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School of Medicine

Pancreatic and Biliary Cancers
What is new in 2024?

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Wake Forest School of Medicine

Neo Adjuvant Pancreas Ca

Background

Study	Randomization	Resectablitiy	# Patients	OS in months	Other Endpoints
PREOPERATIVE					
PREOPANC-1 Versteijne E JCO 40: 11 ,2022	G+XRT-S 119 pts S- G 127 pts	Resectable or borderline resectable	119 x 127	15.7 (N) x 14.3 (S) 5-y OS 20.5% x 6.5% (HR 0.73, p=0.025)	R0 71% (N) x 40% (S) (p<.001)
Preop-02/JSA 05 JCO 37 S4;A189, 2019	GS1 x 2-S –GS1 x 6 S- GS1 x 6	Resectable	182 x 180	36.7 (9N) x 26.6(S) HR 0.72 p=0.015	No reported change in resection rates

RANDOM PHASE II AIO-NEONAX TRIAL

Resectable PDAC: Perioperative or Adjuvant Gemcitabine/nab-Paclitaxel

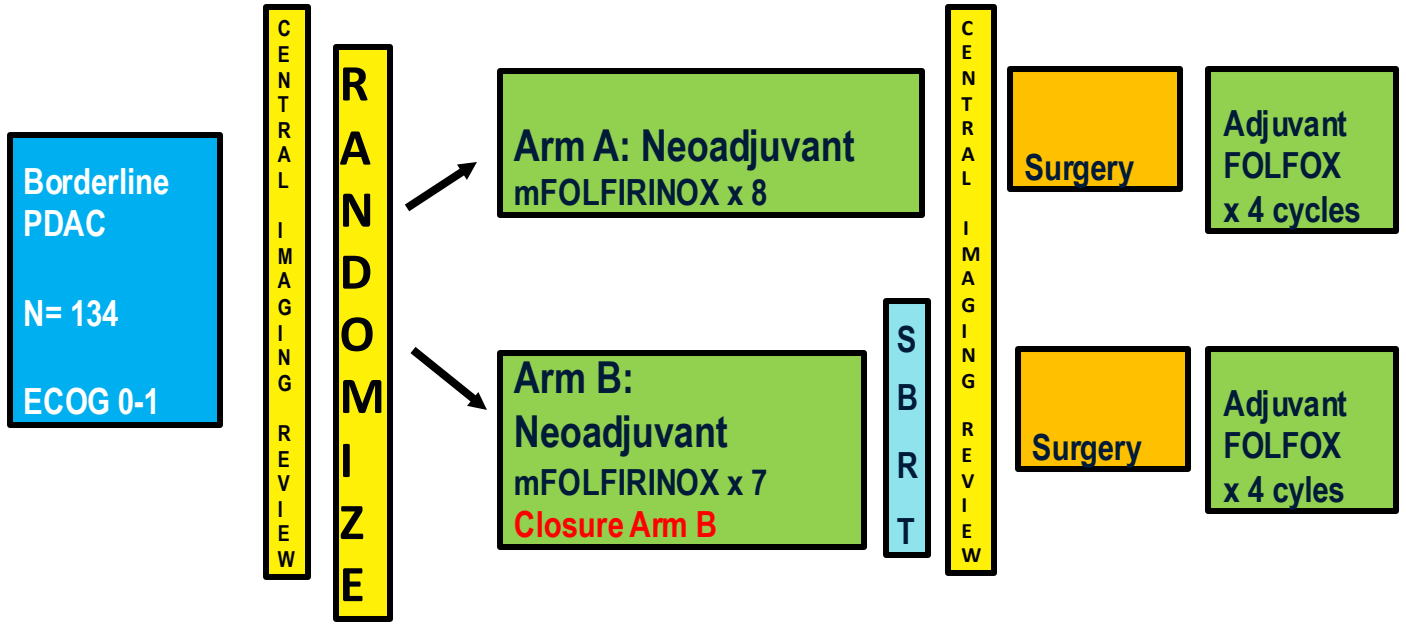
Randomized phase II, 2-arm trial; N= 127 (22 German centers)
Arm A: 2 pre-operative, 4 post-operative cycles gemcitabine/nab-paclitaxel
Arm B: Adjuvant gemcitabine/nab-paclitaxel x 6 cycles
Primary endpoint: DFS @ 18 m (55%)

	Arm A Neoadjuvant/Adjuvant	Arm B Adjuvant
DFS @ 18 m (primary)	32.2%	41.4%
pN0	33.3%	29.5%
R0 resection rate	87.8%	67.4%
Median OS	25.2 m	16.7 m
Median DFS	11.5 m	5.9 m

Ettich, TJ…Sufferlein, T. ASCO, 2022 [Abstr 4133]. NCT02047513

A021501 BORDERLINE RESECTABLE PDAC

Randomized Phase II mFOLFIRINOX +/- SBRT



Interim analysis: R0 after
N= 30/arm → early closure of SBRT arm (<11 R0/ 30)

Primary endpoint: 18-month OS in each arm (no comparison)

