Incidental Gallbladder Cancer:

Making the case for neoadjuvant therapy.

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

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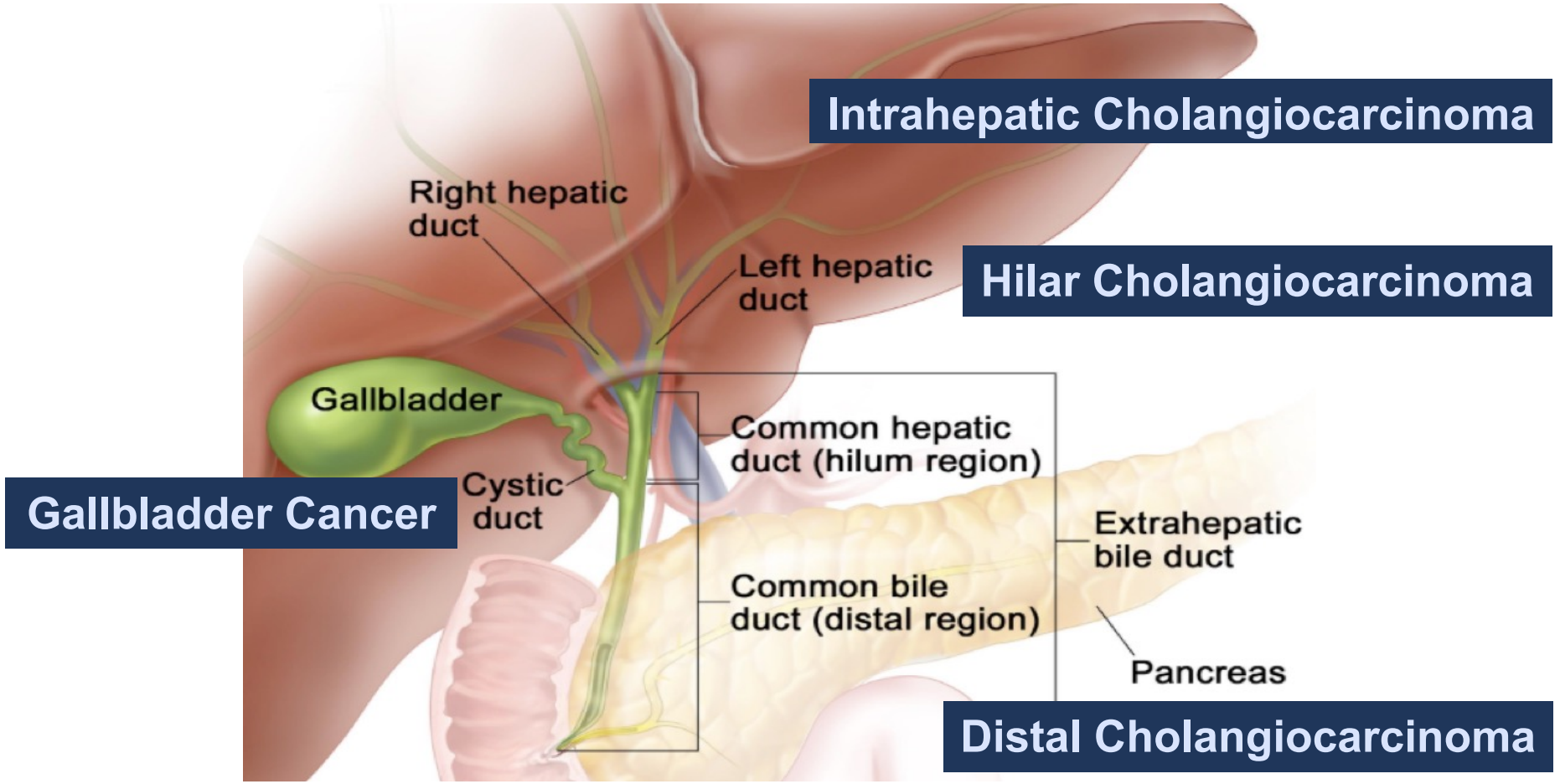
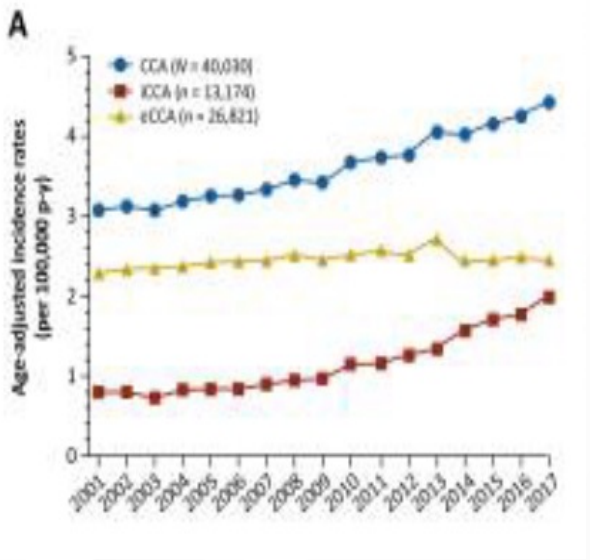
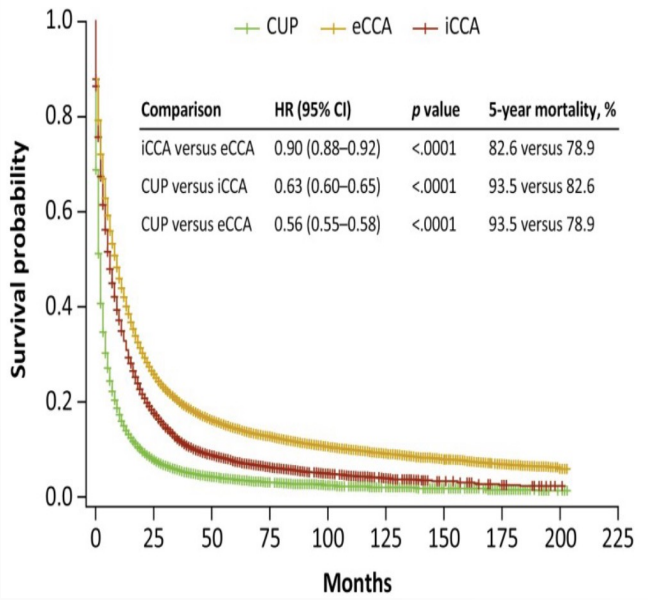
Biliary Tract Cancers (BTCs)



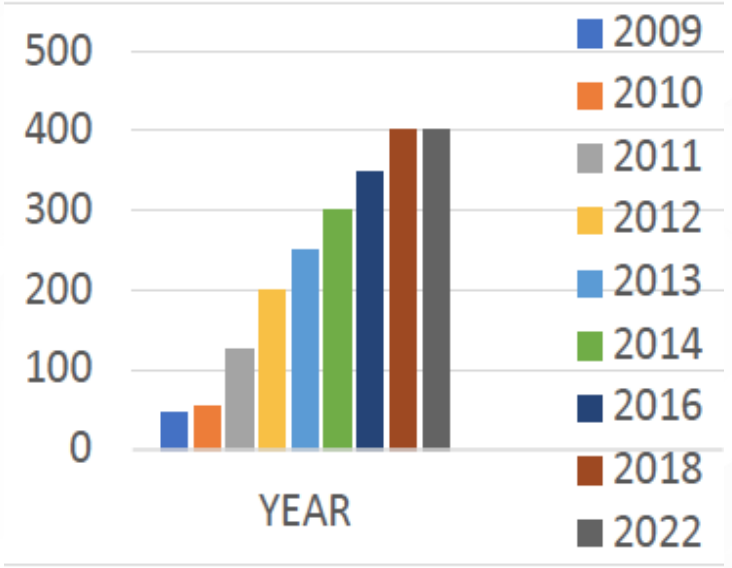
NCI Bile Duct Cancer PDQ 2017

Rising Incidence of Cholangiocarcinoma





Comparison	HR (95% CI)	*p* value	5-year mortality, %
iCCA versus eCCA	0.90 (0.88–0.92)	<.0001	82.6 versus 78.9
CUP versus iCCA	0.63 (0.60–0.65)	<.0001	93.5 versus 82.6
CUP versus eCCA	0.56 (0.55–0.58)	<.0001	93.5 versus 78.9



Obesity's link to cancer: Texas has nation's highest liver cancer mortality rate^

In the city of Houston, the observed number of intrahepatic bile duct cancers was significantly greater than expected in Texas

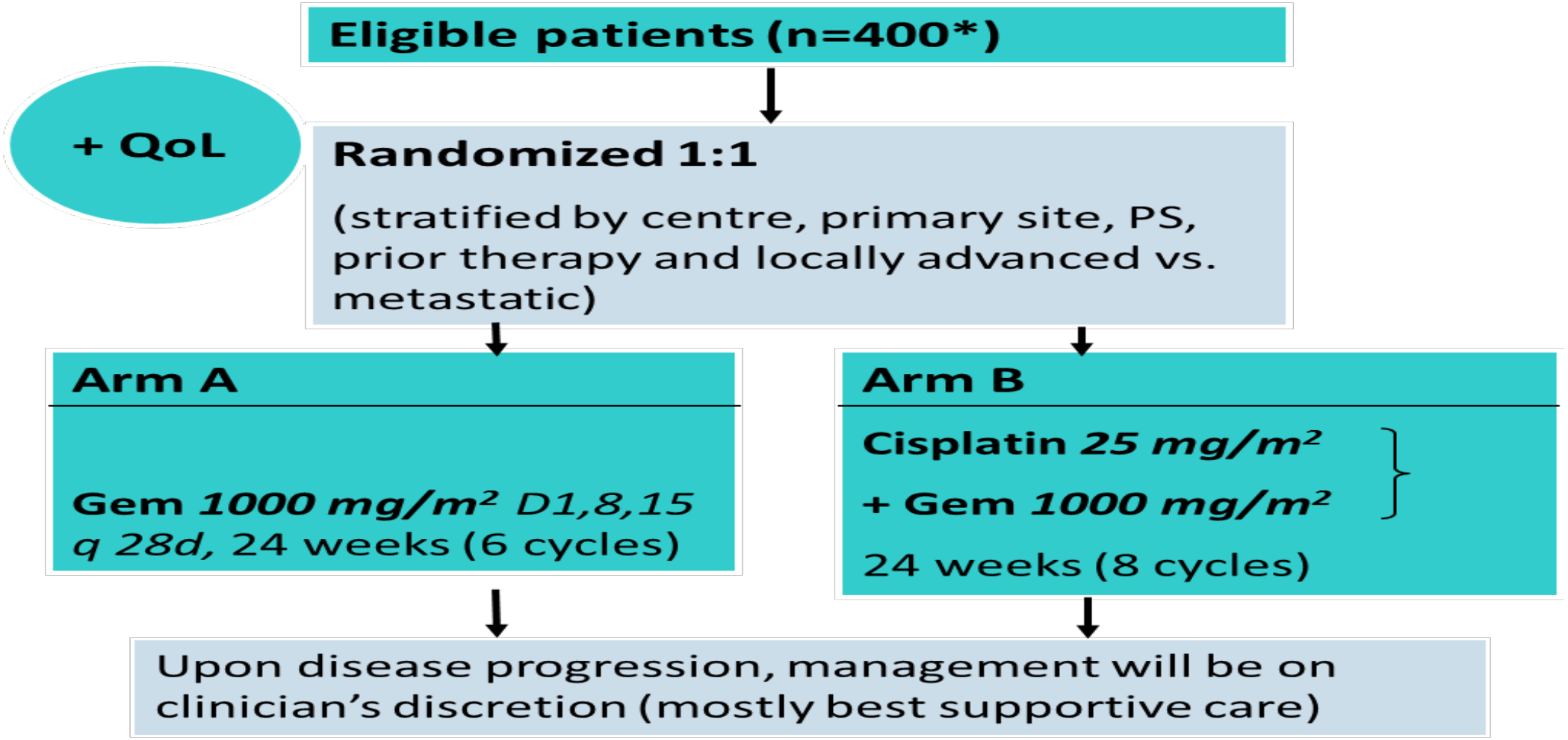
Javle M, et al. *Oncologist.* 2022.

^https://www.tmc.edu/news/2019/03/obesitys-link-to-cancer/#single-article-body

TIMELINE FOR NEW AGENTS IN BILIARY CANCERS

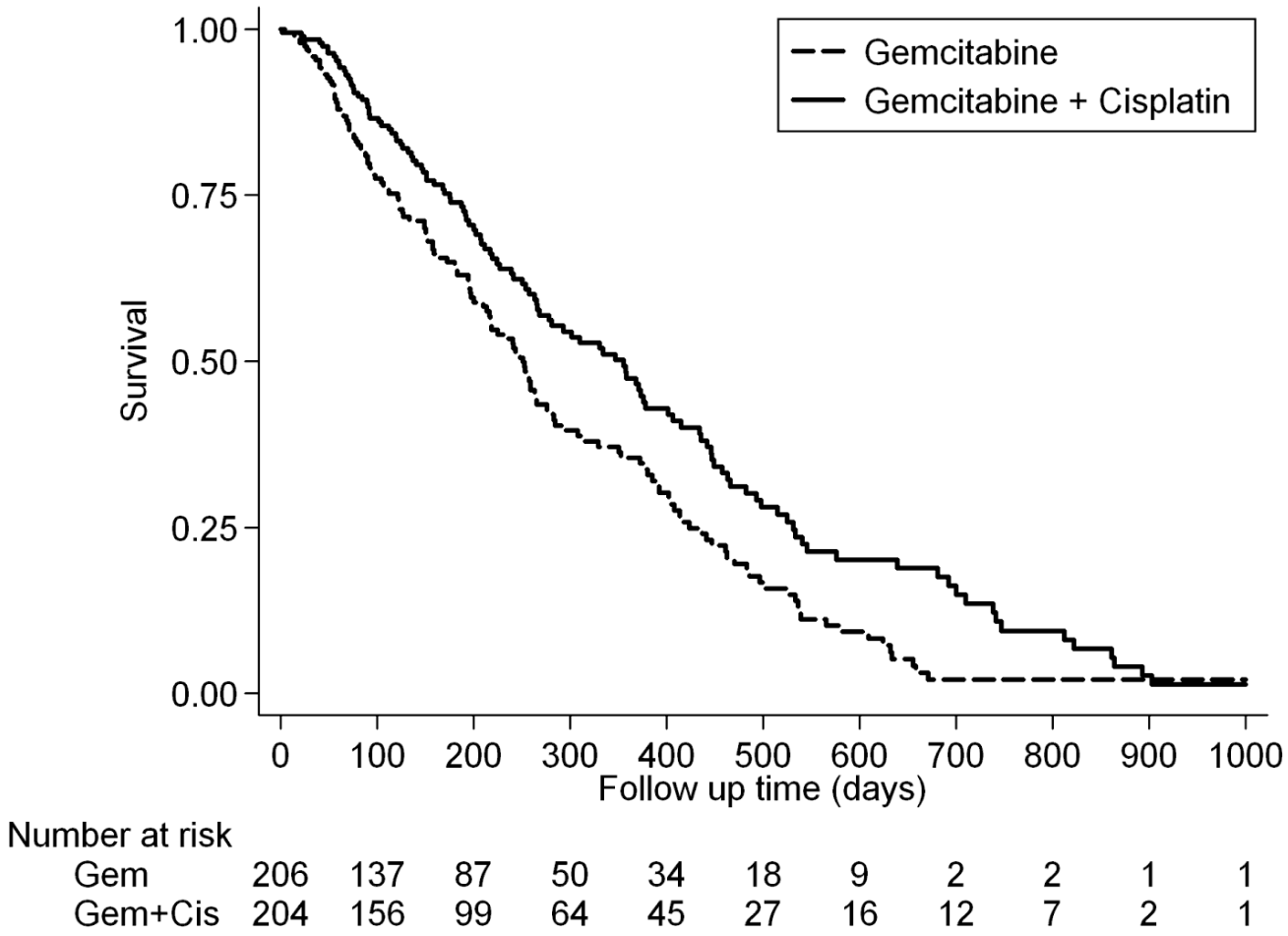
Pre-2010	The dark ages: No SOC
2010	**Gemcitabine and cisplatin improves survival compared with single agent gemcitabine**
2010-2018	No drug or drug combination is better than Gemcitabine and cisplatin 1L
2018	**Gem/cis + S1 superior to Gem/cis in Asian patients**
2019	**FOLFOX superior to ASC**
2020	**Pemigatinib FDA approved**
2021	**Infigratinib FDA approved*** **Ivosidenib FDA approved**
2021	**NalIRI superior to 5FU (phase 2)** **Dabrafenib + Trametinib (BRAF V600E)** **Trastuzumab + Pertuzumab (Her2/neu)**
2021-2	**Derazantinib pivotal study competed.**
2022	**Durvalumab, Futibatinib FDA approved**
2023	**Keynote-966 Pembrolizumab; Zanidatamab, Tucatinib, Trastuzumab-Deruxtecan** **Pembrolizumab approved first line**

ABC-02 – ADVANCED BILIARY CANCER



1. Valle, et al, NEJM. 2010

Phase 3 ABC-02 trial: survival data (ITT)



Treatment arm	Gem	Gem+Cis
Number of patients	n=206	n=204
Deaths, n (%)	141 (68.5)	122 (59.8)
Median survival, months	8.3	11.7
Log-rank p-value	0.002	
HR (95% CI)	0.70 (0.54–0.89)	

