Randomized phase II trial of S-1 plus irinotecan versus S-1 plus paclitaxel as first-line treatment for advanced gastric cancer (OGSG0402)

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I have no relevant relationships to disclose

Background (1)

- JCOG 9205

(Ohtsu A et al; J Clin Oncol 21:54-59, 2003)

5FU alone as reference arm

	5FU	5FU + CDDP	UFT + MMC
No. of pts	105	105	70
Response rate	11%	34%	9%
Median PFS (M)	1.9	3.9	2.4
MST (M)	7.1	7.3	6.0

- JCOG 9912

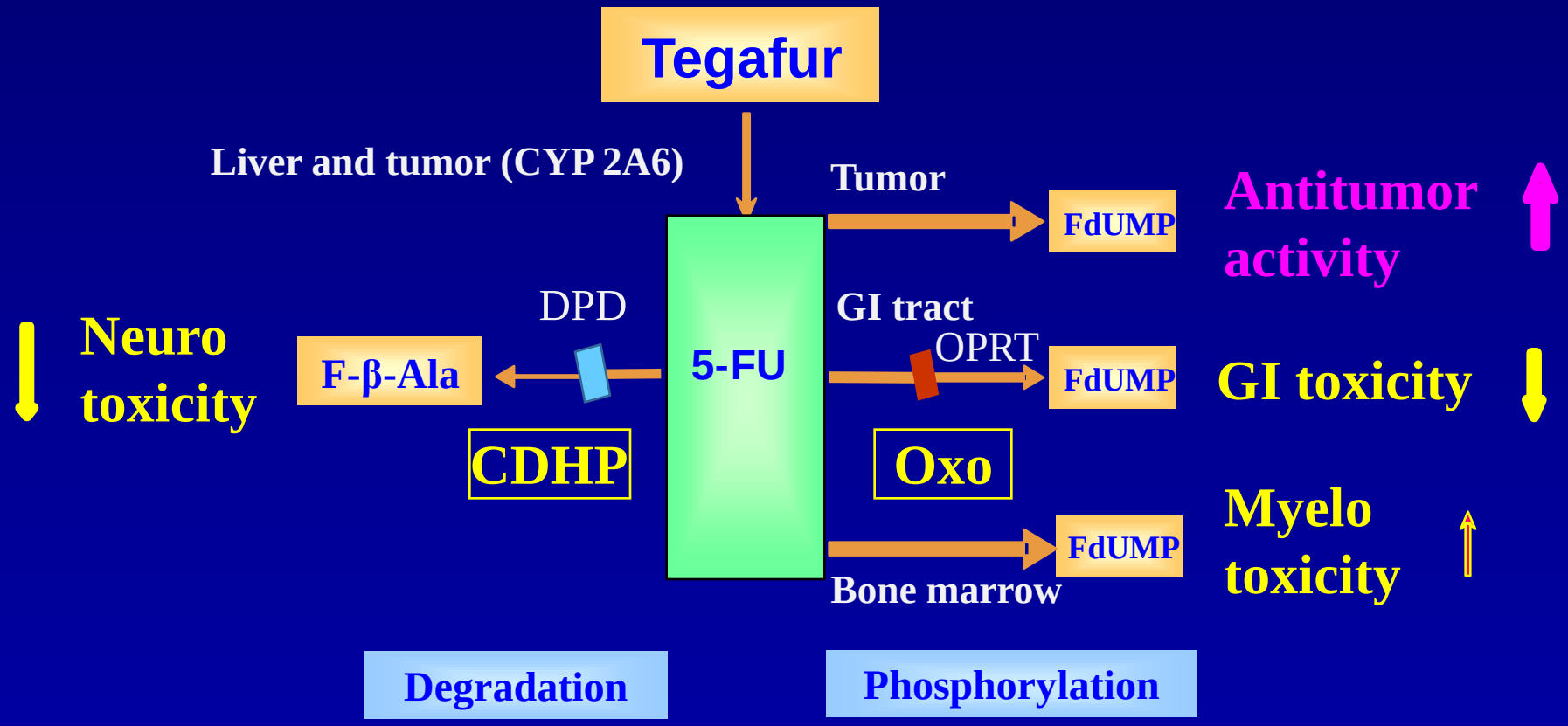
(Boku N et al; ASCO 2007; LBA 4513)

