City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

FINAL GREAT DEBATE

Is there a Role for Regional Therapy in Gastric Cancer? (CON)

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Disclosures

- Grant/Research Support from Merck.
- Consultant for Amgen, Astellas, AstraZeneca, Merck, and Roche.
- On the Speakers Bureau for Bristol Myers Squibb, and Merck.

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.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

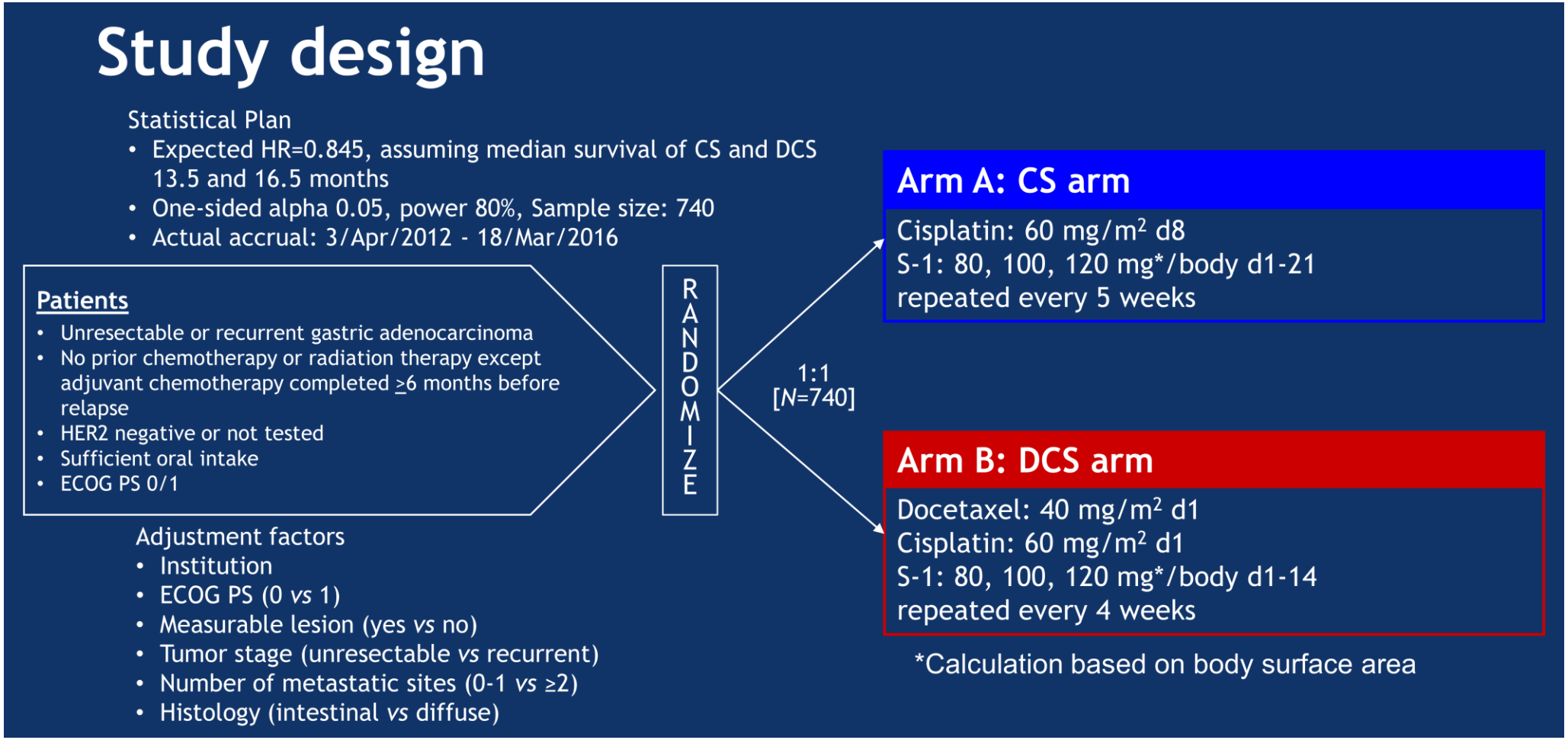
The following CLC & IB components will be addressed in this presentation:

- Underrepresented groups impacted by stomach cancer.

Is HIPEC therapy in its current form ready for prime time in gastric cancer?

- Is more chemotherapy always better?
- What is cytoreductive surgery adding to stage IV disease?
- What is the latest randomized data for HIPEC?

More chemotherapy is not always better – Phase III JCOG 1013 Trial



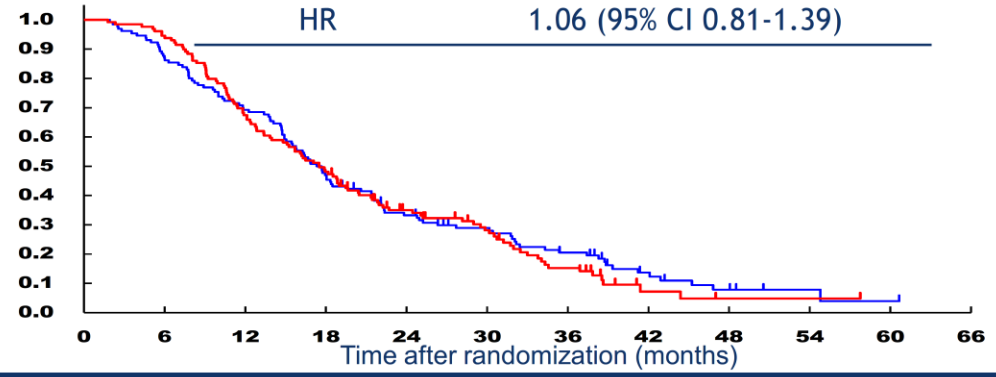
Yamada Y, et al. ASCO 2018. Abstract 4009

