



Most Important Practice-Changing Advances in GI Cancers in 2022

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Disclosures (3 years)

- Consultant/Advisory Board/Steering Committee:
 - AstraZeneca/MedImmune, Merck, Foundation Medicine, Pfizer, Novartis, Ideaya, Astellas, Trisalus, Pionyr
- Travel, accommodations and expenses support:
 - Astellas
- Stock/Ownership:
 - Perthera, Tumor Board Tuesdays, TRICC
- Research funding to my institution:
 - Seattle Genetics, Tesaro, Arcus Bio, Ideaya, Repare Tx, Novartis, Pfizer, Merck, Tizona, Takeda, RenovoRx, Amgen
- I will be discussing “off-label” use of approved and not yet approved therapies
 - Almost by definition
 - Includes: Rucaparib, afatinib, binimetinib, encorafenib, trametinib, dabrafenib, seribantumab, zenocutuzumab, pralsetinib (BLU-667)

Overview - Moving Down the GI Tract

- Updates in upper GI cancers
- Updates in pancreatic cancer
- Updates in biliary cancer
- Updates in HCC
- Updates in colorectal cancer
- Biomarker-guided updates

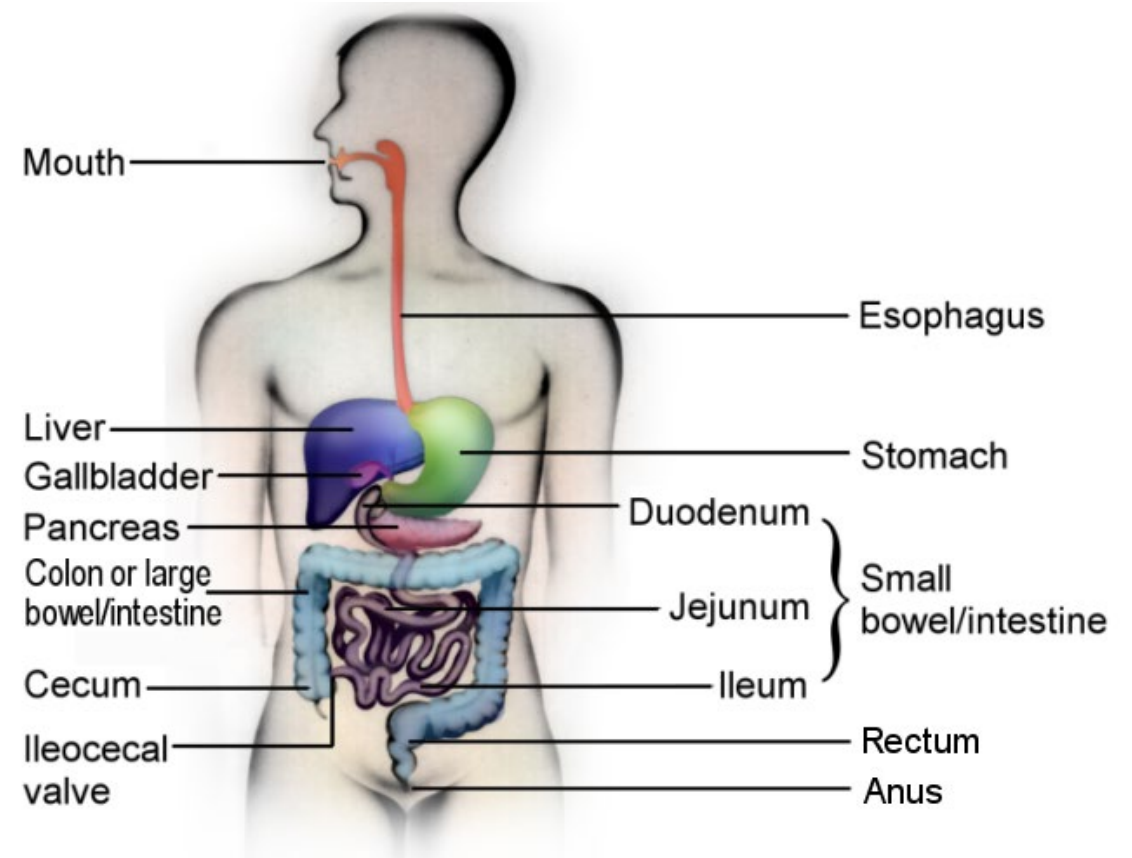


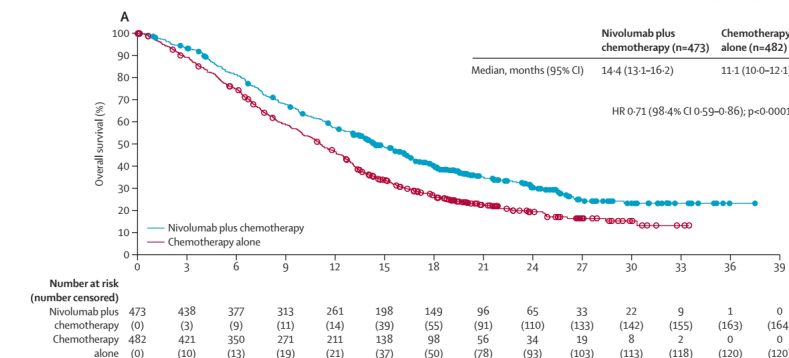
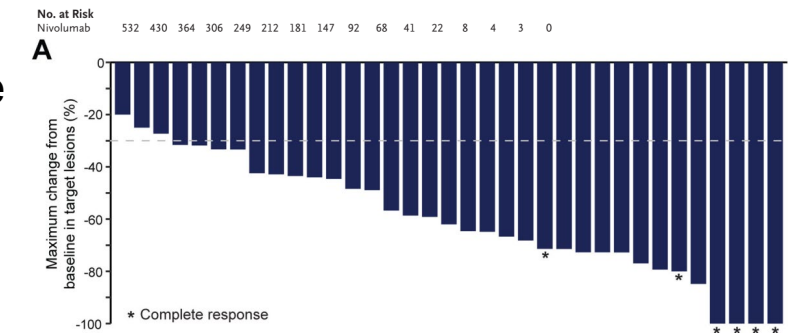
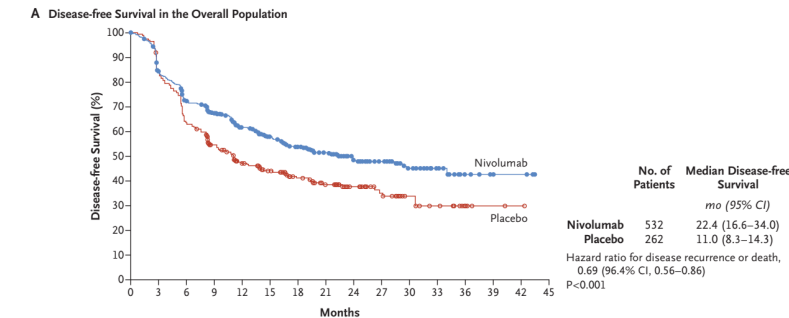
Image from:

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

Updates in Gastroesophageal Cancer?

No Updates for 2022...but as a reminder, Immunotherapy is Indicated for Gastroesophageal Cancers

- Checkmate 577: Adjuvant nivolumab improves disease-free survival for resected esophageal or gastroesophageal junction cancer who had received neoadjuvant chemoradiotherapy and had residual pathological disease
 - Kelly, et al, NEJM, 2021
 - mDFS = 22.4 months with nivolumab vs. 11 months with placebo
- Platinum, 5FU, trastuzumab PLUS pembrolizumab for HER2 positive esophagogastric cancer
 - Janjigian, et al, Lancet Oncology, 2020
 - 91% ORR, mOS = 27.2 months
 - Confirmatory Phase 3 trial (Keynote 811) has completed accrual
- Checkmate 649: Nivolumab improves overall survival when added to 1st line CAPEOX/FOLFOX for metastatic gastroesophageal cancer
 - Janjigian, et al, Lancet Oncology, 2021
 - mOS = 14.4 months with nivolumab vs. 11.1 months with placebo
 - Benefit greatest CPS ≥ 5 tumors



Practical Updates in Pancreatic Cancer

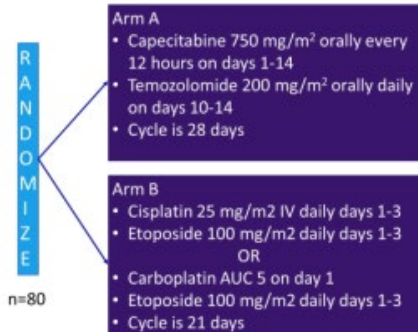
Cis/Carbo-Etoposide vs. Cape-Tem for High Grade GEP-NET

Randomized phase II study of platinum and etoposide (EP) versus temozolomide and capecitabine (CAPTEM) in patients with advanced G3 non-small cell gastroenteropancreatic neuroendocrine neoplasms (GEPNENs): ECOG-ACRIN EA2142

Jennifer R. Eads¹, Paul J. Catalano², George A. Fisher³, Daniel Rubin³, Andrei Iagaru³, David Klimstra⁴, Bhavana Konda⁵, Myron S. Kwong⁶, Jennifer A. Chan⁷, Ana De Jesus-Acosta⁸, Thorvardur R. Halfdanarson⁹, Walid L. Shaib¹⁰, Heloisa P. Soares¹¹, Sung Chul Hong², Terence Z. Wong¹², Peter J. O'Dwyer¹

¹University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; ²Dana Farber Cancer Institute-ECOG-ACRIN Biostatistics Center, Boston, MA; ³Stanford University Medical Center, Palo Alto, CA; ⁴Memorial Sloan Kettering Cancer Center, New York, NY; ⁵Ohio State University Comprehensive Cancer Center, Columbus, OH; ⁶Kaiser Permanente-Santa Teresa-San Jose, San Jose, CA; ⁷Dana Farber Cancer Institute, Boston, MA; ⁸Johns Hopkins University, Sidney Kimmel Cancer Center, Baltimore, MD; ⁹Mayo Clinic, Rochester, MN; ¹⁰Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA; ¹¹Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; ¹²Duke University Medical Center, Durham, NC

STUDY DESIGN

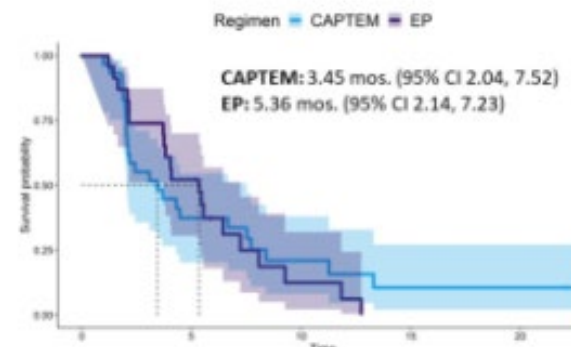


Most Severe Toxicities—evaluable in 57 patients

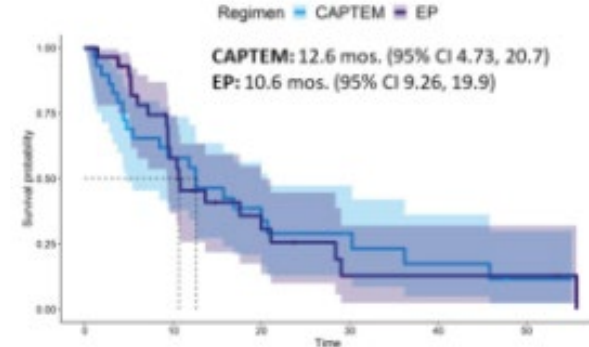
Toxicity	Arm A (n=28)		Arm B (n=29)	
	Grade 3	Grade 4/5*	Grade 3	Grade 4
Anemia	1 (3.6%)	-	8 (27.6%)	-
Febrile neutropenia	-	2 (7.1%)	2 (6.9%)	-
Abdominal pain	2 (7.1%)	-	-	-
Diarrhea	2 (7.1%)	-	-	-
Nausea	2 (7.1%)	-	-	-
Fatigue	-	-	2 (6.9%)	-
Sepsis	-	2 (7.1%)*	-	-
Lymphopenia	1 (3.6%)	-	2 (6.9%)	-
Neutropenia	1 (3.6%)	1 (3.6%)	5 (17.2%)	7 (24%)
Thrombocytopenia	1 (3.6%)	-	2 (6.9%)	2 (6.9%)
Leukopenia	-	2 (7.1%)	4 (13.8%)	2 (6.9%)
Hypomagnesemia	-	-	-	1 (3.4%)

Survival Outcomes

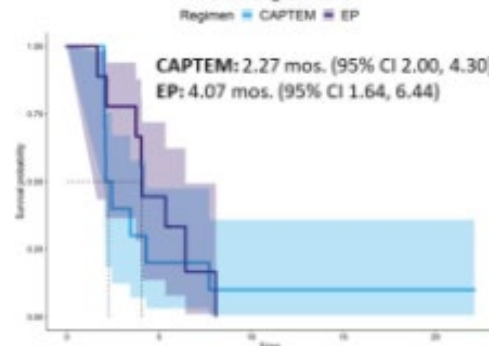
Progression Free Survival Between Treatment Arms



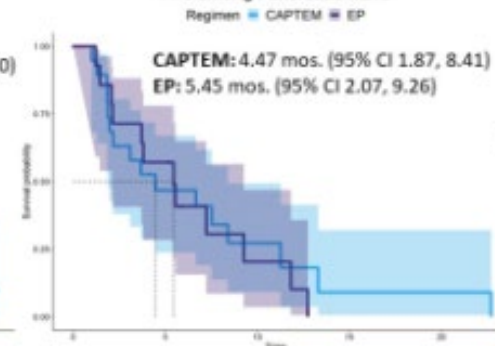
Overall Survival Between Treatment Arms



PFS among GI NETs



PFS among Pancreatic NETs



Response Rate
CAPTEM: 19%
EP: 22%

A Randomized Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors: Final Analysis of Efficacy and Association with MGMT (ECOG-ACRIN E2211)

Pamela L. Kunz¹, Noah Graham^{2,3}, Paul J. Catalano^{2,3}, Halla S. Nimeiri⁴, George A. Fisher Jr⁵, Teri A. Longacre⁵, Carlos J. Suarez⁵, Brock A. Martin⁶, Daniel L. Rubin⁵, James C. Yao⁷, Matthew H. Kulke⁸, Andrew E. Hendifar⁹, James C. Shanks¹⁰, Manisha H. Shah¹¹, Mark M. Zalupski¹², Edmond L. Schmulbach¹³, Diane L. Reidy-Lagunes¹⁴, Jonathan R. Strosberg¹⁵, Terence Z. Wong¹⁶, Peter J. O'Dwyer¹⁷, and Al B. Benson III⁴

