Michael Pishvaian, MD, PhD

Mike Pishvaian is an Associate Professor in the Department of Oncology at Johns Hopkins University. Dr. Pishvaian is an MD and has a PhD in Tumor Biology, having earned both degrees at Georgetown in 2001. He remained at Georgetown after graduation, completing his medical residency in 2004, then his fellowship in Hematology/Oncology in 2007. He served on the faculty at Georgetown until moving to MD Anderson in 2019. At MD Anderson, he was the co-director for Clinical Research at the Zayed Center for Pancreatic Cancer Research. He then moved to Johns Hopkins, and is the Director of the Gastrointestinal, Developmental Therapeutics, and Clinical Research Programs at the National Capital Region Cancer Center. On social media, Dr. Pishvaian is also the Founder of Tumor Board Tuesdays, a case-based weekly discussion on Twitter focusing on interesting biomarker-based therapies.

Dr. Pishvaian is a translational oncologist, focused on providing novel therapies for patients, particularly in the areas of pancreatic cancer and refractory colorectal cancer. His work has been focused in the area of precision medicine, with a special focus on therapy targeted towards homologous recombination DNA repair deficient tumors, and Dr. Pishvaian is a Co-investigator on an NIH RO1 to study mechanisms of resistance to PARP inhibitor-based therapy, and a Co-PI of a U01 grant aimed at studying ex vivo patient derived models of cancer for patients with pancreatic cancer. Dr. Pishvaian also serves as the Alliance Co-Chair of the Pancreatic Cancer subcommittee, and the chair of TARGET-Panc, an ACCRU-supported effort to build biomarker-based clinical trials in Pancreatic Cancer.

Most Important Practice-Changing Advances in GI Cancers in 2023

Michael Pishvaian, MD, PhD
Associate Professor, Department of Oncology
Director of the Gastrointestinal, Developmental Therapeutics, and Clinical Research Programs at the NCR Kimmel Cancer Center at Sibley Memorial Hospital
Johns Hopkins University School of Medicine

Disclosures (3 years)

- Consultant/Advisory Board/Steering Committee:
  - AstraZeneca, Merck, Pfizer, Novartis, Ideaya, Astellas, Trisalus, Pionyr, Seattle Genetics, Merus
- Travel, accommodations and expenses support:
  - Astellas, RenovoRx
- Stock/Ownership:
  - Perthera, Tumor Board Tuesdays, TRICC
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  - AstraZeneca, Exelixis, Caris, Incyte, Ipsen, Natera, Bayer, BMS, Eisai, Foundation Medicine, Pfizer, SeaGen, Taiho, Tempus, Merck, Novartis

Overview - Moving Down the GI Tract

- Updates in upper GI cancers
- Updates in pancreatic cancer
- Updates in biliary cancer
- Updates in colorectal cancer

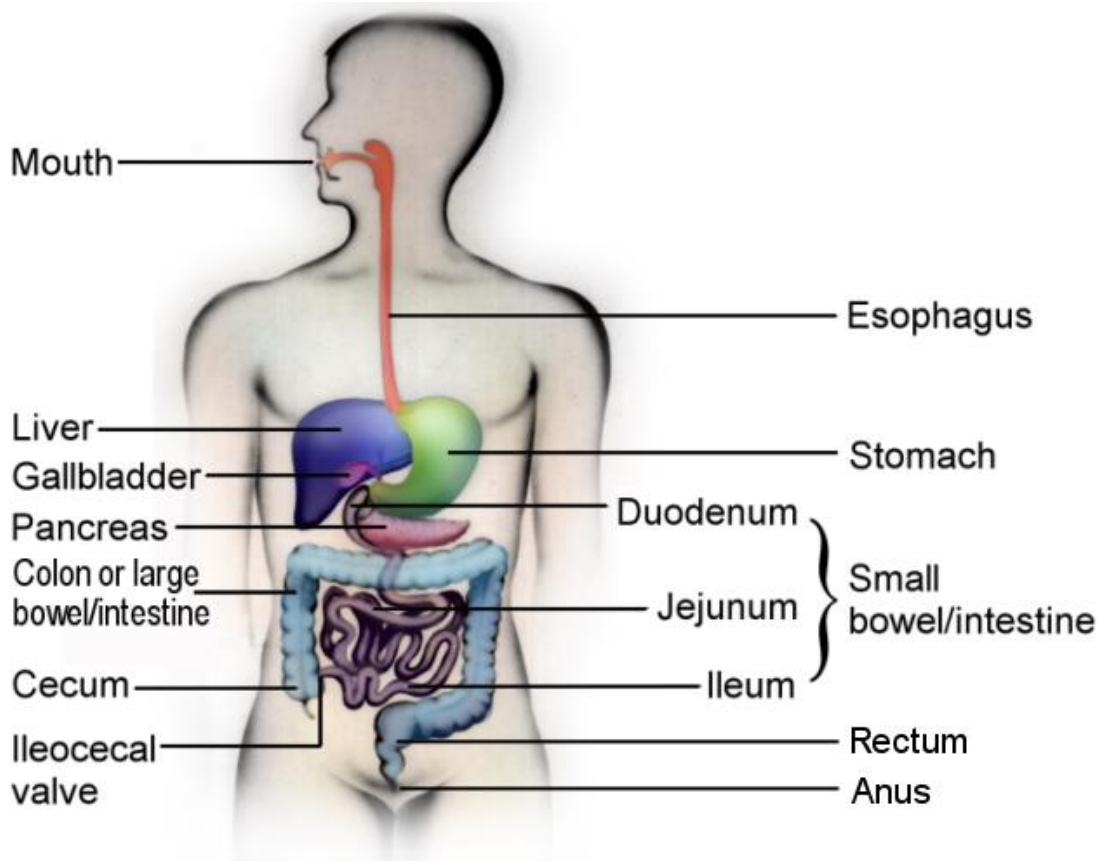


Image from:
https://aboutgimotility.org/wp-content/uploads/sites/14/giguy-web2-labeled.png

Updates in Gastroesophageal Cancer

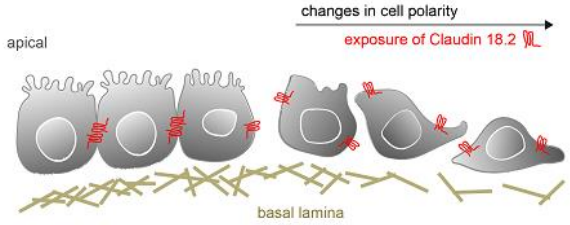
G = Gastric

GEJ = Gastroesophageal Cancer

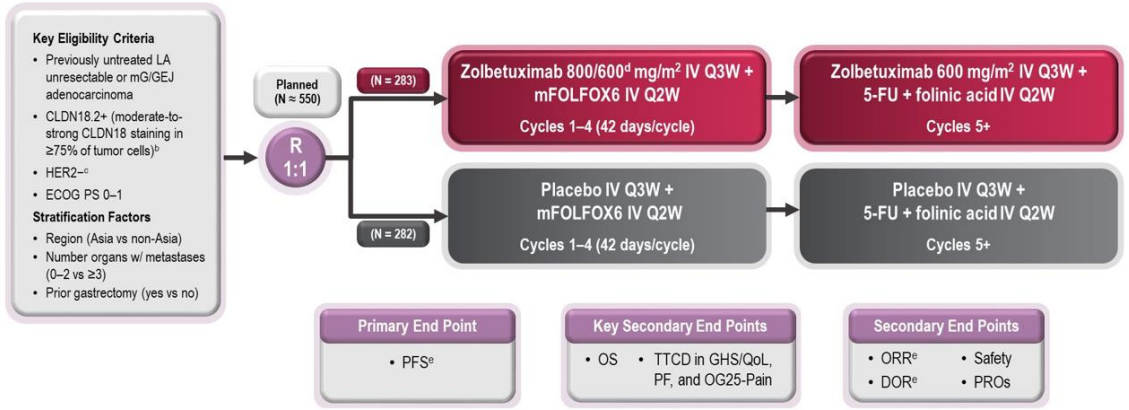
E = Esophageal

Claudin 18.2 – SPOTLIGHT Trial

- Claudin 18.2 is a tight junction protein normally expressed in gastric mucosal cells, and is retained in G/GEJ cancer cells
- But, in cancer cells, tight junctions are disrupted and Claudin 18.2 becomes exposed on the surface of the G/GEJ cancer cells
- Zolebetuximab in an anti-Claudin 18.2 mAb

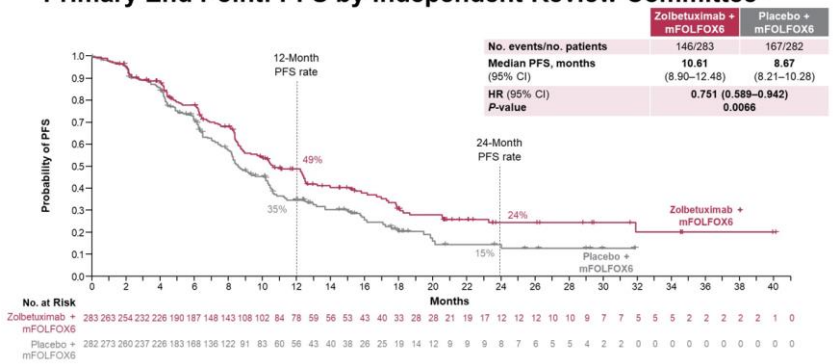


Study Design: SPOTLIGHT
Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial

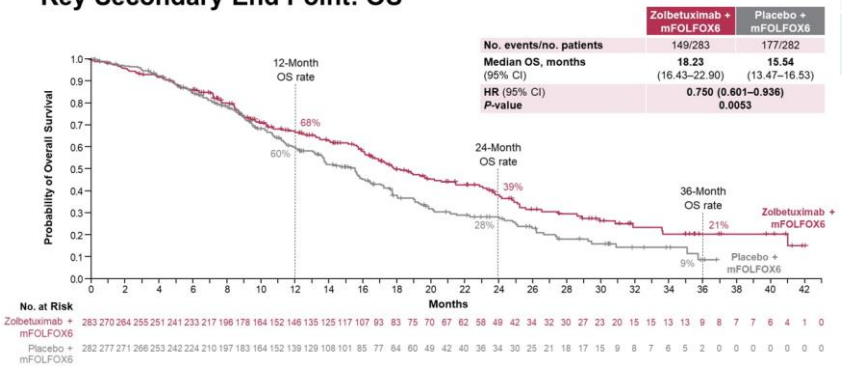


2244 patients screened; 38.5% were Claudin 18.2+

Primary End Point: PFS by Independent Review Committee[a]



Key Secondary End Point: OS



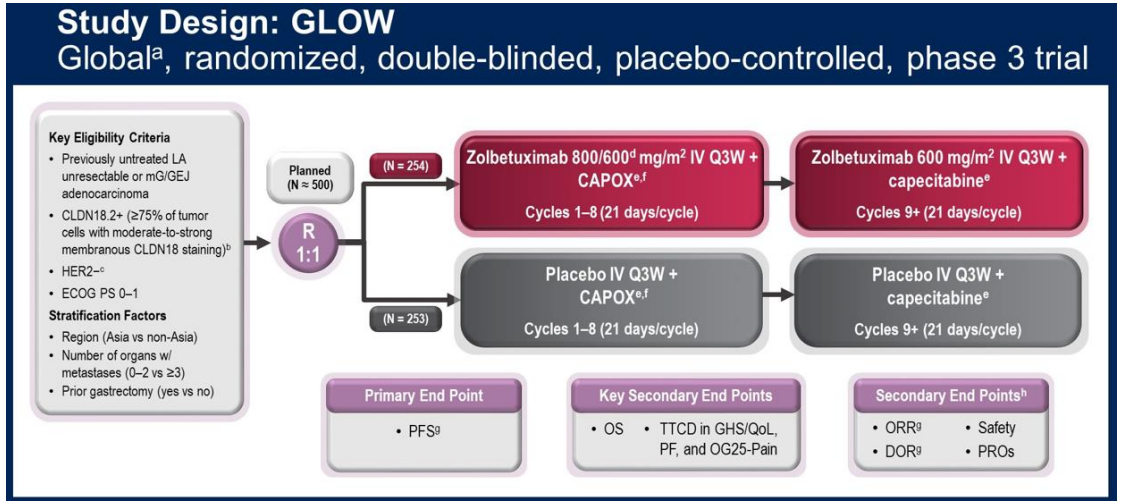
	Zolbe	Placebo
ORR (%)	60.7	62.1
mPFS (mos)	10.61	8.67
mOS (mos)	18.23	15.54

10% MORE Gr3/4 N/V
On target AE

Shitara K, et al, Lancet . 2023 May 20;401(10389):1655-1668. doi: 10.1016/S0140-6736(23)00620-7; Image from https://www.arigobio.com/news/claudin-18.2

Claudin 18.2 – GLOW Trial

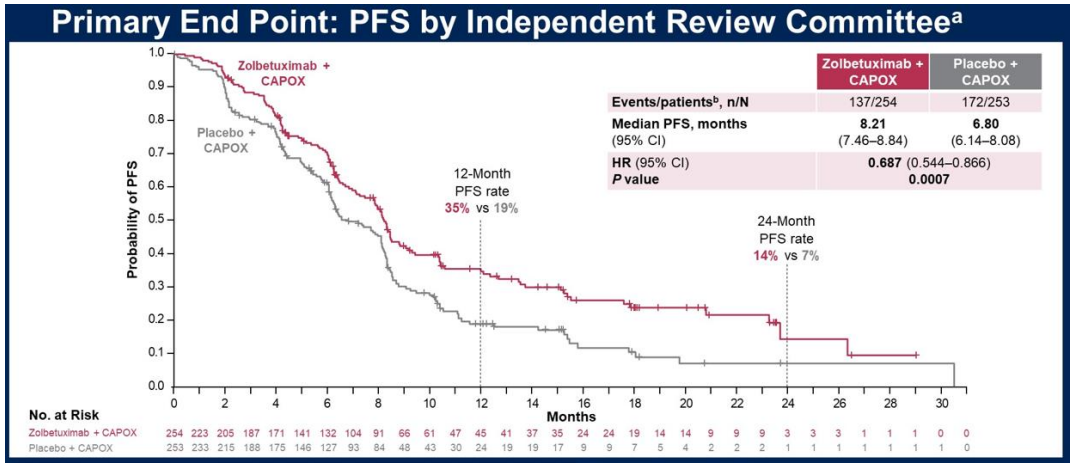
GLOW was a Phase 3 trial of CAPOX +/- Zolbetuximab

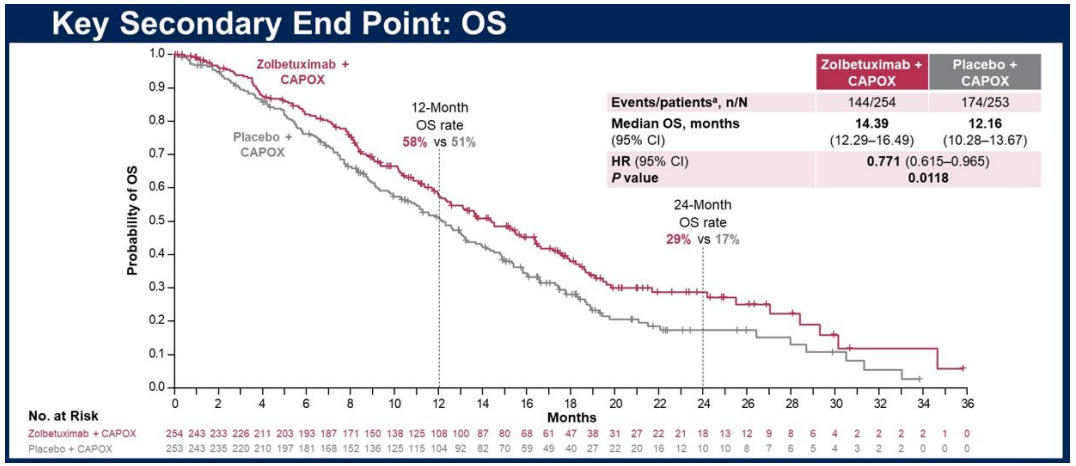


2333 patients screened; 38.4% were Claudin 18.2+

	Zolbe	Placebo
ORR (%)	53.8	48.8
mPFS (mos)	8.21	6.80
mOS (mos)	14.39	12.16

Many, many other Claudin 18.2 targeted therapies in development



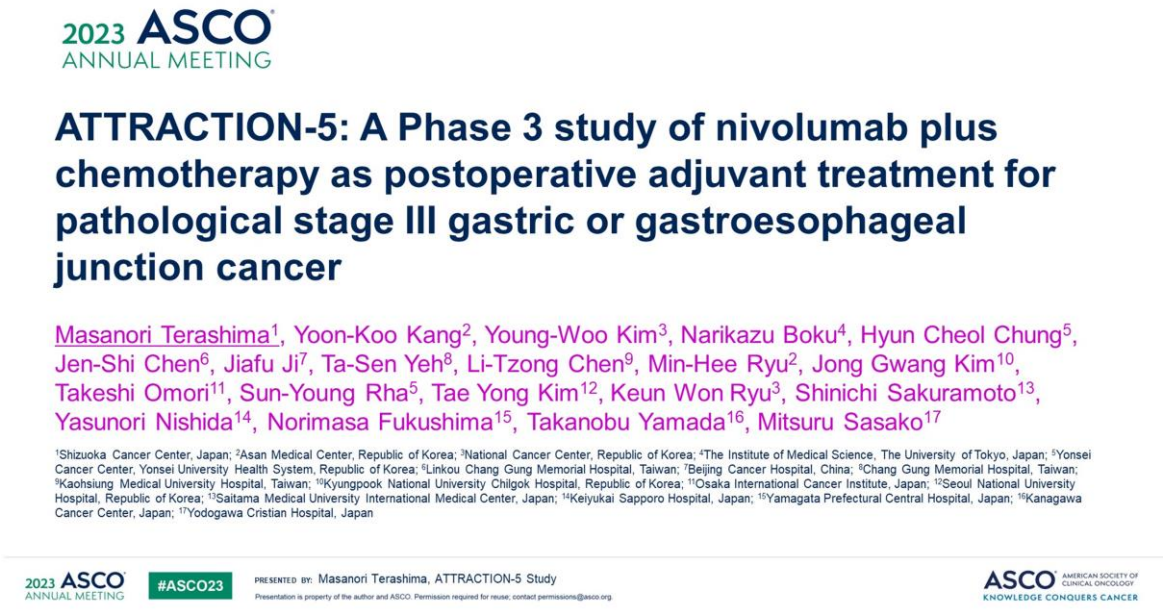


Xu RH, et al, ASCO 2023 Abstract 405736; Image from https://www.arigobio.com/news/claudin-18.2

