



THIRD ANNUAL
ISSPP
Congress 2022

*International Society
for the Study of Pleura
and Peritoneum*



GASTRIC CANCERS

Intraperitoneal Chemotherapy for Treatment and Prevention of Peritoneal Metastases of Gastric Cancer

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- Grant/Research Support from Chugai Pharmaceutical Co., Ltd. and Taiho Pharmaceutical Co, Ltd.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Paclitaxel will be addressed.

Main Topics

1. Long-term **ip chemotherapy via an implanted port** for gastric cancer with peritoneal metastasis (P1)
2. **Gastrectomy after response** to combined ip and systemic chemotherapy
3. Combined ip and systemic chemotherapy **for the prevention of peritoneal metastasis** in type 4 M0 gastric cancer: PHOENIX-GC2 trial

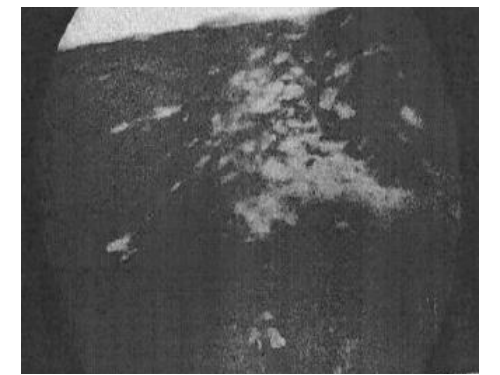
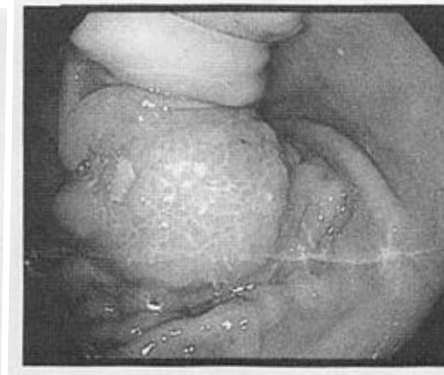
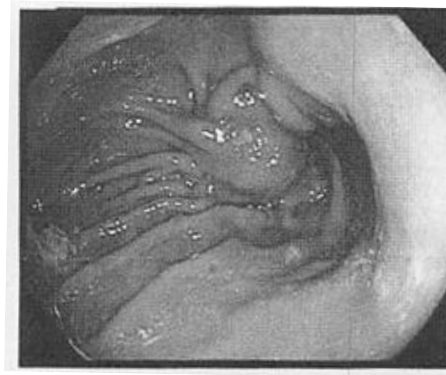
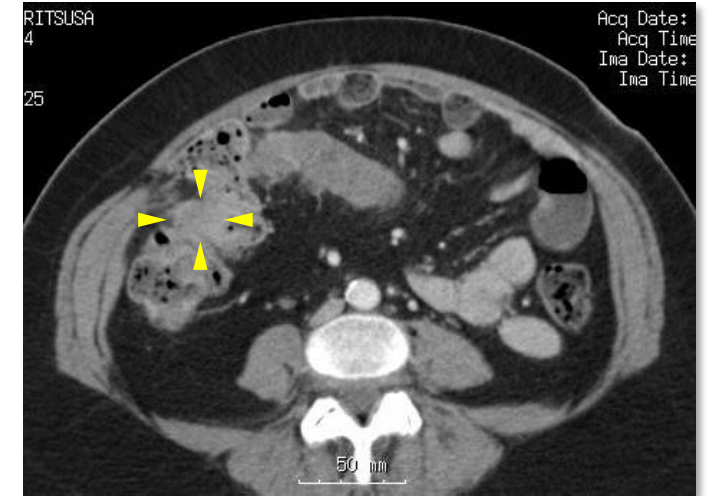
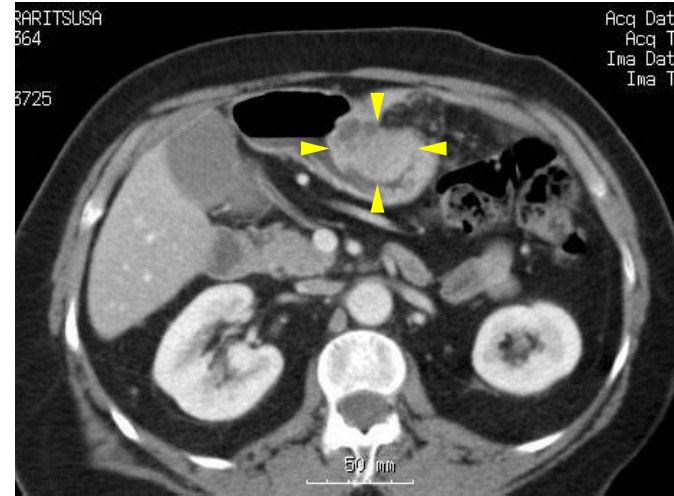
Case presentation

Patient: 58-year-old woman

Dec. 2018

Diagnosed with gastric cancer
(Type 3, mod. diff. adenoca.)
with peritoneal metastasis

Received FLOT in LA



Case presentation

Patient: 58-year-old woman

Dec. 2018

Dx with P1 gastric cancer

Received FLOT in LA

Mar. 2019

Referred to our hospital

Laparoscopy **PCI 21, CY1**

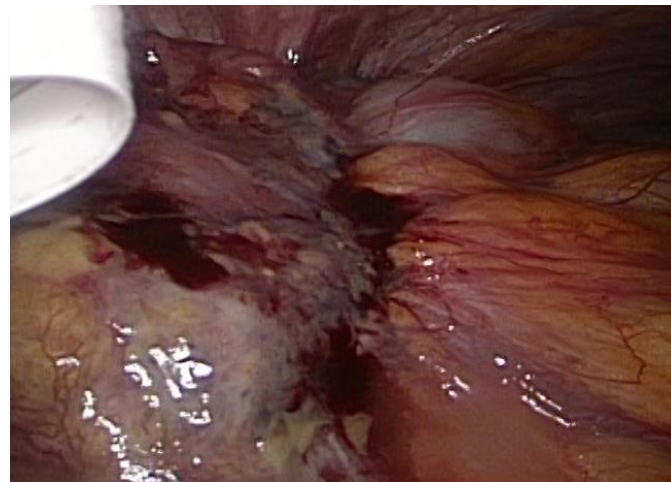
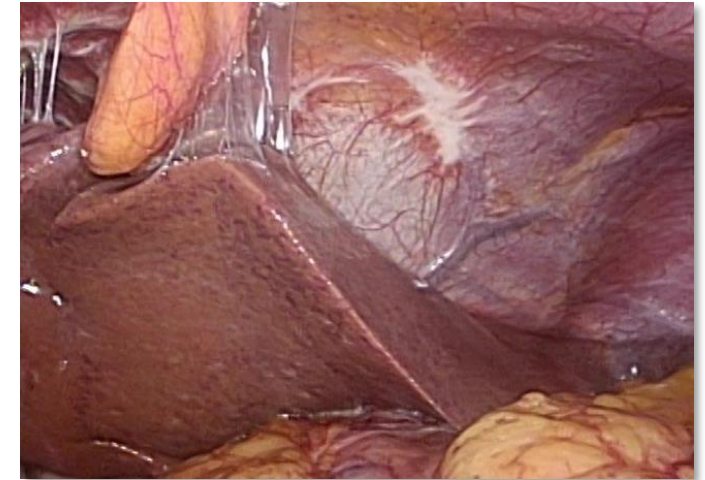
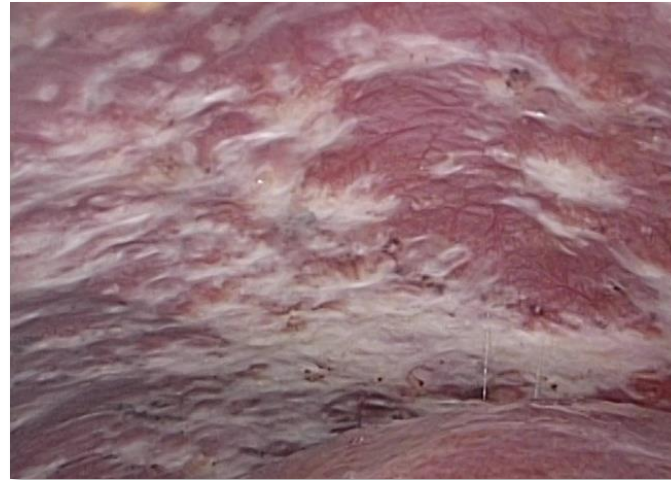
Implanted an IP port

Initiated **FOLFOX plus IP PTX**

Continued treatment in LA

FOLFOX plus IP PTX

-> 5-FU/LV plus IP PTX



Case presentation

Patient: 58-year-old woman

Dec. 2018

Dx with P1 gastric cancer

Received FLOT in LA

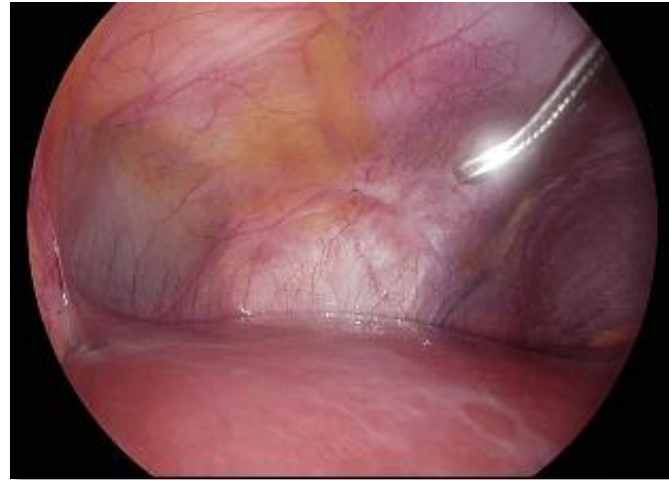
Mar. 2019

Laparoscopy PCI 21, CY1

FOLFOX plus IP PTX

Jun. 2022 2nd-SL **PCI 2, CY0**

Jul. Distal gastrectomy (D2)
with rt. hemicolectomy
ypT3N2M1, ypStage IV



Case presentation

Patient: 58-year-old woman

Dec. 2018

Dx with P1 gastric cancer

Received FLOT in LA

Mar. 2019

Laparoscopy PCI 21, CY1

FOLFOX plus IP PTX

Jun. 2022 2nd-SL PCI 2, CY0

Jul. Distal gastrectomy (D2)

with rt. hemicolectomy

ypT3N2M1, ypStage IV

POD13 IP PTX -> plus 5-FU/LV



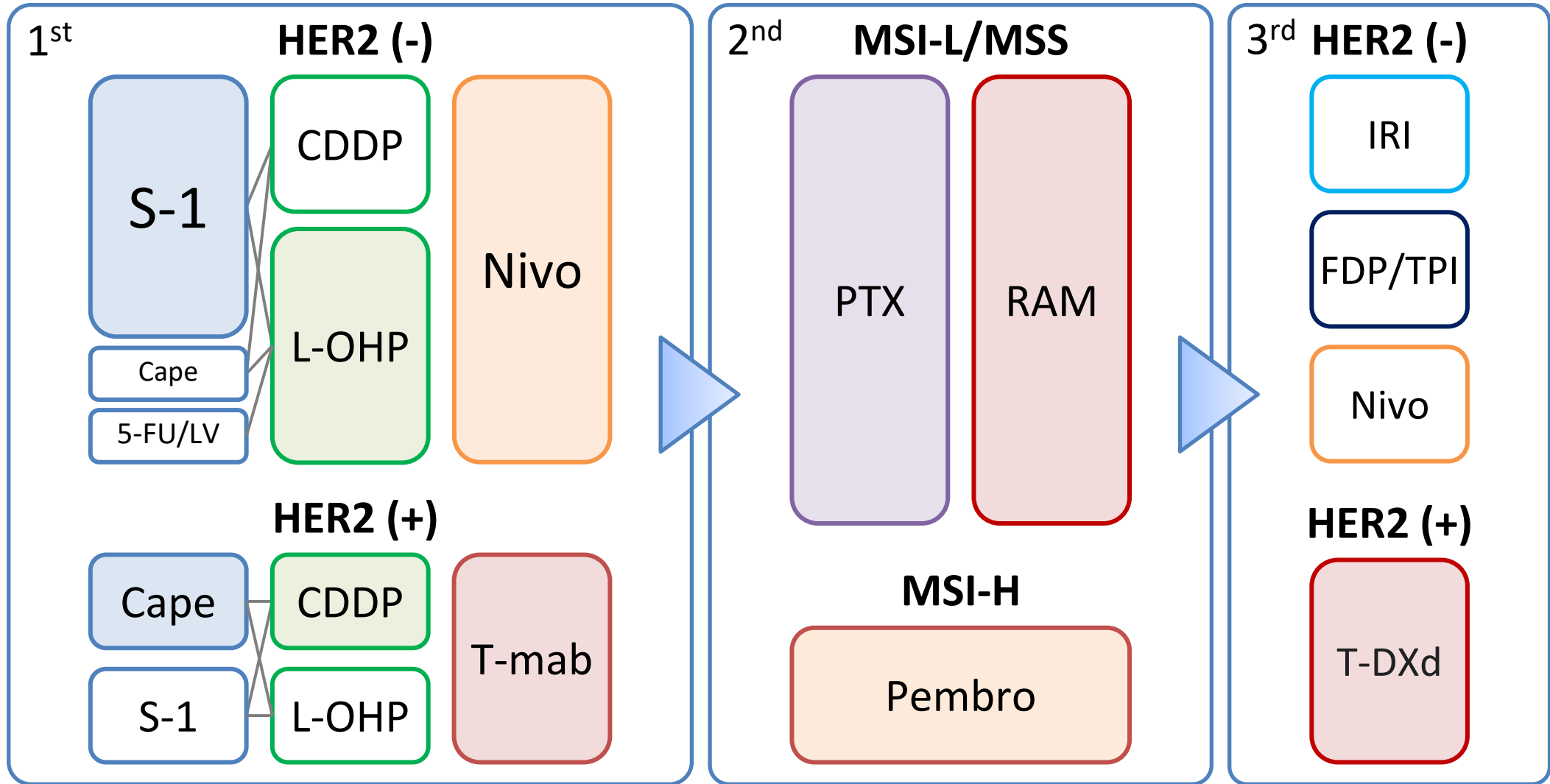
I want to express again my outmost appreciation for everything you have done for me. With your system you have saved my life and brought me to the point when I could have my tumors removed surgically.

When many other doctors gave me no hope at all you gave me this beautiful time since March 2019, when we met for the first time. And much more to come in the future, I hope.

I want to wish you a lot of success in your work.