¹Yale University, ²Dana Farber Cancer Institute, ³ECOG-ACRIN Biostatistics Center, ⁴Northwestern University, ⁵Stanford University, ⁶University of Louisville, ⁷MD Anderson Cancer Center, ⁸Boston University, ⁹Cedars Sinai Medical Center, ¹⁰Saint John's Hospital HealthEast, ¹¹Ohio State Comprehensive Cancer Center, ¹²University of Michigan Comprehensive Cancer Center, ¹³Kaiser Permanente South San Francisco, ¹⁴Memorial Sloan Kettering Cancer Center, ¹⁵Moffitt Cancer Center, ¹⁶Duke University, ¹⁷University of Pennsylvania

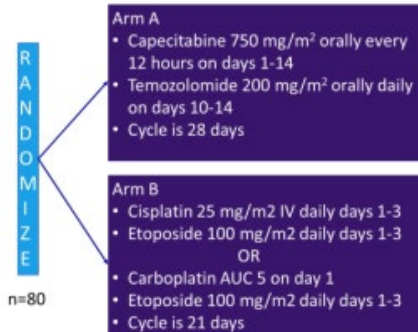
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STUDY DESIGN

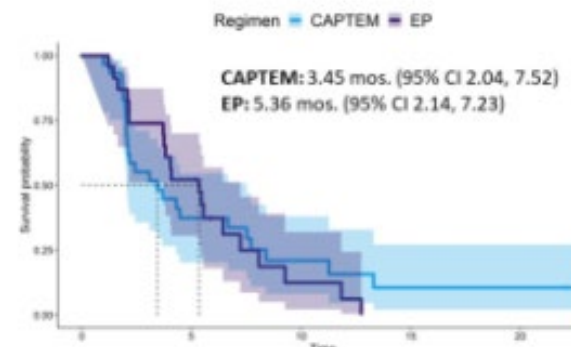


Most Severe Toxicities—evaluable in 57 patients

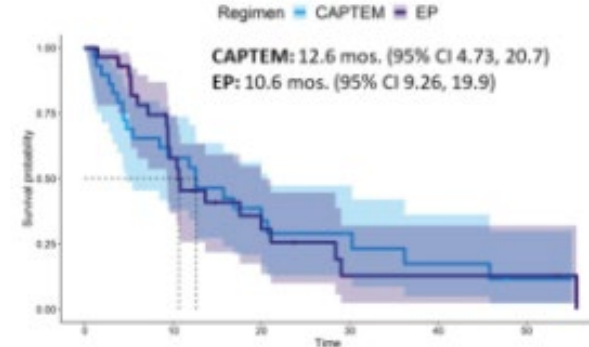
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Abdominal pain	2 (7.1%)	-	-	-
Diarrhea	2 (7.1%)	-	-	-
Nausea	2 (7.1%)	-	-	-
Fatigue	-	-	2 (6.9%)	-
Sepsis	-	2 (7.1%)*	-	-
Lymphopenia	1 (3.6%)	-	2 (6.9%)	-
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Survival Outcomes

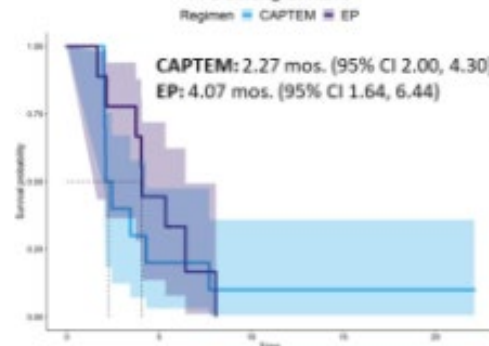
Progression Free Survival Between Treatment Arms



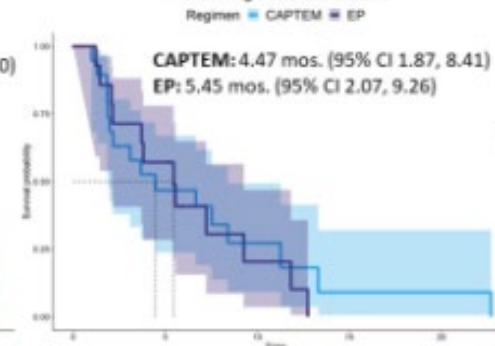
Overall Survival Between Treatment Arms



PFS among GI NETs



PFS among Pancreatic NETs



Response Rate
CAPTEM: 19%
EP: 22%

E2211 Study Design

Key Eligibility:

Progressive,
low/intermediate
grade,
advanced,
pancreatic NETs

Stratified by:

- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

R
1:1

n=72

n=72

ARM A:

Temozolomide 200 mg/m² po QD days 1-5

ARM B:

Capecitabine 750 mg/m² po BID days 1-14
Temozolomide 200 mg/m² QD days 10-14

Cycle length = 28 days; max 13 cycles.
Imaging performed every 12 weeks (RECIST 1.1)

Primary Endpoint:

- PFS (local review)

Secondary Endpoints:

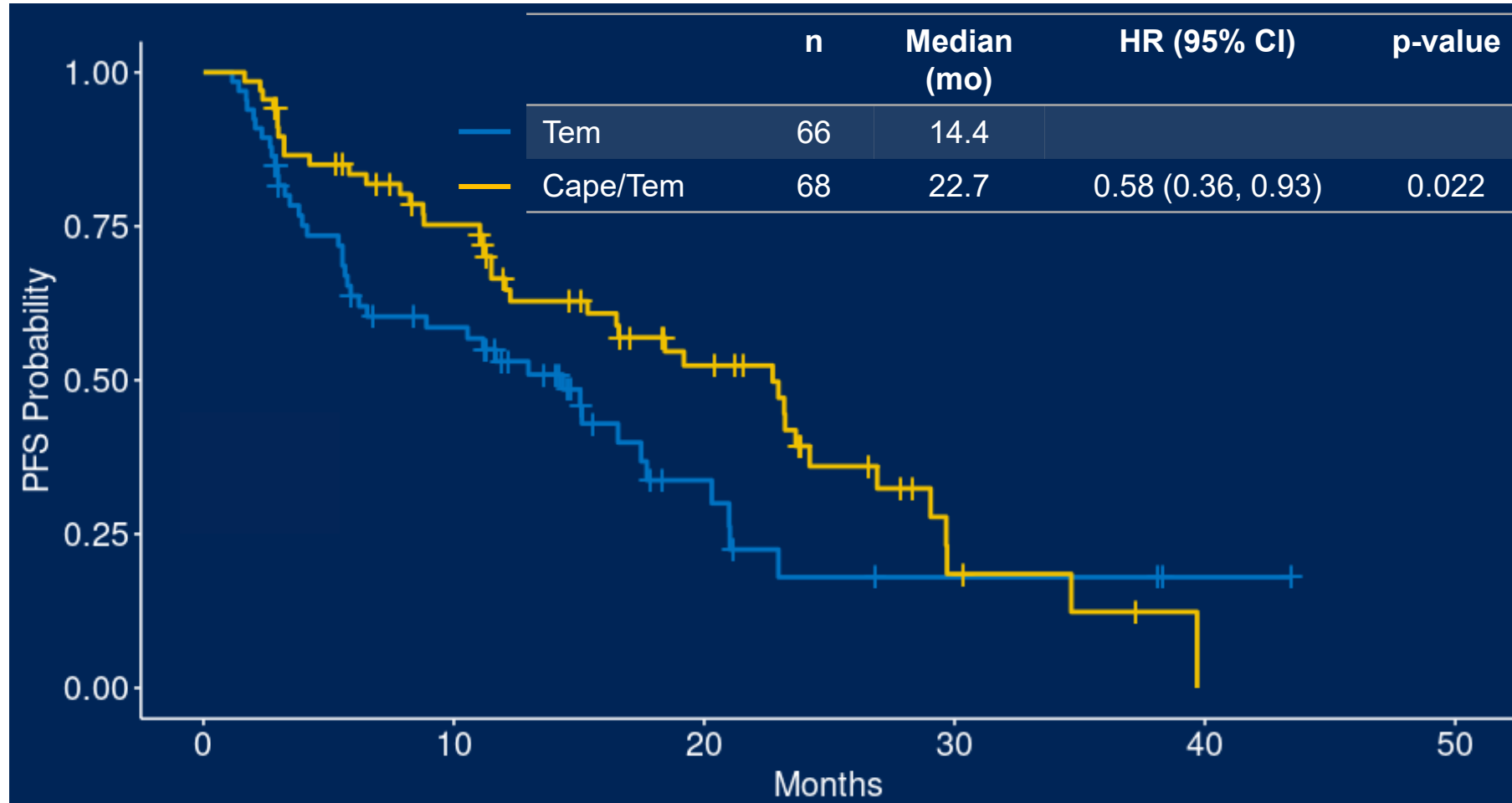
- RR
- OS
- Toxicity

Correlative Endpoints:

- Central Path Review
- MGMT by IHC (H-Score)
- MGMT by promoter methylation

NCT01824875

E2211: Primary Endpoint mPFS



E2211: MGMT Deficiency is Associated with Response

RECIST Response	MGMT (IHC, H-Score)			MGMT (Promoter Methylation)		
	1-2, low	3, high	Total	Negative	Positive	Total
No	30/63 (48%)	29/34 (85%)	59	31/50 (62%)	1/7 (15%)	32
Yes	33/63 (52%)	5/34 (15%)	38	19/50 (38%)	6/7 (85%)	25
Total	63	34	97	50	7	57
	OR [95% CI] = 6.38 [2.19, 18.60]; p = 0.0004			OR [95% CI] = 9.79 [1.09, 87.71]; p = 0.04		

Counts are shown among patients who underwent any MGMT testing (n=97)
 IHC H-Score Categories: Category 1 < 50, Category 2 51-100, Category 3 > 100

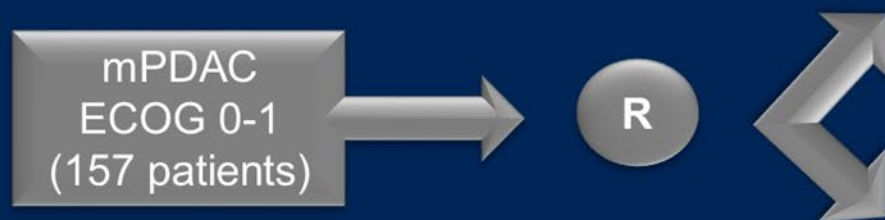
Sequential nab-paclitaxel/gemcitabine followed by modified FOLFOX, for first-line metastatic pancreatic ductal carcinoma (mPDAC): the SEQUENCE trial

A. Carrato, R. Pazo-Cid, T. Macarulla, J. Gallego, P. Jiménez Fonseca, F. Rivera, M^a T. Cano, M Rodríguez-Garrote, C. Pericay, I. Ales, L. Layos, B. Graña, V. Iranzo, I. Gallego-Jimenez, R. García-Carbonero, M. Álvarez Alejandro I. Ruiz de Mena, C. Guillén-Ponce, E. Aranda

On behalf of the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

SEQUENCE trial: Study Design

Open label, randomized, phase II
investigator-initiated trial in 1st-line
mPDAC patients.



Primary endpoint:

- Increased efficacy in terms of 12-month OS rate

Secondary endpoints:

- ORR, TTP, PFS, mOS; quality of life and safety

ClinicalTrial.gov id. NCT02504333

Accrual: 30 months (July 27, 2017-April 16, 2019)

Tumor evaluations every 12 weeks

nab-P/Gem

nab-paclitaxel 125 mg/m² d1,8,15
gemcitabine 1000 mg/m² d1,8,15

Every 4 w until PD, unacceptable toxicity or withdrawal of IC

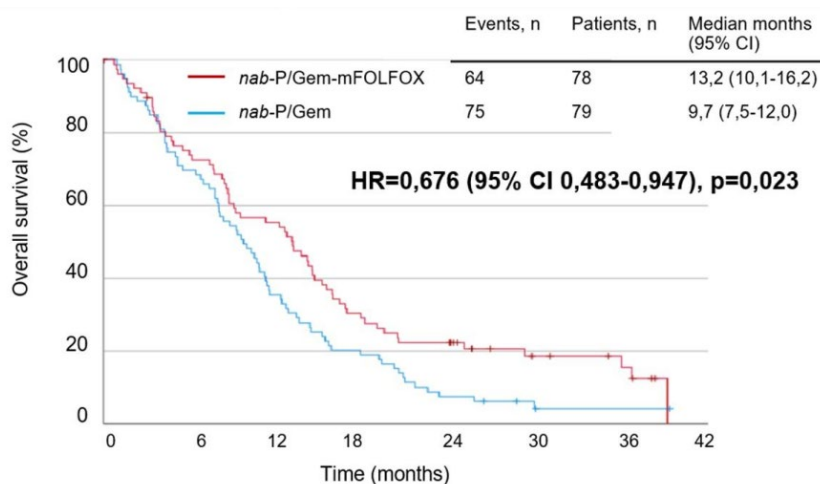
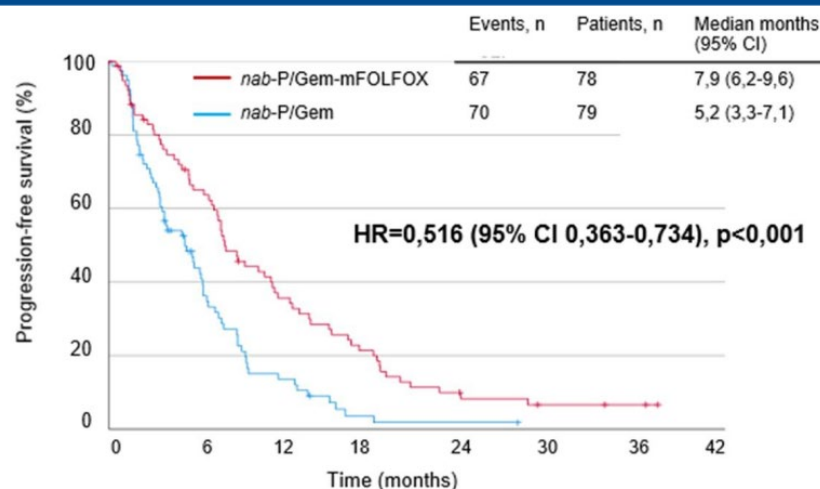
nab-P/Gem-mFOLFOX

nab-paclitaxel 125 mg/m² d1,8,15
gemcitabine 1000 mg/m² d1,8,15
mFOLFOX-6 d29
oxaliplatin 85 mg/m², d29
LV* 400 mg/m², d29
5-FU 400 mg/m² bolus, d29
5-FU 2400 mg/m² 46h CI, d29-30

