Upper GI Hepatobiliary/Pancreatic Cancers

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Disclosure of Conflicts of Interest

Naomi Fei, MD MS, has no financial relationships to disclose.

Outline

- Sequential Chemotherapy: SEQUENCE
- Targeting mutant KRAS in PDAC: KRYSTAL-1
- KRAS WT PDAC: NOTABLE
- Available Trials at UIHC

SEQUENCE trial

- Chemotherapy efficacy may differ in subtypes of pancreatic cancer
  - Classic subtype = mFOLFIRINOX
  - Basal-cell subtype = Gem-Abraxane
- Phase I data has shown promising clinical activity for sequential Gem/Nab-P => mFOLFOX.
- Phase II, open label, randomized trial comparing sequential treatment with Gem-Abraxane followed by mFOLFOX with Gem-Abraxane in 1L metastatic Pancreatic Cancer
  - Primary endpoint: OS
  - Secondary endpoints: ORR, PFS, TTP

SEQUENCE trial: Study Design

SPANISH COOPERATIVE GROUP FOR THE TREATMENT OF DIGESTIVE TUMORS

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

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

Primary endpoint:
- Increased efficacy in terms of 12-month OS rate

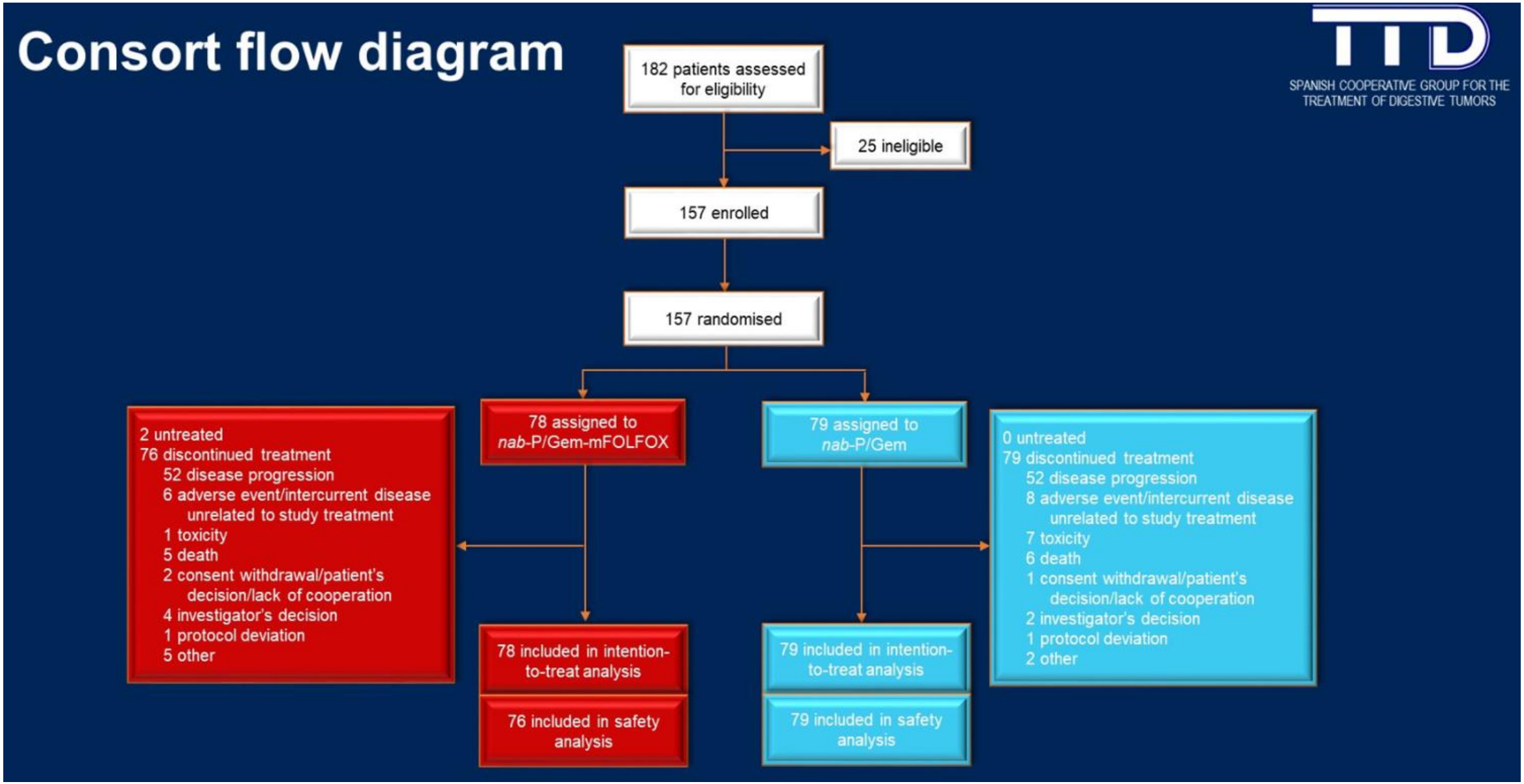
Secondary endpoints:
- ORR, TTP, PFS, mOS; quality of life and safety

ClinicalTrial.gov id. NCT02504333
Accrual: 30 months (July 27, 2017-April 16, 2019)
Tumor evaluations every 12 weeks

