Randomized phase II study of CPT-11 versus PTX versus each combination chemotherapy with S-1 in patients with advanced gastric cancer refractory to S-1 or S-1 plus CDDP

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Background

- S-1 plus cisplatin (SP) is recognized as standard first-line chemotherapy for advanced gastric cancer (AGC)[1] and S-1 monotherapy is recognized as standard adjuvant chemotherapy for locally AGC in Japan[2,3].
- Taxane or CPT-11 are two main options and a retrospective analysis has reported that S-1 combination chemotherapy extended overall survival as second-line chemotherapy for AGC that was resistant to first-line S1-based chemotherapy[4].
- However, second-line chemotherapy for AGC is not established.

Objective and Endpoints

- Objective

  To examine efficacy and safety comparing CPT-11, PTX, and each combination chemotherapy with S-1 refractory to S-1 or SP

- Endpoints

✓ Primary endpoint
-Overall Survival (OS)

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

Study Design

gastric cancer
- Refractory to S-1 or SP as first-line chemotherapy or adjuvant chemotherapy
- Adequate oral intake
- 20-74 y.o
- PS 0-2

R

N=120

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

Group A: CPT

CPT-11 150 mg/m^2, day1, q14days

Group B: PTX

PTX 80 mg/m^2, day1, 8, 15, q28days

Group C1: S-1+CPT

CPT-11 80 mg/m^2, day1, 8
S-1 80 mg/m^2, day1-21, q35days

Group C2: S-1+PTX

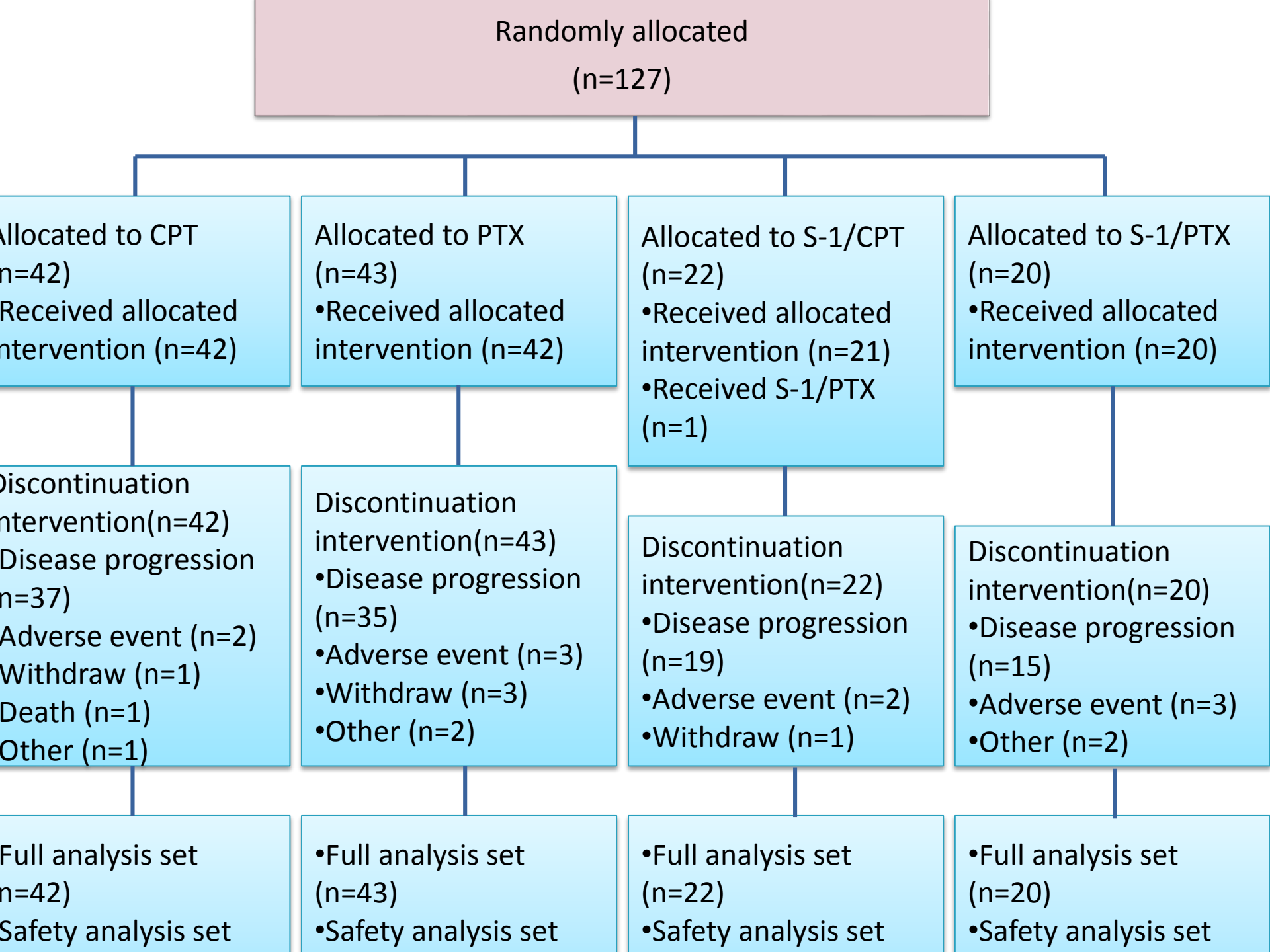
PTX 50 mg/m^2, day1, 15
S-1 80 mg/m^2, day1-14, q21days