With permission and recommendation

Chemotherapy for stage IV gastric cancer



Nivolumab plus Chemo vs. Chemo in the East Asia

Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial

Yoon-Koo Kang, Li-Tzong Chen, Min-Hee Ryu, Do-Youn Oh, Sang Cheul Oh, Hyun Cheol Chung, Keun-Wook Lee, Takeshi Omori, Kohei Shitara, Shinichi Sakuramoto, Ik-Joo Chung, Kensei Yamaguchi, Ken Kato, Sun Jin Sym, Shigenori Kadowaki, Kunihiro Tsuji, Jen-Shi Chen, Li-Yuan Bai, Sung-Yong Oh, Yasuhiro Choda, Hisateru Yasui, Kentaro Takeuchi, Yoshinori Hirashima, Shunsuke Hagihara, Narikazu Boku

PFS

HR 0.68 (98.51% CI 0.51–0.90)

p=0.0007

OS

HR 0.90 (95% CI 0.75–1.08)

p=0.26

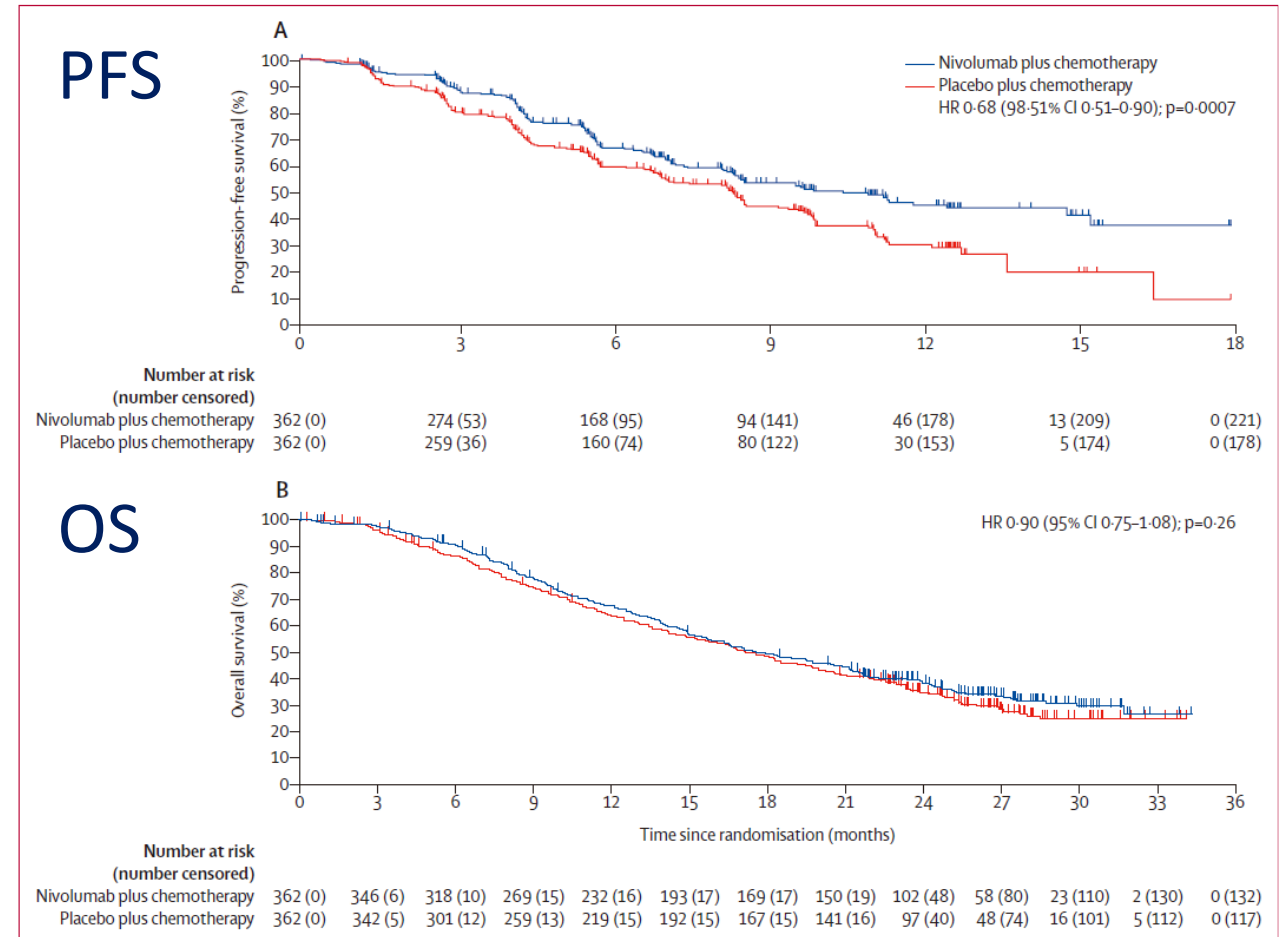


Figure 2: Kaplan-Meier plot of progression-free survival and overall survival
Progression-free survival (interim analysis; A) and overall survival (final analysis; B) by treatment group in all patients. HR=hazard ratio.

Lancet Oncol 2022; 23: 234–47

PFS

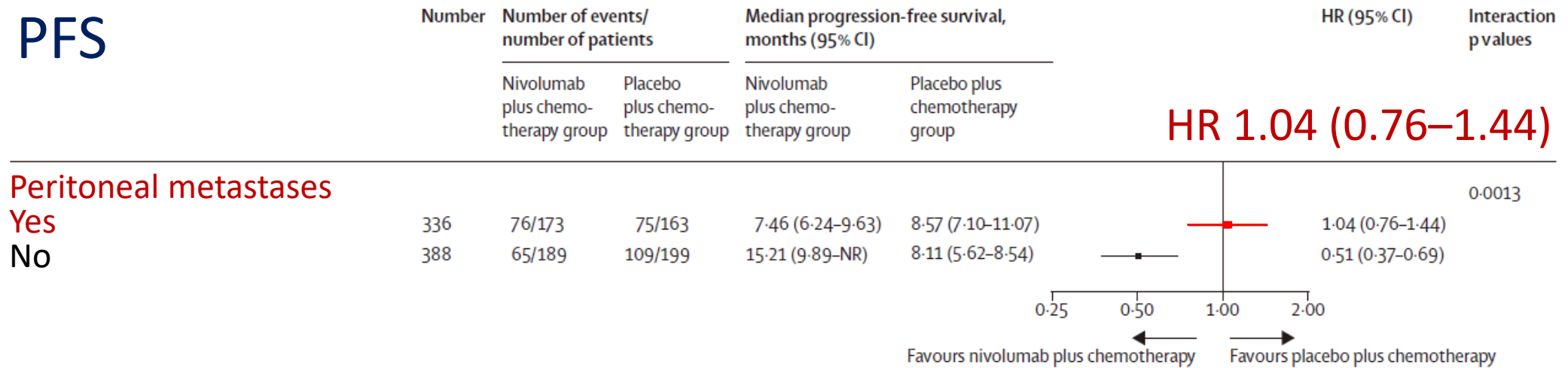


Figure 3: Forest plot of progression-free survival (at the interim analysis) according to patient subgroups

OS

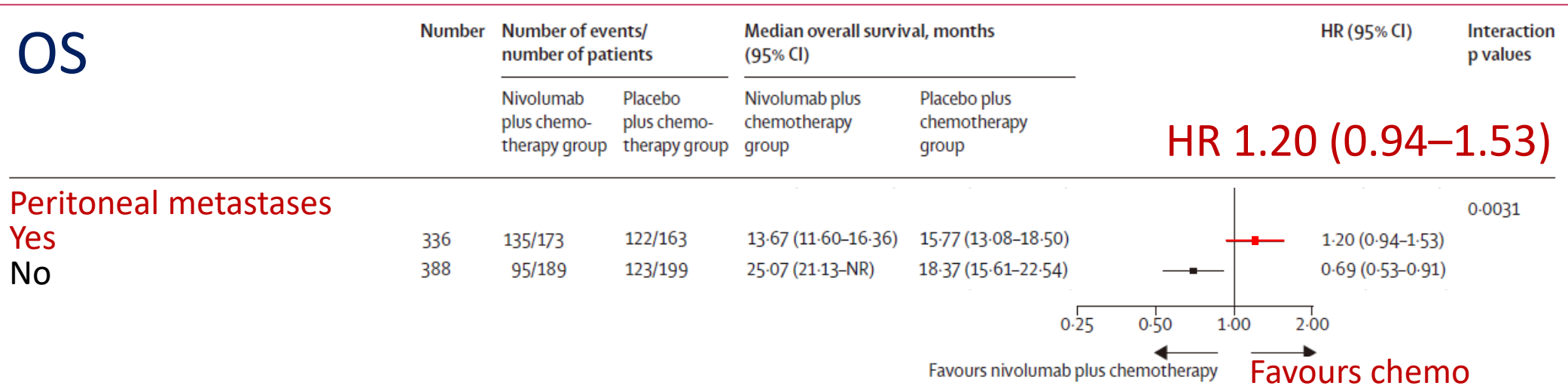
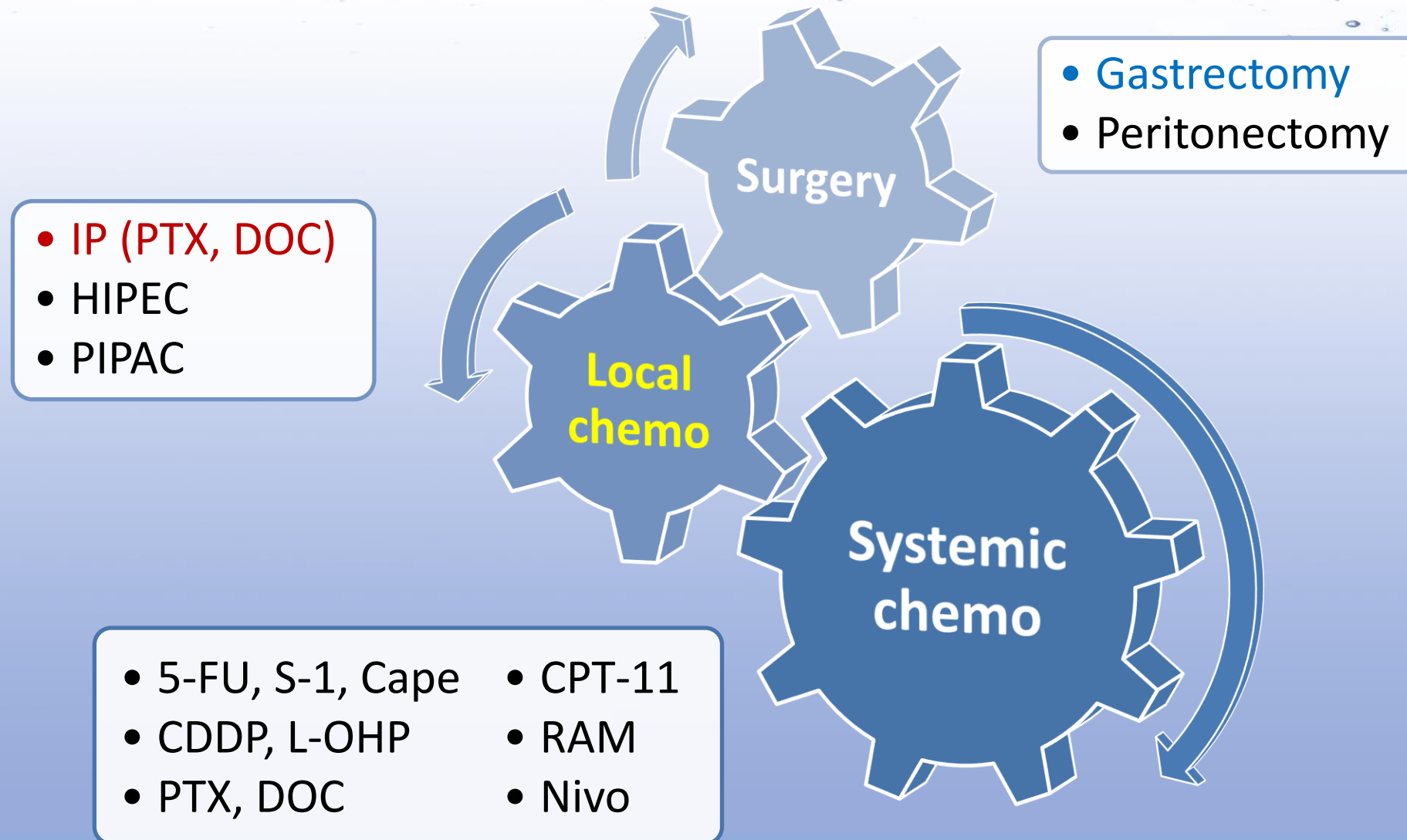
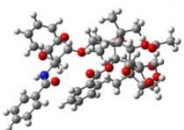


Figure 4: Forest plot of overall survival at the final analysis according to patient subgroups

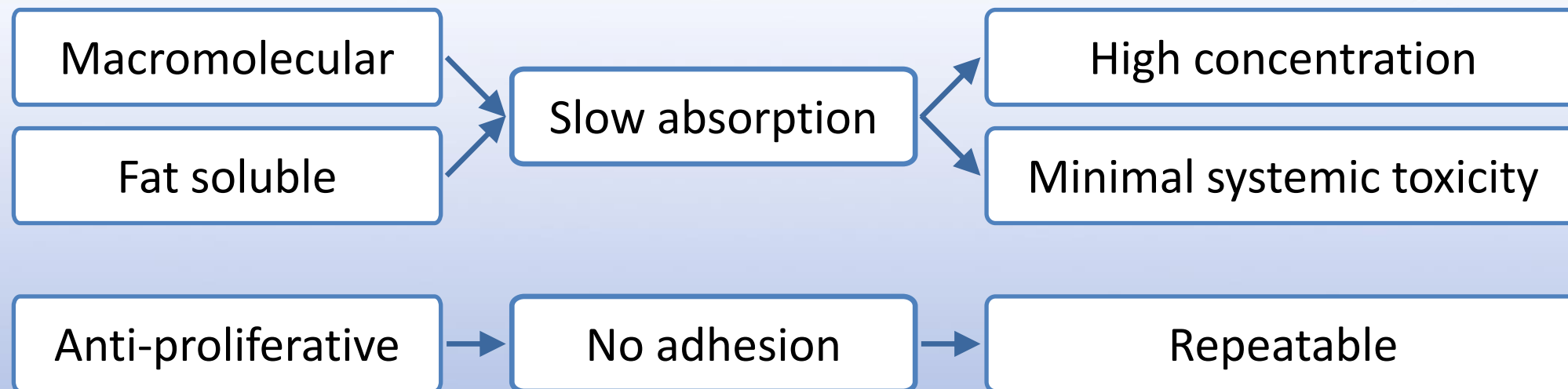
Treatment for GC with peritoneal metastasis



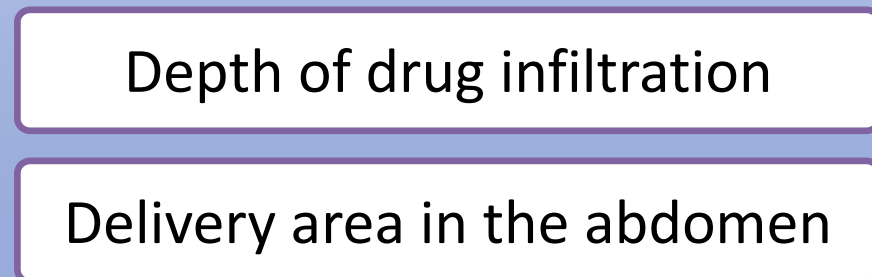


Intraperitoneal taxanes

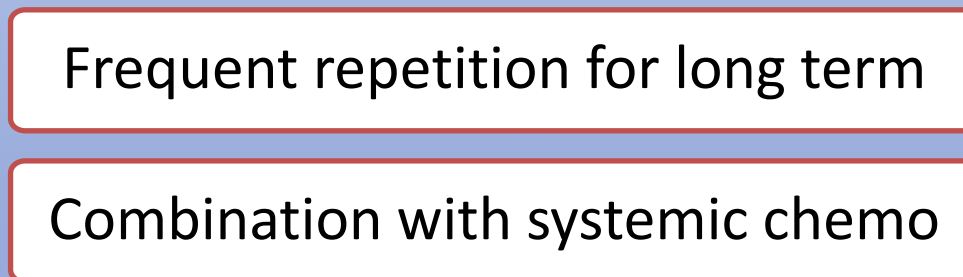
ADVANTAGE



LIMITATIONS



KEYS

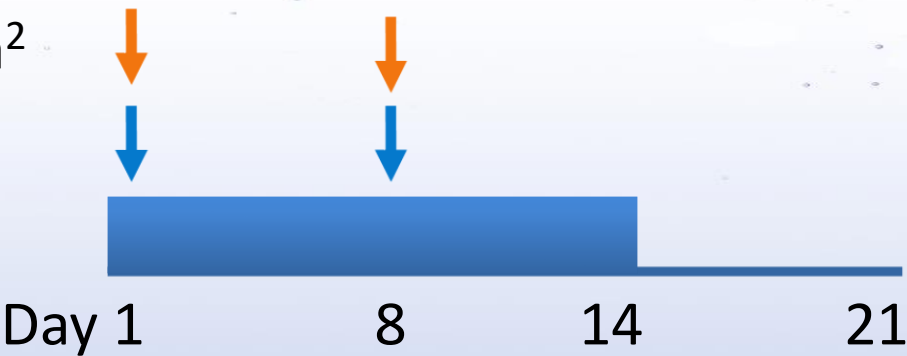


S-1/PTX + IP PTX Phase I Study

IP PTX 20–40 mg/m²

IV PTX 50 mg/m²

S-1 80 mg/m²



Adverse event	Level 1 (n=6) (IP PTX 20 mg/m ²)				Level 2 (n=3) (IP PTX 30 mg/m ²)			
	1	2	3	4	1	2	3	4
Leukopenia	2	1	1	1	1	1	1	
Neutropenia	1	1	1	2			2	
Febrile neutropenia							1	
Anemia	1	5				3		
Thrombocytopenia	1							
Fatigue	3				1			
Anorexia	2	1			2			
Nausea/vomiting	1	2			1			
Diarrhea		3					1	
Abdominal pain	2				1			

DLT

FN, diarrhea
(2/3 in level 2)

