Pancreatic, Biliary Tract and Hepatic Cancers
Recent Advances

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New Orleans Summer Oncology Conference

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2024 ASCO® ANNUAL MEETING

Nivolumab plus ipilimumab vs lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma: first results from CheckMate 9DW

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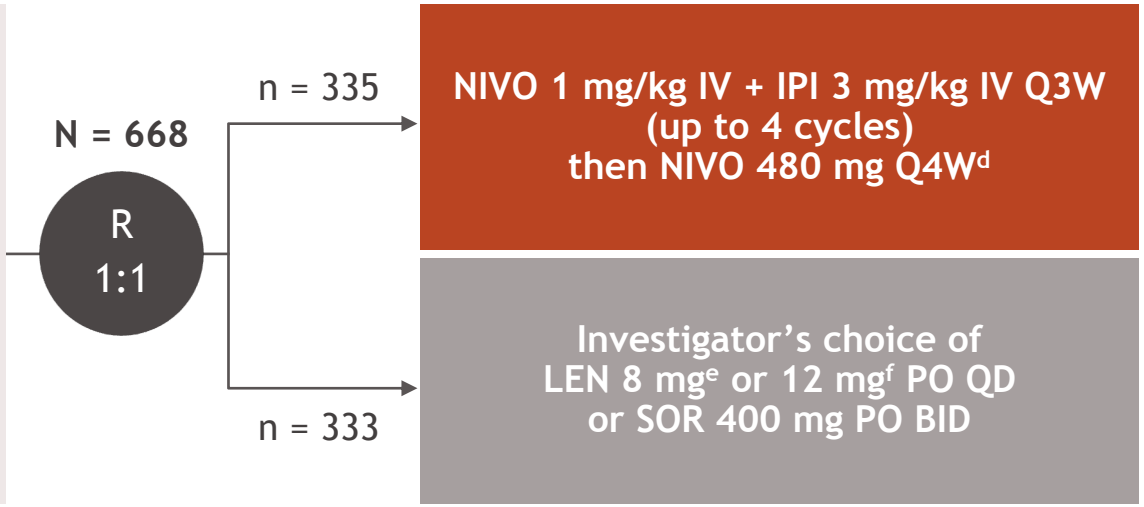
Abstract number LBA4008

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 vs absent)
- AFP (< 400 vs ≥ 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 and 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.

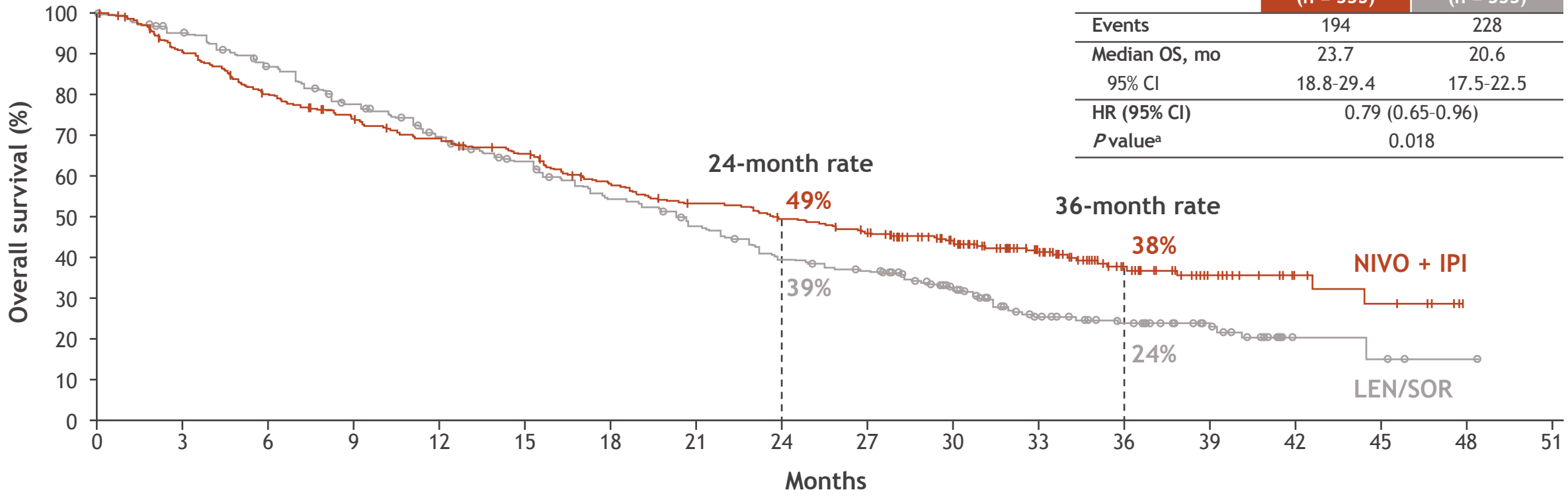
Baseline characteristics

All randomized	NIVO + IPI (n = 335)	LEN/SOR (n = 333)
Median age (range), years	65 (20–86)	66 (20–89)
≥ 65 years	173 (52)	184 (55)
Male, n (%)	271 (81)	277 (83)
Region, n (%)		
Asia	133 (40)	147 (44)
North America/Europe	144 (43)	145 (44)
Rest of the world	58 (17)	41 (12)
Etiology, n (%)[a,b]		
HBV	114 (34)	115 (35)
HCV	90 (27)	96 (29)
Uninfected	124 (37)	119 (36)
Child-Pugh score, n (%)[c]		
5	254 (76)	263 (79)
6	72 (21)	58 (17)
ECOG PS 1, n (%)[d]	102 (30)	89 (27)
BCLC stage, n (%)[e]		
≤ B	89 (27)	88 (26)
C	246 (73)	242 (73)
MVI/EHS, n (%)[b]		
MVI	77 (23)	92 (28)
EHS	188 (56)	172 (52)
MVI/EHS	221 (66)	217 (65)
AFP ≥ 400 ng/ml, n (%)	108 (32)	113 (34)
Prior locoregional therapy, n (%)	142 (42)	158 (47)

[a]7 patients in the NIVO + IPI arm and 3 patients in the LEN/SOR arm were reported as having both HBV and HCV as risk factors for HCC; these patients did not have active co-infection with HBV and HCV. [b]Per CRF. [c]Score ≥ 7: NIVO + IPI, n = 9; LEN/SOR, n = 11. Not reported: LEN/SOR, n = 1. [d]Not reported: LEN/SOR, n = 1. [e]Unknown: LEN/SOR, n = 3.

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

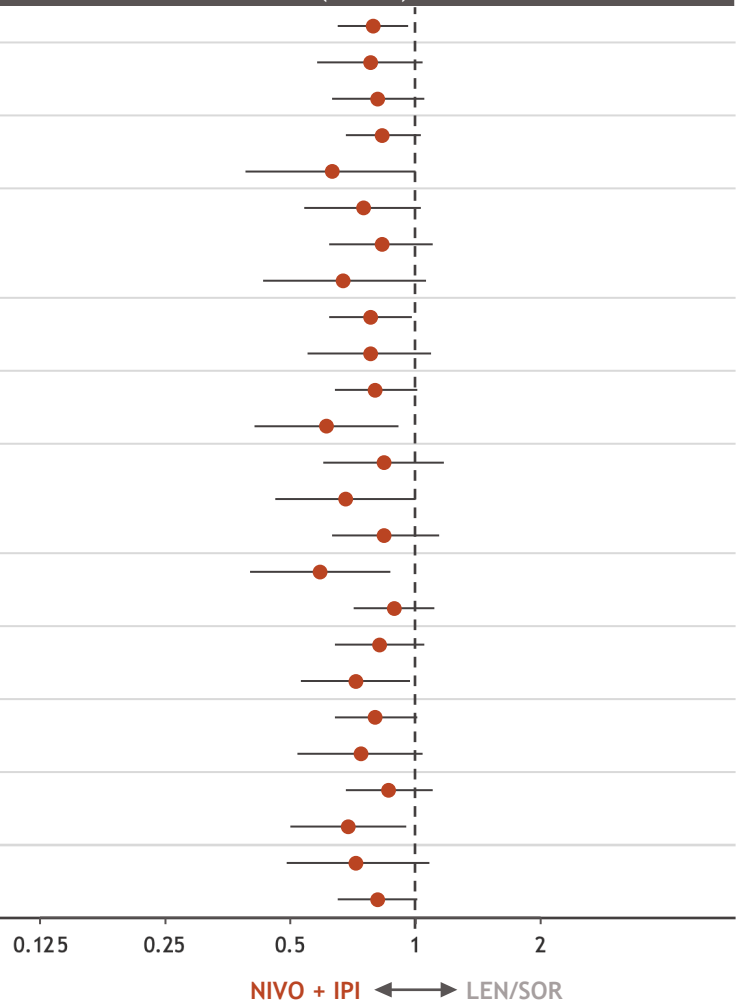
- Statistically significant and clinically meaningful OS benefit with NIVO + IPI vs LEN/SOR
  - Longer median OS and long-term survival benefit with higher OS rates at 24 and 36 months

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.

Overall survival subgroup analysis

Category	Subgroup	Median OS, mo		Unstratified HR
		NIVO + IPI	LEN/SOR	
Overall (N = 668)		23.7	20.6	0.79
Age, years	< 65 (n = 311)	26.8	22.7	0.78
	≥ 65 (n = 357)	18.8	18.2	0.81
Sex	Male (n = 548)	23.0	21.1	0.83
	Female (n = 120)	26.9	17.3	0.63
Region	Asia (n = 280)	34.0	22.5	0.75
	North America/Europe (n = 289)	22.9	19.8	0.83
	Rest of world (n = 99)	18.8	12.4	0.67
ECOG PS[a]	0 (n = 476)	27.9	22.5	0.78
	1 (n = 191)	16.4	15.3	0.78
Child-Pugh score[b]	5 (n = 517)	27.9	23.2	0.80
	6 (n = 130)	18.3	10.3	0.61
Etiology[c,d]	HBV (n = 229)	23.5	22.3	0.84
	HCV (n = 186)	33.0	17.8	0.68
	Uninfected (n = 243)	19.3	18.4	0.84
MVI[c]	Yes (n = 169)	22.9	15.4	0.59
	No (n = 499)	23.9	21.9	0.89
EHS[c]	Yes (n = 360)	18.7	16.6	0.82
	No (n = 308)	33.5	22.5	0.72
MVI/EHS[c]	Yes (n = 438)	19.4	17.7	0.80
	No (n = 230)	33.5	23.0	0.74
Baseline AFP, ng/ml	< 400 (n = 447)	25.9	23.8	0.86
	≥ 400 (n = 221)	16.4	12.1	0.69
BCLC at baseline[e]	≤ B (n = 177)	33.5	27.1	0.72
	C (n = 488)	20.3	17.8	0.81

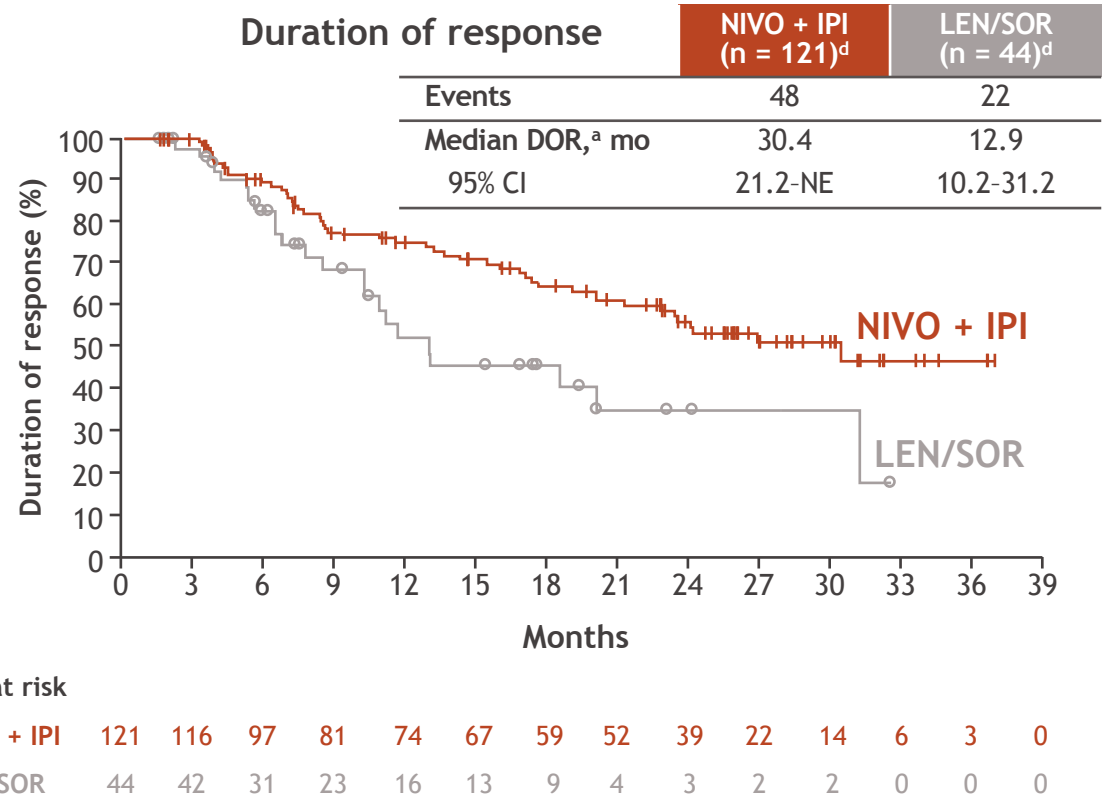
Unstratified HR (95% CI)



Median (range) follow-up, 35.2 (26.8-48.9) months. HRs and 95% CIs from unstratified Cox proportional hazard model. HR is NIVO + IPI over LEN/SOR. HR is not computed for subset categories with 10 or less patients per treatment arm. [a]Not reported, n = 1. [b]Score ≥ 7, n = 20; not reported, n = 1. [c]Per CRF. [d]Reported as having both HBV and HCV as risk factors for HCC, n = 10; these patients did not have active co-infection with HBV and HCV. [e]Unknown, n = 3.

