Pancreatic and Hepatobiliary Updates

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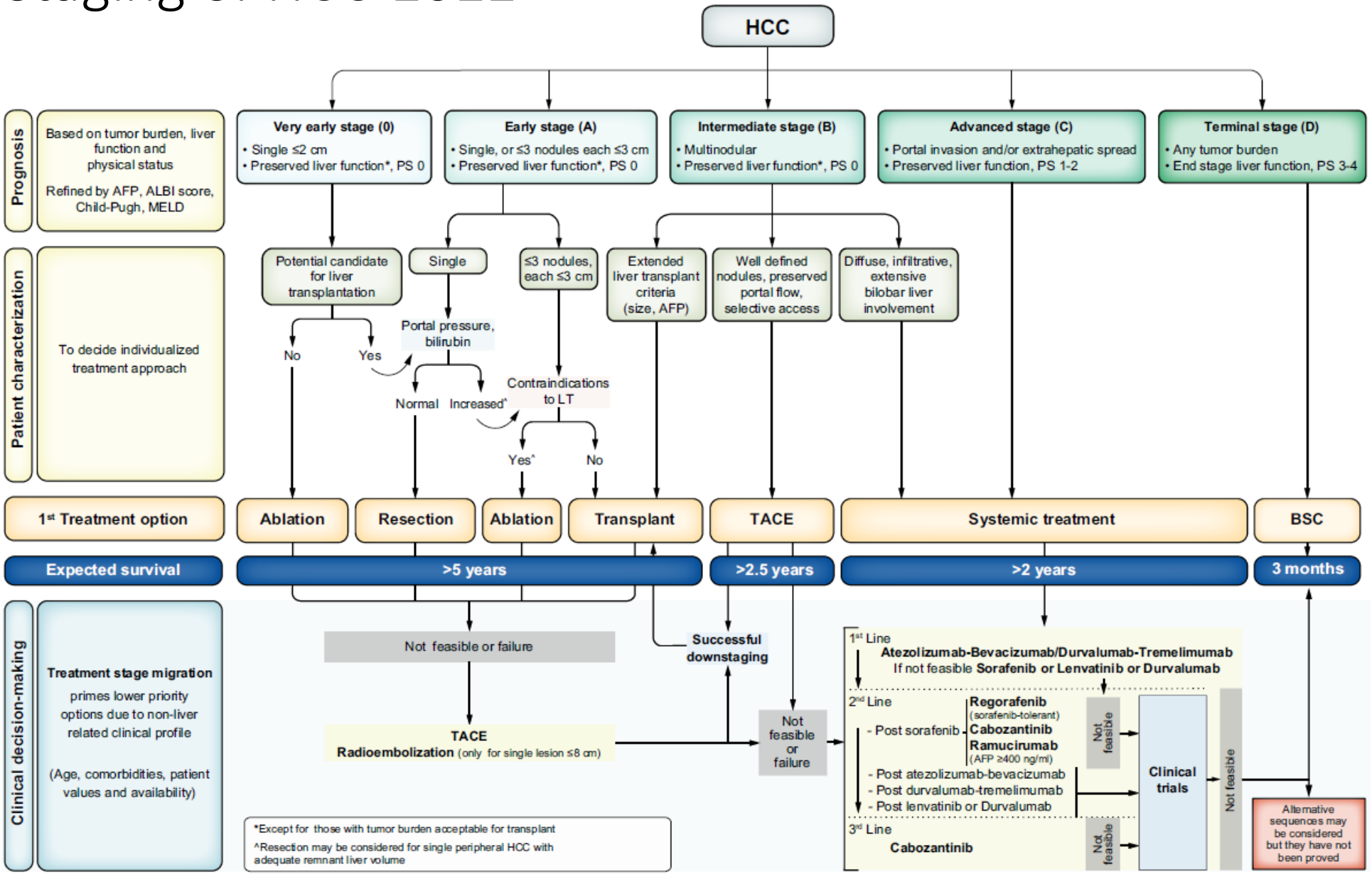
BCLC Staging of HCC-2022



- Reig M et al J Hep 2022

Advanced Stage (BCLC B/C)

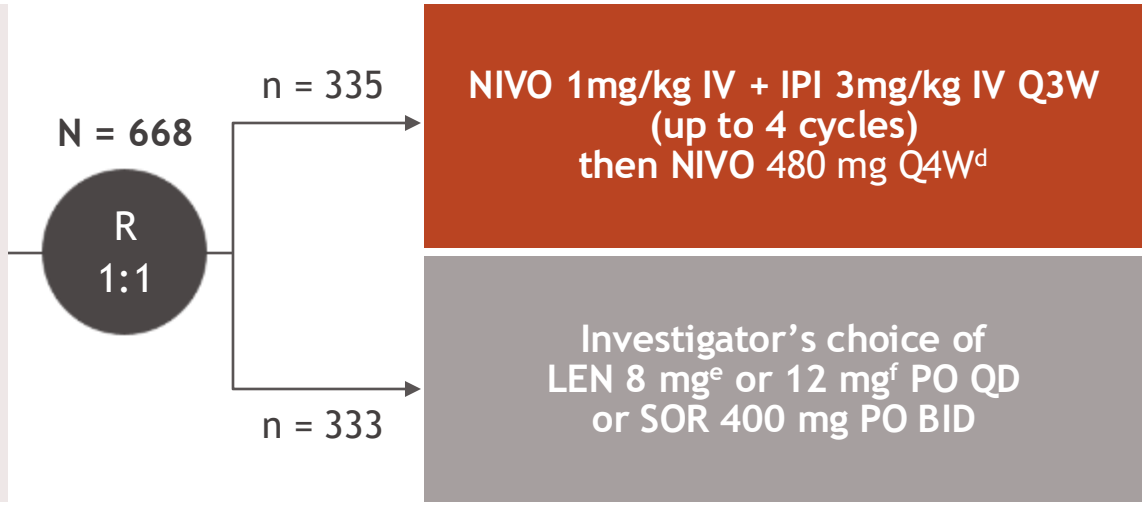
Positive Phase 3 Front-Line Studies in Advanced HCC

	SHARP	REFLECT	IMBRAVE 150	HIMALAYA	CARES 310	CHECKMATE 9DW
Control	placebo	sorafenib	sorafenib	sorafenib	sorafenib	Len (85%)/ sor
Treatment Arm	Sorafenib	Lenvatinib	Atezo-bev	Durva-treme	Rivoceranib/ camrelizumab	Ipi-nivo
VP4 included	yes	no	yes	no	yes	no
HR OS	0.69	0.92 (Non-inf)	0.58	0.78	0.62	0.79
• mOS	10.7 mos	13.6 mos	19.2 mos	16.43 mos	22.1 mos	23.7
HR PFS	0.58 (TTP)	0.66	0.59	0.90 (Not sig)	0.52	0.87 (Not sig)
• mPFS	5.5 mos (TTP)	7.4 mos	6.9 mos	3.78 mos	5.6 mos	9.1
ORR (RECIST)	2%	18.8 %	30%	20%	25%	36%
Reference	Llovet NEJM 2008	Kudo Lancet 2017	Finn NEJM 2020, Cheng J Hep 2022	Abou-Alfa NEJM Evidence 2022	Qin Lancet 2023	Galle ASCO 2024

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)



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

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

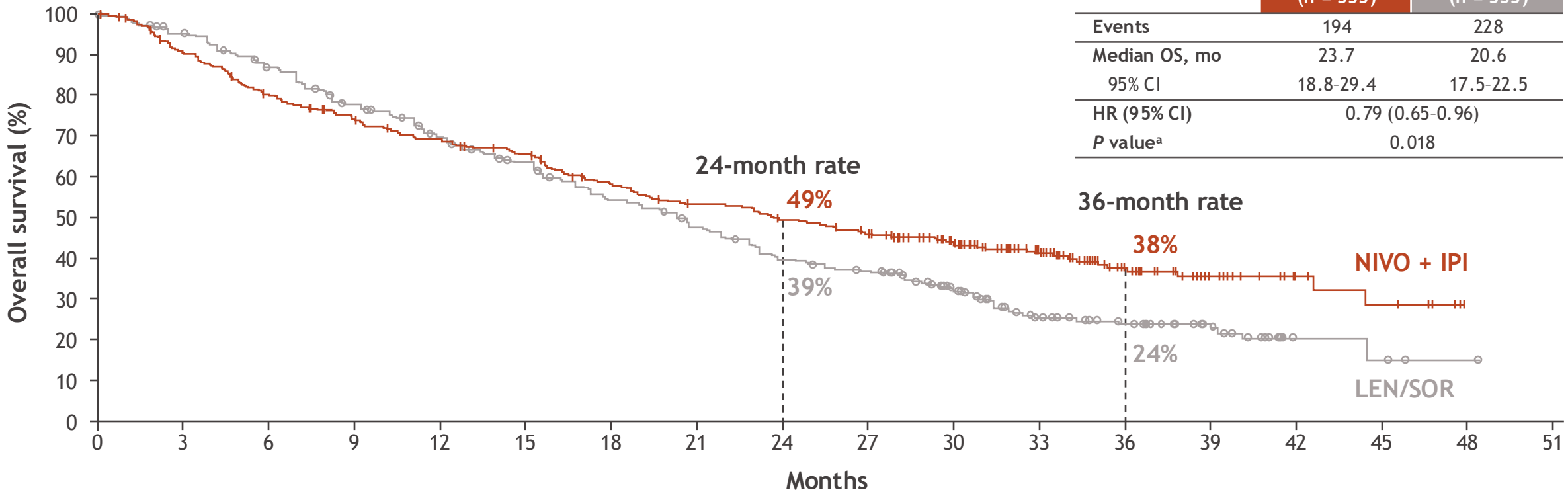
Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO + IPI arm only)

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

- 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



	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	

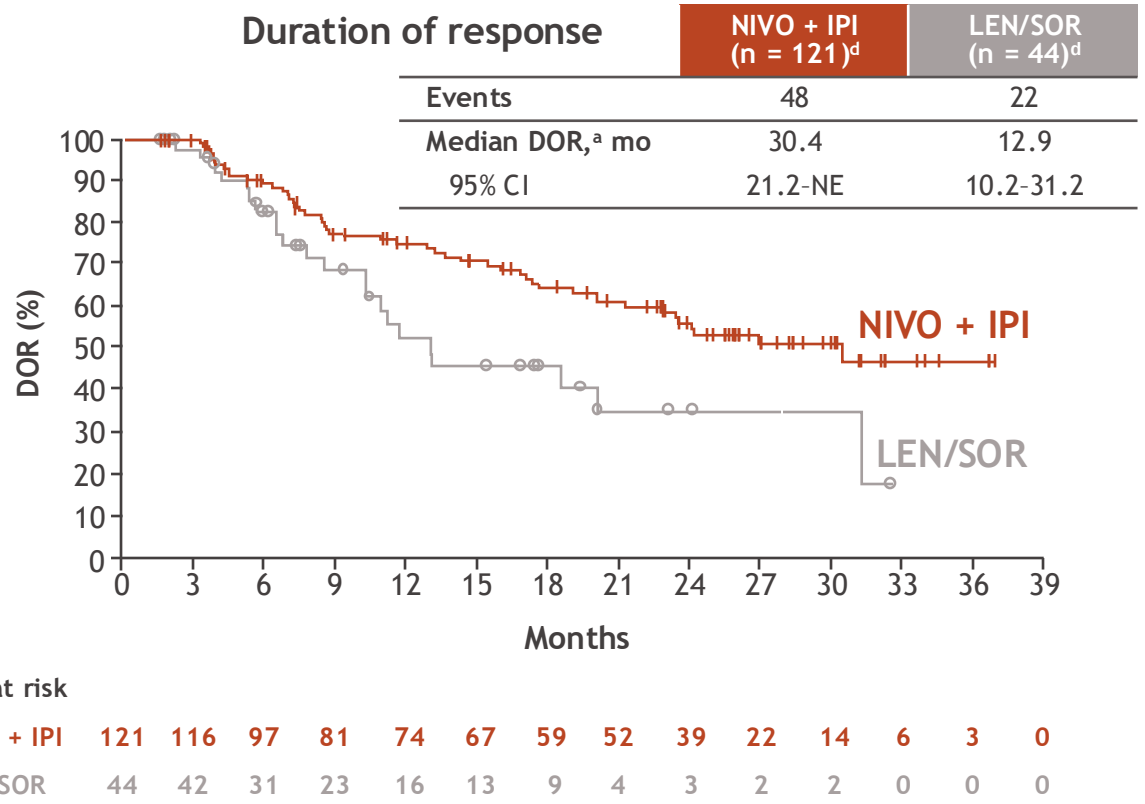
No. at risk																		
NIVO + IPI	335	300	264	239	220	206	179	162	150	137	104	71	42	24	11	8	0	0
LEN/SOR	333	310	280	245	216	194	164	144	116	106	76	44	34	20	4	3	1	0

- 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 (range) follow-up, 35.2 (26.8-48.9) 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.

Response and duration of response

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

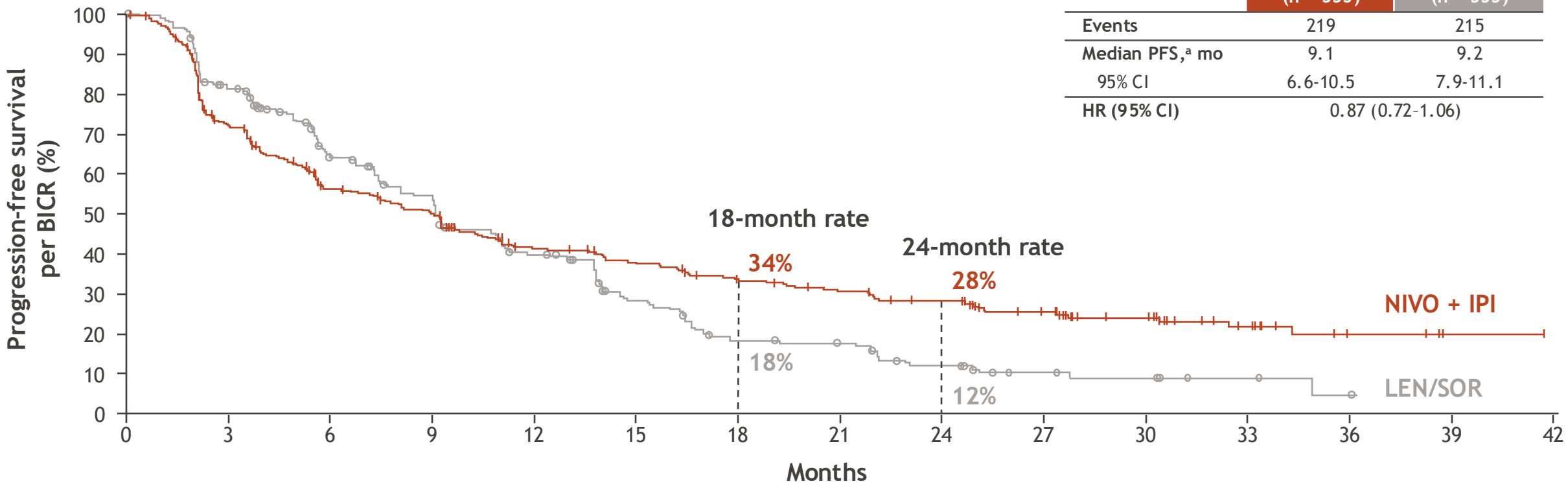


- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs LEN/SOR, with a higher CR rate (7% vs 2%, respectively) and durable responses

Median (range) follow-up, 35.2 (26.8-48.9) months. Symbols represent censored observations. [a]Assessed by BICR based on RECIST v1.1. [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]Number of confirmed responders.

Progression-free survival

	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Events	219	215
Median PFS,[a] mo	9.1	9.2
95% CI	6.6-10.5	7.9-11.1
HR (95% CI)	0.87 (0.72-1.06)	



No. at risk															
NIVO + IPI	335	224	160	140	103	92	78	69	61	45	29	16	6	1	0
LEN/SOR	333	242	164	131	82	52	30	26	16	8	6	3	1	0	0

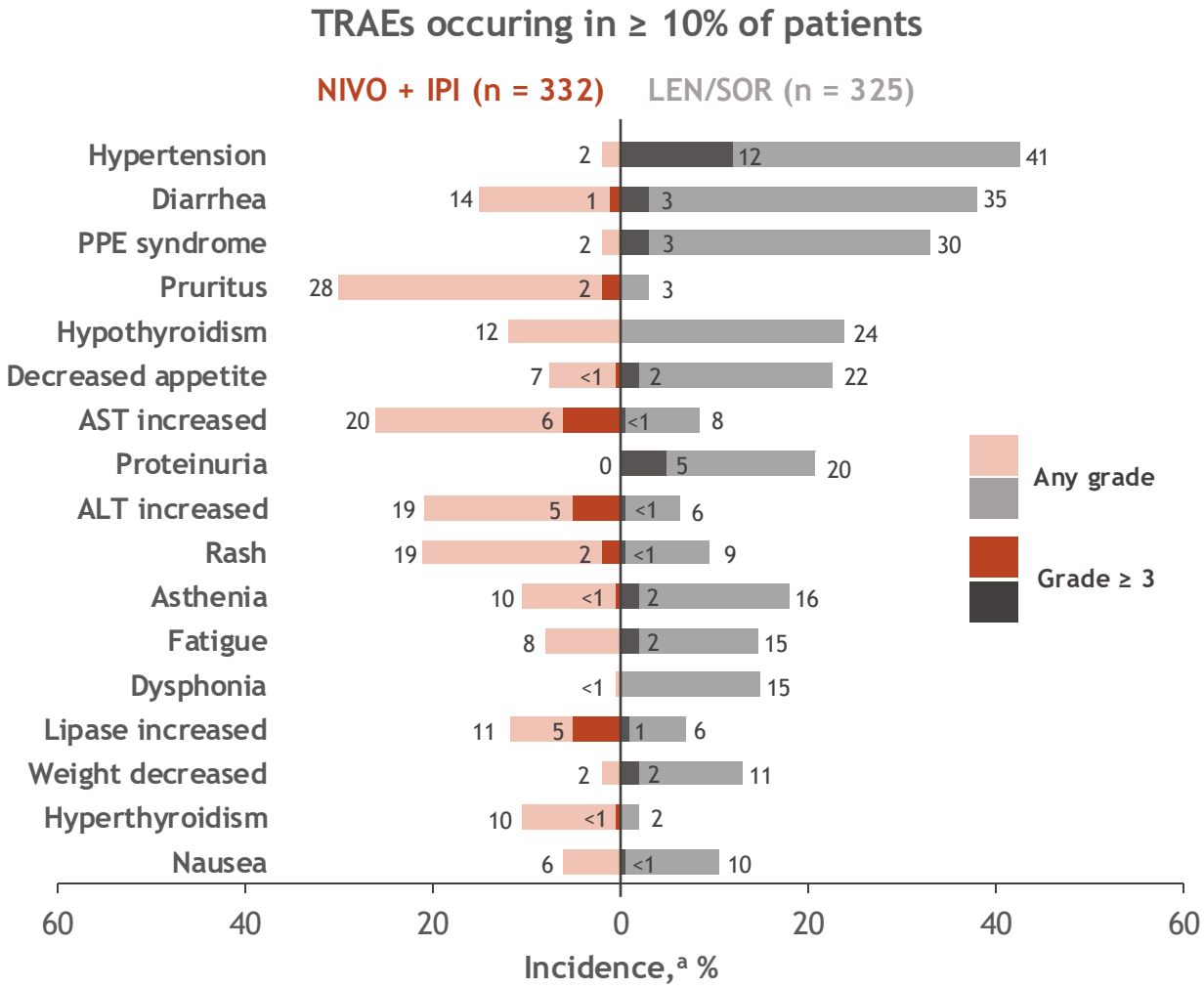
- Numerically higher PFS rates with NIVO + IPI vs LEN/SOR at 18 and 24 months

Median (range) follow-up, 35.2 (26.8-48.9) months. Median PFS 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]Assessed by BICR based on RECIST v1.1.