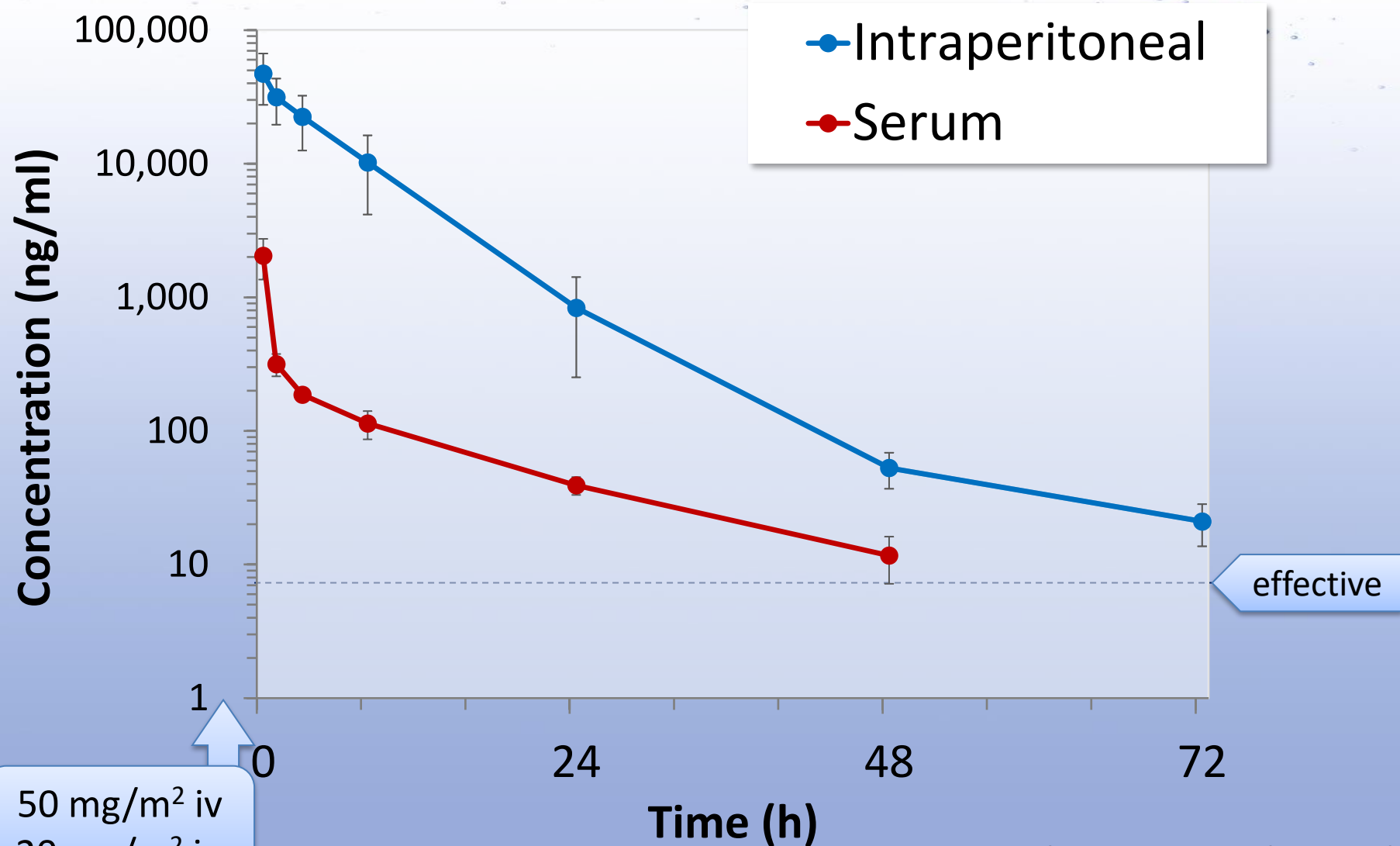
MTD

30 mg/m²

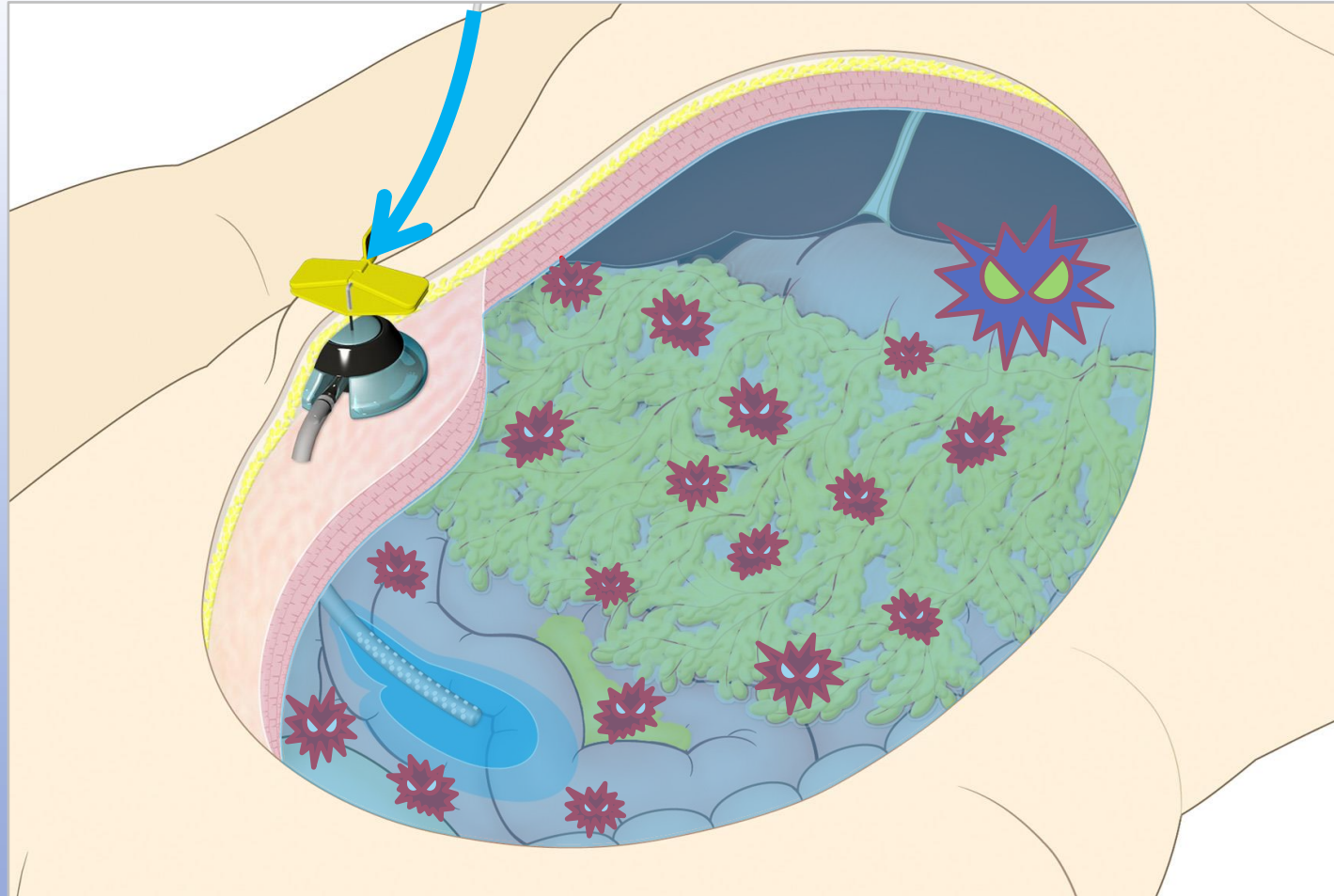
RD

20 mg/m²

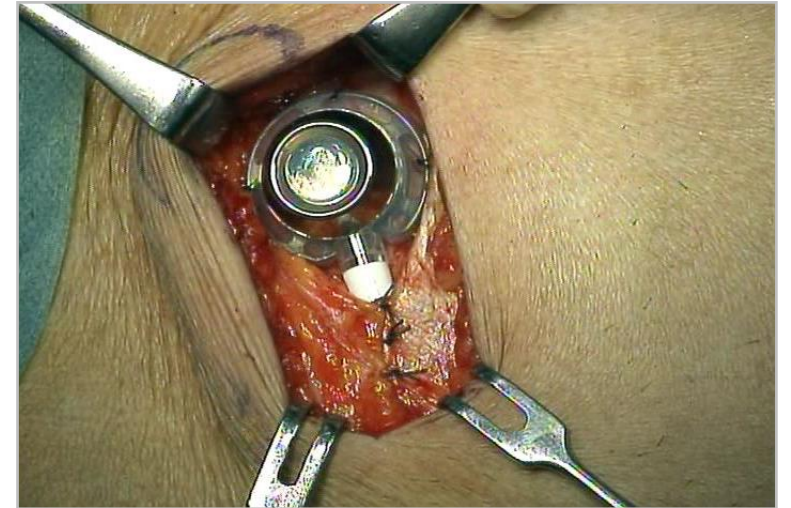
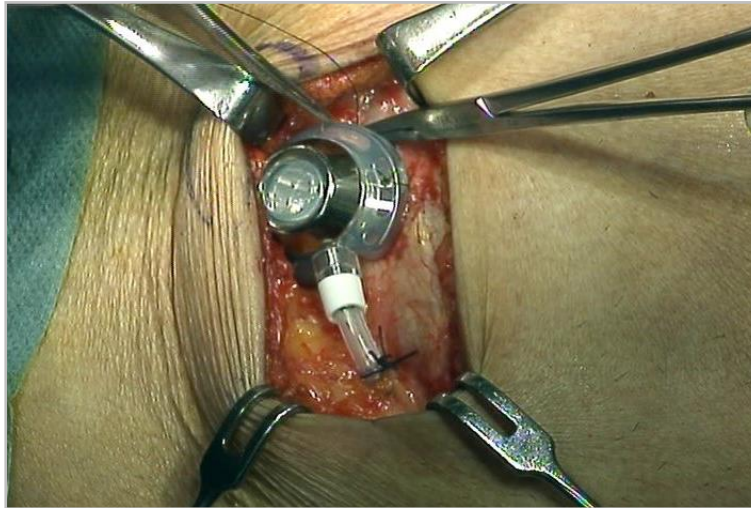
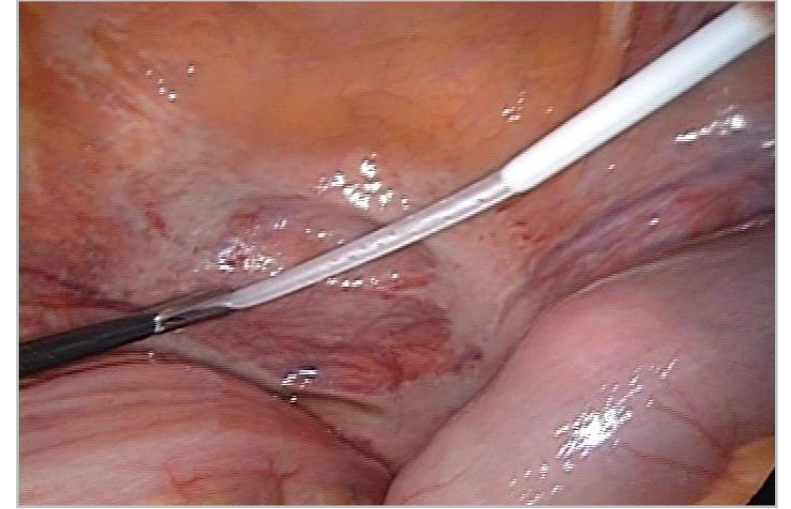
Pharmacokinetics



Intraperitoneal Chemotherapy via a Port



Intraperitoneal Port Implantation



Complications related to the IP port

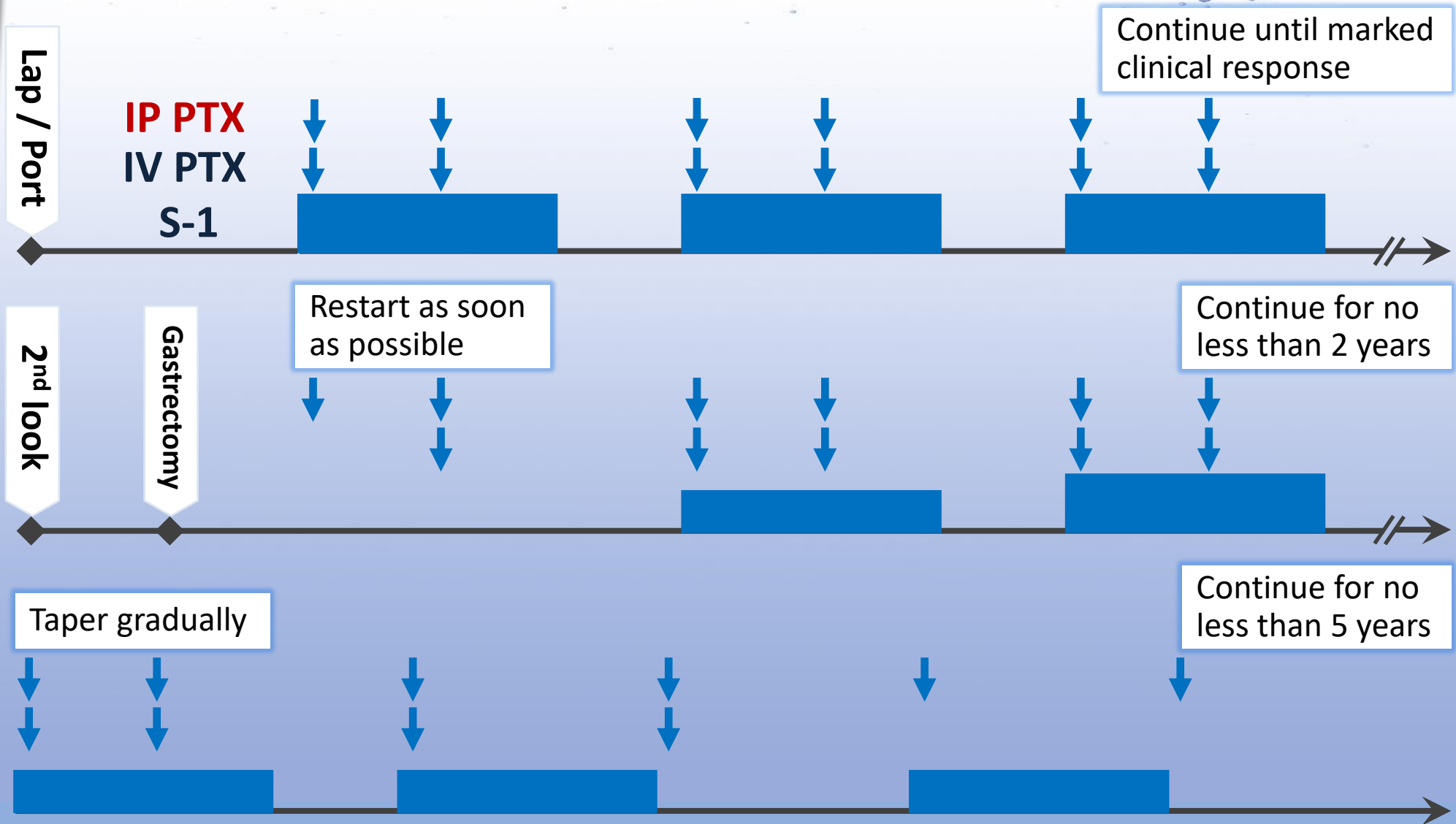
	2005–2011 Tokyo Univ.* ¹	Multicenter clinical trials* ²	GOG172 in ovarian ca.* ³
n	149	222	205
Infection	9 (6%)	7 (3%)	25 (12%)
Obstruction	10 (7%)	7 (3%)	10 (5%)
Leakage or reflux	4 (3%)	4 (2%)	5 (2%)
Access-inability	0 (0%)	0 (0%)	8 (4%)

*¹ Emoto S et al. *Jpn J Clin Oncol* 2012

*² Ishigami H et al. *J Clin Oncol* 2018, Fujiwara et al. *ASCO* 2016, Fukushima et al. *ASCO* 2017

