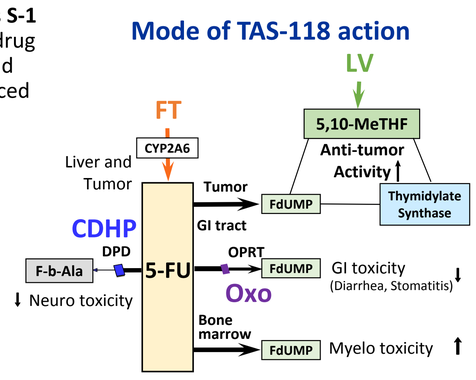
A phase III study of TAS-118 plus Oxaliplatin versus S-1 plus Cisplatin as first-line therapy in patients with advanced gastric cancer (SOLAR)

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Introduction and objectives

- A fluoropyrimidine plus platinum compound has been used as the standard first-line chemotherapy for advanced gastric cancer (AGC)[1,2].
- Oral fluoropyrimidines such as **S-1** which contains **tegafur** (a prodrug of 5-fluorouracil), **gimeracil** and **oteracil potassium** have replaced continuous infusion of fluorouracil and been widely used[3-5].
- The efficacy of fluorouracil is enhanced by leucovorin (LV) which stabilizes the ternary complex formed between fluorodeoxyuridine monophosphate (FdUMP) and thymidylate synthase[6].



- **TAS-118** is an oral drug containing **S-1** plus **leucovorin (LV)**.
- A randomized phase II Japanese study showed that S-1 plus LV and oaxaliplatin was better than S-1 plus cisplatin in terms of response, progression-free survival, and overall survival in patients with AGC[7] (**Table 1**).

Table 1. The result of randomized phase II study for AGC in Japan

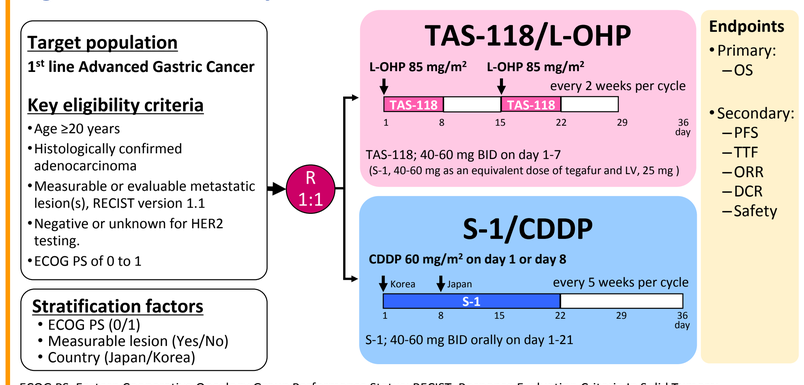
	S-1 plus LV and oxaliplatin (n=47) [a]	S-1 plus cisplatin (n=48) [a]
OS		
Median, months	18.4	12.6
HR (95% CI): *P* value	0.59 (0.37–0.93): *P*=0.023	
PFS		
Median, months	8.3	5.6
HR (95% CI): *P* value	0.60 (0.35–1.02): *P*=0.054	
ORR and DCR		
ORR, n (%)	31 (66)	22 (46)
DCR, n (%)	47 (100)	40 (83)

[a] Full analysis set (FAS)
OS, Overall Survival; HR, Hazard Ratio; CI, Confidence Interval; PFS, Progression-Free Survival; ORR, Overall Response Rate; DCR, Disease Control Rate

Methods

- This randomized, open-label, phase III trial (SOLAR study, NCT02322593; **Figure 1**) was conducted to evaluate the efficacy and safety of TAS-118 plus oxaliplatin vs. S-1 plus cisplatin in patients with AGC in Japan and Korea.
- Tumor response was evaluated every 6 week by CT or MRI.

