HCC Year in Review

Nadine Abi-Jaoudeh, MD, FSIR, CCRP

Disclosures

Consultant–Genentech, Roche

Grant/Research Support–Teclison, Philips Medical Systems, SIRTEX, Guerbet

Major Stock Shareholder–Bruin Biosciences

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No product promotion should be inferred.

Outline

- Focus on major RCT
- Early stage
- Advanced stage

Early Stage HCC

Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial

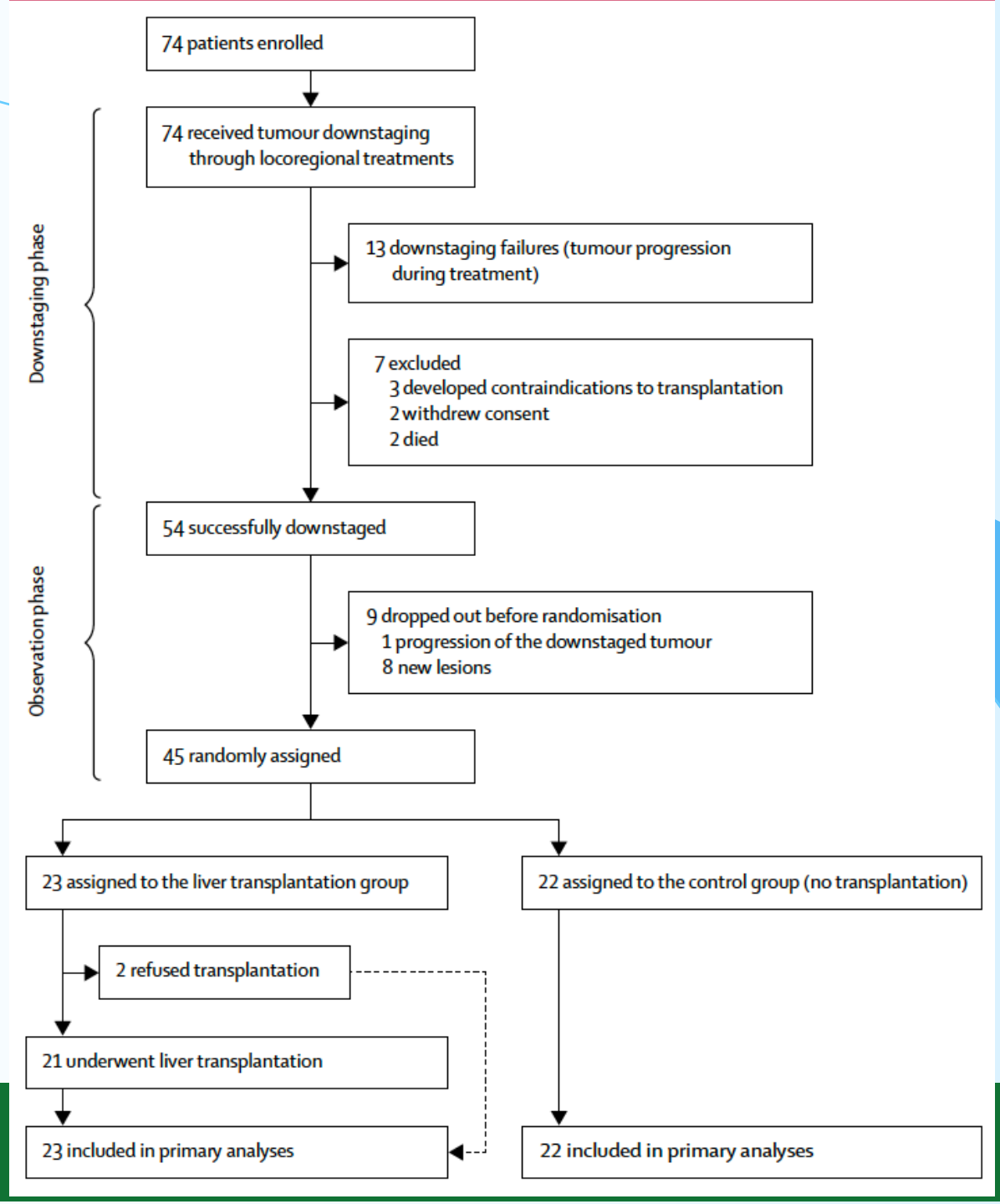
Vincenzo Mazzaferro, Davide Citterio, Sherrie Bhoori, Marco Bongini, Rosalba Miceli, Luciano De Carlis, Michele Colledan, Mauro Salizzoni, Renato Romagnoli, Barbara Antonelli, Marco Vivarelli, Giuseppe Tisone, Massimo Rossi, Salvatore Gruttadauria, Stefano Di Sandro, Riccardo De Carlis, Maria Grazia Lucà, Massimo De Giorgio, Stefano Mirabella, Luca Belli, Stefano Fagiuoli, Silvia Martini, Massimo Iavarone, Gianluca Svegliati Baroni, Mario Angelico, Stefano Ginanni Corradini, Riccardo Volpes, Luigi Mariani, Enrico Regalia, Maria Flores, Michele Droz dit Busset, Carlo Sposito

