Gastric cancer

Perioperative Therapy 2020

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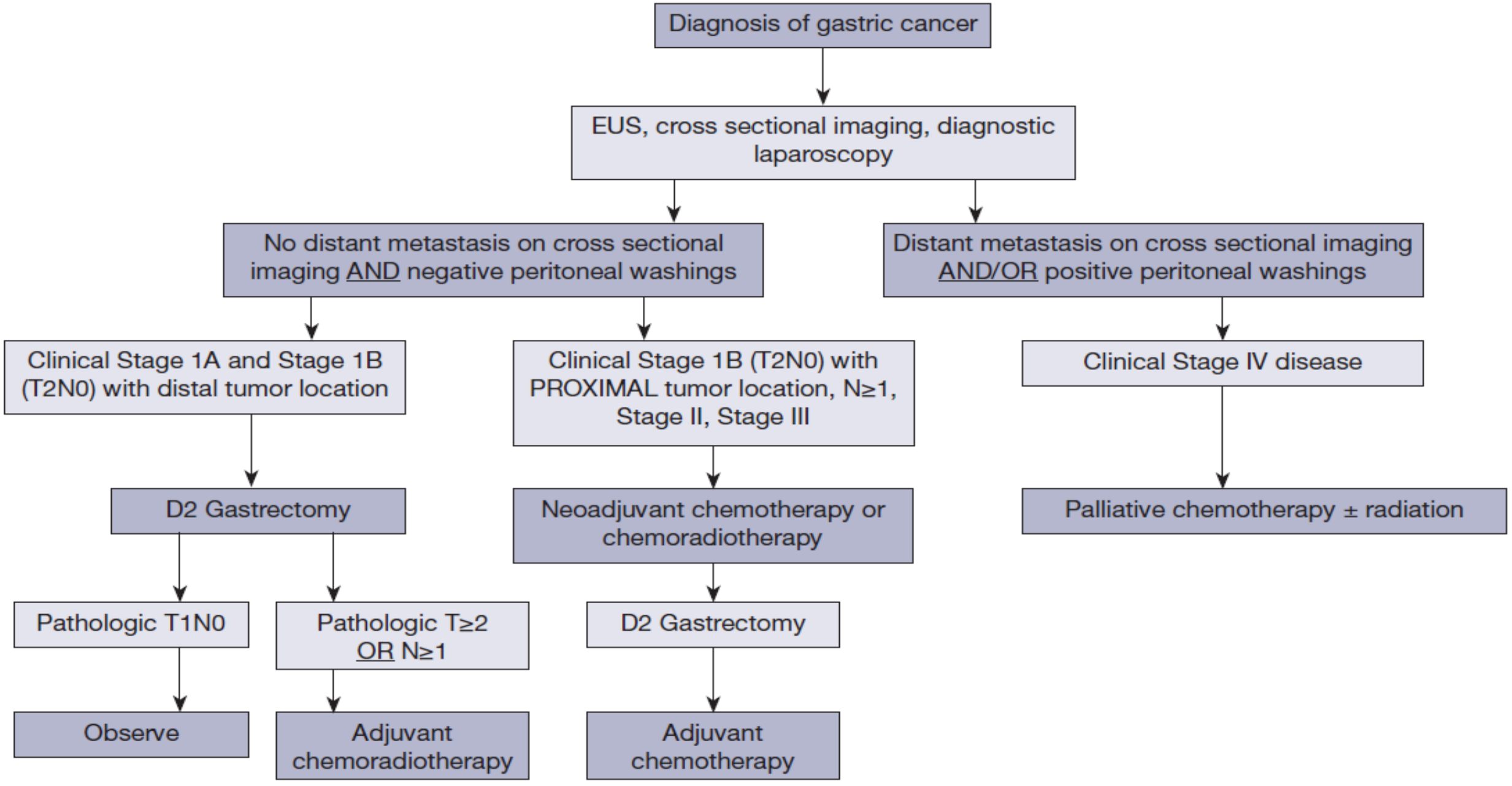
Time line of important clinical trials : 2001- 2020

: ADJUVANT AND NEO-ADJUVANT CHEMORADIATION

: ADJUVANT AND NEO-ADJUVANT CHEMOTHERAPY ALONE


Diagnosis of gastric cancer
EUS, cross sectional imaging, diagnostic laparoscopy
No distant metastasis on cross sectional imaging AND negative peritoneal washings
Distant metastasis on cross sectional imaging AND/OR positive peritoneal washings
Clinical Stage 1A and Stage 1B (T2N0) with distal tumor location
Clinical Stage 1B (T2N0) with PROXIMAL tumor location, N≥1, Stage II, Stage III
Clinical Stage IV disease
D2 Gastrectomy
Neoadjuvant chemotherapy or chemoradiotherapy
Palliative chemotherapy ± radiation
Pathologic T1N0
Pathologic T≥2 OR N≥1
D2 Gastrectomy
Observe
Adjuvant chemoradiotherapy
Adjuvant chemotherapy

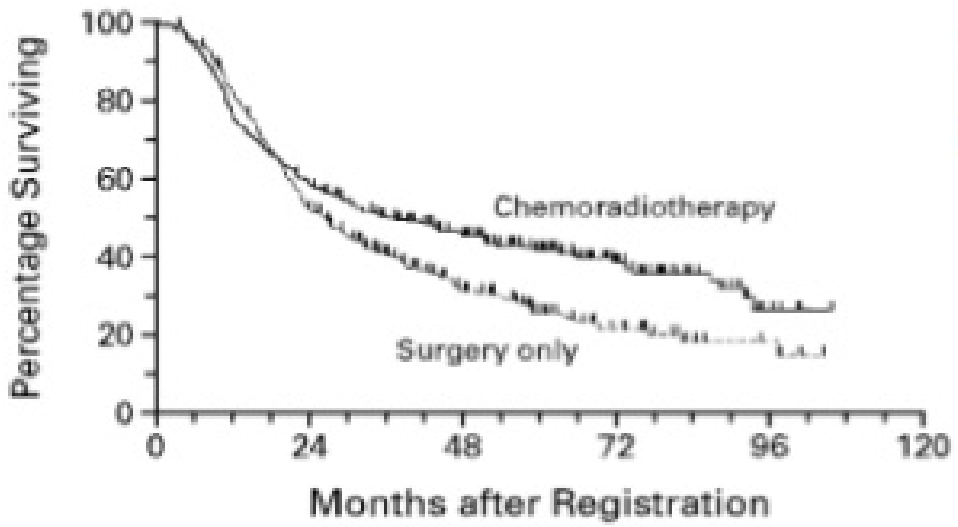
2001

Post-operative Chemoradiation: SWOG 9008/Intergroup 0116 Trial

Resected stage Ib-IV (M0) gastric or OGJ adenocarcinoma n=556 (<D1 resection 54% D1 = 36%, D2 = 10%)

Randomised

- Observation n=275
- 5-FU/LV Chemoradiation (4500Gy) n=281



Macdonald et al., NEJM 2001

Median OS: 27 v 36m

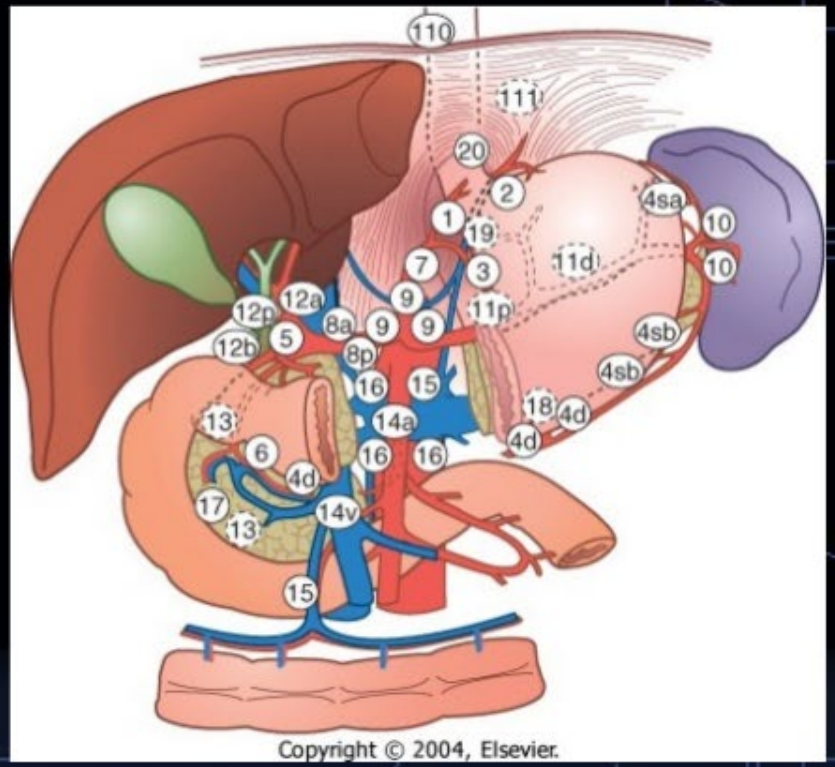
HR for death 1.35; p=0.006

Highly selected population (All had R0 resection + recovered from surgery) yet only 64% completed Rx

Significant Rx related toxicity:
- 1% toxic death
- 73% grade 3/4 AEs

Lymphadenectomy

- 70 % of specimens have nodal metastasis
- D0 - No lymphadenectomy
- D1 - LN included in the greater and lesser omentum
- D2 - LN along the splenic and hepatic arteries, omental bursa and front leaf of the transverse mesocolon. Splenectomy in proximal cancers
- D3 - Removal of para-aortic and retroperitoneal LN



2006 Neoadjuvant chemoradiation

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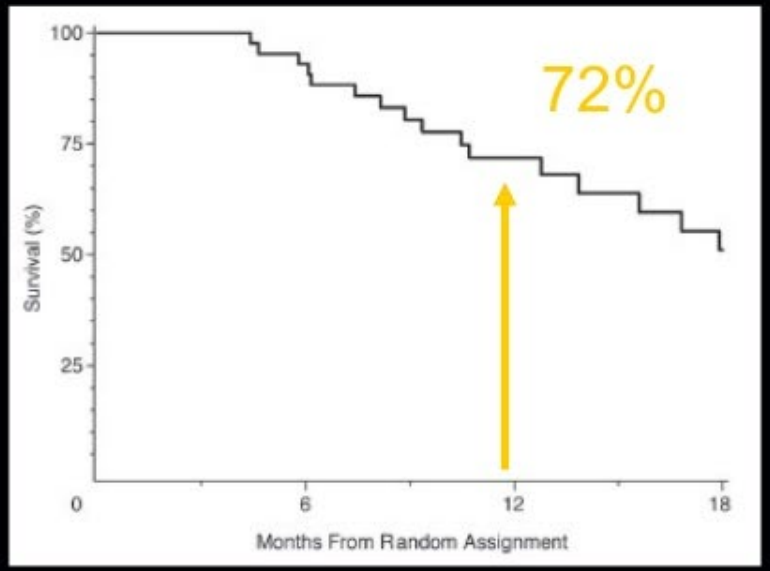
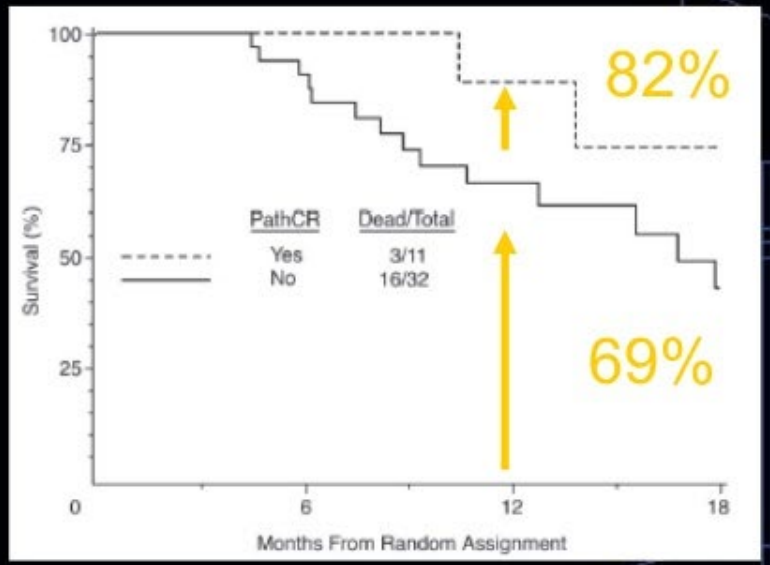
Phase II Trial of Preoperative Chemoradiation in Patients With Localized Gastric Adenocarcinoma (RTOG 9904): Quality of Combined Modality Therapy and Pathologic Response

- Phase II clinical trial J Ajani JCO 2006
- Primary aim: Achievement of a 20 % pathologic complete response in a multinstitutional setting
- Rigorous staging: EUS, laparoscopy, peritoneal lavage
- 20 institutions 43 patients
- 5FU + Cisplatin >>> 4500 cGY + 5fu >>> Surgery
- 50 % had a D2 Lymphadenectomy
- Median follow up 21.6 months
- Path Cr 26 %
- R0 resection 77 %
- Grade 4 toxicity 21%

Cleveland Clinic

Phase II Trial of Preoperative Chemoradiation in Patients With Localized Gastric Adenocarcinoma (RTOG 9904): Quality of Combined Modality Therapy and Pathologic Response





Median survival 23.2 months
Overall survival 72% at one year

Patients who had a pathologic complete response had an Improved survival

Phase II Trial of Preoperative Chemoradiation in Patients With Localized Gastric Adenocarcinoma (RTOG 9904): Quality of Combined Modality Therapy and Pathologic Response

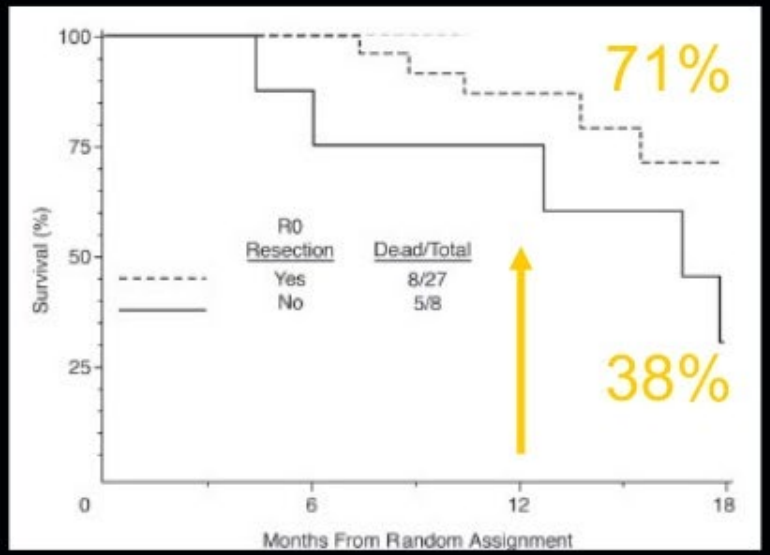


Table 4. Sites of First Failure (n = 43)

Site	No. of Patients	%
Tumor bed (with or without regional nodes)	8	19
Metastases	13	30
Nodes and regional	1	2
Death only (due to study cancer)	1	2
Death only (not due to study cancer)	2	5
No failure	18	42

Patients who underwent an R0 resection had an improved survival

Cleveland Clinic

Phase II Trial of Preoperative Chemoradiation in Patients With Localized Gastric Adenocarcinoma (RTOG 9904): Quality of Combined Modality Therapy and Pathologic Response

- Conclusion
  - A preoperative chemoradiotherapy strategy proved to be succesful in a cooperative group setting with acheivement of a pathological complete response rate of over 20 %
- Critiques
  - Small number of patients
  - Phase II trial
  - No comparison arm
- Based on this results, a preoperative chemoradiation strategy is to be compared with adjuvant chemoradiation in a phase III clinical trial

