COR2ED

THE HEART OF MEDICAL EDUCATION

THE USE OF IMMUNOTHERAPY IN HCC

MICRO LEARNING MODULE ONE:

EFFICACY AND SAFETY

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DEVELOPED BY HCC CONNECT

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EDUCATIONAL OBJECTIVES

Upon completion of this micro learning you will:

1. Recognise the **efficacy of IO and IO combinations**
   - Understand the survival curve when assessing IO treatment
   - Know the place of IO and IO combinations in the treatment landscape for patients with HCC

2. Recognise the **immune-related adverse events (irAEs)**, and potentially additive or synergistic toxicities associated **with IO combinations**
   - Know how to early identify and manage these AEs

3. Be able to implement **IO treatments** for patients with HCC **in clinical practice**

HCC, hepatocellular carcinoma; IO, immunotherapy

CLINICAL TAKEAWAYS

- IO, and in particular IO combinations, are **effective treatments** for patients with advanced HCC
- Survival analysis for IO treatment shifts from median overall survival (OS) to **landmark analysis**
- IO and IO combinations may result in inflammatory side effects, known as **irAEs**. Most of these AEs can be treated with **steroids**

HCC, hepatocellular carcinoma; IO, immunotherapy; irAE, immune-related adverse event

1ST & 2ND LINE SYSTEMIC TREATMENT OPTIONS FOR PATIENTS WITH HCC

TWO TYPES OF SYSTEMIC TREATMENT OPTIONS FOR PATIENTS WITH HCC

IO

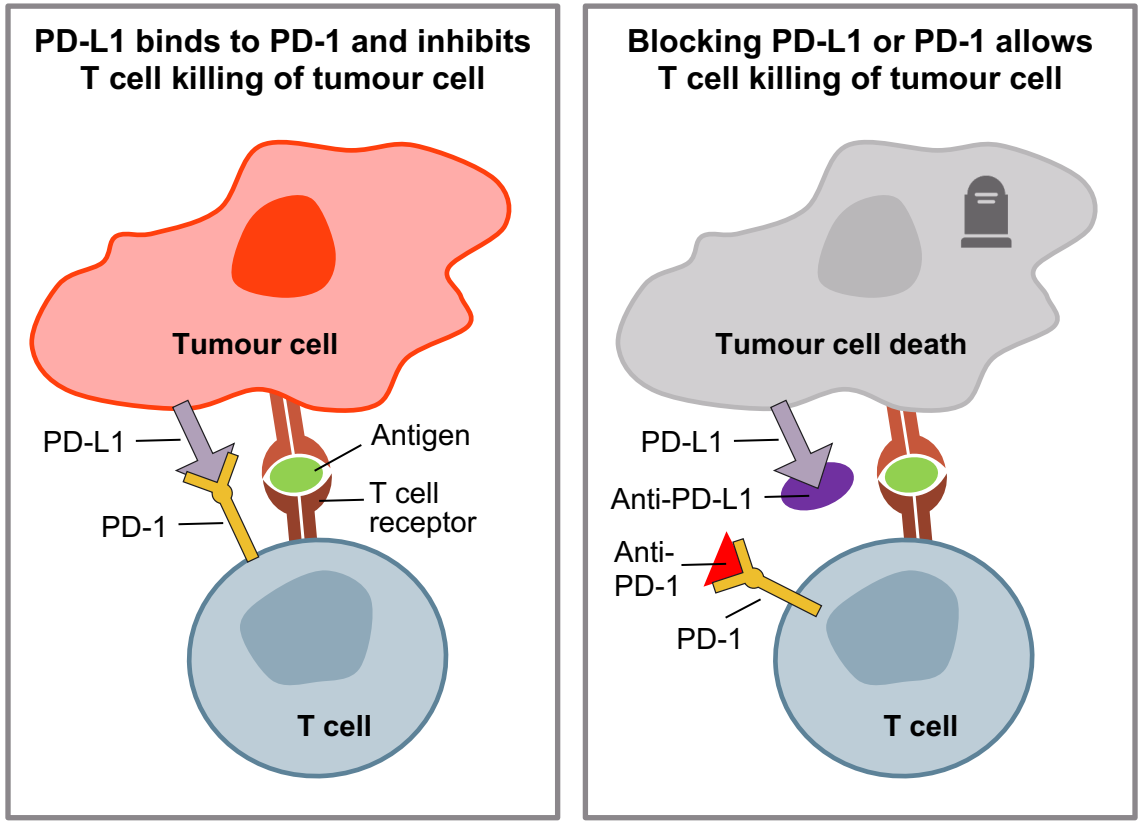


Figure adapted from Terese Winslow LLC[1]

TYROSINE KINASE INHIBITORS (TKIs)

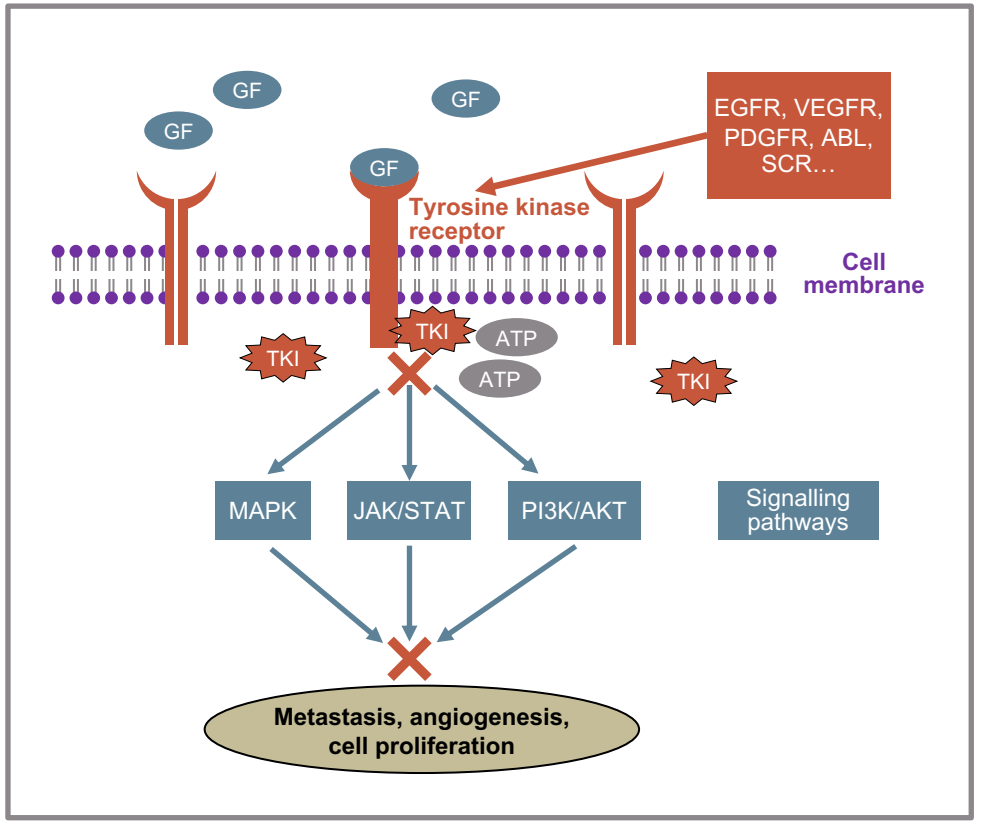
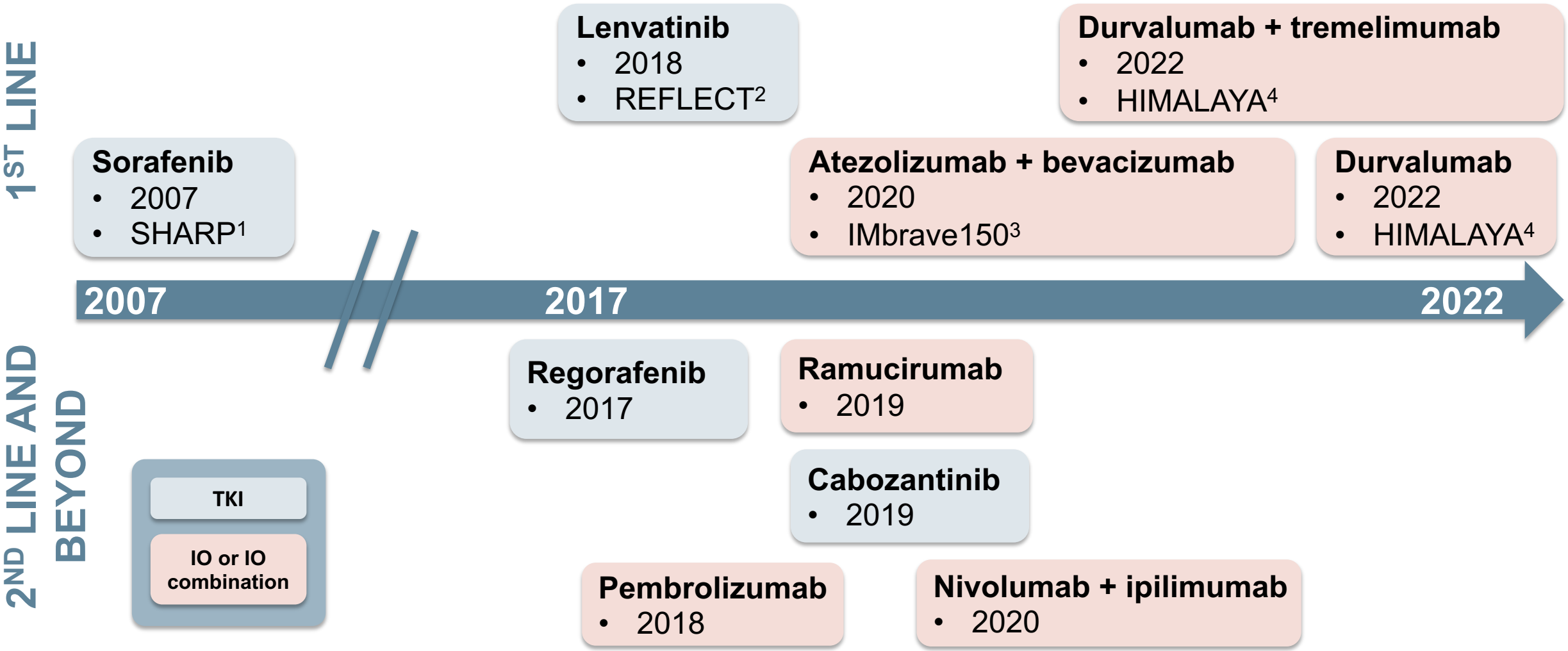


Figure adapted from Gabora K, et al.[2]

ABL, Abelson tyrosine kinase family; AKT, protein kinase B; ATP, adenosine triphosphate; EGFR, endothelial growth factor receptor; GF, growth factor; JAK, Janus kinase protein; MAPK, mitogen-activated protein kinase; PD-1, programmed death 1; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide-3-kinase; SCR, SCR tyrosine kinase family; STAT, signal transducer and activation of transcription protein; VEGFR, vascular endothelial growth factor receptor

1. Terese Winslow LLC. 2015. Available from: https://www.teresewinslow.com/. Accessed March 2023; 2. Gabora K, et al. Drug Metab Rev. 2019;51:562-9