Lancet Oncol 2020; 21: 947–56

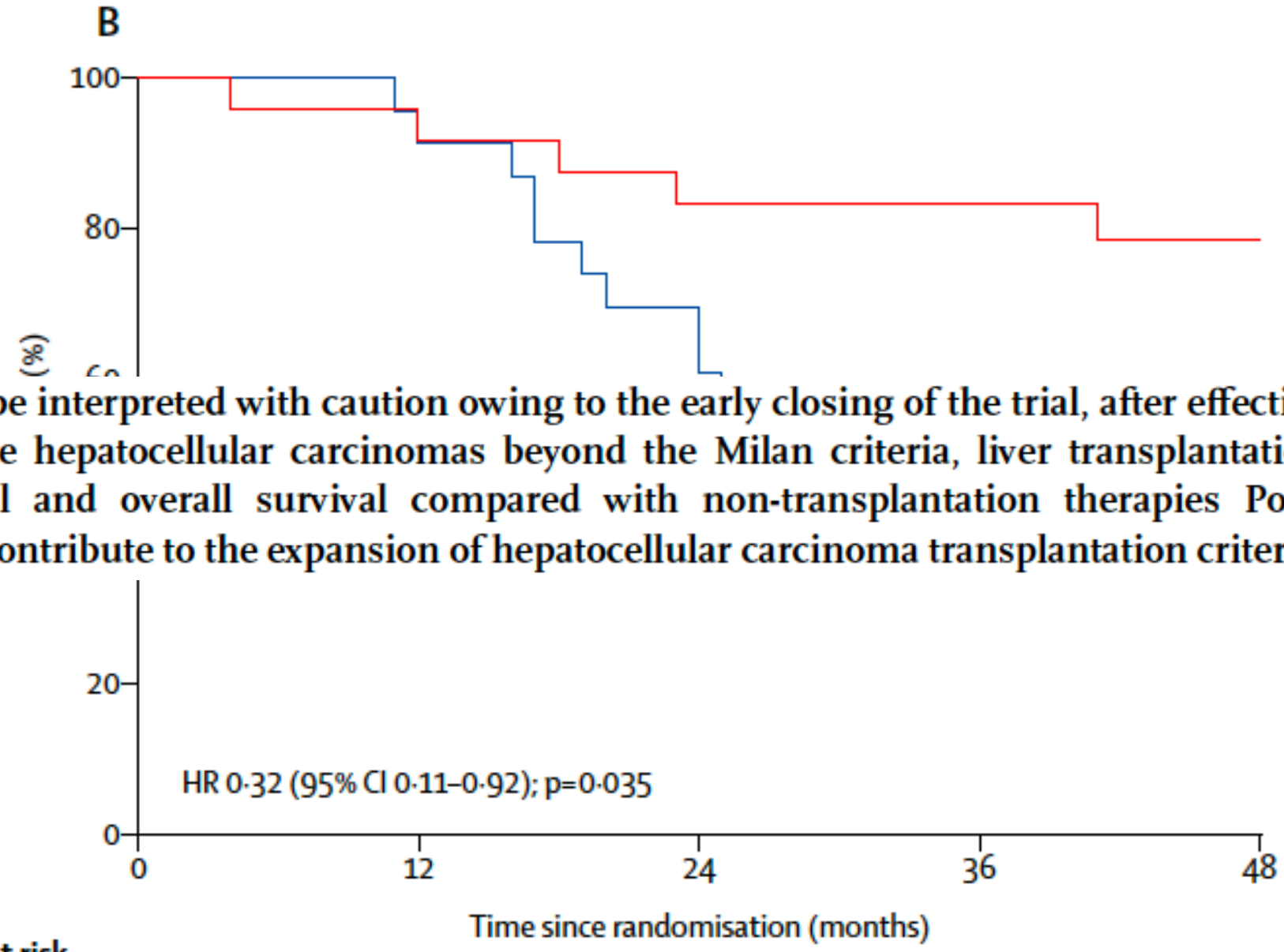
LRT Downstaging to Transplant RCT

- Therapies could be combined, including surgical resection, RFA, MWA, TACE, and SIRT, repeated up to 18 months
- Cycles where series of treatment concluded if 1: CR, 2: best achievable response, 3: technical infeasibility
- At the end of downstaging, tumor response assessed per mRECIST → downstaging failure or success
- Downstaging success → observation phase of 3 months → after which randomization occurred if they sustained tumor response

Mean duration of downstaging = 6 mos.
Mean duration of observation = 3 mos.
Median time on transplant list = 3 mos.
Median time from referral to transplant = 12 mos.



	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%)
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)
Child-Pugh class		
A	21 (91%)	19 (86%)
B	2 (9%)	3 (14%)
Number of nodules	3·0 (2·0–4·0)	3·5 (2·0–4·0)
Largest tumour diameter (mm)	50·0 (40·0–55·5)	40·0 (24·3–54·5)
Sum of the diameters of viable tumour (mm)†	79·0 (70·5–95·5)	71·0 (60·8–93·5)
Tumour burden‡	7·5 (7·0–8·6)	7·0 (6·2–8·1)
α-fetoprotein (ng/mL)	12·4 (7·4–82·1)	8·5 (4·5–63·8)
Met Milan criteria		
Yes	0 (0%)	0 (0%)
No	23 (100%)	22 (100%)
Met Up-to-7 criteria		
Yes	7 (30%)	12 (55%)
No	16 (70%)	10 (45%)
Met UCSF criteria		
Yes	12 (52%)	13 (59%)
No	11 (48%)	9 (41%)
French model		
Low risk (≤2 points)	10 (43%)	11 (50%)
High risk (>2points)	13 (57%)	11 (50%)



Interpretation Although results must be interpreted with caution owing to the early closing of the trial, after effective and sustained downstaging of eligible hepatocellular carcinomas beyond the Milan criteria, liver transplantation improved tumour event-free survival and overall survival compared with non-transplantation therapies Post-downstaging tumour response could contribute to the expansion of hepatocellular carcinoma transplantation criteria.

