Emerging Therapies for advanced BTCs

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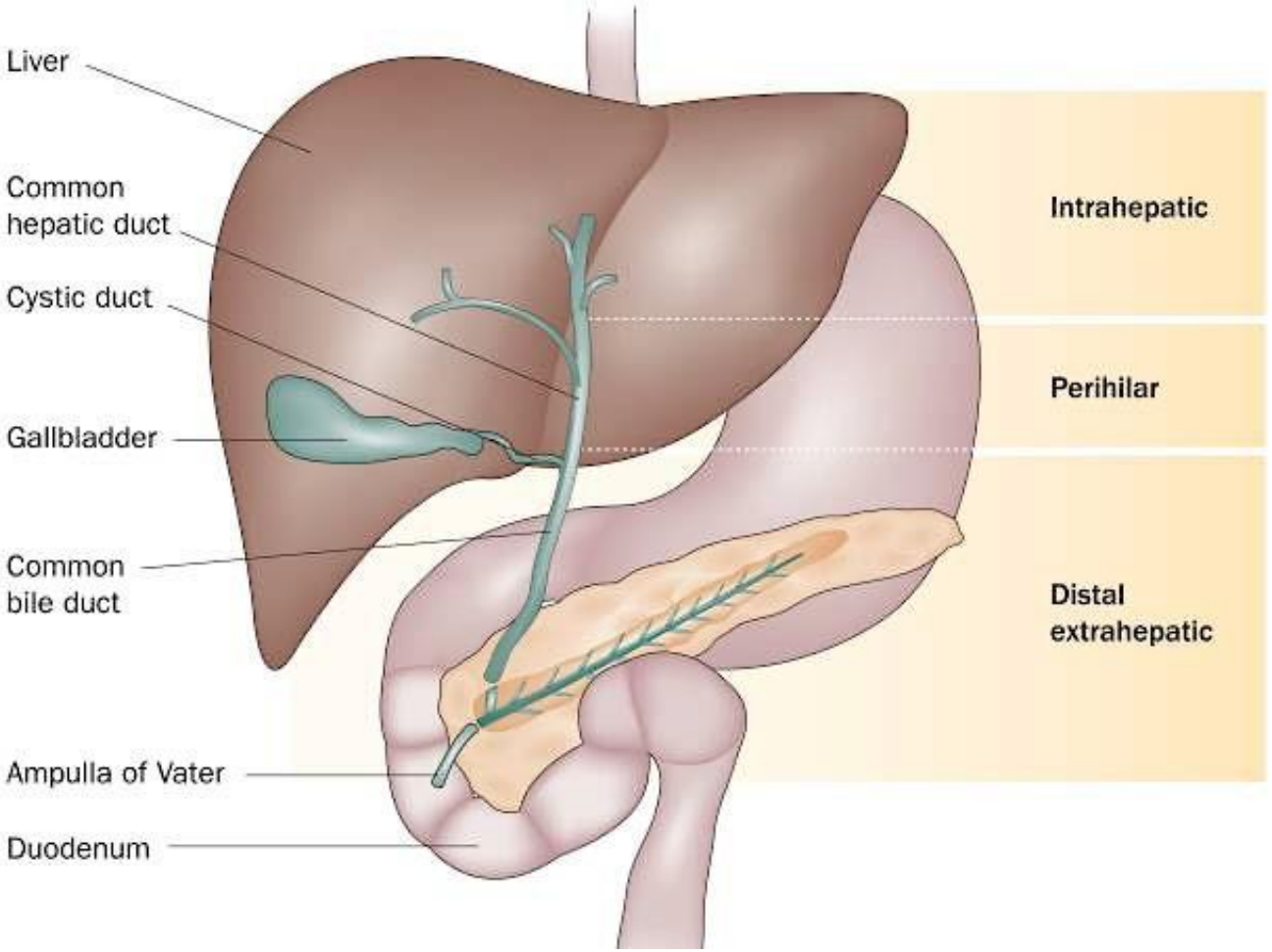
Objectives

- To understand the impact of cholangiocarcinomas
- To recognize the value of mutational analysis in the field of BTCs
- To know the role of IO in metastatic BRC (already been outlined)
- To elaborate on the role of new TKIs in cholangiocarcinoma
- To be able to order the most important mutational chanes needed to be checked for the treatment of metastatic cholangiocarcinoma

Outlines

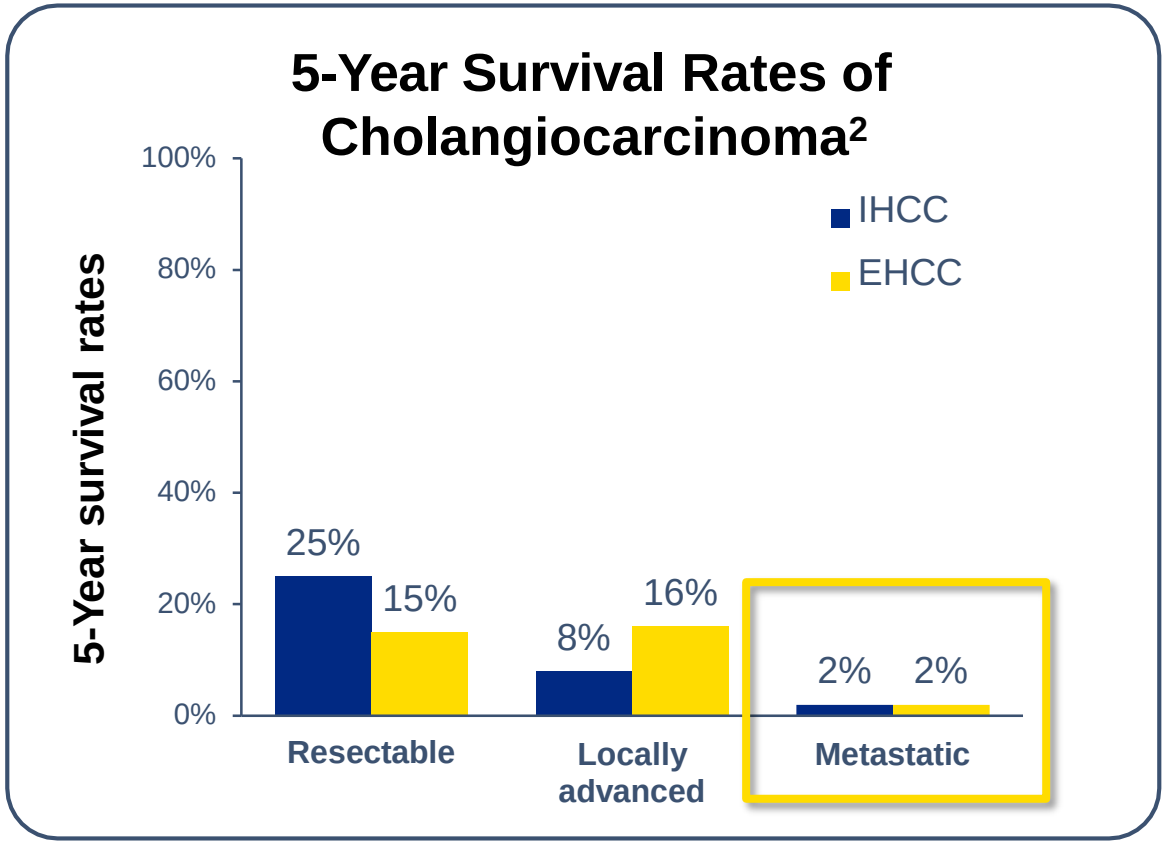
- ***2nd line options***
  - ***Driver's mutations:***
  - ❖ ***FGFR-2 fusion / rearrangments***
    - ➢ Pemigatinib (FIGHT-202)
    - ➢ Futibatinib (FOENIX-CCA2)
    - ➢ Derazanitinib (FIDES-01)
  - ❖ ***IDH-1 mutations:***
    - ➢ Ivosedinib (ClarIDHy)
  - ❖ ***HER-2 positive:***
    - ➢ Trastuzumab + Pertuzumab (myPathway)
    - ➢ Varlitinib + Capecitabine (TreeTOpp)
    - ➢ Trastuzumab Deruxtecan
    - ➢ Zanidatamab
    - ➢ Neratinib
  - ❖ ***Proteasome inhibitor:***
    - ➢ Bortezomib
  - ❖ ***BRAF mutation:***
    - ➢ Dabrafenib + Trametinib (ROAR trial)
- ***Tumor Agnostic / MSI-H:***
  - ➢ Pembrolizumab (Also in TMB-H) (KEYNOTE 158)
  - ➢ Nivolumab
  - ➢ Pembrolizumab + Lenvantinib (LEP)

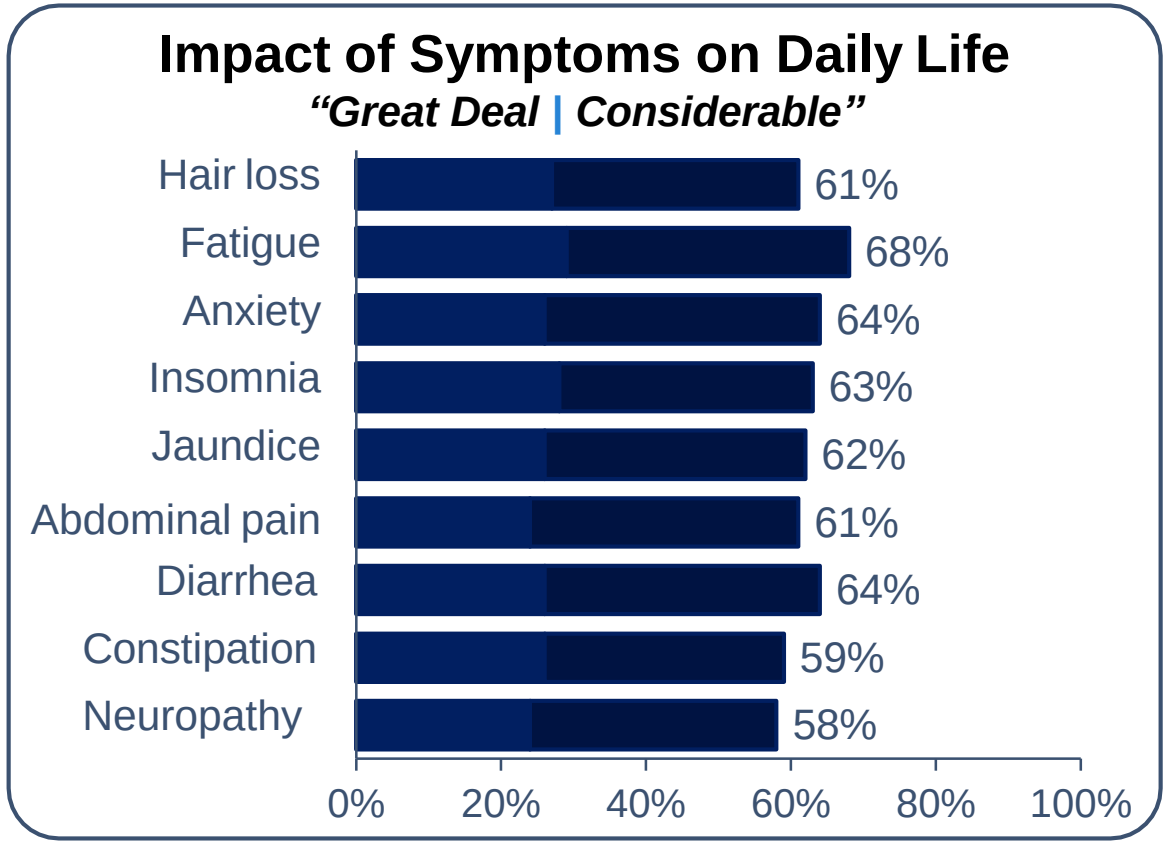
Cholangiocarcinoma Biology and Diagnosis



- Rare, aggressive malignancy[1]
- 2nd most common primary liver malignancy[2]
- **Intrahepatic**: arises from the bile ducts inside the liver[1]
- **Extrahepatic**: includes *perihilar* and *distal* disease which arise from the bile duct outside the liver[2]
- Patients are typically asymptomatic in the early stages of the disease[3]
- >75% of patients have locally advanced or metastatic disease at diagnosis[4]

Poor Prognosis and Symptom Burden





In metastatic CCA median overall survival has remained ≤ 1 year with current single-drug or combination therapy, highlighting the need for new systemic treatment options in this setting[3]

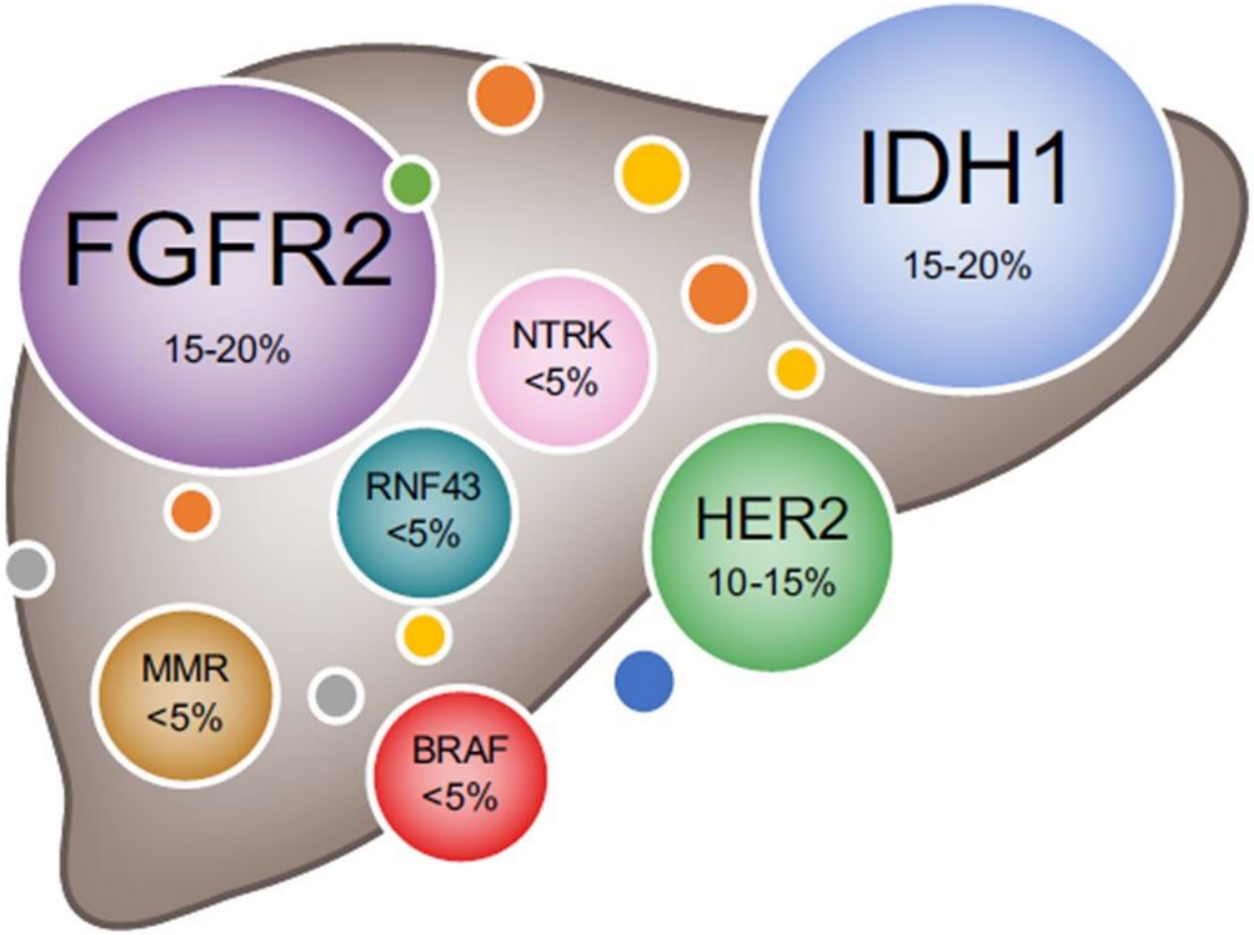
APC, annual percentage change; EHCC, extrahepatic cholangiocarcinoma; IHCC, intrahepatic cholangiocarcinoma

1. SEER Cancer Stats Facts: Common Cancer Sites. Available from: https://seer.cancer.gov/statfacts/html/common.html. Accessed July 7, 2021. 2. American Cancer Society. Survival rates for bile duct cancer. Available from: https://www.cancer.org/cancer/bile-duct-cancer/detection-diagnosis-staging/survival-by-stage.html. Accessed June 29, 2021. 3. Ramírez-Merino N, et al. *World J Gastrointest Oncol*. 2013;5(7):171-6.

Era of Personalized Medicine

BTC - Precision medicine

- BTC-specific
  - IDH-1 mutations
  - FGFR2 fusions
  - Other: BRAF, Her-2
- Disease-agnostic
  - NTRK fusions
  - MMR-deficiency



Lamarca et al Journal of Hepatol 2020

Studies Overview

Personalized medicine

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journal homepage: www.ejcancer.com

Cholangiocarcinoma: what are the options in all comers and how has the advent of molecular profiling opened the way to personalised medicine ?