1ST AND 2ND LINE SYSTEMIC TREATMENT OPTIONS



IO, immunotherapy; TKI, tyrosine kinase inhibitor

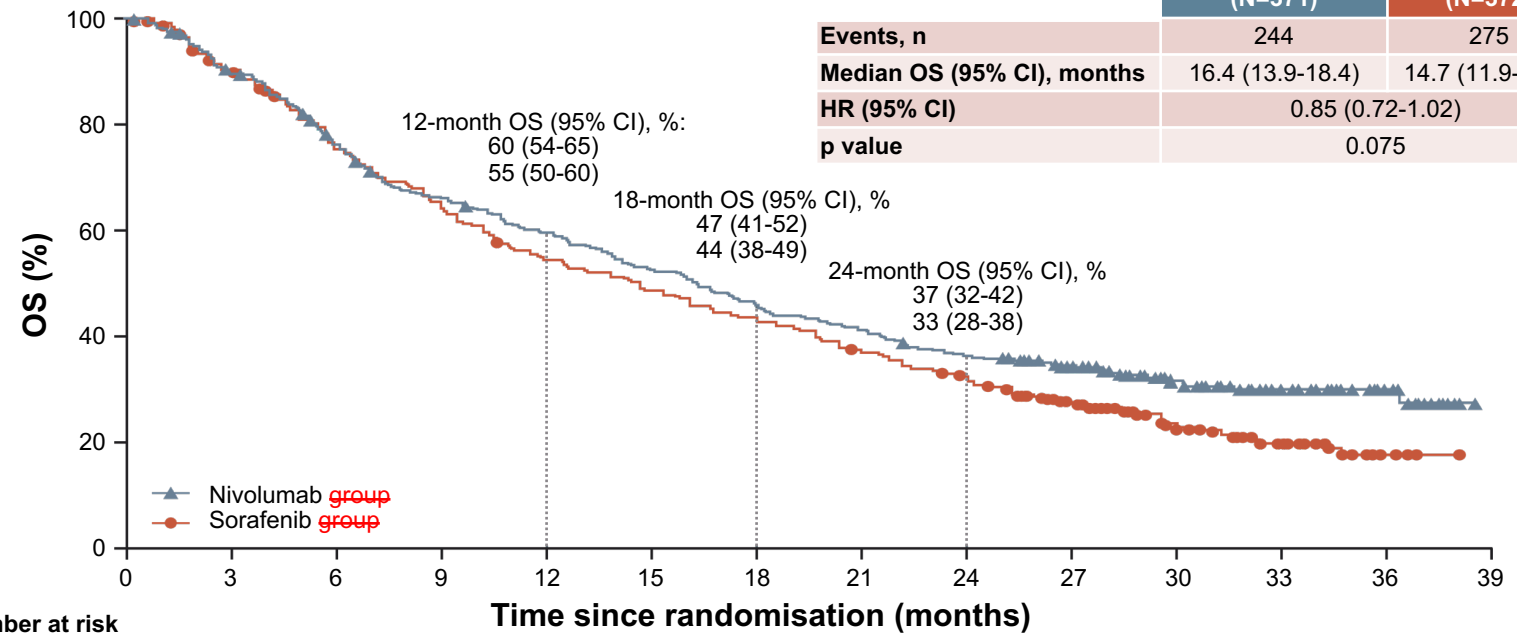
1. Llovet JM, et al. N Engl J Med. 2008;359:378-90; 2. Kudo M, et al. Lancet. 2018;391:1163-73;
3. Cheng A-L, et al. J Hepatol. 2022;76:862-73; 4. Abou-Alfa GK, et al. NEJM Evid. 2022;1:10.1056/EVIDoa2100070

SINGLE-AGENT IO

NIVOLUMAB

SINGLE-AGENT IO THAT DID NOT MEET ITS PRIMARY ENDPOINT IN PHASE 3 STUDY

- Resulted in a durable response in a subset of patients with HCC in a Phase 1/2 study (CheckMate-040)[1]
- Did not show significant OS improvement over sorafenib in a Phase 3 study (CheckMate-459)[2]



	Nivolumab (N=371)	Sorafenib (N=372)
Events, n	244	275
Median OS (95% CI), months	16.4 (13.9-18.4)	14.7 (11.9-17.2)
HR (95% CI)	0.85 (0.72-1.02)	
p value	0.075	

Number at risk (number censored)													
Nivolumab	371 (0)	326 (7)	271 (12)	235 (14)	211 (15)	187 (15)	165 (15)	146 (15)	129 (16)	104 (34)	63 (68)	39 (89)	17 (111)	0 (127)
Sorafenib	372 (0)	328 (8)	274 (12)	232 (12)	196 (14)	174 (14)	155 (14)	133 (15)	115 (17)	80 (36)	47 (58)	30 (69)	7 (90)	0 (97)

Negative trial

Clinically positive:

→ Favourable safety profile

→ Durable response in a subgroup of patients may result in improvement of landmark survival, but not in median OS

Figure adapted from Yau T, et al.[2]

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; IO, immunotherapy; OS, overall survival

1. El-Khoueiry AB, et al. Lancet. 2017;389:2492-502; 2. Yau T, et al. Lancet Oncol. 2022;23:77-90

PEMBROLIZUMAB

SINGLE-AGENT IO THAT DID NOT MEET ITS PRIMARY ENDPOINT IN PHASE 3 STUDY

- Resulted in a durable response in a subset of patients with HCC in a Phase 1/2 study (KEYNOTE-224)[1]
- Did not show significant OS improvement over placebo treatment in a Phase 3 study (KEYNOTE-240)[2]

Best response, %[1]	Patients (N=104)
Objective response	17.3
Complete	1.0
Partial	16.3
Stable disease	44.2
Disease progression	32.7

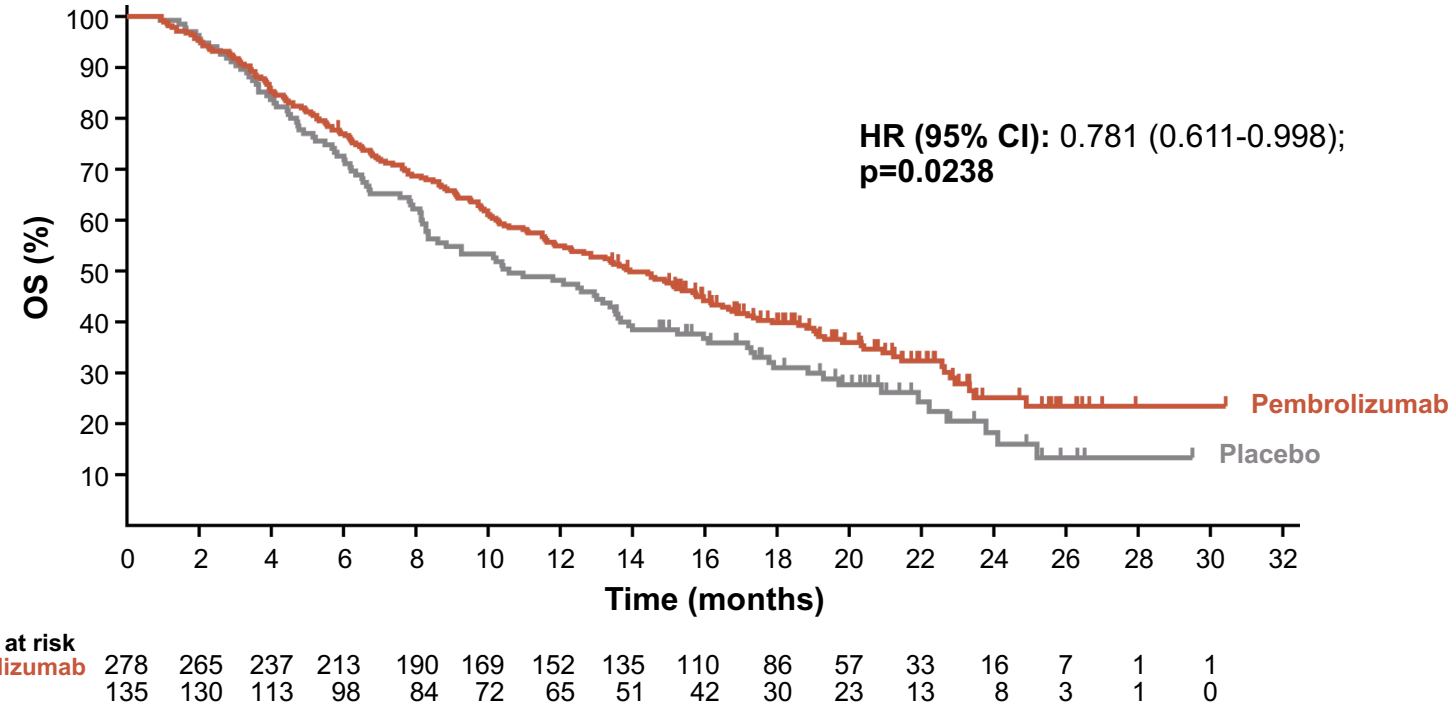


Figure adapted from Finn RS, et al.[2]

CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; IO, immunotherapy; OS, overall survival

1. Zhu AX, et al. Lancet Oncol. 2018;19:940-52; 2. Finn RS, et al. J Clin Oncol. 2019;38:193-202

CHALLENGES WITH SINGLE-AGENT IO

- Nivolumab and pembrolizumab (single IO agents):
  - Did not show significant improvement in OS (CheckMate-459 + KEYNOTE-240)
  - Showed favourable safety profiles

- Response rates from single-agent IO are **relatively low** (14-20%)

- Preclinical studies showed synergistic effects with **IO combination therapy** that demonstrated significant advancement in treating many types of cancers[1]

