PRIMO 2023: Novel Immunotherapy Approaches in Hepatobiliary Malignancies

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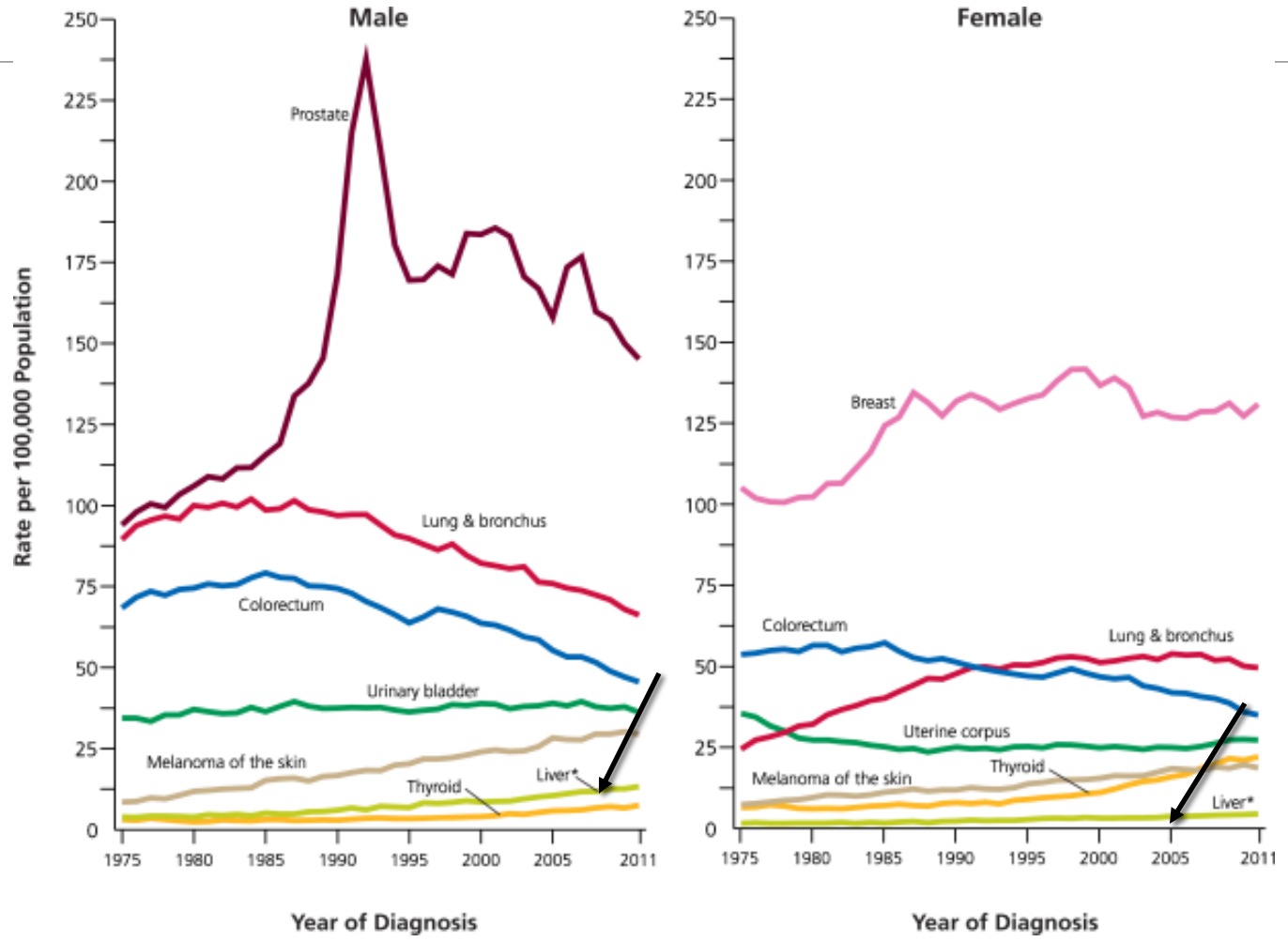
ACS Cancer Statistics

Trends in Incidence Rates for Selected Cancers by Sex, United States, 1975 to 2011



CA: A Cancer Journal for Clinicians
Volume 65, Issue 1, pages 5-29, 5 JAN 2015 DOI: 10.3322/caac.21254
http://onlinelibrary.wiley.com/doi/10.3322/caac.21254/full#caac21254-fig-0003

Biliary Cancers

WE HAVE HOPE! I THINK…

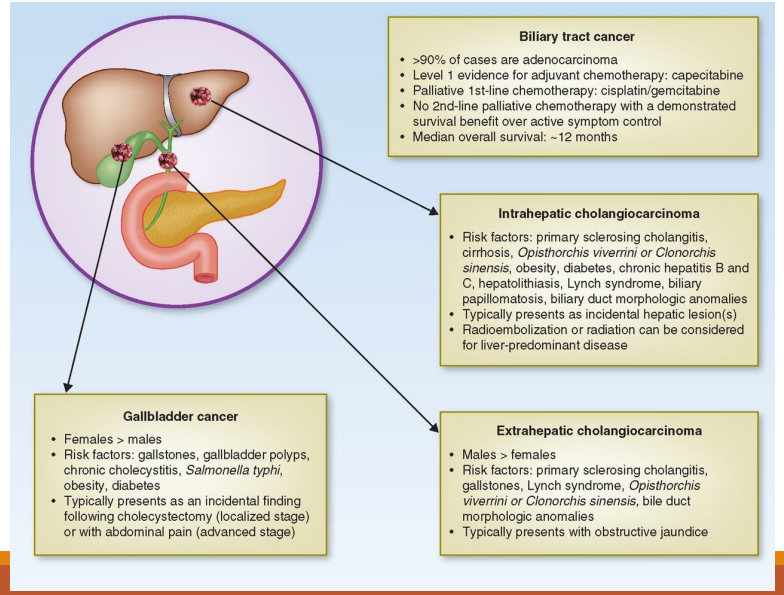
It’s a WHOLE NEW WORLD in CCA…

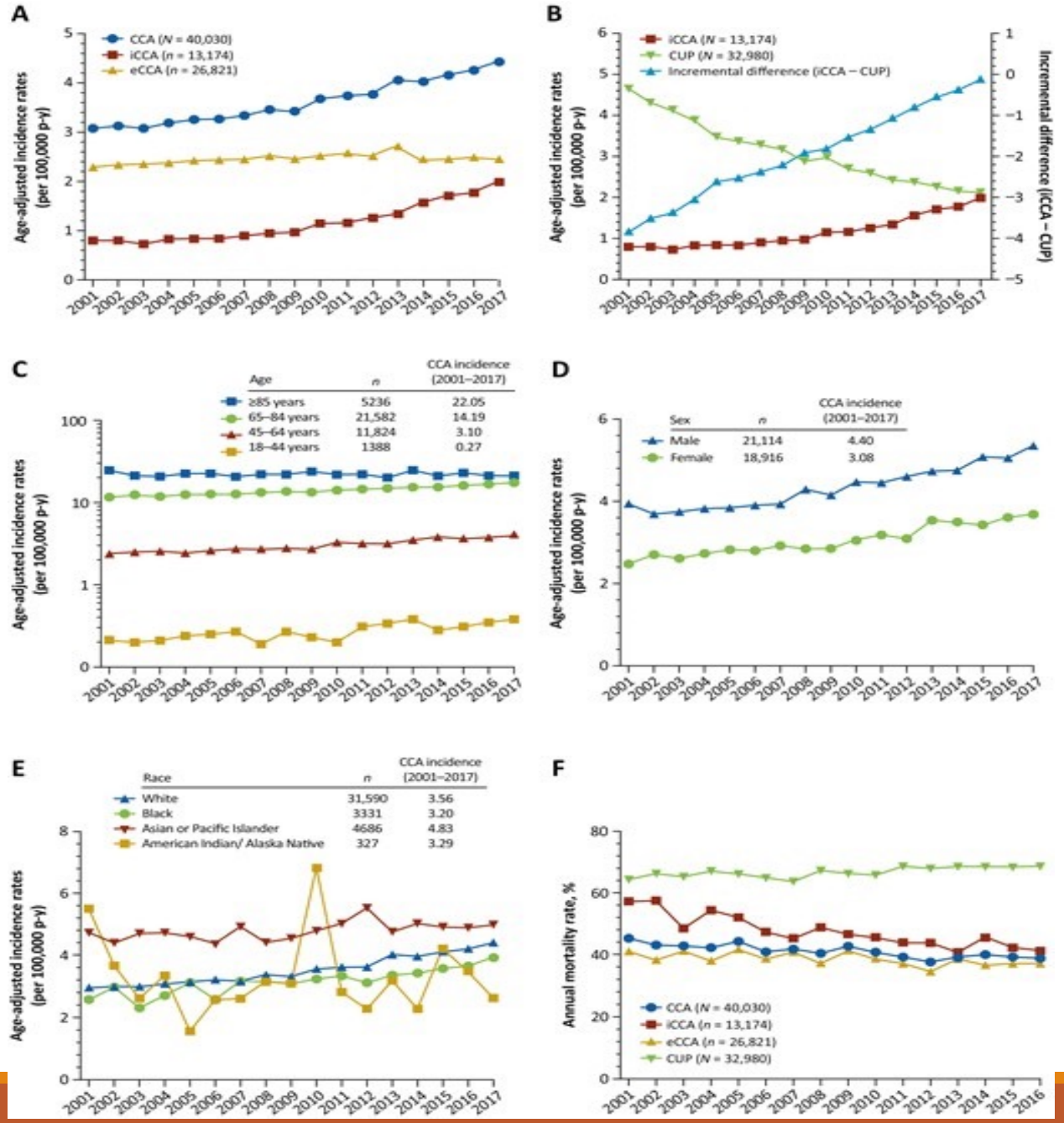
We have historically had gem/cis and that is all

We have historically lumped BTCs together

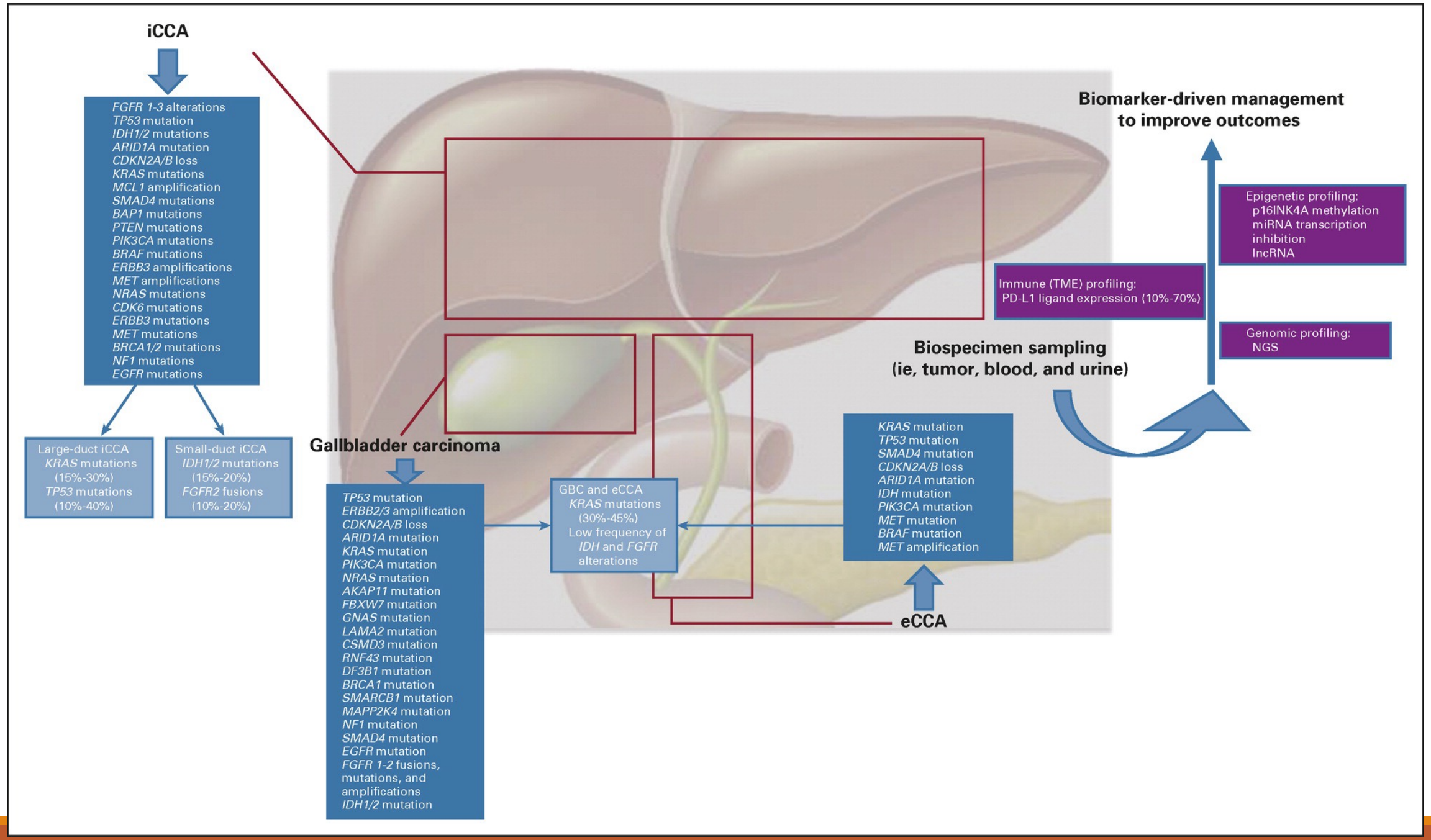
We have historically broken-down subtypes by anatomy