Gael S. Roth [a,*], Cindy Neuzillet [b], Matthieu Sarabi [c,d], Julien Edeline [e],

Actionable alteration *ESCAT class*	Drug name *Drug class*	Trial (Name, ClinicalTrials.gov Identifier or other, reference)	Phase and study design	Population (number, line of treatment)	Primary objectives	Results (final results, intermediate analyses)		
						ORR	mPFS	mOS
IDH1 mutation *ESCAT I-A*	Ivosidenib (AG-120) *IDH1mut -inhibitor*	ClarIDHy NCT02989857 Lancet 2020 [58]	Randomised (2:1) multicentre phase 3 versus Placebo	n = 185 pts L2-L3	OS	Ivosidenib vs Placebo: 2 vs 0%	Ivosidenib vs Placebo: 2.7 vs 1.4 m (HR:0.37; 95% CI:0.25–0.54, p < 0.001)	Ivosidenib vs Placebo: 10.8 vs 9.7 m (HR 0.69, 95%CI: 0.44–1.10 p = 0.060) Placebo (RPSFT-adjusted OS): 6.0 m (HR 0.46 95% CI:0.28–0.75; p = 0.0008)
FGFR2 alterations *ESCAT I–B*	Pemigatinib *FGFR1/2/3 inhibitor*	FIGHT-202 NCT02924376 Lancet Oncol 2020 [59]	Single-arm multicentre phase 2	n = 147 pts (107 pts with FGFR2-fusions) L2+	ORR	Cohort fusion: 35.5% Other alterations: 0%	12 m-PFS: 29% in fusion cohort (0% in other cohorts)	N/A
	Futibatinib *FGFR1-4 inhibitor*	FOENIX-CCA2 NCT02052778 Cancer Res 2021 (Abst) [60]	Single-arm multicentre phase 2	n = 103 pts (78% of pts with FGFR2-fusion) L2+	ORR	41.7%	9.0 m	21.7 m
	Infigratinib (BGJ398) *FGFR1/2/3 inhibitor*	CBGJ398X2204 NCT02150967 J Clin Oncol 2017 [61]	Single-arm multicentre phase 2	n = 61 pts (48 pts with FGFR2-fusions) L2+		14.8% Cohort fusion: 18.8%	5.8 m	N/A
	Derazantinib (ARQ 087) *FGFR1/2/3 inhibitor*	FIDES-01 NCT03230318 J Clin Oncol 2022 (Abst) [62]	Single-arm multicentre phase 2	n = 28 pts L2+	3 m-PFS	8.7%	7.3 m 3 m-PFS: 76.3% 6 m-PFS: 50.3%	N/A
HER amplification/ overexpression *ESCAT I-C*	Trastuzumab-pertuzumab *Anti-HER2 Ab*	myPathway NCT02091141 Lancet Oncol 2021 [64]	Single-arm multicentre phase 2	n = 39 pts L2+	ORR	23%	4.0 m	10.9 m
	FOLFOX-trastuzumab *Chemo + anti-HER2 Ab*	KCSG-HB19-14 NCT04722133 J Clin Oncol 2022 (Abst) [65]	Single-arm multicentre phase 2	n = 34 pts L2-L3	ORR	29.4%	5.1 m	not reached
	Trastuzumab-deruxtecan (T-DXd; DS-8201) *Anti-HER2 Ab*	HERB trial JMA-IIA00423 J Clin Oncol 2022 (Abst) [68]	Single-arm multicentre phase 2	n = 32 pts (24 HER2-positive and 8 HER2-low) L2+	ORR in HER-positive	HER-positive: 36.4% HER2-low: 12.5%	HER-positive: 4.4 m HER2-low: 4.2 m	HER-positive: 7.1 m HER2-low: 8.9 m

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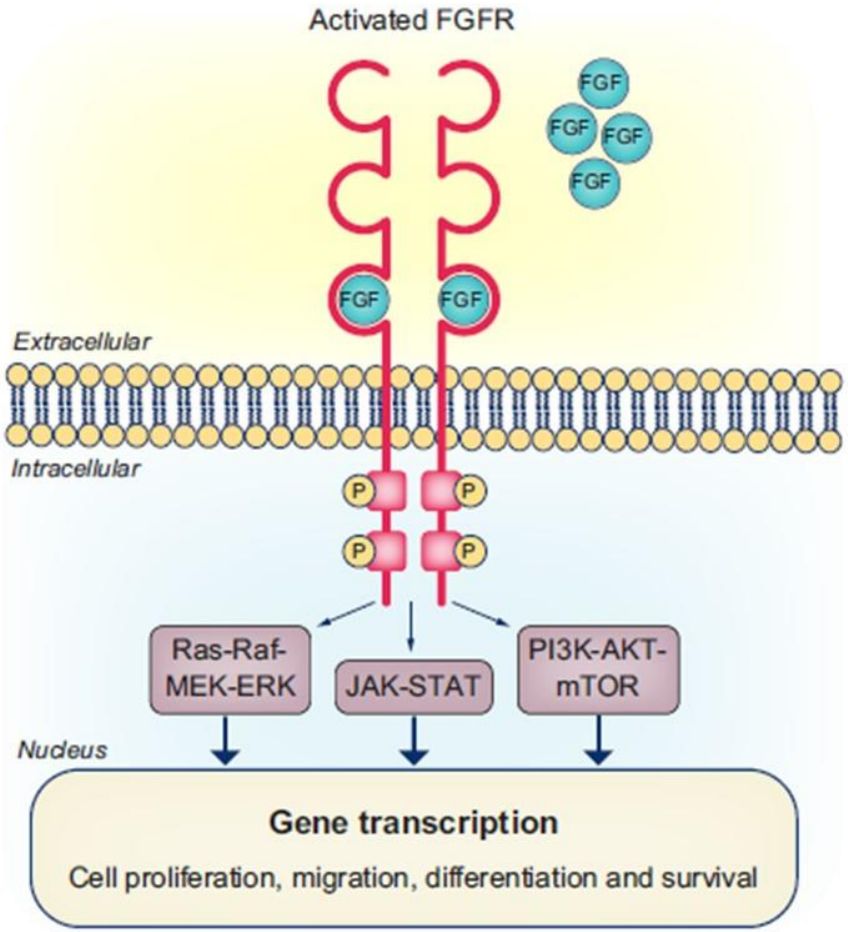
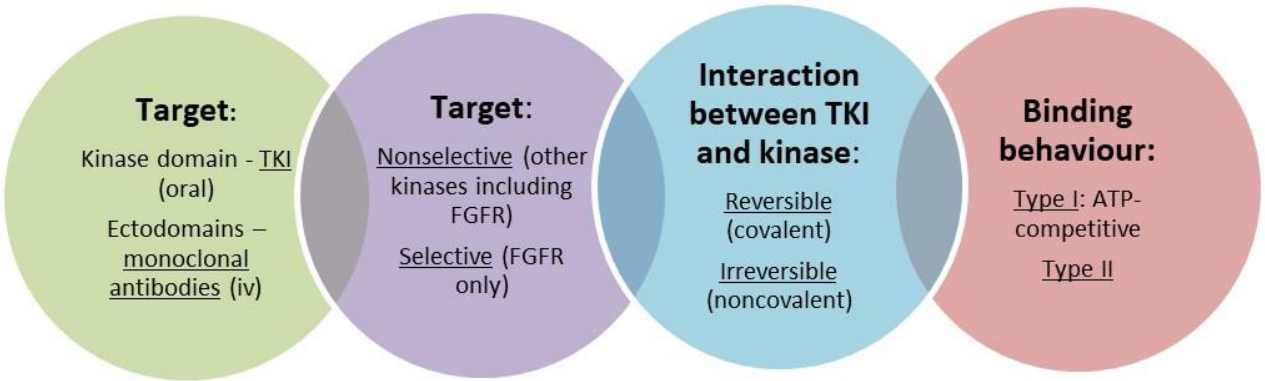
Actionable alteration *ESCAT class*	Drug name *Drug class*	Trial (Name, ClinicalTrials.gov Identifier or other, reference)	Phase and study design	Population (number, line of treatment)	Primary objectives	Results (final results, intermediate analyses)		
						ORR	mPFS	mOS
	conjugated with TOP1 inhibitor Zanidatamab *Bi specific anti-HER2 Ab*	ZWI-ZW25-101 NCT02892123 J Clin Oncol 2021 (Abst) [67]	Single-arm multicentre phase 1	n = 20 pts L2+	Safety/ tolerability	47%	N/A	N/A

Targeting FGFR in CCA

FGFR2 **fusions** (variable partners) identified in ~ 10-20% of iCCA



Multiple iFGFR in development:
Variable mechanism of action



Valle Cancer Disc 2017; Lamarca et al Journal of Hepatol 2020; Dau et al, Cells 2019

FGFR inhibitors in CCA: Present

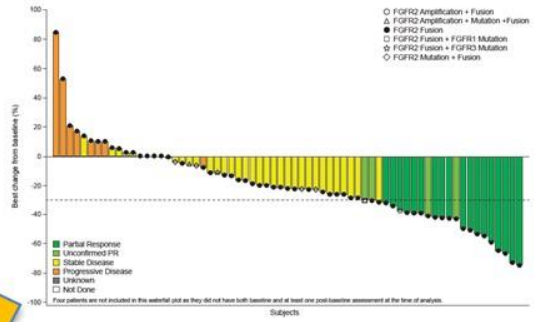
Without head-to-head studies, cross-study comparisons cannot be made

FGFR inhibitor	Company	ORR	Current status
Infigratinib; BGJ398[1,2]	Novartis/QED	26.9%	PROOF trial: 1st line CisGem vs Infigratinib [NCT03773302]; FGFR2 fusions
Derazantinib; ARQ 087[3]	Arqule/ Basilea	20.7%	Ongoing phase II (iCCA) [NCT03230318]; FGFR2 fusions
Pemigatinib; INCB54828[7]	Incyte	37.0% (FGFR2 fusion	FIGHT-302 trial: 1st line CisGem vs Pemigatinib [NCT03656536]; FGFR2 fusions
Futibatinib TAS-120[5]	Taiho	41.7% (FGFR2 fusion); median time to response 1.3 months	FOENIX-CCA3: 1st line CisGem vs Pemigatinib [NCT03656536]; FGFR2 fusions [NCT04093362]

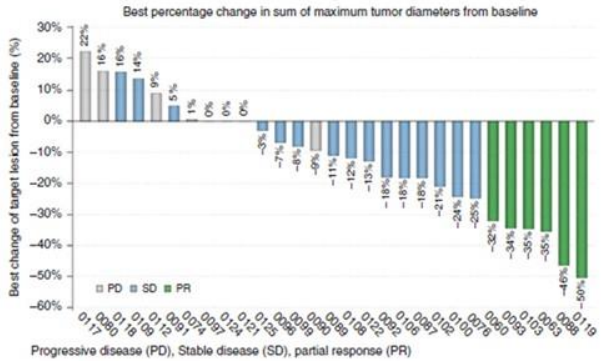
FDA

FDA EMA

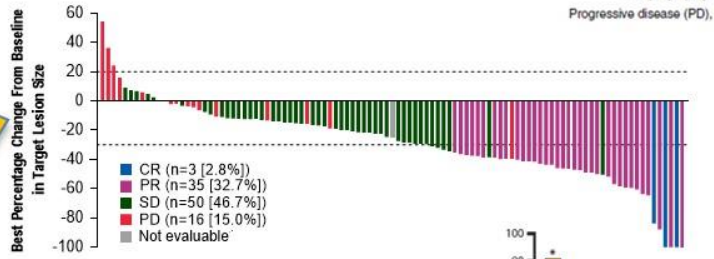
Infigratinib; BGJ398[1,2]



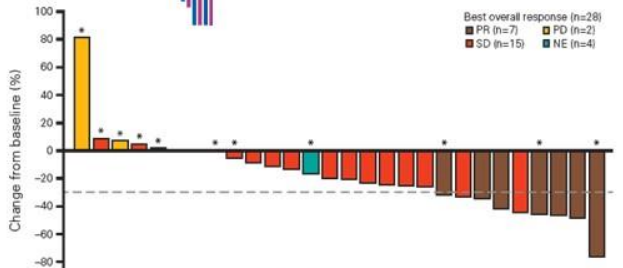
Derazantinib; ARQ 087[3]



Pemigatinib; INCB54828[4]



Futibatinib TAS-120[6]



1. Javle M et al. *J Clin Oncol*. 2017;36:276–82; 2. Javle M, et al. Poster presentation at ESMO 2018. LBA28; 3. Mazzaferro V, et al. *Br J Cancer*. 2018;120:165–71; 4. Vogel A, et al. Oral presentation at ESMO 2019. LBA40; 5. Goyal et al, AACR 2021 DOI: 10.1158/1538-7445.AM2021-CT010 Published July 2021; 6. 5. Tran B, et al. Oral presentation at ESMO-Asia 2018. Abstract 1550; 7. Abou-Alfa et al ASCO 2021

*Prior FGFR inhibitor

Genetic Targets in BTC

Intrahepatic cholangiocarcinoma

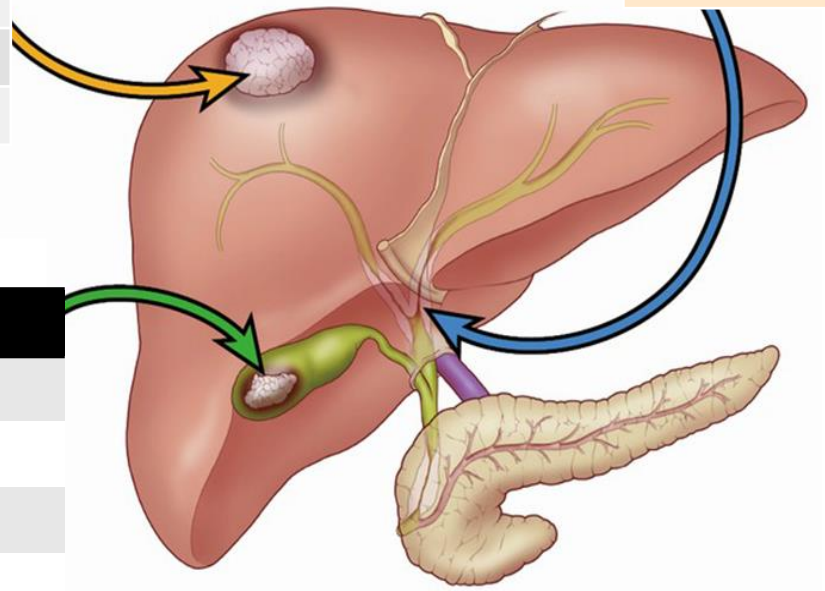
Targetable gene	Prevalence, %
FGFR2 (fusions)	10-20
IDH1/2	22-28
BAP1	15 to 25
BRAF V600 (mutation)[1,2]	5-7

Gall bladder cancer

Targetable gene	Prevalence, %
EGFR	4-13
HER2/neu (amplification)	9
ERB3	0-12
PTEN	0-4
PIK3CA	6-13

Extrahepatic cholangiocarcinoma

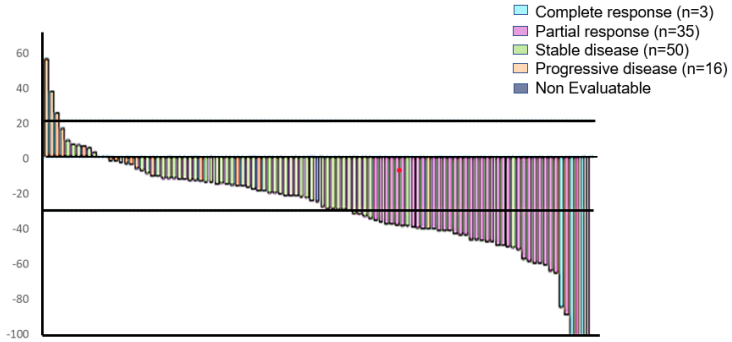
Targetable gene	Prevalence, %
Her2/neu (mutation)	11-20
PRKACA and PRKACB	9
ARID1A	5-12



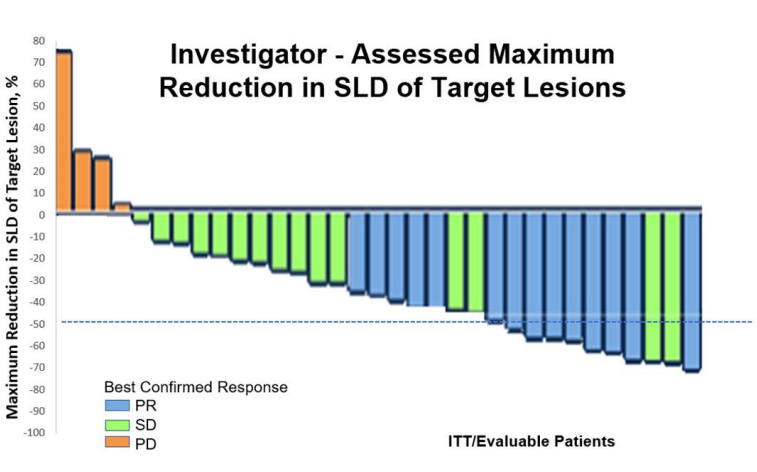
Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. J Gastrointest Oncol. 2016;7(5):797-803

Intrahepatic Cholangiocarcinoma: Clinical Value of Targetable Alterations

FDA, EMA approved



ORR 35.5%, DCR 82%, duration of response 7,5 months
Follow up: 17.8m
mPFS: 6.9m
mOS: 21.1m



Targetable gene	Prevalence %
FGFR2 (fusions)[1]	10-20
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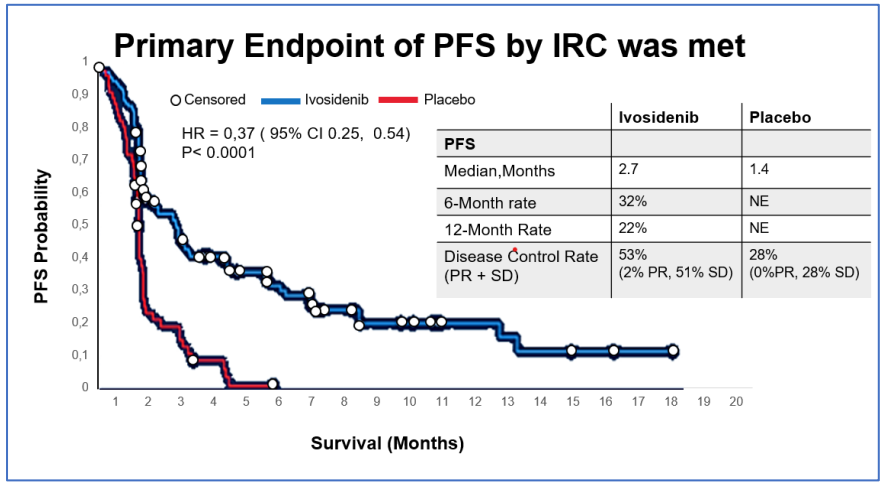
BAP1	15 to 25
BRAF V600 (mutation)[3]	5-7



PFS	Ivosidenib	Placebo
Median,Months	2.7	1.4
6-Month rate	32%	NE
12-Month Rate	22%	NE
Disease Control Rate (PR + SD)	53% (2% PR, 51% SD)	28% (0%PR, 28% SD)

1. Ghassan K Abou-Alfa et al, Lancet Oncol 2020, 2. Ghassan K Abou-Alfa et al, Lancet Oncol 2020, 3. Wainberg et al, ASCO GI 2019

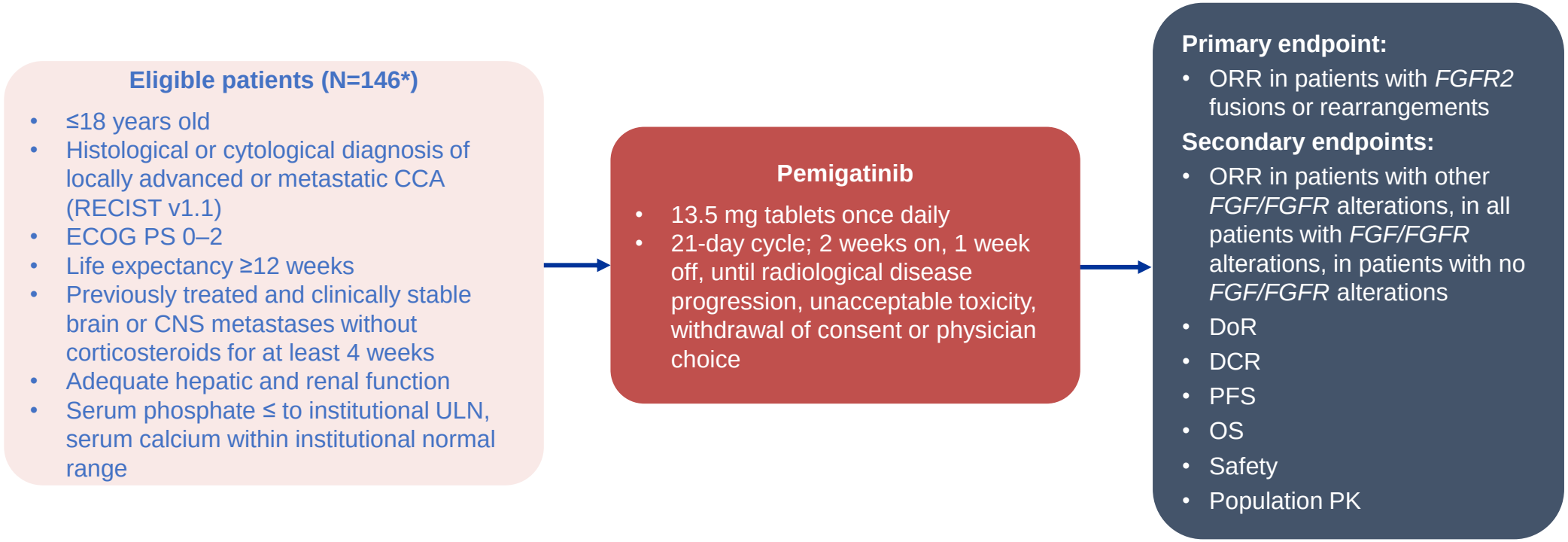
FGFR-2 mutations

Pemigatinib

FIGHT-202

FIGHT-202: pemigatinib for previously treated CCA[1]

- A global, multicenter, open-label, single-arm, phase II study to evaluate the safety and efficacy of pemigatinib in previously treated adult patients with locally advanced or metastatic CCA, with or without *FGF/FGFR* alterations (January 2017–March 2019)



*Includes one patient who did not have confirmed *FGF/FGFR* status centrally confirmed and was not assigned to any cohort
CCA, cholangiocarcinoma; CNS, central nervous system; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ULN, upper limit of normal

1. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21:671–684

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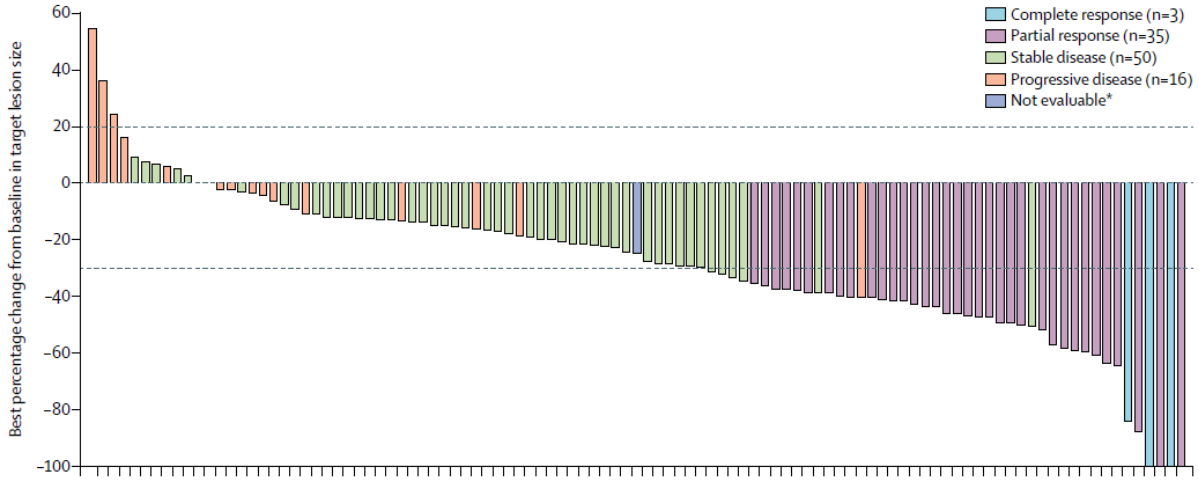
35.5% of patients with *FGFR2* fusions or rearrangements had confirmed objective response[1]

	Endpoint(s)	*FGFR2* fusions or rearrangements (n=107)	Other *FGF/FGFR* alterations (n=20)	No *FGF/FGFR* alterations (n=18)
Primary	ORR[†] (%) (CR+PR)	35.5	0	0
Secondary	DCR (%)	82	40	22
	DoR (median, months)	7.5	–	–
	PFS (median, months)	6.9	2.1	1.7
	OS[‡] (median, months)	21.1	6.7	4.0

Best percentage change from baseline in target lesion size for individual patients with *FGFR2* fusions or rearrangements



*Patient had a decrease in target lesion size but was not evaluable for response using RECIST; [†]Assessed and response confirmed by independent reviewer; [‡]OS data were not mature at cut-off
CR, complete response; DCR, disease control rate; DoR, duration of response; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1

1. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21:671–684

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Hyperphosphatemia was the most common AE[1]

- Across all cohorts, irrespective of cause, hyperphosphatemia was the most common (60%) all-grade AE
- SAEs occurred in 45% of patients
  - Most frequent were abdominal pain, pyrexia, cholangitis and pleural effusion
- 49% of patients died (disease progression was the cause in 42% of patients); no deaths were treatment related

Treatment-related AEs occurring in ≥10% of patients in the total study population*			
	Grade 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hyperphosphatemia†	81 (55)	0	0
Alopecia	67 (46)	0	0
Dysgeusia	55 (38)	0	0
Diarrhea	49 (34)	4 (3)	0
Fatigue	45 (31)	2 (1)	0
Stomatitis	39 (27)	8 (5)	0
Dry mouth	42 (29)	0	0
Nausea	34 (23)	2 (1)	0
Decreased appetite	34 (23)	1 (1)	0
Dry eye	30 (21)	1 (1)	0
Dry skin	22 (15)	1 (1)	0
Arthralgia	16 (11)	6 (4)	0

*Data include one patient who did not have confirmed *FGF/FGFR* status centrally confirmed and was not assigned to any cohort
†The following MedDRA preferred terms related to hyperphosphatemia were combined: blood phosphorus increased; and hyperphosphatemia
AE, adverse event; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event
1. Abou-Alfa GK, et al. *Lancet Oncol.* 2020;21:671–684

FGFR-2 mutations

Futibatinib

FOENIX-CCA2

The NEW ENGLAND JOURNAL of MEDICINE

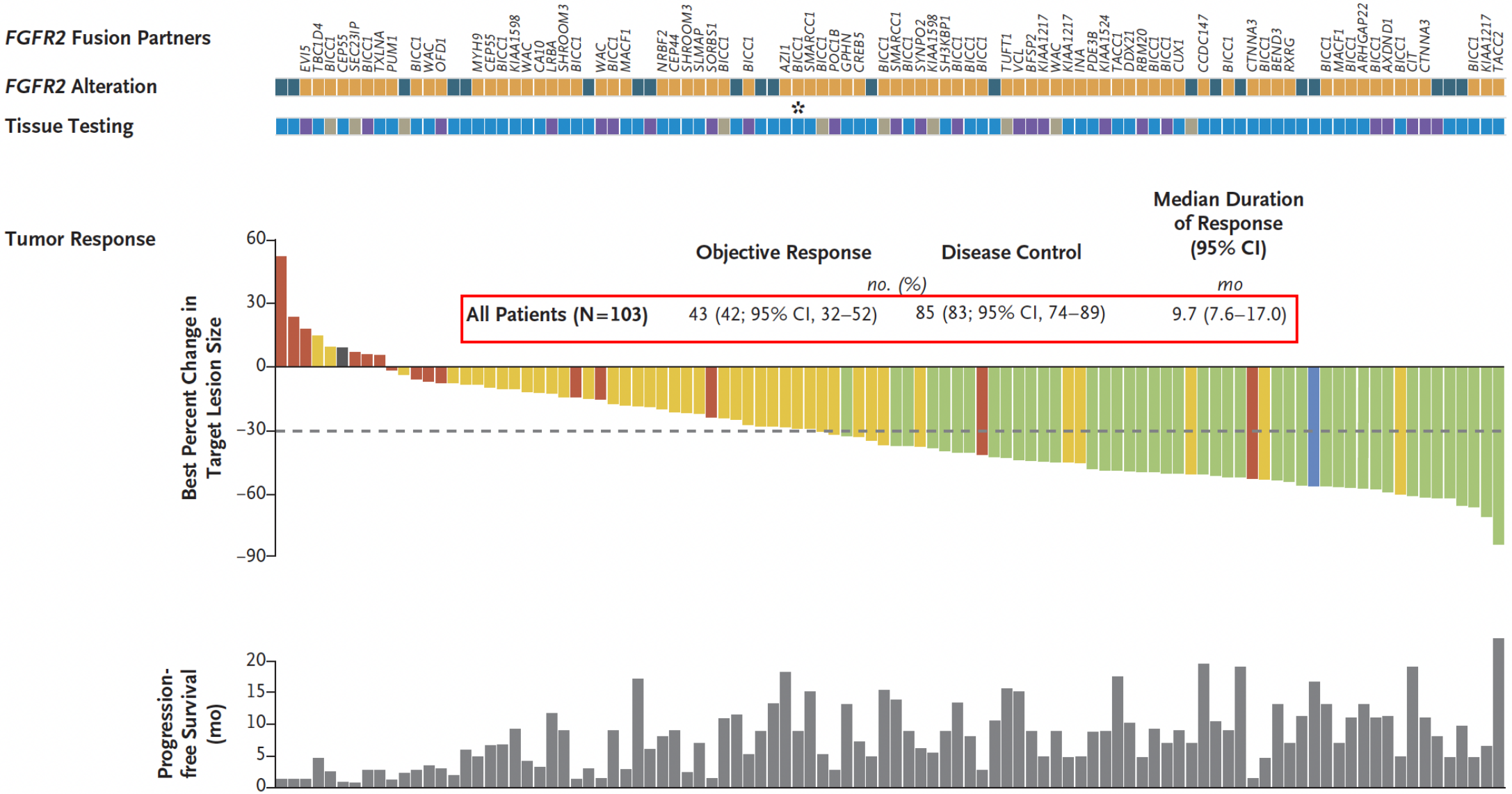
ORIGINAL ARTICLE

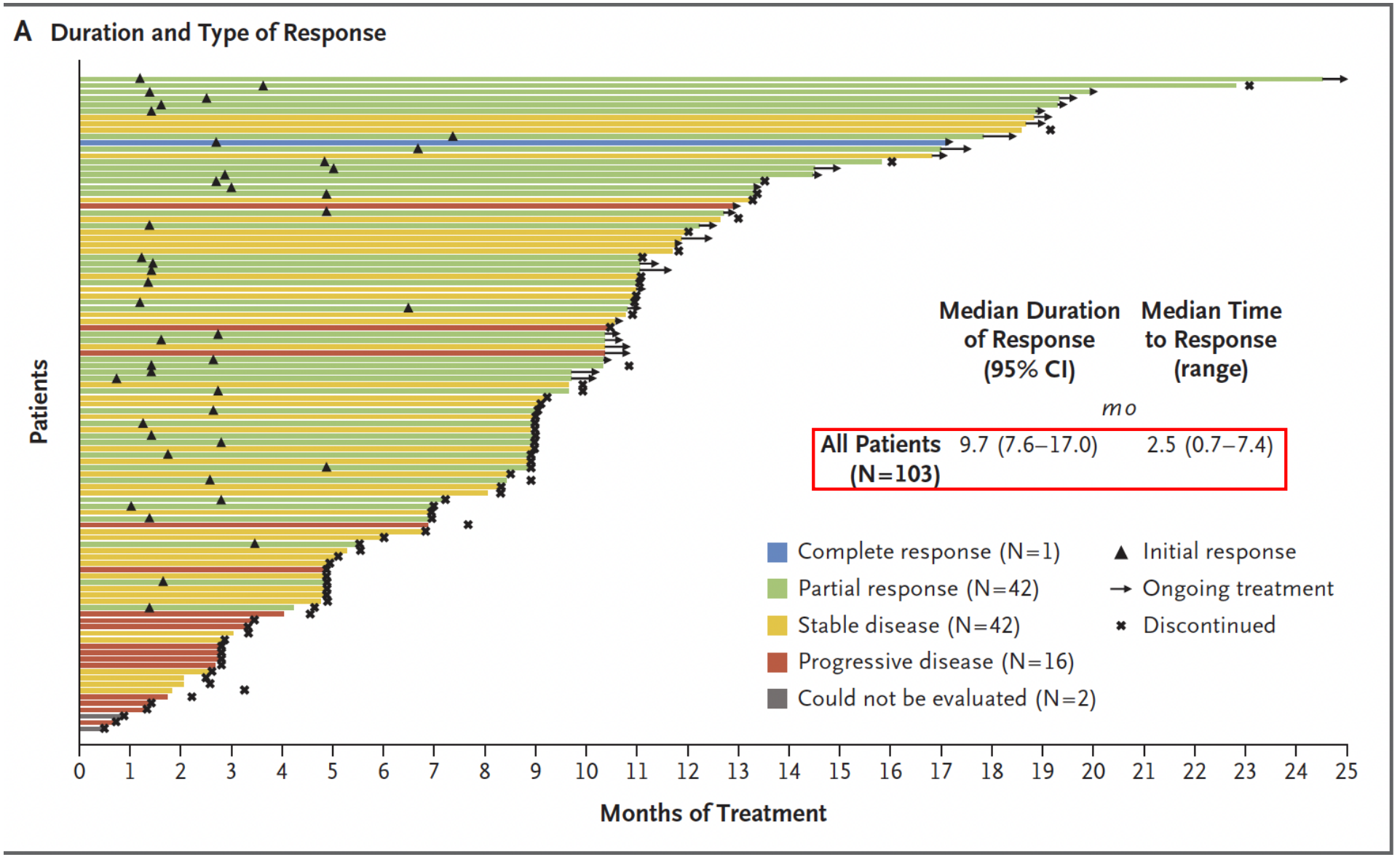
Futibatinib for *FGFR2*-Rearranged Intrahepatic Cholangiocarcinoma

L. Goyal, F. Meric-Bernstam, A. Hollebecque, J.W. Valle, C. Morizane,

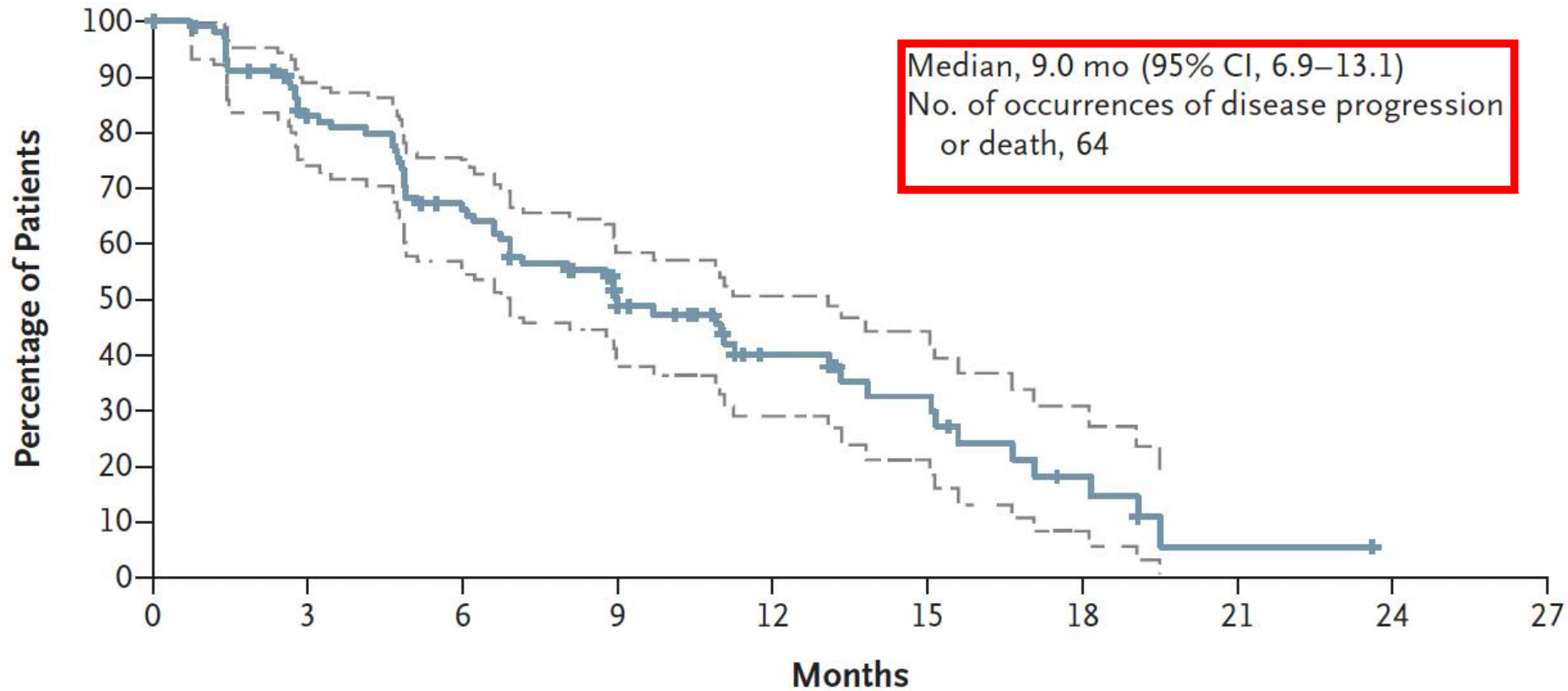
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N = 103)
Age — yr	
Median	58
Range	22–79
Sex — no. (%)	
Female	58 (56)
Male	45 (44)
ECOG performance-status score — no. (%)†	
0	48 (47)
1	55 (53)
Race or ethnic group — no. (%)‡	
White	51 (50)
Asian	30 (29)
Black	8 (8)
Native Hawaiian or Pacific Islander	1 (1)
Unknown	13 (13)
Geographic region — no. (%)	
North America	47 (46)
Europe	28 (27)
Japan	14 (14)
Asia Pacific, excluding Japan	14 (14)
FGFR2 alteration — no. (%)§	
Fusion	80 (78)
Rearrangement	23 (22)
Previous therapy — no. (%)	
Anticancer therapy	103 (100)
Radiotherapy	28 (27)
Anticancer surgery	41 (40)
No. of previous lines of systemic therapy — no. (%)¶	
1	48 (47)
2	31 (30)
≥3	24 (23)
Median time from previous anticancer therapy to first dose of futibatinib (interquartile range) — mo	1.5 (1.0–3.4)


FGFR2 Fusion Partners
FGFR2 Alteration
Tissue Testing
EVI5 TBC1D4 BICC1 CEP55 SEC23IP BICC1 TXLNA PUM1
BICC1 WAC OFD1
MYH9 CEP55 BICC1 KIAA1598 WAC CA10 LRBA SHROOM3 BICC1
WAC BICC1 MACF1
NRBF2 CEP44 SHROOM3 SLMAP SORBS1 BICC1
BICC1
AZI1 BICC1 SMARCC1 BICC1 POC1B GPHN CREB5
BICC1 SMARCC1 BICC1 SYNPO2 KIAA1598 SH3KBP1 BICC1 BICC1 BICC1
TUFT1 VCL BFSP2 KIAA1217 WAC KIAA1217 INA PDE3B KIAA1524 TACC1 DDX21 RBM20 BICC1 BICC1 CUX1
CCDC147
BICC1
CTNNA3 BICC1 BEND3 RXRG
BICC1 MACF1 BICC1 ARHGAP22 BICC1 AXDND1 BICC1 CIT CTNNA3
BICC1 KIAA1217 TACC2
Tumor Response
Objective Response
Disease Control
Median Duration of Response (95% CI)
no. (%)
mo
All Patients (N=103)
43 (42; 95% CI, 32–52)
85 (83; 95% CI, 74–89)
9.7 (7.6–17.0)
Best Percent Change in Target Lesion Size
60
30
0
−30
−60
−90
Progression-free Survival (mo)
20
15
10
5
0

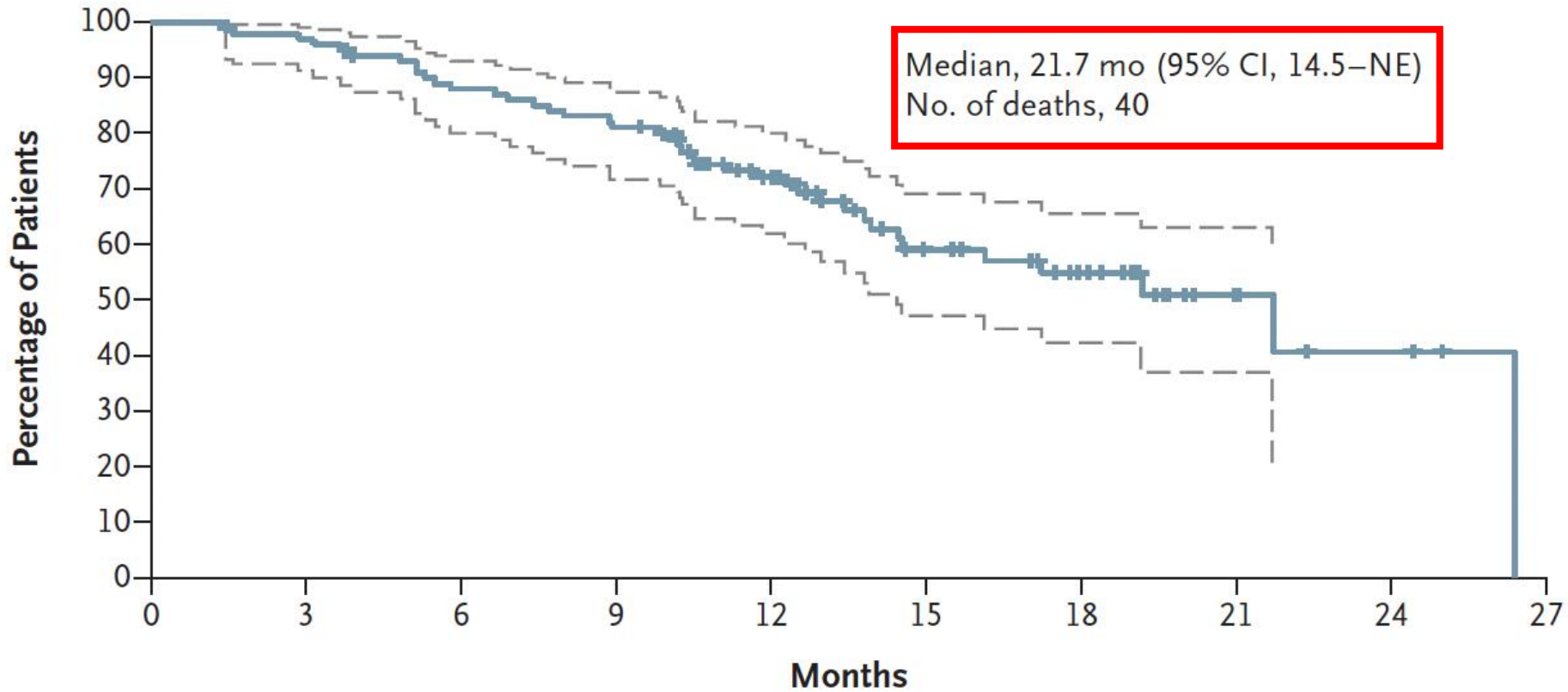

A Duration and Type of Response
Patients
Median Duration of Response (95% CI)
Median Time to Response (range)
mo
All Patients (N=103)
9.7 (7.6–17.0)
2.5 (0.7–7.4)
Complete response (N=1)
Partial response (N=42)
Stable disease (N=42)
Progressive disease (N=16)
Could not be evaluated (N=2)
Initial response
Ongoing treatment
Discontinued
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Months of Treatment

