COR2ED

THE HEART OF MEDICAL EDUCATION

HCC CONNECT
VIRTUAL EXPERTS KNOWLEDGE SHARE

TREATMENT OPTIONS FOR HCC PATIENTS WHO ARE NOT ELIGIBLE FOR OR PROGRESSED ON IO: *CLINICAL CONSIDERATIONS AND WHEN TO SWITCH*

Tuesday 23rd May 2023

TODAY YOU WILL

EXPLORE the outcomes of patients with HCC receiving IO 1st line and determine the right time to switch to 2nd line

KNOW the treatment options for patients with advanced HCC not eligible for IO in 1st line

UNDERSTAND the data supporting 2nd line treatment options for patients with advanced HCC, to enable optimal sequencing

IO, immunotherapy; HCC, hepatocellular carcinoma

AGENDA

TREATMENT OPTIONS FOR HCC PATIENTS WHO ARE NOT ELIGIBLE FOR OR PROGRESSED ON IO: CLINICAL CONSIDERATIONS AND WHEN TO SWITCH

Topic	Facilitator	Duration
Welcome and Introductions	COR2ED/ Prof. Michel Ducreux	5 mins
Reviewing the outcomes in HCC with 1st line IO: when is the right time to switch?	Dr Timon Vandamme	15 mins
Q&A	All	5 mins
What are the treatment options for patients with advanced HCC not eligible for IO in 1st line?	Prof. Michel Ducreux	15 mins
Q&A	All	5 mins
Overview of 2nd line treatment options in advanced HCC: How to achieve optimal sequencing?	Assoc. Prof. Changhoon Yoo	15 mins
Q&A	All	5 mins
Discussion and Q&A	All	15 mins
Future perspectives and summary	Prof. Michel Ducreux	5 mins
Closing remarks	COR2ED	5 mins

HCC, hepatocellular carcinoma; IO, immunotherapy

DEVELOPED BY HCC CONNECT

This programme is developed by HCC CONNECT, an international group of experts in the field of hepatocellular carcinoma.

HCC connect®
POWERED BY COR2ED

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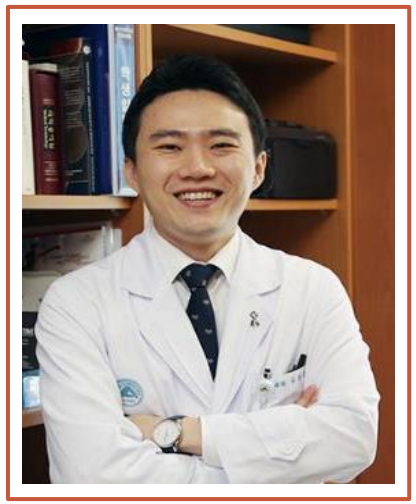
Expert Disclaimers:

- **Prof. Ducreux** has received financial support/sponsorship from Roche, Servier, Pierre Fabre, Amgen, Daiichi Sankyo, MSD, Bayer, Merck Serono, AstraZeneca for advisory boards and from Roche, MSD, BeiGene, Bayer, Merck Serono, Pierre Fabre, Servier for symposium participation
- **Dr Vandamme** has received financial support for consultation from Omnigen BV, Roche, Ipsen, Eisai, ElmediX BV, Bayer and institutional grants from Ipsen and Novartis
- **Assoc. Prof. Yoo** has received financial support/sponsorship from Servier, Bayer, AstraZeneca, MSD, Eisai, Celgene, Bristol Myers Squibb, Debiopharm, Ipsen, Kyowa Kirin, Novartis, Boryung Pharmaceuticals, Merck Serono, Mundipharma, Roche and Janssen

INTRODUCING THE SCIENTIFIC COMMITTEE

Prof. Michel Ducreux
Head of GI Oncology Unit, Department of Medical Oncology, Gustave Roussy France

Dr Timon Vandamme
Medical Oncologist, Digestive and Neuroendocrine Oncology at the University Hospital Antwerp, Belgium



Assoc. Prof. Changhoon Yoo
Medical Oncologist, Department of Oncology, ASAN Medical Center, Seoul, South Korea

KEY CLINICAL TAKEAWAYS

- A substantial part of the advanced HCC patient population **is not eligible for IO 1st line**, such as:
  - Post-liver transplant patients with recurrent HCC
  - Most patients with an active autoimmune disease
- **TKIs**, such as lenvatinib and sorafenib, **are recommended treatments** for these patient groups

- **Switching to 2nd line** after IO 1st line should be considered in case of **toxicity** or **disease progression**
  - Measuring disease progression can be challenging, as there are several methods with different evaluation criteria
  - mRECIST criteria have a powerful ability to discriminate between responders and non-responders

- **Multiple 2nd line treatment** options have been approved in advanced HCC patients
  - There is **lack of solid evidence** for optimal 2nd line regimens after progression on new standard 1st line IO-based combination therapy

HCC, hepatocellular carcinoma; IO, immunotherapy; mRECIST, modified Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor

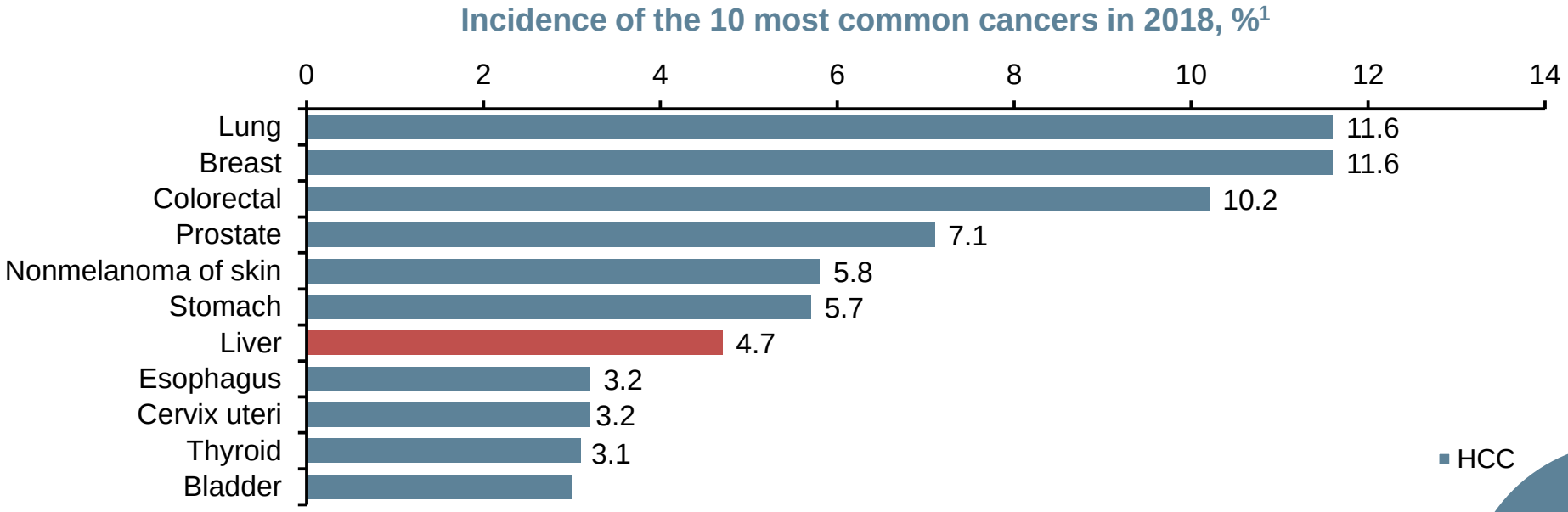
REVIEWING THE OUTCOMES IN HCC WITH 1ST LINE IMMUNOTHERAPY:

WHEN IS THE RIGHT TIME TO SWITCH?

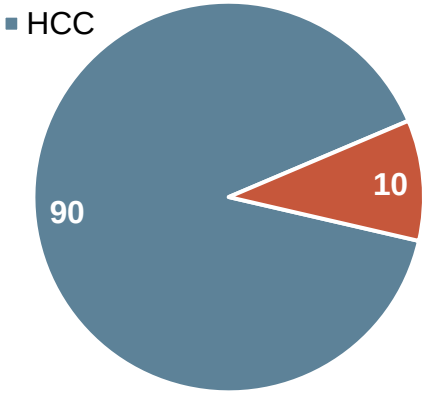
Dr Timon Vandamme

LIVER CANCER IS THE SIXTH MOST COMMON CANCER WORLDWIDE

IT REPRESENTED 4.7% OF ALL 18.1 MILLION NEW CANCER CASES IN 2018[1]



HCC is responsible for 90% of all liver cancers[2]



HCC, hepatocellular carcinoma

1. Bray F, et al. CA Cancer J Clin. 2018;68:394-424; 2. Llovet JM, et al. Nat Rev Dis Primers. 2016;2:16018

WORLDWIDE INCIDENCE OF LIVER CANCER[1]

HIGHEST INCIDENCE IN LOW- AND MIDDLE-INCOME COUNTRIES

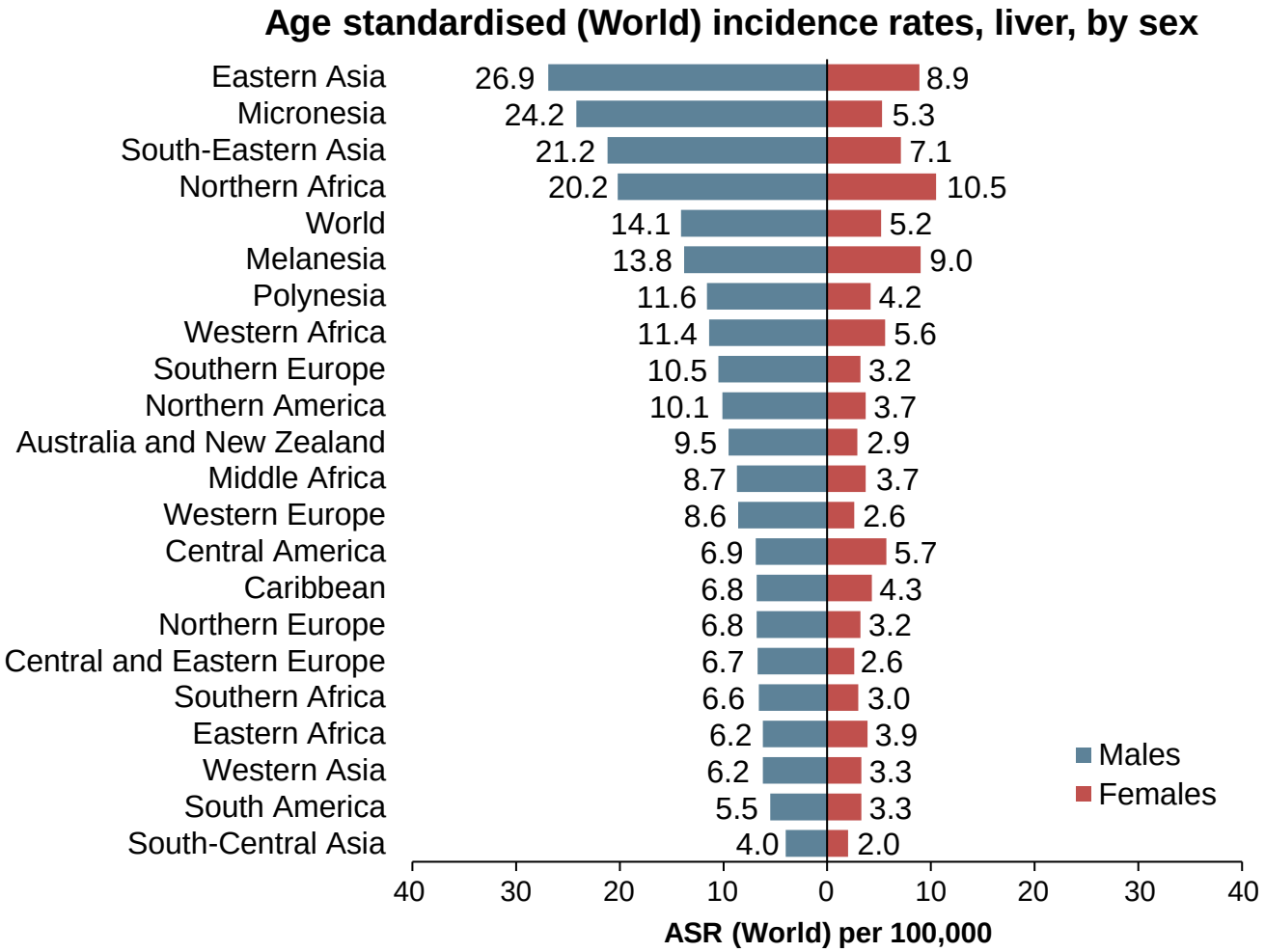


Figure adapted from WHO, Globocan 2020[1]

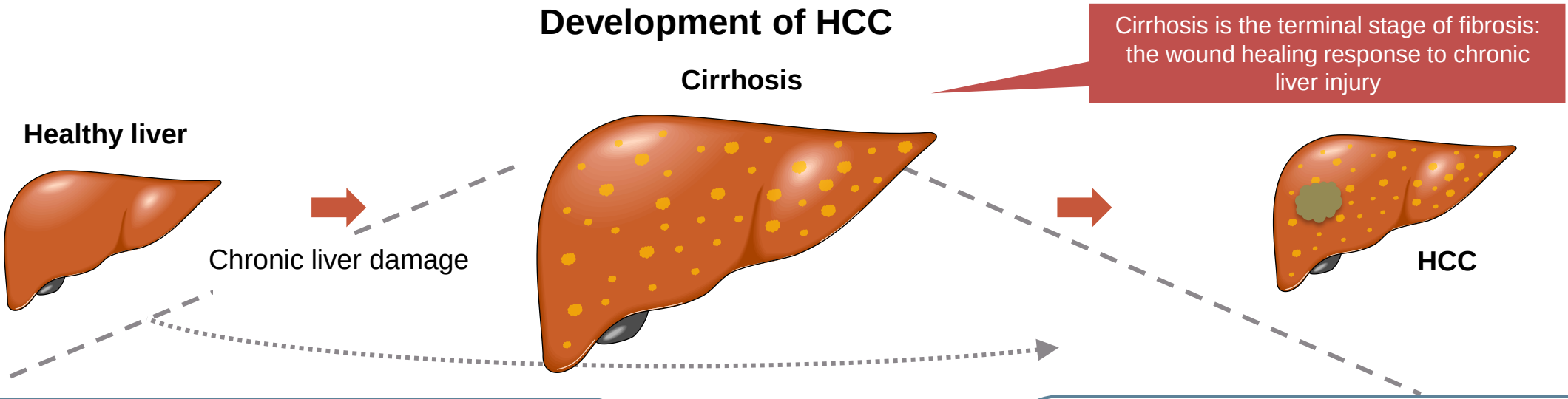
- 75% of the patients are from **low- and middle-income countries**
- **Liver cancer** is the 5th and 9th most common cancer in men and women, respectively
  - **Men have a 3-fold higher risk** of developing liver cancer than women

ASR, age standardised rate

1. WHO, Globocan 2020, online: https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf accessed April 2023; 2. Bray F, et al. CA Cancer J Clin. 2018;68:394-424

CIRRHOSIS IS A PREDISPOSING FACTOR FOR HCC

~85% OF HCC IS CAUSED BY CIRRHOSIS[1]



- Cirrhosis is a consequence of chronic liver inflammation, followed by diffuse hepatic fibrosis[2]
  - Normal hepatic architecture is replaced by regenerative hepatic nodules, leading to liver failure

- The estimated incidence of cirrhosis per 100,000 people ranges from 8.50 in Oceania, 24.45 in Western Europe, to 59.06 in Central Asia 2019[3]
- Liver cirrhosis contributed to nearly 1.5 million (1.4-1.6) deaths in 2019[3]
- Risk factors for cirrhosis include heavy alcohol consumption – 15-20% of heavy alcohol drinkers will develop cirrhosis[4]

HCC, hepatocellular carcinoma

1. Asafo-Agyei KO, Samant H. Hepatocellular Carcinoma. 2023 Feb 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 32644603; 2. Ginès P, et al. Lancet. 2021;398(10308):1359-76; 3. Lan Y, et al. Hepatol Commun. 2023;7(2):e0026.

4. Åberg F, et al. Hepatology. 67(6):2141-9;

POLLING QUESTION

WHAT ARE RECOMMENDED TREATMENT OPTIONS FOR ADVANCED HCC PATIENTS 1ST LINE BY BCLC GUIDELINES?

A. Sorafenib and lenvatinib

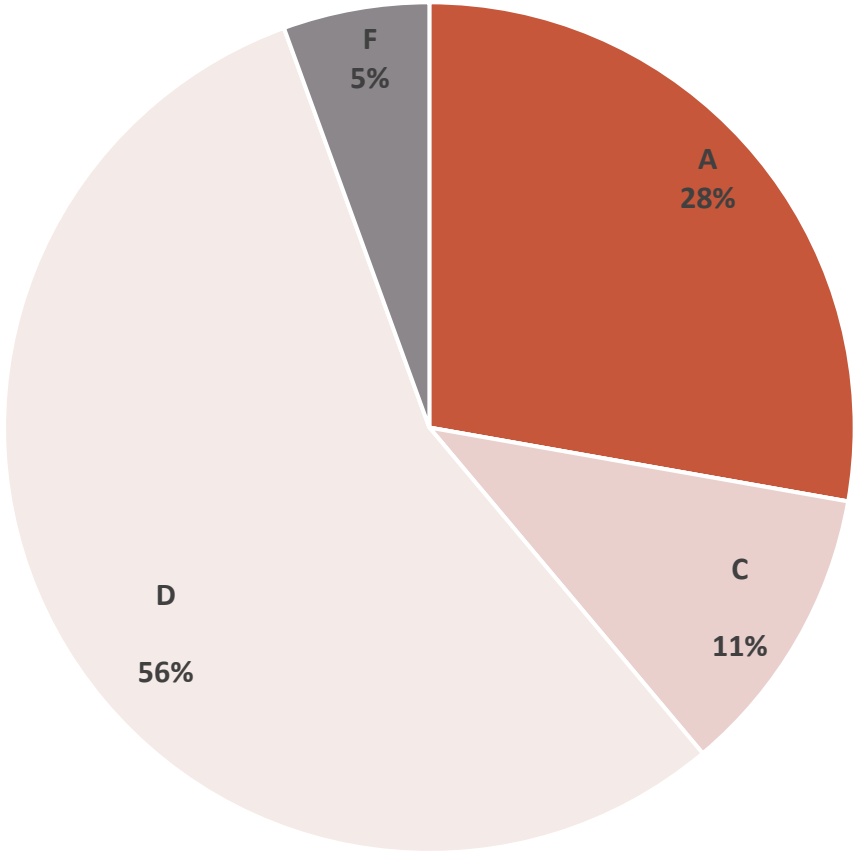
B. Sorafenib, lenvatinib and durvalumab

C. Atezolizumab + bevacizumab, or durvalumab + tremelimumab

D. Atezolizumab + bevacizumab, or durvalumab + tremelimumab, if not feasible sorafenib, lenvatinib and durvalumab ☑

E. All of the above without specific order

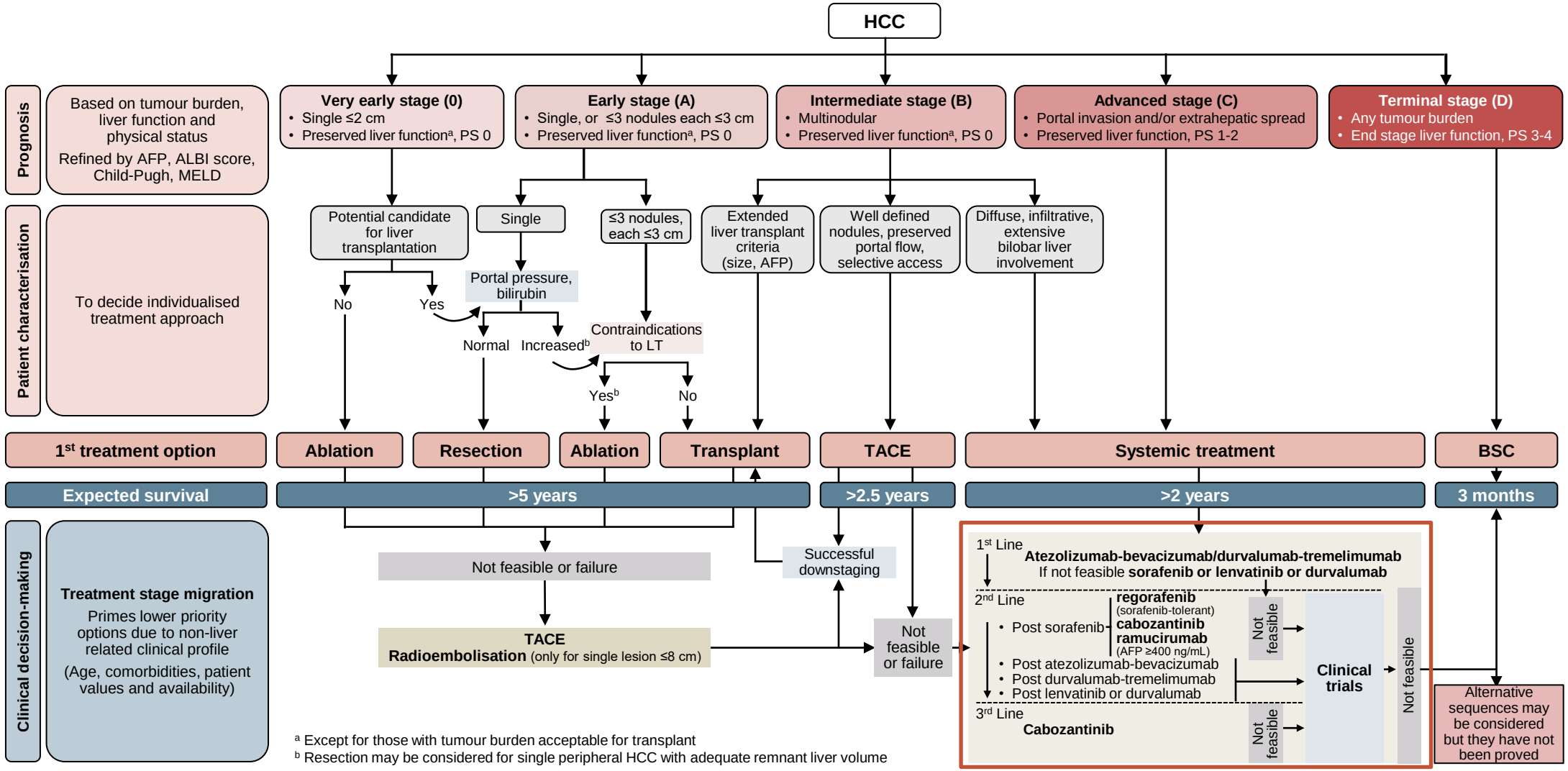
F. I am not sure



BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma

BCLC UPDATED TREATMENT ALGORITHM

MULTIDISCIPLINARY CARE FOR PATIENTS WITH HEPATOBILIARY CANCER



AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model of end-stage liver disease; PS, performance status; TACE, transarterial chemoembolisation