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

Slides Courtesy of Alfredo Carrato, ASCO 2022

Consort flow diagram



Slides Courtesy of Alfredo Carrato, ASCO 2022

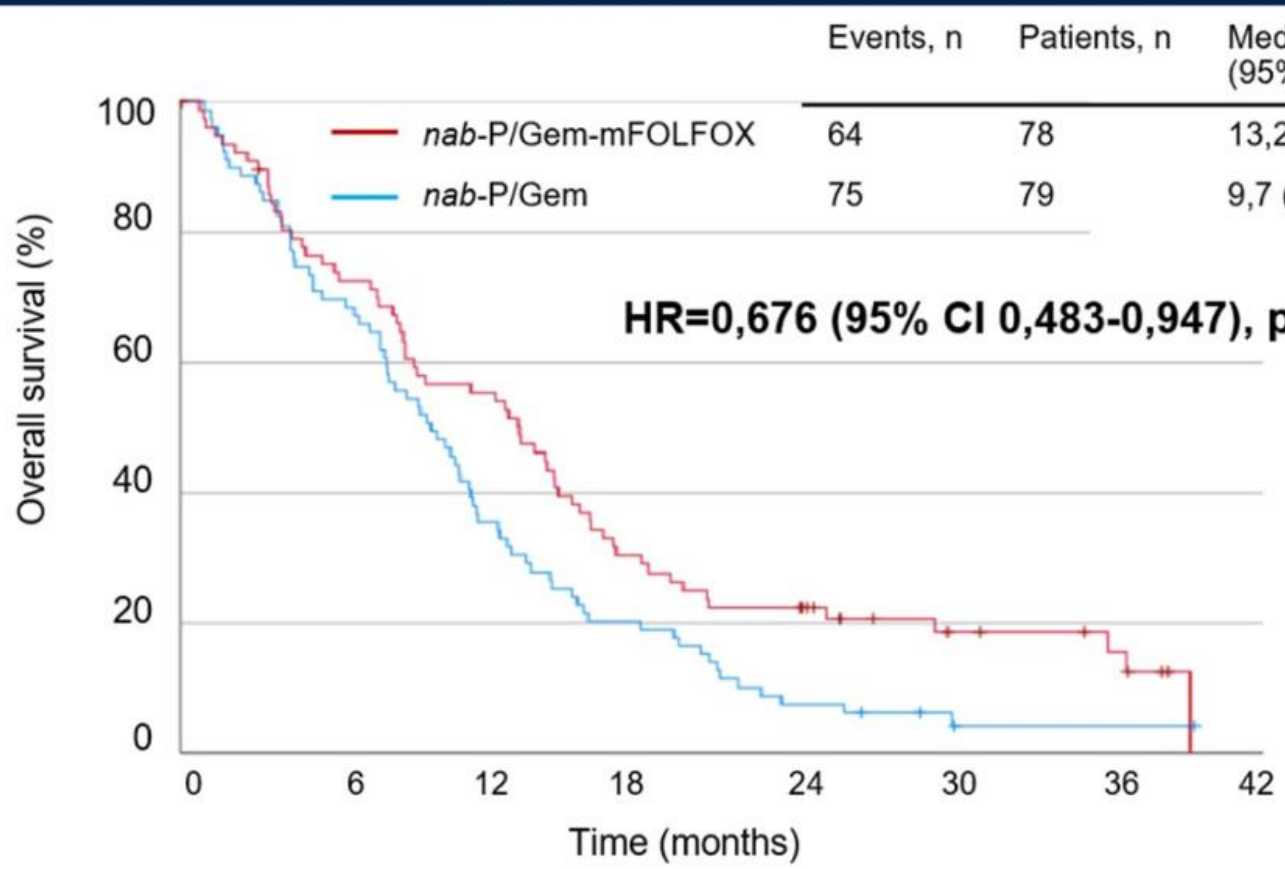
Characteristic N (%)	nab-P/Gem-mFOLFOX (n=78)	nab-P/Gem (n=79)	p-value
Age (years)			
Median (range)	66,0 (38-81)	65,0 (42-84)	0,691
>65 years	40 (51,3%)	35 (44,3%)	0,740
Sex			
Male	41 (52,6%)	36 (45,6%)	0,426
Female	37 (47,4%)	43 (54,4%)	
ECOG performance status			
0	22 (28,2%)	22 (27,8%)	>0,999
1	56 (71,8%)	57 (72,2%)	
PDAC and metastases location*			
Pancreas	67 (85,9%)	71 (89,9%)	0,474
Liver	60 (76,9%)	59 (74,7%)	0,853
Lung	27 (34,6%)	20 (25,3%)	0,226
Peritoneum	21 (26,9%)	25 (31,6%)	0,600
Regional lymph nodes	16 (20,5%)	15 (19,0%)	0,843
Distant lymph nodes	15 (19,2%)	13 (16,5%)	0,682
Bone	5 (6,4%)	1 (1,3%)	0,117
Stomach	1 (1,3%)	0 (0,0%)	0,497
Large intestine	1 (1,3%)	1 (1,3%)	>0,999
Other	16 (20,5%)	9 (11,4%)	0,132
Number of affected organs			
1	2 (2,6%)	3 (3,8%)	0,596
2	26 (33,3%)	35 (44,3%)	
≥ 3	50 (64,1%)	41 (51,9%)	
Prior neo/adjuvant procedures			
Surgery	15 (19,2%)	13 (16,5%)	0,682
Radiotherapy	0 (0,0%)	1 (1,3%)†	0,278
Chemotherapy	5 (6,4%)†	2 (2,5%)†	>0,999

