Randomized phase II study of CPT-11 versus PTX: +/- S1 in advanced gastric cancer refractory to S1 or S1 + platinum (OGSG 0701)

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Conflict of Interest disclosure slide for representative speakers or investigators

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contributions	☐	
research expenses	☐	
fees of testimony, judgment, comment, etc.	☐	
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lecturer fees	☐	
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contributions	☐	
research expenses	☐	
fees of testimony, judgment, comment, etc.	☐	
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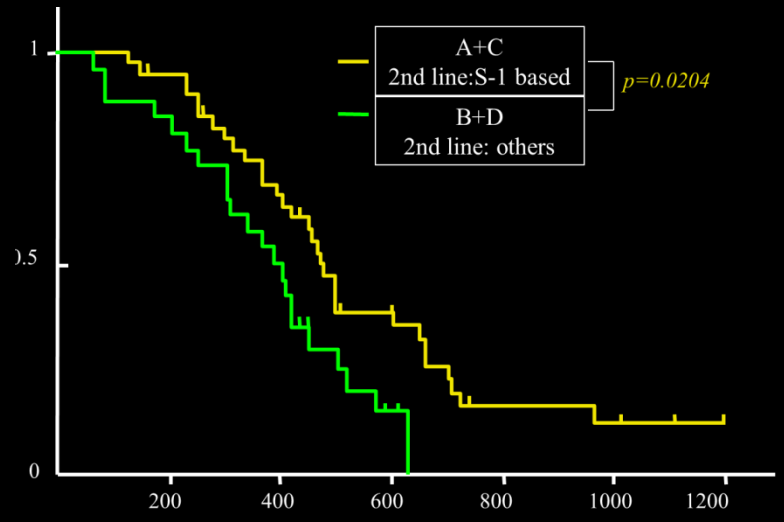
Japanese Society of Medical Oncology

Background

- In Japan, S1 + platinum (SP) is recommended for advanced gastric cancer (AGC) patients as first-line setting[1], and S1 monotherapy is suggested for frail AGC patients or adjuvant setting[2,3].
- However, taxane or CPT-11 were often employed as second-line treatment for the patients who were resistant to S1-containing regimen.
- A retrospective analysis has reported that S1 beyond progression (SBP) extended overall survival as second-line treatment for AGC that was resistant to first-line S1-based chemotherapy[4].



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2. S. Sakuramoto et al. N Engl J Med. 2007 357 1810-20.
3. M. Sasako et al. J Clin Oncol. 2011 29 (33) 4387-93
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OGSG0701 : Study Design

- Advanced gastric cancer
- Refractory to S1 or S1+platinum as first-line
- Adequate oral intake

N=127

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Group A: CPT (n=42)

CPT-11 150 mg/m² day1, q2w

Group B: PTX (n=43)

PTX 80 mg/m², day1, 8, 15, q4w

Group C1: S1+CPT (n=22)

CPT-11 80 mg/m², day1, 15
S1 80 mg/m², day1-21, q5w

Group C2: S1+PTX (n=20)

PTX 50 mg/m², day1, 8
S1 80 mg/m², day1-14, q3w

Stratifications
- Metastatic or recurrent /adjuvant
- PS 0-1/2
- Peritoneal metastasis ＋/ －
- Institution

Objective and Endpoints

Objective

To examine the efficacy and safety comparing CPT-11, PTX, and each combination chemotherapy with S1 refractory to S1 or SP

Endpoints

✓ Primary endpoint
-Overall Survival (OS)

✓ Secondary endpoints
- progression free survival (PFS)
- response rate (RR)
- safety

