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

ASCO Annual '10 Meeting

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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

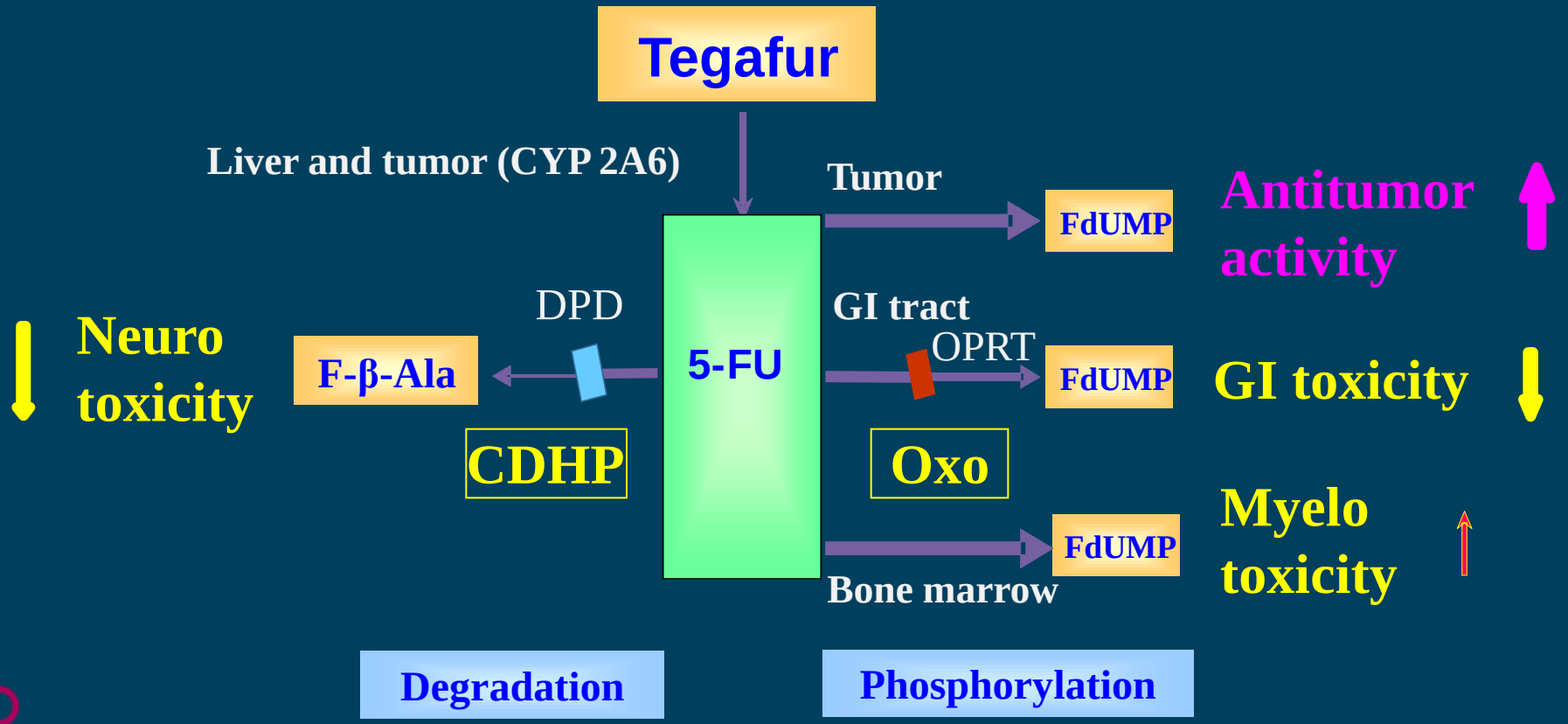
(Boku N et al; ASCO 2007; LBA 4513)

S-1's non-inferiority to 5FU

	5FU	S-1	CPT-11 + 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 S-1 plus irinotecan (OGSG 0002)

CPT-11
bi-weekly, i.v.