riable. †Neoadjuvant and/or adjuvant primary tumour surgical therapy

Slides Courtesy of Alfredo Carrato, ASCO 2022

Overall survival by treatment arm

SPANISH COOPERATIVE GROUP FOR THE TREATMENT OF DIGESTIVE TUMORS



Number at risk

nab-P/Gem-mFOLFOX	78	56	42	22	17	8	5
nab-P/Gem	79	55	28	15	6	2	1

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Primary endpoint: 12-month OS rate

	nab-P/Gem-mFOLFOX (n=78)	nab-P/Gem (n=79)	p-value
12-month OS rate (95% CI)	55,3% [44,2-66,5%]	35,4% [24,9-46,0%]	**0,016**

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Safety analysis

SPANISH COOPERATIVE GROUP FOR THE TREATMENT OF DIGESTIVE TUMORS

Grade ≥3 treatment-related AEs	nab-P/Gem-mFOLFOX (n=76)	nab-P/Gem (n=79)	p-value
Any event	53 (69,7%)*	45 (57,0%)	0,133
Serious events	37 (48,7%)	43 (54,4%)	0,522
Events in ≥5% in either group			
Neurologic toxicity†	12 (15,8%)	12 (15,2%)	> 0,999
Neutropenia	35 (46,1%)	19 (24,1%)	**0,004**
Febrile neutropenia	4 (5,3%)	3 (3,8%)	0,716
Thrombocytopenia	18 (23,7%)	6 (7,6%)	**0,007**
Anaemia	4 (5,3%)	8 (10,1%)	0,369
Asthenia	15 (19,7%)	7 (8,9%)	0,369
Diarrhoea	7 (9,2%)	5 (6,3%)	0,559

*It includes two fatal events (cellulitis and sepsis). †It includes peripheral sensory neuropathy, paraesthesia and/or dysesthesia

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SEQUENCE Trial: Conclusions

- The SEQUENCE schedule in 1L metastatic PDAC demonstrated improvements in 12 month OS rate, ORR, TTP, and PFS when compared with standard treatment of Gem-Abraxane.
- The SEQUENCE schedule demonstrates a manageable safety profile, though higher neurologic events, neutropenia and thrombocytopenia were observed.
- Next Steps: comparison with mFOLFIRINOX

KRAS and Pancreatic Cancer

- KRAS is a membrane bound regulatory protein, transducing signals from activated membrane receptors resulting in cell proliferation and survival.

- Mutant KRAS is a known oncogenic driver, present in 95% of pancreatic cancers
  - Majority KRAS G12D, G12V and G12R, 2% are KRAS G12C