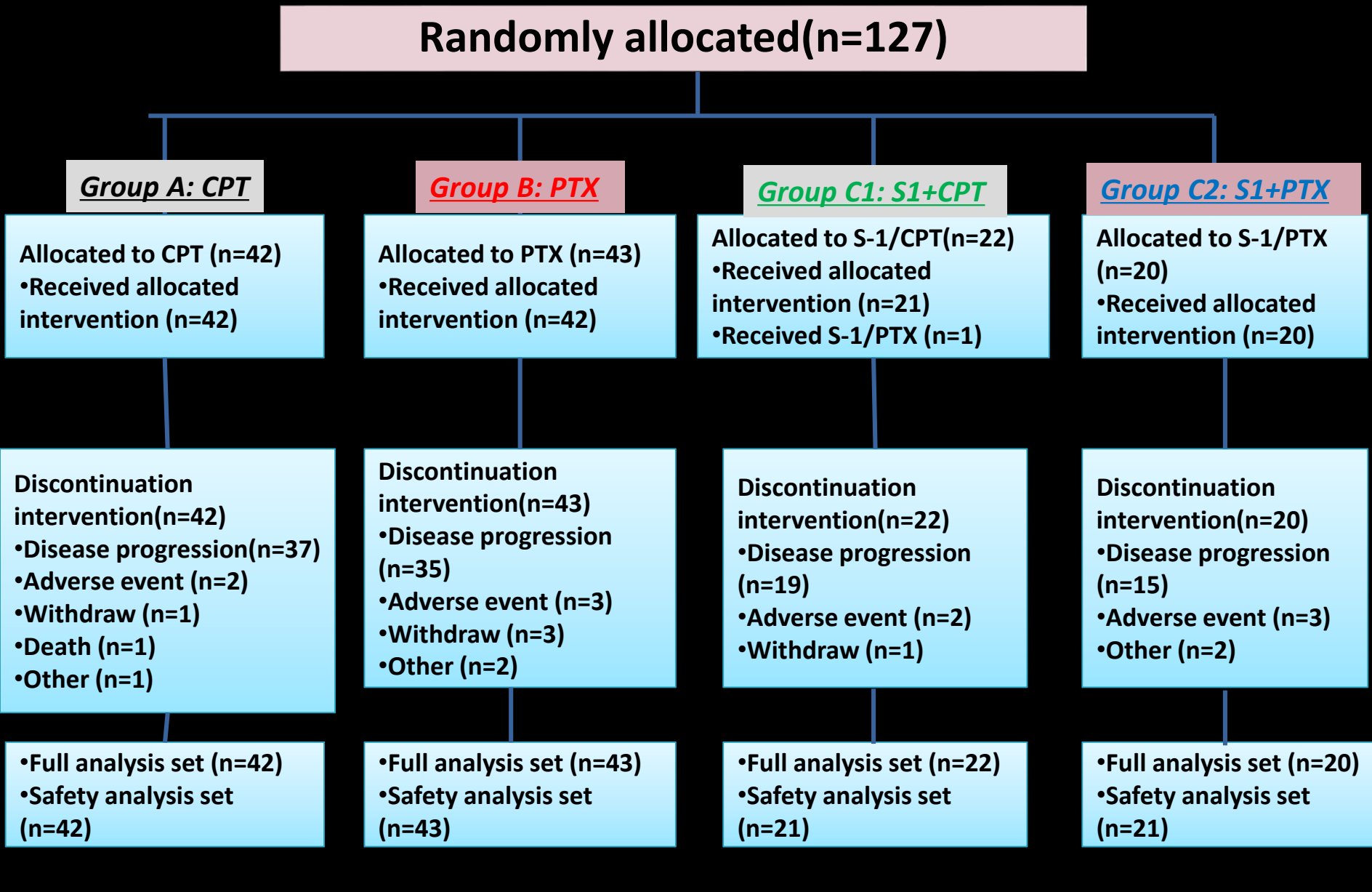
Statistical Considerations

- 2x2 factorial screening design
- Assumed median OS: PTX based (B+C2) 5 months
  CPT based (A+C1) 7 months
- 1-sided α=0.2, a power of β=80%
- Sample size n=100
- Assumed median OS: CPT or PTX (A+B): non-SBP 6 months
  S1 based (C1+C2): SBP 8 months
- 1-sided α=0.2, a power of β=73%
- Sample size n=120
  - ✓ 40 patients/each Group A and Group B,
  - ✓ 20 patients/each Group C1 and Group C2
- Accrual Time: 3 years → 4.5years
- Follow-up Time: 2years → 1 year

Main Inclusion Criteria

- Histologically confirmed gastric cancer
- Disease progression confirmed by imaging technique during first-line chemotherapy with S1 or SP or during adjuvant chemotherapy or within 26 weeks after adjuvant chemotherapy completion with S1
- ECOG performance status 0-2
- Age 20-74
- No severe organ dysfunction
- Written informed consent

Consort Diagram



Patient Characteristics

	Group A CPT (n=42)	Group B PTX (n=43)	Group C1 S1+CPT (n=22)	Group C2 S1+PTX (n=20)
Gender Male/Female	30/12	35/8	15/7	12/8
Age, years Median(range)	65 (44-74)	65 (31-74)	67 (47-73)	63 (37-74)
ECOG PS 0-1/2	42/0	41/2	21/1	20/0
Histology Intestinal/Diffuse	24/18	25/17	11/10	12/8
Prior gastrectomy Yes/No	22/20	21/22	13/9	13/7
Peritoneal metastasis Yes/No	15/27	15/28	7/15	4/16
No. of metastatic sites 0-1/≥2	28/14	31/12	19/3	16/4

