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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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Abstract

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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). Although ToGA study demonstrated that trastuzumab (T-mab) in combination with capecitabine plus cisplatin or fluorouracil plus cisplatin improved the overall survival of patients (pts) with HER2-positive AGC, there was no study evaluating the efficacy and the safety of T-mab in combination with SP regimen.

Methods

Eligibility criteria included gastric or esophagogastric junction adenocarcinoma; HER2-positive confirmed by IHC and/or FISH (IHC 3+ or IHC 2+ and FISH positive); unresectable or recurrent; measurable lesion; no history of chemotherapy or radiotherapy; age≤75; ECOG PS of 0-1; and adequate organ function. Pts received S-1 at 40–60 mg depending on body surface area, po bid, day 1-14, and cisplatin 60 mg/m^2, iv, day 1, plus T-mab 8 mg/ kg, iv, day 1 (6 mg/ kg, iv, d1 from 2nd course), repeated every 3 weeks until disease progression. Primary endpoint was response rate assessed by the RECIST (ver 1.1). The planned sample size was 50 based on the threshold response rate of 35%, the expected rate of 50%, power of 80%, and 1-sided α of 0.1.

Results

A total of 56 pts were enrolled from July 2011 to May 2012. Two pts were ineligible with inadequate renal function and no measurable lesion. Characteristics of 54 eligible pts were as follows: median age of 66 (range 34-75), M/F: 42/12, PS0/1: 42/12, unresectable/recuurent: 51/3, and IHC 2+/3+: 9/45. As one patient did not receive the protocol treatment due to the rapid progression of tumor, the efficacy and the safety analyses were conducted in the full analysis set of 53 pts. The confirmed response rate assessed by the independent review committee was 68%, and the disease control rate was 94%. The response rate without interval confirmation was 75%. The grade 3/4 adverse events (>5% of pts) were as follows: neutropenia 30%, leucopenia 8%, anorexia 21%, diarrhea 8%, hypoalbuminemia 8%, vomiting 6%, and increased creatinine 6%.

Conclusions

T-mab in combination with triweekly SP regimen showed promising antitumor activity and manageable toxicities in pts with HER2-positive AGC.

Background

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- 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

