

The START trial: S-1/doce vs. S-1

Japan Clinical Cancer Research Organization and
Korean Cancer Study Group Inter-Group Study

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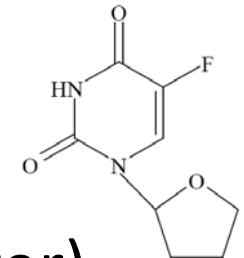
Disclosures / conflicts of interest

- Study grant – Merck
- Lecture honoraries - Merck, Roche, Amgen
- Advisory boards - Merck, Roche, Sanofi-Aventis, BMS
- I never prescribed S-1

S-1

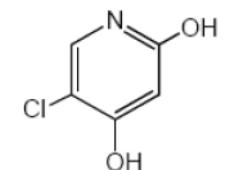
- **Tegafur**

- metabolized to 5-FU
mainly through P450 isoenzyme CYP2A6 (liver)



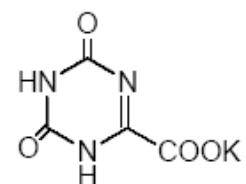
- **Gimeracil**

- inhibits DPD (and 5-FU metabolism)



- **Oteracil**

- inhibits OPRT (orotate phosphoribosyl transferase)
– to decrease GI toxicity



S-1

EMA:

The approved indication is:

“Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with cisplatin”.

20 mg tegafur, 5.8 mg gimeracil, 15.8 mg oteracil

15 mg tegafur, 4.35 mg gimeracil and 11.8 mg oteracil

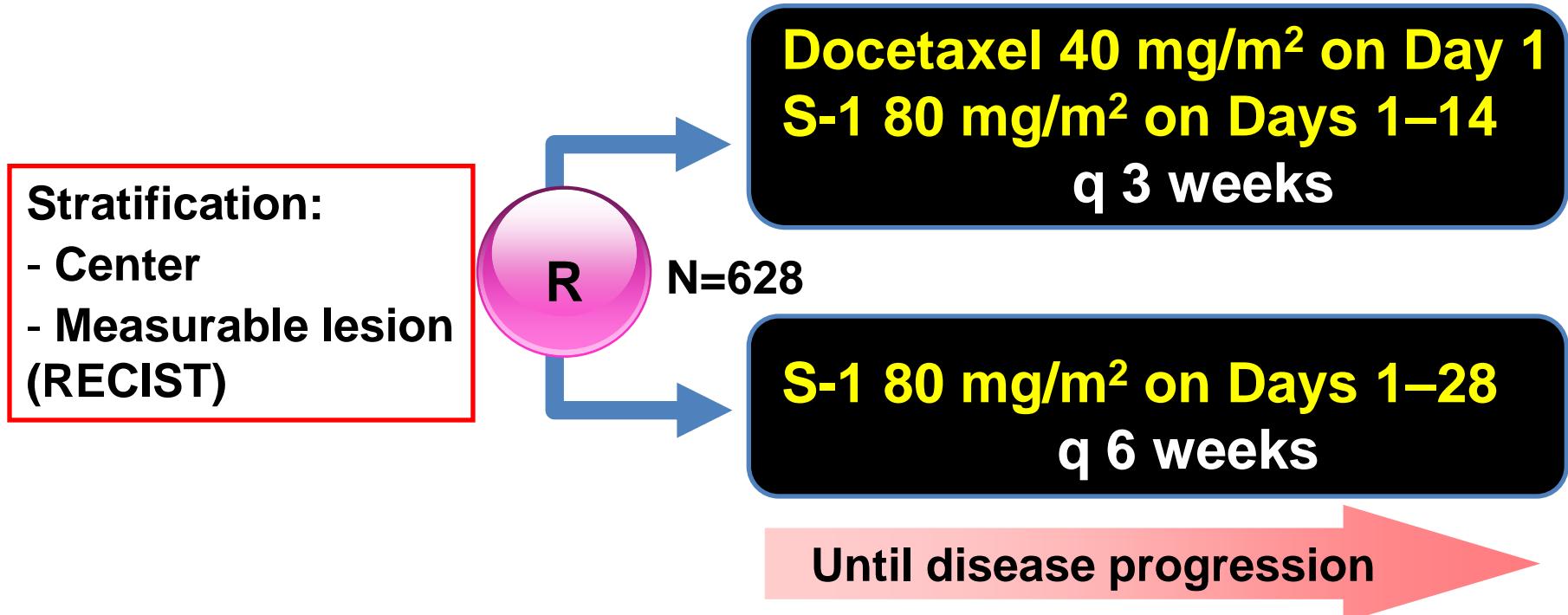
S-1 plus Docetaxel versus S-1 for Advanced Gastric Cancer (START Trial) Update 2012

(NCT 00287768)



Kazuhiro Yoshida, Masashi Fujii, Wasaburo Koizumi, Hoon Kyo Kim,
Yeul Hong Kim, Masahiro Takeuchi, Toshifusa Nakajima,
Japan Clinical Cancer Research Organization and Korean Cancer
Study Group Inter-Group Study