Figure 1. SOLAR study schema



ECOG PS, Eastern Cooperative Oncology Group Performance Status; RECIST, Response Evaluation Criteria In Solid Tumors; R, Randomized; L-OHP, oxaliplatin; CDDP, cisplatin; TTF, Time to Treatment Failure

Statistical assumptions and study conduct

- **Primary endpoint : OS by FAS**
  - Expected OS hazard ratio: 0.75
    - MST 19.33 months with TAS-118/L-OHP vs 14.5 months with S-1/CDDP
    - 19 months of accrual and 19 months of follow-up
    - 85% power and 2-sided significance level of 5% in overall study (adjusted by O'Brien-Fleming method)
  - Required total events: 491, Planned sample size: 686
    - In initial protocol, 437 OS events were planned to be required.
    - The IDMC determined that the required number of OS event should be changed (Mar 2017).
      - More prolonged OS than expected, because of introduction of ramucirumab in the second-line and nivolumab in the third-line.
- **Interim Analysis (IA)**
  - 1st IA for safety when 100 events were confirmed (Jul 2016).
  - 2nd IA for efficacy and safety when 219 events were confirmed (Mar 2017).

MST, Median Survival Time; IDMC, Independent Data Monitoring Committee

Results

- From Jan 2015 to Dec 2016, 711 patients were randomized to either TAS-118 plus oxaliplatin (n=356) or S-1 plus cisplatin (n=355) (**Figure 2**).
- The IDMC recommended to exclude ineligible 19 cases from FAS who were judged at central review by IDMC not to have advanced metastatic gastric cancer in a blinded manner (Mar 2018) (**Figure 2**).
- Data cut-off for primary analysis with 491 events was Mar 2018 (median follow-up time, 15 months).
- Baseline characteristics were well balanced, except for gender (**Table 2**)

Figure 2. Patient disposition

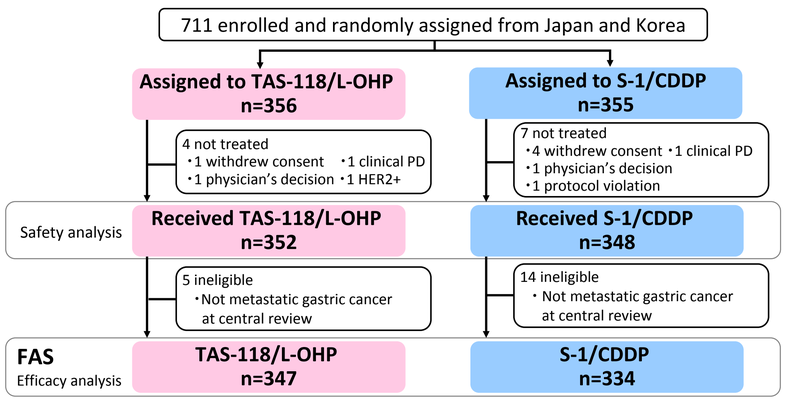


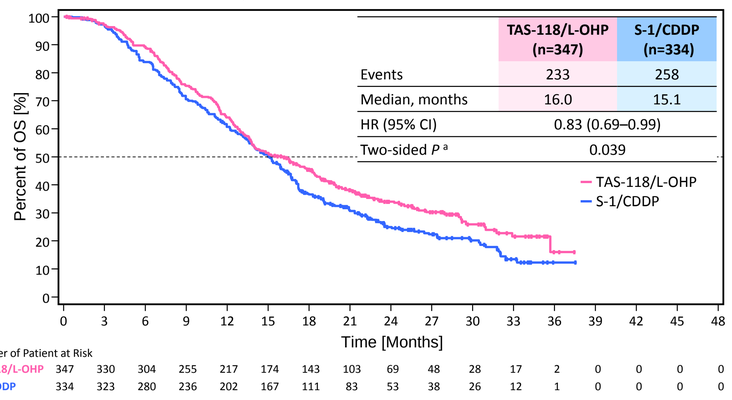
Table 2. Patient baseline characteristics

		TAS-118/L-OHP (n=347) %	S-1/CDDP (n=334) %
Age (years)	Median (min, max)	62.0 (21, 79)	62.0 (26, 80)
Gender [a]	Male	72.3	65.3
	Female	27.7	34.7
Country	Japan	63.7	63.5
	Korea	36.3	36.5
ECOG PS	0	55.3	53.9
	1	44.7	46.1
Measurable Lesion	No	36.6	35.9
	Yes	63.4	64.1
Histological Type (Lauren) [b]	Diffuse	69.5	70.0
	Intestinal	30.3	30.0
	Unknown	0.3	0
Primary Tumor Site	Stomach	95.4	95.5
	EGJ	4.6	4.5
Prior Gastrectomy	No	78.1	80.2
	Yes	21.9	19.8
Disease Status	Metastatic	84.7	88.3
	Recurrent	15.3	11.7
Number of Organ Metastases	1	36.6	34.4
	2	42.1	42.8
	≥3	21.3	22.8
Peritoneal Metastasis	No	61.1	59.9
	Yes	38.9	40.1