S-1's non-inferiority to 5FU

	5FU	S-1	CPT + CDDP
No. of pts	234	234	236
Response rate	9%	28%	38%
PFS (M)	2.9	4.2	4.8
MST (M)	10.8	11.4	12.3

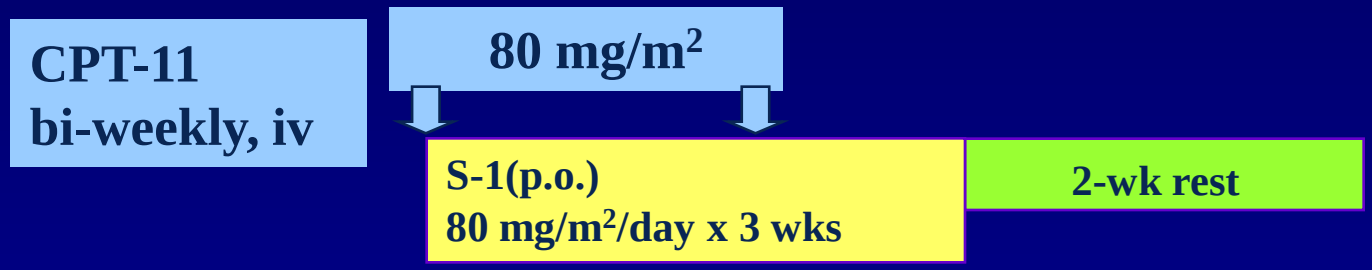
Background (2): S-1

– S-1 is an oral agent containing tegafur, gimeracil (CDHP) and oteracil potassium (Oxo) at a molar ratio of 1:0.4:1.



Background (3a)

- Phase I/II study of S1 plus irinotecan (OGSG 0002)



<Efficacy>

Response rate	47.8 (27.4-68.2) %
1-year survival	52.9 %
MST	394 days

Standard dose of S-1

Body surface area	Daily dose (equivalent to tegafur)
< 1.25m^2	40mg x 2
1.25 - < 1.50m^2	50mg x 2
1.50m^2 ≤	60mg x 2

<Adverse events> (Grade 3 or higher)

Hematological toxicity		Non-hematological toxicity	
Leukopenia	4.3 %	Diarrhea	4.3 %
Neutropenia	8.7 %	Anorexia	4.3 %
Anemia	8.7 %	Nausea/Vomiting	4.3 %

(Takiuchi H et al; Jpn J Clin Oncol 35: 520-5, 2005. Uedo N et al; Oncology 73: 65-71, 2007.)

Background (3b)

- Phase I/II study of S1 plus paclitaxel (OGSG 0105)

