



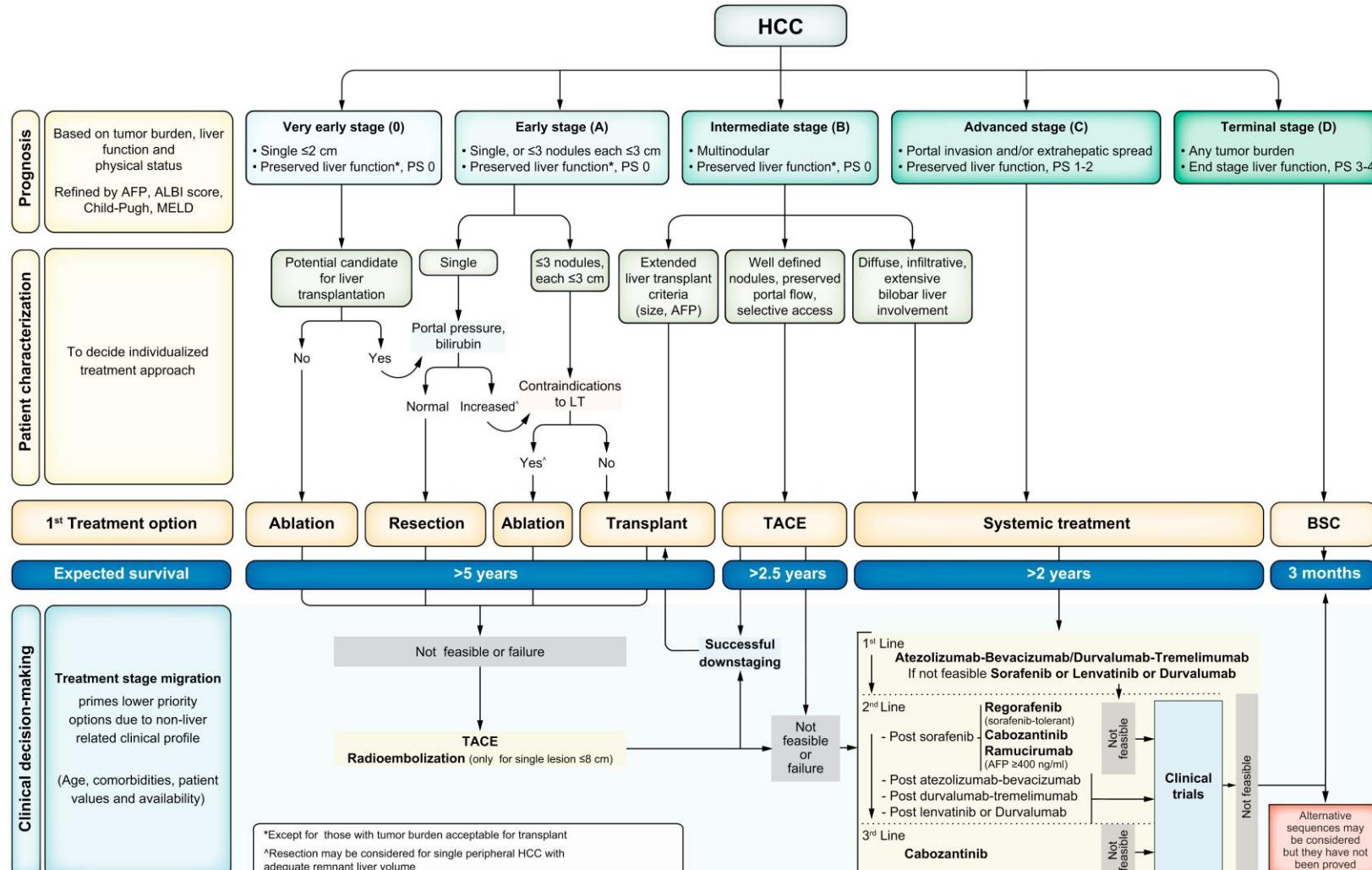
# Evolution of systemic therapies and clinical trials in liver cancer

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# Objectives: Hepatocellular Carcinoma

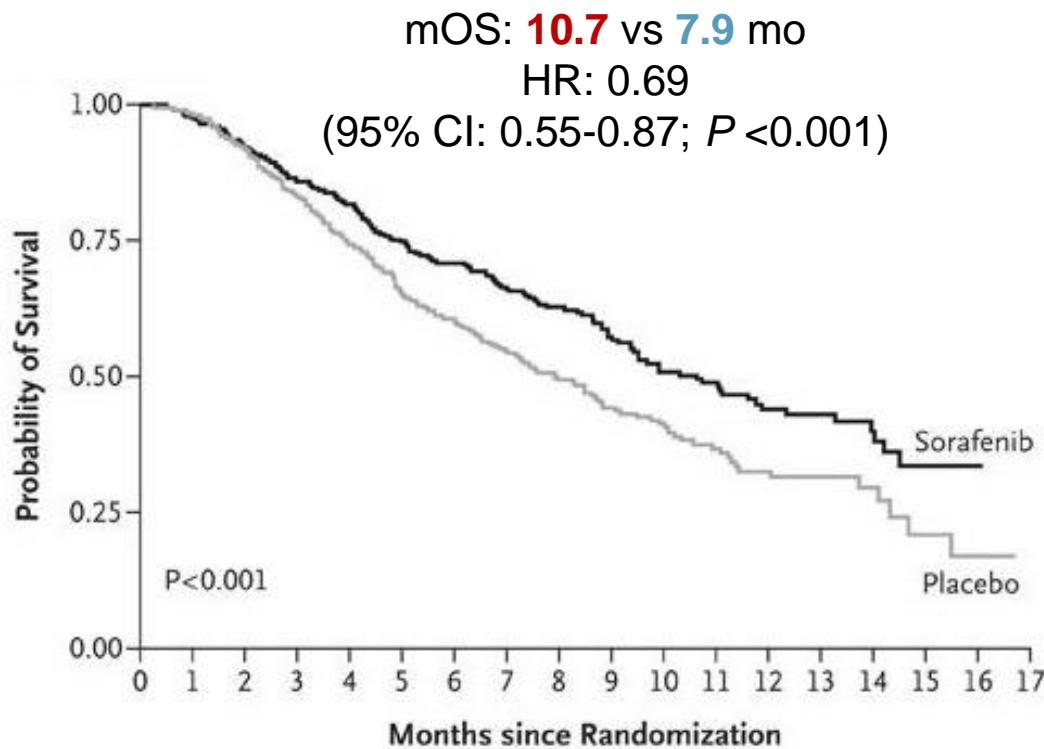
1. **Discuss drug classes of systemic therapy in hepatocellular carcinoma, including efficacy and common toxicities**
  - a) Immune checkpoint inhibitors
  - b) VEGF-targeted monoclonal antibodies
2. **Discuss role for combination therapies and emerging novel targets in hepatocellular carcinoma**