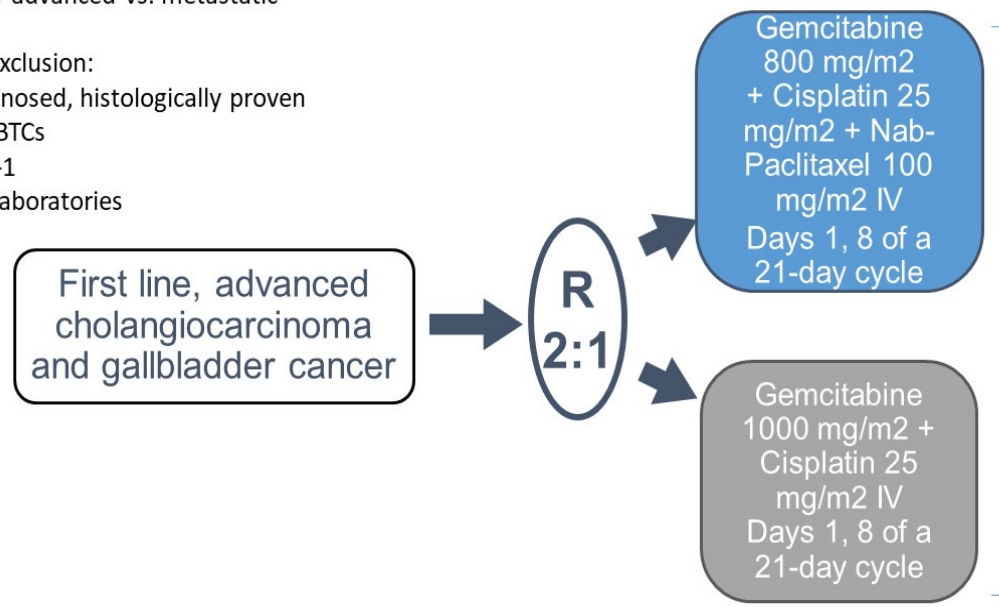
Valle J, et al. *N Engl J Med* 2010;362:1273–1281

SWOG-1815 Phase 3Trial of Gemcitabine, Cisplatin and Nab-paclitaxel vs Gemcitabine and Cisplatin Alone in Patients with Newly-diagnosed Advanced BTC

Study design

Prespecified stratifications factors: tumor type, PS, locally-advanced vs. metastatic

Key Inclusion/Exclusion:
- Newly diagnosed, histologically proven untreated BTCs
- ECOG PS 0-1
- Adequate laboratories



N = 441

FIRST PATIENT IN: 2/2019

CLOSED TO ACCRUAL 2/15/2021

Restage every 3 cycles until progression

Primary EP: OS; **Target HR 0.7**
Secondary: ORR, PFS, DCR, safety, CA 19-9 changes

Archival blood and tissue specimens to be banked

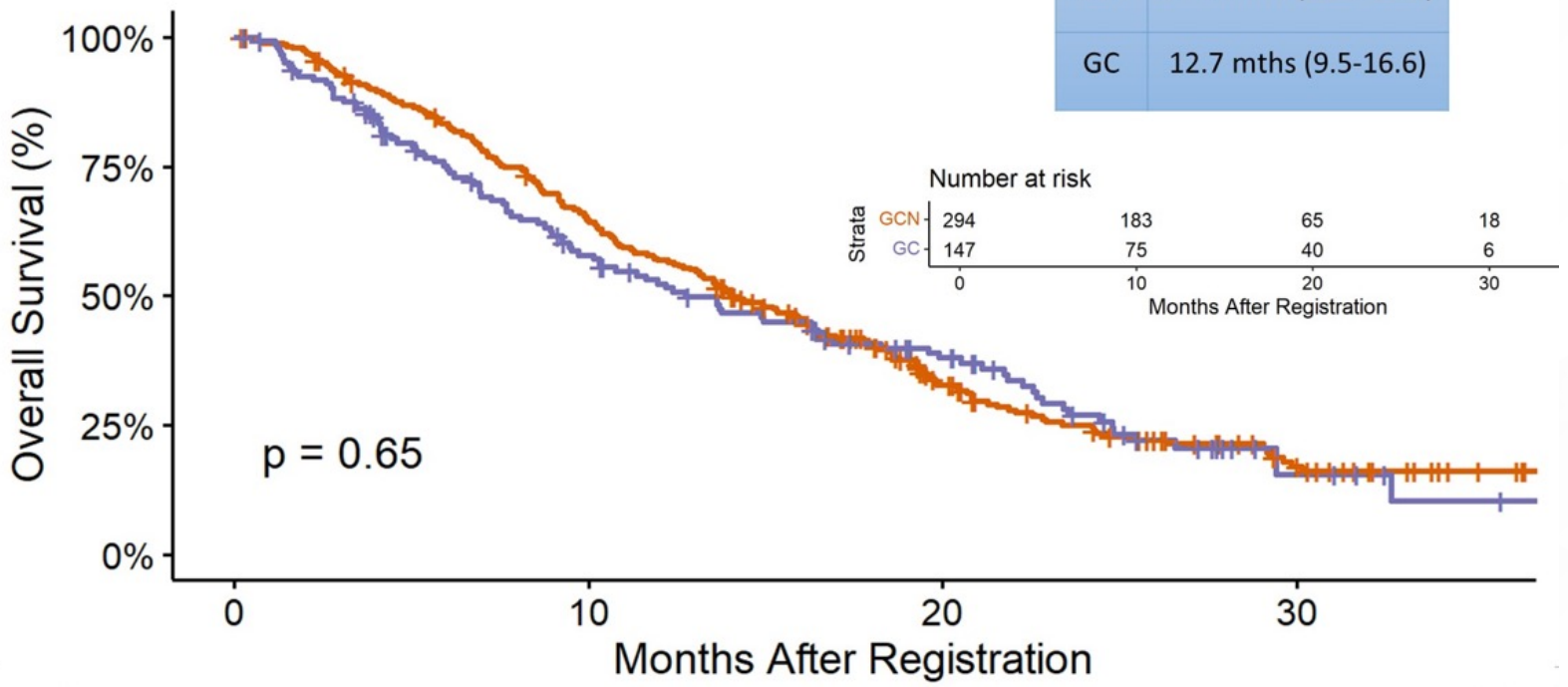
Shroff RT, et al. Presented at: ASCO GI; January 19-21, 2023; San Francisco, California. Abstract LBA490.

SWOG-1815 Trial Did Not Meet Its Primary Endpoint of OS

- The addition of nab-paclitaxel to GC did not improve median OS when compared with GC alone in newly-diagnosed, advanced BTCs
- A survival trend towards GCN was seen in patients with gallbladder cancer and with locally-advanced disease

OS

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



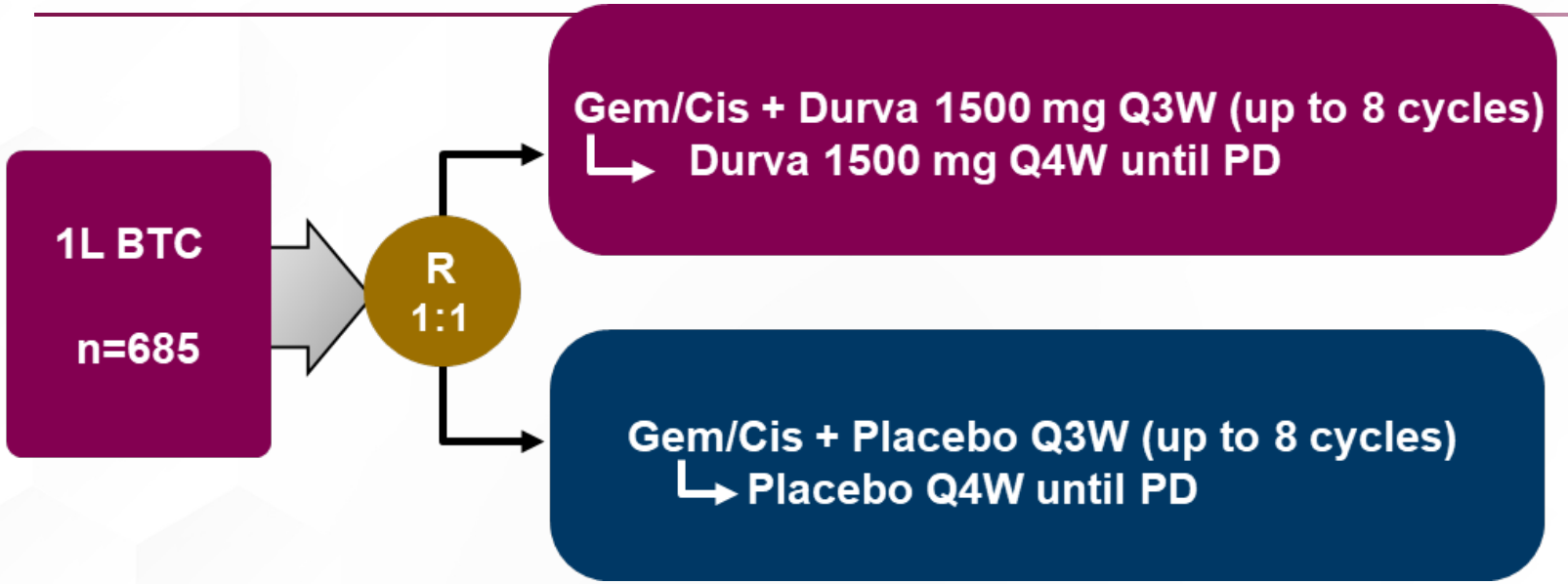
Subgroup analyses: median OS (months)

Disease Site	GCN (CI)	GC (CI)
Intrahepatic CCA	13.6 (11.7-16.1)	13.6 (9.5-19.6)
Extrahepatic CCA	15.8 (9.2-18.5)	16.3 (5.1-29.4)
Gallbladder Adenocarcinoma	17.0 (11.3-20.7)	9.3 (7.0-22.2)

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

Shroff RT, et al. Presented at: ASCO GI; January 19-21, 2023; San Francisco, California. Abstract LBA490.

TOPAZ-1 Study Design: Durvalumab + Chemotherapy in 1L BTC



PRIMARY ENDPOINT

OS

SECONDARY ENDPOINTS

PFS, ORR, DOR, PROs, Safety, Biomarkers (PD-L1), PK/ADA

Patient population

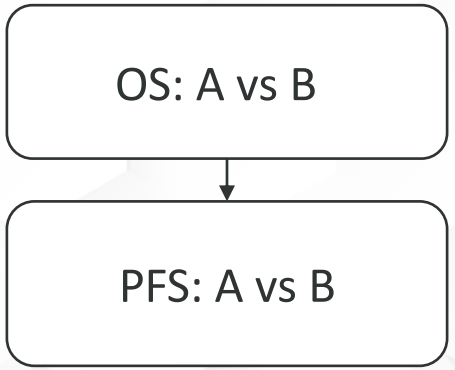
- Locally advanced, or metastatic BTC, or recurrence >6 months from curative surgery or last dose of adjuvant therapy
- Bili ≤2.0 × ULN,
- ECOG PS 0 and 1,
- Must have at least one measurable lesion by RECIST 1.1 at baseline
- Ampullary cancer excluded

Stratification factors

- Disease status (initially unresectable vs recurrent)
- Primary tumor location (ICC, ECC, GBC)

MTP at IA2

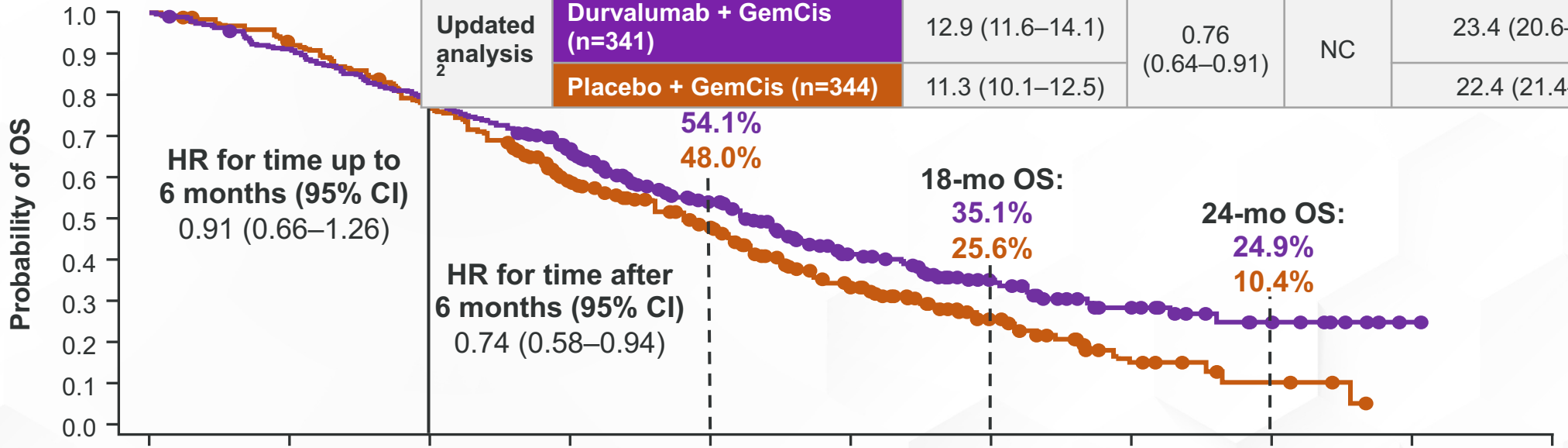
Statistical testing of PFS only if OS is statistically significant



Primary endpoint: OS Was Significantly Improved with Durvalumab + GemCis vs Placebo + GemCis

		Median OS (95% CI), mo	HR (95% CI)	p-value	Median duration of follow-up (95% CI), mo
Primary analysis [1]	Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021*	16.8 (14.8–17.7)
	Placebo + GemCis (n=344)	11.5 (10.1–12.5)			15.9 (14.9–16.9)
Updated analysis [2]	Durvalumab + GemCis (n=341)	12.9 (11.6–14.1)	0.76 (0.64–0.91)	NC	23.4 (20.6–25.2)
	Placebo + GemCis (n=344)	11.3 (10.1–12.5)			22.4 (21.4–23.8)

Kaplan–Meier curve of OS at the primary analysis[1]



No. 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

*Statistical significance cut-off for OS at primary analysis: p=0.03; formal statistical testing was not conducted for the updated analysis.

GemCis, gemcitabine and cisplatin.

1. Oh D-Y, et al. Accessed March 24, 2023. https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200015. 2. Oh D-Y, et al. Presented at ESMO Congress 2022; September 9-13, 2022; Paris, France. Poster 56P.

The Safety Profiles of Durvalumab + GemCis and Placebo + GemCis Were Similar

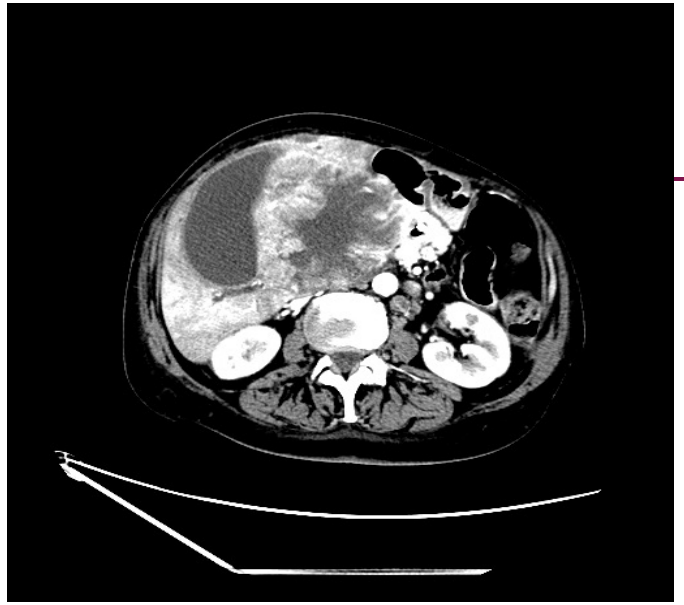
	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Median duration of exposure (range), months[1]		
Durvalumab / placebo	7.3 (0.1–24.5)	5.8 (0.2–21.5)
Gemcitabine	5.2 (0.1–8.3)	5.0 (0.2–8.6)
Cisplatin	5.1 (0.1–8.3)	4.9 (0.2–8.5)
AE, n (%)[2]		
Any AE	336 (99.4)	338 (98.8)
Any TRAE	314 (92.9)	308 (90.1)
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 discontinuation	44 (13.0)	52 (15.2)
Any TRAE leading to discontinuation	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†,1	43 (12.7)	16 (4.7)

*TRAEs leading to death were ischaemic stroke and hepatic failure in the durvalumab treatment group and polymyositis in the placebo treatment group. †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 aetiology.[2]

AE, adverse event; TRAE, treatment-related adverse event.

1. Oh D-Y, et al. *NEJM Evid.* 2022;1(8):EVIDoa2200015. Supplementary Appendix. 2. Oh D-Y, et al. Accessed March 24, 2023. https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200015.