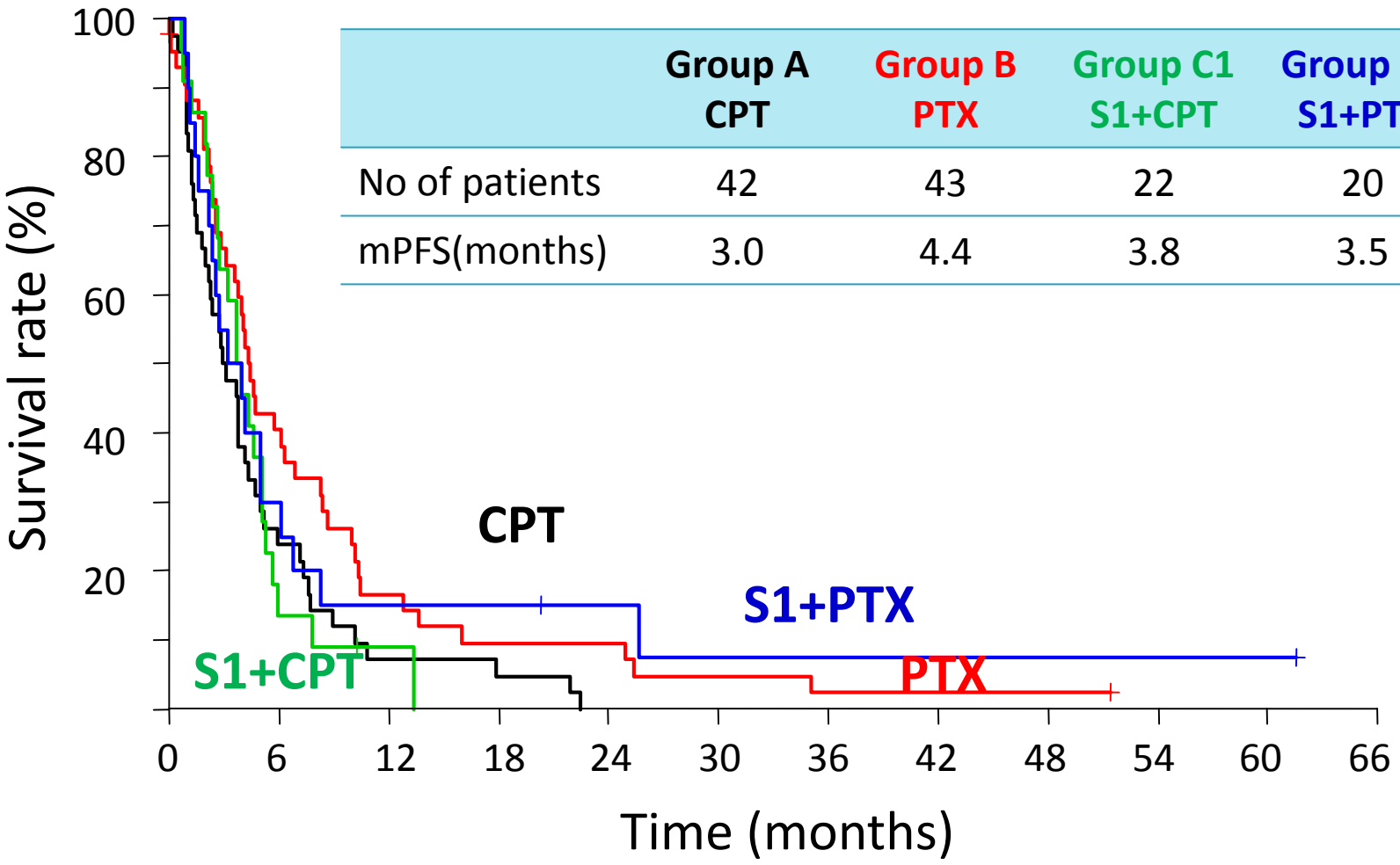
Objective Response Rate

	Group A CPT N = 42	Group B PTX N = 43	Group C1 S1 + CPT N = 22	Group C2 S1 + PTX N = 20
ORR, % (95% CI)	7.1 (1.5-19.5)	16.3(6.8-30.7)	4.5 (0.1-22.8)	5.0 (0.1-24.9)
DCR, % (95% CI)	54.8 (38.7-70.2)	46.5 (31.2-62.3)	59.1 (36.4-79.3)	55.0 (31.5-76.9)

	A+C1 CPT ± S1 N = 64	B+C2 PTX ± S1 N = 63	A+B Non-SBP N = 85	C1+C2 SBP N = 42
ORR, % (95% CI)	4.7 (1.7-15.2)	12.7(5.6-23.5)	11.8 (5.8-20.6)	4.8 (0.6-16.2)
p-value	0.241		0.334	
DCR, % (95% CI)	56.3 (43.3-68.6)	49.2 (36.4-62.1)	50.6 (39.5-61.6)	57.1 (41.0-72.3)
p-value	0.479		0.572	

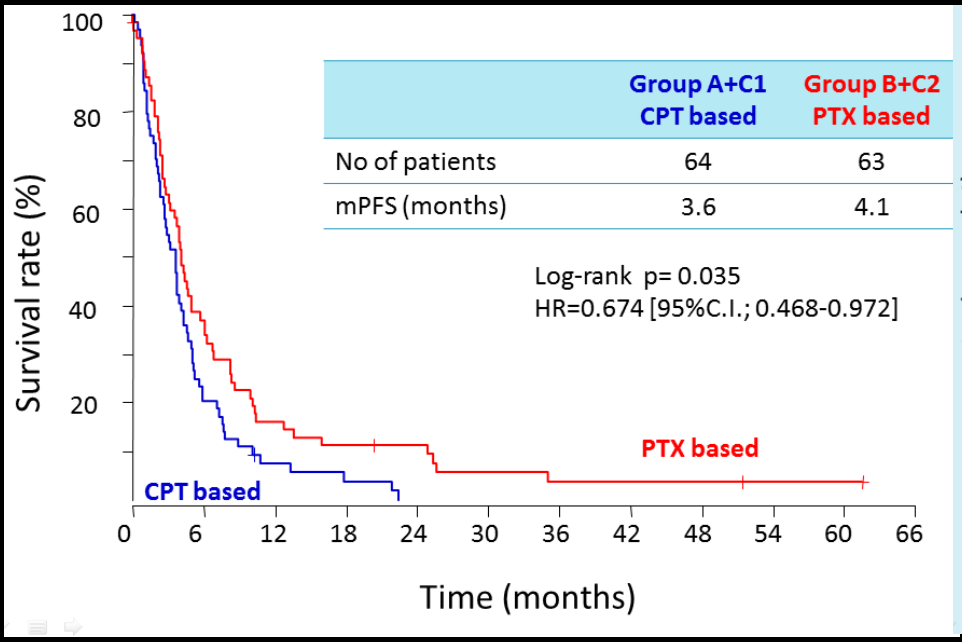
Progression-free Survival

	Group A CPT	Group B PTX	Group C1 S1+CPT	Group C2 S1+PTX
No of patients	42	43	22	20
mPFS(months)	3.0	4.4	3.8	3.5



