Immunotherapy in Hepatocellular Carcinoma

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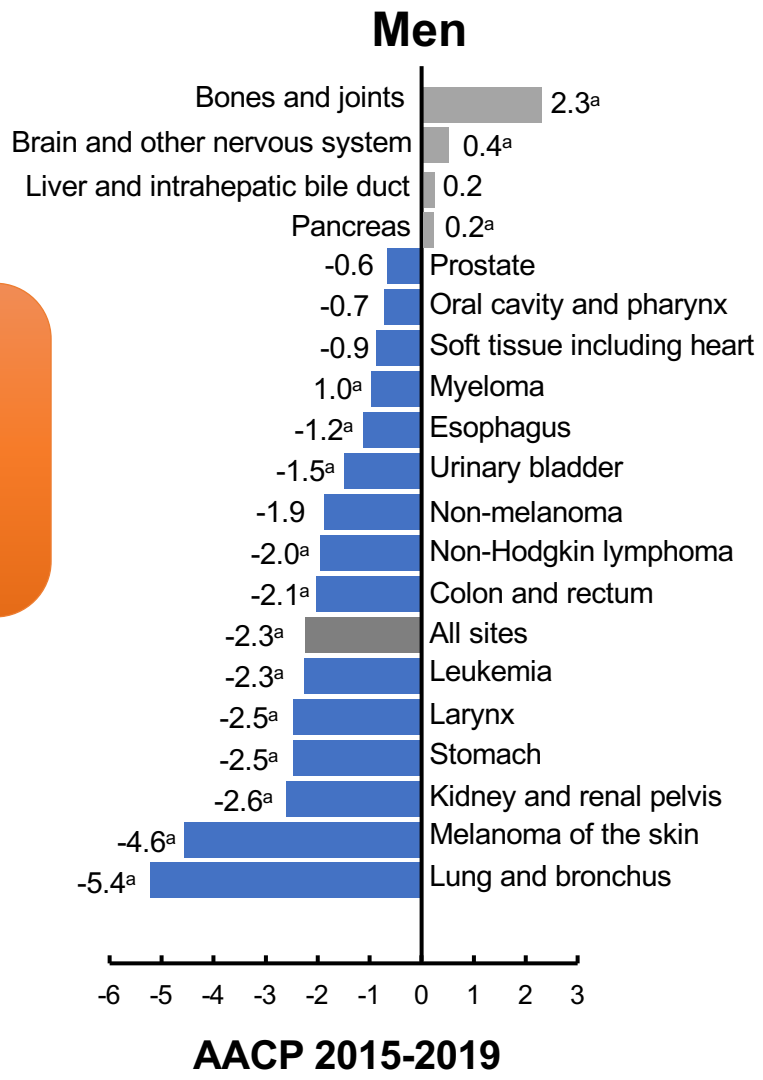
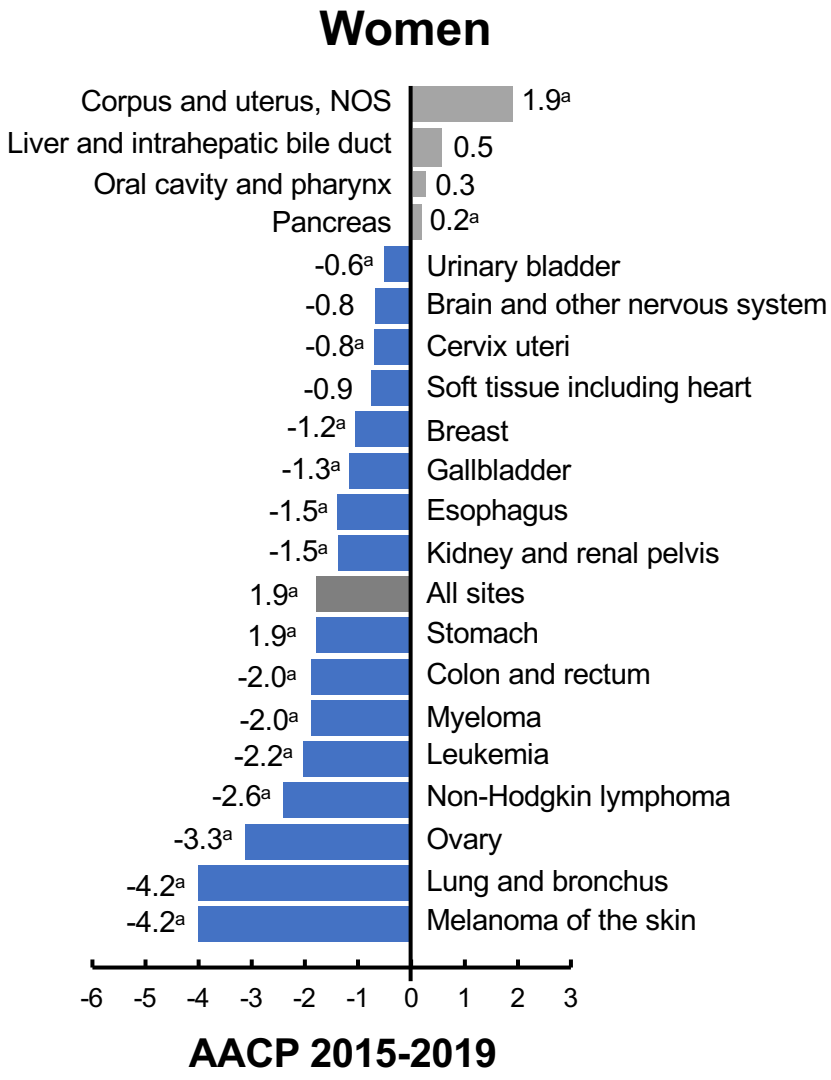
HCC Mortality in the United States Is Increasing

HCC is one of the top drivers of cancer death in the United States (2022 Annual Report)





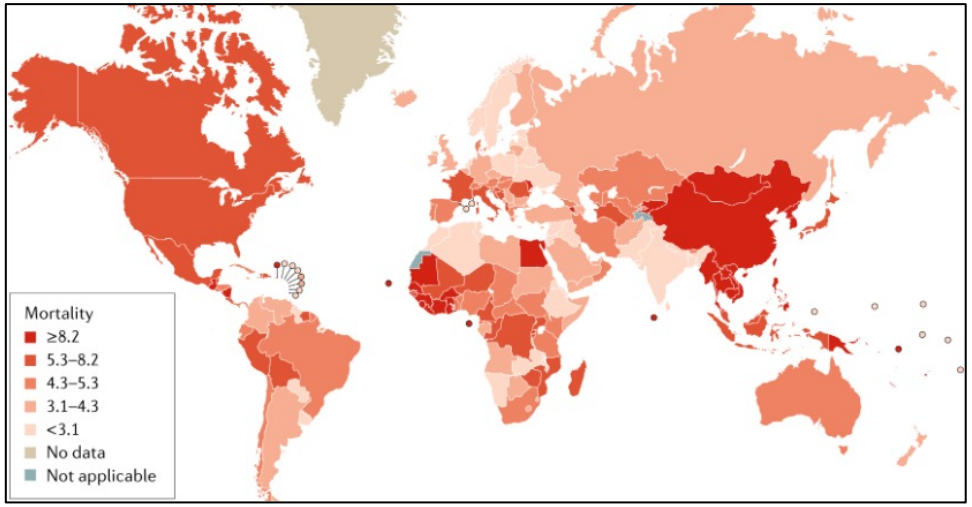
HCC Mortality Is Increasing Globally

905,700 people were diagnosed with liver cancer in 2020

830,200 people died from liver cancer in 2020

Liver cancer ranked **among the top 3 causes of cancer death** in 46 countries in 2020

The number of people diagnosed with or dying from liver cancer globally **could increase by >55% between 2020 and 2040** if current rates do not change



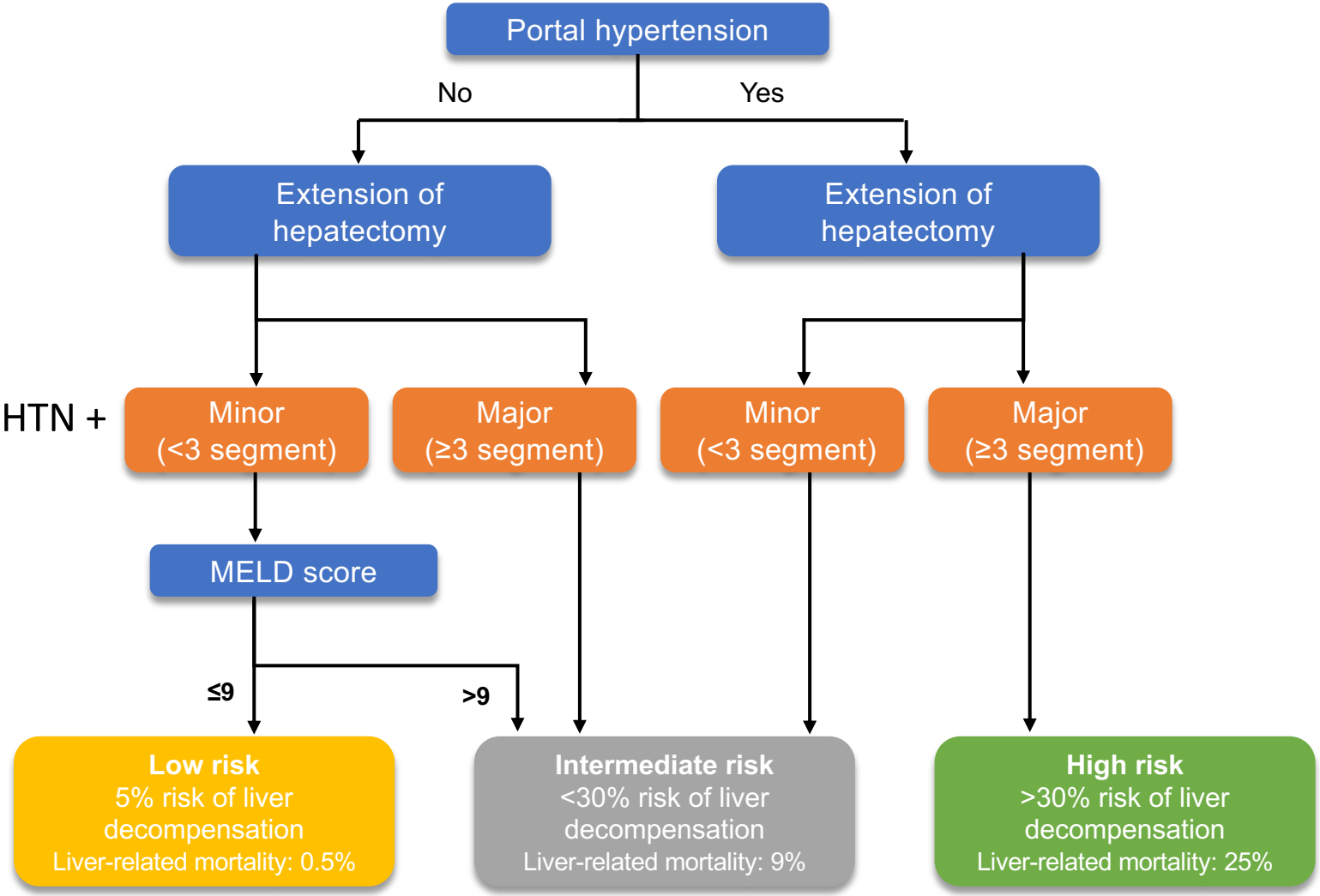
Most Early-Stage HCCs Have an Immunosuppressive Microenvironment

HCC Immune Classes	Immune Class (~30% of HCCs)		Immune Intermediate Class (45% of HCCs)	Immune Excluded Class (~25% of HCCs)
Immune subtypes	Active immune (~20% of HCCs)	Exhausted immune (~10% of HCCs)		
Gene expression and enrichment for signatures	↑ T cells, cytotoxic cells, TLS, macrophages, and PD-1 signaling			↓ T cells, B cells, and cytotoxic cells
	IFN$_\gamma$, *GZMB*, and *PRF1*	Activated stroma		↑ *PTK2*
	Signatures of response to immunotherapy	TGFβ		*CCL4*
		T-cell exhaustion		
DNA structural alterations	↓ chromosomal aberrations		↑ chromosomal aberrations	
• Copy number variations • Mutations				*CTNNB1*
Protein immunohistology	↑ immune cell infiltration, PD-1/PD-L1, and TLS		↓ immune cell infiltration, PD-1/PD-L1, and TLS	
Epigenetic aberrations	192 immune-related genes differentially methylated			

1. Sia D et al. *Gastroenterology*. 2017;153:812-826. 2. Llovet JM et al. *Nat Rev Clin Oncol*. 2018;15:599-616.

Hepatic Resection

- **Guidelines recommend resection only for**
  - Single nodules, *ANY* size
  - No *clinically significant portal HTN* (CSPH = HVPG ≥10 mmHg)
    - ➢ + EV; platelets <100,000 mm^3; or spleen >12 cm
  - Bilirubin <1 mg/dL
  - 5-y OS: 70%; OS significantly less if CSP HTN + bilirubin >1 mg/dL
- **Future liver remnant**
  - ≥20% normal liver
  - ≥30% with fibrosis or steatosis
  - **≥40% in cirrhosis**



HCC Recurrence Rate Is 70%-80% Post Resection

Factors Associated With Outcomes

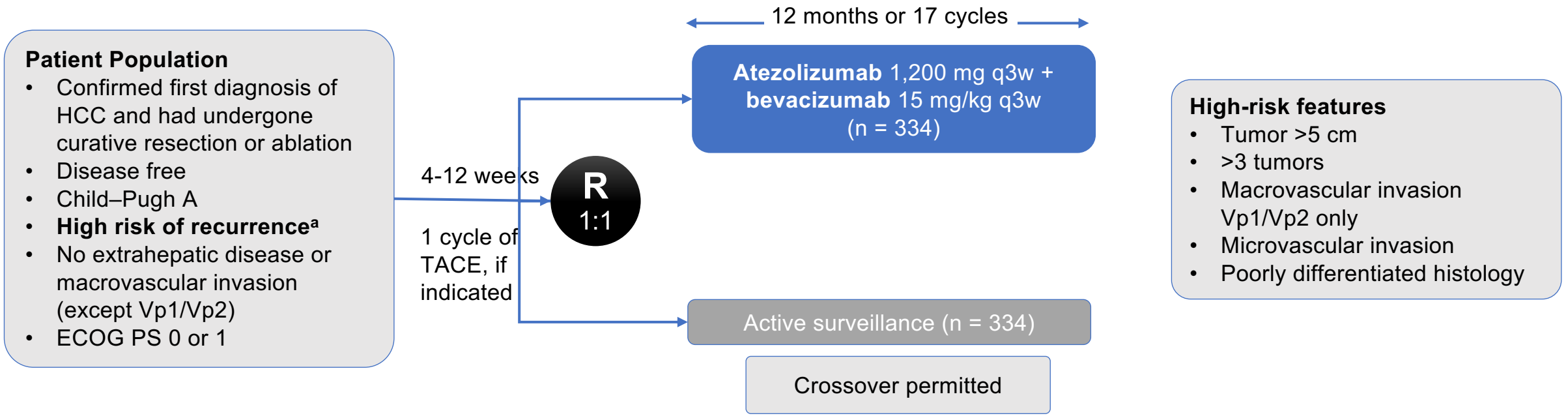
# of nodules (5-y OS)[1]	Single: 57%	≥3: 26%
Tumor size (5-y recurrence)[2]	<5 cm: 32%	>5 cm: 43%
Tumor-free margin (5-y OS)[3]	2 cm: 75%	1 cm: 49%
Blood loss (median OS)[4]	<1L: 68 months <2L: 49 months	>1L: 18 months >2L: 13 months

Sorafenib did not work in the adjuvant setting

Fabricio Souza, Marie-Aude Le Berre, Gerold Meinhardt, Josep M Llovet*, on behalf of the STORM investigators

1. Ikai I et al. *Cancer*. 2004;101:796-802. 2. Vauthey JN et al. *J Clin Onc*. 2002;20:1527-1536. 3. Shi M et al. *Ann Surg*. 2007;245:36-43.
4. Katz SC et al. *Ann Surg.* 2009;249:617-623.

