20 minute
UPDATE ON Pancreatic, Cholangio and Hepatocellular CARCINOMA

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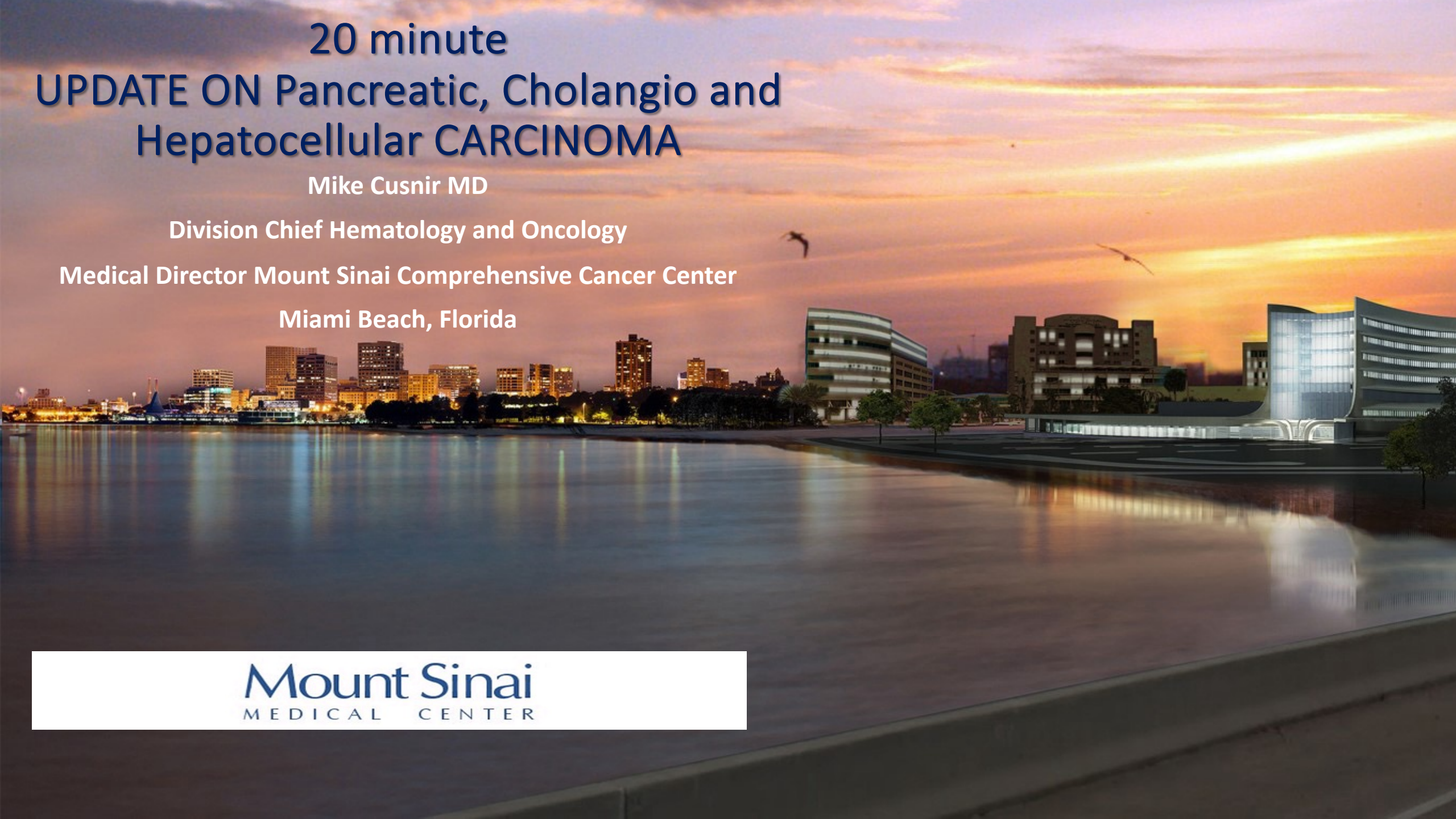
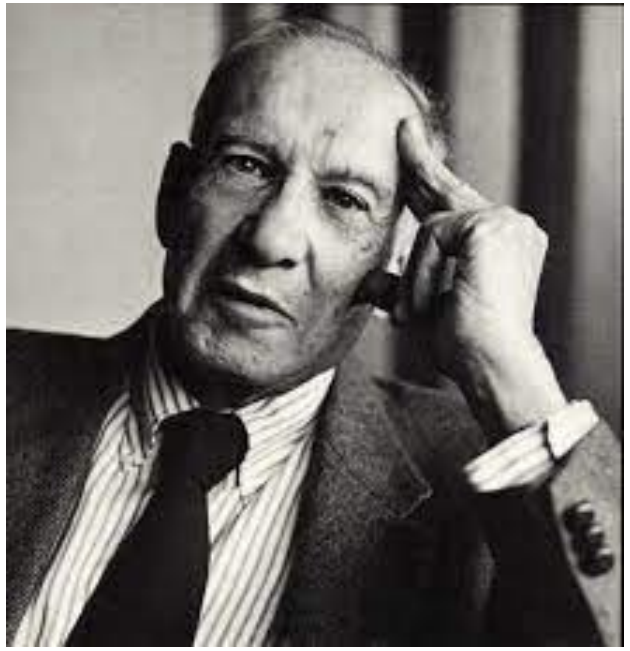


Mount Sinai
MEDICAL CENTER

Pancreatic

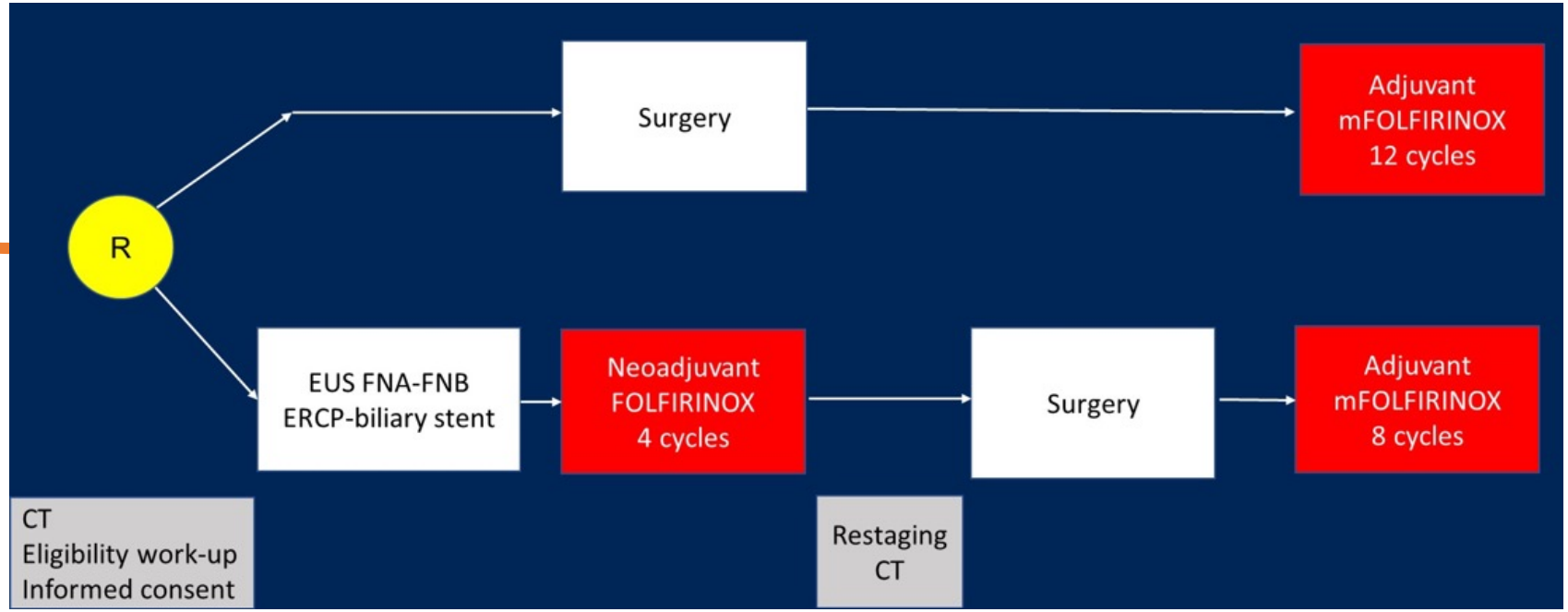
- *Until we can manage time, we can manage nothing else."*

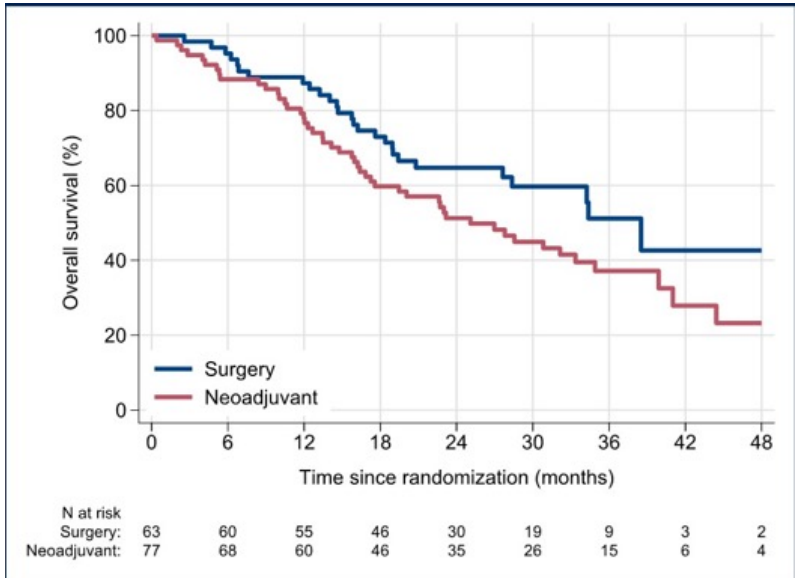


— Peter F. Drucker

5 year survival is now close to 13% up from 5%

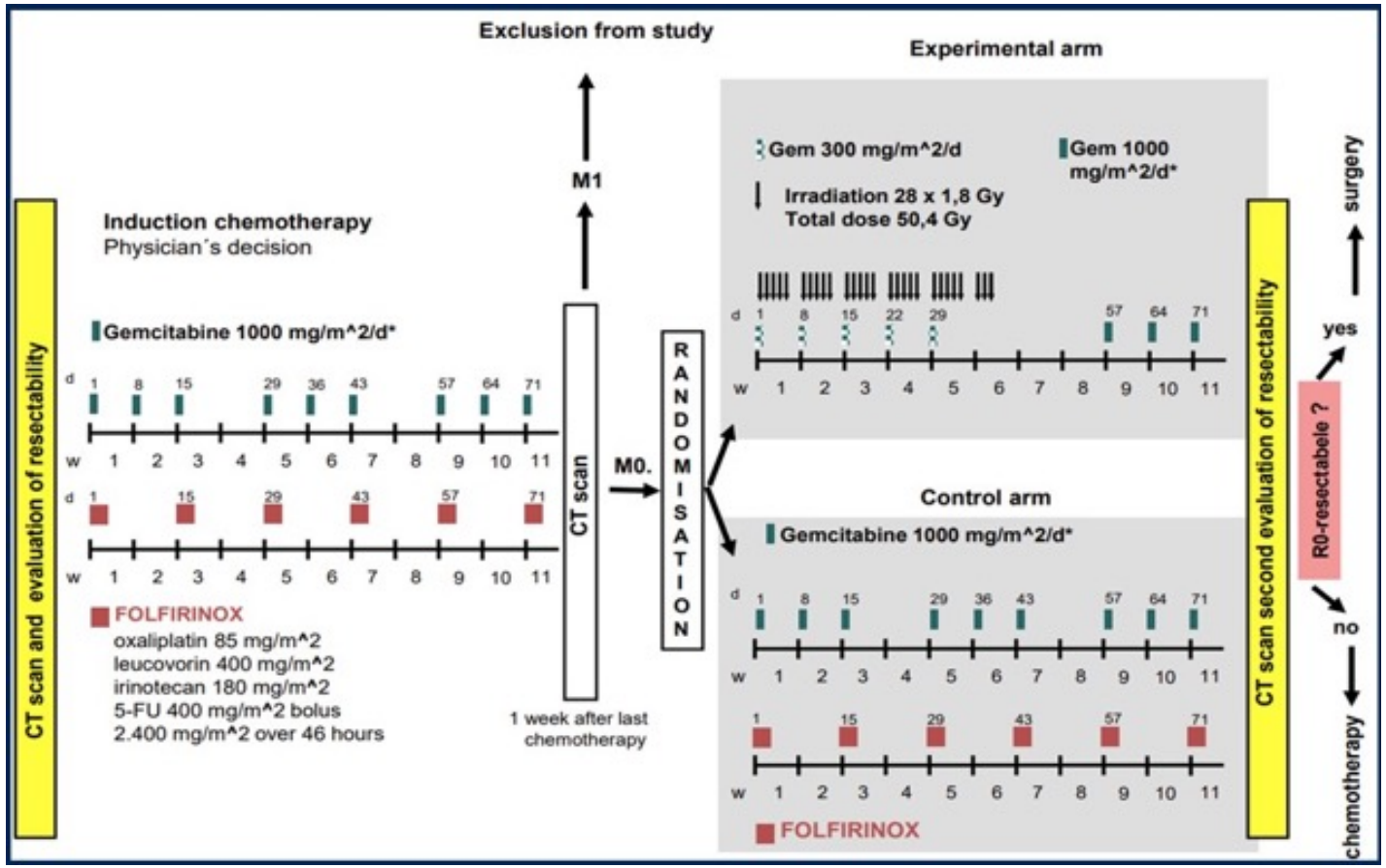
NORPAC



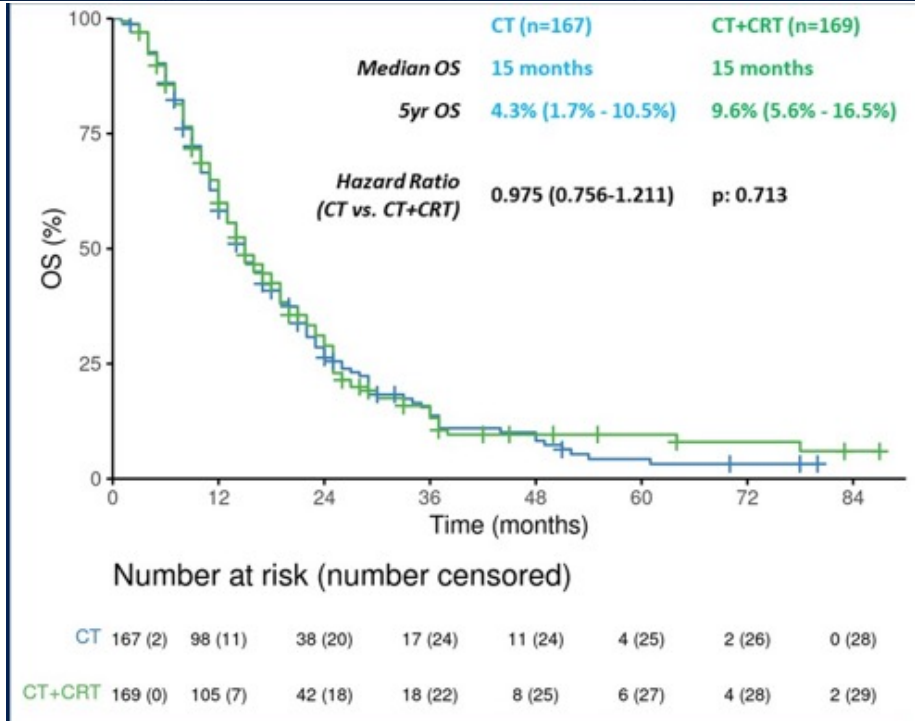


	Neoadjuvant group (n=63)	Upfront surgery (n=56)	p-value
Intention-to-treat			
R0	56%	39%	0.076
N0	29%	14%	0.060
Per-protocol	(n=46)	(n=49)	
R0	59%	33%	0.011
N0	37%	10%	0.002