80 mg/m^2

S-1(p.o.)
80 mg/m^2/day x 3 wks

2-wks rest

<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 S-1 plus paclitaxel (OGSG 0105)

Paclitaxel weekly, i.v.

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

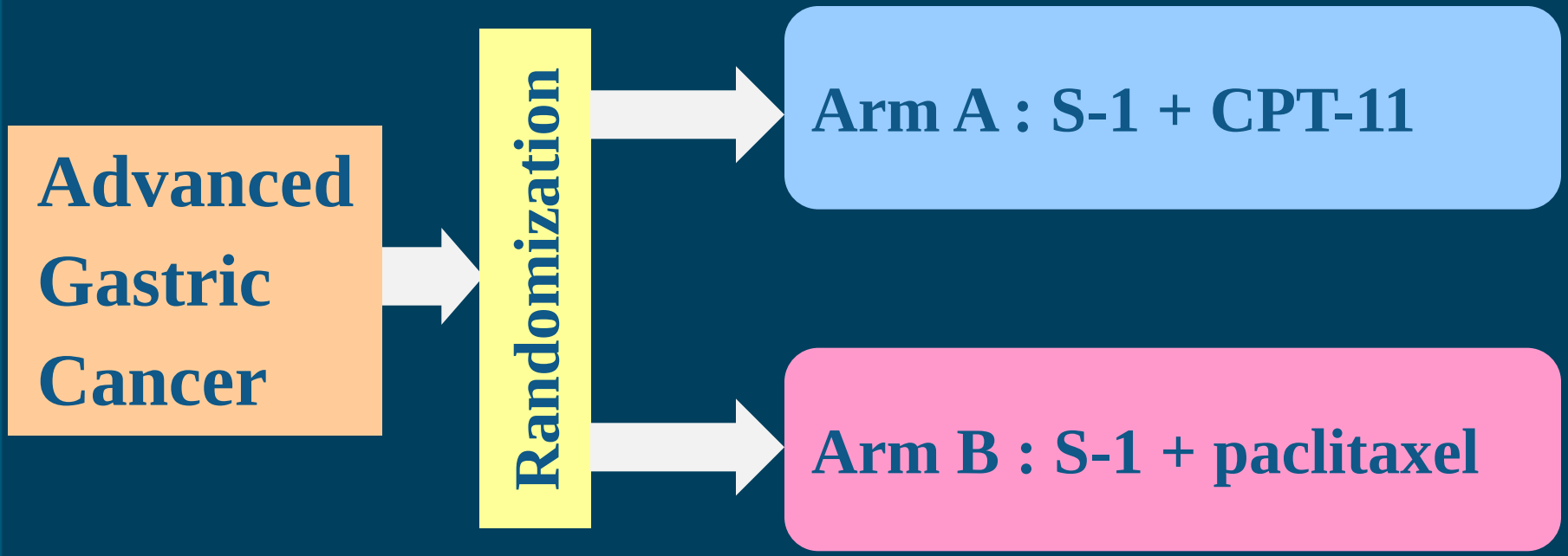
Body surface area	Daily dose (equivalent to tegafur)
< 1.25m^2	40mg x 2
1.25 - < 1.50m^2	50mg x 2
1.50m^2 ≤	60mg x 2

