City of Hope

Multidisciplinary Approaches to Cancer Symposium

Systemic Therapy for Hepatocellular Carcinoma

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Disclosures

- Consultant for Abbvie, Adagene, AstraZeneca, Coherus, Eisai, Exelixis, Genentech, Merck, Sumitomo Pharma
- Grant/Research Support from AstraZeneca

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

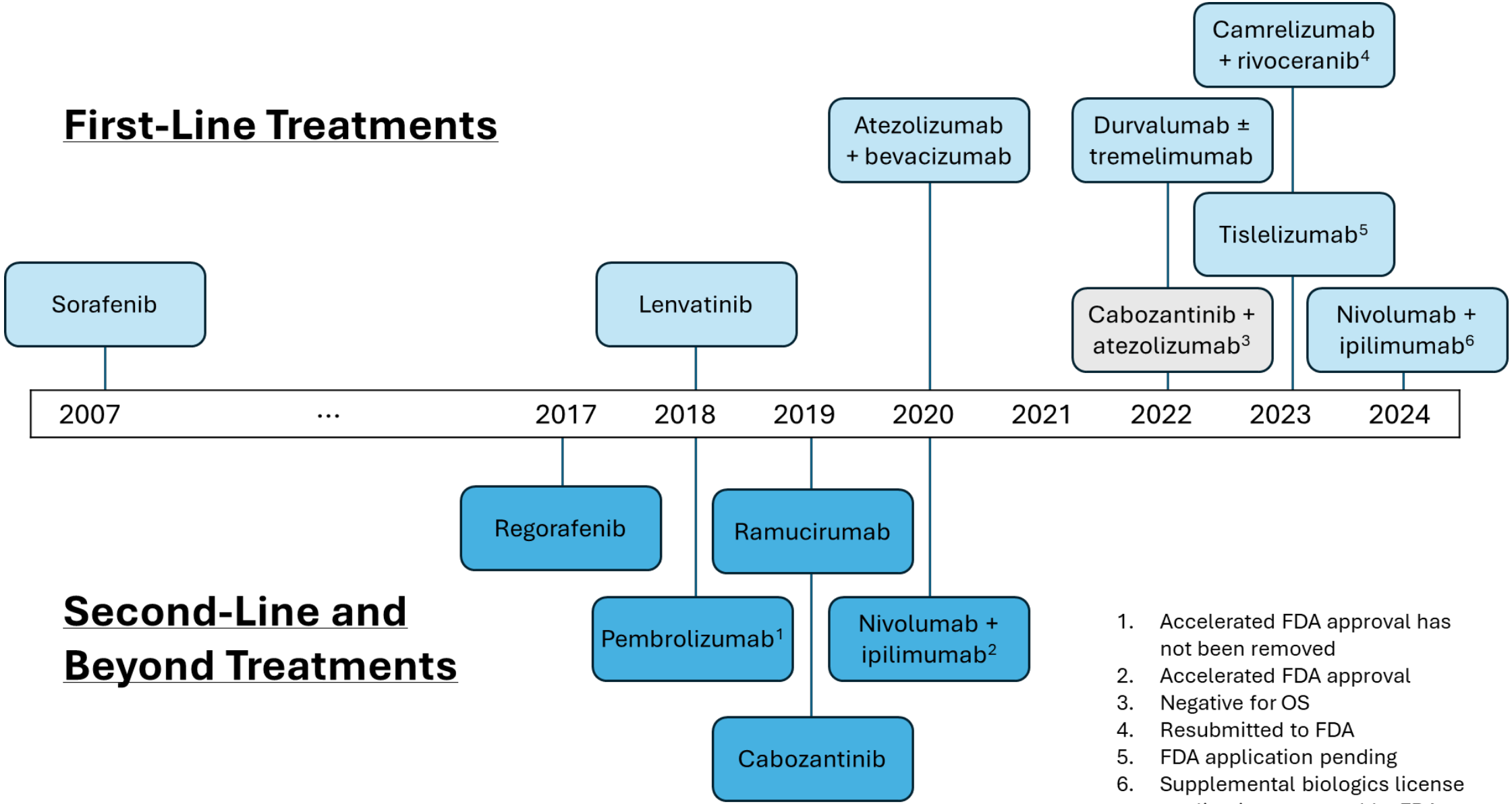
- *Will be discussing clinical trial data for patients with HCC with various therapies so these would not be direct patient care.*

Introduction: Primary Liver Cancer

- Sixth-leading cancer diagnosis; third-leading cause of cancer-related death worldwide[1]
- Hepatocellular carcinoma (HCC) comprises up to 90% of liver cancers[1, 2]
- 5-year survival rates for primary liver cancer:[3]
    - All stages: 21.6%
    - Metastatic/unresectable disease: 3.3%
- Up to 70% of HCC patients have unresectable disease at time of diagnosis[4]
    - Typically limited to **systemic treatments**[2, 4–7]

1. Bray et al. *CA Cancer J Clin* 2024 2. Llovet et al. *Nat Rev Dis Primers* 2021 3. https://seer.cancer.gov/statfacts/html/livibd.html
4. Gholam et al. *Cancers* 2019 5. Li et al. *Cancers (Basel)* 2019 6. Sonbol et al. *JAMA Oncol* 2020 7. Vogel et al. *Lancet* 2022

First-Line Treatments



Second-Line and Beyond Treatments

1. Accelerated FDA approval has not been removed
2. Accelerated FDA approval
3. Negative for OS
4. Resubmitted to FDA
5. FDA application pending
6. Supplemental biologics license application accepted by FDA