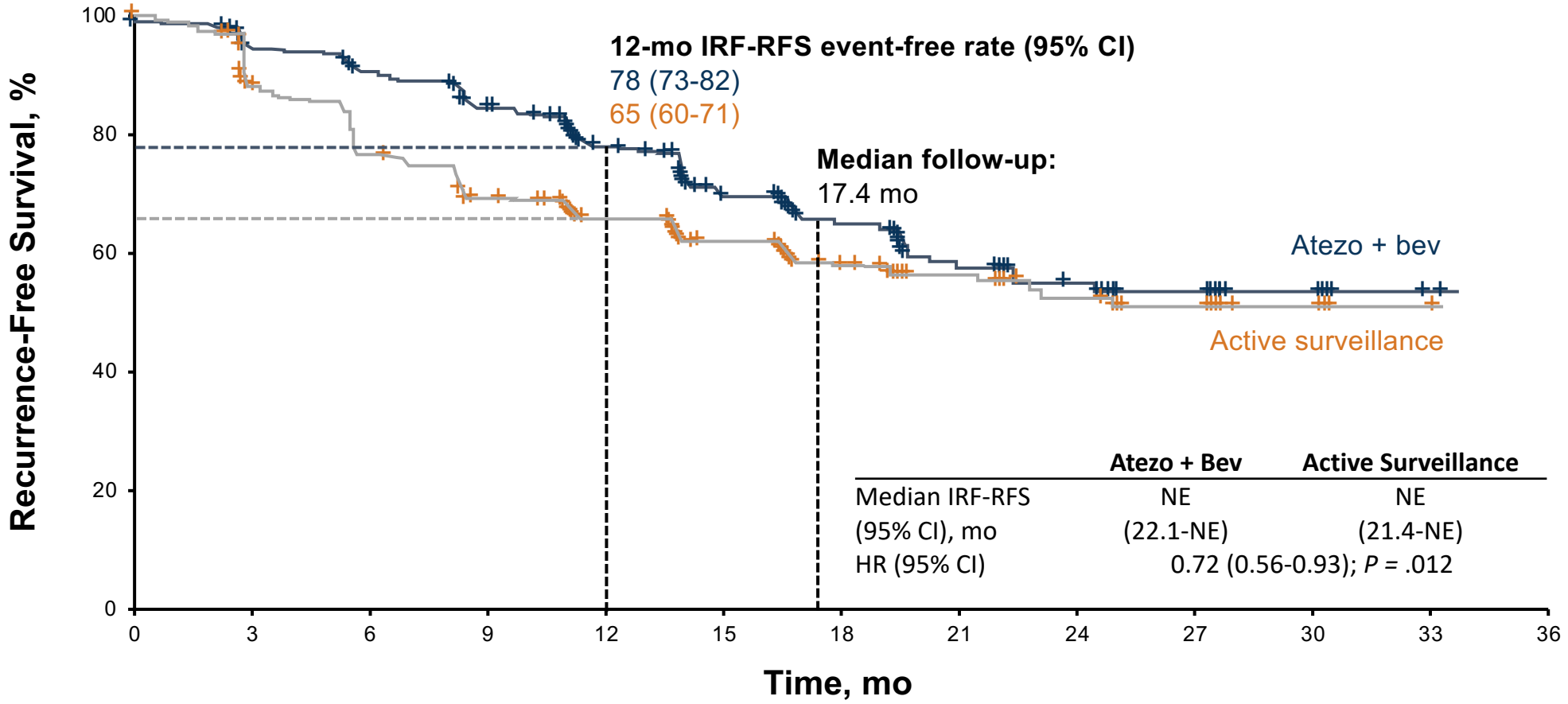
IMbrave050: Atezolizumab + Bevacizumab as Adjuvant Therapy for HCC With High Recurrence Risk



[a] High-risk feature include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology. [b] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1. [c] APAC excluding Japan vs rest of world.

1. Chow P et al. AACR 2023. https://bit.ly/3ZPKzgM. 2. https://clinicaltrials.gov/ct2/show/NCT04102098.

Adjuvant Atezolizumab + Bevacizumab in HCC: RFS Was Significantly Improved

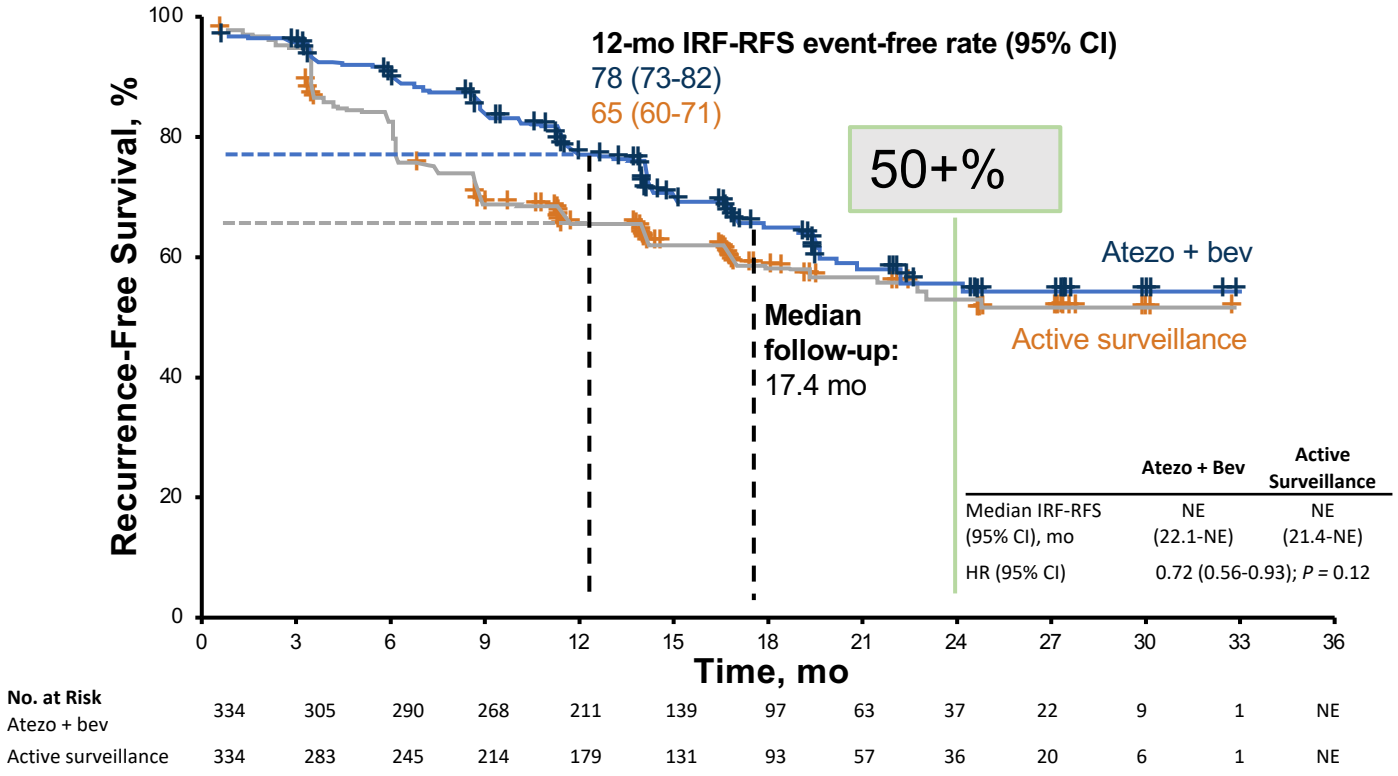


No. at Risk													
Atezo + bev	334	305	290	268	211	139	97	63	37	22	9	1	NE
Active surveillance	334	283	245	214	179	131	93	57	36	20	6	1	NE

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. At clinical cutoff, 110 of 334 patients (33%) in the atezo + bev arm and 133 of 334 (40%) in the active surveillance arm experienced disease recurrence or death. RFS – Recurrence free survival; IRF – Independent Review Facility

1. Chow P et al. AACR 2023. Abstract CT003.

But Will We Improve Overall Survival?



First positive adjuvant study in HCC

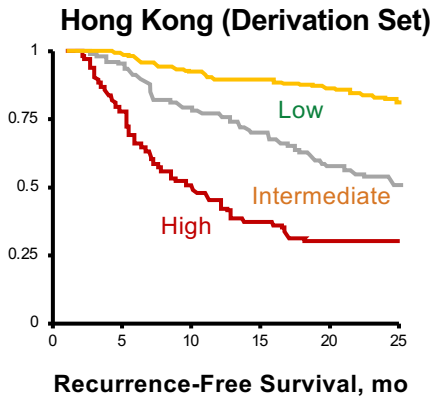
Earlier than expected overlap of RFS

- Less effective to prevent recurrence in the second year
- Delay (instead of preventing) some early recurrences

More mature data on mRFS and 2-y RFS data is important

ERASL, %	1-y RFS	2-y RFS
Low risk	83.9	71
Intermediate risk	68.5	47.5
High risk	38	26.1

Treatment arm "reverts" back to intermediate risk



Pattern of curve: the persistent separation of RFS curves was not observed in this clinical trial

n (%)	Atezo + Bev (n = 334)	Active Surveillance (n = 334)
All deaths	27 (8.1)	20 (6)
Progressive disease	17 (63)	16 (80)
Adverse events	6 (22.2)	1 (5)
Other	4 (14.8)	3 (15)

Deaths from AEs were numerically higher in the treatment arm

1. Chow P et al. AACR 2023. Abstract CT003.

Ongoing Phase 3 Trials of Adjuvant Immunotherapy

- High risk for HCC recurrence after resection or ablation
- Child–Pugh A

IMbrave050[3]	EMERALD-2[1]	CheckMate -9DX[2]	KEYNOTE-937[4]	JUPITER 04[5]
• Atezo + bev vs active surveillance • ECOG PS 0-1 • Primary endpoint: RFS	• Durvalumab ± bevacizumab + vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Nivolumab vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Pembro vs placebo • ECOG PS 0 • AFP <400 ng/mL • Primary endpoints: RFS and OS	• Toripalimab vs placebo • ECOG PS 0 • Primary endpoint: RFS

1. https://clinicaltrials.gov/ct2/show/NCT03847428. 2. https://clinicaltrials.gov/ct2/show/NCT03383458. 3. https://clinicaltrials.gov/ct2/show/NCT04102098.
4. https://clinicaltrials.gov/ct2/show/NCT03867084. 5. https://clinicaltrials.gov/study/NCT03859128.

Rationale for Combining LRT and Systemic Therapy

Intermediate-stage HCC is a heterogeneous entity with variability in tumor burden, distribution, and underlying liver function	Risk of missing the opportunity to reach the point of systemic therapy in cases of liver function deterioration
Efficacy of LRT is affected by tumor burden	Systemic therapy has level 1 evidence of improved survival and high response rates

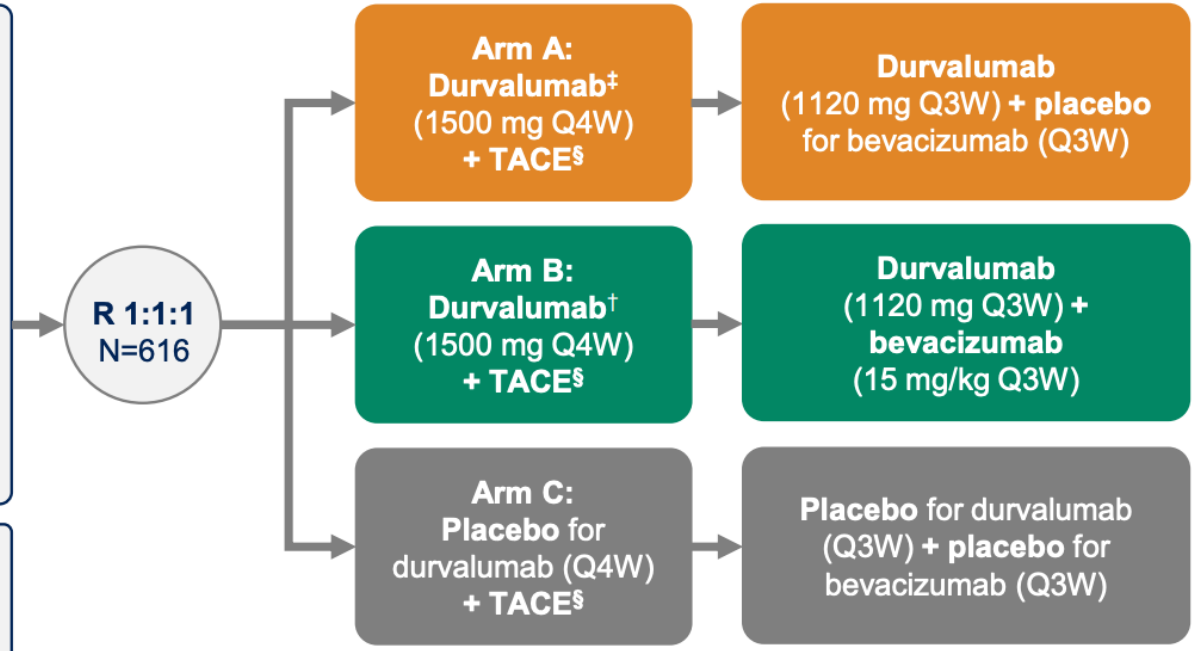
Potential advantages of incorporating systemic therapy earlier include

- Starting effective therapy earlier
- Introducing more effective intervention prior to possible liver decompensation
- Potentially increasing cures

EMERALD-1: A Phase 3 Study Evaluating Durvalumab + Bevacizumab Combined With TACE for Locoregional HCC

Study population*
- Adults with confirmed HCC
- Not amenable to curative therapy, e.g. surgical resection, ablation, transplantation
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG PS 0 or 1
- Measurable disease per mRECIST
- Excludes Vp3 and Vp4
- No prior systemic therapy or TACE†