Every 6 w until PD, unacceptable toxicity or withdrawal of IC

(*) *L-leucovorin* 200 mg/m² or racemic leucovorin 400 mg/m²

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
2 nd Line Tx	55%	40%	0.08*

Quality of life was measured and was similar in both arms

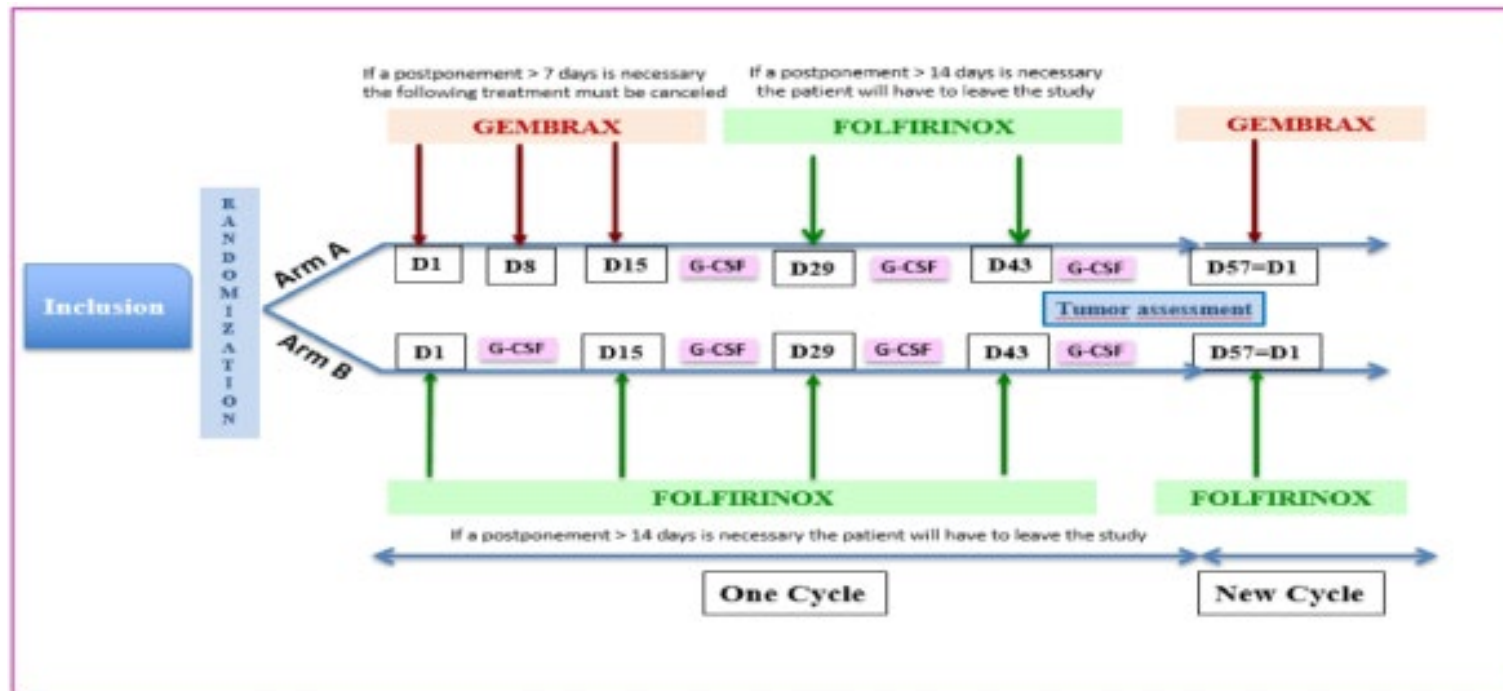
Next Sequence Trial for Pancreatic Cancer

#4190

Efficacy of sequential first-line treatment Gemcitabine plus Nab-paclitaxel (GA) followed by FOLFIRINOX (FFX) versus FOLFIRINOX alone in patients with metastatic pancreatic cancer: GABRINOX2 randomized phase 2 trial

Fabienne PORTALES¹, Eric ASSENAT¹, Emmanuelle SAMALIN¹, Thibault MAZARD¹, Antoine ADENIS¹, Blandine SUCHET GALLET¹, Catherine FIESS¹, Aurore MOUSSION¹, Stéphanie DELAINE¹, Florin GRIGORESCU¹, Sophie GOURGOU¹ and Marc YCHOU¹

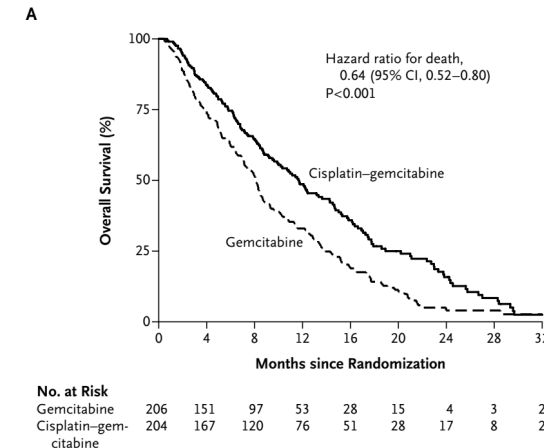
¹Institut du Cancer de Montpellier (ICM), Univ Montpellier, Montpellier, France; ²Centre Hospitalier Universitaire de Montpellier, Hôpital Saint Eloi, Montpellier, France; ³Biostatistics Unit, CTD INCa, ICM-Montpellier Cancer Institute, Montpellier, France.



Practice Changing Trials in Biliary Tract Cancer

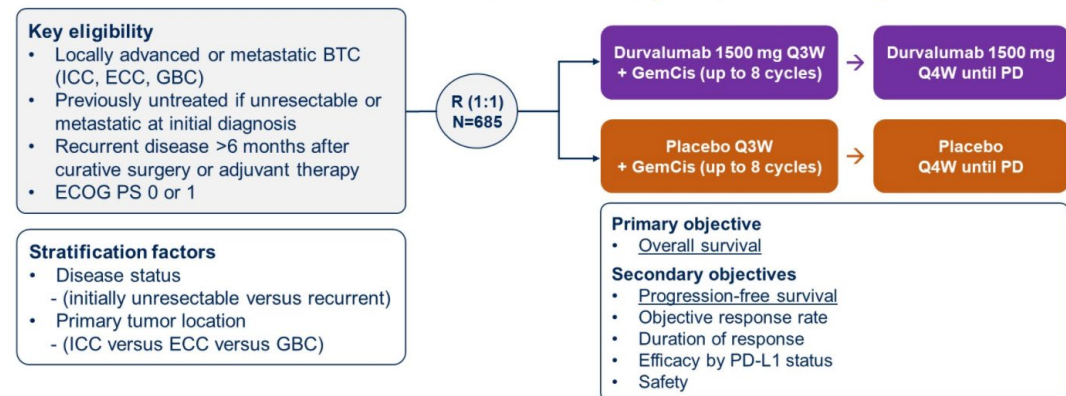
TOPAZ-1: Gem-Cis +/- Durvalumab in Cholangiocarcinoma

- 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



TOPAZ-1 study design

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



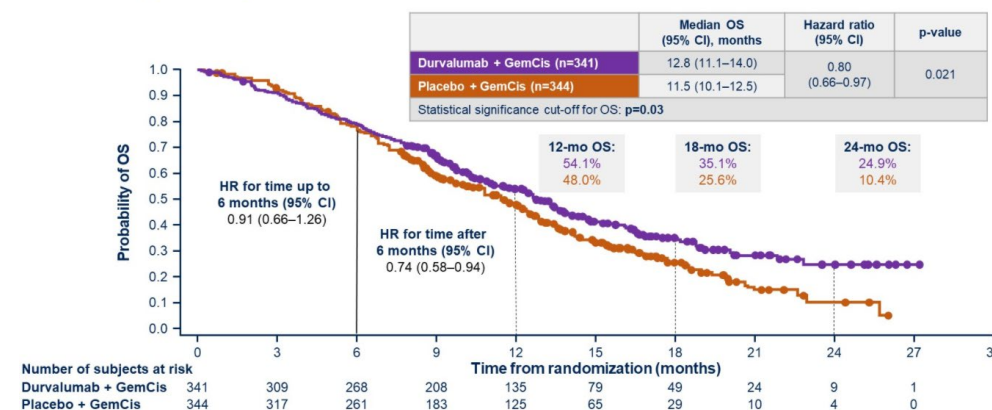
Valle J, et al, NEJM 2010; 362: 1273 – 1281

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

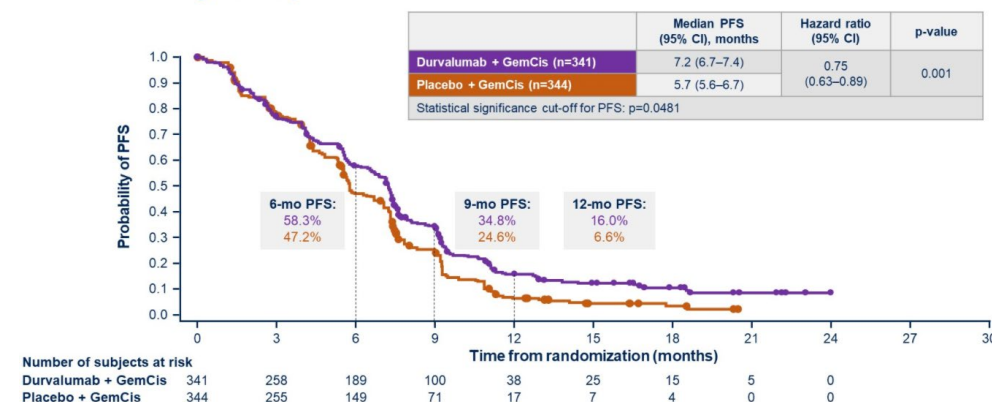
TOPAZ-1: Gem-Cis +/- Durvalumab in Cholangiocarcinoma

- 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 greater 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

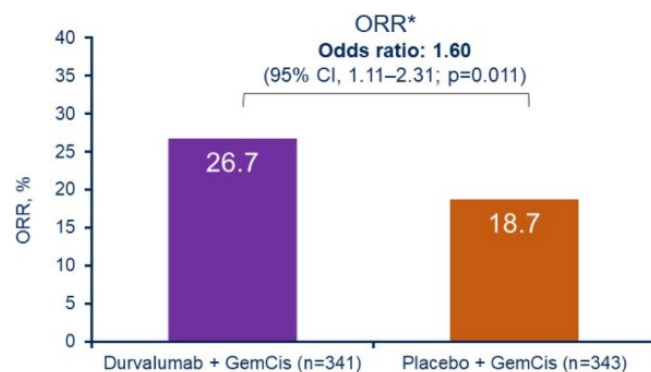


Secondary endpoint: PFS



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

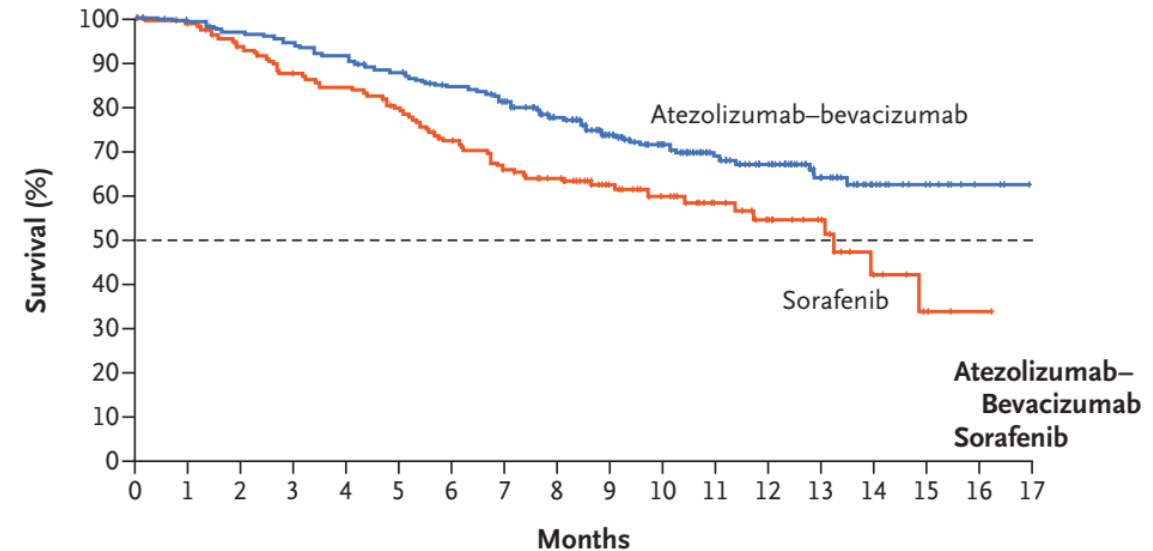
	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Median duration of exposure (range), months		
Durvalumab/placebo	7.33 (0.1–24.5)	5.77 (0.2–21.5)
Gemcitabine	5.19 (0.1–8.3)	5.03 (0.2–8.6)
Cisplatin	5.13 (0.1–8.3)	4.88 (0.2–8.5)
Adverse event, n (%)		
Any AE	336 (99.4)	338 (98.8)
Any TRAE	314 (92.9)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

Practice Changing Trials in Hepatocellular Cancer

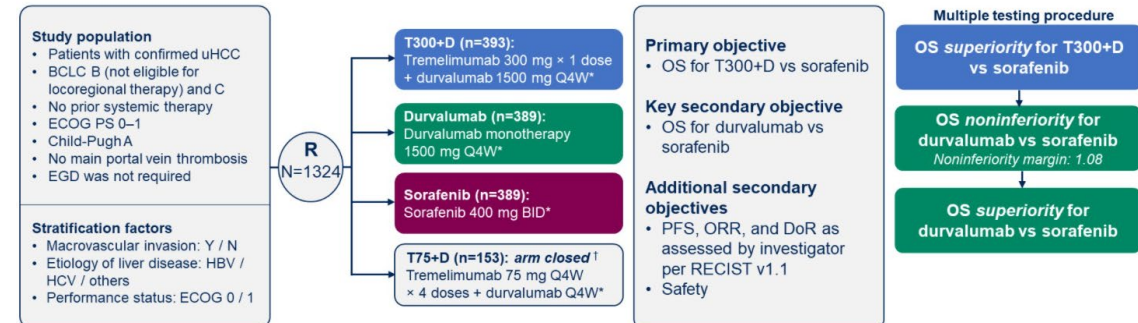
HIMALAYA: Tremilimumab + Durvalumab vs Sorafenib in Hepatocellular Cancer



