AIG HOSPITALS | INSTITUTE OF ONCOLOGY
A unit of Asian Institute of Gastroenterology

PANCREATIC CANCER – NEWER TREATMENT OPTIONS

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Neoadjuvant and adjuvant therapies

METASTATIC PANCREATIC CANCER

Table 1. Approved treatments for pancreatic adenocarcinoma in the U.S.

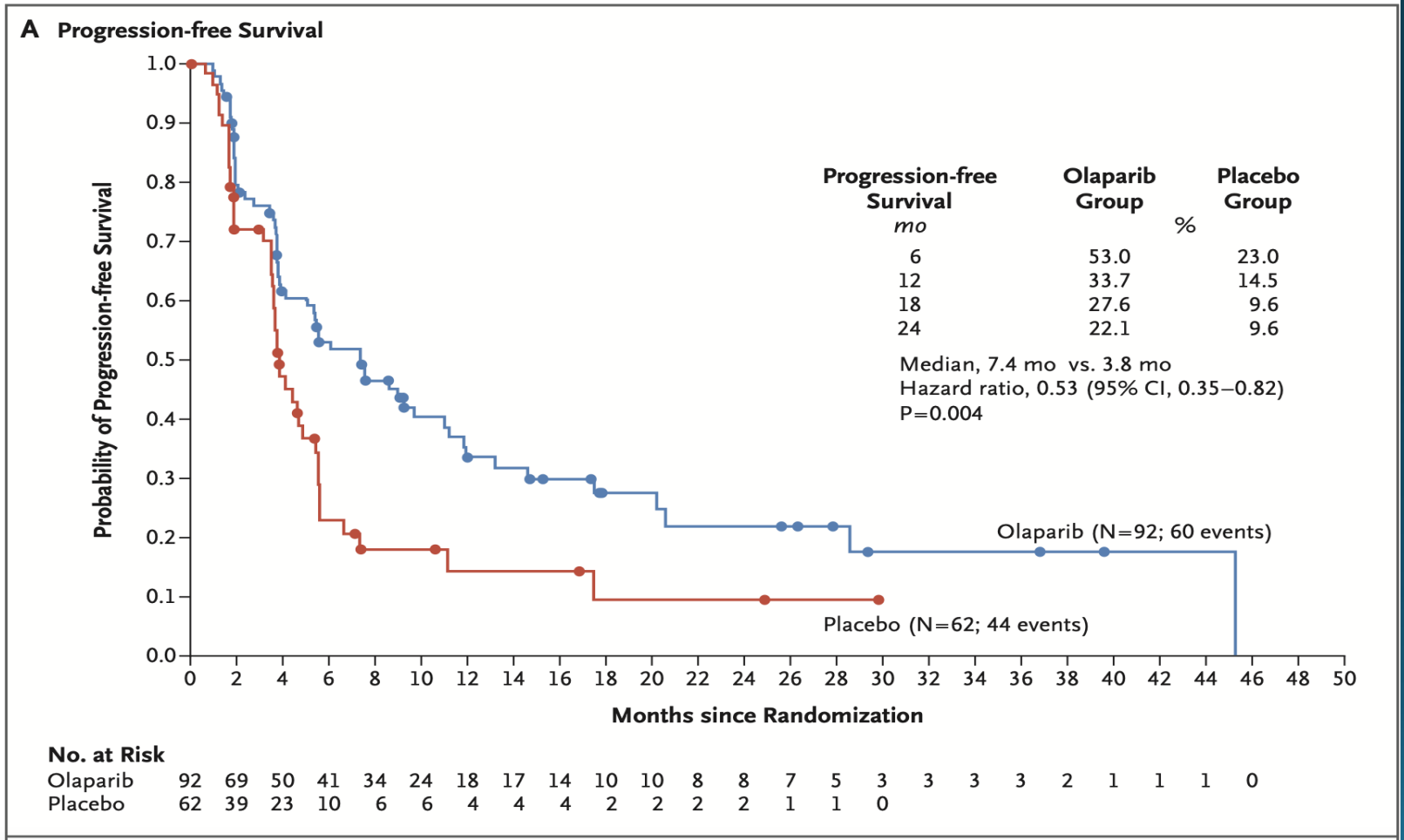
Year	Treatment	Population	Approval
1996	Gemcitabine	Metastatic, 1st line	FDA
2005	Gemcitabine + erlotinib	Metastatic, 1st line	FDA
2010	FOLFIRINOX	Metastatic, 1st line	
2013	Gemcitabine + nab-paclitaxel	Metastatic, 1st line	FDA
2015	5-FU + nal-irinotecan	Metastatic, post gemcitabine	FDA
2016	Gemcitabine + capecitabine	Post-surgery adjuvant	
2017	Pembrolizumab	Microsatellite instability (MSI-Hi) or deficient mismatch repair (dMMR) (approx. 2% prevalence)	FDA tissue agnostic
2018	Modified FOLFIRINOX	Post-surgery adjuvant	
2018	Larotrectinib	NTRK fusions, refractory (approx. 1% prevalence)	FDA, tissue agnostic
2019	Entrectinib	NTRK fusions, refractory (approx. 1% prevalence)	FDA, tissue agnostic
2019	Olaparib	Germline BRCA1/2, maintenance (approx. 5% prevalence)	FDA
2020	Pembrolizumab	High tumor mutation burden (TMB) (approx. 1% prevalence[38]	FDA, tissue agnostic
2021	Dostarlimab-gxly	Mismatch repair deficiency (dMMR) (approx. 2% prevalence)	FDA, tissue agnostic
2022	Dabrafenib plus trametinib	BRAFv600E (less than 1% prevalence)[25]	FDA, tissue agnostic