Stratification factors
- TACE modality (DEB-TACE vs cTACE)
- Geographical region (Japan vs Asia [excluding Japan] vs other)
- Portal vein invasion (Vp1 or Vp2+ / -Vp1 vs none)



Primary endpoint:
- PFS‖ for Arm B vs Arm C using BICR per ***RECIST 1.1***

Key secondary endpoints:
- PFS for Arm A vs Arm C
- OS
- QoL

Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

Lencioni et al, GI ASCO 2024

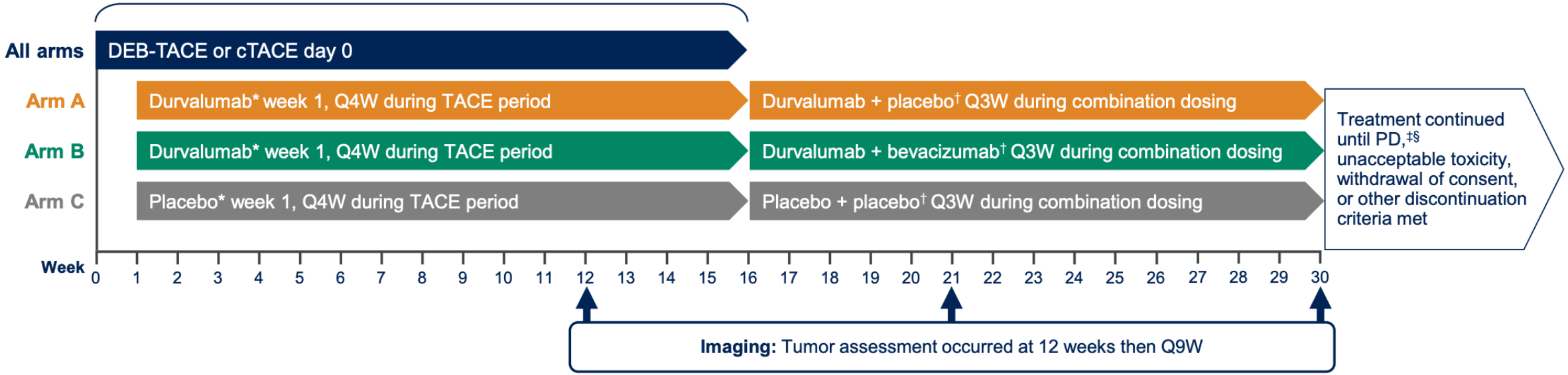
EMERALD-1: Study Schema

Number and timings of TACE at the investigator's discretion:

- 1–4 TACE procedures within 16 weeks

Combination therapy begins after the final TACE procedure

- Median (range) start of combination systemic therapy: 14 (2–113) weeks post first dose of TACE at Day 0



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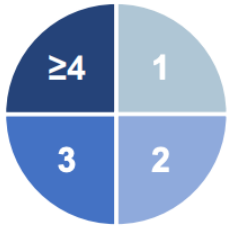
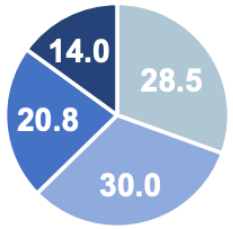
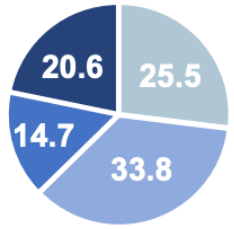
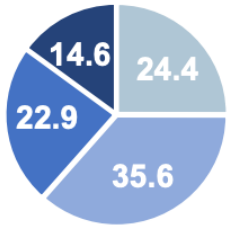
EMERALD-1: Participant Disposition

The majority of participants had 1 or 2 TACE procedures with or without durvalumab

616 participants randomized

	D + TACE	D+B + TACE	Placebos + TACE
Randomized	**207**	**204**	**205**
No. of TACE procedures,* %				
Dosed with durvalumab,† n / N (%)	193 / 207 (93.2%)	193 / 204 (94.6%)	200 / 205 (97.6%)
Dosed with combination n / N (%)	162 / 207 (78.3%)	154 / 204 (75.5%)	155 / 205 (75.6%)
Ongoing study, n / N (%)	**88 / 207 (42.5%)‡**	**89 / 204 (43.6%)§**	**82 / 205 (40.0%)‖**
On durvalumab treatment†	25 / 193 (13.0%)	27 / 193 (14.0%)	27 / 200 (13.5%)
Discontinued study treatment, n / N (%)¶	**168 / 193 (87.0%)****	**166 / 193 (86.0%)††**	**173 / 200 (86.5%)‡‡**
Condition under investigation worsened§§	122 / 193 (63.2%)	85 / 193 (44.0%)	119 / 200 (59.5%)

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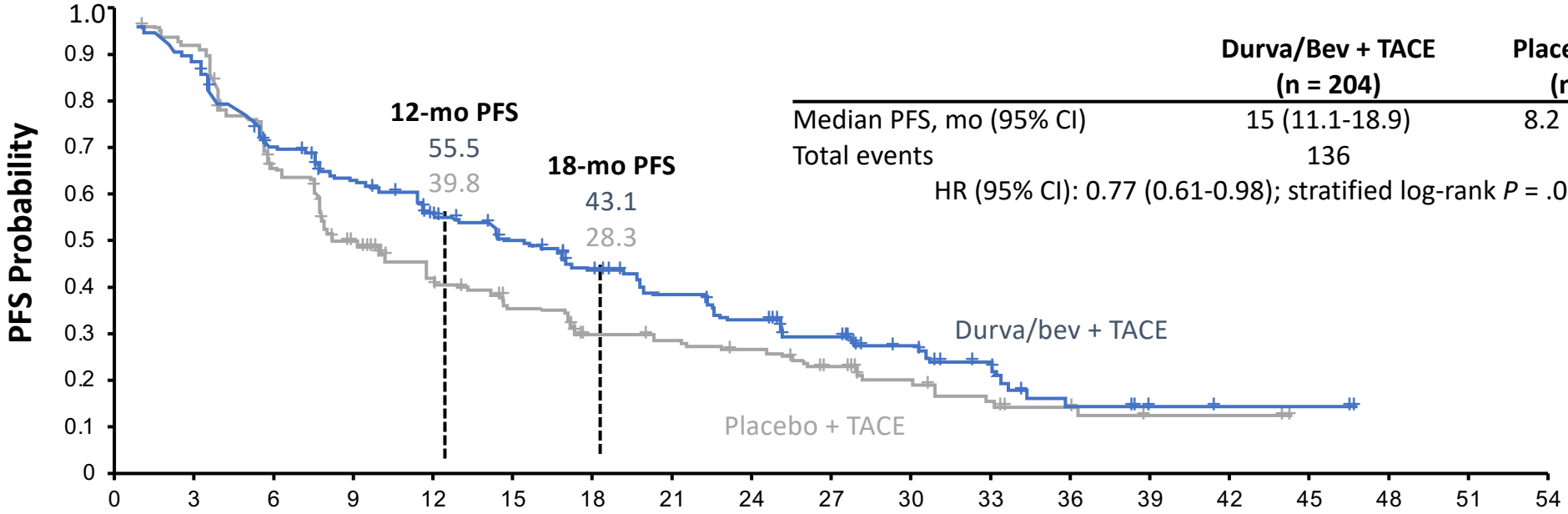
EMERALD-1: Significant PFS Benefit With Durva + Bev + TACE vs TACE Alone



	Durva/Bev + TACE (n = 204)	Placebo + TACE (n = 205)
Median PFS, mo (95% CI)	15 (11.1-18.9)	8.2 (6.9-11.1)
Total events	136	149

HR (95% CI): 0.77 (0.61-0.98); stratified log-rank *P* = .032

No. at Risk

Durva/bev + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0
Placebo + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0

- No significant difference in PFS between the durva + TACE and placebo + TACE arms, suggesting that VEGF-targeting may provide a “boosting effect”
- mTTP: 22 mo vs 10 mo; ORR: 43.6% vs 29.6%; DOR: 22.1 mo vs 16.4 mo

Lencioni et al, GI ASCO 2024

EMERALD-1: Most Common Maximum Grade 3 or 4 TEAEs

Incidence of maximum Grade 3 or 4 AEs was low across all arms, with no unexpected safety signals

AE, n (%)	D + TACE (n=232)	D+B + TACE (n=154)	Placebos + TACE (n=200)
Hypertension	5 (2.2)	9 (5.8)	1 (0.5)
Anemia	10 (4.3)	7 (4.5)	3 (1.5)
Acute kidney injury	4 (1.7)	6 (3.9)	0
Proteinuria	0	6 (3.9)	0
Post-embolization syndrome	8 (3.4)	5 (3.2)	8 (4.0)
Hepatic encephalopathy	1 (0.4)	5 (3.2)	3 (1.5)
Ascites	4 (1.7)	4 (2.6)	3 (1.5)
Hyponatremia	1 (0.4)	4 (2.6)	0
Esophageal varices hemorrhage	0	4 (2.6)	1 (0.5)

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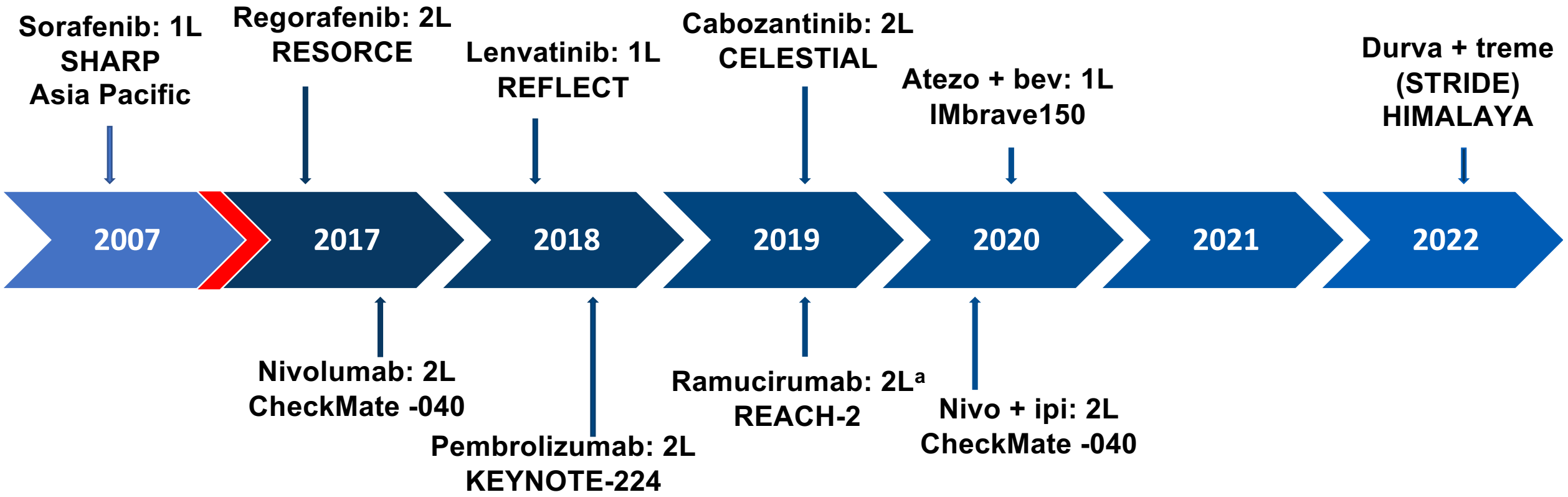
Timeline of Recent Approvals for Systemic Therapy in HCC

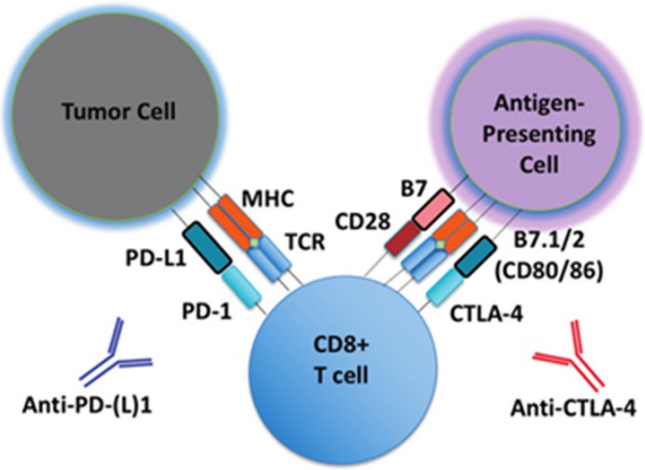


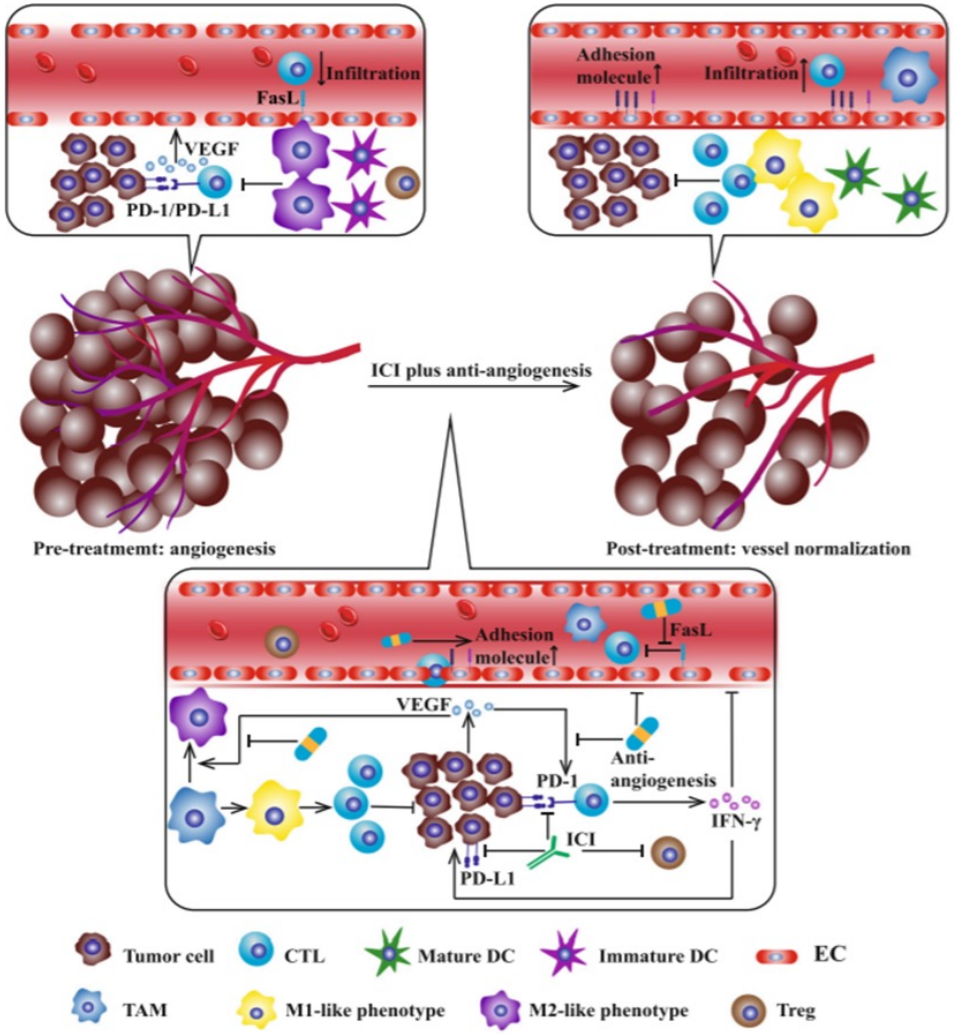
[a] AFP ≥400 ng/mL.

