Navigating HCC Treatment Decision: What Do We Learn From Systemic Treatment

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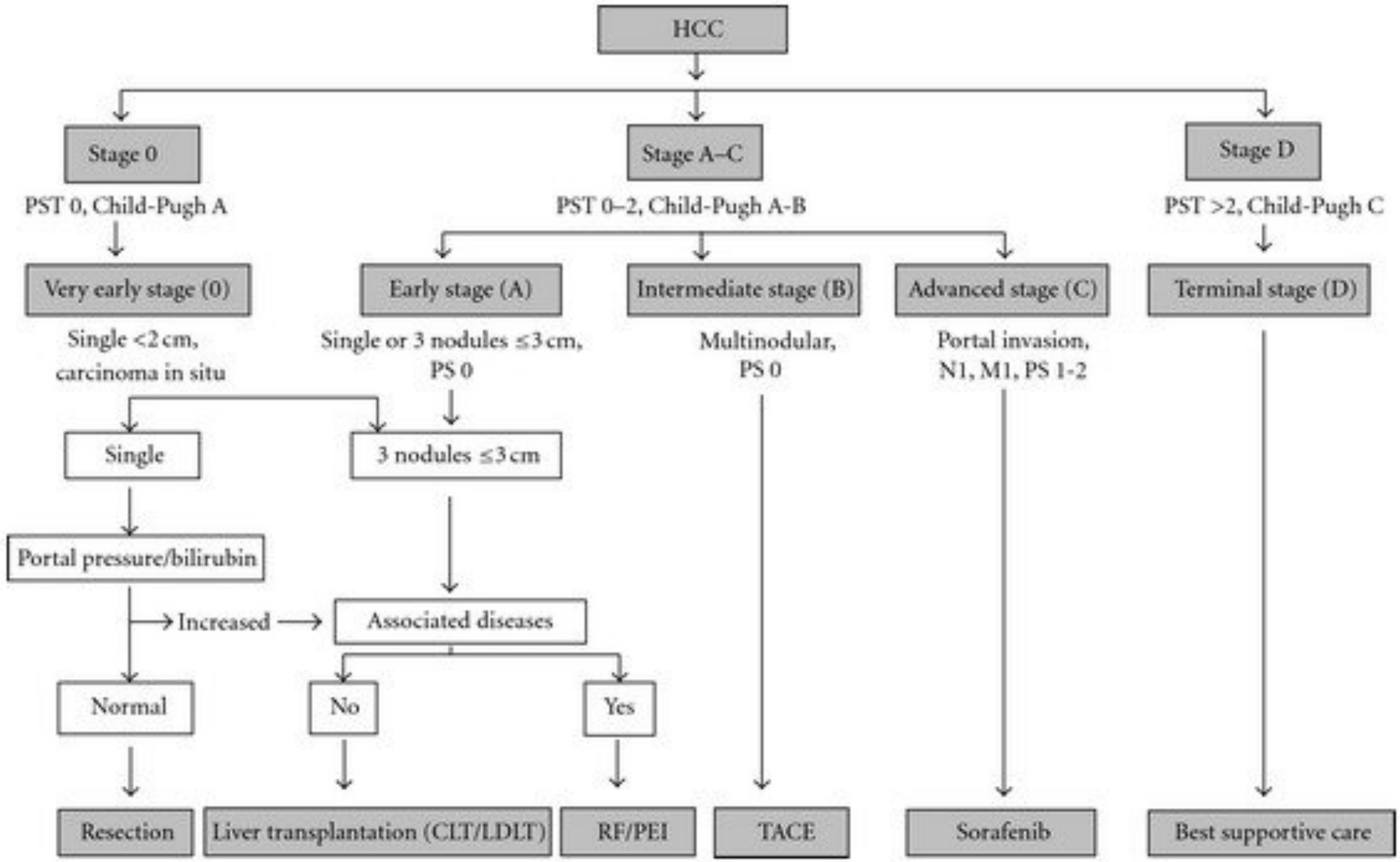
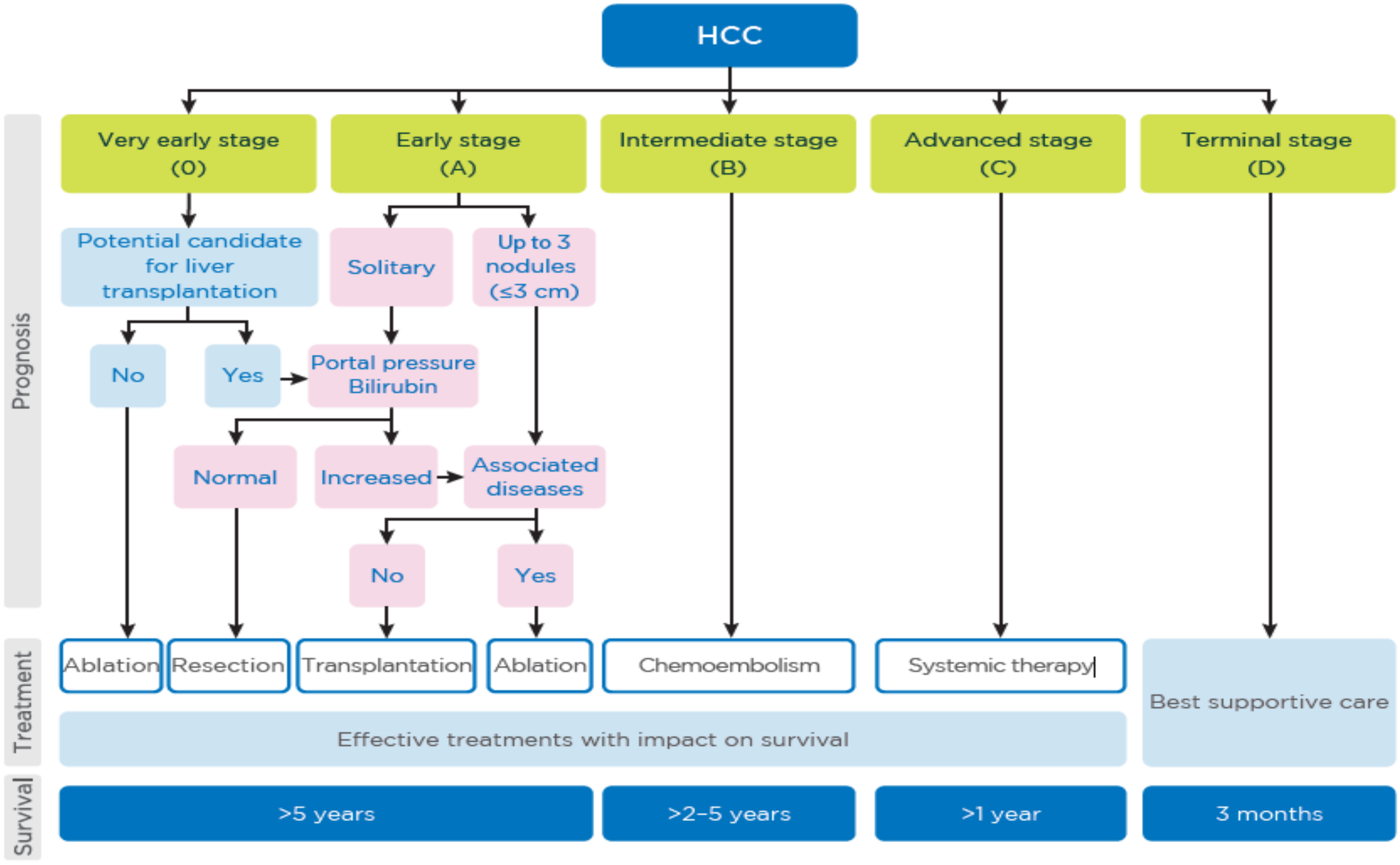
HCC Treatments

In Past



HCC Treatments in BCLS Guideline in 2018



Curative Treatments for Localized HCC

	Resection	Ablation	Transplant
Key points	▪ Noncirrhotics: choice of therapy ▪ Cirrhotics: reserved for CTP A; avoid R hepatectomy ▪ Best for solitary HCC ▪ < 30% eligible	▪ Effective when < 3 cm ▪ Multiple modalities (thermal, chemical, stereotactic radiation) ▪ Minimally invasive	▪ Cures both ▪ MELD exception: Milan criteria, downsizing ▪ Demand > supply
5-yr survival, %	70	40-50	> 70
5-yr recurrence, %	70	70	15

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Liver Embolotherapy

Technique	Mechanism	Advantages	Disadvantages
TAE	Ischemic necrosis induced at arteriolar level via permanent embolic (eg, small particles)	▪ Low cost, no chemotherapy adverse events	▪ Postembolization syndrome may cause PEs
Conventional TACE (cTACE)	Intrahepatic chemotherapy with embolization by ethiodized oil	▪ Strongest evidence supporting benefit from RCT data	▪ Intraoperator technical variation (cTACE) ▪ Systemic release of chemotherapy (cTACE) ▪ Postembolization syndrome
DEB-TACE	Intrahepatic chemotherapy + embolization with slow-release drug-eluting beads	▪ More standardized than cTACE, less systemic release of chemotherapy	▪ More expensive than cTACE ▪ Postembolization syndrome
Radioembolization	Radiation necrosis induced by beta-emitting yttrium-90 microspheres	▪ May improve TTP ▪ Fewer sessions required ▪ No postembolization syndrome ▪ May be safer in adv disease with PVT ▪ Radiation segmentectomy may be curative ▪ FLR hypertrophy from radiation lobectomy can provide tumor control and facilitate resection	▪ Cost: 2-3x more expensive ▪ Requires multidisciplinary coordination ▪ Nontarget delivery may cause severe ulceration ▪ Potential biliary toxicity ▪ Radiation-induced liver disease

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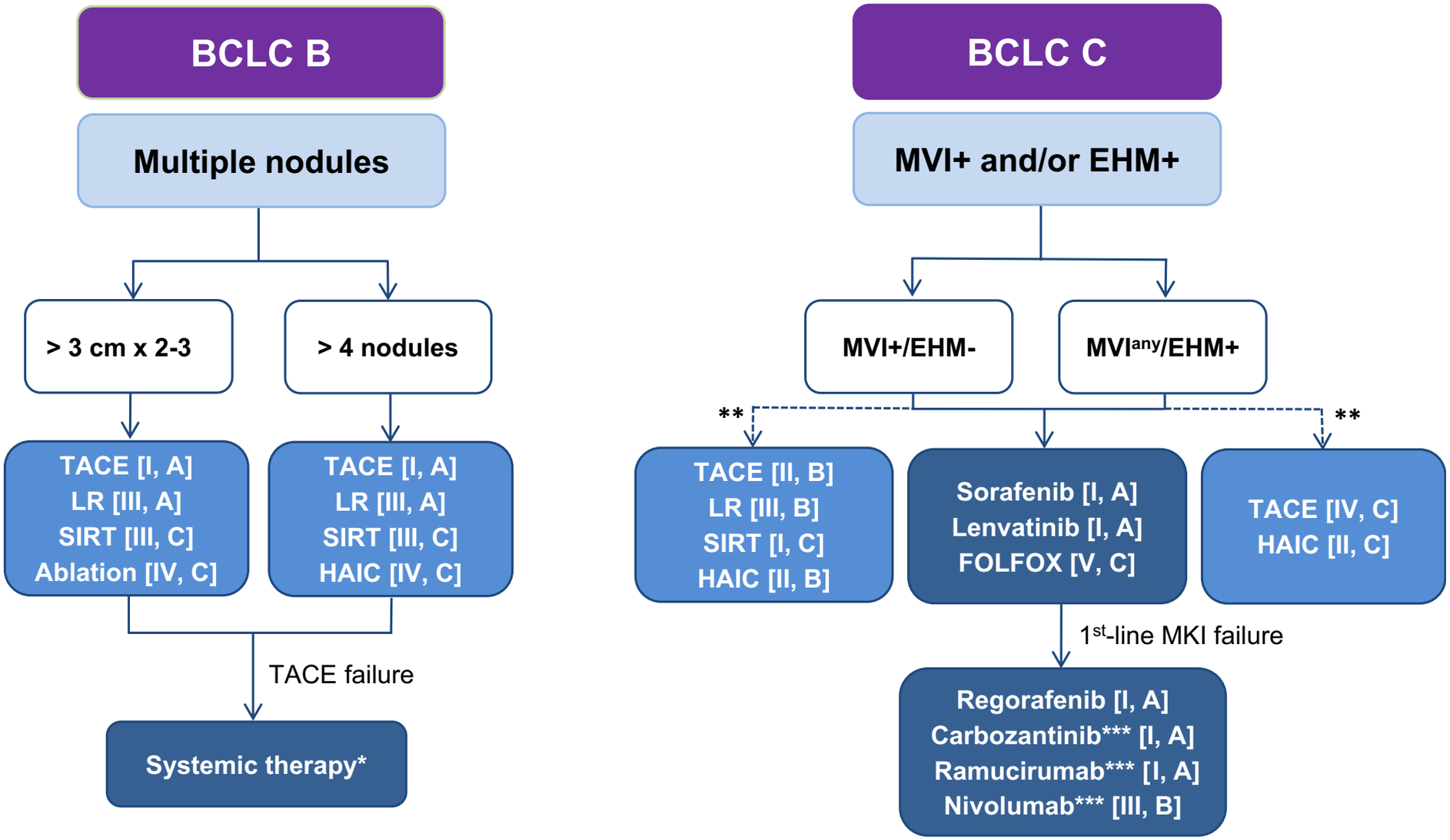
Pan-Asian Treatment

