Stage IIIA, IIIB胃癌に対する S-1+CPT-11併用術後補助化学療法 第II相臨床試験

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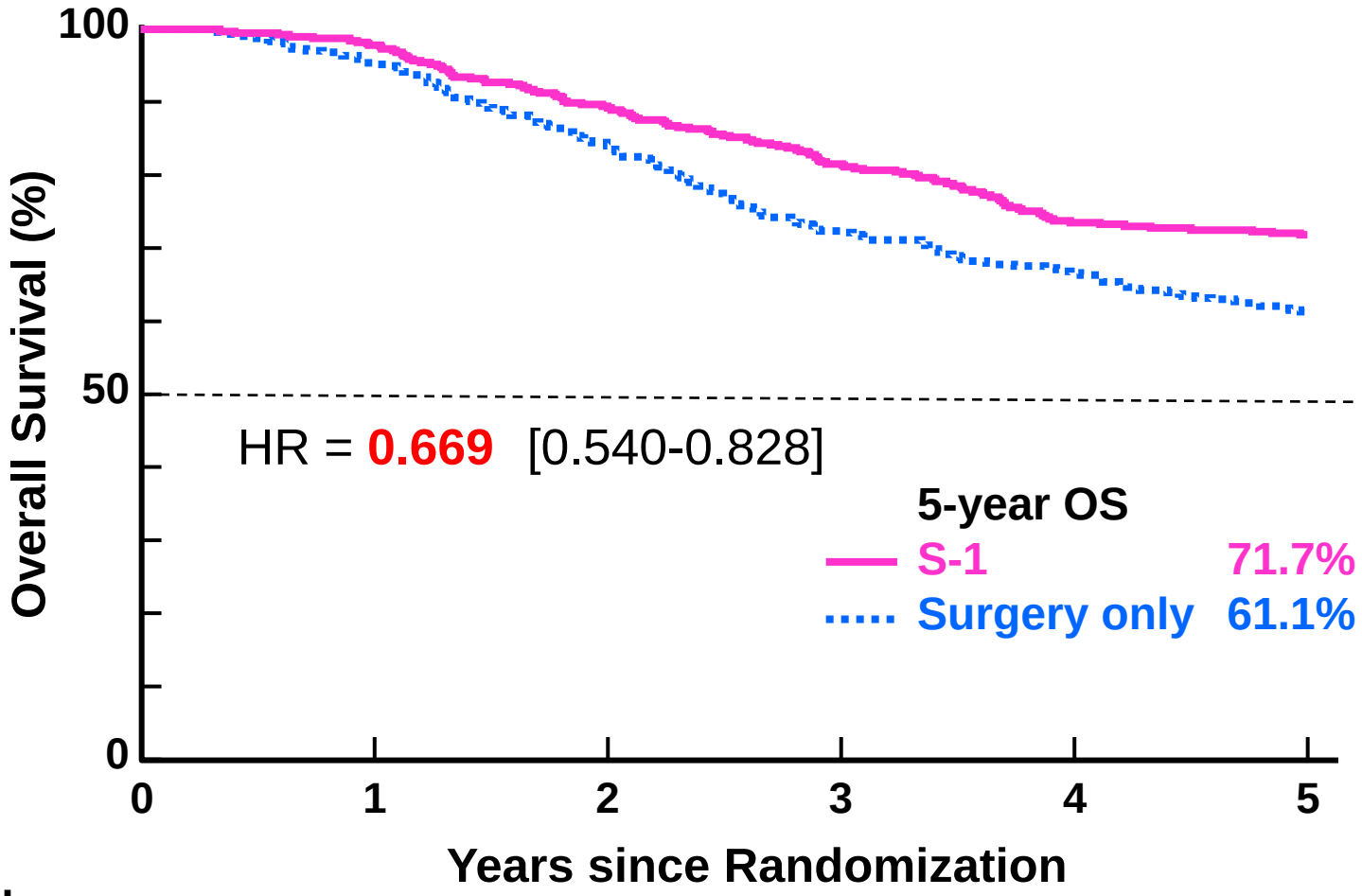
ACTS-GC : Overall survival

(Five-Year Outcomes)

(All randomized)

