

Esophagogastric Cancer: Recent Progress in Adjuvant Therapy and Advance Disease

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Esophageal and Gastric Carcinoma

US Incidence in 2007

- **36,820 new cases**
 - Gastric: 21,260 (58%)
 - Esophagus: 15,560 (42%)
- **4% of U.S. cancer deaths**
 - Esophageal: 90% fatality rate
 - Gastric: 53% fatality rate
- **Male > Female**
- **Decline in Gastric Cancer Incidence**
- **Increase in Esophageal , GE JX, cardia adeno**

Therapy for Local / Regional Disease Esophageal Cancer

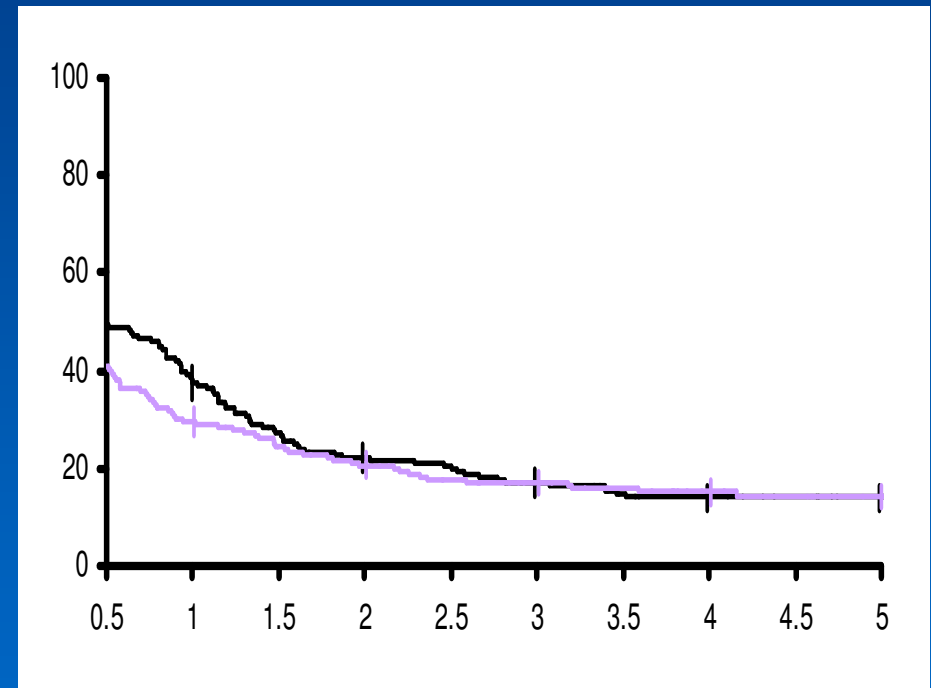
- **Surgery or Chemo
Radiotherapy** alone have been
standard treatment

Esophageal Cancer: Adjuvant Therapy

- Survival with surgery alone: 20-40%
- Adjuvant trials in esophageal cancer have evaluated preop therapy
 - Preop Chemotherapy
 - Preop Chemo + radiotherapy
 - Most common U.S. practice

Esophageal Cancer: Preop Chemotherapy

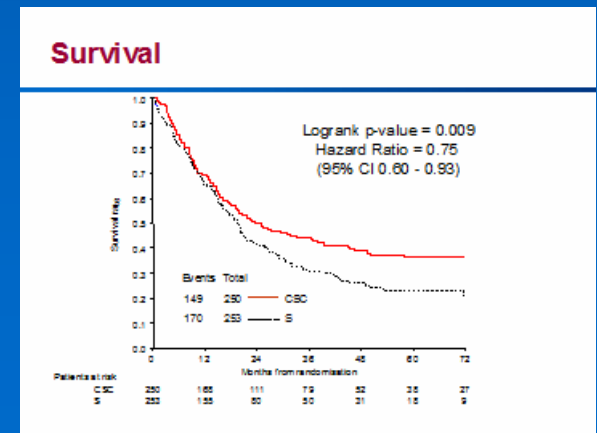
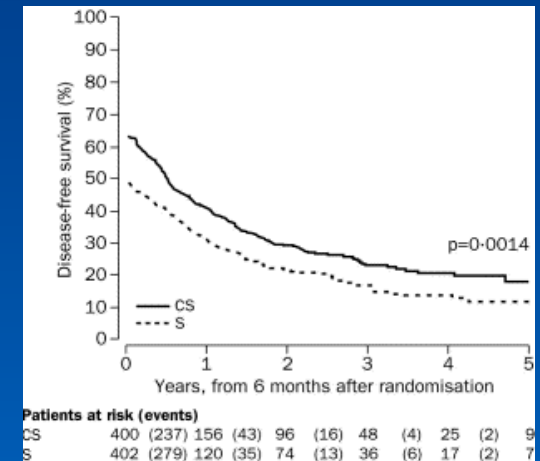
- Negative Trials
- U.S. INT 113
 - 3 pre, 3 post op cycles of 5-FU + Cisplatin
 - 440 pts
 - Adeno 54%, Squamous 46%
 - No improvement in R0 resection rate, disease free or overall survival
 - Path CR 2.5%



Kelsen et al, NEJM 339: 1979; 1998

Esophageal Cancer: Preop Chemotherapy

- Positive trials
- U.K. MRC OEO-2
 - 2 preop cycles of 5-FU + Cisplatin
 - 802 pts
 - Adeno 66%, Squamous 31%
 - 6% increase in R0 resection rate, 9% increase in 2 year OS
 - Path CR 4%
- U.K. MAGIC: pre and post op ECF in gastric cancer
 - 25% of 500 pts had GE junction or distal esophageal adeno
 - No improvement in R0 resection rate, 13% increase in 5 year OS
 - No Path CRs



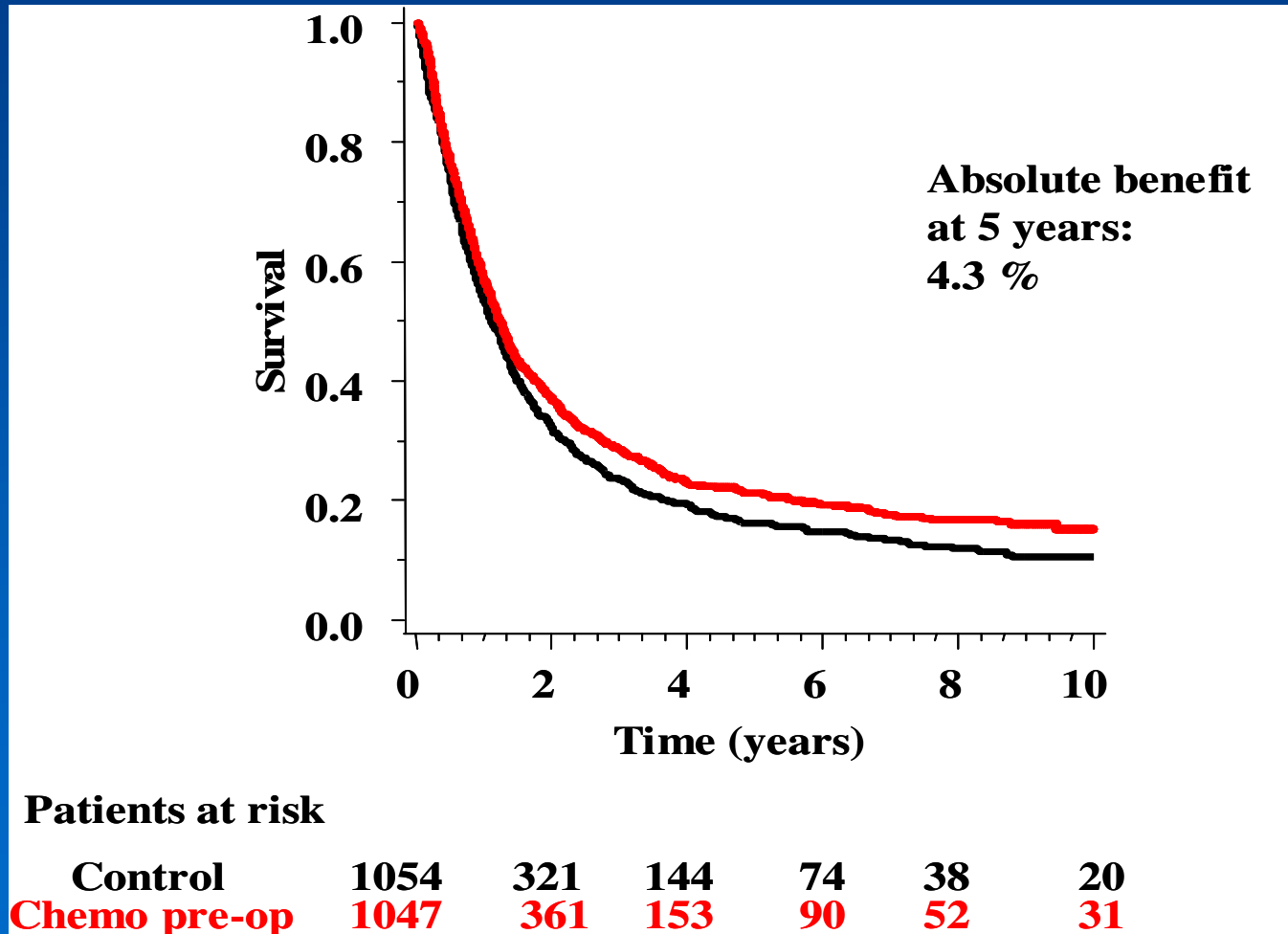
Esophageal Cancer: Consensus on Adjuvant Therapy