[a] Fisher's exact test *P*=0.048. [b] If there are multiple type of histology, select the one which the investigator considered as histologically predominant. If it is difficult to judge the predominant one, select the one which the malignancy is worse.
EGJ, Esophagogastric Junction

- In the primary analysis with 491 events, median OS was 16.0 months in TAS-118 plus oxaliplatin and 15.1 months in S-1 plus cisplatin (HR 0.83; 95% CI 0.69-0.99; stratified log-rank test *P*=0.039) (**Figure 3**).

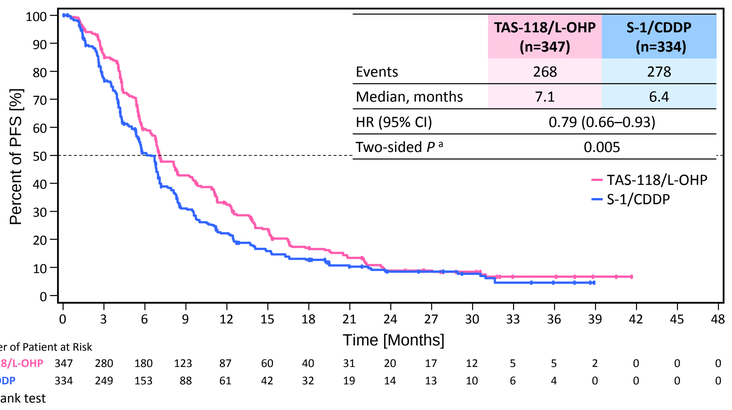
Figure 3. Kaplan-Meier plot of overall survival



[a] Stratified log-rank test (Significance level at primary analysis = 0.048581)

- Median PFS was 7.1 months in TAS-118 plus oxaliplatin and 6.4 months in S-1 plus cisplatin (HR 0.79; 95% CI 0.66-0.93; *P*=0.005) (**Figure 4**).

Figure 4. Kaplan-Meier plot of progression-free survival



[a] Logrank test

- OS subgroup analysis favored TAS-118 plus oxaliplatin over S-1 plus cisplatin in all prespecified subgroups (**Figure 5**).

Figure 5. OS subgroup analysis

		TAS-118/L-OHP (n)	S-1/CDDP (n)	HR (95% CI)
Age (years)	<65	201	194	0.85 (0.68-1.07)
	≥65	146	140	0.78 (0.58-1.03)
Gender	Male	251	218	0.87 (0.70-1.08)
	Female	96	116	0.70 (0.51-0.97)
Country	Japan	221	212	0.86 (0.69-1.09)
	Korea	126	122	0.76 (0.58-1.00)
ECOG PS	0	192	180	0.71 (0.56-0.92)
	1	155	154	1.00 (0.78-1.28)
Measurable Lesion	No	127	120	0.74 (0.55-1.00)
	Yes	220	214	0.87 (0.70-1.09)
Histological Type (Lauren)	Diffuse	241	233	0.82 (0.66-1.01)
	Intestinal	105	100	0.82 (0.59-1.16)
Prior Gastrectomy	No	277	272	0.82 (0.67-0.99)
	Yes	70	62	0.88 (0.56-1.36)
Disease Status	Metastasis	294	295	0.81 (0.67-0.98)
	Recurrent	53	39	0.93 (0.54-1.61)
Number of Organ Metastases	1	127	115	0.88 (0.64-1.20)
	2	146	143	0.89 (0.68-1.16)
	≥3	74	76	0.67 (0.46-0.96)
Peritoneal Metastasis	No	212	200	0.94 (0.75-1.18)
	Yes	135	134	0.66 (0.50-0.87)

0.5 1.0 2.0
←Favours TAS-118/L-OHP Favours S-1/CDDP→

- ORR in TAS-118 plus oxaliplatin and S-1 plus cisplatin were 73.5 % and 50.0 %, respectively (*P*<0.001) (**Table 3**).