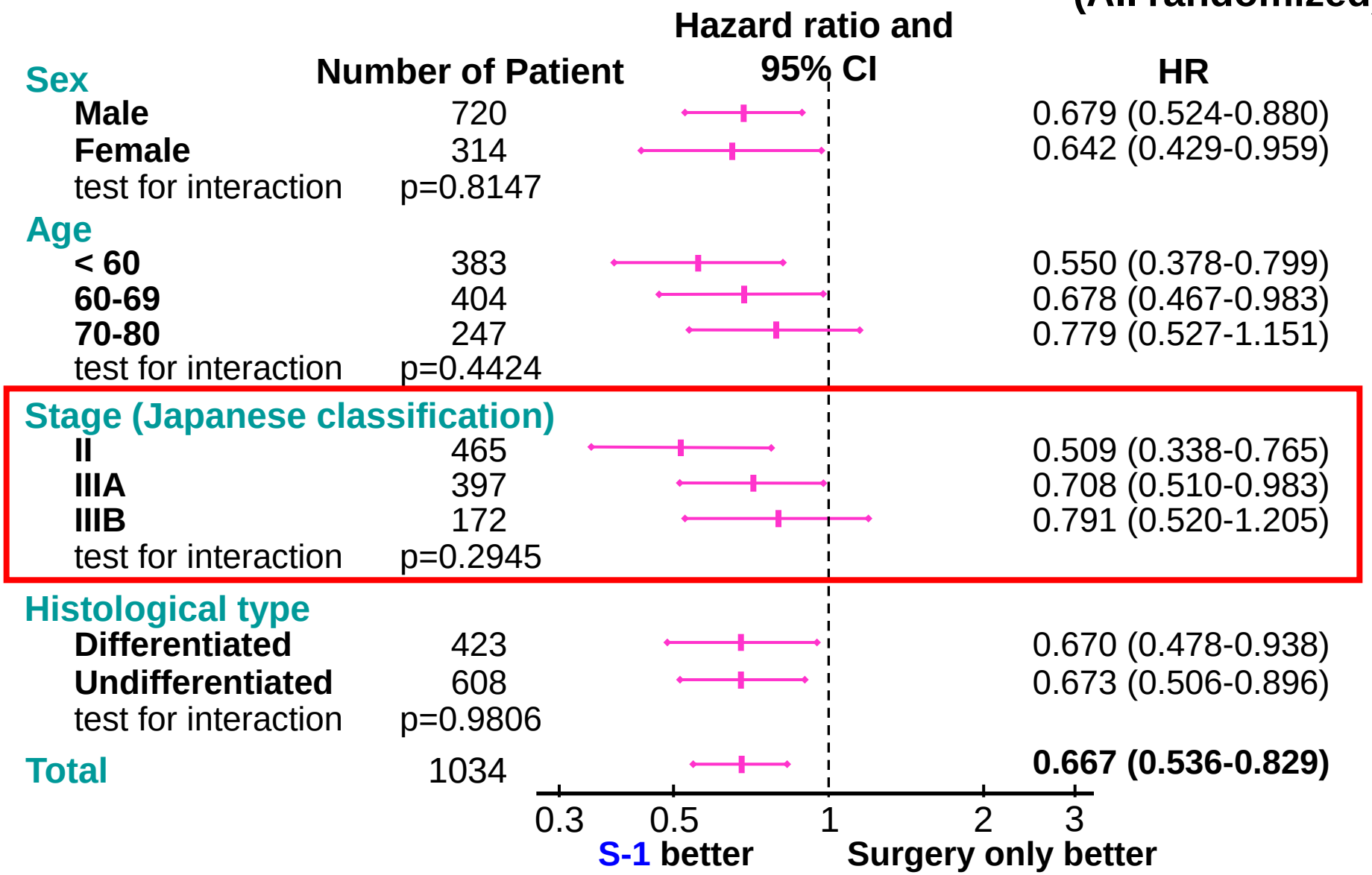


No. at risk						
S-1	529	515	465	416	363	316
Surgery only	530	504	438	365	327	268

Sasako M et al. JCO 2011; 36: 5908.

