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THE STATE UNIVERSITY
OF NEW JERSEY

Medical Approaches for Liver Cancer in 2023

March 4, 2023

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Division of Hematology/Oncology
Department of Medicine
Rutgers NJMS

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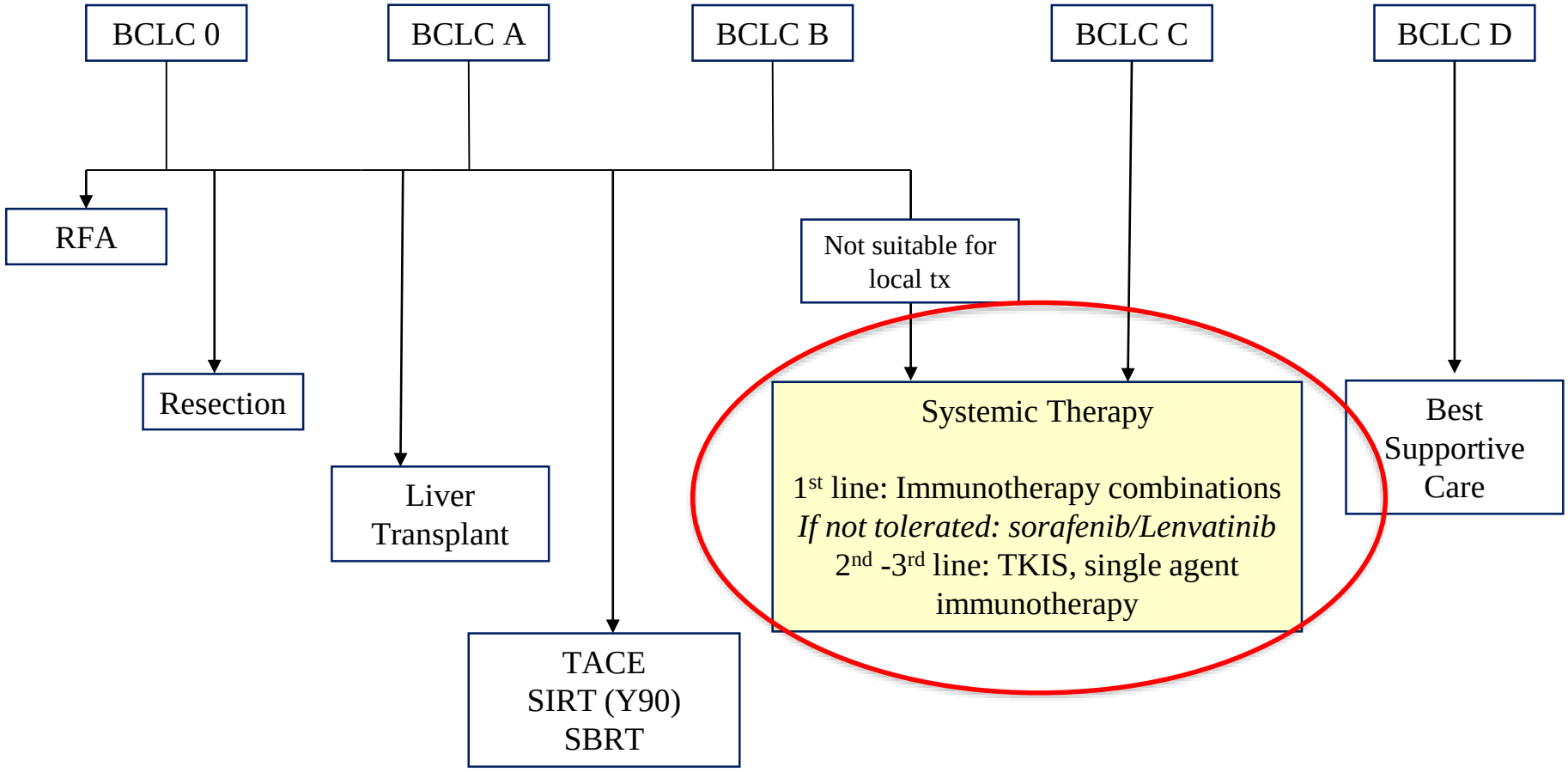
Abbreviated BCLC Staging and Treatment Strategy



Adapted from Vogel et al. ESMO Clinical Practice Guidelines 2021, eUpdate from Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Vogel A, Cervantes A, Chau I et al. Ann Oncol 2018; 29 (Suppl 4): iv238–iv255. and
Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76(3):681–93.

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A brief comment on systemic therapy + TACE...

Trial	Study	Results	Reference
Phase III sorafenib after TACE in Japanese and Korean patients	Post-TACE sorafenib	Negative trial for primary endpoint of TTP, no survival benefit	Kudo M et al; Eu J Cancer 2011. Sep;47(14):2117-27. doi: 10.1016/j.ejca.2011.05.007.
Phase II SPACE trial	DEB-TACE + sorafenib	Negative trial for primary endpoint of TTP, no survival benefit	Lencioni R et al, J Hepatol . 2016 May;64(5):1090-1098. doi: 10.1016/j.jhep.2016.01.012. Epub 2016 Jan 22.
Phase III TACE2 trial	DEB-TACE + sorafenib	Negative for improvement in PFS or OS despite crossover allowed on progression	Meyer T et al, Lancet Gastroenterol Hepatol . 2017 Aug;2(8):565-575. doi: 10.1016/S2468-1253(17)30156-5. Epub 2017 Jun 23.
Phase II TACTICS	TACE (epirubicin or miriplatin) + sorafenib	Negative for OS benefit; however, argued clinically meaningful survival benefit and improved TACE-specific PFS defined as 'untreatable progression'	Kudo M et al, Liver Cancer 2022;11:354–367 https://doi.org/10.1159/000522547
Phase III STAH	TACE (doxorubicin or cisplatin) + sorafenib	Negative for OS benefit though combo improved tumor response/secondary outcomes	Park JW et al, J Hepatol . 2019 Apr;70(4):684-691. doi: 10.1016/j.jhep.2018.11.029. Epub 2018 Dec 6.
Phase III SORAMIC	Y90 + sorafenib	Negative for OS benefit	Ricke, J et al, J Hepatol . 2019 Dec;71(6):1164-1174. doi: 10.1016/j.jhep.2019.08.006. Epub 2019 Aug 14.
Phase III LAUNCH	**TACE + lenvatinib**	**Positive OS benefit and ORR**	**Peng Z et al, J Clin Oncol . 2023 Jan 1;41(1):117-127. doi: 10.1200/JCO.22.00392. Epub 2022 Aug 3.**

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Limited evidence on clinically meaningful benefit of systemic therapy + TACE, particularly in the US

Trial	Study	Results	Reference
Phase III sorafenib after TACE in Japanese and K	Post-TACE sorafenib	Negative trial for primary endpoint of TTP	Kudo M et al; Eu J Cancer 2011. 17-27. 011.05.007.
Phase			J Hepatol 00-1098. doi: 2. Epub 2016 Jan
Phase			roenterol Hepatol 565-575. 253(17)30156- un 23.
Phase			er 2022;11:354– 9/000522547
Pha			Hepatol 4-691. doi: 9. Epub 2018 Dec
S			Hepatol 4-1174. doi: 6. Epub 2019 Aug
Phase III LAUNCH	**TACE + lenvima**	**Positive OS benefit and ORR**	**Peng Z et al, J Clin Oncol . 2023 Jan 1;41(1):117-127. doi: 10.1200/JCO.22.00392. Epub 2022 Aug 3.**

To date, no compelling evidence that systemic therapy + TACE = clinically meaningful benefit; may have more toxicity.

Most studies have been in Asia, where etiology of HCC is different (younger patients, more HBV, less NASH or concomitant comorbidities, many HCC without cirrhosis)

LAUNCH was the first Phase III trial to show OS benefit, but population was entirely Chinese; 87% had hepatitis B; avg age of study population mid 50s; Western population is different → findings have not yet been studied in US population

This is a topic of high interest and subject of many current trials!

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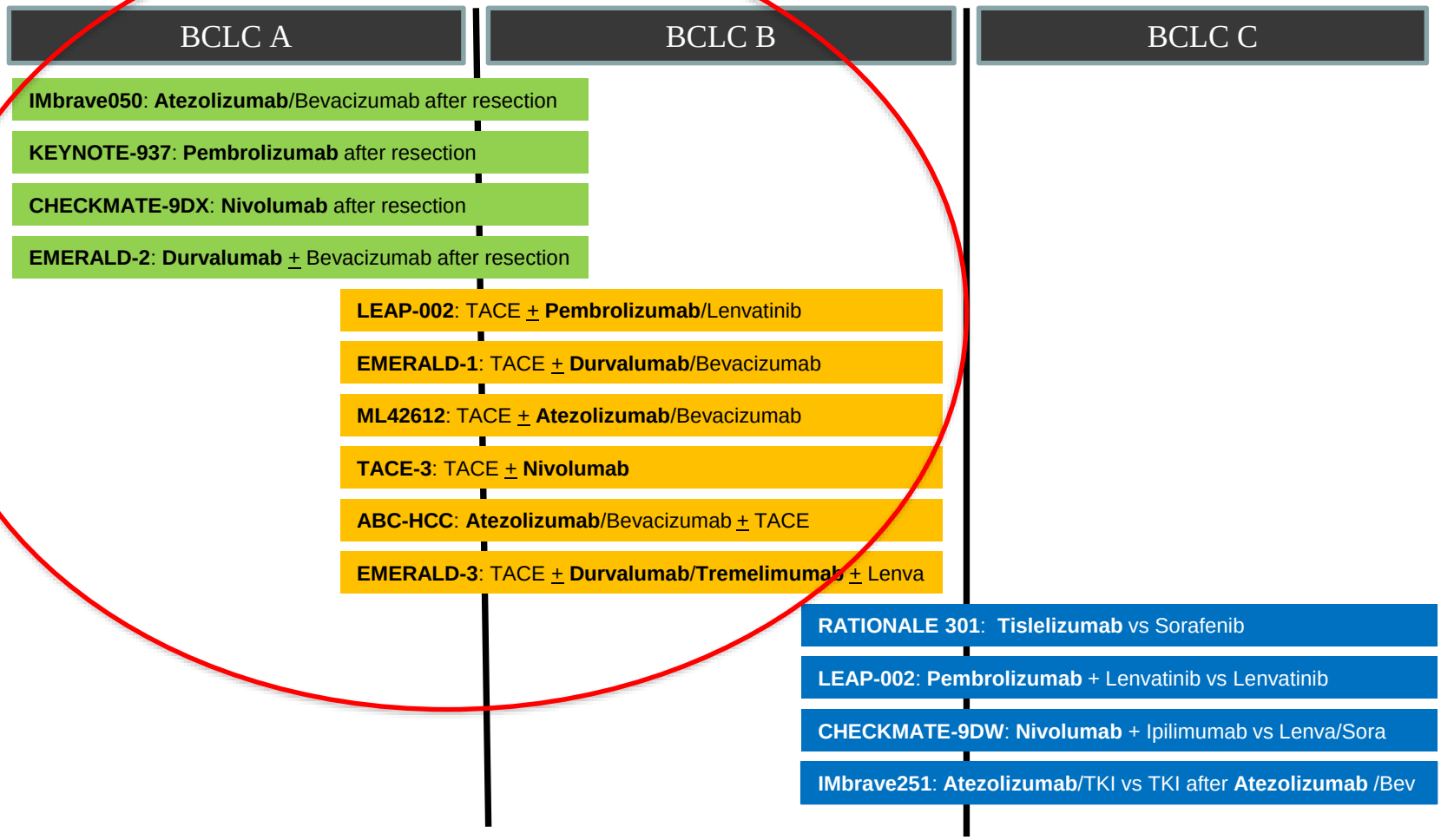
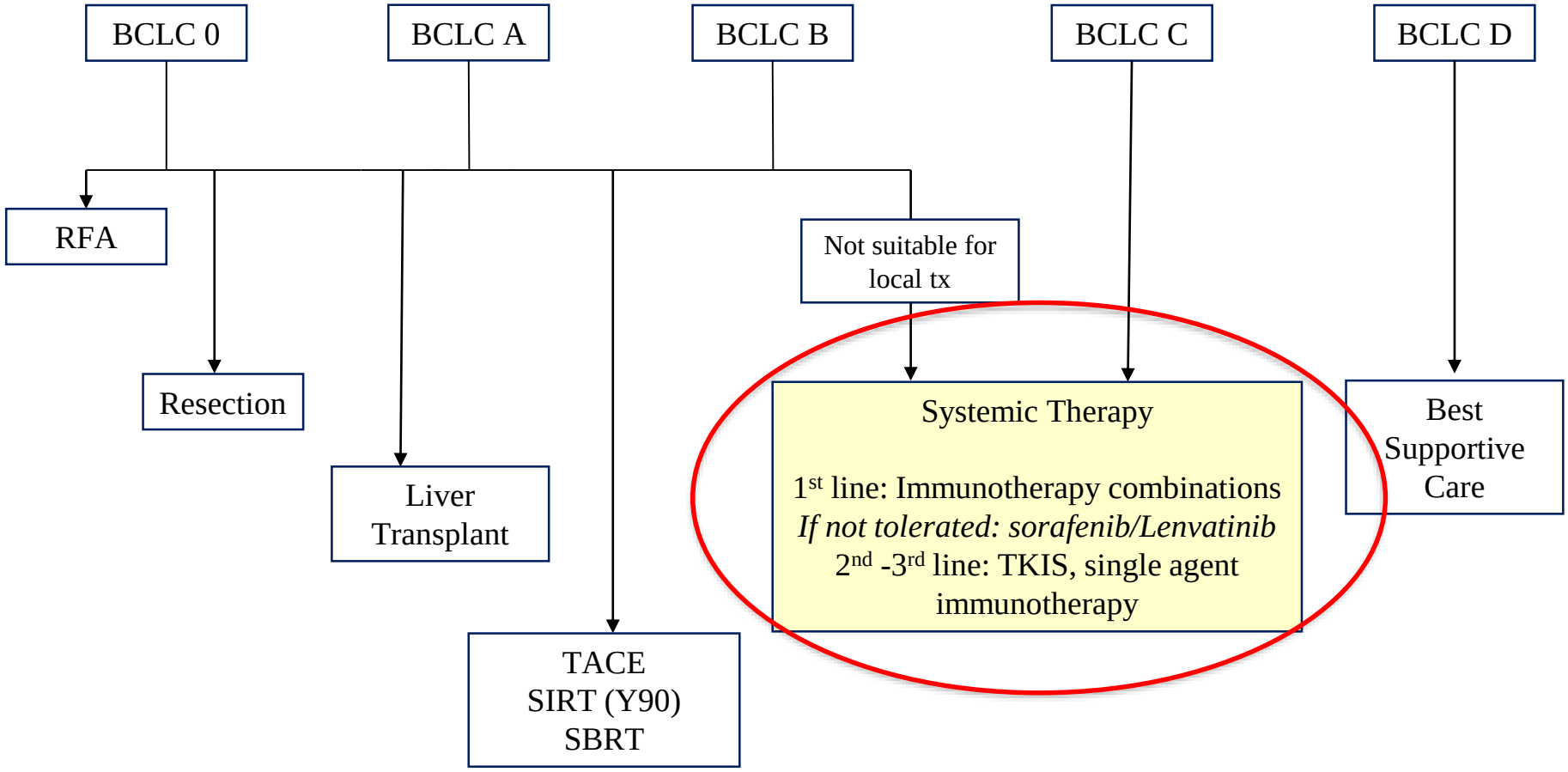
Current Trials in Progress



