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

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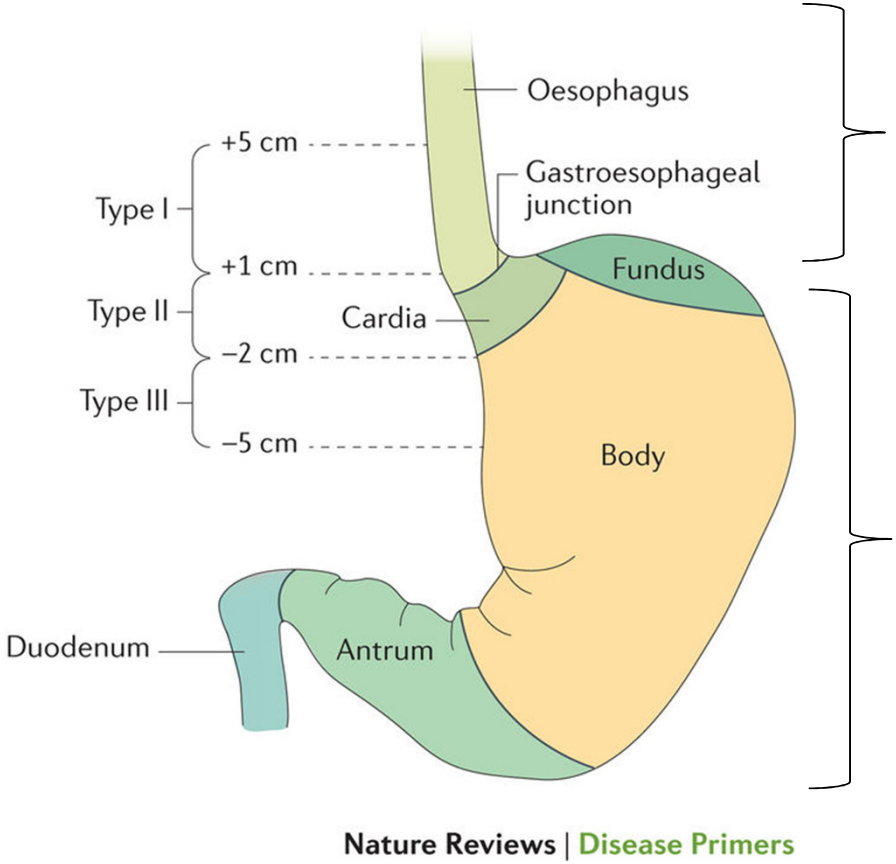
ESMO Gastric Cancer Preceptorship Valencia 2018

DISCLOSURES

Honoraria

BMS, Celgene, Five Prime Therapeutics, Servier, Gritstone Oncology

GASTRIC AND GASTROESOPHAGEAL CANCER NOMENCLATURE



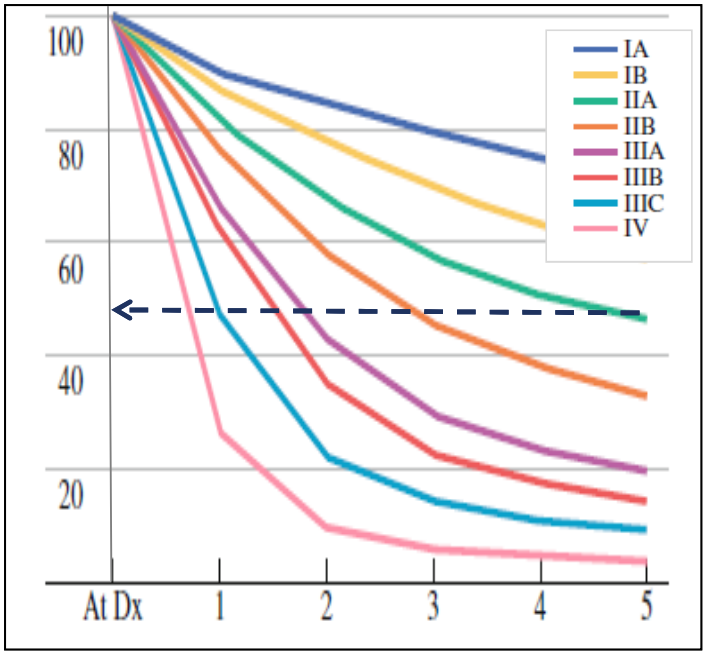
Lower oesophageal, gastroesophageal junction adenocarcinoma
→ ESMO Oesophageal Cancer Guidelines

Gastric cancer
→ ESMO Gastric Cancer Guidelines

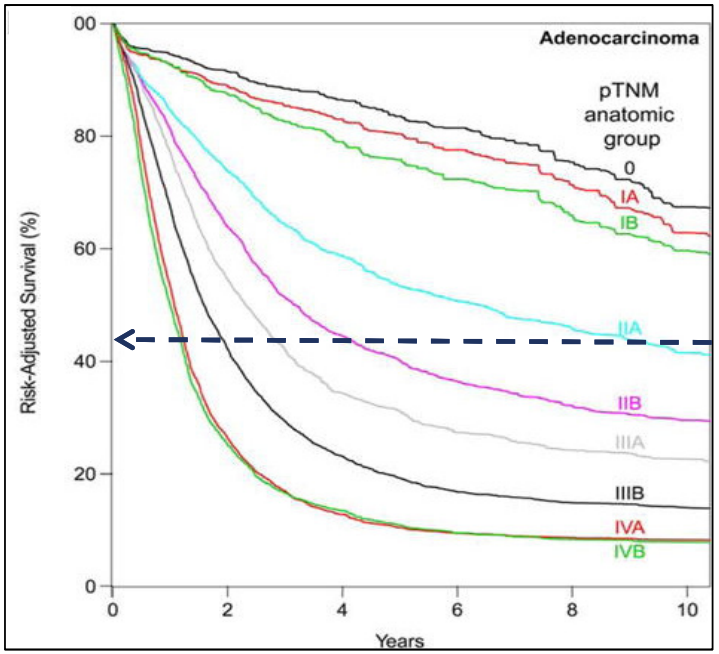
ESMO

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

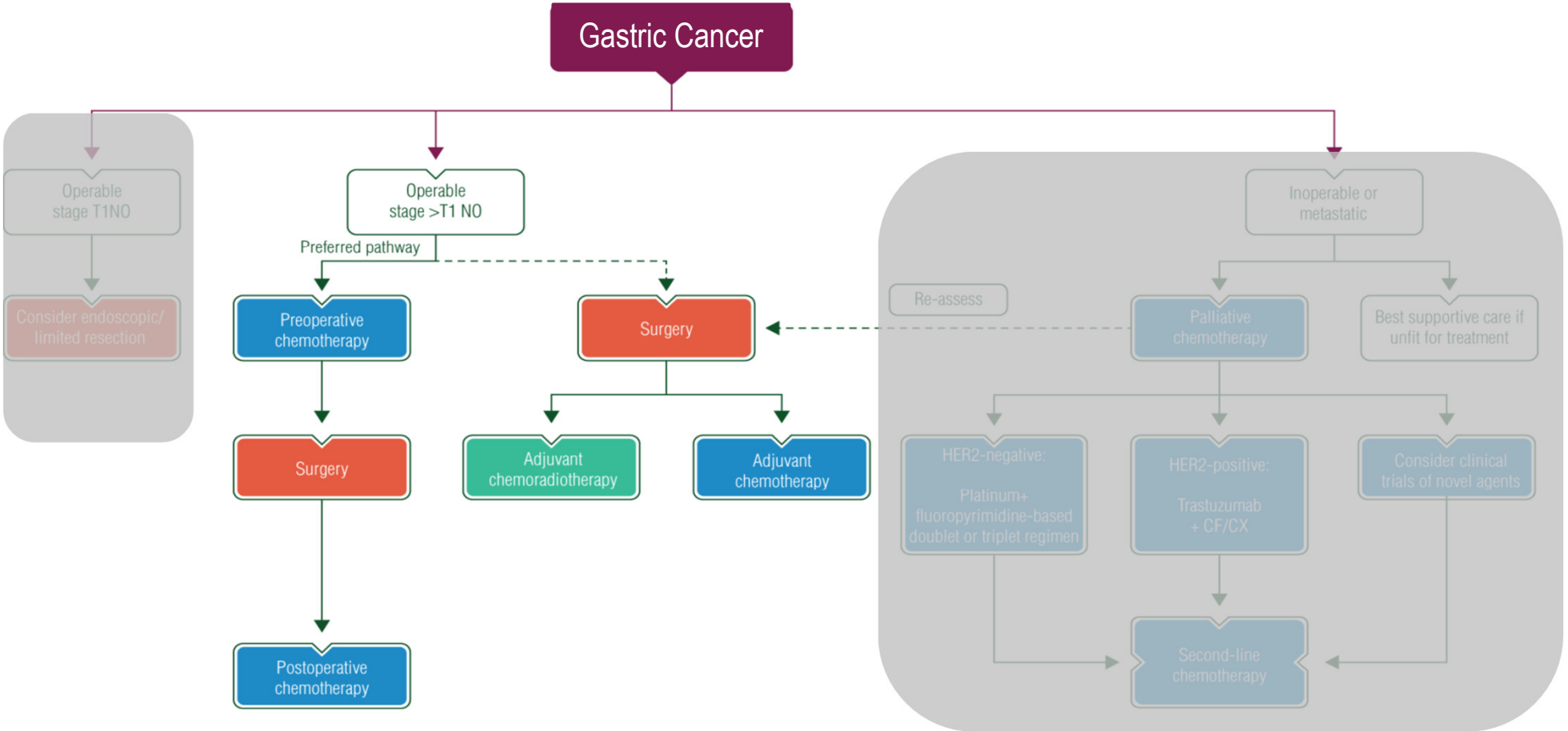


Oesophageal adeno OS surgery alone

Treatment in addition to surgery is required for most patients

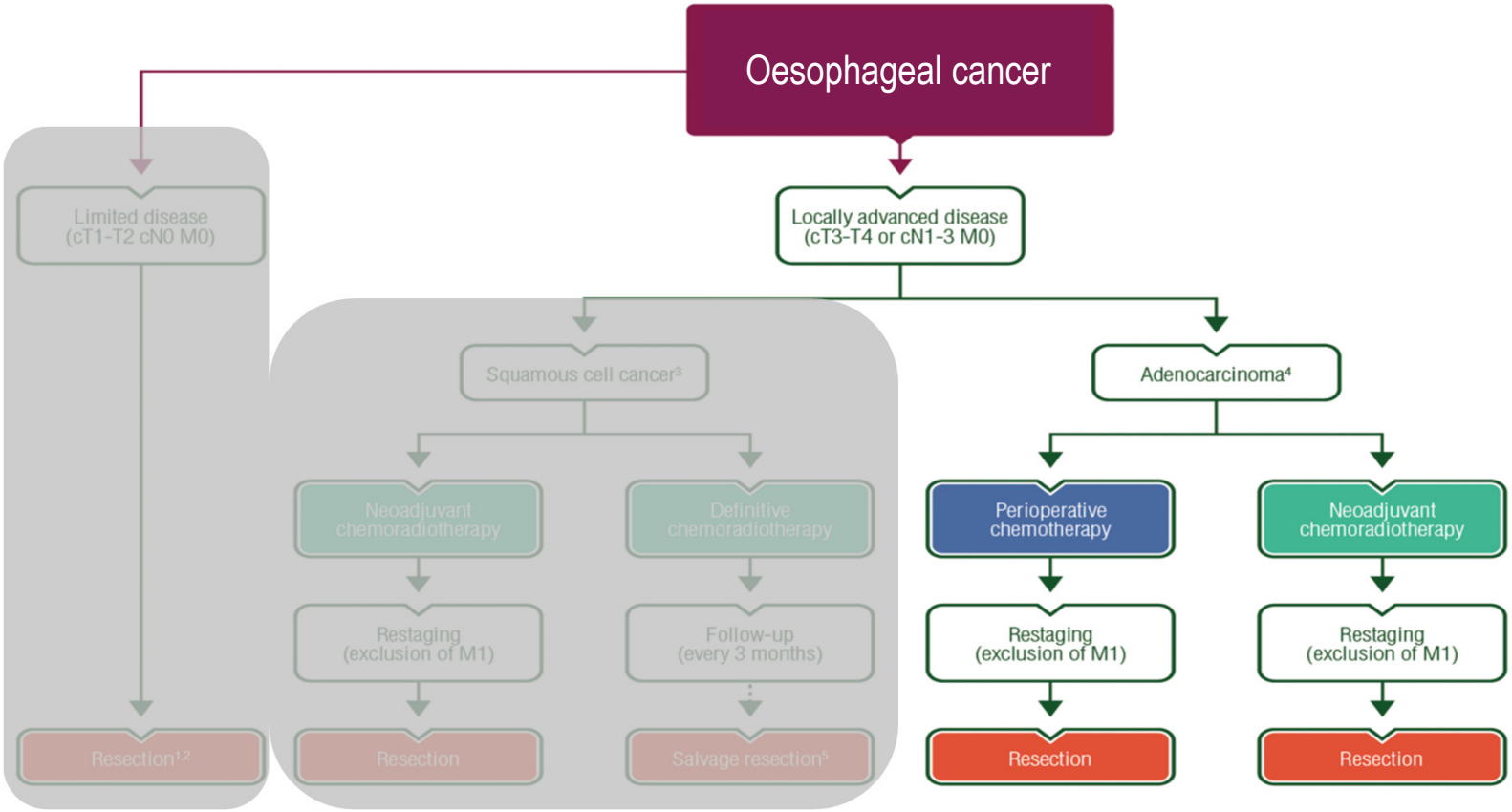
Rice et al, Dis Esophagus. 2016 Nov;29(8):897-905.
Washington et al, Ann Surg Oncol, December 2010, Volume 17, Issue 12