Depending on BCLC staging



HCC Treatment

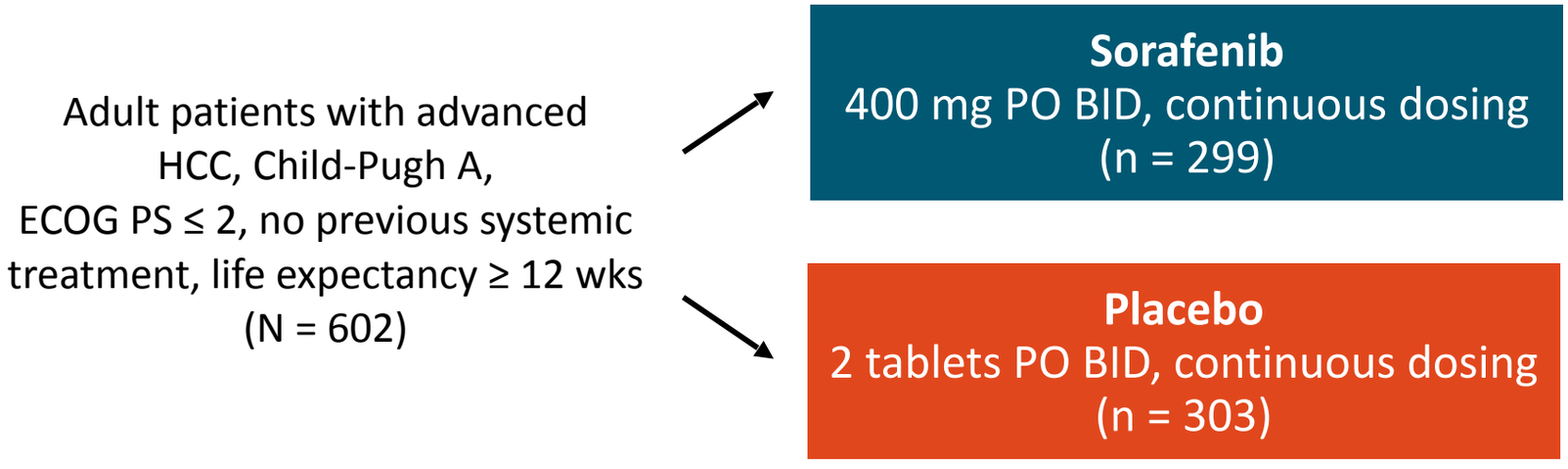
First-line Systemic Therapy

Agent	FDA Indication	Key Trial
Sorafenib	Unresectable HCC	SHARP
Lenvatinib	First-line treatment of patients with unresectable HCC	REFLECT

SHARP

Sorafenib vs. Placebo in Advanced HCC

- Randomized, double-blind phase III trial
  - **Sorafenib: multispecific TKI** with activity against CRAF; BRAF; KIT; FLT-3; RET; RET/PTC; VEGFR-1, -2, -3; PDGFR-ß



- Primary endpoints: OS, time to symptomatic progression
- Secondary endpoints: TTP, disease control rate, safety

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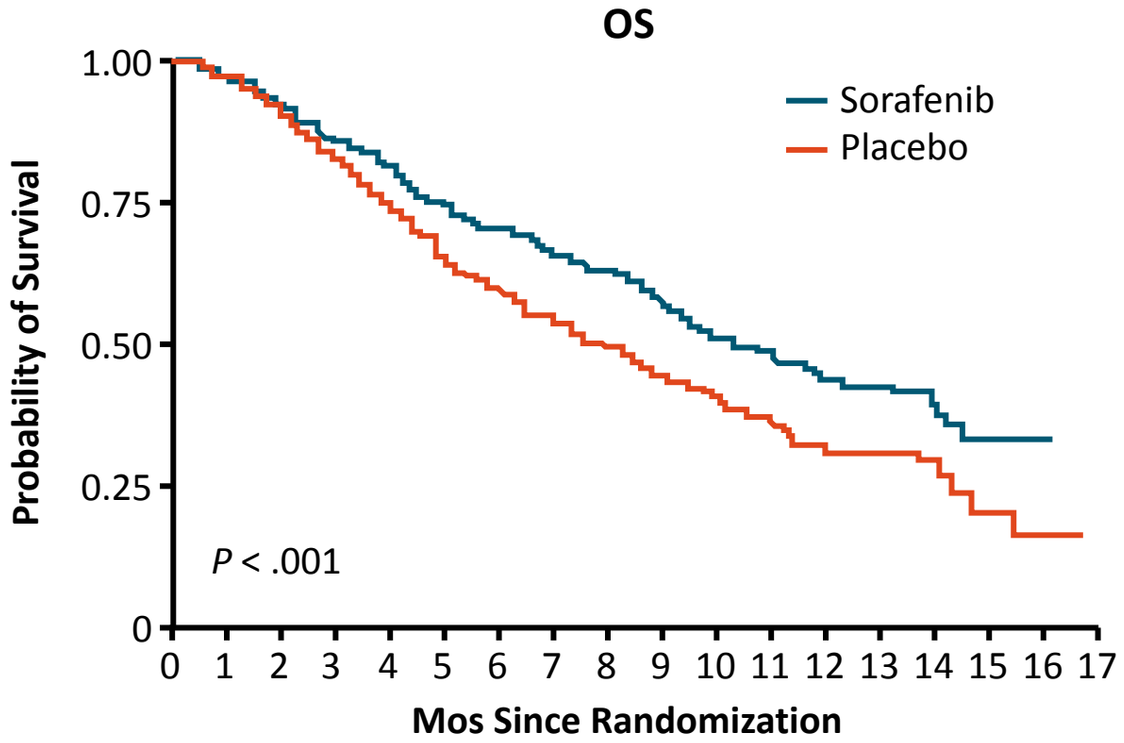
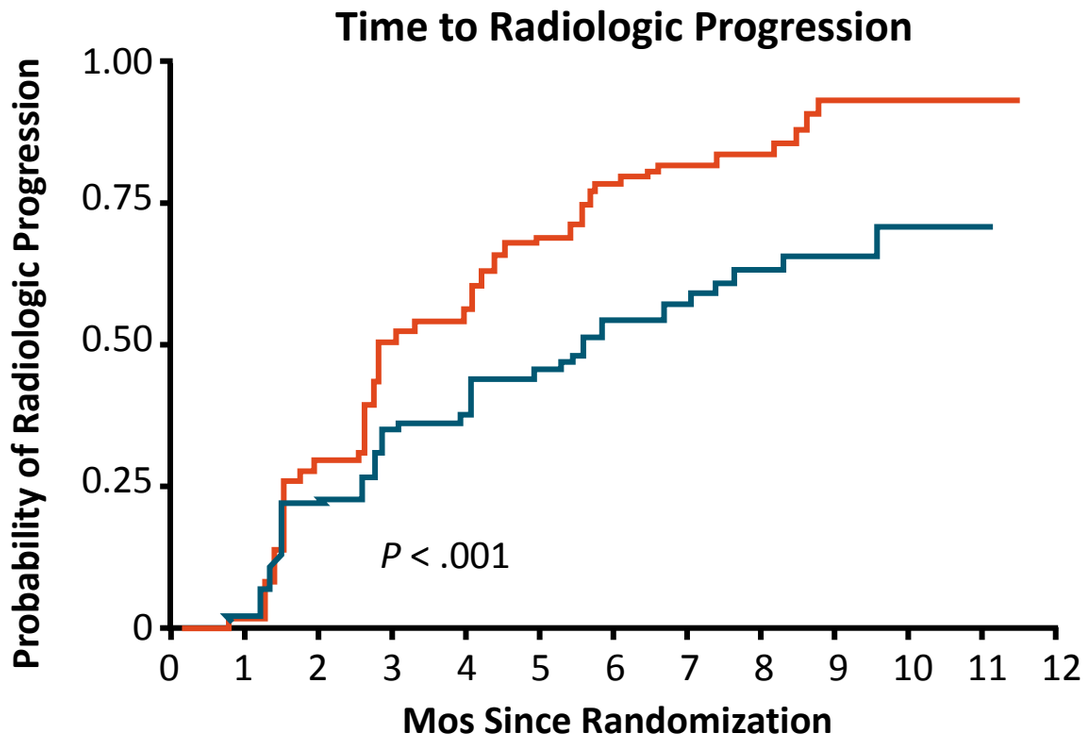
Llovet. NEJM. 2008;359:378.

SHARP

Survival and Progression





- Sorafenib treatment associated with improved OS in nearly all selected subgroups, including those with poorer performance status and macroscopic vascular invasion

Slide credit: clinicaloptions.com

Llovet. NEJM. 2008;359:378.

