Choice of first-line therapy for Advanced HCC.

2025 Debates and Didactics

Haematology and Oncology

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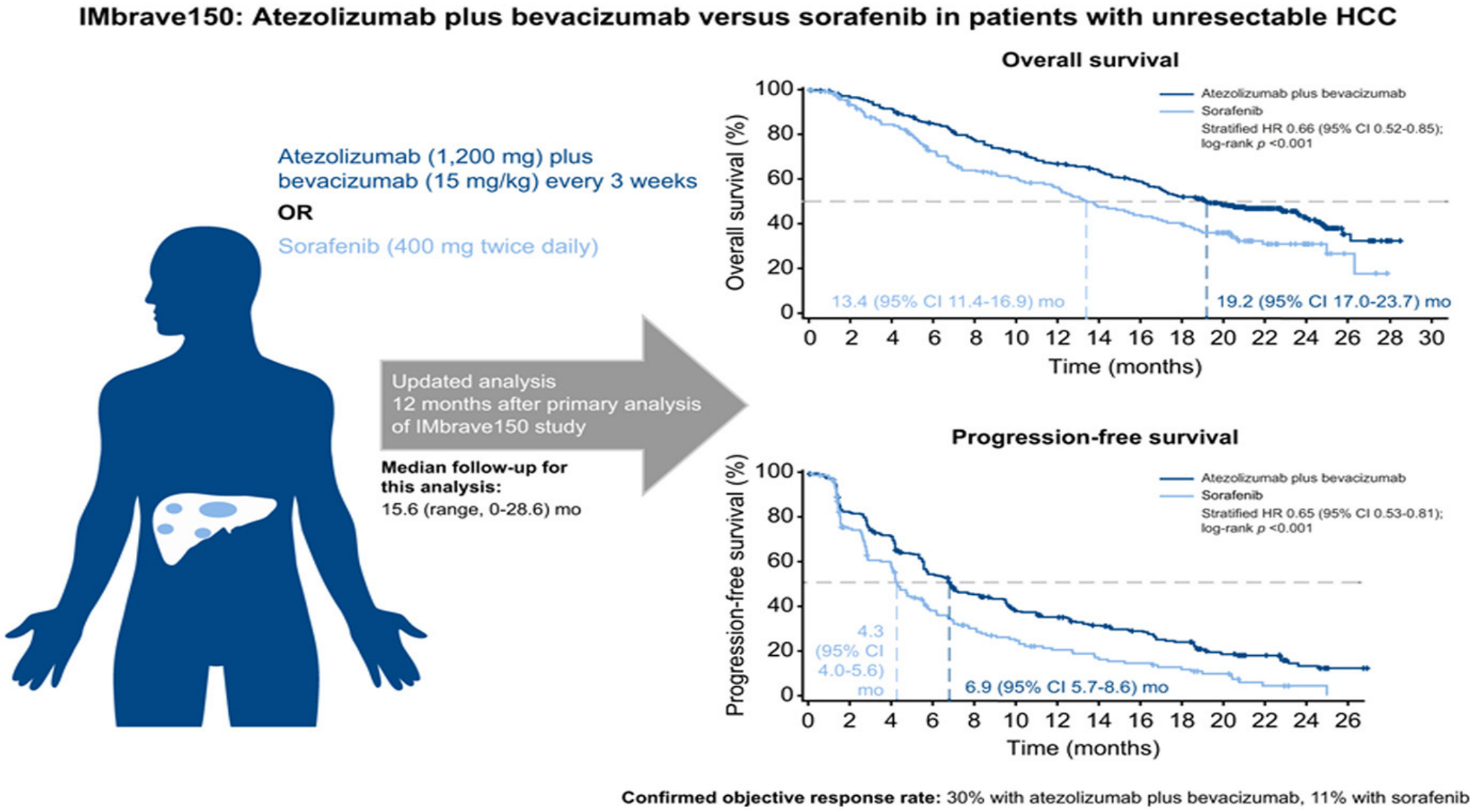
NCI Designated Comprehensive Cancer Center

Disclosures and Disclaimers

Advisory role: Boston Scientific, Jazz, JnJ. AstraZeneca, Ipsen
Research Support: AstraZeneca, Astella Pharmaceuticals, Ipsen, Merck, Eisai, Jazz, SeaGen, Roche
No off- label uses of drugs will be presented.

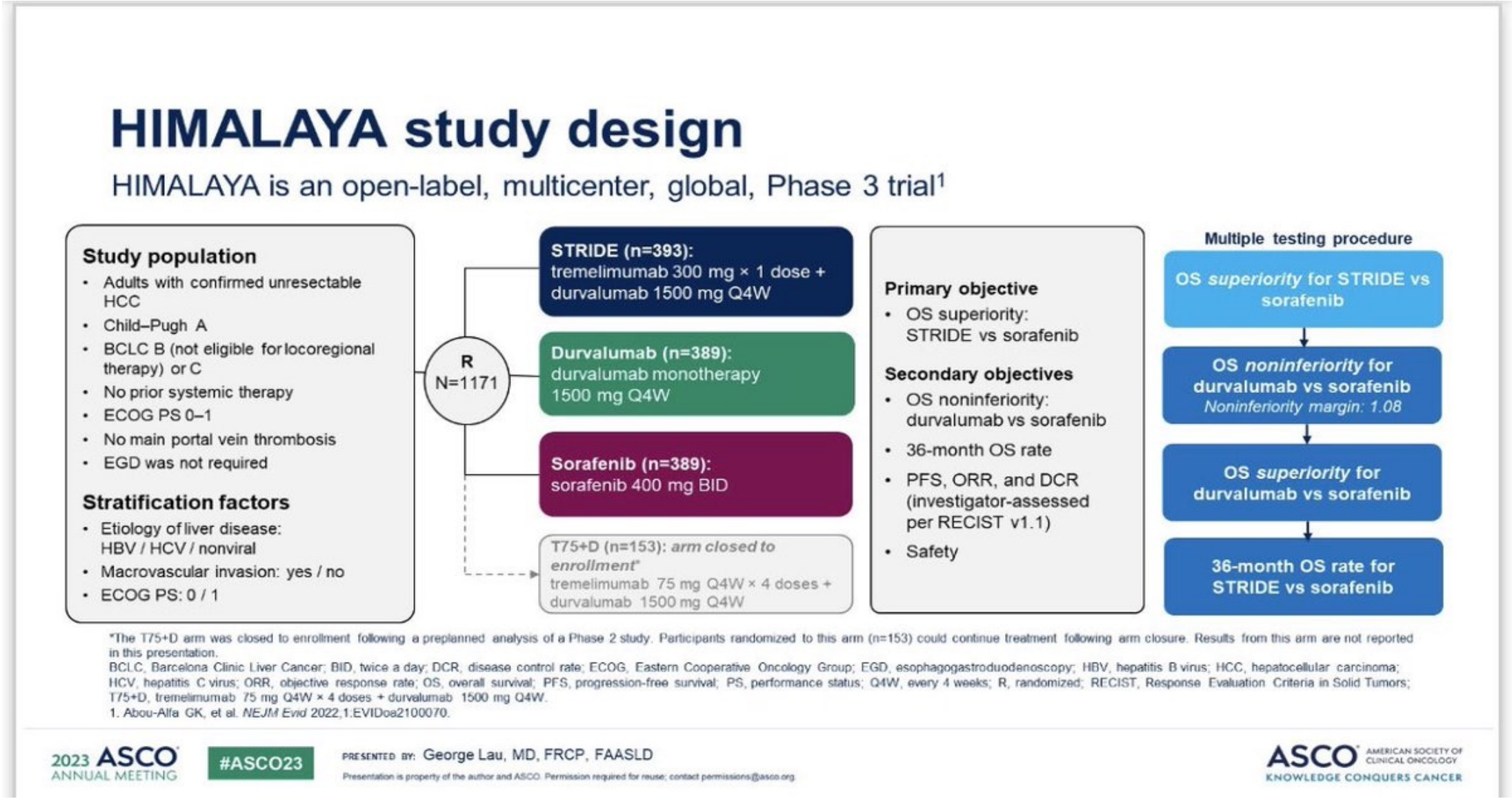
Brave New World: IMBRAVE150 changed the paradigm.