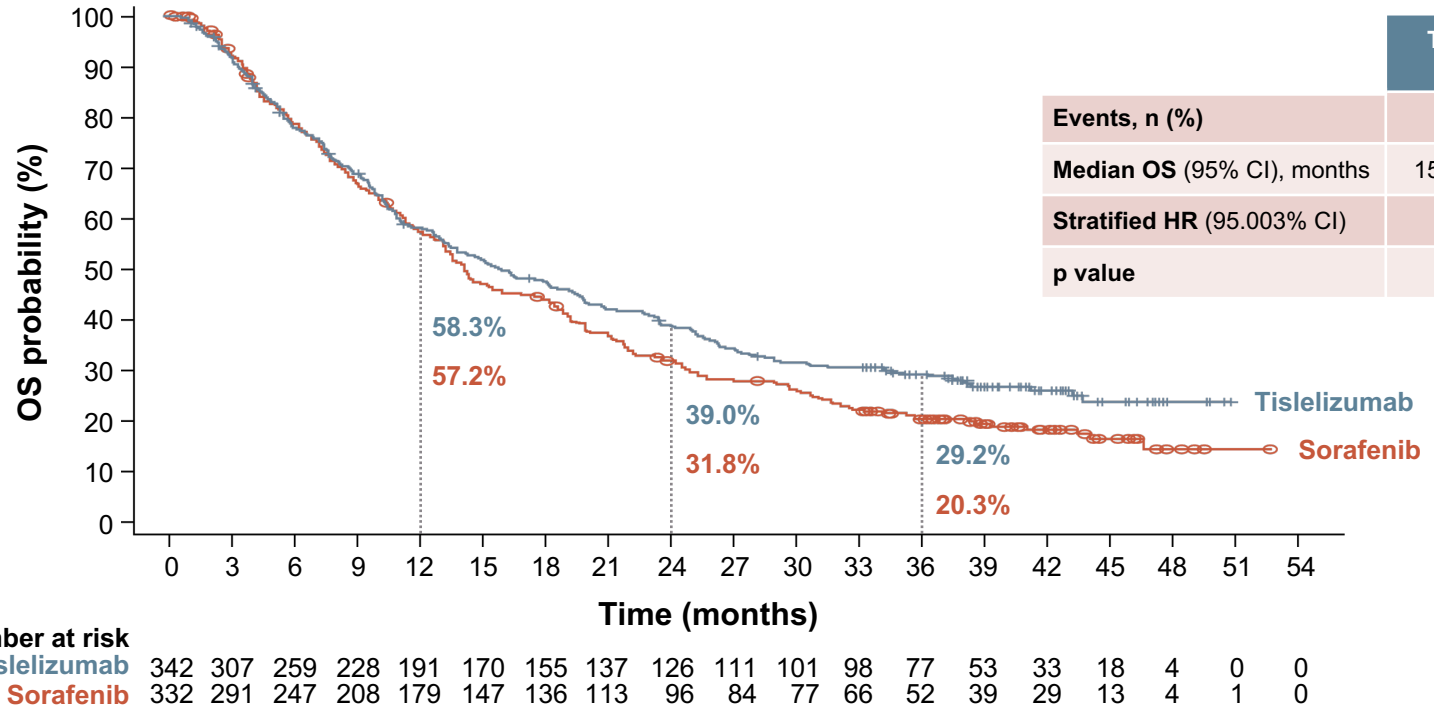
IO, immunotherapy; OS, overall survival

1. Finn RS, Zhu AX. Hepatology. 2021;73 suppl 1:150-7

TISLELIZUMAB

SINGLE-AGENT IO THAT MET ITS PRIMARY ENDPOINT IN PHASE 3 STUDY

- RATIONALE-301 met its primary endpoint of OS noninferiority with tislelizumab versus sorafenib in first-line HCC



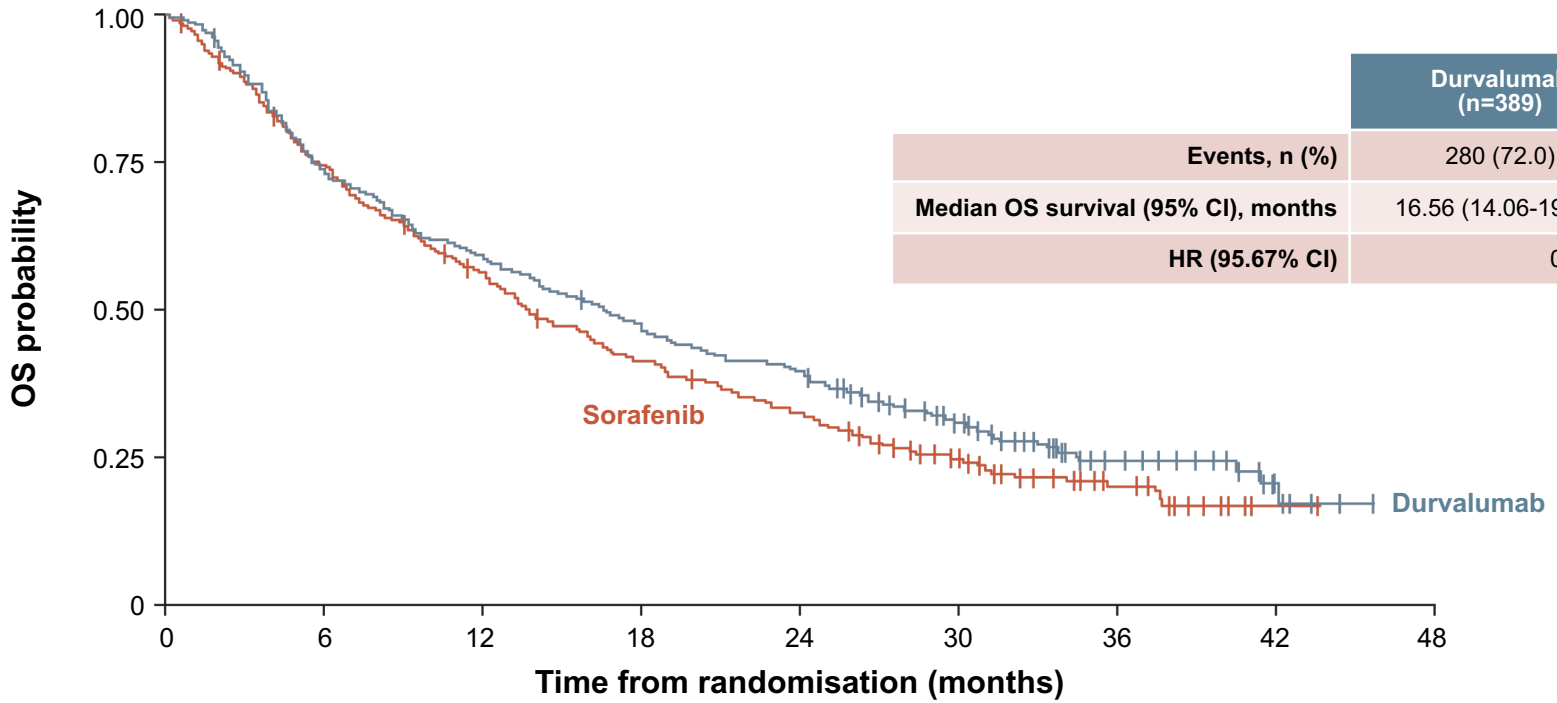
	Tislelizumab (n=342)	Sorafenib (n=332)
Events, n (%)	242 (70.8)	255 (76.8)
Median OS (95% CI), months	15.9 (13.2-19.7)	14.1 (12.6-17.4)
Stratified HR (95.003% CI)	0.85 (0.712-1.019)	
p value	0.0398	

Data cut-off date: 11 July 2022; OS was assessed in the intent-to treat population; Figure adapted from Qin S, et al. 2022
CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; IO, immunotherapy; OS, overall survival
Qin S, et al. Ann Oncol. 2022;33:S1402-3

DURVALUMAB

SINGLE-AGENT IO THAT MET ITS PRIMARY ENDPOINT IN PHASE 3 STUDY

- HIMALAYA met its primary endpoint of OS noninferiority with durvalumab versus sorafenib in HCC



	Durvalumab (n=389)	Sorafenib (n=389)
Events, n (%)	280 (72.0)	293 (75.3)
Median OS survival (95% CI), months	16.56 (14.06-19.12)	13.77 (12.25-16.13)
HR (95.67% CI)	0.86 (0.73-1.03)	

Number at risk									
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Figure adapted from Abou-Alfa GK, et al. 2022

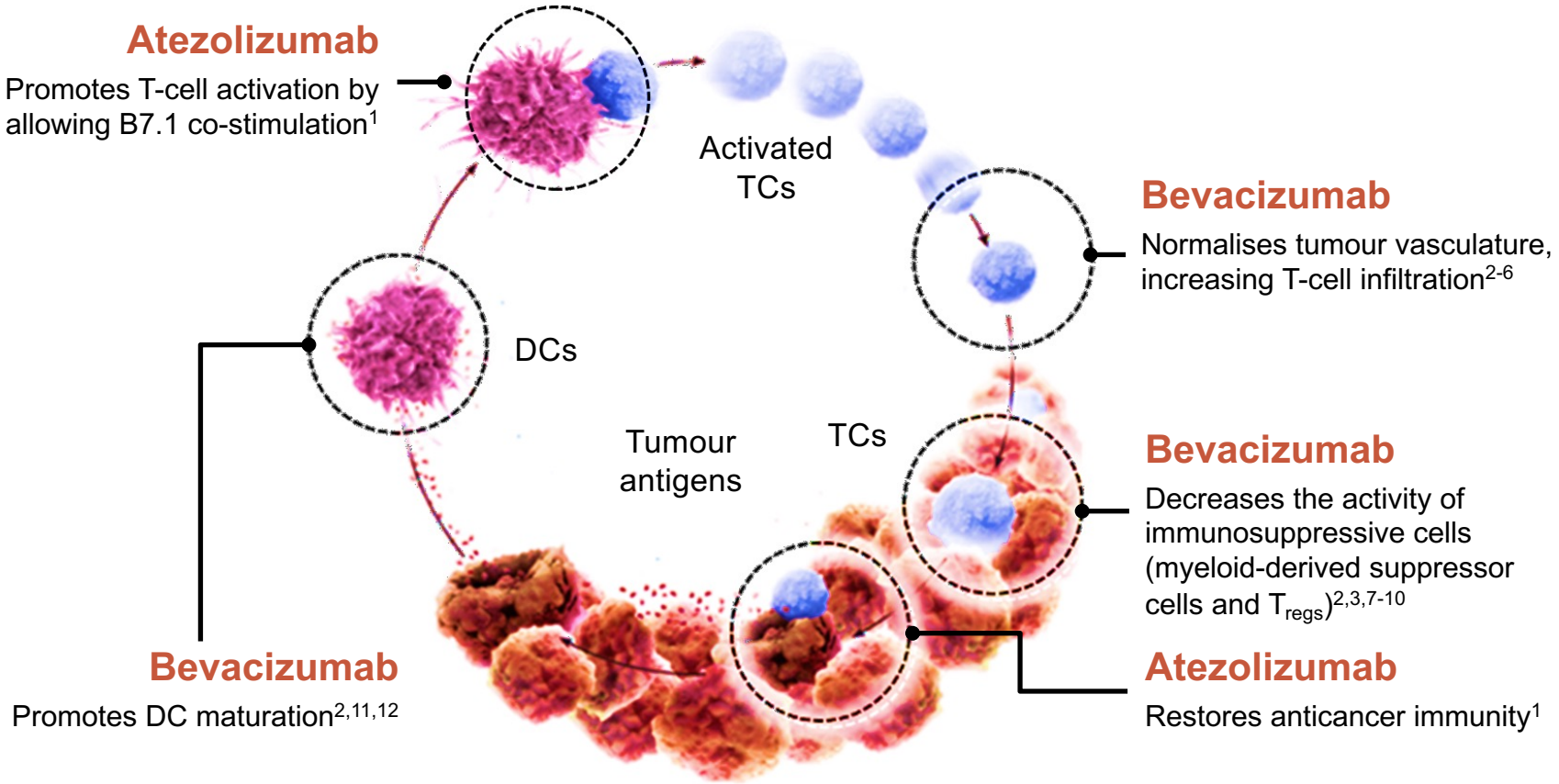
CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; IO, immunotherapy; OS, overall survival

