HCC and Systemic/Radiologic Rx Options

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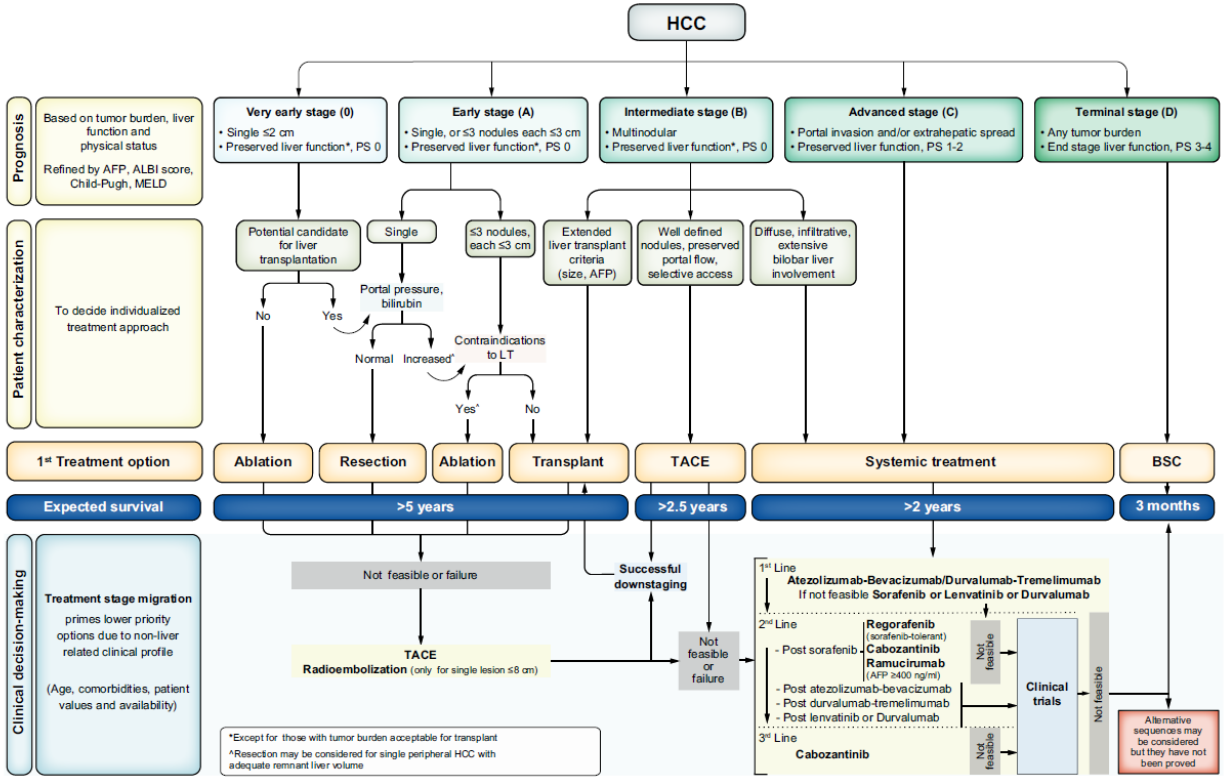
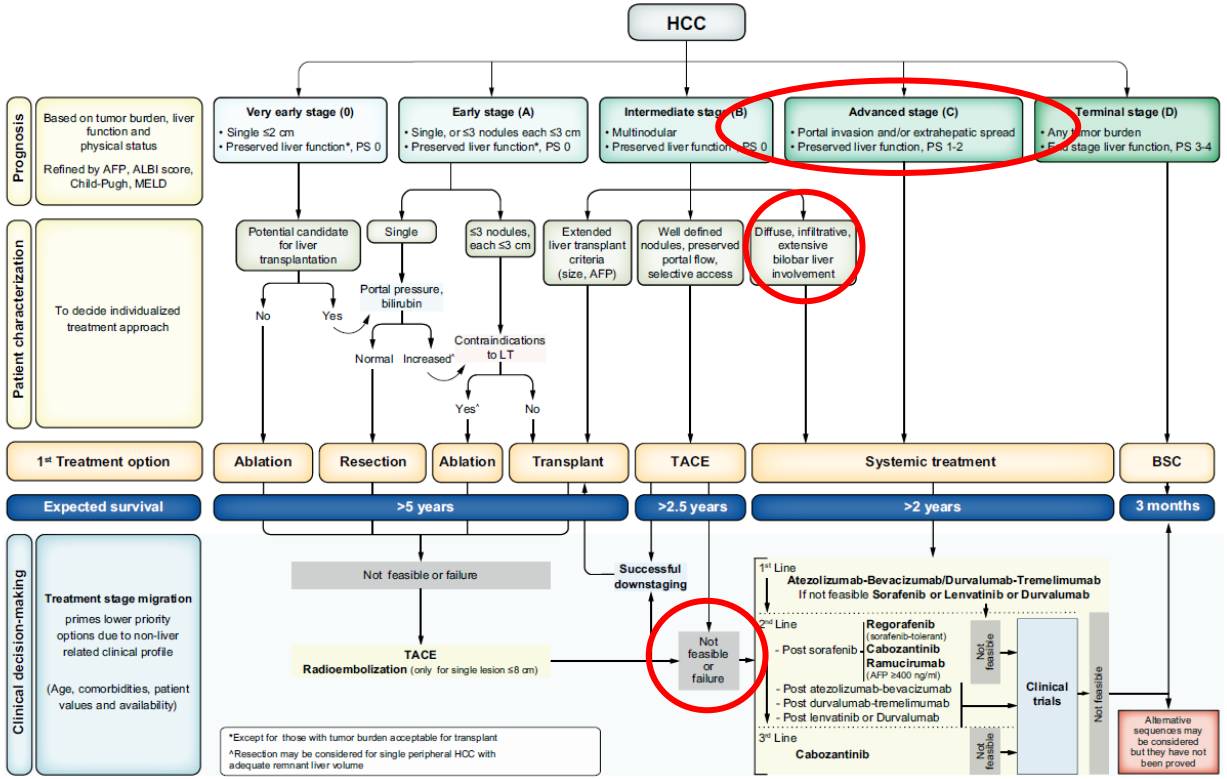
BCLC Management of HCC-2022



Reig M. *J Hep*. 2022.

BCLC Management of HCC-2022



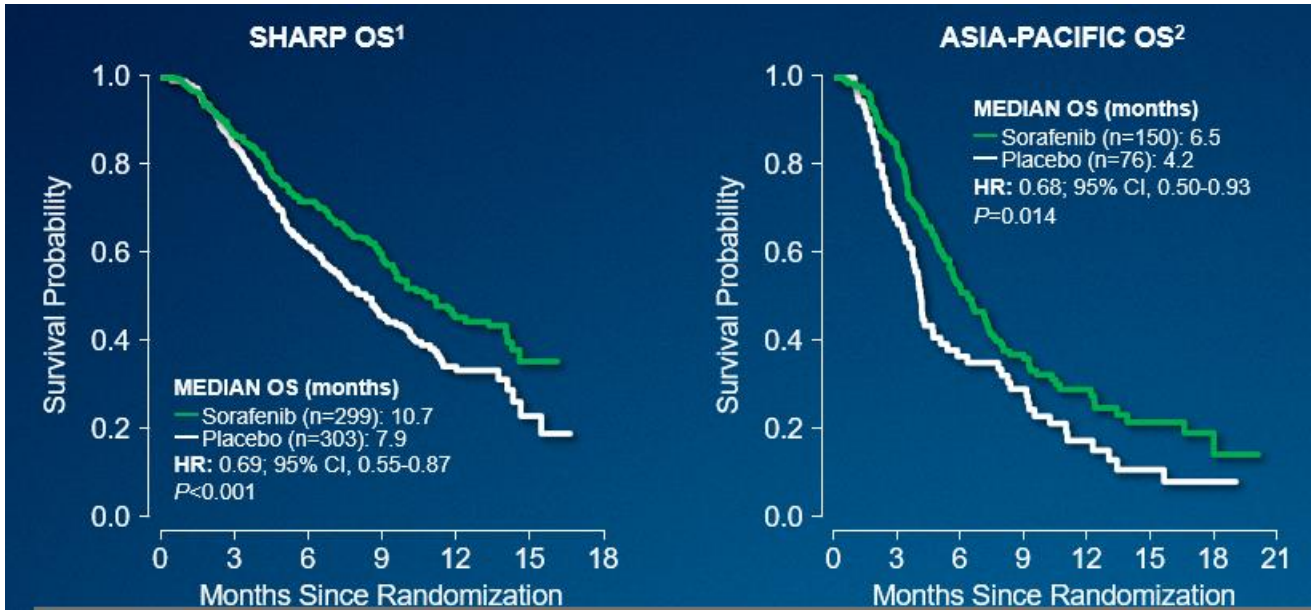
Reig M. *J Hep*. 2022.

Positive Phase 3 Studies in Advanced HCC With FDA Approvals

	SHARP	REFLECT	IMBRAVE 150	HIMALAYA
Control	placebo	sorafenib	sorafenib	sorafenib
Treatment Arm	Sorafenib	Lenvatinib	Atezo-bev	Durva-treme
VP4 included	yes	no	yes	no
HR OS	0.69	0.92 (Non-inf)	0.58	0.78
HR PFS	0.58 (TTP)	0.66	0.59	0.90 (Not sig)
ORR (RECIST)	2%	18.8 %	30%	20%
Reference	Llovet NEJM 2008	Kudo Lancet 2017	Finn NEJM 2020, Cheng J Hep 2022	Abou-alfa NEJM Evidence 2022

Pivotal Trials Demonstrated OS Benefit With Sorafenib in uHCC

Sorafenib consistently increased OS in different patient populations across geographic regions and etiologies

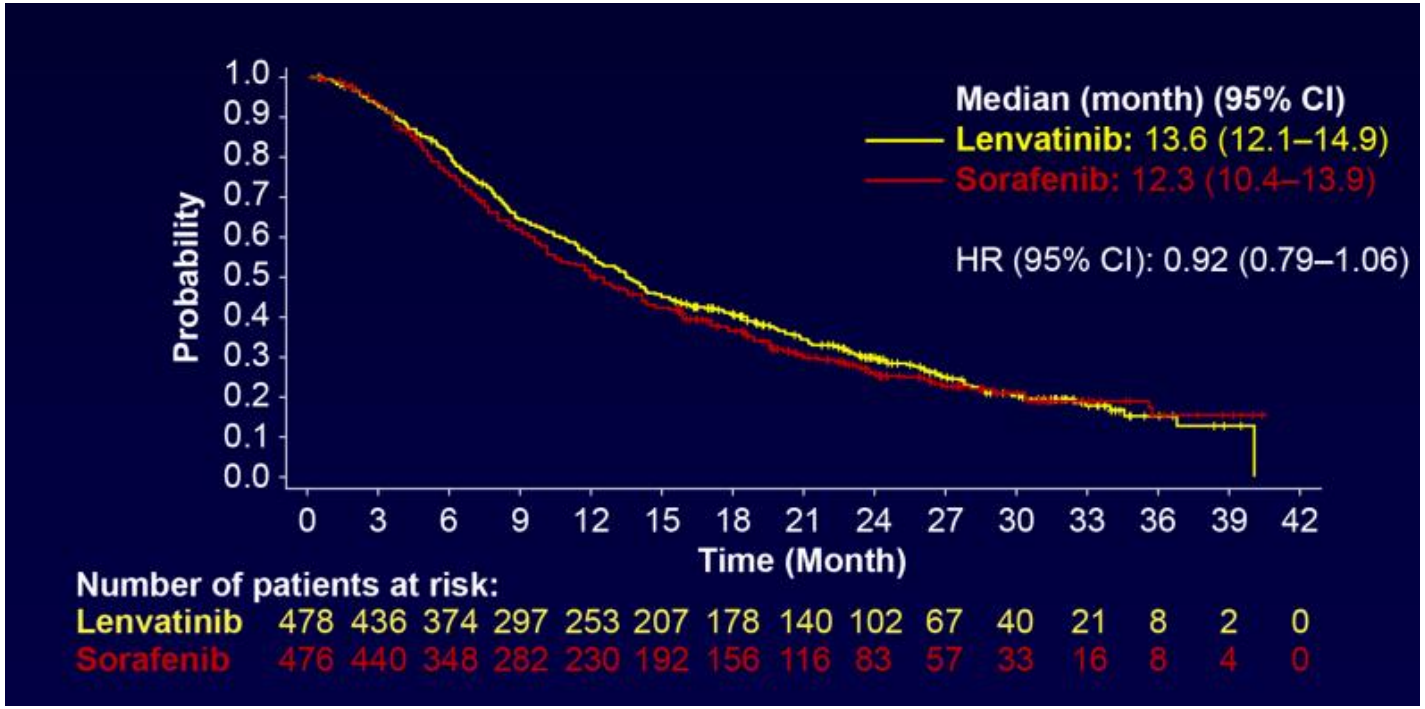


HR=hazard ratio; SHARP=Sorafenib HCC Assessment Randomized Protocol Trial.