But we eventually got smarter and flipped the script…





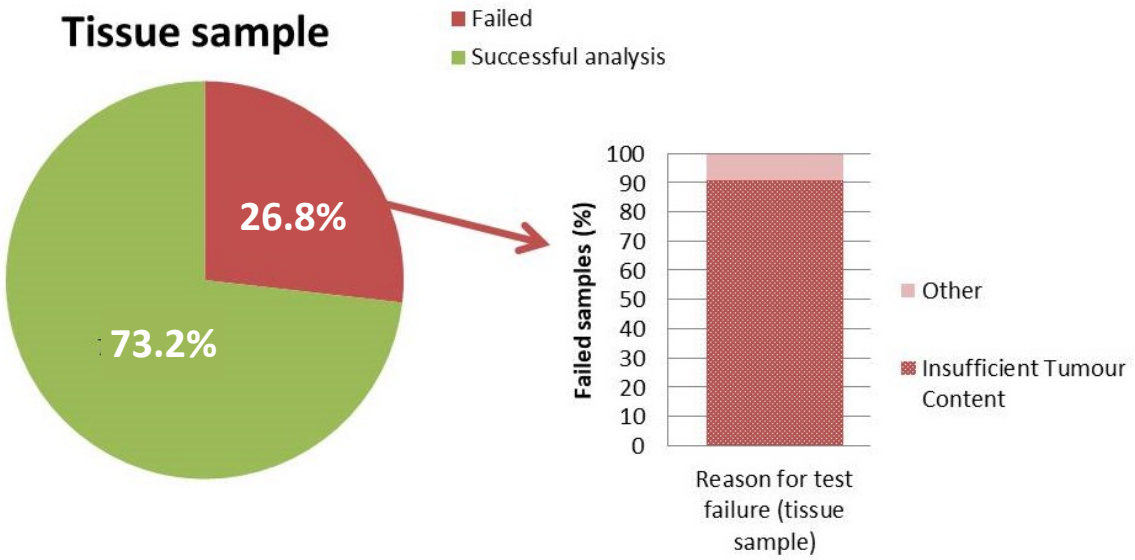
Javle et al, Oncologist 2022



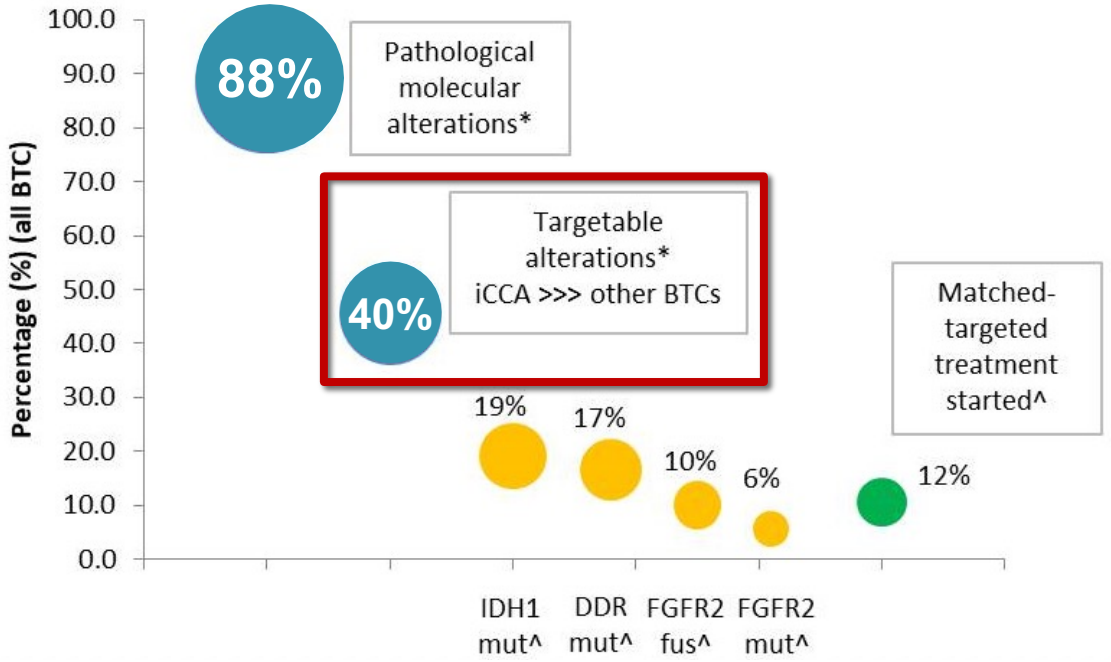
Scott AJ et al, J Clin Oncol 2022

Precision Medicine is not for everyone…

- **Reason #1: Quality tissue sample not always available**
  - Cytology-based diagnosis
  - Failed tissue samples



- **Reason #2: Targetable finding ~40% of patients**
  - ~60%: not suitable for targeted therapies



Novel cytotoxic chemotherapy strategies are required

Slide courtesy of Dr. Lamarca

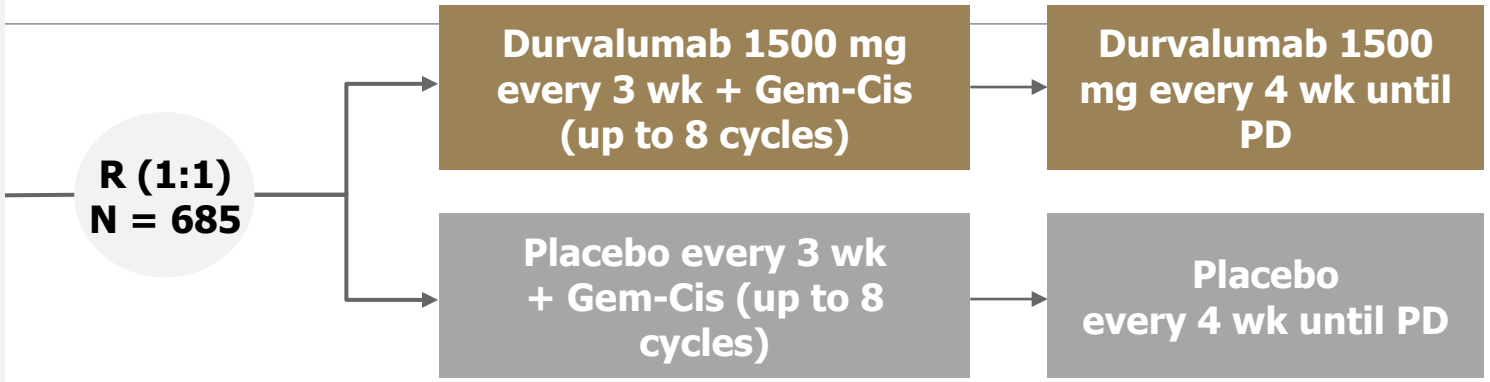
First let’s talk about the big change!

IT ISN’T JUST A GEM/CIS WORLD ANYMORE…IMMUNOTHERAPY!

Shine bright like a TOPAZ: Study Design

TOPAZ-1 Is a Double-Blind, Multicenter, Global, Phase 3 Study

Key eligibility
- Locally advanced or metastatic BTC (iCCA, eCCA, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease > 6 mo after curative surgery or adjuvant therapy
- ECOG PS 0 or 1



Stratification factors
- Disease status
  - (initially unresectable vs recurrent)
- Primary tumor location
  - (iCCA vs eCCA vs GBC)

Primary objective
- OS

Secondary objectives
- PFS
- ORR
- DoR
- Efficacy by PD-L1 status
- Safety

Gem-Cis treatment: gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on days 1 and 8 every 3 wk administered for up to 8 cycles.
GBC, gallbladder cancer; PD, progressive disease.

Oh DY, et al. 2022 ASCO Gastrointestinal Cancers Symposium; January 20-22, 2022; San Francisco, CA. Abstract 378.

Shine bright like a…TOPAZ! Demographics

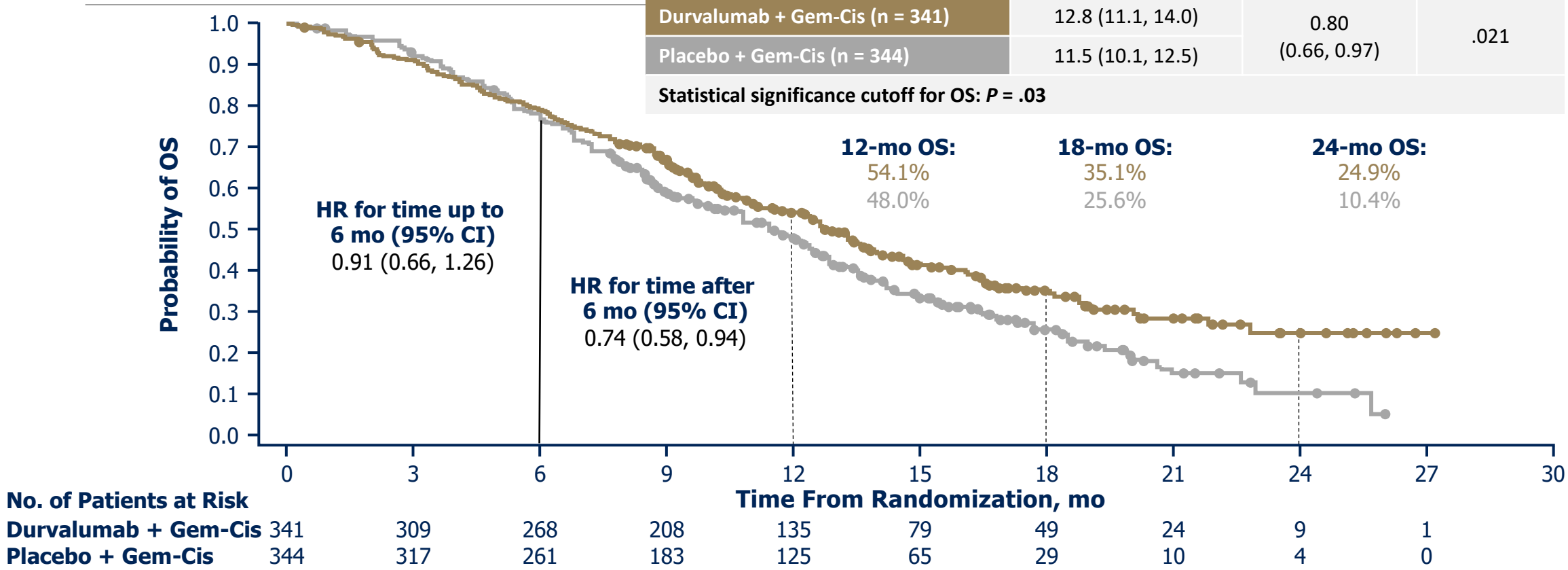
	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Median age (range), years	64 (20–84)	64 (31–85)
Sex, female, n (%)	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
White	131 (38.4)	124 (36.0)
Black or African American	8 (2.3)	6 (1.7)
American Indian or Alaska Native	0	1 (0.3)
Other	17 (5.0)	12 (3.5)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of the world	163 (47.8)	148 (43.0)
ECOG PS 0 at screening, n (%)	173 (50.7)	163 (47.4)
Primary tumor location at diagnosis, n (%)		
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)
Disease status at randomization, n (%)		
Initially unresectable	274 (80.4)	279 (81.1)
Recurrent	67 (19.6)	64 (18.6)
Disease classification at diagnosis,* n (%)		
Metastatic	303 (88.9)	286 (83.1)
Locally advanced	38 (11.1)	57 (16.6)
PD-L1 expression,* n (%)		
TAP ≥1%	197 (57.8)	205 (59.6)
TAP <1%	103 (30.2)	103 (29.9)

*Data missing for remaining patients. Unless otherwise indicated, measurements were taken at baseline.

ECOG, Eastern Cooperative Oncology Group; GemCis, gemcitabine and cisplatin; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

Primary Endpoint
OS

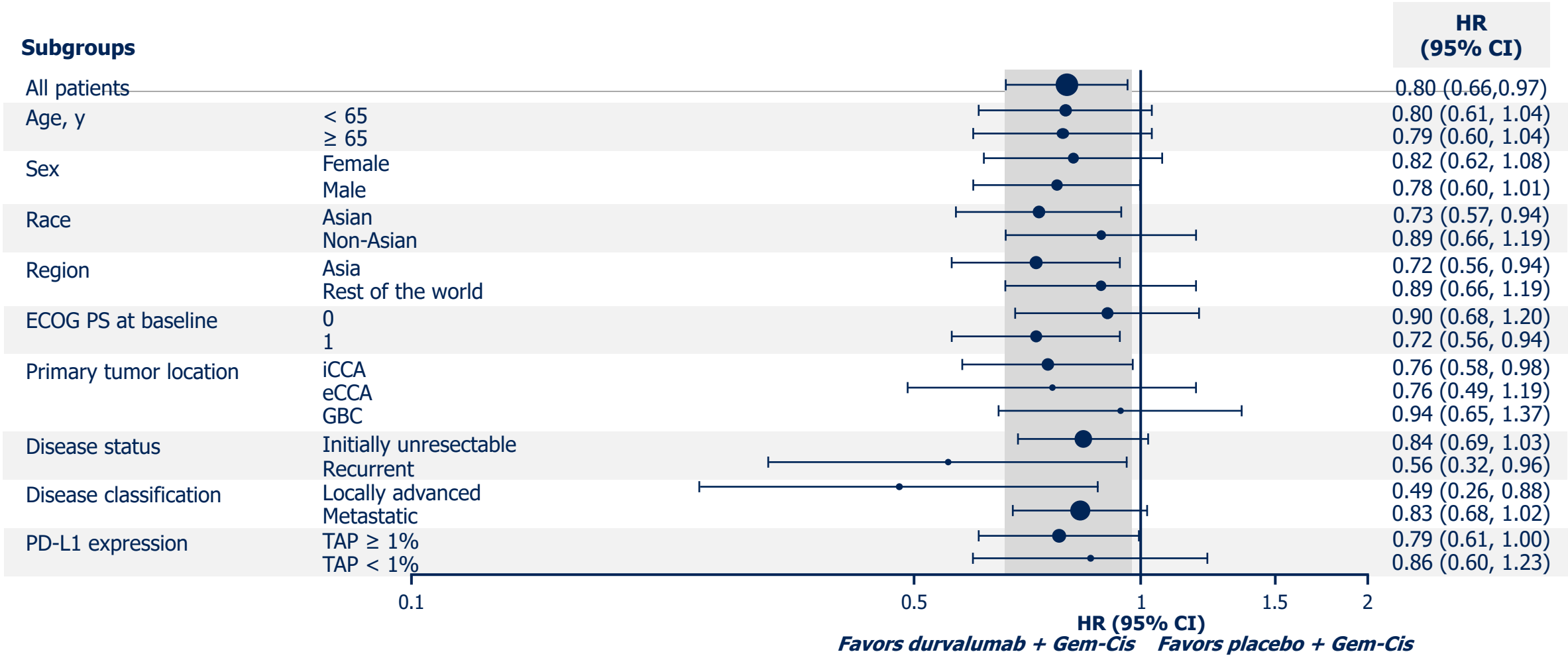
	Median OS (95% CI), mo	HR (95% CI)	*P* Value
Durvalumab + Gem-Cis (n = 341)	12.8 (11.1, 14.0)	0.80 (0.66, 0.97)	.021
Placebo + Gem-Cis (n = 344)	11.5 (10.1, 12.5)		
Statistical significance cutoff for OS: *P* = .03			



