PERSONALAIZED MEDICINE IN CHOLANGIOCARCINOMA

Presented by:
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Disclosure information

Advisory board : ACTERO , KIMIA

I will discuss investigational and off-label drugs in my talk .

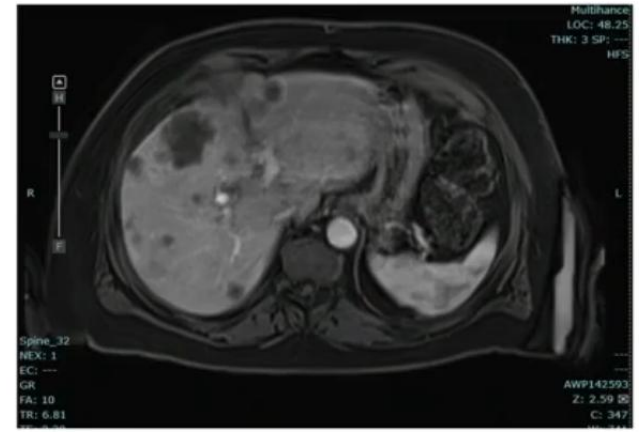
Treatment approach

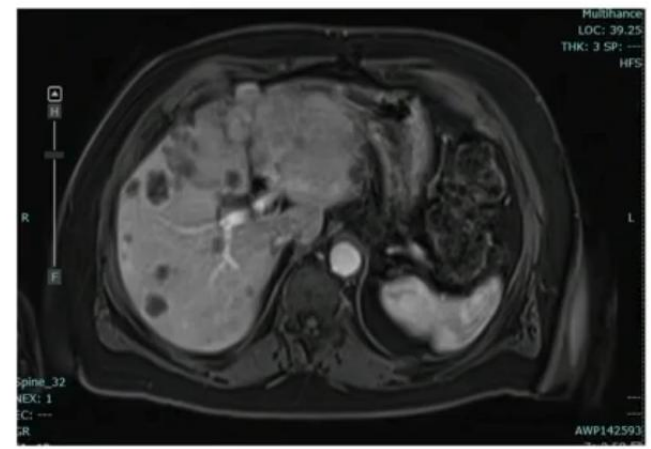
- Chemo immunotherapy

- Biomarker driven therapy

Case: iCCA

- 48 yo F, otherwise healthy, presents with abdominal pain and palpable mass in the epigastric area.
- PE: unremarkable, ECOG PS 0
- Labs show mild elevations in AST/ALT, **CA 19-9 527**, otherwise normal
- CT and PET scan showed multiple liver masses, left portal vein occluded, compression of adjacent hepatic veins.
- US guided liver biopsy showed **poorly differentiated infiltrating adenocarcinoma** with desmoplastic stroma. **+CK7**, -CK20. High grade, intrahepatic CCA



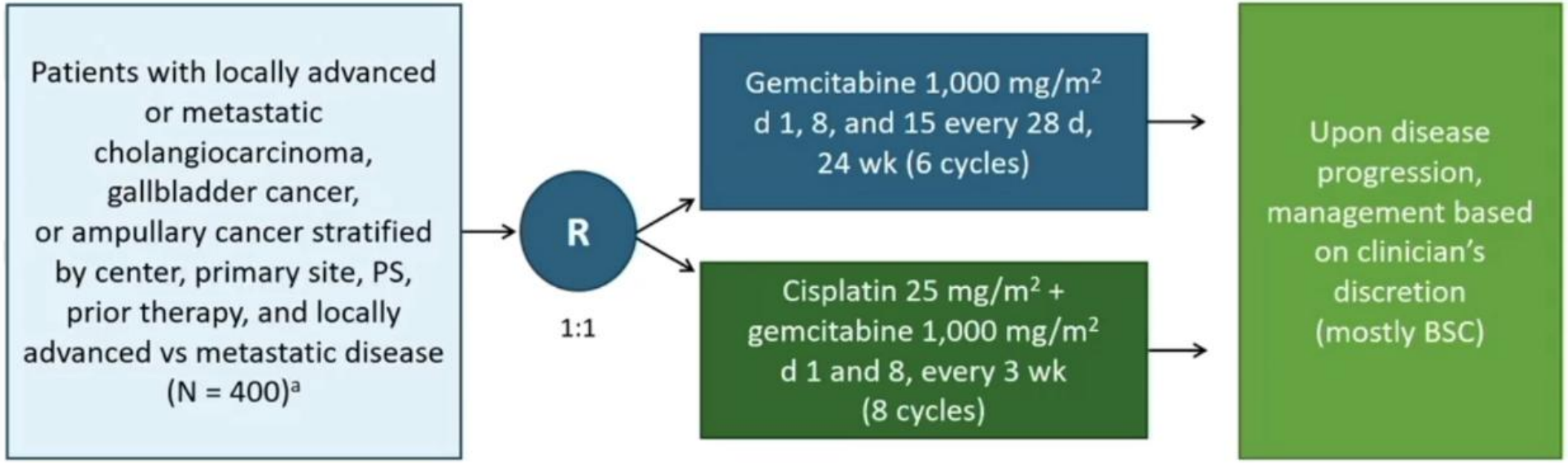


What to do in the first line treatment in 2026 ?

- Conventional Chemo
- Chemo immunotherapy
- Biomarker driven (Targeted therapy)

For along time orphan disease

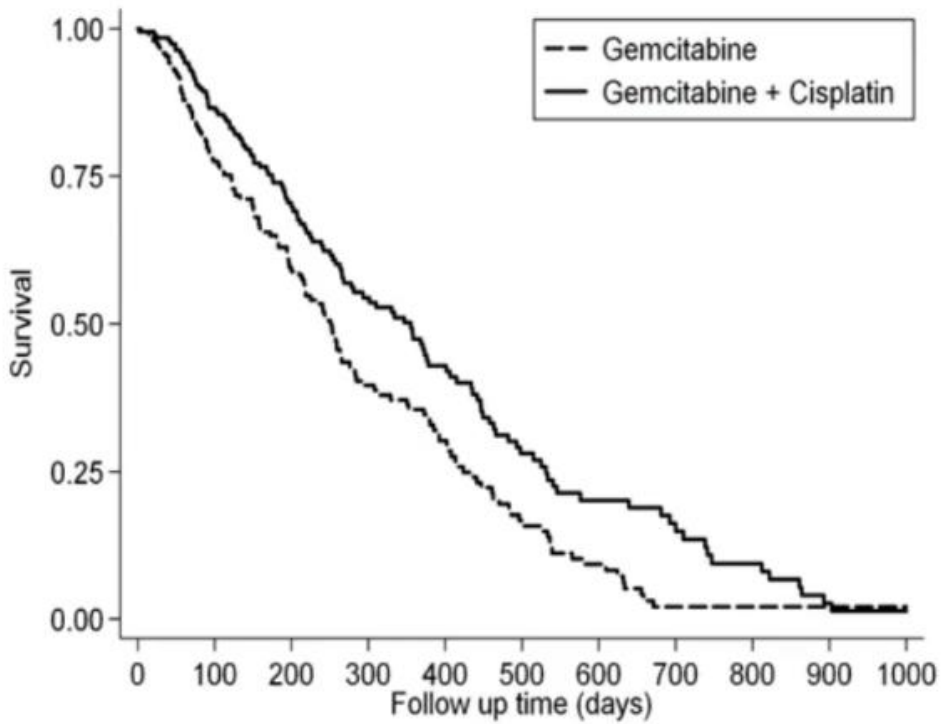
Phase 3 ABC-02 Trial: Gemcitabine vs Cisplatin/ Gemcitabine in Advanced Biliary Cancers



- Primary endpoint: OS
- Secondary endpoints: PFS, tumor response, AEs

+ QOL

ABC-02: Survival Data (ITT)



	Gem	Gem + Cis
Patients, n	206	204
Deaths, n (%)	141 (68.5)	122 (59.8)
Median survival, mo	8.3	11.7
Log rank *P*	.002	
Hazard ratio (95% CI)	0.70 (0.54, 0.89)	

Improving on Gemcitabine and Cisplatin

Combination with checkpoint inhibitors

TOPAZ-1 study design

TOPAZ-1 is a double-blind, multicenter, global, Phase 3 study

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

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

R (1:1)
N=685

Durvalumab 1500 mg Q3W + GemCis (up to 8 cycles) → Durvalumab 1500 mg Q4W until PD

Placebo Q3W + GemCis (up to 8 cycles) → Placebo Q4W until PD

Primary objective
- Overall survival

Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

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.

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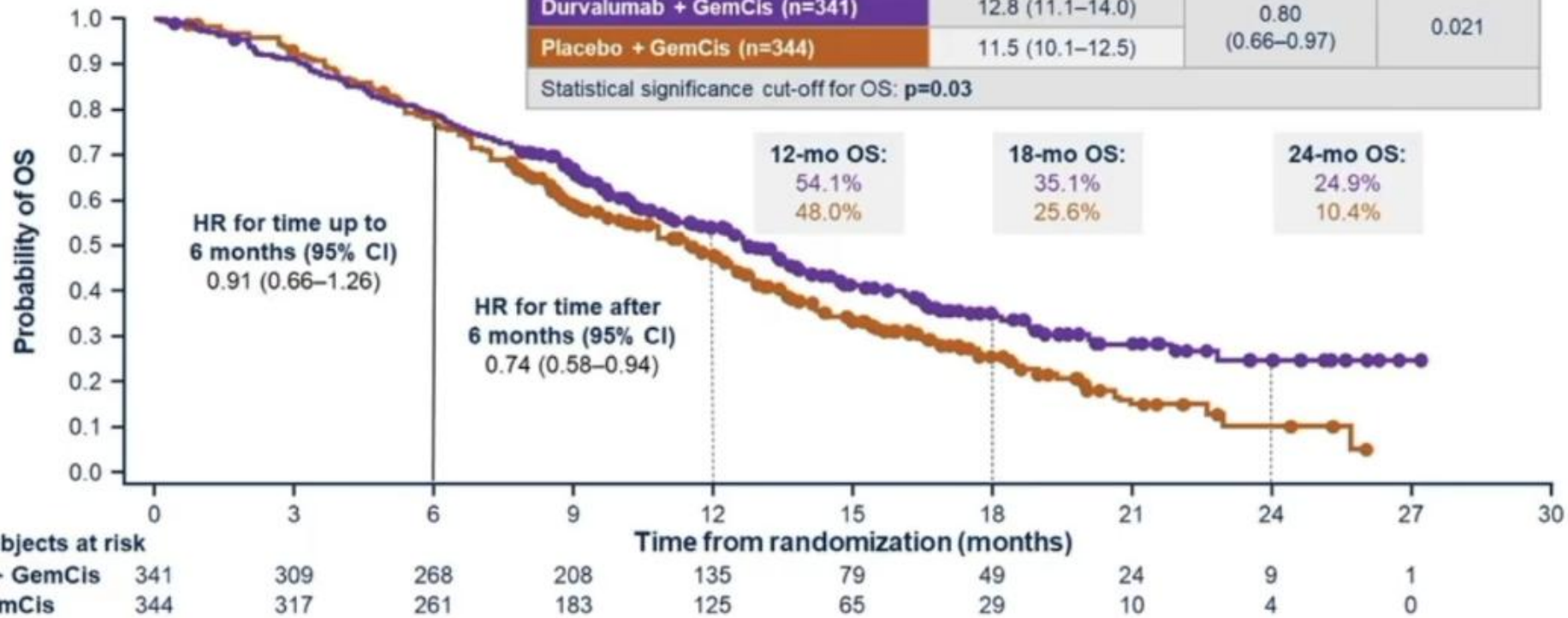
TOPAZ Demographics

	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)

lissing for remaining patients. Unless otherwise indicated, measurements were taken at baseline.

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.

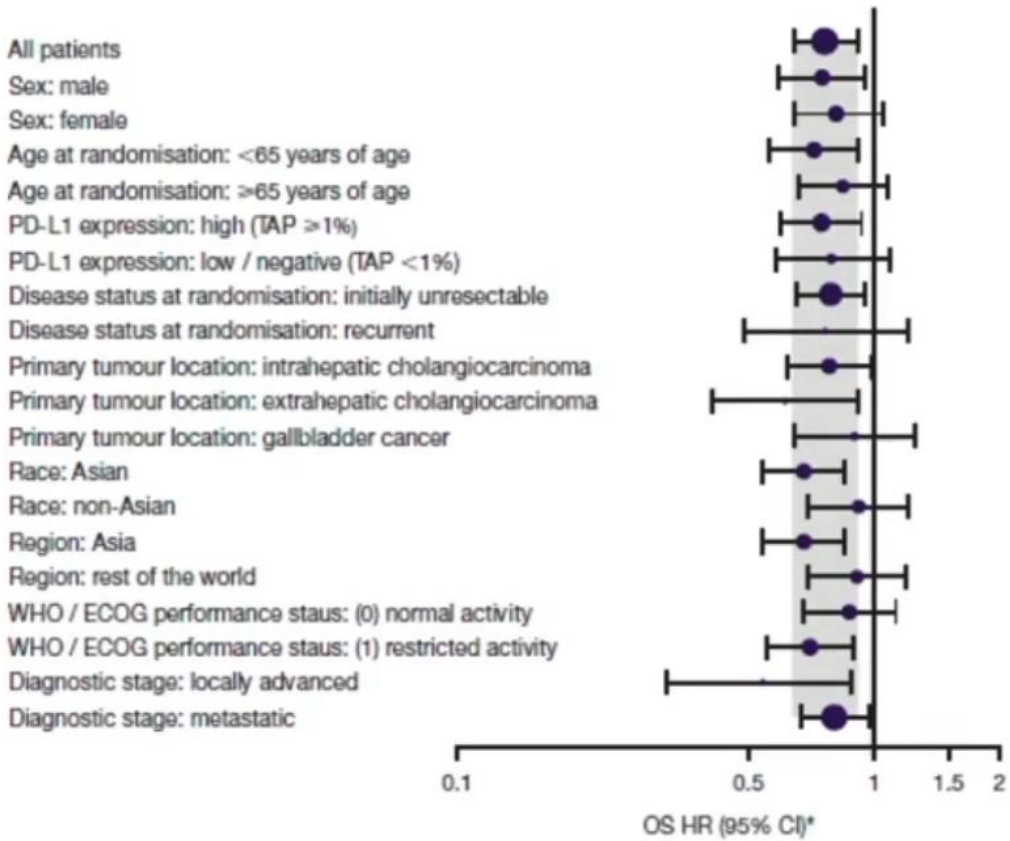
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TOPAZ-1 Outcomes across Subgroups



	Durvalumab + GemCis n/N (%)	Placebo + GemCis n/N (%)	OS HR (95% CI)*
All patients	248 / 341 (72.7)	279 / 344 (81.1)	0.76 (0.64–0.91)
Sex: male	126 / 169 (74.6)	148 / 176 (84.1)	0.75 (0.59–0.95)
Sex: female	122 / 172 (70.9)	131 / 168 (78.0)	0.81 (0.64–1.04)
Age at randomisation: <65 years of age	123 / 181 (68.0)	150 / 184 (81.5)	0.72 (0.56–0.91)
Age at randomisation: ≥65 years of age	125 / 160 (78.1)	129 / 160 (80.6)	0.84 (0.66–1.08)
PD-L1 expression: high (TAP ≥1%)	149 / 199 (74.9)	172 / 207 (83.1)	0.75 (0.60–0.93)
PD-L1 expression: low / negative (TAP <1%)	71 / 103 (68.9)	81 / 103 (78.6)	0.79 (0.58–1.09)
Disease status at randomisation: initially unresectable	209 / 274 (76.3)	240 / 279 (86.0)	0.79 (0.65–0.95)
Disease status at randomisation: recurrent	39 / 67 (58.2)	39 / 64 (60.9)	0.76 (0.49–1.20)
Primary tumour location: intrahepatic cholangiocarcinoma	136 / 190 (71.6)	153 / 193 (79.3)	0.78 (0.62–0.99)
Primary tumour location: extrahepatic cholangiocarcinoma	45 / 66 (68.2)	55 / 65 (84.6)	0.61 (0.41–0.91)
Primary tumour location: gallbladder cancer	67 / 85 (78.8)	71 / 86 (82.6)	0.90 (0.64–1.25)
Race: Asian	134 / 185 (72.4)	174 / 201 (86.6)	0.68 (0.54–0.85)
Race: non-Asian	114 / 156 (73.1)	105 / 143 (73.4)	0.92 (0.70–1.20)
Region: Asia	130 / 178 (73.0)	170 / 196 (86.7)	0.68 (0.54–0.85)
Region: rest of the world	118 / 163 (72.4)	109 / 148 (73.6)	0.91 (0.70–1.18)
WHO / ECOG performance staus: (0) normal activity	126 / 173 (72.8)	125 / 163 (76.7)	0.87 (0.68–1.12)
WHO / ECOG performance staus: (1) restricted activity	122 / 168 (72.6)	154 / 181 (85.1)	0.70 (0.55–0.89)
Diagnostic stage: locally advanced	22 / 38 (57.9)	45 / 57 (78.9)	0.54 (0.32–0.88)
Diagnostic stage: metastatic	226 / 303 (74.6)	234 / 286 (81.8)	0.80 (0.67–0.97)

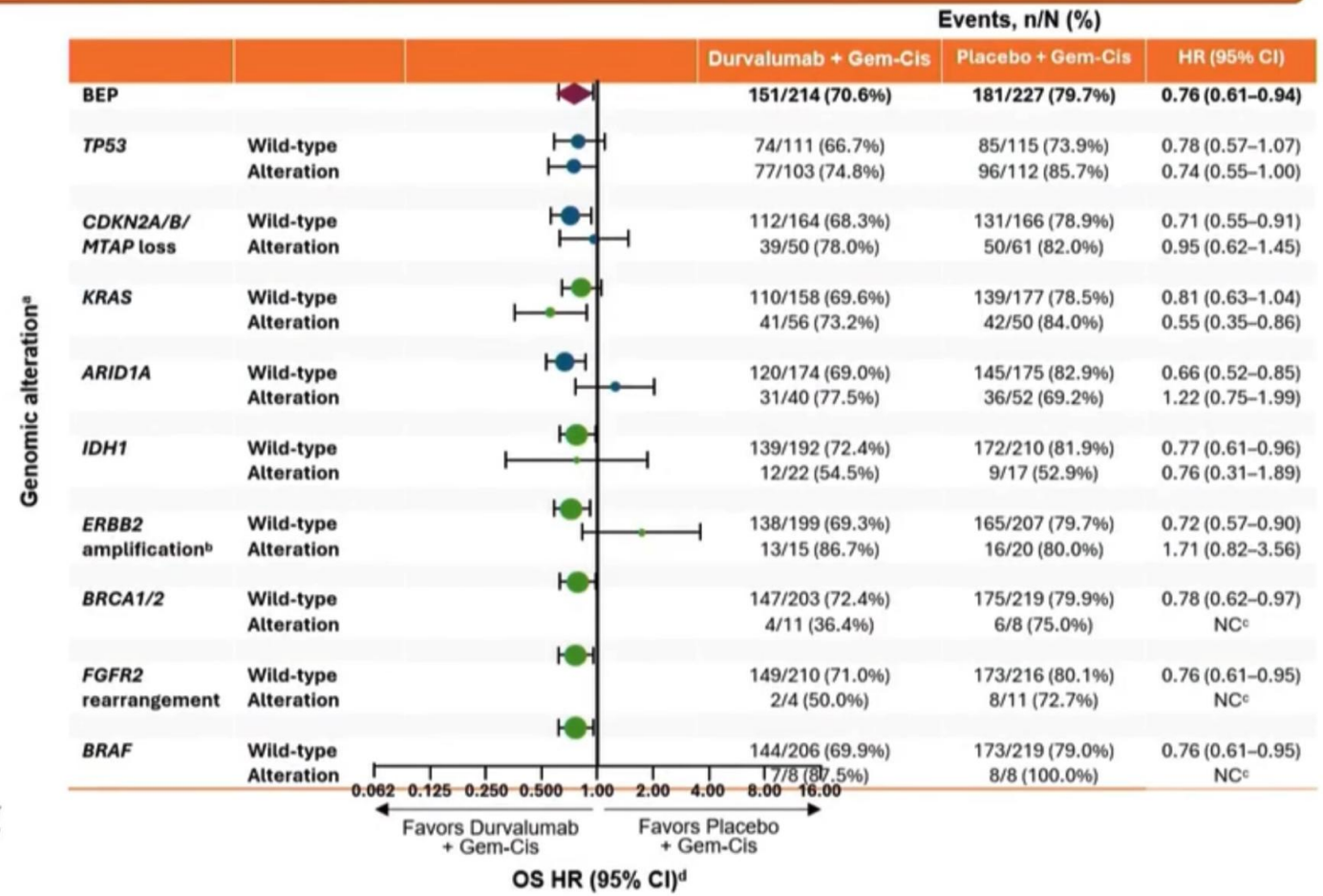
Oh DY et al, NEJM Evid 2022

Oh et al. ESMO Asia 2022

TOPAZ-1: OS by Mutation Status

Durvalumab plus gem-cis is generally effective in patients with clinically actionable and high-prevalence genomic alterations

- Generally, similar OS benefit with durvalumab versus placebo was observed for patients with either wild-type or altered genotypes
- 95% CIs are wide for some genomic alterations due to their low prevalence



[a]Yellow indicates clinically actionable genomic alterations; [b]Correlation of *ERBB2* amplification with ERBB2 overexpression was not confirmed by immunohistochemistry or in-situ hybridization. It is unclear whether *ERBB2* amplification is associated with efficacy outcomes in this population; sample size is limited, and ongoing analysis is continuing to understand the outcomes in this subgroup; [c]HR not calculated if <20 total events occur across treatment arms; [d]Size of dot represents number of events.
Abbreviations and reference in slide notes

Grade 3/4 AEs

Event, n (%)	Durvalumab + GemCis (n=338)	Placebo + GemCis (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)

AE, adverse event; GemCis, gemcitabine and cisplatin; TRAE, treatment-related adverse event.