ESMO GASTRIC CANCER GUIDELINES



Smyth et al, Ann Oncol. 2016;27(suppl_5):v38-v49. doi:10.1093/annonc/mdw350

ESMO OESOPHAGEAL CANCER GUIDELINES



Lordick et al, Ann Oncol. 2016;27(suppl_5):v50-v57. doi:10.1093/annonc/mdw329

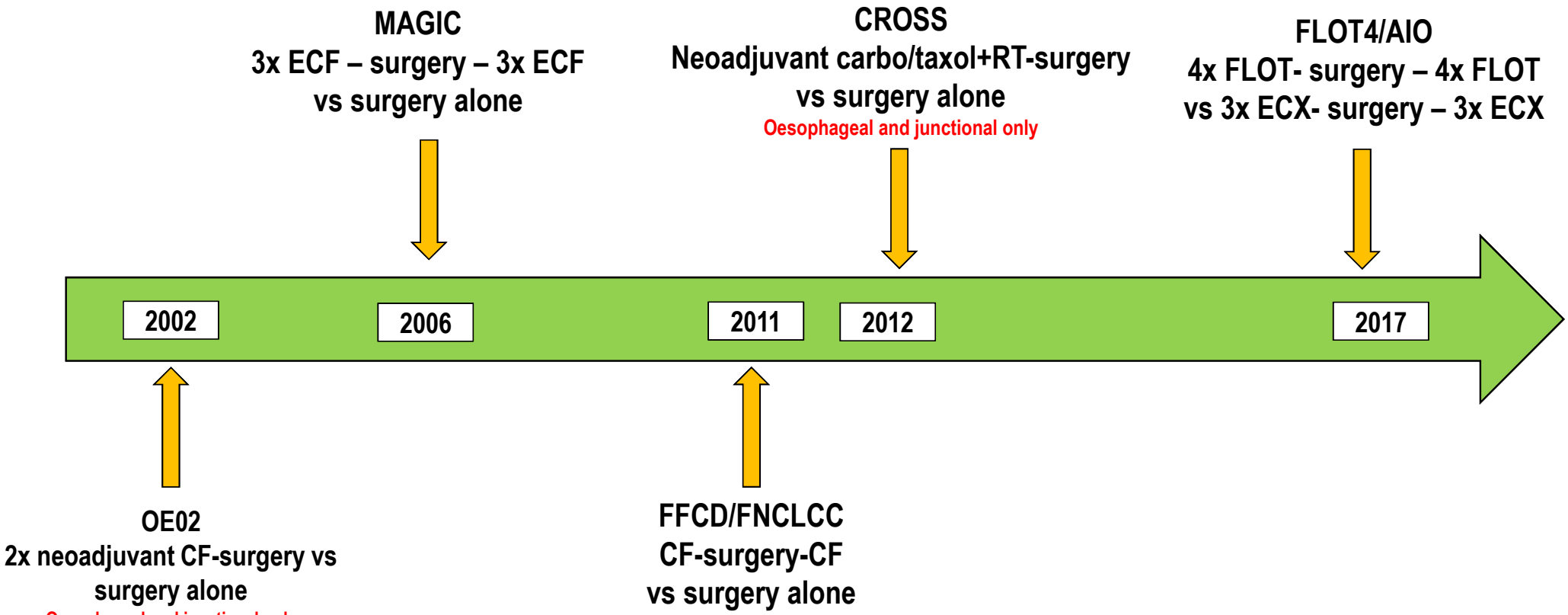
NEOADJUVANT AND PERIOPERATIVE CHEMOTHERAPY

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

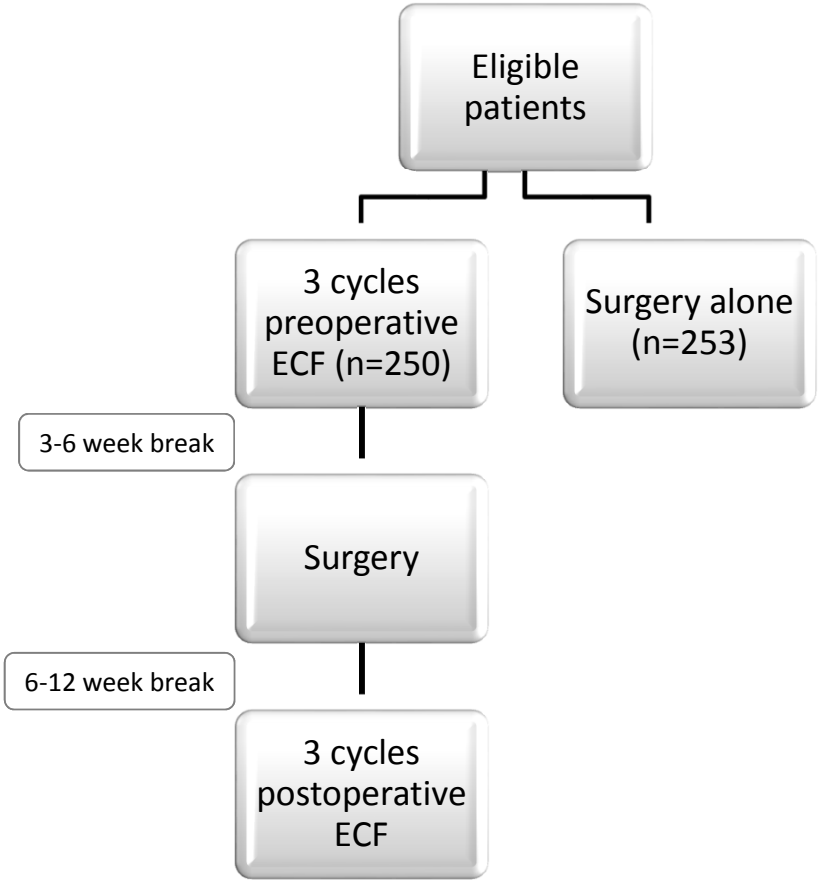
EVOLUTION OF NEOADJUVANT AND PERI-OPERATIVE (CHEMO)THERAPY 2002 - 2017



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



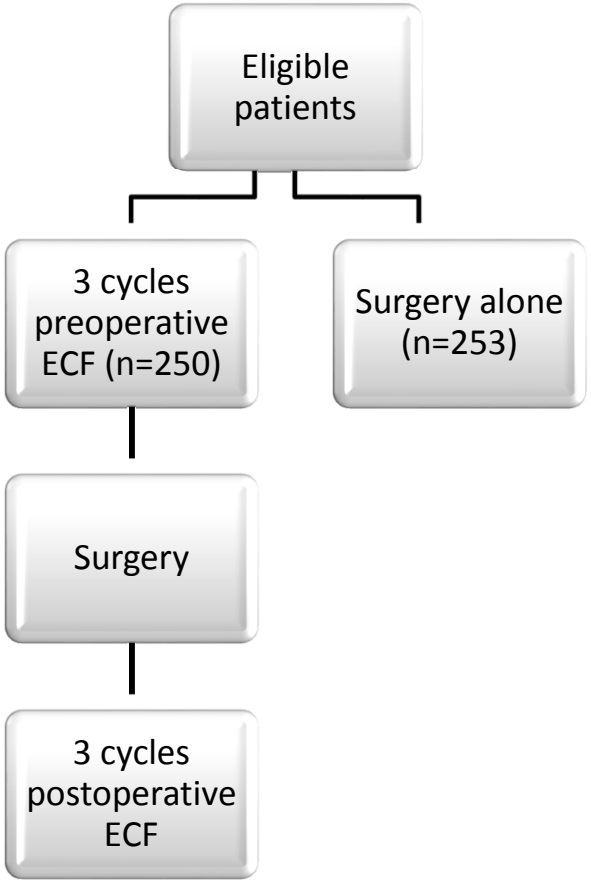
Eligibility criteria
Stage ≥ II gastric, gastroesophageal junction, or lower oesophageal adenocarcinoma (after 1999)
No metastases
ECOG 0-1

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	36 (14%)	37 (15%)
GOJ	30 (12%)	28 (11%)

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

MEDICAL RESEARCH COUNCIL MAGIC TRIAL

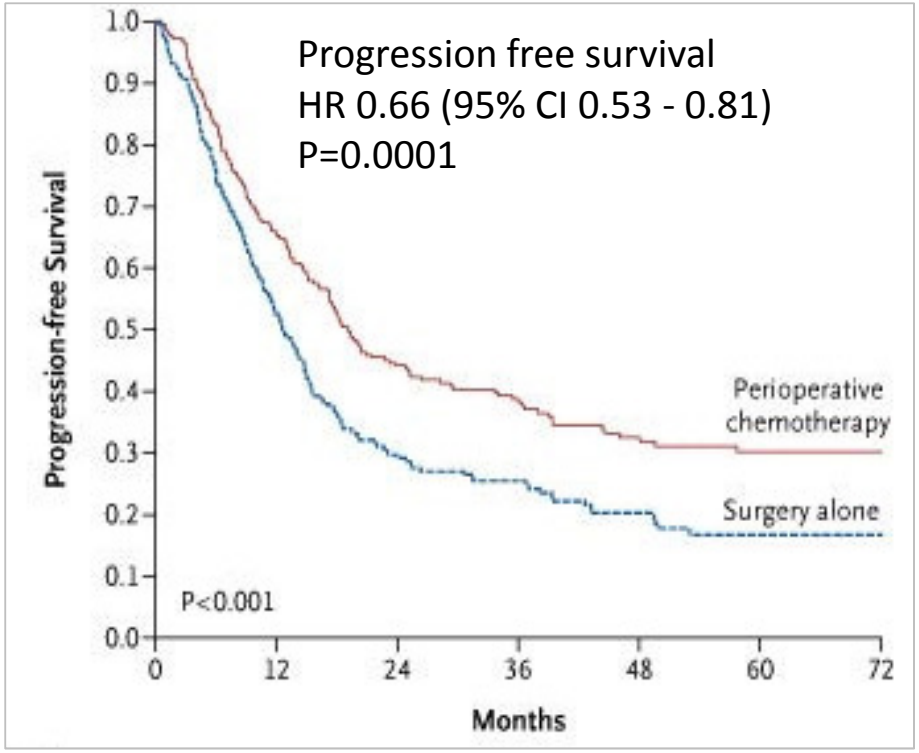


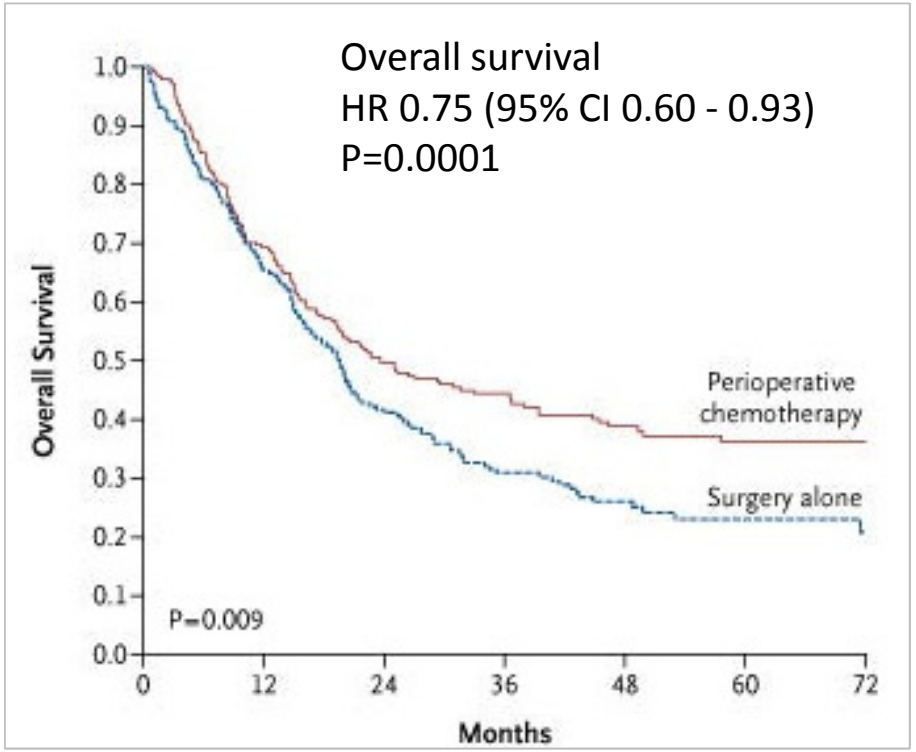
MAGIC post-operative patient characteristics		
	Surgery alone	Chemo + surgery
Surgery		↑ curative resections
Curative	66/250 (66%)	169/244 (69%)
Palliative	70/250 (28%)	44/244 (18%)
Other	17/250 (6%)	27/244 (13%)
ypT stage		↑ early T stage
T1	16/193 (8%)	27/172 (16%)
T2	55/193 (29%)	62/172 (36%)
T3	106/193 (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

MEDICAL RESEARCH COUNCIL MAGIC TRIAL

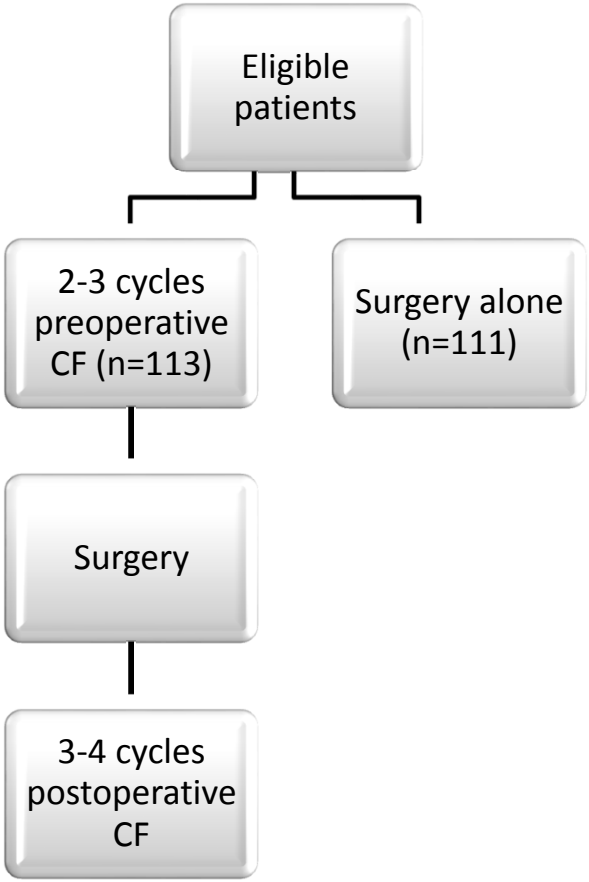




Absolute gain in 5 year survival 13% (23% surgery alone to 36% chemotherapy plus surgery
Median OS benefit approximately 4 months (20 months vs 24 months)