No. of Patients at Risk										
Durvalumab + Gem-Cis	341	309	268	208	135	79	49	24	9	1
Placebo + Gem-Cis	344	317	261	183	125	65	29	10	4	0

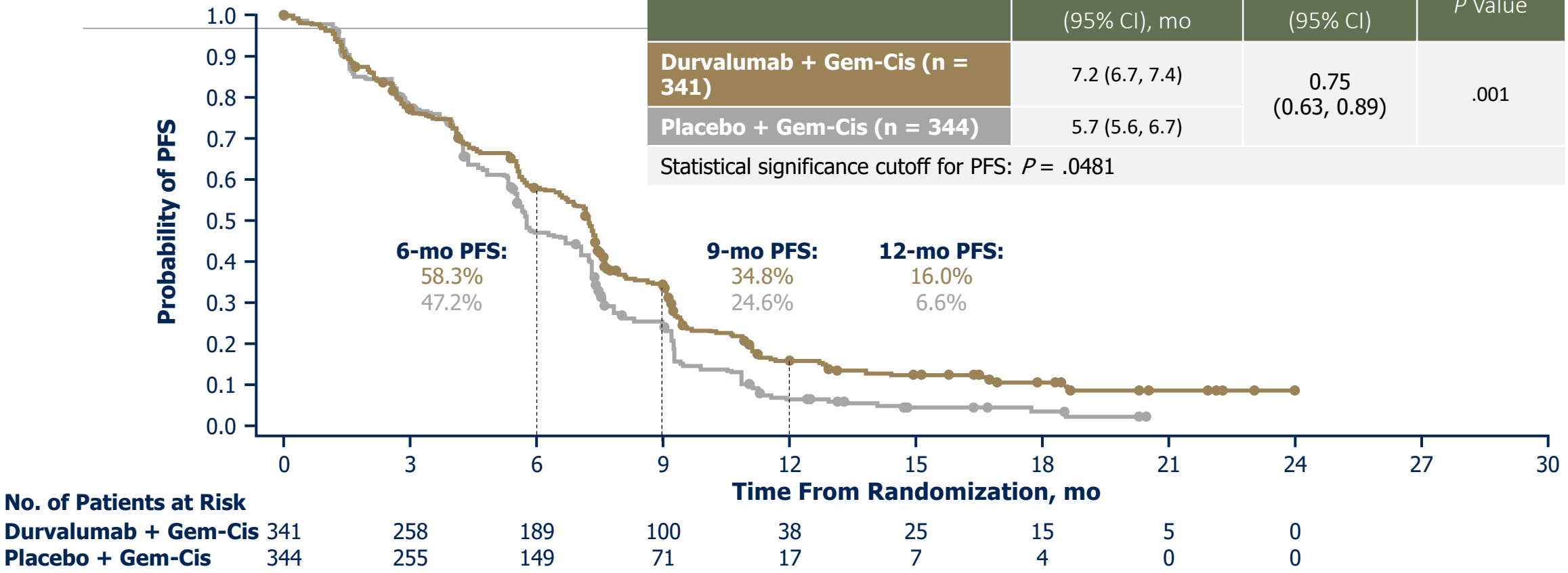
Median duration of f/u (95% CI) was 16.8 (14.8, 17.7) mo with durvalumab + Gem-Cis and 15.9 (14.9, 16.9) mo with placebo + Gem-Cis.

Subgroup Analysis of OS



Secondary Endpoint
PFS

	Median PFS (95% CI), mo	HR (95% CI)	*P* Value
Durvalumab + Gem-Cis (n = 341)	7.2 (6.7, 7.4)	0.75 (0.63, 0.89)	.001
Placebo + Gem-Cis (n = 344)	5.7 (5.6, 6.7)		
Statistical significance cutoff for PFS: *P* = .0481			



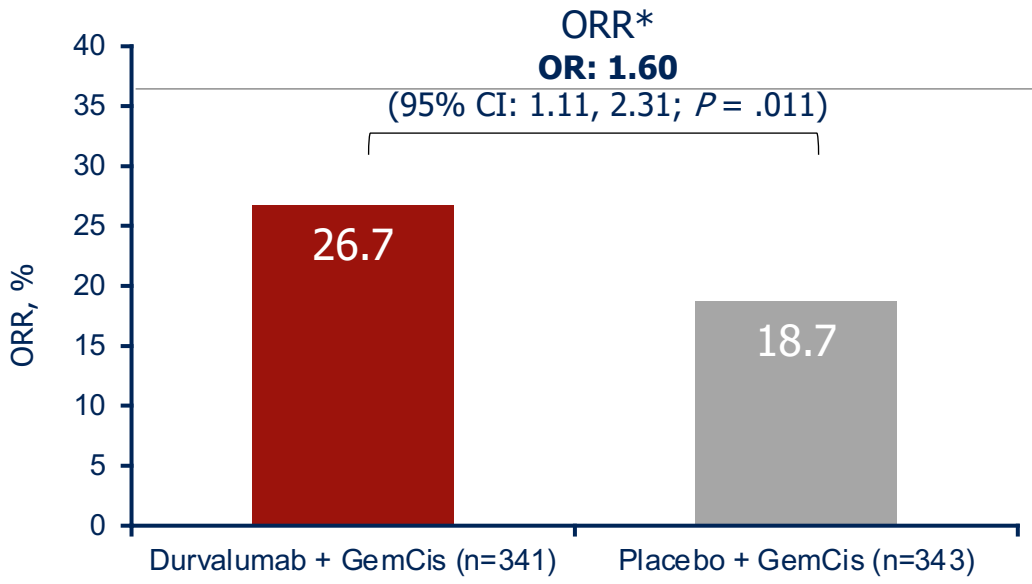
No. of Patients at Risk

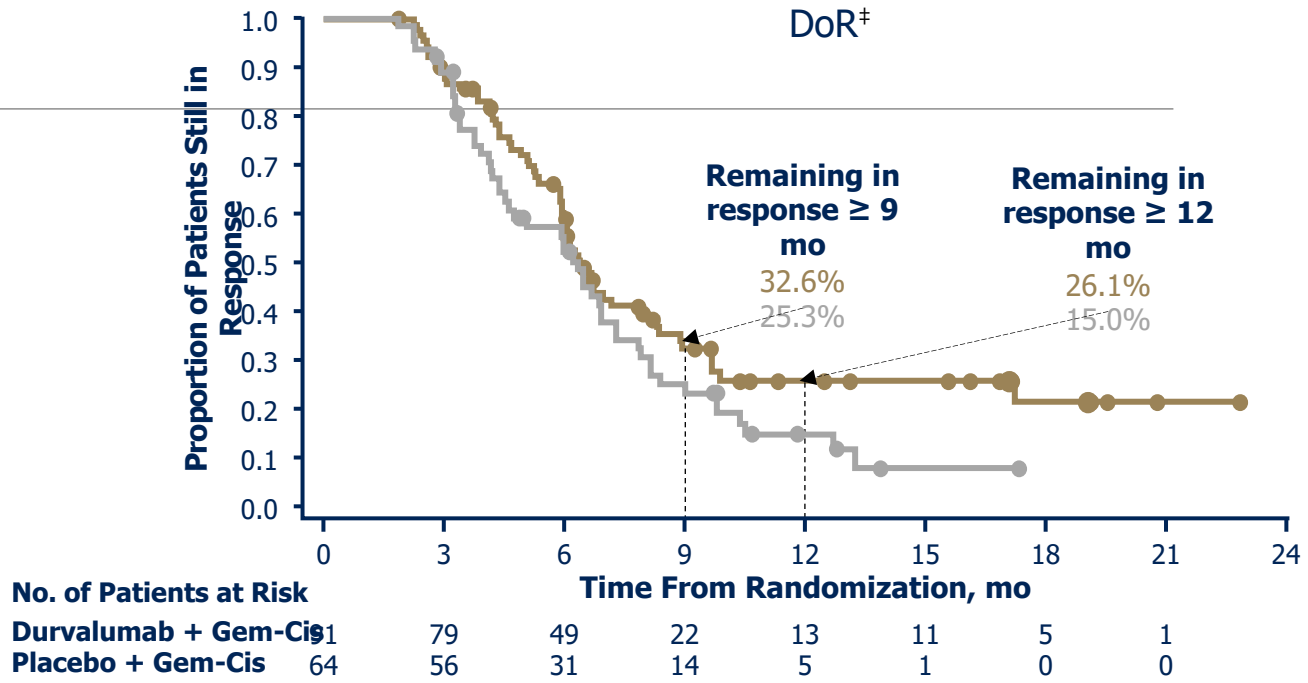
Durvalumab + Gem-Cis	341	258	189	100	38	25	15	5	0
Placebo + Gem-Cis	344	255	149	71	17	7	4	0	0

Median duration of f/u (95% CI) was 9.2 (0.0, 24.0) mo with durvalumab + Gem-Cis and 6.9 (0.0, 20.4) mo with placebo + Gem-Cis.

Oh DY, et al. 2022 ASCO Gastrointestinal Cancers Symposium; January 20-22, 2022; San Francisco, CA. Abstract 378.

Secondary Endpoint
Tumor Response





No. (%)	Durvalumab + Gem-Cis (n = 341)	Placebo + Gem-Cis (n = 343)
ORR	91 (26.7)	64 (18.7)
CR	7 (2.1)	2 (0.6)
PR	84 (24.6)	62 (18.1)
DCR†	291 (85.3)	284 (82.6)

	Durvalumab + Gem-Cis (n = 91)	Placebo + Gem-Cis (n = 64)
Median DoR (quartiles 1-3), mo	6.4 (4.6-17.2)	6.2 (3.8-9.0)
Median TTR (quartiles 1-3), mo	1.6 (1.3-3.0)	2.7 (1.4-4.1)

*By investigator assessments using RECIST v1.1 based on patients in the final analysis set who had measurable disease at baseline. †Analysis of DCR was based on all patients in the full analysis set. ‡Analysis of DoR was based on patients in the full analysis set who had an objective response and measurable disease at baseline.

Oh DY, et al. 2022 ASCO Gastrointestinal Cancers Symposium; January 20-22, 2022; San Francisco, CA. Abstract 378.

Summary of AEs and Treatment Exposure

	Durvalumab + Gem-Cis (n = 338)	Placebo + Gem-Cis (n = 342)
Duration of exposure, median (range), mo		
Durvalumab/placebo	7.33 (0.1-24.5)	5.77 (0.2-21.5)
Gem	5.19 (0.1-8.3)	5.03 (0.2-8.6)
Cis	5.13 (0.1-8.3)	4.88 (0.2-8.5)
AE, No. (%)		
Any AE	336 (99.4)	338 (98.8)
Any trAE	314 (92.9)	308 (90.1)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any grade 3/4 trAE	212 (62.7)	222 (64.9)
Any serious AE	160 (47.3)	149 (43.6)
Any serious trAE	53 (15.7)	59 (17.3)
Any AE leading to D/C	44 (13.0)	52 (15.2)
Any trAE leading to D/C	30 (8.9)	39 (11.4)
Any AE leading to death	12 (3.6)	14 (4.1)
Any trAE leading to death	2 (0.6)	1 (0.3)
Any immune-mediated AE	43 (12.7)	16 (4.7)

Includes AEs with onset date on or after the date of the first dose or AEs that worsened after the first dose. Includes AEs occurring up to 90 d following the date of the last dose or up to the first subsequent therapy.