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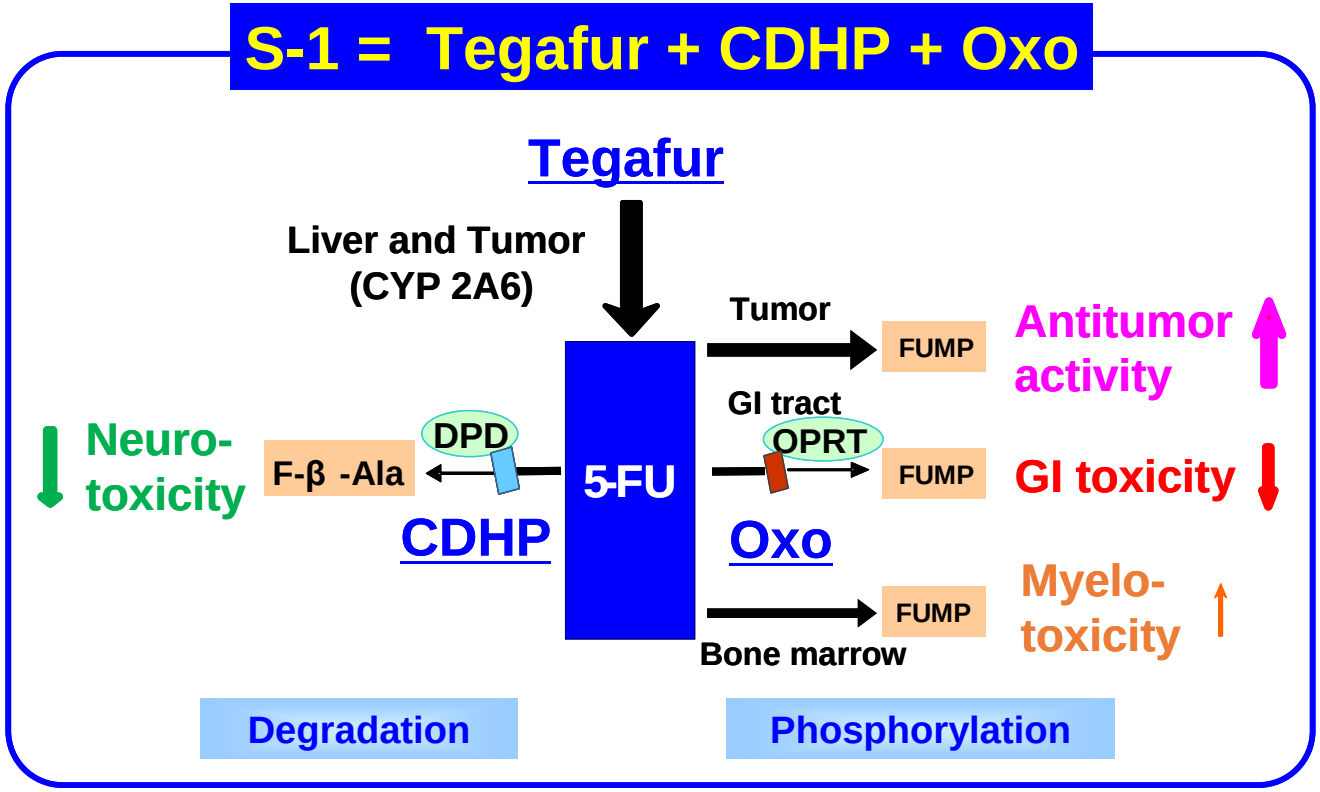
- **S-1 (tegafur, CDHP, Oxo) is an oral "DPD inhibitory fluoropyrimidine (DIF)" widely used to treat various solid tumors in East Asia.**

Biochemical action of S-1



DPD, dihydropyrimidine dehydrogenase
OPRT, orotate phosphoribosyltransferase

Objective

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- To clarify the efficacy and the safety of combined therapy with trastuzumab and SP (3 weekly) in Her2-positive advanced gastric.

- 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

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- 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

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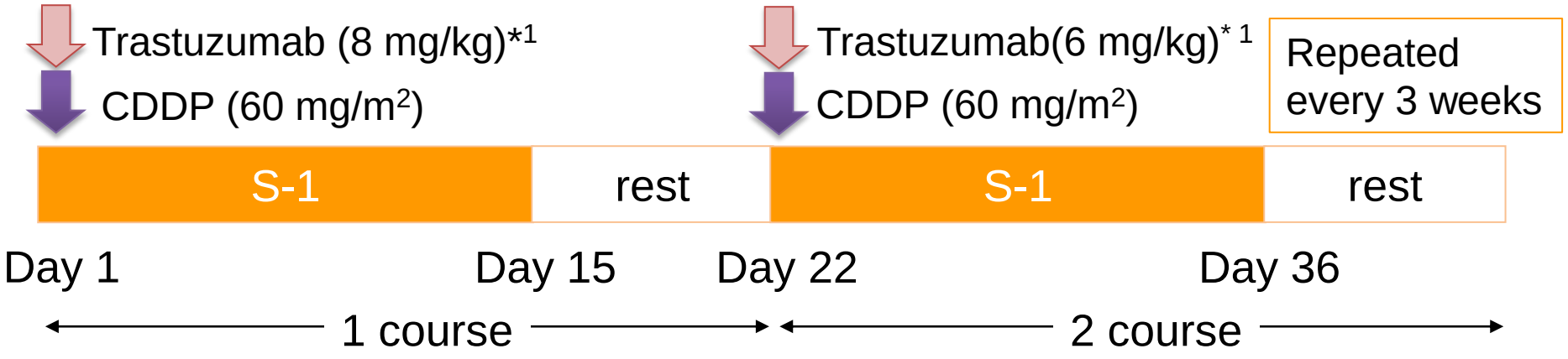
- S-1: a fixed dose of 80, 100, or 120 mg/patient p.o. in 2 divided doses for 14 days, followed by a 7-day rest.
- Trastuzumab, CDDP: day 1.