Rosenzweig *et al. J Cancer Metastasis Treat* 2022;8:46
DOI: 10.20517/2394-4722.2022.58

ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D.,



Overall Survival Results From the POLO Trial: A Phase III Study of Active Maintenance Olaparib Versus Placebo for Germline BRCA-Mutated Metastatic Pancreatic Cancer

Hedy L. Kindler, MD[1] ✉; Pascal Hammel, MD, PhD[2]; Michele Reni, MD[3]; Eric Van Cutsem, MD, PhD[4]; Teresa Macarulla, MD, PhD[5]; Michael J. Hall, MD[6]; ...

- 154 patients were randomly assigned (olaparib, n = 92; placebo, n = 62).
- No statistically significant OS benefit was observed (median 19.0 *v* 19.2 months; hazard ratio [HR], 0.83; 95% CI, 0.56 to 1.22; *P* = .3487).
- Estimated 3-year survival after random assignment was 33.9% versus 17.8%, respectively
- Median time to first subsequent cancer therapy or death, time to second subsequent cancer therapy or death\ and time to discontinuation of study treatment or death significantly favored olaparib.
- PFS 2 non significant

CONCLUSION

- Although no statistically significant OS benefit was observed, the HR numerically favored olaparib, which also conferred clinically meaningful benefits including increased time off chemotherapy and long-term survival in a subset of patients.

Prognostic Factor of PC: K-Ras Wild-type or Mutation

- PC has a worse prognosis either for K-Ras wild-type or mutation type.

Table 1. Disease-Free Survival and Overall Survival by *KRAS*, *CDKN2A*, *SMAD4*, and *TP53* Tumor Status

	Disease-Free Survival (n = 335)						Overall Survival (n = 338)					
			Rate						Rate			
Driver Gene	Patients, No. (%)	Median (IQR), mo	2-y Survival, %	5-y Survival, %	HR (95% CI)[a]	*P* Value[b]	Patients, No. (%)	Median (IQR), mo	2-y Survival, %	5-y Survival, %	HR (95% CI)[a]	*P* Value[b]
KRAS												
Wild-type	27 (8.1)	16.2 (8.9-30.5)	30.2	20.2	1 [Reference]		27 (8.0)	38.6 (16.6-63.1)	63.0	30.2	1 [Reference]	
Mutant	308 (91.9)	12.3 (6.7-27.2)	27.5	12.4	1.72 (1.04-2.84)	.03	311 (92.0)	20.3 (11.3-38.3)	44.5	13.0	1.55 (0.96-2.51)	.08
CDKN2A												
Intact	111 (33.1)	14.8 (8.2-30.5)	31.2	16.9	1 [Reference]		112 (33.1)	24.6 (14.1-44.6)	53.8	19.5	1 [Reference]	
Lost	224 (66.9)	11.5 (6.2-24.5)	26.0	11.5	1.62 (1.19-2.20)	.002	226 (66.9)	19.7 (10.9-37.1)	42.3	11.9	1.44 (1.08-1.91)	.01
SMAD4												
Intact	172 (51.3)	11.5 (6.6-30.1)	27.1	14.4	1 [Reference]		173 (51.2)	21.3 (18.2-26.7)	49.1	15.8	1 [Reference]	
Lost	163 (48.7)	13.6 (7.4-27.0)	28.4	12.3	1.18 (0.90-1.55)	.25	165 (48.8)	20.5 (11.3–39.3)	43.0	12.9	1.07 (0.83-1.38)	.62
TP53												
Wild-type	118 (35.2)	14.8 (8.1-30.5)	31.4	13.9	1 [Reference]		119 (35.2)	24.6 (13.5-44.6)	50.7	18.7	1 [Reference]	
Altered	217 (64.8)	10.8 (6.2-24.5)	25.7	12.6	1.33 (1.02-1.75)	.04	219 (64.8)	20.3 (11.1-37.8)	43.5	12.3	1.18 (0.91-1.53)	.23