Advanced HCC

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investigators*

Advanced HCC

Key Eligibility

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy

(n = 501)

Stratification Criteria

- Region (Asia excluding Japan/ rest of world)
- ECOG/ PS: 0/1
- Macrovascular invasion and/or EHS: presence/absence
- Baseline AFP: >/< 400ng/mL

R 2:1

Atezolizumab 1200 mg IV q3w and Bevacizumab 15mg/kg q3w

Open Label

Sorafenib 400mg BID

Until loss of clinical benefit or unacceptable toxicity

Survival follow-up

Co-primary endpoints:

- OS
- PFS per IRF RECIST 1.1

Secondary endpoints:

- ORR per IRF per RECIST 1.1 + mRECIST
- TTD of QOL

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)

B Survival without Disease Progression

Table 2. Secondary Efficacy Outcomes.*

Variable	RECIST 1.1			HCC-Specific mRECIST		
	Atezolizumab–Bevacizumab (N=326)	Sorafenib (N=159)	Difference (P Value)†	Atezolizumab–Bevacizumab (N=325)	Sorafenib (N=158)	Difference (P Value)†
Confirmed objective response — no. (% [95% CI])‡	89 (27.3 [22.5–32.5])	19 (11.9 [7.4–18.0])	15.4 (<0.001)	108 (33.2 [28.1–38.6])	21 (13.3 [8.4–19.6])	19.9 (<0.001)
Complete response — no. (%)	18 (5.5)	0		33 (10.2)	3 (1.9)	
Partial response — no. (%)	71 (21.8)	19 (11.9)		75 (23.1)	18 (11.4)	
Stable disease — no. (%)	151 (46.3)	69 (43.4)		127 (39.1)	66 (41.8)	
Disease control rate — no. (%)§	240 (73.6)	88 (55.3)		235 (72.3)	87 (55.1)	
Progressive disease — no. (%)	64 (19.6)	39 (24.5)		66 (20.3)	40 (25.3)	
Could not be evaluated — no. (%)	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing — no. (%)	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response at data cutoff — no./total no. (%)	77/89 (86.5)	13/19 (68.4)		84/108 (77.8)	13/21 (61.9)	

bevacizumab																
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE

Table 3. Adverse Events from Any Cause.

Variable	Atezolizumab–Bevacizumab (N=329)	Sorafenib (N=156)
	number (percent)	
Patients with an adverse event from any cause	323 (98.2)	154 (98.7)
Grade 3 or 4 event*	186 (56.5)	86 (55.1)
Grade 5 event†	15 (4.6)	9 (5.8)
Serious adverse event	125 (38.0)	48 (30.8)
Adverse event leading to withdrawal from any trial drug	51 (15.5)	16 (10.3)
Withdrawal from atezolizumab–bevacizumab	23 (7.0)	—
Adverse event leading to dose modification or interruption of any trial drug	163 (49.5)	95 (60.9)
Dose interruption of any trial treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib	—	58 (37.2)

Shown are Kaplan–Meier estimates of the time to deterioration in quality of life in the intention-to-treat population. Tick marks indicate censored data.

Advanced HCC

- Improved OS & PFS
- 40% pts had MVI including portal v.
- Increase in PFS of 2.5 mos. vs. sorafenib
- RR of 27.3% sustained at 6 mp in 88% of those pts w/response
- CP A pts + varices **
- 15% stopped bz of AE + 7% UGI bleeds (vs. 4.5% in sorafenib)

Advanced HCC

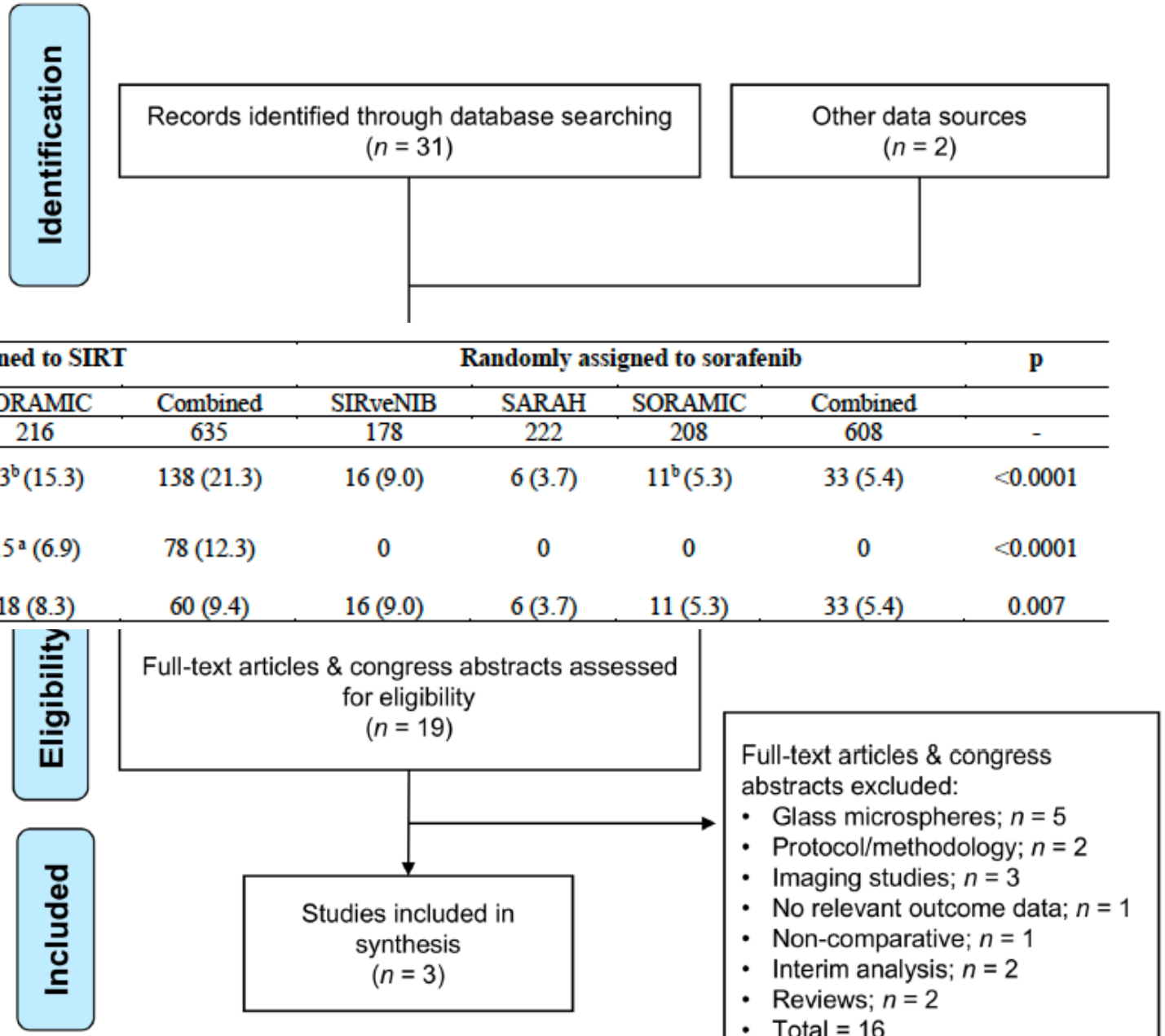
NEMESIS: Non-inferiority, Individual Patient Meta-analysis of Selective Internal Radiation Therapy with Yttrium-90 Resin Microspheres versus Sorafenib in Advanced Hepatocellular Carcinoma