Vogel A et al. Lancet . 2022 Oct 15;400(10360):1345-1362. doi: 10.1016/S0140-6736(22)01200-4. Epub 2022 Sep 6.

Figure from Vogel, A; Oncology Today with Dr Neil Love: Management of **Hepatocellular Carcinoma, Companion Faculty Lecture**. Research To Practice. Nov 21, 2022



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Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76(3):681–93.

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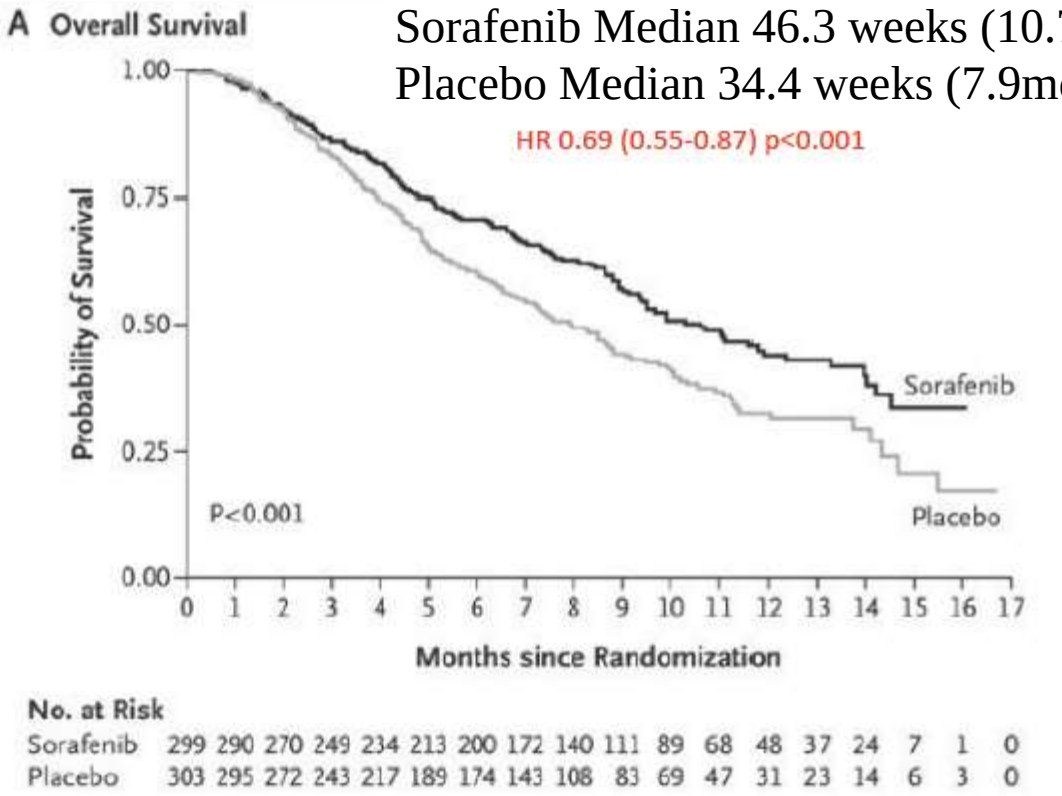
SHARP Trial

Sorafenib Median 46.3 weeks (10.7mo)
Placebo Median 34.4 weeks (7.9mo)



Llovet JM et al, N Engl J Med 2008; 359:378-390
DOI: 10.1056/NEJMoa0708857

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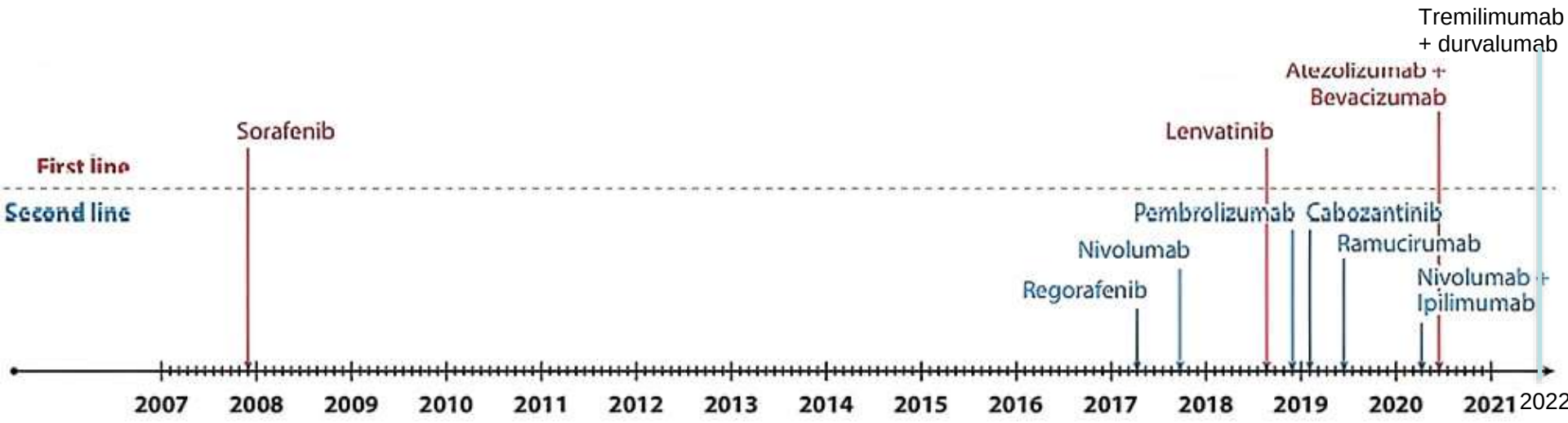
Systemic therapy for those not candidates for LRT

Huang, A., Yang, XR., Chung, WY. *et al.* Targeted therapy for hepatocellular carcinoma. *Sig Transduct Target Ther* **5**, 146 (2020). https://doi.org/10.1038/s41392-020-00264-x



Shannon AH et al, J Hepatocell Carcinoma. 2022; 9: 1247–1261. Published online 2022 Dec 7. doi: 10.2147/JHC.S383922

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Categories of Systemic Therapy

Preferred - Combination

-Atezolizumab/Bevacizumab

-Tremelimumab/Durvalumab

Other options:

Tyrosine Kinase Inhibitors

- Sorafenib*
- Lenvatinib
- Regorafenib
- Cabozantinib
- Ramucirumab (AFP >400 and CPA)

Immunotherapy

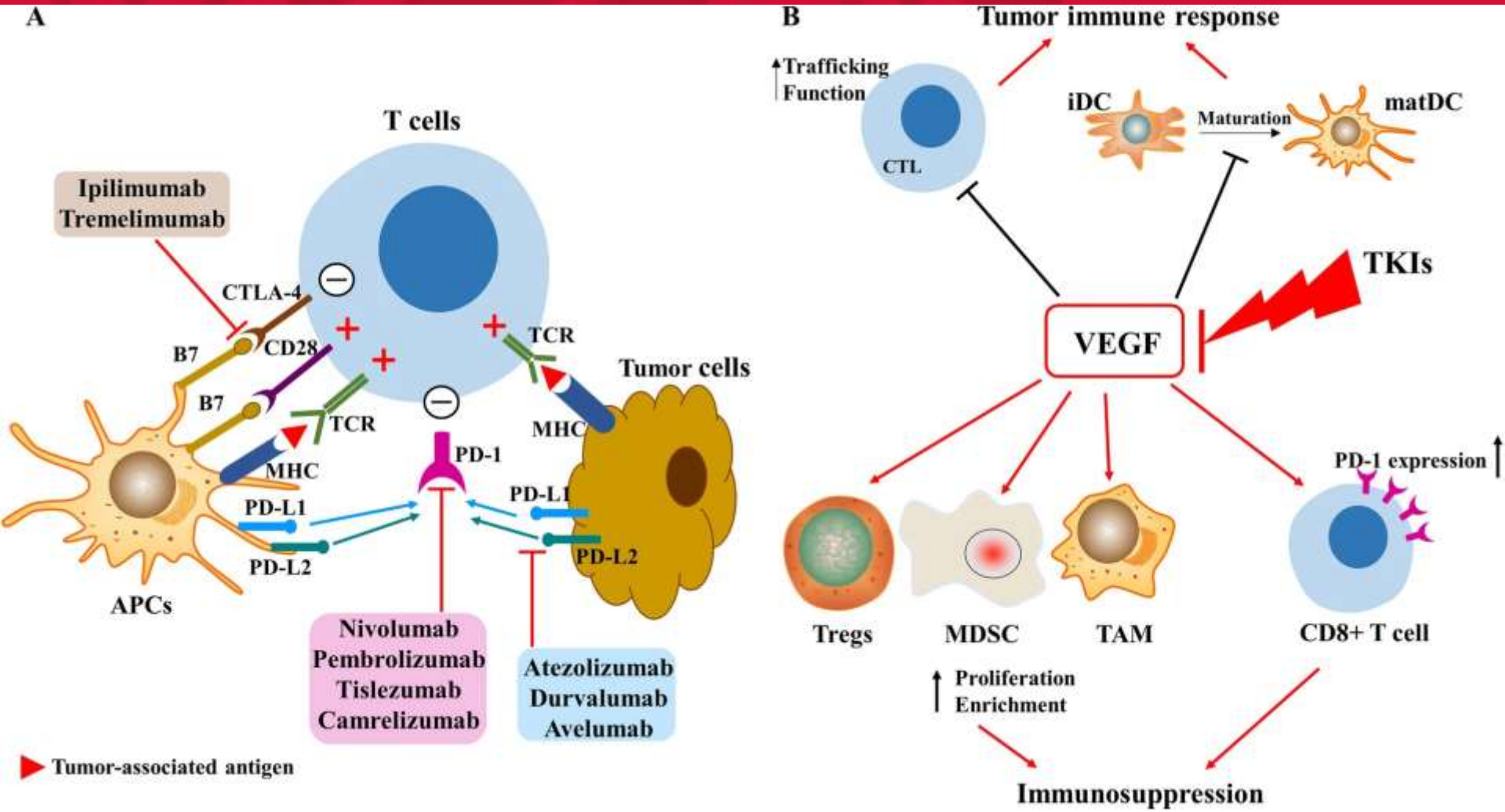
- Nivolumab*
- Durvalumab
- Pembrolizumab