1. JAMA Oncol. 2018;4(3):e173420. doi:10.1001/jamaoncol.2017.3420

Meeting Abstract | 2022 ASCO Annual Meeting II

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Nimotuzumab combined with gemcitabine versus gemcitabine in K-RAS wild-type locally advanced or metastatic pancreatic cancer: A prospective, randomized-controlled, double-blinded, multicenter, and phase III clinical trial.

Shukui Qin, Yuxian Bai, Zishu Wang, Zhendong Chen, Ruihua Xu,

NOTABLE Study design (NCT01074021)

- 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.

R 1:1

Nimotuzumab (400mg, weekly) + Gemcitabine (1000mg/m^2, on days 1, 8, and 15, every four weeks), until disease progression or intolerable toxicity

- **Stratification factors**:
  - Head vs. body or tail
  - Previous surgery (yes *vs* no).
  - Previous treatment of biliary obstruction (yes *vs* no).
  - Previous adjuvant chemotherapy (yes *vs* no).

Placebo (400mg,QW) + Gemcitabine (1000mg/m^2, on days 1, 8, and 15, every four weeks), until disease progression or intolerable toxicity

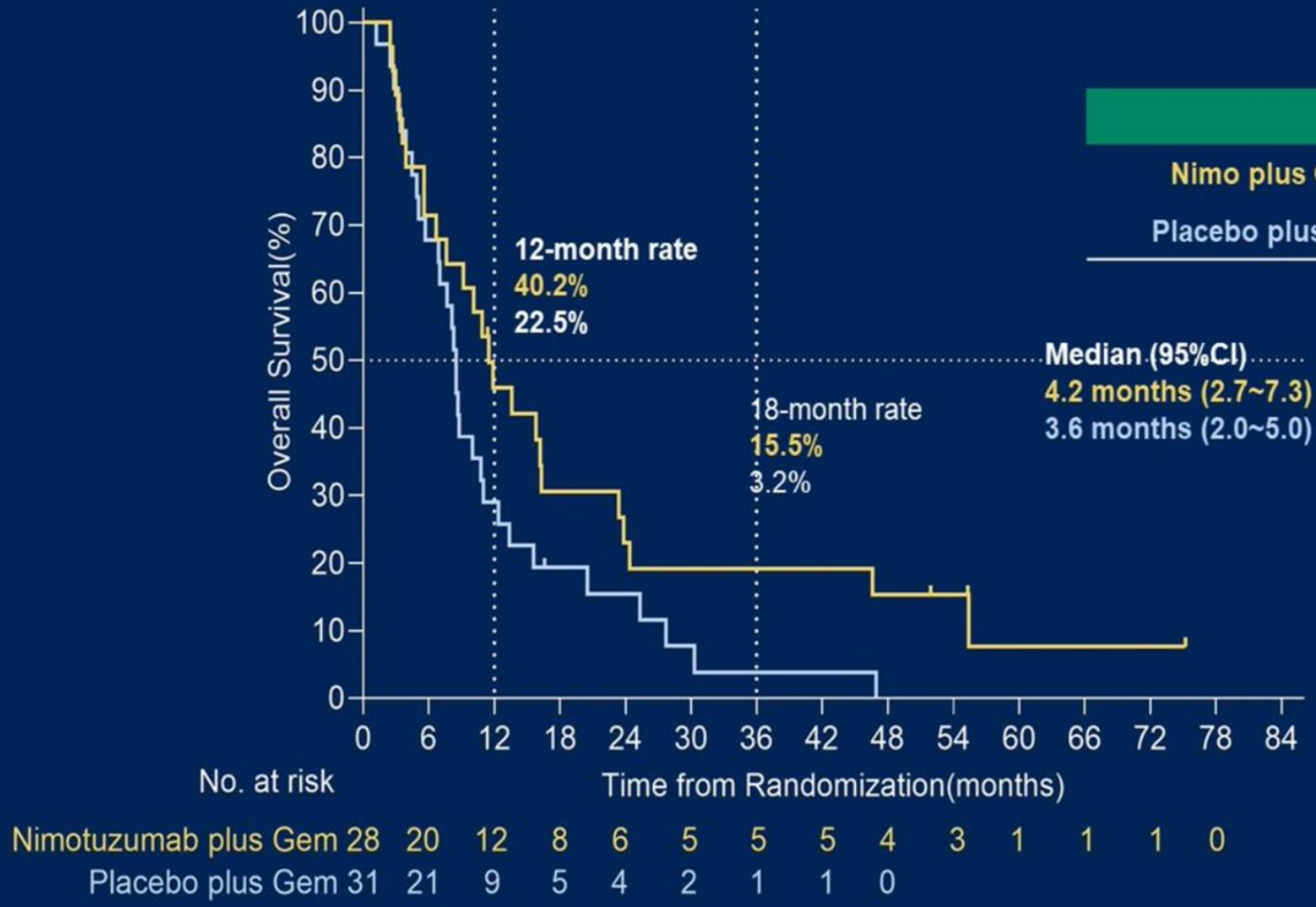
Follow up

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

* OS, overall survival; PFS, progression-free survival; TTP, time to disease progression; ORR, objective response rate; DCR, disease control rate, CBR, clinical benefit response

Progression-Free Survival(Full Analysis Set)

