Imunoterapia v manažmente hepatocelulárneho karcinómu

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Vyhlásenie o konflikte záujmov autora

☐ Nemám potenciálny konflikt záujmov

X Deklarujem nasledujúci konflikt záujmov

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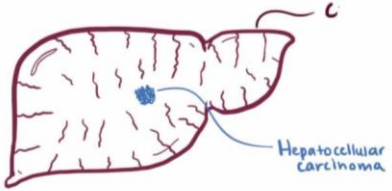
Táto prezentácia/prednáška bola podporená spoločnosťou
Roche Slovensko, s.r.o.

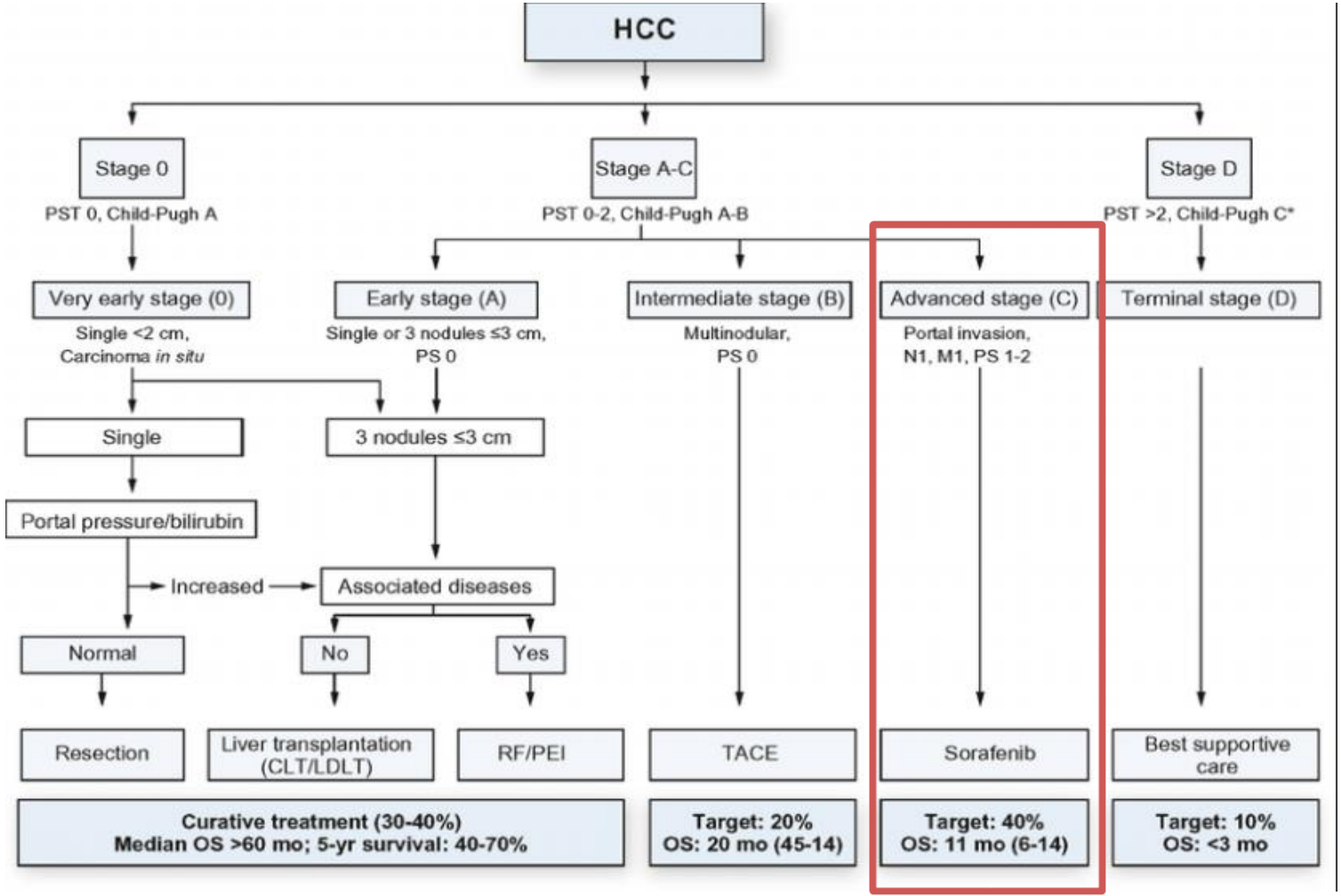
Spoločnosť Roche Slovensko, s.r.o. však nijako neovplyvňovala
obsah, rozsah a ani formulácie textu tejto prezentácie