Progression-free Survival

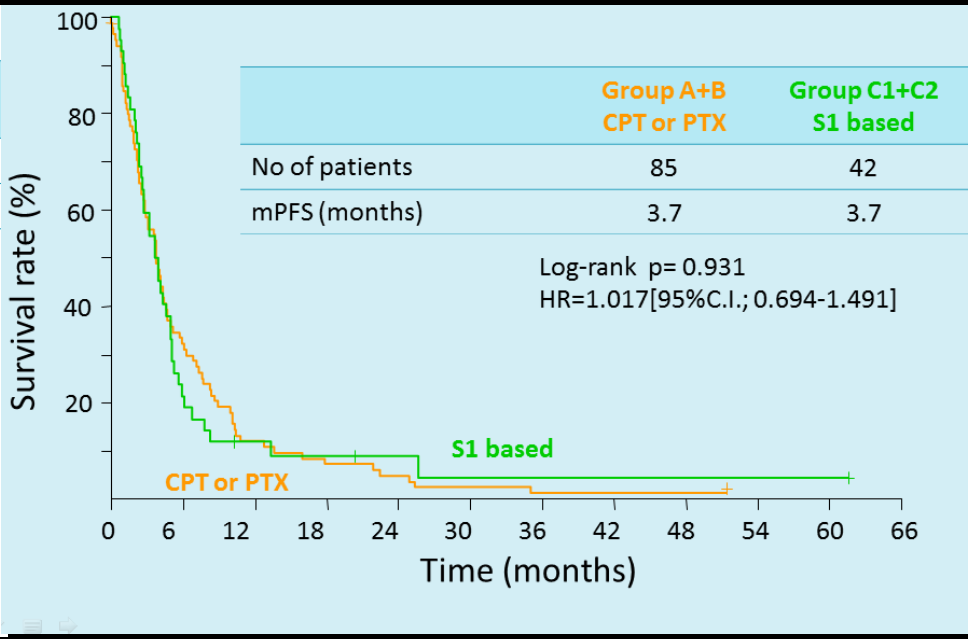
CPT based vs PTX based



	Group A+C1 CPT based	Group B+C2 PTX based
No of patients	64	63
mPFS (months)	3.6	4.1

Log-rank p= 0.035
HR=0.674 [95%C.I.; 0.468-0.972]