Safety and Efficacy of FDA-Approved First-Line Systemic Treatments

	SHARP[1]	REFLECT[2]	IMbrave150[3]	HIMALAYA[4]
	Sorafenib vs Placebo (n=299 vs 303)	Lenvatinib vs Sorafenib (n=478 vs 476)	Atezolizumab + Bevacizumab vs Sorafenib (n=336 vs 165)	Durvalumab + Tremelimumab vs Durvalumab vs Sorafenib (n=393 vs 389 vs 389)
Median OS, months HR (95% CI), p-value	10.7 vs 7.9 0.69 (0.55-0.87), p<0.001	13.6 vs 12.3 0.92 (0.79-1.06), p=NS	19.2 vs 13.4 0.66 (0.52-0.85), p<0.001	16.43 vs 16.56 vs 13.77 0.78 (0.65-0.93), p=0.0035[a, b] 0.86 (0.73-1.03), p=0.0674[c, d]
Median TTP, months HR (95% CI), p-value	5.5 vs 2.8 0.58 (0.45-0.74), p<0.001	7.4 vs 3.7 0.61 (0.51-0.72), p<0.0001	--	5.4 vs 3.8 vs 5.6[e]
Median PFS, months HR (95% CI), p-value	--	7.3 vs 3.6 0.65 (0.56-0.77), p<0.0001	6.9 vs 4.3 0.65 (0.53-0.81), p<0.001	3.78 vs 3.65 vs 4.07 0.90 (0.77-1.05)[a] 1.02 (0.88-1.19)[c]
ORR per RECIST 1.1, %	2.3 vs 0.7	18.8 vs 6.5	30 vs 11	20.1 vs 17.0 vs 5.1
Any-grade AEs, %	98 vs 96	99 vs 99	98 vs 99	97.4 vs 88.9 vs 95.5
Grade 3/4 AEs, %	45 vs 32	75 vs 67	63 vs 57	50.5 vs 37.1 vs 52.4
Grade 5 TRAEs, n	13 vs 29	11 vs 4	23 vs 9	9 vs 0 vs 3

NS: not significant
a: durvalumab + tremelimumab vs sorafenib
b: 96.02% CI
c: durvalumab vs sorafenib
d: 95.67% CI
e: HR and 95% CI not provided

1. Llovet et al. *N Engl J Med* 2008 2. Kudo et al. *Lancet Oncol* 2018
3. Cheng…Li et al. *J Hepatol* 2022 4. Abou-Alfa et al. *NEJM Evid* 2022

CARES-310:A Randomized, Open-Label, International, Multi-Center, Phase 3 Clinical Study of Camrelizumab Plus Rivoceranib Versus Sorafenib as First-Line Therapy in Patients With Advanced Hepatocellular Carcinoma (NCT03764293)

Eligibility Criteria

- Unresectable/metastatic HCC
- BCLC B (unsuitable for radical surgery and/or locoregional treatment) or C
- No prior systemic therapy
- ECOG PS 0 or 1
- Child Pugh A
- At least 1 measurable lesion per RECIST v1.1

Camrelizumab 200 mg IV Q2W + Rivoceranib 250 mg PO QD (n=272)

Sorafenib 400 mg PO BID (n=271)

Treatment until loss of clinical benefit or intolerable toxicity

Stratification factors

- Geographic region (Asia vs non-Asia)*
- MVI/EHS (yes vs no)
- Baseline AFP (<400 vs ≥400 ng/mL)

Primary endpoints

- Progression-free survival per RECIST v1.1 (BIRC)
- Overall survival

Key secondary endpoint

- Objective response rate per RECIST 1.1 (BIRC)

*Note: 82.7% of patients in each arm were from Asia

Qin et al. *Lancet* 2023
Vogel et al. *J Clin Oncol* 2024 (4110)

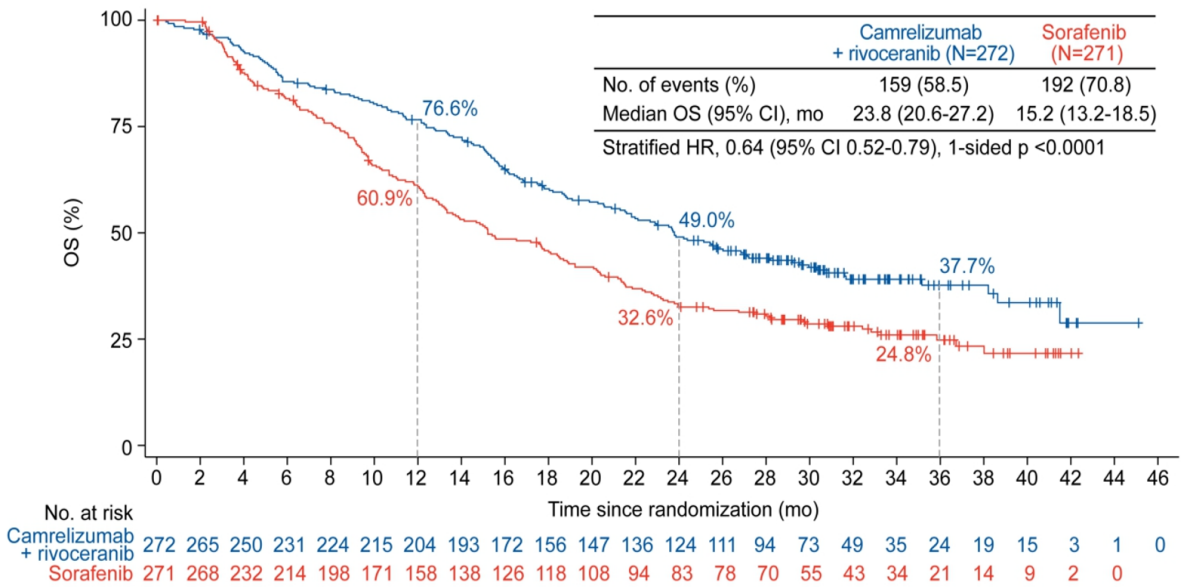
CARES-310: Results

	Camrelizumab/ Rivoceranib (n=272)	Sorafenib (n=271)
Confirmed ORR (95% CI), %	25.4 (20.3-31.0)	5.9 (3.4-9.4)
DCR (95% CI), %	78.3 (72.9-83.1)	53.9 (47.7-59.9)
Best Overall Response, n (%)		
Complete Response	3 (1.1)	1 (0.4)
Partial Response	66 (24.3)	15 (5.5)
Stable Disease	144 (52.9)	130 (48.0)
Progressive Disease	44 (16.2)	99 (36.5)
Not Evaluable	15 (5.5)	26 (9.6)

