A phase II study of trastuzumab in combination with triweekly S-1 plus CDDP in HER2-positive advanced gastric cancer ; OGSG1101, HGCSG1102, T-CORE1101 Intergroup study (HERBIS-1 trial)

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Background

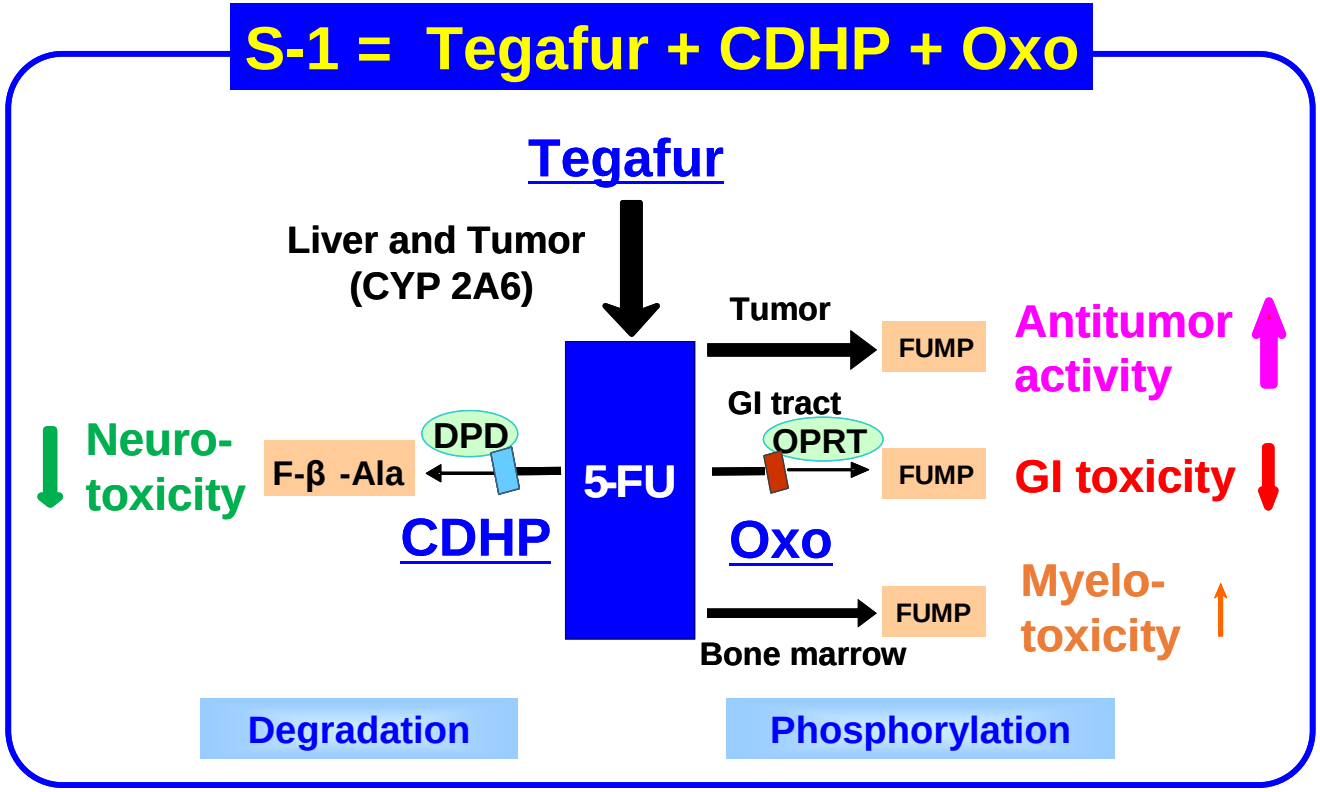
- S-1, an oral fluoropyrimidine, plus cisplatin (SP) regimen is one of the standard chemotherapy as first-line for advanced gastric cancer (AGC) in East Asia.

- However, there was no study evaluating the efficacy and the safety of trastuzumab in combination with SP regimen in patients with HER2-positive AGC.