Table 3. ORR and DCR in patients with measurable lesions

	TAS-118/L-OHP (n=211) [a] %	S-1/CDDP (n=212) [a] %	*P* value [b]
ORR, (95% CI)	**73.5** (67.0-79.3)	**50.0** (43.1-56.9)	<0.001
DCR, (95% CI)	**93.4** (89.1-96.3)	**88.2** (83.1-92.2)	0.092
BOR			
CR	2.8	3.3	
PR	70.6	46.7	
SD	19.9	38.2	
PD	6.2	11.3	
NE	0.5	0.5	

[a] Analysis Set; Tumor Response Evaluable Population, [b] Fisher's exact test
BOR, Best Overall Response; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progression Disease; NE, Not Evaluable

- The most common reason of discontinuation was RESIST PD. (76.7% in TAS-118 plus oxaliplatin and 79.4% in S-1 plus cisplatin)
- Post study treatment was given to 77.5% in TAS-118 plus oxaliplatin and 83.8% in S-1 plus cisplatin (**Table 4**).

Table 4. Reasons of discontinuation and post treatment

	TAS-118/L-OHP (n=347) %	S-1/CDDP (n=334) %
Discontinuation	95.1	97.3
RECIST PD	76.7	79.4
Adverse Events	5.8	4.9
Dose delay over 28 days	2.1	5.2
Surgery after tumor shrinkage	4.8	2.8
Patient's request to discontinue	4.5	1.8
Investigator discretion	6.1	5.8
Post study treatment	77.5	83.8
Chemotherapy	98.9	98.2
Paclitaxel	71.7	76.1
Irinotecan	50.9	49.6
Ramucirumab	58.4	50.0
Nivolumab	18.6	18.9

- The incidences of grade ≥3 adverse events were 69.6% in TAS-118 plus oxaliplatin and 69.3% in S-1 plus cisplatin (**Table 5**).
- The most common grade 3/4 adverse events were stomatitis (3.7% in TAS-118 plus oxaliplatin vs 1.4% in S-1 plus cisplatin), diarrhea (9.4% vs 4.3%), peripheral sensory neuropathy (8.5% vs 0.3%) and weight decreased (5.4% vs 2.9%) (**Table 5**).
- Two treatment-related deaths were reported in TAS-118 plus oxaliplatin.
- No new safety signals were observed in the two treatment arms.

Table 5. Adverse events

	TAS-118/L-OHP (n=352) [a] %		S-1/CDDP (n=348) [a] %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse events	100.0	69.6	98.9	69.3
Anaemia [b]	37.2	15.9	39.7	18.4
Neutropenia [c]	39.8	15.3	48.3	25.3
Thrombocytopenia [d]	31.8	2.0	24.7	5.7
Nausea	60.8	4.0	57.2	3.2
Vomiting	35.8	1.7	27.9	1.7
Stomatitis	**43.5**	**3.7**	**25.3**	**1.4**
Diarrhoea	**58.8**	**9.4**	**42.8**	**4.3**
Constipation	37.5	1.1	41.7	0.0
Decreased appetite	70.7	15.1	68.1	13.2
Dysgeusia	31.8	0.3	23.6	0.0
Peripheral sensory neuropathy	**68.8**	**8.5**	**16.7**	**0.3**
Fatigue	34.9	2.8	31.9	2.6
Weight decreased	**29.0**	**5.4**	**18.1**	**2.9**
AST increased	17.6	2.3	7.5	1.4
Hiccups	9.4	0.0	22.4	0.6
Febrile neutropenia	1.1	1.1	1.7	1.7

Any Grade ≥30% or over 10% differences between arms
[a] As treated Population. [b] Anaemia and/or Haemoglobin Decreased. [c] Neutropenia and/or Neutrophil Count Decreased. [d] Thrombocytopenia and/or Platelet Count Decreased. AST, Aspartate aminotransferase

Conclusions

- This phase III SOLAR study demonstrated the better efficacy of TAS-118 plus oxaliplatin compared to S-1 plus cisplatin as a first-line chemotherapy in AGC.
  - OS: HR 0.83; 95%CI (0.69-0.99); *P*=0.039
  - PFS: HR 0.79; 95%CI (0.66-0.93); *P*=0.005
  - Overall Response rate: 73.5% vs 50.0%; *P*<0.001
- Although non-hematological toxicities of TAS-118 plus oxaliplatin were more frequently observed than S-1 plus cisplatin, their incidences of ≥grade 3 were less than 10%.
- TAS-118 plus oxaliplatin can be a new standard first-line chemotherapy for AGC.

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