Hepatocelulárny karcinóm



- Celosvetovo piate najčastejšie nádorové ochorenie
- Druhá najčastejšia príčina úmrtia na nádorové ochorenie
- Multidisciplinárny prístup pri liečbe skorších štádií je kľúčový
- Lokoregionálna liečba je možná u menej ako polovice pacientov pre pečeňové postihnutie na vrub cirhózy alebo pre pokročilosť ochorenia v čase diagnózy
- Viac ako 70% pacientov po úspešnej resekcii relabuje alebo sa de novo objaví choroba

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:359–86.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30.
3. Jung KW, Won YJ, Oh CM, Kong HJ, Lee DH, Lee KH, Community of Population-Based Regional Cancer Registries Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2014. Cancer Res Treat. 2017;49:292–305.
4. Nagashima I, Hamada C, Naruse K, Osada T, Nagao T, Kawano N, Muto T. Surgical resection for small hepatocellular carcinoma. Surgery. 1996;119:40–5.
5. Kumada T, Nakano S, Takeda I, Sugiyama K, Osada T, Kiriyama S, Sone Y, Toyoda H, Shimada S, Takahashi M, Sassa T. Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. Hepatology. 1997;25:87–92.



European Society for Medical Oncology Guidelines Committee. eUpdate – Hepatocellular Carcinoma Treatment Recommendations. June 2020. Available at https://www.esmo.org/guidelines/gastrointestinal-cancers/hepatocellular-carcinoma/eupdate-hepatocellular-carcinoma-treatment-recommendations3. Accessed October 2020;

Prvá línia

- 2008 – Sorafenib - perorálne podávaný multikinázový inhibítor
  - Inhibuje serín-treonín kinázy Raf-1, Raf-2, tyrozínkinázovú aktivitu VEGF receptorov 1 až 3 a receptor rastového faktora pre krvné doštičky beta
- Prvý liek, ktorý dokázal pozitívne ovplyvniť prežívanie pacientov s pokročilým HCC
- Pozitívne výsledky prežívania v štúdii fázy III – SHARP
  - Predĺžil celkové prežívanie (OS) (z 7.9 na 10.7 mesiaca, $P < 0.001$)
  - Čas do progresie (TTP) (z 2.8 na 5.5 mesiaca, $P < 0.001$)

6. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, et al. SHARP Investigators Study Group Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–90.
7. Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, Song X, Xu J, Poggi G, Omata M, Pitman Lowenthal S, Lanzalone S, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phaseIII trial. J Clin Oncol. 2013;31:4067–75.
8. Desai JR, Ochoa S, Prins PA, He AR. Systemic therapy fr advanced hepatocellular carcinoma: an update. J Gastrointest Oncol. 2017;8:243–55.

Súčasné možnosti prvolíniovej liečby

*** HIGH RISK: Pacienti s viac ako 50% postihnutím parenchýmu, inváziou do žlčovodov alebo do hlavnej portálnej žily**

	Sorafenib (SHARP)[1]	Lenvatinib (REFLECT)[2]	Atezo▼ + bev (IMbrave150)[3,4]
Mechanizmus účinku	TKI	TKI	Anti-PDL1 + anti-VEGF
NCT identifier	NCT00105443	NCT01761266	NCT03434379
1L populácia	●Pokrčilé HCC histologicky potvrdené ●≥1 merateľná lézia podľaRECIST ●Child-Pugh A ●ECOG PS 0–2	●Neresekovateľný HCC, dg. Z histológie, cytológie alebo radiologicky (AASLD kritéria) ●≥1 merateľná lézia podľaRECIST ●BCLC štádium B alebo C ●Child-Pugh A ●ECOG PS 0/1 ●**Nie sú zaradení 'high-risk' pacienti***	●Lokálne pokročilý, metastatický a/alebo neoperovateľný HCC, dg. Z histológie, cytológie alebo radiologicky (AASLD kritéria) ●Merateľné ochorenie podľa RECIST v1.1 ●Child-Pugh A ●ECOG PS 0/1 ●**Zahrnutí 'high-risk' pacienti‡**
Účinnosť	**Sorafenib arm**	**Lenvatinib arm**	**Atezo + bev arm[5]**
Medián OS, mesiace	10.7 (HR vs placebo=0.69)	13.6 (HR vs sorafenib=0.92)	19.2 (HR vs sorafenib=0.66)
Medián PFS, mesiace	4.1 (TTSP)§	7.3¶ / 7.4‖+	6.9¶
ORR, %	2§	19¶ / 24‖+	30¶ / 35‖