Adjuvant Nivolumab After Gastric Cancer Resection

- In 2021, Dr. Janjigian, et al showed that the addition of nivolumab to chemotherapy in metastatic G/GEJ cancer improved mOS
- In 2021, Dr. Kelly, et al showed that the addition of nivolumab post-operatively in patients with E/GEJ cancers with positive residual disease (i.e. a non-CR) after chemoXRT improved OS

- But what about post-operative therapy for GASTRIC cancer?


2023 ASCO ANNUAL MEETING

ATTRACTION-5: A Phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III gastric or gastroesophageal junction cancer

Masanori Terashima[1], Yoon-Koo Kang[2], Young-Woo Kim[3], Narikazu Boku[4], Hyun Cheol Chung[5], Jen-Shi Chen[6], Jiafu Ji[7], Ta-Sen Yeh[8], Li-Tzong Chen[9], Min-Hee Ryu[2], Jong Gwang Kim[10], Takeshi Omori[11], Sun-Young Rha[5], Tae Yong Kim[12], Keun Won Ryu[3], Shinichi Sakuramoto[13], Yasunori Nishida[14], Norimasa Fukushima[15], Takanobu Yamada[16], Mitsuru Sasako[17]

[1]Shizuoka Cancer Center, Japan; [2]Asan Medical Center, Republic of Korea; [3]National Cancer Center, Republic of Korea; [4]The Institute of Medical Science, The University of Tokyo, Japan; [5]Yonsei Cancer Center, Yonsei University Health System, Republic of Korea; [6]Linkou Chang Gung Memorial Hospital, Taiwan; [7]Beijing Cancer Hospital, China; [8]Chang Gung Memorial Hospital, Taiwan; [9]Kaohsiung Medical University Hospital, Taiwan; [10]Kyungpook National University Chilgok Hospital, Republic of Korea; [11]Osaka International Cancer Institute, Japan; [12]Seoul National University Hospital, Republic of Korea; [13]Saitama Medical University International Medical Center, Japan; [14]Keiyukai Sapporo Hospital, Japan; [15]Yamagata Prefectural Central Hospital, Japan; [16]Kanagawa Cancer Center, Japan; [17]Yodogawa Cristian Hospital, Japan

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Masanori Terashima, ATTRACTION-5 Study

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Janjigian Y, et al, Lancet. 2021 Jul 3;398(10294):27-40. doi: 10.1016/S0140-6736(21)00797-2; ; Kelley RJ, et al, N Engl J Med. 2021 Apr 1;384(13):1191-1203. doi: 10.1056/NEJMoa2032125
Terashima M, et al, ASCO 2023, Abstract 4000

Adjuvant Nivolumab After Gastric Cancer Resection

- Phase 3, double-blind, placebo-controlled study of Asian patients (Japan, Korea, Taiwan, China)[a]

Key eligibility criteria
- pStage III GC/GEJC
- D2 or more extended gastrectomy
- ECOG PS 0-1
- Tumor tissue for PD-L1 analysis

Investigator's choice of adjuvant chemotherapy **S-1**[b] or **CapeOX**[c]

R 1:1

N=755

Nivolumab 360 mg IV Q3W + Chemotherapy (N=377)

Placebo IV Q3W + Chemotherapy (N=378)

Primary endpoint:
- RFS per BICR

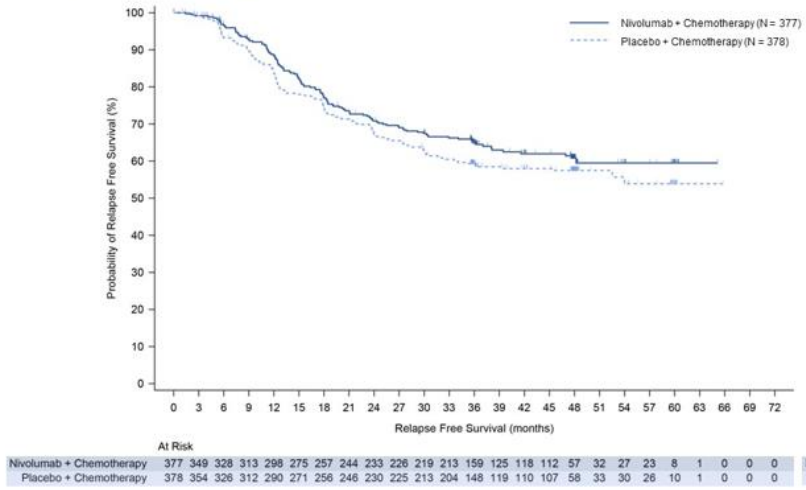
Secondary endpoints:
- RFS per investigator
- OS
- Safety

Stratification factors:
- **Stage (IIIA/IIIB/IIIC)**
- **Country (Japan/Korea/Other)**

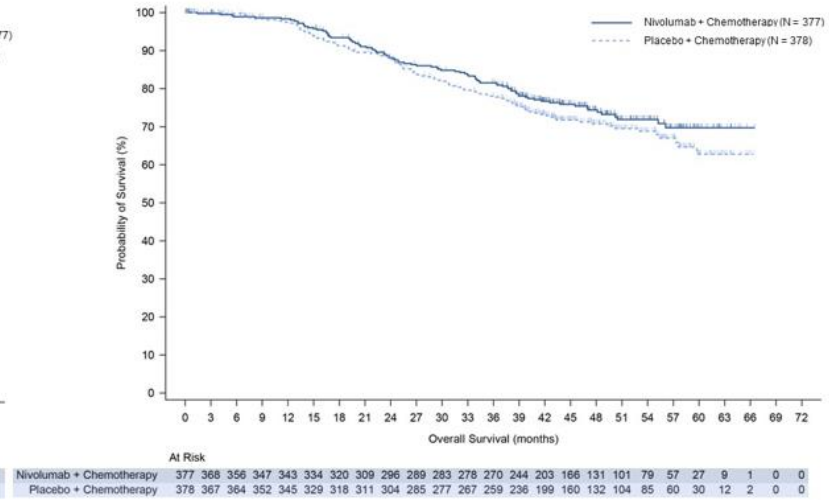
Treatment duration:
- **Up to 1 year (Nivolumab/Placebo, S-1)**
- **Up to 6 months (CapeOX)**

- Planned sample size: 700 patients (assuming HR=0.67; 3-year RFS, 71% vs 60%)

RFS per investigator



OS



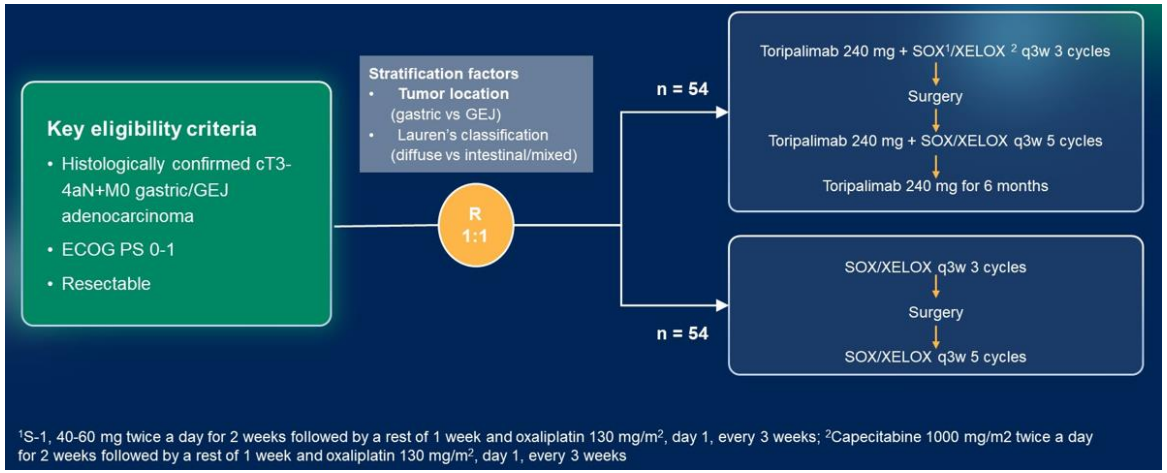
	Nivo	Placebo
mRFS (mos)	NE	NE
3y RFS (%)	68.4	65.3
mOS (mos)	NR	NR
3y OS (%)	81.5	78.0

- No improvement in RFS or OS
- So currently – there is no role for adjuvant nivo for resected gastric cancer

Terashima M, et al, ASCO 2023, Abstract 4000

Perioperative Chemo +/- Toripalimab for Operable G/GEJ Cancer

- Is there any role for neodjuvant/peri-operative anti-PD1 therapy for resectable G/GEJ cancer?
- Yuan, et al assess the addition of toripalimab to peri-operative SOX/XELOX
  - There was an improvement in pathological response (tumor regression grade, TRG)
- But, will that translated to any survival benefit?



Primary endpoint

TRG 0/1: rate of pathological complete response (TRG 0) or near complete response (TRG 1), according to NCCN guideline[1]

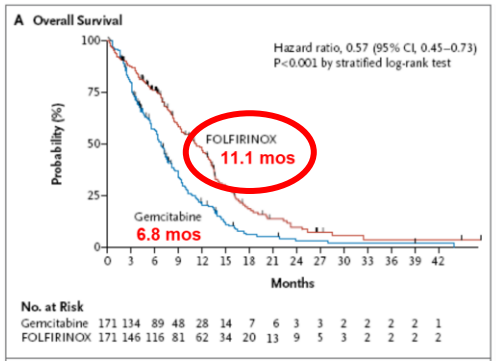
	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)	P value
TRG			
TRG 0 (ypT0N0M0)	**12 (22%)**	**4 (7%)**	0.03
TRG 1	12 (22%)	7 (13%)	
TRG 2	16 (30%)	29 (54%)	
TRG 3	11 (20%)	12 (22%)	
Combined TRG 0-1	**24 (44%)**	**11 (20%)**	0.01
No surgery	3 (6%)	2 (4%)	

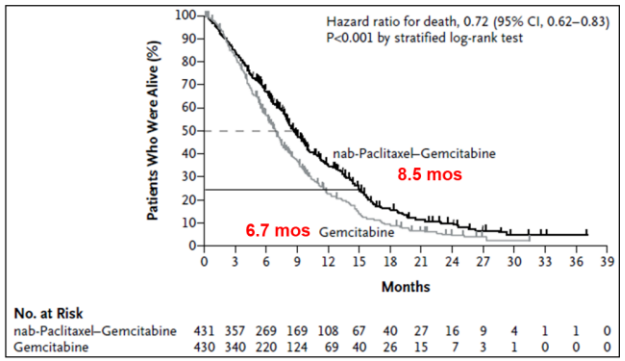
Yuan S, et al, ASCO 2023, Abstract 4001

Updates in Pancreatic Cancer

NALIRIFOX

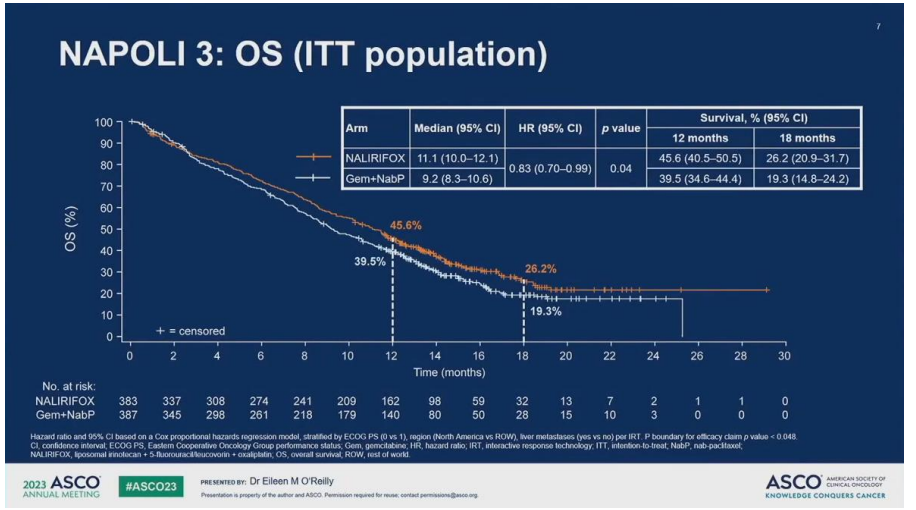
- FOLFIRINOX and Gemcitabine + Nab-paclitaxel have been our SOC regimens for mPDAC for 10+ years
- There has never been a head to head comparison of these two regimens
  - FOLFIRINOX vs. Gemcitabine, Phase III
    - Response rate: 32% vs. 9%
    - Overall survival: 11.1 vs. 6.8 months
  - Gem-nab-pac vs. Gemcitabine, Phase III
    - Response rate: 23% vs. 7%
    - Overall survival: 8.5 vs. 6.7 months

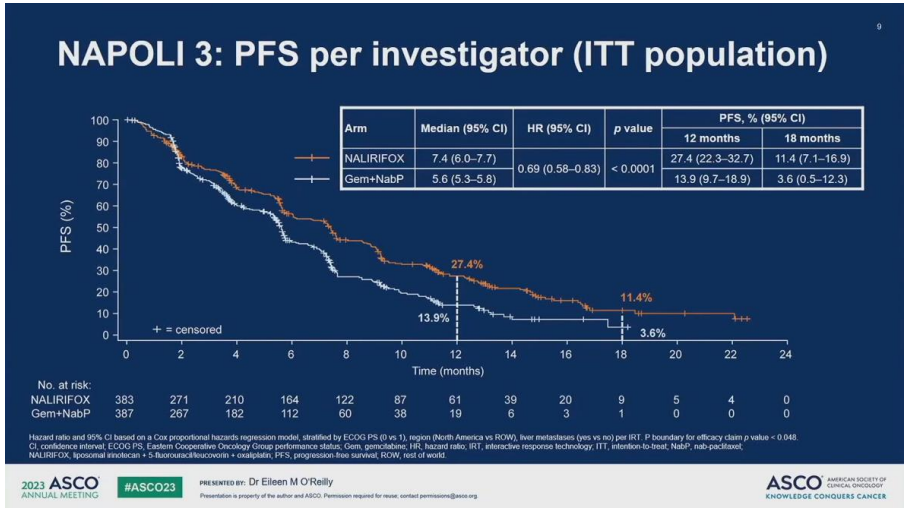




- NAPOLI-3 was a Phase 3 trial comparing NALIRIFOX to gem-nab-pac
  - Improved PFS and OS with NALIRIFOX
  - More GI tox with NALIRIFOX
  - More heme tox with gem-nab-pac