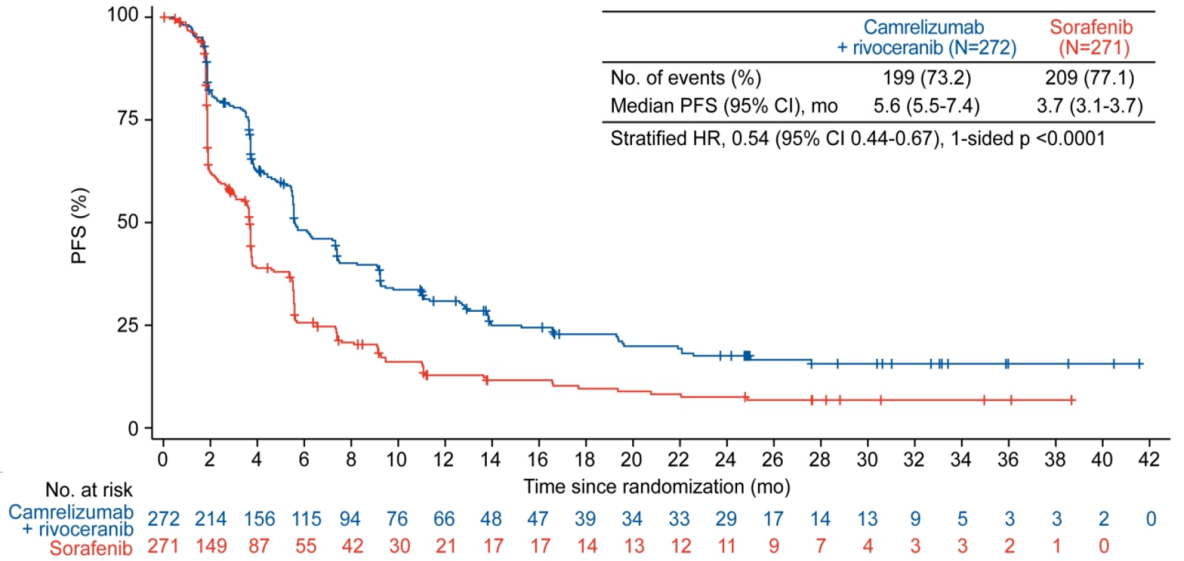
- Improved OS, PFS, and ORR with camrelizumab/ rivoceranib vs sorafenib

  ** Patient demographics may influence results*

Overall Survival



Progression-Free Survival



CheckMate 9DW: A Randomized, Multi-center, Phase 3 Study of Nivolumab in Combination With Ipilimumab Compared to Sorafenib or Lenvatinib as First-Line Treatment in Participants With Advanced Hepatocellular Carcinoma

Eligibility Criteria

- Advanced unresectable HCC
- Not amenable to curative surgical or locoregional therapy
- Child-Pugh A
- ECOG PS 0 or 1
- ≥1 measurable untreated lesion per RECIST 1.1

x Prior systemic therapy
x Vp4 main portal vein invasion

Nivolumab 1 mg/kg IV + Ipilimumab 3 mg/kg IV Q3W for 4 cycles (n = 335)

→ Nivolumab 480 mg IV Q4W

Investigator's choice
Lenvatinib 8 mg or 12 mg PO QD* OR Sorafenib 400 mg PO BID (n = 333**)

→ Treatment until disease progression, unacceptable toxicity, or 2 years of nivolumab

Stratification factors

- Etiology (HBV vs HCV vs nonviral)
- MVI/EHS (present vs absent)
- AFP (<400 vs ≥400 ng/mL)

Primary endpoint

- Overall survival

Secondary endpoints

- ORR and DOR per RECIST 1.1 (BICR)

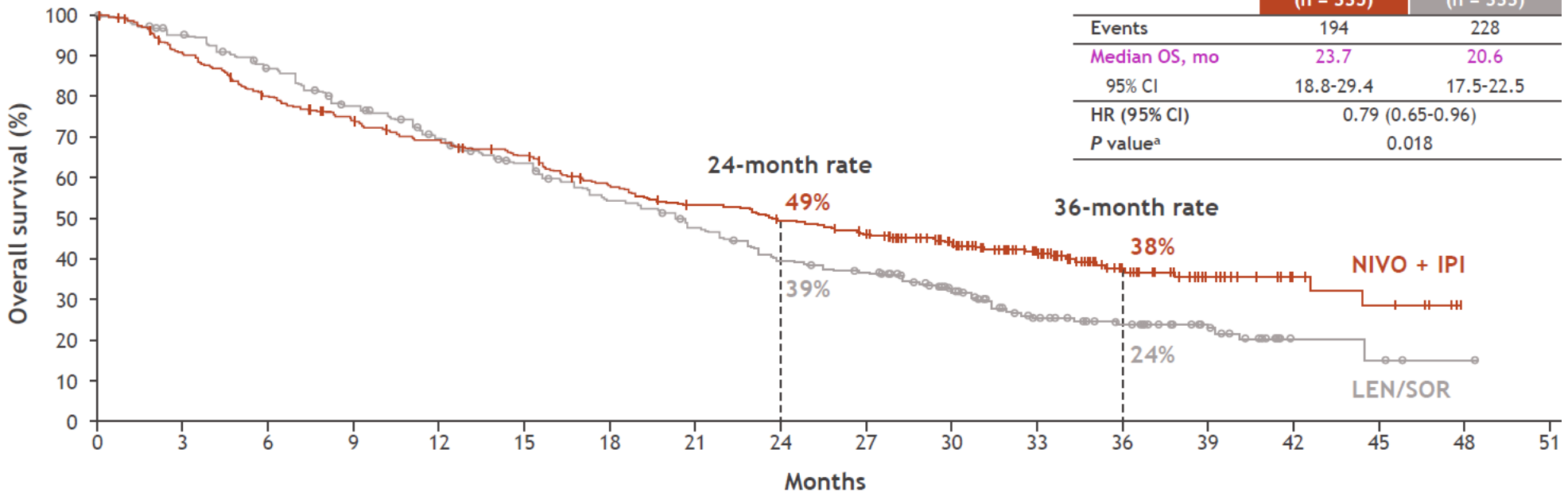
Key exploratory endpoints

- PFS by investigator per RECIST 1.1 (BICR)
- PFS2 by investigator
- Safety

* 8 mg QD if body weight <60 kg; 12 mg QD if body weight ≥60 kg
** Among 325 treated patients, 275 (85%) received lenvatinib

Galle et al. *J Clin Oncol* 2024 (LBA4008)
Decaens et al. *Ann Oncol* 2024 (965MO)

CheckMate 9DW: Overall Survival



	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	194	228
Median OS, mo	23.7	20.6
95% CI	18.8-29.4	17.5-22.5
HR (95% CI)	0.79 (0.65-0.96)	
P value[a]	0.018	

No. at risk																		
NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months

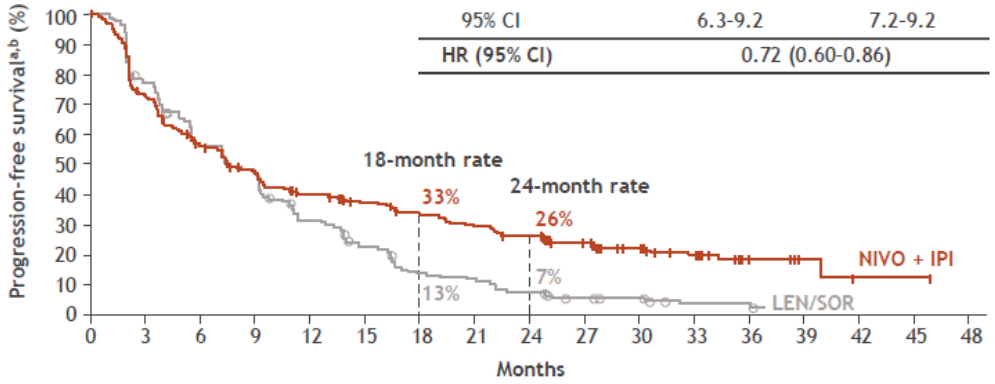
Median OS is estimated using Kaplan-Meier methodology. HR and 95% CI from stratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. Symbols represent censored observations. [a]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257.