SHARP

Select Treatment-Related AEs

AEs, %	Sorafenib (n = 297)			Placebo (n = 302)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Constitutional symptoms						
▪ Fatigue	46	9	1	45	12	2
▪ **Weight loss**	**30**	**2**	**0**	**10**	**1**	**0**
Dermatology/skin						
▪ Rash/desquamation	19	1	0	14	0	0
▪ **HFSR**	**21**	**8**	**0**	**3**	**< 1**	**0**
▪ **Alopecia**	**14**	**0**	**0**	**2**	**0**	**0**
Gastrointestinal						
▪ **Diarrhea**	**55**	**10**	**< 1**	**25**	**2**	**0**
▪ Anorexia	29	3	0	18	3	< 1
▪ Nausea/vomiting	39	3	0	31	5	0
Hepatic dysfunction	11	2	1	8	2	1

Slide credit: clinicaloptions.com

REFLECT

Lenvatinib vs Sorafenib in unresectable HCC

Phase 3, global, randomized, open-label, noninferiority study

Patients with unresectable HCC (n=954)

- No prior systemic therapy for unresectable HCC
- ≥ 1 Measurable target lesion per mRECIST
- BCLC stage B or C
- Child-Pugh score A
- ECOG PS ≤ 1
- Adequate organ function
- Patients with ≥ 50% liver occupation, clear bile duct invasion, or portal vein invasion at the main portal vein (Vp4) were excluded

Stratification

- Region: (Asia- pacific or Western)
- MVI and/or EHS: (yes or no)
- ECOG PS: (0 or 1)
- Body weight: (<60 kg or ≥ 60kg)

Randomization 1:1

Lenvatinib (n=478)

8mg (BW < 60KG) or 12 mg (BW ≥ 60kg) once daily

sorafenib (n=476)

400mg twice daily

Primary endpoint:
- OS

Secondary endpoint:
- PFS
- TTP
- ORR
- Quality of life
- PK lenvatinib exposure parameters

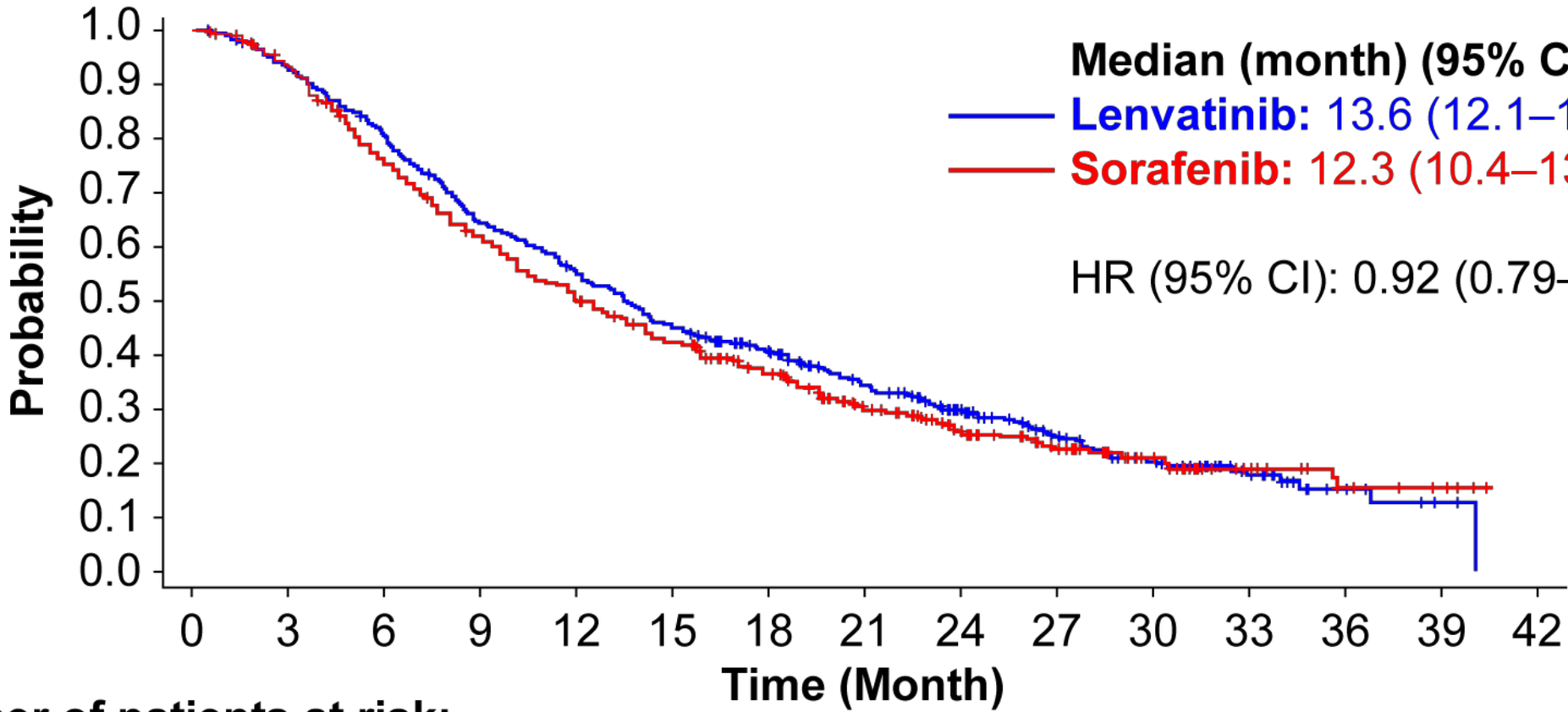
Tumour assessments were performed according to mRECIST by the investigator

Tumour assessments were performed every 8 weeks using CT or MRI, regardless of dose interruptions, and until radiologic disease progression

Kudo M *et al*. *Lancet* 2018;391:1163-1173.

REFLECT

Overall Survival



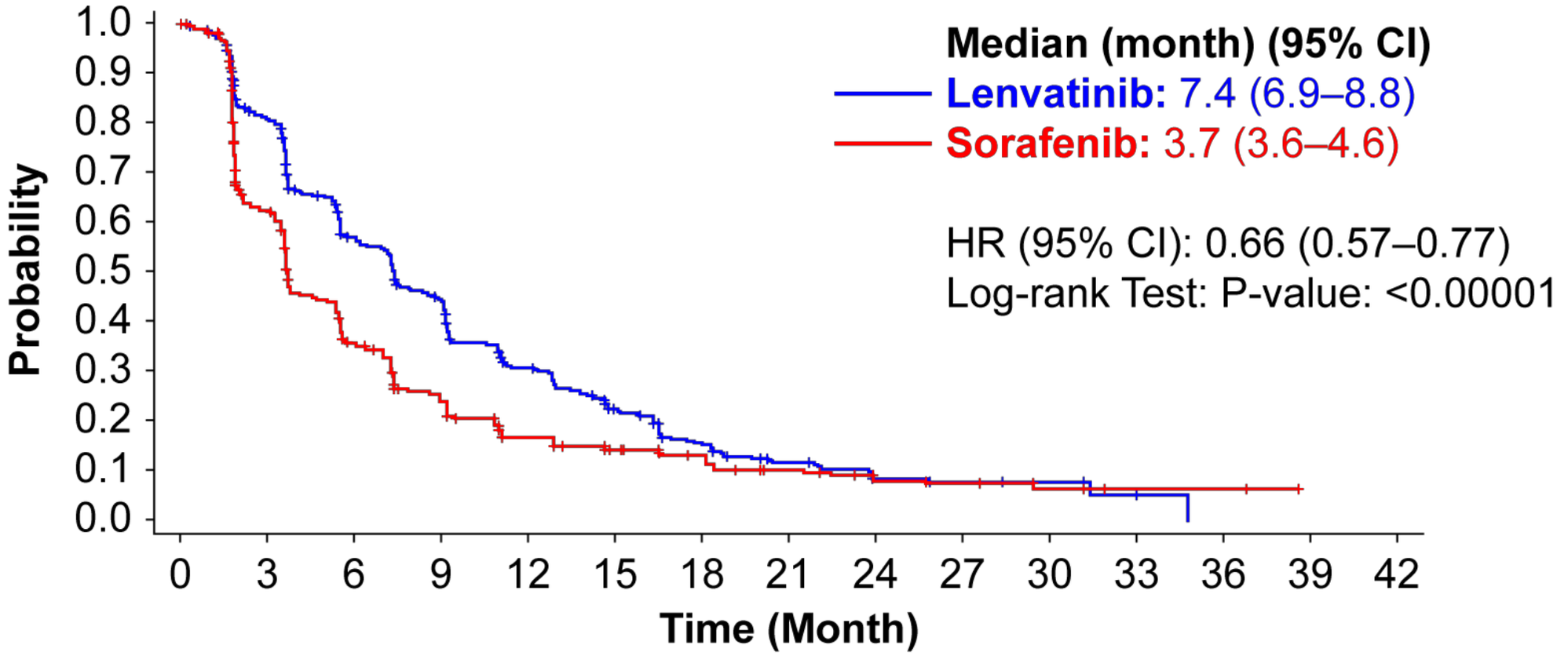
Number of patients at risk:

Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

Kudo M *et al*. *Lancet* 2018;391:1163-1173.

REFLECT

Progression-Free Survival



Number of patients at risk:

Lenvatinib	478	345	223	172	106	69	44	28	14	9	4	2	0	0
Sorafenib	476	262	140	94	56	41	33	22	14	9	4	2	2	0

Kudo M *et al*. *Lancet* 2018;391:1163-1173.

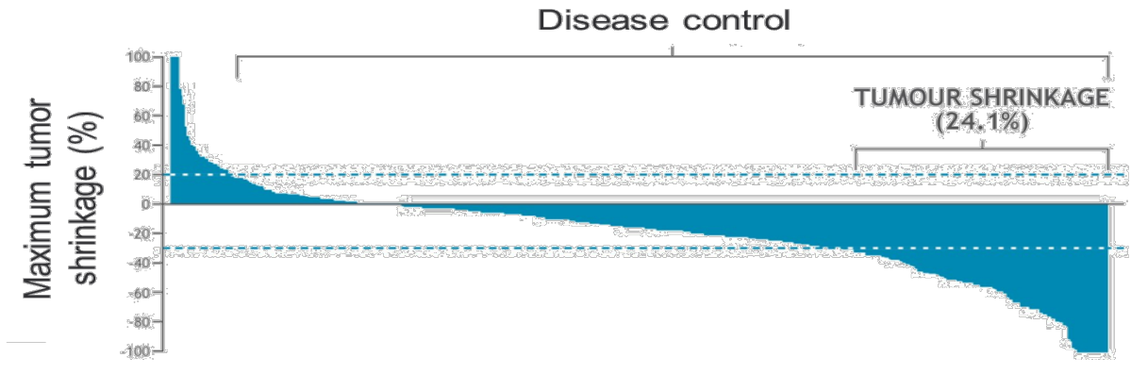
REFLECT

Tumor Assessment

n, (%)	Lenvatinib (n = 478)	sorafenib (n = 476)	Odds Ratio (95% CI)
ORR 95% CI	115 (**24.1**) 20.2–27.9	44 (9.2) 6.6–11.8	3.13 (2.15–4.56) P < 0.0001
CR	6 (1.3)	2 (0.4)	
PR	109 (22.8)	42 (8.8)	
SD	246 (51.5)	244 (51.3)	
Durable SD	167 (34.9)	139 (29.2)	
PD	71 (14.9)	147 (30.9)	
Unknown/NE	46 (9.6)	41 (8.6)	
DCR n (%) 95% CI	361 (**75.5**) 71.7–79.4	288 (60.5) 56.1–64.9	

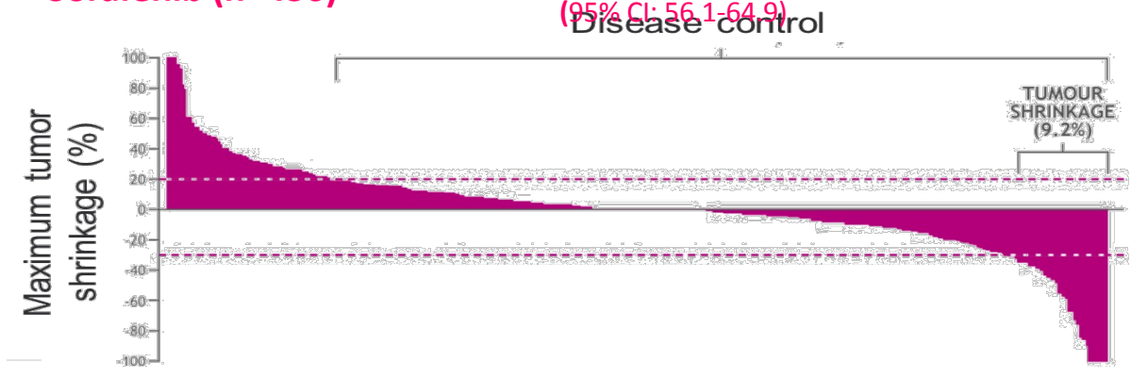
Lenvatinib (n=433)

Disease control rate: 75.5%
(95% CI: 71.7-79.4)



Sorafenib (n=436)

Disease control rate: 60.5%
(95% CI: 56.1-64.9)



Kudo M *et al*. *Lancet* 2018;391:1163-1173.

