFS per RECIST v1.1

	Atezolizumab + bevacizumab (n=49)	Sorafenib (n=24)
Median PFS, months	12.6	8.6
HR (95% CI)	0.64 (0.36–1.12)	



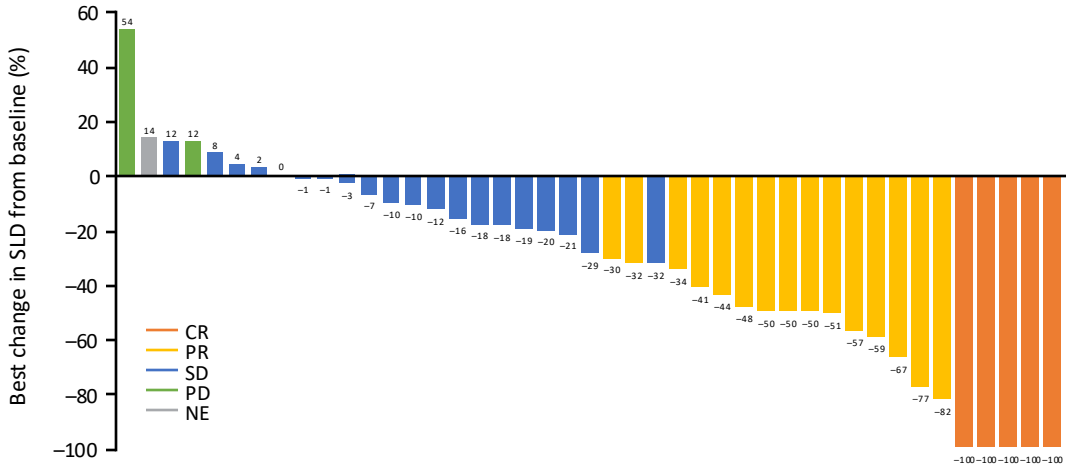
Clinical response per IRF-assessed RECIST v1.1	Atezolizumab + bevacizumab (n=46)	Sorafenib (n=23)
Confirmed ORR, n (%)	20 (43)	6 (26)
Median DOR, months	14.2	12.4

DOR, duration response; IRF, independent-review facility; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1

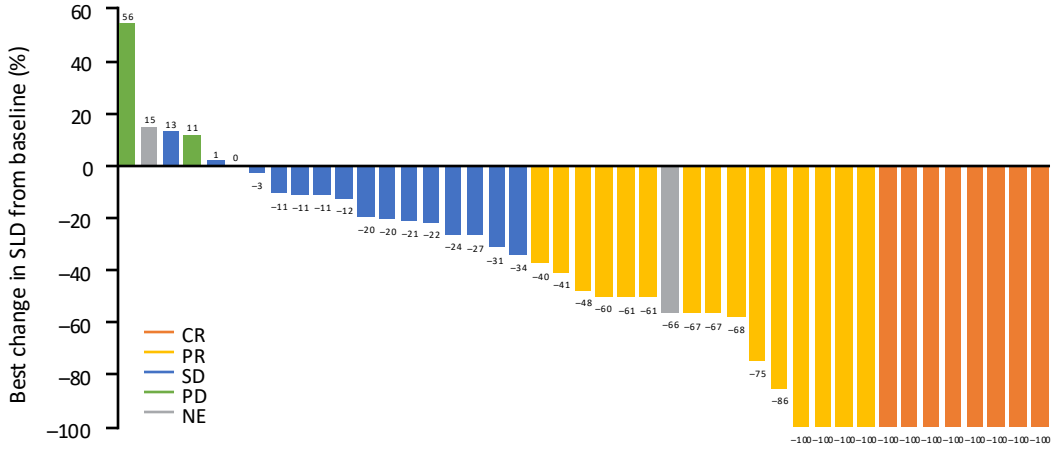
Kudo et al. Liver Cancer 2023.

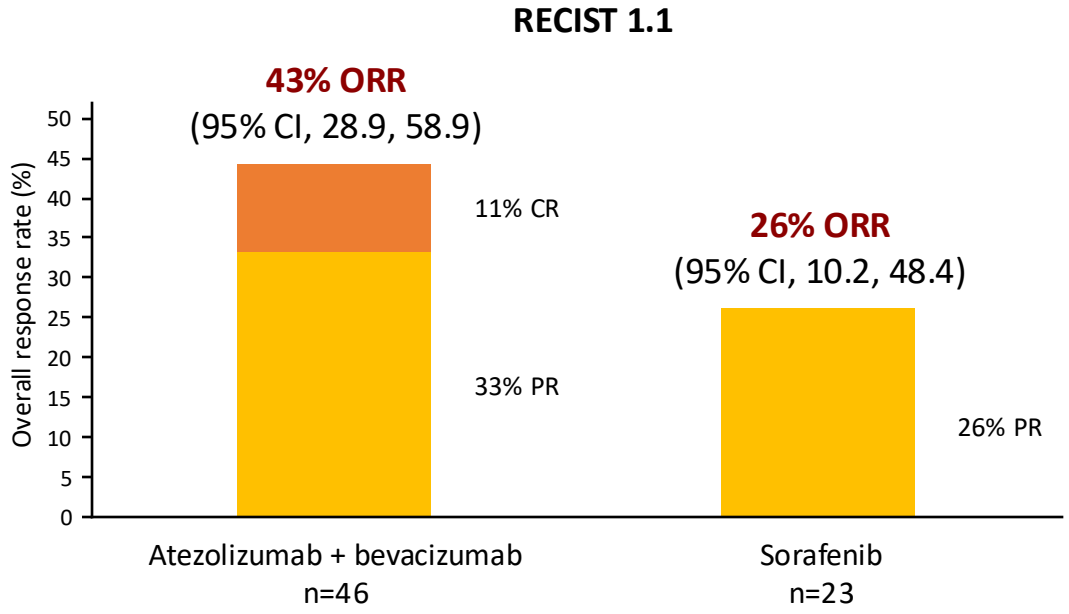
IMbrave150: ORR of BCLC B patients

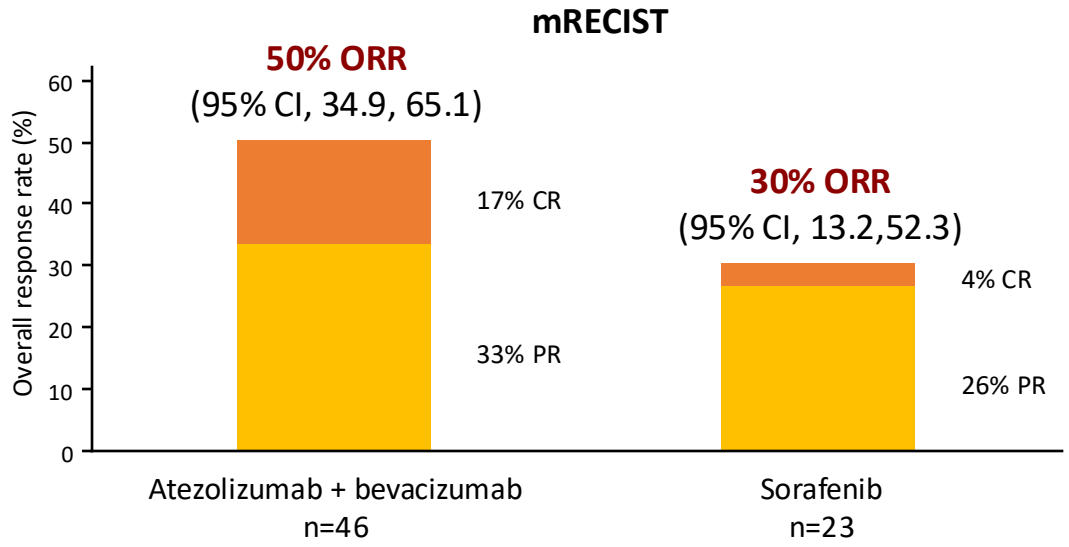
Best change in SLD of target lesions from baseline by RECIST 1.1



Best change in SLD of target lesions from baseline by mRECIST







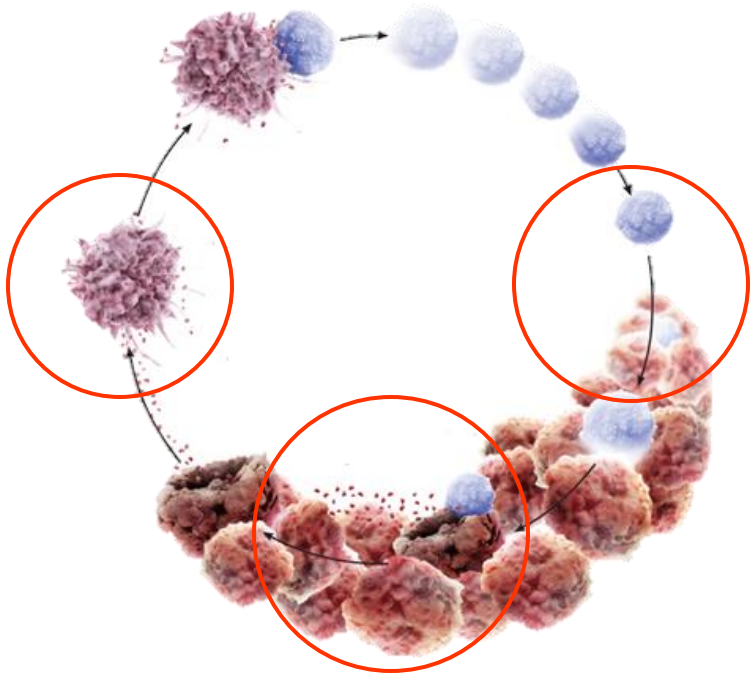
Kudo M, et al. Liver Cancer. 2022;12(3):238-250

Can we improve outcomes of TACE alone with systemic immunotherapies?

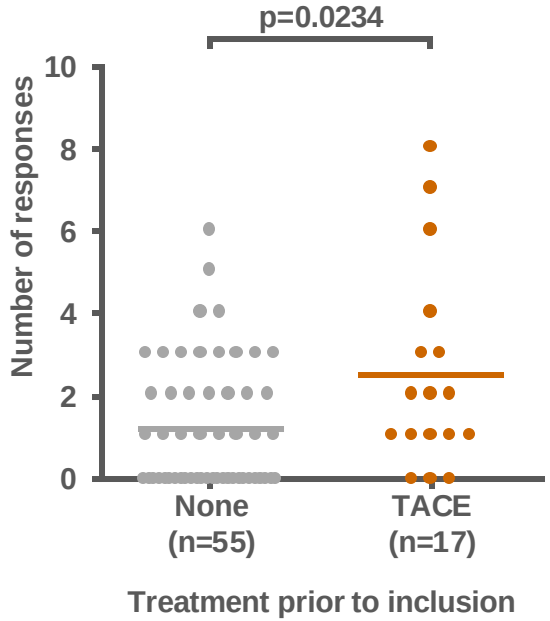
There is an immunobiologic rationale for combinations with locoregional therapy

TACE is a locoregional inducer of ICD[1]

TACE-induced ICD may act at various stages of the cancer immunity cycle[2]



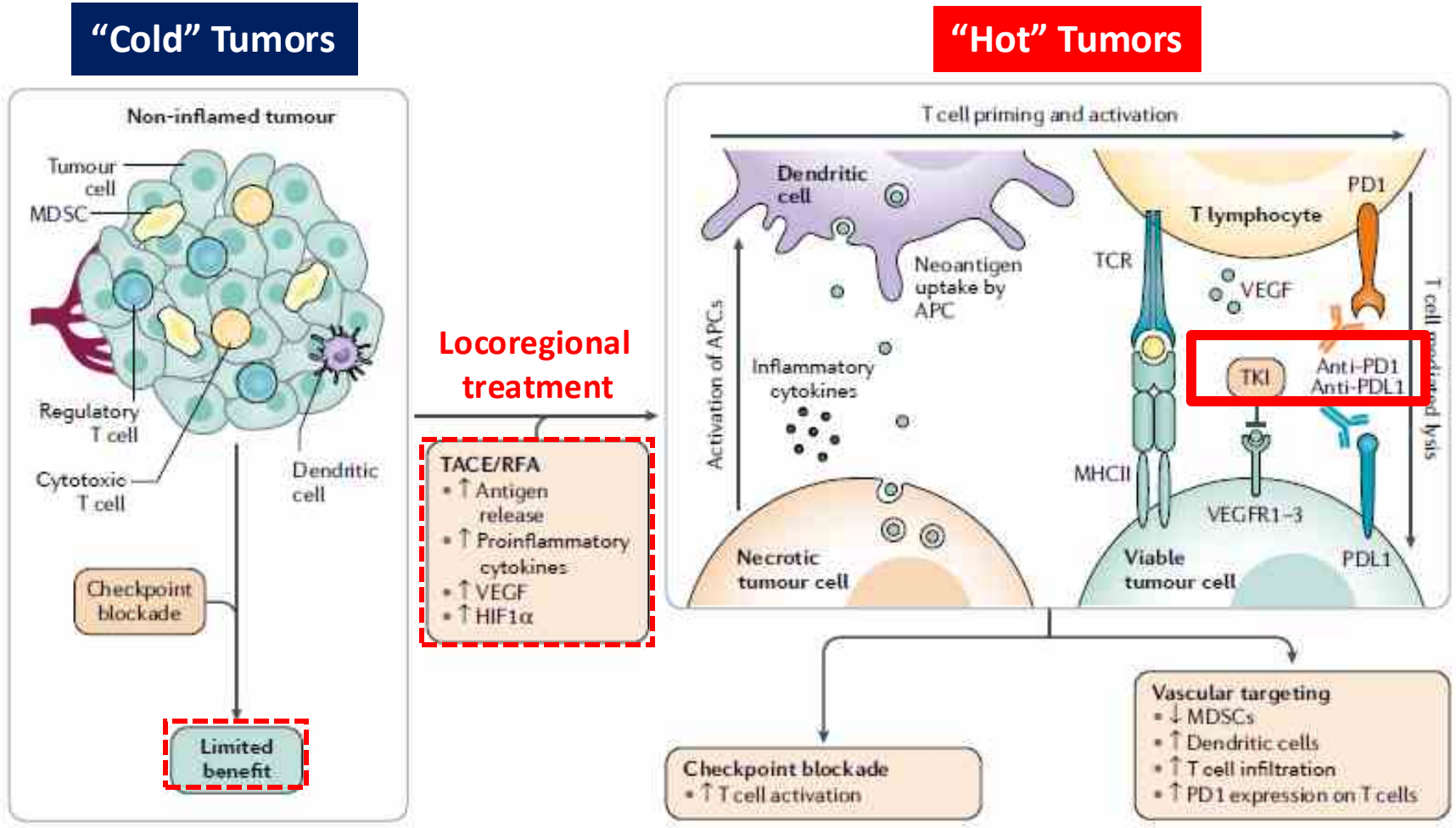
TACE enhances CD8 immune responses against tumour-associated antigens[3]



ICD, immunogenic cell death

1. Reynders et al. Cancer Treat Rev 2015; 2. Galluzi et al. Nat Rev Immunol 2017
3. Adapted from Flecken et al. Hepatology 2014

There is an immunobiologic rationale for combinations with locoregional therapy



Adapted from Nat Rev Gastroenterol Hepatol. 2021 Jan 28.