Galle et al. *J Clin Oncol* 2024 (LBA4008)
Decaens et al. *Ann Oncol* 2024 (965MO)

CheckMate 9DW: Progression-Free Survival

Progression-free survival

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	242	281
Median PFS,[a,b] mo	7.5	7.5
95% CI	6.3-9.2	7.2-9.2
HR (95% CI)	0.72 (0.60-0.86)	

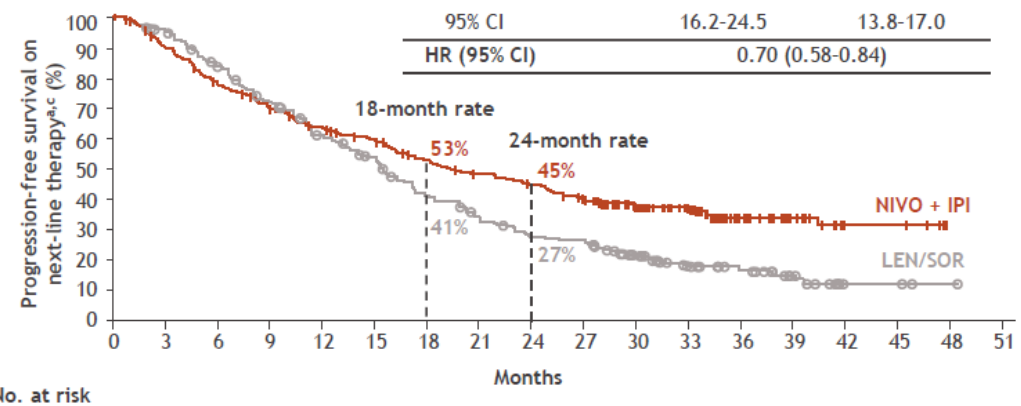


No. at risk

NIVO + IPI	335	236	173	143	114	101	89	78	69	53	35	23	9	3	1	1	0
LEN/SOR	333	243	170	140	88	62	34	28	18	11	8	3	2	0	0	0	0

Progression-free survival on next-line therapy (PFS2)

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	206	257
Median PFS2,[a,c] mo	19.3	15.4
95% CI	16.2-24.5	13.8-17.0
HR (95% CI)	0.70 (0.58-0.84)	



No. at risk

NIVO + IPI	335	298	256	228	205	189	163	148	136	120	90	61	33	18	6	6	0	0
LEN/SOR	333	310	269	229	190	162	124	101	80	76	50	32	25	13	3	3	1	0

- Numerically higher PFS[b] rates with NIVO + IPI vs LEN/SOR at 18 and 24 months
- PFS2[c] favored NIVO + IPI over LEN/SOR with a 30% reduction in the risk of death or disease progression on subsequent systemic therapy
- Subsequent systemic anticancer therapies were received by 38% vs 52% of patients in the NIVO + IPI vs LEN/SOR arm; subsequent immunotherapies were received by 13% vs 35% of patients, respectively

[a]Assessed by investigator based on RECIST v1.1. [b]Time from randomization to first documented radiological progression or death. [c]Time from randomization to documented progression (radiological or clinical) after next-line of therapy (i.e. subsequent systemic anticancer therapy) or death or to the start of second next-line systemic therapy.

Galle et al. *J Clin Oncol* 2024 (LBA4008)
Decaens et al. *Ann Oncol* 2024 (965MO)

CheckMate 9DW: Response

	NIVO + IPI (n=335)	LEN/SOR (n=333)
ORR,[a] % (95% CI)	36 (31-42)	13 (10-17)
P-value[b]	<0.0001	
Best overall response,[a] %		
Complete response	7	2
Partial response	29	11
Stable disease[c]	32	62
Progressive disease	20	14
Not evaluable	12	11
Median TTR (range),[a, d] months	2.2 (1.1-11.6)	3.7 (0.6-11.2)
Median DOR (95% CI),[a, d] months	30.4 (21.2-NE)	12.9 (10-2.31.2)

[a] Assessed by BICR per RECIST 1.1. [b] Two-sided p-value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: P-value ≤0.025. [c] Includes non-CR/non-PD: NIVO+IPI, n=6 (2%), LEN/SOR, n=7 (2%). Non-CR/non-PD refers to patients with persistence of one or more non-target lesion(s). [d] In confirmed responders (NIVO + IPI: n = 121; LEN/SOR: n = 44).

