Chemotherapy in metastatic gastric cancer:
Two vs Three drugs?
Which one to choose over another?
How to sequence?

Advanced Gastroesophageal Cancers

- ~ 46,000 new gastric and esophageal cancer cases and ~ 27,000 deaths estimated for 2020; up to 30% of patients with gastroesophageal cancers present with metastatic disease[1,2]
  - Median OS for patients with advanced gastroesophageal cancer generally < 12 months[3]
- First-line treatment for advanced disease is generally selected based on patient age/functional status and biomarker findings
  - Frequently consists of chemotherapy (singlet/doublet/triplet regimens based on patient fitness) ± trastuzumab (if HER2 overexpressed)

1. Siegel. CA Cancer J Clin. 2020;70:7. 2. SEER Stomach Cancer 2020. 3. Tabernero. ASCO 2019. Abstr LBA4007.

PALLIATIVE chemotherapy compared to BSC … improves survival and quality of life

		Chemo	BSC	HR	95%CI
Murad Cancer 1993	FAMTX	30	10	0,33	0,17 - 0,64
Pyrhonen BJC 1995	FEMTX	21	20	0,25	0,25 - 0,47
Scheithauer Ann Hematol 1996	ELF	52	51	0,49	0,33 - 0,74
total		103	81	0,39	0,28 - 0,52

Cochrane DatabaseSystRev. 2010 Mar 17;3:CD004064

overall survival : 11 m vs 4,3 m, p < 0,00001

Prognostic Factors

- PS gr 2 or 3
- Hepatic Metastases
- Peritoneal Carcinomatosis
- Alkaline Phosph > 100 UI

ECF vs FAMTX
ECF vs MCF
Fuc vs FUcMMC

1080 patients

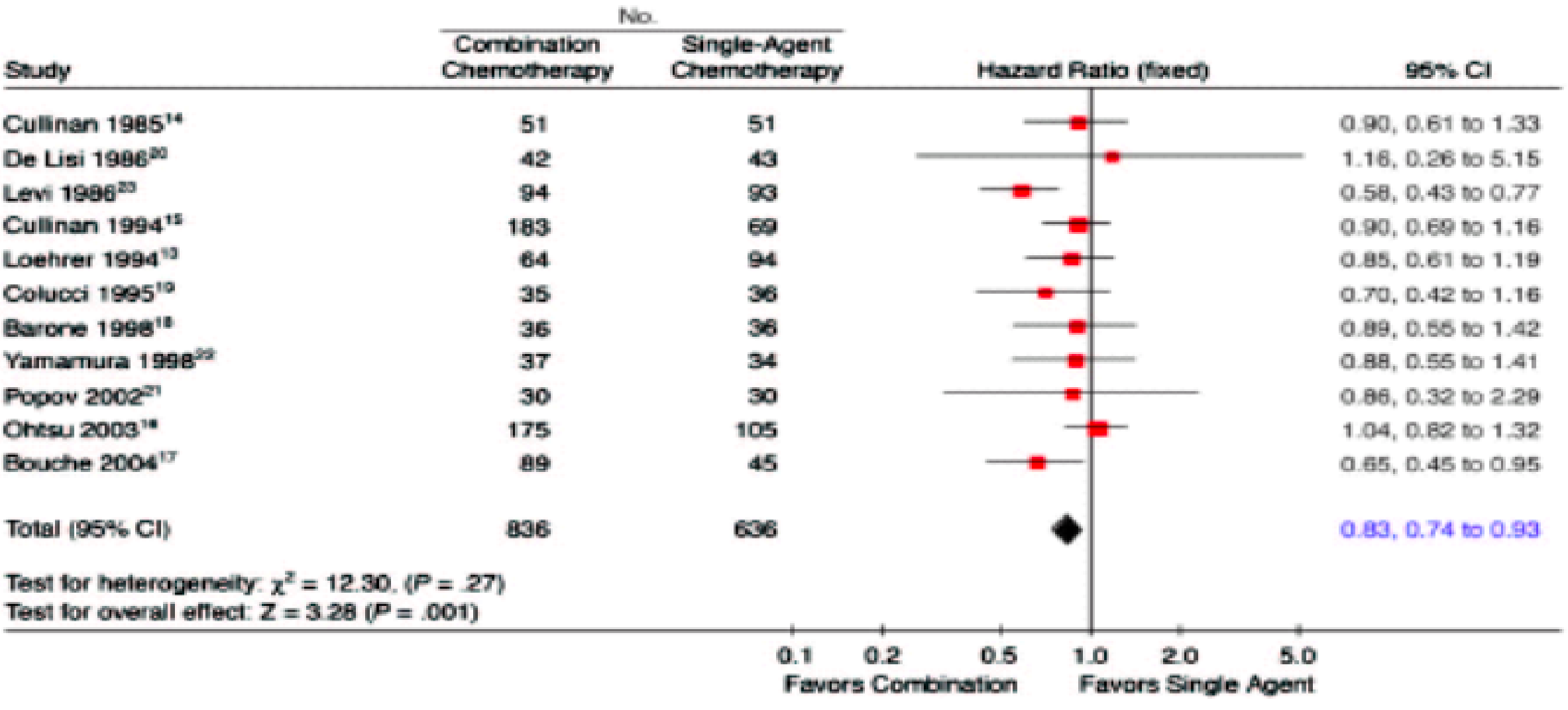
0 = « good »	:	11.8 months
1 or 2 = intermediate:		7.4 months
3 or 4 = poor	:	4.1 months

Chau et al. J Clin Oncol 2004

Cytotoxics in advanced gastric cancer

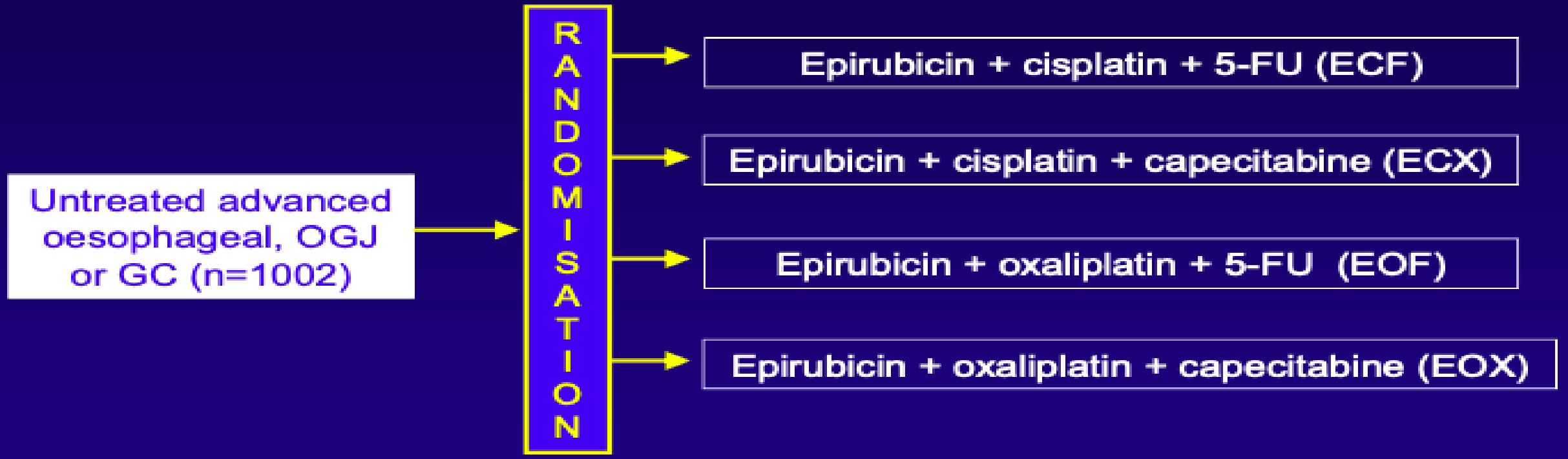
- Fluoropyrimidines: IV 5-FU vs oral
  - ✓ Capecitabine
  - ✓ S1
- Platinums
  - ✓ oxaliplatin versus cisplatin
- Taxanes:
  - ✓ docetaxel
  - ✓ paclitaxel
- Topo-isomerase inhibitors: irinotecan
- Anthracyclines: epirubicin

Chemo : Combo Vs Single



Wagner A et al. JCO 2006;24: 2902-9

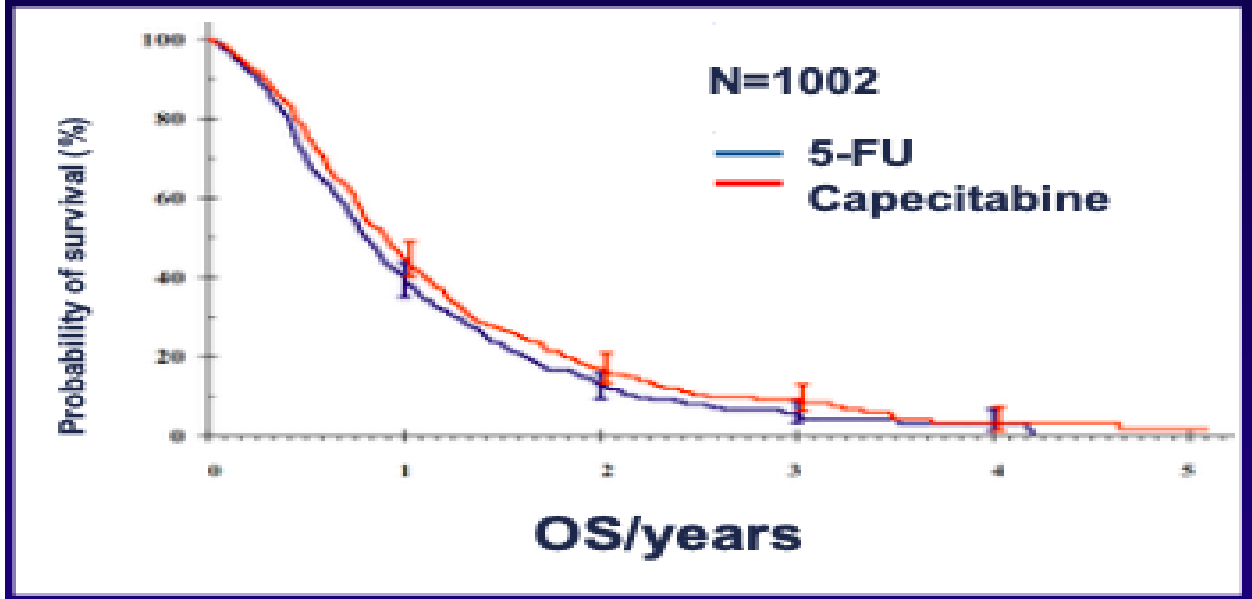
REAL-2: study in advanced gastric & oesophageal adenocarcinoma