Cunningham D et al. N Engl J Med 2006;355:11-20

FFCD/FNCLCC TRIAL



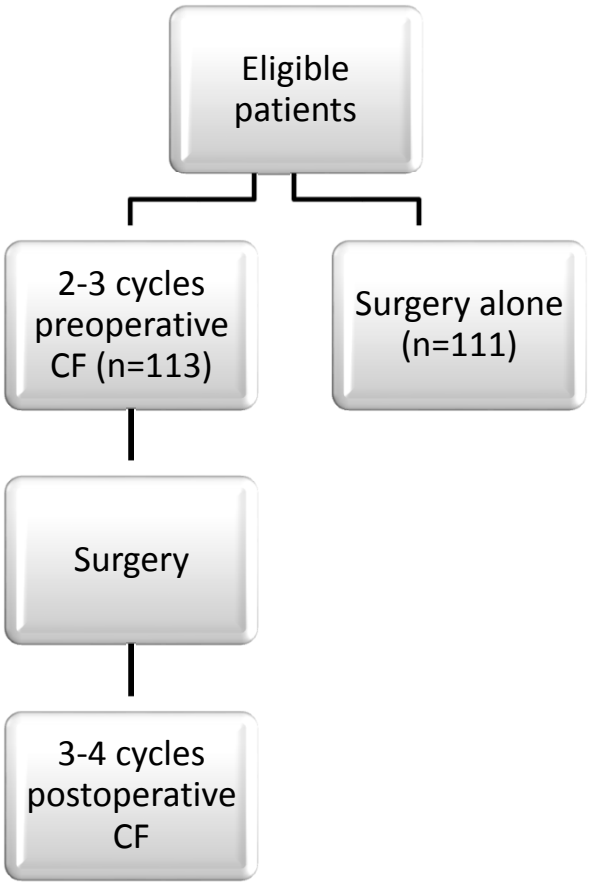
Eligibility criteria
Lower oesophageal or GOJ adenocarcinoma (gastric after 1998)
No metastases
ECOG 0-1

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

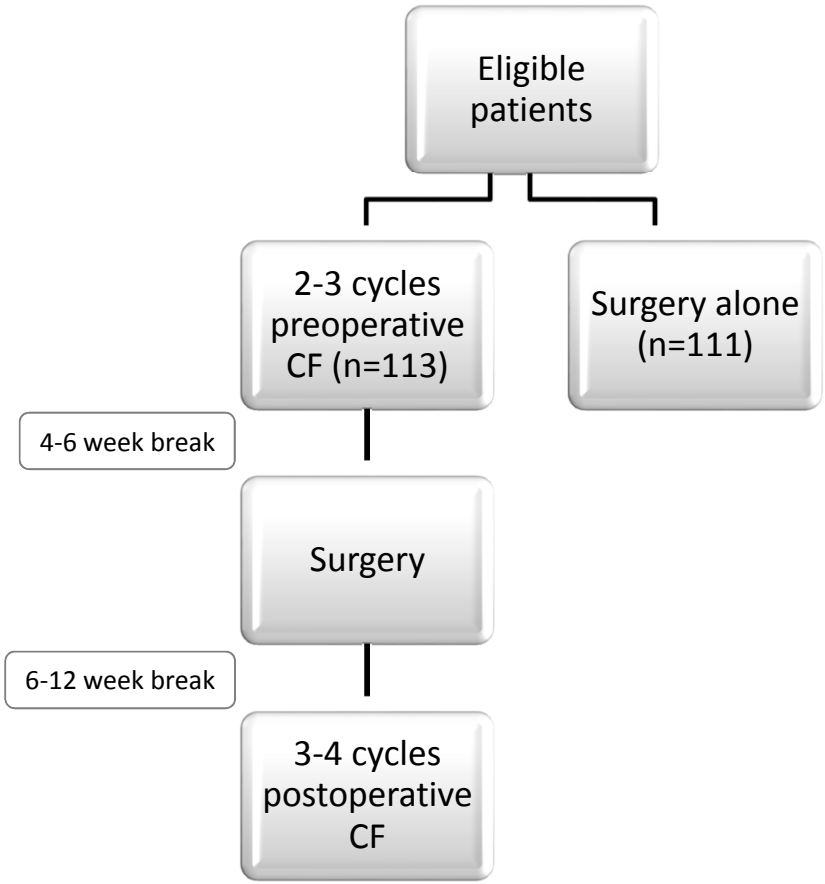


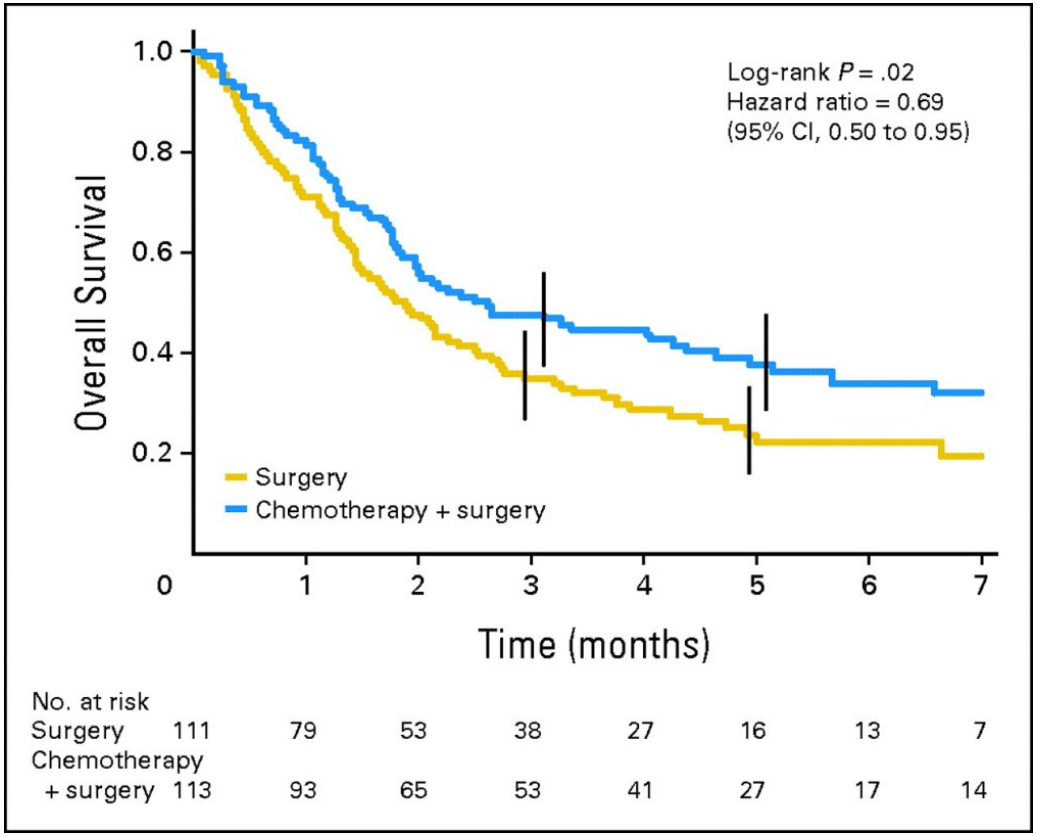
FFCD/FNCLCC post-operative patient characteristics		
	Surgery alone	Chemo + surgery
Surgery		↑ curative surgery
No resection	11 (10%)	7 (6%)
R0	81(74%)	95(87%)
R1	6 (5%)	4 (4%)
R2	11(10%)	2(2%)
Rx	1(1%)	1(1%)
ypT stage		↑ early T stage
T0	(8%)	3 (3%)
T1-2	(29%)	38 (39%)
T3-4	(55%)	57 (58%)
ypN Stage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

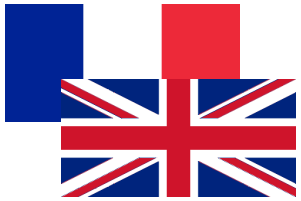
FFCD/FNCLCC TRIAL





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

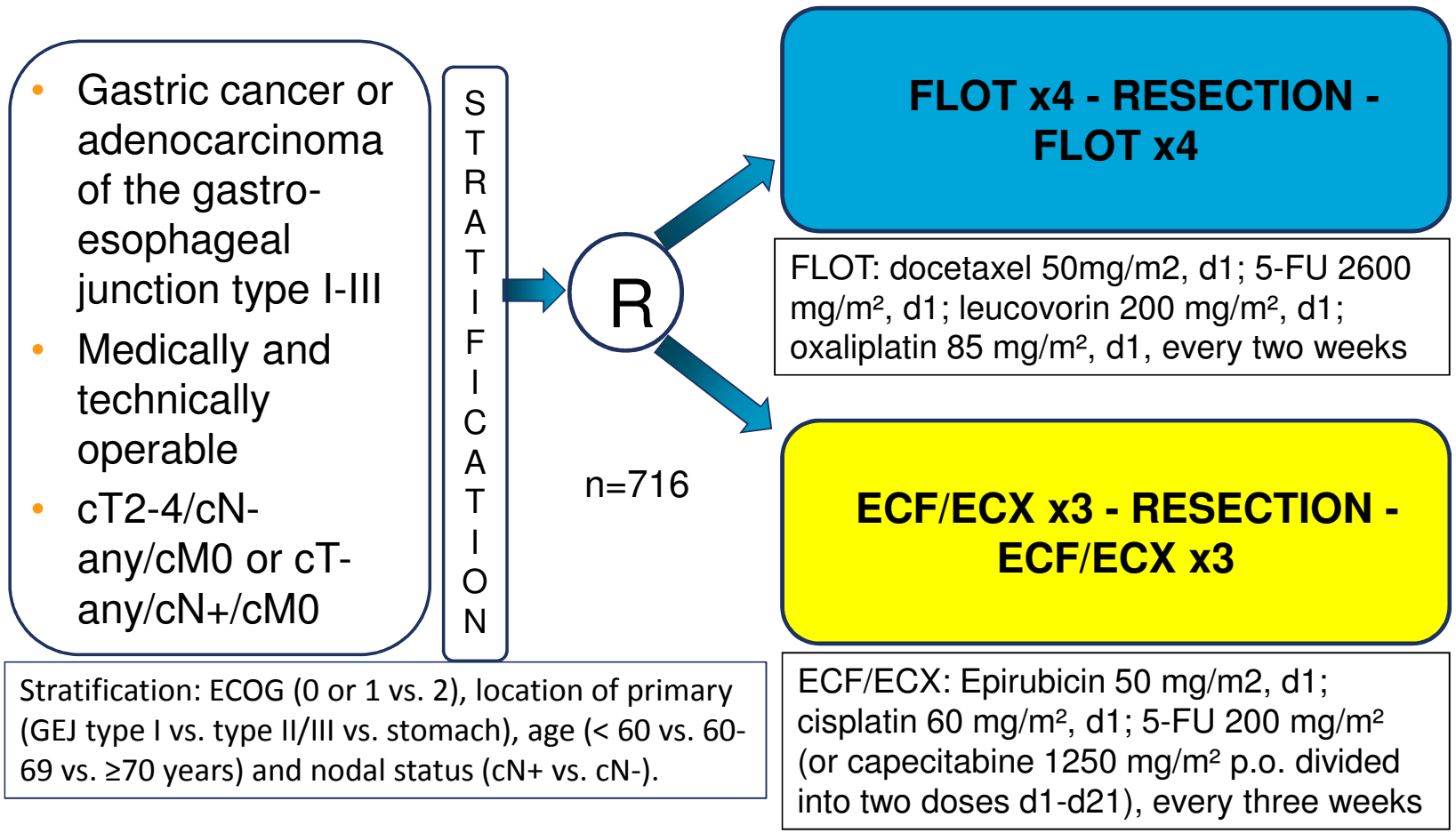


LESSONS FROM MAGIC AND FFCD TRIALS

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

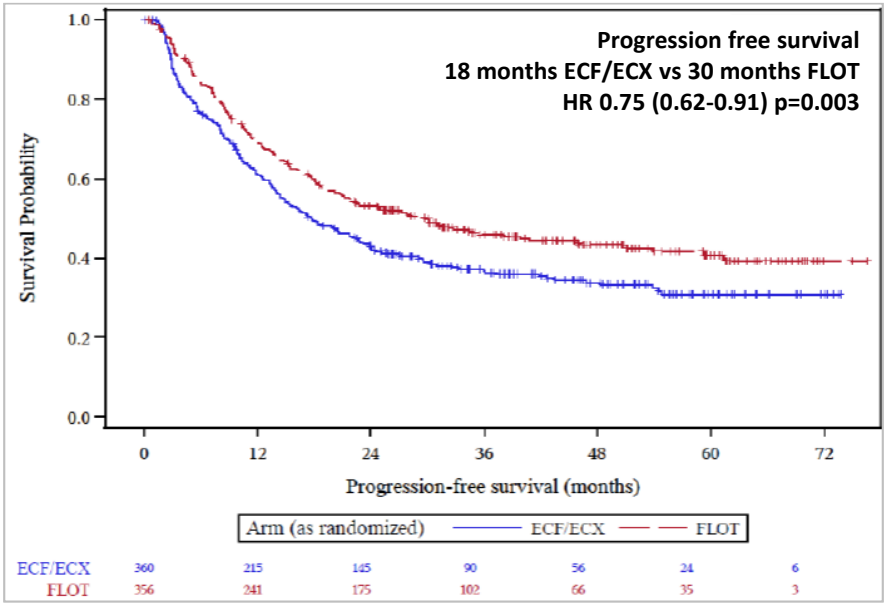
✓Surgical morbidity and mortality was not increased by use of FLOT chemotherapy

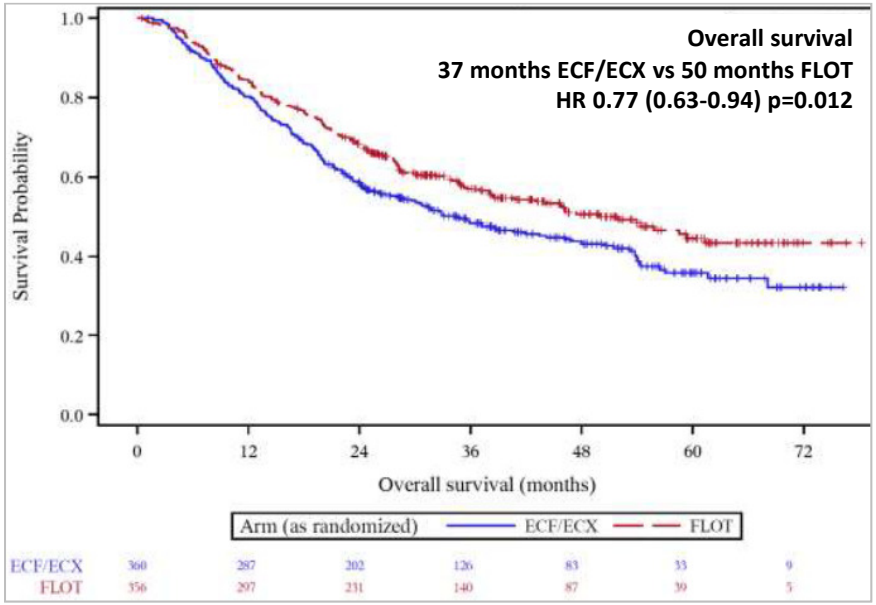
FLOT VS ECX PATHOLOGICAL OUTCOMES

	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

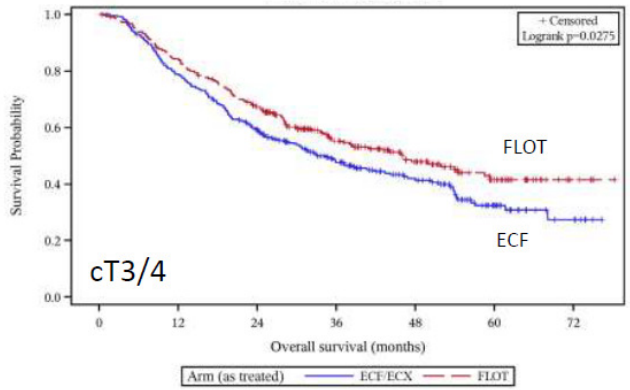
Grade 3-4 >5%	ECF/ECX (N=354)	FLOT (N=354)	P-value (Chi-Square)
Diarrhea	13 (4%)	34 (10%)	0.002
Vomiting	27 (8%)	7 (2%)	<0.001
Nausea	55 (16%)	26 (7%)	0.001
Fatigue	38 (11%)	25 (7%)	
Infections	30 (9%)	63 (18%)	<0.001
Leukopenia	75 (21%)	94 (27%)	
Neutropenia	139 (39%)	181 (51%)	0.002
Sensory	7 (2%)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