Case of Gallbladder Cancer



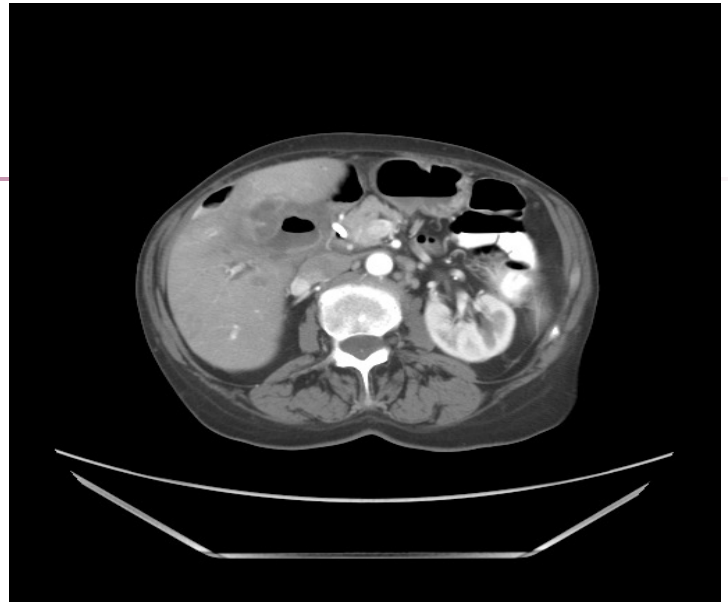
Feb 2022

62 Y/F presenting with painless jaundice, abdominal distention, obstruction at level of CBD.

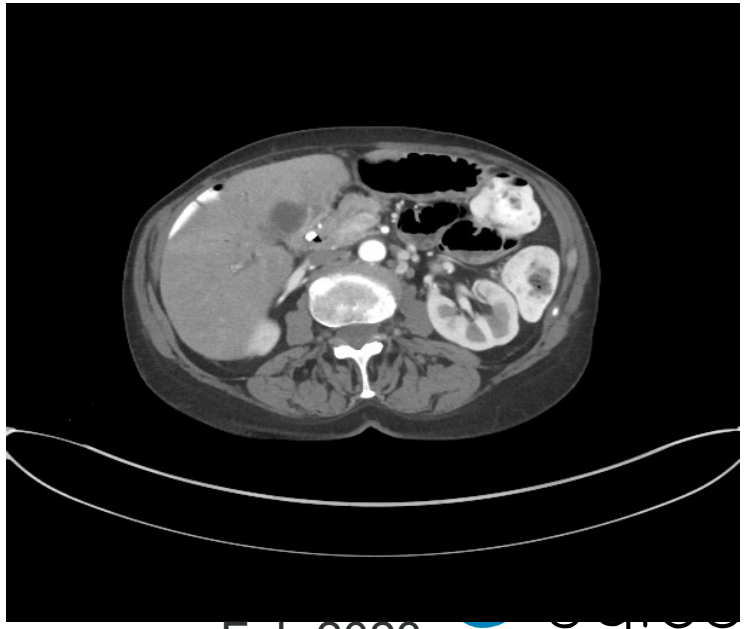
Large mass involving GB neck, hepatoduodenal ligament, liver mets and regional nodes.

Pathology: Poorly differentiated adenoca, IHC suggests biliary primary.

NGS: BRCA2 (somatic), PDL1+, TMB=6 mut/MB



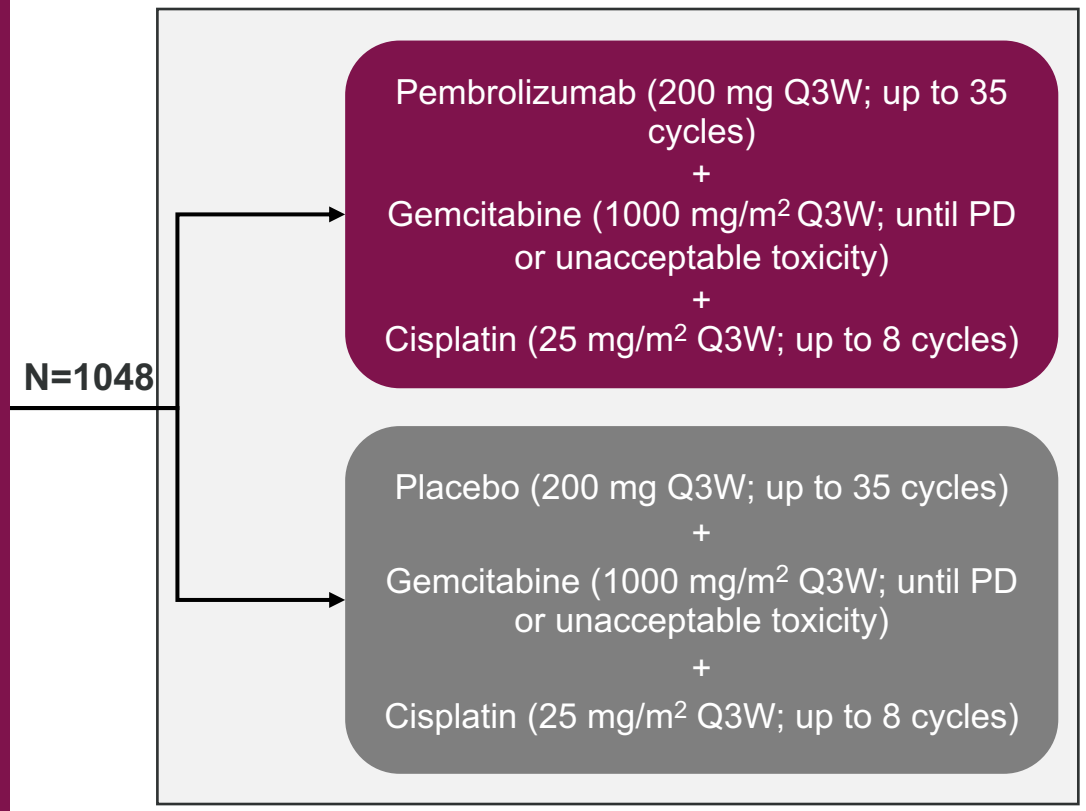
May 2022



Feb 2023

KEYNOTE-966: pembrolizumab plus GemCis versus GemCis alone in first-line advanced and/or unresectable BTC

Screening/baseline:
- Histologically confirmed diagnosis of advanced (metastatic) and/or unresectable (locally advanced) BTC (ampullary cancer excluded)
- Measurable disease based on RECIST v1.1, as determined by the site investigator
- No prior systemic therapies
- No CNS metastases and/or carcinomatous meningitis
- Participants with a history of hepatitis B/C can be enrolled if they meet study criteria
- Availability of archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion
- Life expectancy >3 months
- Adequate organ function



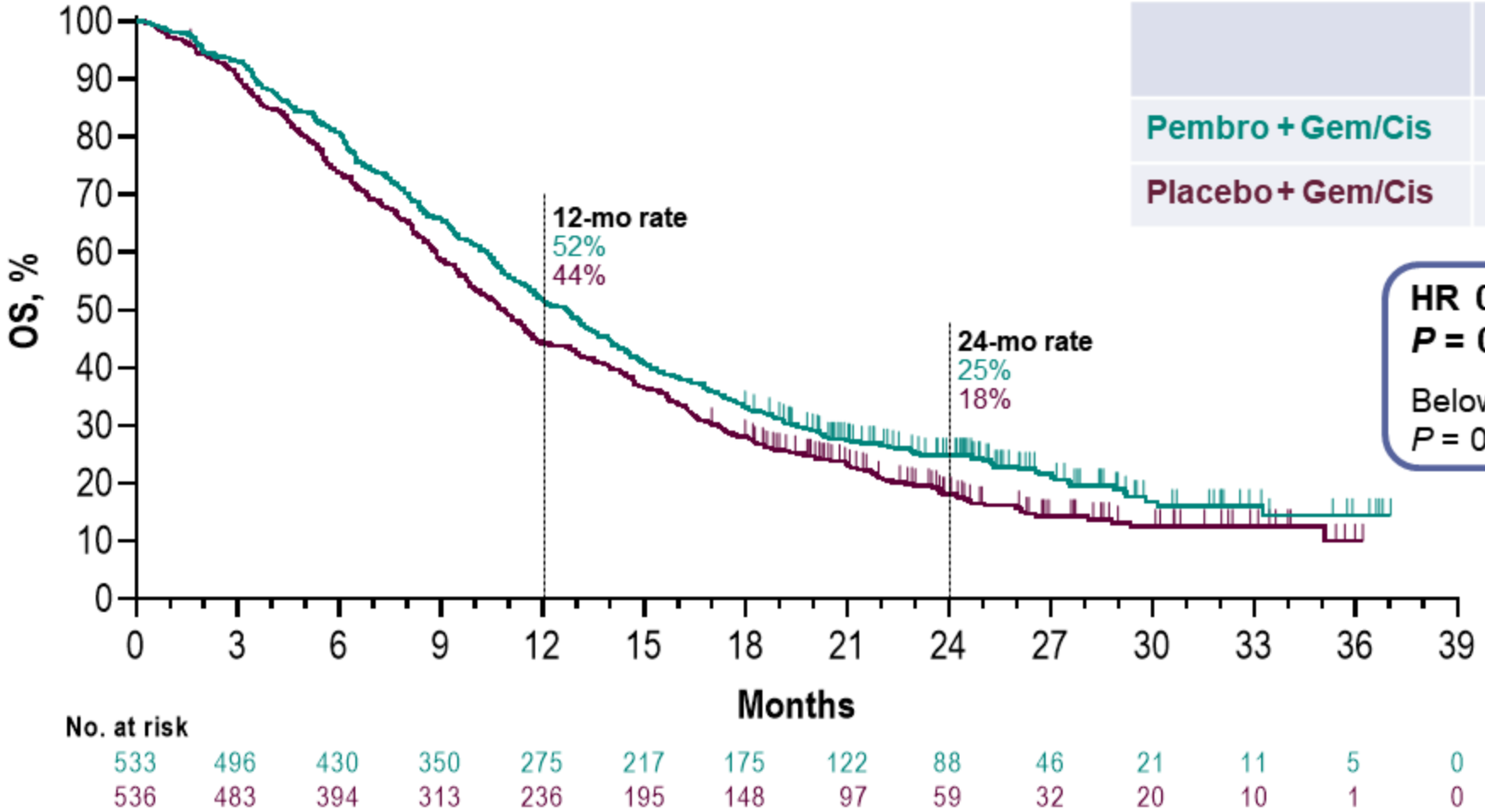
Status	Active, not recruiting
Estimated completion date	August 31, 2023

Primary objective:
- OS

Secondary objectives:
- ORR (RECIST v1.1; BICR)
- DOR (RECIST v1.1; BICR)
- PFS (RECIST v1.1; BICR)

Safety outcomes:
- Number of patients experiencing more than one adverse event
- Discontinuations due to adverse events

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.

Incidence of mutations in targetable pathways in biliary cancers

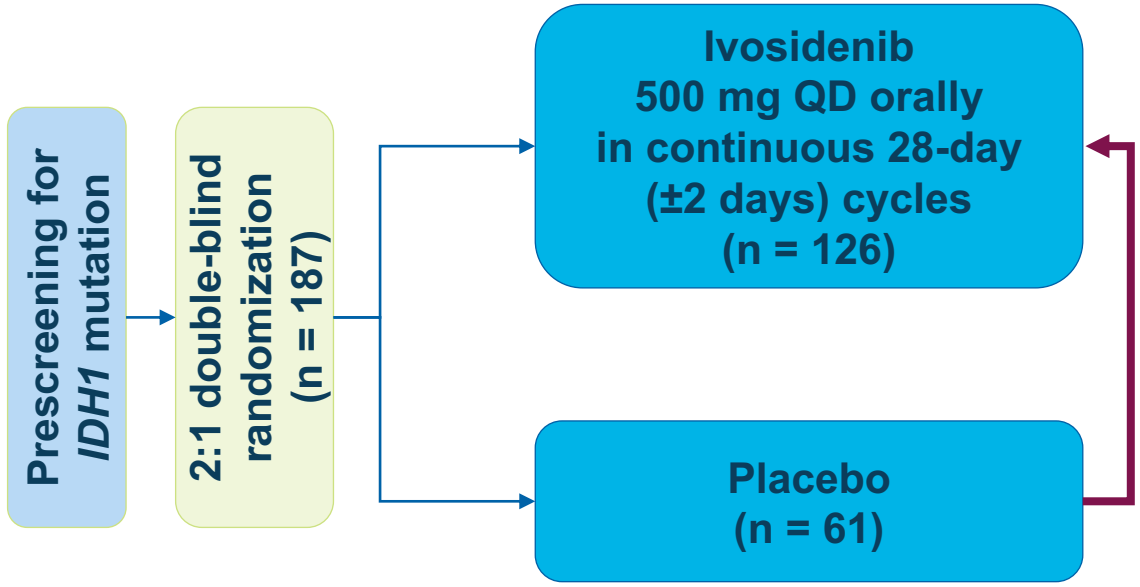
CGP findings	ICCA	ECCA	GBC
Total GA/patient	3.6	4.4	4.0
CRGA/patient	2.0	2.1	2.0
ERBB2 amplifications	4%	**11%**	**16%**
BRAF substitutions	**5%**	**3%**	1%
KRAS substitutions	22%	42%	11%
PI3KCA substitutions	5%	**7%**	14%
FGFR1–3 fusions and amplifications	**11%**	0	3%
CDKN2A/B loss	27%	17%	19%
IDH1/2 substitutions	**20%**	0	0
ARID1A alterations	18%	12%	13%
MET amplifications	2%	0	1%

Javle M, et al. *Cancer* 2016;122:3838–3847

ClarIDHy: Study design and endpoints

Key eligibility criteria

- ≥ 18 years of age
- Histologically confirmed diagnosis of CCA
- Centrally confirmed m*IDH1*[a] status by NGS
- ECOG PS score 0 or 1
- 1−2 prior therapies (at least 1 gemcitabine- or 5-FU-containing regimen)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function

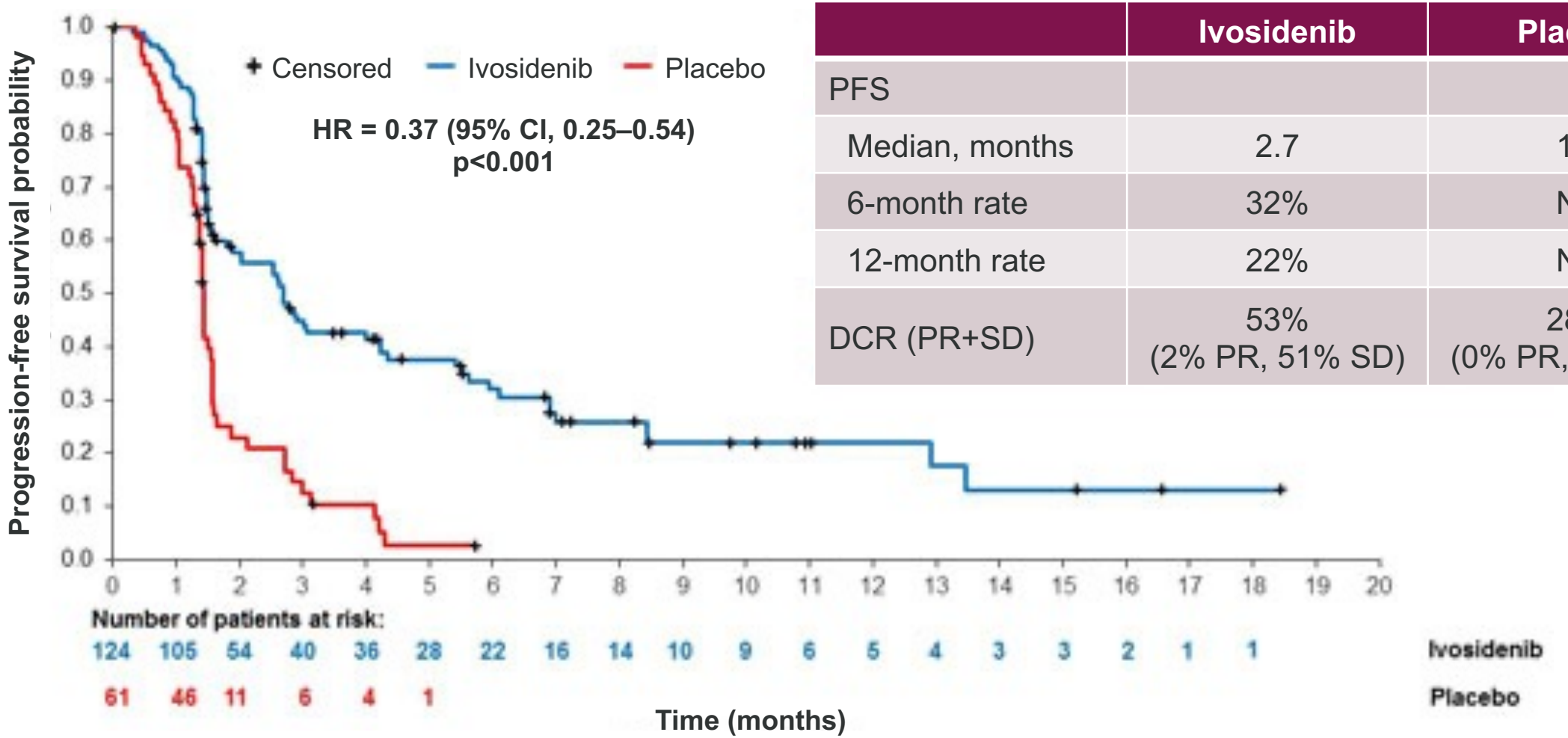


[b]Assessed using EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-BIL21, and PGI questions

ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = 5-level EuroQoL-5 Dimension questionnaire; FU = fluorouracil; NGS = next-generation sequencing; PGI = Patient Global Impression; QD = once daily; QLQ-BIL21 = Cholangiocarcinoma and Gallbladder Cancer module; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST = Response Evaluation Criteria in Solid Tumors

