Data You Should Know: Most Influential Publications Over the Past Year

Ziv J Haskal, FSIR

Professor of Radiology/IR Division

Editor in Chief, *JVIR*

Disclosures

Ziv Haskal, FSIR: Consultant – Becton Dickinson, WL Gore and Associates, Boston Scientific, Medtronic, Varian; Grant/Research Support –Bluegrass Medical, Ethicon

Brand names are included in this presentation for participant clarification purposes only.

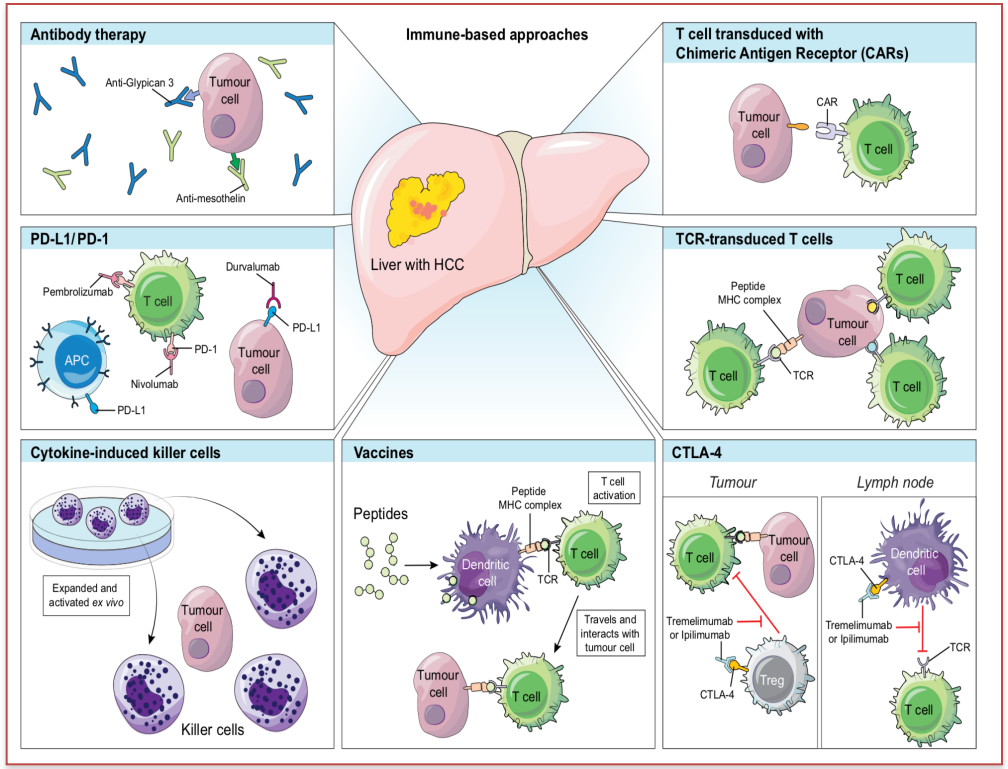
No product promotion should be inferred.

In a short time…

- I'll highlight a variety of relevant oncology papers that I would suggest bear familiarity and close reading.
- I'll assume that we already all read the IR journals, so my focus is to source from *non-IR journals, specifically.*

Atezolizumab for Unresectable HCC

- Two trials: NEJM (July 2020) and Lancet Oncology (June 2020)
- Angiogenesis (and immune evasion) are notable in HCC – hypervascular, high VEGF
- PD-L1-PD-1 immune checkpoint inhibitors enhance tumor specific T-cell responses
- Phase 3 trials had not convincingly shown clinical benefit to HCC patients (CheckMate 040/459, Keynote-224/ 240)



Approved First-Line Options (for Medical Care of Unresectable HCC) Have Been…

- Multikinase inhibitors like sorafenib, levantinib (targeting VEGF angiogenic pathways)
- Mild HCC effect has occurred with solo bevacizumab (which is also immunomodulatory in other cancer combos)

- …Hence testing of atezolizumab and bevaz for stronger combined anti-tumor immune responses

Cohort Demographics

Majority (78–88%) of enrollees had **extrahepatic disease**, **macrovascular invasion**, or both → *high burden of disease*

	Group A: atezolizumab plus bevacizumab (n=104)	Group F	
		Atezolizumab plus bevacizumab (n=60)	Atezolizumab monotherapy (n=59)
Median age, years	62 (23–82)	60 (22–82)	63 (23–85)
18–40	6 (6%)	3 (5%)	2 (3%)
41–64	61 (59%)	36 (60%)	32 (54%)
≥65	37 (36%)	21 (35%)	25 (42%)
Sex			
Male	84 (81%)	54 (90%)	49 (83%)
Female	20 (19%)	6 (10%)	10 (17%)
Ethnicity			
White	20 (19%)	14 (23%)	9 (15%)
Asian	75 (72%)	45 (75%)	47 (80%)
Black or African American	7 (7%)	1 (2%)	2 (3%)
Native Hawaiian or other Pacific Islander	0	0	1 (2%)
Unknown	2 (2%)	0	0
Geographical region			
Asia excluding Japan	59 (57%)	39 (65%)	39 (66%)
Rest of the world*	45 (43%)	21 (35%)	20 (34%)

Lancet Oncology (June 2020)

	Group A: atezolizumab plus bevacizumab (n=104)	Group F	
		Atezolizumab plus bevacizumab (n=60)	Atezolizumab monotherapy (n=59)
(Continued from previous page)			
ECOG performance status			
0	52 (50%)	27 (45%)	25 (42%)
1	52 (50%)	33 (55%)	34 (58%)
Child-Pugh score			
A5	77 (74%)	43 (72%)	42 (71%)
A6	21 (20%)	17 (28%)	17 (29%)
A7	6 (6%)	0	0
Barcelona Clinic Liver Cancer stage			
A4	0	0	2 (3%)
B	10 (10%)	6 (10%)	4 (7%)
C	94 (90%)	54 (90%)	53 (90%)
α-Fetoprotein at baseline ≥400 ng/mL	37 (36%)	18 (30%)	19 (32%)
Present macrovascular invasion	55 (53%)	20 (33%)	25 (42%)
Present extrahepatic spread	74 (71%)	40 (67%)	39 (66%)
Present macrovascular invasion or extrahepatic spread	91 (88%)	47 (78%)	50 (85%)
Bile duct invasion	5 (5%)	0	2 (3%)
Main portal vein invasion	14 (13%)	6 (10%)	5 (8%)
Liver occupancy ≥50%	10 (10%)	2 (3%)	3 (5%)
Cause of hepatocellular carcinoma			
Hepatitis B virus	51 (49%)	34 (57%)	32 (54%)
Hepatitis C virus	31 (30%)	11 (18%)	10 (17%)
Non-viral†	22 (21%)	15 (25%)	17 (29%)
Alcohol use			
Current	14 (13%)	7 (12%)	6 (10%)
Never	32 (31%)	14 (23%)	21 (36%)
Previous	58 (56%)	39 (65%)	32 (54%)

Endpoints:

Lancet Oncology (June 2020)

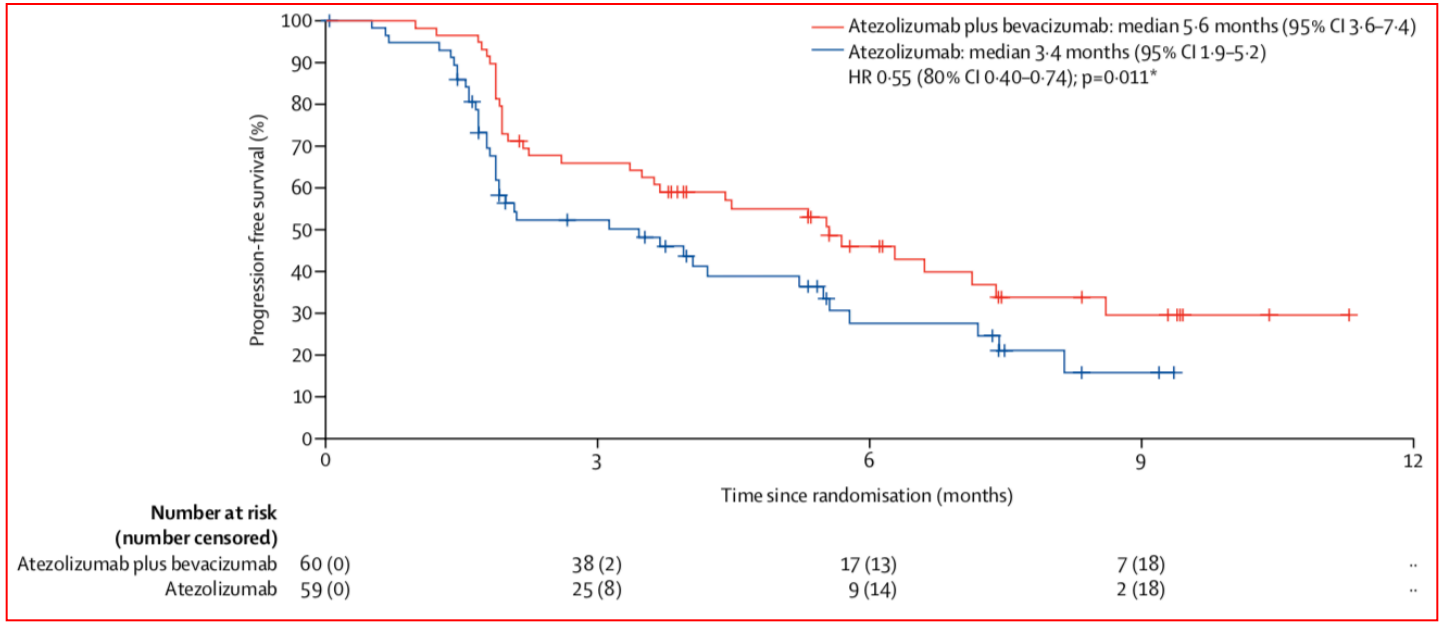
- Objective Response Rate, RECIST 1.1, mRECIST, PFS
- Tolerable safety profile