2006

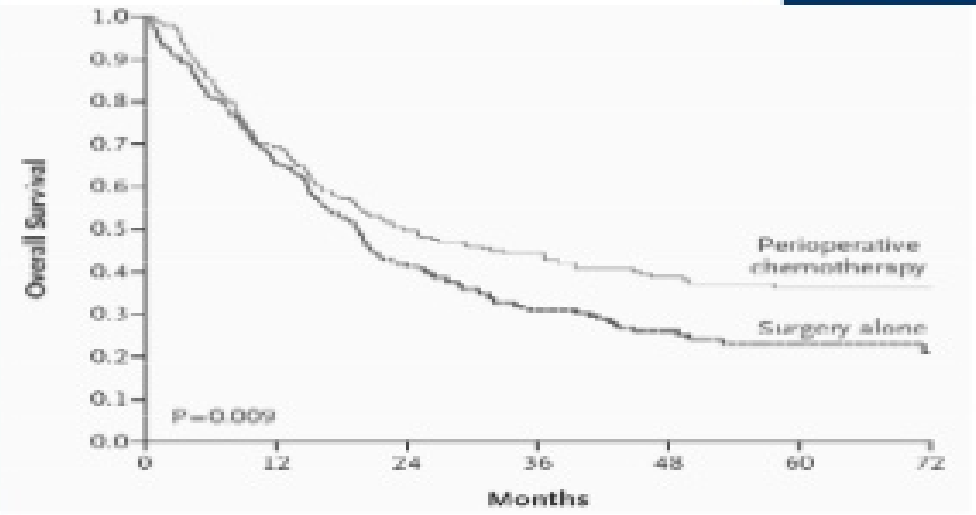
Peri-operative Chemotherapy: The MRC MAGIC Trial

Resectable adenocarcinoma of the stomach, OGJ or lower oesophagus n=503

→ Randomised

→ Pre-operative ECX x3 → Surgical resection within 3-6/52 → Post-operative ECX x3 within 6-12/52

→ Surgical resection within 6/52



Median OS: 24 v 20 months
5 yr OS: 36% v 23%
13% OS benefit for ECF

HR for death 0.75, p=0.009

Pre-op chemo well tolerated (5% did not complete pre-op Rx due to toxicity)
No increase in post-op complications

Cunningham et al., NEJM 2006

2013

31 May – 4 Jun 2013 | Chicago, USA

ASCO Annual Meeting

Cleveland Clinic

3 Jul – 6 Jul 2013 | Barcelona, Spain

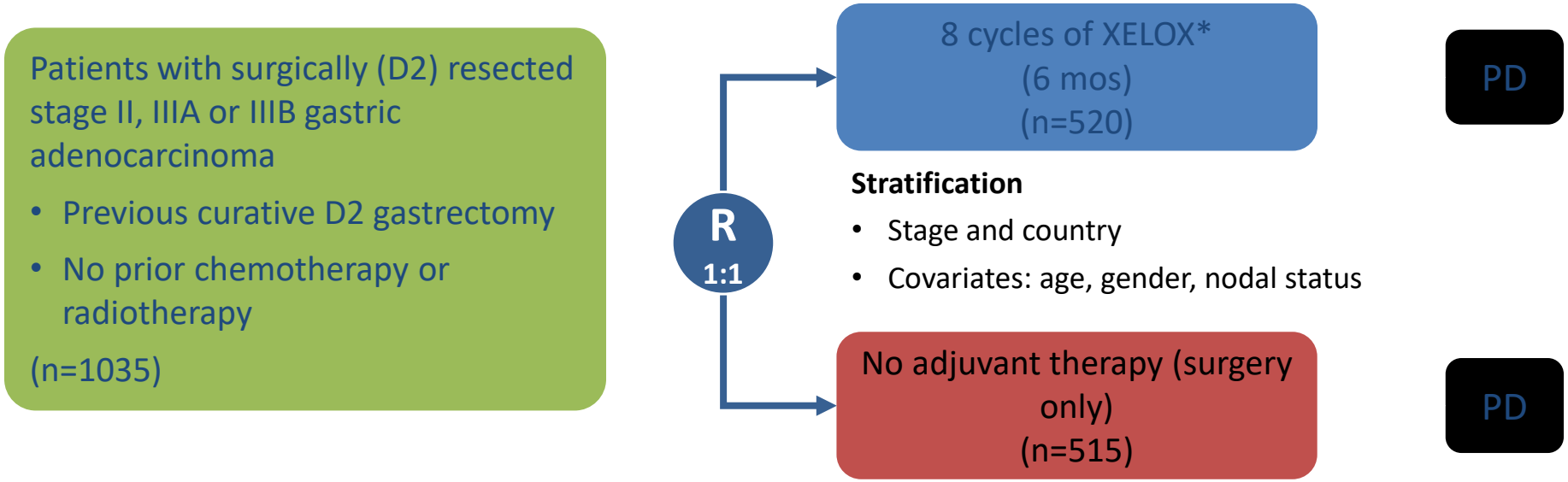
WCGIC

27 Sep – 1 Oct 2013 | Amsterdam, Netherlands

ESMO-ECCO

O-0007: Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: final results from the CLASSIC trial – *Noh SH et al*

- Study objective
  - To prospectively examine adjuvant capecitabine+oxaliplatin vs. surgery alone in patients with gastric cancer included in the CLASSIC trial



Primary endpoint

- 3-year OS (previously reported)

Secondary endpoints

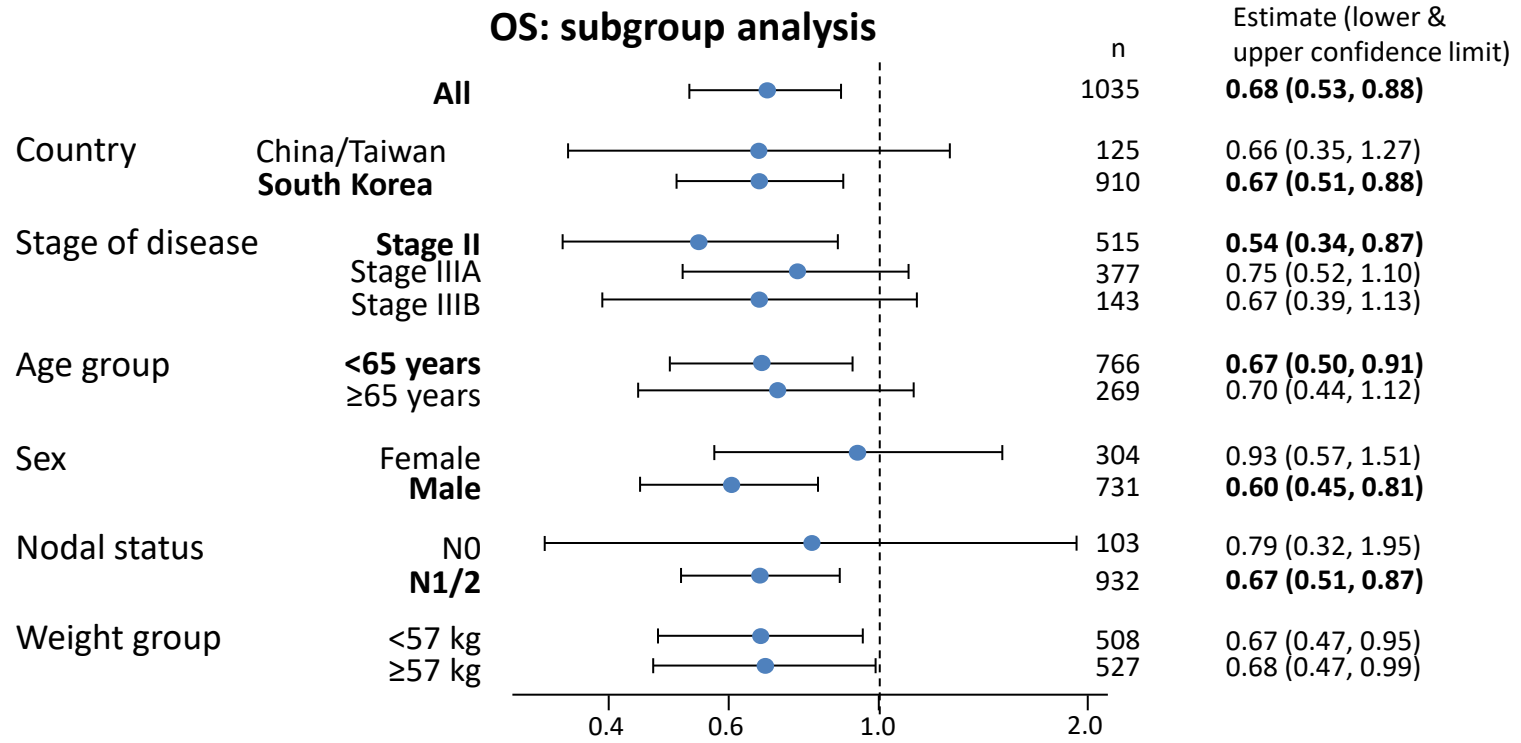
- 5-year OS, 5-year DFS, safety

*Capecitabine 1000 mg/m^2 bid d1–14 q3w plus oxaliplatin 130 mg/m^2 d1 q3w

Noh et al. Ann Oncol 2013; 24(4): iv11–iv24, O-0007

O-0007: Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: final results from the CLASSIC trial – *Noh SH et al*

- Key results
  - The 5-year OS rate for XELOX was significantly higher vs. surgery alone (78 vs. 69%, p=0.0029)
    - There was a 34% reduction in risk of death with XELOX vs. surgery alone (stratified HR 0.66, 95% CI: 0.51, 0.85; p=0.0015)



Noh et al. Ann Oncol 2013; 24(4): iv11–iv24, O-0007

O-0007: Adjuvant capecitabine and oxaliplatin (XELOX) for gastric cancer after D2 gastrectomy: final results from the CLASSIC trial – *Noh SH et al*

- Key results (continued)
  - The 5-year relapse free rate was significantly higher with XELOX vs. surgery alone (68 vs. 53%; p<0.0001)
    - There was a 42% reduction in risk of relapse with XELOX vs. surgery alone (stratified HR 0.58, 95% CI: 0.47, 0.72; p<0.0001)
- **Conclusions**
  - **Adjuvant XELOX provided a DFS benefit that translated to an OS benefit**
    - **The 34% (HR 0.66) reduction in risk of death at 5 years was greater than that previously reported at 3 years (28%, HR 0.72)**
  - **Postoperative adjuvant therapy with XELOX was an effective and well-tolerated option for patients with operable stage II / III gastric cancer following D2 gastrectomy**
  - **Adjuvant XELOX should be considered as a standard treatment for patients with operable gastric cancer**

Noh et al. Ann Oncol 2013; 24(4): iv11–iv24, O-0007

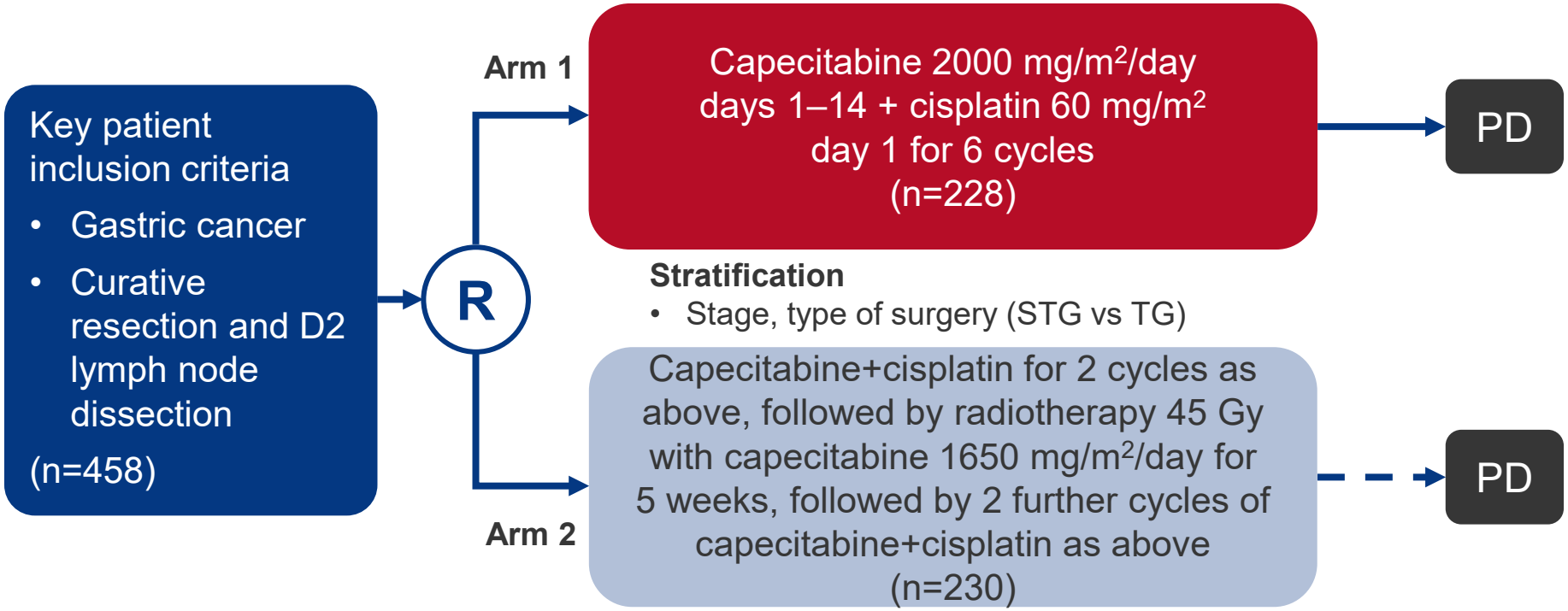
2014


16 – 18 Jan 2014 | San Francisco, USA
Gastrointestinal Cancers Symposium
Cleveland Clinic


31 May – 3 Jun 2014 | Chicago, USA
ASCO Annual Meeting

4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

- **Study objective**
  - To determine whether the addition of RT to capecitabine/cisplatin CT can improve survival in patients with D2 dissected gastric cancer



Primary endpoint

- 3-year DFS

Secondary endpoints

- OS, toxicity profile, exploratory biomarkers

Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)

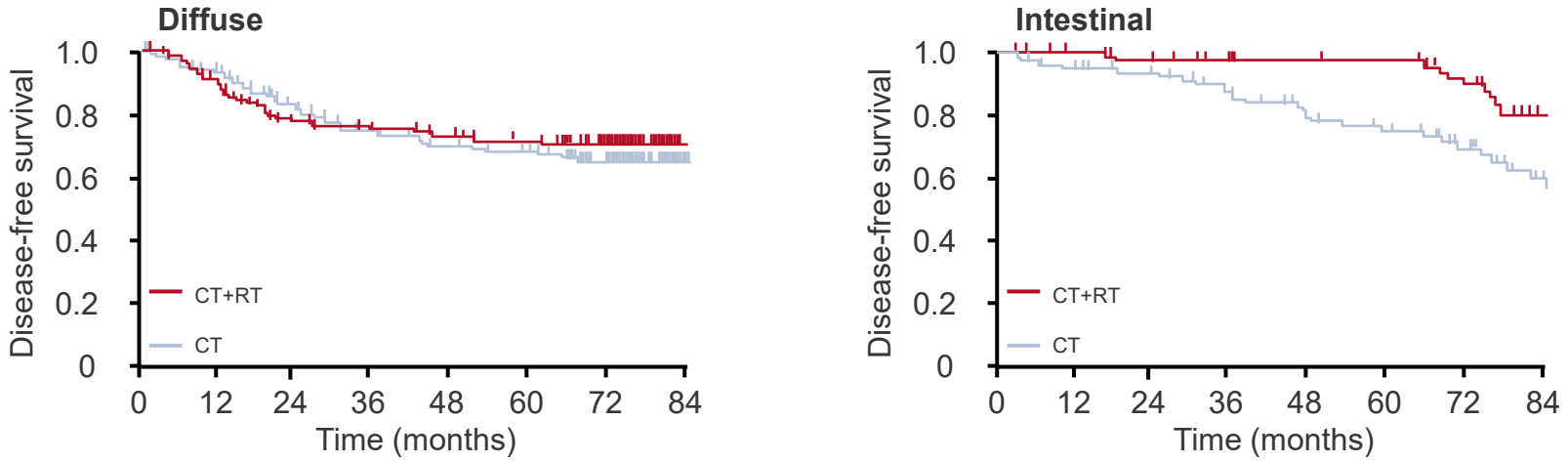
4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

- **Key results**

Survival (CT+RT vs CT alone)	HR (95% CI)	p value*
DFS	0.74 (0.52, 1.05)	0.9222
OS	1.13 (95% CI: 0.78, 1.65)	0.5272

  - 3-year DFS for CT+RT vs CT alone:
    - In lymph node-positive disease (n=396) was 76% vs 72% (p=0.04)
    - In intestinal type gastric cancer (n=163) was 94% vs 83% (p=0.001; Figure)

DFS by Lauren classification



Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)

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4008: Phase III trial to compare capecitabine/cisplatin (XP) versus XP plus concurrent capecitabine-radiotherapy in gastric cancer (GC): The final report on the ARTIST trial – Lee J et al