Cheng A et al. J. Hepatol. 2022, 76, 862–873

In defense of IO +IO in HCC

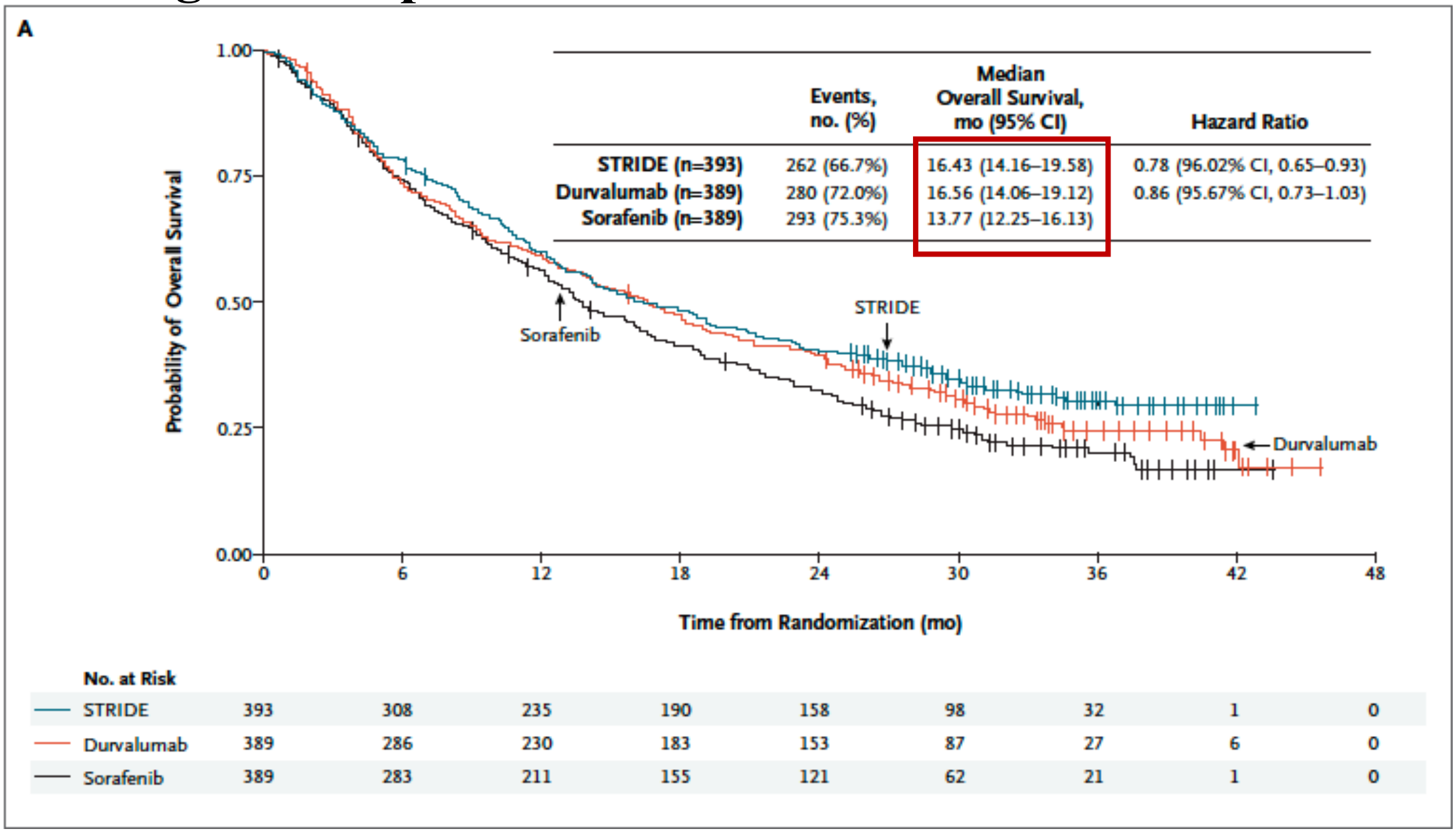
Marching forward with STRIDE



*The T75+D arm was closed to enrollment following a preplanned analysis of a Phase 2 study. Participants randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.
BCLC, Barcelona Clinic Liver Cancer; BID, twice a day; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGD, esophagogastroduodenoscopy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q4W, every 4 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; T75+D, tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W.

