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Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX or S-IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE)

: a multicenter, randomized, open-label, three-arm, phase 2/3 trial

Akihiro Ohba[1], Masato Ozaka[2], Gakuto Ogawa[1], Takuji Okusaka[1], Satoshi Kobayashi[3], Taro Yamashita[4], Masafumi Ikeda[5], Ichiro Yasuda[6], Kazuya Sugimori[7], Naoki Sasahira[2], Kenji Ikezawa[8], Ikuya Miki[9], Naohiro Okano[10], Nobumasa Mizuno[11], Masayuki Furukawa[12], Hirofumi Shirakawa[13], Yusuke Sano[1], Hiroshi Katayama[1], Junji Furuse[3], Makoto Ueno[3]

[1]National Cancer Center Hospital, Tokyo; [2]Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo; [3]Kanagawa Cancer Center, Yokohama; [4]Kanazawa University, Kanazawa; [5]National Cancer Center Hospital East, Kashiwa; [6]University of Toyama, Toyama; [7]Yokohama City University Medical Center, Yokohama; [8]Osaka International Cancer Institute, Osaka; [9]Hyogo Cancer Center, Hyogo; [10]Kyorin University, Tokyo; [11]Aichi Cancer Center Hospital, Nagoya; [12]Kyushu Cancer Center, Fukuoka; [13]Tochigi Cancer Center, Utsunomiya.

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DECLARATION OF INTERESTS

Akihiro Ohba

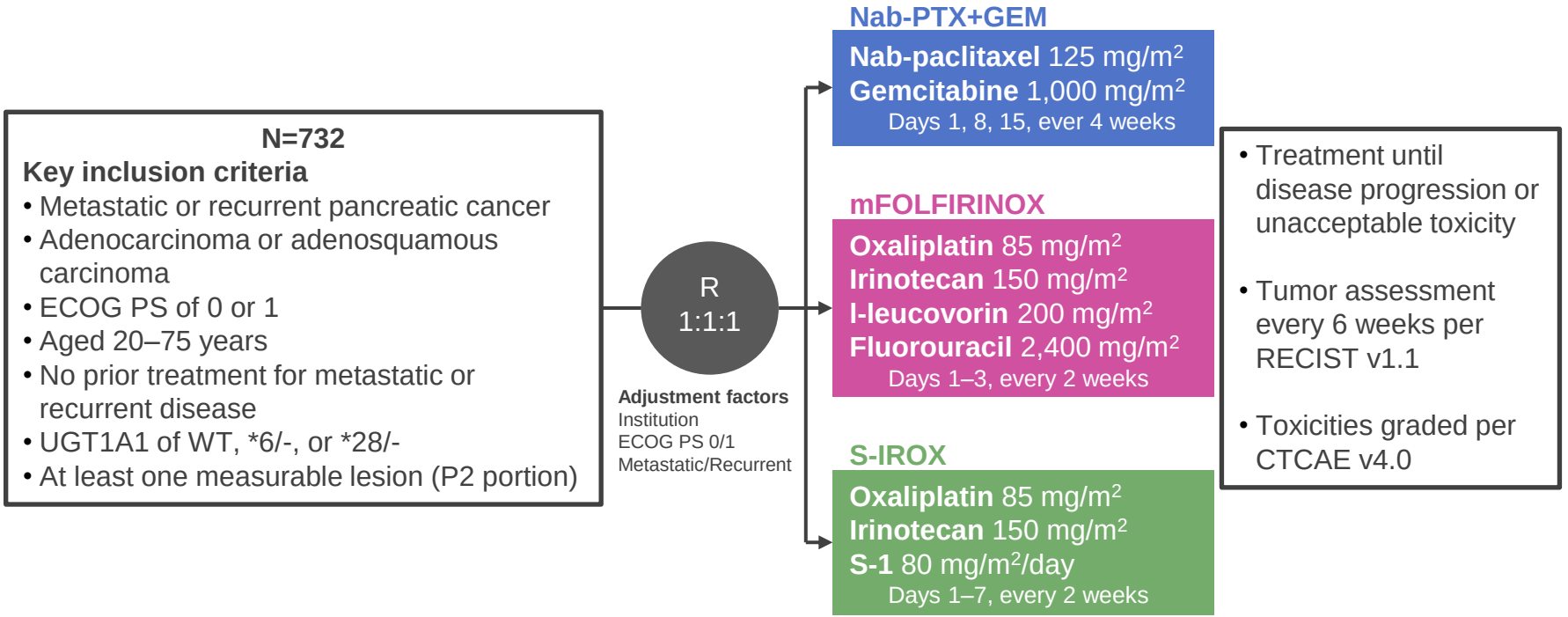
Invited Speaker (Personal): Yakult, Ono, Servier, Taiho, Eisai
Advisory Board (Personal): Zymeworks
Local PI (Institutional): Ono, Chugai, Novartis