Background

- **S-1 (tegafur, CDHP, Oxo) is an oral "DPD inhibitory fluoropyrimidine (DIF)" widely used to treat various solid tumors in East Asia.**

Biochemical action of S-1



DPD, dihydropyrimidine dehydrogenase
OPRT, orotate phosphoribosyltransferase

Objective

- To clarify the efficacy and the safety of combined therapy with trastuzumab and SP (3 weekly) in HER2-positive advanced gastric cancer.

- Primary end point:
  - Response rate (RR)
- Secondary end point:
  - Progression free survival (PFS)
  - Overall Survival (OS)
  - Time to treatment Failure (TTF)
  - Safety

Under follow-up (immature)

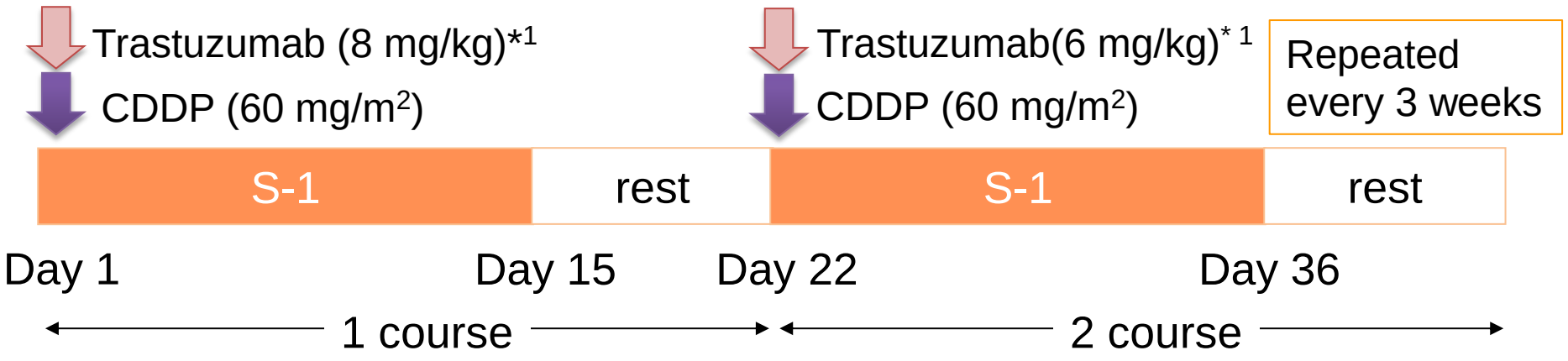
Main Eligibility Criteria

- Histologically proven gastric or gastroesophageal junction cancer which is unresectable or recurrent
- Measurable disease (RECIST 1.1 criteria)
- HER2-positive confirmed by IHC and/or FISH (IHC 3+ or IHC 2+ and FISH positive)
- No previous chemotherapy or radiotherapy
- Age ≤ 75
- ECOG PS 0-1
- Adequate organ function
- Written Informed consent

Treatment schedule

- S-1: a fixed dose of 80, 100, or 120 mg/patient p.o. in 2 divided doses for 14 days, followed by a 7-day rest.
- Trastuzumab, CDDP: day 1.

Body Surface Area (BSA: m^2)	Initial Dose of S-1 (mg/day as tegafur)
<1.25	40 × 2
1.25 to <1.50	50 × 2
≥1.50	60 × 2