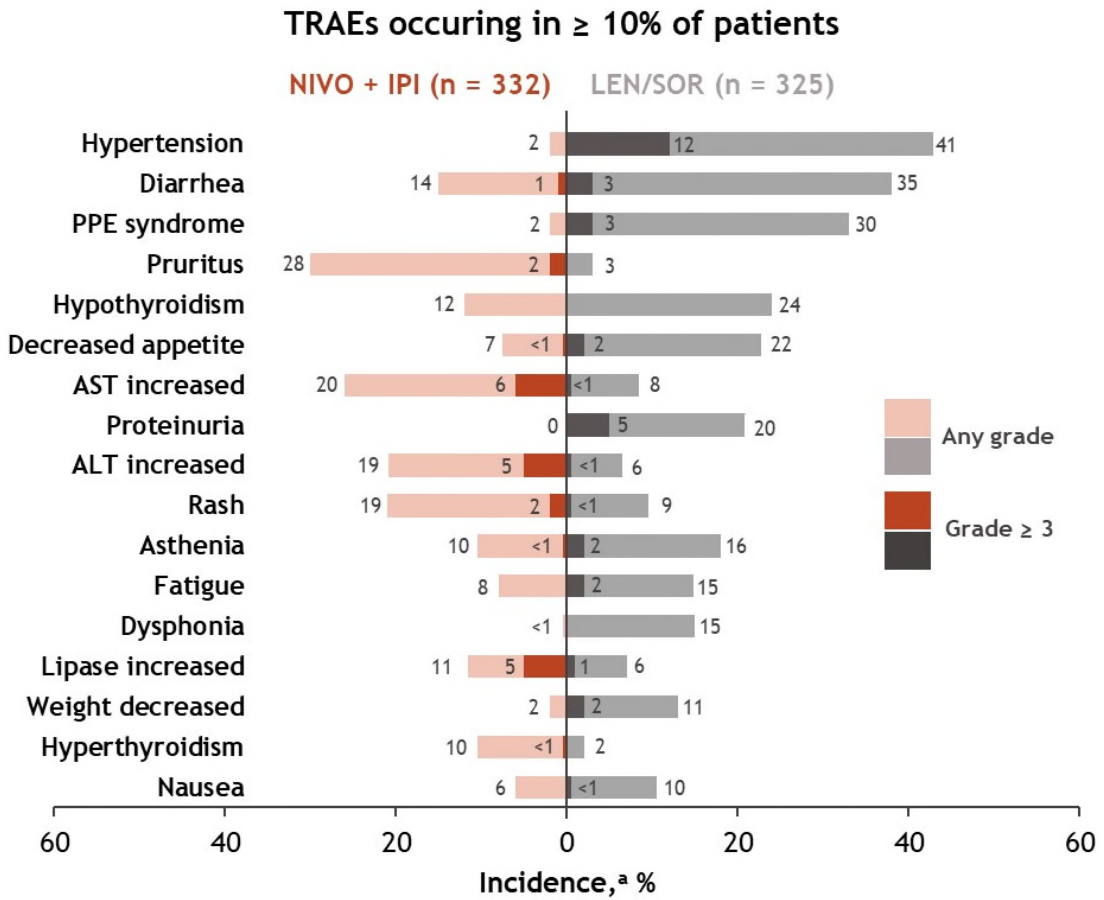
- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs LEN/SOR
  - Higher complete response rate, longer median duration of response
  - Responses to NIVO + IPI observed regardless of HCC etiology

Best reduction from baseline	NIVO + IPI (n=282)[a]	LEN/SOR (n=285)[a]
Median (IQR), %	-27.6 (-65.3 to 0.0)	-13.2 (-25.8 to 0.0)
Reduction, n (%)	210 (74)	207 (73)
> 50%	103 (37)	22 (8)
> 75%	50 (18)	12 (4)

[a] Response-evaluable patients defined as those with a best overall response of CR, PR, SD, non-CR/non-PD, or PD; target lesion(s) assessed at baseline; and ≥1 on-study assessment of all baseline target lesion(s).

Galle et al. *J Clin Oncol* 2024 (LBA4008)
Decaens et al. *Ann Oncol* 2024 (965MO)

CheckMate 9DW: Safety



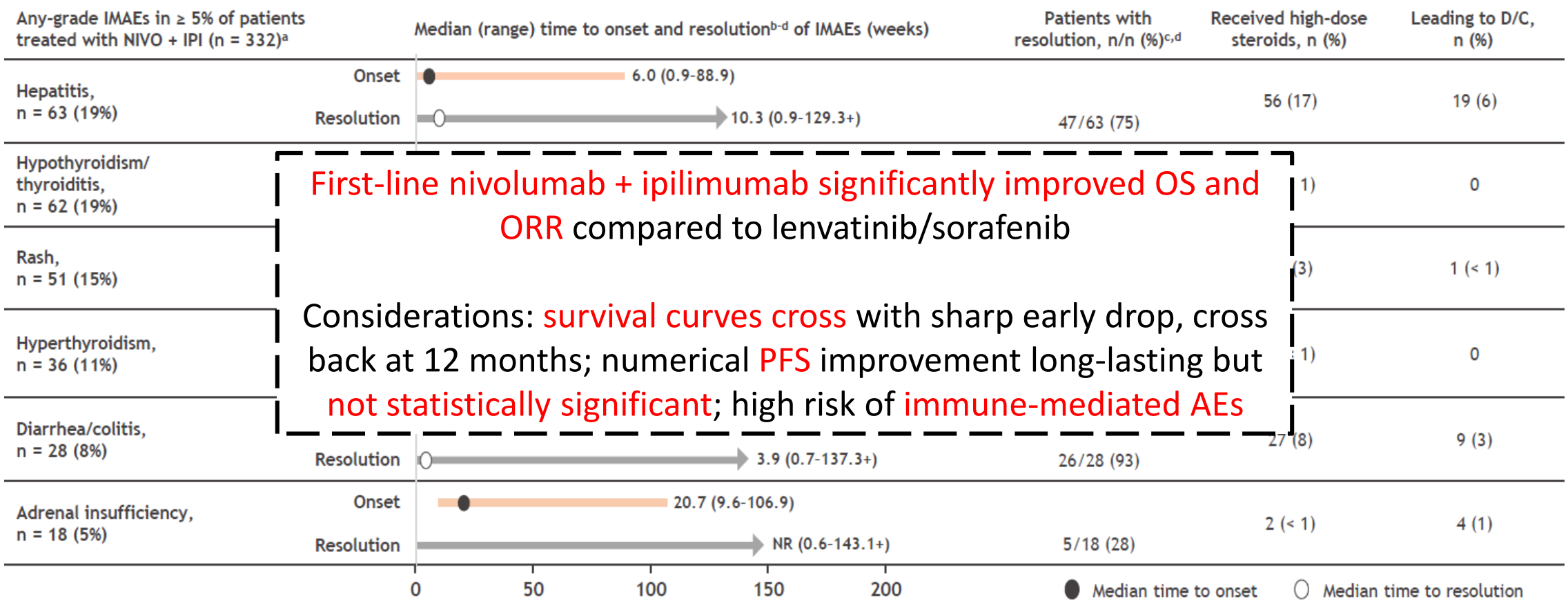
All treated patients, n (%)	NIVO + IPI (n=332)	LEN/SOR (n=325)
Median (range) duration of treatment, months	4.7 (<1 to 24.4)	6.9 (<1 to 45.8)

All treated patients, n (%)	NIVO + IPI (n=332)		LEN/SOR (n=325)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	278 (84)	137 (41)	297 (91)	138 (42)
Serious TRAEs	94 (28)	83 (25)	47 (14)	42 (13)
TRAEs leading to discontinuation	59 (18)	44 (13)	34 (10)	21 (6)
Treatment-related deaths[b]	12 (4)[c]		3 (<1)[d]	

[a] Includes events reported between first dose and 30 days after last dose of study therapy.
[b] Treatment-related deaths were reported regardless of time frame.
[c] TRAEs leading to death in the NIVO+IPI arm included immune-mediated hepatitis (n=4), hepatic failure (n=3), hepatic insufficiency (n=1), decompensated cirrhosis (n=1), diarrhea-colitis (n=1), autoimmune hemolytic anemia (n=1), and dysautonomia (n=1).
[d] TRAEs leading to death in the LEN/SOR arm included hepatorenal syndrome (n=1), ischemic stroke (n=1), and acute kidney injury (n=1).

