Imunoterapie hepatocelulárního karcinomu
Běžná praxe na dohled

Jiří Tomášek
Masarykův onkologický ústav, Brno

PragueONCO 2019

HCC staging – TNM nestačí

Staging určuje prognózu a léčbu.

Většina pacientů má hepatopatii.

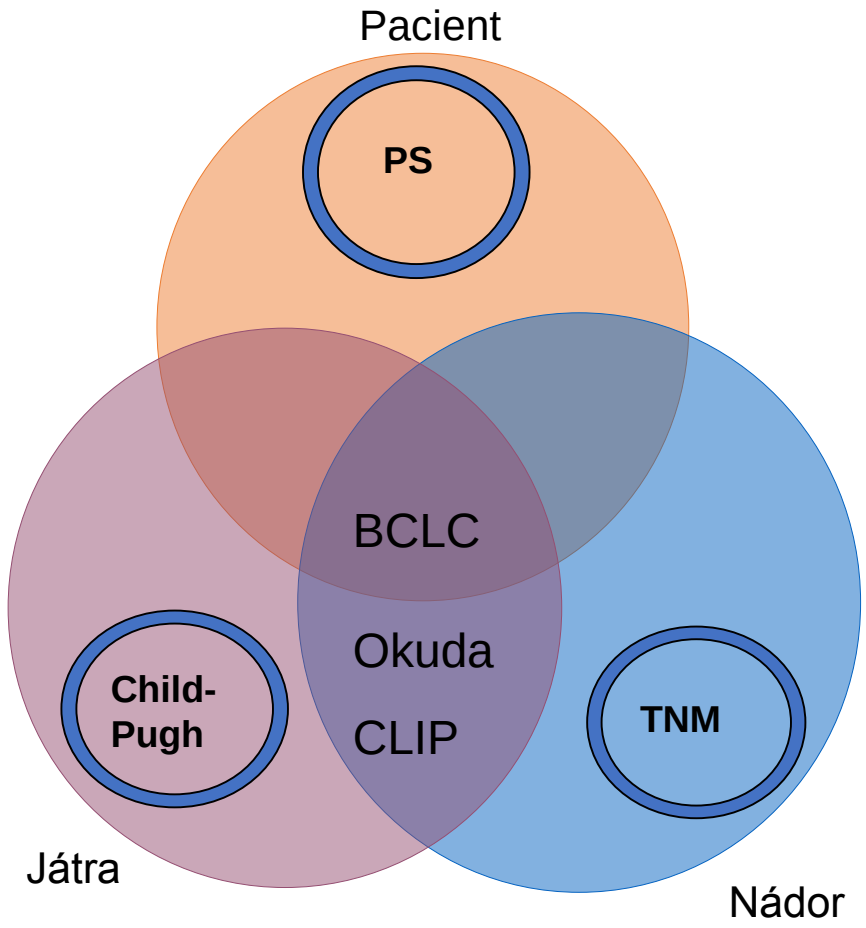
Nejsou jednoduché prognost. faktory

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)



Nová klasifikace TNM (UICC 8. vydání)

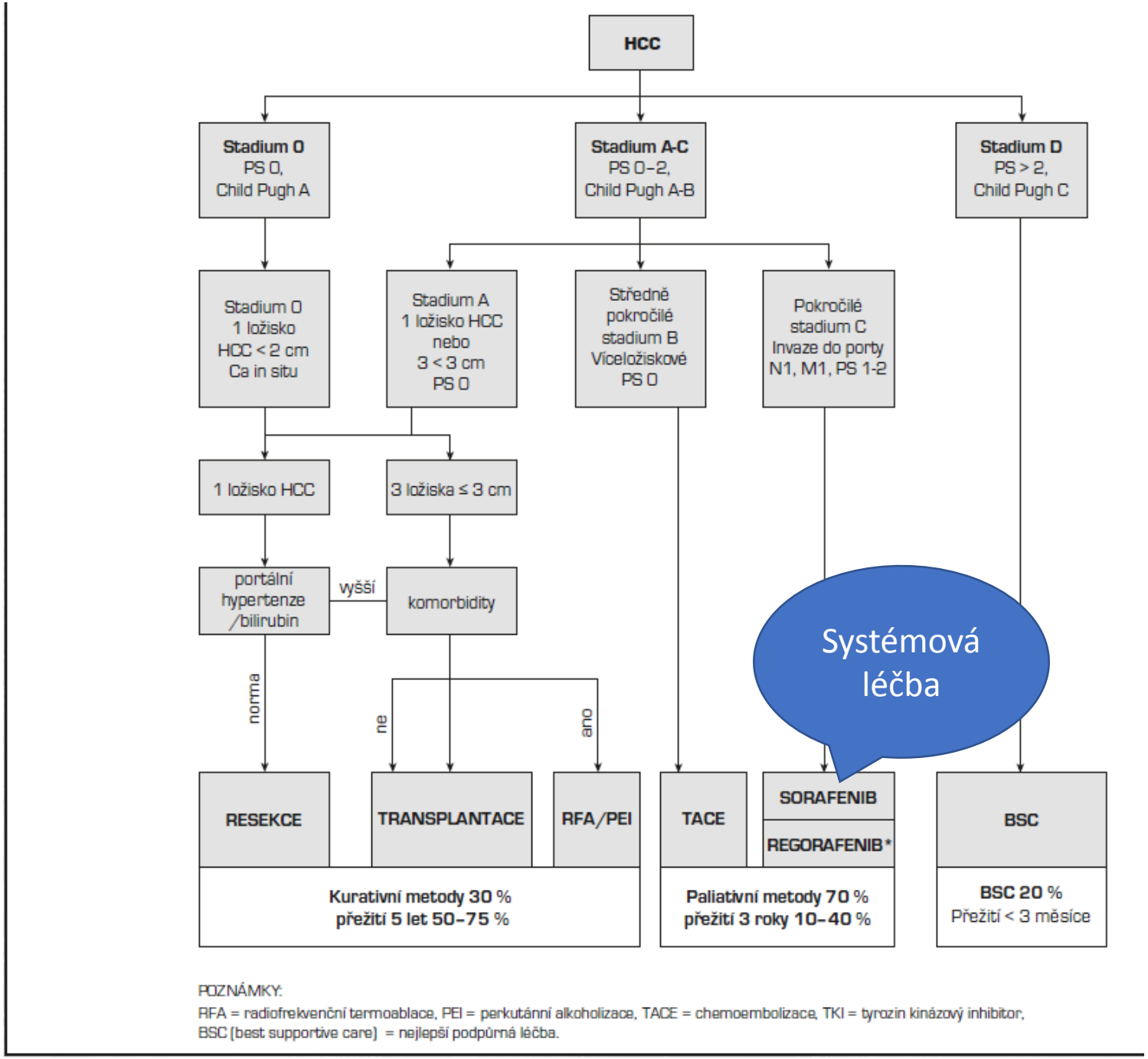
Table 3. UICC 8th edition staging system for hepatocellular carcinoma [49]

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.