# BCLC Staging and Treatment



# Systemic Therapy: Sorafenib

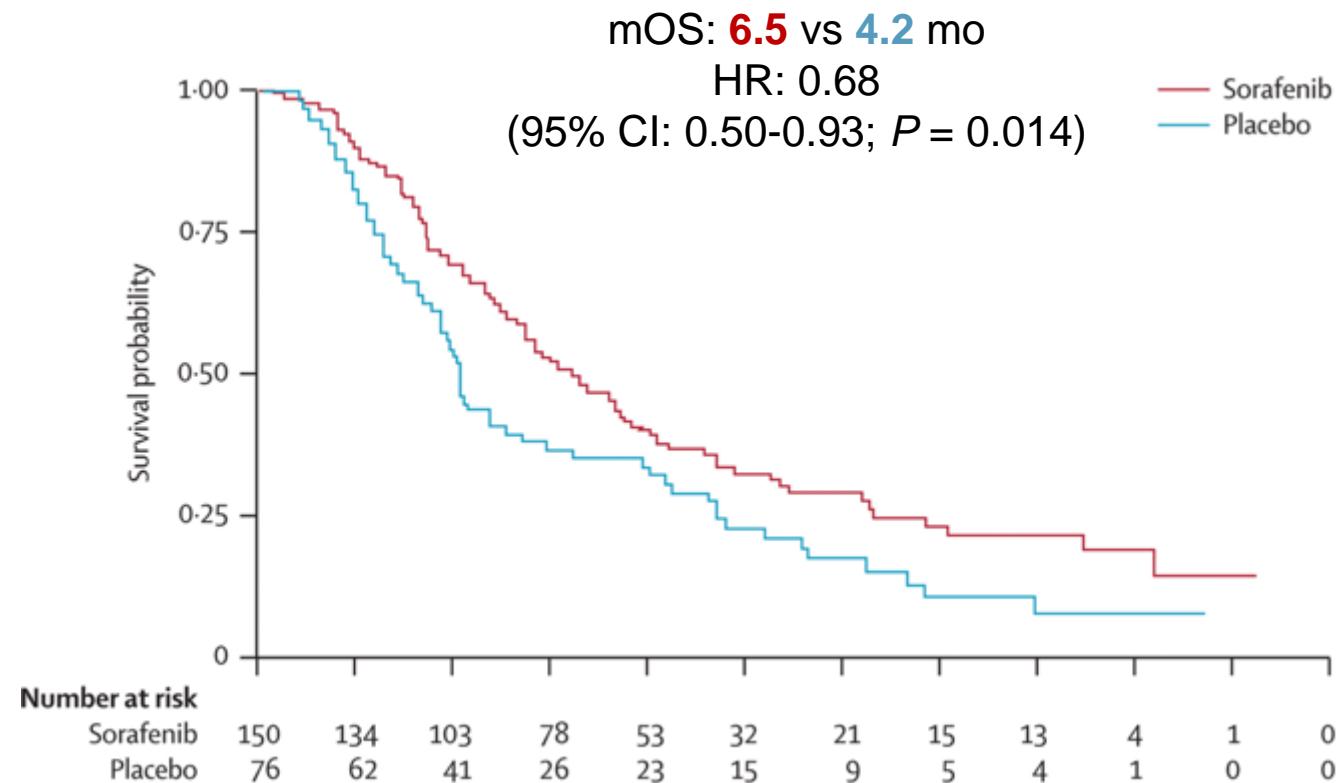
## SHARP



### No. at Risk

Sorafenib	299	290	270	249	234	213	200	172	140	111	89	68	48	37	24	7	1	0
Placebo	303	295	272	243	217	189	174	143	108	83	69	47	31	23	14	6	3	0

## Asia-Pacific



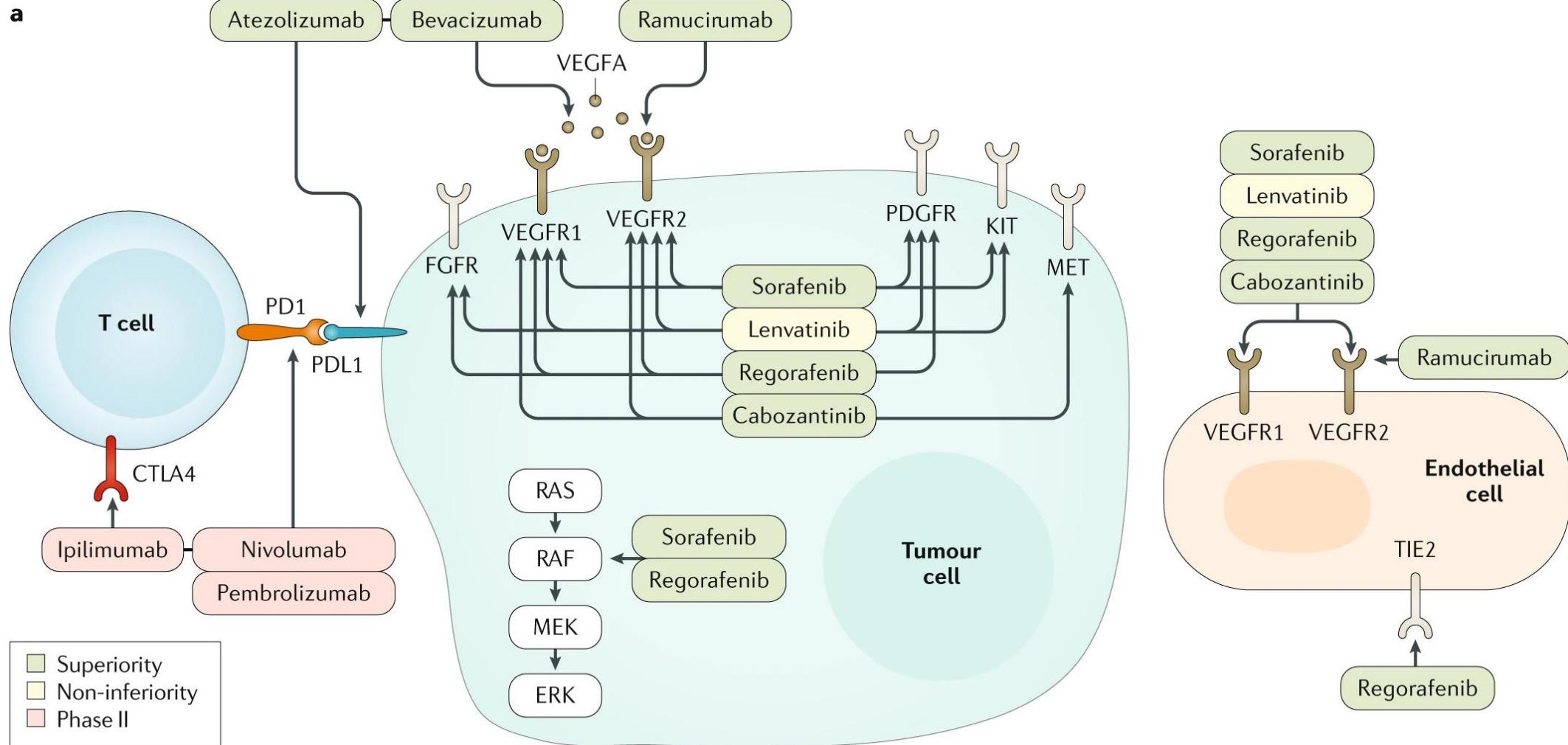
Llovet JM et al. N Engl J Med. 2008 Jul 24;359(4):378-90.