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Immune-mediated AEs

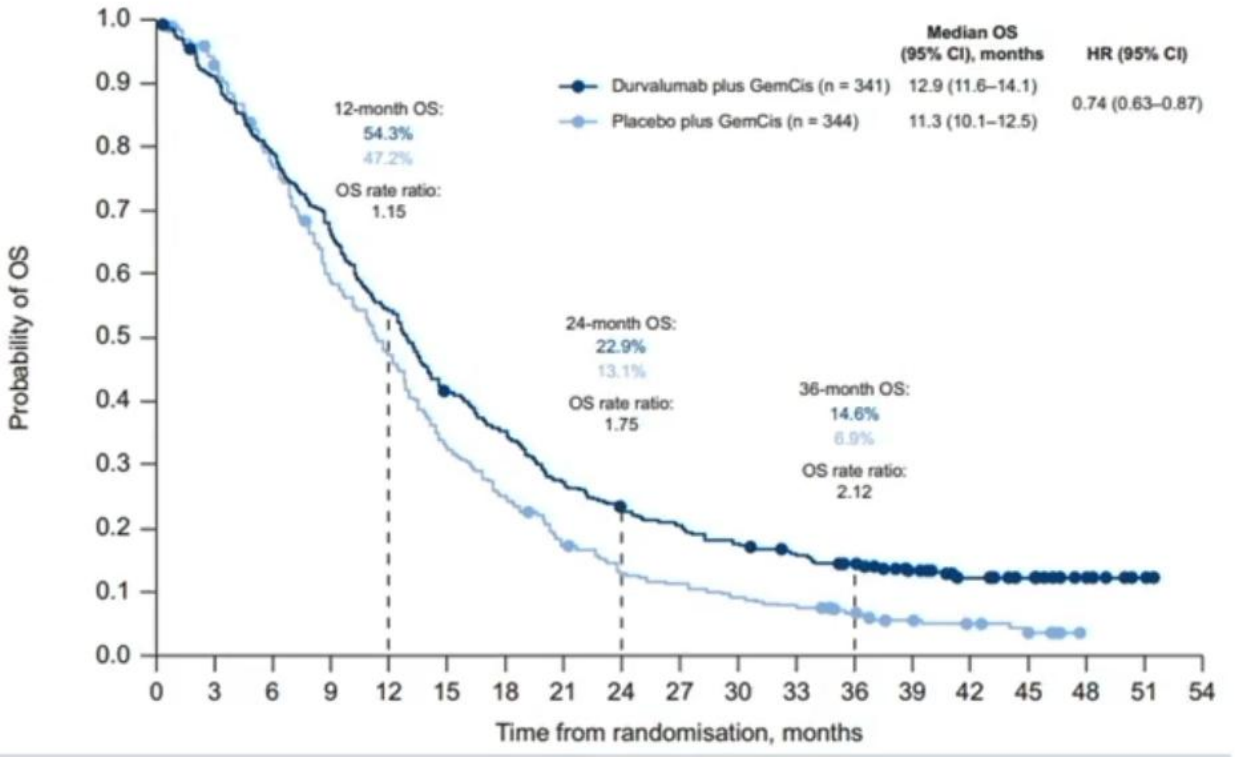
Event, n (%)	Durvalumab + GemCis (n=338)		Placebo + GemCis (n=342)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any immune-mediated AE*	43 (12.7)	8 (2.4)	16 (4.7)	5 (1.5)
Hypothyroid events	20 (5.9)	0	5 (1.5)	0
Dermatitis/rash	12 (3.6)	3 (0.9)	1 (0.3)	0
Pneumonitis	3 (0.9)	1 (0.3)	2 (0.6)	1 (0.3)
Hepatic 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 adverse event 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.
AE, adverse event; GemCis, gemcitabine and cisplatin.

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Oh DY et al, NEJM Evid 2022
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Updated 3-year survival from TOPAZ



Extended long-term survivors
alive ≥30 months from randomization

Higher in Durvalumab group
17% vs 8.7%

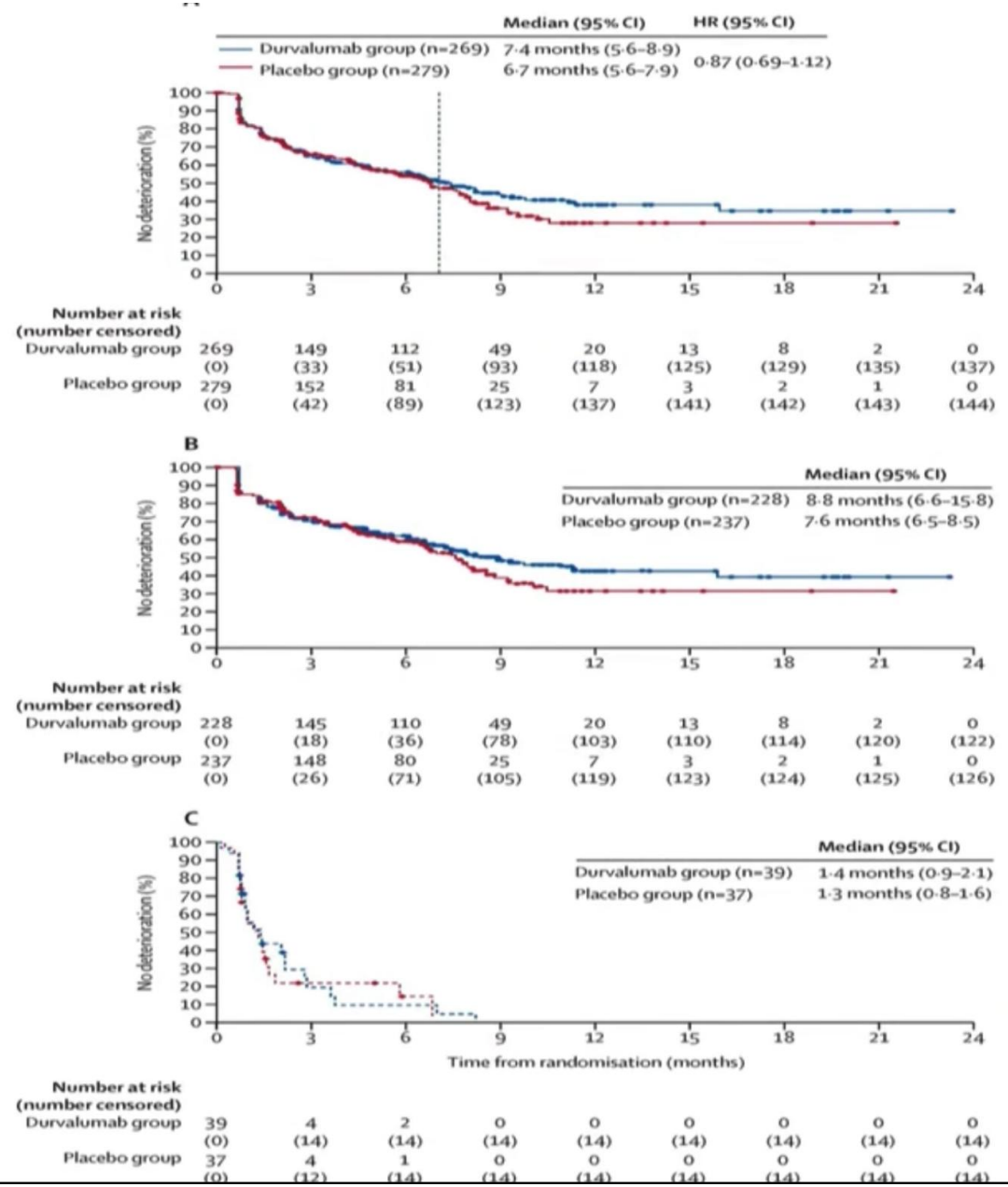
Included all clinically relevant subgroups

Oh DY et al, J of Hepatol 2025

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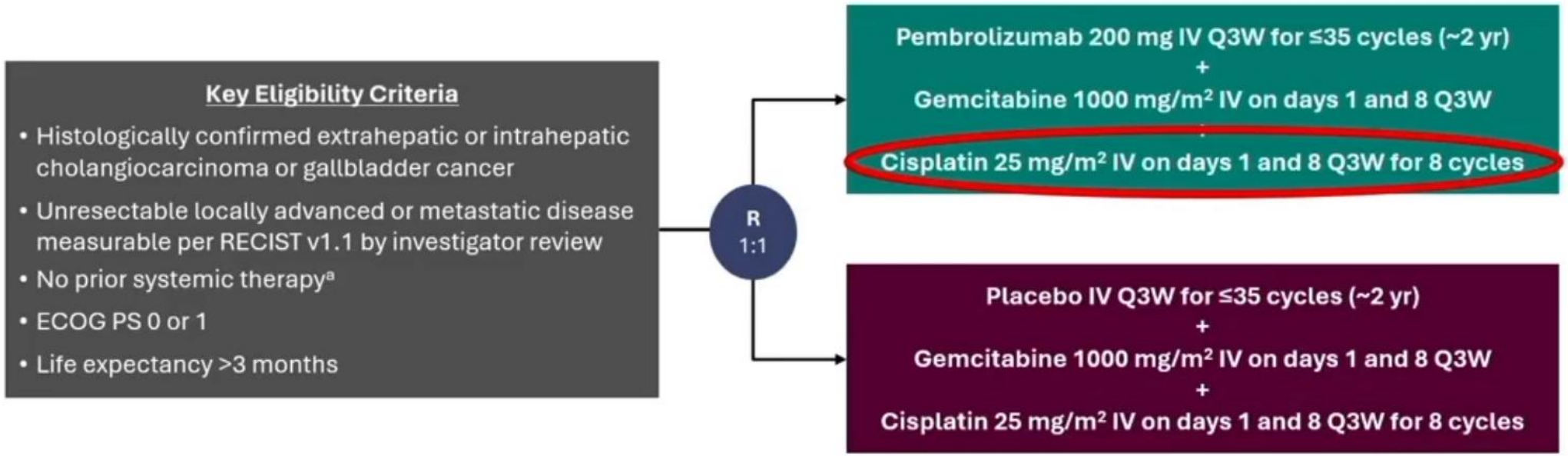
TOPAZ-1: QOL

- No difference in time to deterioration in global health status or quality of life, functioning, and symptoms
- Median time to deterioration of global health status or quality of life was 7·4 months (95% CI 5·6 to 8·9) in the durvalumab group and 6·7 months (5·6 to 7·9) in the placebo group (hazard ratio 0·87 [95% CI 0·69 to 1·12])
- Authors concluded that the addition of durvalumab to gemcitabine and cisplatin “did not have a detrimental effect on patient-reported outcomes”



Burris et al, Lancet Oncol 2024

KEYNOTE-966 Study Design
Randomized, Double-Blind, Phase 3 Trial



Stratification Factors
- Geographic region (Asia vs not Asia)
- Disease stage (locally advanced vs metastatic)
- Site of origin (extrahepatic vs gallbladder vs intrahepatic)

- **Primary End Point:** OS
- **Secondary End Points:** PFS, ORR, and DOR assessed per RECIST v1.1 by blinded, independent central review (BICR) and safety

Kelley RK et al, Lancet 2023

INTERNAL

Baseline Characteristics

	Pembro + Gem/Cis (n = 533)	Placebo + Gem/Cis (n = 536)
Median age (IQR), years	64 (57-71)	63 (55-70)
Male	280 (53%)	272 (51%)
Race		
American Indian or Alaska Native	2 (<1%)	1 (<1%)
Asian	245 (46%)	250 (47%)
Black or African American	11 (2%)	3 (1%)
Multiple	5 (1%)	2 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0
White	256 (48%)	268 (50%)
Missing	13 (2%)	12 (2%)
Geographic region		
Asia	242 (45%)	244 (46%)
Not Asia	291 (55%)	292 (54%)
ECOG PS 1	274 (51%)	308 (57%)

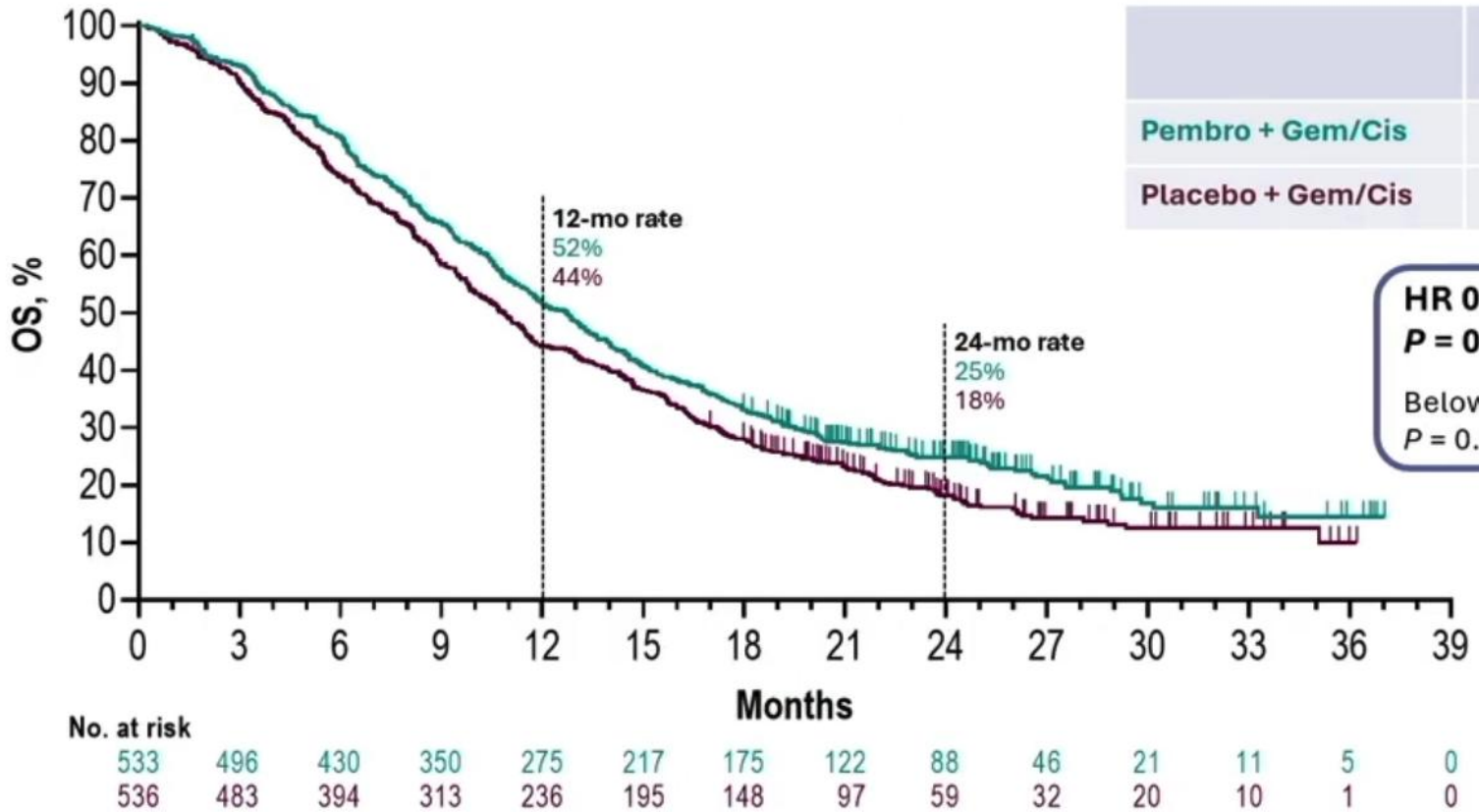
	Pembro + Gem/Cis (n = 533)	Placebo + Gem/Cis (n = 536)
Site of origin		
Extrahepatic	98 (18%)	105 (20%)
Gallbladder	115 (22%)	118 (22%)
Intrahepatic	320 (60%)	313 (58%)
Disease status		
Locally advanced	60 (11%)	66 (12%)
Metastatic	473 (89%)	470 (88%)
Biliary stent or drain	33 (6%)	41 (8%)
Prior neoadjuvant or adjuvant chemo	50 (9%)	48 (9%)
Antibiotics within 1 month of study start	291 (55%)	273 (51%)
MSI-H status[a]	6 (1%)	4 (1%)
PD-L1 CPS ≥1[b]	363 (68%)	365 (68%)
HBV infection[c]	164 (31%)	165 (31%)
HCV infection[d]	19 (4%)	14 (3%)

[a]94 (18%) in the pembro group and 110 (21%) in the placebo group had unknown MSI status. [b]57 (11%) in the pembro group and 61 (11%) in the placebo group had unknown PD-L1 CPS. [c]14 (3%) in the pembro group and 16 (3%) in the placebo group had chronic HBV infection (ie, HBsAg positive or HBV DNA ≥20 IU/mL). 150 (28%) and 149 (28%), respectively, had clinically resolved HBV infection (ie, HBsAg negative, anti-HBc positive, and HBV DNA <20 IU/mL). 3 (1%) and 5 (1%), respectively, had missing HBV status. [d]1 (<1%) in the pembro group and 1 (<1%) in the placebo group had active HCV infection (ie, anti-HCV positive with detectable HCV RNA). 18 (3%) and 13 (2%), respectively, had prior HCV infection (ie, anti-HCV positive with undetectable HCV RNA). 0 and 2 (<1%), respectively, had missing HCV status.
Data cutoff date: December 15, 2022.

INTERNAL

Kelley RK et al, Lancet 2023

Overall Survival at Final Analysis



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

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

Below the signficance boundary of *P* = 0.0200

Data cutoff date: December 15, 2022.

INTERNAL

Kelley RK et al, Lancet 2023

KEYNOTE-966: 3-Year Data

- Median follow-up: 36.6 months
- Comparable safety profiles for PEMBRO and placebo – no difference in grade 3-5 toxicity
- Median duration of response, months (range)
  - PEMBRO+GC: 8.3 (1.2+ to 44.3+)
  - Placebo+GC: 6.9 (1.1+ to 41.1+)

Overall Survival



Outcomes[a]	D+GC (n=341)	PBO+GC (n=344)
Median OS, months (95% CI)	12.7 (11.5-13.6)	10.9 (9.9-11.6)
OS HR, (95% CI)	0.86 (0.75-0.98), nominal *P* = .0099	

Keynote-966 Safety

	Pembrolizumab plus gemcitabine and cisplatin group (n=529)				Placebo plus gemcitabine and cisplatin group (n=534)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	73 (14%)	287 (54%)	133 (25%)	31 (6%)	83 (16%)	270 (51%)	130 (24%)	49 (9%)
Decreased neutrophil count	73 (14%)	167 (32%)	90 (17%)	0	74 (14%)	171 (32%)	82 (15%)	0
Anaemia	171 (32%)	150 (28%)	2 (<1%)	0	159 (30%)	150 (28%)	4 (1%)	0
Nausea	221 (42%)	12 (2%)	0	0	234 (44%)	12 (2%)	0	0
Decreased platelet count	117 (22%)	64 (12%)	30 (6%)	0	105 (20%)	67 (13%)	40 (7%)	0
Fatigue	161 (30%)	25 (5%)	1 (<1%)	0	150 (28%)	22 (4%)	0	0
Constipation	184 (35%)	2 (<1%)	0	0	187 (35%)	3 (1%)	0	0
Decreased appetite	137 (26%)	6 (1%)	1 (<1%)	0	140 (26%)	15 (3%)	0	0
Decreased white blood cell count	80 (15%)	57 (11%)	4 (1%)	0	80 (15%)	44 (8%)	3 (1%)	0
Pyrexia	127 (24%)	12 (2%)	0	0	99 (19%)	5 (1%)	0	0
Vomiting	108 (20%)	14 (3%)	0	0	121 (23%)	7 (1%)	0	0
Diarrhoea	92 (17%)	11 (2%)	0	0	87 (16%)	10 (2%)	0	1 (<1%)
Abdominal pain	82 (16%)	10 (2%)	0	0	103 (19%)	19 (4%)	0	0
Rash	87 (16%)	3 (1%)	0	0	47 (9%)	2 (<1%)	0	0
Increased aspartate aminotransferase	72 (14%)	16 (3%)	0	0	77 (14%)	19 (4%)	2 (<1%)	0
Increased alanine aminotransferase	75 (14%)	12 (2%)	0	0	99 (19%)	14 (3%)	0	0
Hypomagnesaemia	74 (14%)	5 (1%)	0	0	73 (14%)	5 (1%)	1 (<1%)	0
Pruritus	77 (15%)	0	0	0	51 (10%)	0	0	0
Asthenia	64 (12%)	10 (2%)	1 (<1%)	0	76 (14%)	19 (4%)	0	0
Peripheral oedema	73 (14%)	0	0	0	78 (15%)	7 (1%)	0	0

Data are n (%).

Kelley RK et al, Lancet 2023

Response by Regimen

TOPAZ

Investigator assessed %	Durvalumab + Gem-Cis	Placebo + Gem-Cis
ORR	26.7	18.7
CR	2.1	0.6
PR	24.6	18.1
DCR†	85.3	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)

KN-966

BICR %	Pembrolizumab + Gem-Cis	Placebo + Gem-Cis
ORR	29%	28%
CR	3%	2%
PR	27%	27%
DCR†	?	?

Median DOR (95% CI) at 1st Interim

Pembro + Gem/Cis: 9.7 mo (6.9-12.2)

Placebo + Gem/Cis: 6.9 mo (5.7-8.2)

INTERNAL

Other attempts to improve first-line outcomes

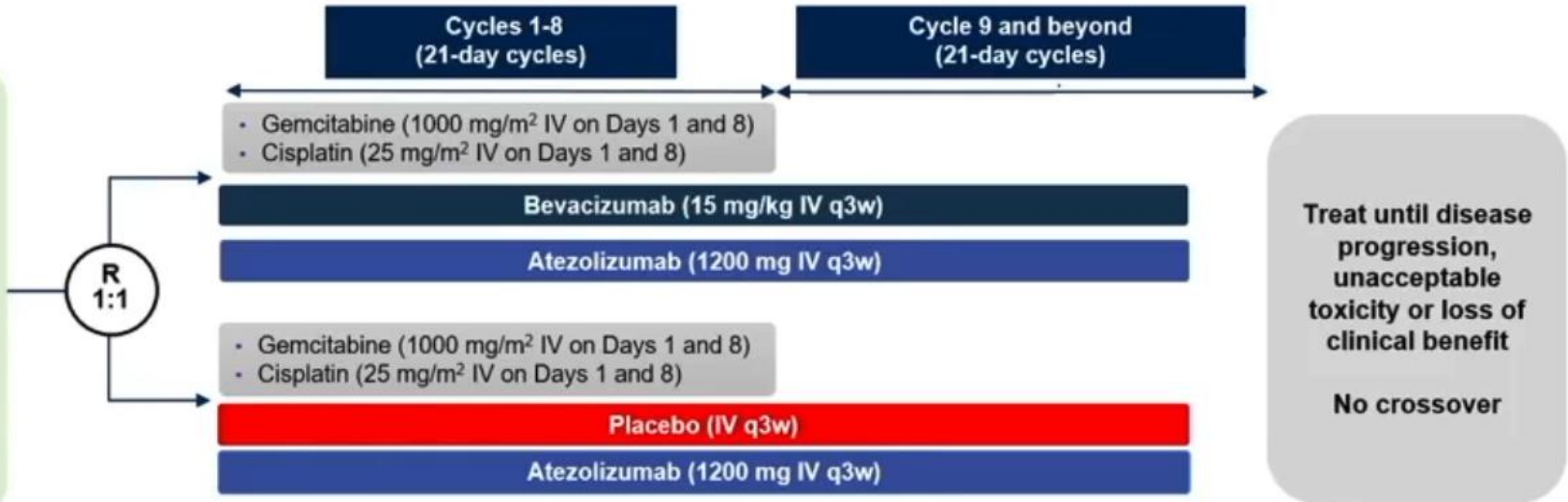
Addition of anti-VEGF therapy

Triplet chemotherapy

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.