	NFOX	Gnab
ORR (%)	41.8	36.2
mOS (mos)	11.1	9.2
mPFS (mos)	7.4	5.6

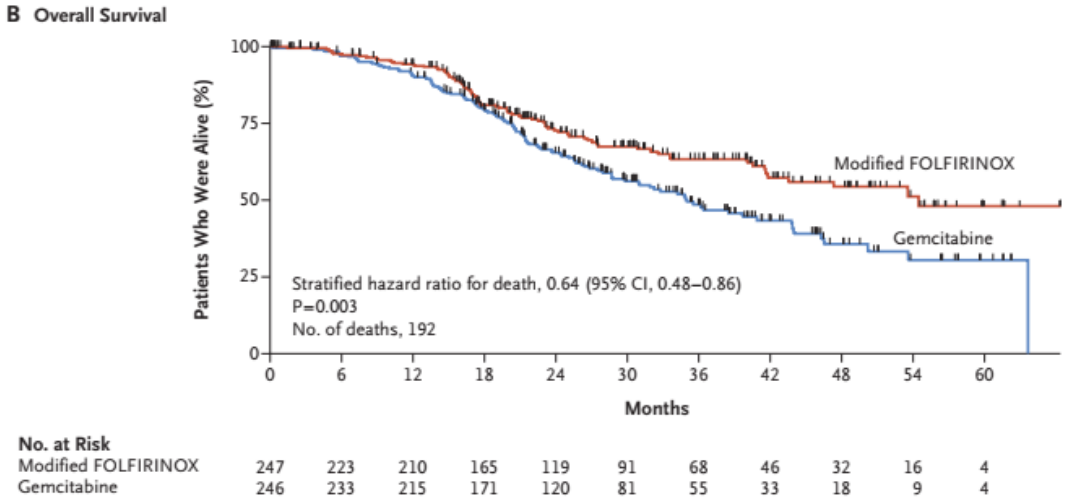




Conroy T, et al. N Engl J Med. 2011;364:1817-1825; Von Hoff, NEJM, 2013, 369(18): 1691-1703 ; Wainberg, ZA, ASCO GI 2023, Abs LBA661

Perioperative Therapy for PDAC

- Adjuvant FOLFIRINOX for patients with resected pancreatic cancer has unequivocally shown improved survival compared to gemcitabine
  - mOS improved from 40 months → 54.5 months*
- Trials such as PREOPANC-1 have shown that neoadjuvant chemoradiotherapy improves survival over immediate surgery for resectable pancreatic cancer
  - mOS 13.7 months → 17.1 months*
  - *(These two trials have very different starting points)
- So it is perfectly reasonable to hypothesize that neoadjuvant/perioperative FOLFIRINOX would improve OS compared to immediate surgery



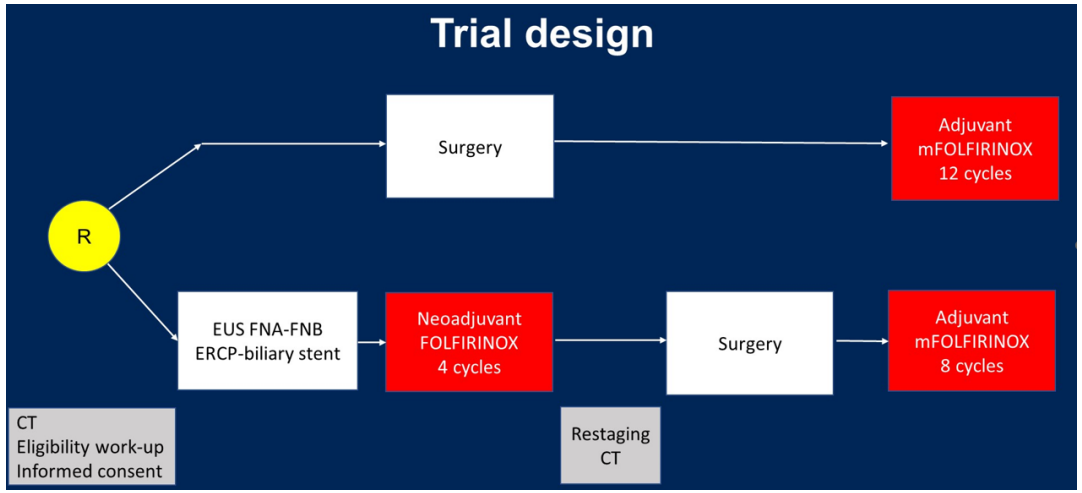
Outcome	Preoperative Radiochemotherapy (n = 119)	Immediate Surgery (n = 127)	HR	*P* Value
Median OS, mos (ITT population)*	**17.1**	**13.7**	**0.74**	**.074**
▪ Subset with R0/R1 resection†	**42.1**	**16.8**	**NR**	**< .001**
Resection rate, n (%)	72 (60)	91 (72)	--	.065
R0 resection rate, n/N (%)	45/72 (63)	28/91 (31)	--	< .001
Median DFS, mos	9.9	7.9	0.71	.023
Median distant metastases–free interval, mos	18.4	10.6	0.71	.013
Median locoregional recurrence-free interval, mos	Not reached	11.8	0.55	.002
Serious AEs, n (%)	55 (46)	49 (39)	--	.28

*Preliminary analysis; only 149/176 events. †Preoperative radiochemotherapy, n = 72; immediate surgery, n = 91.

Conroy T. N Engl J Med. 2018 Dec 20;379(25):2395-2406. doi: 10.1056/NEJMoa1809775; Versteijne E, et al, J Clin Oncol. 2020 Jun 1;38(16):1763-1773

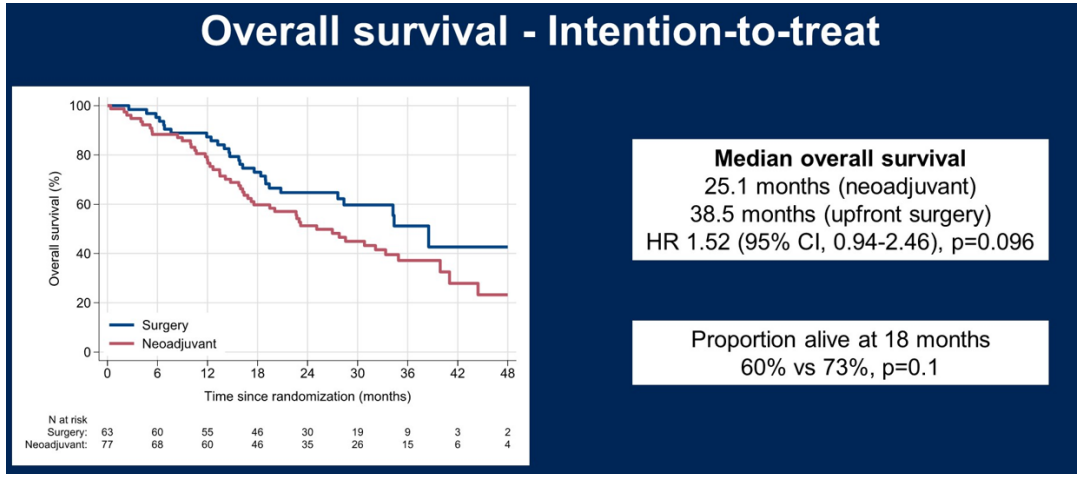
Perioperative Therapy for PDAC

- Labori KJ, et al presented the NORPACT-1 trial of perioperative FOLFIRINOX vs. upfront surgery for resectable pancreatic cancer
  - Operable PDAC head cancers per NCCN guidelines – no arterial involvement
  - Study designed to detect an ***improvement*** in OS at 18 months from 50% → 70%
  - ~20% of pre-op chemo patients did not have surgery
- Patients treated with FOLFIRINOX had a ***worse*** 18 month OS!
  - Despite a much better R0 resection rate
- This has shaken our certainty – but there are two large randomized Phase 3 trials accruing that will hopefully answer this question definitively



Histopathology

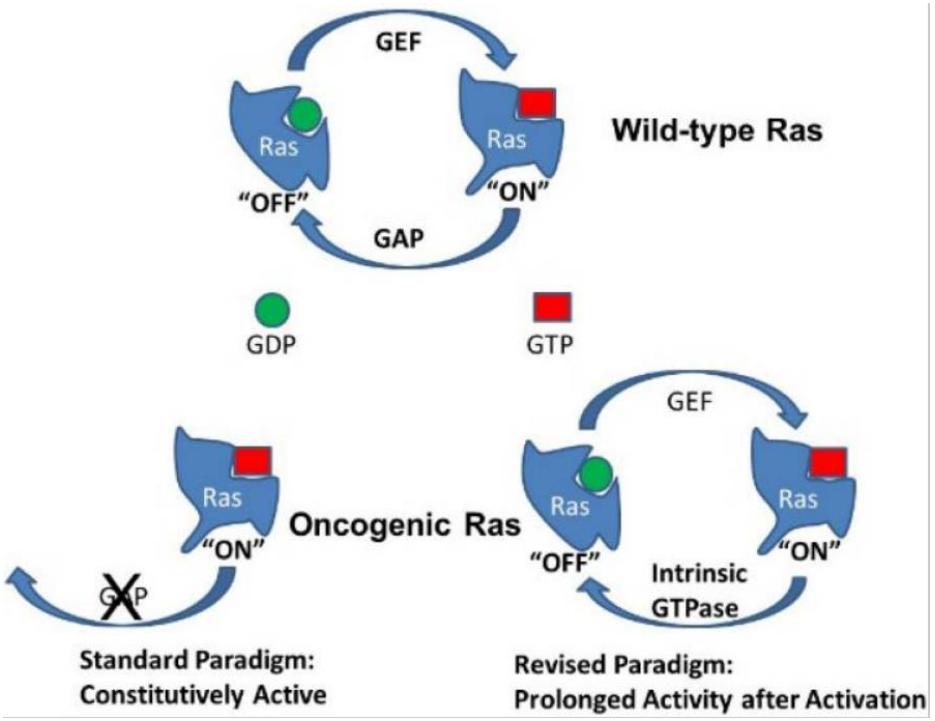
	Neoadjuvant group (n=63)	Upfront surgery (n=56)	p-value
Intention-to-treat			
R0	56%	39%	0.076
N0	29%	14%	0.060
Per-protocol	(n=46)	(n=49)	
R0	59%	33%	0.011
N0	37%	10%	0.002

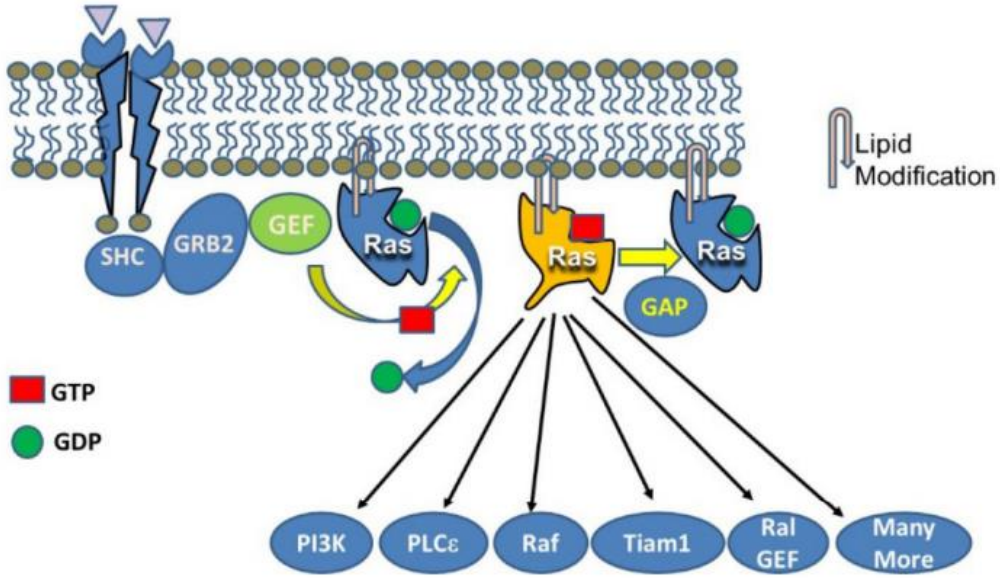


Labori KJ, et al, ASCO 2023, LBA4005

KRAS Mutations in Pancreatic Cancer

- *KRAS* mutations occur in 90 – 95% of pancreatic cancers
  - *KRAS* mutations are a key event in the initiation and development of PDAC

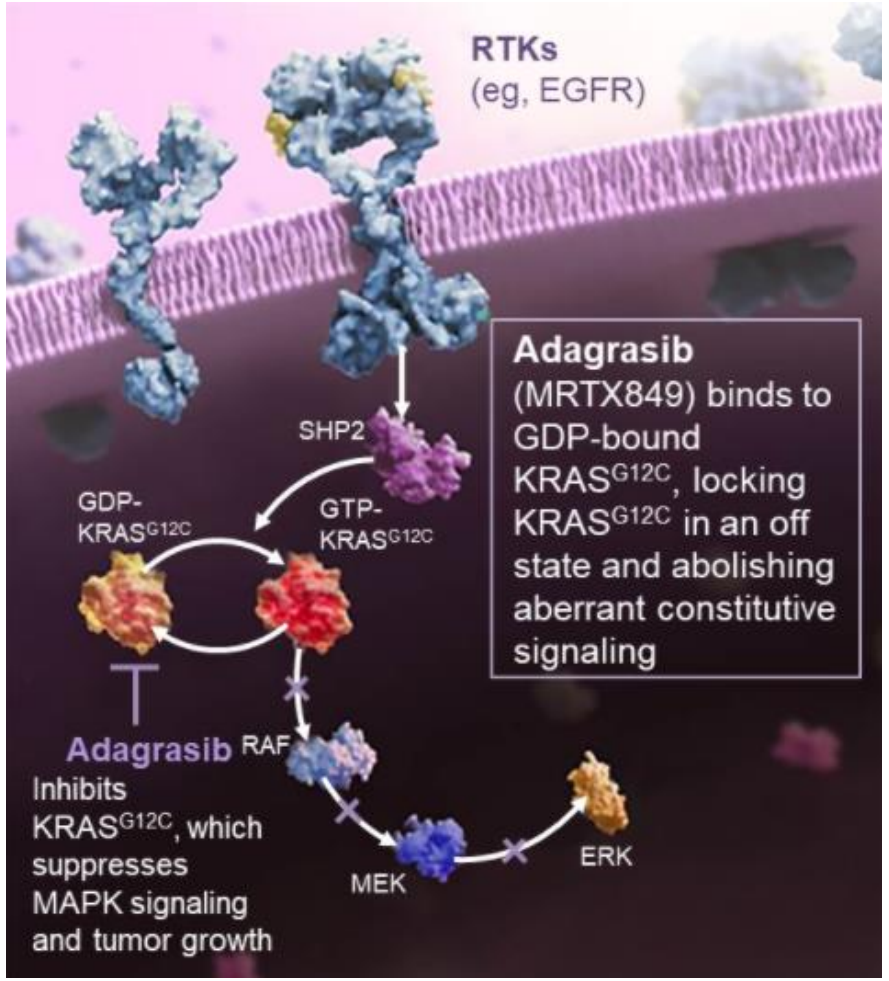




Craig Logsdon and Weiqin Lu, Int J Bio Sci, 2016; 12(3): 338–346

KRYSTAL-1: Adagrasib in KRAS^{G12C} Mutated Pancreatic Cancer

- *KRAS* mutations occur in 90 – 95% of PDACs
  - 80% are KRAS^{G12D} or KRAS^{G12V}
  - 2% are KRAS^{G12C}
- KRAS cycles between a GTP-on state and a GDP-off state
  - The protein resynthesis half life is 24 hours
- Adagrasib covalently binds to KRAS^{G12C} in its GDP-off state
- Phase II monotherapy in solid tumors
  - Mostly pancreatic cancers (n = 21)
  - Other GI cancers (n = 29; biliary n = 12)
  - All had at least 1 line of Tx

