GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

NEO- AND ADJUVANT TREATMENT FOR GASTRIC CANCER: THE ROLE OF CHEMOTHERAPY

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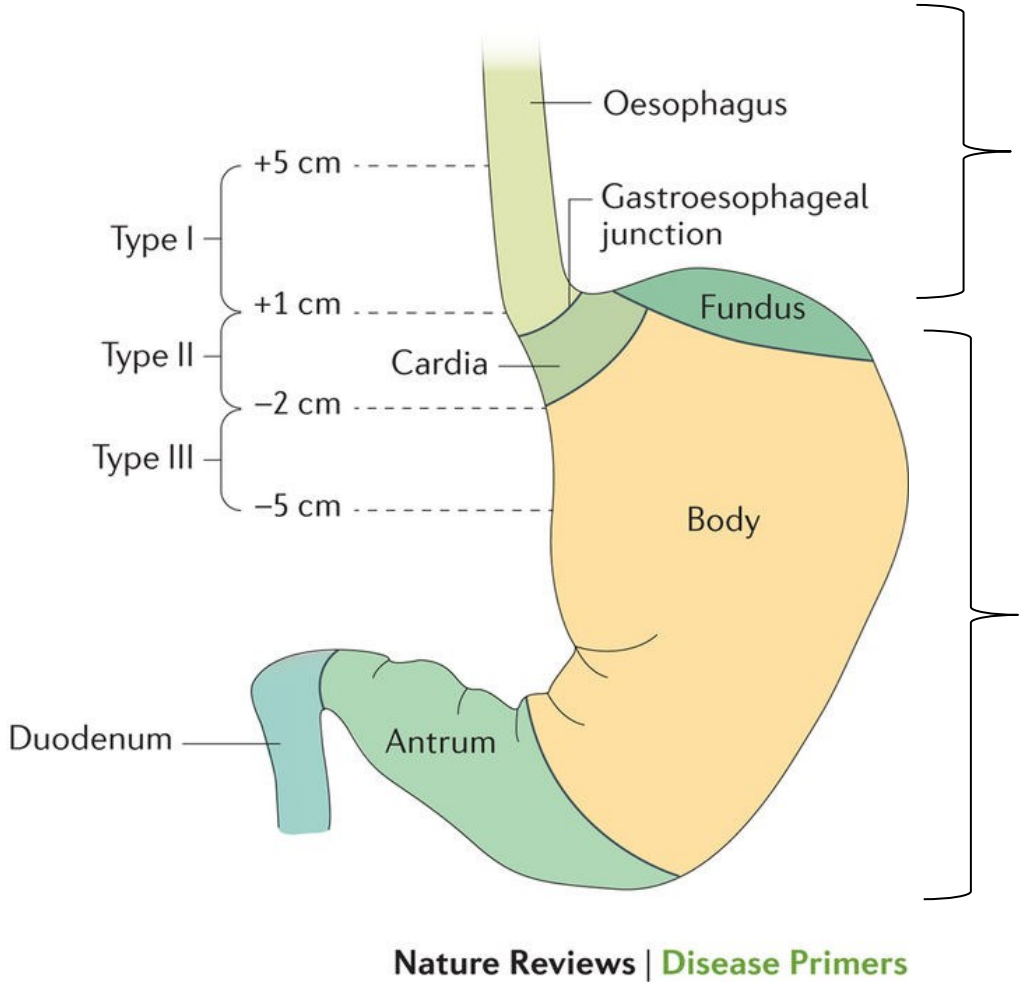
symposium Upper GI & HPB oncologie 28 mrt maastricht

GASTRIC AND GASTROESOPHAGEAL CANCER NOMENCLATURE

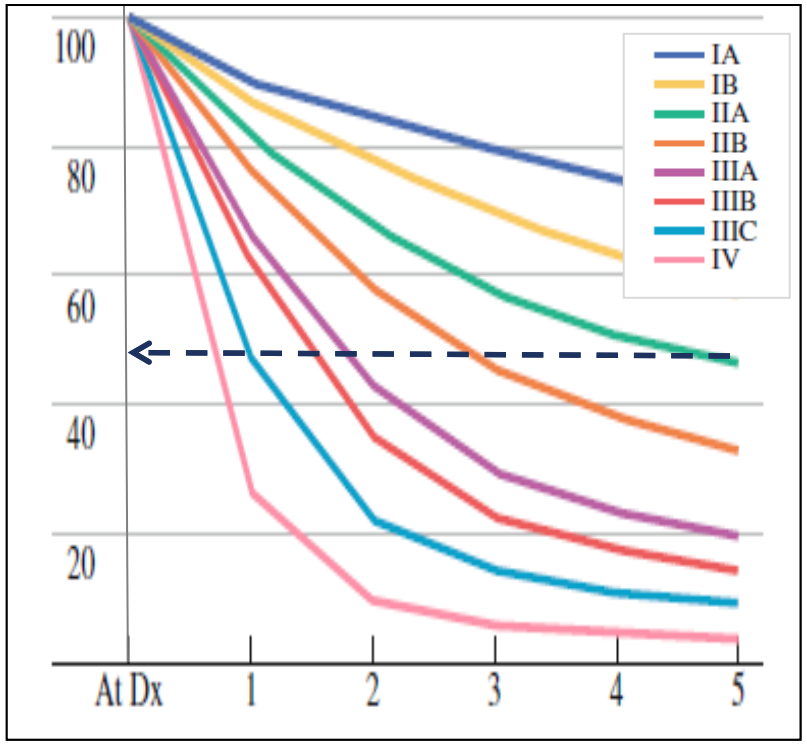


Lower oesophageal, gastroesophageal junction adenocarcinoma
→ ESMO Oesophageal Cancer Guidelines

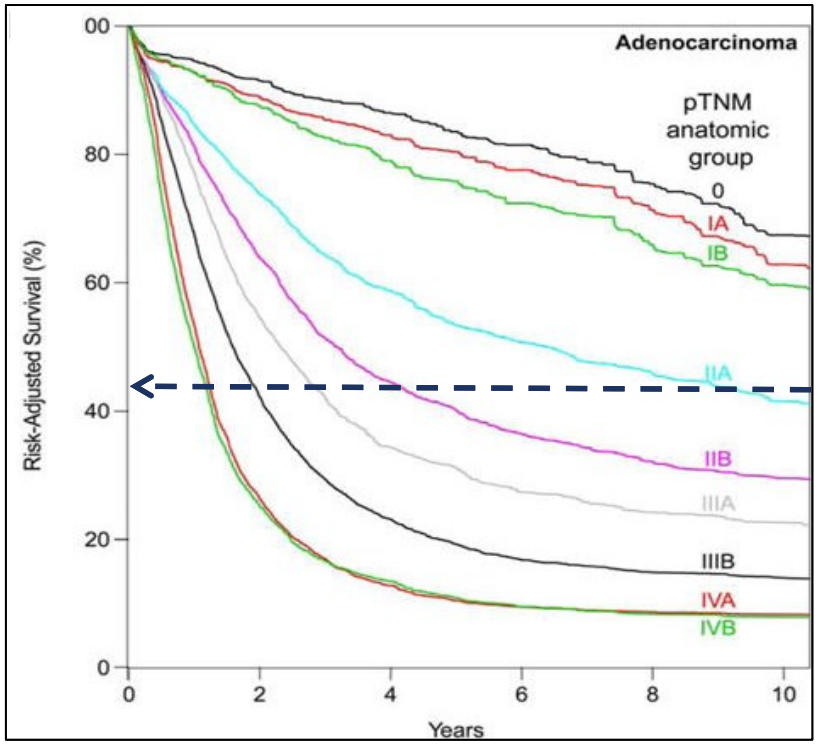
Gastric cancer
→ ESMO Gastric Cancer Guidelines

Ajani et al, Nat Rev Dis Primers. 2017 Jun 1;3:17036. doi: 10.1038/nrdp.2017.36

SURVIVAL FROM OG CANCER WITH SURGERY ALONE



Gastric cancer OS surgery alone



Oesophageal adeno OS surgery alone

Treatment in addition to surgery is required for most patients

Rice et al, Dis Esophagus. 2016 Nov;29(8):897-905.
Washington et al, Ann Surg Oncol, December 2010, Volume 17, Issue 12

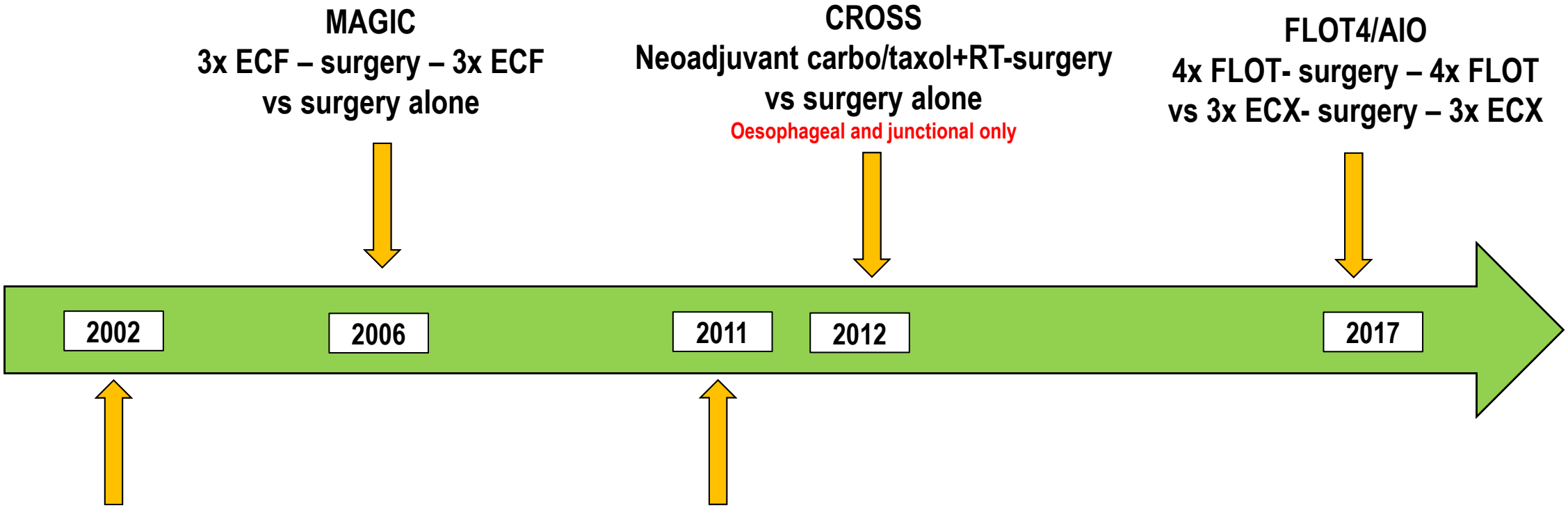
NEOADJUVANT AND PERIOPERATIVE CHEMOTHERAPY

AIMS OF NEOADJUVANT AND PERI-OPERATIVE CHEMOTHERAPY

- Downstage the tumour
- Increase R0 resection rate
- Treat micrometastatic disease
- Improve overall survival

Neoadjuvant and perioperative chemotherapy is more commonly used in non-Asian countries where tumours are frequently locally advanced and require downstaging prior to successful resection

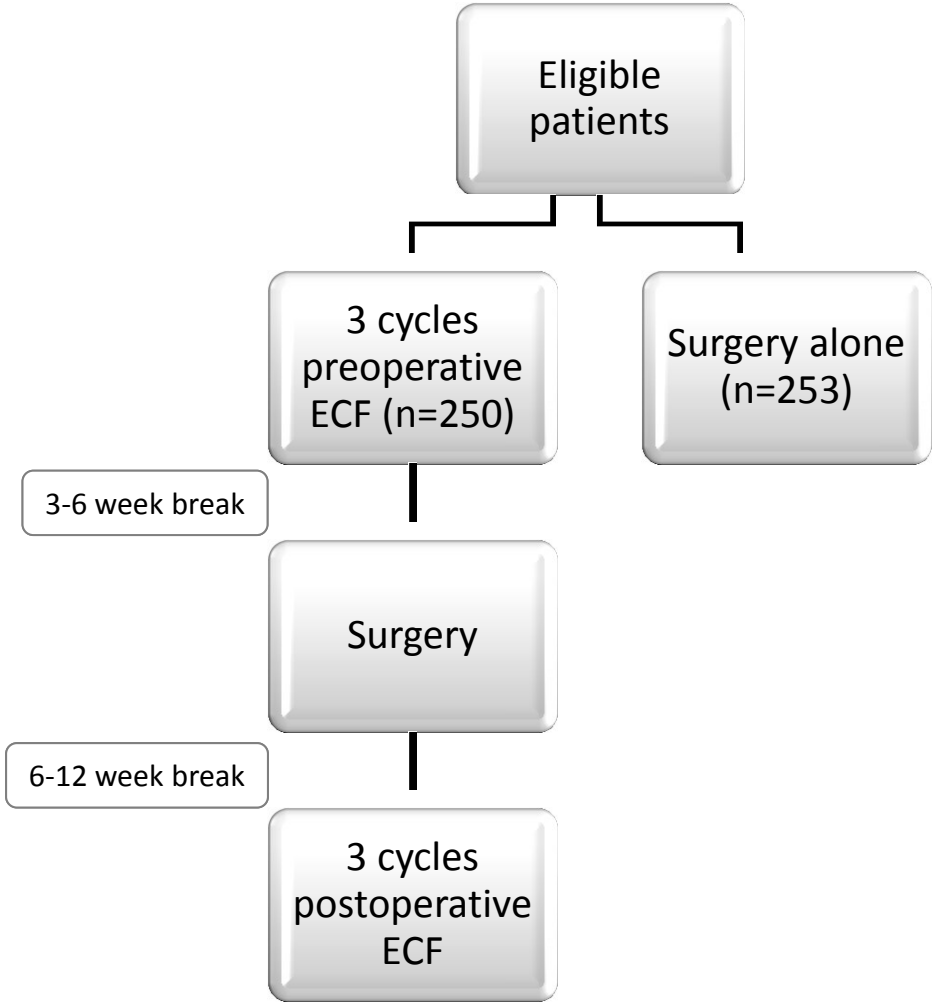
EVOLUTION OF NEOADJUVANT AND PERI-OPERATIVE (CHEMO)THERAPY 2002 - 2017



CF, cisplatin + 5-fluourouracil; ECF epirubicin + CF; FLOT. 5-fluororuraci, leucovorin, oxaliplatin, docetaxel

1. OE02 Trial Group, Lancet 2002
2. Cunningham D, *et al*. N Engl J Med 2006.
3. Ychou M, *et al*. J Clin Oncol. 2011
4. Van Hagen et al, N Engl J Med 2012
5. Al-Batran S, et al. ASCO Annual Meeting 2017

MEDICAL RESEARCH COUNCIL MAGIC TRIAL



Eligibility criteria

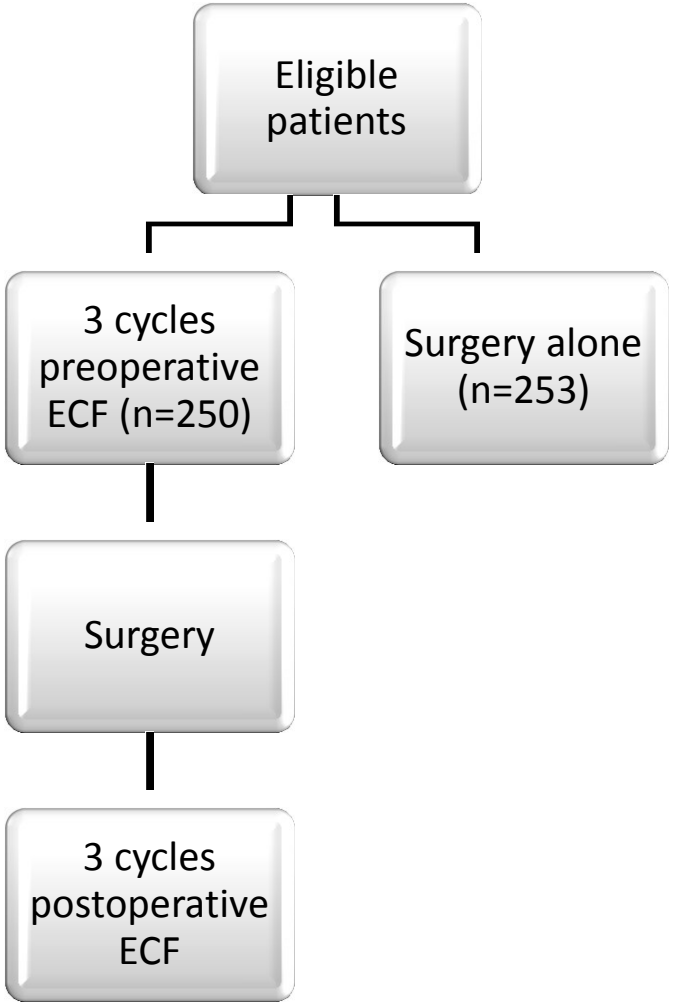
Stage ≥ II gastric, gastroesophageal junction, or lower oesophageal adenocarcinoma (after 1999)
No metastases
ECOG 0-1

MAGIC preoperative patient characteristics

	Surgery alone	Chemo + surgery
Median age	62	62
Sex Male Female	 191 (75%) 62 (25%)	 205 (82%) 45 (18%)
Site of disease		
Gastric	187 (74%)	185 (74%)
Oesophagus GOJ	36 (14%) 30 (12%)	37 (15%) 28 (11%)

ECF, epirubicin 50mg/m^2, cisplatin 60mg/m^2 and continuous 5-fluorouracil 200mg/m^2/d