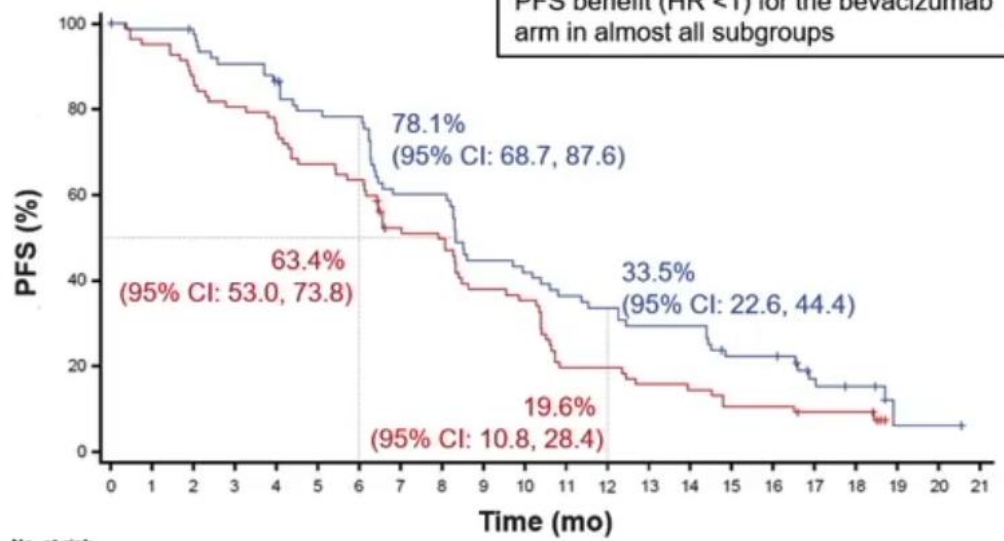
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Updated PFS and OS

Primary endpoint: PFS	Atezo + Bev + CisGem (n=79)[a]	Atezo + PBO + CisGem (n=83)
No. of events (%)	63 (80)	73 (88)
Median PFS (95% CI), mo	8.3 (6.8, 10.6)	7.9 (6.2, 8.5)
Stratified HR[b] (95% CI)	0.67 (0.46, 0.95)	

Secondary endpoint: OS	Atezo + Bev + CisGem (n=79)[a]	Atezo + PBO + CisGem (n=83)
No. of events (%)	47 (59)	48 (58)
Median OS (95% CI), mo	14.9 (11.6, 18.0)	14.6 (11.2, NE)
Stratified HR[b] (95% CI)	0.97 (0.64, 1.47)	

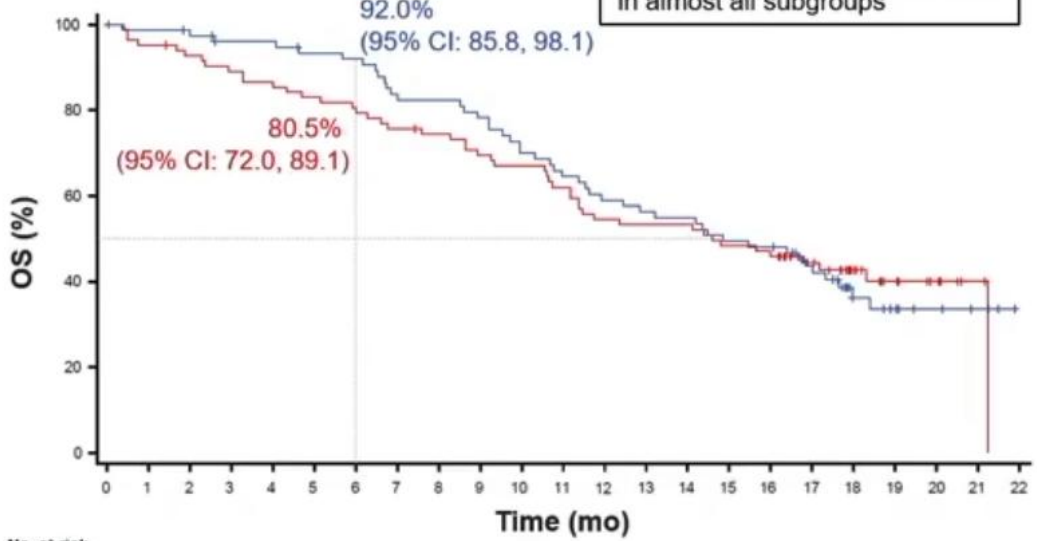
Descriptive subgroup analysis showed a PFS benefit (HR <1) for the bevacizumab arm in almost all subgroups



No. at risk

Atezo + Bev + CisGem	78	74	73	67	63	57	56	43	43	32	30	26	24	21	21	15	15	9	7	1	1	NE
Atezo + PBO + CisGem	83	78	72	66	63	55	52	40	38	29	27	15	15	12	11	8	8	6	6	NE	NE	NE

Similar HR for OS was observed in almost all subgroups



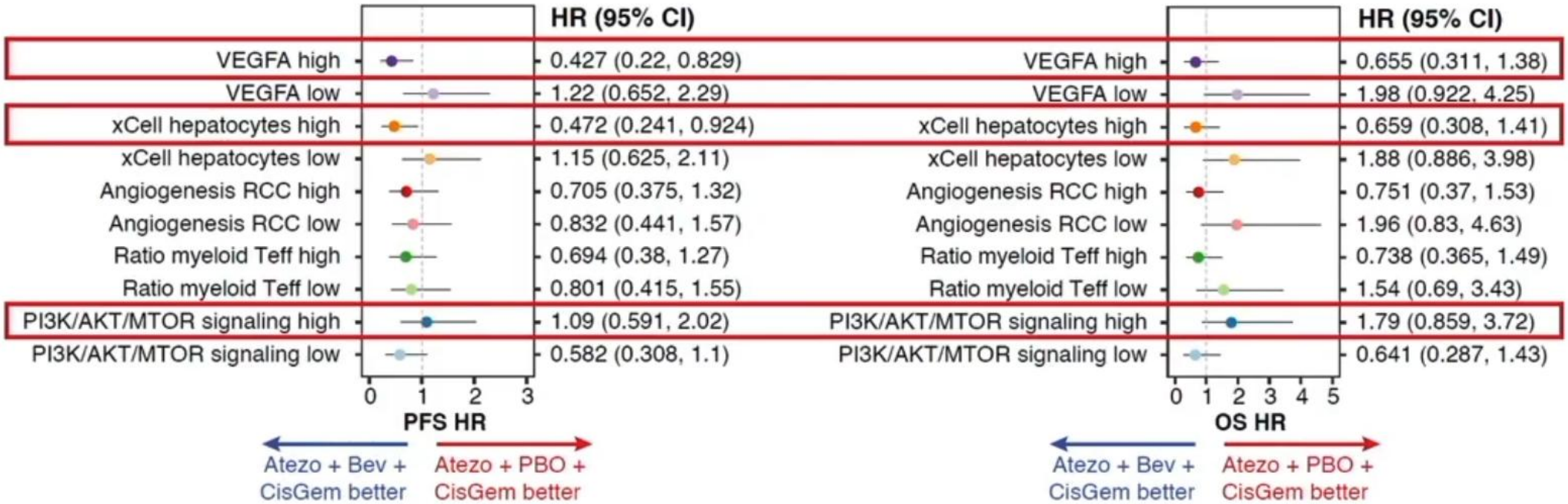
No. at risk

Atezo + Bev + CisGem	78	76	75	71	71	68	67	60	60	57	51	47	43	41	40	36	35	28	14	11	6	4	NE
Atezo + PBO + CisGem	83	79	76	73	71	68	66	62	60	56	54	50	44	43	43	39	38	28	19	11	7	2	NE

Median follow-up duration: 18.8 mo. Clinical cutoff: Jan 16, 2023. CI, confidence interval; NE, not estimable.
[a] A patient with a missing death date was excluded from the Kaplan-Meier curve. [b] Stratified analysis. Stratification factors are location of primary tumor (iCCA vs eCCA vs GBC) and geographic region (Asia vs rest of world).

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Exploratory endpoint: Gene expression and signatures



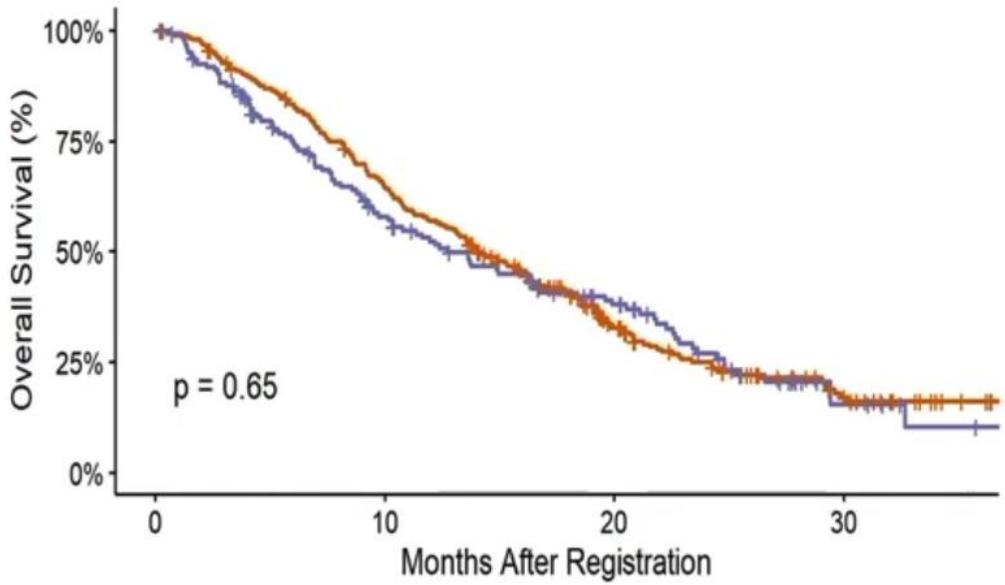
- High VEGFA gene expression and enrichment of hepatocytes may be associated with longer PFS and OS in patients treated with Atezo + Bev + CisGem
- High PI3K/AKT/MTOR pathway activation may be associated with less clinical benefit in the Atezo + Bev + CisGem arm compared with the Atezo + PBO + CisGem arm

Median follow-up duration: 18.8 mo. Clinical cutoff: Jan 16, 2023.

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INTERNAL

SWOG 1815: A Phase III Randomized Trial of Gemcitabine, Cisplatin, and Nab-Paclitaxel versus Gemcitabine and Cisplatin in Newly Diagnosed, Advanced Biliary Tract Cancers

Arm	Median (CI)
GCN	14.0 mths (12.6-16.3)
GC	12.7 mths (9.5-16.6)



OS by stage of disease

Disease Stage	GCN (mths)	GC (mths)
Locally-Advanced	19.2	13.7
Metastatic	13.1	12.7

Response by stage of disease

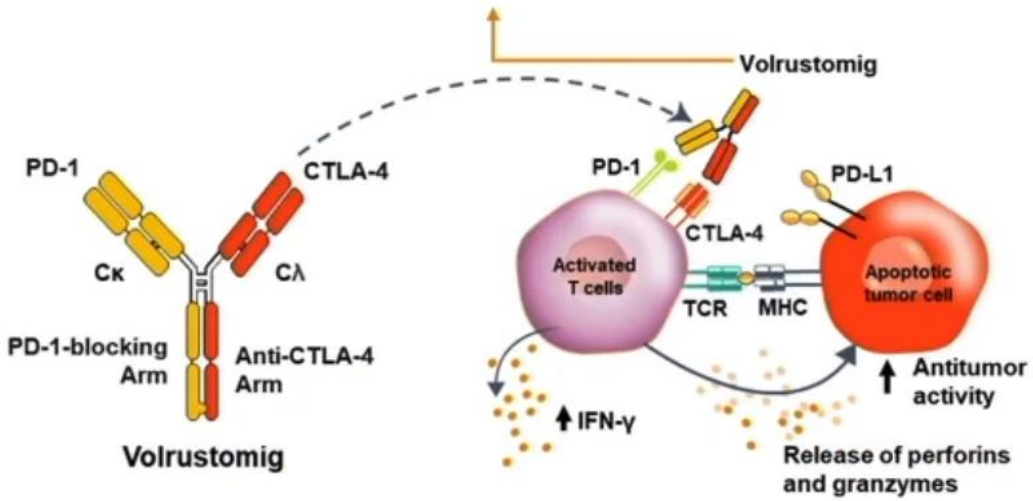
	GCN		GC	
Locally-Advanced	N (74)	%	N (40)	%
Overall Response	20	28	5	21
Disease Control Rate	36	87	16	69

Data in locally advanced disease is hypothesis generating: possible role in peri-operative setting?

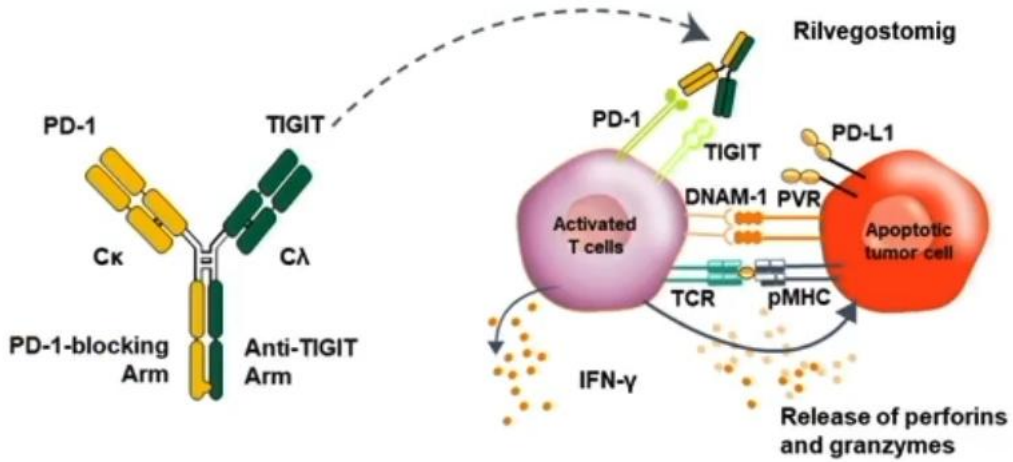
Shroff R et al, GI Cancers Symposium 2023

Expanding checkpoint inhibition beyond PD-1/PD-L1

Volrustomig-Anti-PD-1/Anti-CTLA-4 bispecific antibody



Rilvegostomig-Anti-PD-1/Anti-TIGIT bispecific antibody



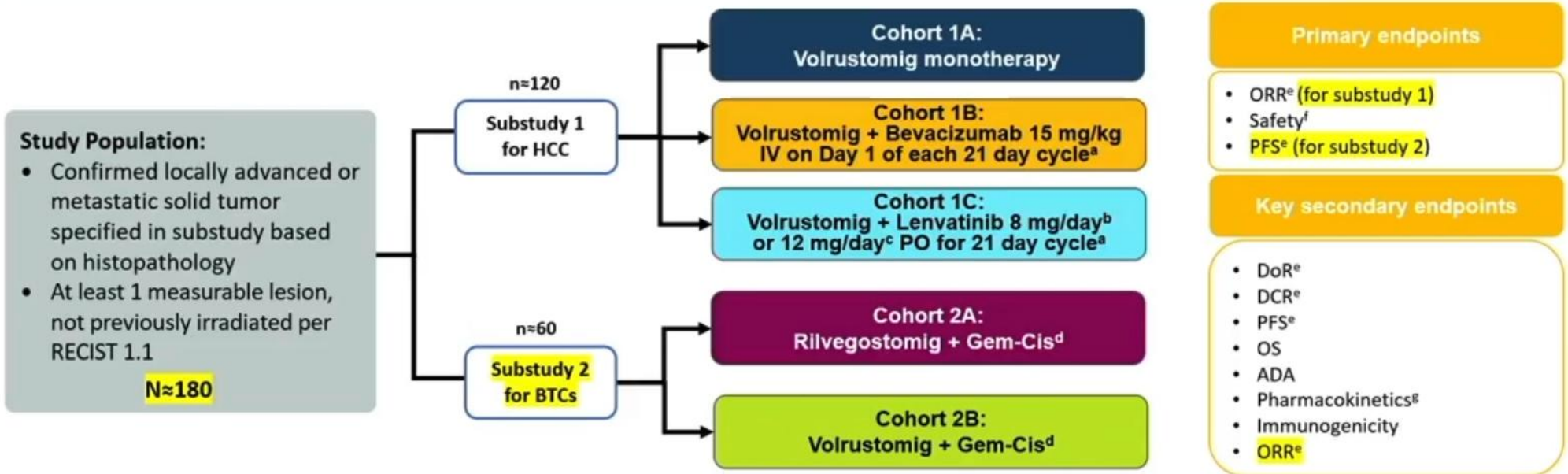
INTERNAL

GEMINI-HPB: Study Design

MoA: Volrustomig | MoA: Rilvegostomig

Phase II, non-randomized, open-label, uncontrolled, multicenter, global study

To evaluate the preliminary efficacy, safety tolerability of volrustomig as monotherapy and volrustomig or rilvegostomig in combination with anticancer agentands in patients with advanced hepatobiliary cancer (HCC, BTCs, etc.)



Primary endpoints

- ORR[e] (for substudy 1)
- Safety[f]
- PFS[e] (for substudy 2)

Key secondary endpoints

- DoR[e]
- DCR[e]
- PFS[e]
- OS
- ADA
- Pharmacokinetics[g]
- Immunogenicity
- ORR[e]

INTERNAL

Summary 1

- Checkpoint inhibitors targeting PD-1 or PD-L1 in combination with gemcitabine and cisplatin resulted in improved outcomes for first-line biliary tract cancers
  - Incremental but modest benefit
- Triplet chemotherapy with gemcitabine, cisplatin, and nab-paclitaxel did not improve OS; there is a possible benefit in a subset of patient groups
  - Potential future role in locally advanced, neoadjuvant setting?
- Addition of anti-VEGF therapy improved PFS and appears to benefit a subset of patients
  - Not powered for OS
  - Provides rational for PD-1/VEGF bispecifics in first line setting
- Ongoing trials evaluating bispecifics (TIGIT/PD1, CTLA4/PD1)

Back to our case

- Gem /cis plus durvalumab (PR)

Followed by durvalumab maintenance for 9 month

At 12-month progression of disease was noted

What to do next ?

- Conventional Chemo

- Driver driven therapy

Molecular Genetics of Biliary Tract Cancers by Anatomic Location

Actionable Alterations

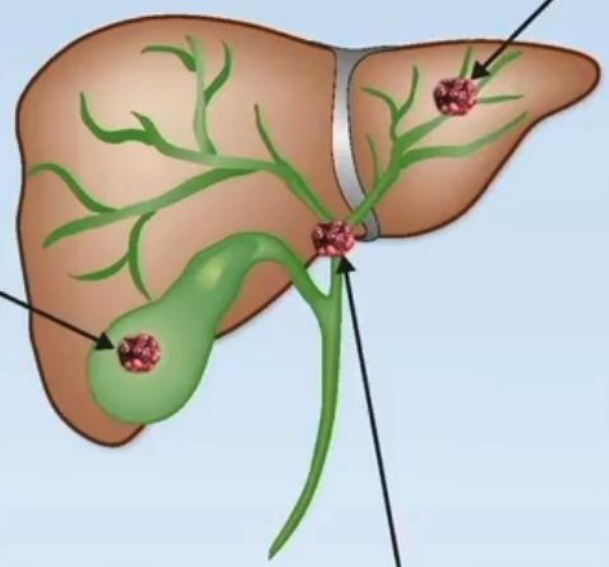
40-50% ICC

10-20% ECC

20-30% GBCA

Available Therapies in BTC

BTC Therapies in Trials



GBCA

- *TP53* mutation (47.1–59%)
- *ERBB2/3* amplification (9.8–19%)
- *CDKN2A/B* loss (5.9–19%)
- *ARID1A* mutation (13%)
- *KRAS* mutation (4–13%)
- *PIK3CA* mutation (5.9–12.5%)
- *NRAS* mutation (6.3%)
- *BRAF* mutation (1–5.9%)
- *AKAP11* mutation (5.9%)
- *FBXW7* mutation (5.9%)
- *GNAS* mutation (5.9%)
- *LAMA2* mutation (5.9%)
- *CSMD3* mutation (5.9%)
- *RNF43* mutation (3.9%)
- *SF3B1* mutation (3.9%)
- *BRCA1* mutation (3.9%)
- *SMARCB1* mutation (3.9%)
- *MAP2K4* mutation (3.9%)
- *CPNE4* mutation (3.9%)
- *POLE* mutation (3.9%)
- *GLTSCLR1* mutation (3.9%)
- *NALCN* mutation (3.9%)
- *ARID1B* mutation (3.9%)
- *NF1* mutation (3.9%)
- *RB1* mutation (3.9%)
- *SMAD* 4 mutation (3.9%)
- *EGFR* mutation (3.9%)
- *FLG* mutation (3.9%)
- *FGFR1–3* fusions, mutations and amplifications (3%)
- *RGPD3* mutation (2%)
- *IDH1/2* mutation (1.5%)

ECC

- *KRAS* mutation (8.3–42%)
- *TP53* mutation (40%)
- *SMAD4* mutation (21%)
- *CDKN2A/B* loss (17%)
- *ERBB2/3* amplification (11–17%)
- *ARID1A* mutations (12%)
- *IDH1/2* mutation (0–7.4%)
- *PIK3CA* mutation (7%)
- *MET* mutation (3.7%)
- *BRAF* mutations (3%)
- *MET* amplification (1%)

ICC

- *FGFR1–3* fusions, mutations and amplifications (11–45%)
- *TP53* mutation (2.5–44.4%)
- *IDH1/2* mutation (4.9–36%)
- *ARID1A* mutations (6.9–36%)
- *CDKN2A/B* loss (5.6–25.9%)
- *KRAS* mutation (8.6–24.2%)
- *MCL1* amplifications (21%)
- *SMAD4* mutation (3.9–16.7%)
- *MLL3* mutation (14.8%)
- *BAP1* mutation (13.0%)
- *PTEN* mutation (0.6–11%)
- *ARAF* mutation (11%)
- *RNF43* mutation (9.3%)
- *ROBO2* mutation (9.3%)
- *GNAS* mutation (9.3%)
- *PIK3CA* mutations (3–9%)
- *BRAF* mutations (3–7.1%)
- *ERBB3* amplification (7%)
- *MET* amplification (2–7%)
- *NRAS* mutation (1.5–7%)
- *CDK6* mutation (7%)
- *ERBB3* mutation (7%)
- *PEG3* mutation (5.6%)
- *XIRP* mutation (5.6%)
- *RB1* mutation (5.0%)
- *MET* mutation (4.7%)
- *BRCA1/2* mutation (4%)
- *NF1* mutation (4%)
- *TSC1* mutation (4%)
- *RADIL* mutation (3.7%)
- *NDC80* mutation (3.7%)
- *PCDHA13* mutation (3.7%)
- *LAMA2* mutation (3.7%)
- *EGFR* mutation (1.5–2%)
- *CTNNB1* mutation (0.6^)

Valle JW et al. *Cancer Discov.* 7(9):943-962.