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[b]	< 0.0001	
Best overall response,[a] %		
Complete response	7	2
Partial response	29	11
Stable disease[c]	32	62
Progressive disease	20	14
Not evaluable	12	11
Median TTR (range),[a] mo	2.2 (1.1-11.6)	3.7 (0.6-11.2)

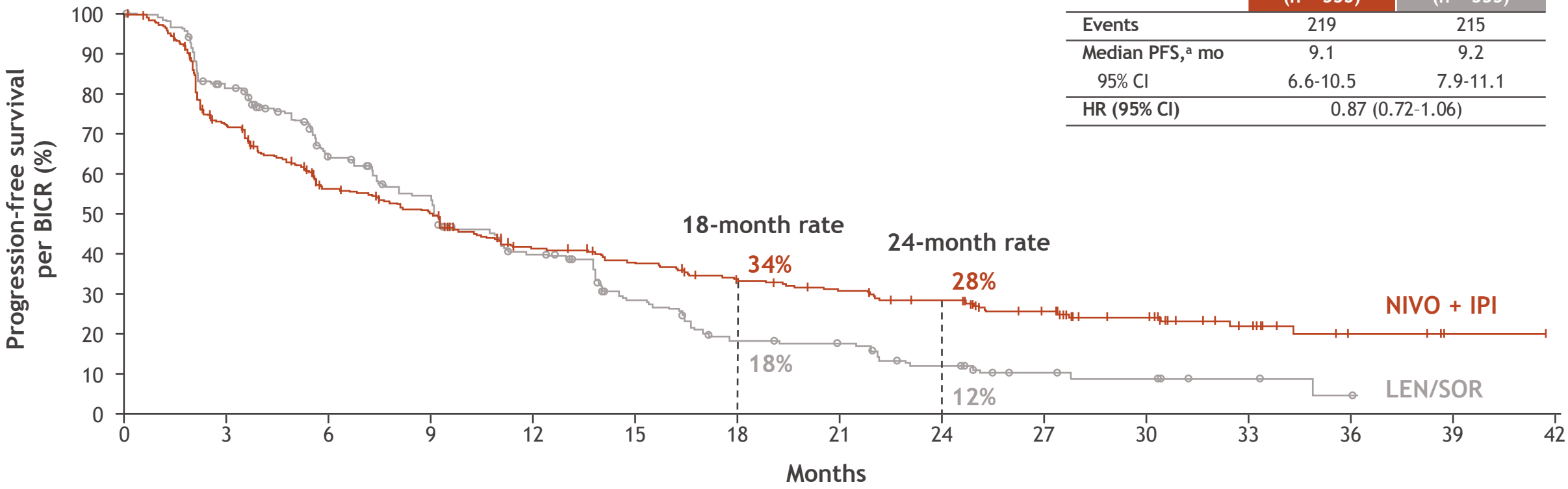


- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs LEN/SOR, with a higher complete response rate (7% vs 2%, respectively) and durable responses

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

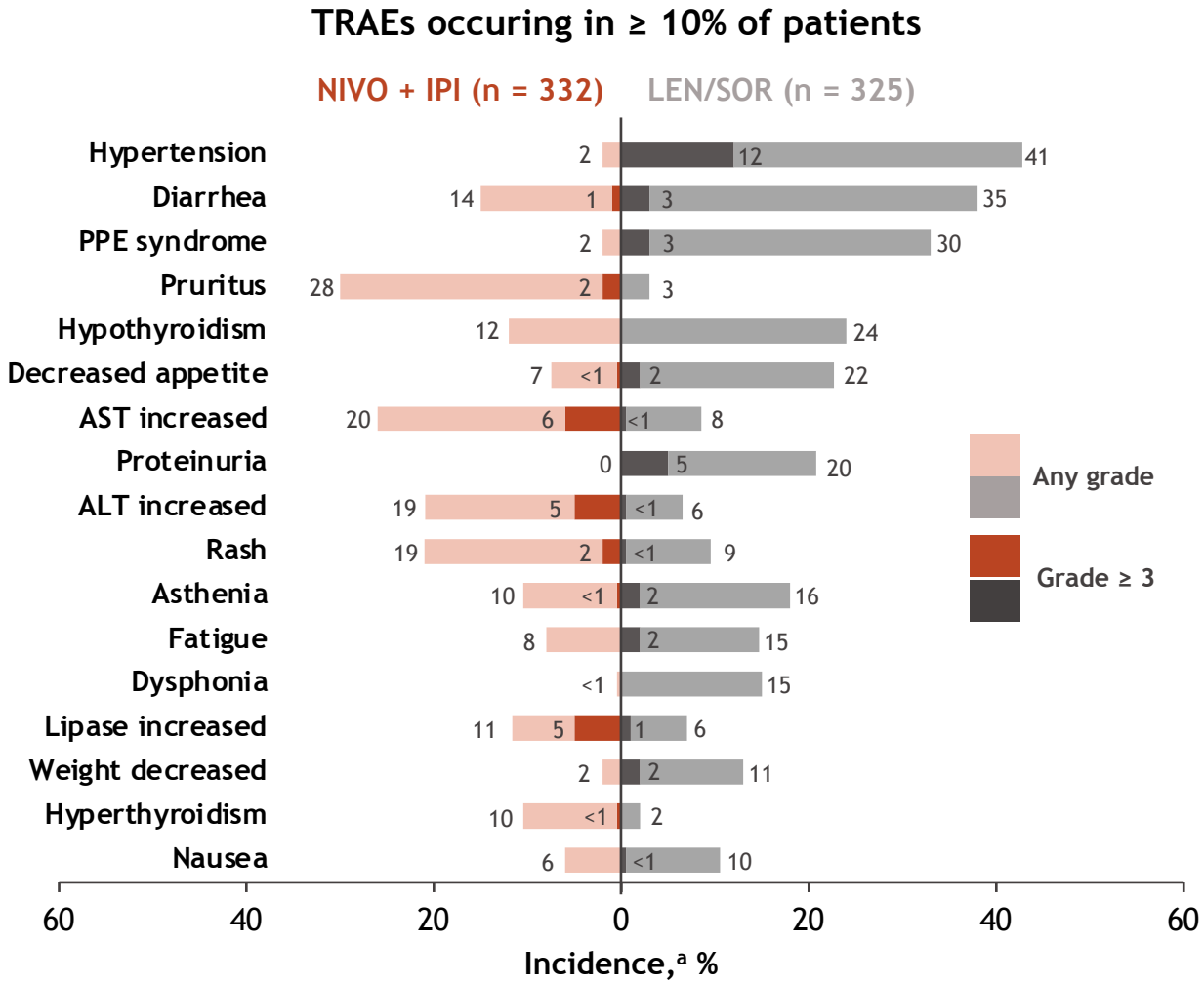
- Numerically higher PFS rates with NIVO + IPI vs LEN/SOR at 18 and 24 months

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, mo	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, occurring within 100 days after the last dose of study treatment, regardless of causality, and, with the exception of endocrine events, are treated with immune-modulating medication

	Atezo + Bev[1,3]	Durva + Treme[2]	Durva[2]	Ipi + Nivo[4]
OS (mth)	19.2	16.4	16.6	23.7
2 year OS	NR	40.5%	39.6%	49%
3 year OS	NR	30.7%	24.7%	38%
4 year OS.	NR	25.2%	19.3%	N/A
PFS (mth)	6.9	3.78	3.65	9.1
RR	30%	20.1%	17%	36%
DOR (mth)	18.1	22.3	16.8	30.4
TTR (mth)	NR	2.17	2.09	2.2

1. Finn et al NEJM 2020 ; 2. Abou-Alfa et al NEJM Evid 2022; 3. Cheng et al J Hep 2022 ; 4. Galle et al ASCO 2024

ASCO Gastrointestinal Cancers Symposium

EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization

Riccardo Lencioni*[1], Masatoshi Kudo[2], Joseph Erinjeri[3], Shukui Qin[4], Zhenggang Ren[5], Stephen L Chan[6], Yasuaki Arai[7], Jeong Heo[8], Anh Mai[9], Jose Escobar[10], Yamil Alonso Lopez Chuken[11], Jung-Hwan Yoon[12], Won Young Tak[13], Tanita Suttichaimongkol[14], Mohamed Bouattour[15], Shi-Ming Lin[16], Magdalena Żotkiewicz[17], Stephanie Udoye[18], Gordon J Cohen[18], **Bruno Sangro*[19]**

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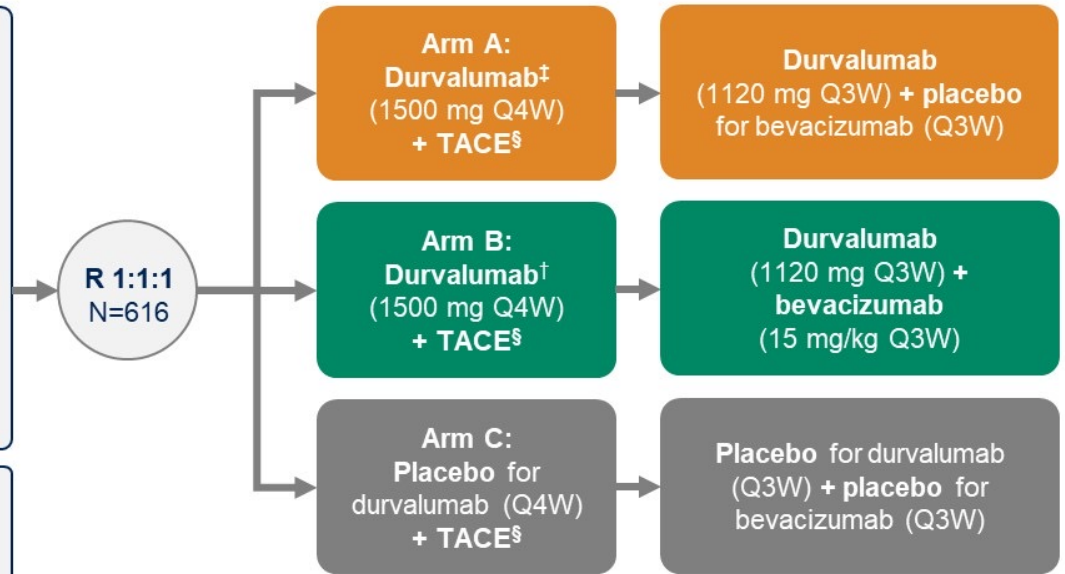
**Co-principal investigators*

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.