Background

- Nab-paclitaxel plus gemcitabine and FOLFIRINOX (including modified regimens) are recommended as first-line treatments for metastatic pancreatic cancer in patients with good performance status[1,2].
- Although NALIRIFOX demonstrated superiority over nab-paclitaxel plus gemcitabine recently[3], there is no direct comparison between nab-paclitaxel plus gemcitabine and modified FOLFIRINOX.
- S-IROX (S-1, irinotecan, and oxaliplatin) showed promising activity (ORR of 51.1%) in a phase 1b trial in advanced pancreatic cancer[4].
- Therefore, we aimed to compare the efficacy and safety of these three regimens in a phase 2/3 trial.

[1]New Engl J Medicine. 2011;364(19):1817–25. [2]New Engl J Medicine. 2013;369(18):1691–703. [3]J Clin Oncol. 2023;41(4_suppl):LBA661. [4]Eur J Cancer. 2022;174:40–7.

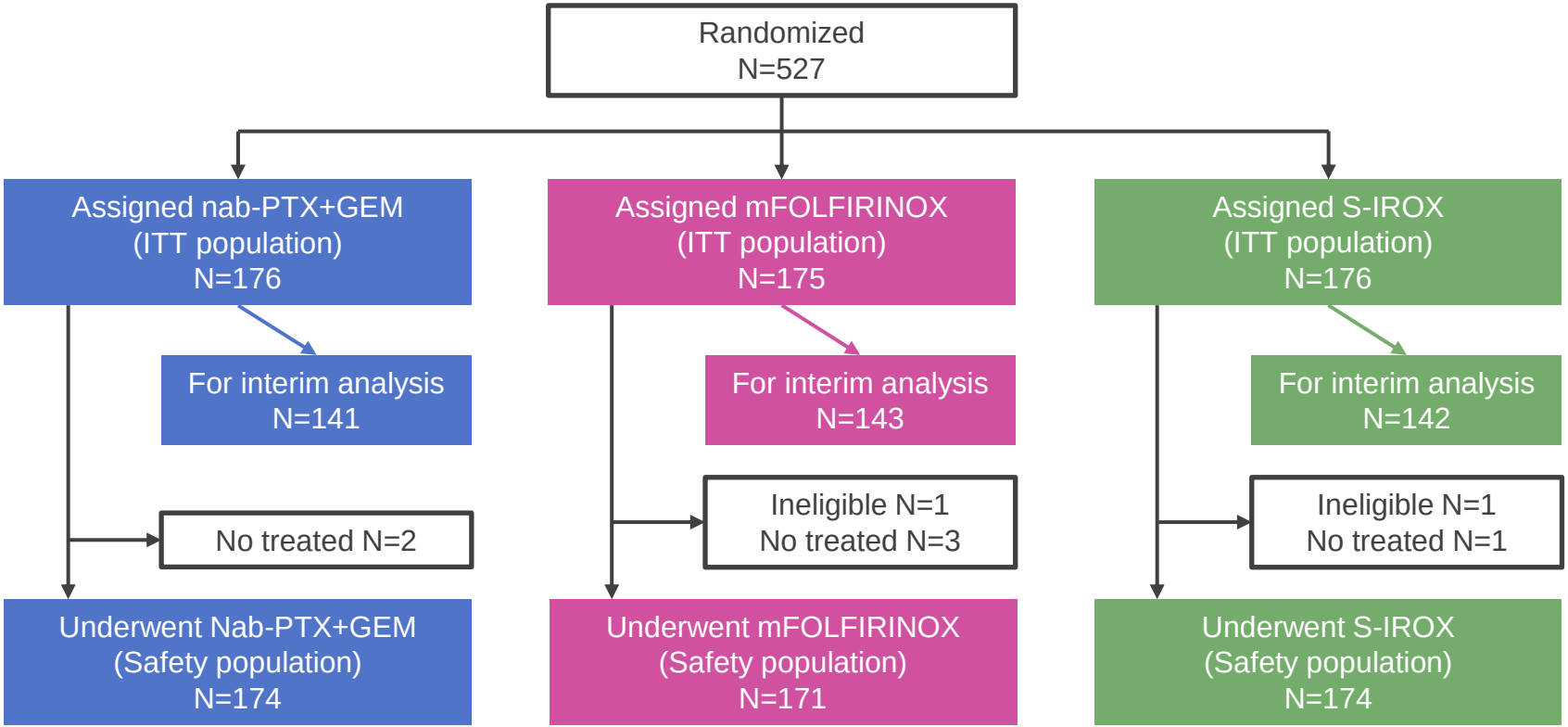
JCOG1611 (GENERATE): Trial Design



Endpoints and Statistical Considerations

- **Phase 2 portion**
  - Primary endpoint: ORR of S-IROX arm
  - Planned N=45; 90% power with a one-sided alpha of 10%; threshold ORR 20%, expected ORR 40%.
  - ➢ This was met in June 2020, and the phase 3 portion continued as a three-arm trial.
- **Phase 3 portion**
  - Primary endpoint: OS
  - Planned N=732; assumed MST as 11 months in nab-PTX+GEM and 15 months in mFOLFIRINOX and S-IROX (HR=0.73); 80% power with a one-sided alpha of 1.25% for each.
  - Secondary endpoints: PFS, ORR, AEs, serious AEs, dose intensity
  - One interim analysis after 50% of patients were enrolled was preplanned to determine whether continuing patient enrollment was reasonable.
  - ➢ This was done in March 2023, and the trial was terminated early.

Trial Population



Patient disposition

	Nab-PTX+GEM (n=176)	mFOLFIRINOX (n=175)	S-IROX (n=176)
Primary reason for protocol treatment discontinuation, n (%)			
Progressive disease	92 (52.3)	85 (48.6)	84 (47.7)
Adverse event	42 (23.9)	60 (34.3)	52 (29.5)
Death	1 (0.6)	0 (0)	2 (1.1)
Patient's decision	2 (1.1)	2 (1.1)	2 (1.1)
Due to early trial termination	33 (18.8)	25 (14.3)	32 (18.2)
Other	6 (3.4)	3 (1.7)	4 (2.3)