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

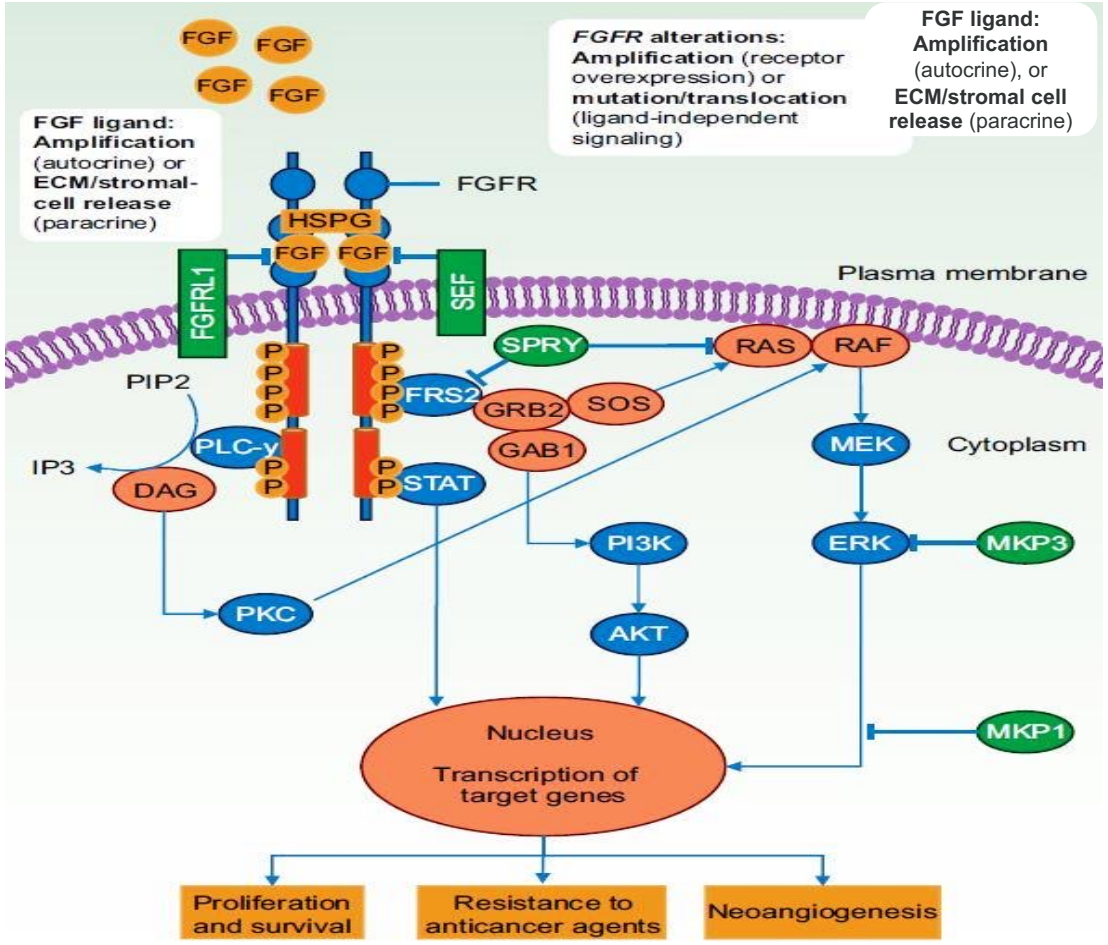
Phase 3 ClarIDHy trial: IDH1 inhibitor ivosidenib vs placebo in second-line setting: PFS by IRC



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

Abou-Alfa GK, et al. Presented at: ESMO Congress 2019; 27 September–01 October 2019; Barcelona, Spain. Abs LBA10
NE, not estimated

Mechanisms of FGFR Signaling



Cholangiocarcinoma:

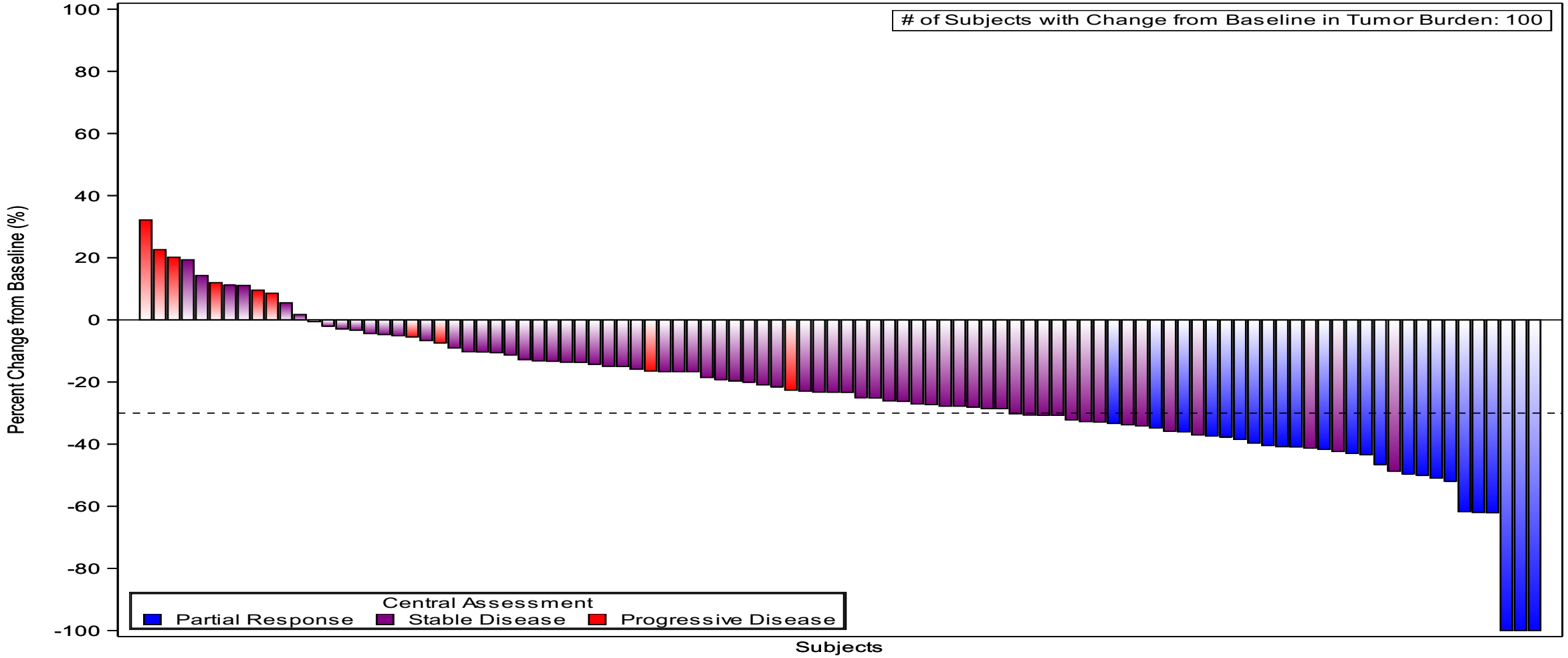
'Clinical Phenotype'

- Stage of cancer: earlier disease stage
- Age: higher proportion of patients aged <40 years
- Ethnicity: Caucasian > Asians; Women> Men
- Better clinical prognosis as compared with FGFR wt
- Distinct pattern of concurrent mutations: CDKN2A/B, TP53, KRAS associated with poor prognosis

Touat M, et al. *Clin Cancer Res* 2015;21:2684–2694

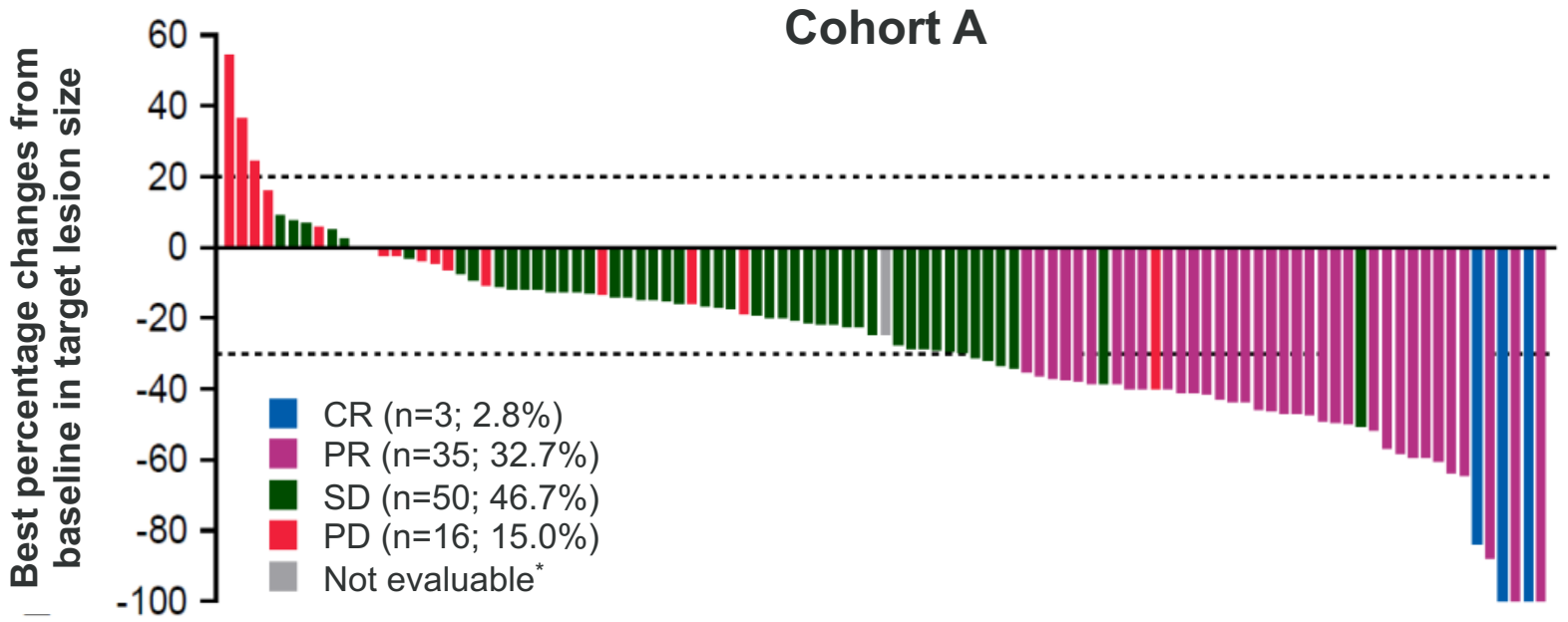
Jain. JCO Precision Oncology - published online January 17, 2018

Efficacy of infigratinib in *FGFR2* fusion-positive CCA



Javle M, et al. Presented at ASCO-GI, January 17, 2021. Abstract 265.

Phase 2 FIGHT-202 trial: pemigatinib in locally advanced or metastatic CCA



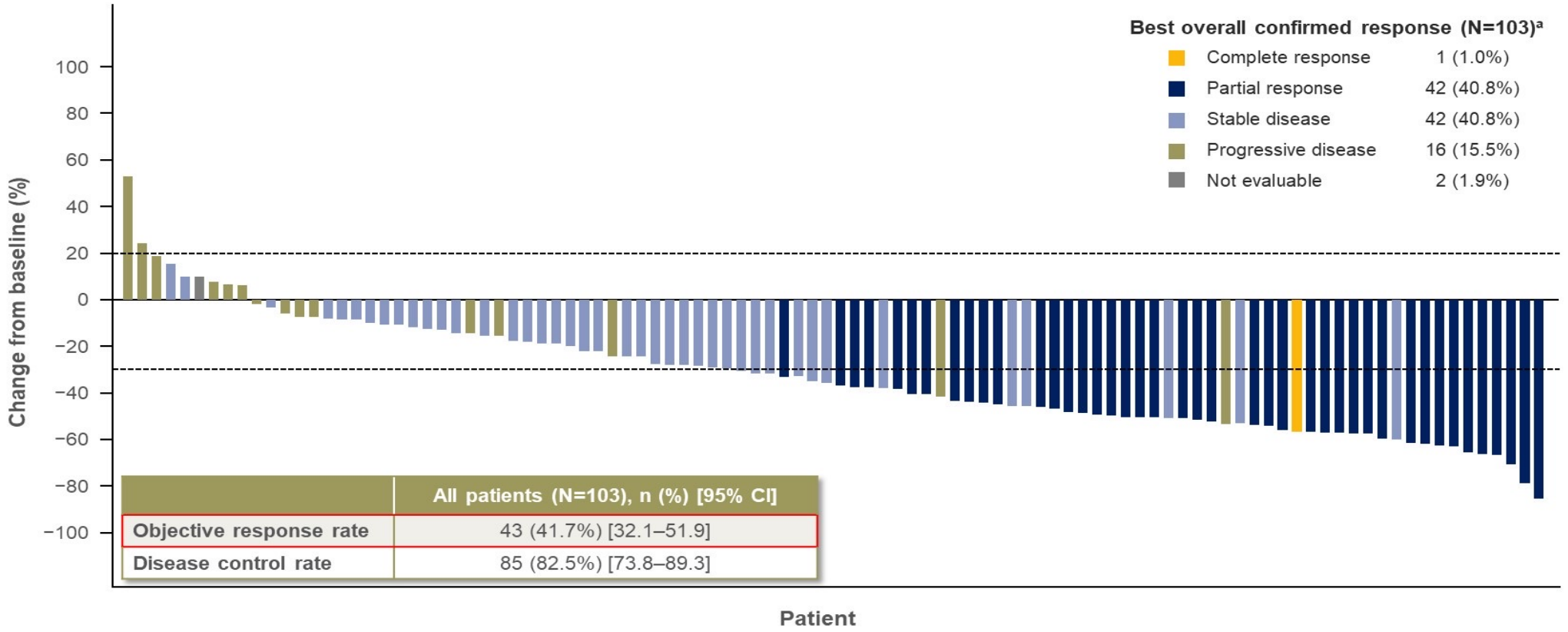
Variable	Cohort A (n=107) *FGFR2* fusions/rearrangements	Cohort B (n=20) Other *FGF/FGFR* genetic alterations	Cohort C (n=18) No *FGF/FGFR* genetic alterations
ORR, % (95% CI)	35.5 (26.50–45.35)	0	0
Best OR,[a] n (%)			
CR	3 (2.8)	0	0
PR	35 (32.7)	0	0
SD	50 (46.7)	8 (40.0)	4 (22.2)
PD	16 (15.0)	7 (35.0)	11 (61.1)
Not evaluable[a]	3 (2.8)	5 (25.0)	3 (16.7)
Median DoR, months (95% CI)	7.5 (5.7–14.5)	—	—
DCR (CR + PR + SD), % (95% CI)	82 (74–89)	40 (19–64)	22 (6–48)

*Patient had a decrease in target lesion size but was not evaluable for response per RECIST v1.1

Vogel A, et al. ESMO Congress 2019; 27 September–01 October 2019; Barcelona, Spain. Abs LBA40

FOENIX CCA2

Futibatinib in Intrahepatic Cholangiocarcinoma: Best Percent Change in Target Lesion Size



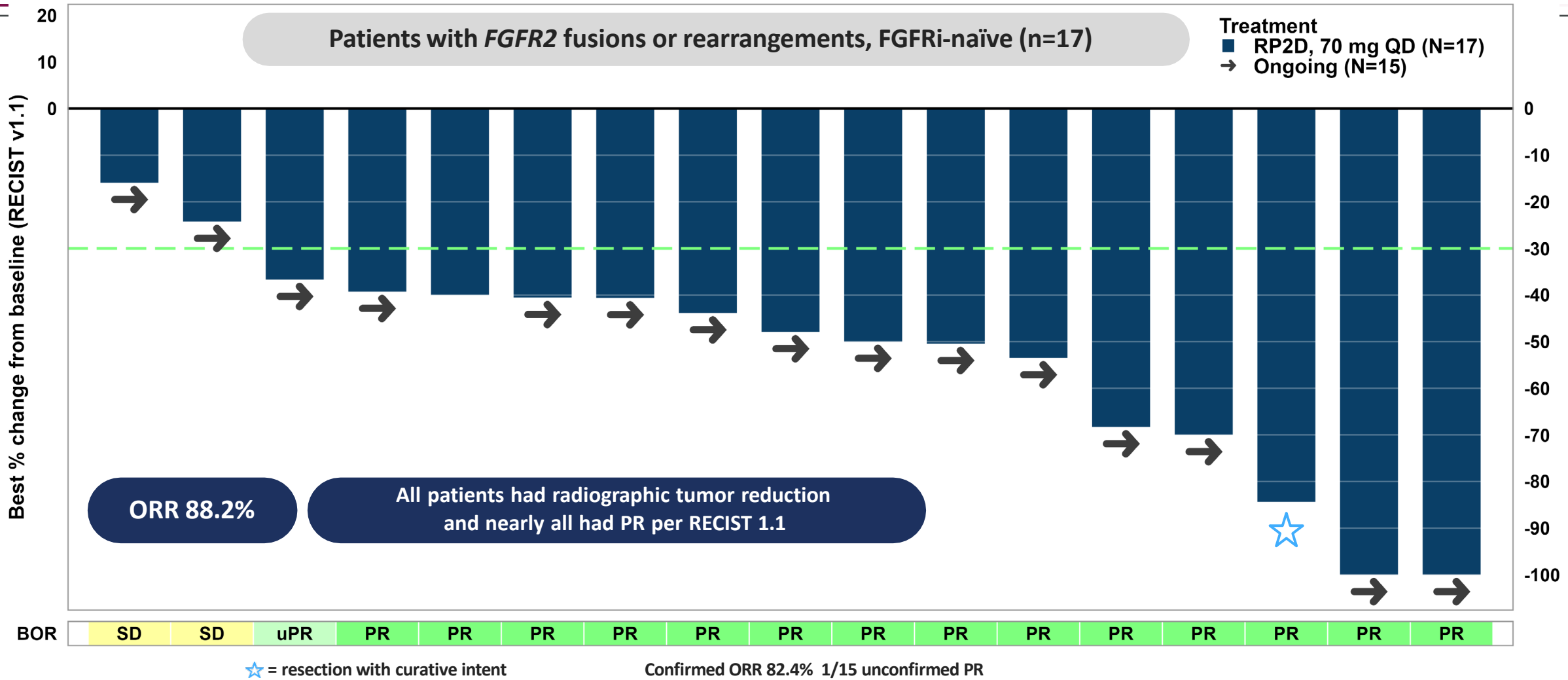
	All patients (N=103), n (%) [95% CI]
Objective response rate	43 (41.7%) [32.1–51.9]
Disease control rate	85 (82.5%) [73.8–89.3]

[a]Assessed by independent central review

Data cutoff: May 29, 2021. Dotted horizontal lines represent partial response (≥30% reduction in lesion size) and progressive disease (≥20% increase) per RECIST v1.1.
RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Goyal L, et al. *J Clin Oncol*. 2022;40(16_suppl):4009.