Second line

ABC-06 study design

Phase III, randomised, open-label

Inclusion criteria

- Histo/cytologically verified **advanced BTC**

  ECOG performance score 0-1

  Progression after 1st-line CisGem
- Max **6 weeks progression to randomisation**
- Adequate haematological, renal & hepatic function

R

Arm A

Active Symptom Control (ASC)

- May include: biliary drainage, antibiotics, analgesia, steroids, anti-emetics etc
- 4-weekly clinical review

Arm B

Active Symptom Control + mFOLFOX

- Chemotherapy every 14 days for up to 12 cycles
- Day 1: Oxaliplatin 85mg/m^2, L-folinic acid 175 mg (or folinic acid 350 mg), 5 FU 400 mg/m^2 (bolus), 5 FU 2400 mg/m^2 46 hours continuous infusion
- 4-weekly clinical review after chemotherapy
- 3-monthly radiological assessment

Follow up

- **Overall survival** = primary end-point
- Until death or until completion of 12 months after enrolment of the final patient (whichever happened first)

Platinum sensitivity (yes vs. no; determined from first-line CisGem*)
Serum albumin (<35 vs. ≥35 g/L)
Stage (locally advanced vs. metastatic disease)

*determined from first-line CisGem: sensitive (progression after three months (90 days) of day 1 of the last cycle of 1st-line CisGem), refractory (progression during 1st line CisGem), resistant (progression within the first three months (90 days) after completion of day 1 of the last cycle of 1st line CisGem). CisGem: cisplatin and gemcitabine; BTC: biliary tract cancer; ECOG: Eastern Cooperative Oncology Group

SWOG CANCER RESEARCH NETWORK

INTERNAL

Lamarca A, et al, ASCO 2019

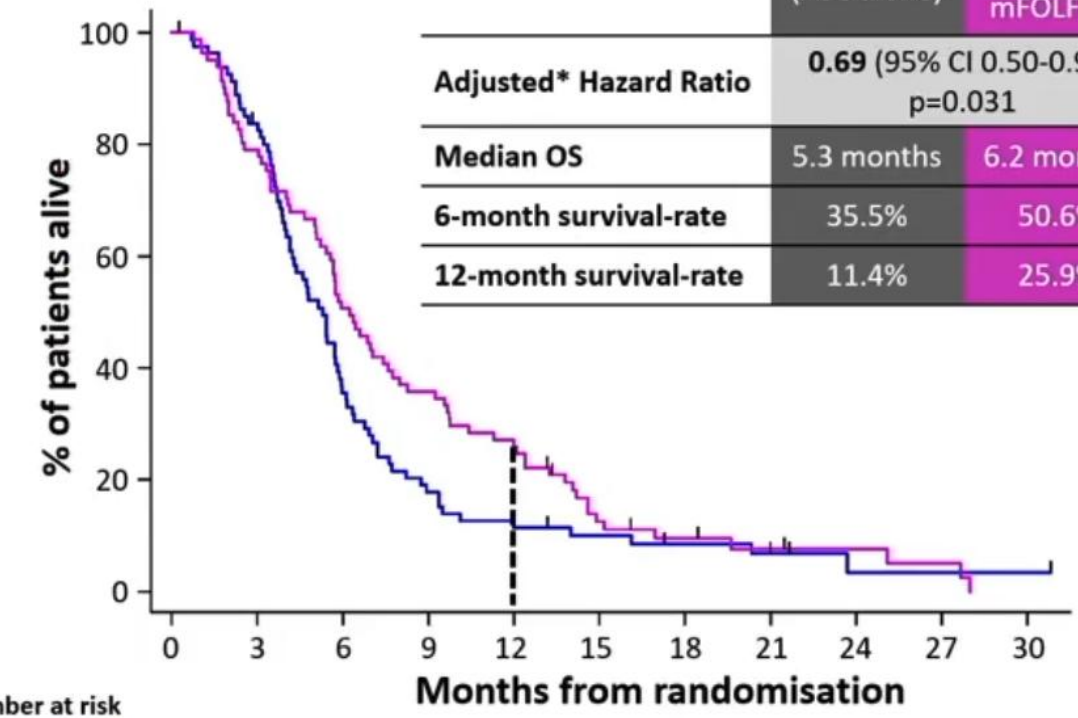
NCI National Clinical Trials Network NCI Community Oncology Research Program

Primary end-point: Overall Survival (ITT)

- The **primary end-point was met**: adjusted* HR was 0.69 (95% CI 0.50-0.97; p=0.031) for OS in favour of ASC + mFOLFOX arm (vs ASC)

- No marked evidence was identified against the key proportional hazards assumption**; which confirmed the validity of using the Cox Regression analysis

Overall survival by trial arm



	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

*adjusted for platinum sensitivity, albumin and stage
**proportional hazards assumption test p-value 0.6521
ITT: intention-to-treat analysis; ASC: active symptom control

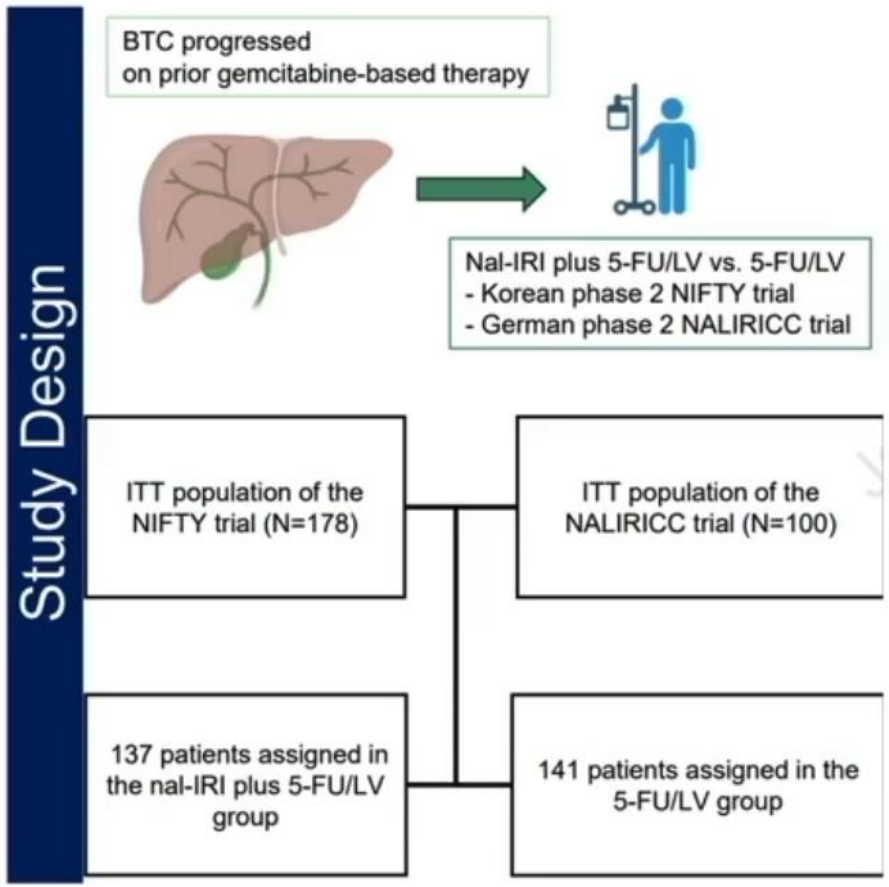
Modest Benefit of Second-Line Chemotherapy in BTC

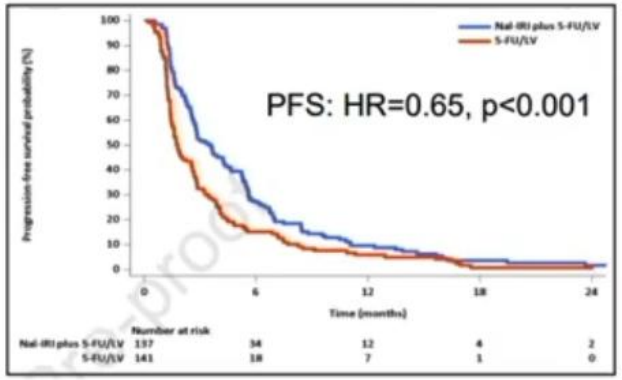
	ABC-06 FOLFOX vs Active Symptom Control (N = 162)	NIFTY 5-FU/LV/Nal-Iri vs 5-FU/LV (N = 174)	NALIRICC 5-FU/LV/Nal-Iri vs 5-FU/LV (N = 174)
	Phase 3	**Phase 2**	**Phase 2**
Primary Endpoint	**OS**	**PFS**	**PFS**
Median OS, mo, HR (95% CI)	6.2 vs 5.3 mo HR 0.69 (0.50-0.97) p=0.031	8.6 vs 5.3 mo HR 0.68 (0.48–0.95) p=0.02	6.90 vs 8.21 mo HR 1.082 (0.681-1.720)
Median PFS, mo, HR (95% CI)	4.0 mo	4.2 vs 1.7 mo HR 0.61 (0.44–0.86) p=0.004	2.64 vs 2.30 mo HR 0.867 (0.559-1.345)
ORR, %	5% (DCR 33%)	12.5% vs 3.5% p=0.043	14.3% vs 3.9%

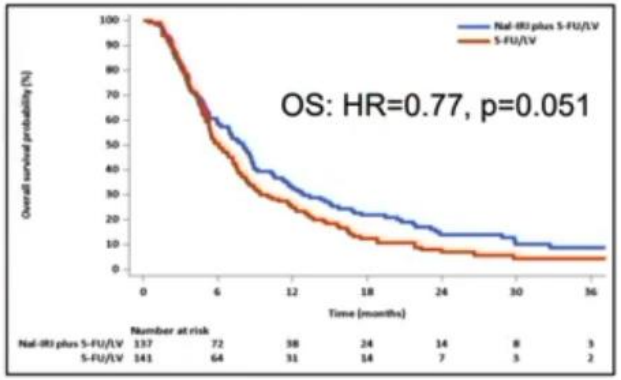
Lamarca A et al. *Lancet Oncol.* 2021;22(5):690-701; Yoo C et al. *Lancet Oncol.* 2021;22(11):1560-1572; Vogel A et al. ESMO 2022. Abstract 53MO.

INTERNAL

Pooled Analysis of NIFTY and NALIRICC

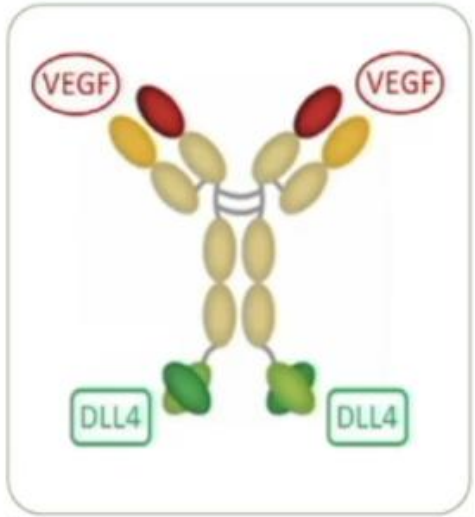




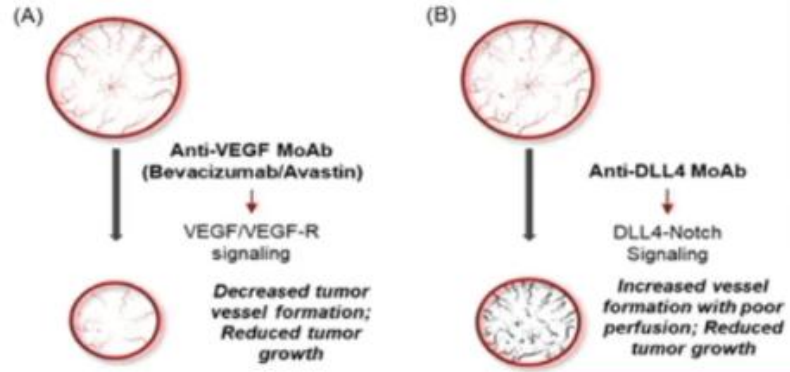


Woo C et al, J Hepatol 2025

CTX-009

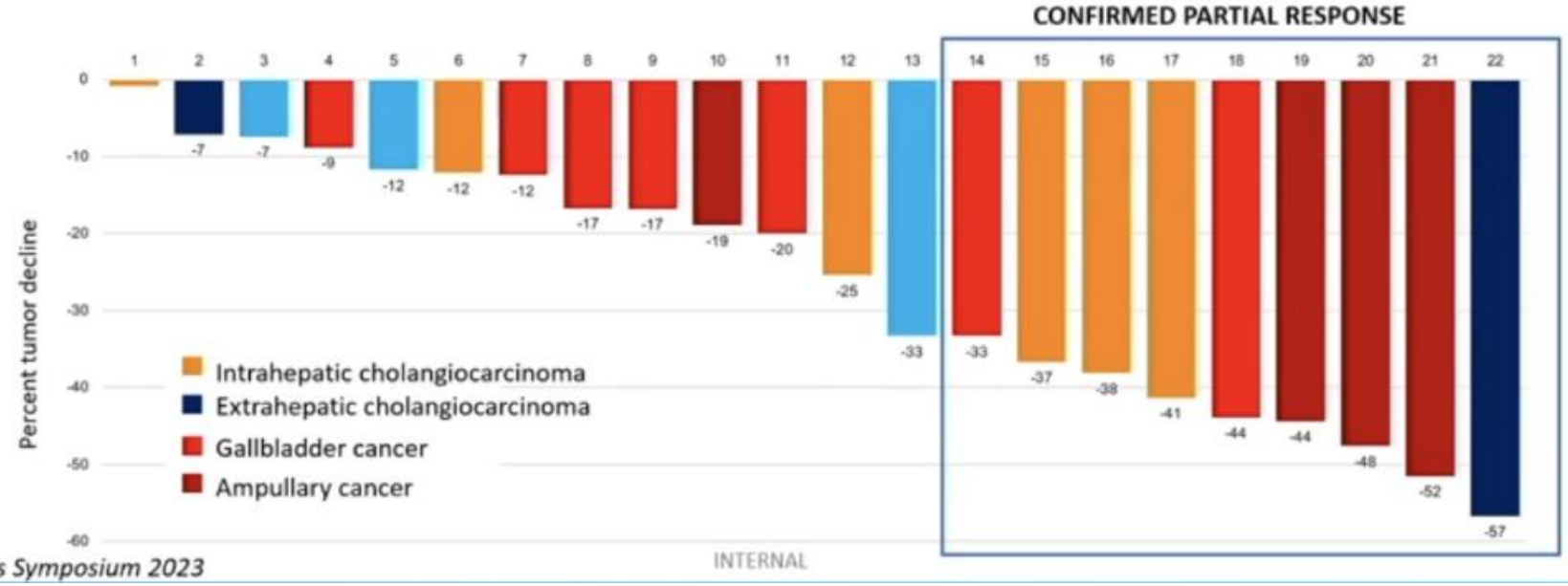


Dual blockade of DLL4 and VEGF overcomes VEGF resistance



ORR = 37.5%
CBR = 91.5%

Phase Ib: CTX-009 and paclitaxel

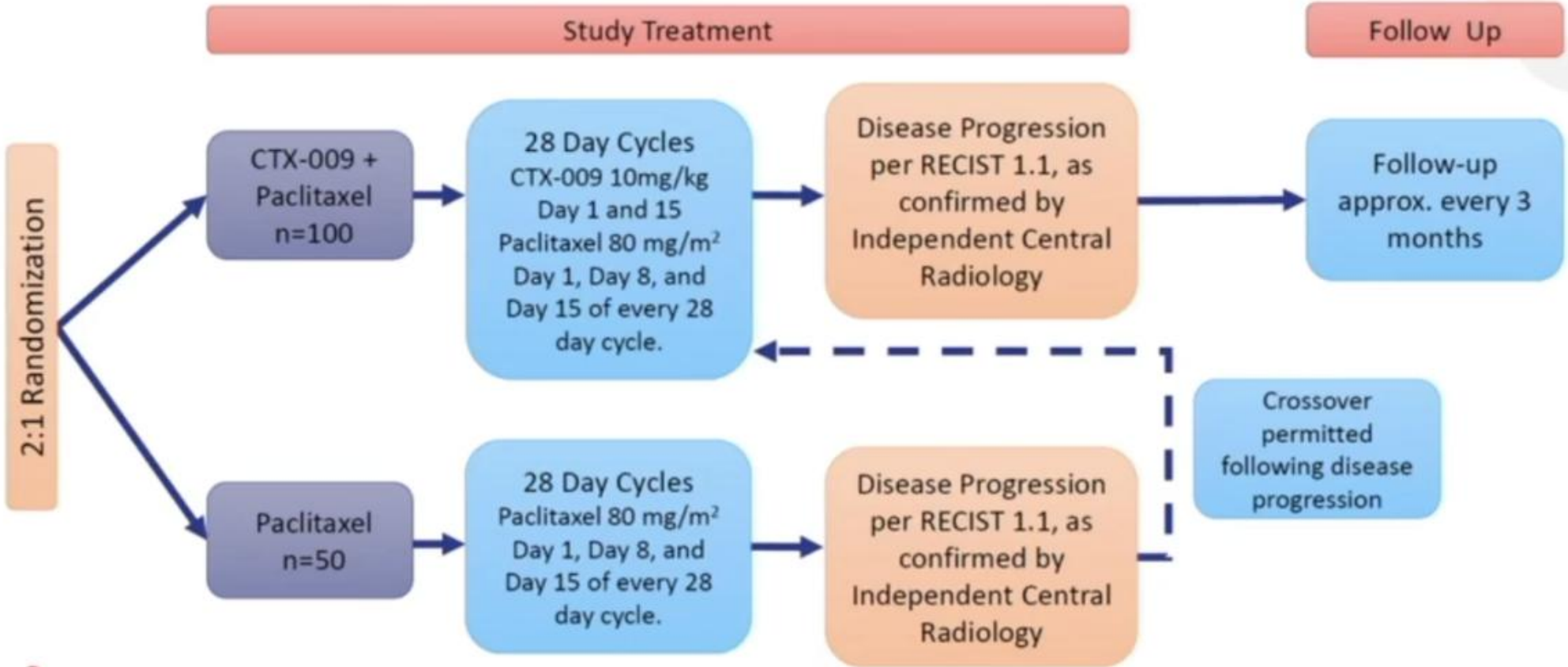


Oh DY et al, ASCO GI Cancers Symposium 2023

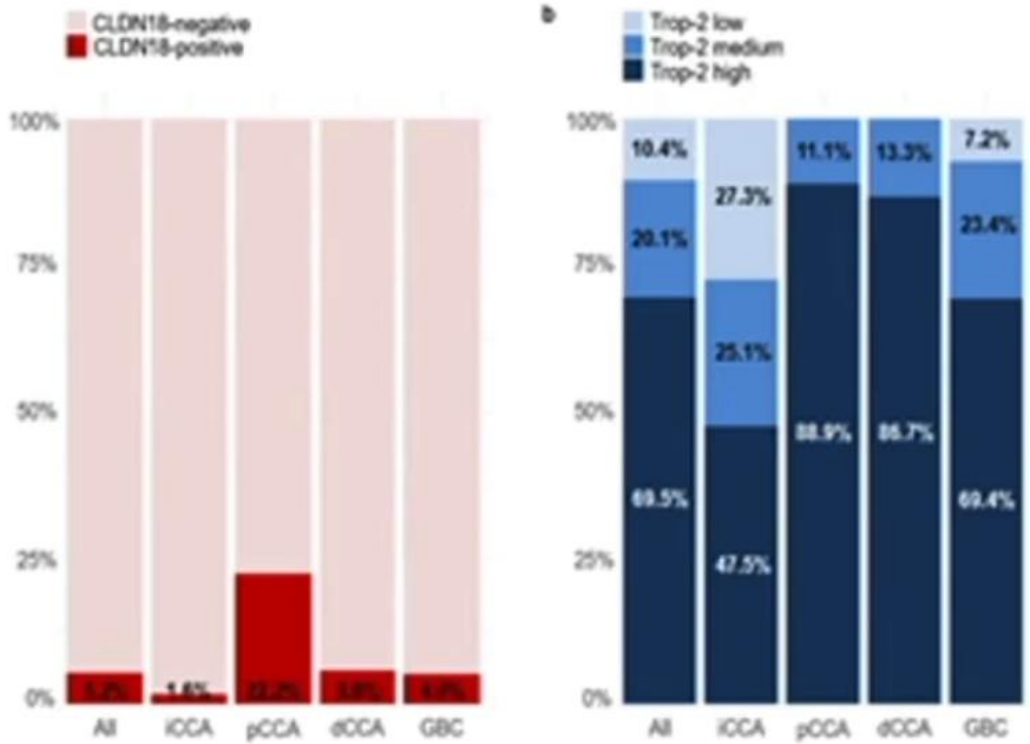
INTERNAL

Phase 2/3 U.S. BTC Study Design

Patients who have received one prior line of therapy

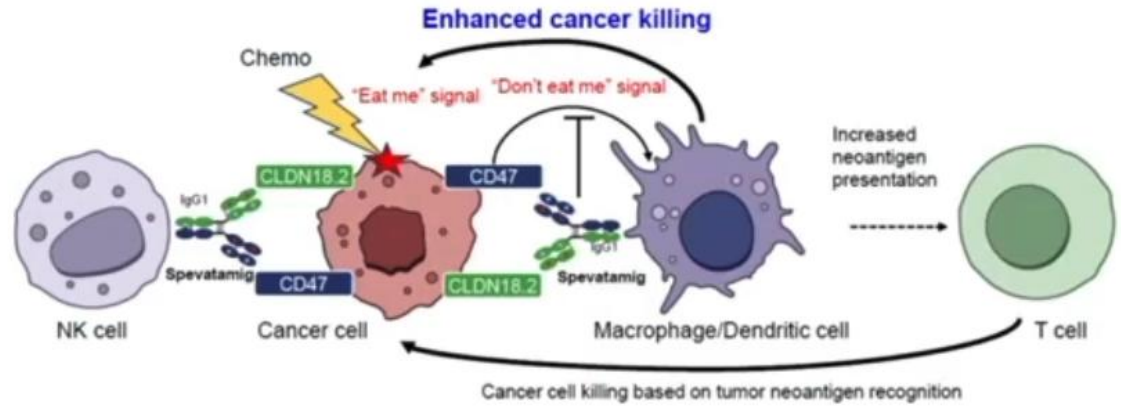


Novel and Emerging Targets for Biliary Tract Cancers



Shin Y et al, ASCO GI Cancers Symposium 2026

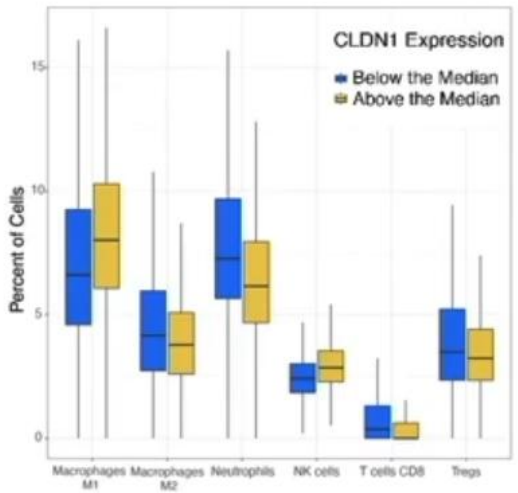
Spevatamig (PT886) Bispecific antibody targeting CD47 and Claudin 18.2
TWINPEAK study: NCT05482893