REFLECT

Select Treatment-Emergent AEs

AE, %	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Total	99	75	99	67
HFSR	**27**	**3**	**52**	**11**
Hypertension	**42**	**23**	**30**	**14**
Diarrhea	39	4	46	4
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Fatigue	30	4	25	4
Alopecia	**3**	**0**	**25**	**0**
Proteinuria	**25**	**6**	**11**	**2**
Dysphonia	**24**	**< 1**	**12**	**2**
Nausea	20	1	14	1

Kudo M *et al*. *Lancet* 2018;391:1163-1173.

Hand-Foot Skin Reaction

- General principle is to treat the hyperkeratosis and skin inflammation
    - Creams or ointments containing urea, ammonium lactate, or salicylic acid
- Topical corticosteroids may help reduce grade 2 or higher inflammation
- In general, when grade 3 or intolerable, treatment should be withheld until symptoms resolve
    - May be restarted at a lower dose

HCC Treatment

First-line Systemic Therapy

Agent	FDA Indication	Key Trial
Sorafenib	Unresectable HCC	SHARP
Lenvatinib	First-line treatment of patients with unresectable HCC	REFLECT

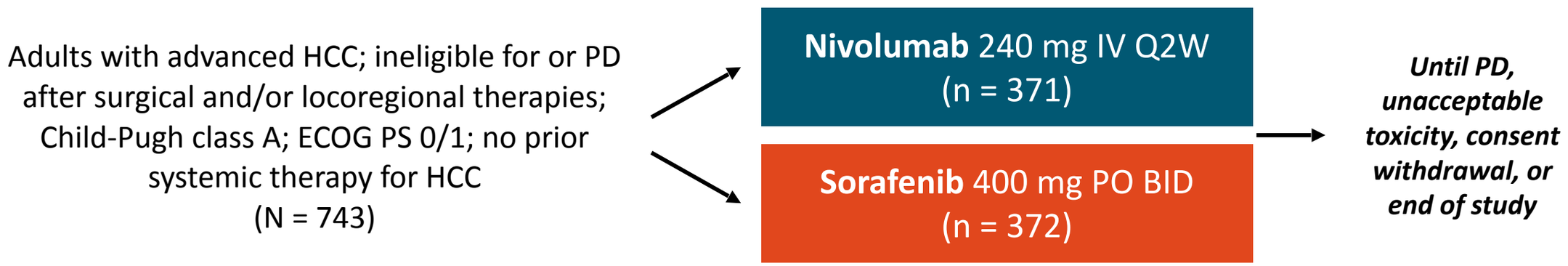
- Sorafenib improves survival vs placebo
- Lenvatinib noninferior to sorafenib for OS, but increases response rates and delays progression vs sorafenib

- Do **IO** have a role in first-line therapy?

CheckMate 459

Nivolumab vs. Sorafenib as 1st-line Therapy

- International, open-label, randomized phase III trial (minimum follow-up: 22.8 mos)



- Primary endpoint: OS
  - Predefined threshold for statistical significance: HR of 0.84 (*P* = .0419)
- Secondary endpoints: PFS, ORR, association between PD-L1 expression and efficacy

Slide credit: clinicaloptions.com

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

CheckMate 459

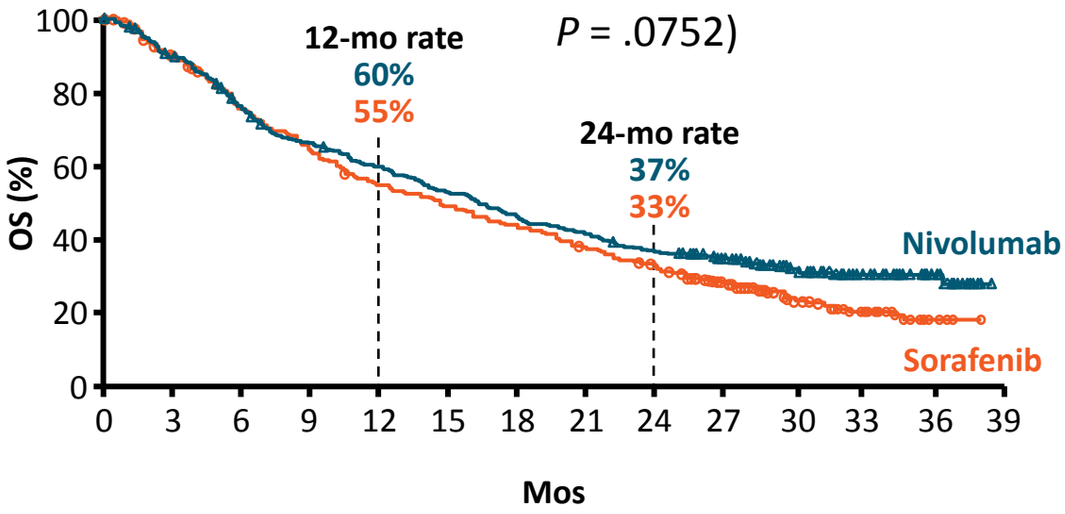
Overall Survival and Progression-Free Survival

Median OS, Mos (95% CI)

Nivolumab 16.4 (13.9-18.4)

Sorafenib 14.7 (11.9-17.2)

HR: 0.85 (95% CI: 0.72-1.02; *P* = .0752)

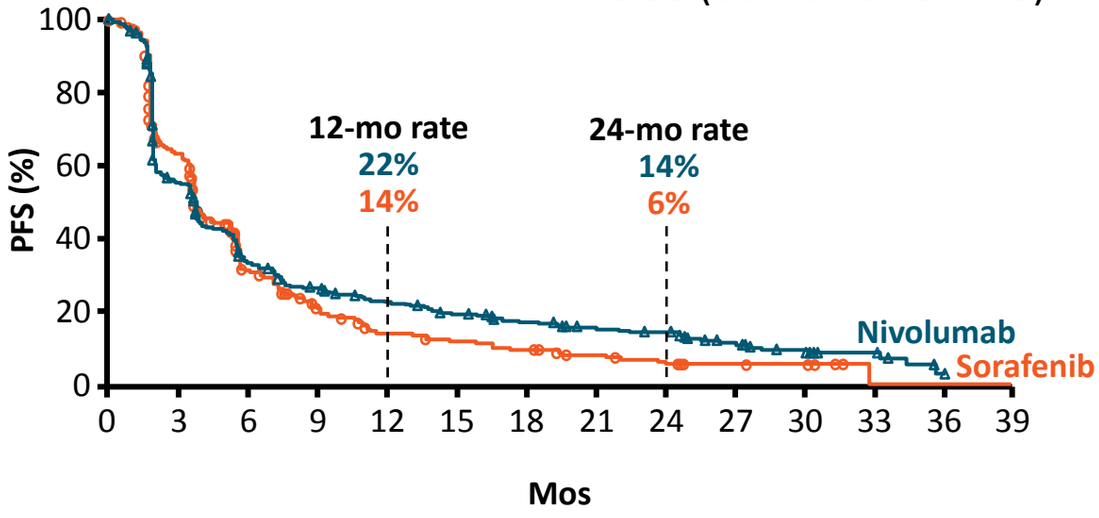


Median PFS, Mos (95% CI)

Nivolumab 3.7 (3.1-3.9)

Sorafenib 3.8 (3.7-4.5)

HR: 0.93 (95% CI: 0.79-1.10)



- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit
- ORR: nivolumab, 15%; sorafenib, 7%

Slide credit: clinicaloptions.com

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

CheckMate 459

Subsequent Therapy

Treatment, n (%)	Nivolumab (n = 371)	Sorafenib (n = 372)
Any subsequent therapy	181 (49)	195 (53)
Systemic therapy	140 (38)	170 (46)
▪ Tyrosine kinase inhibitor	132 (36)	86 (23)
▪ Chemotherapy	15 (4)	25 (7)
▪ Investigational agent	10 (3)	40 (11)
▪ Immuno-oncology agent	7 (2)	76 (20)
▪ Other	2 (1)	4 ()
Local therapy	63 (17)	61(16)
Radiotherapy	52 (14)	38 (10)
Surgery	10 (3)	14 (4)

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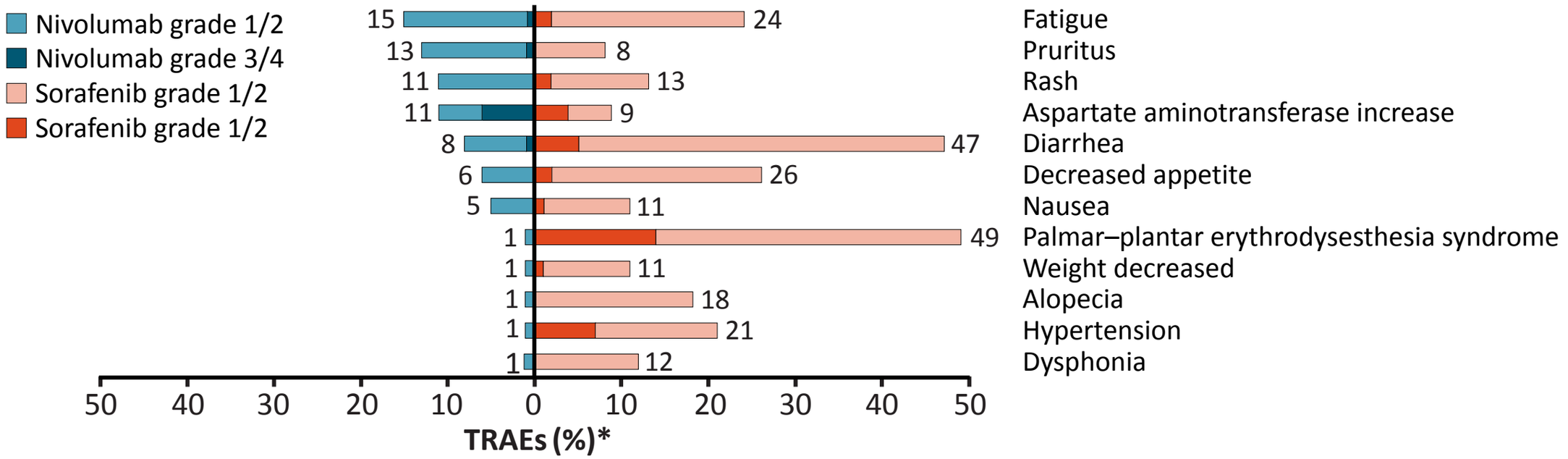
Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

CheckMate 459

Treatment-Related Adverse Effects



- Nivolumab demonstrated an improved safety profile compared with sorafenib, with fewer grade 3/4 TRAEs and TRAEs leading to discontinuation vs sorafenib
  - Grade 3/4 TRAEs: nivolumab, 22%; sorafenib, 49%

*Occurring in > 10% of patients in either treatment arm.

Slide credit: clinicaloptions.com

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

Atezolizumab + Bevacizumab in Untreated, Unresectable HCC

Randomized Phase Ib Study

Patients with unresectable HCC; ECOG PS 0/1; Child-Pugh up to B7 for Arm A/Child-Pugh A for Arm F; no prior systemic therapy or antibodies to CTLA-4 or PD-1/L1

Arm A → **Atezolizumab** 1200 mg IV Q3W + **Bevacizumab** 15 mg/kg IV Q3W (n = 104)

Arm F →

- **Atezolizumab** 1200 mg IV Q3W + **Bevacizumab** 15 mg/kg IV Q3W (n = 60)
- **Atezolizumab** 1200 mg IV Q3W (n = 59)

Treat until loss of benefit or unacceptable toxicity; follow-up for survival

- Arm A primary endpoint: ORR
- Arm F primary endpoint: PFS
- Study includes first randomized analysis in HCC of ICI + VEGF inhibitor vs ICI alone

Slide credit: clinicaloptions.com

Lee. ESMO 2019. Abstract LBA39.