Galle et al. *J Clin Oncol* 2024 (LBA4008)
Decaens et al. *Ann Oncol* 2024 (965MO)

CheckMate 9DW: Immune-Mediated AEs



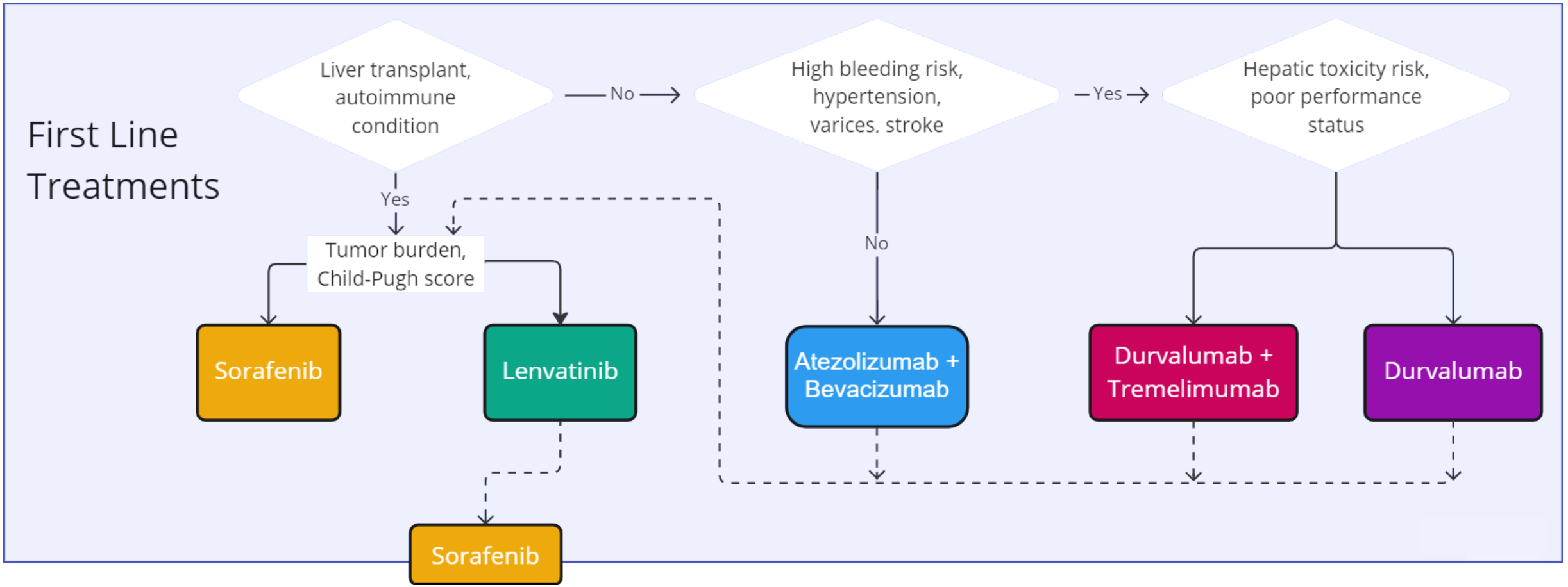
First-line nivolumab + ipilimumab significantly improved OS and ORR compared to lenvatinib/sorafenib

Considerations: survival curves cross with sharp early drop, cross back at 12 months; numerical PFS improvement long-lasting but not statistically significant; high risk of immune-mediated AEs

→ indicates ongoing events. + indicates a censored value. [a]IMAEs are specific events considered as potential immune-mediated events by investigator, occurring within 100 days after the last dose of study treatment, regardless of causality, and, with the exception of endocrine events, are treated with IMM. [b]From Kaplan-Meier estimates. [c]Time to resolution measured from the date of IMAE onset; patients who experienced IMAE without worsening from baseline grade were excluded from time to resolution analysis. Events without a stop date or with a stop date equal to the death and grade 5 events were considered unresolved. [d]Some endocrine IMAEs were considered unresolved due to continuing need for hormone replacement therapy.

Galle et al. *J Clin Oncol* 2024 (LBA4008)
Decaens et al. *Ann Oncol* 2024 (965MO)

First-Line Treatment Landscape



Adapted from Li et al. *Cancers (Basel)* 2019

Summary of Efficacy and Safety of Key Second-Line Trials

	RESORCE[1]	CELESTIAL[2]	REACH-2[3]	CheckMate 040[4,5]	KEYNOTE-240[6]
	Regorafenib vs Placebo (n=379 vs 194)	Cabozantinib vs Placebo (n=470 vs 237)	Ramucirumab vs Placebo (n=197 vs 95)	Nivolumab + Ipilimumab Cohort* (n=50)	Pembrolizumab vs Placebo (n=278 vs 135)
Median OS, months HR (95% CI), p-value	10.6 vs 7.8 0.63 (0.50-0.79), p<0.0001	10.2 vs 8.0 0.76 (0.63-0.92), p=0.005	8.5 vs 7.3 0.71 (0.53-0.95), p=0.020	22.8	13.9 vs 10.6 0.78 (0.61-1.00), p=0.0238
Median TTP, months HR (95% CI), p-value	3.9 vs 1.5 0.41 (0.34-0.51), p<0.0001	--	3.0 vs 1.6 0.427 (0.313-0.582), p<0.0001	--	--
Median PFS, months HR (95% CI), p-value	3.4 vs 1.5 0.43 (0.35-0.52), p<0.0001	5.2 vs 1.9 0.44 (0.36-0.52), p<0.001	2.8 vs 1.6 0.452 (0.339-0.603), p<0.0001	--	3.0 vs 2.8 0.775 (0.609-0.987), p=0.0186
ORR per RECIST 1.1, %	7 vs 3	4 vs <1	4.6 vs 1.1	32	18.3 vs 4.4
Any-grade AEs, %	100 vs 93	99 vs 92	--	--	96.4 vs 90.3
Any-grade TRAEs, %	93 vs 52	--	11 vs 5	94	60.9 vs 48.5
Grade 3/4 AEs, %	66 vs 39	68 vs 36	--	--	52.7 vs 46.3
Grade 3/4 TRAEs, %	50 vs 17	--	--	53	18.6 vs 7.5
Grade 5 TRAEs, n	7 vs 2	6 vs 1	3 vs 0	1	1 vs 0

