Expanding Treatment Options for Advanced Biliary Tract Cancer

2023 Debates and Didactics

Haematology and Oncology

Olumide Gbolahan

Assistant Professor

GI Oncology

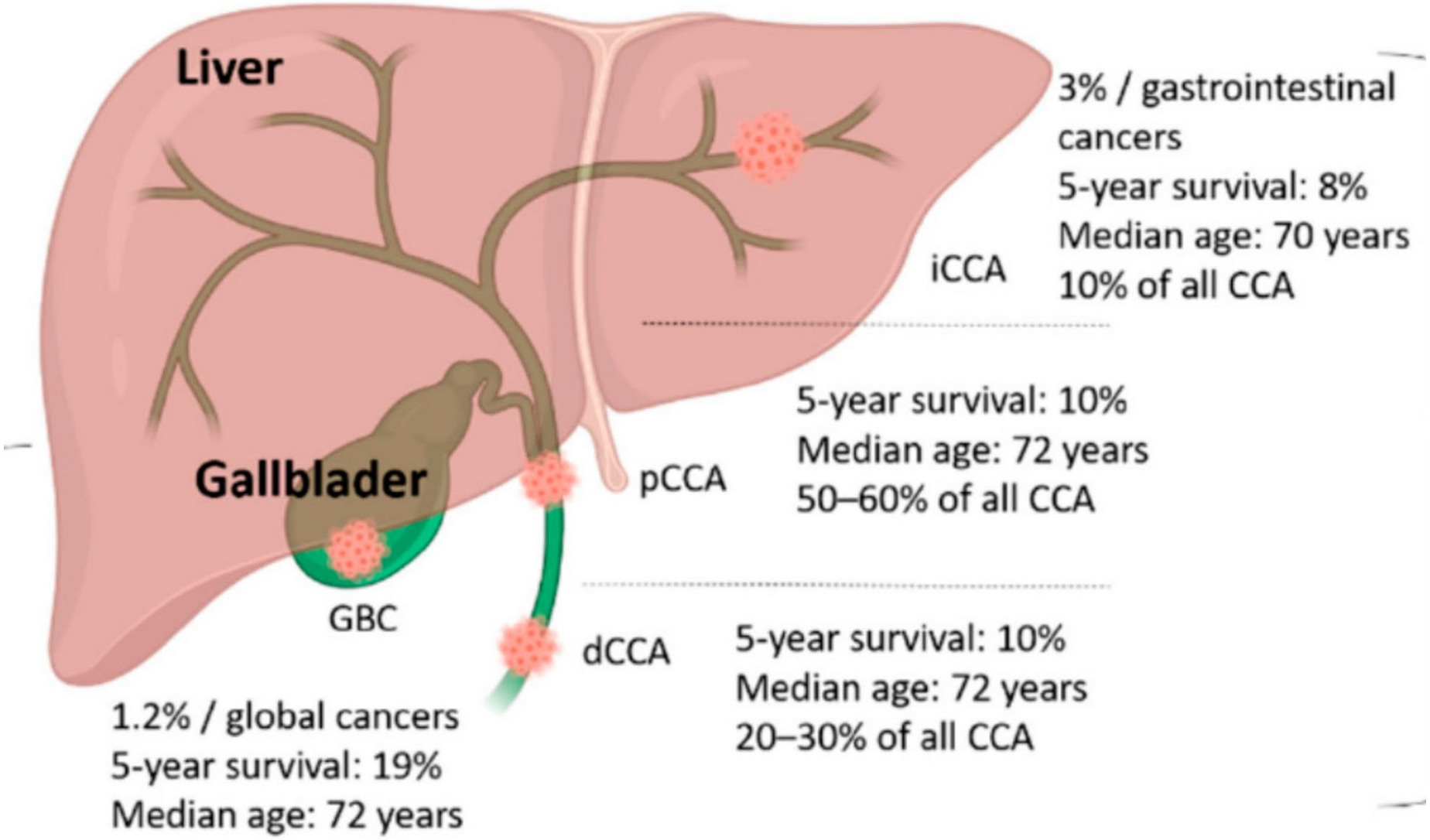
EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

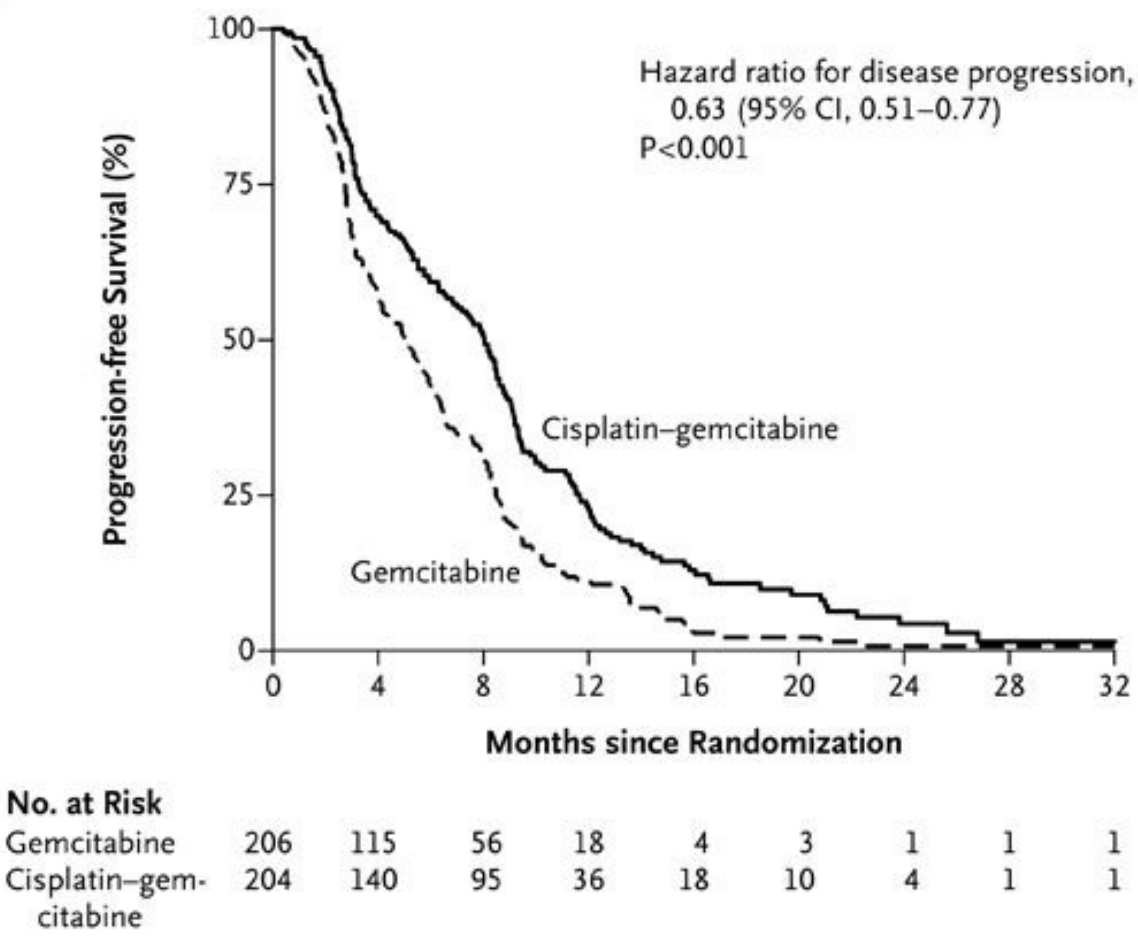
Disclosures

Advisory role: Exelixis, Incyte, QED therapeutics
Research Support: AstraZeneca, Astellas Pharmaceuticals, Ipsen, Merck, Eisai, BMS, Relay Therapeutics, Novartis, Pfizer, Genentech. No off- label use of drugs will be presented.