Abou-Alfa GK, et al. J Clin Oncol. 2022;4 suppl:379

1ST LINE IO-BASED COMBINATION TREATMENTS: EFFICACY AND SAFETY

ATEZOLIZUMAB + BEVACIZUMAB

IMMUNE CHECKPOINT INHIBITOR (ANTI-PD-L1) + ANTI-VEGF



- Bevacizumab (anti-VEGF) is an antiangiogenic agent with additional immunomodulatory effects
- In combination, bevacizumab may enhance the efficacy of atezolizumab by reversing VEGF-mediated immunosuppression to promote anticancer T-cell activity

DC, dendritic cell; PD-L1, programmed death-ligand 1; TC, T cell; T_{reg}, regulatory T cell; VEGF, vascular endothelial growth factor

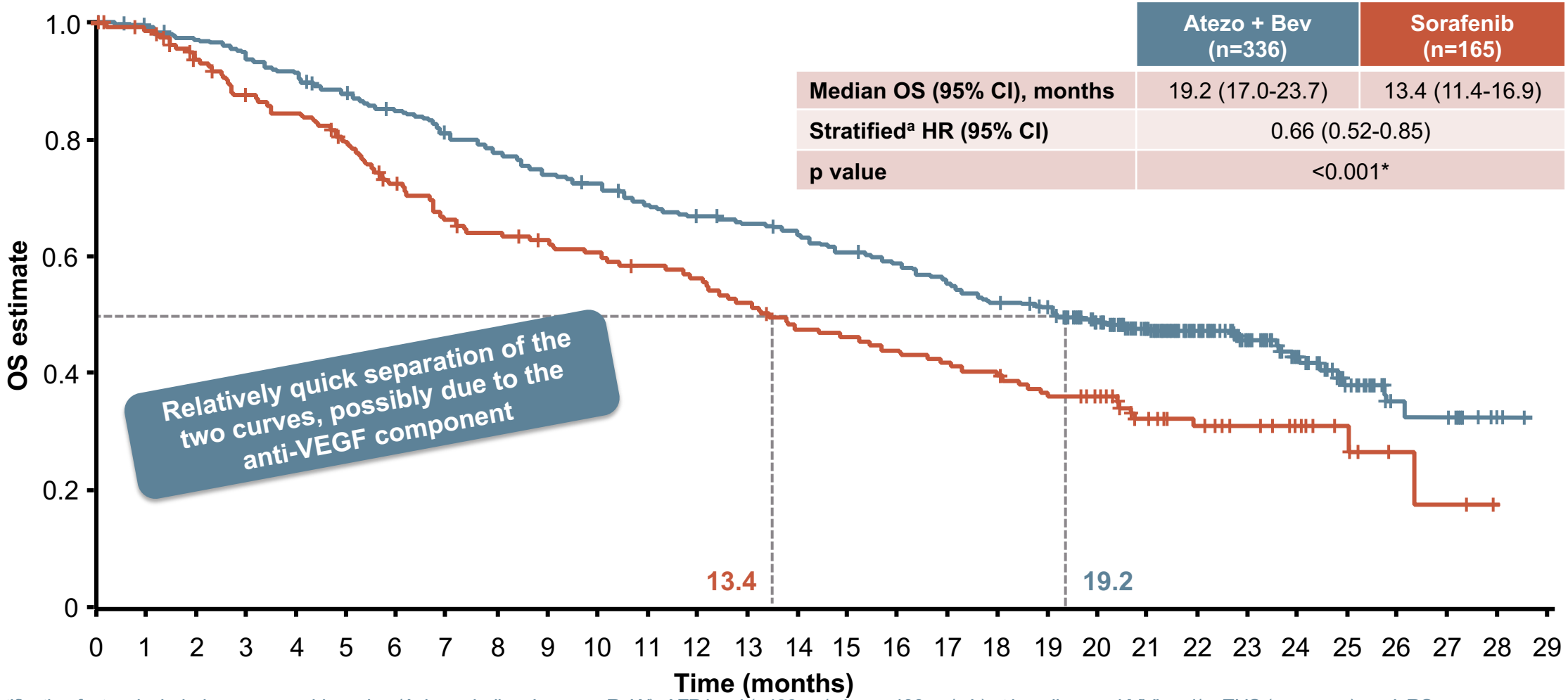
1. Chen DS, Mellman I. Immunity. 2013;39:1-10; 2. Hegde PS, et al. Semin Cancer Biol. 2018;52:117-24; 3. Wallin JJ, et al. Nat Commun. 2016;7:12624; 4. Goel S, et al. Physiol Rev. 2011;91:1071-121; 5. Motz GT, et al. Nat Med. 2014;20:607-15; 6. Hodi FS, et al. Cancer Immunol Res. 2014;2:632-42; 7. Gabrilovich DI, Nagaraj S. Nat Rev Immunol. 2009;9:162-74; 8. Roland CL, et al. PLoS One. 2009;4:e7669; 9. Facciabene A, et al. Nature. 2011;13;475:226-30; 10. Voron T, et al. J Exp Med. 2015;212:139-48; 11. Gabrilovich DI, et al. Nat Med. 1996;2:1096-103; 12. Oyama T, et al. J Immunol. 1998;160:1224-32

ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150)

UPDATED ANALYSIS: OS BENEFIT VERSUS SORAFENIB

Approved as first line in 2020 by the FDA and EMA

	Atezo + Bev (n=336)	Sorafenib (n=165)
Median OS (95% CI), months	19.2 (17.0-23.7)	13.4 (11.4-16.9)
Stratified[a] HR (95% CI)	0.66 (0.52-0.85)	
p value	<0.001*	



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

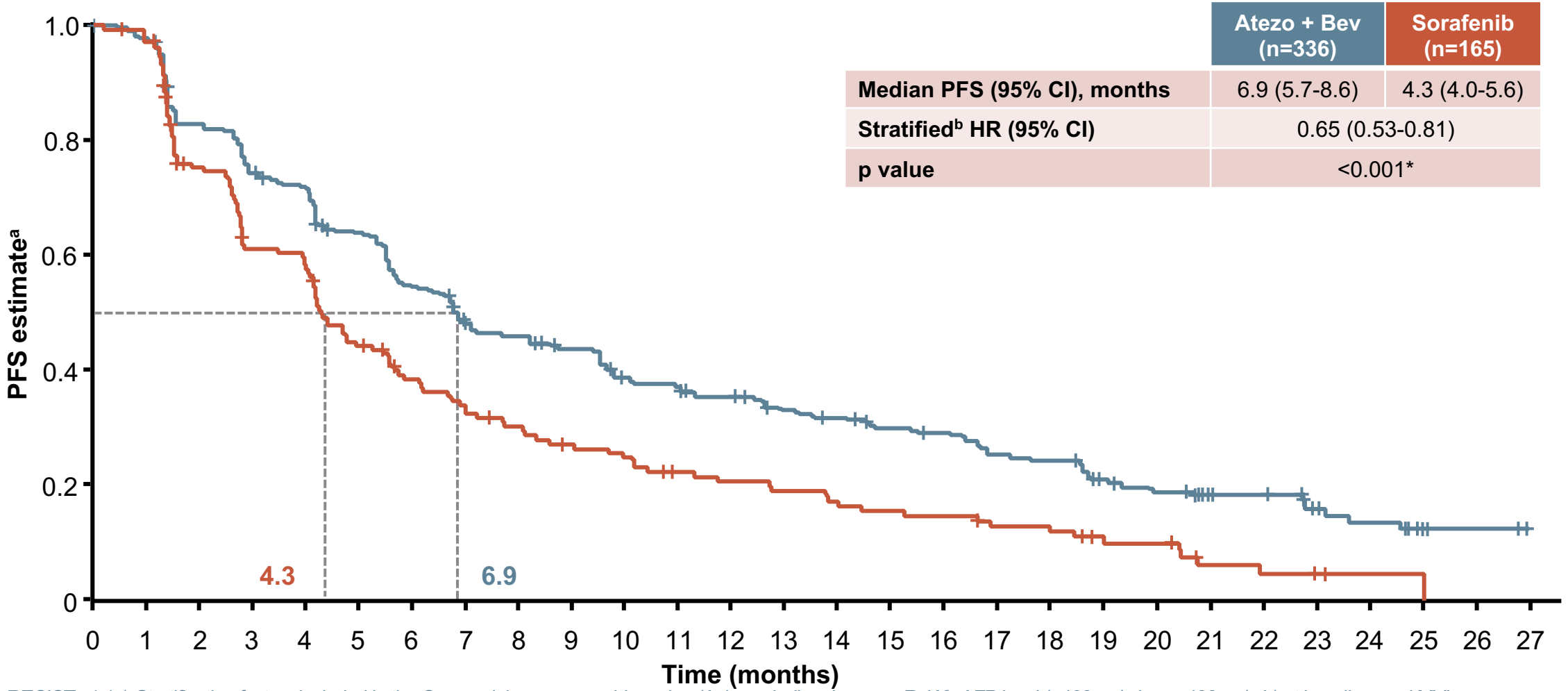
AFP, alpha fetoprotein; Atezo, atezolizumab; Bev, bevacizumab; CI, confidence interval; EHS, extrahepatic spread; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; HR, hazard ratio; IxRS, interactive voice/web response system; MVI, macrovascular invasion; OS, overall survival; RoW, rest of world; VEGF, vascular endothelial growth factor

Cheng A-L, et al. J Hepatol. 2022;76:862-73

ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150)

UPDATED ANALYSIS: PFS BENEFIT VERSUS SORAFENIB

	Atezo + Bev (n=336)	Sorafenib (n=165)
Median PFS (95% CI), months	6.9 (5.7-8.6)	4.3 (4.0-5.6)
Stratified[b] HR (95% CI)	0.65 (0.53-0.81)	
p value	<0.001*	



[a] IRF, RECIST v1.1; [b] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs RoW), AFP level (<400 ng/mL vs ≥400 ng/mL) at baseline, and MVI and/or EHS (yes vs no) per IxRS; * p value for descriptive purposes only

Atezo, atezolizumab; Bev, bevacizumab; CI, confidence interval; EHS, extrahepatic spread; HR, hazard ratio; IRF, independent review facility; IxRS, interactive voice/web response system; MVI, macrovascular invasion; PFS, progression-free survival; RoW, rest of world; RECIST, Response Evaluation Criteria in Solid Tumours

Cheng A-L, et al. J Hepatol. 2022;76:862-73

ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150)

UPDATED ANALYSIS: SAFETY SUMMARY

Event	Atezo + Bev (n=329)	Sorafenib (n=156)
Median treatment duration, months	**Atezo: 8.4; Bev: 7.0**	**2.8**
AEs, n (%)		
All grade, any cause	322 (98)	154 (99)
Treatment-related	284 (86)	148 (95)
Grade 3 or 4[b], n (%)	207 (63)	89 (57)
Treatment-related[b]	143 (43)	72 (46)
SAE	160 (49)	51 (33)
Treatment-related	76 (23)	25 (16)
Grade 5, n (%)	23 (7)	9 (6)
Treatment-related	6 (2)	1 (<1)
AE leading to withdrawal from any component	72 (22)	18 (12)
AE leading to withdrawal from both components	34 (10)	0
AE leading to dose interruption of any study treatment	195 (59)	68 (44)
AE leading to dose modification of sorafenib[c]	0	58 (37)

[a] Safety-evaluable population; [b] Highest grade experienced; [c] No dose modification allowed for the atezolizumab + bevacizumab arm
AE, adverse event; Atezo, atezolizumab; Bev, bevacizumab; SAE, serious adverse event