* Arm A: Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg Q3W x4, then Nivolumab 240 mg Q2W

1. Bruix et al. *Lancet* 2017 2. Abou-Alfa et al. *N Engl J Med* 2018 3. Zhu et al. *Lancet Oncol* 2019
4. El-Khoueiry et al. *Lancet Oncol* 2017 5. Yau et al. *JAMA Oncol* 2020 6. Finn et al. *J Clin Oncol* 2020

Factors to Consider for Subsequent Treatment

- All currently available second-line HCC treatments were based on trials with patients who previously progressed on or were unable to tolerate sorafenib
    - **Lack of data available on second-line and beyond treatments following treatment with lenvatinib, atezolizumab + bevacizumab, or durvalumab ± tremelimumab**

An Open-Label Study of Regorafenib in Combination With Pembrolizumab in Patients With Advanced or Metastatic Hepatocellular Carcinoma After PD-1/PD-L1 Immune Checkpoint Inhibitors (ICIs)

Eligibility Criteria

- Unresectable advanced HCC
- Progression on ONLY ONE anti-PD-1/PD-L1–containing ICI regimen
- Age ≥18 years
- Child-Pugh A
- BCLC B or C
- ECOG PS 0-1

x Fibrolamellar and mixed HCC/cholangiocarcinoma subtypes
x Experienced any AE ≥Grade 3 or any immune-related toxicity that led to permanent discontinuation of ICI in first-line setting
x Persistent proteinuria ≥Grade 3
x Known active CNS metastases and/or carcinomatous meningitis

Cohort 1
Atezolizumab + Bevacizumab (n=68)

Cohorts defined by prior ICI treatment

Cohort 2
Any Other ICI Regimen (n=27)

Regorafenib 90 mg PO QD*
3 weeks on/1 week off +
Pembrolizumab 400 mg IV Q6W

* Regorafenib dose could be escalated to 120 mg QD after cycle 1 if tolerated

Primary objective
- ORR per RECIST 1.1 (independent central review)

Secondary objectives
- ORR (investigator assessment)
- Duration of response
- Safety

Exploratory objectives
- Pharmacodynamics
- Overall survival
- Progression-free survival
- Disease control rate

El-Khoueiry et al. *J Clin Oncol* 2024 (4007)

Regorafenib + Pembrolizumab: Results

Response, n (%)	Cohort 1 (n=68)[1] Atezolizumab + Bevacizumab	Cohort 2 (n=27)[1] Any Other ICI
ORR	4 (5.9)	3 (11.1)
DCR (CR, PR, SD)	37 (54.4)	20 (74.1)
Best Overall Response		
CR	0	0
PR	4 (5.9)	3 (11.1)
SD	33 (48.5)	17 (63.0)
PD	22 (32.4)	5 (18.5)
Not evaluable	9 (13.2)	1 (3.7)
Not applicable[2]	0	1 (3.7)
Median PFS, months (95% CI)	2.8 (2.4-3.9)	4.2 (2.9-6.8)
Median OS, months (95% CI)	NE (9.9-NE)	NE (NE-NE)

[1] All patients received regorafenib + pembrolizumab. Cohorts were defined by prior treatment: Cohort 1 = atezolizumab + bevacizumab; Cohort 2 = any other ICI regimen (alone or combination). [2] No detection of measurable or non-measurable disease at baseline nor of progressive disease at follow-up timepoints (central assessment).

Adverse event, n (%)	All patients (n=95)[1]	
	TEAE	Drug-related TEAE
Any grade[2]	95 (100)	83 (87)
Grade 3	53 (56)	35 (37)
Grade 4	5 (5)	3 (3)
Grade 5	3 (3)	1 (1)[4]
Serious	43 (45)	19 (20)
Leading to dose modification[3]	70 (74)	51 (54)
Leading to discontinuation of regorafenib	15 (16)	10 (11)
Leading to discontinuation of pembrolizumab	8 (8)	4 (4)
Leading to discontinuation of both study drugs	7 (7)	3 (3)
Immune-related AE	21 (22)	21 (22)

Percentages may not add to 100% due to rounding. Graded by CTCAE version 5.
[1] All patients received regorafenib + pembrolizumab. Cohorts were defined by prior treatment: Cohort 1 = atezolizumab + bevacizumab; Cohort 2 = any other ICI regimen (alone or combination). [2] Worst grade listed. [3] Dose interruptions or reductions due to AEs that did not lead to a subsequent permanent discontinuation of the same study drug. Pembrolizumab was not dose-reduced. [4] One grade 5 drug-related TEAE was listed as cardiac arrest related to both study drugs.

Factors to Consider For Subsequent Treatment

	Sorafenib[1–4]	Lenvatinib[5]

Factors to Consider	- **GIDEON study** included **Child-Pugh B and C** patients
	
	- mOS decreased as Child-Pugh score increased
	
	- More **serious AEs** and **AEs leading to discontinuation** in **Child-Pugh B and C** patients
	
	- Better response in patients **with low neutrophil to lymphocyte ratio** and **liver-confined disease**
	
	- Improved OS in patients **negative for HBV/positive for HCV**
		- **ORR** per RECIST 1.1: **18.8%**
		
		- **TRAEs**:
		  - Any grade: 94% of patients
		  - Grade 3/4: 57% of patients
		  - Serious: 18% of patients
		
		- **23%** of patients experienced **Grade ≥3 hypertension**
		
		- REFLECT **exclusion criteria**:
		  - ≥50% liver involvement
		  - Bile duct or main portal vein invasion

1. Galle et al. *Future Oncol* 2021 2. Marrero et al. *J Hepatol* 2016 3. Lim et al. *J Gastroenterol Hepatol* 2015
4. Jackson et al. *J Clin Oncol* 2017 5. Kudo et al. *Lancet Oncol* 2018