Epidemiology of Biliary Tract Cancer

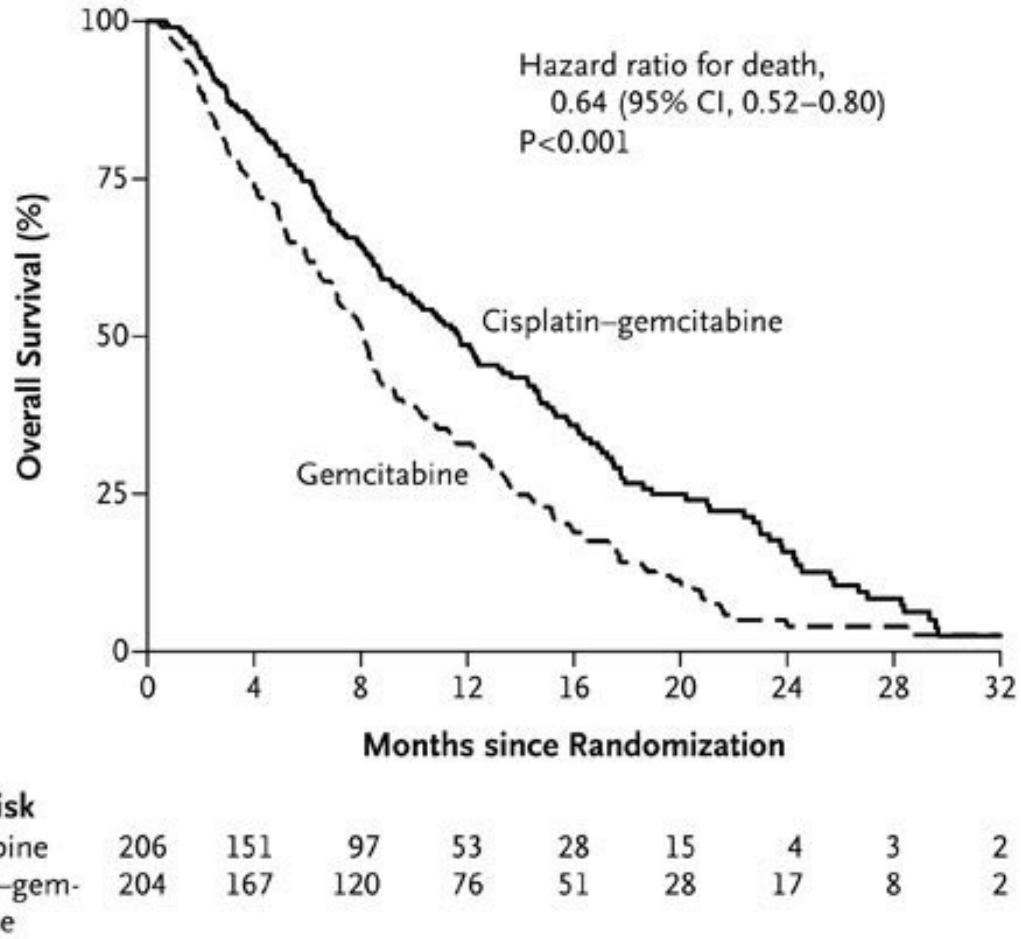


First line systemic treatment- ABC-02



No. at Risk									
Gemcitabine	206	115	56	18	4	3	1	1	1
Cisplatin–gemcitabine	204	140	95	36	18	10	4	1	1

mPFS 8 vs 5 months

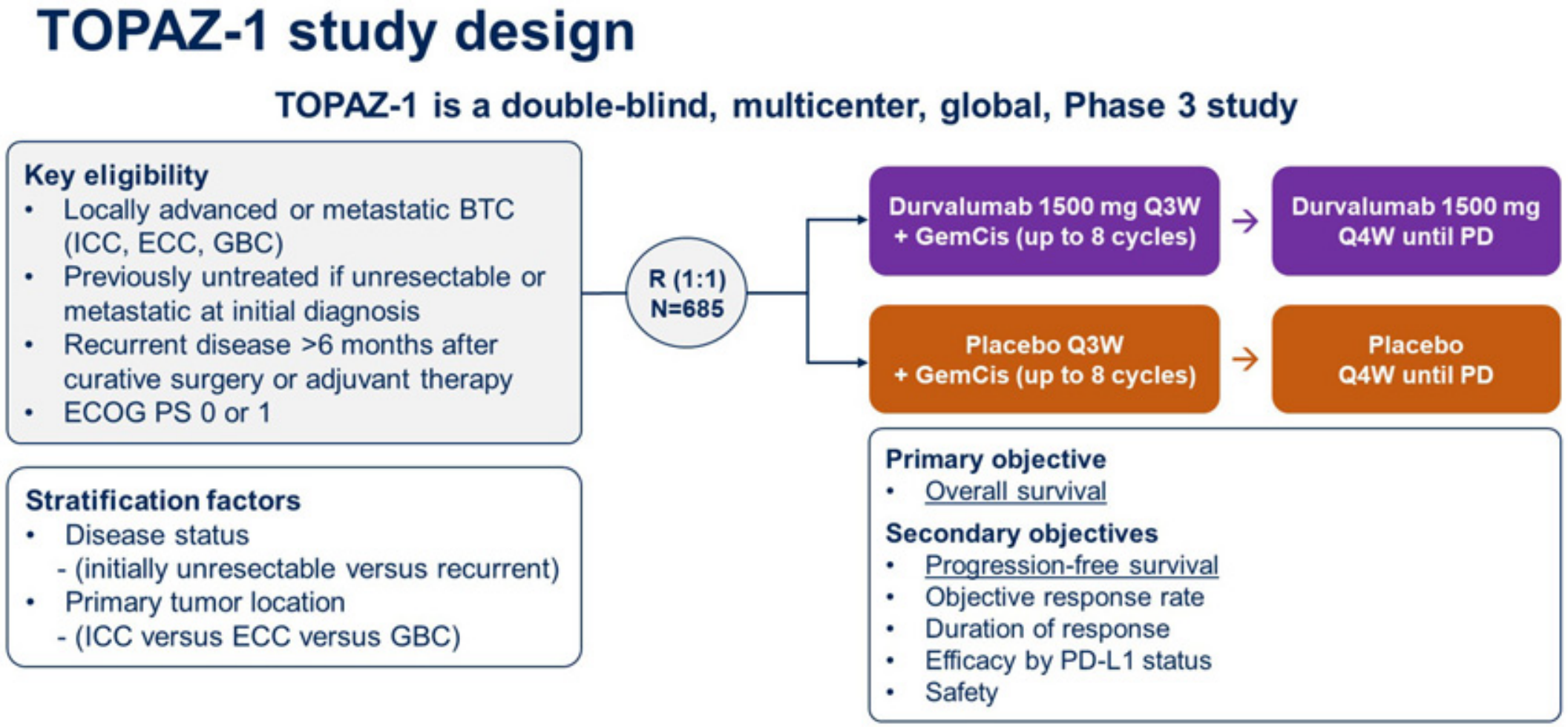


No. at Risk									
Gemcitabine	206	151	97	53	28	15	4	3	2
Cisplatin–gemcitabine	204	167	120	76	51	28	17	8	2

mOS 11.7 vs 8.1 months

N Engl J Med 2010; 362:1273-1281

Immunotherapy moves the needle- TOPAZ -1



GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

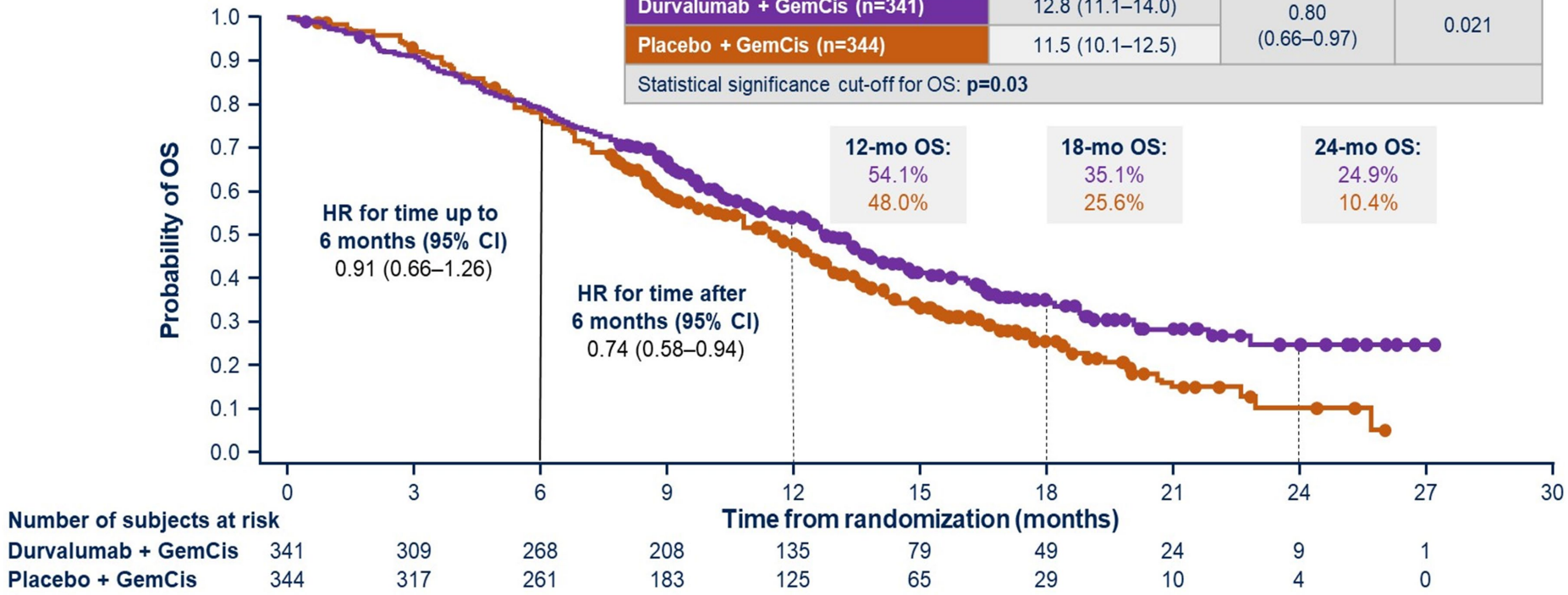
BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