Reig M, et al. J Hepatol. 2022;76:681-93

BCLC UPDATED TREATMENT ALGORITHM

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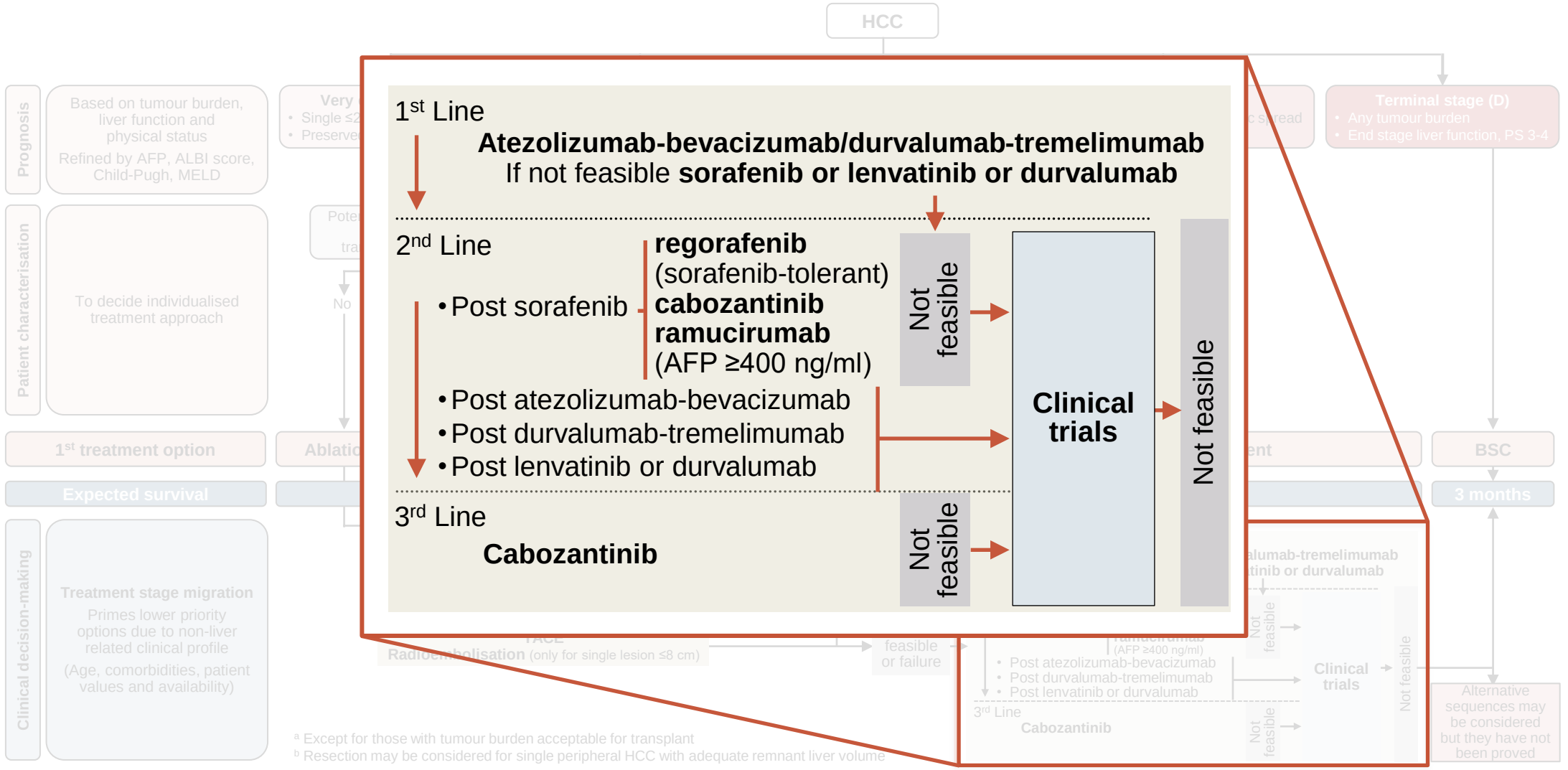

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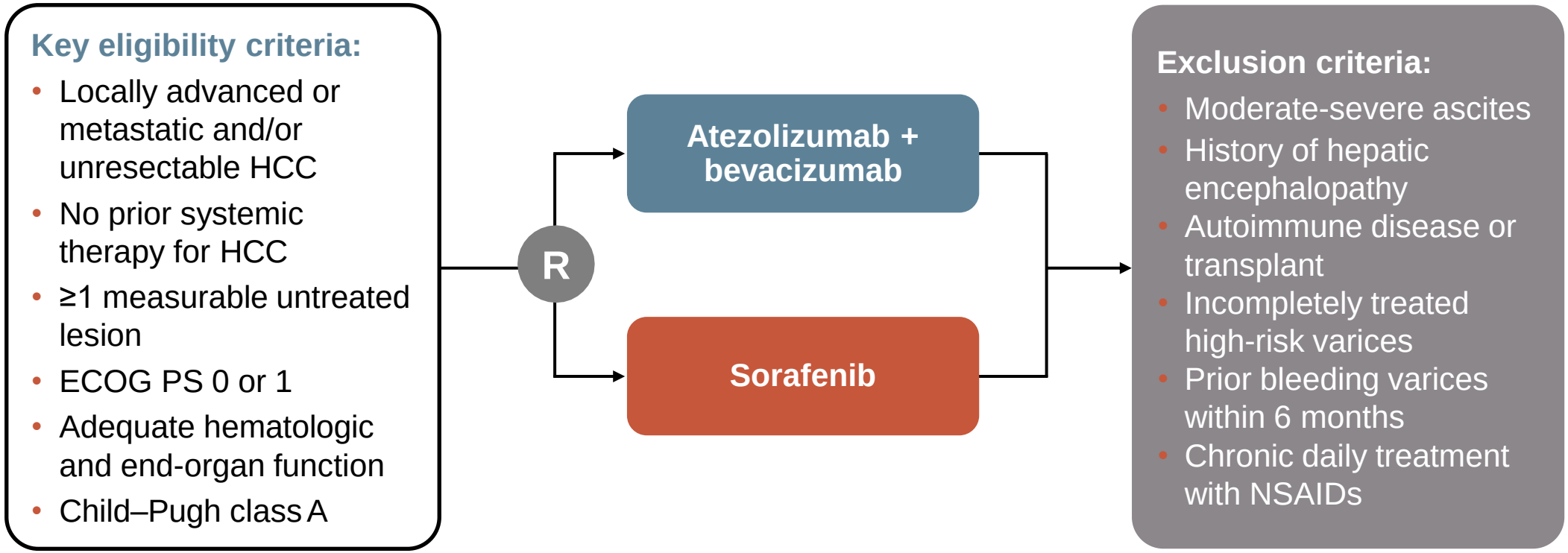
Reig M, et al. J Hepatol. 2022;76:681-93

ATEZOLIZUMAB + BEVACIZUMAB COMBINATION

ANTI-PD-L1 + VEGFi: IMbrave150

Study design



Primary endpoints: overall survival and progression free survival

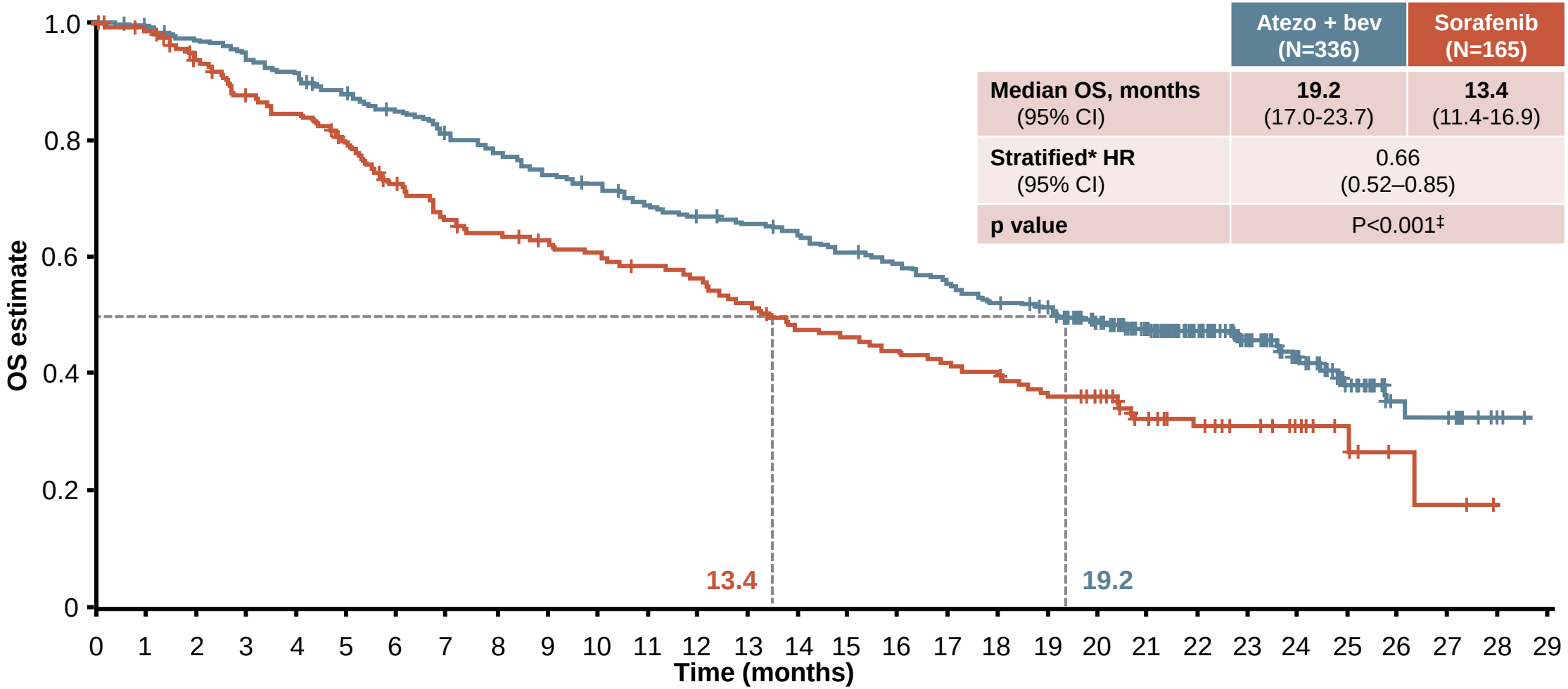
ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; NSAID, nonsteroidal anti-inflammatory drug; PD-L1, programmed death-ligand 1; VEGFi, vascular endothelial growth factor inhibitor

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905. Finn RS, et al. J Clin Oncol. 2021;39(3_suppl):267-267. Source: https://clinicaltrials.gov/ct2/show/NCT03434379

ATEZOLIZUMAB + BEVACIZUMAB COMBINATION

MEDIAN OS WAS 5.8 MONTHS LONGER THAN SORAFENIB[1]

Updated analysis 12 months after the primary analysis of IMbrave150



	Atezo + bev (N=336)	Sorafenib (N=165)
Median OS, months (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 value	P<0.001‡	

*Stratification factors included are geographic region (Asia excluding Japan vs RoW), AFP level (<400ng/mL vs ≥400ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS
‡p value for descriptive purposes only

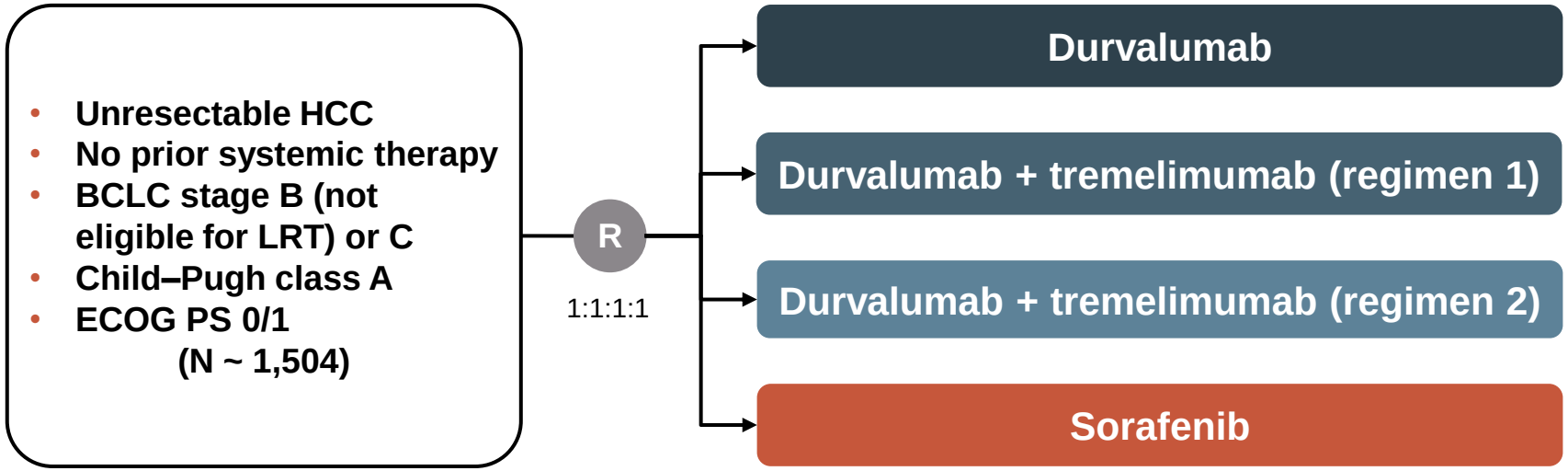
AFP, alpha fetoprotein; atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; EHS, extrahepatic spread; HR, hazard ratio; IxRS, interactive voice/web response system; MVI, microvascular invasion; OS, overall survival; RoW, rest of world

1. Cheng A-L, et al. J Hepatology. 2022;76(4):862-73

DURVALUMAB + TREMELIMUMAB COMBINATION

ANTI-PD-L1 + ANTI-CTLA4: HIMALAYA

Study design



- **Primary endpoint:** OS
- **Key secondary endpoints:** TTP, PFS, ORR, DCR, DoR, safety and tolerability

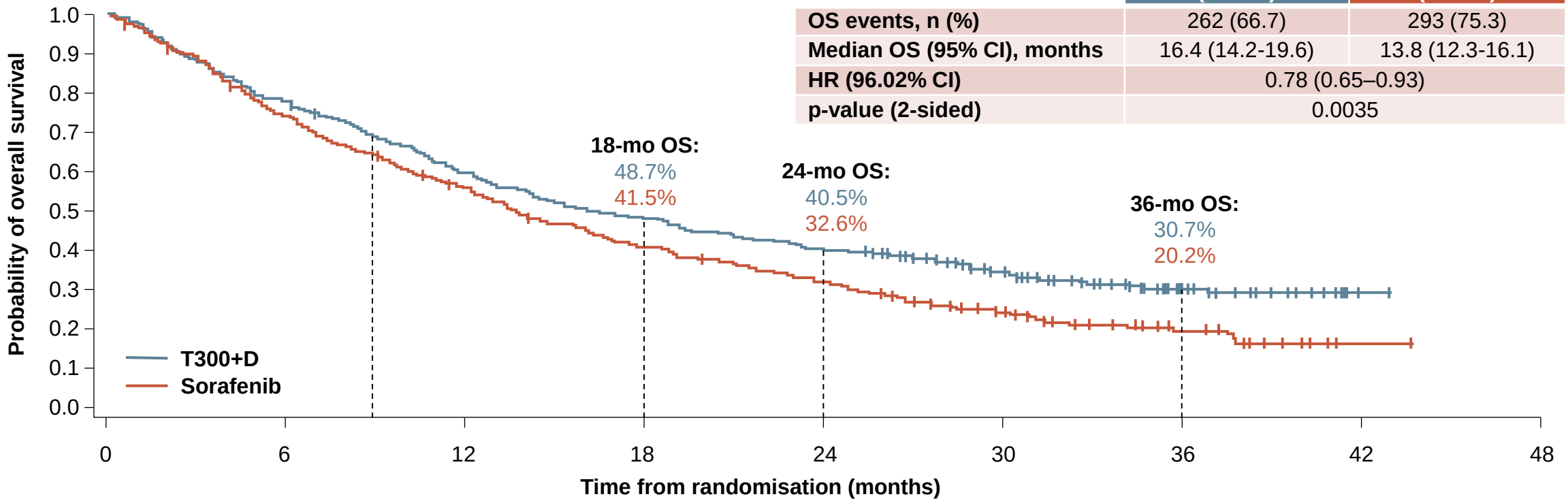
BCLC, Barcelona Clinic Liver Cancer; CTLA4, cytotoxic T-lymphocyte associated protein 4; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; LRT, local regional treatment; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TTP, time to progression

Source: https://clinicaltrials.gov/ct2/show/NCT03298451

DURVALUMAB + TREMELIMUMAB COMBINATION

PRIMARY ENDPOINT: SIGNIFICANT BENEFIT IN OVERALL SURVIVAL 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 (0.65–0.93)	
p-value (2-sided)	0.0035	



No.at risk									
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.7-34.5) months for T300+D and 32.23 (95% CI, 30.4-33.7) months for sorafenib.

CI, confidence interval; HR, hazard ratio; OS, overall survival; Q4W, every 4 weeks; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W

1Abou-Alfa GK, et al. NEJM Evid. 2022;1.8

SAFETY

TIME TO SWITCH TO 2ND LINE THERAPY & RE-CHALLENGING

IMMUNE-RELATED ADVERSE EVENTS ASSOCIATED WITH IMMUNE CHECKPOINT BLOCKADE

10 QUESTIONS RELEVANT TO THE MANAGEMENT OF IMMUNE RELATED ADVERSE EVENTS[1]

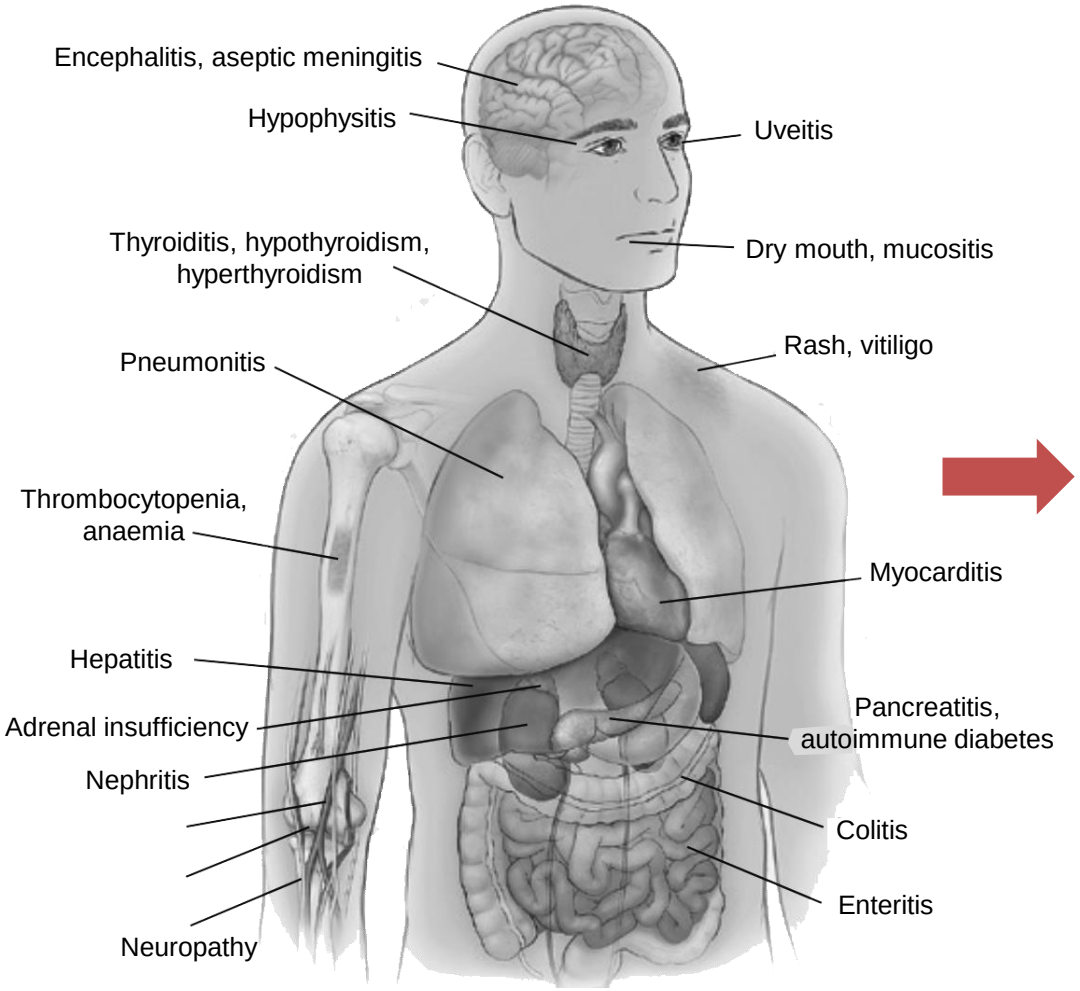


Figure adapted from Postow et al. 2018[1]

1. Why do they occur?
2. How are they generally treated?
3. When do they occur?
4. Why do they occur in some patients and not others?
5. Are they associated with the efficacy of immune checkpoint blockade?
6. Does immunosuppression to treat such adverse events reduce the antitumor efficacy of treatment?
7. Are there unintended effects of immunosuppression to treat adverse events?
8. Is it safe to restart treatment after a major adverse event?
9. Is it necessary to restart treatment after resolution of an adverse event?
10. Is it safe to treat patients at potentially increased risk for such adverse events?