B **Progression-free Survival**



No. at Risk	103	79	61	36	19	12	5	1	0
No. with Censored Data	—	7	2	11	11	4	2	1	1

C Overall Survival



No. at Risk	103	99	88	81	55	31	21	6	3	0
No. with Censored Data	—	1	2	0	18	16	8	14	2	2

Table 2. Treatment-Related Adverse Events Reported in at Least 10% of the Patients.*

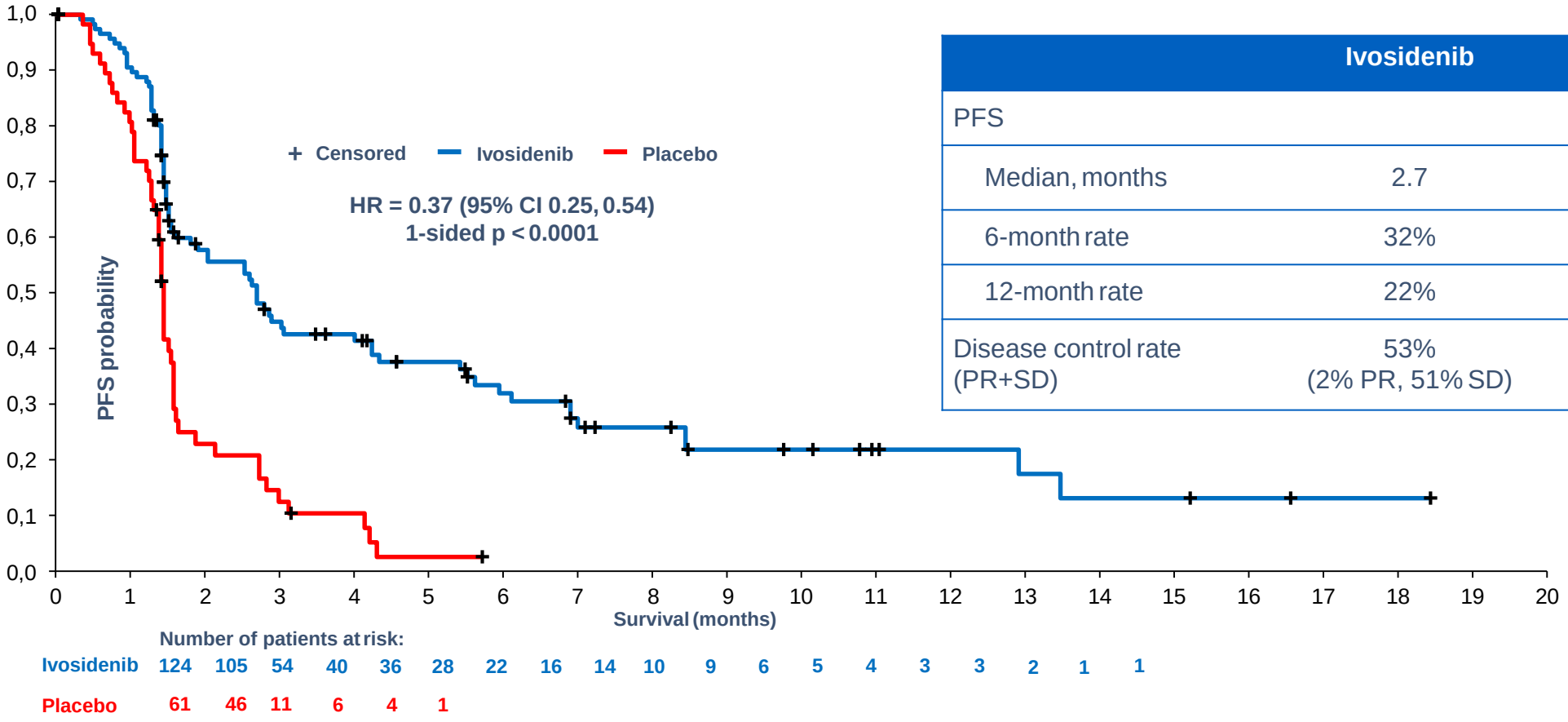
Event	All Patients (N = 103)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
	number of patients (percent)				
Any adverse event	102 (99)	8 (8)	35 (34)	58 (56)	1 (1)
Hyperphosphatemia	88 (85)	10 (10)	47 (46)	31 (30)	0
Alopecia	34 (33)	26 (25)	8 (8)	0	0
Dry mouth	31 (30)	28 (27)	3 (3)	0	0
Diarrhea	29 (28)	21 (20)	8 (8)	0	0
Dry skin	28 (27)	22 (21)	6 (6)	0	0
Fatigue	26 (25)	15 (15)	5 (5)	6 (6)	0
Palmar–plantar erythrodysesthesia syndrome	22 (21)	3 (3)	14 (14)	5 (5)	0
Stomatitis	21 (20)	10 (10)	5 (5)	6 (6)	0
Dysgeusia	19 (18)	12 (12)	7 (7)	0	0
Increased aspartate aminotransferase level	19 (18)	11 (11)	1 (1)	7 (7)	0
Dry eye	18 (17)	14 (14)	3 (3)	1 (1)	0
Constipation	17 (17)	12 (12)	5 (5)	0	0
Nail disorder	16 (16)	9 (9)	7 (7)	0	0
Onycholysis	16 (16)	8 (8)	8 (8)	0	0
Increased alanine aminotransferase level	15 (15)	5 (5)	5 (5)	4 (4)	1 (1)
Nail discoloration	14 (14)	12 (12)	2 (2)	0	0
Onychomadesis	14 (14)	6 (6)	7 (7)	1 (1)	0
Decreased appetite	13 (13)	6 (6)	7 (7)	0	0
Myalgia	12 (12)	9 (9)	3 (3)	0	0
Nausea	12 (12)	7 (7)	3 (3)	2 (2)	0
Arthralgia	10 (10)	9 (9)	1 (1)	0	0
Muscle spasms	10 (10)	8 (8)	1 (1)	1 (1)	0

IDH-1 mutation

Ivosednib

ClarIDHy

Primary Endpoint of PFS by IRC



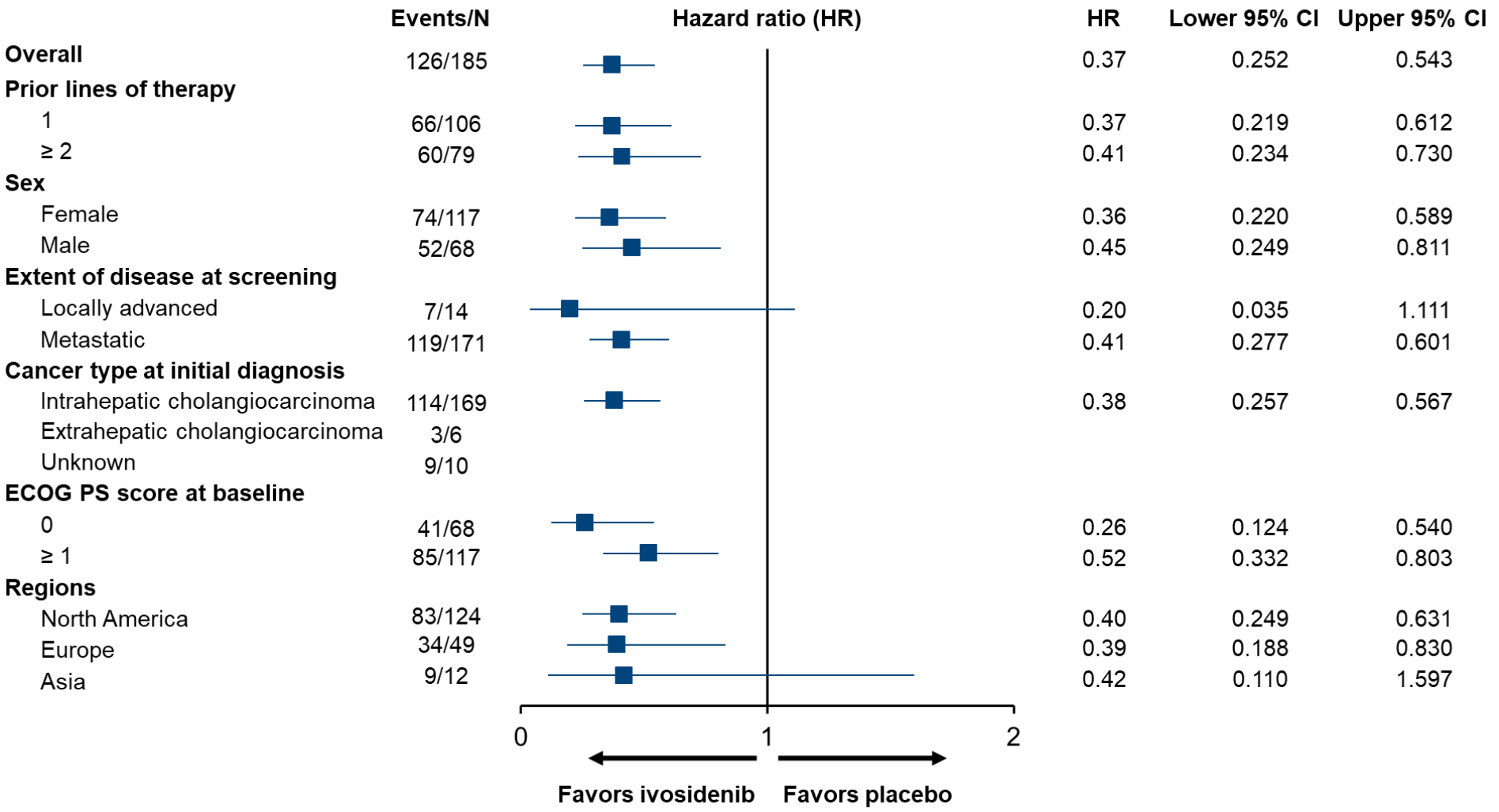
	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

- PFS rate was 32% at 6 months and 22% at 12 months for ivosidenib; no patients on placebo were progression free at 6 months

NE = not estimable; PR = partial response; SD = stable disease

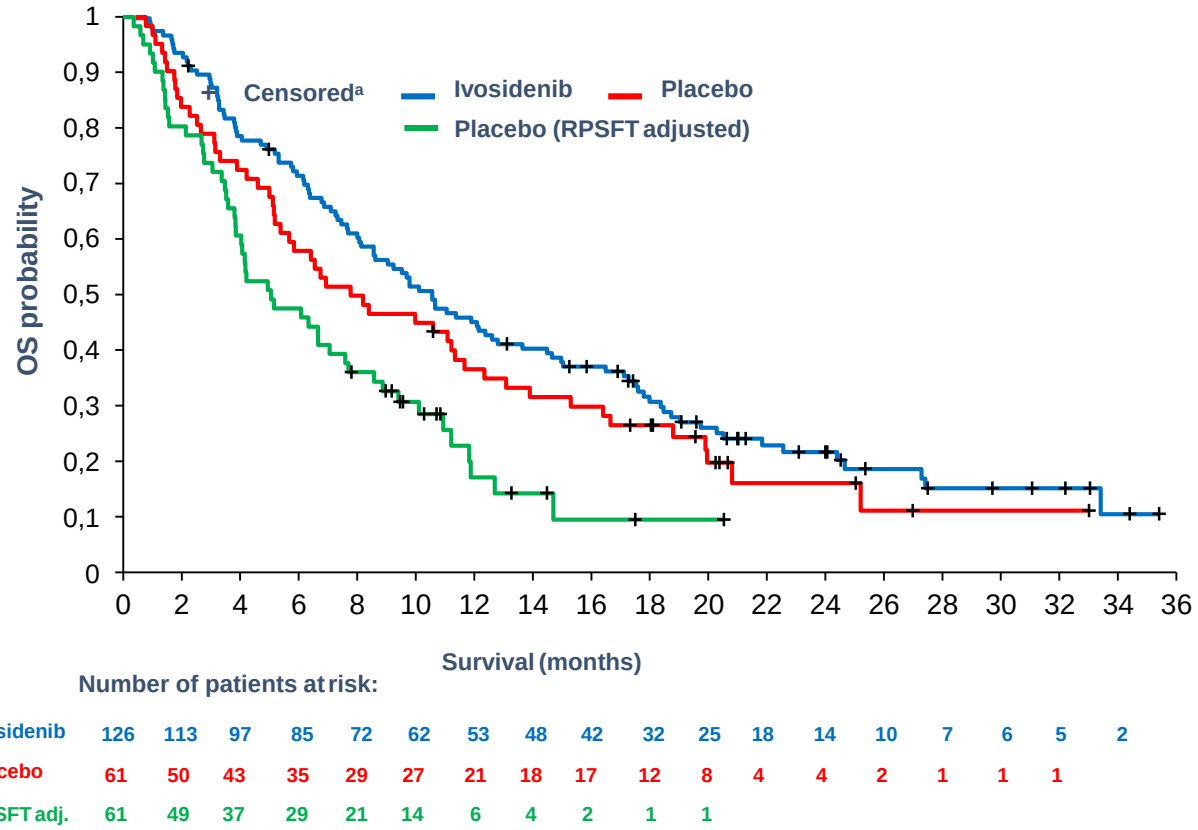
Abou-Alfa GK et al. *Lancet Oncol* 2020;21:796−807.

PFS by IRC: Ivosidenib Efficacy across Subgroups[a]



[a]Subgroups with number of events ≤ 5 or number of patients ≤ 10 were not plotted. All randomized patients as of 31Jan2019; Abou-Alfa GK et al. *Lancet Oncol* 2020;21:796−807.

Overall Survival: Final analysis[1-3]



	Ivosidenib n = 126	Placebo n = 61
Number of events (%)	100 (79.4)	50 (82.0)
Median OS, months	10.3	7.5
HR (95% CI)	0.79 (0.56, 1.12)	
1-sided p-value	0.093	
6-month OS rate, %	69	57
12-month OS rate, %	43	36

- The median OS in the placebo arm after adjustment for crossover was 5.1 months
- (HR = 0.49 [95% CI 0.34, 0.70]; 1-sided p < 0.0001)

All randomized patients as of 31May2020
[a]Patients without documentation of death at the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was earlier
OS, overall survival
1. Zhu AX, et al. *ASCO-GI 2021*: Oral presentation 266. 2. Abou-Alfa GK, et al. *ASCO 2021*: Poster presentation 4069. 3. Zhu AX, et al. JAMA Oncol. 2021 [Submitted].

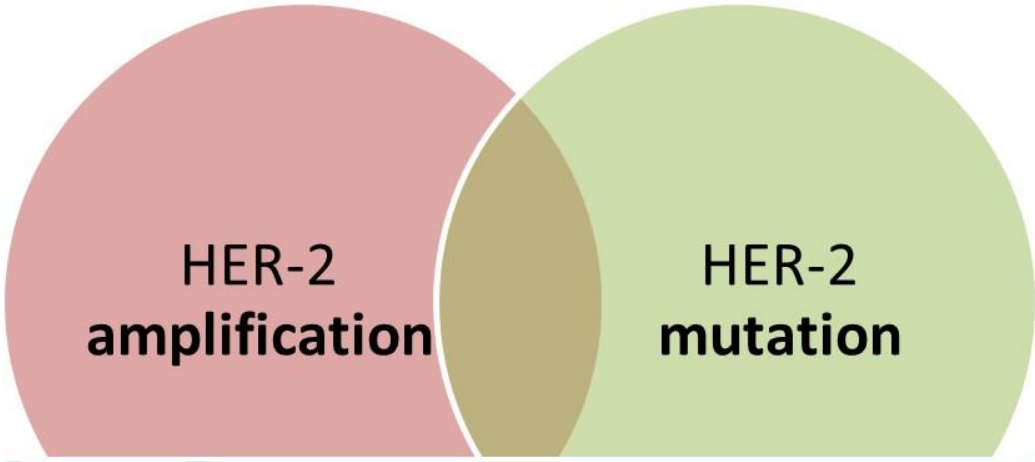
FGFR inhibitors in CCA: Future

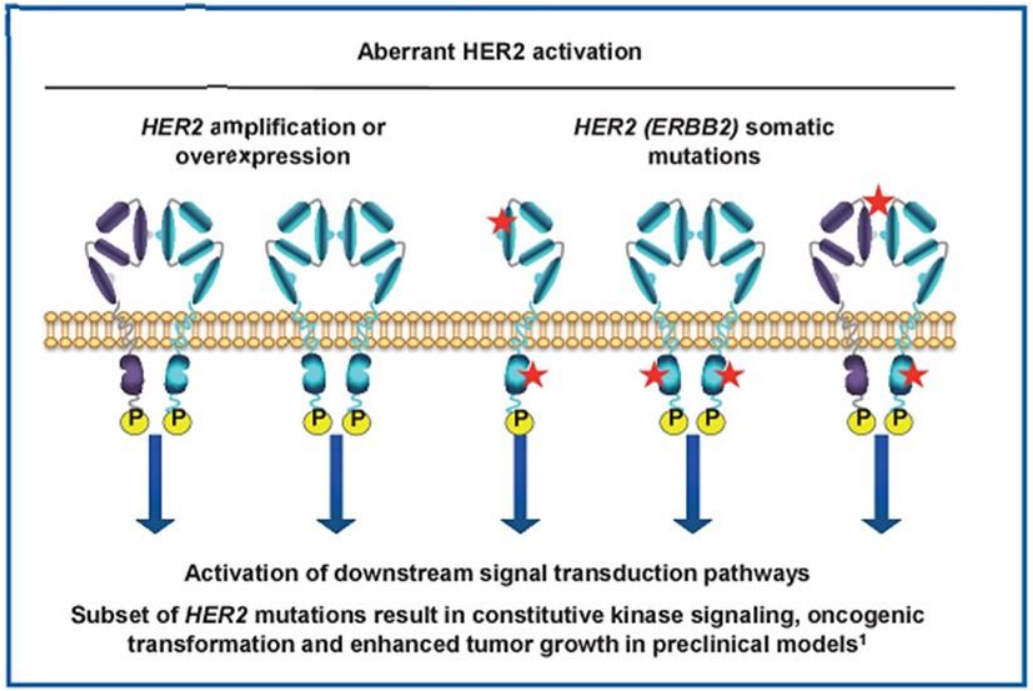
- Exploring their role in the first-line setting:
  - Pemigatinib/Inf
- Other alternatives: co sequencing strategies?
- Mechanisms of primary/secondary resistance?

How can we overcome drug resistance??