ACTS-GC : Subgroup Analysis（OS）

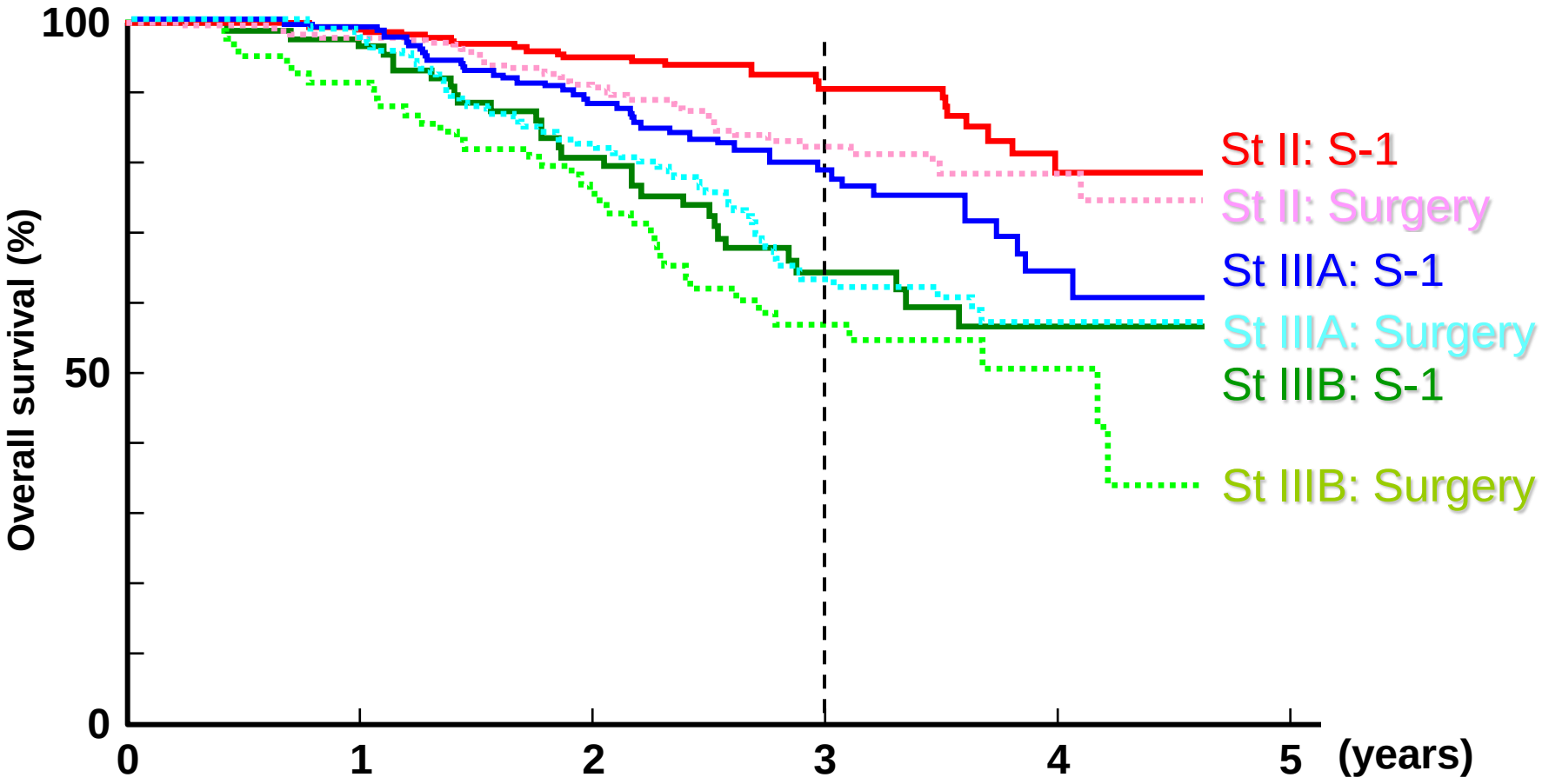
(All randomized)



Sasako M et al. JCO 2011; 36: 5908.

ACTS-GC : stage II, IIIA, and IIIB

(Eligible)



Sakuramoto S et al. NEJM 2007; 357: 1810-20.