Key ongoing trials in intermediate-stage HCC

	Study name	n	Investigational arm(s)	Control arm	Primary endpoint(s)	Target population	BCLC
TACE + systemic therapy vs TACE	EMERALD-1[1]	724	TACE + durvalumab + bevacizumab / TACE + durvalumab	TACE + placebo	PFS (BICR)	TACE-eligible Not eligible for curative	A, B, C
	EMERALD-3[2]	725*	TACE + tremelimumab + durvalumab + lenvatinib / TACE + tremelimumab + durvalumab	TACE	PFS (BICR) in lenvatinib arm vs control arm	TACE-eligible Not eligible for curative	A, B, C
	LEAP-012[3]	450*	TACE + pembrolizumab + lenvatinib	TACE + placebo (IV + oral)	PFS (RECIST 1.1 by BICR) and OS	TACE-eligible Not eligible for curative	A, B
	TACE-3[4]	522*	TACE + nivolumab	TACE	OS and TTTP	TACE-eligible Not eligible for curative	A, B, C
	TALENTACE[5]	342	TACE + atezolizumab + bevacizumab	TACE	PFS (INV) and OS	TACE-eligible Not eligible for curative	
Systemic therapy vs TACE	ABC-HCC[6]	434*	Atezolizumab + bevacizumab	TACE	Time to failure of treatment strategy	TACE-eligible Not eligible for curative	A, B, C
	REPLACE[7]	496*	Pembrolizumab + regorafenib	TACE or TARE	PFS (INV; mRECIST)	Intermediate-stage	B

Information based on clinicaltrials.gov (accessed September 2024)
*Estimated enrolment
TTTP, time to TACE progression
Product/indication not approved. Experimental use

1. NCT03778957; 2. NCT05301842; 3. NCT04246177
4. NCT04268888; 5. NCT04712643; 6. NCT04803994; 7. NCT04777851

EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)

R 1:1:1
N=616

Arm A: Durvalumab‡ (1500 mg Q4W) + TACE§	Durvalumab (1120 mg Q3W) + placebo for bevacizumab (Q3W)
Arm B: Durvalumab† (1500 mg Q4W) + TACE§	Durvalumab (1120 mg Q3W) + bevacizumab (15 mg/kg Q3W)
Arm C: Placebo for durvalumab (Q4W) + TACE§	Placebo for durvalumab (Q3W) + placebo for bevacizumab (Q3W)

Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.

BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

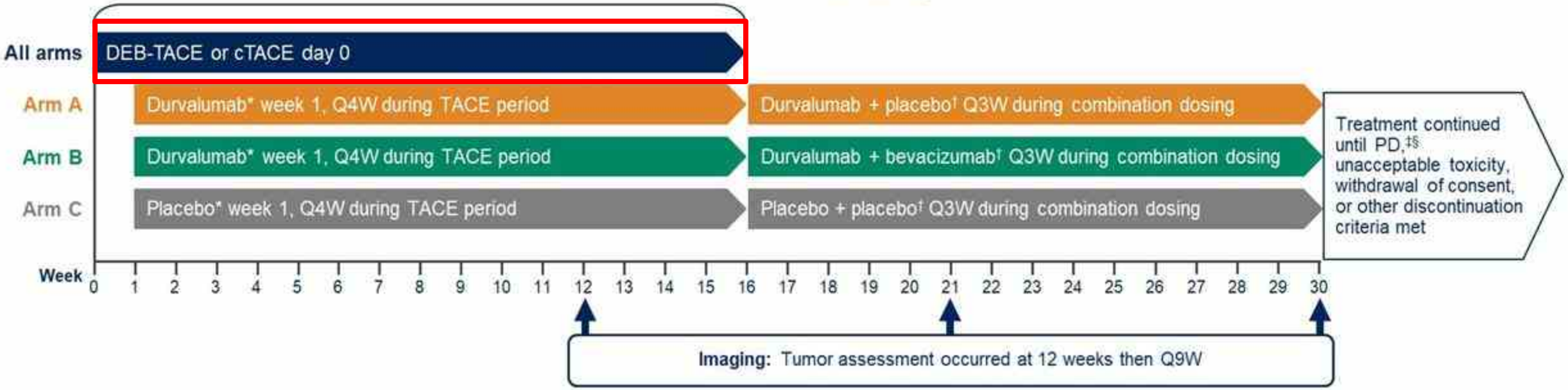
EMERALD-1 study schema

Number and timings of TACE at the investigator's discretion:

- 1–4 TACE procedures within 16 weeks

Combination therapy begins after the final TACE procedure

- Median (range) start of combination systemic therapy: 14 (2–113) weeks post first dose of TACE at Day 0



*Durvalumab / placebo started at least 7 days after TACE; doses moved to accommodate TACE if necessary. Durvalumab 1500 mg. †Durvalumab / placebo Q4W until ≥14 days after last TACE. †Durvalumab 1120 mg. Bevacizumab 15 mg/kg. Durvalumab / bevacizumab / placebos Q3W. ‡Investigator-determined mRECIST-defined radiological disease progression. §Participants with mRECIST-defined progression may continue to receive study treatment, including additional TACE, at the discretion of the investigator and participant, and in consultation with the AstraZeneca study physician.

cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead-transarterial chemoembolization; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; TACE, transarterial chemoembolization; Q3W / Q4W / Q9W, every 3 / 4 / 9 weeks.

PRESENTED BY: Riccardo Lencioni, MD

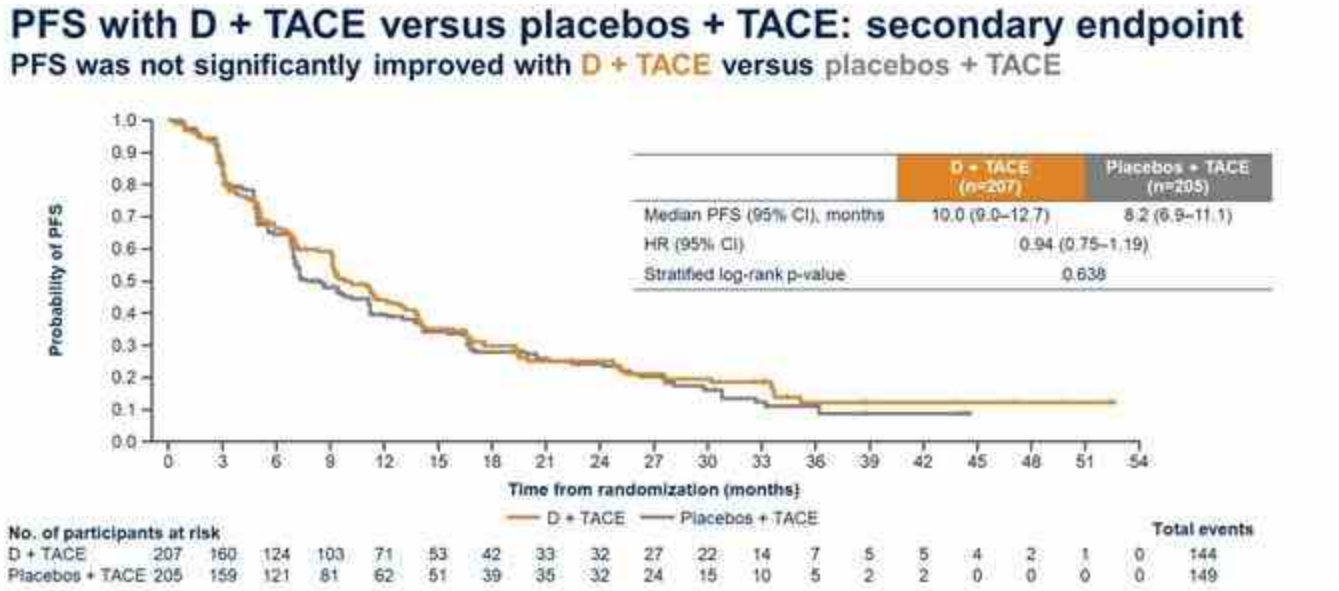
Baseline characteristics

Baseline characteristics were generally well balanced

		D + TACE (n=207)*	D+B + TACE (n=204)*	Placebos + TACE (n=205)*
Age (years)	Median	65.0	64.5	66.0
Sex, n (%)	Male	156 (75.4)	162 (79.4)	163 (79.5)
Geographical region, n (%)	Japan	15 (7.2)	15 (7.4)	15 (7.3)
	Asia (non-Japan)	108 (52.1)	107 (52.4)	107 (52.1)
	Others	84 (40.5)	82 (40.1)	83 (40.4)
TACE modality, n (%)	DEB-TACE	81 (39.1)	84 (41.2)	84 (41.0)
	cTACE	123 (59.4)	119 (58.3)	120 (58.5)
Etiology of liver disease, n (%)	HBV	70 (33.8)	75 (36.8)	74 (36.1)
	HCV	48 (23.2)	42 (20.6)	54 (26.3)
	Non-viral	88 (42.5)	86 (42.2)	76 (37.1)
BCLC stage, n (%)	A	59 (28.5)	51 (25.0)	49 (23.9)
	B	114 (55.1)	117 (57.4)	122 (59.5)
	C	33 (15.9)	35 (17.2)	31 (15.1)
Portal vein invasion, n (%)	No	194 (93.7)	188 (92.2)	192 (93.7)
	Yes	13 (6.3)	16 (7.8)	13 (6.3)
Screening ECOG PS, n (%)	0	173 (83.6)	167 (81.9)	175 (85.4)
	1	34 (16.4)	37 (18.1)	30 (14.6)
Baseline PD-L1†, n (%)	High (≥1%)	63 (30.4)	61 (29.9)	64 (31.2)
	Low (<1%)	97 (46.9)	93 (45.6)	88 (42.9)
	Unknown	47 (22.7)	50 (24.5)	53 (25.9)
Child-Pugh score, n (%)	A	201 (97.1)	200 (98.0)	201 (98.0)
	B	6 (2.9)	4 (2.0)	4 (2.0)
ALBI at baseline, n (%)	Grade 1	107 (51.7)	117 (57.4)	126 (61.5)
	Grade ≥2	100 (48.3)	87 (42.6)	79 (38.5)
Tumor burden at baseline, n (%)	Within up-to 7 criteria (≤7)	97 (46.9)	97 (47.5)	102 (49.8)
	Beyond up-to-7 criteria (>7)	110 (53.1)	106 (52.0)	103 (50.2)
HAP score, n (%)	A	63 (30.4)	66 (32.4)	64 (31.2)
	B	72 (34.8)	74 (36.3)	75 (36.6)
	C	52 (25.1)	41 (20.1)	48 (23.4)
	D	20 (9.7)	20 (9.8)	18 (8.8)
	Missing	0	3 (1.5)	0

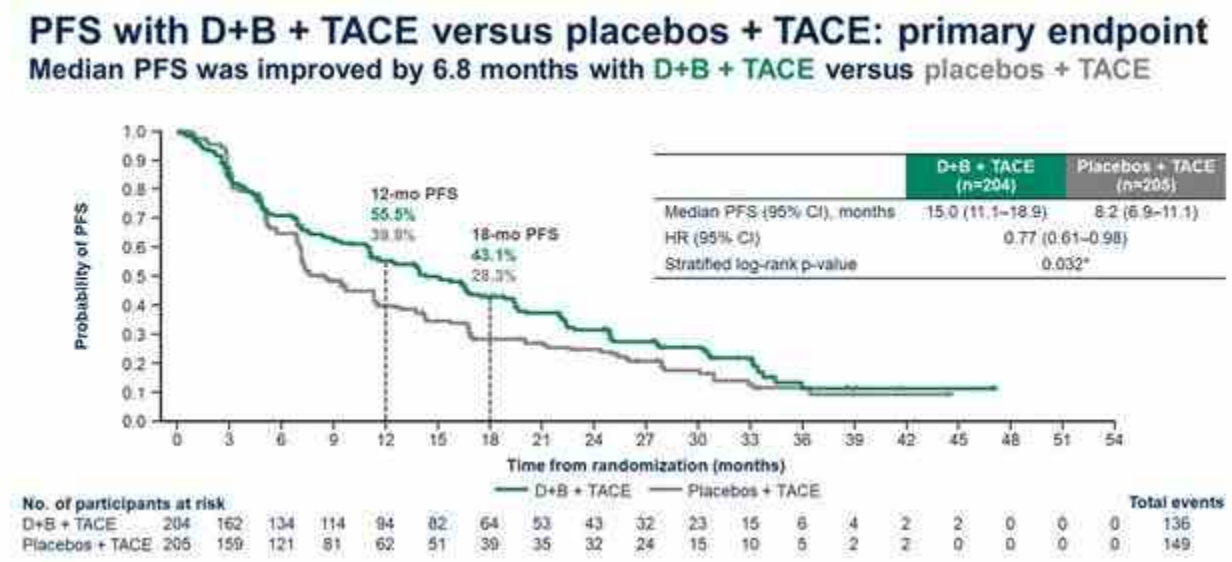
*ITT: all randomized participants with treatment groups assigned in accordance with the randomization, regardless of the treatment actually received. †Baseline PD-L1 TAP expression.
ALBI, albumin-bilirubin; B, bevacizumab; BCLC, Barcelona Clinical Liver Cancer; cTACE, conventional transarterial chemoembolization; D, durvalumab; DEB-TACE, drug-eluting bead-transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; HAP, hepatoma arterial-embolization prognostic; HBV, hepatitis B virus; HCV, hepatitis C virus; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; PS, performance status; TACE, transarterial chemoembolization; TAP, tumor area positivity.