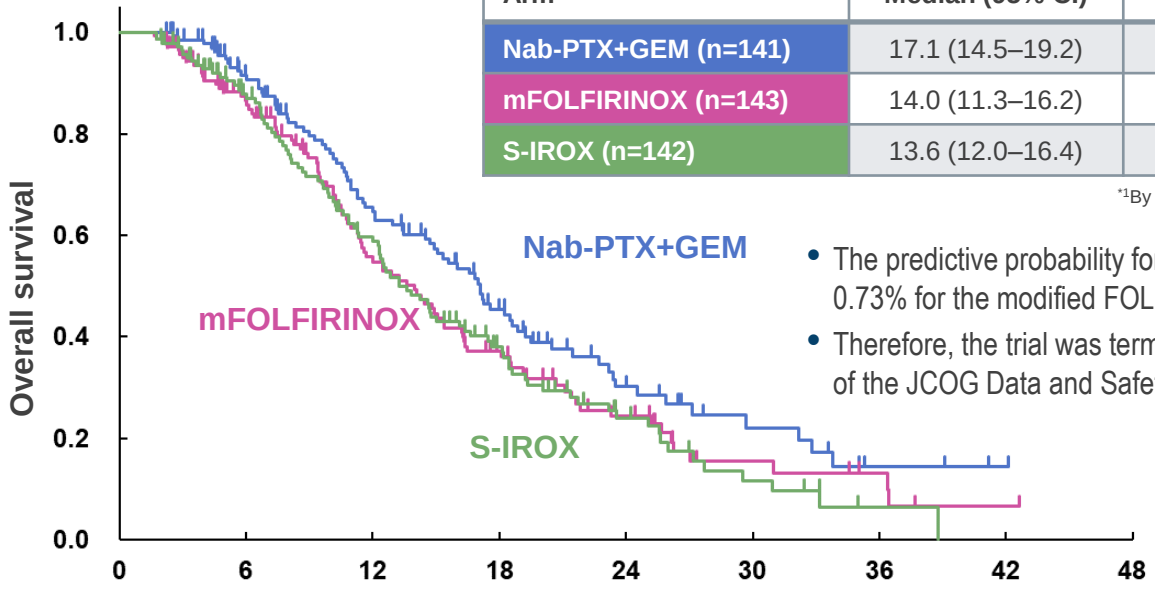
Patient Baseline Characteristics

	Nab-PTX+GEM (N=176)	mFOLFIRINOX (N=175)	S-IROX (N=176)
Median age (range), years	65 (38–75)	67 (45–75)	65 (35–75)
Sex, female, n (%)	89 (50.6)	71 (40.6)	64 (36.4)
ECOG PS 0, n (%)	118 (67.0)	118 (67.4)	119 (67.6)
Pathology, n (%) Adenocarcinoma Adenosquamous Ca	 171 (97.2) 5 (2.8)	 171 (97.7) 4 (2.3)	 173 (98.3) 3 (1.7)
Disease status, n (%) Metastatic Recurrent	 165 (93.8) 11 (6.3)	 167 (95.4) 8 (4.6)	 167 (94.9) 9 (5.1)
Number of metastatic sites, n (%) 1 2 ≥3	 116 (65.9) 44 (25.0) 16 (9.1)	 103 (58.9) 51 (29.1) 21 (12.0)	 109 (61.9) 50 (28.4) 17 (9.7)
Liver metastasis, n (%)	117 (66.5)	124 (70.9)	124 (70.5)
Pancreatic tumor location, n (%) Head Body/Tail	 68 (38.6) 108 (61.4)	 68 (38.9) 107 (61.1)	 70 (39.8) 106 (60.2)
CA 19-9, n (%) <37 U/mL ≥37 U/mL	 33 (18.8) 143 (81.2)	 39 (22.3) 136 (77.7)	 28 (15.9) 148 (84.1)

Overall Survival (Interim Analysis: Mar 2023)

Arm	Median (95% CI)	HR (95% CI)*1	One-sided p*2
Nab-PTX+GEM (n=141)	17.1 (14.5–19.2)	–	
mFOLFIRINOX (n=143)	14.0 (11.3–16.2)	1.31 (0.97–1.77)	0.9622
S-IROX (n=142)	13.6 (12.0–16.4)	1.35 (1.00–1.82)	0.9769