Main Inclusion Criteria

- Histologically confirmed gastric cancer
- disease progression confirmed by imaging technique during first-line chemotherapy with S-1 or SP or during adjuvant chemotherapy or within 26 weeks after adjuvant chemotherapy completion with S-1
- ECOG performance status 0-2
- Age 20-74
- No severe organ dysfunction
- Written informed consent

Statistical Considerations

- Sample size n=120
  - ✓40 patients/each Group A and Group B,
  - ✓20 patients/each Group C1 and Group C2
- Estimated median OS: 7 months, threshold median OS: 4 months
- Enrollment: 5 years, Follow-up: 2 years
- 1-sided α=0.1, a power of β=80%
- Intension-to-treat basis

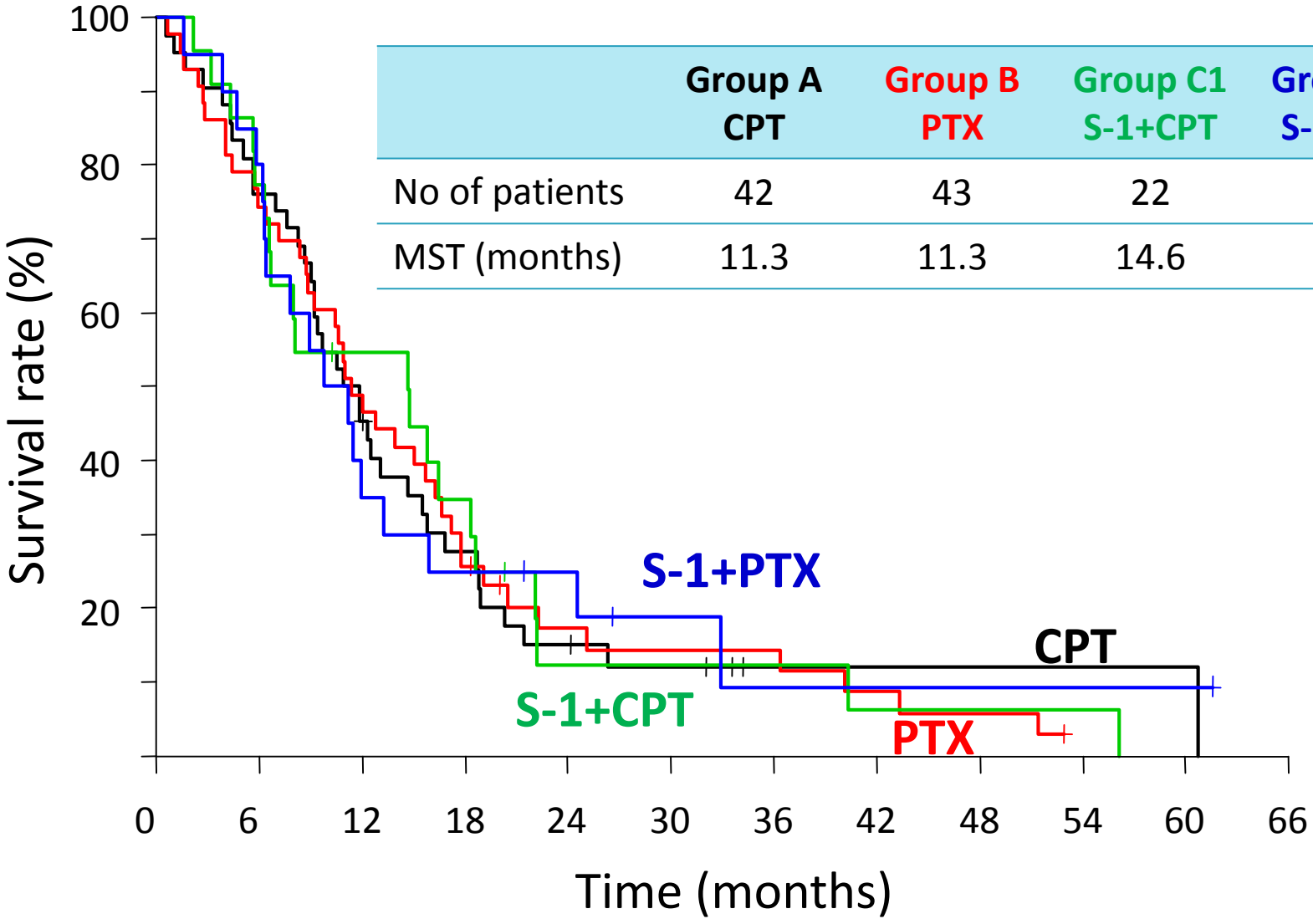

Randomly allocated
(n=127)
llocated to CPT
n=42)
Received allocated
ntervention (n=42)
Allocated to PTX
(n=43)
•Received allocated
intervention (n=42)
Allocated to S-1/CPT
(n=22)
•Received allocated
intervention (n=21)
•Received S-1/PTX
(n=1)
Allocated to S-1/PTX
(n=20)
•Received allocated
intervention (n=20)
Discontinuation
ntervention(n=42)
Disease progression
n=37)
Adverse event (n=2)
Withdraw (n=1)
Death (n=1)
Other (n=1)
Discontinuation
intervention(n=43)
•Disease progression
(n=35)
•Adverse event (n=3)
•Withdraw (n=3)
•Other (n=2)
Discontinuation
intervention(n=22)
•Disease progression
(n=19)
•Adverse event (n=2)
•Withdraw (n=1)
Discontinuation
intervention(n=20)
•Disease progression
(n=15)
•Adverse event (n=3)
•Other (n=2)
Full analysis set
n=42)
Safety analysis set
•Full analysis set
(n=43)
•Safety analysis set
•Full analysis set
(n=22)
•Safety analysis set
•Full analysis set
(n=20)
•Safety analysis set