MEDICAL RESEARCH COUNCIL MAGIC TRIAL



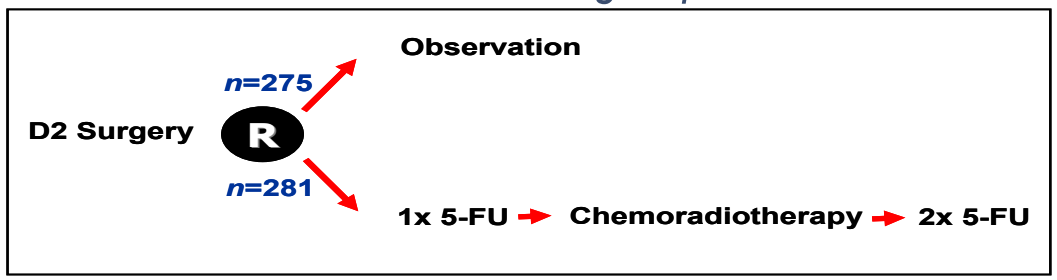
MAGIC post-operative patient characteristics		
	Surgery alone	Chemo + surgery
Surgery		↑ curative resections
Curative	66/250 (66%)	169/244 (69%)
Palliative	70/250 (28%)	44/244 (18%)
Other	17/250 (6%)	27/244 (13%)
ypT stage		↑ early T stage
T1	16/193 (8%)	27/172 (16%)
T2	55/193 (29%)	62/172 (36%)
T3	106/193 (55%)	75/172 (44%)
T4	16/193 (8%)	8/172 (4%)
ypN Stage (gastric)		↑ early N stage
N0	42/156 (27%)	42/135 (31%)
N1	68/156 (43%)	72/135 (53%)
N2	34/156 (23%)	19/135 (14%)
N3	12/156 (8%)	2/135 (2%)

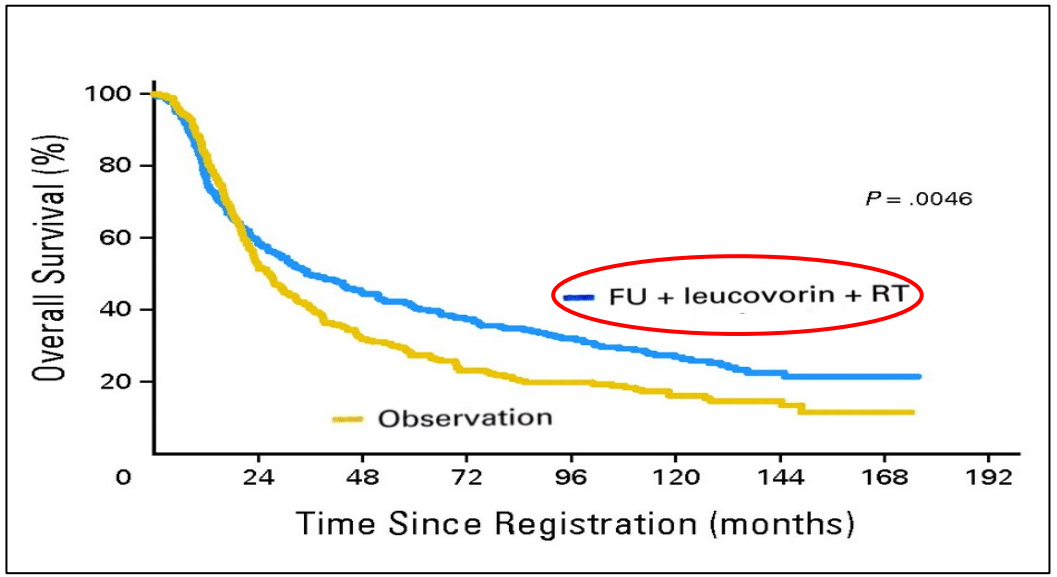
Peri-operative chemotherapy leads to tumour **downstaging**

ECF, epirubicin 50mg/m^2, cisplatin 60mg/m^2 and continuous 5-fluorouracil 200mg/m^2/d

evidence-based (neo-)adjuvant strategies (1)

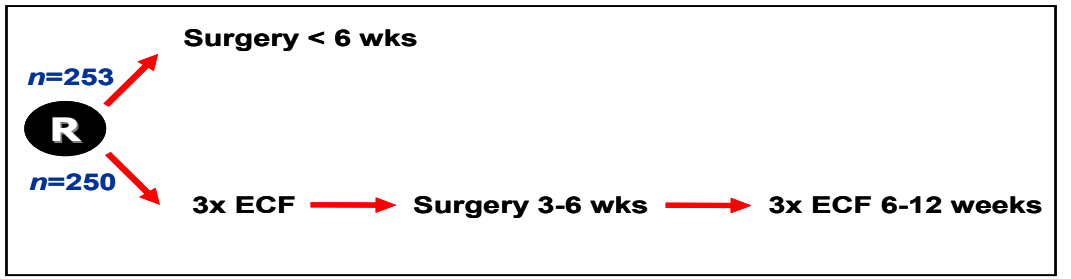
SWOG-Intergroup 0116 Trial

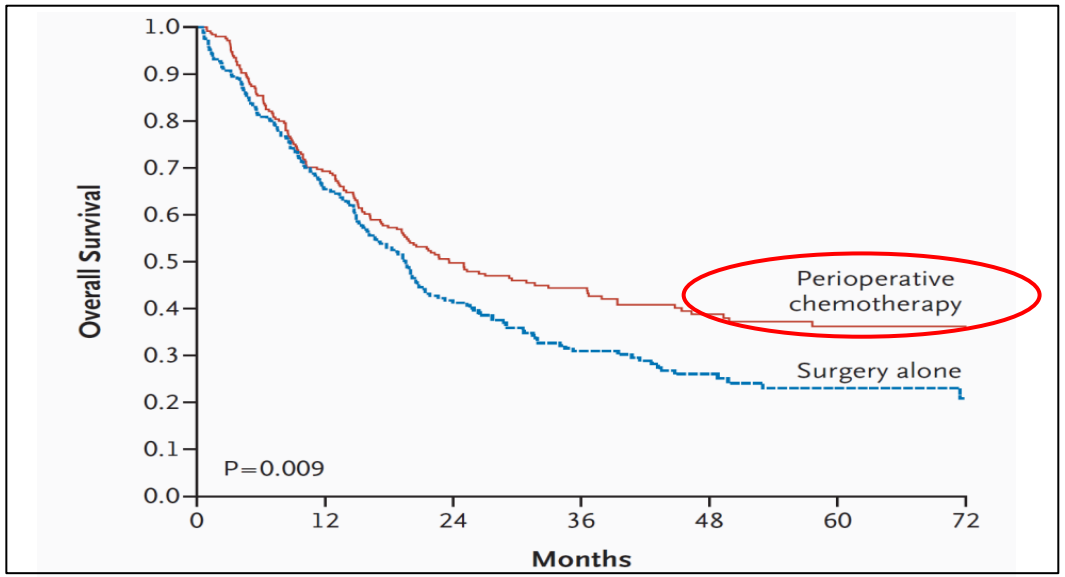




Macdonald et al. NEJM 2001; Smalley et al. JCO 2012

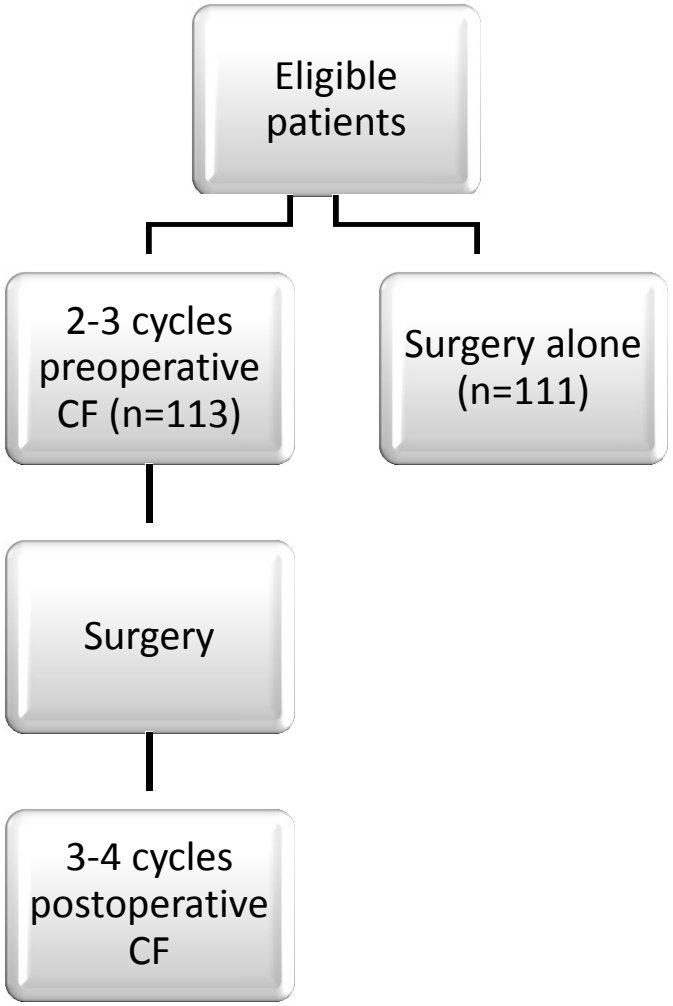
MAGIC Trial





Cunningham et al. NEJM 2006

FFCD/FNCLCC TRIAL



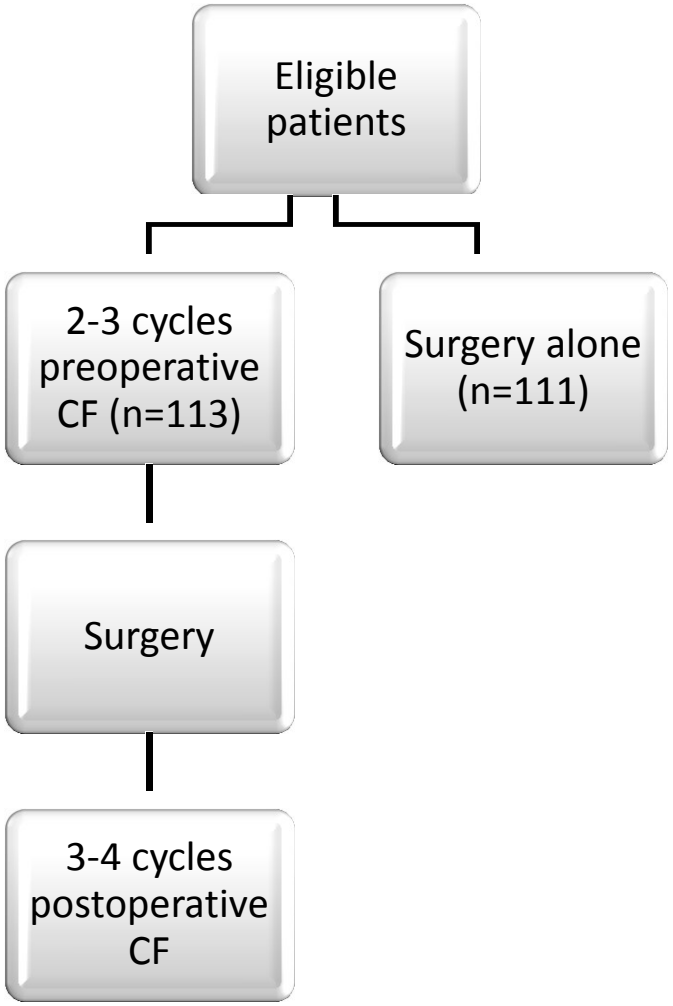
Eligibility criteria
Lower oesophageal or GOJ adenocarcinoma (gastric after 1998)
No metastases
ECOG 0-1

FFCD/ACCORD preoperative patient characteristics

	Surgery alone	Chemo + surgery
Median age	63	63
Sex Male Female	 91 (82%) 20 (18%)	 96 (85%) 17 (15%)
Site of disease Gastric Oesophagus GOJ	 28 (13%) 15 (25%) 70 (62%)	 27(9%) 10 (24%) 74(67%)

CF, cisplatin 100mg/m^2 and continuous 5-fluorouracil 800mg/m^2/d day 1-5 q 28d

FFCD/FNCLCC TRIAL

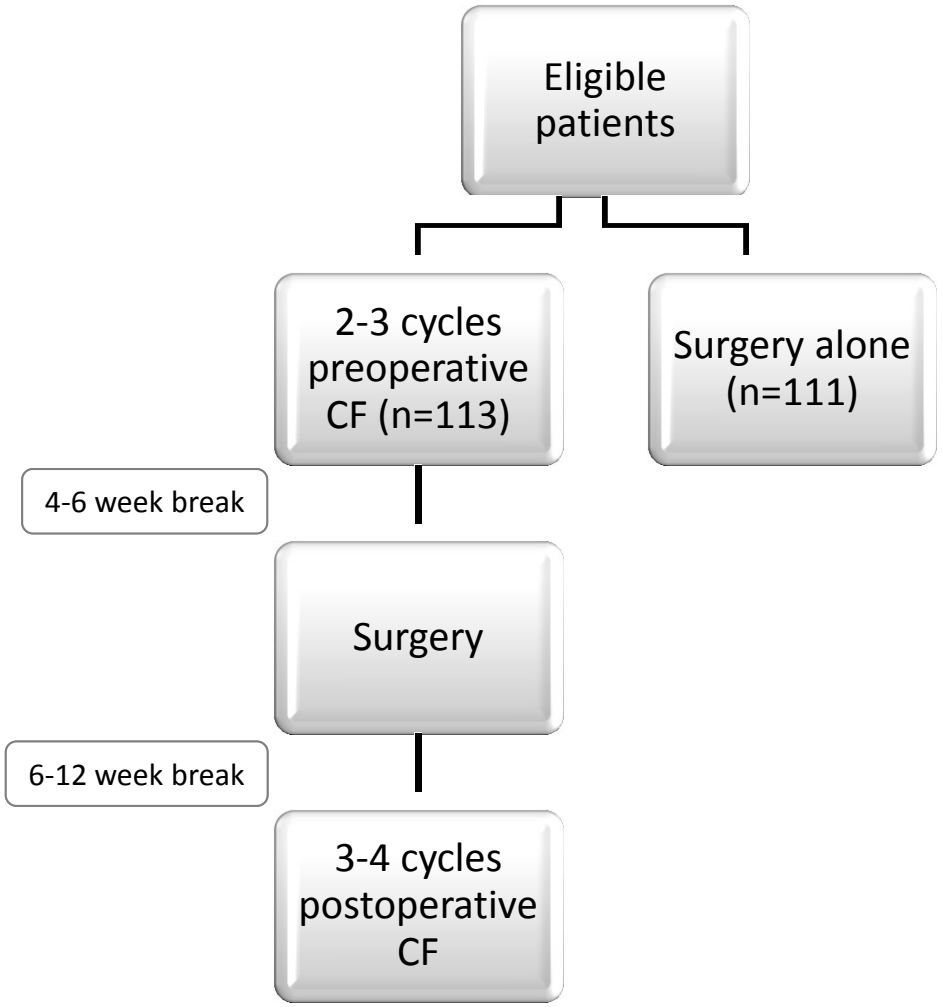


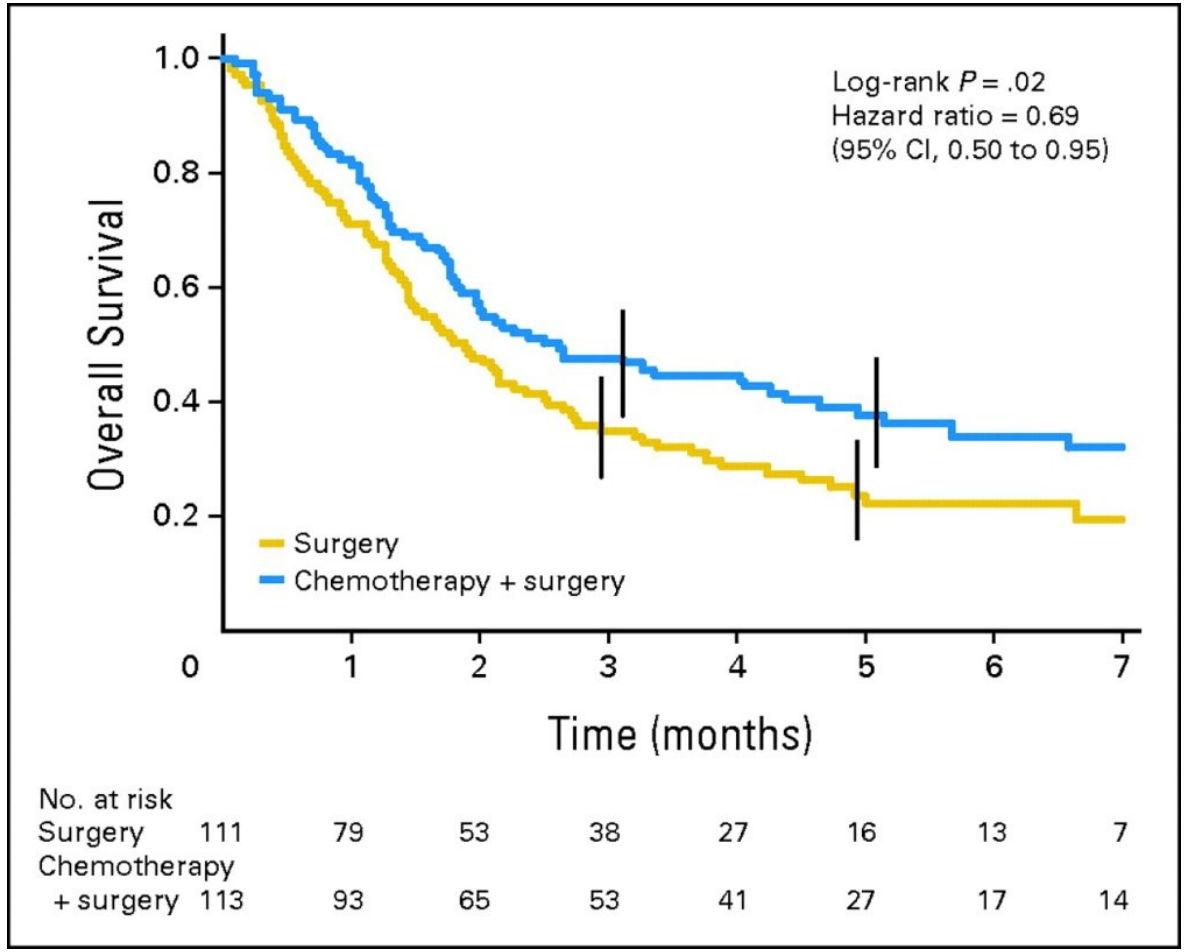
FFCD/FNCLCC post-operative patient characteristics		
	Surgery alone	Chemo + surgery
Surgery		↑ curative surgery
No resection	11 (10%)	7 (6%)
R0	81(74%)	95(87%)
R1	6 (5%)	4 (4%)
R2	11(10%)	2(2%)
Rx	1(1%)	1(1%)
ypT stage		↑ early T stage
T0	(8%)	3 (3%)
T1-2	(29%)	38 (39%)
T3-4	(55%)	57 (58%)
ypN Stage (gastric)		↑ early N stage
N0	17 (20%)	32(33%)
N+	68 (80%)	66(67%)