Non-SBP vs SBP

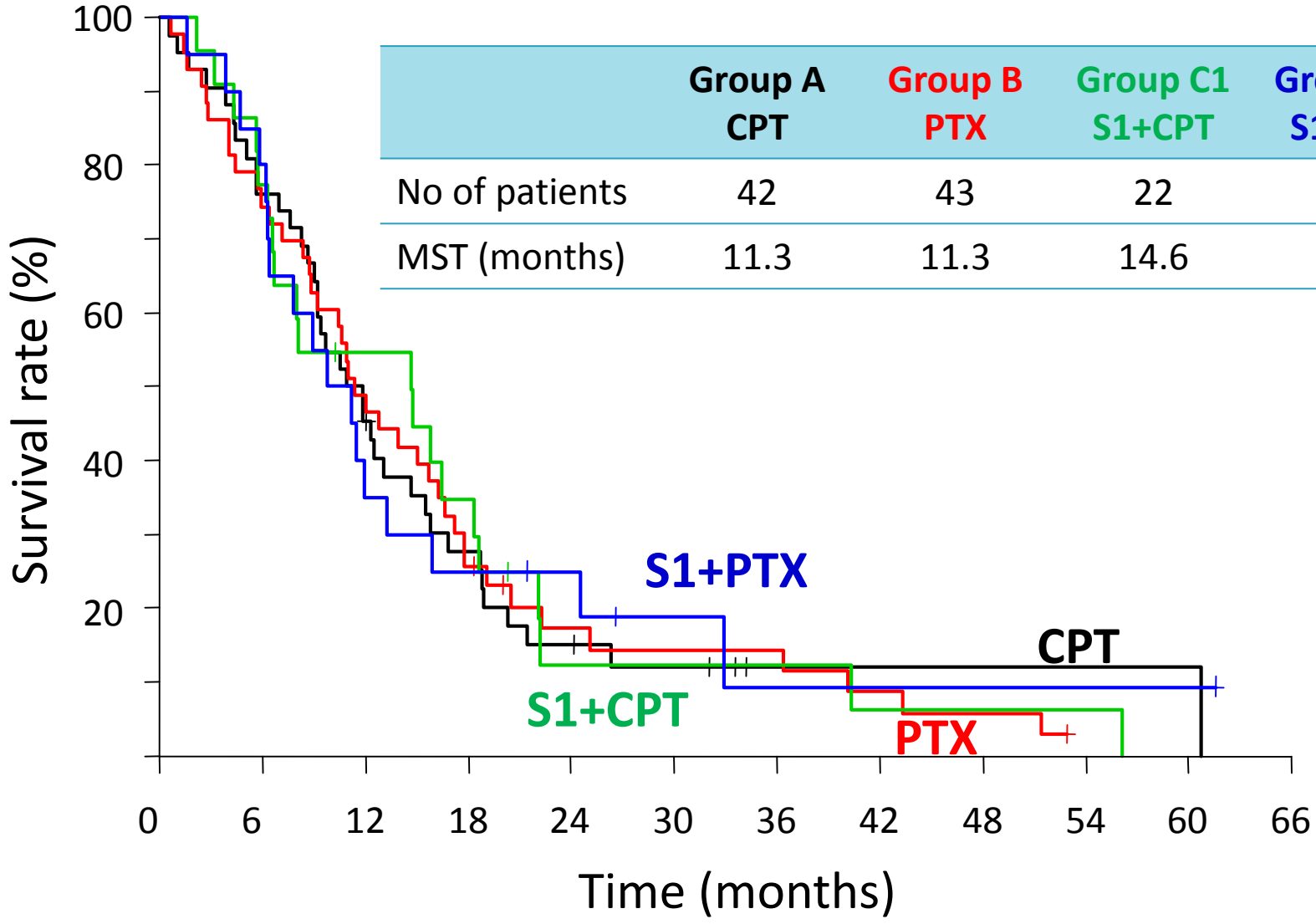


	Group A+B CPT or PTX	Group C1+C2 S1 based
No of patients	85	42
mPFS (months)	3.7	3.7

Log-rank p= 0.931
HR=1.017[95%C.I.; 0.694-1.491]

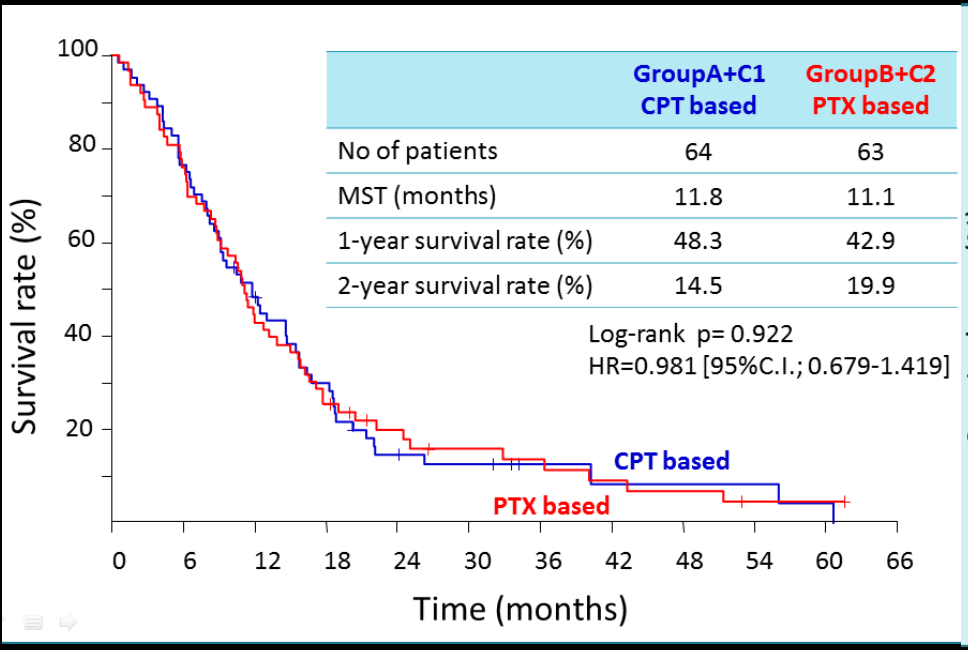
Overall Survival

	Group A CPT	Group B PTX	Group C1 S1+CPT	Group C2 S1+PTX
No of patients	42	43	22	20
MST (months)	11.3	11.3	14.6	10.5