Efficacy of adjuvant therapy for gastric cancer

- **INT-0116 study**:

  Post-op chemoradiation (CRT) (5FU+ LV) prolonged OS and DFS after D0/1 surgery. (NEJM 2001)

- **MAGIC trial**:

  Peri-op chemotherapy (ECF) prolongs OS and DFS. (NEJM 2006)

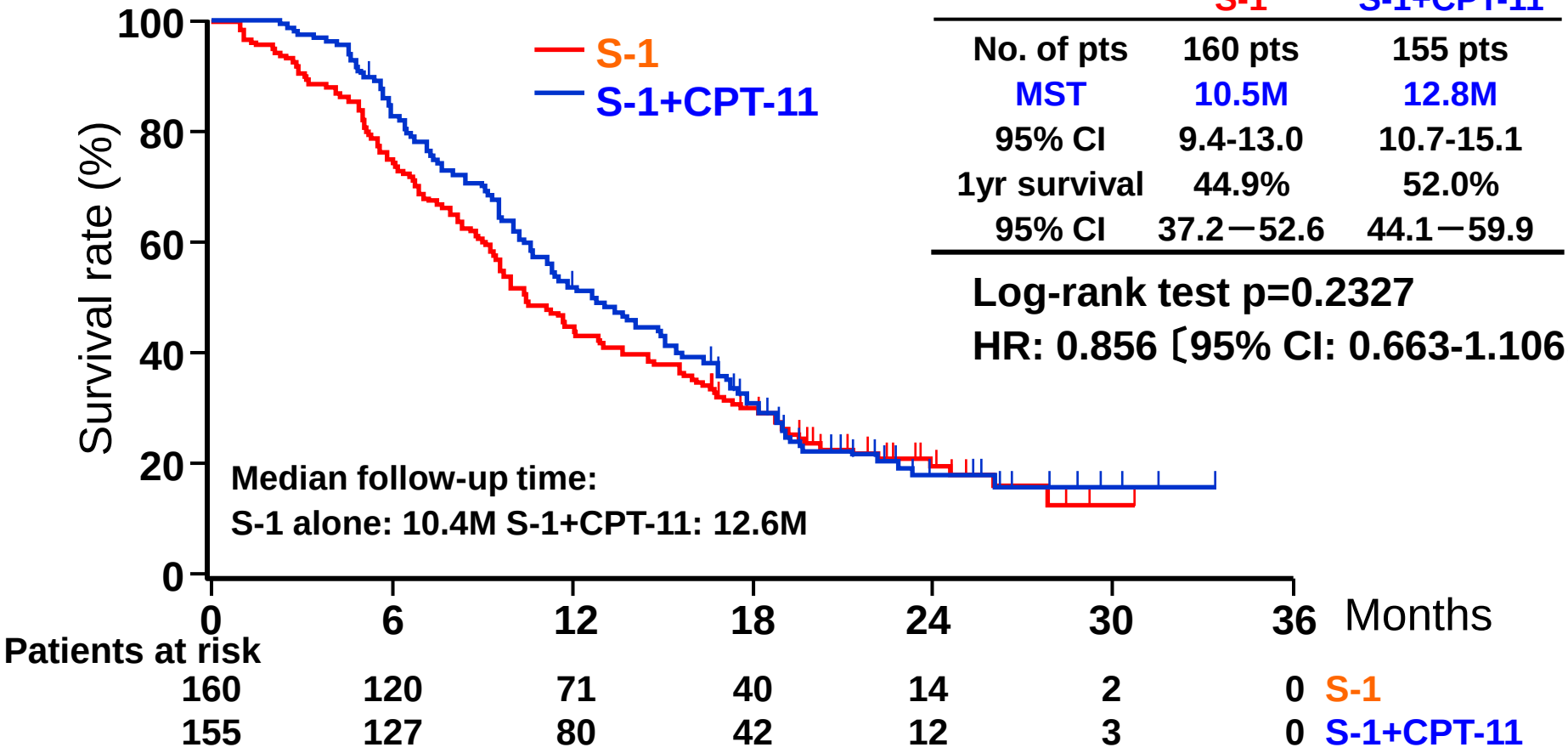
- **ACTS-GC trial** :

  Post-op chemotherapy (S-1) prolonged OS and DFS after D2 surgery. (NEJM 2007)

- **CLASSIC trial** :

  Post-op chemotherapy (XELOX) prolonged DFS after D2 surgery. (ASCO 2011)

GC0301/TOP-002 Phase III study



	S-1	S-1+CPT-11
No. of pts	160 pts	155 pts
MST	10.5M	12.8M
95% CI	9.4-13.0	10.7-15.1
1yr survival	44.9%	52.0%
95% CI	37.2－52.6	44.1－59.9

Log-rank test p=0.2327

HR: 0.856〔95% CI: 0.663-1.106〕

Narahara H. et al. Gastric Cancer 2011, 14:72-80.