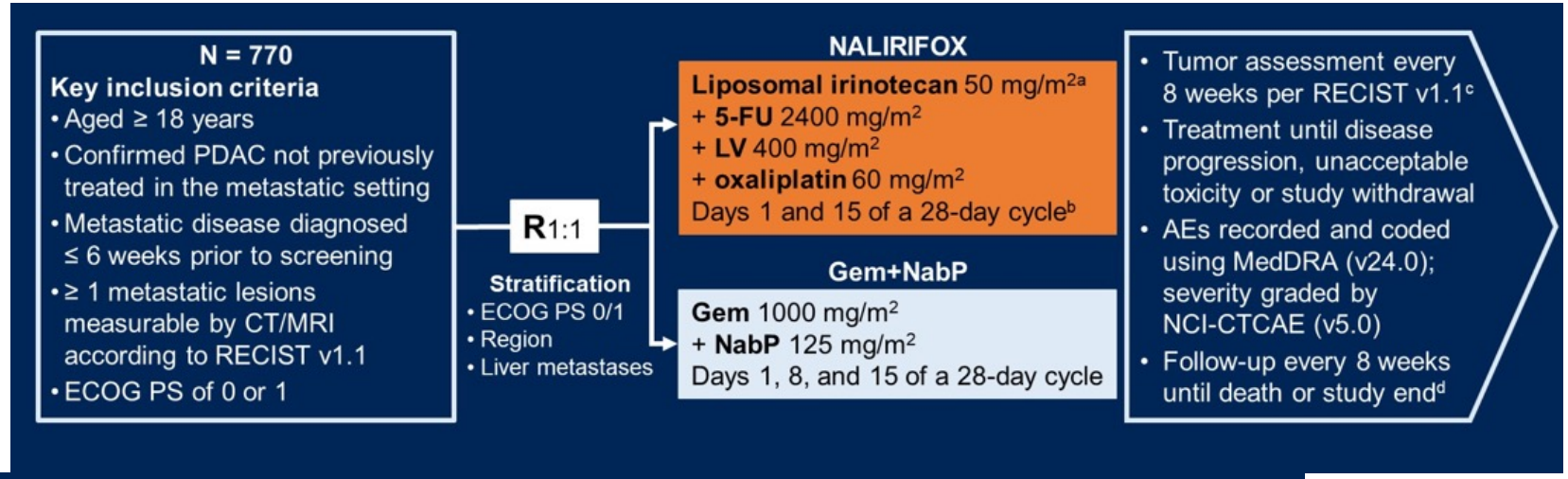
CONKO 007



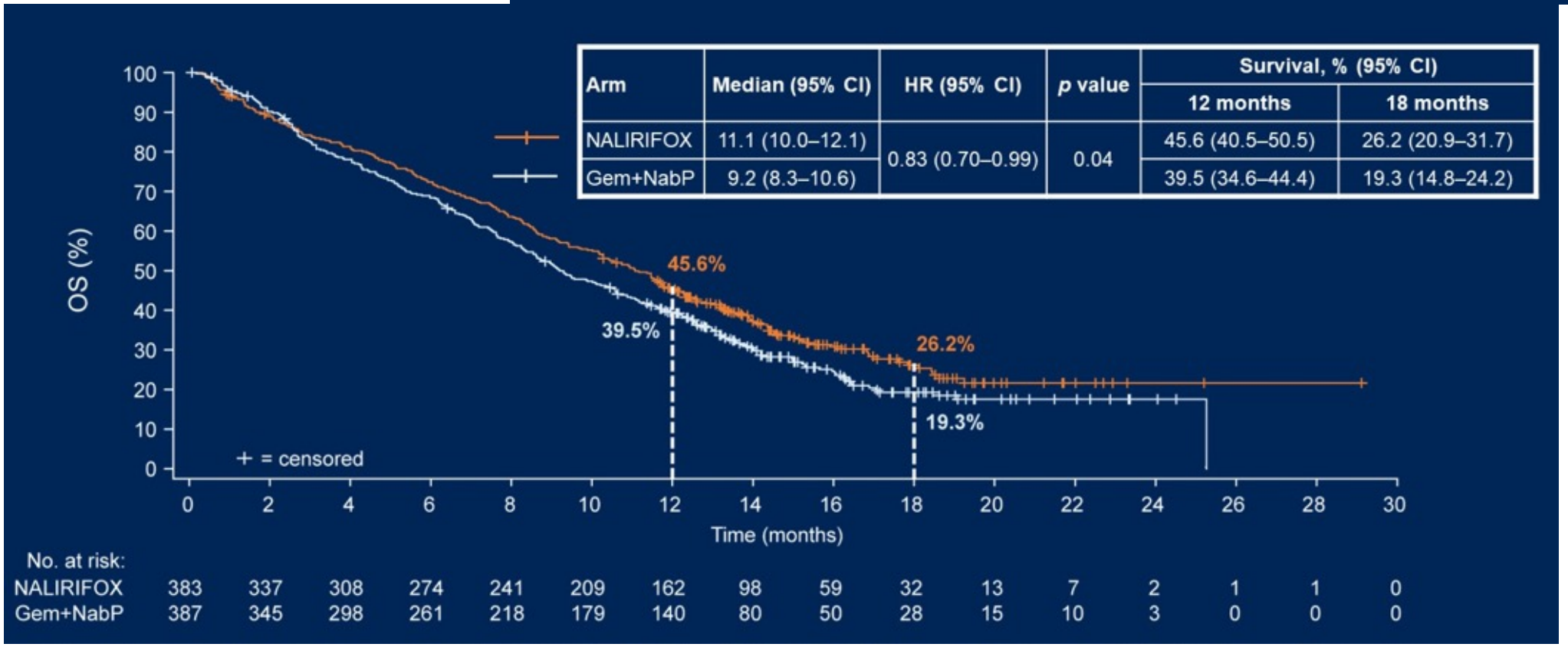
	CT (n=167)	CT+CRT (n=169)	p-value
Resection performed, No. (%)	60 (36)	62 (37)	0.91
pCR, No. (%)	1 (.6)	11 (7)	0.0055
R0 resection, No. (%)	30 (18)	43 (25)	0.1126
R1 resection, No. (%)	16 (10)	5 (3)	0.0133
R2, Rx resection, No. (%)	14 (8)	14 (8)	1.0000
CRM negative, No. (%)	15 (9)	29 (17)	0.0348
CRM positive, No. (%)	27 (16)	11 (7)	0.0057
CRM missing data, No. (%)	4 (2)	8 (5)	
Deceased within 30 days after resection, No. (%)	5 (3)	4 (2)	0.7494



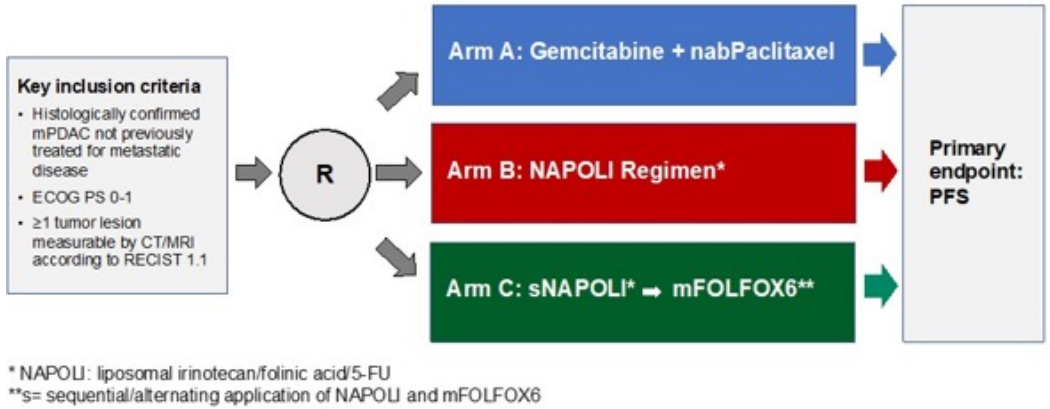
NAPOLI 3

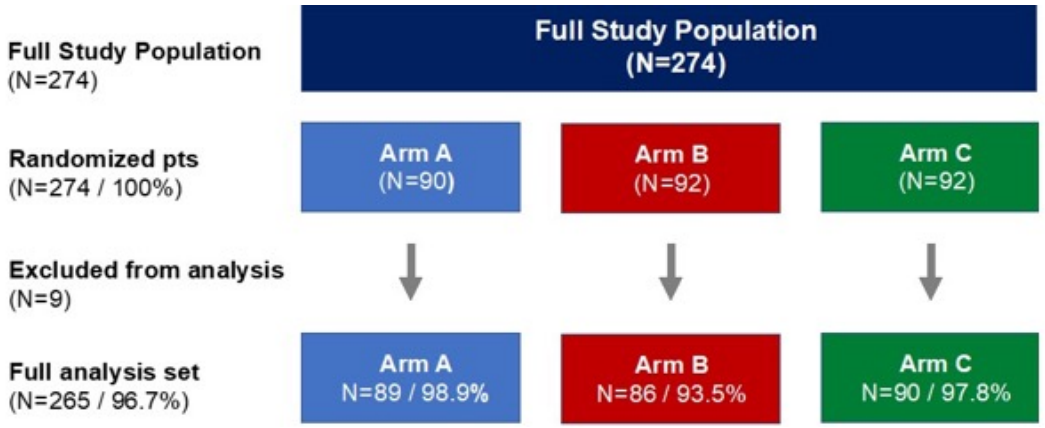


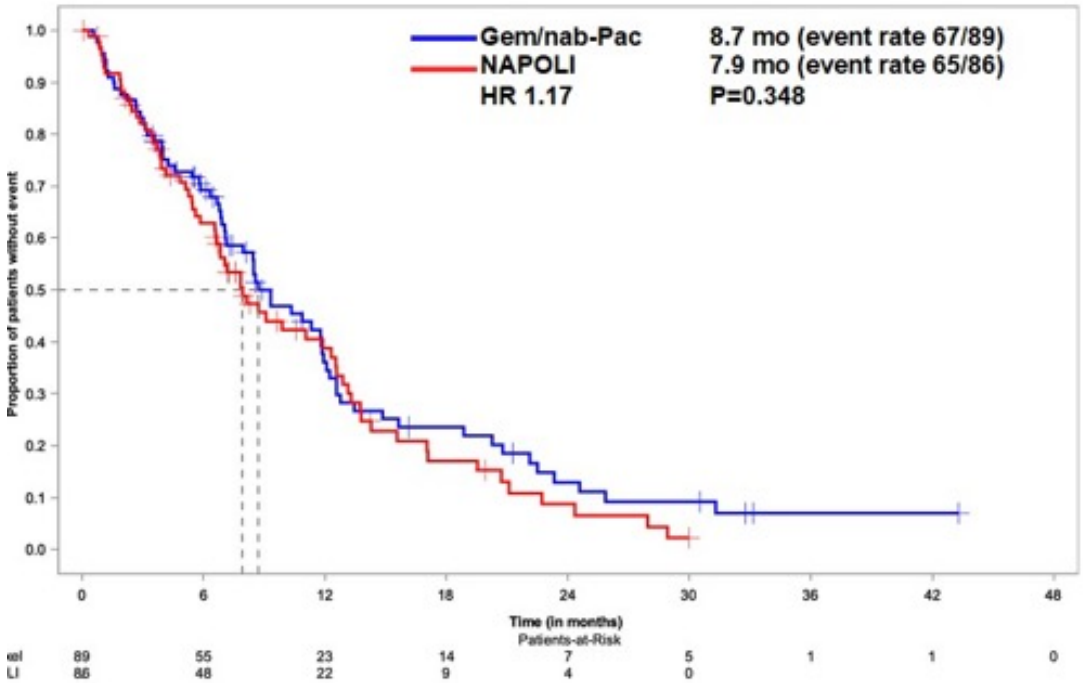
Arm	Median (95% CI)	HR (95% CI)	*p* value	Survival, % (95% CI)	
				12 months	18 months
NALIRIFOX	11.1 (10.0–12.1)	0.83 (0.70–0.99)	0.04	45.6 (40.5–50.5)	26.2 (20.9–31.7)
Gem+NabP	9.2 (8.3–10.6)			39.5 (34.6–44.4)	19.3 (14.8–24.2)

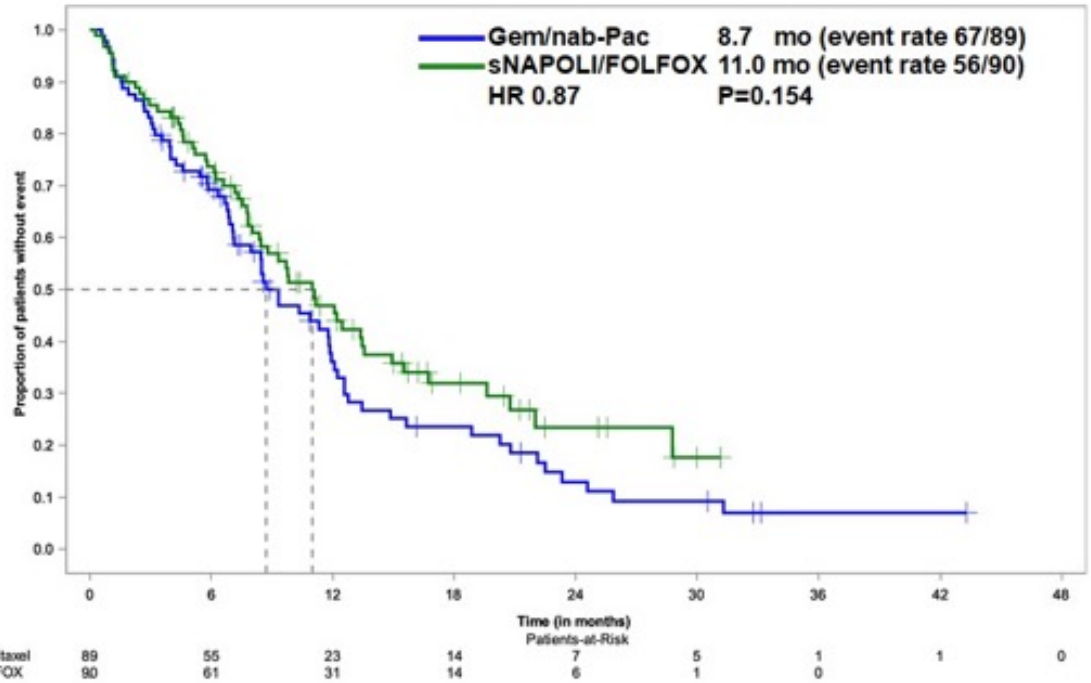


FOOTPATH

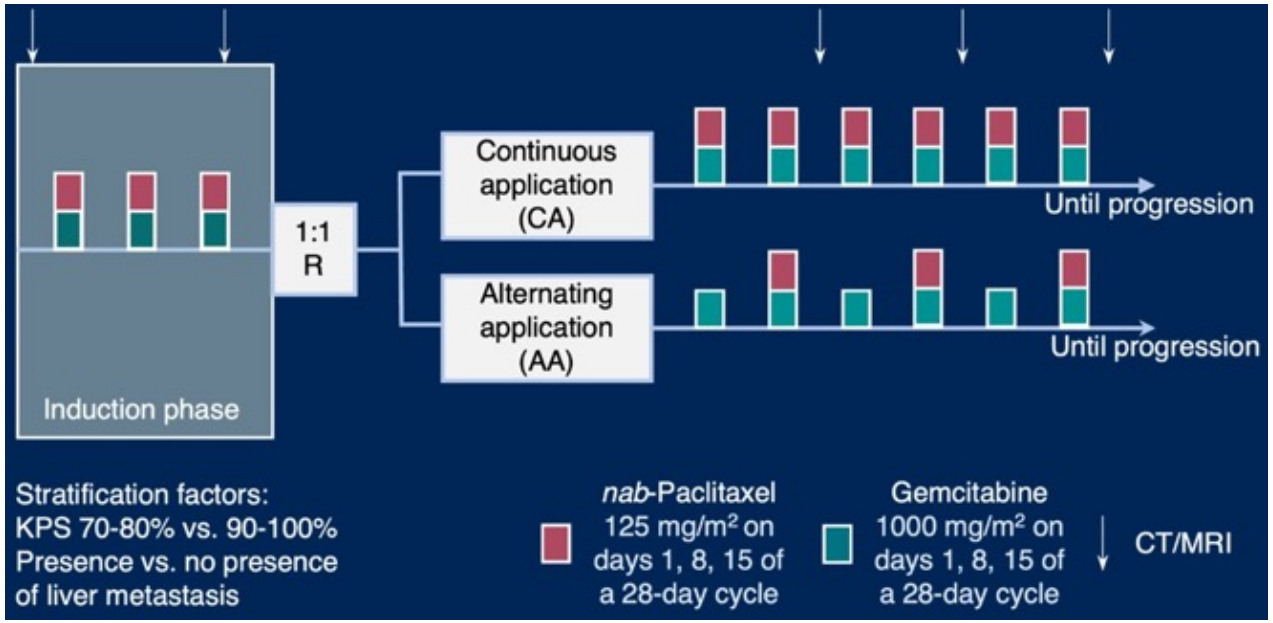

Key inclusion criteria
• Histologically confirmed mPDAC not previously treated for metastatic disease
• ECOG PS 0-1
• ≥1 tumor lesion measurable by CT/MRI according to RECIST 1.1
R
Arm A: Gemcitabine + nabPaclitaxel
Arm B: NAPOLI Regimen*
Arm C: sNAPOLI* ➡ mFOLFOX6**
Primary endpoint: PFS
* NAPOLI: liposomal irinotecan/folinic acid/5-FU
**s= sequential/alternating application of NAPOLI and mFOLFOX6

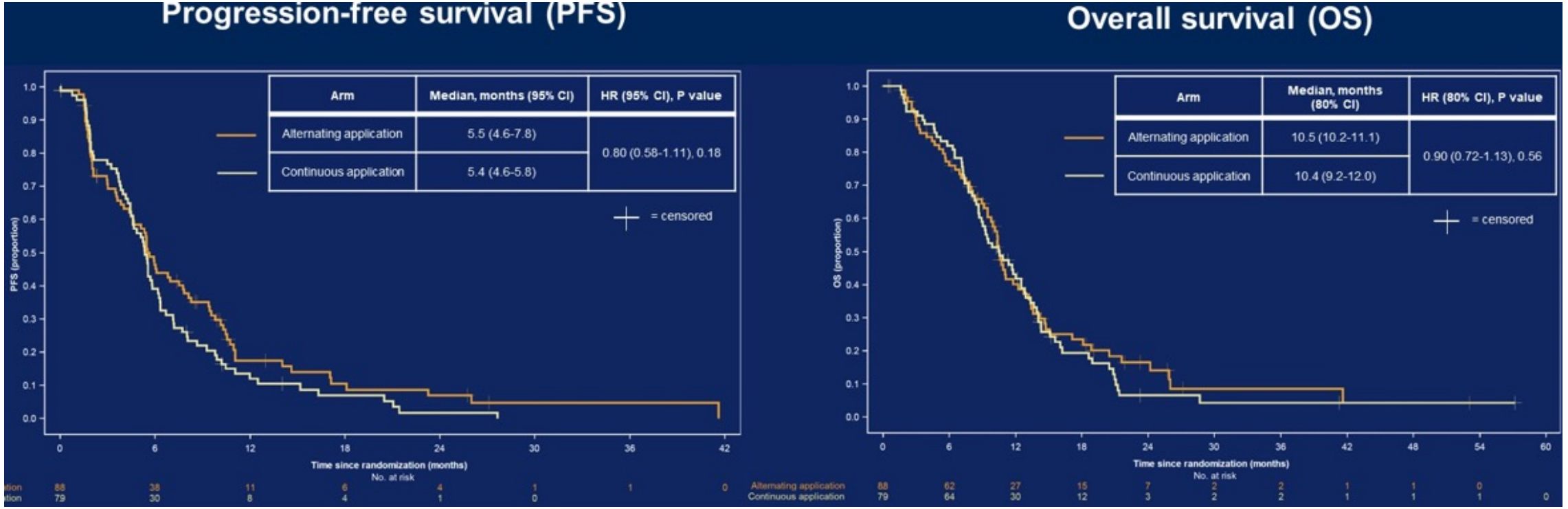

Full Study Population (N=274)
Full Study Population (N=274)
Randomized pts (N=274 / 100%)
Arm A (N=90)
Arm B (N=92)
Arm C (N=92)
Excluded from analysis (N=9)
Full analysis set (N=265 / 96.7%)
Arm A N=89 / 98.9%
Arm B N=86 / 93.5%
Arm C N=90 / 97.8%


Gem/nab-Pac 8.7 mo (event rate 67/89)
NAPOLI 7.9 mo (event rate 65/86)
HR 1.17 P=0.348
Proportion of patients without event
Time (in months)
Patients-at-Risk


Gem/nab-Pac 8.7 mo (event rate 67/89)
sNAPOLI/FOLFOX 11.0 mo (event rate 56/90)
HR 0.87 P=0.154
Proportion of patients without event
Time (in months)
Patients-at-Risk
Gemcitabine plus nab-Paclitaxel 89 55 23 14 7 5 1 1 0
seq.-NAPOLI-FOLFOX 90 61 31 14 6 1 0

ALPACA


Induction phase
1:1
R
Continuous application (CA)
Alternating application (AA)
Until progression
Until progression
Stratification factors:
KPS 70-80% vs. 90-100%
Presence vs. no presence of liver metastasis
nab-Paclitaxel 125 mg/m² on days 1, 8, 15 of a 28-day cycle
Gemcitabine 1000 mg/m² on days 1, 8, 15 of a 28-day cycle
CT/MRI


Progression-free survival (PFS)
Arm
Median, months (95% CI)
HR (95% CI), P value
Alternating application
5.5 (4.6-7.8)
0.80 (0.58-1.11), 0.18
Continuous application
5.4 (4.6-5.8)
= censored
PFS (proportion)
Time since randomization (months)
No. at risk
Overall survival (OS)
Arm
Median, months (80% CI)
HR (80% CI), P value
Alternating application
10.5 (10.2-11.1)
0.90 (0.72-1.13), 0.56
Continuous application
10.4 (9.2-12.0)
= censored
OS (proportion)
Time since randomization (months)
No. at risk
Alternating application 88 62 27 15 7 2 2 1 1 0
Continuous application 79 64 30 12 3 2 2 1 1 0