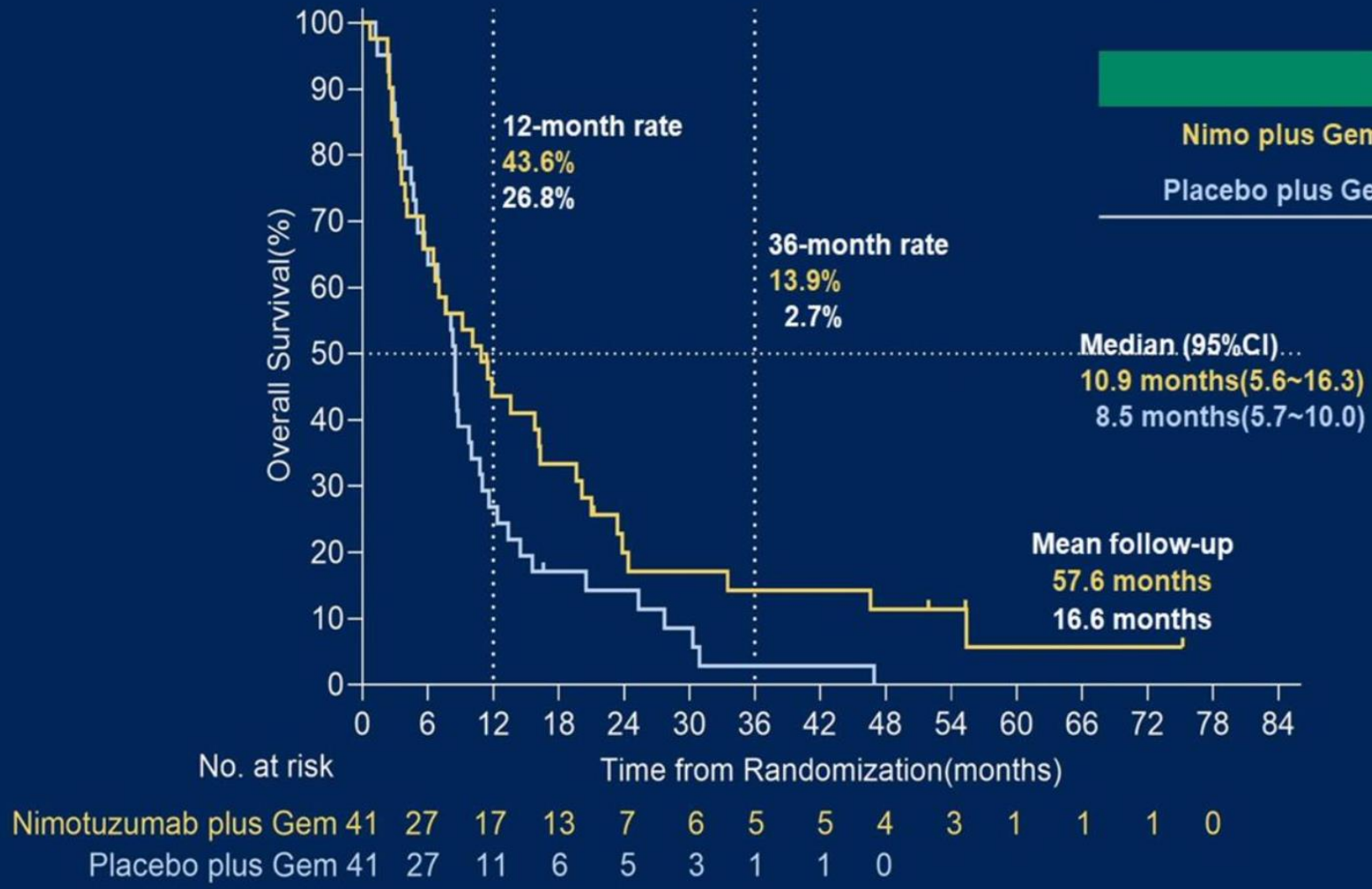


	mPFS	HR(95%CI)	*P*
Nimo plus Gem	4.2 months	0.56	RMST-log
Placebo plus Gem	3.6 months	(0.12-0.99)	*P*=0.013

- 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

Overall Survival (Full Analysis Set)



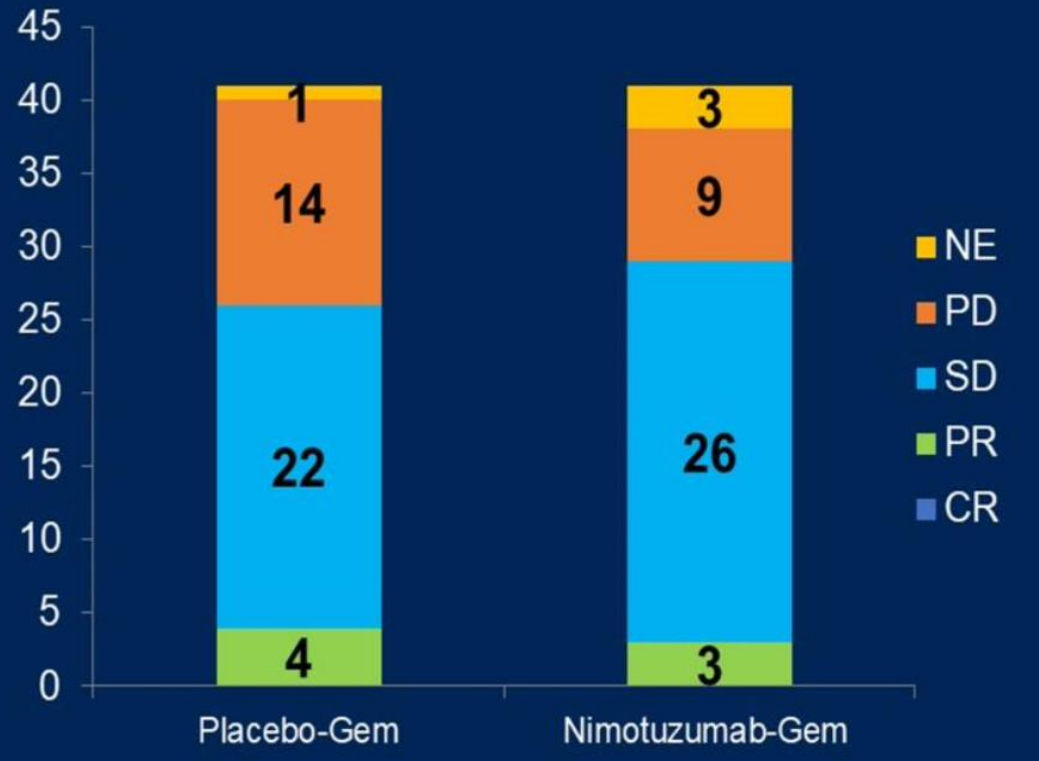
	mOS	HR(95%CI)	*P*
Nimo plus Gem	10.9 months	0.50	RMST-Log
Placebo plus Gem	8.5 months	(0.06-0.94)	*P=0.024*

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

* 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

Overall Response Rate & Disease Control Rate

- The disease control rate (DCR) of the Nimo plus Gem was slightly improved, compared with placebo plus Gem group ($P = 0.641$).