- **Something more than surgery alone should be done**
- **Adenocarcinoma**
 - Preoperative chemotherapy improves overall survival
 - MAGIC: 13% improvement at 5 yr
 - MRC 0E0-2: 9% improvement at 2 yr
 - No clear impact on rate of R0 resection
- **Addition of RT to chemotherapy**
 - Improves rates of curative resection in some trials
 - Achieves pathologic complete responses in 10-30%
 - Phase III trials: only 2 of 5 recent trials showed a survival benefit for preop chemo + RT

Meta Analysis Preop Chemo in Esophageal Cancer: Thirion (ASCO 2007 Abs 4512)

- Updated, individual pt data from preop chemo trials
- Squamous and adeno
 - 9 trials OS: 2102 pts
 - 7 trials DFS: 1849 pts
- 2 dominant trials:
 - U.S. INT 113 (467 pts)
 - U.K. MRC OEO-2 (802 pts)
- Overall survival improvement, HR of 0.87 ($p = 0.0033$)
 - Translates into 4% improvement in OS at 5 yrs
 - Adeno 7%, Squamous 4%

Primary End-point: Overall Survival

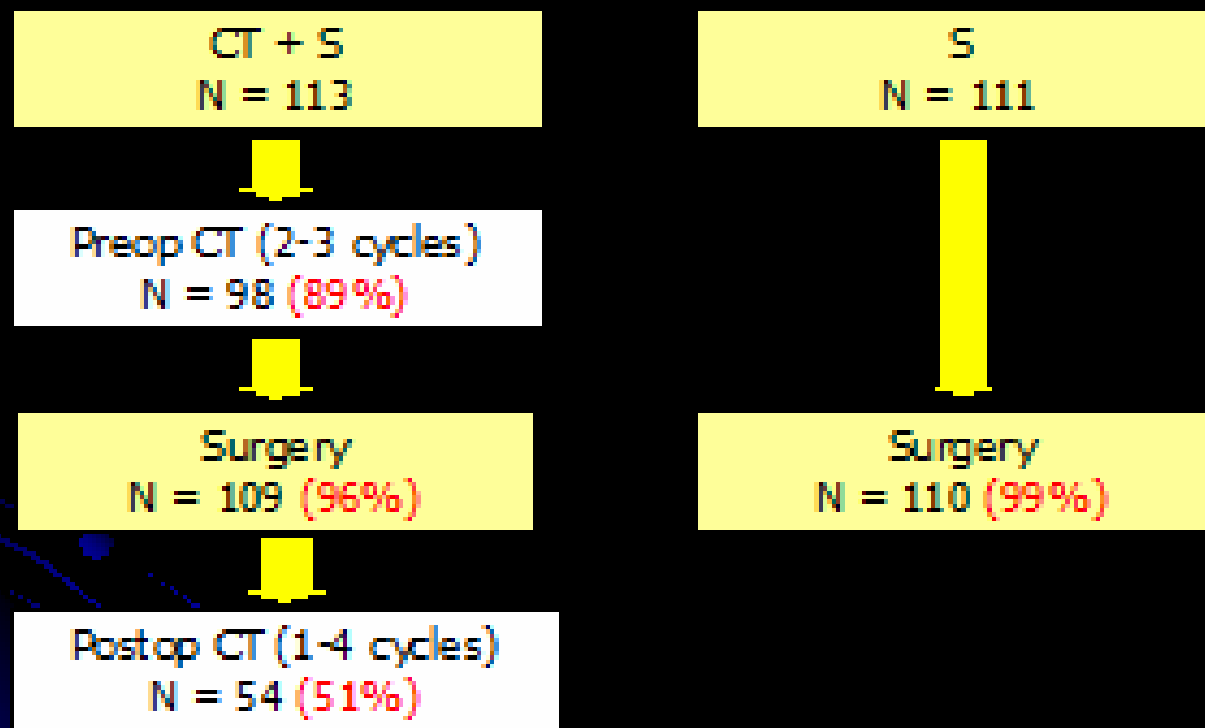


Squamous: 4%

Adeno: 7%

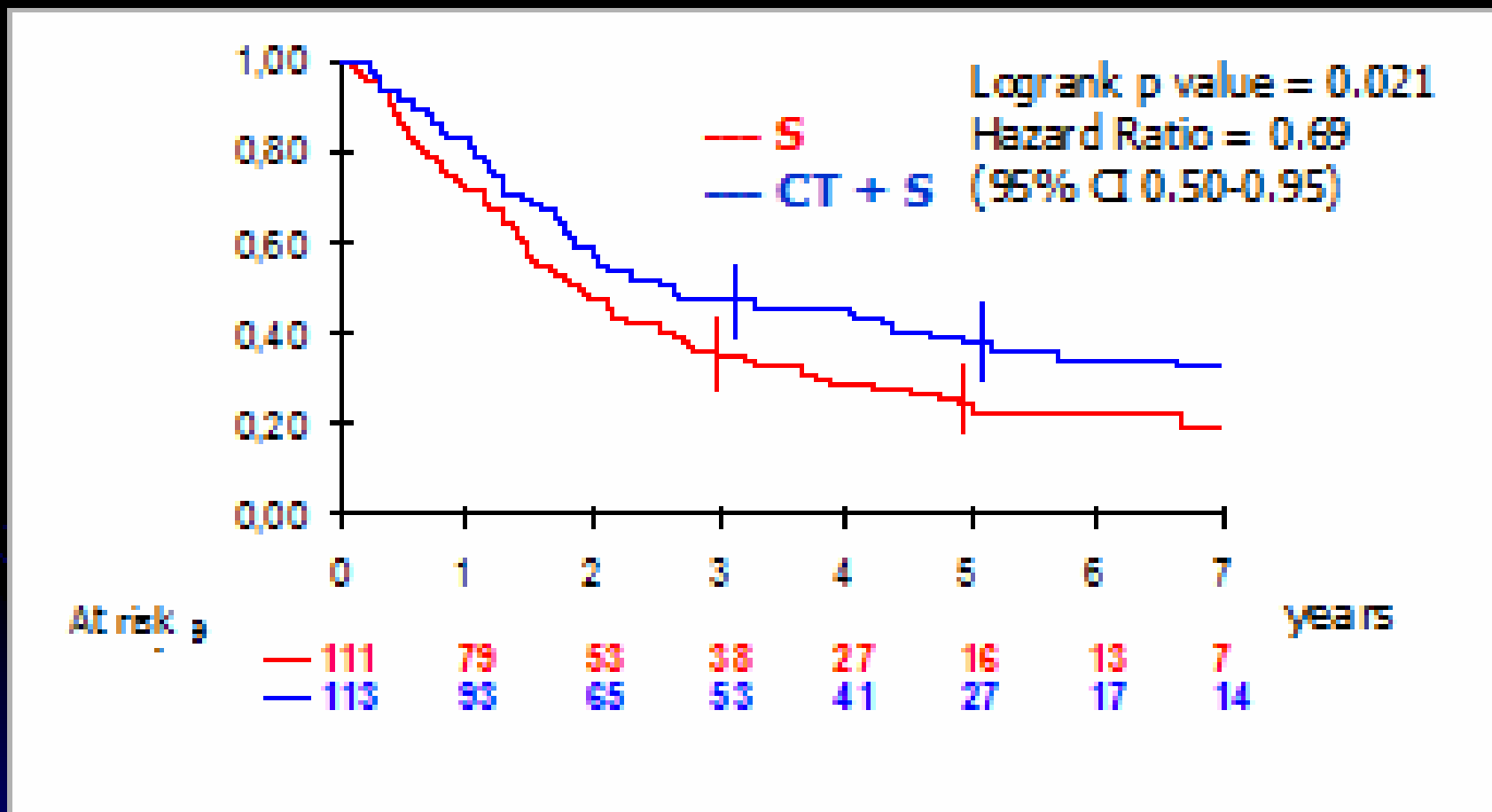
Boige et al (ASCO 2007, Abs 4510): Preop Chemo in Esophageal and Gastric Cancer: FFCD / FNLC