*³ Walker JL et al. *Gynecol Oncol* 2006

Treatment schedule



Effect of long-term ip chemotherapy via a port



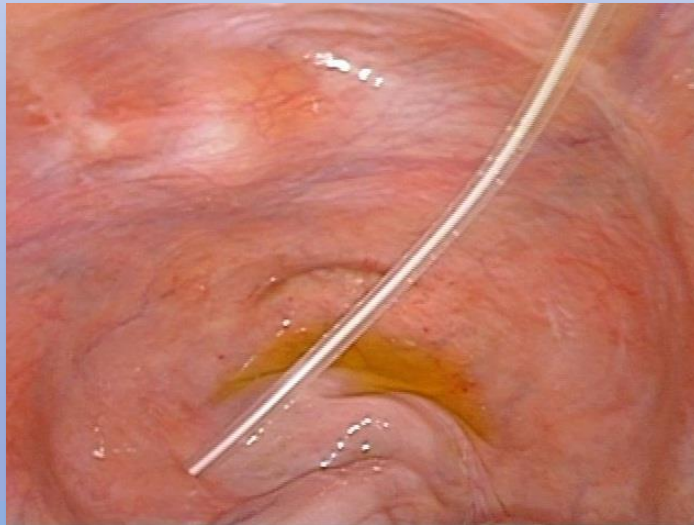
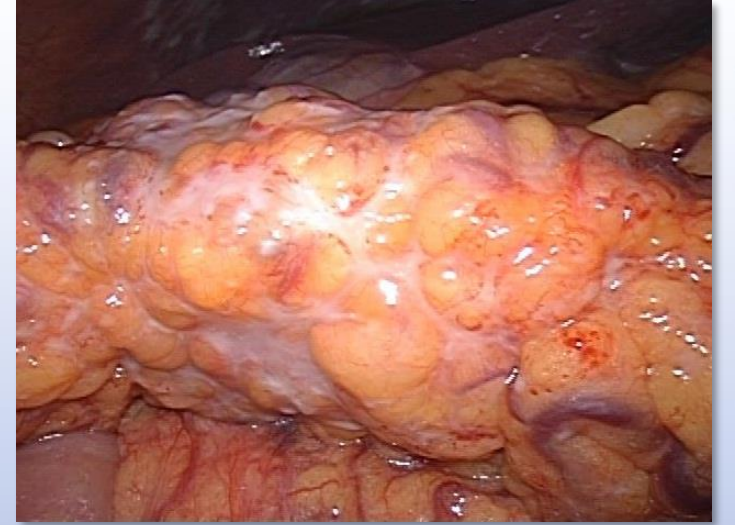
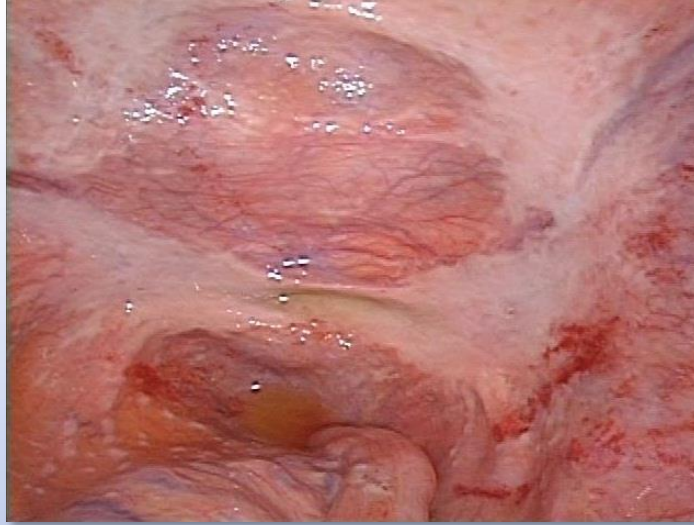
Before chemotherapy



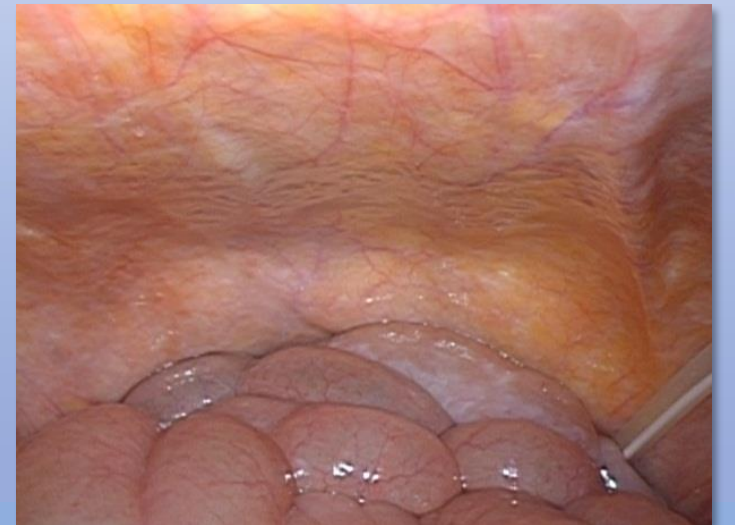
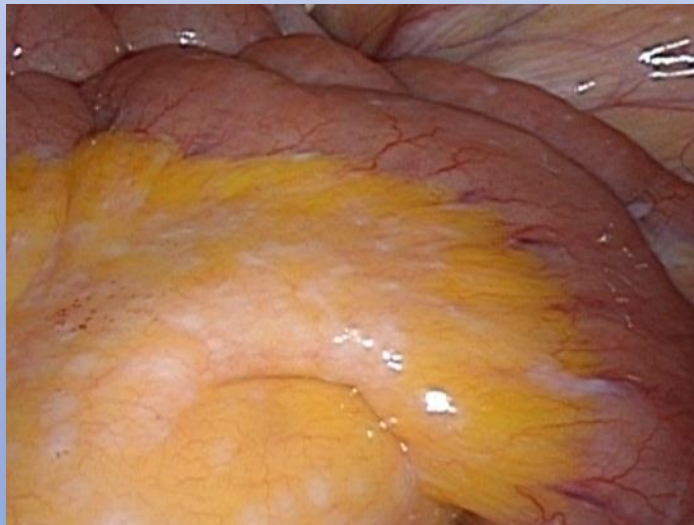
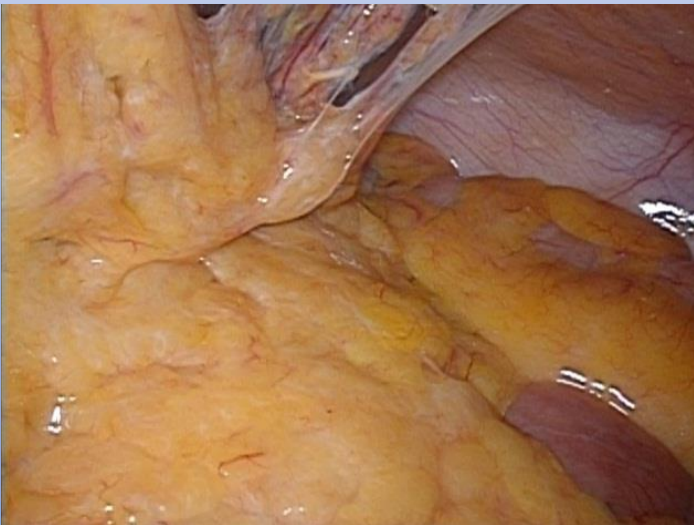
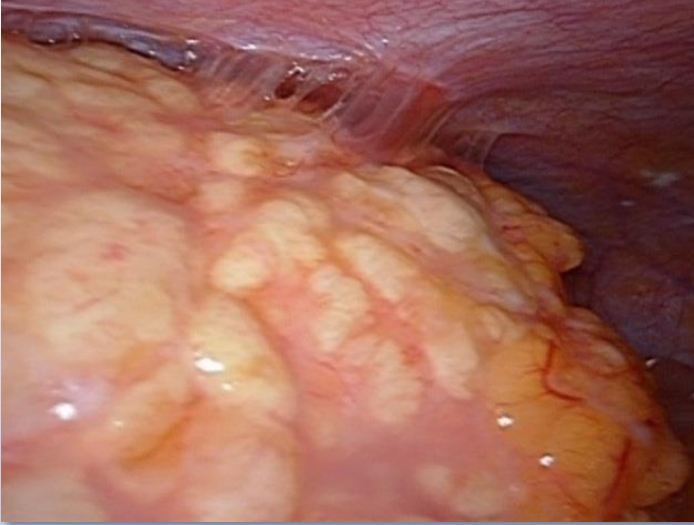
After 6 months of chemotherapy



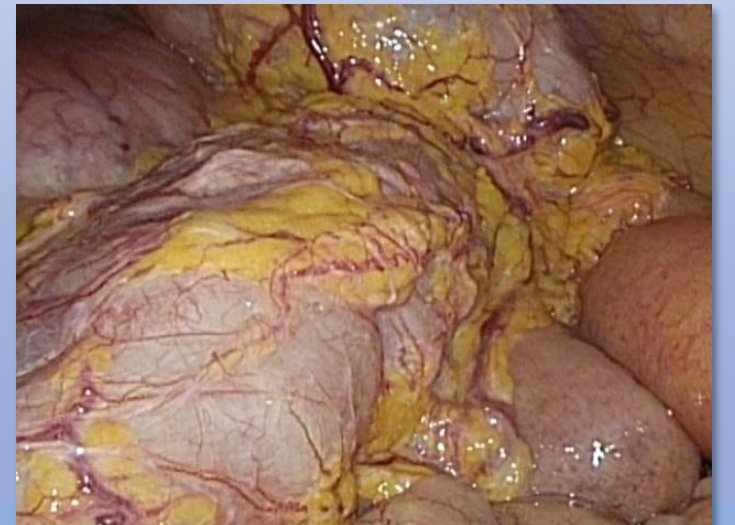
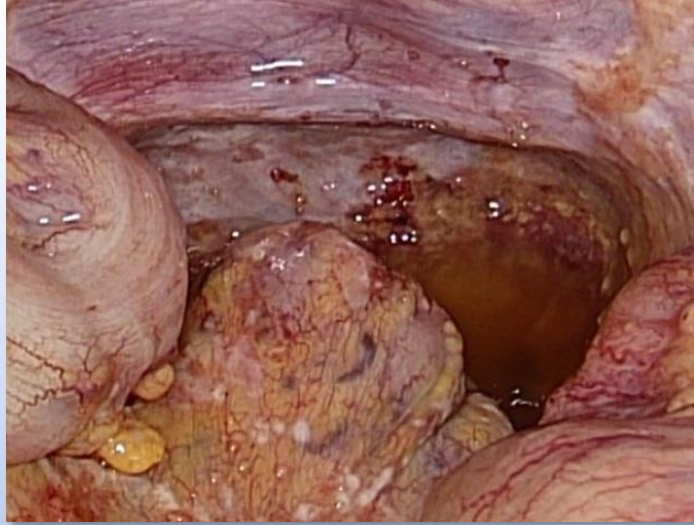
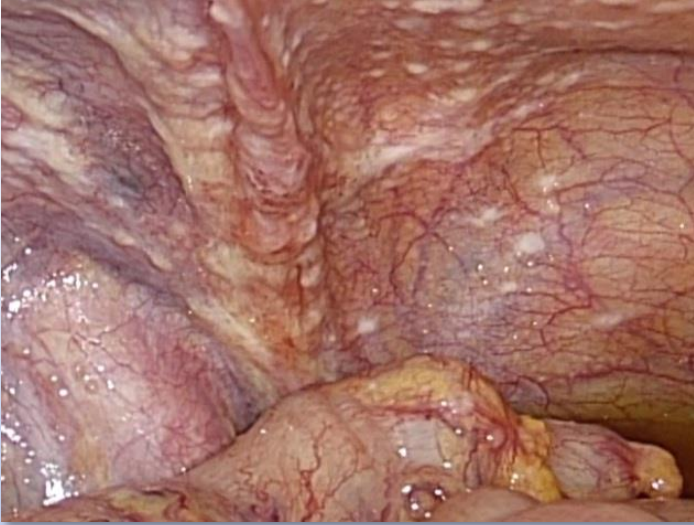
Response to IP chemotherapy



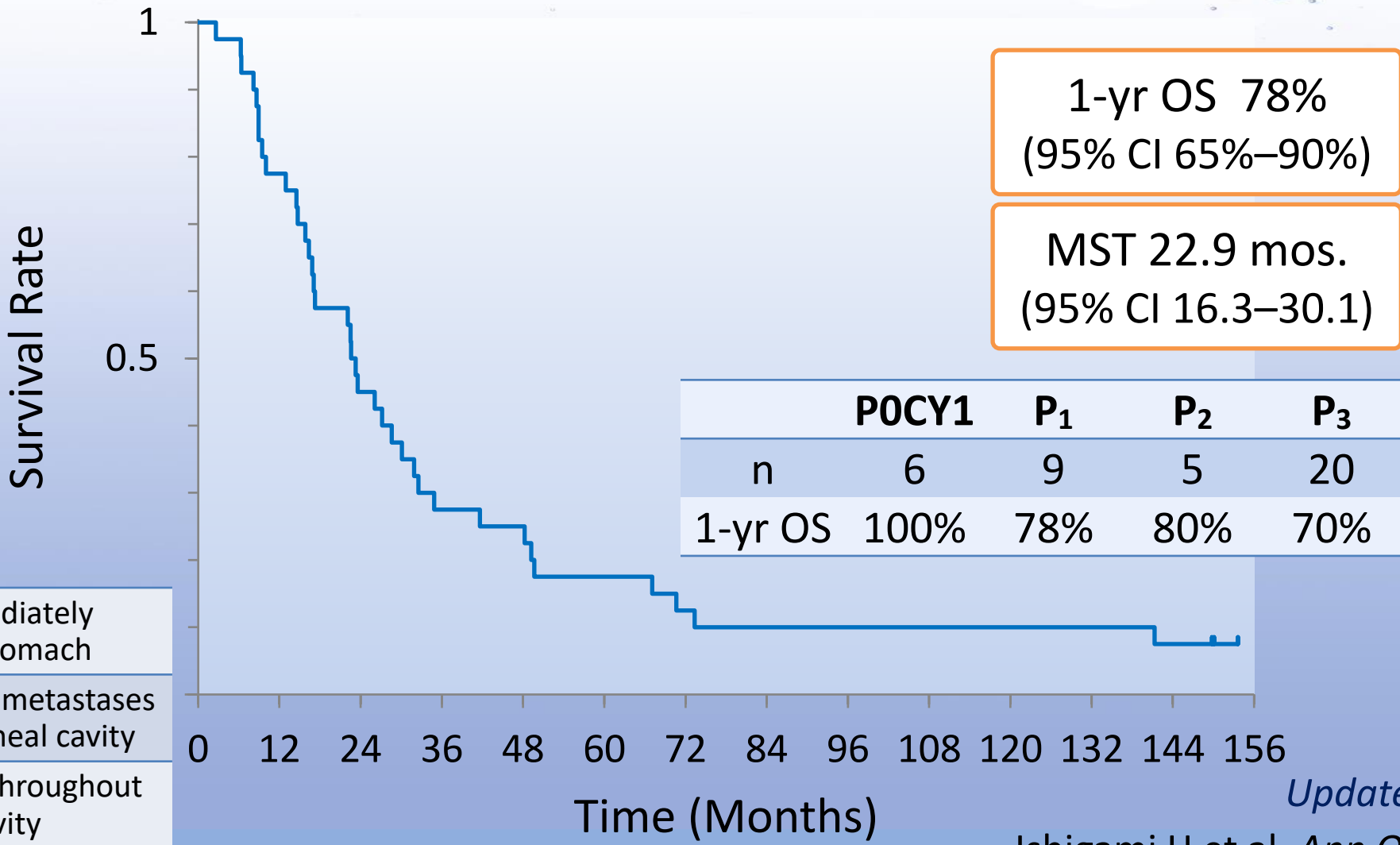
Response to IP chemotherapy



Response to IP chemotherapy



Overall Survival

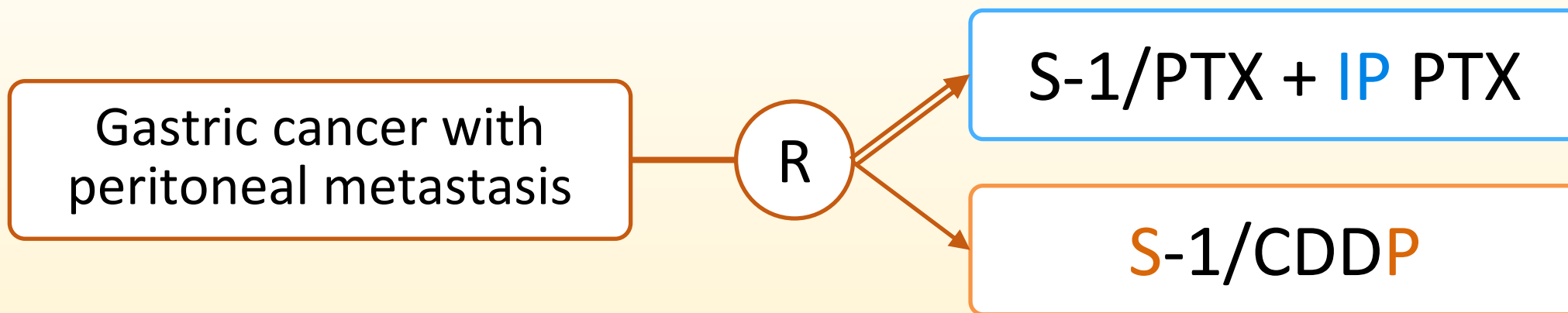


P ₁	Metastases immediately adjacent to the stomach
P ₂	Several scattered metastases within the peritoneal cavity
P ₃	Numerous mets throughout the peritoneal cavity



2011-2016

PHOENIX-GC Trial



Key Eligibility Criteria

- Peritoneal metastasis
- No or <2mo. prior chemo
- No prior gastrectomy
- No other distant metastasis
- No frequent ascites drainage