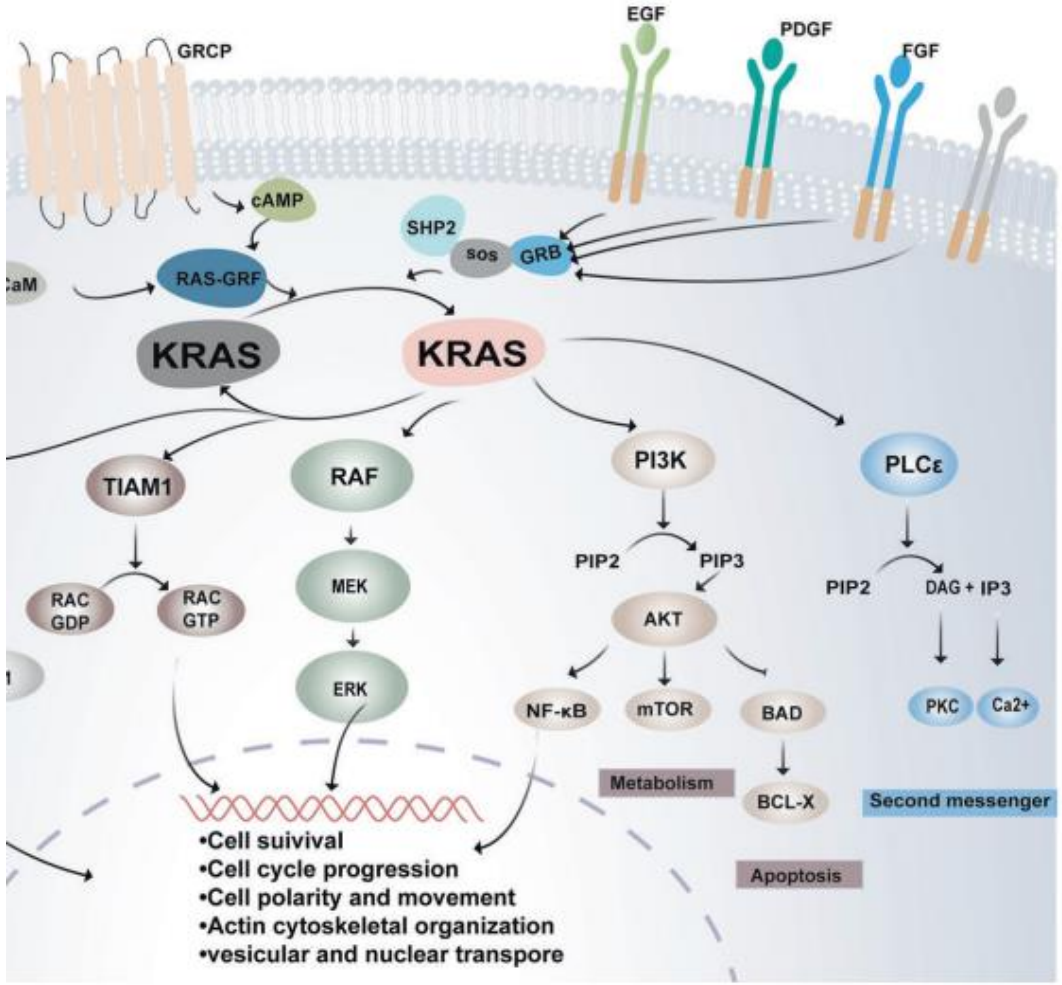


Figure from Huang et al., *Sig Transduct Target Ther* (2021)

Inhibiting KRASG12C

- KRAS switches between inactive (GDP) and active (GTP) conformations
- Mutant KRAS G12 is resistant to GAP, resulting in persistent activation.
- **Adagrasib (MRTX849)** is a covalent inhibitor of KRASG12C, binding and locking it in an inactive GDP-bound state.

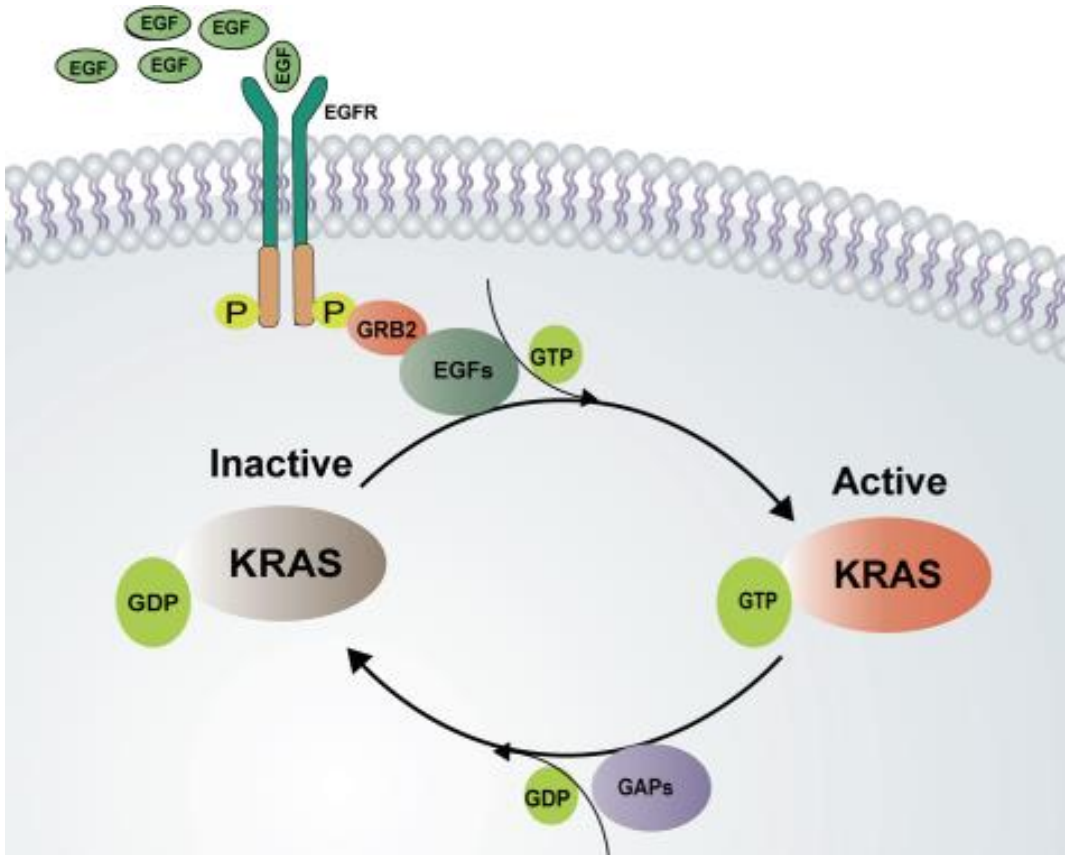


Figure from Huang et al., *Sig Transduct Target Ther* (2021)

KRYSTAL-1:

- Phase 1/2 multicohort study evaluating adagrasib as monotherapy / in combination in solid tumors with KRAS G12C mutation
  - Previously treated unresectable/metastatic PDAC with $KRAS^{G12C}$
- Study endpoints: clinical activity, safety, and PK