Treatment-related adverse events

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).

Immune-mediated adverse events

All treated patients, n (%)	NIVO + IPI (n = 332)			
	Any grade	Grade 3/4	Received high-dose steroids	Leading to discontinuation
Patients with IMAEs[a]	191 (58)	93 (28)	96 (29)	42 (13)
Hepatitis	63 (19)	51 (15)	56 (17)	19 (6)
Hypothyroidism/thyroiditis	62 (19)	1 (< 1)	2 (< 1)	0
Rash	51 (15)	14 (4)	10 (3)	1 (< 1)
Hyperthyroidism	36 (11)	2 (< 1)	3 (< 1)	0
Diarrhea/colitis	28 (8)	15 (5)	27 (8)	9 (3)
Adrenal insufficiency	18 (5)	6 (2)	2 (< 1)	4 (1)
Hypophysitis	9 (3)	4 (1)	3 (< 1)	4 (1)
Pneumonitis	7 (2)	3 (< 1)	6 (2)	3 (< 1)
Nephritis and renal dysfunction	5 (2)	3 (< 1)	3 (< 1)	2 (< 1)
Hypersensitivity	4 (1)	0	3 (< 1)	0
Diabetes mellitus	2 (< 1)	2 (< 1)	0	0

- The majority of IMAEs were grade 1 or 2, were manageable, and did not result in treatment discontinuation

[a]IMAEs are specific events considered as potential immune-mediated events by investigator, and include events reported between first dose and 100 days after last dose of study therapy, with the exception of endocrine events, which are treated with immune-modulating medication.

Early Stage (BCLC 0/A)

Ongoing Phase 3 Trials of Adjuvant Immunotherapy[1-4]

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

EMERALD-2	CheckMate-9DX	IMbrave050	KEYNOTE-937
• Durvalumab ± bevacizumab + vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Nivolumab vs placebo • ECOG PS 0-1 • Primary endpoint: RFS	• Atezolizumab + bevacizumab vs active surveillance • ECOG PS 0-1 • Primary endpoint: RFS	• Pembrolizumab vs placebo • ECOG PS 0 • AFP <400 ng/mL • Primary endpoint: RFS and OS

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

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

4-12 weeks

1 cycle of TACE, if indicated

R 1:1

12 months or 17 cycles

Atezolizumab 1200 mg q3w + bevacizumab 15 mg/kg q3w (n=334)

Active surveillance (n=334)

Recurrence[b] or unacceptable toxicity

Survival follow-up

Crossover permitted

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[b]

ClinicalTrials.gov, NCT04102098. ECOG PS; Eastern Cooperative Oncology Group performance status; Q3W, every three weeks; 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] Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

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High-risk criteria by curative treatment

Curative treatment	Criteria for high risk of HCC recurrence
Resection	▪ ≤3 tumors, with **largest tumor >5 cm** regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ▪ **≥4 tumors**, with largest tumor ≤5 cm regardless of vascular invasion,[a] or poor tumor differentiation (Grade 3 or 4) ▪ ≤3 tumors, with largest tumor ≤5 cm with **vascular invasion**,[a] and/or **poor tumor differentiation** (Grade 3 or 4)
Ablation[b]	▪ 1 tumor >2 cm but ≤5 cm ▪ Multiple tumors (≤4 tumors), all ≤5 cm

[a] Microvascular invasion or minor macrovascular portal vein invasion of the portal vein—Vp1/Vp2.
[b] Ablation must be radiofrequency ablation or microwave ablation.

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Baseline characteristics were balanced across treatment arms

Characteristic	Atezo + bev (n=334)	Active surveillance (n=334)
Median age (range), years	60 (19-89)	59 (23-85)
Male sex, n (%)	277 (82.9)	278 (83.2)
Ethnicity, n (%)		
Asian	276 (82.6)	269 (80.5)
White	35 (10.5)	41 (12.3)
Other	23 (6.9)	24 (7.2)
Geographic region, n (%)		
Asia Pacific excluding Japan | rest of world	237 (71.0) | 97 (29.0)	238 (71.3) | 96 (28.7)
ECOG PS score, n (%)		
0 | 1	258 (77.2) | 76 (22.8)	269 (80.5) | 65 (19.5)
PD-L1 status, n (%)[a,b]		
≥1% | <1%	154 (54.0) | 131 (46.0)	140 (50.2) | 139 (49.8)
Etiology, n (%)		
Hepatitis B	209 (62.6)	207 (62.0)
Hepatitis C	34 (10.2)	38 (11.4)
Non viral | unknown	45 (13.5) | 46 (13.8)	38 (11.4) | 51 (15.3)
BCLC stage at diagnosis, n (%)		
0	2 (0.6)	3 (0.9)
A	287 (85.9)	277 (82.9)
B	25 (7.5)	32 (9.6)
C	20 (6.0)	22 (6.6)

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. BCLC; Barcelona Clinic Liver Cancer.
[a] n=285 for atezo + bev and 279 for active surveillance. [b] PD-L1 expression is defined as the total percentage of the tumor area covered by tumor and immune cells stained for PD-L1 using the SP263 immunohistochemistry assay (VENTANA).

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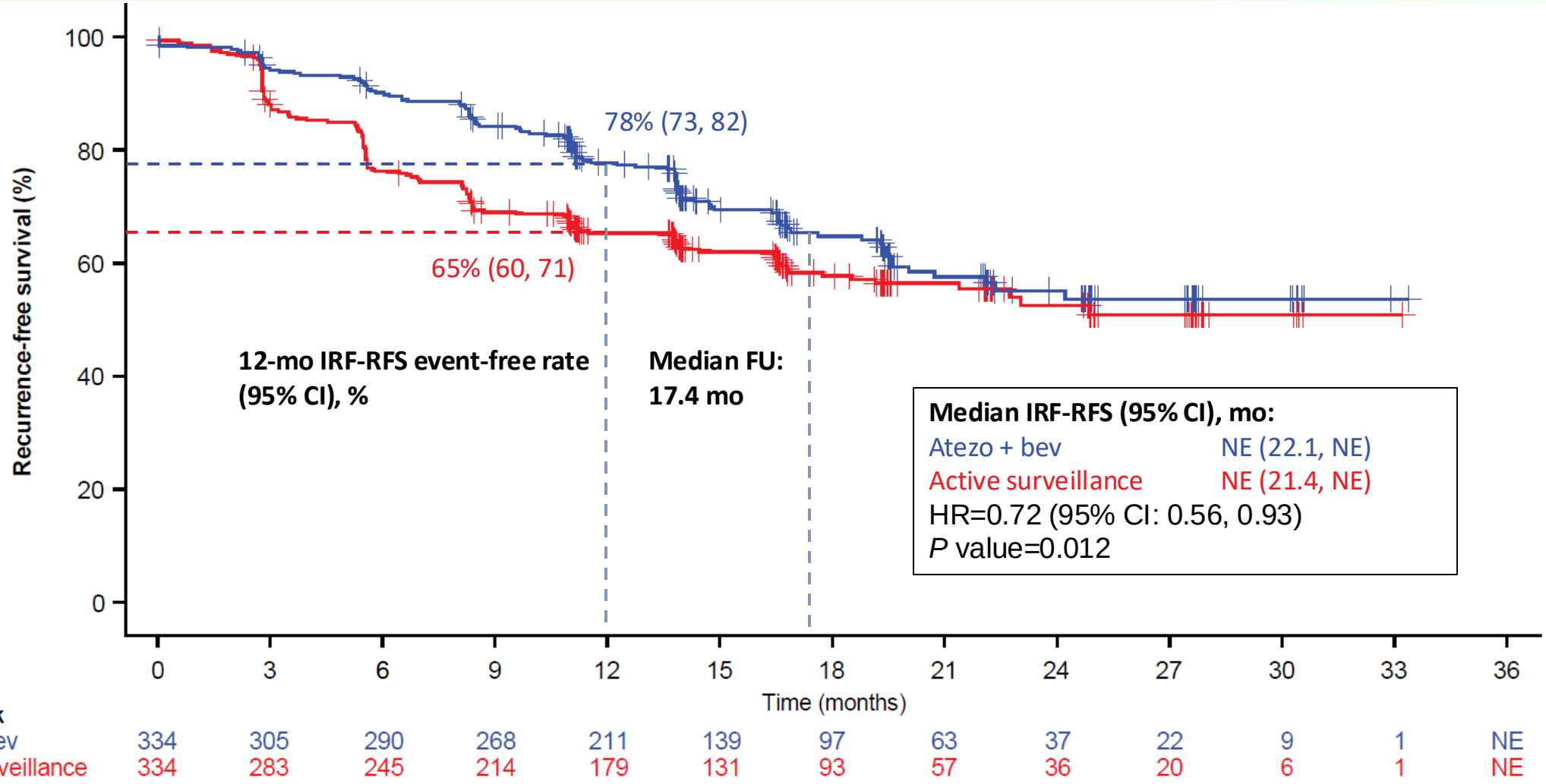
Primary endpoint: IRF-assessed RFS was significantly improved with atezo + bev vs active surveillance



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.
FU, follow-up; NE, not estimable. HR is stratified. *P* value is a log rank.

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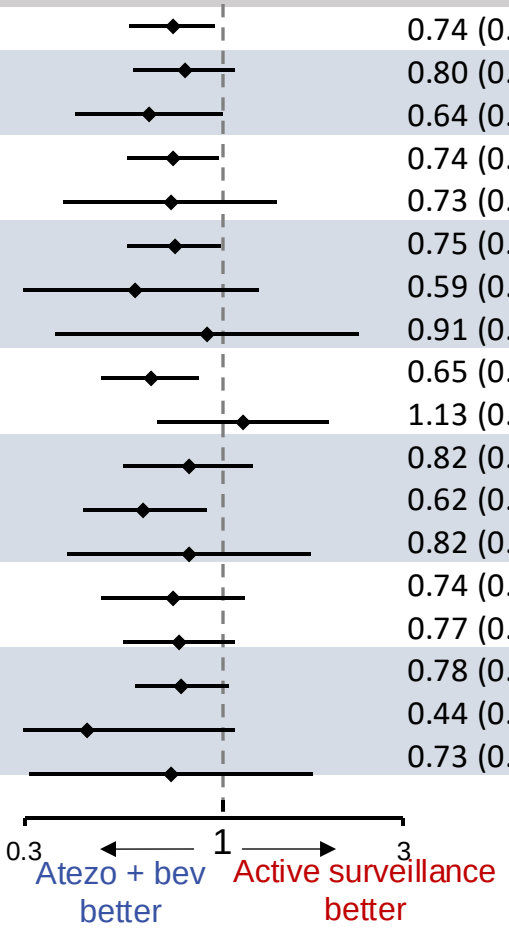
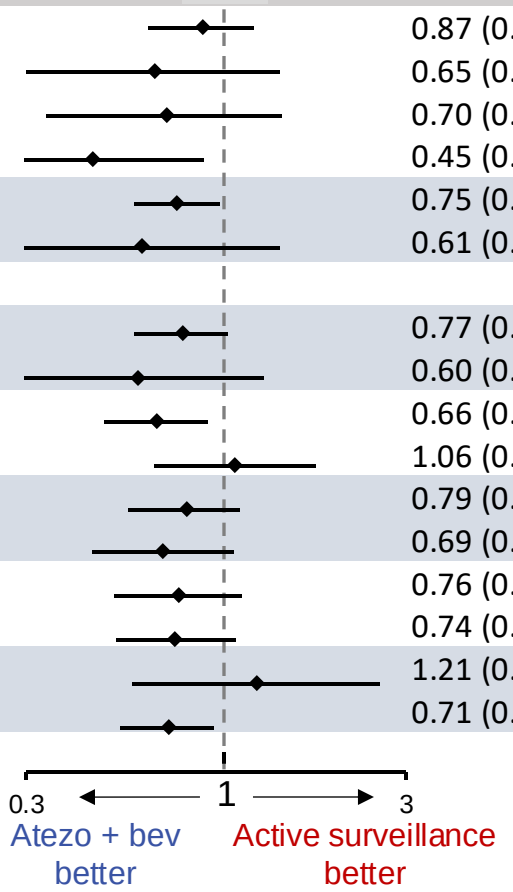
IRF-assessed RFS subgroups

Baseline risk factors	No. of patients	Unstratified HR (95% CI)
All patients	668	0.74 (0.57, 0.95)
<65 years old	427	0.80 (0.58, 1.08)
≥65 years old	241	0.64 (0.41, 1.00)
Male	555	0.74 (0.56, 0.98)
Female	113	0.73 (0.38, 1.40)
Asian	545	0.75 (0.56, 0.99)
White	78	0.59 (0.28, 1.25)
Other race	45	0.91 (0.36, 2.29)
ECOG PS 0	527	0.65 (0.48, 0.87)
ECOG PS 1	141	1.13 (0.67, 1.91)
PD-L1 ≥1%	294	0.82 (0.55, 1.20)
PD-L1 <1%	270	0.62 (0.43, 0.91)
Unknown PD-L1	104	0.82 (0.39, 1.71)
1 high-risk feature[a]	311	0.74 (0.48, 1.14)
≥2 high-risk features[a]	274	0.77 (0.55, 1.08)
BCLC 0/A	569	0.78 (0.59, 1.04)
BCLC B	57	0.44 (0.18, 1.08)
BCLC C	42	0.73 (0.31, 1.73)



Baseline risk factors	No. of patients	Unstratified HR (95% CI)
Hepatitis B etiology	416	0.87 (0.63, 1.20)
Hepatitis C etiology	72	0.65 (0.30, 1.40)
Non-viral etiology	83	0.70 (0.34, 1.42)
Unknown etiology	97	0.45 (0.23, 0.89)
Resection	585	0.75 (0.58, 0.98)
Ablation	83	0.61 (0.26, 1.41)
In patients who underwent resection		
1 tumor	526	0.77 (0.58, 1.03)
>1 tumors	59	0.60 (0.28, 1.27)
Tumor size >5 cm	327	0.66 (0.48, 0.91)
Tumor size ≤5 cm	258	1.06 (0.65, 1.74)
mVI present	354	0.79 (0.56, 1.10)
mVI absent	231	0.69 (0.45, 1.06)
Poor tumor differentiation	245	0.76 (0.51, 1.12)
No poor tumor differentiation	340	0.74 (0.52, 1.07)
Received TACE	66	1.21 (0.57, 2.59)
Did not receive TACE	519	0.71 (0.53, 0.94)



Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.
mVI, microvascular invasion. [a] Patients who underwent ablation were categorized as "not applicable."

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Safety summary

	Atezo + bev (n=332)	Active surveillance (n=330)	IMbrave150[1,2] (n=329)
Treatment duration, median, mo	Atezo: 11.1 Bev: 11.0	NA	Atezo: 7.4 Bev: 6.9
Patients with ≥1 AE, n (%)	326 (98.2)	205 (62.1)	323 (98.2)
Treatment-related AE	293 (88.3)	NA	276 (83.9)
Grade 3/4 AE, n (%)	136 (41.0)	44 (13.3)	186 (56.5)
Treatment-related Grade 3/4 AE	116 (34.9)	NA	117 (35.6)
Serious AE, n (%)	80 (24.1)	34 (10.3)	125 (38.0)
Treatment-related serious AE	44 (13.3)	NA	56 (17.0)
Grade 5 AE, n (%)	6 (1.8)	1 (0.3)	15 (4.6)
Treatment-related Grade 5 AE	2 (0.6)[a]	NA	6 (1.8)
AE leading to dose interruption of any study treatment, n (%)	155 (46.7)	NA	163 (49.5)
AE leading to withdrawal from any study treatment, n (%)	63 (19.0)	NA	51 (15.5)

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. In safety-evaluable patients. AE, adverse event. NA, not available.
[a] Esophageal varices hemorrhage and ischemic stroke; 1 was related to atezo and bev and the other was related to bev only.
1. Finn et al. NEJM 2020. 2. Data on file.