- **Key results**

Grade 3–4 AEs, n (%)	CT (N=226)		CT+RT (N=227)	
	Grade 3	Grade 4	Grade 3	Grade 4
Nausea	28 (12)	0	28 (12)	0
Vomiting	8 (4)	0	7 (3)	0
Diarrhoea	4 (2)	1 (0)	2 (1)	0
Stomatitis	3 (1)	0	4 (2)	0
Constipation	2 (1)	0	2 (1)	0
Hand-foot syndrome	5 (2)		7 (3)	
Anaemia	3 (1)	1 (0)	1 (0)	0
Neutropenia	79 (35)	13 (6)	99 (44)	11 (5)
Thrombocytopenia	0	0	2 (1)	0

- **Conclusions**
  - **Overall, this trial was negative with no significant difference in DFS with the addition of RT to CT compared with CT alone**
  - **Subgroup analyses showed a potential benefit of RT in patients with intestinal type and lymph node-positive gastric cancer**

Lee et al. J Clin Oncol 2014; 32 (suppl 5; abstr 4008)

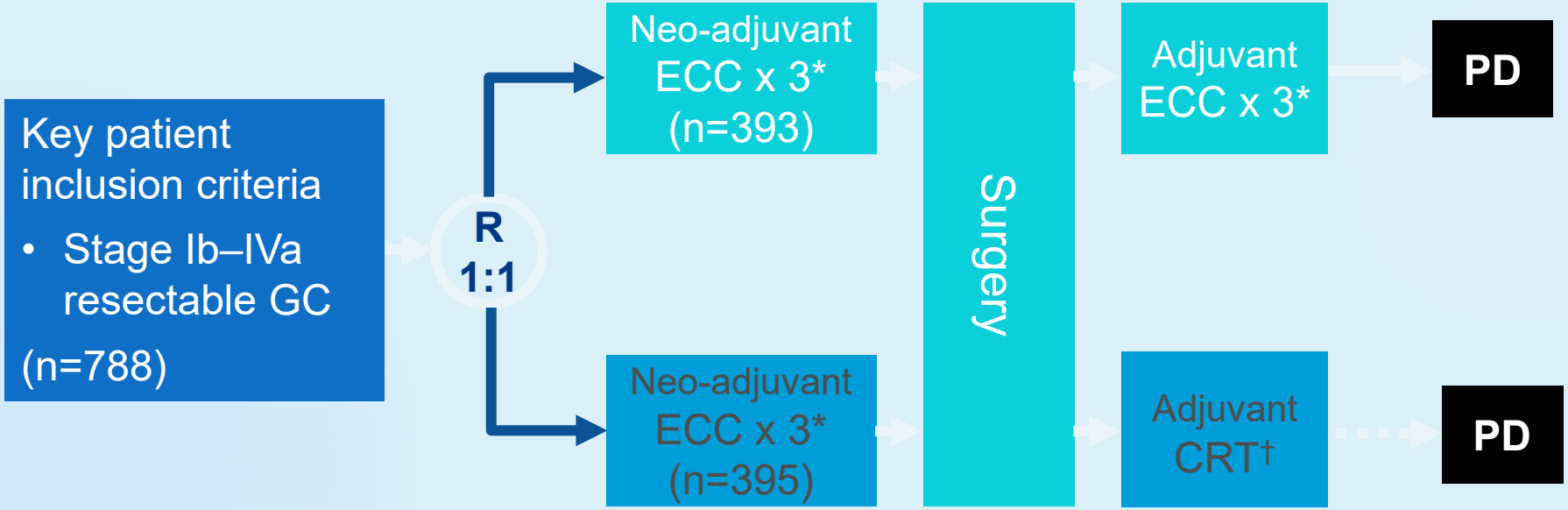
2016

Cleveland Clinic

4000: A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study – Verheij M, et al

Study objective

- **To investigate the efficacy and safety of CRT vs CT following neo-adjuvant CT and surgery in patients with resectable GC**



PRIMARY ENDPOINT(S)

- OS

SECONDARY ENDPOINTS

- DFS
- Safety, QoL

*3 cycles of ECC (epirubicin, cisplatin/oxaliplatin + capecitabine);
†45 Gy in 25 fractions + cisplatin q1w + capecitabine qd.

Note: Based on data from abstract only

Verheij et al. J Clin Oncol 2016; 34 (suppl): abstr 4000

4000: A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study – Verheij M, et al

Key results

- **Treatment completed: 46% with CT vs 55% with CRT**
- **After a median follow-up of 50 months, 405 patients had died**

	CT	CRT
5-year OS, %	41.3	40.9
p-value	0.99	

Grade ≥3 AEs	CT	CRT
Haematological, %	44	34
p-value	0.01	
Gastrointestinal, %	37	42
p-value	0.14	

Conclusion

- **Only ~50% of patients completed the treatment**
- **No significant difference in OS was observed between postoperative CT vs CRT in patients with resectable GC**

Note: Based on data from abstract only

Verheij et al. J Clin Oncol 2016; 34 (suppl): abstr 4000

2017

Cleveland Clinic

4004: Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/ leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 – Al-Batran S-E, et al

Cleveland Clinic

Study objective

- To evaluate the efficacy of FLOT vs. ECF/ECX as a perioperative treatment for patients with resectable gastric or GEJ adenocarcinoma

Key patient inclusion criteria

- Gastric cancer or adenocarcinoma of the gastro-oesophageal junction type I–III
- Medically and technically operable
- cT2–4/cN-any/cMO or cT-any/ cN+/cMO

(n=716)

R

FLOT x4 – RESECTION – FLOT x4 (n=356)

Stratification

- ECOG PS (0 or 1 vs. 2)
- Location of primary (GEJ type I vs. type II/III vs. stomach)
- Age (<60 vs. 60–69 vs. 70 years)
- Nodal status (cN+ vs. cN-)

ECF/ECX x3 – RESECTION – ECF/ECX x3

PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, complete resection rate, surgical morbidity/mortality, safety

FLOT: docetaxel 50 mg/m^2 D1; 5FU 2600 mg/m^2 D1; leucovorin 200 mg/m^2 D1; oxaliplatin 85 mg/m^2 D1q2w

ECF/ECX: epirubicin 50 mg/m^2 D1; cisplatin 60 mg/m^2 D1; 5FU 200 mg/m^2 (or capecitabine 1250 mg/m2 PO divided into 2 doses D1–D21) q3w

Al-Batran S-E, et al. J Clin Oncol 2017;35(Suppl):Abstr 4004

4004: Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/ leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 – Al-Batran S-E, et al

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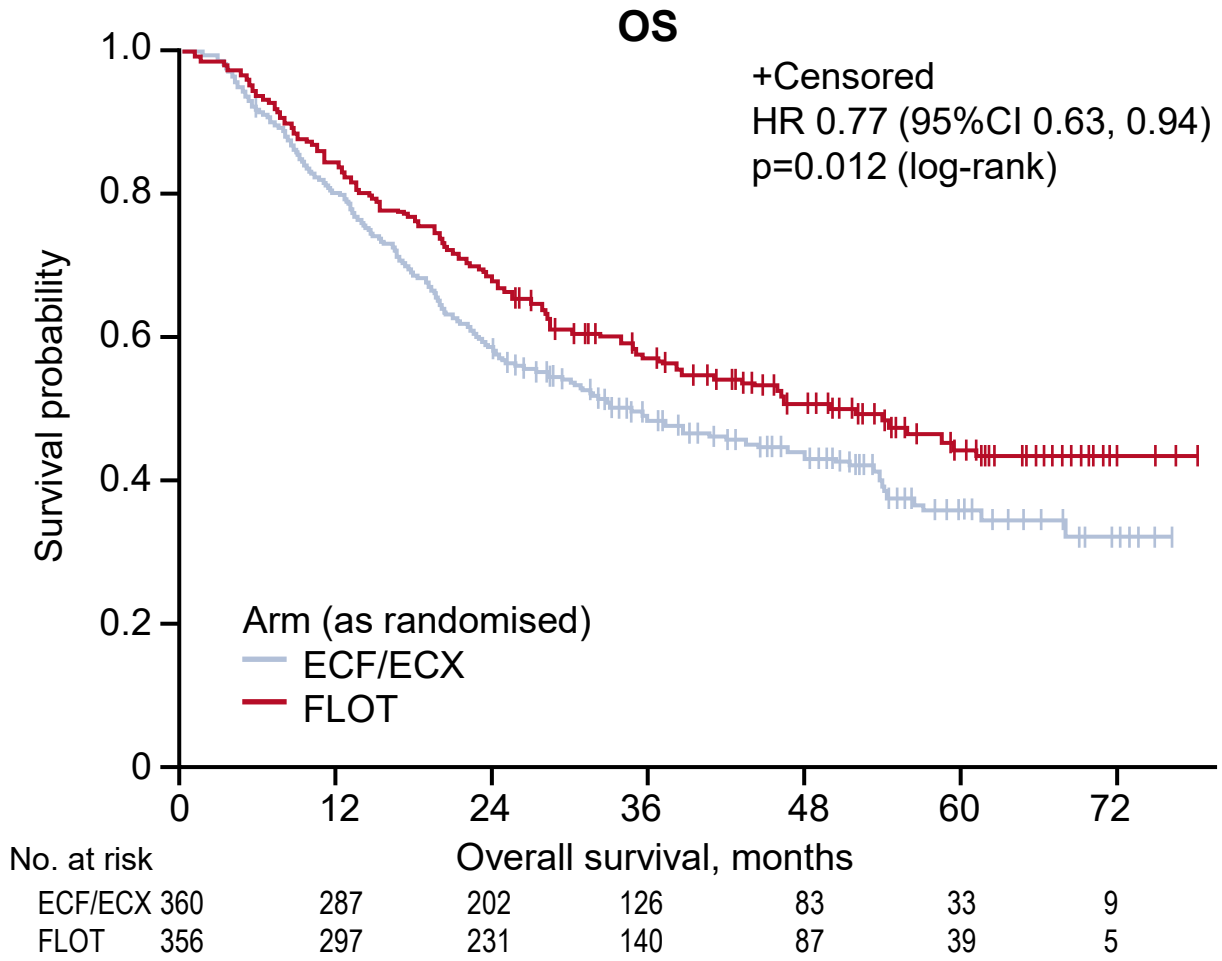
Key results

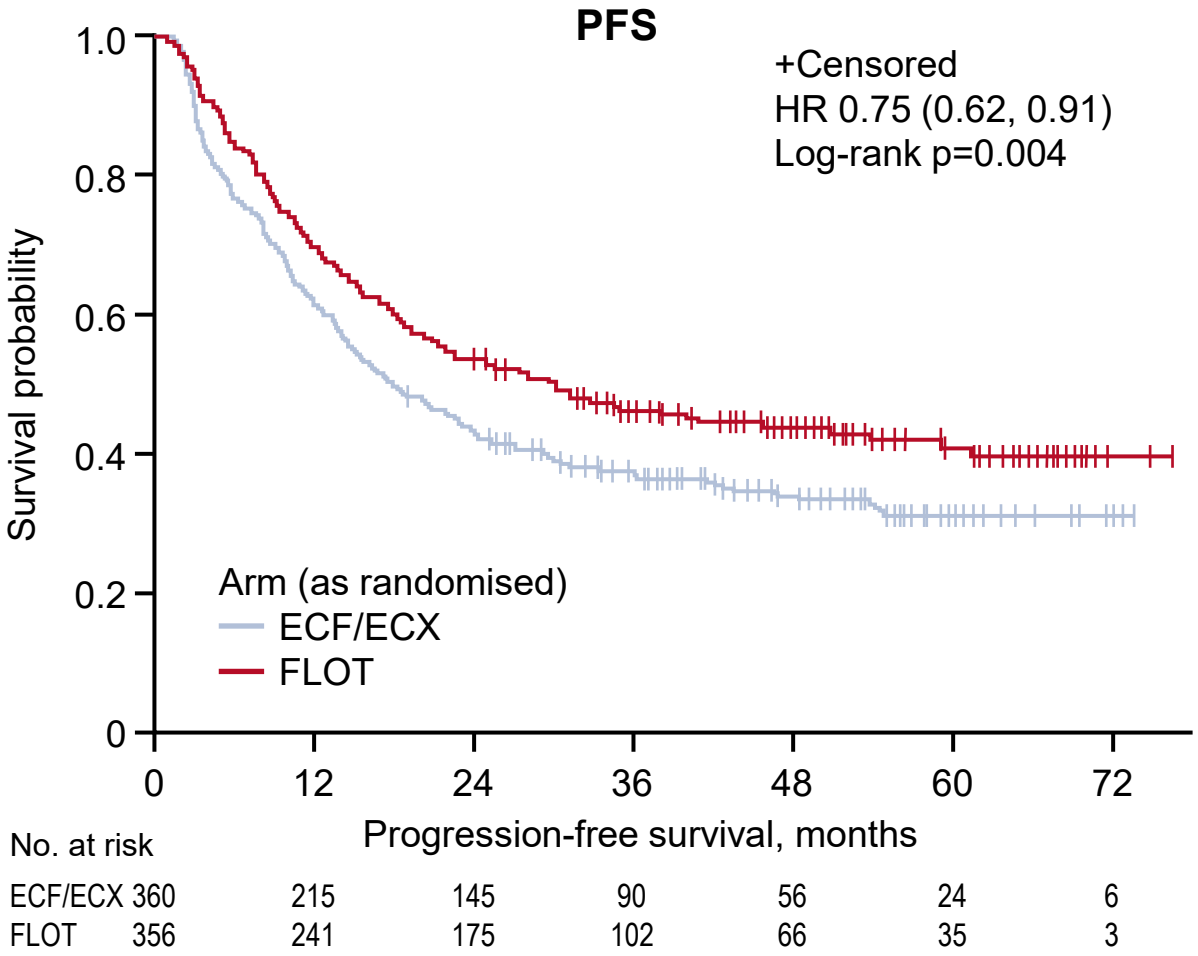


	ECF/ECX	FLOT
mOS, months (95%CI)	35 (27, 46)	50 (38, NA)
Projected OS rate, %		
2-year	59	68
3-year	48	57
5-year	36	45

Al-Batran S-E, et al. J Clin Oncol 2017;35(Suppl):Abstr 4004

4004: Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/ leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 – Al-Batran S-E, et al

Key results (cont.)



	ECF/ECX	FLOT
mPFS, months (95%CI)	18 (15, 22)	30 (21, 44)
Projected PFS rate, %		
2-year	43	53
3-year	37	46
5-year	31	41

Al-Batran S-E, et al. J Clin Oncol 2017;35(Suppl):Abstr 4004

4004: Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/ leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 – Al-Batran S-E, et al

Cleveland Clinic

Key results (cont.)