1. Llovet J et al. *N Engl J Med*. 2008;359:378-390; 2. Cheng A-L et al. *Lancet Oncol*. 2009;10:25-34.

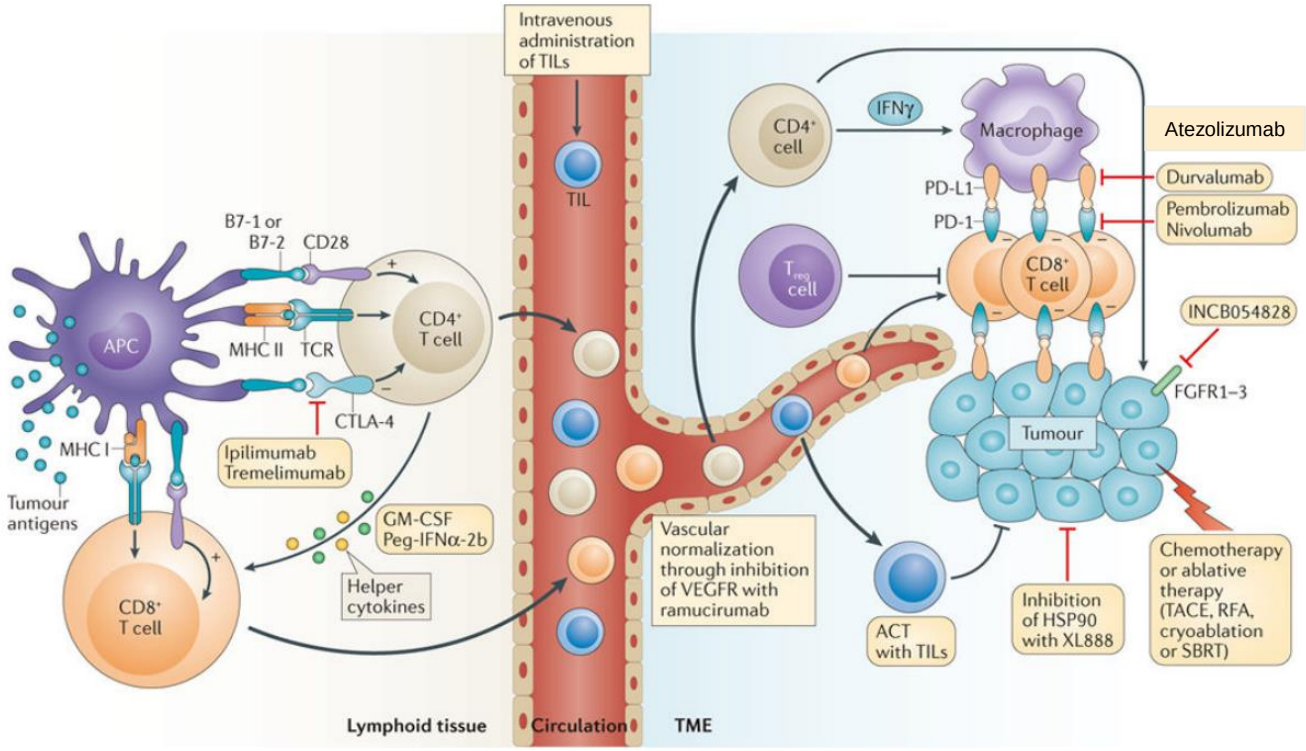
REFLECT Study

Primary Endpoint: Kaplan-Meier Estimate of OS



Kudo M, Finn RS, Qin S et al. *Lancet*. 2018.

Targeting the Immune System in Cancer



Rizvi. *Nat Rev Clin Oncol.* 2018;15:95.

Phase III Nivolumab vs. Sorafenib 1st Line CheckMate 459

Key eligibility criteria
- Histologically confirmed advanced HCC not eligible for surgical and/or LRT; or progressive disease after surgical and/or LRT
- Child-Pugh class A
- ECOG PS 0 or 1
- Systemic therapy naive

Stratification factors
- Etiology Vascular invasion and/or EHS
- Geography (Asia vs non-Asia)

R 1:1

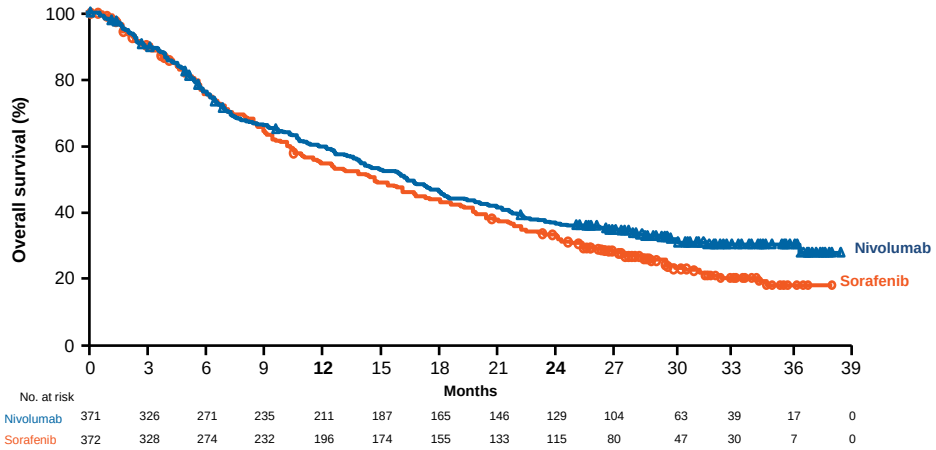
N = 743

Nivolumab
240 mg IV Q2W
n = 371

Sorafenib
400 mg po BID
n = 372

Objectives
- Primary – OS
- Secondary – ORR, PFS, efficacy PD-L1 status
- Exploratory – HRQoL using FACT-Hep

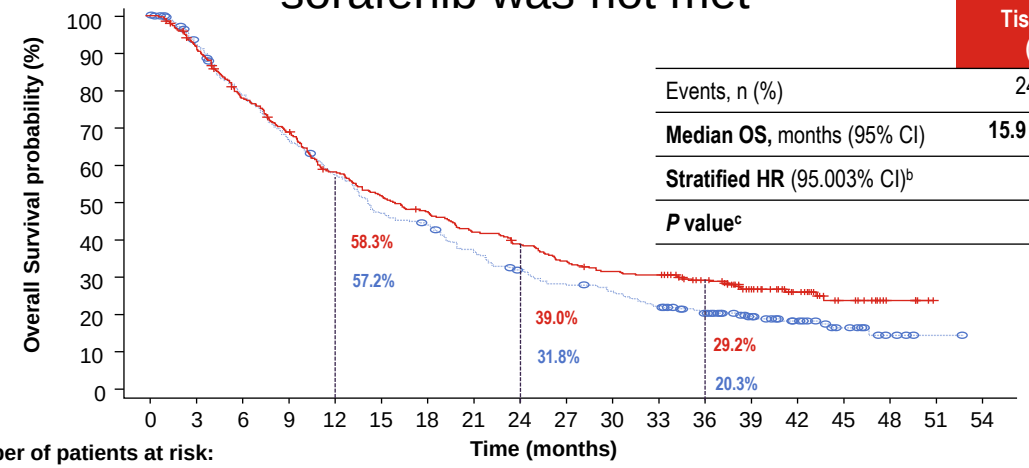
	Nivolumab (n = 371)	Sorafenib (n = 372)	HR (95% CI)[b]	P value[c]
Median OS (95% CI),[a] months	16.4 (13.9–18.4)	14.7 (11.9–17.2)	0.85 (0.72–1.02)	0.0752



Yau T, Park JW, Finn RS et al Annals of Oncology (2019) 30 (suppl_5): v851-v934.

RATIONALE-301: Overall Survival

Tislelizumab demonstrated OS noninferiority[a] vs sorafenib; OS superiority vs sorafenib was not met



	Tislelizumab (n=342)	Sorafenib (n=332)
Events, n (%)	242 (70.8)	255 (76.8)
Median OS, months (95% CI)	**15.9** (13.2, 19.7)	**14.1** (12.6, 17.4)
Stratified HR (95.003% CI)[b]	**0.85** (0.712, 1.019)	
***P* value**[c]	**0.0398**	

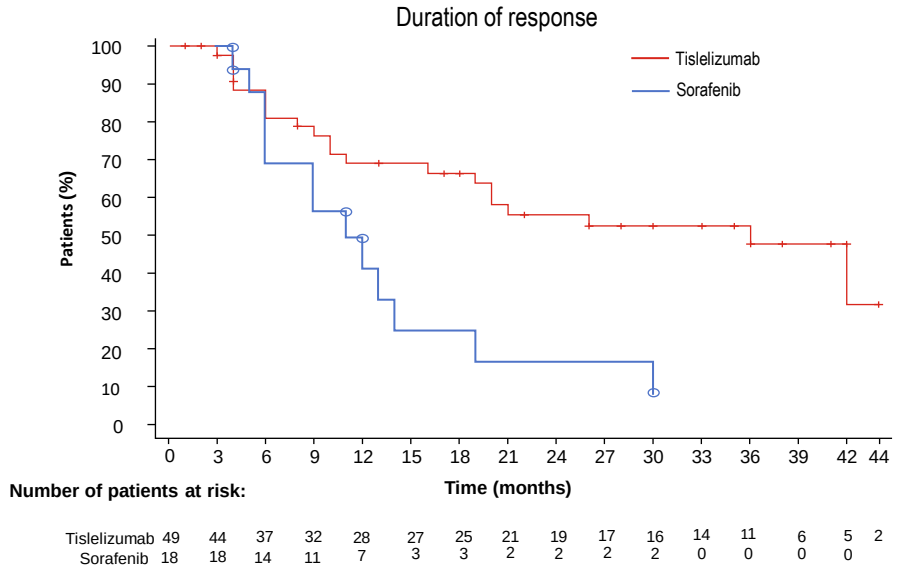
Masatoshi Kudo

Data cutoff: July 11, 2022. OS was assessed in the ITT population. [a]Prespecified boundary of NI: upper bound of 95.003% CI of stratified HR <1.08; pre-specified boundary of superiority: one-sided *P* value <0.0223 (approximate HR <0.8352). [b]HR was based on a Cox proportional hazard model including treatment as a covariate, geography (Asia [including Japan] vs rest of world [EU/US]), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (HCV vs other), and ECOG PS (0 vs 1) as stratification factors. [c]One-sided stratified log-rank test. Abbreviations: CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; HCV, hepatitis C virus; HR, hazard ratio; ITT, intent-to-treat; NI, non-inferiority; OS, overall survival.