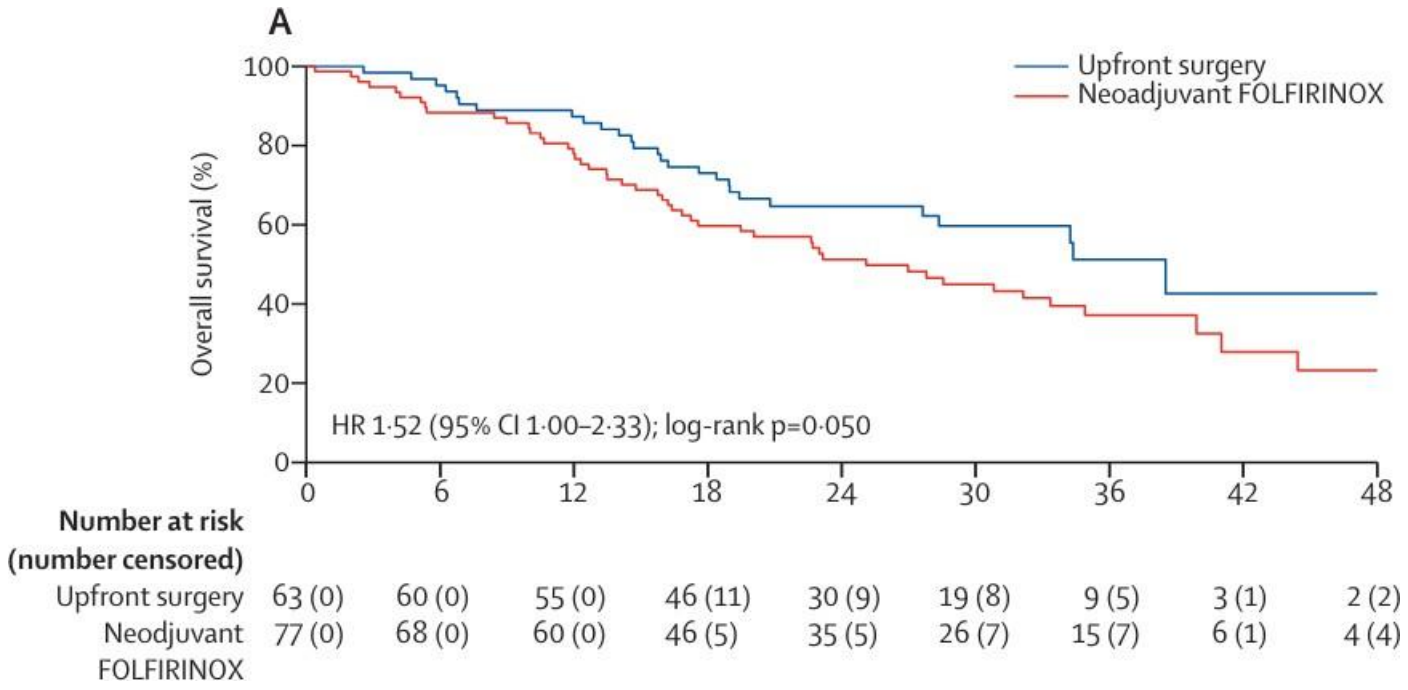
*Alternative to SBRT – HIGRT

NCT02839343 M. Katz, PI

A021501 BORDERLINE RESECTABLE PDAC

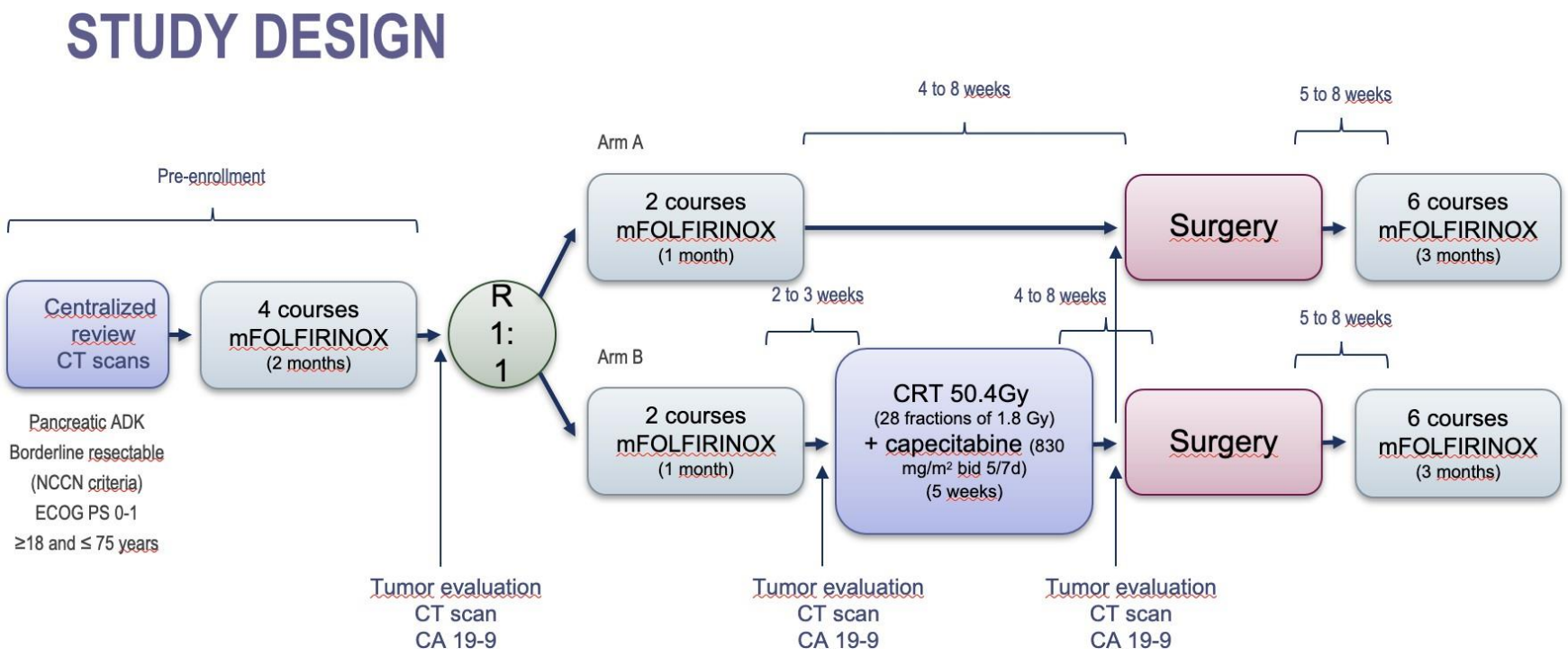
- ARM A FOLFIRINOX;
  - **Median OS (95): 29.8 (21.1 – NE) mo**
  - 18-mo OS rate: 66.4**% CI** (55.6 – 79.2%)
- ARM B FOLFIRINOX→RT
  - **Median OS (95% CI): 17.1 (12.8 – 24.4) mo**
  - 18-mo OS rate: 47.3 (35.8 – 62.5%)

NORPAC-1 DIFFERENT RESULTS



Labori, et al. Lancet Gastronterol Hepatol 2024

ESMO 2024 PANDAS/PRODIGE 44 trial

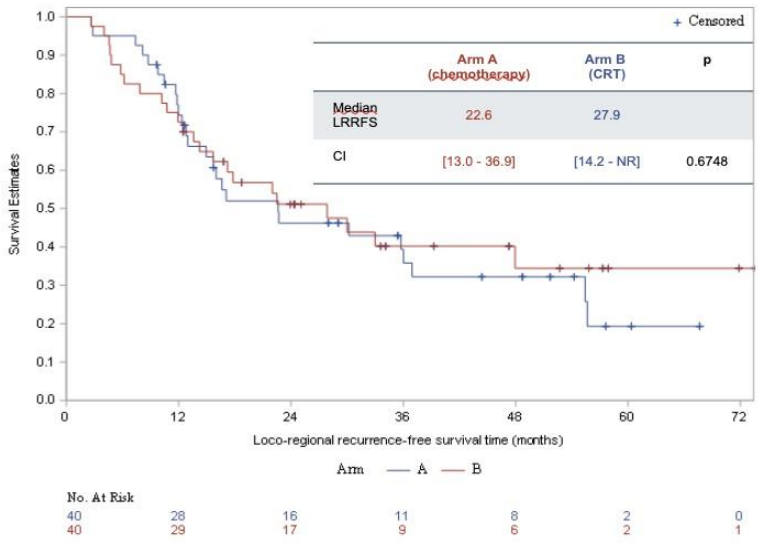


Primary objective: R0 resection rate

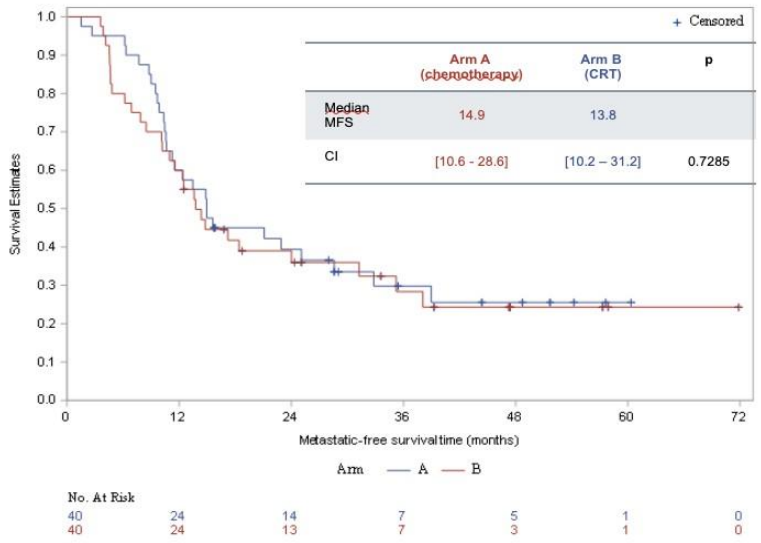
		Arm A (chemotherapy) N=40	Arm B (CRT) N=40	p-value
R0 Resection rate	**Yes** / No N (%)	**20 (50)** / 20 (50)	**18 (45)** / 22 (55)	0.8230
Resection (R0 or R1)	Yes / No N (%)	37 (92.5) / 3 (7.5)	31 (77.5) / 9 (22.5)	0.1149
ypCR	No N (%)	37 (100) (3 missing)	31 (100) (9 missing)	