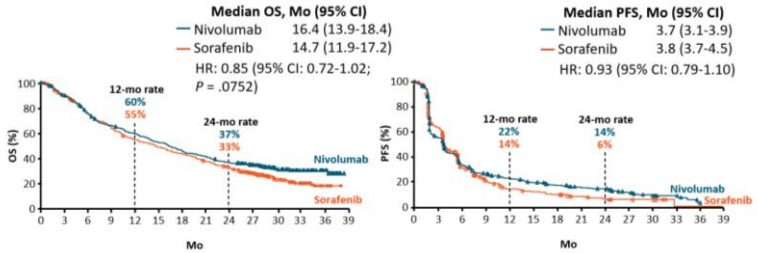
Cross-trial comparisons and conclusions should be not be made based on this side-by-side table.
***Patients with ≥50% liver occupation, obvious invasion of the bile duct, or invasion at the main portal vein**
‡Patients with MVI of the main portal trunk or the portal vein branch contralateral to the primarily involved lobe, bile duct invasion, or ≥50% hepatic involvement; §RECIST; ¶RECIST v1.1; ‖HCC mRECIST; +INV assessed
AASLD, American Association for the Study of Liver Diseases; PD-L1, programmed death ligand-1
TTSP, time to symptomatic progression; VEGF, vascular endothelial growth factor

▼ Tento liek je predmetom ďalšieho monitorovania. To umožní rýchle získanie nových informácií o bezpečnosti. Od zdravotníckych pracovníkov sa vyžaduje, aby hlásili akékoľvek podozrenia na nežiaduce reakcie na www.sukl.sk/sk/bezpecnost-liekov, neziaduce.ucinky@sukl.sk. Táto informácia môže byť tiež hlásená spoločnosti Roche na slovakia.drug_safety@roche.com alebo +421 905 400 503.

1. Llovet et al. N Engl J Med 2008; 2. Kudo et al. Lancet 2018
3. Cheng et al. ESMO Asia 2019. Abstract LBA3; 4. Finn et al. N Engl J Med 2020 5. Finn. NEJM. 2020;382:1894

Miesto imunoterapie v liečbe HCC

CheckMate 459 (Nivolumab vs Sorafenib as First-line Therapy): OS and PFS

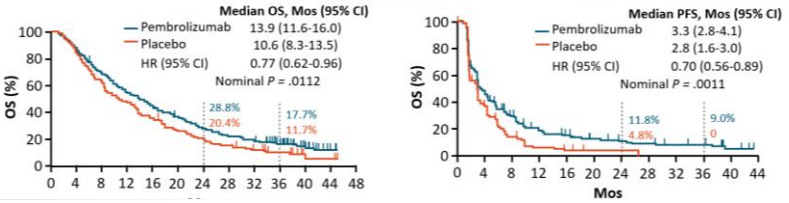


- Predefined threshold of statistical significance for OS with nivolumab not met, although nivolumab demonstrated clinical benefit
- ORR: nivolumab, 15%; sorafenib, 7%

Yau. ESMO 2019. Abstr LBA38_PR.

KEYNOTE-240: Pembrolizumab for Patients With Previously Treated HCC

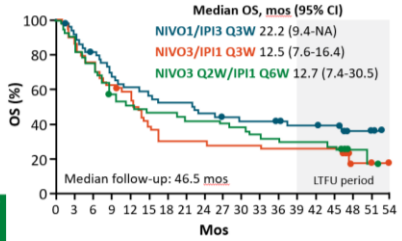
- Randomized, double-blind phase III trial of **pembrolizumab** vs **placebo** (both with BSC) for pts with advanced HCC with intolerance to or PD on or after sorafenib; Child-Pugh A (N = 413)
  - Failed to reach prespecified level of statistical significance for OS, PFS in primary analysis (prespecified *P* = .0174 [OS] and *P* = .002 [PFS] required) (median f/u 10.6-13.8 mos); updated analysis with additional 18 mos f/u



CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC

- Open-label phase I/II trial of 3 different dosing schemes of **nivolumab + ipilimumab** for patients with advanced HCC and prior sorafenib treatment; Child-Pugh score A5-A6; ECOG PS 0/1
- Dosing:
  - **NIVO1/IPI3 Q3W**: nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (4 doses)
  - **NIVO3/IPI1 Q3W**: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses), each followed by nivolumab 240 mg Q2W
  - **NIVO3 Q2W/IPI1 Q6W**: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W

	NIVO1/IPI3 Q3W (n = 50)	NIVO3/IPI1 Q3W (n = 49)	NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR, % (95% CI)	32 (20-47)	31 (18-45)	31 (18-45)



- Nivo + ipi approved for patients with HCC who have been previously treated with sorafenib

Yau. JAMA Oncol. 2020;6:e204564. El-Khoueiry. ASCO GI 2021. Abstr 269.