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Grade 3/4 AEs

Event, No. (%)	Durvalumab + Gem-Cis (n = 338)	Placebo + Gem-Cis (n = 342)
Any grade 3/4 AE (≥ 5%)		
Anemia	80 (23.7)	77 (22.5)
Neutrophil count decreased	71 (21.0)	88 (25.7)
Neutropenia	68 (20.1)	72 (21.1)
Platelet count decreased	33 (9.8)	29 (8.5)
Cholangitis	22 (6.5)	11 (3.2)
Thrombocytopenia	16 (4.7)	18 (5.3)
White blood cell count decreased	15 (4.4)	20 (5.8)
Any grade 3/4 trAE (≥ 2%)		
Neutrophil count decreased	70 (20.7)	87 (25.4)
Neutropenia	65 (19.2)	69 (20.2)
Anemia	64 (18.9)	64 (18.7)
Platelet count decreased	27 (8.0)	26 (7.6)
White blood cell count decreased	14 (4.1)	20 (5.8)
Thrombocytopenia	12 (3.6)	18 (5.3)
Fatigue	9 (2.7)	8 (2.3)
Leukopenia	7 (2.1)	2 (0.6)
Asthenia	4 (1.2)	7 (2.0)

Immune-Mediated AEs

Event, No. (%)	Durvalumab + Gem-Cis (n = 338)		Placebo + Gem-Cis (n = 342)	
	Any Grade	**Grade ≥ 3**	Any Grade	**Grade ≥ 3**
Any immune-mediated AE*	43 (12.7)	8 (2.4)	16 (4.7)	5 (1.5)
Hypothyroid events	20 (5.9)	0	5 (1.5)	0
Dermatitis/rash	12 (3.6)	3 (0.9)	1 (0.3)	0
Pneumonitis	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.3)
Hepatic events	4 (1.2)	2 (0.6)	2 (0.6)	1 (0.3)
Adrenal insufficiency	4 (1.2)	0	1 (0.3)	0
Diarrhea/colitis	2 (0.6)	1 (0.3)	1 (0.3)	1 (0.3)
Hyperthyroid events	2 (0.6)	0	0	0
Type 1 diabetes mellitus	1 (0.3)	1 (0.3)	0	0
Pancreatic events	1 (0.3)	0	2 (0.6)	1 (0.3)
Hypophysitis	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	0	0
Renal events	0	0	2 (0.6)	0
Myositis	0	0	1 (0.3)	1 (0.3)
Other rare/miscellaneous[†]	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)

*An immune-mediated AE is defined as an event that is associated with drug exposure and consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology.

[†]The events in the "other rare/miscellaneous" category were immune-mediated arthritis in the durvalumab group and arthritis in the placebo group.

Oh DY, et al. 2022 ASCO Gastrointestinal Cancers Symposium; January 20-22, 2022; San Francisco, CA. Abstract 378.

Demographics, baseline clinical characteristics, and subsequent therapy by primary tumour location

- Most patients with ICC or GBC presented with initially unresectable disease at baseline
- There was some variability in extent of disease between treatment arms
- The use of subsequent anti-cancer therapy was lower in patients receiving durvalumab versus placebo across all primary tumour locations

	Intrahepatic cholangiocarcinoma (N=383)		Extrahepatic cholangiocarcinoma (N=131)		Gallbladder cancer (N=171)	
	Durvalumab + GemCis (n=190)	Placebo + GemCis (n=193)	Durvalumab + GemCis (n=66)	Placebo + GemCis (n=65)*	Durvalumab + GemCis (n=85)	Placebo + GemCis (n=86)
Median age (range), years	64.0 (20–84)	63.0 (42–85)	65.0 (41–82)	65.0 (45–80)	62.0 (39–84)	64.0 (31–83)
Female sex, n (%)	87 (45.8)	93 (48.2)	22 (33.3)	24 (36.9)	63 (74.1)	51 (59.3)
Asia region, n (%)	100 (52.6)	111 (57.5)	35 (53.0)	42 (64.6)	43 (50.6)	43 (50.0)
Disease status: *Initially unresectable*, **n (%)**	170 (89.5)	173 (89.6)	35 (53.0)	35 (53.8)	69 (81.2)	71 (82.6)
Disease status: *Recurrent*, **n (%)**	20 (10.5)	20 (10.4)	31 (47.0)	29 (44.6)	16 (18.8)	15 (17.4)
Extent of disease: *Locally advanced*, **n (%)**	24 (12.6)	31 (16.1)	7 (10.6)	13 (20.0)	7 (8.2)	13 (15.1)
Extent of disease: *Metastatic*, **n (%)**	166 (87.4)	162 (83.9)	59 (89.4)	51 (78.5)	78 (91.8)	73 (84.9)
ECOG PS: *0*, **n (%)**	98 (51.6)	91 (47.2)	33 (50.0)	33 (50.8)	42 (49.4)	39 (45.3)
ECOG PS: *1*, **n (%)**	92 (48.4)	102 (52.8)	33 (50.0)	32 (49.2)	43 (50.6)	47 (54.7)
PD-L1 expression: *TAP ≥1%*, **n (%)**	107 (56.3)	103 (53.4)	43 (65.2)	44 (67.7)	47 (55.3)	58 (67.4)
PD-L1 expression: *TAP <1%*, **n (%)**	66 (34.7)	69 (35.8)	12 (18.2)	13 (20.0)	25 (29.4)	21 (24.4)
PD-L1 expression: *Missing*, **n (%)**	17 (8.9)	21 (10.9)	11 (16.7)	8 (12.3)	13 (15.3)	7 (8.1)
Subsequent anti-cancer therapy, n (%)	84 (44.2)	99 (51.3)	23 (34.8)	29 (44.6)	38 (44.7)	42 (48.8)

***Patient E2801004 was randomised as a patient with recurrent disease via IVRS in error. This patient did not receive any study treatment**

ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC, intrahepatic cholangiocarcinoma; IVRS, interactive voice response system; PD-L1, programmed cell death ligand-1; PS, performance status, TAP, tumour area positivity

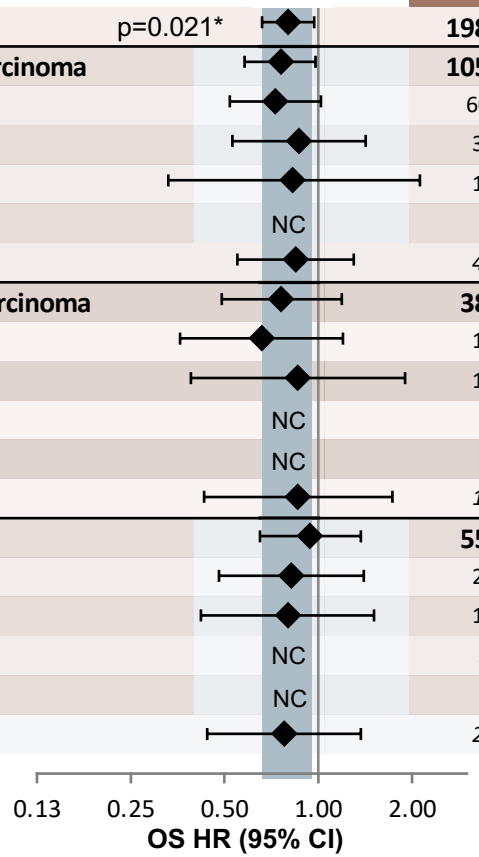
He et al, ESMO GI 2022

OS by primary tumour location and region

OS HRs were <1, favouring durvalumab, across primary tumour locations

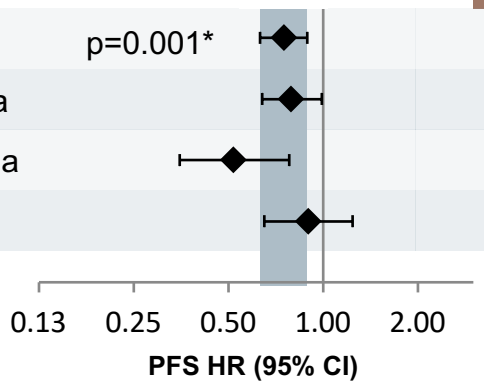
- OS benefit with durvalumab was consistent in patients with ICC and ECC, and in patients with GBC in Asia, Europe, and North America

	Durvalumab + GemCis (N=341)		Placebo + GemCis (N=344)		OS HR[†] (95% CI)
	Events, n/N (%)	Median OS (95% CI), mo	Events, n/N (%)	Median OS (95% CI), mo	
Full analysis set[1]	**198/341 (58.1)**	**12.8 (11.1–14.0)**	**226/344 (65.7)**	**11.5 (10.1–12.5)**	**0.80 (0.66–0.97)[‡]**
Intrahepatic cholangiocarcinoma	**105/190 (55.3)**	**13.5 (11.9–15.1)**	**126/193 (65.3)**	**11.5 (9.8–12.8)**	**0.76 (0.58–0.98)[§]**
Asia	60/100 (60.0)	13.0 (9.8–14.6)	81/111 (73.0)	11.4 (9.2–12.5)	0.73 (0.52–1.02)[§]
Europe	31/61 (50.8)	13.5 (9.5–18.8)	35/61 (57.4)	14.0 (8.0–18.3)	0.87 (0.53–1.42)[§]
North America	11/21 (52.4)	15.1 (6.8–NC)	9/18 (50.0)	13.3 (5.3–NC)	0.83 (0.33–2.12)[§]
South America	3/8 (37.5)	NR (2.3–NC)	1/3 (33.3)	NR (8.0–NC)	NC[‖]
Europe + North America	*42/82 (51.2)*	*13.7 (10.9–18.1)*	*44/79 (55.7)*	*13.6 (8.5–17.7)*	*0.85 (0.55–1.30)[§]*
Extrahepatic cholangiocarcinoma	**38/66 (57.6)**	**12.7 (9.8–16.6)**	**42/65 (64.6)**	**12.1 (7.8–14.4)**	**0.76 (0.49–1.19)[§]**
Asia	18/35 (51.4)	16.6 (12.6–NC)	27/42 (65.3)	12.8 (7.7–17.3)	0.66 (0.36–1.20)[§]
Europe	14/23 (60.9)	9.1 (8.7–NC)	12/19 (63.2)	14.4 (7.0–NC)	0.86 (0.39–1.90)[§]
North America	5/6 (83.3)	11.0 (0.9–NC)	3/4 (75.0)	9.6 (3.4–NC)	NC[‖]
South America	1/2 (50.0)	NR (10.0–NC)	0	NC	NC[‖]
Europe + North America	*19/29 (65.5)*	*9.8 (8.7–16.2)*	*15/23 (65.2)*	*12.1 (7.0–14.4)*	*0.86 (0.43–1.73)[§]*
Gallbladder cancer	**55/85 (64.7)**	**10.7 (8.9–13.2)**	**58/86 (67.4)**	**11.0 (8.7–12.8)**	**0.94 (0.65–1.37)[§]**
Asia	25/43 (58.1)	13.3 (9.0–20.1)	29/43 (67.4)	12.6 (8.4-17.7)	0.82 (0.48–1.40)[§]
Europe	18/24 (75.0)	9.6 (5.2–11.1)	22/27 (81.5)	8.1 (4.9–11.0)	0.80 (0.42–1.51)[§]
North America	5/10 (50.0)	12.2 (2.6–NC)	4/6 (66.7)	10.2 (5.7–NC)	NC[‖]
South America	7/8 (87.5)	8.1 (0.9–NC)	3/10 (30.0)[¶]	NR (2.0–NC)	NC[‖]
Europe + North America	*23/34 (67.6)*	*10.3 (6.6–12.2)*	*26/33 (78.8)*	*8.7 (6.0–11.0)*	*0.78 (0.44–1.37)[§]*



He et al, ESMO GI 2022

PFS by primary tumour location



	Durvalumab + GemCis (N=341)		Placebo + GemCis (N=344)		PFS HR† (95% CI)
	Events, n/N (%)	Median PFS (95% CI), mo	Events, n/N (%)	Median PFS (95% CI), mo	
Full analysis set[1]	**229/341 (67.2)**	**7.2 (6.7–7.4)**	**252/344 (73.3)**	**5.7 (5.6–6.7)**	**0.75 (0.63–0.89)‡**
Intrahepatic cholangiocarcinoma	154/190 (81.1)	7.3 (6.5–7.5)	167/193 (86.5)	6.0 (5.6–7.2)	0.79 (0.64–0.99)§
Extrahepatic cholangiocarcinoma	50/66 (75.8)	7.6 (6.9–9.1)	55/65 (84.6)	5.7 (5.4–7.2)	0.52 (0.35–0.78)§
Gallbladder cancer	72/85 (84.7)	6.1 (5.5–7.2)	75/86 (87.2)	5.6 (4.2–7.2)	0.90 (0.65–1.24)§

- PFS HR was statistically significant in the full analysis set for durvalumab plus GemCis versus placebo plus GemCis

*Two-sided p-value. Threshold of significance for the interim analysis was 0.0481. †Durvalumab plus GemCis versus placebo plus GemCis. ‡Calculated from a stratified Cox proportional hazards model. §Calculated from an unstratified Cox proportional hazards model

CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, months; PFS, progression-free survival

1. Oh D-Y, et al. *NEJM Evid* Published online 1 June 2022. doi:10.1056/EVIDoa2200015

He et al, ESMO GI 2022

ORR and DoR by primary tumour location

	Full analysis set (N=684)[1]		Intrahepatic cholangiocarcinoma (N=383)		Extrahepatic cholangiocarcinoma (N=131)		Gallbladder cancer (N=171)	
	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)	Durvalumab + GemCis (n=190)	Placebo + GemCis (n=193)	Durvalumab + GemCis (n=66)	Placebo + GemCis (n=65)*	Durvalumab + GemCis (n=85)	Placebo + GemCis (n=86)
ORR,† %	**26.7**	**18.7**	24.7	15.5	28.8	15.6	29.4	27.9
ORR OR (95% CI)	**1.60 (1.11–2.31)**		1.79 (1.07–2.97)		2.18 (0.92–5.16)		1.08 (0.55–2.09)	
Median TTR, mo	**1.6**	**2.7**	2.8	2.7	1.4	2.6	1.4	2.7
Median DoR,‡ mo	**6.4**	**6.2**	6.0	6.0	8.9	6.2	6.0	6.6
DoR ≥9 mo, %	**32.6**	**25.3**	28.3	24.0	43.3	23.3	33.2	27.5
DoR ≥12 mo, %	**26.1**	**15.0**	18.9	12.0	43.3	23.3	27.6	16.5

- ORR benefit for durvalumab plus GemCis was consistent and durable across primary tumour locations