INTERNAL

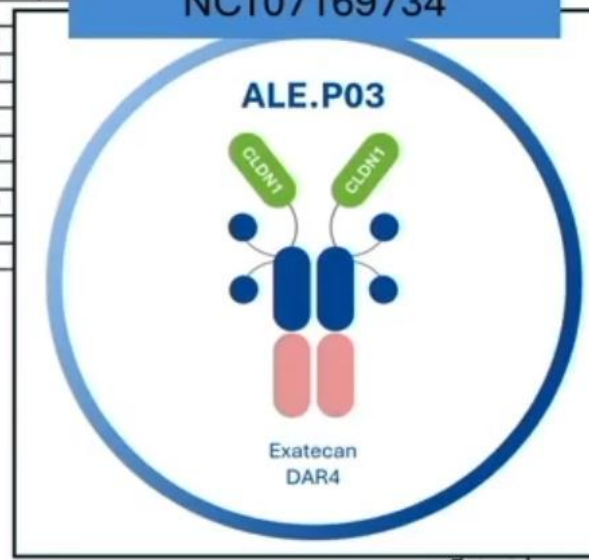
Novel and emerging targets for Biliary Tract Cancers: Claudin-1

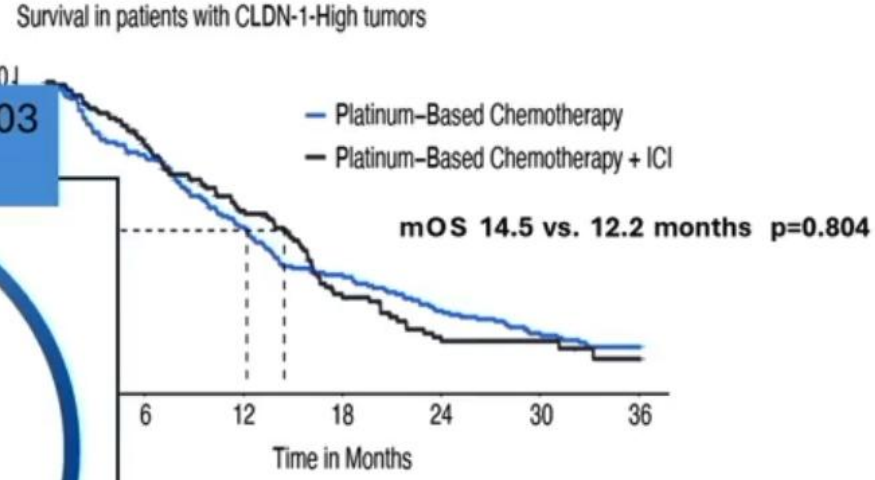
TUMOR CHARACTERISTICS | CLINICAL OUTCOMES	CLDN-L	CLDN-H	OVERALL	p-value
Biliary Tract Cancer (BTC) Subtype				
IHCC	294 (31%)	680 (72%)	974 (51%)	
EHCC	212 (22%)	50 (5.3%)	262 (14%)	
Gallbladder	324 (34%)	93 (9.8%)	417 (22%)	
Cholangiocarcinoma NOS	118 (12%)	126 (13%)	244 (13%)	
First-Line Therapy				
Chemotherapy	167 (50%)	171 (53%)	338 (52%)	
Chemotherapy + IO	165 (50%)	150 (47%)	315 (48%)	
Best Response (by 90 Days)				
Complete Response	6 (3.1%)	0 (0%)	6 (1.6%)	
Partial Response	61 (31%)	45 (26%)	106 (29%)	
Stable Disease	44 (23%)	49 (29%)	93 (26%)	
Progressive Disease	83 (43%)	76 (45%)	159 (44%)	
Median Overall Survival (OS) (months)				
	10.2 mths	12.2 mths		

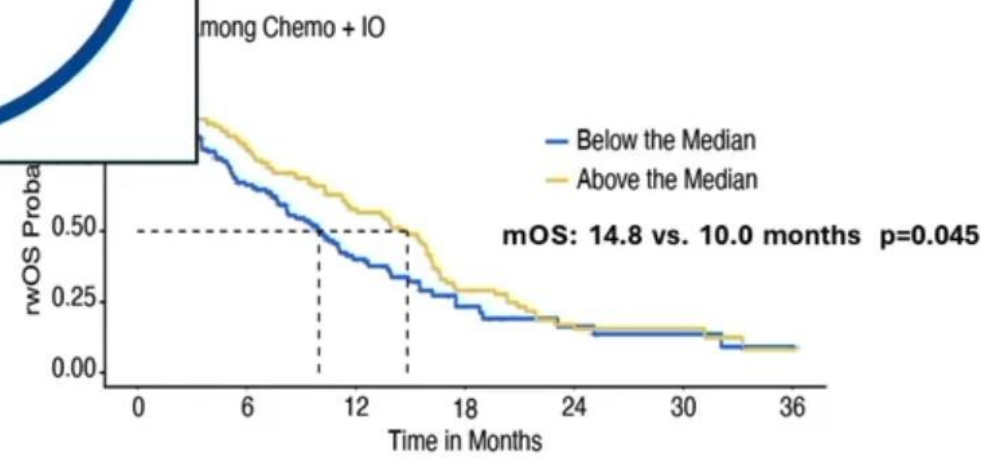


CLDN1-H expression was associated with a significantly higher percentage of M1 macrophages and NK cells and lower M2 macrophages, CD8 T-cells, Tregs and neutrophils (all $p < 0.001$).
There was no difference in *PDL1* (*22c3*) status by *CLDN1* expression.

Phase I study of ALE.P03
NCT07169734







Hanna D et al, ASCO GI Cancers Symposium 2026

Summary 2 and Conclusions

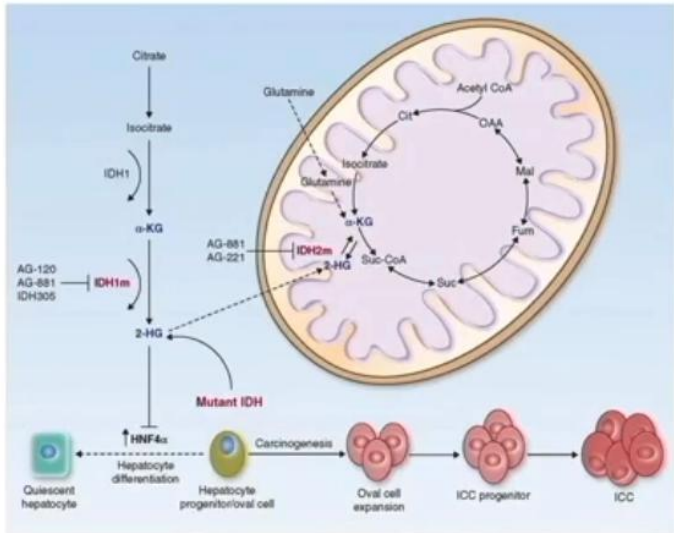
- Chemotherapy benefit in second line and beyond is limited
  - FOLFOX
  - Irinotecan or NalIRI
  - ? Paclitaxel
- Looking forward to survival outcomes from Tovecimig (CTX-009) trial
- Multiple novel and emerging targets
  - Antibody drug conjugates
  - Bispecifics and cell engagers

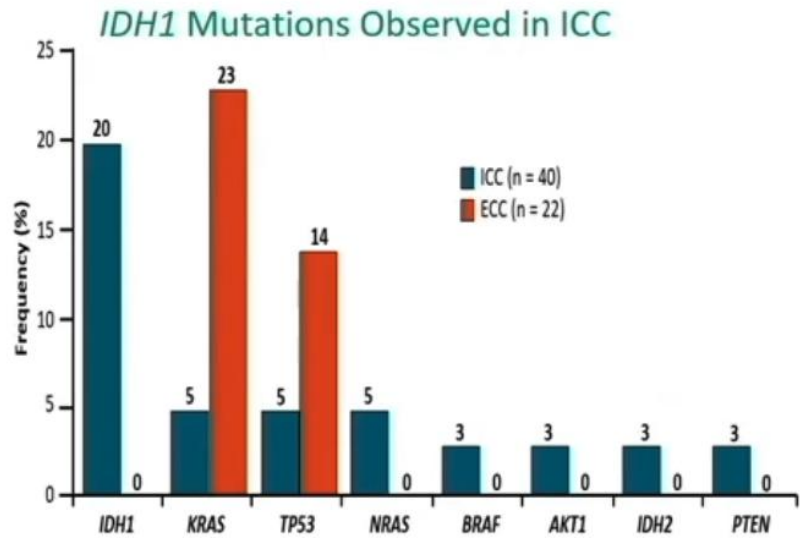
- Improved outcomes with targeted therapies for molecular subsets

Biomarker-Driven Therapy in Biliary Tract Cancer

BTC –Targeting IDH-1

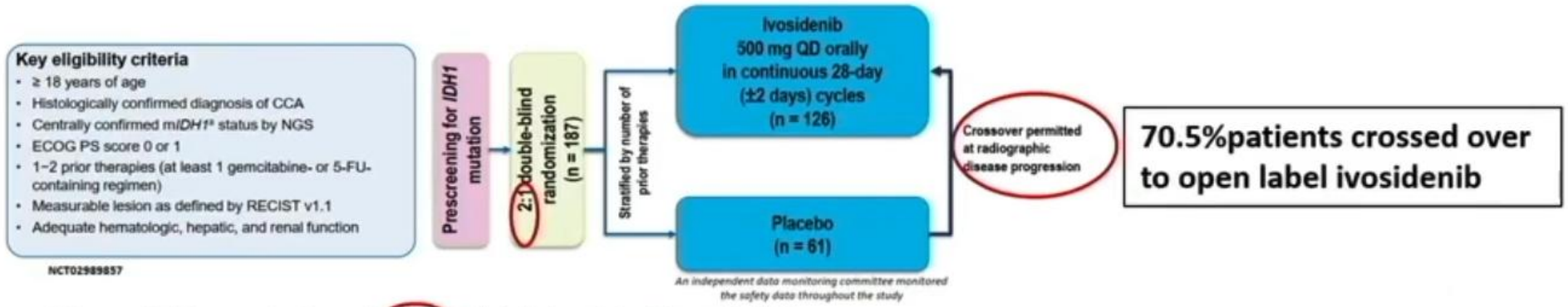
- IDH1 mutations occur in up to 20% of iCCA
- Accumulation of oncometabolite d-2-HG which promotes oncogenesis
- Prognostic value in glioma, not clear in BTC
- Ivosidenib (AG-120) is a first in class, oral, small-molecule inhibitor of mutant IDH1





Valle et al. Cancer Discov. 2017;7(9):943-962: Borger. Oncologist. 2012;17:72.

BTC –Targeting IDH-1, ClarIDy study



70.5%patients crossed over to open label ivosidenib

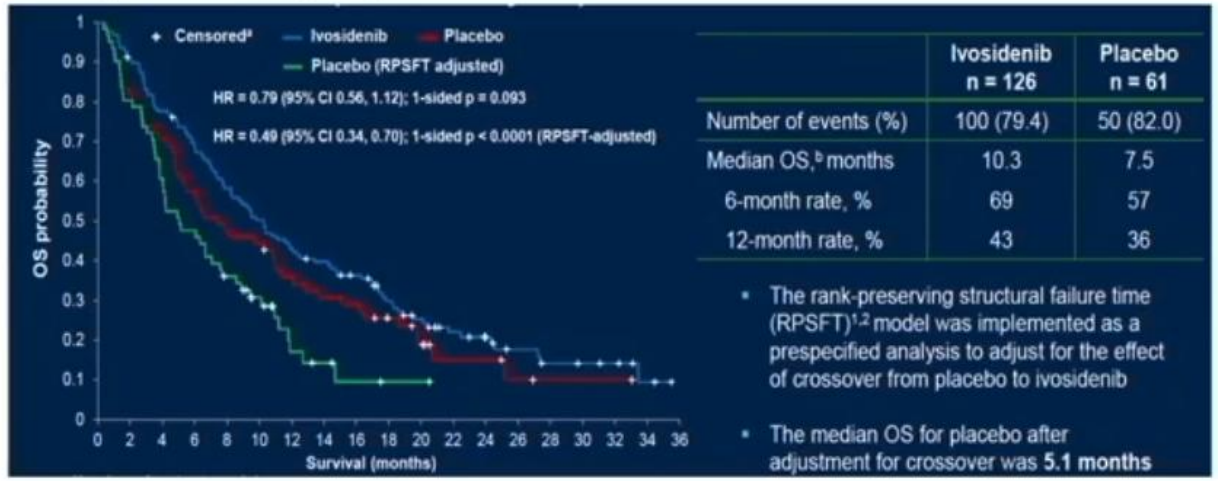
- **Primary endpoint:** progression-free survival (PFS) by blinded independent radiology center (IRC)
- **Key secondary endpoints:** overall survival (OS); objective response rate; PFS by local review; pharmacokinetics/pharmacodynamics; health-related quality of life (HRQOL)[b]; safety and tolerability

PFS (final analysis)



	Ivosidenib	Placebo
PFS[a]		
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)

OS (final analysis)



	Ivosidenib n = 126	Placebo n = 61
Number of events (%)	100 (79.4)	50 (82.0)
Median OS,[b] months	10.3	7.5
6-month rate, %	69	57
12-month rate, %	43	36

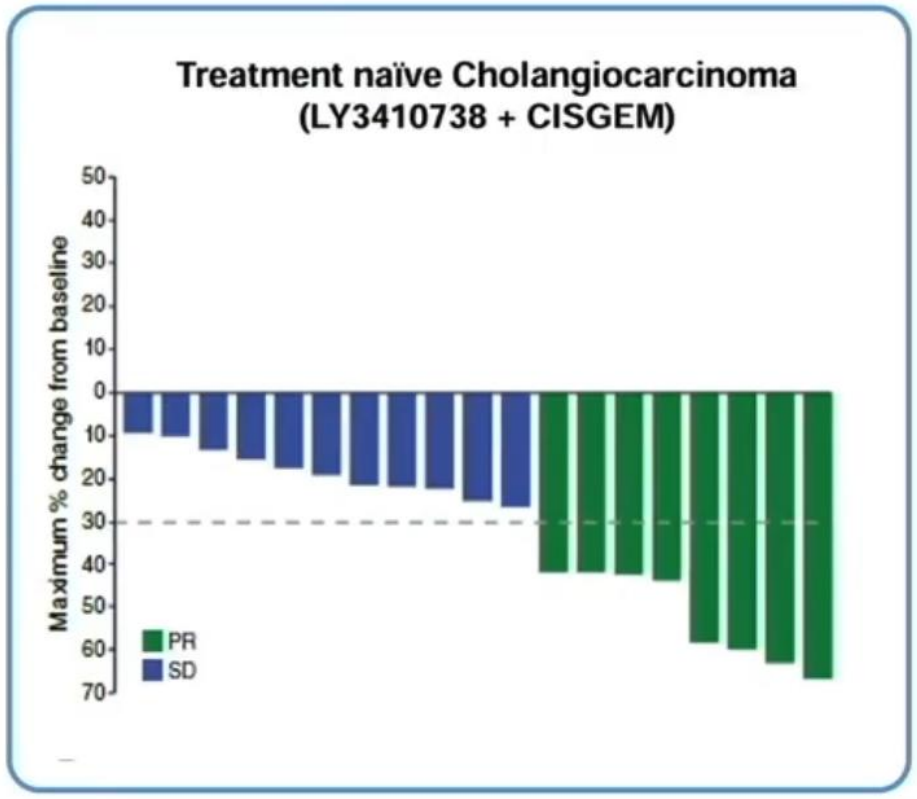
- The rank-preserving structural failure time (RPSFT)[1,2] model was implemented as a prespecified analysis to adjust for the effect of crossover from placebo to ivosidenib
- The median OS for placebo after adjustment for crossover was **5.1 months**

vorasidenib

BTC-TARGETING IDH1

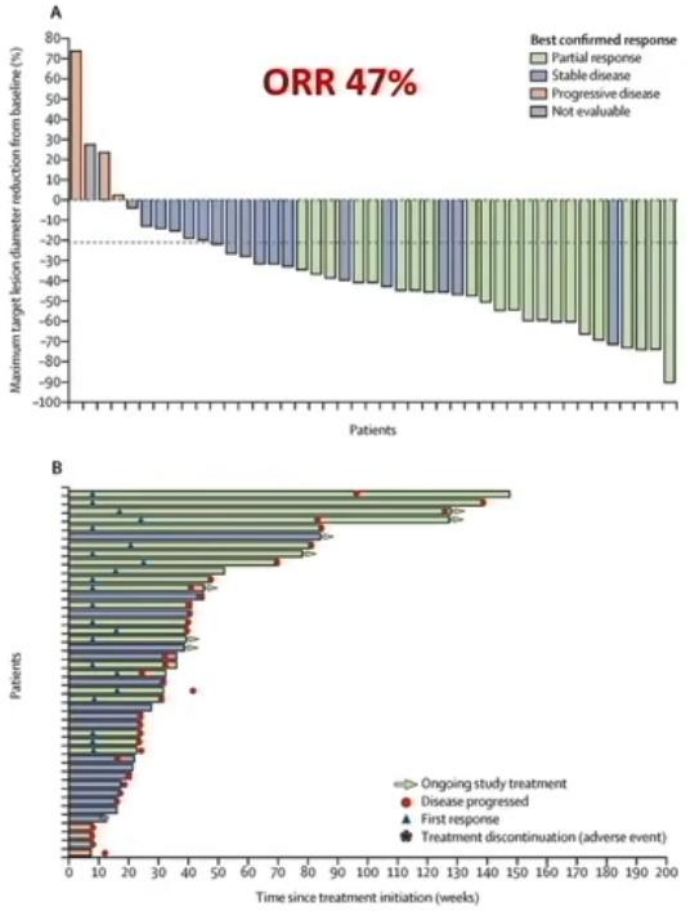
Study of LY3410738 Administered to Patients With Advanced Solid Tumors With IDH1 or IDH2 Mutations

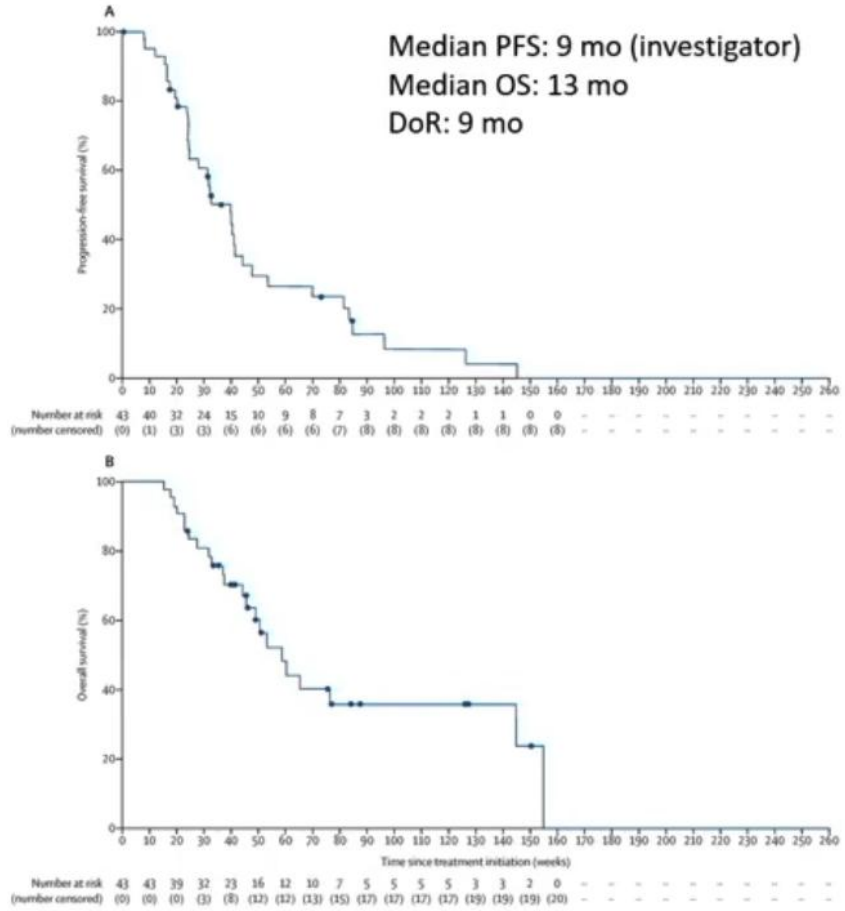
- LY3410738, a potent, covalent inhibitor of IDH1/2
  - Designed to overcome second-site mutations and "isoform switch"
- Monotherapy (refractory setting, n=58)
  - ORR 5.2%, DCR 56.9%
- LY3410738 +GEM/CIS (19 pts) 1st line
  - ORR 42.1%, mPFS 10.2
- LY3410738 + durvalumab (refractory setting, n=6)
  - SD 100%



Valle JW, et al. *Cancer Discov*. 2017; Borger DR, et al. *Oncologist*. 2012; Cleary JM, et al. *NPJ Precis Oncol*. 2022; Harding JJ, et al. *Cancer Discov*. 2018. Harding JJ, et al. *Ann Oncol*. 2023, Harding J. et al CCR 2026
BID, twice daily; BTC, biliary tract cancer; IDH1/2, isocitrate dehydrogenase 1/2; mPFS, median progression-free survival; NE, not evaluable; ORR, objective response rate; PD, progressive disease; QD, once daily; RP2D, recommended phase 2 dose; SD, stable disease.