1. Cheng A-L, et al. J Hepatol. 2022;76:862-73

ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150)

PRIMARY ANALYSIS: BLEEDING EVENTS WERE TYPICALLY LOW IN GRADE AND UNRELATED TO VARICES

Bleeding event, %	IMbrave150[1]			
	Atezo + Bev (n=336)		Sorafenib (n=165)	
	Any grade	Grade 3 or 4[a]	Any grade	Grade 3 or 4[a]
Varices at baseline	**26**		**26**	
Treated at baseline	11		14	
All-grade bleeding/ haemorrhage events	25		17	
Epistaxis	**10.3**	0	**4.5**	0.6
Oesophageal varices haemorrhage	2.4	1.8	0.6	0.6
GI haemorrhage	2.4	1.2	1.9	1.9
Upper GI haemorrhage	1.2	0.6	1.3	1.3

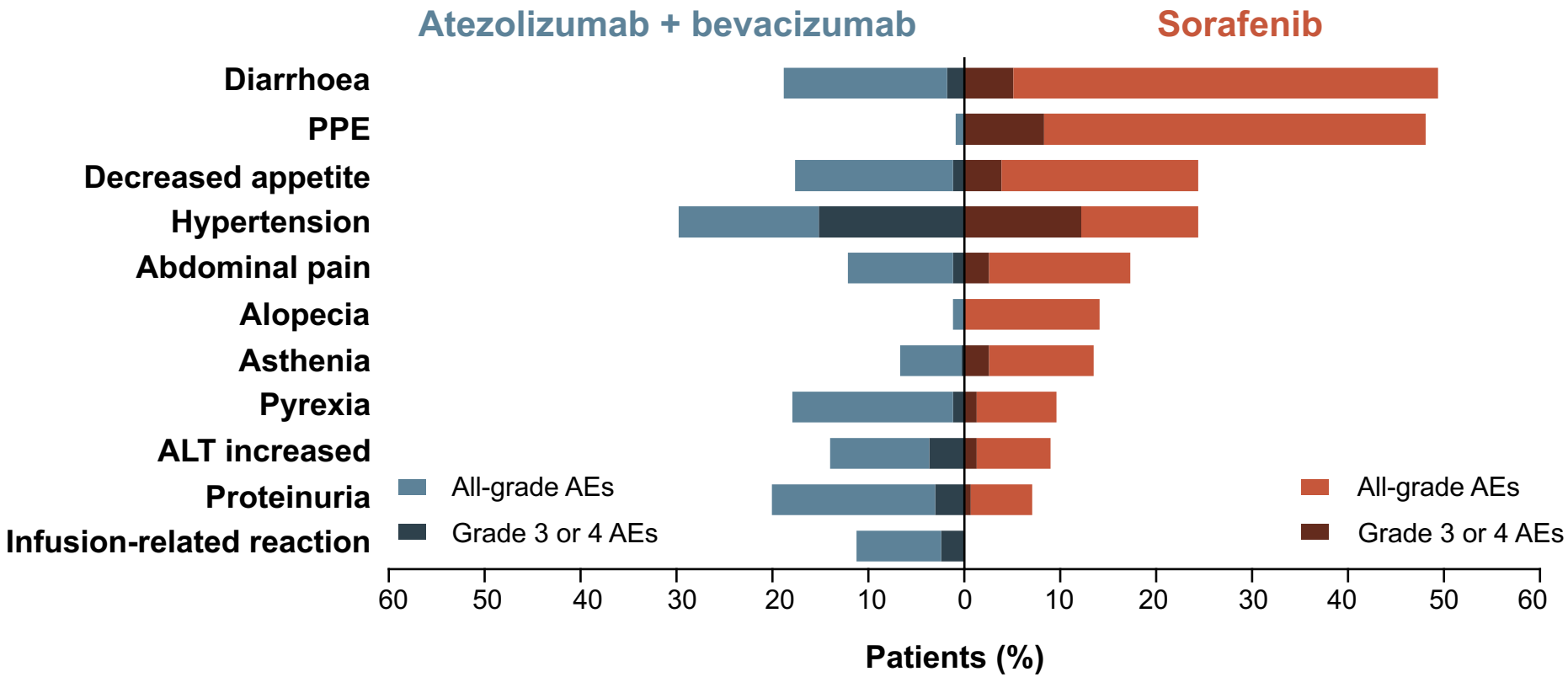
[a] Highest grade assigned

Atezo, atezolizumab; Bev, bevacizumab; GI gastrointestinal

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

ATEZOLIZUMAB + BEVACIZUMAB (IMbrave150)

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



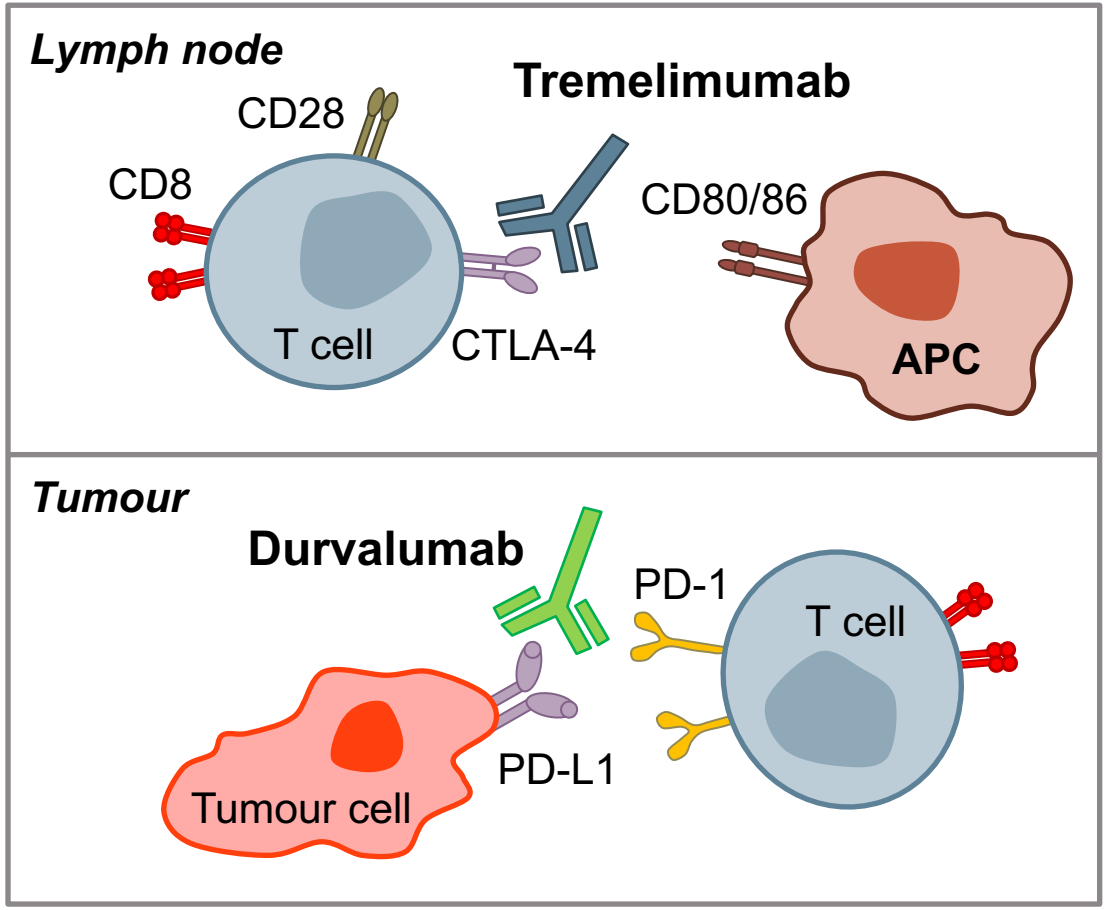
AE, adverse event; ALT, alanine aminotransferase; PPE, palmar-plantar erythrodysaesthesia

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

TREMELIMUMAB + DURVALUMAB[1]

IMMUNE CHECKPOINT INHIBITORS ANTI-CTLA-4 + ANTI-PD-L1

Approved as first line in 2022 by the FDA and EMA



Mechanism of action[1,2]

STRIDE regimen:

- Novel combination
- Single high-priming dose of tremelimumab (anti-CTLA-4)
- Regular interval durvalumab (anti-PD-L1)

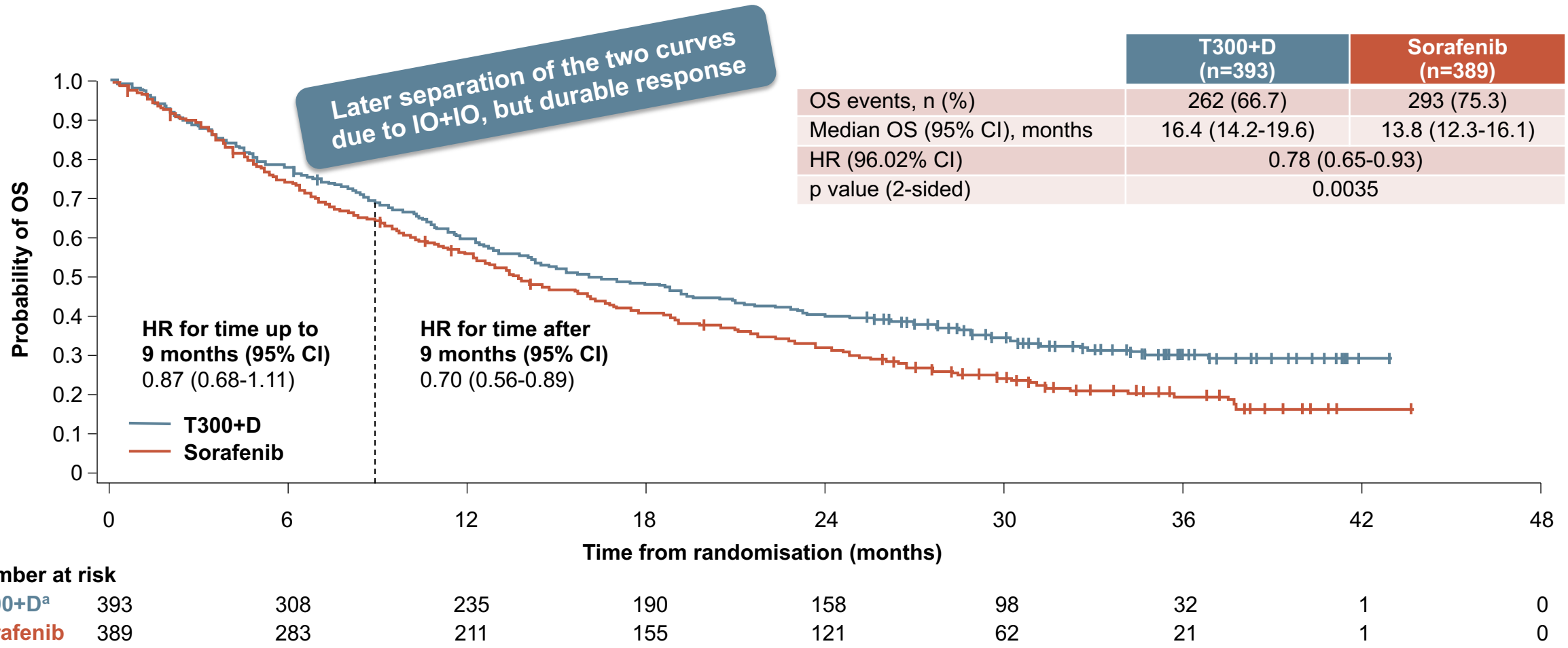
APC, antigen presenting cells; CD, cluster of differentiation; CTLA-4, cytotoxic T lymphocyte antigen 4; EMA, European medicines Agency; FDA, U.S. Food and Drug Administration; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; STRIDE, Single Tremelimumab Regular Interval Durvalumab