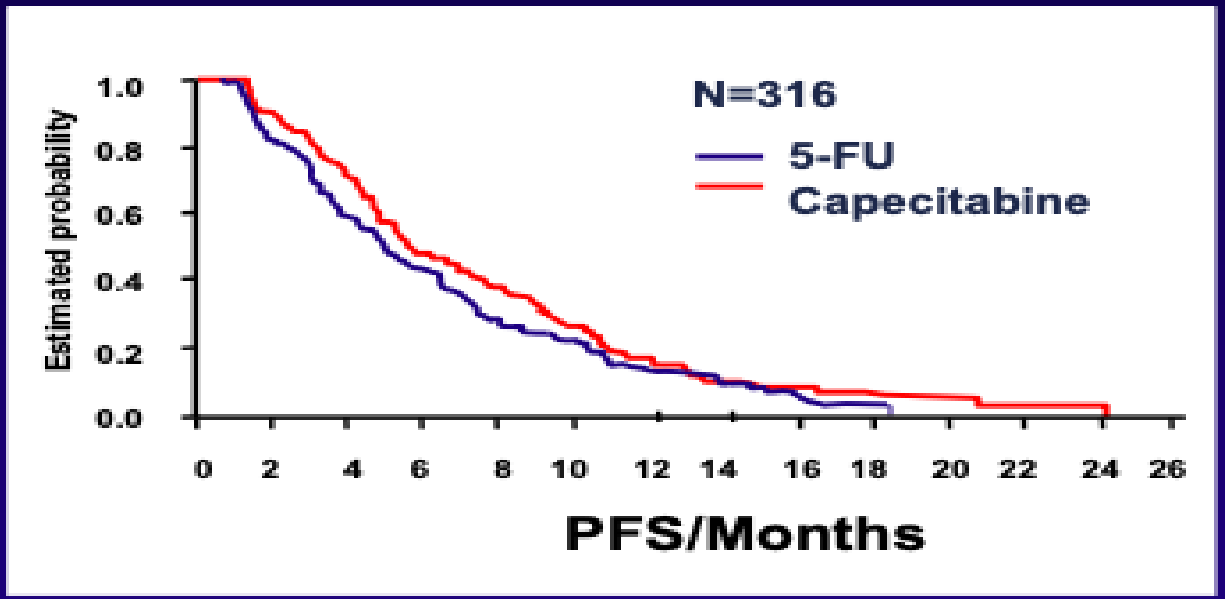
Cunningham D et al. NEJM 2008

TRIALS DEMONSTRATING NON-INFERIORITY FOR CAPECITABINE

REAL-2[1]



ML17032[2]



Primary endpoint:

Overall survival

HR 0.86 (0.80–0.99)*

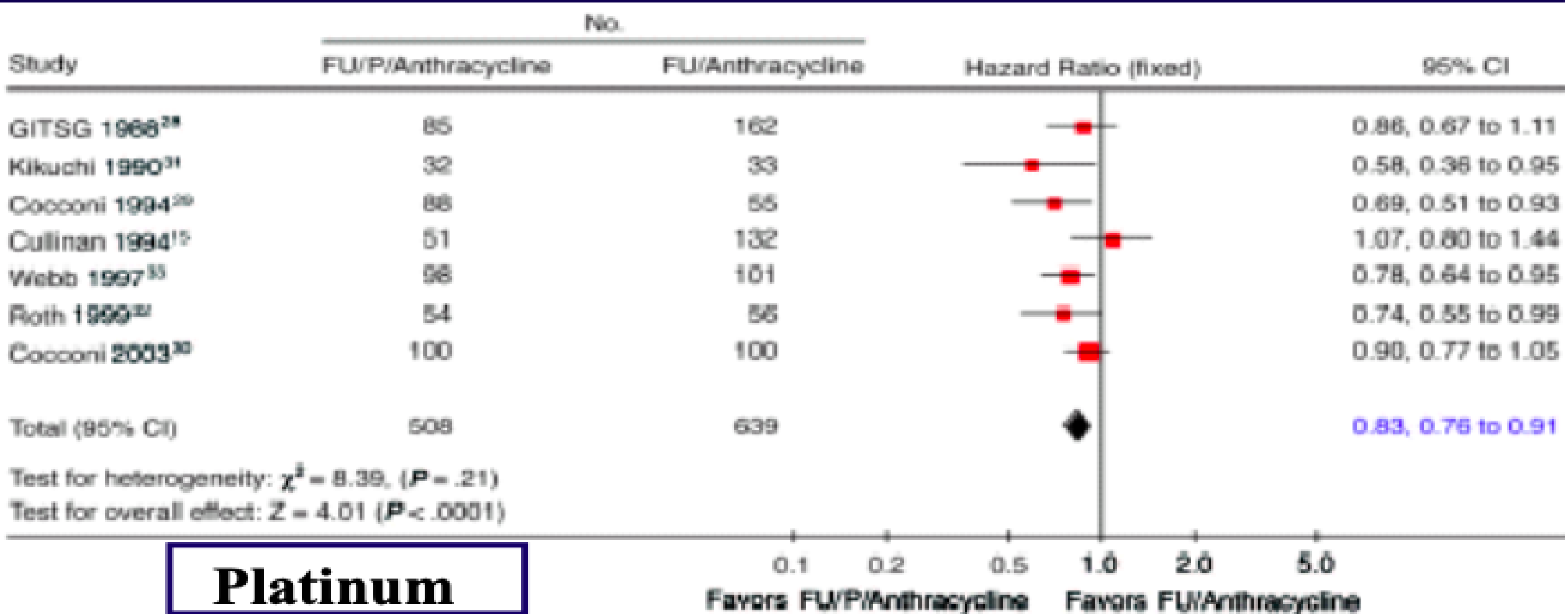
Progression-free survival

HR 0.81 (0.63–1.04)*

*Per protocol population

[1]Cunningham et al. NEJM 2008; [2]Kang et al. Ann. Oncol 2009

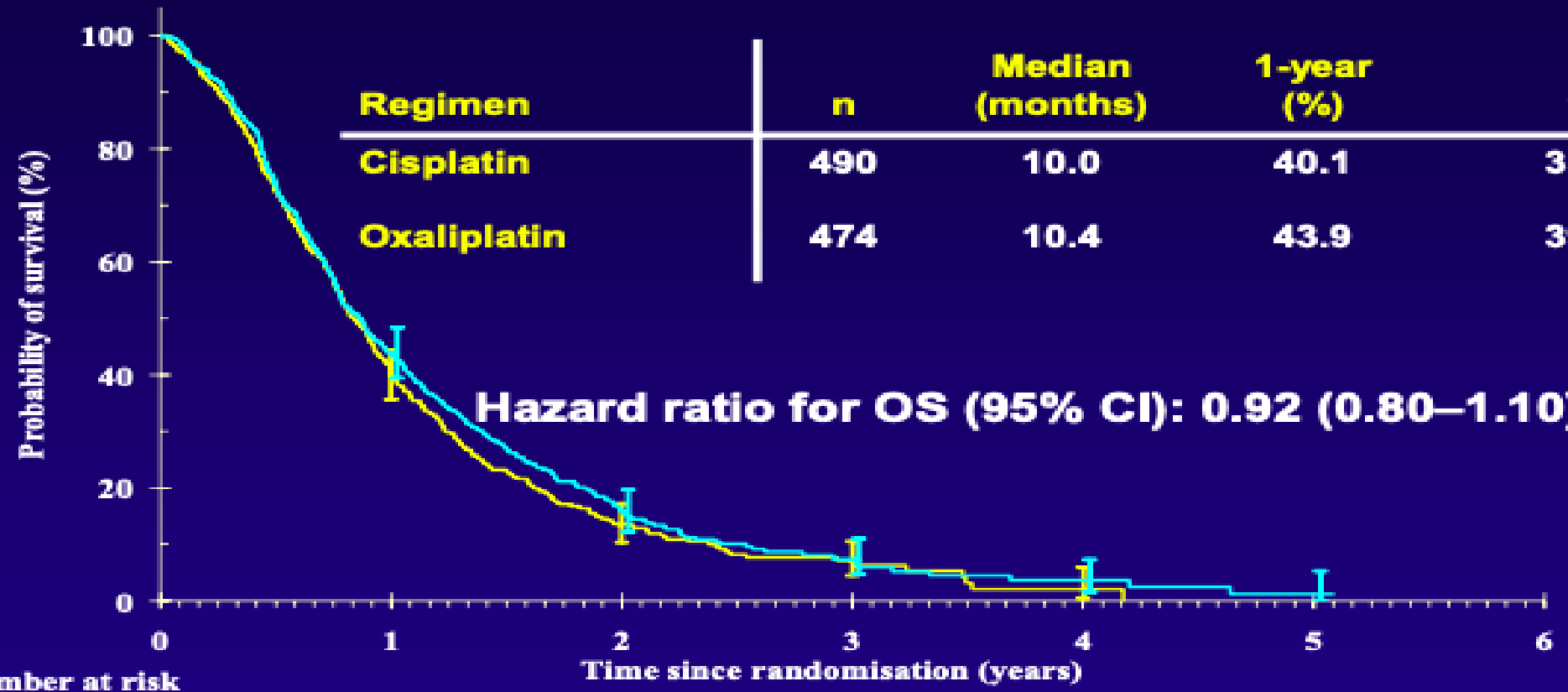
Treatment of advanced gastric cancer: role of cisplatin