	Independent review facility-assessed (RECIST 1.1)		Independent review facility-assessed (mRECIST)		Investigator-assessed (RECIST 1.1)	
	Atezolizumab plus bevacizumab (n=60)	Atezolizumab monotherapy (n=59)	Atezolizumab plus bevacizumab (n=60)	Atezolizumab monotherapy (n=59)	Atezolizumab plus bevacizumab (n=60)	Atezolizumab monotherapy (n=59)
Median progression-free survival, months (95% CI)	5·6 (3·6–7·4)	3·4 (1·9–5·2)	5·6 (3·6–7·4)	3·4 (1·9–5·2)	5·7 (3·5–9·3)	2·0 (1·9–3·7)
Hazard ratio (80% CI)*	0·55 (0·40–0·74)†	..	0·54 (0·40–0·74)	..	0·44 (0·33–0·60)	..
Events	35 (58%)	39 (66%)	34 (57%)	39 (66%)	35 (58%)	44 (75%)
Confirmed objective response, % (95% CI)	20% (11–32)	17% (8–29)	27% (16–40)	17% (8–29)	13% (6–25)	9% (3–19)
Complete response	1 (2%)	3 (5%)	3 (5%)	3 (5%)	0	0
Partial response	11 (18%)	7 (12%)	13 (22%)	7 (12%)	8 (13%)	5 (8%)
Stable disease	28 (47%)	19 (32%)	25 (42%)	19 (32%)	33 (55%)	20 (34%)
Progressive disease	17 (28%)	25 (42%)	16 (27%)	25 (42%)	17 (28%)	31 (53%)
Disease control‡	40 (67%)	29 (49%)	41 (68%)	29 (49%)	41 (68%)	25 (42%)
Median duration of response, months (95% CI)	Not reached (NE)	Not reached (3·7–NE)	Not reached (NE)	Not reached (3·7–NE)	Not reached (5·5–NE)	Not reached (NE)
Median time to radiographic progression, months (95% CI)	5·6 (3·7–NE)	3·1 (1·9–5·5)	5·6 (3·7–NE)	3·1 (1·9–5·5)	7·5 (3·8–9·4)	2·0 (1·9–3·7)

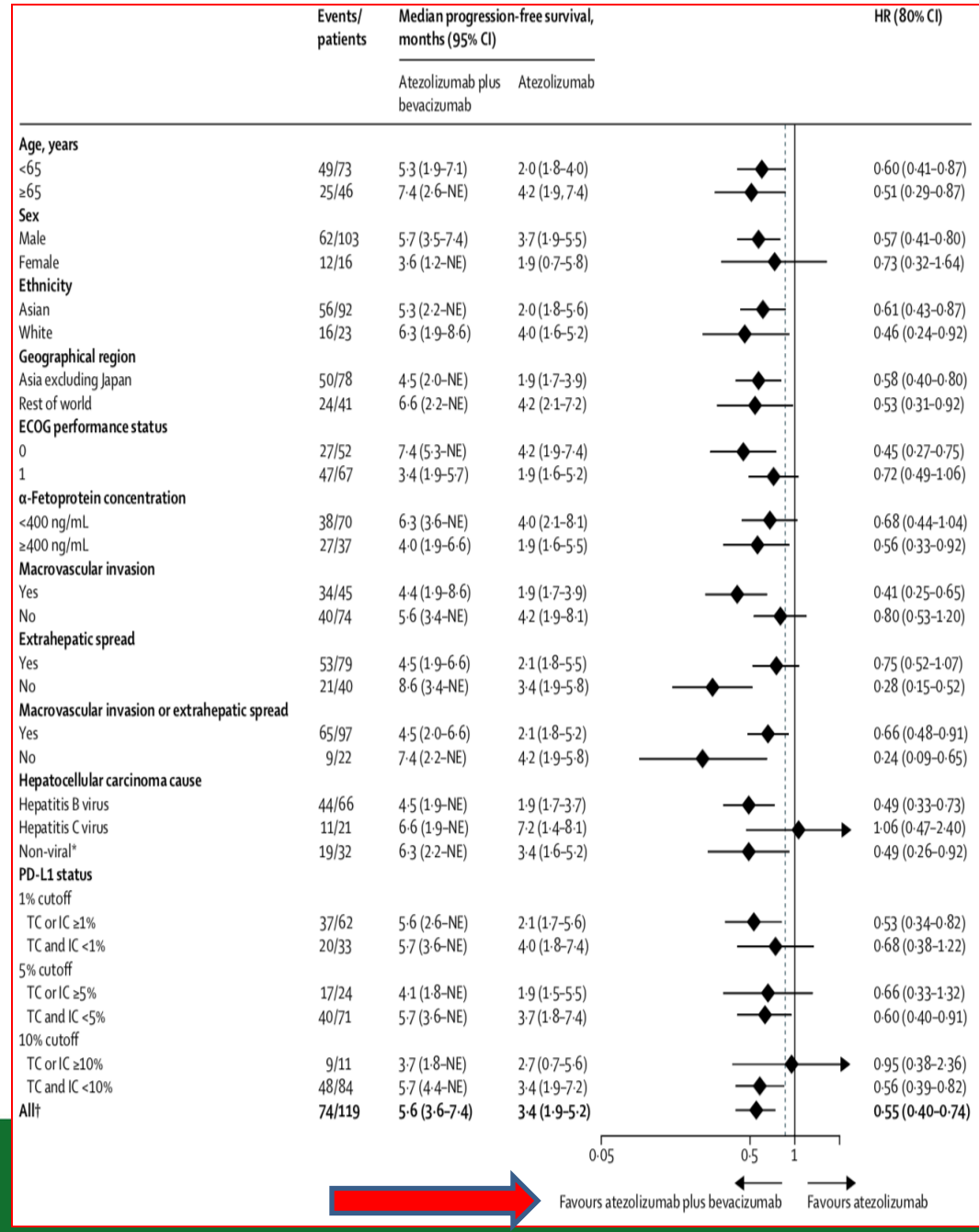
Data are n (%) unless otherwise specified. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. mRECIST=hepatocellular carcinoma-specific modified RECIST. NE=not estimable. *Stratified. †p=0·011. ‡Disease control is the sum of complete response, partial response, and stable disease.

Median overall survival was not reached in either treatment group (atezo + beva: 95% CI 8·3 months to not estimable; atezo mono-Rx : 8·2 months to not estimable)

16 (27%) of 60 patients in the combination therapy group died, and 18 (31%) of 59 in the monotherapy group died *by* the data cutoff



- ORR (36% group A) & disease control rates (71% in group A) in atezo + beva pts were clinically meaningful
- 1º PFS endpoint was met (in group F) → significant/clinically meaningful improvement of 2·2 months in median PFS
- reduction in risk of progression or death with atezo + beva compared with atezo-monoRx.

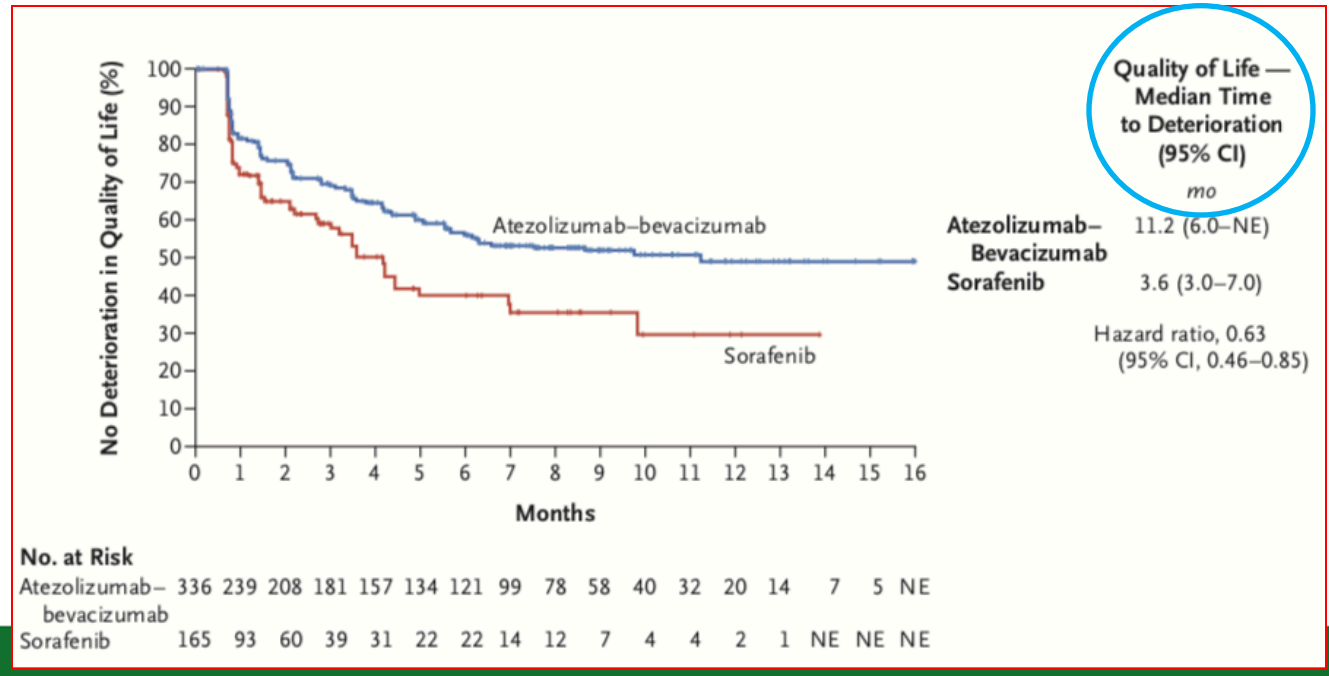


Atezolizumab plus Bevacizumab ('IMBrave150') in Unresectable Hepatocellular Carcinoma NEJM May 2020