<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

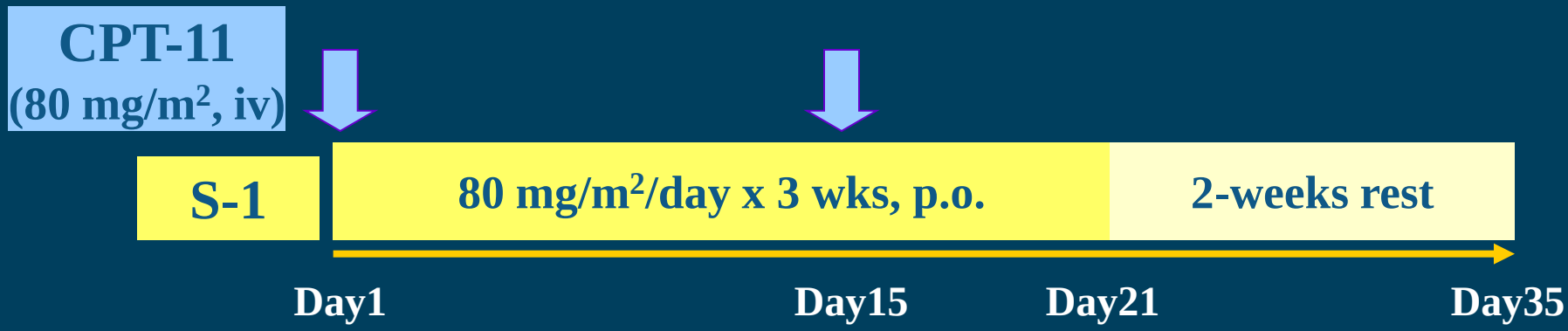
Latest analysis: 1/8/2010

Eligibility criteria

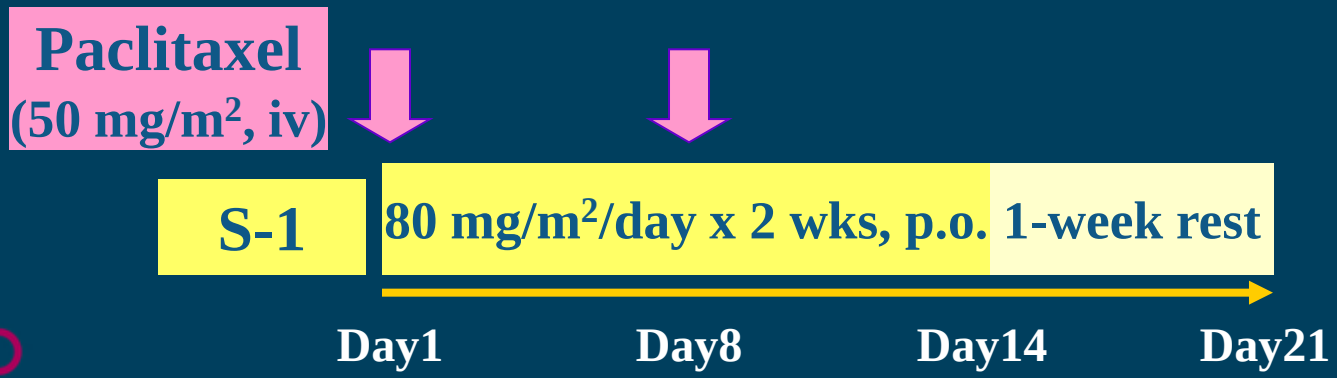
- Histologically proven unresectable advanced or recurrent gastric cancer with measurable lesions
- No prior chemotherapy except adjuvant CTX completed 4 weeks or more before entry
- PS of 2 or less on the ECOG scale
- Aged 20-75 years
- Tolerance of oral feeding
- Life expectancy of at least 3 months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