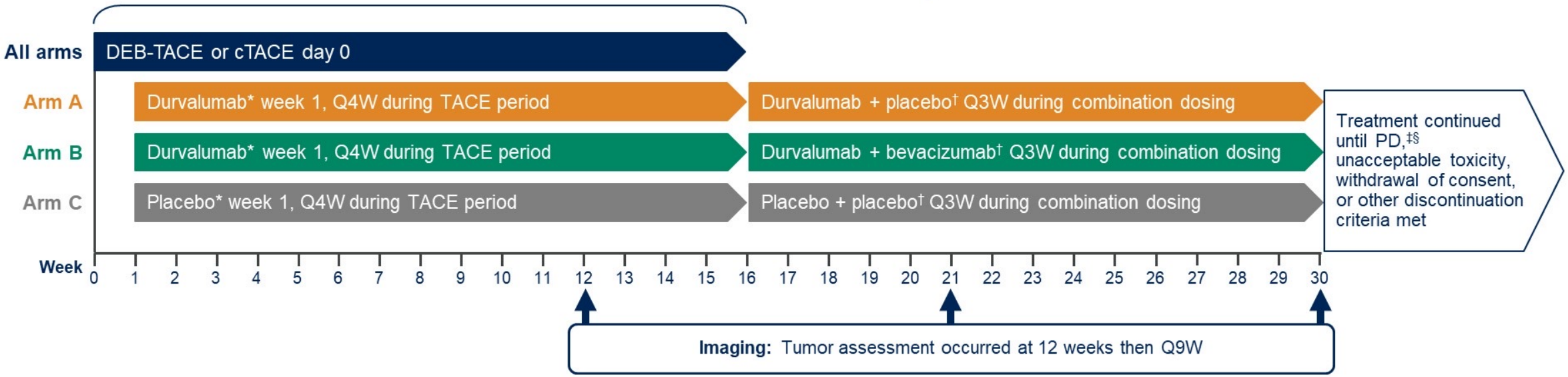
EMERALD-1 study schema

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



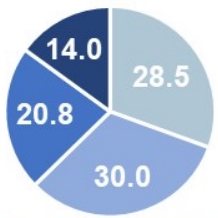
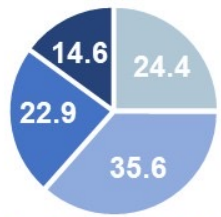
*Durvalumab / placebo started at least 7 days after TACE; doses moved to accommodate TACE if necessary. Durvalumab 1500 mg. Durvalumab / placebo Q4W until ≥14 days after last TACE. †Durvalumab 1120 mg. Bevacizumab 15 mg/kg. Durvalumab / bevacizumab / placebos Q3W. ‡Investigator-determined mRECIST-defined 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.

PRESENTED BY: Riccardo Lencioni, MD

Participant disposition

The majority of participants had 1 or 2 TACE procedures with or without durvalumab

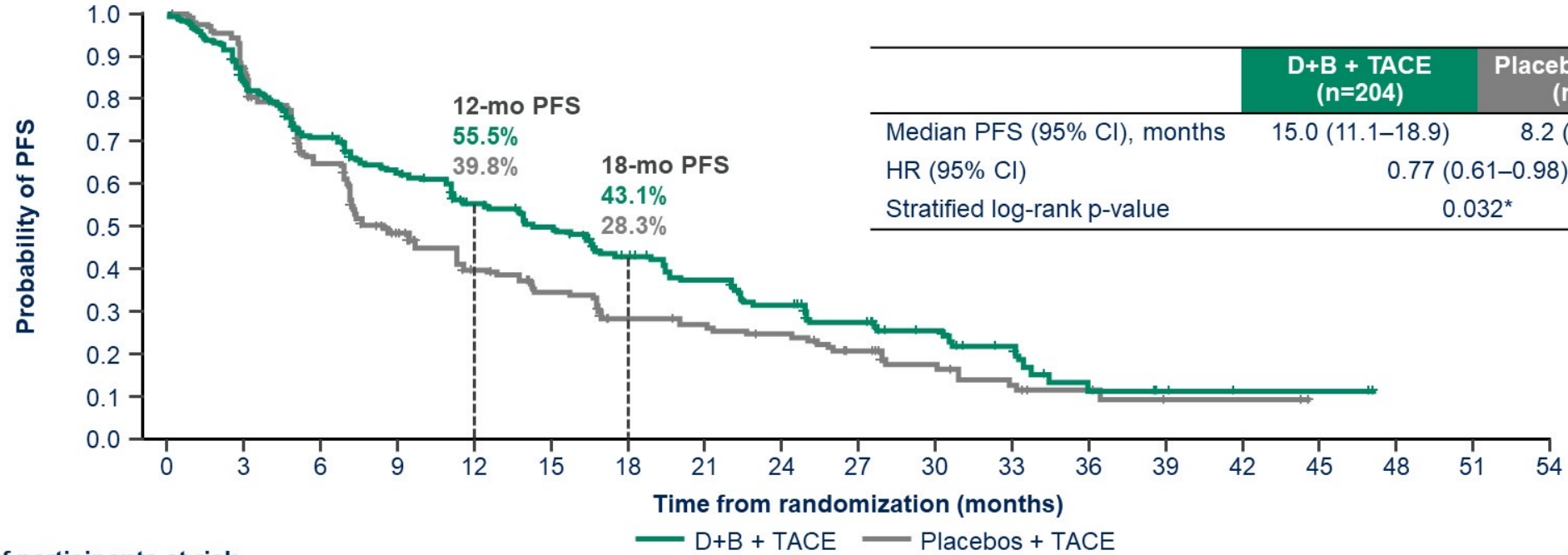
	D + TACE	D+B + TACE	Placebos + TACE
	616 participants randomized		
Randomized	**207**	**204**	**205**
No. of TACE procedures,* %				
Dosed with durvalumab,† n / N (%)	193 / 207 (93.2%)	193 / 204 (94.6%)	200 / 205 (97.6%)
Dosed with combination n / N (%)	162 / 207 (78.3%)	154 / 204 (75.5%)	155 / 205 (75.6%)
Ongoing study, n / N (%)	**88 / 207 (42.5%)‡**	**89 / 204 (43.6%)§**	**82 / 205 (40.0%)‖**
On durvalumab treatment†	25 / 193 (13.0%)	27 / 193 (14.0%)	27 / 200 (13.5%)
Discontinued study treatment, n / N (%)¶	**168 / 193 (87.0%)****	**166 / 193 (86.0%)††**	**173 / 200 (86.5%)‡‡**
Condition under investigation worsened§§	122 / 193 (63.2%)	85 / 193 (44.0%)	119 / 200 (59.5%)

*Number of TACE procedures given prior to disease progression. Some participants had additional TACE procedures beyond progression, while remaining on the study. †Participants in arm C (placebos + TACE) received placebo for durvalumab. ‡57.5% no longer ongoing study: 51.2% due to death; 5.8% due to withdrawal by participant; 0.5% due to other. §56.4% no longer ongoing study: 51.5% due to death; 4.4% due to withdrawal by participant; 0.5% due to other. ‖60.0% no longer ongoing study: 52.7% due to death; 7.3% due to withdrawal by participant. ¶Other reasons for 'discontinued study treatment' include AEs, participant decision, severe non-compliance to protocol, development of study-specific discontinuation criteria, lost to follow-up, due to COVID-19 pandemic, or other. **10.9% due to AEs; 7.3% due to participant decision; 5.2% due to other. ††22.8% due to AEs; 12.4% due to participant decision; 4.7% due to other. ‡‡8.0% due to AEs;12.5% due to participant decision; 6.0% due to other. §§Clinical or objective progression, or investigator determined participants no longer benefitting from treatment.

AE, adverse event; B, bevacizumab; D, durvalumab; TACE, transarterial chemoembolization.

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)

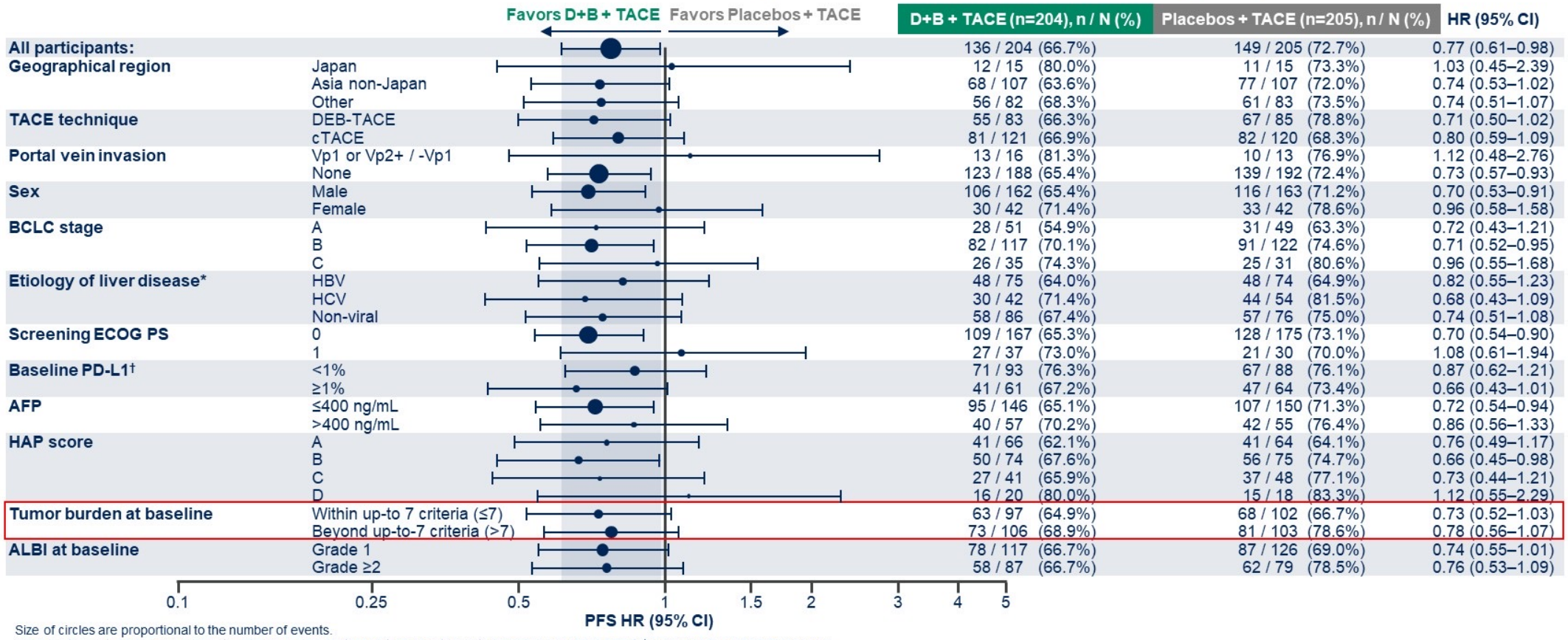
*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

