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Multicenter randomized phase II study comparing alternate-day oral therapy using S-1 with the standard regimen as a first-line treatment for patients with locally advanced and metastatic pancreatic cancer: PAN-01 study.

Masayuki Sho[1], Atsushi Shimizu[2], Hiroaki Yanagimoto[3], Shoji Nakamori[4], Takuji Okusaka[5], Hiroshi Ishii[6], Masayuki Kitano[7], Kazuya Sugimori[8], Hiroyuki Maguchi[9], Shinichi Ohkawa[10], Hiroshi Imaoka[11], Daisuke Hashimoto[12], Kazuki Ueda[13], Hiroko Nebiki[14], Tatsuya Nagakawa[15], Hiroyuki Isayama[16], Yasuhiro Hagiwara[17], Yasuo Ohashi[18], Hiroki Yamaue[2]

[1]Department of Surgery, Nara Medical University, Kashihara, Japan; [2]Second Department of Surgery, Wakayama Medical University, Wakayama, Japan; [3]Department of Surgery, Kansai Medical University, Hirakata, Japan; [4]Department of Hepatobiliary and Pancreatic Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; [5]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan; [6]Clinical Research Center, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [7]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan; [8]Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan; [9]Center for Gastroenterology, Teine Keijinkai Hospital, Sapporo, Japan; [10]Division of Hepatobiliary and Pancreatic Oncology, Kanagawa Cancer Center, Yokohama, Japan; [11]Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan; [12]Department of Gastroenterological Surgery, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; [13]Second Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan; [14]Department of Gastroenterology, Osaka City General Hospital, Osaka, Japan; [15]Second Department of Gastroenterology, Hokkaido P.W.F.A.C. Sapporo-Kosei General Hospital, Hokkaido, Japan; [16]Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [17]Department of Biostatistics, Division of Health Sciences and Nursing, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [18]Department of Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo, Japan.

Comprehensive Support Project

Background

- S-1 is an active agent for the treatment of pancreatic cancer (PC). GEST study has previously shown the noninferiority of S-1 to gemcitabine in advanced PC.
- The standard regimen of 4 weeks of administration followed by 2 weeks of rest frequently causes adverse effects.
- To induce the effect of S-1 while reducing toxicity, alternate-day administration may be a treatment option.

Study design

Non-inferiority

Patients with unresectable PC (N=190) → R → 1 : 2

Arm A
Standard daily administration
4-wks daily followed by 2-wks rest

Arm B
Alternate-day administration
4 days a week

Stratification factors
- Institution
- Locally advanced (LAPC) or Metastatic (MPC)

Study aim

- To clarify the efficacy and toxicity of alternate-day administration of S-1 compared to the standard regimen for advanced PC.

- Primary endpoint: Overall Survival (OS)
- Secondary endpoints: Progression-free Survival (PFS), Time to Treatment Failure (TTF), Response rate (RR), Adverse Events (AEs), Quality of Life (EQ-5D, EORTC-QLQ-C30)

Key eligibility criteria

- Pathologically confirmed unresectable PC
- Aged between 20 and 79 years
- PS 0 or 1 (ECOG)
- No prior chemotherapy/radiotherapy

Statistics

180 patients required
- Alpha error: 0.05, Power: 80%
- Non-inferiority threshold HR: 1.33

Non-inferiority was considered to be shown if Bayesian posterior probability of HR < 1.15 was at least 90% with non-informative prior
- 95% credible interval was also calculated for HR

CONSORT diagram

Patients enrolled (N=190)
Arm A (Standard, N=65) Arm B (Alternate-day, N=125)

Eligible (N=188)
Arm A (N=64) Arm B (N=124)

Ineligible (N=2)
Arm A (N=1) Arm B (N=1)

Full Analysis Set (N=185)
Arm A (N=64) Arm B (N=121)

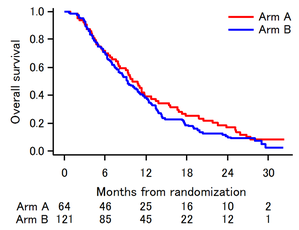
No treatment (N=3)
Arm B (N=3)

- From 31 institutions
- Enrollment period: Aug 2012 – Aug 2013
- Median follow-up time: 9.5 months
- Number of death events: 169

Patient characteristics

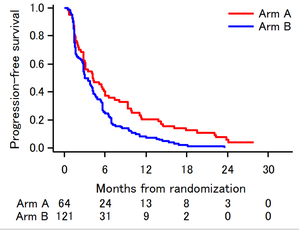
	Arm A (N=64)	Arm B (N=121)	*P* value
Age: Median (range)	68 (46-78)	66 (40-79)	0.275
Gender: M/F	35/29	72/49	0.528
BMI	20.8	21.2	0.797
LAPC/MPC	15/49	28/93	0.964
PS: 0/1	43/21	77/44	0.630

Survival analysis



Median OS
Standard (A) 10.4 M
Alternate (B) 9.4 M

HR=1.19 (95%CI: 0.86-1.64)
Probability of HR < 1.15: 42.5%



Median PFS
Standard (A) 4.2 M
Alternate (B) 3.0 M

HR=1.65 (95%CI: 1.20-2.29)
Probability of HR < 1.15: 1.4%

Response	CR	PR	SD	PD
Arm A	1(2%)	8(13%)	35(56%)	18(29%)
Arm B	0(0%)	12(10%)	64(54%)	43(36%)

Mantel trend test P=0.31

Median TTF
Arm A: 3.0 M (2.0-4.2)
Arm B: 3.0 M (2.4-3.8)

Adverse events

	Arm A (N=65)		Arm B (N=122)		P_{trend} value
	Any	≧ G3	Any	≧ G3	
Anorexia	38 (59%)	7 (11%)	61 (50%)	5 (4%)	0.04
Fatigue	39 (60%)	3 (5%)	52 (43%)	2 (2%)	0.02
Pigmentation	16 (25%)	-	9 (7%)	-	<0.001
Pneumonitis	5 (8%)	1 (2%)	2 (2%)	0 (0%)	0.03

Summary

- PAN-01 did not show the noninferiority of alternate-day administration to standard regimen in overall survival.
  Median OS: 9.4 M vs 10.4 M (HR, 1.19; 95% CI, 0.86-1.64).
- PAN-01 demonstrated that alternate-day administration was significantly worse than standard regimen in tumor progression .
  Median PFS: 3.0 M vs 4.2 M (HR, 1.65; 95% CI, 1.20-2.29).
- Anorexia, Fatigue, Pigmentation, and Pneumonitis were more common in standard regimen than alternate-day administration .

Conclusion

- This study failed to demonstrate the noninferiority of alternate-day administration of S-1 to standard regimen as a first-line chemotherapy in unresectable pancreatic cancer.

Acknowledgement

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Masayuki Sho, MD., Ph.D., email: m-sho@naramed-u.ac.jp,

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