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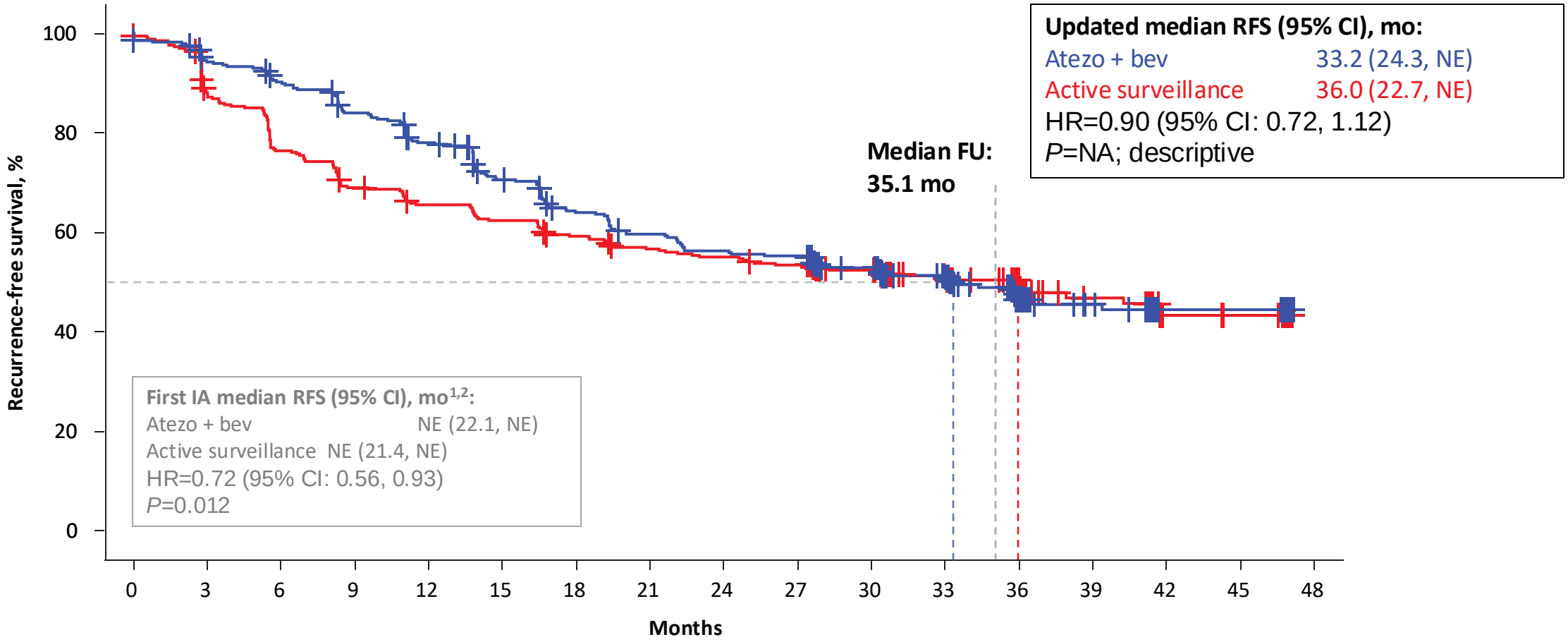
Early RFS benefit was not maintained with longer follow-up



No. at risk																	
Atezo + bev	334	305	290	268	245	216	191	177	167	164	147	123	62	45	18	18	NE
Active surveillance	334	285	247	221	207	197	185	175	170	164	145	124	63	42	16	14	NE

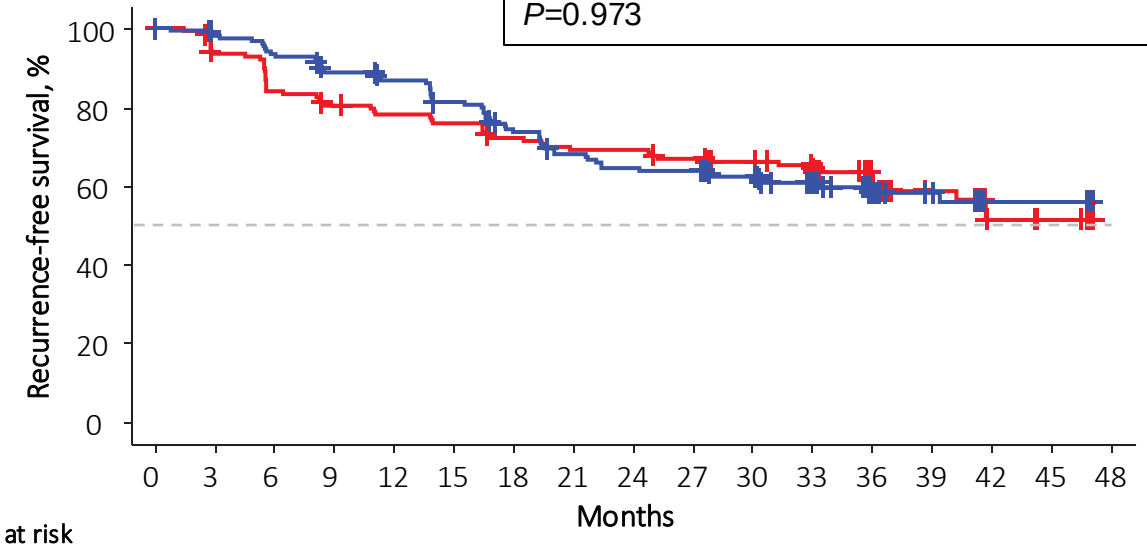
Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. At clinical cutoff, 162 of 334 patients (49%) in the atezo + bev arm and 164 of 334 (49%) in the active surveillance arm experienced disease recurrence or death. HRs are stratified. *P* values are log rank.
FU, follow-up; NA, not applicable; NE, not estimable. 1. Qin et al. Lancet 2023. 2. Chow et al. AACR 2023 [abstract CT003].

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

RFS among resection patients was numerically better in those who were outside up-to-7 criteria

Within up-to-7 criteria

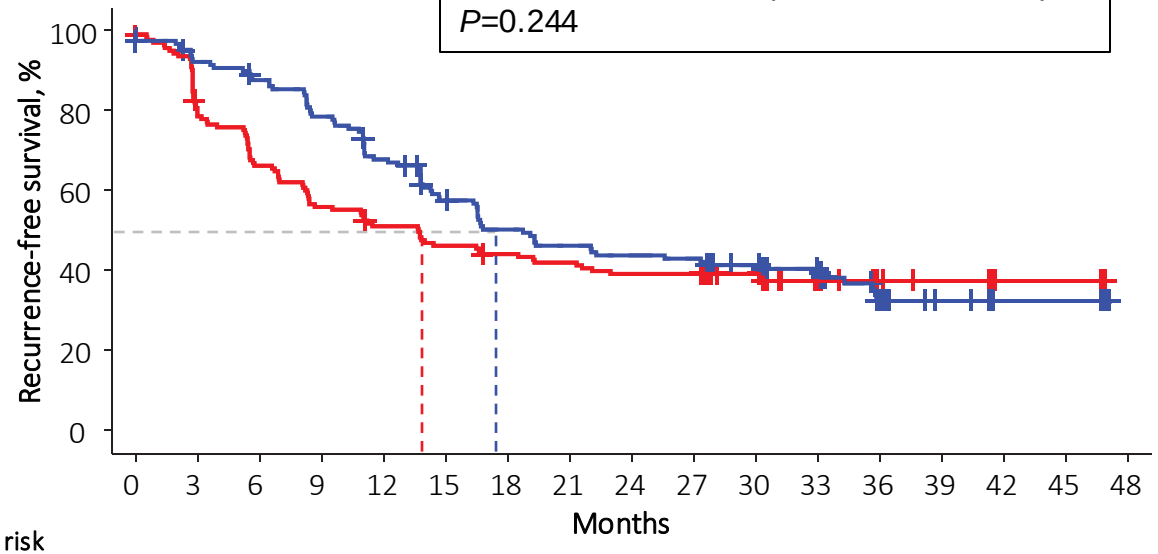
Post hoc median RFS (95% CI), mo:
Atezo + bev NE (35.9, NE)
Active surveillance NE (36.1, NE)
Unstratified HR=1.01 (95% CI: 0.70, 1.46)
P=0.973



No. at risk																	
Atezo + bev	158	148	141	132	127	118	105	96	91	90	84	70	35	26	7	7	NE
Active surveillance	144	128	115	109	105	102	96	92	92	88	83	75	42	27	9	7	NE

Outside up-to-7 criteria

Post hoc median RFS (95% CI), mo:
Atezo + bev 16.9 (14.7,27.6)
Active surveillance 13.7 (8.4,19.4)
Unstratified HR=0.84 (95% CI: 0.62, 1.13)
P=0.244



No. at risk																	
Atezo + bev	135	122	115	103	88	72	62	57	54	53	46	39	18	11	7	7	NE
Active surveillance	148	117	96	81	73	66	62	59	55	55	45	35	11	9	5	5	NE

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

First post-recurrence treatment

	Atezo + bev (n=147)	Active surveillance (n=156)
Curative intent, n (%)	49 (33.3)	59 (37.8)
Resection	28 (19.0)	28 (17.9)
Radiofrequency ablation	17 (11.6)	17 (10.9)
Microwave ablation	4 (2.7)	13 (8.3)
Other	0	1 (0.6)
Locoregional, n (%)	45 (30.6)	18 (11.5)
Embolisation	32 (21.8)	13 (8.3)
Radiation	13 (8.8)	5 (3.2)
Systemic therapy, n (%)	33 (22.4)	72 (46.2)
Atezolizumab + bevacizumab	3 (2.0)	61 (39.1)
Immunotherapy	2 (1.4)	2 (1.3)
Immunotherapy + TKI/immunotherapy + VEGF(R) mAb	11 (7.5)	2 (1.3)
Other	4 (2.7)	1 (0.6)
TKI	12 (8.2)	6 (3.8)
VEGF(R) mAb	1 (0.7)	0

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. Recurrence was assessed by the investigator. For the active surveillance arm, resection/radiofrequency ablation/microwave ablation received at crossover screening and crossover atezo + bev treatment, whichever was the first, was included. mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor; VEGF(R), vascular endothelial growth factor (receptor).

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

Recurrence patterns

First post-baseline unequivocal recurrence

	Atezo + bev (n=334)	Active surveillance (n=334)
Patients with recurrence, n	141	160
Location of recurrence, n (%)		
Intrahepatic only	103 (73.0)	109 (68.1)
Extrahepatic only	35 (24.8)	44 (27.5)
Both intra- and extrahepatic	3 (2.1)	7 (4.4)
Outside Milan criteria, n (%)		
Yes	51 (36.2)	67 (41.9)
No	89 (63.1)	89 (55.6)
NA[a]	1 (0.7)	4 (2.5)
Outside up-to-7 criteria, n (%)		
Yes	51 (36.2)	67 (41.9)
No	89 (63.1)	89 (55.6)
NA[a]	1 (0.7)	4 (2.5)

Patients with intrahepatic recurrence
(regardless of extrahepatic recurrence)

	Atezo + bev (n=334)	Active surveillance (n=334)
Intrahepatic recurrence, n	106	116
Macrovascular invasion, n (%)		
Yes	14 (13.2)	15 (12.9)
No	92 (86.8)	100 (86.2)
Not evaluable	0	1 (0.9)
Tumour liver lobe invasion, n (%)		
Unilobar	99 (93.4)	110 (94.8)
Bilobar	7 (6.6)	6 (5.2)

Clinical cutoff: 3 May 2024; median follow-up duration: 35.1 mo. [a] Patients were considered NA for Milan and up-to-7 criteria if they did not have extrahepatic spread or MVI and had ≥1 non-measurable lesion.

Yopp et al.
IMbrave050 update
https://ter.li/q4cyl1

Intermediate Stage (BCLC B)

Key ongoing trials in intermediate-stage HCC

	Study name	No. of patients enrolled	Investigational arm(s)	Control arm	Primary endpoint(s)
TACE + systemic therapy vs TACE	EMERALD-1[1]	724	TACE + durvalumab + bevacizumab TACE + durvalumab	TACE + placebo	PFS (BICR)
	EMERALD-3[2]	725*	TACE + tremelimumab + durvalumab + lenvatinib TACE + tremelimumab + durvalumab	TACE	PFS (BICR) in lenvatinib arm vs control arm
	LEAP-012[3]	450*	TACE + pembrolizumab + lenvatinib	TACE + placebo (IV + oral)	PFS (RECIST 1.1 by BICR) and OS
	TACE-3[4]	522*	TACE + nivolumab	TACE	OS and TTTP
	TALENTACE[5]	342	TACE + atezolizumab + bevacizumab	TACE	PFS (INV) and OS
Systemic therapy vs TACE	ABC-HCC[6]	434*	Atezolizumab + bevacizumab	TACE	Time to failure of treatment strategy
	REPLACE[7]	496*	Pembrolizumab + regorafenib	TACE or TARE	PFS (INV; mRECIST)

Information based on clinicaltrials.gov (accessed September 2024)
*Estimated enrolment
TTTP, time to TACE progression
Producto/indicación no autorizada. Uso experimental. Product/indication not approved. Experimental use

1. NCT03778957; 2. NCT05301842; 3. NCT04246177
4. NCT04268888; 5. NCT04712643; 6. NCT04803994; 7. NCT04777851

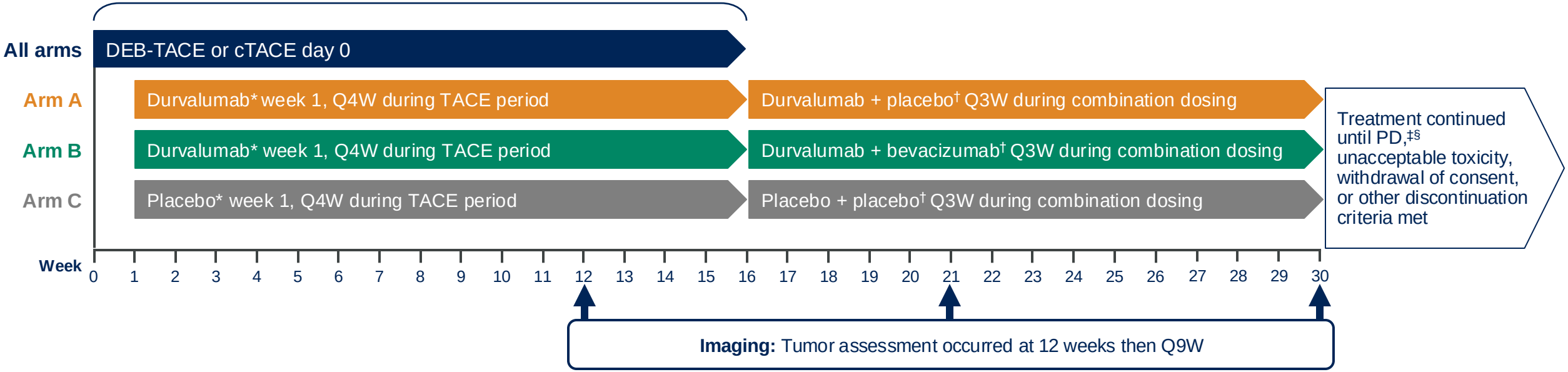
EMERALD-1 study schema

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

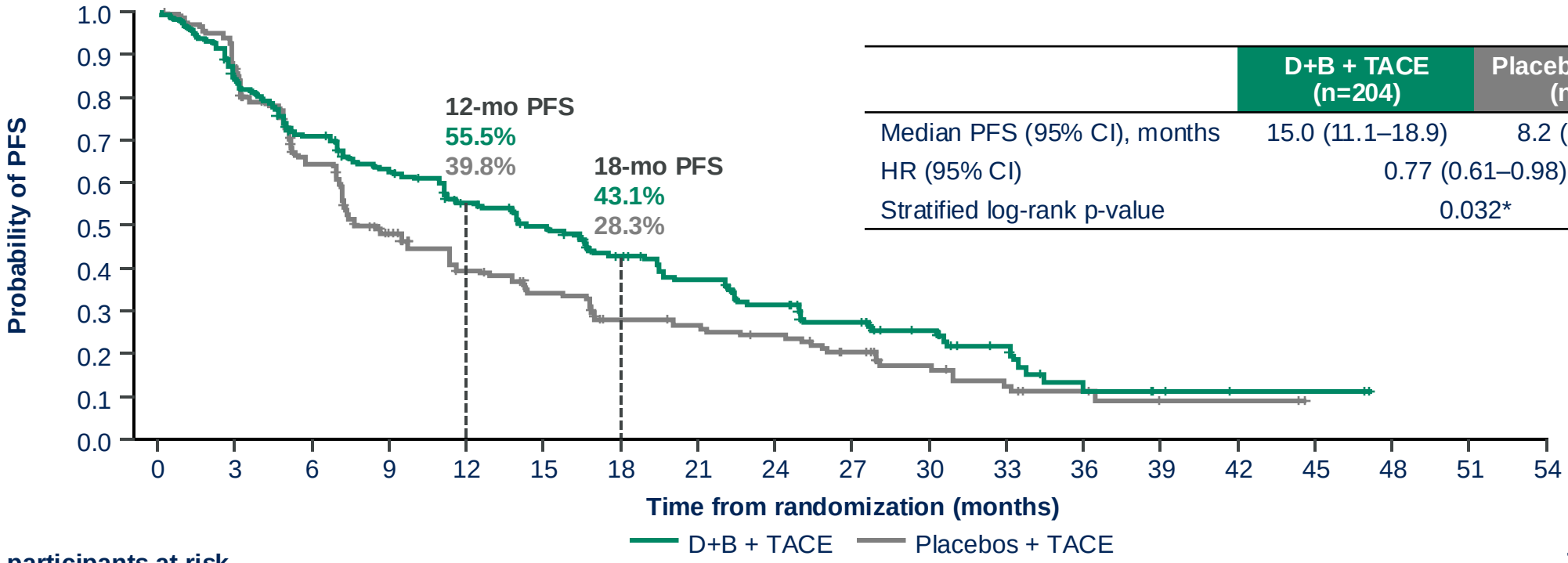


*Durvalumab / placebo started at least 7 days after TACE; doses moved to accommodate TACE if necessary. Durvalumab 1500 mg. Durvalumab / placebo Q4W until ≥14 days after last TACE. †Durvalumab 1120 mg. Bevacizumab 15 mg/kg. Durvalumab / bevacizumab / placebos Q3W. ‡Investigator-determined mRECIST-defined radiological disease progression. §Participants with mRECIST-defined progression may continue to receive study treatment, including additional TACE, at the discretion of the investigator and participant, and in consultation with the AstraZeneca study physician.

cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead-transarterial chemoembolization; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; TACE, transarterial chemoembolization; Q3W / Q4W / Q9W, every 3 / 4 / 9 weeks.