GC0301/TOP-002 Phase III study

Response Rate: measurable (n=187)

➢Criteria : RECISTv1.0

	No. of pts	Response					Response Rate (95% CI)
		CR	PR	SD	PD	NE	
S-1+CPT-11	94	0	39	40	12	3	41.5 % (31.4-52.1)
S-1	93	0	25	35	30	3	26.9 % (18.2-37.4)

p=0.035

Treatment Courses

	S-1+CPT-11 (q5 wks)	S-1 (q6 wks)
No. of pts	160	155
Median (range)	4 (1-25)	3 (1-19)

Narahara H. et al. Gastric Cancer 2011, 14:72-80.

Objectives

- **To evaluate the feasibility and safety of adjuvant S-1 plus CPT-11 in pts with stage III GC who underwent D2 gastrectomy.**
- **Primary endpoint**
  - **Feasibility of the 4 cycles administration of S-1 plus CPT-11**
- **Secondary endpoints**
  - **Feasibility of S-1 for 1 year**
  - **Safety**
  - **Recurrence free survival (RFS)**
  - **Overall survival (OS)**

Definition of feasibility in this protocol

$$\text{Treatment completing rate} = \frac{\text{Full analysis set} - \text{No. of discontinued Pts by adverse events}}{\text{No. of all Patients}} \times 100$$

Definition of feasibility was

" treatment completing rate is over 75% (6/8 times) of CPT-11
and 66.6% (8/12 weeks) of S-1
for 4 cycles of S-1 plus CPT-11 therapy"

Statistical considerations

- **Sample Size**: **40 pts**
  - determined to reject completing rate of 50%

    under the expectation of 75%

    with a power of 90% and a two-sided α of 5%
- **Planned accrual & follow-up**: 2 yrs & 5 yrs
- **Actual accrual**: **45 pts** from 12 institutions

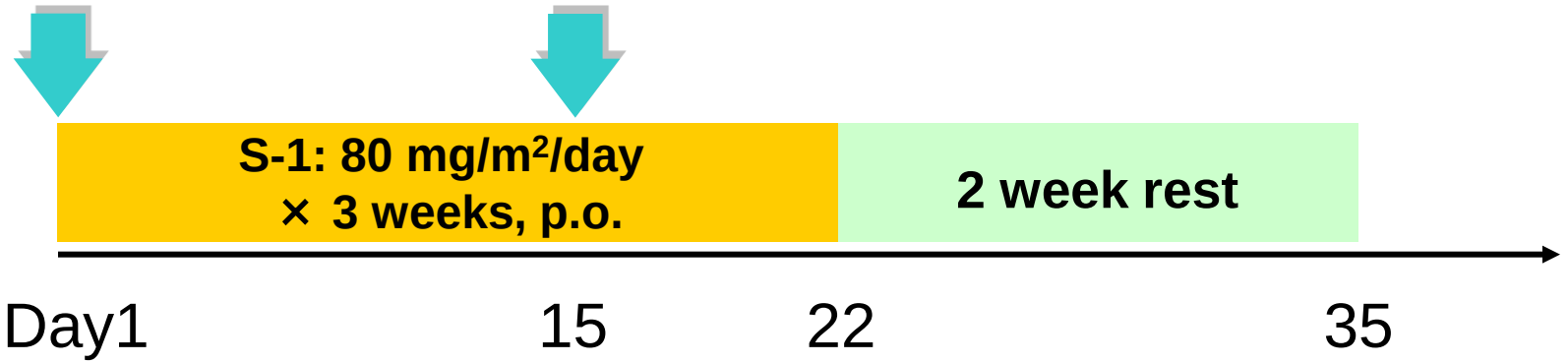
  12/2008 – 4/2010

Treatment schedule

- Patients were enrolled within **4-8 weeks after surgery**.
- ①Combination therapy of **S-1** and **CPT-11** : for **4 cycles**

CPT-11 : 80mg/m^2

Uedo N. et al. Oncology 2007, 73: 65-71.