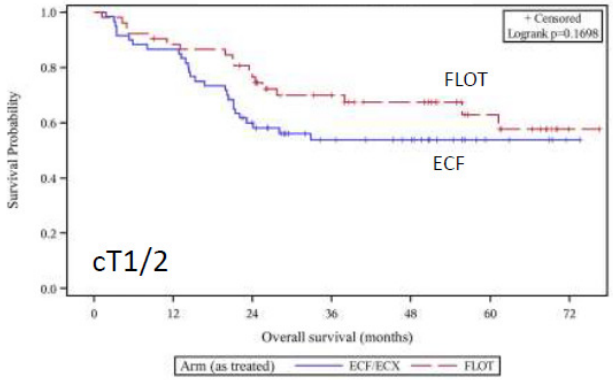
FLOT VS ECF/X TREATMENT TOLERABILITY

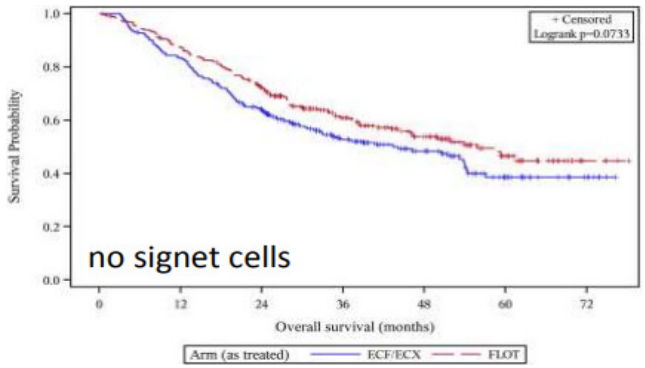
	ECF/ECX (n=360)	FLOT (n=356)
Completed pre-operative chemo	327 (91%)	320 (90%)
Surgery	340 (94%)	336 (94%)
Started post-operative chemo Completed protocol post-op chemo	187 (52%) 133 (37%)	213 (60%) 162 (46%)

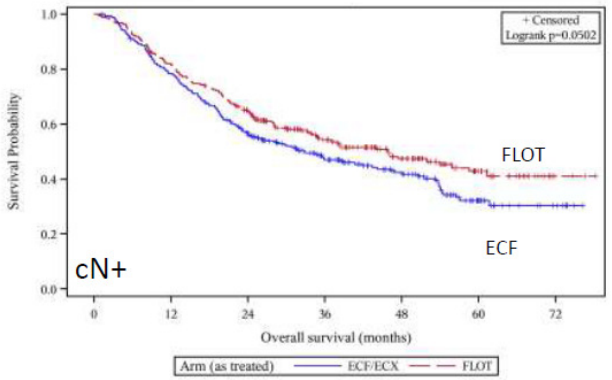
✓Patients treated with FLOT were more likely to commence post-operative chemotherapy, and those who commenced post-operative FLOT were more likely to complete post-operative chemotherapy

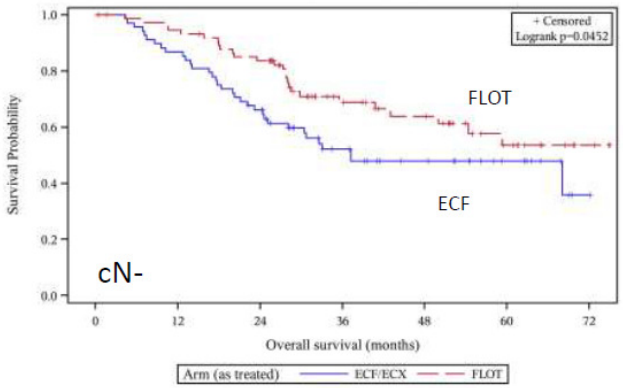
BENEFIT OF FLOT IN ALL PROGNOSTIC GROUPS

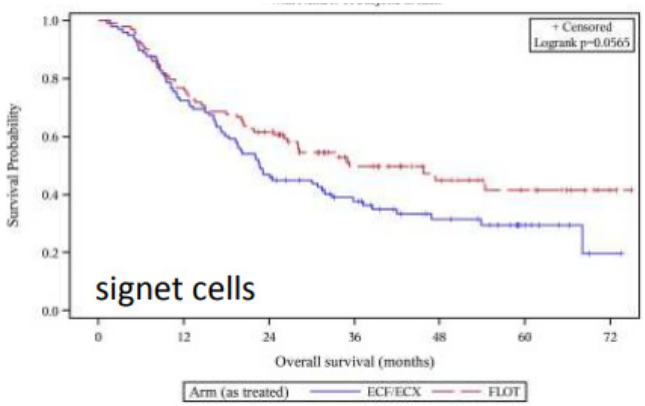












al Batran et al, ESMO 2017

PERI-OPERATIVE CHEMOTHERAPY: TAKE HOME MESSAGES

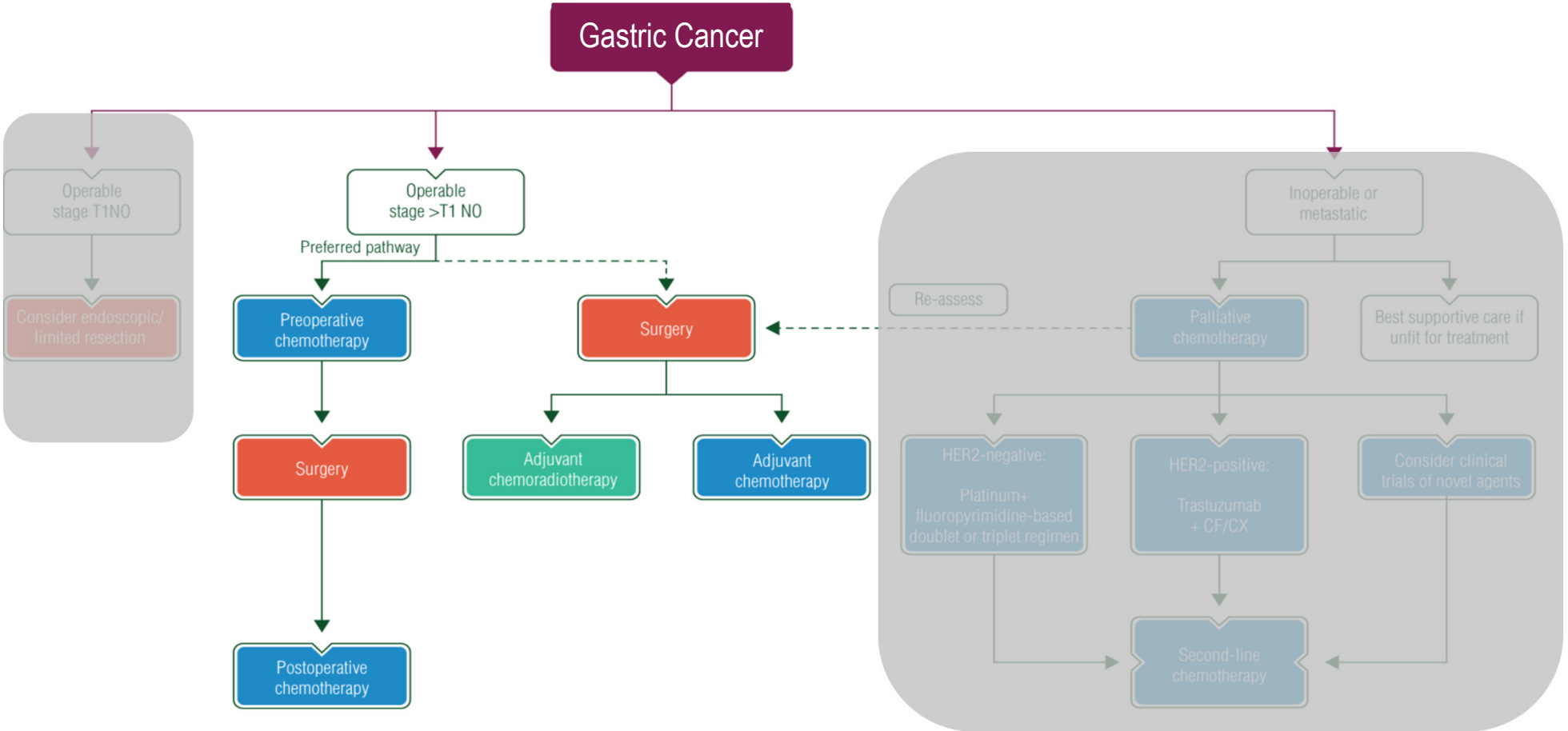
FLOT is the new gold standard treatment for patients who receive peri-operative chemotherapy and surgery for operable gastroesophageal cancer

- In patients are not suitable for triplet chemotherapy, doublet chemotherapy can be considered
- Doublets can be cisplatin or oxaliplatin based

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

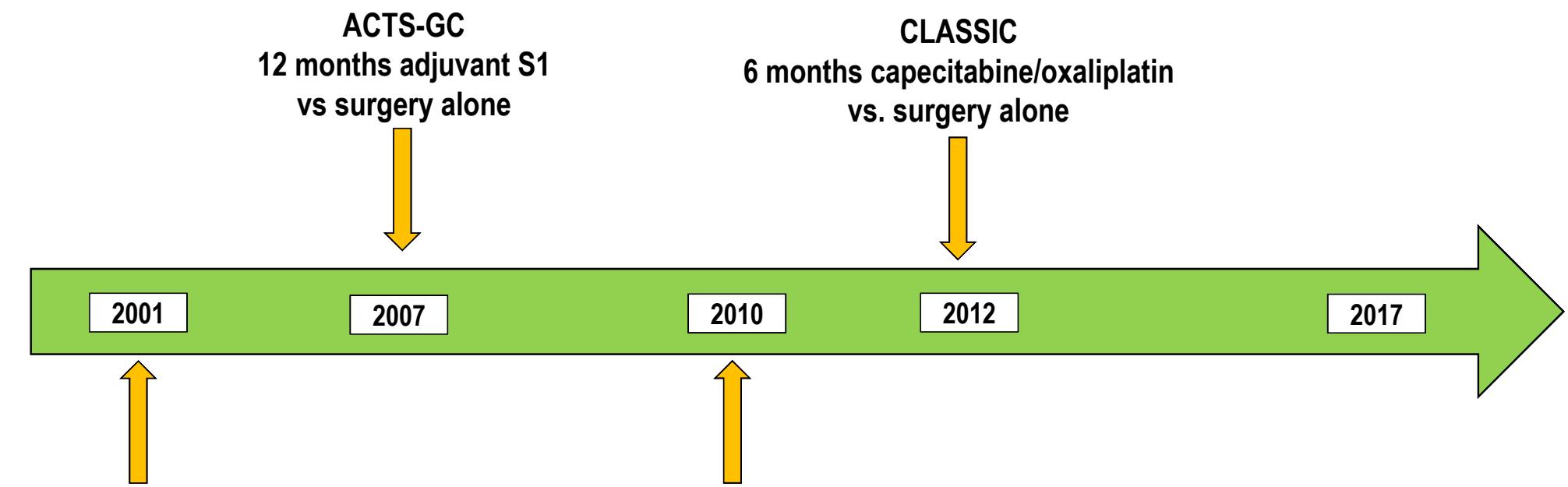
ADJUVANT CHEMOTHERAPY

ESMO GASTRIC CANCER GUIDELINES



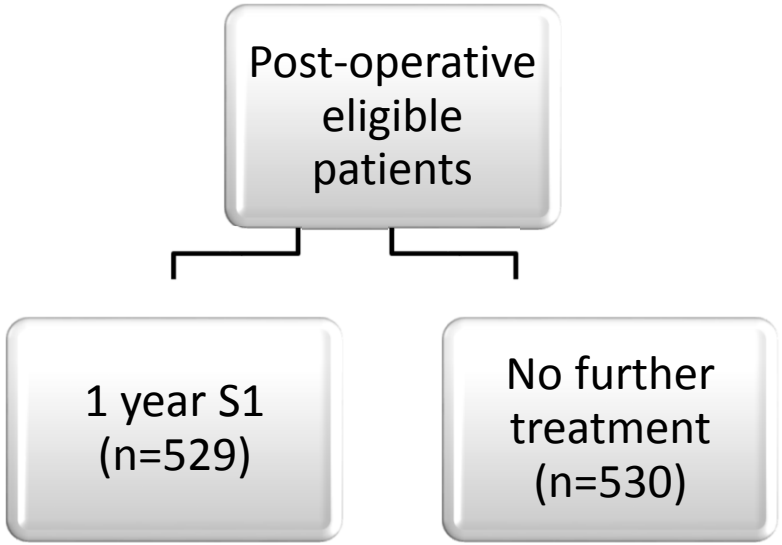
Smyth et al, Ann Oncol. 2016;27(suppl_5):v38-v49. doi:10.1093/annonc/mdw350

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

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

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%)