Platinum

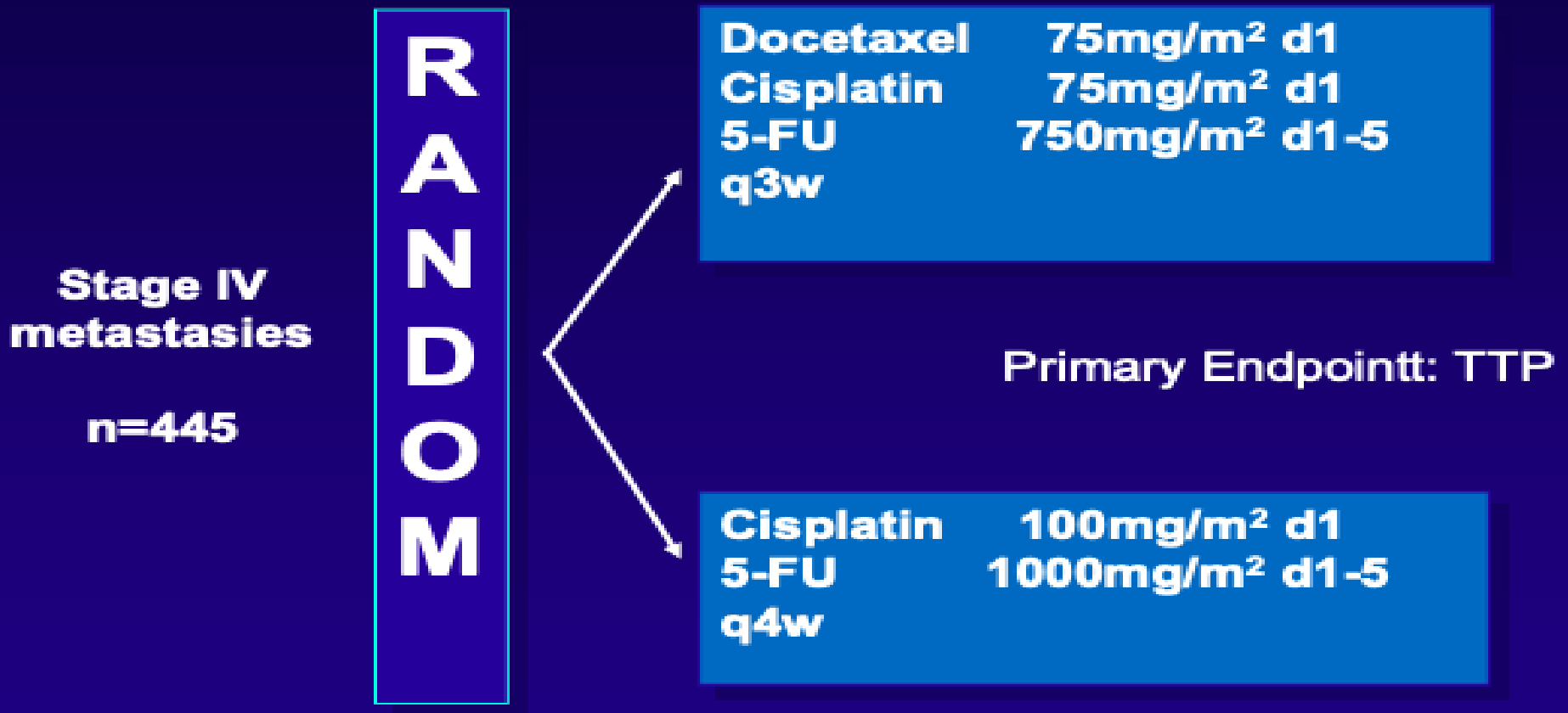
REAL-2: oxaliplatin- vs cisplatin-based chemotherapy

Regimen	n	Median (months)	1-year (%)	95% CI
Cisplatin	490	10.0	40.1	35.7–48.4
Oxaliplatin	474	10.4	43.9	39.4–49.0



Cunningham D, et al. N Engl J Med 2008.

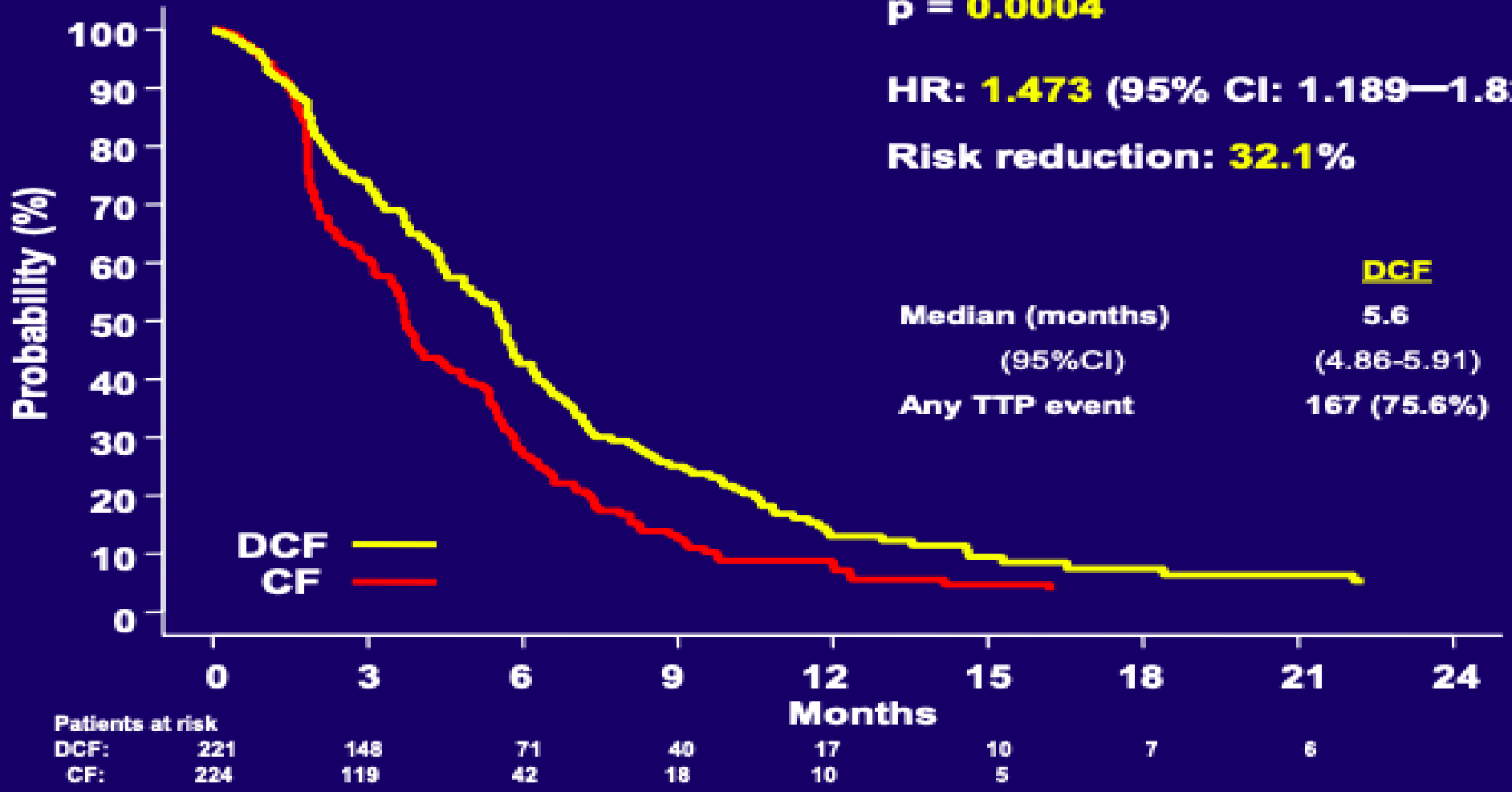
Docetaxel in addition to DDP + 5-FU
TAX325



Primary Endpointt: TTP

Van Cutsem et al. *J Clin Oncol* 2006; 24: 4991-7

Docetaxel in gastric cancer – TTP



p = 0.0004

HR: 1.473 (95% CI: 1.189—1.825)