Slide credit: clinicaloptions.com

:C who have been previously treated with sorafenib

Slide credit: clinicaloptions.com

IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib v prvej línii liečby HCC

- Multicenter, randomized, open-label phase III trial[1]
  - GO30140: randomized phase Ib study showed potential benefit of atezolizumab + bevacizumab for patients with advanced HCC (ORR 36%)[2]

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
(n = 336)

Sorafenib 400 mg BD
(n = 165)

Treatment until PD or intolerable toxicity

- Coprimary endpoints: OS and PFS

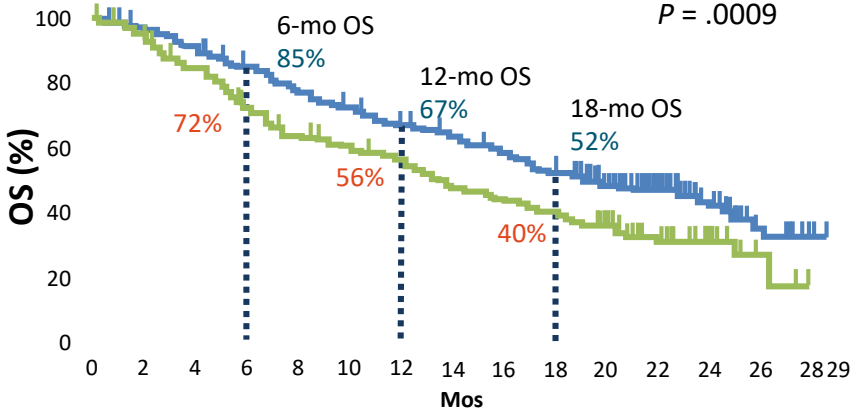
*Trial included subgroups of high-risk patients excluded from other contemporary phase III trials: ~ 40% had macrovascular invasion; specifically included patients with 50% hepatic involvement or main portal vein invasion or invasion of the portal vein branch contralateral to the primarily involved lobe.

1. Finn. NEJM. 2020;382:1894. 2. Lee. Lancet Oncol. 2020;21:808.

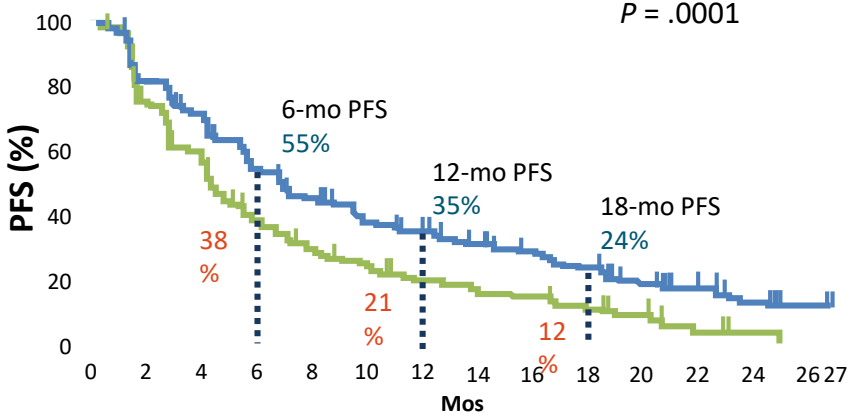
IMbrave150: Aktualizované OS a PFS

- Primary analysis OS/PFS HR: 0.58/0.59 (median f/u 8.6 mos)

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median OS, mos (95% CI)	**19.2** (17.0-23.7)	**13.4** (11.4-16.9)
Stratified HR (95% CI)	0.66 (0.52-0.85)	
	P = .0009	



	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median PFS, mos (95% CI)	**6.9** (5.7-8.6)	**4.3** (4.0-5.6)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
	P = .0001	



Median follow-up: 15.6 mos.

Finn. NEJM. 2020;382:1894. Finn. ASCO GI 2021. Abstr 267.

Slide credit: clinicaloptions.com

IMbrave150: Aktualizovaná odpoveď

	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR,% (95% CI)	**30 (32-35)**	**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, mos (95% CI)	**18.1 (14.6-NE)**	**14.9 (4.9-17.0)**	**16.3 (13.1-21.4)**	**12.6 (6.1-17.7)**

Finn. NEJM. 2020;382:1894. Finn. ASCO GI 2021. Abstr 267.