RATIONALE-301: Overall Response Rate by IRC

Tislelizumab was associated with a higher ORR and more durable responses vs sorafenib

	Tislelizumab (n=342)	Sorafenib (n=332)
ORR, n (%) [95% CI][a]	49 (14.3) [10.8, 18.5]	18 (5.4) [3.2, 8.4]
Best overall response, n (%)[a]		
CR	10 (2.9)	1 (0.3)
PR	39 (11.4)	17 (5.1)
SD	94 (27.5)	137 (41.3)
PD	166 (48.5)	117 (35.2)
Undetermined[b]	26 (7.6)	50 (15.1)
Non-CR/non-PD[c]	7 (2.0)	10 (3.0)
Responders	**Tislelizumab (n=49)**	**Sorafenib (n=18)**
Median DoR, months (95% CI)	36.1 (16.8, NE)	11.0 (6.2, 14.7)
Patients with ongoing response, n (%)[d]	20/28 (71.4)	2/5 (40.0)



Masatoshi Kudo

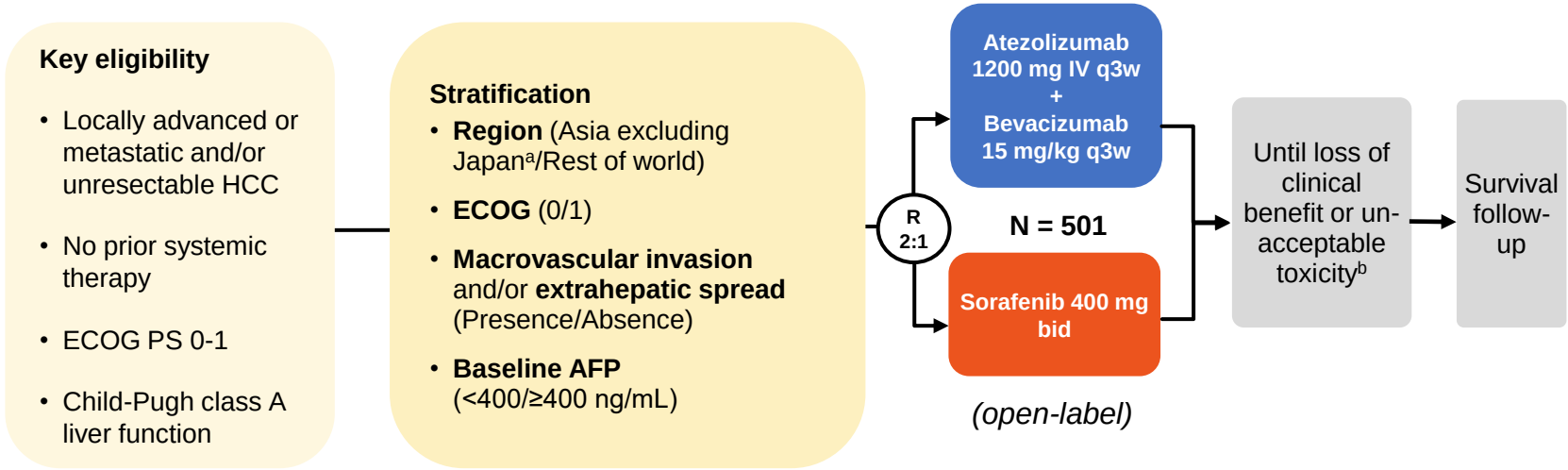
Data cutoff: July 11, 2022. ORR was assessed in the ITT population. [a]Confirmed responses; [b]Patients with no postbaseline tumor assessment (not assessable) or a nonevaluable tumor assessment. [c]Patients were assessed as non-CR/non-PD if the IRC was not able to identify the target lesions at screening. Patients with no target lesions were evaluated based on the assessment of nontarget lesions or the presence of new lesions. [d]Patients who had PD or died were excluded from this analysis. Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; IRC, independent review committee; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Phase 3 IO Combination Studies in HCC

- IO + VEGF antibody
  - Atezolizumab + bevacizumab (IMBrave 150) (Positive)
  - Sintilimab + IBI305 (ORIENT 32) (Positive)
- IO + TKI
  - Atezolizumab+ cabozantinib (COSMIC 312) (Negative)
  - Pembrolizumab + lenvatinib (LEAP 002) (Negative)
  - Camrelizumab + apatinib (Positive)
- IO +IO
  - Durvalumab + tremilimumab (HIMALAYA) (Positive)
  - Nivolumab + ipilimumab (9DW) (ongoing)

IO + VEGF Antibody

IMbrave150 Study Design



Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

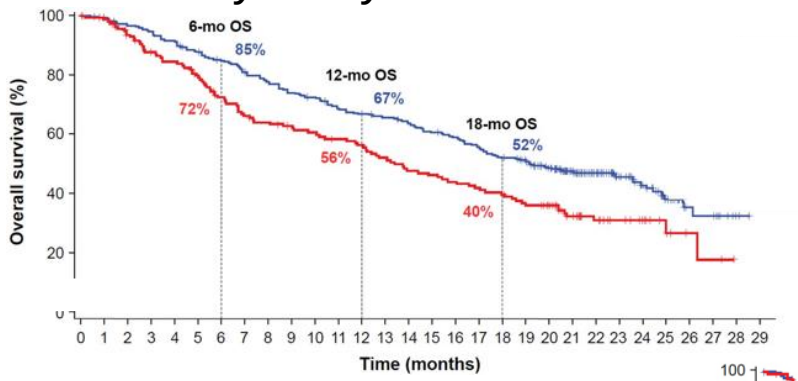
Secondary endpoints included:
- IRF-assessed ORR, DOR per RECIST 1.1 and HCC mRECIST[b]
- PROs: TTD[c] of QOL, physical and role functioning (EORTC QLQ-C30)
- Safety and tolerability assessed based on the nature, frequency and severity of AEs per NCI CTCAE version 4.0

Finn et al. *New Engl J Med.* 2020.
[a] Japan is included in rest of world. [b] Tumor assessment by computed tomography or magnetic resonance imaging was done at baseline and every 6 weeks until 54 weeks, then every 9 weeks thereafter.
[c] Time from randomization to first decrease from baseline of ≥ 10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
AFP, α-fetoprotein; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer; IRF, independent review facility; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; QOL, quality of life; TTD, time to deterioration.

IMbrave150 Trial

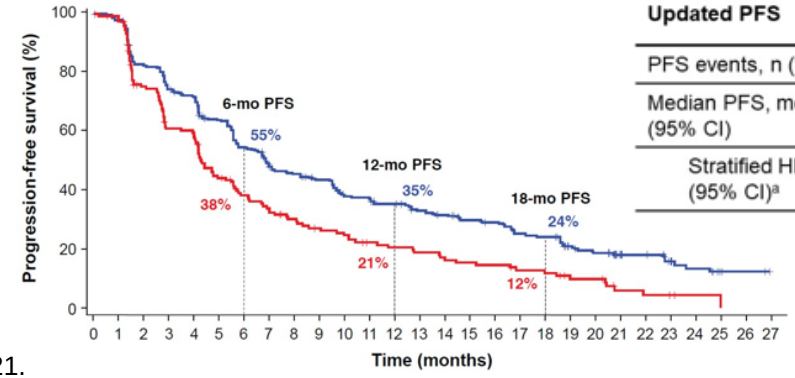
Key Efficacy Data: Updated OS and PFS

– Primary analysis OS/PFS HR: 0.58/0.59 (median follow-up: 8.6 mo)



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

– Median follow-up: 15.6 mo



Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	

Finn RS et al. *NEJM*. 2020; Finn RS et al. *ASCO GI*. 2021.

Updated Response and Duration of Response

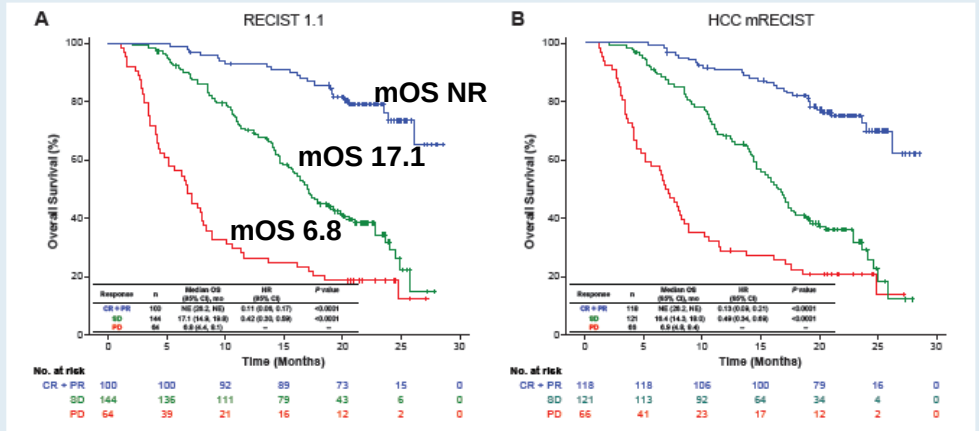
	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Cheng AL. *J Hep*. 2022.
Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. DCR, disease control rate.
[a] Only patients with measurable disease at baseline were included in the analysis of ORR.
[b] Only confirmed responders were included in the analysis of ORR and DOR.

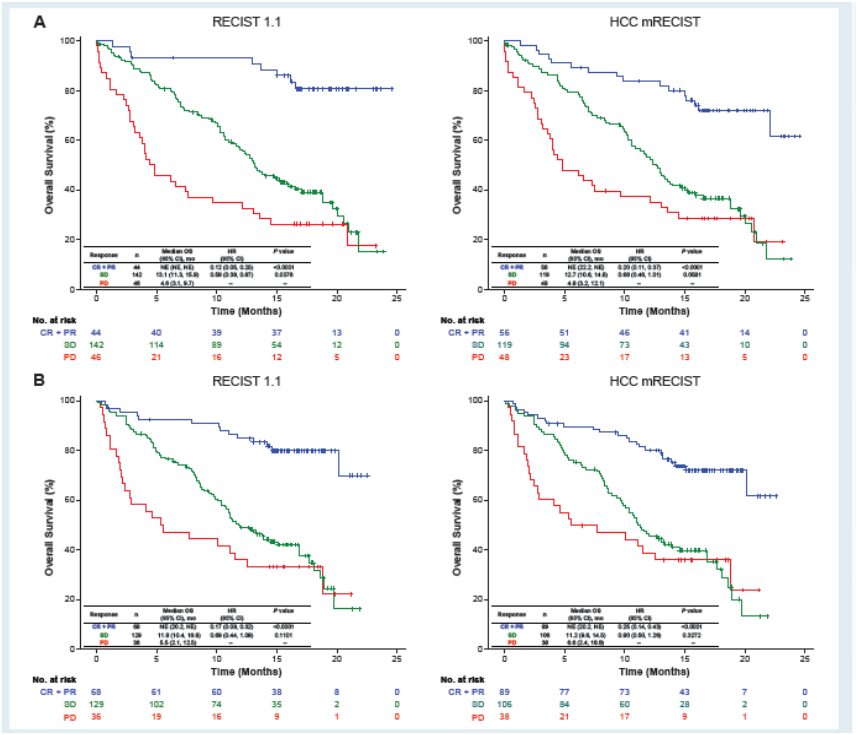
Best Response and OS From ImBrave 150

- OS by BOR per RECIST 1.1 and HCC mRECIST is shown in Figure 2

Figure 2. OS in Patients (Atezolizumab + Bevacizumab Arm) With Confirmed Response vs SD vs PD per (A) RECIST 1.1 and (B) HCC mRECIST



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

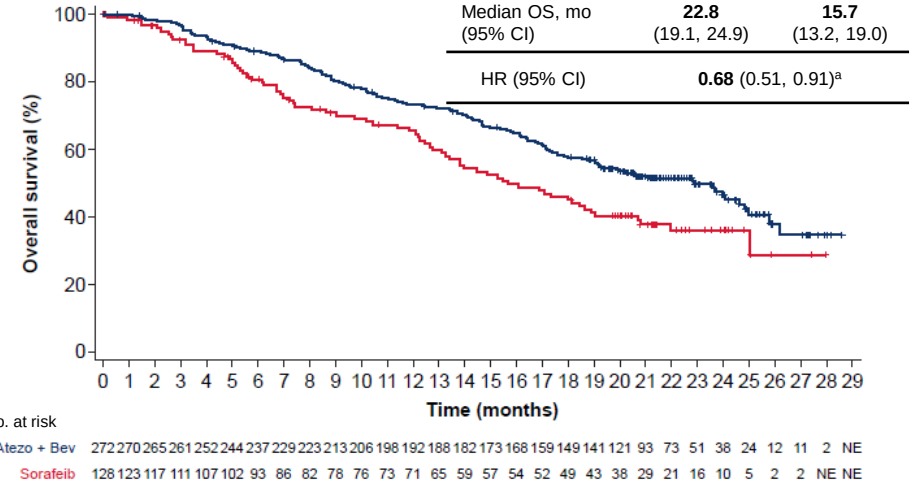


Ducreux et al. *ASCO*. 2021.