EMERALD-1: Bevacizumab played a critical role in driving difference in PFS outcomes



10.0 vs 8.2 mon

Arm A
Without VEGF inhibition
PFS: HR 0.94 (p=0.638)



15.0 vs 8.2 mon

Arm B
With VEGF inhibition
PFS: HR 0.77 (p=0.032)

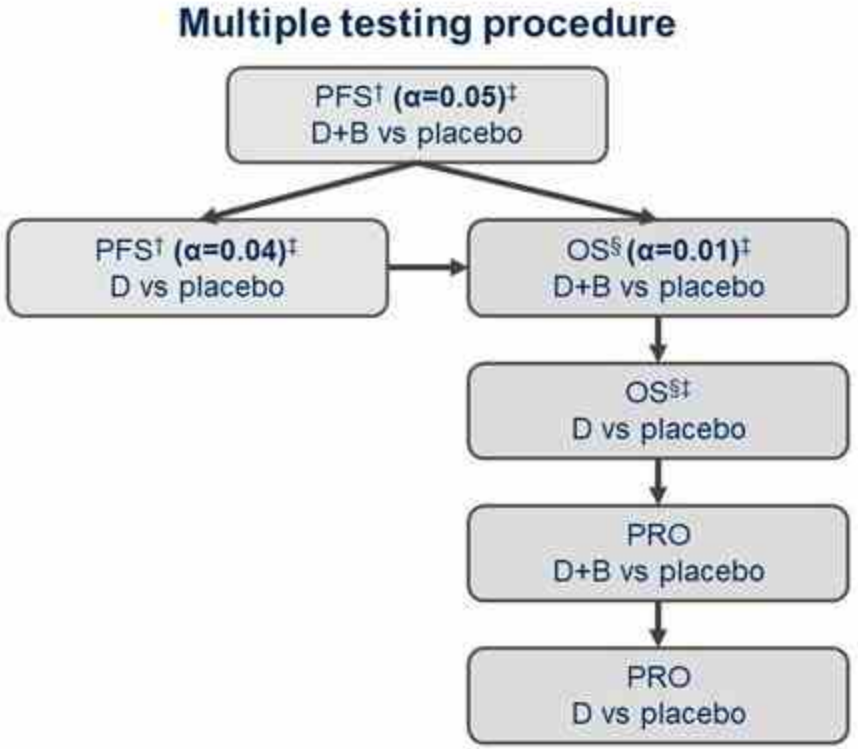
R Lencioni et al. ASCO GI 2024.

EMERALD-01: Longer follow-up for Overall Survival needed

Statistical Considerations

Pre-planned analysis	Approximate target maturity for arms B and C per protocol*
Interim PFS	58%
Final PFS	72%
Interim OS	51%
Final OS	64%

- At data cut-off, Sep 11, 2023, the final PFS analysis and interim OS analysis co-occurred
- OS was not statistically significant at the interim analysis: EMERALD-1 is ongoing for the final analysis of OS and remains blinded to investigators and participants



*Across the durvalumab plus bevacizumab plus TACE arms and the placebos plus TACE arm. †The final analysis for PFS occurred at analysis 2 out of 4 pre-planned analyses. ‡2-sided α. §The final analysis for OS will occur at analysis 4 out of 4 pre-planned analyses.
B, bevacizumab; D, durvalumab; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes.

R Lencioni, M Kudo, J Erinjeri, et al. ASCO GI 2024

LEAP-012 Study Design (NCT04246177)

Key Eligibility Criteria

- Confirmed HCC not amenable to curative treatment
- ≥1 measurable HCC lesion per RECIST v1.1
- All lesions treatable with TACE in 1 or 2 sessions
- No portal vein thrombosis or extrahepatic disease
- Child-Pugh liver class A
- ECOG PS of 0 or 1

R 1:1

Lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) PO QD
+
Pembrolizumab 400 mg IV Q6W (up to 2 years)
+
TACE[b]

Placebo PO QD + Placebo IV Q6W (up to 2 years)
+
TACE[b]

Stratification Factors

- Study site
- Alpha fetoprotein (≤400 ng/mL vs >400 ng/mL)
- ECOG PS (0 vs 1)
- ALBI grade (1 vs 2 or 3)
- Tumor burden score[1,a] (≤6 vs >6 but ≤12 vs >12)

End Points

- Primary: PFS[c] and OS
  - IA1 is the **final analysis** for PFS
  - Initial alpha of 0.025 (1-sided) allocated to PFS; passed to OS if PFS is statistically significant
- Secondary: ORR,[c,d] DOR,[c,d] DCR,[c,d] TTP,[c,d] PFS,[d] and safety

1. Wang Q et al. *J Hepatol*. 2019;70:893-903.

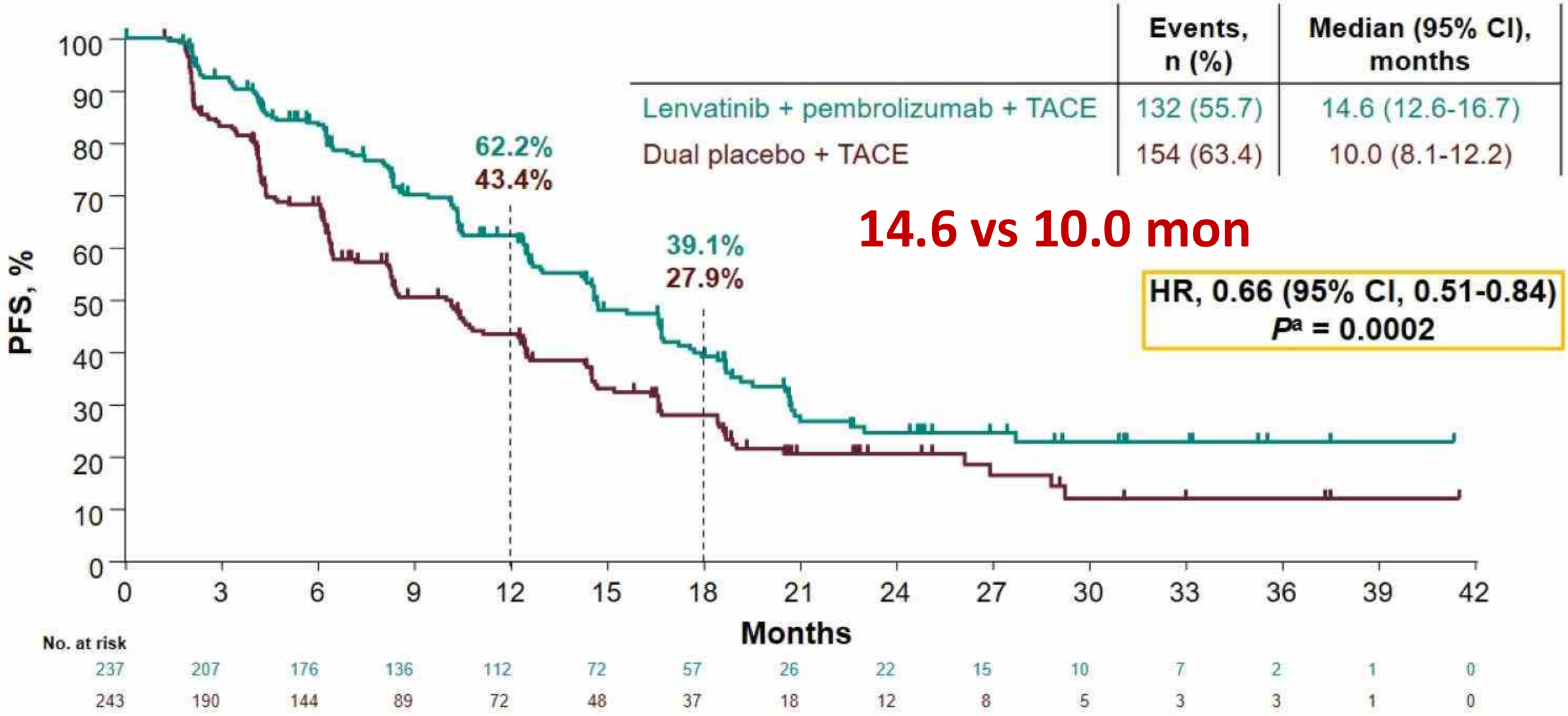
[a]Largest tumor in centimeters + number of tumors. [b]2-4 weeks after the start of systemic therapy with a maximum of 2 treatments per tumor (4 total) and no more than 1 treatment per month.
[c]Per RECIST v1.1 by BICR. [d]Per mRECIST by BICR.

Baseline Characteristics

	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 243
Age, median (range), yrs	65.0 (31-87)	66.0 (21-85)
Age, ≥65 yrs	128 (54.0)	137 (56.4)
Sex, male	192 (81.0)	206 (84.8)
Geographic region, Asia (without Japan)	135 (57.0)	137 (56.4)
ECOG PS 0	216 (91.1)	213 (87.7)
HBV status – positive[a]	153 (64.6)	144 (59.3)
HCV status – positive[b]	42 (17.7)	39 (16.0)
Viral etiology[c]	179 (75.5)	167 (68.7)
Alcohol etiology	107 (45.1)	112 (46.1)
AFP ≤400 ng/mL	200 (84.4)	203 (83.5)
Child-Pugh score A5	204 (86.1)	217 (89.3)
BCLC stage[d]		
A	80 (33.8)	68 (28.0)
B	135 (57.0)	146 (60.1)
C	21 (8.9)	29 (11.9)
ALBI grade 1[e]	171 (72.2)	174 (71.6)
Tumor burden score[1,f]		
≤6	112 (47.3)	116 (47.7)
>6 and ≤12	120 (50.6)	117 (48.1)
>12	5 (2.1)	10 (4.1)

1. Wang Q et al. *J Hepatol*. 2019;70:893-903. [a]Defined as a positive result for anti-HBc, HBsAg or HBV DNA; 2 patients had missing HBV status in each treatment group. [b]3 patients had missing HCV status in the lenvatinib + pembrolizumab + TACE group. [c]4 patients in the lenvatinib + pembrolizumab + TACE group and 1 patient in the dual placebo + TACE group had missing viral etiology. [d]1 patient had BCLC stage 0 in the lenvatinib + pembrolizumab + TACE group. [e]1 patient had missing ALBI grade in the lenvatinib + pembrolizumab + TACE group; no patients had an ALBI grade of 3. [f]Largest tumor in centimeters + number of tumors. Data are n (%) unless otherwise noted. Data cutoff date for IA1: January 30, 2024.

Progression-Free Survival per RECIST v1.1 by BICR



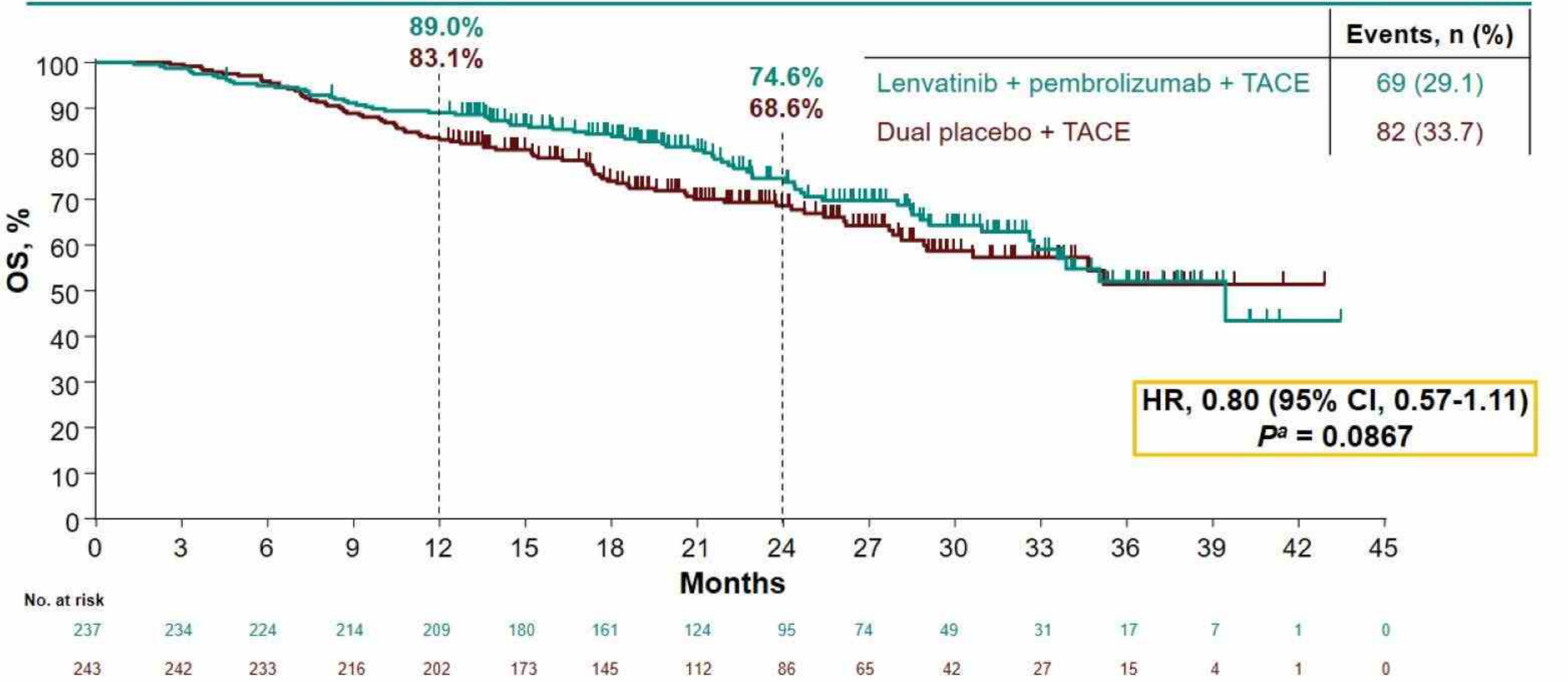
	Events, n (%)	Median (95% CI), months
Lenvatinib + pembrolizumab + TACE	132 (55.7)	14.6 (12.6-16.7)
Dual placebo + TACE	154 (63.4)	10.0 (8.1-12.2)