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

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

50 patients

CONSORT diagram

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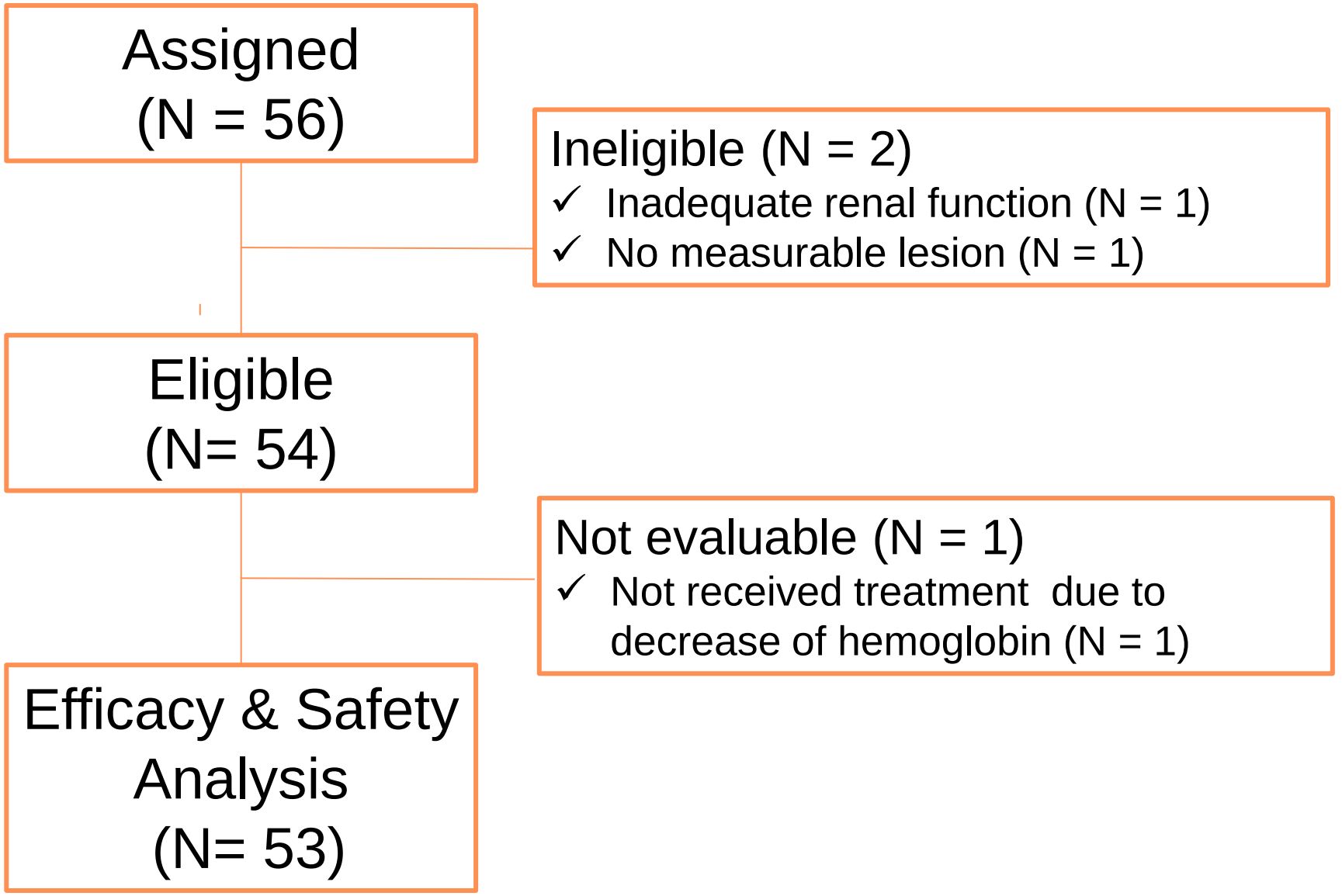