RLY-4008
Response per RECIST 1.1 at RP2D (70 mg QD)

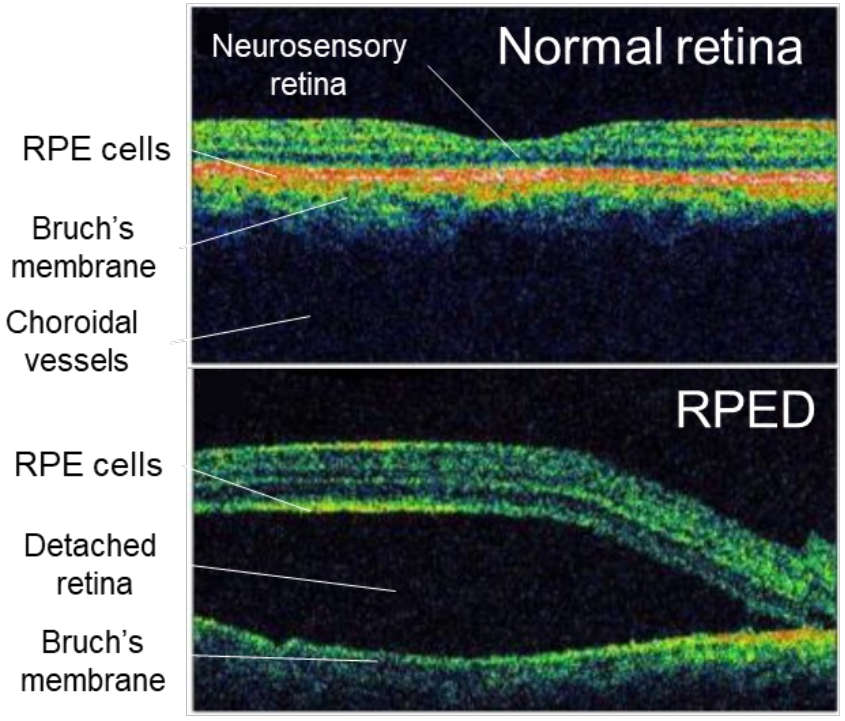


PARIS 2022 ESMO congress

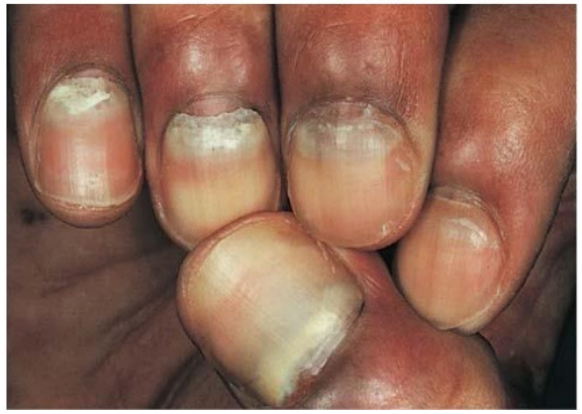
Hollebecque A et al., Efficacy of RLY-4008, a highly selective FGFR2 inhibitor in patients with an FGFR2-fusion or rearrangement, FGFR inhibitor-naïve cholangiocarcinoma: ReFocus trial. ESMO 2022.

Notable FGFRi-Related AEs

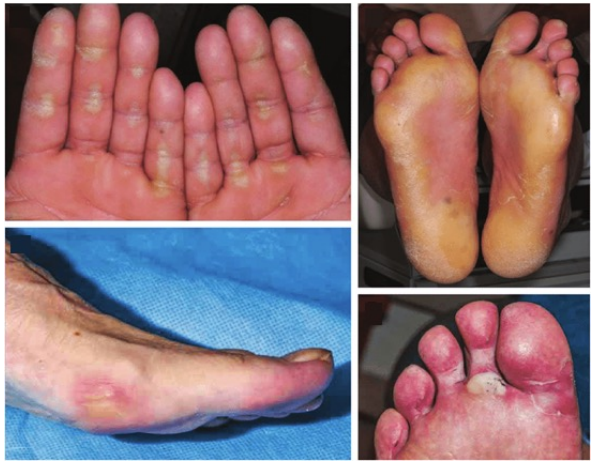
RPED Presentation[1]



Onychomadesis Presentation[2]



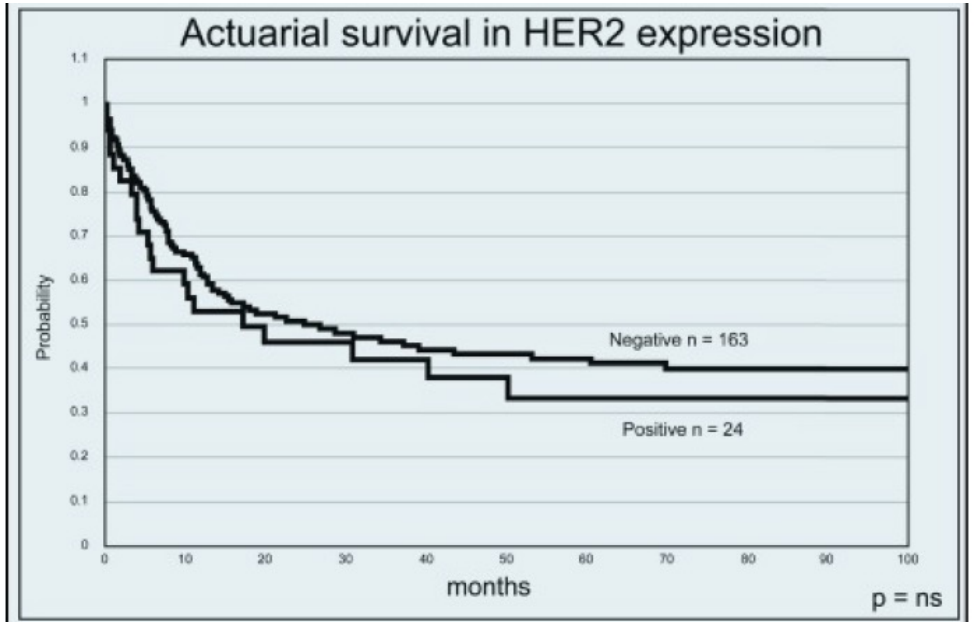
PPE Presentation[3]



HER 2/neu expression GB Cancer

Demographics

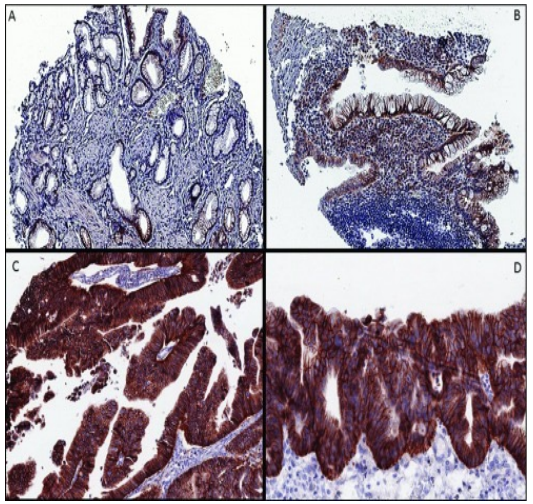
Gender	*n* (total)	Mean age	SD
Female	165	61.6	13.5
Male	22	69.0	14.3
Total	187	62.5	14.4



Gallbladder cancer (N=187)

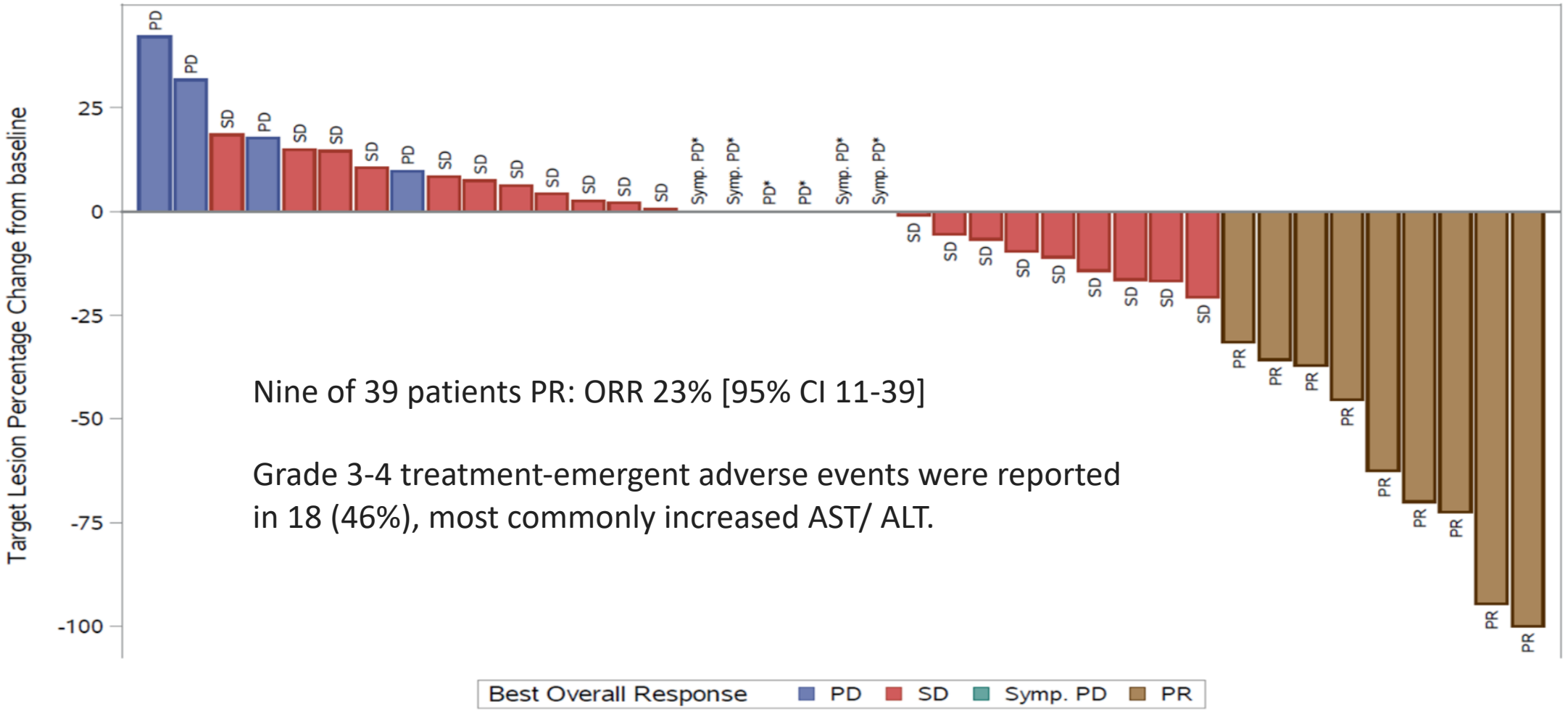
HER2/ neu expression

- 90 (48.1%) stained negative,
- 35 (18.7%) were 1+, 38 (20.3%) were 2+,
- 24 (12.8%) were considered positive (3+)



Gastrointest Cancer Res. 2014 Mar-Apr; 7(2): 42–48

Trastuzumab plus pertuzumab for HER2/neu-amplified BTC

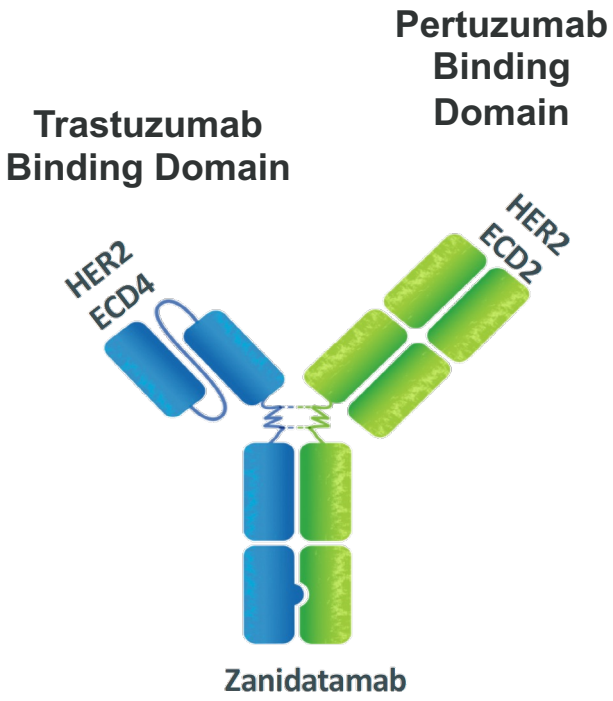


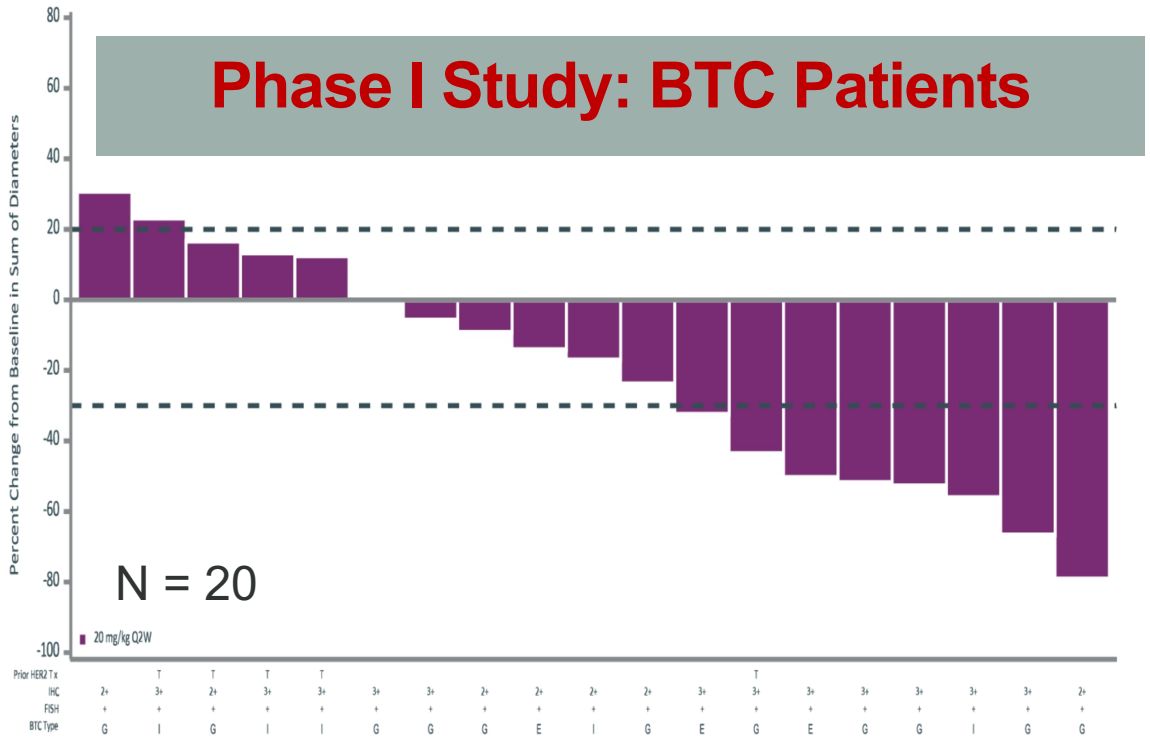
Nine of 39 patients PR: ORR 23% [95% CI 11-39]

Grade 3-4 treatment-emergent adverse events were reported in 18 (46%), most commonly increased AST/ ALT.

Javle M, et al. Lancet Oncol 2021 Sep;22(9):1290-1300.