Cheng AL et al. Lancet Oncol. 2009 Jan;10(1):25-34.

# Currently Approved Systemic Therapies



# Therapeutic Targets in HCC



# Immune Checkpoint Inhibitors

# Immunotherapy Combinations: Targets

Drug	HCC Dosing	Targets
<b>Atezolizumab</b> <b>Bevacizumab</b>	1200mg IV q3weeks 15mg/kg IV q3weeks	PD-L1 VEGF
<b>Tremelimumab</b> <b>Durvalumab</b>	300mg IV x 1 dose 1500mg IV q4weeks	CTLA-4 PD-L1

# 1<sup>st</sup> Line Systemic Therapy: Atezolizumab plus Bevacizumab

**IMbrave150:** phase 3, randomized, multicenter, open-label trial

501 patients at 111 sites in 17 countries

## POPULATION

Advanced HCC  
No prior systemic therapy  
Child Pugh A  
ECOG ≤ 1

## RANDOMIZATION/ STRATIFICATION

Asia vs ROW  
ECOG 0 vs 1  
± MVI/EHS  
AFP </≥ 400

1:2

## INTERVENTION

Atezolizumab 1200mg IV  
Bevacizumab 15mg/kg IV  
q3weeks

Sorafenib 400mg PO BID

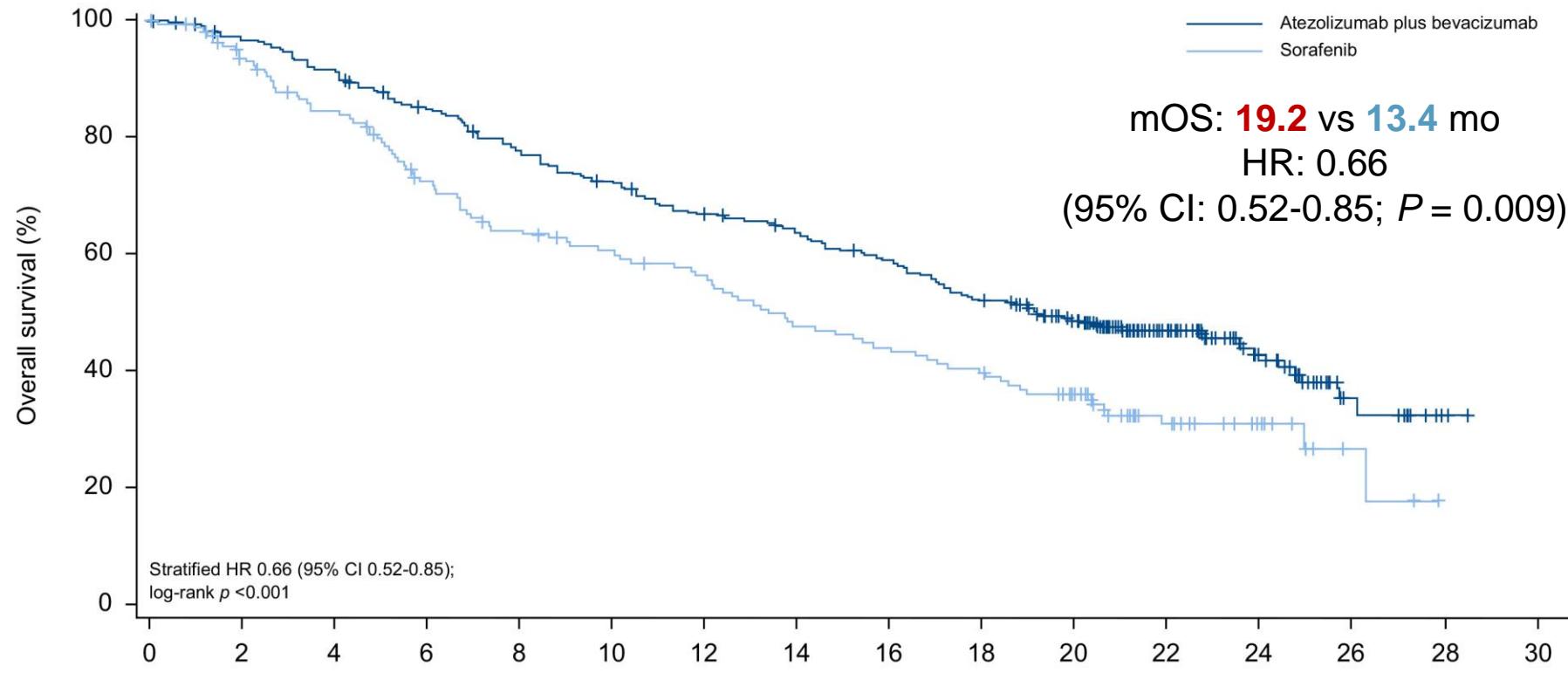
## ENDPOINTS

**Co-Primary:**  
OS, PFS

**Key Secondary:**  
ORR RECIST v1.1  
ORR mRECIST

# IMbrave150 Co-Primary Endpoints: OS

A



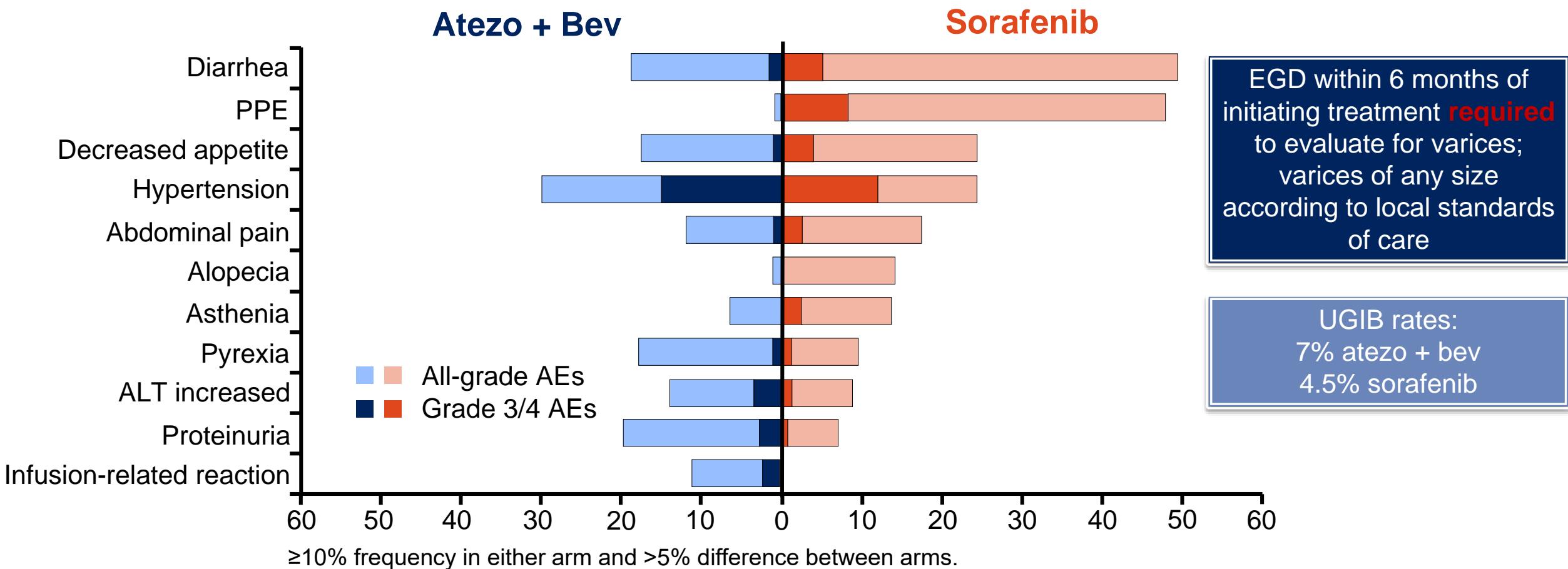
N° at risk (number censored)

Atezolizumab plus bevacizumab	336 (0)	320 (6)	302 (6)	276 (10)	252 (11)	233 (12)	214 (14)	202 (16)	186 (17)	164 (17)	134 (37)	80 (87)	42 (120)	12 (145)	2 (154)	0 (156)
Sorafenib	165 (0)	144 (11)	128 (13)	106 (17)	92 (19)	85 (21)	78 (22)	66 (22)	61 (22)	55 (22)	44 (28)	24 (43)	12 (55)	3 (63)	0 (65)	0 (65)

# IMbrave150: Response Rates

Outcome	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR, % (95% CI)	30 (32-35)	11 (7-17)	35 (30-41)	14 (9-20)
CR, n (%)	25 (8)	1 (<1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing Response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DoR, mo (95% CI)	18.1 (14.6-NE)	14.9 (4.9-17.0)	16.3 (13.1-21.4)	12.6 (6.1-17.7)

# IMbrave150: Safety



# Dual Immune Checkpoint Blockade

## STRIDE

- Single Tremelimumab (*anti-CTLA4*)
- Regular Interval Durvalumab (*anti-PDL1*)

# 1<sup>st</sup> Line Systemic Therapy: Durvalumab plus Tremelimumab

**HIMALAYA:** phase 3, randomized, multicenter, open-label trial

1324 patients

## POPULATION

Advanced HCC  
No prior systemic therapy  
Child Pugh A  
ECOG ≤ 1  
No main PVT  
EGD not required