1. Postow MA, et al. N Engl J Med. 2018;378(2):158-68

IMMUNE-RELATED ADVERSE EVENTS

AFFECTED ORGANS AND MANIFESTATIONS

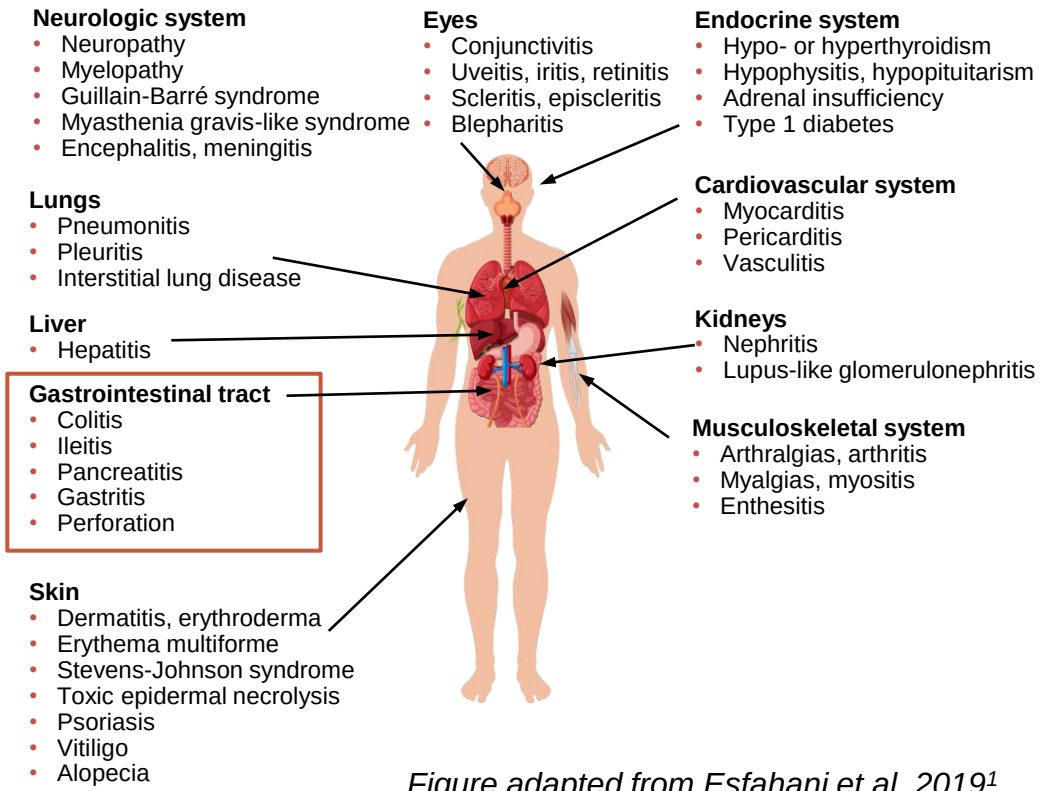


Figure adapted from Esfahani et al. 2019[1]

Timing of occurrence of immune-related events following ipilimumab treatment

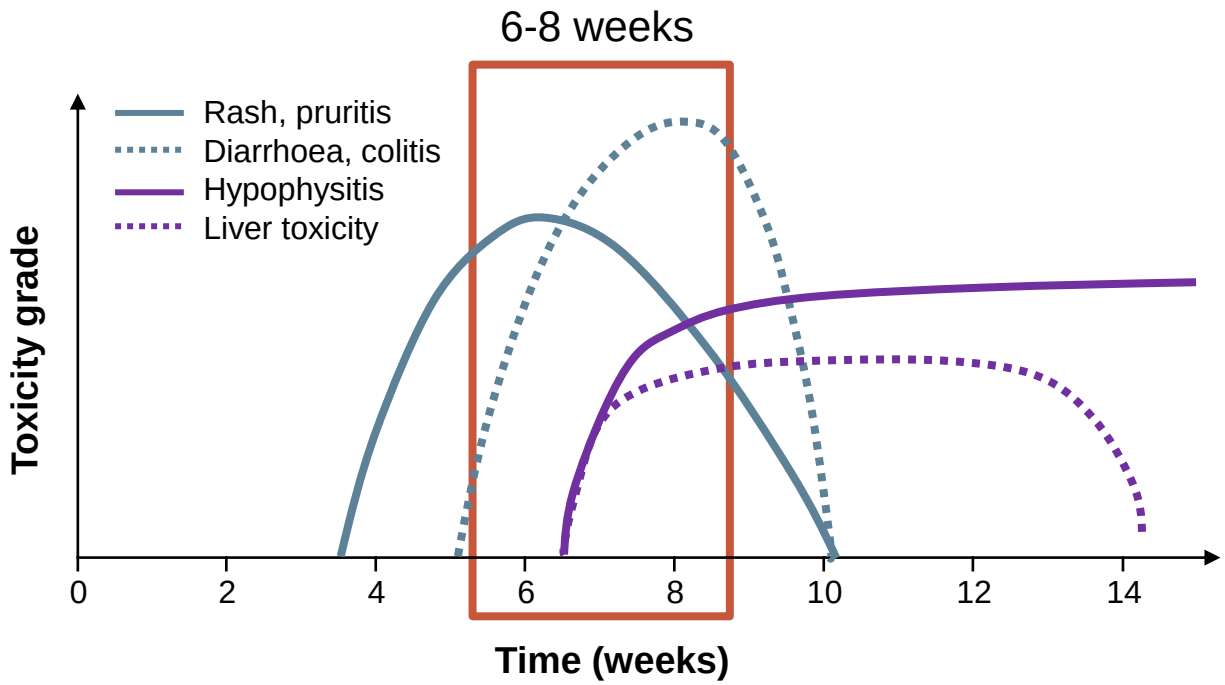


Figure adapted from Haanen et al. 2017[2]

1. Esfahani KH, et al. CMAJ. 2019;191:E40-E46; 2. Haanen JBAG, et al. Ann Oncol. 2017;28:iv119-iv142

ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150):

VARICES AND BLEEDING RISK

rhosis and hepatocellular carcinoma. In this trial, patients had to be evaluated for the presence of varices before enrollment, and varices of any size were assessed and treated as needed according to local standards of care. Overall, the inci-

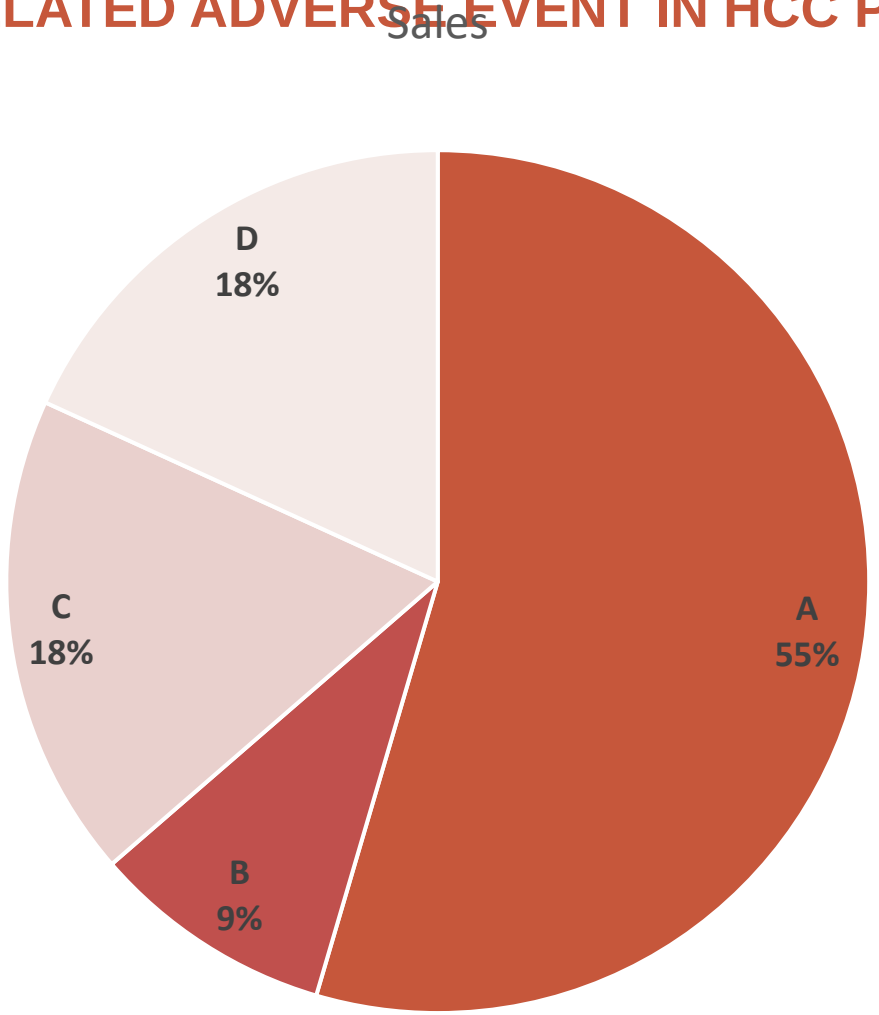
All-causality adverse events of special interest by medical concept	Atezolizumab plus bevacizumab (N=329)		Sorafenib (N=156)	
	All grade	Grade 3 or 4	All grade	Grade 3 or 4
Bevacizumab related, n(%)				
Patients with at least one event	190 (57.8)	76 (23.1)	76 (48.7)	29 (18.6)
Hypertension	102 (31.0)	50 (15.2)	40 (25.6)	19 (12.2)
Bleeding/hemorrhage	83 (25.2)	21 (6.4)	27 (17.3)	9 (5.8)
Proteinuria	70 (21.3)	10 (3.0)	13 (8.3)	1 (0.6)
Thromboembolic event–venous	10 (3.0)	5 (1.5)	5 (3.2)	2 (1.3)
Thromboembolic event–arterial	9 (2.7)	4 (1.2)	2 (1.3)	1 (0.6)
Congestive heart failure	1 (0.3)	0	2 (1.3)	0

Finn R, et al. N Engl J Med. 2020;382(20):1894-905 and supplement;

POLLING QUESTION

WHAT IS THE MOST COMMON IMMUNE RELATED ADVERSE EVENT IN HCC PATIENTS?

A. **Diarrhoea and colitis** ☑
B. Infusion-related reactions
C. Hepatic toxicity
D. Other



HCC, hepatocellular carcinoma

GASTRO INTESTINAL AND HEPATIC IMMUNE-RELATED ADVERSE EVENTS

STEROIDS CAN BE USED FOR MOST IMMUNE-RELATED ADVERSE EVENTS

Different drugs and regimens[1]

DRUG	Diarrhoea, %*	Colitis, %*	Hepatic, %*
• Ipilimumab	34.0 (7.2)	11.6 (6.8)	14.1 (5.5)
• Nivolumab	12.0 (1.0)	1.0 (0.4)	7.1 (1.5)
• Pembrolizumab	10.7 (0.6)	1.9 (1.1)	1.0 (0.6)
• IPI + NIVO – High IPI – Low IPI	 45.0 (9.0) 21.7 (2.8)	 13.0 (8.0) 1.0 (0.5)	 33.0 (20.0) 3.5 (3.0)
• Avelumab	8.5 (0)	/	4.2 (1.6)
• Atezolizumab	15.4 (0.7)	0.3 (0)	0.3 (0.3)
• Durvalumab**	0.7 (0.2)	0.4 (0)	0.7 (0.7)

*Any-grade adverse events (grade ≥3 adverse events)
**percentages reported for durvalumab probably do not reflect the true rate
All data have been averaged

Use of steroids for immune related adverse events in advanced HCC patients in randomised controlled trials

DRUG	Trial	% use of steroids
Nivolumab	Checkmate459	11
Atezolizumab	IMbrave150	12
Durvalumab	HIMALAYA	9.5
STRIDE	HIMALAYA	20
Pembrolizumab/ lenvatinib	LEAP-002	9.6

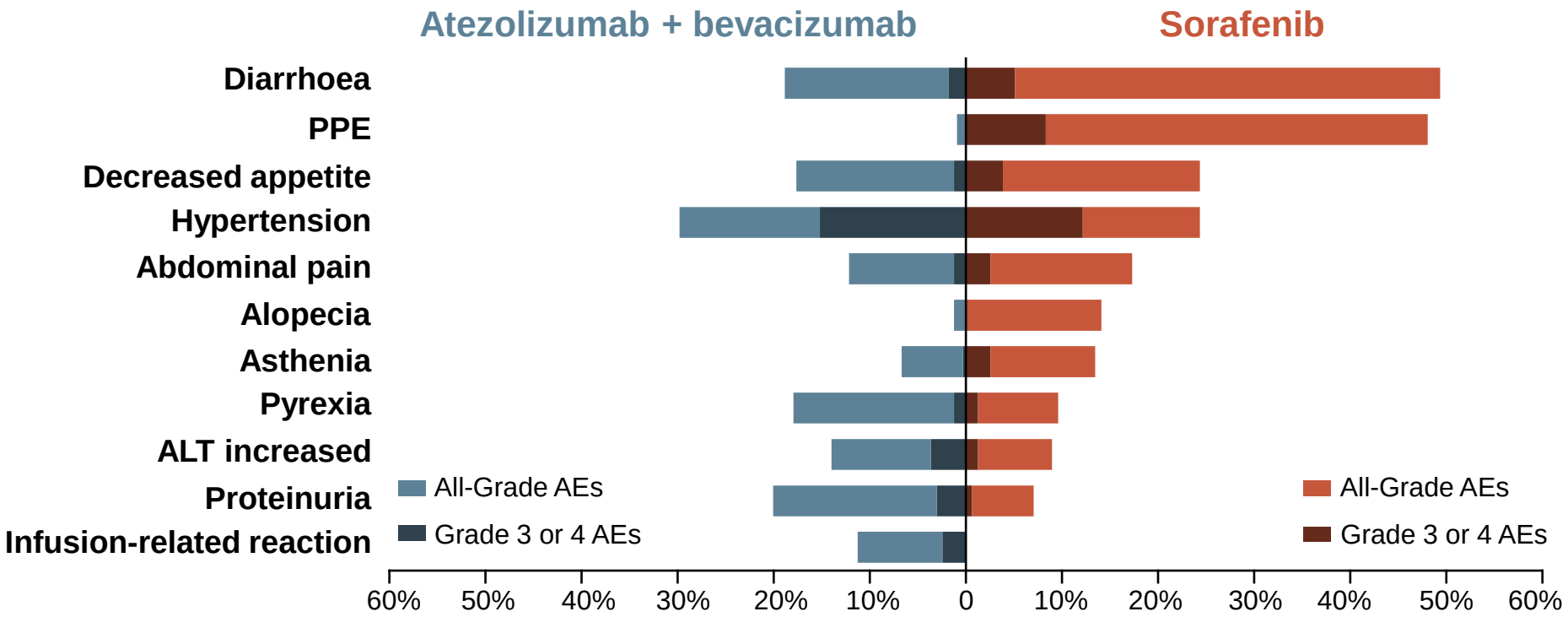
HCC, hepatocellular carcinoma; IPI, ipilimumab; NIVO, nivolumab; STRIDE, Single Tremelimumab Regular Interval Durvalumab

1. Martins F, et al. Nat Rev Clin Oncol. 2019;16(9):563-80

ATEZOLIZUMAB + BEVACIZUMAB COMBINATION

SUMMARY OF ADVERSE EVENTS

≥10% FREQUENCY OF AEs IN EITHER ARM AND >5% DIFFERENCE BETWEEN ARMS



AE, adverse event; ALT, alanine aminotransferase; PPE, palmar-plantar erythrodysaesthesia

Finn RS, et al. N Engl J Med. 2020;382(20):1894-905

RE-CHALLENGING WITH IMMUNE CHECKPOINT INHIBITOR AFTER TOXICITY

ICI-INDUCED ENTERO-COLITIS[1]

Grade 2-4 response to CSs:

- Initiate 4-8-weekly CSs tapering programme
- Upon remission, discuss resuming ICI therapy, weighing oncological benefit against risk of GI irAE recurrence
- In the case of relapse, consider infliximab or vedolizumab as below

Grade 2-4 refractory to CSs:

- Infliximab 5 mg/kg IV in the more severe forms or vedolizumab 300 mg in the more moderate forms and rapid CS tapering
- If no response, consider switching to the other biologic, higher-dose infliximab, faecal microbiota transplantation, ustekinumab, tofacitinib, extracorporeal photopheresis, colectomy and repeat testing for infections

IMMUNE RELATED HEPATOTOXICITY[2]

ICI-related toxicity: Management of hepatitis

Steroid wean:

- Grade 2: Once grade 1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤10 mg
- Grade 3 or 4: Once improved to grade 2, can change to oral prednisolone and wean over 4 weeks; for grade 3, re-challenge only at consultant discretion

Worsening despite steroids:

- If on oral change to IV (methyl)prednisolone
- If on IV add MMF 500-1000 mg bid
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis

CS, corticosteroid; GI, gastrointestinal; ICI, immune checkpoint inhibitor; irAE, immune related adverse event; IV, intravenous; MMF, mycophenolate mofetil

1. Haanen J, et al. Ann Oncol. 2022;33(12)1217-38; 2. Haanen JBAG., et al. Ann Oncol. 2017;28, iv119-iv142.

PROGRESSION

TIME TO SWITCH TO 2ND LINE THERAPY

POLLING QUESTION

HOW WOULD YOU MEASURE PROGRESSION IN HCC PATIENTS?

A. Choi

B. EASL

C. RECIST

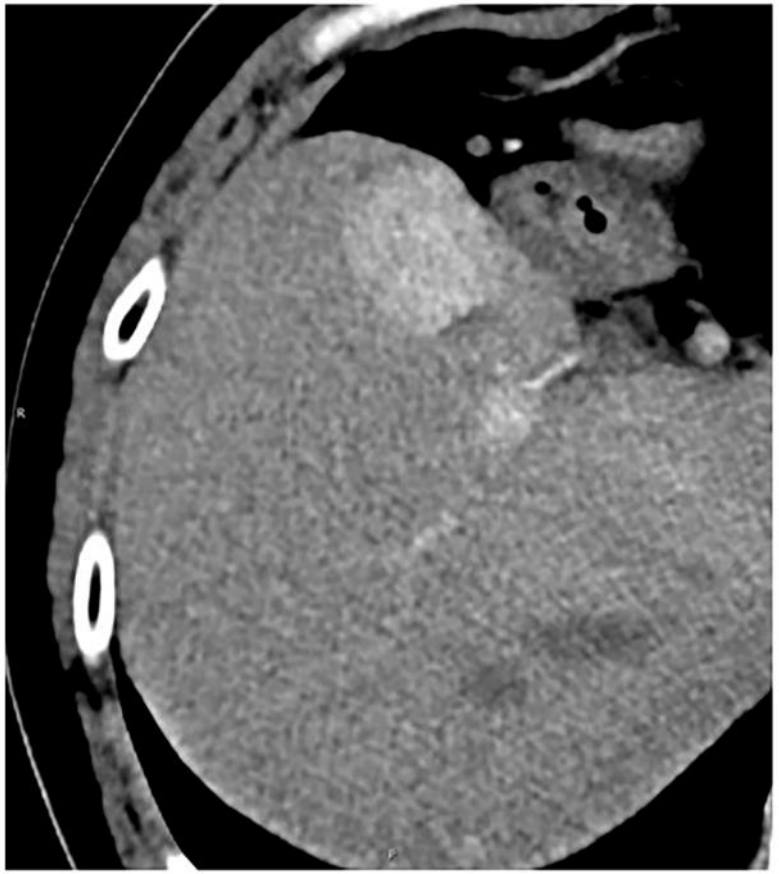
D. mRECIST ☑

E. I am not sure

EASL, European Association for the Study of the Liver (clinical practice guidelines); mRECIST, modified RECIST; RECIST, Response Evaluation Criteria in Solid Tumors

HOW TO MEASURE PROGRESSION IN HCC?

Before start treatment



After immunotherapy

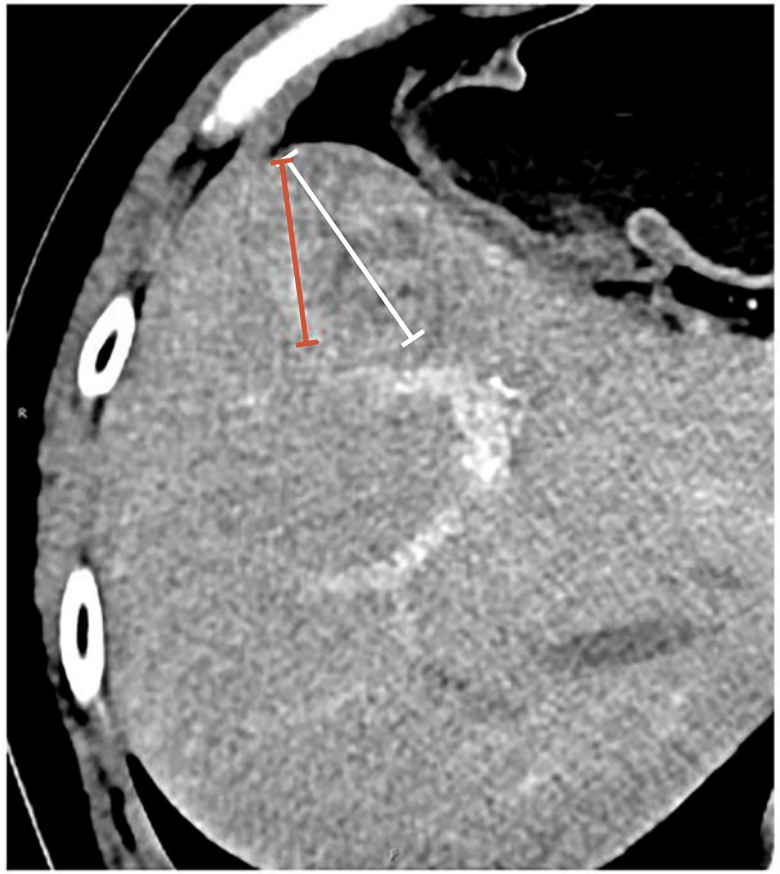


Figure adapted from Zhou et al. 2021[1]

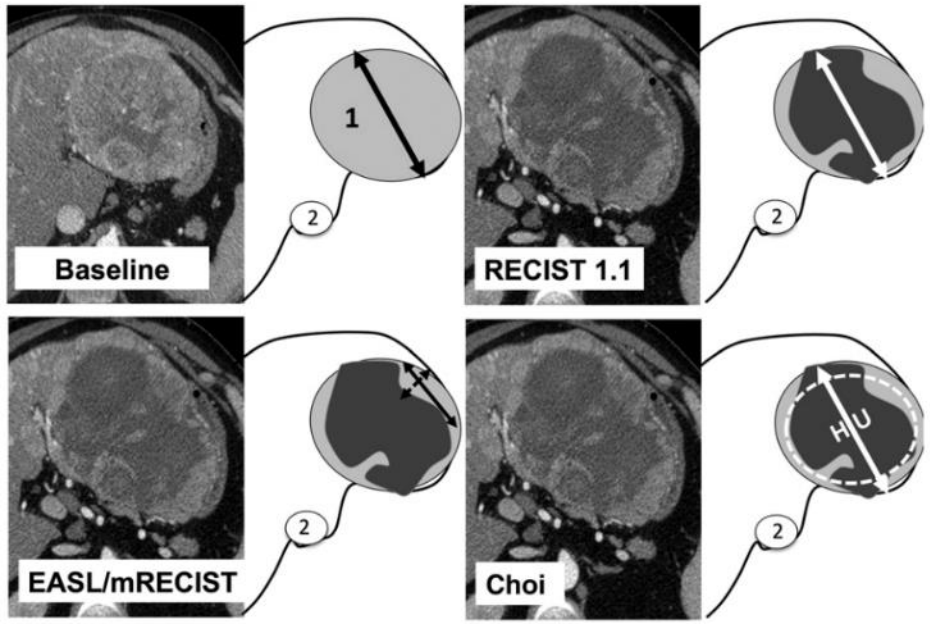
HCC, hepatocellular carcinoma

Zhou, et al. Front Oncol. 2021;11:764189

HOW TO MEASURE PROGRESSION IN HCC?

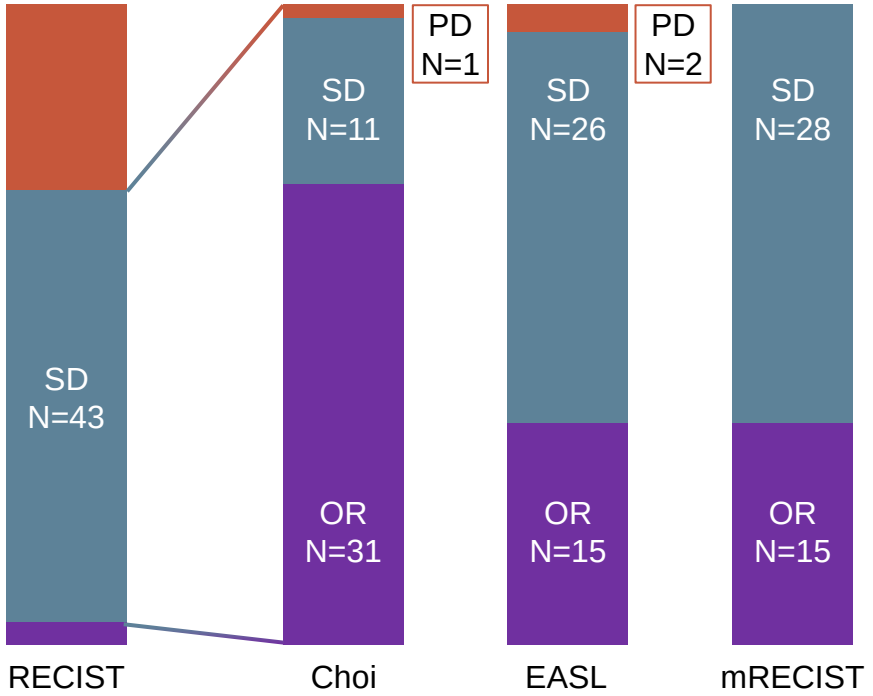
mRECIST CRITERIA HAVE A POWERFUL ABILITY TO DISCRIMINATE BETWEEN RESPONDERS AND NON RESPONDERS

Baseline and post-treatment evaluation



1 = tumour light/dark gray = viable tumour/necrosis
2 = inferior vena cava

Proportions of patients with OR, SD and PD using alternative response criteria



Figures adapted from Ronot et al. 2014

EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; mRECIST, modified RECIST; OR, objective response; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Ronot M, et al. Oncologist. 2014;19:394-402

CONCLUSION

REVIEWING THE OUTCOMES IN HCC WITH 1ST LINE IO: WHEN IS THE RIGHT TIME TO SWITCH?