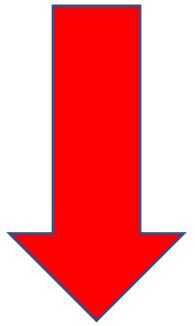
Barcelonská klasifikace (Barcelona Clinical Liver Cancer)

- 5 stadií (0, A, B, C a D) na základě počtu a velikosti ložisek, funkce jater (Child Pughova klasifikace), výkonnostního stavu pacienta, popřípadě dalších faktorů (invaze do portální žíly, extrahepatální šíření)



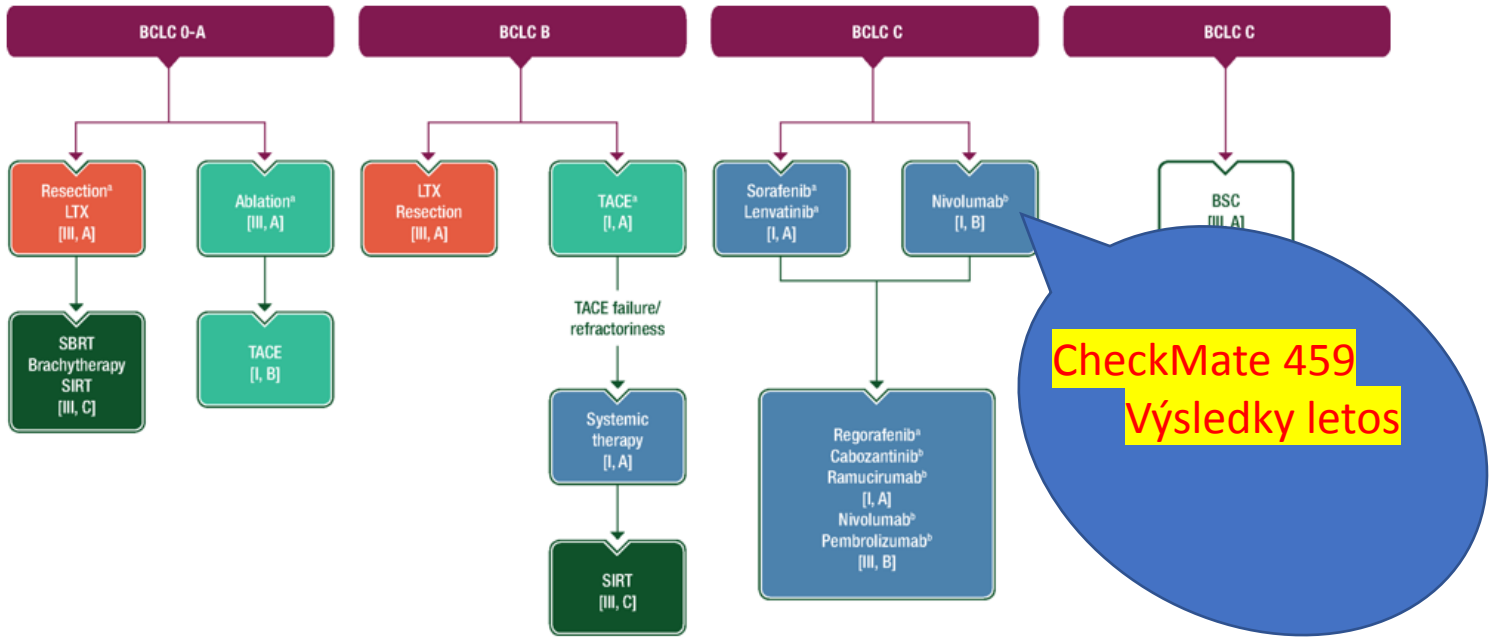
Nové léky pro terapii HCC

- Regorafenib (RESORCE study, 2L vs plb)
- Kabozantinib (CELESTIAL study, 2L vs plb)
- Lenvatinib (REFLECT study 304, 1L vs sorafenib)
- Ramucirumab (REACH study, 2L vs plb)
- Imunoterapie
  - Nivolumab (CheckMate 040)
  - Pembrolizumab
  - Atezolizumab