Atezolizumab + Bevacizumab

- ORR in Arm A -

Response	Atezolizumab + Bevacizumab (n = 104)		
	IRF RECIST 1.1	**IRF HCC mRECIST**	**INV RECIST 1.1**
Confirmed ORR, n (%) (95% CI)	**37 (36)** (26-46)	**41 (39)** (30-50)	**34 (33)** (24-43)
▪ CR	12 (12)	16 (15)	3 (3)
▪ PR	25 (24)	25 (24)	31 (30)
▪ SD	37 (36)	33 (32)	44 (42)
▪ PD	25 (24)	25 (24)	20 (19)
DCR, n (%)	**74 (71)**	**74 (71)**	**78 (75)**
Ongoing response, n/N (%)	**28/37 (76)**	**28/41 (68)**	**24/34 (71)**
Median DOR, mo (95% CI)	**NE** (11.8 – NE)	**NE** (11.8 – NE)	**NE** (11.7 – NE)
DOR range, mo	**1.6+ to 31.0+**	**1.6+ to 31.0+**	**3.5 to 31.0+**
▪ ≥ 9 mo, n (%)	20 (54)	25 (61)	21 (62)
▪ ≥ 12 mo, n (%)	11 (30)	11 (27)	12 (35)

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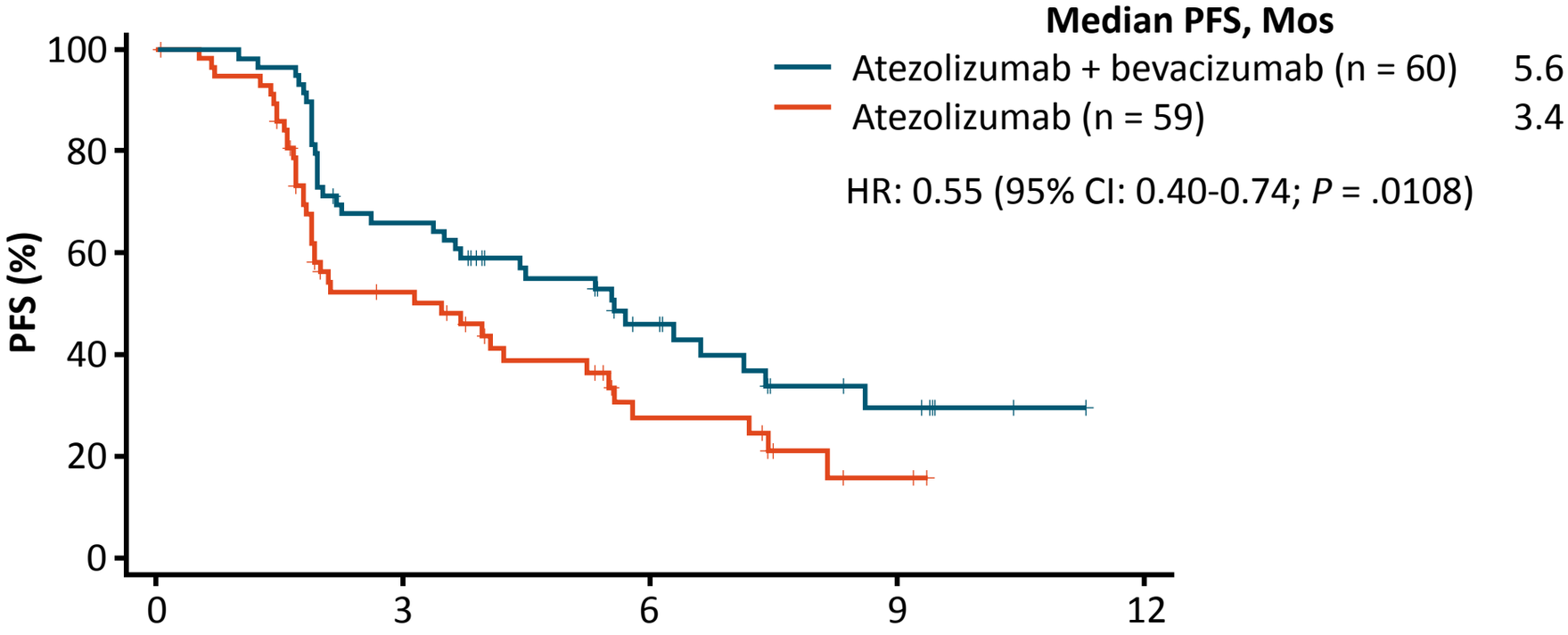
Lee. ESMO 2019. Abstract LBA39.

Atezolizumab + Bevacizumab

- PFS in Arm F -



Median follow-up: 12.4 mos

Lee. ESMO 2019. Abstract LBA39.

IMbrave150

Atezolizumab/Bevacizumab vs Sorafenib

- Multicenter, randomized, open-label, phase III trial

Patients with locally advanced or metastatic and/or unresectable HCC with no previous systemic therapy, Child-Pugh A, and ECOG PS ≤ 1 (N = 501)

Atezolizumab 1200 mg Q3W + **Bevacizumab** 15 mg/kg Q3W

Sorafenib 400 mg BID

Treatment until PD or intolerable toxicity

- Coprimary endpoints: OS and PFS

Slide credit: clinicaloptions.com

Cheng. ESMO Asia 2019. Abstr LBA3.

IMbrave150

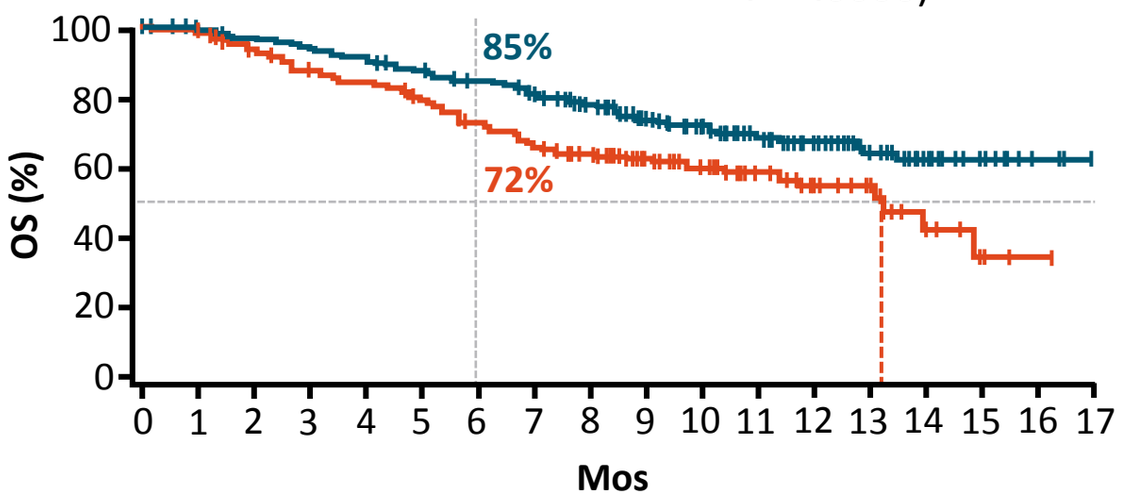
Overall Survival and Progression-Free Survival

Median OS, Mos (95% CI)

Atezo + bev NE

Sorafenib 13.2 (10.4-NE)

HR: 0.58 (95% CI: 0.42-0.79; *P* = .0006)

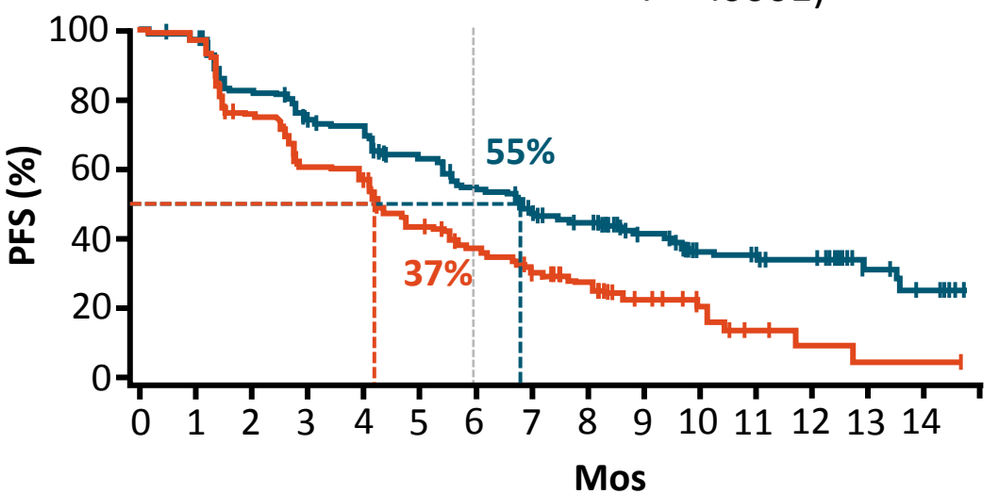


Median PFS, Mos (95% CI)

Atezo + bev 6.8 (5.7-8.3)

Sorafenib 4.3 (4.3-5.6)

HR: 0.59 (95% CI: 0.47-0.76; *P* < .0001)



Median follow-up: 8.6 mos.

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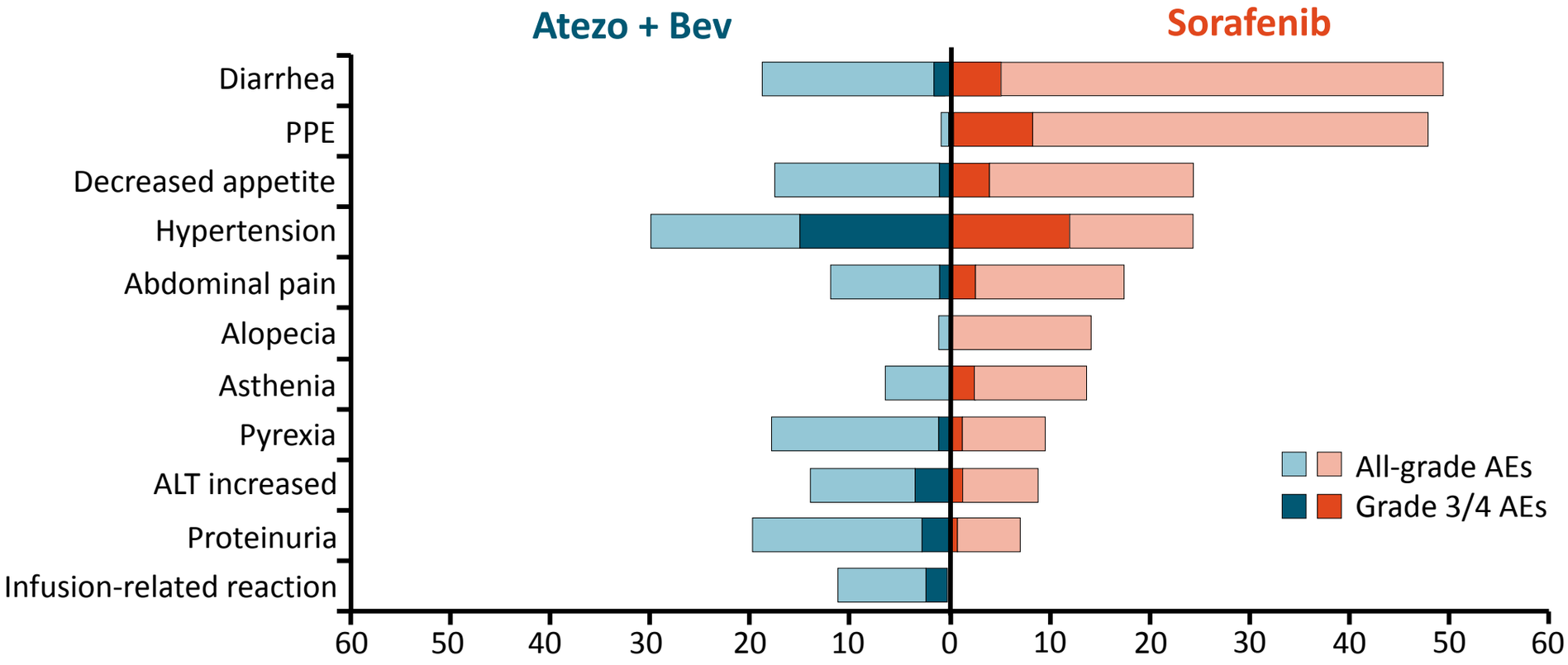
Adverse Effects



≥ 10% frequency in either arm and > 5% difference between arms.