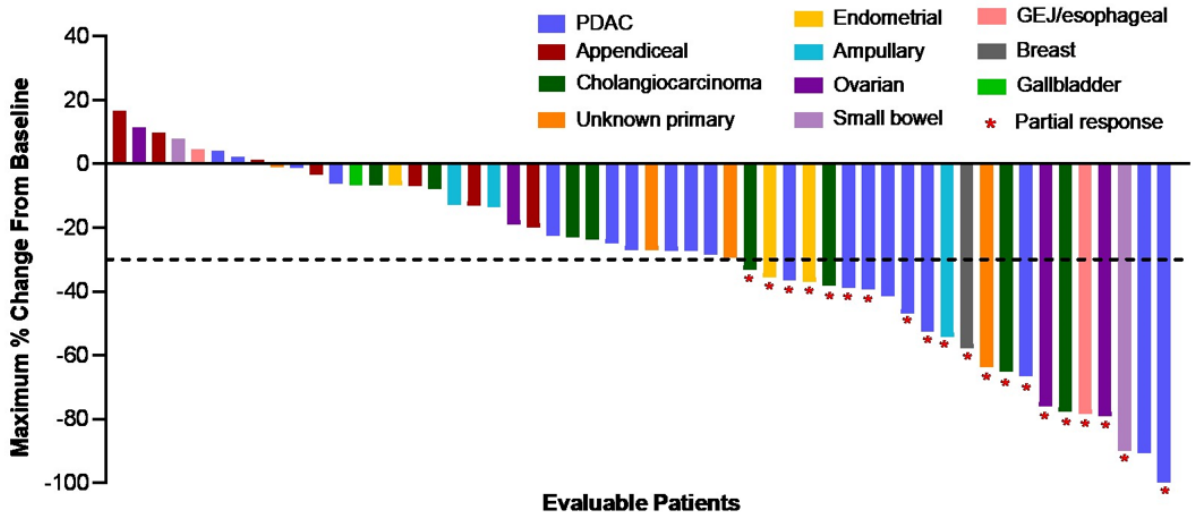


Pant S, et al, ASCO 2023; Bekaii-Saab T, et al, J Clin Oncol. 2023 Apr 26;101200JCO2300434. doi: 10.1200/JCO.23.00434

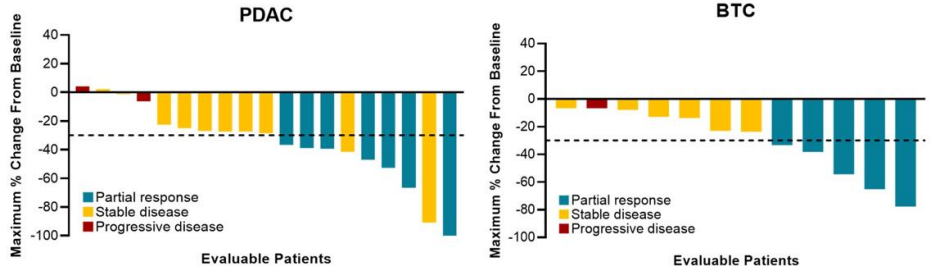
KRYSTAL-1: Adagrasib in KRAS^{G12C} Mutated Pancreatic Cancer

- Adagrasib demonstrated efficacy
  - ORR was 35.1% overall
  - 33% in pancreatic cancer
  - 42% in biliary cancers

Tumor Type	n	ORR, n (%)	DCR, n (%)
All patients	**57[b]**	**20 (35.1)**	**49 (86.0)**
PDAC	**21**	**7 (33.3)**	**17 (81.0)**
BTC	**12**	**5 (41.7)**	**11 (91.7)**
Other GI tumors	**12**	**2 (16.7)**	**10 (83.3)**
Appendiceal	7	0 (0.0)	6 (85.7)
Small Bowel	2	1 (50.0)	2 (100.0)
GEJ/esophageal	3	1 (33.3)	2 (66.7)
Gynecological tumors	**7**	**4 (57.1)**	**6 (85.7)**
Ovarian	4	2 (50.0)	3 (75.0)
Endometrial	3	2 (66.7)	3 (100.0)
Other tumors	**5**	**2 (40.0)**	**5 (100.0)**
Unknown Primary	4	1 (25.0)	4 (100.0)
Breast	1	1 (100.0)	1 (100.0)



- Confirmed objective responses were observed in 20/57 patients (35.1%)
- Disease control was observed in 49/57 patients (86.0%)



- Confirmed ORR of 33.3% (7/21 patients)
- Disease control was observed in 17/21 (81.0%) patients
- Confirmed ORR of 41.7% (5/12 patients)
- Disease control was observed in 11/12 (91.7%) patients

Pant S, et al, ASCO 2023; Bekaii-Saab T, et al, J Clin Oncol. 2023 Apr 26;101200JCO2300434. doi: 10.1200/JCO.23.00434

KRYSTAL-1: Adagrasib in KRAS^{G12C} Mutated Solid Tumors

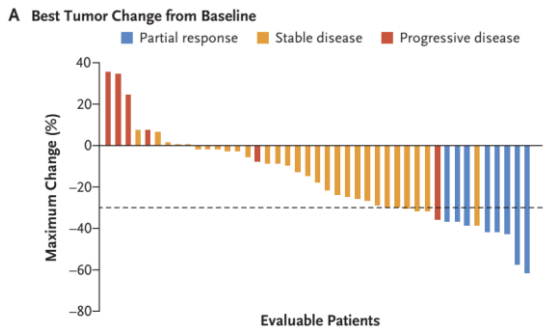
- Adagrasib was adequately tolerated
  - No Grade 4 or Grade 5 adverse events
  - Nausea, vomiting, diarrhea in 40 – 50% of patients
    - But, almost all Grade ≤2
  - 6% Grade 3 fatigue

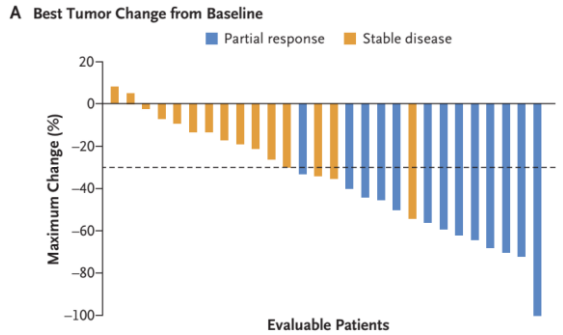
TRAEs, n (%)	Overall solid tumors (N=63)			
	Any Grade	Grade 1	Grade 2	Grade 3
Any TRAEs	**61 (96.8)**	**16 (25.4)**	**28 (44.4)**	**16 (25.4)**
Most Frequent TRAEs[b]				
Nausea	31 (49.2)	23 (36.5)	7 (11.1)	1 (1.6)
Diarrhea	30 (47.6)	21 (33.3)	8 (12.7)	1 (1.6)
Fatigue	26 (41.3)	12 (19.0)	10 (15.9)	4 (6.3)
Vomiting	25 (39.7)	20 (31.7)	4 (6.3)	1 (1.6)
Blood creatinine increase	10 (15.9)	7 (11.1)	3 (4.8)	0 (0.0)
Anemia	9 (14.3)	3 (4.8)	5 (7.9)	1 (1.6)
AST increase	9 (14.3)	7 (11.1)	0 (0.0)	2 (3.2)
Decreased appetite	9 (14.3)	5 (7.9)	4 (6.3)	0 (0.0)
Peripheral edema	9 (14.3)	7 (11.1)	2 (3.2)	0 (0.0)
Electrocardiogram QT prolongation	8 (12.7)	3 (4.8)	1 (1.6)	4 (6.3)
Dysgeusia	7 (11.1)	6 (9.5)	1 (1.6)	0 (0.0)

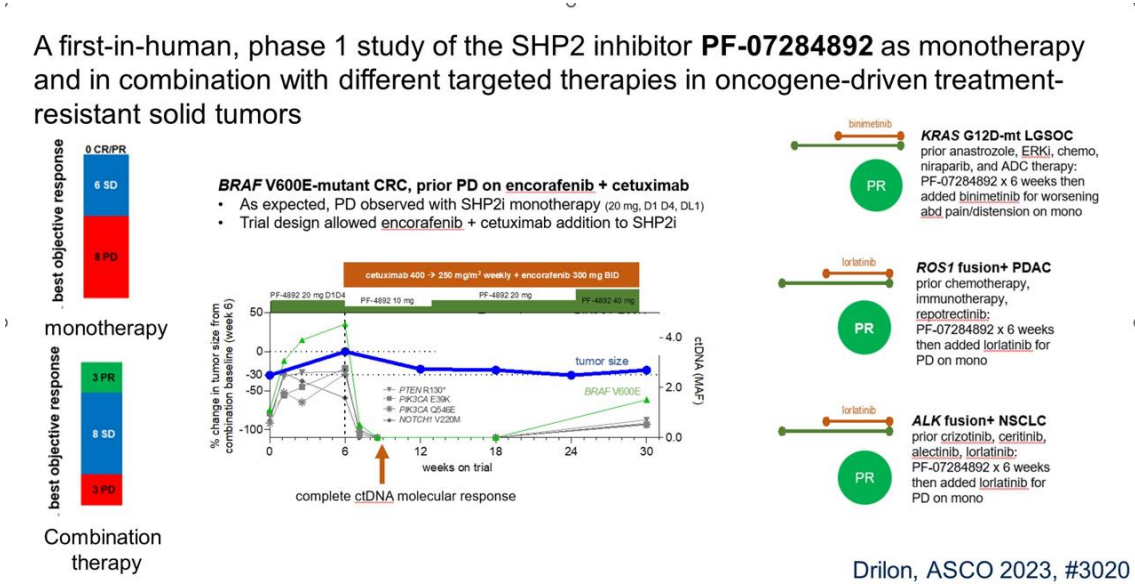
Pant S, et al, ASCO 2023; Bekaii-Saab T, et al, J Clin Oncol. 2023 Apr 26;101200JCO2300434. doi: 10.1200/JCO.23.00434

Targeting RAS/SHP/SOS in Combination

- KRAS inhibitors can be effective
  - But the effect may be short lived
  - Perhaps there will be improved outcomes with combination therapies?
- E.g. Yaeger, et al – Adagrasib +/- cetuximab in $KRAS^{G12C}$-mutated CRC
  - ORR = 23% vs. 46%
  - DOR = 4.3 mos vs. 7.6 mos
- Drillon, et al showed activity of a SHP2 inhibitor, but only in combination
  - E.g. PR with a SHP2i + encorafenib + cetux in a $BRAF^{V600E}$ mutated CRC patient





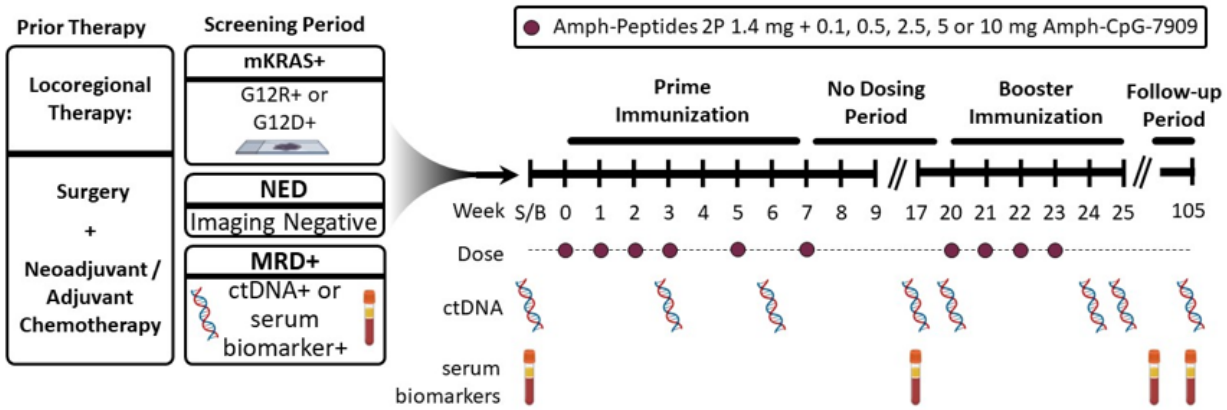


Drilon, ASCO 2023, #3020

N Engl J Med. 2023 Jan 5;388(1):44-54. doi: 10.1056/NEJMoa2212419; Drillon A, et al, ASCO 2023 Abstract 3020

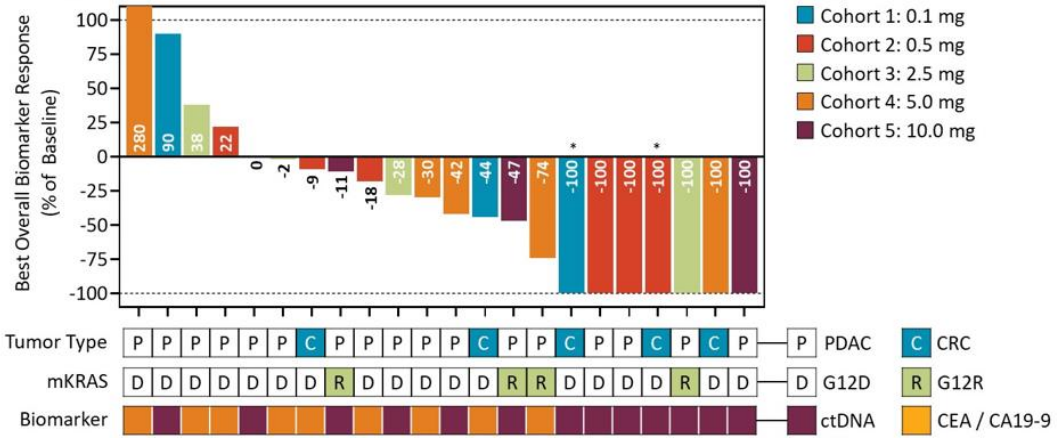
ELI-002 Personalized Vaccine in $KRAS^{G12R/D}$ cancers (Amplify-201)

- KRAS neoantigens are promising immunotherapy targets
- Target patient population that is radiologically NED, but MRD+ (ctDNA+ or tumor marker+)
  - ELI-002 is a $KRAS^{G12D/R}$ and TLR-9 adjuvant targeting cancer vaccine



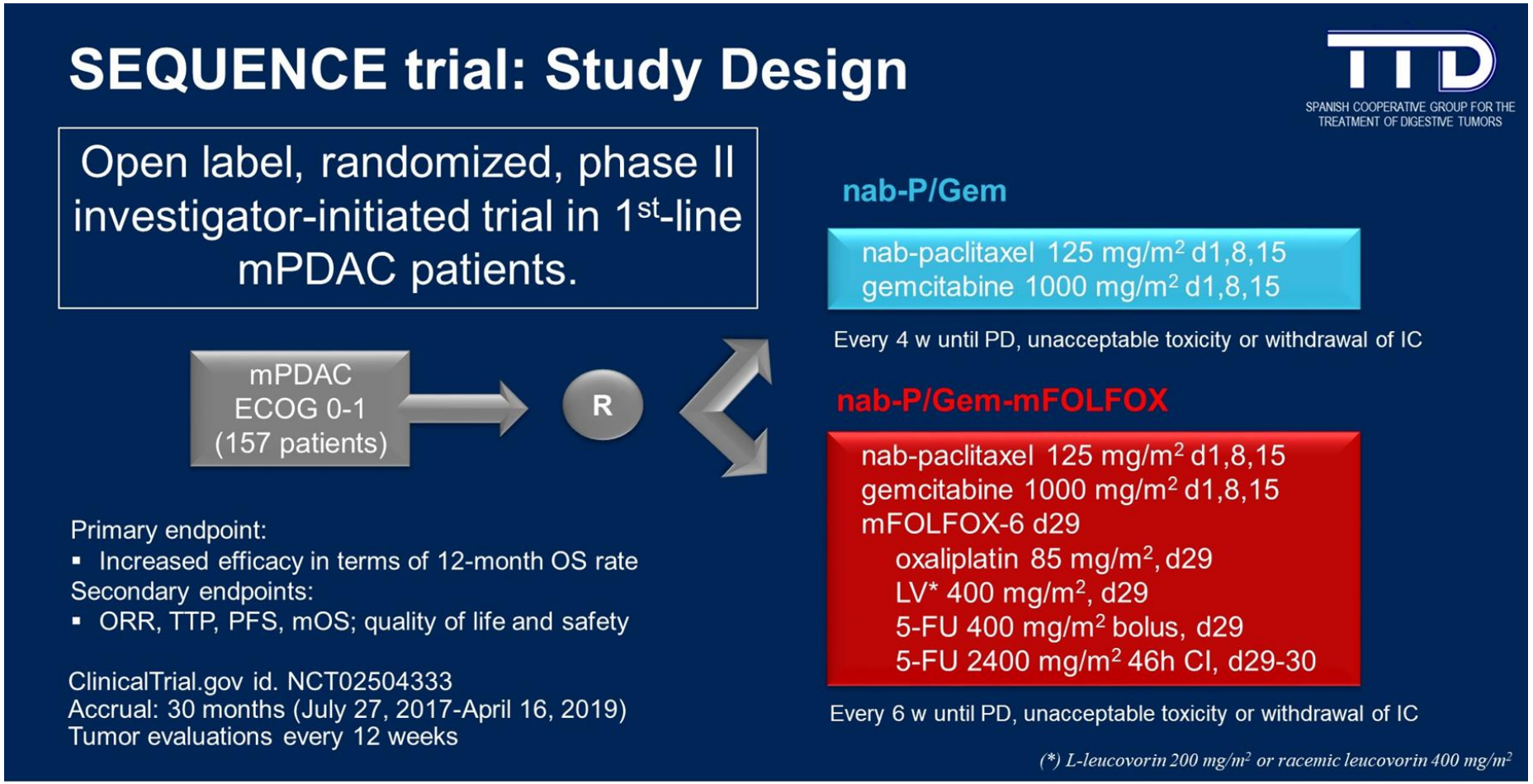
***Reduction** = % decrease from baseline*
- *17/22 (77%)*