Zanidatamab: Bispecific HER2-Targeted Antibody



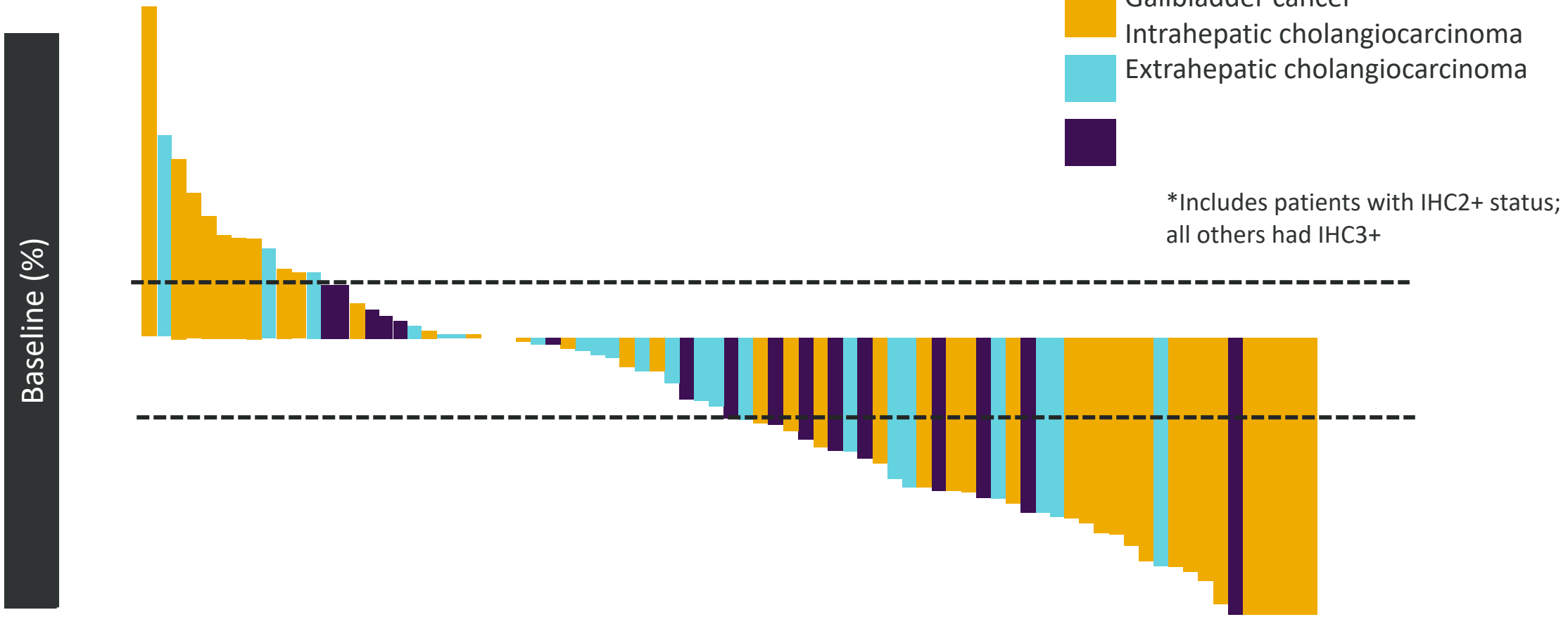


ORR 40% **DCR 65%** **DOR 7.4 mo**

Meric-Bernstam et al, *J Clin Oncol* 2021

HERIZON-BTC-01: Change in Target Lesion Size From Baseline (Cohort 1)

- Target lesions decreased in 68.4% of patients

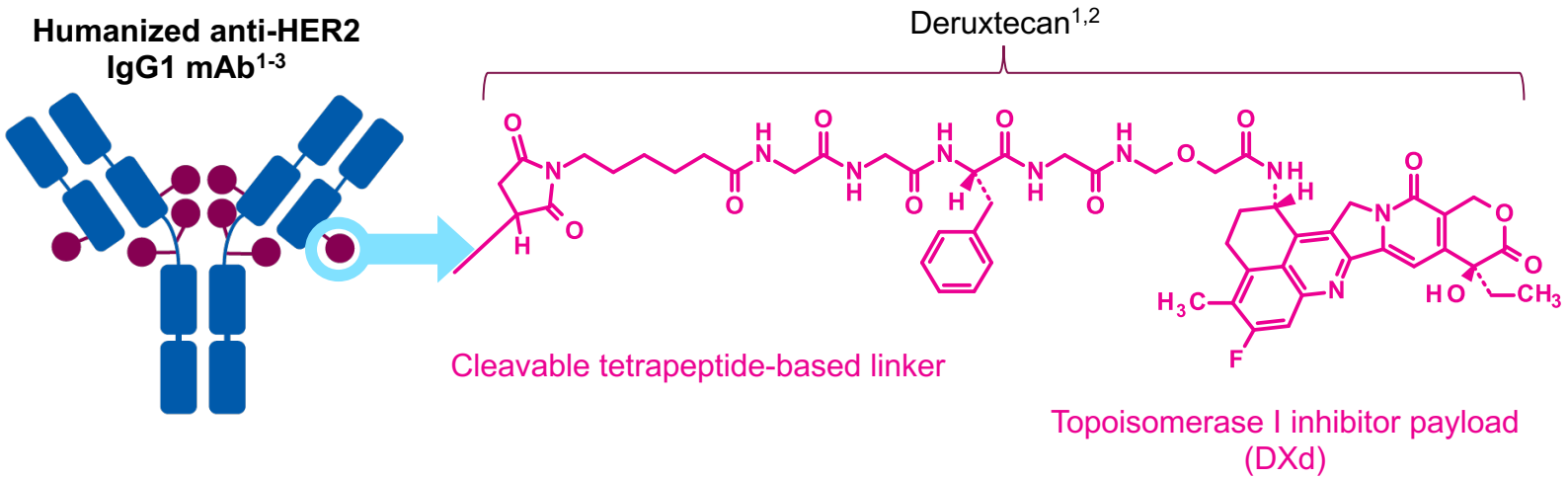


Pant. ASCO 2023. Abstr 4008. Harding. Lancet Oncol. 2023;[Epub].

Trastuzumab deruxtecan (T-DXd) Was Designed With 7 Key Attributes

T-DXd is an ADC composed of 3 parts[1,2]:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



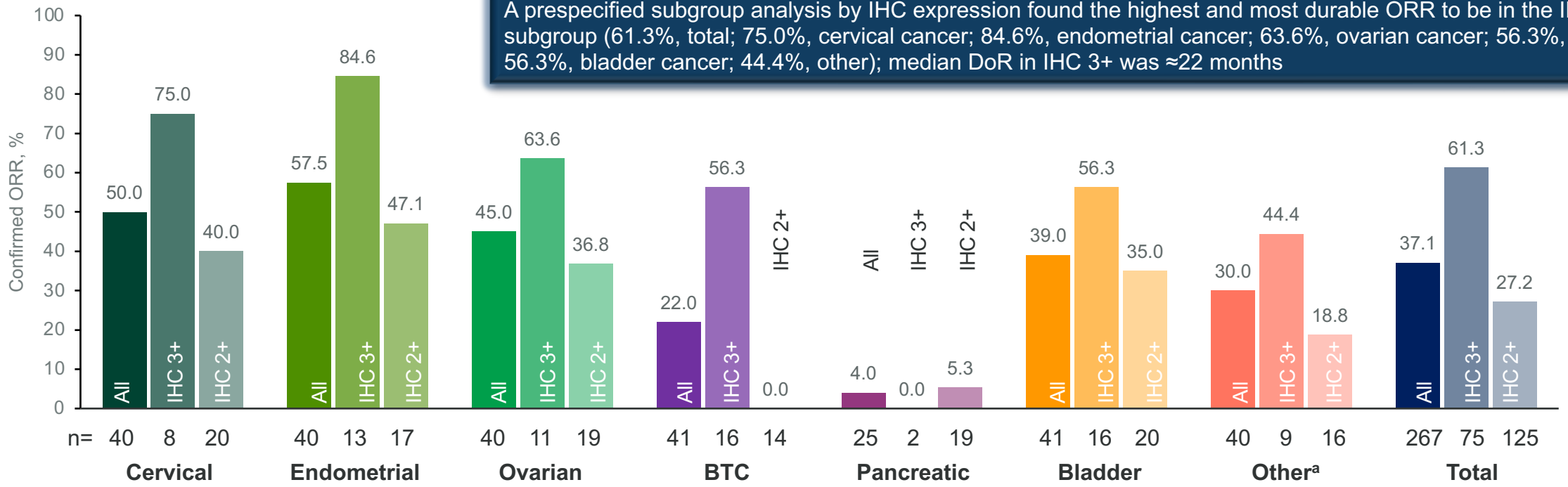
- Payload mechanism of action: topoisomerase I inhibitor[1,2,a]
- High potency of payload[1,2,a]
- High drug to antibody ratio ≈8[1,2,a]
- Payload with short systemic half-life[1,2,a]
- Stable linker-payload[1,2,a]
- Tumor-selective cleavable linker[1,2,a]
- Bystander antitumor effect[1,4,a]

[a] The clinical relevance of these features is under investigation.

1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

Objective Response Rate by HER2 status

A prespecified subgroup analysis by IHC expression found the highest and most durable ORR to be in the IHC 3+ subgroup (61.3%, total; 75.0%, cervical cancer; 84.6%, endometrial cancer; 63.6%, ovarian cancer; 56.3%, BTC; 56.3%, bladder cancer; 44.4%, other); median DoR in IHC 3+ was ≈22 months



	All patients (n=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DoR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DoR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status.

[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.

Meric-Bernstam F et al. Presented at: ASCO Annual Meeting; June 4-6, 2023; Chicago, IL.

Click for abbreviations

Novel Agents in Trials

Compound	Action	Trial Phase
Surufatinib	Angiogenesis	Phase 2/3 (China)
Milademetan	mdm2	Phase 2
BI907828	Mdm2	Phase 2
Pamiparib Olaparib	PARP	Phase 2
CTX009 + Paclitaxel	VEGFR/ DLL	Phase 2
Spartalizumab Dostarlimab PRMT5, MTA inhibitors	PD1 MTAP loss	Phase 2 Phase 2

How Far We Have Come in BTC…

- No drug approved <2020; 6 FDA approvals in 3 years, several NCCN designations
- Immunotherapy for these cancers is a promising area, Gem/cis and Durvalumab/ Pembrolizumab is current standard of care 1L
- The advent of molecular profiling, targeted therapies, multiagent chemotherapy has led to a ‘sea change’ in management of BTC
- IDH1, FGFR, Her2/neu, BRAFV600E, DDR, MTAP loss, Angiogenesis promising areas
- Model for ‘Precision Medicine’ in GI cancers

Sobering Statistics of PDAC

- About 64,050 people (33,130 men and 30,920 women) will be diagnosed with pancreatic cancer.
- About 50,550 people (26,620 men and 23,930 women) will die of pancreatic cancer.
- Represents only 3% of all cancers, but 4th leading cause of cancer deaths
- Incidence rising by 1% annually worldwide
- Majority present at an advanced disease stage
- 5-year survival has improved over the past decade from 5% to 11%

Source: American Cancer Society (www.cancer.org)

TIMELINE FOR DRUG APPROVALS IN PDAC

Pre-1996	The dark ages. Nothing works
1996	Gemcitabine improves survival compared with 5-FU. Gemcitabine is approved for PC
1996-2005	Many agents tested. No drug or drug combination is better than Gemcitabine
2005	Erlotinib + Gemcitabine modestly improves survival compared with Gemcitabine. Erlotinib is approved for PC
2005-2009	More drugs tested. Many more negative trials
2010	FOLFIRINOX improves survival compared with Gemcitabine
2012	*nab*-Paclitaxel + Gemcitabine improves survival compared with Gemcitabine
2016	Nal-IRI + 5FU/ LVF approved for 2nd line therapy for PC
2017	Pembrolizumab approved for MSI-H cancers including pancreatic cancer
2019 **2022-23**	**Olaparib approved for gBRCA PDAC** **Sotorasib, adagrasib KRAS G12c** **NALIRIFOX**

MSI-H

KRAS G12C

FOLFIRINOX vs Gem

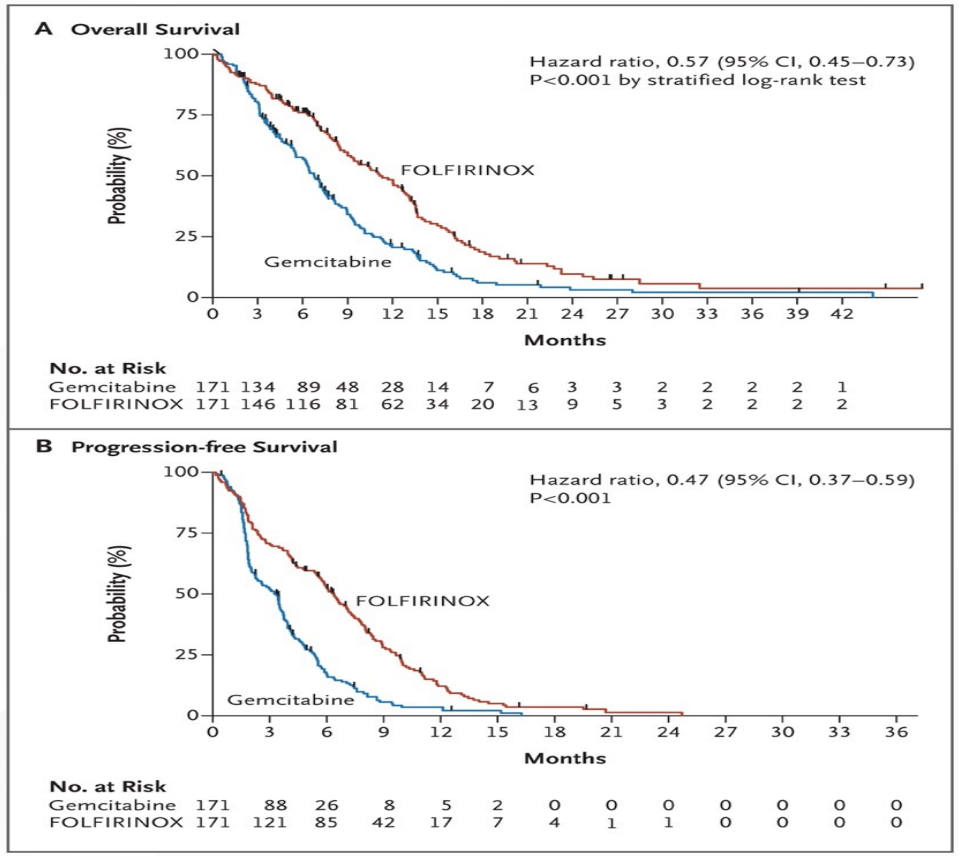


Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

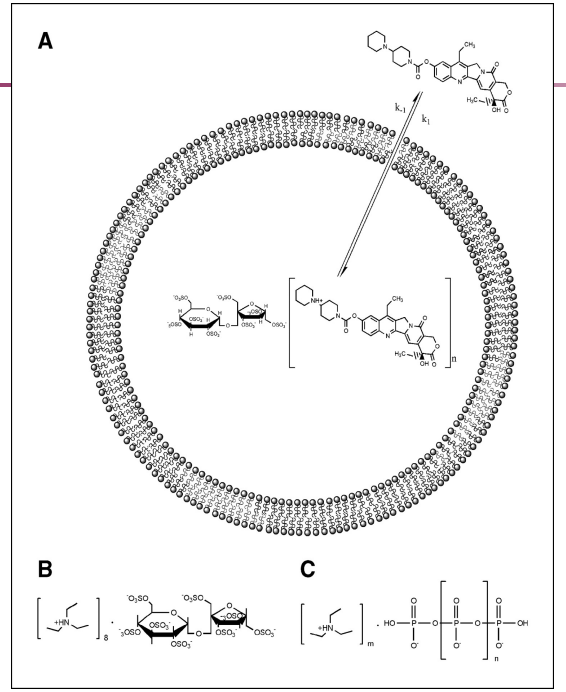
* Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant.

N Engl J Med 2011;364(19):1817-25

Development of Highly Active Nanoliposomal Irinotecan

Liposome formulations of camptothecins have potential for pharmacologic advantages from successful drug delivery

Amelioration of toxicity by preventing premature delivery of the cytotoxic in the body



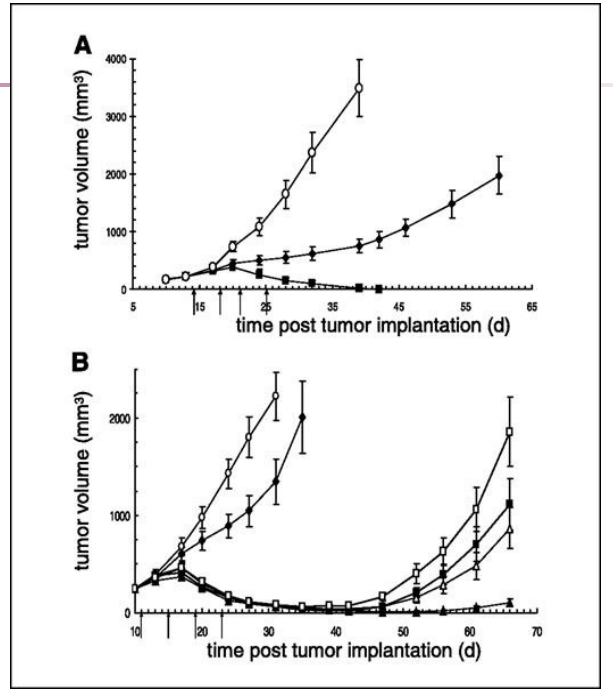
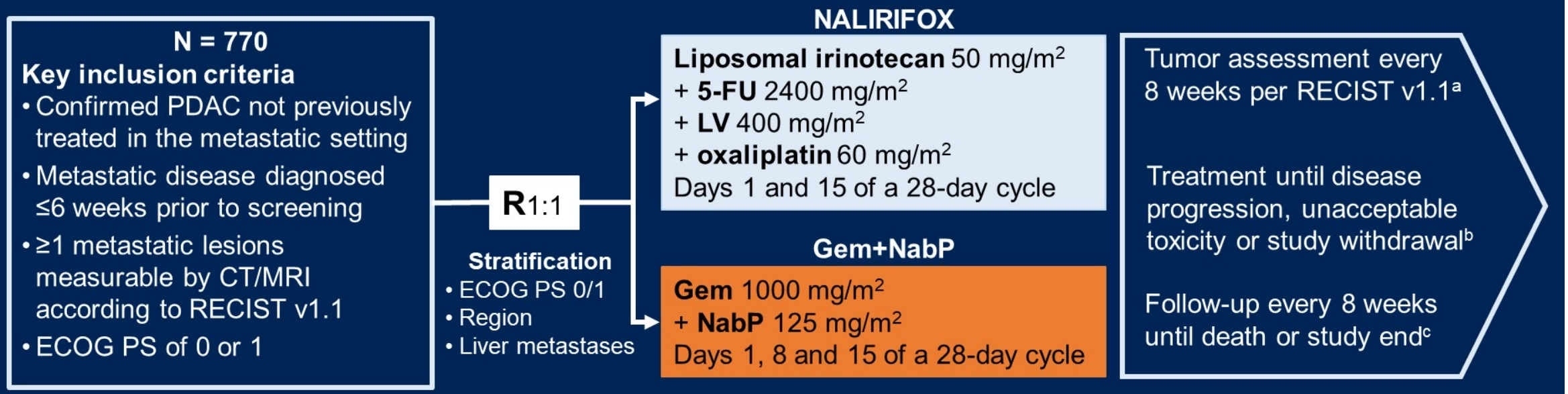