Patient Characteristics

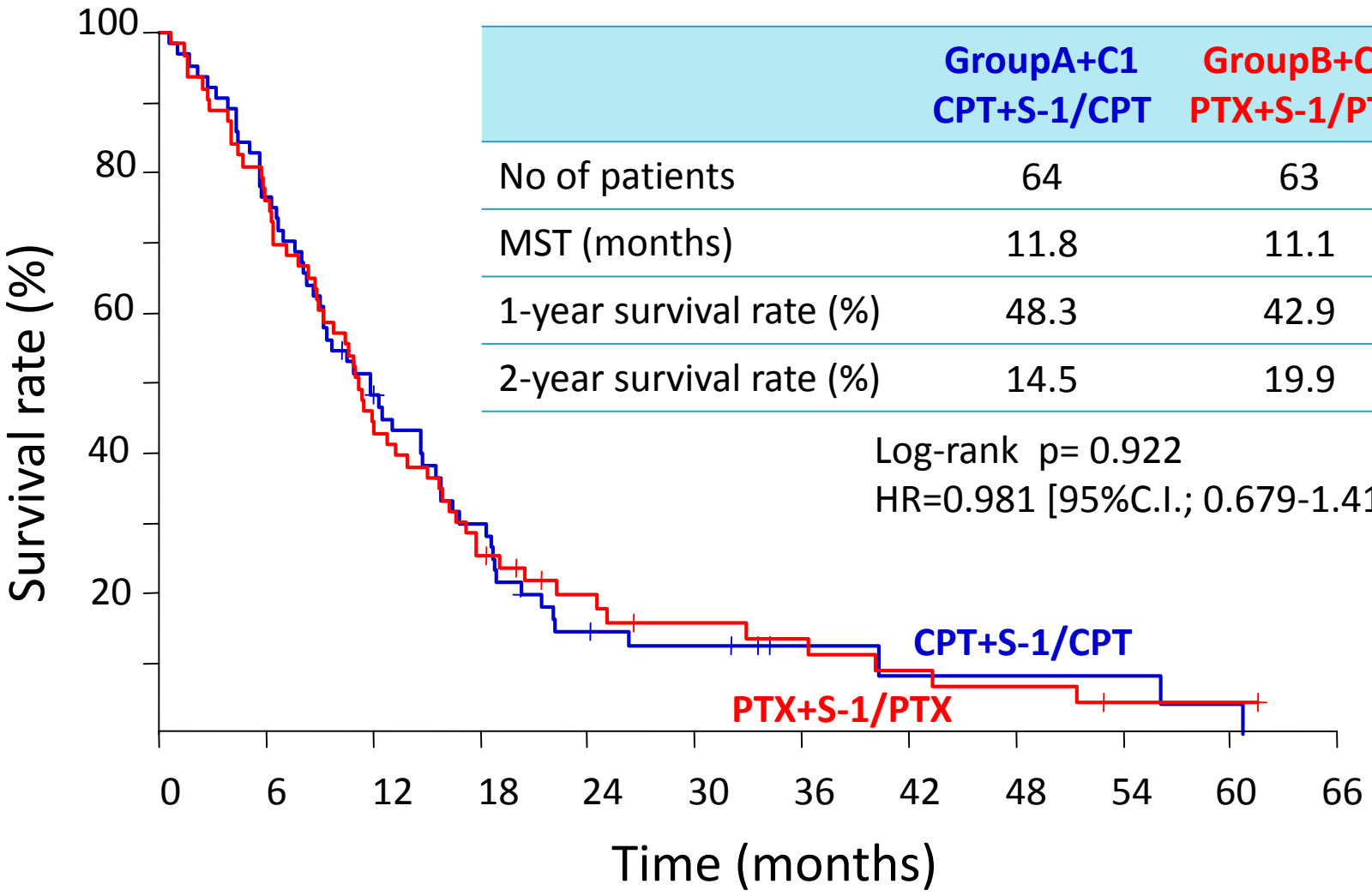
	Group A CPT (n=42)	Group B PTX (n=43)	Group C1 S-1+CPT (n=22)	Group C2 S-1+PTX (n=20)
Sex Male/Female	30/12	35/8	15/7	12/8
Age, years Median(range)	65 (44-74)	65 (31-74)	67 (47-73)	63 (37-74)
ECOG PS 0-1/2	42/0	41/2	21/1	20/0
Histology Intestinal/Diffuse	24/18	25/17	11/10	12/8
Prior gastrectomy Yes/No	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

Overall Survival

	Group A CPT	Group B PTX	Group C1 S-1+CPT	Group C2 S-1+PTX
No of patients	42	43	22	20
MST (months)	11.3	11.3	14.6	10.5