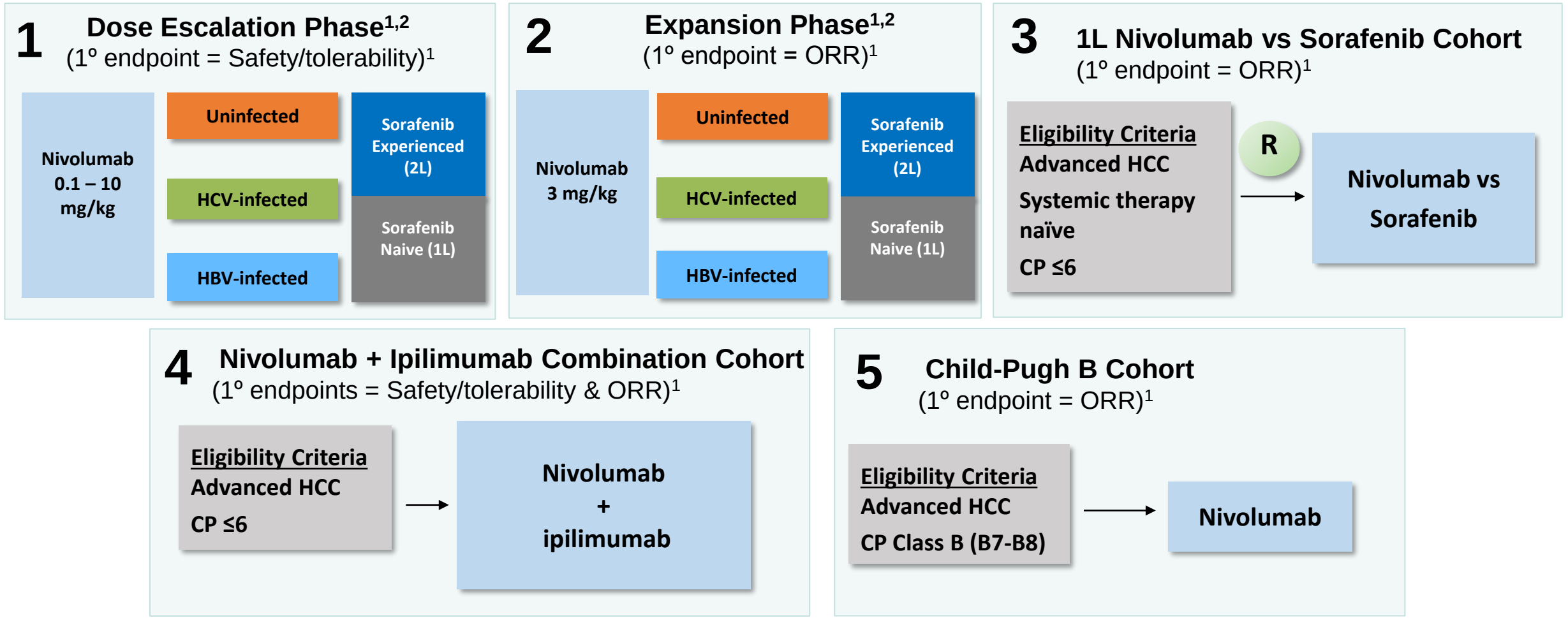
1st line		Months	Significance
Sorafenib[1]	Sorafenib (n=299) vs **placebo** (n=303)	10.7 vs 7.9	*P*<0.001
Lenvatinib[2]	Lenvatinib (n=478) vs **sorafenib** (n=476)	13.6 vs 12.3	*P*<0.001 Lenvatinib is non-inferior to sorafenib

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



Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†
Ann Oncol. 2018;29(Supplement_4):iv238-iv255. doi:10.1093/annonc/mdy308

CheckMate 040 (CA209-040): Study Design



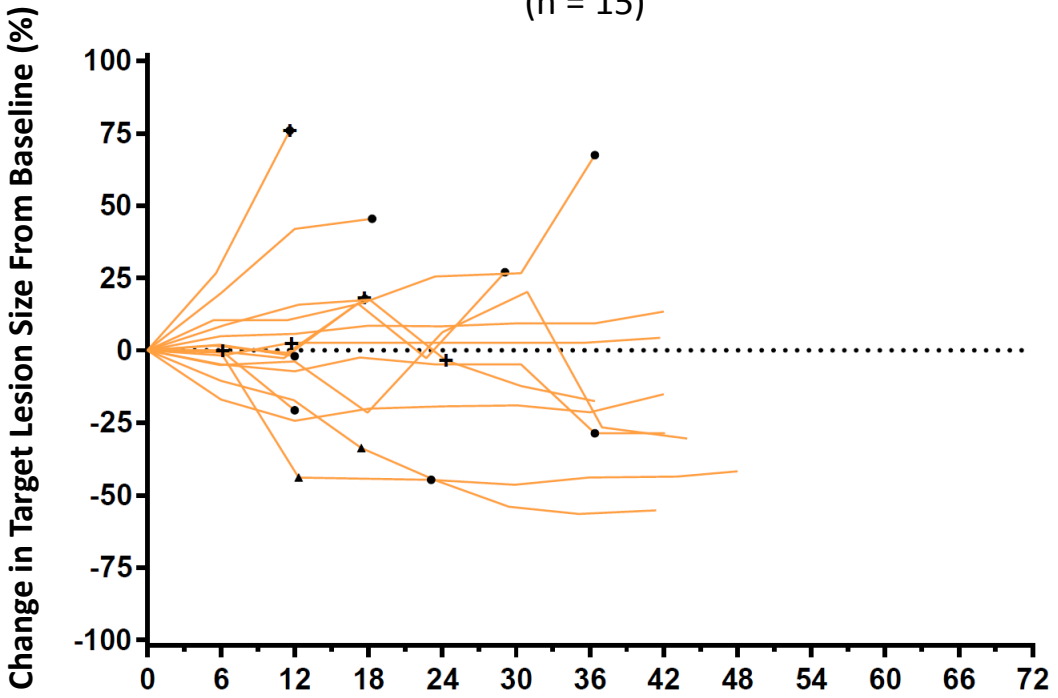
CP, Child-Pugh; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, objective response rate; R, randomized.

1. Clinicaltrials.gov. NCT01658878, https://clinicaltrials.gov/ct2/show/NCT01658878; 2. Melero I, et al. Oral presentation at ASCO GI 2017.