- For more than a decade, sorafenib was the standard of care first line therapy for advanced HCC
- In 2018, Lenvatinib was demonstrated to be non-inferior to sorafenib as first-line therapy for advanced HCC
 - Lenvatinib vs. Sorafenib**
 - mOS 13.6 vs. 12.3 months
 - ORR 18.8 vs. 6.5%
- In 2020, atezolizumab + bevacizumab became the new 1st line standard of care
 - Atezo + Bev vs. Sorafenib**
 - mOS NR vs. 13.2 months
 - ORR 27.3 vs. 11.9%
- HIMALAYA was a Phase III randomized trial of tremilimumab + durvalumab vs. durvalumab alone vs. sorafenib
 - A lower dose tremi + durva arm was closed based on Phase II data
 - Patients with advanced, untreated HCC
 - 1324 patients evenly distributed among 3 arms
 - 1:1:1 randomization



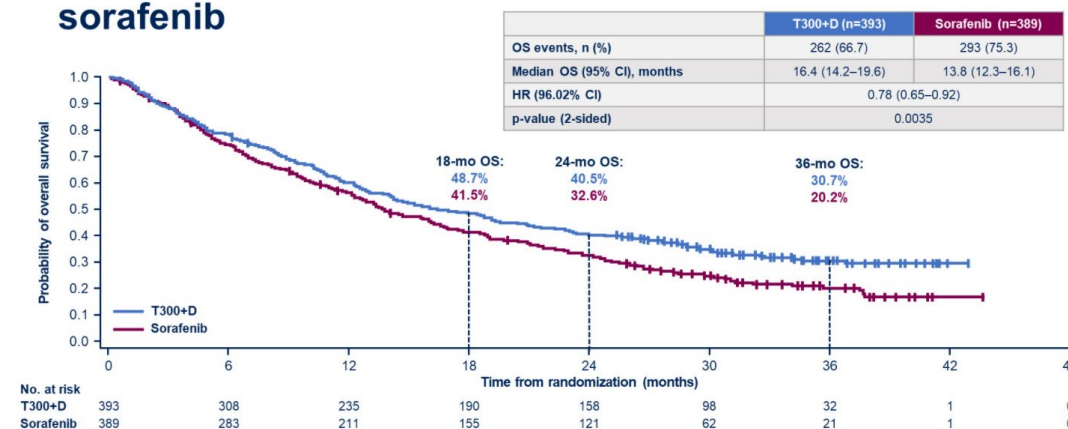
HIMALAYA was an open-label, multicenter, global, Phase 3 trial



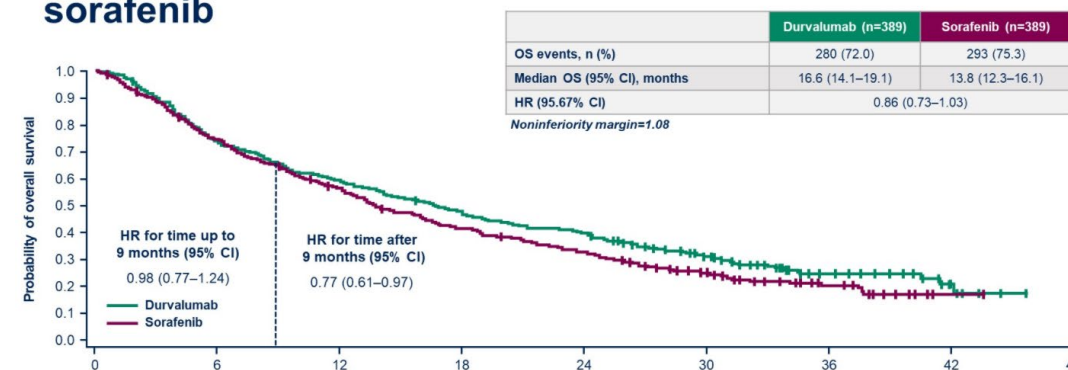
HIMALAYA: Tremilimumab + Durvalumab vs Sorafenib in Hepatocellular Cancer

- Overall survival was significantly greater for tremi + durva vs. sorafenib
 - mOS 16.4 vs. 13.8 months
 - HR = 0.78, $p = 0.0035$
- Secondary objective showed non-inferiority of single agent durvalumab vs. sorafenib
 - mOS 16.6 vs. 13.8 months
 - HR = 0.86
- Overall survival benefit held true for virtually all subgroups analyzed

Primary objective: overall survival for T300+D vs sorafenib



Secondary objective: overall survival for durvalumab vs sorafenib



HIMALAYA: Tremilimumab + Durvalumab vs Sorafenib in Hepatocellular Cancer

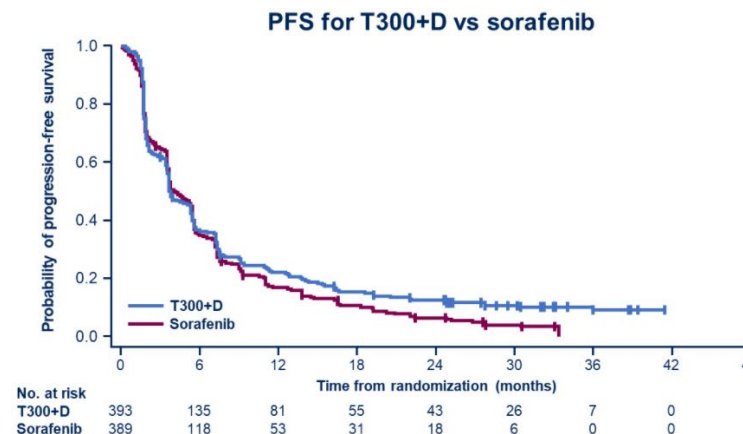


- Progression-free survival was equivalent between tremi + durva vs. sorafenib

- mPFS 3.78 vs. 4.07 months
- HR = 0.90

- Objective response rate was greater for tremi + durva vs. sorafenib

- ORR 20.1 vs. 5.1%



	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
PFS events, n (%)	335 (85.2)	345 (88.7)	327 (84.1)
Median PFS (95% CI), months	3.78 (3.68–5.32)	3.65 (3.19–3.75)	4.07 (3.75–5.49)
PFS HR* (95% CI)	0.90 (0.77–1.05)	1.02 (0.88–1.19)	–
Progression-free at DCO, n (%)	49 (12.5)	32 (8.2)	19 (4.9)
Median TTP (95% CI), months	5.42 (3.81–5.62)	3.75 (3.68–5.42)	5.55 (5.13–5.75)
Treated ≥1 cycle beyond progression, n (%)†	182 (46.9)	188 (48.5)	134 (34.4)

	T300+D (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* n (%)	79 (20.1)	66 (17.0)	20 (5.1)
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months	22.34	16.82	18.43
25 th percentile	8.54	7.43	6.51
75 th percentile	NR	NR	25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ %			
6 months	82.3	81.8	78.9
12 months	65.8	57.8	63.2

HIMALAYA: Tremilimumab + Durvalumab vs Sorafenib in Hepatocellular Cancer



- Adverse events were comparable between tremi + durva vs. sorafenib, although lower with single agent durva
 - Immune-related adverse events were higher in the two immunotherapy arms
- Hepatic hemorrhage was greater with tremi + durva vs. sorafenib
 - But, no increase in esophageal variceal hemorrhage

Event, n (%)	T300+D (n=388)	Durvalumab (n=388)	Sorafenib (n=374)
Any AE	378 (97.4)	345 (88.9)	357 (95.5)
Any TRAE*	294 (75.8)	202 (52.1)	317 (84.8)
Any grade 3/4 AE	196 (50.5)	144 (37.1)	196 (52.4)
Any grade 3/4 TRAE	100 (25.8)	50 (12.9)	138 (36.9)
Any serious TRAE	68 (17.5)	32 (8.2)	35 (9.4)
Any TRAE leading to death	9 (2.3)*	0	3 (0.8)*
Any TRAE leading to discontinuation	32 (8.2)	16 (4.1)	41 (11.0)

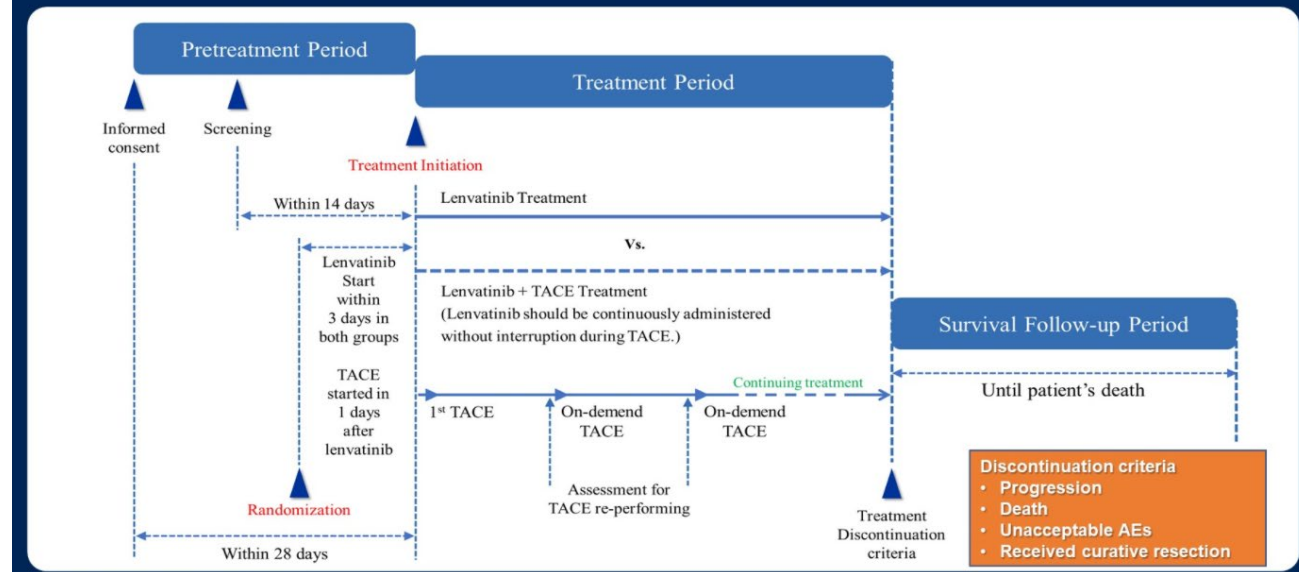
Event, n (%)	T300+D (n=388)		Durvalumab (n=388)		Sorafenib (n=374)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with hepatic SMQ TRAE	66 (17.0)	27 (7.0)	55 (14.2)	20 (5.2)	46 (12.3)	18 (4.8)
Patients with hemorrhage SMQ TRAE	7 (1.8)	2 (0.5)	3 (0.8)	0	18 (4.8)	6 (1.6)
Alanine aminotransferase increased	18 (4.6)	4 (1.0)	22 (5.7)	5 (1.3)	8 (2.1)	3 (0.8)
Aspartate aminotransferase increased	22 (5.7)	9 (2.3)	25 (6.4)	9 (2.3)	10 (2.7)	6 (1.6)
Blood bilirubin increased	6 (1.5)	1 (0.3)	6 (1.5)	0	10 (2.7)	2 (0.5)
Ascites	1 (0.3)	0	0	0	2 (0.5)	0
Hepatic encephalopathy	0	0	0	0	2 (0.5)	1 (0.3)
International normalized ratio increased	4 (1.0)	1 (0.3)	0	0	0	0
Esophageal varices hemorrhage	0	0	0	0	0	0

Event, n (%)	T300+D (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0

LAUNCH: Lenvatinib +/- TACE in Hepatocellular Cancer

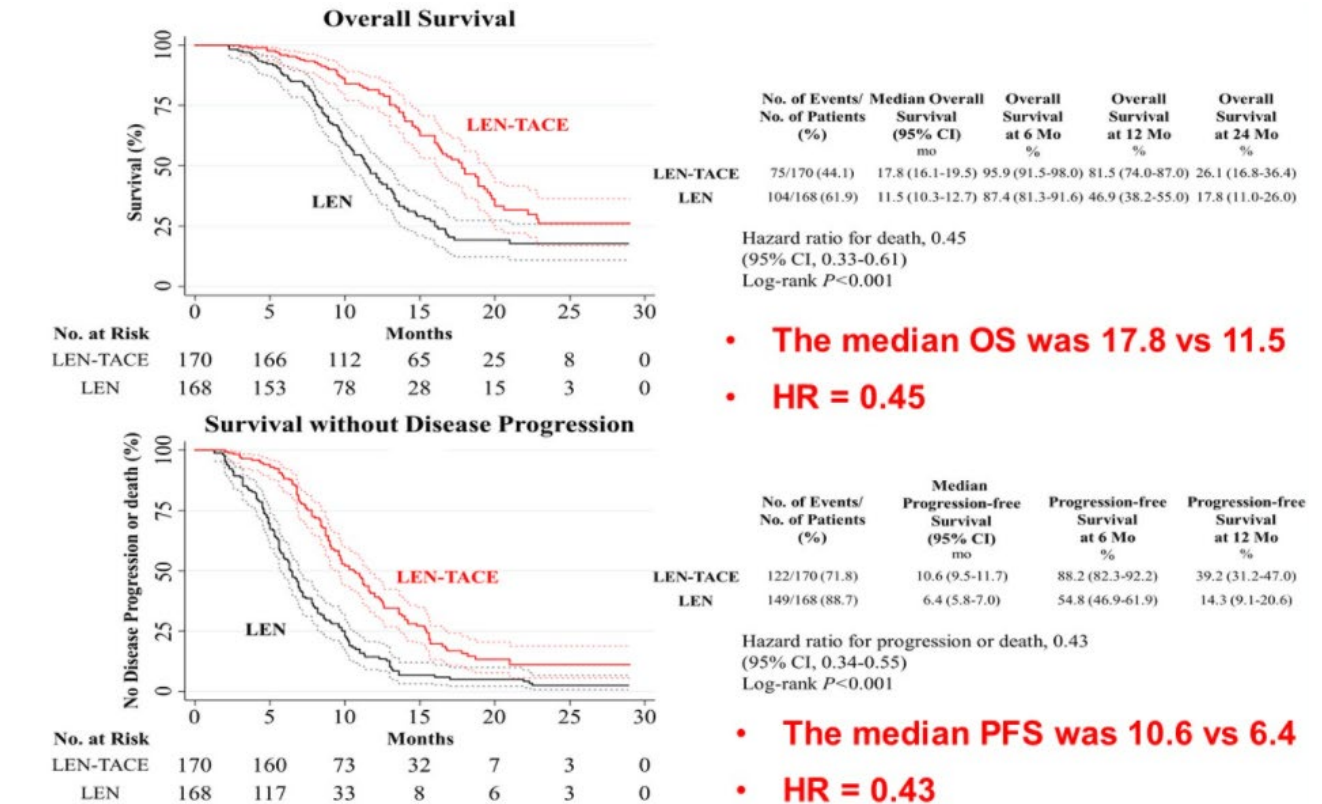
- In 2018, Lenvatinib was shown to be non-inferior to sorafenib as first-line therapy for advanced HCC
 - Lenvatinib vs. Sorafenib
 - mOS 13.6 vs. 12.3 months
 - ORR 18.8 vs. 6.5%
- LAUNCH was a Phase III randomized trial of Lenvatinib +/- TACE
 - Patients with advanced, untreated HCC
 - 1:1 randomization
 - Lenvatinib was administered *during* TACE