Special scenarios

- Dostarlimab for MSI-H/dMMR
- Selpercatinib for RET-fusion+

Majority are only studied/approved for Child-Pugh A except for those with *

Mechanism of Action of HCC Therapies

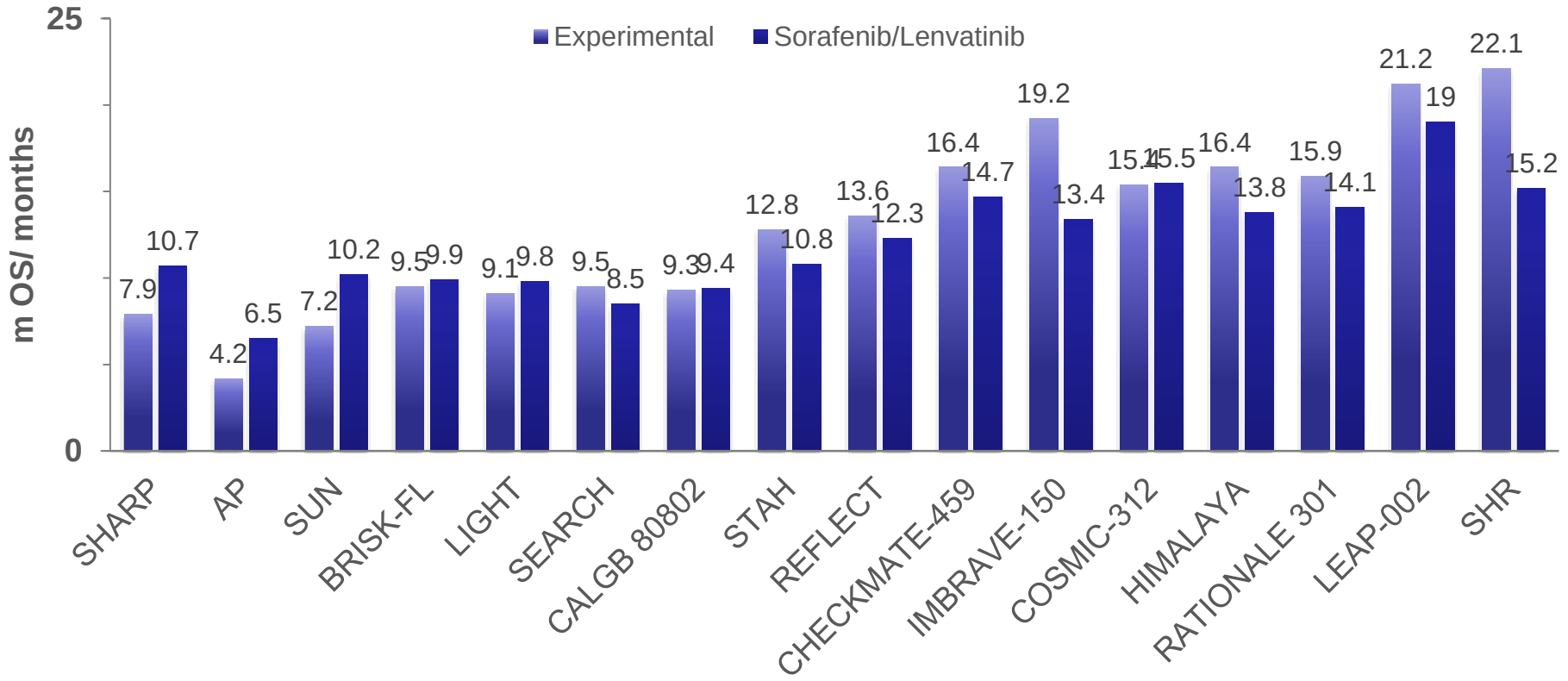


From: Zhang, H., Zhang, W., Jiang, L. *et al.* Recent advances in systemic therapy for hepatocellular carcinoma. *Biomark Res* **10**, 3 (2022). https://doi.org/10.1186/s40364-021-00350-4

***Tislezumab, Camrelizumab, Avelumab are not FDA approved for treatment of HCC**

Recent Progress with Systemic Therapy in Advanced HCC

mOS in phase-III trials



Vogel A et al. Lancet . 2022 Oct 15;400(10360):1345-1362. doi: 10.1016/S0140-6736(22)01200-4. Epub 2022 Sep 6.

Figure from Vogel, A; Oncology Today with Dr Neil Love: Management of **Hepatocellular Carcinoma, Companion Faculty Lecture**. Research To Practice. Nov 21, 2022

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First Line Systemic Therapy

Preferred - Combination

-Atezolizumab/Bevacizumab

-Tremelimumab/Durvalumab

TKIs

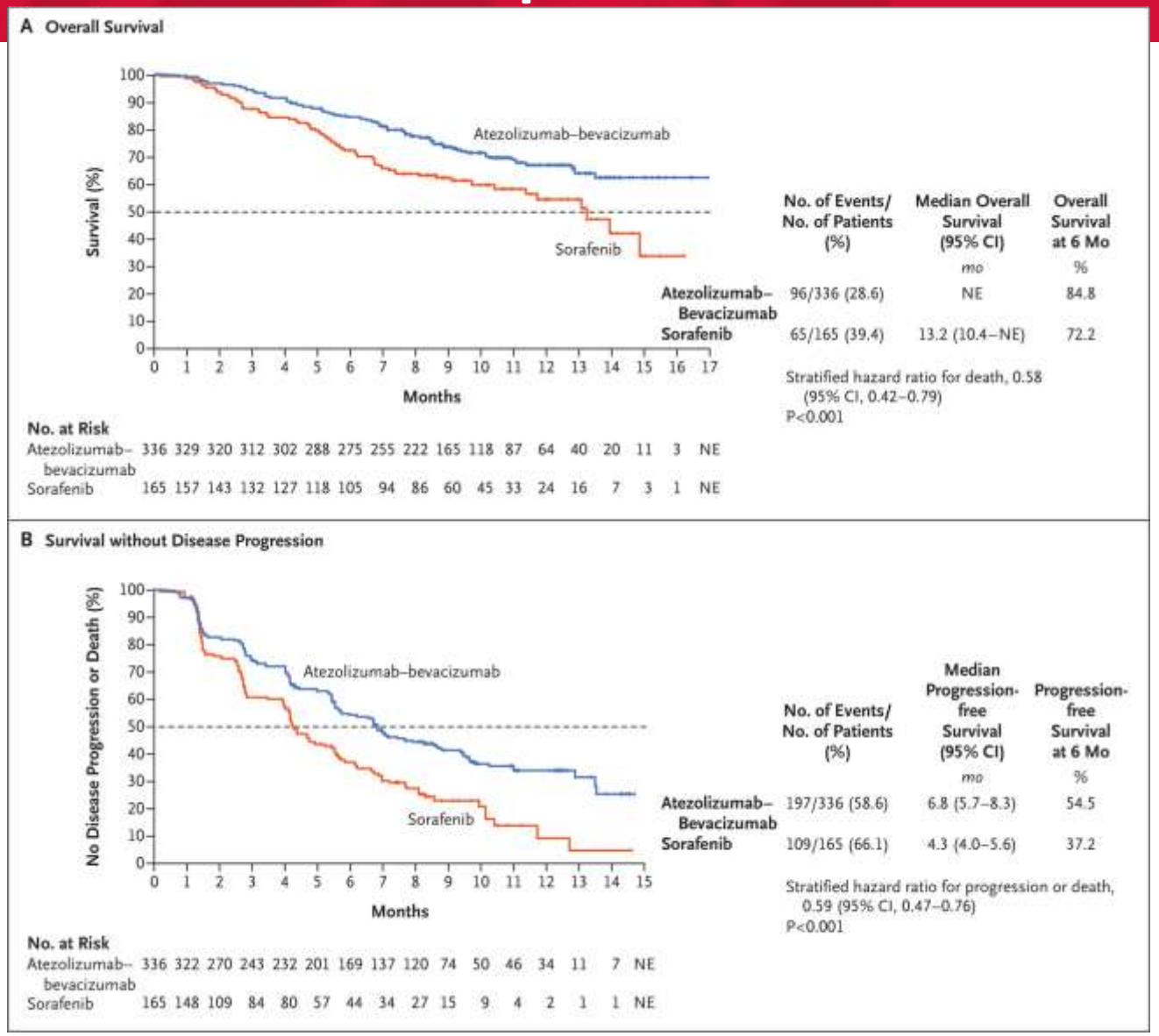
- Sorafenib*
- Lenvatinib

Immunotherapy

- Durvalumab
- Pembrolizumab
- Nivolumab* (only if ineligible for TKI or other anti-angiogenic agents)

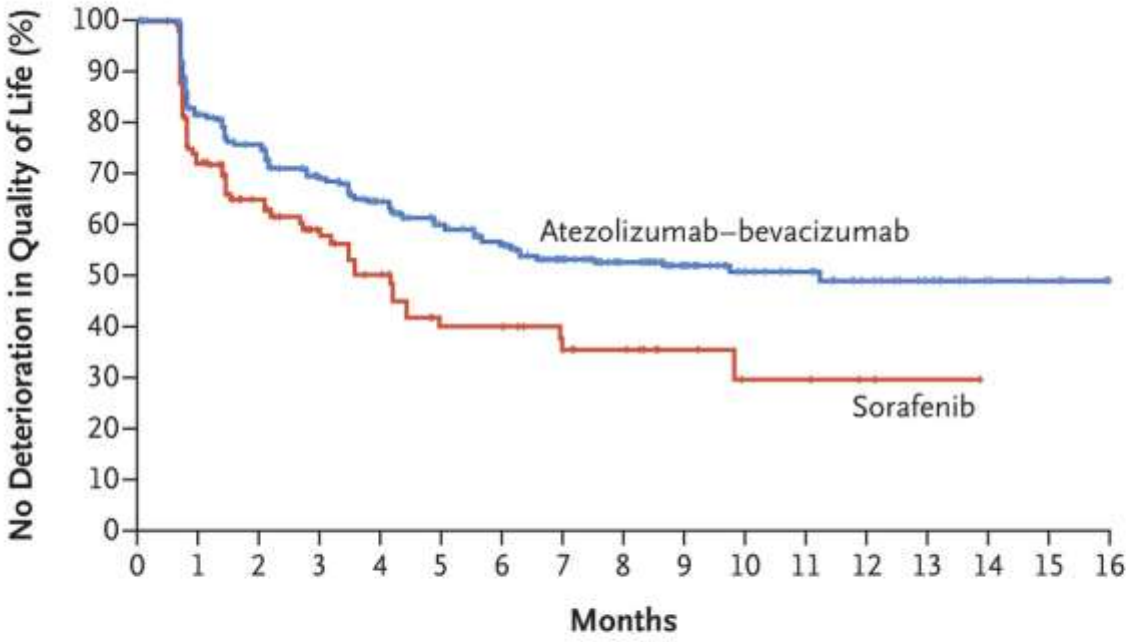
Majority are only studied/approved for CPA except for those with *

IMbrave150 – improved PFS and OS



Finn RS et al, N Engl J Med 2020; 382:1894-1905. DOI: 10.1056/NEJMoa191574

IMBrave150 also improved Time to Deterioration of Quality of Life



Quality of Life — Median Time to Deterioration (95% CI)	*mo*
Atezolizumab–Bevacizumab	11.2 (6.0–NE)
Sorafenib	3.6 (3.0–7.0)

Hazard ratio, 0.63 (95% CI, 0.46–0.85)

No. at Risk

Atezolizumab–bevacizumab	336	239	208	181	157	134	121	99	78	58	40	32	20	14	7	5	NE
Sorafenib	165	93	60	39	31	22	22	14	12	7	4	4	2	1	NE	NE	NE

Finn RS et al, N Engl J Med 2020; 382:1894-1905. DOI: 10.1056/NEJMoa191

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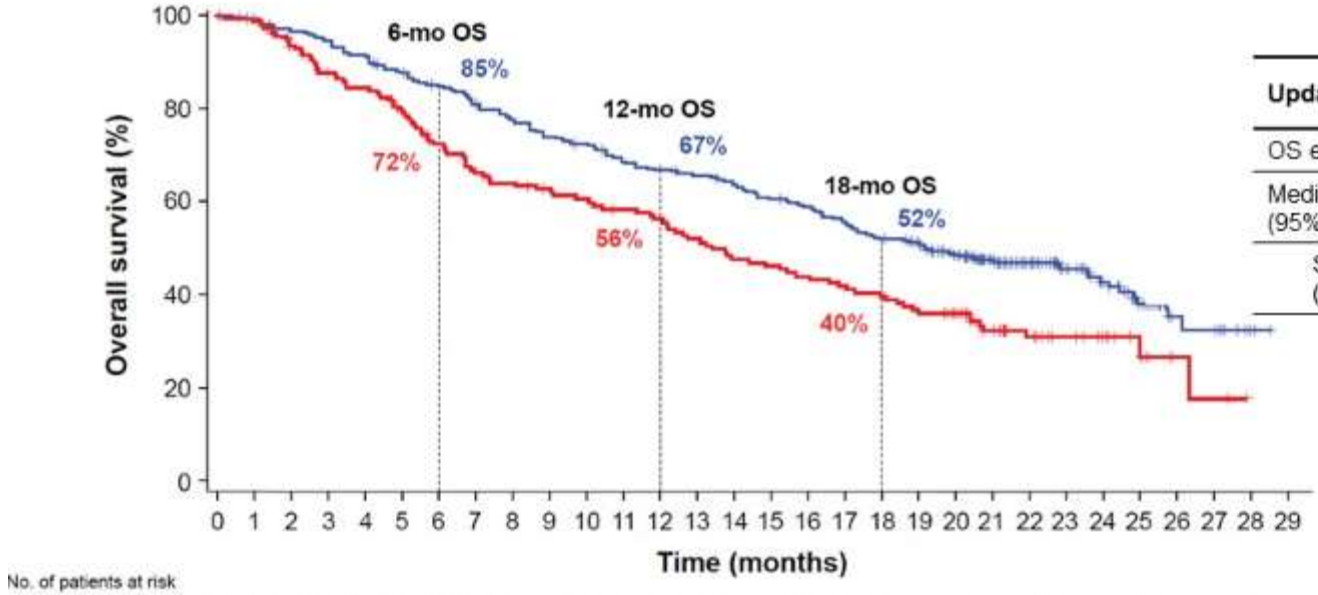
Updated OS for IMbrave150 after longer follow up



Updated OS	Atezo + Bev (336 pts)	Sorafenib (165 pts)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.
[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS). [b] *P* value for descriptive purposes only.