## RANDOMIZATION/ STRATIFICATION

HBV/HCV/other  
ECOG 0 vs 1  
± MVI

1:1

## INTERVENTION

Tremelimumab 300mg x1  
Durvalumab 1500mg IV q4weeks

Durvalumab 1500mg IV q4weeks

Sorafenib 400mg PO BID

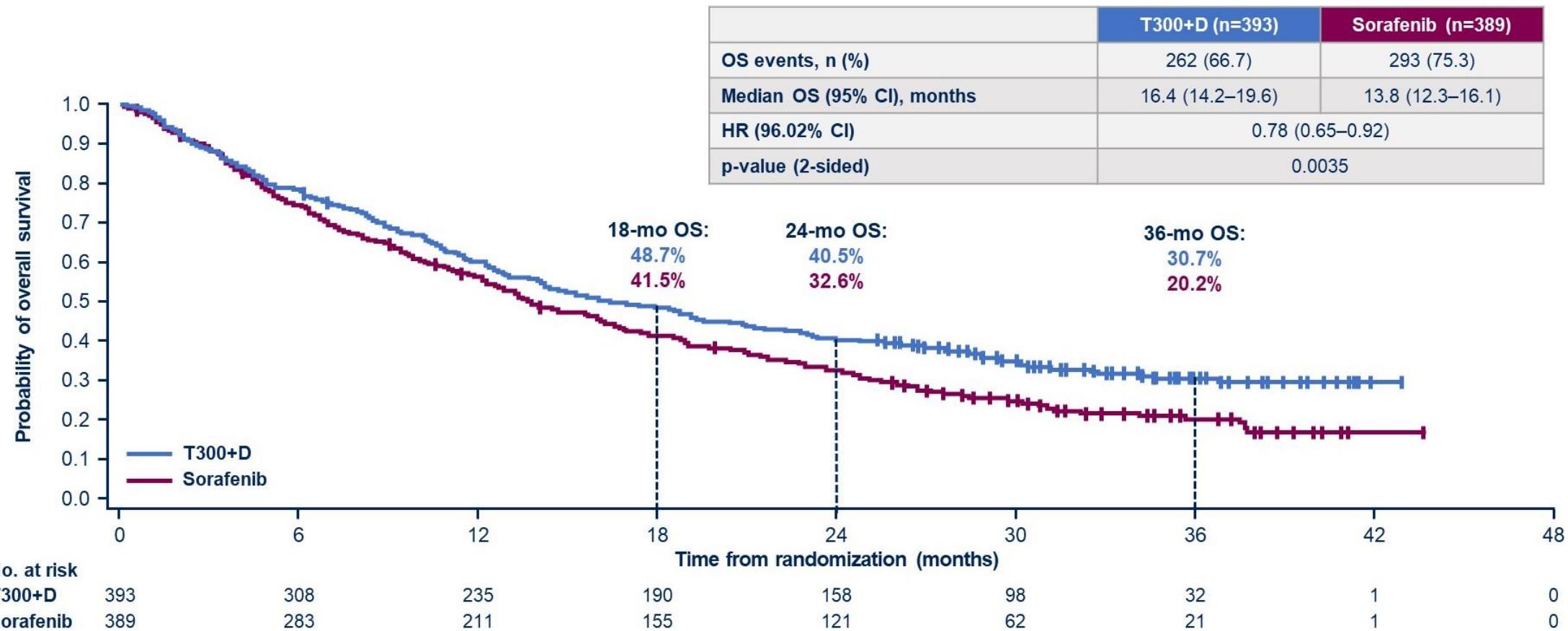
## ENDPOINTS

**Primary:**  
OS (STRIDE vs sorafenib)

**Key Secondary:**  
OS (durva vs sorafenib)

**Other Secondary:**  
PFS, ORR, DoR

# HIMALAYA Primary Endpoint: OS



# HIMALAYA: Response Rates

	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
<b>ORR,* n (%)</b>	<b>79 (20.1)</b>	<b>66 (17.0)</b>	<b>20 (5.1)</b>
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months	22.34	16.82	18.43
25 <sup>th</sup> percentile	8.54	7.43	6.51
75 <sup>th</sup> percentile	NR	NR	25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ %			
6 months	82.3	81.8	78.9
12 months	65.8	57.8	63.2

# HIMALAYA: Safety

Event, n (%)	T300+D (n=388)		Durvalumab (n=388)		Sorafenib (n=374)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
<b>Patients with hepatic SMQ TRAE</b>	66 (17.0)	27 (7.0)	55 (14.2)	20 (5.2)	46 (12.3)	18 (4.8)
<b>Patients with hemorrhage SMQ TRAE</b>	7 (1.8)	2 (0.5)	3 (0.8)	0	18 (4.8)	6 (1.6)
Alanine aminotransferase increased	18 (4.6)	4 (1.0)	22 (5.7)	5 (1.3)	8 (2.1)	3 (0.8)
Aspartate aminotransferase increased	22 (5.7)	9 (2.3)	25 (6.4)	9 (2.3)	10 (2.7)	6 (1.6)
Blood bilirubin increased	6 (1.5)	1 (0.3)	6 (1.5)	0	10 (2.7)	2 (0.5)
Ascites	1 (0.3)	0	0	0	2 (0.5)	0
Hepatic encephalopathy	0	0	0	0	2 (0.5)	1 (0.3)
International normalized ratio increased	4 (1.0)	1 (0.3)	0	0	0	0
Esophageal varices hemorrhage	0	0	0	0	0	0

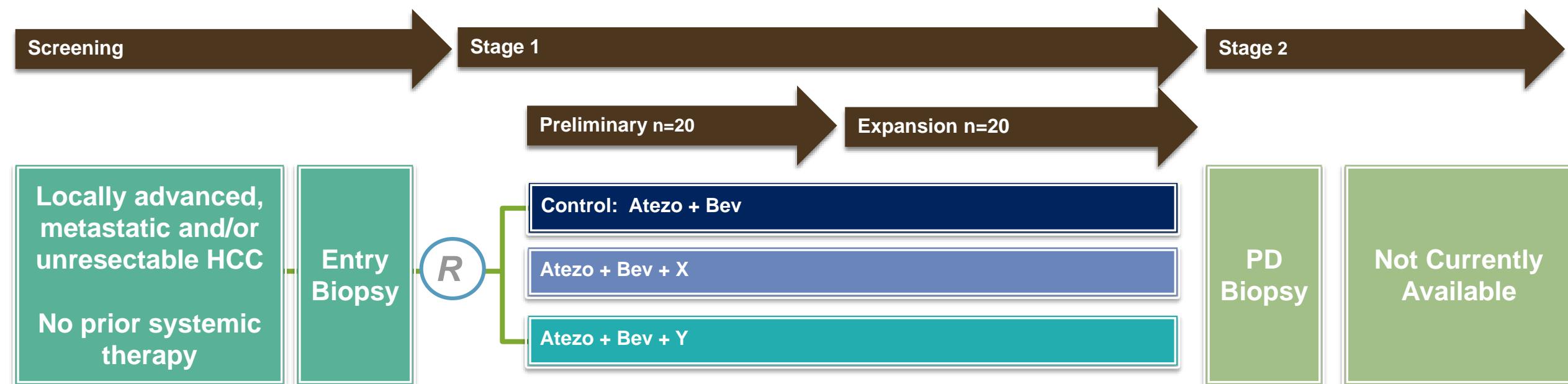
New front-line option for advanced HCC patients that have higher risk of **bleeding** with VEGF-sparing regimen