Table 1. Pharmacokinetic variables for free and nanoliposomal CPT-11 in rats

Formulation	$t_{1/2}$ (h)	AUC_{∞} (μg h/mL)	CL (mL/h)	V_d (mL)	MRT (h)	$t_{1/2}$ CPT-11 release (h)
Free CPT-11	0.27	6.2	1,609	616.4	0.4	–
Ls-CPT-11 [TEA-Pn]	6.80	1,407.8	7.10	69.7	9.8	14.0
Ls-CPT-11 [TEA-SOS]	10.7	2,134.4	4.69	72.3	15.4	56.8

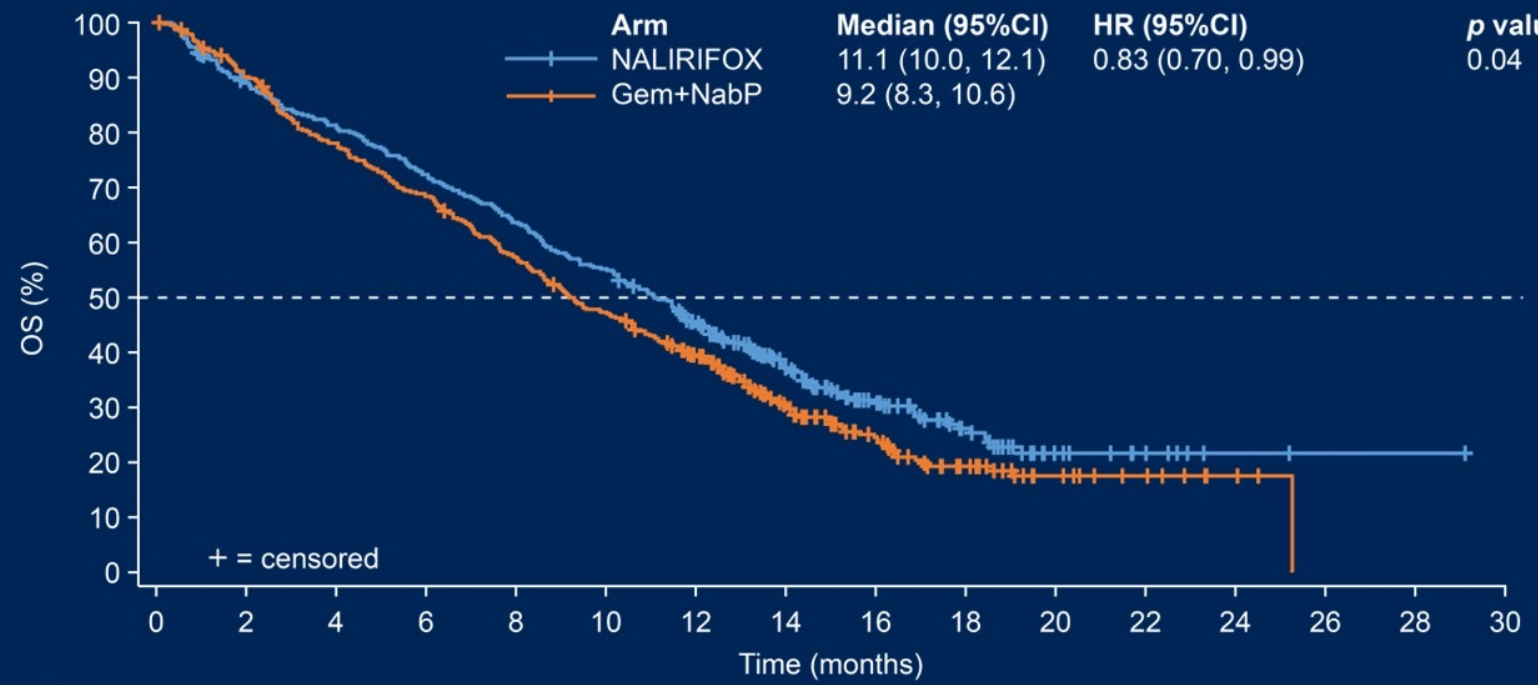
Cancer Res 2006; 66: (6). March 15, 2006

NAPOLI 3: Study design



[a]Tumor assessments (RECIST v1.1) were performed at baseline and every 8 weeks until radiologically progressive disease or until the start of another anti-cancer treatment, whichever came first. [b]Dose delays were permitted; if oxaliplatin was not well tolerated, patients in arm 1 could continue to receive liposomal irinotecan + 5-FU/LV. [c]The study will be completed once all patients have discontinued the study treatment and at least 543 OS events have occurred in randomized patients.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; LV, leucovorin; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

NAPOLI 3: mOS (ITT population)



Stratified by ECOG PS (0 vs 1), region (North America vs ROW), live metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; mOS, median overall survival; NabP, nab-paclitaxel.

NAPOLI 3: Selected any-cause TEAEs in ≥10% of patients

	NALIRIFOX (N = 370)		Gem+NabP (N = 379)	
Any-cause TEAEs in ≥10% of patients, %[a]	**Any grade**	**Grade 3–4**	**Any Grade**	**Grade 3–4**
Hematologic				
Neutropenia / neutrophil count decreased / febrile neutropenia	29.5 / 20.5 / 2.4	14.1 / 9.7 / 2.4	31.9 / 18.7 / 2.6	24.5 / 13.5 / 2.4
Anemia	26.2	10.5	40.4	17.4
Thrombocytopenia / platelet count decreased	13.5 / 10.5	0.8 / 0.8	22.7 / 17.9	3.7 / 2.4
Non-hematologic				
Diarrhea	70.5	20.3	36.7	4.5
Nausea	59.5	11.9	42.7	2.6
Vomiting	39.7	7.0	26.4	2.1
Hypokalemia	31.6	15.1	12.9	4.0
Peripheral neuropathy	17.8	3.2	17.4	5.8
Peripheral sensory neuropathy	15.1	3.5	13.5	2.9
Paresthesia	11.9	0.3	8.7	0.5
Pyrexia	10.5	0.8	23.0	1.6

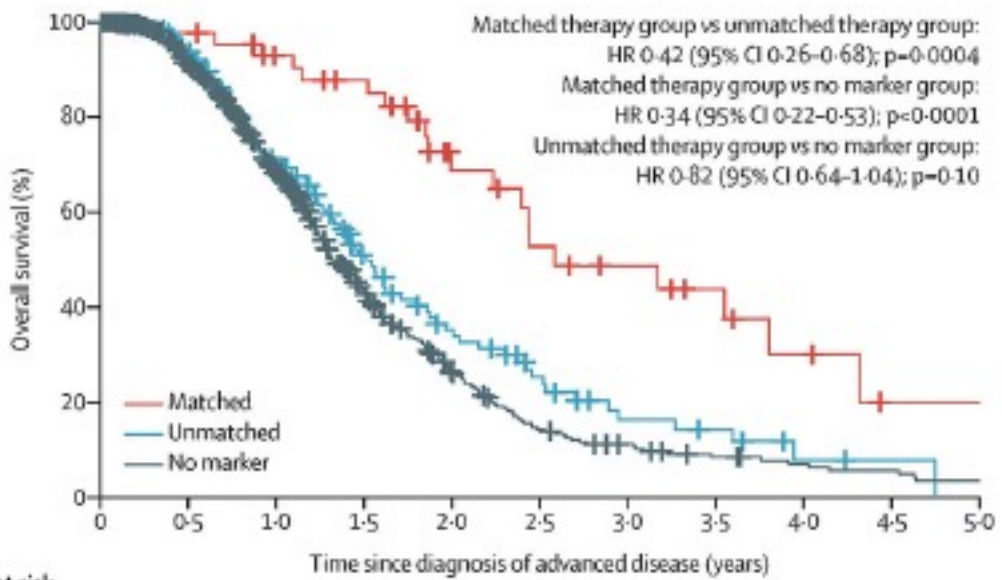
[a]Grouped by system organ class (safety population).
Gem, gemcitabine; NabP, nab-paclitaxel; TEAE, treatment-emergent adverse event.

Grade 3-4 Toxicities (%)

Toxicity	NALIRIFOX	FOLFIRINOX
Neutropenia	14	45.7
Febrile Neutropenia	2.4	5.4
Neuropathy	3.2	9
Diarrhea	20	12
Anemia	10	7.8
Thrombocytopenia	0.8	9

Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial

Most common actionable alteration is DDR



Number at risk (number censored)											
Matched therapy	46	42	36	32	18	13	10	7	4	1	1
	(0)	(3)	(4)	(2)	(8)	(1)	(2)	(2)	(1)	(2)	(0)
Unmatched therapy	143	116	78	44	27	16	8	6	2	1	0
	(0)	(19)	(11)	(15)	(4)	(4)	(3)	(1)	(2)	(1)	(0)
No marker	488	384	241	124	63	33	22	14	10	8	5
	(0)	(66)	(55)	(39)	(15)	(4)	(4)	(3)	(2)	(0)	(0)

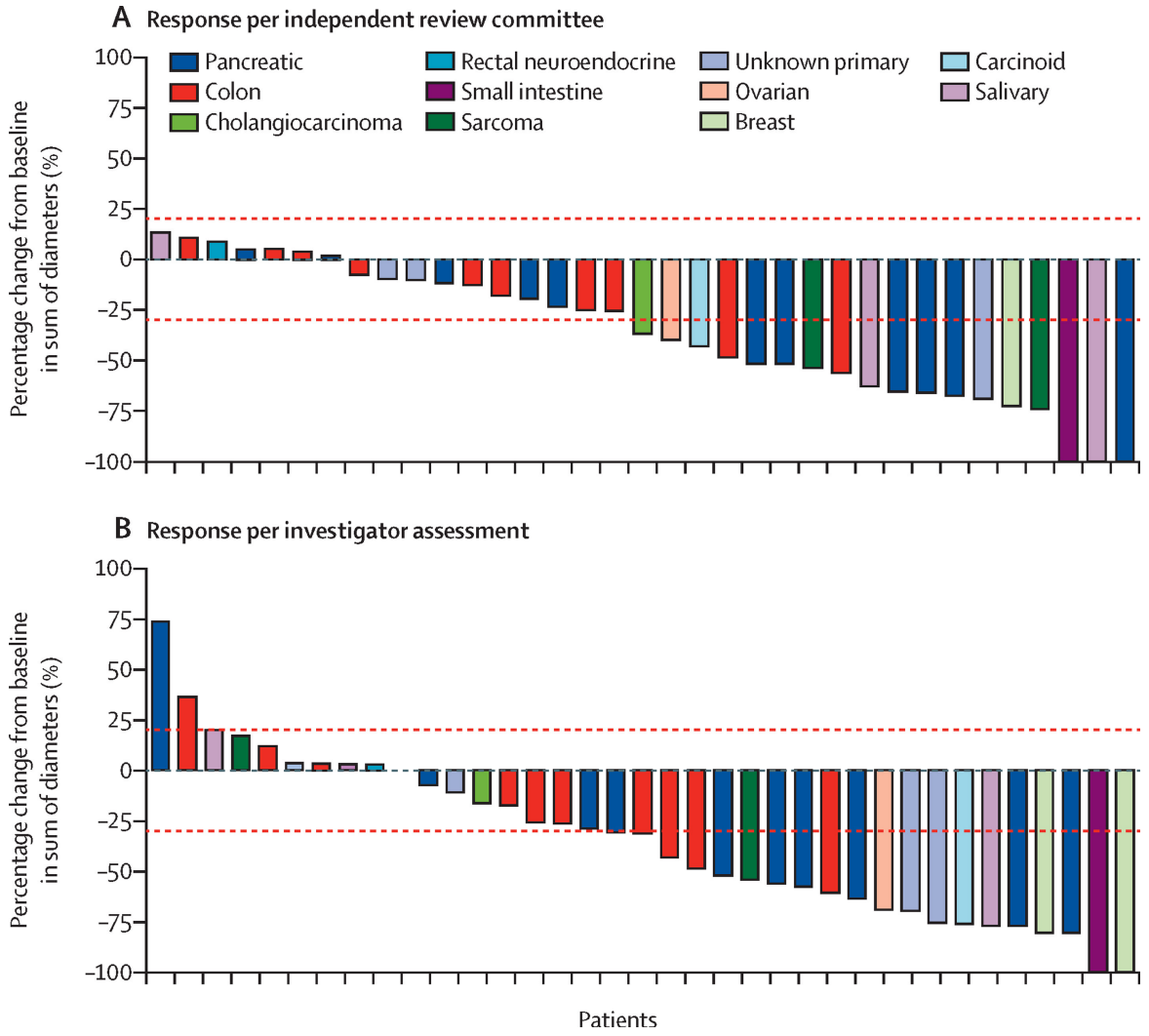
Figure 2.
Overall survival.
HR=hazard ratio.

Pishwain, Lancet Oncology 2020 Apr;21(4):508-518

TARGETED THERAPIES FOR PDAC

- RET fusions
- NTRK fusions
- KRAS
- CDKN2A
- NRG1 fusion
- TROP-2
- DNA damage repair

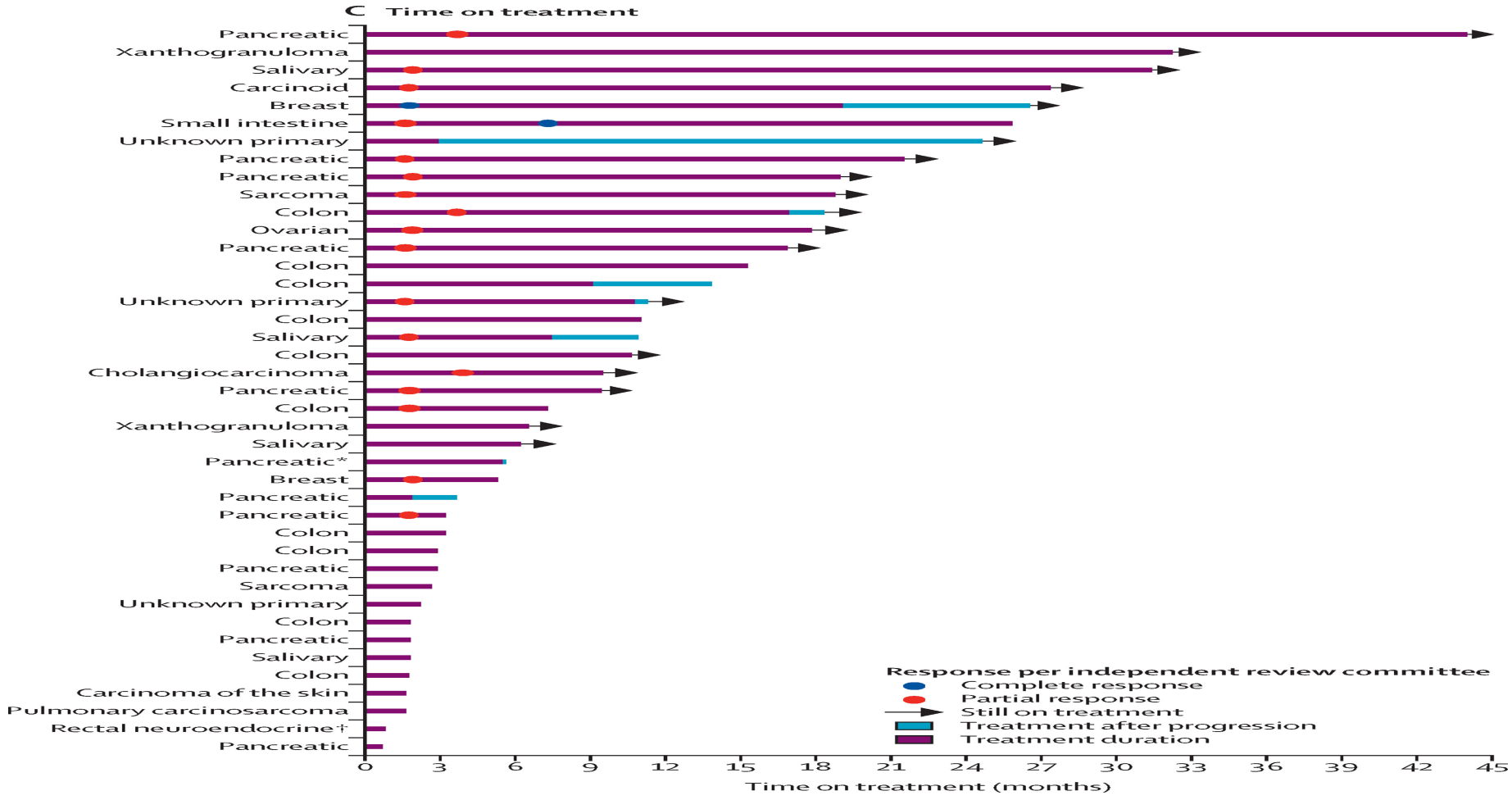
RET FUSION and SELPERCATINIB



1.35% of KRAS wt
0.6% PDAC

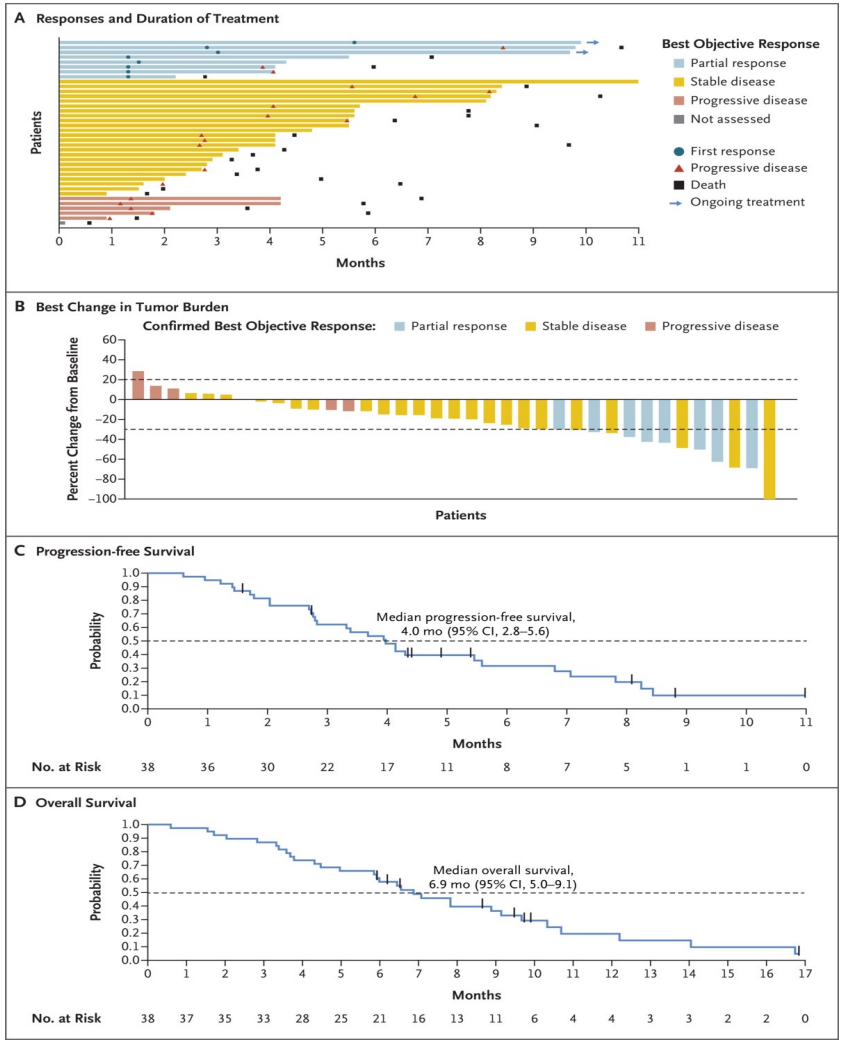
- Subbiah et al, Lancet Oncology, Sept 2022

RET FUSION and SELPERCATINIB



Lancet Oncology, Sept 2022

Efficacy Analyses of Sotorasib Therapy KRAS G12C PDAC.