Patient baseline characteristics

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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

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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)

Relative dose intensity

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Drug	Mean (%)	Median (%)
Trastuzumab	94	95
S-1	73	74
CDDP	75	79

Relative Dose intensity (RDI)

Actual total dose / Planned dose* [%], until discontinuation of drug

* Trastuzumab : 6 mg/kg/3weeks x treatment period (1st course 8 mg/kg)

S-1: 80 or 100 or 120 mg x 2 weeks /3weeks x treatment period

CDDP : 60 mg/m^2/3weeks x treatment period

Overall response rates

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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

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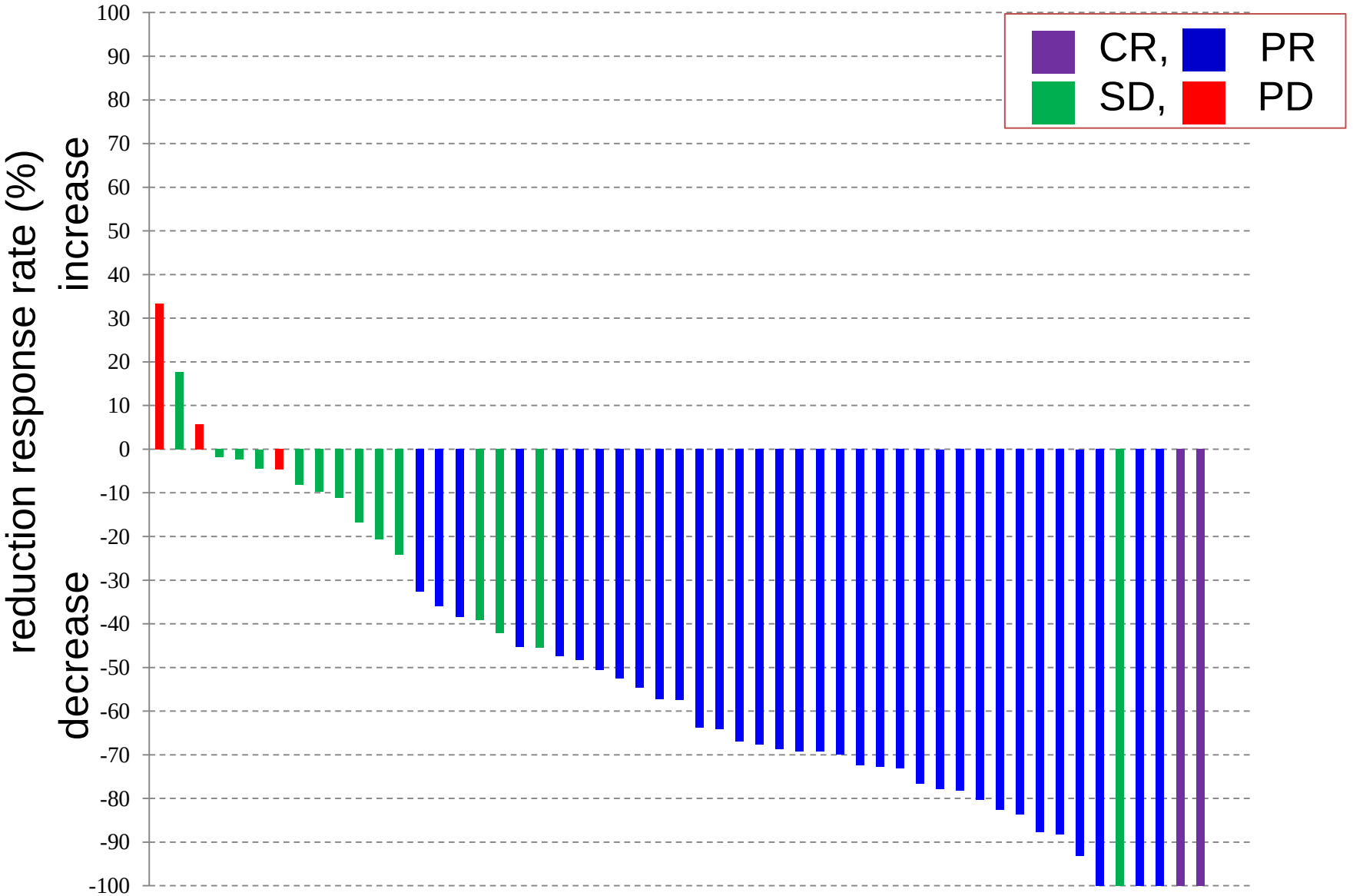
Efficacy analysis population (n = 53)