***Clearance** = 0 MTM/mL on ctDNA assay*
- *7/22 (32%)*



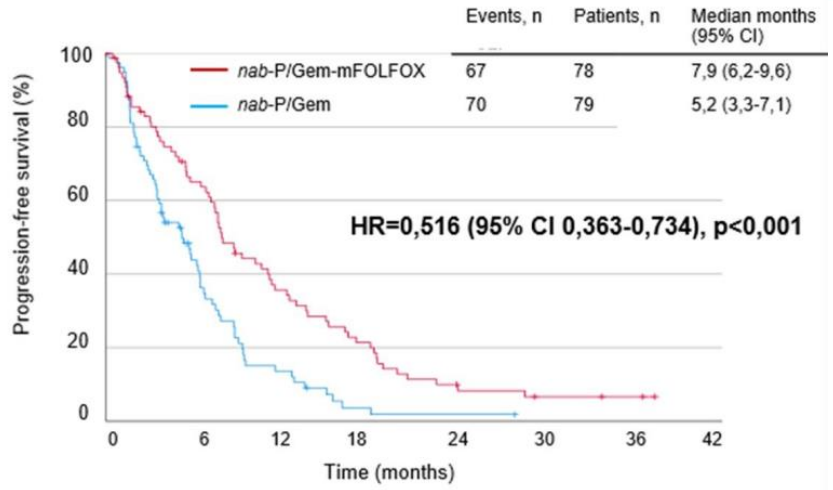
O'Reilly EO, et al, ASCO 2023

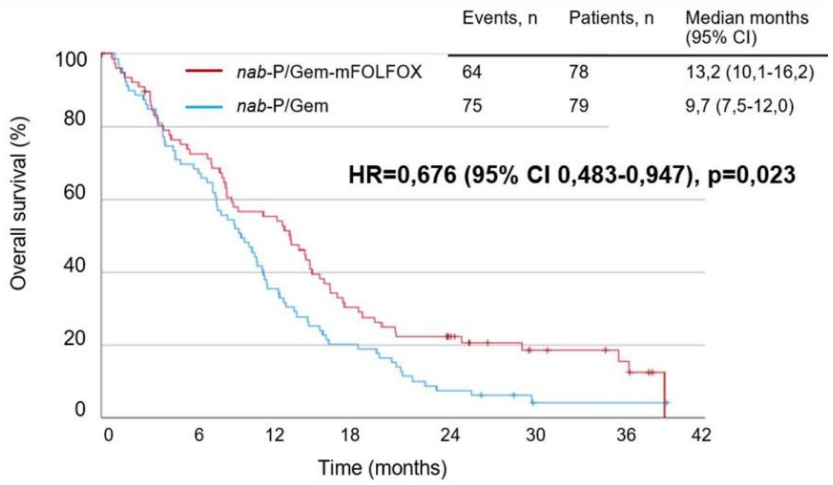
SEQUENCEing Chemotherapy for Pancreatic Cancer



Carrato A, et al, J Clin Oncol 40, 2022 (suppl 16; abstr 4022)

SEQUENCEing Chemotherapy for Pancreatic Cancer



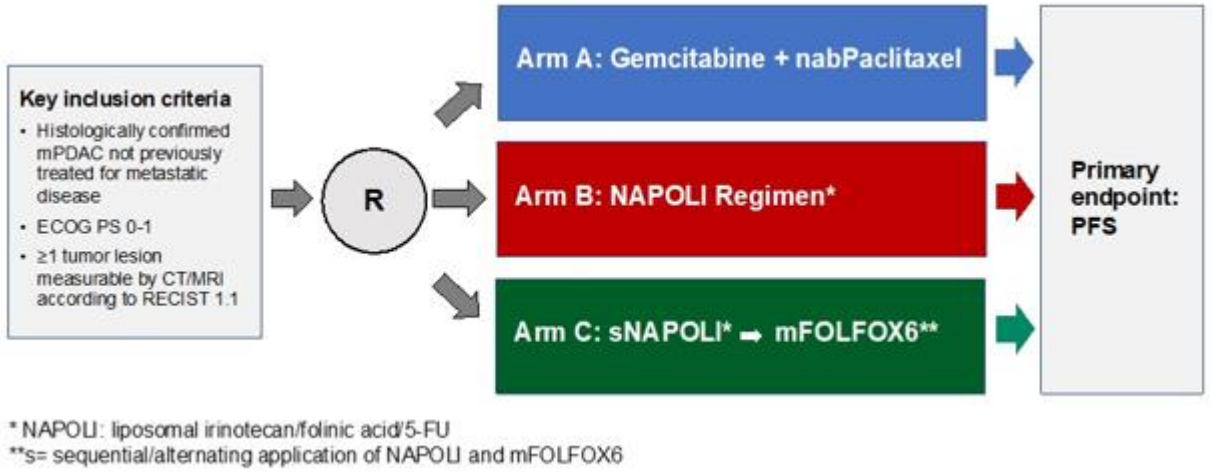


	Gem-Nab-Pac	Gem-Nab-Pac → FOLFOX	P-value
ORR	20%	40%	0.009
mPFS	5.2 months	7.9 months	<0.001
mOS	9.7 months	13.2 months	0.023
12m OS	35%	55%	0.016
2nd Line Tx	55%	40%	0.08*

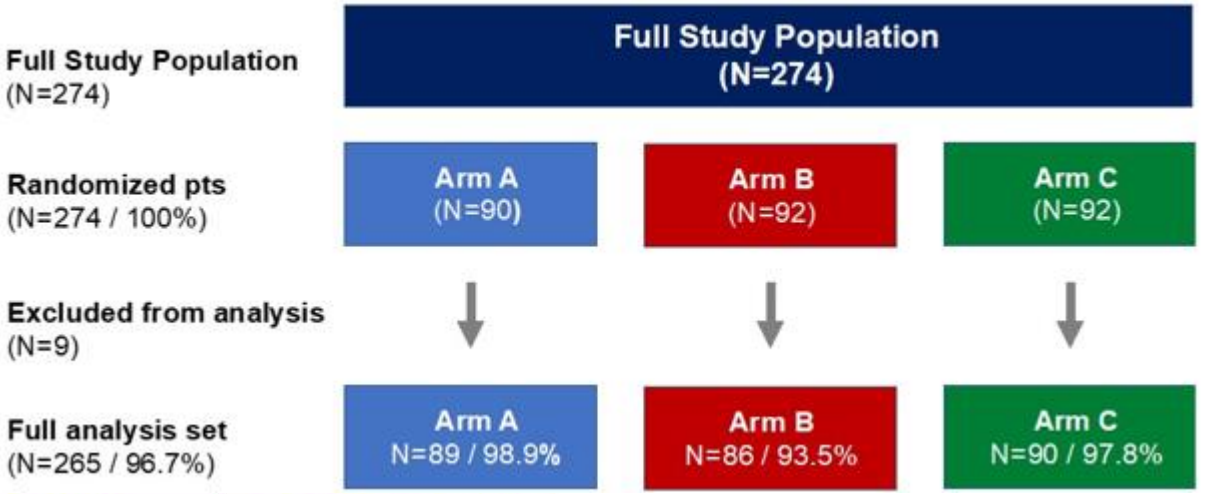
Quality of life was measured and was similar in both arms

Carrato A, et al, J Clin Oncol 40, 2022 (suppl 16; abstr 4022)

A Different Sequencing Trial in Pancreatic Cancer: FOOTPATH



* NAPOLI: liposomal irinotecan/folinic acid/5-FU
**s= sequential/alternating application of NAPOLI and mFOLFOX6

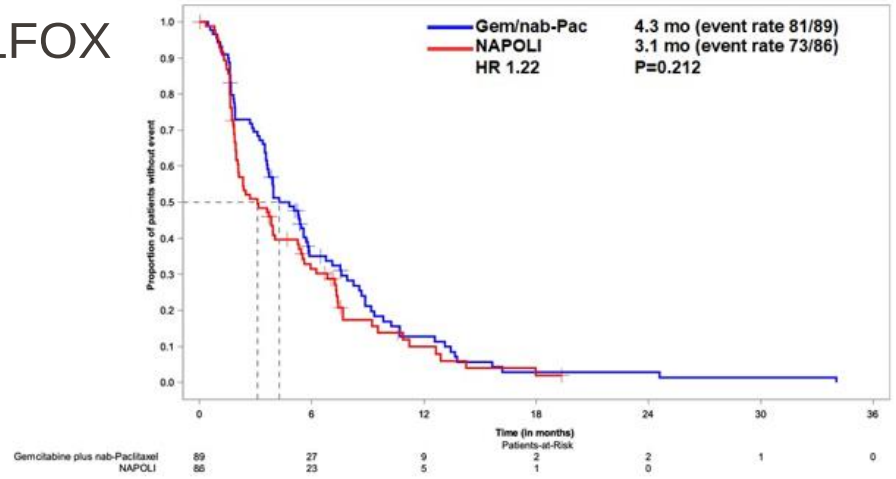


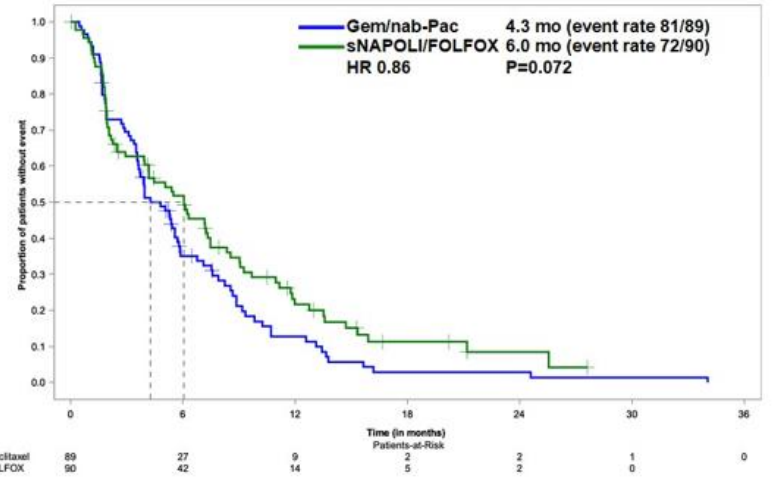
	Arm A (Gem/nabPac) N= 89		Arm B (NAPOLI) N= 86		Arm C (sNAPOLI/mFOLFOX6) N= 90	
AE/SAE	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Hematologic (in %)	66.3	39.3	29.1	11.6	32.2	18.9
Neutropenia	30.3	21.3	9.3	5.8	13.3	6.7
Febrile Neutropenia	1.1	1.1	n/a	n/a	1.1	1.1
Anemia	40.4	16.9	17.4	4.7	15.6	10
Thrombocytopenia	30.3	11.2	2.3	2.3	5.6	2.2
Non-hematologic (in %)						
Diarrhea	38.2	3.4	58.1	11.6	52.2	12.2
Nausea	41.6	3.4	47.7	7.0	45.6	6.7
Vomiting	21.3	1.1	27.9	4.7	28.9	4.4
Hypokalemia	7.9	n/a	15.1	5.8	10	3.3
Peripheral Neuropathy	40.4	6.7	14	n/a	34.4	3.3
Pyrexia	18	2.2	8.1	1.2	8.9	2.2

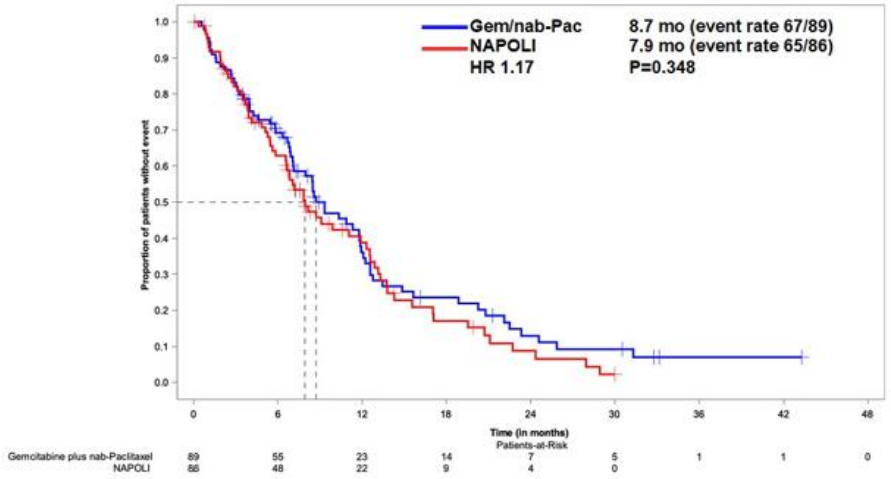
Westphalen B, et al, ASCO 2023 Abstract 4021

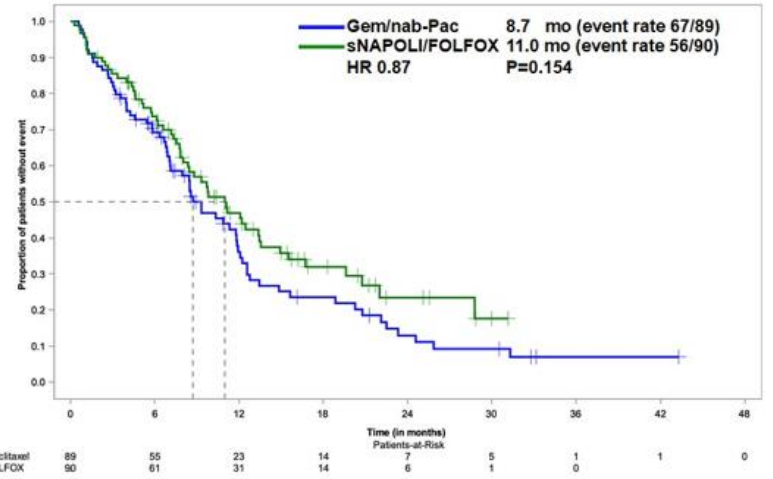
A Different Sequencing Trial in Pancreatic Cancer: FOOTPATH

- Sequential NAPOLI/FOLFOX led to (over GA):
  - An improved PFS
  - Numerically greater OS
  - Greater tolerability







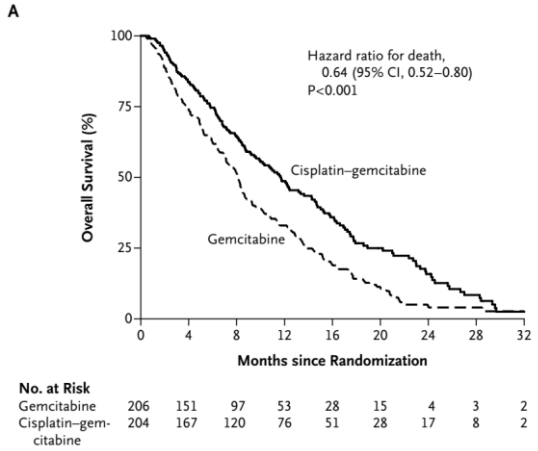


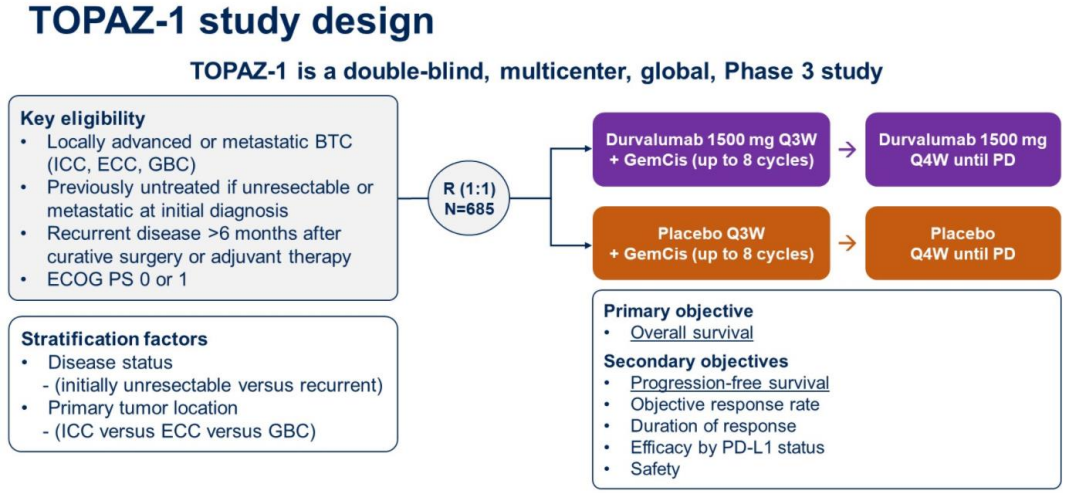
Westphalen B, et al, ASCO 2023 Abstract 4021