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

ACTS-GC TRIAL

Post-operative eligible patients

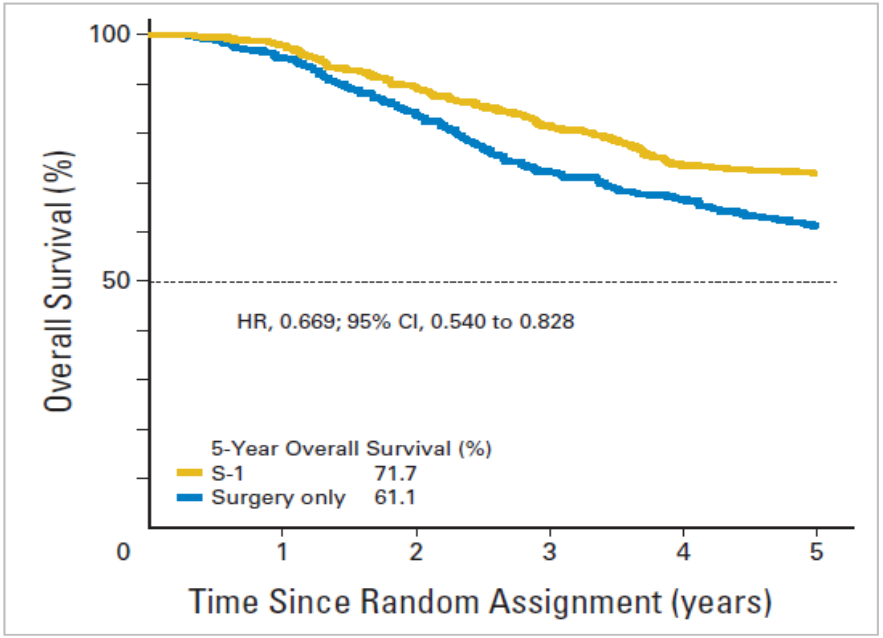
1 year S1 (n=529)

No further treatment (n=530)

Primary Endpoint
Overall survival
Secondary endpoints
Relapse free survival & Safety

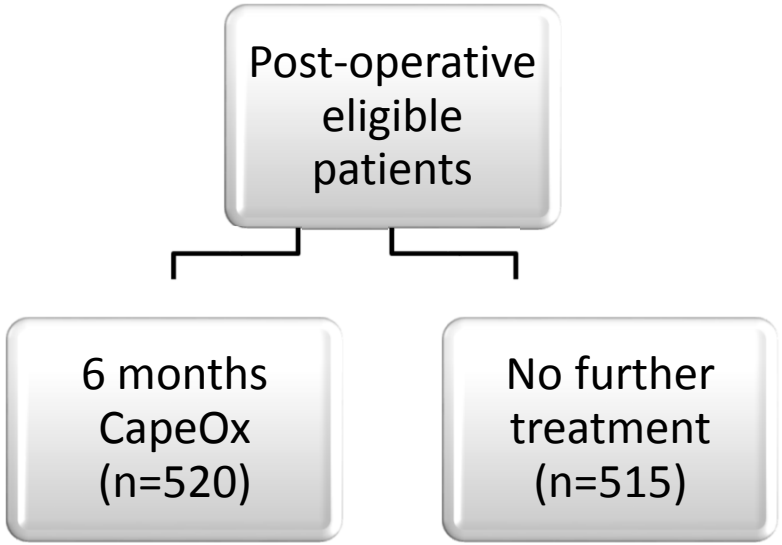
Update ESMO 2017 OPAS-1 study
6 months of S1 not inferior to 12 months

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

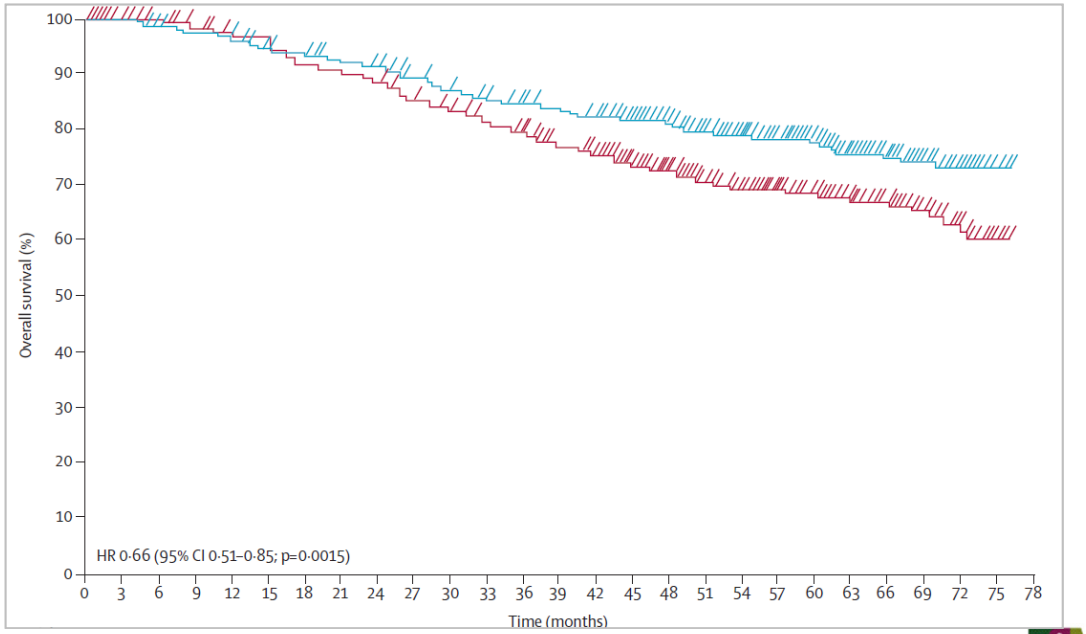
Post-operative eligible patients

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

JACRO-07

Post-operative eligible patients

S1 80mg/m^2 d1-28 q 6 wks x 1 year

(n=459)

Cycle 1: S1 80mg/m^2 d1-14 q21d

Cycle 2-7: docetaxel 40mg/m^2 plus S1 80mg/m^2 d1-14 q21d

Then S1 x 6 months

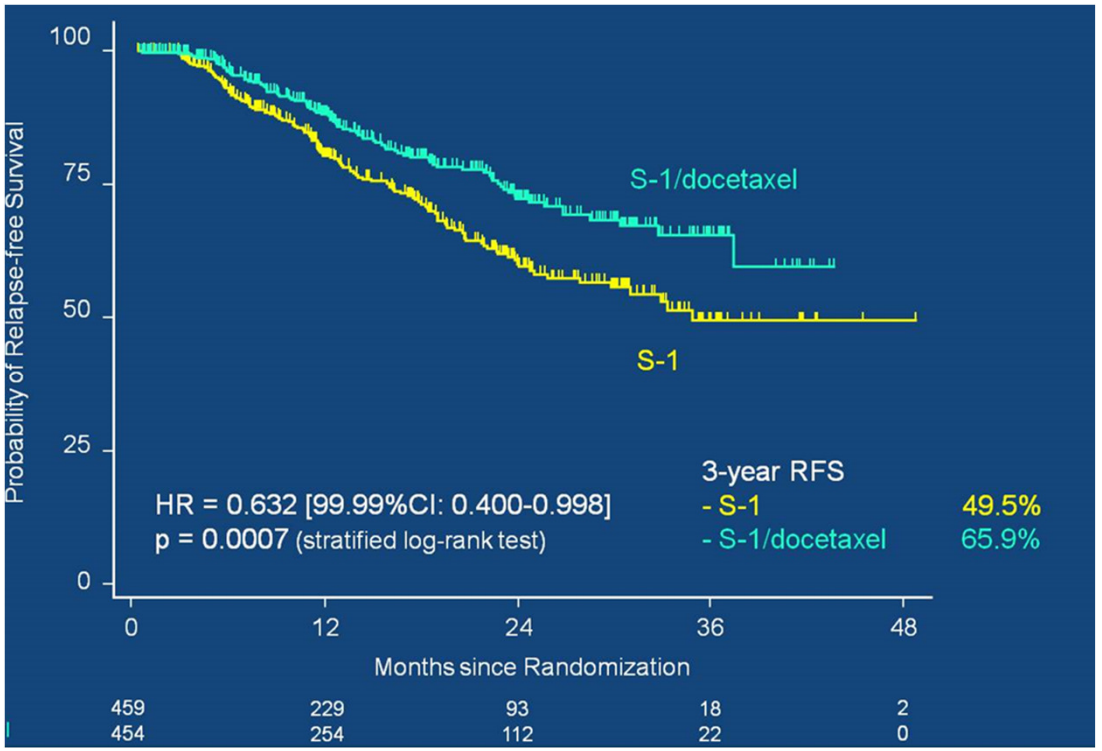
(N=456)

Primary Endpoint

3 year relapse free survival

Secondary endpoints

Overall survival & safety



Relapse free survival

Kodera et al, ASCO 2018

ESMO

JACRO-07

Post-operative eligible patients

S1 80mg/m^2 d1-28 q 6 wks x 1 year

(n=459)

Cycle 1: S1 80mg/m^2 d1-14 q21d

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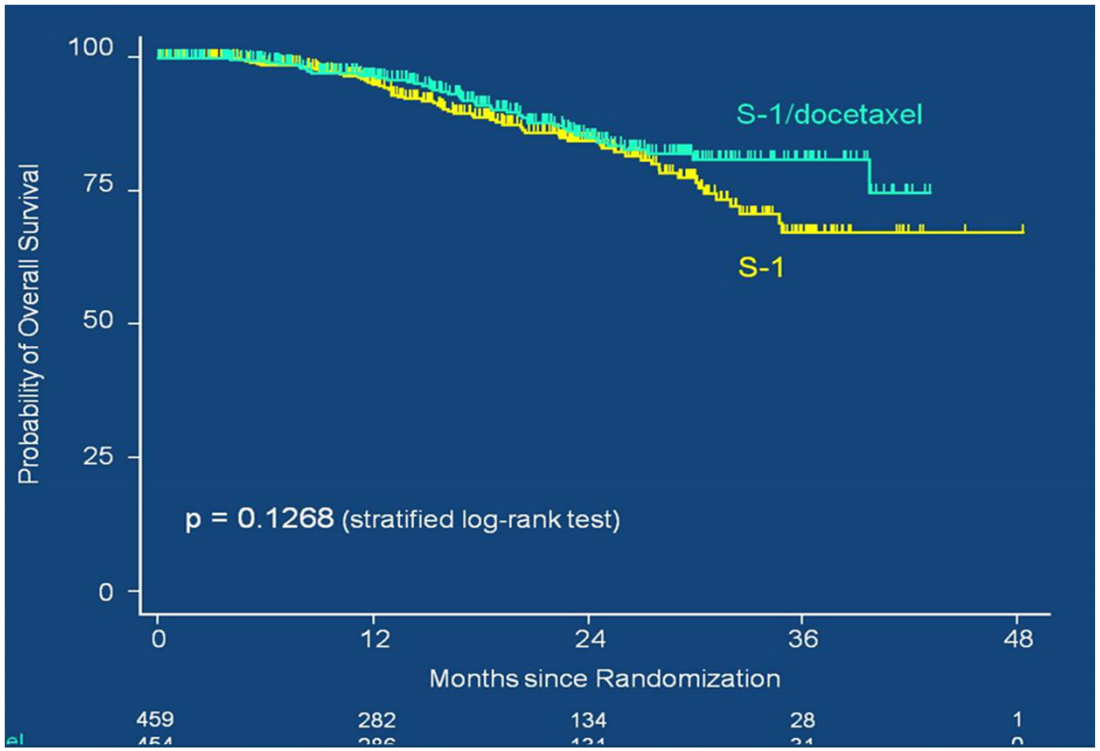
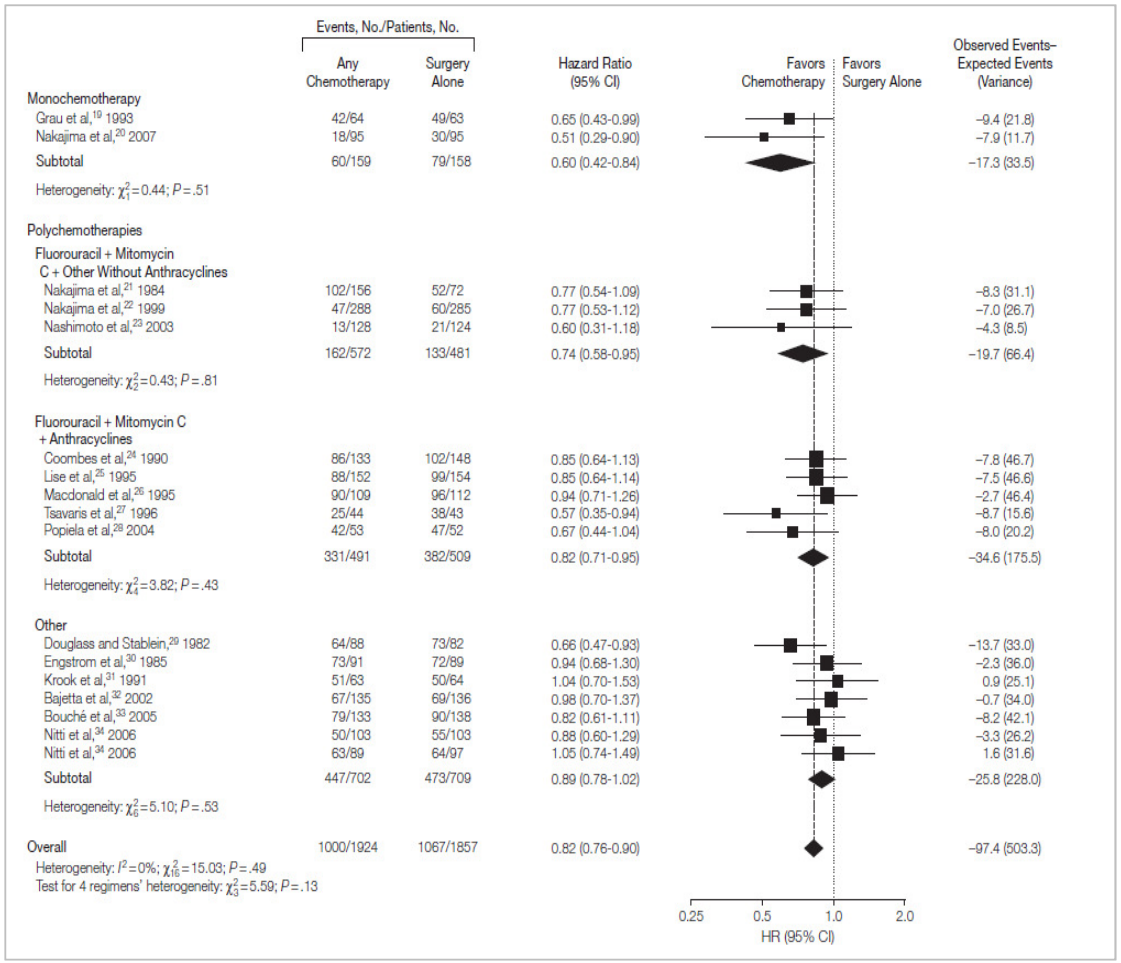


Overall survival

Kodera et al, ASCO 2018

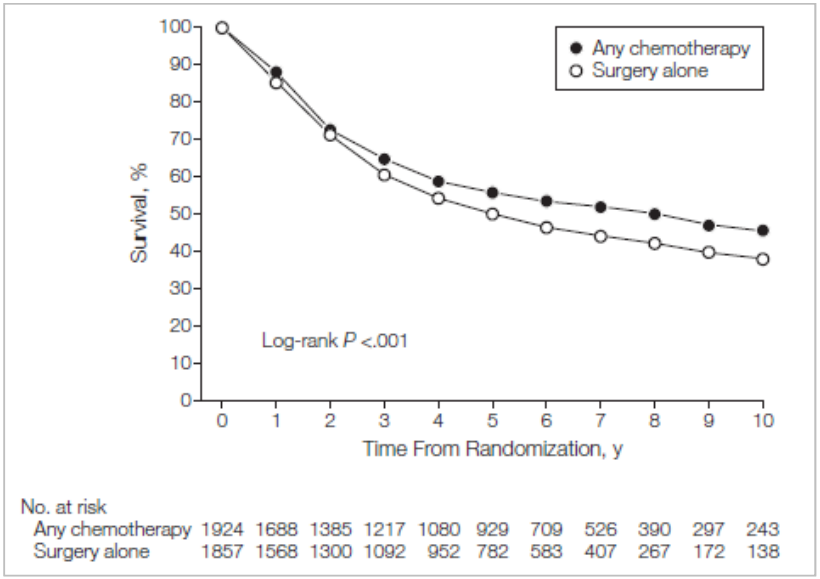
ESMO

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.