Stratification

- Institution
- Prior chemotherapy +/-
- Peritoneal meta.
 P_1/P_{2-3}

Primary Endpoint

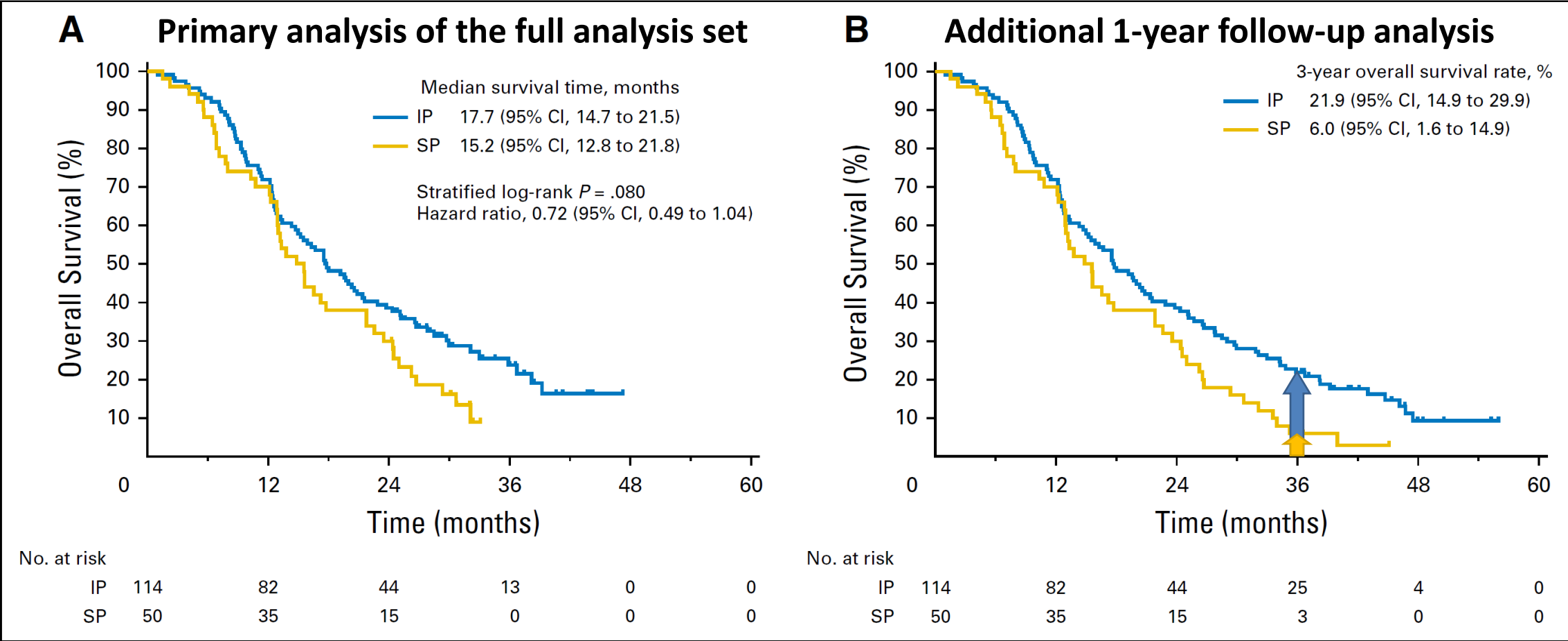
- Overall survival

Secondary Endpoints

- Response rate
- 3-yr OS rate
- Safety



Overall Survival

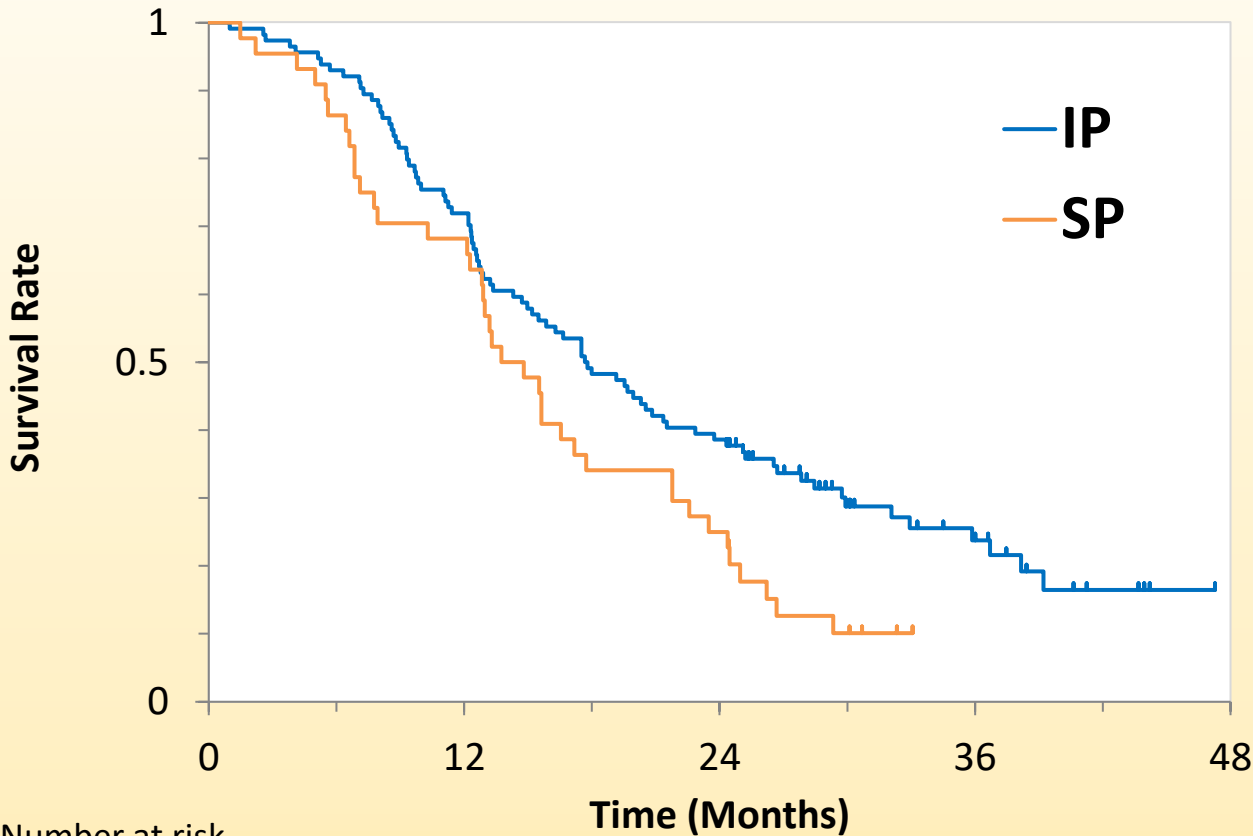


Ishigami H et al. *J Clin Oncol* 2018



Sensitivity analysis for OS

in the PPS* population (n=158)



Number at risk

IP	114	82	44	13
SP	44	30	11	0

Median OS

IP	17.7 mos. (95% CI 14.7–21.5)
SP	14.3 mos. (95% CI 12.1–17.7)

Stratified log-rank test

$p=0.022$

Cox regression analysis

HR 0.64 (95% CI 0.43–0.94)

$p=0.023$

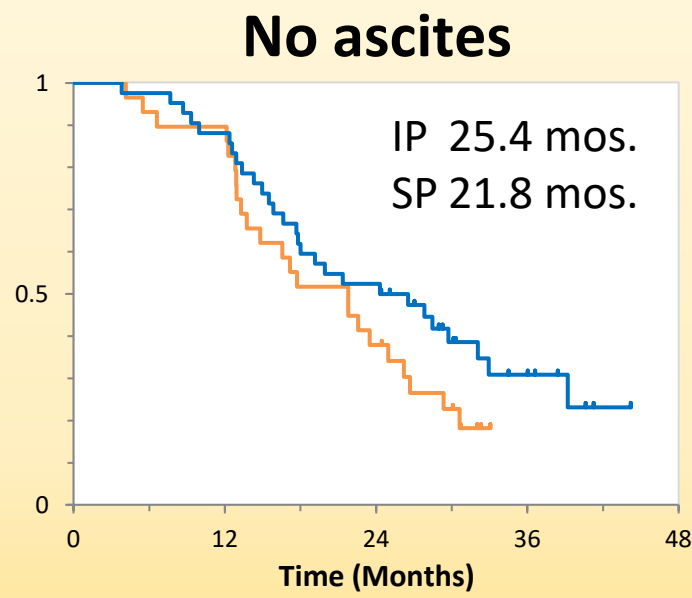
*excluding 6 patients who declined SP and received IP against the protocol



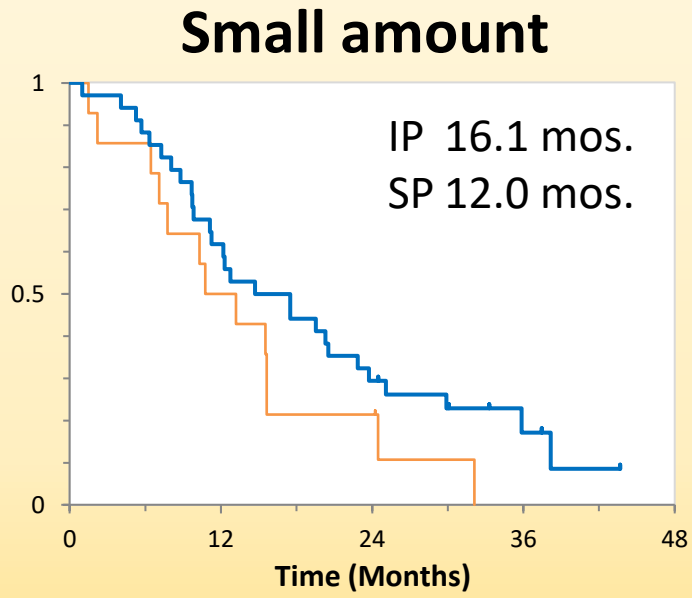
Sensitivity analysis adjusting for ascites

	IP (n=114)	SP (n=50)	p
No ascites	42 (37%)	29 (58%)	
Small amt.	34 (30%)	14 (28%)	0.015
Moderate amt.	38 (33%)	7 (14%)	

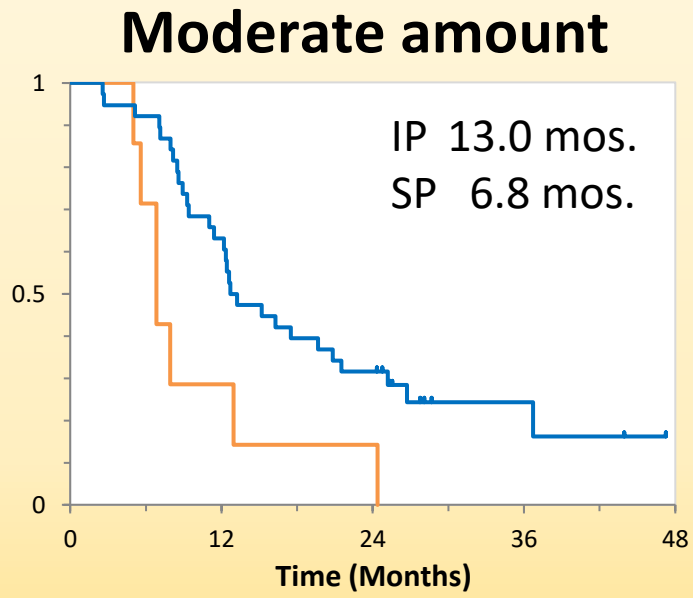
Cox regression analysis
HR 0.59 (95%CI 0.39–0.87)
p = 0.008



HR 0.67 (95%CI 0.38–1.18)



HR 0.65 (95%CI 0.32–1.32)



HR 0.38 (95%CI 0.16–0.90)



Summary

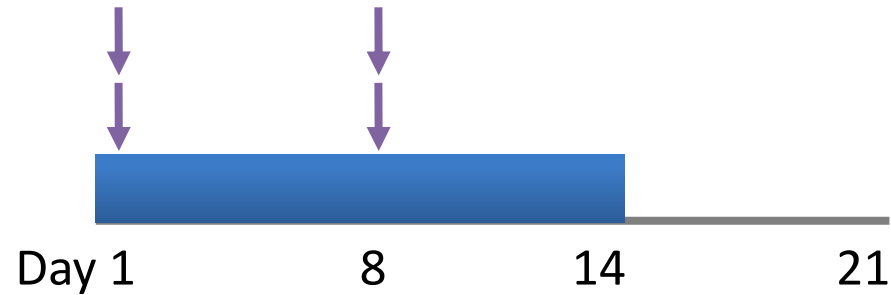
Analysis	p value	HR
Primary analysis	p=0.080	HR 0.72 (95% CI 0.49–1.04)
Additional 1-yr follow-up analysis	p=0.034	HR 0.68 (95% CI 0.48–0.97)
Sensitivity analysis adjusted for ascites	p=0.008	HR 0.59 (95% CI 0.39–0.86)
Sensitivity analysis of PPS*	p=0.022	HR 0.64 (95% CI 0.43–0.94)

*excluding 6 patients in SP with crossover

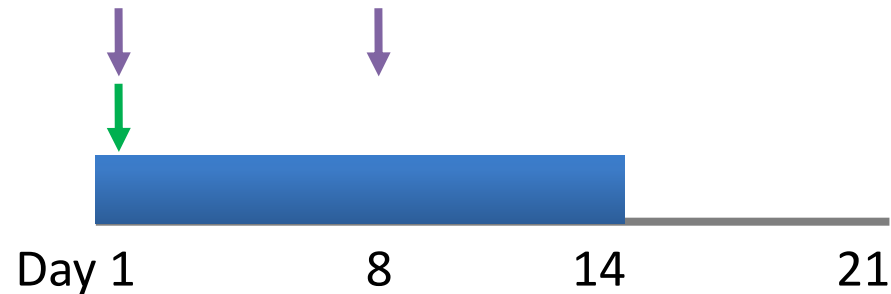
Combination chemotherapy regimens



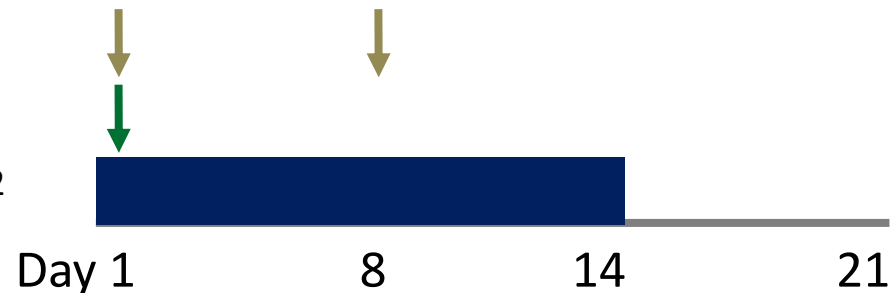
IP PTX 20 mg/m²
IV PTX 50 mg/m²
S-1 80 mg/m²