Loco-regional recurrence-free survival

ITT population



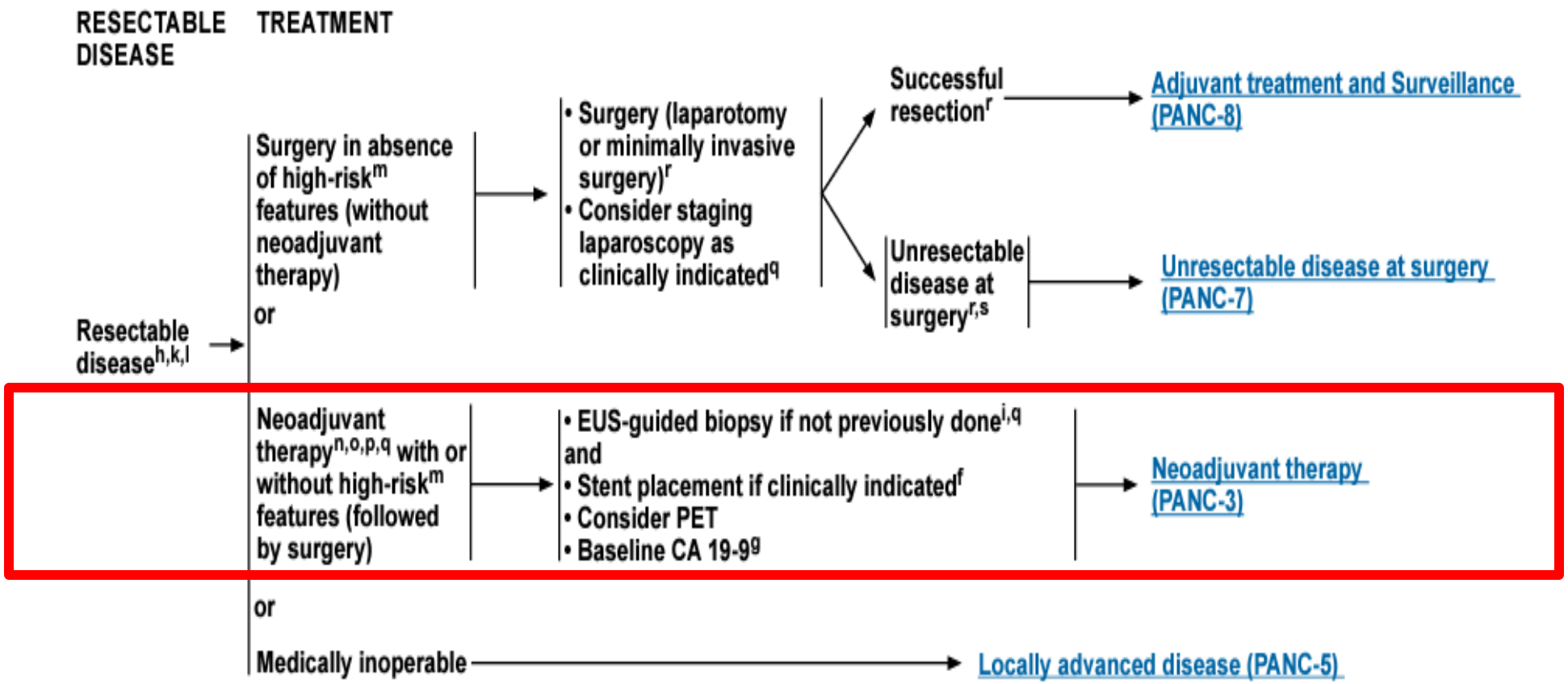
Metastasis-free survival



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Table of Contents
Discussion



METASTATIC PANCREAS CANCER

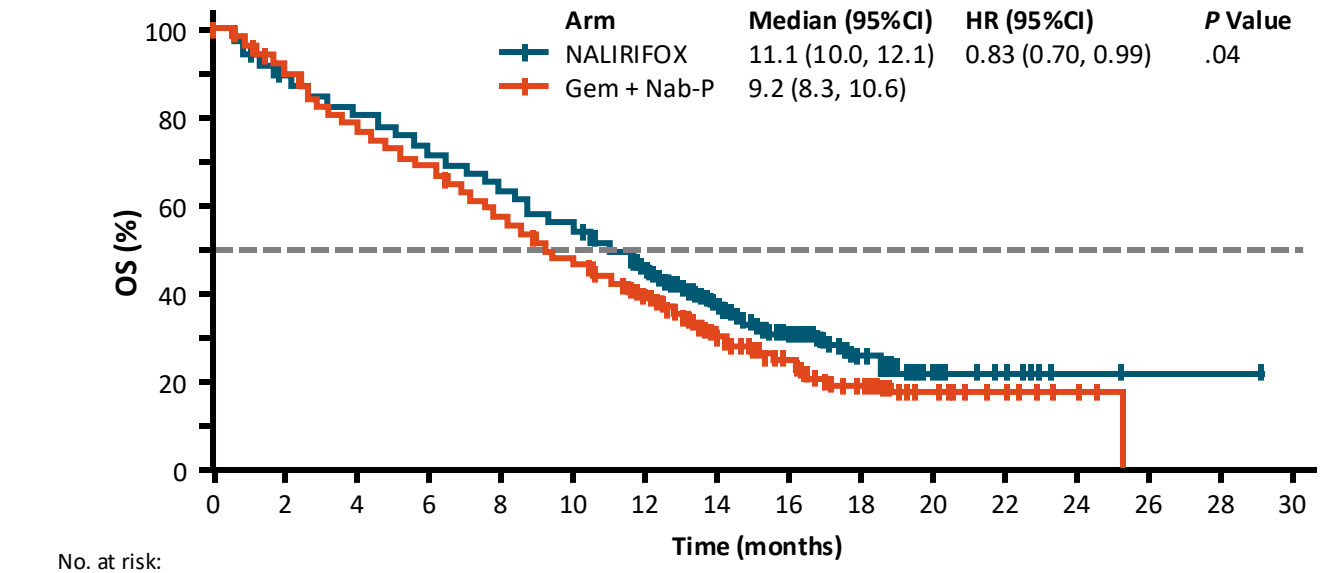
We Have Made Progress in the 1st-Line Pancreas Adeno in the Metastatic Setting