# HIMALAYA: Safety

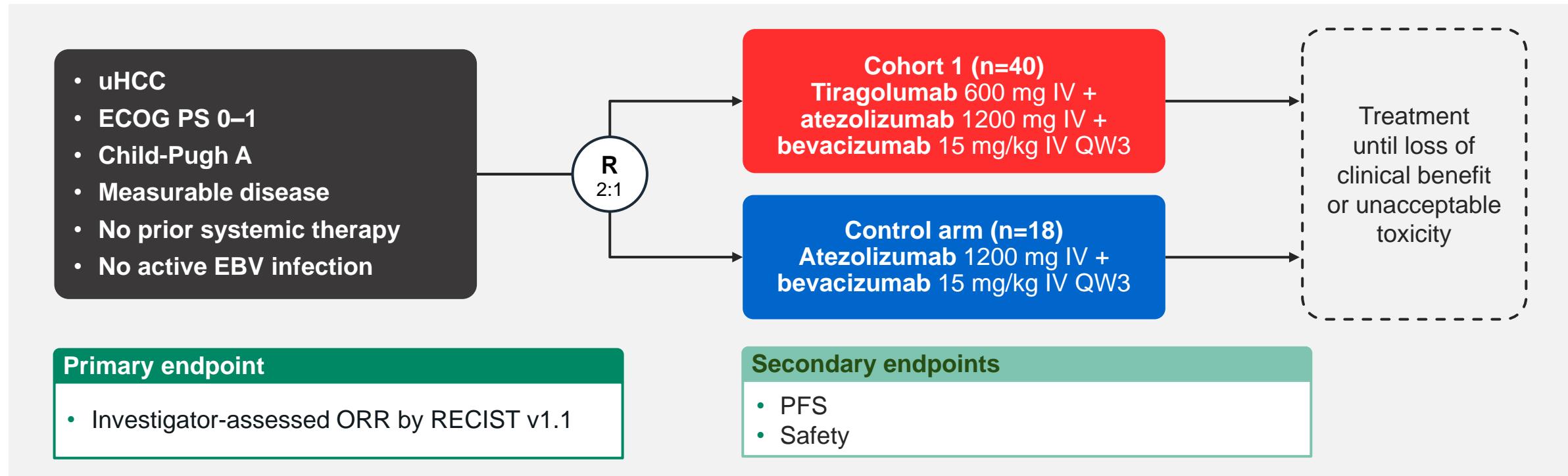
Event, n (%)	T300+D (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
<b>Patients with immune-mediated event</b>	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0

CheckMate-040 study with ipilimumab/nivolumab had **53% grade 3 TRAEs**; STRIDE regimen has improved safety profile