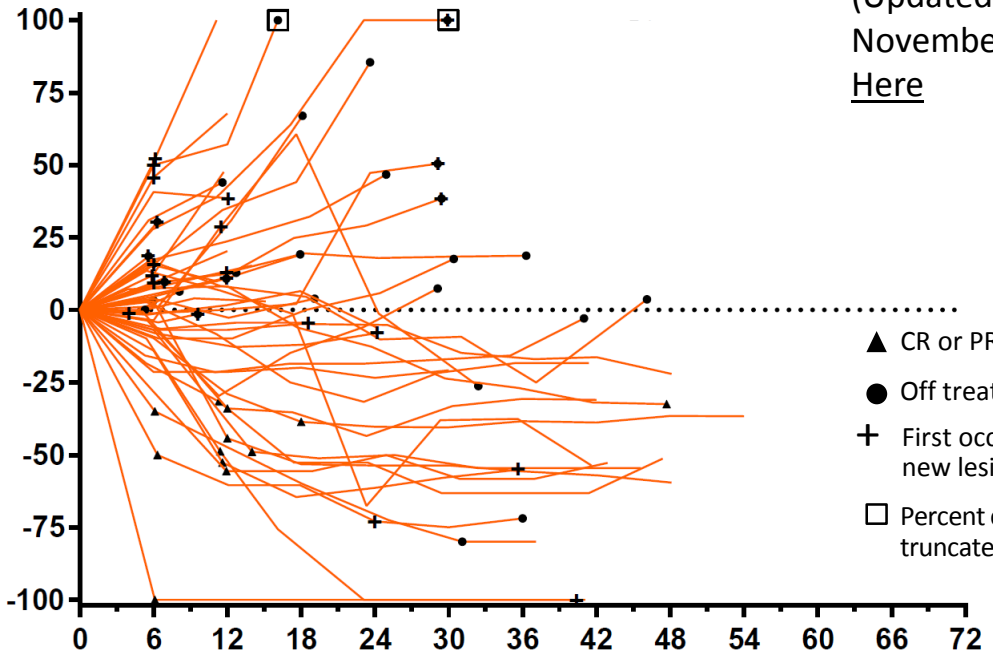
Efficacy Results: Change in Target Lesion From Baseline

Dose Expansion Phase – Investigator Assessment*

Uninfected
Sorafenib Intolerant
(n = 15)



Uninfected
Sorafenib Progressors
(n = 51)



Weeks

*For spider plots by etiology and BICR from EASL 2017 (Updated DBL-November 2016) Click Here

CR, complete response; PR, partial response

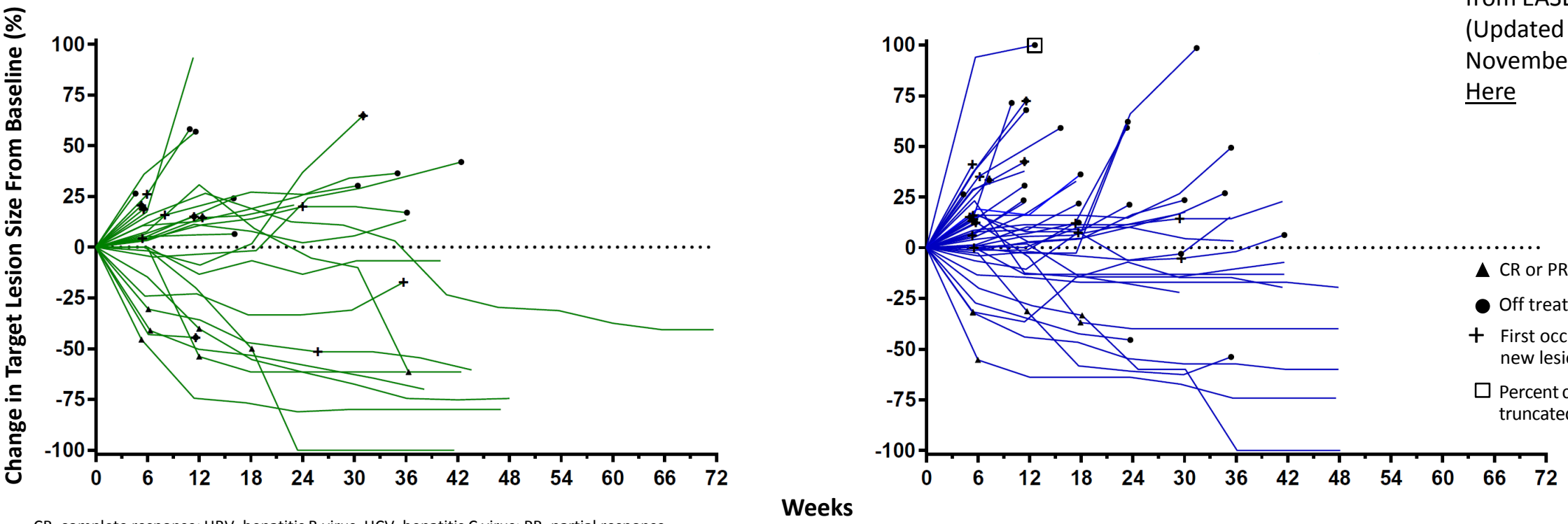
1. Melero I, et al. Oral presentation at ASCO GI 2017.

Efficacy Results: Change in Target Lesion From Baseline

Dose Expansion Phase – Investigator Assessment*

HCV infected
(n = 27)

HBV infected
(n = 42)



*For spider plots by etiology and BICR from EASL 2017 (Updated DBL-November 2016) Click Here

CR, complete response; HBV, hepatitis B virus, HCV, hepatitis C virus; PR, partial response

1. Melero I, et al. Oral presentation at ASCO GI 2017.

Efficacy Results: Best Overall Response

Parameter	Dose Expansion (n = 69)[a]
Objective response, n (%)[b]	**15 (21.7)**
Complete response	0
Partial response	15 (21.7)
Stable disease	30 (43.5)
Progressive disease	22 (31.9)
Not evaluable	2 (2.9)