Trial[1]	Date	Patients (n)	Treatment	Median survival (mo)	P value
Burris et al[2]	1997	126 (unresectable, LA or metastatic pancreatic cancer)	5-FU vs. gemcitabine	4.41 5.65*	Log-Rank Test 0.0025
NCIC[3]	2007	569 (unresectable, LA or metastatic pancreatic cancer)	gemcitabine vs. gemcitabine + erlotinib	5.91 6.24	0.038 (HR = 0.82 [95% CI, 0.69–0.99])
PRODIGE[4]	2011	342 (metastatic)	gemcitabine vs. FOLFIRINOX	6.8 11.1	<0.001 (HR = 0.57 [95% CI, 0.45–0.73])
Ueno, et al[5]	2013	834 (LA, or metastatic pancreatic cancer)	gemcitabine vs. S-1 vs. gemcitabine + S-1	8.8 9.7 10.1	gemcitabine vs. S-1: <0.001 (non-inferiority; HR = 0.96 [97.5% CI, 0.78–1.18]) gemcitabine vs. gemcitabine + S-1: 0.15 (superiority; HR = 0.88 [97.5% CI, 0.71–1.08])
MPACT[6]	2013	861 (metastatic)	gemcitabine vs. gemcitabine + nab-paclitaxel	6.7 8.5	<0.001 (HR = 0.72 [95% CI, 0.62–0.83])

1. Ryan DP, et al. N Engl J Med 2014;371:1039;
2. Burris HA, et al. J Clin Oncol 1997;15:2403;
3. Moore MJ, et al. J Clin Oncol 2007;25:1960;

4.Conroy T, et al. N Engl J Med 2011;364:1817;
5. Ueno H, et al. J Clin Oncol 2013;31:1640;
6. Von Hoff DD, et al. N Engl J Med 2013;369:1691.

NAPOLI: OS (Primary Endpoint)



Wainberg ZA, Melisi D, Macarulla T, et al. Lancet. 2023

NALIRIFOX x FOLFIRINOX

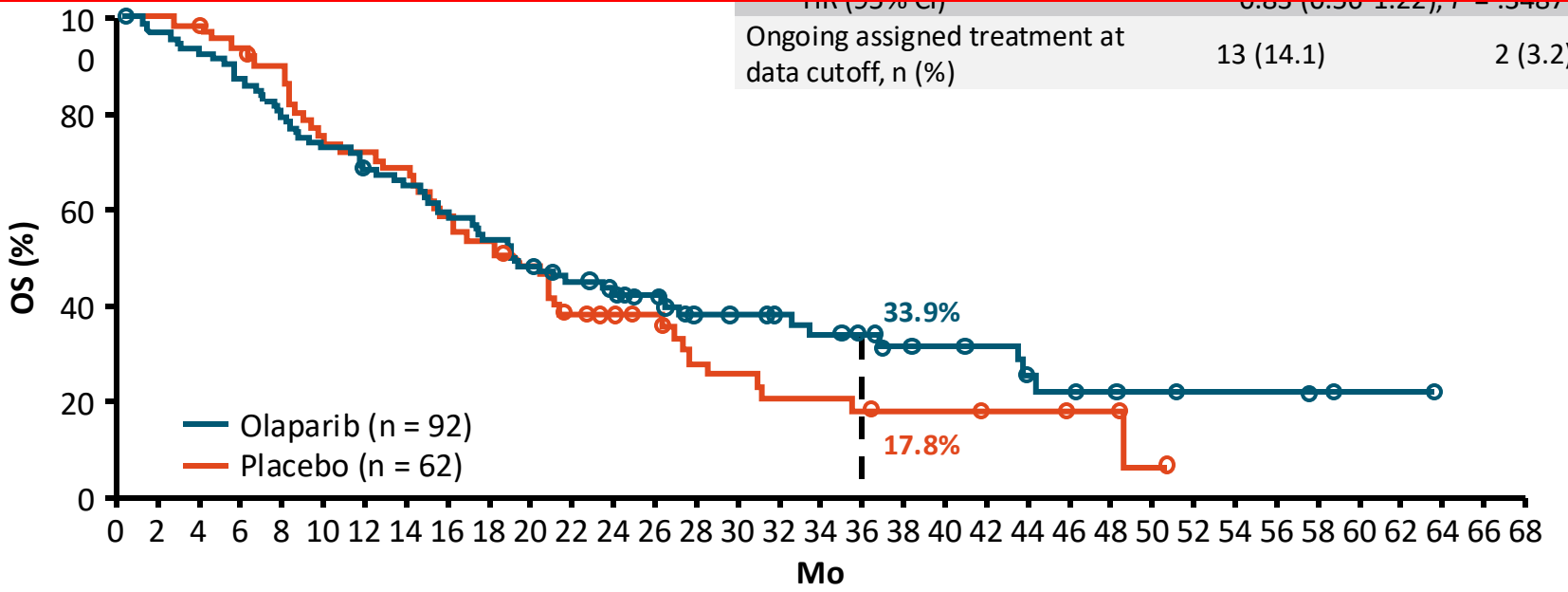
	NALIRIFOX	FOLFIRINOX (PRODIGE)
Median OS	11.2 Months	11.1 Months
Median PFS	7.4 Months	6.4 Months
ORR	41.8%	31.6%
Toxicity	Myelotoxicity, peripheral neuropathy, and GI Toxicity	

O'Reilly et al. Abstract 4006.PASCO 2023

Conroy T, et al. N Engl J Med 2011;364:1817

POLO: Final OS

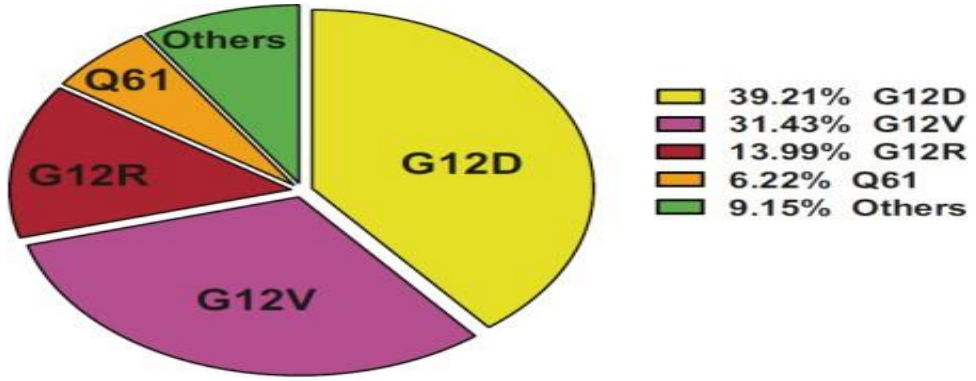
	Olaparib (n = 92)	Placebo (n = 62)
Events, n (%)	61 (66.3)	47 (75.8)
Median OS, mo	19.0	19.2
HR (95% CI)	0.83 (0.56, 1.22); P = .3487	
Ongoing assigned treatment at data cutoff, n (%)	13 (14.1)	2 (3.2)