*1By stratified Cox regression model, *2By stratified log-rank test

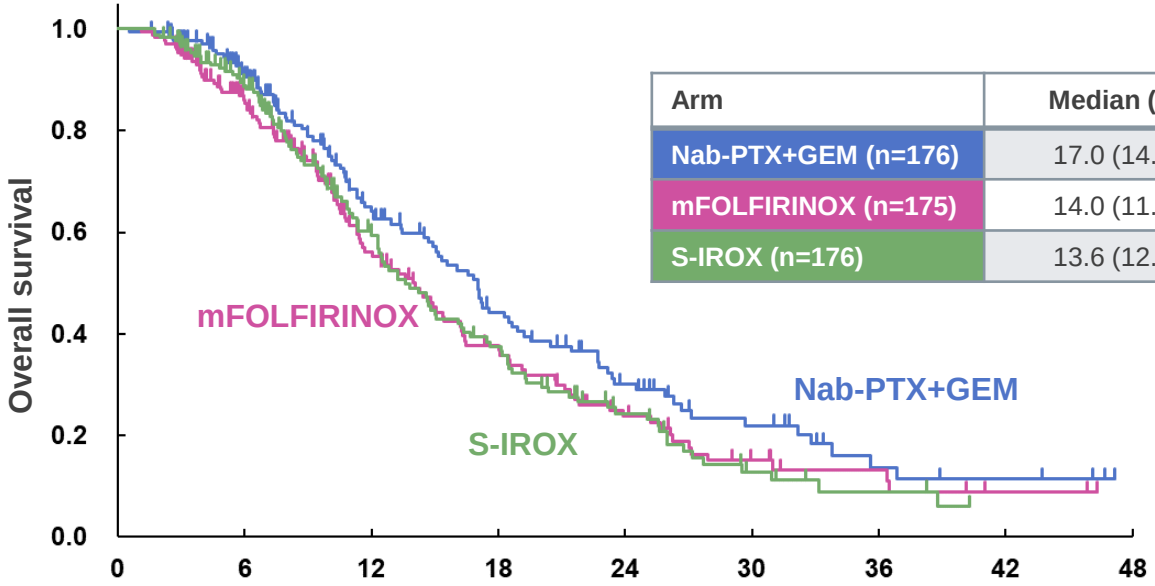


Patients at risk

Nab-PTX+GEM	141	110	73	44	20	9	3	1	0
mFOLFIRINOX	143	104	60	35	18	7	4	1	0
S-IROX	142	104	67	35	16	6	1	0	

- The predictive probability for achieving superiority at the final analysis was 0.73% for the modified FOLFIRINOX arm and 0.48% for the S-IROX arm.
- Therefore, the trial was terminated for futility based on the recommendation of the JCOG Data and Safety Monitoring Committee.

Overall Survival (Updated: May 2023)



Arm	Median (95% CI)	HR (95% CI)*
Nab-PTX+GEM (n=176)	17.0 (14.5–18.9)	–
mFOLFIRINOX (n=175)	14.0 (11.4–16.3)	1.29 (0.98–1.70)
S-IROX (n=176)	13.6 (12.3–16.3)	1.29 (0.98–1.70)

* By stratified Cox regression model

Patients at risk									
Nab-PTX+GEM	176	135	76	47	27	15	6	4	0
mFOLFIRINOX	175	128	66	39	21	10	6	2	0
S-IROX	176	133	68	42	21	8	4	0	