14.6 vs 10.0 mon

HR, 0.66 (95% CI, 0.51-0.84)
P^a = 0.0002

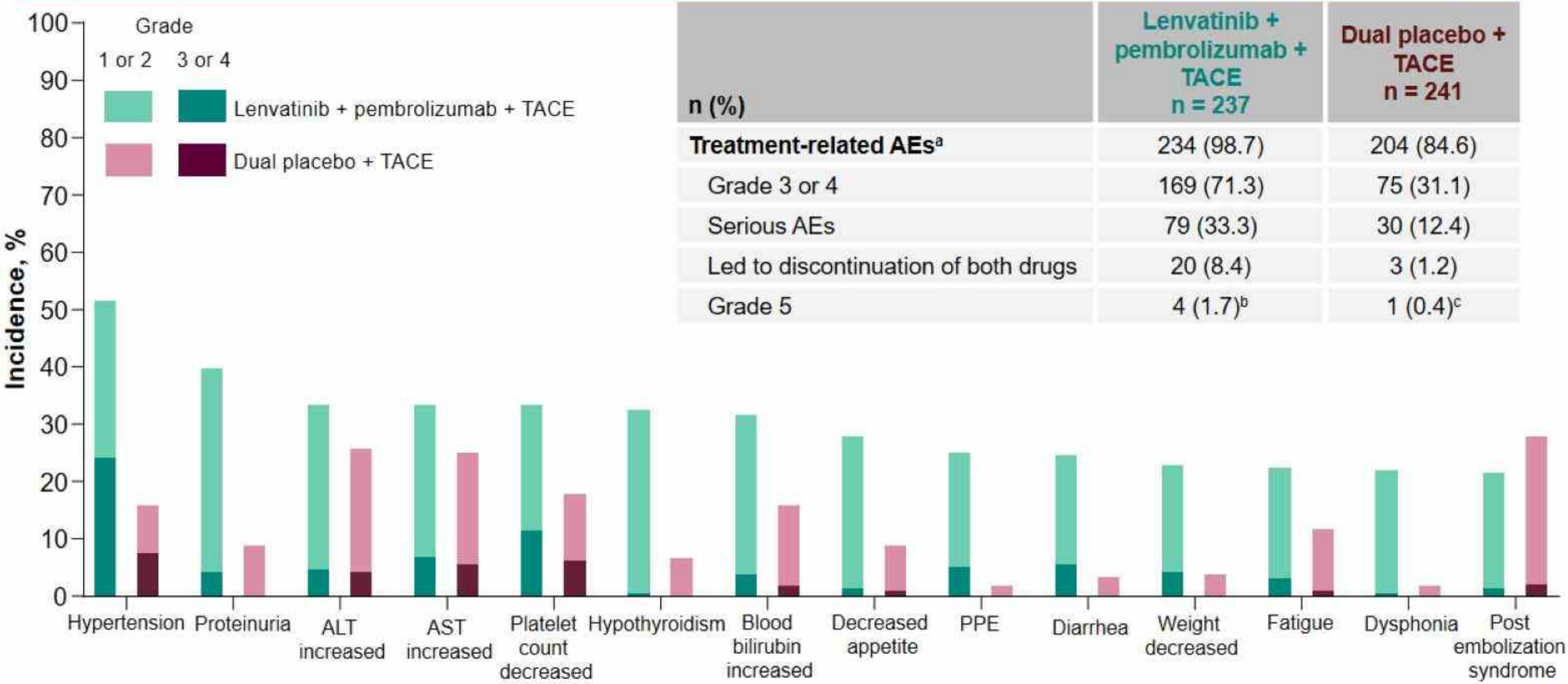
[a]One-sided *P* from re-randomization test; threshold *P* = 0.025. Data cutoff date for IA1: January 30, 2024.

Overall Survival



[a]One-sided *P* from re-randomization test; threshold *P* = 0.0012. Data cutoff date for IA1: January 30, 2024.

Most Common Treatment-Related Adverse Events[a] (≥25%)



n (%)	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 241
Treatment-related AEs[a]	234 (98.7)	204 (84.6)
Grade 3 or 4	169 (71.3)	75 (31.1)
Serious AEs	79 (33.3)	30 (12.4)
Led to discontinuation of both drugs	20 (8.4)	3 (1.2)
Grade 5	4 (1.7)[b]	1 (0.4)[c]

[a]Related to pembrolizumab, lenvatinib, and/or TACE. [b]1 patient each died from hepatic failure, gastrointestinal hemorrhage, myositis, and immune-mediated hepatitis. [c]1 patient died from brain stem hemorrhage.
Data cutoff date for IA1: January 30, 2024.

Response rate in EMRALD-1 and LEAP-012

- **EMRALD-1:**
  - The ORR was **43.6%** with durvalumab and bevacizumab, 41.0% with durvalumab, and 29.6% with TACE alone
  - The complete responses across the 3 arms were rare, with partial responses representing 40.6%, 39.5%, and 27.1% of responses in the durvalumab/ bevacizumab, durvalumab, and TACE-alone arms, respectively.
  - The median duration of response was 22.1 months, 14.0 months, and 16.4 months with durvalumab and bevacizumab, durvalumab, and TACE alone, respectively
- **LEAP-012 :**
  - The ORR was higher in the lenvatinib/ pembrolizumab /TACE arm - **46.8%,** with a **CR rate of 3.4%** and PR rate of 43.5%

Are there synergistic effects of combining immunotherapies with Y90-TARE?

EMERALD-Y90: A Phase 2 Study to Evaluate Transarterial Radioembolization Followed by Durvalumab and Bevacizumab for the Treatment of Unresectable Hepatocellular Carcinoma Eligible for Embolization

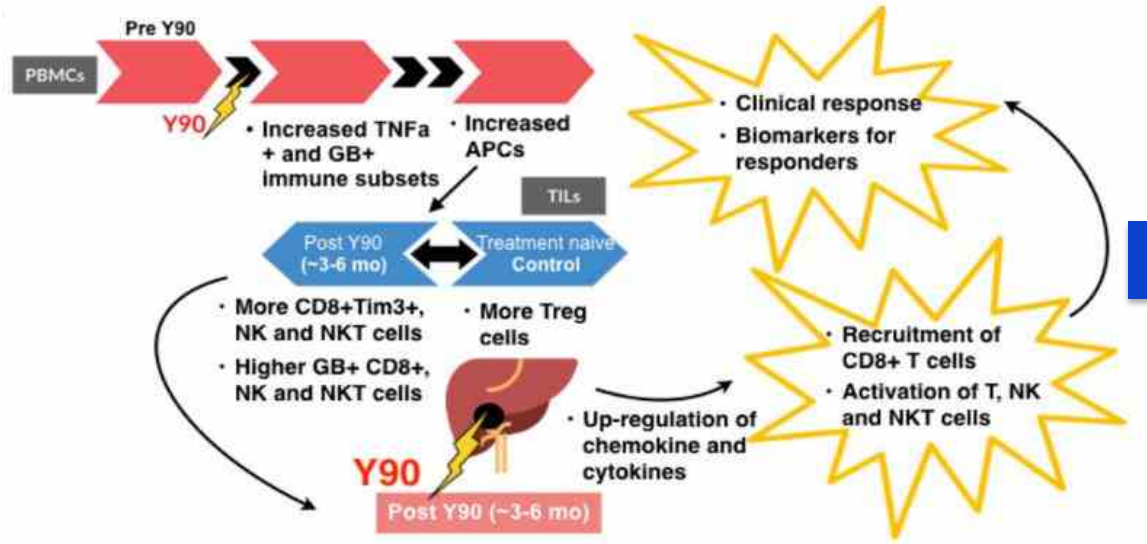
R. Iyer,[1] A. Noonan,[2] B. Spieler,[3] S. White,[4] L. Kulik,[5] D. Underwood,[6] E. Heilbron,[6] B. Nguyen,[6] G. Wetherill,[7] and R. Salem[8]; [1]*Roswell Park Cancer Institute, Buffalo, NY,* [2]*The Ohio State University Comprehensive Cancer Center, Columbus, OH,* [3]*University of Miami, Miami, FL,* [4]*Medical College of Wisconsin, Milwaukee, WI,* [5]*Northwestern Memorial Hospital, Chicago, IL,* [6]*AstraZeneca, Gaithersburg, MD,* [7]*AstraZeneca, Cambridge, United Kingdom,* [8]*Northwestern University, Chicago, IL*

Purpose/Objective(s): In people with hepatocellular carcinomas (HCC), reported median progression-free survival (PFS) following locoregional therapy (LRT; TACE or TARE) is less than one year, highlighting a need for additional treatment options. The Phase 3 EMERALD-1 study (NCT03778957) has shown a statistically significant improvement in PFS with durvalumab + bevacizumab + TACE versus TACE alone in participants (pts) with unresectable HCC (uHCC) eligible for embolization. However, an unmet need still exists for evidence to support additional treatment options in settings where TARE is the preferred treatment modality. The EMERALD-Y90 study evaluates the efficacy and safety of TARE with durvalumab monotherapy (one cycle), followed by durvalumab + bevacizumab in pts with uHCC eligible for embolization; the hypothesis is that this regimen will prolong PFS.

Materials/Methods: EMERALD-Y90 (NCT06040099) is a Phase 2, single-arm study that will enroll approximately 100 pts aged ≥18 years with uHCC (Child-Pugh class A with ECOG PS 0−1) amenable to embolization who are ineligible for, or who have declined treatment with, resection and/or ablation, or liver transplant. Exclusion criteria include having received prior LRT (previous TACE, TARE, or SBRT associated with the curative setting more than 6 months prior to study is permitted, and radiofrequency ablation is permitted if the target lesion was not treated or had subsequently progressed), prior systemic therapy, or having evidence of extrahepatic spread or major portal vein invasion (Vp3/Vp4). Eligible pts will receive partition-based dosing of TARE using Y-90 glass microspheres. Following TARE, pts will receive a single dose of durvalumab 1500 mg followed by durvalumab 1120 mg + bevacizumab 15 mg/kg every three weeks until study completion, disease progression, unacceptable toxicity, or another discontinuation criterion is met. The primary endpoint is PFS (time from

Y90-TARE and Immune Response

- **Higher total radiation doses** and **hypo-fractionation** of **external beam radiation** courses are associated with a greater anti-tumoral immune response.



Lee Y, et al. Blood. 2009;114:589–95.

↑PD-1^{+}/Tim- 3^{+} CD8^{+} T cells in Y90-RE responders

Chew V, et al. Gut. 2018;0:1–12.

- A **significant increase** in tumor-infiltrating lymphocytes (TILs), CD4+ and CD8+ T cells, and granzyme B was observed in resected HCC in Y90-RE*(n=12)* as compared to TACE*(n=16)* and SURG*(n=32)* groups.

Craciun et al. BMC Cancer (2020) 20:135.

Opportunity for synergies with Y90-TARE

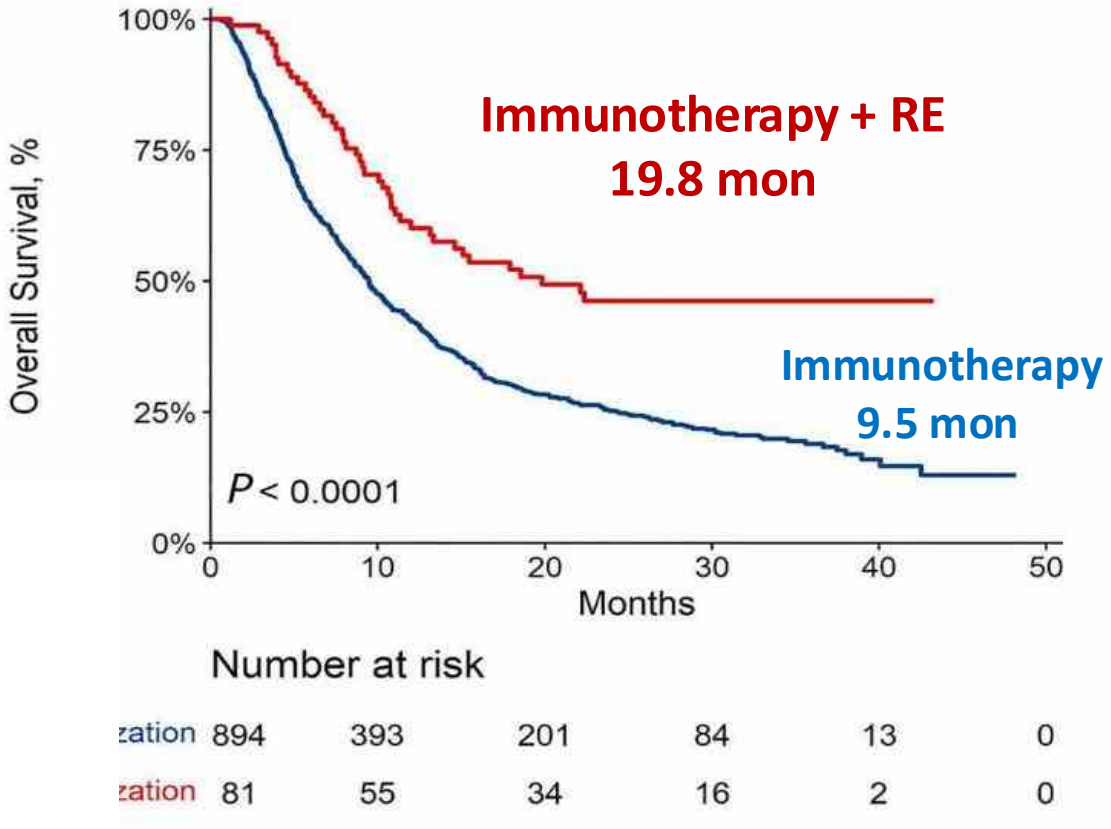
- Radiation therapy and VEGF inhibition have an established synergism with immunotherapy: **enhanced antigen presentation** and **reduced immunosuppressive immune** infiltrate.
- Combining ICI with VEGF blockade and 90Y-TARE might overcome primary resistances.
- Objective Response Rates (ORR) have increased and provided the opportunity for surgical resection of many unresectable cases
  - SIRT (Y90-RE): around 30% (RECIST 1.1, Phase III SIRveNIB)
  - Atezo+Bev: 30% (RECIST 1.1, Phase III IMBrave150)

Synergistic effect of SIRT-Y90 followed by atezolizumab + bevacizumab can enhance effectiveness by increasing anti-tumoral immune response and potentially further increase proportion of resectable HCC

Di Federico A et al. Expert Opin Investig Drugs. 2022;31(4):361-369.
Chew V et al. Gut. 2018;0:1–12.

The National Cancer Database
Patients with advanced HCC diagnosed between 2017~2019, who received combined therapy or immunotherapy alone as first-line treatment.