Treatment schedule

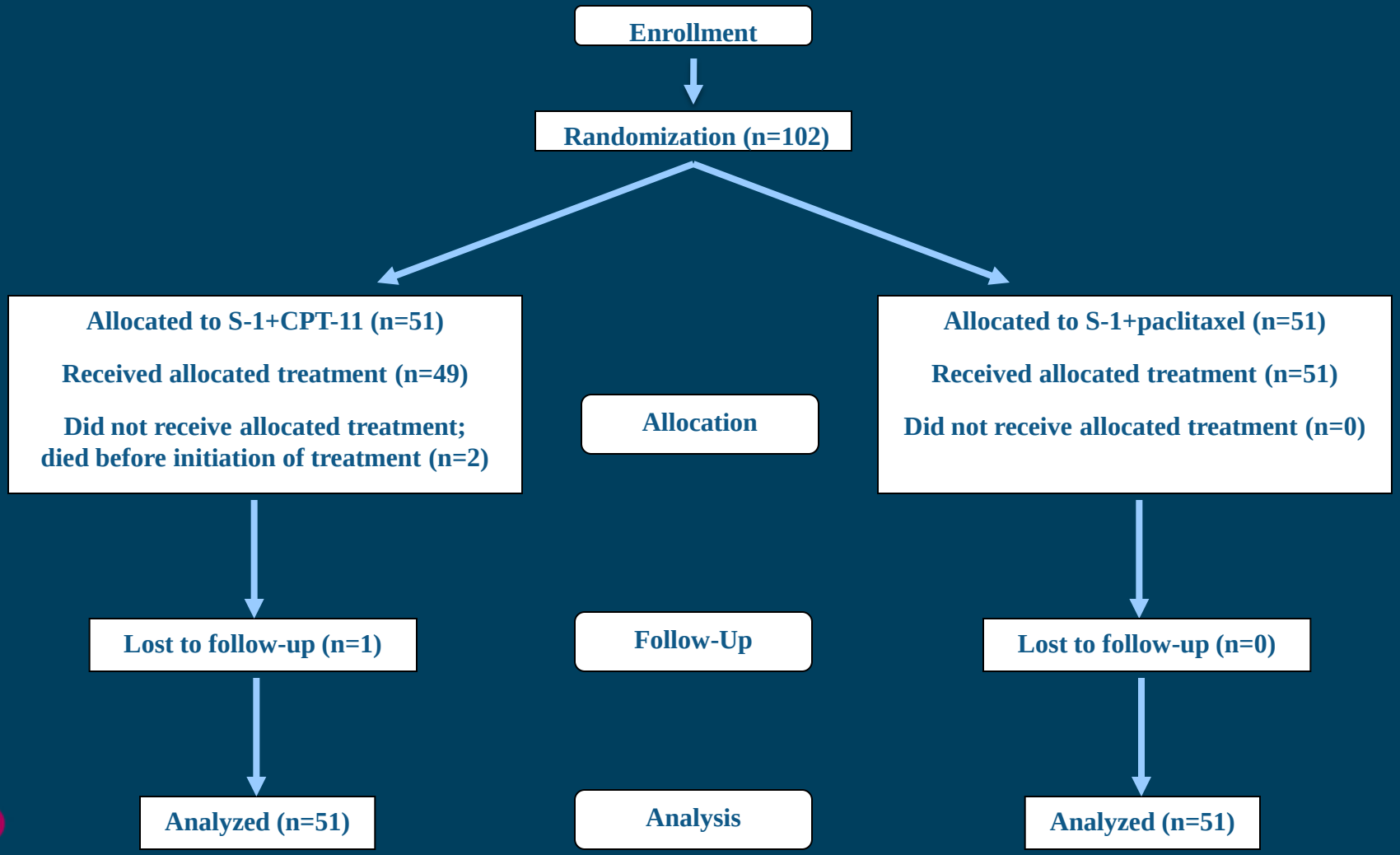
- **Arm A: 5 weeks / course**



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



Patient disposition



Patient characteristics

	S-1+CPT-11 (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-11	48	237	4 (1-16)
S-1+ paclitaxel	51	319	5 (1-40)

Reasons for discontinuation (S-1+CPT-11/S-1+paclitaxel) :

- Progressive disease 70 (33/37) pts
- Adverse events 11 (4/7) pts
- Patient withdrawal 7 (4/3) pts
- Doctor's decision 1 (1/0) 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-11	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-11	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-11(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 3.0.