Overall Survival

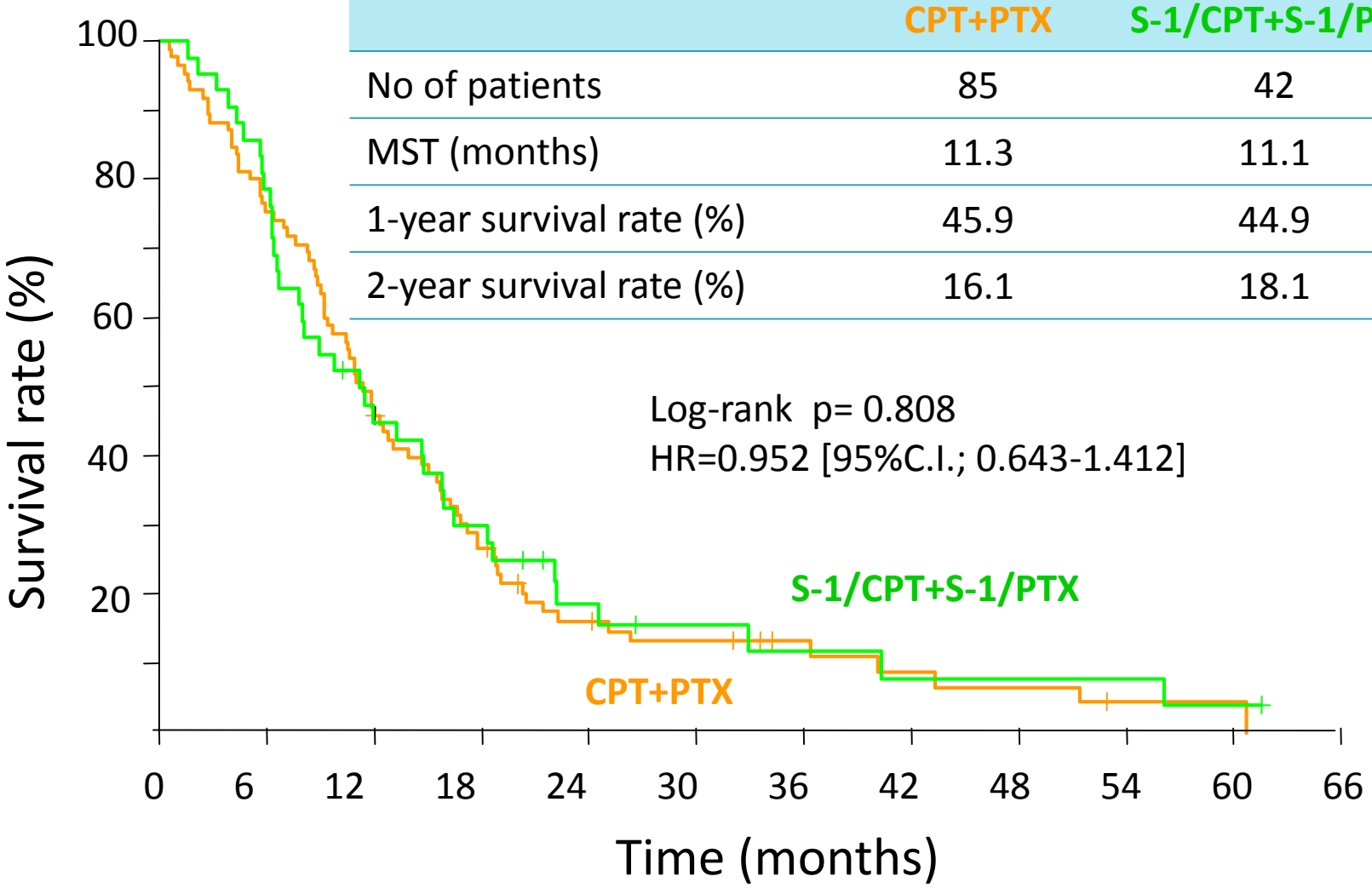


	GroupA+C1 CPT+S-1/CPT	GroupB+C2 PTX+S-1/PTX
No of patients	64	63
MST (months)	11.8	11.1
1-year survival rate (%)	48.3	42.9
2-year survival rate (%)	14.5	19.9