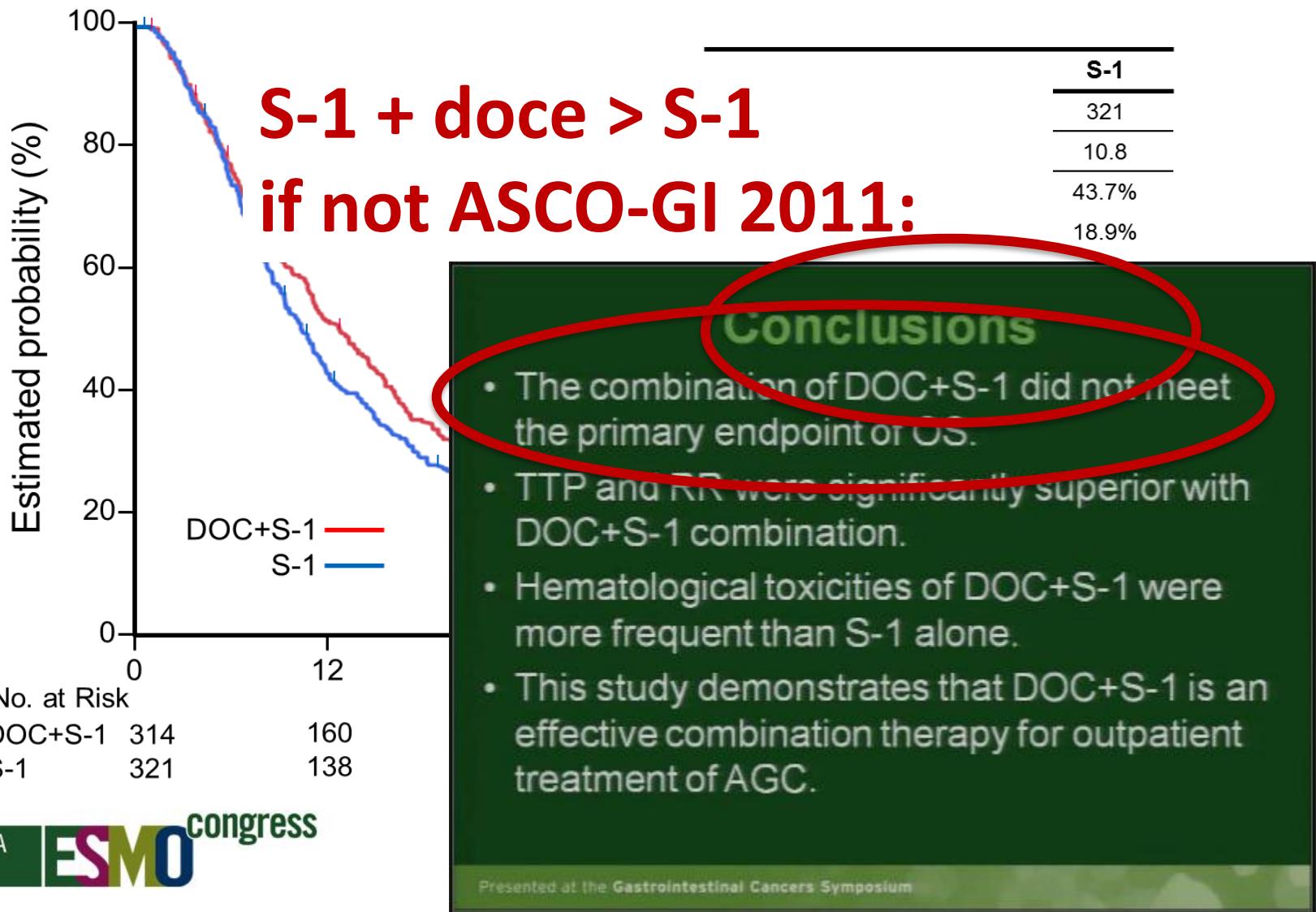
Study Design



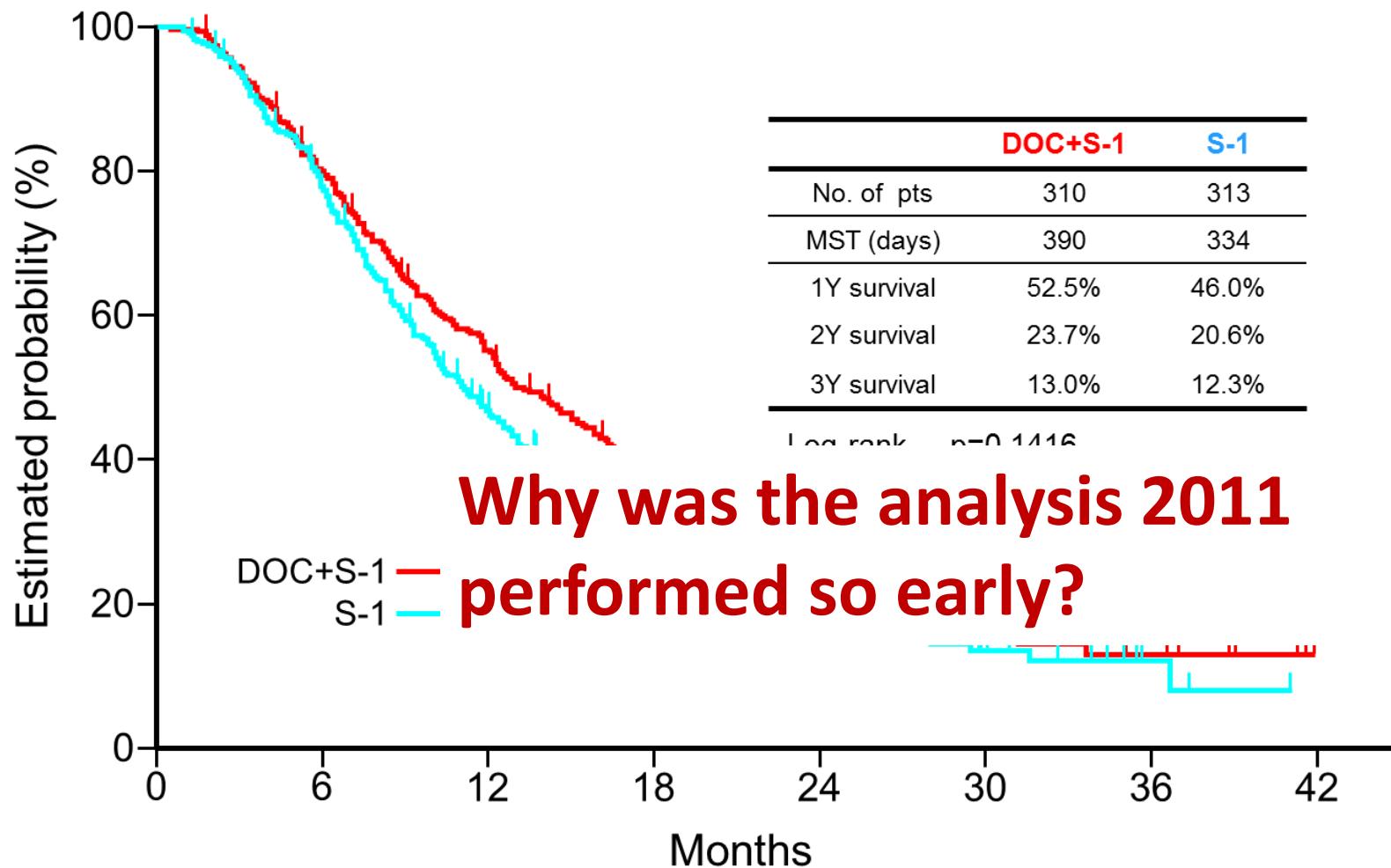
Primary endpoint: OS

Secondary endpoints: PFS, RR, Safety

Overall Survival



Overall Survival (ASCO GI 2011)