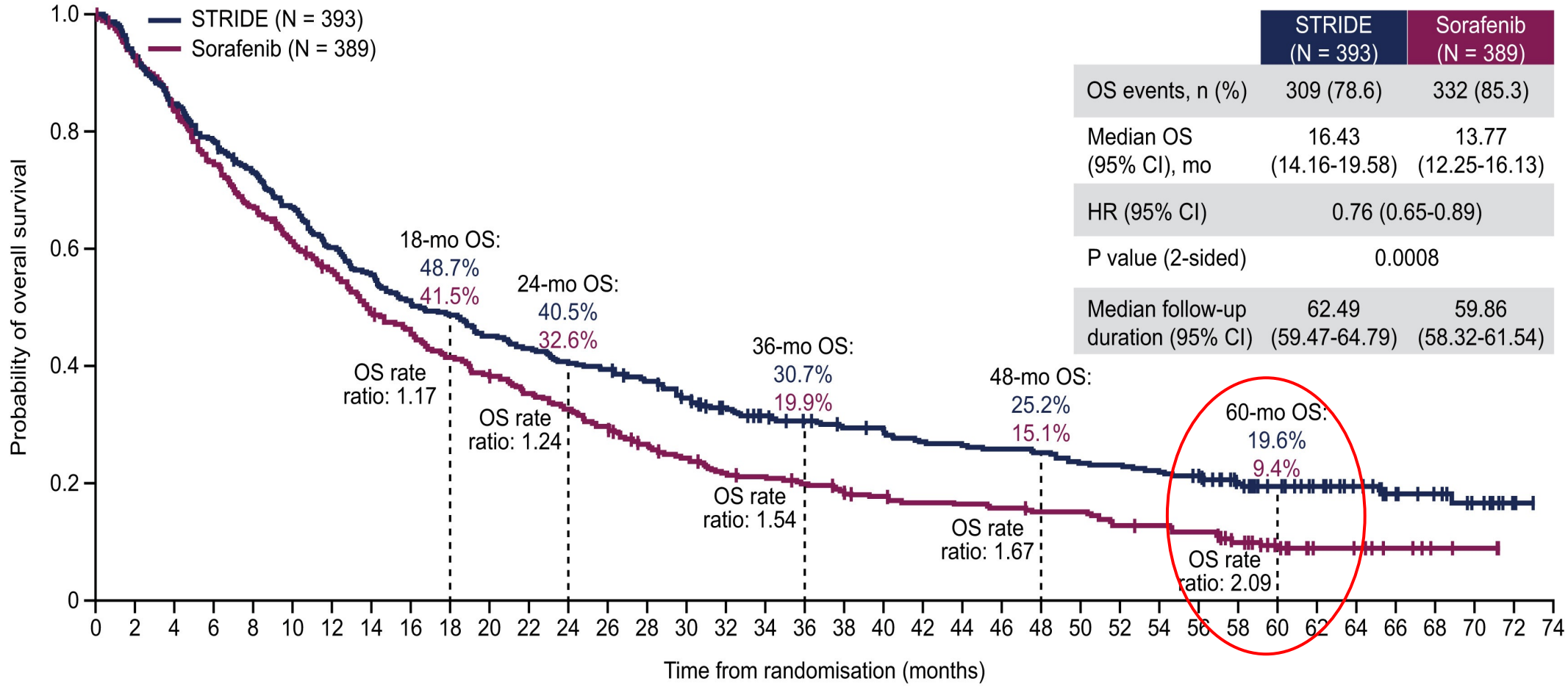
1. Abou-Alfa GK, et al. *NEJM Evid* 2022;1:EVIDoa2100070.

STRIDE regimen improves survival in HCC



Abou-Alfa GK et al NEJM Evid 2022; 1 (8)

Marching forward with STRIDE: the tale of the tail



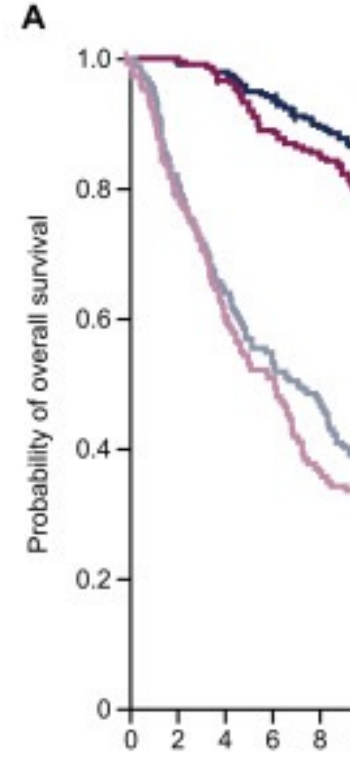
	STRIDE (N = 393)	Sorafenib (N = 389)
OS events, n (%)	309 (78.6)	332 (85.3)
Median OS (95% CI), mo	16.43 (14.16-19.58)	13.77 (12.25-16.13)
HR (95% CI)	0.76 (0.65-0.89)	
P value (2-sided)	0.0008	
Median follow-up duration (95% CI)	62.49 (59.47-64.79)	59.86 (58.32-61.54)

