Nové možnosti systémové léčby HCC a její zařazení do celkového algoritmu terapie

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HCC staging – TNM nestačí

Staging určuje prognózu a léčbu.

Většina pacientů má hepatopatii.

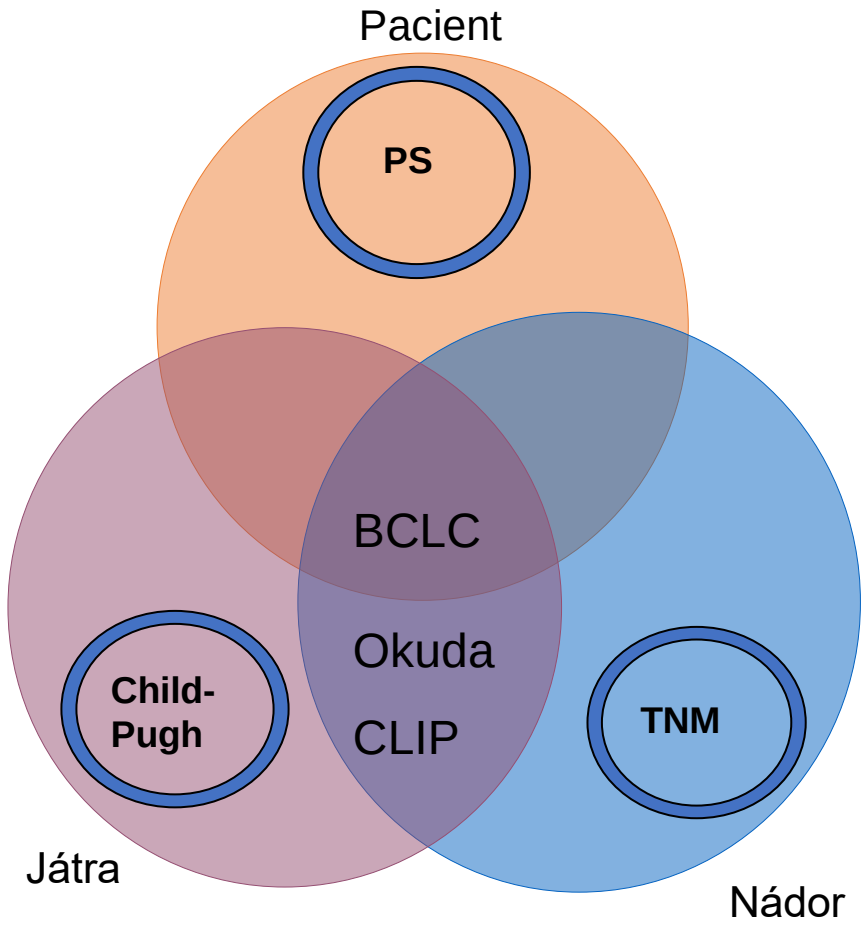
Nejsou jednoduché prognost. faktory

Většina faktorů se mění vývojem nemoci – nádoru i cirhózy

BCLC: Barcelona Clinic Liver Cancer staging systém

Okuda (tumor,bili,alb,ascites)

CLIP (Child-Pugh, tumor,AFP, trombóza portální žíly)



Jaterní funkce – Child Pughova klasifikace

Tabulka 1: Child-Pughova klasifikace funkčního hodnocení jater u pacientů s cirhózou

Klinické a laboratorní parametry	**Bodová hodnota parametrů**		
	1	**2**	**3**
Bilirubin (µmol/l)	< 35	35–50	> 50
Albumin g/l	> 35	28–35	< 28
Ascites	0	Mírný nebo reverzibilní medikací	Střední nebo těžký, refrakterní k medikaci
Encefalopatie	0	mírná (gr 1 a 2)	zřetelná (gr 3 a 4)
INR	< 1,7	1,71–2,20	> 2,20

Zhodnocení: třída A: 5–6 bodů; třída B: 7–9 bodů; třída C: 10–15 bodů

Klasifikace TNM (8. vydání)

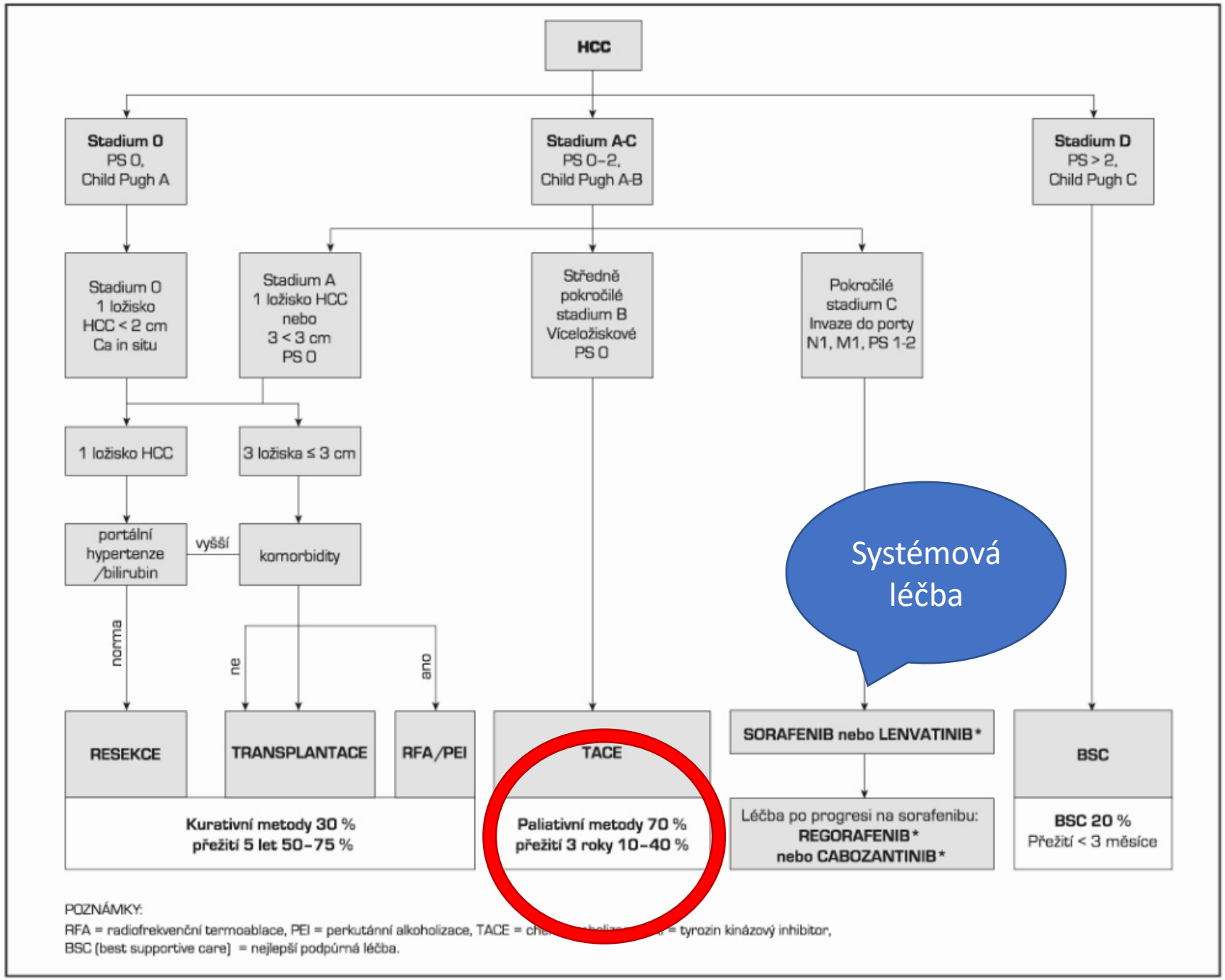
Table 3. UICC 8th edition staging system for hepatocellular carcinoma [49]

T—primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1a	Solitary tumour 2 cm or less in greatest dimension with or without vascular invasion		
T1b	Solitary tumour more than 2 cm in greatest dimension without vascular invasion		
T2	Solitary tumour with vascular invasion more than 2 cm dimension or multiple tumours, none more than 5 cm in greatest dimension		
T3	Multiple tumours any more than 5 cm in greatest dimension		
T4	Tumour(s) involving a major branch of the portal or hepatic vein with direct invasion of adjacent organs (including the diaphragm), other than the gallbladder or with perforation of visceral peritoneum		
N—regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M—distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
Stage—liver			
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

UICC, Union for International Cancer Control.