IP PTX 40 mg/m²
L-OHP 100 mg/m²
S-1 80 mg/m²

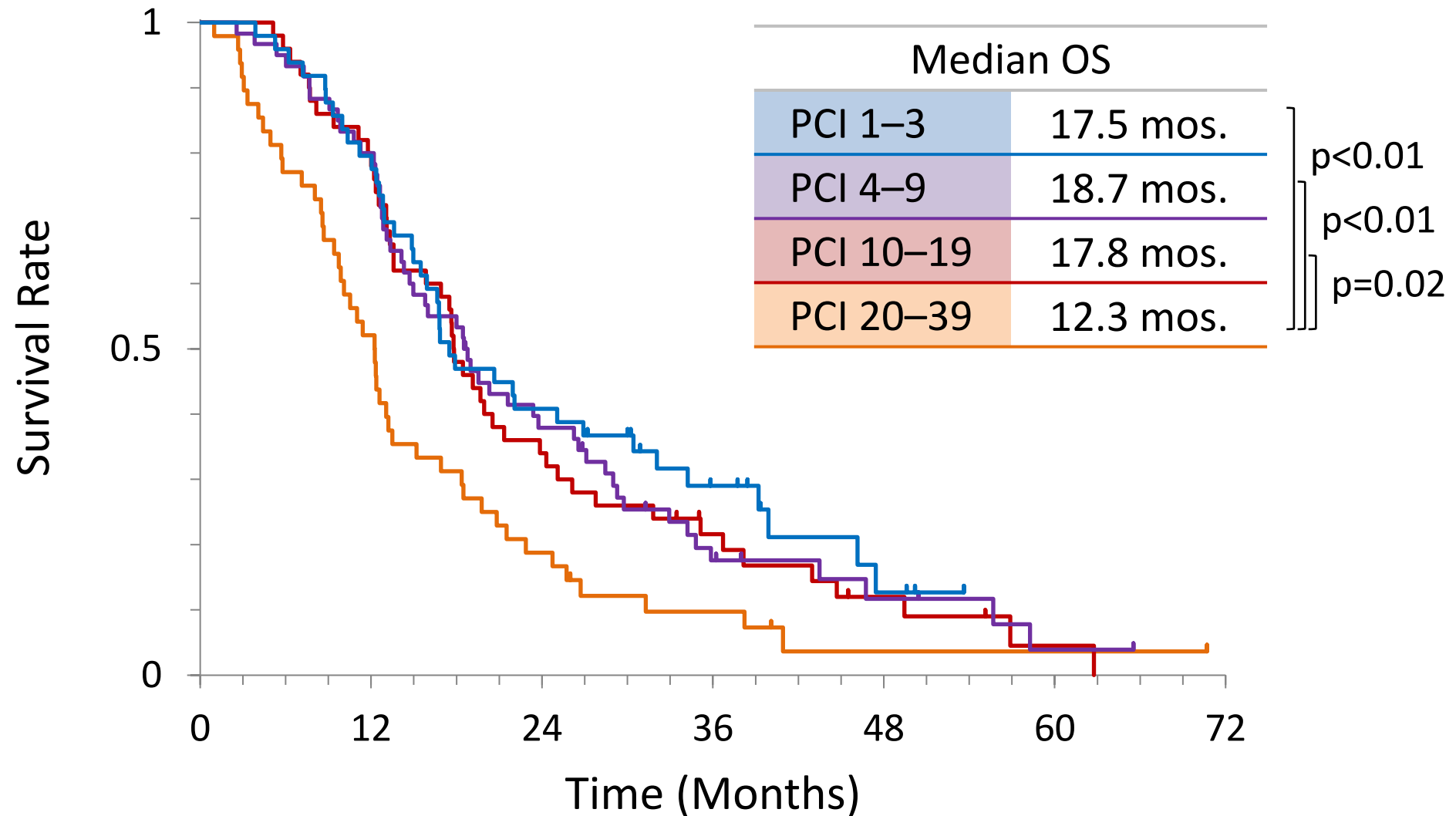


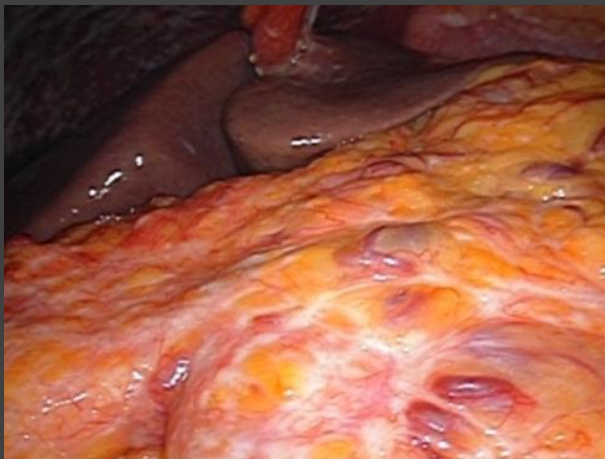
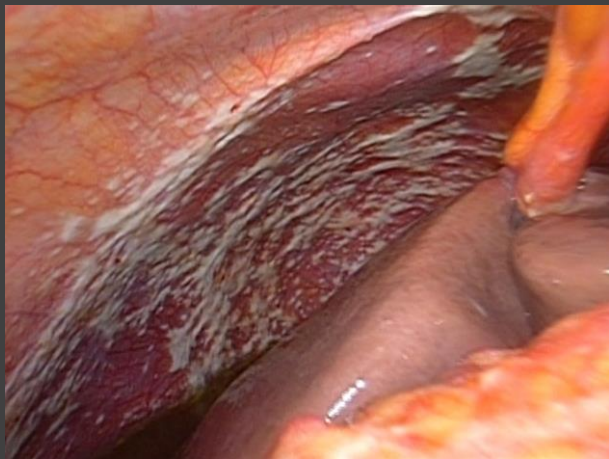
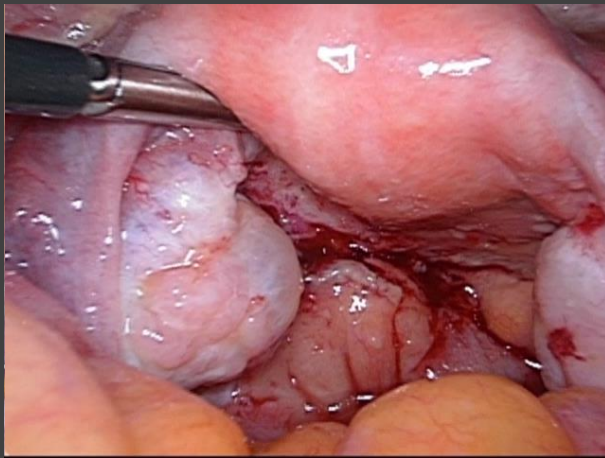
IP DOC 10 mg/m²
CDDP 80 mg/m²
Cape 2,000 mg/m²



Subset analysis of OS by PCI

(n=207)





Surgery after response to chemotherapy



Rationale for Gastrectomy

- Peritoneal metastasis can be controlled by IP chemo
 - Primary tumor is not controlled long-term by chemo
- 

Criteria to proceed to surgery

- Disappearance of cancer cells on peritoneal cytology
 - No unresectable metastasis identified by imaging
- 

2nd -look Laparoscopy Findings

1. Disappearance of macroscopic peritoneal metastasis
 2. Obvious shrinkage of peritoneal metastasis
- 

Laparotomy Findings

- Resectable by standard or extended gastrectomy (excluding PD, thoracotomy, peritonectomy)

Retrospective Study



Objective

To evaluate the safety and efficacy of surgery after response to combination chemotherapy

Patients

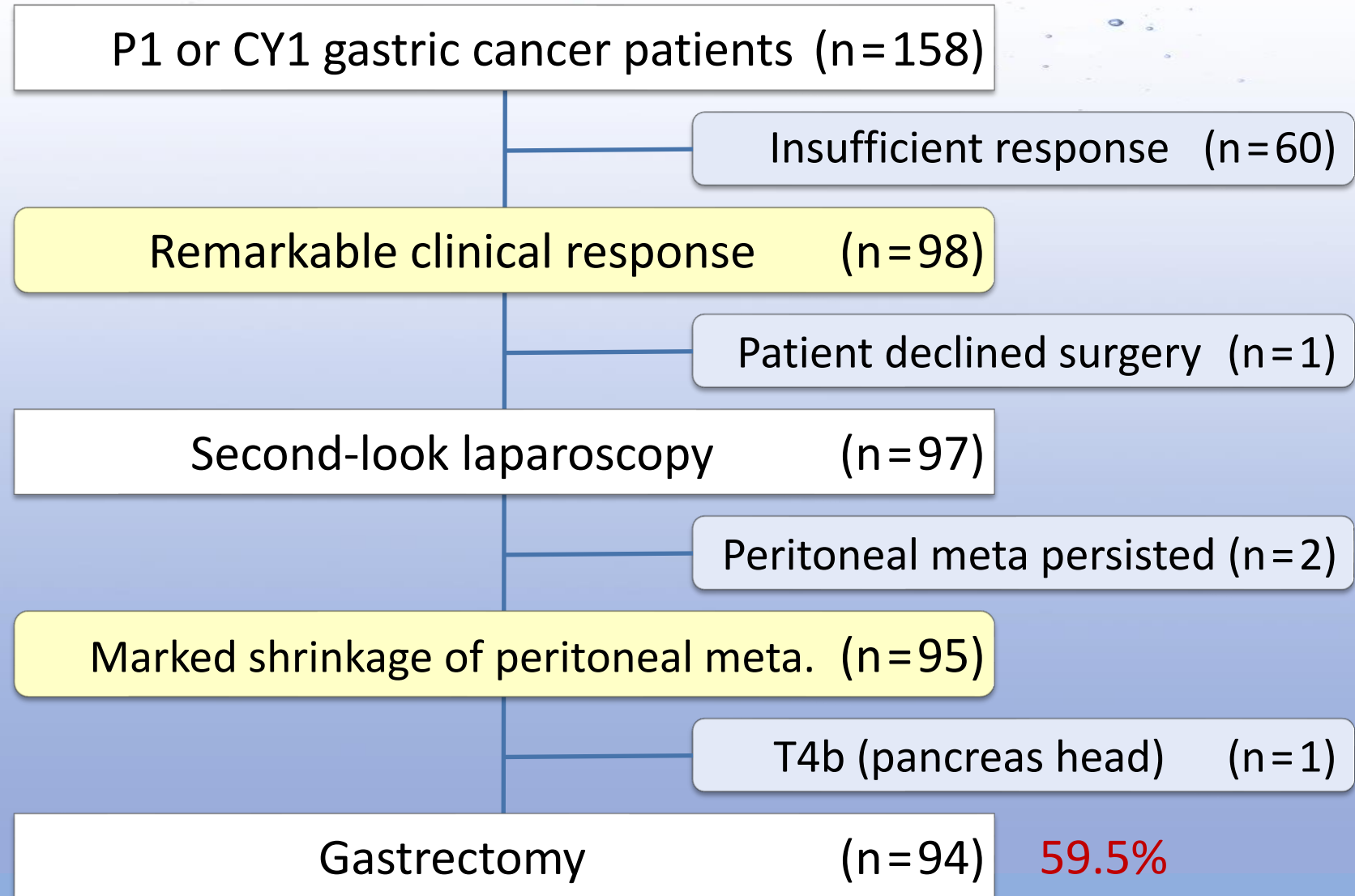
P1 or CY1 gastric cancer patients with the primary tumor treated at the University of Tokyo Hospital between 2005 and 2015

Treatment


Chemotherapy IP PTX/DOC plus systemic chemotherapy

Surgery Gastrectomy with lymph node dissection
Partial peritonectomy as necessary

Clinical Course



Patient characteristics



Characteristic	Surgery (+) (n = 94)	Surgery (-) (n = 64)	P value
Age, years, median (range)	57 (28–86)	58 (23–86)	0.43
Sex Male / Female	48/46	35/29	0.65
ECOG PS 0 / 1 / 2	73/21/0	32/30/2	0.0003
Previous chemotherapy Received/Not received	42/52	25/39	0.48
Macroscopic type Type 0 / 2 / 3 / 4	1/2/34/57	0/0/20/44	0.57
Histological type Diff. / Mixed / Undiff.	10/8/76	7/6/51	0.98
Peritoneal metastasis POCY1 / P ₁ / P ₂ / P ₃	9/5/30/50	2/0/7/55	0.0001
Other distant metastasis None / Ovary / LN	79/11/4	52/5/7	0.22

Chemotherapy before surgery

(n = 94)

Regimen




- S-1/PTX + IP PTX 73
- S-1/oxaliplatin + IP PTX 10
- S-1/cisplatin + IP PTX 1
- Capecitabine/cisplatin + IP DOC 10

Number of courses Median 6 (range 2–33)

Courses	2–3	4–6	7–9	10–12	13–18	22	33
POCY1	8	1					
P ₁	3	1			1		
P ₂	13	9	5	2	1		
P ₃	9	9	11	14	5	1	1

Surgery

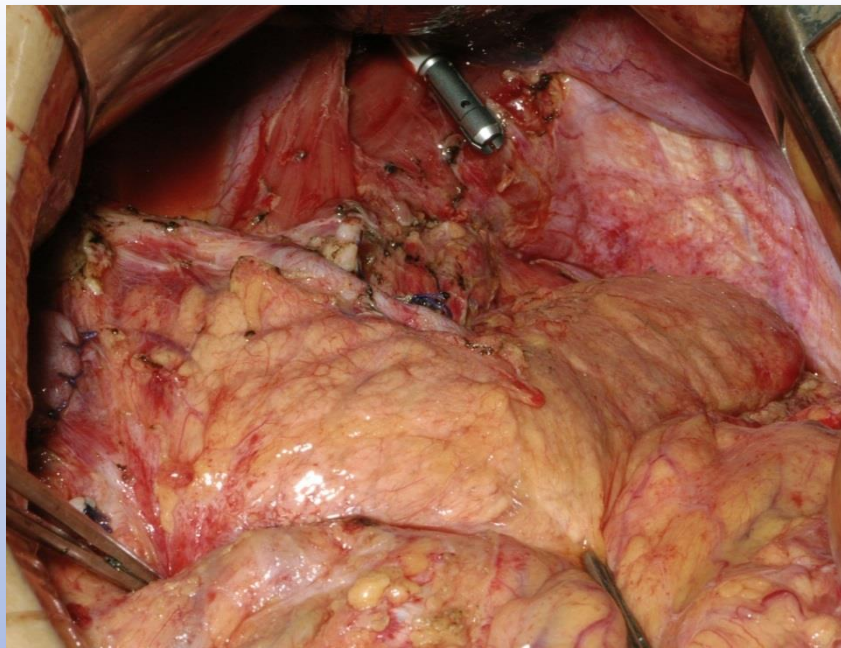
(n = 94)



Total/Distal gastrectomy	87/7
Combined resection	
Spleen	20
Distal pancreas	3
Colon	23
Small intestine	4
Adnexa	9
LN dissection D2-No.10/D2/D3	70/23/1
Operation time	Mdn 295 min
Blood loss	Mdn 660 ml

Lymph node dissection

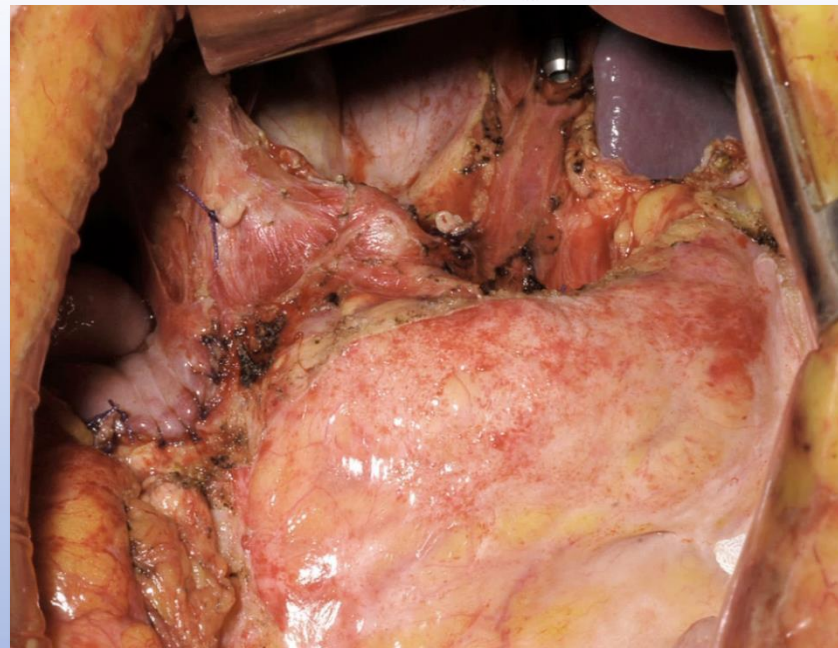
D2



P0CY1 or P₁

R0

D2-No.10



P₂, P₃

R2

- ◆ Splenic hilar node swelling (+)
- ◆ gastrosplenic ligament invasion (+)

Outcomes

(n = 94)

Postoperative complication (Clavien-Dindo G2/3/4/5)

Anastomotic leakage	3/0/0/0
Intra-abdominal abscess	3/0/0/0
Pancreatic fistula	2/0/0/0