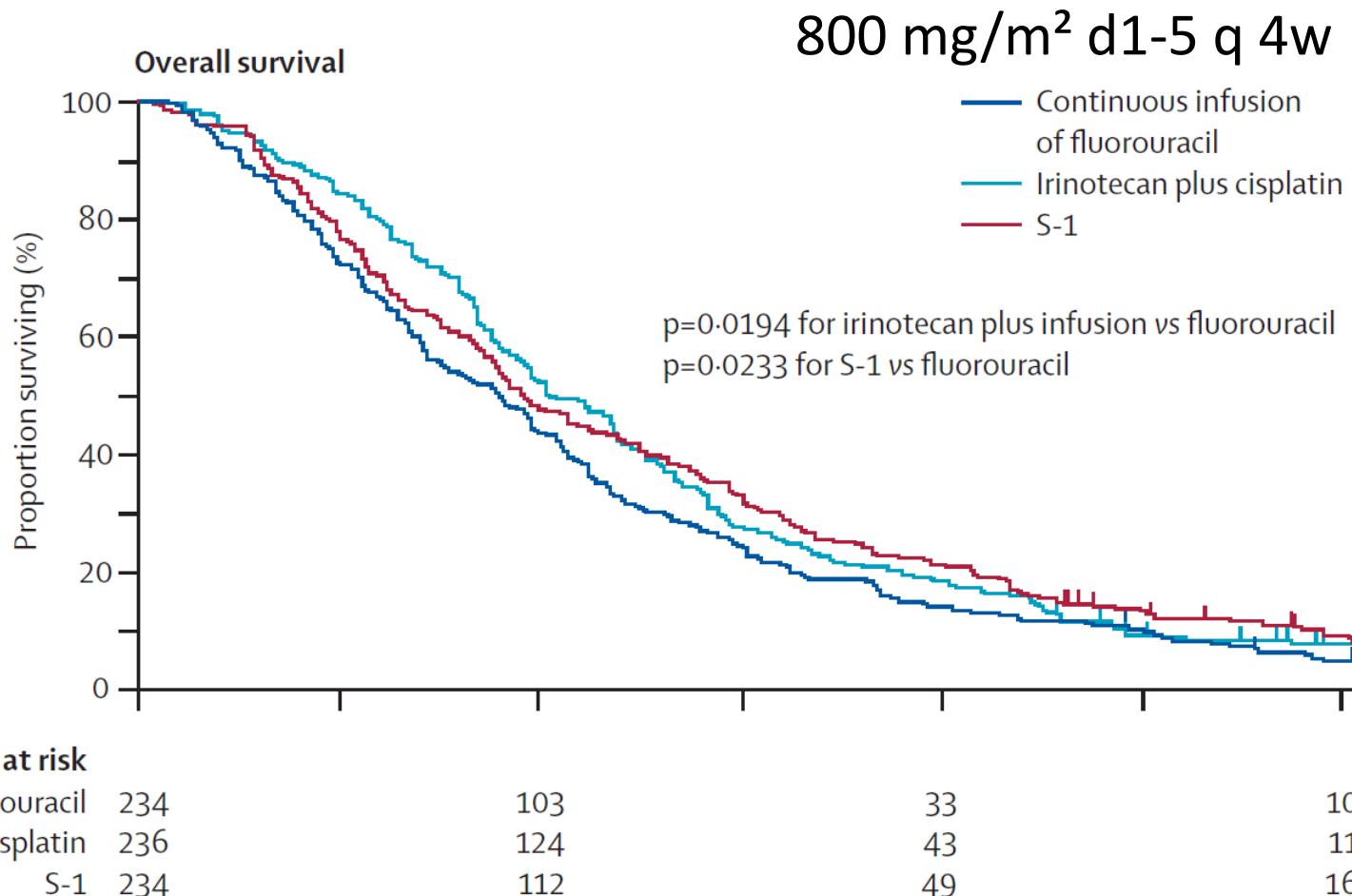
ORIGINAL ARTICLE

Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine

Shinichi Sakuramoto, M.D., Mitsuru Sasako, M.D., Toshiharu Yamaguchi, M.D.,
Taira Kinoshita, M.D., Masashi Fujii, M.D., Atsushi Nashimoto, M.D.,
Hiroshi Furukawa, M.D., Toshifusa Nakajima, M.D., Yasuo Ohashi, Ph.D.,
Hiroshi Imamura, M.D., Masayuki Higashino, M.D., Yoshitaka Yamamura, M.D.,
Akira Kurita, M.D., and Kuniyoshi Arai, M.D., for the ACTS-GC Group*

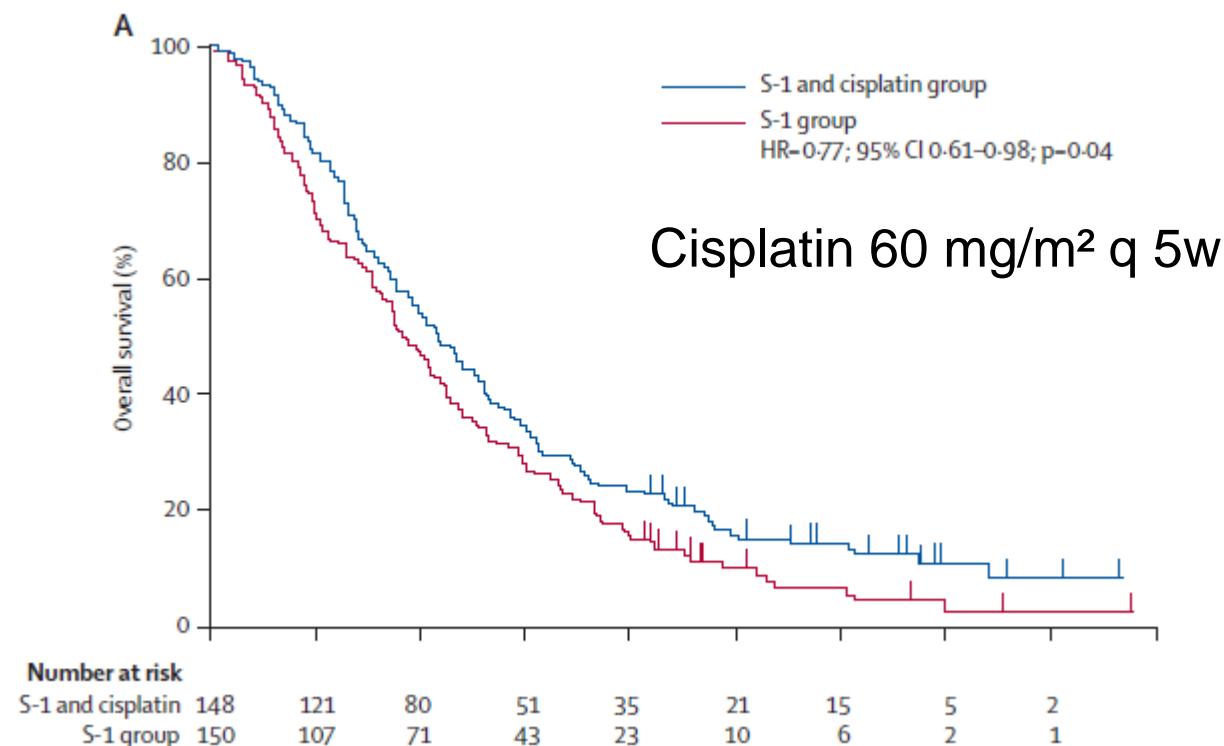
- Is S-1 better than 5-FU?
 - which 5-FU