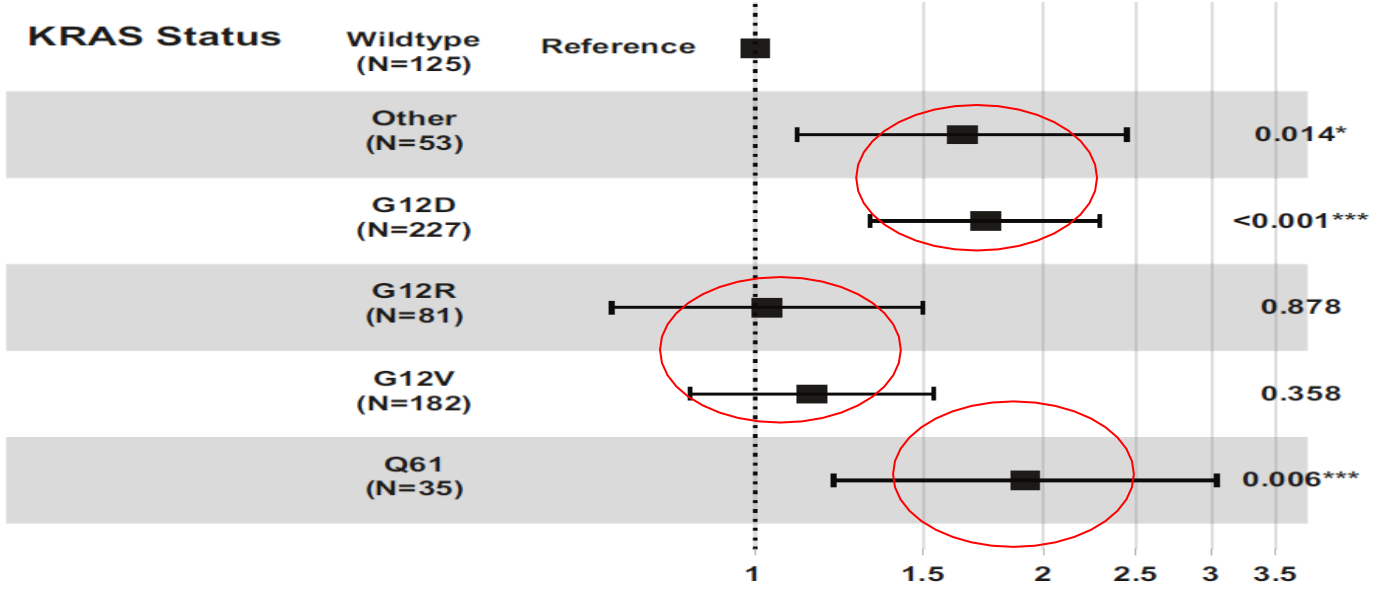


Golan. ASCO GI 2021. Abstr 378.

KRAS MUTATION AS PROGNOSTIC MARKER

- 803 patients
- retrospective





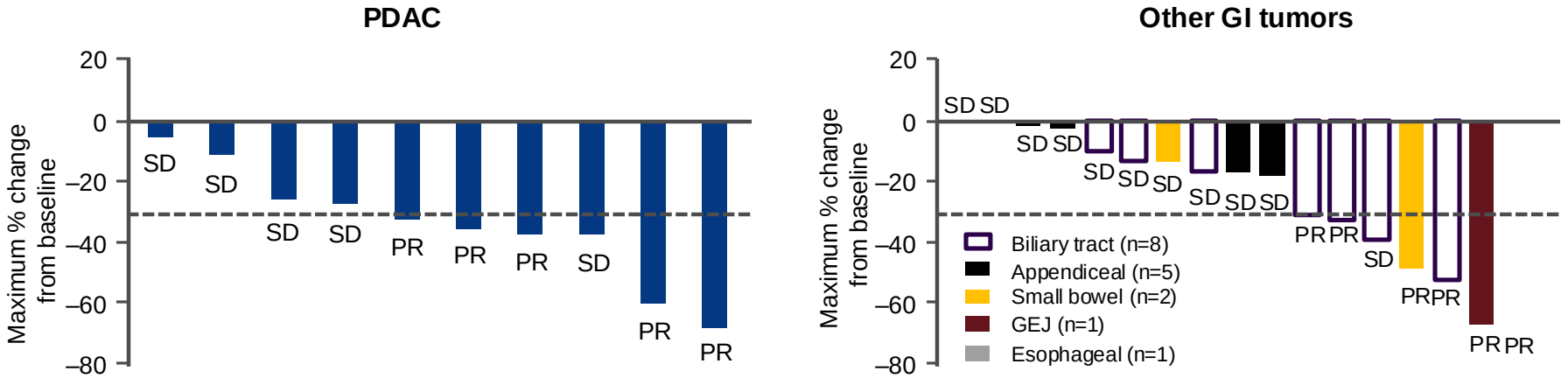
Yousef et al., npj, 2024

KRYSTAL-1: Adagrasib (MRTX849) unresectable or metastatic pancreatic cancer and other gastrointestinal tumors with KRASG12C mutation