Overall Survival

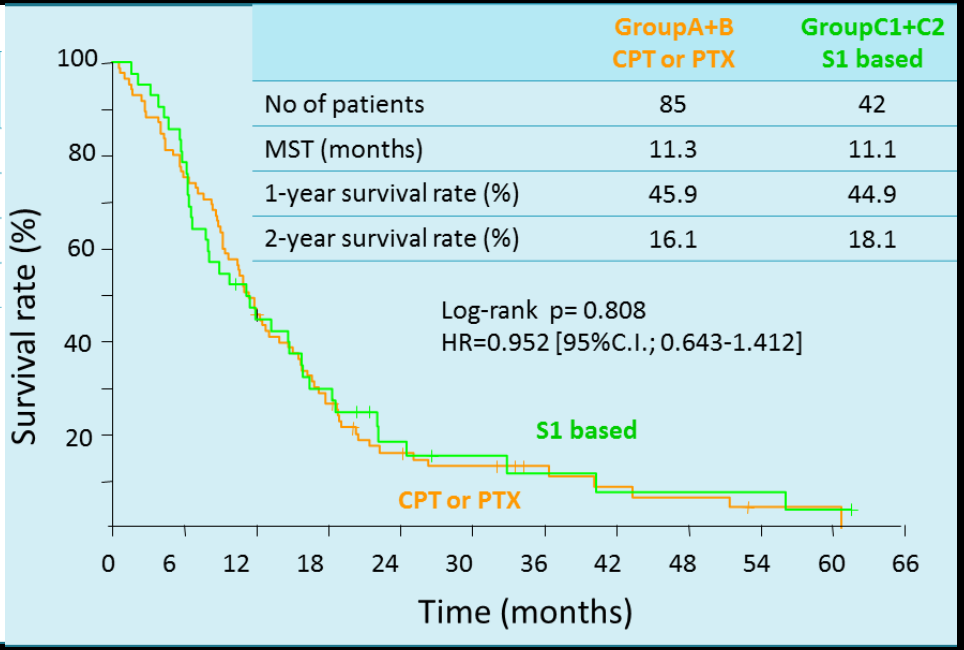
CPT based vs PTX based



	GroupA+C1 CPT based	GroupB+C2 PTX based
No of patients	64	63
MST (months)	11.8	11.1
1-year survival rate (%)	48.3	42.9
2-year survival rate (%)	14.5	19.9

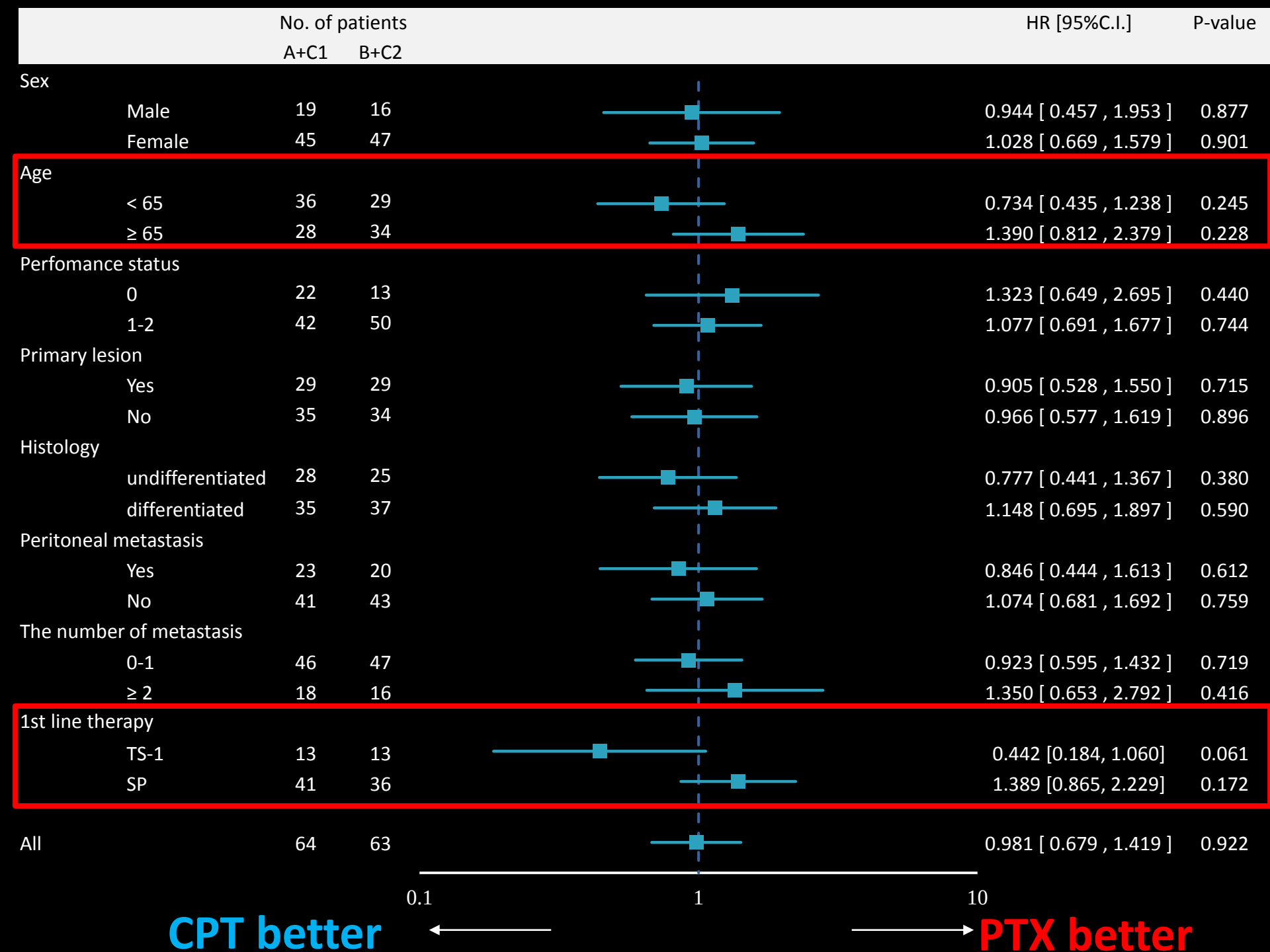
Log-rank p= 0.922
HR=0.981 [95%C.I.; 0.679-1.419]