CHEMOTHERAPY VS. CHEMORADIOTHERAPY

CHEMOTHERAPY VS CHEMORADIOTHERAPY

An ongoing debate

For **GASTRIC** adenocarcinomas **peri-operative chemotherapy (FLOT)** is preferred to post-operative chemotherapy or post-operative chemoradioatherapy because:

- More patients are able to receive chemotherapy before surgery than afterwards.
- Downstaging due to chemotherapy increases rates of R0 resections

However, in cases where surgery has been performed without neoadjuvant chemotherapy, adjuvant treatment may be considered.

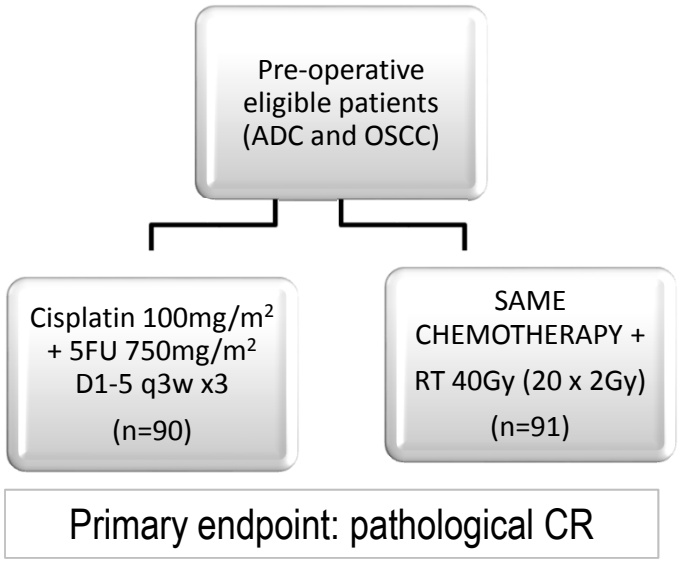
For **GASTROESOPHAGEAL JUNCTIONAL (Siewert Type I/II)** and **OESOPHAGEAL** adenocarcinoma

Perioperative chemotherapy and neoadjuvant chemoradiotherapy are both reasonable choices

Patients selection for treatment depends on the characteristics of the patient, the tumour and local expertise

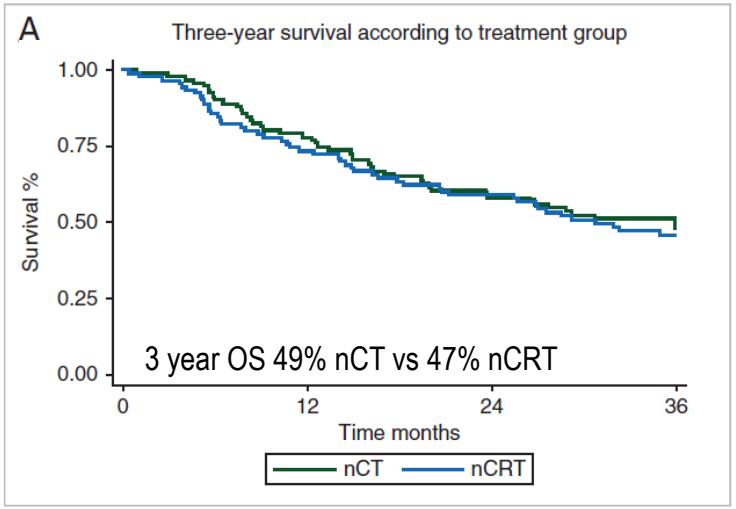
CHEMOTHERAPY VS CHEMORADIOTHERAPY

NeoRes Study



Primary endpoint: pathological CR

NeoRes Study Outcomes		
	CT	CRT
R0	58 (74%)	68 (87%)
Path CR	7(9%)	22 (28%)
30 day mortality	0 (0%)	1(1%)



The NeoRes study treated patients with oesophageal SCC and adenocarcinoma including gastroesophageal junction

Although underpowered for survival, no difference was suggested in OS for chemotherapy vs chemoradiotherapy treated patients, nor in subgroup analysis

Surgical complications were more severe, but not more frequent in patients treated with chemoradiotherapy

Klevebro et al, Ann Oncol. 2016 Apr;27(4):660-7

CHEMOTHERAPY VS CHEMORADIOTHERAPY

Propensity matched analysis neoadjuvant chemotherapy vs CRT

Eligible patients from prospectively maintained databases

OAC or Siewert I/II GEJ

Neoadjuvant chemotherapy plus surgery

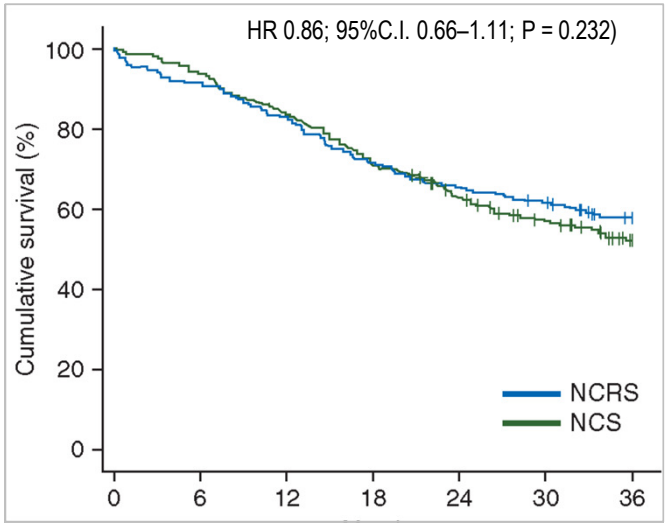
N=221

Neoadjuvant chemoradiotherapy plus surgery

N=221

RETROSPECTIVE

Study Outcomes		
	nCT	nCRT
R0	165 (78%)	204 (92%)
Path CR	11 (5%)	59 (27%)
30 day mortality	1.4%	4.1%
Leak	6.8%	23.1%



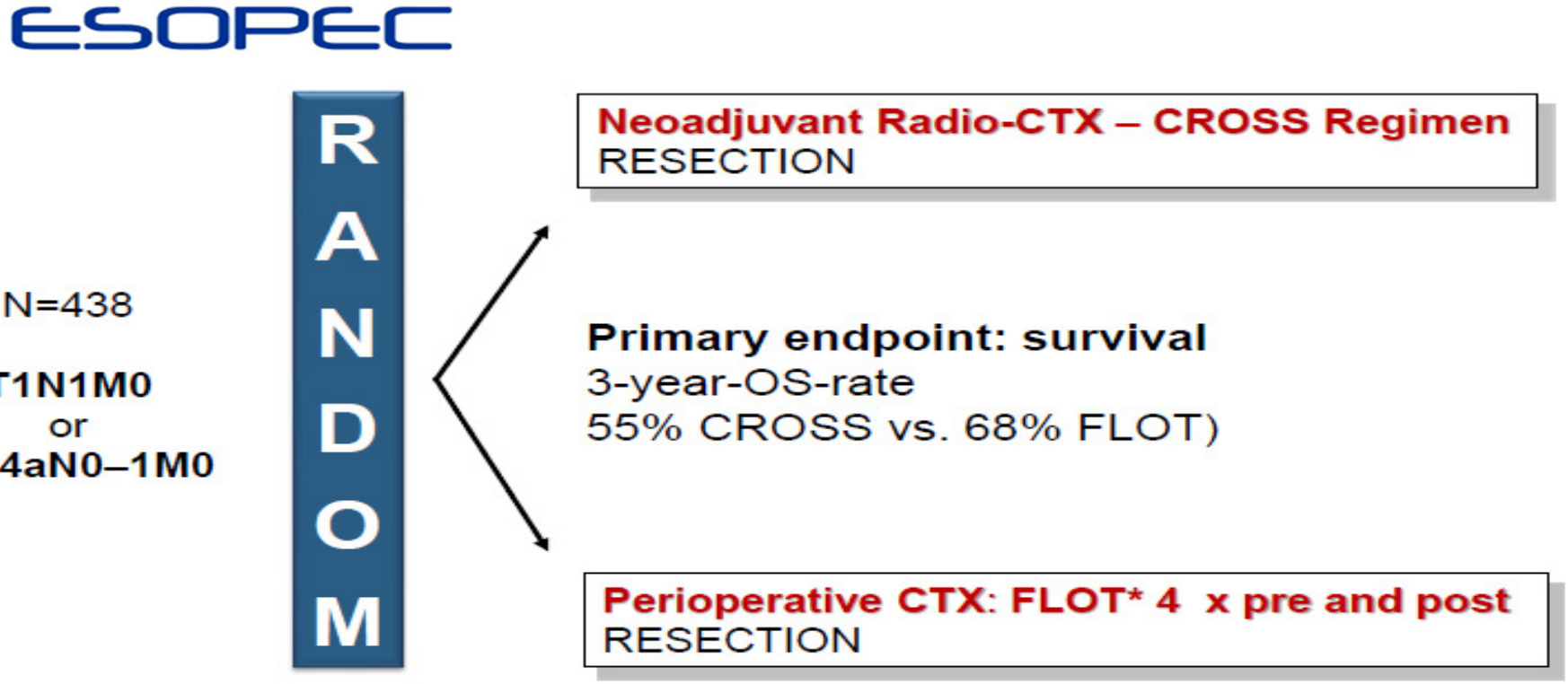
This multicentre European analysis matched patients with resectable oesophageal and Siewert Type I and II junctional cancers treated with neoadjuvant chemotherapy or chemoradiotherapy.

Compared with chemotherapy CRT is associated with improvements in R0 resection rates and pathological complete response, but not in overall survival.

With the exception of anastamotic leaks, morbidity and post-operative mortality were not different between the groups.

Markar et al, Ann Oncol. 2017 Mar 1;28(3):519-527.

Trials which will answer this question
Chemo vs CRT

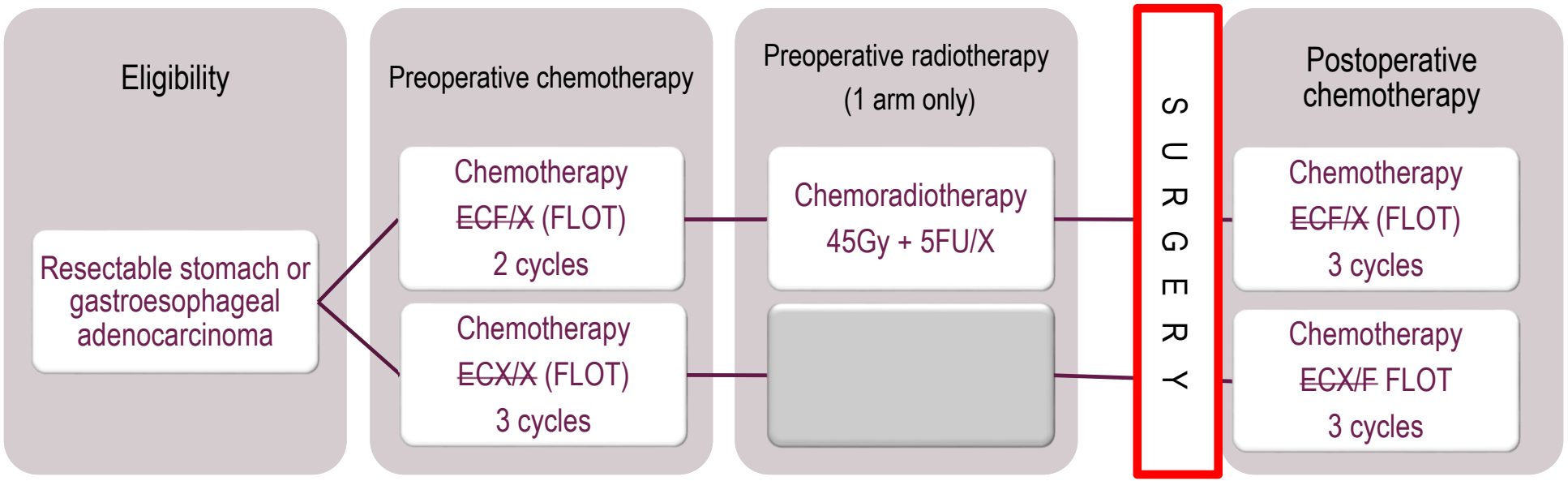


Neo-Aegis (NCT01726452): Same design (n=594)

Hoeppner et al, BMC Cancer. 2016 Jul 19;16:503.
Reynolds et al, BMC Cancer. 2017 Jun 3;17(1):401.