Peri-operative chemotherapy leads to tumour **downstaging**

CF, cisplatin 100mg/m^2 and continuous 5-fluorouracil 800mg/m^2/d day 1-5 q 28d

FFCD/FNCLCC TRIAL





Absolute benefit in OS 14% (24% surgery vs. 38% chemo + surgery)

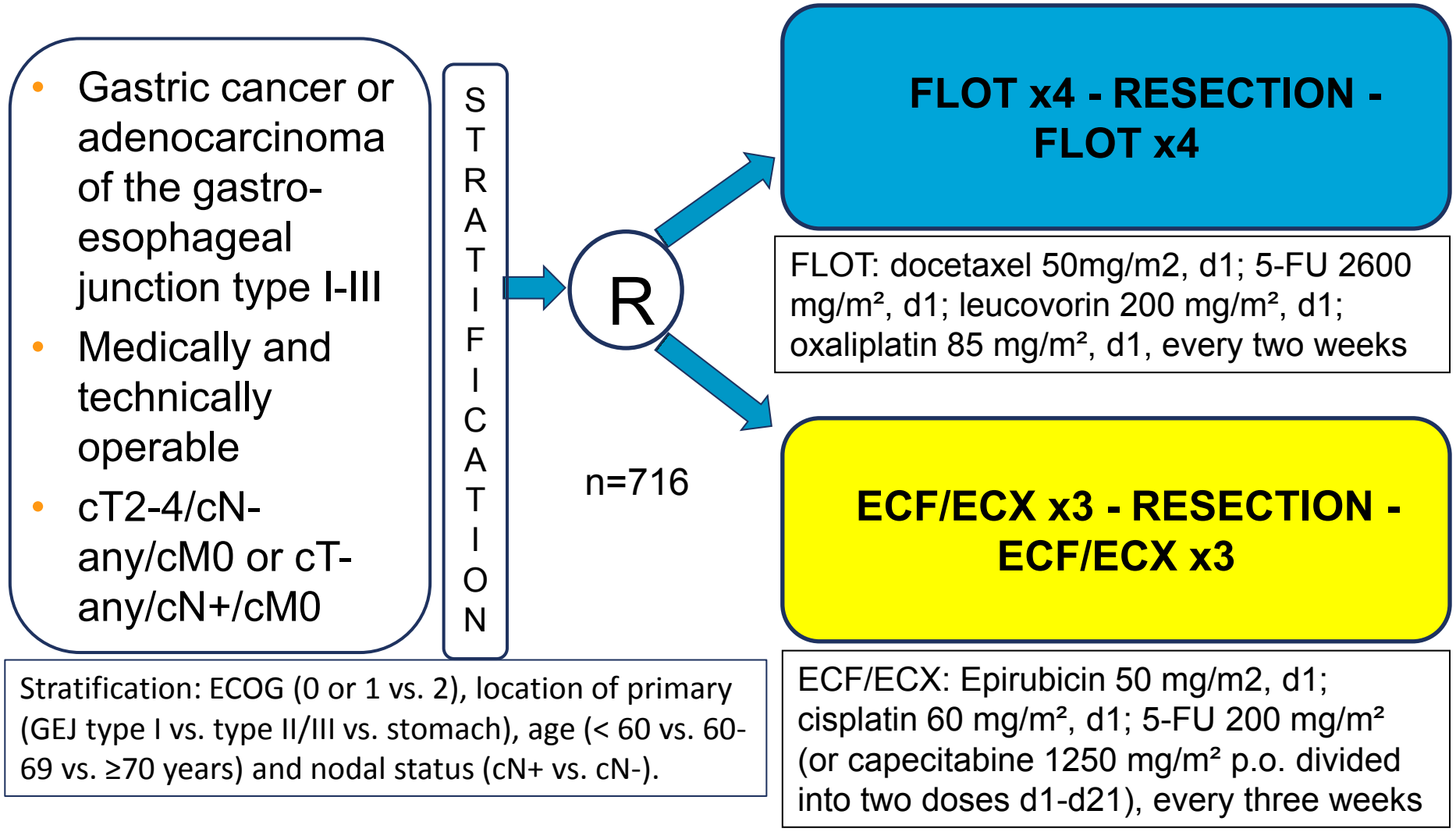
CF, cisplatin 100mg/m^2 and continuous 5-fluorouracil 800mg/m^2/d day 1-5 q 28d

LESSONS FROM MAGIC AND FFCD TRIALS

1. ~10% of patients will not complete pre-operative chemotherapy
2. Approximately 50% of patients are not fit enough for post operative chemotherapy

	MAGIC 3 cycles ECF	FFCD/FNCLCC 2-3 cycles CF
Pre-operative chemotherapy	3 cycles: n= 215 (91%)	1 cycle: n=11 (10%) 2 cycles: n=85 (75%) 3 cycles: n= 13 (12%) 87% had minimum 2 cycles
Surgery	229 (92%)	109 (97%)
Post-operative chemotherapy	Any chemotherapy: n=137 (55%) 3 cycles: n= 104 (42%)	Any chemotherapy: n=54 (50%) 1 cycle: n=6 (6%) 2 cycles: n=7 (6%) 3 cycles: n= 16 (15%) 4 cycles: n=25 (23%)

NEW HORIZON IN PERI-OPERATIVE CHEMOTHERAPY



Primary endpoint OS (ITT)

al Batran et al, ASCO 2017

FLOT BASELINE CHARACTERISTICS

	ECF/ECX N=360		FLOT N=356	
Age				
median	62	-	62	-
>=70	87	24%	85	24%
Sex				
male	265	74%	268	75%
ECOG PS				
0	254	71%	246	69%
1	103	29%	109	31%
2	3	1%	1	<1%
Location				
GEJ Siewert type 1	85	24%	80	23%
GEJ Siewert type 2 or 3	115	32%	118	33%
Stomach	160	44%	158	44%

FLOT VS ECF/X SURGICAL OUTCOMES

	ECF/ECX (n=360)	FLOT (n=356)	
Resection surgery	313/360(87%)	336/356 (94%)	0.001
R0 resection rate	276/360 (77%)	300/356 (84%)	0.011
Any surgical complication	188/341 (55%)	188/345 (55%)	
Median duration hospital stay	16 days	15 days	
Death 90 days	26 (8%)	16 (5%)	

✓Peri-operative FLOT chemotherapy increases the proportion of patients who undergo surgical resection and increases the R0 resection rate compared to ECF/ECX

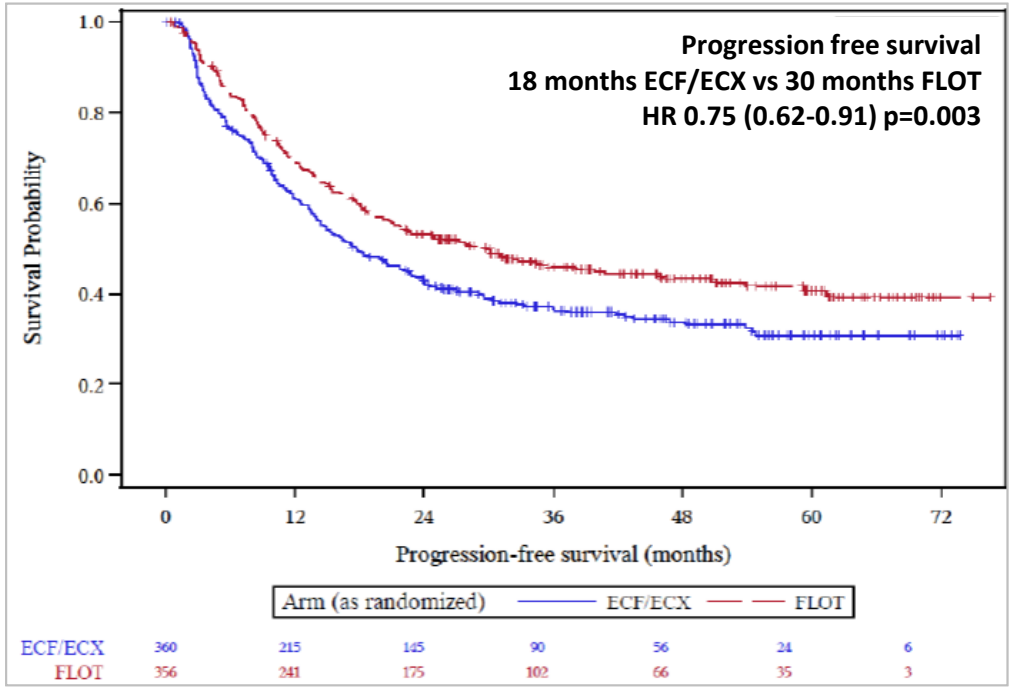
✓Surgical morbidity and mortality was not increased by use of FLOT chemotherapy

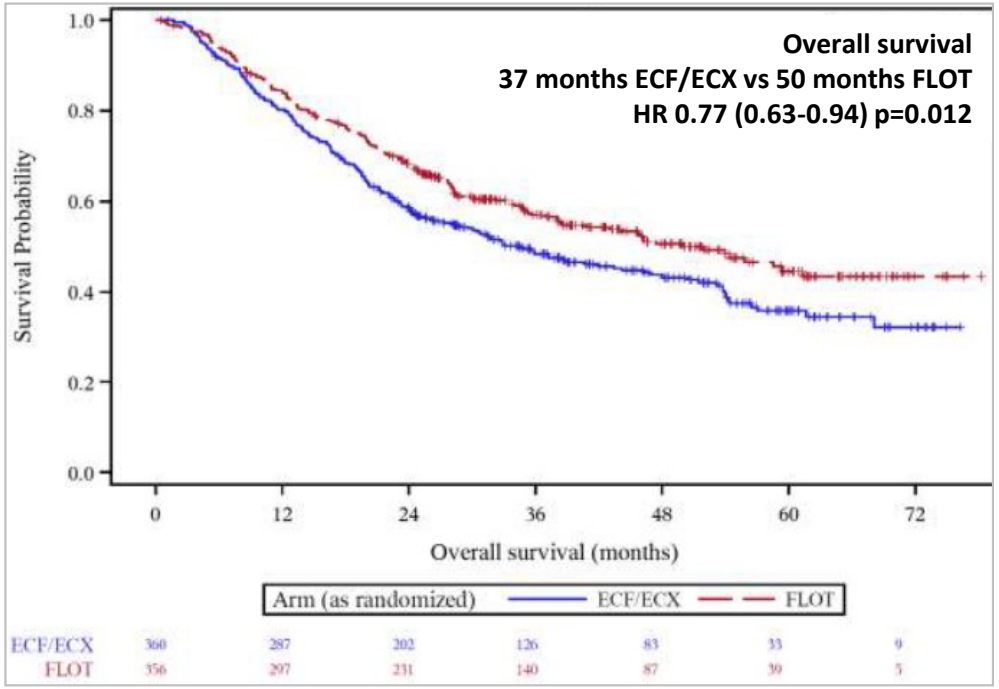
FLOT VS ECX PATHOLOGICAL OUTCOMES

	ECF/ECX (n=360)	FLOT (n=356)	
ypT stage			
≤T1	**53 (15%)**	**88(25%)**	**0.001**
T2	44 (12%)	44(12%)	
T3	175 (49%)	165(46%)	
T4	47(13%)	37(10%)	
NA	41(11%)	22(6%)	
ypN stage			
N0	**146(41%)**	**174(49%)**	**0.029**
N1	44(12%)	55(16%)	
N2	54(15%)	47(13%)	
N3	73(20%)	57(16%)	
NA	43(12%)	23(7%)	

✓Peri-operative FLOT chemotherapy increases the proportion of patients have pathological early stage tumours compared to ECF/X

FLOT IMPROVES PFS AND OS COMPARED TO ECF/X





Projected PFS rates		
	ECF/X	FLOT
2 year	43%	53%
3 year	37%	46%
5 year	31%	41%

Projected OS rates		
	ECF/X	FLOT
2 year	59%	68%
3 year	48%	57%
5 year	36%	45%

FLOT VS ECF/X TOXICITY

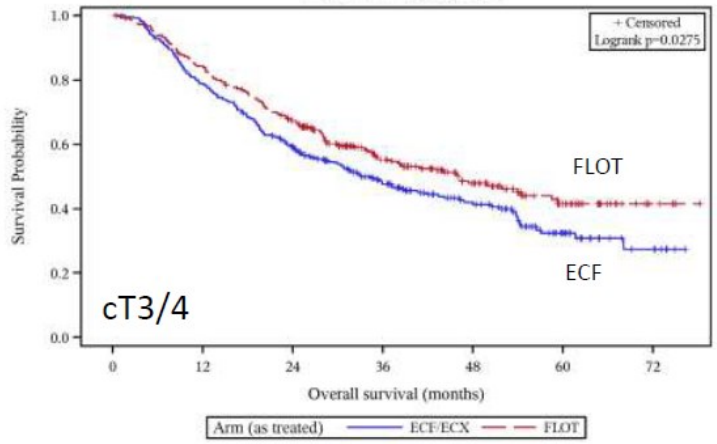
Grade 3-4 >5%	ECF/ECX (N=354)	FLOT (N=354)	P-value (Chi-Square)
Diarrhea	13 (4%)	34 (10%)	0.002
Vomiting	27 (8%)	7 (2%)	<0.001
Nausea	55 (16%)	26 (7%)	0.001
Fatigue	38 (11%)	25 (7%)	
Infections	30 (9%)	63 (18%)	<0.001
Leukopenia	75 (21%)	94 (27%)	
Neutropenia	139 (39%)	181 (51%)	0.002
Sensory	7 (2%)	24 (7%)	0.002
Thromboembolic	22 (6%)	9 (3%)	0.03
Anemia	20 (6%)	9 (3%)	0.04

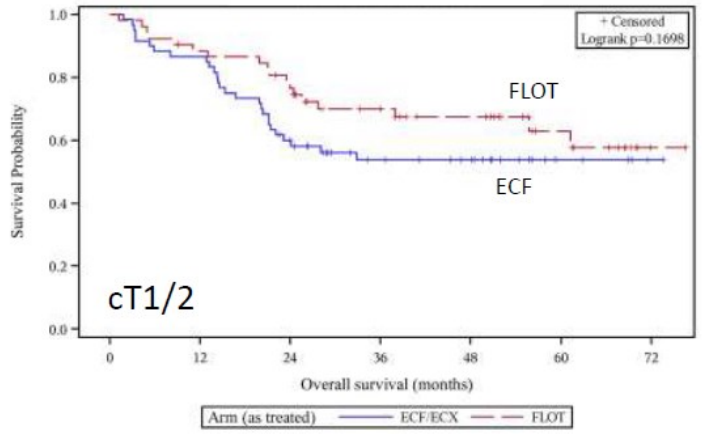
FLOT VS ECF/X TREATMENT TOLERABILITY

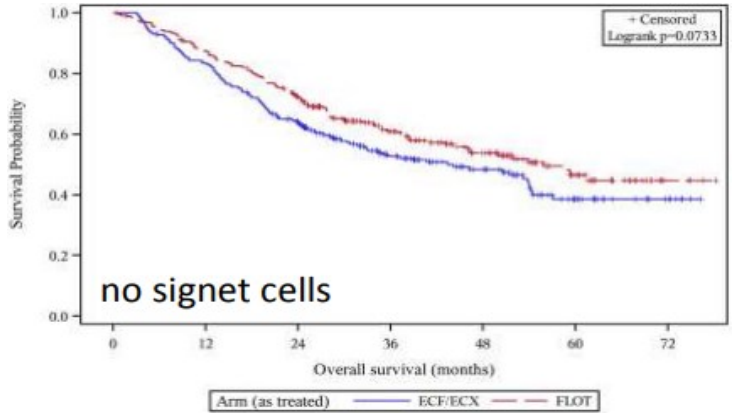
	ECF/ECX (n=360)	FLOT (n=356)
Completed pre-operative chemo	327 (91%)	320 (90%)
Surgery	340 (94%)	336 (94%)
Started post-operative chemo Completed protocol post-op chemo	187 (52%) 133 (37%)	213 (60%) 162 (46%)

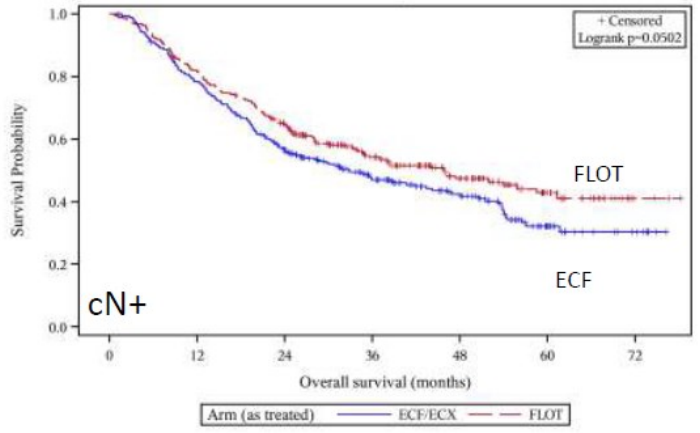
✓Patients treated with FLOT were more likely to commence post-operative chemotherapy, and those who commenced post-operative FLOT were more likely to complete post-operative chemotherapy

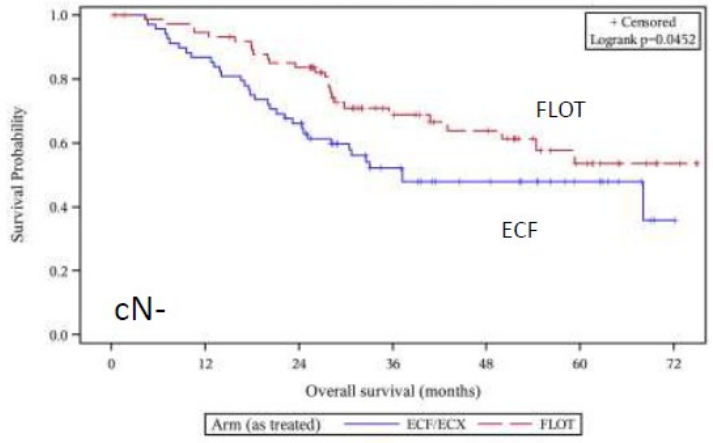
BENEFIT OF FLOT IN ALL PROGNOSTIC GROUPS