Trial profile



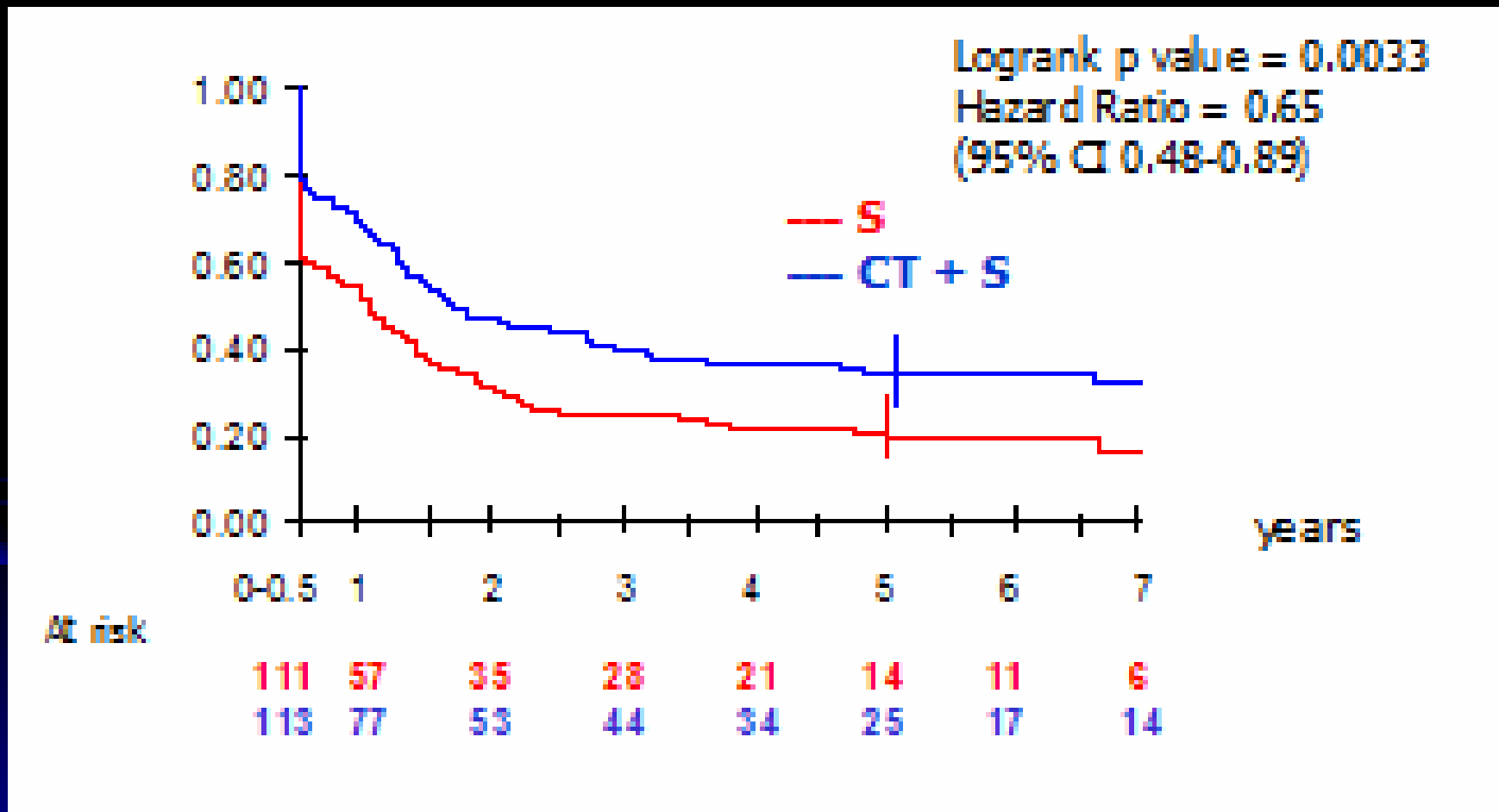
CT = 5-FU + Cisplatin

Overall survival



5-year OS: 24% (16-33%) vs 38% (28-47%)

Disease-free survival



5-year DFS: 21% (14-30%) vs 34% (26-44%)

Preop Chemo in Esophageal Adeno: FFCD / FNLCC Trial

- OS benefit for preop chemo with CF (cisplatin and 5-FU)
- Similar to ECF-MAGIC
 - Epirubicin may not be needed
- 13% rate of improvement in R0 resection rate
- Preop staging: EUS not performed routinely
 - No pre therapy stratification for stage
 - 224 patient trial
 - Differences in 10-15 pts account for the outcome

Preop ChemoRT → Surgery: Esophageal Cancer

- Path CR in 10-40%
- 5 yr OS 25-35%
- Phase III: small, inconclusive (<100-250 patients)
 - Curative Resection rates increased RT + chemo in some trials
 - Local Recurrence reduced
 - Trends toward ↑ Survival
 - Path CR: ↑ Survival
 - Only 2 of 5 Randomized Trials indicate survival benefit

Preop Chemo vs Chemo RT: Meta Analysis

	Trials	Pts	Mort. Reduc	HR	P value	2 yr OS
Chemo	8	1724	10%	0.90	0.05	7%
Adeno			22%	0.78	0.024	
Squam			12%	0.88	0.12	
Chemo RT	10	1209	19%	0.81	0.002	13%
Adeno			25%	0.75	0.02	
Squam			16%	0.84	0.04	

GebSKI et al, Lancet Oncol 8: 226-234; 2007

**PreOperative Chemotherapy or
Radiochemotherapy in Esophago-
gastric Adenocarcinoma Trial**

POET

ASCO 2007

Michael Stahl

on behalf of the

**German Oesophageal Cancer Study
Group**

Treatment

Arm A

PLF 2 x 6 weeks

PLF, 3 weeks

Surgery

1 Week

13

17

21

PLF 2 x 6 weeks

15 x 2 Gy, 3 weeks

Surgery

PE, 1 week

Arm B

P: Cisplatin E: Etoposide
LF: Leukovorin / 5-FU

Erythropoetin alpha recommended in both arms
to keep the Hb-level between 11.5 and 12.5 g/dl

Results at Surgery

	Arm A (n=59)	Arm B (n=60)
■ Patients with S	88.1%	81.7%
■ R0-Resection	69.5%	71.7%
■ R1/R2	13.6%	3.3%
■ Exploration (n)	3	4
	peritoneal mets 2 unresect. 1	peritoneal mets 3 hepatic mets 1

Pathohistologic Results

	Arm A (n=49)	Arm B (n=45)	p
T0N0M0	2.0%	15.6%	0.03
T1-4N0M0	34.7%	48.9%	
T0-4N0M0	36.7%	64.4%	0.01
T0-4N+M0	55.1%	31.1%	
T1-4N+M1	8.2%	4.4%	

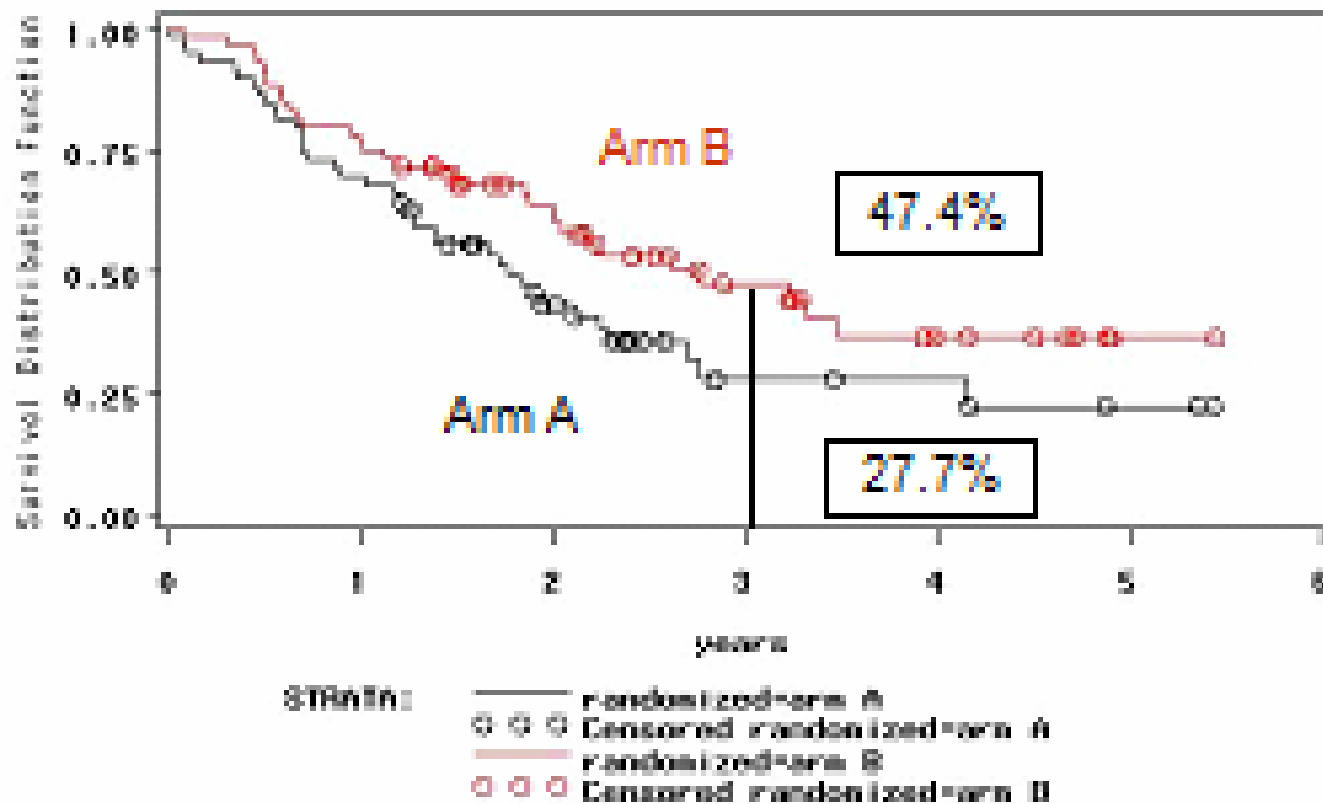
Mortality after Surgery

	Arm A (n=52)	Arm B (n=49)
Hospital mortality	2 (3.8%)	5 (10.2%)*
Pneumonia	1	2
Anastom. leakage	1	2
Kardiac shock	0	1