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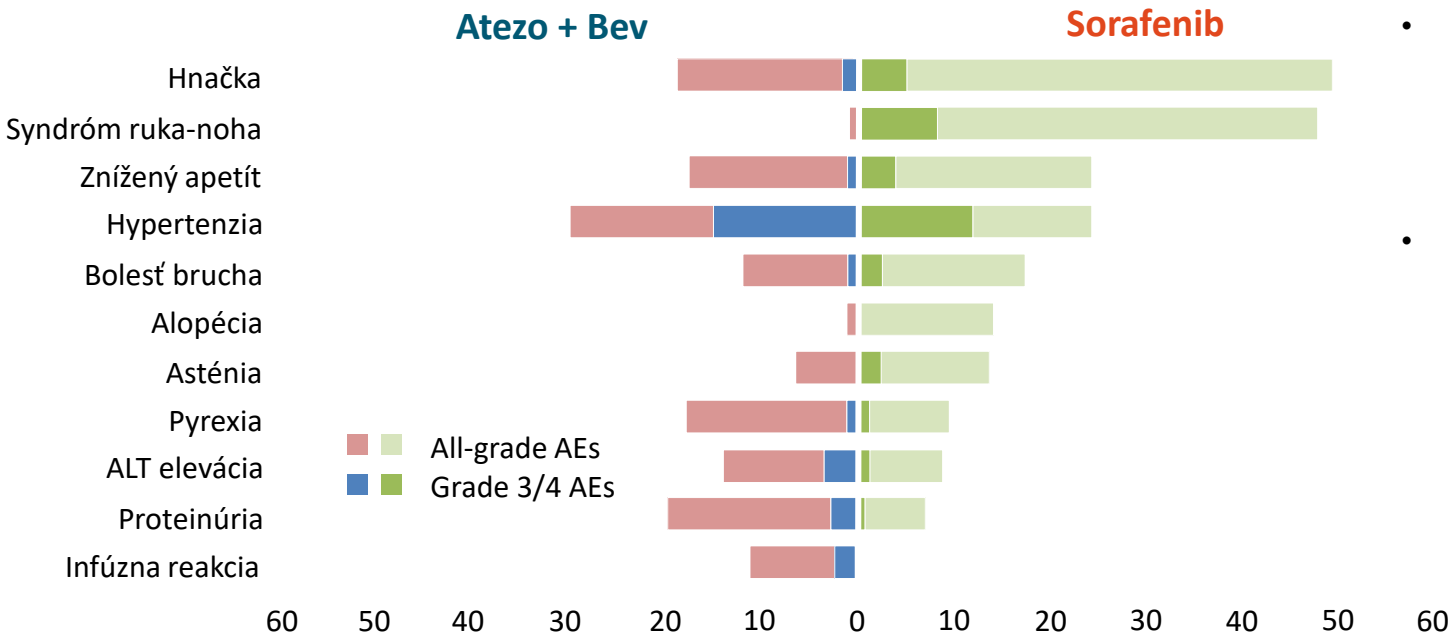
IMbrave150: Bezpečnosť



- EGD within 6 mos of initiating treatment required to evaluate for varices; varices of any size according to local standards of care
- Upper GI bleeding rate in atezo + bev vs sorafenib groups: 7% vs 4.5%; this was consistent with historical data in other studies of bevacizumab in HCC

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

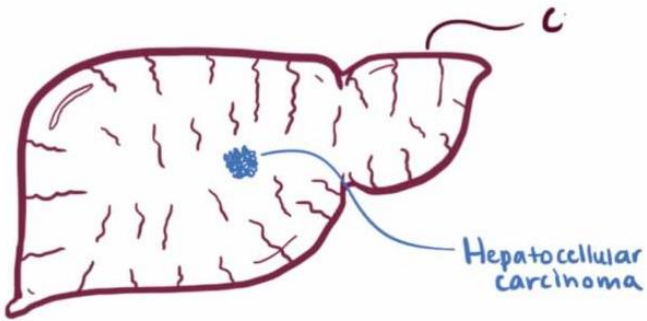
- Patient-reported QoL also improved with atezo + bev vs sorafenib (median TTD: 11.2 vs 3.6 mos)

Cheng. ESMO Asia 2019. Abstr LBA3. Finn. NEJM. 2020;382:1894.

Slide credit: clinicaloptions.com

Na čo si treba dávať pozor pri tejto kombinácii?