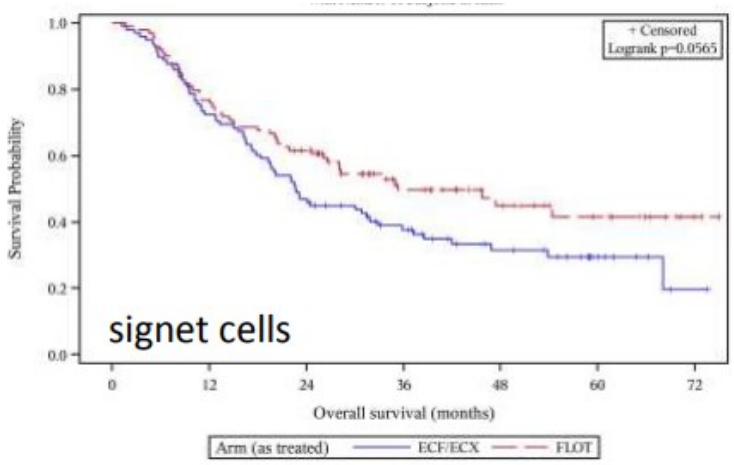












al Batran et al, ESMO 2017

PERI-OPERATIVE CHEMOTHERAPY:

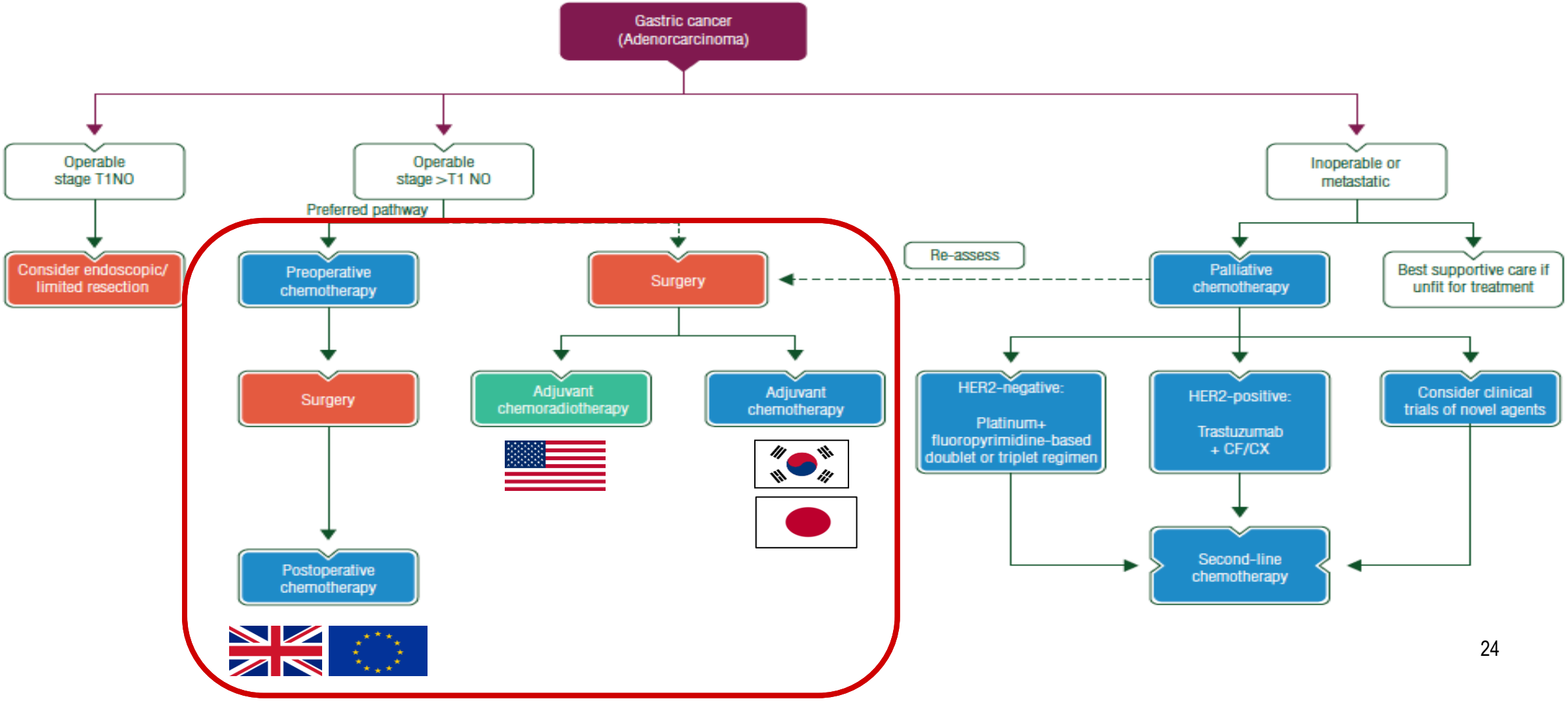
5 year projected OS with FLOT is **45%,** therefore there is still **more work** to do to improve survival for patients treated with peri-operative chemotherapy

ADJUVANT CHEMOTHERAPY

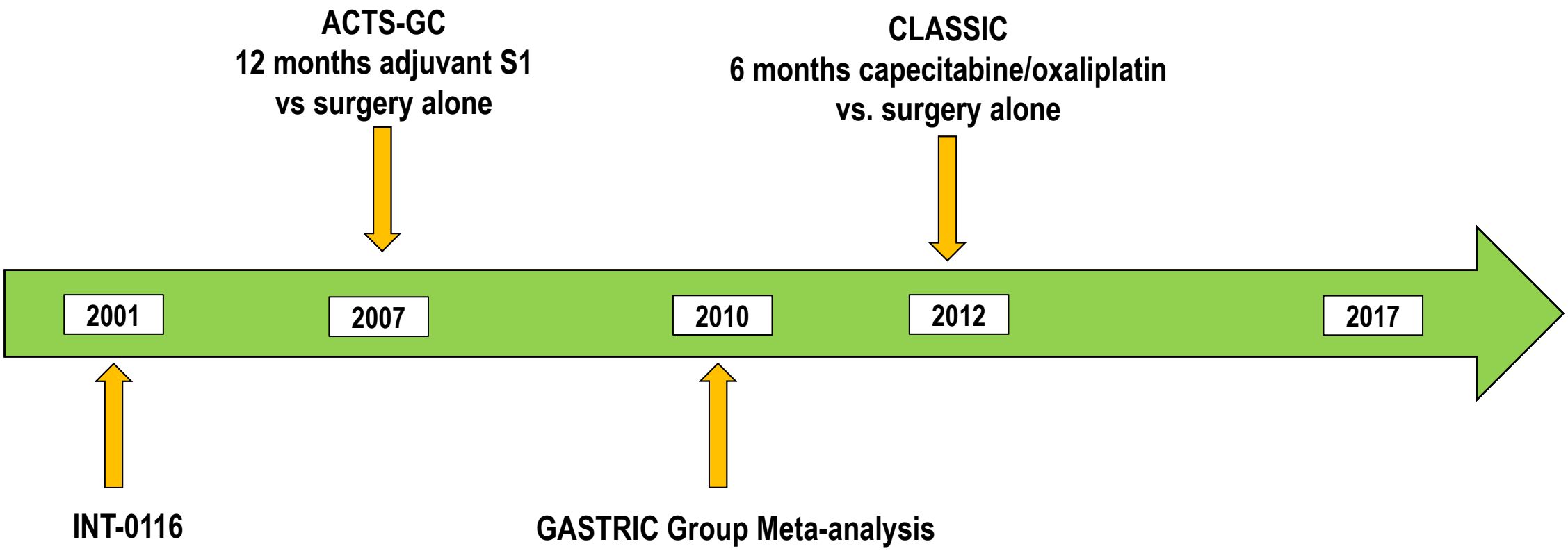
Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Annals of Oncology 27 (Supplement 5): v38–v49, 2016
doi:10.1093/annonc/mdw350

E. C. Smyth[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6] on behalf of the ESMO Guidelines Committee*

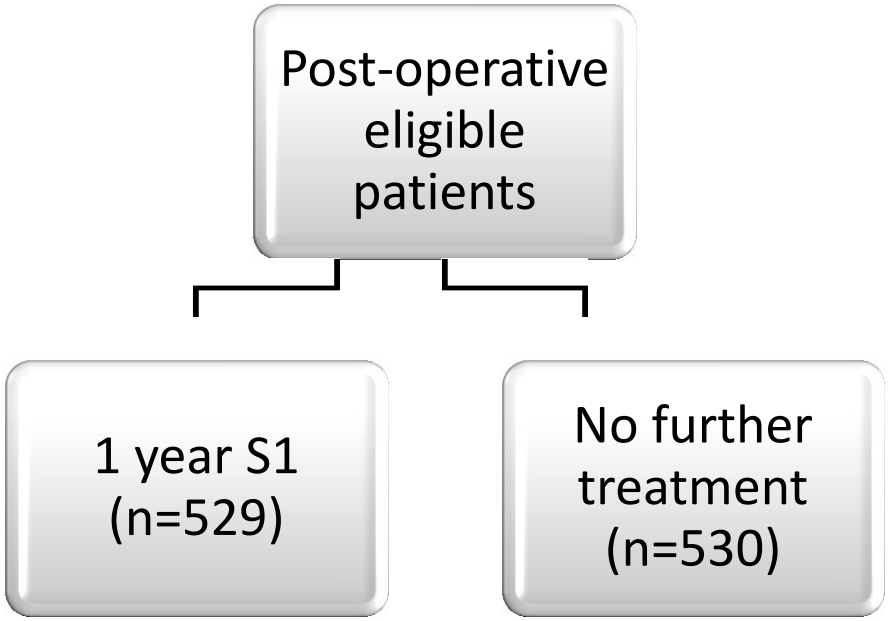


EVOLUTION OF ADJUVANT (CHEMO)THERAPY FOR GASTRIC CANCER 2001 - 2017



1. Macdonald et al, N Engl J Med. 2001 Sep 6;345(10):725-30.
2. Sakuramoto et al, N Engl J Med. 2007 Nov 1;357(18):1810-20.
3. Bang et al, Lancet. 2012 Jan 28;379(9813):315-21.
4. Pignon et al, JAMA. 2010 May 5;303(17):1729-37.

ACTS-GC TRIAL



Primary Endpoint
Overall survival
Secondary endpoints
Relapse free survival & safety

Eligibility criteria
Stage ≥ II (no T1), IIIA or IIIB gastric adenocarcinoma
D2 resection minimum

ACTS-GC patient characteristics

	Surgery alone	Chemo + surgery
Median age	63	63
Sex Male Female	 369 (70%) 161(30%)	 367 (71%) 162(29%)
Stage of cancer II III IV	 282 (53%) 213 (40%) 35 (7%)	 264 (50%) 224 (42%) 40(8%)

S1, 40mg/m2/d x 28 days followed by 2 week break x 1 year

Sakuramoto et al, N Engl J Med. 2007 Nov 1;357(18):1810-20.

ACTS-GC TRIAL

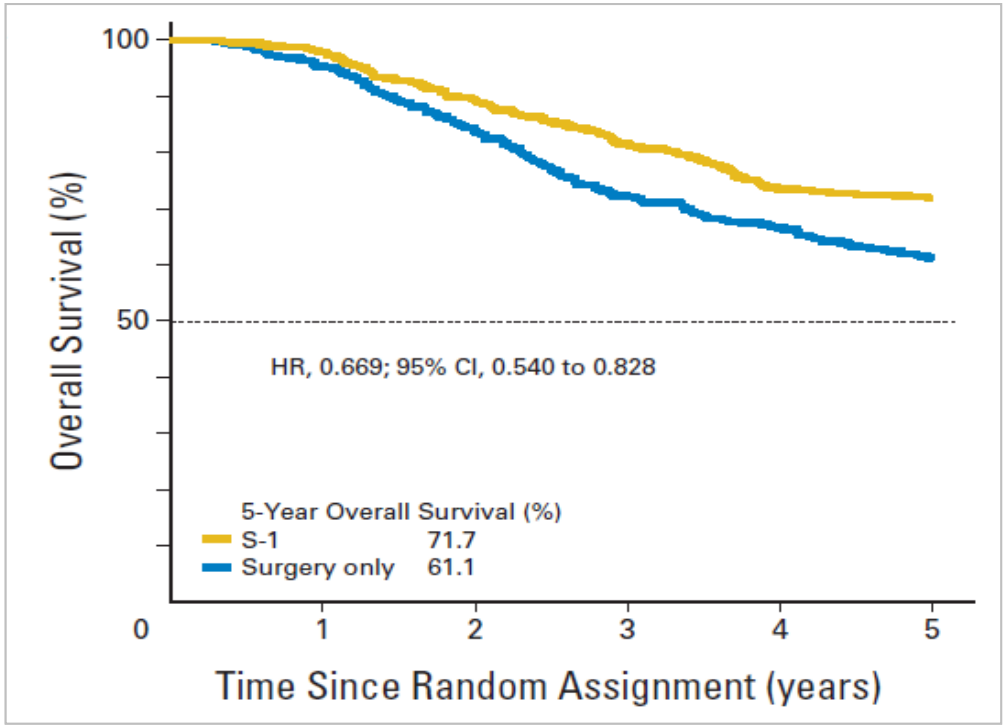
Post-operative eligible patients

- 1 year S1 (n=529)
- No further treatment (n=530)

Primary Endpoint
Overall survival
Secondary endpoints
Relapse free survival & Safety

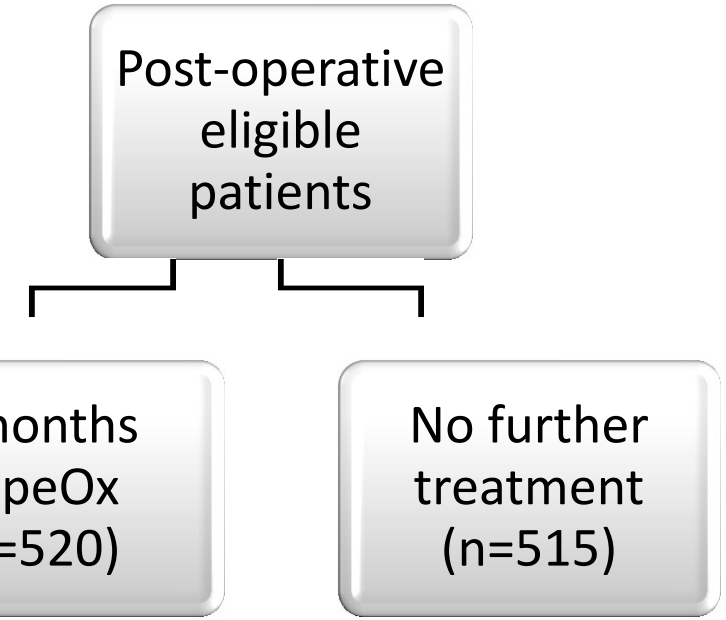
Update ESMO 2017 OPAS-1 study
6 months of S1 not inferior to 12 months

Updated 5 year survival S1 vs surgery alone
All patients 5 year OS 72% vs. 61%
Stage II 5 year OS 84% vs 71%
Stage IIIA 5 year OS 67% vs 57%
Stage IIIB 5 year OS 50% vs 44%



Sasako et al, J Clin Oncol. 2011 Nov 20;29(33):4387-93.

CLASSIC TRIAL



Primary Endpoint
3 year disease free survival
Secondary endpoints
Overall survival & safety

Eligibility criteria
Stage ≥ II, IIIA or IIIB gastric adenocarcinoma
D2 resection minimum

CLASSIC patient characteristics		
	Surgery alone	Chemo + surgery
Median age	56	56
Sex Male Female	 358 (70%) 157(30%)	 373 (72%) 147(28%)
Stage of cancer II III IV	 261 (51%) 253 (49%) 1 (<1%)	 253(49%) 266(51%) 0 (0%)

Bang et al, Lancet. 2012 Jan 28;379(9813):315-21.

CapeOx, capecitabine 1000 mg/m^2 bd D1-14 , plus oxaliplatin 130 mg/m^2 iv D1 q3wks

CLASSIC TRIAL

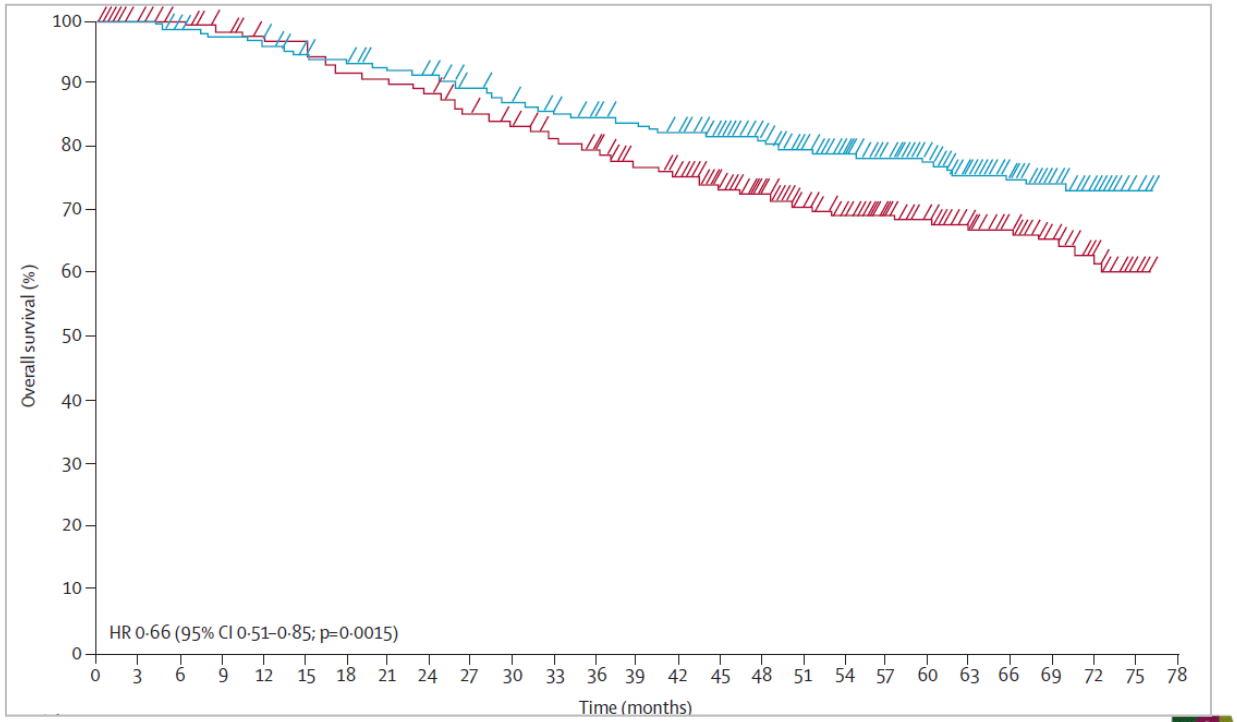
Post-operative eligible patients

6 months CapeOx (n=520)