- ②**S-1** monotherapy : until 1 year after surgery

Eligibility criteria

- Histologically proven gastric adenocarcinoma
- D2 lymph node dissection (curability B)
- Stage III on the JGCA※ classification
- Age 20-75 years
- PS of 1 or less on the ECOG scale
- No prior adjuvant therapy (any chemotherapy, radiation, hormonal therapy etc.)
- Tolerance of oral feeding
- Adequate organ function
- Written informed consent

※JGCA: Japanese Gastric Cancer Association

Patient characteristics

Characteristics	No of pts (n = 45)
Gender (male/female)	22 / 23
Age median (range)	61 (47-75)
PS (0/1)	40 / 5
Stage (IIIA / IIIB)	25 / 20
Histology (intestinal / diffuse / others)	20 / 23 / 2
Complications (+/-)	3 / 42

Feasibility of protocol treatment

- **S-1 plus CPT-11 for 4 cycles**

No. of Pts	Completed	Failed	Treatment completing rate
45	28	17	62.2% (46.5-76.2) p=0.068

Null hypothesis : Treatment completing rate < 50% were not rejected

- **Reasons for discontinuation** 16
  - ・Next course was delayed 1
  - ・Patient withdrawal 11
  - ・Other 4

CPT-11 skipped more than twice 1

Feasibility of protocol treatment

- S-1 plus CPT-11 for each cycle

No. of Course	Completed	Failed	Treatment completing rate
1	35	10	77.8% (62.9-88.8)
2	34	11	75.6% (60.5-87.1)
3	32	13	71.1% (55.7-83.6)
4	29	16	64.4% (48.8-78.1)

- S-1 monotherapy for 1 year

No. of Pts	Completed	Failed	Treatment completing rate
45	23	22	51.1% (35.8-66.3)

Comparison of S-1 compliance

study	OGSG0801	OGSG0604 [1]	Feasibility study [2]	ACTS-GC [3]
Treatment	**S-1+CPT-11**	**S-1+DTX**	**S-1+CDDP**	**S-1 only**
Phase	**II**	**II**	**Feasibility**	**III**
Stage	**III**	**III**	**III**	**II-III**
Compliance:S-1				
3 months	—	**84.9 %**	**100 %**	**87.4 %**
6 months	—	**73.6 %**	**92.1 %**	**77.9 %**
9 months	—	**69.8 %**	**81.8 %**	**70.8 %**
12 months	**51.1%**	**64.2 %**	**70.0 %**	**65.8 %**

[1] *Tamura S et al. Oncology. 2011; 80(5-6): 296.*
[2] *Takahari, D et al. Cancer Chemother Pharmacol. 2011; 67(6): 1423.*
[3] *Sasako M et al. JCO 2011; 36: 5908.*

Adverse events : Hematological (n=45)

	G1	G2	G3	G4	≧G3 (%)
Leukopenia	11	6	2	0	4.4
Neutropenia	8	11	6	0	13.3
Thrombocytopenia	4	1	2	0	4.4
Anemia	22	10	0	0	0

(NCI-CTC version 3.0)

- ✓ For 4 cycles evaluated
- ✓ Treatment-related deaths (TRDs) were 2 pts.