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

PFS with D+B + TACE versus placebos + TACE in key subgroups

PFS benefit with D+B + TACE was generally consistent across subgroups

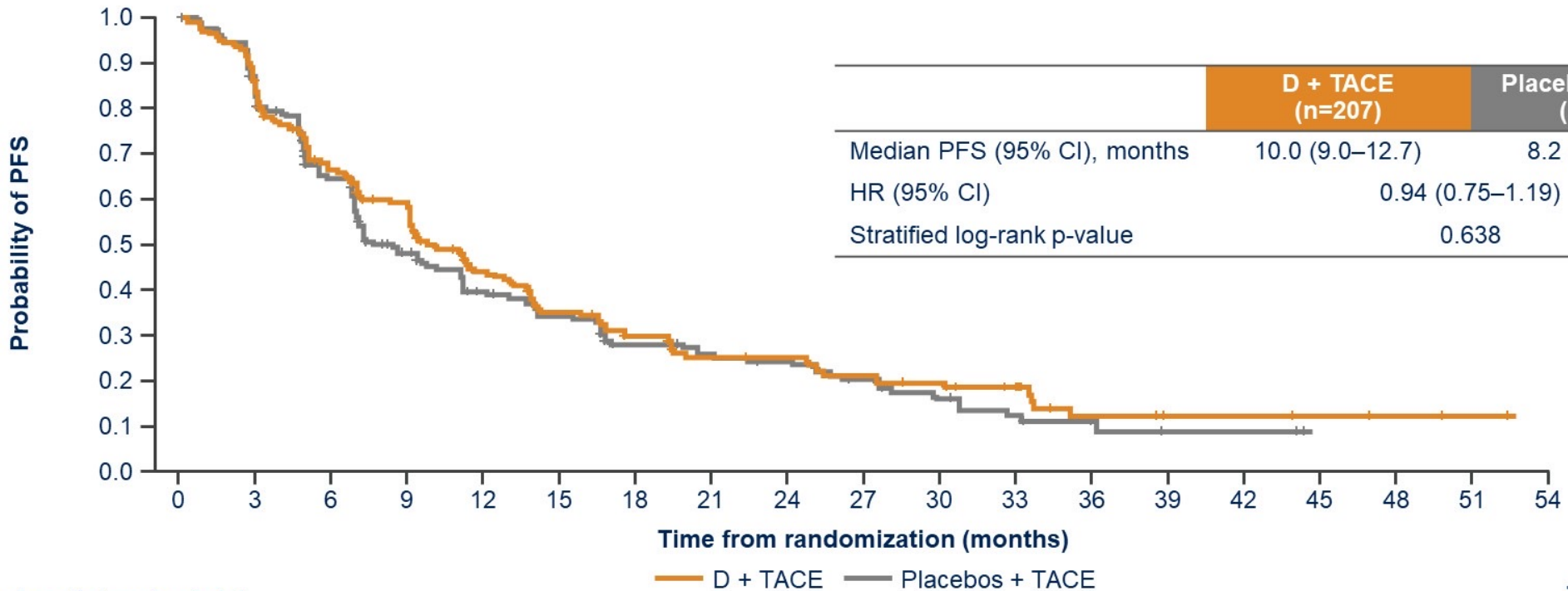


		D+B + TACE (n=204), n / N (%)	Placebos + TACE (n=205), n / N (%)	HR (95% CI)
All participants:		136 / 204 (66.7%)	149 / 205 (72.7%)	0.77 (0.61–0.98)
Geographical region	Japan	12 / 15 (80.0%)	11 / 15 (73.3%)	1.03 (0.45–2.39)
	Asia non-Japan	68 / 107 (63.6%)	77 / 107 (72.0%)	0.74 (0.53–1.02)
	Other	56 / 82 (68.3%)	61 / 83 (73.5%)	0.74 (0.51–1.07)
TACE technique	DEB-TACE	55 / 83 (66.3%)	67 / 85 (78.8%)	0.71 (0.50–1.02)
	cTACE	81 / 121 (66.9%)	82 / 120 (68.3%)	0.80 (0.59–1.09)
Portal vein invasion	Vp1 or Vp2+ / -Vp1	13 / 16 (81.3%)	10 / 13 (76.9%)	1.12 (0.48–2.76)
	None	123 / 188 (65.4%)	139 / 192 (72.4%)	0.73 (0.57–0.93)
Sex	Male	106 / 162 (65.4%)	116 / 163 (71.2%)	0.70 (0.53–0.91)
	Female	30 / 42 (71.4%)	33 / 42 (78.6%)	0.96 (0.58–1.58)
BCLC stage	A	28 / 51 (54.9%)	31 / 49 (63.3%)	0.72 (0.43–1.21)
	B	82 / 117 (70.1%)	91 / 122 (74.6%)	0.71 (0.52–0.95)
	C	26 / 35 (74.3%)	25 / 31 (80.6%)	0.96 (0.55–1.68)
Etiology of liver disease*	HBV	48 / 75 (64.0%)	48 / 74 (64.9%)	0.82 (0.55–1.23)
	HCV	30 / 42 (71.4%)	44 / 54 (81.5%)	0.68 (0.43–1.09)
	Non-viral	58 / 86 (67.4%)	57 / 76 (75.0%)	0.74 (0.51–1.08)
Screening ECOG PS	0	109 / 167 (65.3%)	128 / 175 (73.1%)	0.70 (0.54–0.90)
	1	27 / 37 (73.0%)	21 / 30 (70.0%)	1.08 (0.61–1.94)
Baseline PD-L1†	<1%	71 / 93 (76.3%)	67 / 88 (76.1%)	0.87 (0.62–1.21)
	≥1%	41 / 61 (67.2%)	47 / 64 (73.4%)	0.66 (0.43–1.01)
AFP	≤400 ng/mL	95 / 146 (65.1%)	107 / 150 (71.3%)	0.72 (0.54–0.94)
	>400 ng/mL	40 / 57 (70.2%)	42 / 55 (76.4%)	0.86 (0.56–1.33)
HAP score	A	41 / 66 (62.1%)	41 / 64 (64.1%)	0.76 (0.49–1.17)
	B	50 / 74 (67.6%)	56 / 75 (74.7%)	0.66 (0.45–0.98)
	C	27 / 41 (65.9%)	37 / 48 (77.1%)	0.73 (0.44–1.21)
	D	16 / 20 (80.0%)	15 / 18 (83.3%)	1.12 (0.55–2.29)
Tumor burden at baseline	Within up-to 7 criteria (≤7)	63 / 97 (64.9%)	68 / 102 (66.7%)	0.73 (0.52–1.03)
	Beyond up-to-7 criteria (>7)	73 / 106 (68.9%)	81 / 103 (78.6%)	0.78 (0.56–1.07)
ALBI at baseline	Grade 1	78 / 117 (66.7%)	87 / 126 (69.0%)	0.74 (0.55–1.01)
	Grade ≥2	58 / 87 (66.7%)	62 / 79 (78.5%)	0.76 (0.53–1.09)

Size of circles are proportional to the number of events.
*One participant in each arm had both HBV and HCV. Neither of these participants experienced a PFS event. †Baseline PD-L1 TAP expression.
AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; B, bevacizumab; BCLC, Barcelona Clinical Liver Cancer; CI, confidence interval; cTACE, conventional transarterial chemoembolization; D, durvalumab; DEB-TACE, drug-eluting bead-transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; HAP, hepatoma arterial-embolization prognostic; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PS, performance status; TACE, transarterial chemoembolization; TAP, tumor area positivity.

PFS with D + TACE versus placebos + TACE: secondary endpoint

PFS was not significantly improved with D + TACE versus placebos + TACE



	D + TACE (n=207)	Placebos + TACE (n=205)
Median PFS (95% CI), months	10.0 (9.0–12.7)	8.2 (6.9–11.1)
HR (95% CI)	0.94 (0.75–1.19)	
Stratified log-rank p-value	0.638	

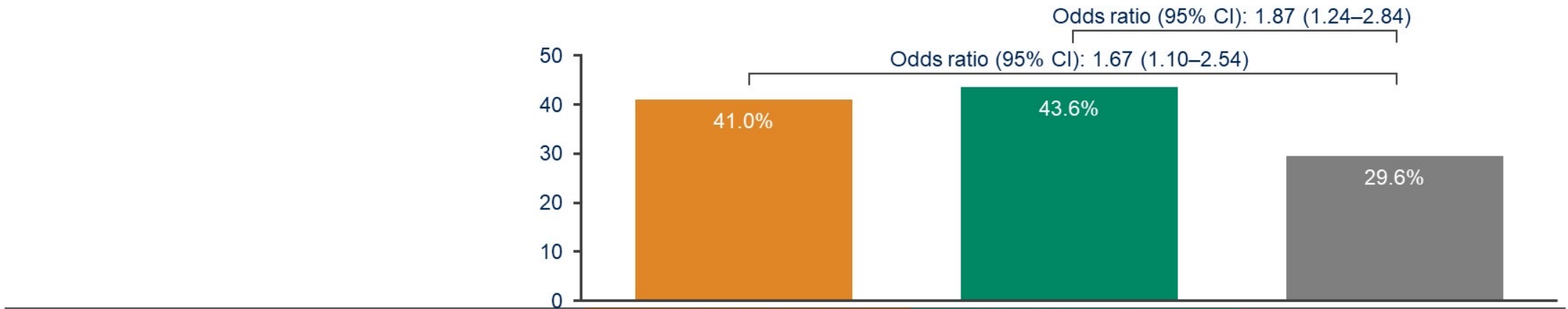
No. of participants at risk

																			Total events
D + TACE	207	160	124	103	71	53	42	33	32	27	22	14	7	5	5	4	2	1	0	144
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 + TACE 11.5 (0.03–52.4) 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 + TACE 27.7 (17.7–30.3) months, Placebos + TACE 26.3 (16.7–30.4) months.
PFS was assessed by BICR (RECIST v1.1)
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.

ORR using BICR per RECIST v1.1

ORR was improved with both D + TACE and D+B + TACE versus placebos + TACE



	D + TACE (n=207)	D+B + TACE (n=204)	Placebos + TACE (n=205)
Participants with measurable disease at baseline	205	202	203
Confirmed response,* n (%)	84 (41.0)	88 (43.6)	60 (29.6)
Complete response, n (%)	3 (1.5)	6 (3.0)	5 (2.5)
Partial response, n (%)	81 (39.5)	82 (40.6)	55 (27.1)
Stable disease ≥20 weeks, n (%)	42 (20.5)	45 (22.3)	63 (31.0)
Median duration of response, (LQ–UQ) months	14.0 (6.9–30.7)	22.1 (11.2–30.3)	16.4 (6.3–26.3)

*Responses included confirmed complete or partial response.
B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; LQ, lower quartile; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization; UQ, upper quartile.

Most common maximum Grade 3 or 4 TEAEs

Incidence of maximum Grade 3 or 4 AEs was low across all arms, with no unexpected safety signals

AE, n (%)	D + TACE (n=232)	D+B + TACE (n=154)	Placebos + TACE (n=200)
Hypertension	5 (2.2)	9 (5.8)	1 (0.5)
Anemia	10 (4.3)	7 (4.5)	3 (1.5)
Acute kidney injury	4 (1.7)	6 (3.9)	0
Proteinuria	0	6 (3.9)	0
Post-embolization syndrome	8 (3.4)	5 (3.2)	8 (4.0)
Hepatic encephalopathy	1 (0.4)	5 (3.2)	3 (1.5)
Ascites	4 (1.7)	4 (2.6)	3 (1.5)
Hyponatremia	1 (0.4)	4 (2.6)	0
Esophageal varices hemorrhage	0	4 (2.6)	1 (0.5)

AEs occurring in ≥2% of participants by preferred term in any arm.
AE, adverse event; B, bevacizumab; D, durvalumab; TACE, transarterial chemoembolization; TEAE, treatment-emergent adverse event.