*Patient E2801004 was randomised as a patient with recurrent disease via IVRS in error. This patient did not receive any study treatment and was not included in this analysis. †Calculated using the Cochran-Mantel-Haenszel test. ‡Calculated using the Kaplan-Meier technique

CI, confidence interval; DoR, duration of response; GemCis, gemcitabine and cisplatin; mo, months; OR, odds ratio; ORR, objective response rate; TTR, time-to-response

He et al, ESMO GI 2022

1. Oh D-Y, et al. *NEJM Evid* Published online 1 June 2022. doi:10.1056/EVIDoa2200015

KEYNOTE-966

Key Eligibilit
- Adults with n
  and/or unres
  locally advar
  histologically
  BTC
- Measurable c
  RECIST v1.1
- No prior syst
  therapy for ac
  unresectable
  advanced BT
- ECOG PS 0

January 25, 2023

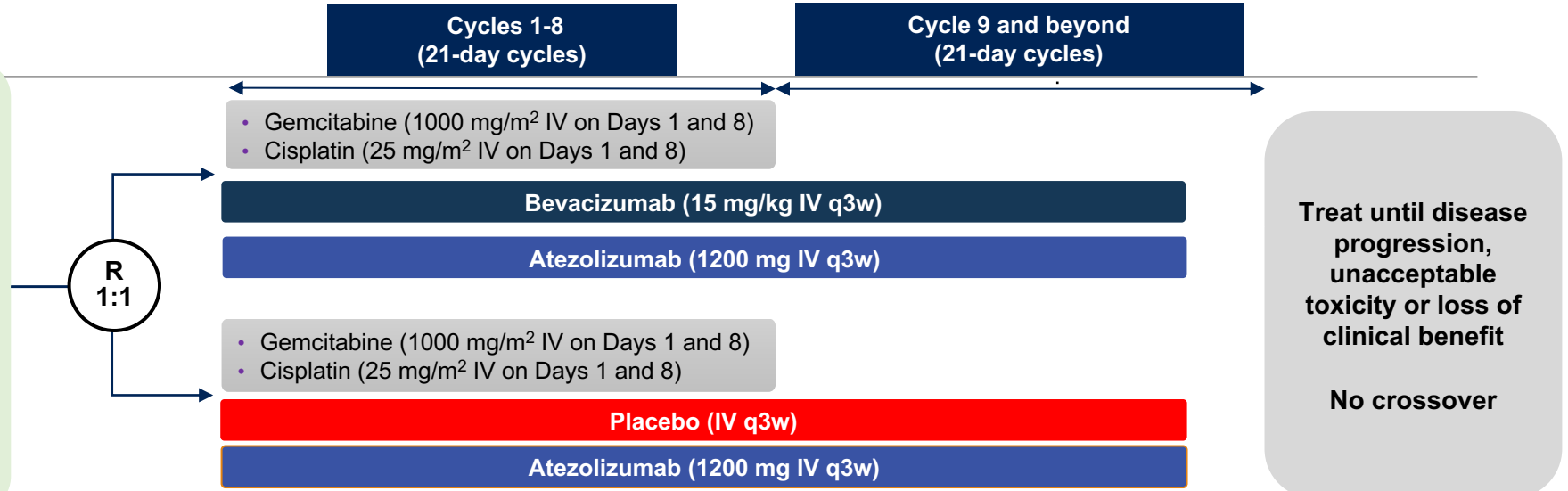
[redacted] (pembrolizumab) Plus Chemotherapy Significantly Improved Overall Survival Versus Chemotherapy in First-Line Advanced or Unresectable Biliary Tract Cancer in KEYNOTE-966 Trial

by BICR
S for
+ Cis
o + Gem

IMbrave151 study design (NCT04677504)

Advanced biliary tract cancer (n=162)

- Histologically confirmed intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma or gallbladder cancer
- ECOG PS 0/1
- Measurable disease per RECIST 1.1
- No prior systemic treatment for advanced BTC
- Screening EGD required for patients at high risk of esophageal varices



Treat until disease progression, unacceptable toxicity or loss of clinical benefit

No crossover

Stratification factors

- Anatomical location of primary tumor (iCCA, eCCA or GBC)
- Metastatic disease (yes or no)
- Geographic region (Asia vs rest of world)

Key endpoints

- **Primary endpoint:** PFS[a]
- **Key secondary endpoints:** ORR,[a] duration of response,[a] DCR,[a] OS, safety, PRO/QOL
- **Exploratory endpoints:** 6-month PFS and OS rates, biomarkers, PRO-CTCAE

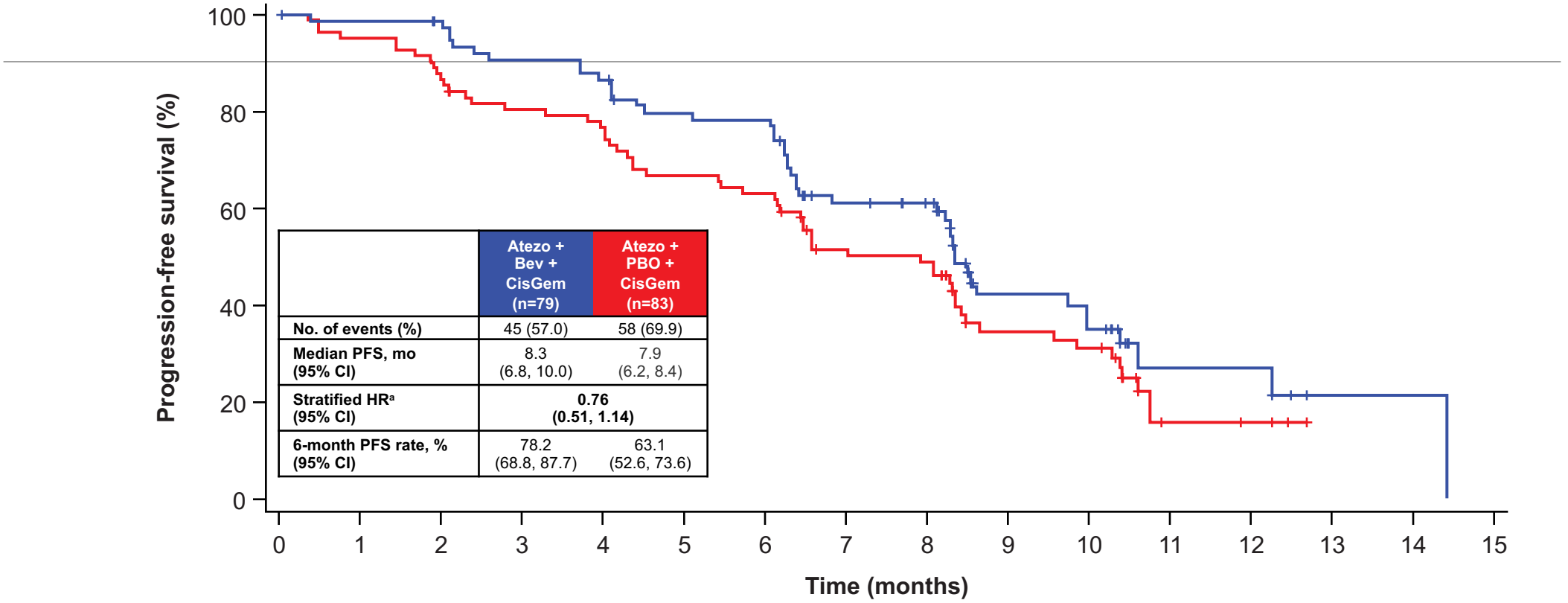
BTC, biliary tract cancer; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gall bladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; QOL, quality of life; q3w, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors. [a]Per investigator assessment by RECIST 1.1.

Patient baseline characteristics

	Atezo + Bev + CisGem (n=79)	Atezo + PBO + CisGem (n=83)	All patients (n=162)
Median age (range), years	61.0 (36-79)	65.0 (37-79)	63.0 (36-79)
Age < 65 years, n (%)	51 (64.6)	38 (45.8)	89 (54.9)
Male, n (%)	49 (62.0)	38 (45.8)	87 (53.7)
Race, n (%)			
White	41 (51.9)	46 (55.4)	87 (53.7)
Asian	37 (46.8)	35 (42.2)	72 (44.4)
Region,[a] n (%)			
Asia	34 (43.0)	35 (42.2)	69 (42.6)
Rest of world	45 (57.0)	48 (57.8)	93 (57.4)
Baseline ECOG PS, n (%)			
0	42 (53.2)	43 (51.8)	85 (52.5)
1	37 (46.8)	40 (48.2)	77 (47.5)
PD-L1 (TAP)[a] status at baseline, n (%)	n=58	n=63	n=121
< 1%	35 (60.3)	33 (52.4)	68 (56.2)
≥ 1%	23 (39.7)	30 (47.6)	53 (43.8)
Metastatic disease,[a] n (%)	n=75	n=80	n=155
Yes	63 (84.0)	64 (80.0)	127 (81.9)
No	12 (16.0)	16 (20.0)	28 (18.1)
Anatomical location of primary tumor,[b] n (%)			
iCCA	45 (57.0)	43 (51.8)	88 (54.3)
eCCA	13 (16.5)	17 (20.5)	30 (18.5)
GBC	21 (26.6)	23 (27.7)	44 (27.2)
Median CA19.9 at baseline (range), kU/L	46.3 (0-199970.0)	66.9 (0-335091.0)	57.2 (0-335091.0)
Prior BTC surgery, n (%)	22 (27.8)	32 (38.6)	54 (33.3)

Atezo, atezolizumab; Bev, bevacizumab; BMI, body mass index; CisGem, gemcitabine plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; PBO, placebo; PD-L1, programmed cell death ligand 1; TAP, tumor area positive score. [a]Per VENTANA SP-263 PD-L1 assay. [b]Per electronic case report form.

Primary endpoint: PFS



	Atezo + Bev + CisGem (n=79)	Atezo + PBO + CisGem (n=83)
No. of events (%)	45 (57.0)	58 (69.9)
Median PFS, mo (95% CI)	8.3 (6.8, 10.0)	7.9 (6.2, 8.4)
Stratified HR[a] (95% CI)	0.76 (0.51, 1.14)	
6-month PFS rate, % (95% CI)	78.2 (68.8, 87.7)	63.1 (52.6, 73.6)

Number at risk

Atezo + Bev + CisGem	79	75	73	67	64	57	56	41	38	18	15	5	5	1	1	NE
Atezo + PBO + CisGem	83	78	72	65	62	54	51	38	36	20	18	4	3	NE	NE	NE

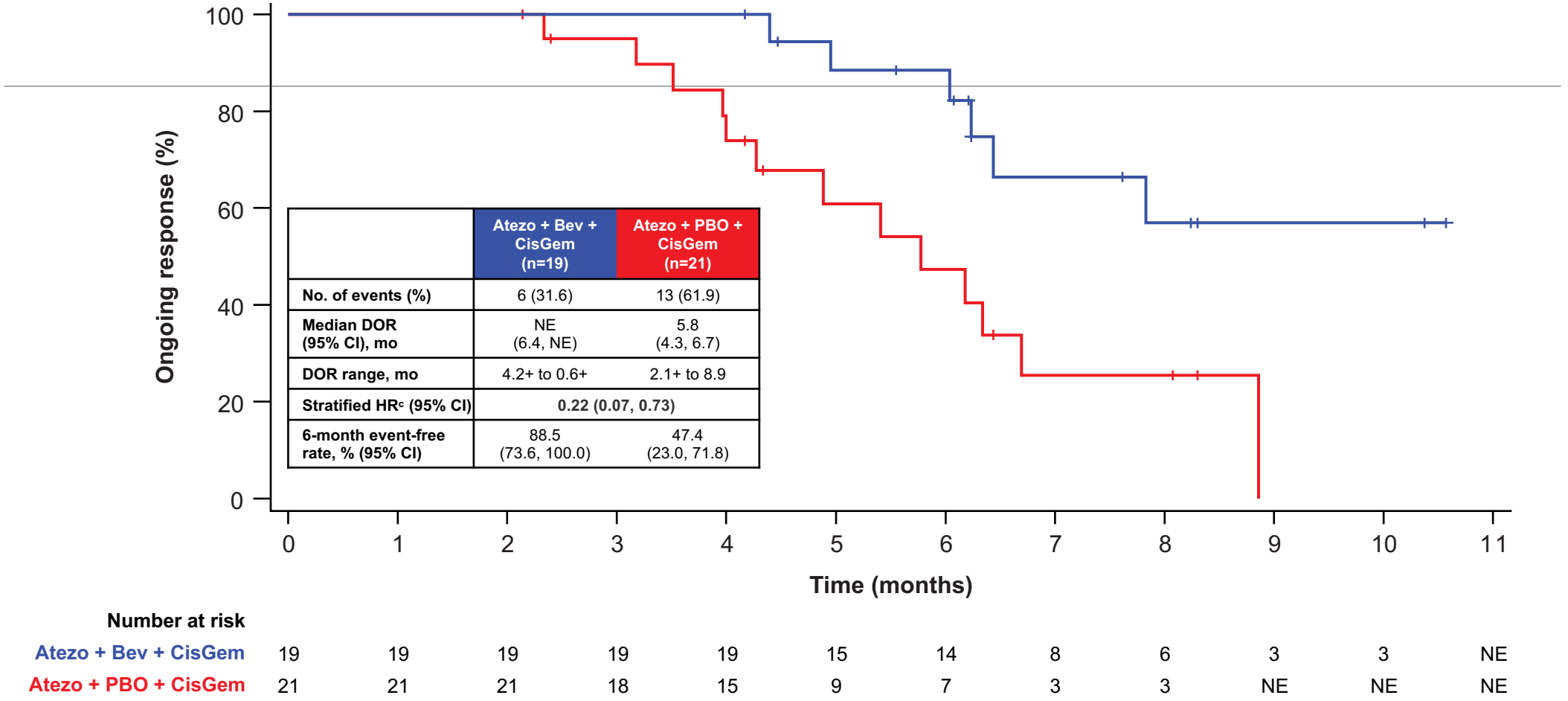
Median follow-up duration: 10.8 months. CCOD: May 16, 2022. Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CI, confidence interval; CisGem, gemcitabine plus cisplatin; eCCA, extrahepatic cholangiocarcinoma; GBC, gall bladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; NE, not estimable; PBO, placebo; PFS, progression-free survival. [a]Stratified analysis. Stratification factors are location of primary tumor (iCCA vs eCCA vs GBC) and geographic region (Asia vs rest of world).