More chemotherapy is not always better – Phase III JCOG 1013 Trial

Key Secondary Endpoint: OS according to histological type

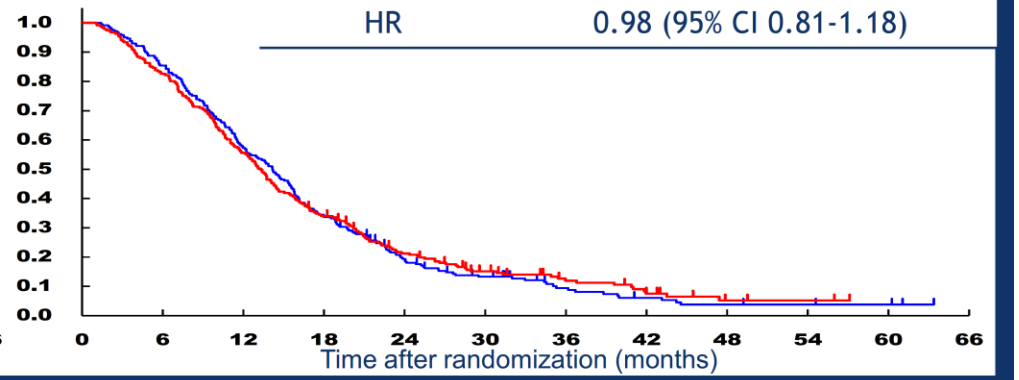
Intestinal type (n=259)

	CS	DCS
Median OS (95% CI)	17.5 m (15.0-20.6)	17.5 m (14.0-20.4)
HR	1.06 (95% CI 0.81-1.39)	



Diffuse type (n=482)

	CS	DCS
Median OS (95% CI)	14.2 m (12.2-15.6)	13.3 m (11.7-14.5)
HR	0.98 (95% CI 0.81-1.18)	



Number at risk (number censored)

CS	130 (0)	113 (0)	90 (0)	61 (0)	40 (4)	31 (4)	21 (1)	10 (5)	5 (1)	2 (3)	1 (0)	0 (1)	241 (0)	206 (0)	138 (0)	82 (0)	43 (5)	26 (4)	14 (6)	8 (1)	5 (0)	4 (1)	3 (1)	0 (3)
DCS	129 (0)	122 (0)	87 (0)	62 (0)	38 (8)	27 (4)	14 (1)	3 (6)	1 (1)	1 (0)	0 (1)	0 (0)	241 (0)	199 (0)	134 (0)	81 (1)	47 (5)	28 (6)	17 (6)	9 (2)	3 (4)	2 (1)	0 (2)	0 (0)

Overall survival was significantly shorter in the diffuse type (median, 13.7 months, 95% CI 12.5-14.6) than in the intestinal type (17.5 months, 15.7-18.9; HR 1.38, 95% CI 1.17-1.62).

Yamada Y, et al. ASCO 2018. Abstract 4009

More chemotherapy can be worse . . .