PANCREATIC CANCER - KRAS

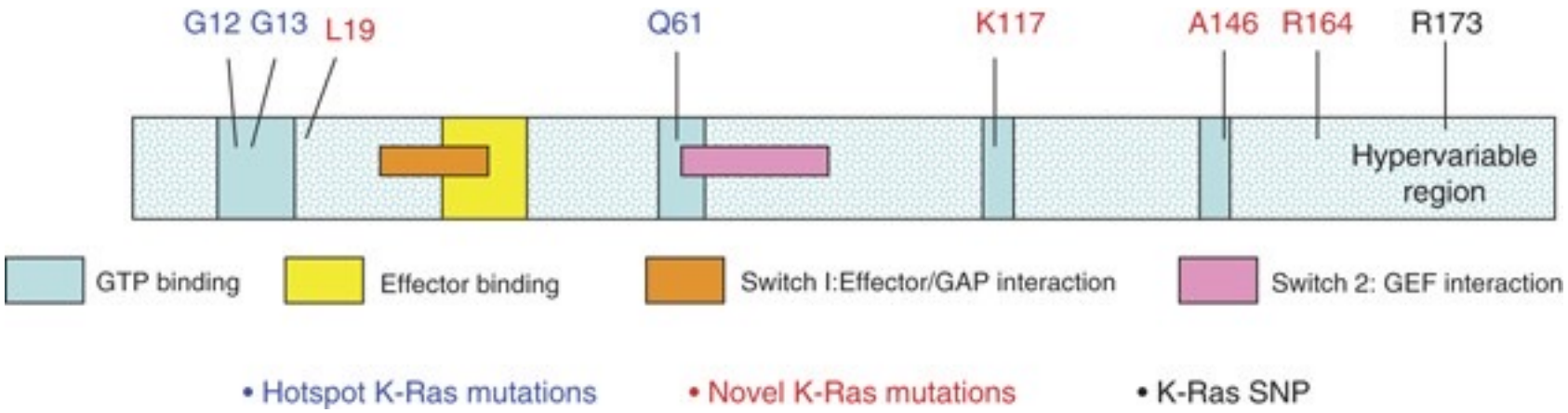
KRAS MUTANT

~90%

KRAS WILD TYPE

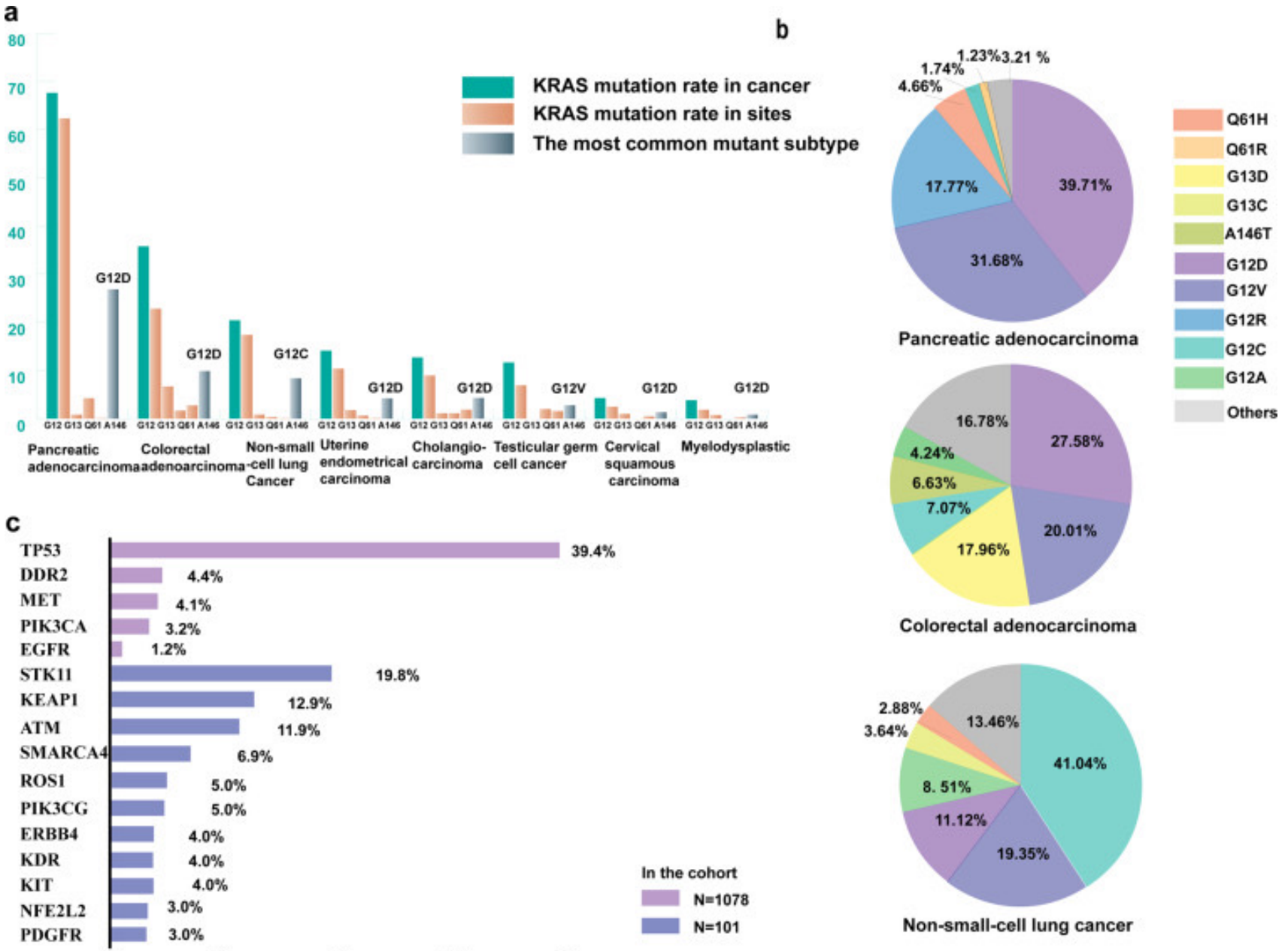
~10%

PANCREATIC CANCER - KRAS



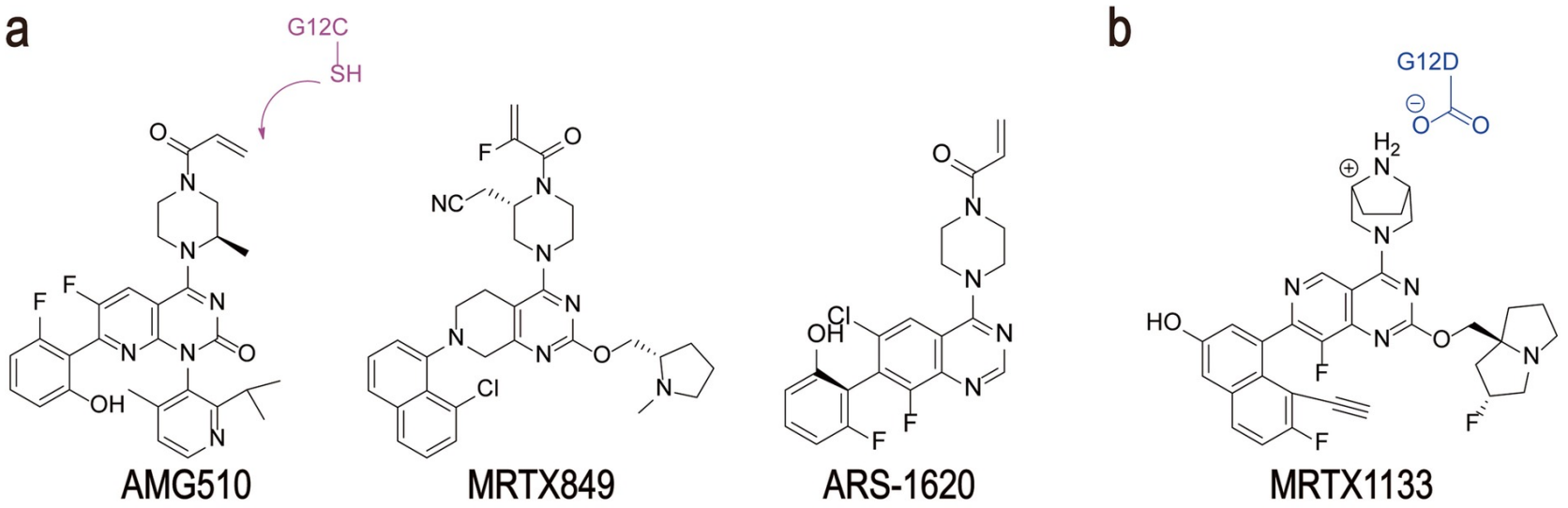
SMITH ET AL, BJC 2010

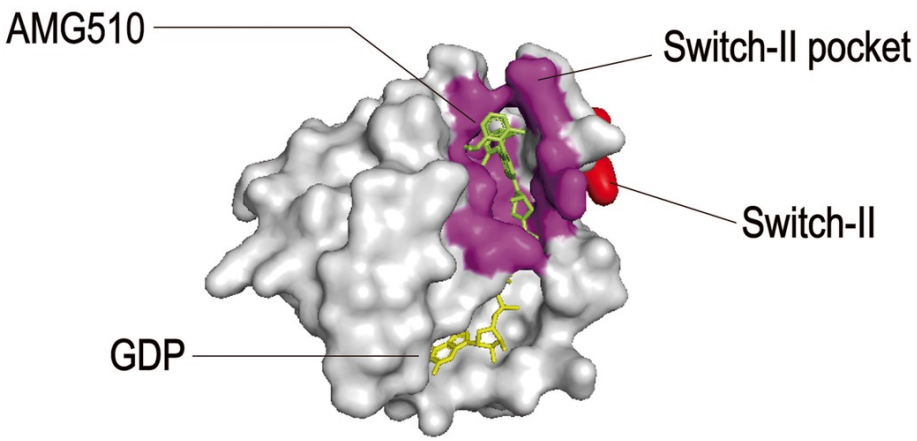
PANCREATIC CANCER - KRAS

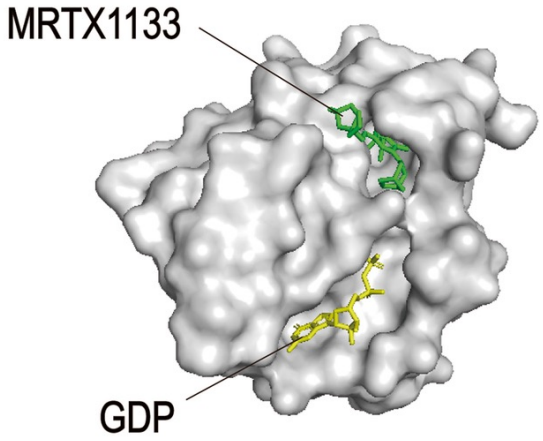


HUANG ET AL, SIG TRANS AND TARG THER 2021

KRAS TARGET SITES FOR NEXT-GEN THERAPIES







ZHU ET AL, MOLECULAR CANCER 2022

KRAS G12C IN PANCREATIC CANCER - SOTORASIB

RESPONSE RATE : 21% (N=38)

PFS : 4 MONTHS

DCR : 84%

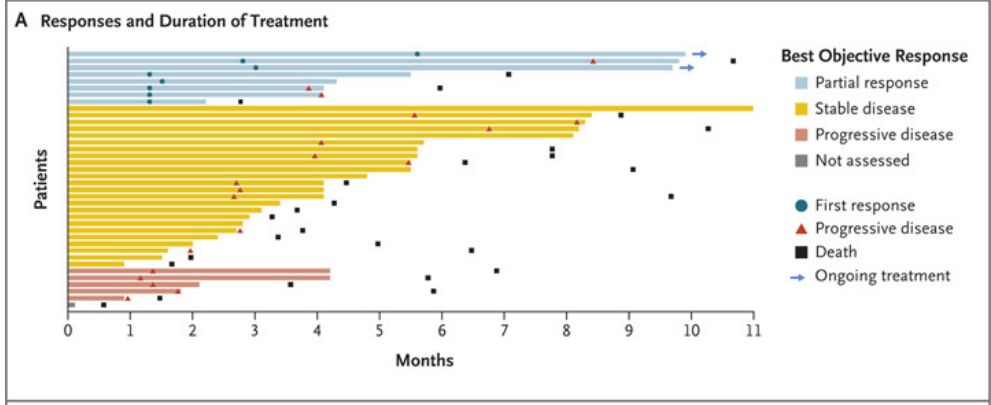
OS : 6.9 MONTHS

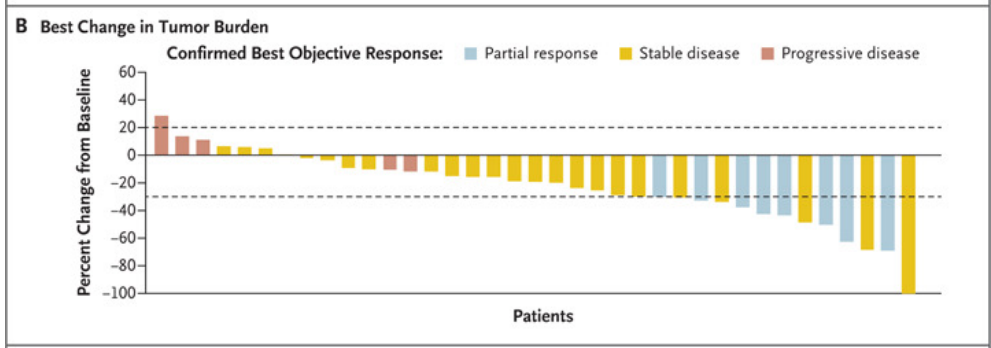
TTR : 1.5 MONTHS

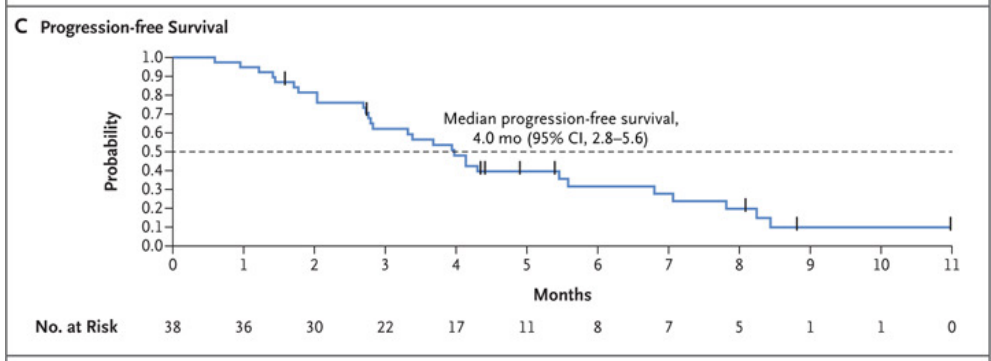
DOR : 5.7 MONTHS

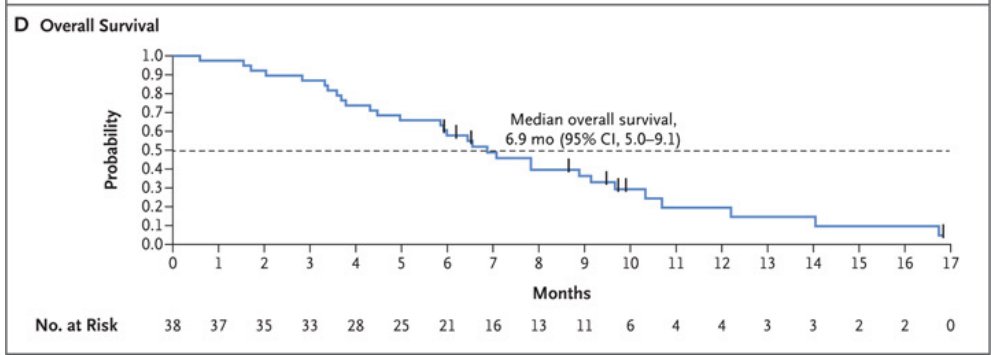
SAFETY : DIARRHEA, NAUSEA, FATIGUE, RASH