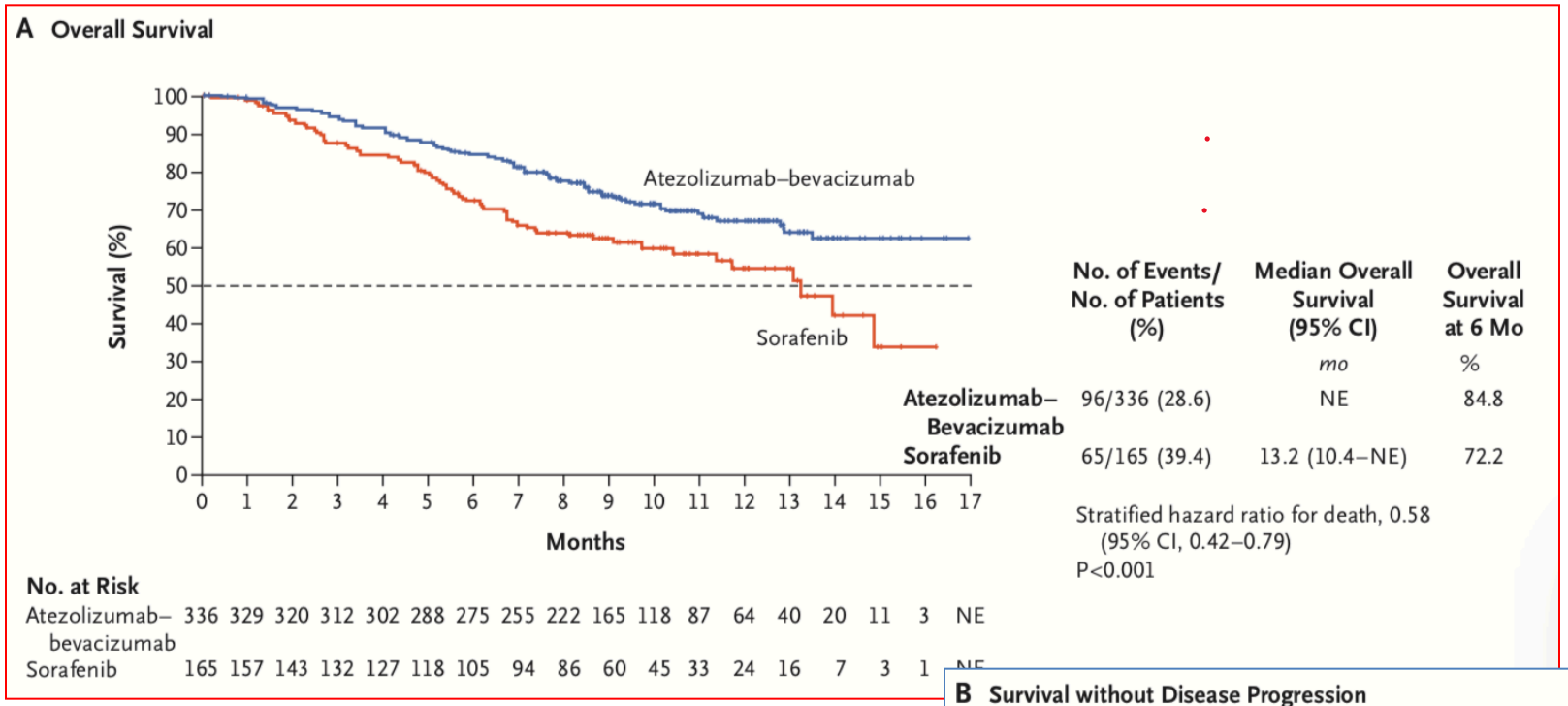
Table 1. Patient Characteristics at Baseline.*

Variable	Atezolizumab–Bevacizumab (N=336)	Sorafenib (N=165)
Median age (IQR) — yr	64 (56–71)	66 (59–71)
Male sex — no. (%)	277 (82)	137 (83)
Geographic region — no. (%)		
Asia, excluding Japan	133 (40)	68 (41)
Rest of the world†	203 (60)	97 (59)
ECOG performance status score — no. (%)‡		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child–Pugh classification — no./total no. (%)§		
A5	239/333 (72)	121/165 (73)
A6	94/333 (28)	44/165 (27)
Barcelona Clinic liver cancer stage — no. (%)¶		
A	8 (2)	6 (4)
B	52 (15)	26 (16)
C	276 (82)	133 (81)
Alpha-fetoprotein ≥400 ng per milliliter — no. (%)	126 (38)	61 (37)
Presence of macrovascular invasion, extrahepatic spread, or both — no. (%)	258 (77)	120 (73)
Macrovascular invasion	129 (38)	71 (43)
Extrahepatic spread	212 (63)	93 (56)
Varices — no. (%)		
Present at baseline	88 (26)	43 (26)
Treated at baseline	36 (11)	23 (14)
Cause of hepatocellular carcinoma — no. (%)		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Nonviral‖	100 (30)	53 (32)
Prior local therapy for hepatocellular carcinoma — no. (%)	161 (48)	85 (52)

- 2:1 randomization
- 73-77% macrovasc invasion &/or extrahep spread
- 93% compliance with QOL questions (from start to cycle 17)



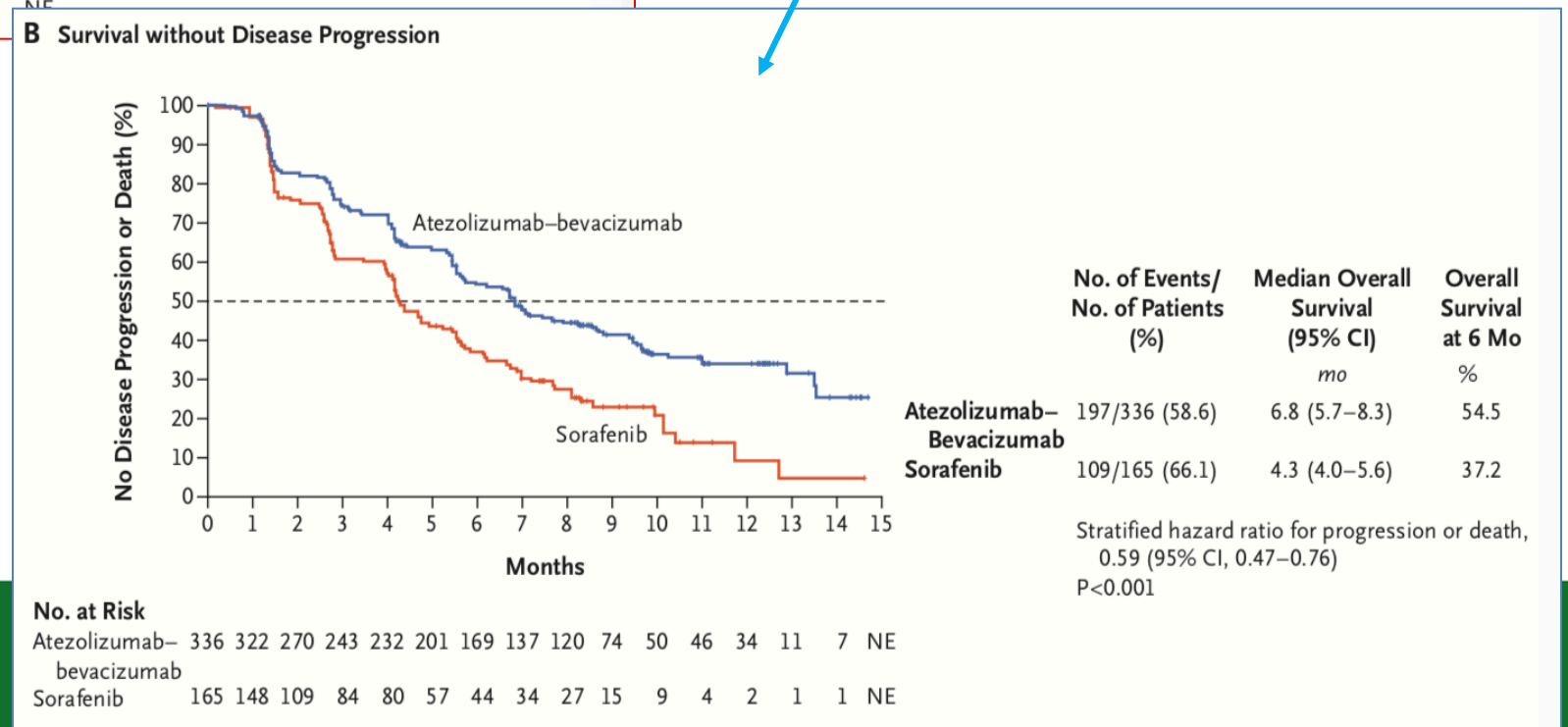
NEJM May 2020



	No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI)	Overall Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death, 0.58 (95% CI, 0.42–0.79)
P<0.001