Finn RS et al, *Journal of Clinical Oncology* 39, no. 3_suppl (January 20, 2021) 267-267. DOI: 10.1200/JCO.2021.39.3_suppl.267

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Also improved ORR *and* CR rates

	Atezo + Bev n = 326 RECIST 1.1	Sor n = 159 RECIST 1.1	Atezo + Bev n = 325 HCC mRECIST	Sor n = 158 HCC mRECIST
Confirmed ORR (95% CI), %	29.8 (24.8, 35.0)	11.3 (6.9, 17.3)	35.4 (30.2, 40.9)	13.9 (8.9, 20.3)
CR, n (%)	25 (7.7)	1 (0.6)	39 (12.0)	4 (2.5)
PR, n (%)	72 (22.1)	17 (10.7)	76 (23.4)	18 (11.4)
SD, n (%)	144 (44.2)	69 (43.4)	121 (37.2)	65 (41.1)
Median DOR (95% CI), mo	18.1 (14.6, NE)	14.9 (4.9, 17.0)	16.3 (13.1, 21.4)	12.6 (6.1, 17.7)

DOR, duration of response; HCC mRECIST, modified RECIST for HCC; NE, not estimable; PR, partial response; SD, stable disease.

Finn RS et al, *Journal of Clinical Oncology* 39, no. 3_suppl (January 20, 2021) 267-267. DOI: 10.1200/JCO.2021.39.3_suppl.267

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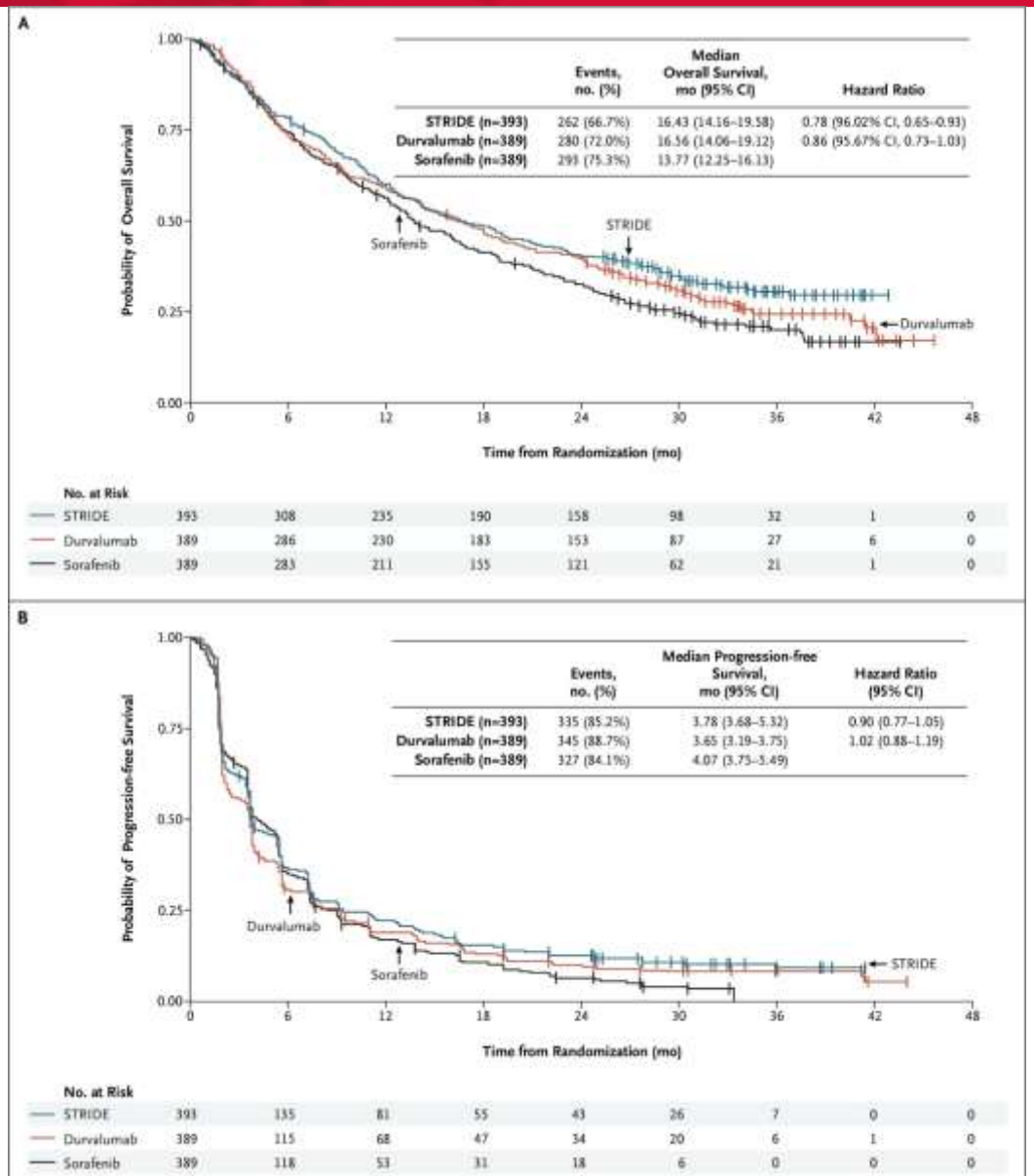
HIMALAYA – improvements in OS; not PFS

- Median OS 16.43 mo Tremelimumab + durvalumab (STRIDE) vs 16.56 mo durvalumab vs 13.77 mo sorafenib
- Median PFS 3.78 STRIDE vs 3.65 durvalumab vs 4.07 sorafenib
- Note – even sorafenib arm had notable longer survival than previous trials



Abou-Alfa GK et al. June 6, 2022. NEJM Evid 2022; 1 (8)
DOI:https://doi.org/10.1056/EVIDoa2100070

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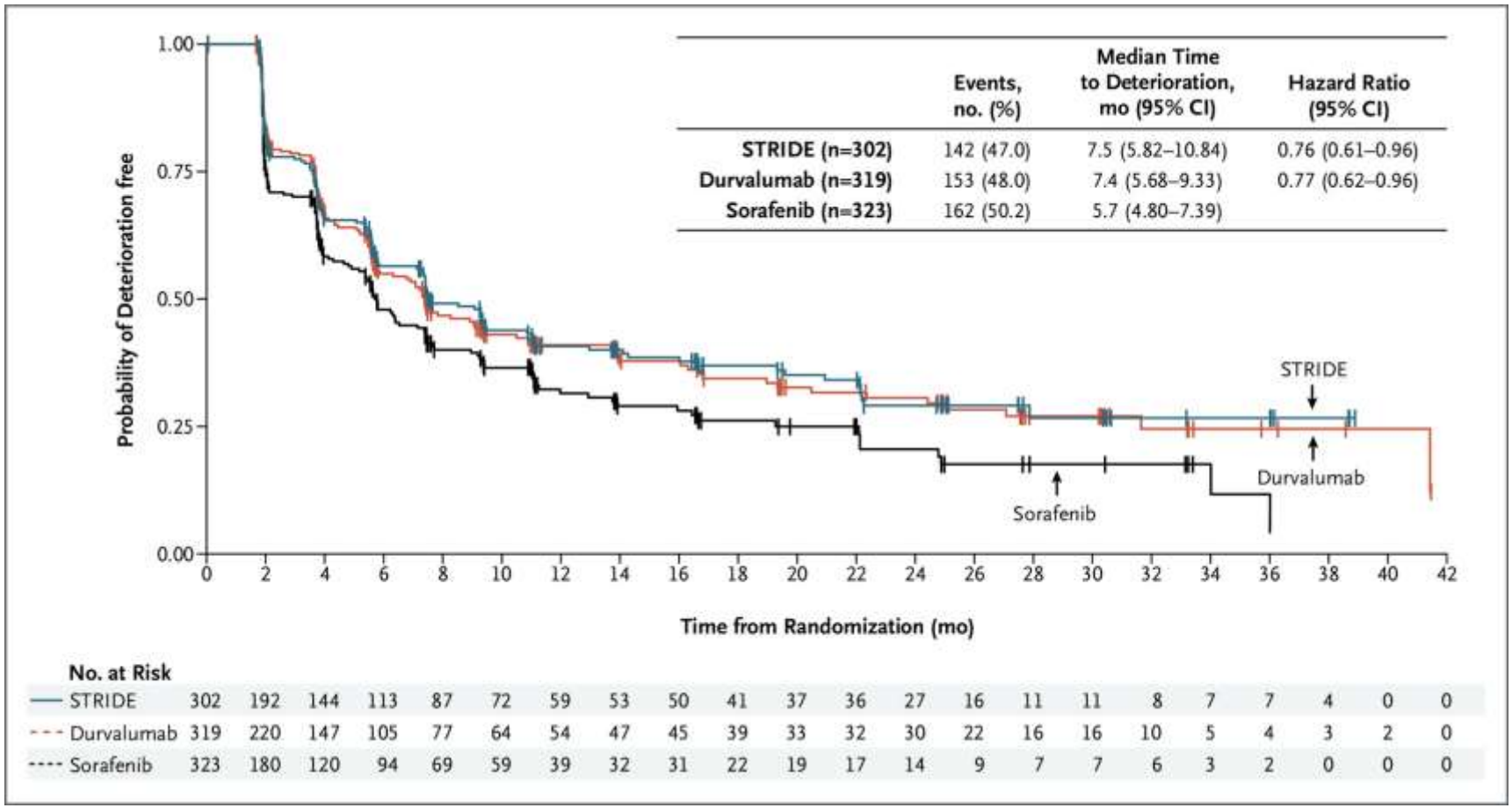
Also Improved Time to Deterioration of Quality of Life