	ECF/ECX (n=354)	FLOT (n=354)	p-value
Grade 3/4 AEs, n (%)			
Diarrhoea	13 (4)	34 (10)	0.002
Vomiting	27 (8)	7 (2)	<0.001
Nausea	55 (16)	26 (7)	0.001
Fatigue	38 (11)	25 (7)	-
Infections	30 (9)	63 (18)	<0.001
Leukopenia	75 (21)	94 (27)	-
Neutropenia	139 (39)	181 (51)	0.002
Sensory	7 (2)	24 (7)	0.002
Thromboembolic	22 (6)	9 (3)	0.03
Anaemia	20 (6)	9 (3)	0.04
Any SAE, n (%)	220 (62)	215 (61)	-
Treatment-related SAE, n (%)	137 (34)	139 (35)	-
Toxic death, n (%)	2 (<1)	2 (<1)	-

Al-Batran S-E, et al. J Clin Oncol 2017;35(Suppl):Abstr 4004

4004: Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/ leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 – Al-Batran S-E, et al

Cleveland Clinic

Conclusions

- In comparison to ECF/ECX, FLOT demonstrated increased rates of curative surgery and prolonged PFS and OS
- The results with FLOT were consistent across subgroups and sensitivity analyses
- Surgical morbidity and mortality, re-surgeries or hospitalization times were not increased
- In perioperative treatment of patients with adenocarcinoma of the stomach or GEJ, FLOT offers a new standard of care

Al-Batran S-E, et al. J Clin Oncol 2017;35(Suppl):Abstr 4004

2017

Cleveland Clinic

Fluorouracil Market Overview

5-FU (5-Fluorouracil)

Discovered in 1957, widely available as generic

IV only

Principal uses: colorectal, breast, gastric, pancreatic, head and neck, ovarian and basal cell cancer

Used in combination with leucovorin, which improves 5-FU antitumor activity

Annual use: 500,000 patients in North America, millions worldwide

Xeloda® (capecitabine)

Oral, prodrug of 5-FU

On the market since 1998, expected generic in the US by 2013/2014

Principal uses: colorectal, breast and gastric cancer

Not used with leucovorin

UFT® (tegafur-uracil)

Developed in Japan during the 1980s

Oral, combining uracil (competitive inhibitor of DPD) and tegafur (prodrug of 5-FU)

Approved in 50 countries, except the US

Principal uses: colorectal, breast, gastric, pancreatic, head and neck, liver, ovarian and basal cell cancer

Used in combination with leucovorin

Teysuno®
(tegafur-gimeracil-oteracil-potassium)

Oral combination of tegafur (prodrug of 5-FU) plus 2 enzyme inhibitors: gimeracil and oteracil

On the market since 1999 in Japan and since 2011 in Europe

Principal uses: gastric, colorectal, head and neck, non-small cell lung, breast, pancreatic cancer

Not used with leucovorin

626PD: A randomized phase III trial comparing 4 courses and 8 courses of S-1 adjuvant chemotherapy for p-stage II gastric cancer: JCOG1104 (OPAS-1) – Yoshikawa T, et al

Study objective

- To evaluate the efficacy of 6 vs. 12 months of S-1 adjuvant CT in patients with stage II gastric cancer

Key patient inclusion criteria

- Histologically proven adenocarcinoma of the stomach – stage II (excl. T1N2-3 and T3N0)
- R0 resection
- Surgery by laparotomy (or laparoscopic approach for stage I)
- ECOG PS 0–1

(n=528)

R

Arm A: 8 courses* (1 year)
S-1 80 mg/m^2 (n=262)

Stratification

- Stage (IIA/IIB)
- Age (<70/≥70 years)
- Surgery (open bursectomy/open non-bursectomy/laparoscopic surgery)
- Institution

Arm B: 4 courses* (6 months)
S-1 80 mg/m^2 (n=266)

PRIMARY ENDPOINT

- RFS

- OS, TTF, safety, proportion of the treatment continuation at each time point

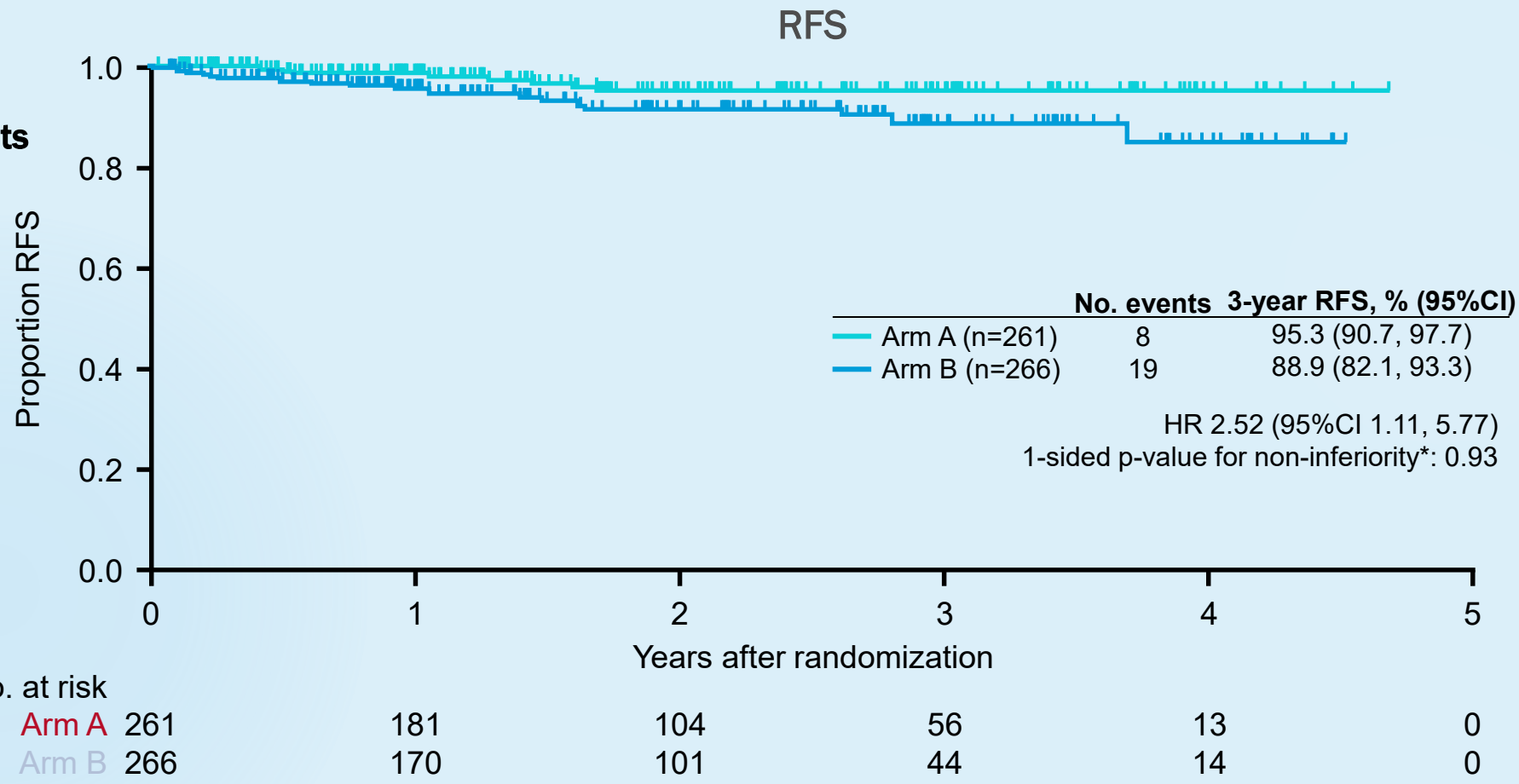
*1 course = 4-weeks on, 2-weeks off

Yoshikawa T, et al. Ann Oncol 2017;28(Suppl 5):Abstr 626PD

626PD: A randomized phase III trial comparing 4 courses and 8 courses of S-1 adjuvant chemotherapy for p-stage II gastric cancer: JCOG1104 (OPAS-1) – Yoshikawa T, et al

Cleveland Clinic

Key results

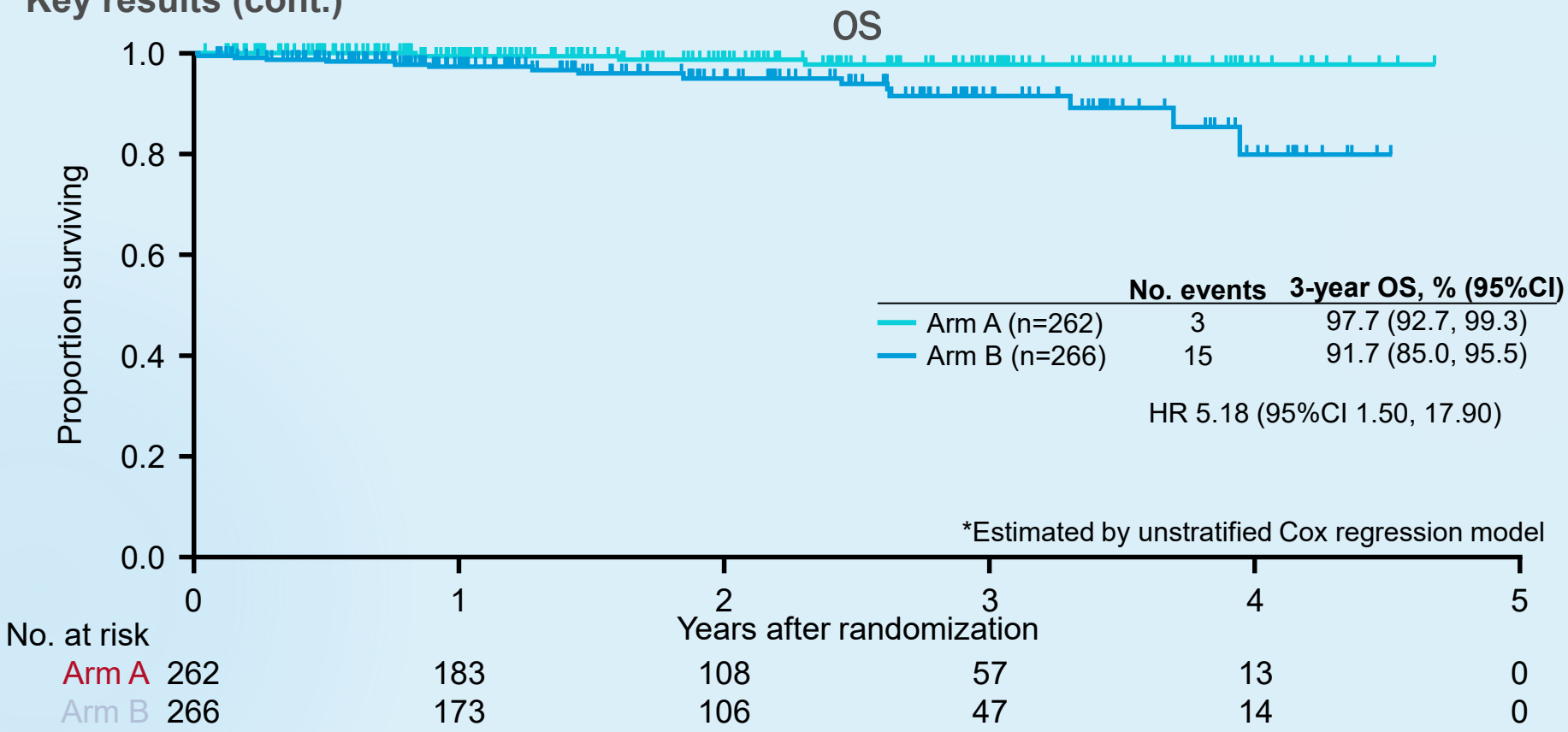


*Estimated by stratified Cox regression model according to p-stage

Yoshikawa T, et al. Ann Oncol 2017;28(Suppl 5):Abstr 626PD

626PD: A randomized phase III trial comparing 4 courses and 8 courses of S-1 adjuvant chemotherapy for p-stage II gastric cancer: JCOG1104 (OPAS-1) – Yoshikawa T, et al

Key results (cont.)



Conclusion

- In patients with pathological stage II gastric cancer, it is possible to continue postoperative S-1 adjuvant CT for up to 1 year

Yoshikawa T, et al. Ann Oncol 2017;28(Suppl 5):Abstr 626PD

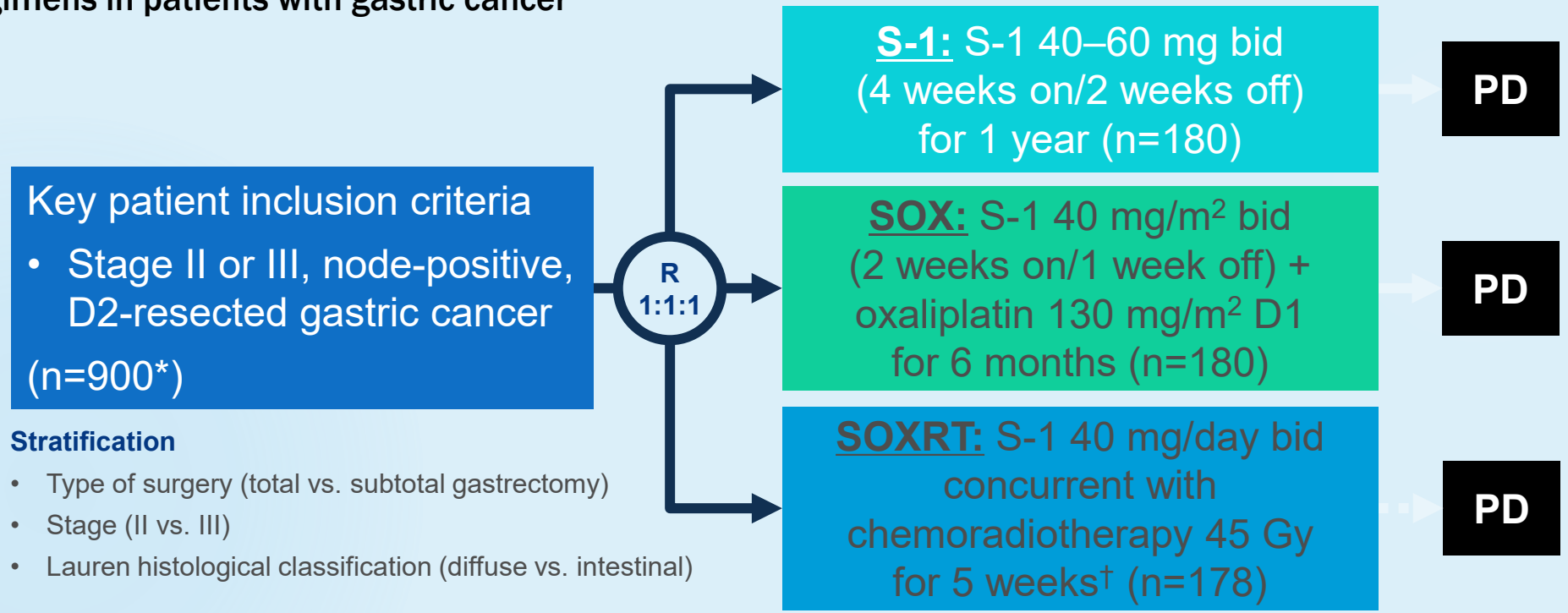
2019

Cleveland Clinic

4001: ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC) – Park SH, et al

Study objective

- To investigate the efficacy and safety of different chemotherapy and chemoradiotherapy regimens in patients with gastric cancer



Stratification

- Type of surgery (total vs. subtotal gastrectomy)
- Stage (II vs. III)
- Lauren histological classification (diffuse vs. intestinal)

PRIMARY ENDPOINT

- DFS

SECONDARY ENDPOINTS

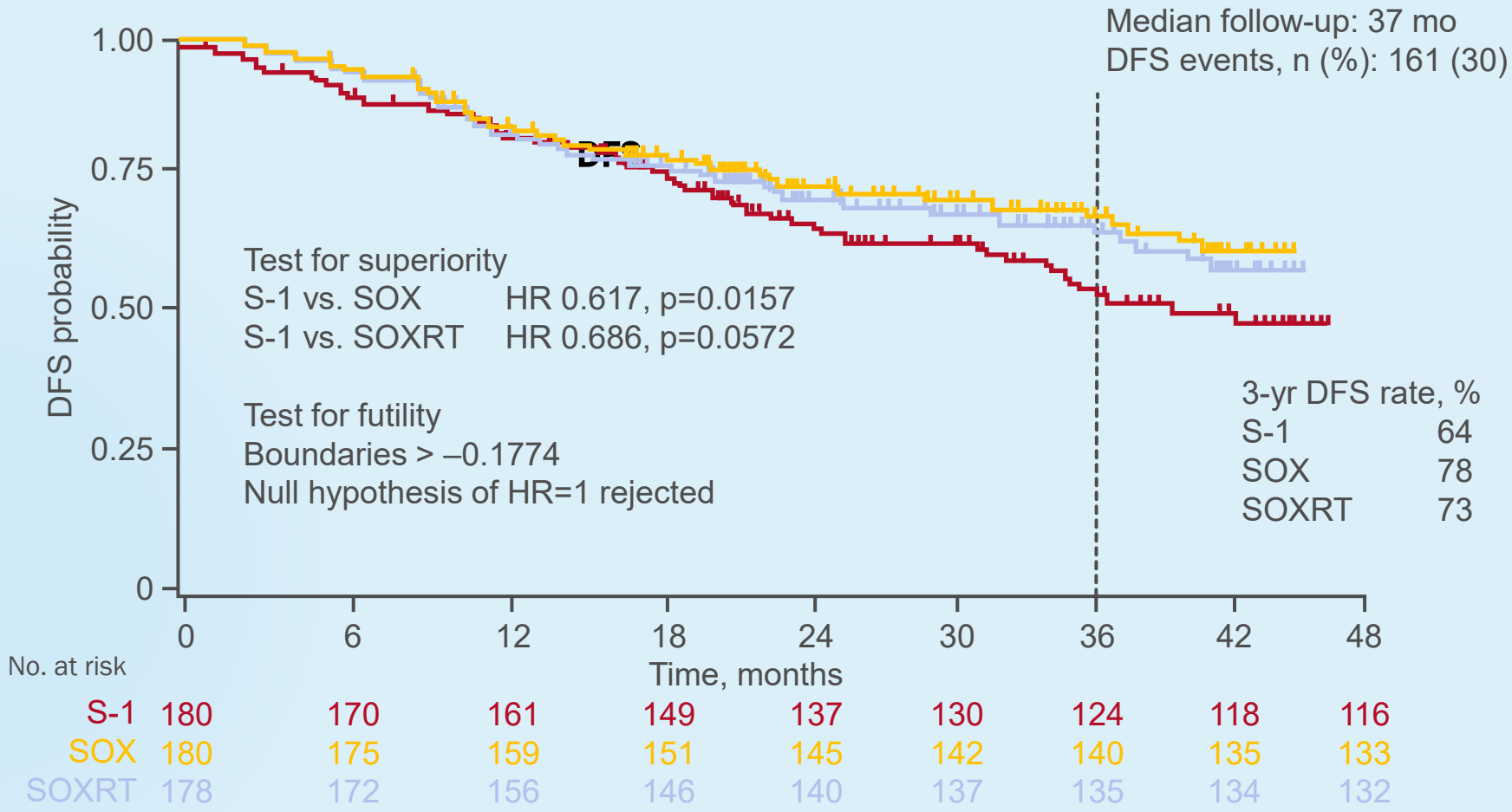
- OS, recurrence, safety

*Interim analysis of 538 patients; †2 cycles prior to adjuvant chemoradiotherapy and 4 cycles after of S-1 40 mg/m² bid (2 weeks on/1 week off) + oxaliplatin 130 mg/m² D1

Park SH, et al. J Clin Oncol 2019;37(suppl):abstr 4001

4001: ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC) – Park SH, et al

Key results



Park SH, et al. J Clin Oncol 2019;37(suppl):abstr 4001

4001: ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC) – Park SH, et al

Key results (cont.)