1. Ghaziani et al. *Curr Treat Options Gastro*. 2021;19:1-18. 2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-unresectable-hepatocellular-carcinoma. 3. Reig M et al. *J Hepatol*. 2022;76:681-693.

Immune Checkpoint Inhibition (ICI): Combination Strategies in Advanced HCC

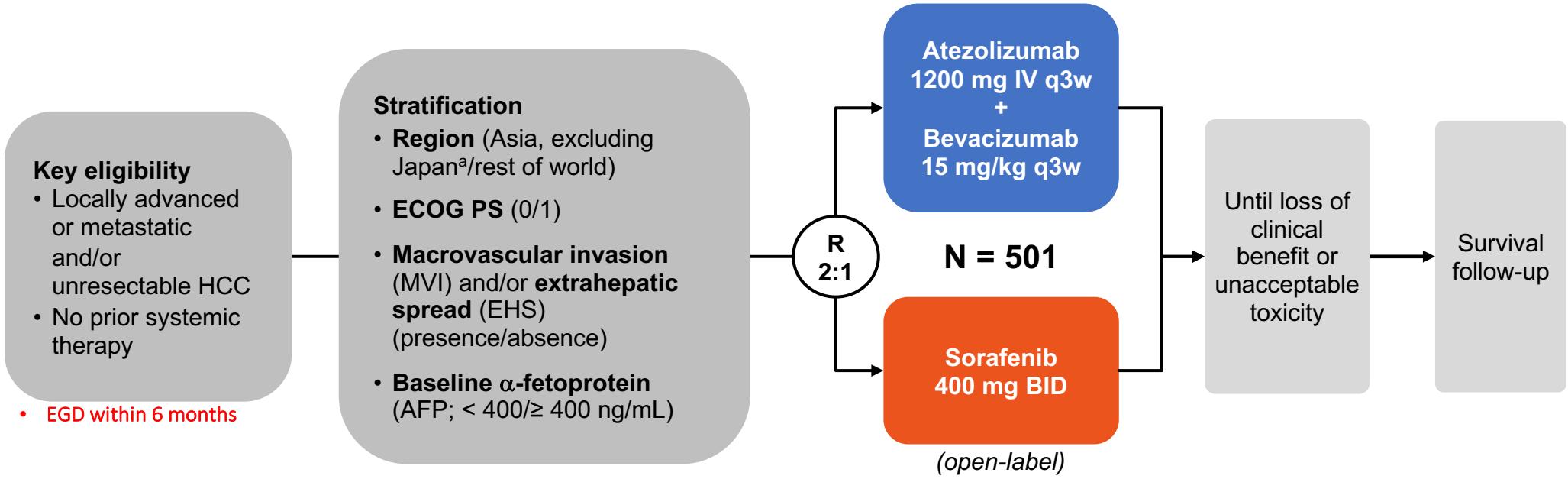
1. ICI + anti-VEGF mAb
2. ICI + anti-angiogenic TKI
3. ICI + ICI





Yi M, et al. Mol Can. 2019;18:60. Foerster F, Galle PR. Cancers (Basel). 2021;13:1962. Aref AR, et al. The Royal Society of Chemistry. 2018;18:3129-3143.

IMbrave 150: Phase 3 Trial of Atezolizumab plus Bevacizumab vs. Sorafenib in 1st Line Advanced HCC



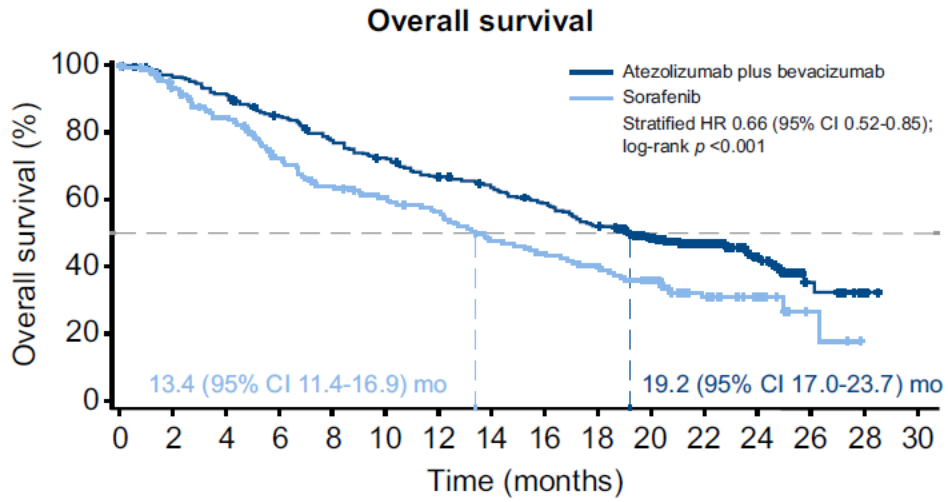
Primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

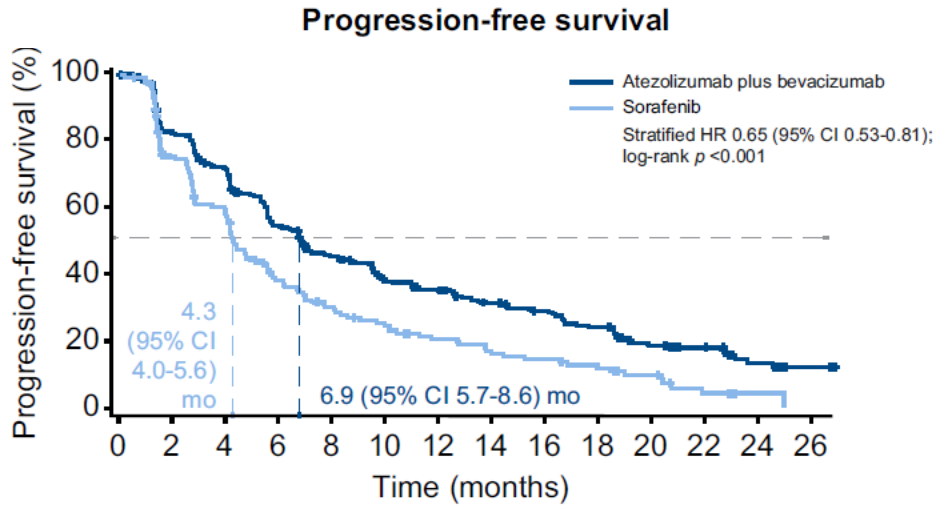
Key secondary efficacy endpoints
- IRF-assessed ORR and DOR per RECIST 1.1
- IRF-assessed ORR and DOR per HCC mRECIST

BID, twice a day; q3w, every 3 weeks; [a]Japan is included in rest of world.

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

IMbrave150: Updated Results





	Updated analysis[a] RECIST 1.1	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**
CR, n (%)	25 (8)	1 (< 1)
PR, n (%)	72 (22)	17 (11)
SD, n (%)	144 (44)	69 (43)
DCR, n (%)	241 (74)	87 (55)
PD, n (%)	63 (19)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**

Established new benchmarks for efficacy in 1st line:
- Median OS 19.2 v. 13.4 months, HR 0.66
- Median PFS 6.9 v. 4.3 months, HR 0.65
- Durable responses in 30%, complete responses in 8%

Acceptable safety in carefully screened population:
- Treatment-related grade 3/4 AE: 43% vs. 46%
- Discontinuation for AE: 15.5% vs. 10.3%

Finn et al. N Engl J Med 2020;382:1894-905; Cheng et al. J Hepatol 2022;76:862-73

Patient-Reported Outcomes from IMbrave150

- EORTC QLQ-C30 and EORTC QLC-HCC18 outcomes favored atezo+beva arm over sorafenib across domains

	Atezolizumab plus bevacizumab group (n=336)		Sorafenib group (n=165)		HR (95% CI)
	Events, n (%)	Median time to confirmed deterioration, months (95% CI)	Events, n (%)	Median time to confirmed deterioration, months (95% CI)	
EORTC QLQ-C30					
Fatigue	164 (49%)	5·7 (4·3–7·1)	78 (47%)	2·1 (1·5–4·8)	0·61 (0·46–0·81)
Pain	131 (39%)	9·7 (7·2–NE)	76 (46%)	2·8 (2·1–4·3)	0·46 (0·34–0·62)
Appetite loss	101 (30%)	NE (NE)	54 (33%)	7·6 (3·5–NE)	0·57 (0·40–0·81)
Diarrhoea	62 (18%)	NE (NE)	63 (38%)	4·4 (3·5–5·6)	0·23 (0·16–0·34)
Nausea and vomiting	55 (16%)	NE (NE)	40 (24%)	NE (5·7–NE)	0·39 (0·26–0·60)
Dyspnoea	82 (24%)	NE (13·2–NE)	43 (26%)	NE (6·3–NE)	0·54 (0·37–0·79)
Insomnia	84 (25%)	NE (13·8–NE)	40 (24%)	NE (7·0–NE)	0·67 (0·46–0·99)
Constipation	75 (22%)	NE (13·9–NE)	32 (19%)	NE (NE)	0·71 (0·46–1·08)
Financial difficulties	60 (18%)	NE (NE)	19 (12%)	NE (NE)	0·94 (0·55–1·60)
Emotional functioning	59 (18%)	NE (NE)	38 (23%)	NE (6·7–NE)	0·47 (0·31–0·71)
Social functioning	120 (36%)	NE (8·3–NE)	55 (33%)	7·4 (3·5–NE)	0·71 (0·51–0·98)
Cognitive functioning	104 (31%)	NE (10·6–NE)	54 (33%)	6·7 (4·2–NE)	0·56 (0·40–0·79)
EORTC QLQ-HCC18					
Fatigue	154 (46%)	5·7 (4·3–9·0)	79 (48%)	2·1 (1·6–2·8)	0·60 (0·45–0·80)
Pain	101 (30%)	NE (NE)	50 (30%)	9·8 (4·3–NE)	0·65 (0·46–0·92)
Jaundice	128 (38%)	10·6 (6·9–NE)	51 (31%)	6·5 (5·6–NE)	0·76 (0·55–1·07)
Abdominal swelling	72 (21%)	NE (NE)	34 (21%)	NE (NE)	0·57 (0·37–0·86)
Body image	135 (40%)	9·0 (6·4–NE)	61 (37%)	4·3 (2·8–NE)	0·71 (0·52–0·97)
Fever	80 (24%)	NE (NE)	37 (22%)	NE (NE)	0·71 (0·47–1·06)
Nutrition	101 (30%)	NE (NE)	52 (32%)	6·9 (3·6–NE)	0·56 (0·40–0·79)
Sex life	72 (21%)	NE (NE)	30 (18%)	NE (NE)	0·82 (0·53–1·26)

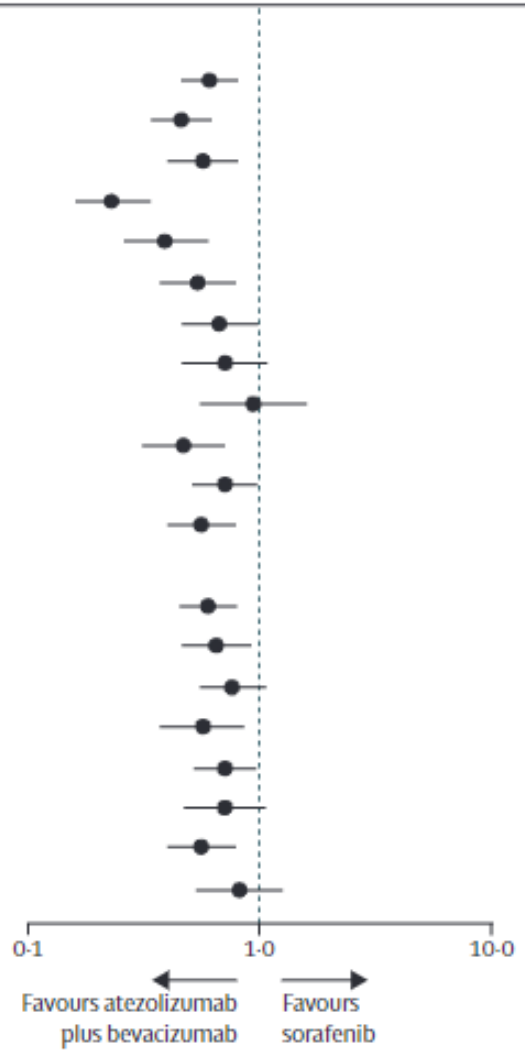


Figure 2: **Time to confirmed deterioration in EORTC QLQ-C30 and EORTC QLQ-HCC18 scales analysed as prespecified and post-hoc endpoints**

Galle et al. Lancet Oncol. 2021;22

HIMALAYA Study Design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial

Study population
- Patients aged ≥18 years with uHCC
- BCLC stage B (not eligible for locoregional therapy) and stage C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

R
N=1324

STRIDE (n=393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

Durvalumab (n=389):
Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389):
Sorafenib 400 mg BID*

T75+D (n=153): *arm closed* †
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

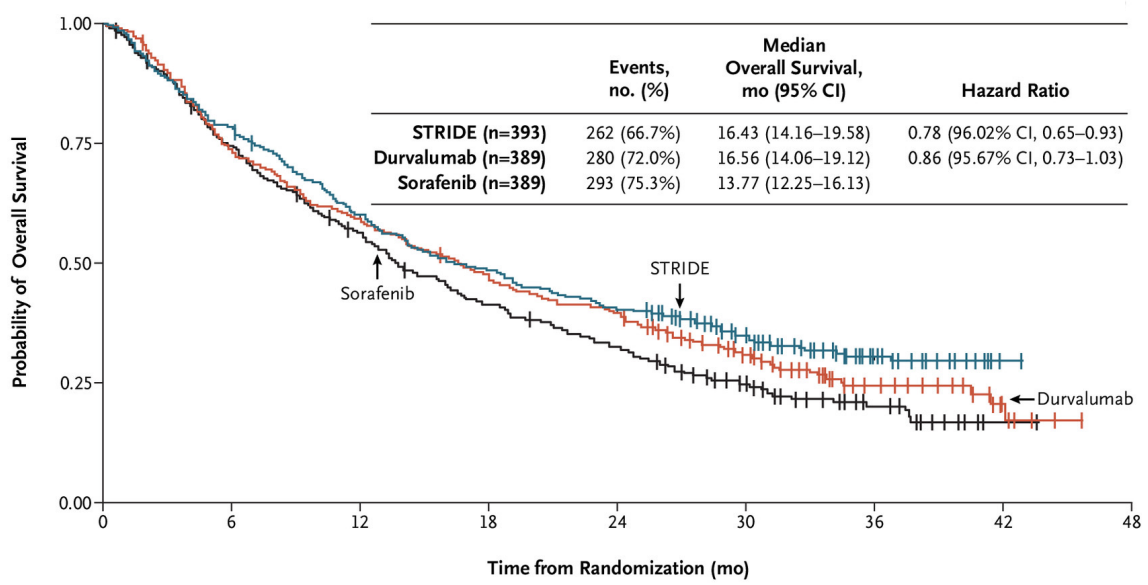
Stratification factors
- Macrovascular invasion: yes vs no
- Etiology of liver disease: HBV vs HCV vs others
- Performance status: ECOG 0 vs 1