Phase 2 ROAR study - Dabrafenib/Trametinib for BRAF V600E





Median PFS: 9 mo (investigator)
Median OS: 13 mo
DoR: 9 mo

On June 22, 2022, the **FDA granted accelerated approval** to dabrafenib plus trametinib for BRAF V600E mutated unresectable solid tumors

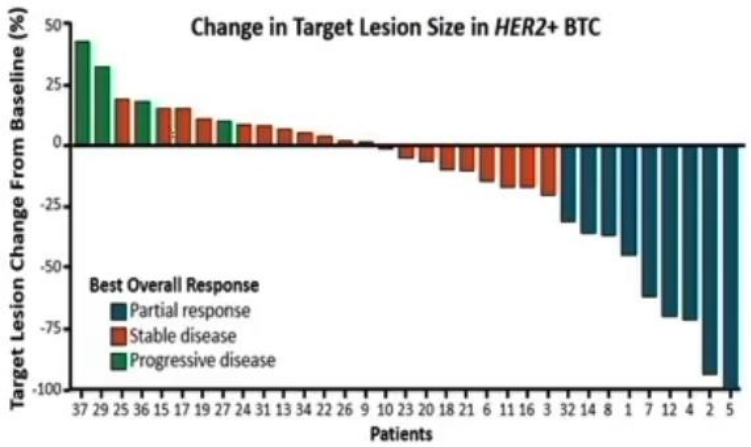
More common in ECC

HER2 pathway inhibition in HER2-driven BTC

NCNN guidelines

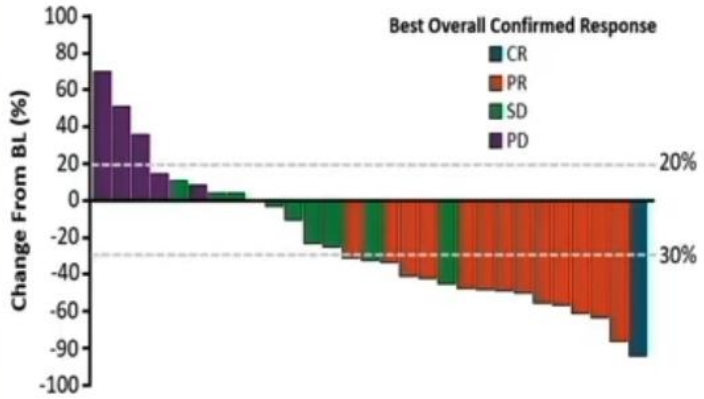
FDA Approved

MyPathway: Trastuzumab + Pertuzumab* for *HER2*-Positive BTC



Efficacy Outcome	n = 39
ORR, %	23
DCR, %	51
Median DoR, mo (range)	10.8 (0.7-25.4)
Median PFS, mo (range)	4.0 (1.8-5.7)
Median OS, mo (range)	10.9 (5.2-15.6)

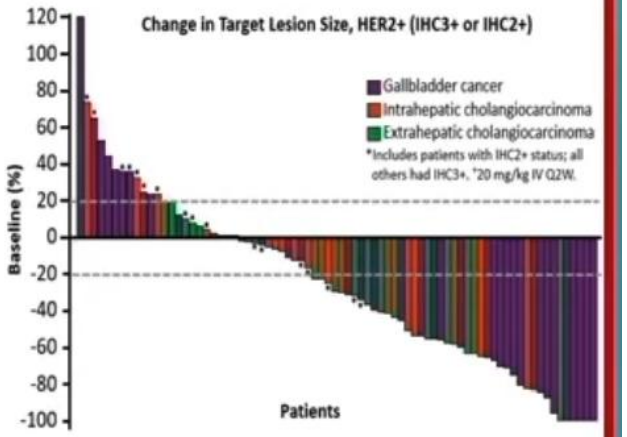
SGNTUC-019: Tucatinib + Trastuzumab for Previously Treated HER2+ or Mutant Advanced BTC



Efficacy Outcome	n = 30
ORR, %	46.7
DCR, %	76.7
mDoR, mo (range)	6.0 (5.5-6.9)
mPFS, mo	5.5 (3.9-8.1)
mOS, mo	15.5 (6.5-16.7)

Tucatinib: oral tyrosine kinase inhibitor that is highly selective for the kinase domain of HER2 w

HERIZON-BTC-01: Zanidatamab for Previously Treated HER2-Amplified Biliary Tract Cancer



Efficacy Outcome	n = 80
ORR, %	41.3
DCR, %	68.8
mDoR, mo (range)	**14.9 (6.0-NE)**
mOS, mo	15.5

Zanidatamab: HER2-targeted bispecific antibody that binds 2 separate HER2 epitopes; preclinical data show greater activity vs trastuzumab ± pertuzumab

**NCCN guideline*

Harding et al. Nature Communications 2023; Javle et al. Lancet Oncology 2021; Meric-Bernstein ASCO 2023; Harding et al. Lancet Oncology 2023; Pant et al. ASCO

Trastuzumab Deruxtecan for Advanced HER2-Expressing Biliary Tract Cancers

- Trastuzumab deruxtecan: an antibody-drug conjugate composed of a humanized monoclonal anti-HER2 antibody, a cleavable linker, and a topoisomerase I inhibitor.
- ILD, requires more careful monitoring and intervention.

FDA Approved Tumor agnostic

Outcomes	HERB	DESTINY Pan-Tumor02
Trial population	Unresectable/recurrent HER2-expressing BTC; refractory or intolerant to gemcitabine-containing therapy (N = 32; n = 24 HER2 high, n = 8 HER2 low)	unresectable or metastatic HER2-expressing (IHC 3+ or 2+) BTC, PD after ≥1 systemic treatment/no alternative treatment options (n = 41*)
ORR, %	**36.4 (HER2 high),** 12.5 (HER2 low)	22 (overall), **56.3 (IHC3+), 0 (IHC2+)**
Median PFS, mo	5.1 (HER2 high), 3.5 (HER2 low)	4.6 (overall), 7.4 (IHC3+), 4.2 (IHC2+)
Median OS, mo	7.1 (HER2 high); 8.9 (HER2 low)	7.0 (overall), 12.4 (IHC3+), 6.0 (IHC2+)
Key AEs	Anemia, neutropenia, leukopenia, **interstitial lung disease (25%)**	Nausea, anemia, neutropenia, **interstitial lung disease (10.5 overall%)**

HER2-low-expressing (defined as IHC/ISH status of 0/+, 1+/−, 1+/+ or 2+/−)

Ohba. ASCO 2022. Abstr 4006. Meric-Bernstam. JCO. 2024:42:47.

HER2 Pathway Inhibition in HER2-Driven BTC Next HERizons

Resistance to HER2-Directed Therapy in BTC

- **Loss of HER2 dependency**
  - Loss of amplification or downregulation of HER2 expression
- **On-target mutations**
  - Mutations that reduce drug binding or alter receptor structure
- **Bypass signaling**
  - Activation of downstream pathways
  - Expansion of non–HER2-driven clones
- **Clinical implications**
  - Combinations/sequencing strategies needed

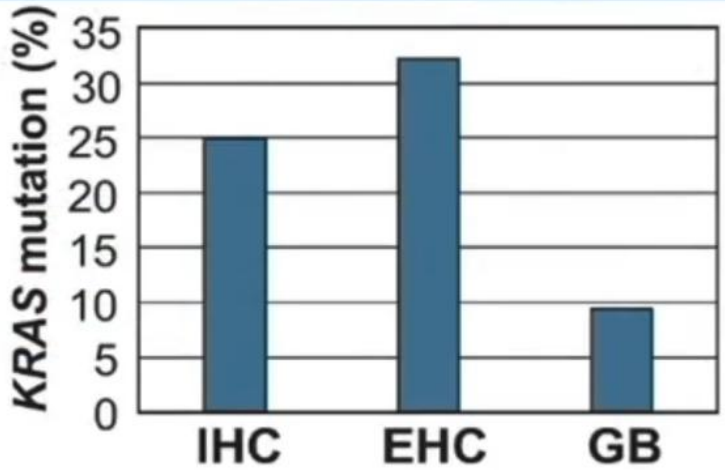
- **HERIZON-BTC-302:**
  A phase 3 study of zanidatamab with SOC therapy vs SOC alone for first-line treatment of HER2-positive advanced/metastatic BTC

- **DESTINY-BTC01:**
  Phase 3 study of T-DXd and rilvegostomig vs SoC in advanced HER2-expressing BTC

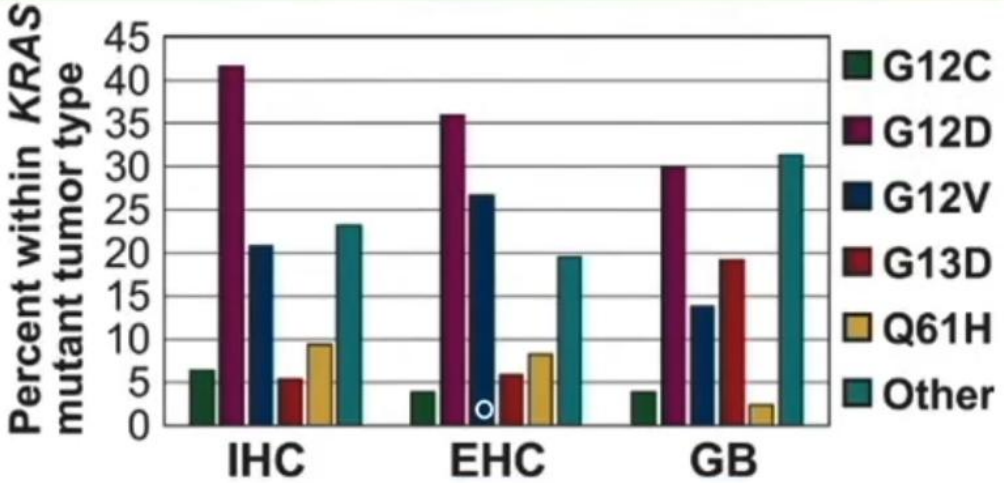
BTC, biliary tract cancer; HER2, human epidermal growth factor receptor 2; SOC, standard of care; T-DXd, trastuzumab deruxtecan.

KRAS Mutations in BTC: Shaping Biomarker-Driven Treatment Strategies

KRAS Mutation Distribution By BTC Types



KRAS Mutation Distribution By Variants



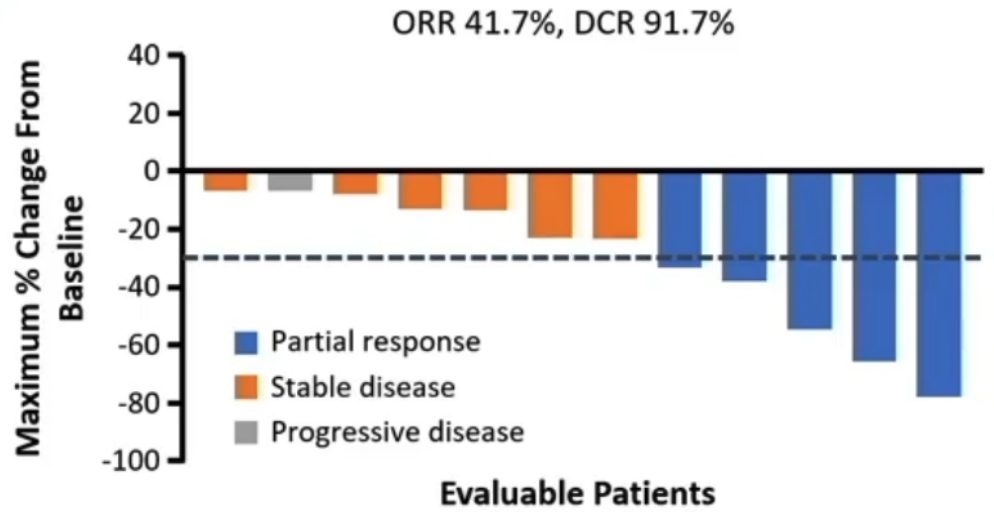
- Data from >7000 BTC
- Overall frequency of *KRAS* mutations in BTC was 23.4% (more common in IHC)
- KRAS variants were significantly associated with poor prognosis.

Iida K, et al. *Esmo Open*. 2025.
BTC, biliary tract cancer; EHC, extrahepatic cholangiocarcinoma; GB, gallbladder; IHC, intrahepatic cholangiocarcinoma; KRAS, Kirsten rat sarcoma viral oncogene homolog.

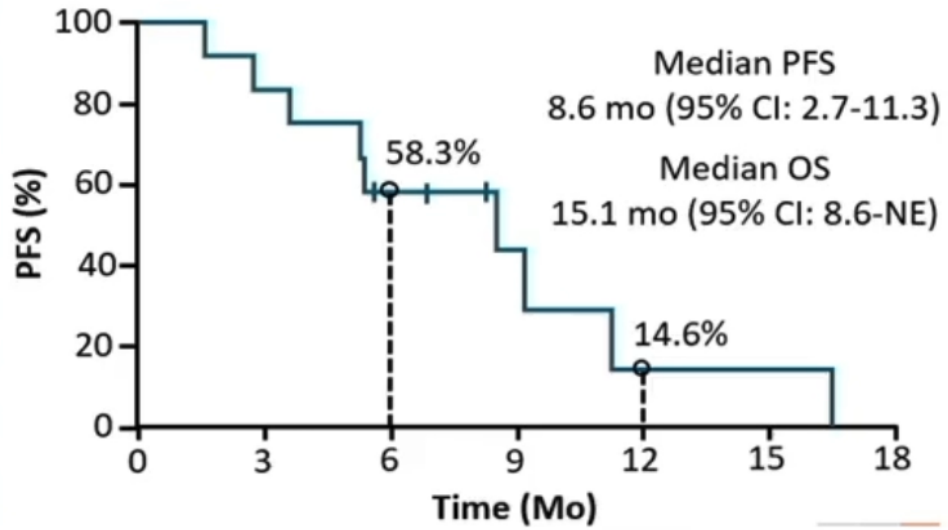
Adagrasib: KRAS G12C Inhibitor

- **Adagrasib:** covalent inhibitor of KRAS G12C; KRAS G12C mutations may occur in ~1% CCA
- KRYSTAL-1: phase 2 study of adagrasib for unresectable/metastatic solid tumors with KRAS G12C mutations and no remaining SoC treatment options; recent report included patients with BTC (n=12)

Response in Patients With BTC



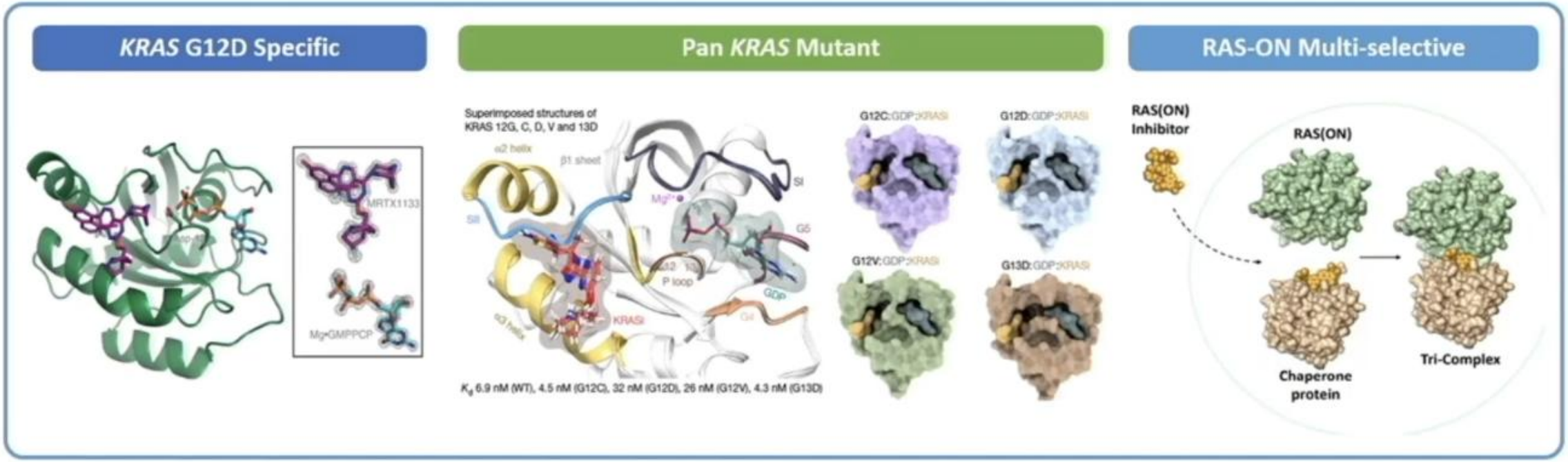
PFS in Patients With BTC



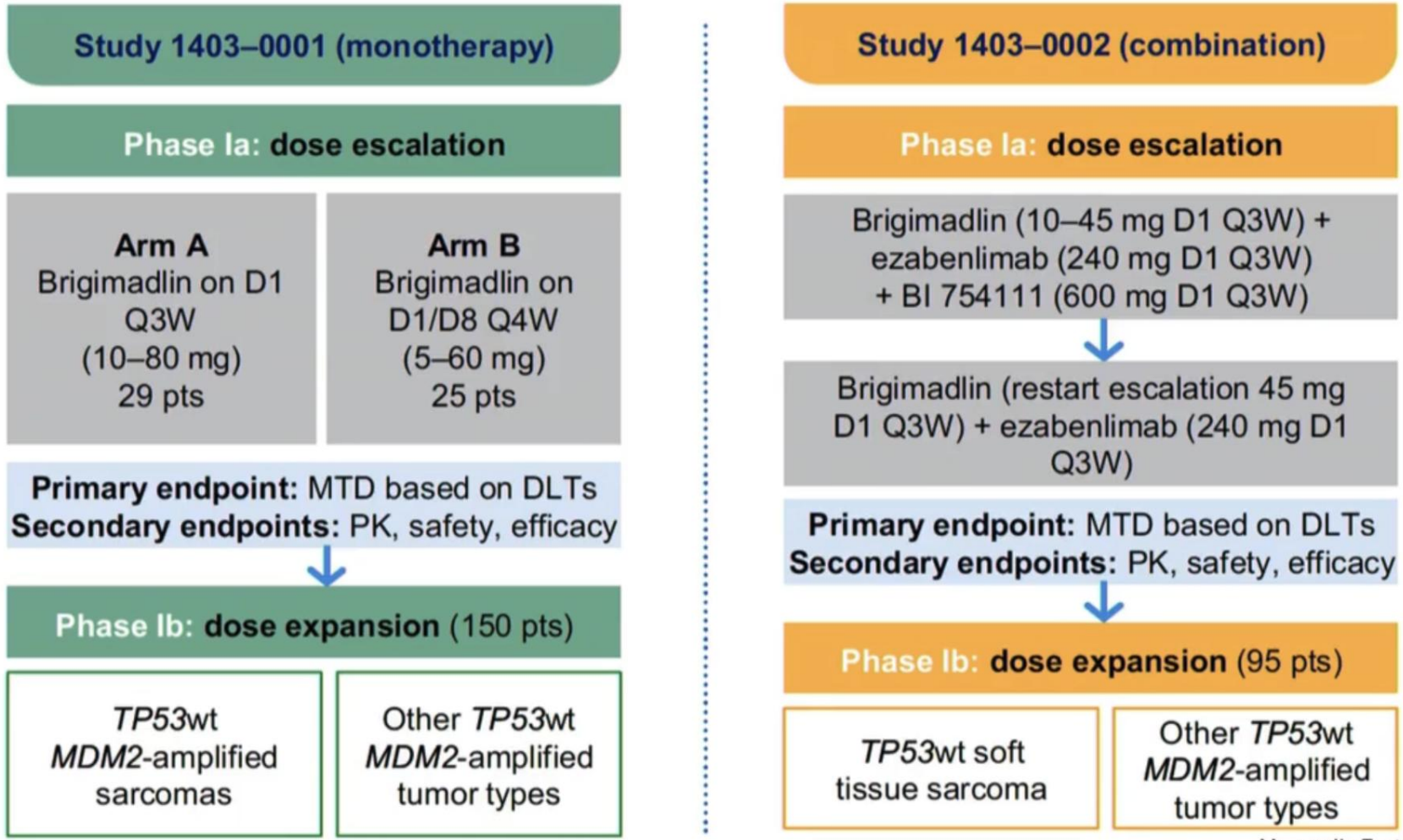
Pant S. *J Clin Oncol*. 2023; Kendre G, et al. *J Hepatol*. 2023.
BTC, biliary tract cancer; CCA, cholangiocarcinoma; DCR, disease control rate; NE, not estimable; ORR, overall response rate; OS,

Daraxonrasib (may be the new option)