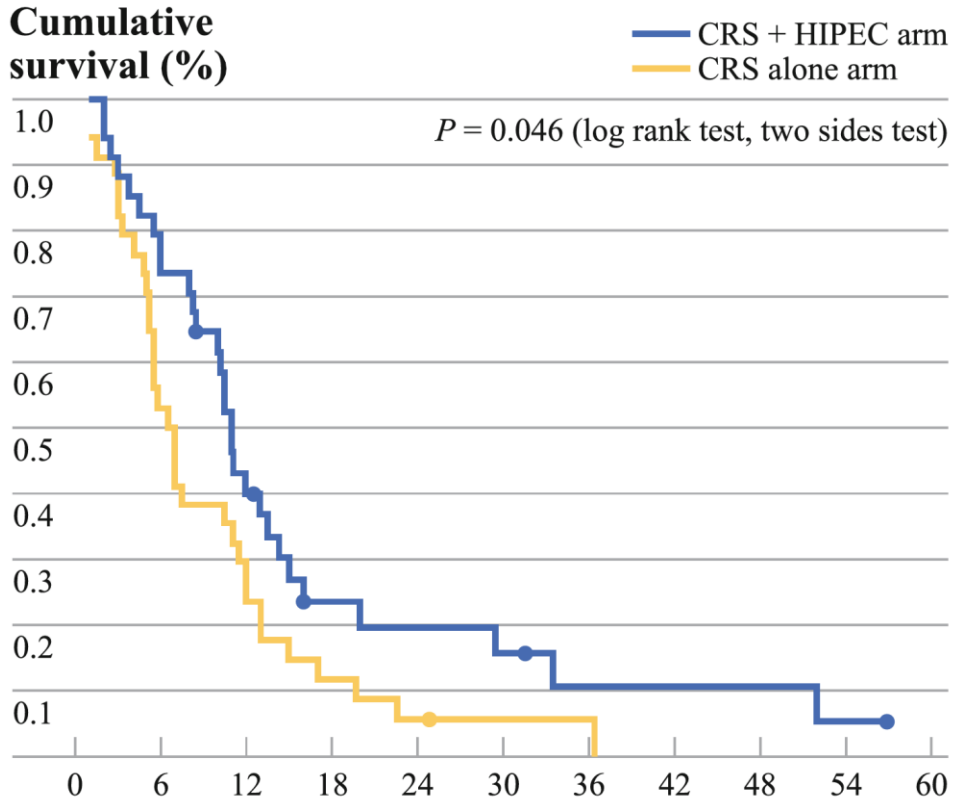
Grade ≥3 adverse events

CTCAE ver.4.0	CS (n=367)		DCS (n=358)	
	n	(%)	n	(%)
Leukocytes	60	(16.4)	120	(33.6)
Neutrophils	117	(32.1)	209	(58.5)
Hemoglobin	89	(24.4)	83	(23.2)
Platelets	31	(8.5)	14	(3.9)
Febrile neutropenia	21	(5.7)	27	(7.6)
Hyponatremia	45	(12.3)	51	(14.3)
Fatigue	42	(11.4)	40	(11.2)
Anorexia	81	(22.1)	94	(26.3)
Diarrhea	27	(7.4)	25	(7.0)
Nausea	27	(7.4)	31	(8.7)
Vomiting	9	(2.5)	8	(2.2)
Mucositis oral	8	(2.2)	9	(2.5)
Treatment-related death	1	(<1)	3	(<1)

Yamada Y, et al. ASCO 2018. Abstract 4009

Chinese Phase III Gastric HIPEC Trial

- 34 patients in each arm, single center, single lead surgeon
- Control arm underperformed?
- No CONSORT Diagram
- 1 of 34 patients in CRS alone arm versus 5 of 34 patient in CRS + HIPEC arm alive at data cutoff

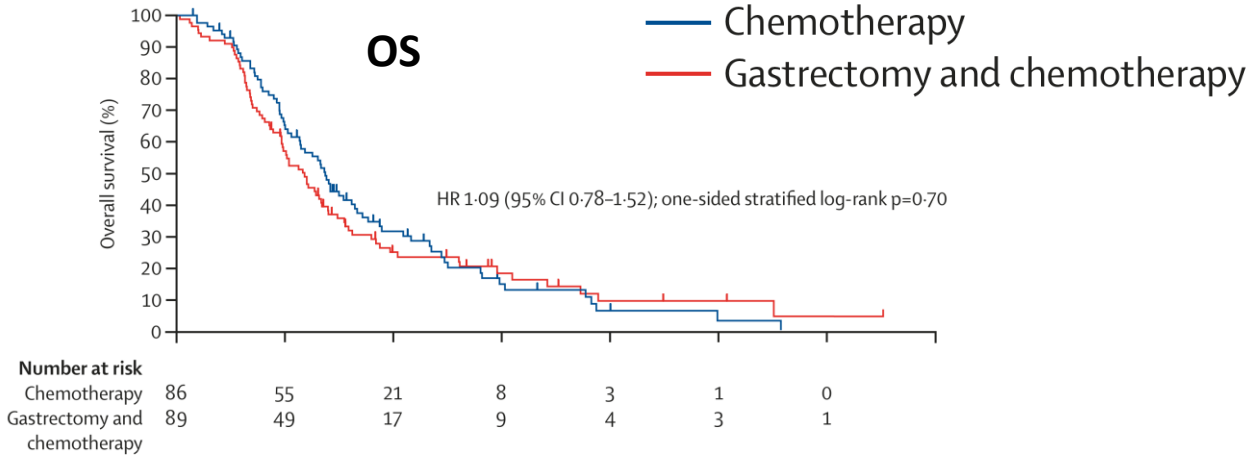


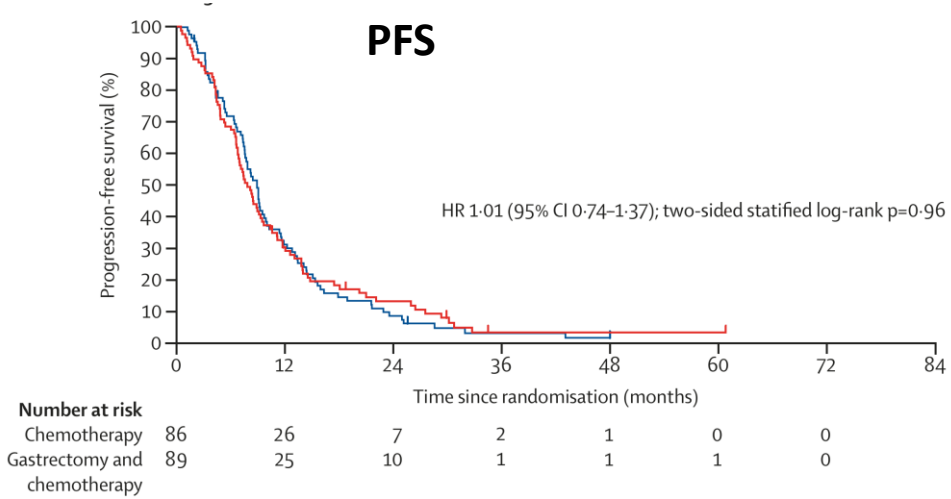
	Patients	Median OS	95% C1
CRS + HIPEC arm	n = 34	6.5 mo	4.8 – 8.2 mo
CRS alone arm	n = 34	11.0 mo	10.0 – 11.9 mo

Yang X, et al. Ann Surg Oncol. 2011;18(6):1575-1581.