Marino Venerito, MD[1*], Maciej Pech, MD[2], Ali Canbay, MD[1], Rossella Donghia, PhD[3], Vito Guerra, PhD[3], Gilles Chatellier, MD[4], Helena Pereira, MSc[4], Mihir Gandhi, PhD[5,6,7], Pierce K.H. Chow, PhD[7*], Valérie Vilgrain, MD, PhD[8*], Peter Malfertheiner, PhD[1,9], Jens Ricke, PhD[1,9*], Gioacchino Leandro, MD[3]

dol:10.2967/jnumed.120.242933

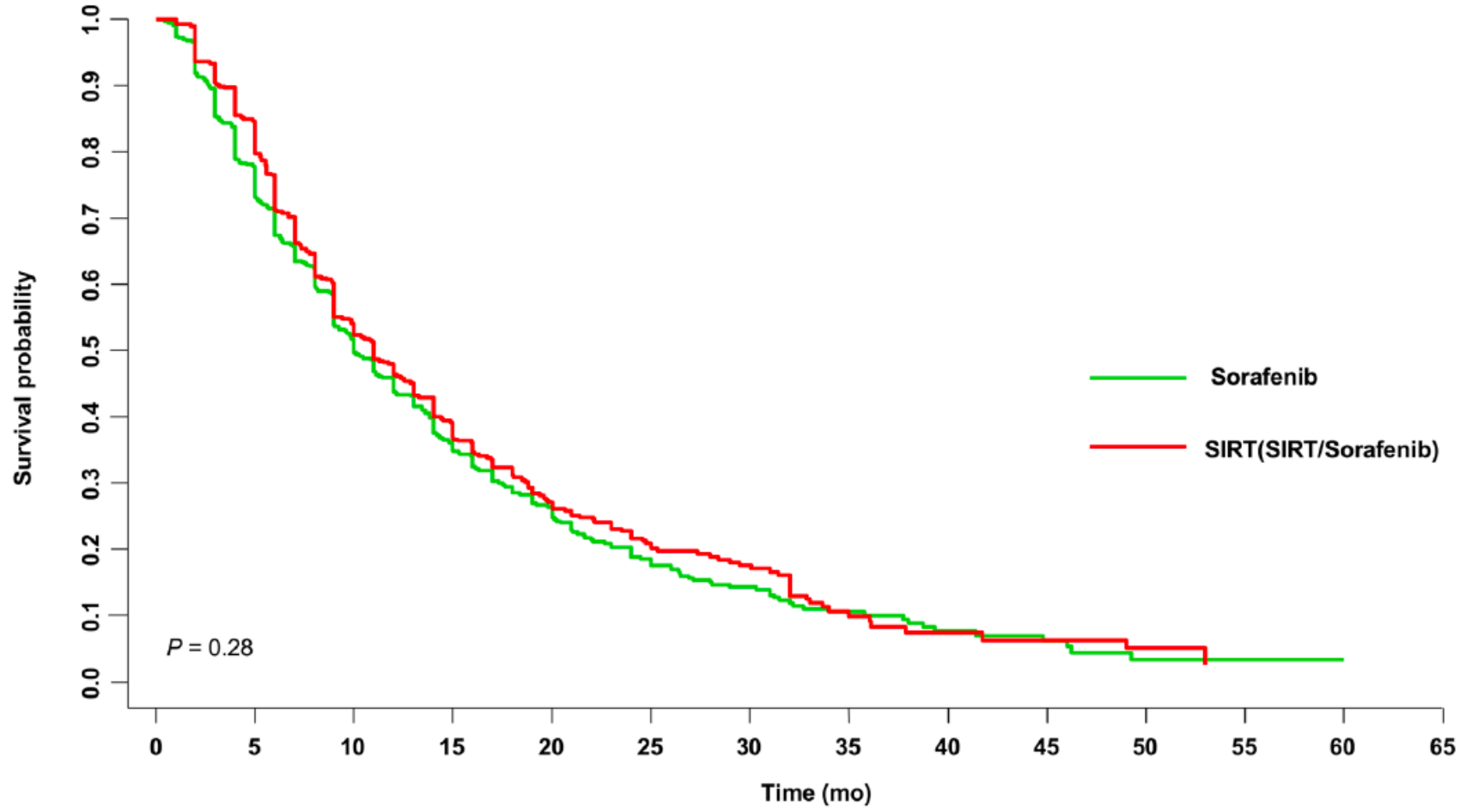
Advanced HCC: NEMESIS

- 3 databases: MEDLINE, Embase, & Cochrane Central Register of Controlled Trials (CENTRAL) & abstracts of EASL, ASCO, ESMO
- RCT w/ SIRT w/ w/out sorafenib vs. sorafenib control arm
- Main outcomes: OS and AE