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IMbrave150

Time to Deterioration in QoL

QoL Parameter	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Mean baseline QoL score (SD)	71.04 (21.07)	68.79 (21.20)
Median TTD, mos (95% CI)	11.2 (6.0-NE)	3.6 (3.0-7.0)
▪ HR (95% CI)	0.63 (0.46-0.85)	
Clinically meaningful QoL deterioration, %*		
▪ Cycle 2	29.9	44.2
▪ Cycle 3	31.5	43.3
▪ Cycle 4	30.2	41.4
▪ Cycle 5	29.6	35.7

Slide credit: clinicaloptions.com

IMbrave150

Time to Deterioration in Physical Functioning

Physical Functioning Parameter	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Mean baseline physical functioning score (SD)	85.73 (16.32)	84.82 (17.75)
Median TTD, mos (95% CI)	13.1 (9.7-NE)	4.9 (3.5-6.2)
▪ HR (95% CI)	0.53 (0.39-0.73)	
Clinically meaningful deterioration, %*		
▪ Cycle 2	24.2	39.5
▪ Cycle 3	21.3	37.0
▪ Cycle 4	22.3	38.6
▪ Cycle 5	22.9	31.4

Slide credit: clinicaloptions.com

IMbrave150

Time to Deterioration in Role Functioning

Role Functioning Parameter	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Mean baseline role functioning score (SD)	85.01 (23.03)	85.75 (21.60)
Median TTD, mos (95% CI)	9.1 (6.5-NE)	3.6 (2.2-6.0)
▪ HR (95% CI)	0.62 (0.46-0.84)	
Clinically meaningful deterioration, %*		
▪ Cycle 2	29.3	41.1
▪ Cycle 3	29.6	42.0
▪ Cycle 4	27.1	37.5
▪ Cycle 5	28.1	31.4

Slide credit: clinicaloptions.com

KEYNOTE-240

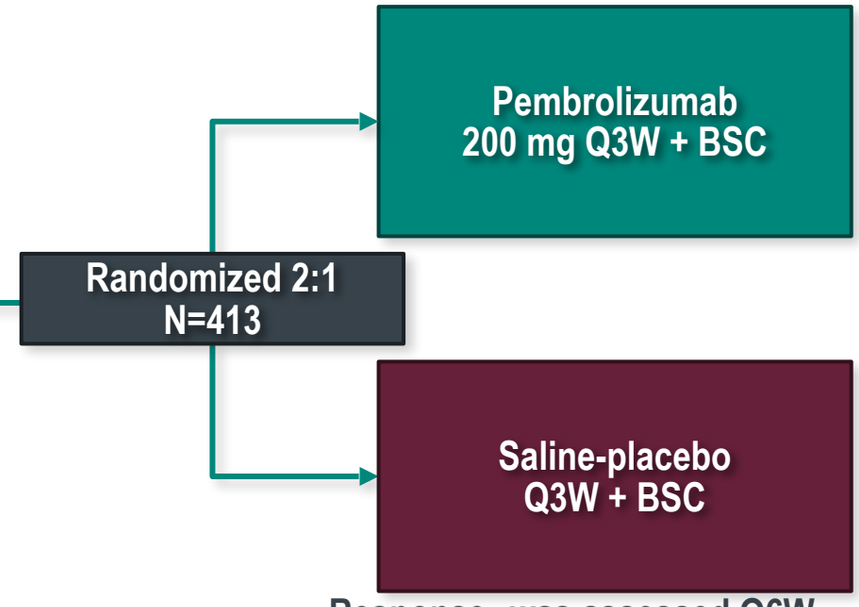
Phase 3 randomized study of pembrolizumab vs best supportive care (BSC) for 2L advanced hepatocellular carcinoma

Key Eligibility Criteria

- Pathologically/radiographically confirmed HCC
- Progression on/intolerance to sorafenib
- Child Pugh class A
- BCLC stage B/C
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Main portal vein invasion was excluded

Stratification Factors

- Geographic region (Asia w/o Japan vs non-Asia w/Japan)
- Macrovascular invasion (Y vs N)
- AFP level (≥200 vs <200 ng/mL)



Response was assessed Q6W

Primary End Point

OS

PFS (RECIST v1.1, central review)

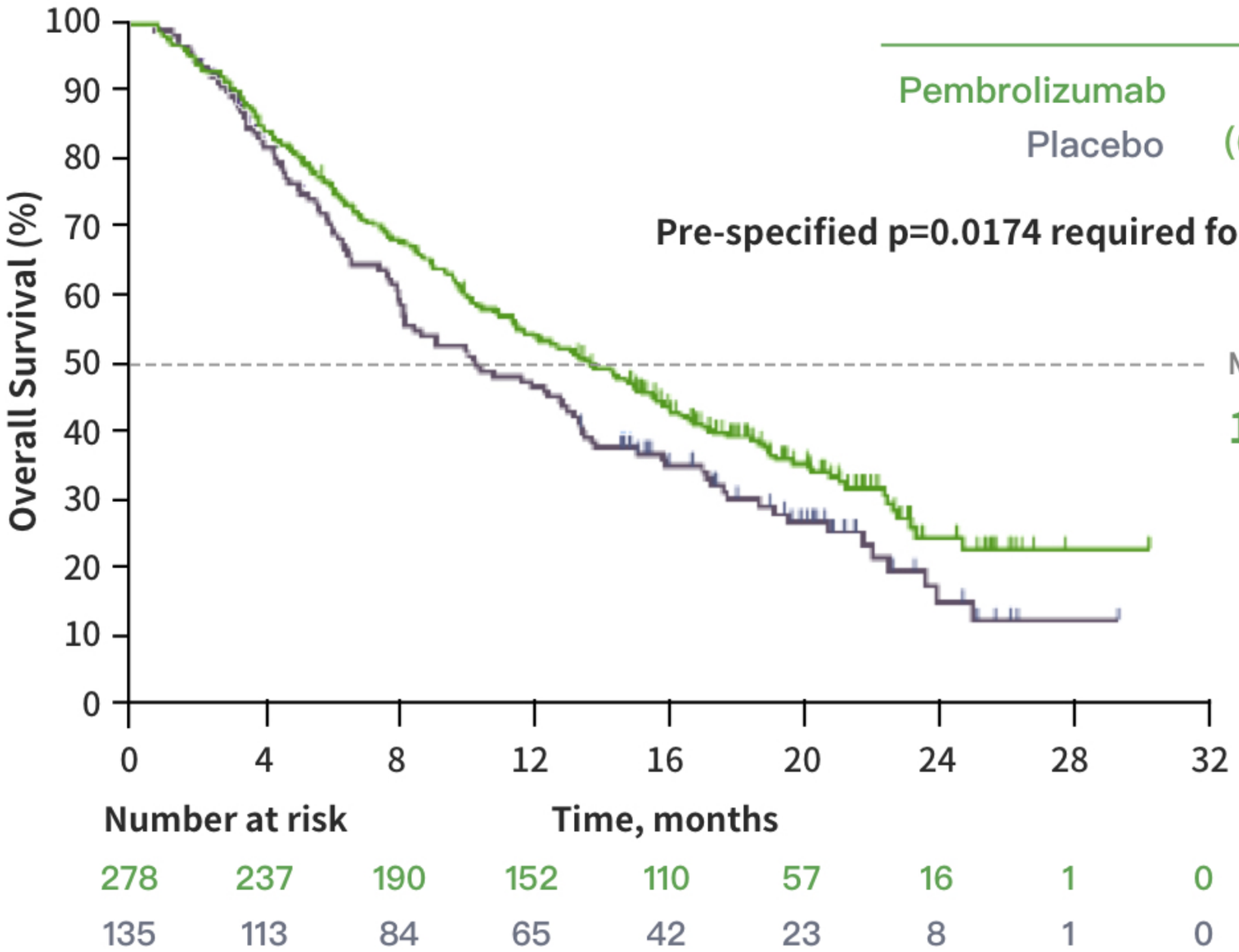
Secondary End Points

ORR, DOR, DCR and TTP (all RECIST v1.1, central review)

Safety and tolerability

KEYNOTE-240

Overall Survival



	HR (95% CI)	p
Pembrolizumab	0.781 (0.611–0.998)	0.0238
Placebo		

Pre-specified p=0.0174 required for statistical significance

Median (95% CI)

13.9 mo (95% CI, 11.6-16.0)

10.6 mo (95% CI, 8.3-13.5)

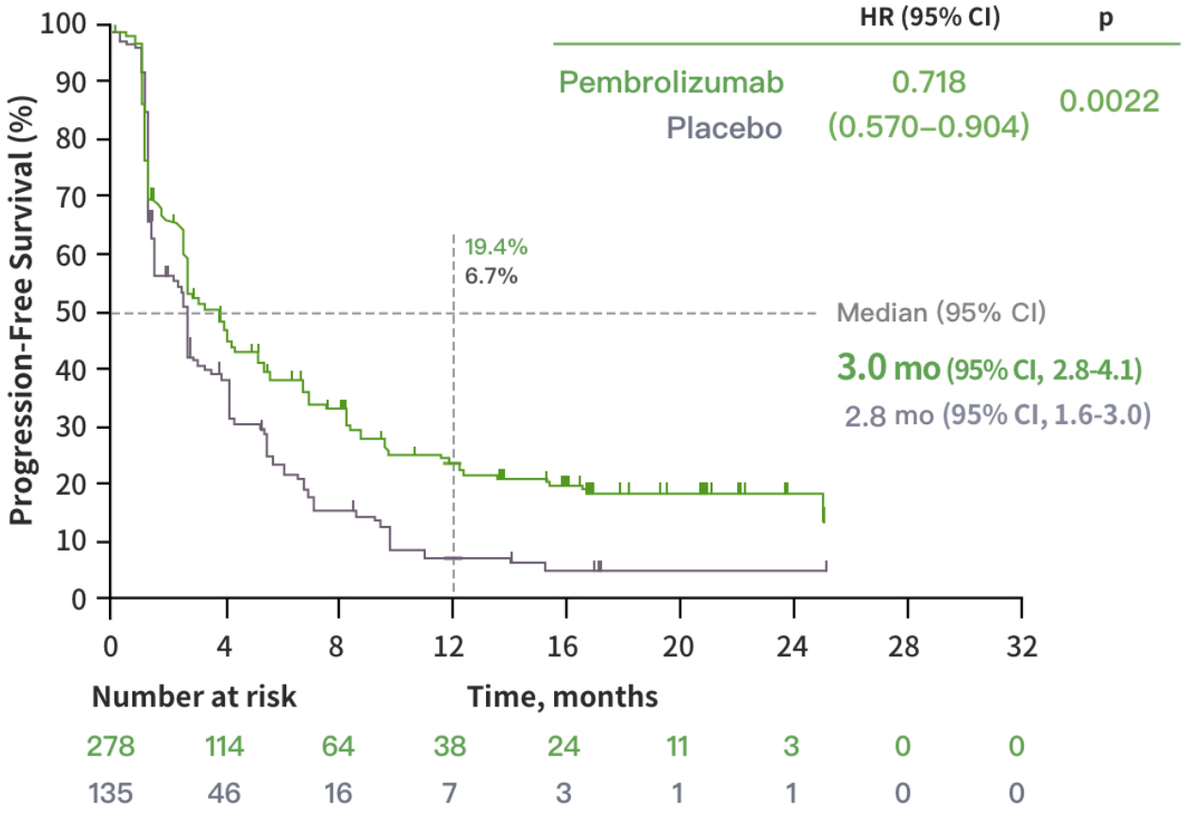
KEYNOTE-240

Progression-Free Survival

Primary Analysis

	Pembro	Placebo
HR (95% CI)	0.775 (0.609-0.987)	
P value	0.0186	
Median (95% CI)	3.0 mo (2.8-4.1)	2.8 mo (2.5-4.1)