What does gastrectomy add for stage IV gastric cancer – Phase III REGATTA Trial

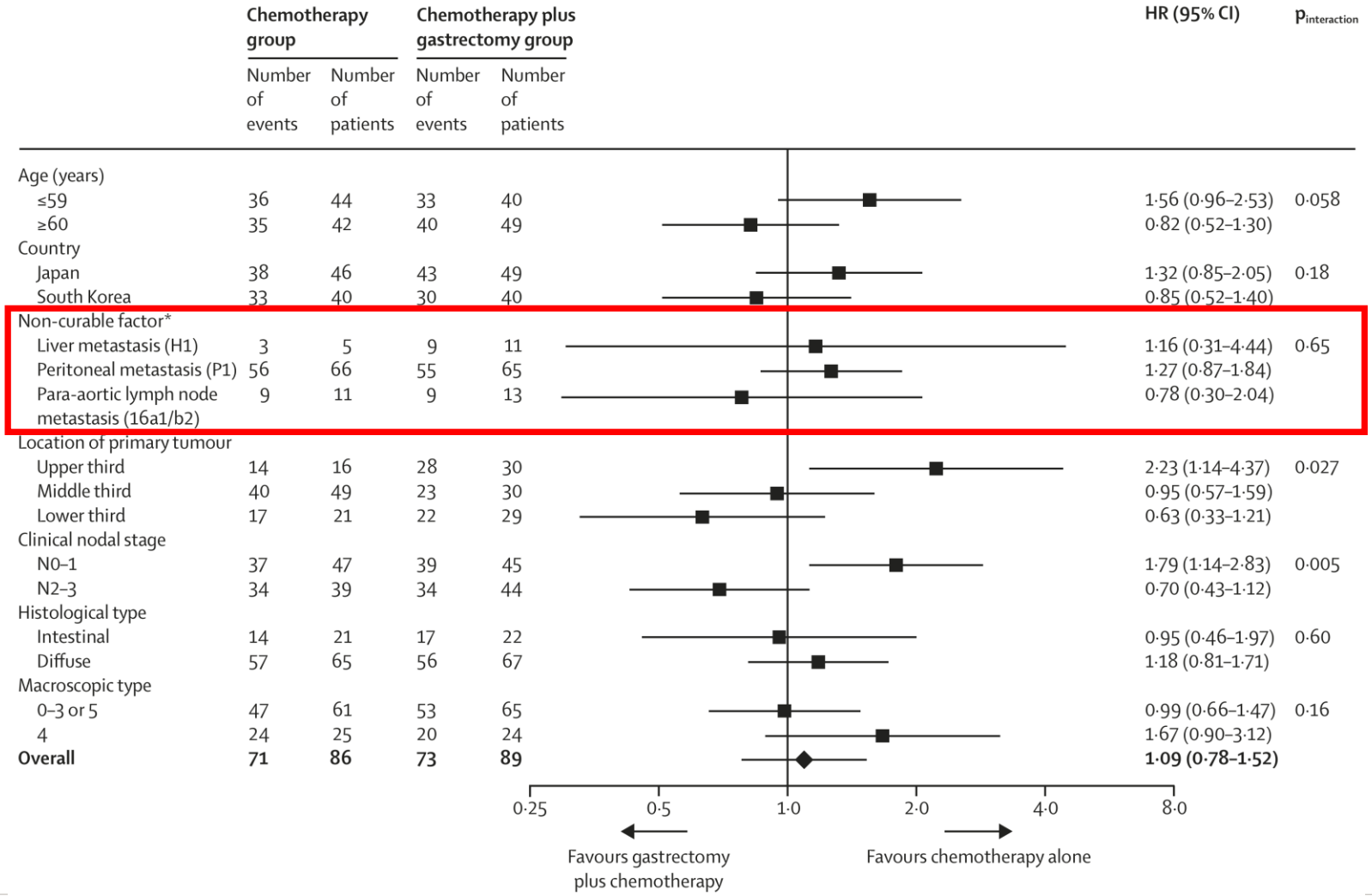
- > 5 years to enroll 175 patients across Japan and Korea
- Enrollment limited to patients with peritoneal metastasis (P1) in the diaphragm or peritoneum caudal to the transverse colon without massive ascites or intestinal obstruction, cT1-3





Fujitani K, et al. Lancet Oncol. 2016;17(3):309-318.