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

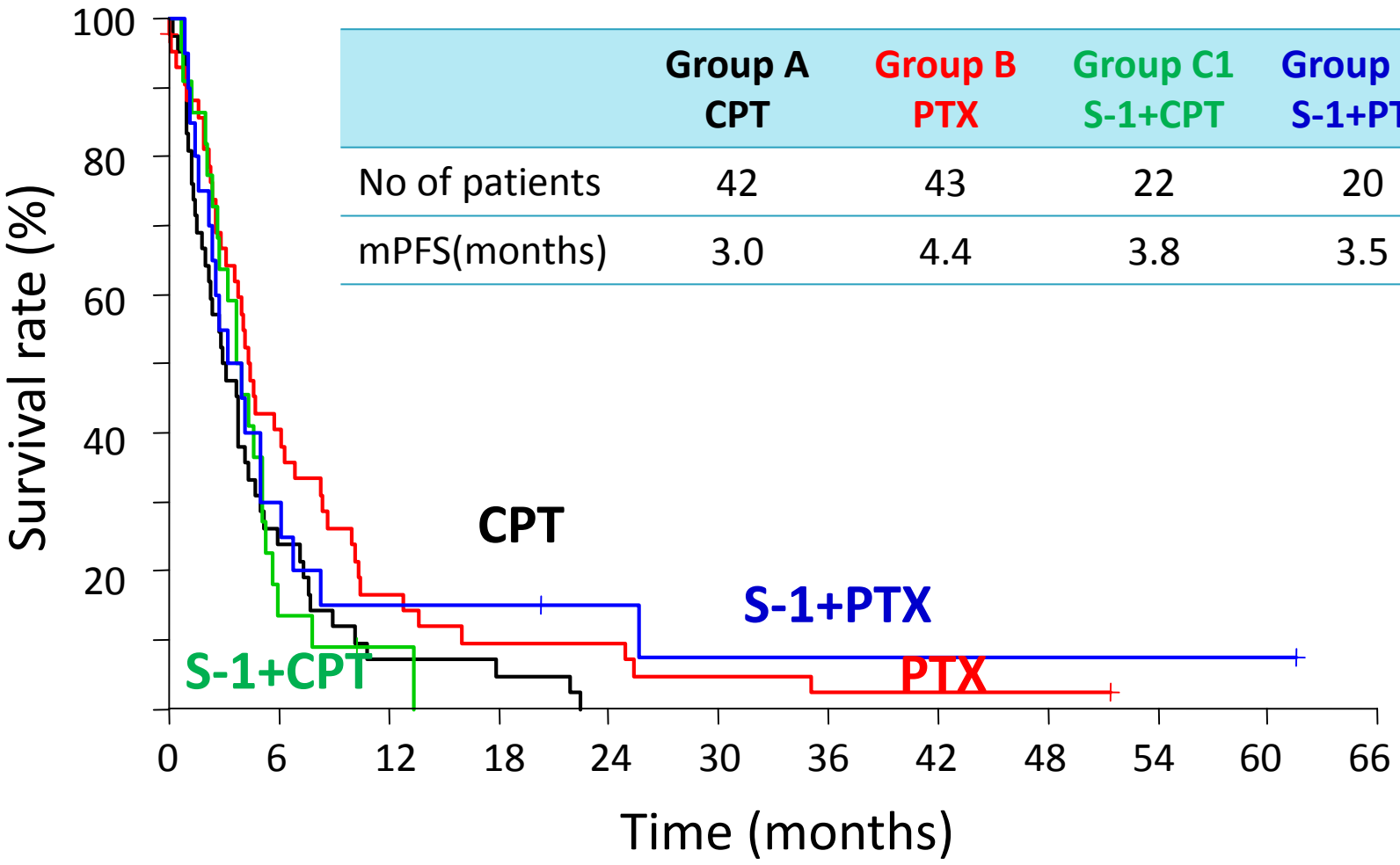
Overall Survival

	GroupA+B CPT+PTX	GroupC1+C2 S-1/CPT+S-1/PTX
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

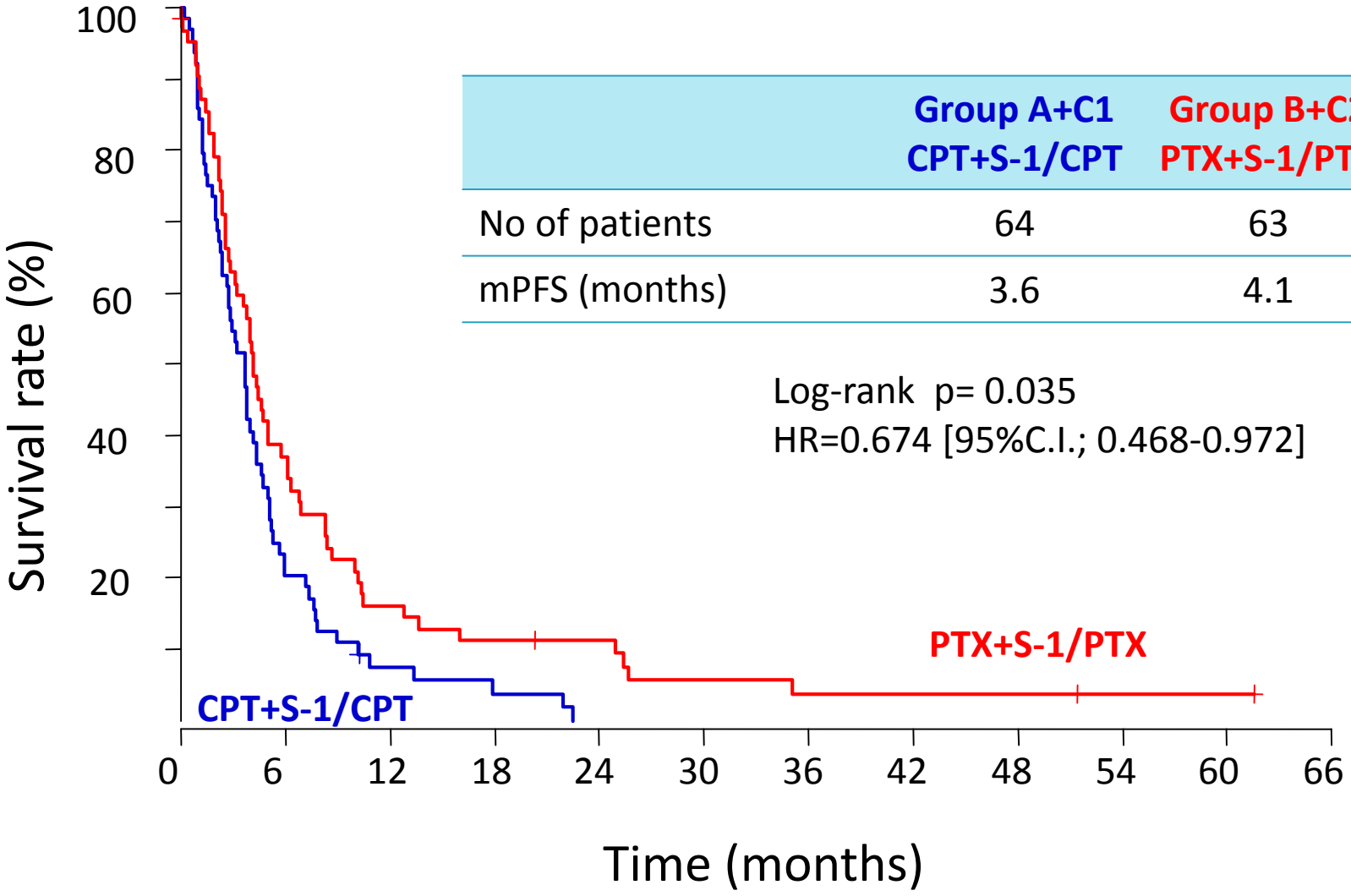


Progression-free Survival

	Group A CPT	Group B PTX	Group C1 S-1+CPT	Group C2 S-1+PTX
No of patients	42	43	22	20
mPFS(months)	3.0	4.4	3.8	3.5