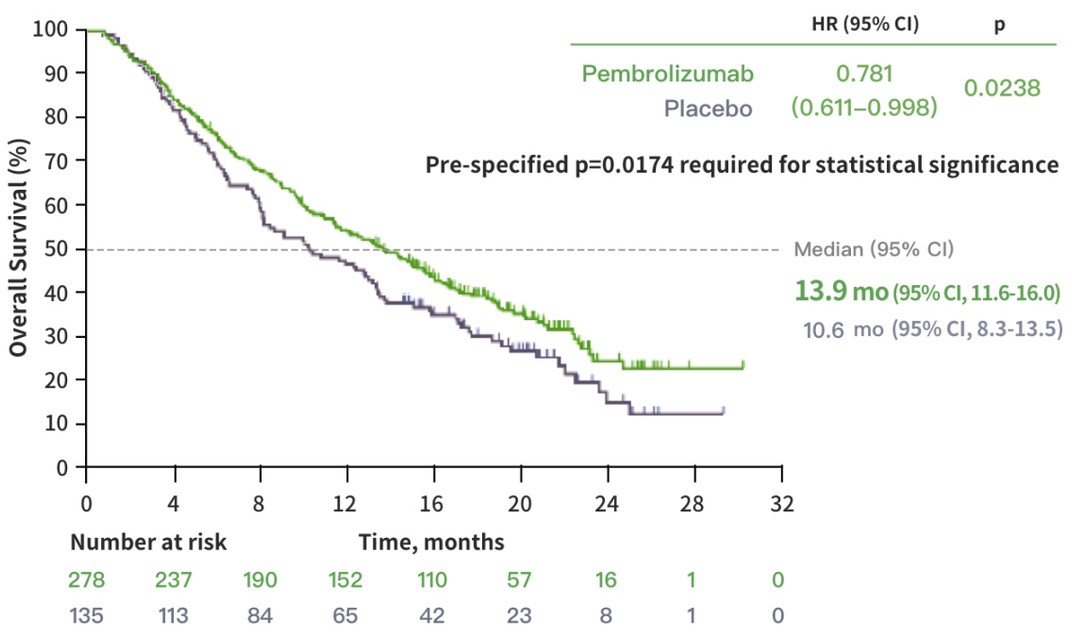
Final Analysis



KEYNOTE-240

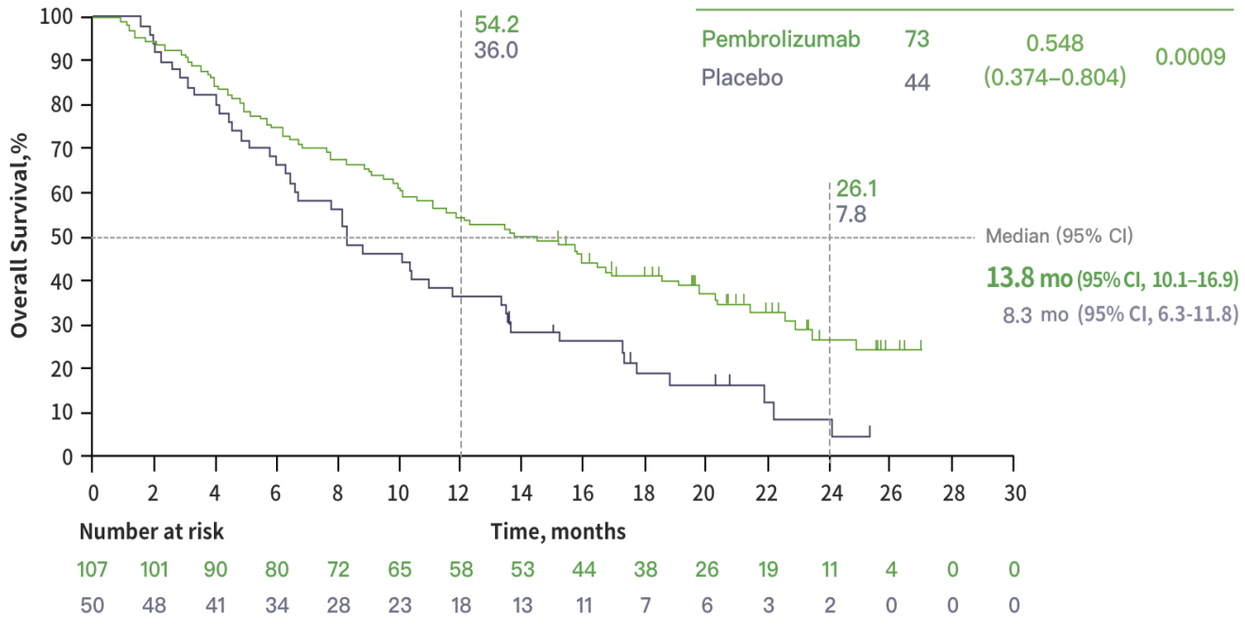
Overall Survival in East-Asia

Overall population [1]



△ = 3.3 mos

East-Asia population [2]

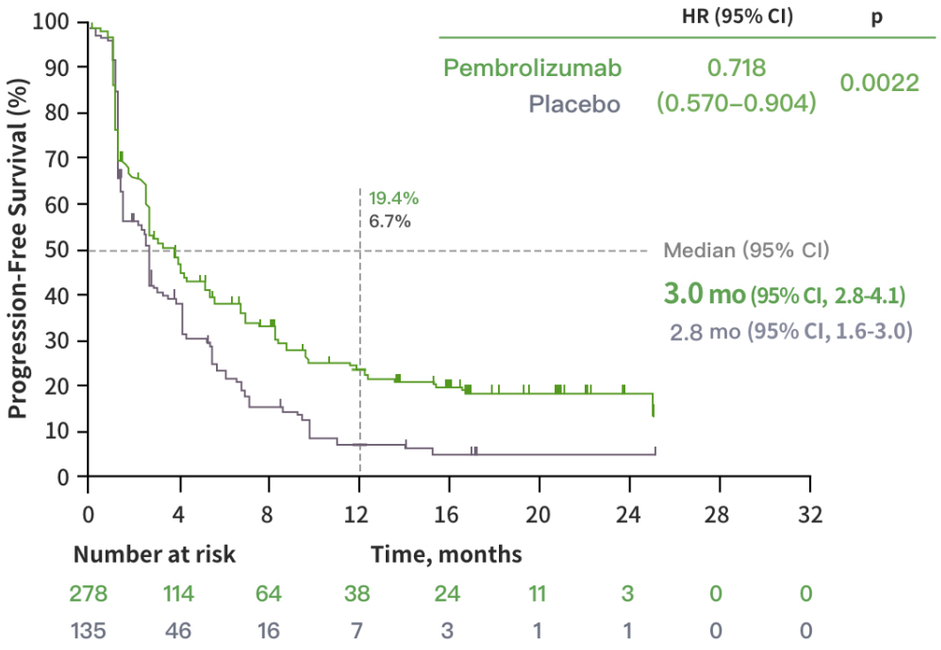


△ = 5.5 mos

KEYNOTE-240

Progression-Free Survival in East-Asia

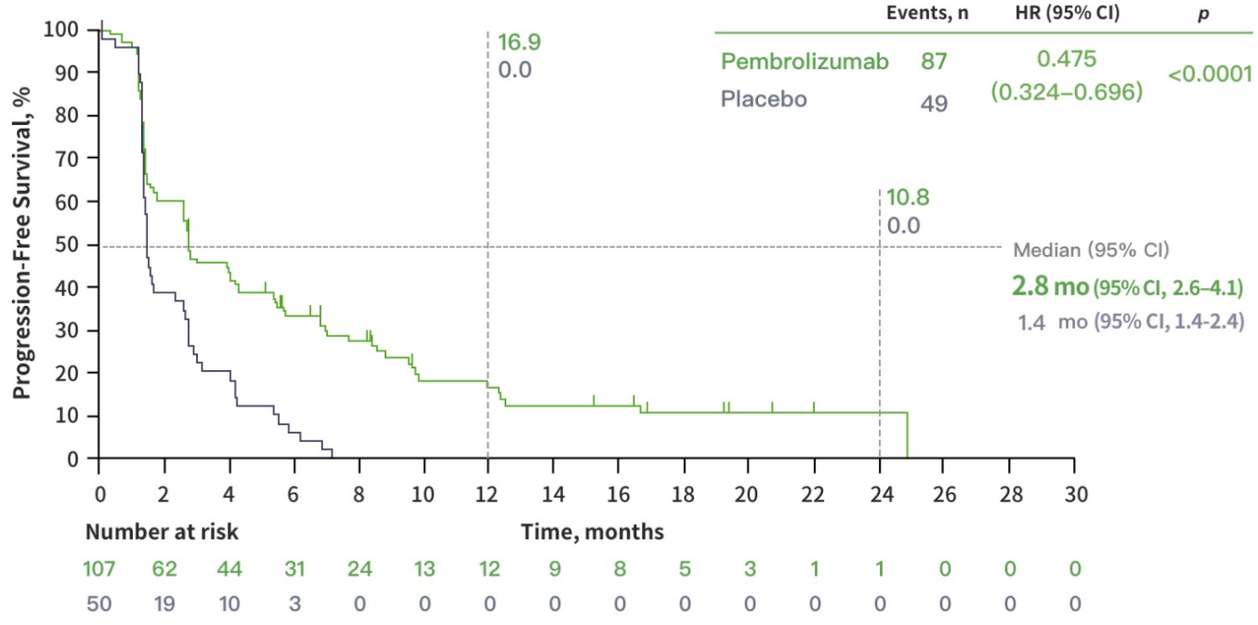
Overall population [1]



	HR (95% CI)	p
Pembrolizumab	0.718 (0.570–0.904)	0.0022
Placebo		

△ = 0.2 mos

East-Asia population [2]



	Events, n	HR (95% CI)	p
Pembrolizumab	87	0.475 (0.324–0.696)	<0.0001
Placebo	49		

△ = 1.4 mos

KEYNOTE-524

Lenvatinib+Pembrolizumab in unresectable HCC

Lenvatinib 12 or 8 mg daily orally (based on body weight)
+**pembrolizumab** 200 mg IV on Day 1 (21-day cycle)

DLT Evaluation (Part 1)
- n=6
- Patients ineligible for other therapies
- Tolerability evaluated by DLTs during Cycle 1

Expansion (Part 2)
- n= ~94
- No prior systemic therapy for uHCC

Key Eligibility Criteria

- uHCC
- BCLC Stage B (not applicable for TACE) or C
- Child-Pugh class A
- ECOG performance status 0-1
- At least 1 measurable target lesion according to mRECIST

Primary Endpoint
- Safety and tolerability
- ORR and DOR by mRECIST and RECIST 1.1 based on IIR (Part 2)

Selected Secondary and Exploratory End Points
- PFS
- TTP
- OS
- PK
- Antidrug antibodies for pembrolizumab

Tumour assessments were performed according to mRECIST by IR and IIR and RECIST v1.1 per IIR*

Patients

- 104 Patients were enrolled
  - DLT part: n = 6
  - Expansion part: n = 98
  - 4 Patients from the DLT part were excluded because of prior sorafenib treatment
- 37 (37%) Patients were still undergoing study treatment at the data cutoff date (October 31, 2019)
  - Both drugs: n = 34
  - Lenvatinib: n = 3

Baseline Characteristic	N = 100
Median age, years (range)	66.5 (47, 86)
Sex, n (%)	
Male	81 (81)
Female	19 (19)
ECOG performance status, n (%)	
0	62 (62)
1	38 (38)
BCLC stage, n (%)	
B	29 (29)
C	71 (71)
Serum AFP level[a], n (%)	
< 400 ng/mL	67 (67)
≥ 400 ng/mL	30 (30)
Child-Pugh Score, n (%)	
5	71 (71)
6	27 (27)
7	2 (2)[b]
MPVI, extrahepatic spread or both, n (%)	62 (62)

AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; MPVI, macroscopic portal vein invasion.