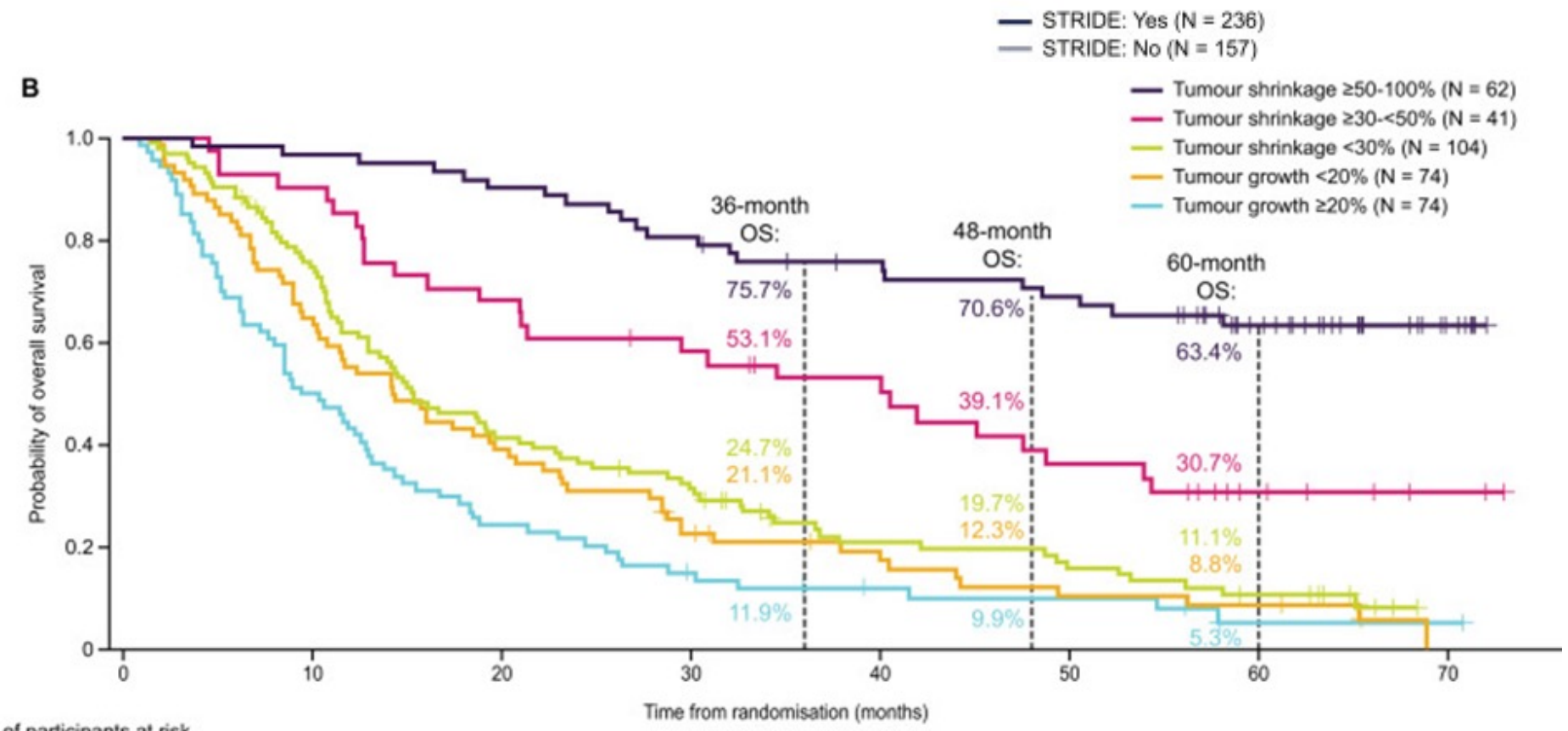
Number of participants at risk

STRIDE	393	365	333	308	285	262	235	217	197	190	176	168	158	154	144	131	118	110	104	98	95	89	87	85	83	77	76	72	68	56	46	40	32	20	15	9	2	0
Sorafenib	389	356	319	283	255	231	211	183	170	155	142	131	121	108	93	84	74	71	66	58	55	51	50	48	45	45	38	37	34	25	18	10	9	6	3	2	0	0

Abou-Alfa GK et al NEJM Evid 2022; 1 (8)

Marching forward with STRIDE: Response Matters





Number of participants at risk

STRIDE: Yes	236	236	231	222	210			
STRIDE: No	157	129	102	86	75			
Sorafenib: Yes	236	236	227	209	201			
Sorafenib: No	153	120	92	74	54			

Number of participants at risk

Tumour shrinkage ≥50-100%	62	60	56	50	43	40	26	6
Tumour shrinkage ≥30-<50%	41	37	28	23	19	13	6	2
Tumour shrinkage <30%	104	76	42	31	17	13	8	0
Tumour growth <20%	74	48	29	16	10	6	5	0
Tumour growth ≥20%	74	37	18	10	6	5	1	1

In defense of IO +IO in HCC

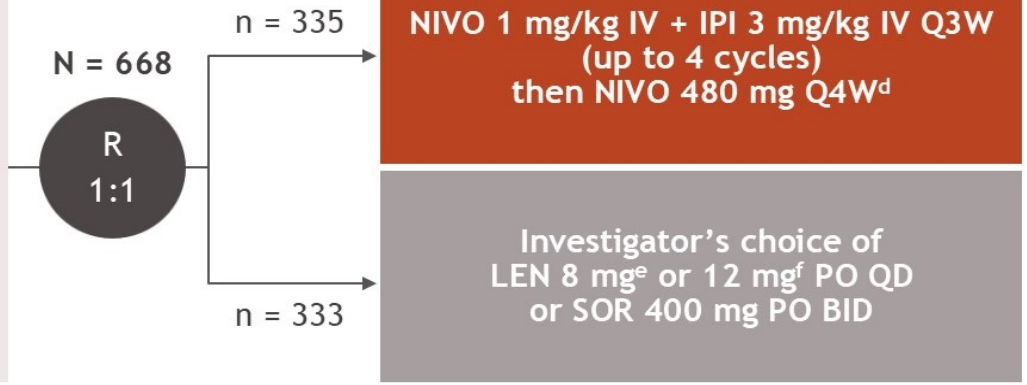
CheckMate with Ipi(3) and Nivo (1)

CheckMate 9DW study design

- CheckMate 9DW is a global, phase 3, randomized, open-label study of NIVO in combination with IPI compared with LEN or SOR as 1L treatment in patients with unresectable HCC[a]

Key eligibility criteria:
- Unresectable HCC[b]
- At least 1 measurable lesion (RECIST v1.1)
- Systemic therapy naive
- Child-Pugh score 5 or 6
- ECOG PS 0 or 1
- No main portal vein invasion (Vp4)

Stratification factors:
- Etiology (HBV vs HCV vs uninfected)[c]
- MVI/EHS (present vs absent)
- AFP (< 400 vs ≥ 400 ng/mL)



Treatment until disease progression, unacceptable toxicity, withdrawal of consent (both arms), or a maximum treatment duration of 2 years (NIVO + IPI arm only)

Among 325 patients treated with LEN/SOR:
275 (85%) received LEN, and 50 (15%) received SOR

Primary endpoint:
- OS

Secondary endpoints:
- ORR and DOR by BICR per RECIST v1.1
- Time to symptom deterioration[g]

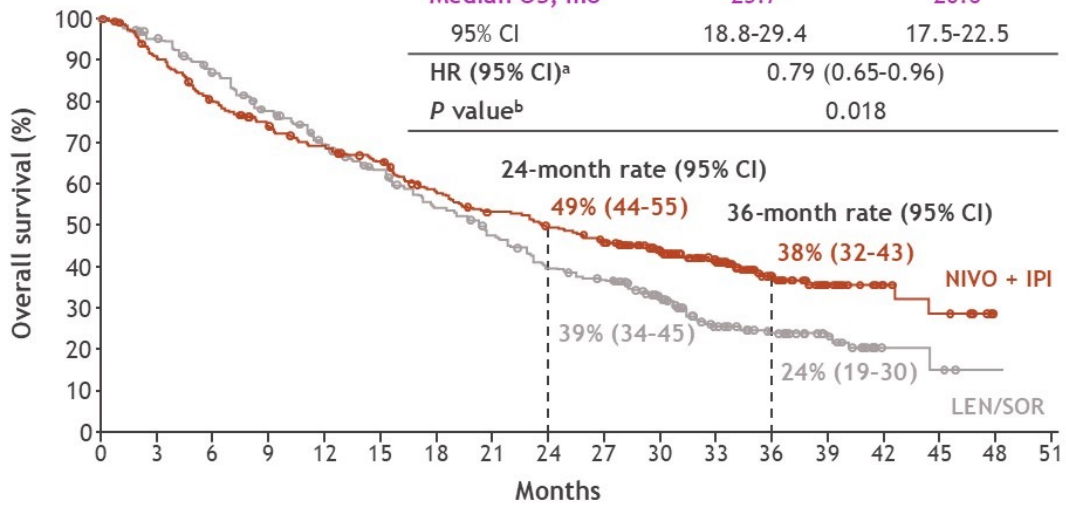
Key exploratory endpoints:
- PFS by BICR per RECIST v1.1
- Safety

- At data cutoff (January 31, 2024), median (range) follow-up[h] was 35.2 (26.8-48.9) months

[a]ClinicalTrials.gov: NCT04039607. [b]Disease not eligible for, or progressive disease after, curative surgical and/or locoregional therapies. [c]Based on central lab serology results for stratification purpose. [d]Minimum of 1 dose of NIVO + IPI is required before proceeding to NIVO monotherapy. [e]If body weight < 60 kg. [f]If body weight ≥ 60 kg. [g]HCS subscale score of the FACT-Hep. [h]Time between randomization date and cutoff date.