NETTER 2

Screening phase

- Patients ≥15 years; N=226
- Advanced, SSTR+, well-differentiated, G2 or G3 GEP-NET (Ki67 ≥10% and ≤55%)
- Diagnosis within last 6 months prior to enrollment
- No prior PRRT or systemic therapy

Randomized treatment phase

R 2:1

- ^{177}Lu-DOTATATE 4 × 7.4 GBq + octreotide LAR (30 mg)* Q8W
- Octreotide control: High-dose octreotide LAR (60 mg) Q4W

PD

Optional treatment extension phase

- Retreatment with ^{177}Lu-DOTATATE (7.4 GBq/200mCi) Q8W × 2–4 cycles†
- Cross-over treatment ^{177}Lu-DOTATATE (7.4 GBq/200mCi) Q8W × 4 cycles + octreotide LAR (30 mg)*

Follow-up phase

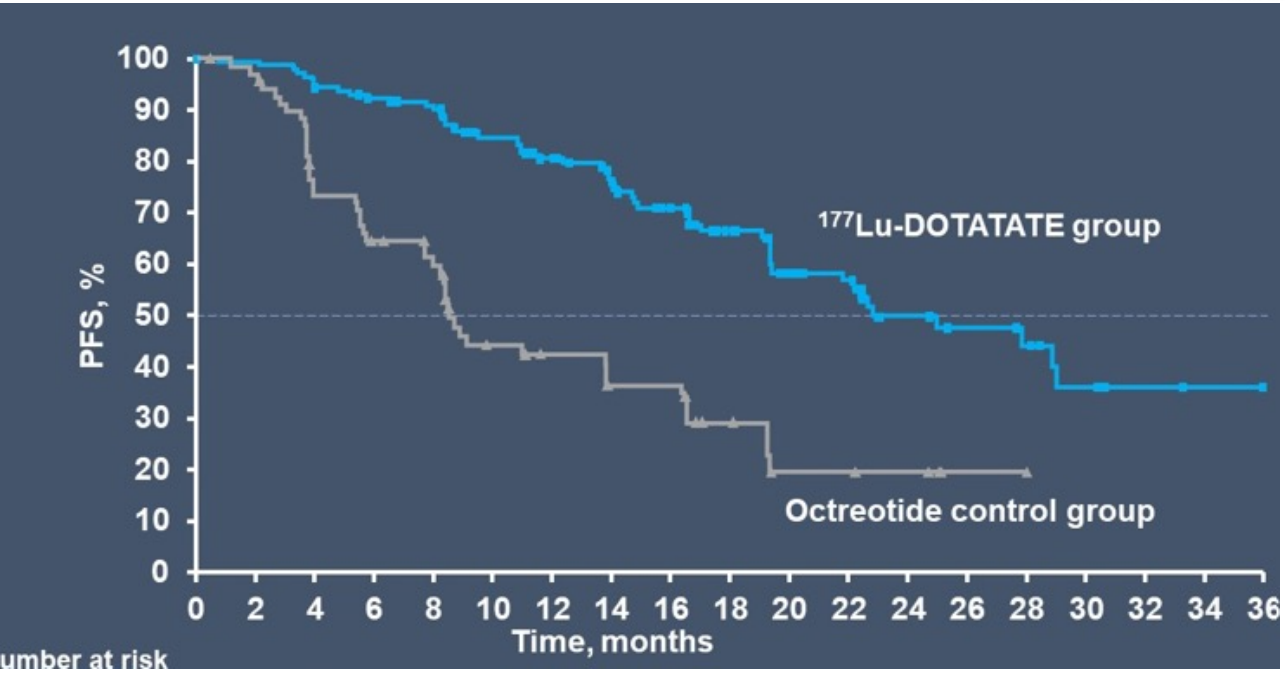
Follow-up visits every 6 months for 3 years

Stratification factors:

- Grade (G2 vs G3)
- Tumor origin (pancreas vs other origin)

Study endpoints:

- Primary: PFS
- Key secondary: ORR, QOL



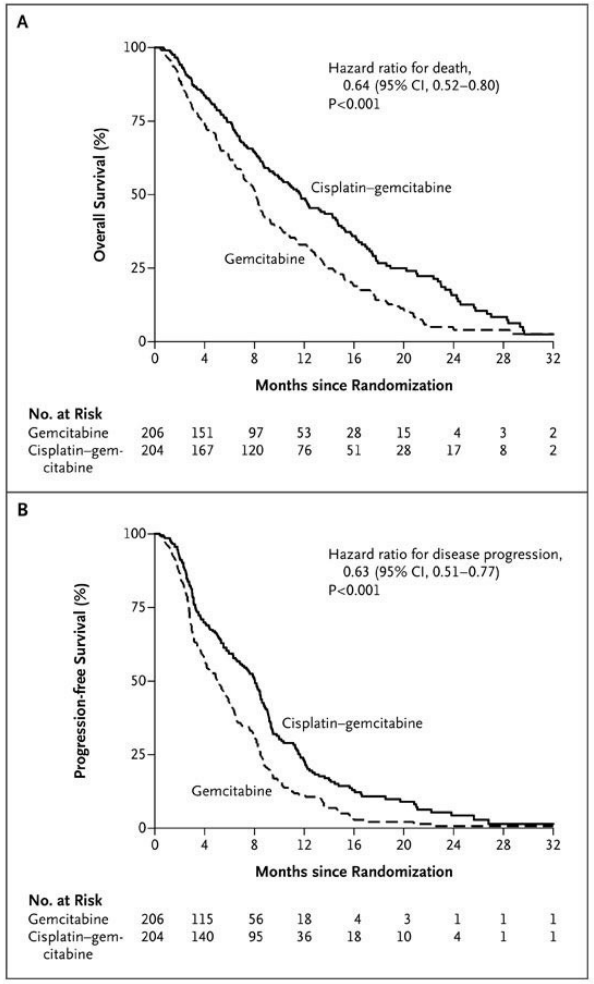
	^{177}Lu-DOTATATE group n=151	Octreotide control group n=75
PFS median, months (95% CI)	22.8 (19.4, NE)	8.5 (7.7, 13.8)
Stratified HR (95% CI)	0.276 (0.182, 0.418)	
p-value	<0.0001	

Cholangio

- Time will not slow down when something unpleasant lies ahead.”

Harry Potter

Outcomes in Patients with Biliary Tract Cancer Who Received Gemcitabine Alone versus Cisplatin plus Gemcitabine.



OS :

- 11.7 months cisplatin–gemcitabine
- 8.1 months gemcitabine group

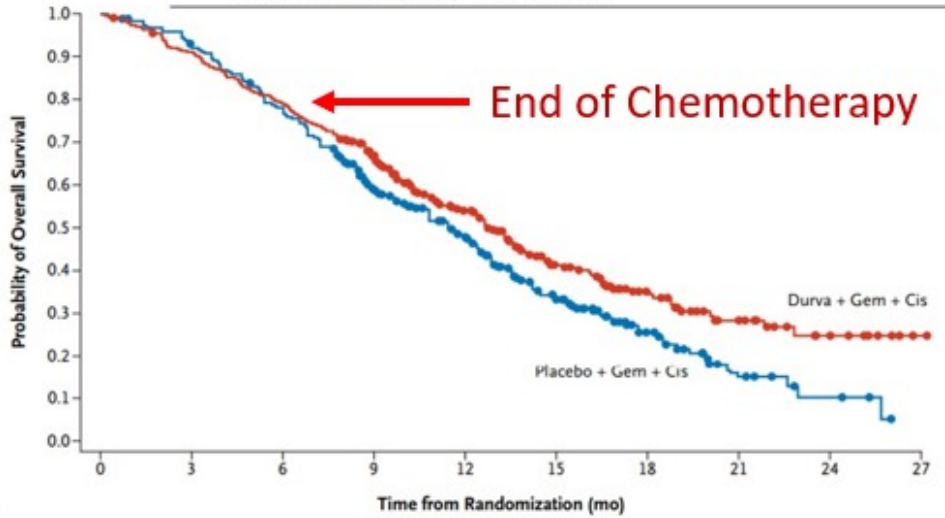
(hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001)

Valle J et al. N Engl J Med 2010;362:1273-1281.

The NEW ENGLAND JOURNAL of MEDICINE

TOPAZ-1: Durva/Gem/Cis vs. Gem/Cis

	Median Overall Survival, mo (95% CI)	Hazard Ratio (95% CI)	Stratified Log-rank P Value
Durva + Gem + Cis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + Gem + Cis (n=344)	11.5 (10.1–12.5)		

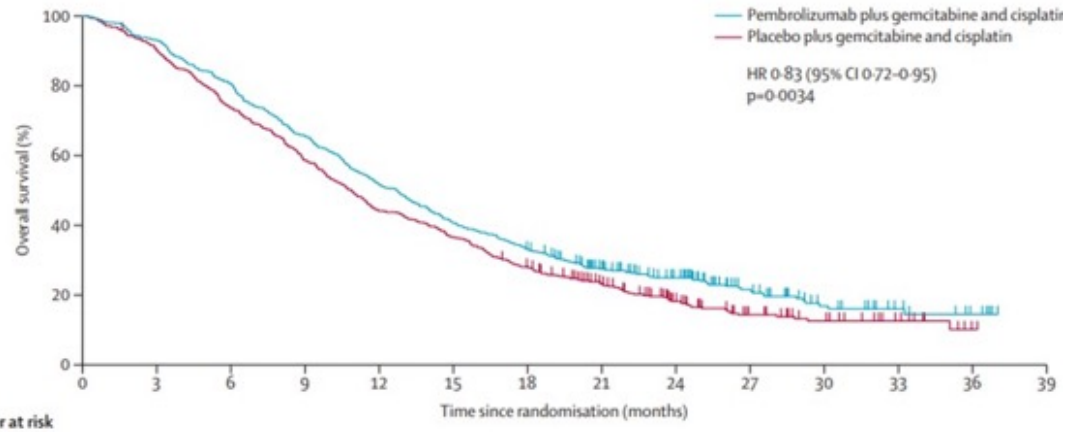


No. at Risk

Durva + Gem + Cis	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1
Placebo + Gem + Cis	344	337	329	317	299	283	261	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0

Oh et al. NEJM 2022;1:EVIDoa2200015.

KEYNOTE-966: Pembro/Gem/Cis vs. Gem/Cis



Number at risk (number censored)

Pembrolizumab plus gemcitabine and cisplatin	533 (0)	496 (0)	430 (0)	350 (0)	275 (0)	217 (0)	175 (1)	122 (26)	88 (50)	46 (83)	21 (100)	11 (109)	5 (114)	0 (119)
Placebo plus gemcitabine and cisplatin	536 (0)	483 (1)	394 (1)	313 (1)	236 (1)	195 (1)	148 (3)	97 (30)	59 (49)	32 (65)	20 (74)	10 (84)	1 (92)	0 (93)

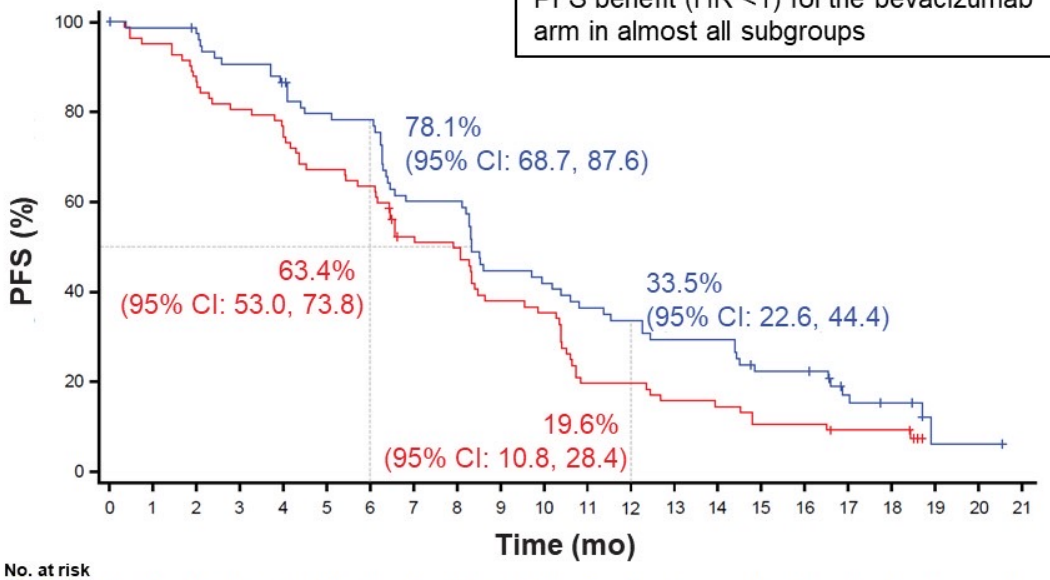
Kelley et al. Lancet 2023;S0140-6736(23)00727-4

Updated PFS and OS

Primary endpoint: PFS	Atezo + Bev + CisGem (n=79)[a]	Atezo + PBO + CisGem (n=83)
No. of events (%)	63 (80)	73 (88)
Median PFS (95% CI), mo	8.3 (6.8, 10.6)	7.9 (6.2, 8.5)
Stratified HR[b] (95% CI)	0.67 (0.46, 0.95)	

Secondary endpoint: OS	Atezo + Bev + CisGem (n=79)[a]	Atezo + PBO + CisGem (n=83)
No. of events (%)	47 (59)	48 (58)
Median OS (95% CI), mo	14.9 (11.6, 18.0)	14.6 (11.2, NE)
Stratified HR[b] (95% CI)	0.97 (0.64, 1.47)	

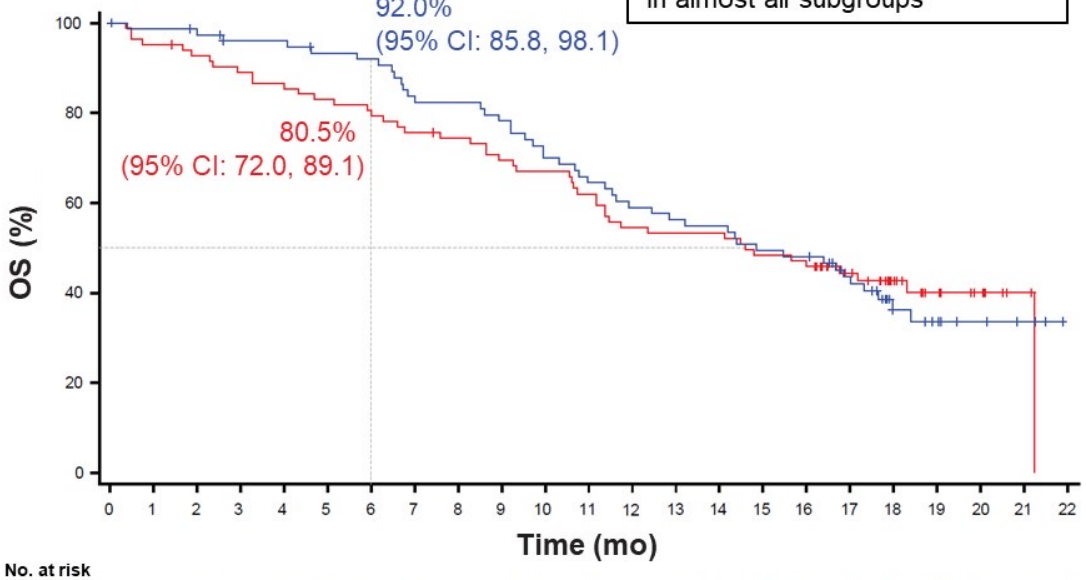
Descriptive subgroup analysis showed a PFS benefit (HR <1) for the bevacizumab arm in almost all subgroups



No. at risk

Atezo + Bev + CisGem	78	74	73	67	63	57	56	43	43	32	30	26	24	21	21	15	15	9	7	1	1	NE
Atezo + PBO + CisGem	83	78	72	66	63	55	52	40	38	29	27	15	15	12	11	8	8	6	6	NE	NE	NE

Similar HR for OS was observed in almost all subgroups

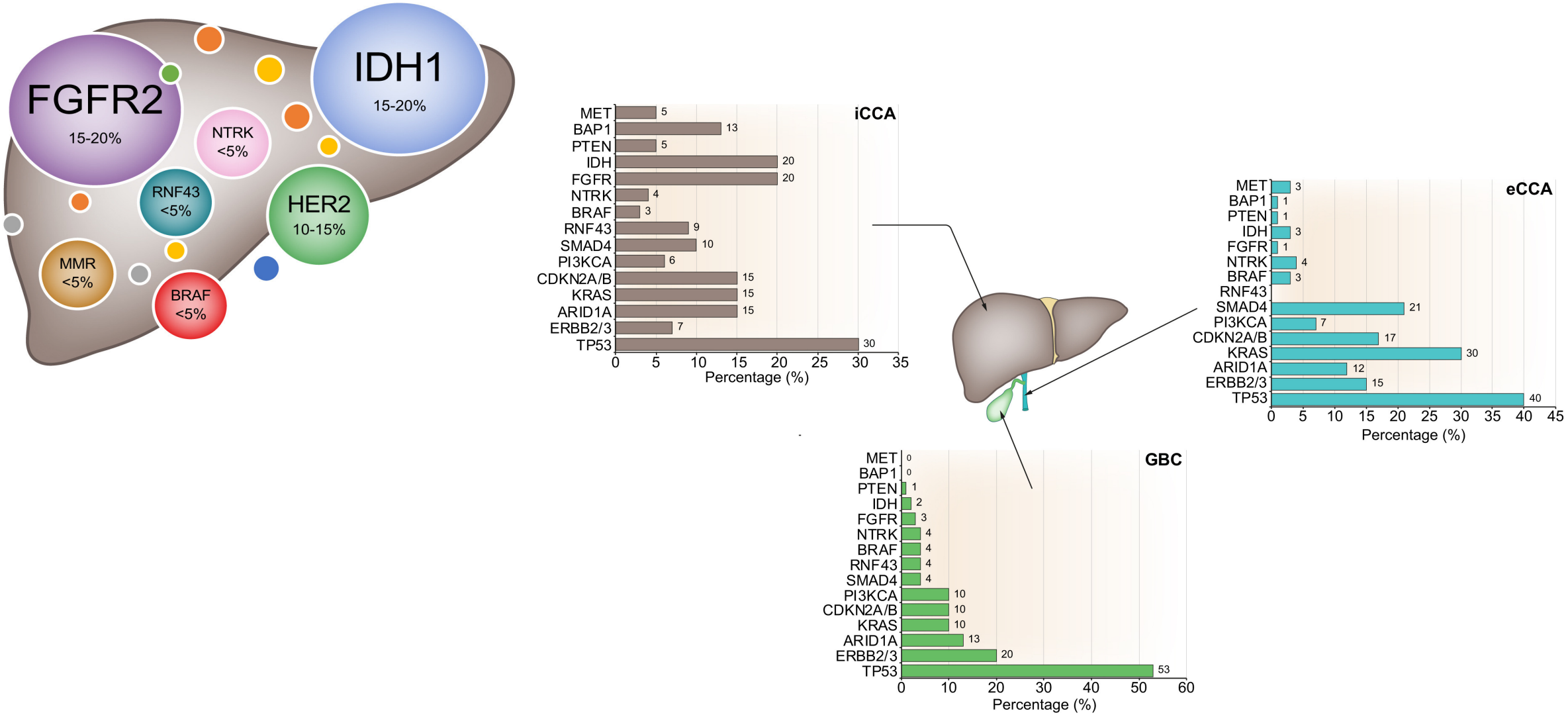


No. at risk

Atezo + Bev + CisGem	78	76	75	71	71	68	67	60	60	57	51	47	43	41	40	36	35	28	14	11	6	4	NE
Atezo + PBO + CisGem	83	79	76	73	71	68	66	62	60	56	54	50	44	43	43	39	38	28	19	11	7	2	NE

Median follow-up duration: 18.8 mo. Clinical cutoff: Jan 16, 2023. CI, confidence interval; NE, not estimable.