No further treatment (n=515)

Primary Endpoint
3 year disease free survival
Secondary endpoints
Overall survival & safety

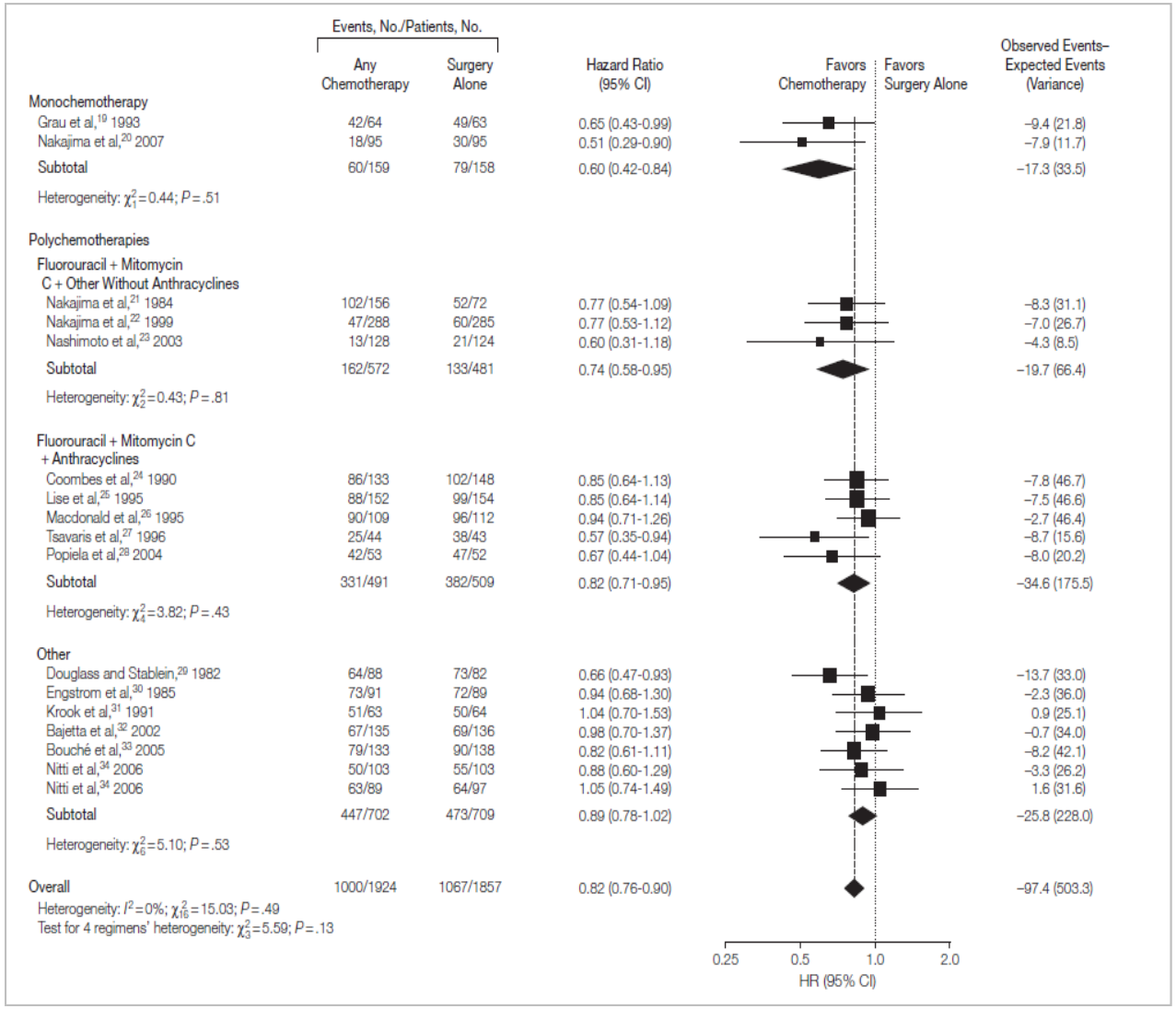
5 year updated survival CapeOx vs surgery alone
All patients 5 year OS 78% vs 69%
Stage II 5 year OS 88% vs 79%
Stage IIIA 5 year OS 70% vs 63%
Stage IIIB 5 year OS 66% vs 45% (compare ACTS GC 50% vs. 44%)



Noh et al, Lancet Oncol. 2014 Nov;15(12):1389-96.

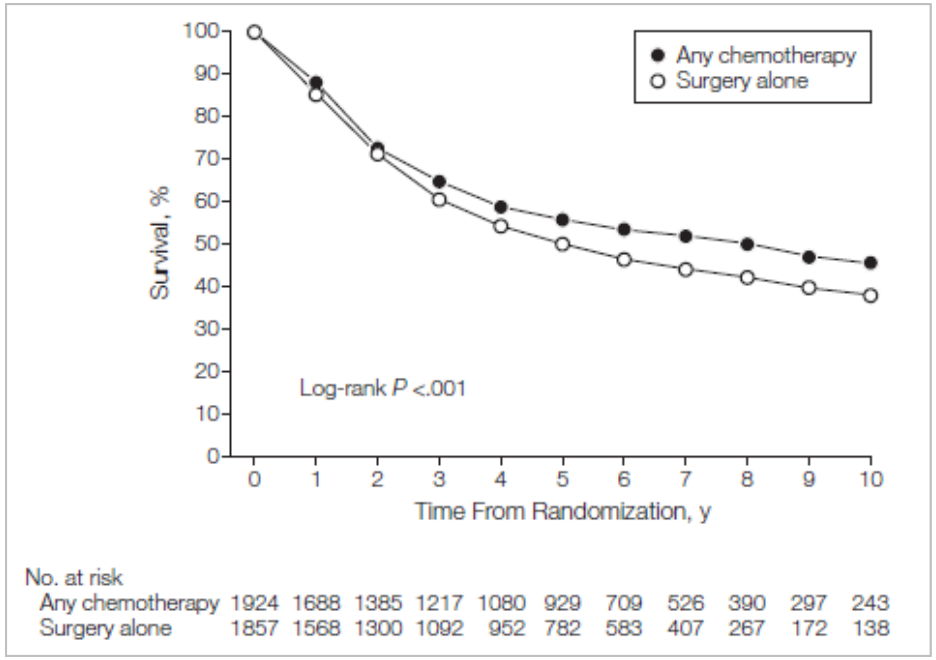
CapeOx, capecitabine 1000 mg/m^2 bd D1-14 , plus oxaliplatin 130 mg/m^2 iv D1 q3wks

ADJUVANT CHEMOTHERAPY FOR NON-ASIAN PATIENTS



Neoadjuvant or peri-operative chemotherapy is preferred due to the downstaging effects associated with this.

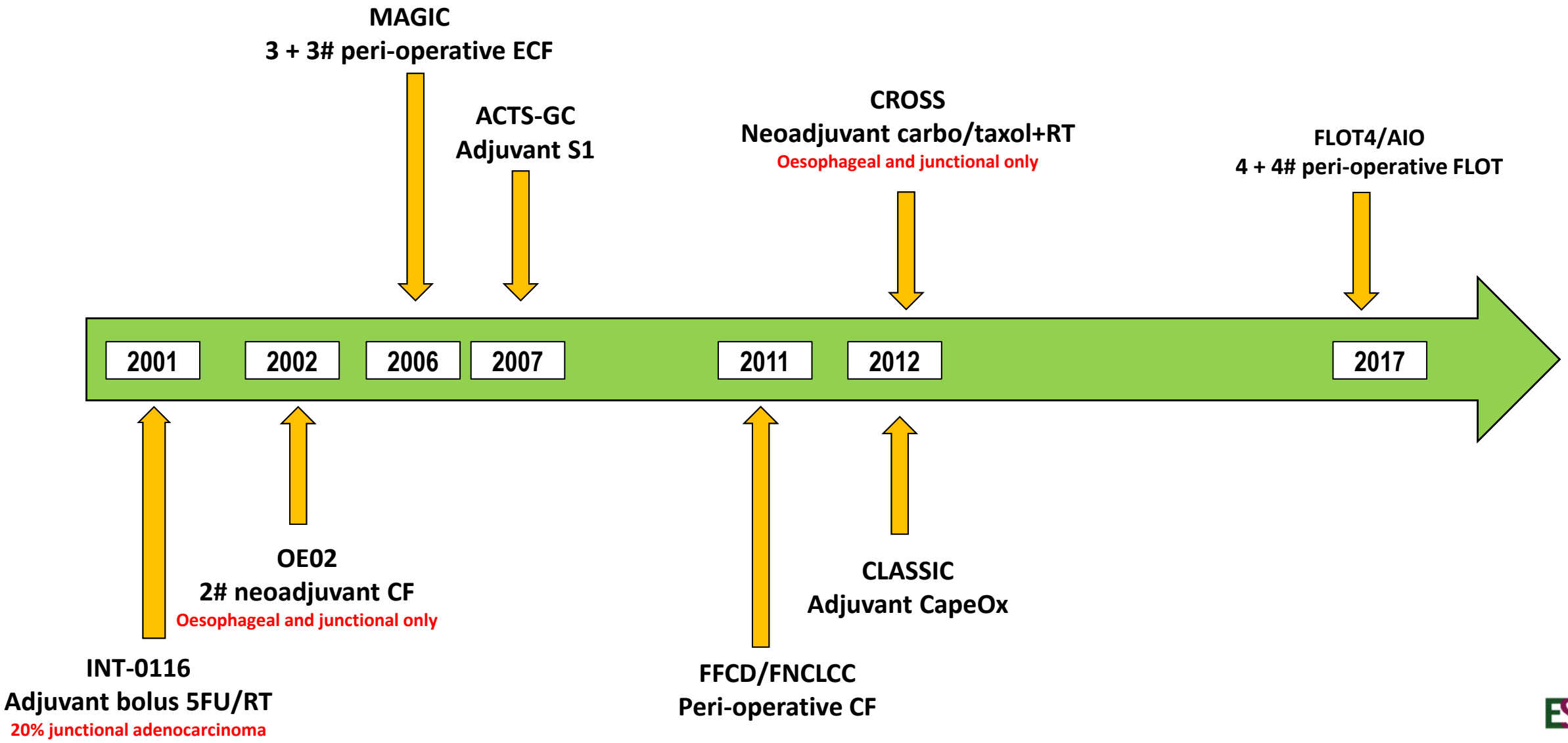
The GASTRIC group meta-analysis suggests a 5.8% absolute OS benefit at 5 years (55.3% to 49.6%) for patients treated with adjuvant chemotherapy .



Paoletti et al, JAMA. 2010 May 5;303(17):1729-37.

Since 2006: 5-Y OS nearly doubled compared with surgery alone

EVOLUTION OF (NEO)ADJUVANT TREATMENT 2002 - 2017



critics trial

Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial

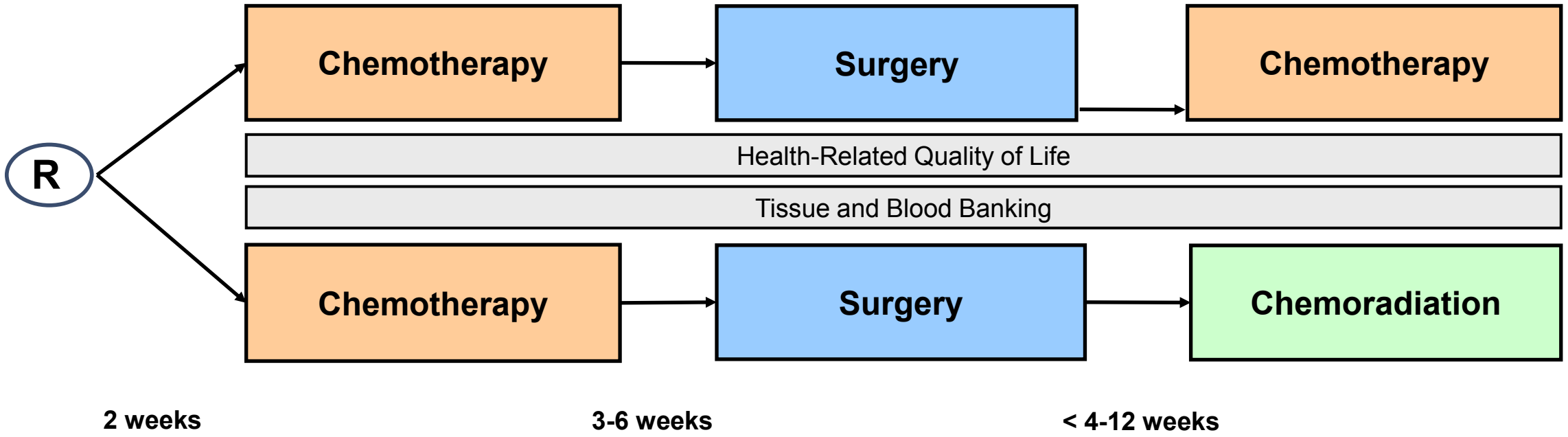
Annemieke Cats, Edwin P M Jansen*, Nicole C T van Grieken, Karolina Sikorska, Pehr Lind, Marianne Nordsmark, Elma Meershoek-Klein Kranenbarg, Henk Boot, Anouk K Trip, H A Maurits Swellengrebel, Hanneke W M van Laarhoven, Hein Putter, Johanna W van Sandick, Mark I van Berge Henegouwen, Henk H Hartgrink, Harm van Tinteren, Cornelis J H van de Velde†, Marcel Verheij†, for the CRITICS investigators‡*

AIM:

To improve survival by combining optimal local and systemic therapy

Lancet Oncol 2018; 19: 616–28

study design



Stratification for:

- ***Center***
- ***Histological type (intestinal, diffuse, mixed, unknown)***
- ***Tumor localisation (gastro-oesophageal junction, proximal, mid, distal stomach)***

Nikken et al. BMC Cancer 2011

treatment details

Chemotherapy: Pre-operative and post-operative: 3x ECC or EOC q 3 wks

Epirubicin 50 mg/m^2 d1, Cisplatin 60 mg/m^2 d1, Capecitabine 1000 mg/m^2 bid days 1-14 *Epirubicin 50 mg/m^2 d1, Oxaliplatin 130 mg/m^2 d1 Capecitabine 625 mg/m^2 bid days 1-21*

Surgery: (Sub)total gastrectomy or oesophagocardiac resection *en bloc* with N1 and N2 lymph nodes

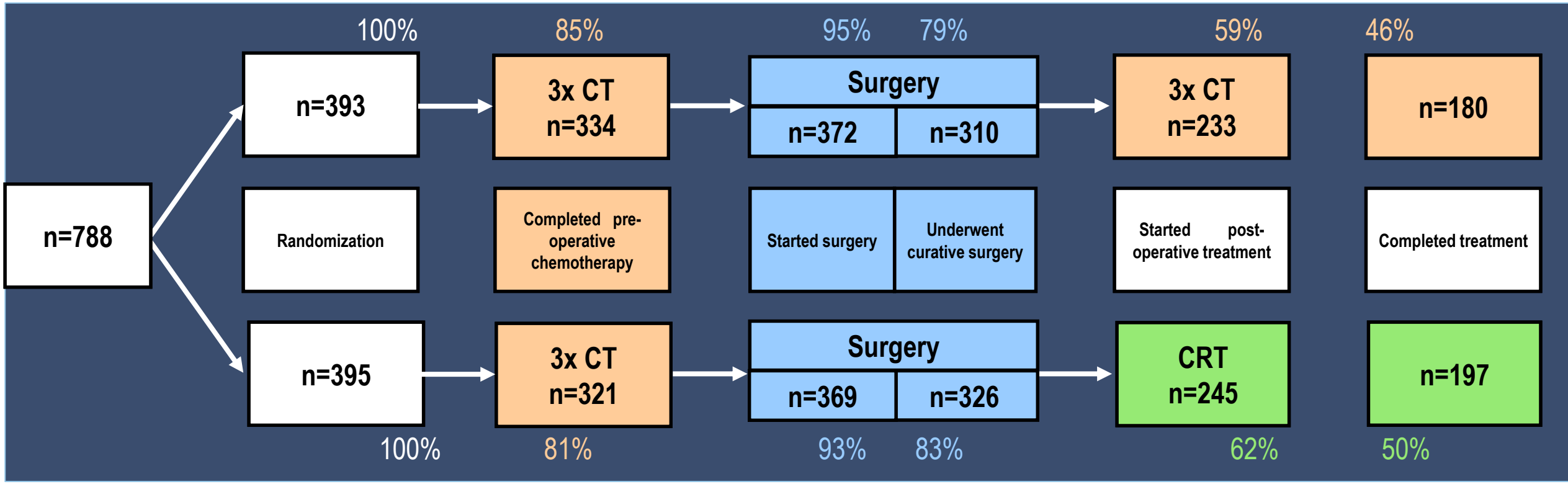
D1$^+$ resection: lymph node stations 1-9 and 11; no splenectomy or pancreatectomy
Removal of ≥15 lymph nodes

Chemoradiation: Post-operative: 45 Gy in 25 fractions combined with CC

3D-CRT or IMRT; CTV includes tumor bed, anastomoses, draining lymph node stations *Concurrent during RT: Cisplatin 20 mg/m^2 weekly; Capecitabine 575 mg/m^2 bid / ddwd*