1,664 eligible patients with advanced-stage HCC
Combined TARE/immunotherapy(N=142) and Immunotherapy alone(N= 1,522)



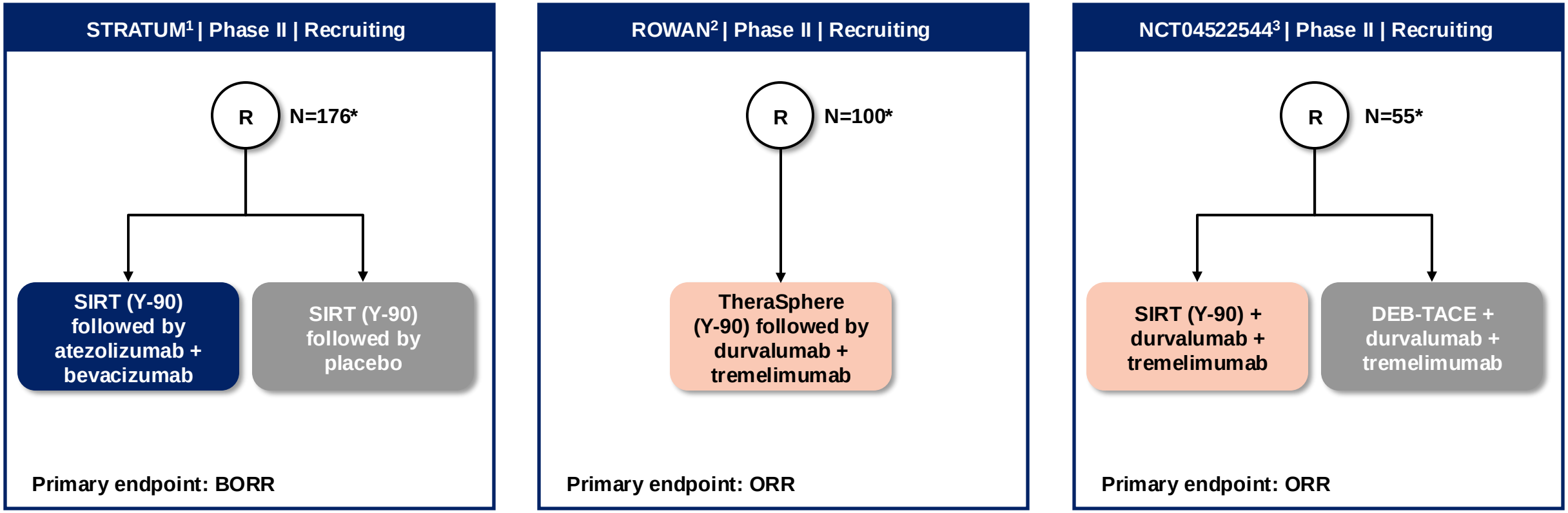
Characteristics	Multivariable	
	Adjusted OR (95% CI)	*P* value
Tumor size (every cm increase)	1.01 (1.00–1.02)	0.044
Treatment		
Immunotherapy only	Reference	
Immunotherapy and TARE	0.50 (0.36–0.68)	<0.001

Combined therapy was independently associated with reduced mortality *(adjusted hazard ratio 0.50, P< 0.001)*

Yeo YH et al. Am J Gastroenterol. 2023;118(12):2201-2211.

Key ongoing combination trials in intermediate-stage HCC with Y90

Y90 + immunotherapy



Information based on clinicaltrials.gov (accessed February 2024). *Estimated enrolment
BORR, best overall response rate; SIRT, selective internal radiation therapy

1. NCT05377034; 2. NCT05063565; 3. NCT04522544

Possibility of “cancer-free, drug-free” status in intermediate uHCC patients?

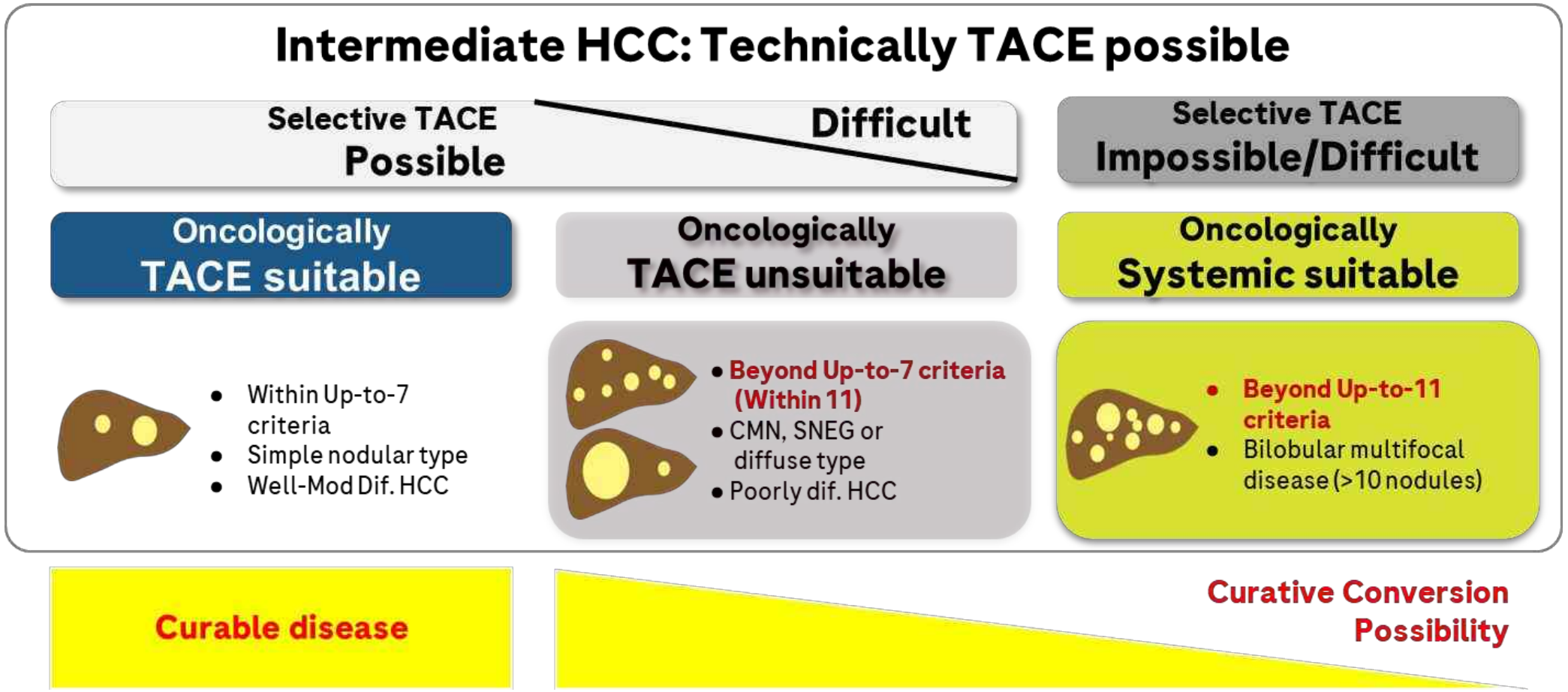
Definition of “clinical CR” and “drug-off criteria” in immunotherapy combined with locoregional therapy

Definition of clinical CR
Fulfilling the following 2 conditions 1. Achievement of CR per mRECIST/RECISTv1.1 evaluated by CT/MRI 2. Continuous normalization of 3 tumor markers (AFP/AFPL-3/PIVKA-II) more than 6 weeks
Drug-off criteria
Fulfilling the following 3 conditions 1. Achievement of CR per mRECIST (RECISTv1.1) by super-selective TACE/RFA/MWA 2. Continuous normalization of 3 tumor markers (AFP/AFP-L3/PIVKA-II) more than 12–24 weeks 3. Complete disappearance of intranodular arterial flow by CEUS

CR, complete response; AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein isoform, lectin affinity; PIVKA-II, protein induced by vitamin K absence or antagonist-II; CEUS, contrast-enhanced ultrasonography. Cited from Kudo et al. [22].

Liver Cancer. 2023 Jul 28;12(4):289-296.

Heterogeneity and possibility of curative conversion in intermediate-stage HCC



CMN, confluent multinodular type; SNEG, simple nodular with extra growth type

Kudo M, et al. Liver Cancer. 2023;12(4):321–338.

A multicenter proof-of-concept study: ABC conversion with TACE-unsuitable patients in intermediate-stage

TACE Unsuitable Intermediate-stage HCC

(1st line Atezo + Bev, Child-Pugh A, Consecutive cases; n=**110**)

Atezo + bev → Curative Conversion +/- Locoregional Tx/Op

Resection	7
Ablation (TACE→RFA/MWA)	13
TACE or LEN-TACE	15
Atezo + Bev only	3
TOTAL	**38**

Clinical complete response rate: **35%** (38/110)
Achievement of drug-free rate: **23%** (n=25/110)

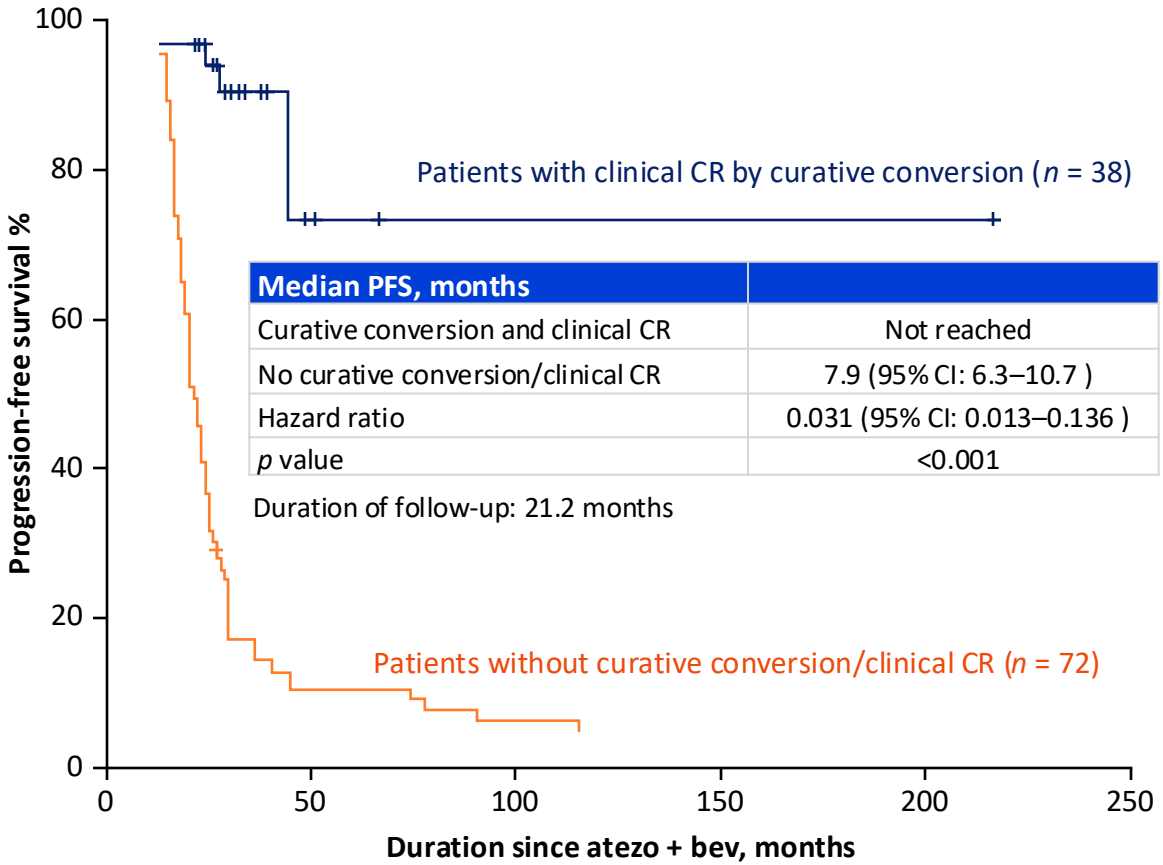
In 25 patients who achieved drug-free status, 7 received resection, 8 received ablation, 10 received super-selective TACE or LEN-TACE with curative intent.

ABC: atezo/bev followed by curative conversion; ABC conversion

Kudo M et al. Liver Cancer. 2023;12:321–338.

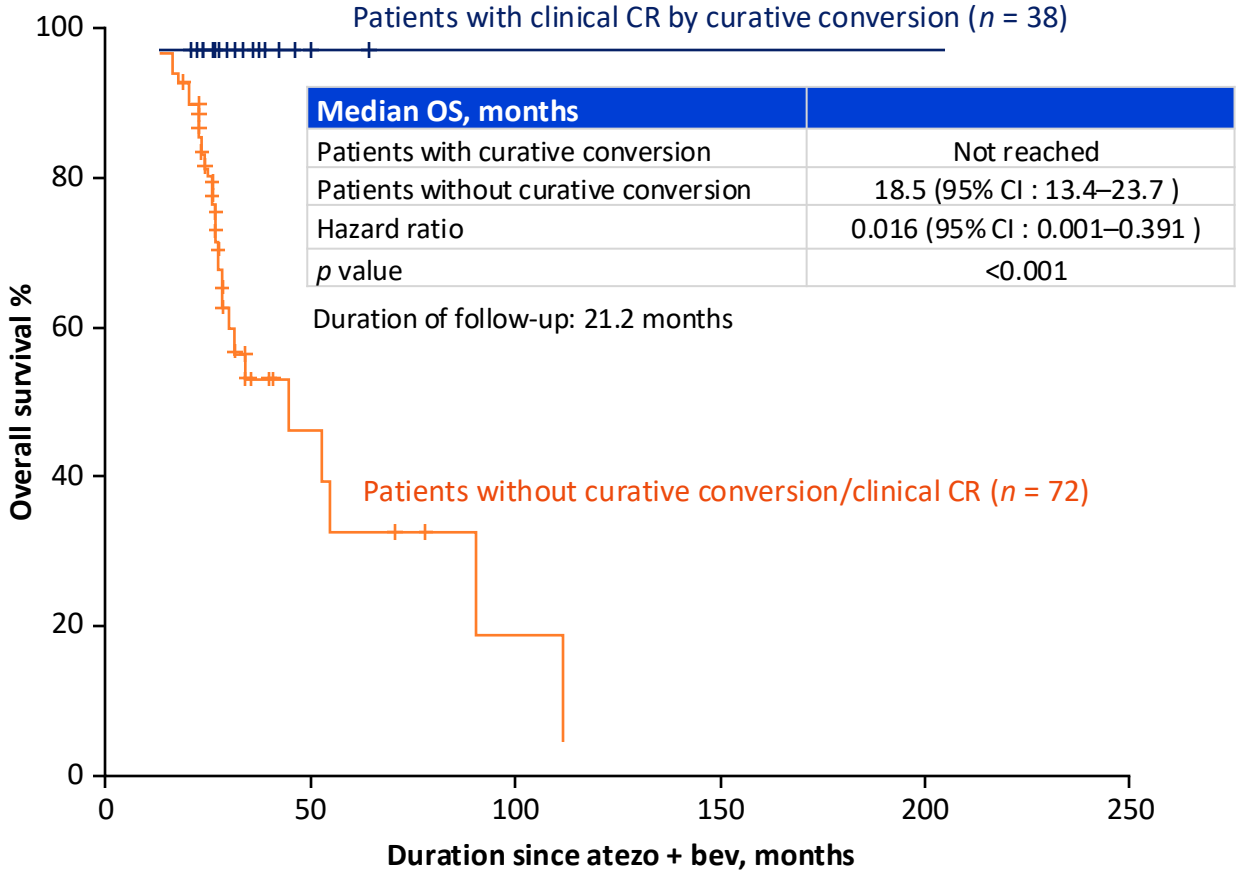
Median PFS and OS since atezo/bev initiation: with or without curative conversion

Median PFS and OS were both **not reached** after 21.2 months of follow up



Median PFS, months	
Curative conversion and clinical CR	Not reached
No curative conversion/clinical CR	7.9 (95% CI: 6.3–10.7)
Hazard ratio	0.031 (95% CI: 0.013–0.136)
p value	<0.001

Duration of follow-up: 21.2 months



Median OS, months	
Patients with curative conversion	Not reached
Patients without curative conversion	18.5 (95% CI : 13.4–23.7)
Hazard ratio	0.016 (95% CI : 0.001–0.391)
p value	<0.001

Duration of follow-up: 21.2 months

Kudo M et al. Liver Cancer. 2023;12:321–338.