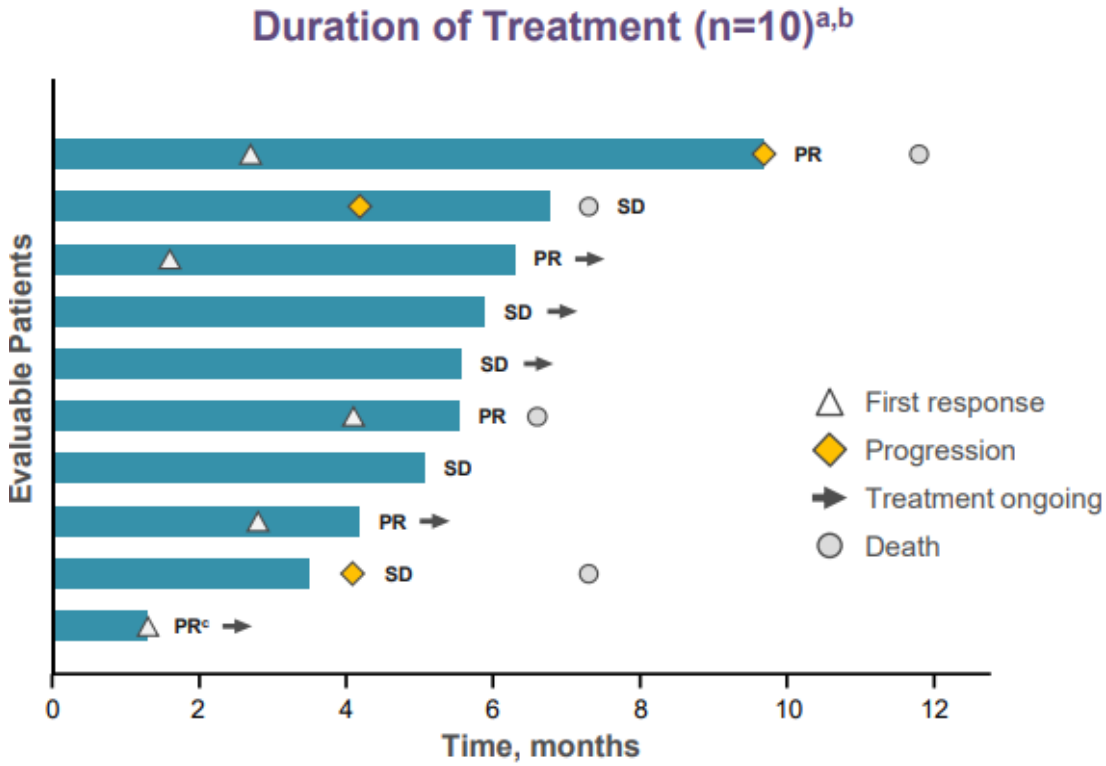
KRYSTAL-1: Demographics

	PDAC (n=12)	Other GI cancers (n=18)	Overall GI cancers[a] (n=30)
Median age, y (range)	66.5 (40–80)	64.0 (54–89)	65.5 (40–89)
Female, n (%)	4 (33)	8 (44)	12 (40)
Race, n (%)			
White	7 (58)	13 (72)	20 (67)
Black or African American	1 (8)	2 (11)	3 (10)
Asian / Other	1 (8) / 3 (25)	1 (6) / 2 (11)	2 (7) / 5 (17)
ECOG PS, n (%)			
0 / 1	0 (0) / 12 (100)	6 (33) / 12 (67)	6 (20) / 24 (80)
Tumor type, n			
PDAC	**12**		**12**
Other GI		**18**	**18**
Biliary tract		8	8
Appendiceal		5	5
Gastro-esophageal junction		2	2
Small bowel		2	2
Esophageal		1	1
Prior lines of systemic anticancer therapy			
Median (range)	2.5 (1–4)[b]	2.0 (1–5)	2.0 (1–5)
1 / 2 / 3 / ≥4 / missing, %	8 / 42 / 42 / 8	22 / 39 / 11 / 22 / 6	17 / 40 / 23 / 17 / 3

Mirati Therapeutics publicly presented data
Bekaii-Saab et al., JCO 2022

KRYSTAL-1: Response

Efficacy outcome[b], n (%)	PDAC (n=10)[c]
Objective response rate	5 **(50)**[e]
Best overall response	
Complete response (CR)	0 (0)
Partial response (PR)	5 (50)[e]
Stable disease (SD)	5 (50)
Disease control rate	10 **(100)**



- Median TTR: 2.8 months
- Median DOR: 6.97 months
- Median PFS: 6.6 months (95% CI 1.0–9.7)
- Treatment ongoing in 50% (5/10) of patients