1. Abou-Alfa GK, et al. NEJM Evid. 2022;1:10.1056/EVIDoa2100070; 2. Kudo M. Liver Cancer. 2019;8:413-26

TREMELIMUMAB + DURVALUMAB (HIMALAYA)

PRIMARY ENDPOINT: SIGNIFICANT BENEFIT IN OS VERSUS 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	



Number at risk

T300+D[a]	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

Data cut-off date: 27 August 2021; Median follow-up: 33.18 (95% CI, 31.74-34.53) months for T300+D and 32.23 (95% CI, 30.42-33.71) months for sorafenib;

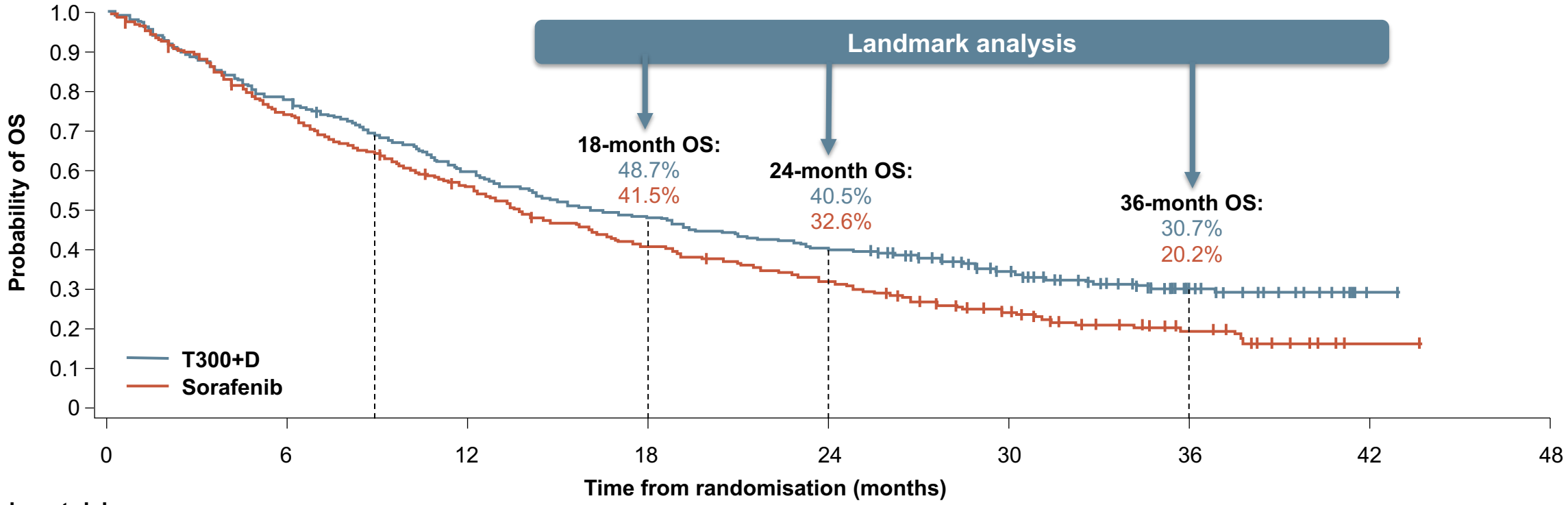
[a] Or: STRIDE

CI, confidence interval; HR, hazard ratio; IO, immunotherapy; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1,500 mg every 4 weeks ~~Q4W~~

Abou-Alfa GK, et al. NEJM Evid. 2022;1:10.1056/EVIDoa2100070

TREMELIMUMAB + DURVALUMAB (HIMALAYA)

SIGNIFICANT BENEFIT IN OS VERSUS SORAFENIB



Number at risk

T300+D[a]	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

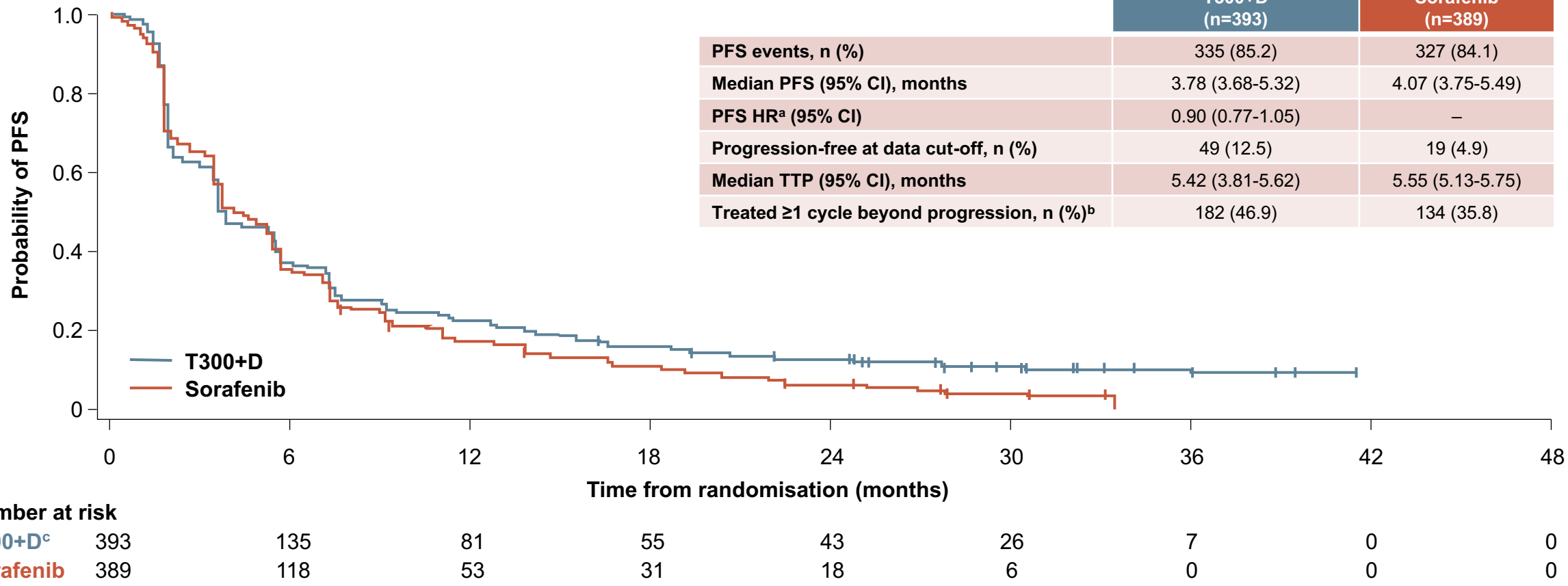
Data cut-off date: 27 August 2021; Median follow-up: 33.18 (95% CI, 31.74-34.53) months for T300+D and 32.23 (95% CI, 30.42-33.71) months for sorafenib; [a] Or: STRIDE

CI, confidence interval; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1,500 mg every 4 weeks

Abou-Alfa GK, et al. NEJM Evid. 2022;1:10.1056/EVIDoa2100070

TREMELIMUMAB + DURVALUMAB (HIMALAYA)

SECONDARY ENDPOINT: NO SIGNIFICANT DIFFERENCE IN MEDIAN PFS VERSUS SORAFENIB



	T300+D (n=393)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68-5.32)	4.07 (3.75-5.49)
PFS HR[a] (95% CI)	0.90 (0.77-1.05)	–
Progression-free at data cut-off, n (%)	49 (12.5)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81-5.62)	5.55 (5.13-5.75)
Treated ≥1 cycle beyond progression, n (%)[b]	182 (46.9)	134 (35.8)

Number at risk

T300+D[c]	393	135	81	55	43	26	7	0	0
Sorafenib	389	118	53	31	18	6	0	0	0

[a] Versus sorafenib; [b] Percent calculated from total patients in the safety analysis set: T300+D (N=388), durvalumab (N=388), sorafenib (N=374); [c] Or: STRIDE
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1,500 mg every 4 weeks; TTP, time to progression

Abou-Alfa GK, et al. NEJM Evid. 2022;1:10.1056/EVIDoa2100070

TREMELIMUMAB + DURVALUMAB (HIMALAYA)

SAFETY SUMMARY: AEs

Event, n (%)	T300+D (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	357 (95.5)
Any TRAE[a]	294 (75.8)	317 (84.8)
Any grade 3 or 4 AE	196 (50.5)	196 (52.4)
Any grade 3 or 4 TRAE	100 (25.8)	138 (36.9)
Any serious TRAE	68 (17.5)	35 (9.4)
Any TRAE leading to death	9 (2.3)[b]	3 (0.8)[c]
Any TRAE leading to discontinuation	32 (8.2)	41 (11.0)

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy; [a] Treatment-related was as assessed by investigator; [b] Nervous system disorder (n=1), acute respiratory distress syndrome (n=1), hepatitis (n=1), myocarditis (n=1), immune-mediated hepatitis (n=2), pneumonitis (n=1), hepatic failure (n=1), myasthenia gravis (n=1); [c] Haematuria (n=1), cerebral haematoma (n=1), hepatic failure (n=1)

AE, adverse event; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1,500 mg every 4 weeks; TRAE, treatment related adverse event

Abou-Alfa GK, et al. NEJM Evid. 2022;1:10.1056/EVIDoa2100070

TREMELIMUMAB + DURVALUMAB (HIMALAYA)

SAFETY: TREATMENT-RELATED HEPATIC OR HAEMORRHAGE SMQ EVENTS

Event, n (%)	T300+D (n=388)		Sorafenib (n=374)	
	All grades	Grade ≥3	All grades	Grade ≥3
Hepatic SMQ TRAE	**66 (17.0)**	**23 (5.9)**	**46 (12.3)**	**17 (4.5)**
Haemorrhage SMQ TRAE	7 (1.8)	2 (0.5)	**18 (4.8)**	4 (1.1)
ALT increased	**18 (4.6)**	4 (1.0)	8 (2.1)	3 (0.8)
Aspartate aminotransferase increased	**22 (5.7)**	9 (2.3)	10 (2.7)	6 (1.6)
Blood bilirubin increased	6 (1.5)	1 (0.3)	10 (2.7)	2 (0.5)
Ascites	1 (0.3)	0	2 (0.5)	0
Hepatic encephalopathy	0	0	2 (0.5)	1 (0.3)
International normalised ratio increased	4 (1.0)	1 (0.3)	0	0
Oesophageal varices haemorrhage	0	0	0	0

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy; Treatment-related was as assessed by investigator