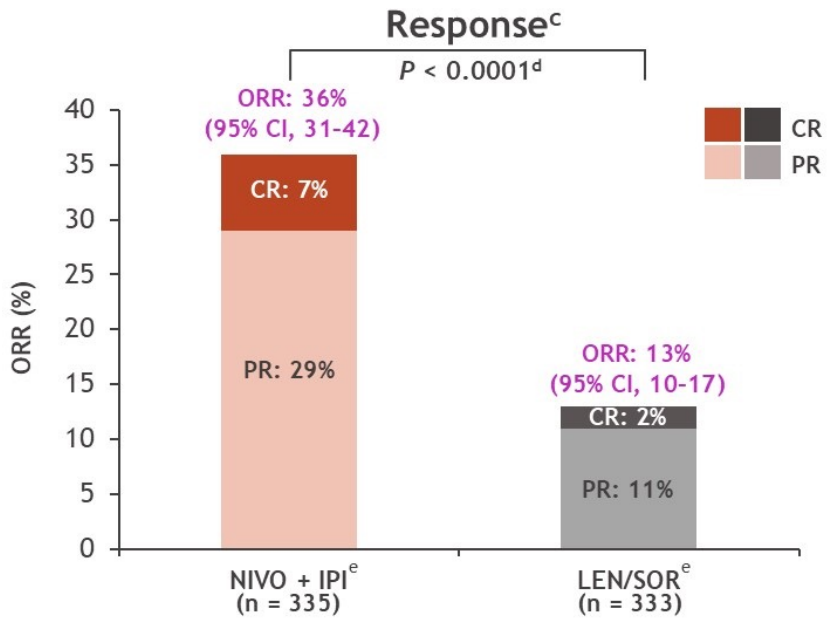
Overall survival, response, and duration of response

	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)[a]	0.79 (0.65-0.96)	
P value[b]	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



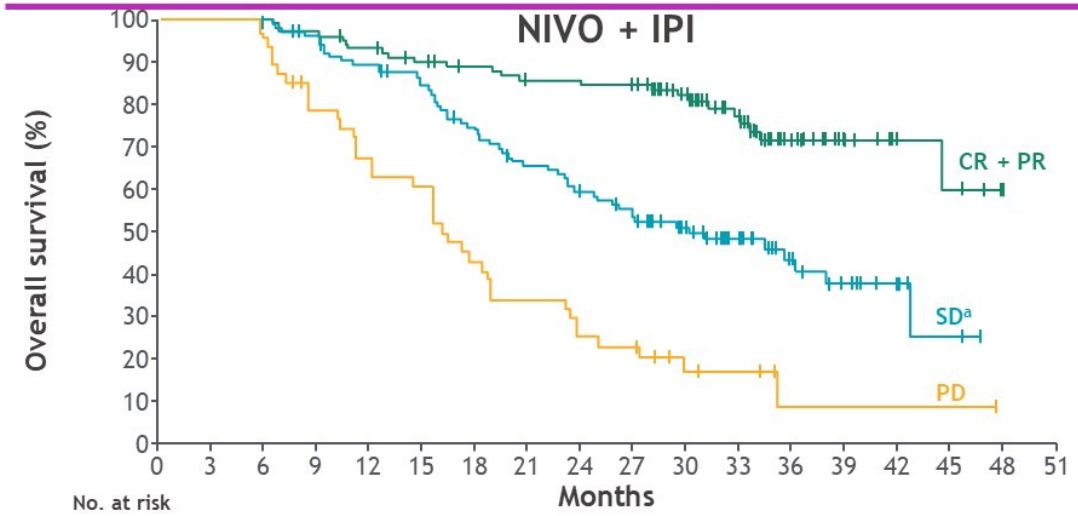
Median TTR (range),[f] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)
Median DOR (95% CI),[f] mo	30.4 (21.2-NE)	12.9 (10.2-31.2)

- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR, with higher OS rates at 24 and 36 months
- Statistically significant and clinically meaningful improvement in ORR by BICR[c] with NIVO + IPI vs LEN/SOR, with a higher CR rate and durable responses

Median (range) follow-up, 35.2 (26.8-48.9) months. [a]HR and 95% CI from stratified Cox proportional hazard model. Symbols represent censored observations. [b]Two-sided *P* value from stratified log-rank test. Boundary for statistical significance: *P* value ≤ 0.0257. [c]Assessed by BICR based on RECIST v1.1. [d]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: *P* value ≤ 0.025. [e]Percentage with BOR of SD (includes non-CR/non-PD, which refers to patients with persistence of 1 or more non-target lesion[s]): NIVO + IPI, 32%; LEN/SOR, 62%. Percentage with BOR of PD: NIVO + IPI, 20%; LEN/SOR, 14%. [f]In confirmed responders (NIVO + IPI: n = 121; LEN/SOR: n = 44).

CheckMate 9DW: Again, response matters

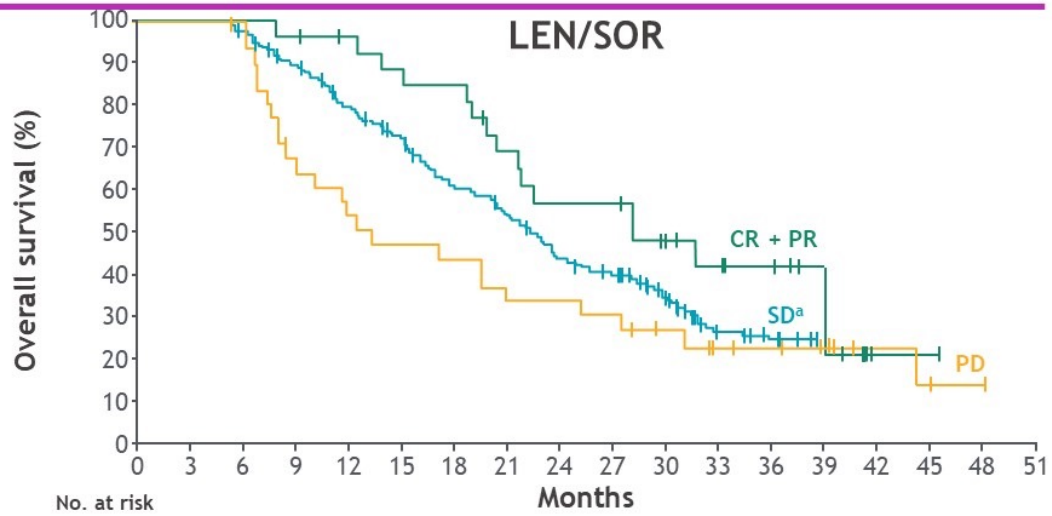
Overall survival by best overall response at 24-week landmark



No. at risk

CR/PR	101	101	101	95	91	86	82	78	77	76	59	41	25	12	6	5	0	0
SDa	105	105	103	98	92	85	72	64	57	49	38	25	15	10	4	2	0	0
PD	47	47	45	35	28	27	19	15	11	10	5	4	1	1	1	1	0	0