*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

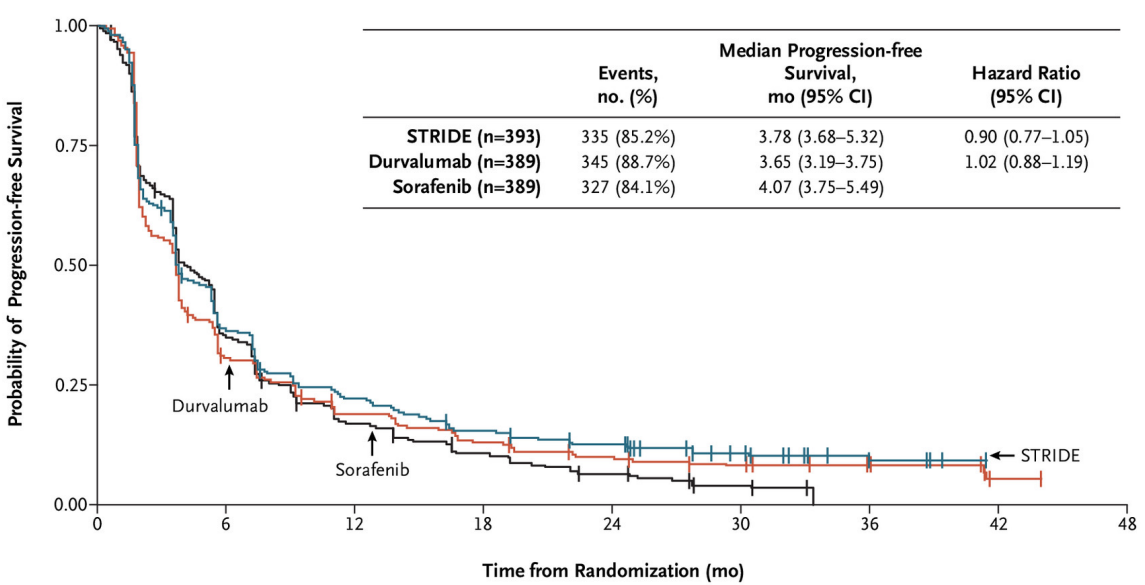
Presented by Ghassan K Abou-Alfa, GI ASCO 2022; Abou-Alfa et al NEJM Evidence 2022; published online June 6, 2022

HIMALAYA Primary and Secondary Endpoints: OS and PFS



	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

No. at Risk									
STRIDE	393	308	235	190	158	98	32	1	0
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0



	Events, no. (%)	Median Progression-free Survival, mo (95% CI)	Hazard Ratio (95% CI)
STRIDE (n=393)	335 (85.2%)	3.78 (3.68–5.32)	0.90 (0.77–1.05)
Durvalumab (n=389)	345 (88.7%)	3.65 (3.19–3.75)	1.02 (0.88–1.19)
Sorafenib (n=389)	327 (84.1%)	4.07 (3.75–5.49)	

No. at Risk									
STRIDE	393	135	81	55	43	26	7	0	0
Durvalumab	389	115	68	47	34	20	6	1	0
Sorafenib	389	118	53	31	18	6	0	0	0

- STRIDE regimen improved OS over sorafenib: Median 16.43 vs. 13.77 mos. (HR 0.78)
- Durvalumab was noninferior to sorafenib for OS (HR 0.86)
- No significant difference in median PFS

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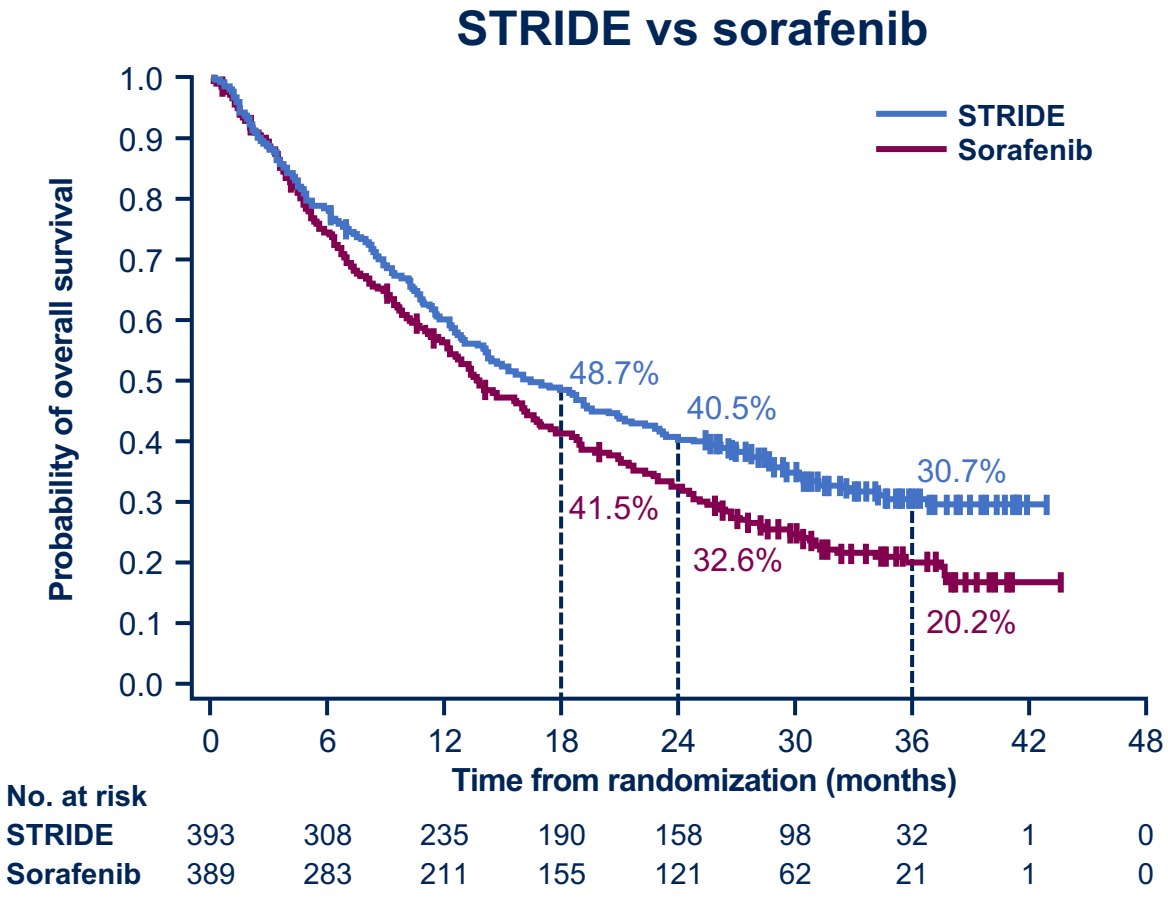
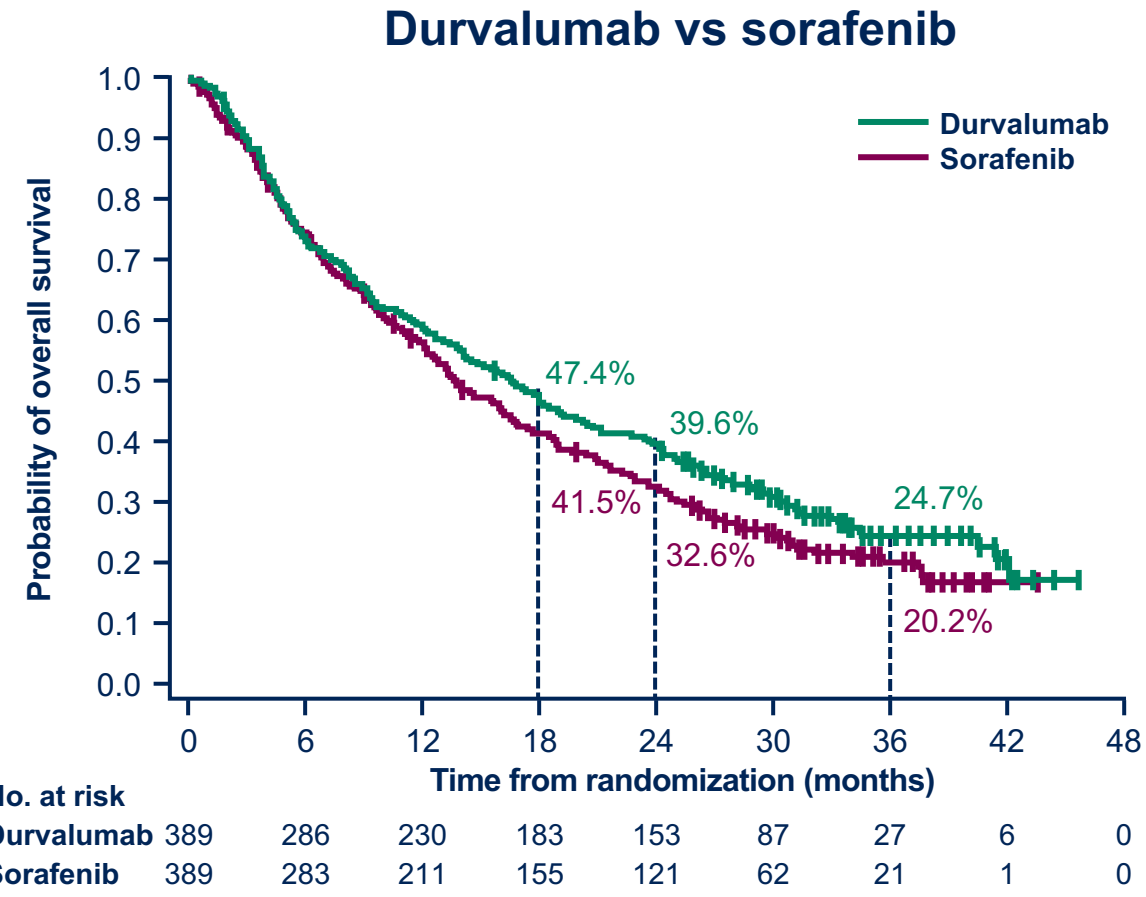
HIMALAYA: Landmark OS analysis





OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

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HIMALAYA: Safety and tolerability

Event, n (%)	STRIDE (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)†	0	3 (0.8)‡
Any TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)
Any grade 3/4 hepatic SMQ TRAE	23 (5.9)	20 (5.2)	17 (4.5)
Any grade 3/4 hemorrhage SMQ TRAE	2 (0.5)	0	4 (1.1)
Any grade 3/4 immune-mediated TRAE	49 (12.6)	24 (6.2)	9 (2.4)
Any immune-mediated AE requiring treatment with high-dose steroids	78 (20.1)	37 (9.5)	7 (1.9)
Any immune-mediated AE leading to discontinuation of study treatment	22 (5.7)	10 (2.6)	6 (1.6)

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. †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). ‡Hematuria (n=1), cerebral hematoma (n=1), hepatic failure (n=1).

AE, adverse event; SMQ, Standardized MedDRA Query; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TRAE, treatment-related adverse event.

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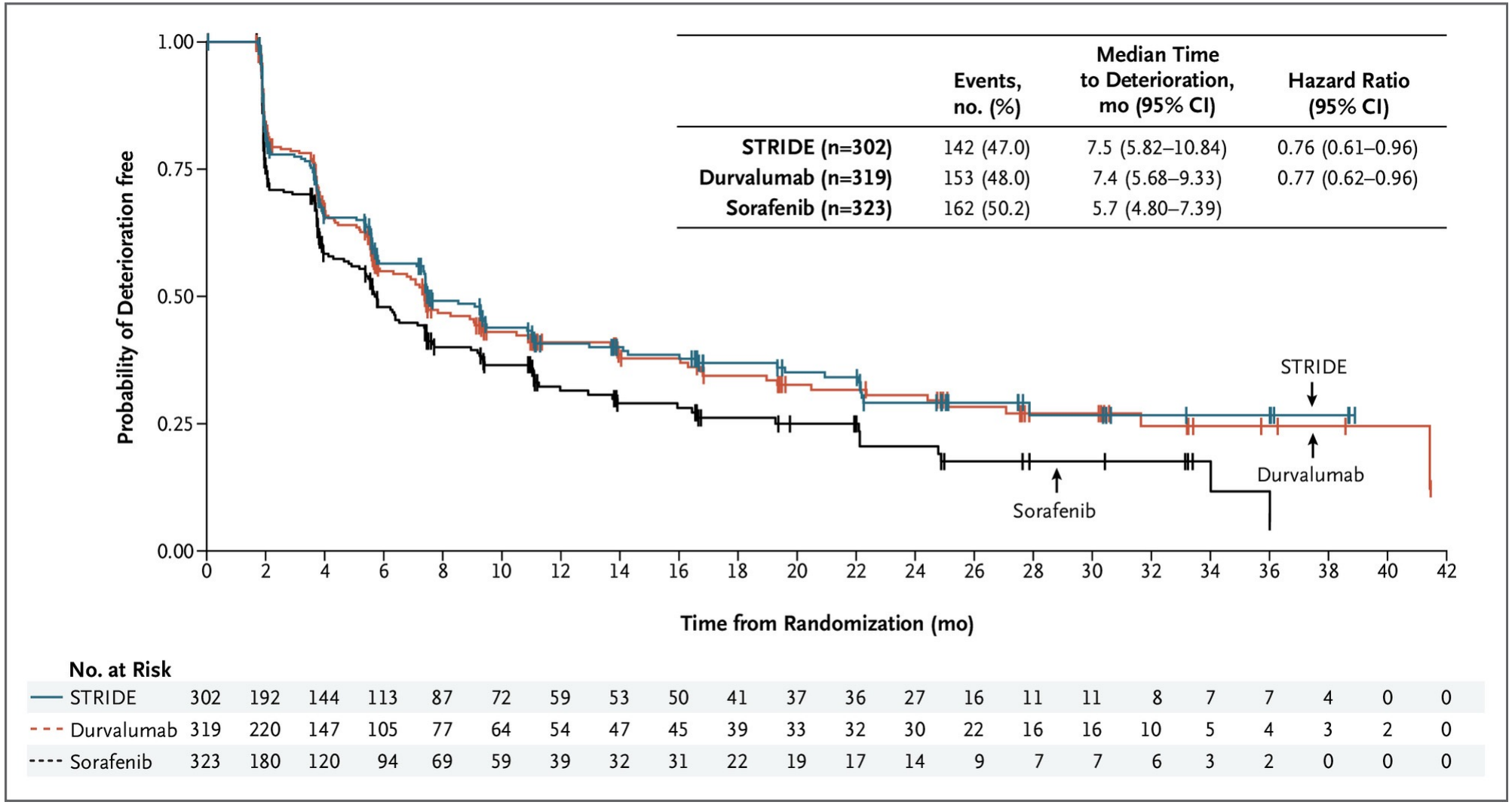
STRIDE and Durvalumab: Preserved QOL vs. Sorafenib