Response to atezolizumab + bevacizumab treatment

An open-label, multicentre, phase 1b study

Tumor assessment was conducted **every 8 weeks**

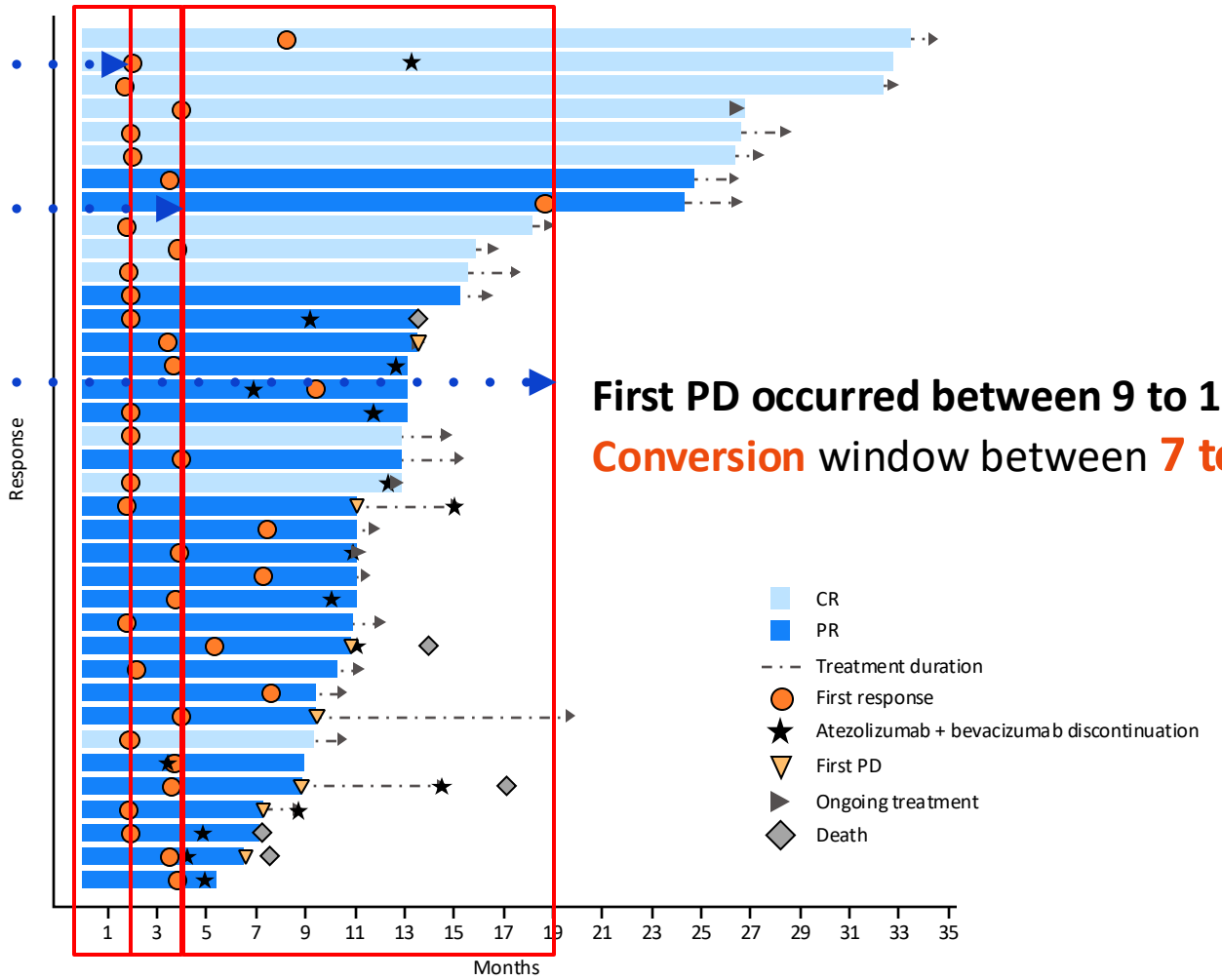
1st response in 2 months: **17/37=45%**

1st response Btw 2nd to 4th months: **13/37=35%**

SD but CR/PR after 5th to 19th months: **7/37= 20%**

80% responded in 16 weeks

20% late responders



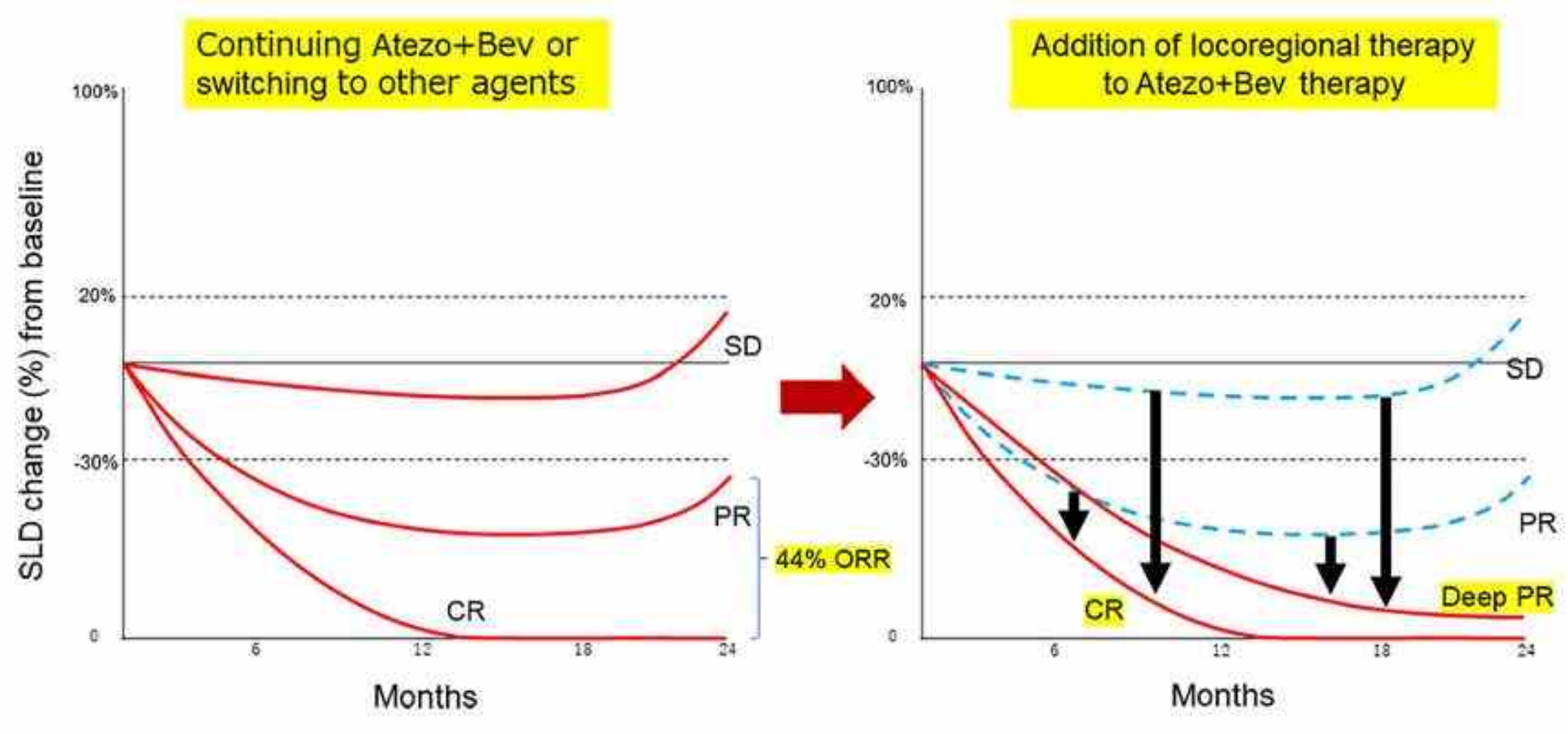
First PD occurred between 9 to 12 months

Conversion window between **7 to 9 months**?

PD, progressive disease

Lee et al. Lancet Oncol. 2020;21:808–820.

Effect of adding locoregional therapy to systemic therapy in intermediate-stage HCC

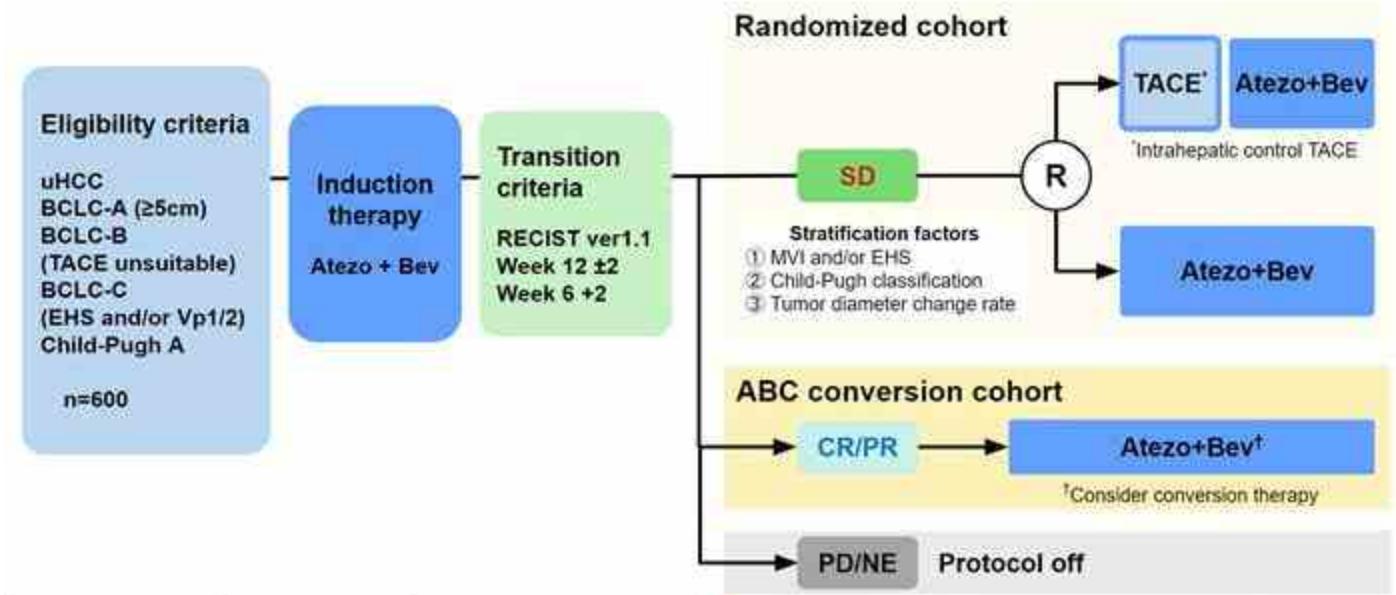


Liver Cancer. 2023 Jul 28;12(4):289-296.