NIVO + IPI	CR + PR (n = 101)	SDa (n = 105)	PD (n = 47)
Events	24	56	38
Median OS, mo	NR	30.0	16.0
95% CI	44.4-NE	23.5-37.8	12.0-18.7
HR (95% CI), CR+PR vs PD		0.14 (0.08-0.24)	
HR (95% CI), SDa vs PD		0.40 (0.26-0.60)	



No. at risk

CR/PR	28	28	28	27	25	23	22	17	14	14	10	7	5	2	1	1	0	0
SDa	212	212	205	186	162	146	120	107	84	76	55	31	24	15	3	2	1	0
PD	31	31	31	20	17	14	13	11	10	9	6	3	2	1	0	0	0	0

LEN/SOR	CR + PR (n = 28)	SDa (n = 212)	PD (n = 31)
Events	15	145	23
Median OS, mo	28.3	22.5	13.5
95% CI	20.6-NE	20.5-24.8	8.7-25.3
HR (95% CI), CR+PR vs PD		0.45 (0.23-0.86)	
HR (95% CI), SDa vs PD		0.69 (0.45-1.08)	

- In both treatment arms, objective response by BICR[b] was associated with improved OS outcomes
  - NIVO + IPI: The HR for CR or PR versus PD was 0.14 and for SD versus PD was 0.40
  - LEN/SOR: The HR for CR or PR versus PD was 0.45 and for SD versus PD was 0.69

Median (range) follow-up, 35.2 (26.8-48.9) months. Symbols represent censored observations. [a]Includes non-CR/non-PD. Non-CR/non-PD refers to patients with persistence of 1 or more non-target lesion(s). [b]Based on RECIST v1.1.

Trial & Regimen	ORR (%)	DOR(months)	PFS (mo) [HR, 95% CI]	OS (mo) [HR, 95% CI]
REFLECT Lenvatinib vs Sorafenib	24.1% vs 9.2%	18.1	7.4 vs 3.7 mo (0.66 [0.57–0.77])	13.6 vs 12.3 mo (0.92 [0.79–1.06]
IMbrave150 Atezo+ Bev vs Sorafenib	30% vs 11%	18.1 vs 14.9	6.9 vs 4.3 mo (0.65 [0.53–0.81])	19.2 vs 13.4 mo (0.66 [0.52–0.85])
HIMALAYA Trem + Durv vs Sorafenib	20.1% vs 5.1%	22.3 mo vs 18.4 mo	3.78 vs 4.07 mo (0.90 [0.77–1.05])	16.4 vs 13.8 mo (0.78 [0.65–0.93])
CheckMate-9DW Nivo + Ipil vs Sor/Len	36% (7% CR)	30.4 mo	9.1 vs 9.2 mo (0.87)	23.7 vs 20.6 mo (0.79)

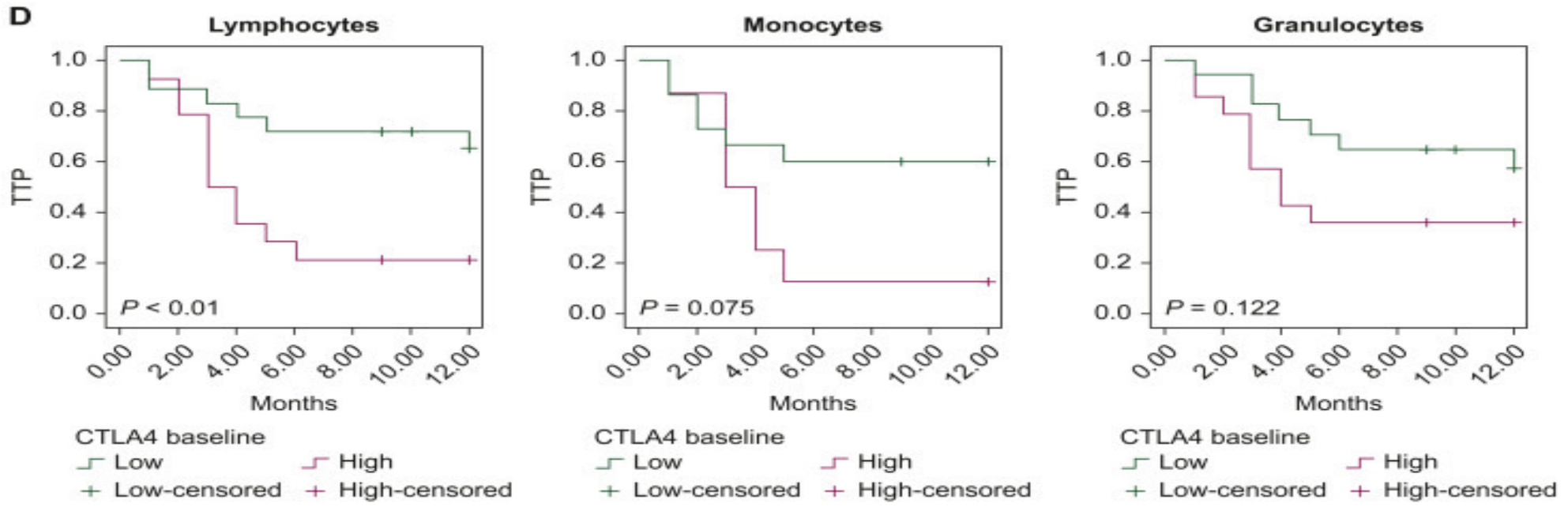
How do we make sense of these?

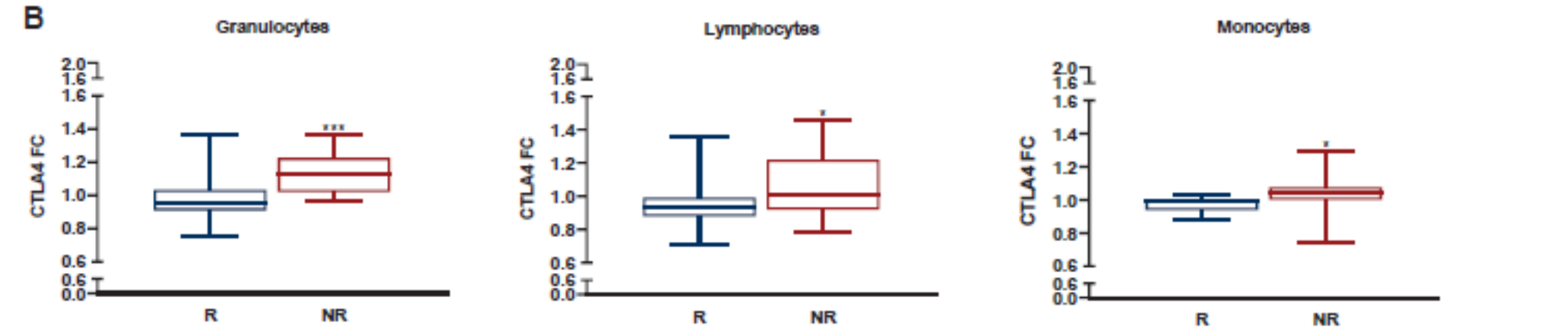
ORIGINAL ARTICLE

Early CTLA4 increase in CD45+ blood cells: an emerging biomarker of atezolizumab–bevacizumab resistance and worse survival in advanced hepatocarcinoma