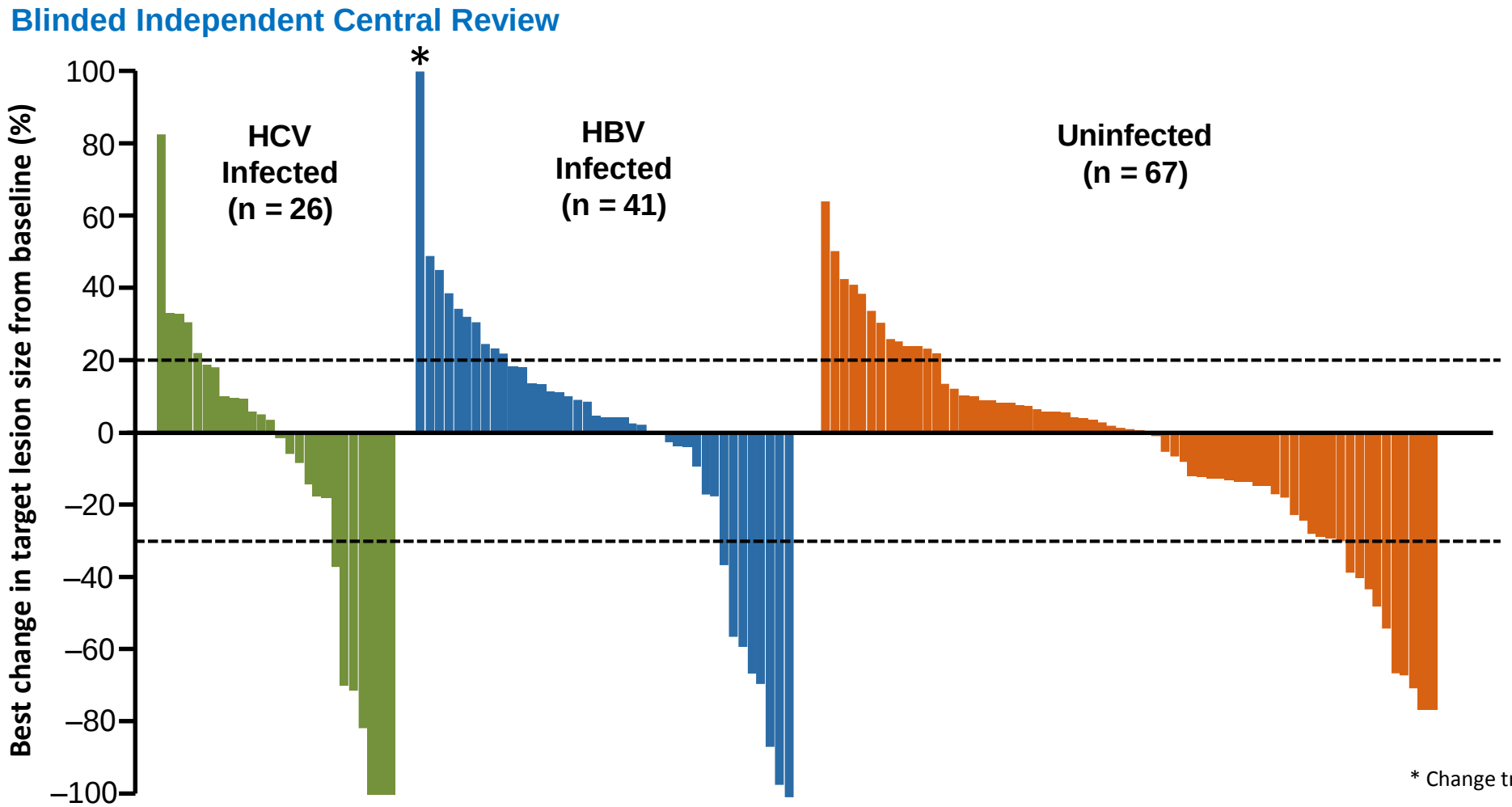
[a] Uninfected (n = 41), HCV infected (n = 20), HBV infected (n = 8). [b] RECIST v1.1 by investigator assessment.

- Overall survival rates at 6 and 9 months in sorafenib-naive patients treated in the dose-expansion phase were 87% and 77%, respectively

HBV, hepatitis B virus; HCV, hepatitis C virus; RECIST v1.1, response evaluation criteria in solid tumors version 1.1.

1. Melero I, et al. Oral presentation at ASCO GI 2017.

Best Change in Target Lesion From Baseline



* Change truncated to 100%.

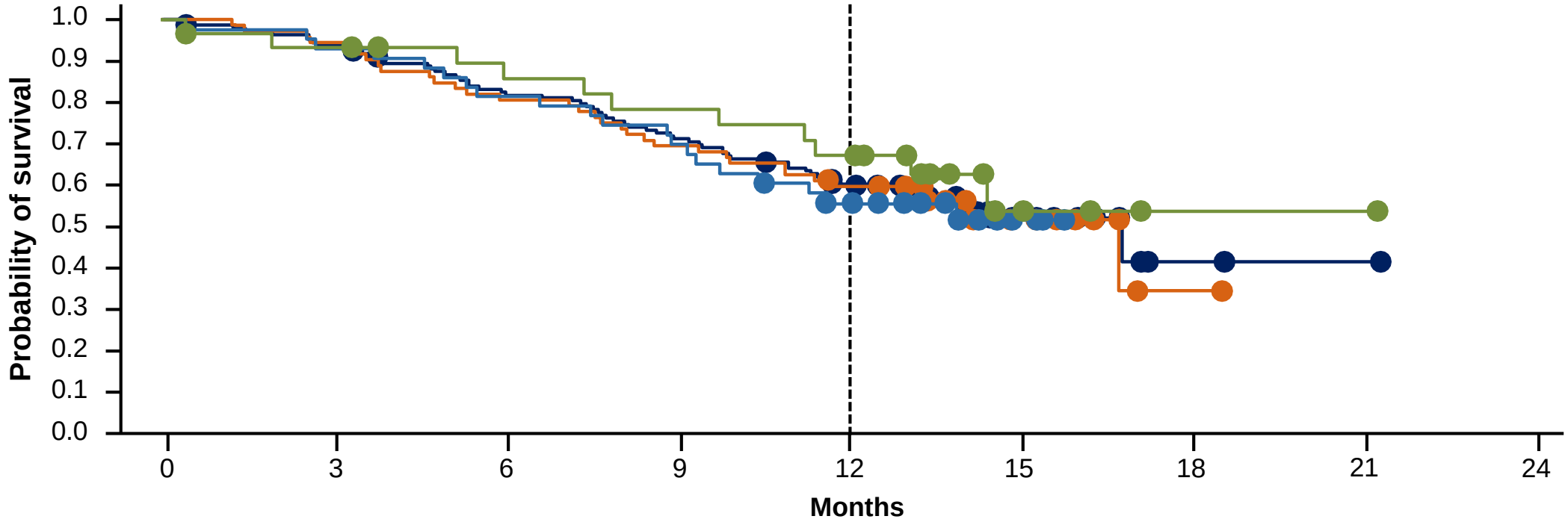
HBV, hepatitis B virus; HCV, hepatitis C virus; INV, investigator; OR, objective response;

1. Sangro B, et al. Oral presentation at EASL 2017.

Overall Survival

	HCV Infected (n = 30)	HBV Infected (n = 43)	Uninfected (n = 72)	All Patients (N = 145)
Median OS (95% CI)[a]	NR	NR	16.7 (11.3–NE)	16.7 (13.2–NE)
12-mo OS rate (95% CI), %[a]	67.1 (46.2–81.4)	55.6 (39.6–69.0)	59.7 (47.4–70.0)	59.9 (51.3–67.4)

[a] Kaplan-Meier method.