Secondary endpoint: ORR

Confirmed response, n (%)	Atezo + Bev + CisGem (n=79)	Atezo + PBO + CisGem (n=83)
ORR[a] **95% CI**	19 (24.1) 15.1, 35.0	21 (25.3) 16.4, 36.0
CR	1 (1.3)	1 (1.2)
PR	18 (22.8)	20 (24.1)
SD	50 (63.3)	45 (54.2)
PD	5 (6.3)	9 (10.8)
Missing/unevaluable[b]	5 (6.3)	8 (9.6)
DCR[c]	62 (78.5)	63 (75.9)

Median follow-up duration: 10.8 months. CCOD: May 16, 2022. Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CI, confidence interval; CisGem, gemcitabine plus cisplatin; CR, complete response; DCR, disease control rate; ORR, objective response rate; PBO, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria for Solid Tumors; SD, stable disease. [a]Confirmed objective response based on investigator assessment per RECIST 1.1. [b]Patients who withdrew from treatment before the first scan were considering missing. Patients for whom a RECIST response assessment was performed, but best response could not be evaluated due to obstruction of view or poor image quality, were considered unevaluable. [c]Censored.

Secondary endpoint: DOR

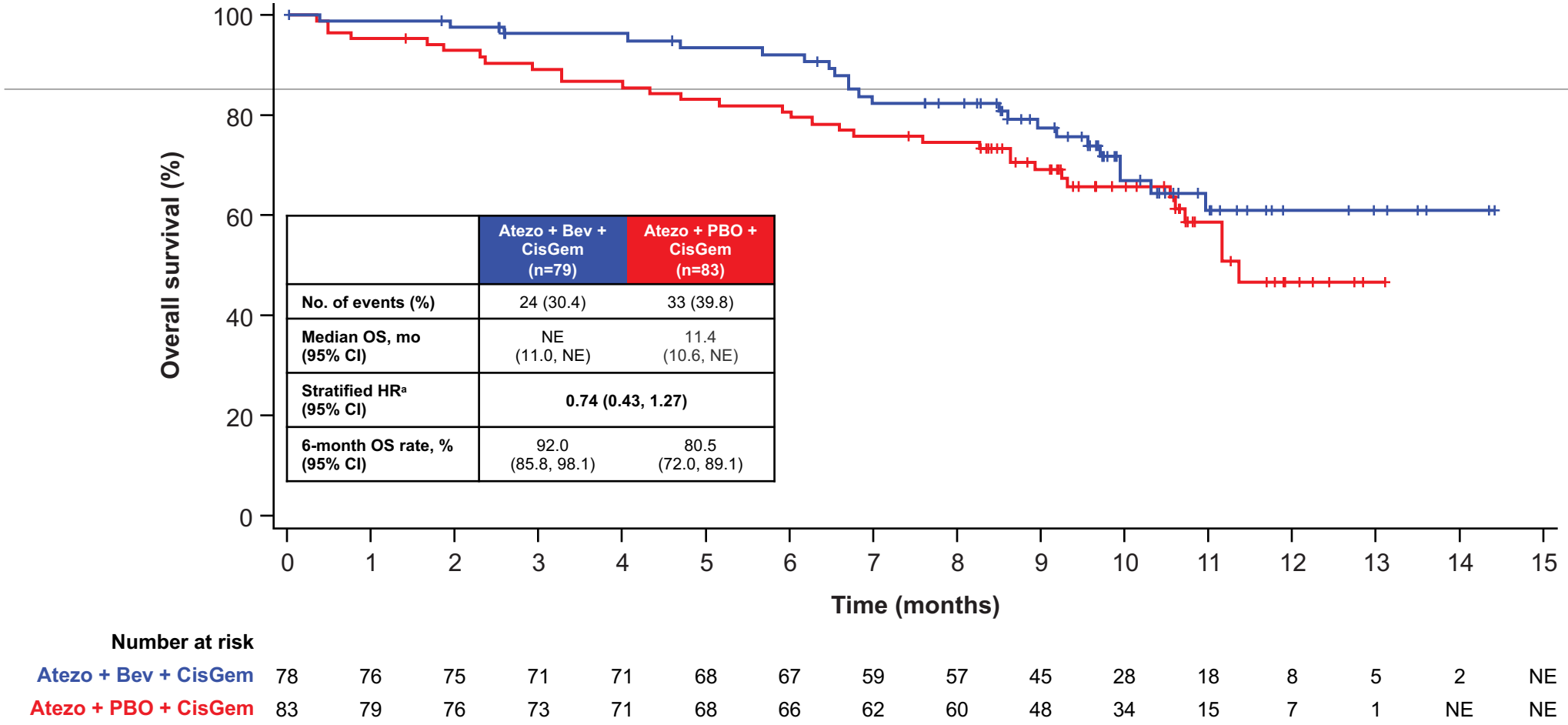


	Atezo + Bev + CisGem (n=19)	Atezo + PBO + CisGem (n=21)
No. of events (%)	6 (31.6)	13 (61.9)
Median DOR (95% CI), mo	NE (6.4, NE)	5.8 (4.3, 6.7)
DOR range, mo	4.2+ to 0.6+	2.1+ to 8.9
Stratified HR[c] (95% CI)	0.22 (0.07, 0.73)	
6-month event-free rate, % (95% CI)	88.5 (73.6, 100.0)	47.4 (23.0, 71.8)

Number at risk												
Atezo + Bev + CisGem	19	19	19	19	19	15	14	8	6	3	3	NE
Atezo + PBO + CisGem	21	21	21	18	15	9	7	3	3	NE	NE	NE

Median follow-up duration: 10.8 months. CCOD: May 16, 2022. Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CI, confidence interval; CisGem, gemcitabine plus cisplatin; DOR, duration of response; eCCA, extrahepatic cholangiocarcinoma; GBC, gall bladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; NE, not estimable; PBO, placebo. [a]Stratified analysis. Stratification factors are location of primary tumor (iCCA vs eCCA vs GBC) and geographic region (Asia vs rest of world).

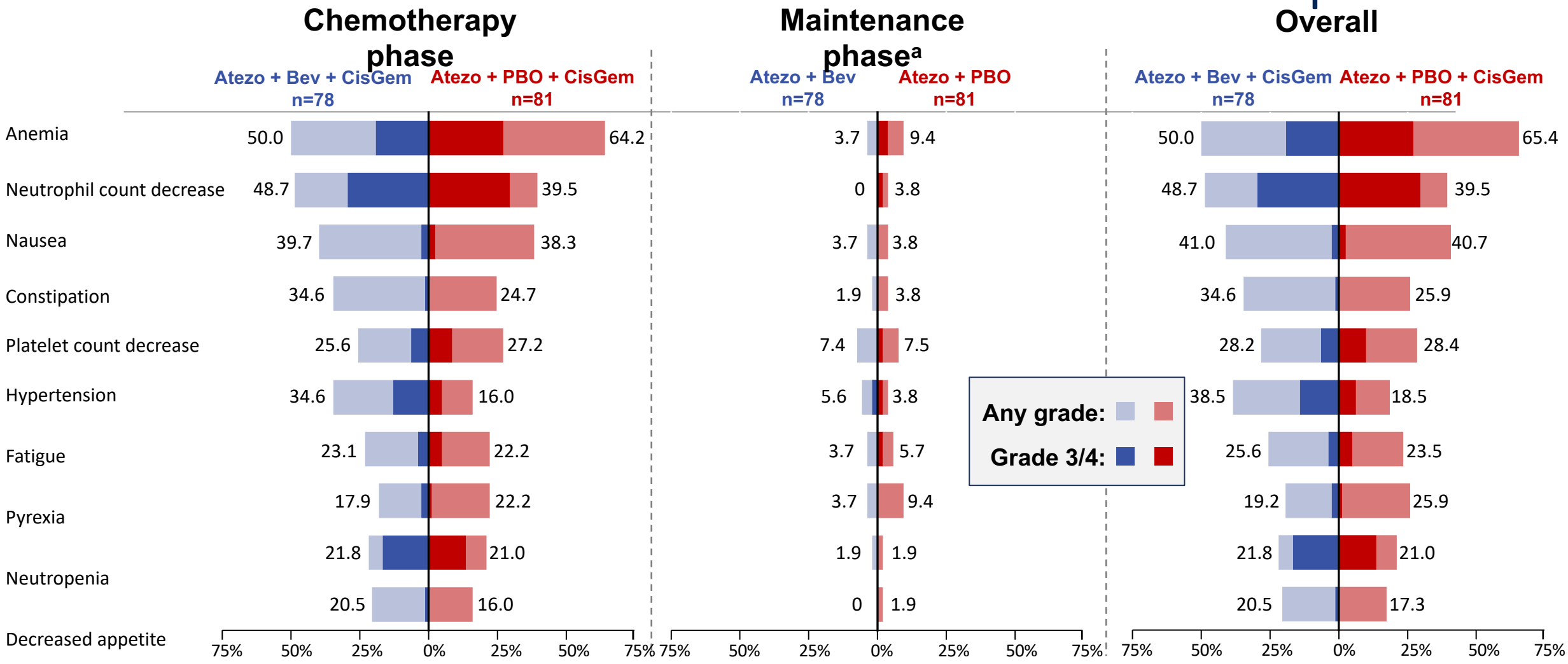
Secondary endpoint: OS



	Atezo + Bev + CisGem (n=79)	Atezo + PBO + CisGem (n=83)
No. of events (%)	24 (30.4)	33 (39.8)
Median OS, mo (95% CI)	NE (11.0, NE)	11.4 (10.6, NE)
Stratified HR[a] (95% CI)	0.74 (0.43, 1.27)	
6-month OS rate, % (95% CI)	92.0 (85.8, 98.1)	80.5 (72.0, 89.1)

Median follow-up duration: 10.8 months. CCOD: May 16, 2022. Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CI, confidence interval; CisGem, gemcitabine plus cisplatin; eCCA, extrahepatic cholangiocarcinoma; GBC, gall bladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; NE, not estimable; OS, overall survival; PBO, placebo. [a]Stratified analysis. Stratification factors are location of primary tumor (iCCA vs eCCA vs GBC) and geographic region (Asia vs rest of world).

AEs with ≥20% incidence by treatment phase

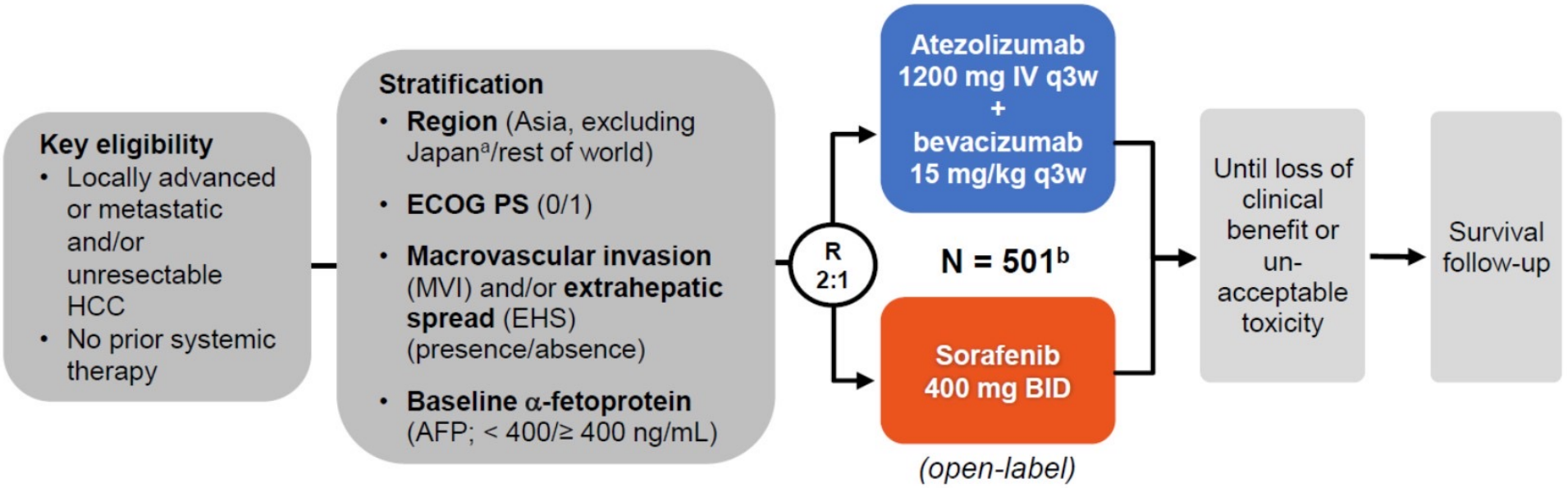


Median follow-up duration: 10.8 months. CCOD: May 16, 2022. AE, adverse event; Atezo, atezolizumab; Bev, bevacizumab; CCOD, clinical cutoff date; CisGem, gemcitabine plus cisplatin; PBO, placebo. [a]Maintenance phase started at Cycle 9 after the completion of 8 cycles of combination chemotherapy treatment administered on a 21-day cycle.