Overall Survival

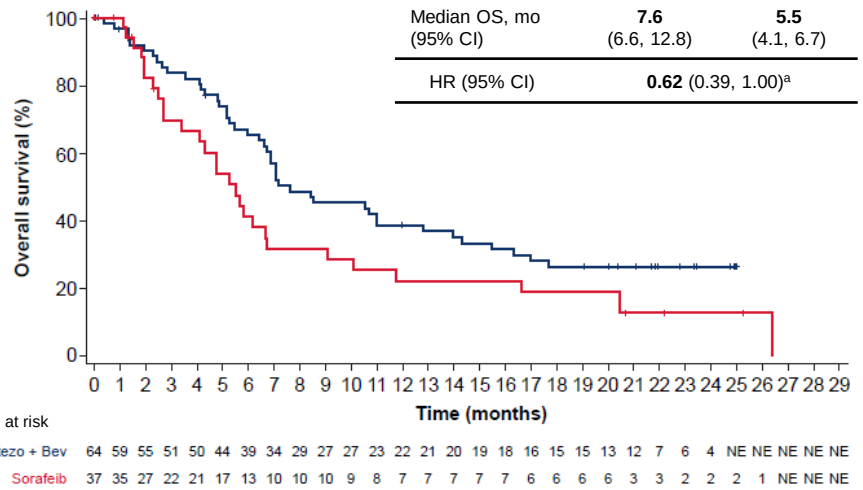
Non–high-risk patients

	Atezo + Bev (n=272)	Sorafenib (n=128)
OS events, n (%)	136 (50)	71 (55)
Median OS, mo (95% CI)	**22.8** (19.1, 24.9)	**15.7** (13.2, 19.0)
HR (95% CI)	**0.68** (0.51, 0.91)[a]	



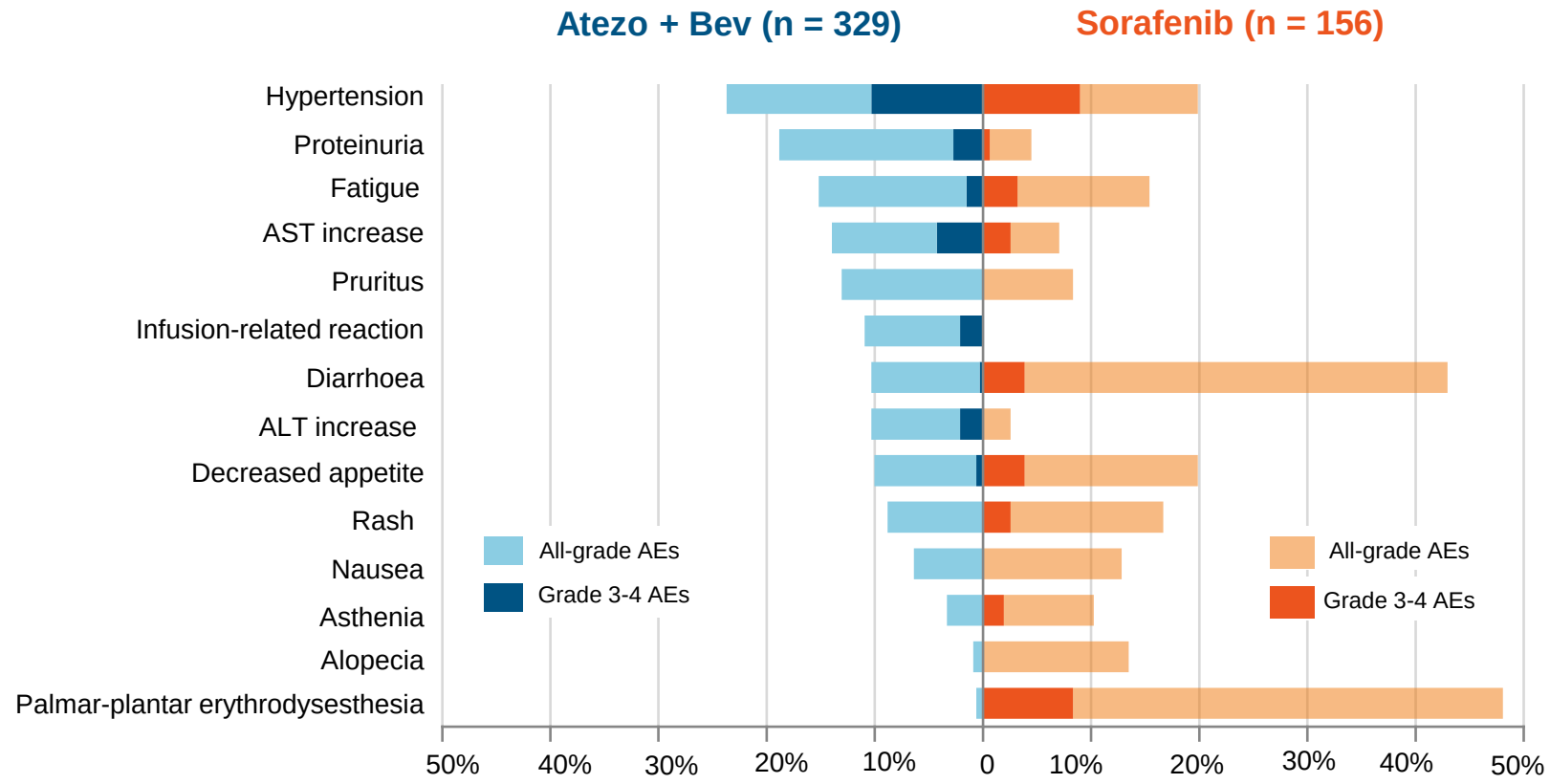
High-risk patients

	Atezo + Bev (n=64)	Sorafenib (n=37)
OS events, n (%)	44 (69)	29 (78)
Median OS, mo (95% CI)	**7.6** (6.6, 12.8)	**5.5** (4.1, 6.7)
HR (95% CI)	**0.62** (0.39, 1.00)[a]	



Finn RS. IMbrave150 high-risk patients [abs #5080].
Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. NE, not evaluable.
[a] OS analysis is descriptive.
https://bit.ly/3vjRqjk

TRAEs: ≥10% Any Grade in Either Arm



Finn et al. *N Engl J Med.* 2020.

Bleeding Events

All-cause AESIs by medical concept and preferred term, n (%)[a]	Atezo + Bev (n = 329)		Sorafenib (n = 156)	
	All grade	**Grade 3-4**	**All grade**	**Grade 3-4**
Bleeding/haemorrhage	83 (25.2)	21 (6.4)	27 (17.3)	9 (5.8)
Bleeding events in > 1% of either group				
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Haematuria	10 (3.0)	1 (0.3)	0	0
Gingival bleeding	9 (2.7)	0	0	0
Oesophageal varices haemorrhage	8 (2.4)	6 (1.8)	1 (0.6)	1 (0.6)
Gastrointestinal haemorrhage	8 (2.4)	4 (1.2)	3 (1.9)	3 (1.9)
Rectal haemorrhage	5 (1.5)	1 (0.3)	3 (1.9)	0
Upper gastrointestinal haemorrhage	4 (1.2)	2 (0.6)	2 (1.3)	2 (1.3)
Haemoptysis	3 (0.9)	0	5 (3.2)	0
Peritoneal haemorrhage	0	0	2 (1.3)	1 (0.6)

SAEs ≥2% in Either Arm

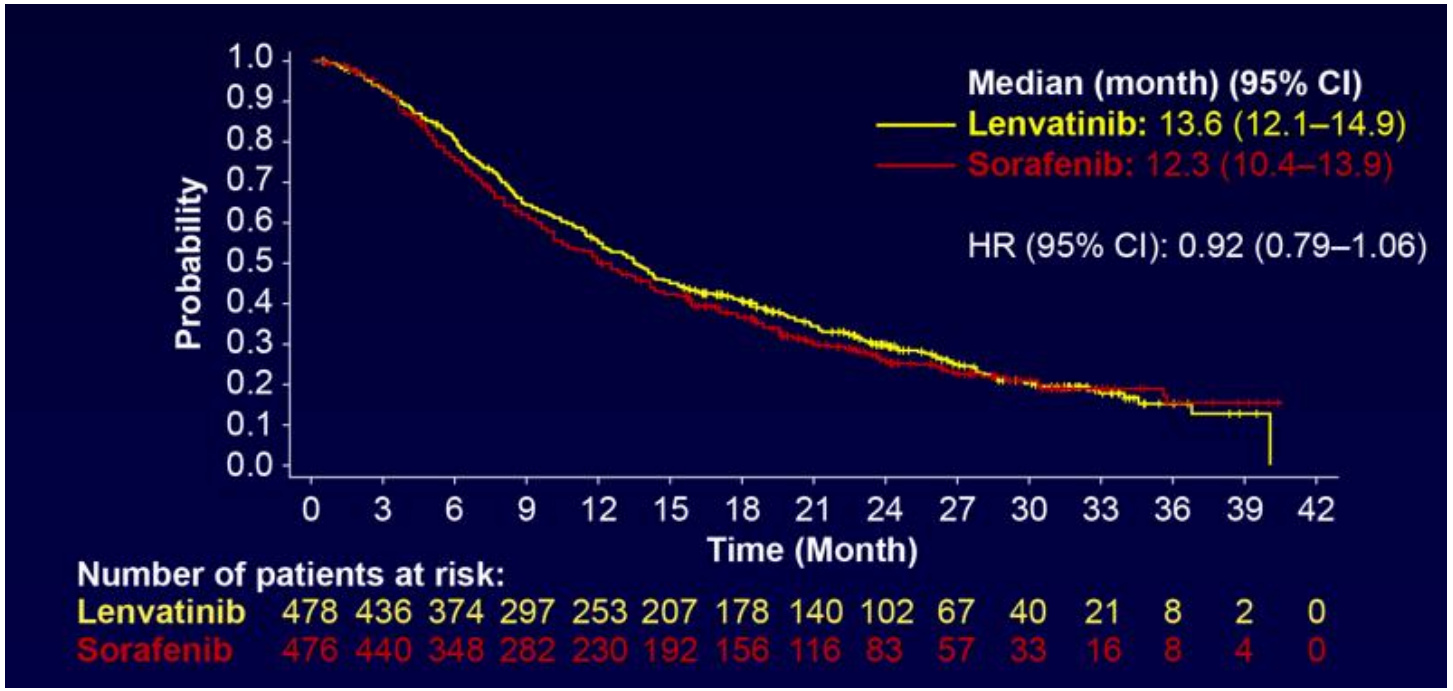
n (%)	Atezo + Bev (n = 329)			Sorafenib (n = 156)		
	Any grade	Grade 3-4	Grade 5	Any grade	Grade 3-4	Grade 5
Gastrointestinal haemorrhage	8 (2.4)	4 (1.2)	3 (0.9)	3 (1.9)	3 (1.9)	0
Oesophageal varices haemorrhage	8 (2.4)	6 (1.8)	1 (0.3)	1 (0.6)	1 (0.6)	0
Pyrexia	7 (2.1)	3 (0.9)	0	2 (1.3)	1 (0.6)	0

Finn et al. *N Engl J Med.* 2020.