HBV, hepatitis B virus; HCV, hepatitis C virus; INV, investigator; NE, not estimable; NR, not reached; OS, overall survival.

1. Sangro B, et al. Oral presentation at EASL 2017.

Nivolumab v II. linii léčby HCC po sorafenibu

Safety

n (%)	HCV Infected (n = 30)		HBV Infected (n = 43)		Uninfected (n = 72)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Patients with any treatment-related AE	25 (83)	9 (30)	30 (70)	4 (9)	53 (74)	11 (15)
Treatment-related AEs (≥ 5%)[a]						
Fatigue	6 (20)	1 (3)	5 (12)	0	24 (33)	2 (3)
Pruritus	8 (27)	1 (3)	9 (21)	0	10 (14)	0
Rash	6 (20)	0	6 (14)	0	11 (15)	1 (1)
Diarrhea	5 (17)	0	4 (9)	1 (2)	11 (15)	1 (1)
Nausea	3 (10)	0	1 (2)	0	8 (11)	0
Dry mouth	1 (3)	0	2 (5)	0	5 (7)	0
Decreased appetite	2 (7)	1 (3)	3 (7)	0	3 (4)	0
Laboratory treatment-related AEs (≥ 5%)[a]						
ALT increased	2 (7)	1 (3)	2 (5)	0	6 (8)	2 (3)
AST increased	2 (7)	2 (7)	1 (2)	0	5 (7)	2 (3)
Blood bilirubin increased[b]	1 (3)	0	0	0	2 (3)	0
Platelet count decreased	2 (7)	2 (7)	6 (14)	2 (5)	0	0

[a] Reported in ≥ 5% of all patients (N = 145), any grade; [b] Blood bilirubin increases were < 5% for all patients.

- Overall safety profile of nivolumab was similar to that of other tumor types with no new safety signals
- Most ALT and AST elevations were reversible with established algorithms

AE, adverse event; HBV, hepatitis B virus; HCV, hepatitis C virus.

1. Sangro B, et al. Oral presentation at EASL 2017.

CheckMate 459 (CA209-459)

Výsledek bude 2019

- CheckMate 459 Study Design[1,2]

Eligibility Criteria **N=726**

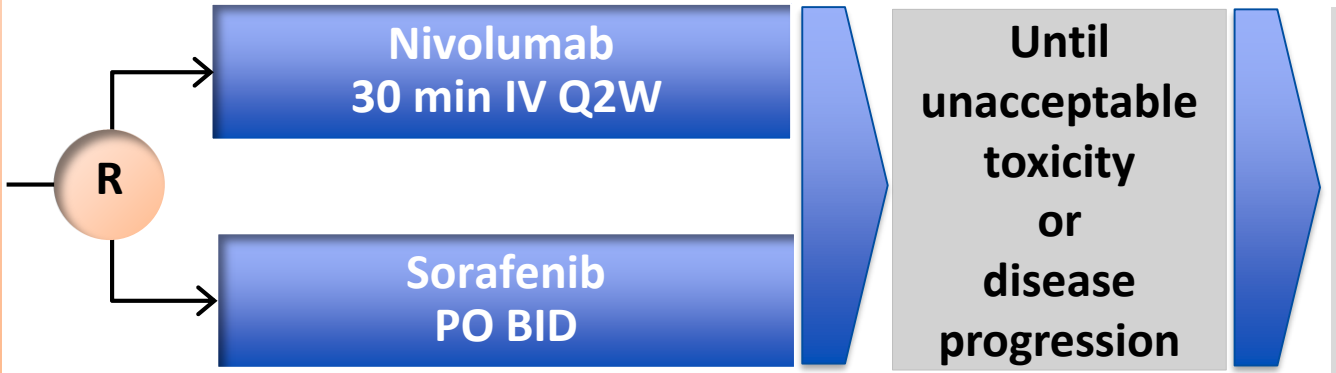
Advanced HCC

Systemic therapy naïve

Locoregional therapy for HCC completed ≥ 4 weeks prior to baseline scan

Child-Pugh Class A

ECOG PS: 0 or 1



Objectives

Primary: OS, TTP (BICR; RECIST v1.1.)

Secondary: ORR, PFS, PD-L1 expression/efficacy

Start Date: November 2015
Estimated Study Completion Date: June 2019
Estimated Primary Completion Date: July 2017
Status: Recruiting
Study Director: Bristol-Myers Squibb

- Tumor imaging assessments
- On-treatment safety assessments
- Viral biomarkers (HBV, HCV)

BICR, blinded independent central review; BID, twice daily; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; IV, intravenous; ORR, overall response rate; OS, overall survival; PD, programmed death; PFS, progression-free survival; PO, orally; PS, performance status; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

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

KEYNOTE-224: Pembrolizumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib

Abstract 209

Zhu AX, Finn RS, Cattan S, Edeline J, Ogasawara S, Palmer DH, Verslype C, Zagonel V, Rosmorduc O, Vogel A, Sarker D, Verset G, Chan SL, Knox JJ, Daniele B, Ebbinghaus S, Ma J, Siegel AB, Cheng A-L, Kudo M

Study Design

- Key eligibility criteria
  - Aged ≥18 years
  - Pathologically confirmed HCC
  - Progression on or intolerance to sorafenib treatment
  - Child-Pugh class A
  - ECOG PS 0-1
  - BCLC stage C or B disease
  - Predicted life expectancy >3 mos

→ **Pembrolizumab**
200 mg q3w
for 2 years or until PD, intolerable toxicity, withdrawal of consent or investigator decision