PRESENTED BY: Do-Youn Oh, MD, PhD

Durvalumab improves survival in BTC- highlights

Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			

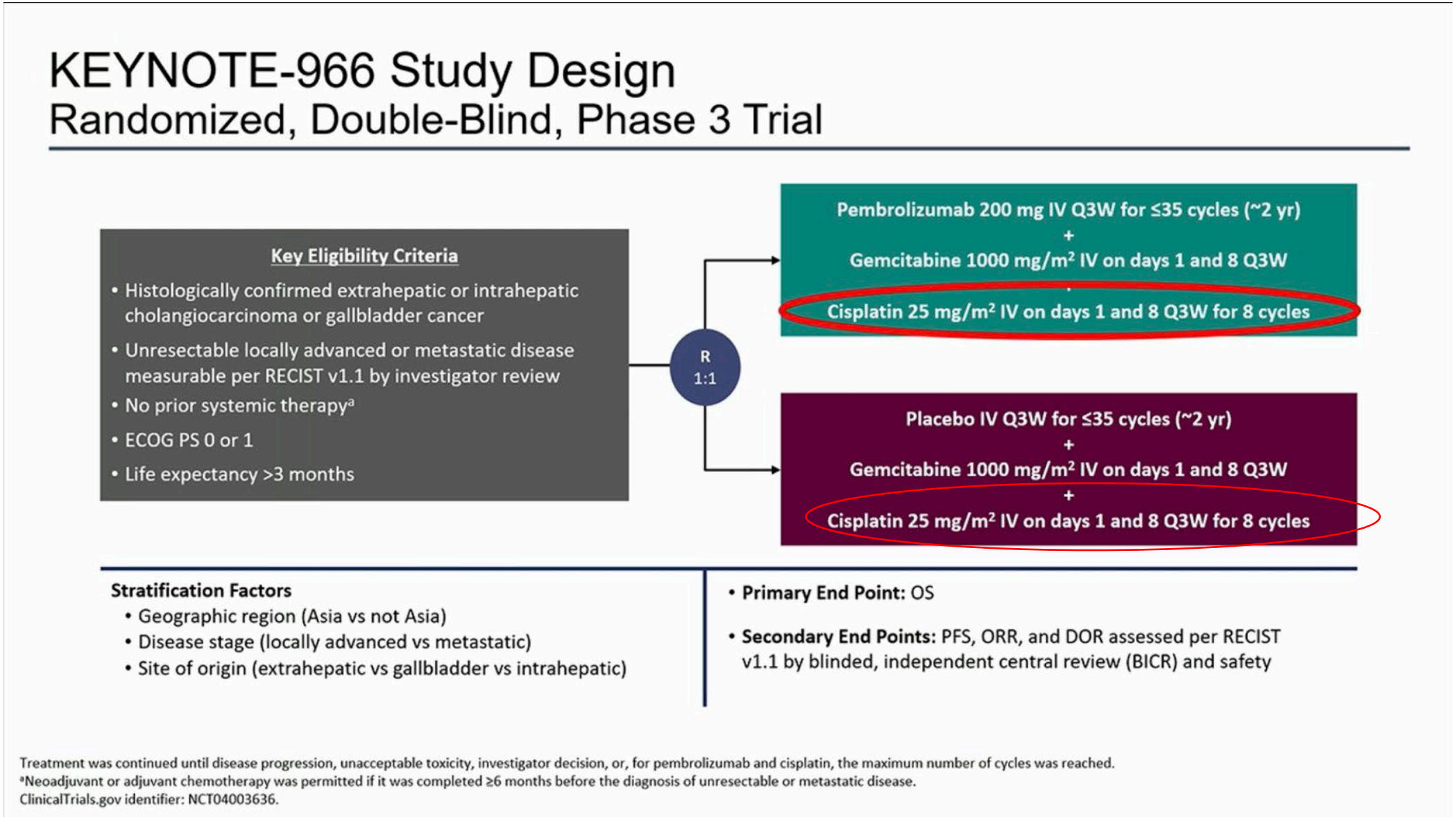


Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

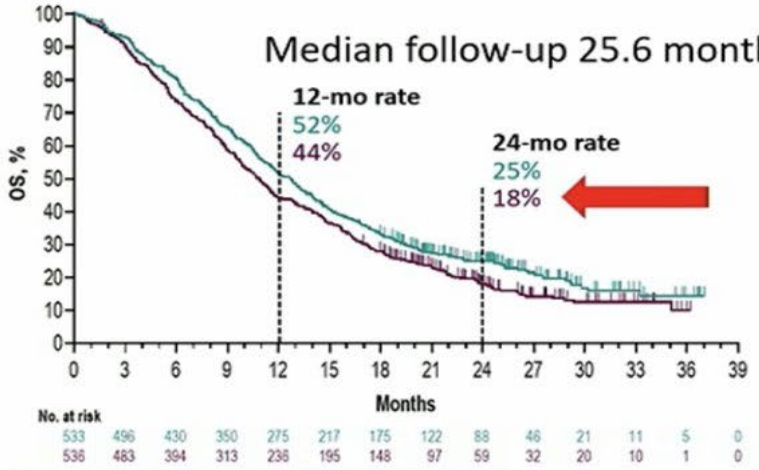
PRESENTED BY: Do-Youn Oh, MD, PhD

Immunotherapy moves the needle- KEYNOTE 966



Immunotherapy moves the needle- Pembrolizumab

Overall Survival at Final Analysis

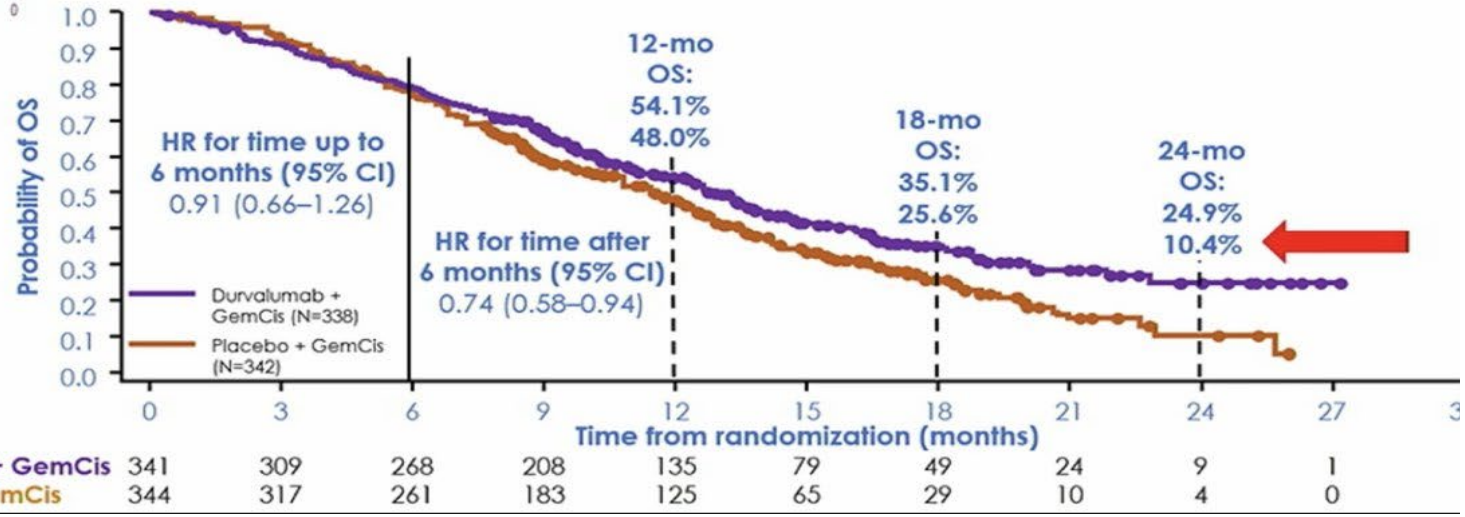


HR 0.83 (95% CI, 0.72-0.95)
***P* = 0.0034**

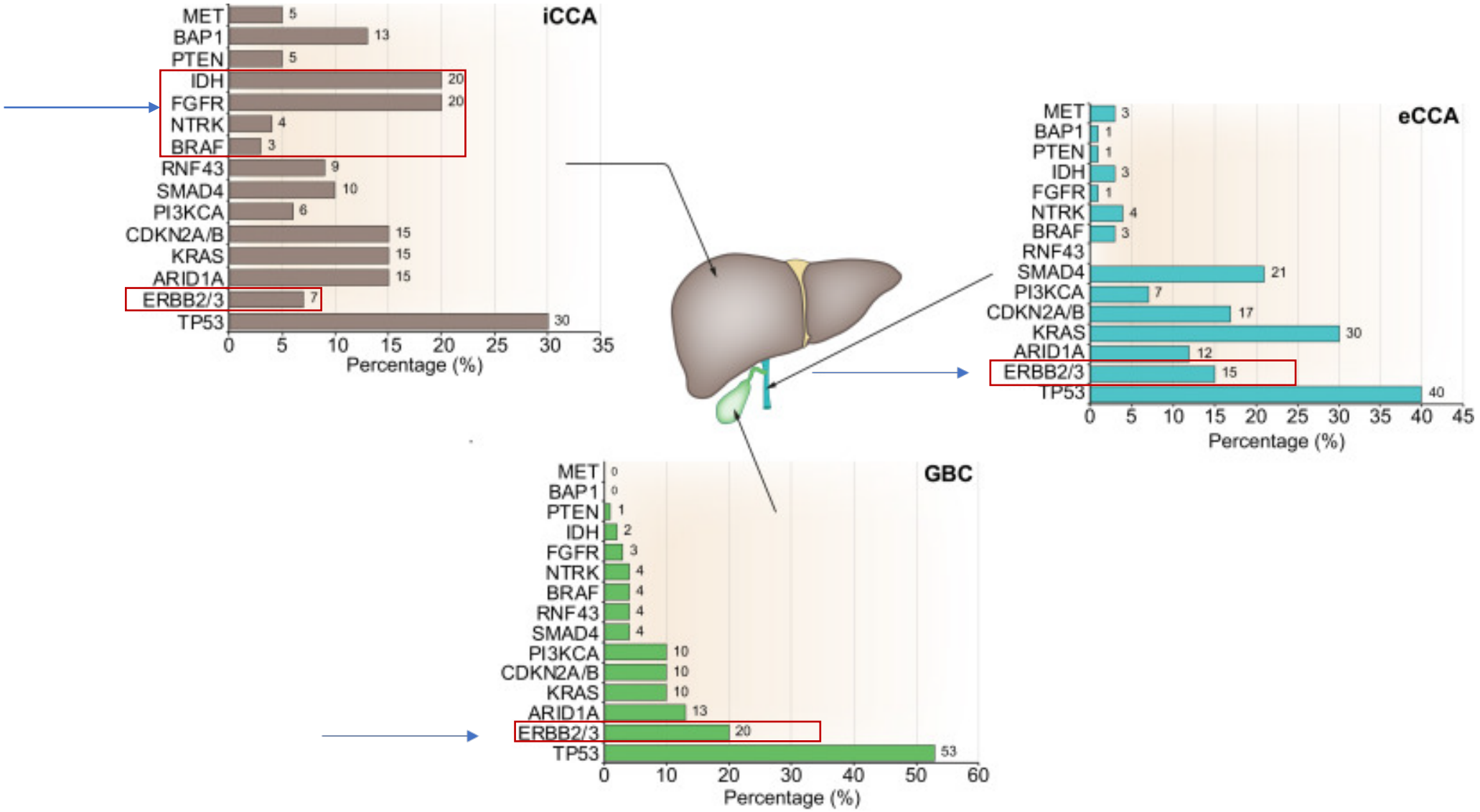
Below the signficance boundary of
P = 0.0200

	Pts w/ Event	Median, mo
Pembro + Gem/Cis	78%	12.7
Placebo + Gem/Cis	83%	10.9

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Median follow-up (95% CI), months	23.4 (20.6–25.2)	22.4 (21.4–23.8)
Median OS (95% CI), months	12.9 (11.6–14.1)	11.3 (10.1–12.5)
HR (95% CI), durvalumab + GemCis vs placebo + GemCis	0.76 (0.64–0.91)	



Molecular profiling in the 2nd line and beyond

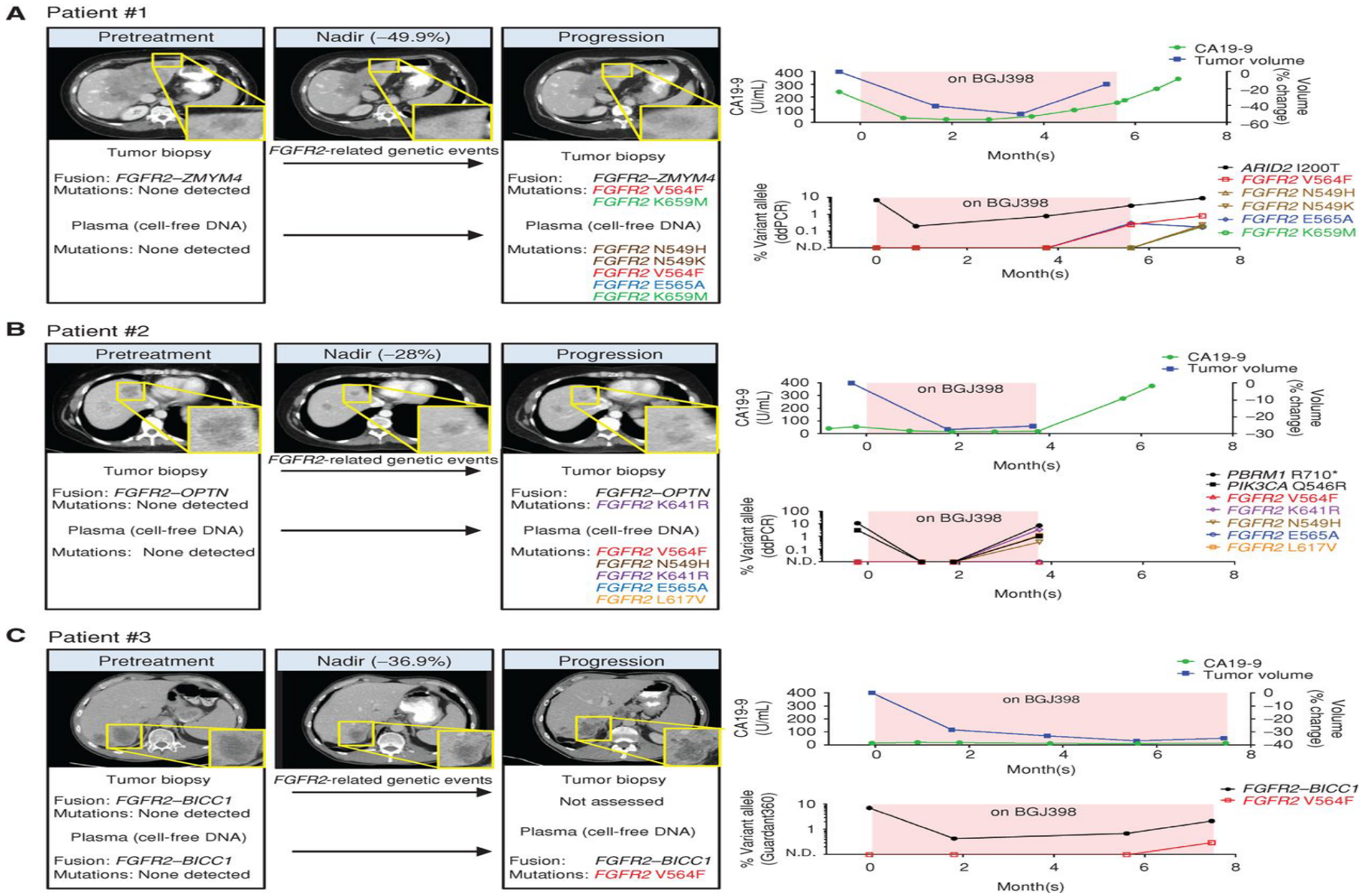


J Hepatol 2020; 73(1): 170-185

Targeting FGR2 fusions.