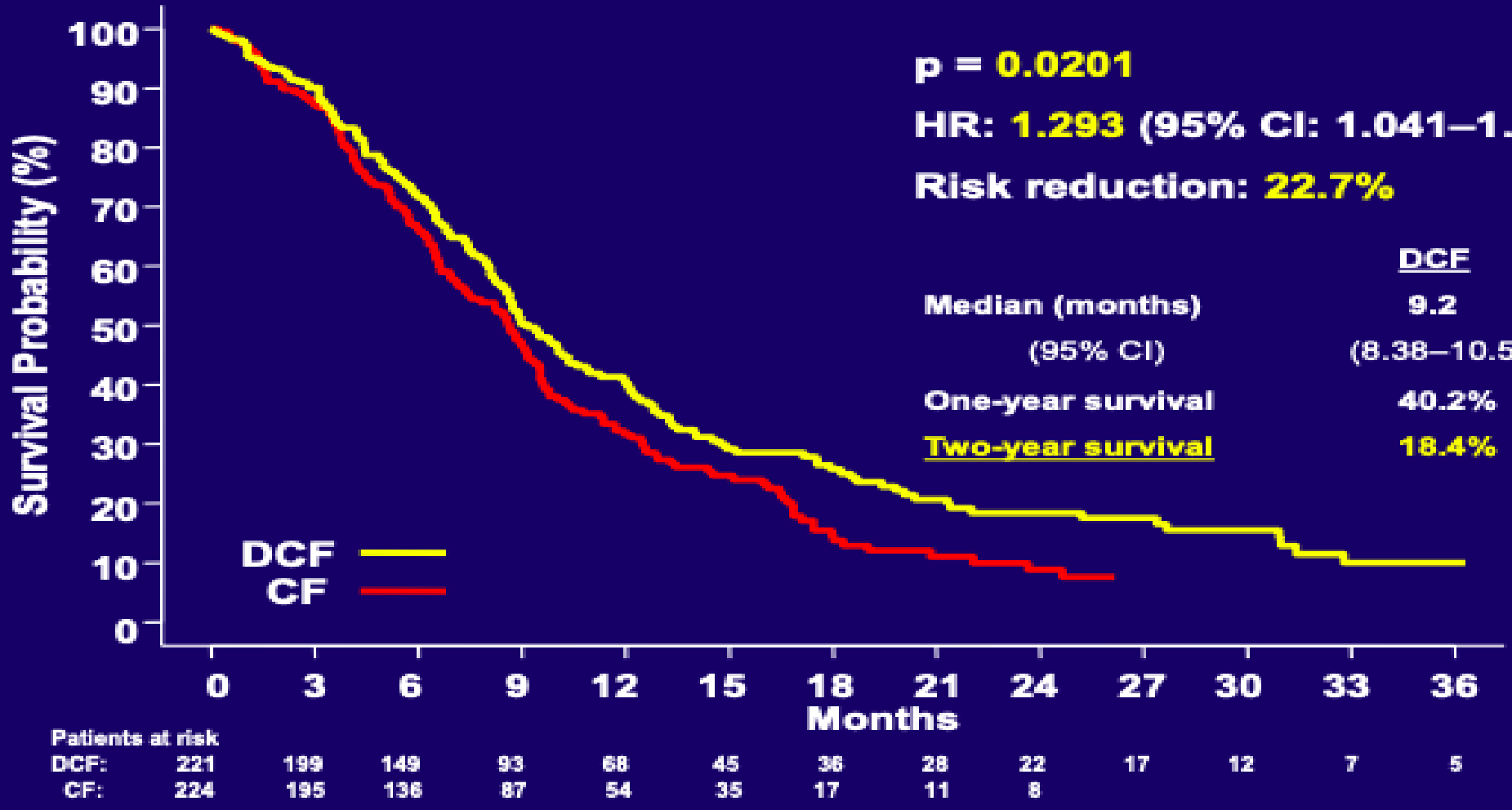
Risk reduction: 32.1%

	DCF	CF
Median (months)	5.6	3.7
(95%CI)	(4.86-5.91)	(3.45-4.47)
Any TTP event	167 (75.6%)	174 (77.7%)

Van Cutsem E et al. J Clin Oncol 2006;24:4991-4991

TAX325: Secondary Efficacy Endpoints

• OVERALL SURVIVAL – Final analysis



p = 0.0201

HR: 1.293 (95% CI: 1.041–1.606)

Risk reduction: 22.7%

	DCF	CF
Median (months)	9.2	8.6
(95% CI)	(8.38–10.58)	(7.16–9.46)
One-year survival	40.2%	31.6%
Two-year survival	18.4%	8.8%