STRICKLER ET AL, NEJM 2023









KRAS G12C IN PANCREATIC CANCER AND BTC - ADAGRASIB

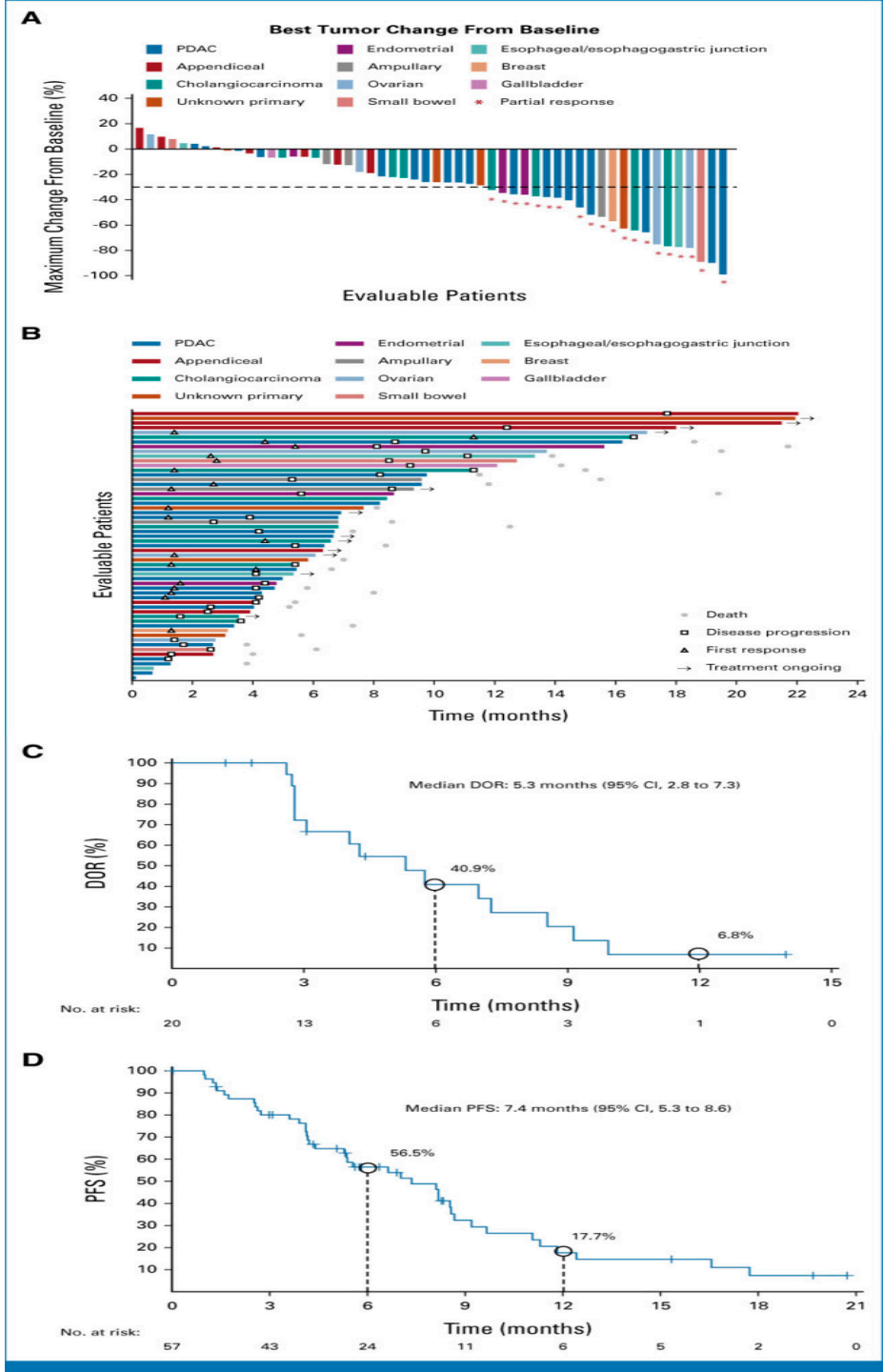
RESPONSE RATE PANCREATIC CA : 33.3% (N=21)

RESPONSE RATE BILIARY TRACT CA: 47.1% (N=12)