IO + TKI

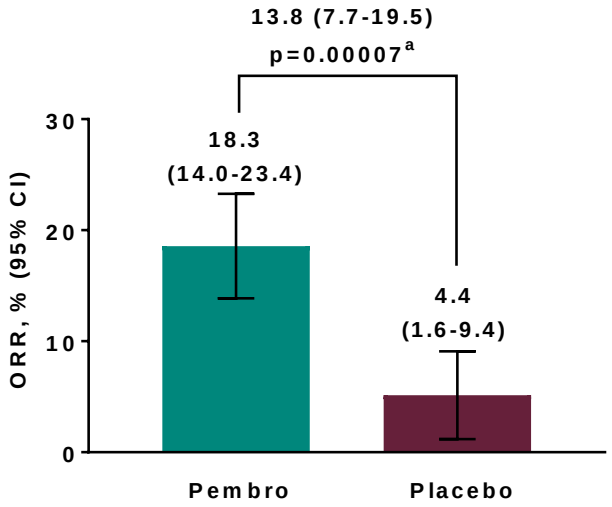
REFLECT Study

Primary Endpoint: Kaplan-Meier Estimate of OS



Kudo M, Finn RS, Qin S et al. *Lancet*. 2018.

KEYNOTE 240 Objective Response Rate at Final Analysis (RECIST 1.1, BICR)



Duration of response, median (range)[b,c]:
- Pembrolizumab: 13.8 mo (1.5+ mo − 23.6+ mo)
- Placebo: not reached (2.8 mo−20.4+ mo)

Response n (%)	Pembrolizumab N=278	Placebo N=135
Best Overall Response		
CR	6 (2.2)	0 (0.0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
SD ≥23 wks	37 (18.3)	20 (14.8)
Progressive Disease	90 (32.4)	57 (42.2)
Disease Control Rate (CR+PR+SD)	173 (62.2)	72 (53.3)

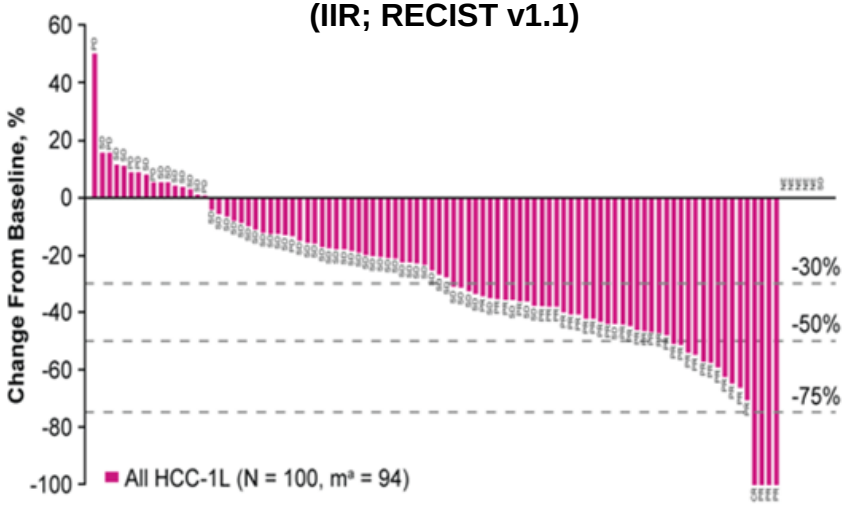
[a]Nominal one-sided P-value based on the Miettinen and Nurminen method stratified by randomization factors. [b]From product-limit (Kaplan-Meier) method for censored data. [c]"+" indicates no PD by the time of last disease assessment.
Data cutoff: Jan 2, 2019.
Finn et al. *J Clin Onc*. 2019.

KEYNOTE-524: Lenvatinib+Pembrolizumab Efficacy Outcomes

Parameter	Lenvatinib + Pembrolizumab (N = 100)
	RECIST v1.1 per IIR
ORR (confirmed responses), n (%) (95% CI)[a]	36 (36) (26.6–46.2)
Best overall response, n (%)	
Complete response	1 (1)
Partial response	35 (35)
Stable disease[b]	52 (52)
Progressive disease	7 (7)
Unknown/not evaluable	5 (5)
Median DOR[c] for confirmed responders, months (95% CI)[d]	12.6 (6.9–NE)
Median TTR for confirmed responders, months (range)	2.8 (1.2–7.7)
Disease control rate, n (%) (95% CI)[a]	88 (88) (80.0–93.6)

[a]The 95% CIs are calculated using an exact method of binomial distribution (Clopper–Pearson method); [b]includes unconfirmed partial response, noncomplete response/nonprogressive disease, and durable stable disease; [c]the Kaplan–Meier method was used for estimating DOR; [d]the 95% CIs are based on a generalized Brookmeyer and Crowley method.

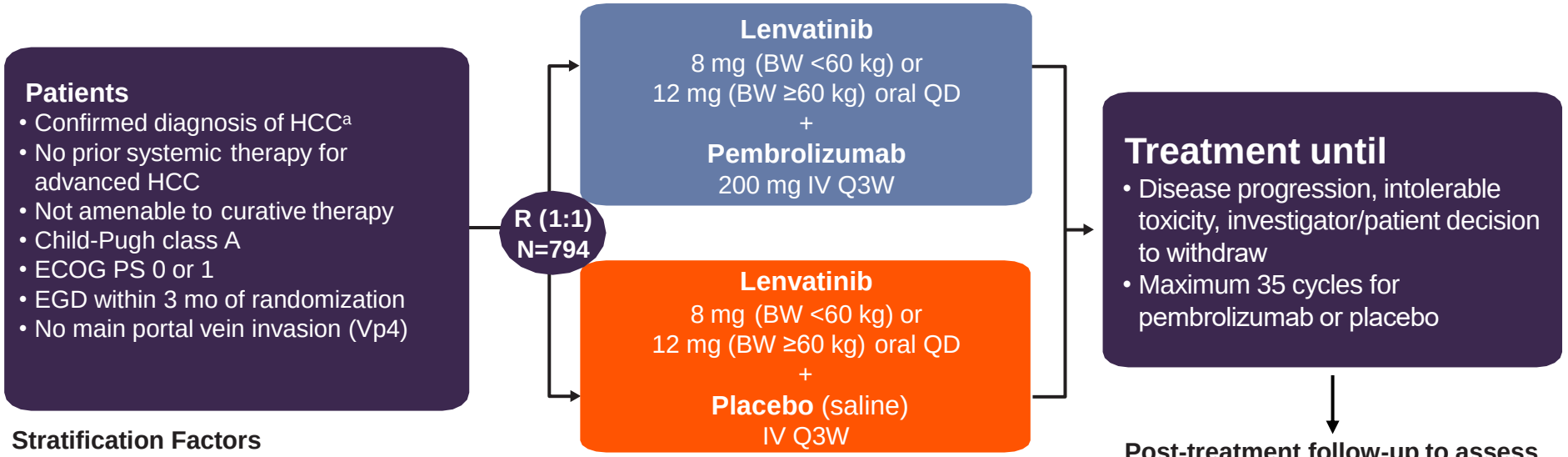
Percentage Change From Baseline in Sum of Diameters of Target Lesions at Postbaseline Nadir (IIR; RECIST v1.1)



[a]m = number of patients with both baseline and postbaseline values for the sum of diameters of target lesions.

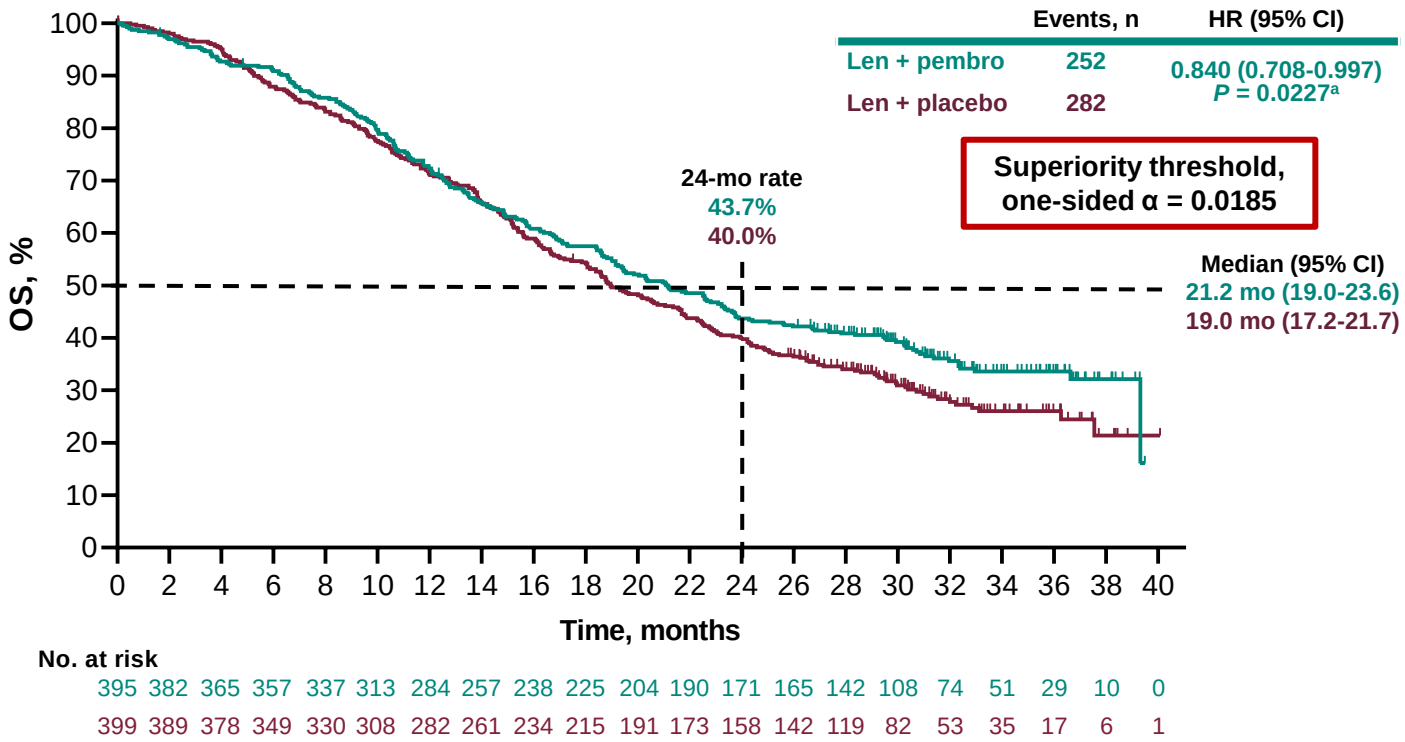
Finn et al. *JCO*. 2020.

LEAP-002 Study Design (NCT03713593)



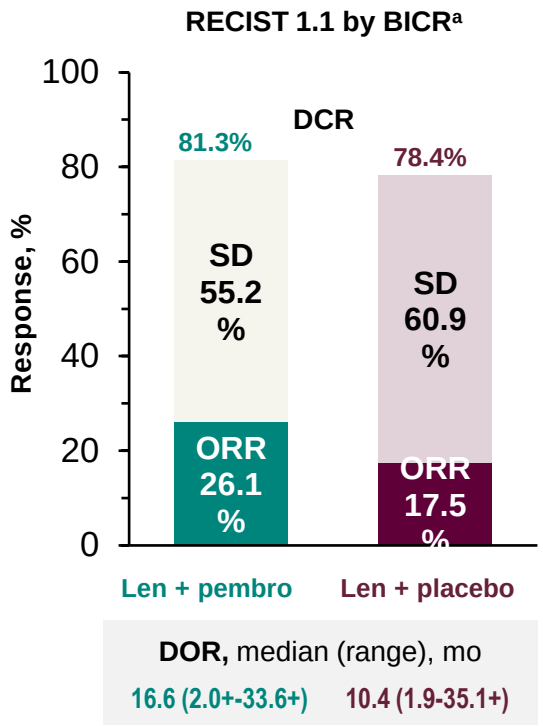
[a]Diagnosis to be confirmed by radiology, histology, or cytology (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible). Radiologic confirmation of diagnosis is provided by the study site. Clinically confirmed diagnosis of HCC (with liver mass ≥1 cm and arterial hypervascularity with washout in the venous phase seen with either triphasic CT or MRI) per American Association for the Study of Liver Diseases criteria. [b]Radiological imaging assessment performed Q9W.