L. Gramantieri[1*], A. Montagner[2], A. Arleo[2], F. Suzzi[2], C. Bassi[3], F. Tovoli[1,2], M. Bruccoleri[4], E. Alimenti[4], F. Fornari[5], M. Iavarone[4], M. Negrini[3], F. Piscaglia[1,2] & C. Giovannini[1,2*]

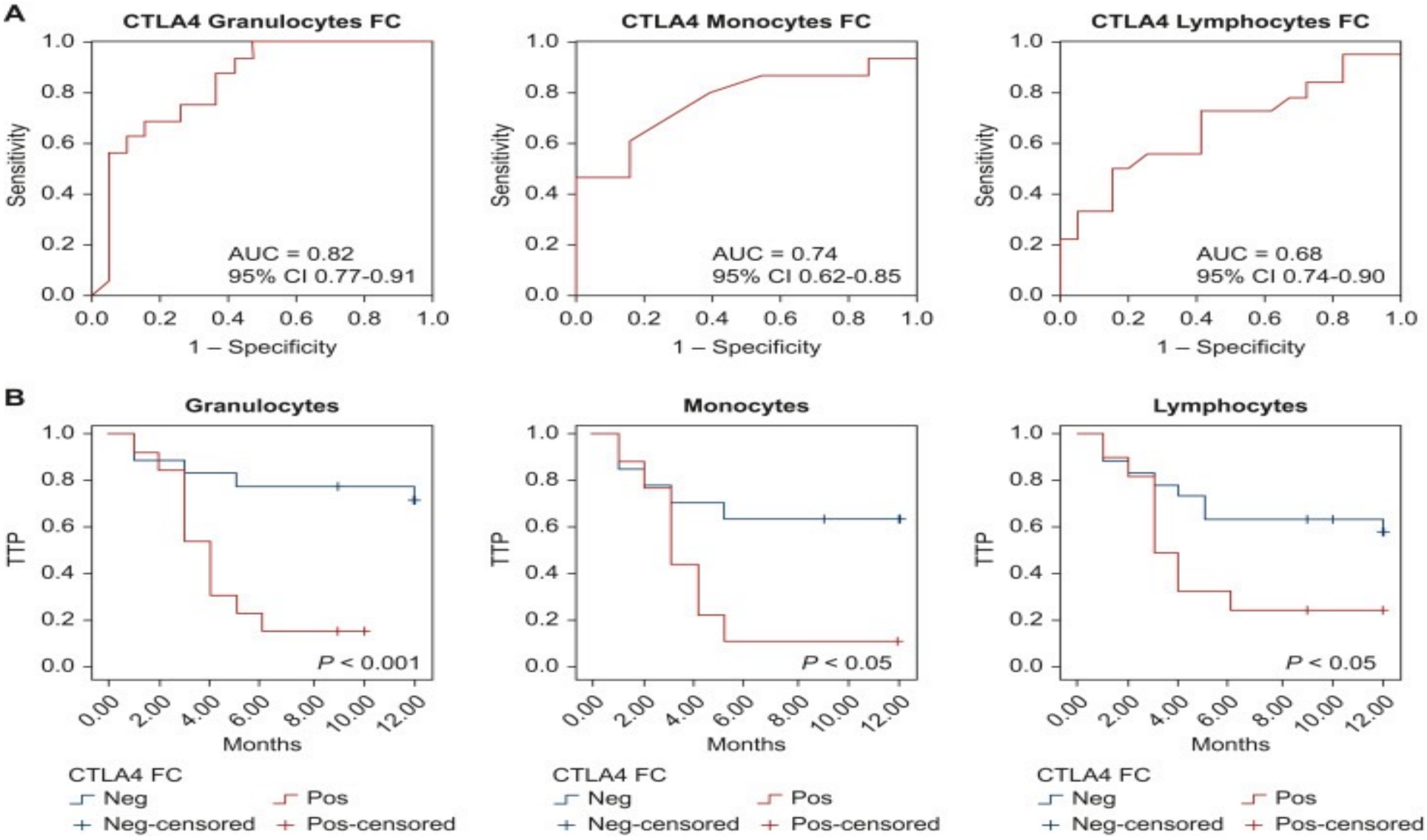
CTLA4 status and response to atezo + bev in HCC





Gramantieri, L. et al. ESMO Open, Volume 10, Issue 3, 104289

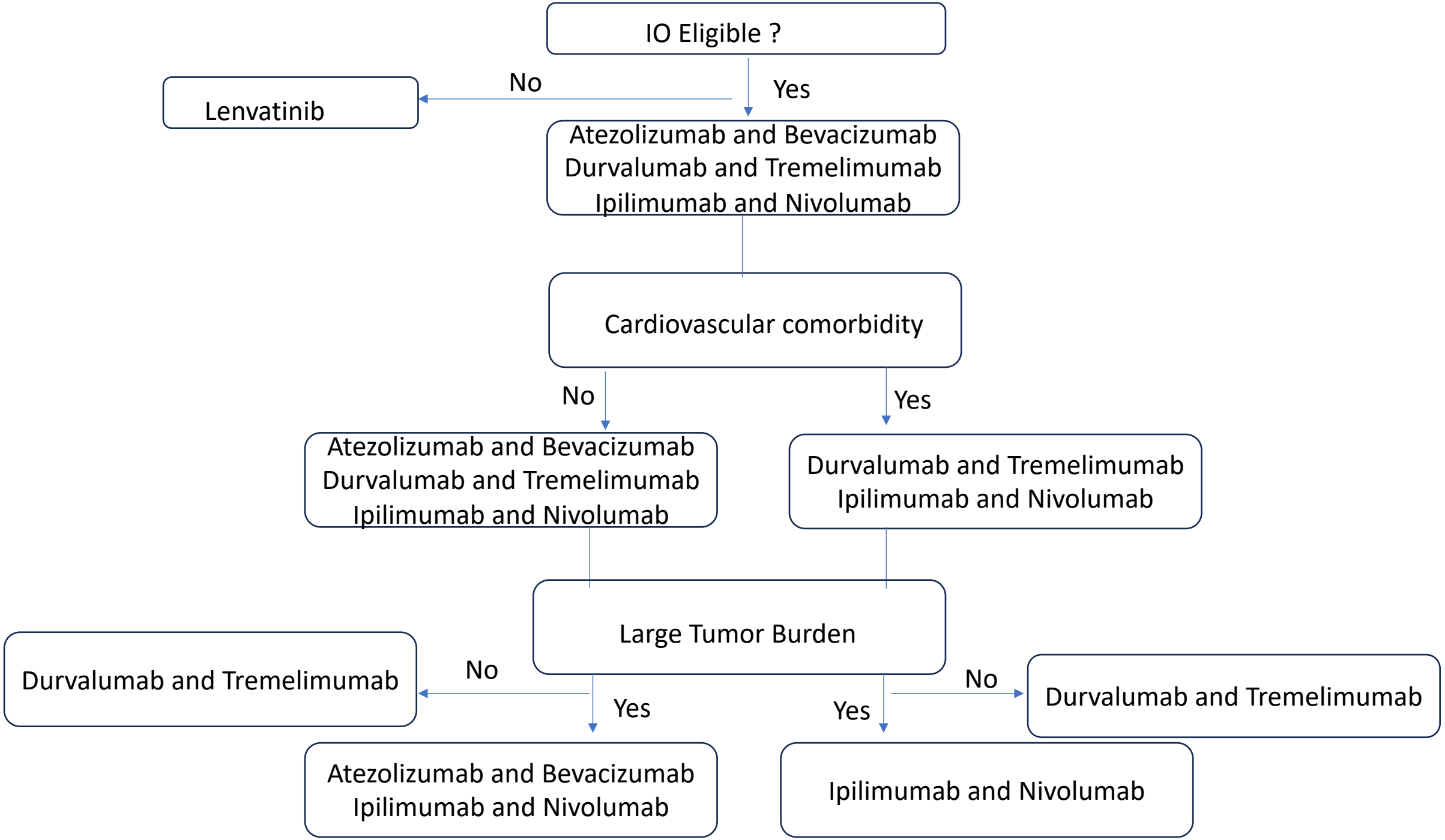
Increase in CTLA4 predicts resistance to atezo+ bev in HCC