Modifikované BCLC schéma
Léky registrované

Modrá kniha ČOS 2019



Indikace transplantace jater u HCC
Milánská kriteria

1. Solitární ložisko ≤ 5cm

2. Do 3 ložisek ≤ 3cm

Bez vaskulární invaze (radiologicky)

Bez mikroangioivaze (histologicky)

…. 5leté přežití 70%

ESMO guidelines HCC

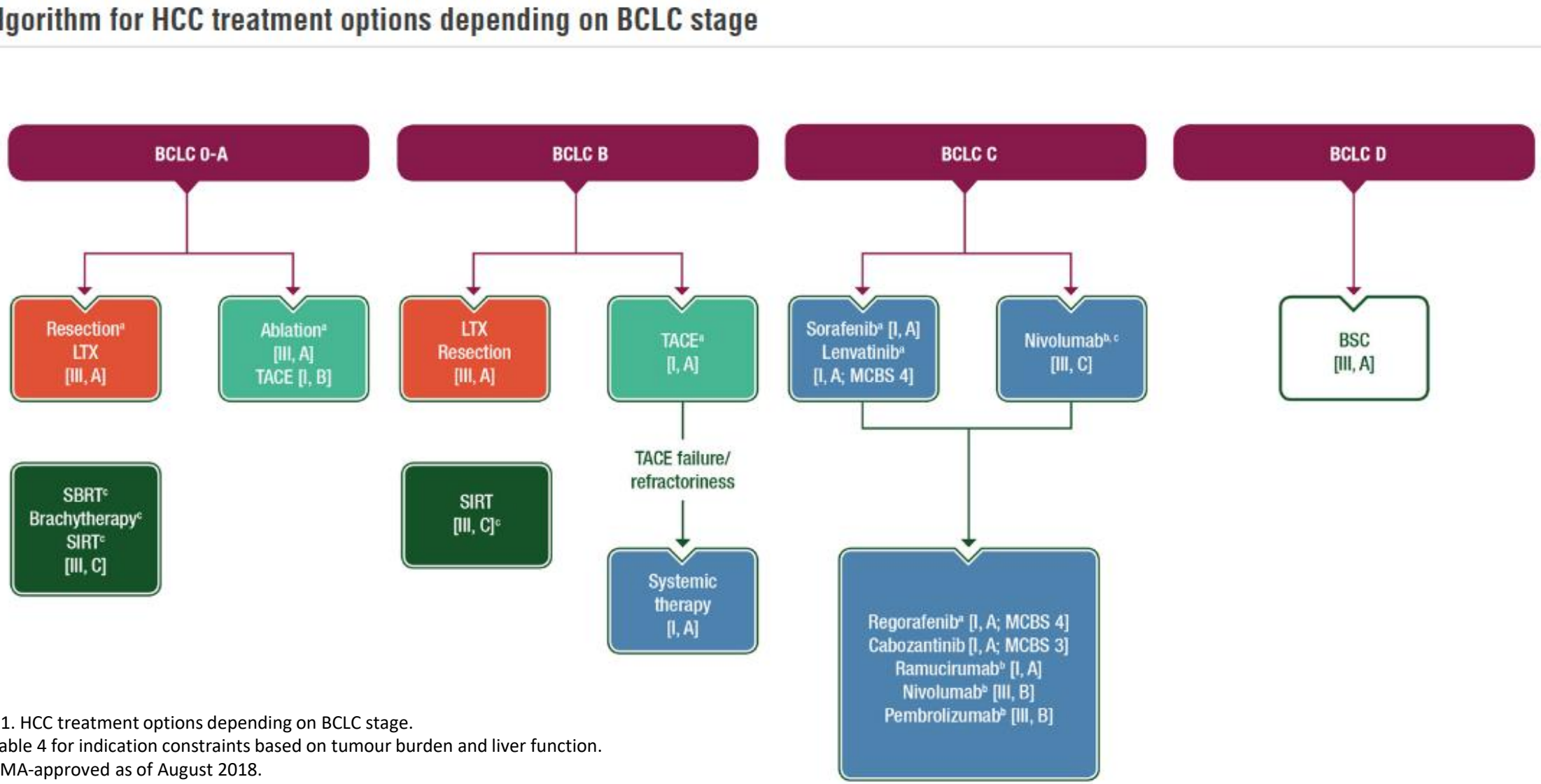


Figure 1. HCC treatment options depending on BCLC stage.
aSee Table 4 for indication constraints based on tumour burden and liver function.
bNot EMA-approved as of August 2018.
BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; EMA, European Medicines Agency; HCC, hepatocellular carcinoma; LTX, liver transplantation; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation.

https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Hepatocellular-Carcinoma/eUpdate-Treatment-Algorithms?hit=some, last accessed 26.1.2020

EASL guidelines HCC (European Association for the Study of the Liver)

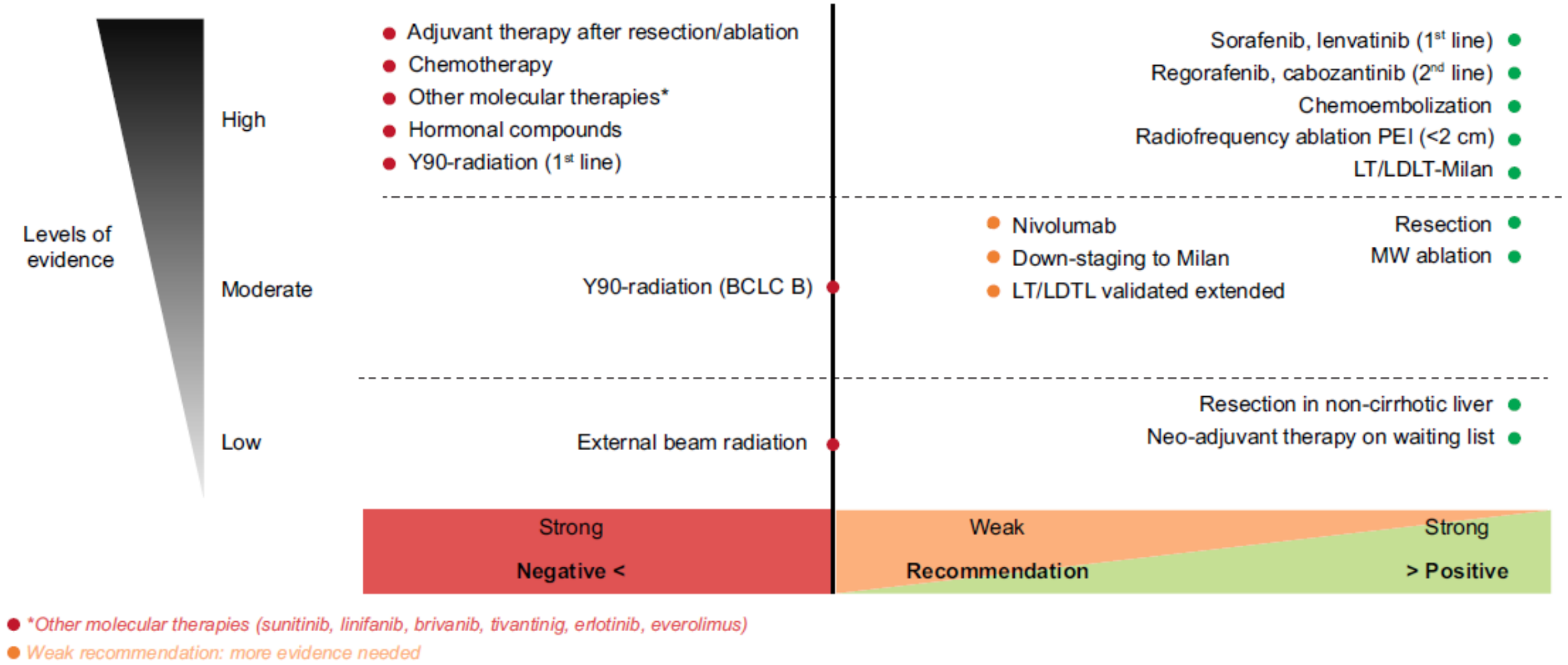


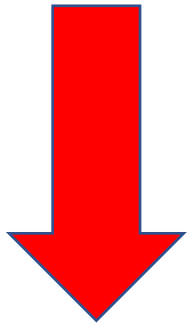
Fig. 9. Representation of EASL recommendations for treatment according to levels of evidence and strength of recommendation (adaptation of the GRADE system). LDLT, living donor liver transplantation; LT, orthotopic liver transplantation; MW, microwave; PEI, percutaneous ethanol injection; RF, radiofrequency ablation

Galle PR *et al*. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology* 2018;69:182-236.