Note early separation of curves persisted



	No. of Events/ No. of Patients (%)	Median Overall Survival (95% CI)	Overall Survival at 6 Mo
		mo	%
Atezolizumab–Bevacizumab	197/336 (58.6)	6.8 (5.7–8.3)	54.5
Sorafenib	109/165 (66.1)	4.3 (4.0–5.6)	37.2

Stratified hazard ratio for progression or death, 0.59 (95% CI, 0.47–0.76)
P<0.001

- Significantly better overall survival and PFS outcomes with atezo + beva vs. sorafenib (no previous systemic Rx)
- Benefit was generally consistent across clinical subgroups

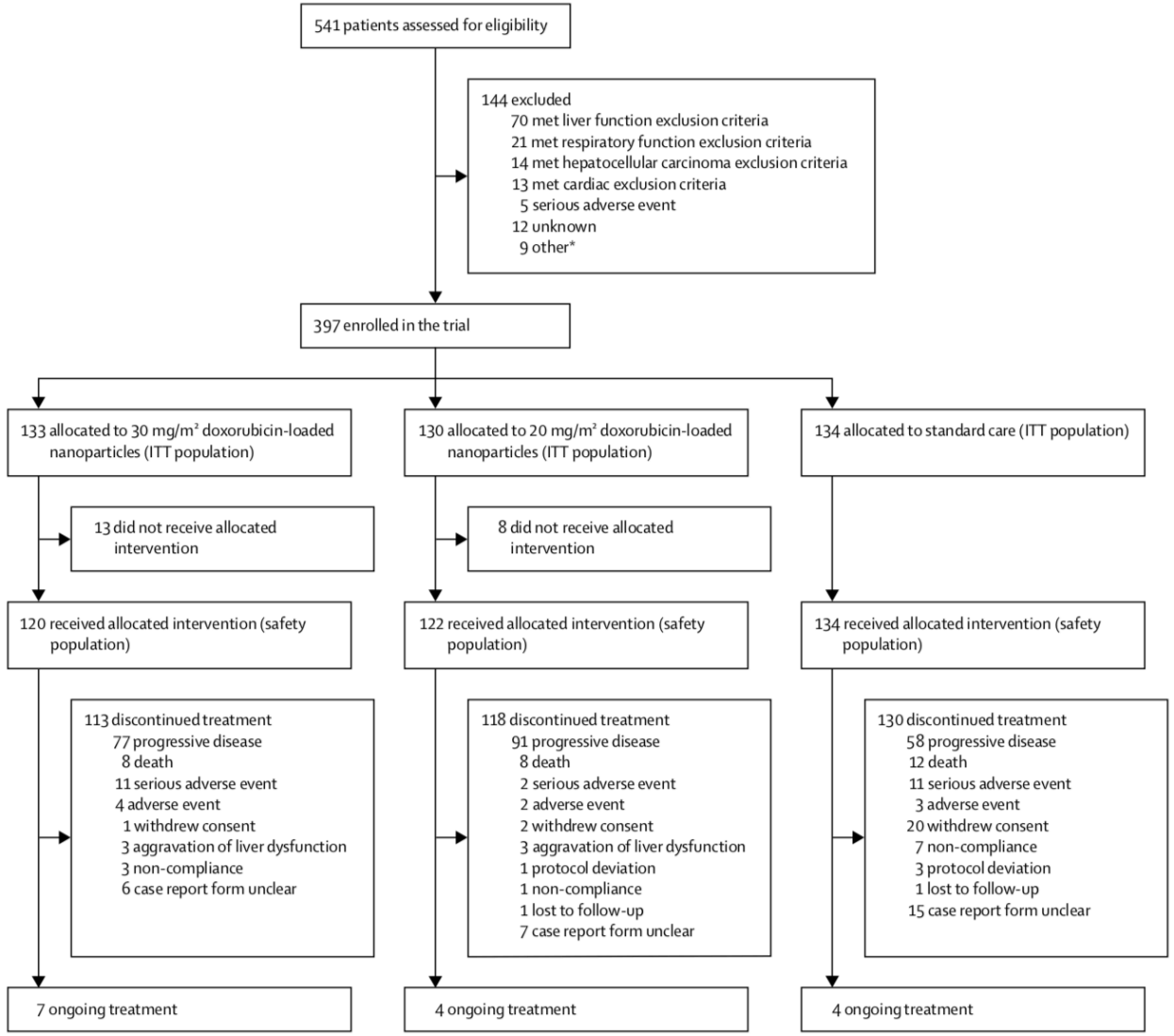
- Momentous — 1st Rx over sorafenib (& 1st phase 3 RCT of Imm-chkpnt inhib in HCC)

HCC Pharma, On the Horizon

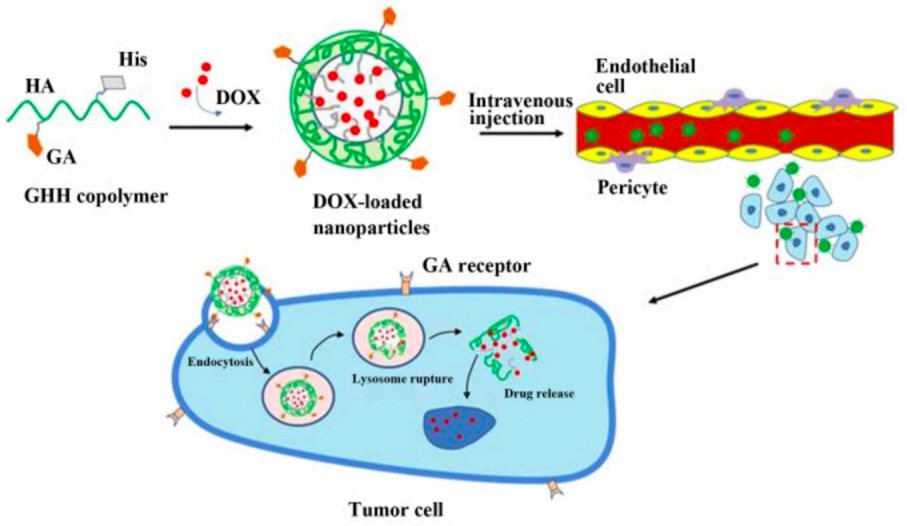
Phase 3 trials of new immune checkpoint inhibitor combinations fall into two general categories:

1. immune checkpoint inhibitors combined with other anti-angiogenic therapies, including multikinase inhibitors lenvatinib (NCT03713593) and cabozantinib (NCT03755791)
2. programmed death 1 or PD-L1 inhibitors combined with cytotoxic T lymphocyte–associated protein 4 inhibitors
   - a phase 3 trial of durvalumab–tremelimumab (NCT03298451) has already completed, and a phase 3 trial of nivolumab–ipilimumab (NCT04039607) is ongoing, following accelerated U.S. regulatory approval for this regimen (which showed durable responses in 33% of patients in a phase 1/2 study)

Doxorubicin-Loaded Nanoparticles for Patients with Advanced Hepatocellular Carcinoma After Sorafenib Treatment Failure (RELIVE): A Phase 3 Randomised Controlled Trial



- **Intravenous** doxo-nanoparticles q4 wks
- Multicenter, open-label, RCT phase 3 (70 sites /11 countries from Europe, USA, Middle East, North Africa)



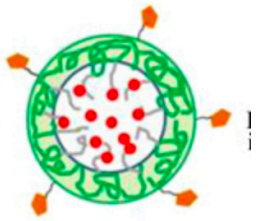
	Pooled experimental group (n=263)	Control group (n=134)
Sex		
Men	224 (85%)	117 (87%)
Women	39 (15%)	17 (13%)
Age, years	67 (60–73)	66 (61–72)
Geographical region		
Europe	237 (90%)	119 (89%)
USA	5 (2%)	3 (2%)
Middle East or North Africa	21 (8%)	12 (9%)
Race		
White	242 (92%)	125 (93%)
Black	5 (2%)	3 (2%)
Asian	5 (2%)	3 (2%)
Other	11 (4%)	3 (2%)
ECOG performance status		
0	150 (57%)	70 (52%)
1	108 (41%)	63 (47%)
2	5 (2%)	1 (1%)
Macrovascular invasion	92 (35%)	46 (34%)
Extrahepatic disease	152 (58%)	83 (62%)
Alpha-fetoprotein of at least 400 ng/mL	108 (41%)	63 (47%)
Child–Pugh class*		
A5	118 (45%)	60 (45%)
A6	105 (40%)	54 (40%)
B7	29 (11%)	17 (13%)
Greater than B7	11 (4%)	3 (2%)
Barcelona Clinic Liver Cancer stage		
A (early)	0%	0%
B (intermediate)	71 (27%)	34 (25%)
C (advanced)	192 (73%)	100 (75%)