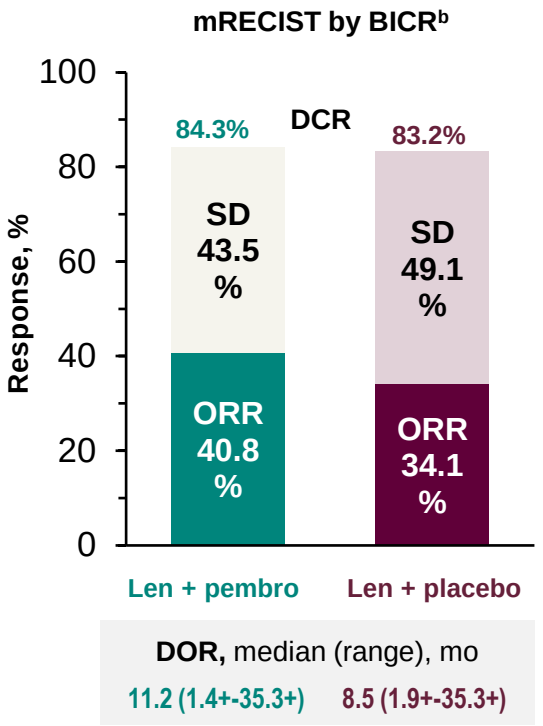
Overall Survival, ITT, FA



[a]Did not reach superiority threshold, one-sided α=0.0185.
Data cutoff date for FA: 21 June 2022; median follow-up: 32.1 months.

Summary of Response and DOR, FA



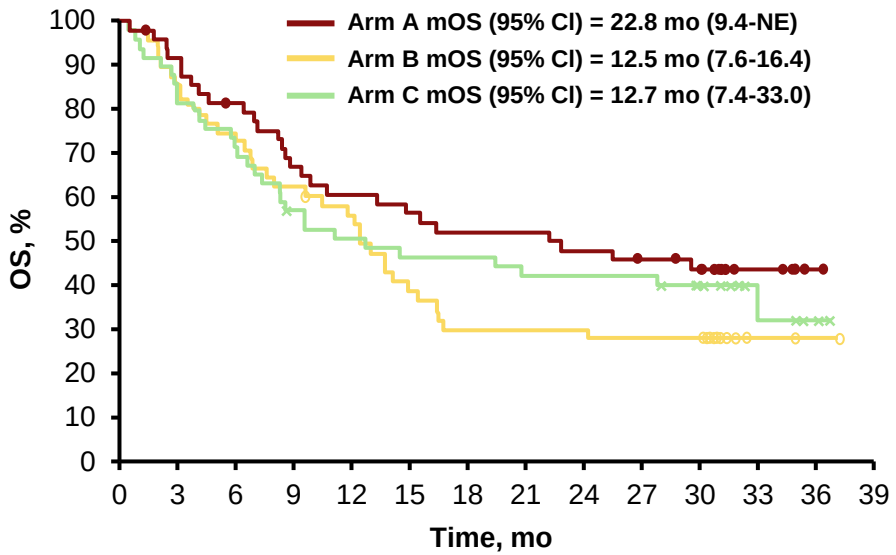


[a]CR=1.5% in both arms; PD=12.2% for len + pembro and 15.0% for len + placebo.
[b]CR=9.4% for len + pembro and 9.5% with len + placebo; PD=9.4% for len + pembro and 10.3% for len + placebo.
Data cutoff date for FA: 21 June 2022.

IO + IO

CheckMate -040: Nivolumab + Ipilimumab Efficacy Results[1]

	Arm A NIVO1/IPI3 Q3W (n = 50)	Arm B NIVO3/IPI1 Q3W (n = 49)	Arm C NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR by BICR using RECIST v1.1, n (%)	16 (32)	15 (31)	15 (31)
BOR, n (%)			
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD	9 (18)	5 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
Unable to determine	3 (6)	4 (8)	4 (8)
DCR, n (%)	27 (54)	21 (43)	24 (49)
Median TTR (range), months	2.0 (1.1–12.8)	2.6 (1.2–5.5)	2.7 (1.2–8.7)
Median DOR (range), months	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)

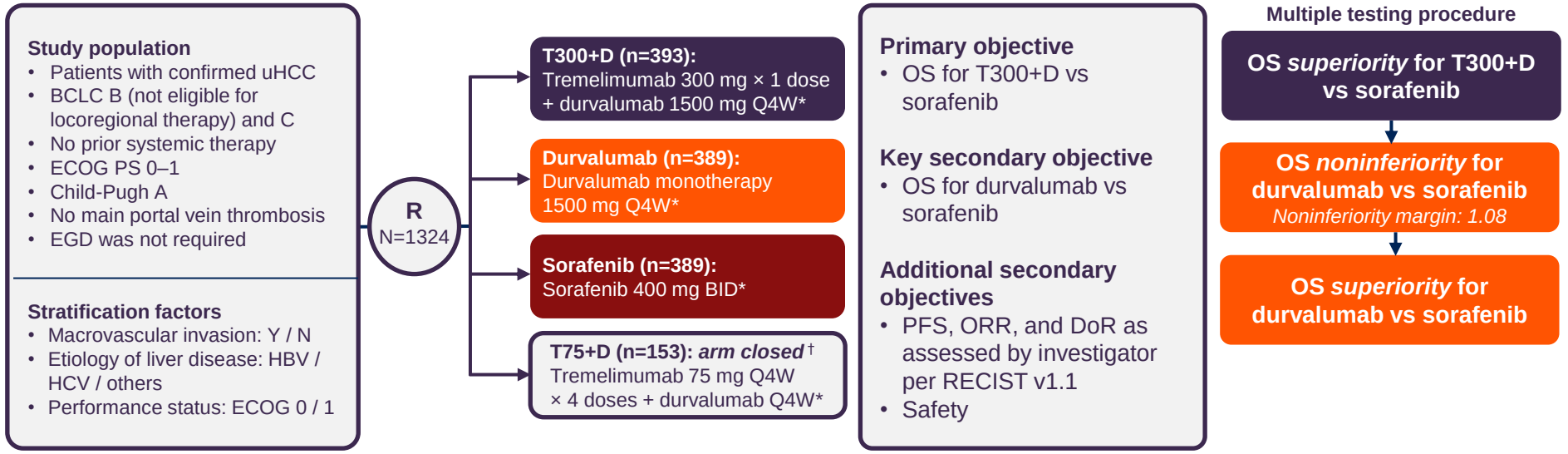


- Similar ORR, DCR, and DOR were observed across treatment arms
  - Consistently high ORR (>30%) was achieved in all treatment arms
  - In total, 7 patients had complete response (4 in arm A and 3 in arm B)
- Arm A: NIVO1/ IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose
- Arm B: NIVO3/ IPI1 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose
- ORR is defined as CR + PR
- SD does not include 2 patients in arm A and 1 patient in arm B who were reported as non-CR/non-PD
- DCR is defined as CR + PR + SD + non-CR/non-PD

1. Yau T. *JAMA Onc*. 2020; 2. El-Khoueiry AB et al. *ILCA*. 2019. Abstract O-13.

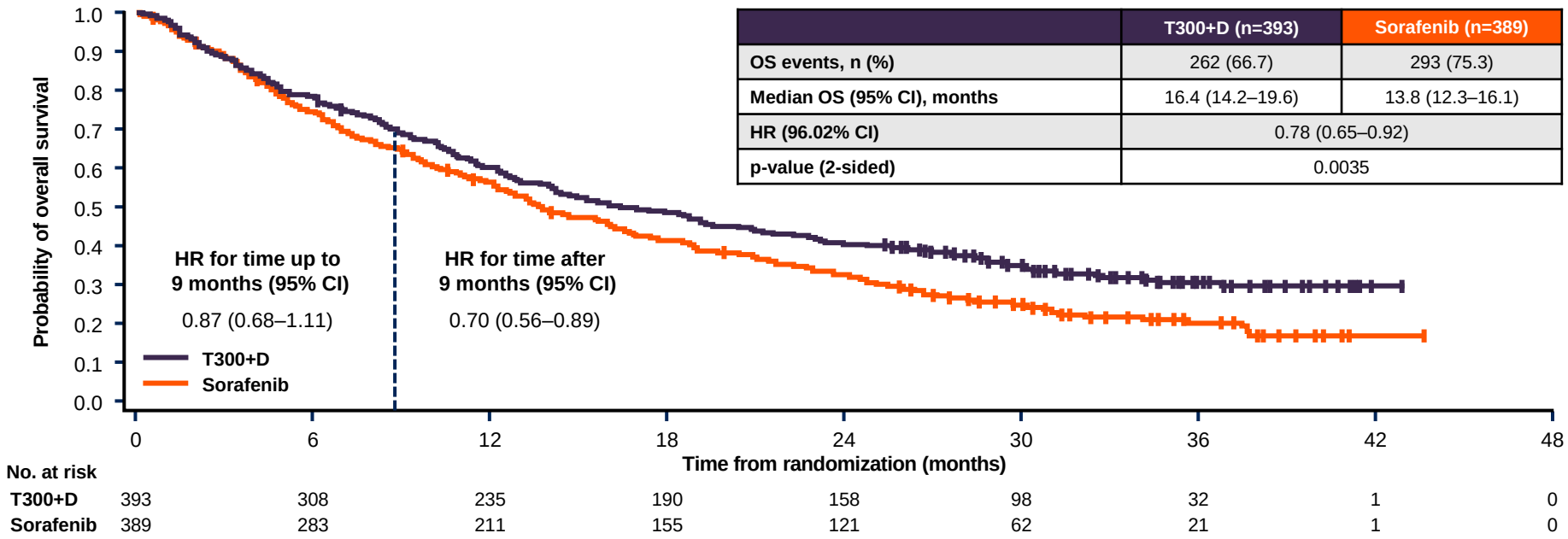
HIMALAYA Study Design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial



*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.
BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks.
Ghassan K Abou-Alfa, MD, MBA

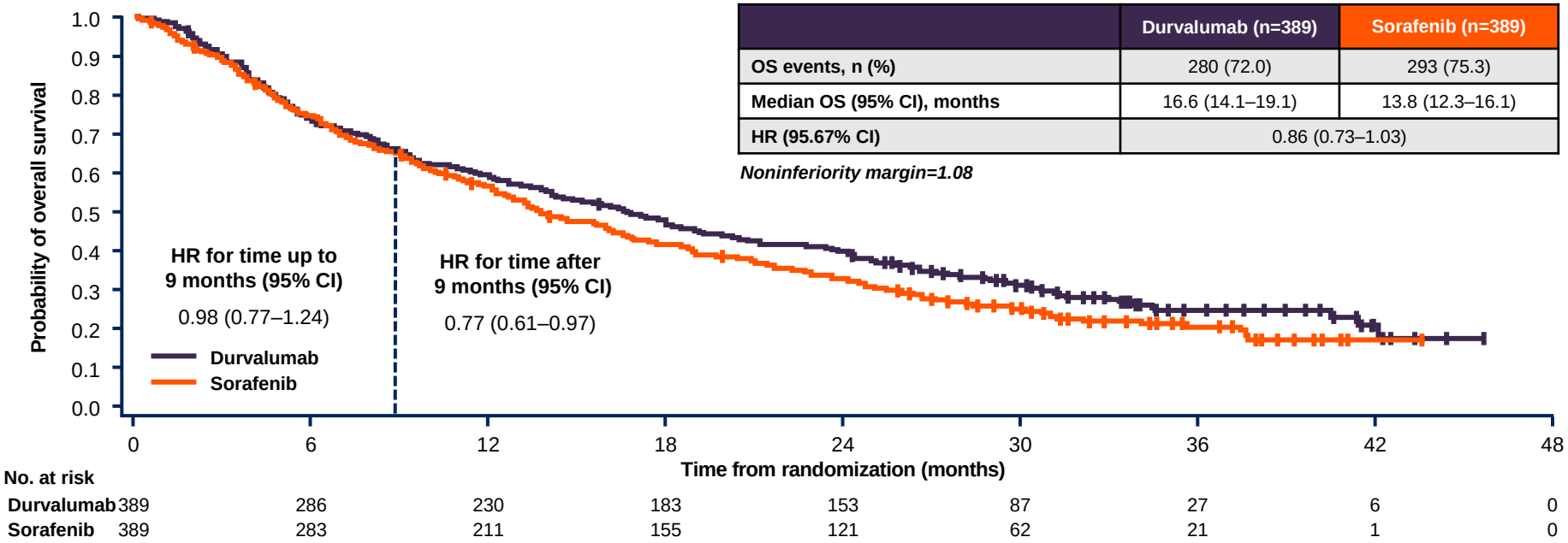
Primary Objective: Overall Survival for T300+D vs Sorafenib



	T300+D (n=393)	Sorafenib (n=389)
OS events, n (%)	262 (66.7)	293 (75.3)
Median OS (95% CI), months	16.4 (14.2–19.6)	13.8 (12.3–16.1)
HR (96.02% CI)	0.78 (0.65–0.92)	
p-value (2-sided)	0.0035	

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74–34.53) months for T300+D and 32.23 (95% CI, 30.42–33.71) months for sorafenib.
CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.
Ghassan K Abou-Alfa, MD, MBA.