JCOG 9912



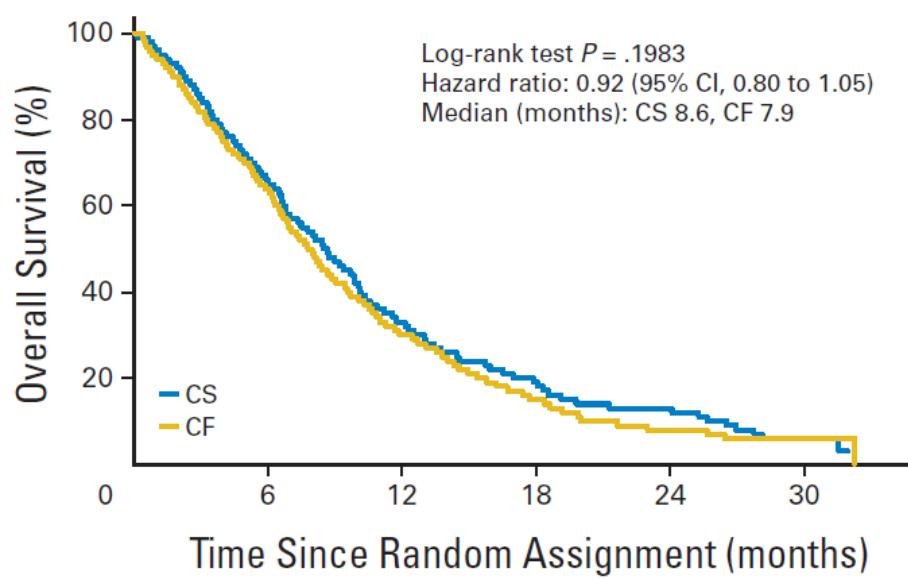
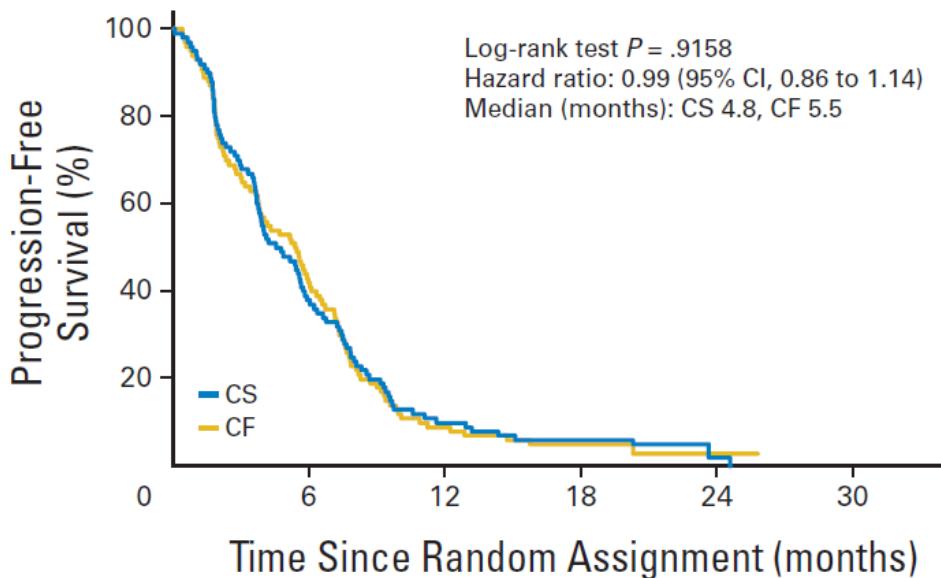
- Is S-1 better than 5-FU?
 - which 5-FU
- Is S-1 monotherapy the standard?

SPIRIT: S-1/cisplatin vs S-1



- Is S-1 better than 5-FU?
 - which 5-FU
- Is S-1 monotherapy the standard?
- Is S-1/Cisplatin better than 5-FU/Cisplatin?

FLAGS trial: S-1/cis vs. 5-FU/cis



S-1 doublets

	n	RR	PFS	OS
S-1/cisplatin	148	(54%)*	6.0	13.0
S-1	150	(31%)*	4.0	11.0
Koizumi Lancet Oncol 2008		p=0.002	HR 0.57 p<0.0001	HR 0.77 p=0.04
S-1/docetaxel	314	(39%)*	5.3	12.5
S-1	321	(27%)*	4.2	10.8
Yoshida ESMO 2012		p=0.005	HR 0.77 p=0.001	HR 0.84 p=0.03

- Is S-1 better than 5-FU?
 - which 5-FU
- Is S-1 monotherapy the standard?
- Is S-1/Cisplatin better than 5-FU/Cisplatin?
- What's the effect of the taxane?
 - and the docetaxel dose...