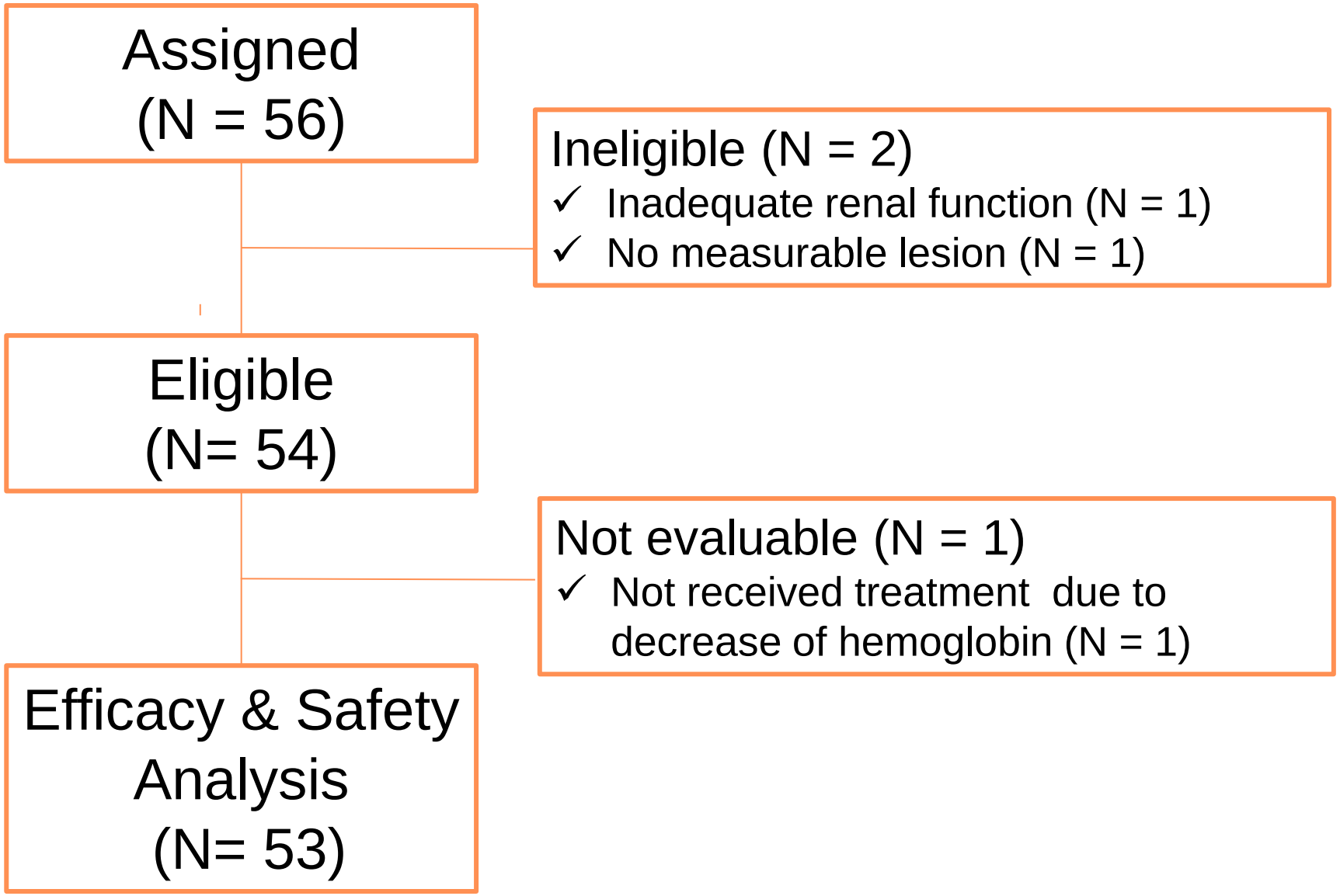
*1: Trastuzumab 8 mg/kg in 1st course, 6mg/kg from 2nd course

Statistical considerations

- The threshold response : 35%
- The expected response : 50%
- Power : 80 %
- 1-sided alpha : 0.1

50 patients

CONSORT diagram



Patient baseline characteristics

Eligible (n = 54)

Characteristics	Number (%)
Age, years	
Median	66
Range	34 – 75
Sex	
Male	42 (77.8)
Female	12 (22.2)
Performance status	
0	42 (77.8)
1	12 (22.2)
Pathological findings	
Differentiated	36 (66.7)
Undifferentiated	18 (33.3)

Patient baseline characteristics

Characteristics	Number (%)
Metastatic sites	
Liver	32 (59.3)
Lymph nodes	44 (81.5)
Lung	5 (9.3)
Peritoneum	5 (9.3)
Bone	2 (3.7)
Other	1 (1.9)
Previous gastrectomy	
No	45 (83.3)
Yes	9 (16.7)
Unresectable/ Recurrent	
Unresectable	51 (94.4)
Recurrent	3 (5.6)
Adjuvant chemotherapy (+)	2
(-)	1
HER2 status	
IHC 2+, FISH positive	9 (16.7)
IHC 3+	45 (83.3)