63 pts treated. 21 PDA

ORR 35.1 %

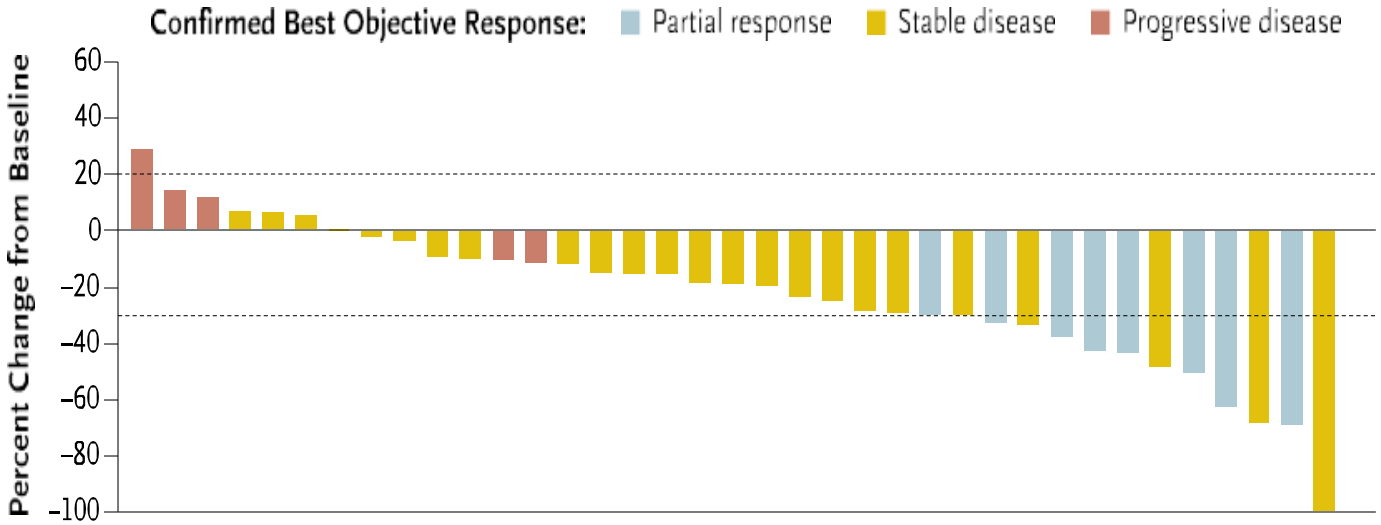
ORR PDA: 33%



Pant S, et al. JCO 2023, A 425082

Sotorasib, the phase 1-2 CodeBreaK 100 trial

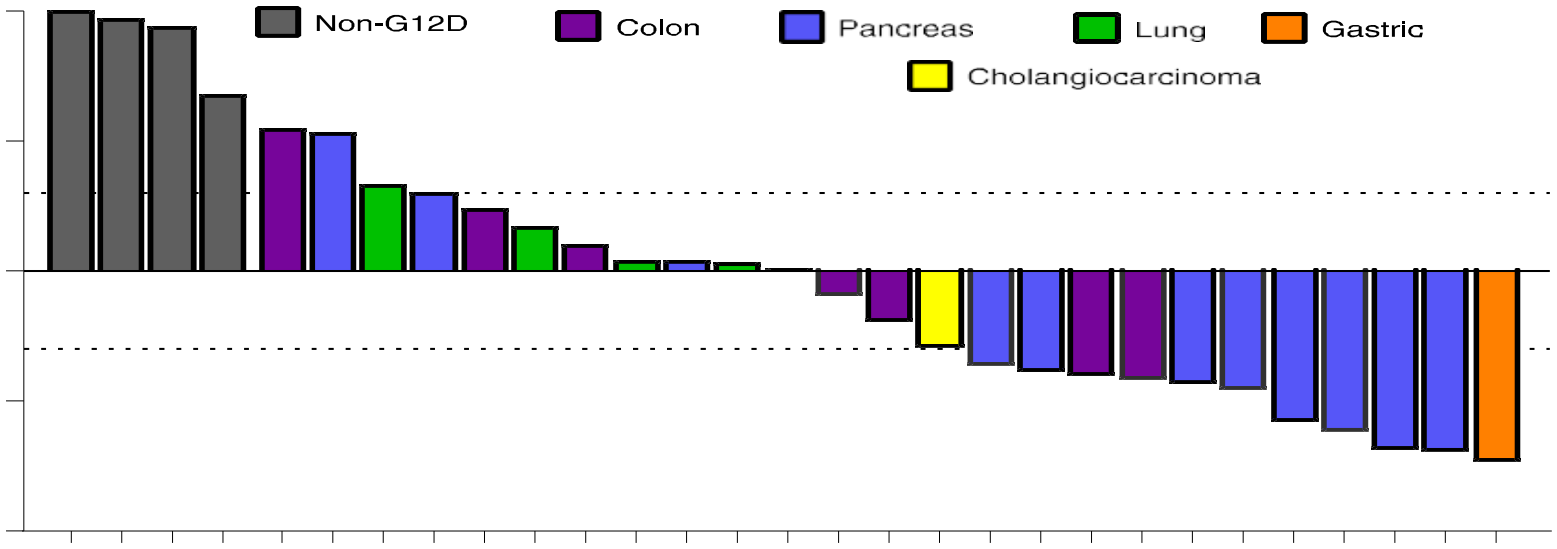
- 38 PDAC patients
  - ORR = 21 %
  - mPFS = 4 months
  - mOS= 6.9 months



Strickler JH, et al. NEJM 2023

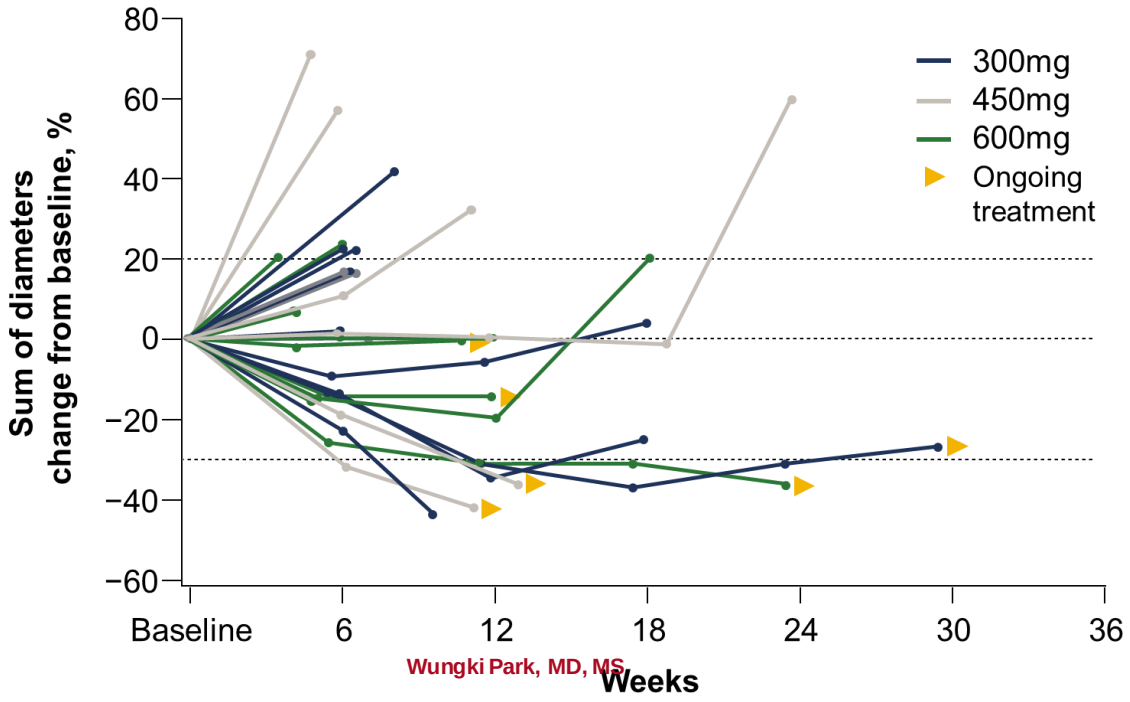
KRAS G12D

- MRTX 1133 shows promise in targeting and inhibiting KRAS G12D activation
- Preclinical data in human tumor xenographs



Wei J, et al. Clin Can Res 2023

Response to ASP3082 300–600mg over time in patients with PDAC Presented at ESMO 2024



- At data cutoff, 6 of 27 (22.2%) patients remained on treatment
- DOR and PFS endpoints were not mature at data cutoff
- For 5 patients with PR, median time to response[a] was 2.6 months (range: 1.4–3.0 months)

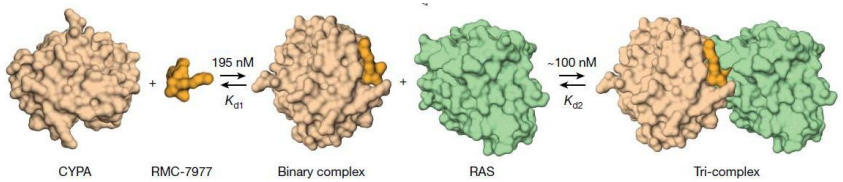
Wungki Park, MD, MS

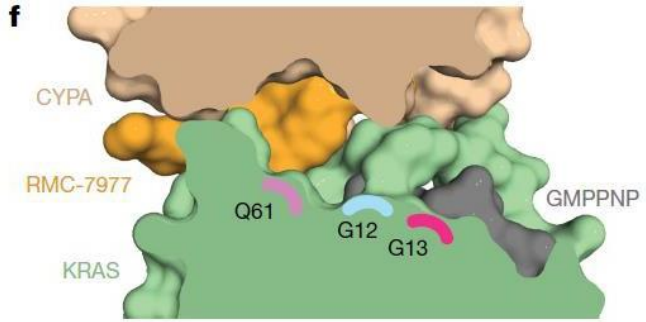
PAN-RAS INHIBITORS
Inhibition of both oncogenic and wild type RAS-GTP

RMC-7977:

- Reversible, tri-complex ***Ras(On)*** multiselective inhibitor
- Active for both mutant and wild-type KRAS, NRAS and HRAS variants
- May be active for KRAS G12C inhibitor Resistance

  Resistance mechanism: Myc copy number gain and YAP–TAZ pathway activation





Holderfield M, et al. Nature 2024
Wasko UN, et al. Nature 2024

RMC-6236: panRAS inhibitor Phase 1 trial

- *KRAS* non G12c patients 2L+ received RMC-6236 administered at doses ranging from 160 mg to 300 mg

  - NSCLC 40: ORR 38% and DCR 34%. Median TTR 1.4 m (1.2-2.7).