Parameters	Pemigatinib	Futibatinib	Infigratinib
Target	FGFR1-3 (reversible)	Pan-FGFR (irreversible)	FGFR1-3 (reversible)
Phase	II	II	II
Sample size	107	103	71
Key Characteristics	Fusions/rearrangements. 1 or more prior systemic therapy		
Regimen	2 weeks on/ 1 off	Continuous	3 weeks on 1 off
ORR	35.5%	42%	31%
Median DoR (m)	7.5 (5.7-14.5)	9.7 (7.6- 17.0)	5.4 (3.7-7.4)
Median PFS (m)	6.9 (6.2-9.6)	9 (6.9- 13.1)	6.8 (5.3- 7.6)
Median OS (m)	21.1 (14.8- NE)	N/A	N/A

Acquired Resistance to FGFR Inhibition- FGFR2 mutations



Cancer Discov. 2017;7(3):252-263. doi:10.1158/2159-8290.CD-16-1000

Futibatinib activity in acquired resistance

FGFR2 Mutation	Kinase Domain Region	Factor Change in IC_{50} vs. Wild-Type *FGFR2*			
		Futibatinib	Pemigatinib	Infigratinib	Erdafitinib
Wild-type	—	1	1	1	1
N550D	Regulatory triad	2	102	81	10
N550K	Regulatory triad	8	164	68	13
V563L	—	3	5	14	1
V565I	Gatekeeper	4	42	>236	1
V565L	Gatekeeper	44	335	>236	23
E566A	Regulatory triad	3	8	12	1
E566G	Regulatory triad	2	6	10	1
K642I	Regulatory triad	2	20	15	22
K642R	Regulatory triad	2	7	16	1
K660M	Activation loop	5	23	63	19