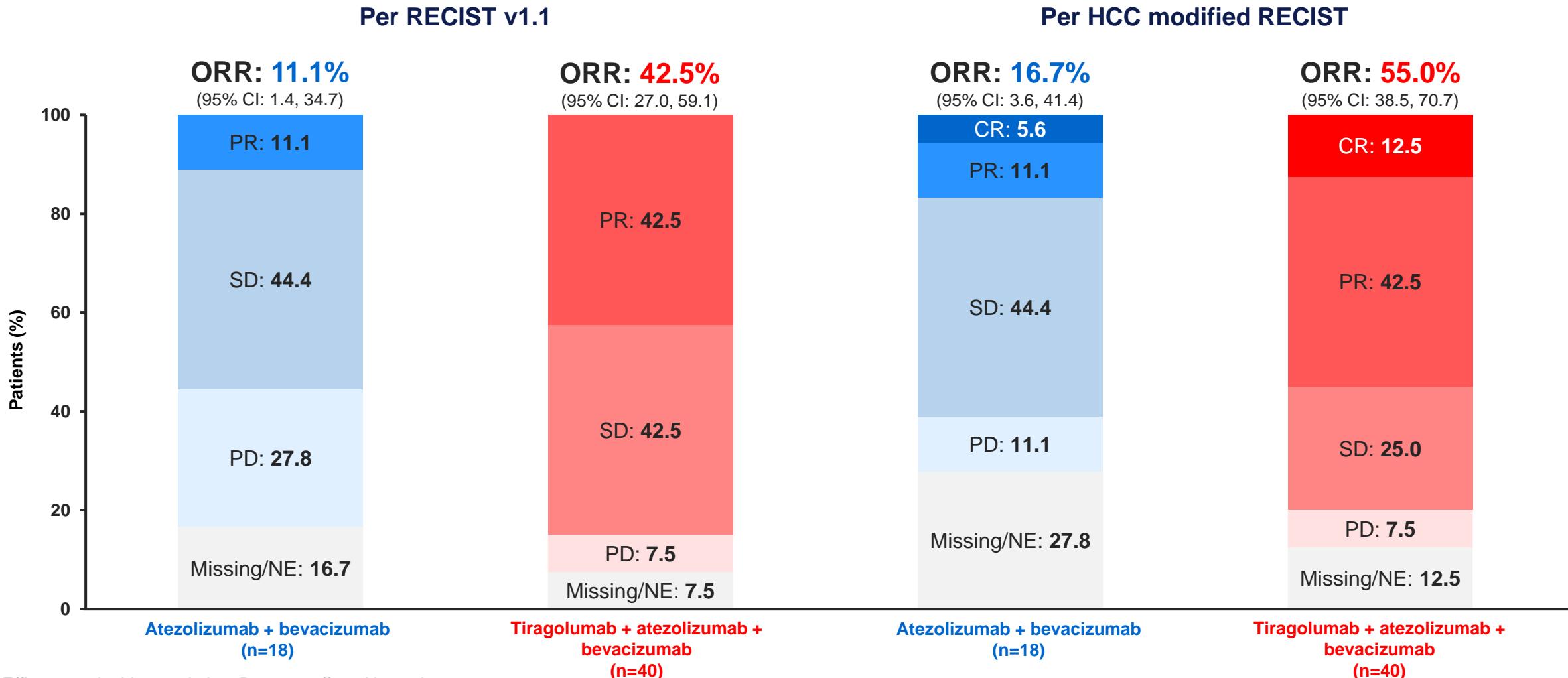
# MORPHEUS: Adaptive Phase 1b/2 Trial