Vybraná data
z klinických studií nových léků

- Regorafenib (RESORCE study, 2L vs plb)
- Cabozantinib (CELESTIAL study, 2L vs plb)
- Lenvatinib (REFLECT study 304, 1L vs sorafenib)
- Ramucirumab (REACH study, 2L vs plb)

- Imunoterapie
  - Nivolumab (CheckMate 040)
  - Pembrolizumab
  - Atezolizumab

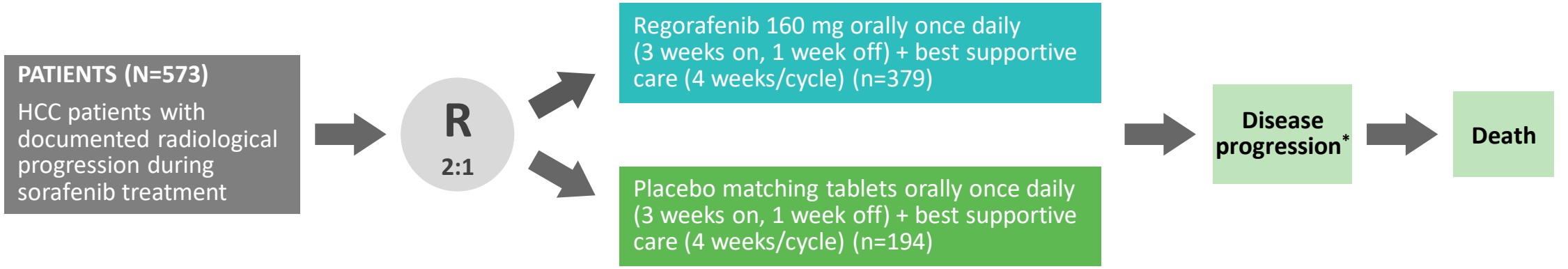


1st line		Months	Significance
Sorafenib[1]	Sorafenib (n=299) vs **placebo** (n=303)	10.7 vs 7.9	*P*<0.001
Lenvatinib[2]	Lenvatinib (n=478) vs **sorafenib** (n=476)	13.6 vs 12.3	*P*<0.001 Lenvatinib is non-inferior to sorafenib

2nd line		Months	Significance
Regorafenib[3]	Regorafenib (n=379) vs **placebo** (n=194)	10.6 vs 7.8	*P*<0.0001
Cabozantinib[4]	Cabozantinib (n=470) vs **placebo** (n=237)	10.2 vs 8.0	*P*=0.0049

Phase III RESORCE: Regorafenib in patients with HCC progressing on prior sorafenib

RESORCE (NCT01774344) was a multinational[a], randomized, double-blind, placebo-controlled, phase III study that evaluated the efficacy and safety of regorafenib in patients with advanced liver cancer who have progressed on prior sorafenib



Stratification:

- Geographic region (Asia vs ROW)
- Macrovascular invasion
- Extrahepatic disease
- ECOG PS (0 vs 1)
- AFP (<400 ng/mL vs ≥400 ng/mL)

Primary Endpoint:

- **OS**

Secondary Endpoints (by modified RECIST for HCC and RECIST 1.1):

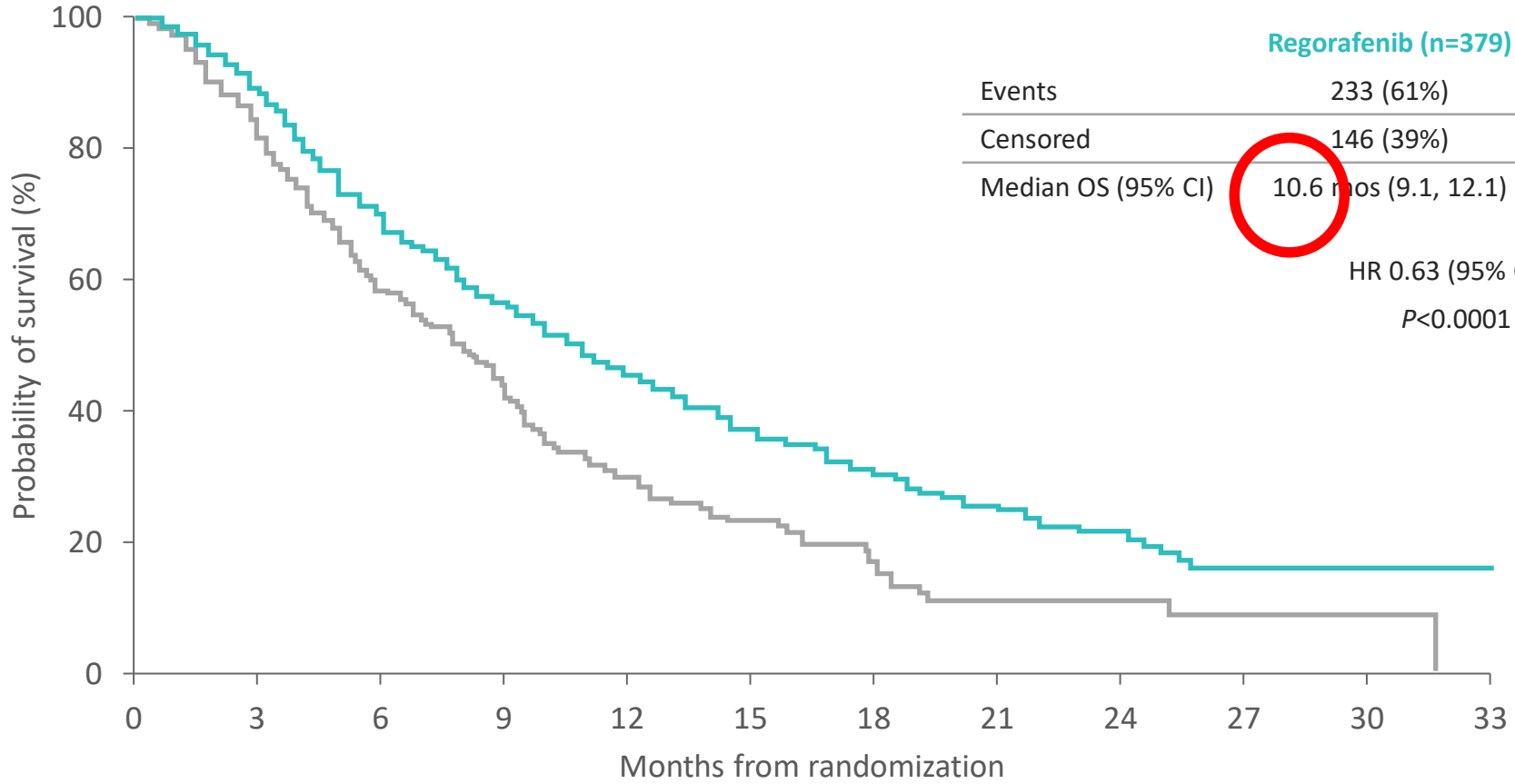
- TTP, PFS, response rate, and disease control rate
- Safety

Other Endpoints:

- Duration of response and duration of stable disease
- HRQoL
- Pharmacokinetic and biomarker analyses

a. 152 centers in 21 countries in North and South America, Europe, Australia, and Asia.
b. Including clinical progression; unacceptable toxicity; withdrawal of patient consent; or discontinuation of therapy by the treating physician.
ECOG PS, Eastern Cooperative Oncology Group performance status.
SOURCE: Bruix J, et al. *Lancet.* 2017 Jan 7;389(10064):56-66.

Phase III RESORCE: Overall survival (OS), Primary endpoint



	Regorafenib (n=379)	Placebo (n=194)
Events	233 (61%)	140 (72%)
Censored	146 (39%)	54 (28%)
Median OS (95% CI)	10.6 mos (9.1, 12.1)	7.8 mos (6.3, 8.8)

HR 0.63 (95% CI: 0.50, 0.79)

P<0.0001 (1-sided)

SOURCE: Bruix J, et al. *Lancet.* 2017 Jan 7;389(10064):56-66.