- HCC is an increasing **global health care challenge**
- **IO** is an **effective standard-of-care 1st line treatment** in advanced HCC with rare but potentially dangerous side-effects
- **Switching to 2nd line** after IO 1st line should be considered in case of **toxicity** or **disease progression**
- **Measuring disease-progression** in HCC can be challenging as there are several methods with different evaluation criteria
  - mRECIST criteria have a powerful ability to discriminate between responders and non-responders

HCC, hepatocellular carcinoma; IO, immunotherapy; mRECIST, modified Response Evaluation Criteria in Solid Tumors

DISCUSSION

PATIENTS WITH ADVANCED HCC NOT ELIGIBLE FOR IO IN 1ST LINE

THE ROLE OF TKIs AS THE PRIMARY TREATMENT OPTION

Prof. Michel Ducreux

HCC, hepatocellular carcinoma; IO, immunotherapy; TKI, tyrosine kinase inhibitor

POLLING QUESTION

WHICH PATIENT GROUP IS ELIGIBLE FOR IO 1ST LINE?

A. Patients with active or uncontrolled auto-immune disease

B. HCC recurrent patients after liver transplantation

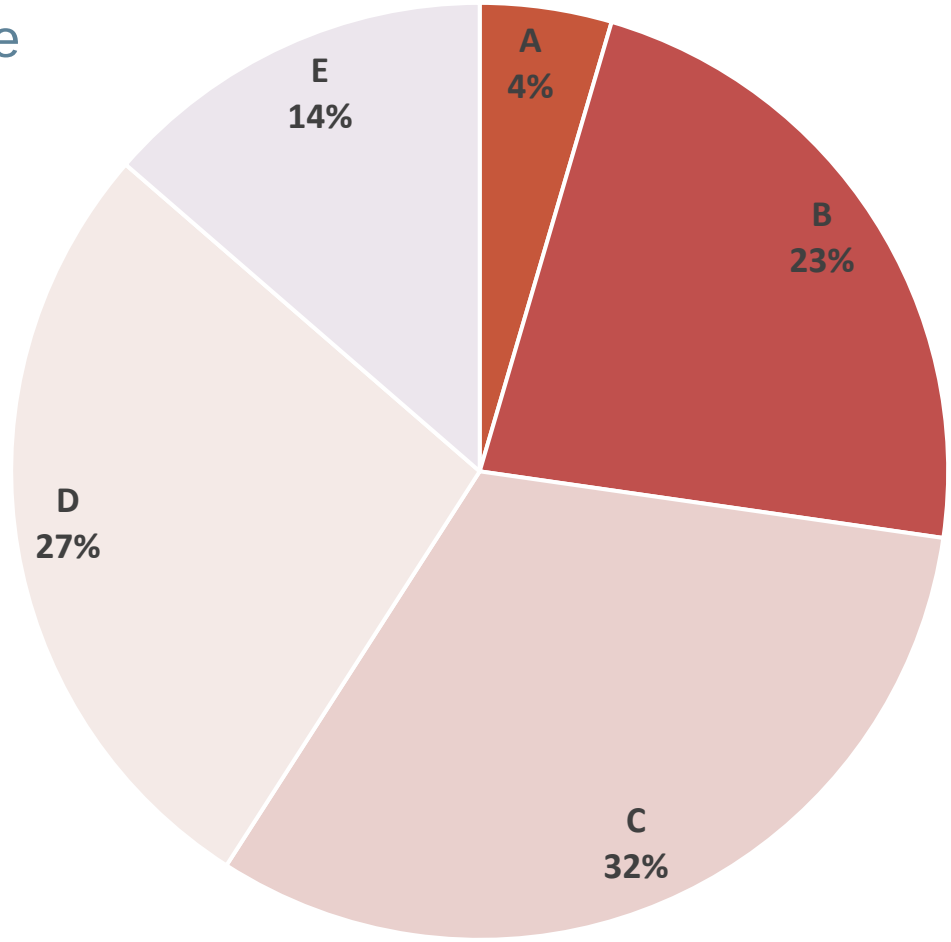
C. Patients with a significant bleeding history ☑

*These patients are now eligible for durvalumab + tremelimumab

A. None of those

B. All of those

C. I am not sure



HCC, hepatocellular carcinoma; IO, immunotherapy

POLLING QUESTION

HOW WOULD YOU TREAT A POST-LIVER TRANSPLANT PATIENT WITH ADVANCED RECURRENT HCC IN 1ST LINE?

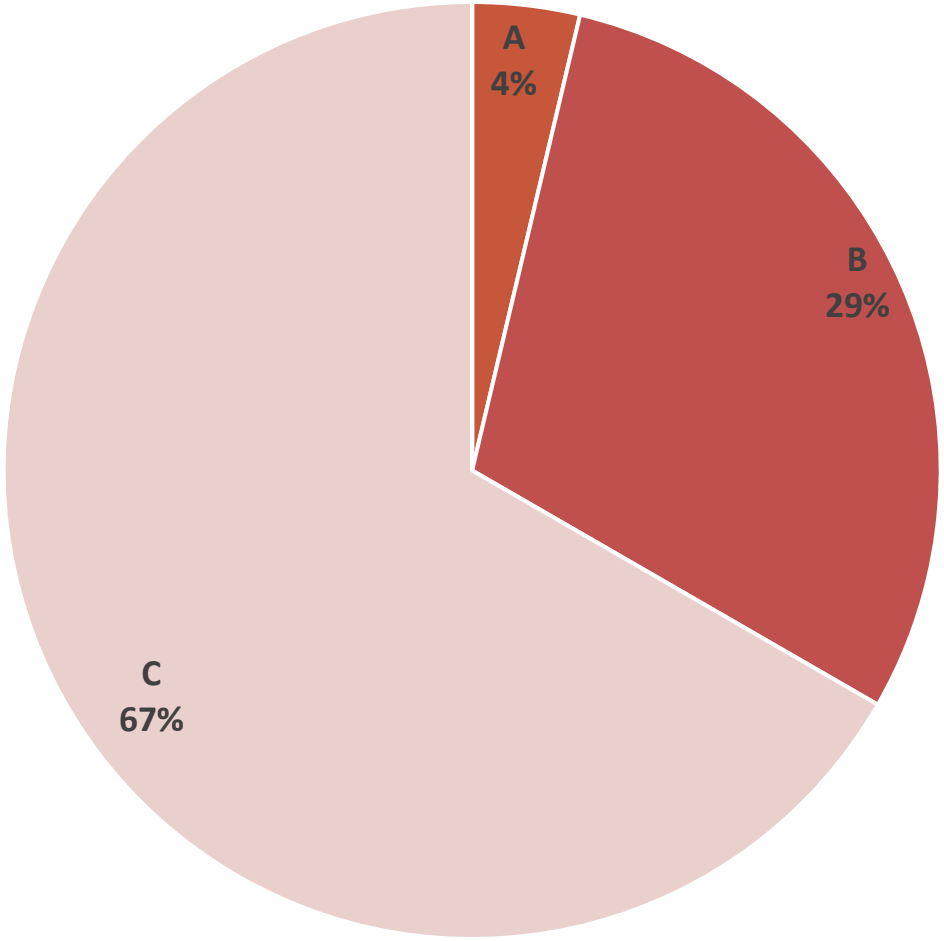
A. With single agent immunotherapy

B. With immunotherapy based combination treatment, such as durvalumab + tremelimumab or atezolizumab + bevacizumab

C. **With TKIs, such as lenvatinib or sorafenib** ☑

D. With chemotherapy

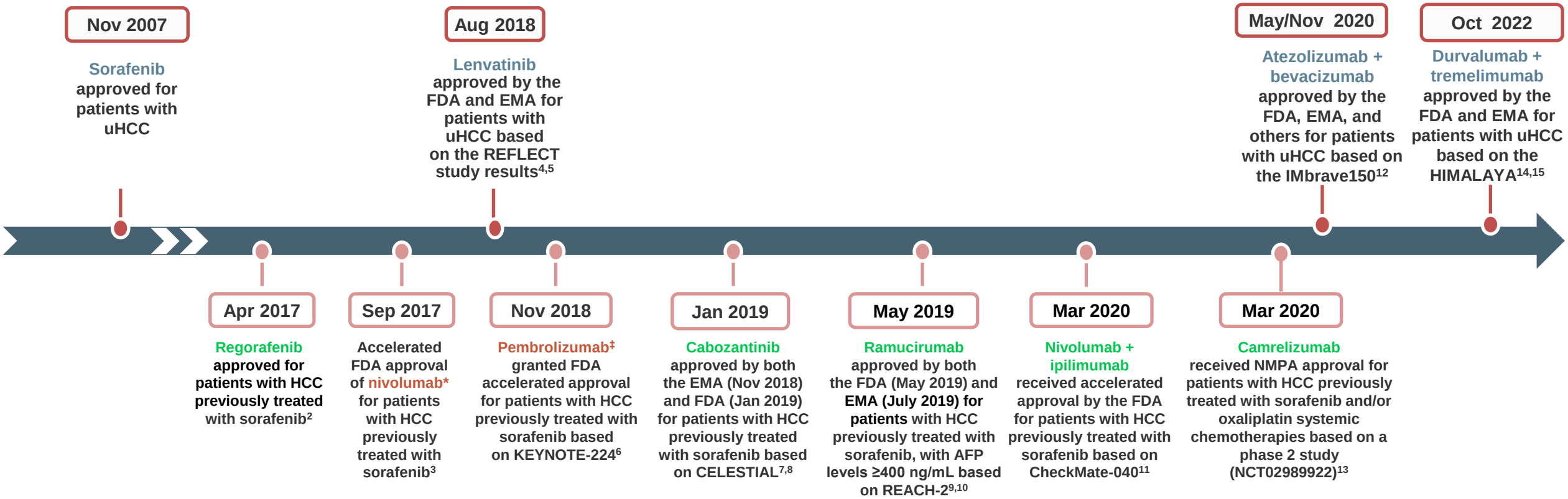
E. I am not sure



HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor

THE HCC SYSTEMIC TREATMENT LANDSCAPE HAS RAPIDLY EVOLVED SINCE 2017

First-line therapies



Second-line therapies

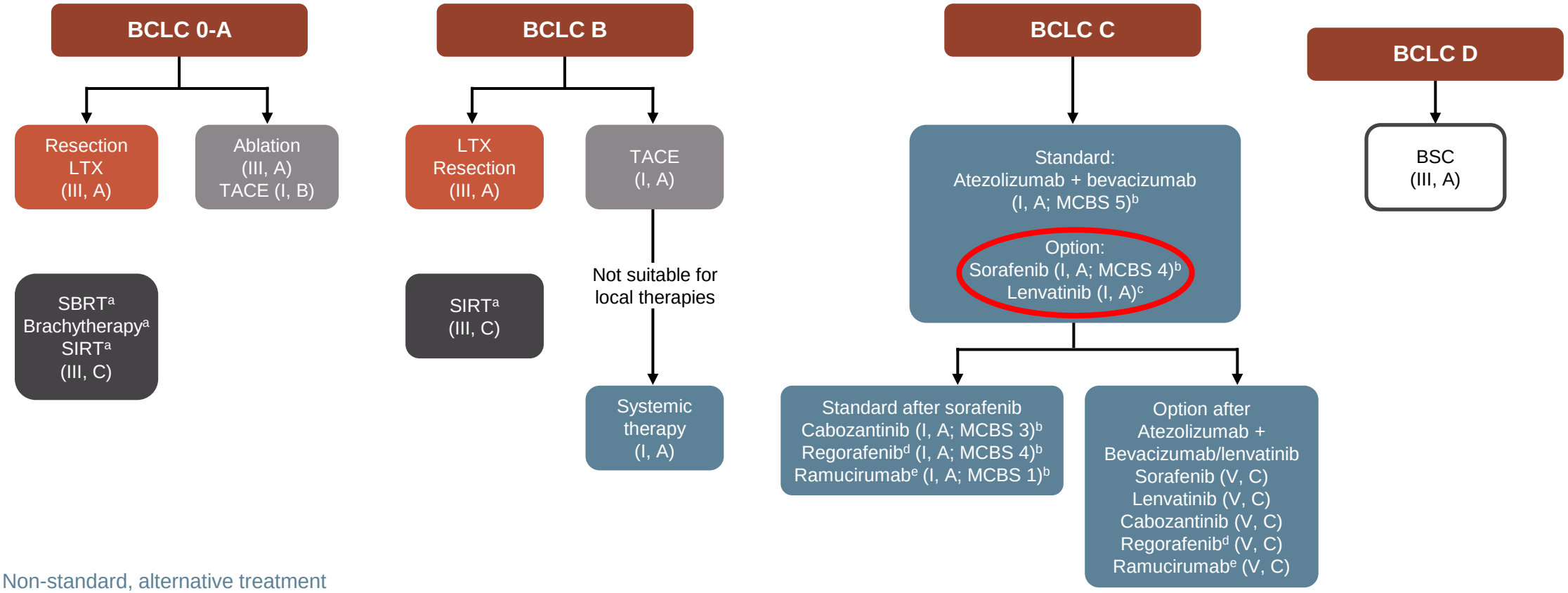
Negative phase 3 trials

AFP, alpha-fetoprotein; EMA, European Medicines Agency; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; NMPA, National Medical Products Administration; OS, overall survival; PFS, progression-free survival; uHCC, unresectable HCC

1. Nexavar (sorafenib) Full Prescribing Information. Bayer HealthCare Pharmaceuticals, Whippany, NJ. 2020 (accessed May 2020); 2. FDA regorafenib in HCC press release. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm555608.htm (accessed May 2020); 3. FDA press release. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm577166.htm (accessed May 2020); 4. FDA press release. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm617185.htm (accessed May 2020); 5. Merck press release. Available from: https://investors.merck.com/news/press-release-details/2018/Eisai-and-Merck-Announce-European-Commission-Grants-Marketing-Authorization-for-LENVIMA-lenvatinib-as-First-Line-Treatment-in-Adults-with-Advanced-or-Unresectable-Hepatocellular-Carcinoma/default.aspx (accessed May 2020); 6. FDA press release. Available from: https://www.fda.gov/drugs/fda-grants-accelerated-approval-pembrolizumab-hepatocellular-carcinoma (accessed May 2020): 7. Ipsen press release. Available from: https://www.ipsen.com/media/press-relases/post_custom_datacustom_datapost_custom_datacustom_dataeuropean-commission-approves-ipsens-cabometyx-cabozantinib-for-the-treatment-of-hepatocellular-carcinoma-in/ (accessed May 2020); 8. FDA press release. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm629512.htm (accessed May 2020): 9. FDA press release https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ramucirumab-hepatocellular-carcinoma (accessed May 2020); 10. Cyramza (ramucirumab) EMA approval. EMA summary of opinion. Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-cyramza-ii-27_en.pdf (accessed May 2020); 11. FDA press release. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma (accessed May 2020); 12. ASCO Post press release. Available from: https://www.ascopost.com/news/may-2020/fda-approves-atezolizumab-plus-bevacizumab-for-patients-with-unresectable-or-metastatic-hcc/ (accessed May 2020); 13. Qin S. et al, Lancet Oncol. 2020;21(4):571-580; 14. Food and Drug Administration. (2022). Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-unresectable-hepatocellular-carcinoma (accessed March 2023). 15. European Medicines Agency. (2022). Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-imjudo_en.pdf (accessed March 2023)

ESMO HCC GUIDELINES E-UPDATE (MARCH 2021)

OPTIONAL SYSTEMIC TREATMENT 1ST LINE: LENVATINIB AND SORAFENIB



[a] Non-standard, alternative treatment
[b] ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee
[c] Non-inferiority to sorafenib established; no evaluable benefit
[d] Regorafenib is not recommended in TKI-naive patients
[e] Ramucirumab is only recommended in patients with an AFP level ≥ 400 ng/mL

AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; EMA, European Medicines Agency; ESMO. European Society for Medical Oncology; HCC, hepatocellular carcinoma; LTx, liver transplantation; MCBS, magnitude of clinical benefit scale; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TKI, tyrosine kinase inhibitor

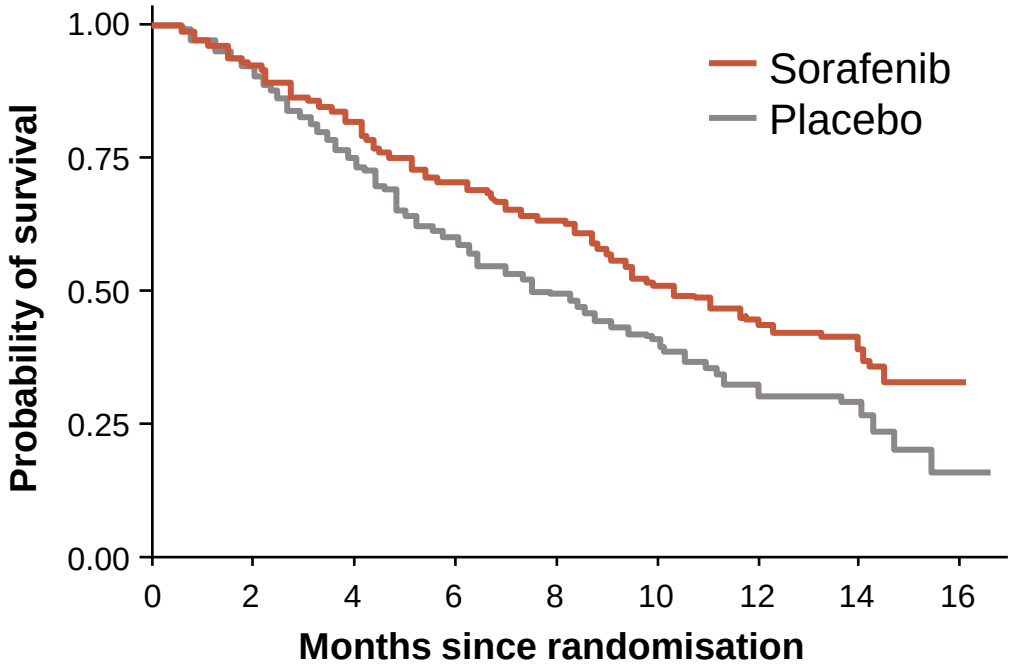
1. Vogel A, et al. Ann Oncol. 32(6):801-5

1ST-LINE TREATMENT OPTIONS FOR PATIENTS NOT ELIGIBLE FOR IO

TKIs SORAFENIB AND LENVATINIB

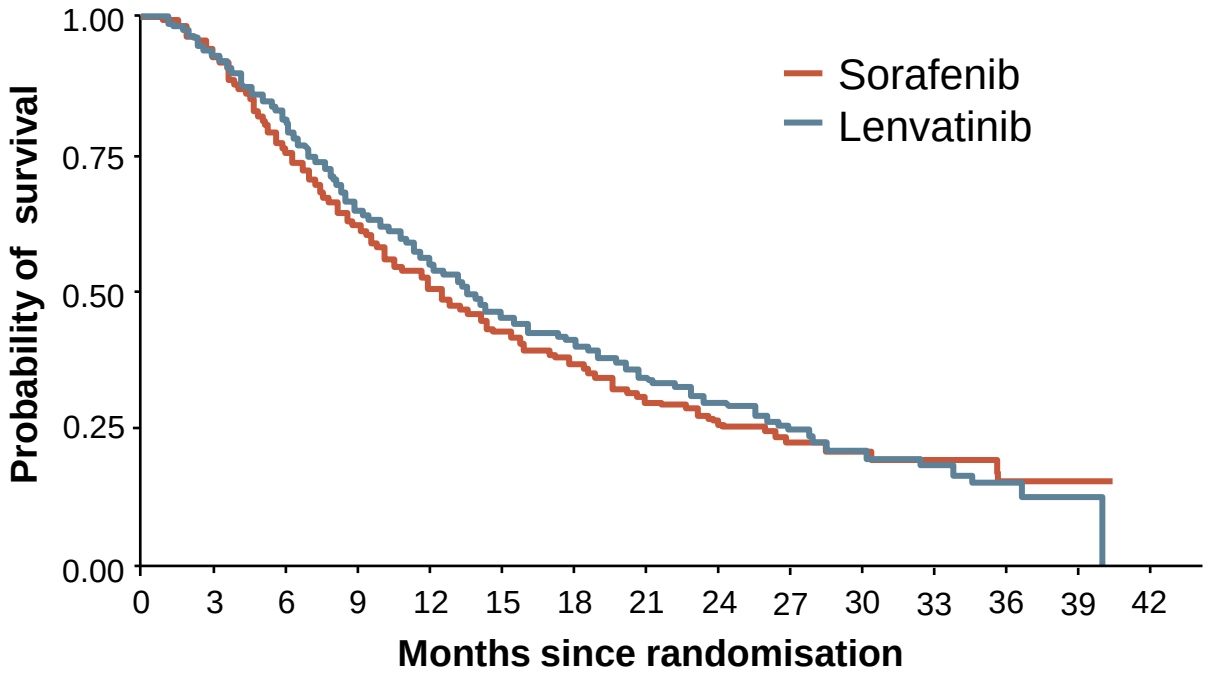
Overall survival in the SHARP trial[1]

Median OS: 10.7 months sorafenib *vs* 7.9 months placebo HR 0.69 (95% CI 0.55-0.87), p<0.001[1]



Overall survival in the REFLECT* trial[2]

Median OS: 13.6 months lenvatinib *vs* 12.3 months sorafenib HR 0.92 (95% CI 0.79-1.06)[2]



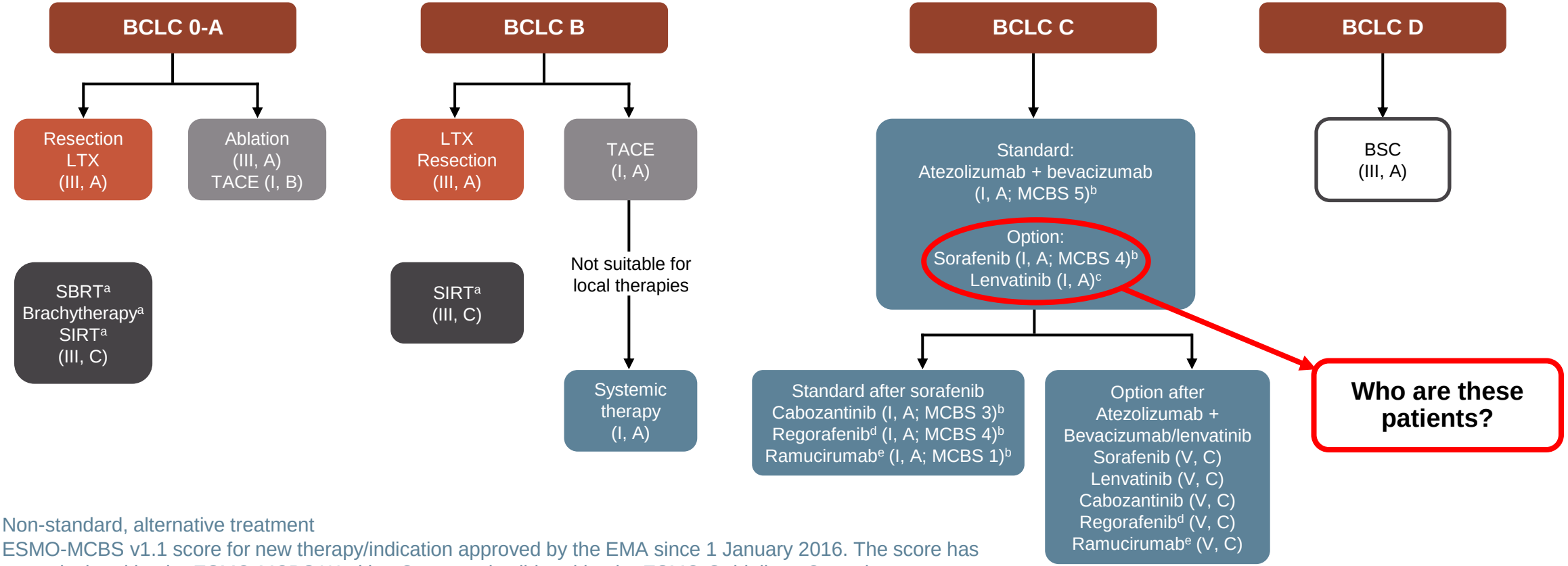
*REFLECT is a randomised phase 3 non-inferiority trial