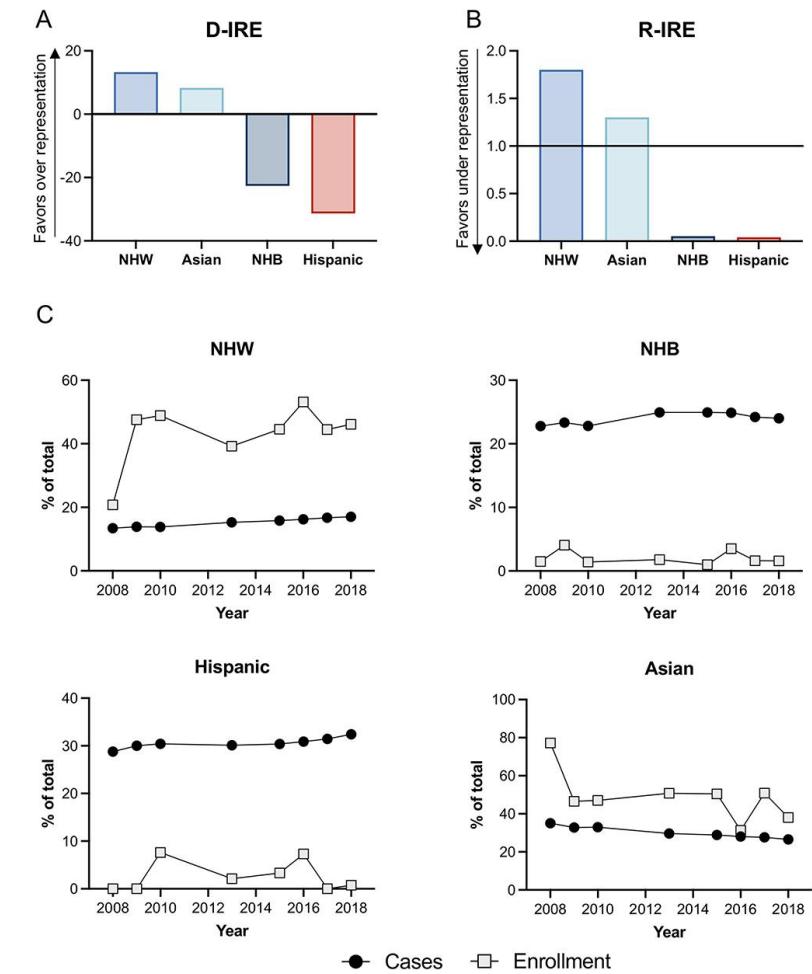
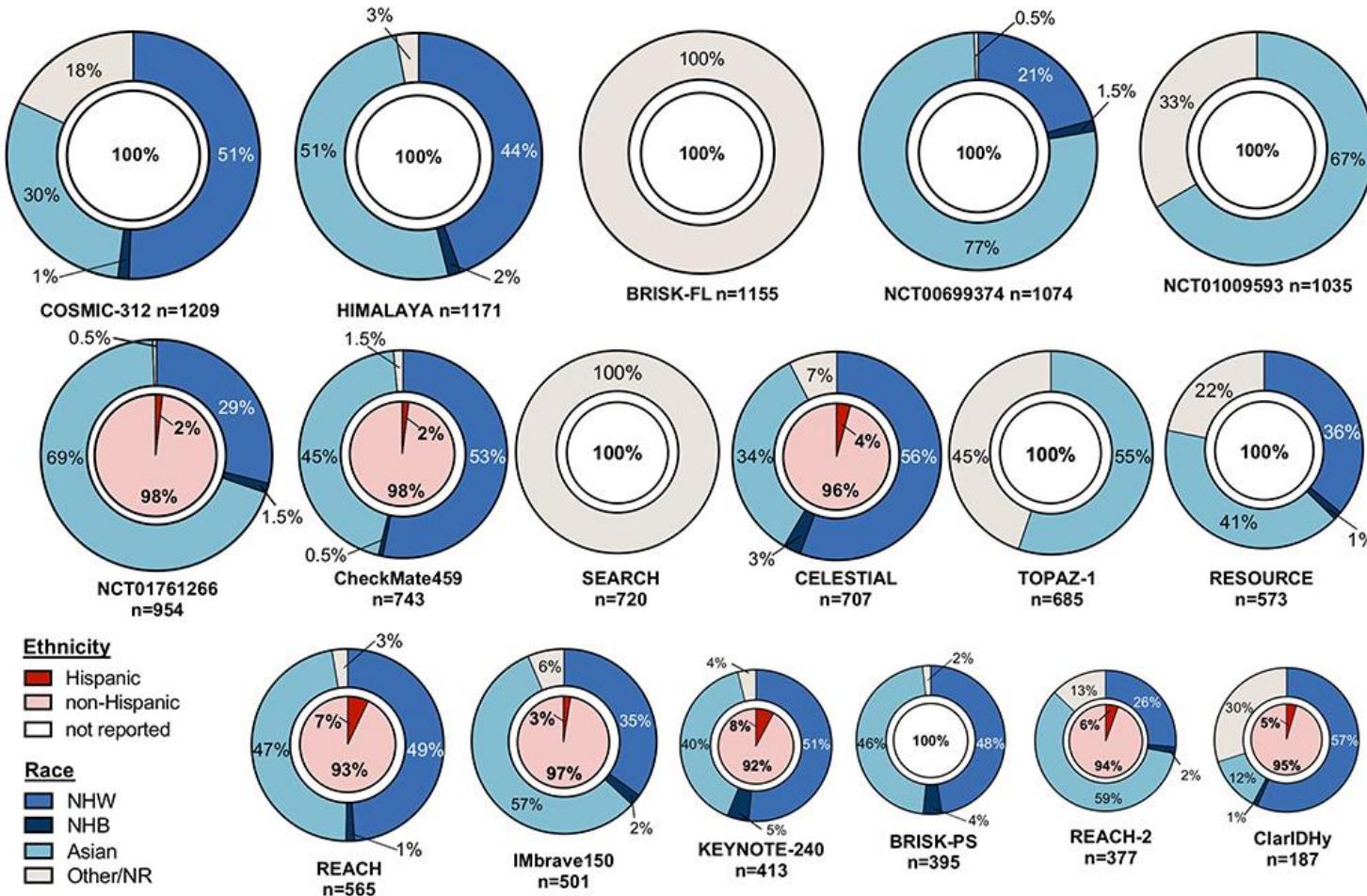
# MORPHEUS: Tiragolumab Arm