Secondary Objective: Overall Survival for Durvalumab vs Sorafenib

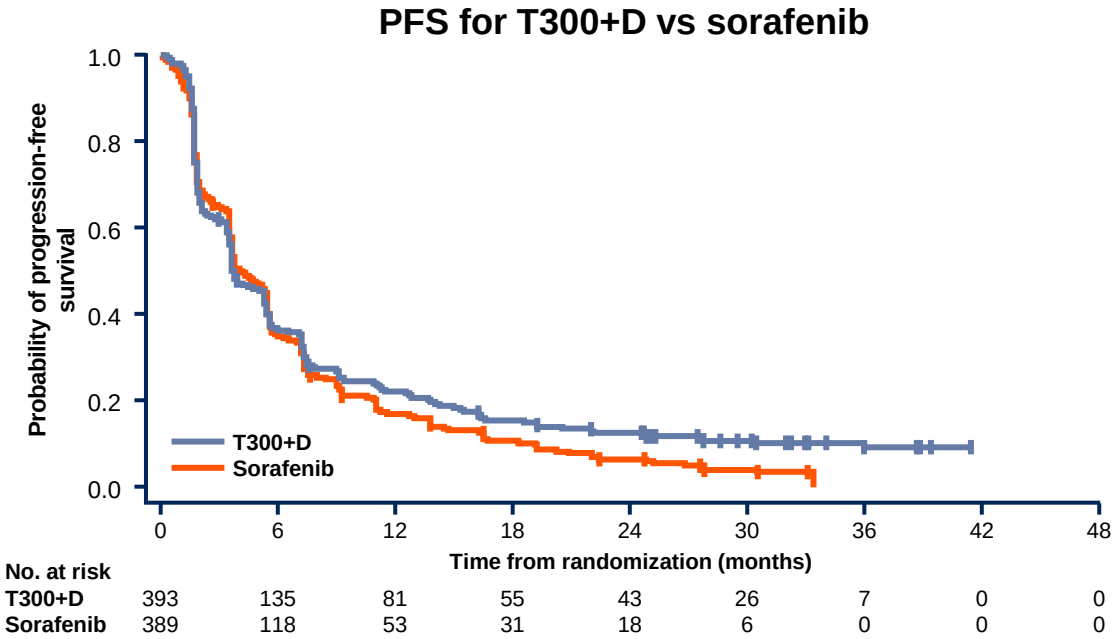


	Durvalumab (n=389)	Sorafenib (n=389)
OS events, n (%)	280 (72.0)	293 (75.3)
Median OS (95% CI), months	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95.67% CI)	0.86 (0.73–1.03)	

Noninferiority margin=1.08

Data cut-off: August 27, 2021. Median duration of follow-up was 32.56 (95% CI, 31.57–33.71) months for durvalumab and 32.23 (95% CI, 30.42–33.71) months for sorafenib.
CI, confidence interval; HR, hazard ratio; NI, noninferiority; OS, overall survival.
Ghassan K Abou-Alfa, MD, MBA.

Progression-Free Survival



	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68–5.32)	3.65 (3.19–3.75)	4.07 (3.75–5.49)
PFS HR* (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	–
Progression-free at DCO, n (%)	49 (12.5)	32 (8.2)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
Treated ≥1 cycle beyond progression, n (%)†	182 (46.9)	188 (48.5)	134 (34.4)

*Versus sorafenib. †Percent calculated from total patients in the safety analysis set: T300+D, N=388; durvalumab, N=388, sorafenib, n=374.
CI, confidence interval; DCO, data cutoff; HR, hazard ratio; PFS, progression-free survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTP, time to progression.
Ghassan K Abou-Alfa, MD, MBA.

Tumor Response

	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* n (%)	**79 (20.1)**	**66 (17.0)**	**20 (5.1)**
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months 25th percentile 75th percentile	22.34 8.54 NR	16.82 7.43 NR	18.43 6.51 25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ % 6 months 12 months	 82.3 65.8	 81.8 57.8	 78.9 63.2

*By investigator assessment according to RECIST v1.1. Responses are confirmed. †Defined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD. ‡Calculated using Kaplan-Meier technique.
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TTR, time to response.
Ghassan K Abou-Alfa, MD, MBA.

Safety and Tolerability

Event, n (%)	T300+D (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)†	0	3 (0.8)‡
Any TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy.

*Treatment-related was as assessed by investigator. †Nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1). ‡Hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1).

AE, adverse event; SMQ, Standardized MedDRA Query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W; TRAE, treatment-related adverse event.

Ghassan K Abou-Alfa, MD, MBA.

Immune-Mediated Adverse Events

Event, n (%)	T300+D (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0

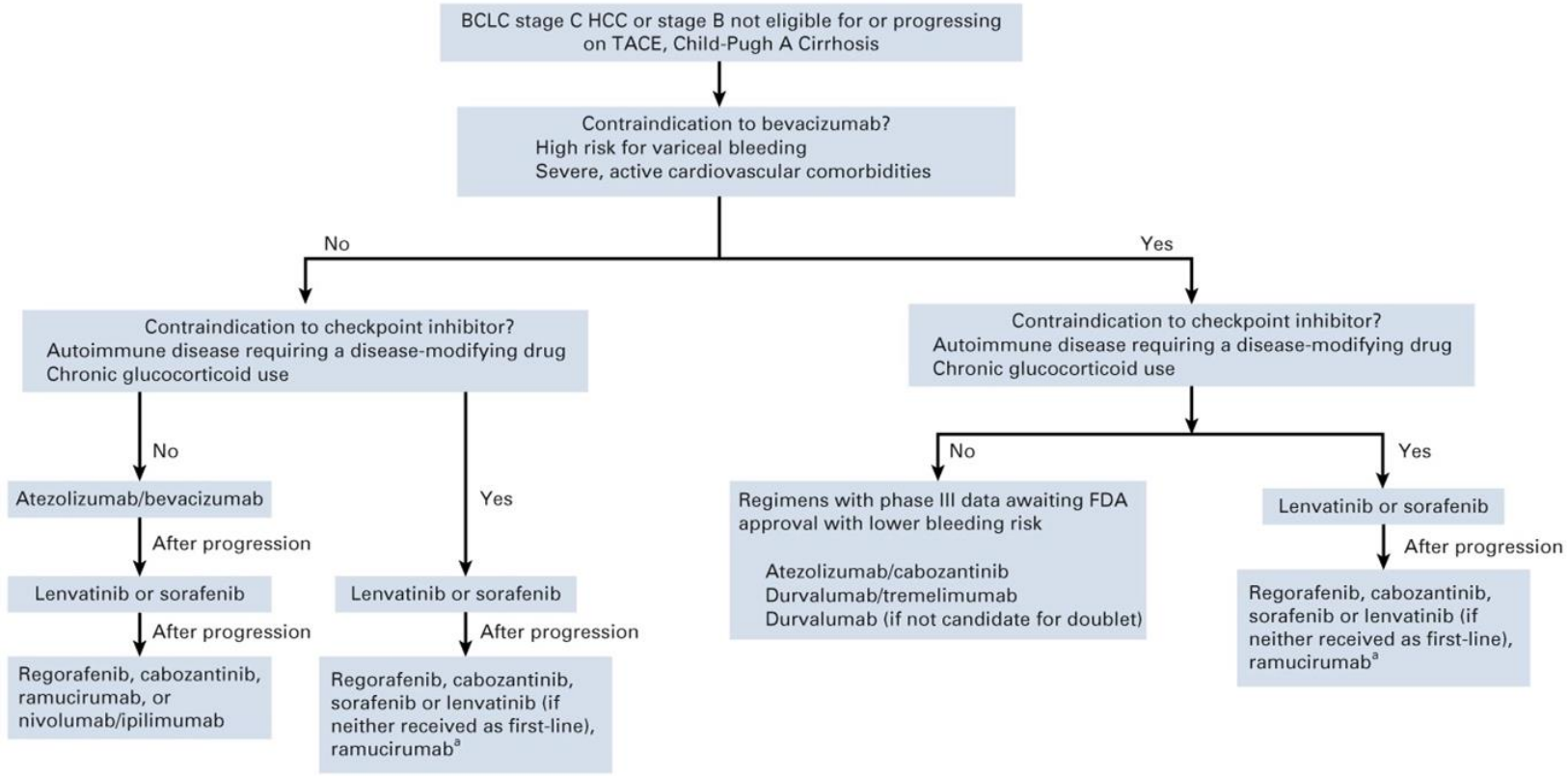
Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm.
T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W.
Ghassan K Abou-Alfa, MD, MBA.

FDA Approved Second Line Systemic Therapies

Study Name	Treatment	Median OS (mos)	Median PFS (mos)	ORR mRECIST;RECIST	Grade 3/4 TRAEs	Most common G3/4	D/C rate
RESORCE	reografenib	10.6	3.1	11%/ 7%	50%	HTN 13% HFSR 13% Fatigue 13%	10%
CELESTIAL	cabozantinib	10.2	5.2	NR/ 7%	68% (all cause)	HFSR 17% HTN 16% Increased ALT 12%	16%
REACH-2 (AFP≥400)	ramucirumab	8.5	2.8	NR/ 5%	NR	HTN 8% Liver injury 4% Proteinuria 2%	11%
KEYNOTE 240/224 (accelerated approval)	pembrolizumab	13.9	3.0	NR/ 18.3%	18.3	Increased AST 13% Increased Bili 7.5% Fatigue 2.5%	6.5%
CheckMate 040, arm A (accelerated approval)	ipilimumab+ nivolumab	22.8	3.9	34%/ 32%	53%	Pruritis 45% Rash 29% Diarrhea 24%	22%

Bruix 2017, Abou-Alfa 2018, Zhu 2019, Finn 2020, Zhu 2018, Yau 2020.
NR- not reported.

Proposed Sequencing Paradigm for Systemic Therapy in HCC



Bejjani and Finn. *JCO Onc Practice*. 2022.

Ongoing Phase 3 Trials of Adjuvant Immunotherapy[1-4]

- High risk for HCC recurrence after resection or ablation
- Child–Pugh class A

EMERALD-2	CheckMate-9DX	IMbrave050	KEYNOTE-937
• Durvalumab ± bevacizumab + vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Nivolumab vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Atezolizumab + bevacizumab vs active surveillance • ECOG PS 0-1 • Primary endpoint: RFS	• Pembrolizumab vs placebo • ECOG PS 0 • AFP <400 ng/mL • Primary endpoint: RFS and OS

1. https://clinicaltrials.gov/ct2/show/NCT03383458; 2. https://clinicaltrials.gov/ct2/show/NCT03867084; 3. https://clinicaltrials.gov/ct2/show/NCT03847428;
2. 4. https://clinicaltrials.gov/ct2/show/NCT04102098.