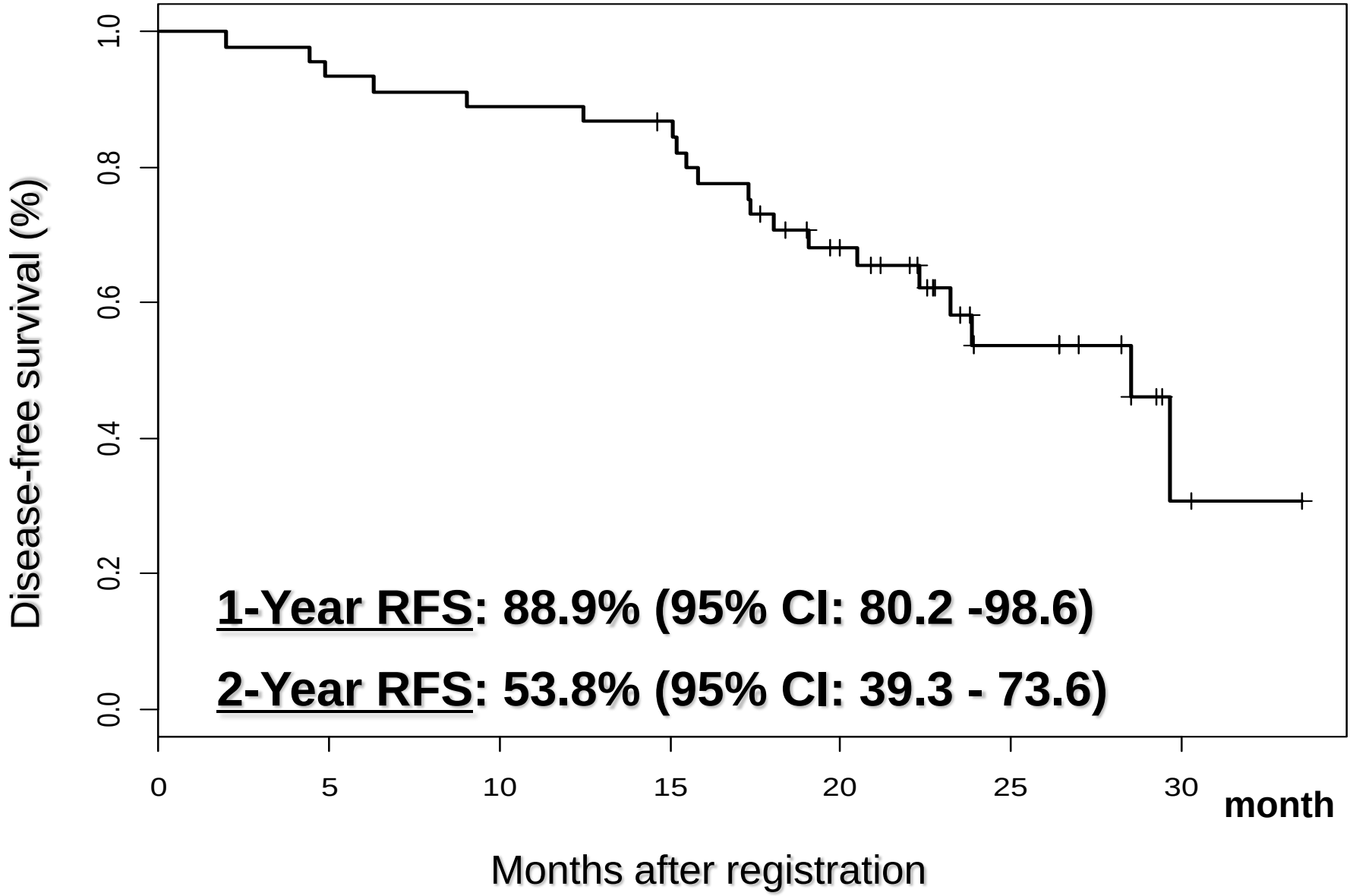
Adverse events : Non-hematological (n=45)

	G1	G2	G3	G4	≧G3 (%)
ALT/AST	12	0	0	0	0
T-Bil	1	1	0	0	0
Nausea	14	10	3	0	6.6
Vomiting	8	5	2	0	4.4
Anorexia	14	12	7	0	15.5
Fatigue	14	13	5	0	11.1
Stomatitis	6	1	0	0	0
Diarrhea	15	4	6	0	13.3