PFS : 5.4 MONTHS

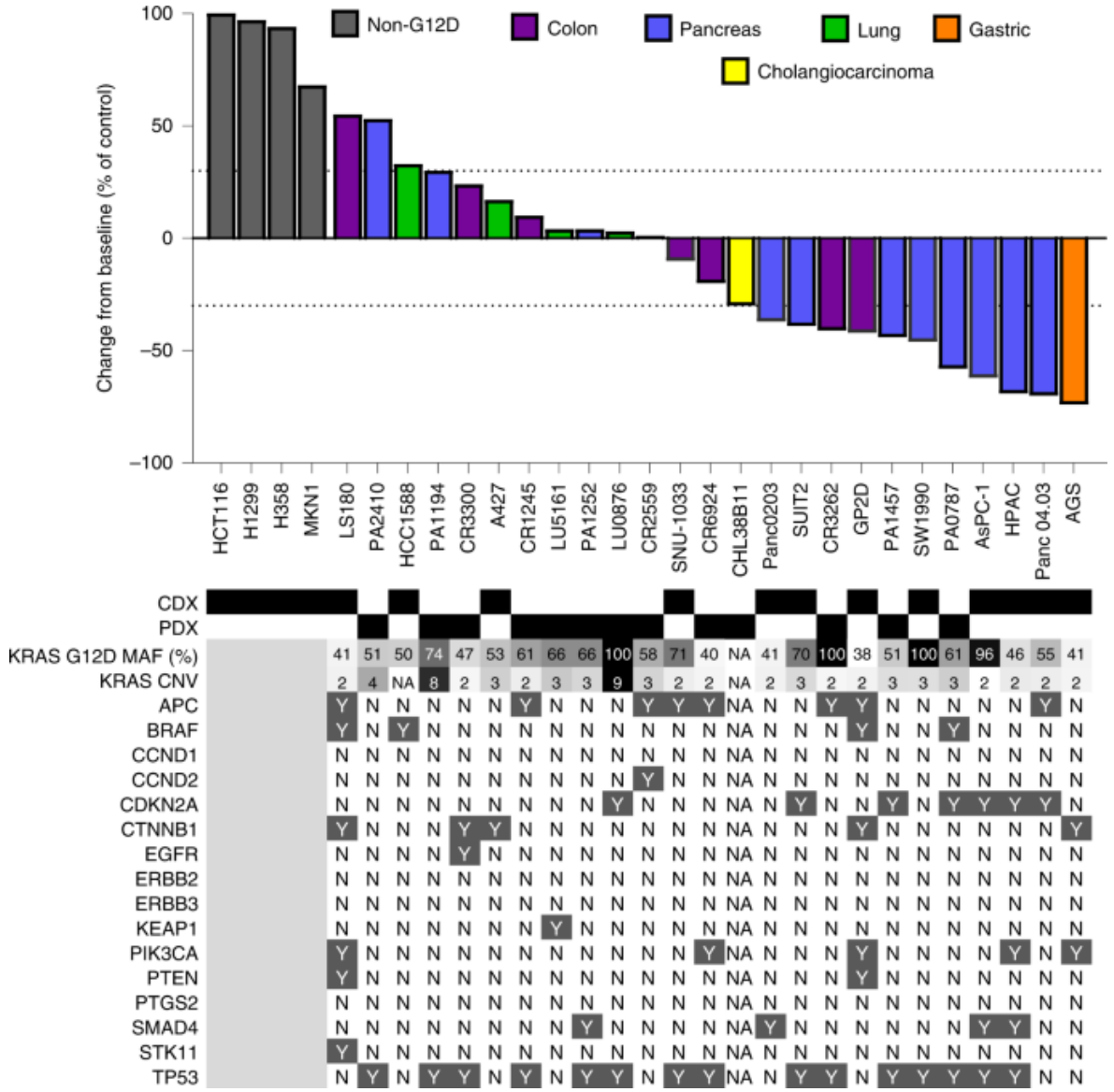
OS : 8 MONTHS

SAFETY : DIARRHEA, NAUSEA, FATIGUE, VOMITING



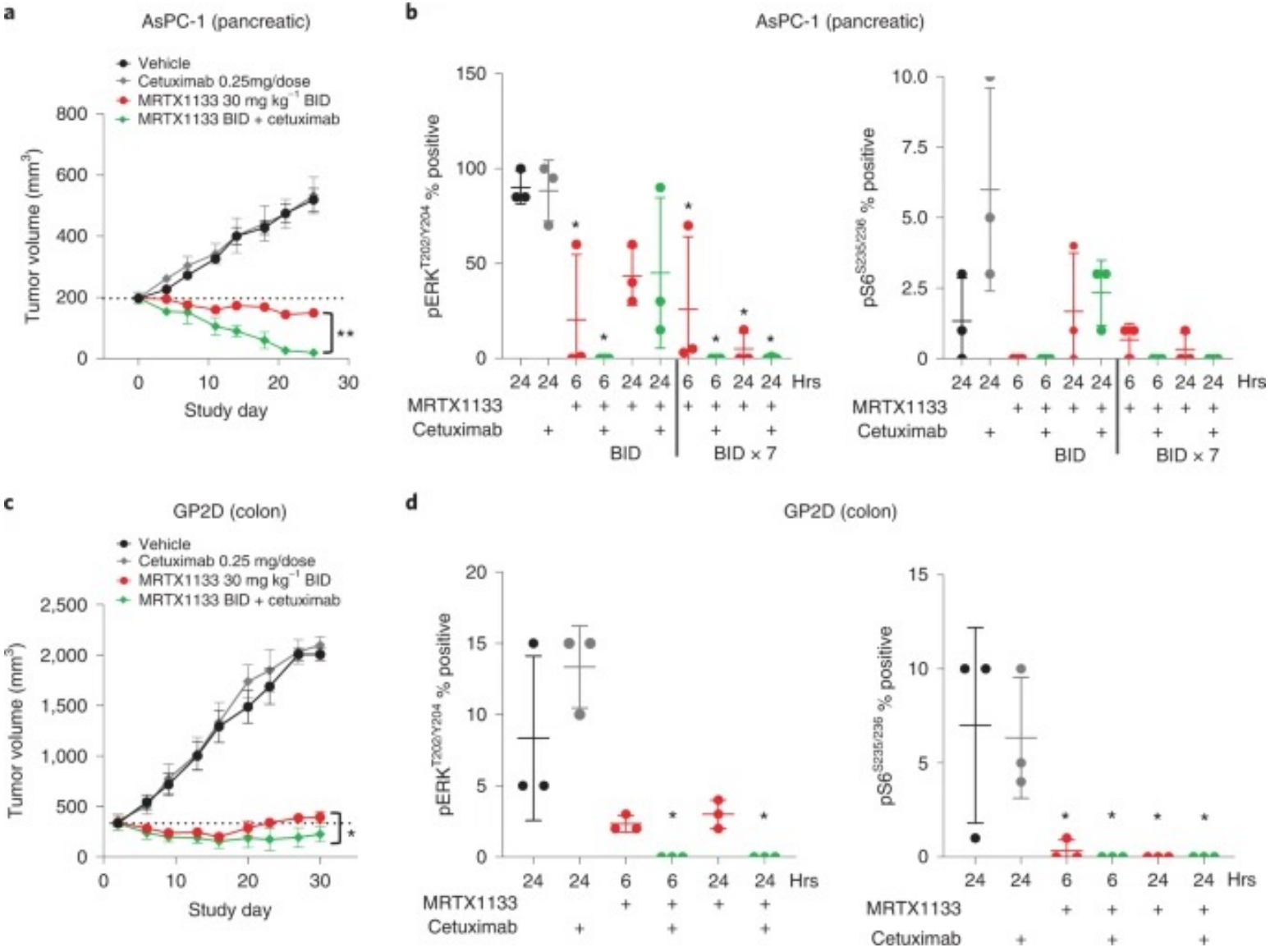
BEKAII-SAAB ET AL, J CLIN ONC 2023

KRAS G12D IN PANCREATIC CANCER – MRTX1133



HALLIN ET AL, NATURE MED 2022

KRAS G12D IN PANCREATIC CANCER – MRTX1133



HALLIN ET AL, NATURE MED 2022

MADRID 2023 ESMO congress

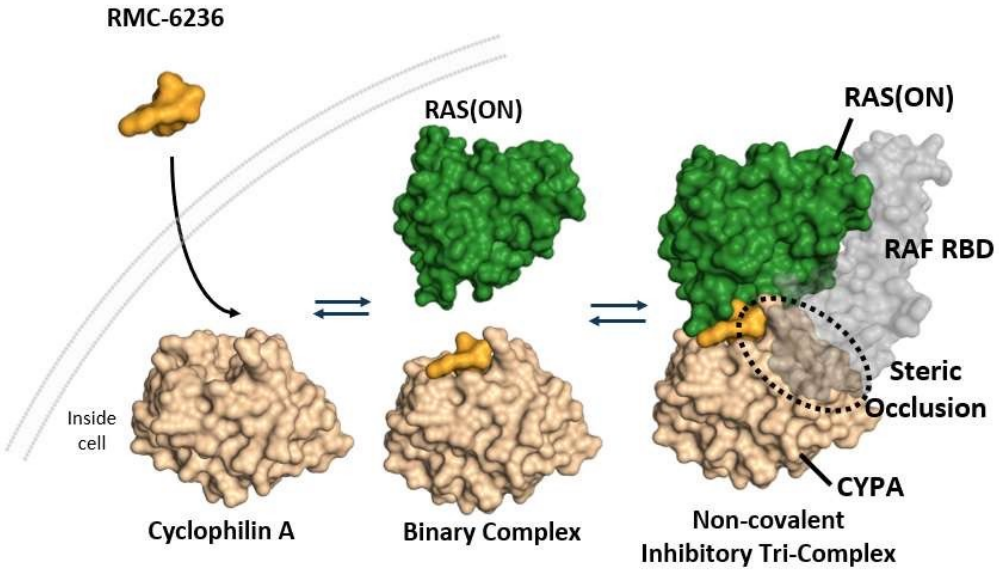
Preliminary Clinical Activity of RMC-6236, a First-in-Class, RAS-Selective, Tri-Complex RAS^{MULTI}(ON) Inhibitor in Patients with KRAS-Mutant Pancreatic Ductal Adenocarcinoma (PDAC) and Non-Small Cell Lung Cancer (NSCLC)

Kathryn C. Arbour[1], Salman Punekar[2], Ignacio Garrido-Laguna[3], David S. Hong[4], Brian M. Wolpin[5], Meredith Pelster[6], Minal Barve[7], Alexander N. Starodub[8], David Sommerhalder[9], Sumit Kar[10], Stephanie Chang[10], Ying Zhang[10], Zeena Salman[10], Xiaolin Wang[10], W. Clay Gustafson[10], Alexander I. Spira[11]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]New York University Medical Center, New York, USA; [3]University of Utah Health – Huntsman Cancer Institute, Salt Lake City, UT, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, USA; [5]Dana Farber Cancer Institute, Boston, USA; [6]Sarah Cannon Research Institute, Nashville, USA; [7]Mary Crowley Cancer Research Center, Dallas, USA; [8]The Christ Hospital – Hematology & Oncology, Cincinnati, USA; [9]NEXT Oncology™, San Antonio, USA; [10]Revolution Medicines, Inc., Redwood City, USA; [11]Virginia Cancer Specialists, NEXT Oncology, Fairfax, USA.

RMC-6236 is a First-in-Class, RAS^{MULTI}(ON) Inhibitor

- RMC-6236 is a novel, oral, non-covalent RAS^{MULTI}(ON) inhibitor that is selective for the active, GTP-bound or ON state of both mutant and wild-type variants of the canonical RAS isoforms
- Preclinical studies have demonstrated deep and sustained regressions across multiple RAS^{MUT} tumor types, particularly PDAC and NSCLC harboring KRAS^{G12X} mutations



KRAS^{G12X} defined as mutation at codon 12 which encodes glycine (G) to X where X = A, D, R, S, or V.
CYPA, cyclophilin A; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog; Mut, mutant; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain.

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ARBOUR ET AL, ESMO 2023

RMC-6236-001 Phase 1 Study Design

Key Eligibility Criteria

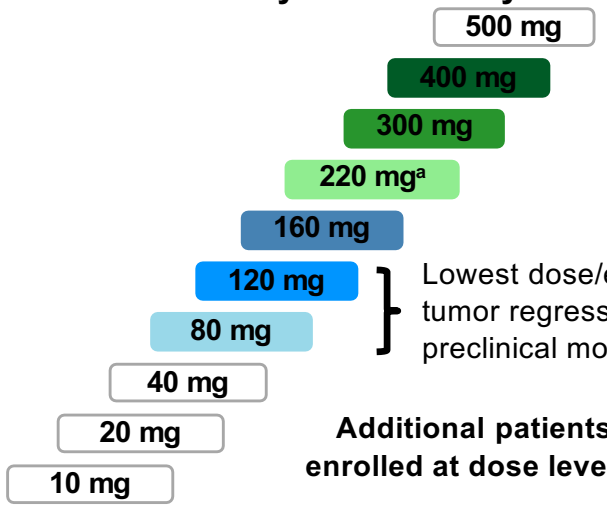
- Advanced solid tumors with KRAS^{G12X} mutations (currently excluding KRAS^{G12C})
- Received prior standard therapy appropriate for tumor type and stage
- ECOG PS 0–1
- No active brain metastases

Key Endpoints

- Safety and tolerability[1]
- Pharmacokinetics
- Anti-tumor activity

Dose Escalation

RMC-6236 administered orally QD, 21-day treatment cycle



Lowest dose/exposure range projected to drive tumor regressions in humans based on preclinical models

Additional patients with NSCLC or PDAC were enrolled at dose levels that cleared DLT evaluation

Dose Expansion / Optimization

DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; QD, once daily.

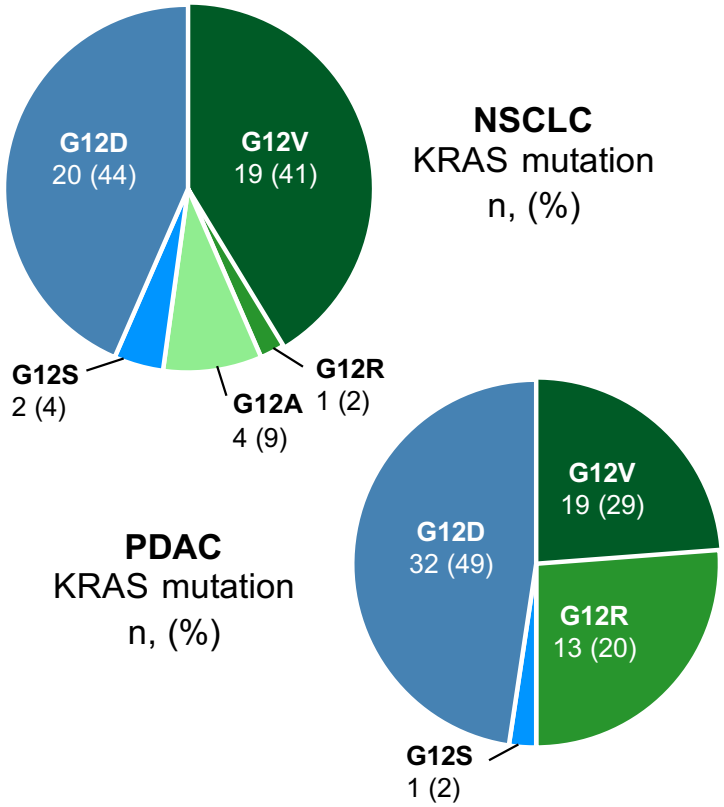
[a]220 mg cleared DLT evaluation and a dose of 200 mg was selected for further expansion/optimization.
KRAS^{G12X} defined as mutation at codon 12 which encodes glycine (G) to X where X = A, D, R, S, or V.

1. Spira A, et al. Presentation at AACR-NCI-EORTC International Conference On Molecular Targets And Cancer Therapeutics; abstract #33378.

ARBOUR ET AL, ESMO 2023

Patient Demographics and Baseline Characteristics

	NSCLC[a] N = 46	PDAC[a] N = 65
Age, median (range), years	65 (31–83)	64 (30–86)
Female, n (%)	25 (54)	31 (48)
ECOG PS, n (%)		
0	11 (24)	20 (31)
1	35 (76)	45 (69)
Smoking status, n (%)		
Current	2 (4)	2 (3)
Past	28 (61)	14 (22)
Never	16 (35)	49 (75)
Number of prior anti-cancer therapies, median (range)	2 (1–6)	3 (1–7)
Select type of prior anti-cancer therapy/regimens, n (%)		
Checkpoint inhibitor[b]	44 (96)	–
Platinum-based chemotherapy	46 (100)	–
FOLFIRINOX	–	45 (69)
Gemcitabine + nab-paclitaxel	–	49 (75)



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Data Extracted 12 Oct 2023.

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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.

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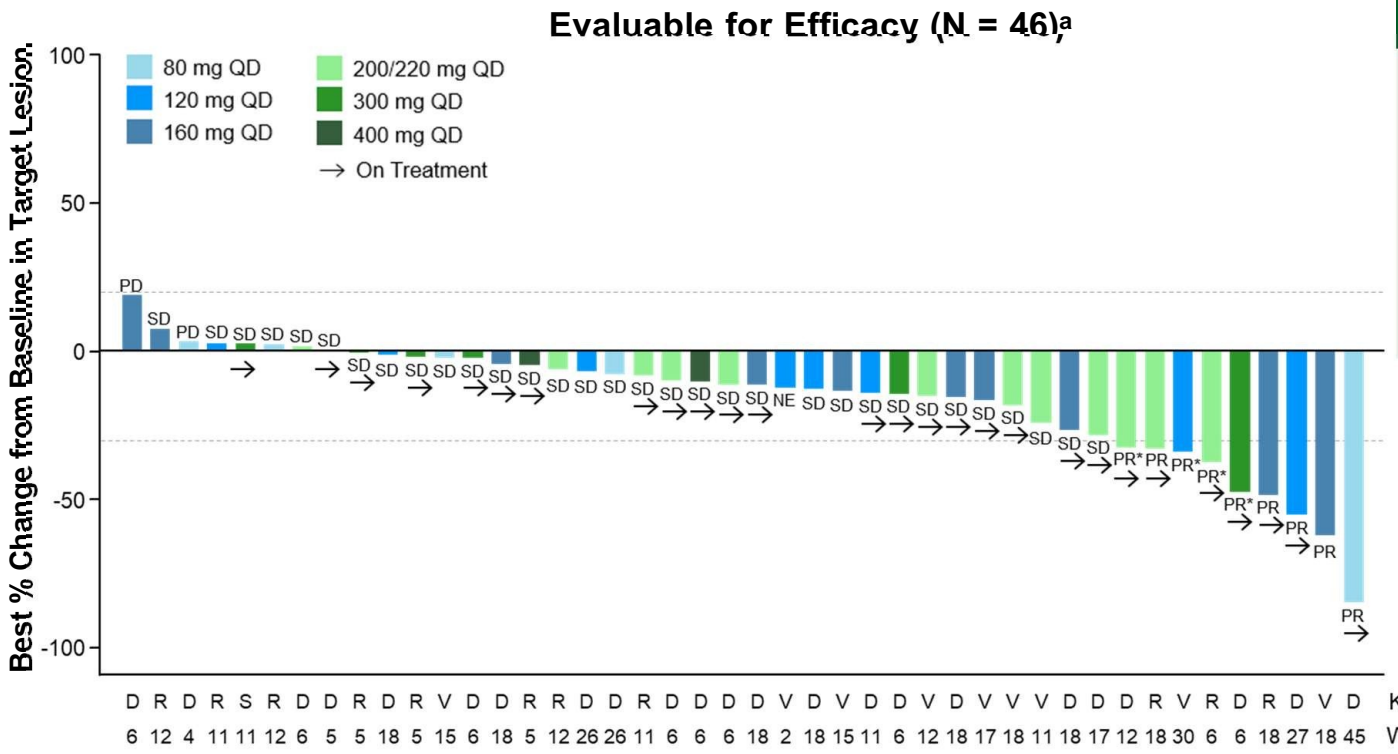
KRAS^{G12X} PDAC: Best Response



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.