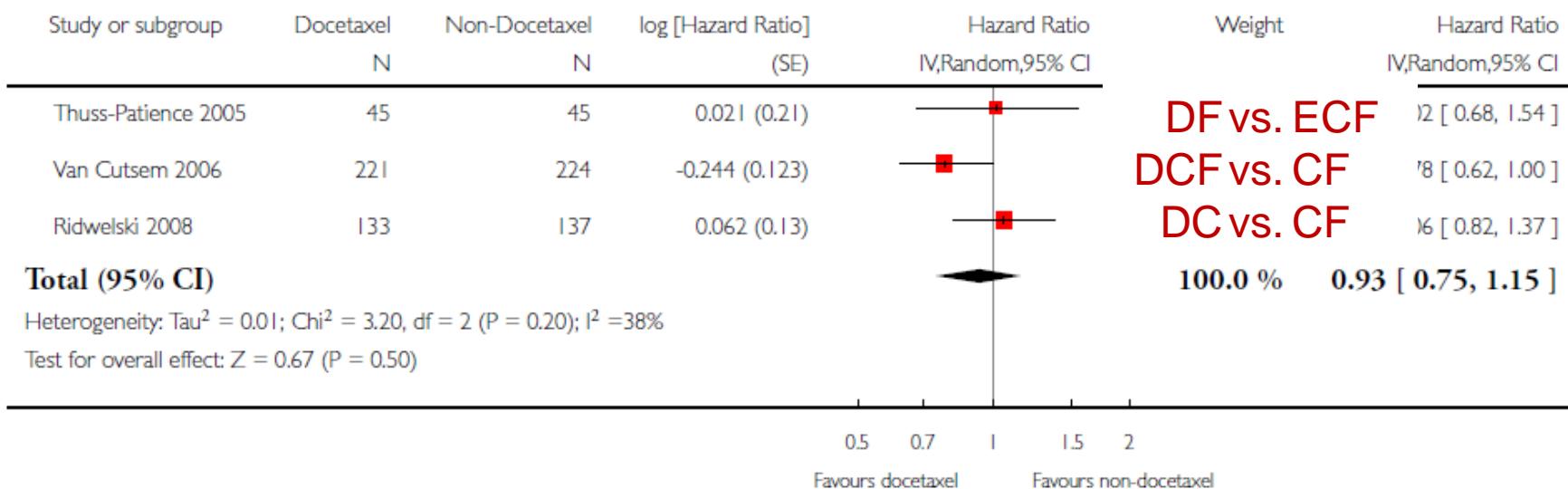
Cochrane

Analysis 6.1. Comparison 6 Docetaxel versus non-docetaxel-containing regimes, Outcome I Overall survival.

Review: Chemotherapy for advanced gastric cancer

Comparison: 6 Docetaxel versus non-docetaxel-containing regimes

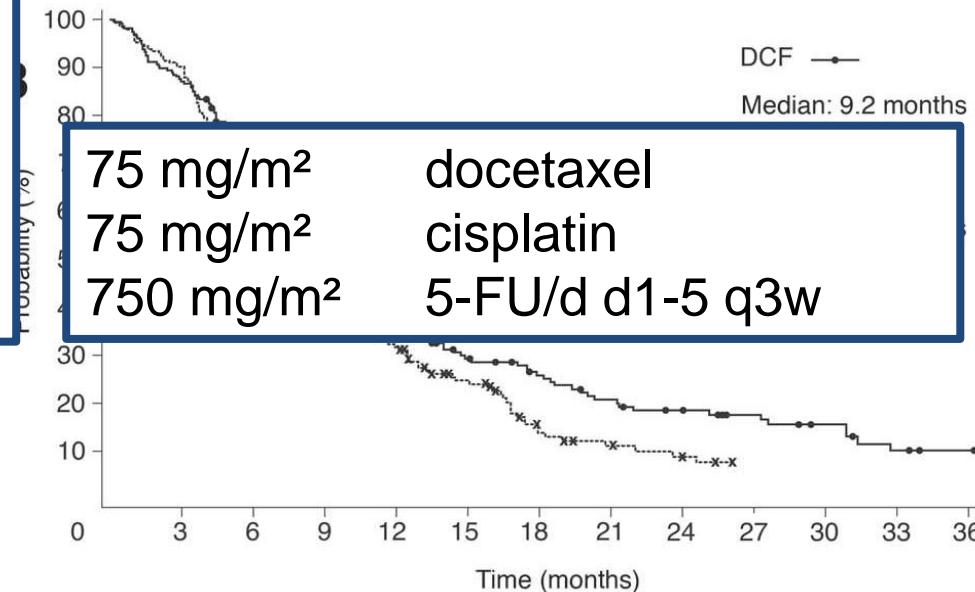
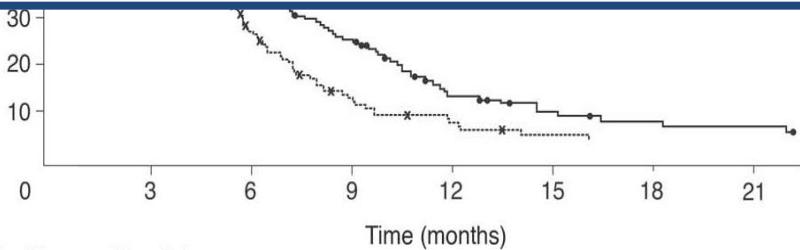
Outcome: I Overall survival