Paclitaxel weekly, iv

50 mg/m^2

S-1(p.o.) 80 mg/m^2/day x 2 wks

1-wk rest

<Efficacy>

Response rate	48.3 (30.1-66.5) %
1-year survival	57.6 %
MST	13.9 M

Standard dose of S-1

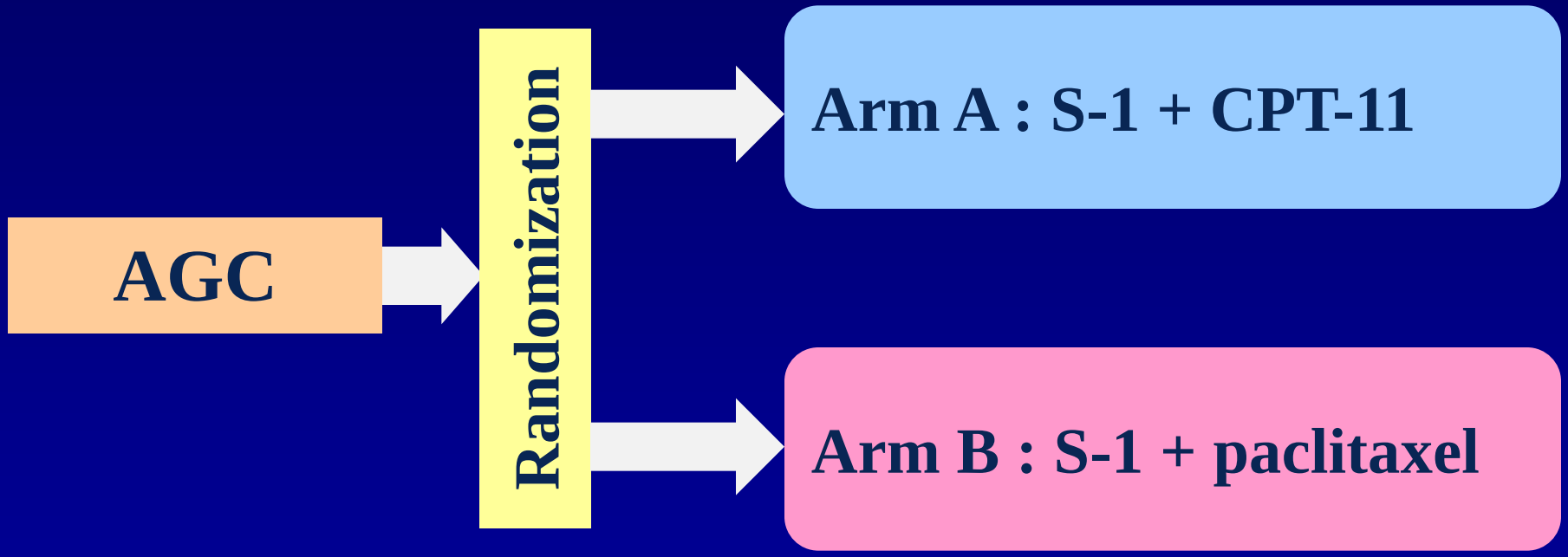
Body surface area	Daily dose (equivalent to tegafur)
< 1.25m^2	40mg x 2
1.25 - < 1.50m^2	50mg x 2
1.50m^2 ≤	60mg x 2

<Adverse events> (Grade 3 or higher)

Hematological toxicity		Non-hematological toxicity	
Leukopenia	0 %	Diarrhea	3.4 %
Neutropenia	3.4 %	Anorexia	0 %
Anemia	0 %	Nausea/Vomiting	0 %

(Fujitani K et al; Oncology 69: 414-20, 2005. Narahara H et al; Oncology 74: 37-41, 2008.)

Study design



Factors adjusted for allocation

(1) Unresectable advanced / recurrent with adjuvant chemotherapy / recurrent without adjuvant chemotherapy

(2) PS 0/1/2

Objectives

- To evaluate the efficacy and safety of S-1 plus irinotecan and S-1 plus paclitaxel as first-line treatments against AGC with an aim of choosing the optimal regimen for a subsequent phase III trial

- Primary endpoint
  - Overall response rate (ORR)
- Secondary endpoints
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Safety

Statistical considerations

Sample size: 50 pts in each arm

determined to reject the ORR of 30% under the expectation of 50% with a power of 80% and a two-sided α of 5%

Planned accrual & follow-up:

2 years & 3 years

Actual accrual: 102 pts from 13 institutions

12/15/2005 - 11/14/2007

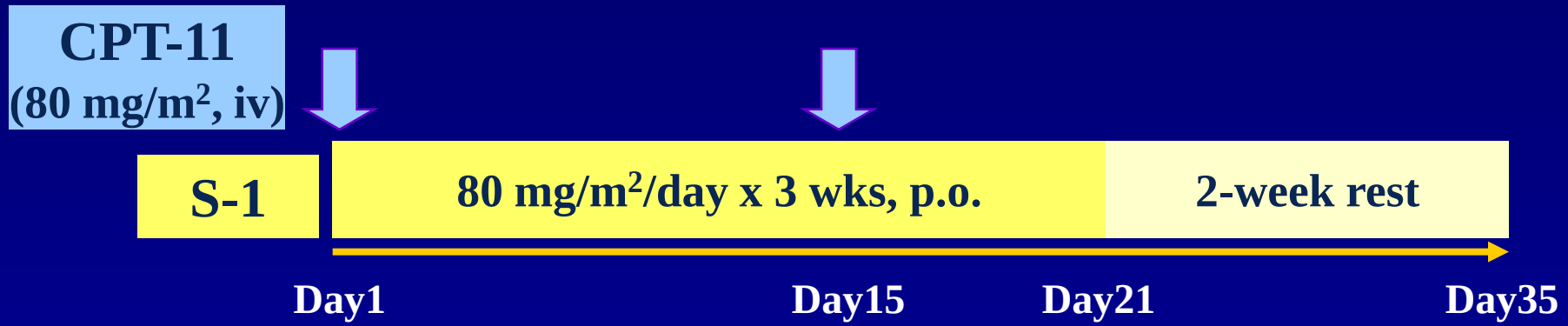
Latest analysis: 12/20/2008

Eligibility criteria

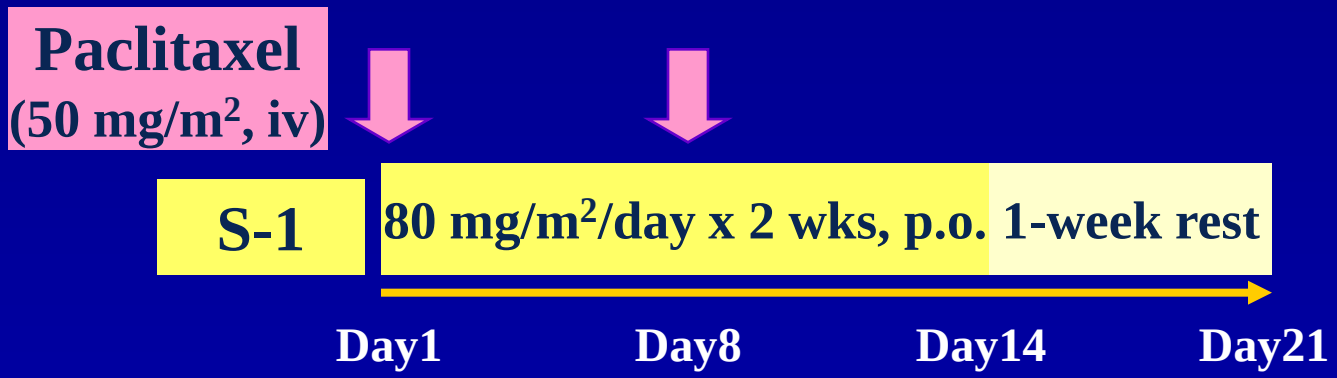
- Histologically proven unresectable advanced or recurrent gastric cancer with measurable lesions
- No prior chemotherapy except adjuvant CTX completed 4 weeks or more before entry
- PS of 2 or less on the ECOG scale
- Aged 20-75 years
- Tolerance of oral feeding
- Life expectancy of at least 3 months
- Adequate organ function
- Written informed consent