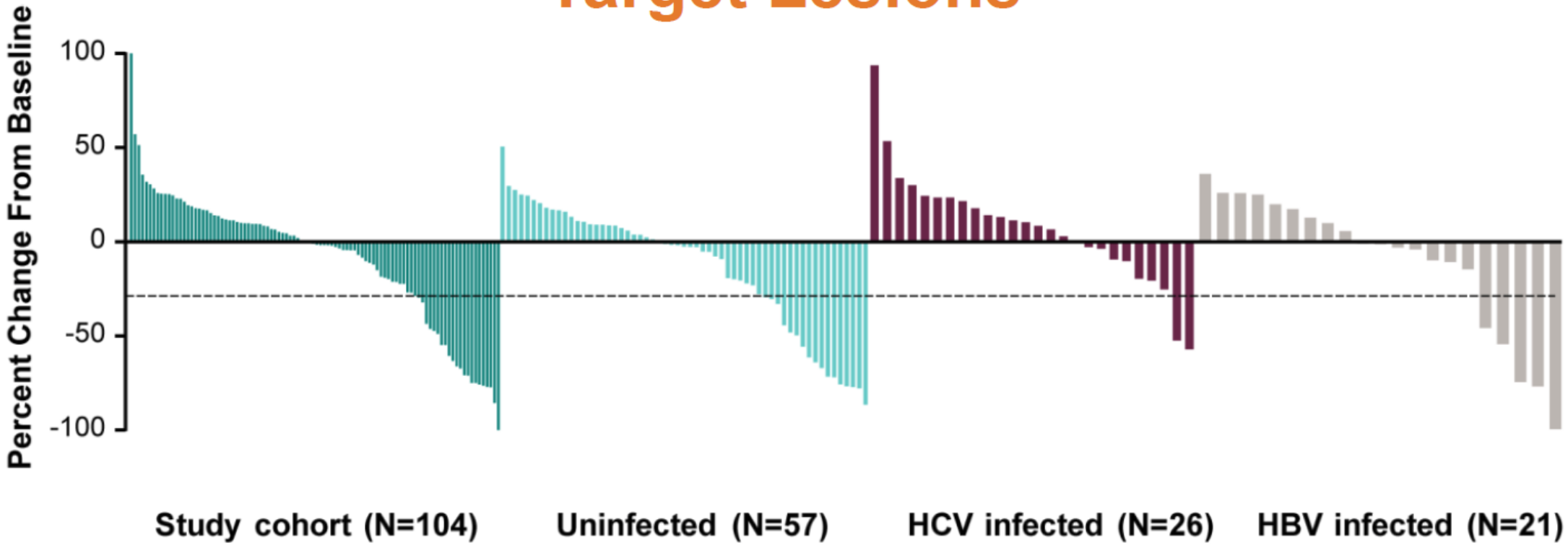
→ **Survival follow-up**

- Response assessed q9w
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability

DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer; ORR, overall response; OS, overall survival; PD, progressive disease; PFS, progression-free survival

Zhu AX, et al. *J Clin Oncol.* 2018;36(suppl 4S): Abstract 209.

Best Percentage Changes From Baseline in Target Lesions



- **Reductions from baseline in tumor target lesion size among HBV- and HCV-uninfected, and HBV- and HCV-infected patients were generally similar to those seen in the overall study cohort**

Based on RESIST v1.1 by central radiology review in patients who had both pre- and post-treatment image measurements. Dotted line is threshold for response.

Zhu AX, et al. *J Clin Oncol.* 2018;36(suppl): Abstract 4020.

Antitumor Activity

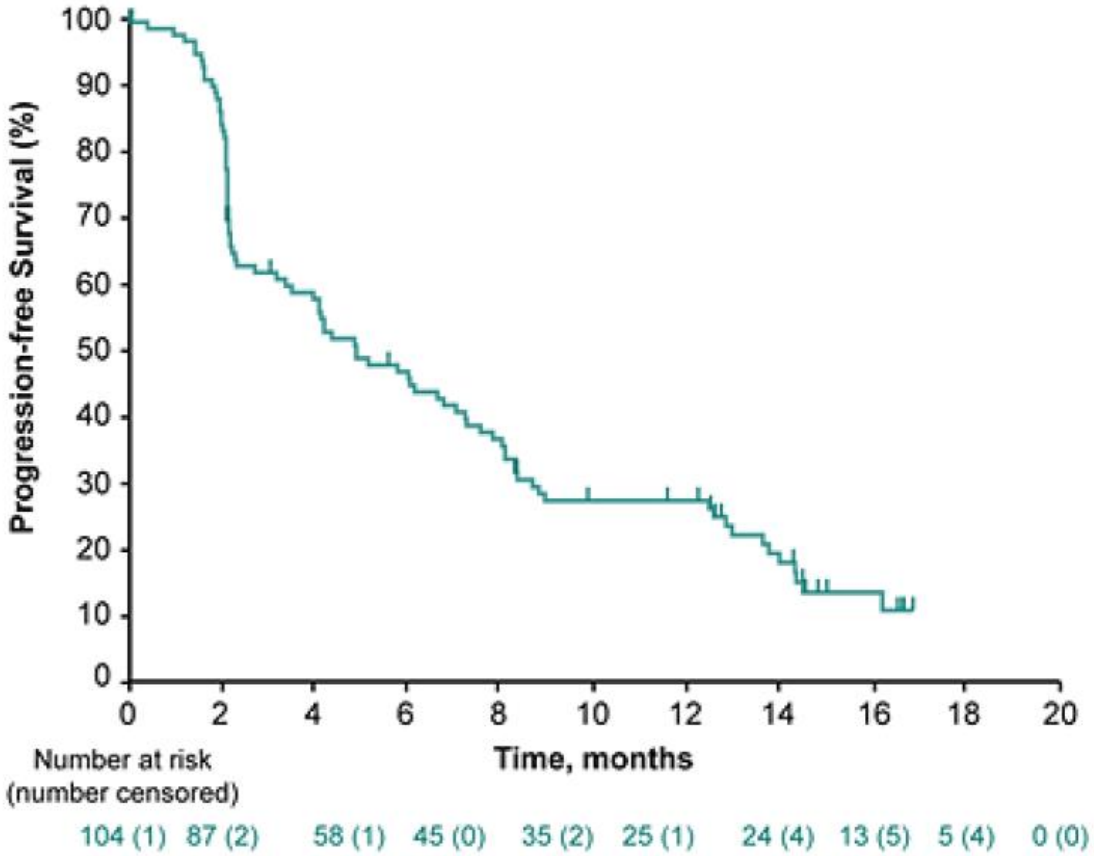
Response[a]	Total N = 104 n (%)	95% CI[b]
ORR (CR + PR)	17 (16.3)	9.8-24.9
Disease control (CR + PR + SD)	64 (61.5)	51.5-70.9
Best overall response		
CR	1 (1.0)	0.0-5.2
PR	16 (15.4)	9.1-23.8
SD	47 (45.2)	35.4-55.3
PD	34 (32.7)	23.8-42.6
No assessment[c]	6 (5.8)	2.1-12.1