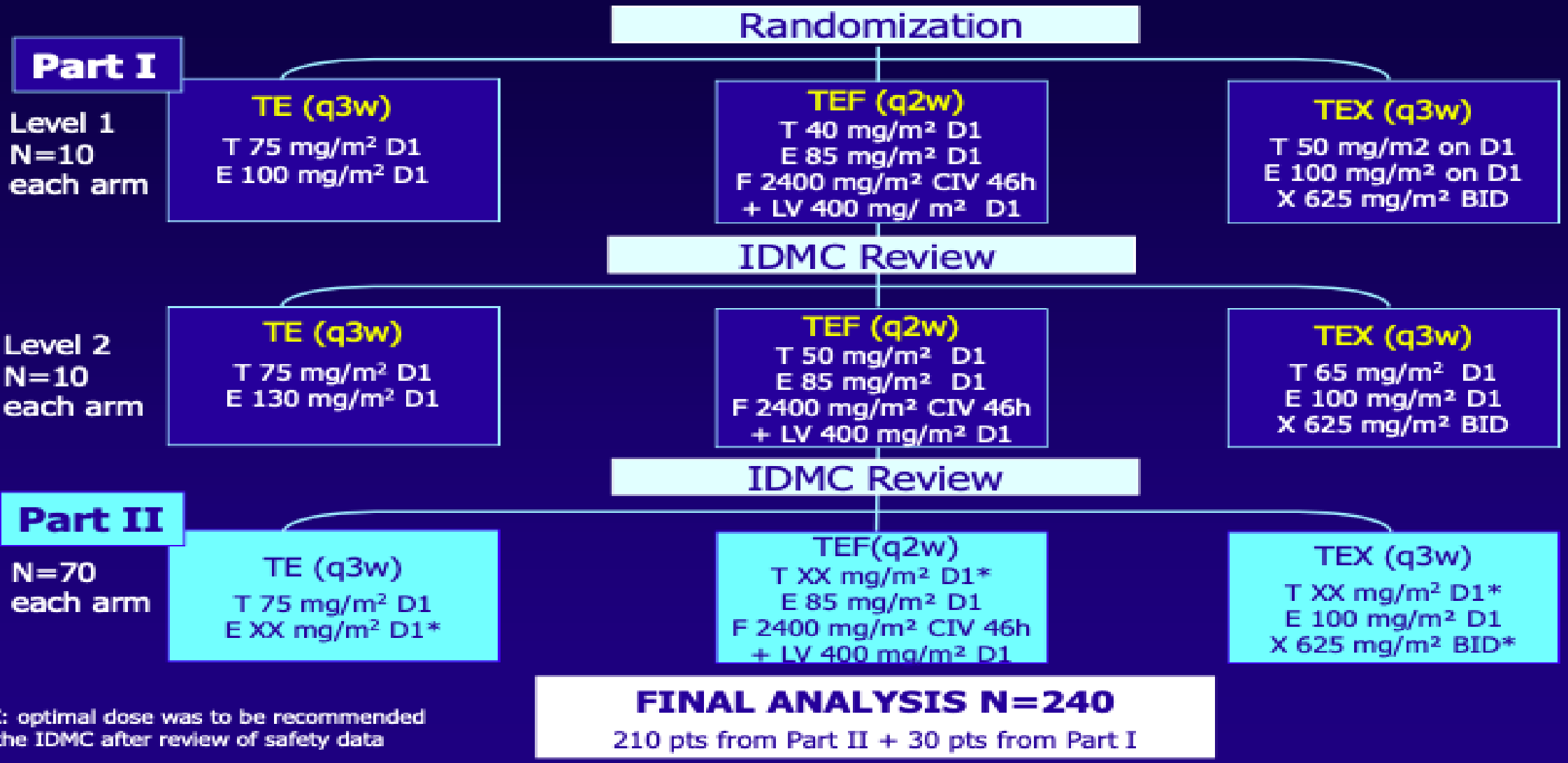
• OVERALL RESPONSE RATE

	DCF	CF	χ^2
% (95% CI)	36.7% (30.3 - 43.4)	25.4% (19.9 - 31.7)	0.0106

Van Cutsem E et al. J Clin Oncol 2006;24:4991-4991

GATE Study

Modified docetaxel regimens

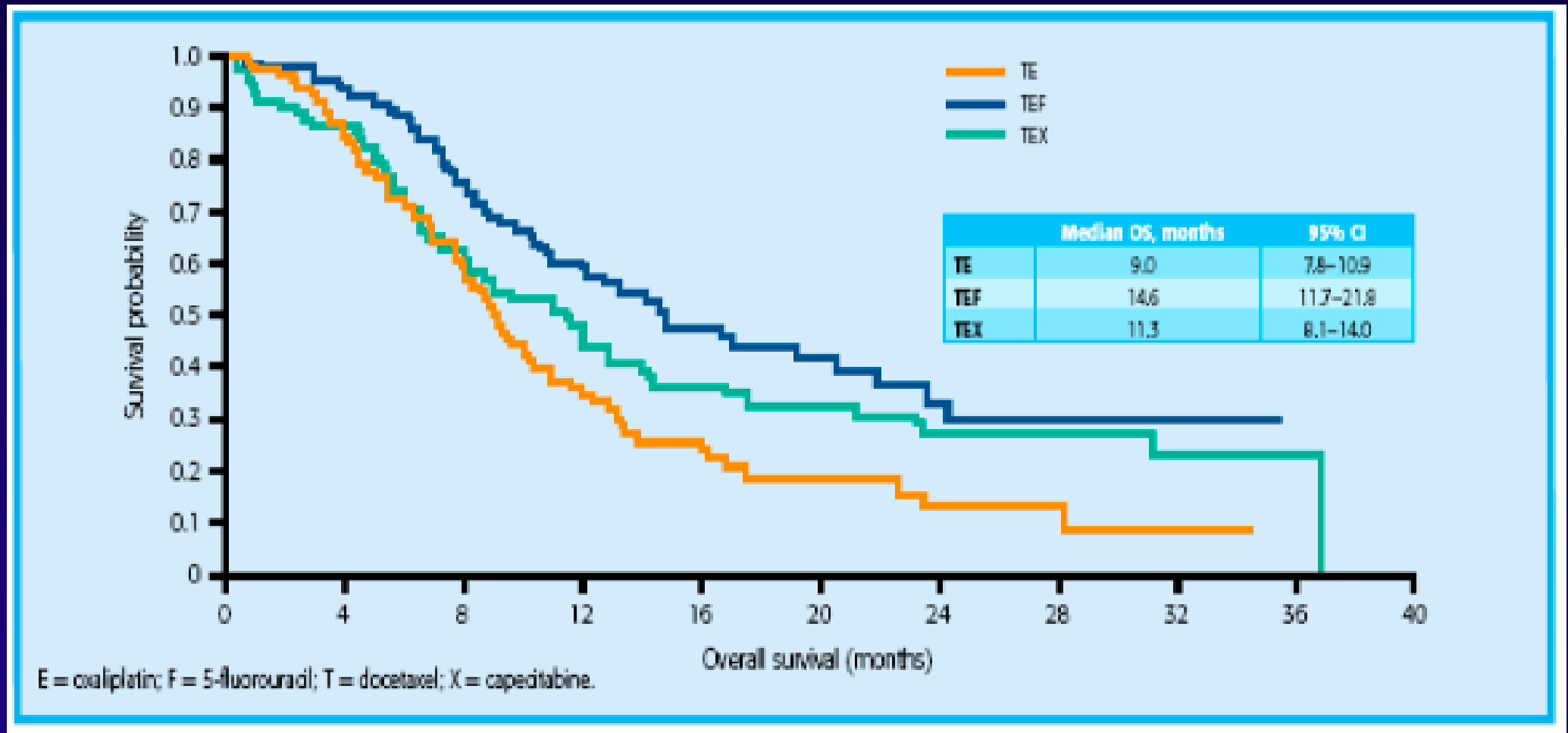


*XX: optimal dose was to be recommended by the IDMC after review of safety data

T, docetaxel; E, oxaliplatin, F, fluorouracil; X, capecitabine; LV, leucovorin; CIV, continuous infusion; IDMC, independent data monitoring committee; D1, day 1

Van Cutsem E et al, Proc ASCO 2011

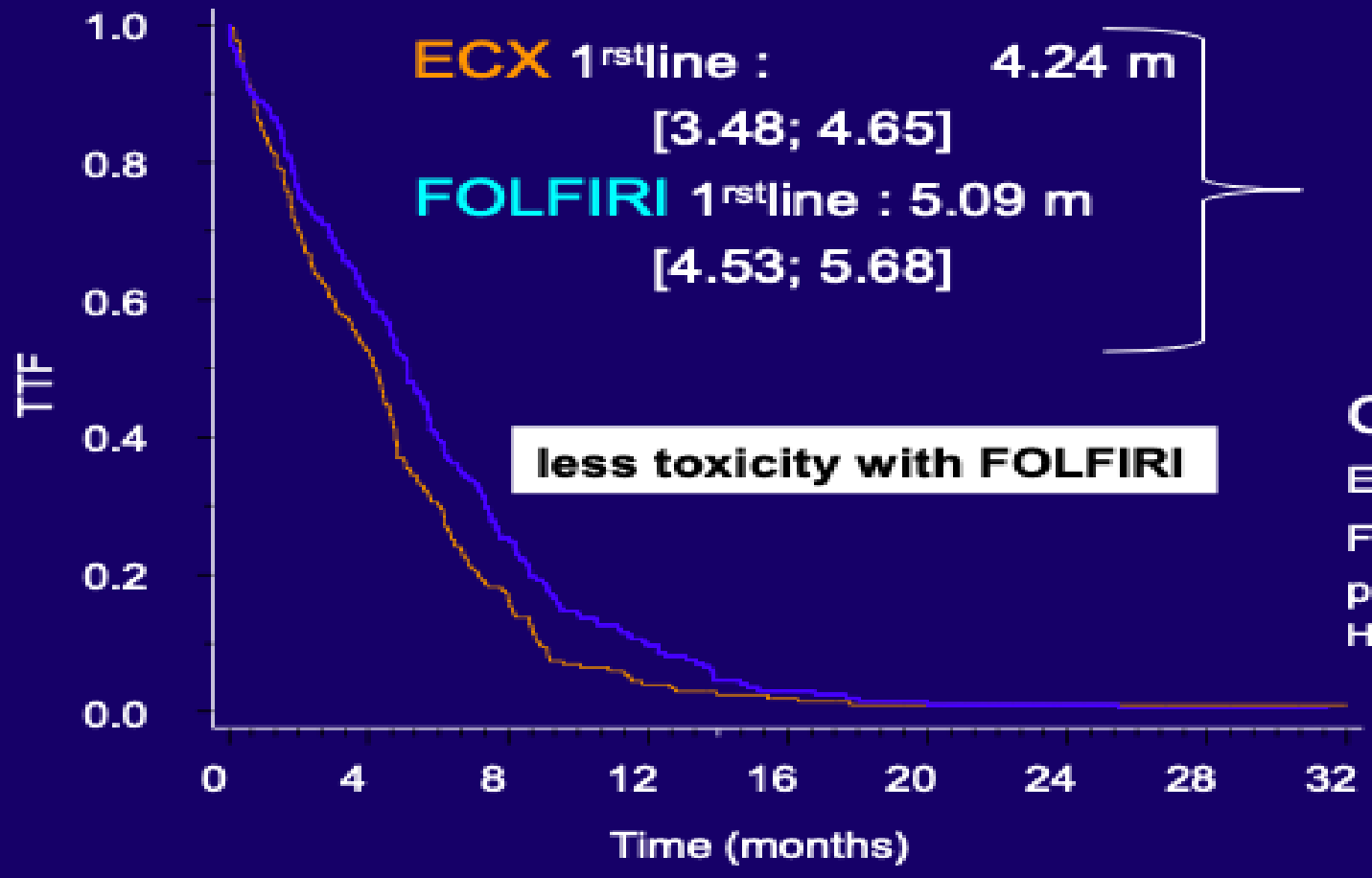
Gate Study: Overall Survival*



	Median OS, months	95% CI
TE	9.0	7.8–10.9
TEF	14.6	11.7–21.8
TEX	11.3	8.1–14.0

E = oxaliplatin; F = 5-fluorouracil; T = docetaxel; X = capecitabine.

FNLCC-GERCOR-FFCD 0307
FOLFIRI / ECX as first line CT : primary objective : Time to First line treatment Failure



ECX 1rstline : 4.24 m
[3.48; 4.65]

FOLFIRI 1rstline : 5.09 m
[4.53; 5.68]

less toxicity with FOLFIRI

p (Log-rank)= 0.008

HR (B vs A)= 0.77 [0.63;0.94]

Overall Survival : NS

ECX 1st line) : 9.49 m.[8.77; 11.14]

FOLFIRI 1st line) : 9.72 m.[8.54; 11.27]

p (Log-rank)= 0.95

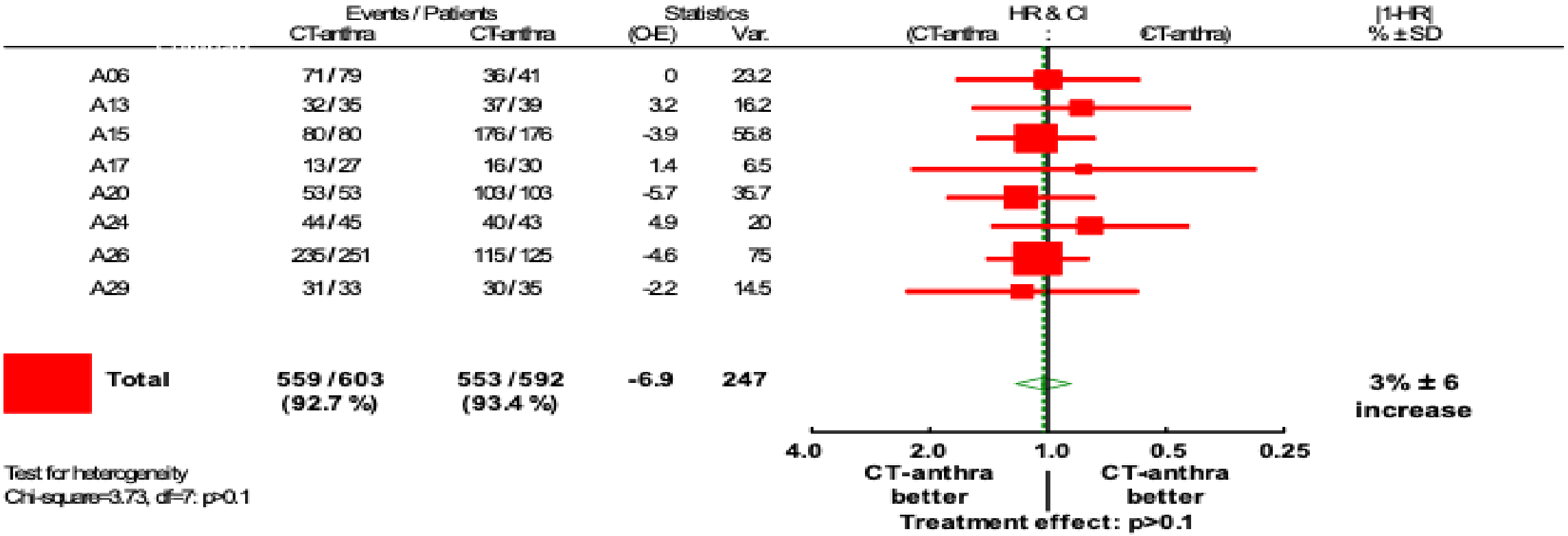
HR (B vs A)= 1.01 [0.82; 1.24]