Study Schema



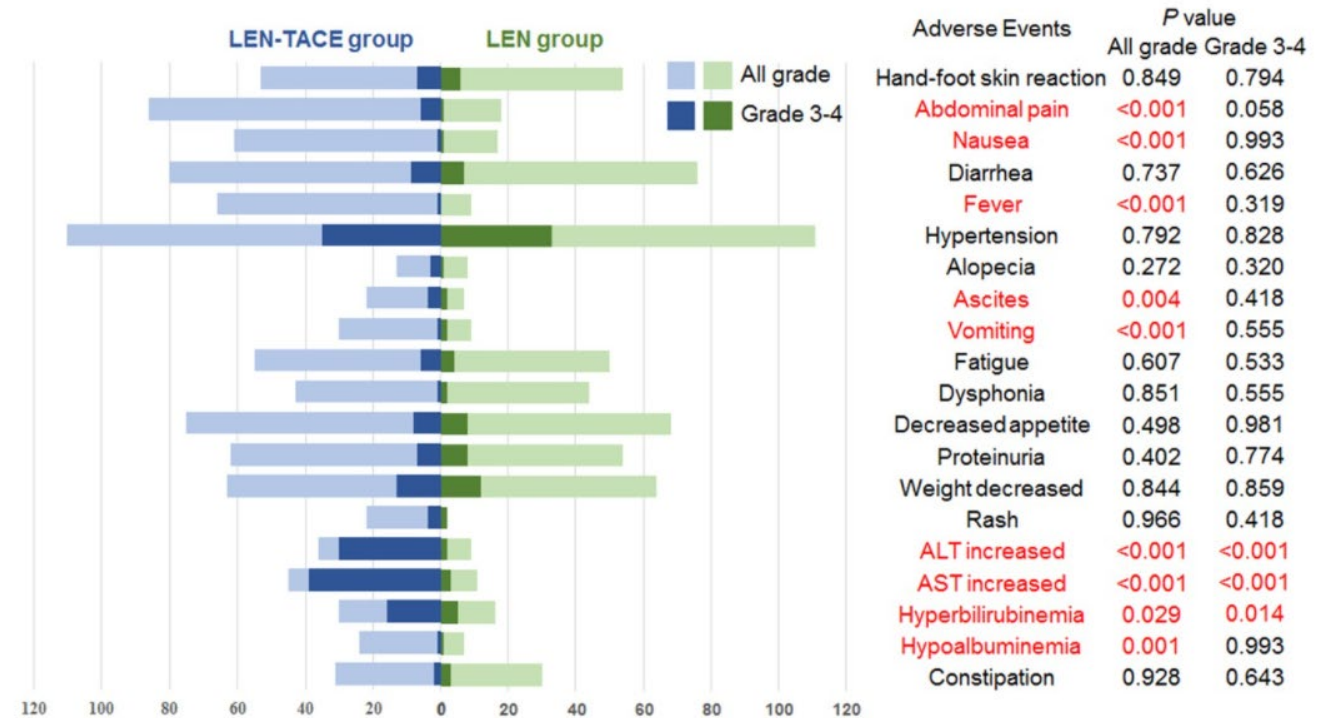
LAUNCH: Lenvatinib +/- TACE in Hepatocellular Cancer

- 338 patients randomized
 - 170 to lenvatinib + TACE
 - 168 to lenvatinib alone
 - Evenly matched
- Response rate was significantly higher with lenvatinib + TACE over lenvatinib alone
 - ORR 45.9 vs. 20.8%
 - DCR 92.4 vs. 72.6%
- Progression-free and overall survival were higher with lenvatinib + TACE vs. lenvatinib alone
 - mPFS 10.6 vs. 6.4 months
 - mOS 17.8 vs. 11.5 months
 - This held true for virtually all subgroups analyzed



LAUNCH: Lenvatinib +/- TACE in Hepatocellular Cancer

- Curative resection
 - 26/162 patients in the lenvatinib + TACE group
 - 2 patients had a complete pathological response
 - 3/165 patients in the lenvatinib alone group
- Adverse events were greater with lenvatinib + TACE over lenvatinib alone
 - BUT...these were mostly attributable to the TACE, and thus were short lived (~2 weeks) with no deaths reported due to AEs
 - Most common with nausea, vomiting, abdominal pain, LFT abnormalities, and fevers



Practice Changing Trials in Colorectal Cancer

Potential Endpoints and Challenges

Phase 3, randomized, open-label, multicenter study (NCT02394795)

Patients with *RAS* WT mCRC

- Unresectable disease
- No previous chemotherapy^a
- Age: 20–79 years
- ECOG performance status 0–1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

N=823

Panitumumab
+mFOLFOX^b

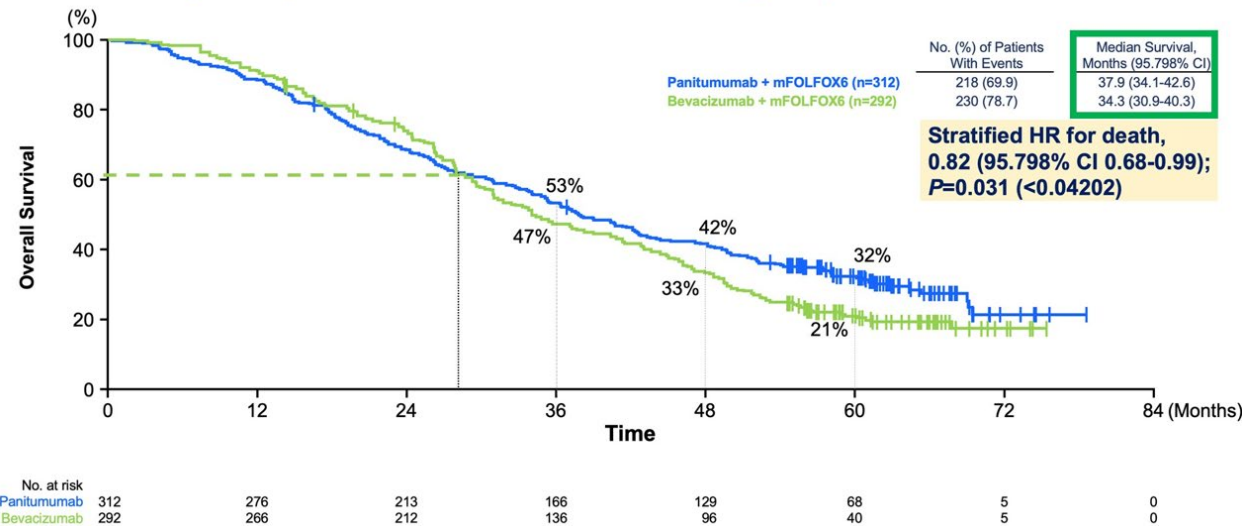
R
1:1

Bevacizumab
+mFOLFOX^b

Stratification factors

- Institution

Primary endpoint: OS in left-sided subgroup



Yoshino T, et al, ASCO LBA01 2022

Practice Changing Biomarker-Specific Trials in GI Cancers

Biliary Tract Cancer is Target Rich

Target	~Frequency in CC	Drug	Benefit	Status
MSI-H/dMMR	3%	Pembrolizumab	ORR 40% ¹	Tumor agnostic approval
TMB >10 mut/Mb	2.4%	Pembrolizumab	ORR 29% ¹	Tumor agnostic approval
<i>NTRK</i> fusion	1%	Larotrectinib	ORR 75% ²	Tumor agnostic approval
<i>FGFR2</i> fusion	14% (intrahepatic)	Pemigatinib or infigratinib	ORR 37% (pemigatinib) ³ ; 23% (infigratinib) ⁴	Cholangiocarcinoma approval
<i>IDH1</i> mutation	10%-20% (intrahepatic)	Ivosidenib	PFS HR: 0.37 ⁵	Cholangiocarcinoma approval
<i>BRAF</i> V600E	4%	Dabrafenib/trametinib	ORR 41% (ROAR) ⁶	Open-label basket study
<i>HER2</i>	9% of BTC* [†]	Pertuzumab/trastuzumab	ORR 23% (MyPathway) ⁷	Open-label basket study
<i>RET</i>	1%	Pralsetinib	Responses ⁸	2/2 PR in basket trial
<i>BRCA1/2</i> , DDR	20%*	PARP inhibitor	Responses reported	Case reports
ROS1	1%	Crizotinib	Response reported	Case reports

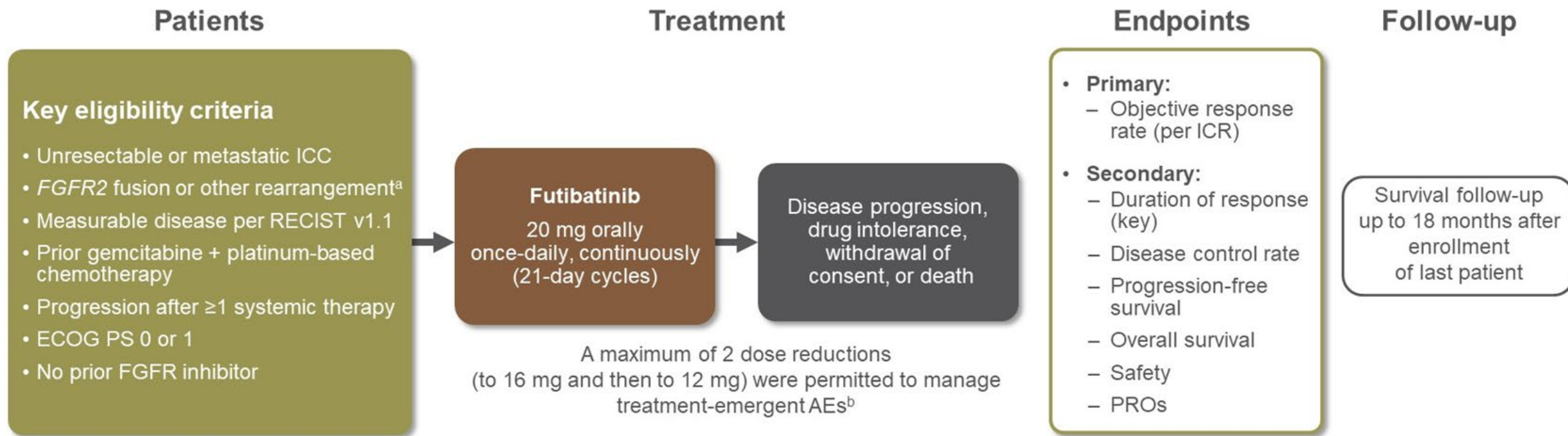
Most common in *extrahepatic or †GB.

Updated Results of the FOENIX-CCA2 Trial: Efficacy and Safety of Futibatinib in Intrahepatic Cholangiocarcinoma Harboring *FGFR2* Fusions/Rearrangements

Lipika Goyal,¹ Funda Meric-Bernstam,² Antoine Hollebecque,³ Chigusa Morizane,⁴ Juan W. Valle,⁵ Thomas B. Karasic,⁶
Thomas A. Abrams,⁷ Robin Kate Kelley,⁸ Philippe Cassier,⁹ Junji Furuse,¹⁰ Heinz-Josef Klümper,¹¹
Heung-Moon Chang,¹² Li-Tzong Chen,¹³ Yoshito Komatsu,¹⁴ Kunihiro Masuda,¹⁵ Daniel Ahn,¹⁶
Kate Li,¹⁷ Karim A. Benhadji,¹⁷ Volker Wacheck,¹⁷ John A. Bridgewater¹⁸

¹Massachusetts General Hospital Cancer Center, Boston, MA, USA; ²University of Texas MD Anderson Cancer Center, Houston, TX, USA; ³Gustave Roussy, Drug Development Department (DITEP), F-94805, Villejuif, France; ⁴National Cancer Center Hospital, Tokyo, Japan; ⁵University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; ⁶Hospital of the University of Pennsylvania, Philadelphia, PA, USA; ⁷Dana-Farber Cancer Institute, Boston, MA, USA; ⁸University of California, San Francisco, CA, USA; ⁹Centre Léon-Bérard, Lyon, France; ¹⁰Kyorin University, Faculty of Medicine, Tokyo, Japan; ¹¹Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands; ¹²Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; ¹³National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan; ¹⁴Hokkaido University Hospital Cancer Center, Hokkaido, Japan; ¹⁵Tohoku University Graduate School of Medicine, Miyagi, Japan; ¹⁶Mayo Clinic, Phoenix, AZ, USA; ¹⁷Taiho Oncology, Inc., Princeton, NJ, USA; ¹⁸UCL Cancer Institute, London, UK

FOENIX-CCA2: Phase 2 Global Study of Futibatinib in *FGFR2* Fusion or Rearrangement–Positive Intrahepatic Cholangiocarcinoma