Phase III REGATTA Trial – Subgroup Analyses

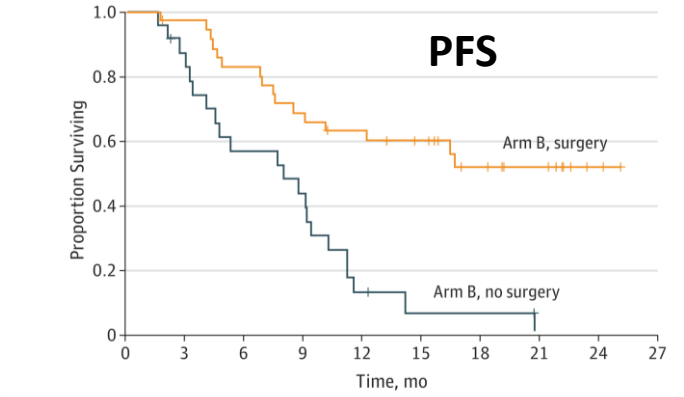


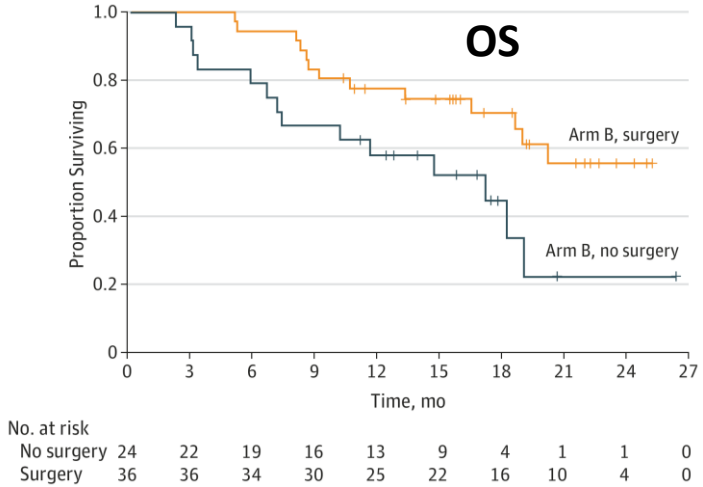
	Chemotherapy group		Chemotherapy plus gastrectomy group		HR (95% CI)	$p_{interaction}$
	Number of events	Number of patients	Number of events	Number of patients		
Age (years)						
≤59	36	44	33	40	1·56 (0·96–2·53)	0·058
≥60	35	42	40	49	0·82 (0·52–1·30)	
Country						
Japan	38	46	43	49	1·32 (0·85–2·05)	0·18
South Korea	33	40	30	40	0·85 (0·52–1·40)	
Non-curable factor*						
Liver metastasis (H1)	3	5	9	11	1·16 (0·31–4·44)	0·65
Peritoneal metastasis (P1)	56	66	55	65	1·27 (0·87–1·84)	
Para-aortic lymph node metastasis (16a1/b2)	9	11	9	13	0·78 (0·30–2·04)	
Location of primary tumour						
Upper third	14	16	28	30	2·23 (1·14–4·37)	0·027
Middle third	40	49	23	30	0·95 (0·57–1·59)	
Lower third	17	21	22	29	0·63 (0·33–1·21)	
Clinical nodal stage						
N0–1	37	47	39	45	1·79 (1·14–2·83)	0·005
N2–3	34	39	34	44	0·70 (0·43–1·12)	
Histological type						
Intestinal	14	21	17	22	0·95 (0·46–1·97)	0·60
Diffuse	57	65	56	67	1·18 (0·81–1·71)	
Macroscopic type						
0–3 or 5	47	61	53	65	0·99 (0·66–1·47)	0·16
4	24	25	20	24	1·67 (0·90–3·12)	
Overall	**71**	**86**	**73**	**89**	**1·09 (0·78–1·52)**	

Fujitani K, et al. Lancet Oncol. 2016;17(3):309-318.

What does cytoreductive surgery add for stage IV gastric cancer – Phase II FLOT3 Trial

- 67 patients enrolled to limited metastatic cohort B, if response then complete surgical cytoreduction with HIPEC if appropriate
- P2 or lower, a few to several scattered metastases to the distant peritoneum, e.g. only ovarian metastases (Krukenberg)
- 2 of 4 patients with limited peritoneal disease underwent resection





Al-Batran SE, et al. JAMA Oncol. 2017;3(9):1237-1244.

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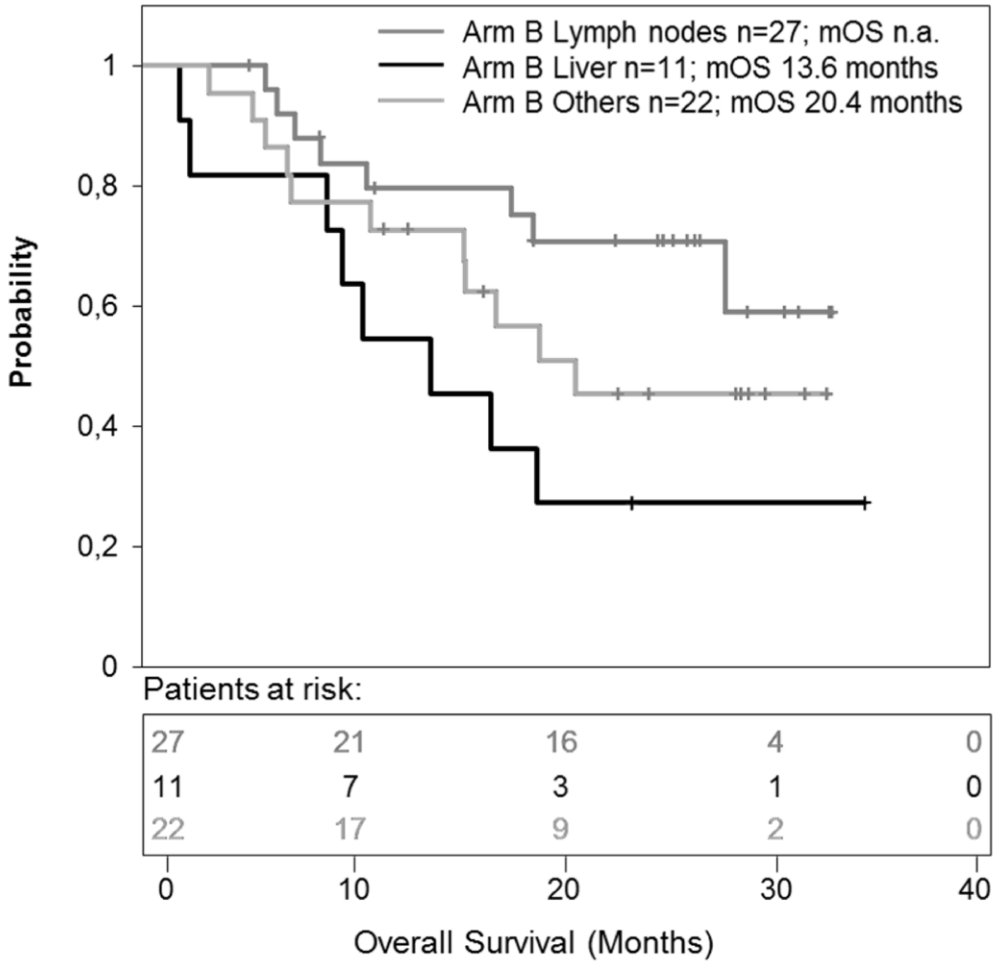