[a] A patient with a missing death date was excluded from the Kaplan-Meier curve. [b] Stratified analysis. Stratification factors are location of primary tumor (iCCA vs eCCA vs GBC) and geographic region (Asia vs rest of world).



Journal of Hepatology 2020 73170-185DOI: (10.1016/j.jhep.2020.03.007)

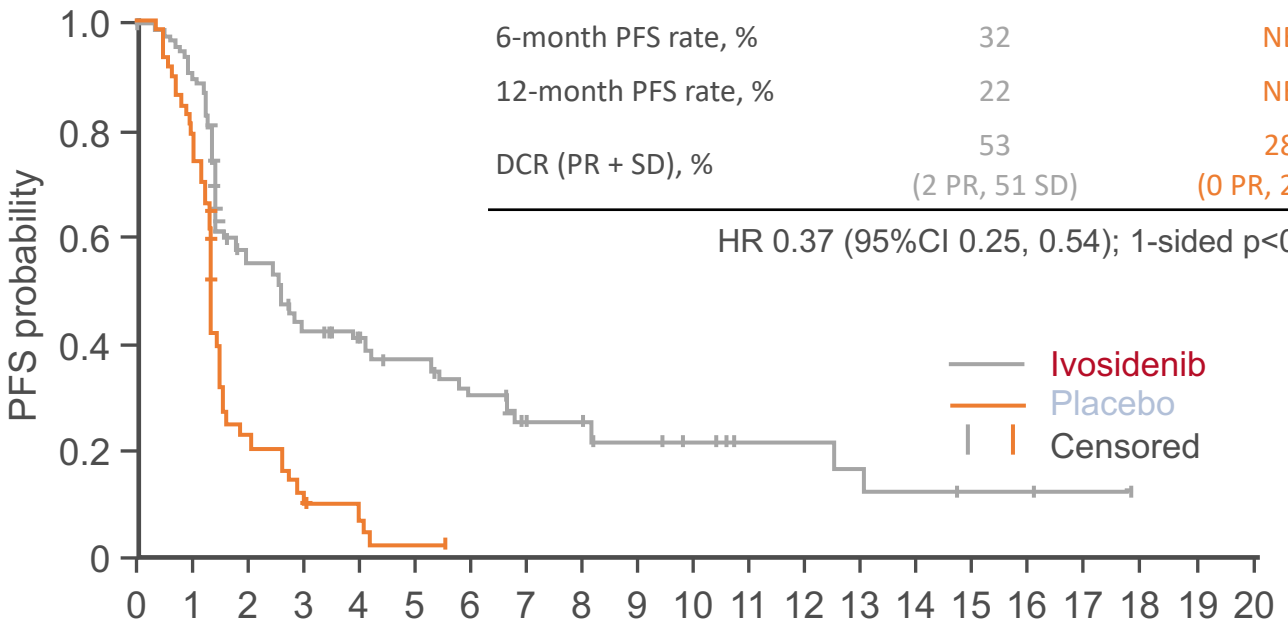
266: Final results from ClarIDHy, a global, phase III, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (IDH1) mutation – Zhu AX, et al

Key results

Progression-free survival

	Ivosidenib	Placebo
mPFS, months	2.7	1.4
6-month PFS rate, %	32	NE
12-month PFS rate, %	22	NE
DCR (PR + SD), %	53 (2 PR, 51 SD)	28 (0 PR, 28 SD)

HR 0.37 (95%CI 0.25, 0.54); 1-sided p<0.0001



No. at risk

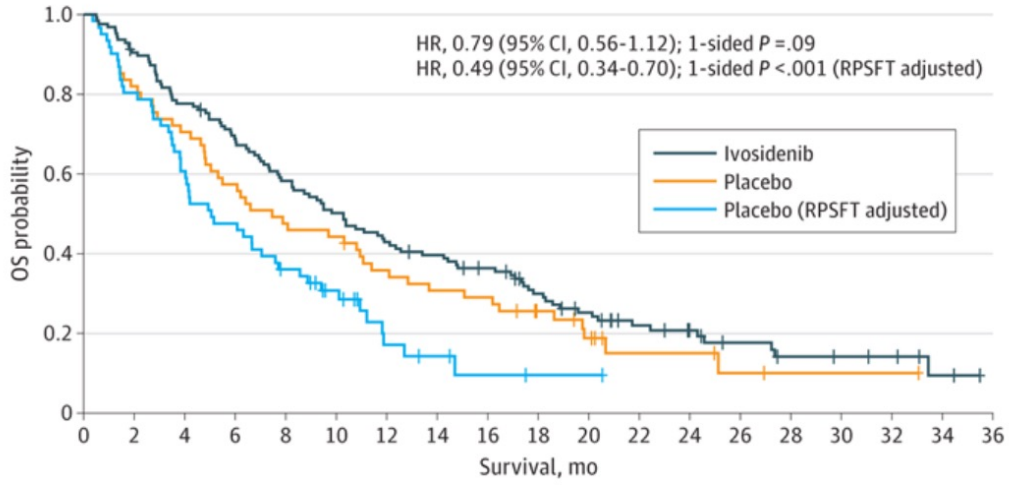
Ivosidenib	124	105	54	40	36	28	22	16	14	10	9	6	5	4	3	3	2	1	1
Placebo	61	46	11	6	4	1													

Zhu AX, et al. J Clin Oncol 2021;39(suppl):abstr 266

From: **Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial**

JAMA Oncol. Published online September 23, 2021. doi:10.1001/jamaoncol.2021.3836

A Overall survival

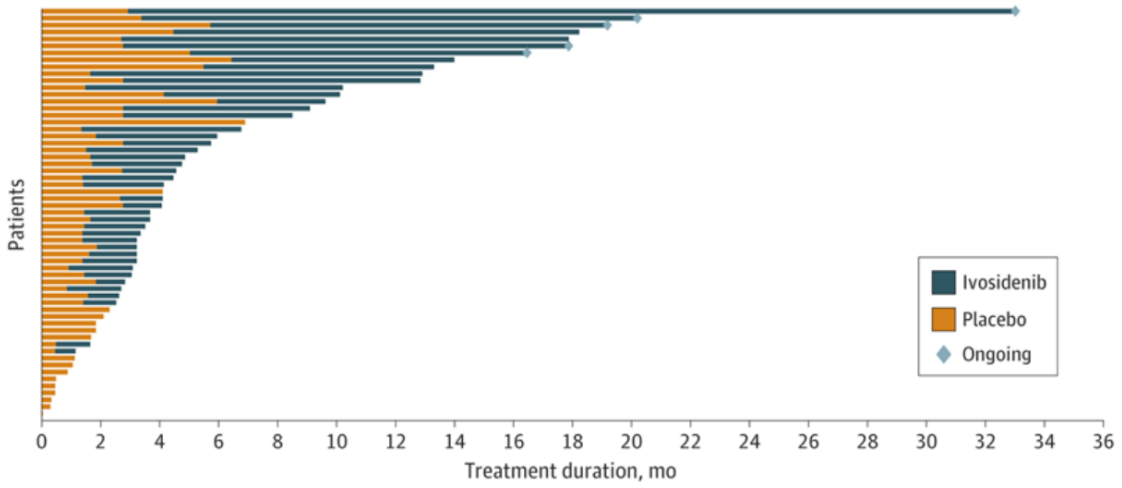


No. at risk

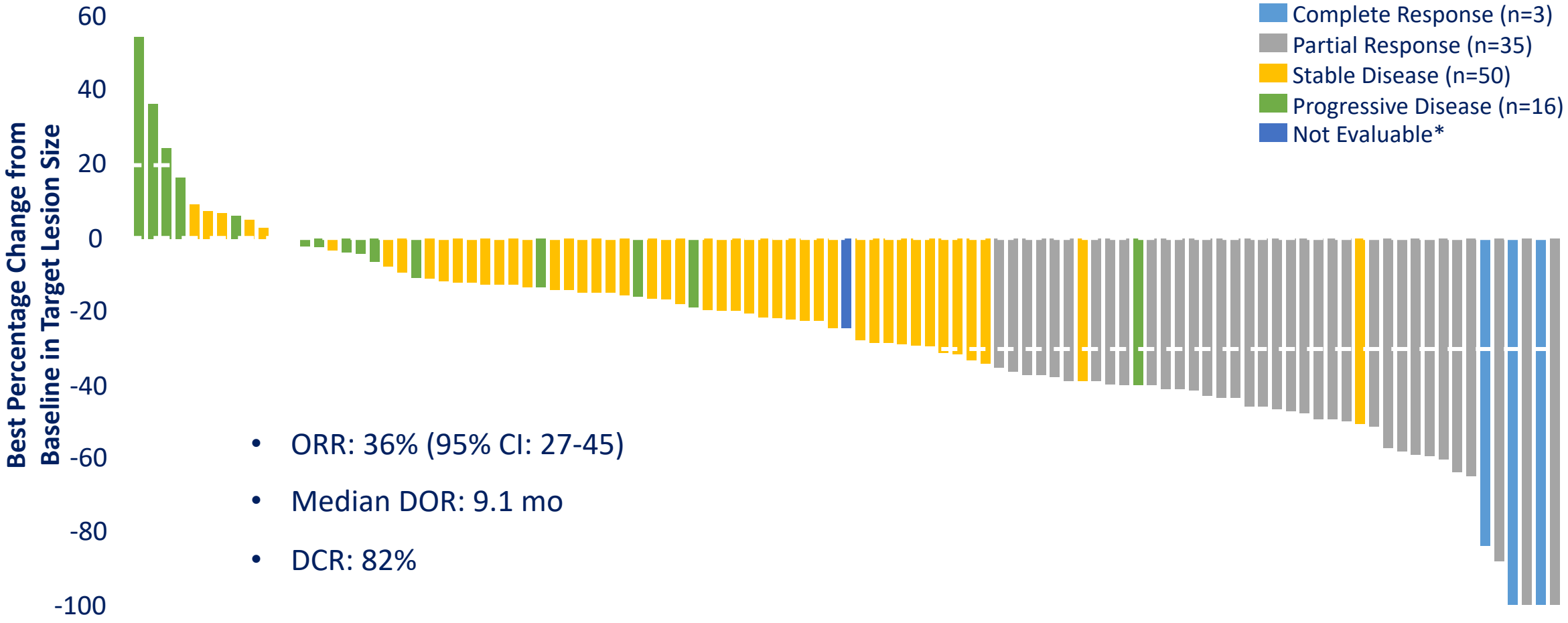
Ivosidenib	126	113	97	85	72	62	53	48	42	32	25	18	14	10	7	6	5	2
Placebo	61	50	43	35	29	27	21	18	17	12	8	4	4	2	1	1	1	
Placebo (RPSFT adjusted)	61	49	37	29	21	14	6	4	2	1	1							

Treatment group	Events/patients, No.	OS, median (95% CI), mo
Ivosidenib	100/126	10.3 (7.8-12.4)
Placebo	50/61	7.5 (4.8-11.1)
Placebo adjusted by RPSFT	49/61	5.1 (3.8-7.6)

C Treatment duration for all patients treated with placebo, including those who crossed over to ivosidenib



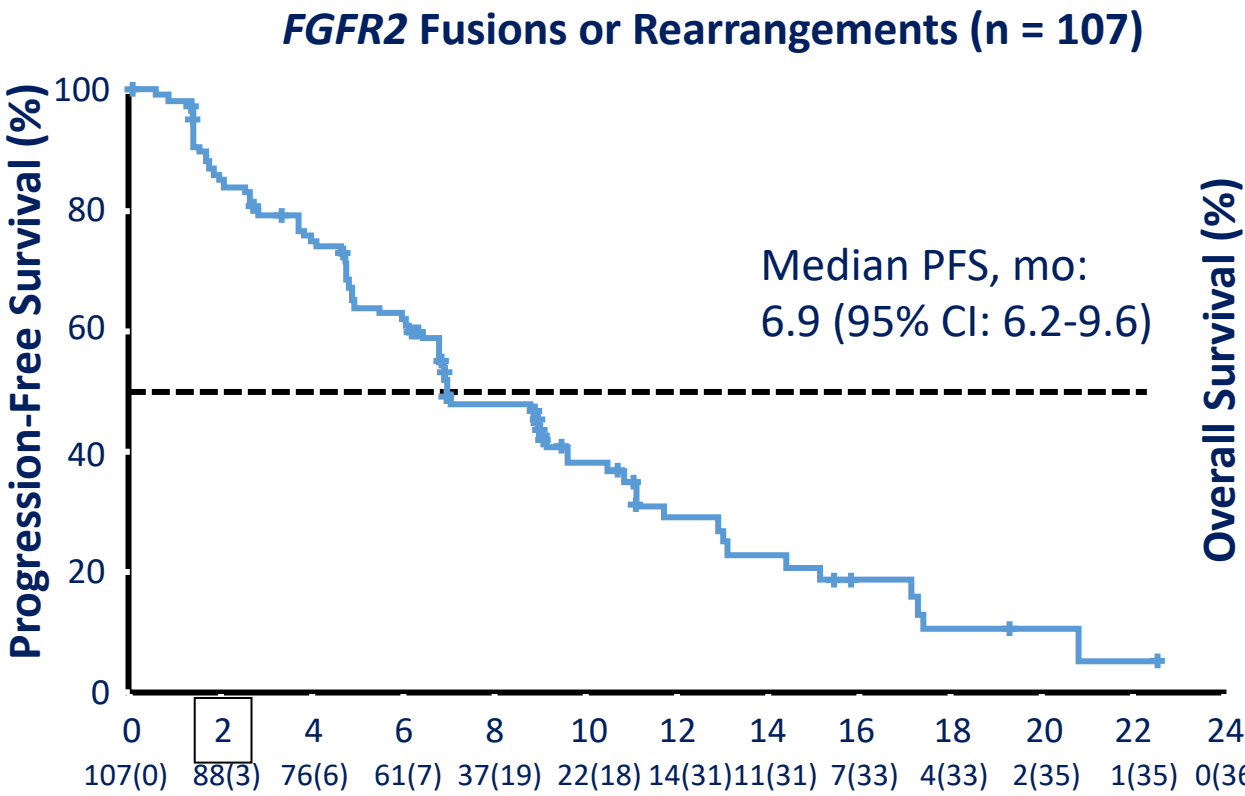
FIGHT-202: Responses in Patients with *FGFR2* Fusion/Rearrangement

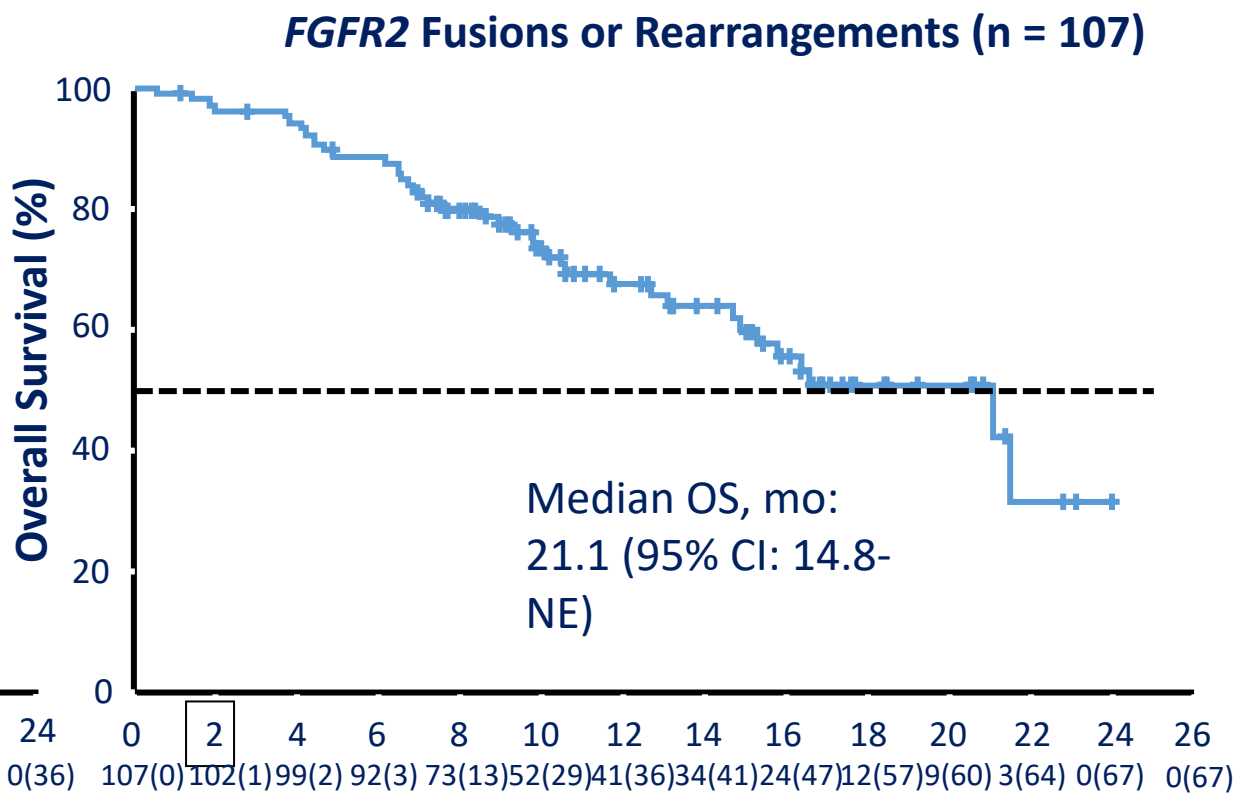


Abou-Alfa. Lancet Oncol. 2020;21:671.

Slide credit: clinicaloptions.com

FIGHT-202: PFS and OS





Abou-Alfa. Lancet Oncol. 2020;21:671.

Slide credit: clinicaloptions.com

HER2 Expression in BTCs

ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; Bp, perihilar; Bd, distal; GBC, gallbladder cancer; AVC, Ampulla of Vater cancer.