Verheij et al. ASCO 2016, Cats et al. Lancet Oncol 2018

study profile



Oats et al. Lancet Oncol 2018

Main Reasons for no post-operative therapy

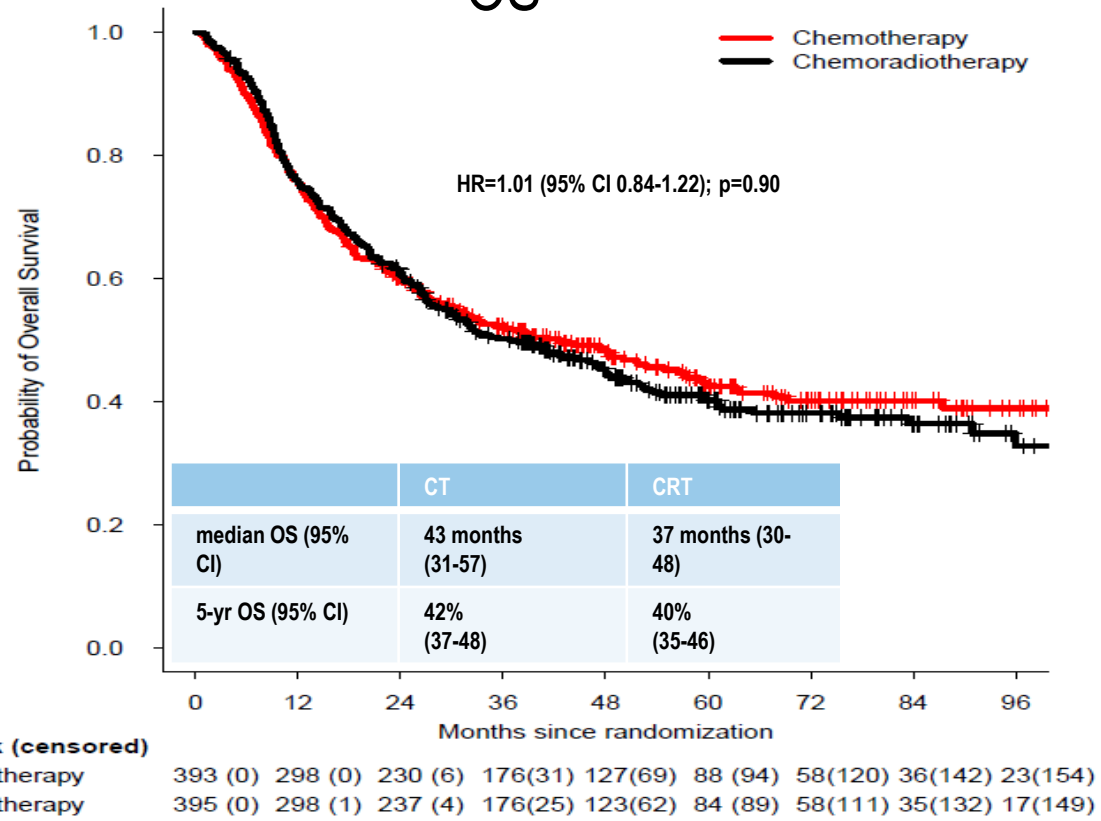
	CT *n* = 393	CRT *n* = 395
	***n* (%)**	***n* (%)**
Progressive or irresectable disease	81 (21)	67 (17)
Death	17 (4)	10 (3)
Treatment-related toxicity	28 (7)	34 (9)
Refusal or poor condition	22 (6)	24 (6)

CT = chemotherapy
CRT = chemoradiotherapy

Hulshof et al. Lancet Oncol 2018

survival

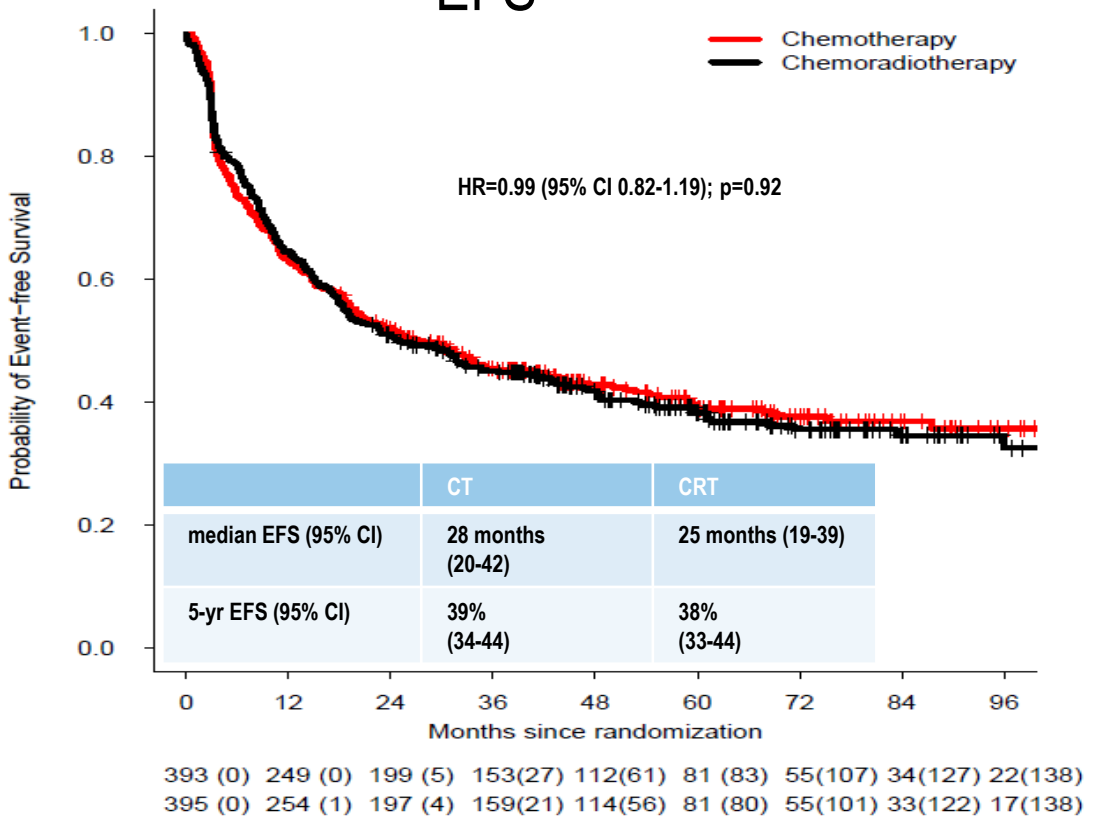
OS



	CT	CRT
median OS (95% CI)	43 months (31-57)	37 months (30-48)
5-yr OS (95% CI)	42% (37-48)	40% (35-46)

Number at risk (censored)									
Chemotherapy	393 (0)	298 (0)	230 (6)	176(31)	127(69)	88 (94)	58(120)	36(142)	23(154)
Chemoradiotherapy	395 (0)	298 (1)	237 (4)	176(25)	123(62)	84 (89)	58(111)	35(132)	17(149)

EFS



	CT	CRT
median EFS (95% CI)	28 months (20-42)	25 months (19-39)
5-yr EFS (95% CI)	39% (34-44)	38% (33-44)

Chemotherapy	393 (0)	249 (0)	199 (5)	153(27)	112(61)	81 (83)	55(107)	34(127)	22(138)
Chemoradiotherapy	395 (0)	254 (1)	197 (4)	159(21)	114(56)	81 (80)	55(101)	33(122)	17(138)

rationale critics II

PATIENT COMPLIENCE IN (NEO)ADJUVANT STUDIES IN GASTRIC CANCER

Studie	Behandelgroep	Behandeling afgerond (%)
SWOG	S→CRT	64%
MAGIC	CT→S→CT	42%
ACTS-GC	S→CT	66%
CLASSIC	S→CT	67%
ARTIST	S→CT	75%
	S→CRT	82%
ST03	CT→S→CT	40%
	CT+B→S→CT+B	37%
TOPGEAR part 1	CT→S→CT	58%
	CT→CRT→S→CT	45%
FLOT4-AIO	CT→S→CT (3xECF/ECX)	37%
	CT→S→CT (4xFLOT)	50%

Rationale

CONCEPTS

- Pre-operative treatment is associated with better patient compliance than post-operative regimens
- Pre-operative treatment increases the likelihood of disease downsizing/ downstaging and radical R0 resections
- Pre-operative paclitaxel/carboplatin-based concurrent chemotherapy and DOC chemotherapy are effective, feasible and safe regimens

AIM

- To optimize pre-operative treatment resectable gastric cancer

CROSS STUDY

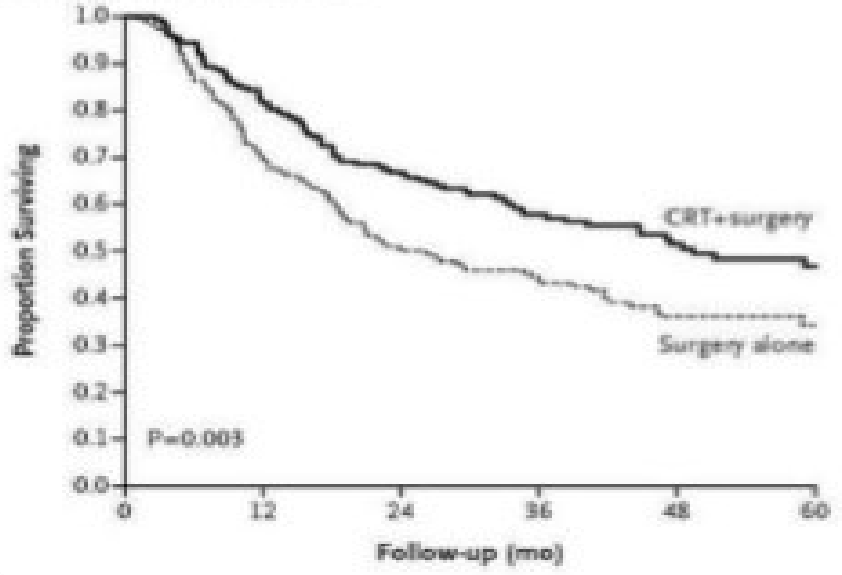
Dutch study

Baseline characteristics

	Neoadjuvant chemoradiotherapy plus surgery (n=178)	Surgery alone (n=188)
Age, years	60 (55–67)	60 (53–66)
Sex		
Women	44 (25%)	36 (19%)
Men	134 (75%)	152 (81%)
Tumour histology		
Squamous cell carcinoma	41 (23%)	43 (23%)
Adenocarcinoma	134 (75%)	141 (75%)
Could not be established	3 (2%)	4 (2%)
Tumour length, cm	4 (3–6)	4 (3–6)
Tumour location		
Proximal third oesophagus	4 (2%)	4 (2%)
Middle third oesophagus	25 (14%)	24 (13%)
Distal third oesophagus	104 (58%)	107 (57%)
Oesophagogastric junction	39 (22%)	49 (26%)
Missing data	6 (3%)	4 (2%)

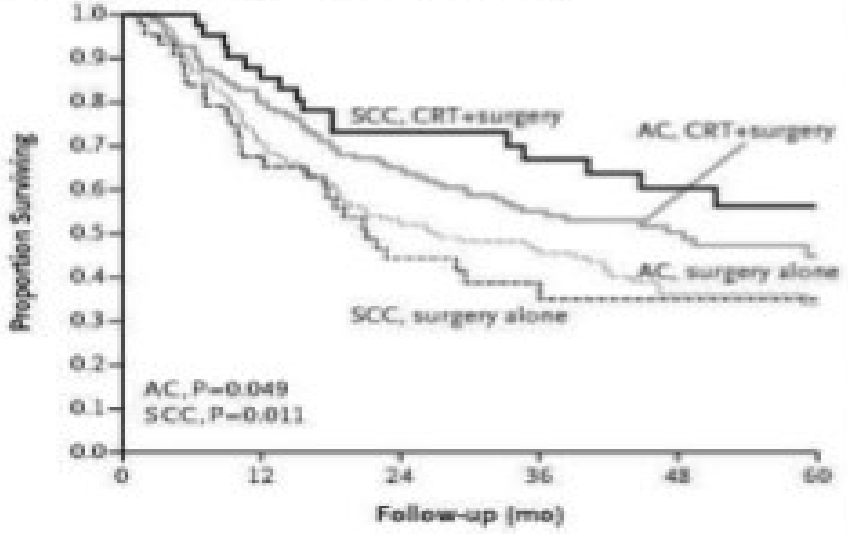
Survival in CROSS study

A Survival According to Treatment Group



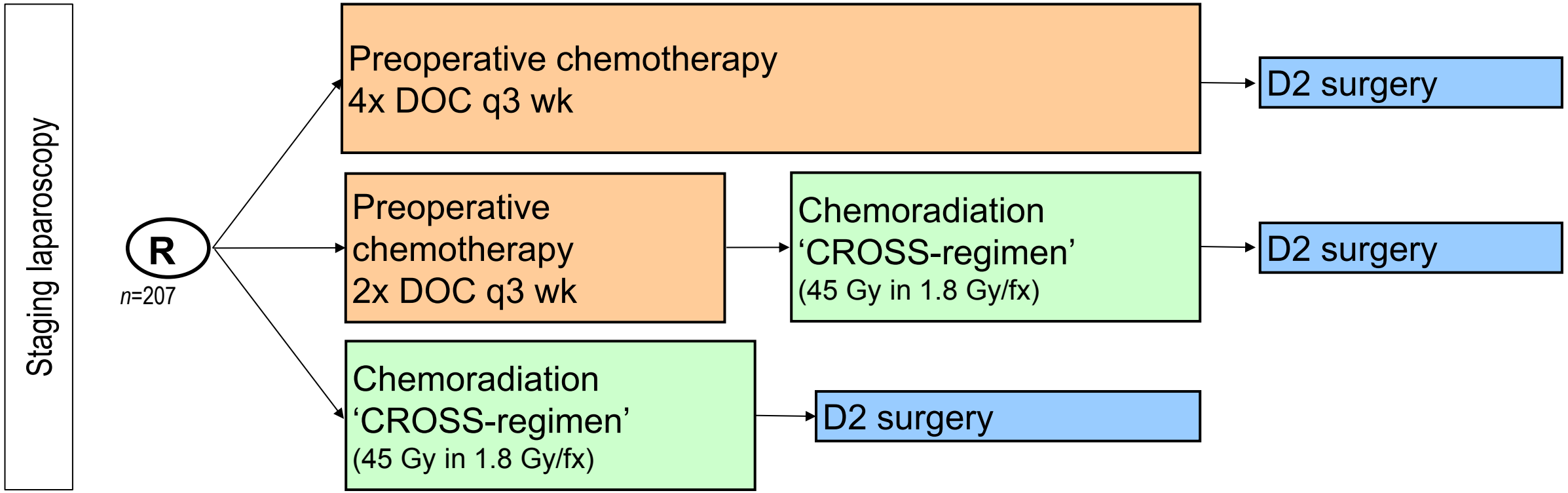
No. at Risk						
CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45

Survival According to Tumor Type and Treatment Group



No. at Risk						
AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

CRITICS II



DOC: docetaxel 50 mg/m² d1, oxaliplatin 100 mg/m² d1, Capecitabine 850 mg/m² bid days 1-14
CROSS: carboplatin AUC 2, paclitaxel 50 mg/m² 5x weekly during chemoradiotherapy

CONCLUSIONS

For treatment of resectable gastric and gastroesophageal cancer:

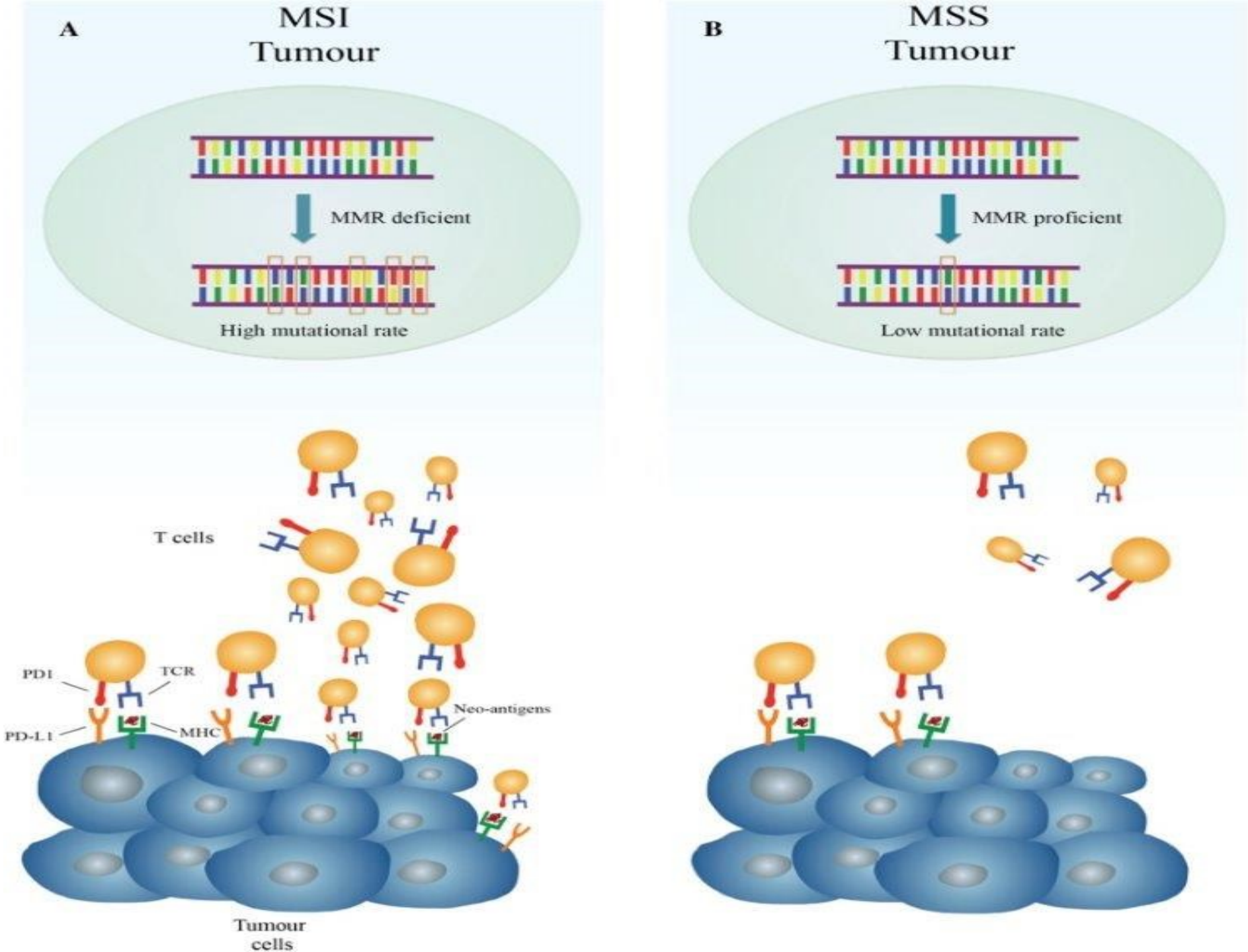
Correct staging and multidisciplinary approach are essential.

For **gastric** adenocarcinoma **peri-operative chemotherapy** is preferred.