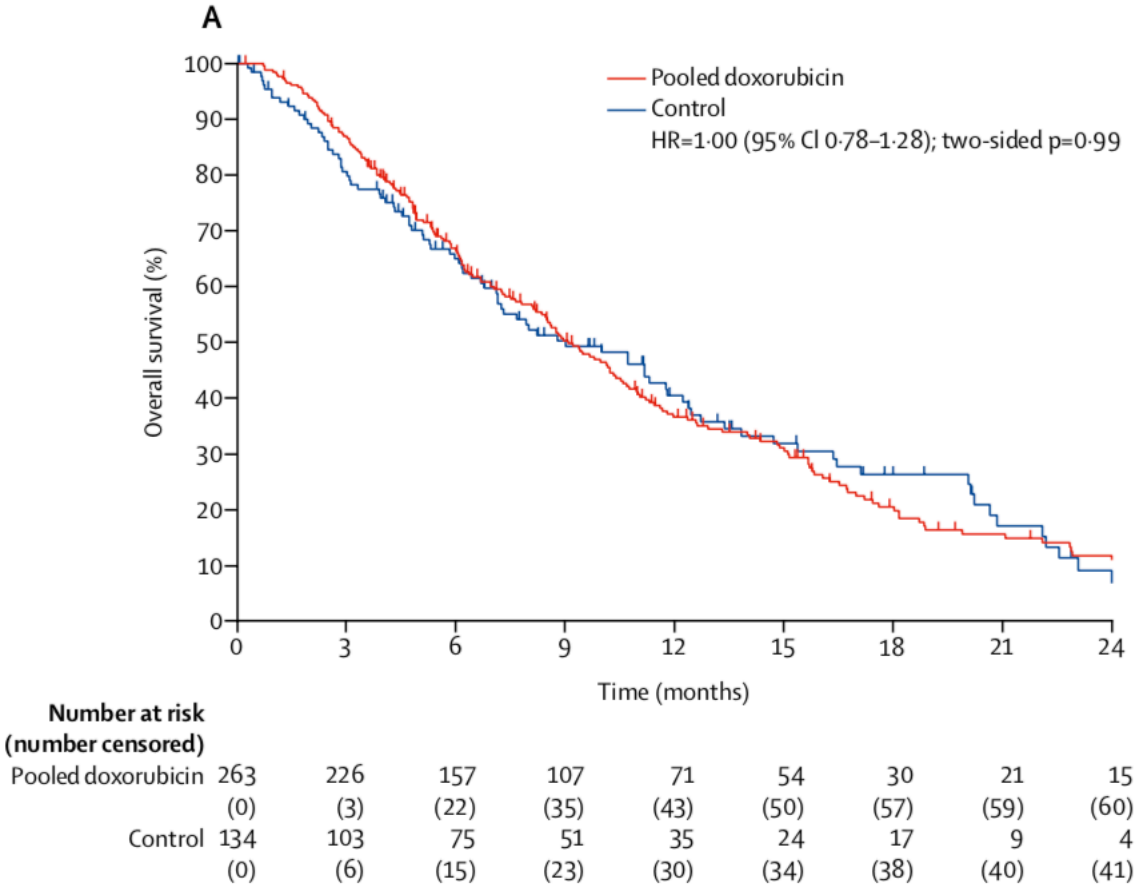
	Pooled experimental group (n=263)	Control group (n=134)
(Continued from previous column)		
Cause of hepatocellular carcinoma†		
Alcohol use	124 (47%)	68 (51%)
Hepatitis C	79 (30%)	38 (28%)
Unknown	39 (15%)	16 (12%)
Non-alcoholic steatohepatitis	34 (13%)	23 (17%)
Hepatitis B	24 (9%)	13 (10%)
Other	26 (10%)	7 (5%)
Number of previous systemic therapies (including sorafenib)		
One (only sorafenib)	205 (78%)	99 (74%)
Two	47 (18%)	26 (19%)
Three or more	11 (4%)	9 (7%)
Reason for sorafenib interruption		
Tumour progression	174 (66%)	96 (72%)
Intolerance to sorafenib	79 (30%)	35 (26%)
Other	10 (4%)	3 (2%)
Duration of sorafenib treatment, months	4·1 (2·4–9·3)	4·9 (2·6–8·7)
Daily sorafenib dose, months	722 (458–800)	800 (600–800)
Previous locoregional treatments before sorafenib‡		
Surgical resection	89 (34%)	40 (30%)
Percutaneous ablations	50 (19%)	24 (18%)
Transarterial chemoembolisation	150 (57%)	78 (58%)
External beam radiotherapy	29 (11%)	9 (7%)

- Outcomes: overall survival, PFS, ORR

No Survival Advantage to Doxorubicin

(Same in Child-Pugh A subset)

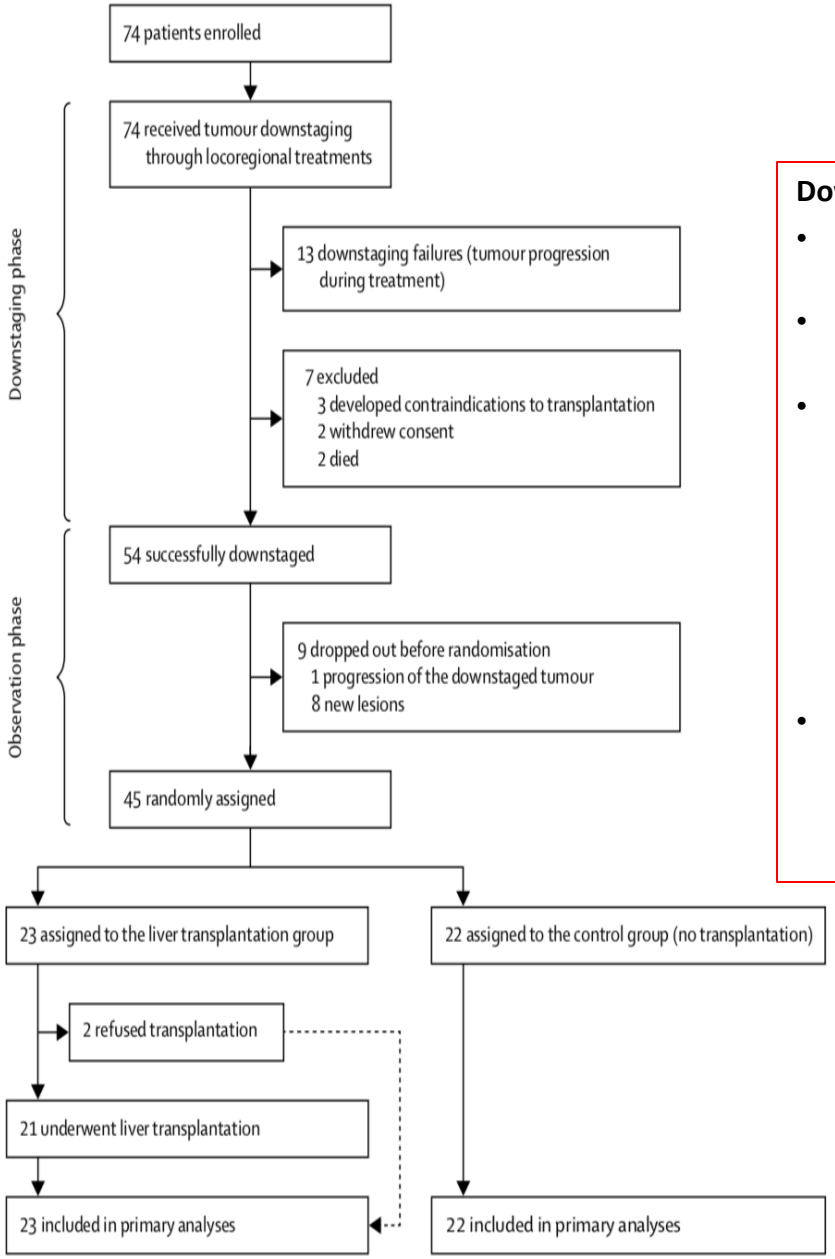




- median overall survival was 9.1 mos. (95% CI 8.1–10.4) in the pooled doxorubicin-loaded nano group and 9.0 mos. (7.1–11.8) in the control group

- Limits:
  - Other phase 3 trials used a placebo as the control group, whereas the control group in RELIVE was standard treatment (per PI)
  - In control group, 55 (41%) of 134 patients received only best supportive care, but 79 (59%) received a systemic anticancer therapy, of whom 37 (47%) were given gemcitabine plus oxaliplatin (GEMOX)

Liver Transplantation in Hepatocellular Carcinoma After Tumour Downstaging (XXL): A Randomised, Controlled, Phase 2b/3 Trial



Downstaging through:

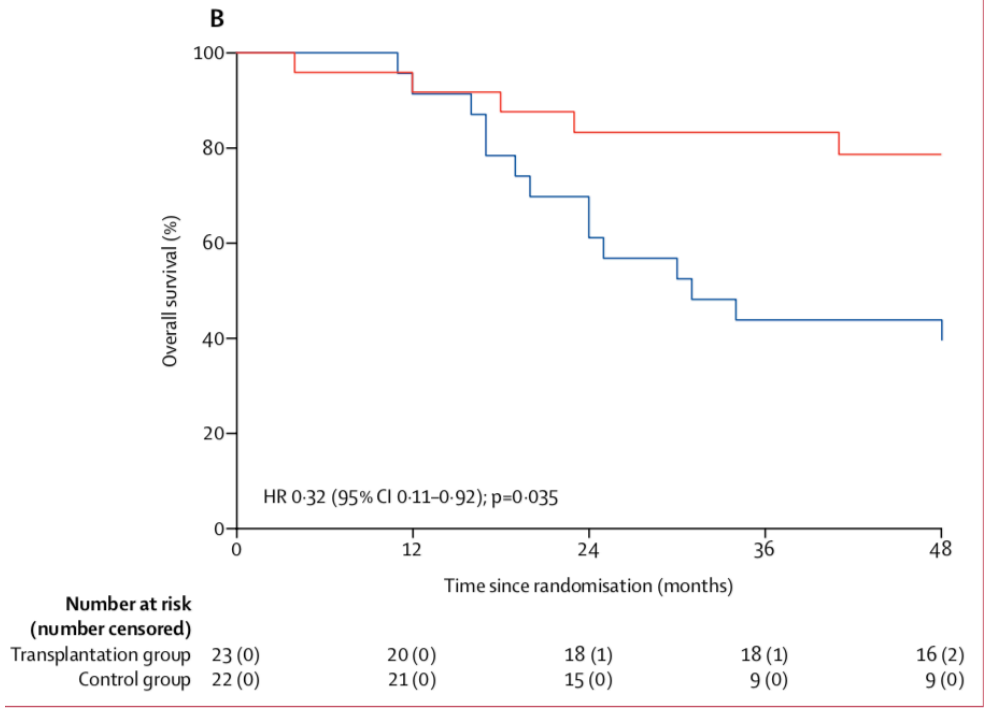
- surgical resection, RFA or microwave, TACE, TARE
- Choice of Rx / schedule were center based.
- Down-staging was considered successful if a patient had a partial response (i.e., reduction of vital, tumor contrast-enhanced areas of ≥50% or decrease in the sum of diameters of viable target lesions of ≥30%) or complete response;
- These patients entered a non-intervention period of no less than 3 months (observation phase).