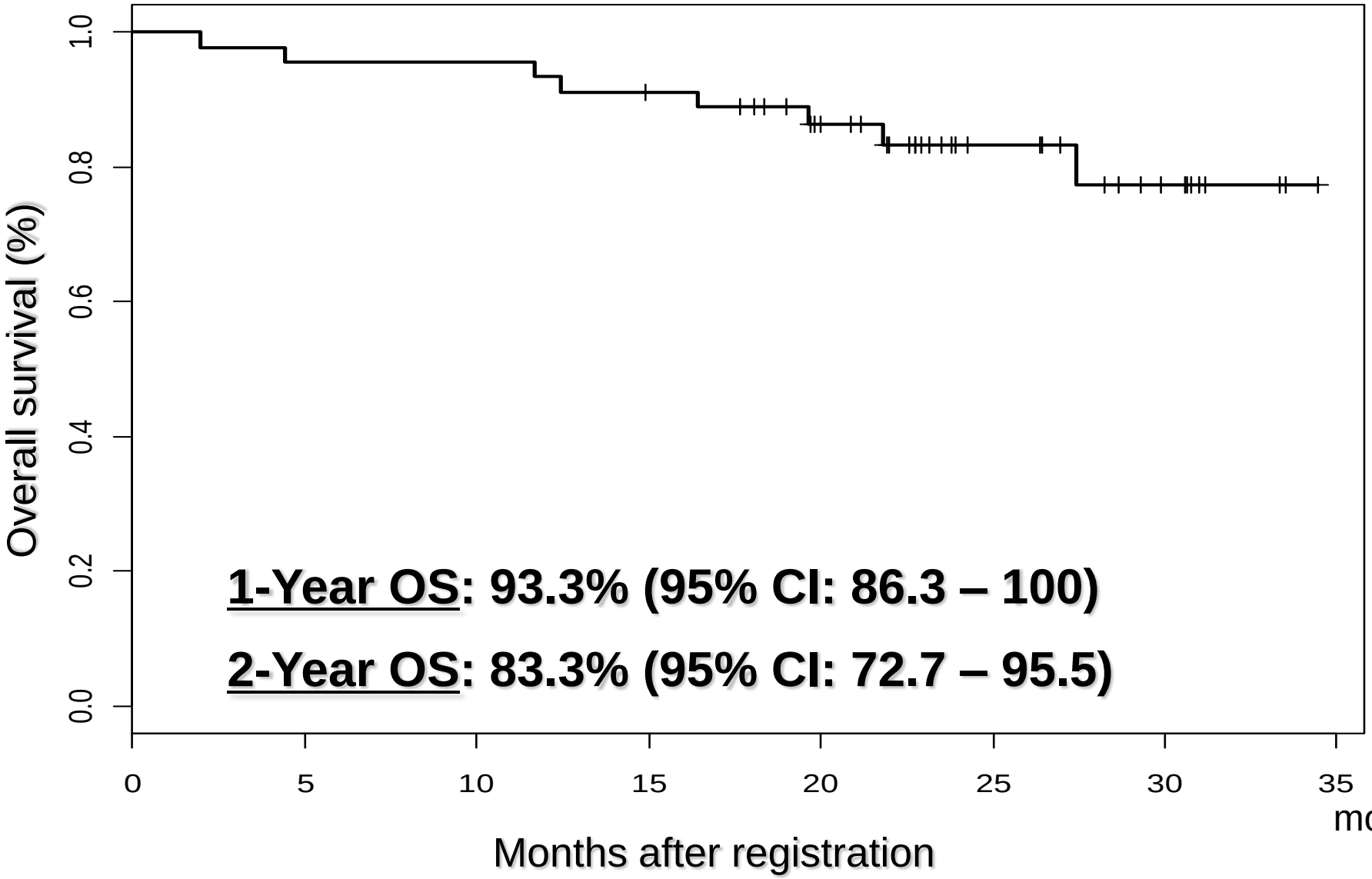
✓ For 4 cycles evaluated

(NCI-CTC version 3.0)

Recurrence free survival (RFS)



Overall survival (OS)



1-Year OS: 93.3% (95% CI: 86.3 – 100)

2-Year OS: 83.3% (95% CI: 72.7 – 95.5)

Summary

- 主要評価項目

  S-1+CPT-11併用療法 4コース治療完遂割合は
  64.4% (95% CI: 48.8-78.1, p=0.068)

- Grade 3以上血液毒性は、
  好中球減少13%、白血球減少4%

- Grade 3以上非血液毒性は、
  食欲不振15.5%、下痢13.3%、疲労倦怠感11%

- Grade 4の有害事象は確認されず

- S-1単独療法の1年間治療完遂割合は 51.1%

Conclusions

- S-1+CPT-11併用術後補助化学療法の
  血液毒性は比較的軽微であったが、
  消化器毒性の発現割合が比較的高かった。
- S-1+CPT-11併用術後補助化学療法は期待した
  治療完遂割合を示すことができなかった。
- S-1単独療法も期待した治療完遂割合を示すことができなかった。
- 今後、さらに生存情報の追跡を予定している。

Participating Institutions

- 北野病院
- NTT西日本大阪病院
- 市立堺病院
- 大阪医療センター
- 貝塚市立病院
- 近畿大学医学部
- 大阪厚生年金病院
- 関西労災病院
- 箕面市立病院
- 阪南中央病院
- 大阪北逓信病院
- 関西電力病院