Hepatocellular Cancer

TALK ABOUT PROGRESS…

IMbrave150 study design



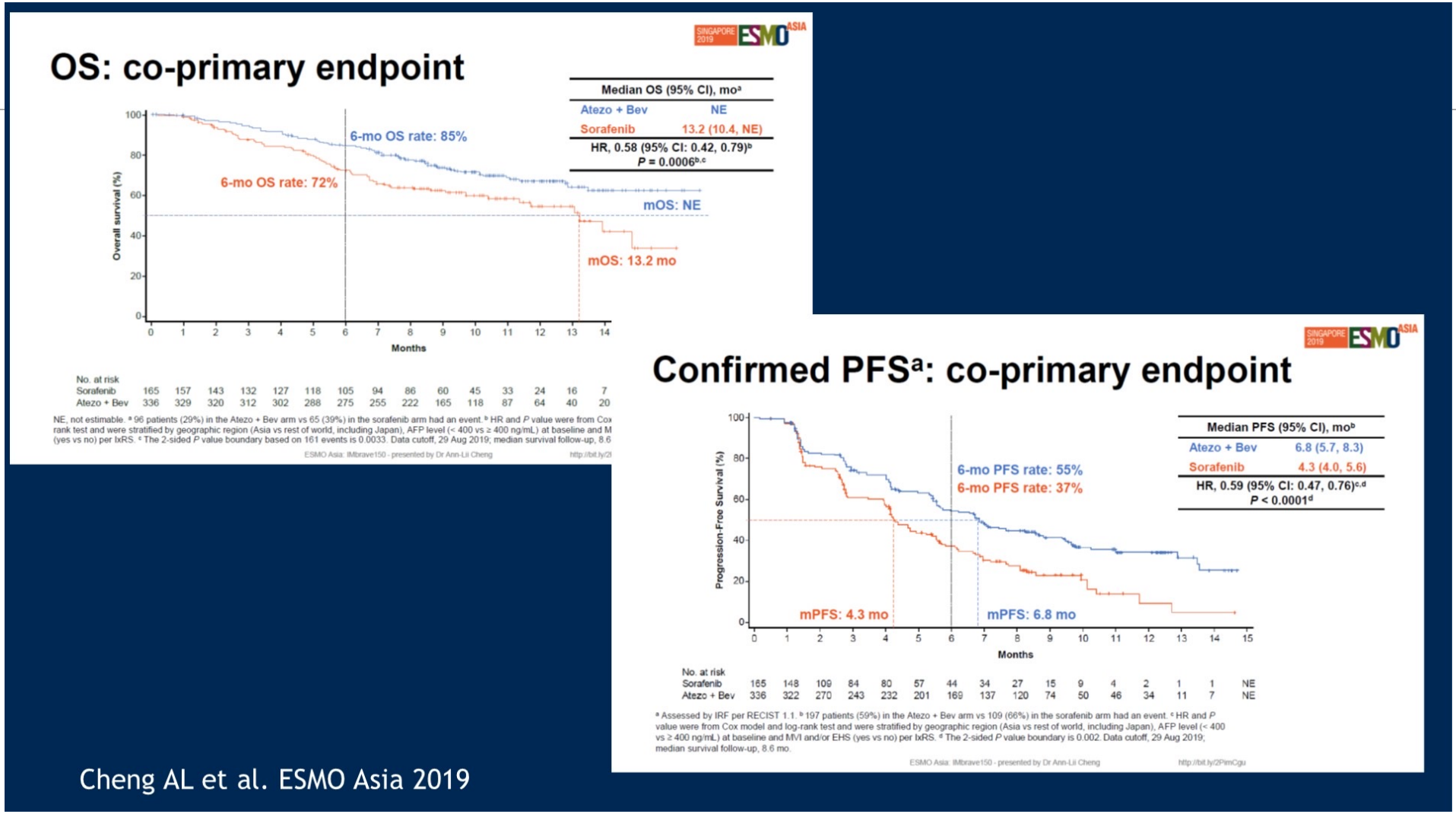
Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

ESMO Asia: IMbrave150 - presented by Dr Ann-Lii Cheng http://bit.ly/2PimCgu 4

IMbrave50: Positive co-primary endpoints



Cheng AL et al. ESMO Asia 2019

Updated Response and DoR

	Updated Analysis* [N (%)]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR	25 (8)	1 (< 1)	39 (12)	4 (3)
PR	72 (22)	17 (11)	76 (23)	18 (11)
SD	144 (44)	69 (43)	121 (37)	65 (41)
DCR	241 (74)	87 (55)	236 (73)	87 (55)
PD	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response	54 (56)	5 (28)	58 (50)	6 (27)
DoR, median (95% CI), mo†	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 months.

Finn RS, et al. N Engl J Med. 2020;382:1894-1905.

AEs From Any Cause

- Median duration of treatment
  - 7.4 mo with atezolizumab
  - 6.9 mo with bevacizumab
  - 2.8 mo with sorafenib
- Dose intensity, mean (SD) and median (range), %
  - 95 (7) and 98 (54-104) for Atezo
  - 93 (10) and 97 (44-104) for Bev
  - 84 (20) and 96 (27-100) for sorafenib
- No specific events were responsible for increased SAE rate in the Atezo + Bev group
- There were no SAEs with a ≥ 2% difference between treatment groups

	Atezo + Bev (n = 329)* N (%)	Sorafenib (n = 156)* N (%)
Patients with an AE from any cause	323 (98.2)	154 (98.7)
Grade 3 or 4 events†	186 (56.5)	86 (55.1)
Grade 5 events‡	15 (4.6)	9 (5.8)
SAEs	125 (38.0)	48 (30.8)
AEs leading to withdrawal from any study drug	51 (15.5)	16 (10.3)
Withdrawal from Atezo + Bev	23 (7.0)	–
AEs leading to dose modification or interruption of any study drug	163 (49.5)	95 (60.9)
Dose interruption of any study treatment	163 (49.5)	64 (41.0)
Dose modification of sorafenib§	–	58 (37.2)

Finn RS, et al. N Engl J Med. 2020;382:1894-1905.

HIMALAYA Study Design

Study population
- Patients with confirmed uHCC
- BCLC B (not eligible for LRT) and C
- No prior systemic therapy
- ECOG PS 0-1
- CP class A
- No main PVT
- EGD was not required

Stratification factors
- Macrovascular invasion: Y/N
- Etiology of liver disease: HBV/HCV/others
- ECOG PS: 0/1

R
N = 1324

T300+D (n = 393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg every 4 wk

Durvalumab (n = 389):
Durvalumab monotherapy 1500 mg every 4 wk

Sorafenib (n = 389):
Sorafenib 400 mg twice daily

T75+D (n = 153): *arm closed*
Tremelimumab 75 mg every 4 wk × 4 doses + durvalumab every 4 wk

Primary objective
- OS for T300+D vs sorafenib

Key secondary objective
- OS for durvalumab vs sorafenib

Additional secondary objectives
- PFS, ORR, and DoR as assessed by investigator per RECIST 1.1
- Safety

Multiple testing procedure

OS *superiority* for T300+D vs sorafenib

↓

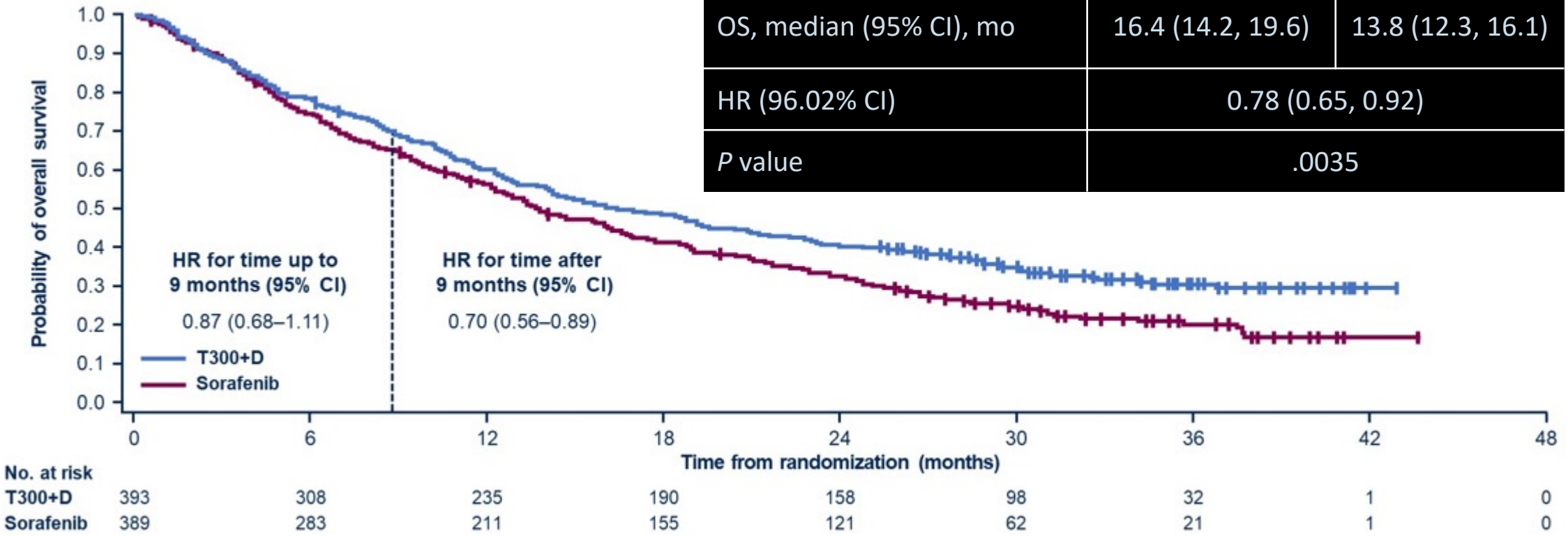
OS *noninferiority* for durvalumab vs sorafenib
Noninferiority margin: 1.08

↓

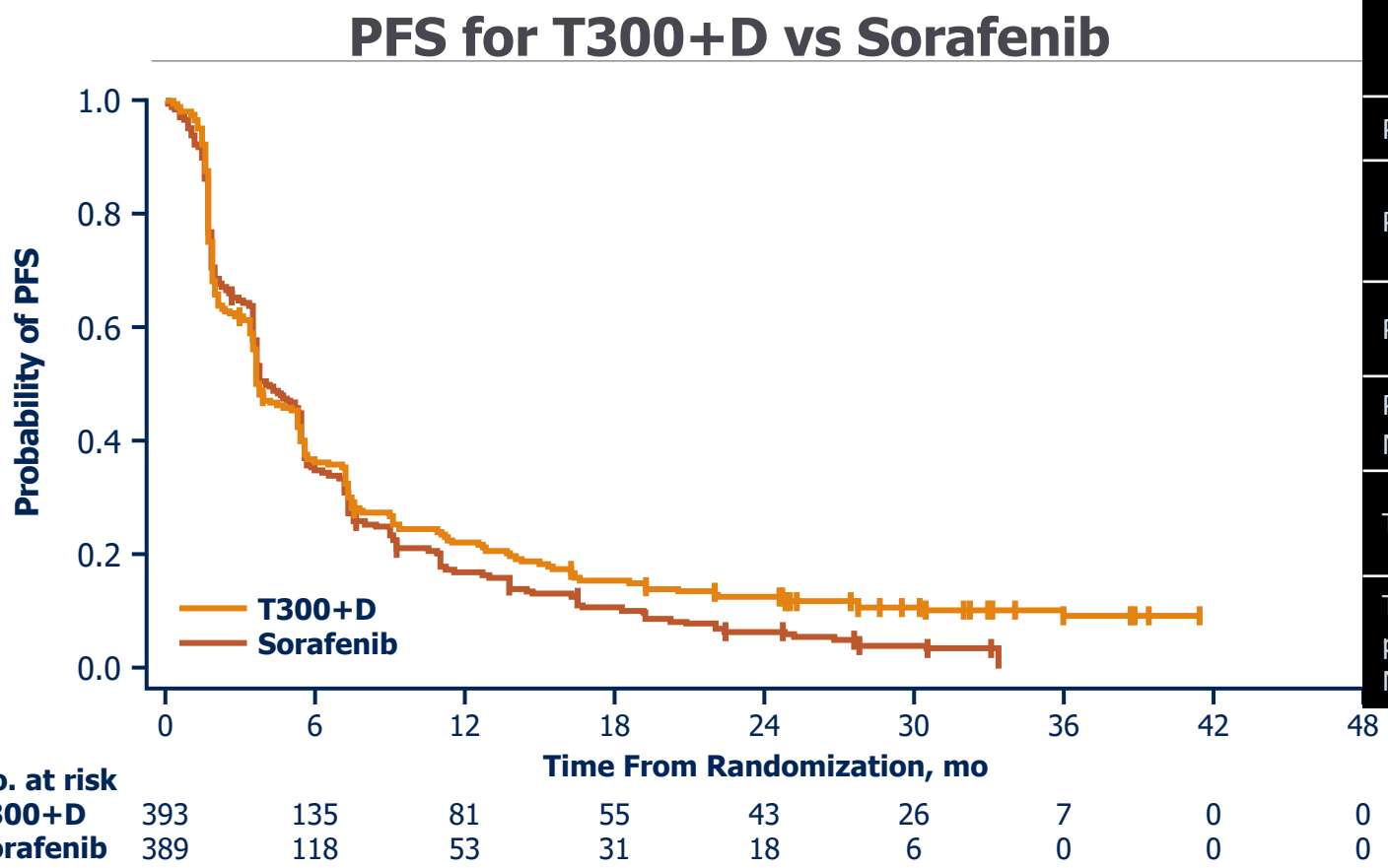
OS *superiority* for durvalumab vs sorafenib