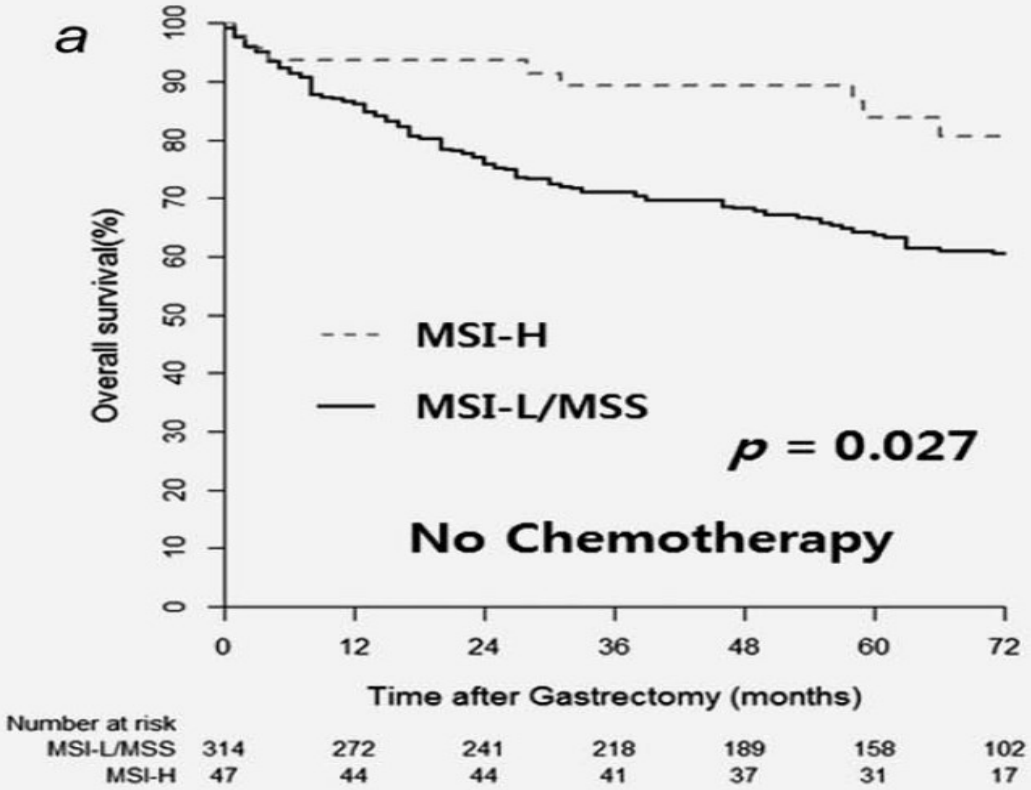
- adjuvant chemotherapy and chemoradiotherapy are possible if a patient has not had any treatment before surgery

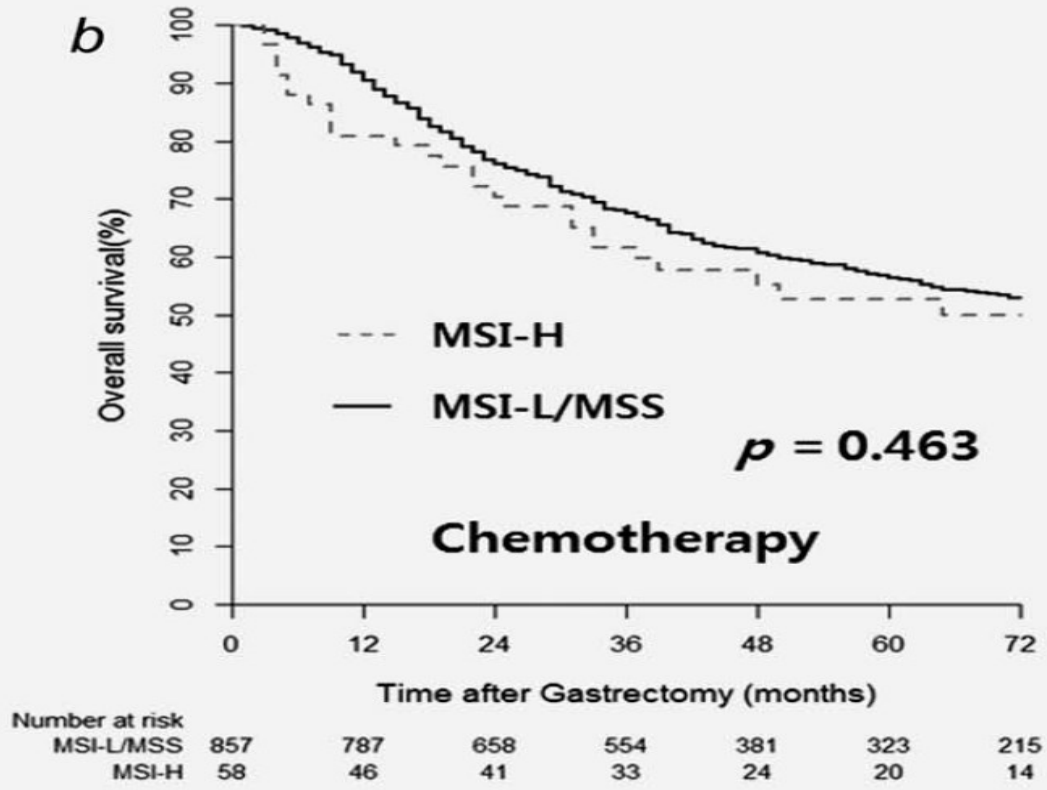
For oesophageal and gastroesophageal junction adenocarcinoma **peri-operative chemotherapy** or **neoadjuvant chemoradiotherapy** are both validated options.

FUTURE DIRECTIONS


A
MSI
Tumour
MMR deficient
High mutational rate
B
MSS
Tumour
MMR proficient
Low mutational rate
T cells
PD1
TCR
PD-L1
MHC
Neo-antigens
Tumour
cells

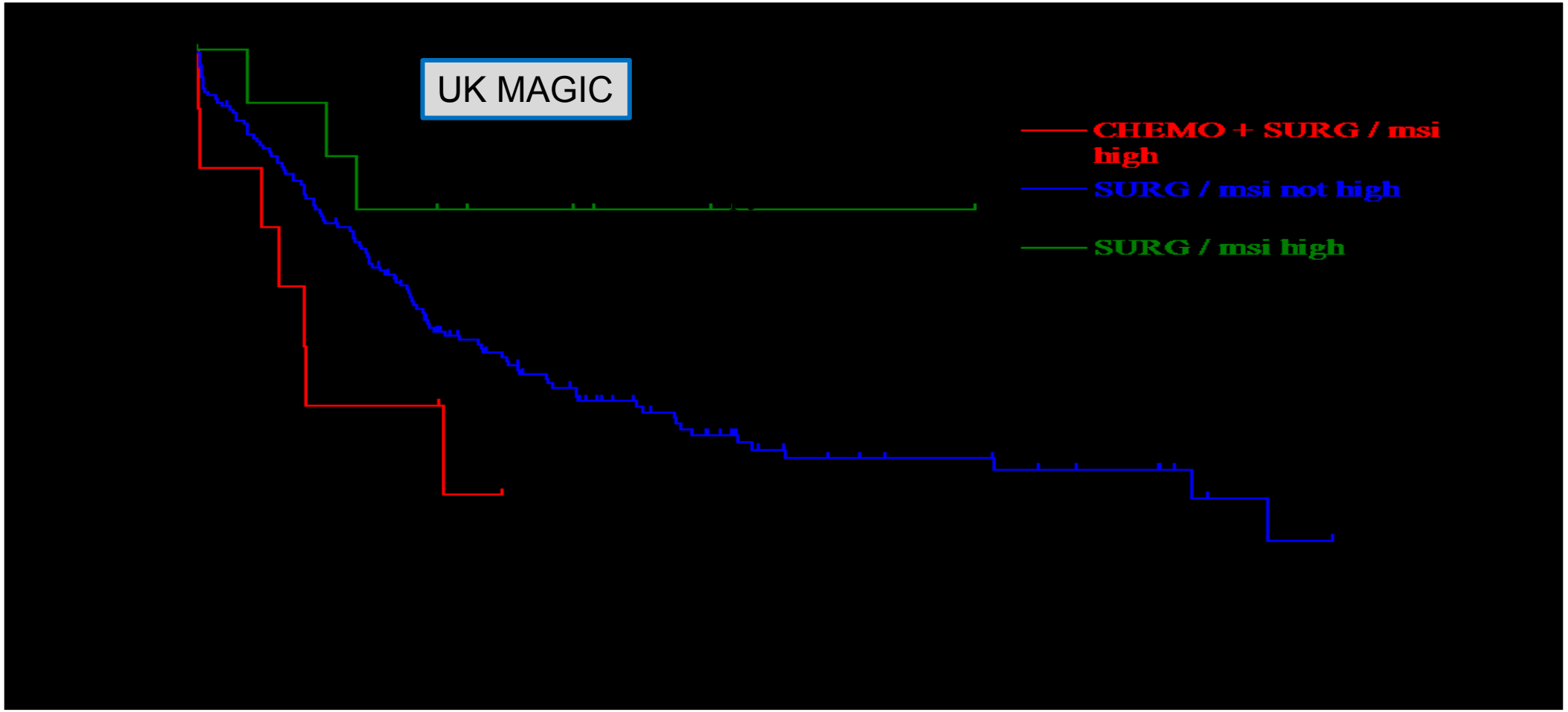
MSI-H Gastric Cancer – Postoperative Chemotherapy





Kim SY et al. *Int. J. Cancer* 2015; 137: 819–825

MSI-H Gastric Cancer – Perioperative Chemotherapy



Smyth E et al. *JAMA Oncol* 2017 Sep 1;3(9):1197-1203

MSI-H Gastric Cancer Stage IV

Response to Pembrolizumab according to MSI Status (n=174)

Response[a]	MSI-High (n=7)		Non-MSI-High (n=167)	
	%	95% CI	%	95% CI
ORR	**57.1**	18.4-90.1	**9.0**	5.1-14.4
CR	14.3	0.4-57.9	2.4	0.7-6.0
PR	42.9	9.9-81.6	6.6	3.3-11.5
DCR	71.4	29.0-96.3	22.2	16.1-29.2

Fuchs CS et al. *JAMA Oncol.* 2018 Mar 15. doi: 10.1001/jamaoncol.2018.0013. [Epub ahead of print]

Perioperative Projects Gastric Cancer

EORTC Gastrointestinal Tract Cancer Group
The future of cancer therapy

Inclusion criteria :
to be defined in detail, e.g.
- Pt eligible for perioperative treatment and potentially eligible for the clinical trials
-Availability of sufficient tumor material
- Informed consent for screening

Step 1:

HER-2+
MSI-
testing

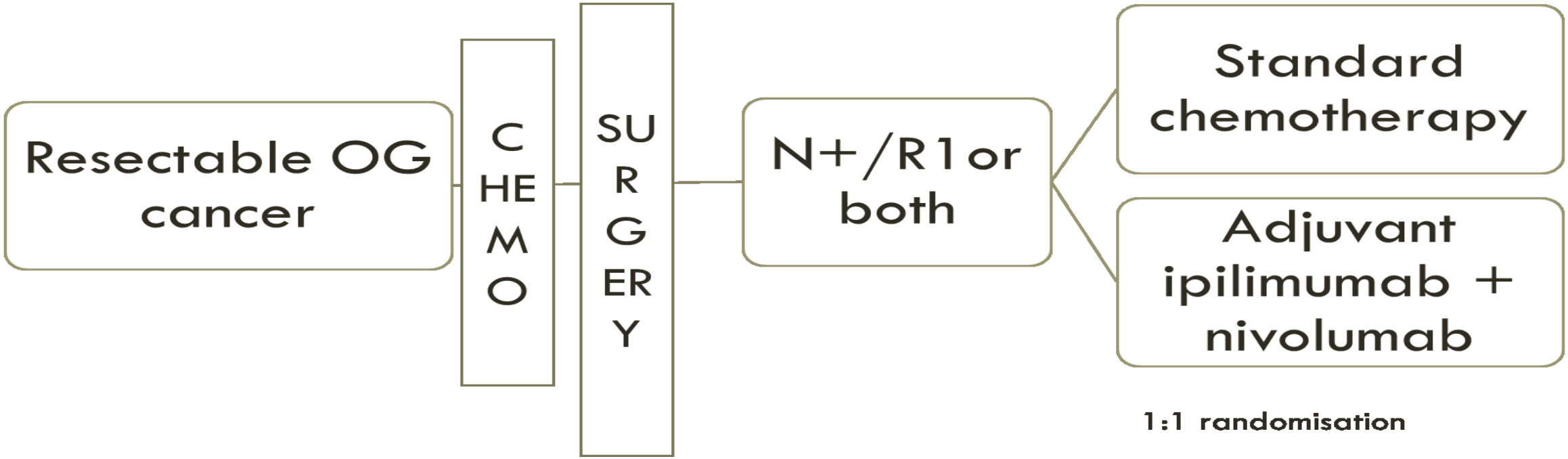
Step 2: proposition of a clinical trial or biobanking

If HER-2 positive	« INNOVATION »
If MSI-high	Immunotherapy study
…….	…..screening for other biomarkers and further trials may be added in the future
Poor Chemo Response	Adjuvant Immunotherapy

Immuno Therapy for Patients at High Risk of Relapse

EORTC Study 1707 VESTIGE (design)

EORTC
European Organisation for Research and Treatment of Cancer
50 years of Progress Against Cancer



Lordick F et al, *EORTC GI Group* 2017

DANK

Voor bijdrage aan deze presentatie

- **Elizabeth C. Smyth,**
- Department of Gastrointestinal Oncology and Lymphoma, Royal Marsden Hospital, London and Sutton, United Kingdom

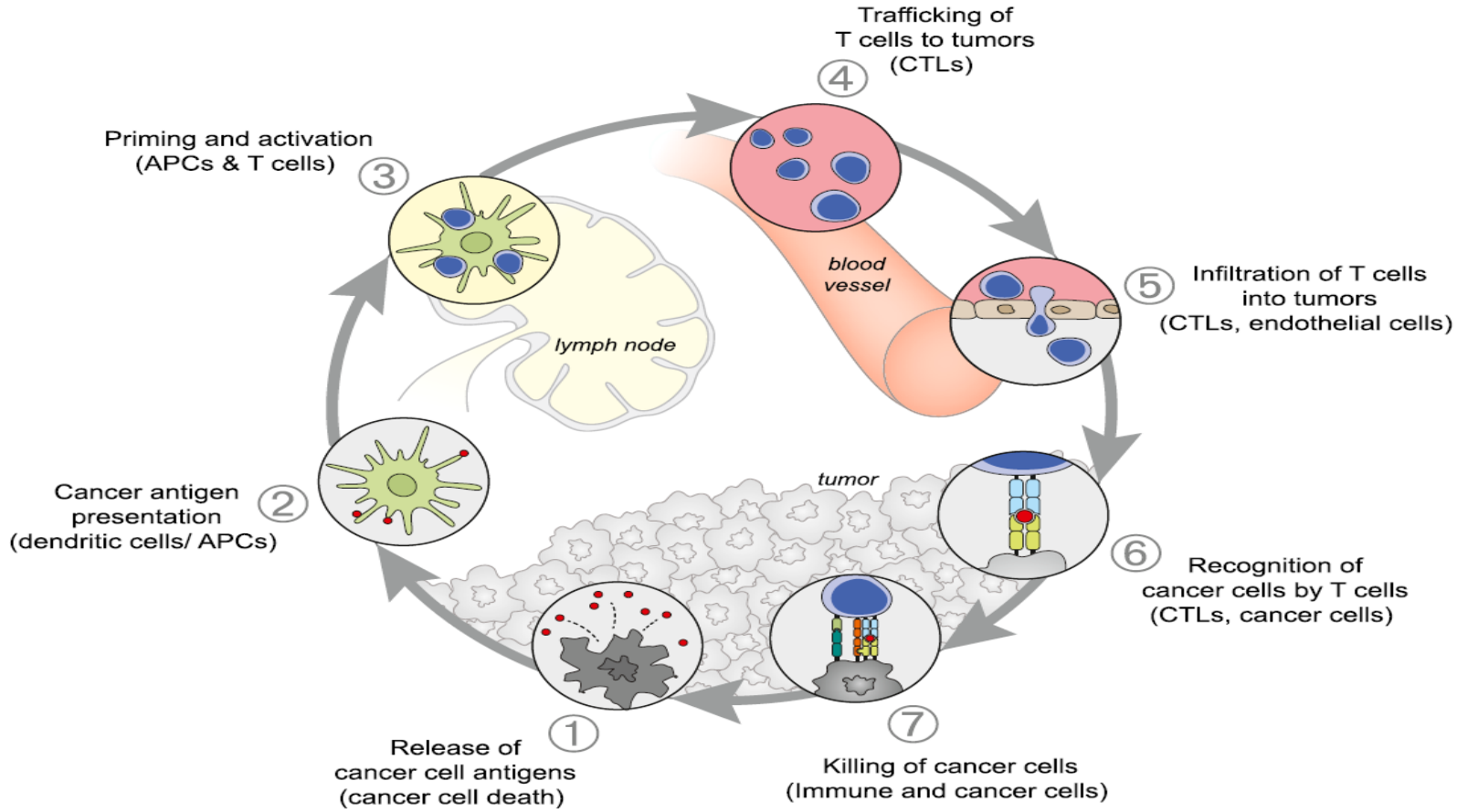
- **Florian Lordick**
  Professor of Oncology
  Director University Cancer Center Leipzig (UCCL)

- **Annemieke Cats**
- Department gastrointestinal Oncology
- Netherlands Cancer Institute