V325: 5-FU/cis vs. 5-FU/cis/doce

Neutropenia

	CF	DCF
- grade 3/4	57%	82%
- febrile/infection	12%	29%



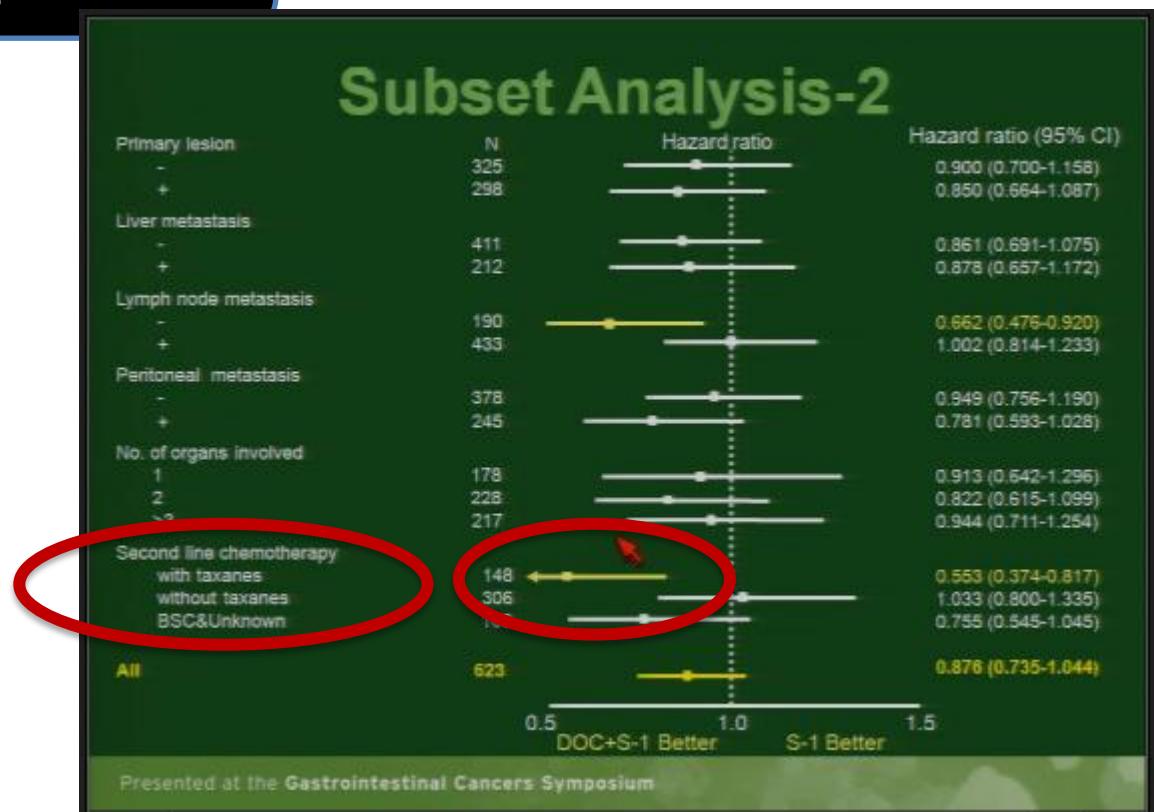
**Docetaxel 40 mg/m² on Day 1
S-1 80 mg/m² on Days 1–14
q 3 weeks**

Adverse Drug Reactions

	DOC+S-1 N=310		S-1 N=313	
	G3 / 4	(≥G3 %)	G3 / 4	(≥G3 %)
Leukocytes	59 / 9	(21.9)	6 / 2	(2.6)
Neutropenia	44 / 46	(29.0)	11 / 2	(4.2)
Platelets	2 / 2	(1.3)	2 / 0	(0.6)
Hemoglobin	30 / 3	(10.6)	20 / 1	(6.7)
Febrile neutropenia	8 / 1	(2.9)	0 / 0	(0.0)
AST	1 / 1	(0.6)	6 / 0	(1.9)
ALT	3 / 0	(1.0)	4 / 0	(1.3)
Bilirubin	3 / 1	(1.3)	4 / 1	(1.6)
Creatinine	0 / 0	(0.0)	1 / 1	(0.6)
Nausea	17 / 0	(5.5)	10 / 0	(3.2)
Vomiting	8 / 1	(2.9)	6 / 1	(2.2)
Diarrhea	9 / 0	(2.9)	14 / 1	(4.8)
Stomatitis	13 / 0	(4.2)	4 / 1	(1.6)
Anorexia	44 / 1	(14.5)	31 / 1	(10.2)
Fatigue	17 / 0	(5.5)	10 / 3	(4.2)
Rash	3 / 0	(1.0)	6 / 0	(1.9)
Treatment related death	1 (0.3%)		0 (0.0%)	

The taxane dose

**Docetaxel 40 mg/m² on Day 1
S-1 80 mg/m² on Days 1–14
q 3 weeks**



CRC-like regimens?