Mirati Therapeutics publicly presented data
Bekaii-Saab et al., JCO 2022

KRYSTAL-1: Treatment Related Adverse Events

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

- No Grade 4 or 5 TRAEs
- No TRAEs led to discontinuation

Mirati Therapeutics publicly presented data
Bekaii-Saab et al., JCO 2022

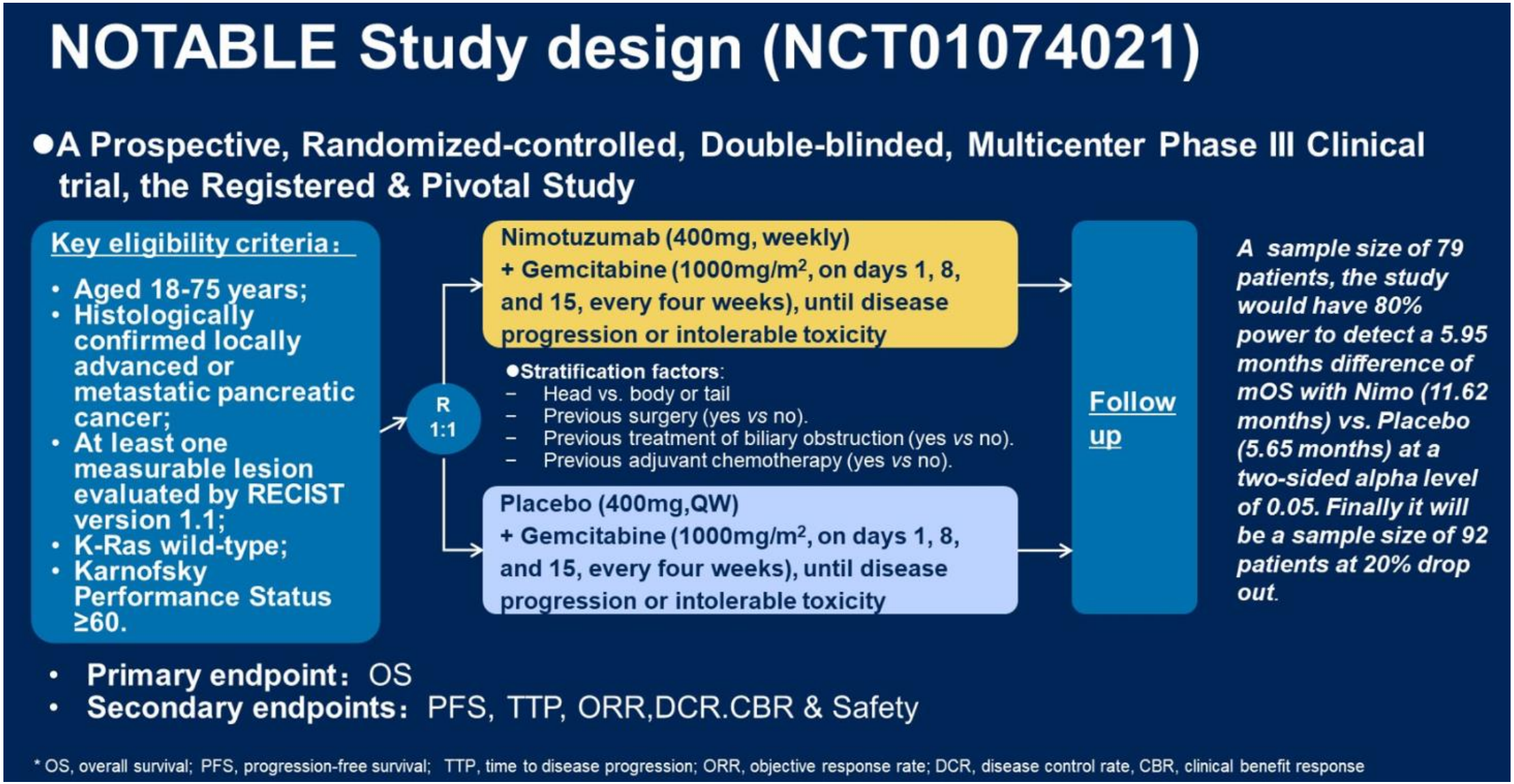
KRYSTAL-1 Conclusions

- Adagrasib monotherapy is well tolerated with manageable safety profile
- Adagrasib monotherapy demonstrated promising clinical activity in pretreated patients with PDAC harboring KRASG12C
- Future directions:
  - New KRAS agents binding other alleles / pan-KRAS inhibitors
  - Combination strategies with drugs aimed at RAS effector pathway (MAPK, PIK3CA)

NOTABLE: KRAS WT Pancreatic Cancer

- This Phase III study evaluated Nimotuzumab + Gemcitabine in KRAS WT locally advanced / metastatic pancreatic adenocarcinoma
- Nimotuzumab is a humanized anti-EGFR mAB inhibiting EGFR signaling and potentiating EGFR degradation.
- Primary Endpoint: OS
- Secondary Endpoints: PFS, Safety, ORR

NOTABLE Study design (NCT01074021)



Slides courtesy of Shukui Quin, M.D. as presented ASCO 22

Qin S, Bai Y, Wang Z, et al: Nimotuzumab combined with gemcitabine versus gemcitabine in K-RAS wild-type locally advanced or metastatic pancreatic cancer. 2022 ASCO Annual Meeting. Abstract LBA4011.

NOTABLE study :Baseline characteristics

- Both groups were well balanced regarding to baseline demographic and clinical characteristics.

	Nimotuzumab plus Gem (n=41)	Placebo plus Gem (n=41)	*P*-value
Age (yr, Mean±SD)	55.0±11.22	57.5±8.89	*0.265*
Gender-male, n(%)	27(65.9)	24(58.5)	*0.494*
Previous surgery, n(%)	23(56.1)	23(56.1)	*>0.999*
Course of disease (<1 year), n(%)	34(82.9)	37(90.2)	*0.331*
Disease type, n(%)			*0.787*
locally advanced	9(22.0)	8(19.5)	
metastatic	32(78.0)	33(80.5)	
Tumors site, n(%)			*0.949*
Head	17(41.5)	17(41.5)	
Body	6(14.6)	7(17.1)	
Tail	18(43.9)	17(41.5)	
Previous adjuvant chemotherapy, n(%)	3(7.3)	3(7.3)	*>0.999*
Previous adjuvant radiotherapy, n(%)	1(2.4)	1(2.4)	*>0.999*
Previous treatment of biliary obstruction, n(%)	4(9.8)	4(9.8)	*>0.999*