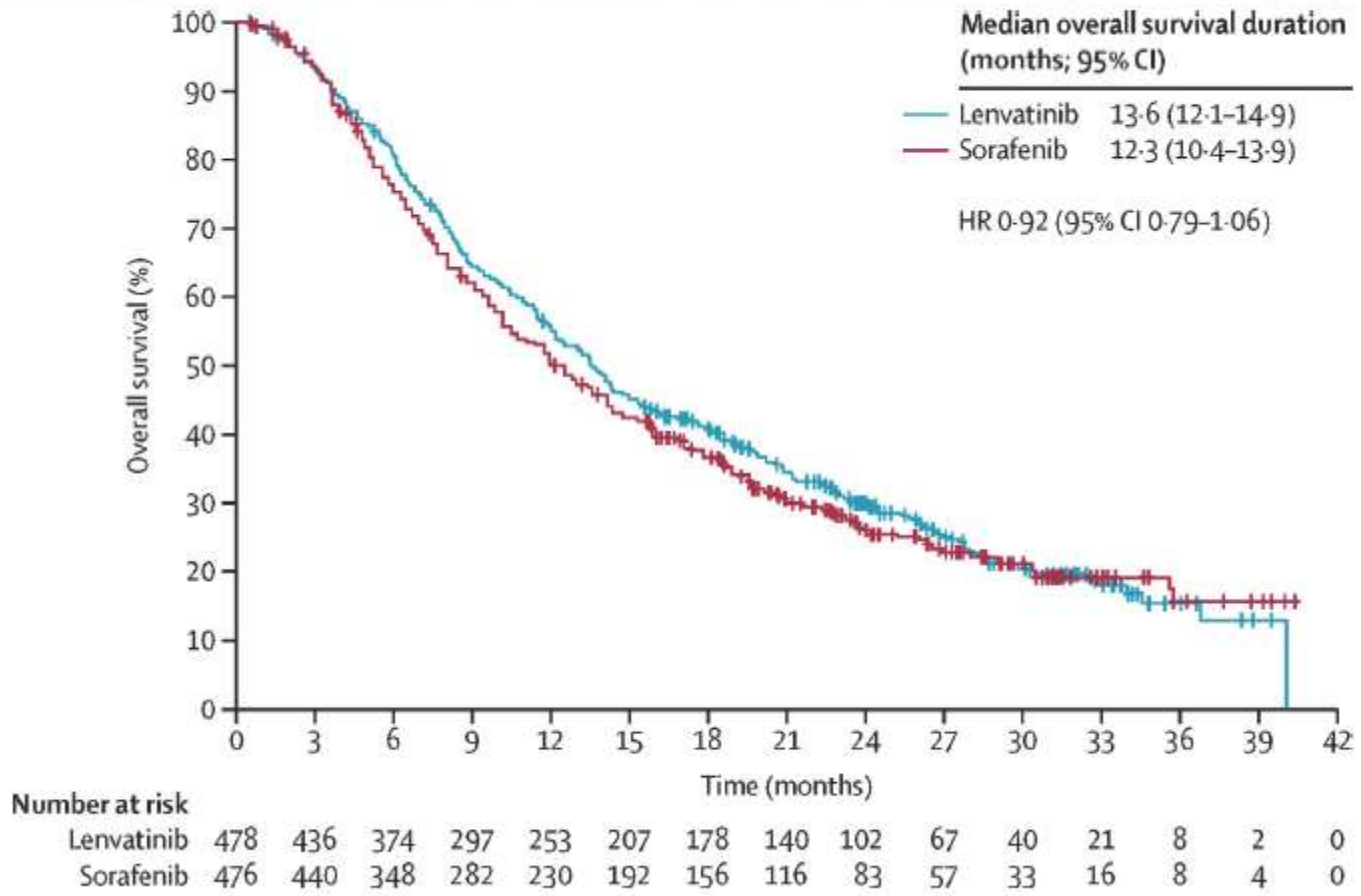
	Events, no. (%)	Median Time to Deterioration, mo (95% CI)	Hazard Ratio (95% CI)
STRIDE (n=302)	142 (47.0)	7.5 (5.82–10.84)	0.76 (0.61–0.96)
Durvalumab (n=319)	153 (48.0)	7.4 (5.68–9.33)	0.77 (0.62–0.96)
Sorafenib (n=323)	162 (50.2)	5.7 (4.80–7.39)	

No. at Risk																						
STRIDE	302	192	144	113	87	72	59	53	50	41	37	36	27	16	11	11	8	7	7	4	0	0
Durvalumab	319	220	147	105	77	64	54	47	45	39	33	32	30	22	16	16	10	5	4	3	2	0
Sorafenib	323	180	120	94	69	59	39	32	31	22	19	17	14	9	7	7	6	3	2	0	0	0

Grade 3/4 treatment-emergent adverse events occurred for 50.5% of patients with STRIDE, 37.1% with durvalumab, and 52.4% with sorafenib.

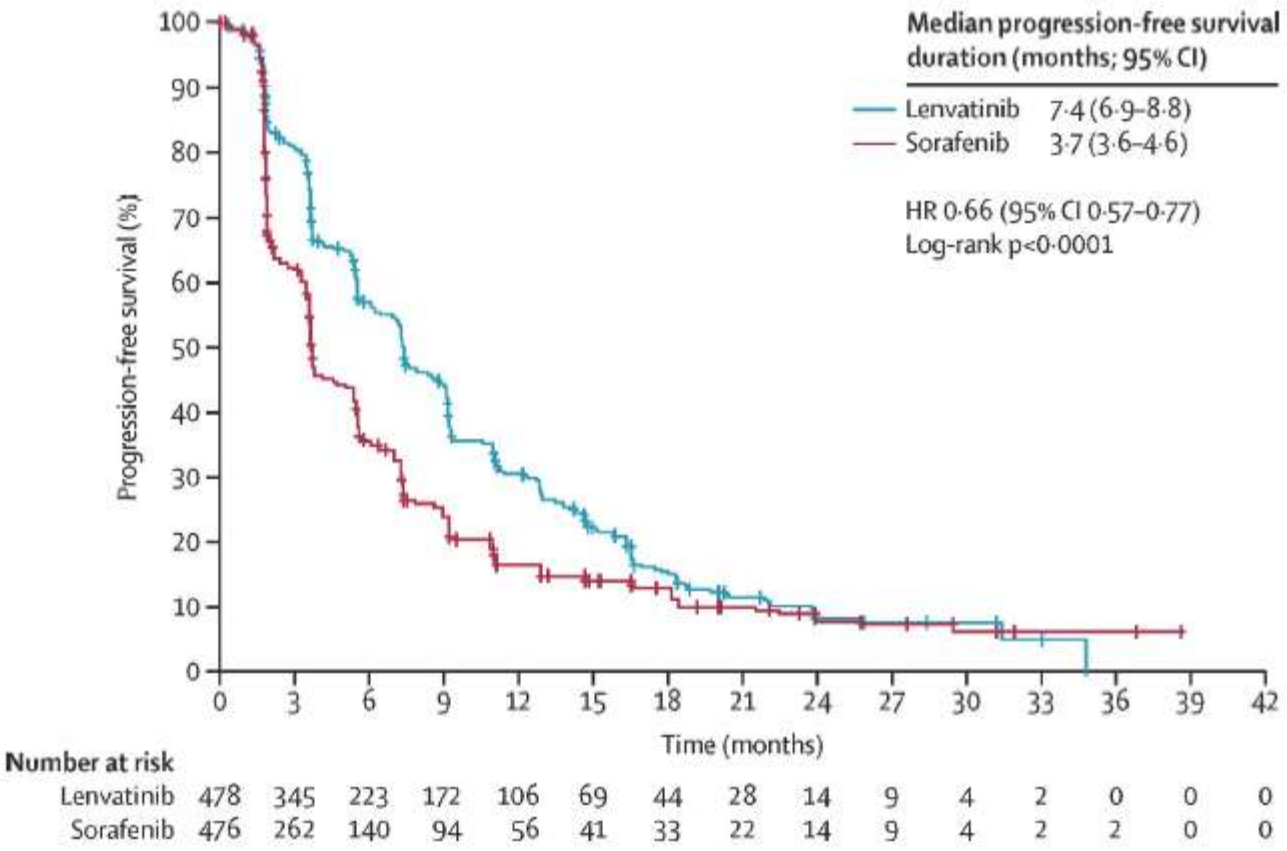
Abou-Alfa GK et al. June 6, 2022. NEJM Evid 2022;
DOI:https://doi.org/10.1056/EVIDoa2100070

REFLECT - Lenvatinib non-inferior to Sorafenib for OS



Kudo M et al, Lancet. 2018 Mar 24;391(10126):1163-1173. doi: 10.1016/S0140-6736(18)30207-1.

Lenvatinib non-inferior to Sorafenib for PFS

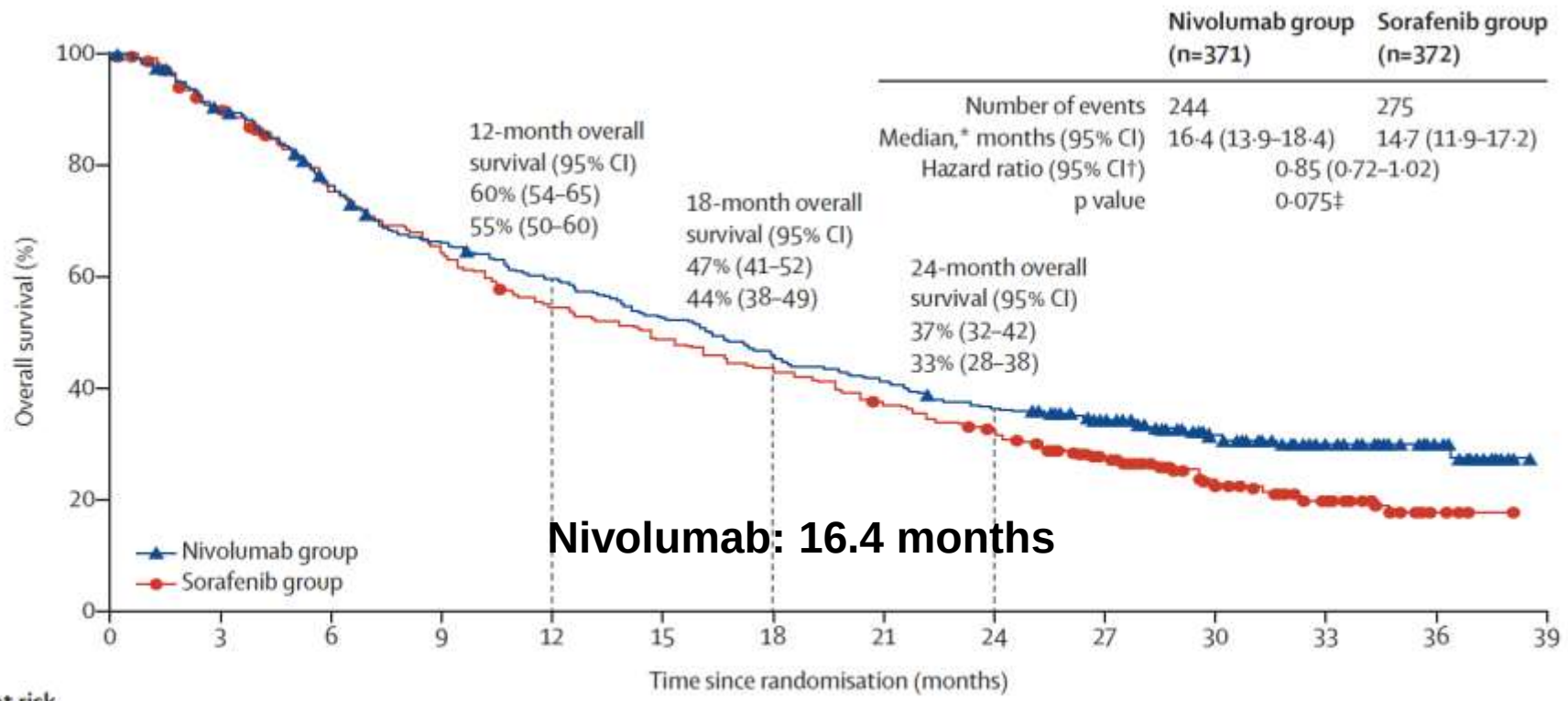


Kudo M et al, Lancet. 2018 Mar 24;391(10126):1163-1173. doi: 10.1016/S0140-6736(18)30207-1.

Efficacy of anti-PD1/PD-L1 in 1st line phase-III trials

A

Checkmate-459: Nivolumab



Number at risk (number censored)														
Nivolumab group	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 group	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)

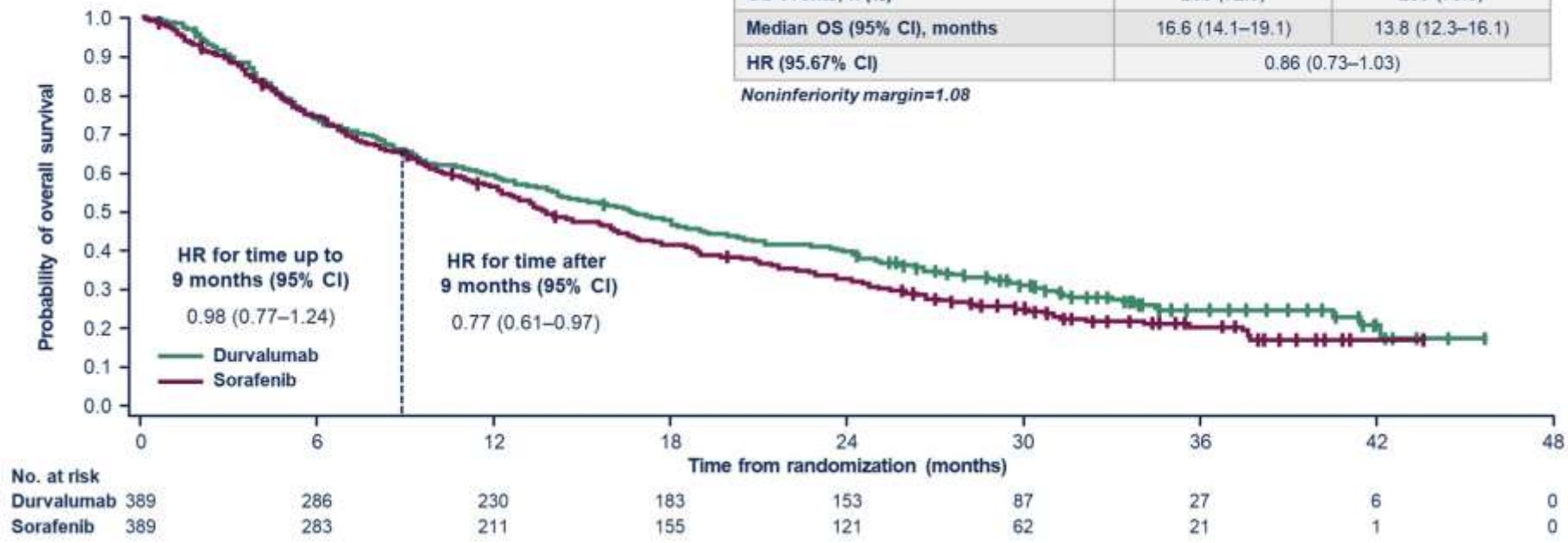
Yau T, et al.Lancet Oncol. 2022 Jan;23(1):77-90. doi: 10.1016/S1470-2045(21)00604-5. Epub 2021 Dec 13.