Updates in Biliary Tract Cancer

TOPAZ-1: Gem-Cis +/- Durvalumab in Cholangiocarcinoma

- For more than a decade, gemcitabine + cisplatin has been the standard of care in advanced biliary cancer
  - Gem-cis vs. gemcitabine alone
    - mOS 11.7 vs. 8.1 months
    - ORR 26.1 vs. 15.5%
- TOPAZ-1 was a Phase III randomized trial of gemcitabine + cisplatin +/- durvalumab for advanced biliary cancer
  - ***Note that gem-cis was stopped in both arms after 8 cycles***
  - Patients with advanced, untreated biliary cancer
  - 685 patients were randomized
    - 1:1 randomization
    - Balanced arms



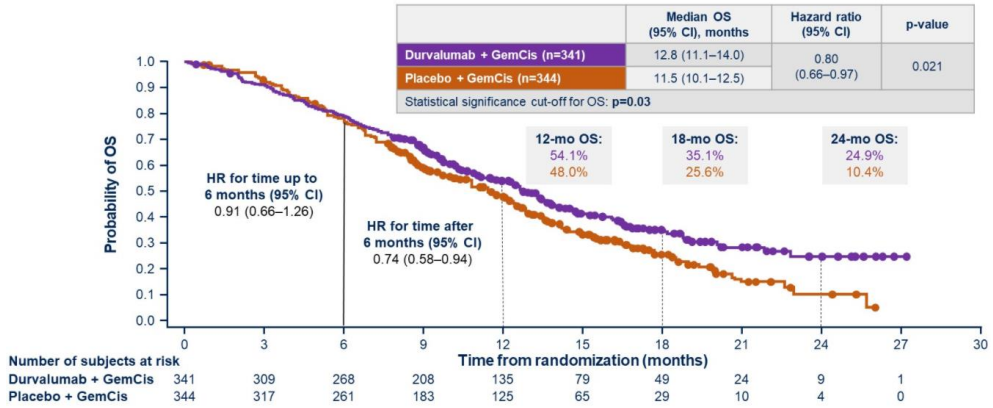


Valle J, et al, NEJM 2010; 362: 1273 – 1281
Oh DY, et al, 2022 ASCO Gastrointestinal Cancers Symposium, Abstract 378

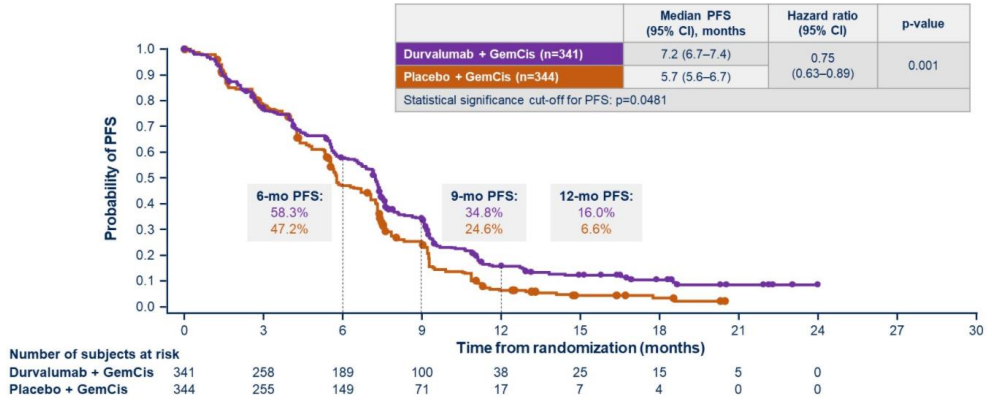
TOPAZ-1: Gem-Cis +/- Durvalumab in Cholangiocarcinoma

- Overall survival was significantly greater for gem-cis-durva vs. gem-cis
  - mOS 12.8 vs. 11.5 months
  - HR = 0.80, p = 0.021
  - HR after 6 months was 0.74
- Progression-free survival was significantly gr eater for gem-cis-durva vs. gem-cis
  - mPFS 7.2 vs. 5.7 months
  - HR = 0.75, p = 0.001
- Overall survival benefit held true for virtually all subgroups analyzed including PD-L1 status

Primary endpoint: OS



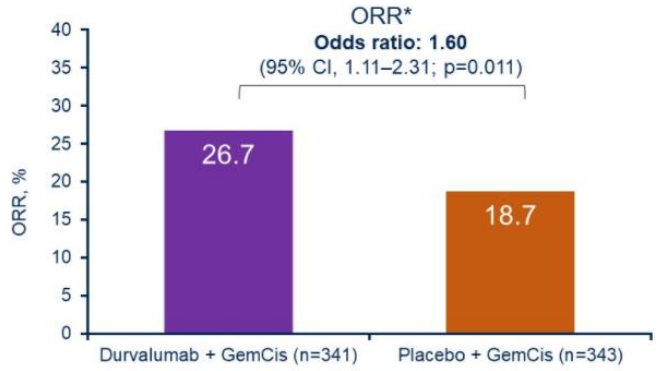
Secondary endpoint: PFS



Oh DY, et al, 2022 ASCO Gastrointestinal Cancers Symposium, Abstract 378

TOPAZ-1: Gem-Cis +/- Durvalumab in Cholangiocarcinoma

- Objective response rate was greater for gem-cis-durva vs. gem-cis
  - ORR 26.7 vs. 18.7%
- Adverse events were very similar between the two arms
  - Any Grade 3/4 AEs 75.7 vs. 77.8%



	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=343)
ORR, n (%)	91 (26.7)	64 (18.7)
CR, n (%)	7 (2.1)	2 (0.6)
PR, n (%)	84 (24.6)	62 (18.1)
DCR, n (%)†	291 (85.3)	284 (82.6)

Summary of AEs and treatment exposure

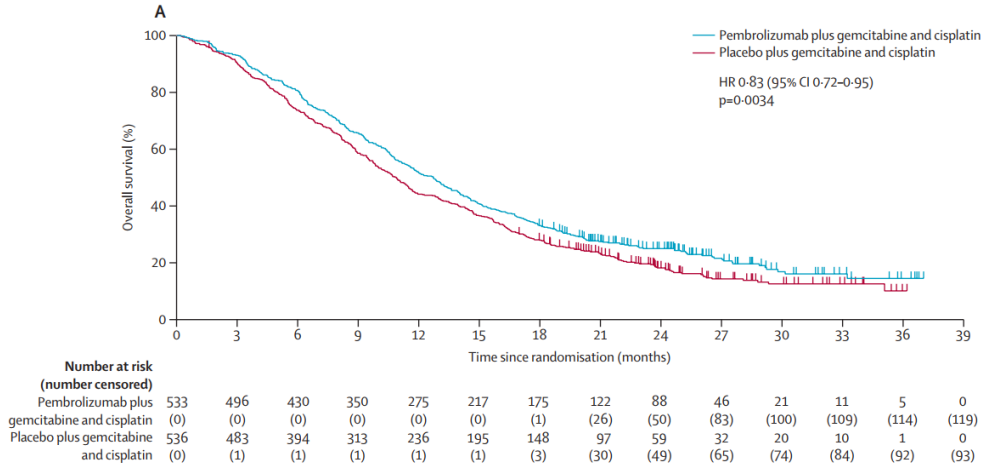
	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Median duration of exposure (range), months		
Durvalumab/placebo	7.33 (0.1–24.5)	5.77 (0.2–21.5)
Gemcitabine	5.19 (0.1–8.3)	5.03 (0.2–8.6)
Cisplatin	5.13 (0.1–8.3)	4.88 (0.2–8.5)
Adverse event, n (%)		
Any AE	336 (99.4)	338 (98.8)
Any TRAE	314 (92.9)	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	43 (12.7)	16 (4.7)

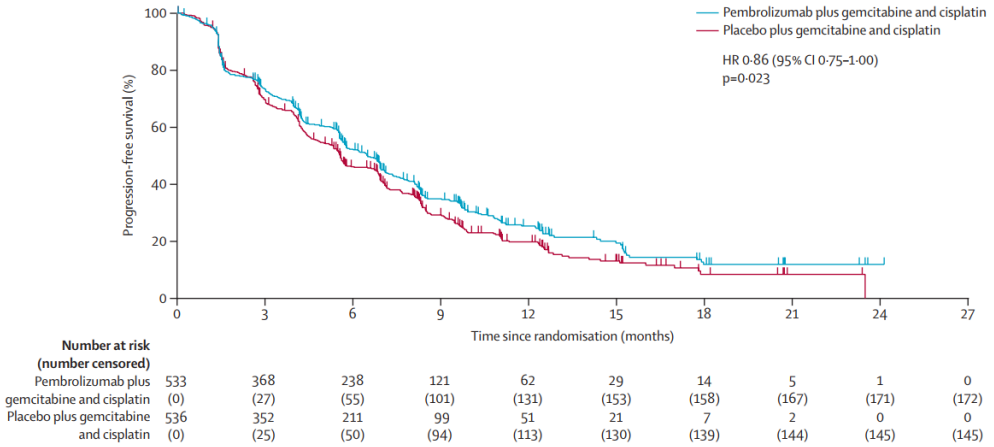
Oh DY, et al, 2022 ASCO Gastrointestinal Cancers Symposium, Abstract 378

KEYNOTE-966: Gem-Cis +/- Pembro in Cholangiocarcinoma

- In April, 2023, Dr. Kelley presented a very similar trial
- KEYNOTE-966 was a Phase III randomized trial of gemcitabine + cisplatin +/- pembrolizumab in advanced biliary cancer
  - ***Here ONLY cisplatin was stopped in both arms after 8 cycles (gem was continued)***
  - Outcomes were very similar to TOPAZ-1

	TOPAZ-1		KEYNOTE-966	
	Gem-Cis	Gem-Cis-Durva	Gem-Cis	Gem-Cis-Pembro
ORR (%)	19	27	29	29
mPFS (mos)	5.7	7.2	5.6	6.5
mOS (mos)	11.5	12.8	10.9	12.7

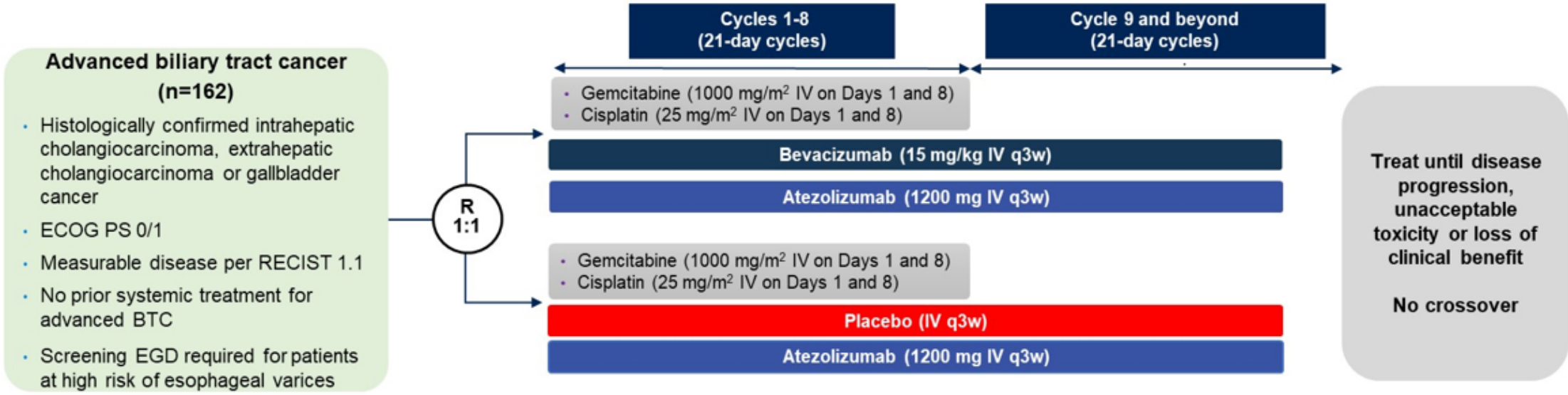




Kelley RR, et al, Lancet. 2023 Jun 3;401(10391):1853-1865. doi: 10.1016/S0140-6736(23)00727-4. Epub 2023 Apr 16. PMID: 37075781

IMbrave151: Gem/Cis + Bev + Atezo in Advanced Biliary Tract Cancer

IMbrave151 study design (NCT04677504)



Stratification factors

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

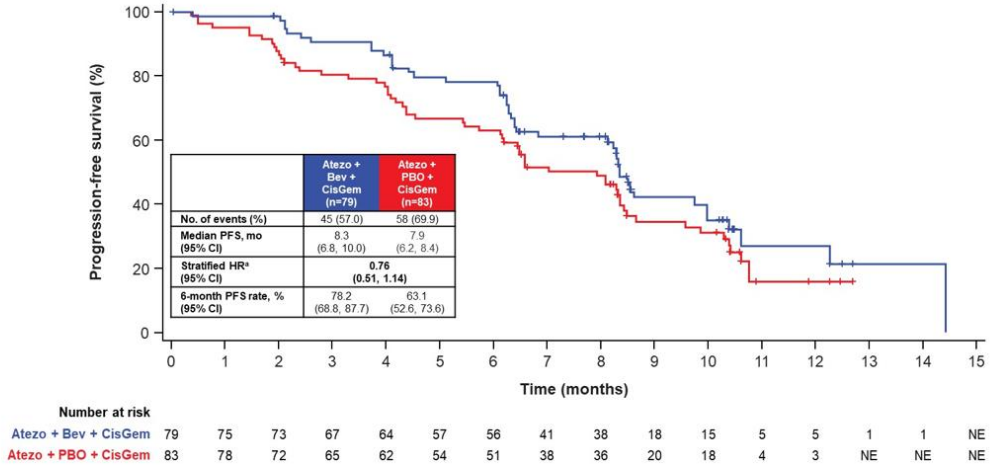
Key endpoints

- **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

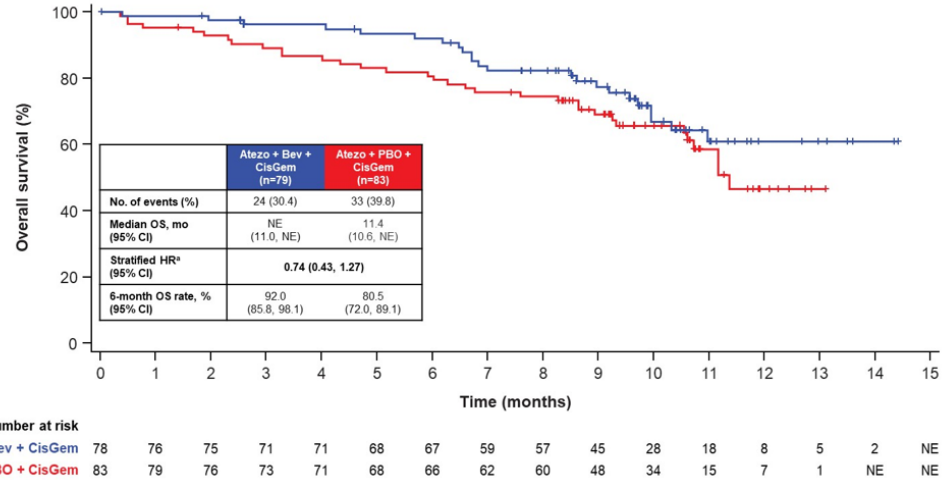
El-Khoueiry A, et al, 2023 ASCO Gastrointestinal Cancers Symposium, Abstract 491