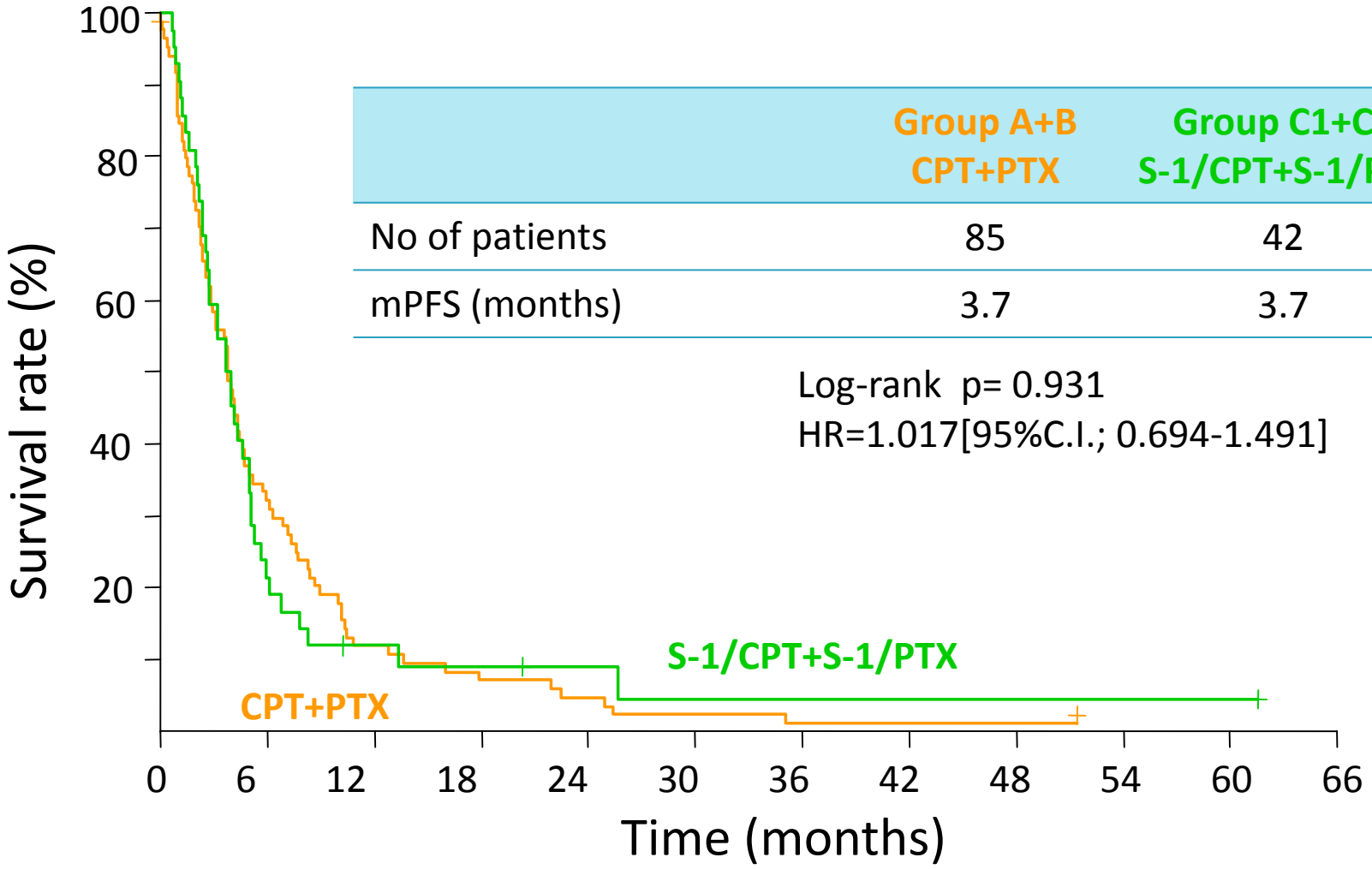
Progression-free Survival



	Group A+C1 CPT+S-1/CPT	Group B+C2 PTX+S-1/PTX
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]