HER-2 mutations

Targeting HER-2 in BTC





Harding et al ASCO GI 2021

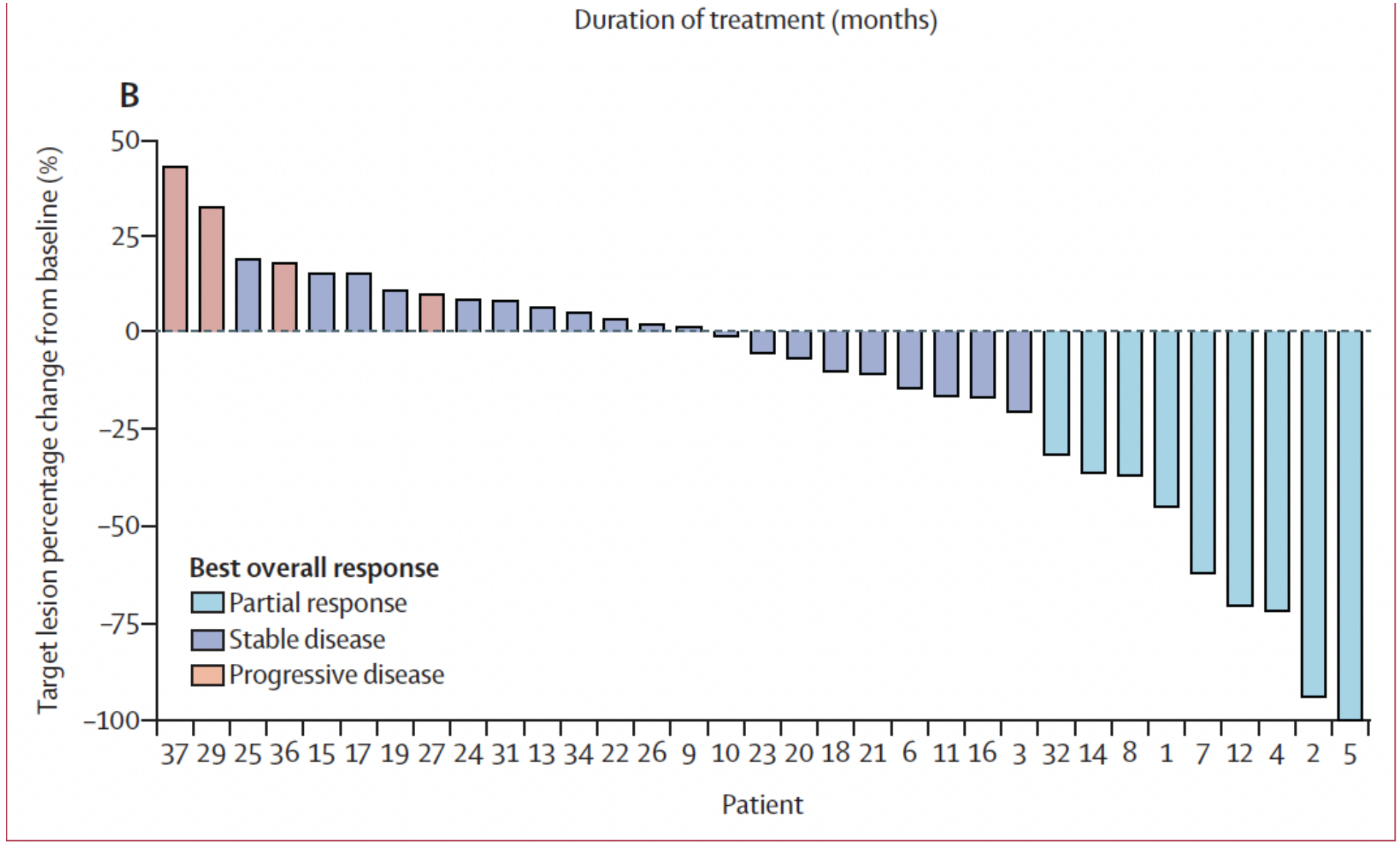
HER-2 mutations

Trastuzumab + Pertuzumab

myPathway trial

Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study

Milind Javle, Mitesh J Borad, Nilofer S Azad, Razelle Kurzrock, Ghassan K Abou-Alfa, Ben George, John Hainsworth, Funda Meric-Bernstam,


Duration of treatment (months)
B
Target lesion percentage change from baseline (%)
50
25
0
−25
−50
−75
−100
Best overall response
Partial response
Stable disease
Progressive disease
37 29 25 36 15 17 19 27 24 31 13 34 22 26 9 10 23 20 18 21 6 11 16 3 32 14 8 1 7 12 4 2 5
Patient

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Varlitinib plus capecitabine in second-line advanced biliary tract cancer: a randomized, phase II study (TreeTopp)

M. M. Javle[1*], D.-Y. Oh[2], M. Ikeda[3], W.-P. Yong[4], K. Hsu[5], B. Lindmark[5], N. McIntyre[5] & C. Firth[5]

Capecitabine + Varlitinib

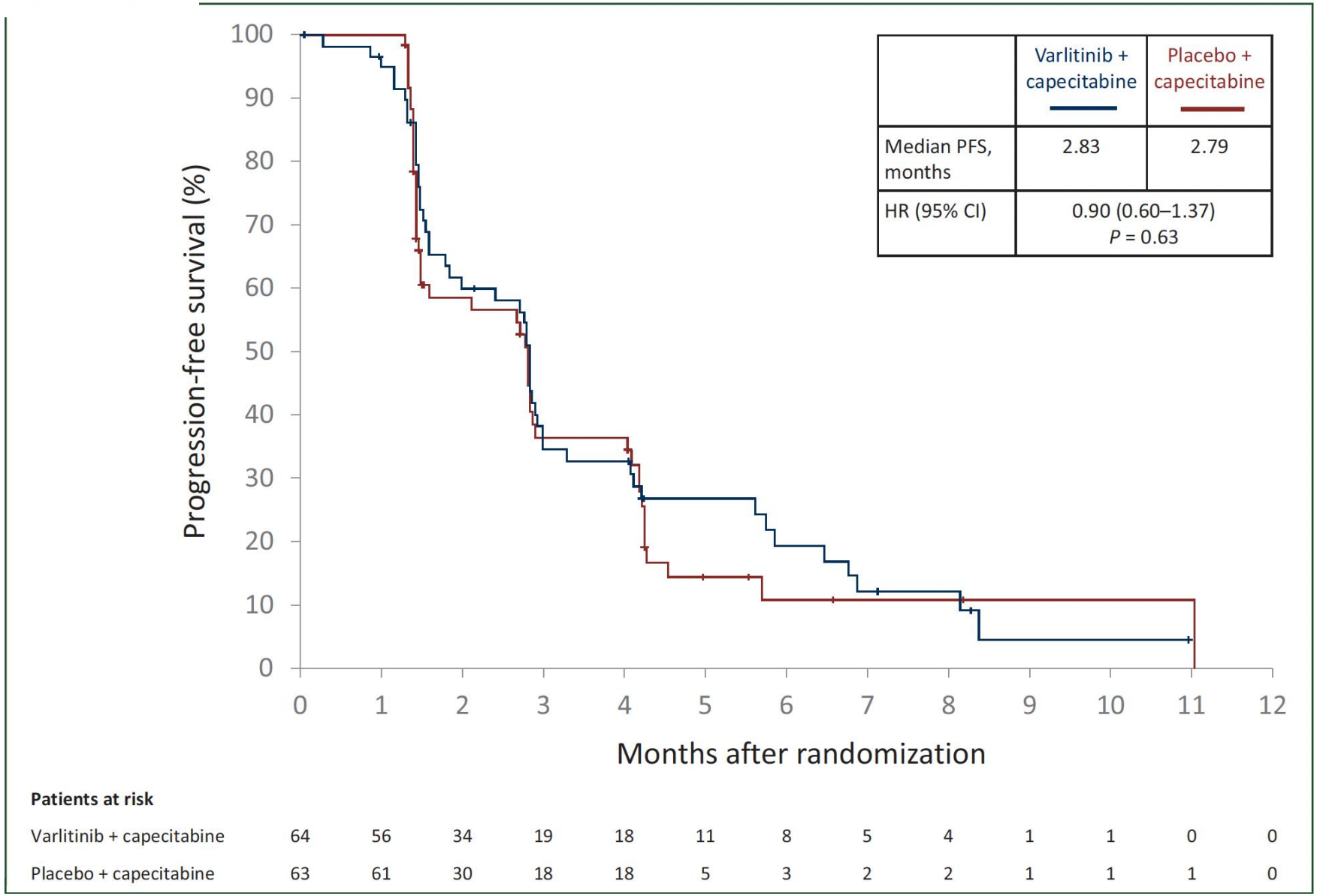
TreeTopp trial

- Varlitinib is a reversible small molecule pan-HER inhibitor targeting EGFR, HER2, and HER4.
- By potently antagonizing EGFR, HER2, and HER4, varlitinib also effectively inhibits heterodimers with HER3, which lacks a kinase domain

Table 2. Summary of responses: randomized population

Responses, *n* (%)	Varlitinib + capecitabine (*n* = 64)	Placebo + capecitabine (*n* = 63)
Objective response	6 (9.4)	3 (4.8)
Complete response	0 (0)	0 (0)
Partial response	6 (9.4)	3 (4.8)
Stable disease	29 (45.3)	34 (54.0)
Progressive disease	24 (37.5)	24 (38.1)
Early death	4 (6.3)	0 (0)
RECIST v1.1 progression	20 (31.3)	24 (38.1)
Non-evaluable	5 (7.8)	2 (3.2)

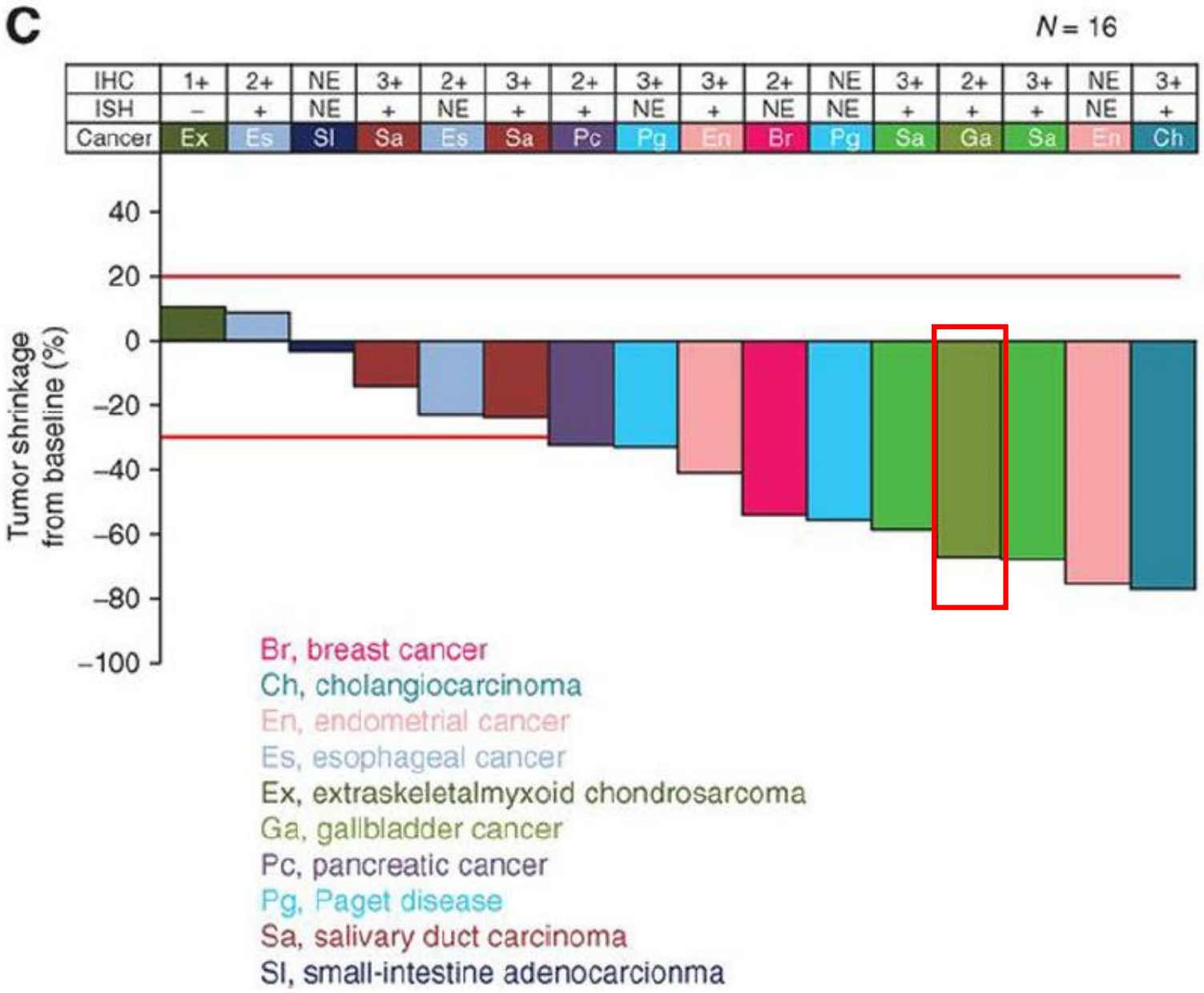
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE



Targeting HER2 with Trastuzumab Deruxtecan: A Dose-Expansion, Phase I Study in Multiple Advanced Solid Tumors

Junji Tsurutani[1,2], **Hiroji Iwata**[3], **Ian Krop**[4], **Pasi A. Jänne**[4], **Toshihiko Doi**[5], **Shunji**

Trastuzumab-Deruxtecan


C
N = 16
IHC 1+ 2+ NE 3+ 2+ 3+ 2+ 3+ 3+ 2+ NE 3+ 2+ 3+ NE 3+
ISH – + NE + NE + + NE + NE NE + + + NE +
Cancer Ex Es Sl Sa Es Sa Pc Pg En Br Pg Sa Ga Sa En Ch
Tumor shrinkage from baseline (%)
40
20
0
–20
–40
–60
–80
–100
Br, breast cancer
Ch, cholangiocarcinoma
En, endometrial cancer
Es, esophageal cancer
Ex, extraskeletalmyxoid chondrosarcoma
Ga, gallbladder cancer
Pc, pancreatic cancer
Pg, Paget disease
Sa, salivary duct carcinoma
Sl, small-intestine adenocarcionma

HER-2 mutations

Zanidatamab

Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or *HER2*-amplified cancers: a phase 1, dose-escalation and expansion study

Funda Meric-Bernstam, Muralidhar Beeram, Erika Hamilton, Do-Youn Oh, Diana L Hanna, Yoon-Koo Kang, Elena Elimova, Jorge Chaves,

RR

	Biliary tract cancer (n=21)	Colorectal cancer (n=26)	Other cancer types (n=36)	Total (n=83)
Confirmed objective response, n (% [95% CI])	8 (38% [18 to 62])	10 (38% [20 to 59])	13 (36% [21 to 54])	31 (37% [27 to 49])
Partial response, n (%)	8 (38%)	10 (38%)	13 (36%)	31 (37%)
Stable disease, n (%)	5 (24%)	10 (38%)	16 (44%)	31 (37%)
Progressive disease, n (%)	8 (38%)	6 (23%)	7 (19%)	21 (25%)
Clinical benefit rate*	38% (18 to 62)	58% (37 to 77)	53% (35 to 70)	51% (39 to 62)
Disease control rate†	62% (38 to 82)	77% (56 to 91)	81% (64 to 92)	75% (64 to 84)
Median duration of response, months‡	8·5 (3·2 to not estimable)	5·6 (2·8 to 16·7)	9·7 (3·7 to not estimable)	6·9 (5·6 to 16·7)
Had event, n/n (%)	6/8 (75%)	9/10 (90%)	7/13 (54%)	22/31 (71%)
Censored, n/n (%)	2/8 (25%)	1/10 (10%)	6/13 (46%)	9/31 (29%)
Progression-free survival, months§	3·5 (1·8 to 6·7)	6·8 (3·5 to 7·8)	5·5 (3·6 to 8·3)	5·4 (3·7 to 7·3)
Had event, n (%)	19/22 (86%)	24/28 (86%)	28/36 (78%)	71/86 (83%)
Censored, n (%)	3/22 (14%)	4/28 (14%)	8/36 (22%)	15/86 (17%)

Data are % (95% CI) or median (95% CI), unless otherwise specified. *Clinical benefit rate was defined as stable disease for 24 weeks or longer or best overall response of complete response or partial response. †Disease control rate was defined as a best overall response of complete response, partial response, or stable disease. ‡Among patients with confirmed response. §Among all patients who received at least one dose.

Table 3: **Anti-tumour activity (in the part 2 response-evaluable population)**

Targeting HER-2 amplification in BTC

- **Novel Her-2 inhibitors are being developed (i.e. Zanidatamab – HER-2 bispecific antibody)**
  - Centrally confirmed HER2 overexpression (immunohistochemistry [IHC] 3+ or IHC 2+/ fluorescence *in situ* hybridization [FISH]+)
  - 20 patients (11 gallbladder cancers, 5 intra- and 4 extra-hepatic cholangiocarcinoma)
  - Partial response rate 47%; median duration of response 6.6 months

Figure 2: Anti-tumor Activity: Zanidatamab

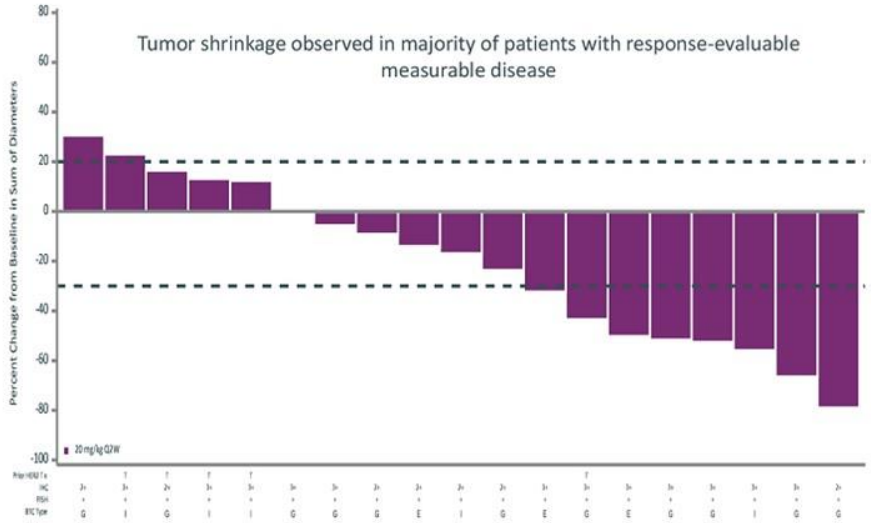


Table 3: Disease Response Endpoints[a] and DOR

	(N = 20)
Confirmed objective response, n (%) (95% CI)	8 (40) (19.1, 63.9)
Partial response	8 (40)
Stable disease	5 (25)
Progressive disease	7 (35)
Disease control rate, n (%)	13 (65)

Duration of response,[b] months	(N=8)
Median (95% CI)	7.4 (3.2, NE)

DOR=duration of response; NE= not estimable.
a, per Investigator Assessment using RECIST 1.1 in response-evaluable patients; b, in response-evaluable patients who had a complete or partial response followed by at least one more response assessment.