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.

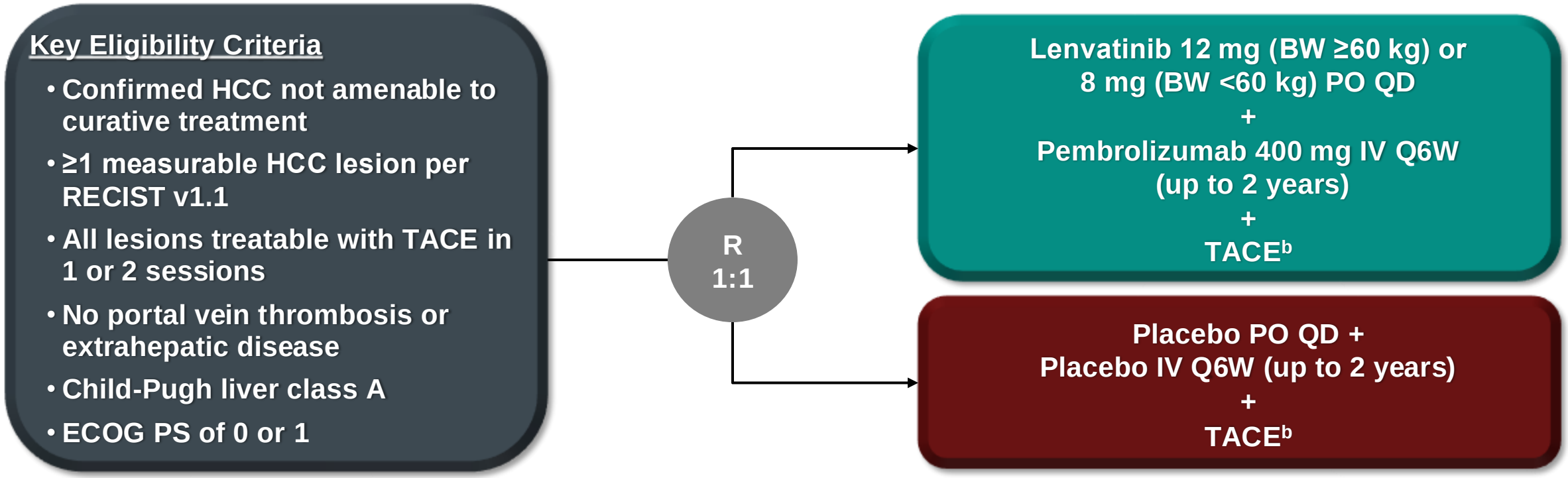
B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

LEAP-012: A Phase 3 Study of Lenvatinib Plus Pembrolizumab Plus Transarterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma

Josep M. Llovet[1]; Richard S. Finn[2]; Zhenggang Ren[3]; Yabing Guo[4]; Guohong Han[5]; Hailan Lin[6]; Jinfang Zheng[7]; Sadahisa Ogasawara[8]; Hailiang Li[9]; Ji Hoon Kim[10]; Haitao Zhao[11]; Chuan Li[12]; David C. Madoff[13]; R. Mark Ghobrial[14]; Anthony B. El-Khoueiry[15]; Arndt Vogel[16]; Xiang Peng[17]; Kalgi Mody[18]; Leonid Dubrovsky[17]; Masatoshi Kudo[19]

[1]Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Division of Hematology/Oncology, Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [3]Zhongshan Hospital, Fudan University, Shanghai, China; [4]Liver Tumor Center, Nanfang Hospital, Southern Medical University, Guangzhou, China; [5]Digestive Diseases Hospital, Xi'an International Medical Center Hospital, Northwest University, Xi'an, China; [6]Fujian Cancer Hospital and Fujian Medical University Cancer Hospital, Fuzhou, China; [7]Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, Haikou, China; [8]Graduate School of Medicine, Chiba University, Chiba, Japan; [9]Henan Cancer Hospital, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; [10]Korea University Guro Hospital, Seoul, Republic of Korea; [11]Peking Union Medical College Hospital, Beijing, China; [12]West China Hospital of Sichuan University, Chengdu, China; [13]Section of Interventional Radiology, Yale School of Medicine, New Haven, CT, USA; [14]Sherrie and Alan Conover Center for Liver Disease and Transplantation, JC Walter Jr. Center for Transplantation, Houston Methodist Hospital, Houston, TX, USA; [15]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [16]Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [17]Merck and Co., Inc., Rahway, NJ, USA; [18]Eisai, Nutley, NJ, USA; [19]Kindai University Faculty of Medicine, Osaka, Japan

LEAP-012 Study Design (NCT04246177)



Stratification Factors

- Study site
- Alpha fetoprotein (≤400 ng/mL vs >400 ng/mL)
- ECOG PS (0 vs 1)
- ALBI grade (1 vs 2 or 3)
- Tumor burden score[1,a] (≤6 vs >6 but ≤12 vs >12)

End Points

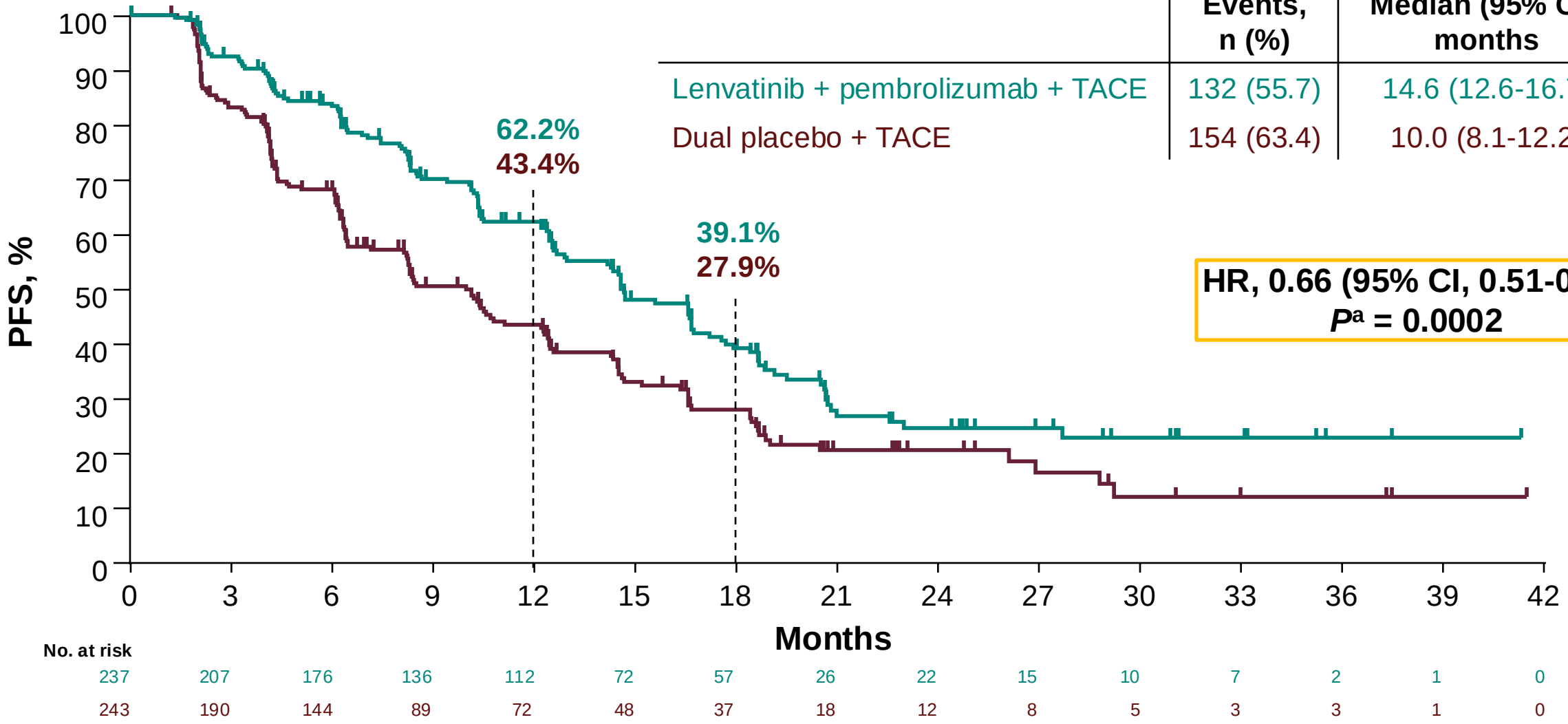
- Primary: PFS[c] and OS
  - IA1 is the final analysis for PFS
  - Initial alpha of 0.025 (1-sided) allocated to PFS; passed to OS if PFS is statistically significant
- Secondary: ORR,[c,d] DOR,[c,d] DCR,[c,d] TTP,[c,d] PFS,[d] and safety

1. Wang Q et al. *J Hepatol.* 2019;70:893-903.

[a]Largest tumor in centimeters + number of tumors. [b]2-4 weeks after the start of systemic therapy with a maximum of 2 treatments per tumor (4 total) and no more than 1 treatment per month.
[c]Per RECIST v1.1 by BICR. [d]Per mRECIST by BICR.

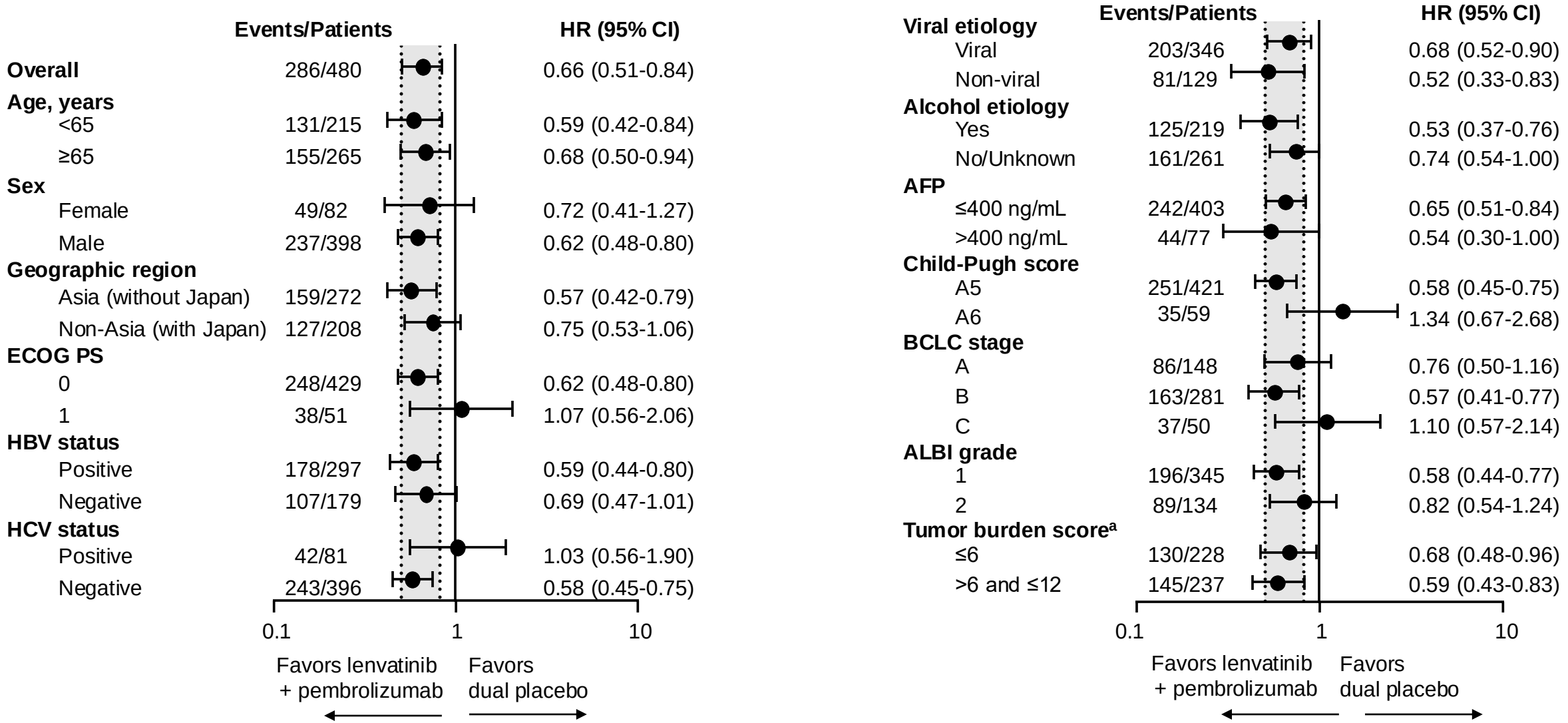
Progression-Free Survival per RECIST v1.1 by BICR

	Events, n (%)	Median (95% CI), months
Lenvatinib + pembrolizumab + TACE	132 (55.7)	14.6 (12.6-16.7)
Dual placebo + TACE	154 (63.4)	10.0 (8.1-12.2)



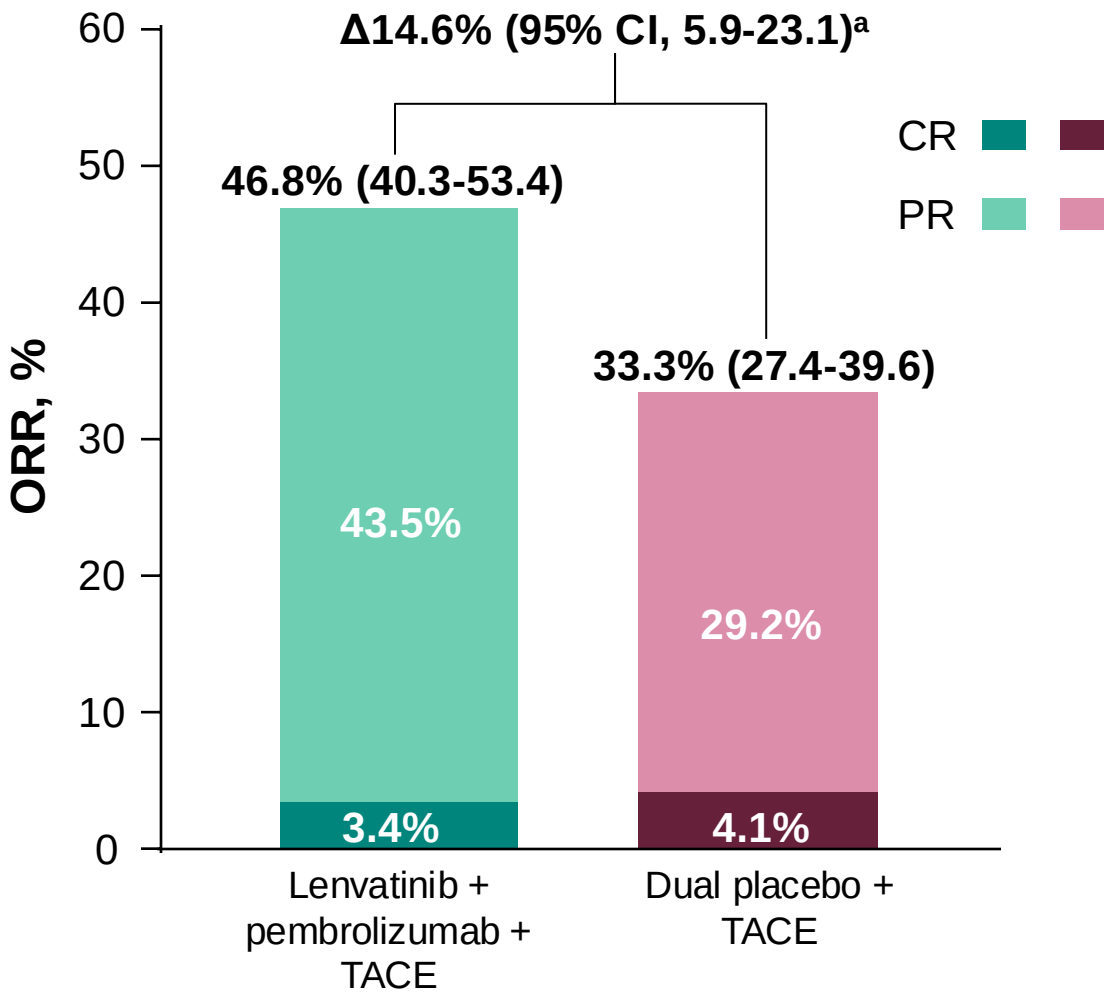
[a]One-sided *P* from re-randomization test; threshold *P* = 0.025. Data cutoff date for IA1: January 30, 2024.

Progression-Free Survival per RECIST v1.1 by BICR in Prespecified Subgroups



[a]Largest tumor in centimeters + number of tumors. Data cutoff date for IA1: January 30, 2024.