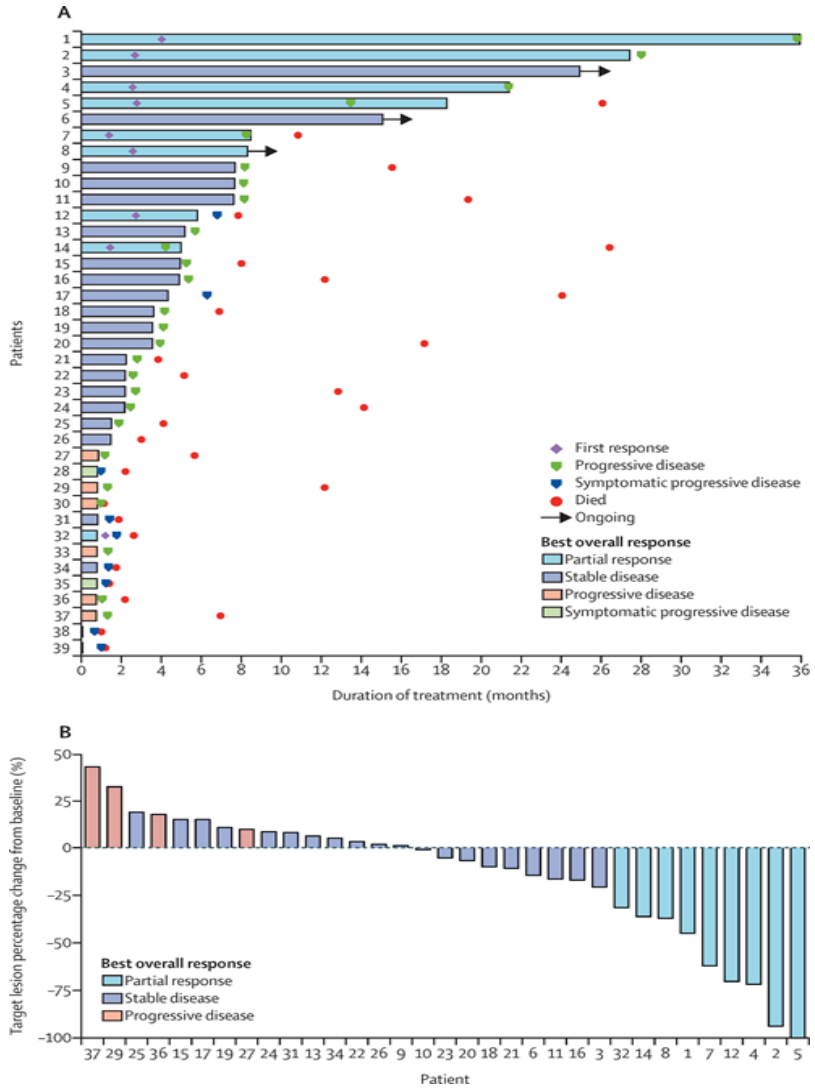
N Engl J Med 2023; 388:228-239

FGFR2 fusion summary

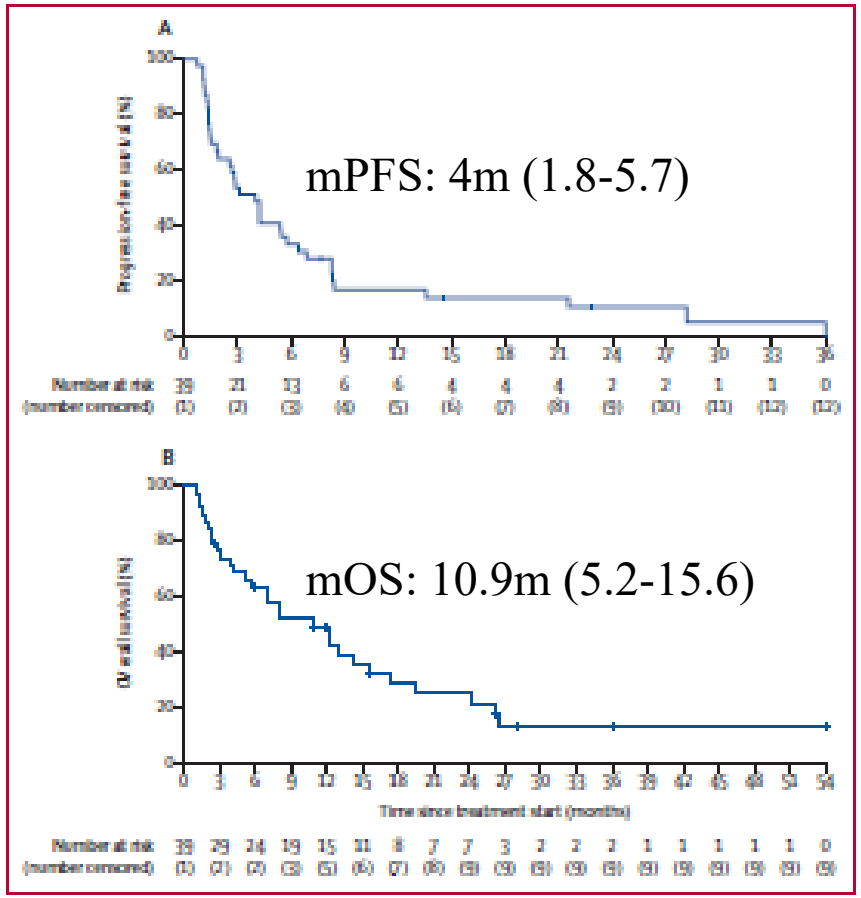
- Next generation sequencing is SoC for advanced BTC
- FGFR2 fusion events occur in 10% of ICC
- The available agents have similar levels of activity in the 2nd line and beyond
- If available, Futibatinib will be my preferred agent.

HER2 Amplification/Overexpression

MyPathway- Trastuzumab and Pertuzumab



ORR- 23%

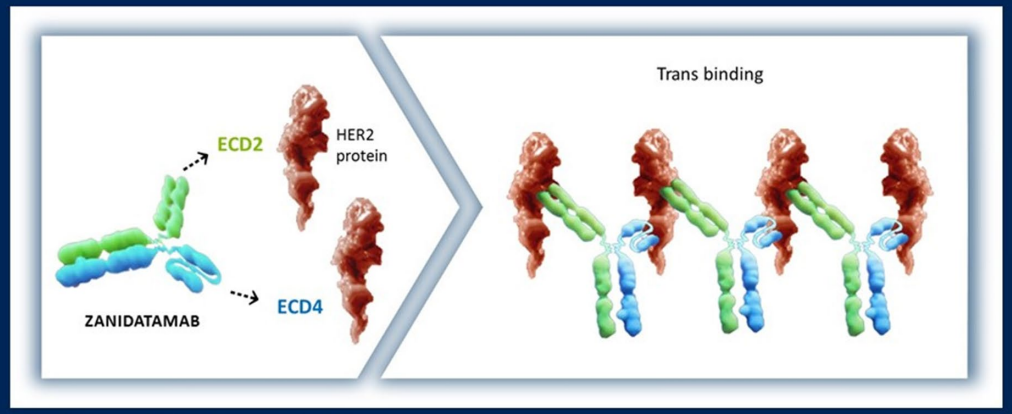


Lancet Oncol. 2021 Sep;22(9):1290-1300

HERIZON –BTC Zanidatamab

Zanidatamab is a HER2-targeted Bispecific Antibody with a Unique Mechanism of Action (MOA)

- Zanidatamab simultaneously binds 2 separate HER2 molecules in *trans*[1]
- Unique binding properties of zanidatamab to HER2 result in multiple MOAs[1]
- Preclinical studies demonstrate greater activity than trastuzumab ± pertuzumab[1]
- Zanidatamab has shown a manageable safety profile and encouraging antitumor activity in patients with HER2-expressing BTC in a Phase 1 trial[2]



ECD = extracellular domain

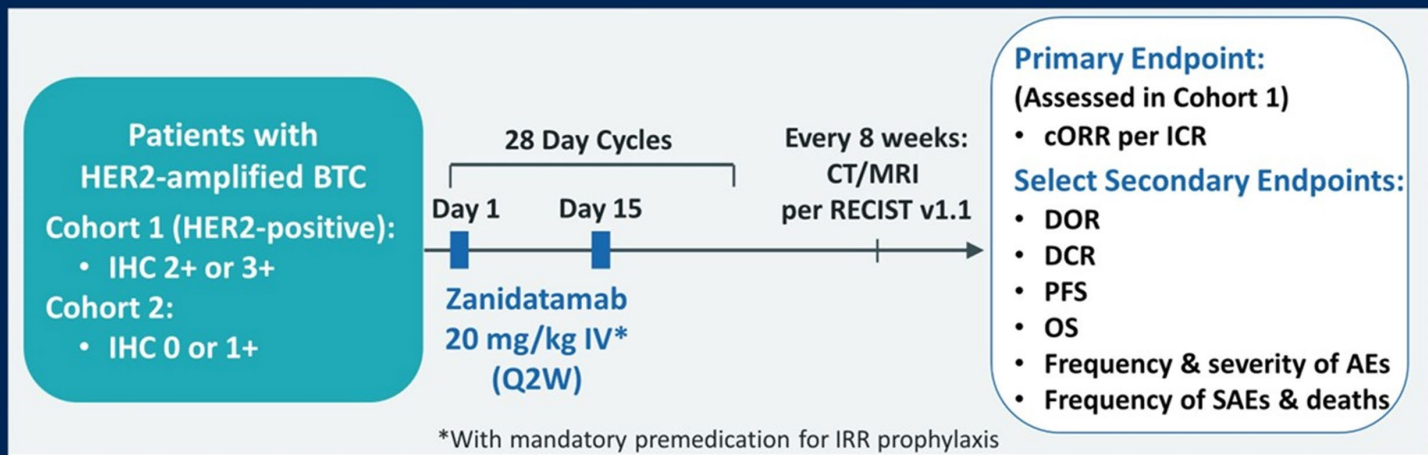
[1] Weisser NE, et al. Nature Commun 2023;14:1394. [2] Meric-Bernstam F, et al. Lancet Oncol 2022;23:1558–1570.