Treatment schedule

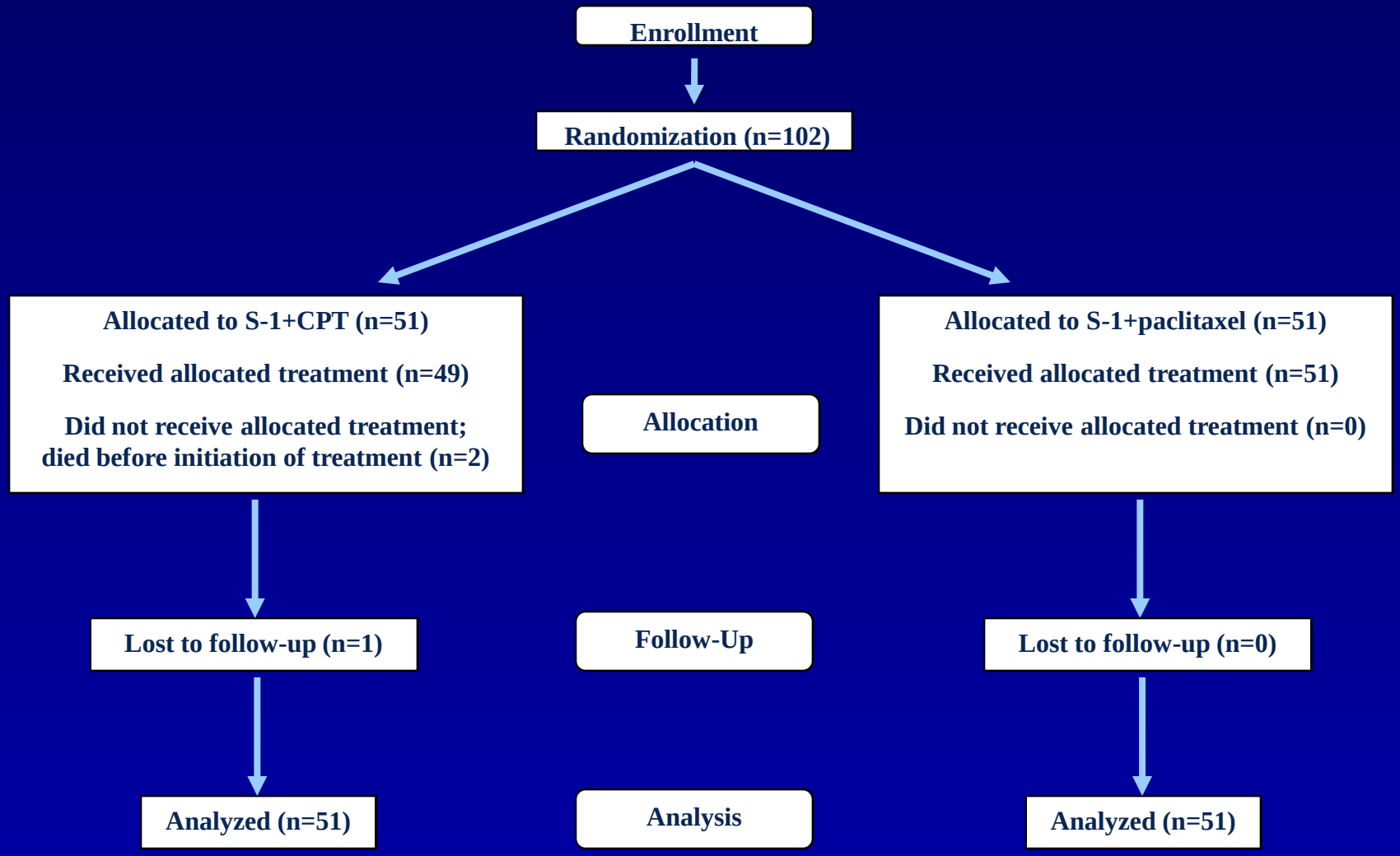
- **Arm A: 5 weeks / course**



- **Arm B: 3 weeks / course**



Patient disposition



Patient characteristics

	S-1+CPT (n=51)	S-1+paclitaxel (n=51)
Gender (male/female)	38/13	38/13
Age median (range)	64 (25-75)	62 (30-75)
PS (0/1/2)	41/8/2	39/12/0
Histology (intestinal/diffuse/others)	28/22/1	33/16/2
Primary lesions (+/-)	37/14	37/14
Advanced/recurrent	40/11	40/11
Recurrent pts after adjuvant chemotherapy (+/-)	3/8	1/10

Number of treatment courses

	No. of pts	Total no. of courses	Median (range)
S-1+CPT	48	237	4 (1-16)
S-1+ paclitaxel	51	319	5 (1-40)

Reasons for discontinuation (S-1+CPT/S-1+paclitaxel) :

- Progressive disease 73 (35/38) pts
- Adverse events 11 (4/7) pts
- Patient withdrawal 5 (3/2) pts
- Doctor's decision 1 (1/0) pt
- Still on treatment 1 (0/1) pt
- Others 8 (5/3) pts

Anti-tumor effect (RECIST)

	No. of pts	Response					Response rate (%) (95%CI)	Chi-square test (p-value)
		CR	PR	SD	PD	NE		
S-1+CPT	51	2	15	17	8	9	33.3% (20.8-47.9)	0.841
S-1+ paclitaxel	51	1	15	18	11	6	31.4% (19.1-45.9)	

- ORR was determined by extra-mural review
- Tumor lesions were assessed every other month after initiation of treatment
- Null hypotheses (ORR≤30%) were not rejected in both arms (S-1+CPT-11: p=0.65, S-1+paclitaxel: p=0.88)

Anti-tumor effect (best ORR)