	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

Presented by Ghassan K Abou-Alfa, GI ASCO 2022; Abou-Alfa et al NEJM Evidence 2022; published online June 6, 2022

Frontline Systemic Therapy for Advanced HCC

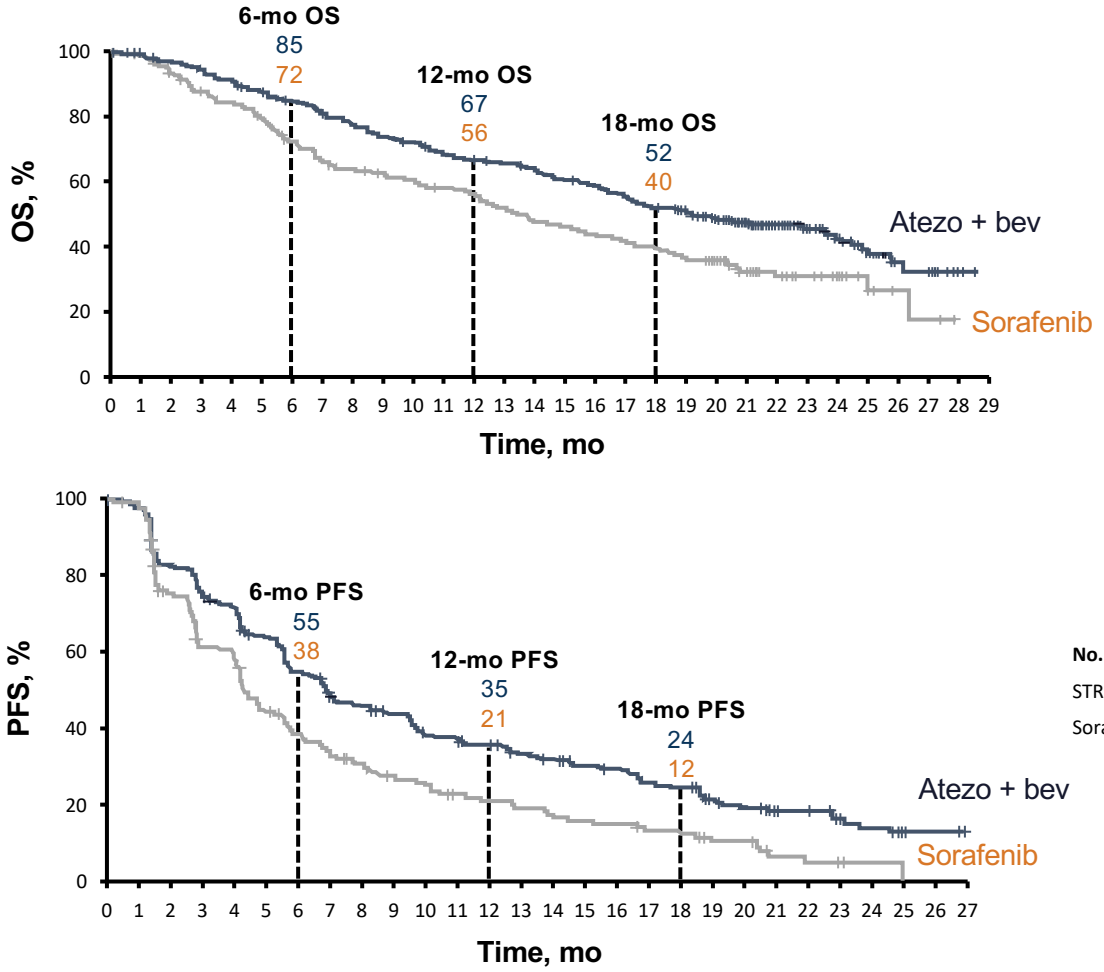
	IMbrave150[1]	HIMALAYA[2, 3]	
Treatment Arm *Patient n*	Atezo/bev *336*	STRIDE *393*	Durvalumab *389*
Control Arm *Patient n*	Sorafenib *165*	Sorafenib *389*	Sorafenib *389*
mOS, mo (95% CI)	19.2 (17.0-23.7)	16.4 (14.2-19.6)	16.56 (14.0-19.1)
mPFS, mo (95% CI)	6.9 (5.7-8.6)	3.78 (3.68-5.32)	3.65 (3.39-3.75)
ORR, % per RESIST 1:1	30	20.1	17.0
mDOR, % per RESIST 1:1	18.1	22.34	16.8

Atezo, atezolizumab; bev, bevacizumab; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; OS, overall survival; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

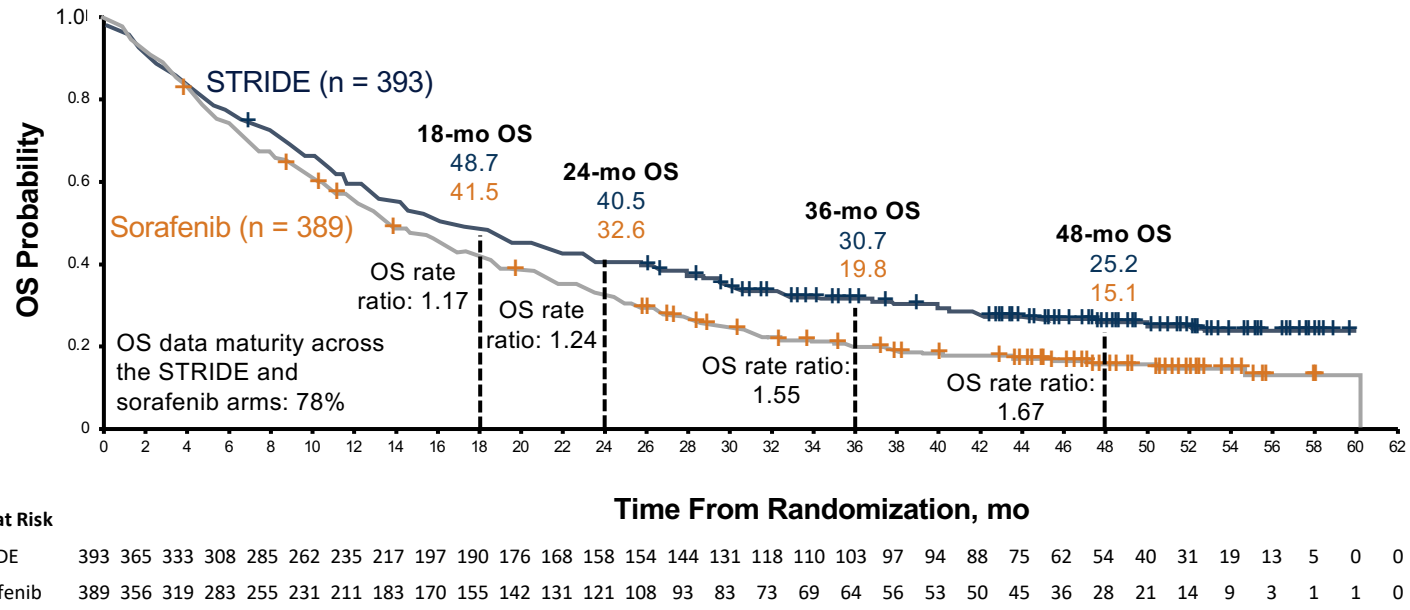
1 Finn RS, et al. *N Engl J Med*. 2020;382(20):1894-1905. 2. Sangro et al. ESMO GI 2023. Abstract SO-15. 3. Abou-Alfa G et al. *NEJM Evid.* 2022;1(8).

How Do We Analyze Data for Immunotherapy Options?

IMbrave150: OS vs PFS[1]



HIMALAYA: 48-month landmark analysis: the "long tail"' of immunotherapy[2]

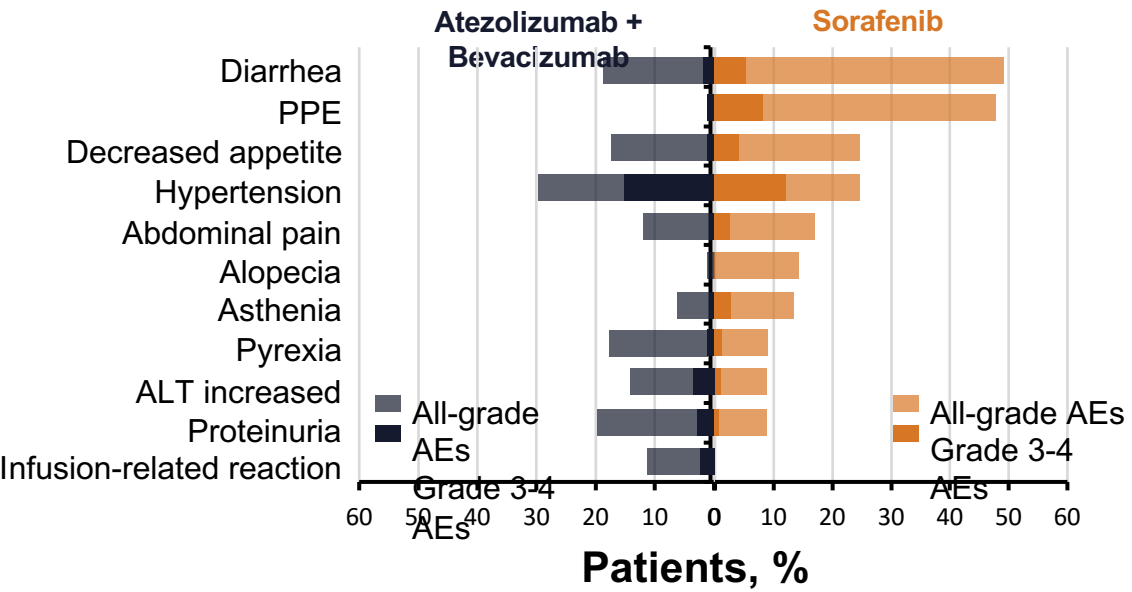


No. at Risk																															
STRIDE	393	365	333	308	285	262	235	217	197	190	176	168	158	154	144	131	118	110	103	97	94	88	75	62	54	40	31	19	13	5	0	0
Sorafenib	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	83	73	69	64	56	53	50	45	36	28	21	14	9	3	1	1	0

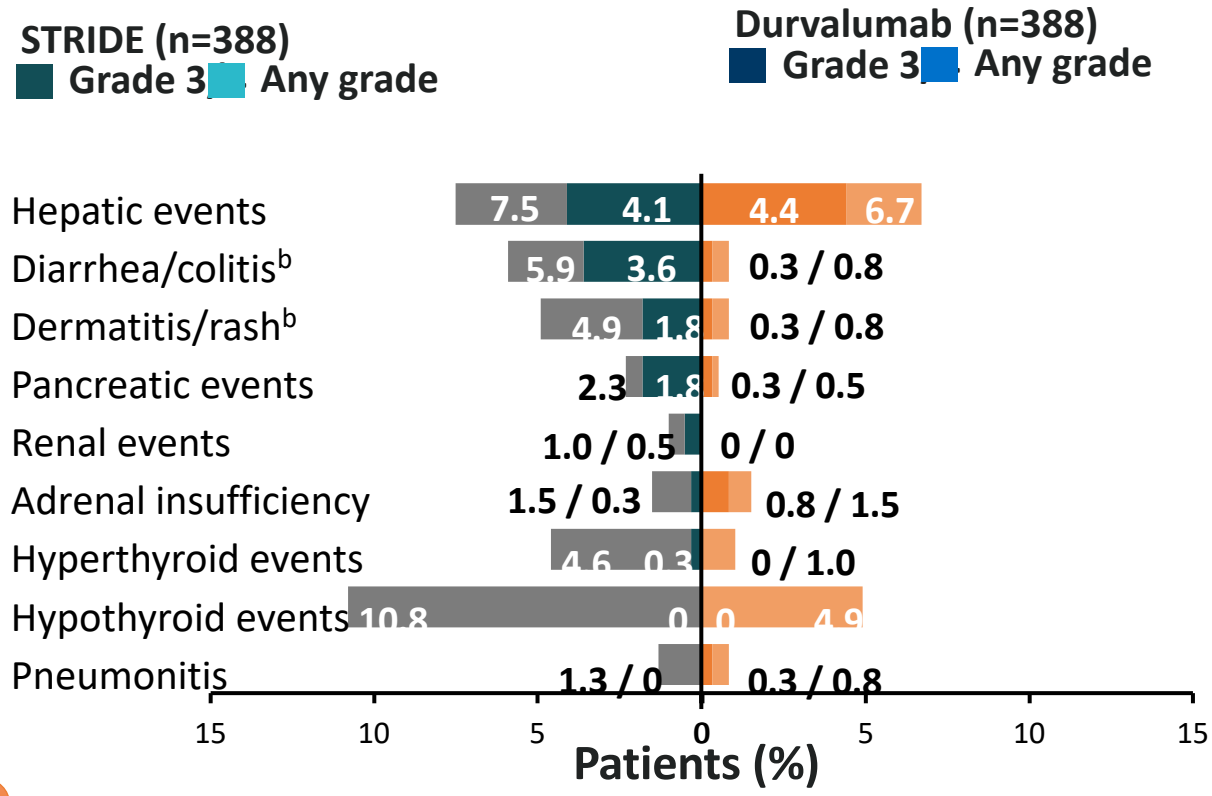
1. Cheng AL et al. *J Hepatol*. 2022;76:862-873. 2. Sangro et al. ESMO GI 2023. Abstract SO-15.