- **Atezolizumab[1]**
  - History of organ transplant
  - History of autoimmune disease
  - Immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies

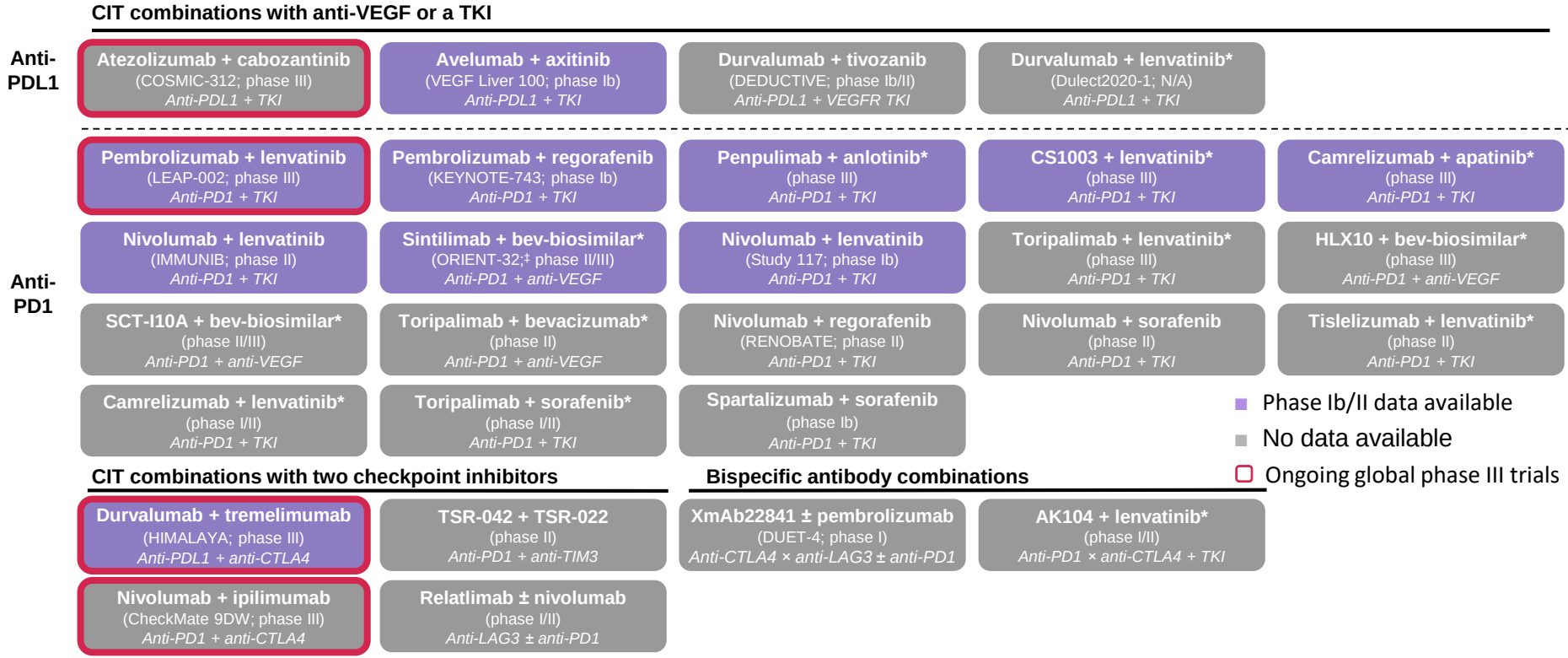


- **Bevacizumab[2]**
  - GI perforations
  - Surgery in last 28 days; incompletely healed wound
  - Recent hemoptysis or major bleed (variceal bleeding)
  - Fistula
  - Uncontrolled hypertension
  - > 2 g proteinuria
  - Congestive heart failure

1. SPC Atezolizumab 2. SPC Bevacizumab

Slide credit: clinicaloptions.com

1L kombinačná liečba s imunoterapiouv rámci klinických skúšaní



*China only; ‡Met primary endpoints (OS and PFS) at interim analysis
CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LAG3, lymphocyte activation gene-3; PD-1, programmed cell death protein 1
TIM3, T-cell immunoglobulin and mucin-domain containing gene-3; VEGFR, vascular endothelial growth factor receptor

Source: ClinicalTrials.gov (13 November 2020)

Prehľad hlavných štúdií fázy Ib/II: účinnosť a bezpečnosť

	KEYNOTE-524 (phase Ib)[1,2]	Tremelimumab/durvalumab (phase II)[3]			CheckMate-040 (phase I/II)[4]		
	Lenvatinib + pembrolizumab (N=100)	T300 + D (n=75)	D (n=104)	T75 + D (n=84)	Nivo + cabo[4] (n=36)	Nivo + cabo[4] + ipi (n=35)	Nivo + ipi** (2L only)[5] (n=49)
Median OS, (95% CI) months	**22.0** (20.4–NE)	**18.7** (10.8–27.3)	**13.6** (8.7–17.6)	**11.3** (8.4–15.0)	**21.5** (13.1–NE)	**NE** (15.1–NE)	**22.8** (9.4–NE)
Median PFS, (95% CI) months	**8.6** (7.1–9.7)*	**2.2** (1.9–5.4)	**2.1** (1.8–2.8)	**1.9** (1.8–2.4)	**5.4** (3.2–10.9)	**6.8** (4.0–14.3)	**NA**
ORR,* %	36‡§	24‖	11‖	10‖	19+	29+	32‖
All-grade TRAEs, %	95	82	60	70	89	94	94
Grade 3/4 TRAEs, %	64	35	18	23	47	71	53
TRAEs leading to treatment discontinuation, %	6¶	11	8	6	NA	NA	22‡‡