Overall response rates

* Assessed by the independent review committee

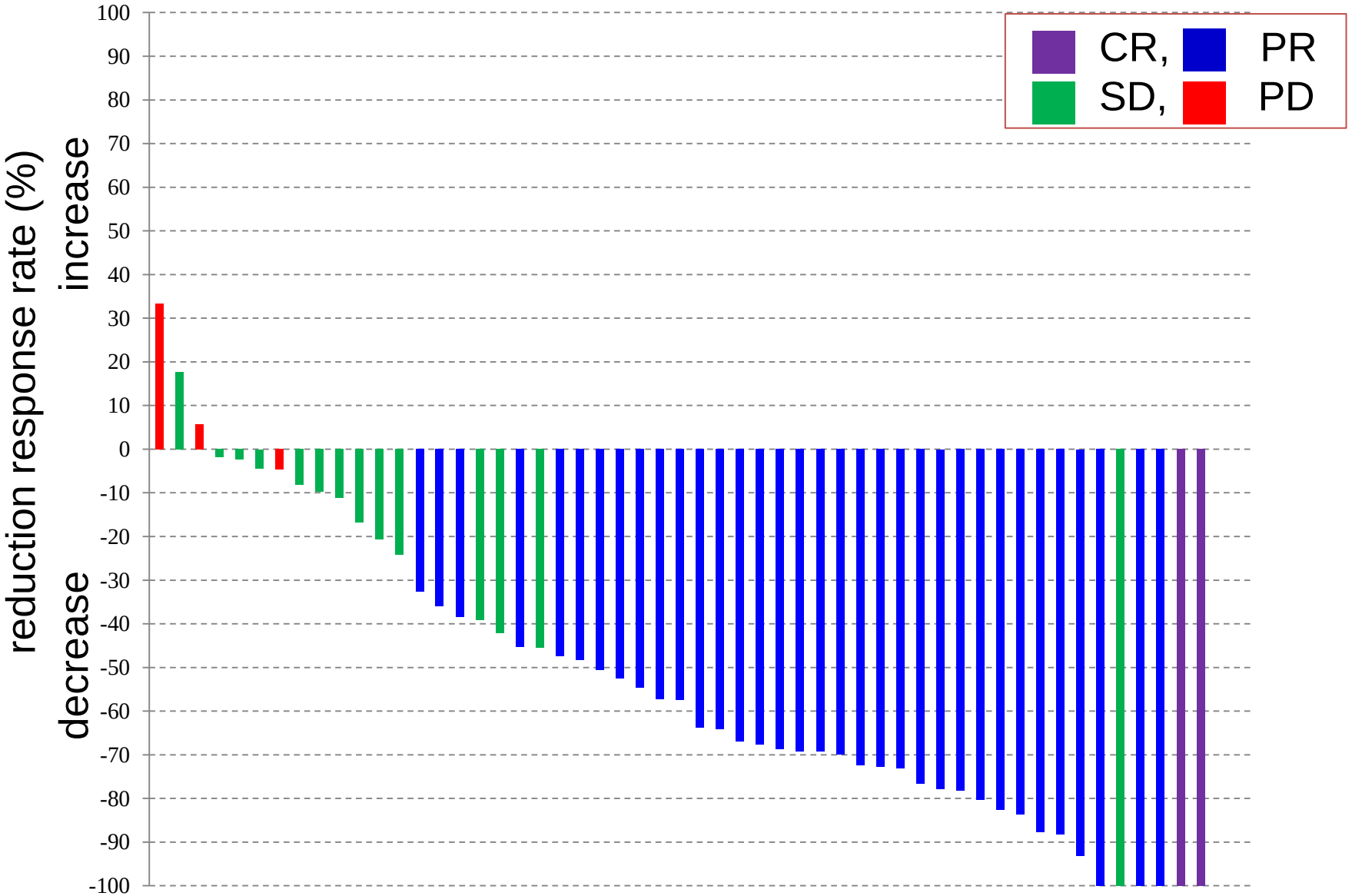
Efficacy analysis population (n = 53)

Variable	Number (%)
Complete response	2 (3.8)
Partial response	34 (64.2)
Stable disease	14 (26.4)
Progressive disease	3 (5.7)
Objective response rate	36 (**67.9**)
95% CI	(53.7 – 80.1)
80% CI	(58.3 – 76.4)
Disease control rate	50 (94.3)
95% CI	(84.3 – 98.9)

The response rate without confirmation was 75.5% (95% CI, 61.7 to 86.2%).