IMbrave151: Gem/Cis + Atezo +/- Bev in Advanced Biliary Tract Cancer

Primary endpoint: PFS



Secondary endpoint: OS



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

El-Khoueiry A, et al, 2023 ASCO Gastrointestinal Cancers Symposium, Abstract 491

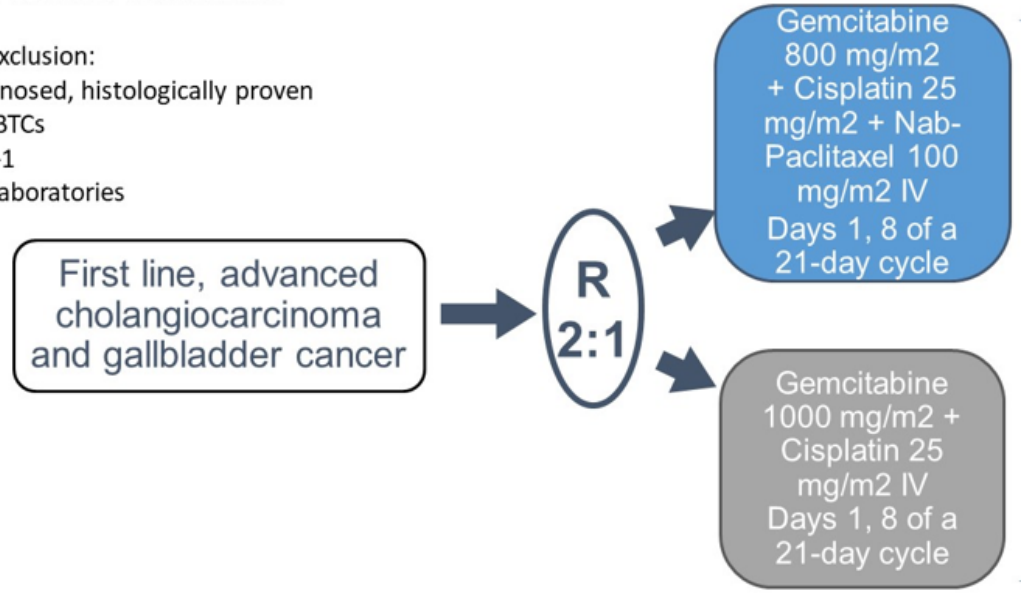
SWOG 1815: Gem, Cis, +/- Nab-pac in Advanced Biliary Tract Cancer

- In a Phase 2 single arm trial, Gem-Cis-Nab-pac resulted in a mOS of 19.2 months
  - Based on this, a randomized Phase 3 trial was designed

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



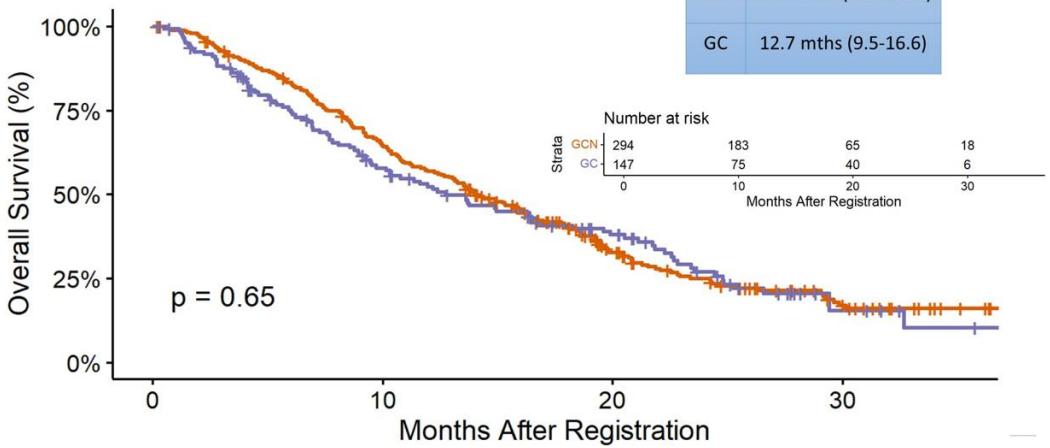
Primary EP: OS; **Target HR 0.7**
Secondary: ORR, PFS, DCR, safety, CA 19-9 changes

Shroff R, et al JAMA Oncol 2019; Shroff R, et al, 2023 ASCO Gastrointestinal Cancers Symposium, Abstract LBA490

SWOG 1815: Gem, Cis, +/- Nab-pac in Advanced Biliary Tract Cancer

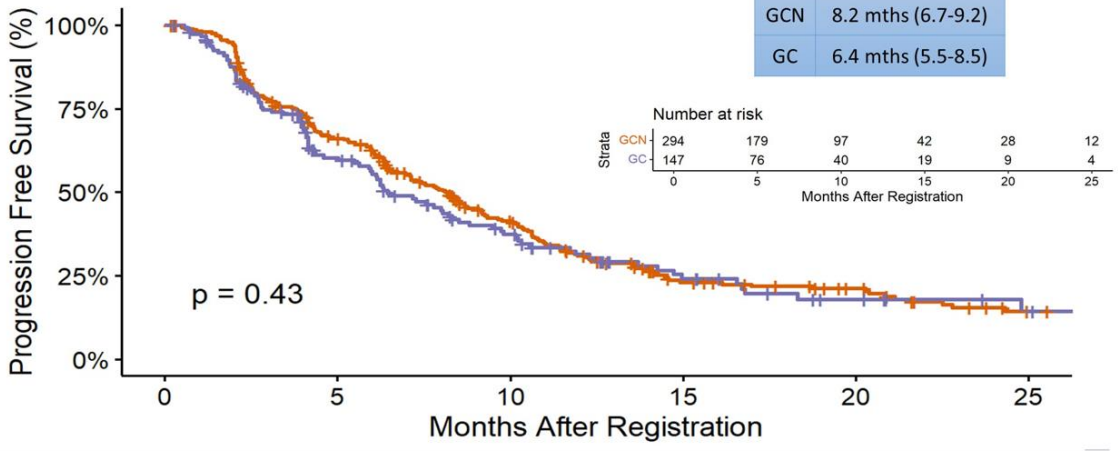
Overall Survival

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



Progression-Free Survival

Arm	Median (CI)
GCN	8.2 mths (6.7-9.2)
GC	6.4 mths (5.5-8.5)



Overall Response Rate

	GCN		GC	
	N (289)	%	N (143)	%
Complete Response	6	2	1	1
Partial Response	84	29	30	21
Stable/No Response	134	46	67	47

Overall Response Rate (ORR) = 31% versus 22% (ns)
Disease Control Rate (DCR) = 77% versus 69% (ns)

Gr 3-4 Treatment-Related Adverse Events

Treatment-Related Adverse Event	GCN Grade 3-4 N (%)	GC Grade 3-4 N (%)
Anemia	95 (33%)	30 (22%)
Neutropenia	105 (37%)	37 (28%)
Thrombocytopenia	56 (20%)	20 (15%)
Leukopenia	72 (25%)	14 (10%)
Diarrhea	13 (5%)	1 (0.7%)
Fatigue	26 (9%)	8 (6%)
Sepsis	12 (4%)	3 (2%)
Peripheral Sensory Neuropathy	10 (4%)	1 (0.7%)

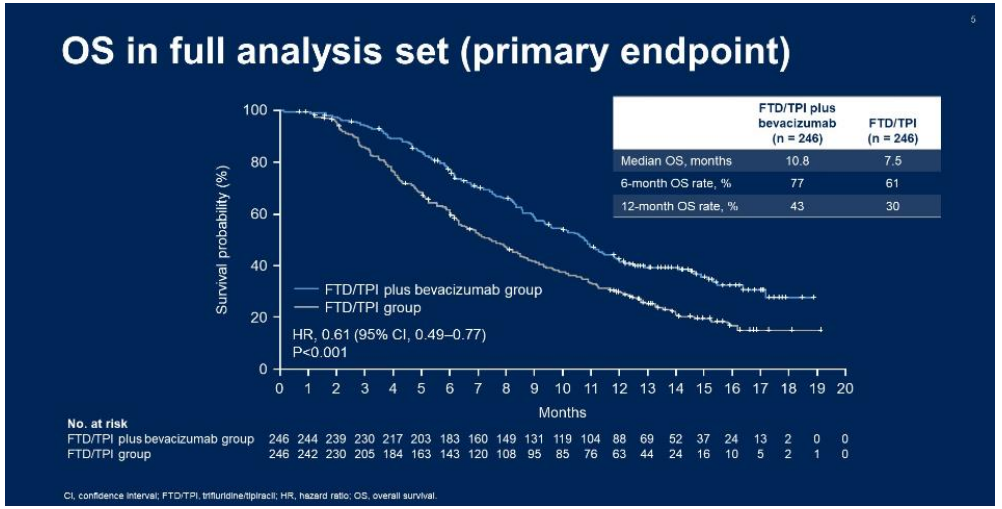
*Included if incidence ≥5% of patients.

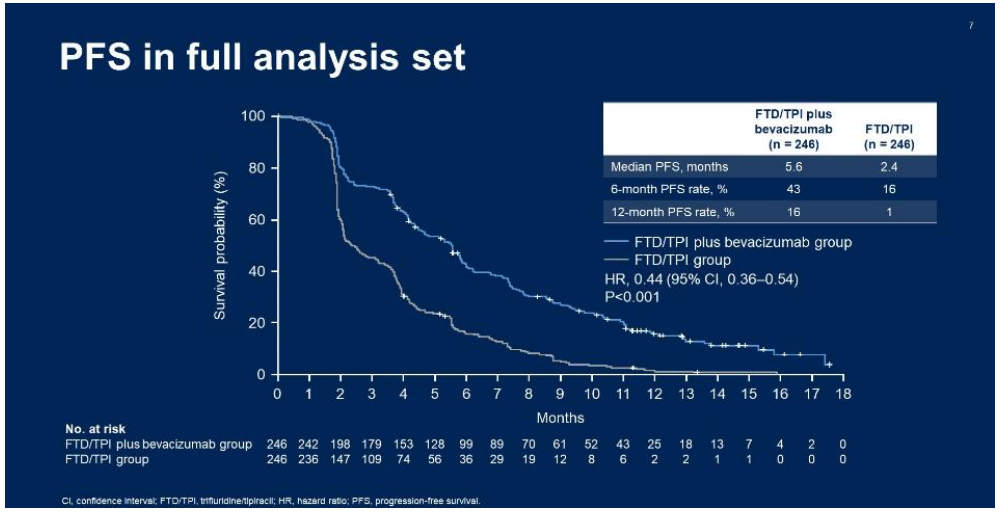
Shroff R, et al JAMA Oncol 2019; Shroff R, et al, 2023 ASCO Gastrointestinal Cancers Symposium, Abstract LBA490

Practice Changing Trials in Colorectal Cancer

SUNLIGHT: TAS-102 +/- Bevacizumab as 3rd Line Tx for Metastatic Colorectal Cancer

- The Phase 3 SUNLIGHT study of TAS-102 +/- Bev as 3rd line therapy for mCRC
  - mOS 10.8 mos for the combo vs. 7.5 mos for TAS-102
  - This was a practice affirming study
  - But, pleasantly surprised by the magnitude of benefit





Tabernero J, et al, ASCO GI 2023 Abstract 4

Management of Locally Advanced Rectal Cancer

- Since ~2005, this was the paradigm for the management of locally advanced rectal cancer

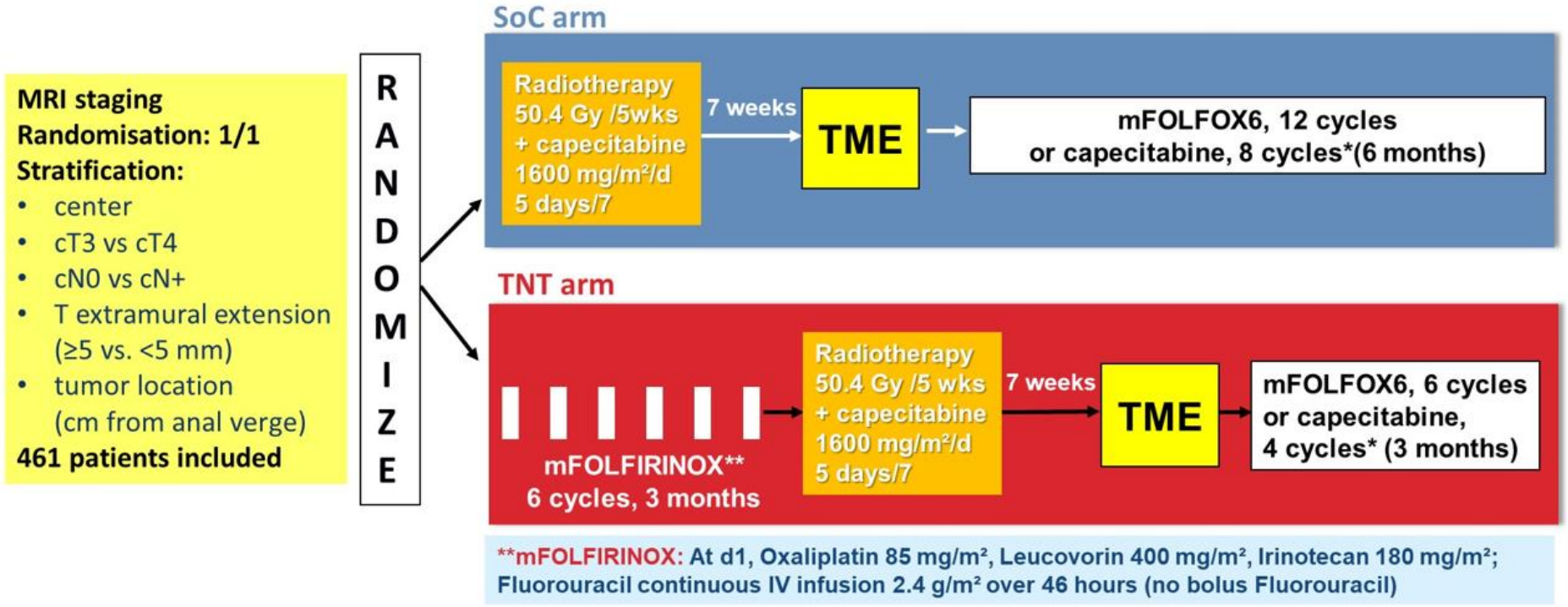
Courtesy of Shrag D, ASCO 2023

Management of Locally Advanced Rectal Cancer

- But many new questions arose:
  - What kind of radiation is better – short course or long course?
  - Could more or all of the chemotherapy be given preoperatively?
  - Could surgery be avoided altogether (watchful waiting, non-operative management)?
  - Could radiation be avoided?
- Unfortunately, there is no absolute best management of locally advanced rectal cancer
  - More than ever decisions need to be made on a case-by-case basis, taking into account in the particular wishes/priorities of the patient

PRODIGE 23: Total Neoadjuvant mFOLFIRINOX vs. Preoperative ChemoRT in Locally Advanced Rectal Cancer

- Patients were randomized to SOC (at that time) vs. “TNT” with FOLFIRINOX
  - TNT is really a misnomer – patients still received adjuvant chemotherapy for 3 months



*according to center choice throughout the study; adjuvant chemotherapy was mandatory in both arms regardless of ypTNM stage.

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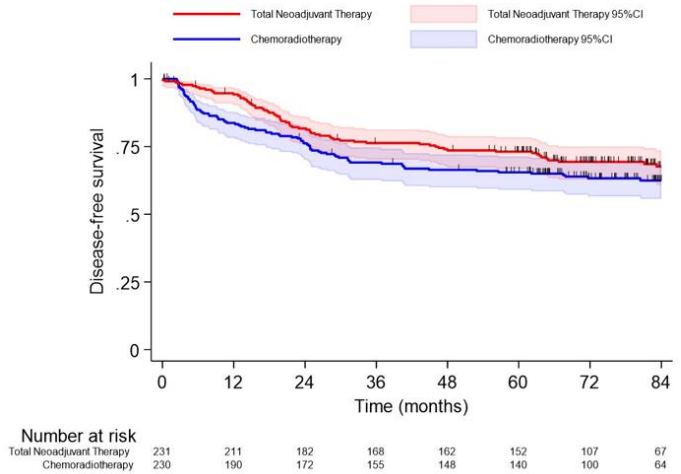
PRODIGE 23: Total Neoadjuvant mFOLFIRINOX vs. Preoperative ChemoRT in Locally Advanced Rectal Cancer

Disease-Free Survival



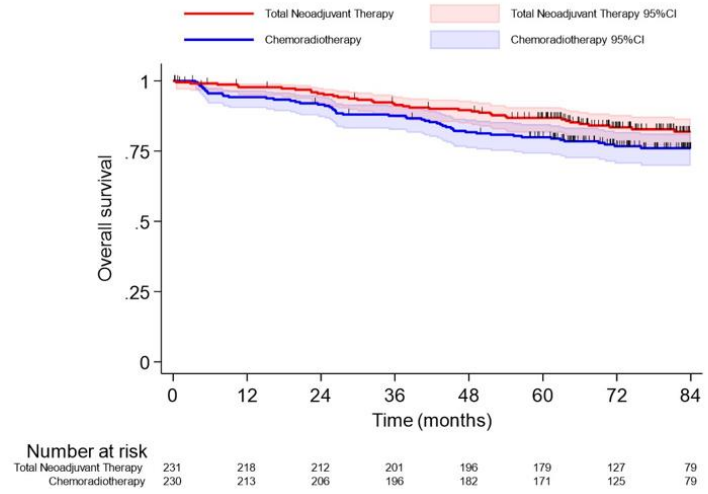
155 events

7-yr DFS rate:
- 67.6% [95%CI: 60.7-73.6] TNT arm
- 62.5% [95%CI: 55.6-68.6] SoC arm

5-yr DFS rate:
- 73.1% [95%CI: 66.8-78.4] TNT arm
- 65.5% [95%CI: 58.9-71.3] SoC arm

RMST (7-yr), months:
5.73 [0.05-11.41] DFS benefit for TNT arm
p=0.048

Overall Survival



98 events.