CI, confidence interval; HR, hazard ratio; IO, immunotherapy; OS, overall survival; TKI, tyrosine kinase inhibitor

1. Llovet JM, et al. N Engl J Med. 2008;359(4):378-90; 2. Kudo M, et al. Lancet. 2018;391(10126):1163-73

ESMO HCC GUIDELINES E-UPDATE (MARCH 2021)

OPTIONAL SYSTEMIC TREATMENT 1ST LINE: LENVATINIB AND SORAFENIB



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1. Vogel A, et al. Ann Oncol. 32(6):801-5

PATIENTS WITH LIVER TRANSPLANTATION

PATIENTS WITH LIVER TRANSPLANTATION

LIVER TRANSPLANTATION CAN BE CURATIVE, BUT HCC RECURS IN 10-16% OF PATIENTS[1]

- Retrospective study with 121 HCC recurrent patients[2]
  - Median time to recurrence: 14 months
  - 41% early recurrence (<1 year)
  - 31% treated with curative intent
  - 42% palliative treatment
  - 26% supportive care only

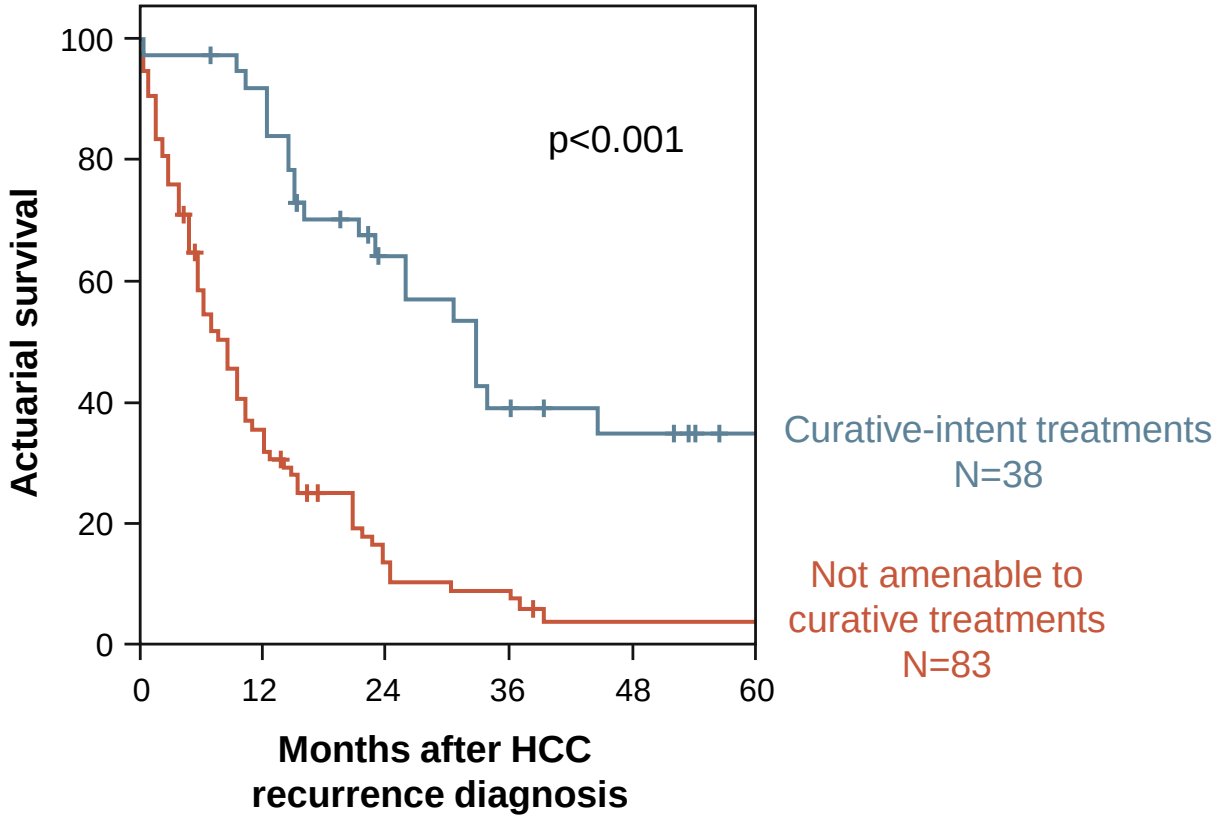


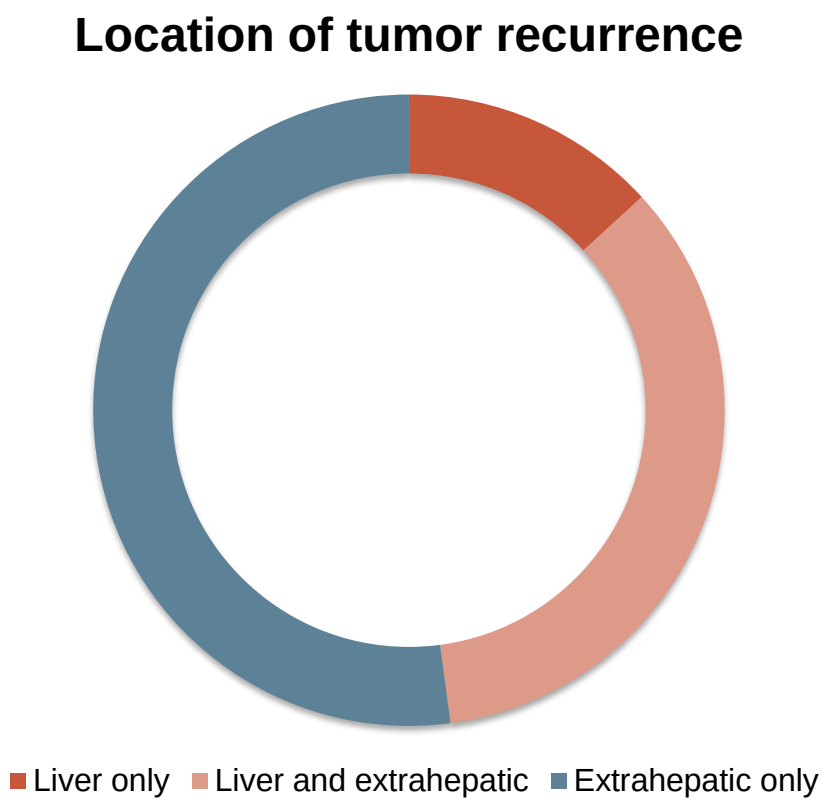
Figure adapted from Saposochin et al. 2015[2]

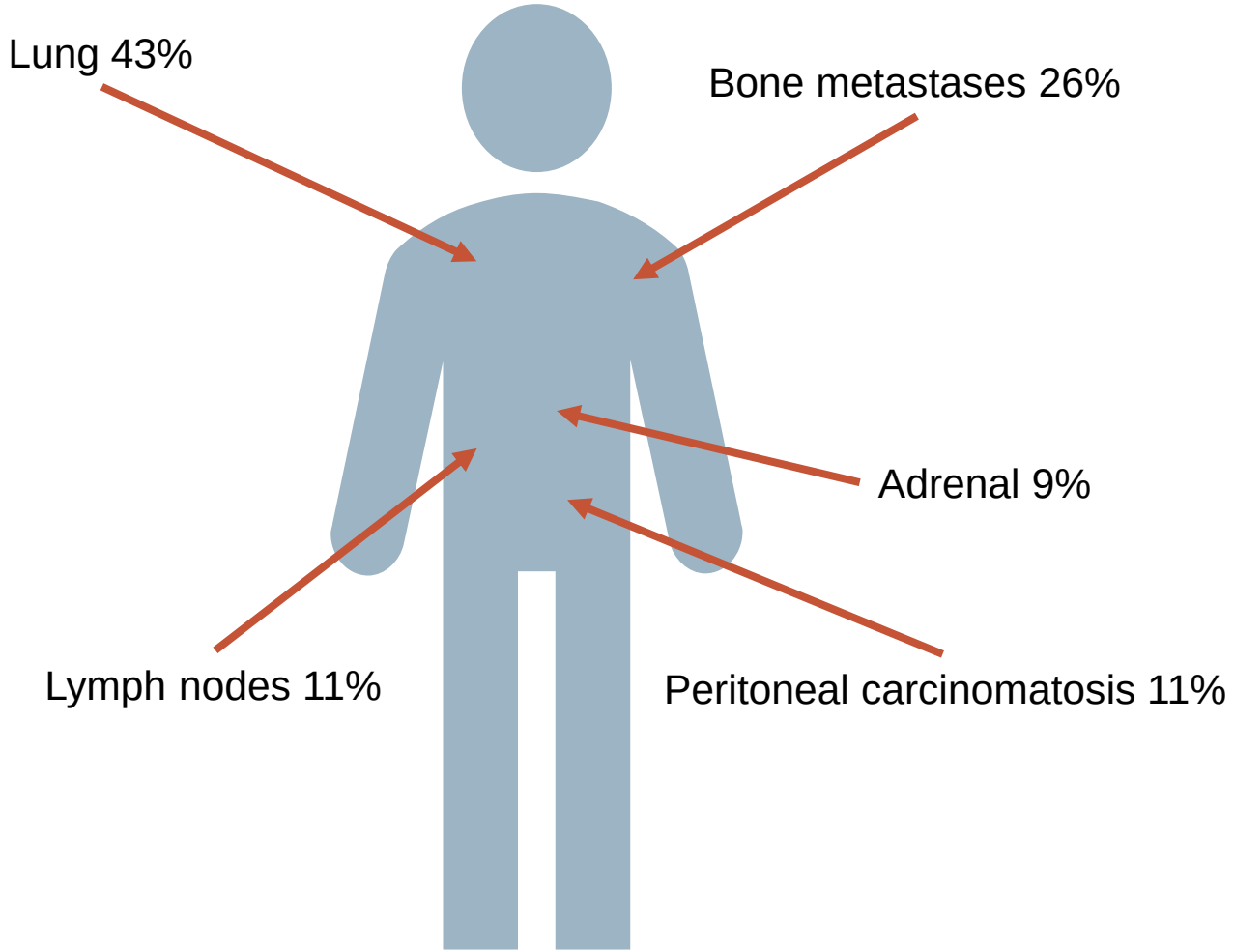
HCC, hepatocellular carcinoma

1. Rimassa L, et al. J Hepatol. 2021:74;P931-43; 2. Sapisochin G, et al. Ann Surg Oncol. 2015;22:2286-94

PATIENTS WITH LIVER TRANSPLANTATION

TYPE OF RECURRENCE (N=121)



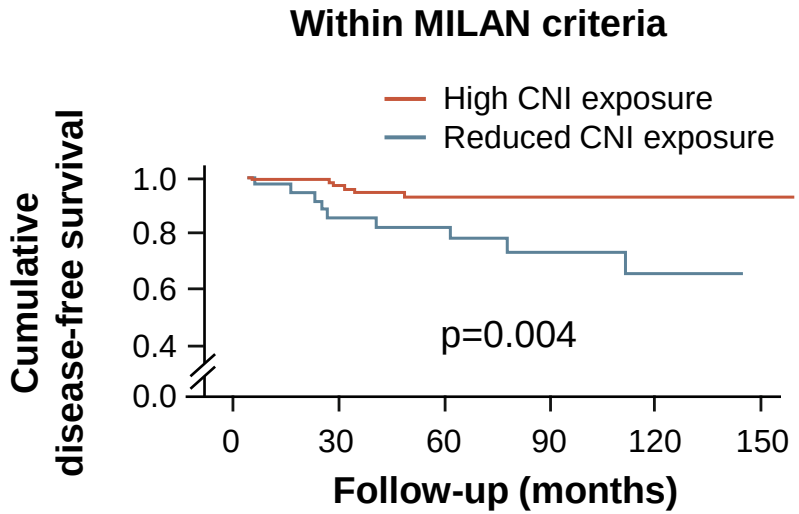


Sapisochin G, et al. Ann Surg Oncol. 2015;22:2286-94

PATIENTS WITH LIVER TRANSPLANTATION

ROLE OF IMMUNO-SUPPRESSION IN THE INCIDENCE OF RECURRENCE

- 219 patients, Milan criteria
  - **HCC recurrence rates: 17.6% at 5 years**
  - Not influenced by use of corticosteroids and antimetabolites
  - Similar with cyclosporine and tacrolimus
  - But: higher exposure to calcineurin inhibitors within the first month after liver transplantation associated with higher risk of recurrence: 27.7% versus 14.7 at 5 years



HCC recurrence % (No. at risk)	1 year	3 years	5 years
High CNI exposure (n=36)	5.7 (32)	14.7 (27)	22 (21)
Reduced CNI exposure (n=106)	1 (99)	5.5 (79)	7 (48)

Figure adapted from Rodiguez-Peralvarez et al. 2013

Little information is available on the safety of IO therapy in patients with liver or other solid organ transplants since they were excluded from trials

CNI, calcineurin inhibitor; HCC, hepatocelular carcinoma; IO, immunotherapy

Rodriguez-Peralvarez M, et al. J Hepatol. 2013;59:1193-9

PATIENTS WITH LIVER TRANSPLANTATION

HIGH REJECTION RISK WITH IMMUNOTHERAPY

Prior organ transplantation	Checkpoint inhibitor	Allograft rejection, no./reported cases (%)	Median time to rejection, days (range)
Hepatic	Ipilimumab	1/3 (33)	13
	Nivolumab	2/4 (50)	12.5 (7-18)
	Pembrolizumab	1/3 (33)	7
	Ipilimumab followed by pembrolizumab	0/1 (0)	
	All	4/11 (36)	10 (7-18)

Table adapted from Abdel-Wahab et al. 2019

PATIENTS WITH LIVER TRANSPLANTATION

SORAFENIB AND LENVATINIB FOR RECURRENT HCC PATIENTS

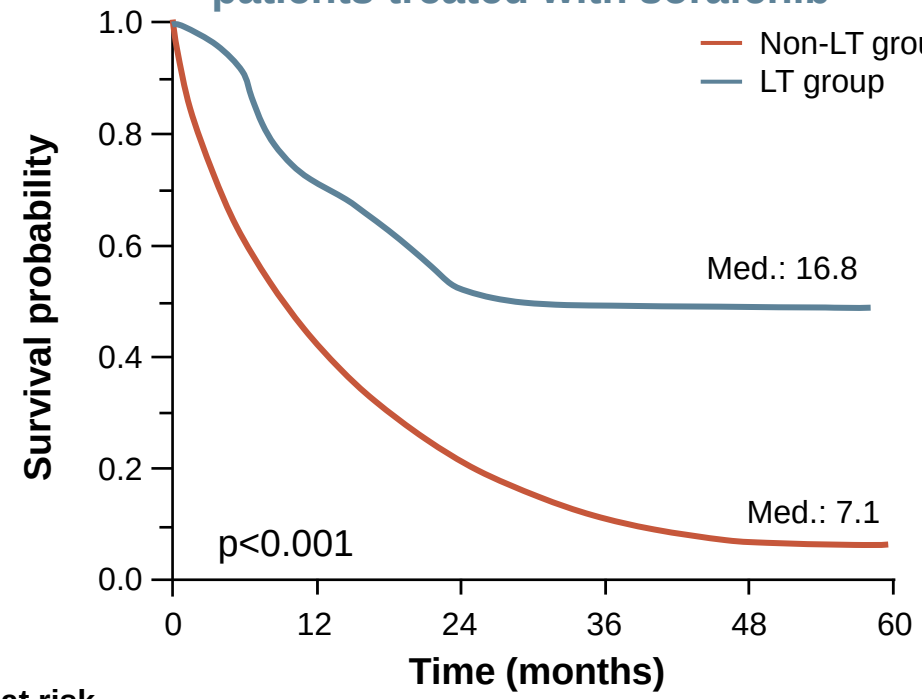
HCC, hepatocelular carcinoma

PATIENTS WITH LIVER TRANSPLANTATION

SORAFENIB PROVIDES CLINICAL BENEFIT TO PATIENTS WITH RECURRENT HCC

- **Sorafenib** has demonstrated improvements in OS vs BSC in the **post-transplant setting**[1-3]
  - Patients with liver transplantation are typically excluded from RCTs[4]
- **Patient outcomes with liver transplantation may be better** than without due to preserved liver function

Retrospective study:
OS by prior transplantation status of patients treated with sorafenib[5]



Numbers at risk						
Non-LT group	790	186	80	27	13	9
LT group	42	20	8	6	3	1

Figure adapted from Lee et al. [5]

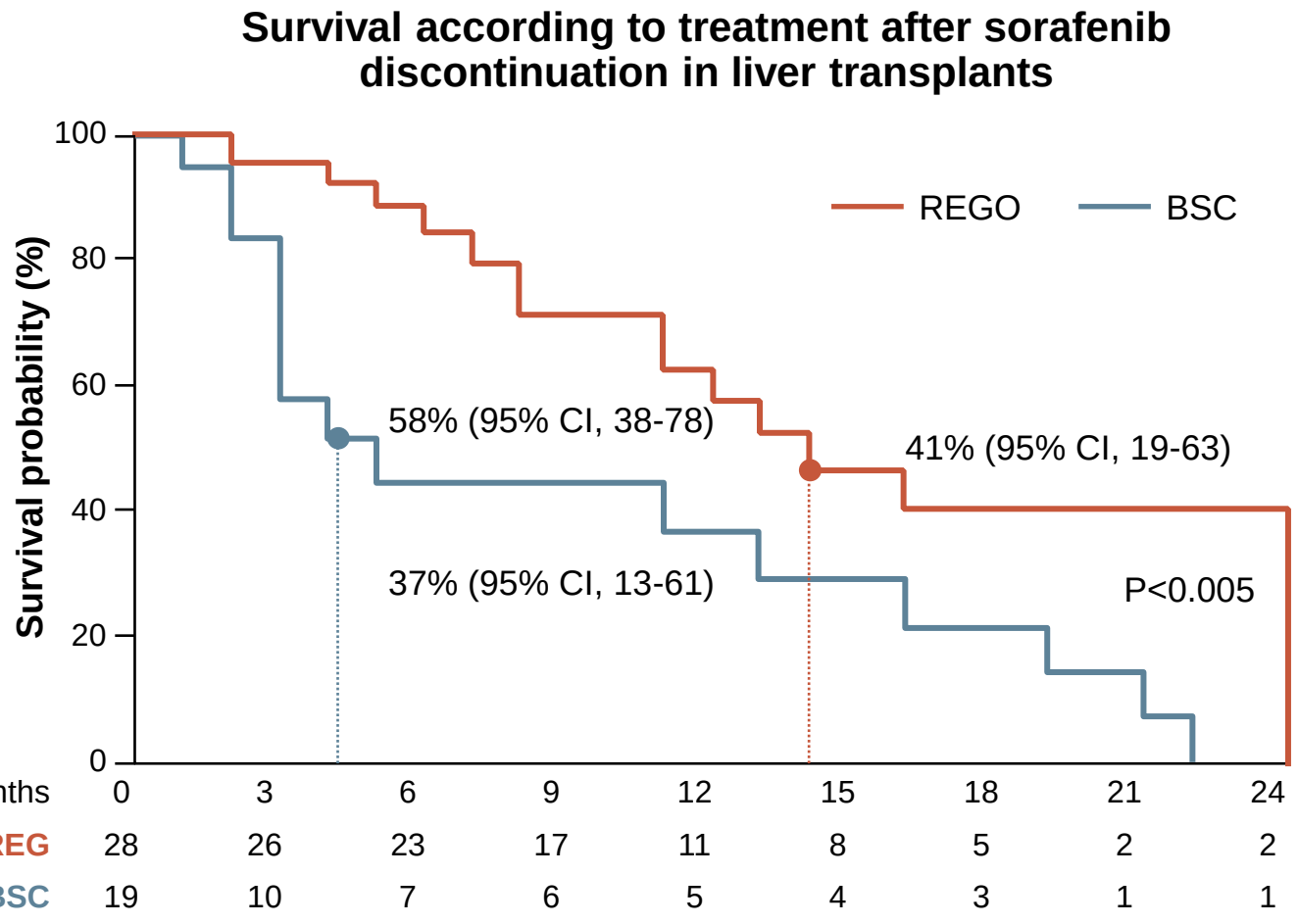
BSC, best supportive care; HCC, hepatocellular carcinoma; LT, liver transplantation; Med., median; OS, overall survival; RCT, randomised controlled trial

1. Kang SH, et al. J Korean Med Sci. 2018;33:e283; 2. Sposito C, et al. J Hepatol. 2013;59:59-66; 3. de'Angelis N, et al. Prog Transplant. 2016;26:348-355; 4. Masi G, et al. Poster P-024; presented at EASL Digital Liver Cancer Summit 2021. Abstract P-024; 5. Lee SK, et al. Hepatol Int. 2021;15:137-45

THE SORAFENIB-REGORAFENIB SEQUENCE

EXTENDING SURVIVAL IN HCC RECURRENCE AFTER LIVER TRANSPLANTATION

Retrospective, multicenter, international study of 32 patients who discontinued sorafenib due to progression



Patients still at risk									
Months	0	3	6	9	12	15	18	21	24
REG	28	26	23	17	11	8	5	2	2
BSC	19	10	7	6	5	4	3	1	1

The median OS was:
14 months (95% CI, 9-19)
sorafenib-regorafenib 4.5 months (95% CI, 0-15)
sorafenib-BSC P<0.005

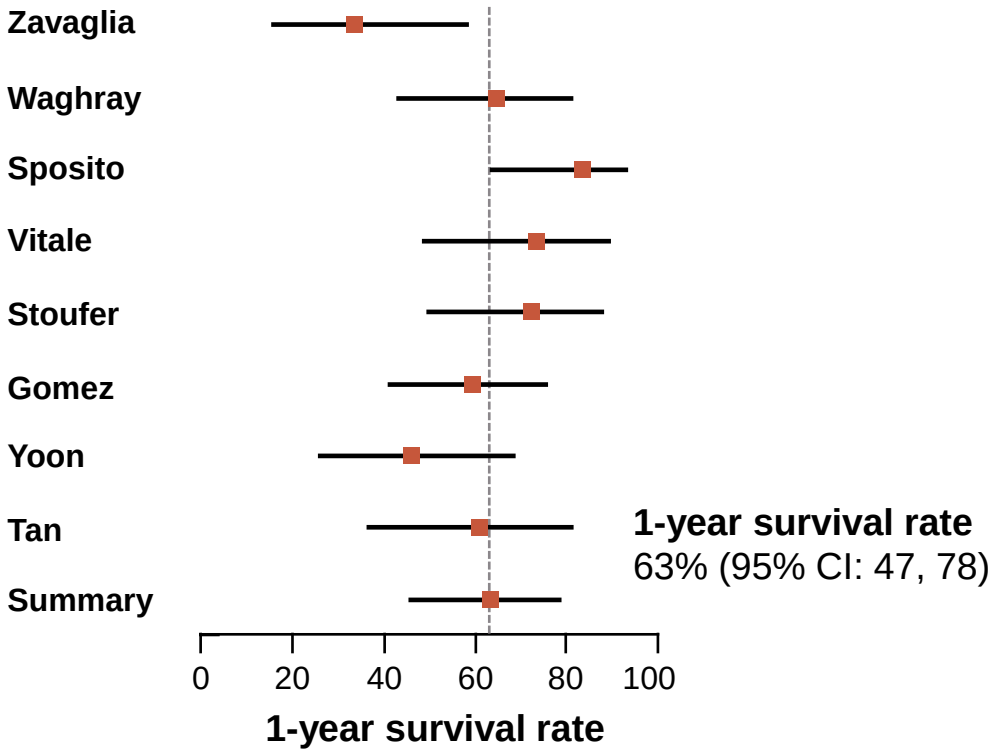
Median OS from the start of sorafenib was:
32.6 months (95% CI, 18-46)
sorafenib-regorafenib
14.3 months (95% CI, 7-21)
sorafenib-BSC
P=0.001 (secondary endpoint)