	No. of pts	Response					Response rate (%) (95%CI)	Chi-square test (p-value)
		CR	PR	SD	PD	NE		
S-1+CPT	51	2	17	21	6	5	37.3% (24.1-51.9)	1.000
S-1+ paclitaxel	51	2	16	22	6	5	35.3% (22.4-49.9)	

- ORR was determined by extra-mural review
- For assessment of best ORR, determination of CR or PR did not require confirmation performed at least 4 weeks later
- Tumor lesions were assessed every other month after initiation of treatment

Adverse events：hematological toxicity

	S-1+CPT(n=48) G3/4 (≥G3)	S-1+paclitaxel (n=51) G3/4 (≥G3)
Leukopenia	7/0 (15%)	0/0 (0%)
Neutropenia	8/1 (19%)	1/0 (2%)
Anemia	6/0 (13%)	2/1 (6%)
Thrombocytopenia	0/0 (0%)	0/1 (2%)
Infection/febrile neutropenia	1/0 (2%)	0/0 (0%)

NCI-CTC version 2.0.

＊ No treatment-related deaths (TRDs) occurred during the study

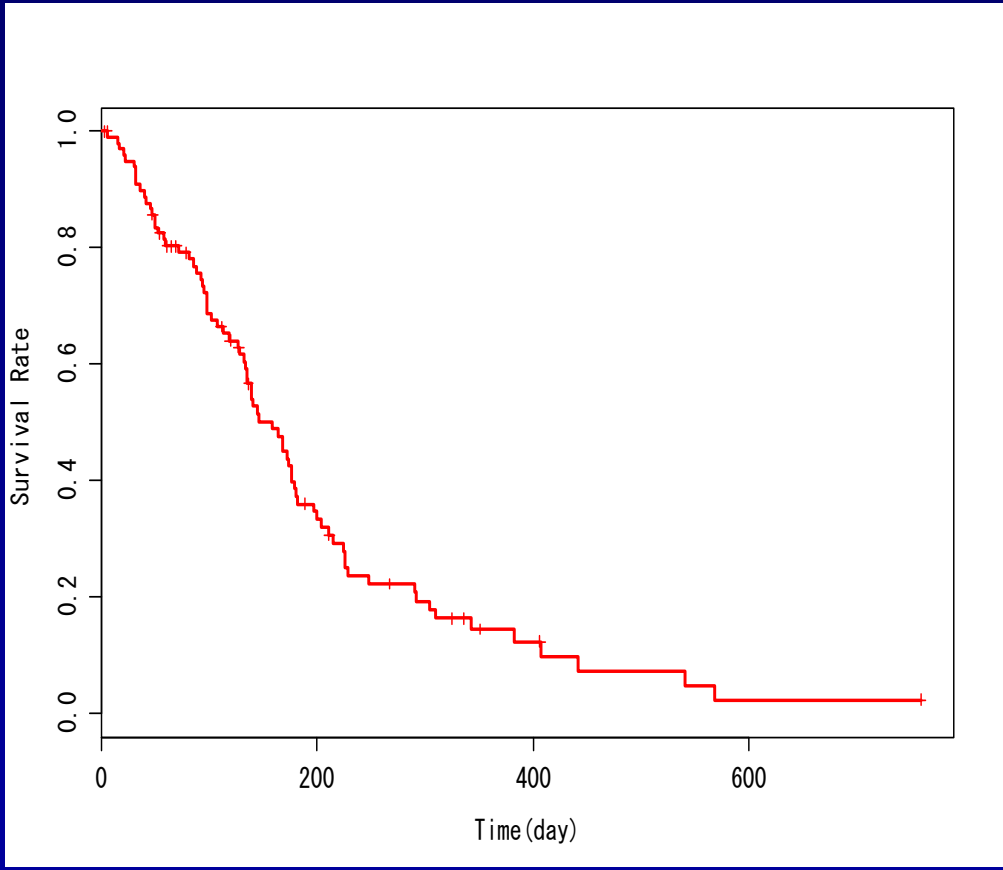
Adverse events：non-hematological toxicity

	S-1+CPT (n=48) G3/4 (≥G3)	S-1+paclitaxel (n=51) G3/4 (≥G3)
Diarrhea	3/0 (6%)	1/0 (2%)
Nausea/Vomiting	2/0 (4%)	3/0 (6%)
Fatigue	2/0 (4%)	1/0 (2%)
Stomatitis	1/0 (2%)	0/0 (0%)
Anorexia	6/0 (13%)	5/0 (10%)
Creatinine	0/0 (0%)	0/0 (0%)
T-Bil	1/0 (2%)	1/0 (2%)
AST (GOT)	0/0 (0%)	1/0 (2%)
ALT (GPT)	0/0 (0%)	2/0 (4%)

NCI-CTC version 2.0.