7-yr OS:
- 81.9% [95%CI: 75.8-86.7] TNT arm
- 76.1% [95%CI: 69.8-81.3] SoC arm

5-yr OS:
- 86.9% [95%CI: 81.6-90.7] TNT arm
- 80.0% [95%CI: 74.1-84.6] SoC arm

RMST (7-yr), months:
4.37 [0.35-8.38] benefit for TNT arm
p=0.033

Cumulative incidence of rectal cancer recurrences

- Disease free and overall survival were greater with TNT

Results	TNT	SoC
Local		
At 5 years	4.7% [95%CI: 2.5-8.5]	6.4% [95%CI: 3.8-10.8]
At 7 years	5.3% [95%CI: 2.9-9.3]	8.1% [95%CI: 4.9-13.3]
Metastatic*		
At 5 years	18.4% [95%CI: 13.8-24.2]	26.6% [95%CI: 21.2-33.0]
At 7 years	20.7% [95%CI: 15.6-27.0]	27.7% [95%CI: 22.2-34.2]
Alive with metastases	19/44 (43%)	21/60 (35%)

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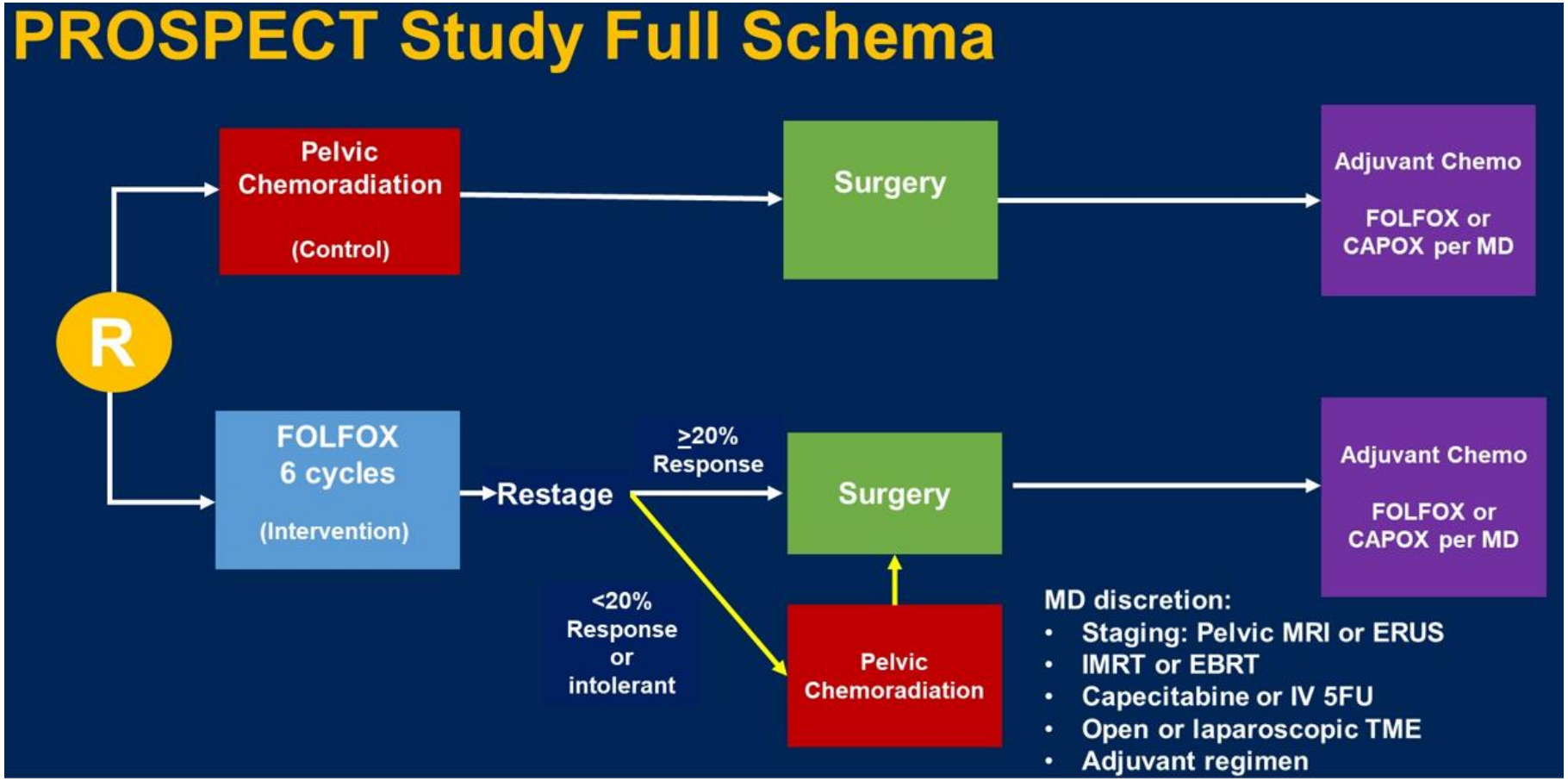
PROSPECT: Preoperative Chemotherapy with *Selective* Chemoradiation in Locally Advanced Rectal Cancer

- Hypothesis: Some rectal cancer patients can be cured WITHOUT pelvic radiation



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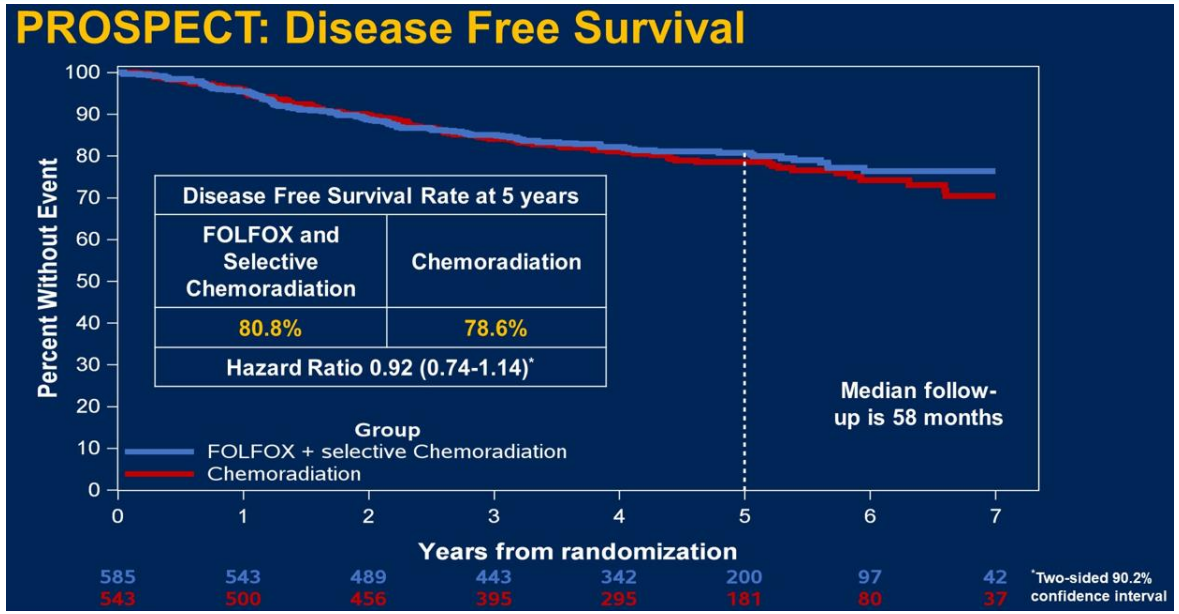
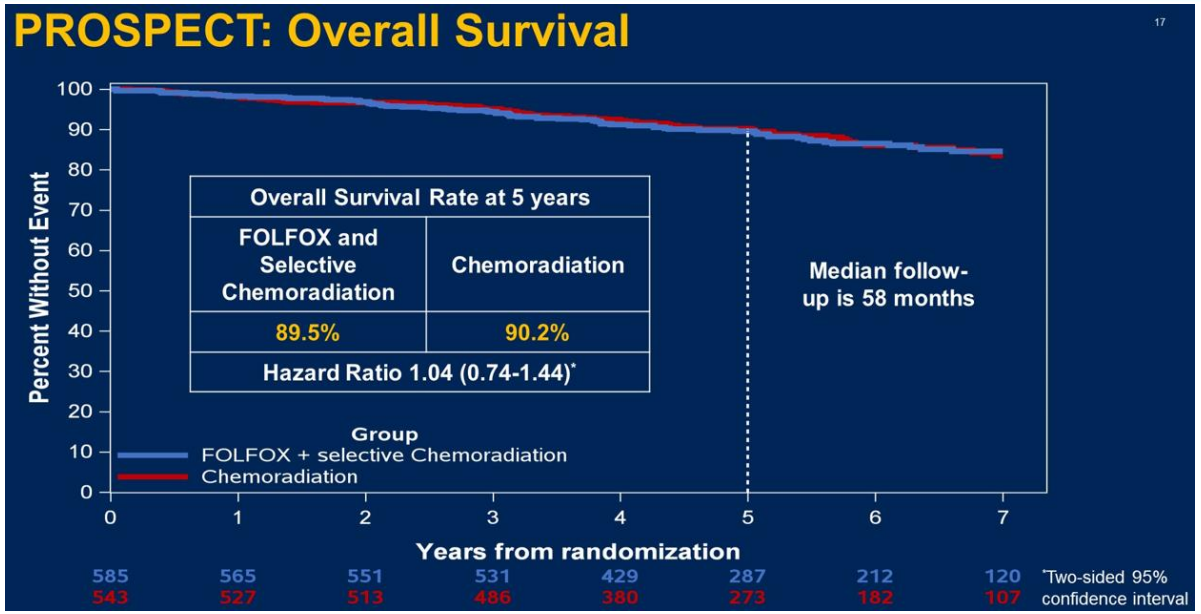
PROSPECT: Preoperative Chemotherapy with *Selective* Chemoradiation in Locally Advanced Rectal Cancer





- The trial DID meet its primary endpoint
  - TNT with SELECTIVE radiation was NON-INFERIOR to chemo radiation for DFS and OS
  - Interestingly, the PathCR rate was similar with TNT with SELECTIVE radiation as it was with chemoradiation
  - But ONLY 9% of Pts in the TNT arm received radiation

Surgical and Pathologic Endpoints

Secondary endpoints in participants who completed Surgery	FOLFOX and Selective Pelvic Chemoradiation N=535	Pelvic Chemoradiation N=510
Complete (R0) Rectal Resection	99%	97%
Low Anterior Resection Rate	98%	98%
Pathologic Complete Response	22%	24%
Positive Radial margin	1.2%	1.5%

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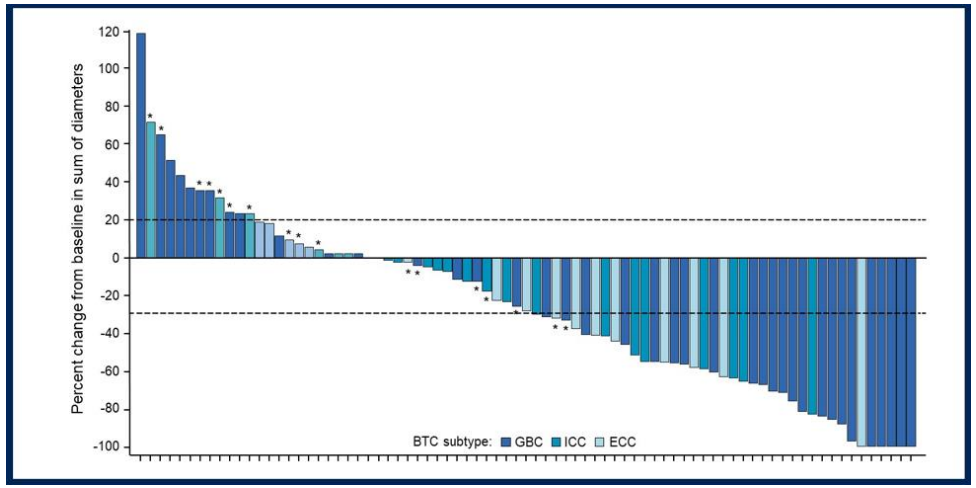
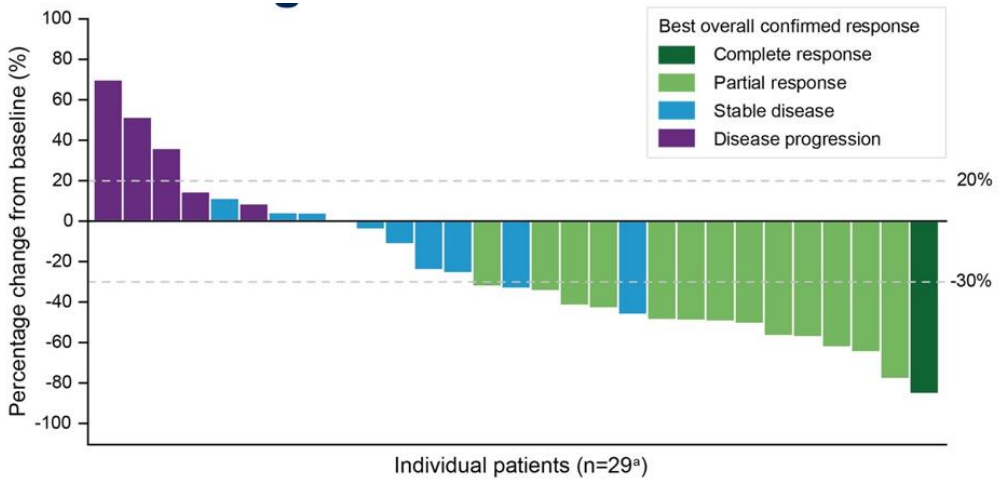
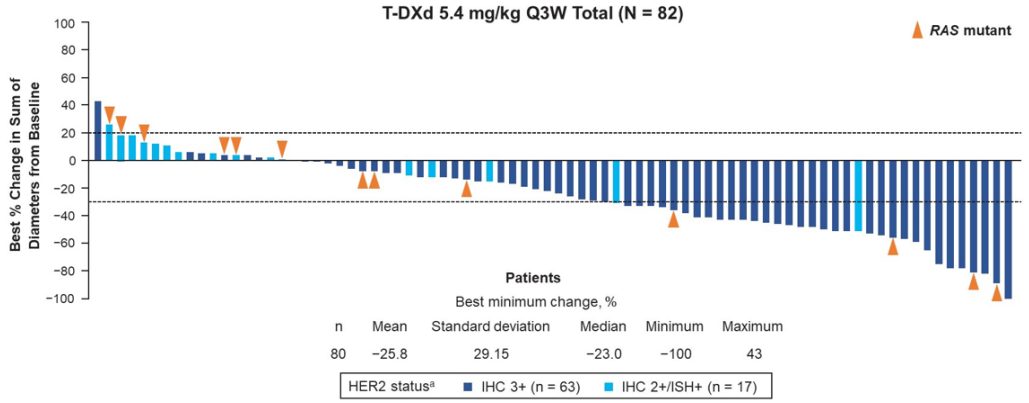
One More Slide…

HER2 Targeted Therapy for GI Cancers





- Three important trials demonstrating significant activity of HER2-targeted therapy in GI cancers
  - Dr. Pant – 41% ORR in 80 HER2+ BTC patients treated with zanidatamab (novel bivalent antiHER2 Ab)
  - Dr. Nakamura – 47% ORR in 30 HER2+ BTC patients treated with tucatinib + trastuzumab
  - Dr. Raghav – 38% ORR in 82 HER2+ CRC patients treated with T-DXd



- Most important lesson – TEST YOUR PATIENTS

Nakamura, et al, ASCO 2023; Pant, et al, ASCO 2023; Raghav, et al, ASCO 2023

Thank you and Questions?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