	Randomly assigned to SIRT				Randomly assigned to sorafenib				p
	SIRveNIB	SARAH	SORAMIC	Combined	SIRveNIB	SARAH	SORAMIC	Combined	
Total assigned	182	237	216	635	178	222	208	608	-
Did not receive allocated treatment, n (%)	52 (28.6)	53 (22.4)	33[b] (15.3)	138 (21.3)	16 (9.0)	6 (3.7)	11[b] (5.3)	33 (5.4)	<0.0001
Liver-to-lung shunting/ Ineligible for SIRT for technical reasons, n (%)	37 (20.3)	26[a] (11.0)	15[a] (6.9)	78 (12.3)	0	0	0	0	<0.0001
Other reasons[c] n (%)	15 (8.2)	27[a] (11.4)	18 (8.3)	60 (9.4)	16 (9.0)	6 (3.7)	11 (5.3)	33 (5.4)	0.007

Figure 1 PRISMA flow diagram for the review



Number at risk (Number failure)

Sorafenib	513 (113)	388 (127)	249 (73)	159 (40)	99(28)	59(13)	39(9)	24(5)	12(2)	8(3)	3(0)	2 (0)	1(0)
SIRT-(SIRT/Sorafenib)	410 (64)	339 (120)	214 (57)	140 (41)	84 (18)	54(8)	37(13)	15(4)	7 (1)	6(1)	4(1)	0 (0)	0 (0)

Table 1 Comparison of tumor responses (RECIST 1.1) in the per-protocol population of the SIRveNIB and SARAH trials[a]

	SIRT			Sorafenib			
	SIRveNIB	**SARAH**	**Combined**	**SIRveNIB**	**SARAH**	**Combined**	**p-value[b]**
	123	174	297	142	206	348	
ORR (CR+PR) (%)	27 (21·9)	32 (18·4)	59 (19·9)	3 (2·1)	23 (11·2)	26 (7·5)	<0·0001
DCR (CR+PR+SDis) (%)	72 (58·5)	115 (66·1)	187 (63·0)	67 (47·2)	148 (71·8)	215 (61·8)	0·81
CR (%)	0 (0·0)	4 (2·3)	4 (1·3)	0 (0·0)	2 (1·0)	2 (0·6)	0·42
PR (%)	27 (21·9)	28 (16·1)	55 (18·5)	3 (2·1)	21 (10·2)	24 (6·9)	<0·0001
SDis (%)	45 (36·6)	83 (47·7)	128 (43·1)	64 (45·1)	125 (60·7)	189 (57·3)	0·005
PD (%)	27 (21·9)	49 (28·2)	76 (25·6)	41 (28·9)	40 (19·4)	81 (23·3)	0·23
Not done/not evaluable	24 (19·5)	10	34 (11·4)	34 (23·9)	18	52 (14·9)	0·20

SIRT as initial therapy is non inferior to sorafenib in terms of OS and has a better safety profile

Table 2 Treatment-related adverse events in the safety population of the SIRveNIB, SARAH and SORAMIC trials

Arm	SIRT				Sorafenib		
Study	SIRveNIB	SARAH	SORAMIC[a]	Combined	SIRveNIB	SARAH	SORAMIC
AE (%)	41/130 (31.5)	173/226 (77.0)	113/159 (71.1)	327/515 (63.5)	121/162 (74.7)	203/216 (94.0)	139/197 (70.6)
AE ≥3 (%)	17/130 (13.1)	92/226 (41.0)	40/159 (25.2)	149/515 (28.9)	61/162 (37.7)	136/216 (63.0)	52/197 (26.4)
SAEs (%)	6/130 (4.6)	45/226 (20)	63/159 (39.6)	114/515 (22.1)	15/162 (9.3)	56/216 (26.0)	78/197 (39.6)

AE: adverse events; SAE: serious adverse events;
[a] in the SIRT arm 114/159 patients received sorafenib after SIRT.

Incidence of treatment related AE >3 grade in SIRvsNIB + SARAH was < in SIRT vs Sorafenib (30.6% vs 52.1% p=0.0002)
In SORAMIC the incidence of AE was slightly higher in SIRT+sorafenib gr vs. sorafenib alone w/out stats significance