AE, adverse event; ALT, alanine aminotransferase; MedRA, Medical Dictionary for Regulatory Activities; SMQ, standardised MedRA query; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1,500 mg every 4 weeks; TRAE, treatment-related adverse event

Abou-Alfa GK, et al. NEJM Evid. 2022;1:10.1056/EVIDoa2100070

TREMELIMUMAB + DURVALUMAB (HIMALAYA)

SAFETY: irAEs

Event, n (%)	T300+D (N=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
irAEs	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)
Hepatic event	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)
Diarrhoea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)
Pancreatic event	9 (2.3)	7 (1.8)	7 (1.8)	0
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0
Hyperthyroid event	18 (4.6)	1 (0.3)	2 (0.5)	0
Hypothyroid event	42 (10.8)	0	1 (0.3)	0
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)
Renal event	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)

Includes AEs with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm

AE, adverse event; irAE, immune-related adverse event; T300+D, tremelimumab 300 mg × 1 dose + durvalumab 1,500 mg every 4 weeks

Abou-Alfa GK, et al. NEJM Evid. 2022;1:10.1056/EVIDoa2100070

irAEs MANAGEMENT

irAEs CAN BE TREATED WITH STEROIDS

CTCAE v5.0 grade definition	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ICI modification	• Continue ICI • Consider withholding ICI for suspected pneumonitis or myocarditis during diagnostic work-up	• Withhold ICI until ≤ grade 1 (except for hypothyroidism, adrenalitis, limited rash, or sensory neuropathy) • ICI can be resumed after completion of steroid taper • Consider permanent discontinuation for pneumonitis, myocarditis, or peripheral neuromotor syndromes based on clinical judgement	• Permanently discontinue CTLA-4 inhibitors in any event • Permanently discontinue PD-1 and PD-L1 inhibitors except for hypothyroidism, adrenal insufficiency, nephritis, or rash that resolve within 30 days	• Permanently discontinue any ICI
Monitoring	• Monitor within 2 weeks, or more frequently, depending on irAE and clinical judgement	• Refer to the specialist • Monitor within 1 week, or more frequently, depending on irAE and clinical judgement	• Monitor every 2-3 days, or more frequently, depending on irAE and clinical judgement • Refer to the specialist	• Continuous monitoring during hospitalisation
Medical therapy	• Not needed	• Initiate steroids (prednisone at 0.5-1.0 mg/kg/day or equivalent p.o. or i.v.) • Decision to start steroids can be differed a few days for nephritis • If it worsens, treat as grade 3	• Initiate steroids immediately (prednisone at 1-2 mg/kg/day or equivalent i.v.); i.v. route for pneumonitis, diarrhoea, and others based on clinical judgement • If no improvement, consider infliximab, particularly for pneumonitis and colitis	• Manage as grade 3

CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T lymphocyte antigen 4; ICI, immune checkpoint inhibitor, irAE; immune-related adverse event; i.v., intravenous(ly); PD-1, programmed death 1; PD-L1, programmed death-ligand 1

Sangro B, et al. J Hepatol. 2020;72:320-41

UNDERSTANDING THE SURVIVAL CURVE

UNDERSTANDING THE SURVIVAL CURVE

IO+IO COMBINATION THERAPIES: RAISING THE TAIL OF THE CURVE

- **An IO+IO combination therapy**, such as durvalumab + tremelimumab
  - **Needs weeks to months** to build an antitumour response, following initiation of therapy
  - **Raises the tail of the survival curve** compared to conventional therapy and thus shows a **durable response**

- **Different analysis for efficacy,** such as landmark analysis, in clinical trials should therefore be considered[1,2]

Typical Kaplan–Meier survival curves observed with IO therapies versus conventional therapies

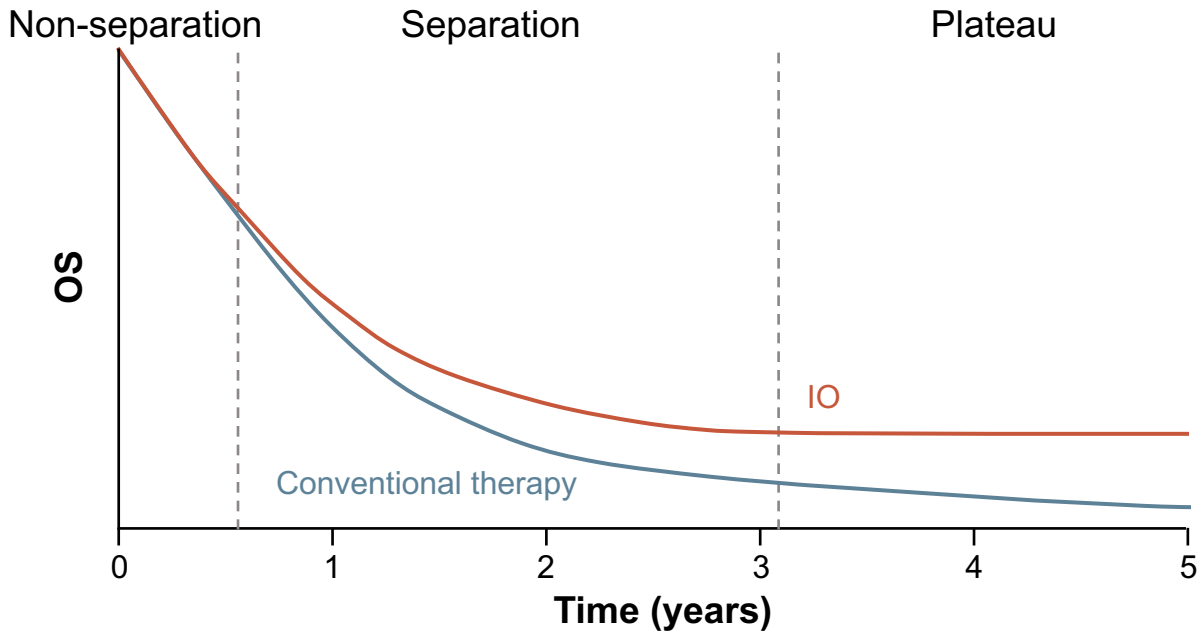


Figure adapted from Quinn C, et al. 2020[3]
IO, immunotherapy

1. Harris SJ, et al. Cancer Biol Med. 2016;13:171-93; 2. Anagnostou V, et al. Clin Cancer Res. 2017:23:4959-69; 3. Quinn C, et al. J Immunother Cancer. 2020;8:e000648

UNDERSTANDING THE SURVIVAL CURVE

LANDMARK ANALYSIS DESIGNATES CERTAIN TIMEPOINTS IN THE FOLLOW-UP PERIOD

Landmark OS[1]

- Multiple landmark rates can be used[1]
- Can be extracted at any time point of interest[1]
- Represents **what matters to patients and their doctors**, by showing what to expect in 1-, 3-, and 5-years' time

The use of landmark survival rates

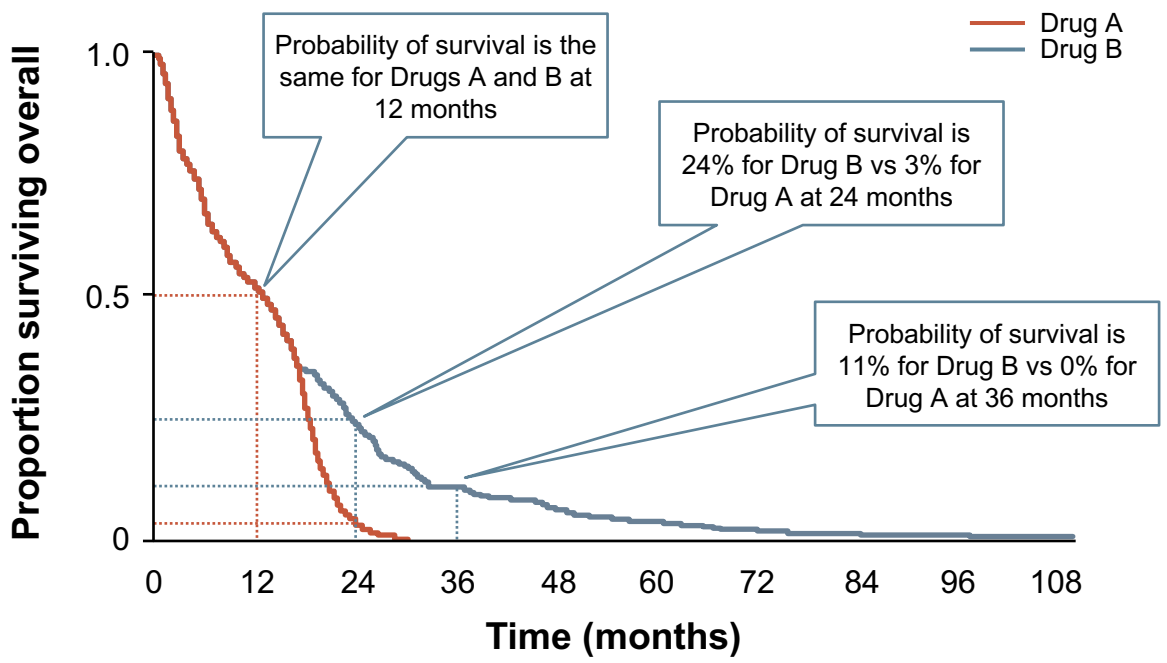


Figure adapted from Chan E, et al. 2018[1]
OS, overall survival

1. Chan E, et al. OncoImmunology. 2018;8:e1343774

UNDERSTANDING THE SURVIVAL CURVE

IO+IO COMBINATION THERAPIES: RAISING THE TAIL OF THE CURVE

- **The different characteristics of the survival curves** for IO and conventional therapies suggest:
  - To consider using atezolizumab + bevacizumab (IO+anti-VEGF) for more aggressive, bulky tumours
  - To consider using durvalumab + tremelimumab (IO+IO) for less aggressive tumours

Effects of IO and targeted therapy on melanoma survival curves

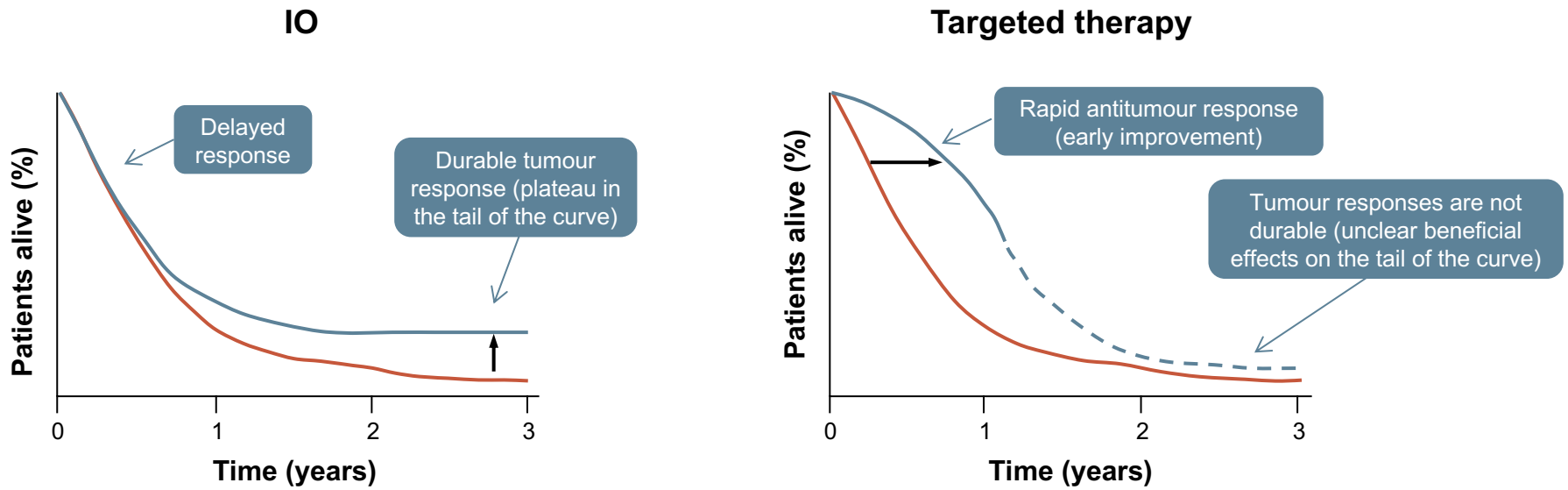


Figure adapted from Ribas A et al. 2012[1]