Trials which will answer this question
Peri-operative chemo vs peri-operative chemo +RT

TOPGEAR

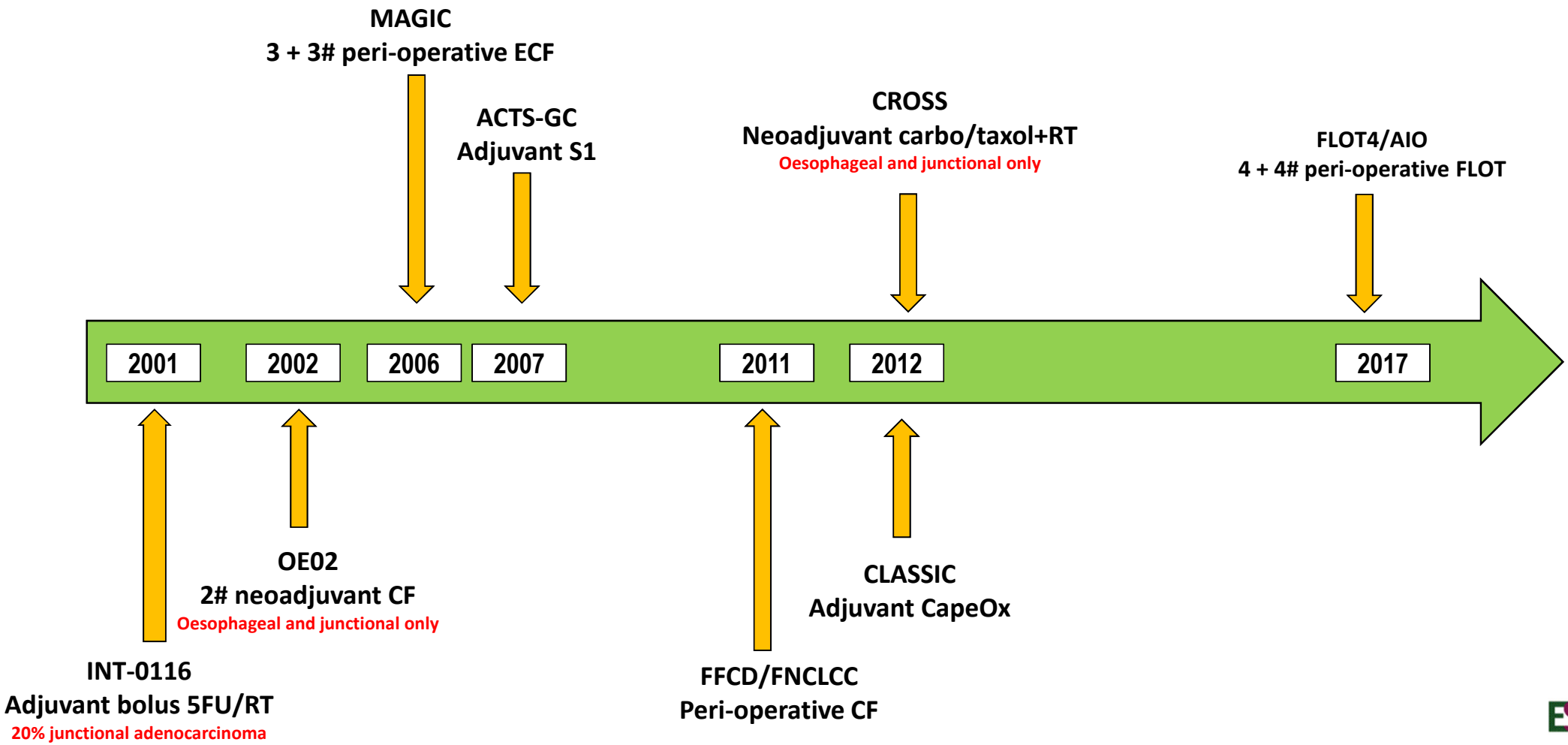


FLOT to replace ECF/X

Leong et al, BMC Cancer. 2015 Jul 21;15:532.

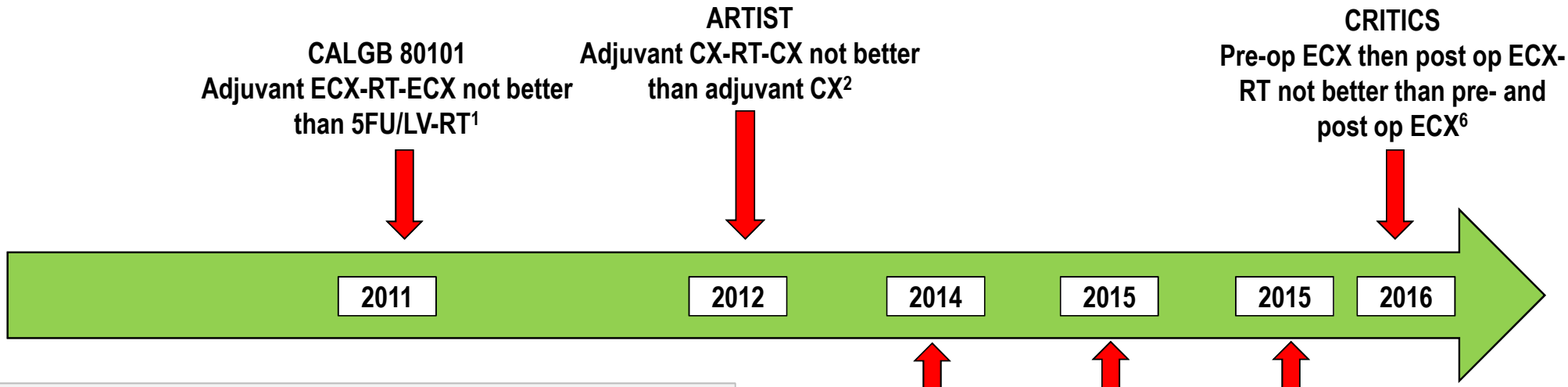
BIOMARKERS FOR PERIOPERATIVE CHEMOTHERAPY

EVOLUTION OF (NEO)ADJUVANT TREATMENT 2002 - 2017



NEGATIVE TRIALS OF (NEO)ADJUVANT TREATMENT 2012-2016

More is not always better

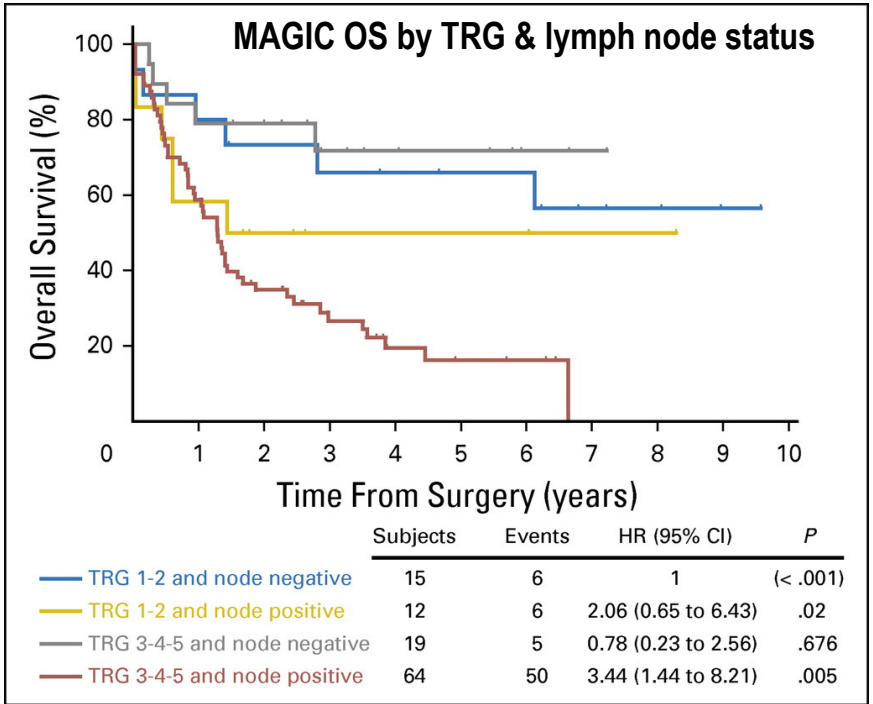


None of the following were effective in improving overall survival

Intensification of chemo in adjuvant chemo-RT (CALGB 80101)
Addition of RT to adjuvant chemo (ARTIST)
Intensification of adjuvant chemotherapy (ITACA-S)
Intensification of neoadjuvant treatment with anthracycline (OEO5)
Addition of RT to standard peri-operative treament (CRITICS)
Addition of bevacizumab (ST03)

1. Fuchs et al, ASCO 2011, 2. Lee et al, J Clin Oncol. 2012 Jan 20;30(3):268-73., 3. Bajetta et al, Ann Oncol. 2014 Jul;25(7):1373-8. 4. Alderson et al, Lancet Oncol. 2017 Sep;18(9):1249-1260. 5. Cunningham et al, Lancet Oncol. 2017 Mar;18(3):357-370. 6. Verheij et al, ASCO 2016

RISK STRATIFICATION USING TUMOUR REGRESSION GRADING



Lymph nodes are the most important prognostic marker following chemotherapy and surgical resection

EORTC VESTIGE Study design

CI: F. Lordick

Gastric or EGJ adenocarcinoma stage Ib-IV

Completed pre-operative chemo with a fluoropyrimidine-platinum containing regimen

Duration of neoadjuvant chemotherapy: 6 weeks - 12 weeks

Total or partial gastrectomy with at least D1 LND; Minimum of 15 lymph nodes evaluated

Age ≥ 18 years

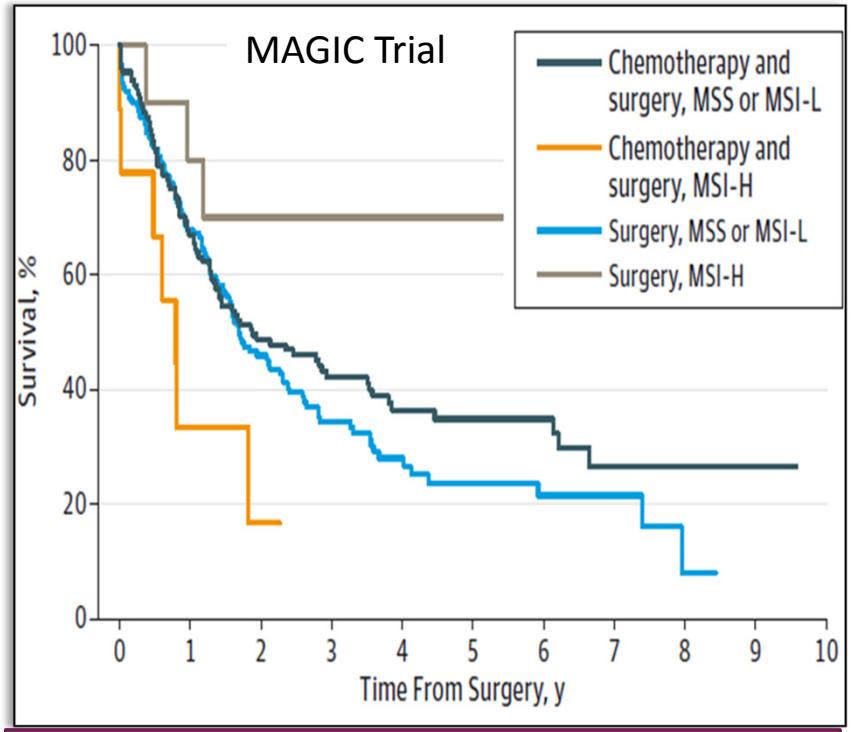
Control arm: Postoperative chemotherapy (completion of the perioperative tx) according to standards:
Fluoropyrimidine/platinum based (CF/CX/ECF/ECX/EOX/FOLFOX/ CapeOx/FLOT/DCF).

Experimental arm:
Nivolumab 3mg/kg q2w x 1y
Ipilimumab 1mg/kg q6wkx 1y

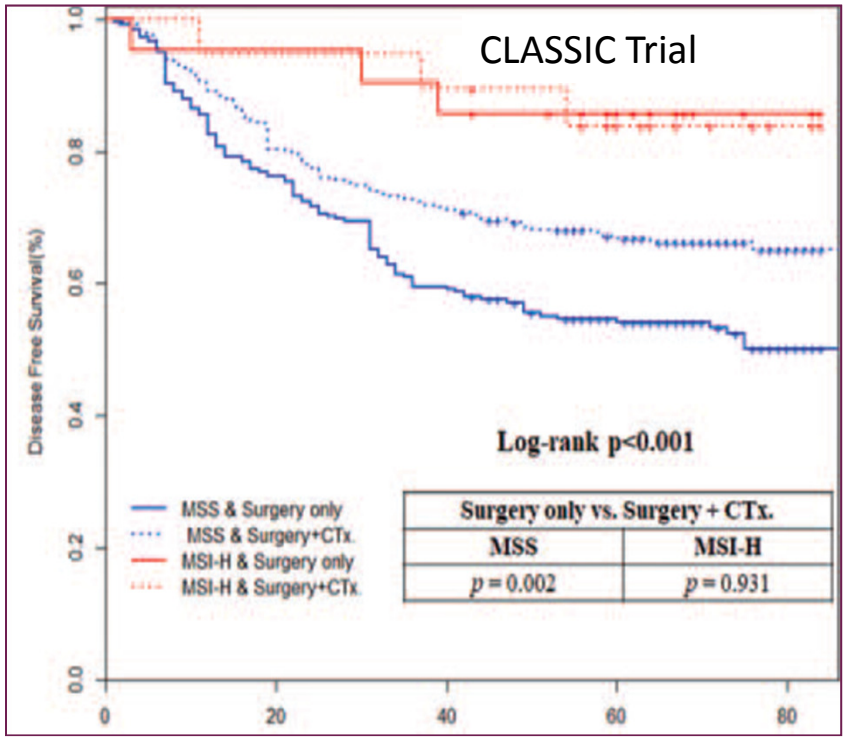
Follow-up:
- Clinical examination and CT scan of the chest and abdomen every 3 months during year 1 and 2 following randomization
- and then every 6 months until year 5 or death or documented recurrence

Smyth et al, J Clin Oncol. 2016 Aug 10;34(23):2721-7.