Advanced HCC

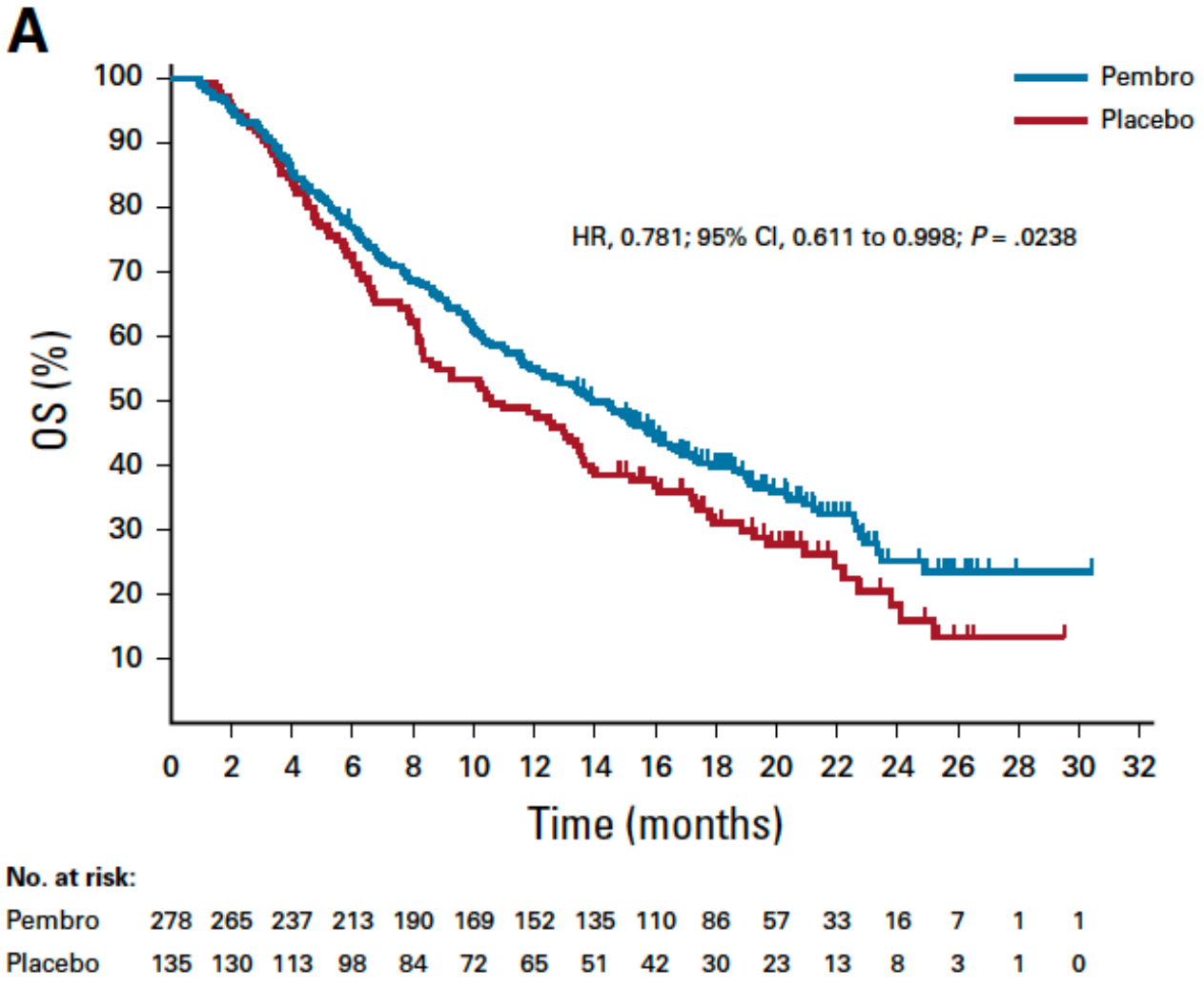
Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial

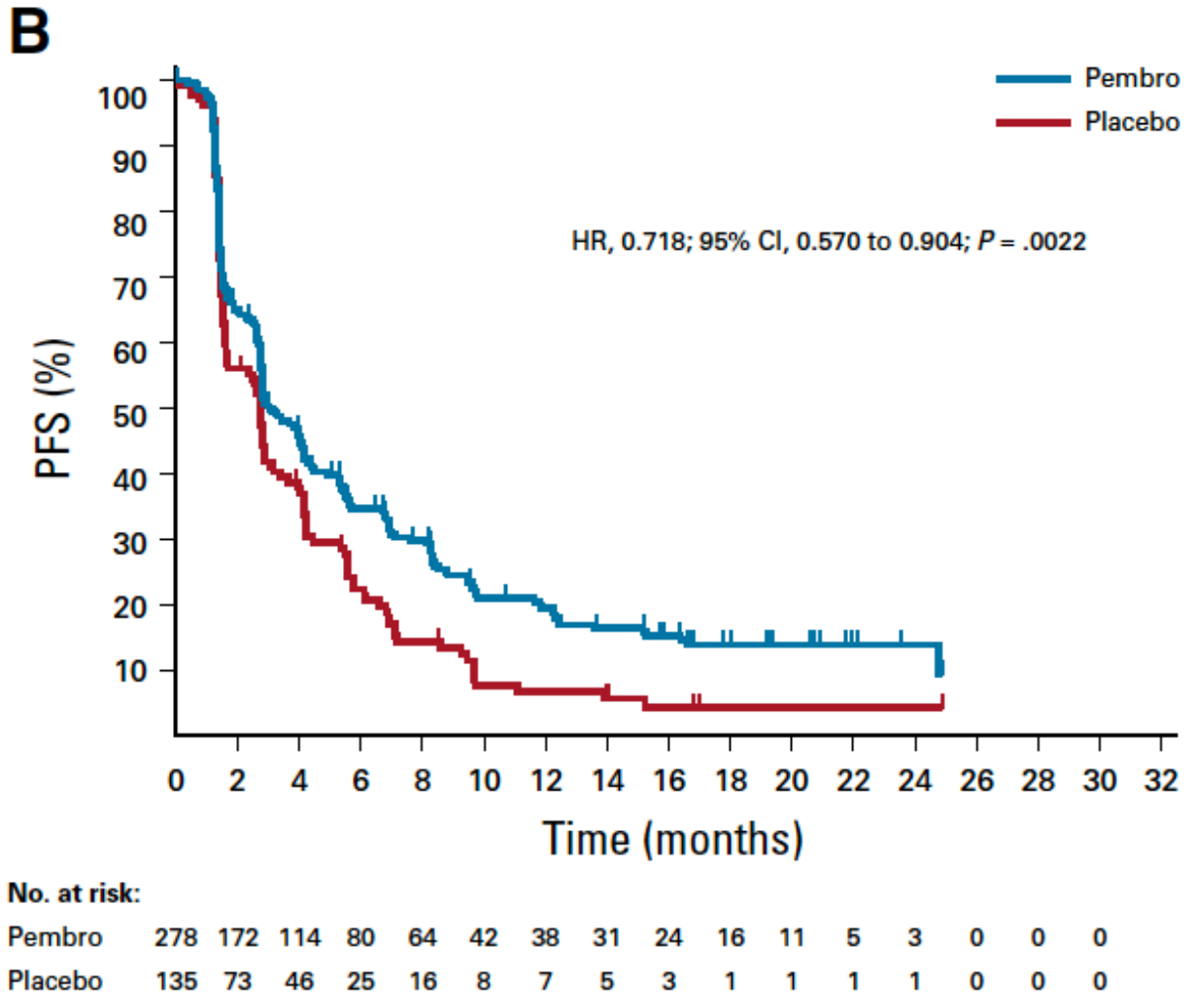
J Clin Oncol 38:193-202. © 2019 by American Society of Clinical Oncology