⇒ FOLFIRI offers a Better profile in 1rst line treatment…

Guimbaud R et al ASCO 2010

GASTRIC - Metaanalysis

Any CT without anthracyclines *vs.* any CT with anthracyclines



Treatment effect P = 0.66

Bouche O, X Paoletti et al, Metaanalysis – GASTRIC 2009

Original Research Article

http://www.ijhsr.org/

Gastric Cancer- Clinical Profile from a Single Center Experience in South India

Giri GV, Lakshmaiah. KC Govind Babu.K, Linu Abraham Jacob, Suresh Babu M.C, Lokanatha D, Suparna

Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India

International Journal of Health Sciences and Research Vol.9; Issue: 12; December 2019

Table 1: Stage wise distribution of DFS in adjuvant and OS in metastatic (including range)

STAGE	NUMBER	MEDIAN AGE	M: F	SURGERY	CHEMO	RT
I	2	62	2 to 0	Radical and subtotal gastrectomy	None	none
II	12	55	8 to 4	12 patients- 1 subtotal, 8 distal, 1 total gastrectomy , THE in 2 patients	Adjuvant CF in subtotal, 5 ECF in distal, two distal – no chemotherapy, one distal –adjuvant ECF, ECF in total, NACT- ECF in 1 THE, no chemotherapy in the other	none
III	3	60	3 to 0	1 distal, 1 post radical and 1 THE	Mc Donald's in the 1st, no chemotherapy in the post radical & 1 ECF in THE	1 patient with Mc Donald's
IV	8	44	4 to 4	none	Palliative – 5 ECF, 1 DCF and 1 FOLFOX	none
Locally advanced	22	56	16 to 6	none	18 patients – 10 received ECF, 3 patients DCF, 2 patients CF, 1 patient Carboplatin+paclitaxel, 2 patients received docetaxel+cisplatin	

THE= Transhiatal esophagectomy; CF= cisplatin, 5-fluorouracil; ECF = epirubicin, cisplatin, 5-fluorouracil;NACT= neo-adjuvant chemotherapy; DCF = docetaxel, cisplatin, 5-fluorouracil

Original Article

Efficacy and safety of first-line systemic chemotherapy with epirubicin, cisplatin plus 5-fluorouracil and docetaxel, cisplatin plus 5-fluorouracil regimens in locally advanced inoperable or metastatic gastric or gastroesophageal junction adenocarcinoma: A prospective phase II study from South India

Babu KG, Chaudhuri T, Lakshmaiah KC, Dasappa L, Jacob LA, Babu MCS, Rudresha AH, Lokesh KN, Rajeev LK

Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

Indian J Cancer 2017;54:47-51

Table 1: Patient characteristics at baseline

Variables	ECF (*n*=30)	DCF (*n*=28)	Total (*n*=58)
Median age in years (range)	53 (35-62)	50 (31-58)	52 (31-62)
Male gender (%)	18 (60)	19 (67.8)	37 (63.8)
ECOG PS (%)			
0-1	28 (93.3)	28 (100)	56 (96.5)
2	2 (6.7)	0	2 (3.5)
Extent of disease at baseline (%)			
Locally advanced inoperable	2 (6.6)	2 (7.1)	4 (6.9)
Metastatic	28 (93.4)	26 (92.9)	54 (93.1)
Site of primary tumor (%)			
GEJ	2 (6.6)	2 (7.2)	4 (6.9)
Body of the stomach	22 (73.4)	21 (75)	43 (74.1)
Pylorus and antrum	6 (20)	5 (17.8)	11 (19)
Grade of primary tumor (%)			
Grade 1	2 (6.6)	1 (3.6)	3 (5.2)
Grade 2	19 (63.4)	20 (71.4)	39 (67.3)
Grade 3	9 (30)	7 (25)	16 (27.5)
Site of metastases (%)			
Liver	18 (60)	19 (67.8)	37 (63.8)
Nonregional lymph node	8 (26.6)	8 (28.6)	16 (27.6)
Lung	3 (10)	2 (7.1)	5 (8.6)
Peritoneum	8 (26.7)	9 (32.1)	17 (29.3)
Ovary	2 (6.7)	3 (10.7)	5 (8.6)
Number of metastatic sites involved (%)			
0 or 1	6 (20)	8 (28.6)	14 (24.1)
2	13 (43.3)	11 (39.3)	24 (41.4)
≥3	11 (36.7)	9 (32.1)	20 (34.5)

GEJ=Gastroesophageal junction; ECF=Epirubicin, cisplatin plus 5-FU; DCF=Docetaxel, cisplatin plus 5-FU; FU=Fluorouracil; ECOG=Eastern Cooperative Oncology Group; PS=Performance status

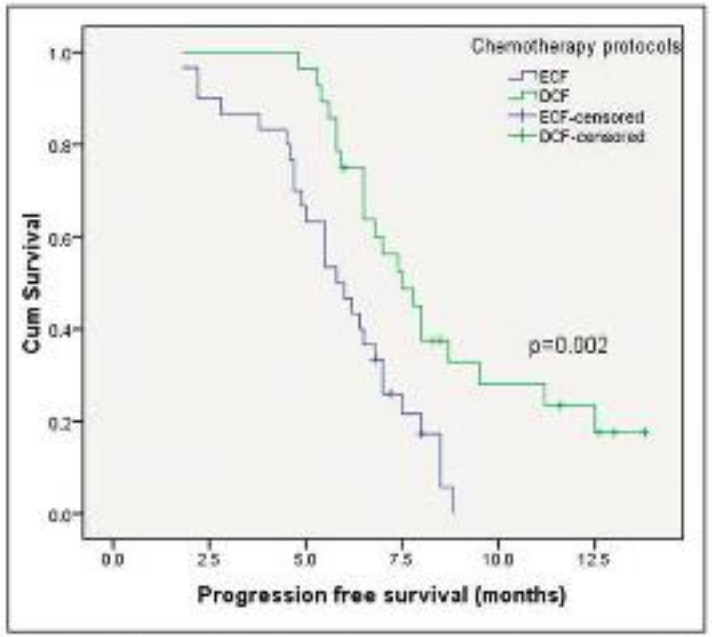


Figure 1: Kaplan–Meier estimates of progression-free survival (in months) of the patients treated with epirubicin, cisplatin plus 5-fluorouracil and docetaxel, cisplatin plus 5-fluorouracil regimens

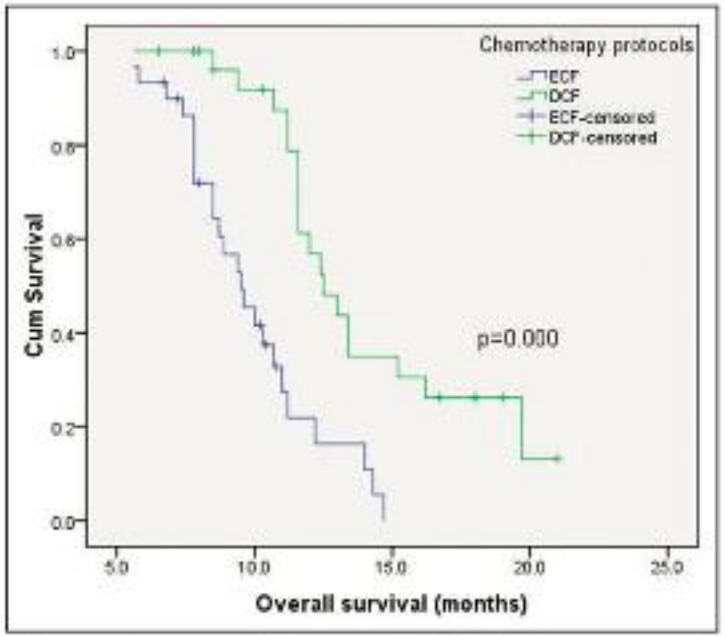
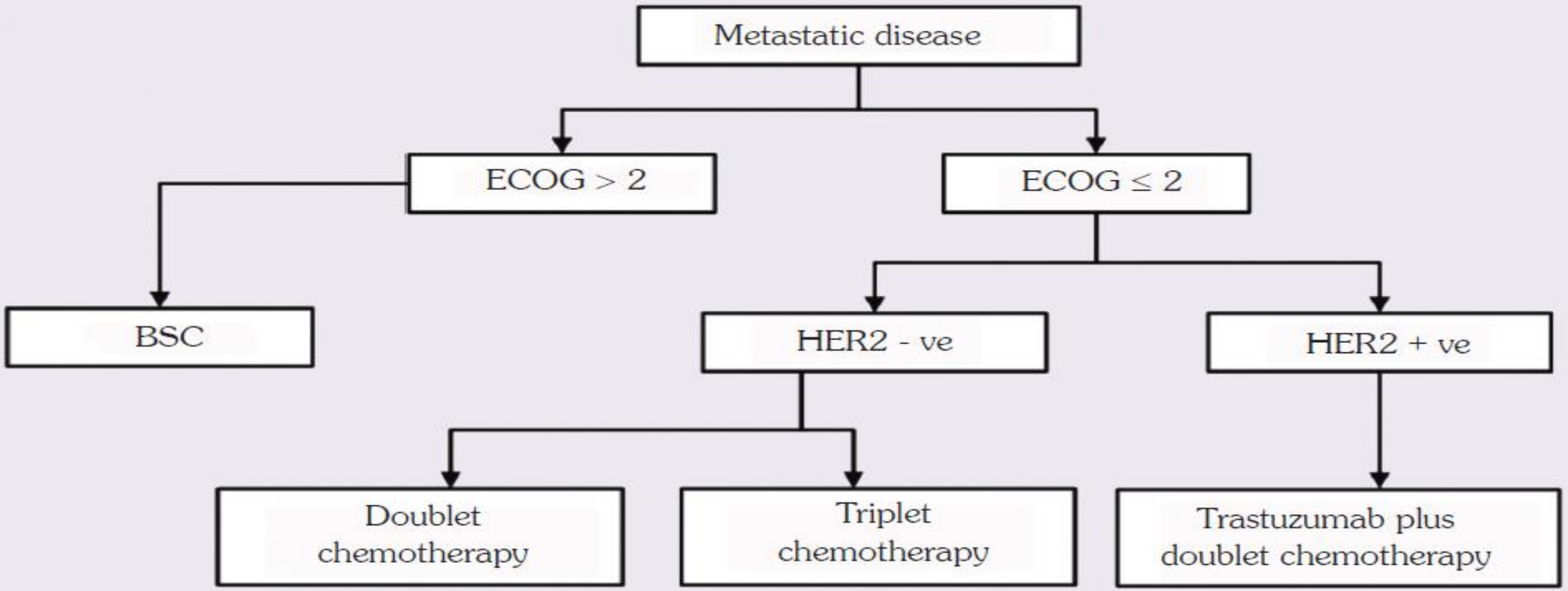