- In BTCs, HER2 overexpression, gene amplification, or both have been reported in several studies, and HER2-positive rates in GBC, ECC, and ICC are estimated to be 30%, 10–20%, and 5%, respectively.[1]
- Through our preliminary study, we confirmed that the HER2 expression patterns in BTCs are more similar to those of gastric cancer than breast cancer, including heterogeneity.
- We also recently reported on the HER2 expression status according to the guidelines for HER2 testing in gastroesophageal adenocarcinoma in 454 cases (Table).[2]

	ICC	ECC-Bp	ECC-Bd	GBC	AVC
HER2-positive rate (%)	3.7	3.0	18.5	31.3	16.4

1. Cancer Discov 2017;7:943–62. 2. Hum Pathol 2020;105:9.

Primary endpoint: Confirmed ORR (BICR)

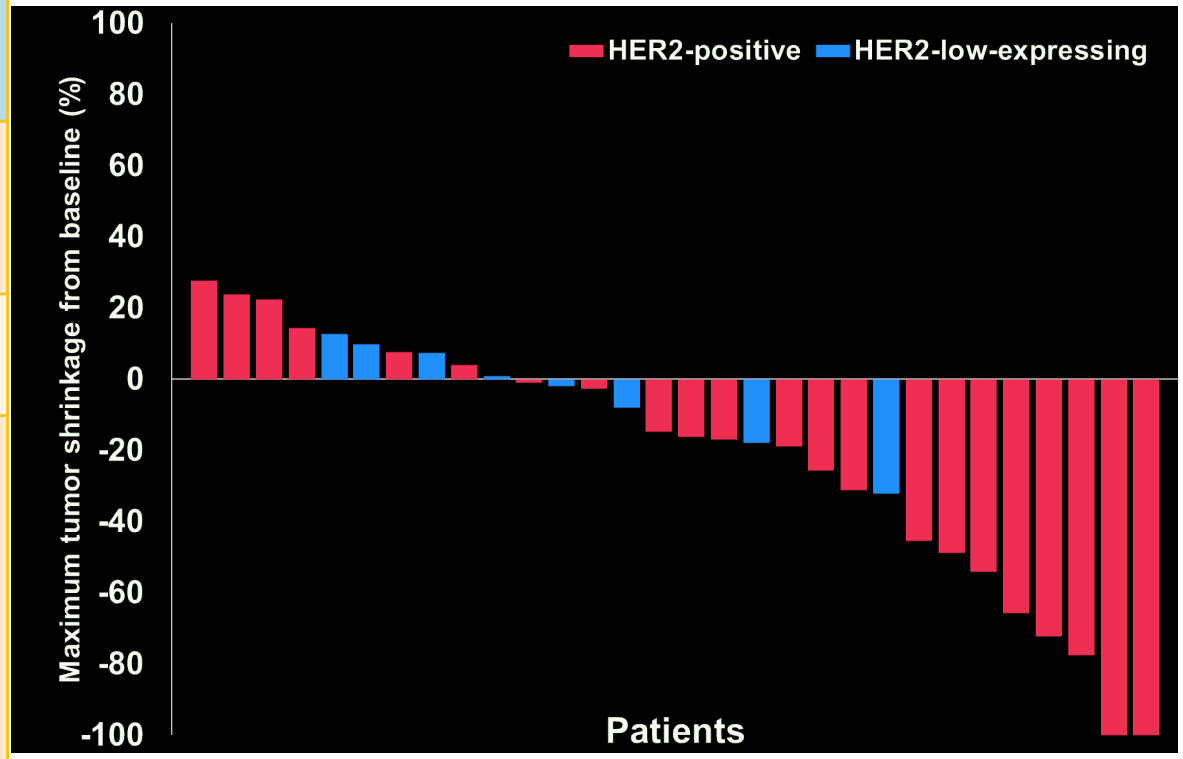
BICR, blinded independent central review; DCR, disease control rate;
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

- Tumor response

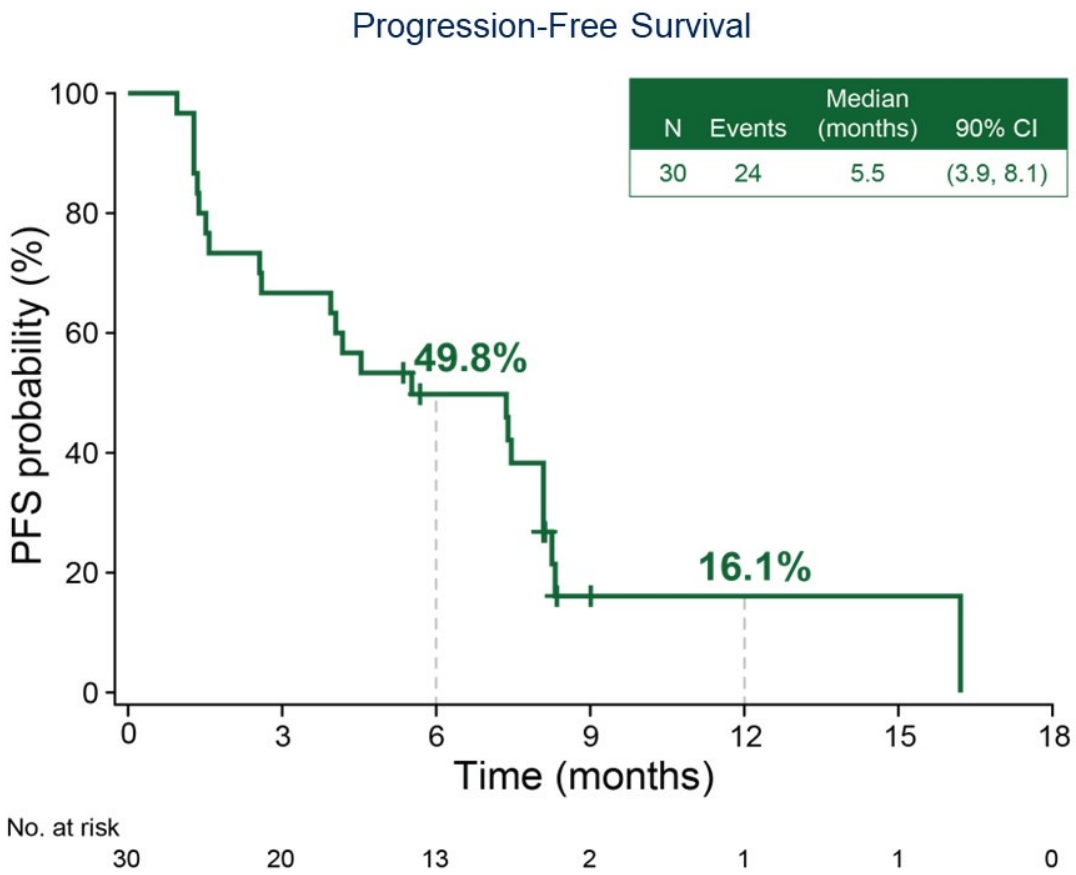
*: P =0.01

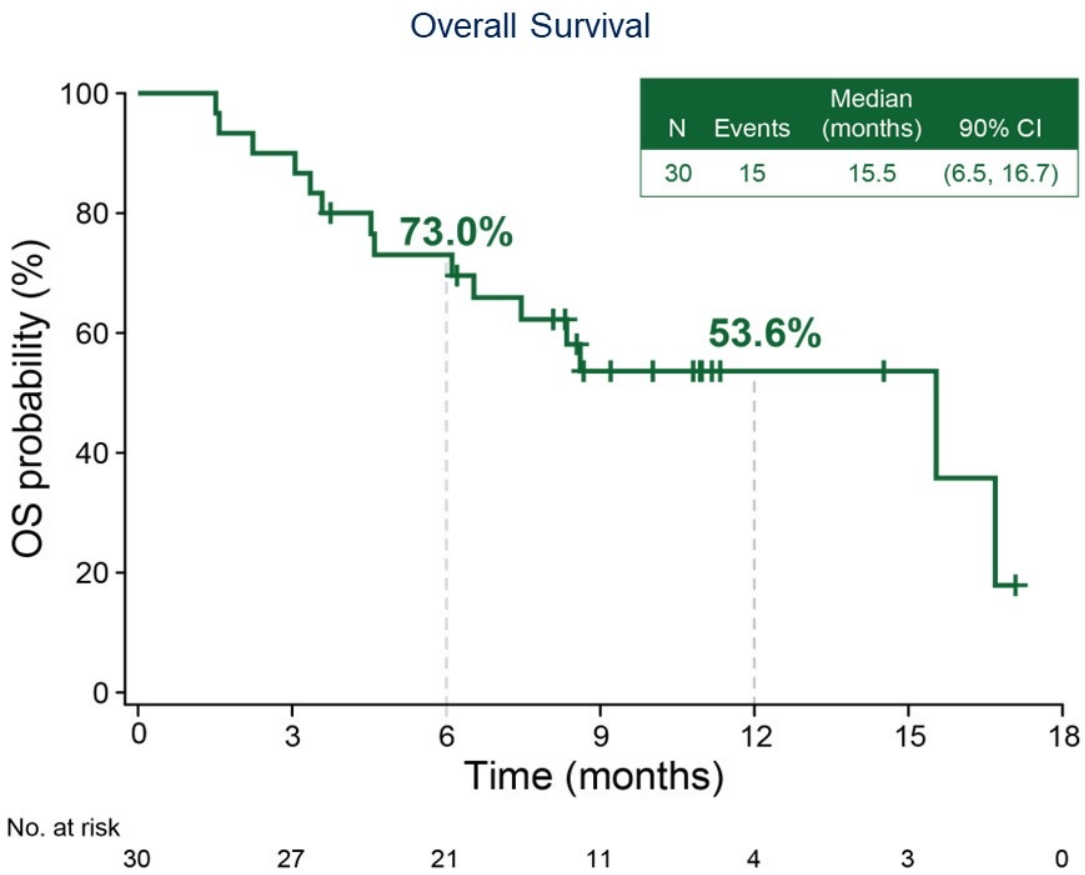
	HER2-positive (n=22)	HER2-low-expressing (n=8)	All pts (n=30)
Confirmed ORR	**36.4%**	12.5%	30.0%
(90% CI)	**(19.6-56.1)***	–	–
(95% CI)	(17.2–59.3)	(0.3–52.7)	(14.7–49.4)
Confirmed DCR	81.8%	75.0%	80.0%
(95% CI)	(59.7–94.8)	(34.9–96.8)	(61.4–92.3)
Confirmed best response, n (%)			
CR	2 (9.1)	0 (0)	2 (6.7)
PR	6 (27.3)	1 (12.5)	7 (23.3)
SD	10 (45.5)	5 (62.5)	15 (50.0)
PD	3 (13.6)	1 (12.5)	4 (13.3)
NE	1 (4.5)	1 (12.5)	2 (6.7)

- Best percentage change



Progression-Free Survival and Overall Survival

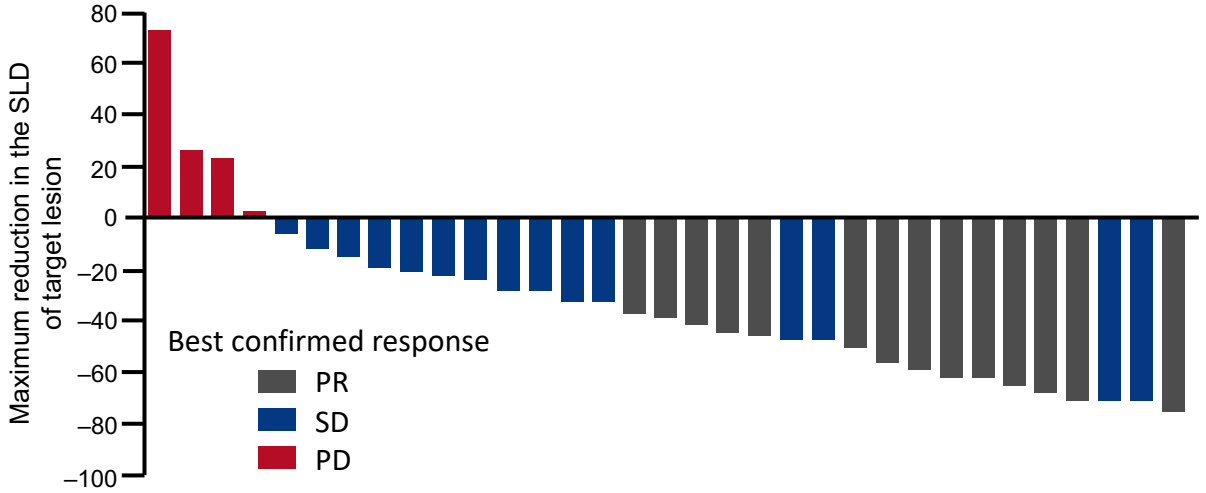




Data cutoff: Jan 30, 2023.
PFS, progression-free survival; OS, overall survival.

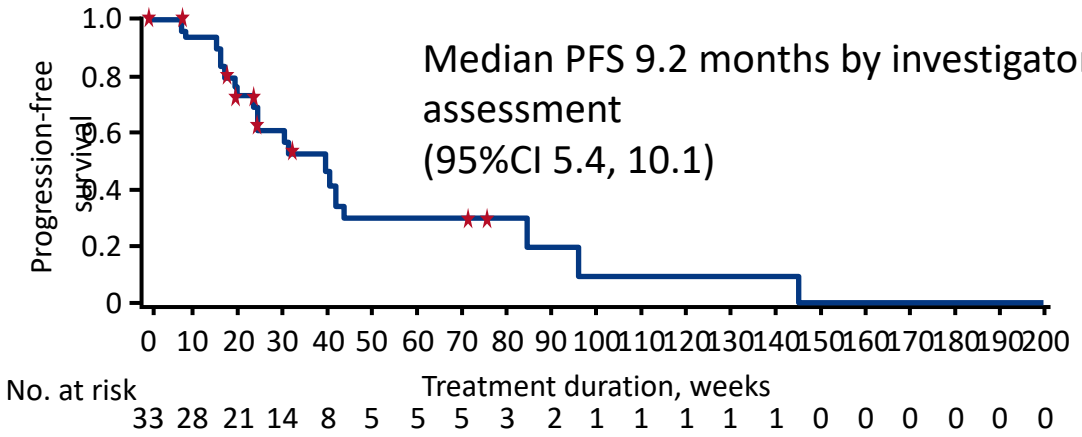
187: Efficacy and safety of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E-mutated biliary tract cancer (BTC): A cohort of the ROAR basket trial – Wainberg ZA, et al

Key results



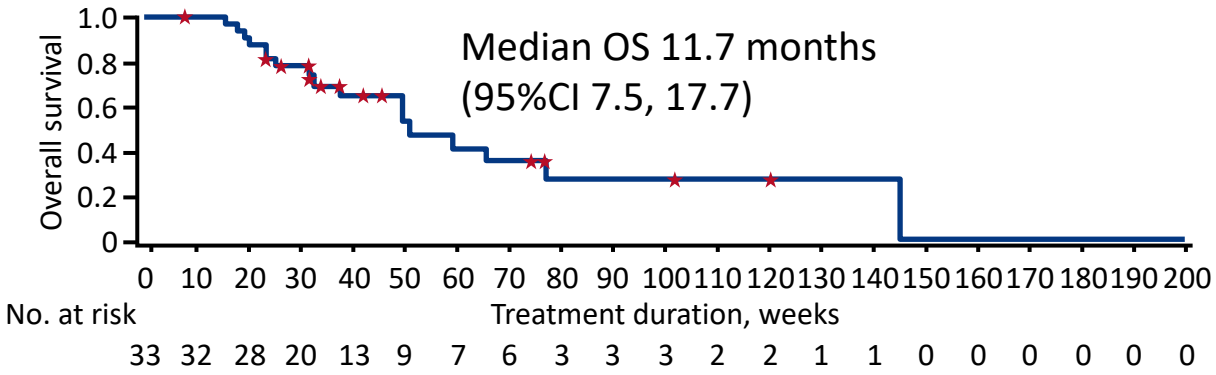
PFS

Median PFS 9.2 months by investigator assessment
(95%CI 5.4, 10.1)



OS

Median OS 11.7 months
(95%CI 7.5, 17.7)



Wainberg ZA, et al. J Clin Oncol 2019;37(Suppl):Abstr 187

Targeted Therapies in BTCs

IDH1, isocitrait dehydrogenase 1; FGFR2, fibroblast growth factor receptor 2; mPFS, median progression-free survival; mo, months.

- Novel molecular targets were found to be attractive for BTCs in several trials.
- However, these targets are limited populations among BTCs, and the remaining targeted agents have not been sufficiently evaluated.

Target	**IDH1**	**FGFR2**		**BRAF^{V600E}**	**HER2**	
Agent	Ivosidenib[1]*	Pemigatinib[2]*	Infigratinib[3]*	Dabrafenib + Trametinib[4]	Pertuzumab + Trastuzumab[5]	TDx
Phase	3	2	2	2	2	2
n	124	146	108	43	39	30
ORR (%)	2.4	35.5	23.1	46.5	23.1	30.0
mPFS (mo)	2.7	6.9	7.3	9	4.0	5.1

*: FDA approved; **: Not reported.

1. Lancet Oncol 2020;21:796. 2. Lancet Oncol 2020;21:671. 3. Lancet Gastroenterology Hepatology 2021;6:803. 4. Lancet Oncol 2020;21:1234. 5. Lancet Oncol 2021;22:1290.