Richard S. Finn, MD[1]; Baek-Yeol Ryoo, MD, PhD[2]; Philippe Merle, MD, PhD[3]; Masatoshi Kudo, MD, PhD[4]; Mohamed Bouattour, MD[5]; Ho Yeong Lim, MD[6]; Valeriy Breder, MD, PhD[7]; Julien Edeline, MD, PhD[8]; Yee Chao, MD, PhD[9]; Sadahisa Ogasawara, MD[10]; Thomas Yau, MD[11]; Marcelo Garrido, MD[12]; Stephen L. Chan, MD[13]; Jennifer Knox, MD[14]; Bruno Daniele, MD[15]; Scot W. Ebbinghaus, MD[16]; Erluo Chen, MPH[16]; Abby B. Siegel, MD[16]; Andrew X. Zhu, MD, PhD[17]; and Ann-Lii Cheng, MD, PhD[18]; on behalf of the KEYNOTE-240 investigators

Keynote-240

- RCT double blind 119 MC 27 countries
- Adv HCC progression or intolerance to sorafenib, BCLC stage C or B not amenable or refractory to LRT, ECOG 0 or 1
- Exclusion of previous systemic therapy other than sorafenib specifically PD-L1, PD-1... ascites, PVT, EHS, & HE
- Randomization 2:1 PD-1 Pembo (200mg) q3w vs saline q3w *35c
- Endpoints: OS, PFS





Median PFS was 3 mos. for pembro vs 2.8 mos. for placebo (HR, 0.718; 95% CI 0.570 to 0.904 p = 0.0022)

Median OS was 13.9 mos. for pembro vs. 10.6 mos. for placebo (HR, 0.781 95% CI 0.611 to 0.998 p = 0.238)

TABLE 2. Summary of Response in Intention-to-Treat Population by Central Radiology Review per RECIST (version 1.1)

Parameter	No. (%) Pembrolizumab (n = 278)	Placebo (n = 135)
Objective response*	51 (18.3)	6 (4.4)
95% CI	14.0 to 23.4	1.6 to 9.4
Estimated treatment difference†	13.8	
95% CI	7.7 to 19.5	
P‡	.00007	
Best overall response§		
CR	6 (2.2)	0 (0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
≥ 23 weeks‖	37 (13.3)	20 (14.8)
PD	90 (32.4)	57 (42.2)
Not evaluable	7 (2.5)	3 (2.2)
Not assessable¶	8 (2.9)	3 (2.2)
DCR#	173 (62.2)	72 (53.3)

Advanced HCC

TABLE 3. AEs Resulting From Any Cause in As-Treated Population

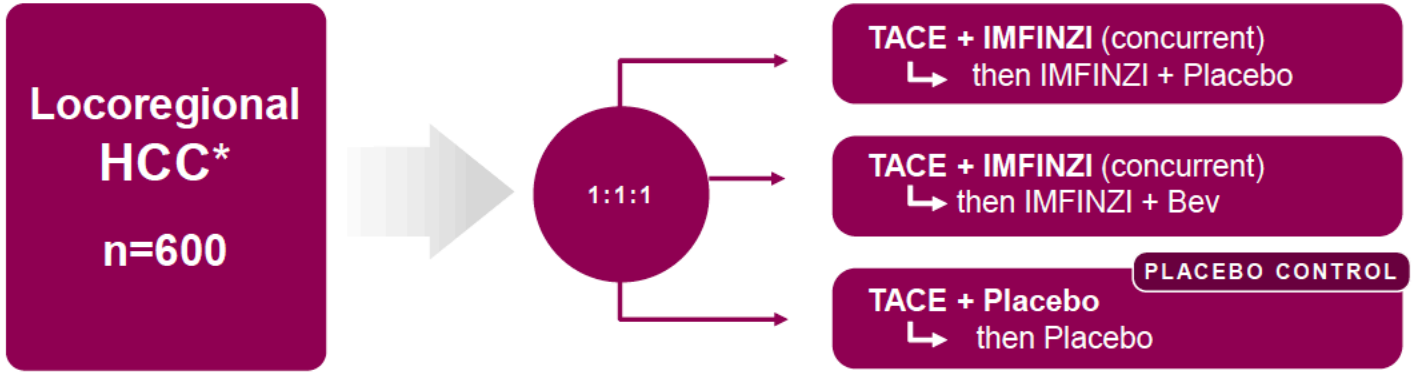
	No. (%)			
	Pembrolizumab (n = 279)		Placebo (n = 134)	
AE	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any	269 (96.4)*	145 (52.0)	121 (90.3)*	62 (46.3)
Leading to discontinuation of treatment	48 (17.2)	40 (14.3)	12 (9.0)	7 (5.2)
Leading to death	7 (2.5)	0 (0)	4 (3.0)	0 (0)
Leading to death attributed to treatment†	1 (0.4)‡	0 (0)	0 (0)	0 (0)

- Keynote did not meet endpoints of improving survival
- DCR and favorable toxicity but no improvement in OS or PFS

Several exciting therapeutic options

EMERALD-1 (Phase III): Study Design
Randomized, double-blind, locoregional HCC

IMFINZI and bevacizumab in combination with transarterial chemoembolization (TACE) in locoregional HCC



PRIMARY ENDPOINT

PFS (RECIST1.1, BICR)