MANCHESTER 1824 The University of Manchester

Galdy Cancer Met Reviews 2017; Meric-Bernstam ASCO GI 2021

NHS Foundation Trust

HER-2 mutations

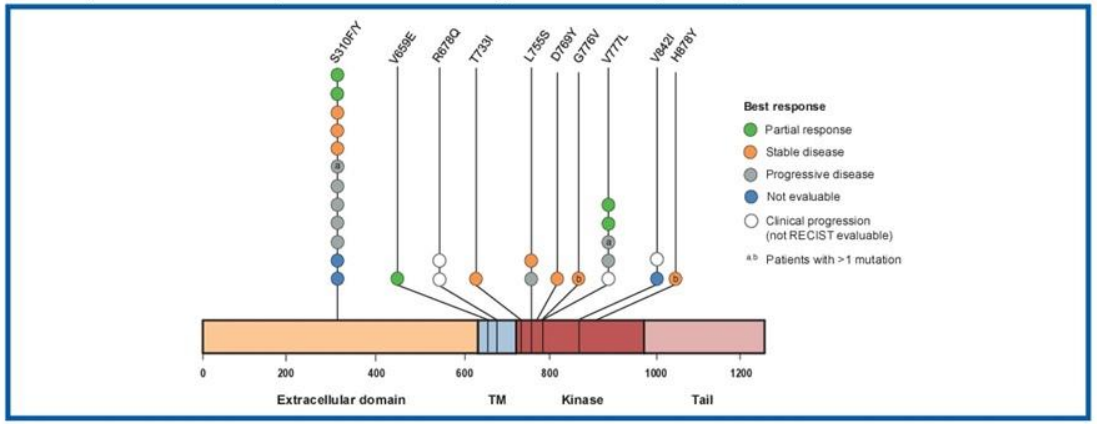
Neratinib

Targeting HER-2 mutations in BTC

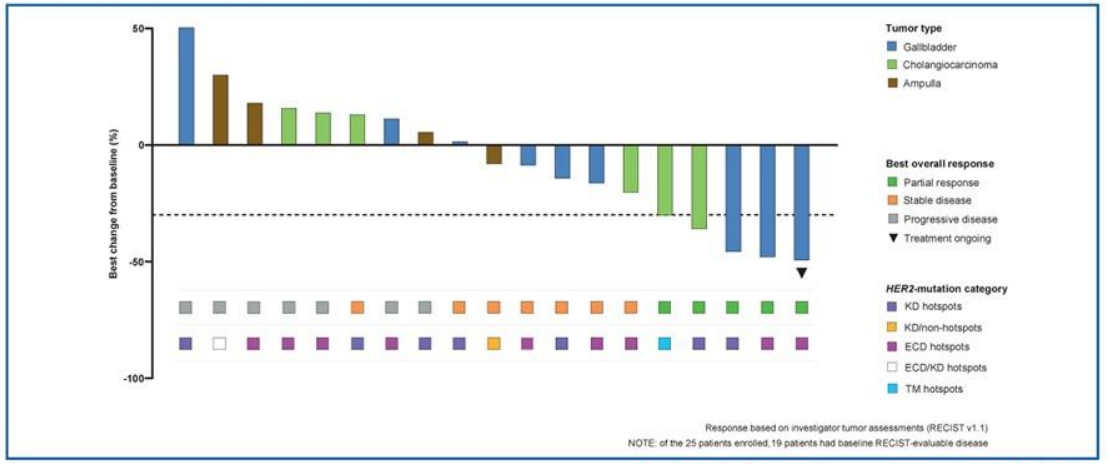
- **HER2 mutations in ~2–5% of biliary tract cancers (BTC)**

- **SUMMIT phase II pan-tumour study**
  - Neratinib, a pan-HER irreversible tyrosine kinase inhibitor
  - Biliary cohort: patients with activating somatic HER-2 mutations recruited (n= 25)
    - gallbladder (40%); intrahepatic (24%); extrahepatic (20%); ampulla of Vater (16%)
  - The S310F/Y variant accounted for nearly half of HER2 mutations (n=11).
  - ORR 12% (95% CI 3–31%)
  - Median PFS 2.8 (95% CI 1.1–3.7) months

Distribution of mutations in efficacy evaluable, HER2-mutant advanced biliary tract cancer patients receiving neratinib (n=25)



Best percentage change in target lesion size from baseline in efficacy-evaluable patients (n=19)



Harding et al ASCO GI 2021

BRAF mutations

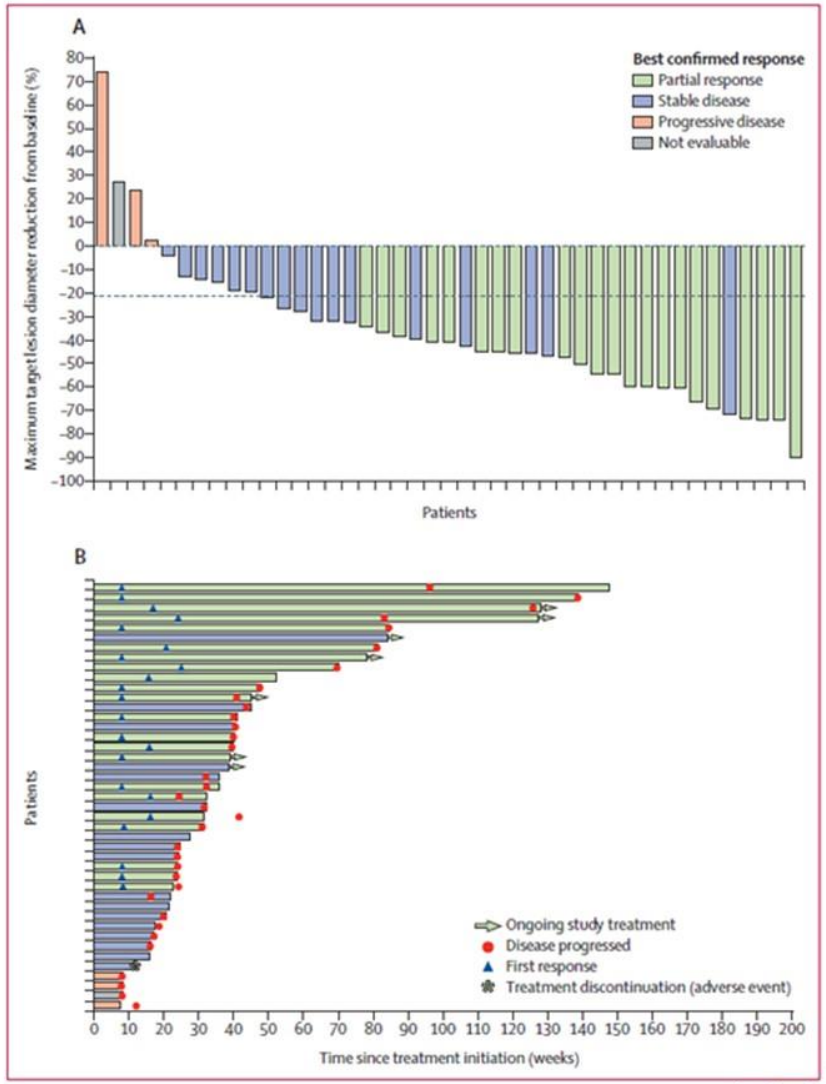
Dabrafenib + Trametinib

Dabrafenib and trametinib: mBRAF V600E

- **Phase II study; n=43**

- ORR 51% (95% CI 36-67) – investigator assessed
- **ORR 47% (95% CI 31-62)** – central review
- Duration of response: 9 months (95% CI 6-14)
- PFS: 9 months (95% CI 5-10)
- OS: 14 months (95% CI 10-33)

➢ **Promising activity and manageable safety profile.**



Subbiah et al, LancetOncol 2020

Proteasome Inhibitor

Bortezomib

A Phase II Trial of the Proteasome Inhibitor Bortezomib in Patients With Advanced Biliary Tract Cancers

Crystal S. Denlinger,[1] Neal J. Meropol,[2] Tianyu Li,[3] Nancy L. Lewis,[4]

Single arm Phase II study

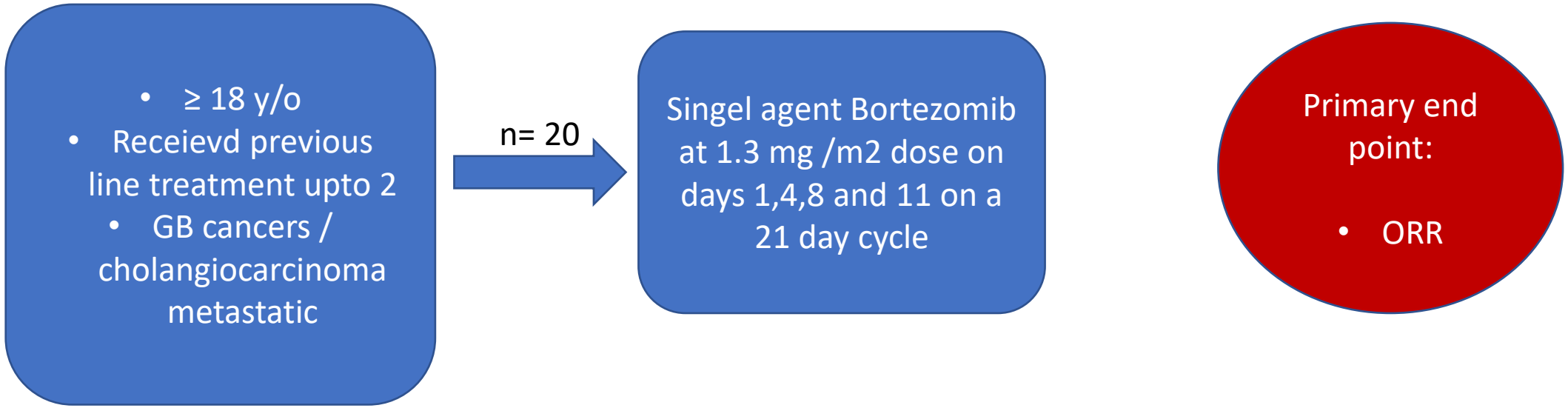
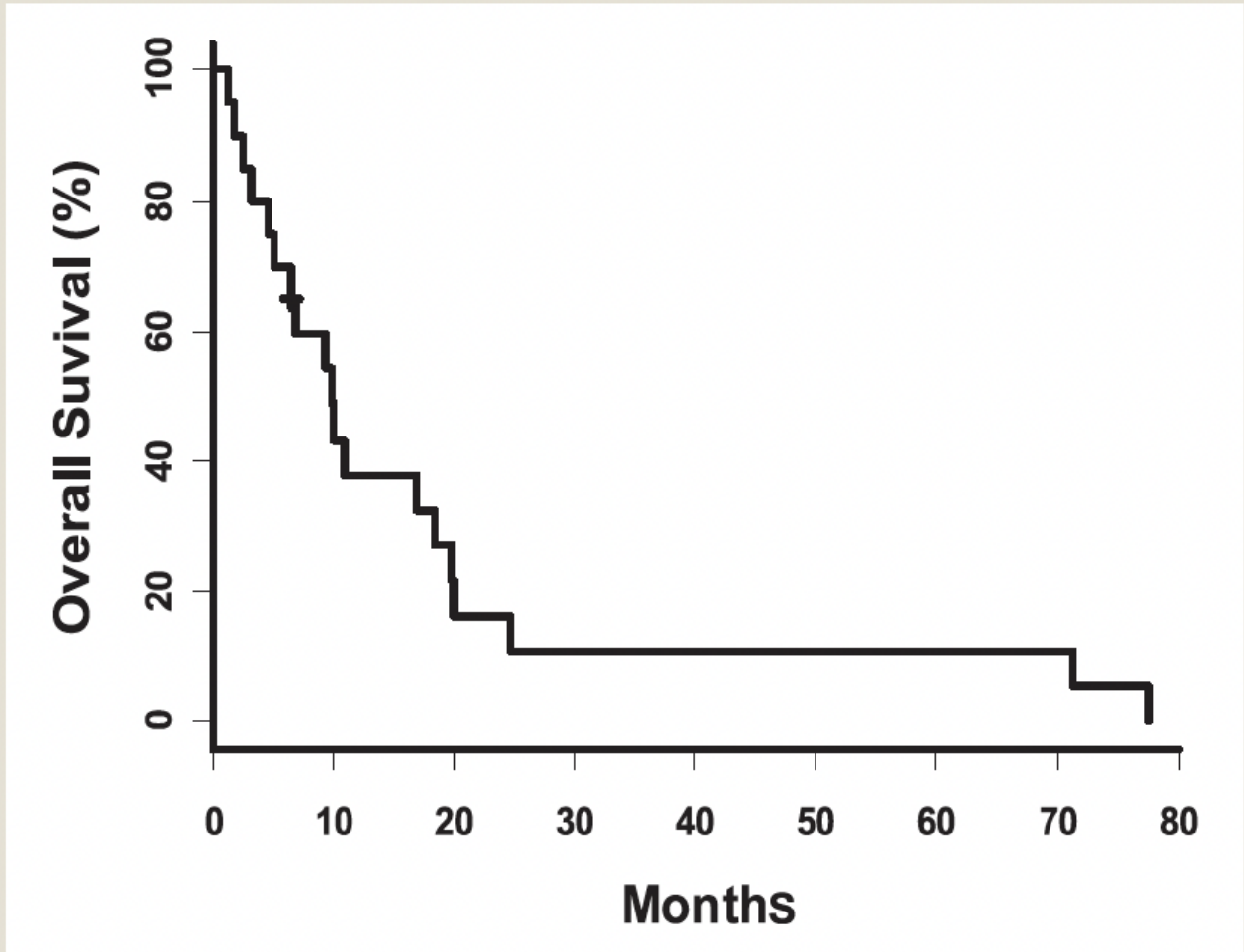


Figure 1 Overall Survival for all Patients Treated With Bortezomib



Conclusion

Our data demonstrate that single-agent bortezomib has minimal clinical activity as defined by tumor response in adenocarcinomas of the biliary tract. However, the rate of stable disease, time to progression, and overall survival are comparable to other studies of single agents in this disease. Currently, combination chemotherapy

IO in subsequent lines

Pembrolizumab

Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

Aurelien Marabelle, MD, PhD[1]; Dung T. Le, MD[2]; Paolo A. Ascierto, MD[3]; Anna Maria Di Giacomo, MD[4]; Ana De Jesus-Acosta, MD[2];

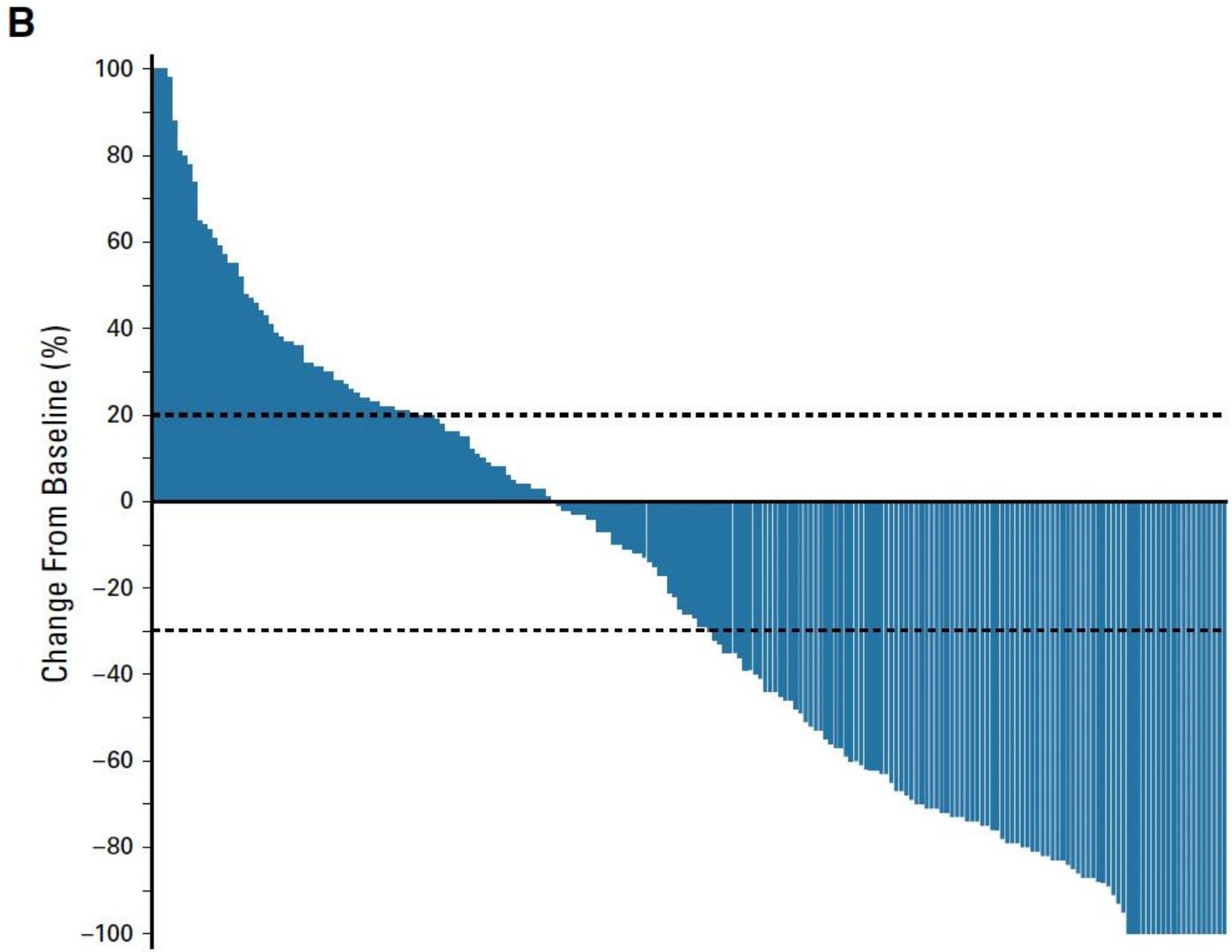
KEYNOTE-158

Median age, years (range)	60.0 (20-87)
≥ 65	87 (37.3)
Sex	
Male	96 (41.2)
Female	137 (58.8)
ECOG performance status	
0	113 (48.5)
1	120 (51.5)
Disease stage	
MX	1 (0.4)
M0	10 (4.3)
M1	212 (91.0)
Unknown	10 (4.3)
Brain metastases	4 (1.7)
Median sum of target lesions at baseline, mm (range)	65.8 (10.2-394.5)
Prior (neo) adjuvant therapy	55 (23.6)
Prior lines of therapy for recurrent/ metastatic disease	
0*	7 (3.0)
1	87 (37.3)
2	61 (26.2)
3	41 (17.6)
≥ 4	37 (15.9)
Cancer type of primary diagnosis	
Endometrial	49 (21.0)
Gastric	24 (10.3)
Cholangiocarcinoma	22 (9.4)
Pancreatic	22 (9.4)
Small intestine	19 (8.2)
Ovarian	15 (6.4)
Brain	13 (5.6)
Sarcoma	9 (3.9)
Neuroendocrine tumor	7 (3.0)
Cervical	6 (2.6)
Prostate	6 (2.6)
Adrenocortical	5 (2.1)
Breast	5 (2.1)
Thyroid	5 (2.1)
Urothelial	5 (2.1)
Mesothelioma	4 (1.7)
Small-cell lung cancer	4 (1.7)
Renal	3 (1.3)