Grade 3–4 AEs, n (%)	S-1 (n=180)	SOX (n=179)	SOXRT (n=177)
Anaemia	7 (4)	14 (8)	12 (7)
Neutropenia	2 (1)	5 (3)	5 (3)
Nausea	2 (1)	2 (1)	0
Vomiting	1 (1)	4 (2)	0
Constipation	0	0	0
Diarrhoea	7 (4)	3 (2)	4 (2)
Anorexia	5 (3)	7 (4)	2 (1)
Fatigue	2 (2)	4 (2)	0
Skin	0	0	0
Neuropathy	0	21 (12)	11 (6)

Conclusions

- **In patients with stage II/III node-positive, D2-resected gastric cancer, adjuvant SOX and SOXRT demonstrated longer DFS than S-1 alone**
- **All three regimens were generally well tolerated**

Park SH, et al. J Clin Oncol 2019;37(suppl):abstr 4001

2019

Cleveland Clinic

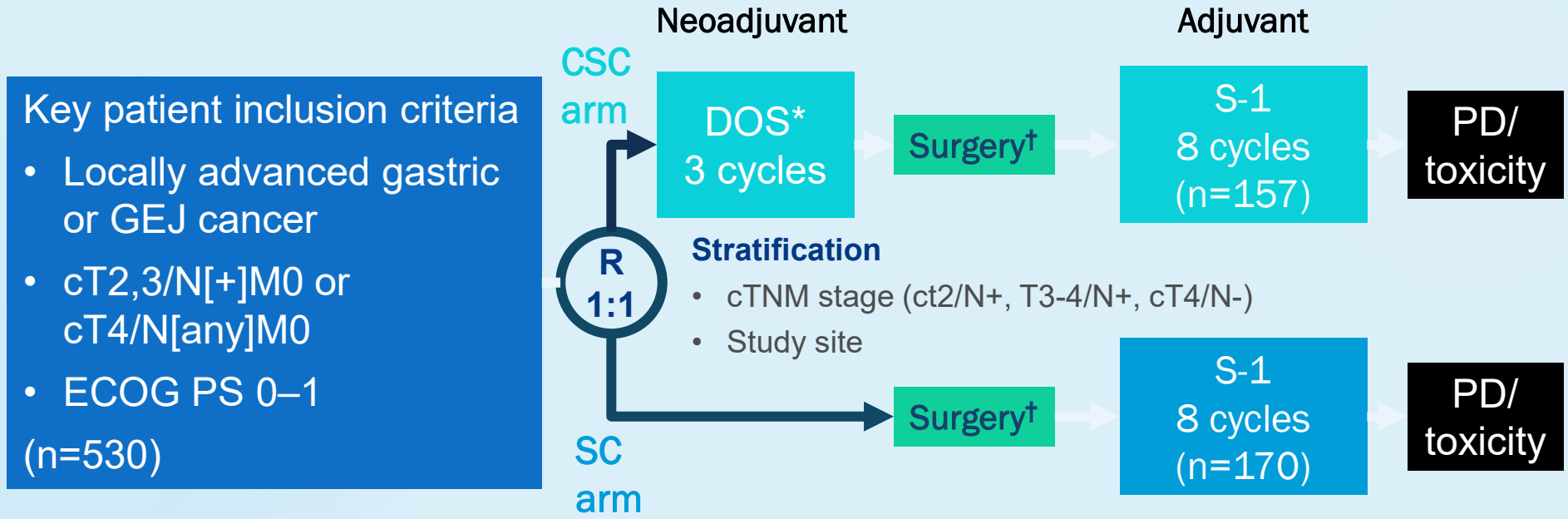
ESMO 2019 Congress

27 Sept – 01 Oct 2019 | Barcelona, Spain

LBA41: Phase III randomized study of neoadjuvant chemotherapy (CT) with docetaxel(D), oxaliplatin(O) and S-1(S) (DOS) followed by surgery and adjuvant S-1, vs surgery and adjuvant S-1, for resectable advanced gastric cancer (GC) (PRODIGY) – Kang Y-K, et al

Study objective

- To investigate the efficacy and safety of neoadjuvant chemotherapy with DOS followed by surgery and adjuvant S-1 compared with surgery + adjuvant S-1 in patients with advanced gastric cancer



PRIMARY ENDPOINT

- 3-year PFS (FAS)

SECONDARY ENDPOINTS

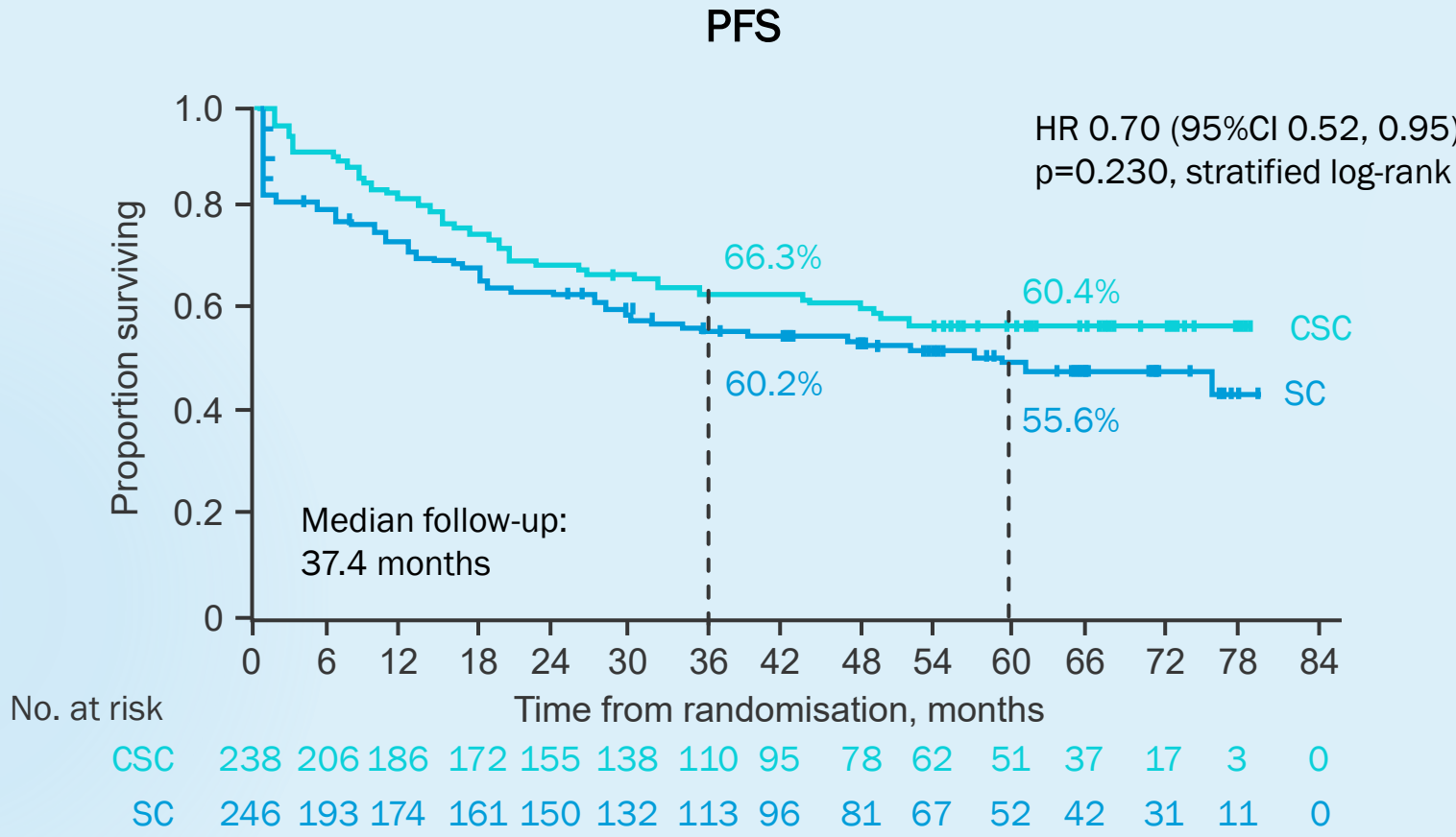
- R0 resection rate, postoperative pathological stage, OS, safety

*Docetaxel 50 mg/m^2 iv D1, oxaliplatin 100 mg/mg^2 iv D1, S-1 40 mg/m^2 po bid D1–14; †gastrectomy + D2 LN dissection

Kang Y-K, et al. Ann Oncol 2019;30(suppl):abstr LBA41

LBA41: Phase III randomized study of neoadjuvant chemotherapy (CT) with docetaxel(D), oxaliplatin(O) and S-1(S) (DOS) followed by surgery and adjuvant S-1, vs surgery and adjuvant S-1, for resectable advanced gastric cancer (GC) (PRODIGY) – Kang Y-K, et al

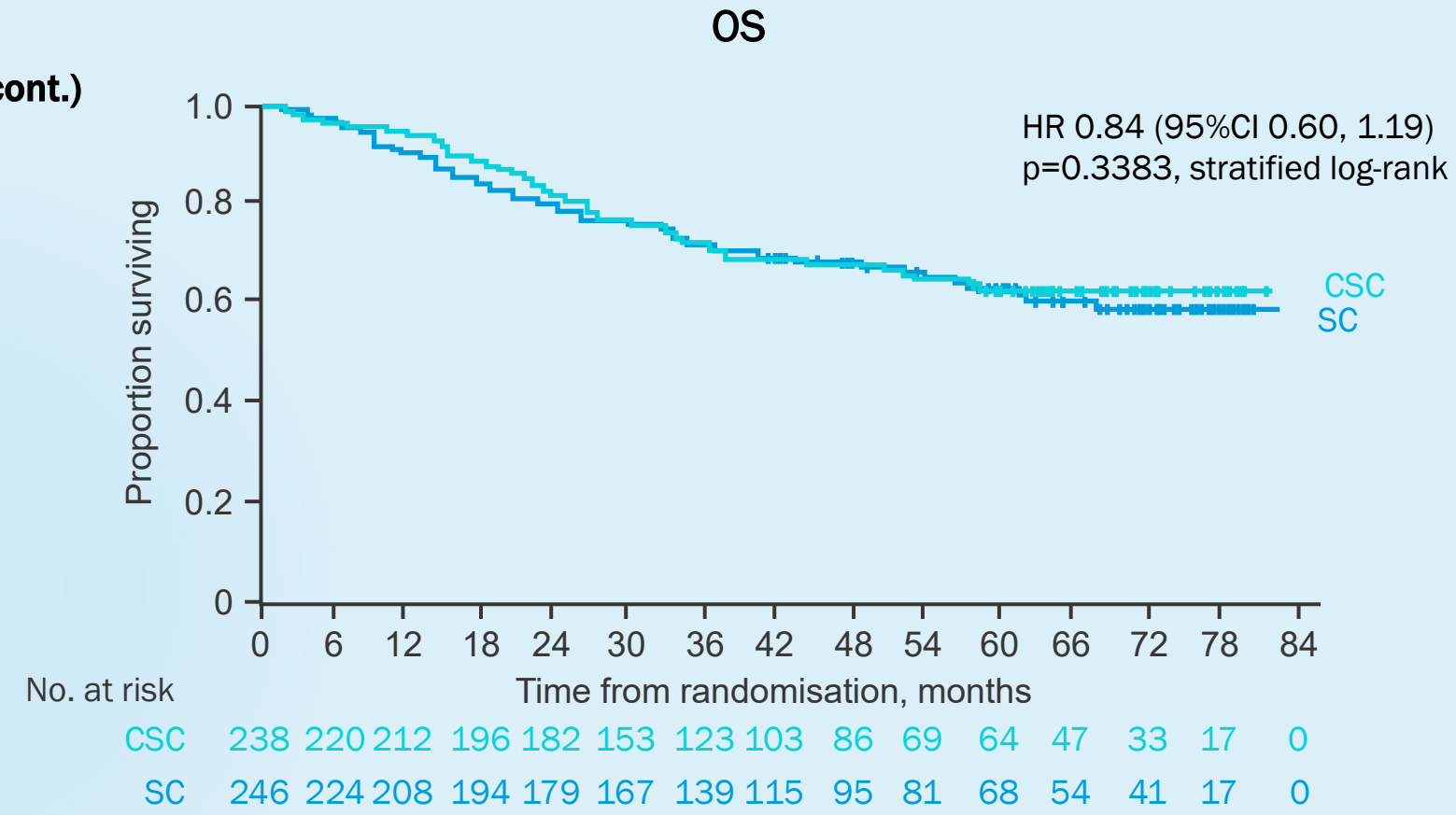
Key results



Kang Y-K, et al. Ann Oncol 2019;30(suppl):abstr LBA41

LBA41: Phase III randomized study of neoadjuvant chemotherapy (CT) with docetaxel(D), oxaliplatin(O) and S-1(S) (DOS) followed by surgery and adjuvant S-1, vs surgery and adjuvant S-1, for resectable advanced gastric cancer (GC) (PRODIGY) – Kang Y-K, et al

Key results (cont.)



Kang Y-K, et al. Ann Oncol 2019;30(suppl):abstr LBA41

LBA41: Phase III randomized study of neoadjuvant chemotherapy (CT) with docetaxel(D), oxaliplatin(O) and S-1(S) (DOS) followed by surgery and adjuvant S-1, vs surgery and adjuvant S-1, for resectable advanced gastric cancer (GC) (PRODIGY) – Kang Y-K, et al

Key results (cont.)