SECONDARY ENDPOINTS

OS, PFS (mRECIST), ORR, PROs, Safety

STRATIFICATION FACTORS

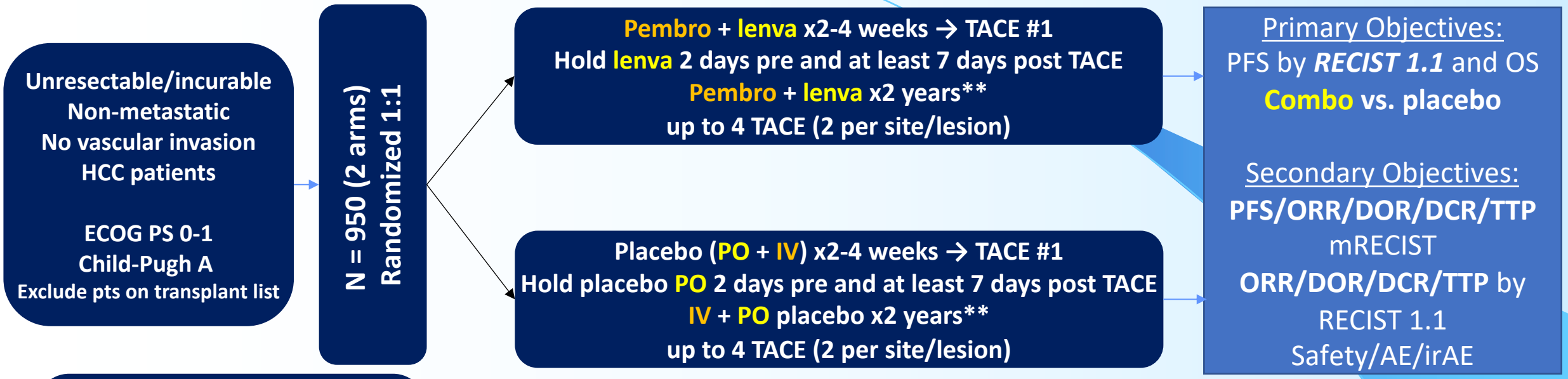
- TACE modality (DEB-TACE vs cTACE)
- Regions (Japan vs Asia non-Japan vs Other)
- Portal Vein Invasion (Vp1/Vp2 vs None)

DOSING

- **During TACE**: IMFINZI 1500mg IV Q4W
- **After TACE**: completion: combination dosing will be Q3W IMFINZI 1120mg IV + Q3W Bevacizumab 15mg/kg IV

*Patient requirements: Unsuitable for curative therapy e.g., surgical resection, ablation, transplantation, No prior TACE, No extrahepatic disease, Child Pugh A-B7, ECOG: 0 or 1, Exclude Vp3 and Vp4, No prior systemic therapy

LEAP-012 Trial Design



Stratification Criteria:
- Study Site
- AFP ≤ 400 vs. AFP >400
- ECOG PS 0 vs. 1
- ALBI Grade 1 vs. 2 or 3
- Tumor burden (6 and 12 rule)*

*3 categories: (largest tumor size in cm) + (number of tumors)

≤ 6 versus **> 6 but ≤ 12** versus **> 12**

**Lenvatinib/PO placebo may be continued beyond 2 years if clinical benefit

- New intrahepatic lesions must meet LI-RADS 5 criteria to be considered "unequivocal" by RECIST 1.1

COSMIC Trial

This is a multicenter, randomized, open-label, controlled Phase 3 trial of cabozantinib in combination with atezolizumab versus sorafenib in subjects with advanced HCC who have not received previous systemic anticancer therapy.

The study has three treatment groups:

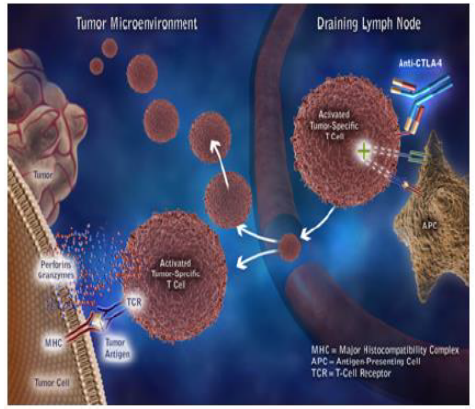
- Cabozantinib in combination with atezolizumab
- Sorafenib
- Single-agent cabozantinib

A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with Unresectable Hepatocellular Carcinoma (HIMALAYA)

Tremelimumab

Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is the central inhibitor of T-cell activation[1]

- Blocks the CTLA-4 receptor on T cells
  - Enhances and prolongs natural T-cell activation
- Fully human IgG2 antibody with a half- life of 22 days
- Studied in 31 clinical trials to date[2]
  - First clinical trial began enrollment in 2002
  - Registration program was focused on melanoma
- Manageable safety profile has been demonstrated with more than 1,200 patients enrolled in clinical studies



Durvalumab:

Durvalumab key attributes

- Immunogenicity impacting PK-PD at Phase 3 dose (10mg/kg) not a clinically significant issue
- Sustained exposure through dosing interval (>1 year)
- Uniquely engineered human IgG1κ mAb
  - Triple mutation in Fc domain removes ADCC activity
- High affinity and selectivity
  - Does not bind to PD-L2
- >1000 patients treated (monotherapy and in combination)

Study Population

- Patients aged ≥18 years with unresectable HCC
- BCLC stage B not eligible for loco-regional therapy and stage C
- No prior systemic therapy
- ECOG PS 0-1
- Child Pugh class A

Randomised N = 1200 patients

R

1 **Durvalumab 1500mg Q4W + Tremelimumab 75mg x 4 doses Q4W (N = 300)**

1 **Durvalumab 1500mg Q4W + Tremelimumab 300mg x 1 dose (N = 300)**

1 **Durvalumab monotherapy 1500mg Q4W (N = 300)**

1 **Sorafenib 400mg BID (N = 300)**

- **Primary Endpoint:** OS
- **Secondary Endpoints:** ORR, DCR, PFS, Safety, Biomarkers, PRO

CONCLUSIONS

- Very busy, exciting year in HCC
- A lot more to come in the near future
- Combination therapies is the way to go, and we need to deliver some of the systemic options locally

Thank You for Your Attention