KRAS is an Actionable Target in Oncology: Beyond G12C



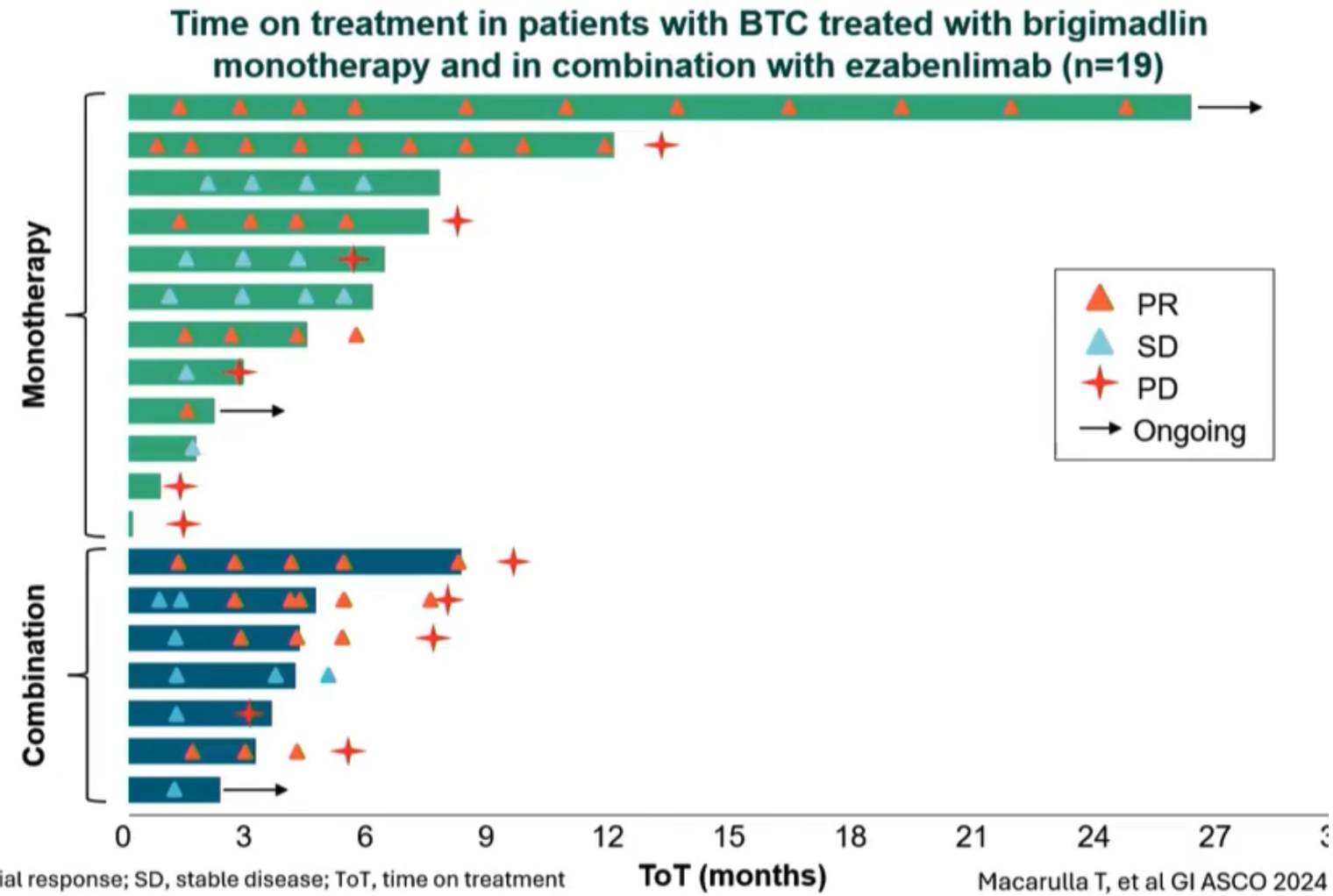
MDM2 as a target: Brigmadlin



Macarulla T, et al GI ASCO 2024

MDM2 AS A TARGET: BRIGMADLIN

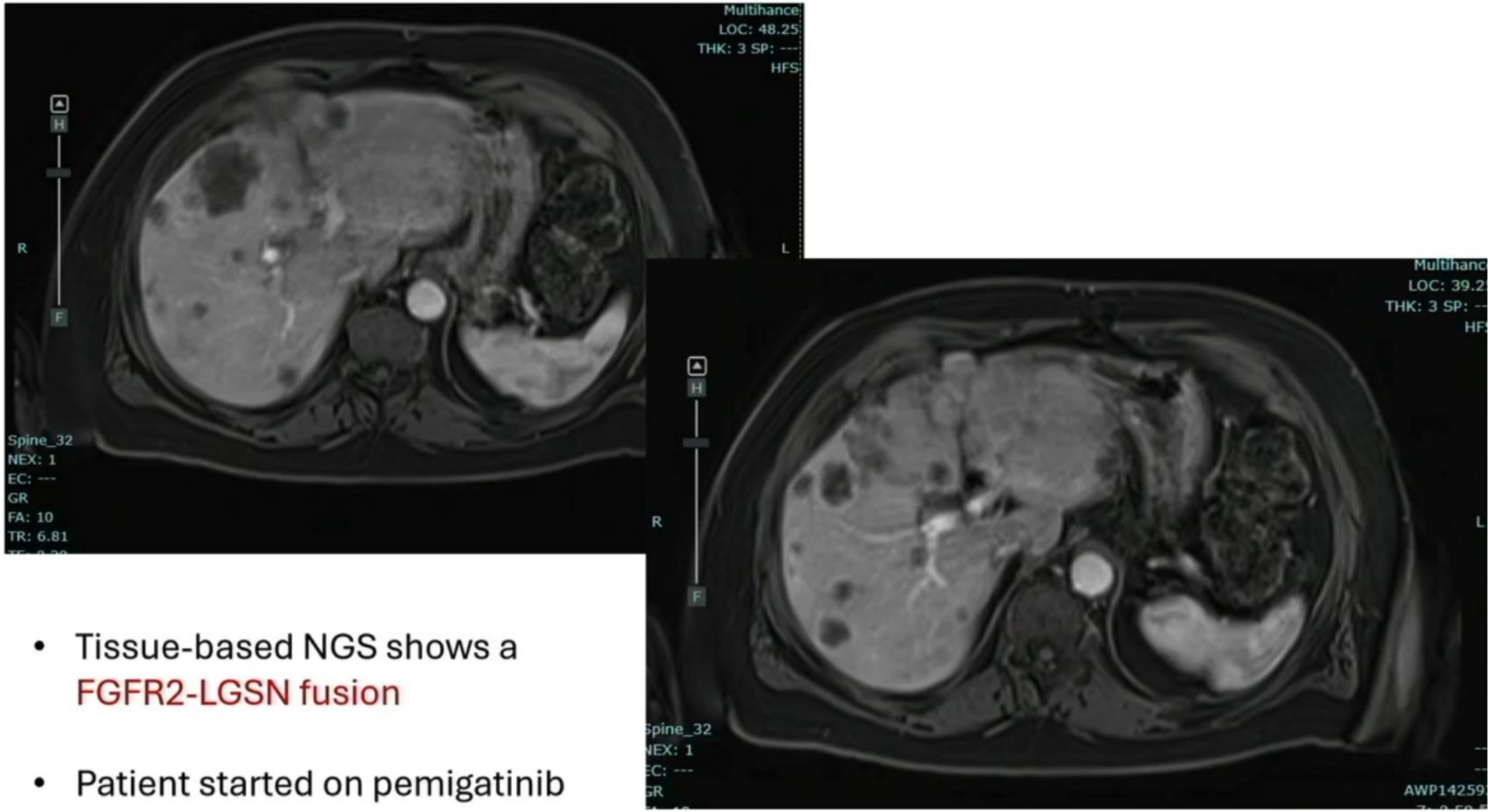
- As of October 2023, 23 patients with BTC have been enrolled across both trials,16 in the monotherapy trial and 7 in the combination trial
- 12 of 16 patients with BTC in the monotherapy trial were response-evaluable:
  - 4 patients have achieved confirmed PR and 6 have achieved SD
- All 7 patients with BTC in the combination trial were response-evaluable:
  - 4 patients have achieved confirmed PR and 3 have achieved SD



BTC, biliary tract cancer; PD, progressive disease; PR, partial response; SD, stable disease; ToT, time on treatment

Macarulla T, et al GI ASCO 2024

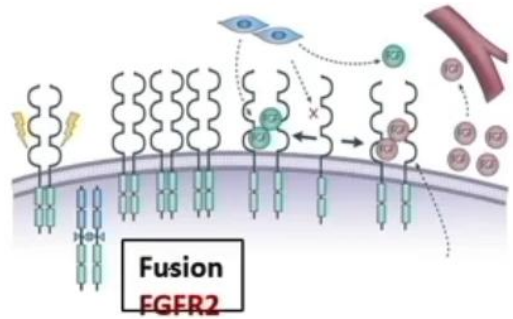
Back to our case



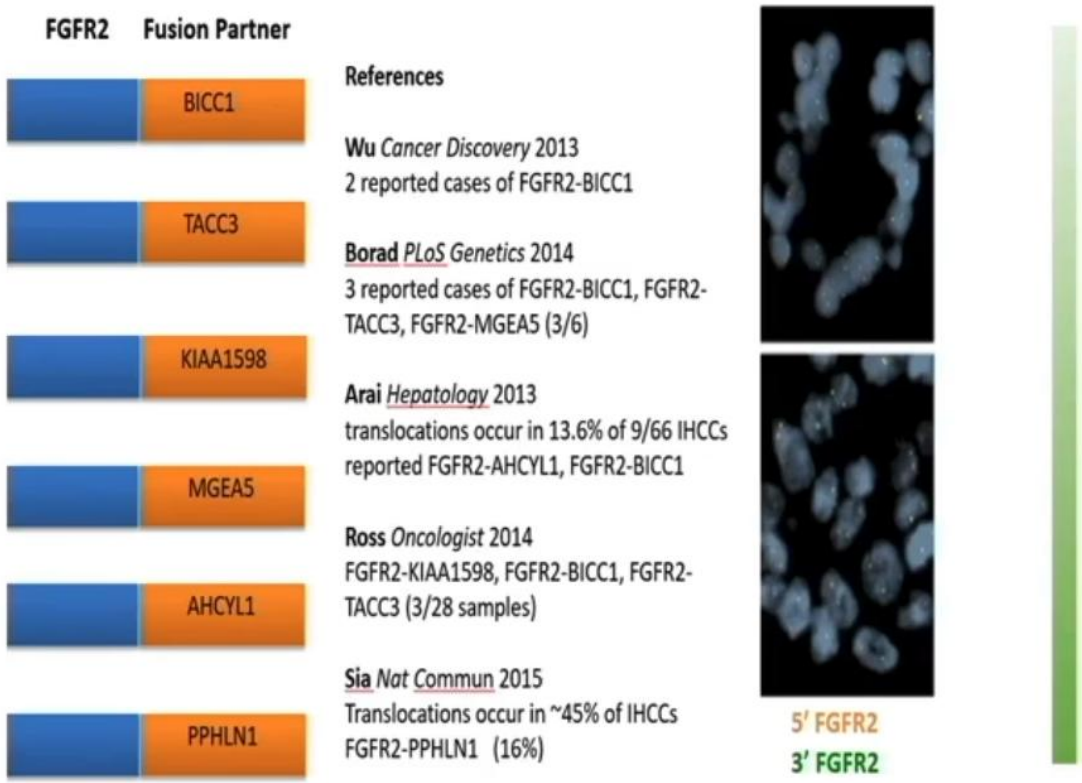
- Tissue-based NGS shows a FGFR2-LGSN fusion
- Patient started on pemigatinib

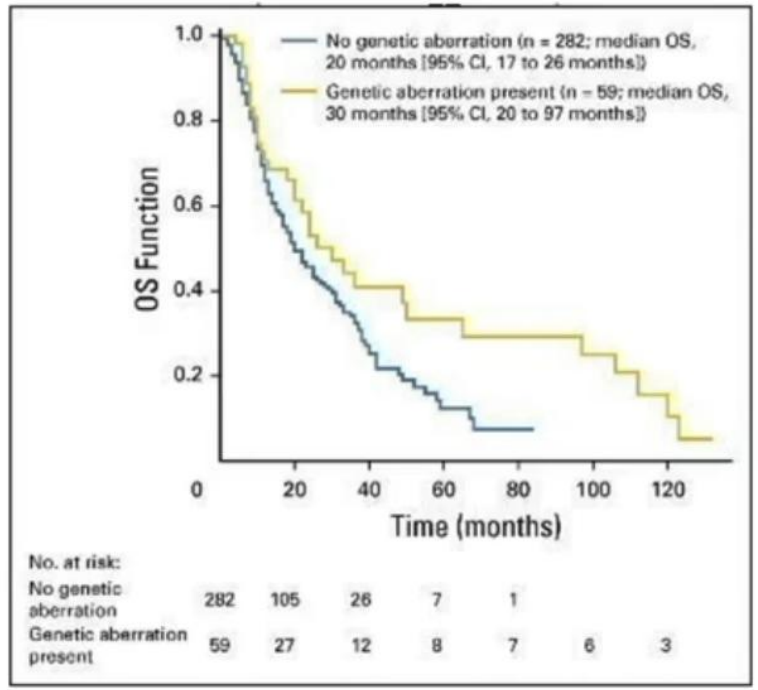
FGFR2 Fusions

- **FGFR2 fusions/rearrangements** in 10-13% of iCCA
- Represents a unique subtype, more in younger, female patients with an indolent disease course.



- iCC (16%)



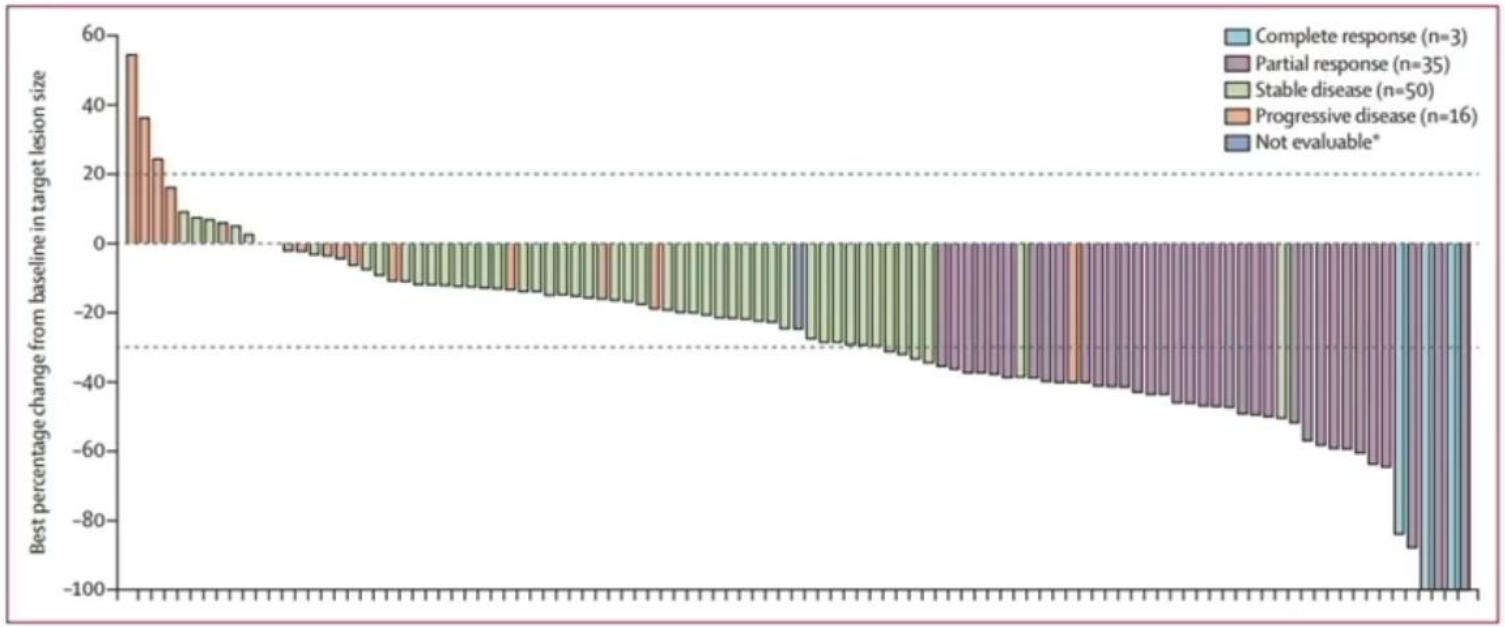


Turner & Gross 2010. Rev Cancer 10(2):116; Valle et al. Cancer Disc 2017; Jain et al. JCO Prec Onc 2018

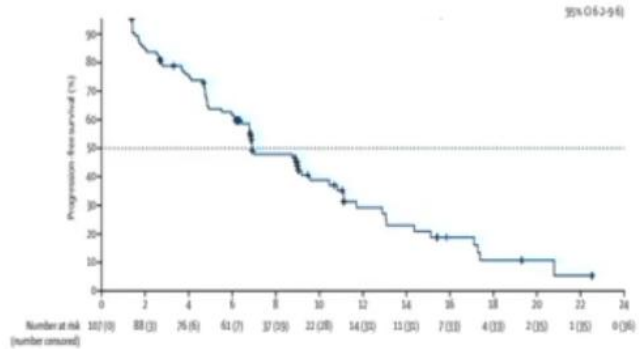
Pemigatinib in CCA with FGFR2 rearrangement or fusion

Pemigatinib, ATP Competitive; FGFR1-3 inhibitor

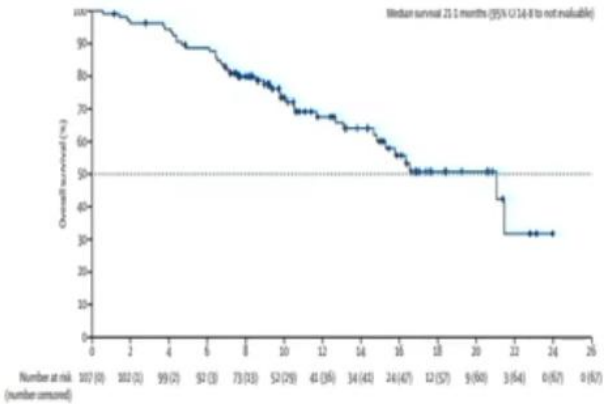
- ORR 37% DCR 82% and mDOR 7.5 months



mPFS 7.0 months



mOS 21.1months)



Abou Alfa et al., Lancet Oncol 2020; Vogel A. et al. Presented at ESMO World Congress on Gastrointestinal Cancer 2022

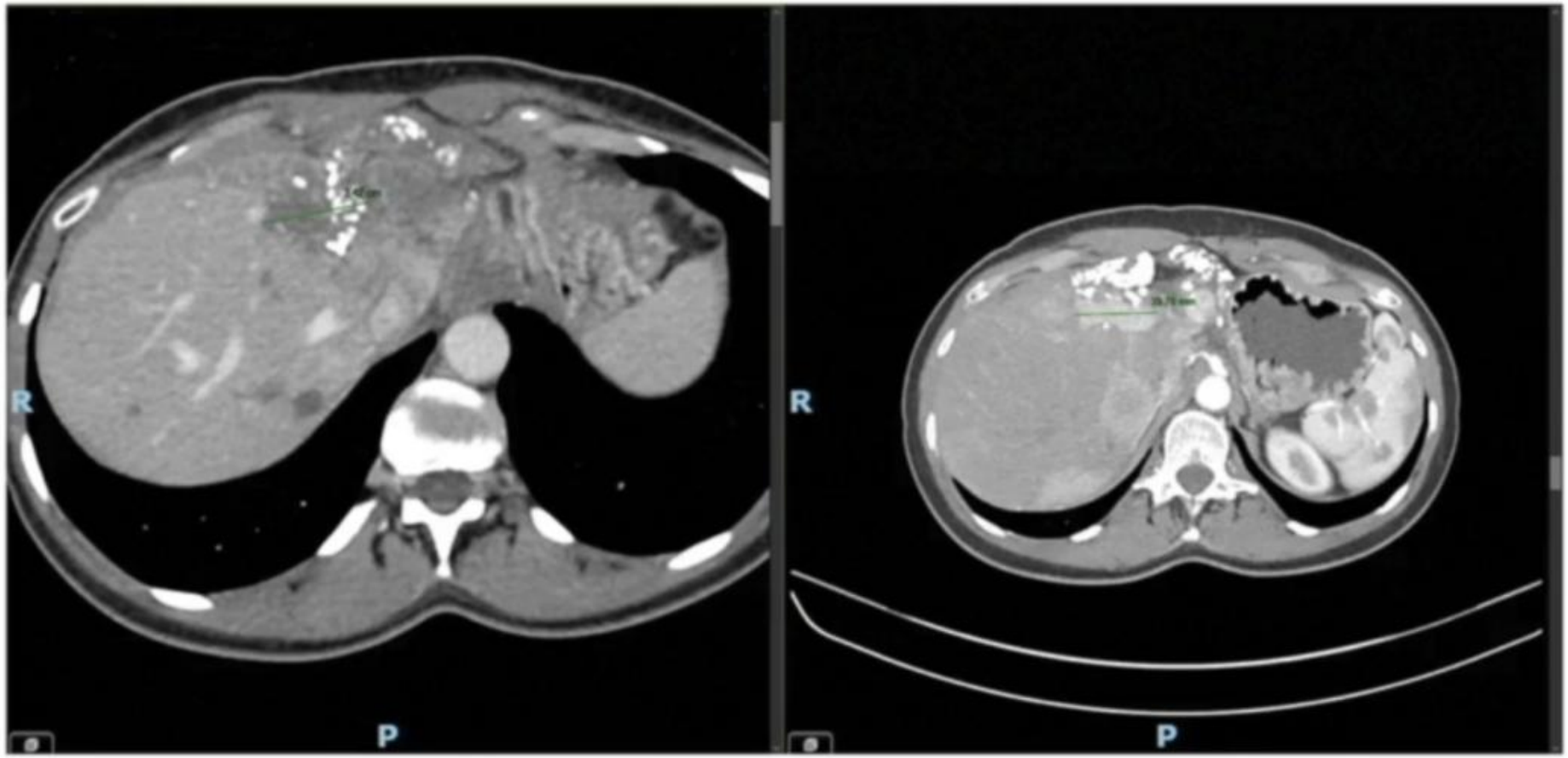
Key Toxicities of FGFR Inhibitors

Hyperphosphatemia, cutaneous toxicity (dry skin, painful/discolored nails, dry eyes [corneal abrasions], dry mouth), retinal toxicity (central serous retinopathy)

AE, %	Pemigatinib (N = 146)[1]		Futibatinib (N = 103)[2]	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Hyperphosphatemia	**55**	**0**	**85**	**30**
Alopecia	49	0	34	0
Diarrhea	47	3	39	1
Nail toxicity	43	2	47	2
Fatigue	42	5	37	8
Stomatitis	35	5	30	6
Dry eye	35	1	25	1
Constipation	35	1	39	0

Abou-Alfa. Lancet Oncol. 2020;21:671. Goyal. NEJM. 2023;388:228.
Slide courtesy of Dr. Pishvaian

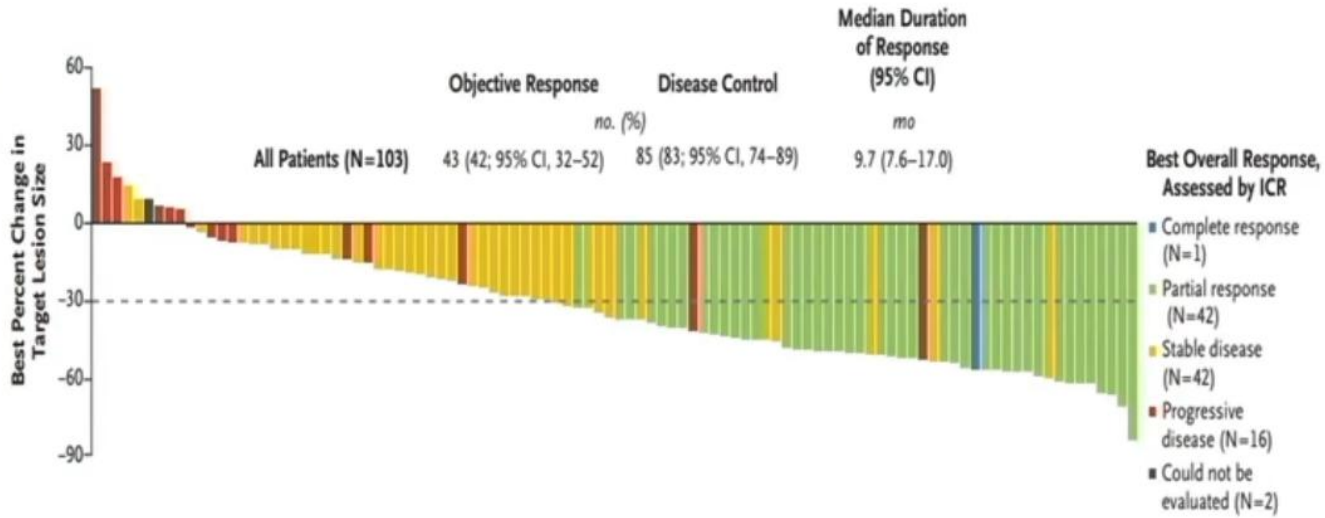
Progression to pemigatinib after ~ 9 months
Decision to switch to futibatinib



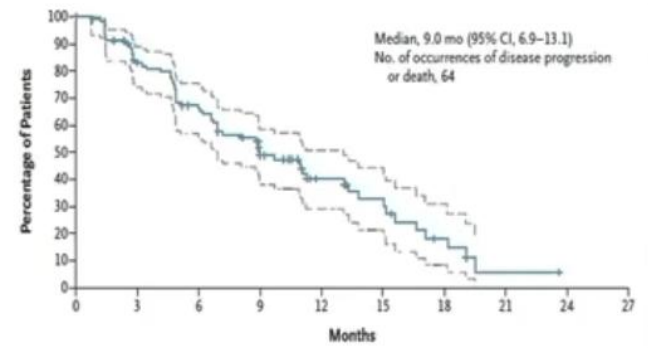
Futibatinib: Phase 2 Study with ORR primary endpoint