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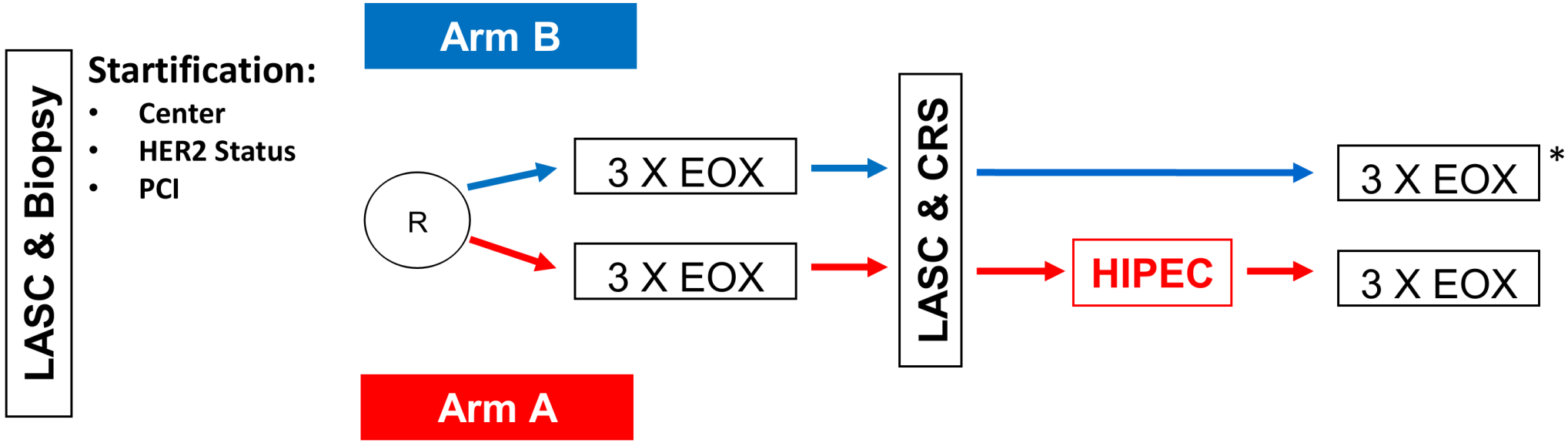
Latest randomized data for CRS + HIPEC – Phase III GASTRIPEC I Trial



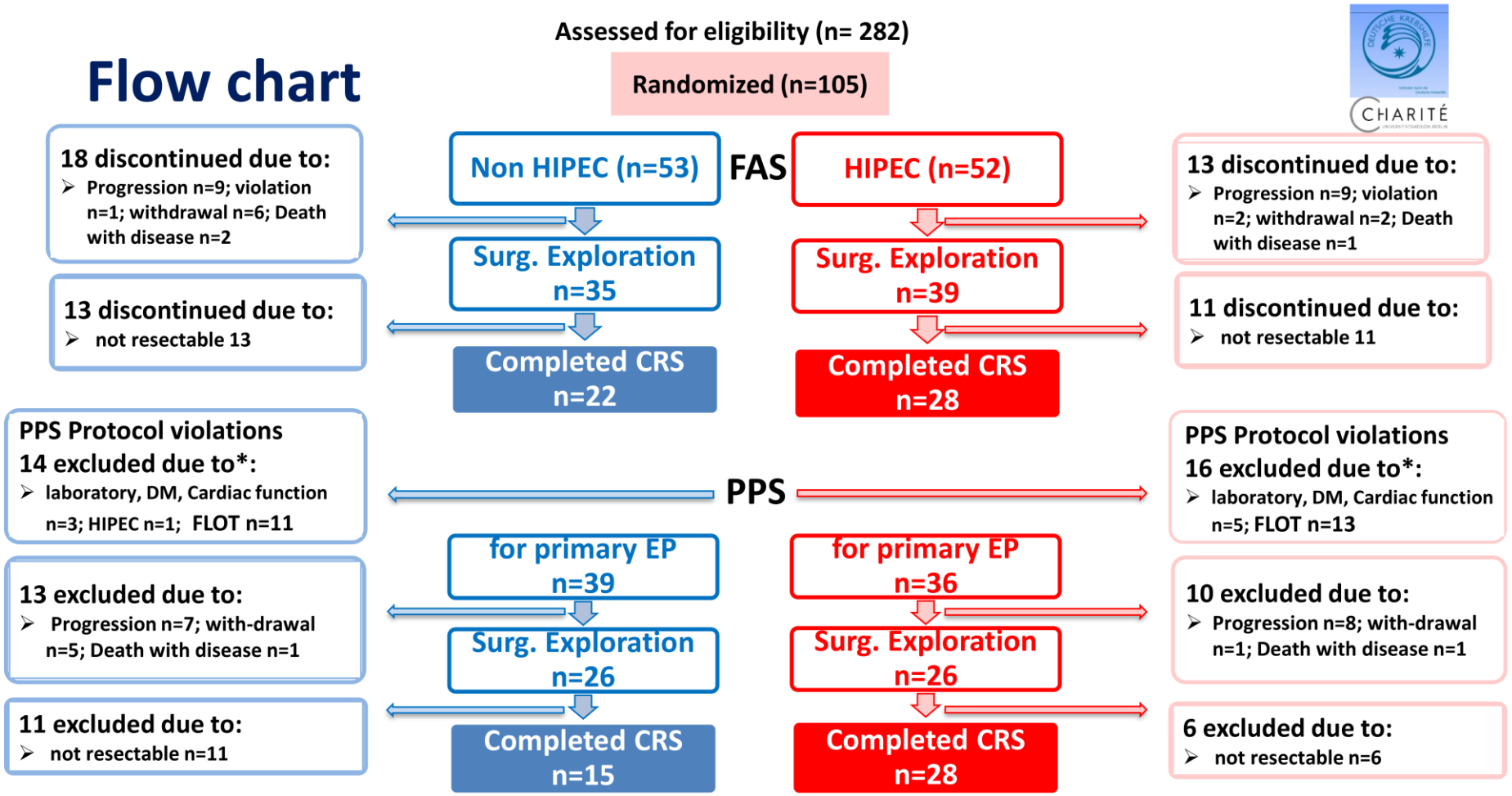
HER 2 Status negativ: Epirubicin 50 mg/m²; **Oxaliplatin** 130 mg/m²; **Capecitabin** 625 mg/m² q3w
HER 2 Status positiv: Cisplatin 80mg/m²; **Capecitabin** 1000mg/m²po; **Trastuzumab** 3cycl:8-6-6 mg/kg q3w
HIPEC: Cisplatin 75 mg/m² i.p.; **Mitomycin** 15 mg/m² i.p.; **60** minutes, > 41°C