* Fisher's exact p = 0.26

Overall Survival

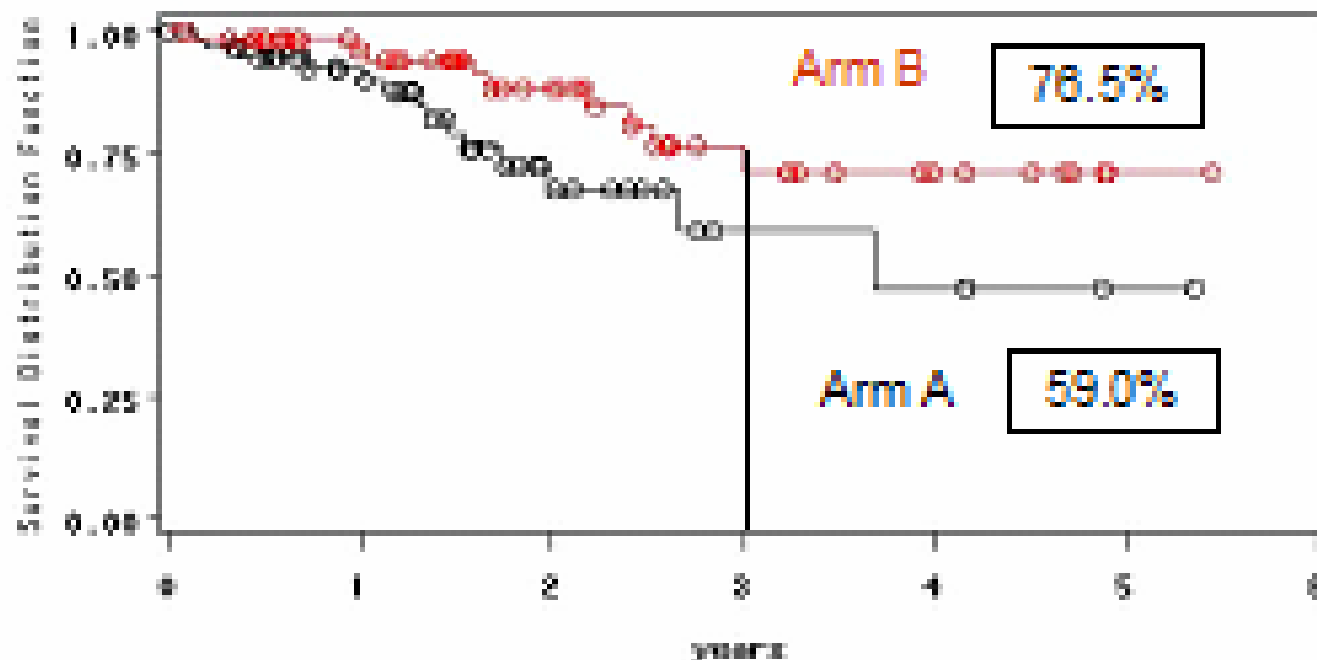
POET
GOeCSG



Logrank
 $p = 0.07$
HR Arm B vs. A
0.67 (0.41-1.07)

Follow-up 45.6 mo

Freedom from Local Tumor Progression



STRATA: — randomized=arm A
○ ○ ○ Censored randomized=arm A
— randomized=arm B
○ ○ ○ Censored randomized=arm B

Logrank
 $p = 0.06$
HR Arm B vs. A
0.45 (0.19 - 1.05)

Esophageal Cancer: Preop Chemo, RT, or Both? Conclusions

- **Esophageal Adeno**

- Preop Chemo improves survival and is feasible
- RT + Chemo: trends toward improved OS, more path CR's, reduced local recurrence
- At the cost of greater toxicity

- **Esophageal Squamous**

- Preop Chemo less certain survival benefit
- RT + Chemo:
 - As primary therapy without surgery is acceptable
 - Surgery after chemo rt: in selected patients
 - Improved local control → no improvement in survival

Gastric, Esophageal Cancer: PET scan response to Induction Chemo

- **Ott (Gastric):** Preoperative chemo with cisplatin-based regimen
- PET scan at baseline and on day 14
- PET responders (35% decline SUV): 2 yr survival 89%
- PET nonresponders: 2 yr survival 26%
- PET prognostic for survival

- **Weber (Esophageal):** 40 pts, induction chemo, PET at 14 days
- > = 35% response on PET:
- PET responders had improved 2 yr survival (60% vs 37%)

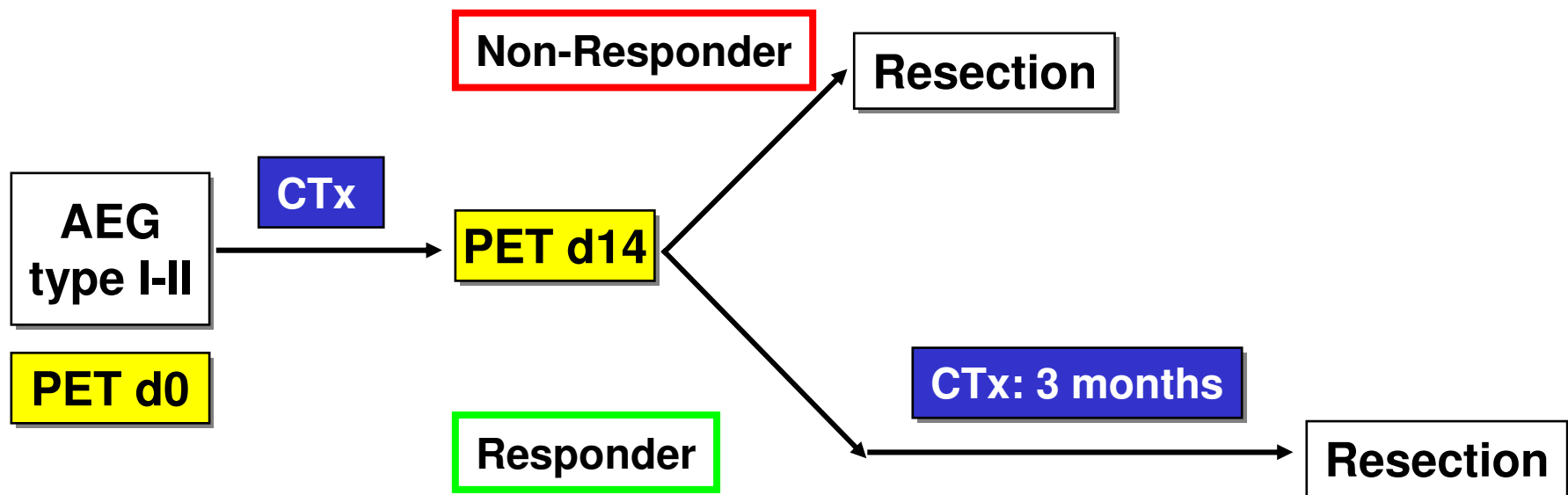
- **Lordick (Esophageal): MUNICON Trial:** PET non responders referred for immediate surgery, responders completed preop therapy