＊ One grade 4 cerebral infarction occurred 7 days after the completion of the 3rd course of treatment in the S-1 + CPT arm

Integrated PFS of both arms



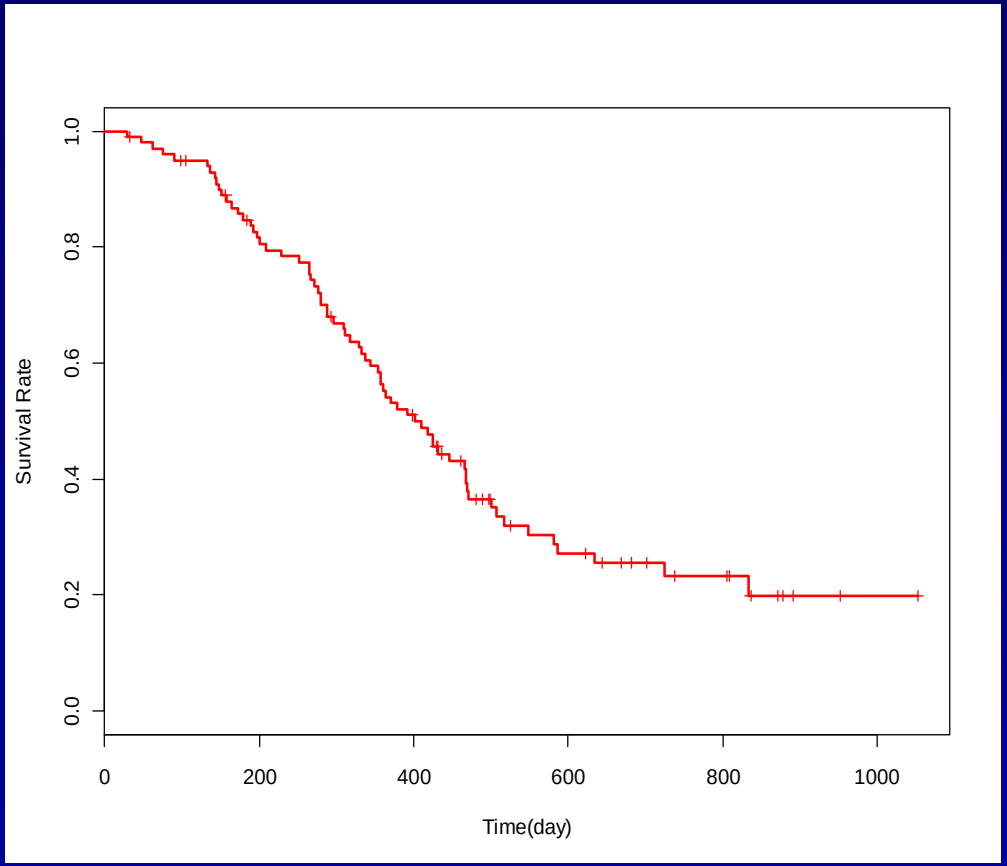
PFS (median) = 158 days
(95% CI, 133 - 180 days)

1-year PFS = 13.4 %
(95% CI, 7.3 - 24.5 %)

Follow-up is ongoing

Events	**75 pts**
Censors	**26 pts**
Median follow-up time	**128 days**

Integrated OS of both arms



OS (median) = 402 days
(95% CI, 354 - 470 days)

1-year OS = 54.0 %
(95% CI, 44.9 – 65.0 %)

Follow-up is ongoing

Events	**68 pts**
Censors	**33 pts**
Median follow-up time	**370 days**

Summary

- ORR was 33.3% for the S-1+CPT arm and 31.4% for the S-1+paclitaxel arm on RECIST, with no significant difference between the two.
- Both arms were well tolerated although grade 3/4 neutropenia (19% vs. 2%) and anemia (13% vs. 6%) were more frequent in the S-1+CPT arm.
- The integrated median PFS and OS of both arms was 158 days and 402 days, respectively.