Futibatinib, Covalently-binding; FGFR1-4 inhibitor

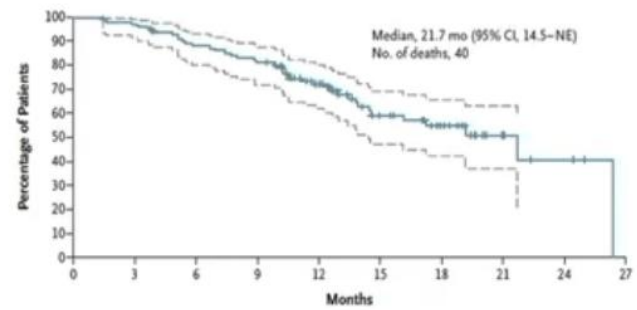
- ORR 42%; Median duration of response 9.7 months



mPFS 9.0



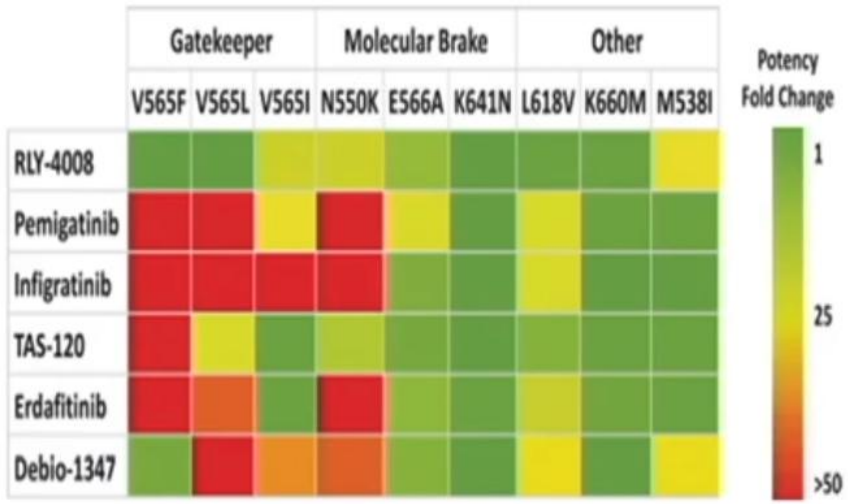
mOS 21.7

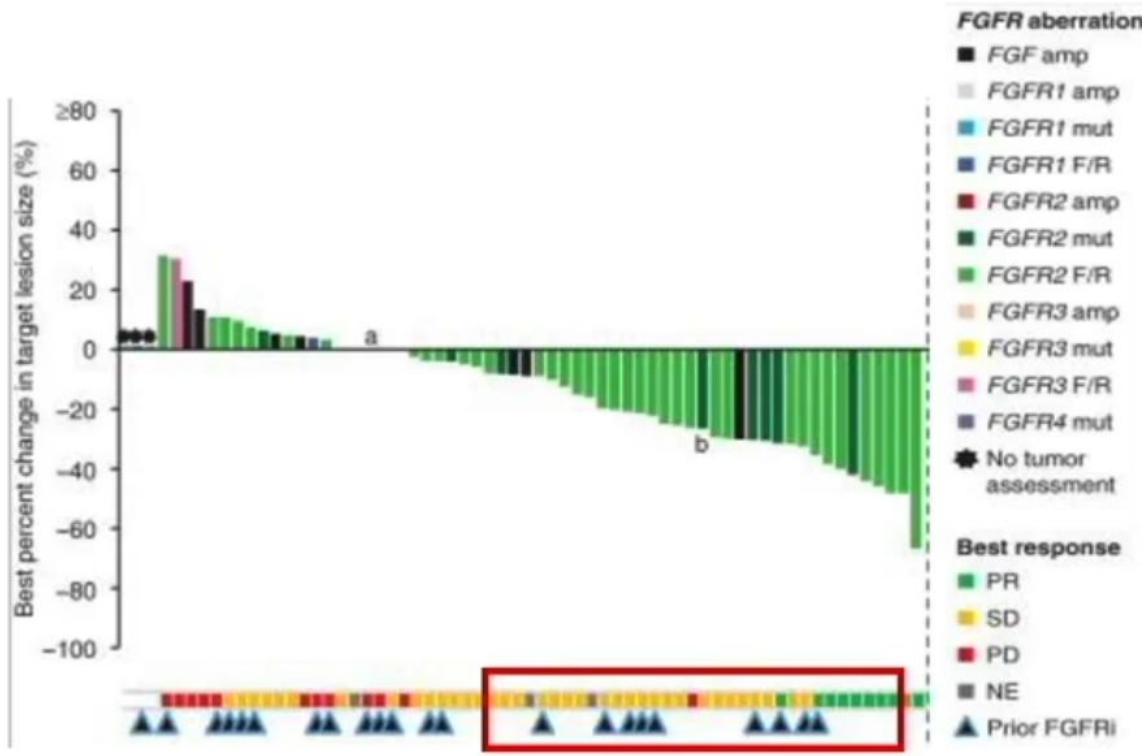


Goyal. et al. NEJM 2023

Futibatinib *might* overcome resistance induced by ATP-competitive FGFRi

The V565F gatekeeper as the greatest challenge

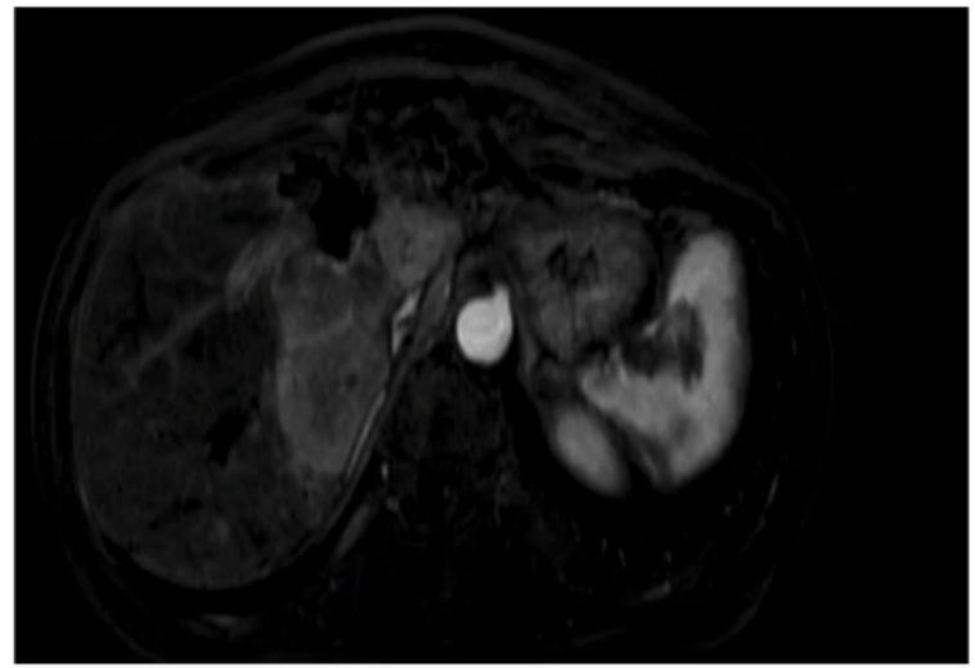




Twenty-eight patients (33.7%) were previously treated with another FGFR inhibitor.

Progression to futibatinib

- ctDNA showed with FGFR2-LGSN fusion (31%), **FGFR2 V564L** (2.5%)

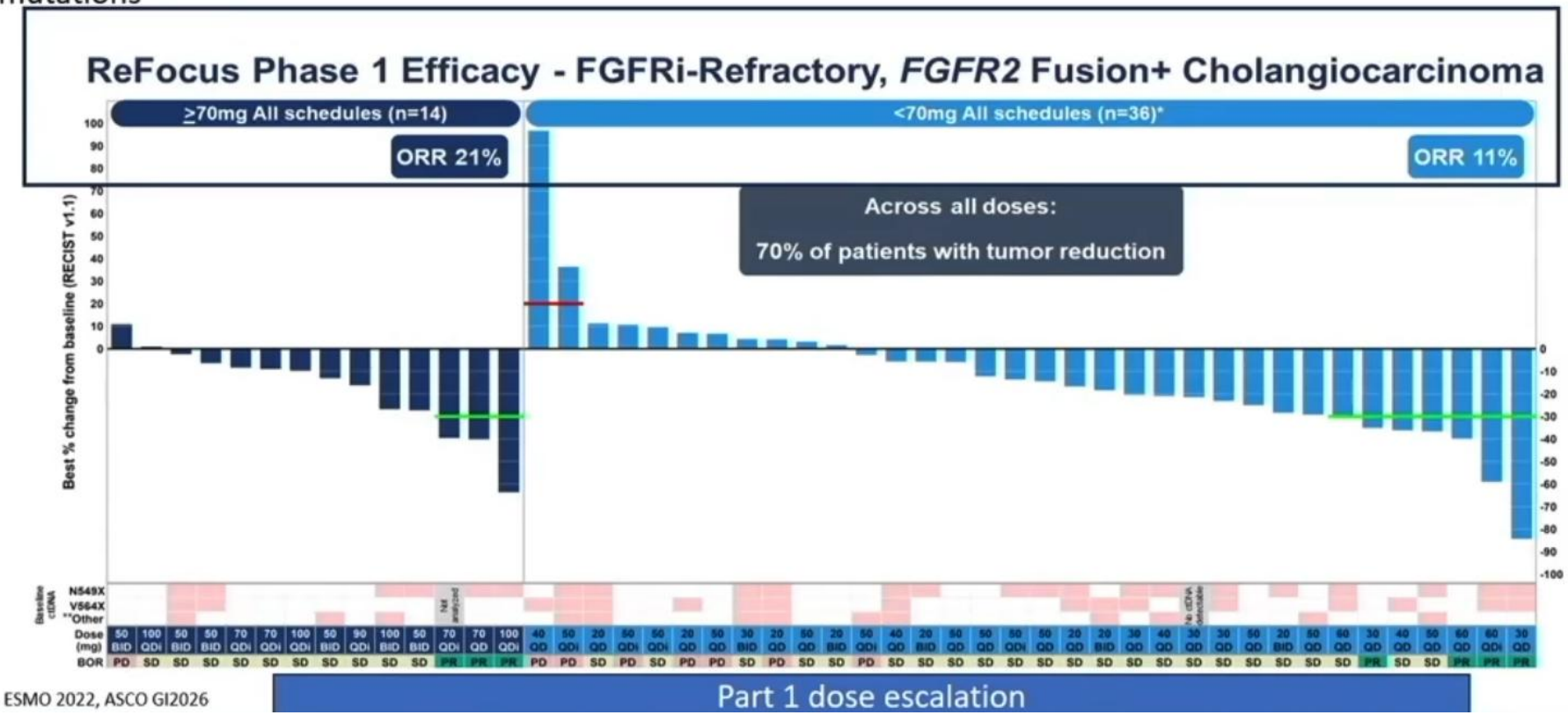


For gate keeper mutations

ReFocus Trial – Lirafugratinib (irreversible FGFR2 inhibitor)

- advanced/metastatic CCA FGFR2 f/r previously treated with **≥1 systemic therapy and FGFRi-naive**
  - treated with oral Lirafugratinib 70 mg
  - ORR 47%, DOR 11.8 mos, mPFS 11.3, mOS 22.8

- RLY-4008 exhibits activity in pan-FGFR inhibitor resistant FGFR2-fusion cholangiocarcinoma regardless of FGFR2 resistance mutations

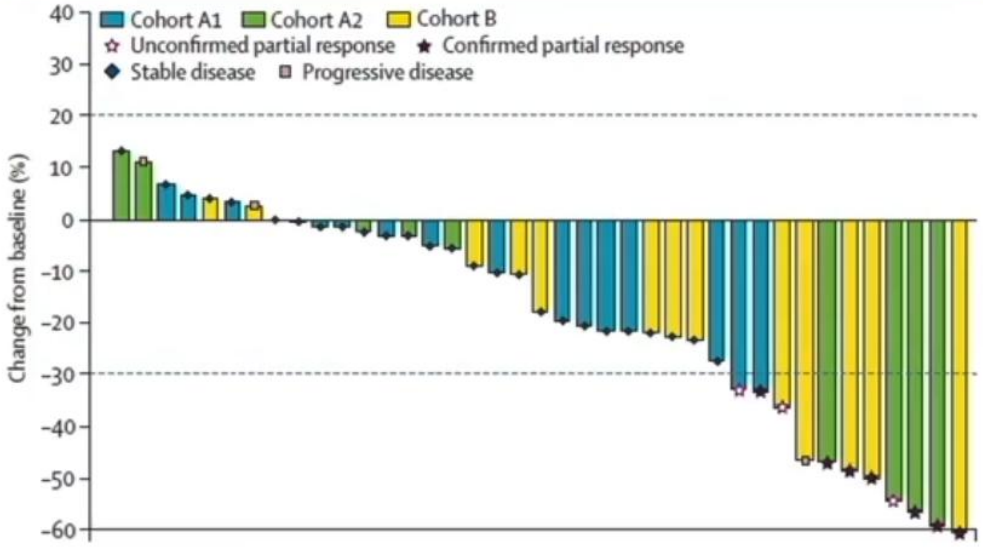


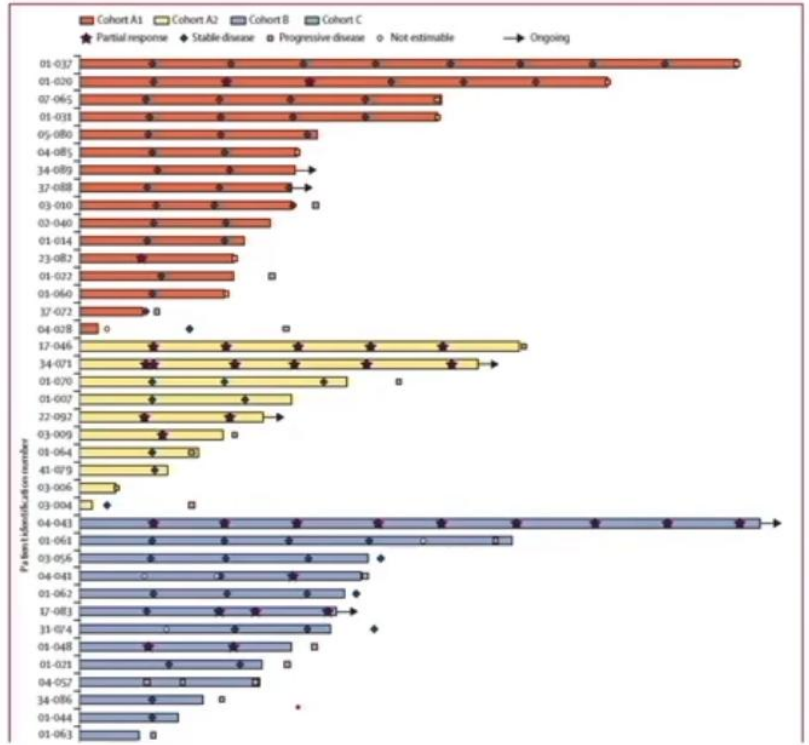
Hollebecque A. ESMO 2022, ASCO GI2026

Tinengotinib for Advanced Cholangiocarcinoma

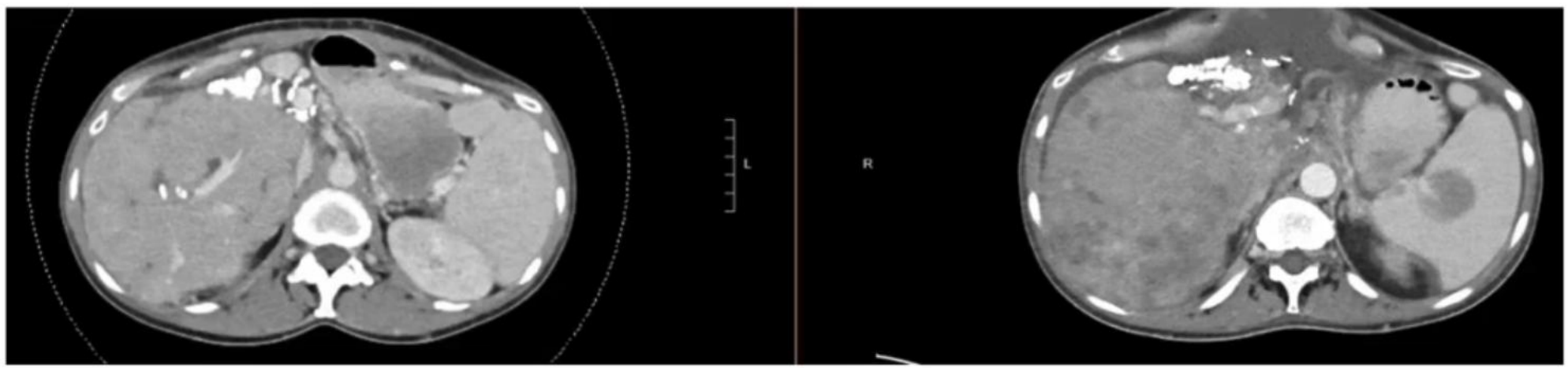
- Multicohort phase II study of tinengotinib 10 mg QD for patients with advanced CCA who had received ≥1 prior systemic chemotherapy
  - Cohort A1 (n-=18): *FGFR2* fusions with PD on prior FGFR inhibitor;
  - Cohort A2 (n=11): ***FGFR2* fusions with PD after response to FGFR inhibitor;**
  - Cohort B (n=13): other *FGFR* alterations;

- **Cohort A1** : ORR 6.3% , DCR 100%, mDOR 9.8, mPFS 5.6
- **Cohort A2** : ORR 30.0% , DCR 30%, mDOR 9.5. mPFS 4.2
- Cohort B : ORR 23.1%, DCR 84.6. mDOR NE, mPFS 7.3





- Patient enrolled in ***clinical trial SURF201*** "A multicenter, open-label, first-in-human study of TYRA-200 in advanced iCCA and other solid tumors with activating FGFR2 gene alterations (SURF201).
  - TYRA-200 is an orally bioavailable FGFR1/2/3 inhibitor designed to specifically address clinically observed acquired resistance alterations in FGFR2.
- 1st scan PR (-57%)
- C3 D1; ctDNA with **FGFR2 fusion (0.4%), V564L resolved**
- C4 D1; CA 19-9 = 74, CT PR (-70.92%) from baseline, -31.69% from nadir/prior).



Key Points

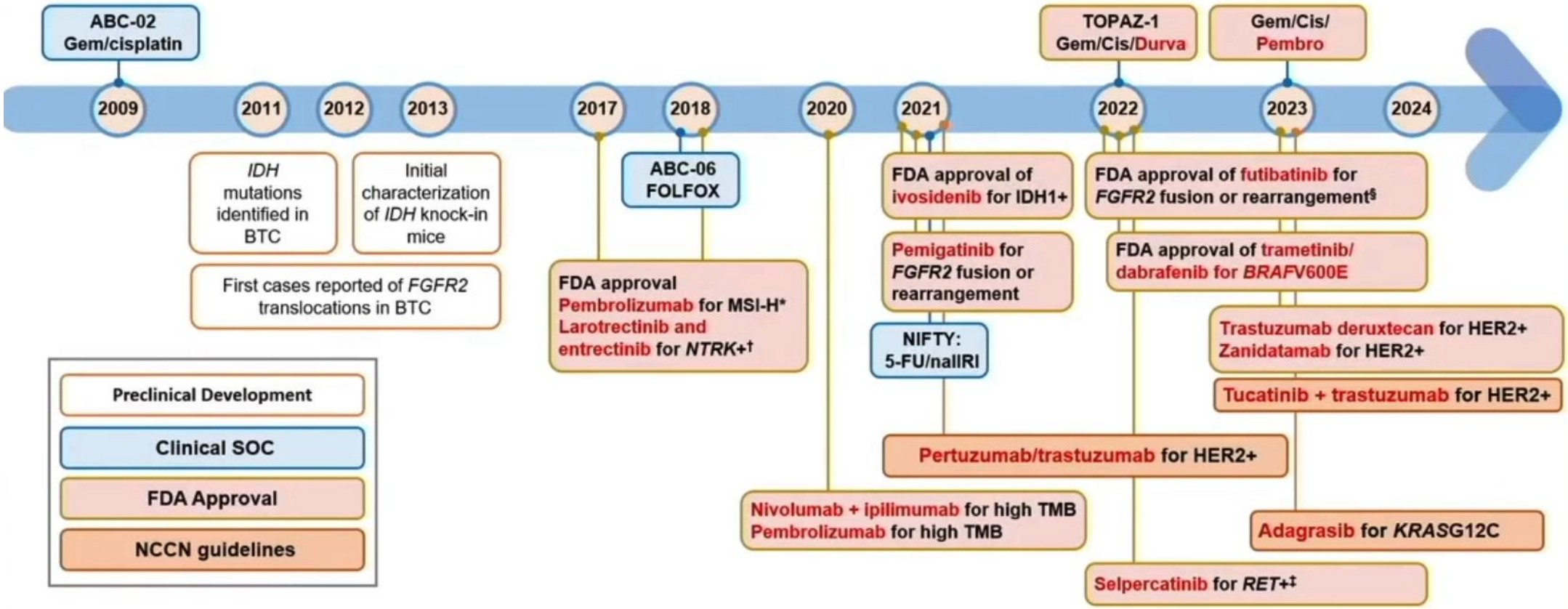
- BTC comprise a group of cancers with unique molecular characteristics.
- Clear role for PROFILING ALL BTC patients
  - FGFR, IDH, BRAF and HER2 (and NTRK and MSI-H/HTMB) are validated therapeutic targets. And more are coming

- Basket trials and umbrella trials are important and welcome to capture multiple and rare targets in a rare populations

- Importance of trial referral and enrollment

- Potential clinical utility of liquid biopsy for diagnosis and monitoring
  - Liquid biopsy can be a powerful tool to:
    - follow intratumor heterogeneity
    - guide treatment
    - drug development

Many New Options for Advanced BTC



*Dostarlimab approved in 2021. †Repotrectinib approved in 2024. ‡Pralsetinib included in NCCN BTC guidelines. §Erdafitinib added to NCCN BTC guidelines in 2025.
5-FU, fluorouracil; BRAFV600E, b-raf proto-oncogene serine/threonine kinase mutation at codon 600; BTC, biliary tract cancer; FGFR2, fibroblast growth factor receptor 2; FOLFOX, leucovorin + fluorouracil + oxaliplatin; Gem, gemcitabine; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase; nalIRI, nanoliposomal irinotecan;
NCCN, National Comprehensive Cancer Network; NTRK, neurotrophic receptor tyrosine kinase; RET, rearranged during transfection; SOC, standard of care; TMB, tumor mutational burden.