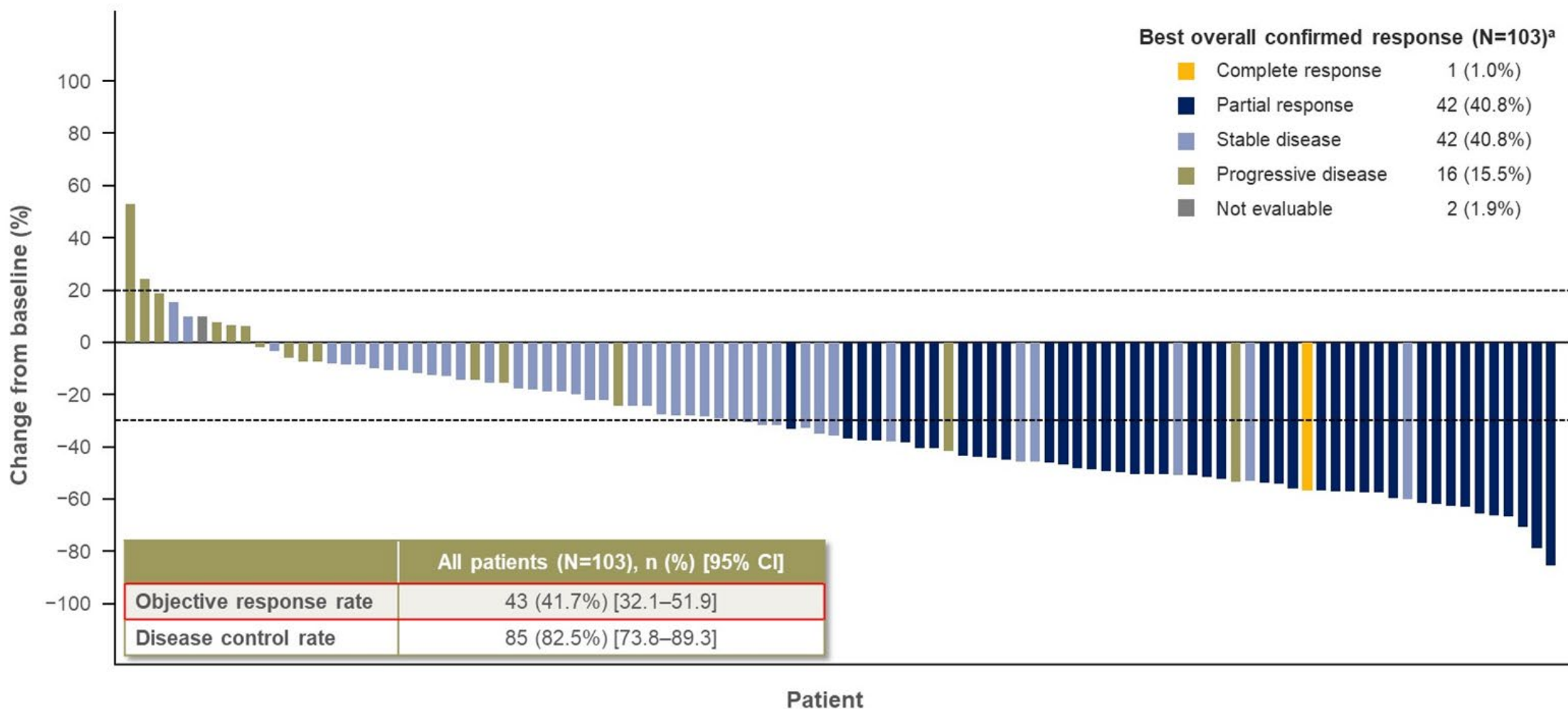


- At the time of the final data cutoff (May 29, 2021), median follow-up was 25.0 months, and 96/103 patients (93%) had discontinued treatment
- The median number of treatment cycles was 13.0, for a median treatment duration of 9.1 months

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; ICC, intrahepatic cholangiocarcinoma; ICR, independent central radiology review; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1; PRO, patient-reported outcome.

^aIdentified centrally in tumor tissue by Foundation Medicine (FMI) or by local laboratory testing of tumor tissue or circulating tumor DNA. ^bTreatment was discontinued if treatment-emergent AEs did not resolve after 2 dose modifications or if the next cycle of treatment was delayed >21 days.

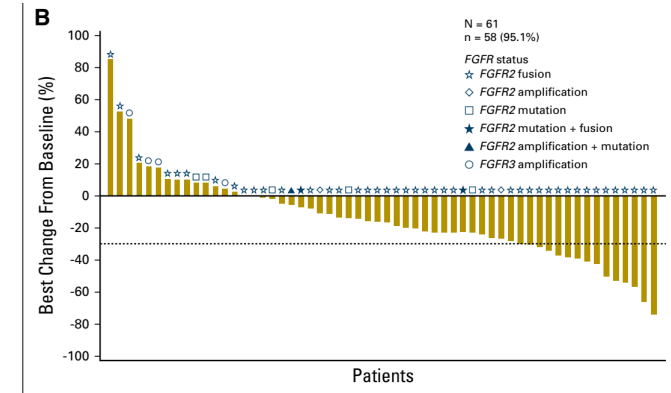
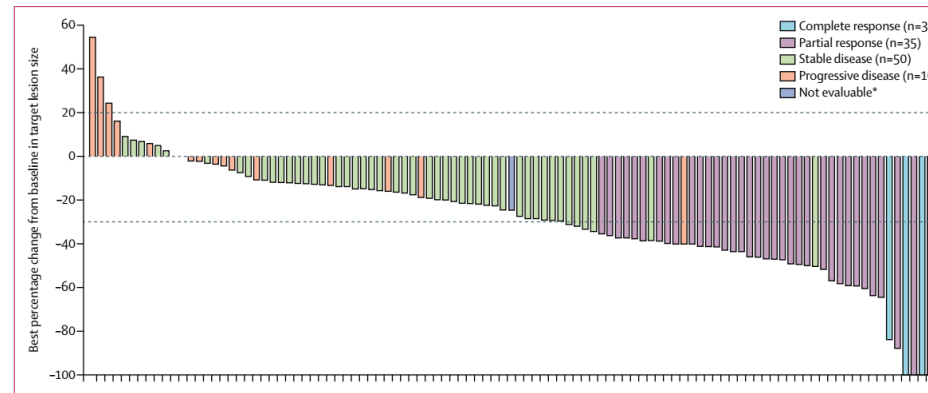
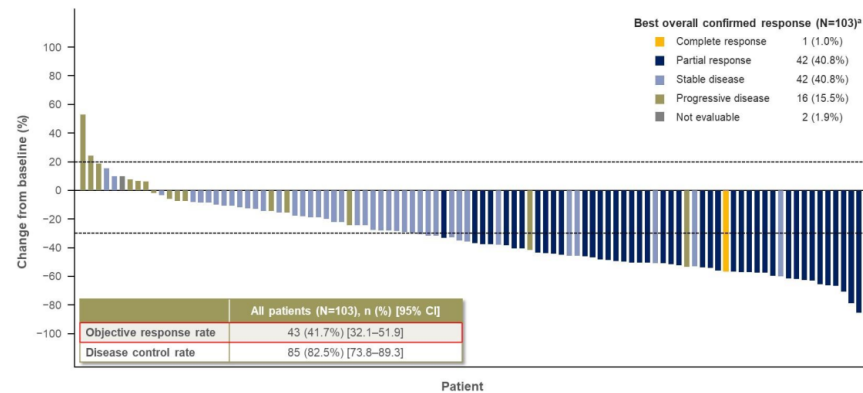
Futibatinib in Intrahepatic Cholangiocarcinoma: Best Percent Change in Target Lesion Size



^aAssessed by independent central review

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

FGFR Inhibitors in Cholangiocarcinoma



¹FOENIX-CCA2 trial: Futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements

103 patients

103 with FGFR2 fusions/rearrangements

ORR = 42%

DCR = 83%

mPFS = 8.9 Months

mOS = 20.0 months

²FIGHT-202: Pemigatinib in Previously Treated Cholangiocarcinoma With FGFR2 Fusions

146 patients

107 with FGFR2 fusions/rearrangements

ORR = 35%

DCR = 85%

mPFS = 6.9 Months

mOS = 21.1 months

³Infigratinib in Patients With FGFR-Altered Advanced Cholangiocarcinoma

61 patients

48 with FGFR2 fusions

ORR = 19%

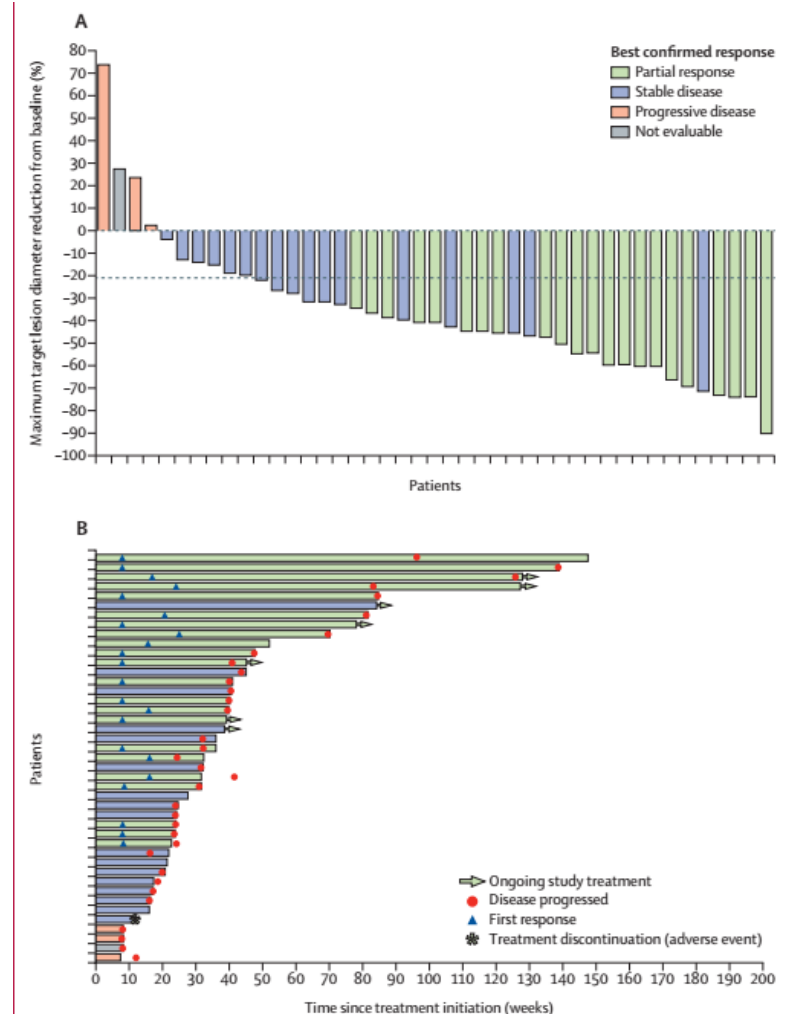
DCR = 83%

mPFS = 5.8 Months

mOS = not reported

ROAR: Dabrafenib + trametinib in BRAF^{V600E}-mutated cholangiocarcinoma

- Multi-disease basket trial
- 43 BRAF^{V600E}-mutated cholangiocarcinoma patients
- Objective Response Rate – 51%
- *Slide included because the FDA approved Dabrafenib + trametinib for all BRAF^{V600E}-mutated solid tumors in 2022*



HER2-Targeted Therapy for HER2 Amplified CRC

HERACLES: Trastuzumab + Lapatinib

- 27 evaluable HER2 positive ($\geq 2+$) and KRAS WT mCRC patients
 - Had prior Ox, Iri, 5FU, Bev, and Cetux
 - Objective Response Rate – 30% (One CR)
 - mPFS – 4.3 months
 - mOS – 11.5 months
- Compendia listed option for HER2+ mCRC**

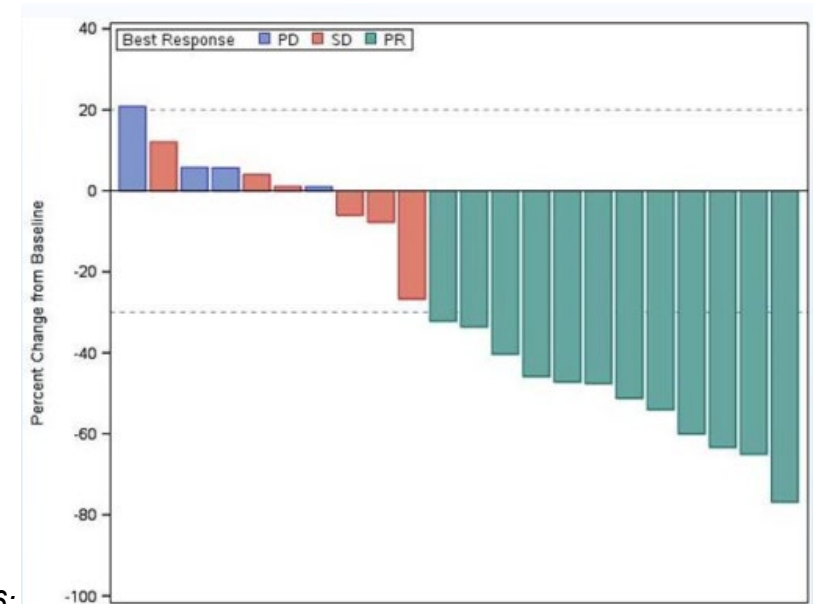


Sartore-Bianchi A, et al, Lancet Oncol 2016;17:738–46;

Strickler JH, et al, ESMO, 2019

MOUNTAINEER: Trastuzumab + Tucatinib

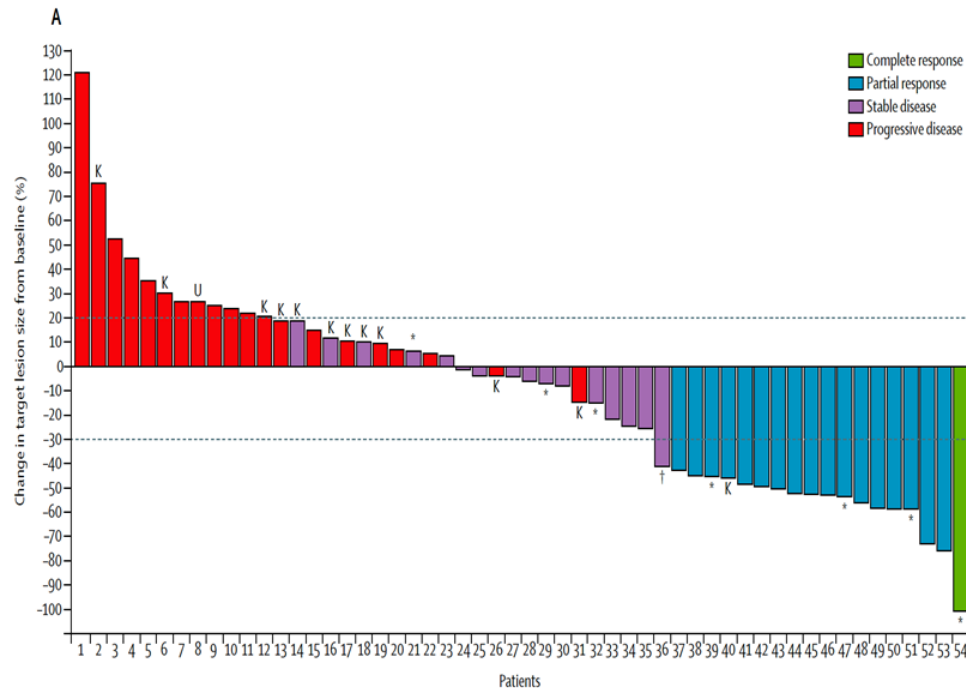
- 26 evaluable HER2 positive ($\geq 2+$) and KRAS WT mCRC patients
 - Objective Response Rate – 52%
 - mDOR – 10.4 months
 - mPFS – 8.1 months
 - mOS – 18.7 months
- Ongoing Phase III Trial**