[a]Confirmed best response by independent central review per RECIST v1.1. [b]Based on binomial exact confidence interval method. [c]Subjects who had a baseline assessment by investigator review or central radiology but no post-baseline assessment on the data cutoff date including discontinuing or death before the first post-baseline scan.
Data cutoff date: Aug 24, 2017.
CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease

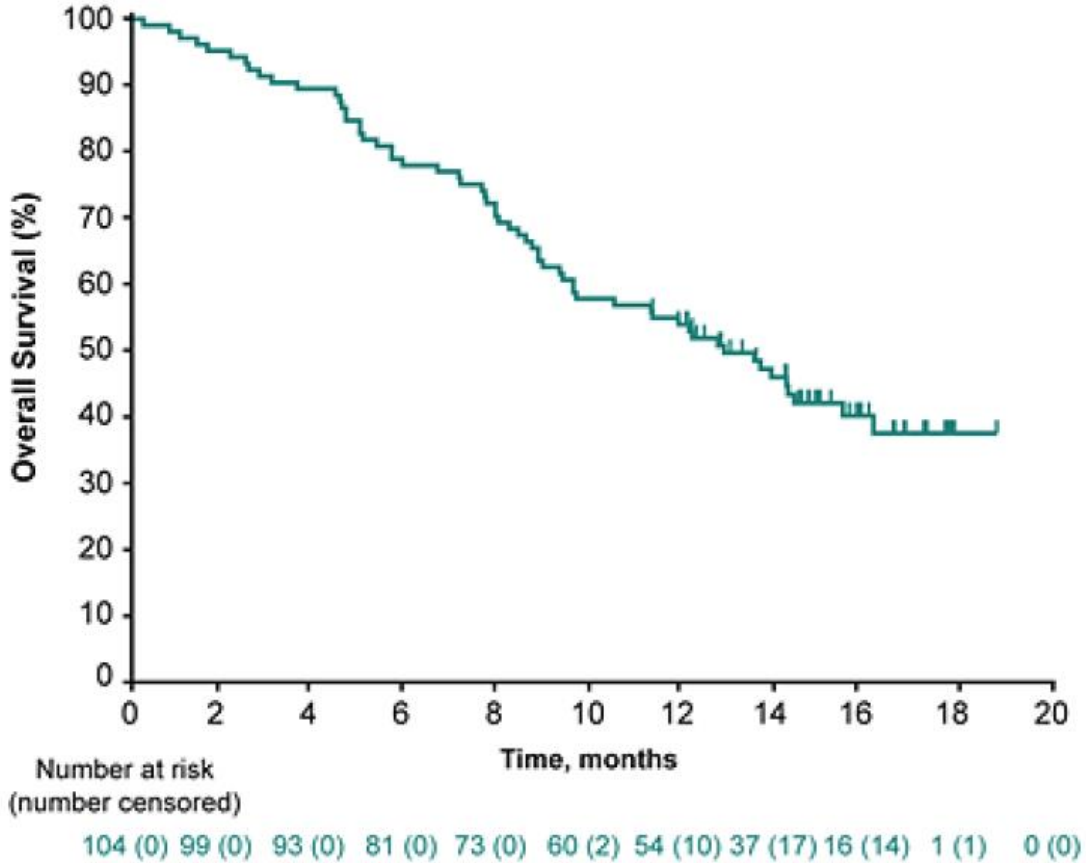
Zhu AX, et al. *J Clin Oncol.* 2018;36(suppl 4S): Abstract 209.

Progression-Free and Overall Survival

Median (95% CI) mo = 4.9 mo (95% CI 3.4-7.2)
Estimated 12-mo rate = 28%



Median (95% CI) mo = 12.9 mo (95% CI 9.7-15.5)
Estimated 12-mo rate = 54%



Estimates of PFS and OS in the all patients-as-treated population by Kaplan-Meier method. PFS was assessed per RESIST version 1.1 by central radiology review.

Zhu AX, et al. *J Clin Oncol.* 2018;36(suppl): Abstract 4020.

Treatment-Related Adverse Events

Adverse Events[a]	Total N = 104 n (%)
≥1 event	76 (73.1)
≥Grade 3	26 (25.0)
Led to discontinuation	7 (6.7)
Led to death[b]	1 (1.0)
Occurred in ≥10% of patients (all grades)	22 (21.2)
Fatigue	13 (12.5)
Aspartate aminotransferase increased	10 (9.6)
Diarrhea	10 (9.6)
Pruritus	22 (21.2)
Hepatic-related[c]	
Immune-mediated	3 (2.9)
Viral flare	0 (0)

[a]Attributed to treatment by investigator. [b]Esophagitis ulcerative. [c]Sponsor assessed.

Zhu AX, et al. *J Clin Oncol.* 2018;36(suppl 4S): Abstract 209.

Imunoterapie u HCC – otázky

- Jaká kritéria k hodnocení používat?
  - RECIST 1.1, mRECIST, iRECIST

- Kombinace imunoterapie a cílené léčby
- Imunoterapie v adjuvanci po resekci nebo ablaci HCC
- Prediktivní biomarkery? ….. Exprese PD-L1 to není….
- Posun systémové léčby k časnějším fázím onemocnění ?
- Otázka 1. linie : CHeckMate 459