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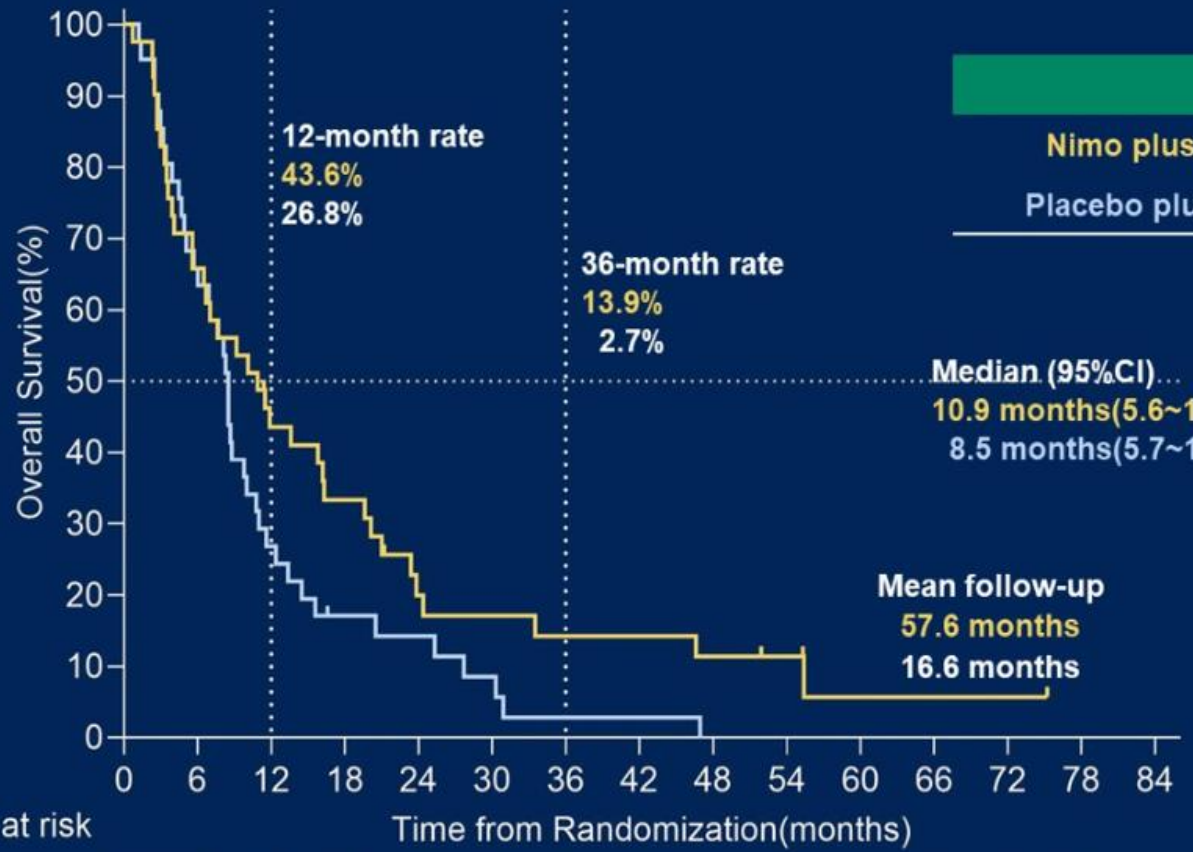
Overall Survival (Full Analysis Set)



	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

- Nimo plus Gem regime improved mOS compared with Placebo plus Gem, with a decrease of 50% mortality risk.

No. at risk

Nimotuzumab plus Gem 41	27	17	13	7	6	5	5	4	3	1	1	1	0
Placebo plus Gem 41	27	11	6	5	3	1	1	0					

* There was a violation of the proportional hazards (PH) because the two survival curves cross. Restricted Mean Survival Time (RMST) method (RMSTREG procedure, log-linear models) was used to estimate hazard risk. The adjusted HR with 95% CI was used as primary estimate of the difference between the arms, stratified by tumor location, previous surgery history, previous treatment of bile obstruction, previous adjuvant chemotherapy history at baseline. Data cut-off, Nov.23,2021.

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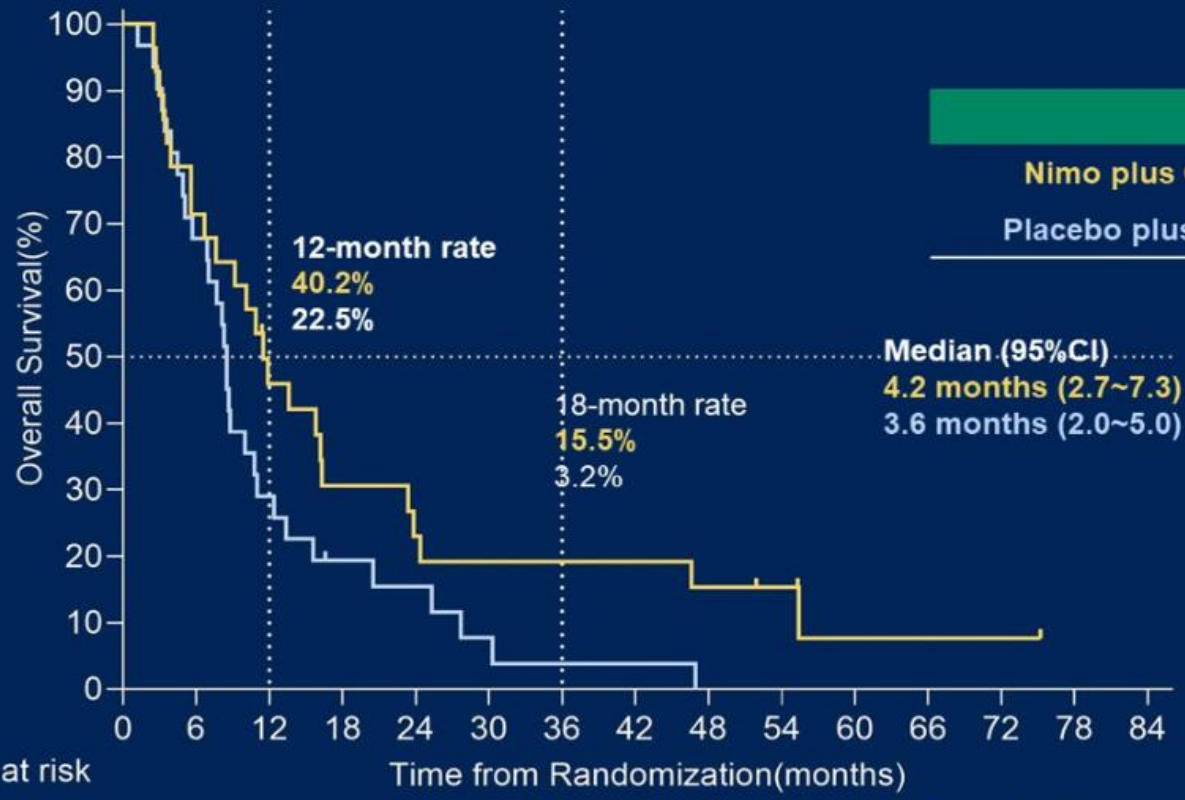
Progression-Free Survival(Full Analysis Set)