Factors to Consider For Subsequent Treatment

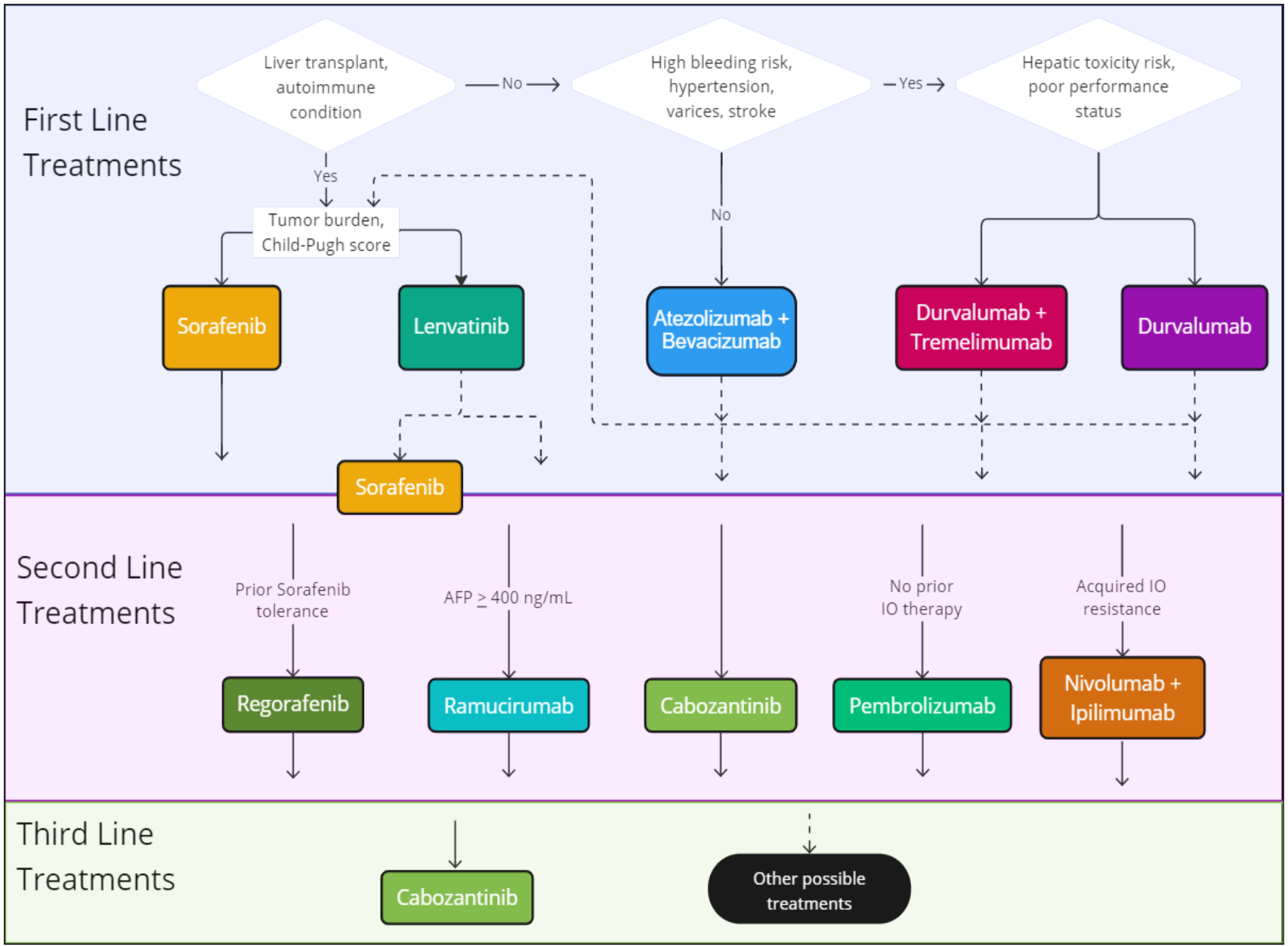
	Regorafenib[1]	Cabozantinib[2–5]	Ramucirumab[6]
Factors to Consider	- Eligibility limited to **sorafenib-tolerant patients** (≥400 mg/day for ≥20 of last 28 days of treatment) who progressed while on sorafenib - **High rates of TEAEs** (93% regorafenib vs 52% placebo) - **Serious AEs** in 10% of patients - 54% of patients had **dose reductions/delays**; 10% **discontinued** due to TRAEs	- Patients allowed **up to 2 prior lines of therapy** - **High rates of grade 3/4 AEs** (68% vs 36%) - May be tolerated/effective in patients with **Child-Pugh B** disease or **prior anti-PD-1/L1** treatment - 62% of patients had **dose reductions**; 16% **discontinued** due to TRAEs	- Approved for patients with baseline **AFP ≥400 ng/mL** and prior sorafenib treatment - 11% **discontinued** treatment due to TRAEs - 5% of patients had **dose reductions**; 6% had **dose delays** due to AEs

1. Bruix et al. *Lancet* 2017 2. Abou-Alfa et al. *N Engl J Med* 2018 3. El-Khoueiry et al. *BMC Cancer* 2022
4. Abou-Alfa et al. EASL Liver Cancer Summit 2020 (PB02-04) 5. Chan et al. *J Hepatol* 2024 6. Zhu et al. *Lancet Oncol* 2019

Factors to Consider For Subsequent Treatment

	Pembrolizumab[1–4]	Nivolumab + Ipilimumab[5–9]
Factors to Consider	**Role of immunotherapy for patients previously treated with anti-PD-1/L1 immunotherapy is unclear**	
	- **KEYNOTE-240** trended towards clinical benefit; **no statistical significance** for OS or PFS - **KEYNOTE-394** met its co-primary endpoints of OS and PFS in **Asian patients** - **Regorafenib + pembrolizumab after first-line immunotherapy** did not meet primary ORR endpoint; no new safety signals observed	- 20% of patients in **CheckMate 040** Arm A experienced **grade 3/4 hepatic immune-mediated AEs** - **22% discontinued** due to toxicity - May be tolerated/effective in patients who received **prior anti-PD-1/L1** treatment - **Positive first-line data from CheckMate 9DW** may reduce number of patients receiving this regimen in the second-line or later setting

1. Finn et al. *J Clin Oncol* 2020 2. Kudo et al. *Liver Cancer* 2021 3. Qin et al. *J Clin Oncol* 2022 (383) 4. El-Khoueiry et al. *J Clin Oncol* 2024 (4007) 5. Yau et al. *JAMA Oncol* 2020 6. Wong et al. *J Immunother Cancer* 2021 7. Roessler et al. *J Cancer Res Clin Oncol* 2022 8. Galle et al. *J Clin Oncol* 2024 (LBA4008) 9. Decaens et al. *Ann Oncol* 2024 (965MO)



Adapted from Li et al. *Cancers (Basel)* 2019

Conclusions

- The systemic treatment landscape for advanced HCC continues to rapidly evolve
- Treatment planning/sequencing requires consideration of multiple factors
- Recently completed/ongoing clinical trials have potential to further improve clinical outcomes for patients at multiple stages of their treatment journey

Thank you

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