	CSC (n=238)	SC (n=246)
O&C or bypass only	3 (1.4)	18 (7.3)
R2 resection	0	7 (2.9)
R1 resection	5 (2.3)	10 (4.1)
R0 resection	**214 (96.4)**	**211 (85.8)**
Total gastrectomy	120 (56.1)*	120 (56.9)
Subtotal gastrectomy	94 (43.9)	91 (43.1)
D2 dissection	210 (98.1)	207 (98.1)
No. of LN dissected, mean (SD)	44.2 (19.5)	50.8 (18.6)

Grade ≥3 TEAEs occurring in ≥5%, n (%)	CSC (n=238)
Haematological	
Neutropenia	30 (12.6)
Febrile neutropenia	22 (9.2)
Gastrointestinal	
Diarrhoea	12 (5.0)
Treatment-related mortalities	2 (0.8)†

Conclusion

- **In patients with advanced gastric or GEJ cancer, the use of neoadjuvant chemotherapy followed by surgery and adjuvant S-1 demonstrated better R0 resection rates and tumour downstaging as well as improved PFS compared with surgery followed by adjuvant S-1 and was generally well-tolerated**

*p<0.0001; †1 febrile neutropenia associated and 1 unknown cause

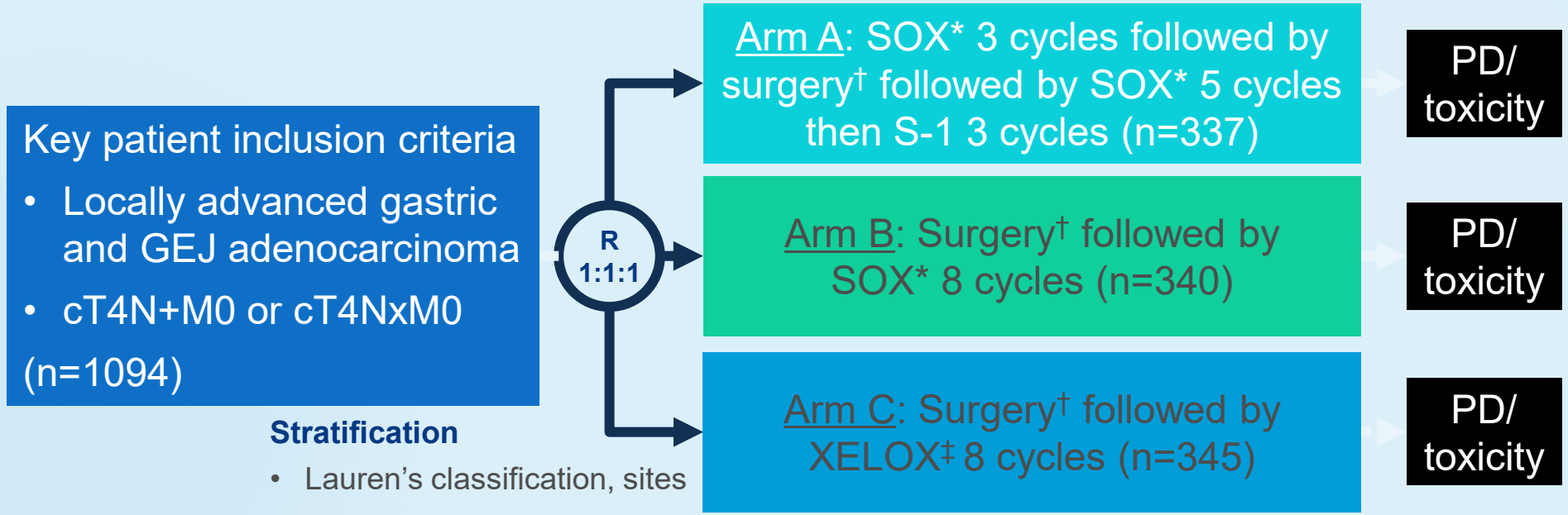
Kang Y-K, et al. Ann Oncol 2019;30(suppl):abstr LBA41

LBA42: Perioperative chemotherapy of oxaliplatin combined with S-1 (SOX) versus postoperative chemotherapy of SOX or oxaliplatin with capecitabine (XELOX) in locally advanced gastric adenocarcinoma with D2 gastrectomy: A randomized phase III trial (RESOLVE trial) – Ji J, et al

Cleveland Clinic

Study objective

- **To investigate the efficacy and safety of perioperative chemotherapy with SOX compared with postoperative chemotherapy with SOX or XELOX in patients with locally advanced gastric cancer**



PRIMARY ENDPOINT

- 3-year DFS

SECONDARY ENDPOINTS

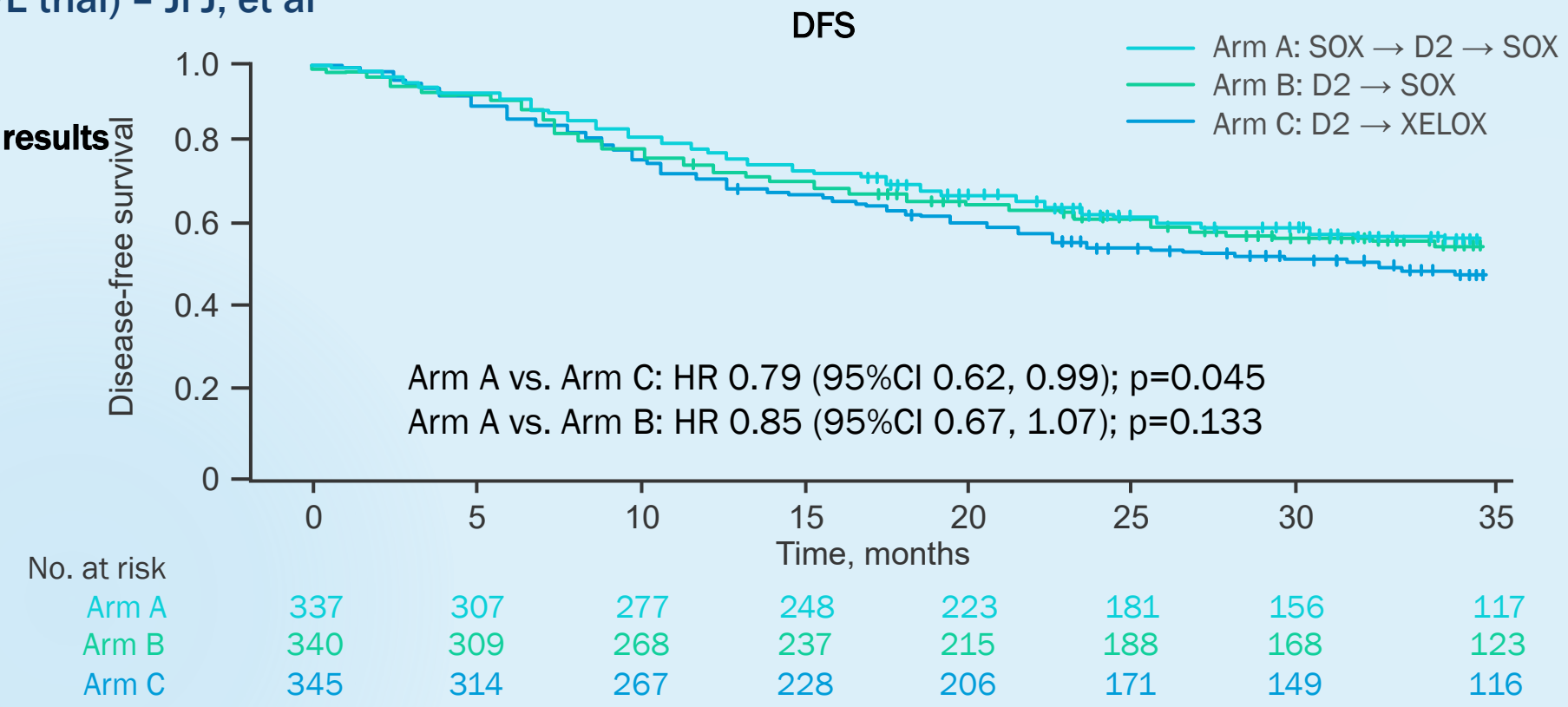
- 5-year OS, safety

***S-1 40–60 mg bid D1–14 + oxaliplatin 130 mg/mg^2 iv D1 q3w; †D2 gastrectomy;** ‡capecitabine 1000 mg/m^2 bid D1–14 + oxaliplatin 130 mg/m^2 iv D1 q3w

Ji J, et al. Ann Oncol 2019;30(suppl):abstr LBA42

LBA42: Perioperative chemotherapy of oxaliplatin combined with S-1 (SOX) versus postoperative chemotherapy of SOX or oxaliplatin with capecitabine (XELOX) in locally advanced gastric adenocarcinoma with D2 gastrectomy: A randomized phase III trial (RESOLVE trial) – Ji J, et al

Key results



	Arm A: SOX→ D2 → SOX	Arm B: D2 → SOX	Arm C: D2 → XELOX
3-year DFS, %	62.02	60.29	54.78

Ji J, et al. Ann Oncol 2019;30(suppl):abstr LBA42

LBA42: Perioperative chemotherapy of oxaliplatin combined with S-1 (SOX) versus postoperative chemotherapy of SOX or oxaliplatin with capecitabine (XELOX) in locally advanced gastric adenocarcinoma with D2 gastrectomy: A randomized phase III trial (RESOLVE trial) – Ji J, et al

Key results (cont.)

Chemotherapy-related AEs, n (%)	Arm A (n=337)	Arm B (n=340)	Arm C (n=345)	p-value
Neutropenia	118 (40.0)	85 (36.2)	88 (33.9)	0.322
Leukopenia	85 (28.8)	68 (28.9)	63 (25.2)	0.384
Thrombocytopenia	93 (31.5)	53 (25.6)	37 (14.2)	<0.001
Anaemia	59 (20.0)	39 (16.6)	37 (14.2)	0.198
Nausea	48 (16.3)	30 (12.8)	45 (17.3)	0.343
ALT/AST increase	58 (19.7)	28 (11.9)	36 (13.9)	0.036
Fatigue	30 (10.2)	24 (10.2)	20 (7.7)	0.527
Vomiting	30 (10.2)	16 (6.8)	25 (9.6)	0.377
Sensory neuropathy	23 (7.8)	16 (6.8)	21 (8.1)	0.862
Diarrhoea	16 (5.4)	17 (7.2)	11 (4.2)	0.37

Ji J, et al. Ann Oncol 2019;30(suppl):abstr LBA42

LBA42: Perioperative chemotherapy of oxaliplatin combined with S-1 (SOX) versus postoperative chemotherapy of SOX or oxaliplatin with capecitabine (XELOX) in locally advanced gastric adenocarcinoma with D2 gastrectomy: A randomized phase III trial (RESOLVE trial) – Ji J, et al

Conclusions

- **In patients with locally advanced gastric cancer, perioperative chemotherapy followed surgery and postoperative chemotherapy demonstrated significant improvement in DFS compared with postoperative XELOX while postoperative SOX was found to be non-inferior to postoperative XELOX**
- **Both perioperative and postoperative SOX showed no differences to postoperative XELOX with regards to surgical morbidity, mortality and safety**

Ji J, et al. Ann Oncol 2019;30(suppl):abstr LBA42

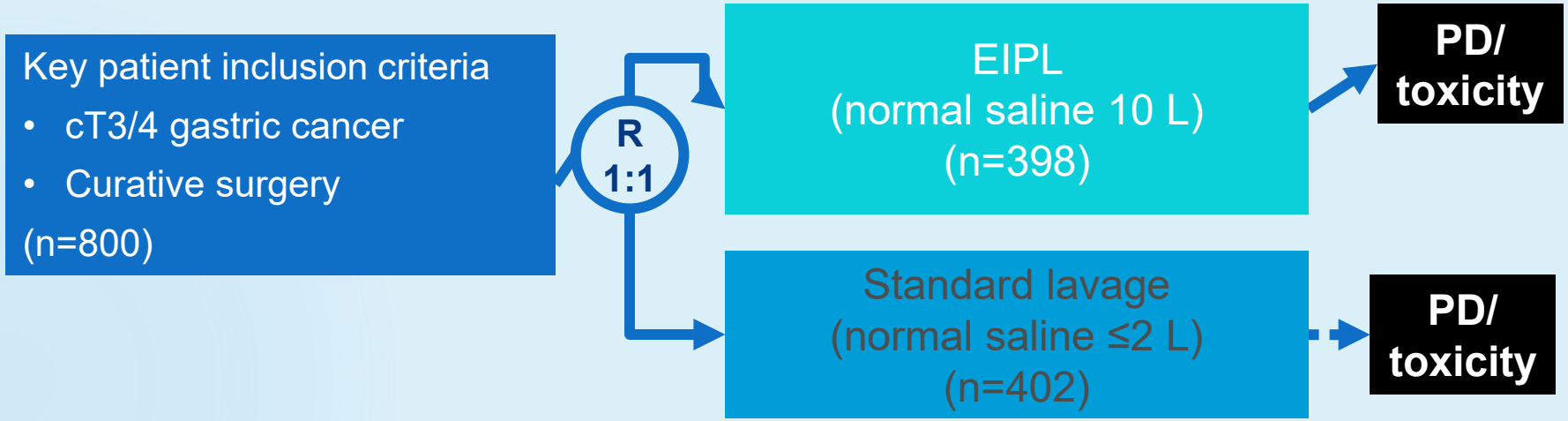
ASCO GI 2020

Cleveland Clinic

279: Extensive peritoneal lavage after curative gastrectomy for gastric cancer study (EXPEL): An international multicenter randomized controlled trial – So JB, et al

Study objective

- **To evaluate the efficacy and safety of surgery + extensive intraoperative peritoneal lavage (EIPL) in patients with gastric cancer**



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- DFS, peritoneal recurrence, safety

Trial terminated early after futility analysis

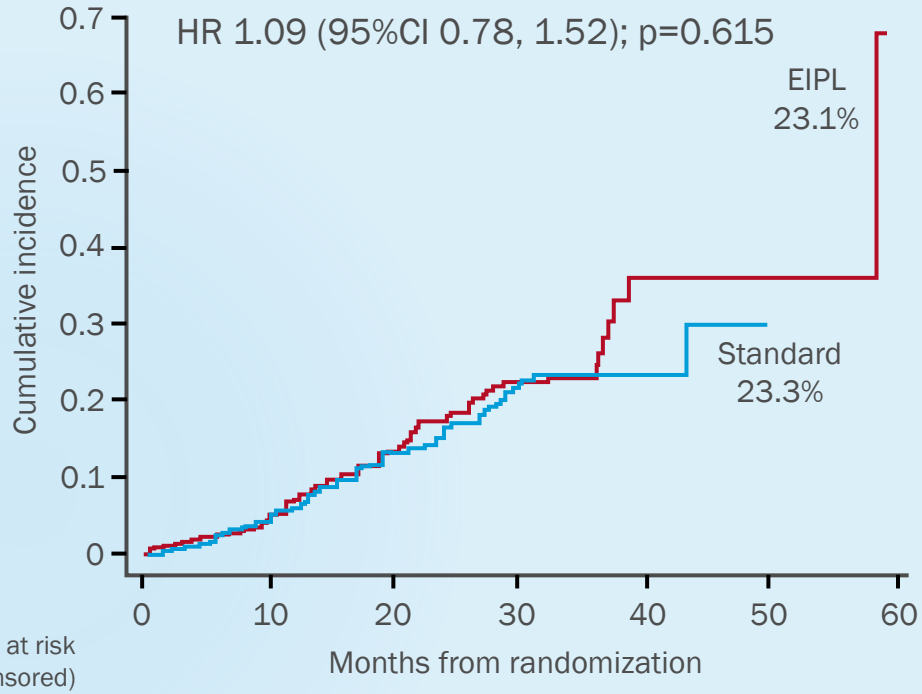
So JB, et al. J Clin Oncol 2020;38(suppl):abstr 279

279: Extensive peritoneal lavage after curative gastrectomy for gastric cancer study (EXPEL): An international multicenter randomized controlled trial – So JB, et al

Key results

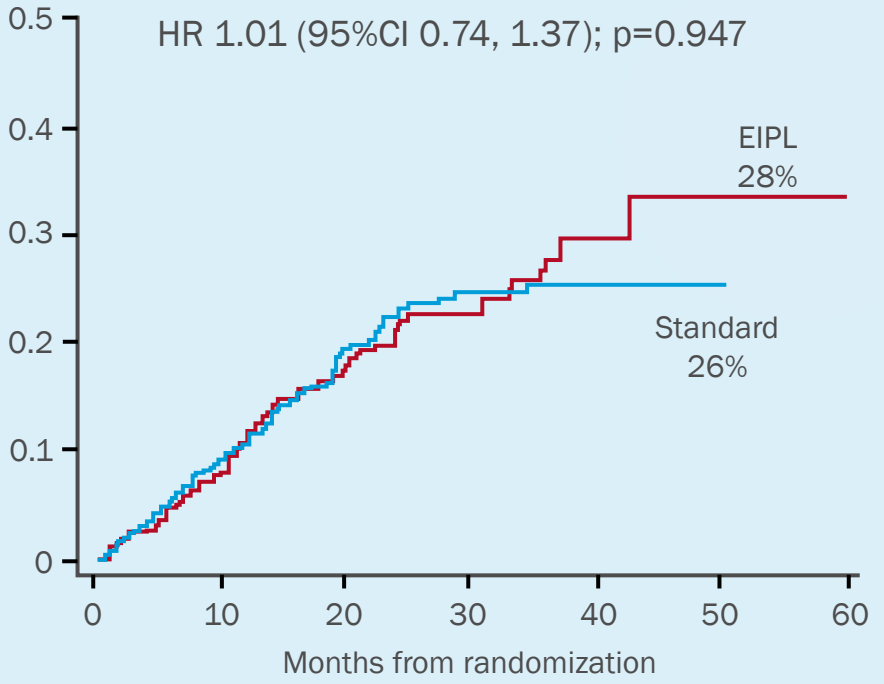
OS

Cumulative incidence of mortality



DFS

Cumulative incidence of recurrence



No. at risk (censored)													
EIPL	396 (0)	351 (16)	234 (30)	142 (20)	22 (7)	6 (0)	0 (1)	396 (0)	327 (32)	203 (31)	126 (10)	21 (7)	5 (1)	0 (0)
Standard	401 (0)	348 (17)	233 (28)	142 (19)	16 (2)	0 (1)	0 (0)	401 (0)	325 (37)	205 (32)	131 (11)	15 (2)	0 (0)	0 (0)

So JB, et al. J Clin Oncol 2020;38(suppl):abstr 279

279: Extensive peritoneal lavage after curative gastrectomy for gastric cancer study (EXPEL): An international multicenter randomized controlled trial – So JB, et al

Key results (cont.)