BSC, best supportive care; CI, confidence interval; HCC, hepatocellular carcinoma; OS, overall survival; REGO, regorafenib;
Iavarone M, et al. Liver Transpl. 2021;27(12):1767-78

PATIENTS WITH LIVER TRANSPLANTATION

META-ANALYSIS SHOWS 1-YEAR SURVIVAL RATE OF 63% FOR PATIENTS TAKING SORAFENIB FOR HCC RECURRENCE POST-LIVER TRANSPLANTATION

1-year survival rates of patients treated with sorafenib for HCC recurrence after LT in eight studies using a random-effects model (n=113)



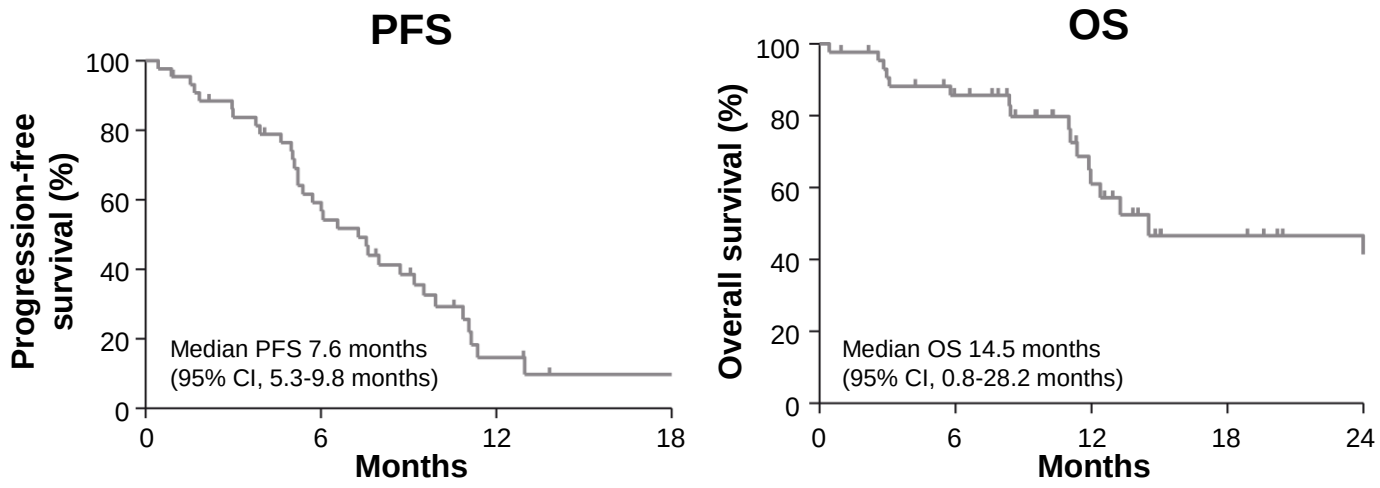
CI, confidence interval; HCC, hepatocellular carcinoma; LT, liver transplantation

Mancuso A, et al. Dig and Liv Dis. 2015;47:324-30

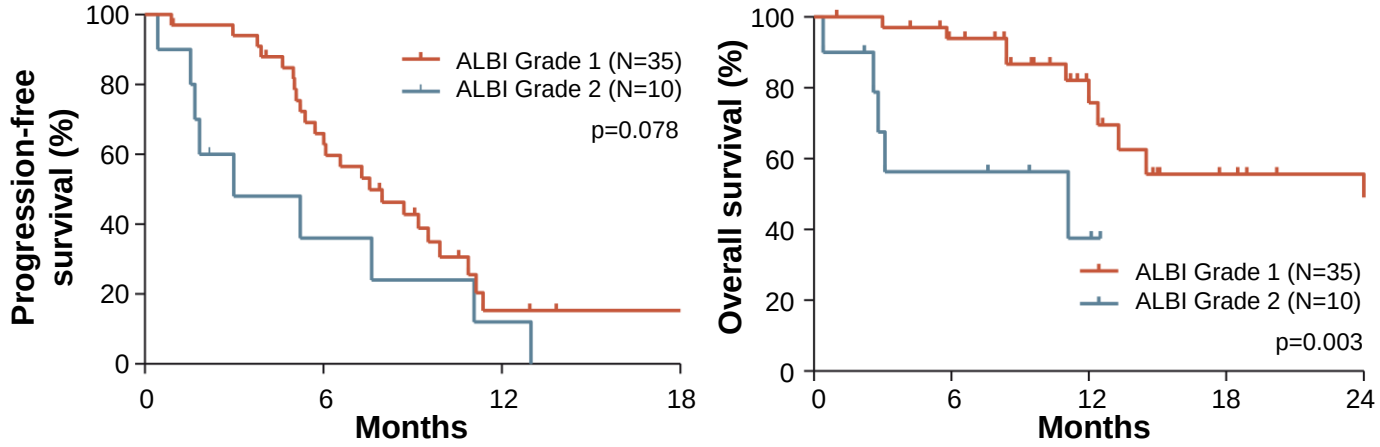
PATIENTS WITH LIVER TRANSPLANTATION

FEW DATA ON LENVATINIB IN PATIENTS WITH RECURRENT HCC

- 45 patients
  - 43 Child-Pugh A
    - 78% ALBI 1
    - 22% ALBI 2
- ORR: 20%
- Median PFS: 7.6 months
- Median OS: 14.5 months



According to ALBI score



ALBI, Albumin-Bilirubin; CI, confidence interval; HCC, hepatocellular carcinoma; PFS, progression free survival; ORR, objective response rate; OS, overall survival

Bang K, et al. Cancer Med. 2023;12(3):2572-9

BEFORE LIVER TRANSPLANTATION

- **The role of neoadjuvant treatment** including immunotherapy **is less clear**
- Immunotherapy pre liver transplantation may **facilitate down staging** of unresectable HCC bridging to liver transplantation eligibility
- However, higher risk of **donor graft rejection**
- Limited data in the literature[1]
  - 10 patients
  - 80% objective response rate
  - 100% disease control rate
  - Biopsy-proven acute rejection incidence: 30%
  - 2 patients died from rejection

HCC, hepatocellular carcinoma

1. Qiao Z-Y, et al. Front Immunol. 2021;12:653437

PATIENTS WITH AUTO-IMMUNE DISEASE (AID)

PATIENTS WITH AUTO-IMMUNE DISEASE
HAVE ROUTINELY BEEN EXCLUDED FROM CLINICAL TRIALS

- Patients with HCC may suffer from:
  - Hepatobiliary auto-immune diseases
    - Primary biliary cholangitis
    - Primary sclerosing cholangitis
    - Auto-immune hepatitis
  - Other auto-immune diseases
    - Rheumatoid arthritis
    - Type 1 diabetes
    - Psoriasis
    - Hypothyroidism
- Data on the safety of immunotherapy in individuals with pre-existing AID are limited and **restricted to case reports and retrospective cohorts**
  - 45 – 85 patients
  - Studies including a large variety of AIDs, which makes impossible to draw firm conclusions

AID, auto-immune disease; HCC, hepatocellular carcinoma

Pinter M, et al. Gut. 2021;70:204-14

PATIENTS WITH AUTO-IMMUNE DISEASE

IMMUNOTHERAPY CAN LEAD TO ADVERSE EFFECTS

In a multicenter retrospective cohort study[1] of patients with pre-existing autoimmune disease receiving ICI as cancer treatment (n=112) over a median follow up of 8 months:

- 71% of patients had a flare of a pre-existing autoimmune disease and/or another immune-related adverse effects related to ICI treatment
- 47% of patients had flares of pre-existing autoimmune disease
  - 30% had severe flares
- 42% of patients had other immune-related adverse effects
  - 40% had severe effects

AIDs with a potential high mortality on reactivation, such as neurological disorders or hepatobiliary disorders are underrepresented in such studies

AID, auto-immune disease; ICI, immune checkpoint inhibitor

Tison A, et al. Arthritis Rheumatol. 2019;71:2100-11

PATIENTS WITH AUTO-IMMUNE DISEASE

CONTRAINDICATION FOR IMMUNOTHERAPY

Recent recommendations suggest:

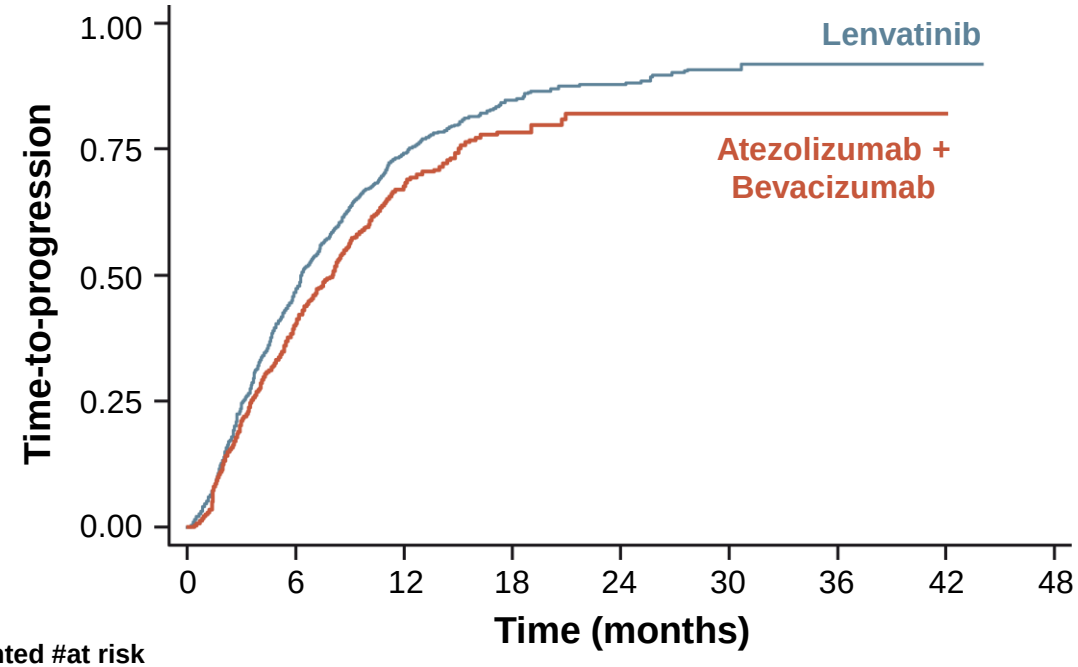
“Immunotherapy should be avoided when reactivation of autoimmune disease may be life-threatening, in those with neurological or neuromuscular disease or in those on high doses of immunosuppression”

Pinter M, et al. Gut 2021;70:204-14

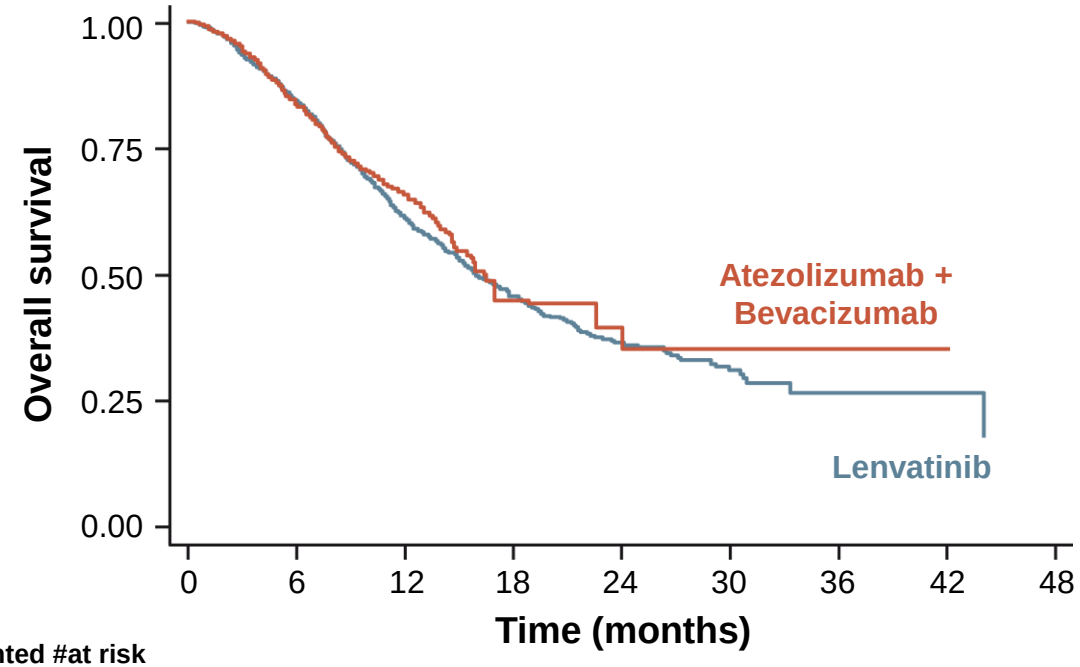
LENVATINIB VS ATEZOLIZUMAB + BEVACIZUMAB IN REAL LIFE

NO MEANINGFUL DIFFERENCE IN OVERALL SURVIVAL

- 1341 patients treated with lenvatinib
- 864 with atezolizumab + bevacizumab



Weighted #at risk									
Atezo + Bev	864	399	114	22	4	4	4	2	0
Lenvatinib	1343	582	196	64	33	11	1	1	0



Weighted #at risk									
Atezo + Bev	864	581	255	43	9	5	5	2	0
Lenvatinib	1343	918	476	220	110	36	5	4	2

atezo, atezolizumab; bev, bevacizumab

Casadei-Gardini A, et al. Eur J Cancer. 2023;180:9-20

PATIENTS WITH A SIGNIFICANT BLEEDING HISTORY

POLLING QUESTION

WHAT WOULD BE THE PREFERRED 1ST LINE TREATMENT FOR PATIENTS WITH A SIGNIFICANT BLEEDING HISTORY?

A. Durvalumab

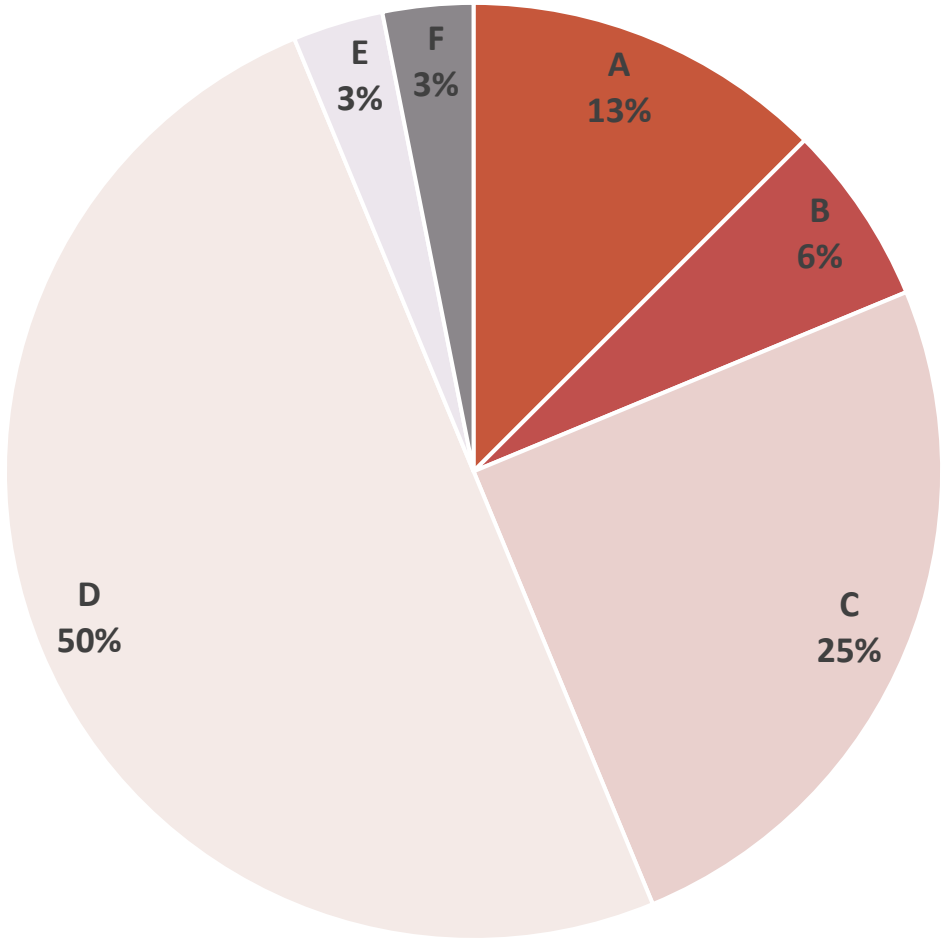
B. Lenvatinib

C. Sorafenib

D. **Durvalumab + tremelimumab** ☑

E. Atezolizumab + bevacizumab

F. I am not sure

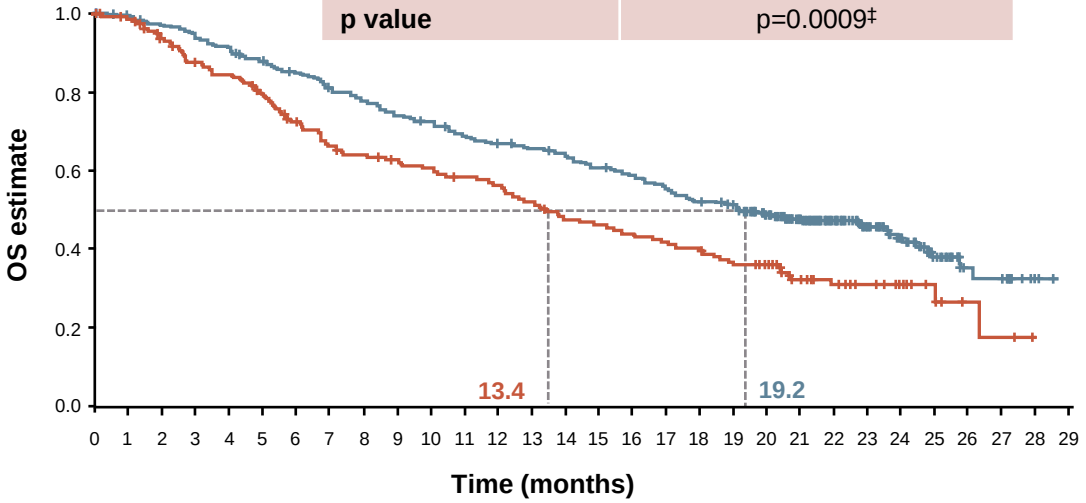


PATIENTS WITH A SIGNIFICANT BLEEDING HISTORY

NO LONGER A CONCERN

When patients are not good candidates for **atezolizumab + bevacizumab**[1]

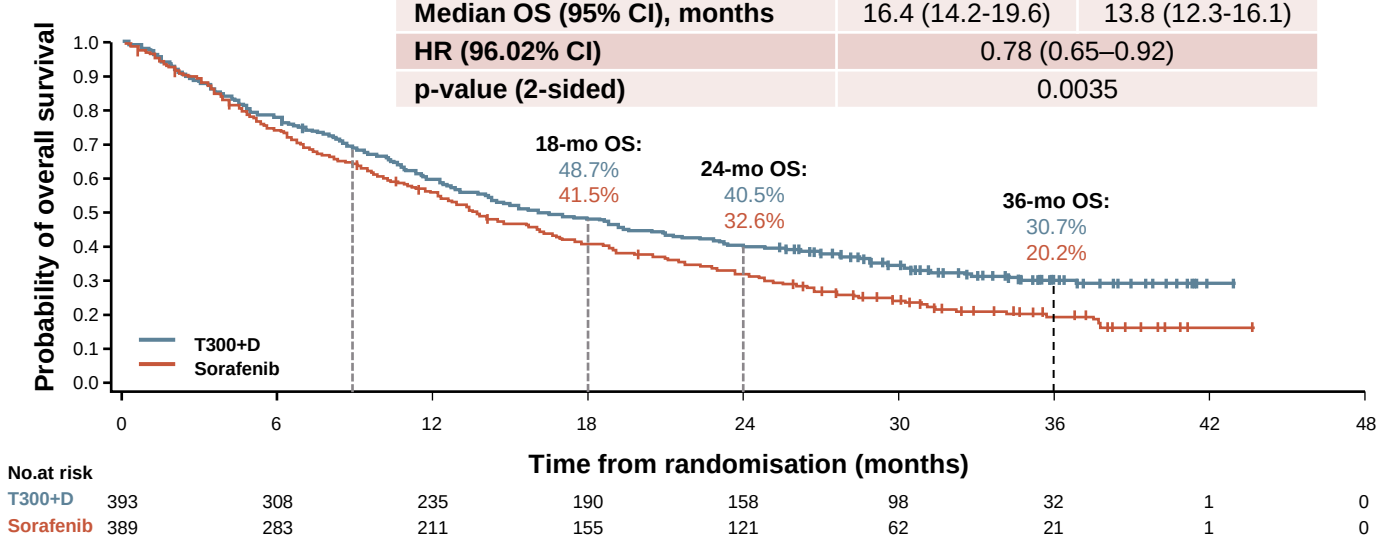
	Atezo + bev (N=336)	Sorafenib (N=165)
Median OS, months (95% CI)	**19.2** (17.0-23.7)	**13.4** (11.4-16.9)
Stratified* HR (95% CI)	0.66 (0.52-0.85)	
p value	p=0.0009‡	



*Stratification factors included are geographic region (Asia excluding Japan vs RoW), AFP level (<400ng/mL vs ≥400ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS;
‡p value for descriptive purposes only

When to consider patients for treatment with **durvalumab + tremelimumab**[2]

	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.