	mPFS	HR(95%CI)	*P*
Nimo plus Gem	4.2 months	0.56	RMST-log
Placebo plus Gem	3.6 months	(0.12-0.99)	*P*=0.013

No. at risk

Nimotuzumab plus Gem	28	20	12	8	6	5	5	5	4	3	1	1	1	0
Placebo plus Gem	31	21	9	5	4	2	1	1	0					

- Nimo plus Gem improved mPFS compared with placebo plus Gem, with a decrease of 44% disease progression risk.

*Restricted Mean Survival Time (RMST) method (RMSTREG procedure, log-linear models) was used to estimate hazard risk. The adjusted HR with 95% CI was used as primary estimate of the difference between the arms, stratified by tumor location, previous surgery history, previous treatment of bile obstruction, previous adjuvant chemotherapy history at baseline. Data cut-off, Nov.23,2021

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Safety profile (2)

- The common grade 3 adverse drug reactions (ADRs) were neutrophil counts reduction, platelet count reduction and etc.
- No grade 4-5 adverse drug reactions occurred.

ADRs(>10%) Preferred term	Nimo plus Gem (n=45)				Placebo plus Gem (n=45)			
	Grade 1	Grade 2	Grade 3	Total	Grade 1	Grade 2	Grade 3	Total
Neutrophil count reduction n(%)	9(20.0)	9(20.0)	4(8.9)	12(26.7)	9(20.0)	8(17.8)	3(6.7)	11(24.4)
Platelet count reduction n(%)	9(20.0)	4(8.9)	3(6.7)	10(22.2)	8(17.8)	5(11.1)	4(8.9)	9(20.0)
AST increased n(%)	9(20.0)	0	0	9(20.0)	8(17.8)	1(2.2)	0	9(20.0)
ALT increased n(%)	6(13.3)	0	0	6(13.3)	9(20.0)	2(4.4)	0	10(22.2)
Leukocyte count reduction n(%)	5(11.1)	9(20.0)	5(11.1)	12(26.7)	7(15.6)	7(15.6)	4(8.9)	12(26.7)
Anemia n(%)	5(11.1)	5(11.1)	1(2.2)	7(15.6)	9(20.0)	3(6.7)	1(2.2)	10(22.2)
Rash n(%)	4(8.9)	2(4.4)	0	6(13.3)	3(6.7)	1(2.2)	1(2.2)	4(8.9)
Fatigue n(%)	3(6.7)	3(6.7)	2(4.4)	5(11.1)	5(11.1)	2(4.4)	1(2.2)	6(13.3)
Fever n(%)	3(6.7)	2(4.4)	1(2.2)	5(11.1)	2(4.4)	0	0	2(4.4)

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NOTABLE: Conclusionsn

- Nimotuzumab with gemcitabine increases OS and PFS in patients with KRAS WT locally advanced or metastatic pancreatic cancer
- Nimotuzumab and gemcitabine display a good safety profile
- Next steps: nimotuzumab and combination chemotherapy

UIHC Trials in PDAC

- Resectable/Borderline Resectable:
  - **ALLIANCE**: Perioperative mFOLFIRINOX and surery vs. upfront surgery followed by adjuvant mFOLFIRINOX
  - **AMPLIFY-201**: A study of ELI-002 as adjuvant therapy in KRASmut PDAC with MRD+.
- Locally Advanced:
  - **TIGER-PAC**: Intra-arterial gemcitabine vs. IV Gemcitabine and Nab-paclitaxel following radiotherapy for LAPC
  - **GRECO-2**: A Phase II study of SBRT + GC4711 in unresectable/borderline resectable, nonmetastatic pancreatic cancer
- Metastatic:
  - **PACMAN**: Phase II trial of High-dose ascorbate + Gem/Abraxane vs. Gem/Abraxane in metastatic pancreatic Ca

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