Phase 3 RCT IMPACT: Efficacy of Atezolizumab plus Bevacizumab in combination with TACE for uHCC

Objective

- To evaluate whether **the addition of TACE to Atezo plus Bev** improves OS **in patients with SD** (RECIST v1.1) after Atezo-Bev.
- To investigate the proportion of patients who achieve disease free (mRECIST CR) with the addition of **curative conversion** and the prognosis of patients who had CR or PR on imaging assessment after Atezo-Bev



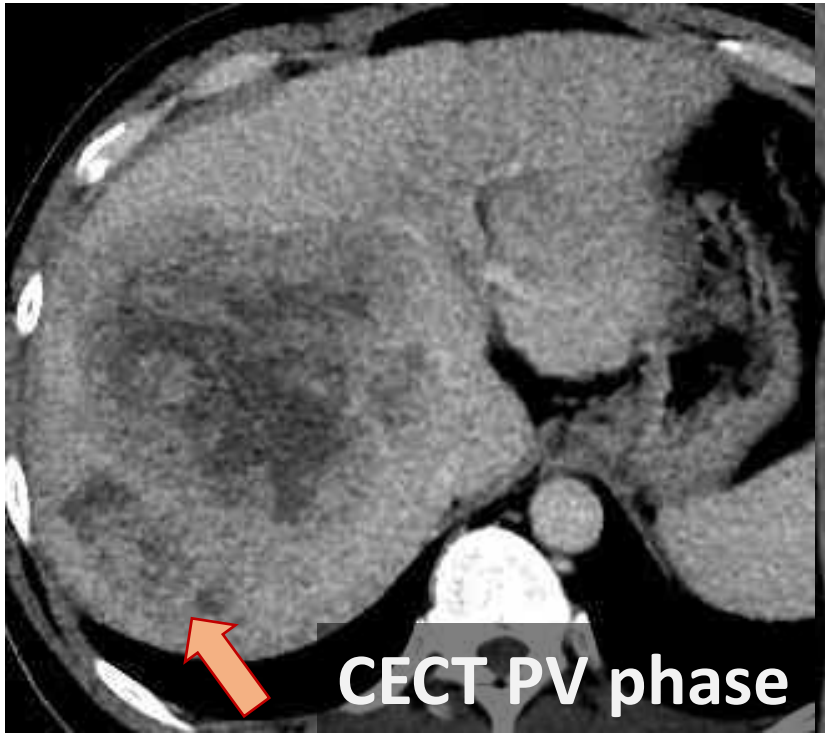
	Primary endpoint	Secondary endpoint
Randomized cohort (patients with SD)	OS	PFS, ORR, DOR, time to CR, conversion rate, safety
Conversion cohort (patients with CR or PR)	Conversion rate	OS, PFS, ORR, DOR, time to CR, safety

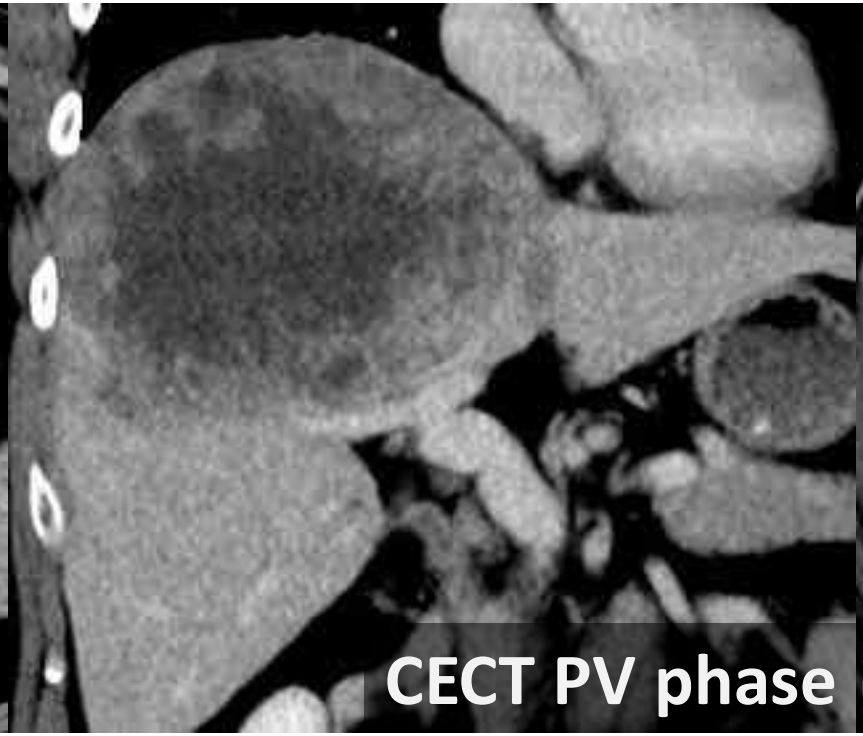
- **Planned enrollment:** 600 patients in the induction phase and 315 patients in the randomized cohort at 100 sites
- **Registration period:** 2.5 years
- **Follow-up period:** 2.5 years from the last enrollment date

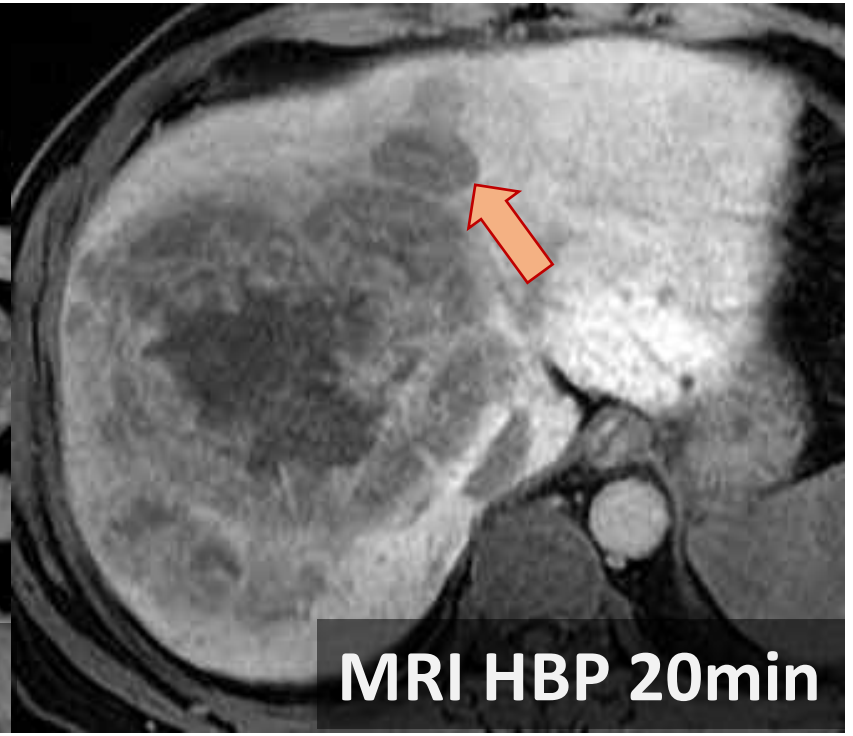
iver Cancer. 2024;13(3):227-234.

50/M, chronic HBV infection, BCLC B (but suspected Rt Vp1-2 invasion), 13cm tumor(main), AFP 7283 ng/mL, Child-Pugh A

Aug, 2022





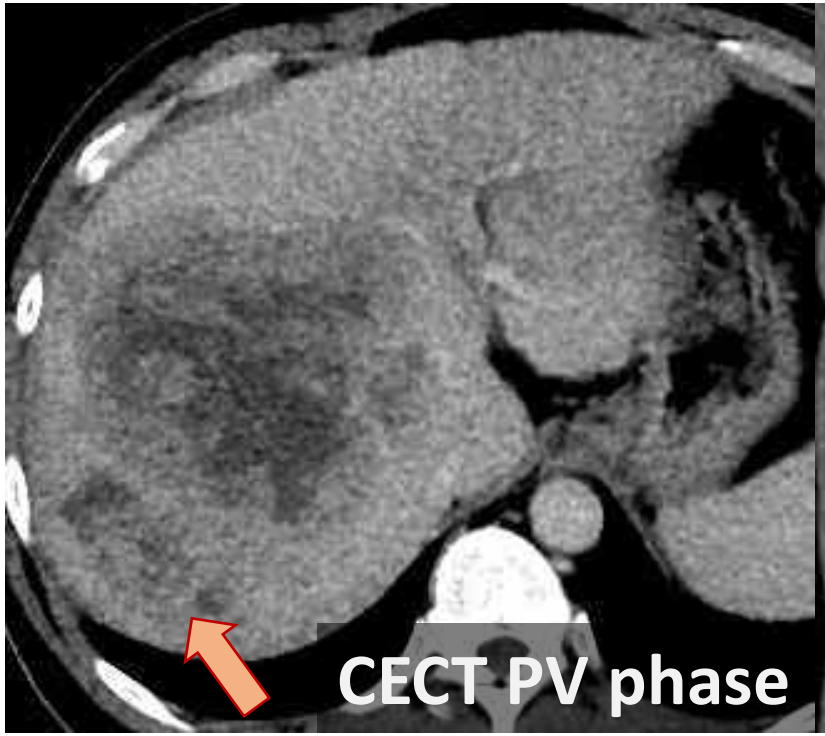


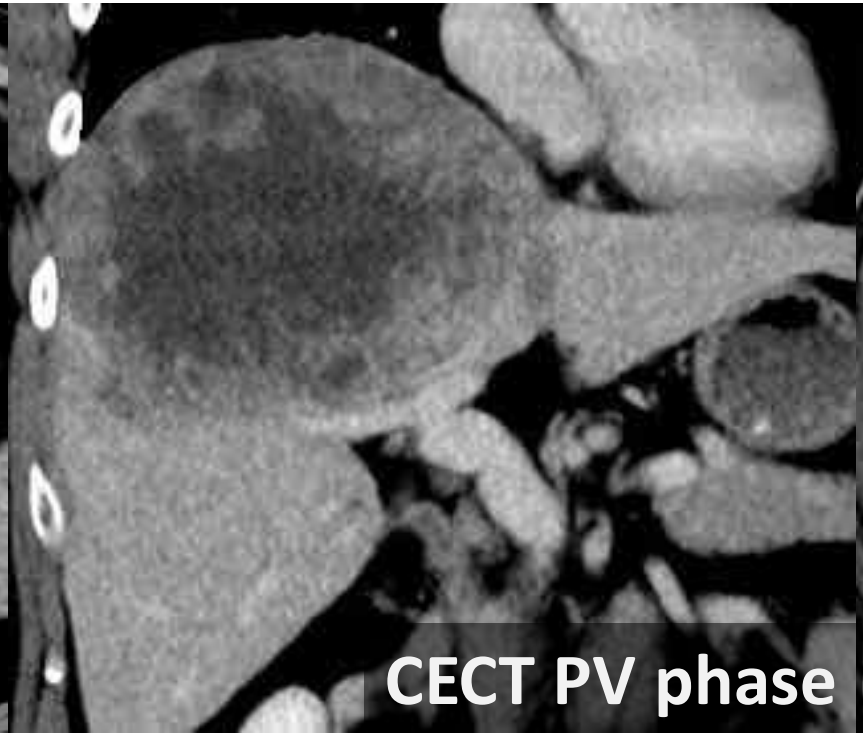
50/M, chronic HBV infection, BCLC B (but suspected Rt Vp1-2 invasion), 13cm tumor(main), AFP 7283 ng/mL, Child-Pugh A