Lancet Onc July 2020.
Mazzaferro et al.

	Transplantation group (n=23)	Control group (n=22)
Age, years	54·8 (51·7–58·8)	59·1 (51·2–62·0)
Sex		
Male	22 (96%)	21 (95%)
Female	1 (4%)	1 (5%)
Body-mass index, kg/m²	26·7 (25·2–28·1)	25·5 (22·9–26·5)
Cause of liver disease		
Hepatitis C virus	11 (48%)	17 (77%)
Hepatitis B virus	5 (22%)	2 (9%)
Alcohol or metabolic	6 (26%)	2 (9%)
Other	1 (4%)	1 (5%)
Disease presentation		
First diagnosis	22 (96%)	17 (77%)
Recurrent hepatocellular carcinoma	1 (4%)	5 (23%)
Downstaging procedures		
TACE only	12 (52%)	10 (45%)
RFA, SIRT, or surgery only	5 (22%)	3 (14%)
RFA	2 (9%)	2 (9%)
SIRT	1 (4%)	0 (0%)
Surgery*	2 (9%)	1 (5%)
Combinations of treatments	6 (26%)	9 (41%)
At least one of:		
TACE	17 (74%)	18 (82%)
RFA	8 (35%)	9 (41%)
SIRT	1 (4%)	1 (5%)
Surgical resection	4 (17%)	3 (14%)
Number of treatment sessions		
1	10 (43%)	8 (36%)
2	8 (35%)	5 (23%)
3	4 (17%)	3 (14%)
>3	1 (4%)	6 (27%)
MELD score	8 (7–10)	7 (7–9)

Liver Transplantation in Hepatocellular Carcinoma After Tumour Downstaging (XXL): A Randomised, Controlled, Phase 2b/3 Trial

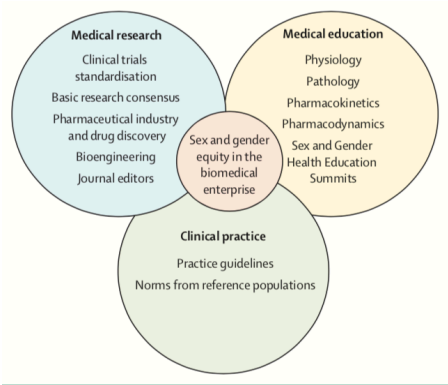
- First study to assess liver transplant benefit in downstaged HCC patients outside Milan criteria
- Significantly longer patient survival led to early study closure
- Post-transplantation survival in patients with partial tumor responses (26·5 months) was nearly triple that of patients who had complete responses (9·9 months)
- Results are comparable to patients who are transplanted within Milan criteria
- Affirms role of HCC downstaging as a selection tool for liver transplantation



Lancet Onc July 2020. Mazzaferro et al.

Sex and Gender: Modifiers of Health, Disease, and Medicine

- **Review article** on how sex is a genetic modifier of disease pathophysiology, clinical presentation, response to Rx, biology, patient and doctor behaviors, and chronic diseases such as:
  - heart disease, **cancer**, COPD, stroke, Alzheimer's, diabetes, influenza, CKD, chronic liver disease, etc.



Mandatory primer.
Consider the gaps IR/IO literature

Lancet August 2020. Jarvis et al.

…banish the 70kg man

	Sex differences		Gender differences, women compared with men
	Male sex	Female sex	
Heart disease	Younger age; more obstructive coronary artery disease; more heart failure with reduced ejection fraction	Older age; more coronary microvasculardysfunction; more heart failure with preserved ejection fraction	Underdiagnosed inflammatory airway disease; less evidence-based treatment; higher myocardial infarction mortality; fewer heart transplantations, although more frequent donors
Cancer	Higher prevalence and mortality; genetic cell autonomouspredisposition; stimulatory role of testosterone after puberty in hepatocellular carcinoma	Lower prevalence and mortality for some cancers; higher expression of X-encoded tumour suppressors; protective effect of oestrogen after puberty in hepatocellular carcinoma	Not identified
COPD and asthma	COPD: higher prevalence; asthma: higher prevalence before puberty	COPD: early onset with less tobacco exposure; majority of non-smoking COPD; high exacerbation rates; immune dysregulation; decline in lung function at menopause; asthma: higher prevalence in middle-age; premenstrual asthma; improves after menopause	COPD: smoking advertisements targeting women in the 1960s; increased smoking rates; often misdiagnosed; suffer from comorbid conditions, anxiety, and depression
Ischaemic stroke	Younger age of onset	Older age of onset; sex-specific risk factors: hypertensive disorders of pregnancy, gestational diabetes, contraception; aspirin provides greater benefit for women in primary prevention	Often undertreated; poorer outcome because of oldage; higher disability, poststroke depression, and social isolation
Alzheimer's disease	Lower prevalence; more likely diagnosed with mild cognitive impairment	Higher prevalence; apolipoprotein E epsilon 4 provides four times higher risk; risk increase with pregnancy, hypertensive disorders of pregnancy, early menopause, and late initiation of menopausal hormone therapy; clinical course is faster	Better performance on verbal memory tests; often delayed or missed diagnosis; greater burden of disease caregiving
Type 2 diabetes	More frequent impaired fasting glycaemia; testosterone deficiency predisposes and testosterone therapy protects	More frequent impaired glucose tolerance; greater clustering of cardiovascular risk factors; menopause predisposes and oestrogen therapy protects	Undertreatment of type 2 diabetes in women
Influenza	Predominant in young boys	Predominant in adults; morbidity and mortality are higher, especially in pregnant women; higher antibody titres following vaccination	Different roles and occupations lead to exposure to different strains of influenza A virus; higher vaccine hesitancy and lower vaccine receipt
Chronic kidney disease	More rapid rate of progression; testosterone might be deleterious	Higher prevalence; risk increases with hypertensive disorders of pregnancy; oestrogens might be protective	Receive fewer kidney transplants; receive fewer arteriovenous fistulas; potential dialysis overdose or administration of larger amounts of erythropoietin-stimulating agents
Chronic liver diseases	Higher risk of primary sclerosing cholangitis, chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma; higher prevalence of alcoholic liver disease; higher risk of NAFLD, fibrosis, and mortality; testosterone is protective against NAFLD; NASH resolution requires moderate bodyweight reduction	Higher risk of primary biliary cholangitis and autoimmune hepatitis; higher susceptibility to alcoholic liver disease; protected from NAFLD and fibrosis before menopause but not after menopause; oestrogens are protective against NAFLD, whereas testosterone is detrimental; greater weight loss is required for NASH resolution	Greater weight loss is required for NASH resolution
Depression	Less frequent but more lethal suicide attempts; irritability, aggression, violence, substance abuse, risky behaviour, and somatic complaints	Higher prevalence; hyperphagia, weight gain, hypersomnia, anxiety; role for gonadal hormones in depression	More likely to be diagnosed

COPD=chronic obstructive pulmonary disease. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis.

Table: **Sex and gender differences in leading causes of mortality**

JAMA Oncology | Original Investigation

Nov 2019

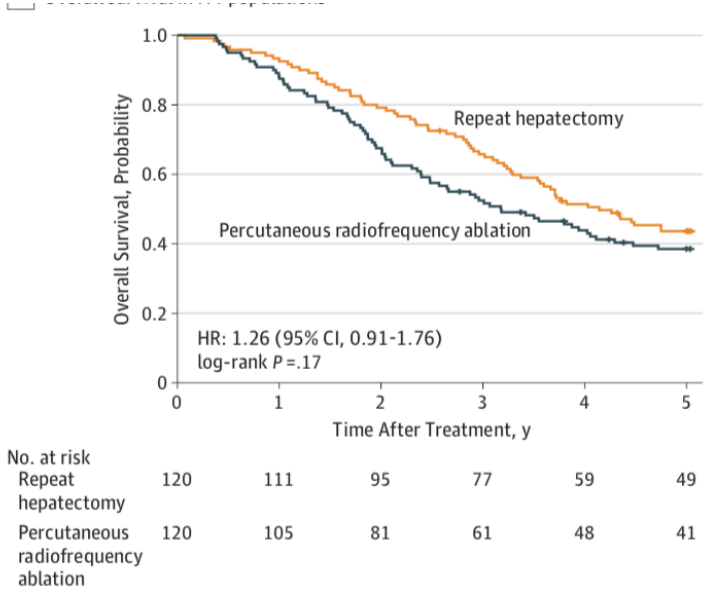
Long-term Effects of Repeat Hepatectomy vs Percutaneous Radiofrequency Ablation Among Patients With Recurrent Hepatocellular Carcinoma