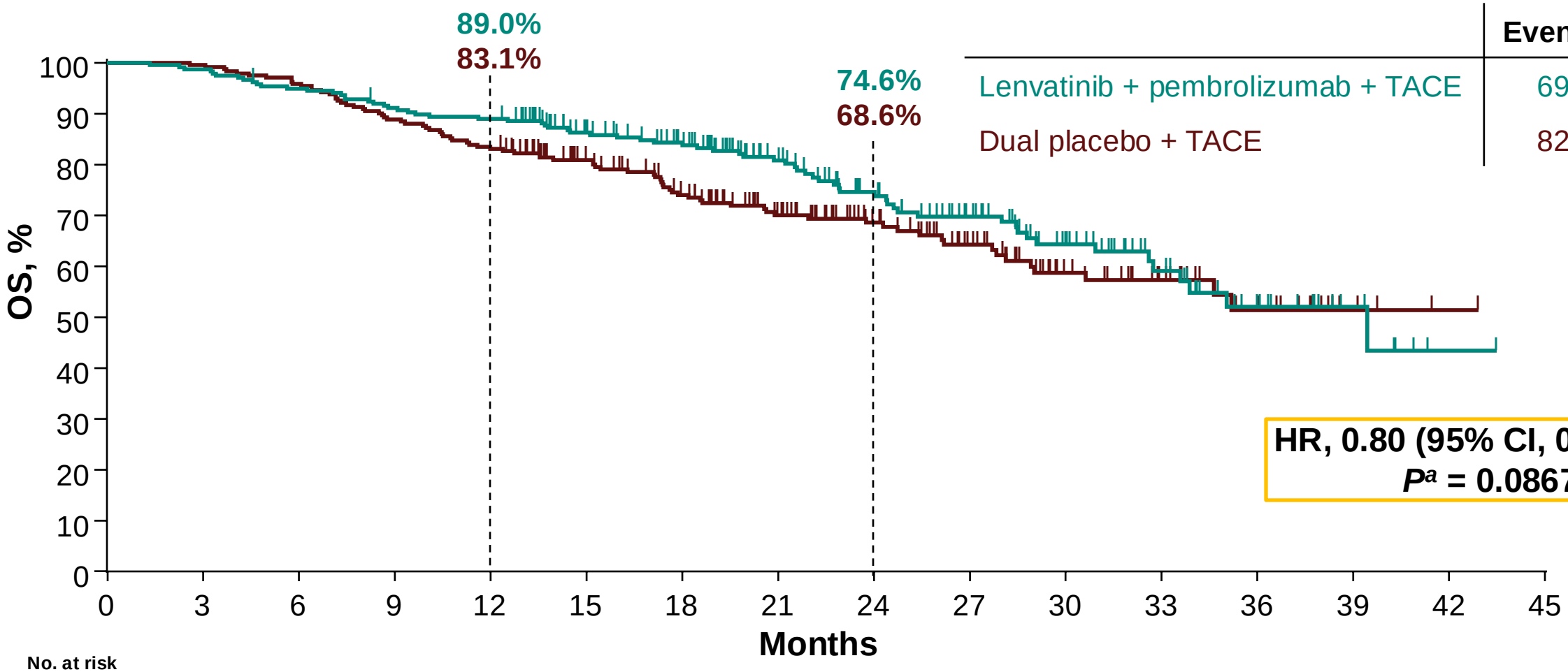
Objective Response Rate per RECIST v1.1 by BICR



	Lenvatinib + pembrolizumab + TACE n = 237	Dual placebo + TACE n = 243
Best overall response, % (95% CI)[b,c]		
Complete response	3.4 (1.5-6.5)	4.1 (2.0-7.4)
Partial response	43.5 (37.1-50.0)	29.2 (23.6-35.4)
Stable disease	42.6 (36.2-49.2)	48.1 (41.7-54.6)
Progressive disease	6.8 (3.9-10.7)	14.8 (10.6-19.9)
Duration of response, median (range), months	12.6 (1.3+ to 39.1+)	10.7 (2.0+ to 39.5+)
Disease control rate	89.5 (84.8-93.1)	81.5 (76.0-86.2)

[a]Estimated from stratified analysis. [b]Patients with insufficient data for assessment of response: 2.1% in the lenvatinib + pembrolizumab + TACE group and 1.6% in the dual placebo + TACE group. [c]Patients without postbaseline assessments: 1.7% in the lenvatinib + pembrolizumab + TACE group and 2.1% in the dual placebo + TACE group. Data cutoff date for IA1: January 30, 2024.

Overall Survival



	Events, n (%)
Lenvatinib + pembrolizumab + TACE	69 (29.1)
Dual placebo + TACE	82 (33.7)

HR, 0.80 (95% CI, 0.57-1.11)
***P*[a] = 0.0867**

No. at risk

237	234	224	214	209	180	161	124	95	74	49	31	17	7	1	0
243	242	233	216	202	173	145	112	86	65	42	27	15	4	1	0

[a]One-sided *P* from re-randomization test; threshold *P* = 0.0012. Data cutoff date for IA1: January 30, 2024.

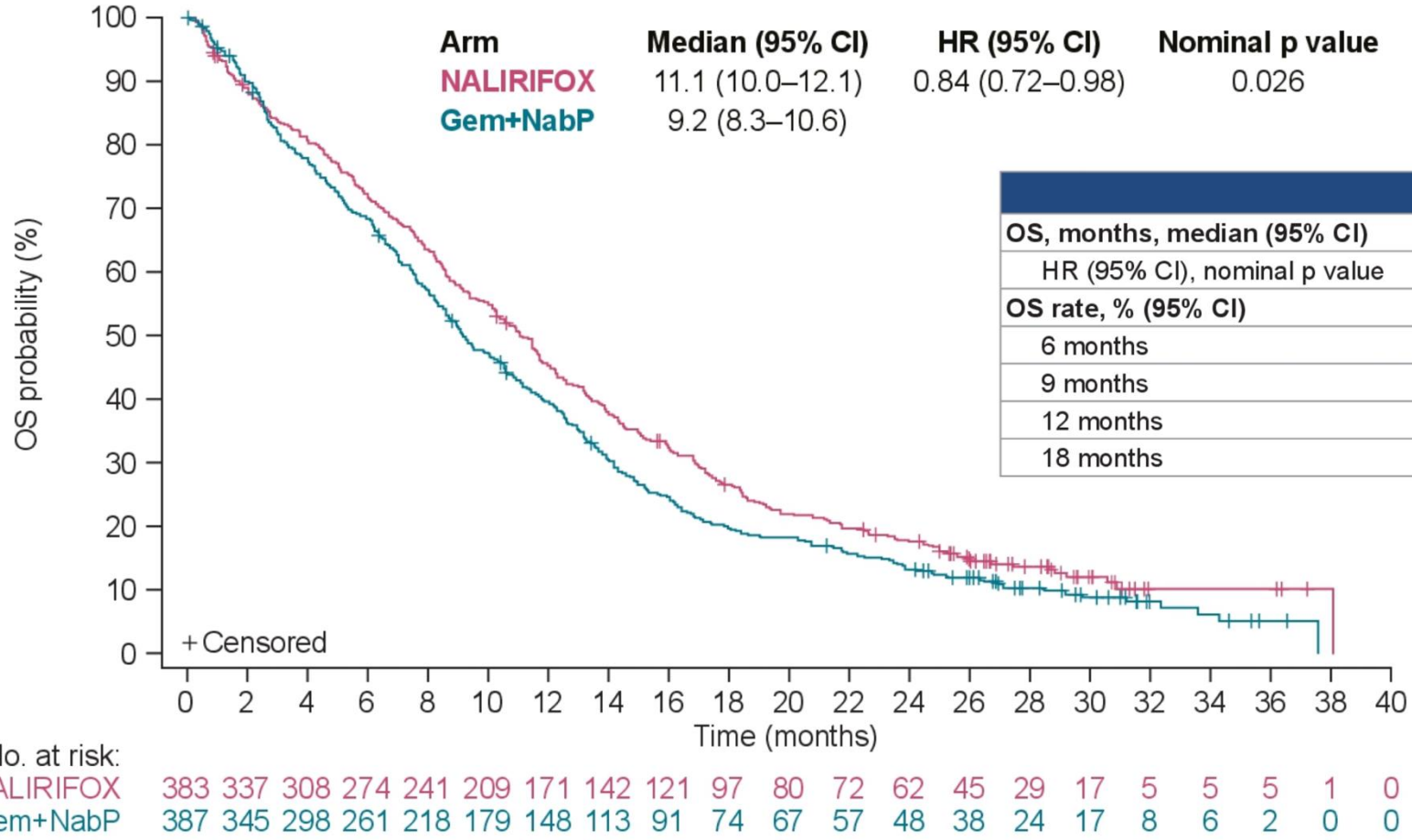
Pancreatic Ca

FOLFIRINOX and Nab-Paclitaxel + Gemcitabine in Advanced PDAC: Phase 3 Trial Results[1,2]

Parameter	FOLFIRINOX	Nab-Paclitaxel + Gemcitabine
N	342	861
Location(s)	France	North America, Eastern and Western Europe, Australia
Eligibility criteria, PS	ECOG 0-1	KPS 70-100%
Head/non-head, % (location)	39/61	44/56
Median OS, mo	11.1	8.5
Median PFS, mo	6.4	5.5
Toxicity (grade 3/4),%	Fatigue: 23.6 Neutropenia: 45.7 Sensory: 9	Fatigue: 17 Neutropenia: 38 Sensory: 17
Poorer PS patients?	N/A	Benefit maintained in KPS 70%-80% patients
QoL data	Yes	No
Biomarker data	N/A	SPARC: not predictive

1. Conroy T et al. *N Engl J Med*. 2011;364(19):1817-1825. 2. Von Hoff DD et al. *N Engl J Med*. 2013;369(18):1691-1703.

NAPOLI 3: Updated OS Analysis With 29-month Follow-up



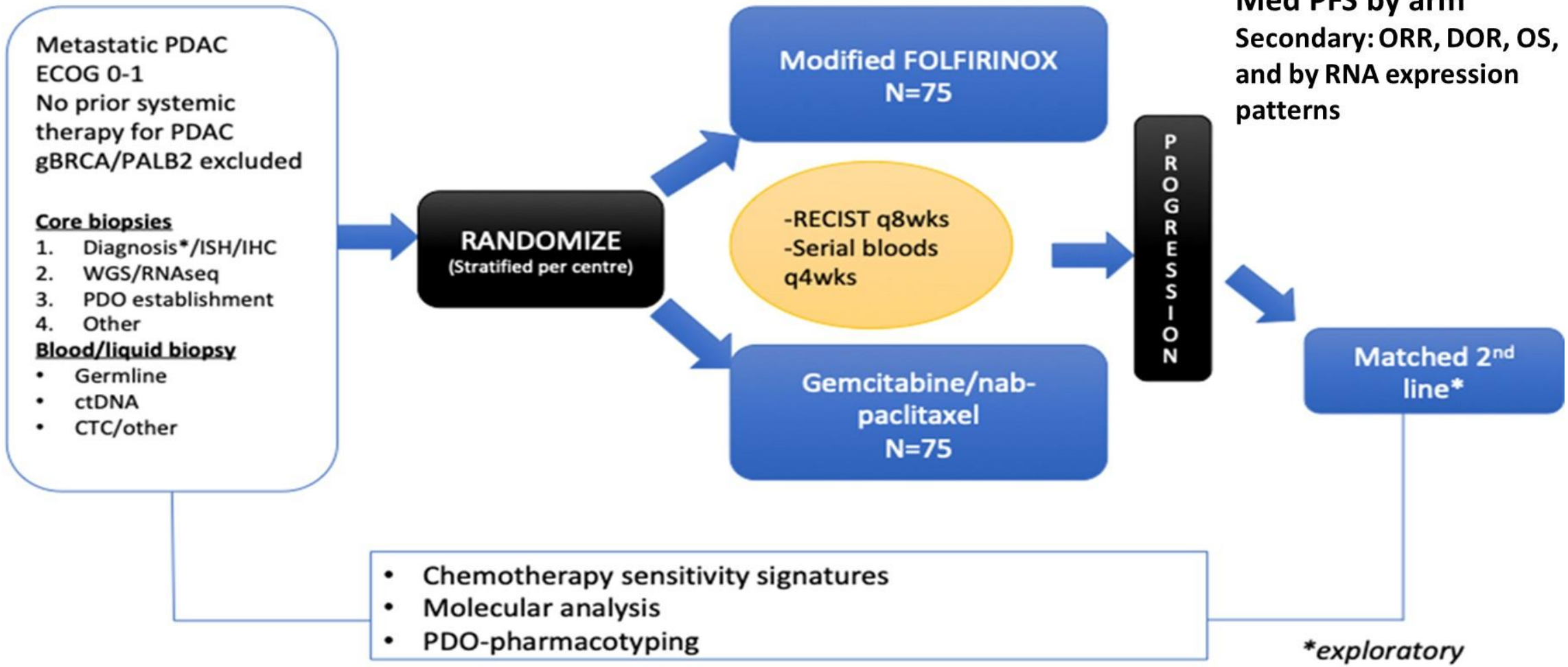
	NALIRIFOX (n = 383)	Gem+NabP (n = 387)
OS, months, median (95% CI)	11.1 (10.0–12.1)	9.2 (8.3–10.6)
HR (95% CI), nominal p value	0.84 (0.72–0.98); 0.026	
OS rate, % (95% CI)		
6 months	72.4 (67.6–76.6)	68.4 (63.5–72.8)
9 months	58.1 (53.0–62.9)	51.8 (46.7–56.7)
12 months	45.6 (40.5–50.5)	39.6 (34.7–44.5)
18 months	26.6 (22.2–31.1)	20.0 (16.1–24.1)

CI, confidence interval; Gem, gemcitabine; HR, hazard ratio; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival.

Hussein MA et al. 2024 ASCO Annual Meeting. Abstract 4136.

PASS-01 Schema: Randomized phase II trial (n = 150)

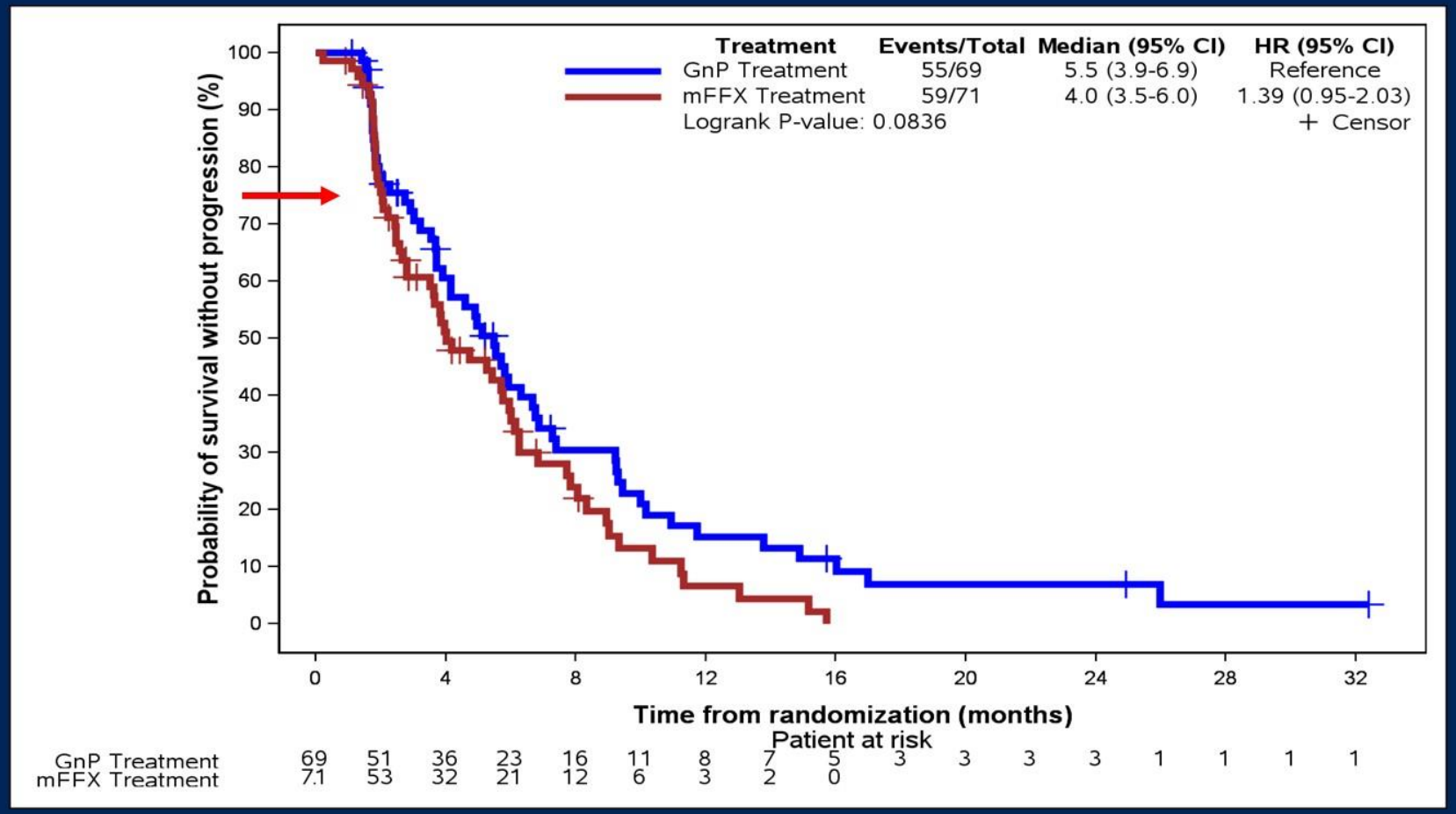
Primary endpoint:
Med PFS by arm
Secondary: ORR, DOR, OS, and by RNA expression patterns



+Eligible histological variants to also include mucinous adenocarcinoma or adenosquamous carcinoma

Knox J et al. 2024 ASCO Annual Meeting. Abstract LBA4004.

PASS-01 PFS (Primary endpoint, per protocol)



P=0.08
Met statistical difference favoring GnP.