Ongoing Phase 3 Trials of Immunotherapy With LRT[1-4]

- Unsuitable for curative therapy (eg, surgical resection, ablation, transplantation)
- Disease amenable to TACE; no metastasis

EMERALD-1	CheckMate -74W	LEAP-012	TACE-3
• Durvalumab ± bevacizumab + TACE vs TACE + placebo • Child–Pugh A-B7 • ECOG PS 0 or 1 • Primary endpoint: PFS	• Nivolumab ± ipilimumab + TACE vs TACE + placebo • ECOG PS 0-1 • Primary endpoint: OS and TTTP	• Pembrolizumab + lenvatinib + TACE vs TACE + placebo • Primary endpoint: PFS and OS	• Nivolumab + TACE vs TACE • Child-Pugh A • ECOG PS 0-1 • Primary endpoint: OS and TTTP

1. https://clinicaltrials.gov/ct2/show/NCT03383458; 2. https://clinicaltrials.gov/ct2/show/NCT03867084; 3. https://clinicaltrials.gov/ct2/show/NCT03847428;
2. 4. https://clinicaltrials.gov/ct2/show/NCT04102098.

Radioembolization for HCC

Radioembolization for Hepatocellular Carcinoma Using Yttrium-90 Microspheres: A Comprehensive Report of Long-term Outcomes

RIAD SALEM,*,‡,§ ROBERT J. LEWANDOWSKI,* MARY F. MULCAHY,‡ AHSUN RIAZ,* ROBERT K. RYU,* SAAD IBRAHIM,* BASSEL ATASSI,* TALIA BAKER,§ VANESSA GATES,* FRANK H. MILLER,* KENT T. SATO,* ED WANG,§ RAMONA GUPTA,* AL B. BENSON,‡ STEVEN B. NEWMAN,‡ REED A. OMARY,* MICHAEL ABECASSIS,‡ and LAURA KULIK‖

Radioembolization with Yttrium-90 Glass Microspheres in Hepatocellular Carcinoma: European Experience on Safety and Long-Term Survival

Philip Hilgard,[1] Monia Hamami,[2] Amr El Fouly,[1] André Scherag,[3] Stefan Müller,[2] Judith Ertle,[1] Till Heusner,[4] Vito R. Cicinnati,[1] Andreas Paul,[5] Andreas Bockisch,[2] Guido Gerken,[1] and Gerald Antoch[4]

Survival After Yttrium-90 Resin Microsphere Radioembolization of Hepatocellular Carcinoma Across Barcelona Clinic Liver Cancer Stages: A European Evaluation

Bruno Sangro,[1] Livio Carpanese,[2] Roberto Cianni,[3] Rita Golfieri,[4] Daniele Gasparini,[5] Samer Ezziddin,[6] Philipp M. Paprottka,[7] Francesco Fiore,[8] Mark Van Buskirk,[9] Jose Ignacio Bilbao,[10] Giuseppe Maria Ettorre,[11] Rita Salvatori,[12] Emanuela Giampalma,[4] Onelio Geatti,[13] Kai Wilhelm,[14] Ralf Thorsten Hoffmann,[7] Francesco Izzo,[15] Mercedes Iñarrairaegui,[1] Carlo Ludovico Maini,[16] Carlo Urigo,[3] Alberta Cappelli,[17] Alessandro Vit,[5] Hojjat Ahmadzadehfar,[6] Tobias Franz Jakobs,[7] and Secondo Lastoria,[18] on behalf of the European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY)

Yttrium-90 Radioembolization for Intermediate-Advanced Hepatocellular Carcinoma: A Phase 2 Study

Vincenzo Mazzaferro,[1] Carlo Sposito,[1] Sherrie Bhoori,[1] Raffaele Romito,[1] Carlo Chiesa,[2] Carlo Morosi,[3] Marco Maccauro,[2] Alfonso Marchianò,[3] Marco Bongini,[1] Rodolfo Lanocita,[3] Enrico Civelli,[3] Emilio Bombardieri,[2] Tiziana Camerini,[4] and Carlo Spreafico[3]

Salem R, et al. *Gastroenterology*. 2010;138:52–64; Hilgard P, et al. *Hepatology*. 2010;52:1741–9; Sangro B, et al. *Hepatology.* 2011;54:868–78; Mazzaferro V, et al. *Hepatology.* 2013.

Institutional Decision to Adopt Y90 as Primary Treatment for Hepatocellular Carcinoma Informed by a 1,000-Patient 15-Year Experience

Riad Salem,[1-3] Ahmed Gabr,[1] Ahsun Riaz,[1] Ronald Mora,[1] Rehan Ali,[1] Michael Abecassis,[3] Ryan Hickey,[1] Laura Kulik,[4] Daniel Ganger,[4] Steven Flamm,[4] Rohi Atassi,[1] Bassel Atassi,[1] Kent Sato,[1] Al B. Benson,[2] Mary F. Mulcahy,[2] Nadine Abouchaleh,[1] Ali Al Asadi,[1] Kush Desai,[1] Bartley Thornburg,[1] Michael Vouche,[1] Ali Habib,[1] Juan Caicedo,[3] Frank H. Miller,[5] Vahid Yaghmai,[5] Joseph R. Kallini,[1] Samdeep Mouli,[1] and Robert J. Lewandowski[1-3]

- 1000 HCC patient, 15 year experience
- Overall Survival data, both censored and intention-to-treat
- Comprehensive review of data, AEs

Salem et al. *Hepatology*. 2018.

TABLE 4. Survival

CP	UNOS	N	OS (Censored*) Median (Months)	95% CI	*P* Value	OS (ITT) Median (Months)	95% CI	*P* Value	Transplanted N (%)	Resected N (%)
A	T1/T2	194	61	(37-80)	<**0.0001**	120	(80-120)	<**0.0001**	67 (35)	15 (8)
	T3	102	35.7	(25-44)		39	(30-56)		10 (10)	15 (14.5)
	T4a	75	17	(11-22)		17	(13-24)		4 (5)	1 (1)
	T4b	92	11.3	(8-14)		12	(8.7-14.3)		5 (5)	1 (1)
	M/N	43	9	(7.8-13.0)		9	(7.8-13.0)		0 (0)	1 (2)
B	T1/T2	152	27	(20.3-30.0)	<**0.0001**	64	(32.8-118.0)	<**0.0001**	69 (45)	1 (0.5)
	T3	63	20	(14.7-35.0)		24.3	(15.0-46.7)		11 (17)	0 (0)
	T4a	65	11.5	(6.4-13.5)		11.8	(8.8-15.0)		4 (6)	0 (0)
	T4b	122	6.2	(4.8-7.6)		6.2	(4.8-7.6)		2 (2)	1 (1)
	M/N	48	4.3	(2.7-6.4)		4.3	(2.7-6.4)		0 (0)	0 (0)
C	T1/T2	22	NR	—	<**0.0001**	NR	—	<**0.0001**	12 (50)	0 (0)
	T3	4	14.8	—		14.8	—		1 (25)	0 (0)
	T4a	7	3.6	(1.6-4.6)		3.6	(1.6-16.0)		1 (14)	0 (0)
	T4b	9	2.5	(2.3-4.8)		2.5	(2.3-4.8)		0 (0)	0 (0)
	M/N	2	1.7	(1.7-2.3)		1.7	(1.7-2.3)		0 (0)	0 (0)
BCLC	Child Pugh									
A	A	158	47.3	(39.5-80.3)	<**0.0001**	102	(80-120)	**0.005**	49 (31)	16 (10)
	B	105	27	(21.0-30.2)		38	(29-118)		46 (44)	1 (1)
B	A	91	25	(17.3-30.5)	**0.037**	30	(21.4-33.0)	0.2	9 (10)	5 (5)
	B	61	15	(12.3-19.0)		16	(12.6-24.5)		8 (13)	0 (0)
C	A	257	15	(13.8-17.7)	<**0.0001**	16.6	(14.5-20.6)	<**0.0001**	28 (11)	12 (5)
	B	284	8	(6.8-9.5)		8.4	(6.8-10.0)		32 (11)	1 (0.5)
D	C†	30	4.6	(2.5-6.0)		—	—		—	0 (0)
	C‡	14	—	—		92% alive at 5 years	—		14 (31)	0 (0)

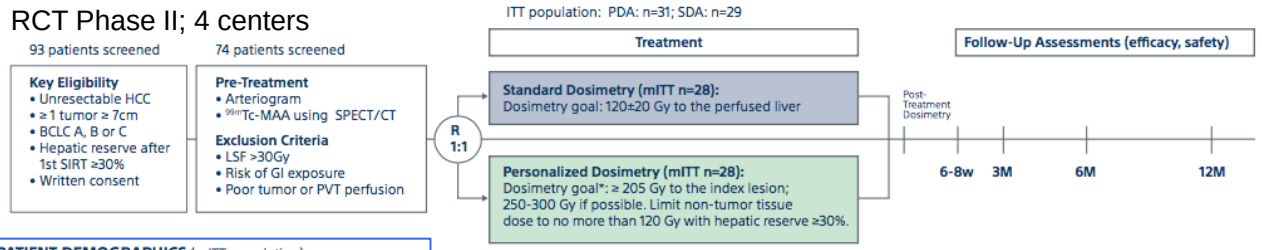
*Censored to resection/LT; †Nontransplanted; ‡Transplanted.
Abbreviation: NR, not reached.
Salem et al. *Hepatology*. 2018.

Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial

Etienne Garin, Lambros Tselikas*, Boris Guiu, Julia Chalaye, Julien Edeline, Thierry de Baere, Eric Assenat, Vania Tacher, Corentin Robert, Marie Terroir-Cassou-Mounat, Denis Mariano-Goulart, Giuliana Amaddeo, Xavier Palard, Antoine Hollebecque, Marilyne Kafrouni, Hélène Regnault, Karim Boudjema, Serena Grimaldi, Marjolaine Fourcade, Hicham Kobeiter, Eric Vibert, Samuel Le Sourd, Lauranne Piron, Danièle Sommacale, Sophie Laffont, Boris Campillo-Gimenez, Yan Rolland, on behalf of the DOSISPHERE-01 Study Group†*

Y90: Personalization Matters

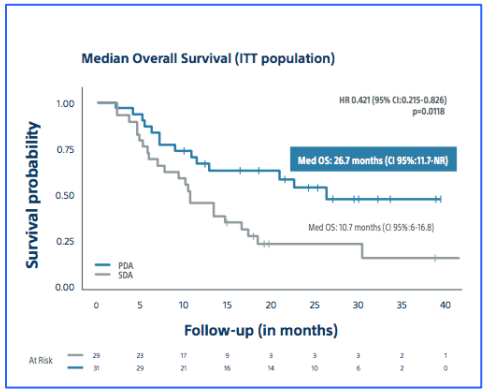
RCT Phase II; 4 centers



PATIENT DEMOGRAPHICS (mITT population)

Parameter	PDA (n=28)	SDA (n=28)
Age (median±SD)	64.8±10.1	62.5±13.1
Male (%)	92.9	92.9
Underlying cirrhosis (%)	85.7	85.7
Child-Pugh Status (%)	CP A5: 78.6 CP A6: 21.4 CP B7: 0	CP A5: 78.6 CP A6: 21.4 CP B7: 0
Mean Total Bilirubin (µM/L±SD)	14.63±6.43	13.63±5.78
ECOG (%)	0: 57.1 1: 42.9	0: 46.4 1: 53.6
PVT present (%)	67.9	75.0
Index lesion (mean, cm)	10.36±2.44	10.67±2.79
Tumoral involvement (mean±SD)	23.01±13.95	23.97±14.2

*No significant difference in baseline characteristics between groups



Garin et al. *Lancet Gastroenterol Hepatol*. 2022.

Conclusions

- We have made tremendous progress in improving the survival of patients with advanced HCC
- The introduction of IO in the front-line setting is practice changing
- Not every patient will be a candidate for IO combinations
  - Consider TKIs or single agent IO
- Recent data with single-agent TKI (LEAP 002/lenvatinib) demonstrates a clinically meaningful change in the natural history of HCC with OS
- Studies evaluating the role of IO in earlier stage disease are ongoing

Acknowledgements:

- Ronald Busuttil MD, PhD
- Saeed Sadeghi, MD
- Seong Kim, NP
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- IR (Gomes, Lu, McWilliams, Padia, Raman)
- Surgery (Agopian, DiNorcia, Farmer, Kaldas)
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