MSI FOR PERSONALISED TREATMENT IN RESECTABLE GC



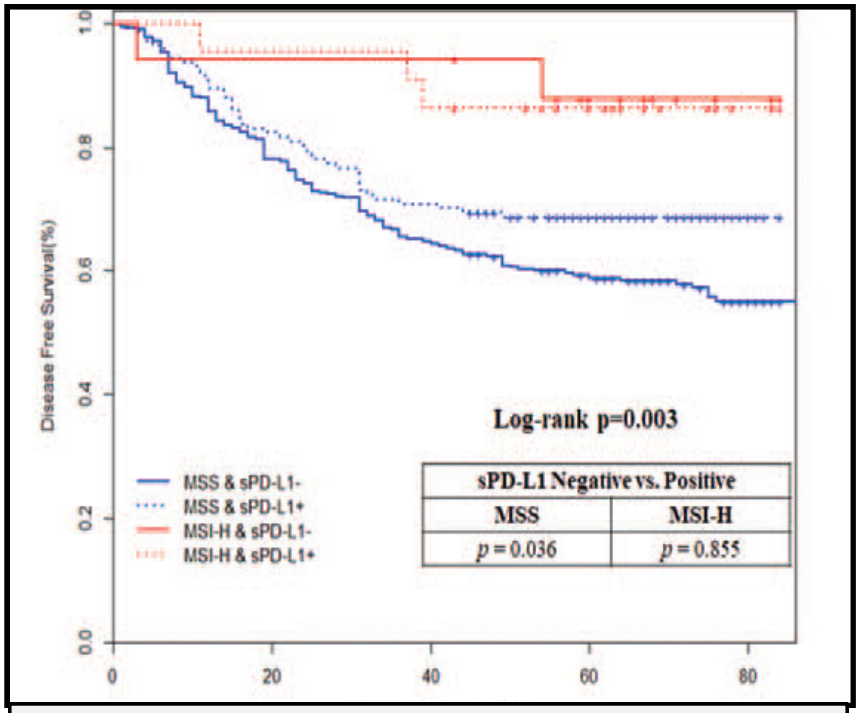
No benefit to perioperative chemotherapy in MSI-H gastric cancer, possible detriment observed (small numbers)



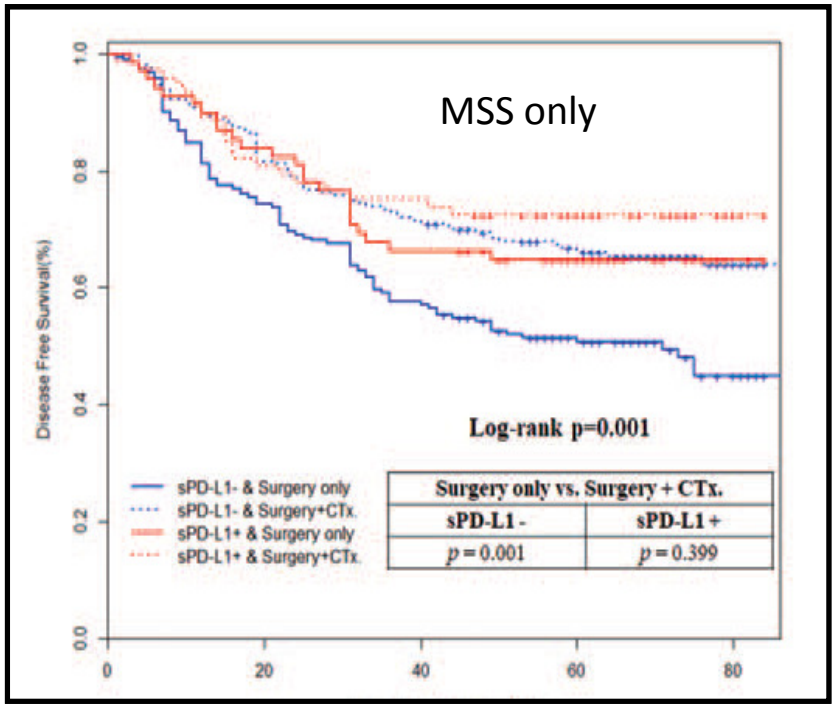
No benefit to adjuvant chemotherapy in MSI-H gastric cancer

Smyth et al, JAMA Oncol. 2017 Sep 1;3(9):1197-1203.,
Choi et al,. Ann Surg; 2018,

PD-L1 AS A BIOMARKER IN OPERABLE GC:
PROGNOSTIC AND PREDICTIVE EFFECTS OF MSI AND PD-L1 IN CLASSIC



PD-L1 is prognostic in MSS patients in the trial as a whole

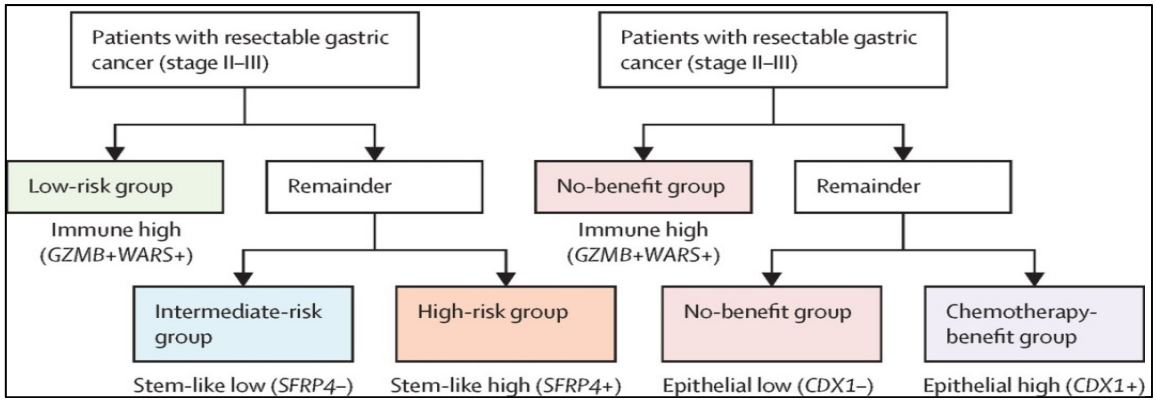


Chemo appears to benefit MSS PD-L1 negative patients > MSS PD-L1 positive

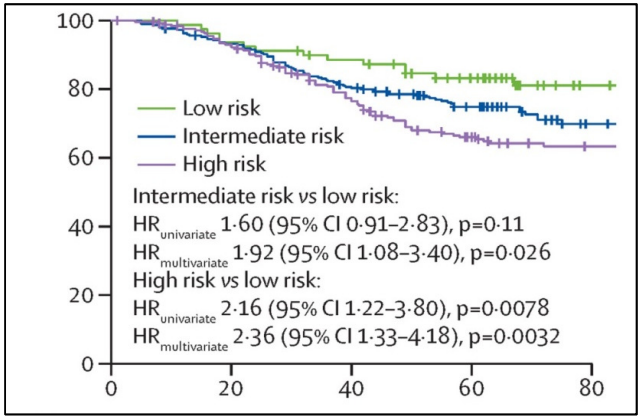
Choi et al, Ann Surg 2018

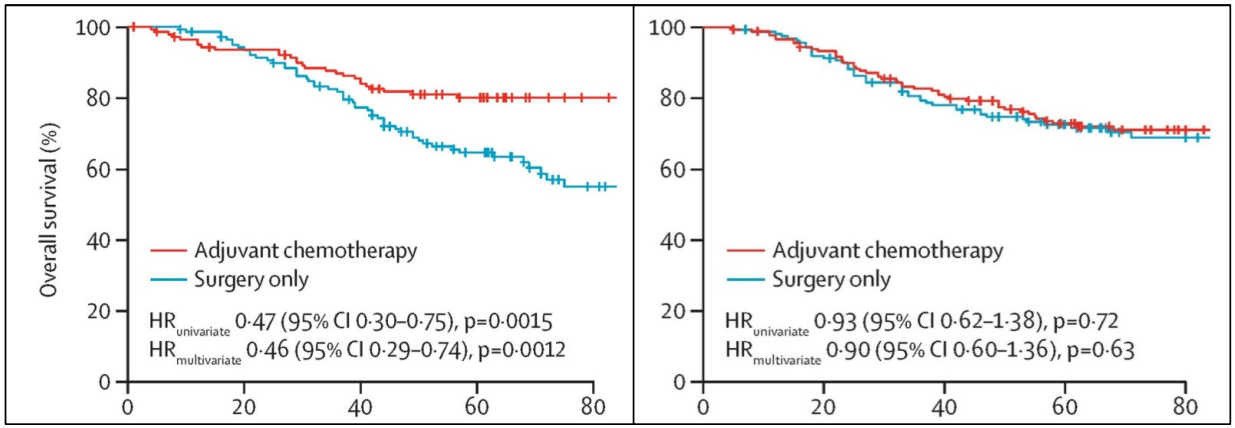
PROGNOSTIC AND PREDICTIVE GENE SIGNATURES IN CLASSIC

Prognostic



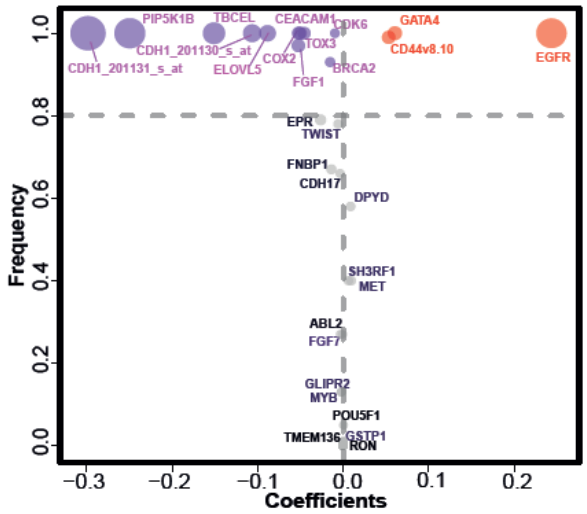
Predictive

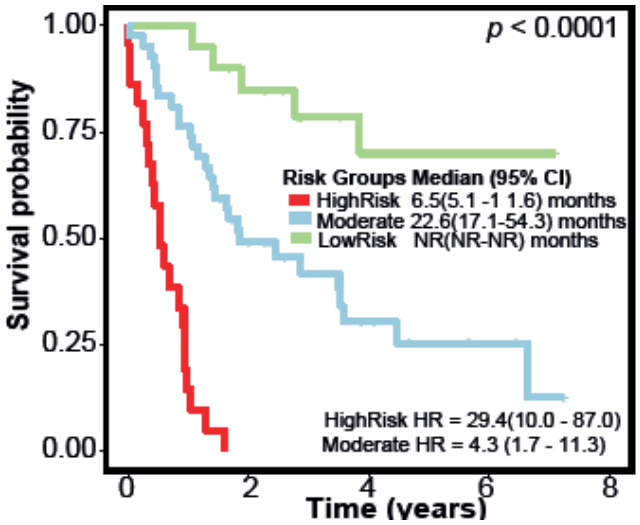


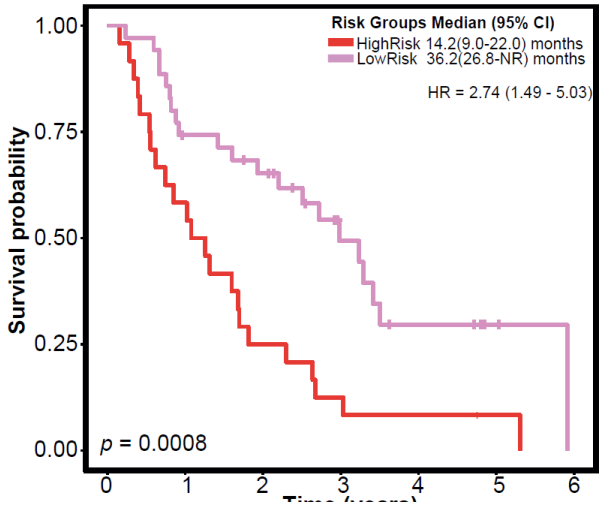


Cheong et al, Lancet Oncol. 2018 May;19(5):629-638.

PROGNOSTIC POST-CHEMOTHERAPY GENE SIGNATURE MAGIC







Prognostic gene selection

Smyth, Sadanandam et al, accepted, Annals of Oncology

BIOMARKERS

Take home messages

- Lymph node metastases are a more important prognostic marker than tumour regression grade
- Mismatch repair deficient tumours do not appear to benefit from perioperative or neoadjuvant chemotherapy
- Gene signatures show promise for selection for chemotherapy, however require prospective validation.

CANCER RESEARCH UK

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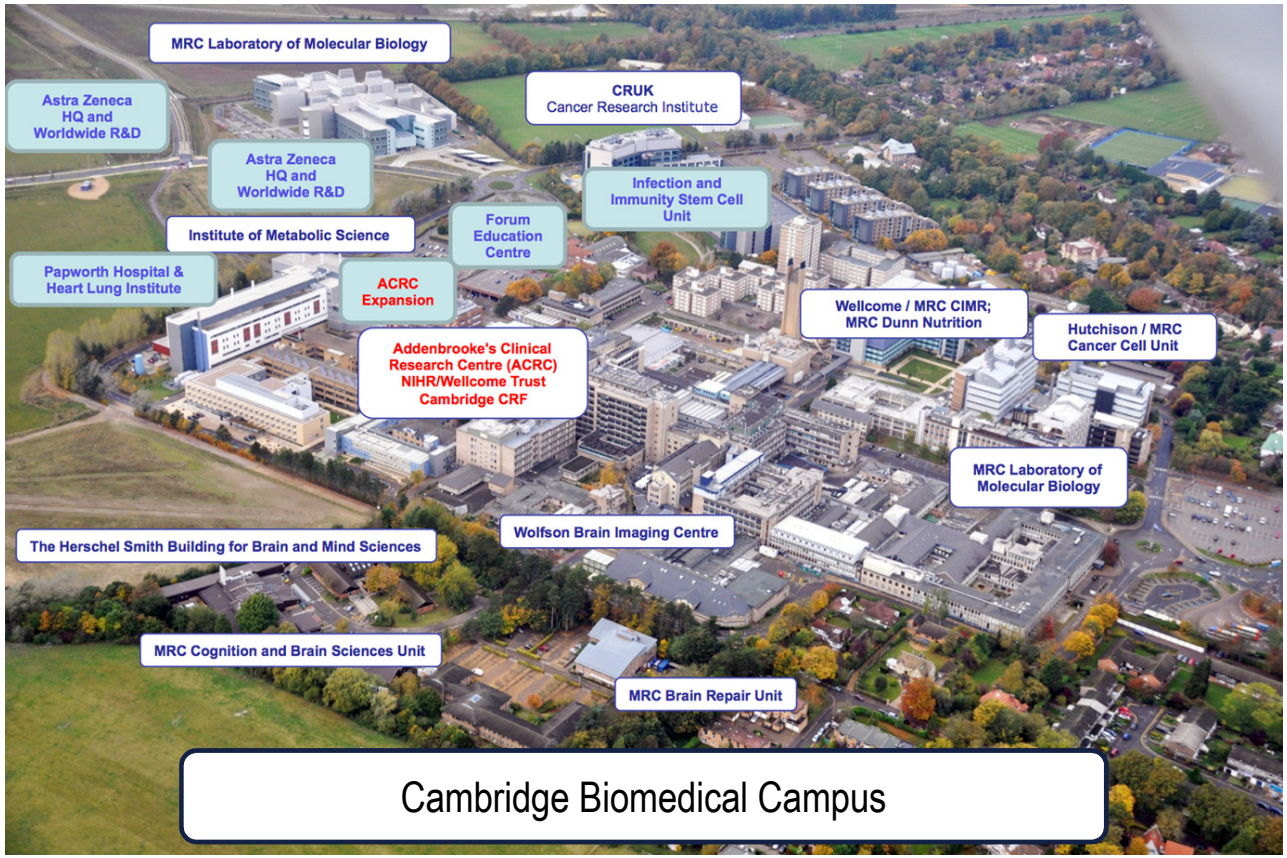
Leading science for better health



Cambridge Biomedical Campus

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