- Use of PET to change induction therapy

Ott 520, Proc ASCO 21:2002
Lancet Oncol 2007

Weber J Clin Oncol 19:3058;2001 Lordick

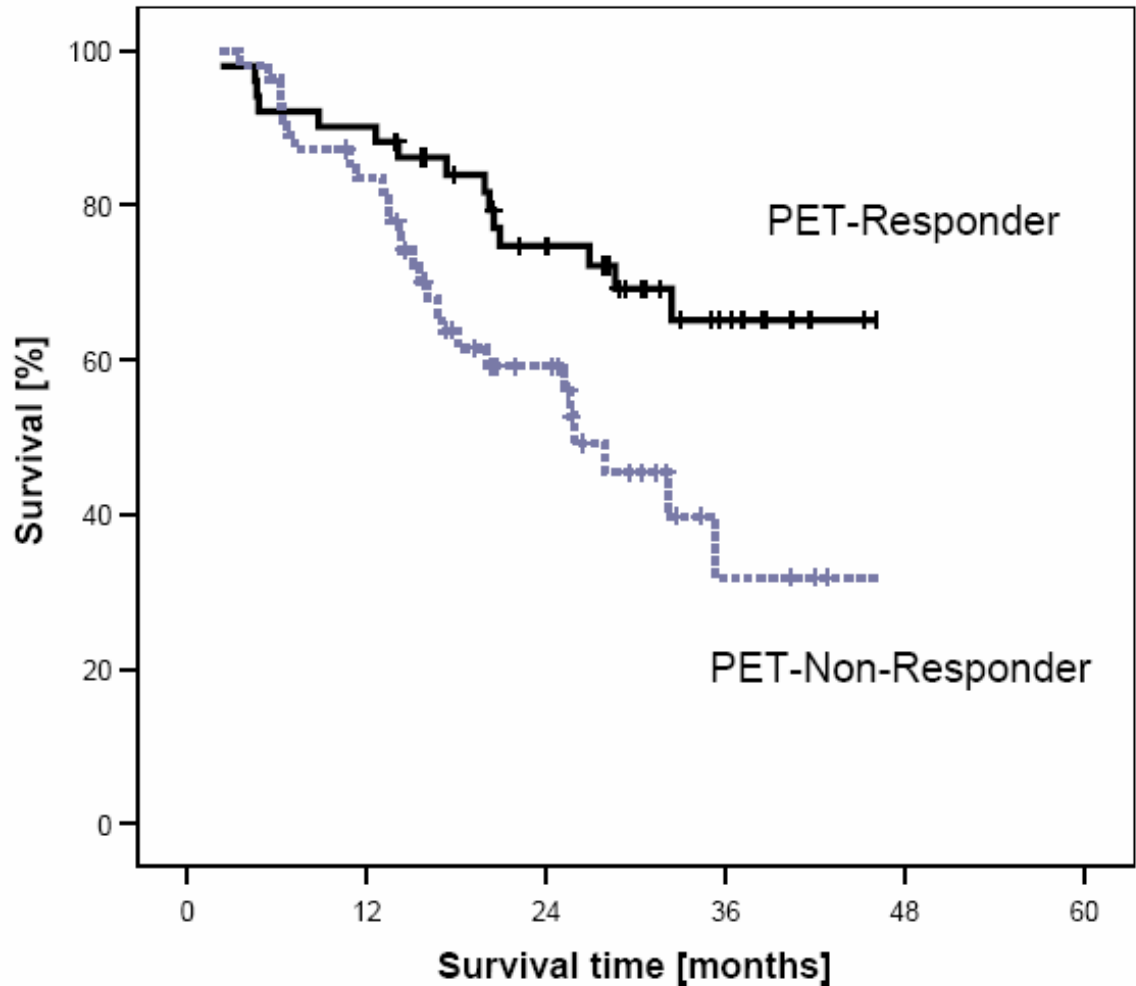
Treatment Plan: MUNICON-1 trial



Response definition: Decrease of the $SUV_{\text{mean}} \text{ PET}_{\text{d14}} / \text{PET}_{\text{baseline}} \geq 35\%$

Weber et al. *J Clin Oncol* 2001;19:3058-65 Ott et al. *J Clin Oncol* 2006;24:4692-8

Overall survival (intention-to-treat-analysis)



**Median survival
[95% CI] in months:**

**Metabolic Responder:
Not reached**

**Metabolic Non-Responder:
25.8 [19.4; 32.3]**

Hazard ratio **2.13** [1.14-3.99]

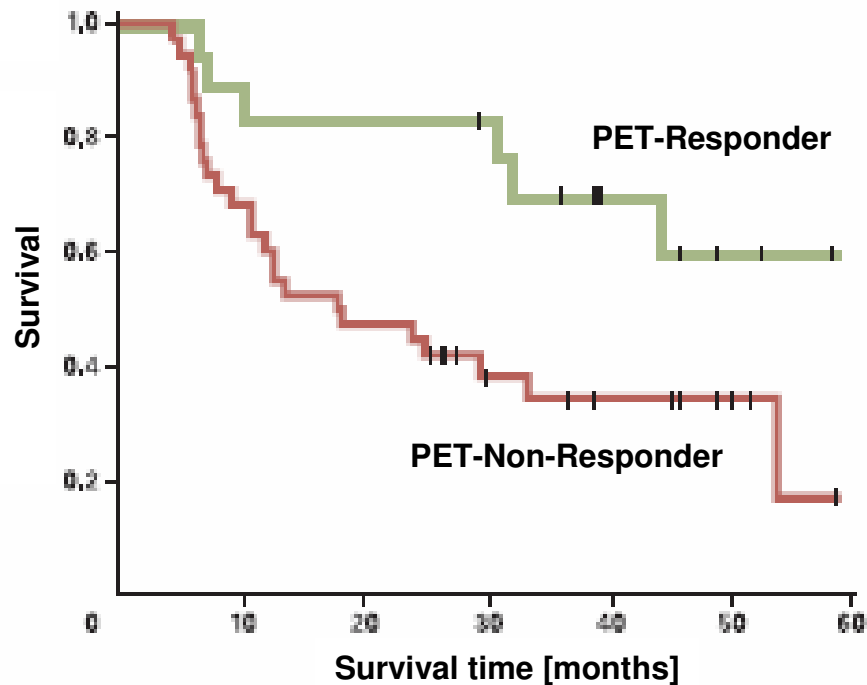
Log-rank p-value: **p<0.015**

Median follow-up: 28.0 months

Comparison with historic cohort

[Ott et al. J Clin Oncol 2006;24:4692-8](#)

CTx for 12 weeks in all patients



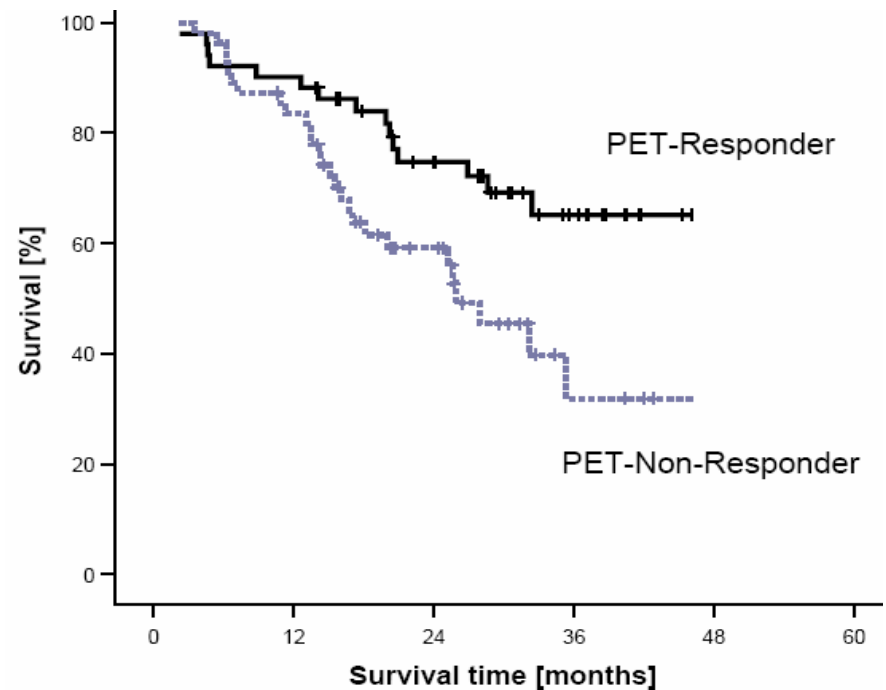
Survival (median)

Responders: not reached

Non-Responders: 18 months

[MUNICON-1 study; 2007](#)

CTx stopped after 2wks in Non-Responders



Survival (median)

Responders: not reached

Non-Responders: 26 months

New Agents In Combined ChemoRT

- **CALGB 80302: Irinotecan/Cisplatin → Irino/Cis/RT → Surgery**
 - Phase II, serial PET scan
- **ECOG 1202: Irinotecan/Cis vs Paclitaxel/Cis + RT → surgery**
 - Path CR's 14-16%
 - Adenocarcinoma
- **RTOG 04036: Paclitaxel, Cisplatin, RT + / - Cetuximab**
- **SWOG S0-356: Oxaliplatin + 5-FU + XRT: preop**
- **MSKCC, Minnie Pearl: Irino/Cis/RT, 5-FU/Carbo/Taxol/RT + Bevacizumab**
- **DFCI: Irino/Cis/RT + Cetuximab**