  - PDAC 46 pts: ORR s 20% and DCR 87%. Median TTR 3.3 months (0.2-10.9).

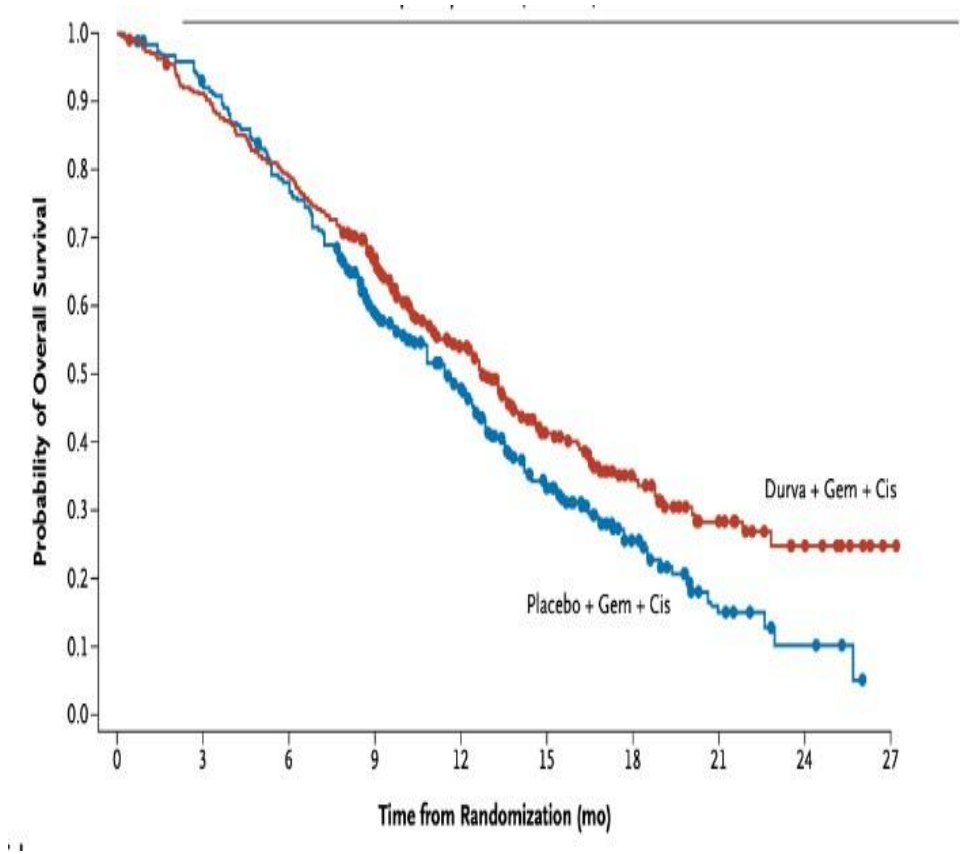
    - M mOS in PDAC not reached

✓ **RASolute302, A Randomized, Phase 3 trial comparing RMC-6236 to chemotherapy in 2L is planned**

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

Metastatic Biliary Cancers

TOPAZ-1 Efficacy Results



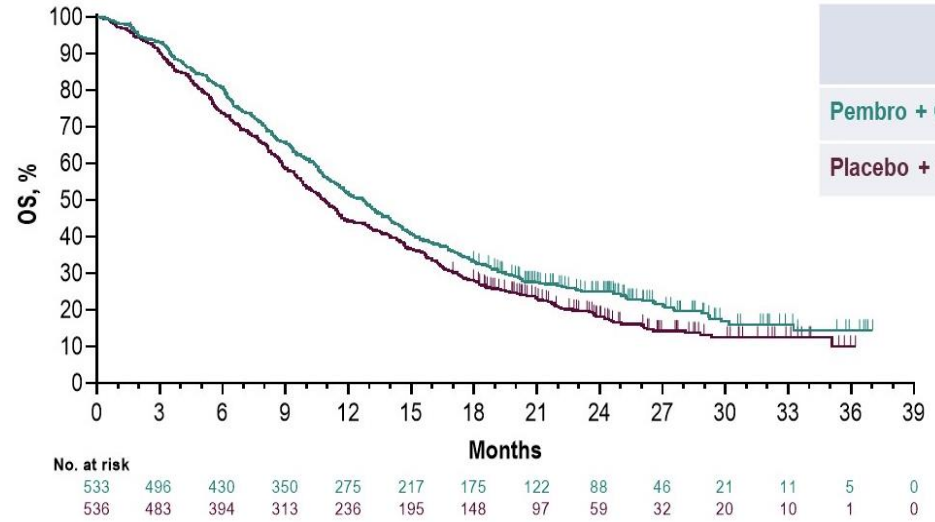
	GEM/DDP/D (n=341)	GEM/DDP/P (n=343)	HR (C.I.) [P Value]
mOS (months)	12.8	11.5	0.8 (0.66-0.97) [0.021]
PFS (months)	7.2	5.7	0.75(0.63-0.89) [0.001]
ORR (%)	26.7	18.7	
DCR	85.3	82.6	

Do-Youn O et al, N Engl J Med Evidence June 2022

Study Update at 41 months: 3- Year survival (14,6% *vs* 6,9%; HR=0,74; CI 95%: 0,63-0,87) in favor chemo+**durvalumabe**

[*Lancet Gastroenterol Hepatol 9:694, 2024*]

KEYNOTE 966
Pembro+Gem+Cis vs GemCis



	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

- KEYNOTE-966 showed similar safety profiles between the pembrolizumab and placebo groups[1]
  - 70% of patients treated with pembrolizumab + gem/cis had grade 3 or 4 treatment-related adverse events vs 69% for placebo + gem/cis

[1]Kelley et al. Lancet 2023; 2023;S0140-6736(23)00727-4.