Mean time from randomization to treatment 3.3 days

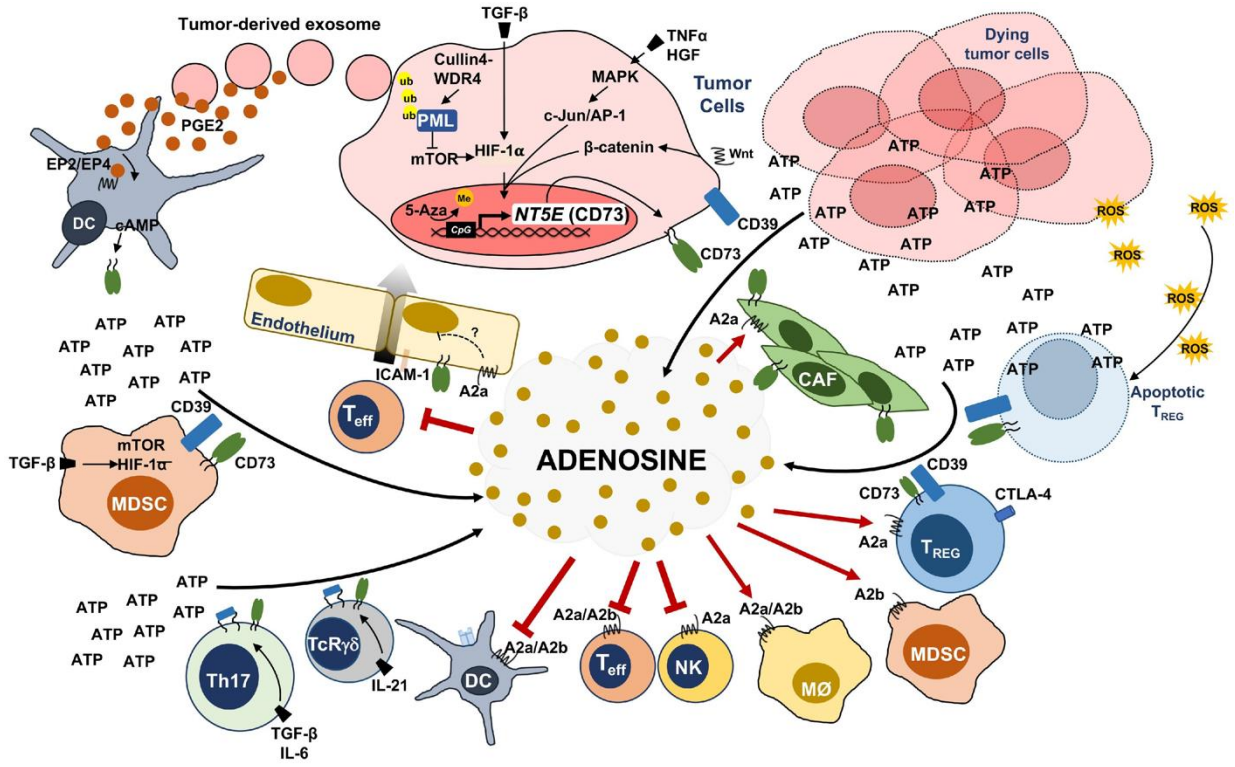
Data lock Mar 1, 2024
Med F/U 7 months
114/139 events

Knox J et al. 2024 ASCO Annual Meeting. Abstract LBA4004.

Pancreatic Ca: What's new?

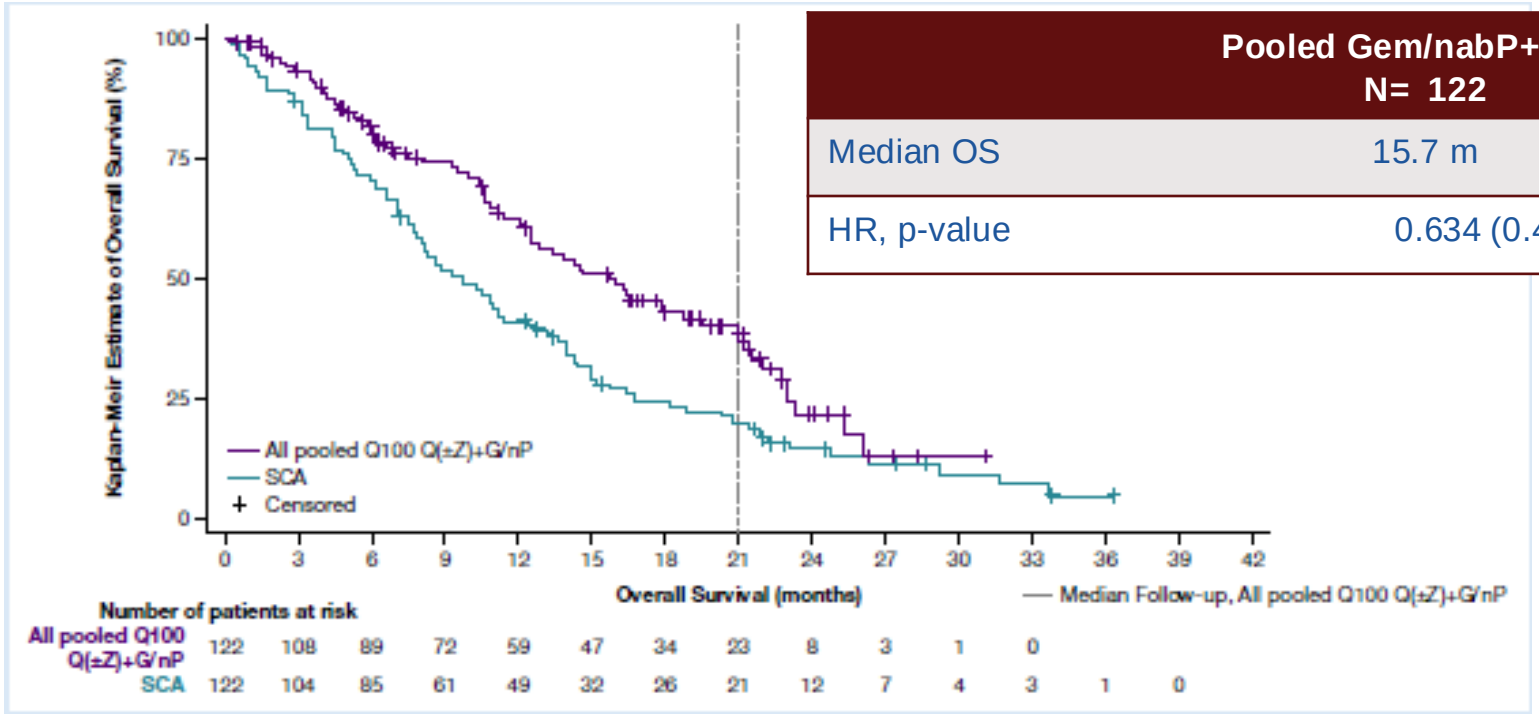
Elevated CD73 Expression and Adenosine Mediated Immune Suppression

- PDAC tumor immune microenvironment:
- High levels CD73
- CD73 expression associated with *KRAS* mutant phenotype
- High CD73 expression associated with worse outcome



Tahkola K et al. *Virchows Arch*. 2021;478(2):209-217. Zhao J et al. *Pancreatology*. 2021;21(5):942-949. Silva-Vilches C et al. *Front Immunol*. 2018;9:2581. Allard D et al. *Immunol Lett*. 2019;205:31-39.

ARC-8: Phase I/IB: Gem/Nab-P + Quemliclustat (anti-CD73) +/- Zimberelimab (anti-PD1) vs SOC Synthetic Control

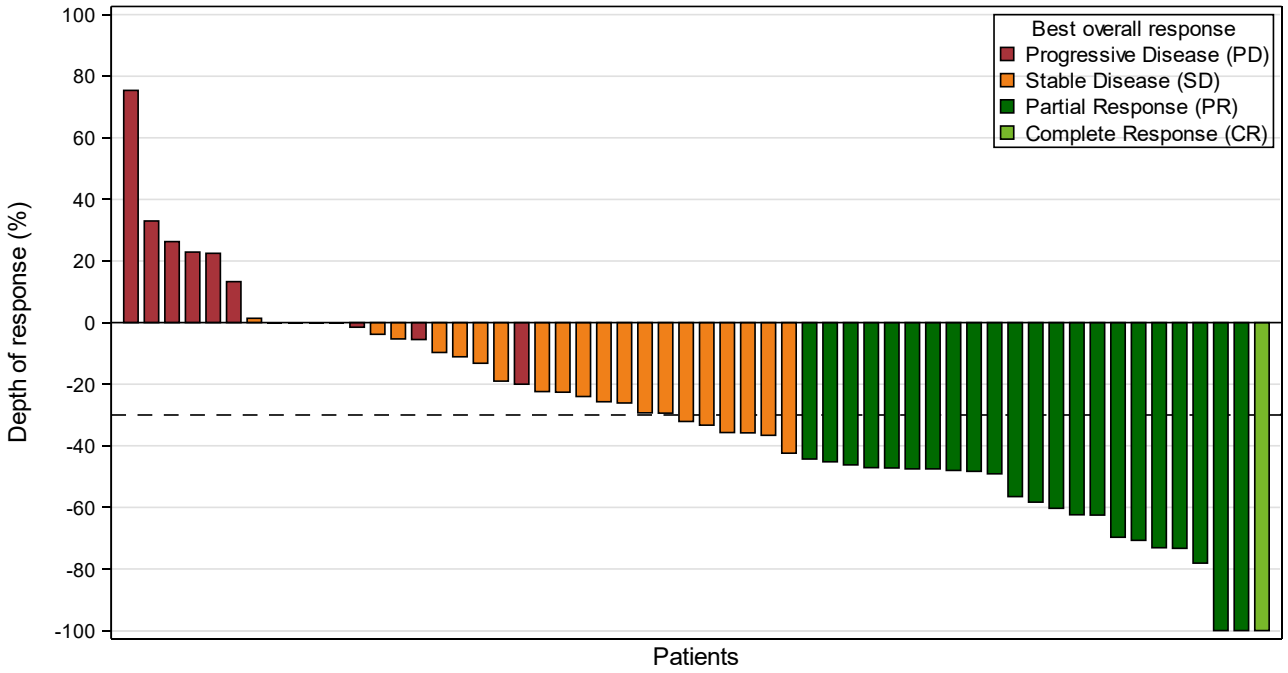


	Pooled Gem/nabP+Q+/-Z N= 122	SOC Control N= 122
Median OS	15.7 m	9.8 m
HR, p-value	0.634 (0.471, 0.854); p= 0.0030	

- Randomized phase III (2024) PRISM-1: Gemcitabine/nab-paclitaxel +/- Quemliclustat/placebo

Wainberg Z et al. 2024 ASCO GI. Abstract 665.

OPTIMIZE-1: Phase Ib/II Mitazalimab (anti-CD40) + mFFX



Abbreviations: N = number of patients in analysis set and treatment group, n = number of patients with non-missing value. The reference line indicates value -30.

N= 57 (of 70)	Statistic
ORR	23 (40%)
DCR	45 (79%)---------+2
Median OS	12.5 m (7.5- NR)
Med PFS	7.7 m (5.8- 11.3)
Overall Survival	14.3 m (10- 21.6)

- Phase II dose mitazalimab 900 ug/kg
- Phase III trial planned

Van Laethem JL et al. *Lancet Oncol*. Published online May 31, 2024.

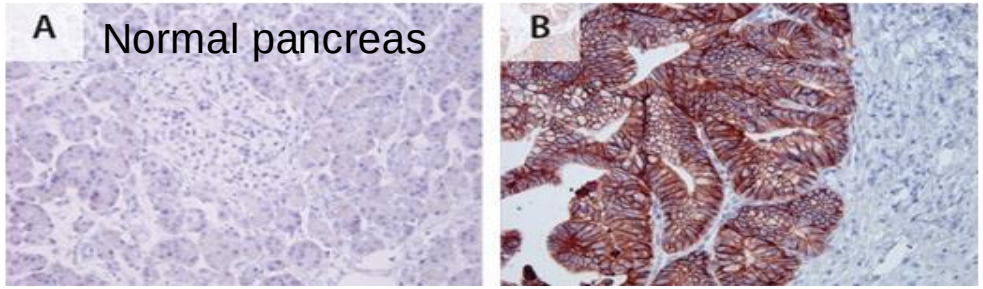
Claudin 18.2: Metastatic PDAC 1L
Randomized Phase II Gemcitabine/nab-Paclitaxel +/- Zolbetuximab (accrued)

Metastatic PDAC
CLDN 18.2(+)
ECOG 0-1
N= 357

2: 1

Gemcitabine/nab-Paclitaxel + Zolbetuximab (N= 238)
1000 mg/m^2 day 1 (load), 600 mg/m^2 day 1, 15

Gemcitabine/nab-Paclitaxel (N= 119)



Zolbetuximab: mAb IgG1 CLDN 18.2: ADCC, CDC

Primary endpoint: OS
10.5 m → 15.0; 80% power, 2-sided 0.05, HR 0.776

Eligibility: CLDN 18.2 mod/strong ≥ 75% tumor cells (IHC)

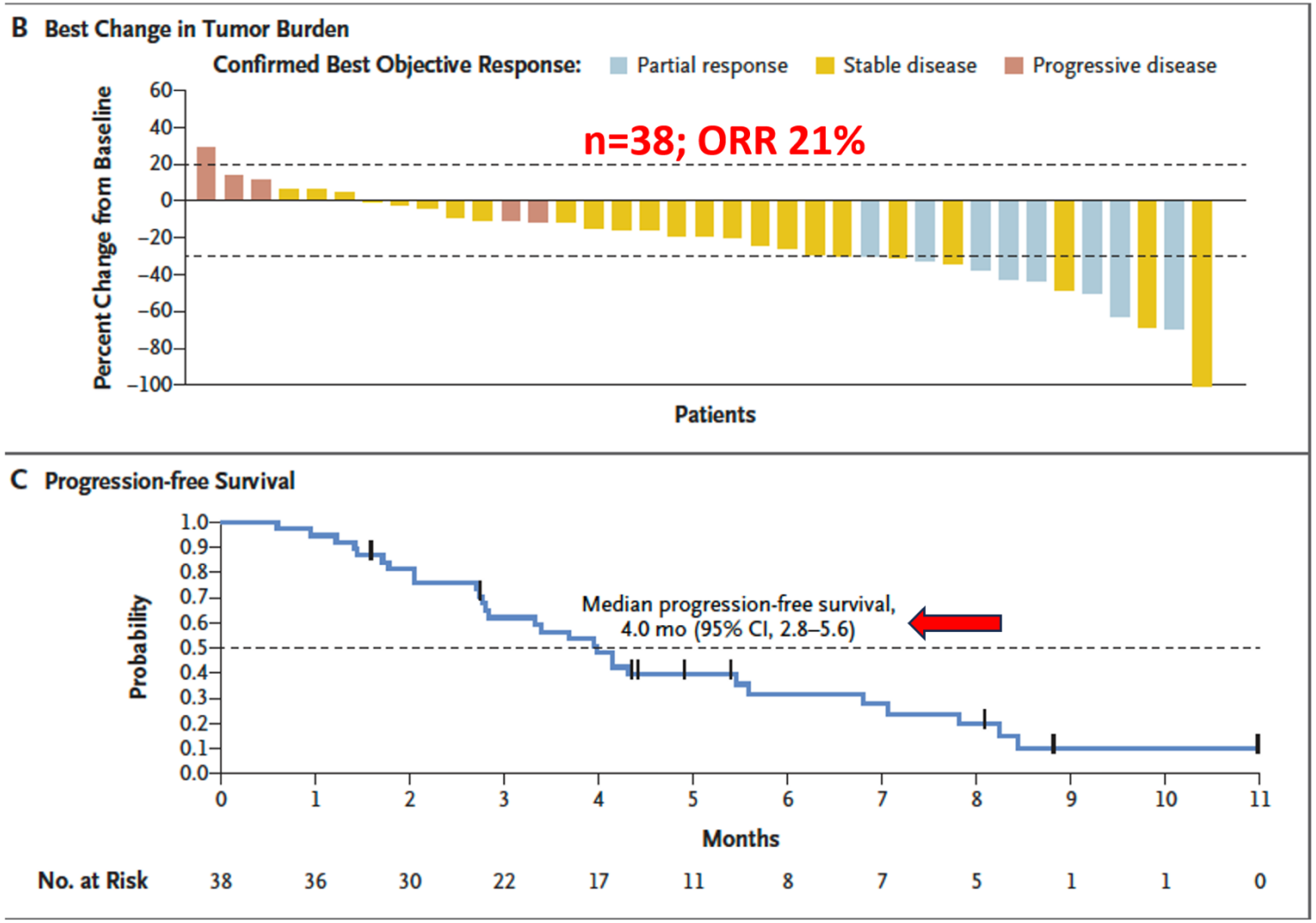
Park W et al. 2022 ASCO Annual Meeting. Abstract TPS4186. NCT03816163.