AFP, alpha fetoprotein; CI, confidence interval; EHS, extrahepatic spread; HR, hazard ratio; IxRS, interactive voice/web response system; MVI, microvascular invasion; OS, overall survival; Q4W, every 4 weeks; RoW, rest of world; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W

1. Cheng AL, et al. J Hepatol. 2022;76(4):862-73 ; 2. Abou-Alfa GK, et al. NEJM Evid. 2022;1.8

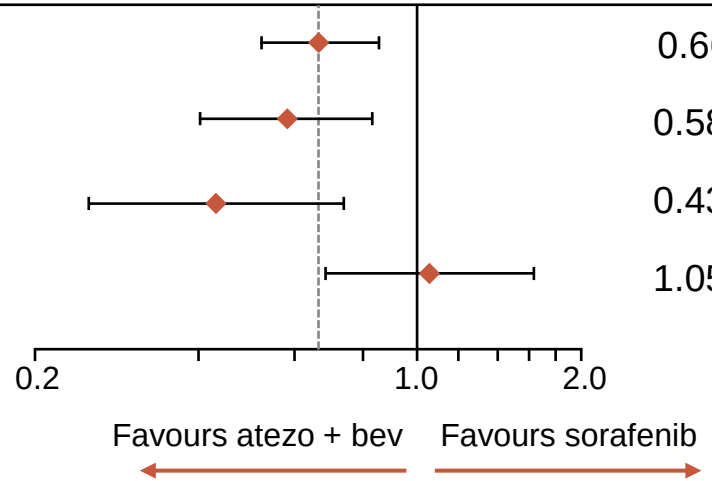
ETIOLOGY OF THE LIVER DISEASE

THE IMPACT OF UNDERLYING LIVER DISEASE ON TREATMENT EFFICACY

VIRAL VS. NON-VIRAL ETIOLOGY

The atezolizumab + bevacizumab combination seems to be less effective in non-viral HCC

Characteristic (n)	Atezo + Bev mOS, mo	Sorafenib mOS, mo	HR (95% CI)
All patients (501)	19.2	13.4	0.66 (0.52-0.85)
Hepatitis B virus HCC (240)	19.0	12.4	0.58 (0.40, 0.83)
Hepatitis C virus HCC (108)	24.6	12.6	0.43 (0.25, 0.73)
Non-viral HCC (153)	17.0	18.1	1.05 (0.68, 1.63)



Limitations :
Small sample size
Study not powered for subgroup analysis

Clinical cut-off date: 31 August 2020; median follow-up: 15.6 months
**HRs are from unstratified analyses*

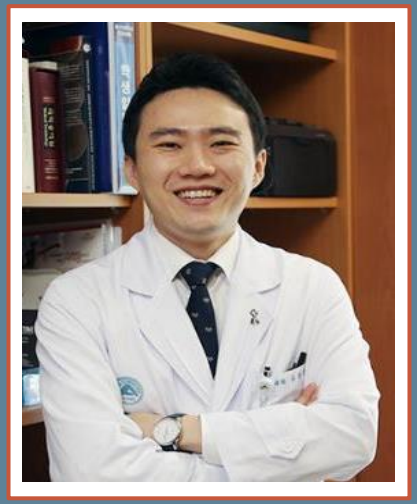
atezo, atezolizumab; bev, bevacizumab; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; mo, months; mOS, median OS; mPFS, median PFS; OS, overall survival; PFS, progression-free survival

Cheng AL, et al. J Hepatol. 2022;76(4):862-73

DISCUSSION

OVERVIEW OF 2ND LINE TREATMENT OPTIONS IN ADVANCED HCC

HOW TO ACHIEVE OPTIMAL SEQUENCING?



Assoc. Prof. Changhoon Yoo

HCC, hepatocellular carcinoma

POLLING QUESTION

WHAT ARE RECOMMENDED 2ND LINE OPTIONS POST SORAFENIB ACCORDING TO THE BCLC GUIDELINE?

A. Atezolizumab + bevacizumab

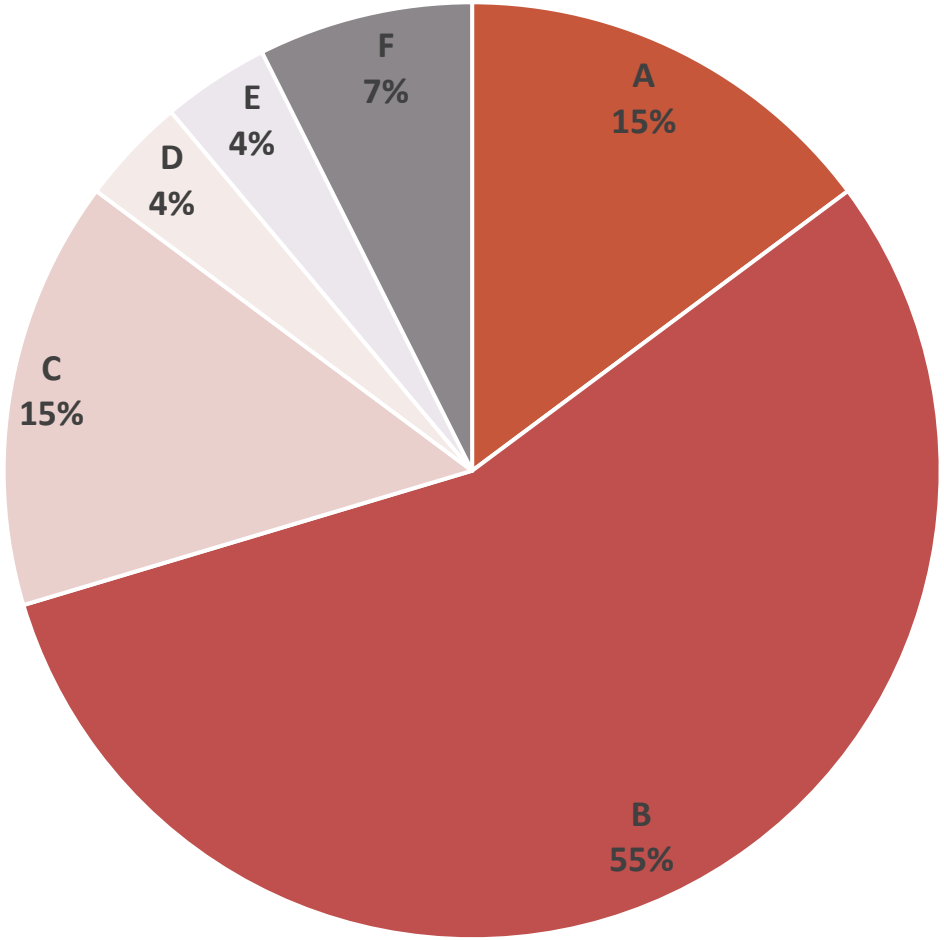
B. Regorafenib, cabozantinib, and ramucirumab ☑

C. Durvalumab + tremelimumab

D. Durvalumab

E. Lenvatinib

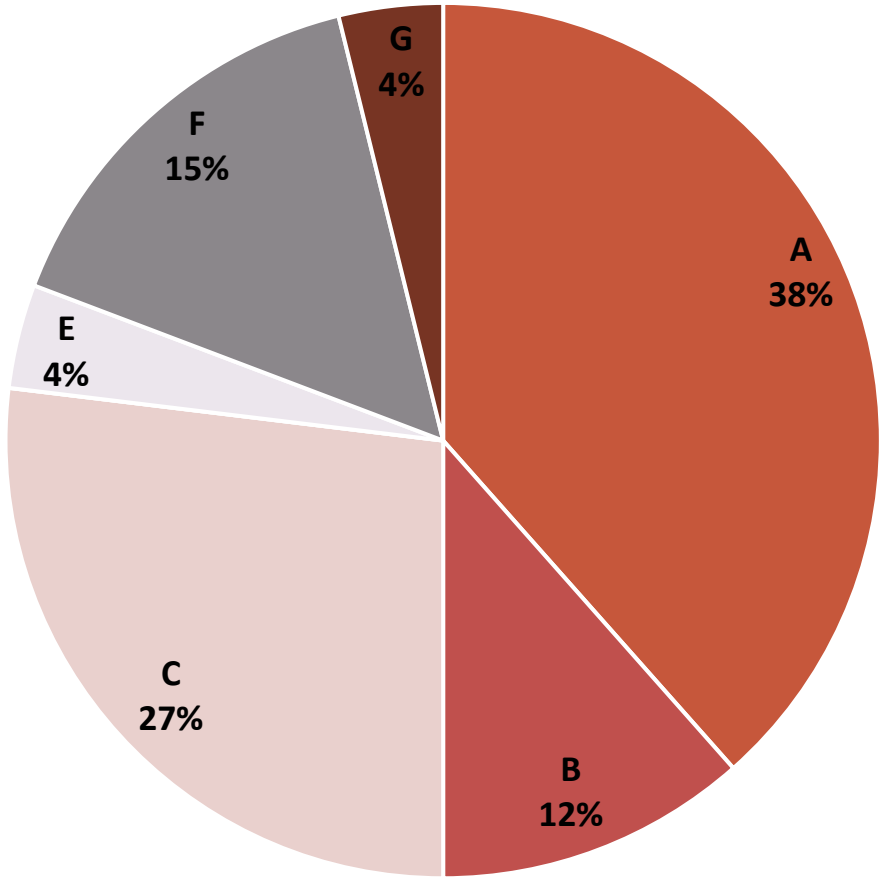
F. I am not sure



POLLING QUESTION

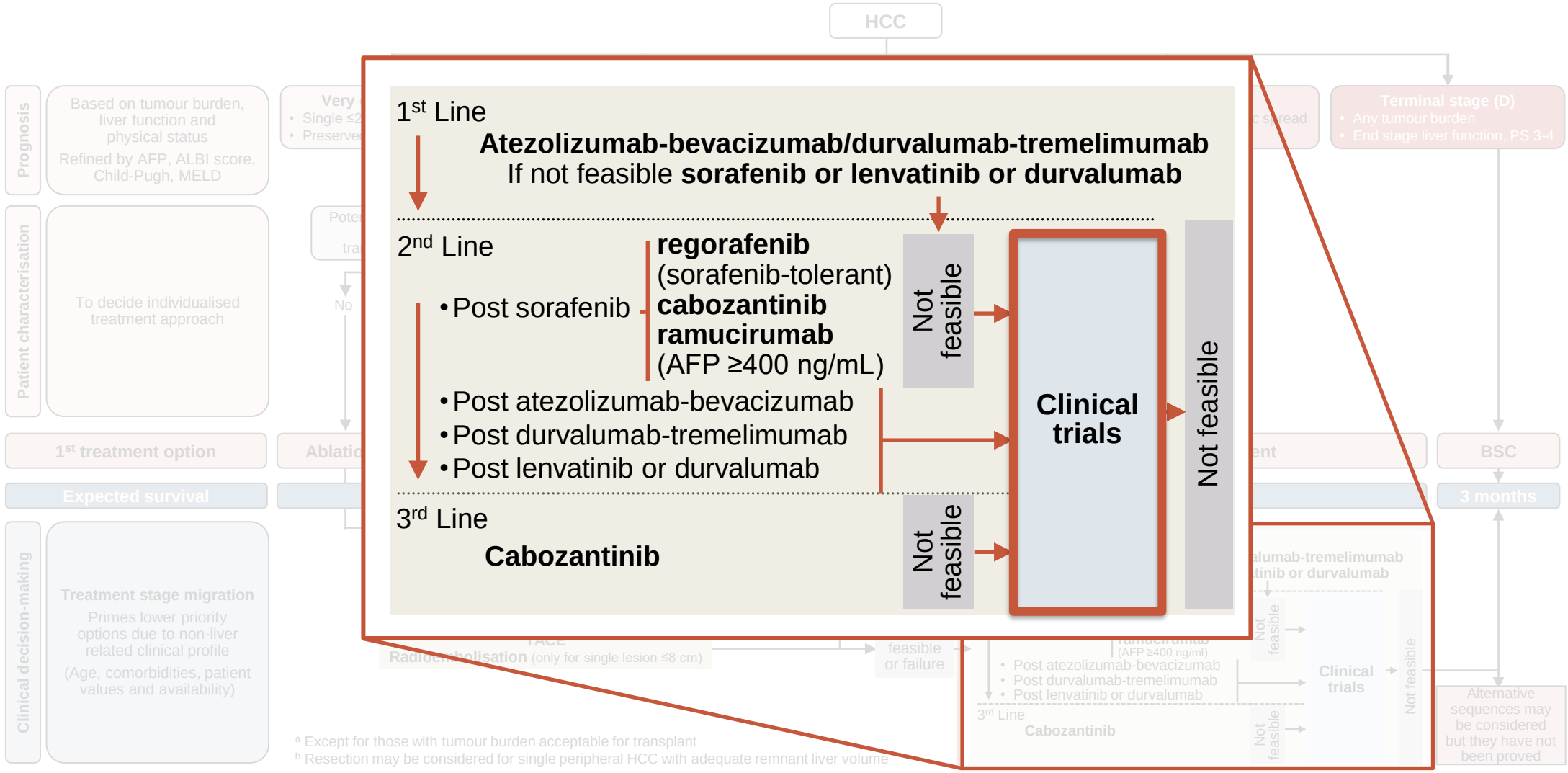
HOW WOULD YOU TREAT AN ADVANCED HCC PATIENT WHO PROGRESSED ON IO-BASED COMBINATION TREATMENTS?

A. **Clinical trial** ☑
B. Sorafenib
C. Lenvatinib
D. Regorafenib
E. Cabozantinib
F. Atezolizumab + bevacizumab (if not used previously)
G. Durvalumab + tremelimumab (if not used previously)



IO, immunotherapy

THE BCLC GUIDELINE RECOMMENDS CLINICAL TRIALS AFTER PROGRESSION
IN DAILY PRACTICE, MOST PHYSICIANS NEED TO CHOOSE ONE OF APPROVED AGENTS



AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model of end-stage liver disease; PS, performance status; TACE, transarterial chemoembolisation

Reig M, et al. J Hepatol. 2022;76:681-93

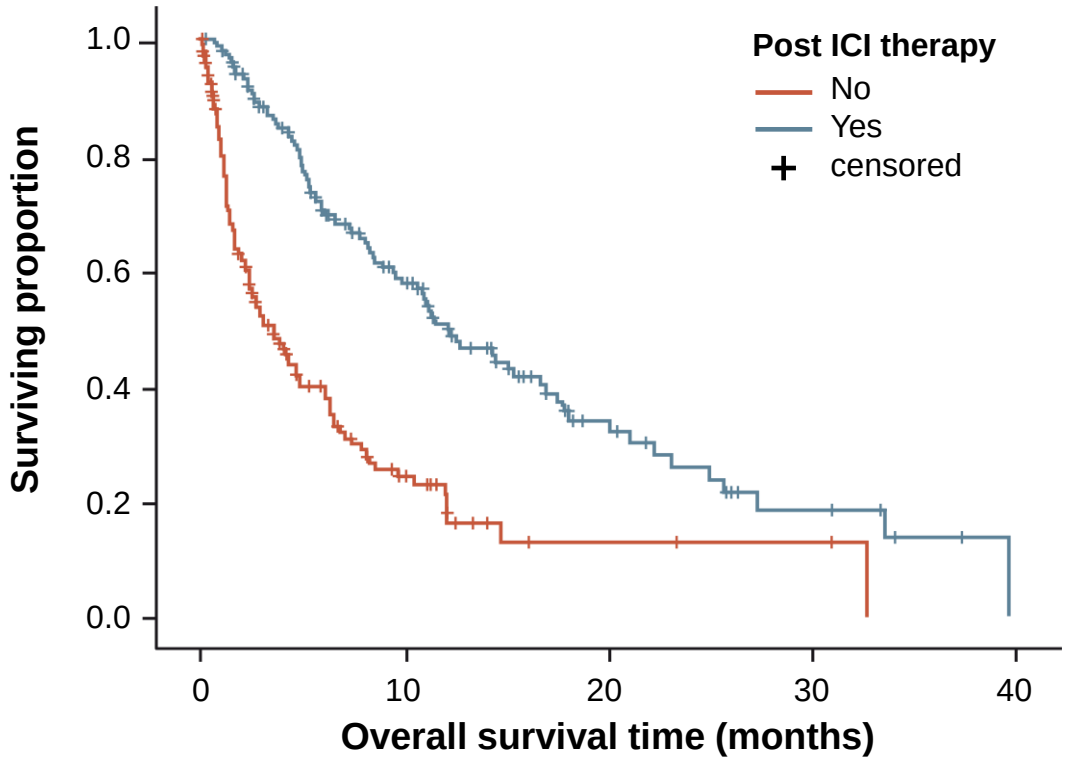
RETROSPECTIVE ANALYSIS OF HCC PATIENTS TREATED WITH IMMUNOTHERAPY

POST-IMMUNOTHERAPY TREATMENT WAS ASSOCIATED WITH PROLONGED OS

POST-TKI TREATMENT SUGGESTED PRESERVED EFFICACY IN TERMS OF OS

420 patients

From USA, Europe and Asia



Details of subsequent therapies received during survival follow-up following immunotherapy (N=165)

Number of subsequent lines received	N (%)
1	115 (67.9)
2	32 (19.4)
>3	13 (7.9)
Treatments received	
TKI sorafenib lenvatinib regorafenib cabozantinib ramucirumab	109 (66.1) 49 (44.9) 31 (28.4) 33 (30.3) 13 (11.9) 6 (5.5)
Radiotherapy	28 (16.9)
Immunotherapy	21 (12.7)
Transarterial chemoembolization/Y90	19 (11.5)
Chemotherapy	9 (5.5)
Surgery	6 (3.6)
Radiofrequency/microwave ablation	4 (2.4)
Other	23 (13.9)

HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; OS, overall survival; TKI, tyrosine kinase inhibitor; Y90, Yttrium-90

Sharma R, et al. Hepatol Commun. 2022;6(7):1776-1785

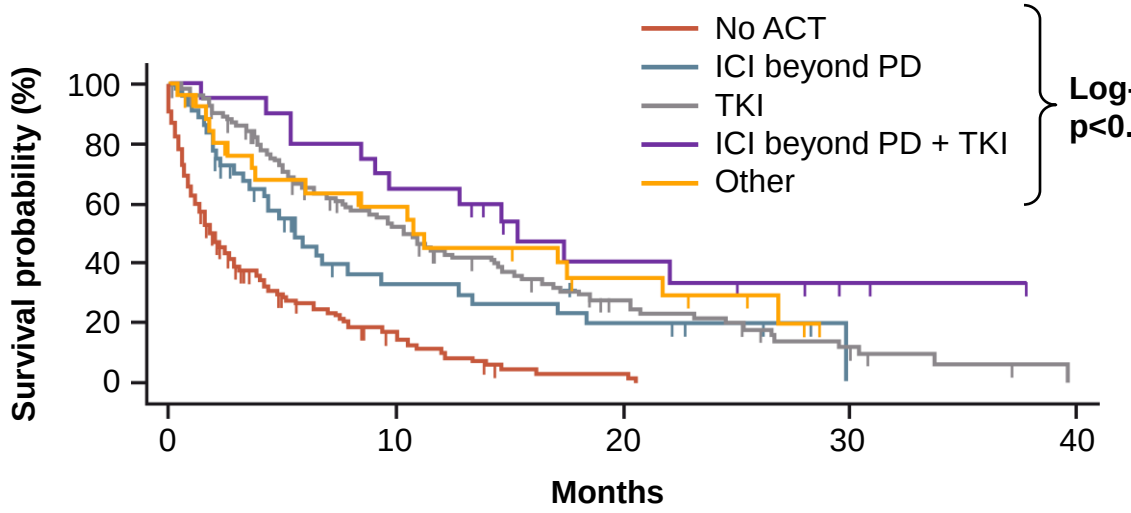
PATTERNS OF PROGRESSION AFTER IMMUNOTHERAPY

CONTINUATION OF IO AND SWITCHING TO TKIs WERE BOTH ASSOCIATED WITH IMPROVED PPS

The median OS of these 271 patients from the initial diagnosis of HCC was 32.7 months (IQR 17.1–56.8)

- No post-progression anticancer therapy
  - 1.9 months (95% CI: 1.3-2.7)
- ICIs beyond PD only
  - 5.6 months (95% CI: 3.5-9.4)
- Post-PD tyrosine kinase inhibitors (TKIs)
  - 10.4 months (95% CI: 7.7-14.4)
- ICIs beyond PD followed by TKIs
  - 15.3 months (95% CI: 8.5-22.0)
- Other post-PD anticancer therapies
  - 10.8 months (95% CI: 3.7-21.7)

Post-progression survival in HCC patients treated with ICI



No. at risk					
No ACT	165	16	2	0	0
ICI beyond PD	44	10	6	0	0
TKI	108	47	19	5	0
ICI beyond PD + TKI	20	13	6	2	0
Other	27	13	6	0	0

ACT, anticancer therapy; CI, confidence interval; ICI, immune checkpoint inhibitor; IO, immunotherapy; PD, progressive disease; PPS, post-progression survival

Talbot T, et al. Liver Int. 2023;43:695-707

OPTIMAL SEQUENCING AFTER PROGRESSION ON IO

POLLING QUESTION

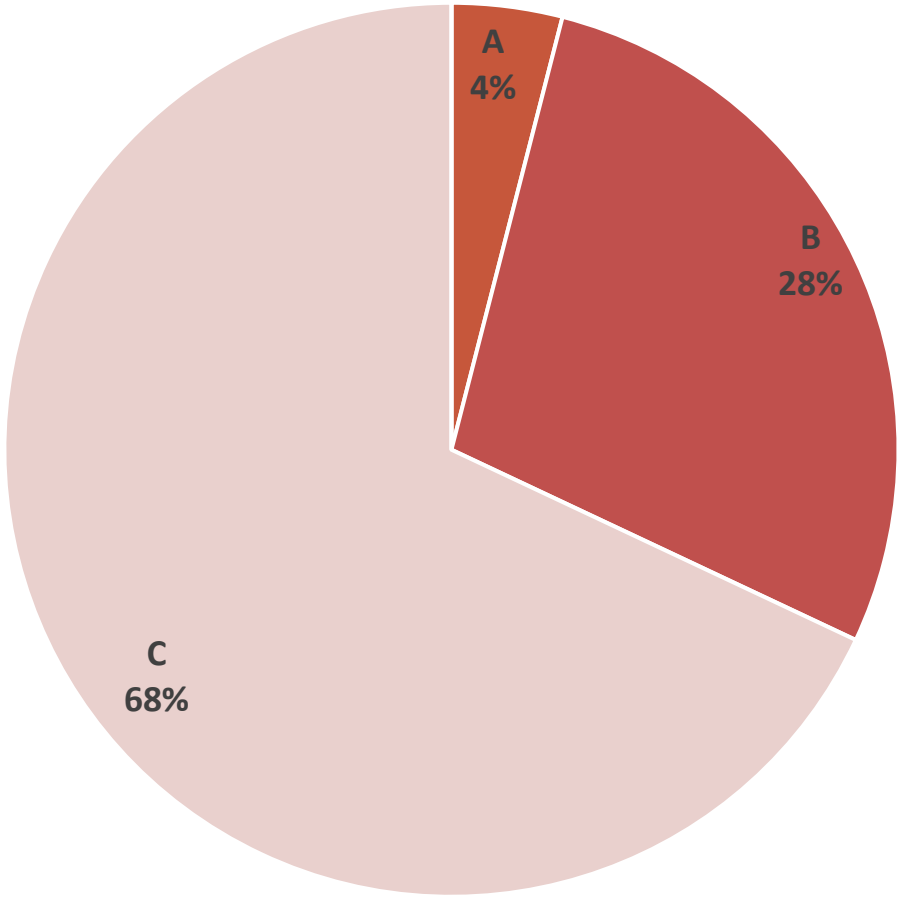
IS THERE ANY OPTIMAL SEQUENCING AFTER PROGRESSING ON IO?

A. Yes

B. No

C. Not yet ☑

D. I am not sure



IS THERE ANY OPTIMAL SEQUENCING AFTER PROGRESSION ON IO?

NOT ENOUGH EVIDENCE EITHER FROM PROSPECTIVE OR RETROSPECTIVE STUDIES

Is efficacy shown in prior registration phase 3 studies reproduced after progression on IO?