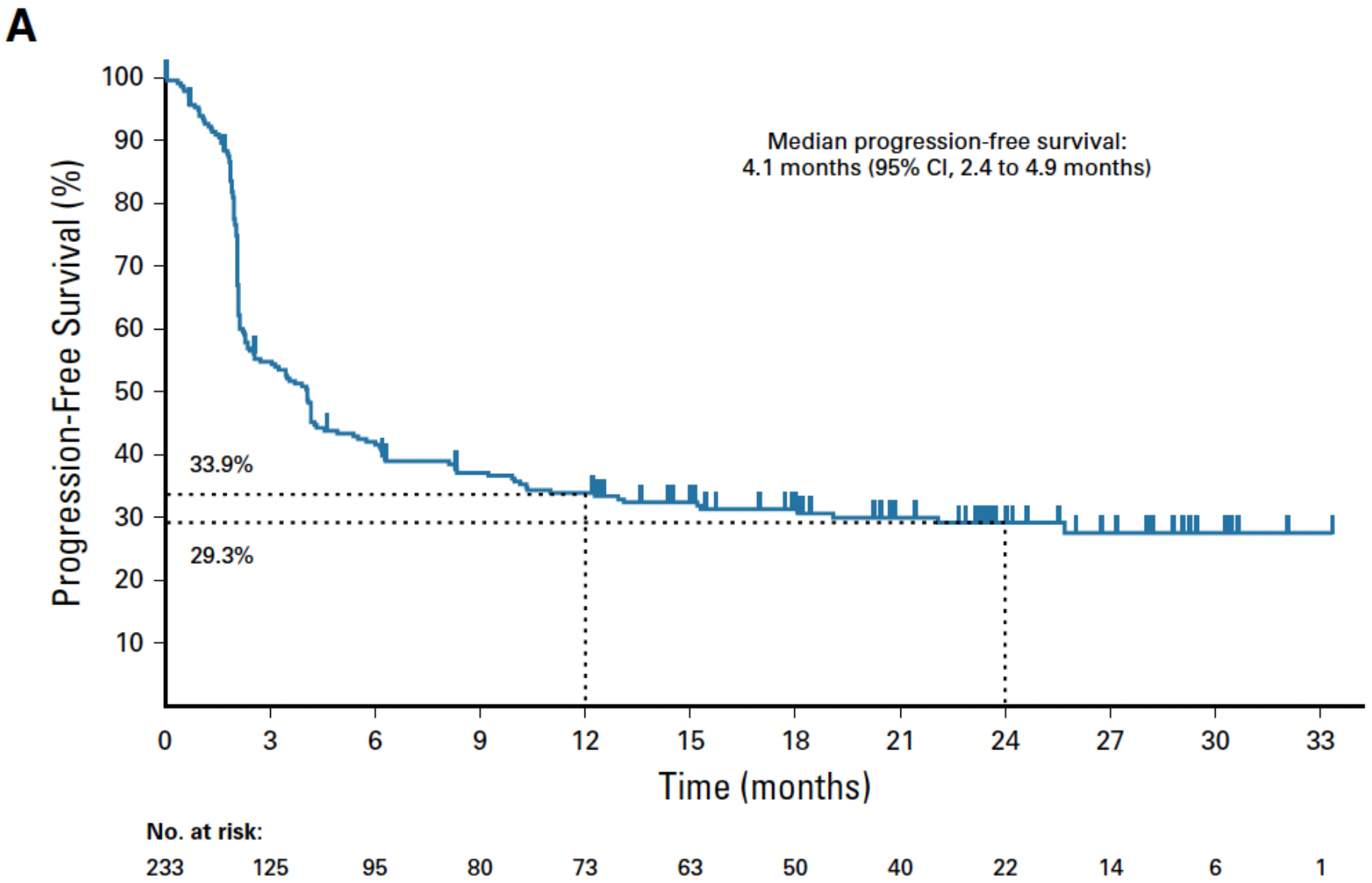
ORR

Response	Evaluable Patients (N = 233)
Objective response	
No. (%; 95% CI)	80 (34.3; 28.3 to 40.8)
Median time to response, months (range)*	2.1 (1.3-10.6)
Median duration of response, months† (range)	NR (2.9-31.3+)
Best overall response, No. (%)	
Complete response	23 (9.9)
Partial response	57 (24.5)
Stable disease	42 (18.0)
Progressive disease	92 (39.5)
Nonevaluable	2 (0.9)
No assessment‡	17 (7.3)
Kaplan-Meier estimate of patients with extended duration of response, months†, No. (%)	
≥ 12	58 (86.9)
≥ 18	40 (79.9)
≥ 24	14 (77.6)

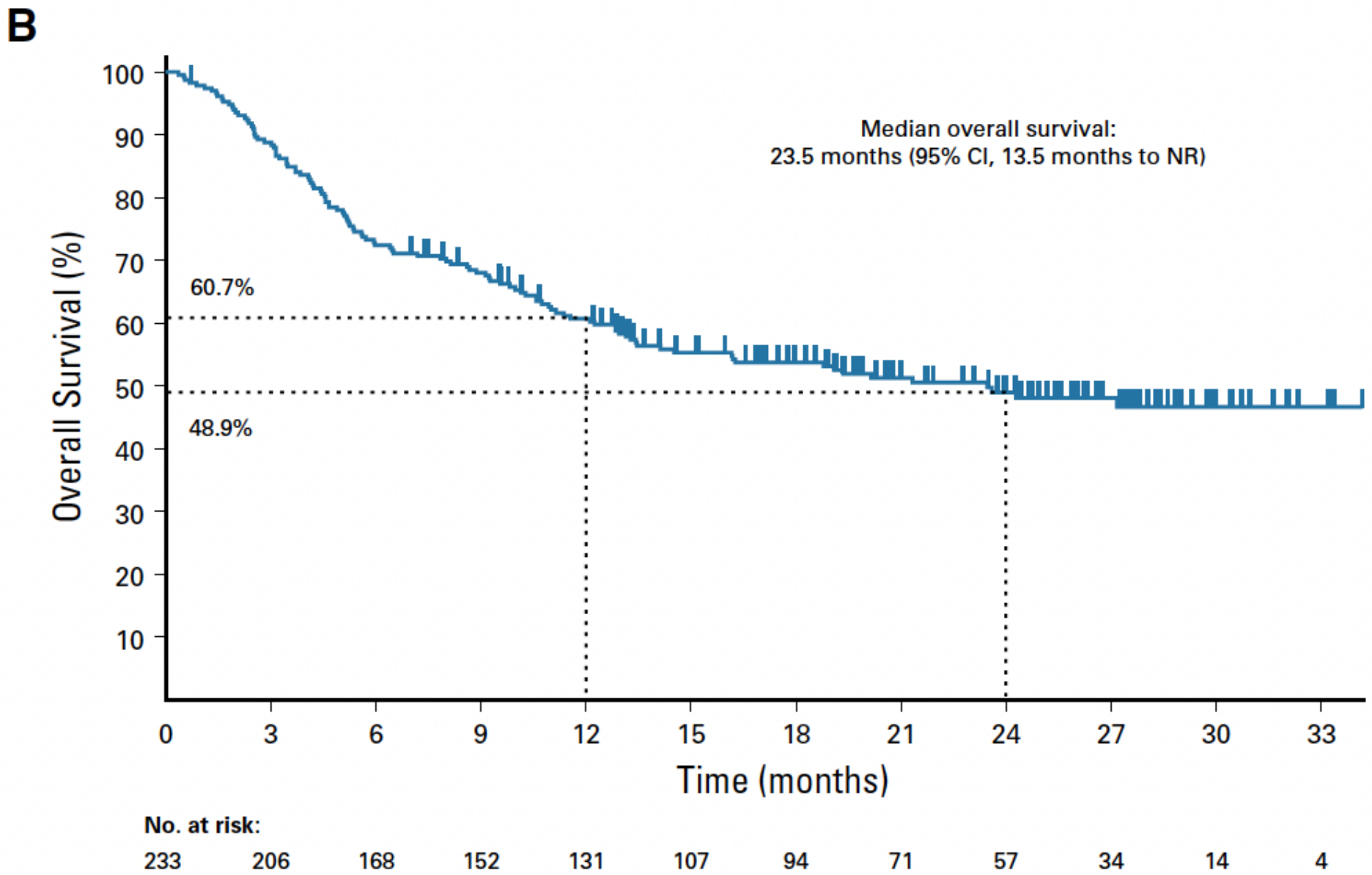
RR



PFS


A
Progression-Free Survival (%)
100
90
80
70
60
50
40
30
20
10
Median progression-free survival:
4.1 months (95% CI, 2.4 to 4.9 months)
33.9%
29.3%
0
3
6
9
12
15
18
21
24
27
30
33
Time (months)
No. at risk:
233
125
95
80
73
63
50
40
22
14
6
1

OS


B
Median overall survival:
23.5 months (95% CI, 13.5 months to NR)
60.7%
48.9%
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
3
6
9
12
15
18
21
24
27
30
33
Time (months)
No. at risk:
233
206
168
152
131
107
94
71
57
34
14
4

KEYNOTE-966

Pembrolizumab in combination with gemcitabine and cisplatin for the treatment of advanced biliary tract cancer: phase 3 KEYNOTE-966 trial in progress

R.K. KELLEY[1], A. VOGEL[2], R.S. FINN[3], J. FURUSE[4], J. EDELINE[5], Z. REN[6], S.-C. SU[7], U. MALHOTRA[7], A.B. SIEGEL[7], J.W. VALLE[8]

AIM

- KEYNOTE-966 (NCT04003636) is an international, randomized, double-blind, phase 3 study that will evaluate pembrolizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin in patients with metastatic and/or unresectable locally advanced BTC

METHOD

Objectives

Dual Primary

- To compare progression-free survival (PFS) assessed by blinded independent central review (BICR) per RECIST v1.1 and overall survival (OS) for pembrolizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin

Secondary

- To evaluate the following for pembrolizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin
  - ORR assessed by BICR per RECIST v1.1
  - DOR assessed by BICR per RECIST v1.1
  - Safety and tolerability

Exploratory

- To evaluate the following for pembrolizumab + gemcitabine + cisplatin compared with placebo + gemcitabine + cisplatin
  - Disease control rate assessed by BICR per RECIST v1.1
  - Health-related quality of life (EuroQol 5-dimension, 5-level questionnaire [EQ-5D-5L], European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 [QLQ-C30], and EORTC Quality of Life Questionnaire Cholangiocarcinoma and Gallbladder Cancer [QLQ-BIL21])
  - Molecular and genetic biomarkers

Study Design and Patients

- Approximately 788 patients will be randomly assigned 1:1 to receive pembrolizumab or placebo in combination with gemcitabine + cisplatin (**Figure 1**)

Patient Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Histologically confirmed advanced (metastatic) and/or unresectable (locally advanced) BTC (intrahepatic or extrahepatic cholangiocarcinoma or gallbladder cancer) • Measurable disease based on RECIST v1.1, as determined by the site investigator • Past or ongoing HCV infection or controlled HBV infection in participants who meet protocol-specified criteria • ECOG PS 0 or 1 • Adequate organ function • Tumor tissue for biomarker analysis	• Past systemic therapy for advanced (metastatic) or unresectable (locally advanced) BTC (intrahepatic or extrahepatic cholangiocarcinoma or gallbladder cancer) • Ampullary cancer, small cell cancer, neuroendocrine tumors, lymphoma, sarcoma, and/or mucinous cystic neoplasms • Active autoimmune disease necessitating systemic treatment in the past 2 years • Past major surgery with ongoing grade >1 toxicity and/or complications • Past therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137)

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; HBV, hepatitis B virus; HCV, hepatitis C virus.

Nivolumab

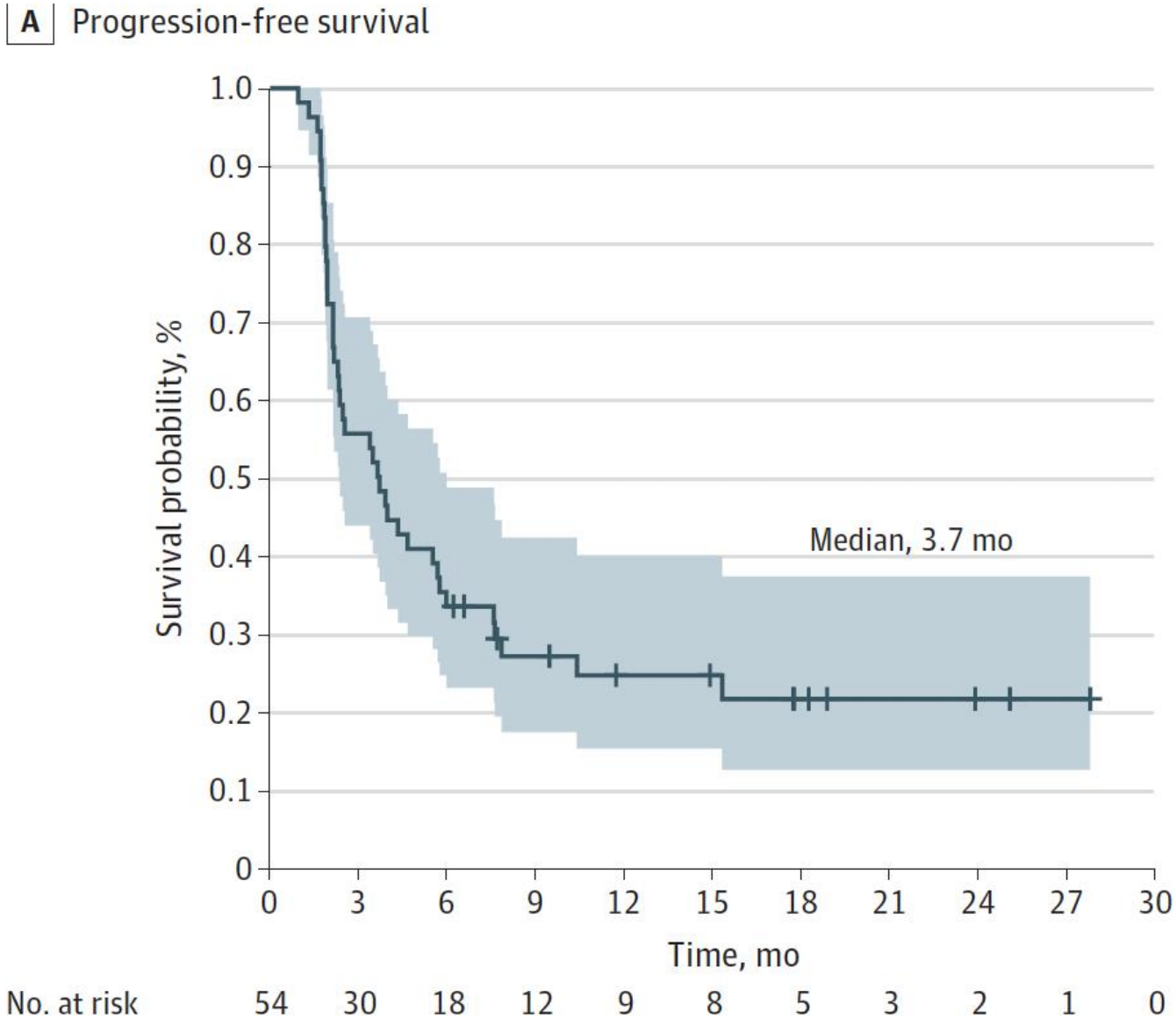
JAMA Oncology | Original Investigation

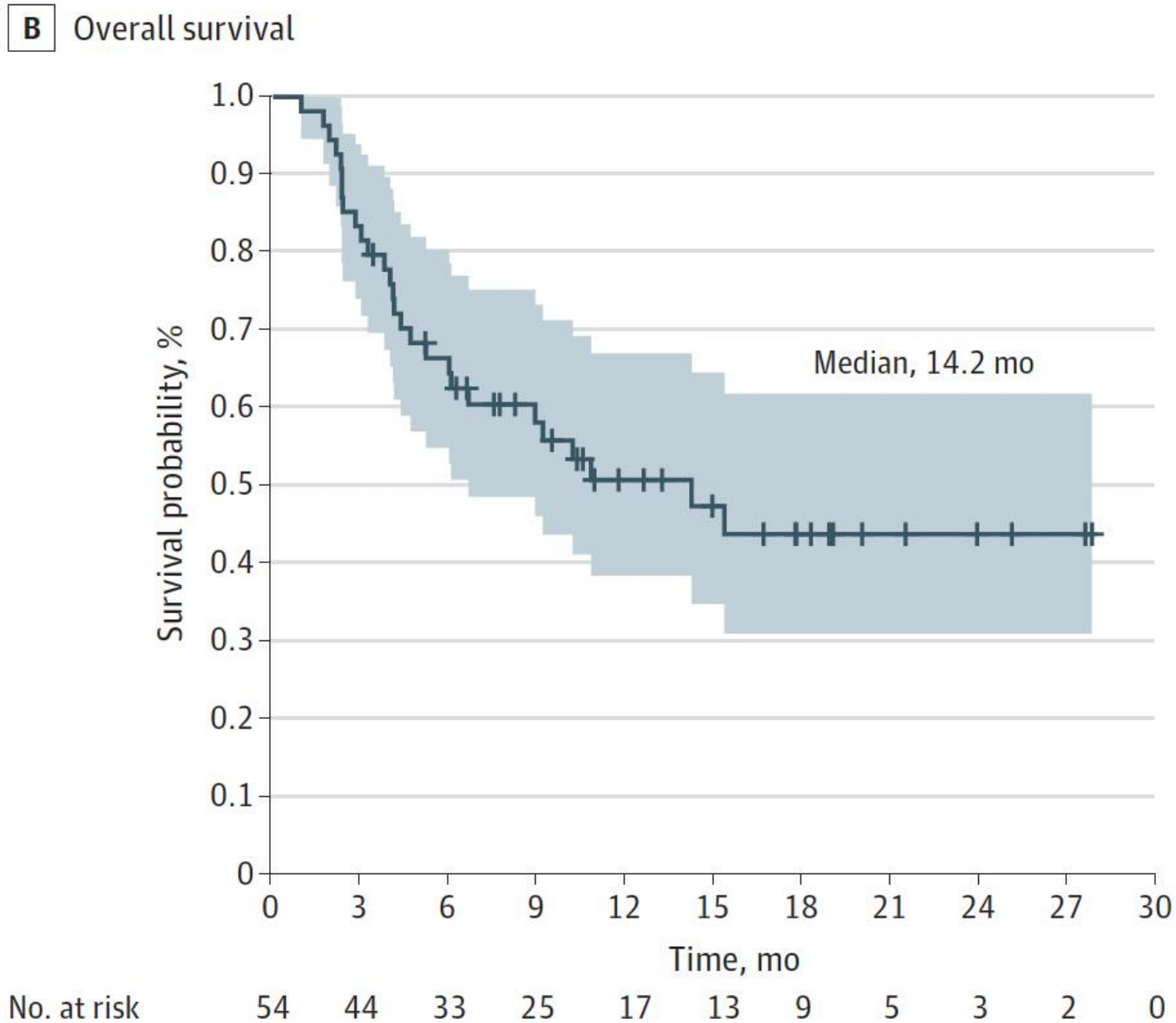
A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer

Richard D. Kim, MD; Vincent Chung, MD; Olatunji B. Alese, MD; Bassell F. El-Rayes, MD; Daneng Li, MD;

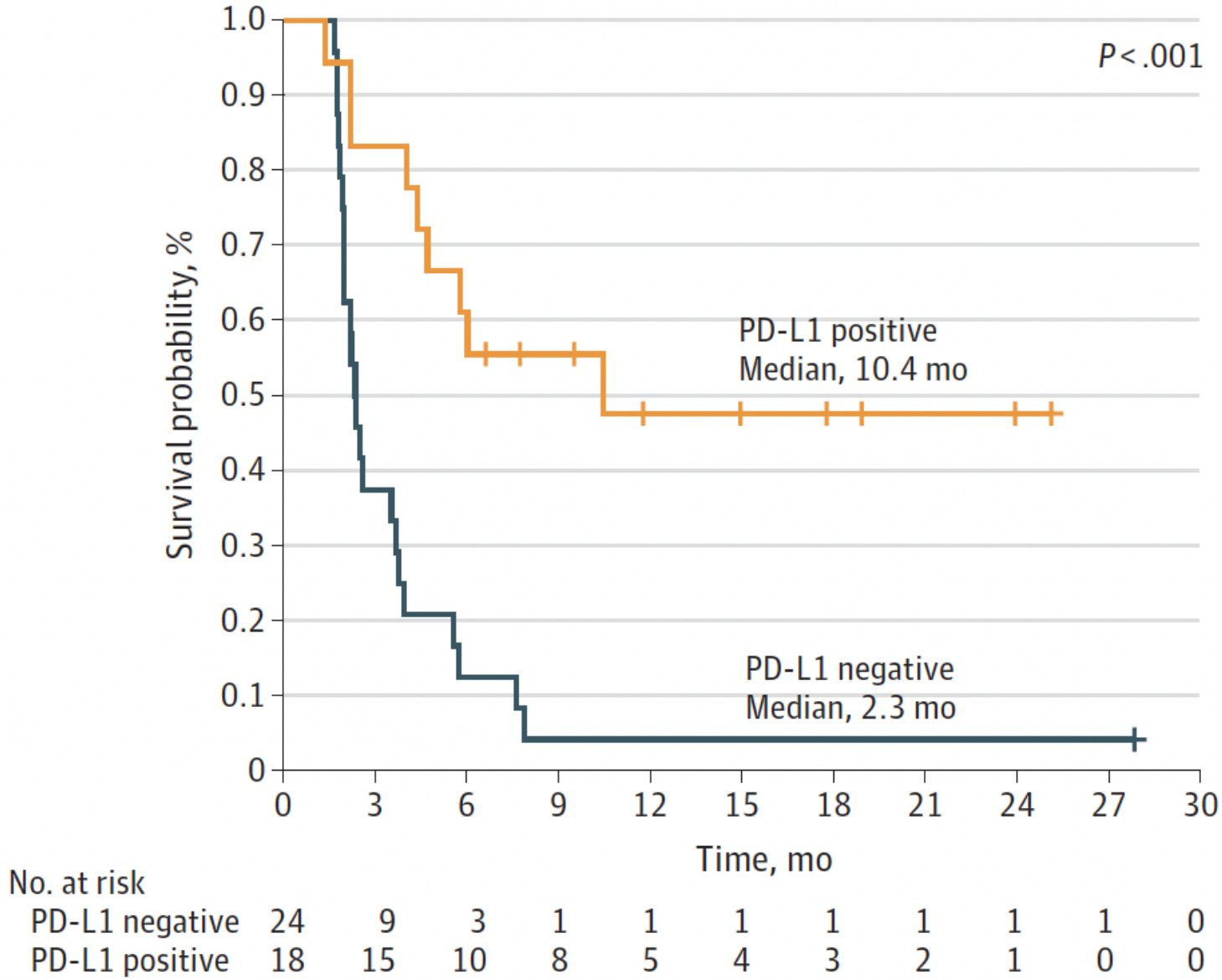
Table 1. Best Overall Response and Disease Control Rate