Waterfall plot

Efficacy analysis population (n = 53)



Adverse Events

Safety analysis population (n = 53)

Event	Any Grade (%)		G3-4 (%)	
Leukopenia	38	(71.7)	4	(7.5)
Neutropenia	30	(56.6)	18	(34.0)
Febrile neutropenia	2	(3.8)	2	(3.8)
Anemia	34	(64.2)	7	(13.2)
Thrombocytopenia	26	(49.1)	0	(0.0)
Creatinine increased	24	(45.3)	3	(5.7)
Total bilirubin increased	7	(13.2)	0	(0.0)
AST increased	9	(17.0)	0	(0.0)
ALT increased	13	(24.5)	0	(0.0)
Hypoalbuminemia	21	(39.6)	2	(3.8)

Adverse Events

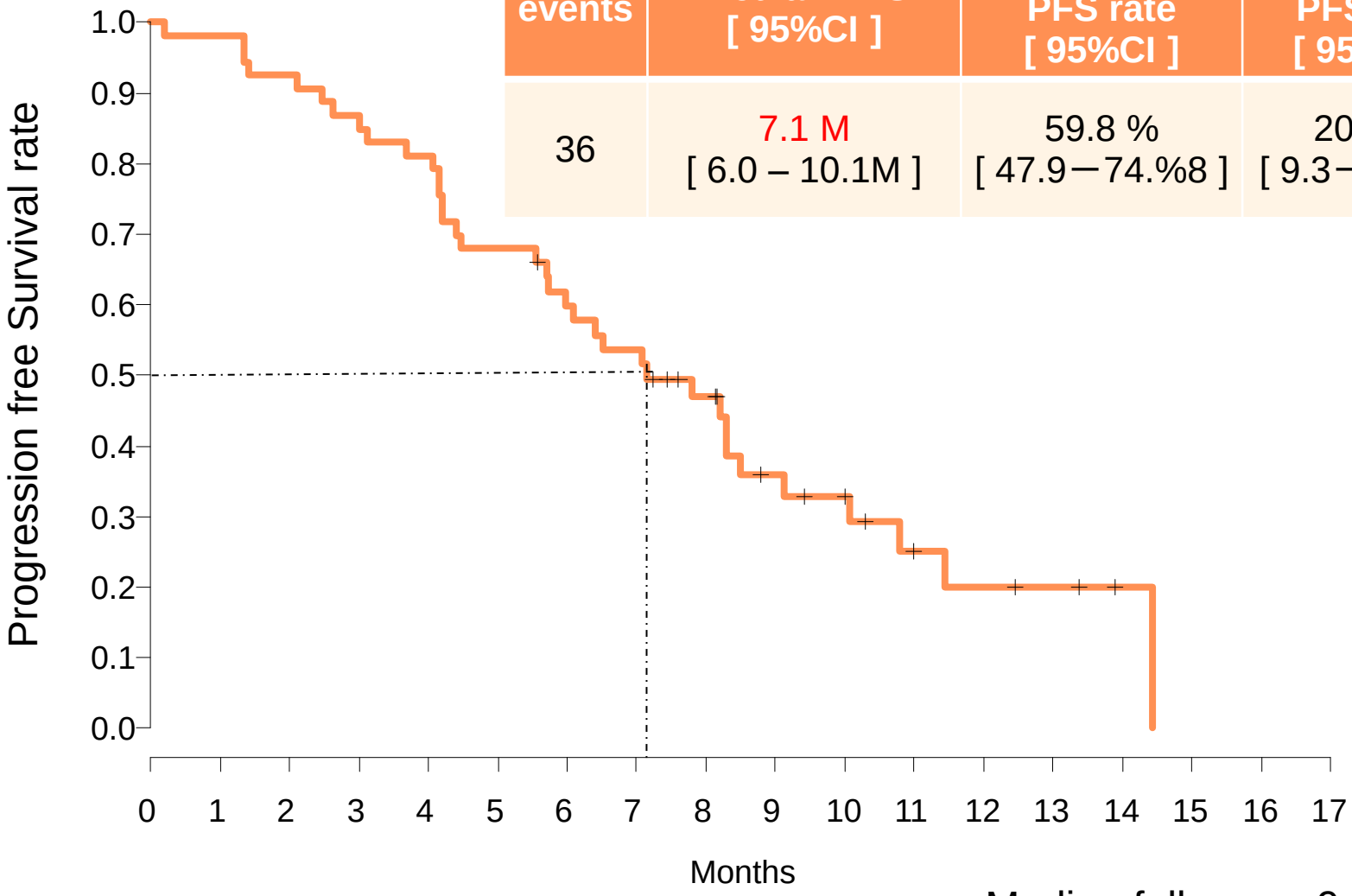
Safety analysis population (n = 53)