Efficacy of anti-PD1/PD-L1 in 1st line phase-III trials

HIMALAYA: Durvalumab

	Durvalumab (n=389)	Sorafenib (n=389)
OS events, n (%)	280 (72.0)	293 (75.3)
Median OS (95% CI), months	16.6 (14.1–19.1)	13.8 (12.3–16.1)
HR (95.67% CI)	0.86 (0.73–1.03)	

Noninferiority margin=1.08



Durvalumab: 16.6 months

Abou-Alfa GK et al. June 6, 2022. NEJM Evid 2022; 1 (8). DOI:https://doi.org/10.1056/EVIDoa2100070

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Subsequent Systemic therapy

TKIs

- Sorafenib
- Lenvatinib
- Regorafenib
- Cabozantinib
- Ramicurumab (AFP >400 and CPA)

Immunotherapy

- Nivolumab*
- Pembrolizumab
- Nivolumab + Ipilimumab

Specific Scenarios

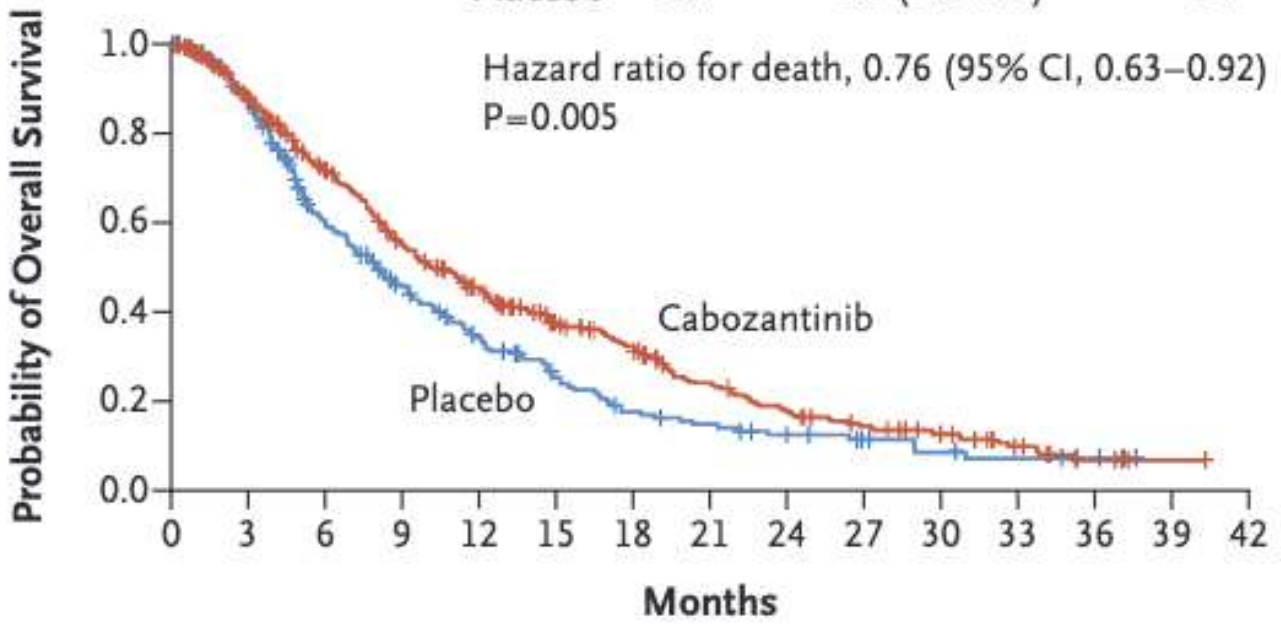
- Dostarlimab for MSI-H/dMMR
- Selpercatinib for RET-fusion+

Note, none of these have been studied after first line Atezo/bev or PDL1

Post Sorafenib – TKI and anti-VEGFR

CELESTIAL: Cabozantinib vs placebo

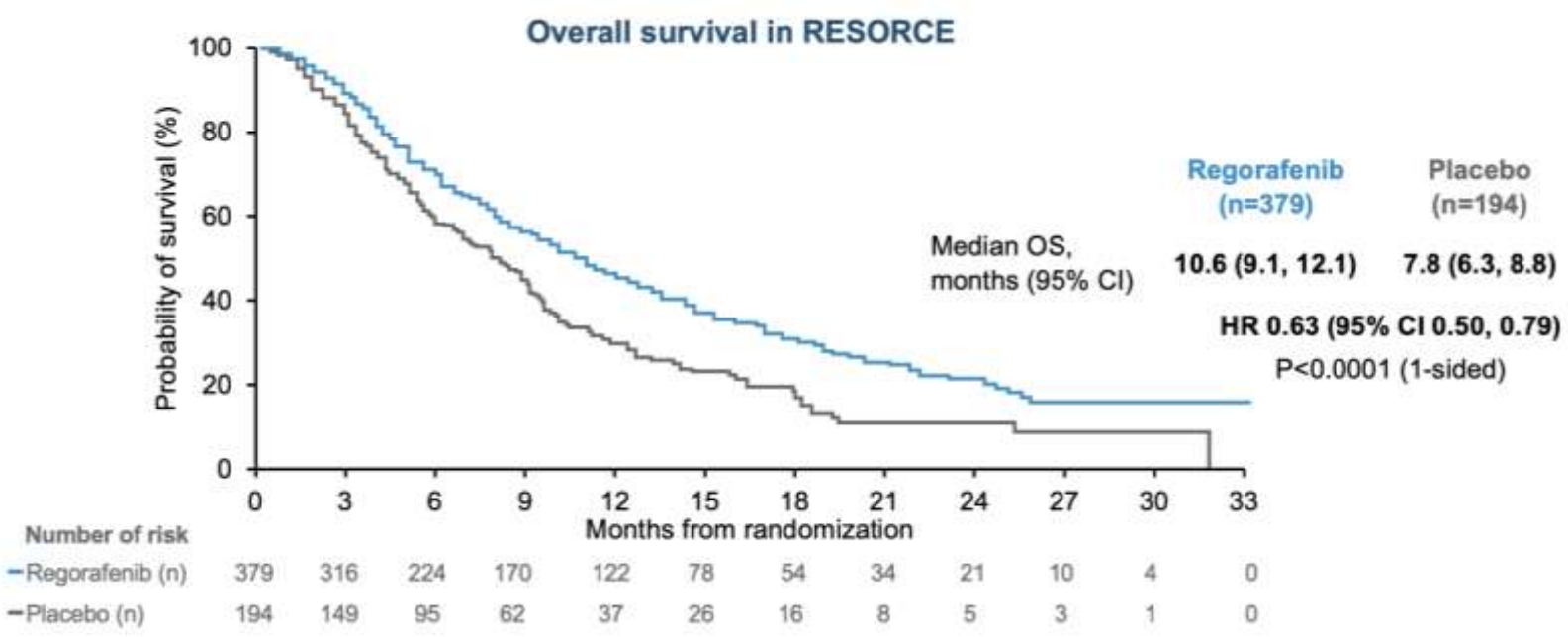
	No. of Patients	Median Overall Survival *mo (95% CI)*	No. of Events
Cabozantinib	470	10.2 (9.1–12.0)	317
Placebo	237	8.0 (6.8–9.4)	167



Abou-Alfa GK, N Engl J Med 2018;379:54-63. DOI: 10.1056/NEJMoa1717002

Post Sorafenib – TKI and anti-VEGFR

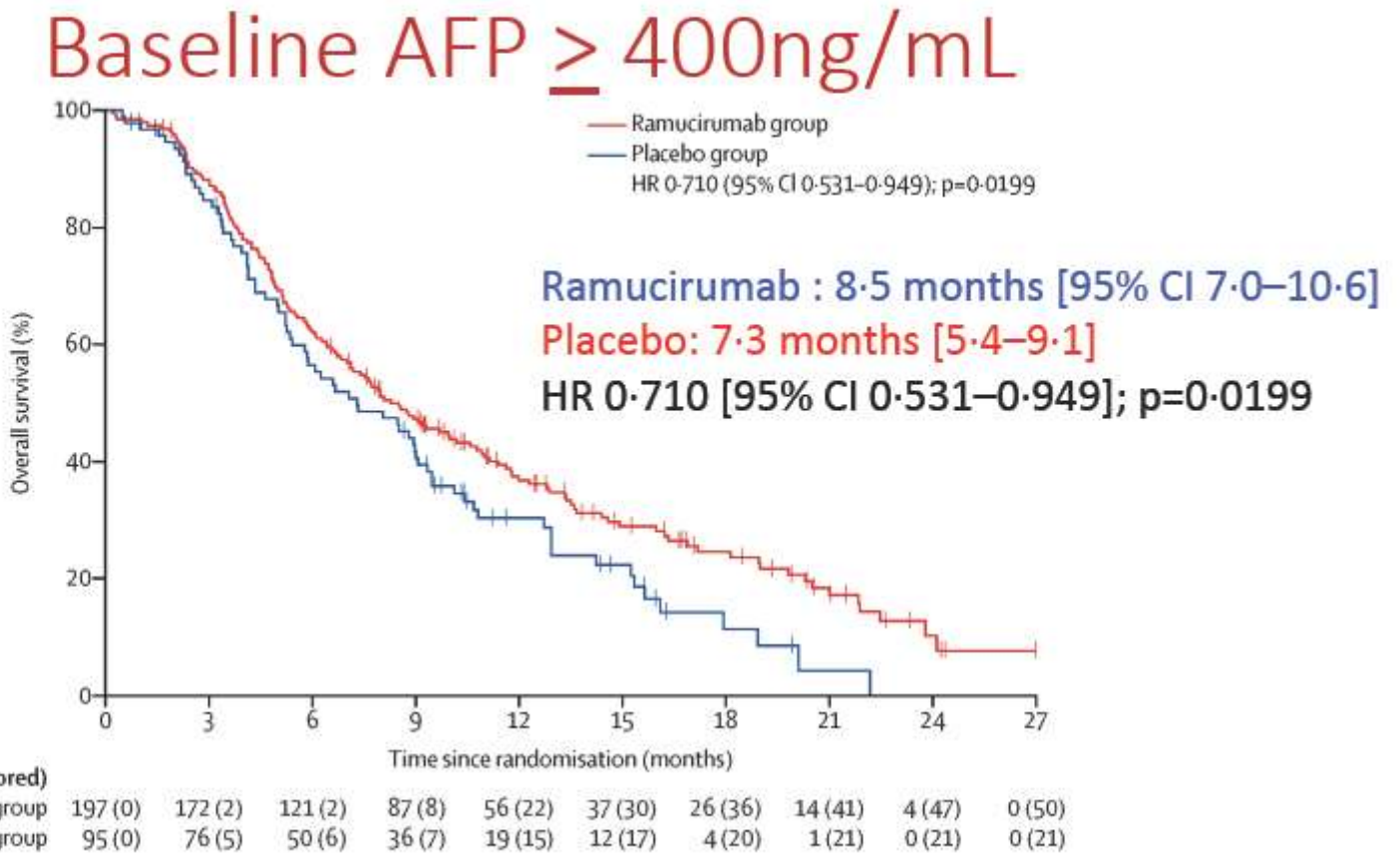
RESORCE: Regorafenib vs placebo



Bruix et al, Lancet. 2017 Jan 7;389(10064):56-66. doi: 10.1016/S0140-6736(16)32453-9. Epub 2016 Dec 6.
,