Gastric Cancer: Adjuvant Therapy

- **Post operative Chemo**
 - Negative Phase III Trials
 - JCOG NEJM 2007: S-1: 10% improved 5 yr OS
- **Post op Chemoradiotherapy (U.S.)**
- **Pre operative Chemotherapy (U.K.)**
- **Intra Peritoneal Chemotherapy**

JCOG: S-1 Adjuvant Therapy

- 1000 patients with gastric cancer post D2 resection
- Observation vs 12 months S-1
 - 40 mg/m²/day x 4 weeks, 2 weeks rest
 - 78% completed 6 mos, 71% 12 mos
 - Grade 3 / 4 toxicity rare (nausea, diarrhea 3-4%)
- 50% AJCC Stage II, 40% Stage III
- 45% T3-4, 90% N+
- Overall survival benefit found at first analysis at 2 years

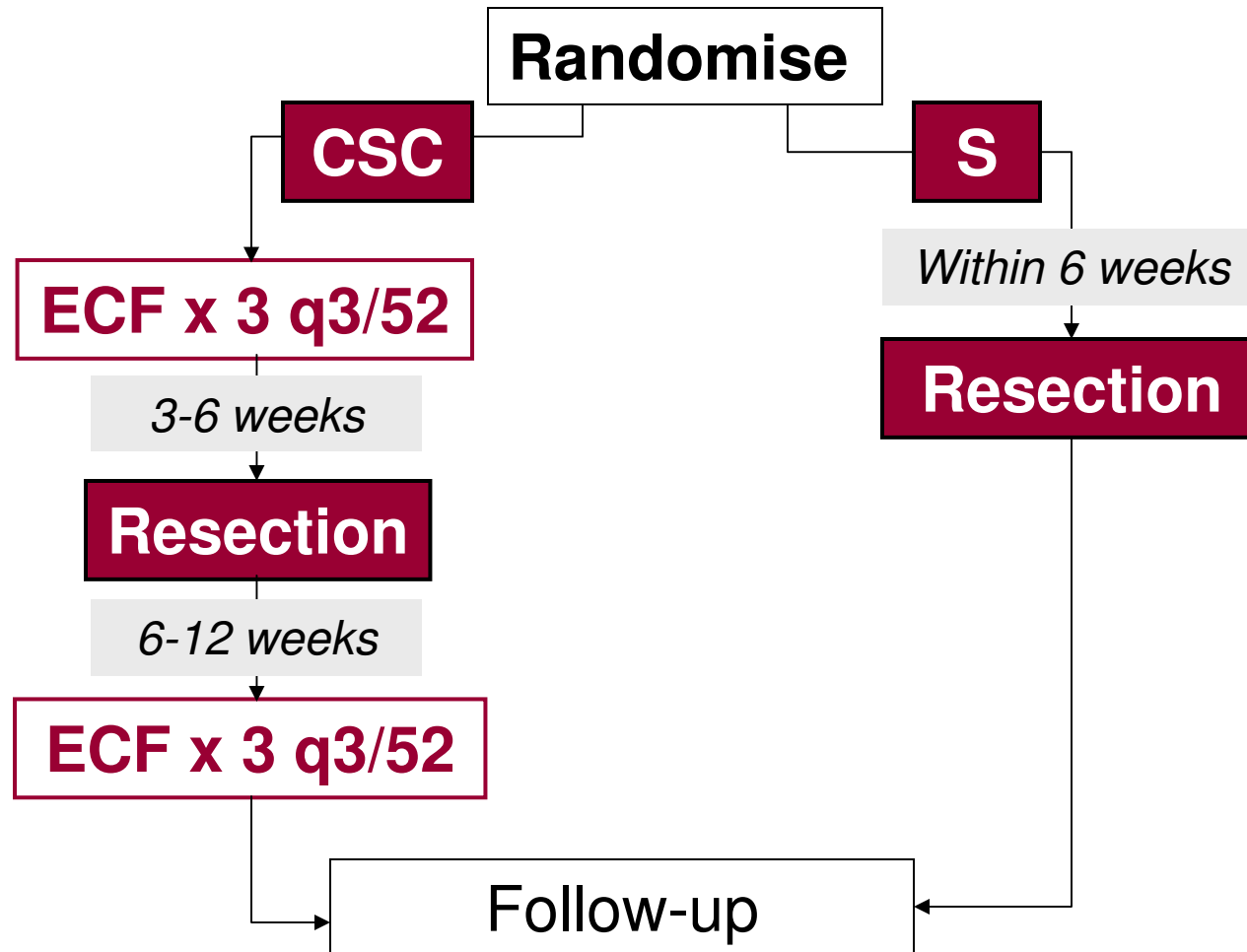
NEJM 2007

JCOG: S-1 Adjuvant Therapy

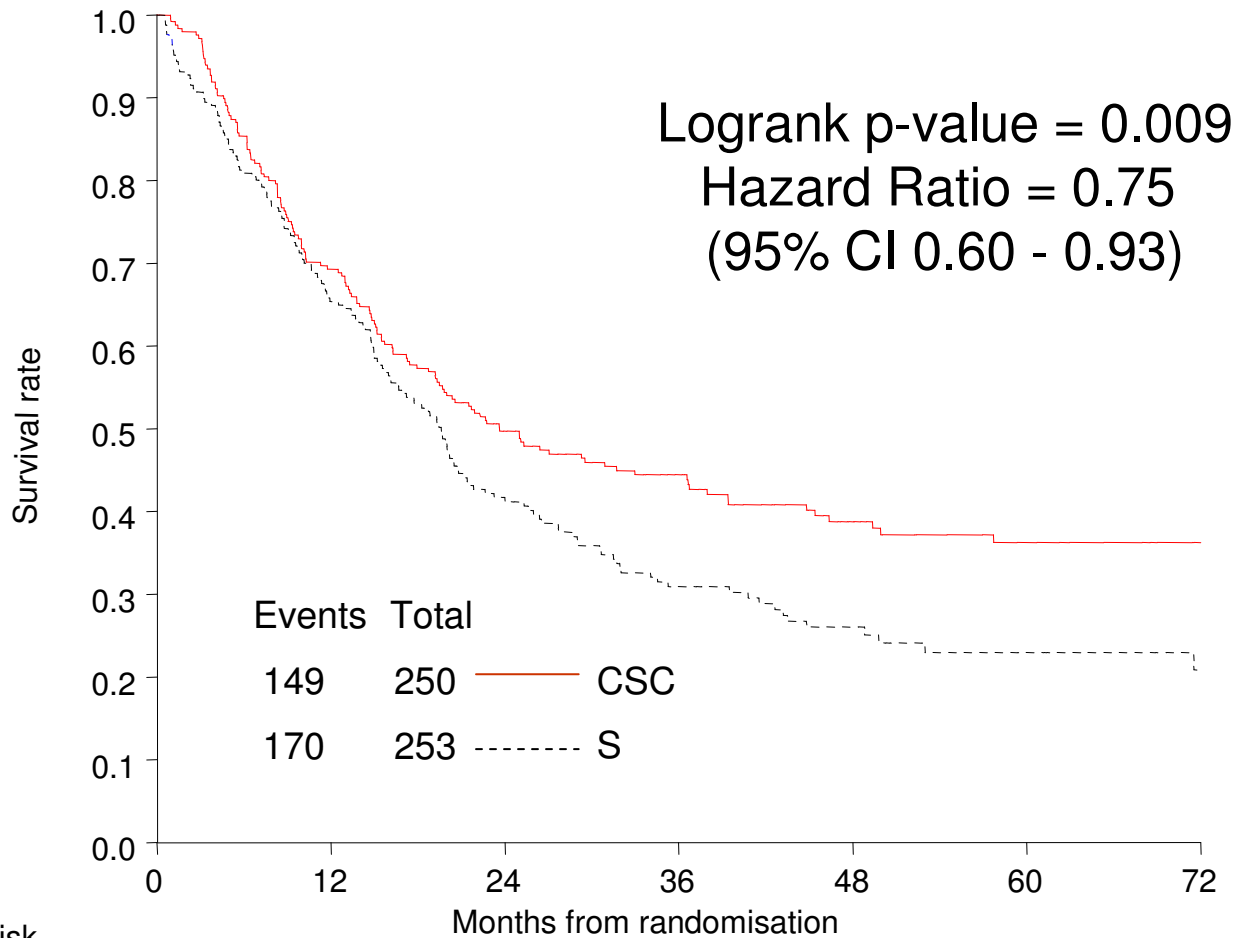
- S-1: 3 yr OS 80%
- vs Surgery: 3 yr OS 70%, HR 0.62, $p < 0.001$
- End the argument that “better surgery” negates a benefit of adjuvant therapy
- Similar benefit (10%) compared to MAGIC (ECF) and U.S. INT (5-FU/LV)
- Questions role of RT
- Questions role of single agent vs combination therapy
- Future: next question to add a targeted agent!