Prior 1st line	Lenvatinib	Sorafenib	
Prior ≥ 2nd line	Regorafenib	Cabozantinib	Ramucirumab
	Ipilimumab + nivolumab		

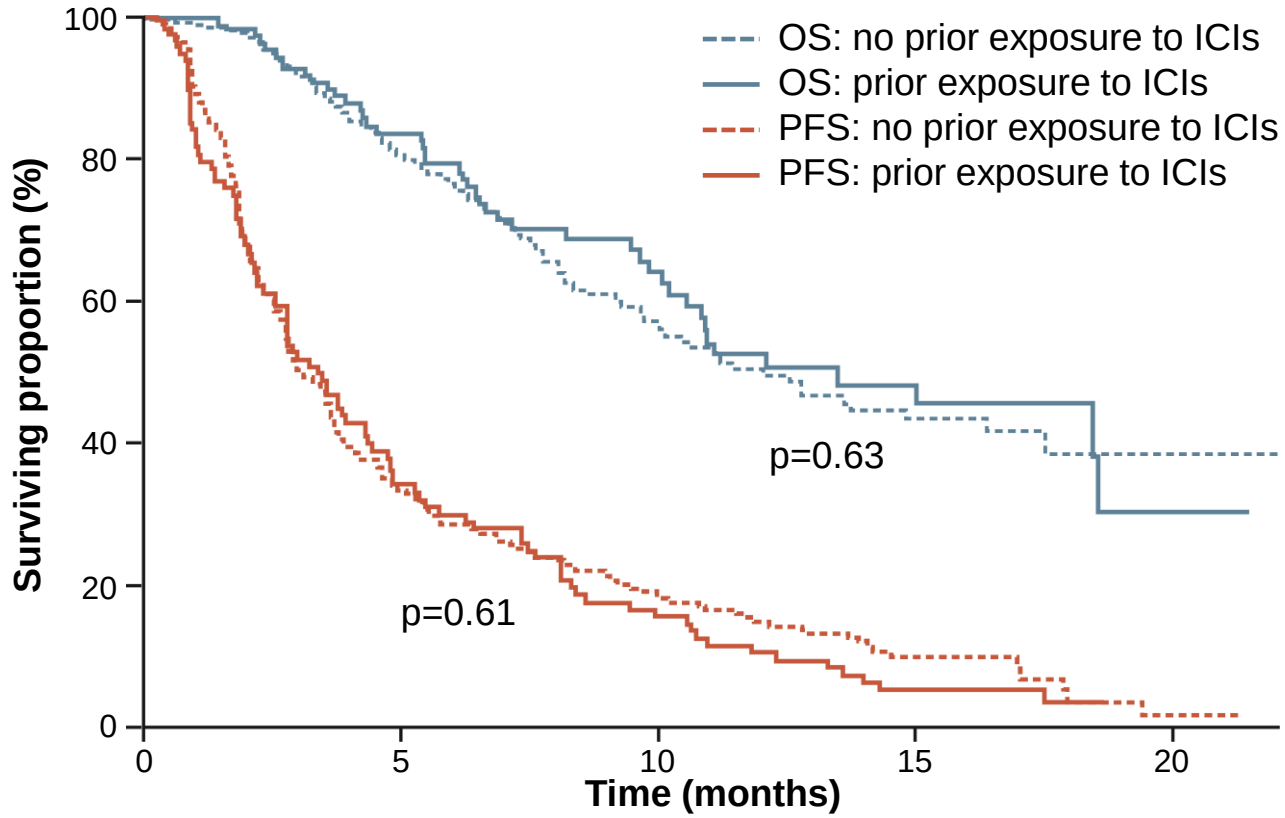
IO, immunotherapy

SUBSEQUENT MKI AFTER ICI: REGORAFENIB

NO SIGNIFICANT DIFFERENCE IN PFS OR OS ACCORDING TO THE TREATMENT LINES, AND PRIOR EXPOSURE TO IMMUNE CHECKPOINT INHIBITORS

KCSG (Korean Cancer Study Group) multicenter retrospective study

440 patients from nine Korean centers



The real-life clinical outcomes of regorafenib for patients who progressed on prior systemic therapy including ICIs were consistent with the phase 3 trial results

ICI, immune checkpoint inhibitor; MKI, multi-targeted kinase inhibitor; OS, overall survival; PFS, progression free survival

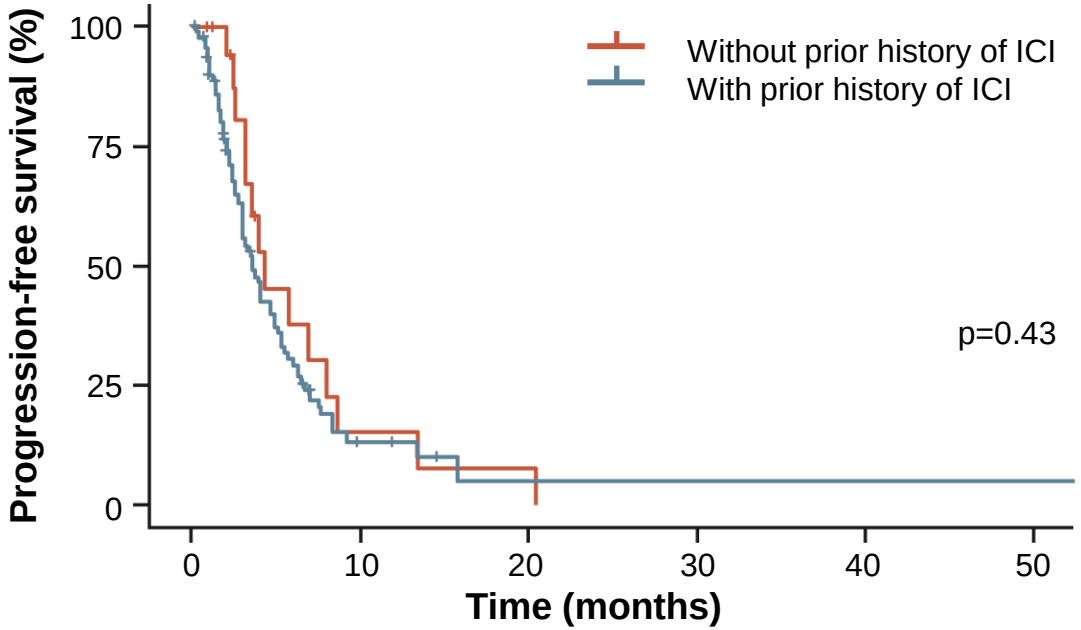
Yoo C, et al. Liver Int. 2020;40(9):2263-71.

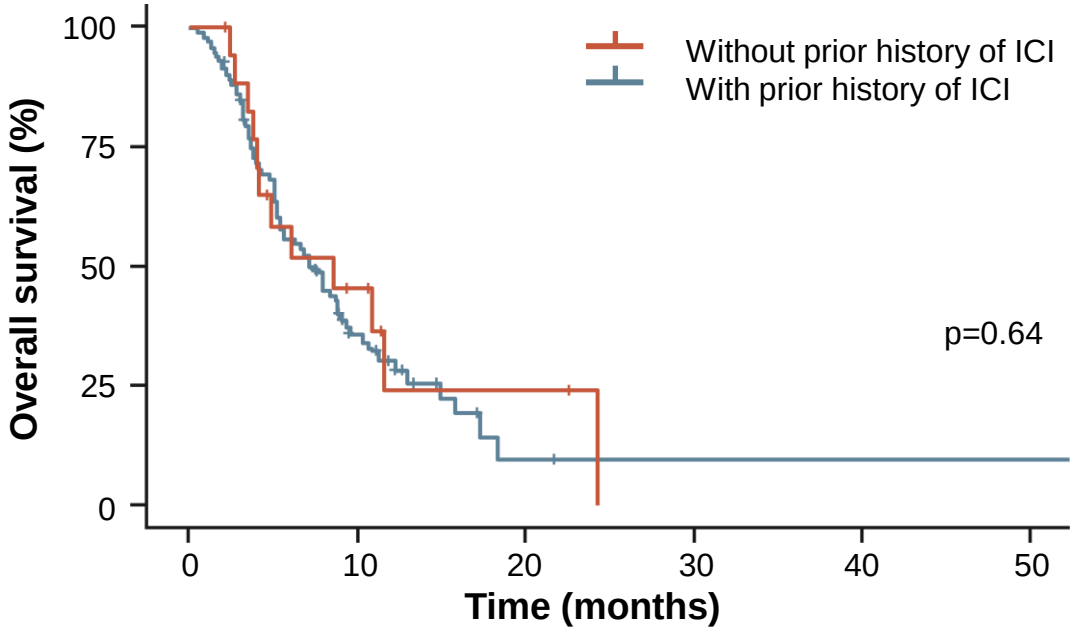
SUBSEQUENT MKI AFTER ICI: CABOZANTINIB

NO DIFFERENCE IN TERMS OF PFS AND OS WITH CABOZANTINIB ACCORDING TO THE PRIOR EXPOSURE TO IMMUNE CHECKPOINT INHIBITORS

Korean multicenter retrospective study

- Multicenter (n=3) study for 110 patients: 82% of patients received cabozantinib as ≥4th line therapy
- 85% of patients received immune checkpoint inhibitors previously





Limitations of prior data for post-IO treatment:
Mostly ICI monotherapy, not atezolizumab + bevacizumab or durvalumab + tremelimumab

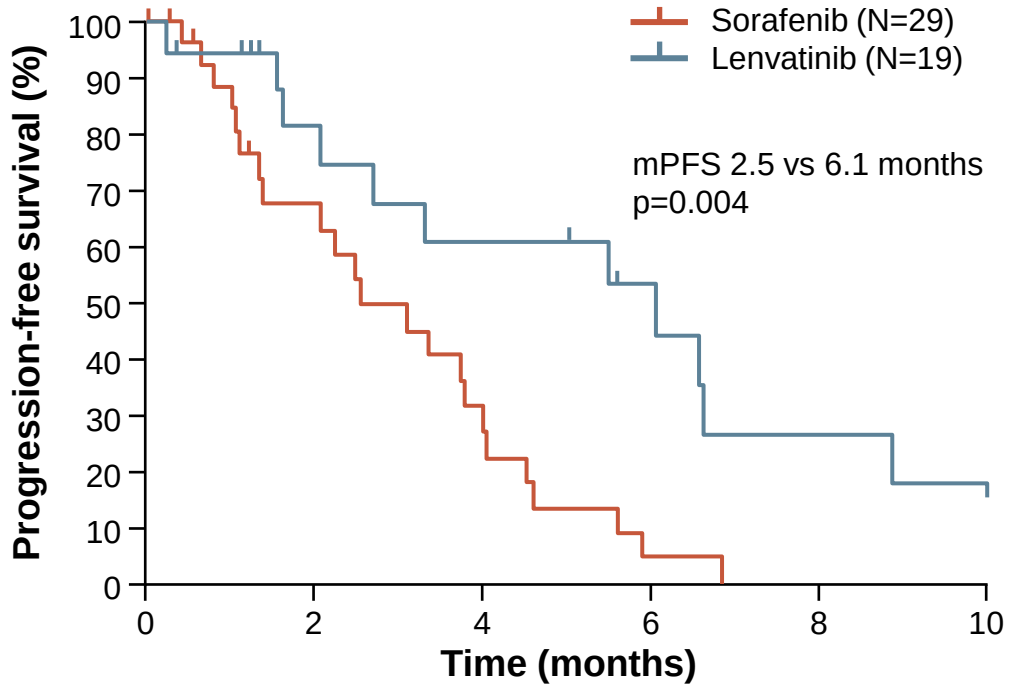
ICI, immune checkpoint inhibitor; IO, immunotherapy; MKI, multi-targeted kinase inhibitor; OS, overall survival; PFS, progression free survival

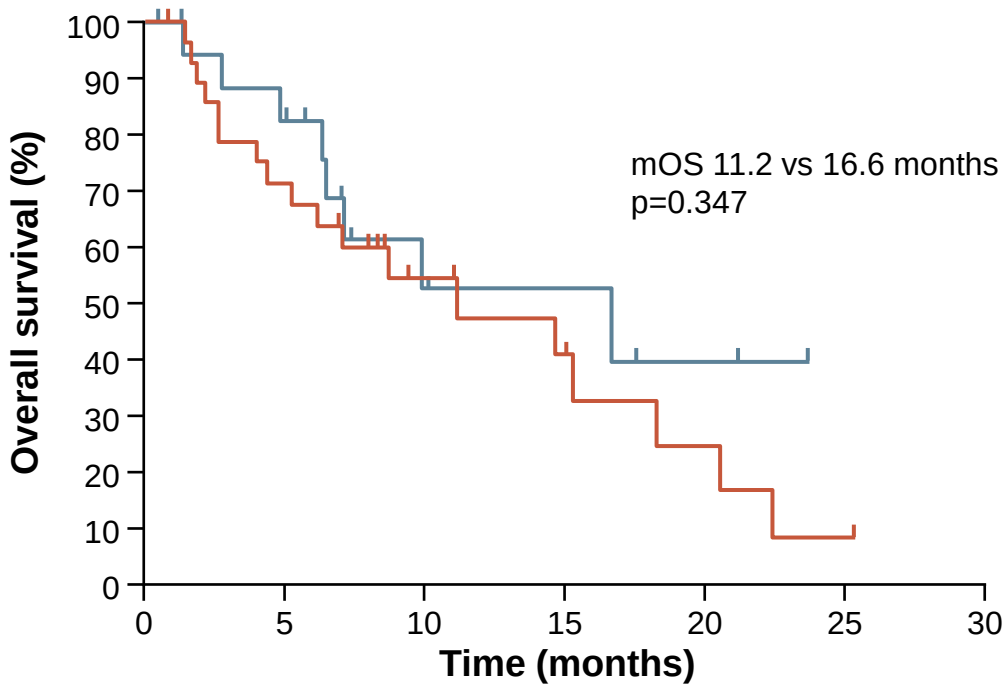
Bang YH, et al. Ther Adv Med Oncol. 2022;14:1-12

CLINICAL OUTCOMES WITH TKIs AFTER PROGRESSION ON ATEZOLIZUMAB + BEVACIZUMAB

SORAFENIB VS LENVATINIB IN RETROSPECTIVE STUDY

49 pts from Korea, HK and Singapore who received TKI after progression on 1st line atezolizumab + bevacizumab*





*One patient received cabozantinib – data not shown

Lenvatinib showed better PFS than sorafenib
No statistical difference in OS between lenvatinib and sorafenib

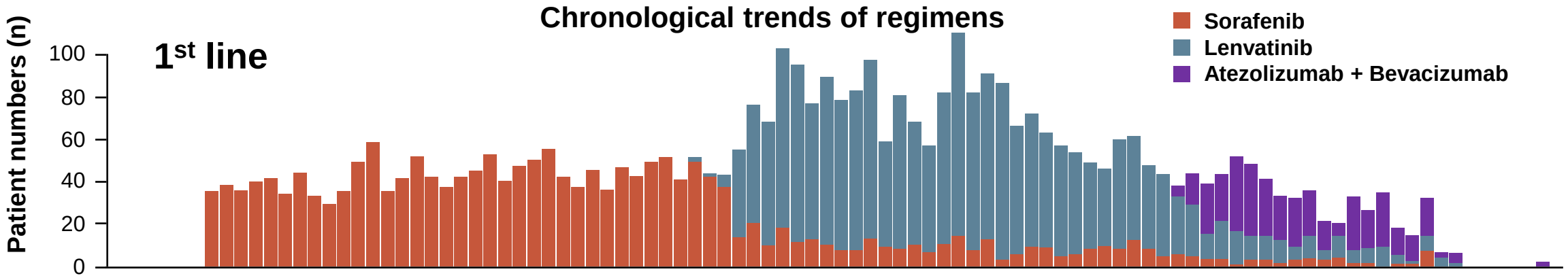
Limitation: Small sample size

atezo, atezolizumab; bev, bevacizumab; HK, Hong Kong; mOS, median OS; mPFS, median PFS; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitor

Yoo C, et al. Liver Cancer. 2021;10(2):107-114

JAPANESE REAL-WORLD REGISTRY STUDY OF SYSTEMIC TREATMENT OF HCC

DEMONSTRATING THE EFFICACY OF VARIOUS TREATMENT SEQUENCES



Treatment efficacy of 2nd line therapy

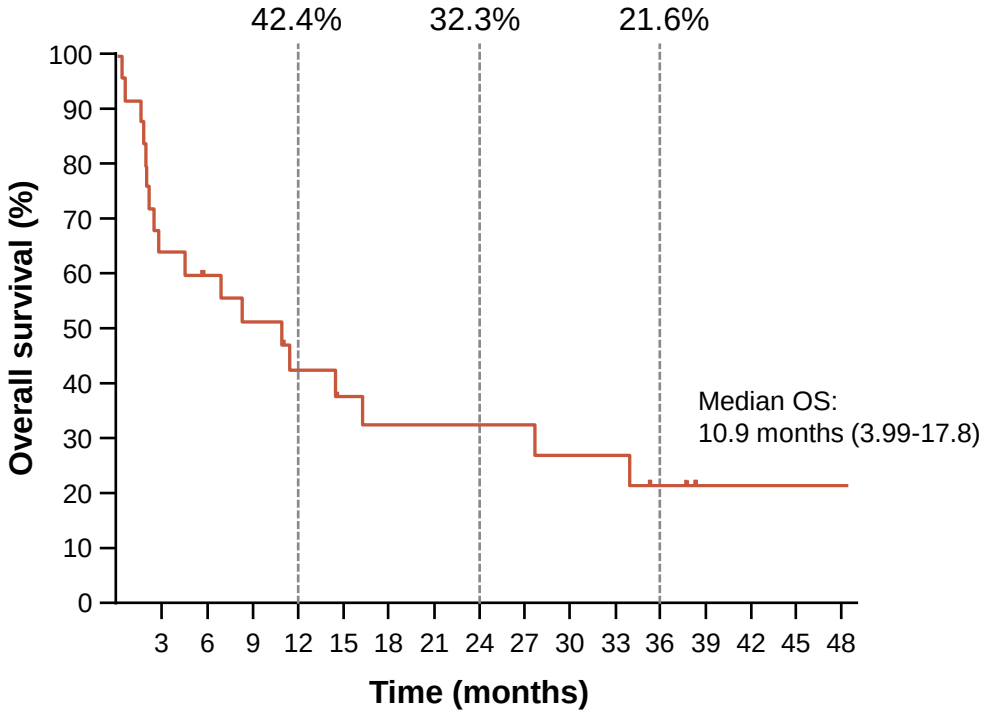
1st line	2nd line	N	RR/DCR (%/%)	Tx duration (days)
Atezolizumab + Bevacizumab	Ongoing	148		
	Sorafenib	8	0/40 (n=5)	25 (11-ND)
	Regorafenib	0		
	Lenvatinib	72	14.9/80.9 (n=47)	87 (64-141)
	Ramucirumab	6	0/100 (n=2)	28 (28-ND)
	Cabozantinib	3	0/50 (n=2)	18 (9-ND)

DCR, disease control rate; HCC, hepatocellular carcinoma; ND, not determined; RR, response rate; Tx, treatment

Asaoka Y, J Clin Oncol. 2023. 41(no. 4_suppl):510-510 (presented at ASCO; poster #510)

ANY ROLE OF ICI RECHALLENGE (ANTI-CTLA-4) IN POST-IO SETTING?

IPILIMUMAB + NIVOLUMAB OR PEMBROLIZUMAB AFTER PROGRESSION ON PRIMARILY NIVOLUMAB OR PEMBROLIZUMAB MONOTHERAPY*



- 25 patients were included
- Objective response rate of patients with primary resistance to prior ICI: 16.7%

?

Would there be a potential role of durvalumab + tremelimumab or ipilimumab + nivolumab after progression on atezolizumab + bevacizumab?

Ipilimumab + nivolumab or pembrolizumab can achieve durable antitumor activity and encouraging survival outcomes in HCC patients who had prior treatment with ICIs

Limitation: Small retrospective study

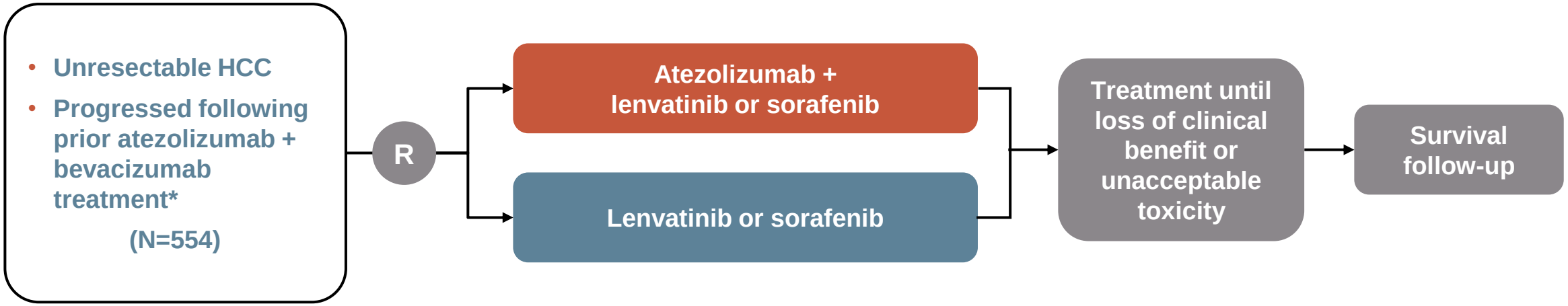
*4% progressed on atezolizumab + bevacizumab

CTLA-4, cytotoxic T-lymphocyte associated protein-4; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; IO, immunotherapy; OS, overall survival

Wong JSL, et al. J Immunother Cancer. 2021;9(2):e001945

IMbrave251: 2nd line atezolizumab + TKI vs TKI alone after progression on atezolizumab + bevacizumab

Site selects the choice of TKI: lenvatinib or sorafenib



Efficacy objectives
- **Primary:** OS
- **Secondary:** PFS,* ORR,* DoR,* TTP,* TTD in PROs

Safety objective
- Percentage of patients with AEs

Exploratory
- Number of patients with anti-drug antibodies to atezolizumab
- Serum concentration of atezolizumab

*INV-assessed per RECIST v1.1

AE, adverse event; AFP, alpha fetoprotein; ALBI, albumin-bilirubin; DoR, duration of response; HBV/HCV, hepatitis B/C virus; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression free survival; ORR, objective response rate; PRO, patient-reported outcome; TKI, tyrosine kinase inhibitor; TTD, time to deterioration; TTP, time to progression

ClinicalTrials.gov.Identifier: NCT04770896 https://clinicaltrials.gov/ct2/show/NCT04770896 accessed April 2023

CONCLUSION

OVERVIEW OF 2ND LINE TREATMENT OPTIONS IN ADVANCED HCC – HOW TO ACHIEVE OPTIMAL SEQUENCING?

- There is **lack of solid evidence** for optimal second-line regimens after progression on new standard 1st line IO-based combination therapy
- **Previously approved drugs as 1st line or subsequent-line therapy** may be used for these patients, if there are no adequate clinical trials
- Multiple small retrospective studies suggest that the **efficacy outcomes of post-IO TKIs are comparable** to those in registration studies
  - Multiple prospective studies are ongoing for regorafenib, cabozantinib, and lenvatinib

HCC, hepatocellular carcinoma; IO, immunotherapy; TKI, tyrosine kinase inhibitor

DISCUSSION

KEY CLINICAL TAKEAWAYS

- A substantial part of the advanced HCC patient population **is not eligible for IO 1st line**, such as:
  - Post-liver transplant patients with recurrent HCC
  - Most patients with an active autoimmune disease
- **TKIs**, such as lenvatinib and sorafenib, **are recommended treatments** for these patient groups

- **Switching to 2nd line** after IO 1st line should be considered in case of **toxicity** or **disease progression**
  - Measuring disease progression can be challenging, as there are several methods with different evaluation criteria
  - mRECIST criteria have a powerful ability to discriminate between responders and non-responders

- **Multiple 2nd line treatment** options have been approved in advanced HCC patients
  - There is **lack of solid evidence** for optimal 2nd line regimens after progression on new standard 1st line IO-based combination therapy

HCC, hepatocellular carcinoma; IO, immunotherapy; mRECIST, modified Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor

ANY QUESTIONS?
PANEL DISCUSSION

FUTURE PERSPECTIVES

- As IO-based combination regimens are globally established as 1st line treatments, there is a need to **study optimal sequencing after progression** on these regimens
  - Multiple prospective trials and registry studies are ongoing

- **Novel methods for response evaluation** such as circulating tumoral DNA could facilitate treatment decision-making in the future

- **The role of liver transplantation after IO** needs further studies

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