1-2% PDAC

N Engl J Med 2023; 388:33-43

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy of Sotorasib Therapy.

Table 2. Efficacy of Sotorasib Therapy.*

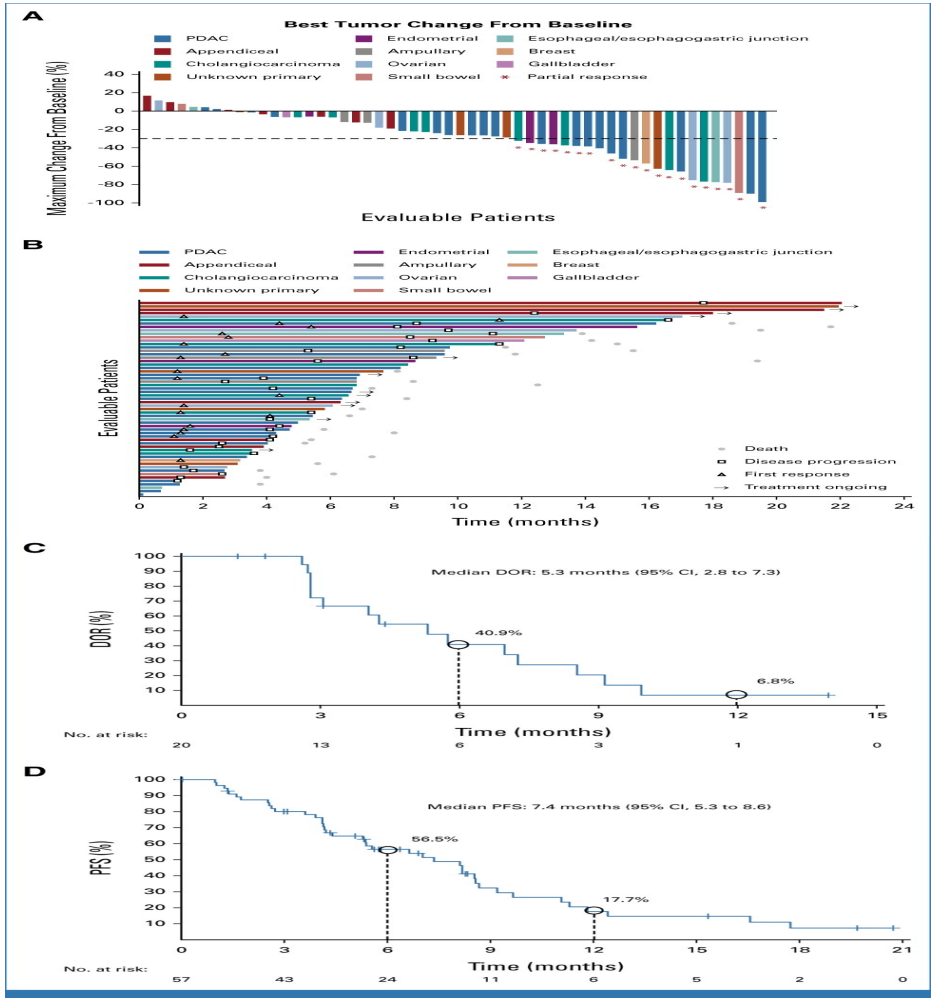
Variable	Phase 1 (N = 12)	Phase 2 (N = 26)	Combined Phase 1–2 (N = 38)
Best overall response — no. (%)†			
Confirmed complete response	0	0	0
Confirmed partial response	3 (25)	5 (19)	8 (21)
Stable disease	6 (50)	18 (69)	24 (63)
Progressive disease	2 (17)	3 (12)	5 (13)
Could not be evaluated	0	0	0
Not assessed	1 (8)	0	1 (3)
Percentage of patients with objective response (95% CI) — %	25 (6–57)	19 (7–39)	21 (10–37)
Percentage of patients with disease control (95% CI) — %‡	75 (43–95)	89 (70–98)	84 (69–94)
Median time to objective response (range) — mo§	1.4 (1.3–1.5)	2.8 (1.3–5.6)	1.5 (1.3–5.6)
Median duration of response (95% CI) — mo§¶	—	—	5.7 (1.6–NE)

* An objective response was defined as a complete or partial response. NE denotes could not be evaluated.
† The best overall response was determined by blinded independent central review.
‡ Disease control was defined as an objective response or stable disease.
§ The median time to objective response and the median duration of response were calculated for the patients who had a confirmed objective response.
¶ The median duration of response (Kaplan–Meier estimates) is not provided for individual phases because of the small number of patients.

N Engl J Med 2023; 388:33-43

The NEW ENGLAND JOURNAL of MEDICINE

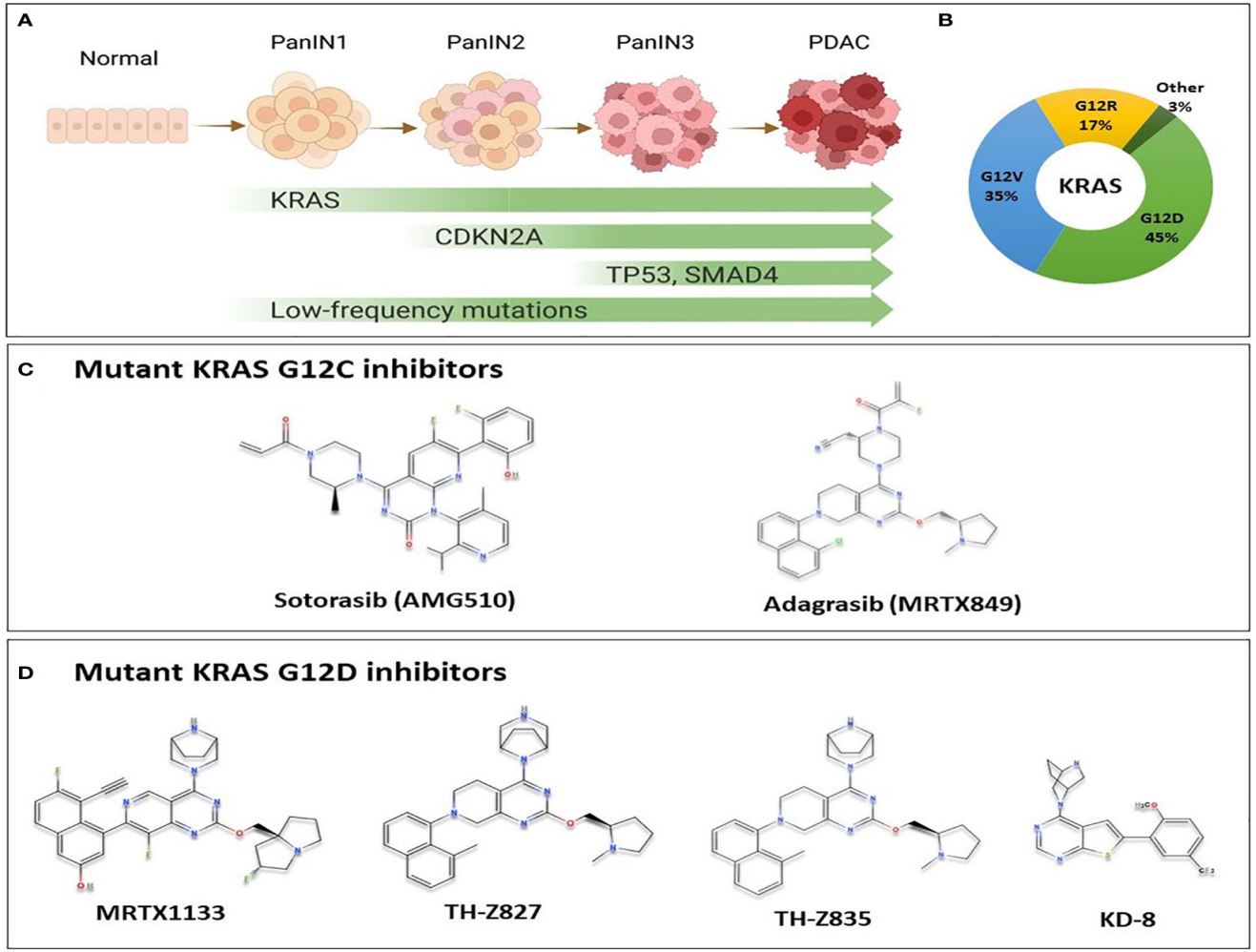
Adagrasib in KRAS G12C PDAC and BTC



57 patients, objective responses in 20 (35.1%) patients including 7/21 (33.3%) responses in pancreatic and 5/12 (41.7%) in biliary tract cancers. The median duration of response was 5.3 months and median PFS was 7.4 months

Published in: Tanios S. Bekaii-Saab; Rona Yaeger; Alexander I. Spira; Meredith S. Pelster; Joshua K. Sabari; Navid Hafez; Minal Barve; Karen Velastegui; Xiaohong Yan; Aditya Shetty; Hirak Der-Torossian; Shubham Pant; *Journal of Clinical Oncology* 2023 414097-4106.
DOI: 10.1200/JCO.23.00434

KRAS G12D: HAS THE FRONTIER BEEN BREACHED?



Front. Oncol., 29 November 2022

RMC 6236

- RMC-6236 targets KRAS proteins in the active (ON) state harboring any mutation at the G12 position
- RMC-6236 also targets wild-type KRAS and KRAS with mutations at other positions, such as the glycine located at position 13 (G13) and the glutamine at position 61 (Q61).
- As of September 11, 2023, a total of 131 patients had been treated with RMC-6236 in this trial.
- Confirmed objective responses were observed in tumors harboring G12D, G12V or G12R mutations.

	ESMO presentation	ESMO abstract
Cutoff	Oct 12, 2023	April 24, 2023
N	111	33
N – NSCLC	46	11
N – pancreatic cancer	65	22
ORR – NSCLC	38% (15/40)*	75% (3/4)^
ORR – pancreatic cancer	20% (9/46)**	20% (2/10)^

Ann Oncol. 2023;34(suppl 2):S458

PARP inhibitors as maintenance therapy for gBRCA/ PALB2

- POLO trial: Olaparib FDA approved indication
- RUCAPANC2: Phase 2 study of rucaparib; study of 42 patients. PFS 13.1 mos, OS 23.5 mos- now NCCN Category 2A
- Niriparib +/- Ipilimumab/ Nivolumab: failed to meet 6 mo PFS endpoint, high toxicity

  IO + PARP remains an area for development

Reiss: JCO 41; 2023

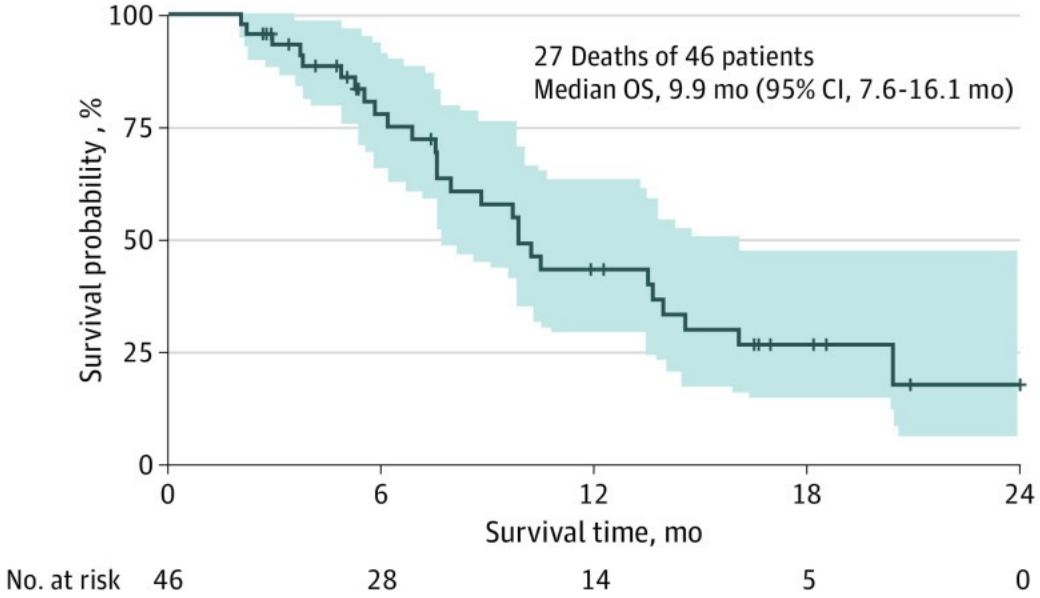
Reiss, Lancet Oncology 23; 1009-20; 2022

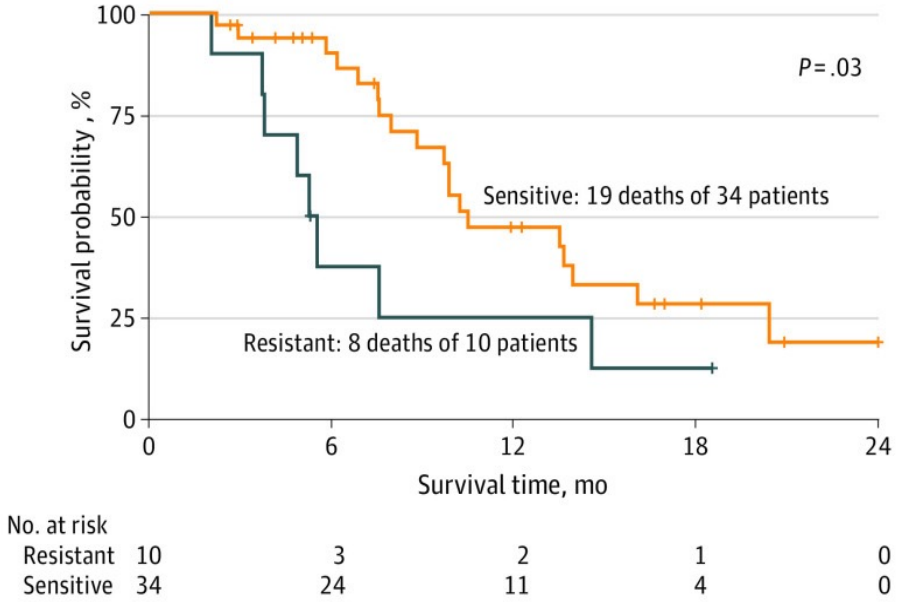
JAMA Oncology | Original Investigation

Olaparib Monotherapy for Previously Treated Pancreatic Cancer With DNA Damage Repair Genetic Alterations Other Than Germline *BRCA* Variants

Findings From 2 Phase 2 Nonrandomized Clinical Trials

Milind Javle, MD; Einat Shacham-Shmueli, MD; Lianchun Xiao, MS; Gauri Varadhachary, MBBS, MD; Naama Halpern, MD, MBA; David Fogelman, MD; Ben Boursi, MD; Syeda Uruba, MBBS, MPH; Ofer Margalit, MD, PhD; Robert A. Wolff, MD; Talia Golan, MD





Patients with DDR but excluding BRCA/ PALB2
ATM (m common)
May experience benefit with PARP-i

Finally, a change in trajectory in PDAC…

- OS with chemotherapy unchanged over a decade
- NALIRINOX is an option to consider 1L
- The advent of targeted therapies, particularly the KRAS directed agents is likely to be transformative; alone or with immunotherapy for advanced PDAC
- GL and somatic genetic profiling now indicated for PDAC