HER2-Targeted Therapy for HER2 Amplified CRC

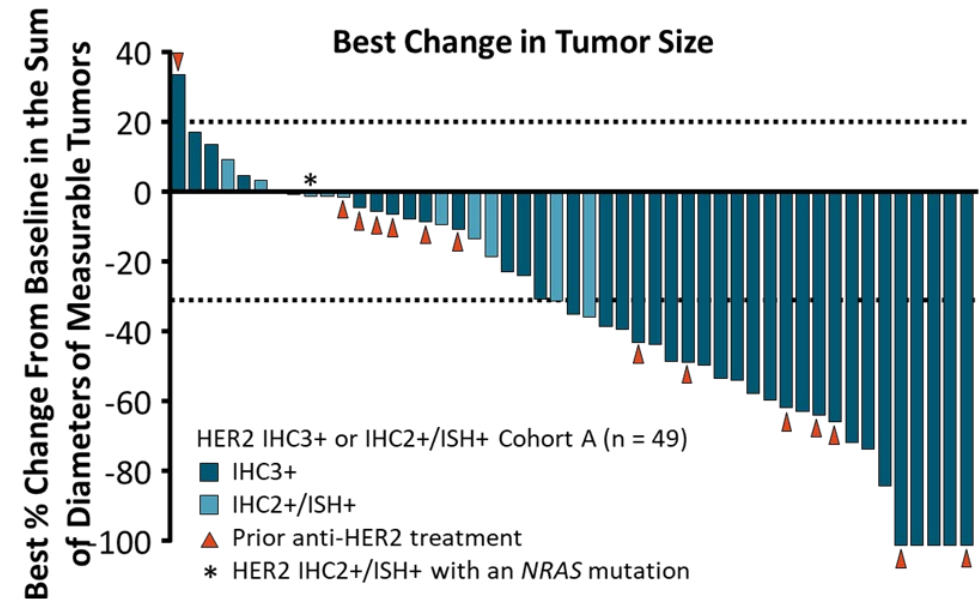
My PathWay: Trastuzumab + pertuzumab

- Her2+, heavily treated patients
- N = 84
- ORR: 32%
- Compendia listed option for HER2+ mCRC**



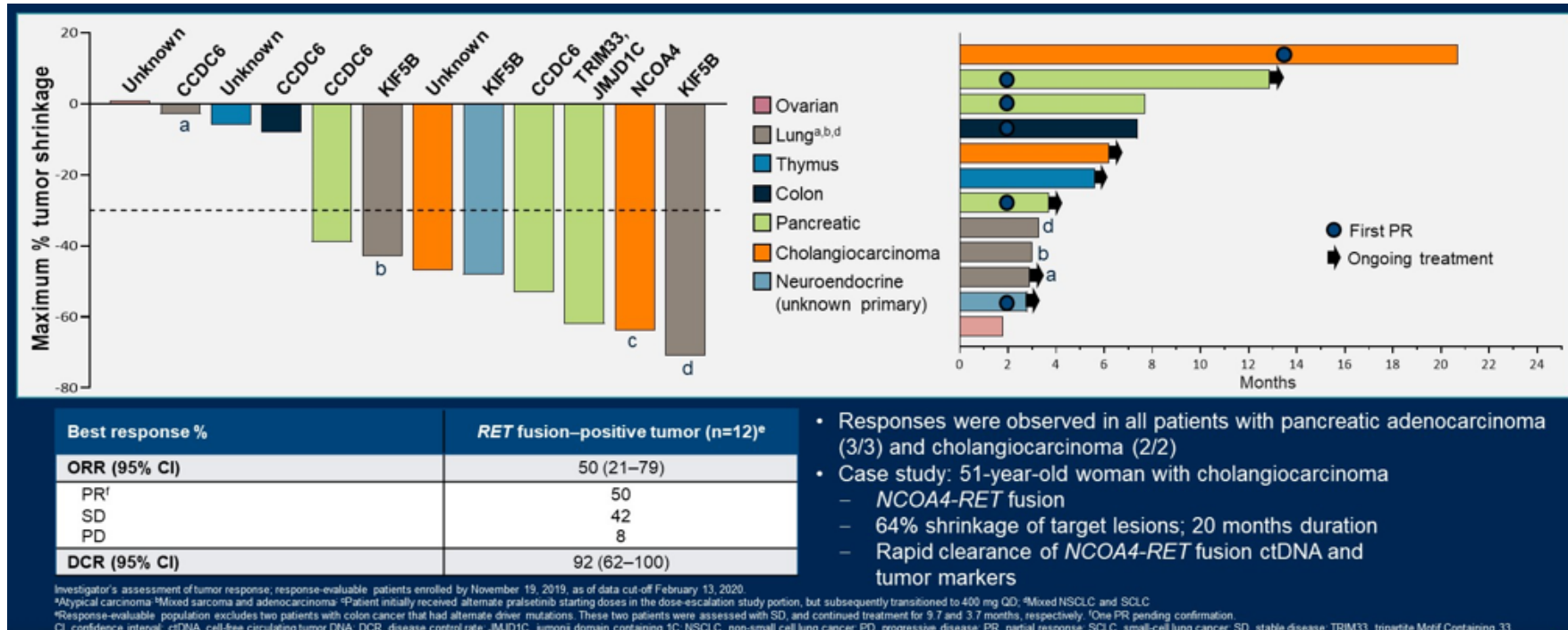
DESTINY-CRC01 trial with T-DXd

- HER2-targeted antibody-drug conjugate – trastuzumab + a TOPO-1 inh payload
- Phase II, N = 78
- Her2+ CRC, 2+ prior Tx (including prior Her2 directed therapies)
- ORR 45% (1 CR, 23 PR); DCR 83%; mPFS 6.9 mo; OS not reached
- Interstitial lung disease in 9% of patients

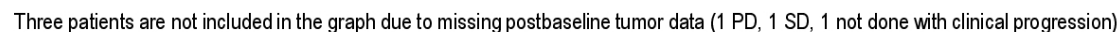


RET Fusions

- Pralsetinib (BLU-667) in RET fusion-positive tumors
 - 3 pancreatic cancer patients



- ### Tumor Burden Change from Baseline



Wild-Type KRAS

KRAS-GDP Inactive $\rightleftharpoons$ KRAS-GTP Active

GDP $\rightarrow$ GTP

Normal Signaling

Mutant KRAS^{G12C}

KRAS^{G12C}-GDP Inactive $\rightleftharpoons$ KRAS^{G12C}-GTP Active

G12C $\rightarrow$

Oncogenic Signaling

Mutant KRAS^{G12C} Inhibited by Sotorasib (Proposed INN for AMG 510)

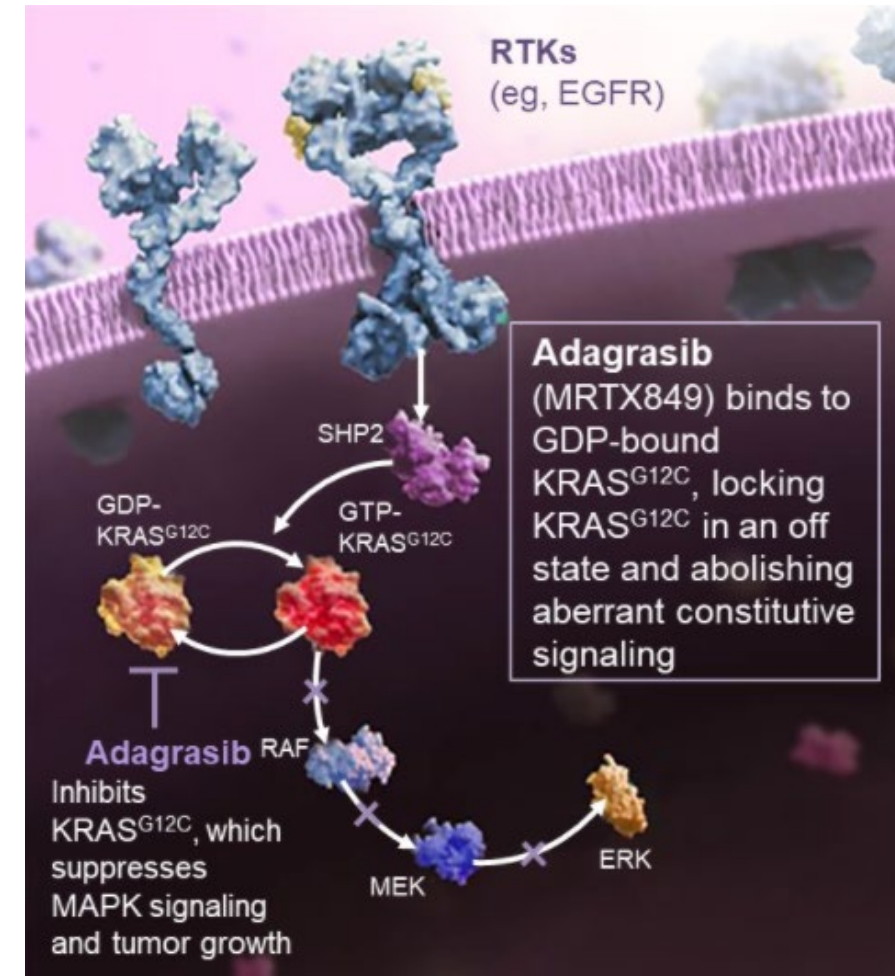
KRAS^{G12C}-GDP Inactive $\nrightarrow$ KRAS^{G12C}-GTP Active

Sotorasib (AMG 510)

INHIBITS: Oncogenic Signaling

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

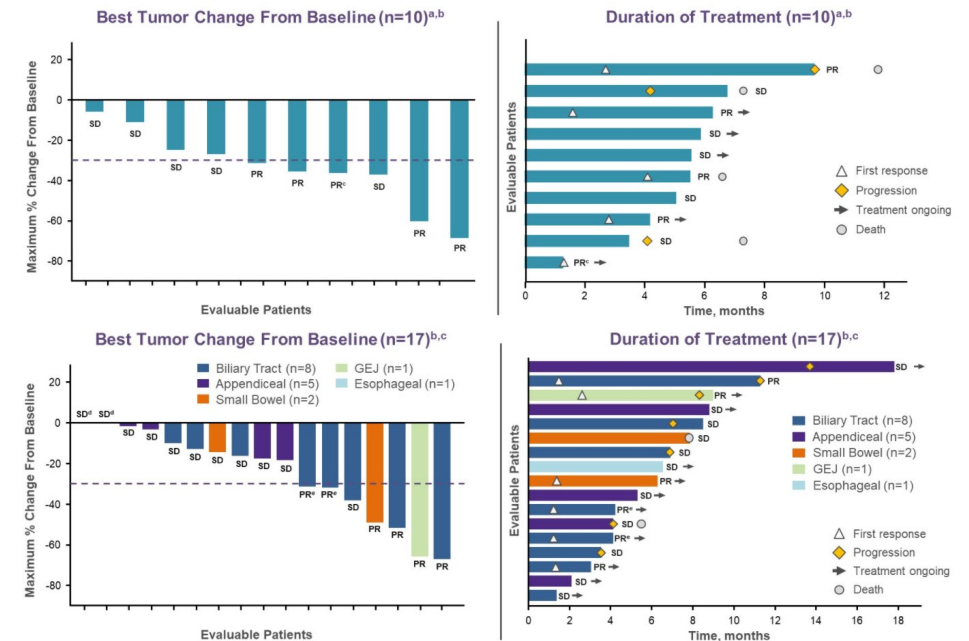
- KRAS mutations occur in 90 – 95% of PDACs
 - 80% are KRAS^{G12D} or KRAS^{G12V}
 - 2% are KRAS^{G12C}
- KRAS cycles between a GTP-on state and a GDP-off state
 - The protein resynthesis half life is 24 hours
- Adagrasib covalently binds to KRAS^{G12C} in its GDP-off state
- Phase II monotherapy cohort in GI cancers
 - Mostly pancreatic cancers (n = 12)
 - Other GI cancers (n = 18; biliary n = 8)
 - All had at least 1 line of Tx



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

- Adagrasib demonstrated efficacy
 - ORR was 41% overall
 - 50% in pancreatic cancer
 - 50% in biliary cancers
 - Disease control rate (including SD through at least 1st scan) = 100%
- PDAC
 - mDOR = 7 months
 - mPFS = 6.6 months
- Other GI cancers
 - mDOR = 8 months
 - mPFS = 8 months

Efficacy outcome ^b , n (%)	PDAC (n=10) ^c	Other GI cancers (n=17) ^d	Overall GI cancers ^a (n=27) ^{e-d}
Objective response rate	5 (50) ^e	6 (35) ^f	11 (41) ^g
Best overall response			
Complete response (CR)	0 (0)	0 (0)	0 (0)
Partial response (PR)	5 (50) ^e	6 (35) ^f	11 (41) ^g
Stable disease (SD)	5 (50)	11 (65)	16 (59)
Disease control rate	10 (100)	17 (100)	27 (100)



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

- Adagrasib was adequately tolerated
 - No Grade 4 or Grade 5 adverse events
 - Nausea, vomiting, diarrhea in 40 – 50% of patients
 - But, only 2% Grade 2 nausea
 - 7% Grade 3 fatigue
- *Need to TEST pancreatic cancer patients*