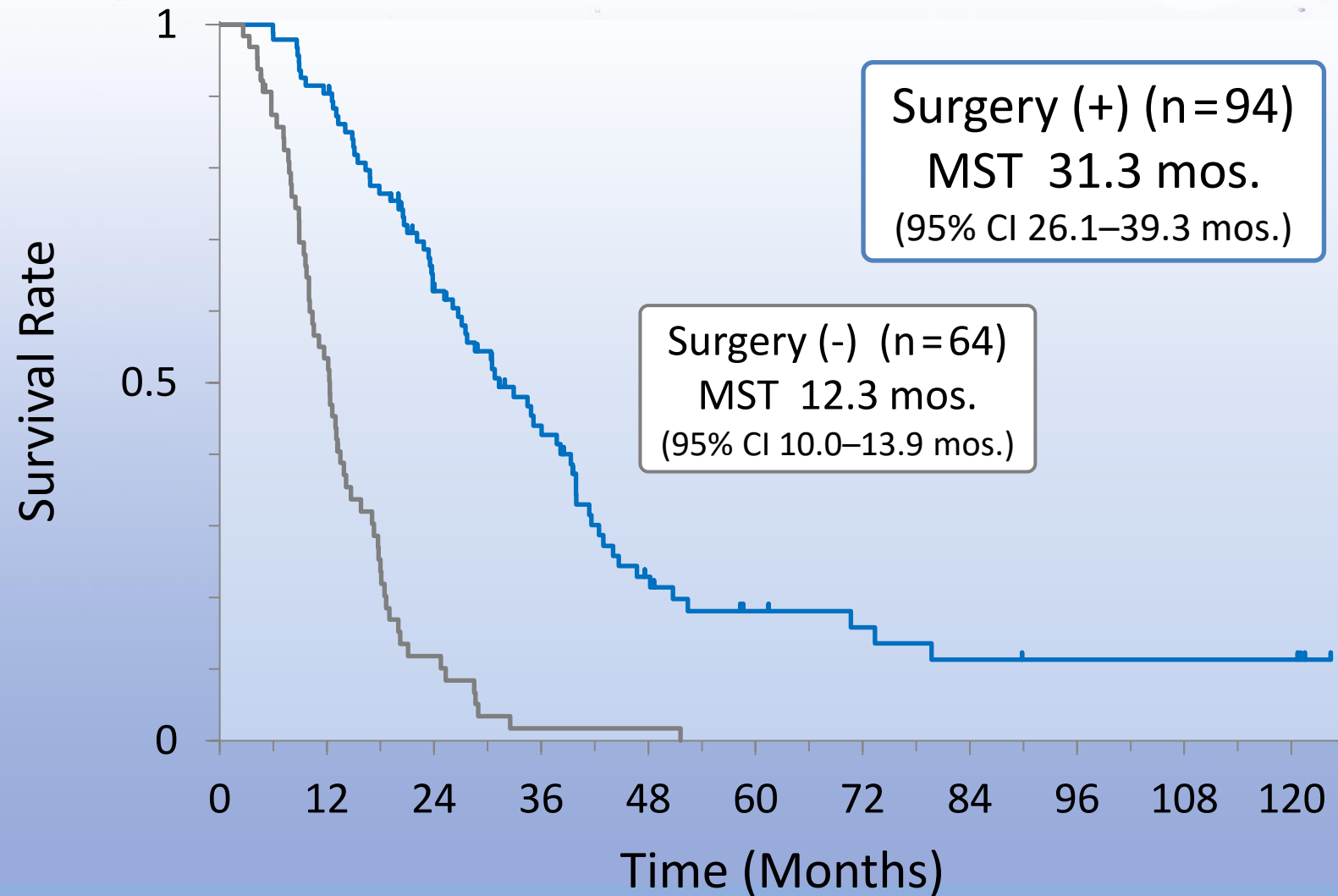
Residual tumor status

R0/R1/R2 **61 (65%)/16/17**

Histological response

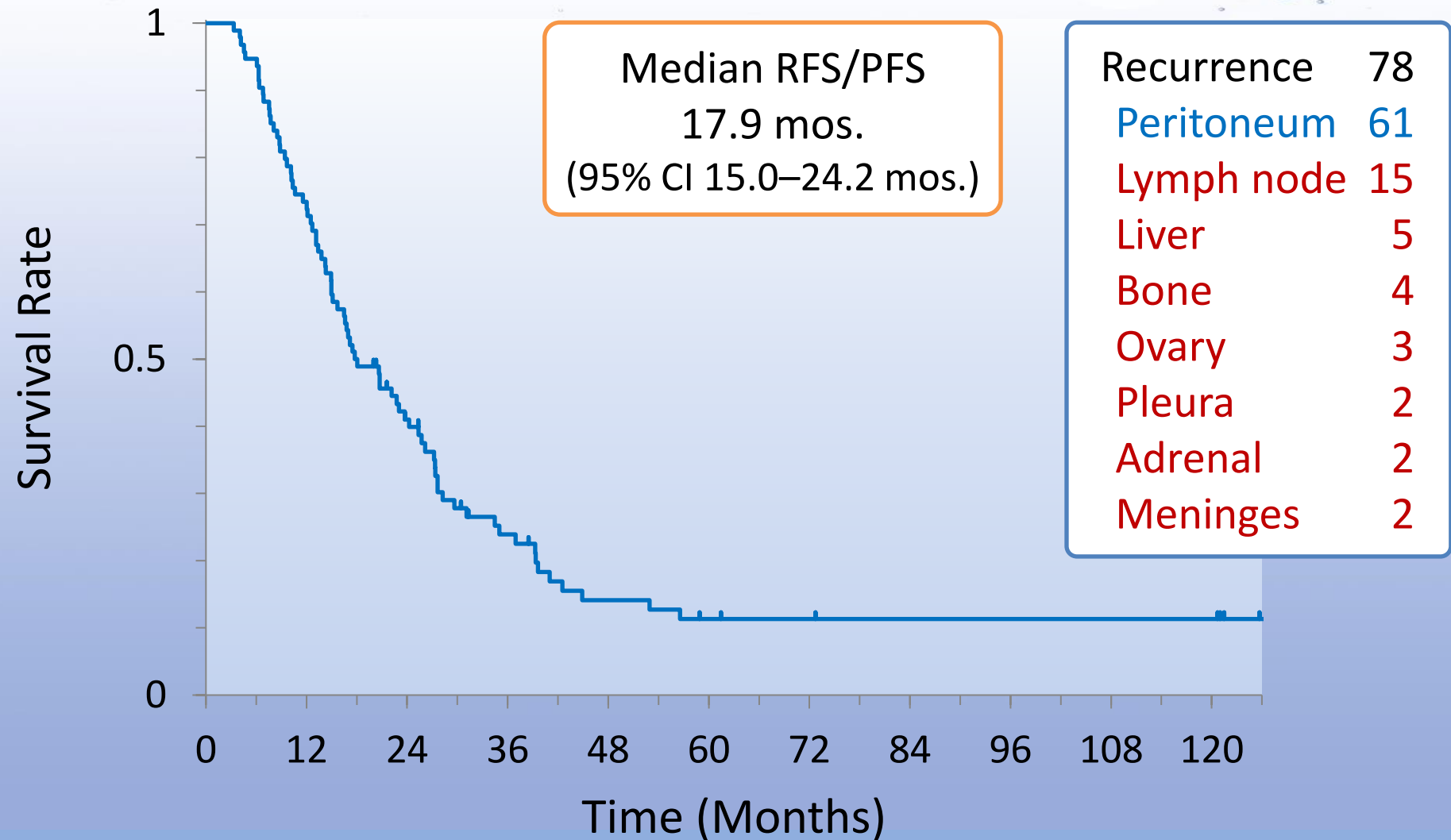
Grade	G0	G1a	G1b	G2	G3
Viable tumor	All	≥ 2/3	1/3–2/3	< 1/3	None
n	2	48	22	20	2
(%)	(2%)	(51%)	(23%)	(21%)	(2%)

Overall Survival



Relapse/Progression Free Survival

(n = 94)



Summary



•**PHOENIX-GC trial**

- ✦ MST 17.7 months vs. 15.2 months (S-1/CDDP)
- ✦ Primary analysis: stratified log-rank $p=0.080$
- ✦ Adjusted for ascites: HR 0.59 (95%CI 0.39–0.87)
- ✦ 3-year OS 21.9% vs. 6.0%

Other combination regimens

- ✦ Equal to PHOENIX regimen in 1-year OS

•**Surgery after response to chemotherapy**

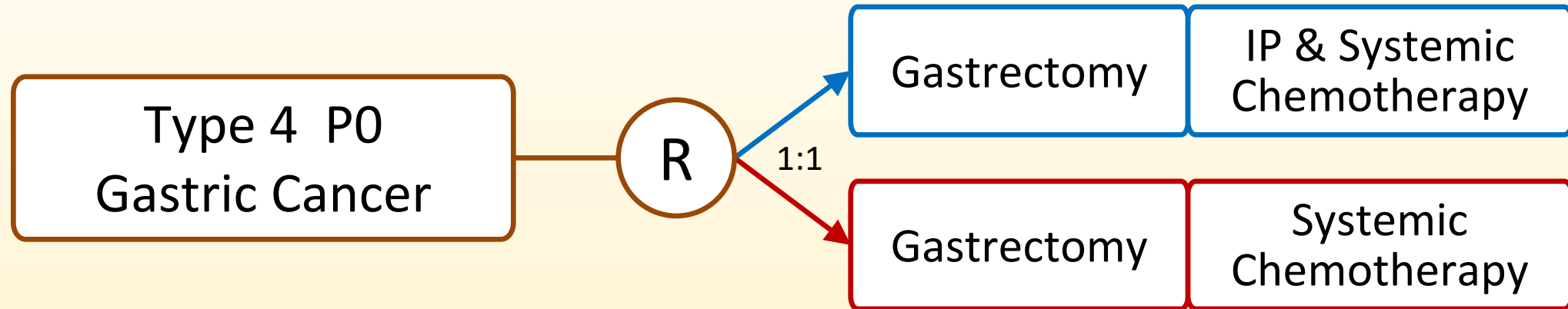
- ✦ MST 31.3 months, RFS/PFS 17.9 months
- ✦ Postoperative complication ($\geq G2$) 10%

HIPEC vs PIPAC vs Long-term IP for gastric cancer

Key factors	HIPEC	PIPAC	Long-term IP
Potency of the drug	★ ★	★	★ ★ ★
Intraperitoneal concentration	★ ★	★ ★	★ ★
Duration of tumor exposure	★	★ ★	★ ★ ★
Depth of drug infiltration	★ ★ ★	★ ★ ★	★ ★
Frequency & duration of Tx	★	★ ★	★ ★ ★



PHOENIX-GC2 trial



Key Eligibility Criteria

- Suspected invasion beyond the subserosal layer (cT3–4)
- No organ metastasis (cM0)
- Irrespective of peritoneal cytology findings (CY0/CY1)

Stratification

- Institution
- Clinical N stage (JCGC 13th ed.)

Primary Endpoint

- Disease free survival

Secondary Endpoints

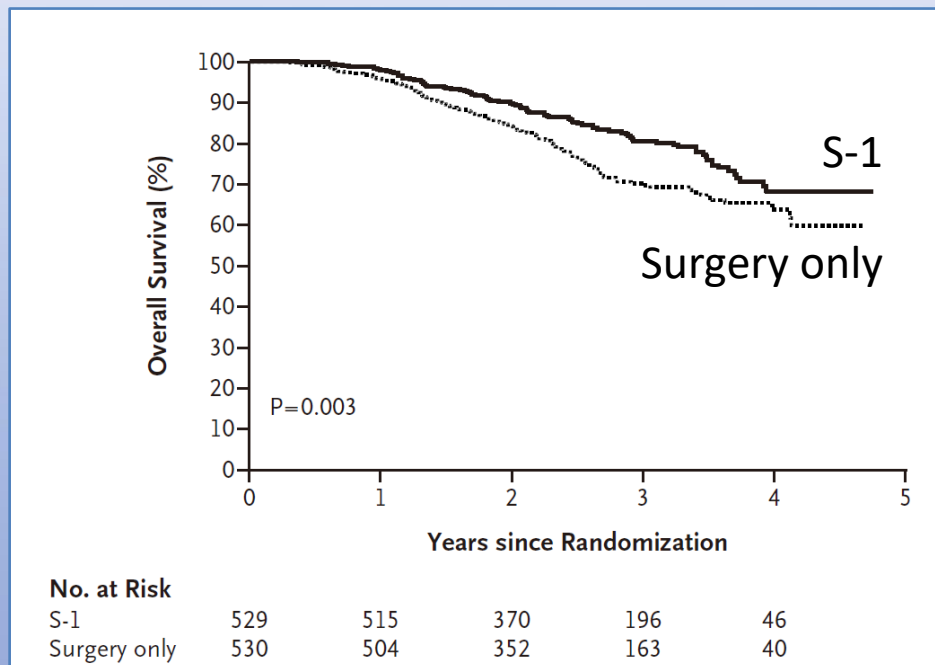
- Overall survival
- Safety etc.

Treatment for stage II–III (M0) GC

Gastrectomy

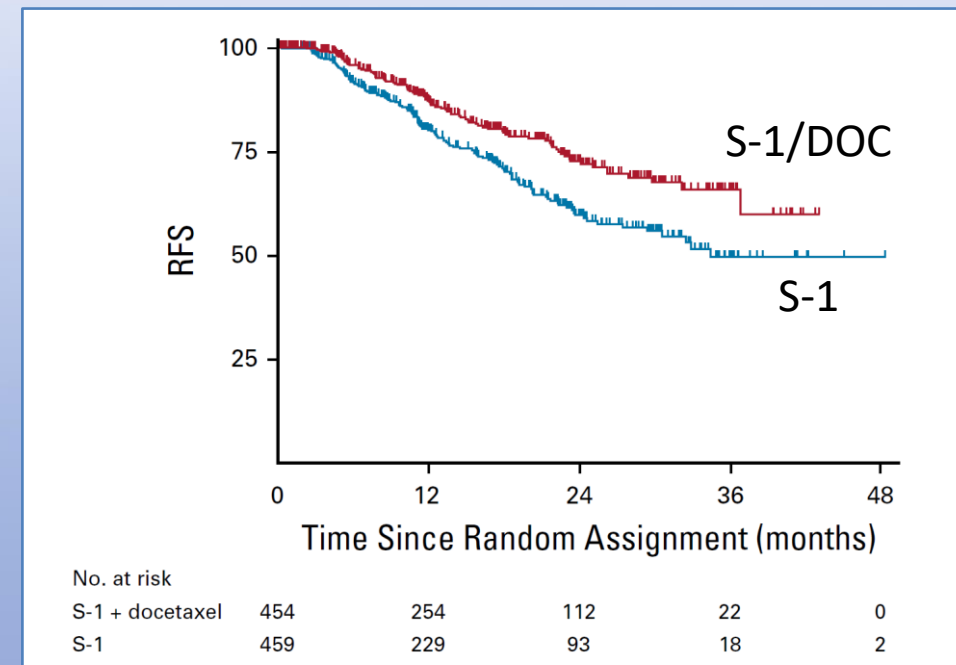
adjuvant CTX (S-1, S-1/DOC, CapeOX, SOX)

ACTS-GC Trial



Sakuramoto S et al. *NEJM* 2007

JACCRO GC-07 (START-2) Trial



Yoshida K, Kodera Y et al. *JCO* 2019

Treatment for stage II–III (M0) GC



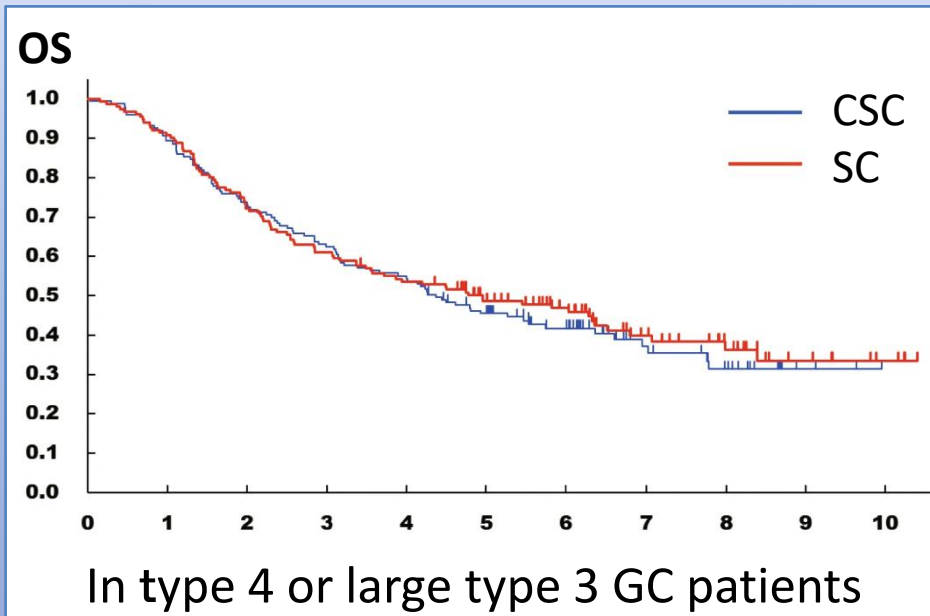
NAC (CS, DOS)