[a]Data were missing for 3 patients.
[b]These 2 patients were enrolled in violation of the protocol.

Safety

- Median duration of exposure
  - Overall treatment duration[a]: 7.9 months
    - Range: 0.2 to 31.1
  - Lenvatinib: 7.6 months
    - Range: 0.2 to 31.1
  - Pembrolizumab: 7.4 months
    - Range: 0.03 to 23.5
- 95% Of patients had ≥ 1 TRAE
- 67% Of patients had grade ≥ 3 TRAEs
  - Grade 3: 63%
  - Grade 4: 1%
  - Grade 5: 3%

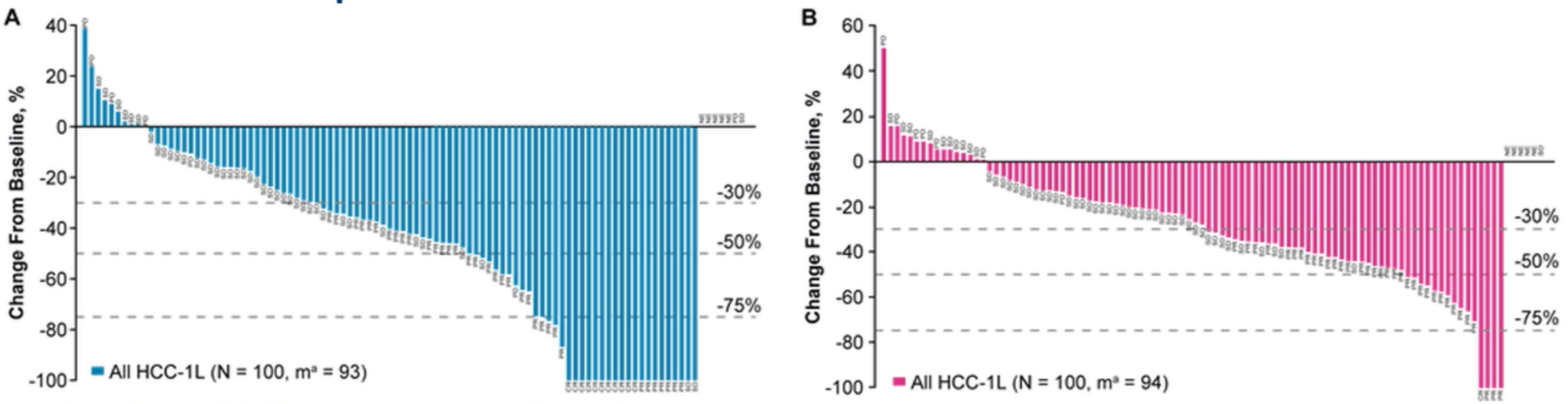
Most Common TRAEs (≥ 25% of Patients With Any-Grade TRAE)

Preferred term, n (%)	N = 100			
	Any Grade	Grade 1	Grade 2	Grade 3
Hypertension	36 (36)	1 (1)	18 (18)	17 (17)
Diarrhea	35 (35)	19 (19)	11 (11)	5 (5)
Fatigue	30 (30)	12 (12)	14 (14)	4 (4)
Decreased appetite	28 (28)	12 (12)	16 (16)	0
Hypothyroidism	25 (25)	11 (11)	14 (14)	0

- Grade 5 TRAEs
  - Acute respiratory failure/acute respiratory distress syndrome (n = 1)
  - Abnormal hepatic function (n = 1)
  - Intestinal perforation (n = 1)
- Grade 4 TRAE
  - Leukopenia/neutropenia (n = 1)

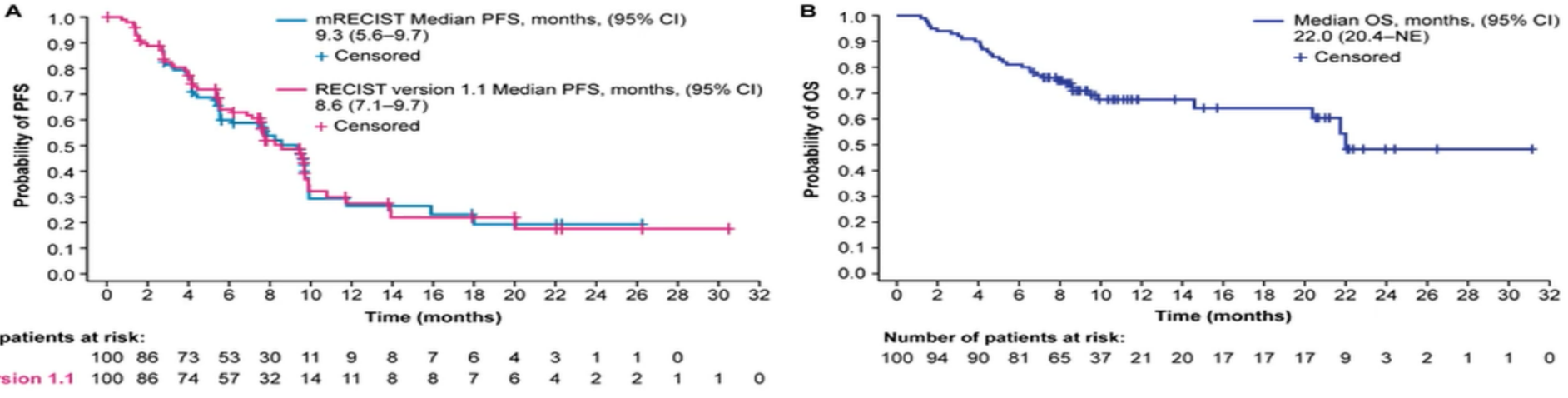
[a]The duration between the earliest start date of the first dose of either medication and the latest date of last dose of either medication.
TRAE, treatment-related adverse event.

Percentage Change From Baseline in Sums of Diameters of Target Lesions (A) by mRECIST per IIR and (B) by RECIST Version 1.1 per IIR



[a]Number of patients with both baseline and postbaseline sum of diameters of target lesions.

Kaplan–Meier Estimates of (A) PFS, by mRECIST and RECIST Version 1.1 per IIR; and (B) OS (Efficacy Analysis Set)



1L, first-line; CI, confidence interval; IIR, independent imaging review; (m)RECIST, (modified) Response Evaluation Criteria In Solid Tumors; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Efficacy Summary

Parameter	N = 100		
	mRECIST per IIR	RECIST Version 1.1 per IIR	mRECIST per Investigator Review
ORR (confirmed), n (%) (95% CI)[a]	46 (46) (36.0-56.3)	36 (36) (26.6-46.2)	41 (41) (31.3-51.3)
Best overall response, n (%)			
Complete response	11 (11)	1 (1)	5 (5)
Partial response	35 (35)	35 (35)	36 (36)
Stable disease[b]	42 (42)	52 (52)	45 (45)
Progressive disease	7 (7)	7 (7)	7 (7)
Unknown/not evaluable	5 (5)	5 (5)	7 (7)
Median DOR[c], months (95% CI)[d]	8.6 (6.9-NE)	12.6 (6.9-NE)	12.6 (6.2-18.7)
Median TTR, months (range)	1.9 (1.2, 5.5)	2.8 (1.2, 7.7)	2.7 (1.2, 11.8)
DCR, n (%) (95% CI)[a]	88 (88) (80.0-93.6)	88 (88) (80.0-93.6)	86 (86) (77.6-92.1)

[a]The 95% CIs are calculated using 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.

Conclusions

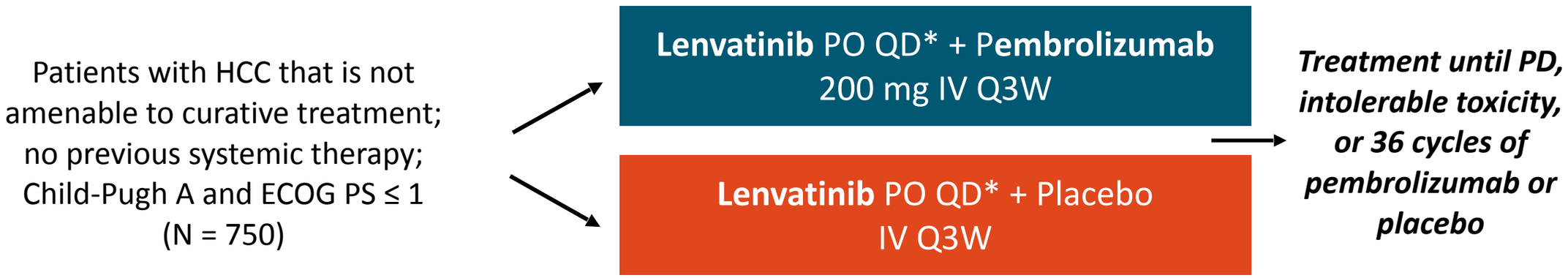
- Multikinase inhibition with lenvatinib plus PD-1 inhibition with pembrolizumab resulted in promising antitumor activity, as evidenced by a high ORR and DCR
  - ORR: 46% by mRECIST and 36% by RECIST v1.1
  - DCR: 88% by mRECIST and RECIST v1.1
- There were no new or unexpected toxicities resulting from lenvatinib plus pembrolizumab combination therapy
- An ongoing phase 3 trial (LEAP-002; NCT03713593) is assessing lenvatinib in combination with pembrolizumab, versus lenvatinib monotherapy, as a first-line therapy option for patients with uHCC

CI, confidence interval; DCR, disease control rate; DOR, duration of response; IIR, independent imaging review; (m)RECIST, (modified) Response Evaluation Criteria In Solid Tumors; NE, not estimable; ORR, objective response rate; PD-1, programmed death receptor-1; TTR, time to response; uHCC, unresectable hepatocellular carcinoma.

LEAP-002

Lenvatinib/Pembrolizumab vs Lenvatinib

- Multicenter, double-blind, phase III trial



*Body weight < 60 kg, 8 mg; body weight ≥ 60 kg, 12 mg.

- Primary endpoints: PFS, OS
- Secondary endpoints: ORR, DoR, DCR, TTP, safety

Llovet. ASCO 2019. Abstr TPS4152. NCT03713593.

Phase III Trials Assessing Immune Checkpoint Inhibitors for First-Line Systemic Therapy

Study	Agent(s)	Findings
Checkmate-459[1]	Nivolumab vs sorafenib	Predefined threshold of statistical significance for OS with nivolumab not met
IMbrave150[2,3]	Atezolizumab + bevacizumab vs sorafenib	Press release: increased OS, PFS with atezolizumab + bevacizumab Randomized phase Ib study: improved PFS with atezolizumab + bevacizumab vs atezolizumab
LEAP-002[4]	Lenvatinib + pembrolizumab vs lenvatinib	Ongoing
HIMALAYA[5]	Durvalumab + tremelimumab vs sorafenib	Ongoing
COSMIC-312[6]	Cabozantinib ± atezolizumab vs sorafenib	Ongoing
CheckMate 9DW[7]	Nivolumab + ipilimumab vs sorafenib or lenvatinib	Ongoing

Slide credit: clinicaloptions.com

1. Yau. ESMO 2019. Abstr LBA38_PR. 2. Lee. ESMO 2019. Abstract LBA39. 3. Finn. ASCO 2018. Abstr TPS4141. 4. Llovet. ASCO 2019. Abstr TPS4152. 5. Abou-Alfa. ASCO 2018. Abstr TPS4144. 6. Kelley. ASCO 2019. Abstr TPS4157. 7. NCT04039607.

Conclusion

- Sorafenib improves survival vs placebo
- Lenvatinib noninferior to sorafenib for OS, but increases response rates and delays progression vs sorafenib
- Single-agent immune checkpoint inhibitors have not met endpoints in phase III studies to date; however, combinations are showing promise