OS Subgroup Analyses

Factors		Nab-PTX+GEM (events/N)	mFOLFIRINOX (events/N)	S-IROX (events/N)	mFOLFIRINOX vs. Nab-PTX+GEM HR [95% CI]	S-IROX vs. Nab-PTX+GEM HR [95% CI]
Age	(Years)					
	< 65	47/86	38/67	50/86	1.06 [0.69-1.62]	1.03 [0.69-1.53]
	≥ 65	49/90	68/108	58/90	1.46 [1.01-2.12]	1.56 [1.07-2.29]
Sex						
	Male	44/87	61/104	70/112	1.26 [0.86-1.86]	1.13 [0.77-1.65]
	Female	52/89	45/71	38/64	1.32 [0.88-1.98]	1.51 [0.98-2.32]
ECOG PS						
	0	63/118	75/118	74/119	1.43 [1.02-2.00]	1.36 [0.97-1.90]
	1	33/58	31/57	34/57	1.03 [0.63-1.69]	1.16 [0.72-1.87]
Tumor location						
	Head	34/68	40/68	39/70	1.19 [0.76-1.89]	1.26 [0.79-2.02]
	Body/Tail	62/108	66/107	69/106	1.37 [0.97-1.94]	1.31 [0.93-1.84]
Disease status						
	Metastatic	93/165	103/167	104/167	1.33 [1.00-1.76]	1.30 [0.98-1.72]
	Recurrent	3/11	3/8	4/9	0.71 [0.14-3.54]	1.21 [0.27-5.56]
Liver metastasis						
	No	24/59	25/51	32/52	1.19 [0.68-2.09]	1.54 [0.91-2.62]
	Yes	72/117	81/124	76/124	1.35 [0.98-1.86]	1.19 [0.86-1.65]
Number of metastatic sites						
	0-1	61/116	51/103	65/109	0.98 [0.68-1.42]	1.29 [0.91-1.84]
	2	24/44	40/51	32/50	2.10 [1.25-3.56]	1.39 [0.81-2.38]
	3 or more	11/16	15/21	11/17	1.12 [0.51-2.46]	0.84 [0.36-1.95]
CA19-9 (U/mL)						
	< 37	14/33	24/39	15/28	1.53 [0.78-3.01]	1.61 [0.78-3.37]
	37≤ , <2183	38/76	41/70	51/86	1.42 [0.91-2.22]	1.47 [0.96-2.24]
	≥ 2183	44/67	41/66	42/62	1.09 [0.71-1.67]	1.05 [0.68-1.60]
Overall		96/176	106/175	108/176	1.29 [0.98-1.70]	1.29 [0.98-1.70]

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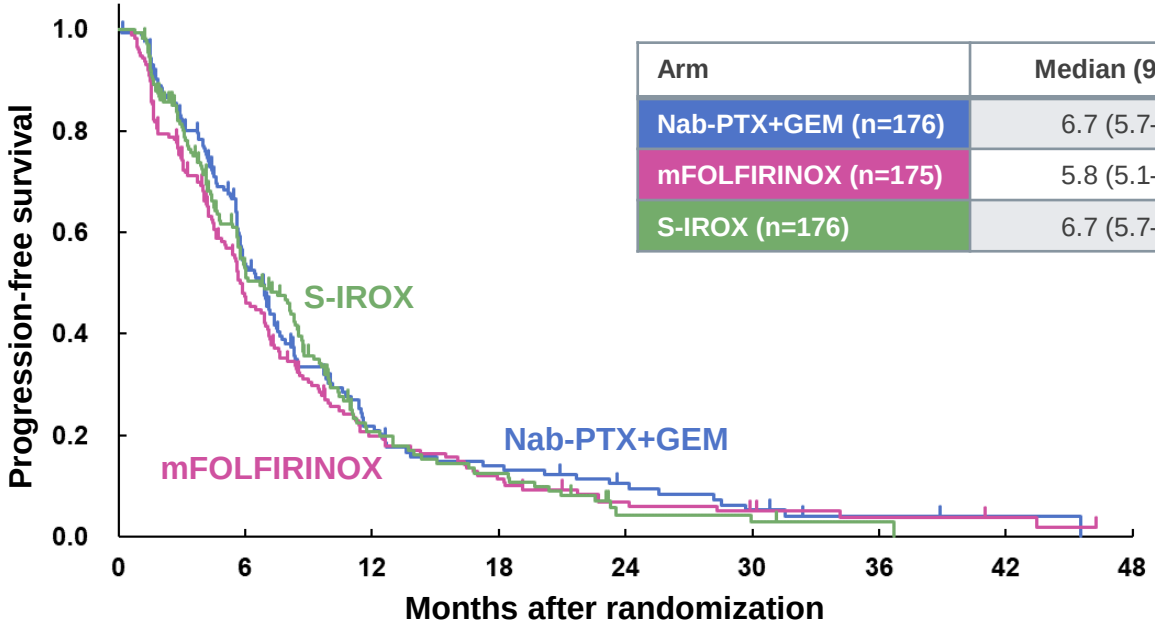
Progression-free Survival