Progression-free Survival

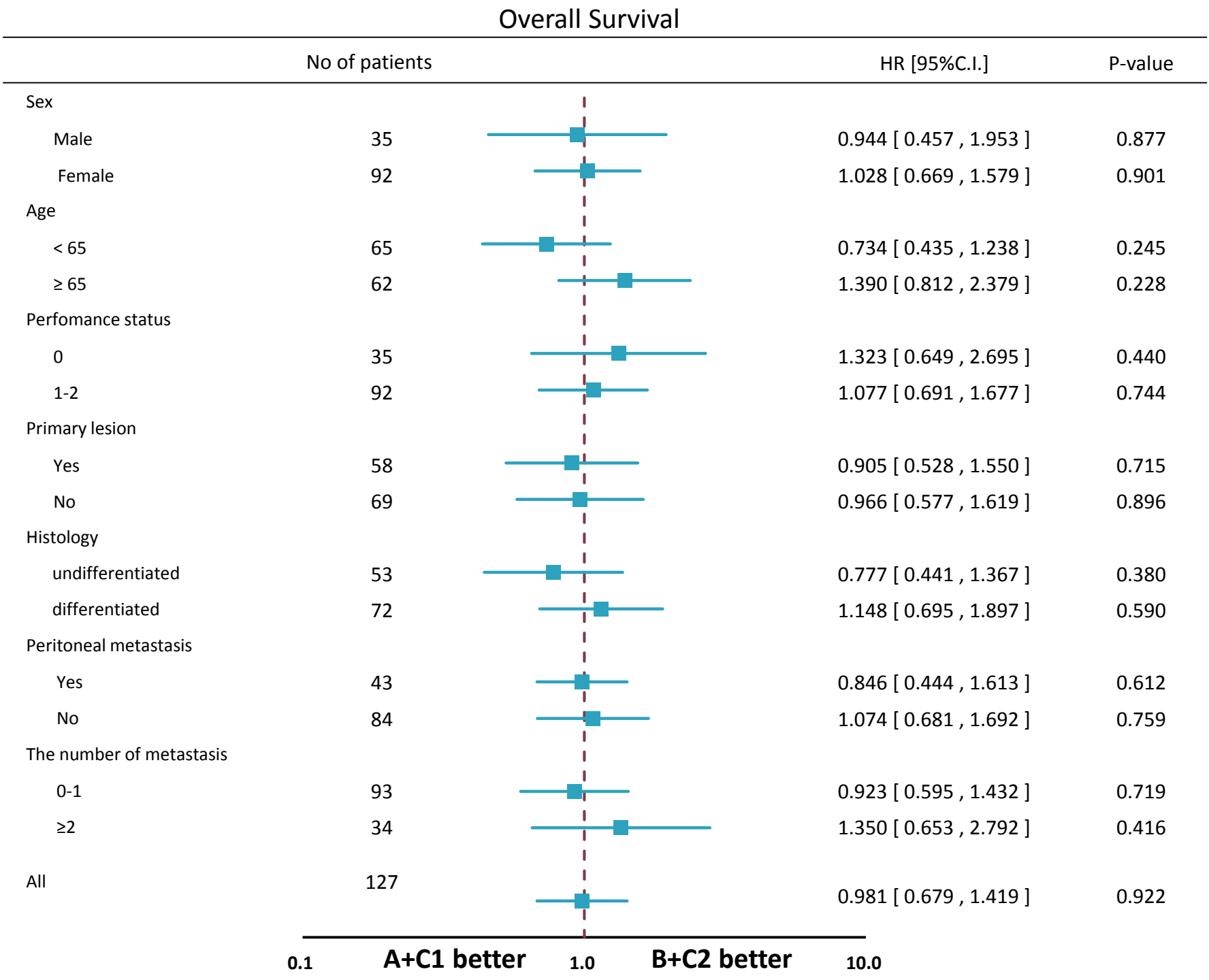


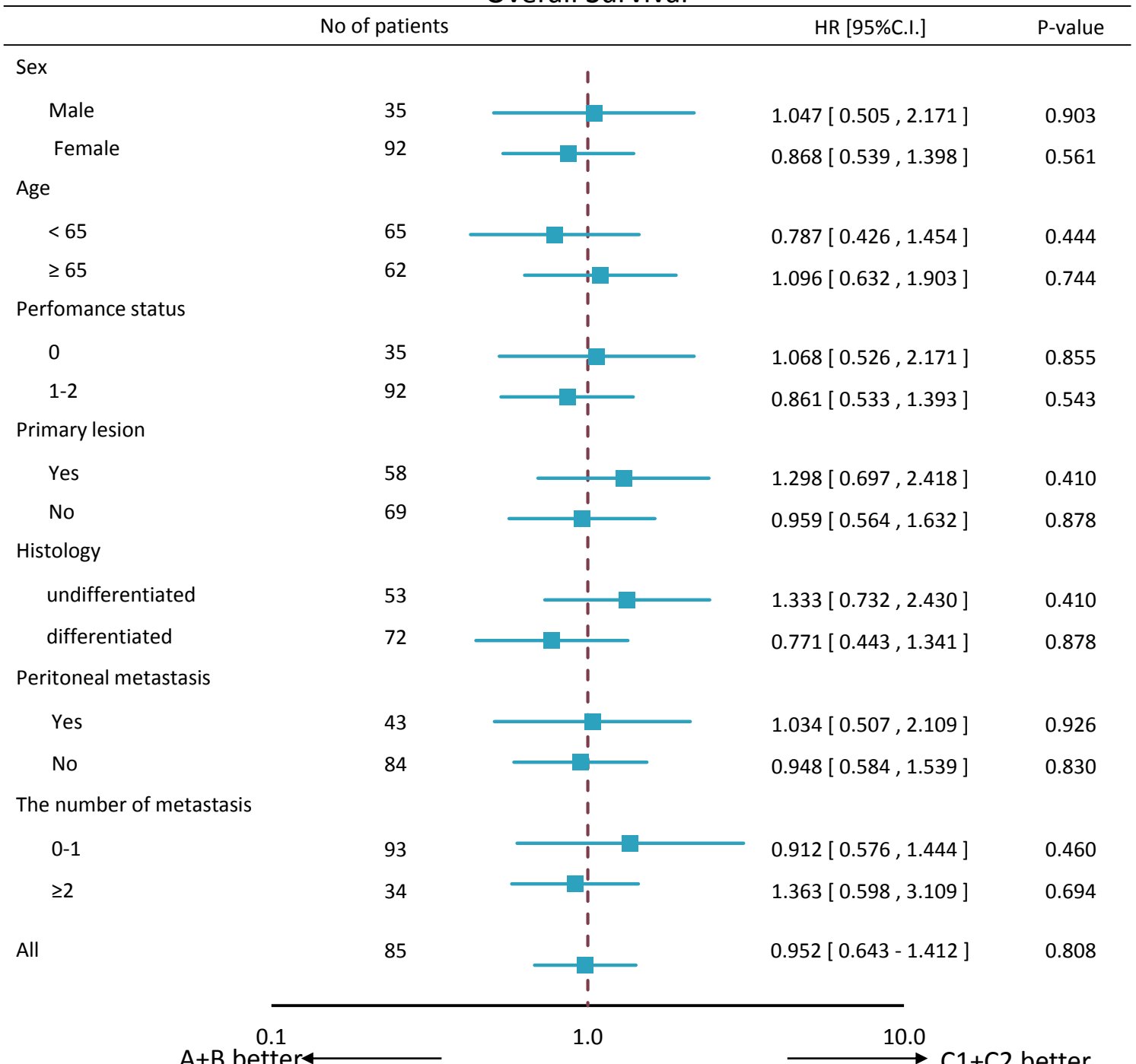
	Group A+B CPT+PTX	Group C1+C2 S-1/CPT+S-1/PTX
No of patients	85	42
mPFS (months)	3.7	3.7