Event	Any Grade (%)		G3-4 (%)	
Anorexia	41	(77.4)	12	(22.6)
Nausea	31	(58.5)	1	(1.9)
Vomiting	12	(22.6)	3	(5.7)
Stomatitis	17	(32.1)	1	(1.9)
Diarrhea	21	(39.6)	4	(7.5)
Constipation	10	(18.9)	0	(0.0)
Fatigue	32	(60.4)	2	(3.8)
Skin rash	13	(24.5)	0	(0.0)
Epistaxis	4	(7.5)	0	(0.0)
Edema	8	(15.1)	0	(0.0)
Dysgeusia	10	(18.9)	0	(0.0)
Hypertension	2	(3.8)	0	(0.0)
Infusion Related Reaction	2	(3.8)	0	(0.0)

Progression-free Survival（PFS）

Efficacy analysis population (n = 53)

events	median PFS [95%CI]	6-month PFS rate [95%CI]	1-year PFS rate [95%CI]
36	7.1 M [6.0 – 10.1M]	59.8 % [47.9－74.%8]	20.1 % [9.3－41.4%]



Median follow up：9.2 Months

Reasons of discontinuation

Eligible (n = 54)

Status/Reason	Number
Under protocol treatment	8
Discontinuation of protocol treatment	46
Reason for discontinuation	
1. Progression of disease	25
2. Adverse event	11
3. Patient refusal (related adverse event)	2
4. Patient refusal (not related adverse event)	0
5. Operation by treatment effect	4
6. Discontinuation before protocol treatment	1[*1]
7. Other	3

*1: Due to decrease of hemoglobin

Conclusion

- SP plus trastuzumab showed high response rate of 67.9% (80% CI 58.3 – 76.4%; 95% CI:53.7 – 80.1%).
- Median PFS, the secondary endpoint, was reached in 7.1 months.
- The main grade 3/4 adverse events were as follows: neutropenia 34.0%, leucopenia 7.5%, anorexia 22.6%, diarrhea 7.5%, vomiting 5.7%, and increased creatinine 5.7%.
- This regimen showed promising activity and acceptable toxicity for HER2 positive advanced gastric cancer.

Acknowledgement

- Name of primary sponsor：Osaka Gastrointestinal cancer chemotherapy Study Group (OGSG)
- This study was conducted by the collaborative group of Osaka Gastrointestinal cancer chemotherapy Study Group (OGSG) , Hokkaido Gastrointestinal Cancer Study Group (HGCSG) and Tohoku Clinical Oncology Research and Education Society (T-CORE) with funding from TAIHO Pharmaceutical Co. Ltd., Japan.

Participating Institutions

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Osaki Citizen Hospital
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Osaka Rosai Hospital
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Osaka Red Cross Hospital
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National Hospital Organization Hokkaido Medical Center
Yamagata Prefectural Central Hospital
Hirosaki University School of Medicine
National Hospital Organization Sendai Medical Center
Miyagi Cancer Center
Suita Municipal Hospital
Osaka General Medical Center
Hyogo Prefectural Nishinomiya Hospital
Kansai Rosai Hospital
Tokusima Red Cross Hospital
Kurume University School of Medicine
Beppu Medical Center

And we thank all of the patients and their families.