- **The 3-year cumulative incidence of peritoneal recurrence was 7.9% for EIPL and 6.6% for standard lavage (HR 1.33 [95%CI 0.73, 2.42]; p=0.347**

AEs, n	EIPL			Standard lavage		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Anastomotic stump leak	2	6	2	0	5	1
Bleeding	1	2	3	2	2	2
Intra-abdominal abscess	3	1	0	2	3	0
Superficial wound infection	5	1	1	1	0	0
Abnormal liver function	3	3	0	0	1	0
Bowel perforation	0	2	1	0	1	0
Pancreatic fistula	1	0	0	0	1	0
Myocardial infarction	0	1	1	0	0	0
Other	6	5	10	7	12	1

Conclusions

- **In patients with gastric cancer, EIPL failed to reduce the risk of peritoneal recurrence and did not improve survival after surgery**

So JB, et al. J Clin Oncol 2020;38(suppl):abstr 279

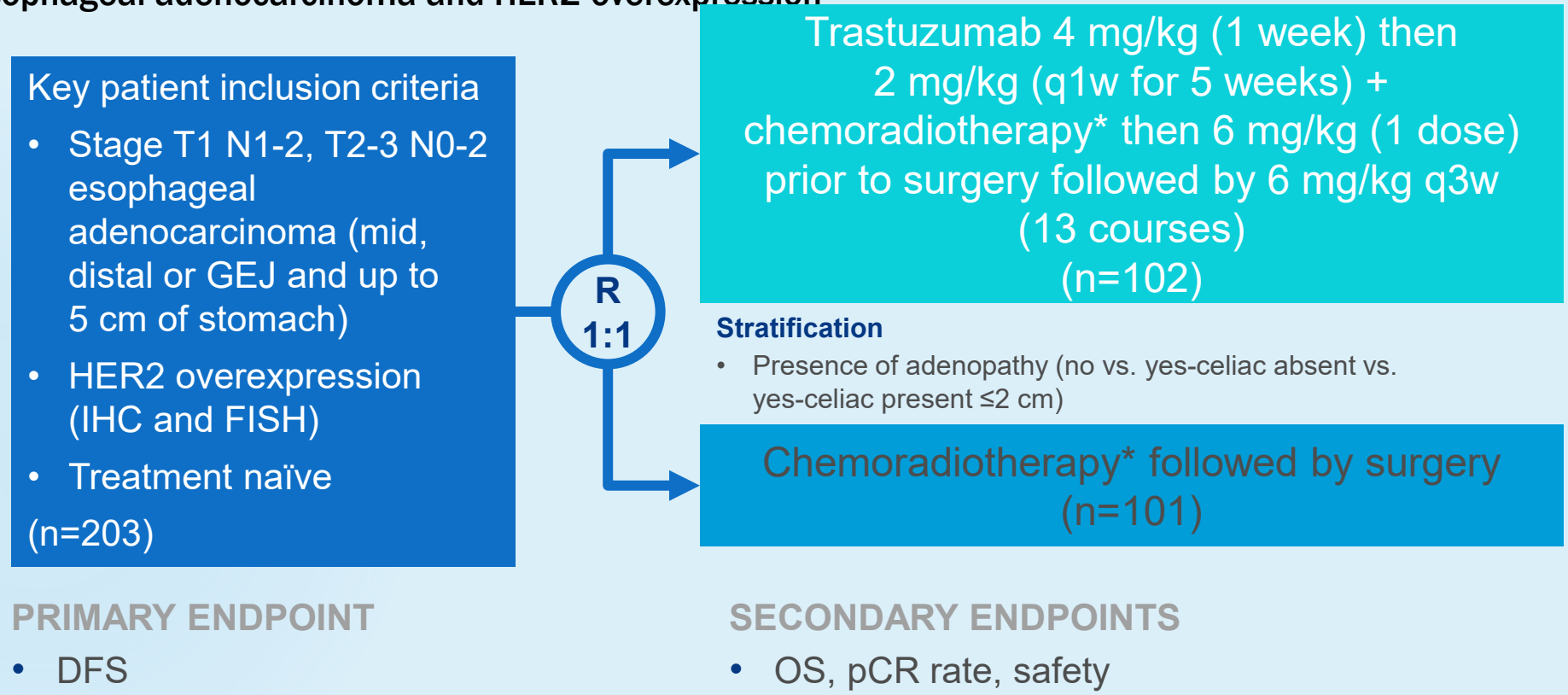
ASCO 2020

Cleveland Clinic

4500: Trastuzumab with trimodality treatment for esophageal adenocarcinoma with HER2 overexpression: NRG Oncology/RTOG 1010 – Safran H, et al

Study objective

- **To evaluate the efficacy and safety of trastuzumab + trimodality treatment for patients with esophageal adenocarcinoma and HER2 overexpression**



PRIMARY ENDPOINT

- DFS

SECONDARY ENDPOINTS

- OS, pCR rate, safety

*Paclitaxel 50 mg/m^2 + carboplatin AUC2 (6 weeks) with radiation (50.4 Gy in 28 fractions)

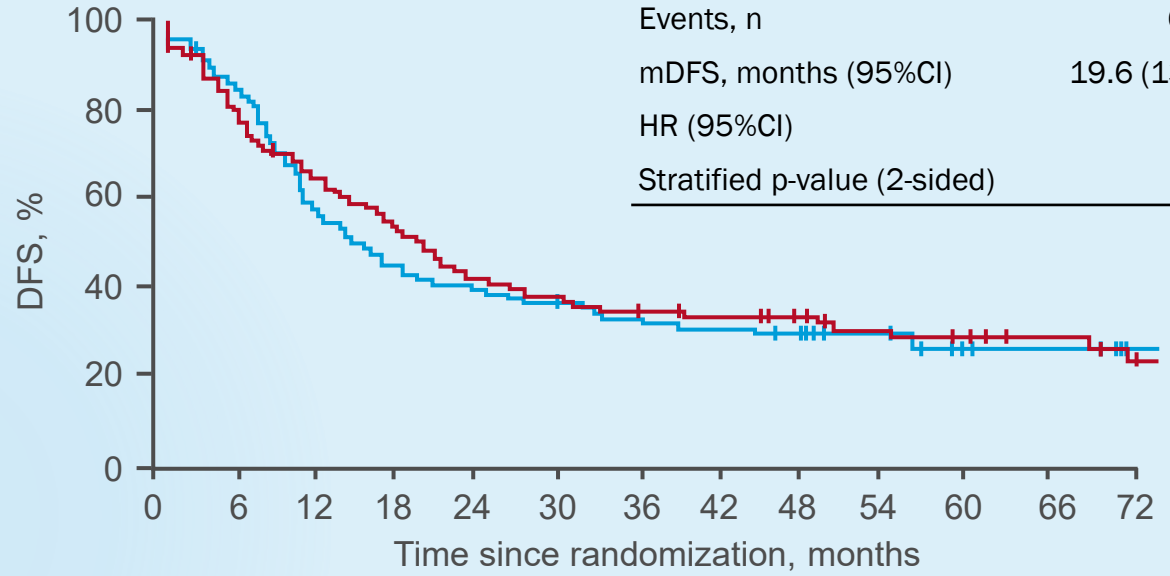
Safron H, et al. J Clin Oncol 2020;38(suppl);abstr 4500

4500: Trastuzumab with trimodality treatment for esophageal adenocarcinoma with HER2 overexpression: NRG Oncology/RTOG 1010 – Safran H, et al

Key results

DFS

	Trastuzumab + CRT (n=98)	CRT (n=96)
Events, n	68	67
mDFS, months (95%CI)	19.6 (13.5, 26.2)	14.2 (10.5, 23.0)
HR (95%CI)	0.97 (0.69, 1.36)	
Stratified p-value (2-sided)	0.85	



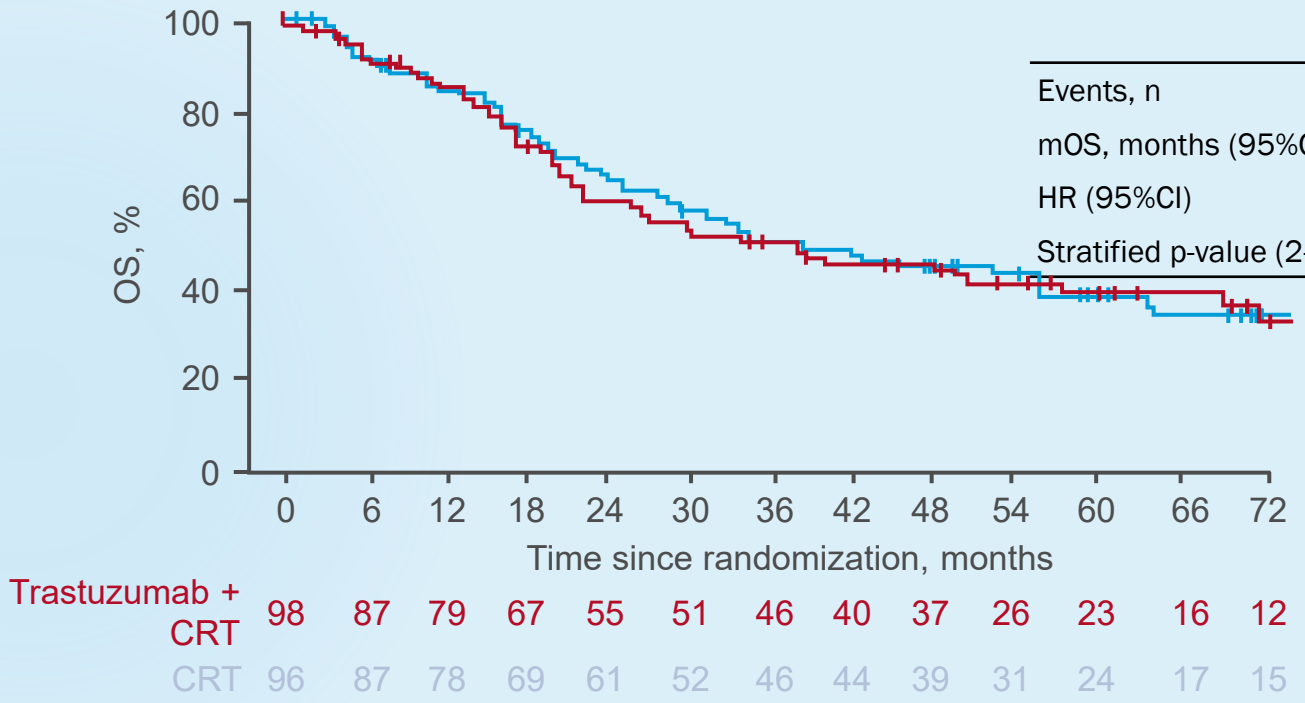
Trastuzumab + CRT	98	72	60	48	39	35	32	29	26	20	19	13	10
CRT	96	77	51	42	37	33	30	28	26	22	17	14	13

Safron H, et al. J Clin Oncol 2020;38(suppl);abstr 4500

4500: Trastuzumab with trimodality treatment for esophageal adenocarcinoma with HER2 overexpression: NRG Oncology/RTOG 1010 – Safran H, et al

Key result

- No significant differences in pCR rate: 27% trastuzumab + CRT and 29% for CRT (p=0.71)



	Trastuzumab + CRT (n=98)	CRT (n=96)
Events, n	54	55
mOS, months (95%CI)	38.5 (26.2, 70.4)	38.9 (29.0, 64.5)
HR (95%CI)	1.01 (0.69, 1.47)	
Stratified p-value (2-sided)	0.95	

Safron H, et al. J Clin Oncol 2020;38(suppl);abstr 4500

4500: Trastuzumab with trimodality treatment for esophageal adenocarcinoma with HER2 overexpression: NRG Oncology/RTOG 1010 – Safran H, et al

Key results (cont.)

Select grade ≥3 TRAEs, n (%)	Trastuzumab + CRT (n=95)	CRT (n=96)
Any	66 (69)	76 (79)
Hematologic	53 (56)	55 (57)
Cardiac disorders	5 (5)	3 (3)
GI disorders	28 (29)	20 (21)
Infections	11 (12)	7 (7)
Metabolism and nutrition	12 (13)	19 (20)

Conclusion

- **In patients with esophageal adenocarcinoma and HER2 overexpression, no improvements in DFS, OS or pCR or increased toxicity were observed with the addition of trastuzumab to trimodality treatment**

Safron H, et al. J Clin Oncol 2020;38(suppl);abstr 4500

ESMO 2020

Cleveland Clinic

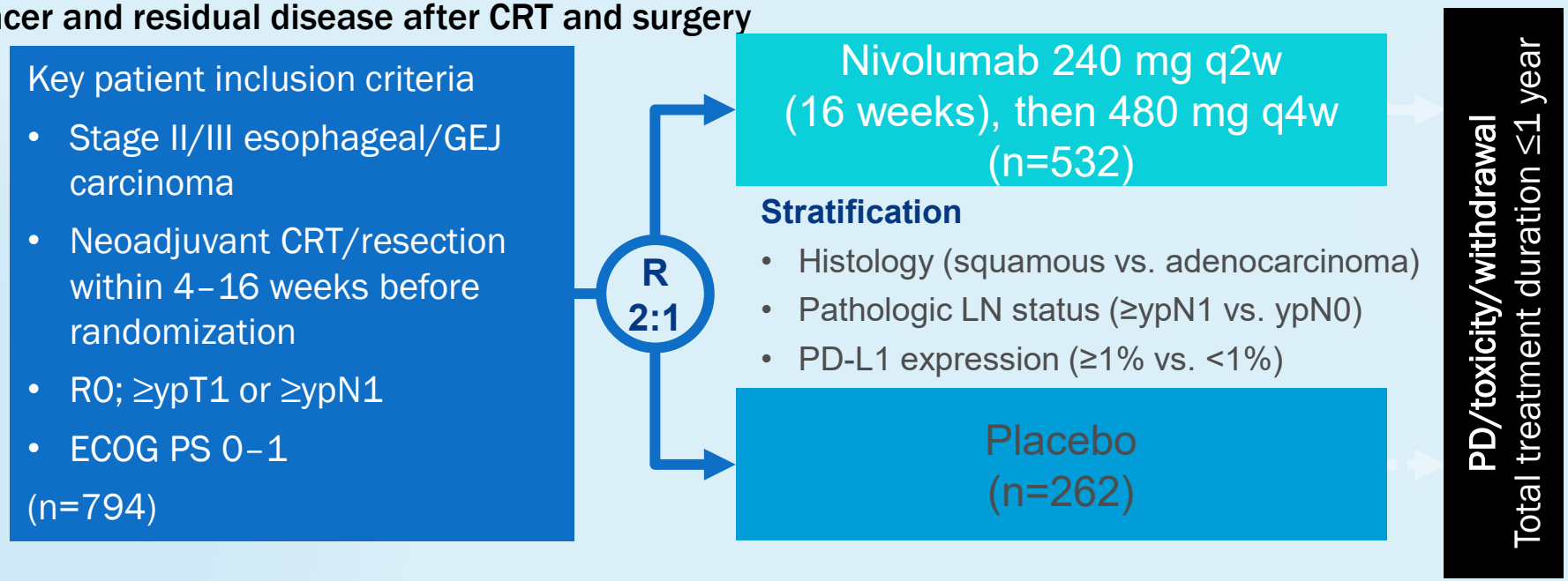
ESMO Virtual Congress 2020

19–21 September 2020

LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Study objective

- To evaluate the safety and efficacy of adjuvant nivolumab in patients with esophageal/GEJ cancer and residual disease after CRT and surgery