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

Adverse Events

	CPT (n=42)		PTX (n=43)		S-1+CPT (n=21)		S-1+PTX (
Adverse Events	All N (%)	≥ G3 N (%)	All N (%)	≥ G3 N (%)	All N (%)	≥ G3 N (%)	All N (%)
Leukocytopenia	25 (59.5)	5 (12.0)	18 (41.9)	3 (7.0)	13 (61.9)	1 (4.8)	12 (57.1)
Neutropenia	30 (71.4)	12 (28.6)	19 (44.2)	7 (16.3)	14 (66.7)	5 (23.8)	13 (61.9)
Hemoglobin	36 (85.7)	3 (7.1)	32 (74.4)	4 (9.3)	16 (76.2)	3 (14.3)	19 (90.5)
Thrombocytopenia	14 (33.3)	2 (4.8)	9 (20.9)	1 (2.3)	5 (23.8)	0 (0)	4 (19.0)
Febrile neutoropenia	0 (0)	0 (0)	5 (11.6)	5 (11.6)	0 (0)	0 (0)	0 (0)
Bilirubin	9 (21.4)	0 (0)	5 (11.6)	0 (0)	7 (33.3)	0 (0)	5 (23.8)
AST	9 (21.4)	1 (2.4)	13 (30.2)	2 (4.7)	5 (23.8)	0 (0)	7 (33.3)
ALT	8 (19.0)	1 (2.4)	10 (23.3)	1 (2.3)	5 (23.8)	0 (0)	4 (19.0)
Nausea	16 (38.0)	3 (7.1)	11 (25.6)	1 (2.3)	12 (57.1)	2 (9.5)	8 (38.1)
Vomiting	10 (23.8)	2 (4.8)	3 (7.0)	1 (2.3)	4 (19.0)	0 (0)	3 (14.3)


Overall Survival
No of patients
HR [95%C.I.]
P-value
Sex
Male 35 0.944 [0.457 , 1.953] 0.877
Female 92 1.028 [0.669 , 1.579] 0.901
Age
< 65 65 0.734 [0.435 , 1.238] 0.245
≥ 65 62 1.390 [0.812 , 2.379] 0.228
Perfomance status
0 35 1.323 [0.649 , 2.695] 0.440
1-2 92 1.077 [0.691 , 1.677] 0.744
Primary lesion
Yes 58 0.905 [0.528 , 1.550] 0.715
No 69 0.966 [0.577 , 1.619] 0.896
Histology
undifferentiated 53 0.777 [0.441 , 1.367] 0.380
differentiated 72 1.148 [0.695 , 1.897] 0.590
Peritoneal metastasis
Yes 43 0.846 [0.444 , 1.613] 0.612
No 84 1.074 [0.681 , 1.692] 0.759
The number of metastasis
0-1 93 0.923 [0.595 , 1.432] 0.719
≥2 34 1.350 [0.653 , 2.792] 0.416
All 127 0.981 [0.679 , 1.419] 0.922
0.1
A+C1 better
1.0
B+C2 better
10.0


Overall Survival
No of patients
HR [95%C.I.]
P-value
Sex
Male
35
1.047 [0.505 , 2.171]
0.903
Female
92
0.868 [0.539 , 1.398]
0.561
Age
< 65
65
0.787 [0.426 , 1.454]
0.444
≥ 65
62
1.096 [0.632 , 1.903]
0.744
Perfomance status
0
35
1.068 [0.526 , 2.171]
0.855
1-2
92
0.861 [0.533 , 1.393]
0.543
Primary lesion
Yes
58
1.298 [0.697 , 2.418]
0.410
No
69
0.959 [0.564 , 1.632]
0.878
Histology
undifferentiated
53
1.333 [0.732 , 2.430]
0.410
differentiated
72
0.771 [0.443 , 1.341]
0.878
Peritoneal metastasis
Yes
43
1.034 [0.507 , 2.109]
0.926
No
84
0.948 [0.584 , 1.539]
0.830
The number of metastasis
0-1
93
0.912 [0.576 , 1.444]
0.460
≥2
34
1.363 [0.598 , 3.109]
0.694
All
85
0.952 [0.643 - 1.412]
0.808
0.1
1.0
10.0
A+B better
C1+C2 better

Conclusion

- The difference in OS between CPT-11 and PTX, and the efficacy of S-1 sequential therapy were not observed in second-line chemotherapy for AGC refractory to S-1 or SP.

References

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