Regorafenib in patients with unresectable hepatocellular carcinoma (uHCC) in routine clinical practice: Interim analysis of the prospective, observational REFINE trial ASCO GI 2020, Abstract 542

Table 2. Treatment duration and dosing

	Regorafenib (N=498)
Duration of treatment, months*	
Median (range)	3.7 (<1–19.0)
Initial daily dose, n (%)	
160 mg	286 (57)
120 mg	63 (13)
80 mg	141 (28)
40 mg	8 (2)
Any treatment modification†, n (%)	267 (54)
Dose reduction	203 (41)
Dose escalation	95 (19)
Dose interruption	138 (28)
Dose restart	68 (14)
Treatment modification within the first 4 weeks, n (%)	179 (36)

Regorafenib – nežádoucí účinky

Table 5. Overview of TEAEs by time after treatment start

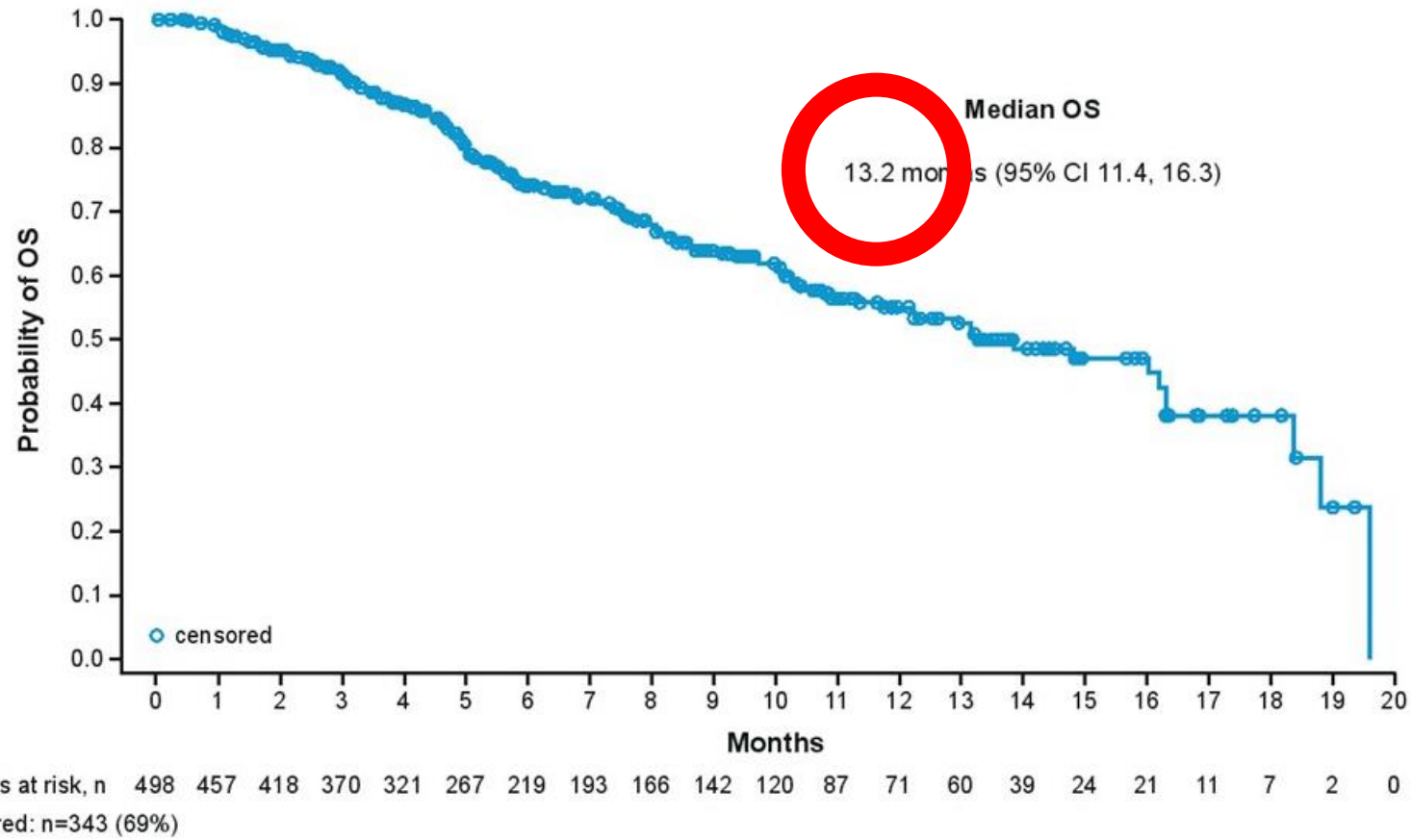
TEAE, n (%)	Regorafenib (N=498)		
	Any time	≤56 days*	≤84 days†
Any	419 (84)	372 (75)	399 (80)
Grade 3	146 (29)	97 (19)	121 (24)
Grade 4	14 (3)	7 (1)	9 (2)
Grade 5	55 (11)	26 (5)	29 (6)
Leading to dose reduction	134 (27)	111 (22)	121 (24)
Leading to dose interruption	124 (25)	94 (19)	105 (21)
Leading to permanent discontinuation	123 (25)	73 (15)	87 (17)

Coded by MedDRA v22.1. Graded by NCI-CTCAE v4.03.
*Corresponds to two theoretical cycles of regorafenib; †Corresponds to three theoretical cycles of regorafenib.
MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Regorafenib – reálná praxe, n = 498

- The median OS was 13.2 months (95% CI 11.4, 16.3) (Figure 2)

Figure 2. Overall survival



CI, confidence interval; OS, overall survival.

CELESTIAL - design studie s cabozantinibem

Randomizovaná, dvojitě zaslepená studie; *cíl: efektivita cabozantinibu u pacientů s HCC předléčených sorafenibem*

Pacienti s pokročilým HCC (N=760)

- Histologicky potvrzená diagnóza HCC nevhodná ke kurativní léčbě
- Child-Pugh skóre A
- Předchozí léčba sorafenibem
- Pacienti po progresi na alespoň jedné předchozí systémové HCC terapii
- Možné až dva předchozí systémové léčebné režimy
- ECOG PS 0 nebo 1
- Bez přítomnosti nekontrolovatelné hypertenze, definované jako trvalý STK >150 mm Hg nebo DTK >100 mm Hg navzdory optimální antihypertenzní léčbě

Rrandomizace 2:1

Cabozantinib 60 mg PO denně

Placebo PO denně

Stratifikace

- Etiologie onemocnění (HBV, HCV, jiné)
- Region (Asie, jiné)
- Přítomnost makrovaskulární invaze a/nebo extrahepatálního rozšíření (ano/ne)

Hodnocení každých 8 týdnů (RECIST 1.1)

Léčba přetrvávala do ztráty klinického benefitu nebo netolerovatelné toxicity

Crossover nebyl povolen

Primární endpoint:

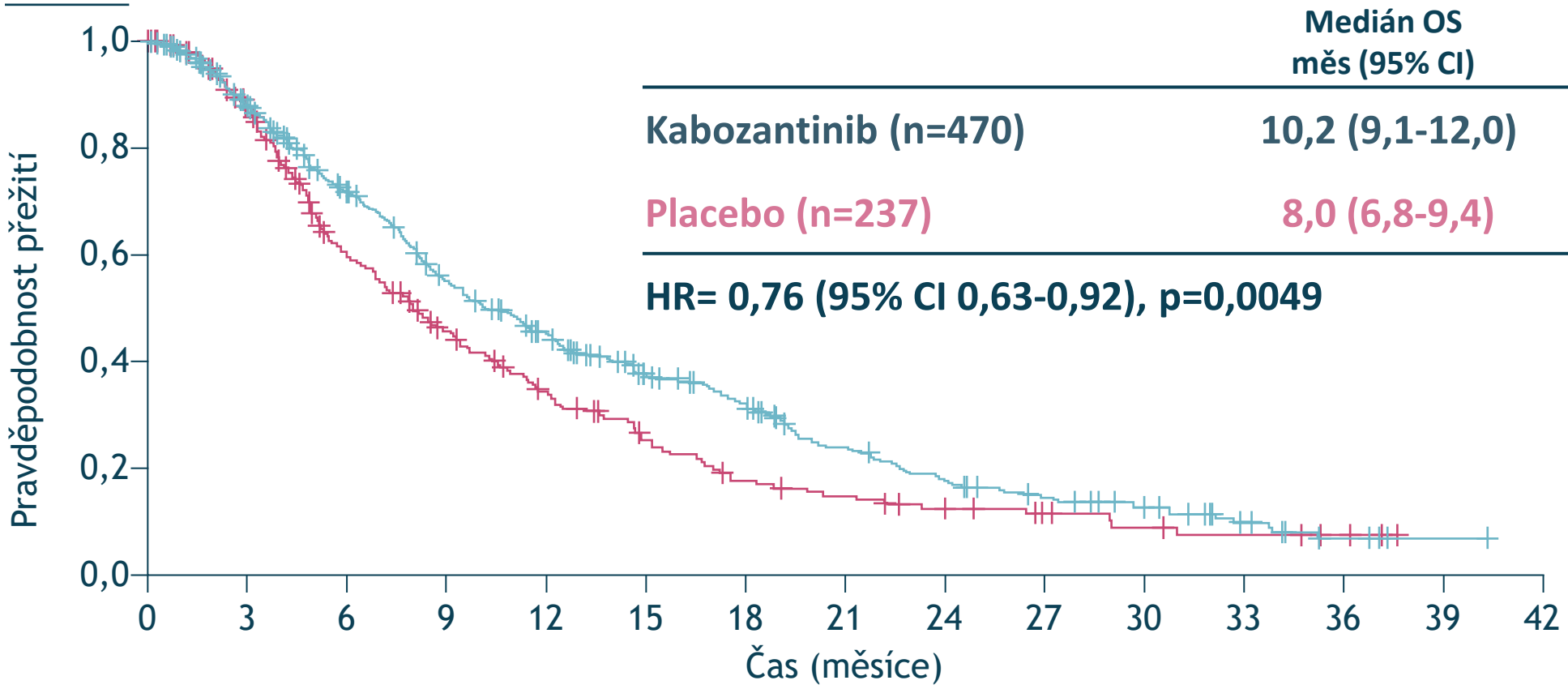
Celkové přežití (OS)

Sekundární endpointy:

Čas do progrese (PFS) a výskyt objektivní léčebné odpovědi (ORR)

Abou-Alfa GK *et al*. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379:54-63.

CELESTIAL: OS



	Medián OS měs (95% CI)	Počet úmrtí
Kabozantinib (n=470)	10,2 (9,1-12,0)	317
Placebo (n=237)	8,0 (6,8-9,4)	167

HR= 0,76 (95% CI 0,63-0,92), p=0,0049

Počet pacientů s rizikem

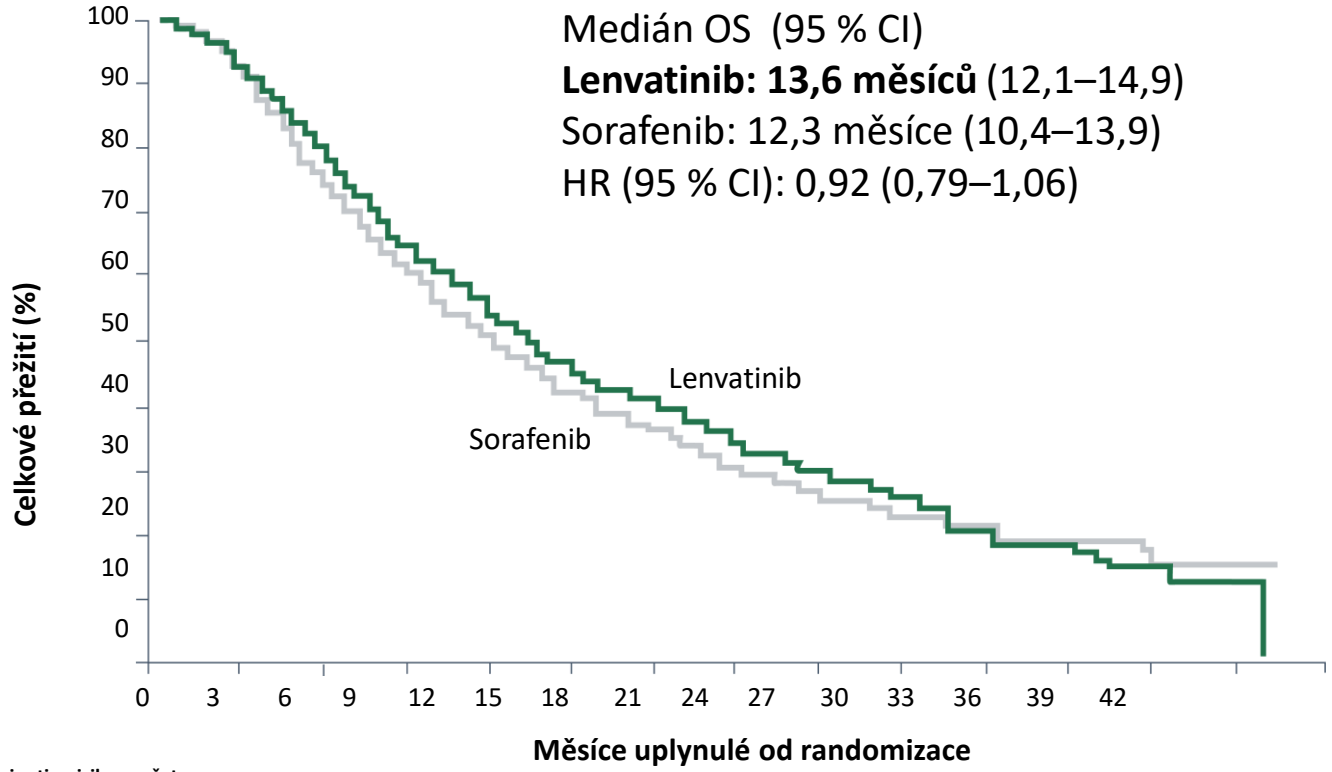
Kabozantinib	470	382	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

Abou-Alfa GK *et al*. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379:54-63.

Klinická studie III. fáze REFLECT – **lenvatinib** (OS primární cíl)

- Lenvatinib prokázal noninferioritu (OS) [1]

Medián OS (95 % CI)
Lenvatinib: 13,6 měsíců (12,1–14,9)
Sorafenib: 12,3 měsíce (10,4–13,9)
HR (95 % CI): 0,92 (0,79–1,06)



Pacienti v riziku, počet

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

- CI: interval spolehlivosti; HR: míra ohrožení;
- 1. Kudo M et al. Lancet. 2018;391:1163–1173; 2. Cheng AL et al. J Clin Oncol. 2013;31:4067–4075; 3. Johnson PJ et al. J Clin Oncol. 2013;31:3517–3524; 4. Cainap C et al. J Clin Oncol. 2015;33:172–179; 5. Zhu AX et al. J Clin Oncol. 2015;33:559–566.