Figure 2: Kaplan–Meier estimates of overall survival (in months) of the patients treated with epirubicin, cisplatin plus 5-fluorouracil and docetaxel, cisplatin plus 5-fluorouracil regimens

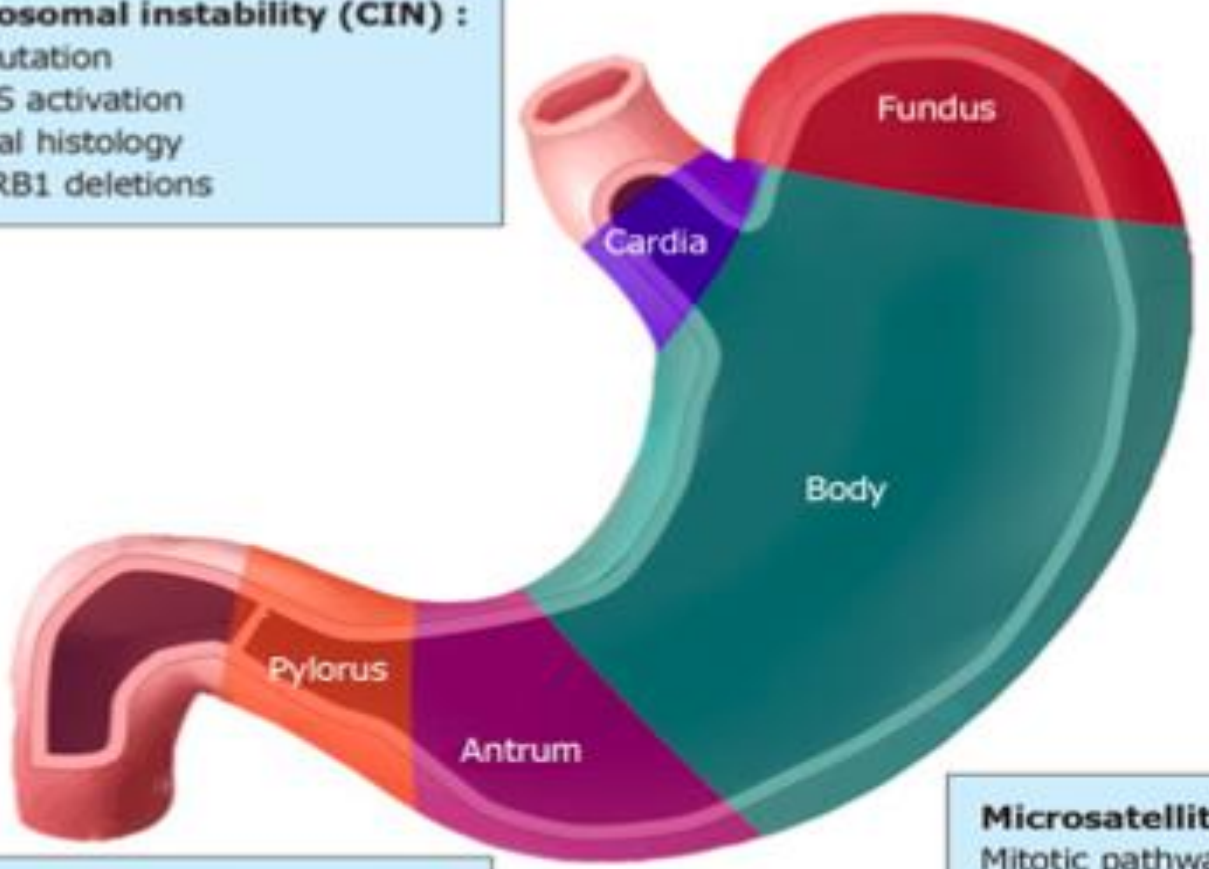
Treatment Algorithm for Metastatic Gastric Cancer



ECOG, Eastern Cooperative Oncology Group; BSC, best supportive care

Precision medicine in gastric cancer

Chromosomal instability (CIN) :
TP53 mutation
RTK-RAS activation
Intestinal histology
CDH1, RB1 deletions

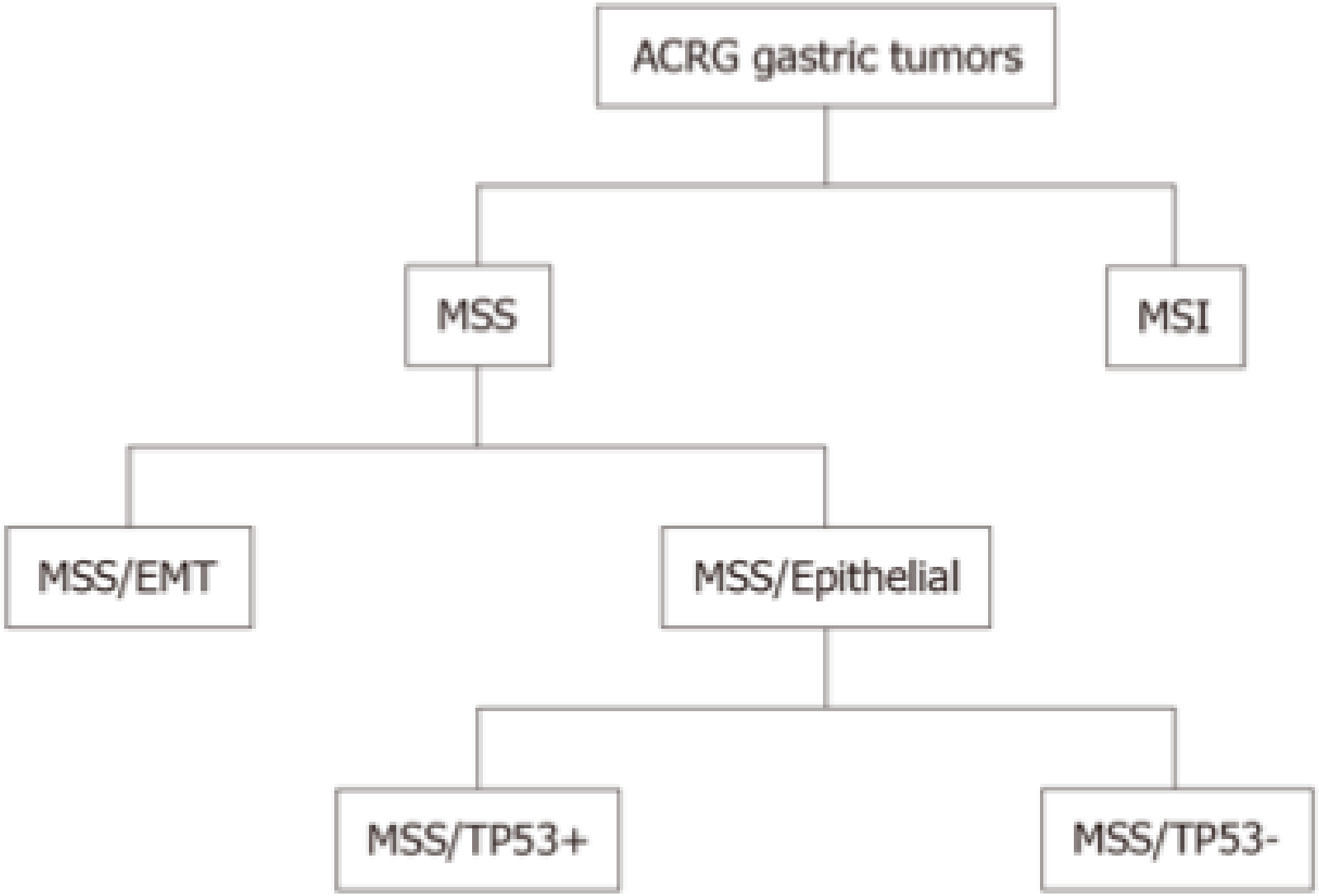


Epstein-Barr virus (EBV) :
CDKN2A silencing
PIK3CA mutation
JAK2 amplification
PDL-1/2 overexpression

Genomically stable (GS) :
CDH1, RHOA, ARDI1A, mutations
CLDN18-ARHGAP fusion
Diffuse histology
Cell adhesion

Microsatellite instable (MSI) :
Mitotic pathways activated
Methylation of DNA mismatch repair genes (MLH1 silencing)
Hypermutation of PI3KCA, ERBB3, RNF43, PTEN, KRAS, TP53, ARID1A

World J Gastrointest Oncol 2019 October 15; 11(10): 804-829


ACRG gastric tumors
MSS
MSI
MSS/EMT
MSS/Epithelial
MSS/TP53+
MSS/TP53-

FDA-Approved Indications for Checkpoint Inhibitors in Gastroesophageal Cancers

Indication	Pembrolizumab	Nivolumab
Gastric	▪ Recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma expressing **PD-L1 (CPS ≥ 1**) with PD on or after ≥ 2 previous therapies including fluoropyrimidine- and platinum-containing chemotherapy ± HER2-targeted therapy	
Esophageal	▪ Recurrent locally advanced or metastatic esophageal squamous cell carcinoma expressing **PD-L1 (CPS ≥ 10)** with PD after ≥ 1 previous lines of systemic therapy	▪ Unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after previous fluoropyrimidine- and platinum-based chemotherapy
Tumor agnostic	▪ Unresectable or metastatic **MSI-H or MMR deficient** solid tumors progressing after previous treatment with no satisfactory alternative treatment options ▪ Unresectable or metastatic **TMB-H (≥ 10 mut/Mb)** solid tumors progressing after previous treatment with no satisfactory alternative treatment options	

Nivolumab PI. Pembrolizumab PI.