Safety Considerations and Summary of Bleeding Events

IMBrave150



HIMALAYA

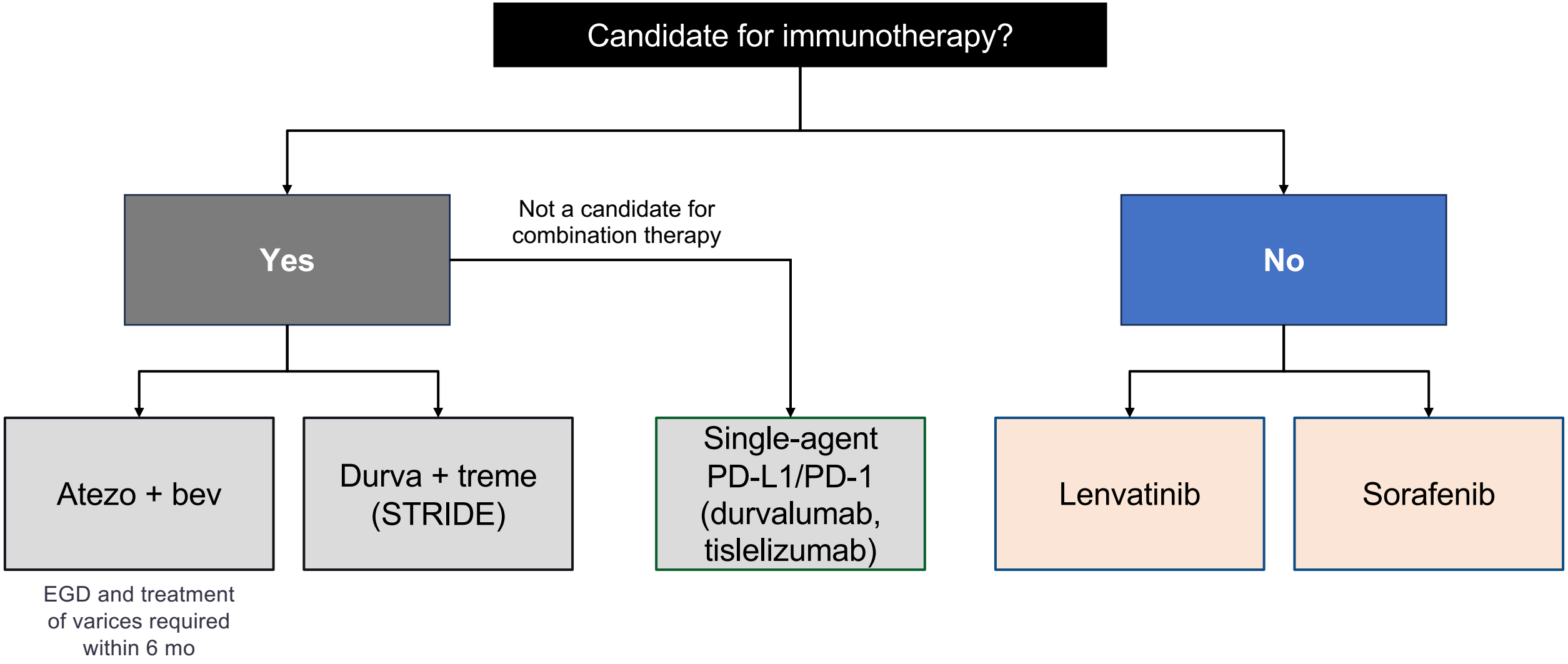


Bleeding events: Grade 3/4 bleeding/hemorrhage with atezo + bev was 6.4% versus 5.8% for sorafenib

[a] Safety-evaluable population.

1. Finn RS et al. *N Engl J Med.* 2020;382:1894-1905.

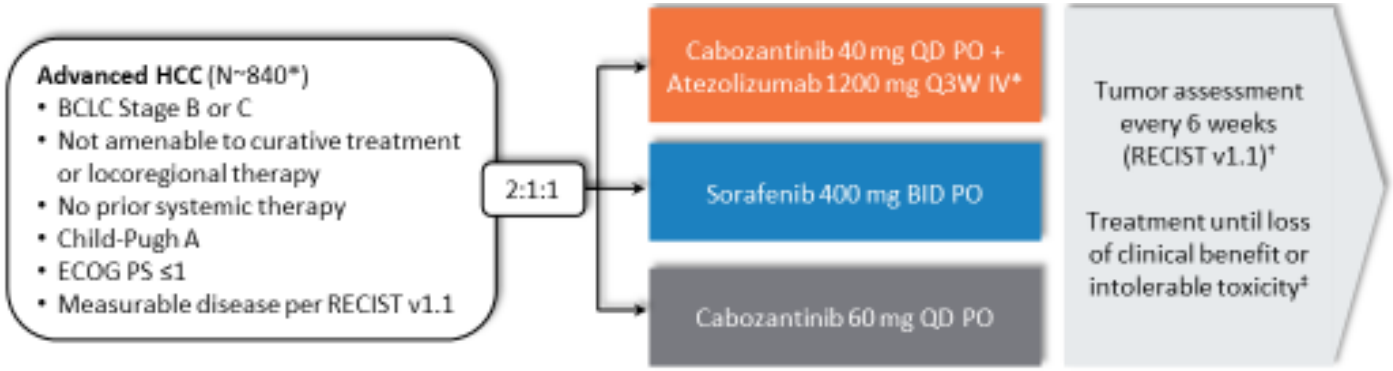
Take-Homes for Selection of 1L Therapy for Advanced HCC

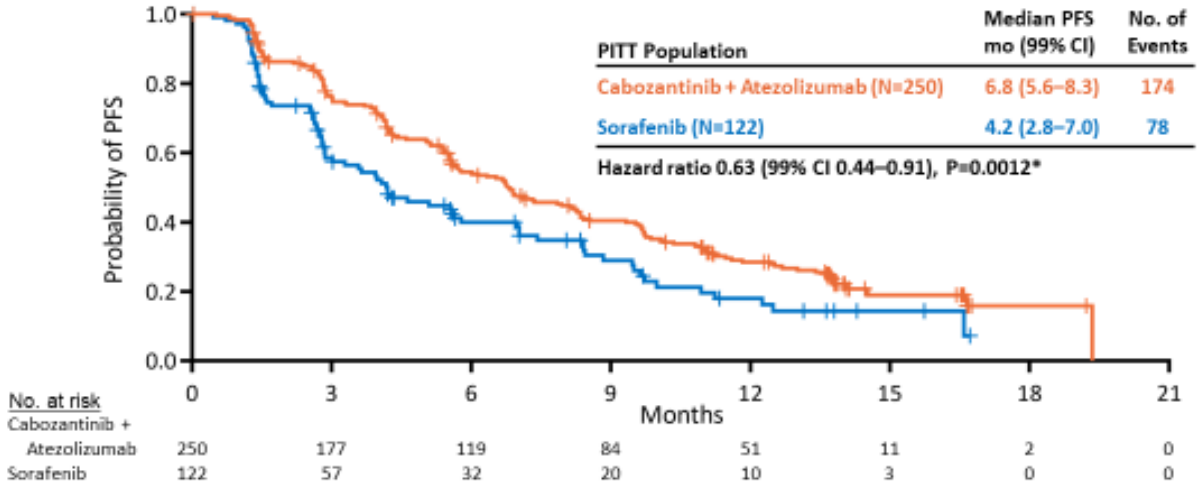


Note: Disease aggressiveness can also inform 1L treatment decisions

ICI + TKI Combinations in HCC: Mixed Results in Recent Phase 3 Trials

- COSMIC-312: Cabozantinib plus atezolizumab versus sorafenib as first-line systemic treatment for advanced HCC



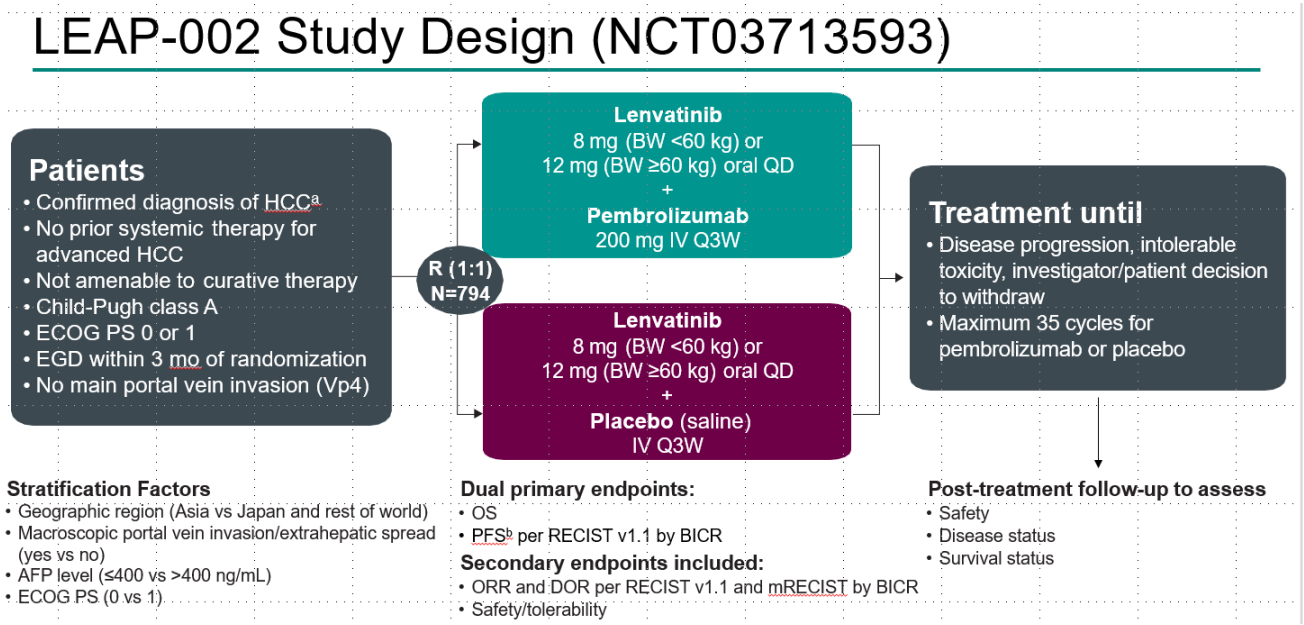


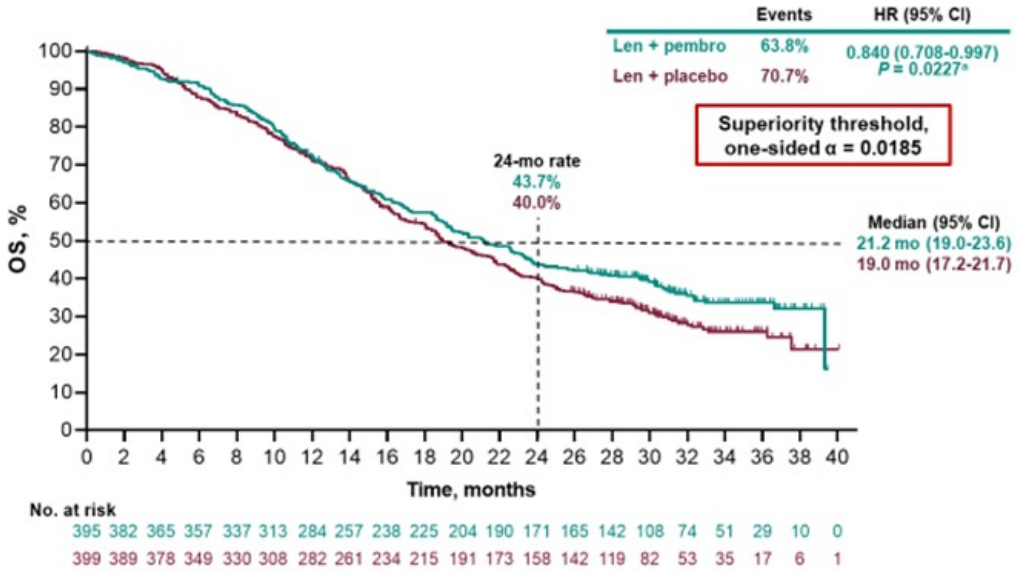
- Improved PFS but no difference OS
  - PFS: Median 6.8 vs. 4.2 mos., HR 0.63
  - OS: Median 15.4 vs. 15.5 mos., HR 0.90
- New Drug Application (NDA) not submitted

Kelley et al. Lancet Oncol 2022;23(9):995-1008

ICI + TKI Combinations in HCC: Mixed Results in Recent Phase 3 Trials, *cont.*

- LEAP-002: Lenvatinib plus pembrolizumab versus Lenvatinib as First-Line Therapy for Advanced HCC





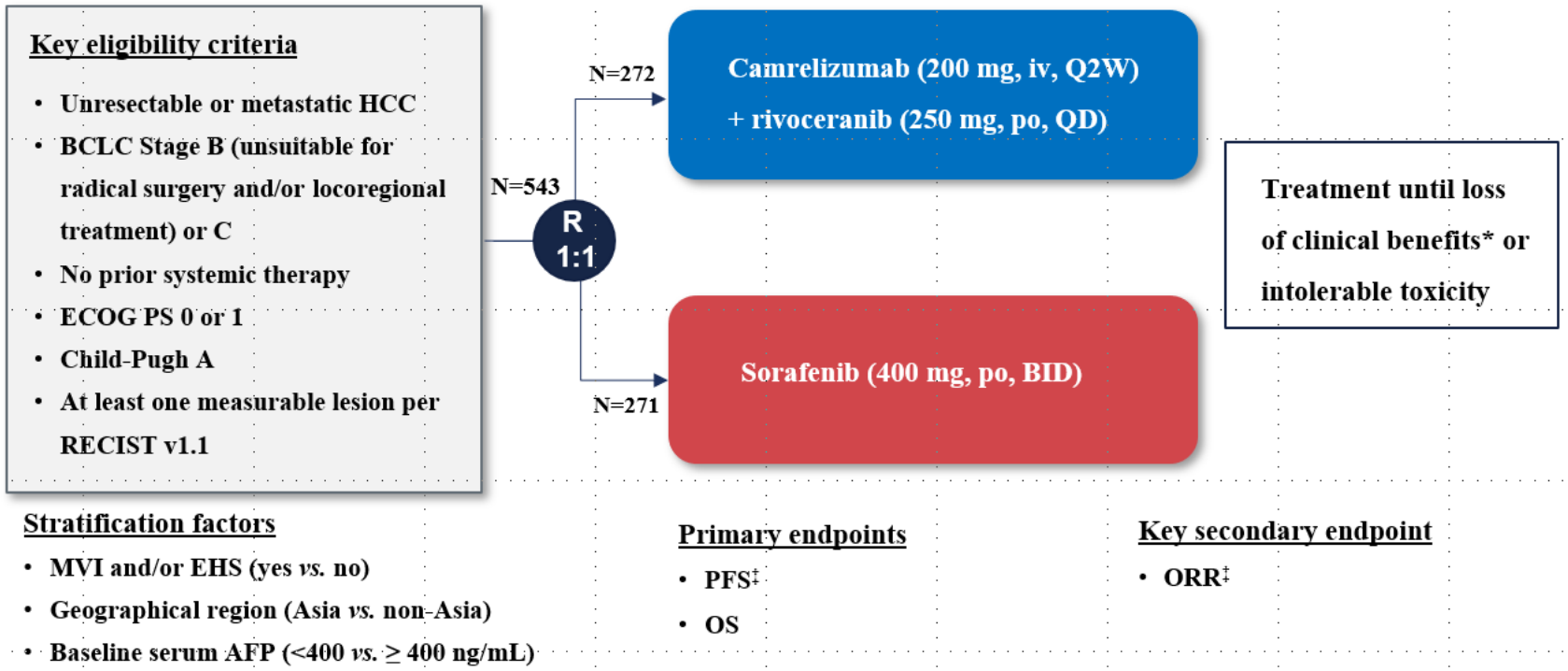
- No difference OS or PFS
  - OS: Median 21.2 vs. 19.0 mos. (HR 0.840)
  - PFS: Median 8.2 vs. 8.0 mos. (HR 0.867)
- Unexpectedly long OS and PFS for lenvatinib control arm

Finn et al. ESMO 2022, Abstract LBA34

ICI + TKI Combinations in HCC: Mixed Results in Recent Phase 3 Trials

Phase 3 trial of Camrelizumab + Rivoceranib (Apatinib)