NEJM 2007

Design: MAGIC Trial



Overall Survival



Patients at risk

CSC	250	168	111	79	52	38	27
S	253	155	80	50	31	18	9

MAGIC TRIAL: Preop Chemo in Gastric Cancer

- **Significant down staging**
 - No improvement in rate of R0 resection, no path CR
- **Survival Improved**
- **Supports preop chemo as a standard of care**
- **Survival benefit + 13%, without RT**
 - Comparable to U.S. 5-FU + RT: + 10%

MAGIC TRIAL: Preop Chemo in Gastric Cancer

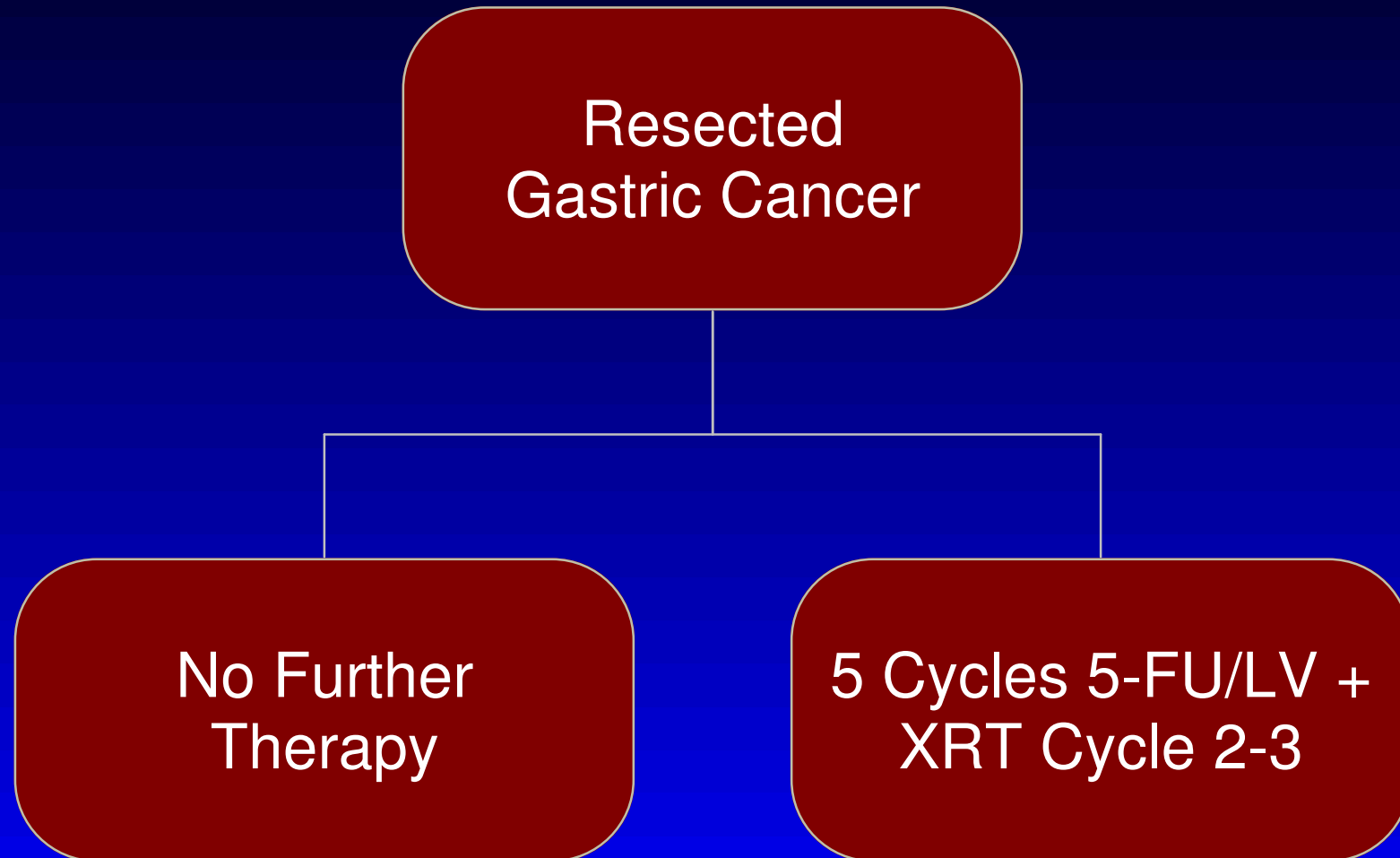
- Is radiotherapy required as part of adjuvant therapy?
- Future Trial Questions
 - Preop Chemo + / - RT → Surgery
 - Preop Chemo → Surgery , → Post op Chemo + / - RT
 - CRITICS Trial (NL)
 - Pre vs Post Op Therapy?

MAGIC 2 Trial

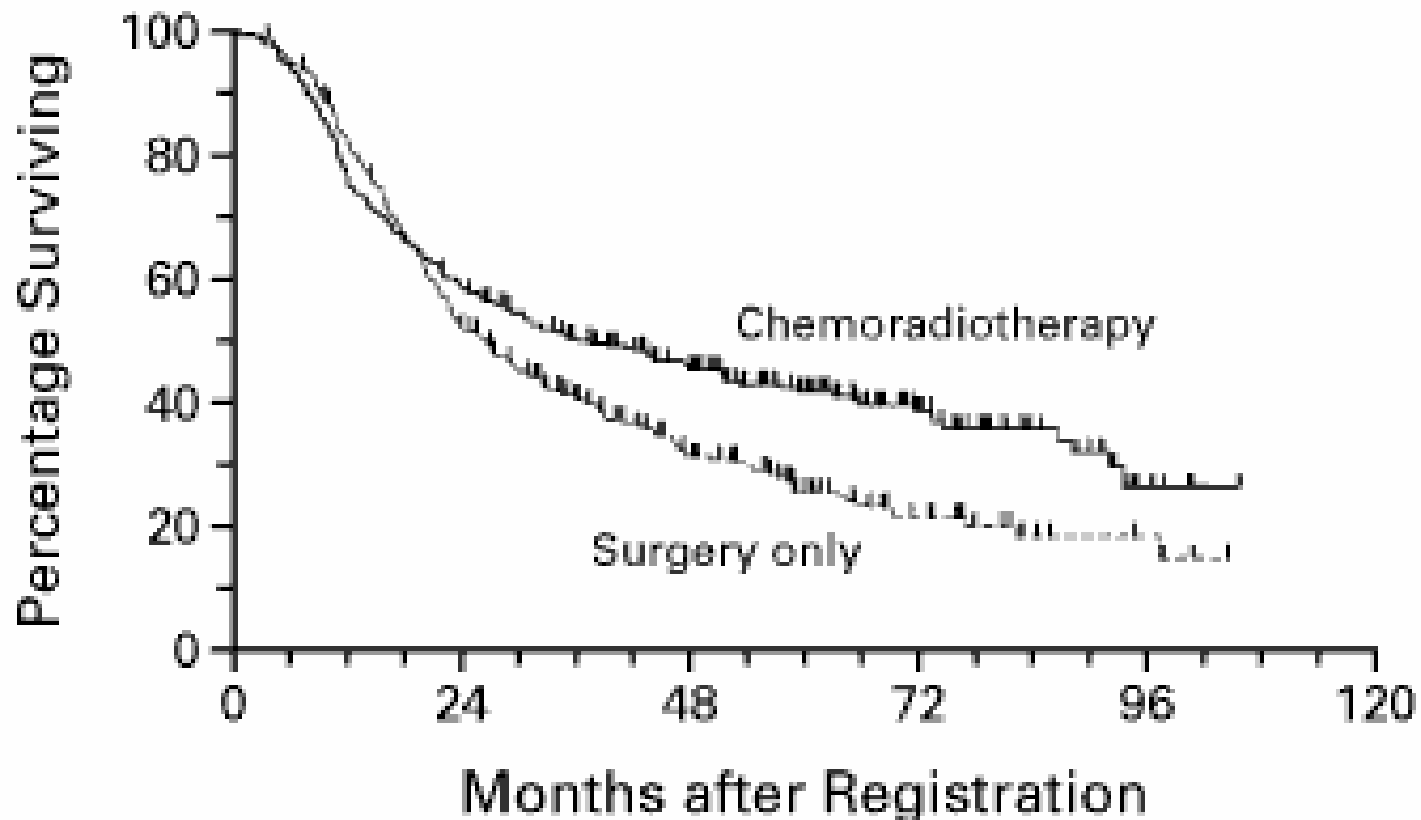
- **MAGIC 2:**
- **3 cycles of pre, 3 cycles of post op chemo**
- **ECX: epirubicin, cisplatin, capecitabine**
- **Randomization: + / - Anti VEGF Antibody Bevacizumab (Avastin)**

U.S. Intergroup 116 (SWOG 9008)

Gastric Cancer: Post Op 5-FU + RT



Overall Survival: INT 116, Post Op 5-FU, LV, RT



Macdonald NEJM 345: 725-730; 2001

New U.S. Intergroup Trial (CALGB 80101)

- **Post op RT + CIV 5FU**
- **Randomization of Systemic Chemotherapy**
 - ECF (Epirubicin, Cisplatin, 5-FU) vs
 - 5-FU/LV

Adjuvant Therapy: Chemo, RT or Both?