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

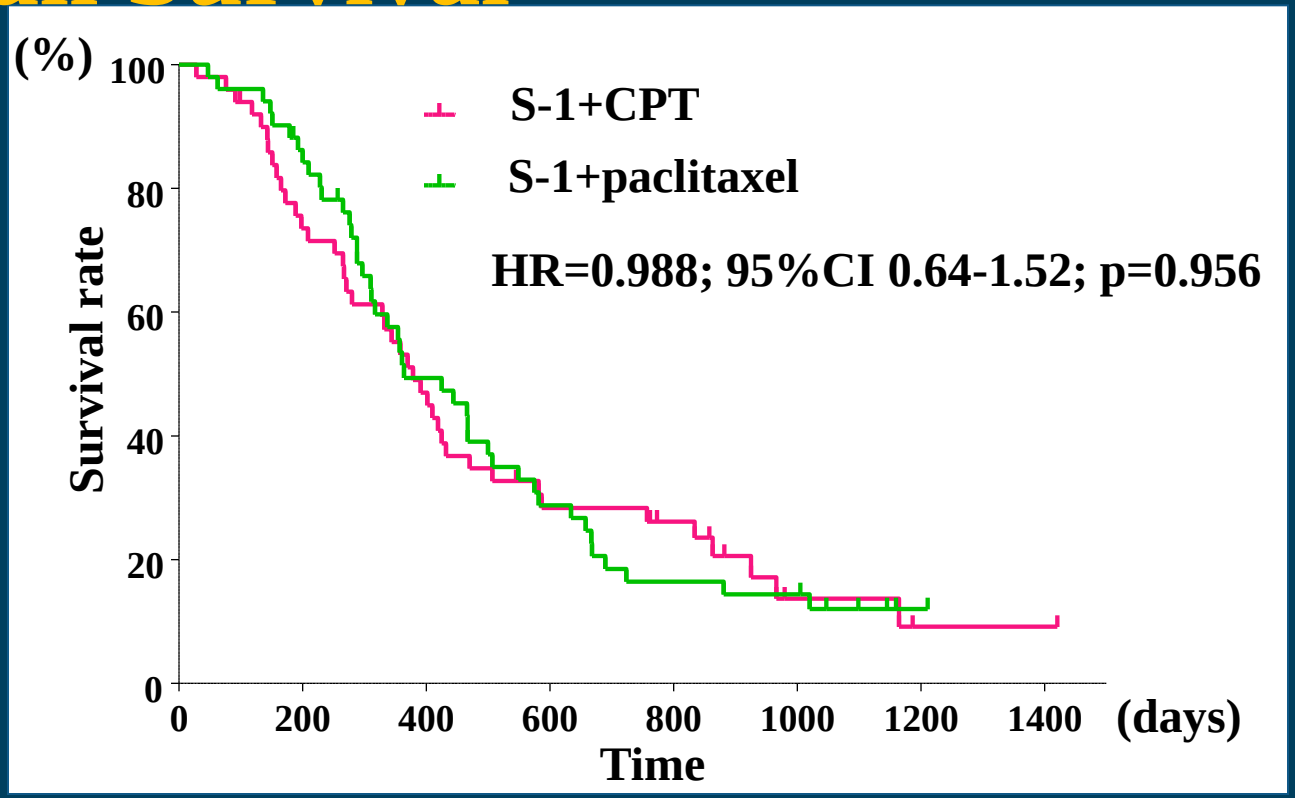
Adverse events : non-hematological toxicity

	S-1+CPT-11 (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 3.0.