	No. (%) (n = 46)			
	RECIST, version 1.1		iRECIST	
Best overall response	Investigator review	Central review	Investigator review	Central review
CR (iCR)	0	0	0	0
PR (iPR)	10 (22)	5 (11)	10 (22)	6 (13)
	1 Unconfirmed	1 Unconfirmed	1 Unconfirmed	1 Unconfirmed
SD (iSD)	17 (37)	18 (39)	18 (39)	22 (48)
PD (iUPD + iCPD)	19 (41)	23 (50)	18 (39)	18 (39)
Disease control rate	27 (59)	23 (50)	28 (61)	28 (61)


A Progression-free survival
Survival probability, %
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Median, 3.7 mo
0 3 6 9 12 15 18 21 24 27 30
Time, mo
No. at risk 54 30 18 12 9 8 5 3 2 1 0


B
Overall survival
Survival probability, %
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Median, 14.2 mo
0
3
6
9
12
15
18
21
24
27
30
Time, mo
No. at risk
54
44
33
25
17
13
9
5
3
2
0

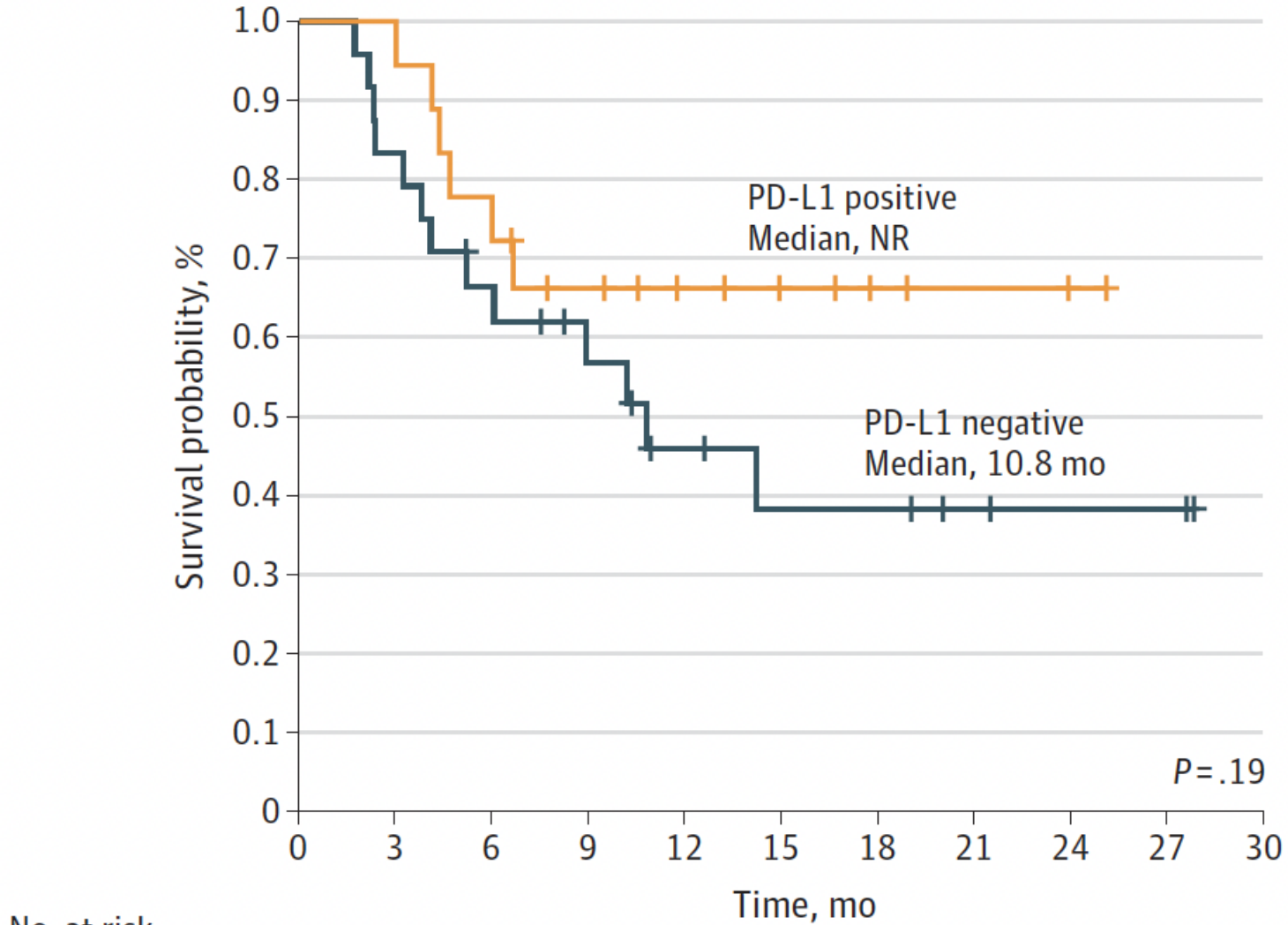
C Progression-free survival by PD-L1 status



No. at risk

PD-L1 negative	24	9	3	1	1	1	1	1	1	1	0
PD-L1 positive	18	15	10	8	5	4	3	2	1	0	0

D Overall survival by PD-L1 status



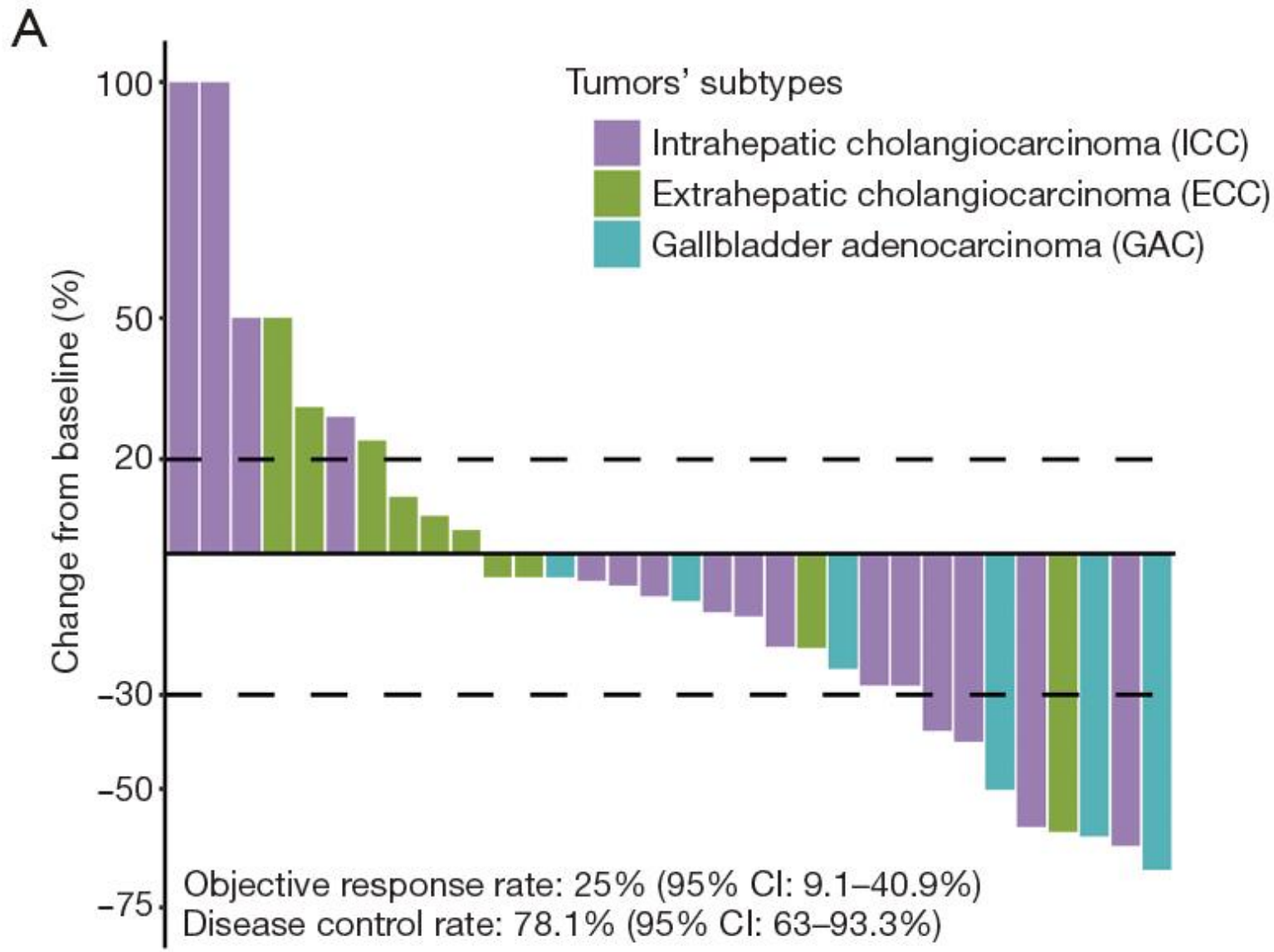
No. at risk

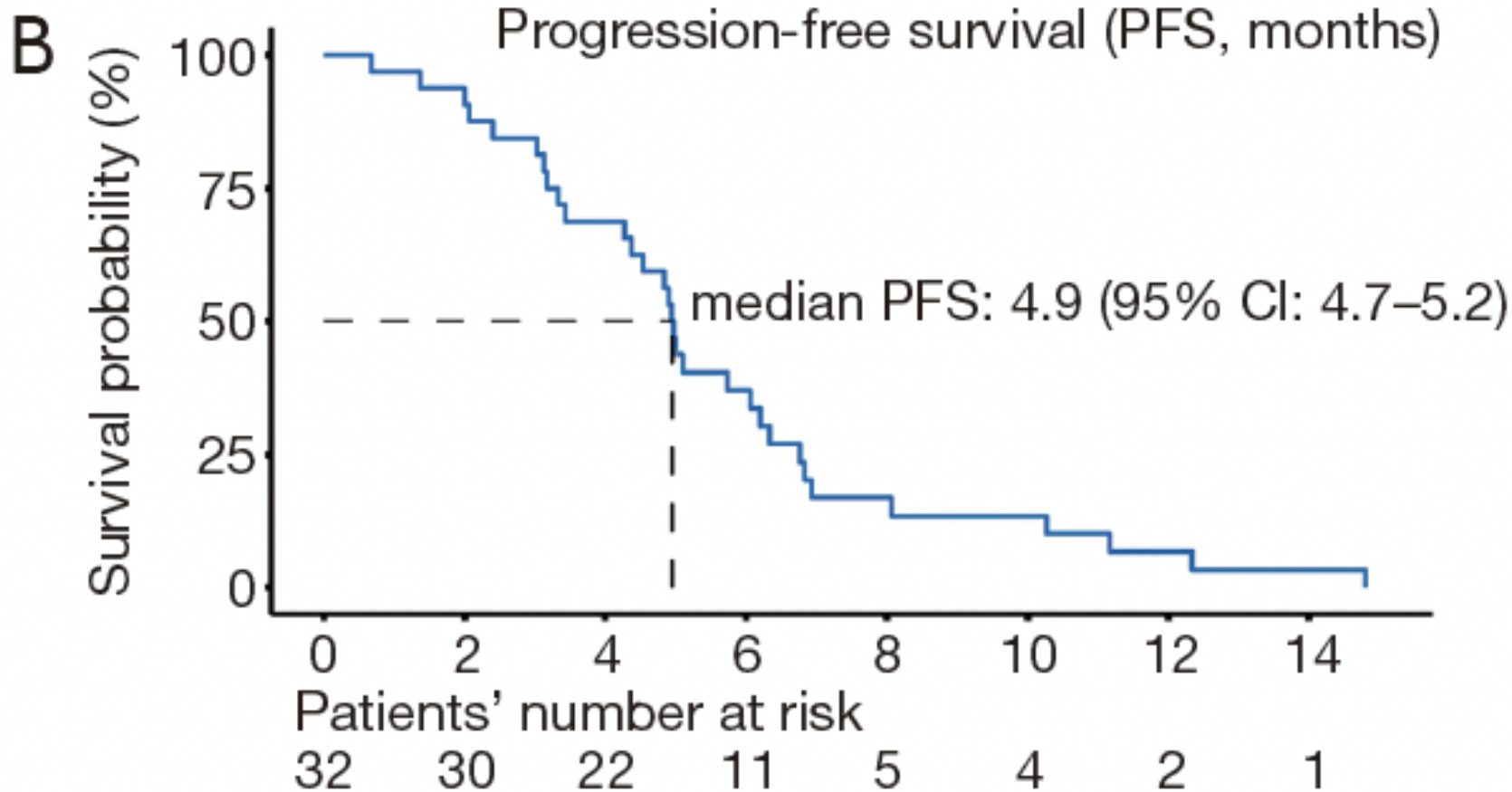
PD-L1 negative	24	20	15	11	7	5	5	3	2	2	0
PD-L1 positive	18	17	13	10	7	5	3	2	1	0	0

Pembrolizumab combined with lenvatinib as non-first-line therapy in patients with refractory biliary tract carcinoma

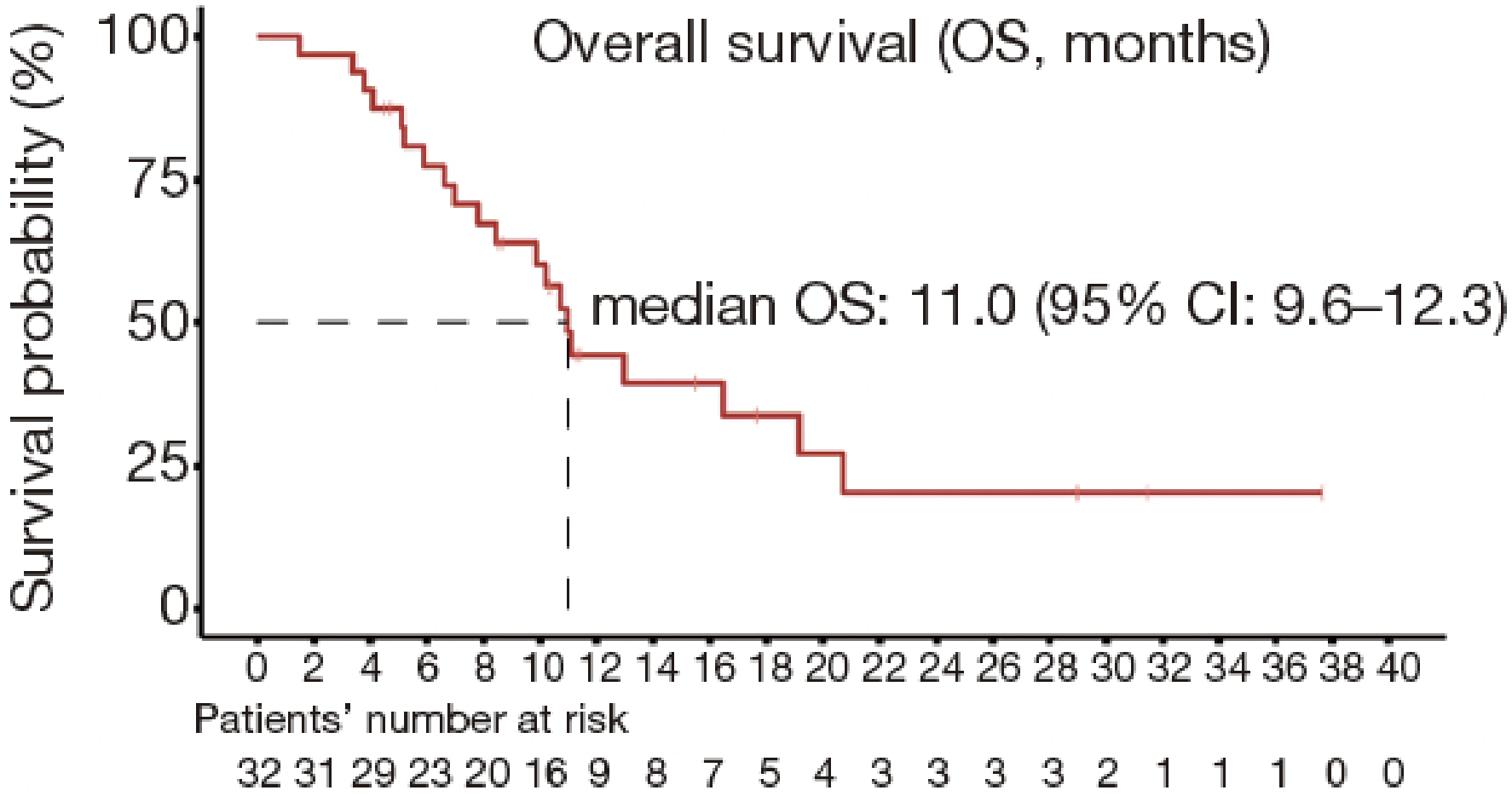
LEP

Pembrolizumab + Lenvantinib


A
Tumors' subtypes
Intrahepatic cholangiocarcinoma (ICC)
Extrahepatic cholangiocarcinoma (ECC)
Gallbladder adenocarcinoma (GAC)
Change from baseline (%)
100
50
20
−30
−50
−75
Objective response rate: 25% (95% CI: 9.1–40.9%)
Disease control rate: 78.1% (95% CI: 63–93.3%)


B
Progression-free survival (PFS, months)
Survival probability (%)
100
75
50
25
0
median PFS: 4.9 (95% CI: 4.7–5.2)
0
2
4
6
8
10
12
14
Patients' number at risk
32
30
22
11
5
4
2
1

C


Overall survival (OS, months)
Survival probability (%)
100
75
50
25
0
median OS: 11.0 (95% CI: 9.6–12.3)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Patients' number at risk
32 31 29 23 20 16 9 8 7 5 4 3 3 3 3 2 1 1 1 0 0

ORR

Therapeutic response assessment	Evaluable patients (n=32)
Confirmed objective response rate (%, 95% CI)	25% (9.1–40.9%)
Complete response (CR, n, %)	0
Partial response (PR, n, %)	8 (25%)
Stable disease (SD, n, %)	17 (53%)
Progressive disease (PD, n, %)	7 (22%)
Disease control rate (%, 95% CI)	78.1% (63–93.3%)
Clinical benefit rate (%, 95% CI)	40.5% (22.6–58.6%)
Progression-free survival (median, 95% CI, months)	4.9 (4.7–5.2)
Overall survival (median, 95% CI, months)	11.0 (9.6–12.3)

THANK YOU