# MORPHEUS: Tiragolumab Arm



# Hispanic Patients are Underrepresented in Phase III Clinical Trials for Advanced Liver Cancer

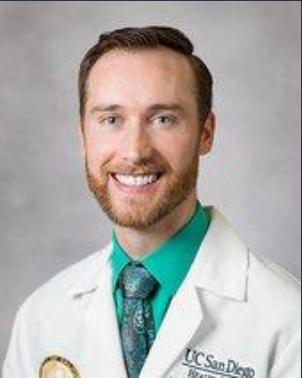


# Conclusions

- Systemic therapy options for HCC now include four FDA-approved first-line agents (atezolizumab plus bevacizumab, durvalumab plus tremelimumab, lenvatinib, and sorafenib) and six second-line agents (regorafenib, cabozantinib, nivolumab, pembrolizumab, ipilimumab plus nivolumab, and ramucirumab)
- Combination strategies have improved efficacy and are becoming standard of care
- Optimal sequence of therapy remains to be determined
- Biomarker-driven discovery with translation to matched clinical trials will be imperative in improving responses and outcomes
- Clinical trials are available at UC San Diego Moores Cancer Center for patients across stages of HCC

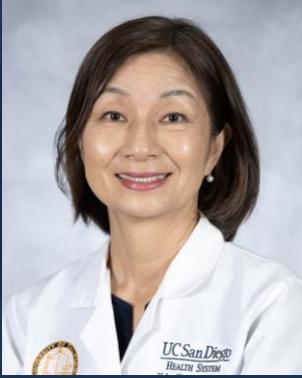
# Multi-Disciplinary Team

## Medical Oncology



Adam Burgoyne

## Hepatology



Yuko Kono

## Surgery



Jason Sicklick

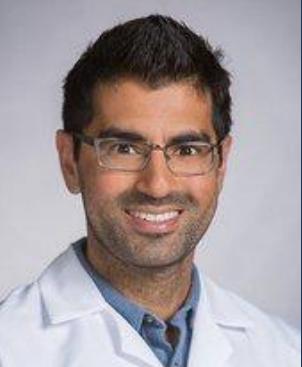


Gabriel Schnickel

## Interventional Radiology

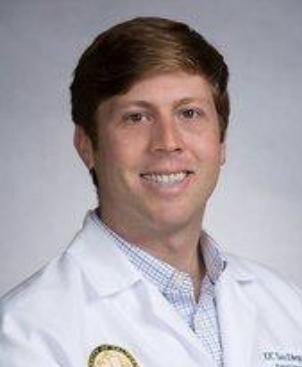


Zach Berman



Jeet Minocha

## Radiation Oncology



Daniel Simpson

## Diagnostic Radiology



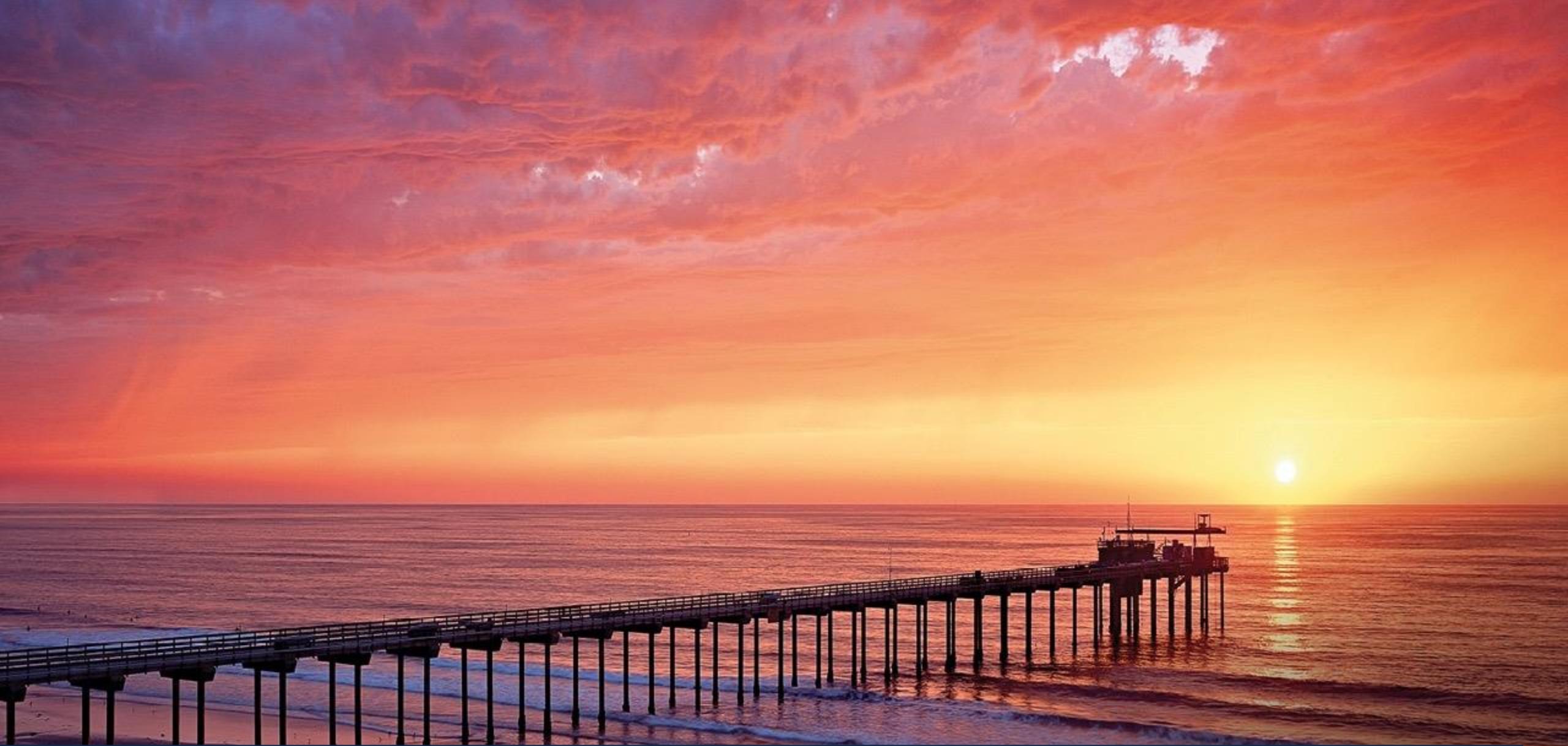
Claude Sirlin



Cynthia Santillan



Kathryn Fowler



Questions?

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