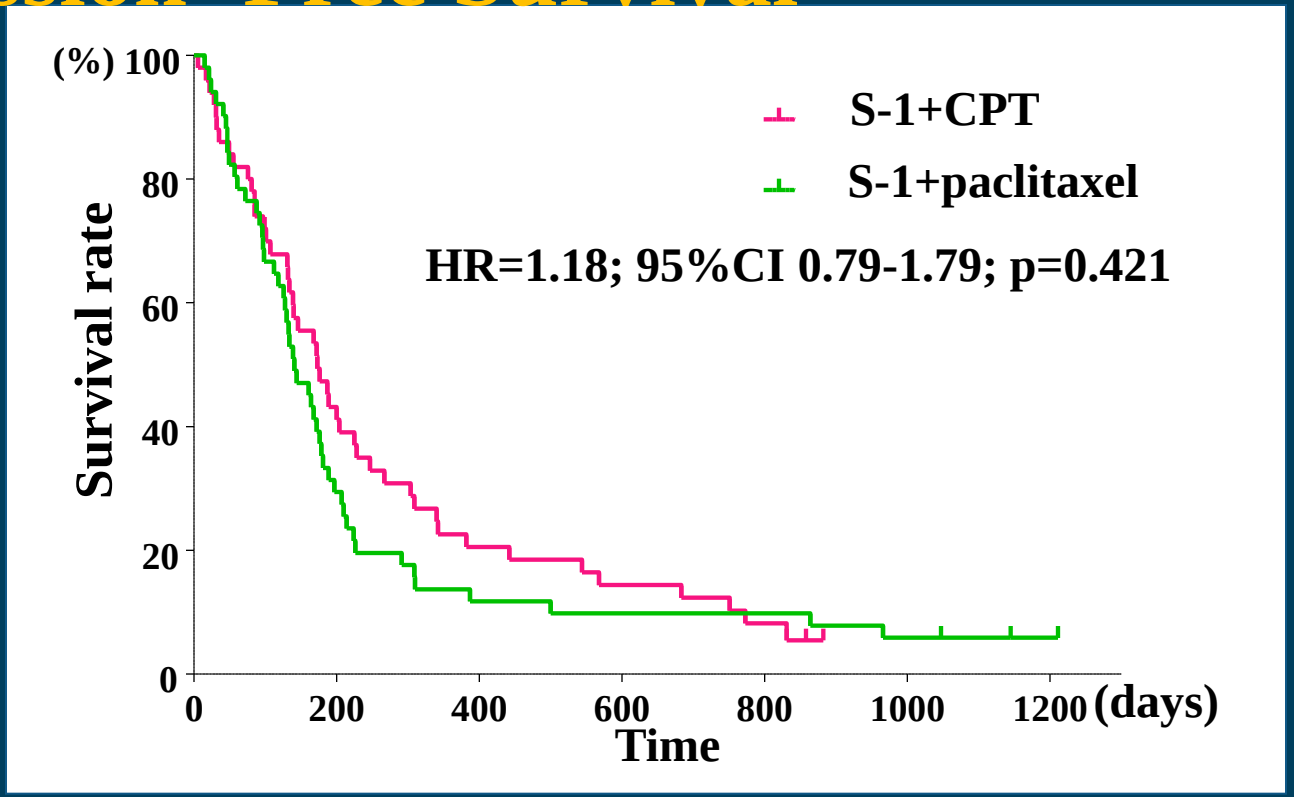
* One grade 4 cerebral infarction occurred 7 days after the completion of the 3rd course of treatment in the S-1 + CPT-11 arm

Overall Survival



	Events	MST (95% CI)	1-year OS (95% CI)
S-1+CPT -11(n=50)	41	379 days (280 – 507 days)	53.1% (40.9 – 69.1 %)
S-1+paclitaxel (n=51)	43	364 days (311 - 549 days)	49.4 % (37.2 – 65.6 %)

Progression- Free Survival



	Events	median PFS (95% CI)	1-year PFS (95% CI)
S-1+CPT-11 (n=50)	46	173 days (134 - 247 days)	22.6 % (13.5 – 38.0 %)
S-1+paclitaxel (n=51)	48	141 days (126 - 181 days)	13.7 % (6.9 – 27.3 %)

Conclusions

- Both S-1+CPT-11 and S-1+paclitaxel were well tolerated in patients with AGC.
- Predicted ORR was not achieved by either regimen.
- Neither of them could demonstrate favorable PFS or OS.
- Either regimen couldn't be optimal for a phase III trial.