ORR: 29% vs 29%

J Clin Oncol 42: abstr 4093, 2024

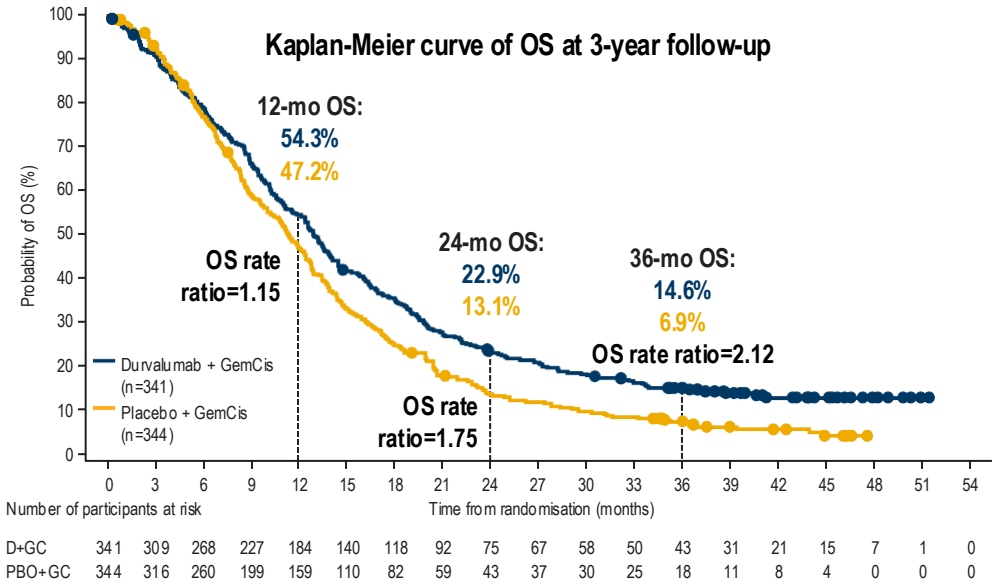
TOPAZ-1 VS KEYNOTE 966

	TOPAZ 1[1]	Keynote 966[2]
Median OS	12.9 vs 11.3 (HR 0.74 from 0.80 in FA)	12.7 vs 10.9 (HR 0.86 from 0.83 in FA)
ORR	26.7 vs 18.7 FA (55 % vs 40% in LTS)	28.7 vs 28.7 but DOR was 8.3 vs 6.9
N	685	1069
Median F/u	42.9 months	36.6 months

1. Do et al, ESMO 2024
2. Finn et al, ASCO 2024

3-YEAR OS UPDATE

OS benefit with durvalumab + GemCis continued at the updated data



	Primary analysis[1,*] DCO: Aug 11, 2021		3-year follow-up[†] DCO: Oct 23, 2023	
	D+GC (n=341)	PBO+GC (n=344)	D+GC (n=341)	PBO+GC (n=344)
Median OS[‡] (95% CI), months	12.8 (11.1–14.0)	11.5 (10.1–12.5)	12.9 (11.6–14.1)	11.3 (10.1–12.5)
OS HR[§] (95% CI)	0.80 (0.66–0.97)		0.74 (0.63–0.87)	

Usually driven by tail of curve

At 36-months, the survival rate in the durvalumab + GemCis arm was more than double the survival rate in the placebo + GemCis arm

Targets Biliary Tract Cancers

- IDH-1 mutations
- FGFR2 fusions
- BRAF
- Her-2 (ERBB2)
- Immunotherapy

FGFR2 inhibitors

Agent	Trial N size	RR (%)	PFS (m)	DOR (m)	OS (m)
Pemigatinib	107	37	7.0	9.1	17.5
Futibatinib	103	41.7	8.9	9.7	21.7
Derazantinib	103	21.4	7.8		
Erdafitinib	78	55%	8.5	6.9	18.1
infigratinib	**108**	**23.1**	**7.3**		

First Line Trials with FGFR2 Inhibitors
Pemigatinib , Infigratinib, and Futibatinib

All are non selective FGFR inhibitors (FGFR 1-4)

Lancet Onc 2020
Lancet Gastro Hepato 2021
Goyal L, et al NEJM 2023
ESMO 2021

FGFR 2 Inhibitors toxicity

- Hyperphosphatemia (FGFR1)
- Eye disorders
- Stomatitis
- Fatigue
- Diarrhea (FGFR4)

REFOCUS TRIAL: Lirafrugatinib
Highly Selective FGFR2 Inhibitor Activity Resistance Mutations

	FGFRi-naïve CCA N = 25	Prior-FGFRi CCA N = 50
ORR n(%) [95% CI]	13 (52% [31.3%-72.2%])	7 (14% [5.8%-26.7%])
mDOR mo (range)	8.2 (1.9-18.6)	5.6 (1.9-7.4)
DCR n (%)	22 (88%)	40 (80%)

No reported G3 or G4 Hyperphosphatemia or G3 or G4 Diarrhea

Jborad et al : ournal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 4009.

Targeting HER-2

- **Pertuzumab and trastuzumab: phase 2a study (**Javle Lancet Oncol 2021**)**
  - 39 patients previously treated HER2 amplification, HER2 overexpression, or both
  - RR 23 %. Median DOR: 10.8 months. Median OS: 10.9 months
    - Higher activity in extrahepatic BTC RR: 40% (ampullary); 31% (GBC)

- **Neratinib, a pan-HER irreversible tyrosine kinase inhibitor** Harding ASCO 2022
  - 25 pts with activating somatic HER2 mutations (GB 40%, ICC24%, EHCC20%, AV 16%)
  - RR 16% and PFS 2.8 months. Median OS 5.4 months

ZANIDATAMAB Herizon- BTC-01 UPDATE

- Median f/u 21.9 mths
- ORR of 41.3% (investigator assessed)
- Median DOR was 14.9 months
- Median OS was 15.5 months

- FDA Accelerated Approval 11/20/24 previously treated, unresectable/metastatic HER2-positive (IHC 3+) BTC

Pant S, et al ASCO 2024

Targeting HER-2
Trastuzumab deruxtecan
FDA Approved (2024)

- 30 pts recurrent or unresectable:
- RR 36.4% and 12.5%. PFS 5.1 and 3.2 months in HER 2 + and HER 2 low
- DOR in Her 2 +: 7.4 months
- ILD: ≥ Grade 3: 12.5%

Ohba et al: A 4006, ASCO 2022

DESTINY Pan Tumor 02

- 41pts recurrent or unresectable:
- RR 22% (all 9 pts 3+)
- DOR 8.6 months
- PFS 4.6 - 7.4m (3+)
- OS 7.0 m -12.4m (3+)

Oh DY et al: Poster 4090, ASCO 2024

PRINCIPLES OF SYSTEMIC THERAPY[a]

Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens

- Durvalumab + gemcitabine + cisplatin (category 1)[e,f,g,4]
- Pembrolizumab + gemcitabine + cisplatin (category 1)[f,g,5]

Other Recommended Regimens

- Gemcitabine + cisplatin (category 1)[6]
- Capecitabine + oxaliplatin
- FOLFOX
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[h]

Preferred Regimens

- FOLFOX[7]

Other Recommended Regimens

- FOLFIRI[8]
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[9]
- Regorafenib (category 2B)[10]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

Useful in Certain Circumstances

- Targeted therapy (BIL-C 3 of 5)
- Nivolumab (category 2B)[f,g,11]

[a] Order does not indicate preference.
[e] Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy.
[f] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] For patients who have not been previously treated with a checkpoint inhibitor when used as subsequent-line therapy because there is a lack of data for use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[h] Treatment selection depends on clinical factors including previous treatment regimen/agent, somatic molecular testing results, and extent of liver dysfunction.

References

Thanks For The Attention!