Arm	Median (95% CI)	HR (95% CI)
Nab-PTX+GEM (n=176)	6.7 (5.7–7.4)	–
mFOLFIRINOX (n=175)	5.8 (5.1–6.9)	1.15 (0.91–1.45)
S-IROX (n=176)	6.7 (5.7–8.3)	1.07 (0.84–1.35)

Patients at risk

Nab-PTX+GEM	176	78	26	16	10	5	2	1	0
mFOLFIRINOX	175	74	28	16	8	5	3	2	0
S-IROX	176	78	23	14	3	2	1	0	

Tumor Response

Patients with measurable lesion (n=515)

	Nab-PTX+GEM (n=175)	mFOLFIRINOX (n=170)	S-IROX (n=170)
Objective response rate % 95% CI	 35.4 28.4–43.0	 32.4 25.4–39.9	 42.4 34.8–50.2
Disease control rate % 95% CI	 83.4 77.1–88.6	 72.9 65.6–79.5	 81.8 75.1–87.3
Best response, n (%) Complete response Partial response Stable disease Progressive disease Not evaluable	 0 (0) 62 (35.4) 84 (48.0) 20 (11.4) 9 (5.1)	 1 (0.6) 54 (31.8) 69 (40.6) 31 (18.2) 15 (8.8)	 0 (0) 72 (42.4) 67 (39.4) 21 (12.4) 10 (5.9)

Subsequent Anti-cancer Therapy

	Nab-PTX+GEM (n=176)	mFOLFIRINOX (n=175)	S-IROX (n=176)
Second-line therapy, n (%)	105 (59.7)	111 (63.4)	110 (62.5)
Chemotherapy	103 (58.5)	110 (62.9)	109 (61.9)
Chemoradiotherapy	2 (1.1)	1 (0.6)	1 (1.6)
Third-line therapy, n (%)	50 (28.4)	48 (27.4)	50 (28.4)
Chemotherapy	49 (27.8)	46 (26.3)	50 (28.4)
Chemoradiotherapy	1 (0.6)	2 (1.1)	0 (0)

Adverse Events (≥Grade 3; ≥5% of patients in either arm)

Safety population (n=519)

Event, %	Nab-PTX+GEM (n=174)	mFOLFIRINOX (n=171)	S-IROX (n=174)
Neutropenia	60.3	51.5	38.7
WBC decreased	34.5	22.2	16.1
Anemia	10.9	10.5	10.9
Thrombocytopenia	4.6	4.7	8.6
Febrile neutropenia	3.4	8.8	7.5
Neuropathy	10.9	8.2	7.5
Infection	10.9	16.4	8.6
ALT increased	10.9	11.7	11.5
AST increased	8.1	9.4	6.9
Anorexia	5.2	22.8	27.6
Fatigue	2.9	4.1	6.3
Nausea	2.3	8.8	10.3
Diarrhea	1.1	8.8	23.0

Conclusions

- GENERATE (JCOG1611) was terminated for futility because the planned interim analysis determined it is unlikely that the superiority of modified FOLFIRINOX or S-IROX over nab-paclitaxel plus gemcitabine could be demonstrated.
- The median OS was 17.0 months in the nab-paclitaxel plus gemcitabine arm, 14.0 months in the modified FOLFIRINOX arm, and 13.6 months in the S-IROX arm.
- ≥Grade 3 GI toxicities were more frequent in the modified FOLFIRINOX and S-IROX arms than in the nab-paclitaxel plus gemcitabine arm.
- Compared to modified FOLFIRINOX or S-IROX, nab-paclitaxel plus gemcitabine is recommended as the first-line treatment for patients with metastatic or recurrent pancreatic cancer.

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JCOG Data Center and Operations Office

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Hyogo Cancer Center
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National Hospital Organization Shikoku Cancer Center
Kochi Health Sciences Center
National Kyushu Cancer Center
Kyushu University Hospital
Nagasaki University Hospital
Kagoshima University Hospital

European Society for Medical Oncology (ESMO)

Via Ginevra 4, CH-6900 Lugano

T. +41 (0)91 973 19 00

esmo@esmo.org

esmo.org