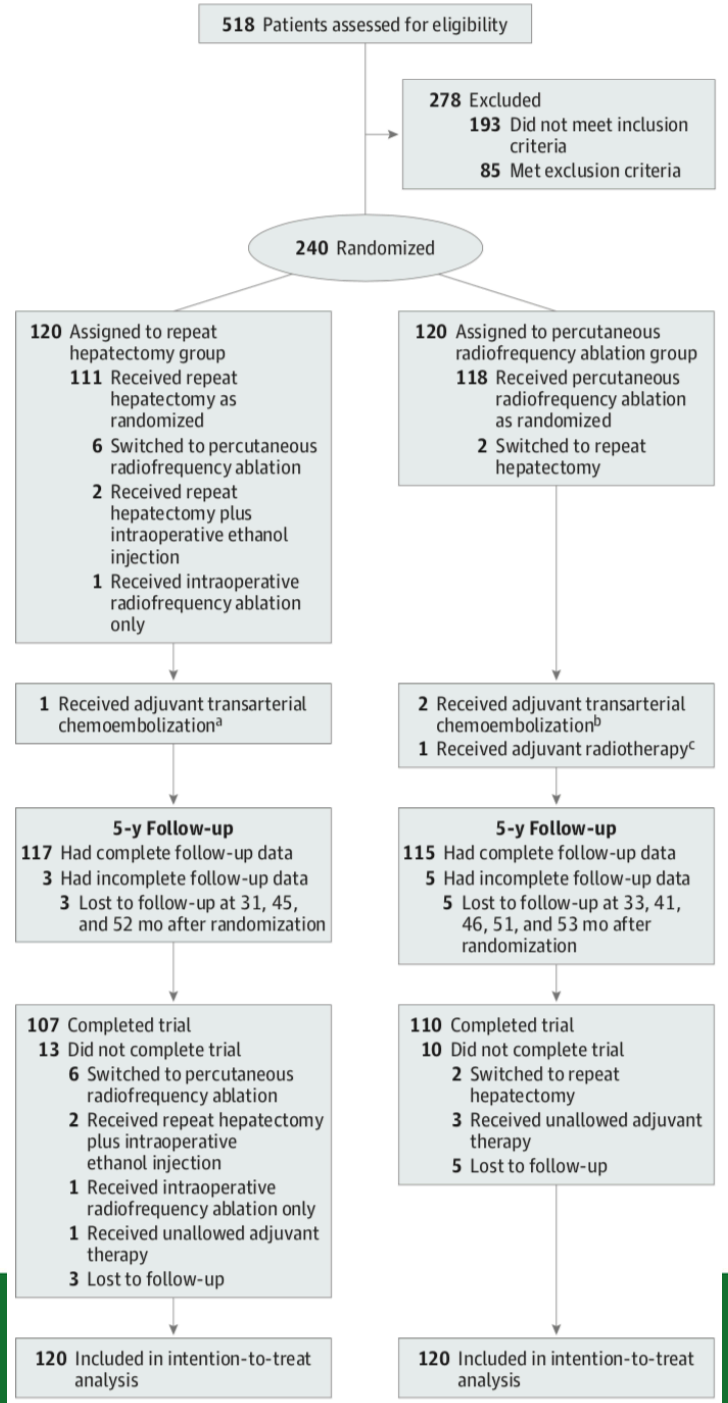
A Randomized Clinical Trial

Yong Xia, MD; Jun Li, MD; Guanghua Liu, MD; Kui Wang, MD; Guojun Qian, MD; Zhenhua Lu, MD; Tian Yang, MD; Zhenlin Yan, MD; Zhengqing Lei, MD; Anfeng Si, MD; Xuying Wan, MD; Han Zhang, MD; Chunfang Gao, MD; Zhangjun Cheng, MD; Timothy M Pawlik, MD, PhD; Hongyang Wang, MD, PhD; Wan Yee Lau, MD, FRCS; Mengchao Wu, MD; Feng Shen, MD, PhD

No 5-yr survival difference (but surgery better for larger masses)

Variable	OS HR (95% CI)	OS *P* Value	rRFS HR (95% CI)	rRFS *P* Value
Initial hepatectomy stage data				
Tumor diameter, >5 vs ≤5 cm	1.62 (1.13-2.30)	.008	1.55 (1.11-2.17)	.01
Multiple vs single tumors[a]	2.22 (1.48-3.45)	<.001	2.53 (1.72-3.72)	<.001
Incomplete vs complete tumor capsule	NA	NA	1.56 (1.12-2.17)	.009
MVI present vs absent	2.14 (1.50-3.06)	<.001	1.61 (1.14-2.27)	.007
Recurrent stage data				
AFP level >200 vs ≤200 ng/mL	1.63 (1.15-2.30)	.006	1.47 (1.06-2.05)	.021
RHCC diameter >3 vs ≤3 cm[b]	1.77 (1.25-2.49)	.001	1.51 (1.09-2.10)	.015
TTR ≤12 vs >12 mo	1.74 (1.19-2.56)	.001	1.97 (1.37-2.83)	<.001





- **Conventional Chemoembolization Plus Radiofrequency Ablation versus Surgical Resection for Single, Medium-Sized Hepatocellular Carcinoma: Propensity-Score Matching Analysis** Lee, Hyo-jae et al. JVIR Volume 30, 284 - 292.e1
- **Comparison of Radiofrequency Ablation and Hepatic Resection for the Treatment of Hepatocellular Carcinoma 2 cm or Less** Huang, Yuqian et al. JVIR Volume 29, 1218 - 1225.e2
- **Combined Therapy of Transcatheter Arterial Chemoembolization and Radiofrequency Ablation versus Surgical Resection for Single 2–3 cm Hepatocellular Carcinoma: A Propensity-Score Matching Analysis** Lee, Hyo-jae et al. JVIR Volume 28, 1240 - 1247.e3
- **Thermal Ablation versus Surgical Resection for the Treatment of Stage T1 Hepatocellular Carcinoma in the Surveillance, Epidemiology, and End Results Database Population** Mironov, Oleg et al. JVIR Volume 28,, 325 - 333

Stereotactic body radiation therapy *vs.* radiofrequency ablation in Asian patients with hepatocellular carcinoma

Nalee Kim[1], Jason Cheng[2], Inkyung Jung[3], Ja Der Liang[4], Yu Lueng Shih[5], Wen-Yen Huang[6], Tomoki Kimura[7], Victor H.F. Lee[8], Zhao Chong Zeng[9], Ren Zhenggan[10], Chul Seung Kay[11], Seok Jae Heo[3], Jong Yoon Won[12], Jinsil Seong[1,*]

- Retrospective, n = 2,064 patients (7 hospitals): 1,568 and 496 in the RFA and SBRT groups
- At baseline, the SBRT group had unfavorable features c/w RFA group: BCLC stage (B-C 65% vs. 16%), tumor size (median 3.0 cm vs. 1.9 cm), and frequent history of liver-directed treatment (81% vs. 49%, all p < 0.001)
- Median f/up 27.7 mos.: 3-year cumulative local recurrence rates in the SBRT and RFA groups were 21.2% and 27.9% (p < 001)
- After adjusting for clinical factors, SBRT had significantly lower risk of local recurrence than RFA in both the entire (hazard ratio [HR] 0.45, p < 0.001) and matched (HR 0.36, p < 0.001) cohorts. In subgroup analysis, SBRT was associated with superior local control in small tumors (<−3 cm)

Kim N, et al. *J Hepatol.* 2020;3:121-9

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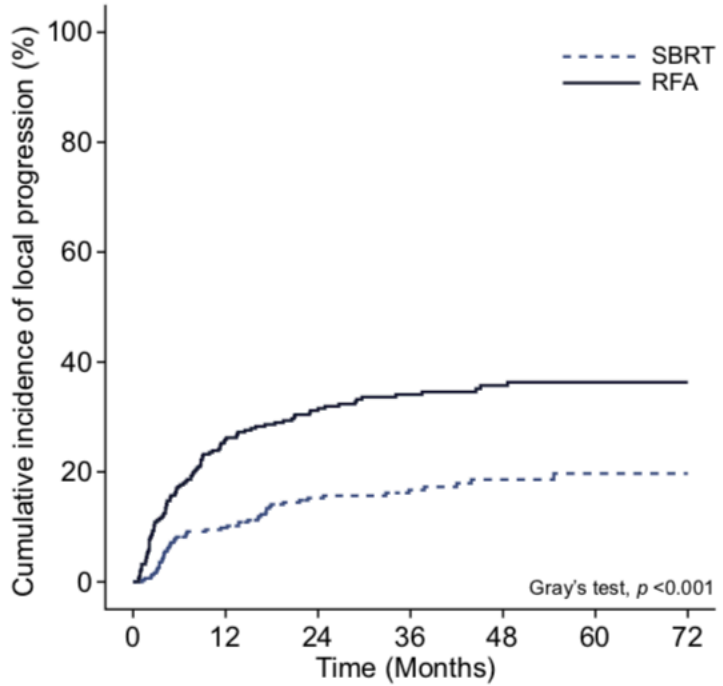
Results Held in All Locations, eg, Subphrenic, > 3cm



No. at risk							
SBRT	313	236	153	90	43	17	5
RFA	313	197	134	84	49	26	14

Ablation zone: SBRT group had a frequent decline in Child-Pugh score 3 months post-treatment; this pattern reversed after another 3 months. The irradiation volume in SBRT was larger than the ablated area after RFA, which could translate into liver function deterioration

Several factors: local selection biases, socioeconomic status, patient preference, and cost may have influenced the decision for local treatment