Antibody-Drug Conjugates in Development in PDAC

NCT	Therapeutic	Mechanism/Target	N	Study Design
NCT0591535	Enfortumab vedotin	NECTIN-4, MMAE	28	Phase II, single arm, two-stage; ORR
NCT04843709	MRG004A	Tissue factor/CD142	181	Phase I, II
NCT06131840	SGN-CEACAM5C	CEA, Topo-1	410	Phase I, II
NCT06219941	AZD0901	Claudin 18.2, MMAE	390	Phase II, multiple arms

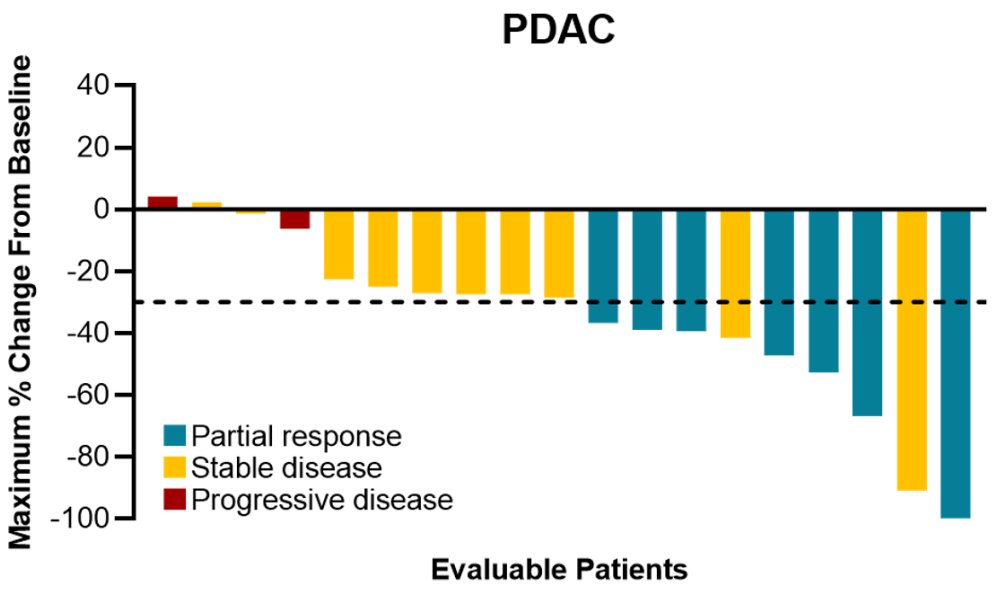
Many other targets
EGFR, mesothelin, Trop 2, HER3, MUC1, Gypican-1 (GPC-1), CD71, DR5, C-MET, EphA2

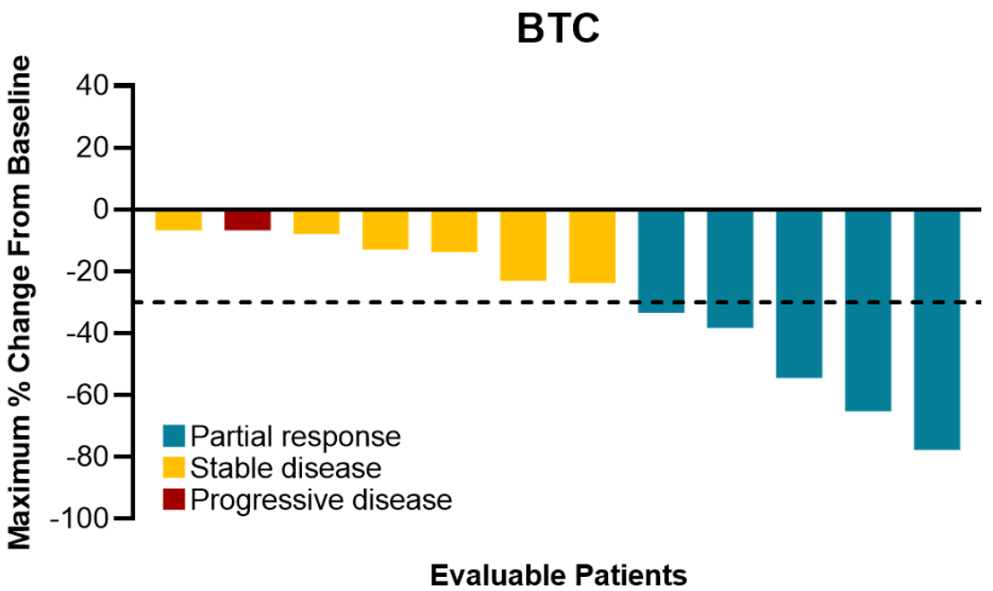
Sotorasib in Pancreatic Cancer



Strickler JH et al. *N Engl J Med*. 2023;388(1):33-43.

Adagrasib in Patients With PDAC and BTC: Best Tumor Change From Baseline





- Confirmed ORR of 33.3% (7/21 patients)
- Disease control was observed in 17/21 (81.0%) patients

- Confirmed ORR of 41.7% (5/12 patients)
- Disease control was observed in 11/12 (91.7%) patients

All results are based on BICR; data as of October 1, 2022 (median follow-up: 16.8 months)

A First-in-Human Phase 1 Study of LY3537982, a Highly Selective and Potent KRAS G12C Inhibitor in Patients with KRAS G12C-Mutant Advanced Solid Tumors

- LY3537982's unique pharmacologic properties permit high target occupancy at low absolute exposures, potentially allowing for safer combinations with less toxicity[4]

	LY3537982	Adagrasib	Sotorasib
pERK H358 IC_{50} (nM)	0.65 (2h, n=5)	14 (3h)[5]	13.5 (2h, n=2)
Active RAS H358 IC_{50} (nM)	3.35 (2h, n=6)	89.9 (n=1)	47.9 (n=3)
Kinact/Ki ($M^{-1}s^{-1}$)	522,000	35,000[5]	9,900[6]
Predicted TO Range	>90% trough[a]	60%[a]	45-70%[a]

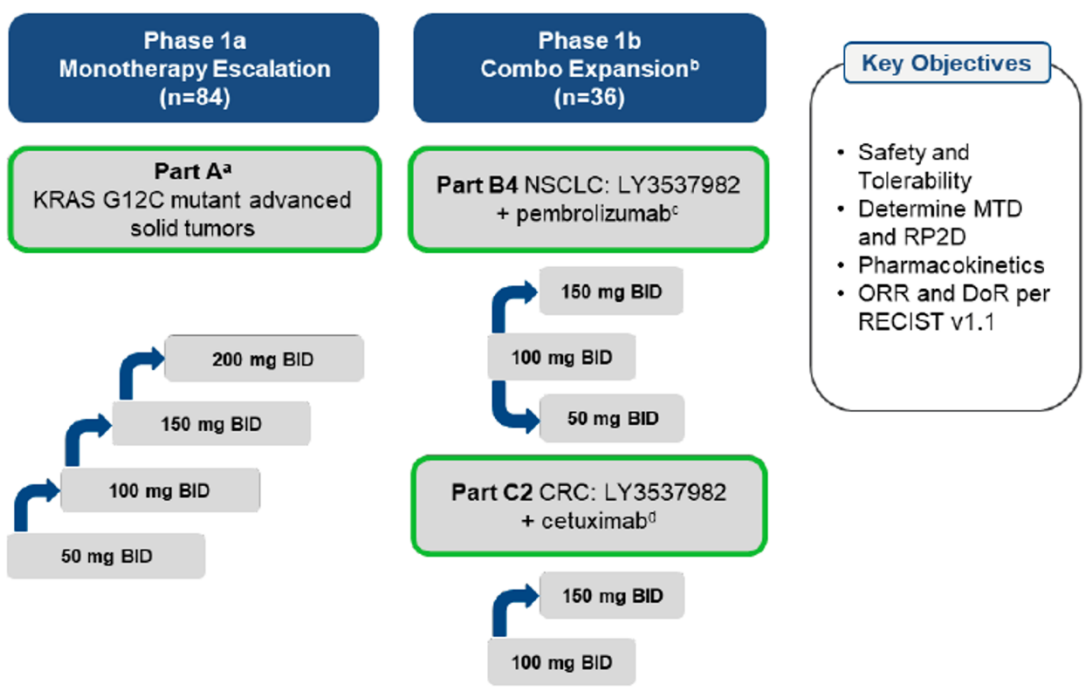
Tumor type, n (%)	
NSCLC	26 (31)
Without prior KRAS G12C inhibitor	9 (11)
With prior KRAS G12C inhibitor	17 (20)
CRC	23 (27)
Pancreatic Cancer	14 (17)
Other[b]	21 (25)

Phase 1a Eligibility
- Age ≥18
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Locally/metastatic solid tumor
- Locally assessed KRAS G12C mutation

Phase 1a Design
- mTPI-2 design
- 21-day cycle (DLT evaluation period)
- Intrapatient dose escalation allowed

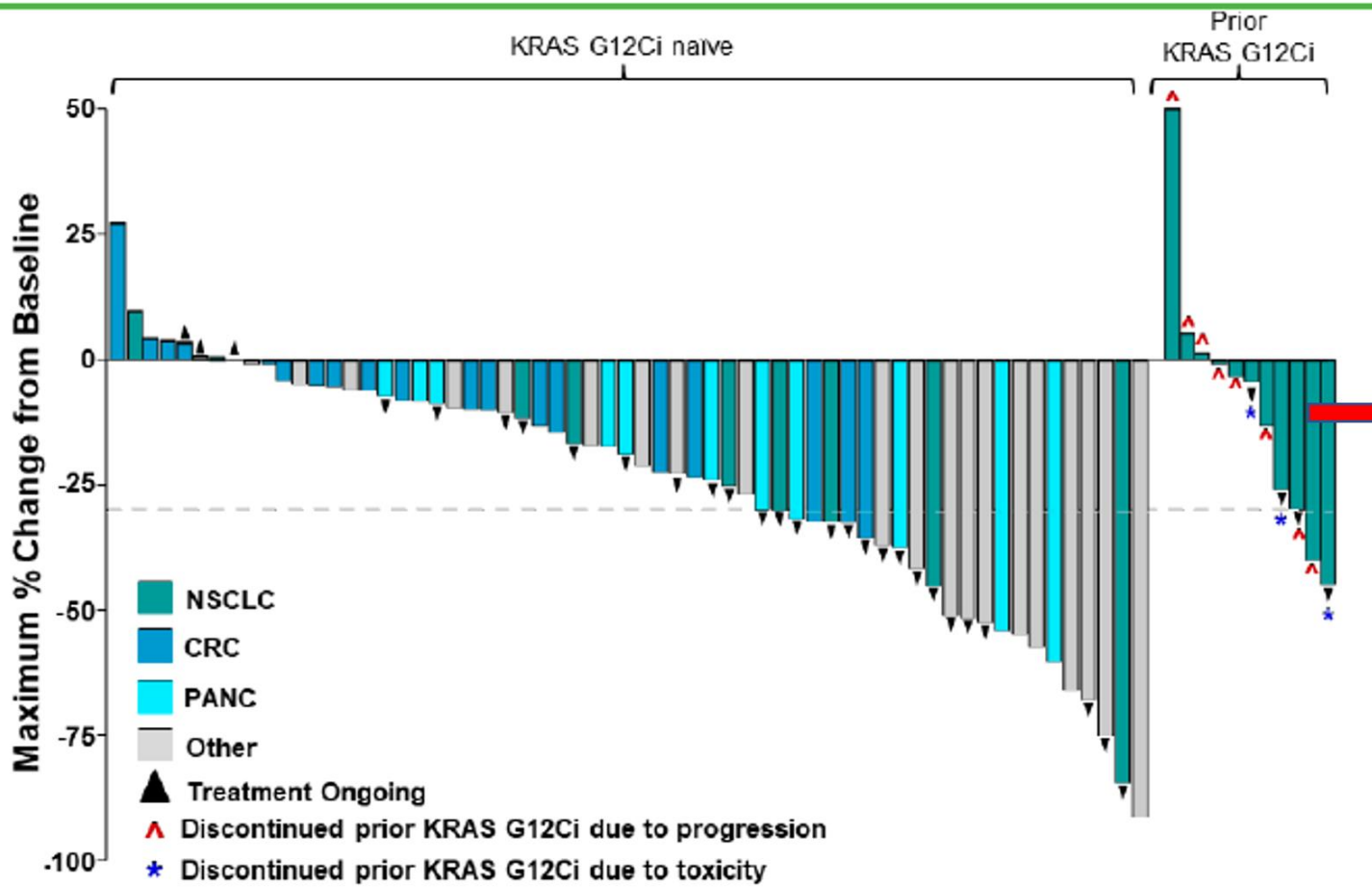
B4 Eligibility
- Prior chemotherapy, anti-PD-(L)1, KRAS G12C inhibitor allowed

C2 Eligibility
- Prior fluoropyrimidine, oxaliplatin, and irinotecan required



Key Objectives
- Safety and Tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- ORR and DoR per RECIST v1.1

Murciano-Goroff YR et al. 2023 AACR Annual Meeting. Abstract CT028.



n=12; ORR 42%

Efficacy Evaluable Patients[a] (n = 75)	ORR[b]	DCR[b]
NSCLC (G12Ci naïve)	38% (3/8)	88% (7/8)
NSCLC (prior G12Ci)	7% (1/14)	64% (9/14)
Colorectal	10% (2/20)	90% (18/20)
Pancreatic	42% (5/12)	92% (11/12)
Other[c]	52% (11/21)	95% (20/21)

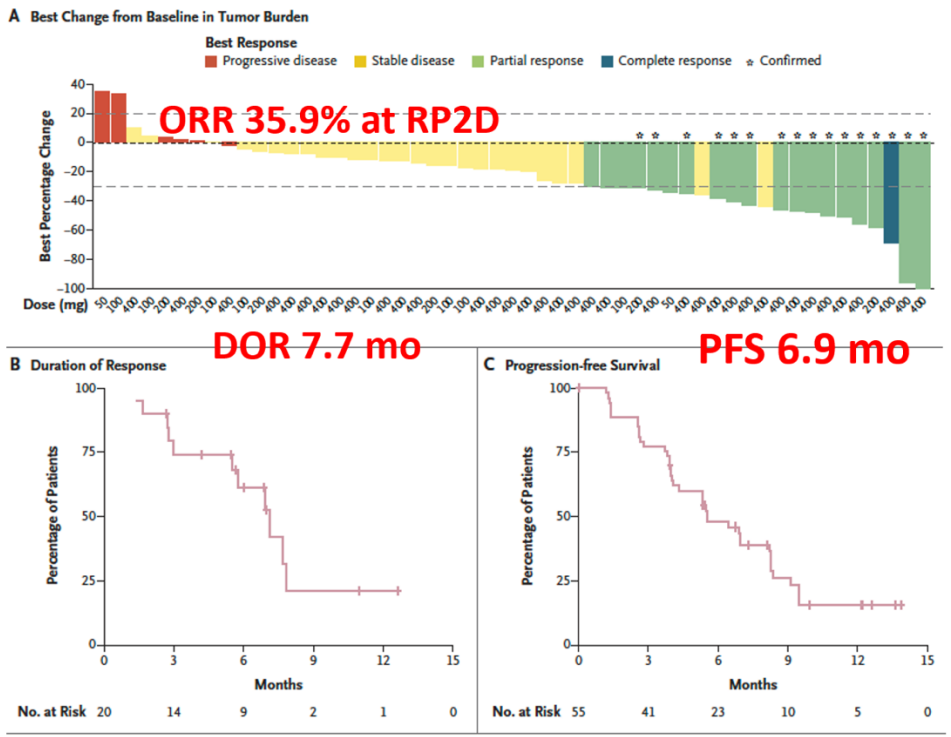
- **Responses observed at all dose levels**
- **Median time to response 1.4 months**
- **At a median follow-up of 4.2 months, 73% of responses remain ongoing**

Murciano-Goroff YR et al. 2023 AACR Annual Meeting. Abstract CT028.

Divarasib (GDC 6036)

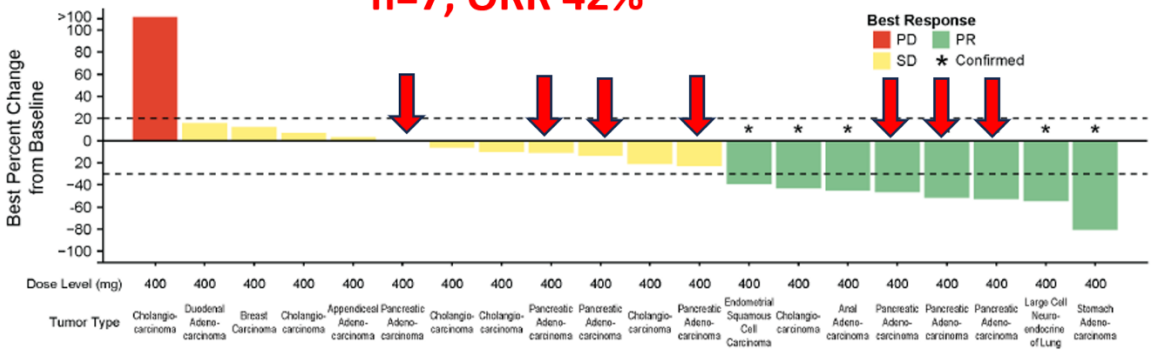
Characteristic	NSCLC (N=60)	Colorectal Cancer (N=55)	Other Solid Tumors† (N=22)	All Patients (N=137)
Median age (range) — yr	67 (43–82)	62 (34–81)	64 (30–85)	65 (30–85)

Potent and Highly Selective



Pancreatic Cancer

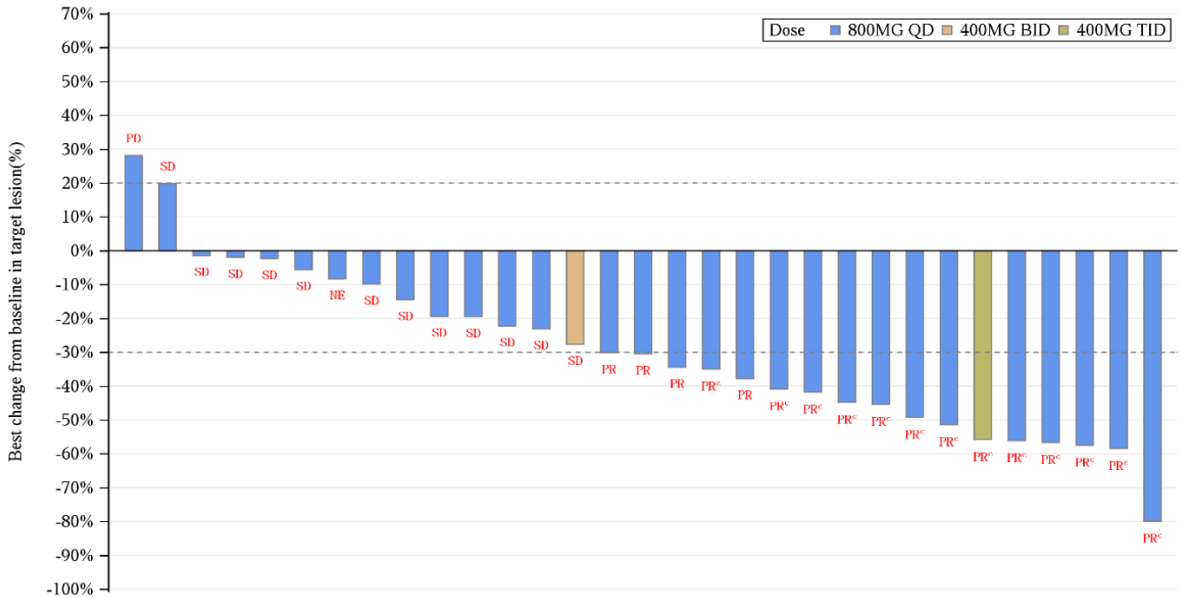
n=7; ORR 42%



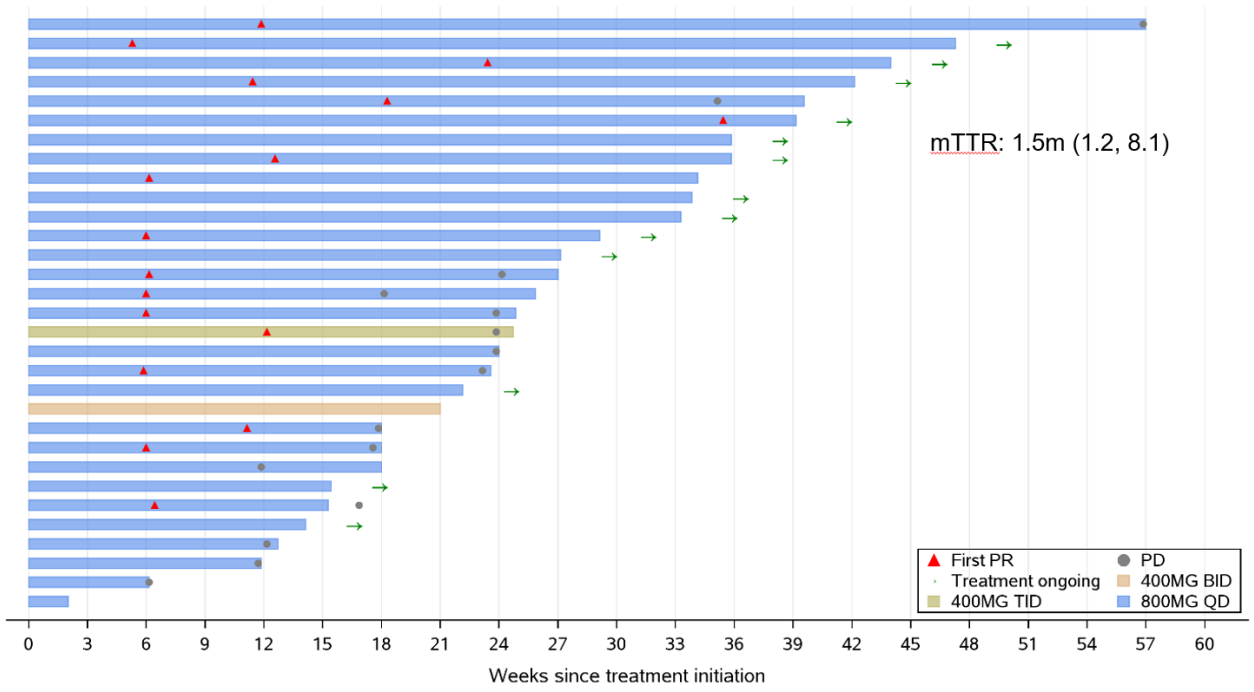
Sacher A et al. *N Engl J Med*. 2023;389(8):710-721.