Cross-trial comparisons and conclusions should be not be made based on this side-by-side table.
*RECIST v1.1; ‡IIR assessed; §Confirmed ORR; ¶Withdrawal from both components; ‖BICR assessed
+INV assessed; **Approved dose for patients with prior sorafenib treatment: nivo 1mg/kg + ipi 3mg/kg q3w (4 doses), then nivo 240mg q2w (data shown) or 480mg q4w (data not available);[6,7] ‡‡Discontinuation due to study drug toxicity. BICR, blinded independent central review; IIR, independent imaging review; NA, not available

1. Finn et al. J Clin Oncol 2020; 2. Zhu et al. ASCO 2020. Abstract 4519
3. Kelley et al. ASCO 2020. Abstract 4508; 4. Yau et al. ASCO GI 2020. Abstract 478
5. Yau et al. ASCO 2019. Abstract 4012; 6. SPC Opdivo
7. SPC Yervoy

Prebiehajúce štúdie fázy III

	LEAP-002: Lenvatinib + pembrolizumab	HIMALAYA Durvalumab ± tremelimumab	CheckMate-9DW: Nivolumab + ipilimumab	COSMIC-312 Cabozantinib + atezo	IMbrave150 Atezo + bev
Mechanism of action	TKI + anti-PD1	Anti-PDL1 + anti-CTLA4	Anti-PD1 + anti-CTLA4	TKI + anti-PDL1	Anti-PDL1 + anti-VEGF
NCT identifier	NCT03713593	NCT03298451	NCT04039607	NCT03755791	NCT03434379
Patient population	1L advanced HCC Child-Pugh class A	1L advanced HCC Child-Pugh class A Excludes patients with main portal vein tumour thrombosis	1L advanced HCC Child-Pugh class A	1L advanced HCC Child-Pugh class A	1L locally advanced or metastatic and/or unresectable HCC Child-Pugh class A 'High-risk' patients included§
Primary endpoints	PFS* OS	OS	OS	PFS* OS	OS PFS*
Data availability	Phase Ib data available[1,2] NCT03006926	Phase II data available[3] NCT02519348	Phase II data available[4‡] NCT01658878	No early phase data available	Phase III data available;[5,6] Phase I data available[7] NCT02715531

*Per RECIST v1.1; ‡Phase II trial of nivolumab + cabozantinib ± ipilimumab. This is different to the Phase III combination; §Patients with MVI of the main portal trunk or the portal vein branch contralateral to the primarily involved lobe, bile duct invasion, or ≥50% hepatic involvement

1. Finn et al. J Clin Oncol 2020; 2. Zhu et al. ASCO 2020. Abstract 4519
3. Kelley et al. ASCO 2020. Abstract 4508; 4. Yau et al. ASCO GI 2020. Abstract 478
5. Cheng et al. ESMO Asia 2019. Abstract LBA3; 6. Finn et al. N Engl J Med 2020
7. Lee et al. Lancet Oncol 2020

NCCN odporúčania 1.2021

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Hepatocellular Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

First-Line Systemic Therapy

Preferred Regimens

- Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)[a,b,c,1]

Other Recommended Regimens

- Sorafenib (Child-Pugh Class A [category 1] or B7)[d,e,2,3]
- Lenvatinib (Child-Pugh Class A only)[4,5] (category 1)

Useful in Certain Circumstances

- Nivolumab[b,6] (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B)
- FOLFOX (category 2B)[f]

Subsequent-Line Therapy[g] if Disease Progression[h]

Options

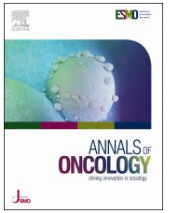
- Regorafenib (Child-Pugh Class A only) (category 1)[i,7]
- Cabozantinib (Child-Pugh Class A only) (category 1)[i,8]
- Ramucirumab (AFP ≥400 ng/mL only) (category 1)[i,9]
- Lenvatinib (Child-Pugh Class A only)
- Sorafenib (Child-Pugh Class A or B7)[d,e]

Other Recommended Regimens

- Nivolumab (Child-Pugh Class A or B)[b,j,10-12]
- Nivolumab + ipilimumab (Child-Pugh Class A only)[b,i,13]
- Pembrolizumab (Child-Pugh Class A only)[b,j,k,14] (category 2B)

https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

ESMO odporúčania – update 2021



- **Atezolizumab plus bevacizumab**, which showed superior efficacy compared with sorafenib, is recommended as standard of care in first-line therapy of patients with advanced HCC and received European Medicines Agency (EMA) approval in late 2020 [ESMO-MCBS v1.1 score 5].