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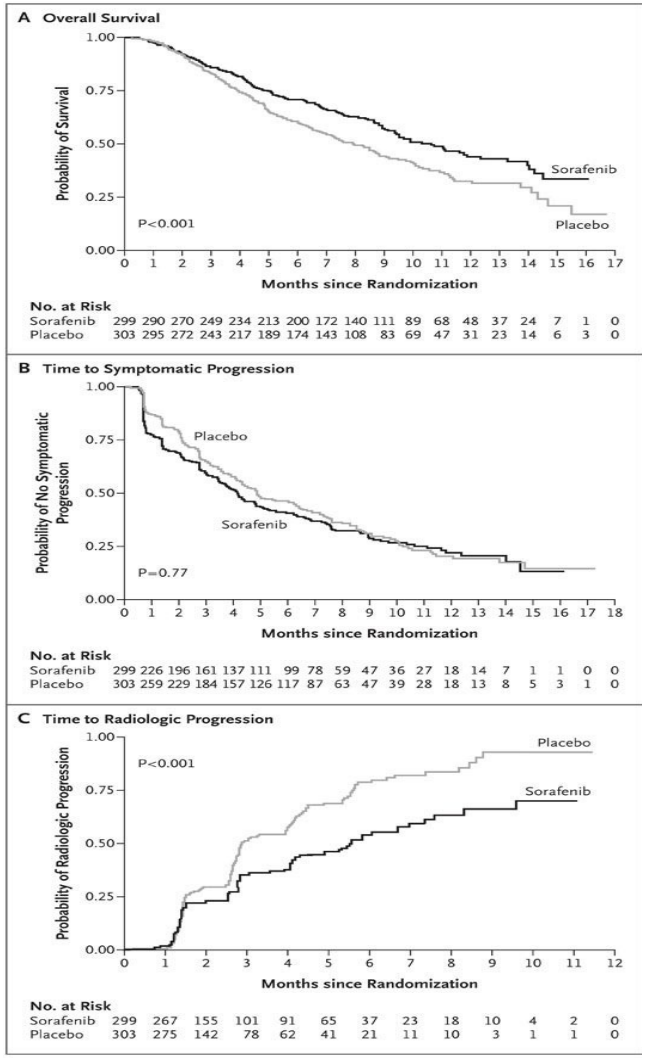
HCC

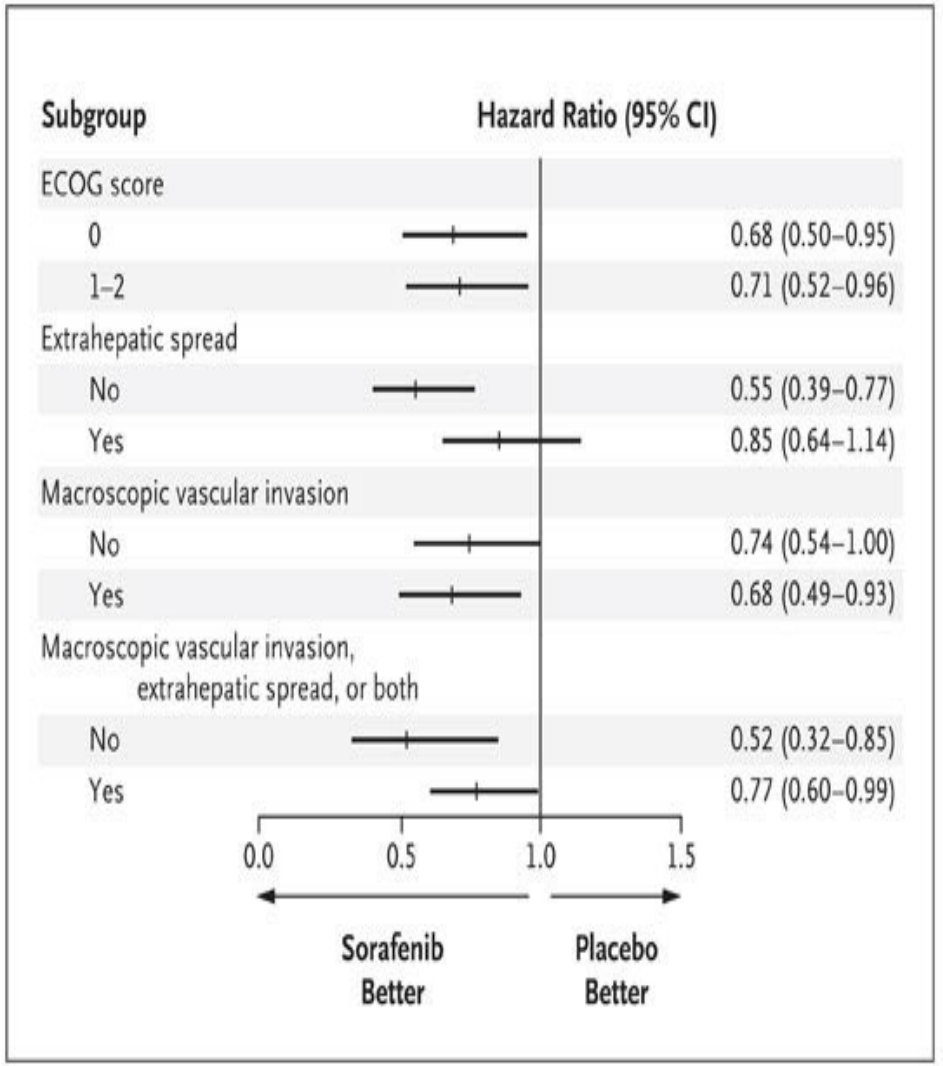
- Time is what we want most but what we use worst.”

William Penn

Kaplan–Meier Analysis of Overall Survival, the Time to Symptomatic Progression, and the Time to Radiologic Progression

- OS
  - 10.7 months sorafenib
  - 7.9 months placebo(P<0.001).
- Time to symptomatic progression
  - 4.1 months Sorafenib
  - 4.9 months Placebo (P=0.77).
- Time to radiologic progression
  - 5.5 months sorafenib
  - 2.8 months placebo group (P<0.001).

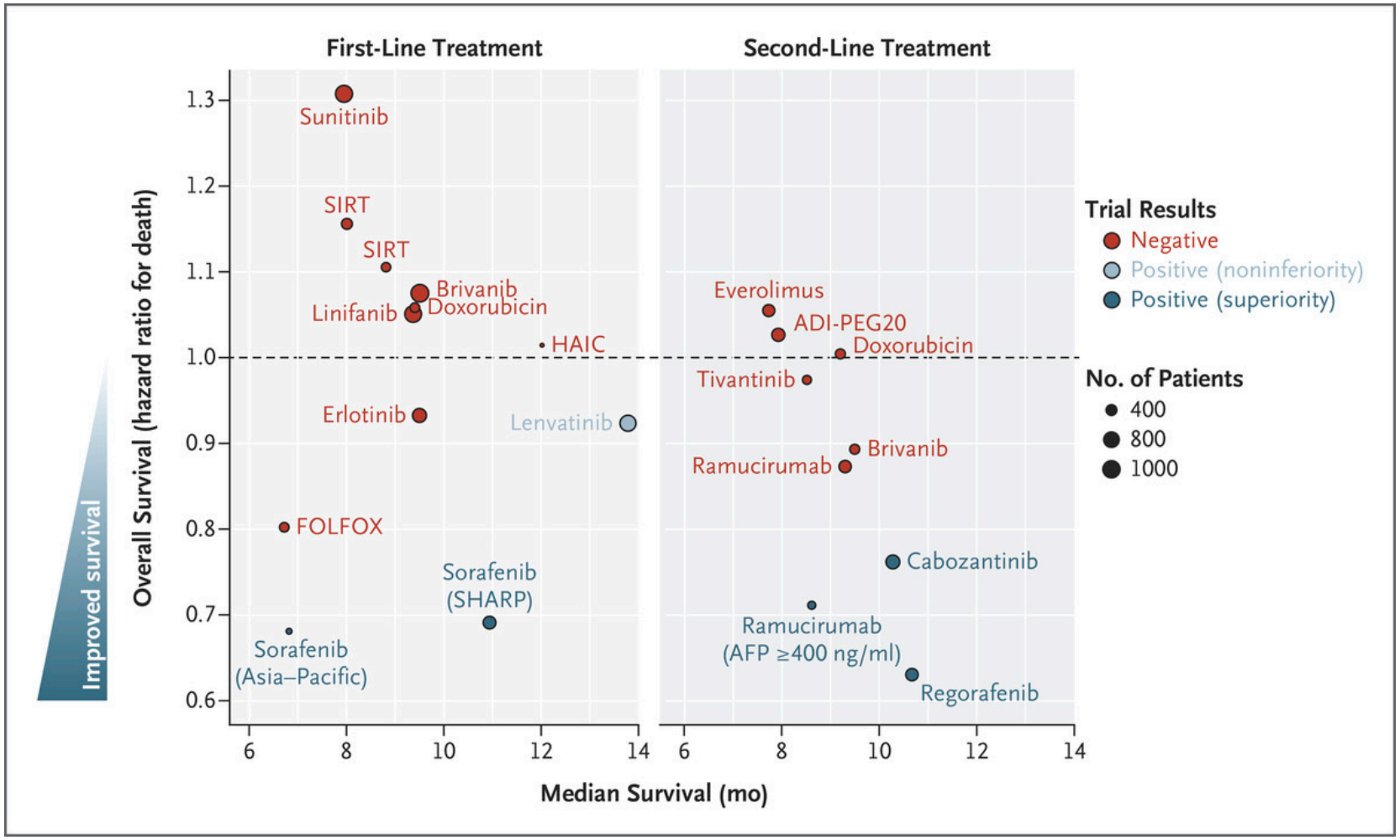




Llovet JM et al. N Engl J Med 2008;359:378-390.

The NEW ENGLAND JOURNAL of MEDICINE

Systemic Therapies Tested in Phase 3 Trials for the Management of Advanced Hepatocellular Carcinoma.



A Villanueva. N Engl J Med 2019;380:1450-1462.

The NEW ENGLAND JOURNAL of MEDICINE

2023 ASCO ANNUAL MEETING

Outcomes by occurrence of immune-mediated adverse events with tremelimumab plus durvalumab in the Phase 3 HIMALAYA study in unresectable hepatocellular carcinoma

George Lau,[1] Ann-Lii Cheng,[2] Bruno Sangro,[3] Masatoshi Kudo,[4] Robin Kate Kelley,[5] Won Young Tak,[6] Antonio Gasbarrini,[7] Maria Reig,[8] Ho Yeong Lim,[9] David Tougeron,[10] Enrico N. De Toni,[11] Vincent C. Tam,[12] Kabir Mody,[13] Jun Gong,[14] Carrie L. McCoy,[15] Charu Gupta,[16] Mallory Makowsky,[15] Alejandra Negro,[15] Ghassan K. Abou-Alfa[17,18]

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PRESENTED BY: George Lau, MD, FRCP, FAASLD

HIMALAYA study design

HIMALAYA is an open-label, multicenter, global, Phase 3 trial[1]

Study population

- Adults with confirmed unresectable HCC
- Child–Pugh A
- BCLC B (not eligible for locoregional therapy) or C
- No prior systemic therapy
- ECOG PS 0–1
- No main portal vein thrombosis
- EGD was not required

Stratification factors

- Etiology of liver disease: HBV / HCV / nonviral
- Macrovascular invasion: yes / no
- ECOG PS: 0 / 1

R
N=1171

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 to enrollment****
tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W

Primary objective

- OS superiority: STRIDE vs sorafenib

Secondary objectives

- OS noninferiority: durvalumab vs sorafenib
- 36-month OS rate
- PFS, ORR, and DCR (investigator-assessed per RECIST v1.1)
- Safety

Multiple testing procedure

OS *superiority* for STRIDE vs sorafenib

↓

OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

↓

OS *superiority* for durvalumab vs sorafenib

↓

36-month OS rate for STRIDE vs sorafenib

*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.

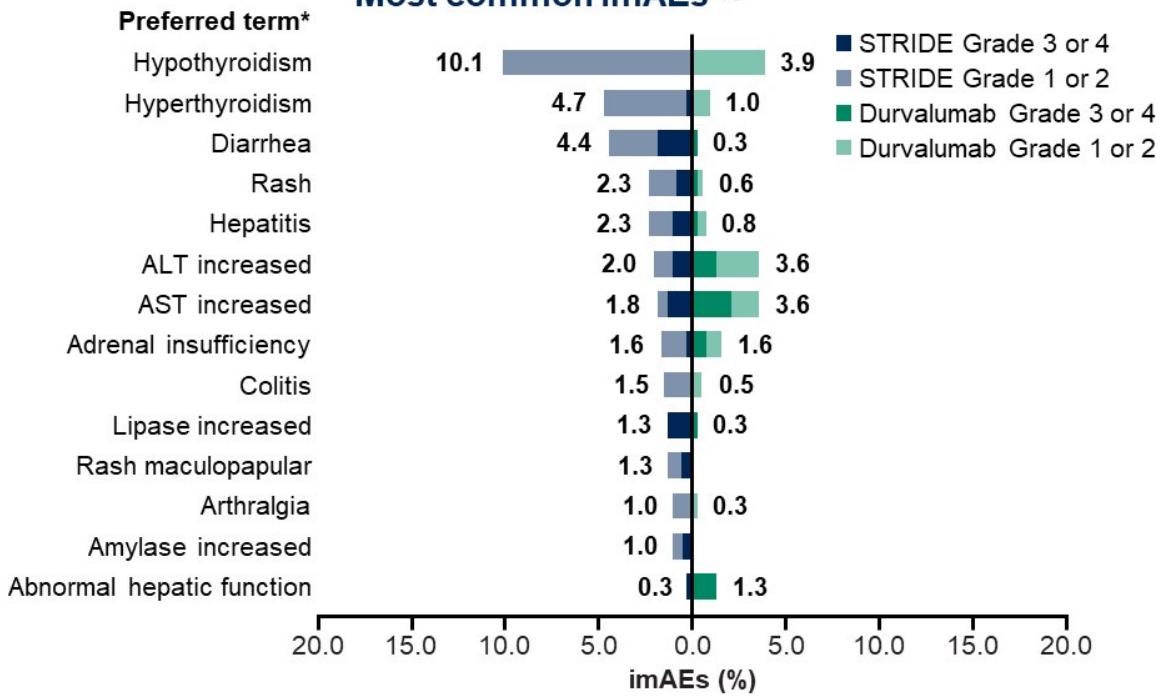
BCLC, Barcelona Clinic Liver Cancer; BID, twice a day; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; EGD, esophagogastroduodenoscopy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ORR, objective response rate; OS, overall survival; PFS, progression-free 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.

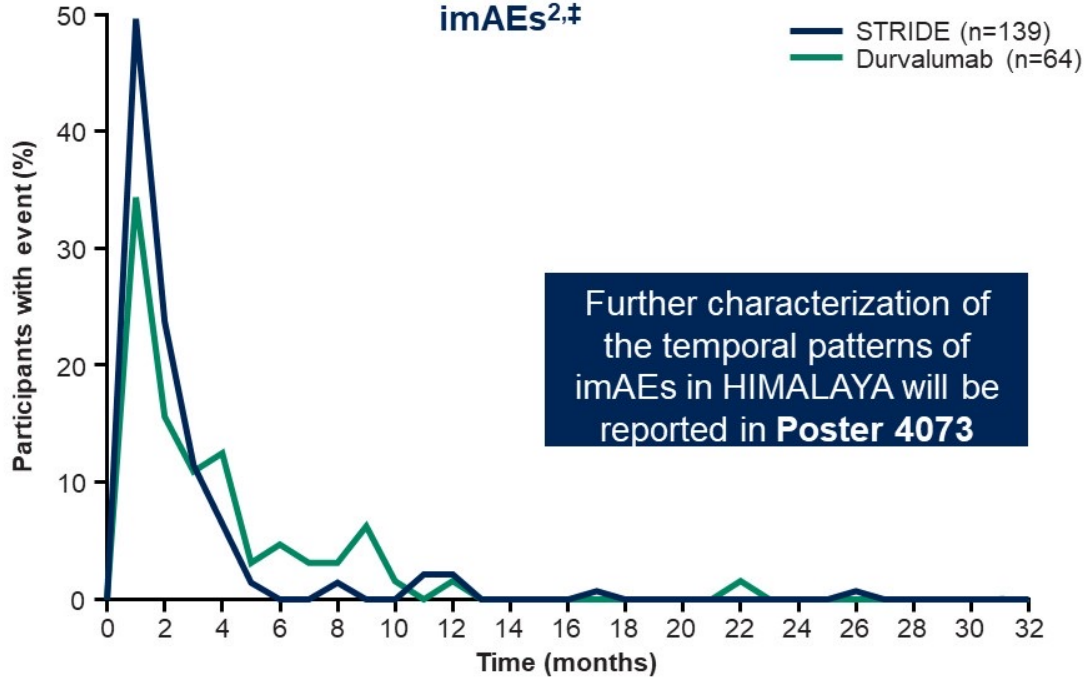
imAEs in HIMALAYA

Most imAEs with STRIDE or durvalumab were low grade, and most occurred within the first 3 months of treatment[1,2]

Most common imAEs[1,†]



Overall frequency of any imAE by time in participants with imAEs[2,‡]



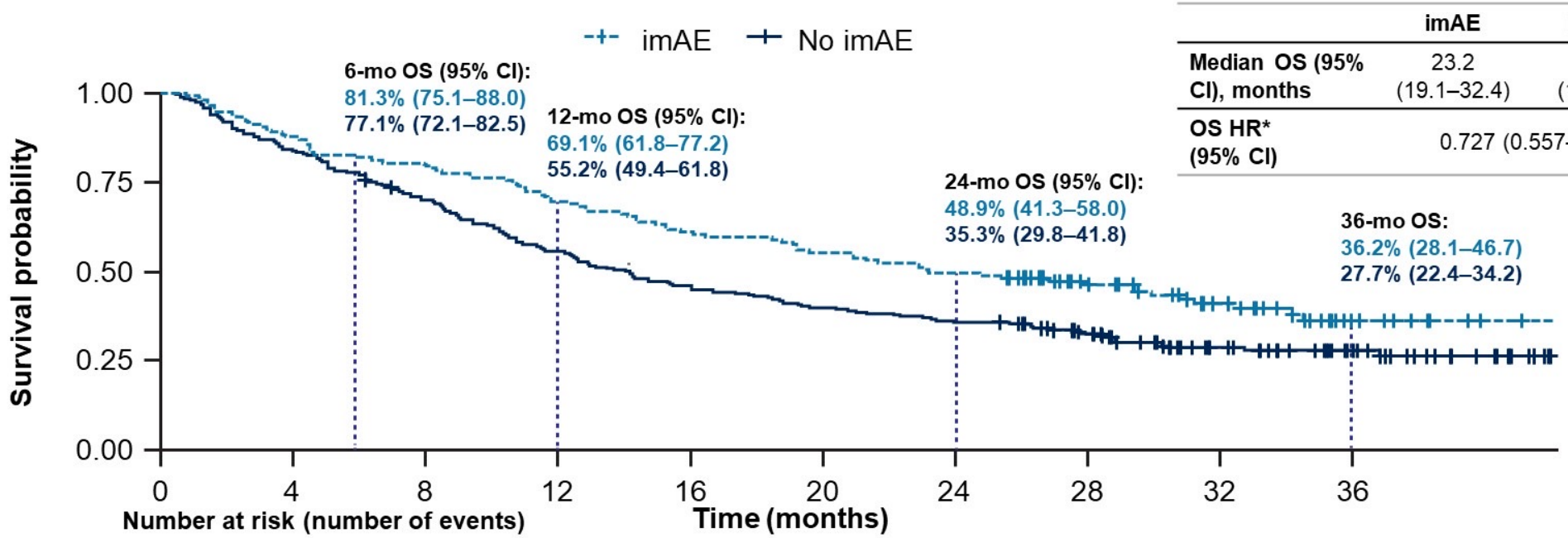
Further characterization of the temporal patterns of imAEs in HIMALAYA will be reported in **Poster 4073**

*Preferred term was as reported by the investigator. †imAEs that occurred in ≥1% of participants in the in the STRIDE or durvalumab treatment arms are included. ‡The percentage of participants with an event is the number of participants who experienced ≥1 imAE event at each time interval divided by the number of participants who experienced ≥1 imAE event at any time; includes first imAE only, regardless of grade.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; imAE, immune-mediated adverse event.

1. Sangro B, et al. Presented at: ILCA 2022 16th Annual Conference; September 1–4, 2022; Madrid, Spain. Oral presentation O-28. 2. Lau G, et al. Poster presented at: ASCO Annual Meeting 2023; June 2–6, 2023; Chicago, IL. Poster 4073.