1st patient in 4/2014; last patient in 06/20

*Cunningham D, et al., N Engl J Med 2008;358:36-46

Rau B, et al. ESMO 2021. Abstract 1376O

Latest randomized data for CRS + HIPEC – Phase III GASTRIPEC I Trial

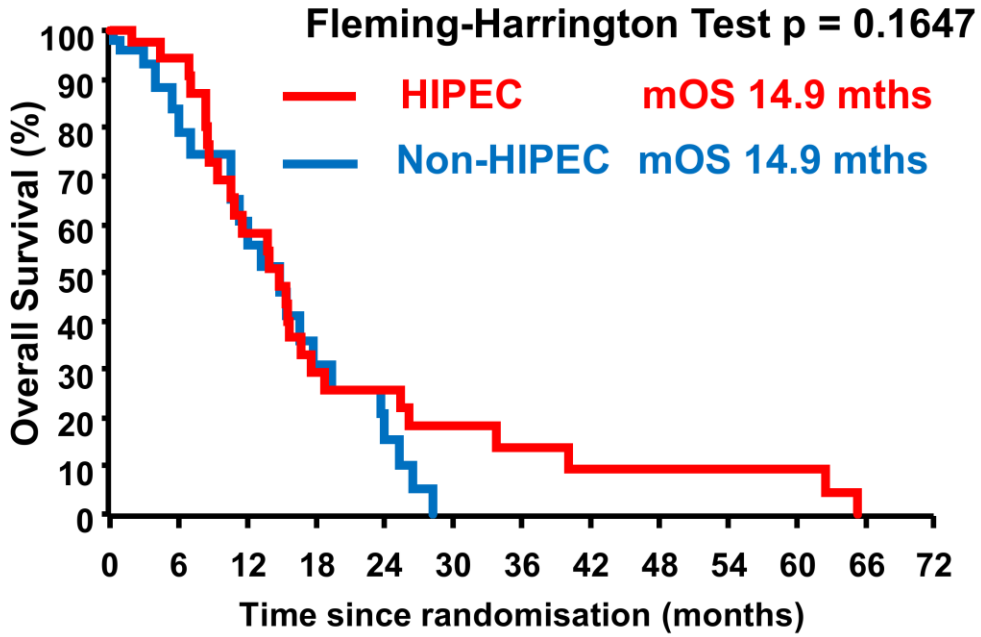


FAS: Full Analysis Set; PPS: Per Protocoll Set; CRS: cytoreductive surgery; surg.: surgical; EP: end point; * multiple violations possible

Rau B, et al. ESMO 2021. Abstract 1376O

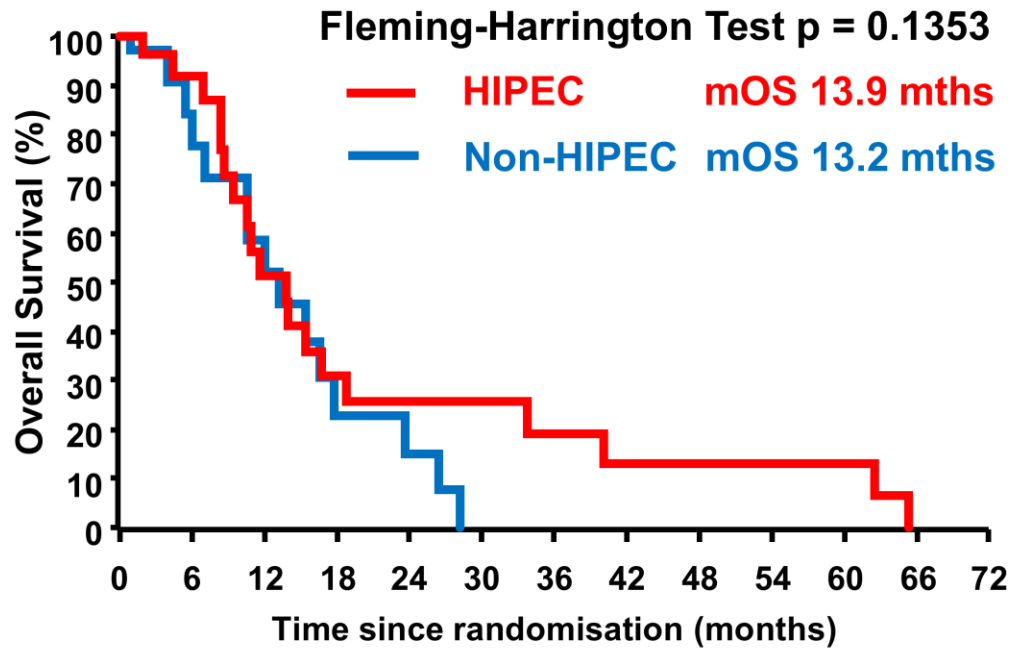
Phase III GASTRIPEC I Trial – Primary Endpoint OS Analysis