Study Design



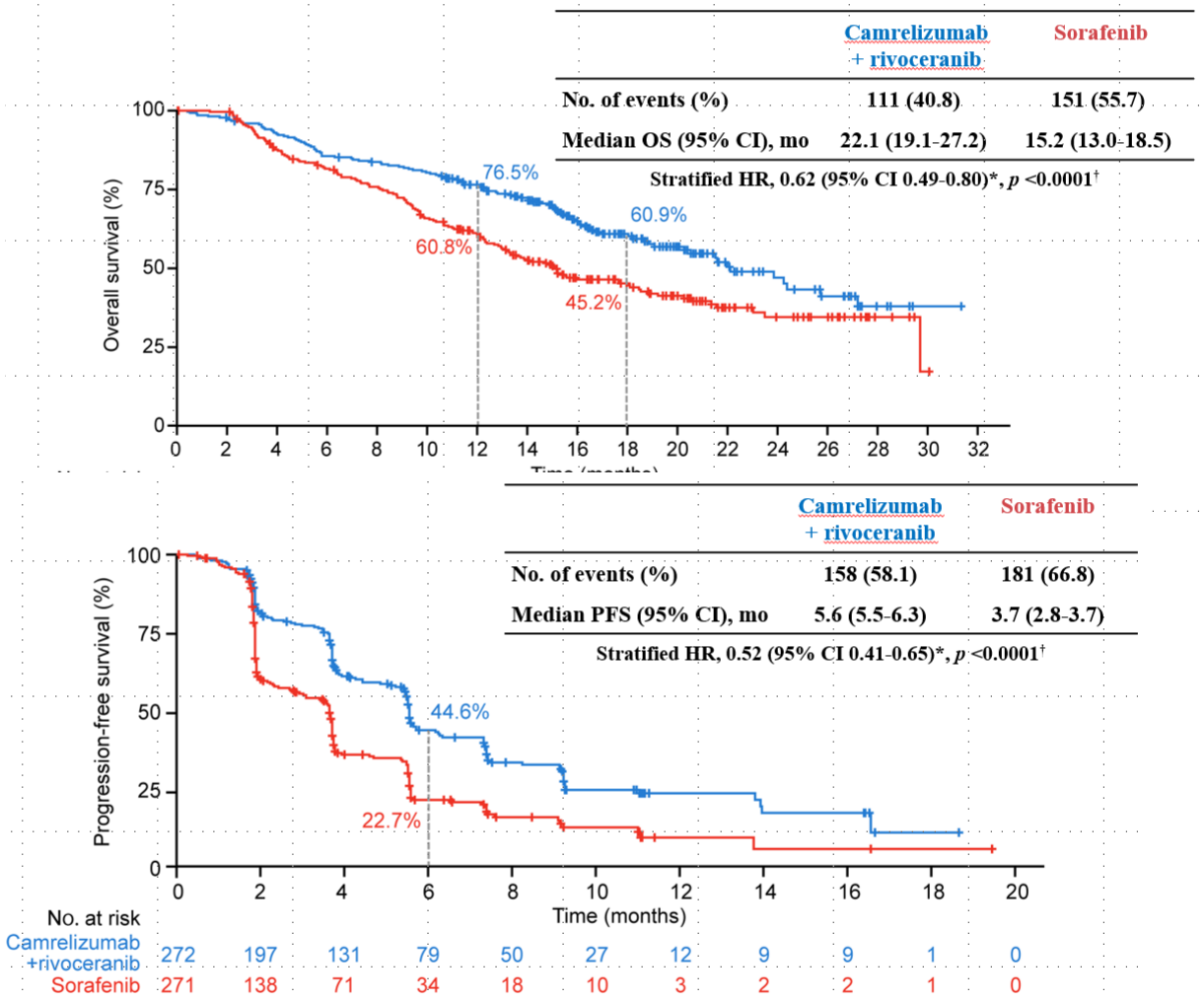
Characteristic	Camrelizumab + rivoceranib (N=272)	Sorafenib (N=271)
Age, years	58 (48-66)	56 (47-64)
Male	227 (83.5)	230 (84.9)
Geographical region		
Asia*	225 (82.7)	224 (82.7)
Non-Asia†	47 (17.3)	47 (17.3)
Etiology‡		
HBV	208 (76.5)	197 (72.7)
HCV	22 (8.1)	29 (10.7)
Non-viral¶	42 (15.4)	45 (16.6)

- Enrolled predominantly Asian, HBV+ population

Qin et al. ESMO 2022, Abstract LBA35

Camrelizumab + Rivoceranib

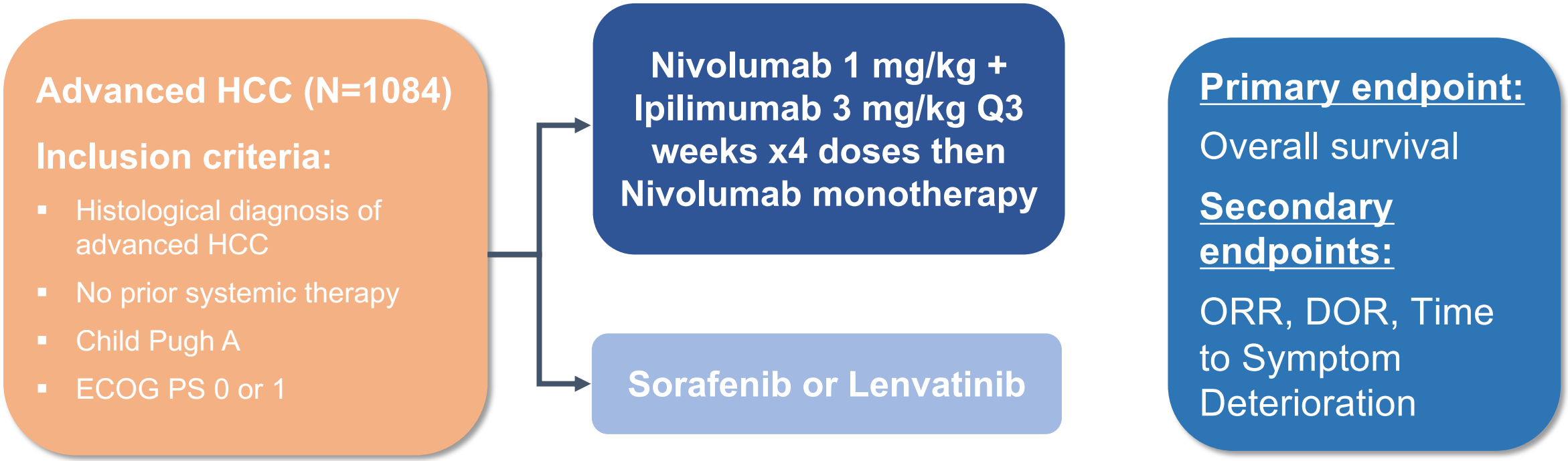
- Improved OS and PFS:
  - OS: Median 22.1 vs. 15.2 mos. (HR 0.62)
  - PFS: Median 5.6 vs. 3.7 mos. (HR 0.52)
  - ORR 25.4% vs. 5.9% by RECIST 1.1
- Safety:
  - Discontinuation any component in 24.3%
  - Grade 3-4 TRAE 80.5%
  - Any grade hemorrhage 32%, grade ≥3 3.3%
  - Grade ≥3 related hepatotoxicity 33.1%
    - Steroids required in 16.2%



Qin et al. ESMO 2022, Abstract LBA35

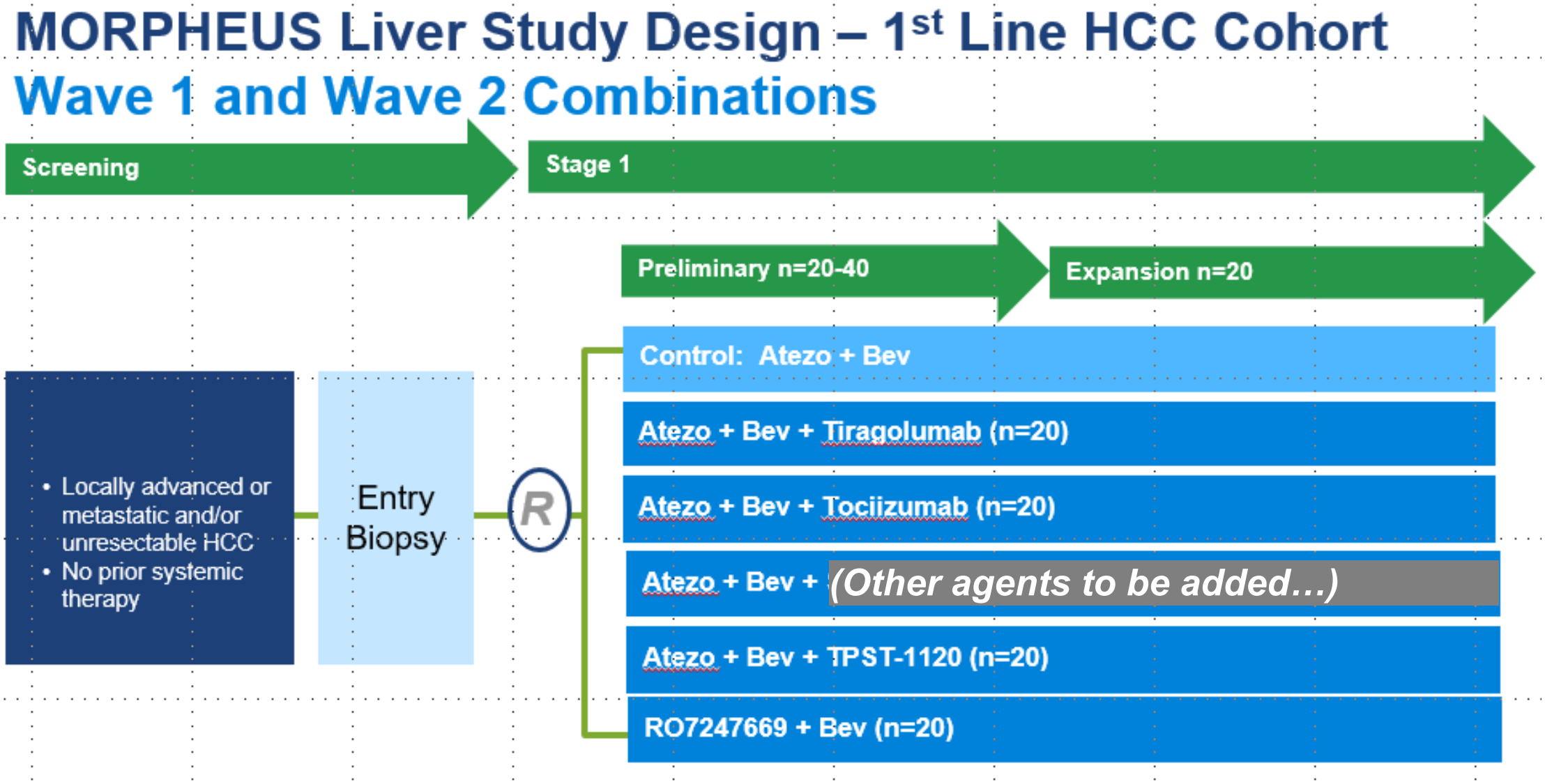
Ongoing Trial: Checkmate 9DW

- Phase 3 Trial of Nivolumab + Ipilimumab vs. SOC in 1st line HCC
- Randomized Open-Label Study



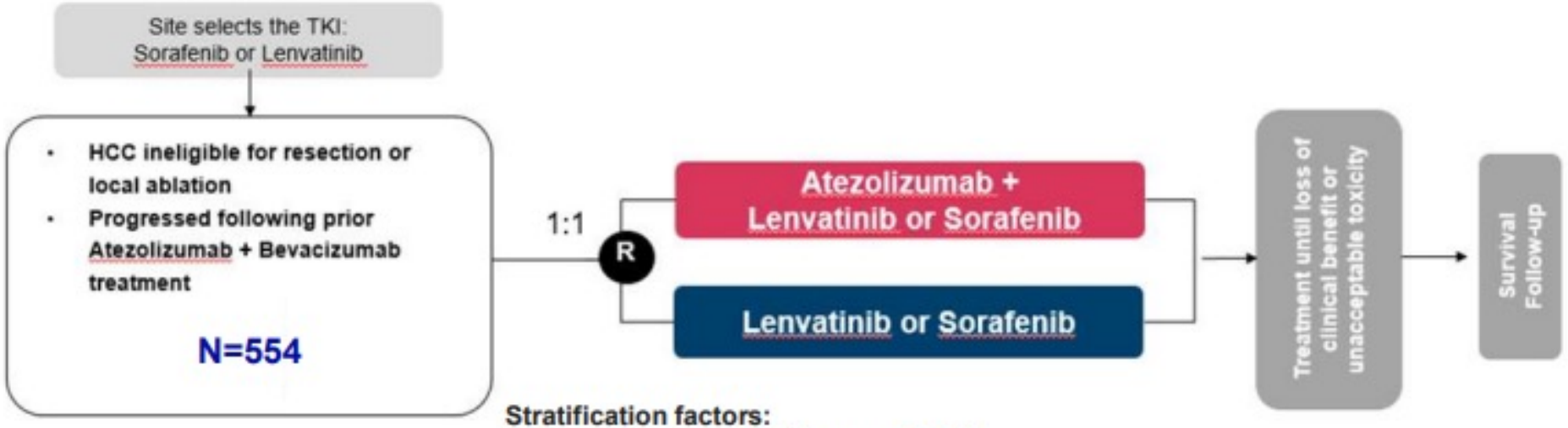
www.clinicaltrials.gov, NCT04039607

Ongoing Phase 1b/2 Platform Trial: MORPHEUS Liver



www.clinicaltrials.gov, NCT4524871

IMbrave251 Study Design *(2nd Line post Atezo+Bev)*



Stratification factors:
- **Selected TKI** (lenvatinib vs sorafenib)
- **Disease aetiology** (HBV/HCV infection vs non-viral)
- **ALBI score at baseline** (Grade 1 vs Grade 2 and 3)
- **AFP**

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

Safety objective
- Incidence and severity of AEs

Exploratory objectives
- Biomarkers
- Pharmacokinetics

www.clinicaltrials.gov, NCT04770896

Conclusions and Future Directions

- Multiple systemic treatment options for advanced HCC
  - Improve OS, ORR, and QOL compared to sorafenib
  - Enable individualized treatments according to comorbidities/AE profiles
- New ICI combination regimens are being studied in advanced stages as well as in earlier stages including adjuvant and in combination with liver-directed therapy
  - IMbrave050 may establish new role for adjuvant atezo+bev
  - EMERALD-1 demonstrates benefit for Durva/Bev with TACE
- Future studies are needed to:
  - Identify new combinations to overcome primary and acquired resistance
  - Determine safety and efficacy in broader HCC populations (e.g. Child Pugh B hepatic dysfunction, Vp4, post-transplant)
  - Define relevant biologic subgroups and biomarkers to predict response

Thank you!

Questions?