OS by imAE occurrence for STRIDE

A numerical improvement in OS was observed in participants who had an imAE versus those who did not



	imAE	No imAE
Median OS (95% CI), months	23.2 (19.1–32.4)	14.1 (11.6–17.9)
OS HR* (95% CI)	0.727 (0.557–0.948)	

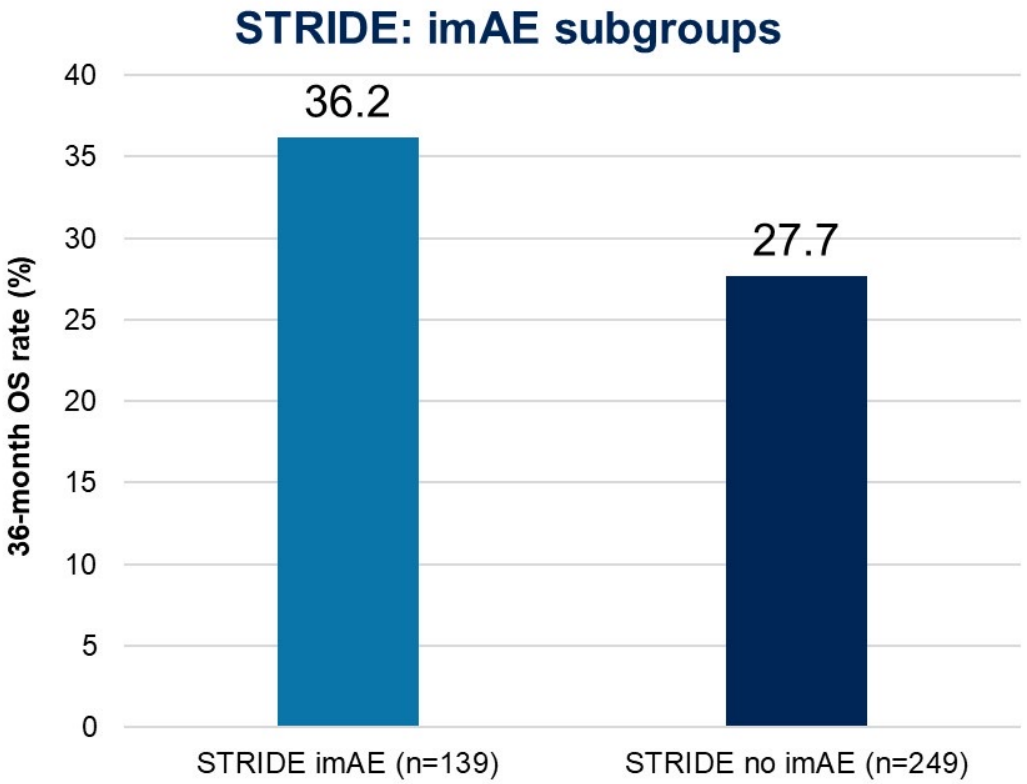
*OS HRs and 95% CIs were calculated using Cox modeling, with imAEs as a time-varying covariate to properly account for immortal time bias and stratified by etiology, ECOG (0 / 1), and macrovascular invasion (yes / no) for participants with versus without imAEs of any grade.

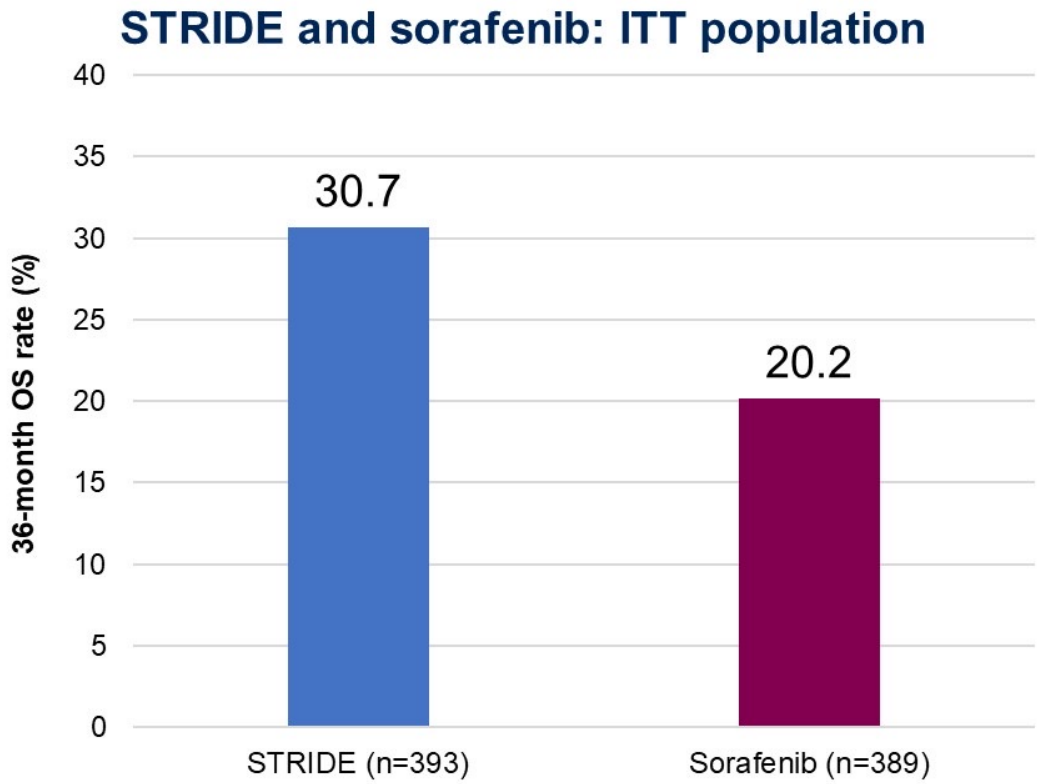
CI, confidence interval; HR, hazard ratio; imAE, immune-mediated adverse event; OS, overall survival.

PRESENTED BY: George Lau, MD, FRCP, FAASLD

Landmark 36-month OS rates for STRIDE in imAE subgroups

OS rates at 36 months were higher with STRIDE than with sorafenib (ITT population) irrespective of imAE occurrence

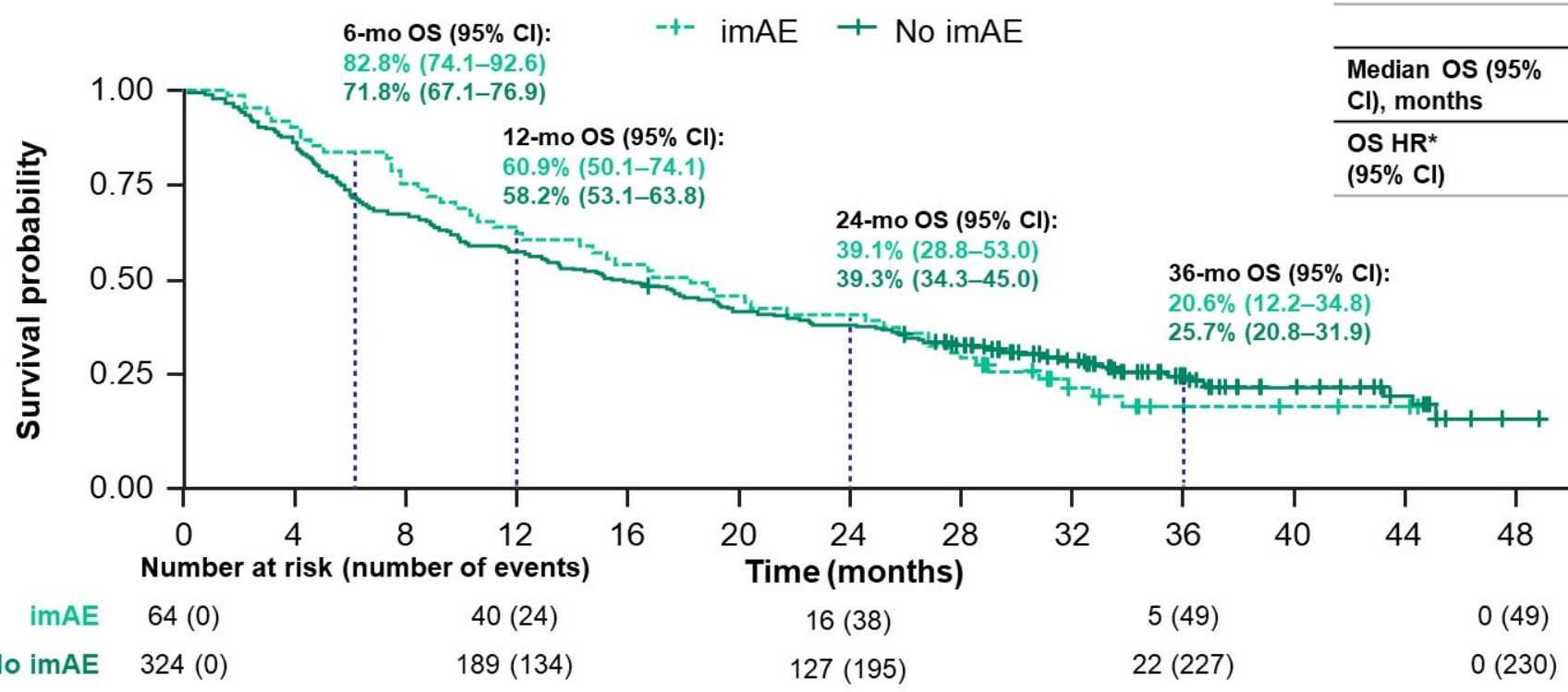




imAE, immune-mediated adverse event; ITT, intent-to-treat; OS, overall survival.

OS by imAE occurrence for durvalumab

OS was similar for participants treated with durvalumab with or without imAEs



	imAE	No imAE
Median OS (95% CI), months	17.8 (13.8–25.1)	16.5 (13.1–19.4)
OS HR* (95% CI)	1.136 (0.820–1.574)	

*OS HRs and 95% CIs were calculated using Cox modeling, with imAEs as a time-varying covariate to properly account for immortal time bias and stratified by etiology, ECOG (0 / 1), and macrovascular invasion (yes / no) for participants with versus without imAEs of any grade.
CI, confidence interval; HR, hazard ratio; imAE, immune-mediated adverse event; OS, overall survival.

PRESENTED BY: George Lau, MD, FRCP, FAASLD

Cross comparison between trials: let's do what we are not supposed to

	IMBRAVE 150	HIMALAYA (STRIDE)	VEGF TKI
Median OS	**19.2 m** vs 13.4 m (HR 0.66, CI 0.52-0.85)	**16.4 m** vs 13.8 m (HR 0.68 , CI 0.65-0.93)	**13.6 m**
>/= Grade 3 Adverse Events (AEs)	43%	25.8%	36.9%
Grade 5 therapy related	2% half bleeding related	2.3%	<1%
imAEs >/= Gr 3	Possibly around 11%	12.6%	NA

- Are imAEs to be considered as early markers or response to therapy with STRIDE regimen?
- Improved AE profile and better QoL makes a strong case to consider this regimen.
- Need data on cost-effectiveness to further inform our decisions

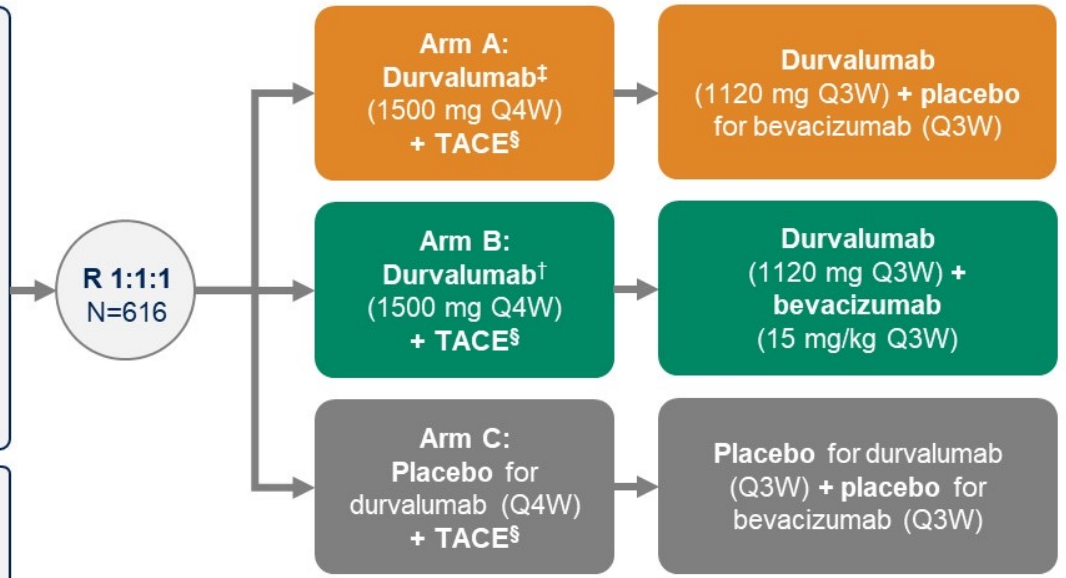
Abou-Alfa et.al., NEJM Evid 2022;1(8)
Cheng wt.al., Journ of Hepatology, Volume 76, Issue 4, April 2022, Pages 862-873

EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study

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

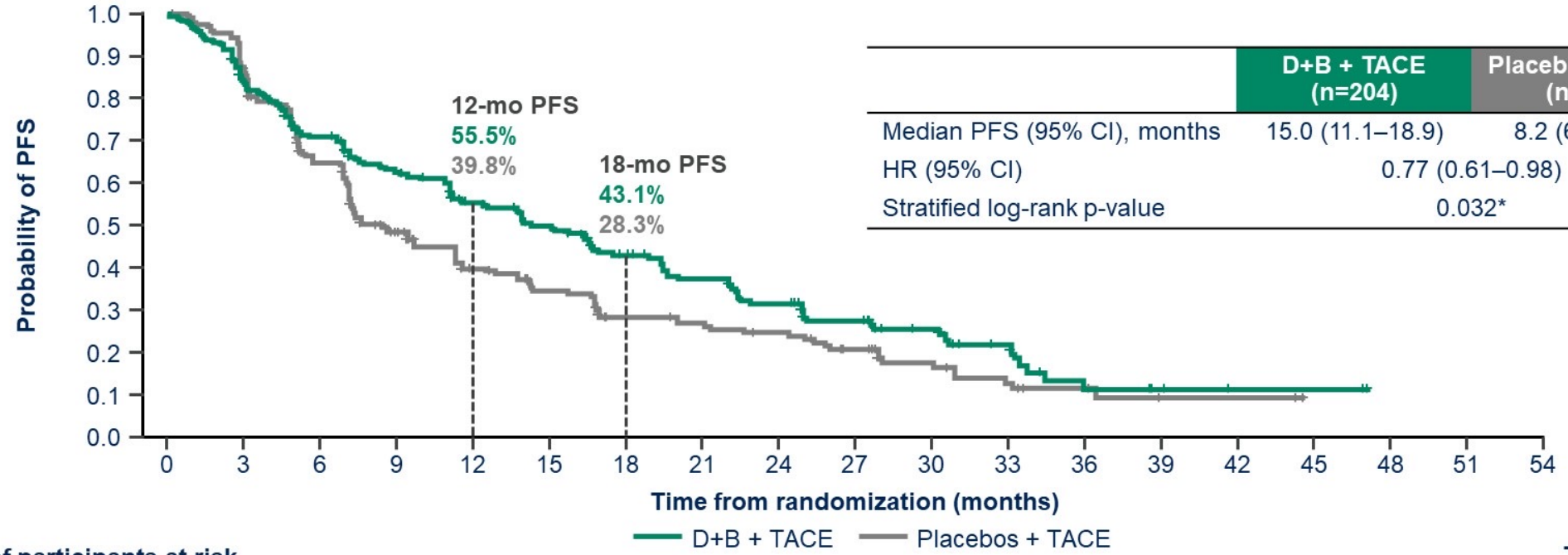
Other secondary endpoints:
- ORR and TTP using BICR per ***RECIST 1.1***
- Safety
- PFS, ORR, and TTP using investigator and BICR per ***mRECIST***

*Upper endoscopy to evaluate varices and risk of bleeding was required within 6 months of randomization. †Prior use of TACE or TAE is acceptable if it was used as part of therapy with curative intent, but not if it was used as the sole modality in curative therapy. ‡Durvalumab / placebo started ≥7 days after TACE. §DEB-TACE or cTACE. Participants will receive up to 4 TACE procedures within the 16 weeks following Day 1 of their first TACE procedure. ‖Only new lesions consistent with progression that were not eligible for TACE occurring prior to the first on study imaging at 12 weeks were considered progression events; standard mRECIST progression criteria were used after the 12-week imaging.

BICR, blinded independent central review; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead-transarterial chemoembolization; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W / Q4W, every 3 / 4 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TAE, transarterial embolization; TTP, time to progression.

PFS with D+B + TACE versus placebos + TACE: primary endpoint

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

No. of participants at risk																			Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

Median (range) duration of follow-up in censored participants, D+B + TACE 16.7 (0.03–47.1) months, Placebos + TACE 10.3 (0.03–44.3) months. **Median (95% CI) duration of follow-up** in all participants using the reverse Kaplan-Meier method, D+B + TACE 22.2 (16.7–27.3) months, Placebos + TACE 26.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1)

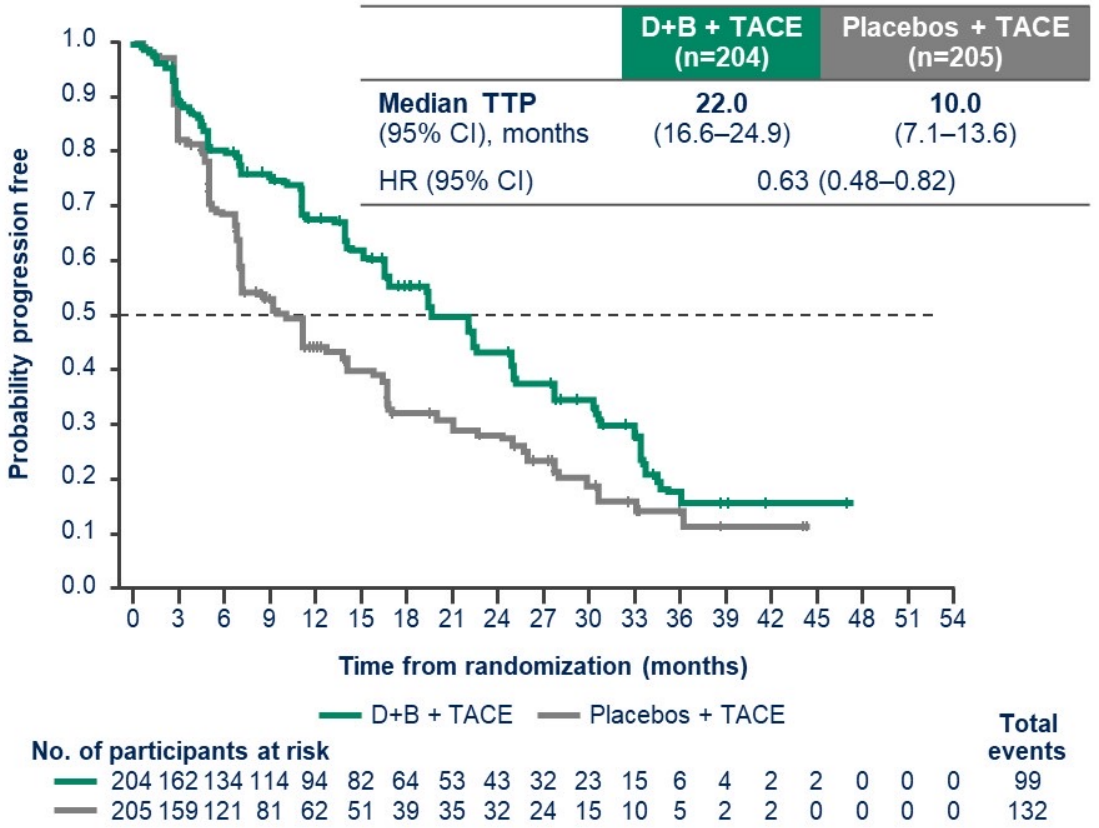
*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