Slide credit: clinicaloptions.com

Molecular Testing in Gastric Cancer

- Recommended molecular testing
  - HER2 (IHC or FISH, NGS for amplification)
  - **dMMR/MSI (IHC/PCR, other techniques)**
  - **PD-L1 (IHC)**
  - **TMB**
  - NTRK (RNA fusion)
- Germline
  - CDH-1 and a long list of others (FAP, Lynch, etc)

Slide credit: clinicaloptions.com

Select Ongoing or Recently Completed Phase III Studies of ICIs for Gastroesophageal Cancers

First-line Treatment for Advanced Disease			
Study	**Phase**	**Treatment**	**Population**
KEYNOTE-811 (NCT03615326)	III	Pembrolizumab + trastuzumab vs CT + trastuzumab	Previously untreated locally advanced unresectable or metastatic HER2+ gastric/GEJ adenocarcinoma
KEYNOTE-859 (NCT03675737)	III	Pembrolizumab + CT vs CT	Previously untreated locally advanced unresectable or metastatic HER2- gastric/GEJ adenocarcinoma
CheckMate 649 (NCT02872116)	III	Nivolumab + ipilimumab or nivolumab + CT vs CT	Previously untreated advanced or metastatic gastric/GEJ adenocarcinoma
CheckMate 648 (NCT03143153)	III	Nivolumab + ipilimumab or nivolumab + CT vs CT	Previously untreated advanced, recurrent or metastatic esophageal SCC
KEYNOTE-590 (NCT03189719)	III	Pembrolizumab + CT vs CT	Previously untreated locally advanced unresectable or metastatic adenocarcinoma or SCC of the esophagus or GEJ adenocarcinoma
KEYNOTE-975 (NCT04210115)	III	Pembrolizumab + CRT vs CRT	Previously untreated unresectable esophageal adenocarcinoma

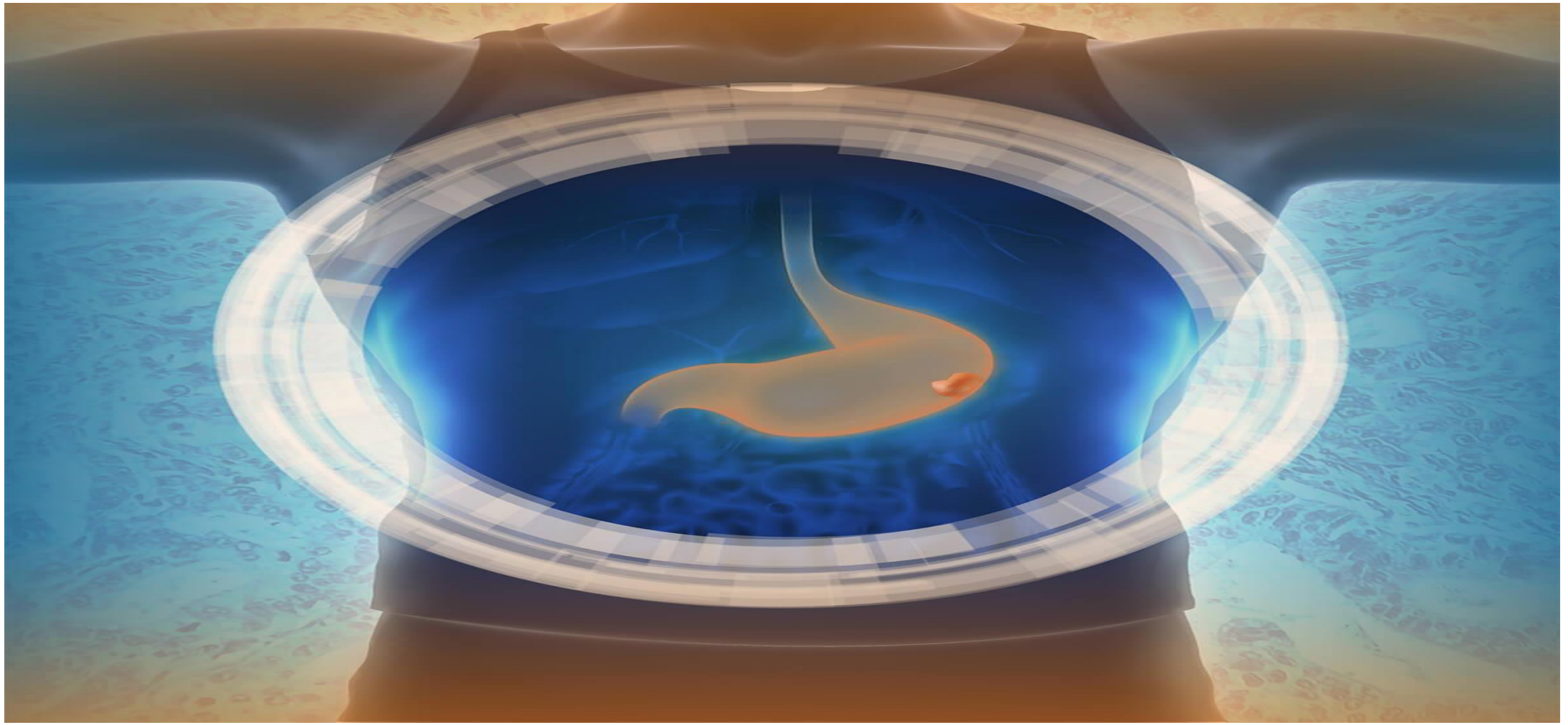
Slide credit: clinicaloptions.com

Select Ongoing or Recently Completed Phase III Studies of ICIs for Gastroesophageal Cancers

Neoadjuvant/Adjuvant Treatment for Resectable Disease			
Study	**Phase**	**Treatment**	**Population**
KEYNOTE-585 (NCT03221426)	III	Perioperative pembrolizumab + CT vs CT	Previously untreated localized gastric/GEJ adenocarcinoma
CheckMate 577 (NCT02743494)	III	Adjuvant nivolumab vs placebo	Resected esophageal/GEJ cancer
ATTRACTION-5 (NCT03006705)	III	Adjuvant nivolumab + CT vs CT	Resected gastric/GEJ adenocarcinoma
NCT03604991	II/III	Perioperative nivolumab + ipilimumab + CRT vs CRT	Previously untreated esophageal/GEJ adenocarcinoma; surgical candidate

Slide credit: clinicaloptions.com

How I treat gastric adenocarcinoma



Alsina M, Miquel JM, Diez M, et al. How I treat gastric adenocarcinoma. ESMO Open 2019

First line studies

Clinical trial	N	Treatment	OS		PFS		ORR	P value
(A) First-line chemotherapy treatment								
The V325 Trial *Van Cutsem* *J Clin Oncol 2006*	445	DPF PF	9.2 m 8.6 m	HR 1.29 p=0.02	5.6 m* 3.7 m	HR 1.47 p<0.01	37% 25%	0.01
The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) Trial *Cunningham* *NEJM 2008*	1002	EPF EPC EOF EOC	9.9 m 9.9 m 9.3 m 11.2 m	Non-inferiority meet	6.2 m 6.7 m 6.5 m 7 m		40.7% 46.4% 42.4% 47.9%	
The ML17302 Trial *Kang* *Ann Oncol 2009*	316	CP FP	10.5 m 9.3 m	HR 0.85 p=0.008	5.6 m 5.0 m	HR 0.81 p<0.01	46% 32%	0.020
The FLAGS Trial *Ajani* *J Clin Oncol 2010*	1053	P-S1 P-F	8.6 m 7.9 m	HR 0.92 p=0.2	4.8 m 5.5 m	HR 0.99 p=0.92	29.1% 31.9%	0.40
The French Intergroup Trial *Guimbaud* *J Clin Oncol 2014*	416	EPC FOLFIRI	9.49 m 9.72 m	HR 1.01 p=0.95	5.29 m 5.75 m	HR 0.99 p=0.96	39.2% 37.8%	

- **The addition of epirubicin to a chemotherapy doublet has not definitively demonstrated an OS advantage and slightly increases toxicity. In contrast, the addition of docetaxel offers a small benefit in OS but with considerable toxicity with the original docetaxel, cisplatin and 5-FU (DCF) .**

- **This latter fact together with the fact that taxanes can be given in the second line makes the use of this drug in the first-line setting rare .**

- **The original DCF regimen, or better the analogous and less toxic FLOT regimen, should only be considered in young/fit patients and if a very quick response is needed.**

Thank You