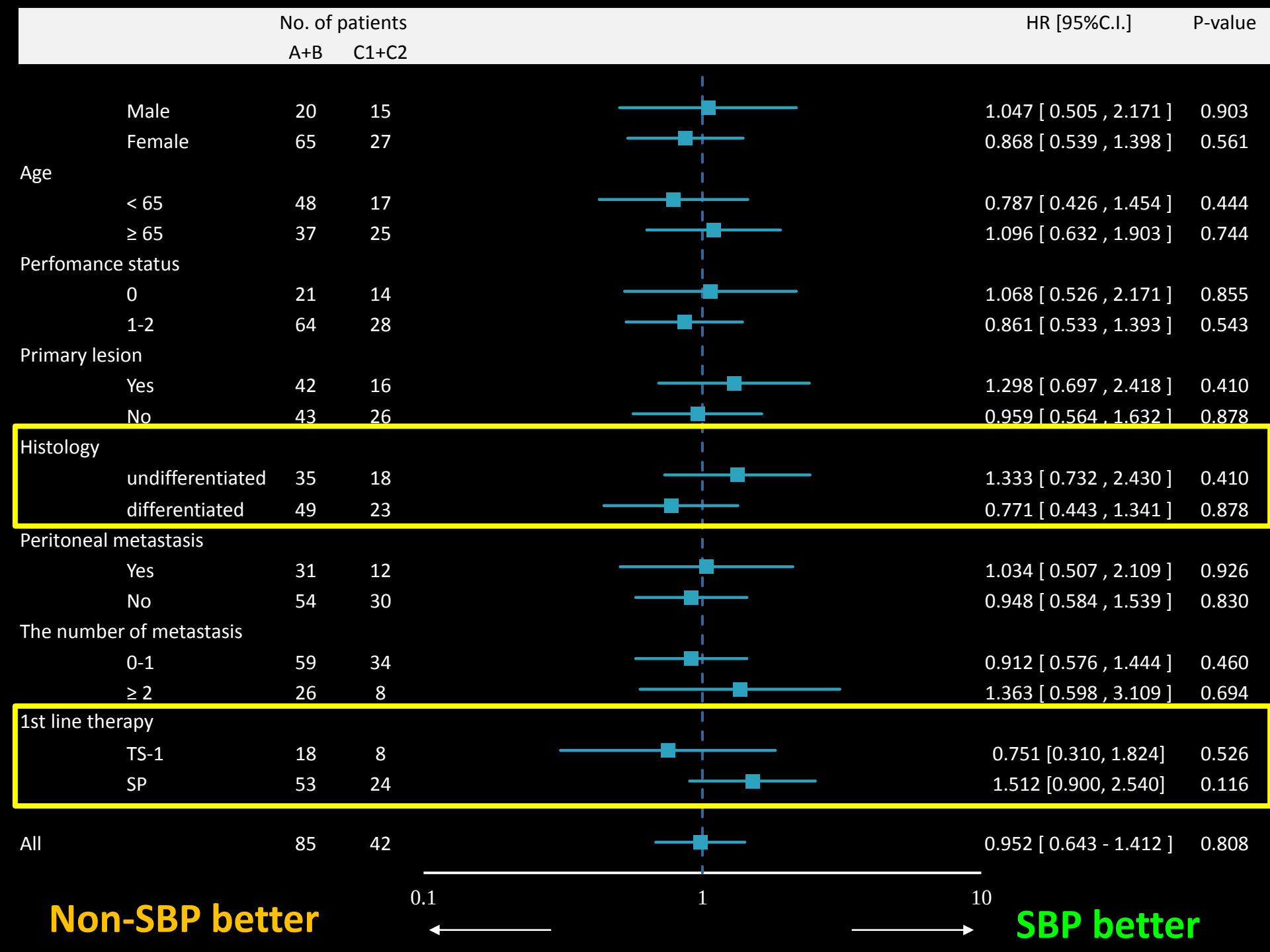
Non-SBP vs SBP



	GroupA+B CPT or PTX	GroupC1+C2 S1 based
No of patients	85	42
MST (months)	11.3	11.1
1-year survival rate (%)	45.9	44.9
2-year survival rate (%)	16.1	18.1

Log-rank p= 0.808
HR=0.952 [95%C.I.; 0.643-1.412]


No. of patients
A+C1
B+C2
HR [95%C.I.]
P-value
Sex
Male 19 16 0.944 [0.457 , 1.953] 0.877
Female 45 47 1.028 [0.669 , 1.579] 0.901
Age
< 65 36 29 0.734 [0.435 , 1.238] 0.245
≥ 65 28 34 1.390 [0.812 , 2.379] 0.228
Perfomance status
0 22 13 1.323 [0.649 , 2.695] 0.440
1-2 42 50 1.077 [0.691 , 1.677] 0.744
Primary lesion
Yes 29 29 0.905 [0.528 , 1.550] 0.715
No 35 34 0.966 [0.577 , 1.619] 0.896
Histology
undifferentiated 28 25 0.777 [0.441 , 1.367] 0.380
differentiated 35 37 1.148 [0.695 , 1.897] 0.590
Peritoneal metastasis
Yes 23 20 0.846 [0.444 , 1.613] 0.612
No 41 43 1.074 [0.681 , 1.692] 0.759
The number of metastasis
0-1 46 47 0.923 [0.595 , 1.432] 0.719
≥ 2 18 16 1.350 [0.653 , 2.792] 0.416
1st line therapy
TS-1 13 13 0.442 [0.184, 1.060] 0.061
SP 41 36 1.389 [0.865, 2.229] 0.172
All 64 63 0.981 [0.679 , 1.419] 0.922
0.1
1
10
CPT better
PTX better