		Nimo plus Gem	Placebo plus Gem	*P*-value
All	ORR	7.3%	9.8%	*>0.05*
	DCR	68.3%	63.4%	
No surgery history of bile obstruction	ORR	8.1%	11.1%	*>0.05*
	DCR	75.7%	58.3%	

* A Cochran-Mantel-Haenszel test was used to compare response rates

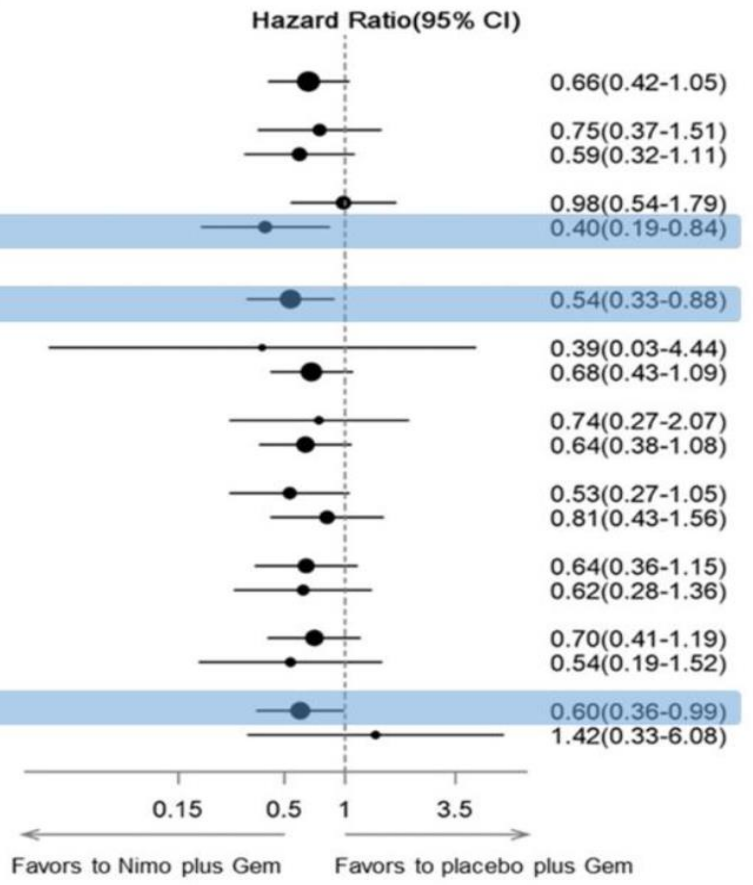
CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluated

Objective response rate (ORR) is the number of PR and CR in FAS
Disease control rate (DCR) is the number of PR, CR and SD in FAS

Subgroup Analyses of Overall Survival

- Nimo plus Gem reduced mortality risk up to 60%, especially for no surgery history

Subgroups	Nimo plus Gem group Events/N	Nimo plus Gem group mOS (mon)	Placebo plus Gem group Events/N	Placebo plus Gem group mOS(mon)	Hazard Ratio(95% CI)
All patients	36/41	10.9	40/41	8.5	0.66(0.42-1.05)
Tumors site					
Head	15/17	11.5	17/17	8.5	0.75(0.37-1.51)
Body or tail	21/24	9.7	23/24	8.4	0.59(0.32-1.11)
Previous surgery					
Yes	22/23	9.2	22/23	10.0	0.98(0.54-1.79)
No	14/18	15.8	18/18	6.0	0.40(0.19-0.84)
Previous treatment of biliary obstruction					
Yes		3.5		13.1	
No	32/37	11.9	36/37	8.5	0.54(0.33-0.88)
Previous adjuvant chemotherapy					
Yes	2/3	37.5	2/3	25.3	0.39(0.03-4.44)
No	34/38	9.7	38/38	8.2	0.68(0.43-1.09)
Disease type					
Locally advanced	8/9	16.2	8/8	13.1	0.74(0.27-2.07)
Metastatic	28/32	10.1	32/33	8.1	0.64(0.38-1.08)
KPS score					
60-80	19/21	11.9	19/19	8.5	0.53(0.27-1.05)
90-100	17/20	10.5	21/22	8.5	0.81(0.43-1.56)
Gender					
Male	24/27	7.6	24/24	5.4	0.64(0.36-1.15)
Female	12/14	19.6	16/17	9.8	0.62(0.28-1.36)
Age					
<65 years	29/33	10.9	29/30	8.3	0.70(0.41-1.19)
≥65 years	7/8	15.3	11/11	8.7	0.54(0.19-1.52)
Course of disease					
<1 year	30/34	9.7	37/37	8.1	0.60(0.36-0.99)
≥1 year	6/7	19.6	3/4	25.3	1.42(0.33-6.08)