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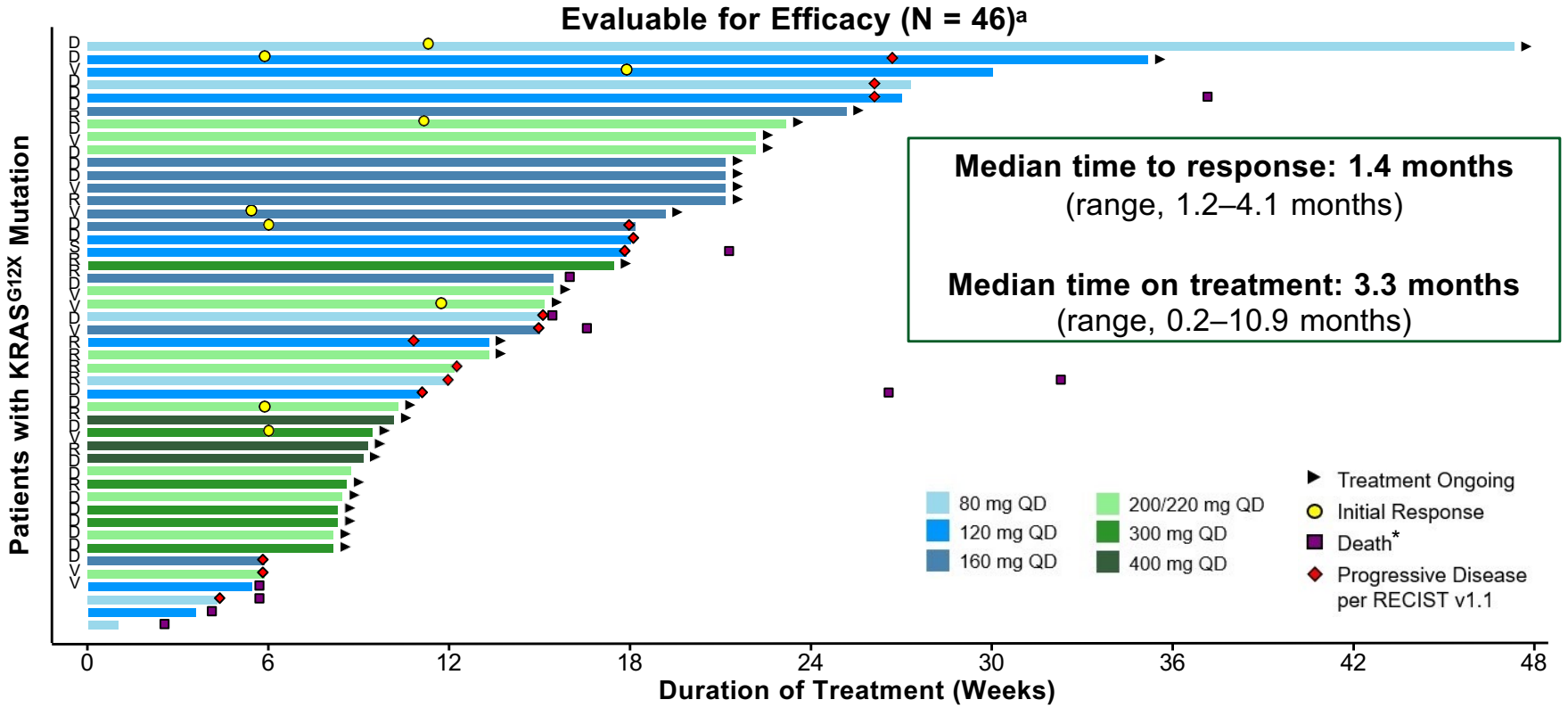
KRAS^{G12X} PDAC: Duration of Treatment and Responses



[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date. *Death due to PD (n = 9), Death due to unrelated AE (n = 2).

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Case Report: Patient with $KRAS^{G12R}$ PDAC

Demographics and Baseline Characteristics

- 57-year-old man
- Diagnosed with PDAC in 2022

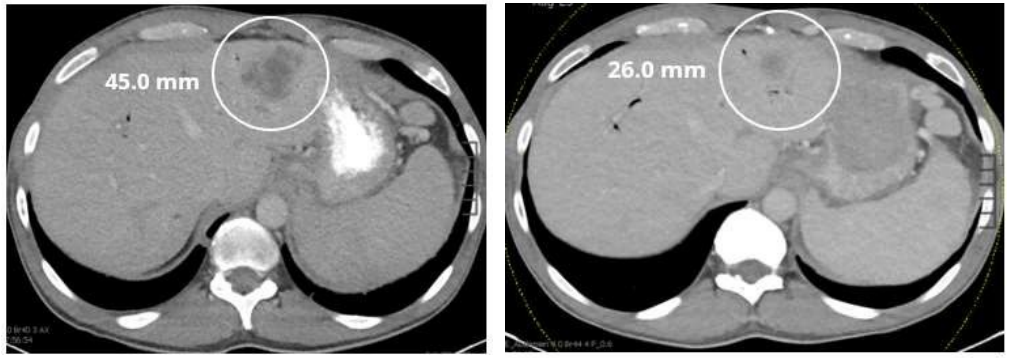
Treatment History

- Prior therapies
  - Gemcitabine/nab-paclitaxel/ canakinumab/spartalizumab
  - FOLFIRINOX

RMC-6236 Treatment Course

- Started at 160 mg QD
- Partial response achieved at Week 6 (confirmed); ongoing

Baseline **On-Treatment, Week 12**



Target Lesion: Segment 2 Liver

Target Lesion	Baseline	On Treatment
1. Segment 2 liver	45 mm	26 mm
2. Lung (medial basilar left lower lobe nodule)	17 mm	6 mm
3. Lung (right lower lobe nodule)	10 mm	6 mm
Sum of Diameters	72 mm	38 mm **(−47% ↓)**
Overall Response (RECIST 1.1)	**--**	**PR**

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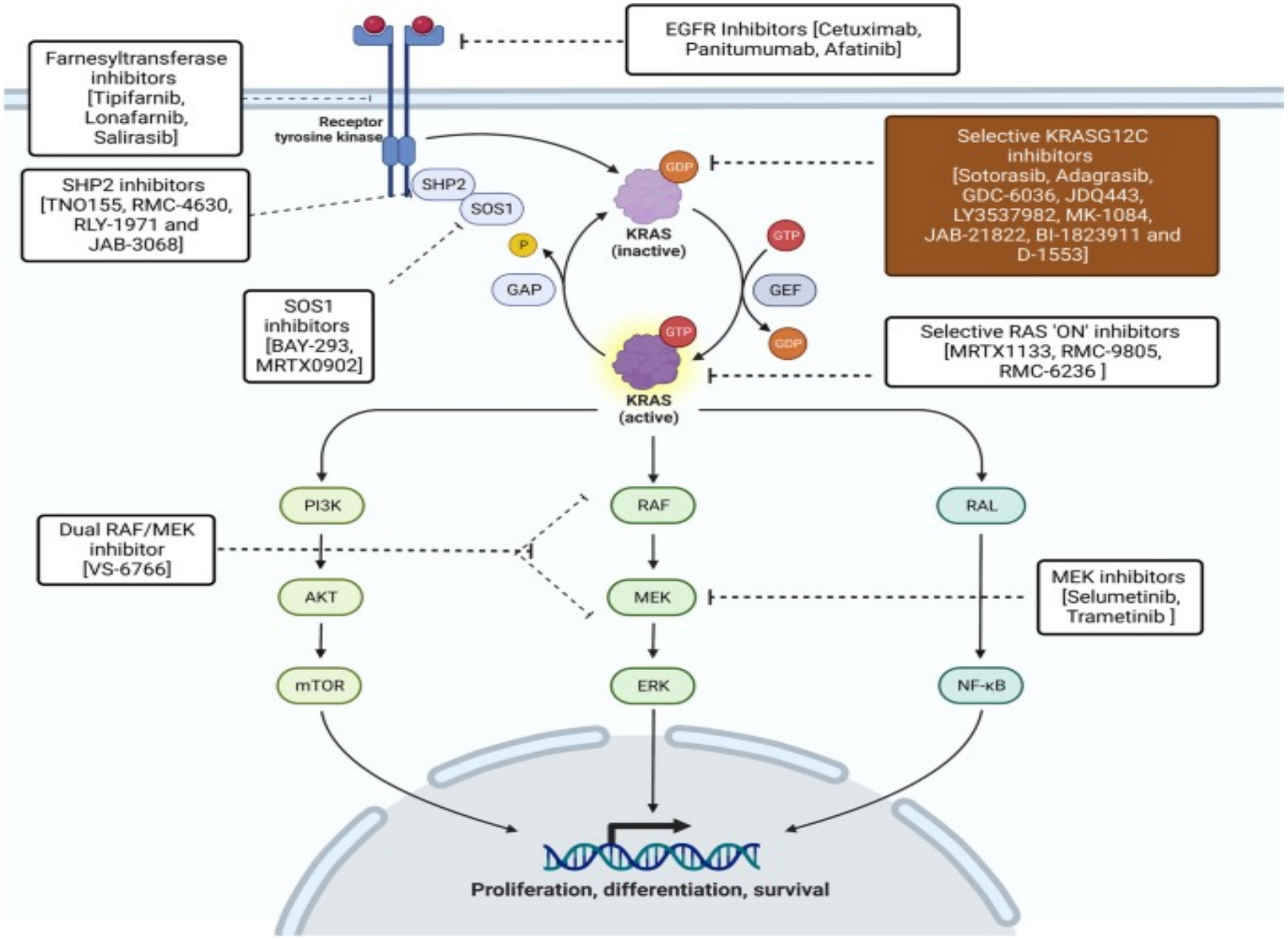
Conclusions

- RMC-6236 is an oral, first-in-class, RAS-selective, RAS^{MULTI}(ON) inhibitor.
- At clinically active doses, RMC-6236 was generally well tolerated.
- RMC-6236 demonstrated encouraging anti-tumor activity in patients with previously treated NSCLC and PDAC across several dose levels and $KRAS^{G12X}$ genotypes, including KRAS mutant genotypes G12D, G12V, and G12R.
- Reduction in KRAS VAF in ctDNA correlated with clinical response across tumor types.
- The dose escalation and dose optimization portion of the study is ongoing and includes plans for monotherapy expansion into additional solid tumor cohorts.
- Preliminary safety and clinical activity data support the ongoing development of RMC-6236 as a single agent and future explorations of RMC-6236 in combination with RMC-6291, immunotherapy, and other anti-cancer therapies.

KRAS : FROM UNDRUGGABLE TO DRUGGABLE



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IMPLICATIONS AND FUTURE DIRECTIONS

1. Immune checkpoint doublets are efficacious in HCC
2. Immune checkpoint inhibitors with TACE can be used in earlier stage HCC
3. KRAS G12C inhibitors have demonstrated efficacy in pancreatic and biliary tract cancers
4. RAS ON inhibitors have shown efficacy in pancreatic cancer

QUESTIONS ?