IO, immunotherapy; VEGF, vascular endothelial growth factor

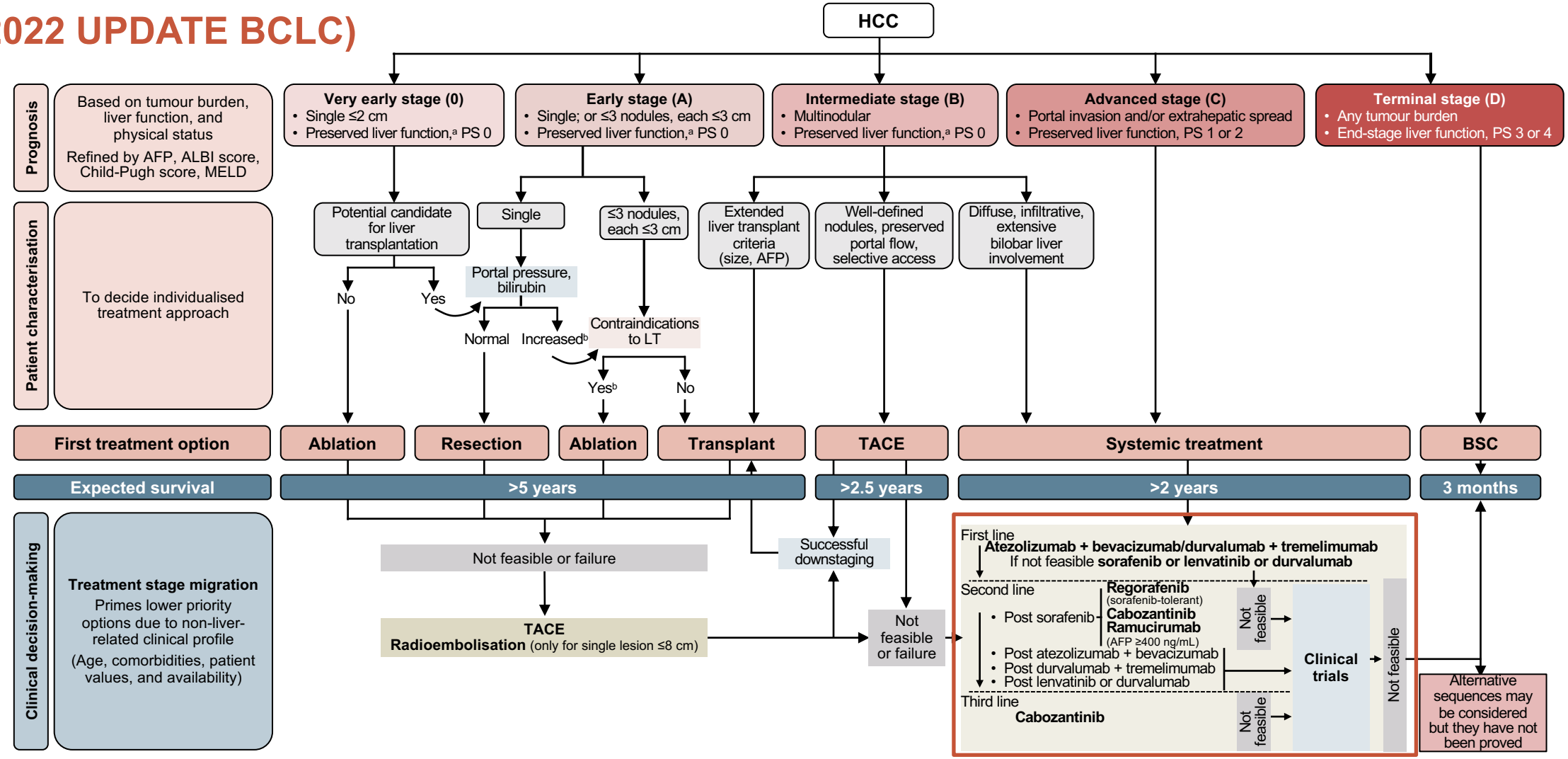
Ribas A, et al. Clin Cancer Res. 2012;18:336-341

IO IN THE FULL SYSTEMIC TREATMENT LANDSCAPE FOR HCC

HCC, hepatocellular carcinoma; IO, immunotherapy

THE PLACE OF IO IN THE TREATMENT LANDSCAPE

MULTIDISCIPLINARY CARE FOR PATIENTS WITH HEPATOBILIARY CANCER (2022 UPDATE BCLC)



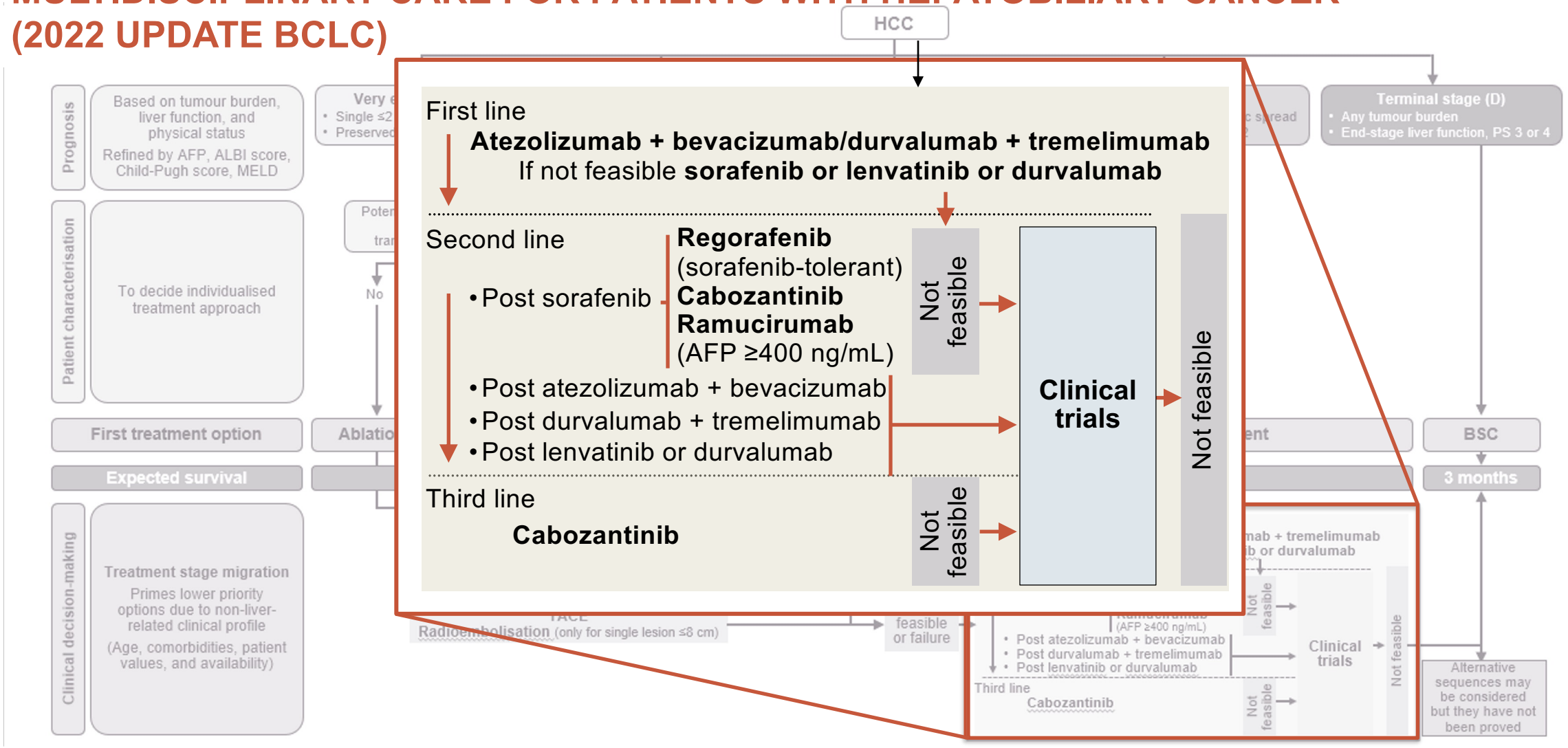
[a] Except for those with tumour burden acceptable for transplant; [b] Resection may be considered for single peripheral HCC with adequate remnant liver volume

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

THE PLACE OF IO IN THE TREATMENT LANDSCAPE

MULTIDISCIPLINARY CARE FOR PATIENTS WITH HEPATOBILIARY CANCER (2022 UPDATE BCLC)



AFP, alpha-fetoprotein;

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

IN CONCLUSION

IN CONCLUSION

- **The treatment landscape for patients with HCC has evolved rapidly over recent years**
- IO, and in particular IO combinations, are **effective treatments** for patients with advanced HCC
- Approved IO and IO combinations as first-line treatment:
  - Atezolizumab + bevacizumab (FDA – May 2020,[1] EMA – Sept 2020[2])
  - Tremelimumab + durvalumab (FDA – Oct 2022,[3] EMA – Dec 2022[4])
- IO and IO combinations may result in inflammatory side effects referred to as **irAEs**
  - Most of these adverse AEs can be treated with **steroids**
- Survival analysis for IO treatment shifts from median OS to **landmark analysis**

AE, adverse event; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; HCC, hepatocellular carcinoma; IO, immunotherapy; OS, overall survival

1. U.S. Food and Drug Administration. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-plus-bevacizumab-unresectable-hepatocellular-carcinoma. Last updated June 2020. Accessed March 2023; 2. European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-tecentriq-ii-39_en.pdf. Last updated September 2020. Accessed March 2023; 3. U.S. Food and Drug Administration. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-unresectable-hepatocellular-carcinoma. Last updated October 2022. Accessed March 2023; 4. European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-imjudo_en.pdf. Last updated December 2022. Accessed March 2023

OUTLOOK TO MODULE 2

THE USE OF IMMUNOTHERAPY IN HCC:

IN-DEPTH SUBGROUP ANALYSES AND CHALLENGES

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