Efficacy of Glecirasib in PDAC

Best Tumor Change from Baseline



Duration of Treatment

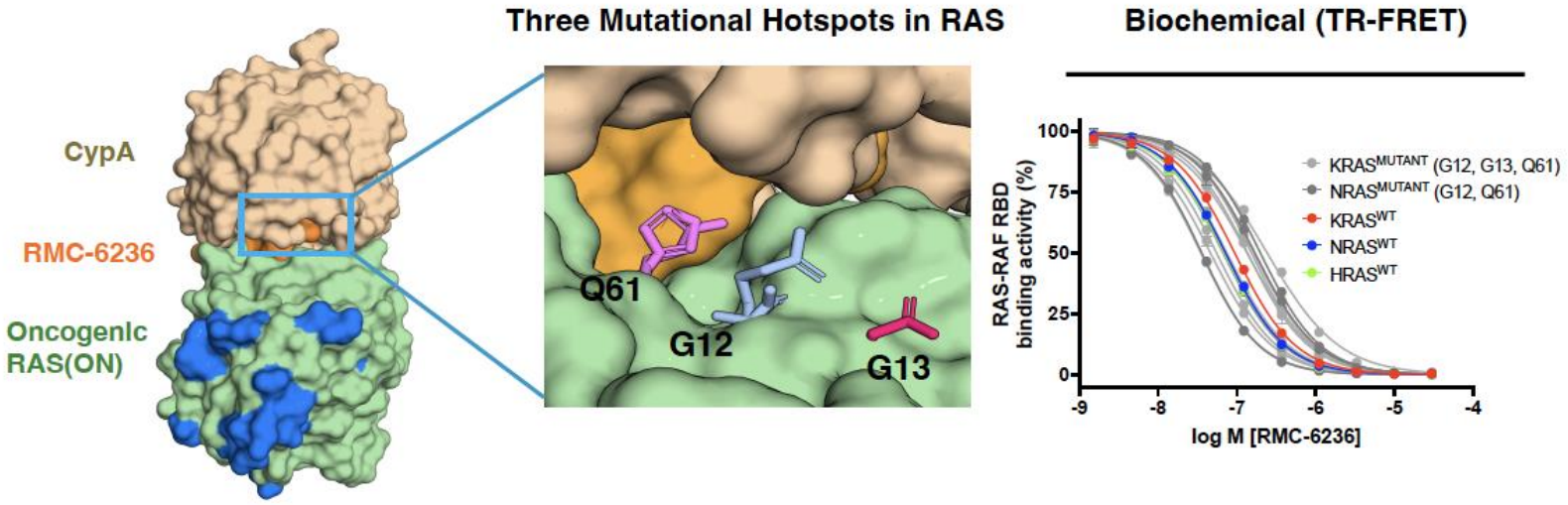


- cORR for PDAC is 41.9%, DCR is 93.5%
- 22.6%(7/31) of patients with PDAC experiencing tumor regression >50%

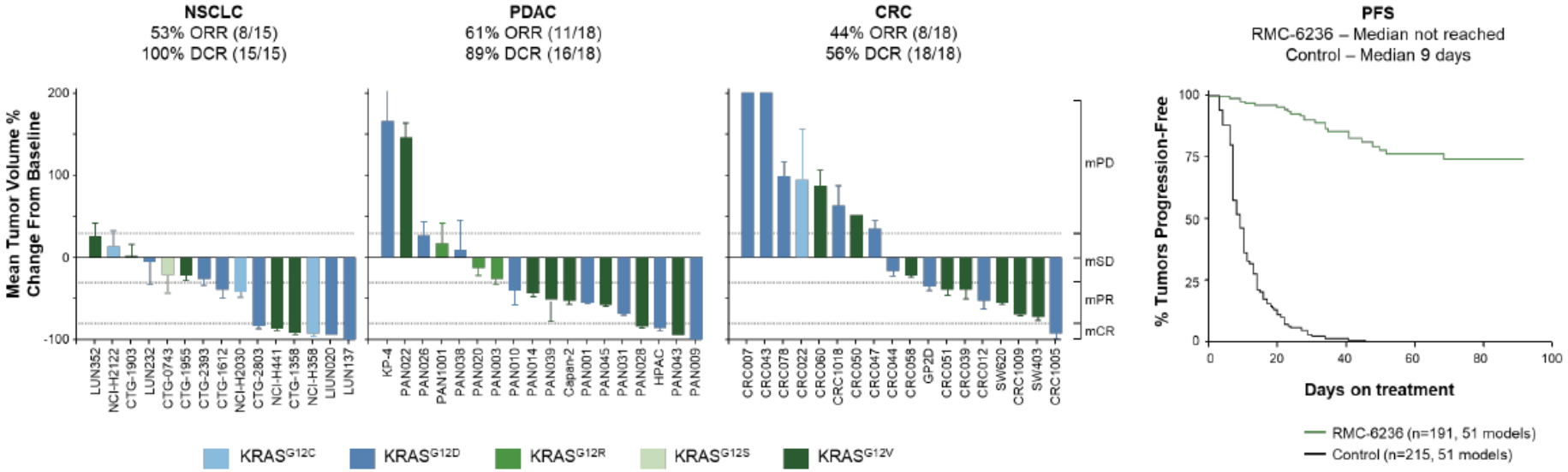
- 41.9% (13/31) of patients on study treatment at the time of data cutoff

Li J et al. 2024 ASCO GI. Abstract 604.

RMC-6236

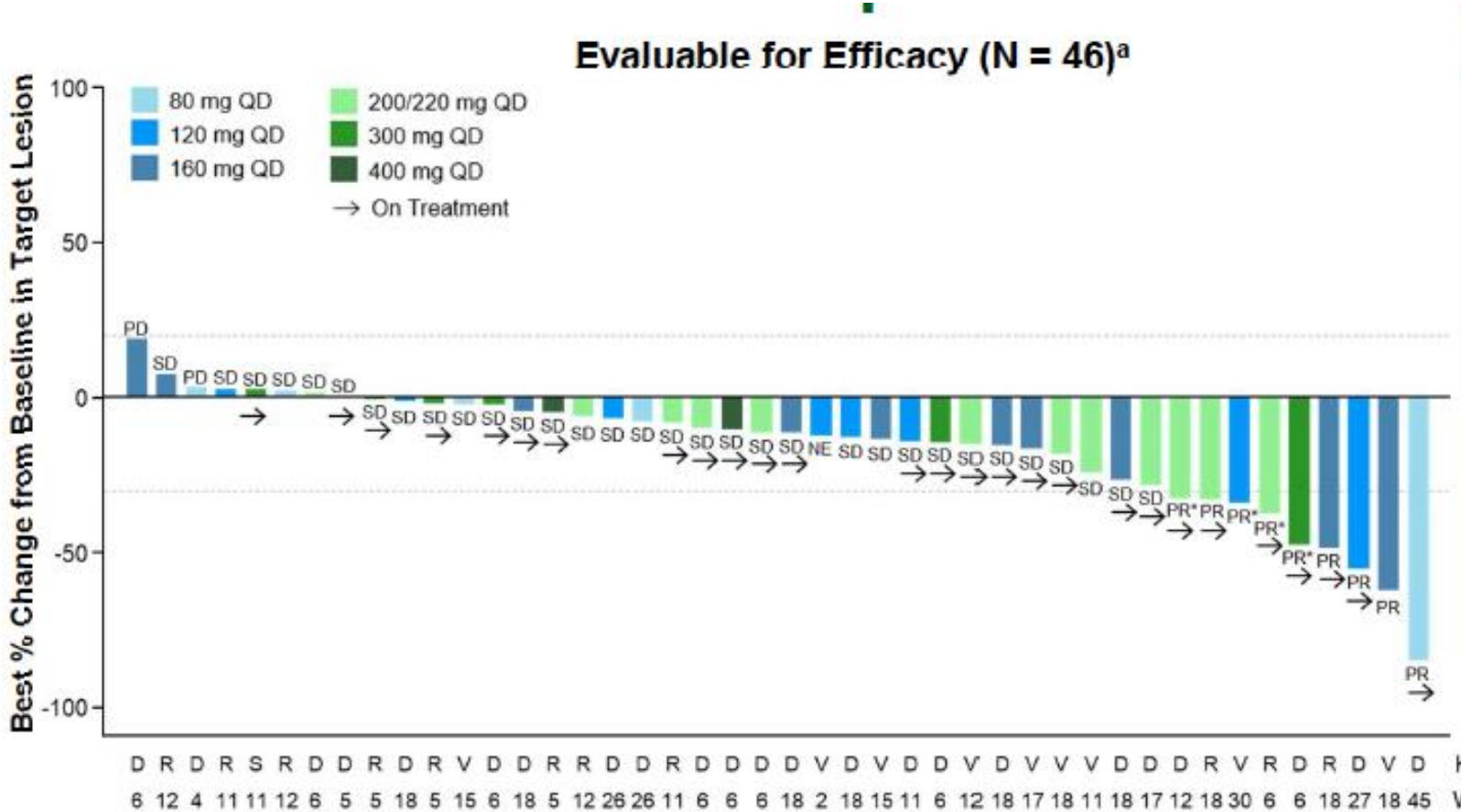


In Vivo Models



Courtesy W. Clay Gustafson. *Revolution Medicine*.

$KRAS^{G12X}$ PDAC Best Response



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
PR	9 (20)
SD	31 (67)
PD	3 (7)
NE[b]	3 (7)
ORR, n (%)	9 (20)
Confirmed, n	5
DCR (CR+PR+SD), n (%)	40 (87)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]Two patients died prior to first post-baseline scan; 1 patient had scan after 11 days of treatment and subsequently died due to PD.

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Data Extracted 12 Oct 2023.

Kathryn C. Arbour, MD

Courtesy: C Gustafson

Summary of Treatment-Related Adverse Events

Patients with NSCLC and PDAC Treated at ≥80 mg QD (N = 111)					
Maximum severity of treatment-related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)					
Rash[a]	58 (52)	25 (23)	7 (6)	0	90 (81)
Nausea	40 (36)	11 (10)	0	0	51 (46)
Diarrhea	28 (25)	14 (13)	1 (1)	0	43 (39)
Vomiting	30 (27)	7 (6)	0	0	37 (33)
Stomatitis	13 (12)	9 (8)	2 (2)	0	24 (22)
Fatigue	11 (10)	6 (5)	0	0	17 (15)
Other select TRAEs, n (%)					
ALT elevation	8 (7)	1 (1)	0	0	9 (8)
AST elevation	8 (7)	0	0	0	8 (7)
Electrocardiogram QT prolonged	1 (1)	0	0	0	1 (1)
TRAEs leading to dose reduction[b], n (%)	0	10 (9)	5 (5)[c]	0	15 (14)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	1 (1)[d]	1 (1)

- Median time on treatment was 2.1 months (range: 0.2–10.9).
- No fatal TRAEs were observed.

[a]Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, erythema, rash erythematous; multiple types of rash may have occurred in the same patient; [b]The most common reason for dose reduction was rash; [c]Grade 3 TRAEs leading to reduction were rash (n = 4), including one patient with a dose reduction due to rash and decreased appetite, and stomatitis (n = 1); [d]One Grade 4 TRAE occurred in a patient with PDAC at the 80 mg dose level who had a large intestine perforation at the site of an invasive tumor that reduced in size while on treatment.
ALT, alanine transaminase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

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Data Extracted 12 Oct 2023.

Courtesy: C Gustafson

More KRAS Inhibitors in the Pipeline: Beyond KRAS^{G12C}

Approved
Recruiting
Active, not recruiting
Completed
Preclinical

- Adagrasib/MRTX849
- BBO-8520
- BI 1823911
- BPI-421286
- D-1553
- D3S-001
- Divarasib/GDC-6036
- GEC255*
- GH35
- Glecirasib/JAB-21822
- HBI-2438
- HS-10370
- IBI351/GFH925
- JNJ-74699157
- LY3537982
- MK-1084
- Opnurasib/JDQ443
- RMC-6291
- Sotorasib/AMG520
- YL-15293

→ KRAS^{G12C}

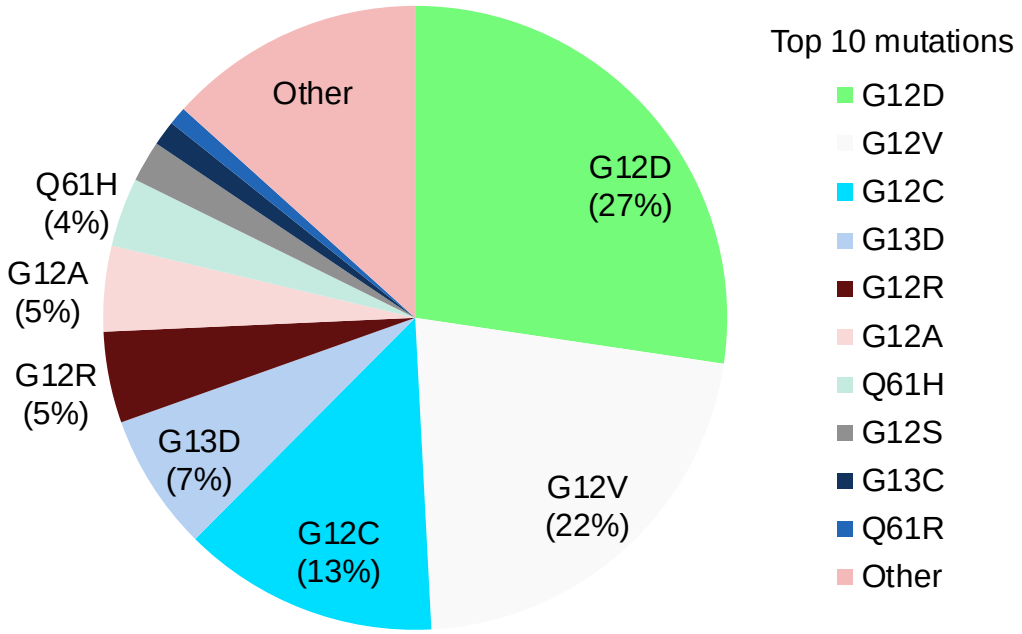
→ KRAS^{G12D}
- ASP3082
- BI-2852
- ERAS-4
- HRS-4642
- JAB-22000
- MRTX1133
- QTX3046
- RMC-9805

→ KRAS^{G13C}
- RMC-8839

→ KRAS^{Q61H}
- RMC-0708

→ KRAS$^{WT/X}$
- BBP-454
- BI-2493
- BI-2865
- JAB-23400
- QTX2024
- RMC-6236
- RSC-1255

KRAS mutations: all cancers



ClinicalTrials.gov

Courtesy: C Der

cBioPortal FOR CANCER GENOMICS GENIE Cohort v13.0

Conclusions (I):

- Front-line IO based regimens have become the standard of care for advanced HCC
- Numerous approved agents with proven activity in HCC are available post-progression
- How best to sequence agents is not determined but patients with preserved performance status should be offered treatment
- At this time there is no role for adjuvant systemic therapy after resection for HCC outside of a clinical trial
  - Ongoing studies are evaluating various regimens
  - Novel vaccine-based approaches in development

Conclusions (II):

- Combination studies in intermediate stage HCC are showing improvements in PFS
  - Will it improve OS?
  - Which patients benefit the most?

- In pancreatic cancer chemotherapy backbones remain standard of care
  - Remember molecular studies for BRCA and other alterations
  - Novel immunotherapy approaches are under study
  - KRAS targeted drugs are showing promise

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