HERIZON-BTC-01 Study Design

- Phase 2b study of zanidatamab monotherapy in patients with HER2-amplified BTC

Key Eligibility Criteria

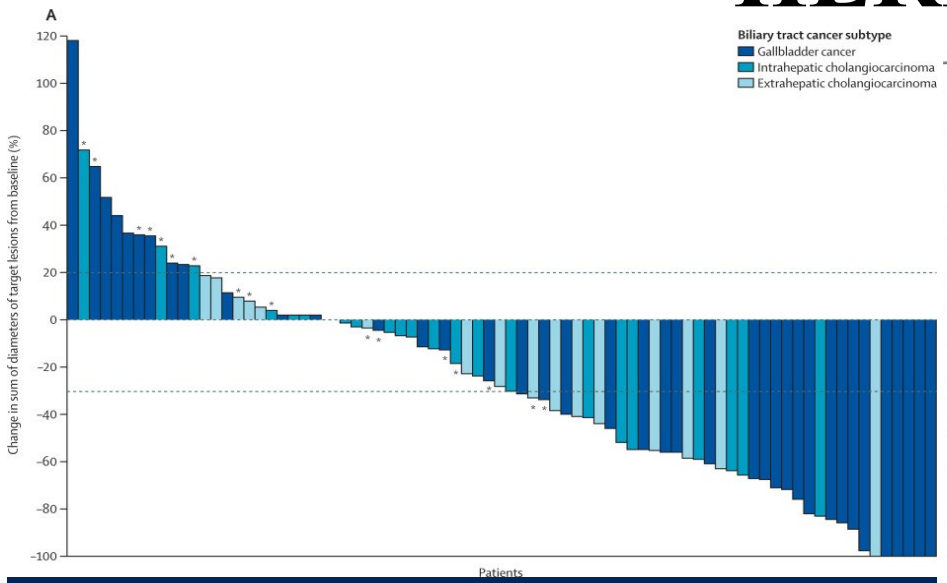
- Locally advanced or metastatic BTC[1]
- Tissue required to confirm HER2 status by central lab
- Progressed after treatment with a gemcitabine-containing regimen
- No prior HER2-targeted therapies
- ECOG PS of 0 or 1



[1] Excludes ampullary

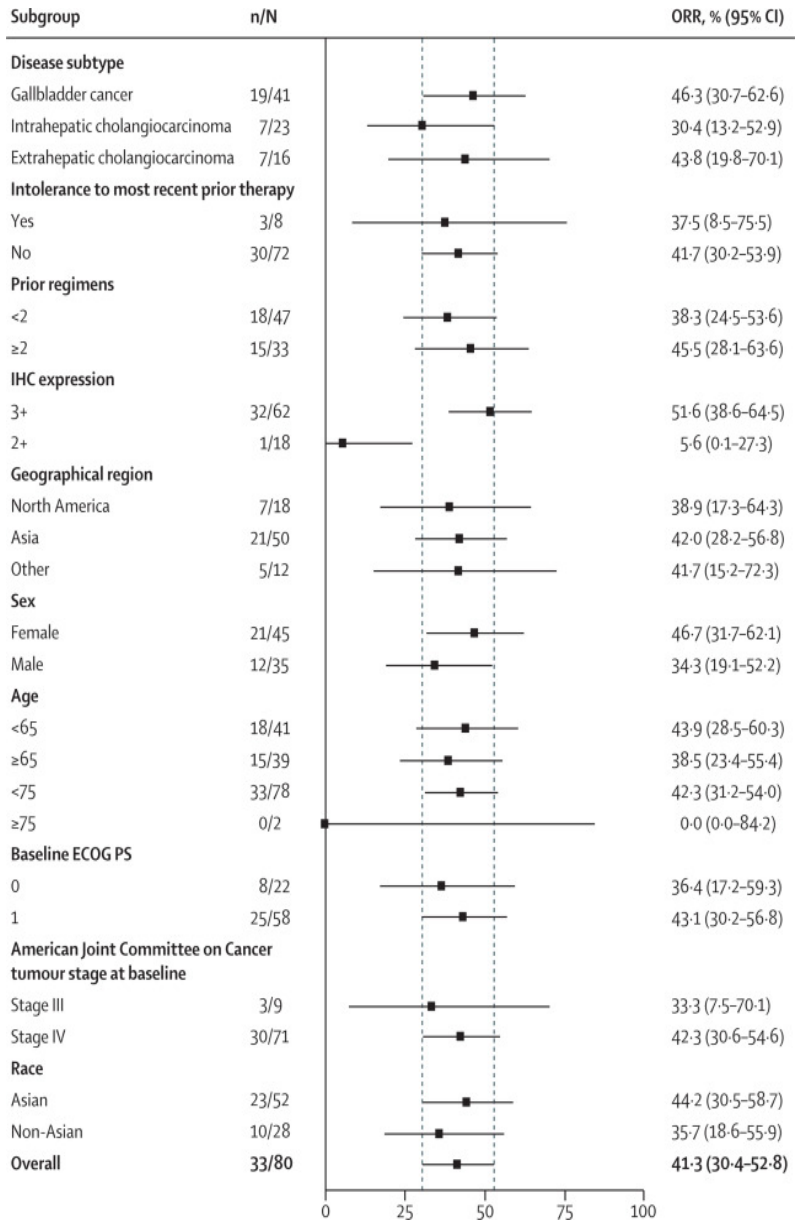
AE = adverse event; cORR = confirmed objective response rate; CT = computed tomography scan; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ICR = independent central review; IHC = immunohistochemistry; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; OS = overall survival; Q2W = every two weeks; RECIST= Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

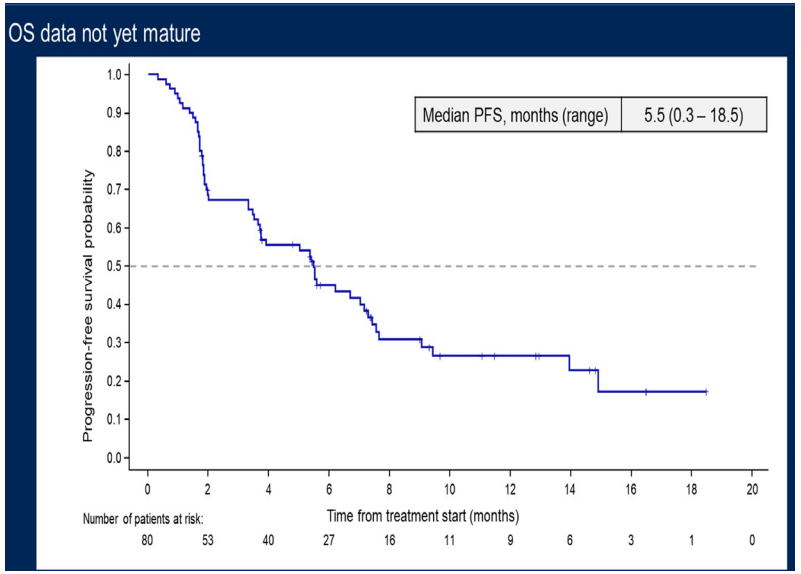
HERIZON BTC Results



- 16 patients had ongoing responses at the time of data cutoff

		By ICR Assessment (N = 80)	By Investigator Assessment (N = 80)
cORR, % (95% CI)		41.3 (30.4, 52.8)	41.3 (30.4, 52.8)
Confirmed BOR, n (%)	CR	1 (1.3)	4 (5.0)
	PR	32 (40.0)	29 (36.3)
	SD	22 (27.5)	21 (26.3)
	PD	24 (30.0)	25 (31.3)
	NE[1]	1 (1.3)	1 (1.3)
DCR [CR + PR + SD], % (95% CI)		68.8 (57.4, 78.7)	67.5 (56.1, 77.6)
CBR [CR + PR + (SD ≥ 6 months)], % (95% CI)		47.5 (36.2, 59.0)	47.5 (36.2, 59.0)





Targeting HER2 Amplifications/Overexpression.