Ramucirumab v II. linii léčby HCC po progresi na sorafenibu

REACH (Overall, N=565; number of patients who had AFP ≥400, n=250)

Stratification factors: Etiology (hepatitis B, hepatitis C, other), geographic regions

- Prior sorafenib
- BCLC stage B/C
- Child-Pugh A
- ECOG PS 0 or 1

Randomization

1:1

- RAM (8 mg/kg IV) Q2W per cycle and BSC
- PBO Q2W per cycle and BSC

Treatment until disease progression or unacceptable toxicity

Primary endpoint:
OS

Secondary endpoints:
PFS, ORR, safety, patient-reported disease-related symptom severity

REACH-2 (N=292)

Stratification factors: Macrovascular invasion (yes vs no), ECOG PS (0 vs 1), geographic regions

- Prior sorafenib
- BCLC stage B/C
- Child-Pugh A
- ECOG PS 0 or 1
- Baseline AFP ≥400 ng/ml

Randomization

2:1

- RAM (8 mg/kg IV) Q2W per cycle and BSC
- PBO Q2W per cycle and BSC

Treatment until disease progression or unacceptable toxicity

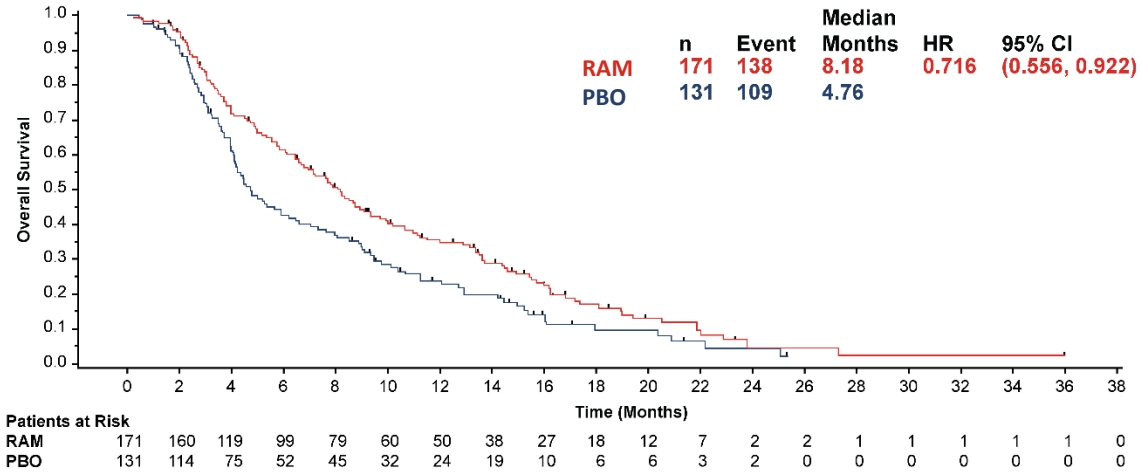
Primary endpoint:
OS

Secondary endpoints:
PFS, ORR, safety, patient-reported disease-related symptom severity

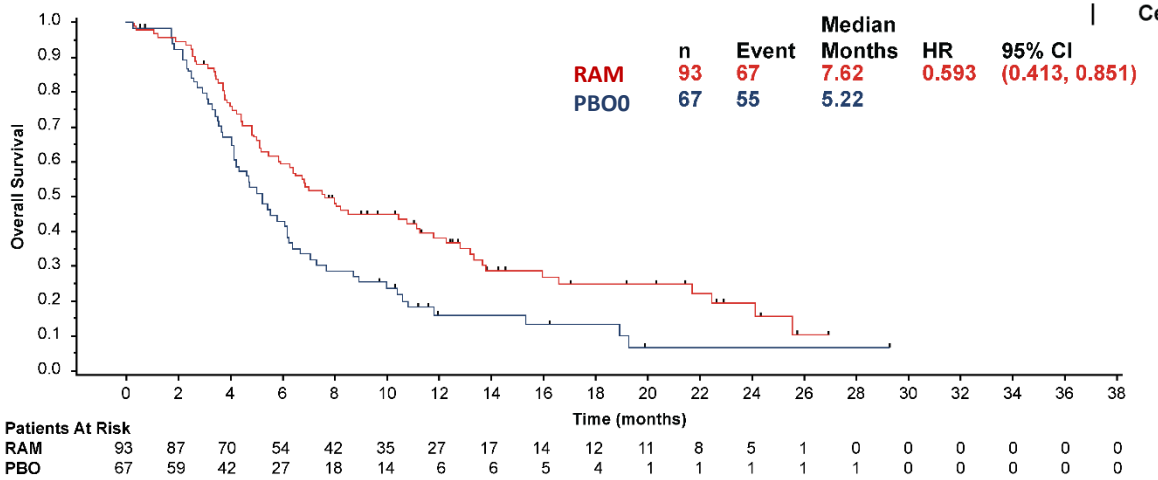
AFP=alpha-fetoprotein; BCLC=Barcelona Clinic Liver Cancer; BSC=best supportive care; ECOG PS=Eastern Cooperative Oncology Group performance status; IV=intravenous; ORR=objective response rate; OS, overall survival; PBO=placebo; PFS=progression-free survival; Q2W=every 2 weeks; RAM=ramucirumab.

Overall Survival – ramucirumab

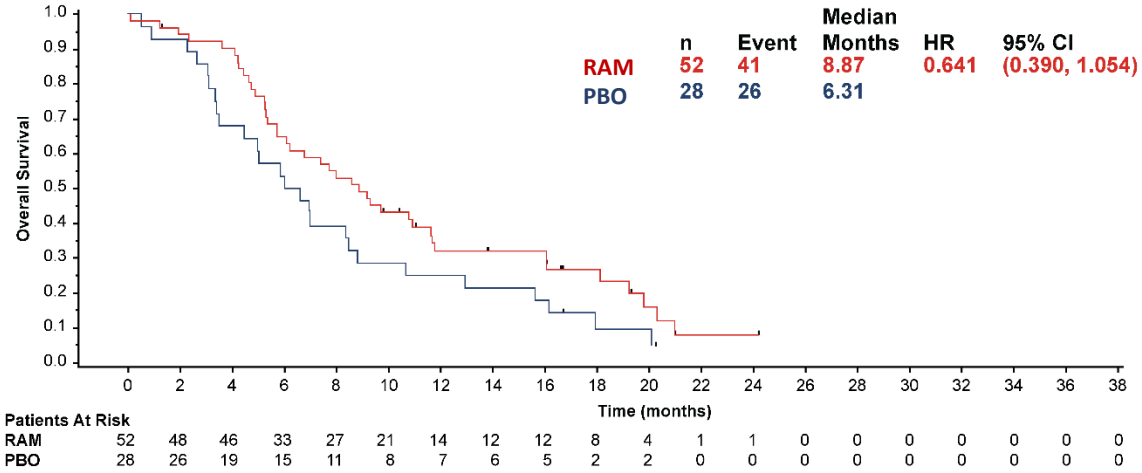
Age <65 years



Age ≥65 to <75 years



Age ≥75 years



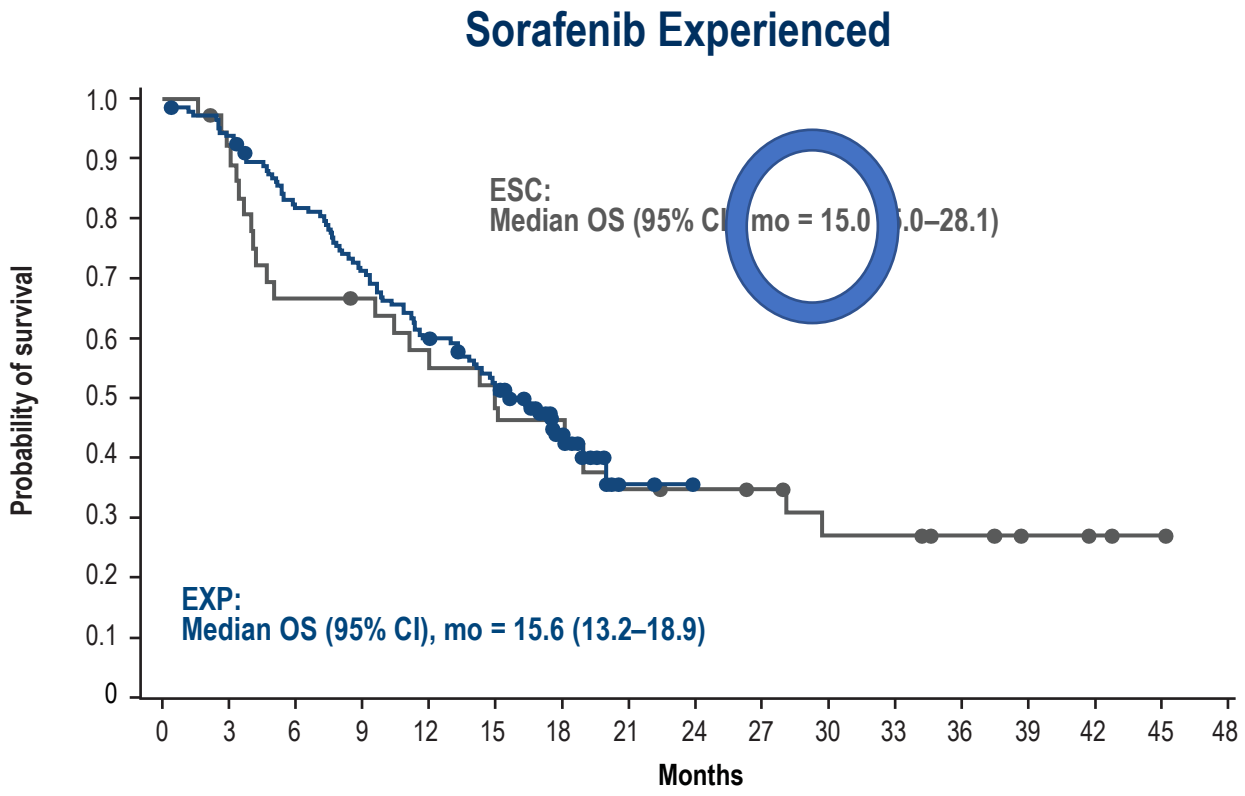
Age (years)	Treatment	Patients (n)	Events	Median OS (months)	Hazard ratio (95% CI)
≤65	RAM	171	138	8.18	0.716 (0.556, 0.922)
	PBO	131	109	4.76	
≥65 to 75	RAM	93	67	7.62	0.593 (0.413, 0.851)
	PBO	67	55	5.22	
≥75	RAM	52	41	8.87	0.641 (0.390, 1.054)
	PBO	28	26	6.31	