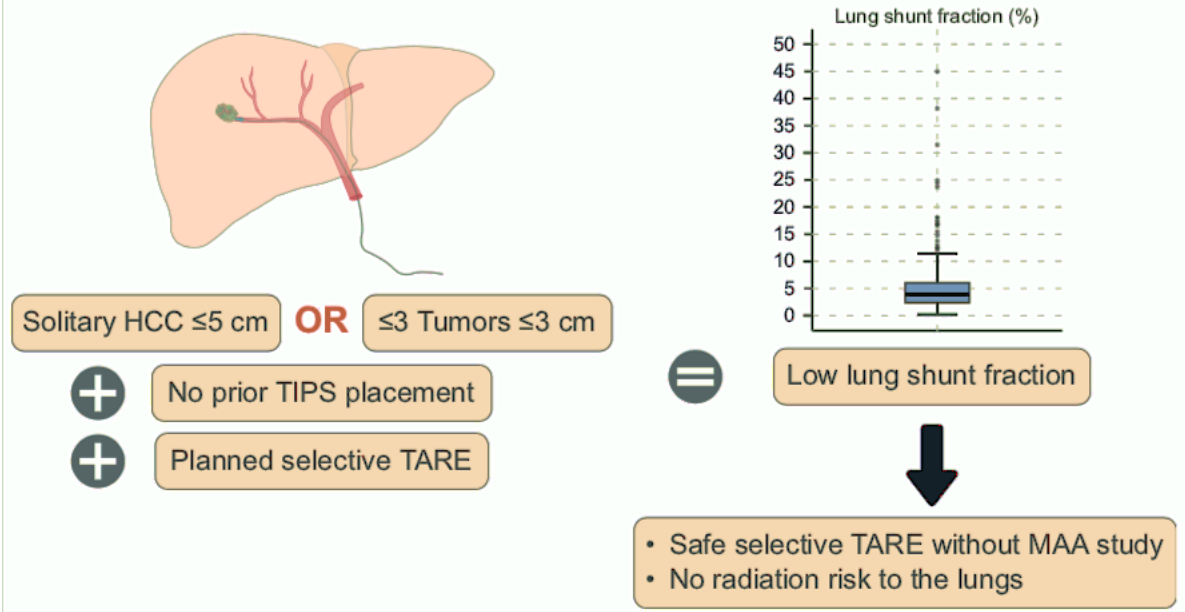
Since both modalities require technical expertise, treatment outcomes may show significant variation among institutions

Kim N, et al. *J Hepatol.* 2020;3:121-9

Streamlining radioembolization in UNOS T1/T2 hepatocellular carcinoma by eliminating lung shunt estimation

Ahmed Gabr[1], Srirajkumar Ranganathan[1], Samdeep K. Mouli[1], Ahsun Riaz[1], Vanessa L. Gates[1], Laura Kulik[2], Daniel Ganger[2], Haripriya Maddur[2], Christopher Moore[2], Elias Hohlastos[1], Nitin Katariya[3], Juan Carlos Caicedo[3], Aparna Kalyan[4], Robert J. Lewandowski[1,3], Riad Salem[1,3,4,*]

J Hepatology. 2020.



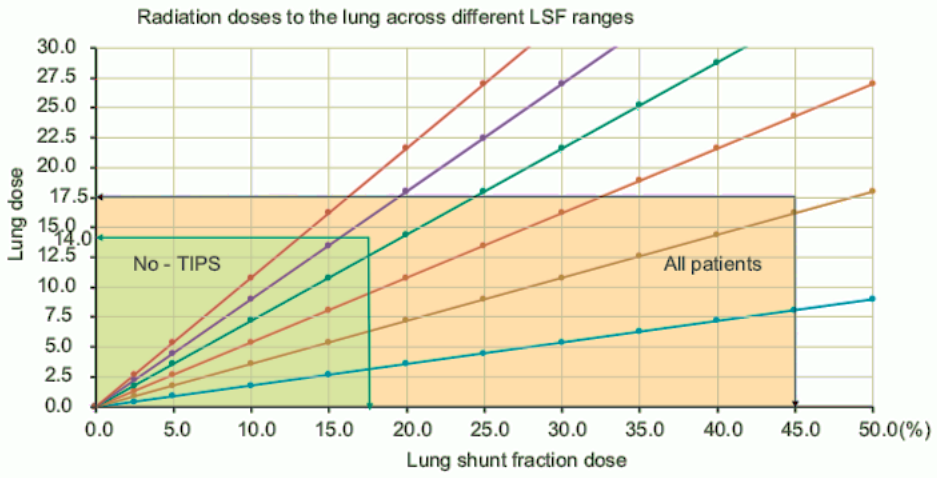


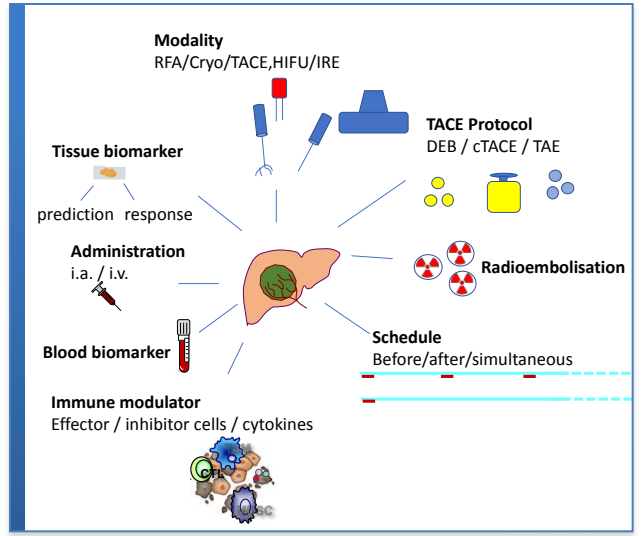
Table 2. Lung shunt fraction distribution among 448 T1/T2 patients.

Lung shunt fraction, range (%)	n	%
≤5	290	65
5.1–10	131	29
10.1–15	14	3
15.1–20	7	1.5
20.1–25	3	0.7
25.1–30	0	0.0
>30	3	0.7

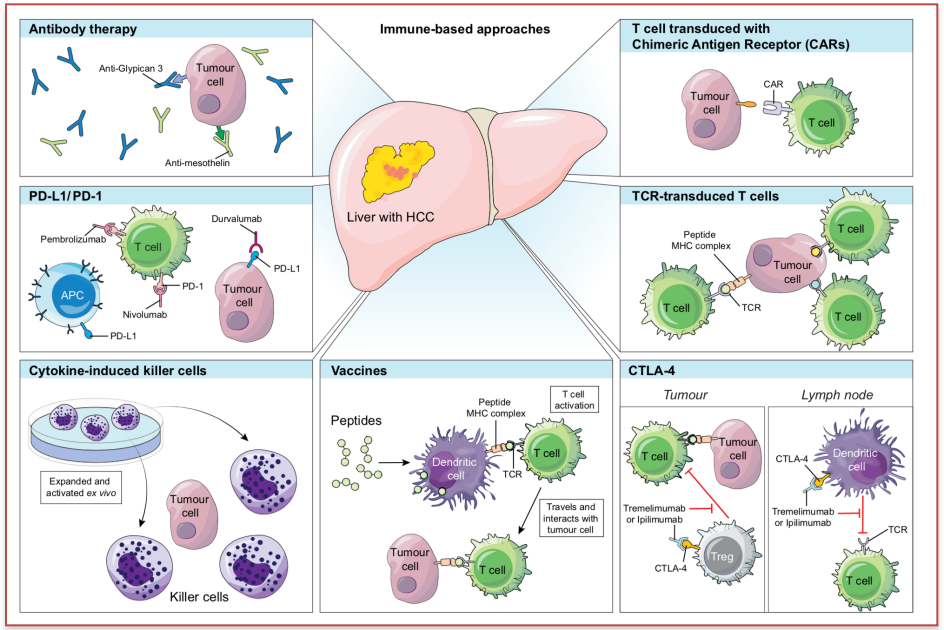
- As part of normal TARE workup and treatment, no patient exhibited an LSF > 45% (arterioportal fistula), and no lung dose exceeded 17.5 Gy
- TIPS patients were excluded (LSF >10%),→ homogenous sample of 410 patients
- Using 0.18 kg as a liver perfused mass, a maximum observed LSF of 18.1%, a dose up to 600 Gy could be prescribed without risk of lung toxicity
- Since most volumes and actual LSF are much lower, these assumptions provide significant safety margin for patients.
- CBCT is important*

Still Good, Past Primers Immunotherapy, HCC

- As CIO attendees, we require relevant expertise: to counsel pts at first consult, in ongoing IO therapy, in recognizing futility of loco-regional therapy, role of adjunct immunotherapy, or in multi-D discussions with colleagues



	CLINICAL TRIAL	Number of patients	Locoregional therapy	Immunomodulator
1	NCT03592706	60	TACE	Immune killer cells
2	NCT03575806	60	TACE	Central memory T cells
3	NCT03572582	49	TACE	Nivolumab
4	NCT03397654	26	TACE	Pembrolizumab
5	NCT03383458	530	Ablation	Nivolumab
6	NCT03143270	14	DEB-TACE	Nivolumab
7	NCT02856815	78	TACE	Immuncell-LC
8	NCT03124498	55	TACE, PEIT, RFA	Autologous cytokine induced killer cells (CIK)
9	NCT02821754	90	TACE, RFA, Cryo	Durvalumab, Tremelimumab
10	NCT02568748	20	TACE	CIK
11	NCT02487017	60	TACE	DC-CIK
12	NCT02837029	35	Y 90 Glass Microspheres	Nivolumab
13	NCT03380130	40	Y90- Microspheres	Nivolumab
14	NCT03033446	40	Y90	Nivolumab
15	NCT03099564	30	Y90	Pembrolizumab
16	NCT03259867	80	TATE	Nivolumab OR Pembrolizumab



J Hepatol. 2018;68:157–166.

Still Good , Past Primers Immunotherapy, HCC

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Conclusions

Scylla and Charybdis