No. of patients
A+B
C1+C2
HR [95%C.I.]
P-value
Male 20 15 1.047 [0.505 , 2.171] 0.903
Female 65 27 0.868 [0.539 , 1.398] 0.561
Age
< 65 48 17 0.787 [0.426 , 1.454] 0.444
≥ 65 37 25 1.096 [0.632 , 1.903] 0.744
Perfomance status
0 21 14 1.068 [0.526 , 2.171] 0.855
1-2 64 28 0.861 [0.533 , 1.393] 0.543
Primary lesion
Yes 42 16 1.298 [0.697 , 2.418] 0.410
No 43 26 0.959 [0.564 , 1.632] 0.878
Histology
undifferentiated 35 18 1.333 [0.732 , 2.430] 0.410
differentiated 49 23 0.771 [0.443 , 1.341] 0.878
Peritoneal metastasis
Yes 31 12 1.034 [0.507 , 2.109] 0.926
No 54 30 0.948 [0.584 , 1.539] 0.830
The number of metastasis
0-1 59 34 0.912 [0.576 , 1.444] 0.460
≥ 2 26 8 1.363 [0.598 , 3.109] 0.694
1st line therapy
TS-1 18 8 0.751 [0.310, 1.824] 0.526
SP 53 24 1.512 [0.900, 2.540] 0.116
All 85 42 0.952 [0.643 - 1.412] 0.808
0.1
1
10
Non-SBP better
SBP better

Adverse Events (Hematological)

	CPT (n=42)		PTX (n=43)		S1+CPT (n=21)		S1+PTX (n=21)	
	All (%)	≥ G3 (%)	All (%)	≥ G3 (%)	All (%)	≥ G3 (%)	All (%)	≥ G3 (%)
Leukocytopenia	59.5	*12.0*	41.9	*7.0*	61.9	*4.8*	57.1	*0*
Neutropenia	71.4	*28.6*	44.2	*16.3*	66.7	*23.8*	61.9	*23.8*
Hemoglobin	85.7	*7.1*	74.4	*9.3*	76.2	*14.3*	90.5	*14.3*
Thrombocytopenia	33.3	*4.8*	20.9	*2.3*	23.8	*0*	19.0	*4.8*
Febrile neutoropenia	0	*0*	11.6	*11.6*	0	*0*	0	*0*

Adverse Events (Non-hematological)

	CPT (n=42)		PTX (n=43)		S1+CPT (n=21)		S1+PTX (n=21)	
Adverse Events	All (%)	≥ G3 (%)	All (%)	≥ G3 (%)	All (%)	≥ G3 (%)	All (%)	≥ G3 (%)
Bilirubin	21.4	0	11.6	0	33.3	0	23.8	4.8
AST	21.4	2.4	30.2	4.7	23.8	0	33.3	0
ALT	19.0	2.4	23.3	2.3	23.8	0	19.0	0
Nausea	38.0	7.1	25.6	2.3	57.1	9.5	38.1	4.8
Vomiting	23.8	4.8	7.0	2.3	19.0	0	14.3	0
Anorexia	64.3	9.5	44.2	2.3	61.9	14.3	66.7	9.5
Diarrhea	40.5	4.8	11.6	0	66.7	9.5	33.3	0
Neuropathy	2.4	0	62.8	0	4.8	0	38.1	0
Fatigue	64.3	4.8	53.5	2.3	61.9	9.5	66.7	4.8

Clinical Trials in second line for AGC

	phase	1st line	Endpoint	Regimen	PFS	OS	RR	n
WJOG 4007	Ⅲ	FU+ platinum	OS	CPT-11 w-PTX	2.3 3.6	8.4 9.5	14 21	223
TCOG GI-0801	Ⅲ	S-1±α	PFS	CPT-11 *CPT-11+CDDP*	*3.03* *4.17*	10.1 10.7	16.4 21.9	130
JACCRO GC-05	Ⅱ/Ⅲ	S-1 ±α (≠ CPT-11)	OS					
OGSG 0701	Ⅱ	S-1± platinum	OS	C/P C/P+S-1	3.7 3.7	11.3 11.1		
ECRIN TRICS	Ⅲ	S-1 alone	OS	CPT-11 CPT-11+CDDP	4.1 4.6	12.7 13.9	15.4 16.9	168
JCOG 0407 (ascites)	Ⅱ	5-FU	OS	Best available 5-FU w.PTX	2.4 3.7	7.7 7.7		100

SBP is not recommended

SBP is not recommended, too.

Conclusion

- **We do not recommend consecutive use of S1 but CPT-11 or PTX monotherapy as second-line treatment in AGC patients who are refractory to S1 or SP.**