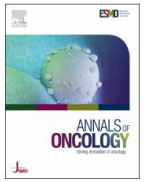
- Immunotherapy in the form of monotherapy has been evaluated in patients in two phase III studies.

  The first-line phase III CheckMate 459 trial, comparing sorafenib with nivolumab as a first-line treatment option, **failed** to meet the primary endpoint of overall survival (OS).

  The second-line phase III KEYNOTE-240 trial of pembrolizumab versus placebo also **failed** to meet its co-primary endpoints of OS and PFS [10]. Neither drug has received EMA approval and they are not recommended as monotherapy for the treatment of advanced HCC.

Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines
Published: 05 March 2021. Authors: ESMO Guidelines Committee

Journal Pre-proof



Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines

A. Vogel, E. Martinelli, on behalf of the ESMO Guidelines Committee

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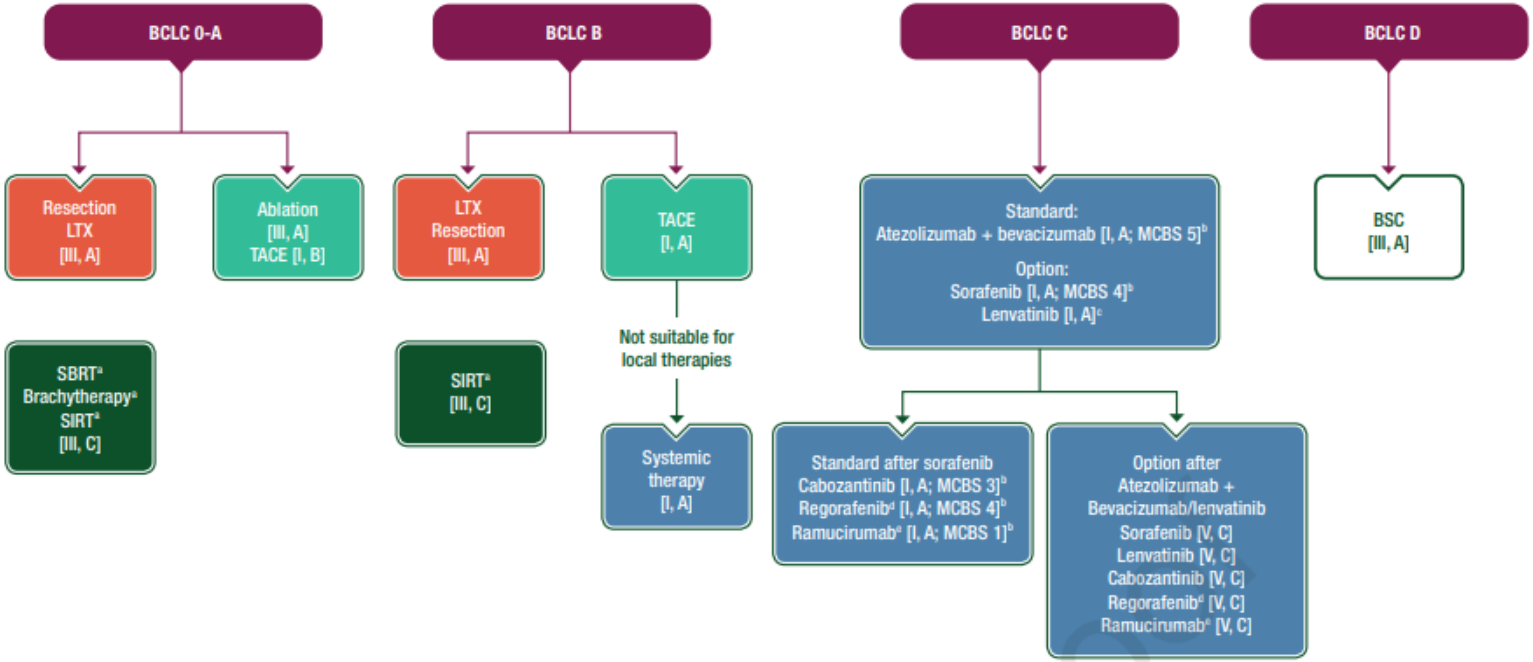

Ďakujem za pozornosť

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