Gastrectomy

adjuvant CTX

JCOG0501 Trial

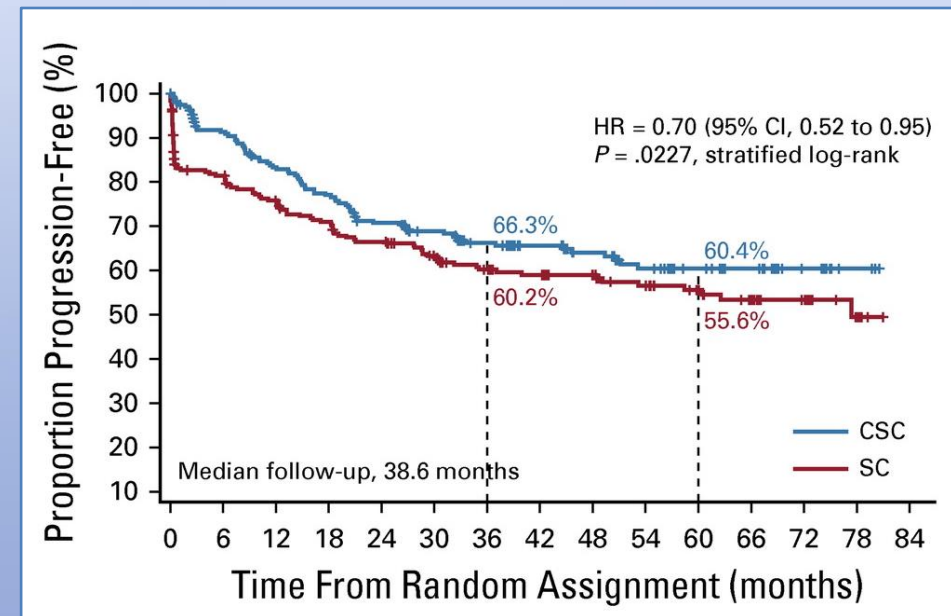
Neoadjuvant CDDP/S-1



Iwasaki Y et al. *Gastric Cancer* 2020

PRODIGY Study

Neoadjuvant DOC/L-OHP/S-1



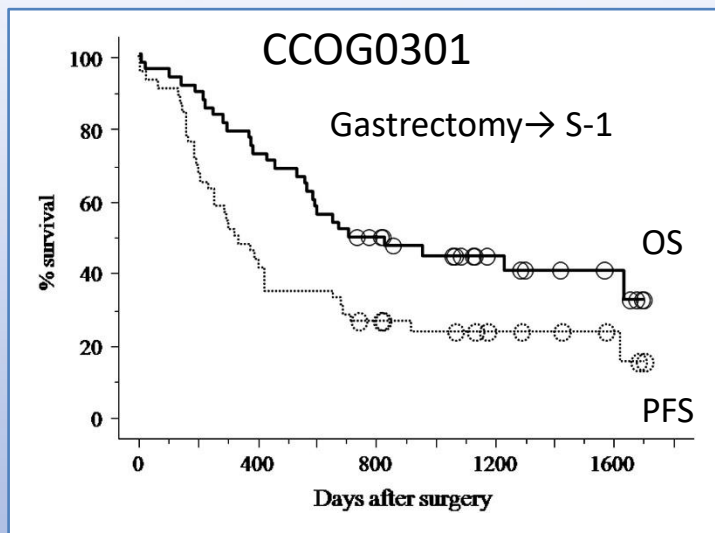
Kang YK et al. *JCO* 2021

Treatment for P0CY1 GC

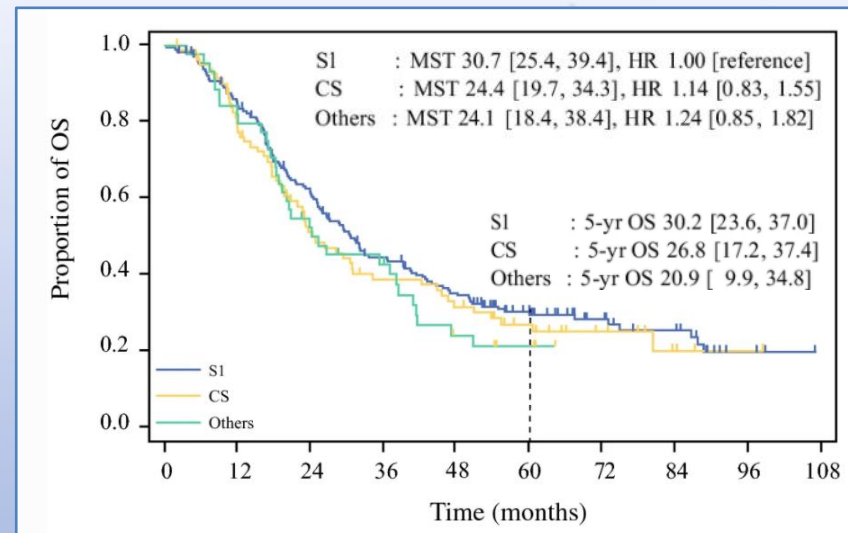
1.

Gastrectomy

CTX (S-1, S-1/CDDP, SOX)



Kodera Y et al. *EJSO* 2009



MST
24–30 mo.

5-yr OS
20%–30%

Yamaguchi T et al. *Ann Surg Oncol* 2020

2.

CTX

Gastrectomy

CTX

3.

CTX



Objectives & Endpoints

Objectives

To verify the superiority of combined ip and systemic chemotherapy over standard systemic chemotherapy in the adjuvant or perioperative setting for type 4 gastric cancer

Primary endpoint

- Disease-free survival (DFS)

Secondary endpoints

- Overall survival, peritoneal recurrence free survival, incidence of adverse events
- Completion rate of preoperative chemotherapy, curative resection rate, histological response rate (in CY1 cases)

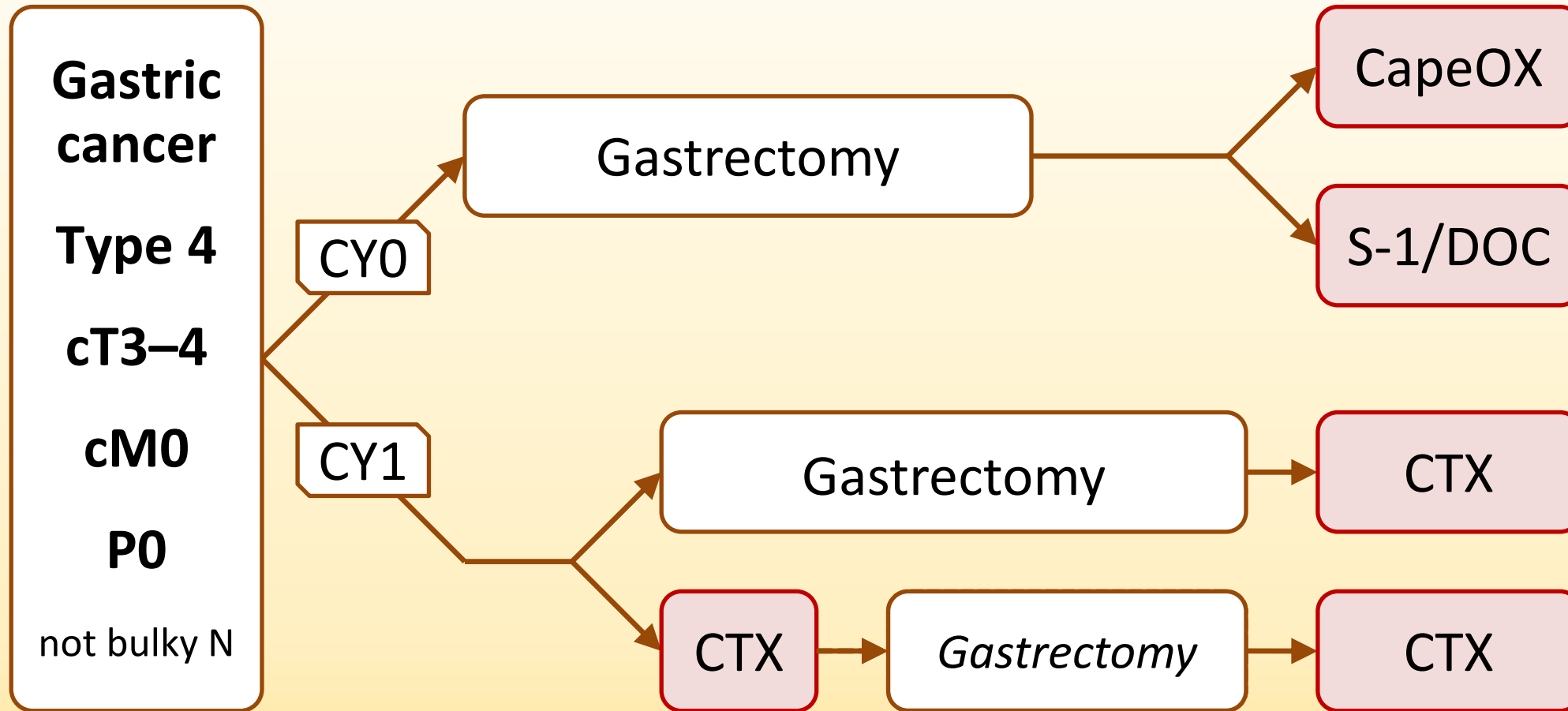


Key Eligibility Criteria

- Pathologically proven common-type gastric adenocarcinoma
- **Type 4** (diffuse infiltrating type) tumor
- Suspected invasion beyond the subserosal layer (**cT3–4**)
- No bulky lymph node metastasis detected by CT (**not bulky N**)
- No apparent distant metastasis detected by diagnostic imaging (**cM0**)
- Age: 20 to 75 years
- ECOG Performance Status: 0 or 1
- No peritoneal metastasis confirmed by the staging laparoscopy (**P0**)
- Either of following conditions
 - Macroscopic curative resection (**R0–1**) in CY0 patients
 - Possible macroscopic curative resection (**R0–1**) in CY1 patients



Standards of Care

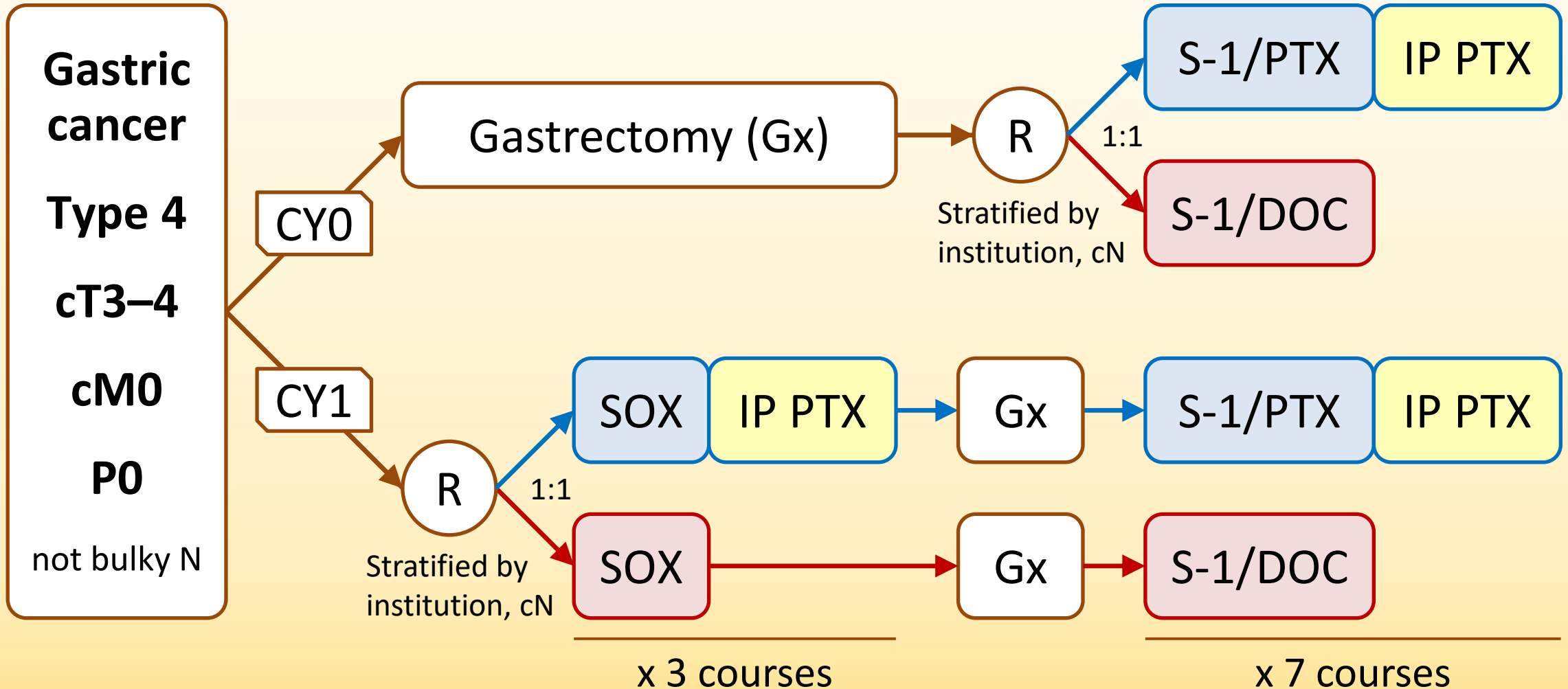


CapeOX, capecitabine/oxaliplatin; DOC, docetaxel; CTX, chemotherapy



Trial design

Multicenter, open-label, randomized, phase III trial



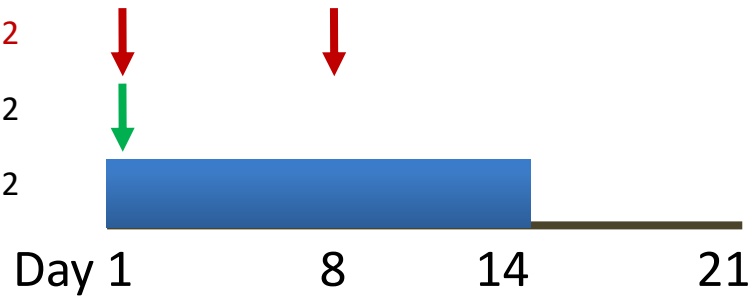


Chemotherapy Regimens

Preoperative

SOX + IP PTX

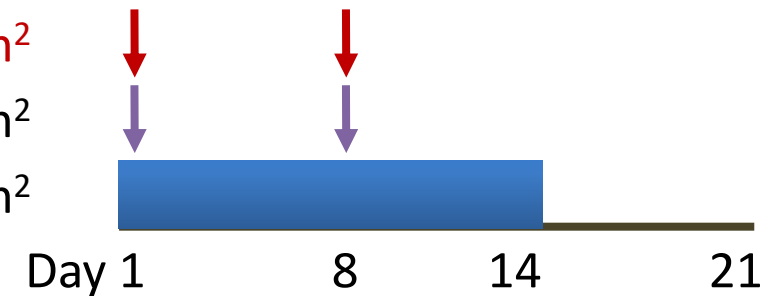
IP PTX 40 mg/m²
L-OHP 100 mg/m²
S-1 80 mg/m²



Postoperative

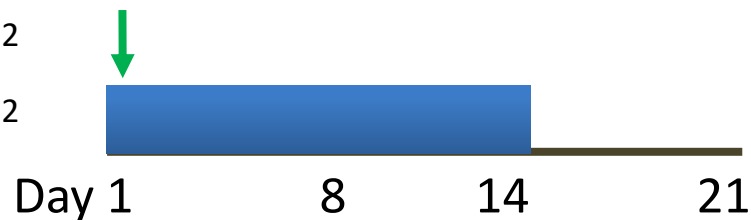
S-1/PTX + IP PTX

IP PTX 20 mg/m²
IV PTX 50 mg/m²
S-1 80 mg/m²



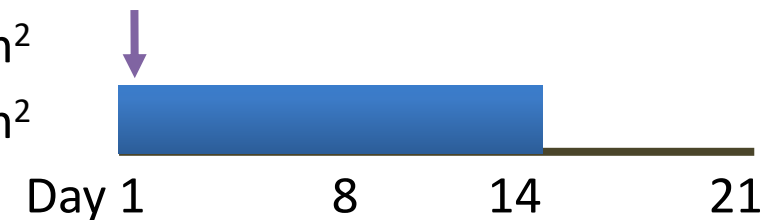
SOX

L-OHP 100 mg/m²
S-1 80 mg/m²



S-1/DOC

DOC 40 mg/m²
S-1 80 mg/m²





Statistical Considerations

Sample size assumptions


- 3-year DFS in the systemic chemotherapy group, 50%
 - Hazard ratio, 0.64
 - Number of patients, CY0:CY1 = 2:1
 - Accrual period, 3 years; follow-up period, 3 years
 - 1-sided $\alpha=0.025$; power 80%
- 157 events are required for the final analysis.
- 300 patients
- Interim analysis is planned at 79 events.



Trial centers

- The University of Tokyo
- Nagoya University
- Kindai University
- Teikyo University
- Niigata Cancer Center Hospital
- Kagoshima University
- Aichi Cancer Center Hospital
- Hyogo College of Medicine
- Kanazawa University
- University of Fukui
- Ibaraki Prefectural Central Hospital
- Osaka International Cancer Institute
- Tokyo Metropolitan Tama Medical Center
- Kyoto Medical Center
- Osaka General Medical Center
- National Center for Global Health and Medicine
- Kanto Rosai Hospital
- Kansai Rosai Hospital
- Kitano Hospital
- Toyonaka Municipal Hospital

- Toho University
- National Kyushu Medical Center
- Kyushu Cancer Center
- Osaka Police Hospital
- Tonan Hospital
- The Cancer Institute Hospital of JFCR
- Yamagata University
- University of Tsukuba
- Jichi Medical University
- Tottori University
- Imamura Hospital
- St. Luke's International Hospital
- Hiroshima City Hospital
- Hiroshima City Asa Citizens Hospital
- Juntendo University Hospital
- Nagasaki University
- Sapporo Medical University
- Komaki City Hospital
- Jichi Medical University Saitama Medical Center
- Nihon University Hospital



Multidisciplinary treatment combining gastrectomy
with IP and systemic chemotherapy is safe
and effective for gastric cancer with
peritoneal metastasis.

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