Post Sorafenib – TKI and anti-VEGFR

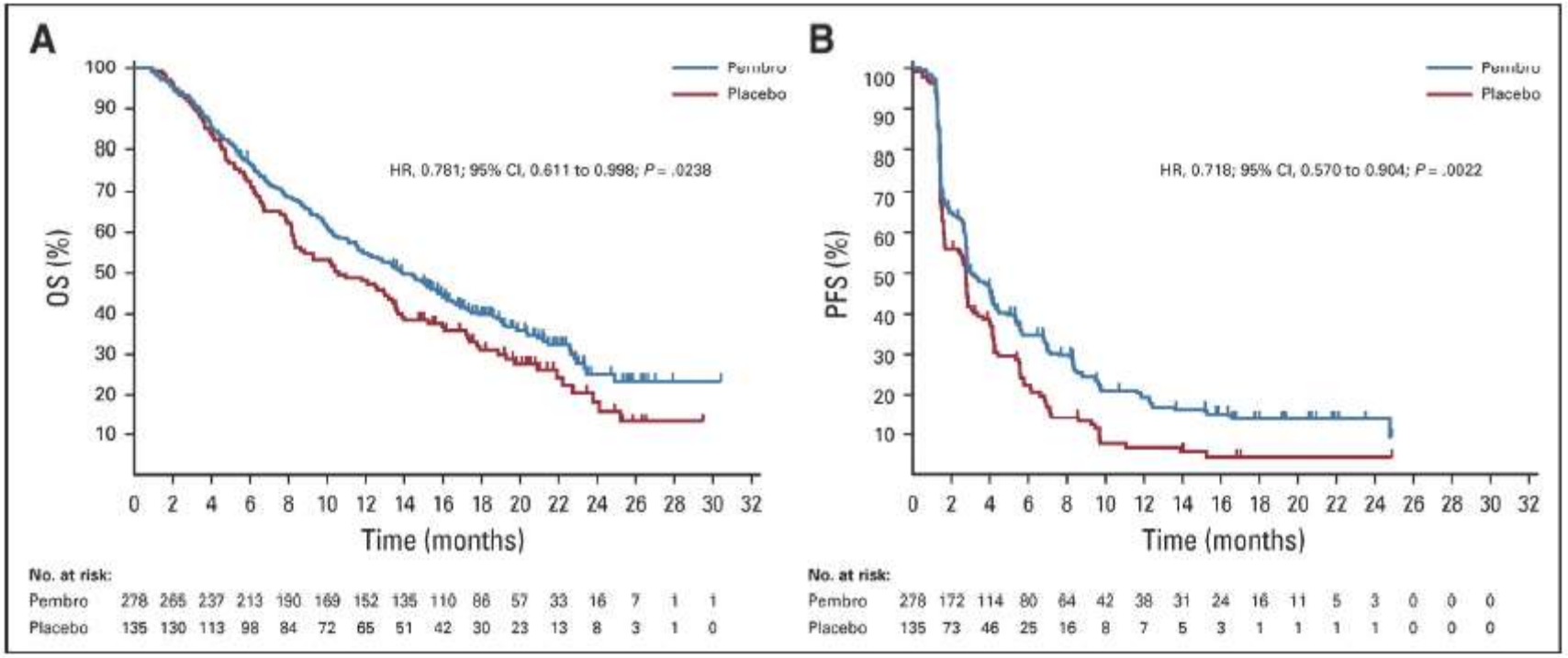
REACH 2: Ramucirumab vs placebo



Zhu A et al. *The Lancet Oncology*, Vol. 20, No. 2, p282–296 and Abou-Alfa, GK, *The Lancet Oncology*, Vol. 20, No. 2, p177–179

Immunotherapy in 2nd line

Keynote 240: Pembrolizumab vs placebo



Finn RS et al. J Clin Oncol. 2020 Jan 20;38(3):193-202. doi: 10.1200/JCO.19.01307. Epub 2019 Dec 2.

Median OS was 13.9 months for pembrolizumab versus 10.6 months for placebo -- not statistically significant but possibly a signal of benefit. Trial was also negative for PFS benefit. No difference in toxicity

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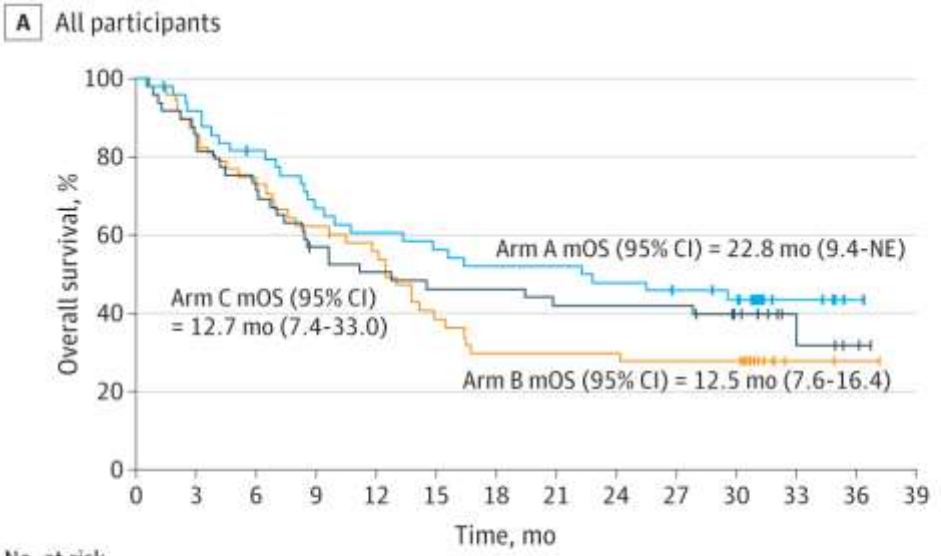
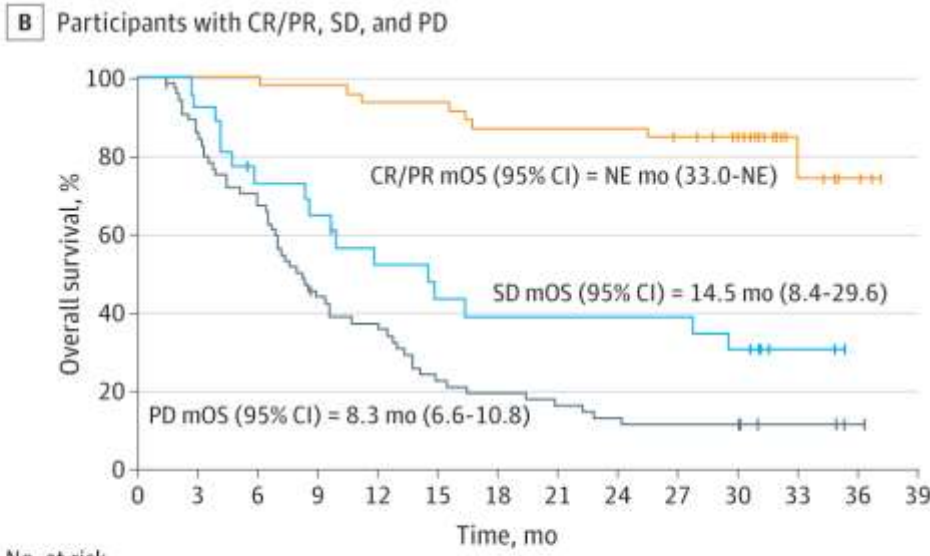
Checkmate 040 – ipi/nivo as dosed in arm A showed improvement in OS and response

- Patients were randomized 1:1:1 to either
- nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, administered every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks (arm A)
- nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, administered every 3 weeks (4 doses), followed by nivolumab 240 mg every 2 weeks (arm B); or
- nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (arm C).



No. at risk (censored)

Arm A	50	45	39	32	29	27	25	25	23	21	19	7	2	0
	(0)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(4)	(16)	(21)	(23)
Arm B	49	41	36	30	26	18	14	14	14	13	13	2	1	0
	(0)	(1)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(13)	(14)	(15)
Arm C	49	42	36	27	24	22	22	20	20	20	15	4	2	0
	(0)	(0)	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(5)	(15)	(17)	(19)



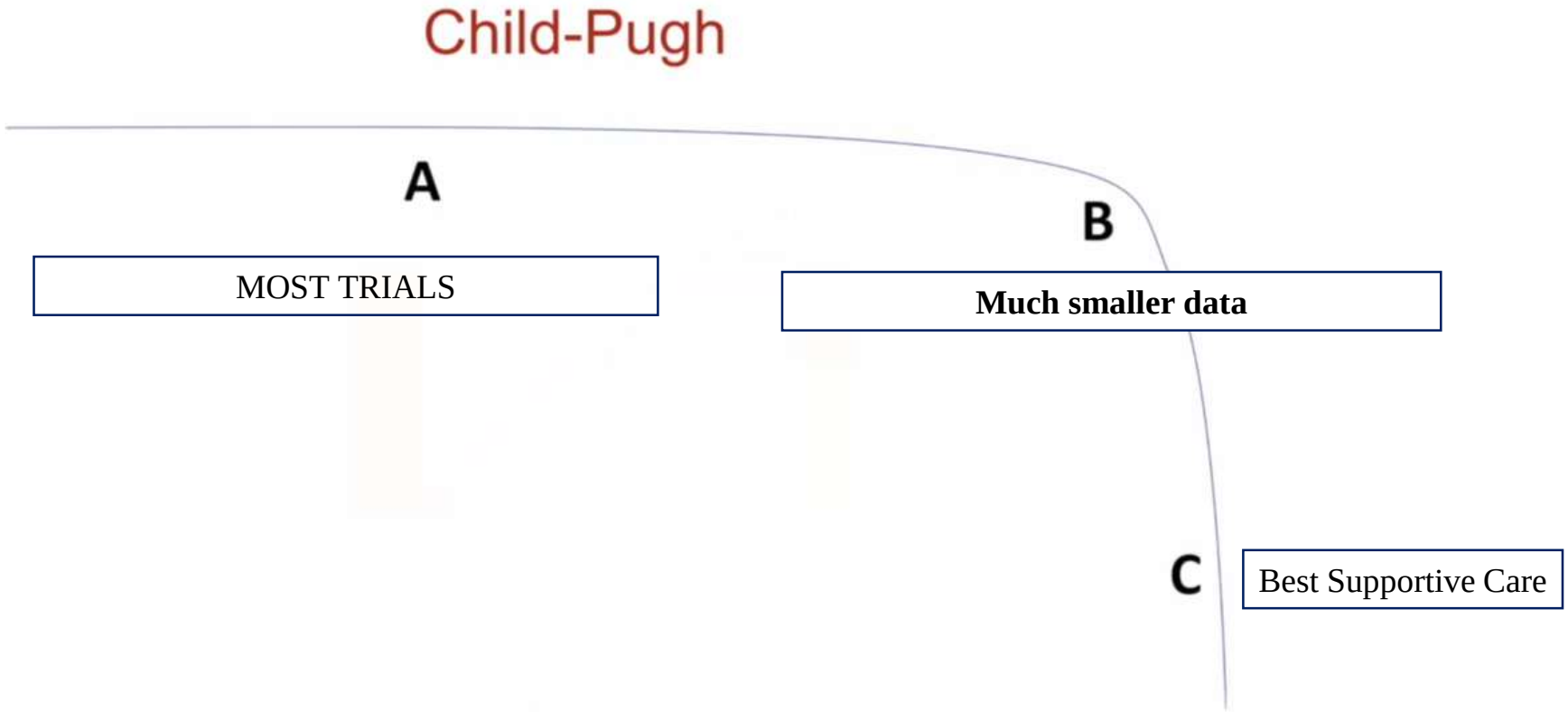
No. at risk (censored)[a]

CR/PR	46	46	46	45	43	43	40	40	40	38	33	7	3	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(6)	(31)	(35)	(38)
SD[b]	26	24	18	16	12	10	9	9	9	9	7	2	0	0
	(0)	(0)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(7)	(9)	(9)
PD	65	55	45	27	23	14	12	10	8	7	7	4	2	0
	(0)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(5)	(7)	(9)

Yau T, Kang Y, Kim T, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564

A note on the patient population in trials

- Clinical trials for HCC commonly use the Child-Pugh Score for assessment of baseline liver function and screening



A note on the patient population in trials

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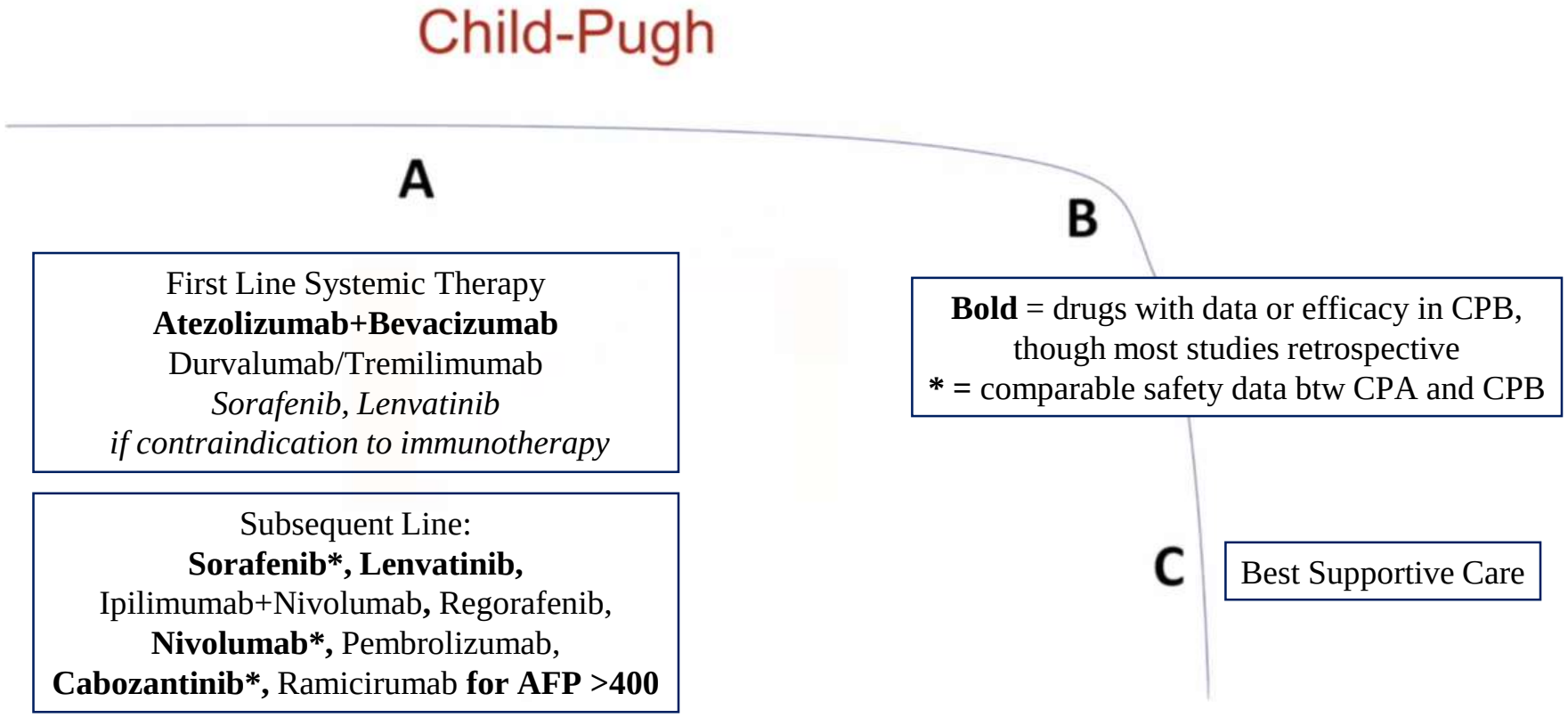