PRIMARY ENDPOINT

- DFS

- OS, safety

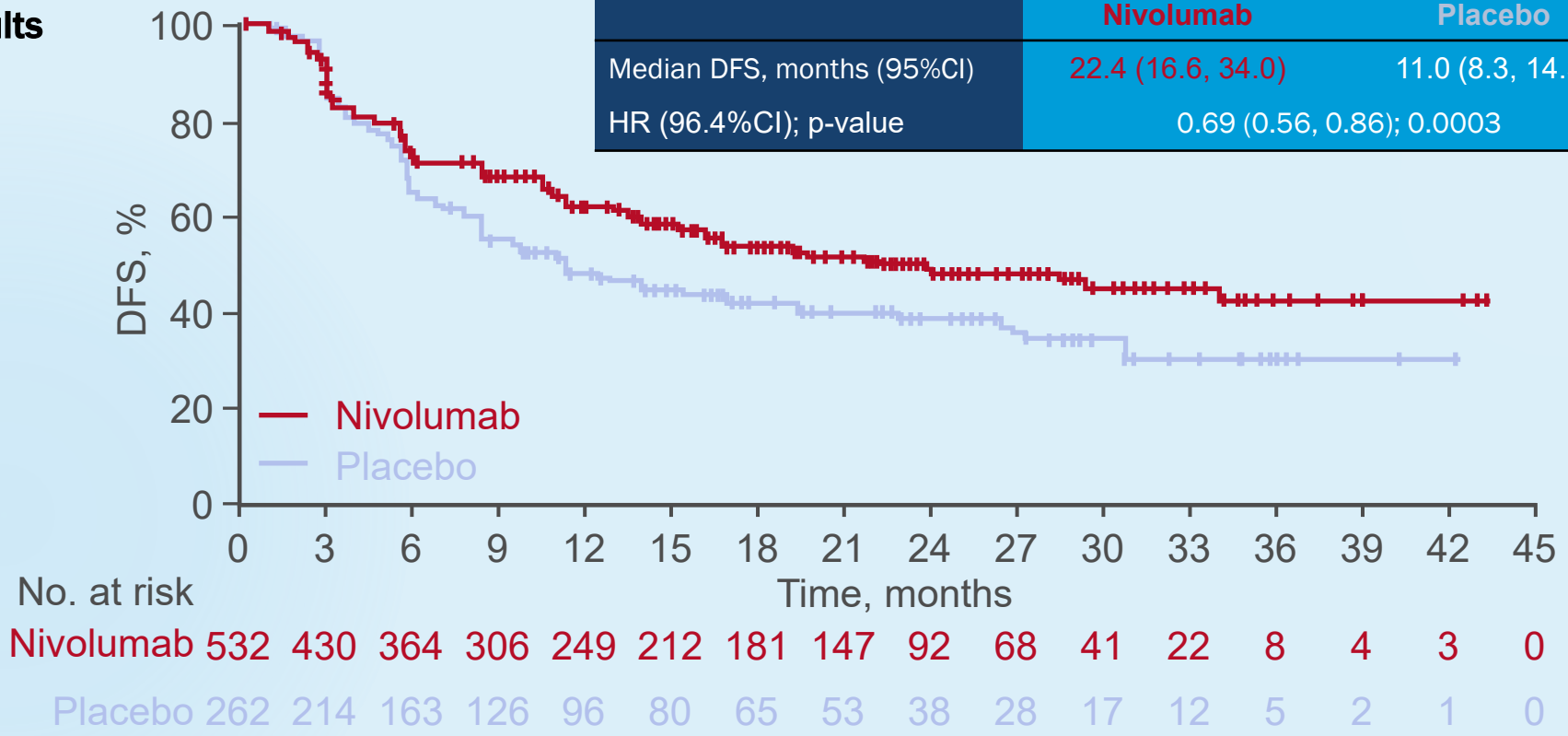
Kelly RJ, et al. Ann Oncol 2020;31(suppl):abstr LBA9

LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Key results

Disease-free survival

	Nivolumab	Placebo
Median DFS, months (95%CI)	22.4 (16.6, 34.0)	11.0 (8.3, 14.3)
HR (96.4%CI); p-value	0.69 (0.56, 0.86); 0.0003	



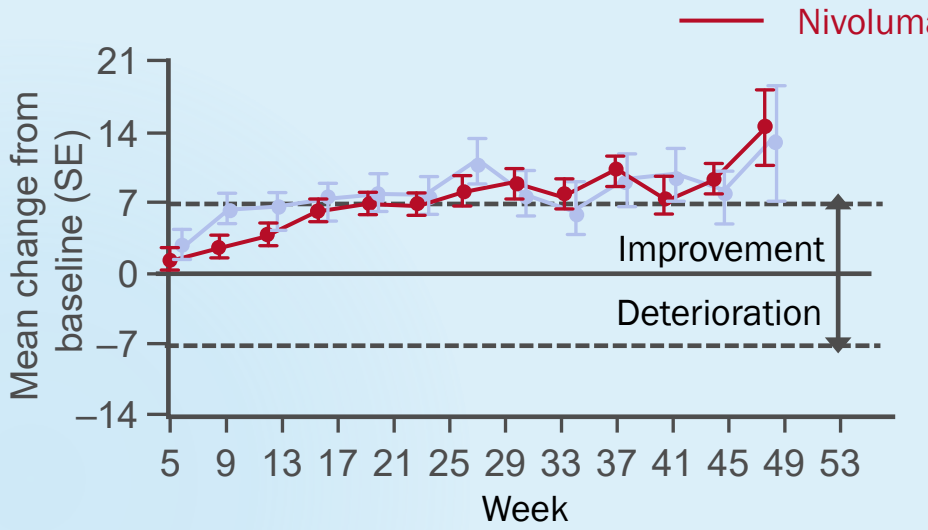
Kelly RJ, et al. Ann Oncol 2020;31(suppl):abstr LBA9

LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Overall health status using EQ-5D-3L

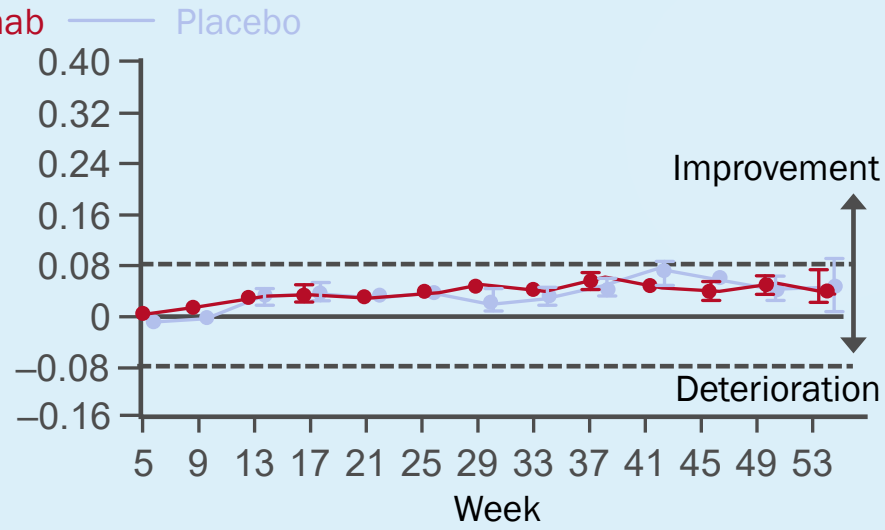
Key results (cont.)

Visual analogue scale



Nivolumab (n=532)	446	420	383	323	312	299	280	283	268	256	241	221	48
Placebo (n=262)	220	219	202	172	169	155	136	131	124	108	100	96	21

Utility index



Nivolumab (n=532)	445	419	386	322	310	300	279	282	265	256	241	221	48
Placebo (n=262)	217	214	198	170	167	154	137	129	123	109	97	95	20

Kelly RJ, et al. Ann Oncol 2020;31(suppl):abstr LBA9

LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Key results (cont.)

AEs, n (%)	Nivolumab (n=532)		Placebo (n=260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any AE	510 (96)	183 (34)	243 (93)	84 (32)
Any TRAE	376 (71)	71 (13)	119 (46)	15 (6)
Serious TRAE	40 (8)	29 (5)	7 (3)	3 (1)
TRAE leading to discontinuation	48 (9)	26 (5)	8 (3)	7 (3)
Selected TRAE				
Endocrine	93 (17)	5 (<1)	6 (2)	0
Gastrointestinal	91 (17)	4 (<1)	40 (15)	3 (1)
Hepatic	49 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (<1)
Renal	7 (1)	1 (<1)	2 (<1)	0
Skin	130 (24)	7 (1)	28 (11)	1 (<1)

Kelly RJ, et al. Ann Oncol 2020;31(suppl):abstr LBA9

LBA9: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study – Kelly RJ, et al

Key results (cont.)

AEs, n (%)	Nivolumab (n=532)		Placebo (n=260)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
TRAEs occurring in ≥10% of patients in either arm				
Fatigue	90 (17)	6 (1)	29 (11)	1 (<1)
Diarrhoea	88 (17)	2 (<1)	39 (15)	2 (<1)
Pruritus	53 (10)	2 (<1)	9 (3)	0
Rash	52 (10)	4 (<1)	10 (4)	1 (<1)

Conclusion

- **In patients with esophageal/GEJ carcinoma and pathological residual disease after neoadjuvant CRT and surgery, adjuvant nivolumab demonstrated significant and clinically meaningful improvement in DFS compared with placebo and was generally well-tolerated**

Kelly RJ, et al. Ann Oncol 2020;31(suppl):abstr LBA9

1421MO: Final results and subgroup analysis of the PETRARCA randomized phase II AIO trial: Perioperative trastuzumab and pertuzumab in combination with FLOT versus FLOT alone for HER2 positive resectable esophagogastric adenocarcinoma – Al-Batran S-E, et al

Study objective

- **To evaluate the efficacy and safety of trastuzumab + pertuzumab + FLOT in patients with resectable HER2-positive esophagogastric adenocarcinoma**

Key patient inclusion criteria
- Resectable esophagogastric adenocarcinoma (cT2–4, cN any, cM0 or T any, cN+, cM0)
- HER2-positive
- ECOG PS ≤2

(n=81)

R 1:1

Trastuzumab* + pertuzumab† + FLOT‡ x4 then resection then trastuzumab* + pertuzumab† + FLOT‡ x4 followed by trastuzumab* + pertuzumab† (9 cycles q3w) (n=40)

FLOT‡ x4 then resection then FLOT‡ x4 (n=41)

Stratification
- ECOG PS (0–1 vs. 2), location of primary tumor (GEJ vs. stomach), age (<60 vs. 60–69 vs. ≥70 years)

PRIMARY ENDPOINT
- pCR

SECONDARY ENDPOINTS
- DFS, OS, R0 rate, safety

*Trastuzumab 8 (loading)/6 mg/kg D1, 22, 43; †pertuzumab 840 mg D1, 22, 43; ‡docetaxel 50 mg/m^2 + oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + 5FU 2600 mg/m^2 D1, 15, 29, 43

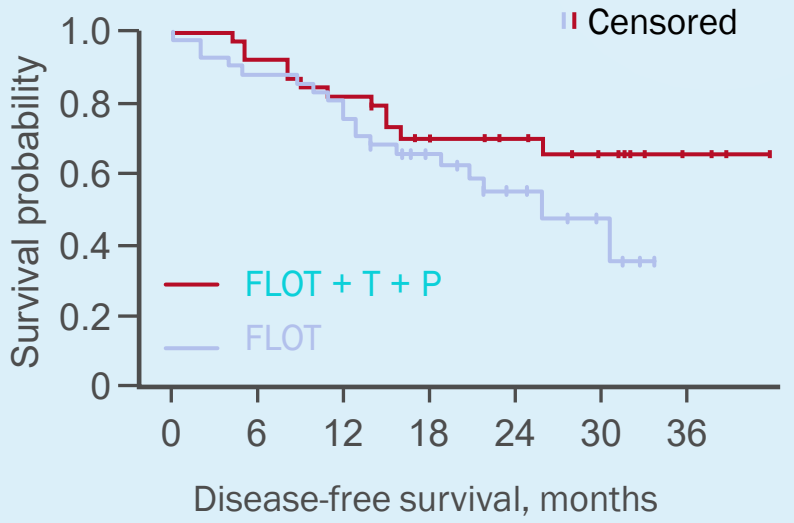
Al-Batran S-E, et al. Ann Oncol 2020;31(suppl):abstr 1421MO

1421MO: Final results and subgroup analysis of the PETRARCA randomized phase II AIO trial: Perioperative trastuzumab and pertuzumab in combination with FLOT versus FLOT alone for HER2 positive resectable esophagogastric adenocarcinoma – Al-Batran S-E, et al

Key results

Outcome, n (%)	Trastuzumab + pertuzumab + FLOT (n=40)	FLOT (n=41)
≤T1	17 (43)	11 (27)
T2	8 (20)	9 (22)
T3	14 (29)	17 (41)
T4	0 (0)	3 (7)
N0	27 (68)	16 (39)
R0 rate (ITT)	37 (93)	37 (90)
pCR	14 (35)	5 (12)
p-value	0.02	

	FLOT + T + P	FLOT
DFS, months (95%CI)	NR	26 (13, NR)
HR (95%CI); p-value	0.576 (0.278, 1.139); p=0.14	
	Median follow-up: 22 months	



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Key results (cont.)

Grade ≥3 AEs, n (%)	Trastuzumab + pertuzumab + FLOT (n=39)	FLOT (n=40)
Any	33 (85)	30 (75)
Leukopenia	9 (23)	5 (13)
Diarrhea	16 (41)	2 (5)
Fatigue	9 (23)	6 (15)

Conclusions

- **In patients with resectable esophagogastric adenocarcinoma, adding trastuzumab + pertuzumab to FLOT provided significant improvement in the pCR, but not R0 resection**
- **There was a higher incidence of AEs in the combination arm**

Al-Batran S-E, et al. Ann Oncol 2020;31(suppl):abstr 1421MO

1424MO: Perioperative FLOT plus ramucirumab versus FLOT alone for resectable esophagogastric adenocarcinoma– Updated results and subgroup analyses of the randomized phase II/III trial RAMSES/FLOT7 of the German AIO and Italian GOIM – Al-Batran S-E, et al

Study objective

- To evaluate the efficacy and safety of perioperative ramucirumab + FLOT in patients with resectable esophagogastric adenocarcinoma

Key patient inclusion criteria

- Resectable gastric or GEJ adenocarcinoma (≥cT2 or cN+)
- No distant metastases
- HER2 negative
- ECOG PS ≤1

(n=180)

R 1:1

Ramucirumab 8 mg/kg q2w + FLOT* (4 cycles) then surgery then ramucirumab 8 mg/kg q2w + FLOT* (4 cycles) followed by ramucirumab (16 cycles) (n=89)

FLOT* (4 cycles) then surgery followed by FLOT* (4 cycles) (n=91)

Stratification

- Tumour site (GEJ vs. gastric)
- Stage (T1/2 vs. T3/4 and/or N+)
- Histology (intestinal vs. diffuse/mixed or unknown)

PRIMARY ENDPOINT

- Response (near or pCR)

SECONDARY ENDPOINTS

- R0 rate, PFS, OS, safety

*Four pre- and postoperative cycles of docetaxel 50 mg/m^2 + oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + 5FU 2600 mg/m^2 q2w

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Key results

Outcome, n (%)	Ramucirumab + FLOT (n=86)	FLOT (n=87)
≤T1	17 (20)	22 (25)
T2	12 (14)	10 (12)
T3	49 (57)	33 (38)
T4	6 (7)	12 (14)
N0	43 (50)	34 (39)
R0 rate, %	97	83
p-value	0.0049	
R0 rate in subgroups, %		
cT4 (8 of 8 vs. 1 of 4)	100	25
Diffuse type	95	77

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Conclusion

- **In patients with resectable esophagogastric adenocarcinoma, adding ramucirumab to FLOT significantly improved the R0 rate**

Al-Batran S-E, et al. Ann Oncol 2020;31(suppl):abstr 1424MO

Summary
Perioperative therapy Gastric Cancer, 2020

- Adjuvant chemoradiation therapy use has declined; when used, needs significant modification
- Neoadjuvant FLOT is the standard of care in 2020, For fit patients, performance status 0-1
- Neoadjuvant FOLFOX, could be used in older patients with performance status 1-2.
- Role of neoadjuvant Xeloda or 5-FU/radiation therapy less defined, but could be used in patients with Locally advanced, borderline resectability.
- Adjuvant XELOX alone is an option as well. S1 not available in the US.
- Immunotherapy/VEGF/Anti Her2 in neoadjuvant setting with FLOT, still in the early phase clinical trials.