Adverse Events

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Safety analysis population (n = 53)

Event	Any Grade (%)		G3-4 (%)	
Leukopenia	34	(64.2)	4	(7.5)
Neutropenia	27	(50.9)	16	(30.2)
Febrile neutropenia	2	(3.8)	2	(3.8)
Anemia	31	(58.5)	5	(9.4)
Thrombocytopenia	20	(37.7)	0	(0.0)
Creatinine increased	17	(32.1)	3	(5.7)
Total bilirubin increased	6	(11.3)	0	(0.0)
AST increased	6	(11.3)	0	(0.0)
ALT increased	13	(24.5)	0	(0.0)
Hypoalbuminemia	21	(39.6)	4	(7.5)

Adverse Events

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Safety analysis population (n = 53)

Event	Any Grade (%)		G3-4 (%)	
Anorexia	39	(73.6)	11	(20.8)
Nausea	28	(52.8)	1	(1.9)
Vomiting	10	(18.9)	3	(5.7)
Stomatitis	14	(26.4)	1	(1.9)
Diarrhea	19	(35.8)	4	(7.5)
Constipation	9	(17.0)	0	(0.0)
Fatigue	31	(58.5)	2	(3.8)
Skin rash	9	(17.0)	0	(0.0)
Epistaxis	4	(7.5)	0	(0.0)
Edema	5	(9.4)	0	(0.0)
Dysgeusia	9	(17.0)	0	(0.0)
Hypertension	2	(3.8)	0	(0.0)
Infusion Related Reaction	2	(3.8)	0	(0.0)

Reasons of discontinuation

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Eligible (n = 54)

Status/Reason	Number
Under protocol treatment	22
Discontinuation of protocol treatment	32
Reason for discontinuation	
1. Progression of disease	18
2. Adverse event	8
3. Patient refusal (related adverse event)	2
4. Patient refusal (not related adverse event)	0
5. Operation by treatment effect	3
6. Discontinuation before protocol treatment	1[*1]
7. Other	0

*1: Due to decrease of hemoglobin

Conclusion

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- SP plus trastuzumab showed high response rate of 67.9% (80% CI 58.3 – 76.4%; 95% CI:53.7 – 80.1%).
- The main adverse events of grade 3 or 4 were neutropenia 30.2%, anorexia 20.8%, anemia 9.4%, diarrhea 7.5% and hypoalbuminemia 7.5%.
- This regimen showed promising activity and acceptable toxicity for HER2 positive advanced gastric cancer.

Acknowledgement

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Participating Institutions

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Osaki Citizen Hospital
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Osaka Rosai Hospital
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National Hospital Organization Osaka National Hospital
Hakodate Central General Hospital
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Yamagata Prefectural Central Hospital
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National Hospital Organization Sendai Medical Center
Miyagi Cancer Center
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Osaka General Medical Center
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