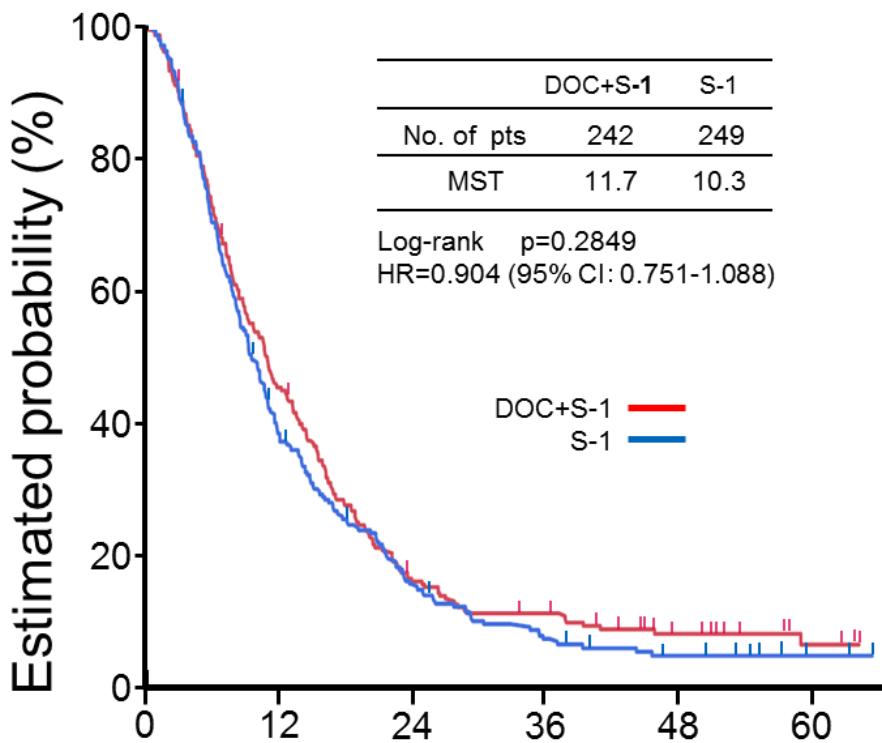
Van Cutsem 2006

	CF	DCF
Neutropenia		
- grade 3/4	57%	82%
- febrile/infection	12%	29%
Grade 3/4		
Diarrhoea	8%	19%
Stomatitis	27%	21%
Vomiting	17%	14%
Fatigue/lethargy	14%	19%
ORR	25%	37%
OS	8.6	9.2

Overall survival by strata :

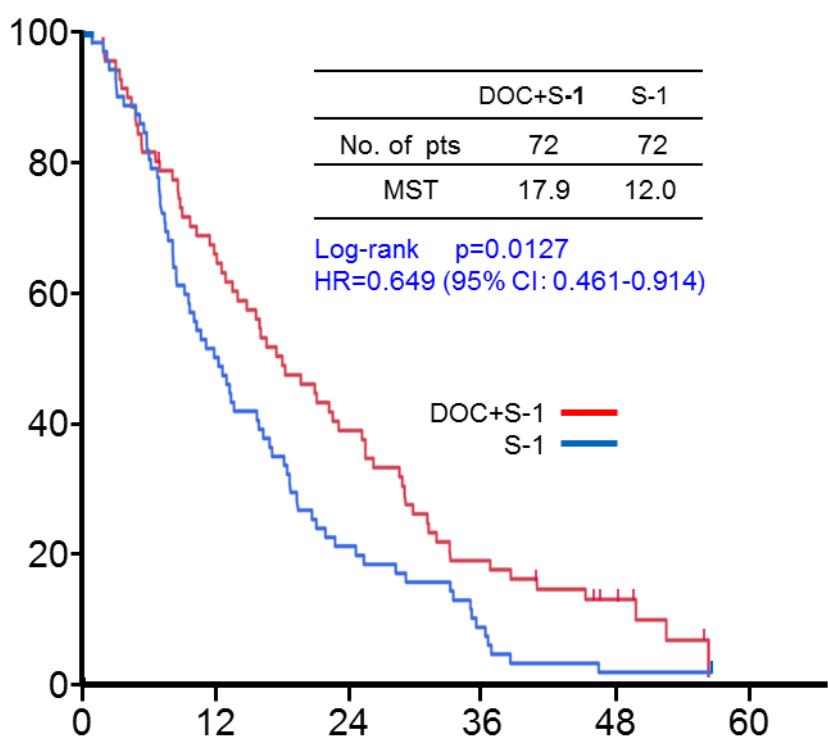
Measurable

N=491



Non-measurable

N=144



The START trial

- will probably not set the/a new standard
 - primary analysis 2011
 - standard arm
- indicates an interesting option
 - toxicity
 - platin-free arm for pharmacodynamic driven trials

I thank Professor Yoshida for sharing the slides.