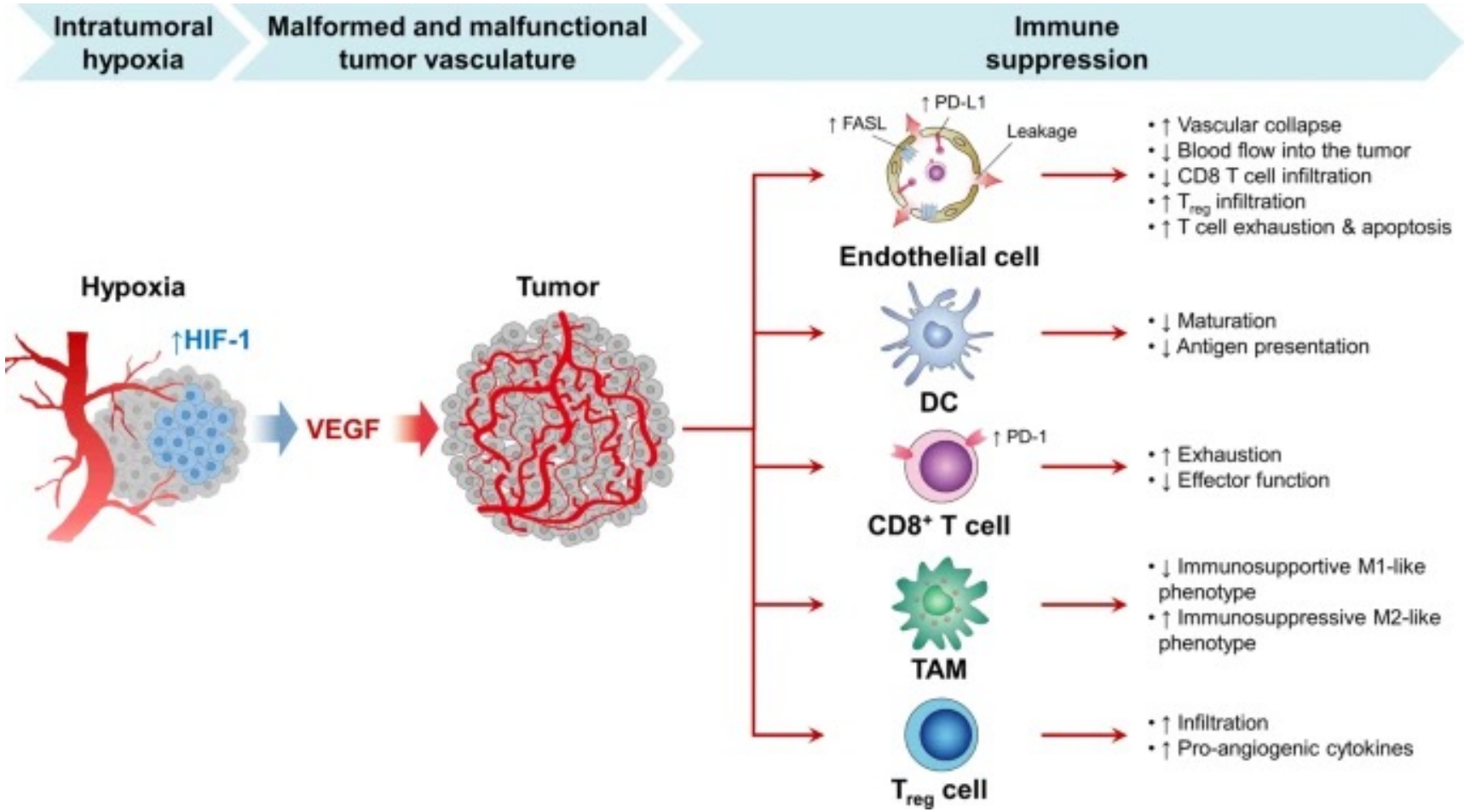
Gramantieri, L. et al. ESMO Open, Volume 10, Issue 3, 104289

Summary

- Abrogating VEGF activity may be important for early response
- Elevated CTLA4+ve cells may suggest resistance to atezo+bev
- Abrogating CTLA4 activity may improve survival further


IO Eligible ?
No
Yes
Lenvatinib
Atezolizumab and Bevacizumab
Durvalumab and Tremelimumab
Ipilimumab and Nivolumab
Cardiovascular comorbidity
No
Yes
Atezolizumab and Bevacizumab
Durvalumab and Tremelimumab
Ipilimumab and Nivolumab
Durvalumab and Tremelimumab
Ipilimumab and Nivolumab
Large Tumor Burden
Durvalumab and Tremelimumab
No
Yes
No
Yes
Durvalumab and Tremelimumab
Atezolizumab and Bevacizumab
Ipilimumab and Nivolumab
Ipilimumab and Nivolumab

The Treaty of ~~Versailles~~ the Golden Isles.



VEGF+ IO vs IO +IO- It's all IO!

Lee WS, et al. Exp Mol Med **52**, 1475–1485 (2020)