Nimo: Nimotuzumab
Gem: Gemcitabine

*HR was calculated by stratified Cox regression for all subjects. Stratified factors were random factors derived from EDC collection. 95% CI was calculated by Wald method. For other subgroups, HR was calculated by un-stratified Cox regression, 95% CI was calculated by Wald method, and mOS was calculated by un-stratified Log-rank method.

nature medicine

ARTICLES

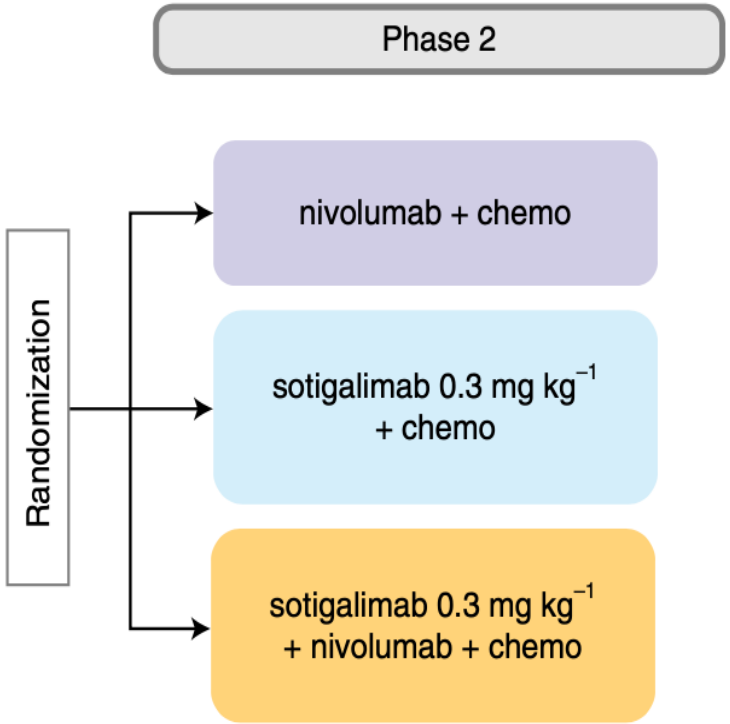
https://doi.org/10.1038/s41591-022-01829-9

Check for updates

OPEN

Sotigalimab and/or nivolumab with chemotherapy in first-line metastatic pancreatic cancer: clinical and immunologic analyses from the randomized phase 2 PRINCE trial

Lacey J. Padrón[1,17] ✉, Deena M. Maurer[1,17], Mark H. O'Hara[2,17], Eileen M. O'Reilly[3],