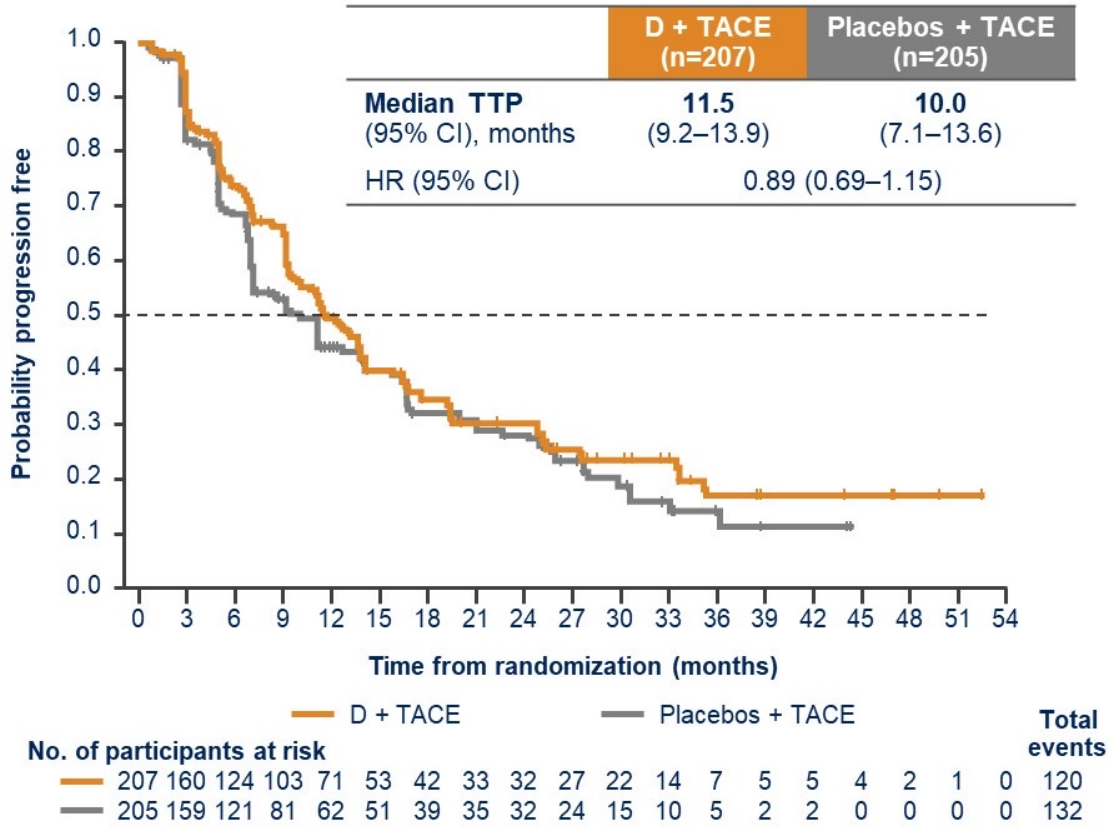
B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

PRESENTED BY: Riccardo Lencioni, MD

TTP

Median TTP was improved by 12 months with D+B + TACE versus placebos + TACE



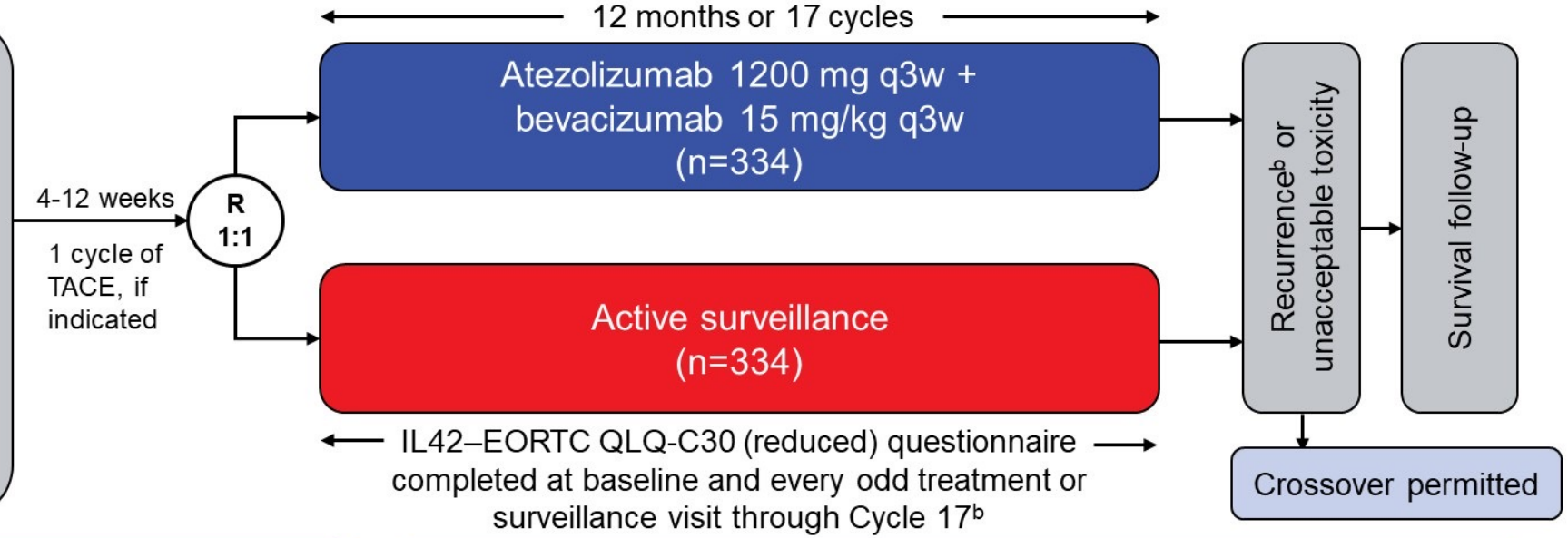


TTP was assessed by BICR (RECIST v1.1)
B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; mo, months; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; TTP, time to progression.

IMbrave050 study design

Patient Population

- Confirmed first diagnosis of HCC and had undergone curative resection or ablation
- Disease free
- Child-Pugh Class A
- High risk of recurrence[a]
- No extrahepatic disease or macrovascular invasion (except Vp1/Vp2)
- ECOG PS 0 or 1



Stratification

- Region (APAC excluding Japan vs rest of world)
- High-risk features and procedures:
  - Ablation
  - Resection, 1 risk feature, adjuvant TACE (yes vs no)
  - Resection, ≥2 risk features, adjuvant TACE (yes vs no)

Primary endpoint

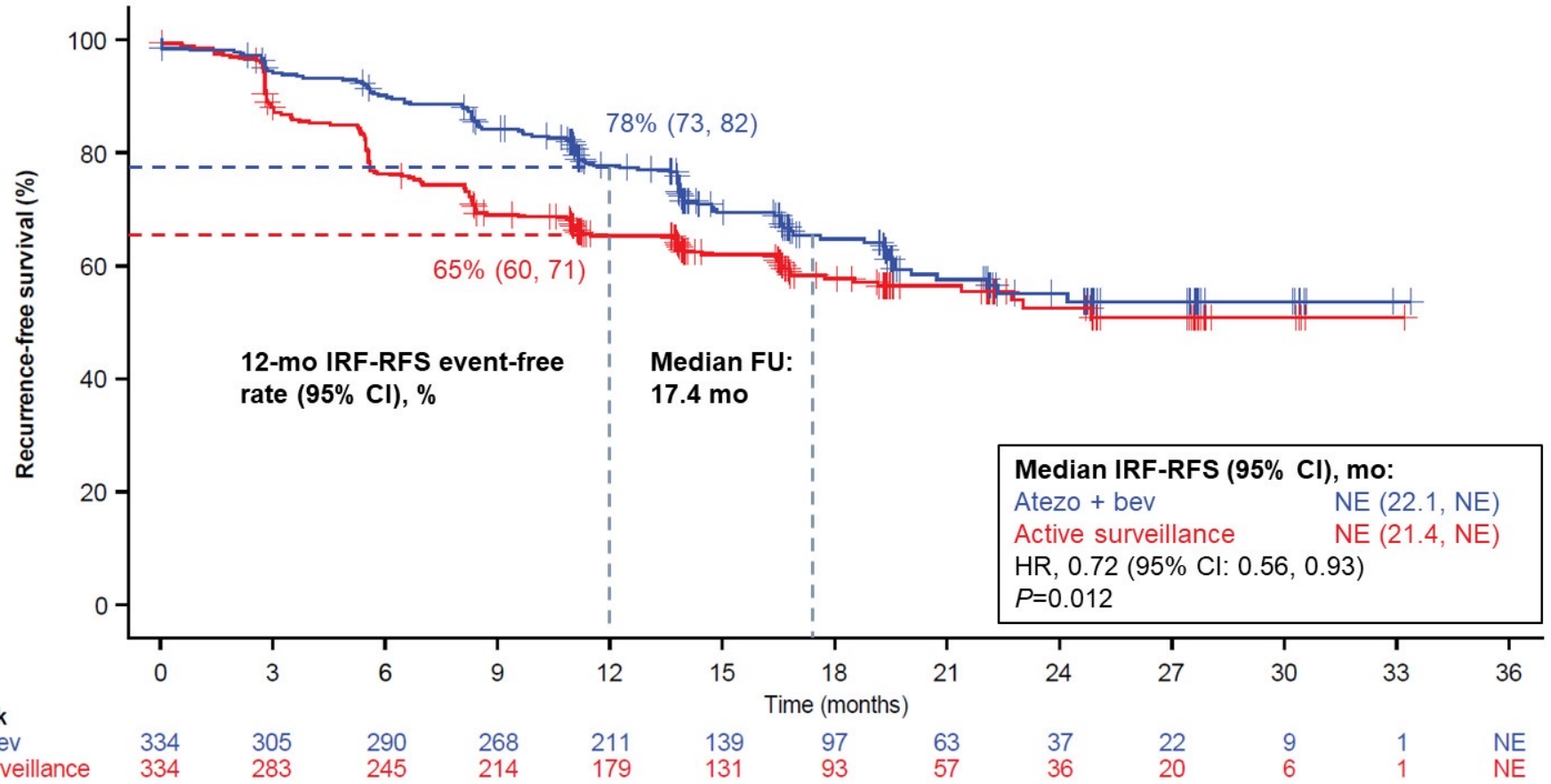
- Recurrence-free survival assessed by the independent review facility[c]

Prespecified exploratory PRO endpoints

- Change from baseline in GHS/QoL, and physical, role, emotional and social functioning
  - Clinically meaningful deterioration was defined as a ≥10-point decrease[2]

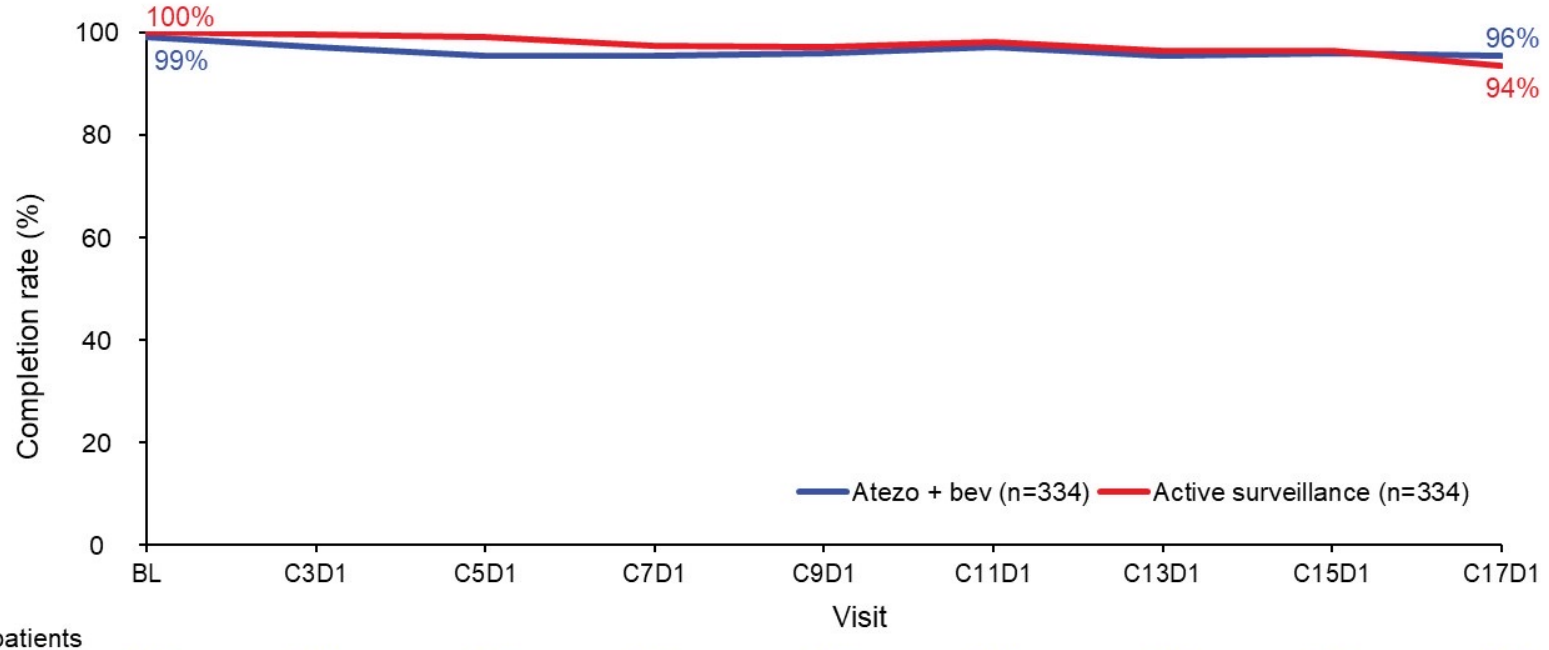
ClinicalTrials.gov, NCT04102098. ECOG, Eastern Cooperative Oncology Group; GHS, global health status; HCC, hepatocellular carcinoma; IL42–QLQ-C30, item-list 42 of the core 30-item quality of life questionnaire; q3w, every 3 weeks; QoL, quality of life; R, randomization; TACE, transarterial chemoembolization.
[a] High-risk features include: tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology. [b] Completion of the IL42–EORTC QLQ-C30 (reduced) questionnaire continued every 12 weeks for 1 year during the follow-up period. [c] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.
1. Chow et al. AACR 2023. Oral CT003. 2. Osoba et al. J Clin Oncol 1998;16:139-44.

Primary endpoint: IRF-assessed RFS was significantly improved with atezo + bev vs active surveillance



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. HR is stratified. *P* value is a log rank.
FU, follow-up; NE, not estimable.
1. Chow et al. AACR 2023. Oral CT003.

IL42–EORTC QLQ-C30 completion rates



No. of patients									
Atezo + bev	333	324	312	289	272	254	242	222	199
Active surveillance	331	326	319	296	282	257	248	230	217

- IL42–EORTC-C30 completion rates remained >93% in both arms from baseline through Cycle 17 of treatment or surveillance[a]
- Interpretation of analyses focused on data through Cycle 17, when over half of the population in each arm remained in the study

[a]Includes responses with ≥1 question completed.
Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.

RAISE

- Primary HCC who underwent radical resection and pathological diagnosis of HCC.
- The most narrow resection margin ≤1 cm.
- No tumor was found on postoperative CT or MR imaging in 4-6 weeks.
- ECOG PS ≤1.
- Child-Pugh score 5-7.
- Satisfactory blood, liver, and kidney function parameters.

Randomization 1:1

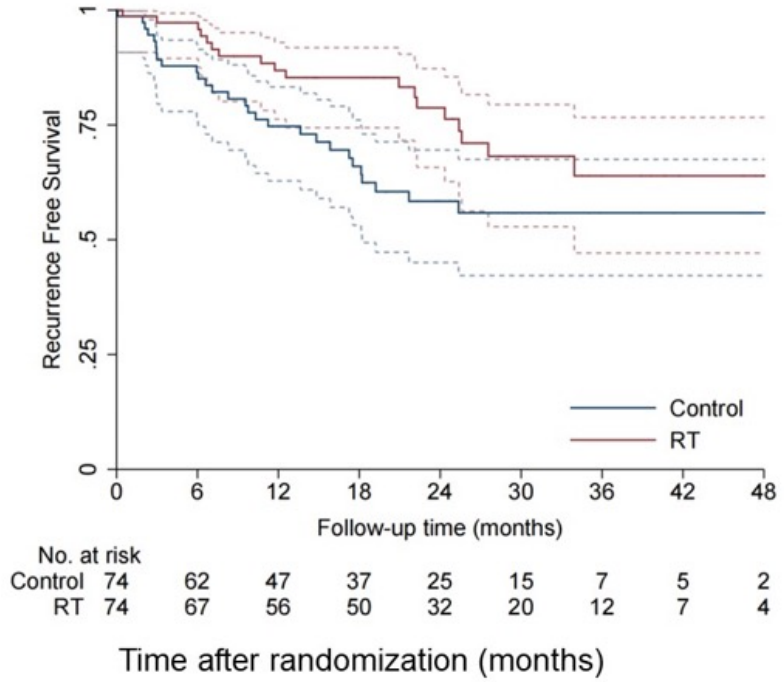
Stratification factors:
- MVI（+ vs -）
- Tumor size（≤5cm vs >5cm）

The radiotherapy group (n=74)
IMRT; 50Gy/25F

The control group (n=74)
Follow-up

- Primary outcome:
  Recurrence Free Survival
- Secondary outcome:
  Time To Recurrence
  Overall Survival,
  Safety

Recurrence-free Survival



Time after randomization (months)

	No. of Events/ No. of Patients	12-month RFS, % (95% CI)	24-month RFS, % (95% CI)
RT group （n = 74）	18/74(24.3%)	86.9 (76.3 to 93.0)	78.7 (65.8 to 87.3)
Control group （n = 74）	28/74(37.8%)	74.7 (62.8 to 83.3)	58.4 (45.1 to 69.6)

- The median follow-up period was 29.4 months
- The 2-year RFS was 78.74% vs 58.39%

  Stratified Hazard ratio, 0.55 (95% CI, 0.30 to 0.99),

  Stratified Log-rank P =0.043

TRIAL	IMBRAVE-050	RAISE
Clinical trial	RCT, Phase III	RCT, Phase II
Treatment- Active arm (vs active surveillance)	Atezolizumab + bevacizumab – 12 mo	Radiotherapy-IMRT (50Gy/25 fractions)
Patient characteristics		
Inclusion criteria	High-risk HCC recurrence	Resection with Margin < 1cm
Single (%), main diameter	91%, 5.3cm	86%, 4.1cm
Microvascular invasion	61%	35%
Study design- Results		
Primary end-point	RFS	RFS
Sample size	668	148
Magnitud of benefit (HR, 95%)	0.72 (0.53-0.98)	0.55 (0.30-0.99)
P value	0.012	0.043
Adverse events (TRAEs G3-4)	35%	<15%

- Time you enjoy wasting is not wasted time.”

Marthe Troly-Curtin