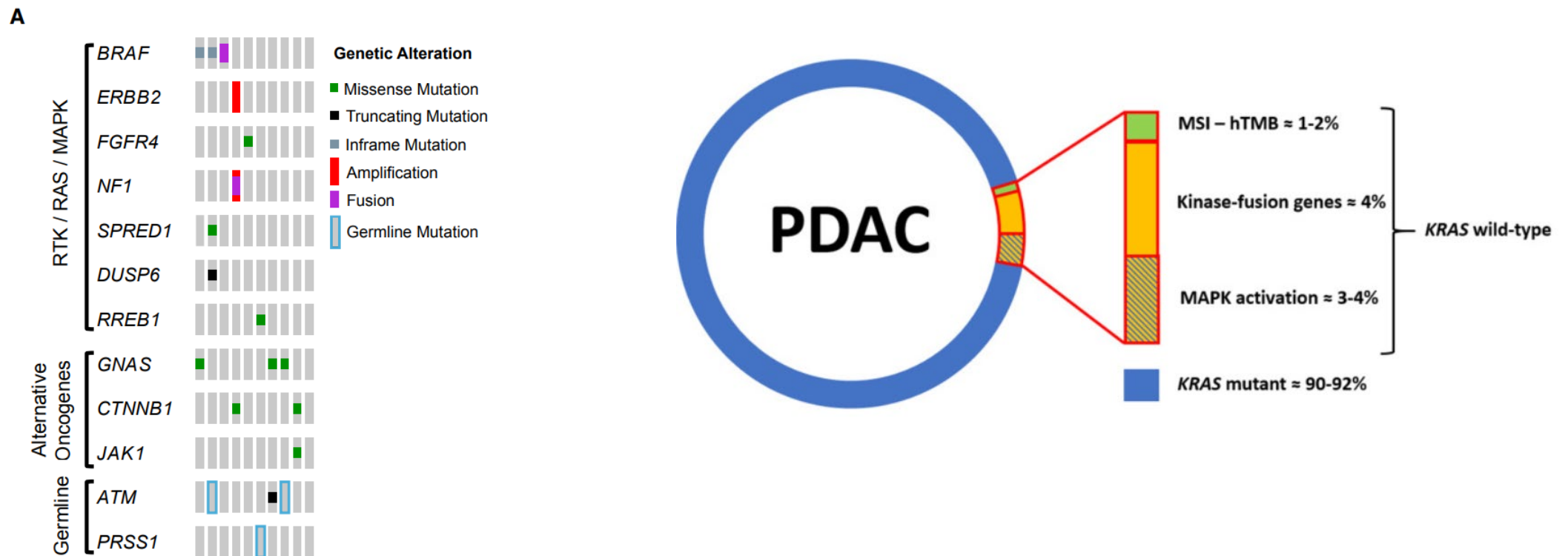
Most Frequent TRAEs ^b		Overall (N=42) ^c	Overall GI cancers ^d (n=30)	
TRAEs, %	Any Grade	Grade 3	Any Grade	Grade 3
Any TRAEs	91	21	87	27
Most frequent TRAEs, %				
Nausea	48	2	50	3
Vomiting	43	0	40	0
Diarrhea	43	0	37	0
Fatigue	29	7	33	10
AST increase	19	2	20	3
Blood creatinine increase	19	0	17	0
Anemia	17	2	20	3
Peripheral edema	17	0	17	0
QT prolongation	14	5	13	7
ALT increase	12	2	13	3
Dysgeusia	12	0	13	0

KRAS Wild Type Pancreatic Cancer

Singhi, et al – 12% *KRAS*^{WT}

Out of 47 *KRAS* wild-type samples, fusions in:

FGFR2 (12), RAF (7), ALK (5), RET (4), MET (2), NTRK1 (2), ERBB4 (1) and FGFR3 (1)

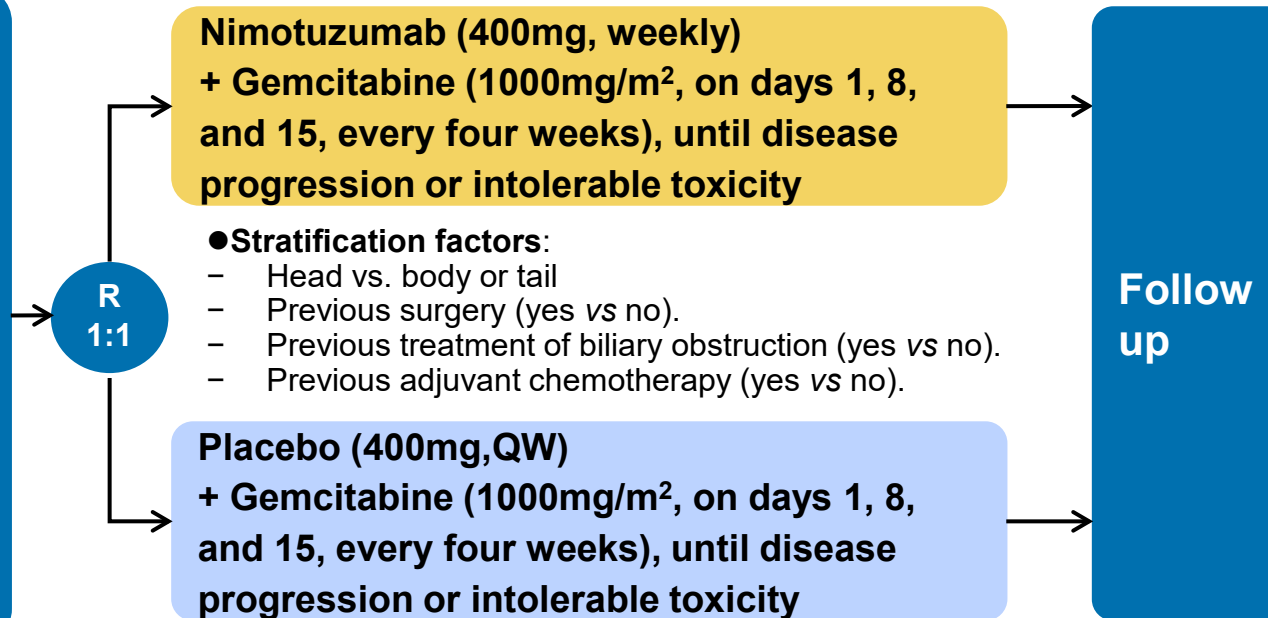


The Notable trial, Qin et al., LBA4011

A Prospective, Randomized-controlled, Double-blinded, Multicenter Phase III Clinical trial, the Registered & Pivotal Study

Key eligibility criteria:

- Aged 18-75 years;
- Histologically confirmed locally advanced or metastatic pancreatic cancer;
- At least one measurable lesion evaluated by RECIST version 1.1;
- K-Ras wild-type;
- Karnofsky Performance Status ≥ 60 .



A sample size of 79 patients, the study would have 80% power to detect a 5.95 months difference of mOS with Nimo (11.62 months) vs. Placebo (5.65 months) at a two-sided alpha level of 0.05. Finally it will be a sample size of 92 patients at 20% drop out.

- **Primary endpoint:** OS
- **Secondary endpoints:** PFS, TTP, ORR, DCR, CBR & Safety

The Notable trial, Qin et al., LBA4011: OS Results

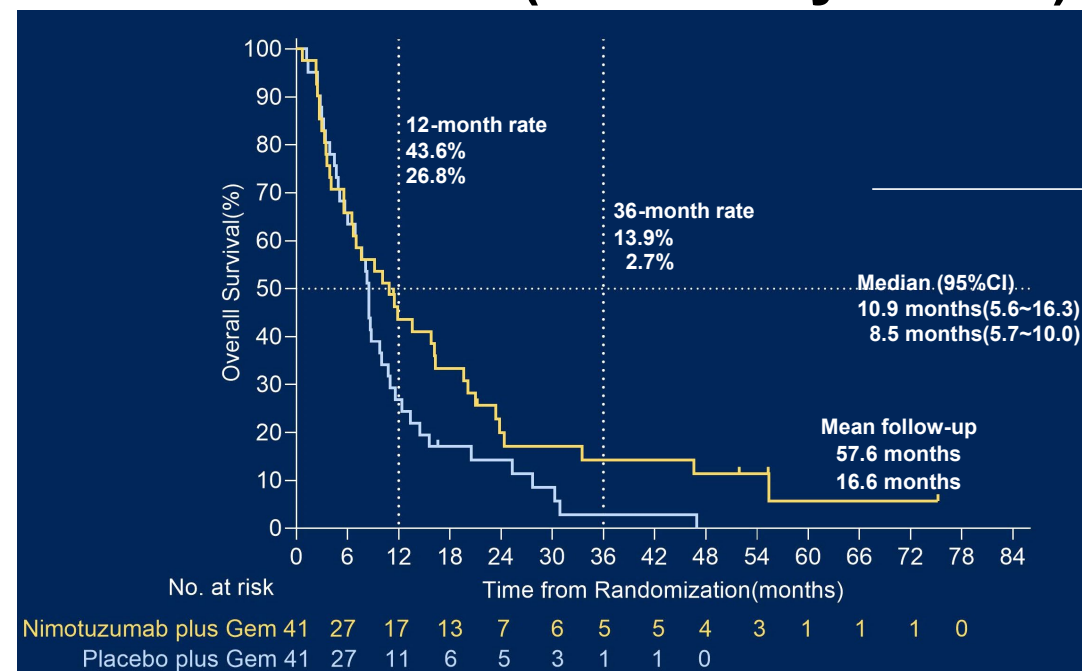
41 patients per arm

Groups well balanced

mOS 10.9 vs. 8.5 months

HR 0.5 (0.06-0.94); $p=0.024$

Overall Survival (Full Analysis Set)



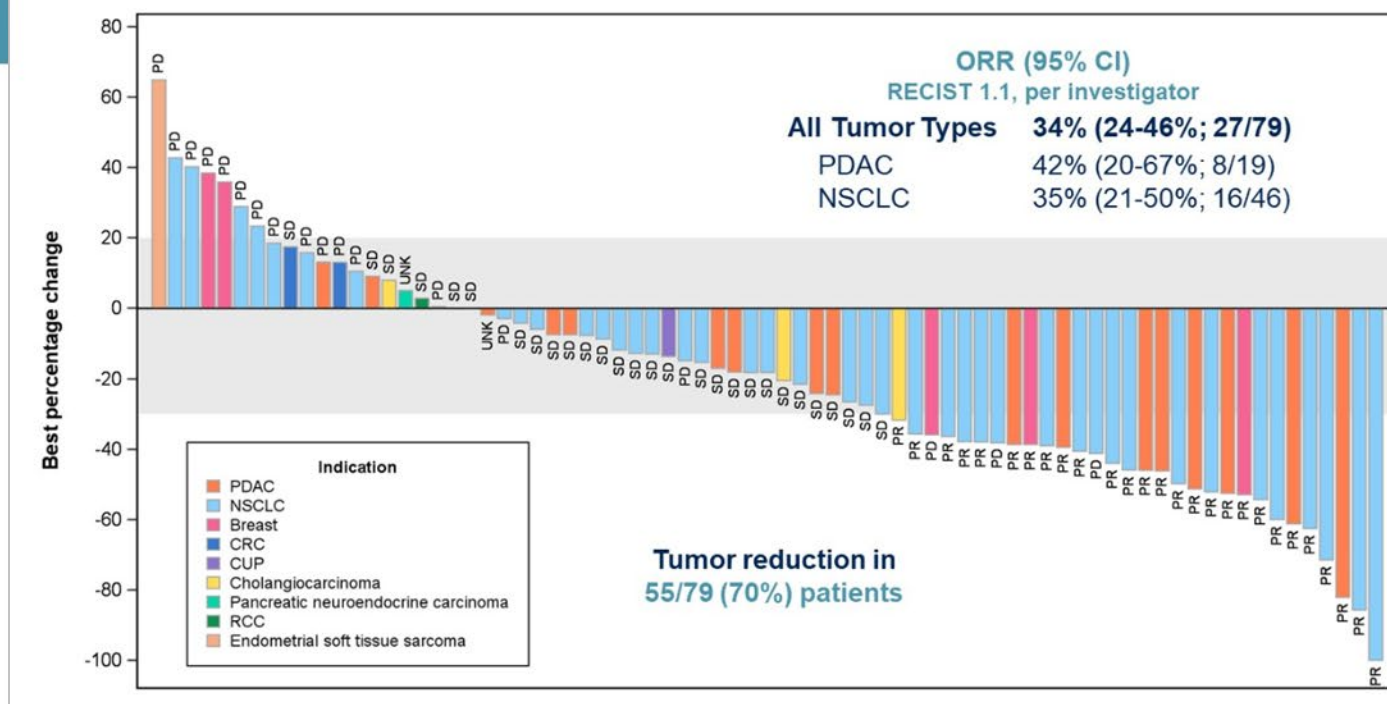
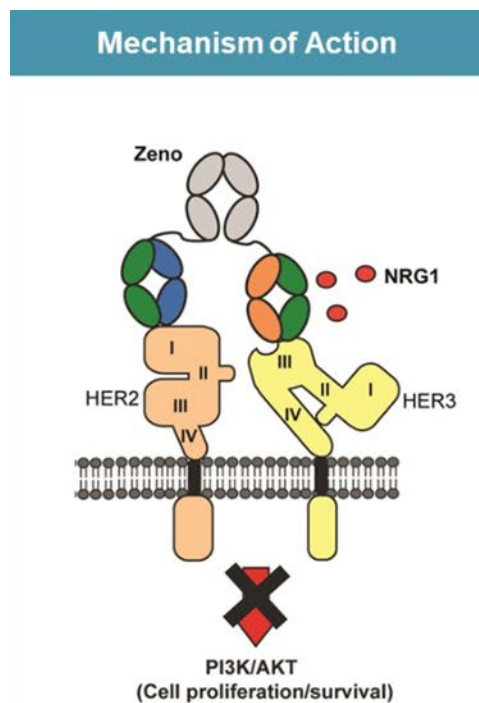
	mOS	HR(95%CI)	P
Nimo plus Gem	10.9 months	0.50	RMST Log
Placebo plus Gem	8.5 months	? 0.06 0.94)	P=0.024

Notable Trial: Analysis

- Significant improvement in OS and PFS by adding nimotuzumab to gemcitabine in patients with KRAS WT mPDAC/LAPC
- BUT...
- Gem is not first line standard in mPDAC/LAPC for ECOG 0-1 patients
 - It would be straightforward to repeat this trial with a mFOLFIRINOX or gem-nab-pac background
- VERY small sample size for a “Phase 3” trial
- No comment on subsequent therapies – and curves separated late
 - Can we make more of an impact getting access to targeted therapies?

Targeted Therapies: Zenocutuzumab, a HER2 x HER3 Bispecific Antibody for NRG1 fusion+ Cancers

- NRG1 fusions occur in <1% of pancreatic cancers
- Enriched in KRASWT cancers
- Zeno: 42% ORR in NRG1 fusion+ PDAC



Thank you and Questions?