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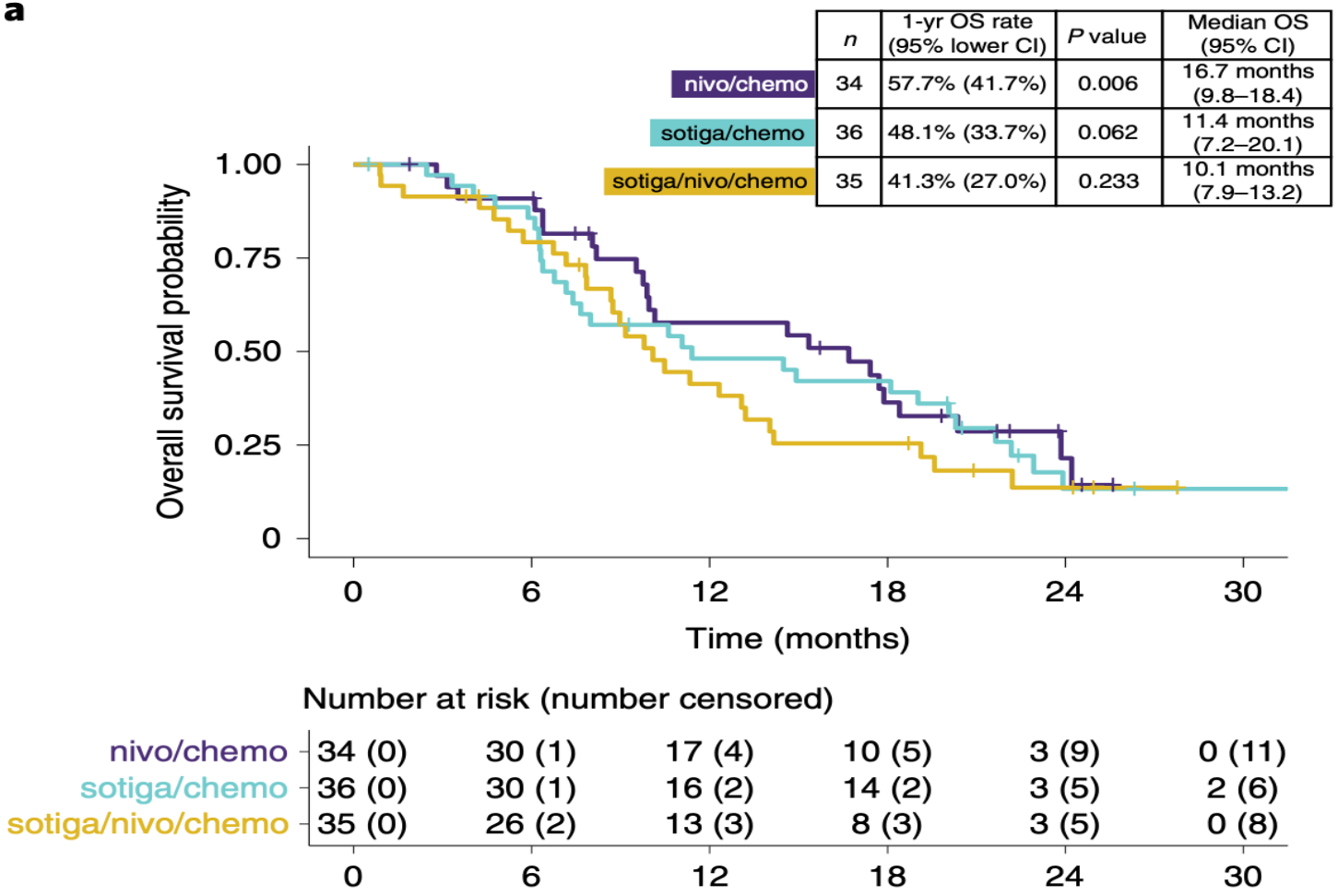

ORIGINAL REPORTS | Gastrointestinal Cancer

Randomized Phase II Study of Nivolumab With or Without Ipilimumab Combined With Stereotactic Body Radiotherapy for Refractory Metastatic Pancreatic Cancer (CheckPAC)

- Primary end point was the clinical benefit rate (CBR)

- Eighty-four patients (41 SBRT/nivolumab and 43 SBRT/nivolumab/ipilimumab)
- CBR was 17.1% (8.0 to 30.6) for patients receiving SBRT/nivolumab and 37.2% (24.0 to 52.1) for SBRT/nivolumab/ipilimumab.

First data for sotorasib in patients with pancreatic cancer with *KRAS* p.G12C mutation: A phase I/II study evaluating efficacy and safety

John H Strickler, Hironaga Satake, Antoine Hollebecque, Yu Sunakawa, Pascale Tomasini, David Lawrence Bajor, ...

Endpoint	Phase I N=12	Phase II N=26	Combined Phase I/II N=38
ORR, n (%)	3 (25.0)	5 (19.2)	8 (21.1)
95% CI[a]	5.49, 57.19	6.55, 39.35	9.55, 37.32
Observed median DoR (range), months	2.8 (1.6, 2.8+)	3.3 (1.4+, 5.8)	2.8 (1.4+, 5.8)
DCR, n (%)	9 (75.0)	23 (88.5)	32 (84.2)
95% CI[a]	42.81, 94.51	69.85, 97.55	68.75, 93.98
Median PFS[b], months	2.79	5.45	3.98

Multiple targets and investigational approaches

- CAR T cell therapy
- DDR pathway inhibitor – LP 184
- MUC5AC antibody in combination with chemotherapy
- Tumour Treating fields – PANOVA 3

TAKE HOME MESSAGES

- Neoadjuvant and adjuvant settings --- Multiple combinations being tried, including RT, Immunotherapy and sequencing
- Metastatic pancreatic and locally advanced – Tisue agnostic drugs available
- Immunotherapy showing some interesting results – however, no conclusive data till now
- Future is in targeted therapies and ? CAR T

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THANK YOU