Note: RAM and PBO were given with best supportive care.

CI=confidential interval; HR=hazard ratio; PBO=placebo; RAM=ramucirumab; OS=overall survival.

Nivolumab: 2. linie systémové léčby : OS CheckMate 040

Sorafenib Experienced (2L)



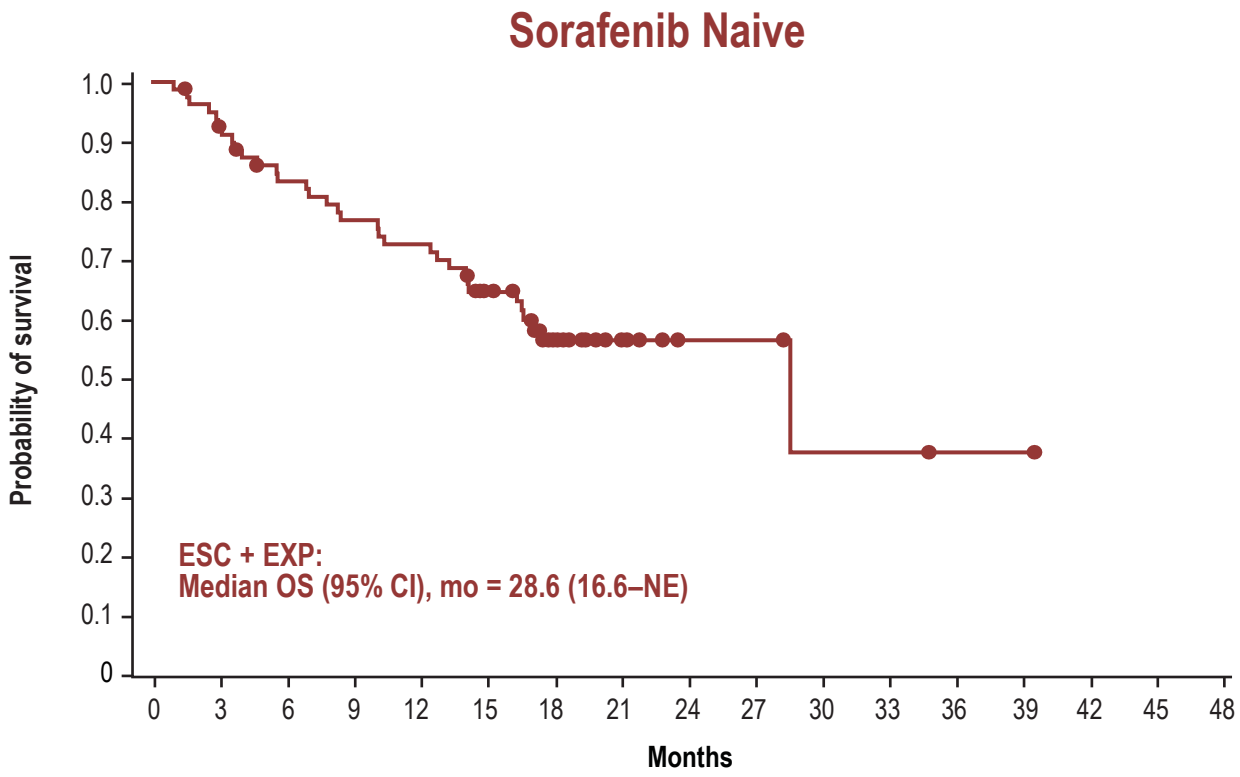
OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

Kaplan-Meier method; closed circles denote censored patients.

1. Crocenzi TS et al. Poster presentation at ASCO 2017. 4013.

Nivolumab: 1. linie systémové léčby : OS CheckMate 040

Sorafenib Naive (1L)

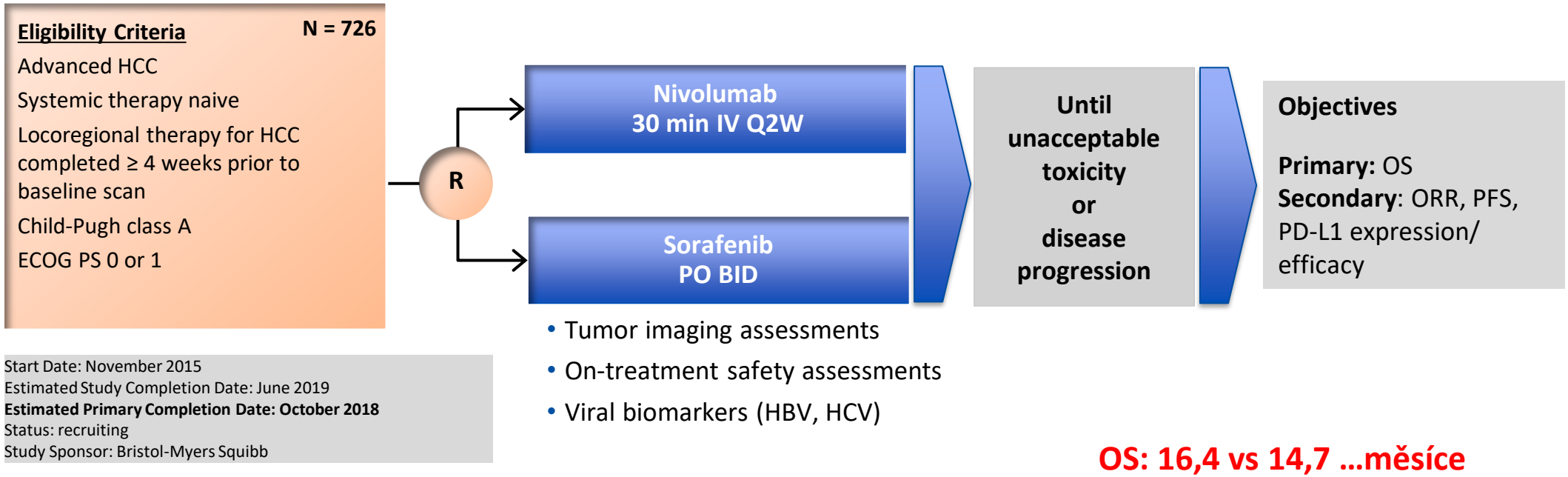


OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

Kaplan-Meier method; closed circles denote censored patients.

1. Crocenzi TS et al. Poster presentation at ASCO 2017. 4013.

CheckMate-459 ….**nivolumab 1. linie HCC**



OS: 16,4 vs 14,7 …měsíce
Nesignifikantní

1. ClinicalTrials.gov. NCT02576509. https://clinicaltrials.gov/ct2/show/NCT02576509; 2. Sangro B, et al. Poster presentation at ASCO 2016. TPS4147.