	MyPathway	HERB	SGNTUC-019	HERIZON-BTC-01
Agents	Trastuzumab + Pertuzumab	Trastuzumab deruxtecan	Tucatinib + Trastuzumab	Zanidatamab
Study Phase	II	II	II	II
Sample Size	39	32 (22)	30	80
Key Characteristic	HER2 by IHC or NGS	*HER2 by IHC	HER2 by IHC or NGS	HER2 by IHC
ORR	23%	36.4%	46.7%	41%
Median DoR(m)	10.8 (0.7-25.4)	NR	6 (5.5- NE)	12.9 (6-NE)
Median PFS (m)	4.0 (1.8- 5.7)	4.4 (2.8-8.3)	5.5 (3.9-8.1)	5.5 (3.7-7.2)
Median OS (m)	10.9 (5.2-15.6)	7.1 (4.7-14.6)	12m OS-53.8%	Not mature
Grade 3AE	46%. Diarrhea (26%)	81%. *ILD (25%)	60% (26%TR)	18%. Diarrhea (5%)

Summary- targeting HER2

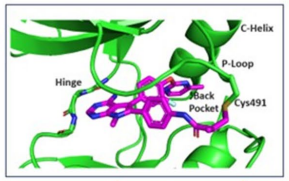
- No FDA approved agents at this time
- NCCN guidelines- Trastuzumab + pertuzumab only
- Zanidatamab given large sample size, AE profile

Emory and Collaborators

FGFR alterations: RLY-4008 (REFOCUS)

RLY-4008: The First Highly Selective FGFR2 Inhibitor

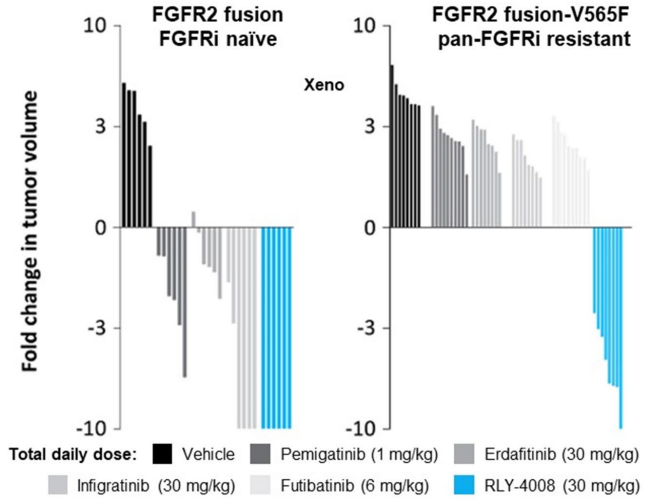
In contrast to pan-FGFRi, RLY-4008 is a potent and selective FGFR2 inhibitor



RLY-4008 selectively inhibits FGFR2 based on unique conformational dynamics[1]

Inhibitor	Mechanism of Action	Biochemical IC50 (nM)[2-5]			
		FGFR1	*FGFR2*	*FGFR3*	*FGFR4*
RLY-4008	Irreversible FGFR2 selective	864.3	3.1	274.1	17,633
Infigratinib	Reversible Pan-FGFRi	1.1	1	2	61
Pemigatinib	Reversible Pan-FGFRi	0.39	0.46	1.2	30
Futibatinib	Irreversible Pan-FGFRi	1.8	1.4	1.6	3.7

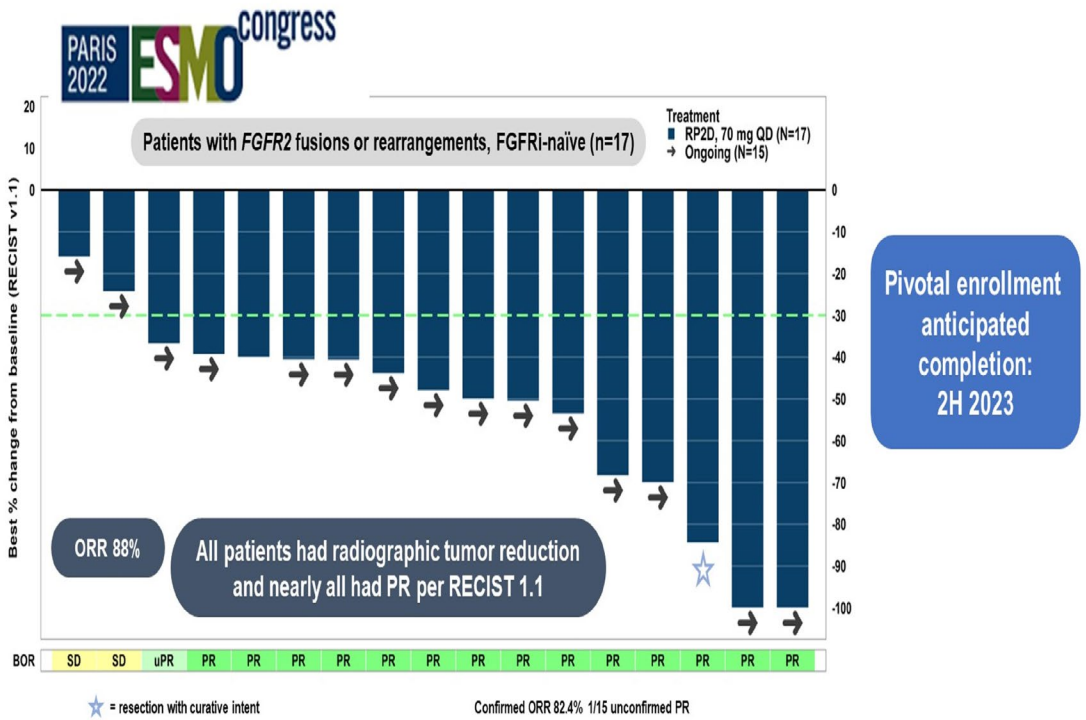
Potent in-vivo activity against FGFRi-sensitive and resistant cholangiocarcinoma[2]



1. Schönherr H. et al. Presented at MedChem GRC meeting; August 7-12,2022. 2. Goyal L. et al. Presented at AACR Annual Meeting; April-9-14;2021. 3.Truseltiq(infigratinib) [package insert]. Brisbane,CA QED Therapeutics; 2021. 4. Pemazyre(pemigatinib) [NDA]. Wilmington, DE;2019. www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213736Orig1s000ChemR.pdf Accessed August 25,2022. 5. Sootome H. et al. *Cancer Res.* 2020;80(22):4986-4997.
FGFRi: fibroblast growth factor receptor inhibitor

RLY-4008 is active in FGFR2+ve Cholangiocarcinoma

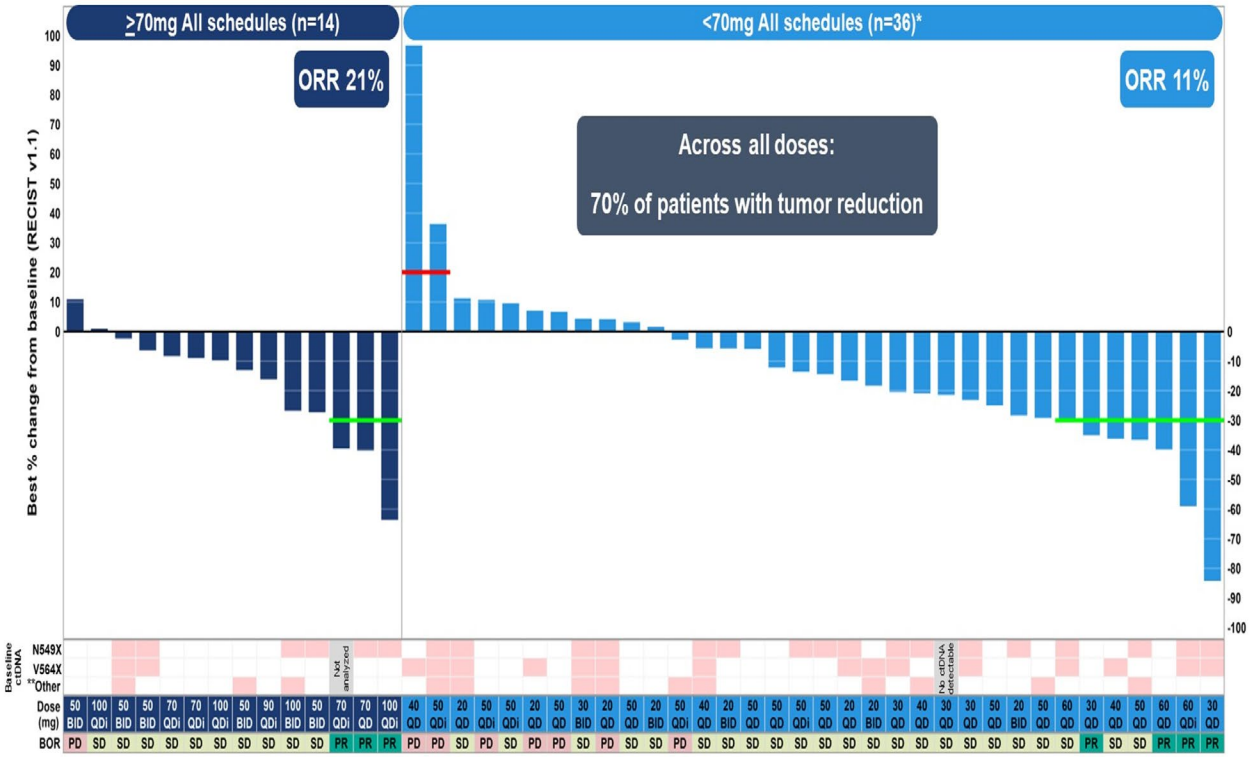
ReFocus Next Steps: Phase 2 Pivotal Cholangiocarcinoma Ongoing