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Clinical Trial and Safety/Efficacy Data for Patients with Child-Pugh B Cirrhosis

Drug	Child-Pugh class	Median OS, months (95% CI)	Median PFS, months (95% CI)	ORR per RECIST v1.1, %	Grade 3 or 4 AEs, %	Grade 3 or 4 TRAEs, %
Sorafenib[3]	A (1,975 patients)	13.6 (12.8, 14.7)	–	–	33	26
	B (669 patients)	5.2 (4.6, 6.3)	–	–	32	22
Lenvatinib[4]	A (413 patients)	13.3 (11.6, 16.1)	6.5 (5.6, 7.4)	42.9[b]	–	54.7
	B[a] (60 patients)	6.8 (2.6, 10.3)	3.7 (1.8, 7.4)	28.3[b]	–	71.7
Atezolizumab plus bevacizumab[5]	A (154 patients)	16.8 (14.1, 23.9)	7.6 (6.2, 8.9)	26	–	Atezolizumab: 15[c] Bevacizumab: 14[c]
	B (48 patients)	6.7 (4.3, 15.6)	3.4 (2.6, 4.2)	21	–	Atezolizumab: 4[c] Bevacizumab: 15[c]
Nivolumab[6]	B (49 patients)	7.6 (4.4, 10.5)	2.7 (1.6, 4.0)	12	24	24
Cabozantinib (vs placebo)[7]	B[a] (51 patients vs 22 patients)	8.5 (7.7, 12.2) vs 3.8 (3.3, 4.8)	3.7 (1.9, 5.2) vs 1.9 (1.7, 2.1)	–	71	–

Figure from Li D et al; Systemic Therapies for Hepatocellular Carcinoma and Child-Pugh B Cirrhosis: How We Treat. ASCO Daily News. June 16, 2022

1.Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study. *J Hepatol*. 2016;65(6):1140-1147.
2.Huynh J, Cho MT, Kim EJH, et al. Post hoc analysis in patients (pts) with unresectable hepatocellular carcinoma (uHCC) who progressed to Child-Pugh B (CPB) liver function in the phase III REFLECT study of lenvatinib (LEN). *J Clin Oncol*. 2021;39:3s (suppl; abstr 298).
3.D'Alessio A, Fulgenzi CAM, Nishida N, et al. Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: a real-world study. *Hepatology*. Published online March 21, 2022.
4.Kudo M, Matilla A, Santoro A, et al. CheckMate 040 cohort 5: a phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis. *J Hepatol*. 2021;75(3):600-609.
5.El-Khoueiry A, Meyer T, Cheng A, et al. Outcomes for patients with advanced hepatocellular carcinoma and Child-Pugh B liver function in the phase 3 CELESTIAL study of cabozantinib vs placebo. *Ann Oncol*. 2020;31:3s (suppl; abstr SO-9):S220.

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Treatment of HCC in Child-Pugh B

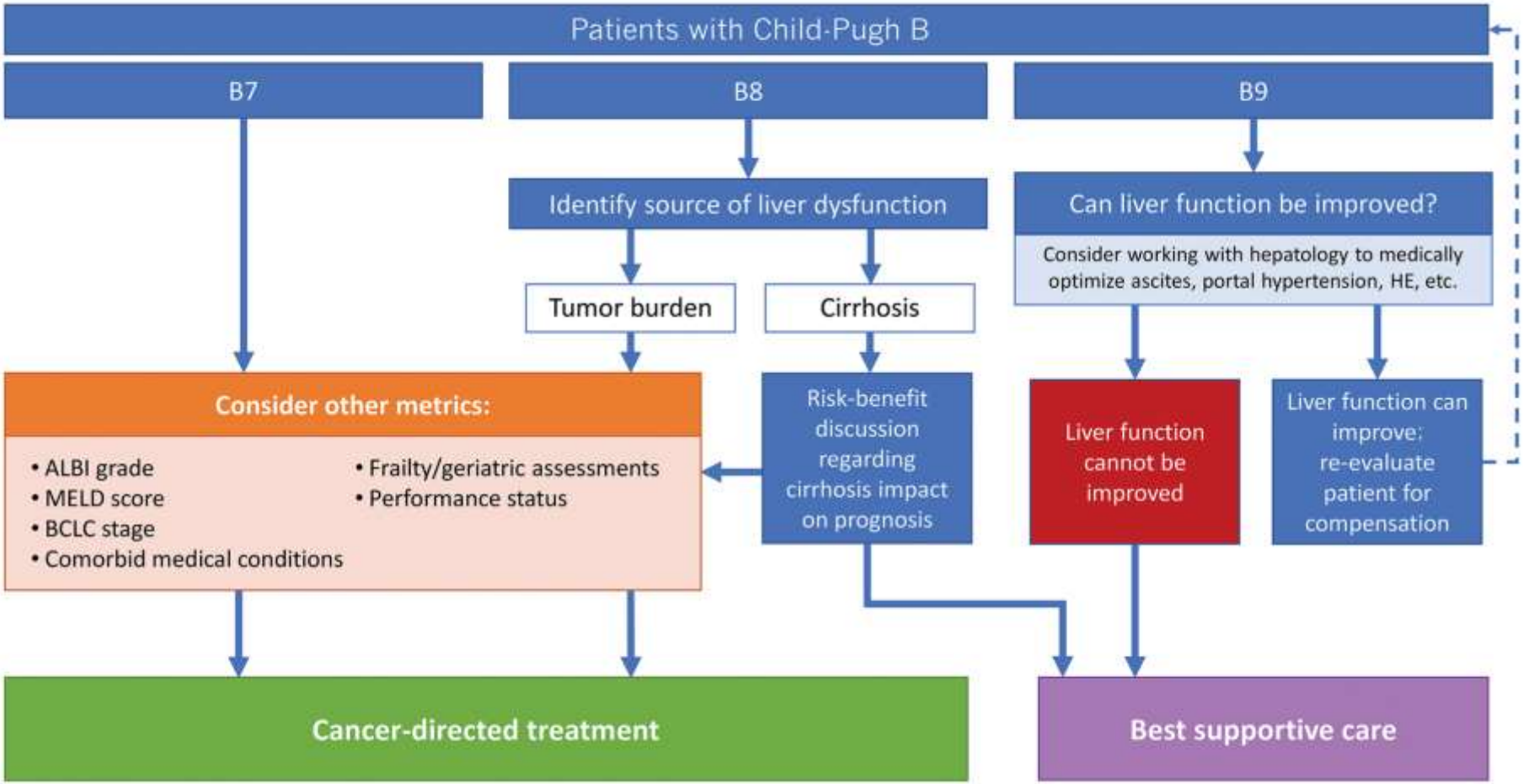

Figure from Li D et al; Systemic Therapies for Hepatocellular Carcinoma and Child-Pugh B Cirrhosis: How We Treat. ASCO Daily News. June 16, 2022

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Future Directions as of 2022

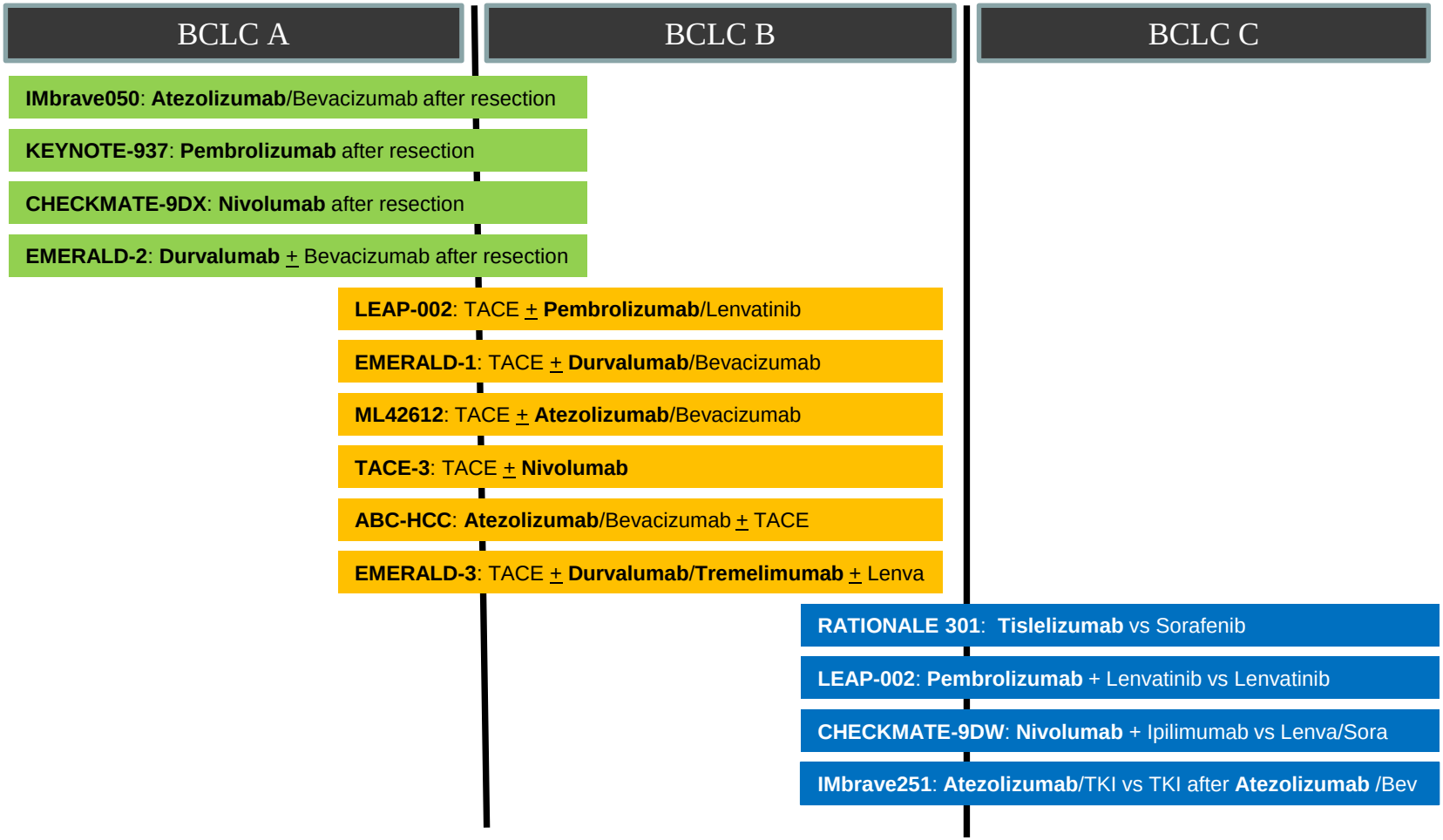

Figure from Vogel, A; Oncology Today with Dr Neil Love: Management of **Hepatocellular Carcinoma, Companion Faculty Lecture**. Research To Practice. Nov 21, 2022

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Post-Test

1. Which systemic therapy combination has shown superiority to sorafenib in the first line setting ?

a) Atezolizumab + Bevacizumab
b) Tremelimumab + Durvalumab
c) A and B
d) None of the above

Post-Test

2. The results of the REFLECT Trial showed that compared to sorafenib, lenvatinib was:

a) Non-inferior to sorafenib in PFS, but not OS
b) Superior to sorafenib
c) Inferior to sorafenib
d) Non-inferior to sorafenib in both OS and PFS