Back up slices

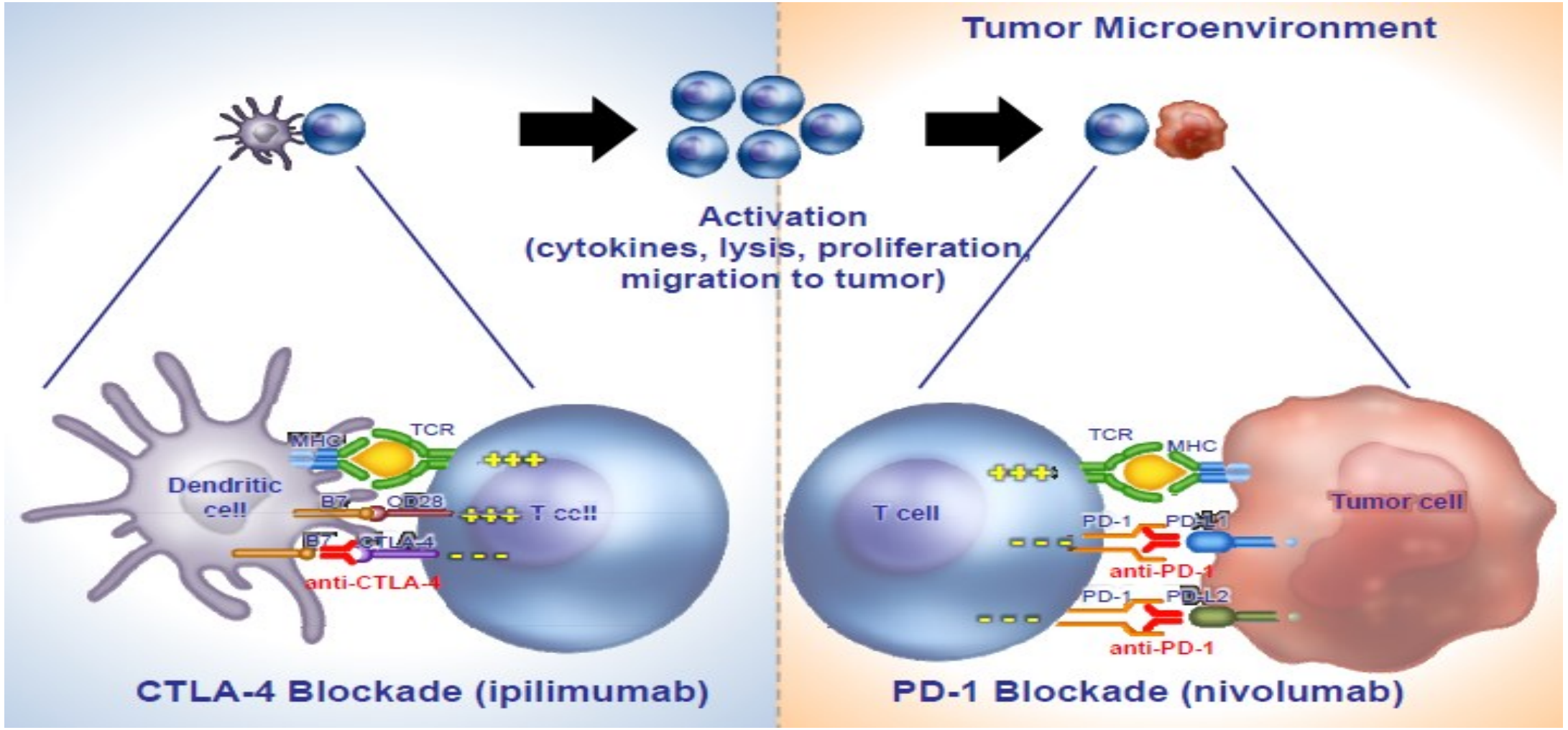
Immune-Therapy

The immune therapy cycle

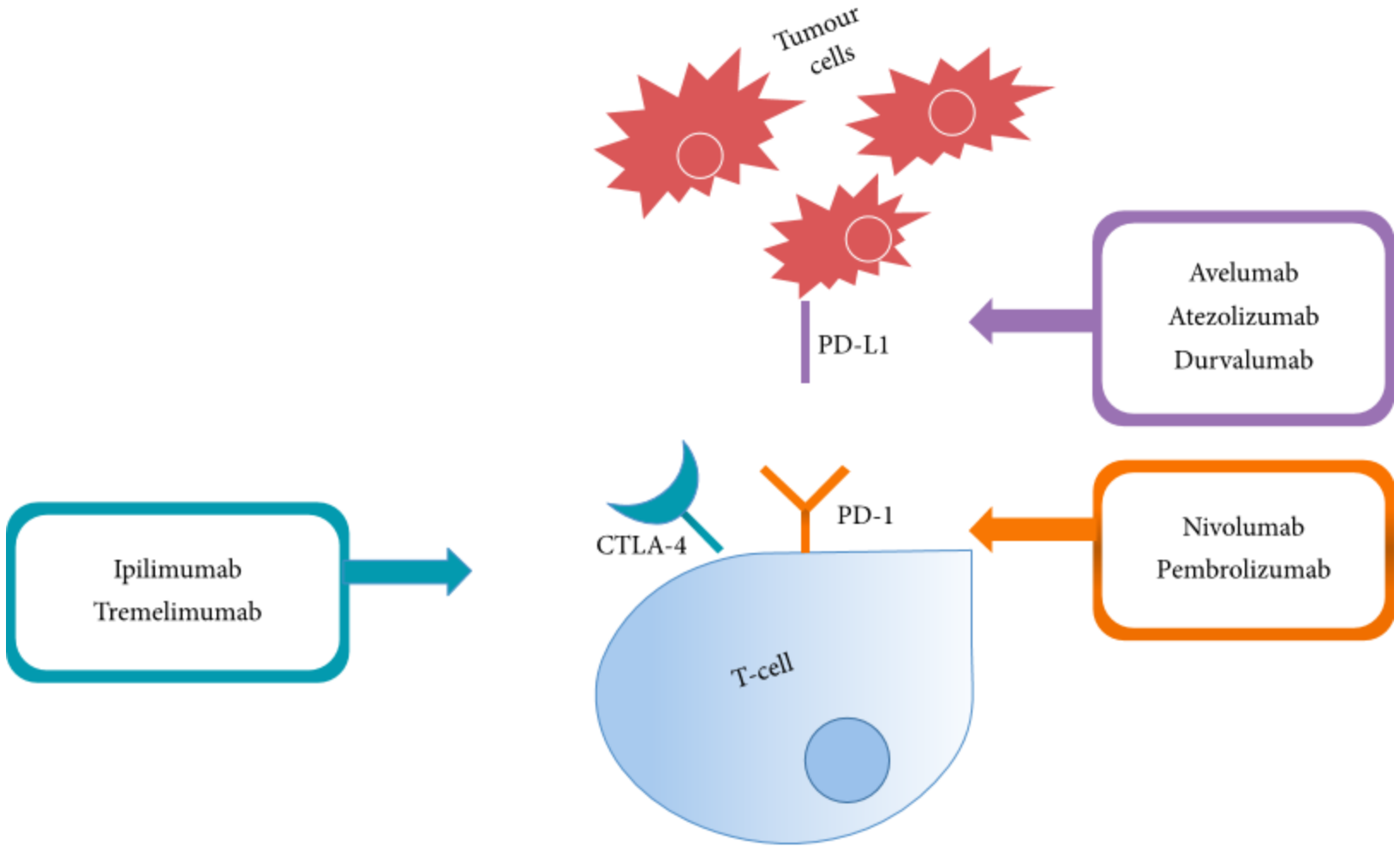


Chen & Mellman, *Immunity* 2013; 39: 1-10

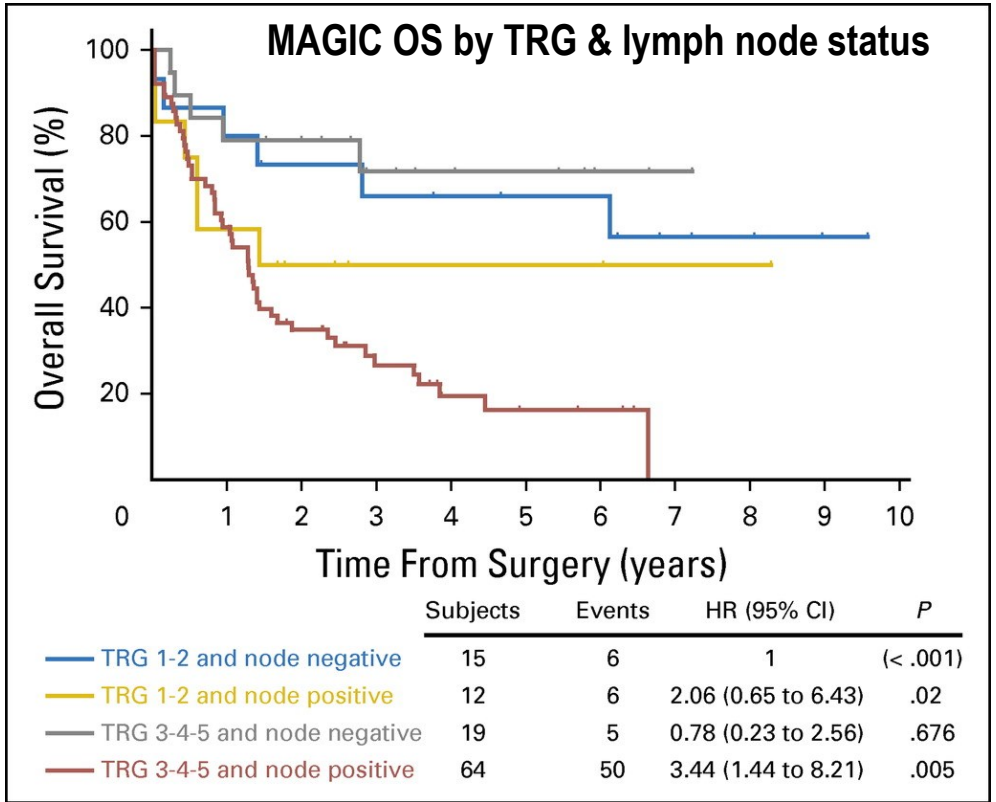
Immune-Therapy



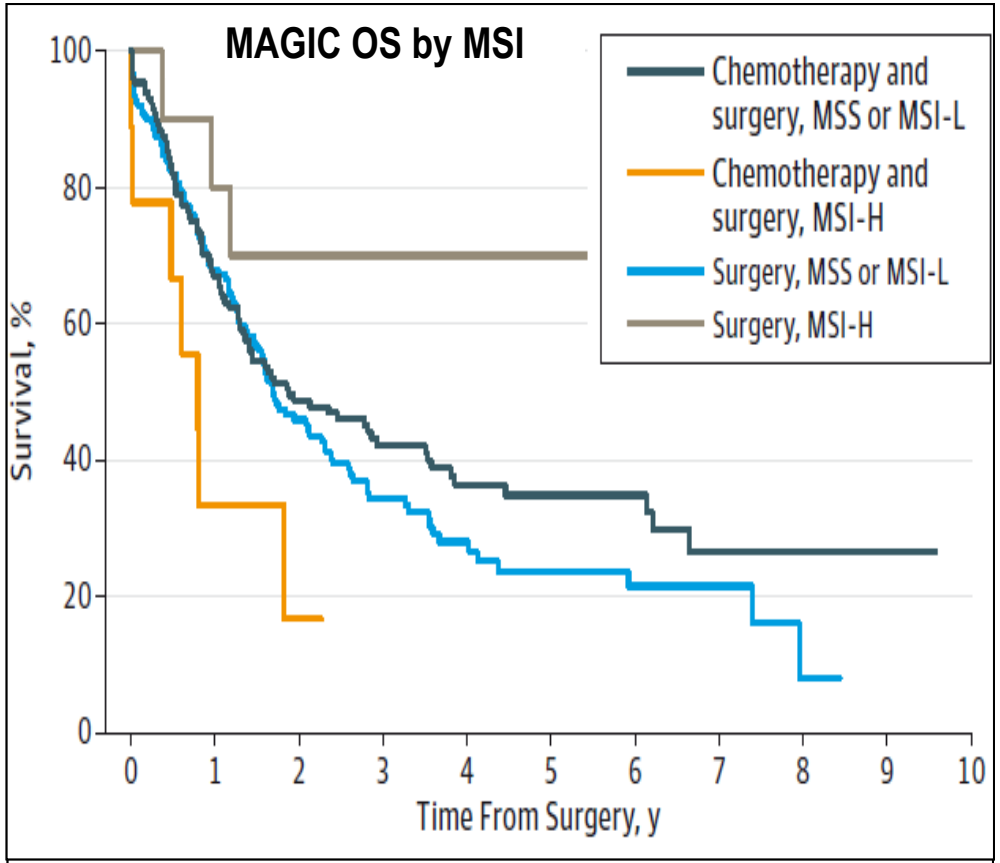
Wolchok JD et al., *N Engl J Med*, 2013, 369: 122-33


Tumour cells
PD-L1
Avelumab
Atezolizumab
Durvalumab
CTLA-4
PD-1
Ipilimumab
Tremelimumab
Nivolumab
Pembrolizumab
T-cell

RISK STRATIFICATION AND PERSONALISED TREATMENT



Limited pathological response and post operative lymph node metastases identify patients with a poor prognosis following peri-operative chemotherapy

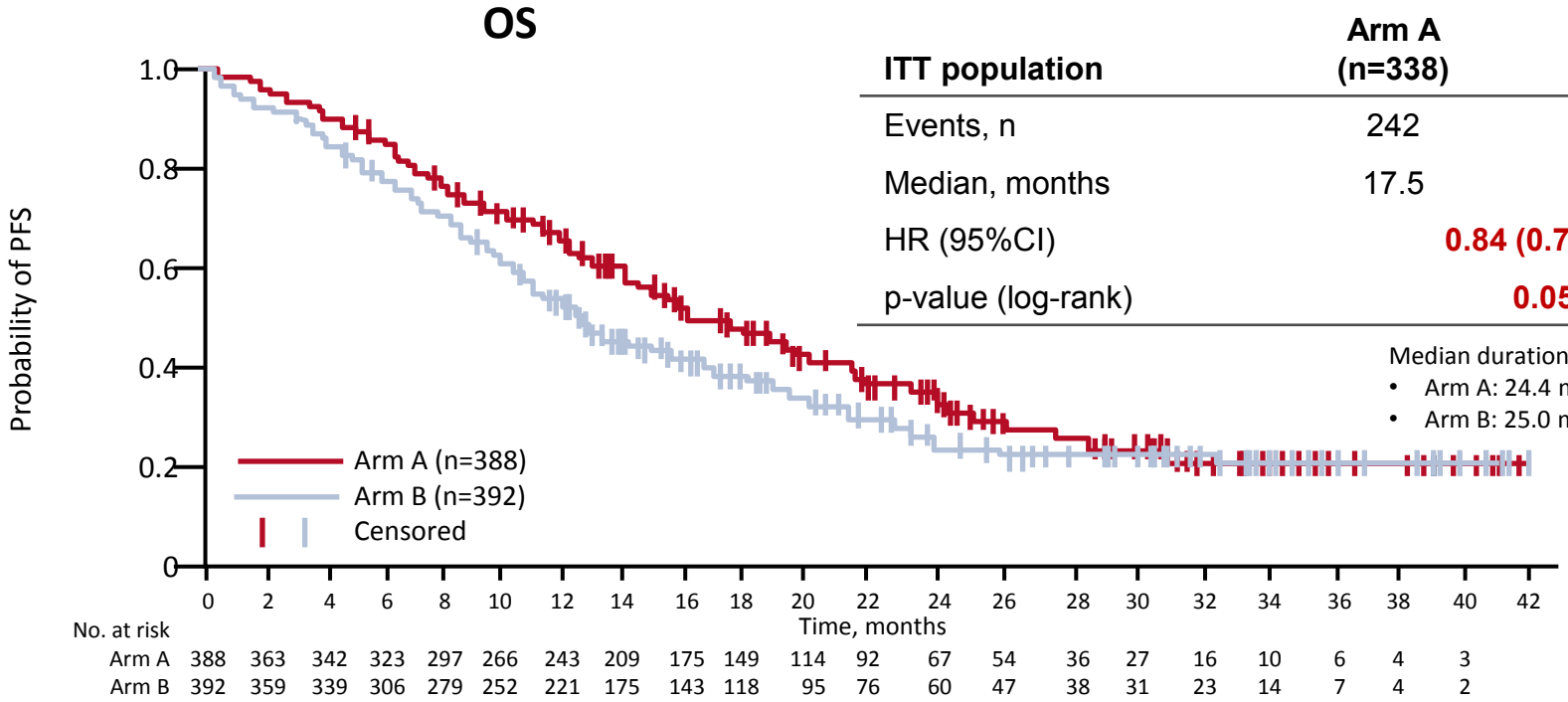


MSI-H (microsatellite unstable) gastric cancer does not benefit from peri-operative chemotherapy

In future, trials might be guided by these and other emerging biomarkers to determine best treatment for each patient

Smyth et al, J Clin Oncol. 2016 Aug 10;34(23):2721-7. Smyth et al, JAMA Oncol. 2017 Sep 1;3(9):1197-1203.

Pertuzumab – Trastuzumab – JACOB Study



ITT population	Arm A (n=338)	Arm B (n=392)
Events, n	242	262
Median, months	17.5	14.2
HR (95%CI)	**0.84 (0.71, 1.00)**	
p-value (log-rank)	**0.0565**	

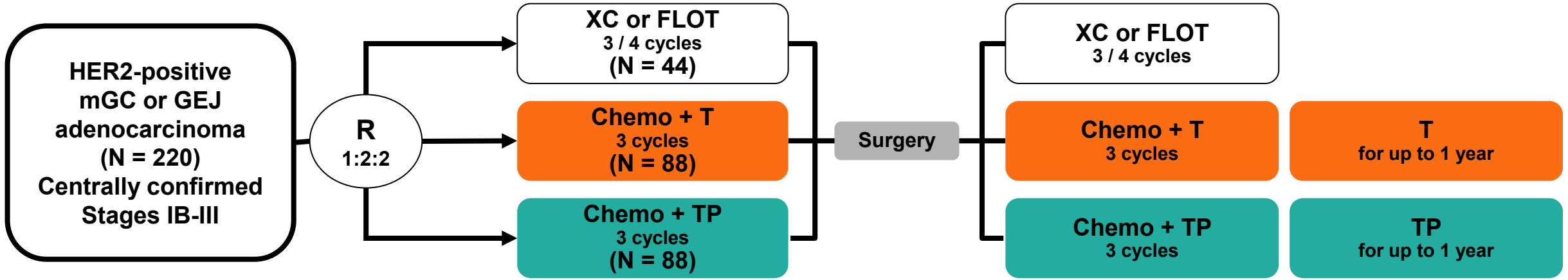
Median duration of survival follow-up
- Arm A: 24.4 months (min–max 22.3–26.1)
- Arm B: 25.0 months (min–max 22.3–28.9)

	Arm A (n=388)	Arm B (n=392)	HR (95%CI)
mPFS, months	8.5	7.0	0.73 (0.62, 0.86)
Response rate (%)	56.7	48.3	Difference 8.4 (0.9, 15.9)

Tabernero J et al. Ann Oncol 2017;28(Suppl 5):Abstr 616O

Perioperative

INNOVATION study



T: Trastuzumab; P: Pertuzumab

- **Primary endpoint:** histopathological near complete response (<10% viable tumour cells) after neoadjuvant therapy
- **Stratification:** histological subtype (intestinal/non-intestinal); Korea versus Europe; stage II versus III; node positive versus node negative