FAS



Patients at risk												
Non HIPEC	53	18	13	6	3	0	0	0	0	0	0	0
HIPEC	52	27	16	8	7	4	3	2	2	2	2	0

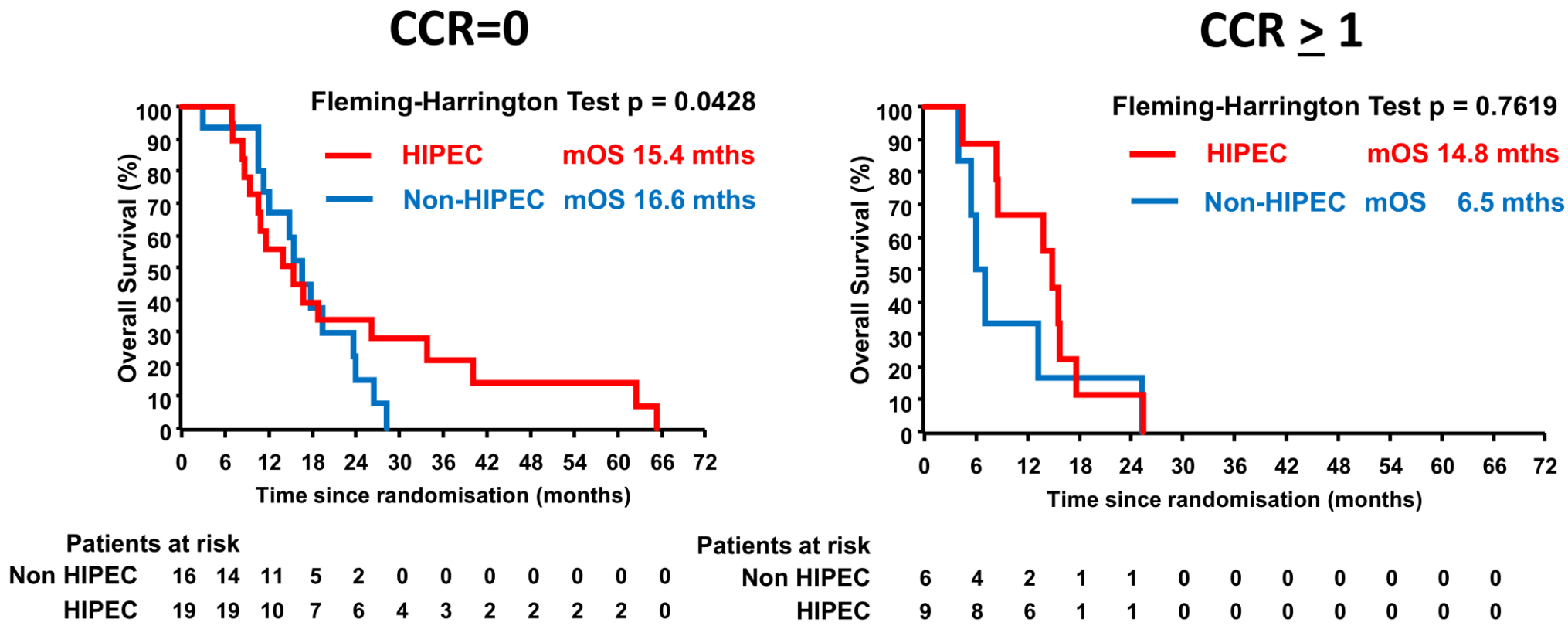
PPS



Patients at risk												
Non HIPEC	39	13	9	3	2	0	0	0	0	0	0	0
HIPEC	36	19	10	6	5	4	3	2	2	2	2	0

Rau B, et al. ESMO 2021. Abstract 1376O

Phase III GASTRIPEC I Trial –OS Analysis by CCR Subgroups



- 5-yr survival ~10% in HIPEC vs. 0% in CRS alone arm, NNT = 10

Rau B, et al. ESMO 2021. Abstract 1376O

Is HIPEC therapy in its current form ready for prime time in gastric cancer? - NO

- Is more chemotherapy always better? – No, taxane triplets confer no survival advantage and more toxicity over doublet chemo regimens
- What is cytoreductive surgery adding to stage IV disease? – Unclear benefit, primary tumor removal alone may even be detrimental despite patient selection
- What is the latest randomized data for HIPEC? – Underpowered but not positive in intent to treat analysis, maybe beneficial for very select patients but selection factors unclear and high percentage of patients will not derive benefit