Primary Objective
OS for T300+D vs Sorafenib

	T300+D (n = 393)	Sorafenib (n = 389)
OS events, N (%)	262 (66.7)	293 (75.3)
OS, median (95% CI), mo	16.4 (14.2, 19.6)	13.8 (12.3, 16.1)
HR (96.02% CI)	0.78 (0.65, 0.92)	
P value	.0035	



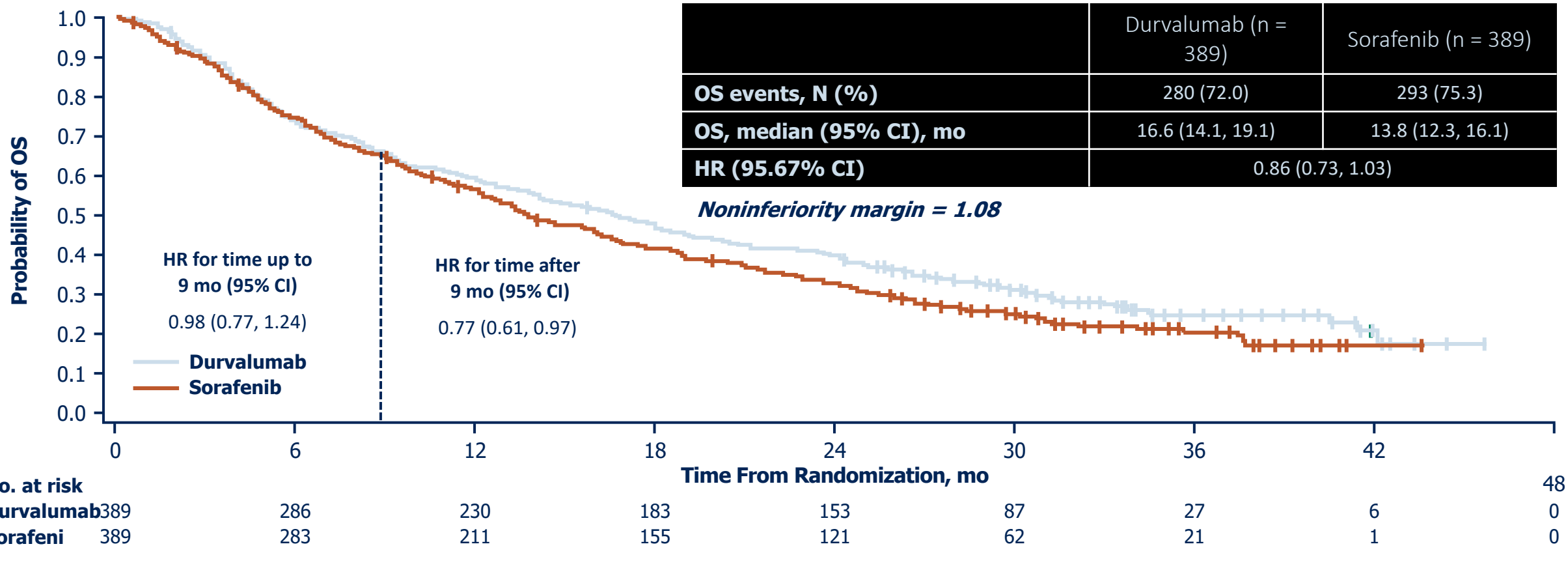
Progression-Free Survival



	T300+D (n = 393)	Durvalumab (n = 389)	Sorafenib (n = 389)
PFS events, N (%)	335 (85.2)	345 (88.7)	327 (84.1)
PFS, median (95% CI), mo	3.78 (3.68, 5.32)	3.65 (3.19, 3.75)	4.07 (3.75, 5.49)
PFS, HR* (95% CI)	0.90 (0.77, 1.05)	1.02 (0.88, 1.19)	–
Progression free at DCO, N (%)	49 (12.5)	32 (8.2)	19 (4.9)
TTP, median (95% CI), mo	5.42 (3.81, 5.62)	3.75 (3.68, 5.42)	5.55 (5.13, 5.75)
Treated ≥ 1 cycle beyond progression, N (%)†	182 (46.9)	188 (48.5)	134 (34.4)

Secondary Objective

OS for Durvalumab vs Sorafenib



	Durvalumab (n = 389)	Sorafenib (n = 389)
OS events, N (%)	280 (72.0)	293 (75.3)
OS, median (95% CI), mo	16.6 (14.1, 19.1)	13.8 (12.3, 16.1)
HR (95.67% CI)	0.86 (0.73, 1.03)	

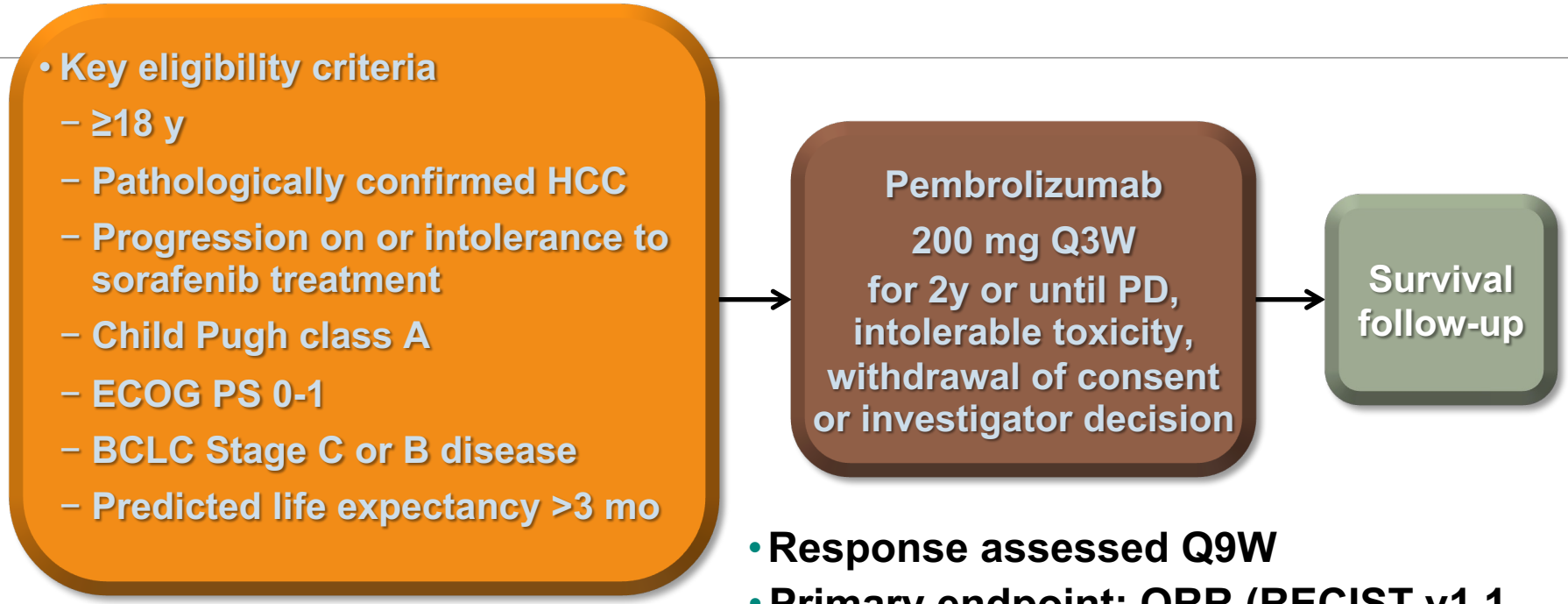
Noninferiority margin = 1.08

No. at risk									
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Safety and Tolerability

Event, N (%)	T300+D (n = 388)	Durvalumab (n = 388)	Sorafenib (n = 374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any trAE	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 trAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious trAE	68 (17.5)	32 (8.2)	35 (9.4)
Any trAE leading to death	9 (2.3)	0	3 (0.8)‡
Any trAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)

KEYNOTE 240: Study Design

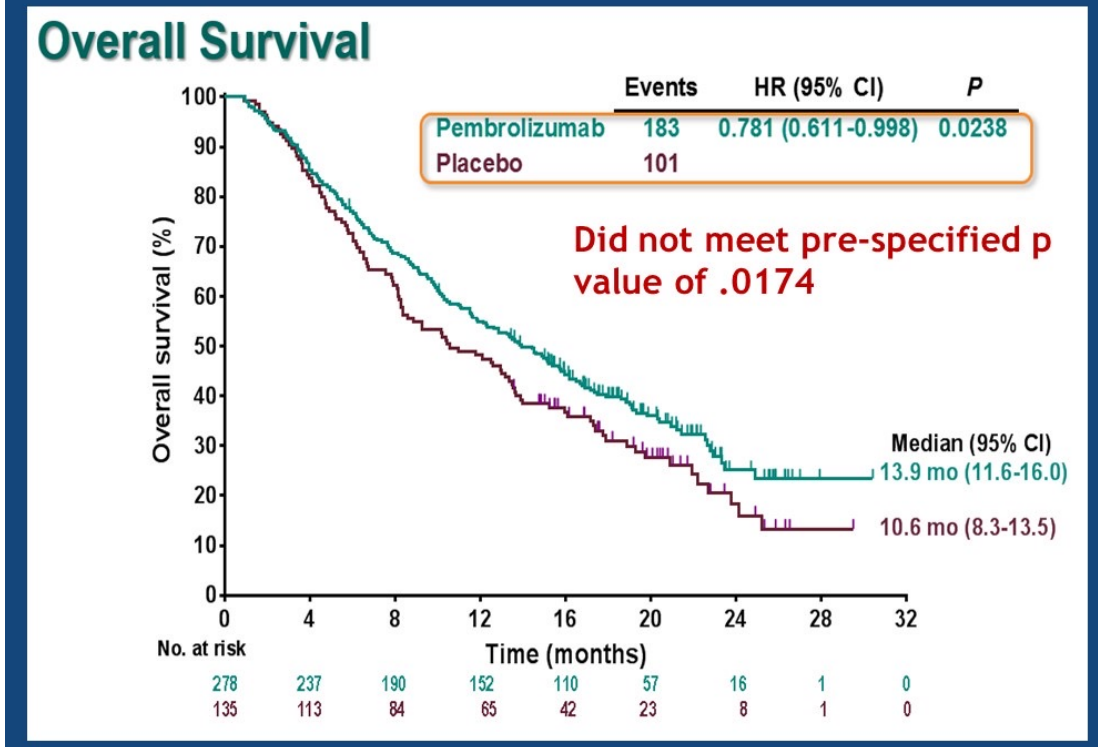


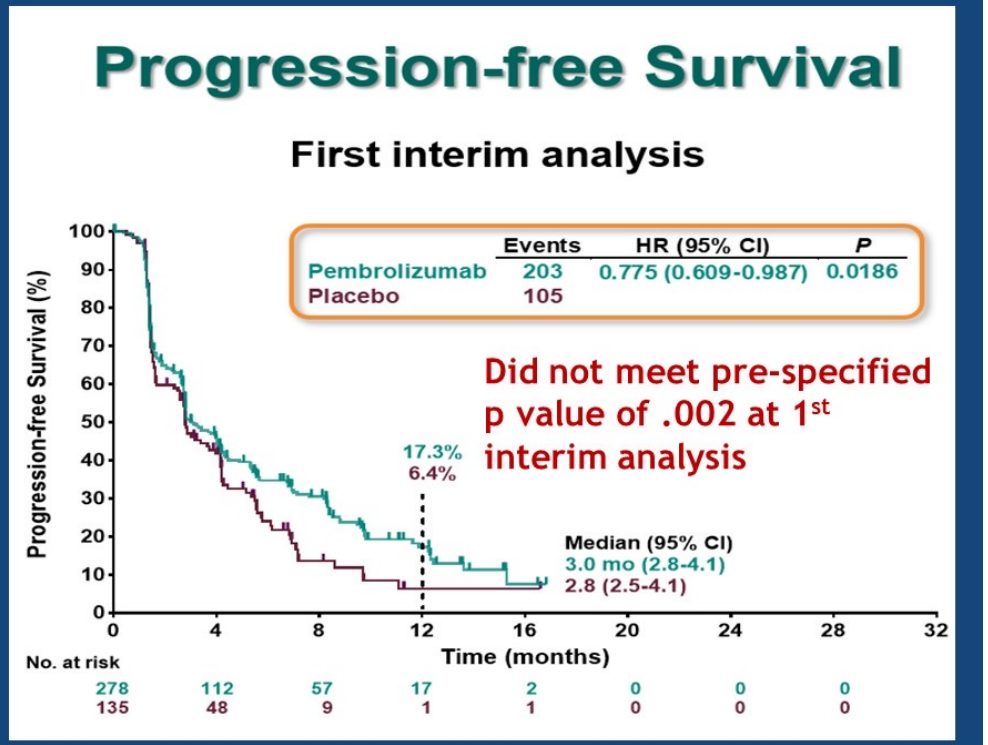
- Response assessed Q9W
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability

KN-240: Response per RECIST (ICR)

	Total N=104
ORR, n (%, 95%CI)*	18 (17, 11-26)
BOR, n (%)†	
CR	1 (1)
PR	17 (16)
SD	46 (44)
PD	34 (33)
No assessment‡	6 (6)
DCR, n (%, 95%CI)§	64 (62, 52-71)
Median time to response, mo (IQR)¶	2.1 (2.1-4.1)
Median DOR, mo (range)¶‖	Not reached (3.1–14.6+)
Response duration ≥9 mo, n (%)¶‖	12 (77)

Results: KEYNOTE-240





PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: William P. Harris, MD

11

Conclusion – IO is the way to go!

It is a new era in the treatment of hepatobiliary cancers and immunotherapy is here to stay!

Needles in haystacks exist – NGS for BTCs is key

Combination approaches will need to be the new focus

We remain hopeful…I am an optimist, after all

Thank you!

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@RACHNATSHROFF