Pivotal enrollment anticipated completion: 2H 2023

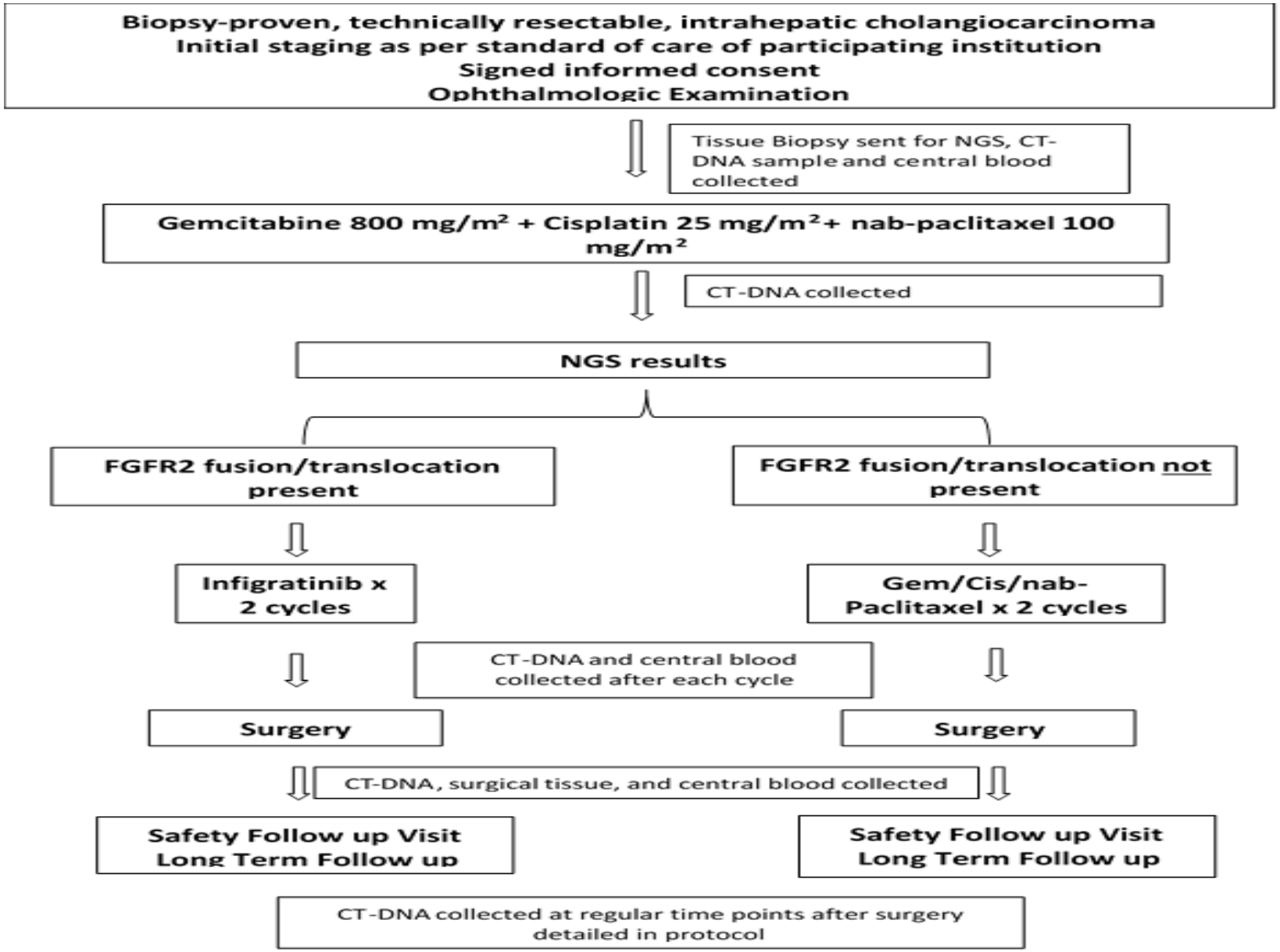
Hollebecque et al. Efficacy of RLY-4008, a highly selective FGFR2 inhibitor in patients (pts) with a FGFR2-fusion or rearrangement (f/r), FGFR inhibitor (FGFRi)-naïve cholangiocarcinoma (CCA): ReFocus trial. Oral Presentation. European Society for Molecular Oncology 2022, Paris, 9-13 October 2022. Data cut-off for ESMO 2022 as of 08/01/2022. ORR: Overall Response Rate, QD: once daily, PR: partial response, uPR: unconfirmed partial response, SD: Stable Disease

ReFocus Phase 1 Efficacy - FGFRi-Refractory, *FGFR2* Fusion+ Cholangiocarcinoma

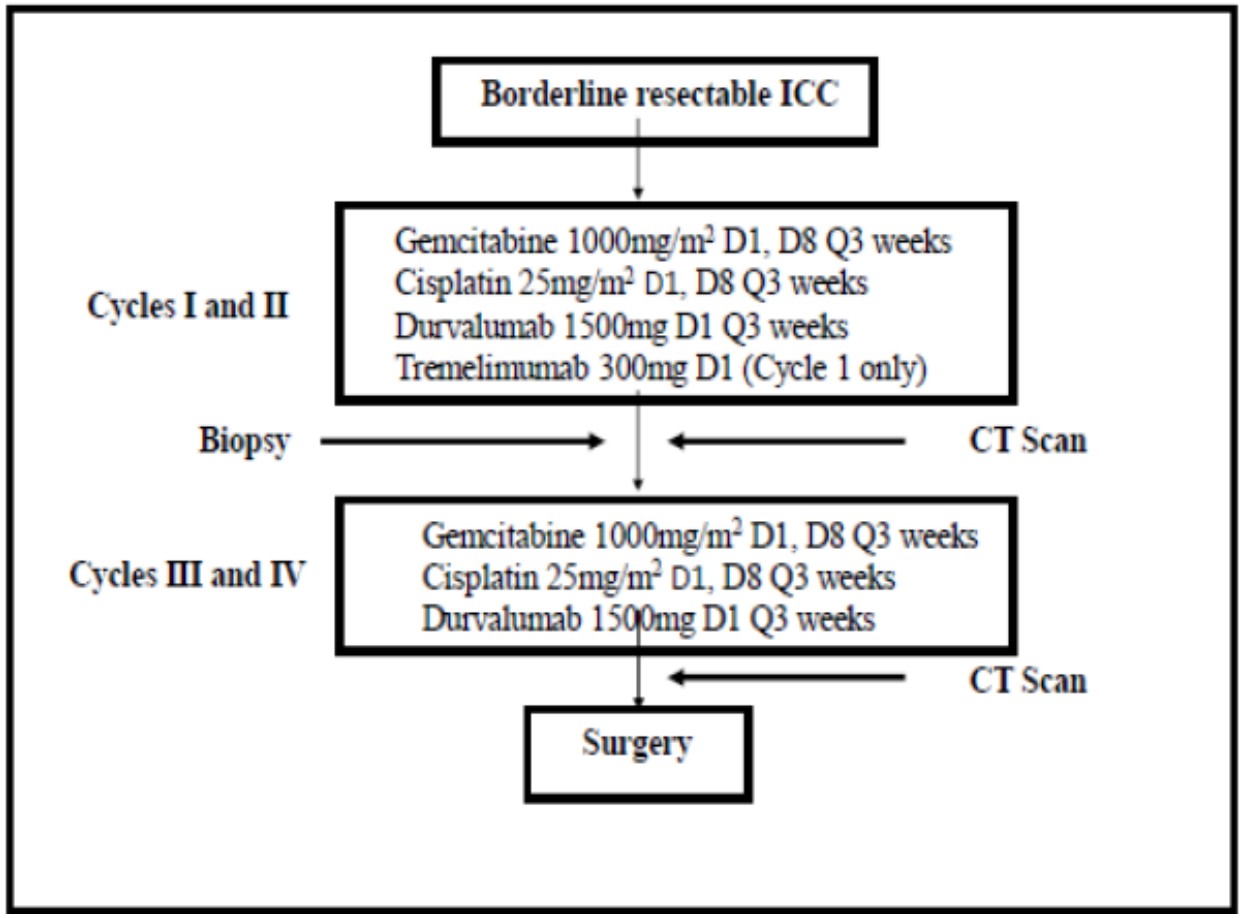


*Waterfall excludes 2 FGFRi-Refractory patients with clinical progressive disease without post baseline tumor assessment.
N549X and V564X correspond to FGFR2 IIIc isoform; X denotes any amino acid substitution
** Other includes FGFR2 mutations other than N549X and V564X (pink), no detectable FGFR2 mutation (white)
Data for Phase 1 Dose Escalation as of 01/30/2023.

Resectable cholangiocarcinoma paradigm shift: OPTIC



Borderline resectable ICC: Neoadjuvant Chemotherapy + STRIDE



Thanks for listening