Discussion

Study	Regimen	Pts	Best ORR (%)	PFS (M)	OS (M)	p-value (OS)
OGSG0402	S-1+CPT	51	37.3	5.2	13.2	-
	S-1+paclitaxel	51	35.3			
GC0301/TOP-002[1] (2008)	S-1+CPT	155	41.5	5.0	12.8	0.233
	S-1	160	26.9	3.4	10.5	
SPIRITS[2] (2007)	S-1+CDDP	148	54.0	6.0	13.0	0.037
	S-1	150	31.1	4.0	11.0	
JCOG 9912[3] (2007)	S-1	234	28	4.2	11.4	0.034 (1-sided)
	5FU	234	9	2.9	10.8	
	CPT+CDDP	236	38	4.8	12.3	0.055

1) Imamura H et al; ASCO-GI 2008; LBA 5
2) Narahara H et al; ASCO 2007; LBA4514
3) Boku N et al; ASCO 2007; LBA4513

Conclusions

- Both S-1+CPT and S-1+paclitaxel were effective and well tolerated in patients with AGC.
- Predicted ORR was not achieved by either regimen.
- Both regimens hold a promise of becoming a standard first line treatment for AGC in terms of overall survival.
- Study follow-up is ongoing and the final analysis of survival will be performed on November 2010.

Participating Institutions

Osaka Medical Center for Cancer and Cardiovascular Diseases

Sakai Municipal Hospital

National Hospital Organization Osaka National Hospital

Minoh City Hospital

Osaka Medical College Hospital

Kinki University School of Medicine

NTT West Osaka Hospital

Kansai Medical University Takii Hospital

Osaka City University Hospital

Kinki Central Hospital of Mutual Aid Association of Public School Teachers

Kumamoto Regional Medical Center

Osaka Seamen's Insurance Hospital

Osaka Saiseikai-Nakatsu Hospital

- Consulting statistician : T. Shimokawa, Yamanashi University

Abstract

Introduction: S1-based regimens are commonly used for advanced gastric cancer (AGC) in Japan. Both S1 plus irinotecan (SI) and S1 plus paclitaxel (SP) have shown an overall response rate (ORR) of 48% in respective phase II trials. This randomized phase II trial evaluated these two S1-based regimens in terms of ORR as first-line treatment for AGC in order to choose the optimal regimen for a phase III trial.

Methods: Patients with previously untreated, locally advanced and/or metastatic measurable gastric adenocarcinoma, a performance status of ≤ 2, and adequate organ function were randomly assigned to receive S-1 (80 mg/m^2/day) for 21 consecutive days plus irinotecan (80 mg/m^2) on days 1 and 15, repeated every 5 weeks for the SI arm, or the same dose of S1 for 14 consecutive days plus paclitaxel (50 mg/m^2) on days 1 and day 8, repeated every 3 weeks for the SP arm. Both treatments were continued until disease progression or intolerable toxicity occurred. Study endpoints included ORR as primary, progression free survival (PFS), overall survival (OS), and toxicity.

Results: One hundred and two patients were enrolled. The median number of cycles administered was 4 (range, 1-16) for the SI arm, and 5 (range, 1-40) for the SP arm. ORR on RECIST was 33.3% (95% CI, 20.8% to 47.9%) for the SI arm (n = 51) and 31.4% (95% CI, 19.1% to 45.9%) for the SP arm (n = 50), with no significant difference between the two. The best ORR was 37.3% (95% CI, 24.1% to 51.9%) for the SI arm and 35.3% (95% CI, 22.4% to 49.9%) for the SP arm. No treatment-related deaths occurred during the study. Both arms were well tolerated although grade 3/4 neutropenia (19% vs. 2%) and anemia (13% vs. 6%) were more frequent in the S-1/CPT arm. The integrated PFS and MST of both arms was 158 days and 402 days, respectively.

Conclusions: Both regimens were effective and well tolerated in patients with AGC. Although predicted ORR was not achieved by either regimen, both regimens hold a promise of becoming a standard first line treatment for AGC in terms of OS. Study follow-up is ongoing and the final analysis of survival will be performed on November 2010.