KEYNOTE-240: Pembro 2. linie HCC

- Randomized, double-blind phase III trial

Stratified by region (Asia without Japan vs non-Asia with Japan), macrovascular invasion (yes vs no), AFP level (≥ vs < 200 ng/mL)

Patients with HCC that progressed on/intolerant to sorafenib; Child-Pugh class A; BCLC stage B/C; ECOG PS ≤ 1; no invasion of main portal vein (N = 413)

Randomized 2:1

Pembrolizumab 200 mg Q3W + **BSC** for up to 35 cycles (n = 278)

Placebo (saline) + **BSC** for up to 35 cycles (n = 135)

PFS: 3,0 vs 2,8 měsíce
Nesignifikantní

OS: 13,9 vs 10,6 měsíce
(HR: 0.781; 95% CI: 0.611-0.998;
***P* = 0,0238)**
Plán byl: 0,0174

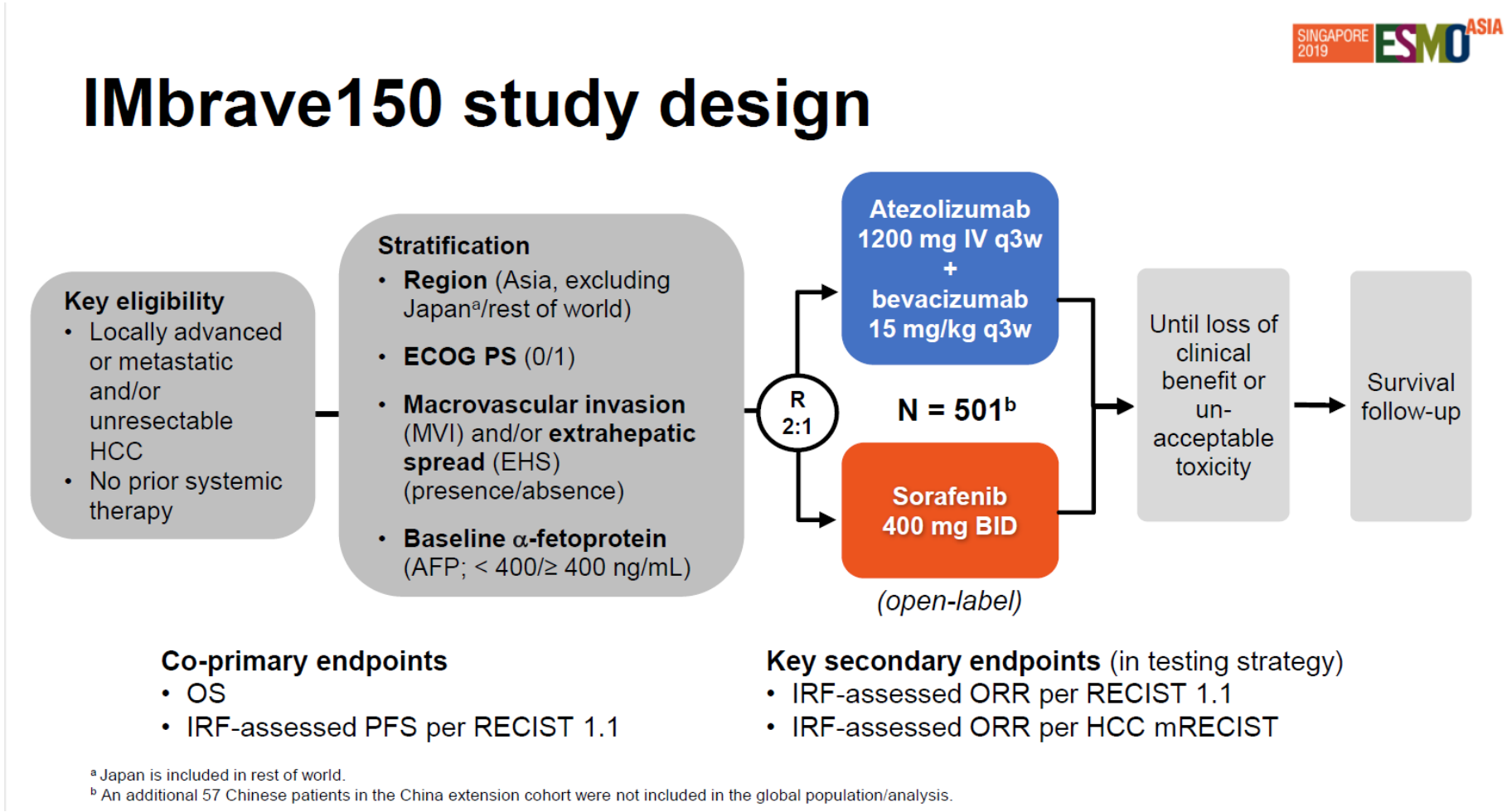
- Coprimary endpoints: PFS,* OS
  - Efficacy boundaries: PFS at first interim cutoff, *P* = .0020 (primary analysis for PFS); OS at final analysis cutoff, *P* = .0174
- Secondary endpoints: ORR,* DoR, DCR, TTP, safety

*PFS, secondary response outcomes centrally reviewed per RECIST v1.1. Response evaluated Q6W.

Finn. ASCO 2019. Abstr 4004. NCT02702401.

Slide credit: clinicaloptions.com

Studie 3 fáze: 1. linie atezo + beva

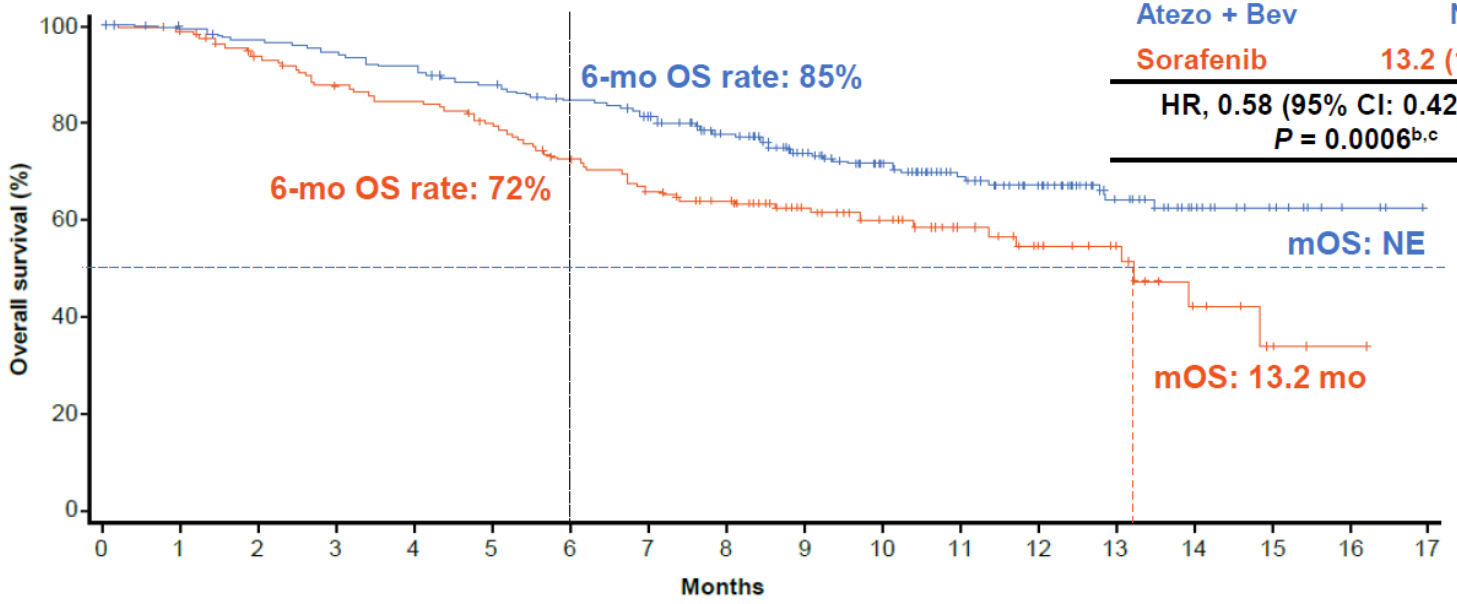


ATEZO + BEVA - OS

SINGAPORE 2019 ESMO ASIA

OS: co-primary endpoint

Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b]	
P = 0.0006[b,c]	



No. at risk																	
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Závěr:

- Multidisciplinární přístup k diagnostice i terapii
- BCLC systém
  - TNM – PS – jaterní funkce
- Resekce – transplantace – ablační metody- TACE
- Systémová terapie :
  - 1. linie: sorafenib nebo lenvatinib
  - 2. linie: regorafenib nebo cabozantinib nebo ramucirumab
  - Imunoterapie … spíše kombinace