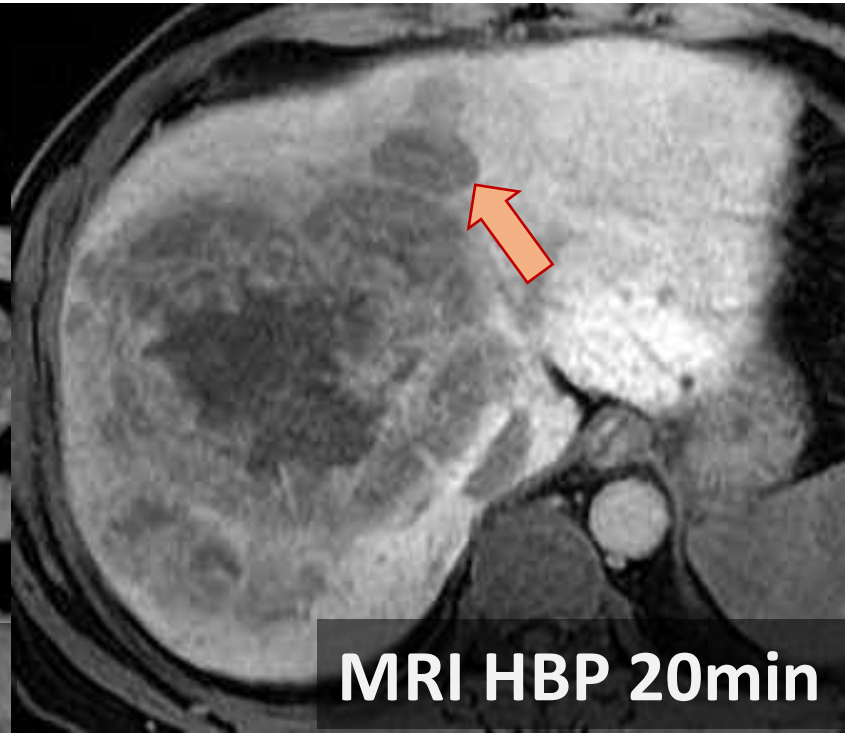
Proton therapy 4/10 Fr

+

Aug, 2022 **Atezo+Beva C1(Aug, 2022) ~ C4(March, 2023)**

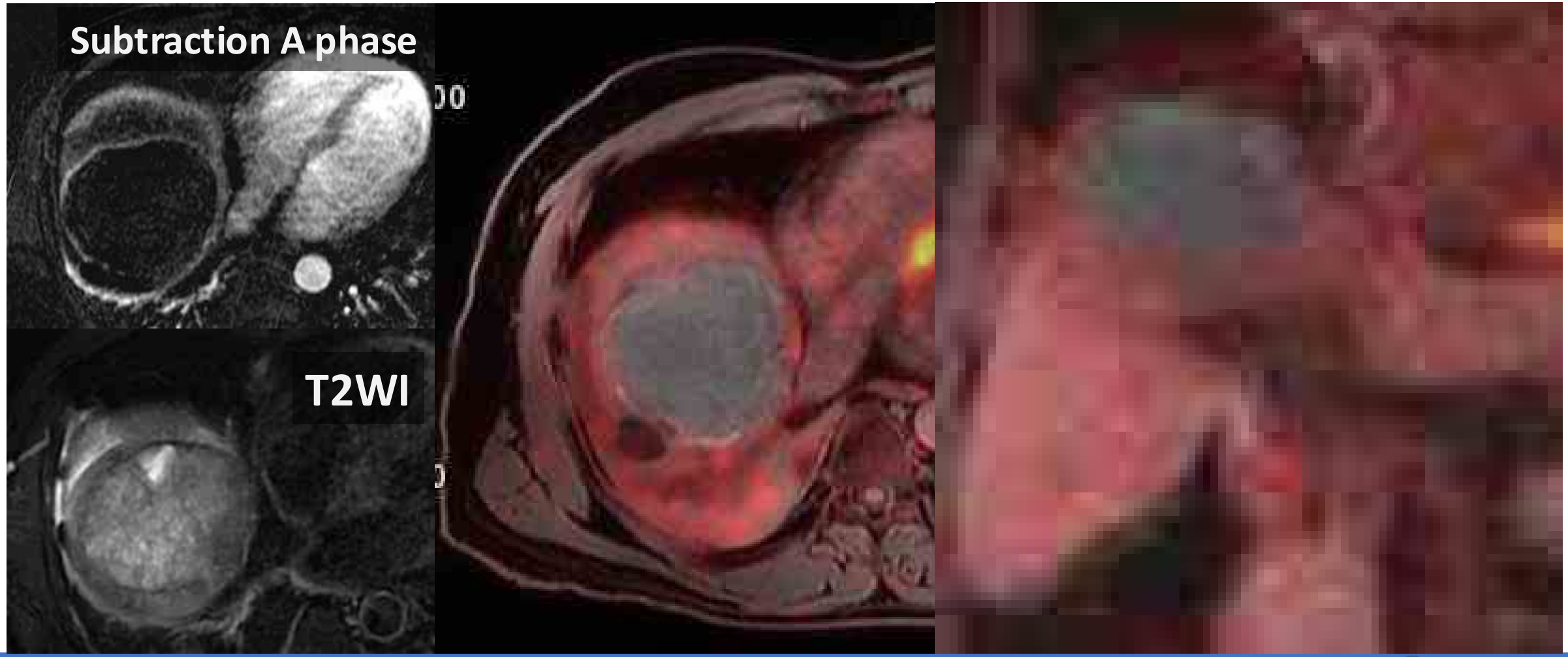


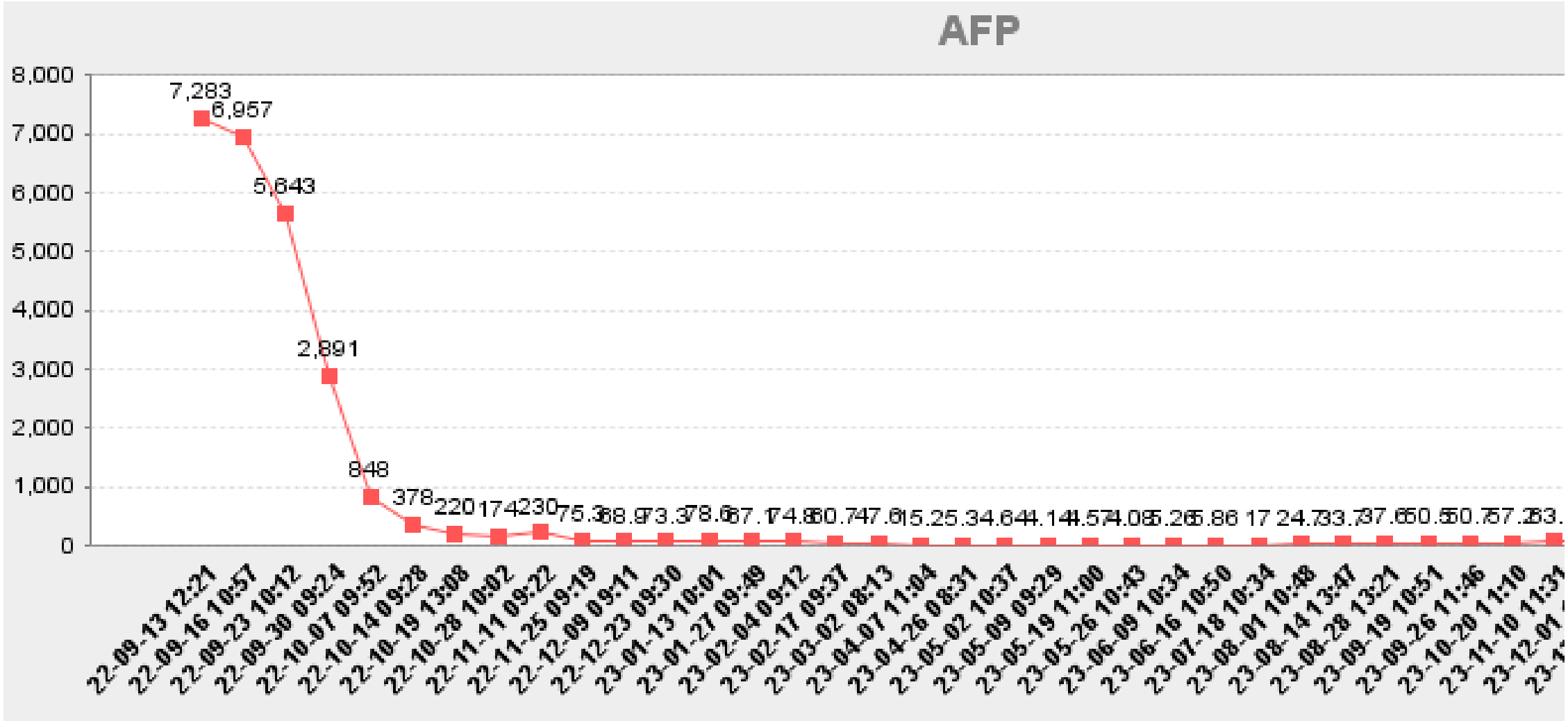




Dec, 2022

Mar, 2023




AFP
8,000
7,000
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6,957
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2,891
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75.3
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22-09-23 10:12
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22-12-23 09:30
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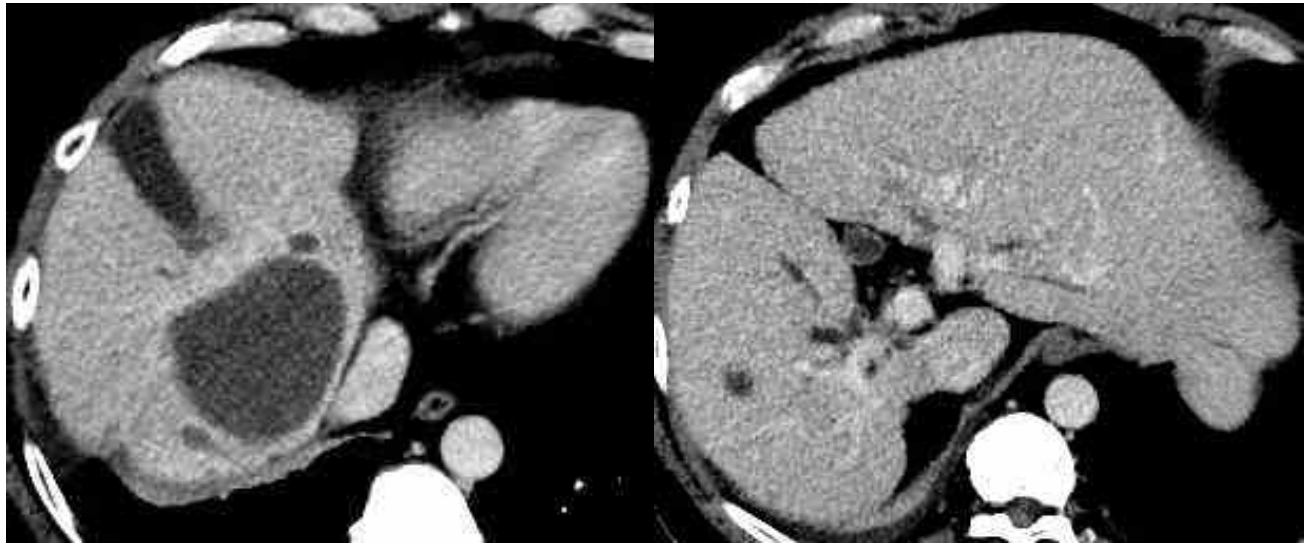
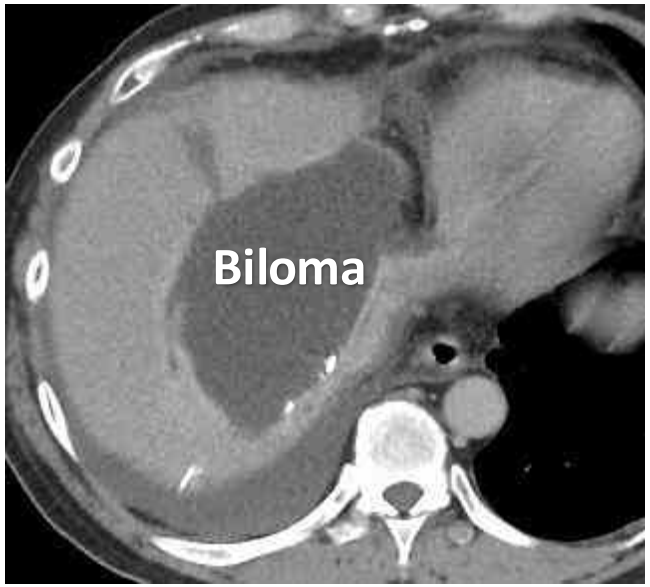
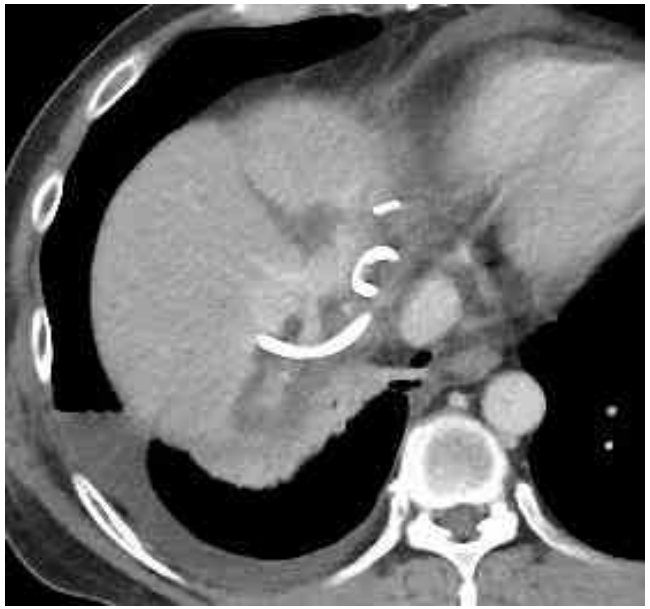
Nov, 2023





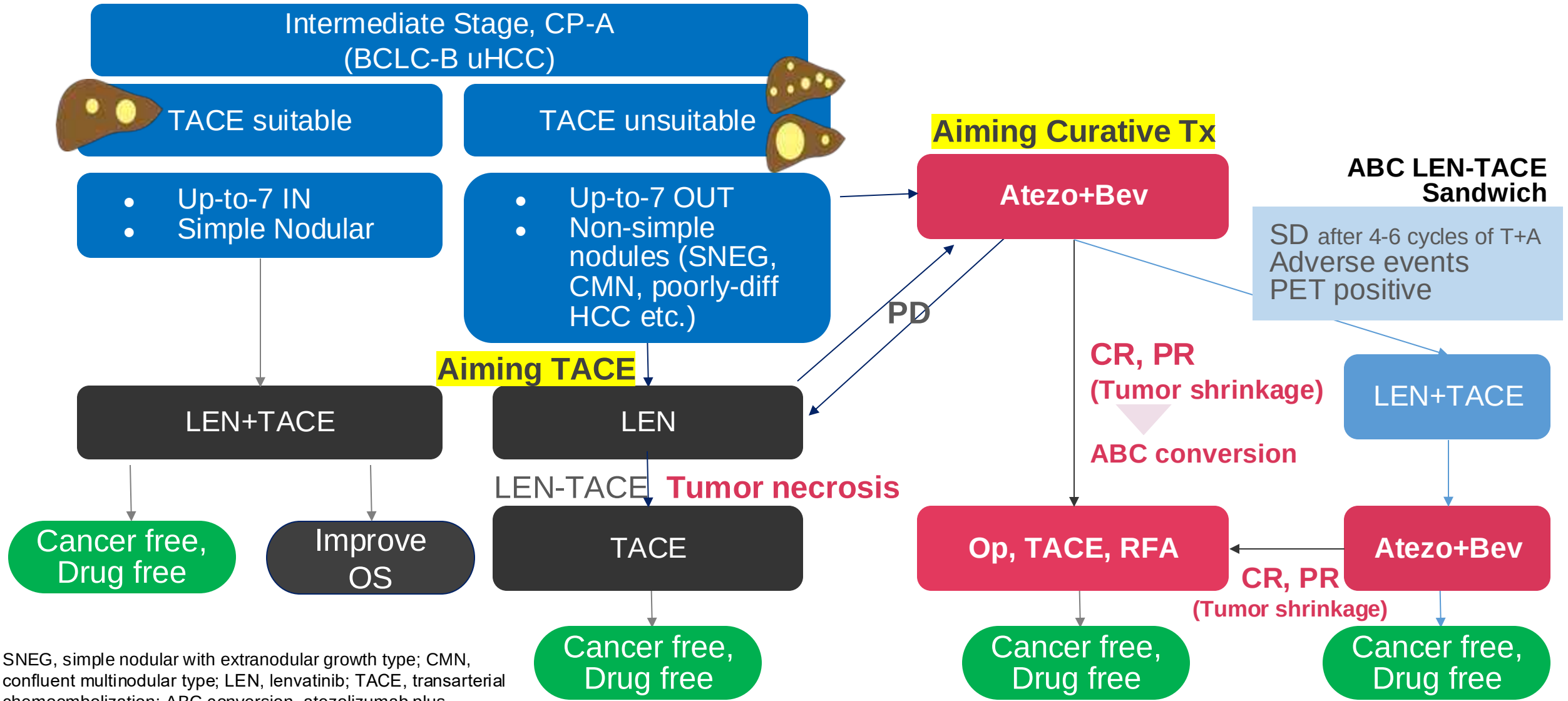


Hand-assisted laparoscopic S4/5/8segmentectomy + cholecystectomy in Dec, 2023 ***(after 8 months of stop A+B)***

MICROSCOPIC FINDING:

Sections of the segment 4/5/8 liver tissue show a completely necrotic tumor. **No viable tumor cells are observed.** Coupled with clinical information, it can be compatible with hepatocellular carcinoma status post therapy with total necrosis.

Systemic-LRT sequence could enable curative conversion for TACE unsuitable patients : New Paradigm Treatment Strategy



SNEG, simple nodular with extranodular growth type; CMN, confluent multinodular type; LEN, lenvatinib; TACE, transarterial chemoembolization; ABC conversion, atezolizumab plus bevacizumab followed by curative conversion therapy

1. Kudo M. Liver Cancer. 2022;11(5):399–406. 2. Kudo M. Liver Cancer. 2023;12:395–404.

Conclusion

- **TACE Suitability and Treatment Evolution**
  - Not all intermediate-stage HCC patients are suitable for TACE
  - Unsuitable tumors: beyond the Up-to-7 criteria, complex tumor types
- **Immunobiologic Potential of TACE and Y90-RE**
  - Not only act as a local treatment but also stimulate systemic anti-tumor immunity
  - This immunologic activation provides a strong rationale for combining locoregional treatments
- **Systemic and Locoregional Therapy Combination**
  - A new paradigm treatment strategy for TACE-unsuitable patients involves combining systemic therapies like Atezo+Bev with locoregional treatments (e.g., LEN+TACE). This combination aims for tumor shrinkage, allowing for potential curative conversion.
- **Challenges with achieving cancer free and drug free status**
  - To achieve curative conversion
  - Long-term Effects and Survivorship
  - Predictive or monitoring Biomarkers
  - Multidisciplinary Approach

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