- Pre post op ECF improves survival in gastric cancer (MAGIC)
- Post op 5-FU/LV + RT improves survival in gastric cancer (U.S. INT)
- Post op S-1 improves survival in gastric cancer after D2 resection

Esophago-Gastric Cancer: Metastatic Disease

- **CIV 5-FU + cisplatin**
 - 4-5 day to 6 week 5-FU infusion
 - RR 20-30%
 - Med S 8-9 months
- **Adding a third drug:**
 - Epirubicin (ECF): RR 40-45%, Med S 9 mos
 - Docetaxel (DCF): RR 36%, Med S 9 mos
 - 10% increment in response rate
 - 1 month increment in survival
- **Capecitabine, oxaliplatin are non inferior**

Is ECF a Superior Regimen?

- **2 phase III trials, 854 pts**
 - ECF (CIV 5-FU) superior to FAMTX (bolus 5-FU)
 - ECF = Mitomycin + CF
 - Absence of difference Epi vs Mito: 3rd drug does not add to CF
 - Meta Analysis (Wagner JCO 2006):
 - Anthracycline + CF: + 2 month survival for gastric but not esophageal cancer
 - Results based on a subset analysis of one trial
- **Supports infusional over bolus 5-FU**
- **Supports lower dose cisplatin (60/m)**

DCF-Supportive Care, Dose Modifications

- **Prophylactic use of growth factors**
 - Grade 3 or 4 neutropenia in 82%
 - Neutropenic fever in 30%
- **Reduce starting dose of docetaxel to 60 mg/m²**
- **Reduce starting dose cisplatin to 60 mg/m²**
 - Supported by dosing of cisplatin in ECF
- **Grade 3 or 4 diarrheal toxicity (20%) and stomatitis (21%)**
 - Reduce 5-FU to 500-600/m²
- **Change dose and schedule to CRC like schedules**
 - FOLFOX or FOLFIRI

DCF: Alternative Regimens

- **DC evaluated in 2 randomized phase II trials**
 - Docetaxel 75-85 mg/m² + Cisplatin 75 mg/m²
 - Response rates 19%-26%, TTP 3.6-5.0 months, OS -10.5-11 mos
 - Neutropenia 76-87%, neutropenic fever 15%-27%
- **DF evaluated in 1 randomized phase II trial**
 - Docetaxel 75 mg/m² + CIV 5-FU 200 mg/m²/daily
 - RR 38%, TTP 5.5 mos, OS 9.5 mos
 - Neutropenia 42%, neutropenic fever 4%
- **DF a more tolerable combination**

Oxaliplatin vs Cisplatin? Colorectal Cancer 5-FU Dosing

- **FLO vs FLP**
 - Oxaliplatin 85/m² vs Cisplatin 50/m² q 2 weeks
- **24 hr CIV 5-FU 2000-2600/m² + LV 200/m² weekly or bi-weekly**
- **210 pts randomized**
- **TTP primary endpoint**

- **Non inferiority for Oxaliplatin**
- **Overall survival data not mature**

	FLO	FLP	<i>P</i>
TTP	5.7 mo	3.8 mo	.081
% RR	34 %	27%	.012

Capecitabine vs 5-FU?

- **XP vs FP**

- Cape 1000/m² BID x 14 days vs CIV 5-FU 800/m²/day x 5days q 3 weeks
- + Cisplatin 80/m²
- 316 pts randomized
- PFS primary endpoint

- **Non inferiority for Capecitabine**

- **Approved in Europe for gastric cancer**

- **Global Trial: XP + / - Bevacizumab**

	XP	FP	<i>P</i>
	n=160	n=156	
%RR	41%	29%	.03
PFS (mo)	5.6	5.0	.0001
OS (mo)	10.5	9.3	.27

REAL-2 Trial: Phase III Comparing Capecitabine With 5-FU and Oxaliplatin With Cisplatin

ECF (N=249)

Epirubicin 50 mg/m² iv 3 wkly
Cisplatin 60 mg/m² iv 3 wkly
5 FU 200 mg/m²/d iv given continuously

ECX (N=241)

Epirubicin 50 mg/m² iv 3 wkly
Cisplatin 60 mg/m² iv 3 wkly
Capecitabine 625 mg/m² bid po continuously

EOF (N=235)

Epirubicin 50 mg/m² iv 3 wkly
Oxaliplatin 130 mg/m² iv 3 wkly
5 FU 200 mg/m²/d iv given continuously

EOX (N=239)

Epirubicin 50 mg/m² iv 3 wkly
Oxaliplatin 130 mg/m² iv 3 wkly
Capecitabine 625 mg/m² bid po continuously

- 2 X 2 Randomization, 8 cycles

- Non-inferiority of X over F and O over C with 1-yr survival of 35% with a 1 side α of 5%

REAL 2: Response

Best overall Response

Response (%)	ECF n=249	ECX n=241	EOF n=235	EOX n=239
Evaluable	246	237	231	234
CR	4.1%	4.2%	2.6%	3.9%
PR	36.6%	42.2%	39.8%	44.0%
CR + PR	40.7%	46.4%	42.4%	47.9%
95% CI	(34.5-46.8)	(40.0-52.8)	(36.1-48.8)	(41.5-54.3)
p-value vs ECF		0.202	0.694	0.112
SD	31.3%	32.1	15.2%	27.8%
PD or died	28.0%	21.5%	24.7%	24.4%

REAL 2: PFS

Progression-free survival (ITT)



REAL 2: Overall Survival

Survival by Regimen (ITT)



REAL 2 Trial

- **EOX arm had highest survival vs ECF**
- **No differences in RR, TTP**
- **REAL 3: ECX + / - Panitumimab**
- **Caveats:**
 - CT scans only performed at 3 and 6 months
 - No confirmation of response
 - No mandated treatment after 6 months
 - No mandated imaging after 6 months
 - First f/u visit mandated at 9 months

Gastric Cancer Chemotherapy: What regimen to use?

- Docetaxel + CF > CF: toxicity
- Irinotecan + CIV 5-FU = CF: less toxicity
- Oxaliplatin + Capecitabine: Non inferior
- Doublets: Platin: + Irinotecan or Taxane or Fluor
Fluor: + Irinotecan or Taxane or Platin

	Oxaliplatin EOX or EOF	Cape ECX or EOX	XP	FLO	FUFIRI	DCF	ECF
Pts	489	513	160	109	170	221	126
%RR	44%	45%	41%	34%	32%	36%	45%
TTP, mos	--	--	5.6	5.5	5.0	5.6	NS
OS, mos	10.9	10.4	10.5	--	9.0	9.2	8.9

S-1

- **S-1: a novel oral fluorouracil formulation**
- **FT: Tegafur, 5-FU prodrug +**
- **CDHP: DPD inhibitor +**
- **Oxo: bowel protectant**
- **Molar ratio of 1.0 : 0.4 : 1.0**
- **Developed as orally absorbed 5-FU preparation with potentially less bowel toxicity**

Gastric Cancer: S-1 vs S-1 + Cisplatin (Abs 4514)

- S-1 vs S-1 + Cisplatin
- S-1 40-60 mg BID x 3 weeks alone,
- vs S-1 + Cisplatin 60 mg/m² day 8, 2 weeks rest
- Primary endpoint OS: 8 mos → 12 mos, 284 pts
- S-1: Active single agent, superior to CIV 5-FU alone
- Combination + cisplatin superior
- S-1 + Cisplatin a new standard in Japan
- FLAGS: Western trial of 5-FU vs S-1 + Cisplatin

	S-1	S-1 + Cisplatin	p
Number	150	148	
RR	31%	54%	0.0018
OS	11 mos	13 mos	0.0366
1 year	47%	54%	
2 year	15%	24%	
PFS	4 mos	6 mos	0.0089
Grade 3/4 Neut	11%	40%	
Grade 3/4 Diarrhea	3%	3%	
Grade 3/4 Nausea	1%	12%	

CPT-11/Cisplatin in Advanced Esophago-gastric Cancer: Phase II Trials

Author	Regimen	Cancer Type	# Patients	Major Response Rate	G3-4 Diarrhea	G4 ANC	Median Survival
Boku. 1999	2-weekly	Gastric	44	48%	20%	57%	9 mo.
Iison. 1999	weekly	Esoph. GE jct.	35	57%	11%	9%	15 mo.
Ajani. 2002	weekly	GE jct. Gastric	38	58%	22%	15%	9 mo.
Ajani. 2002	weekly	GE jct. Gastric	29 pretreated	31%	13%	9%	5 mo.
Satoh. 2002	weekly	Gastric.	15 naive 25 pretx	53% 20%	3%	10%	9.9 mo. 9.0 mo.
Iison*. 2003	weekly	Esoph GE jct.	28	36%	18%	11%	N/A

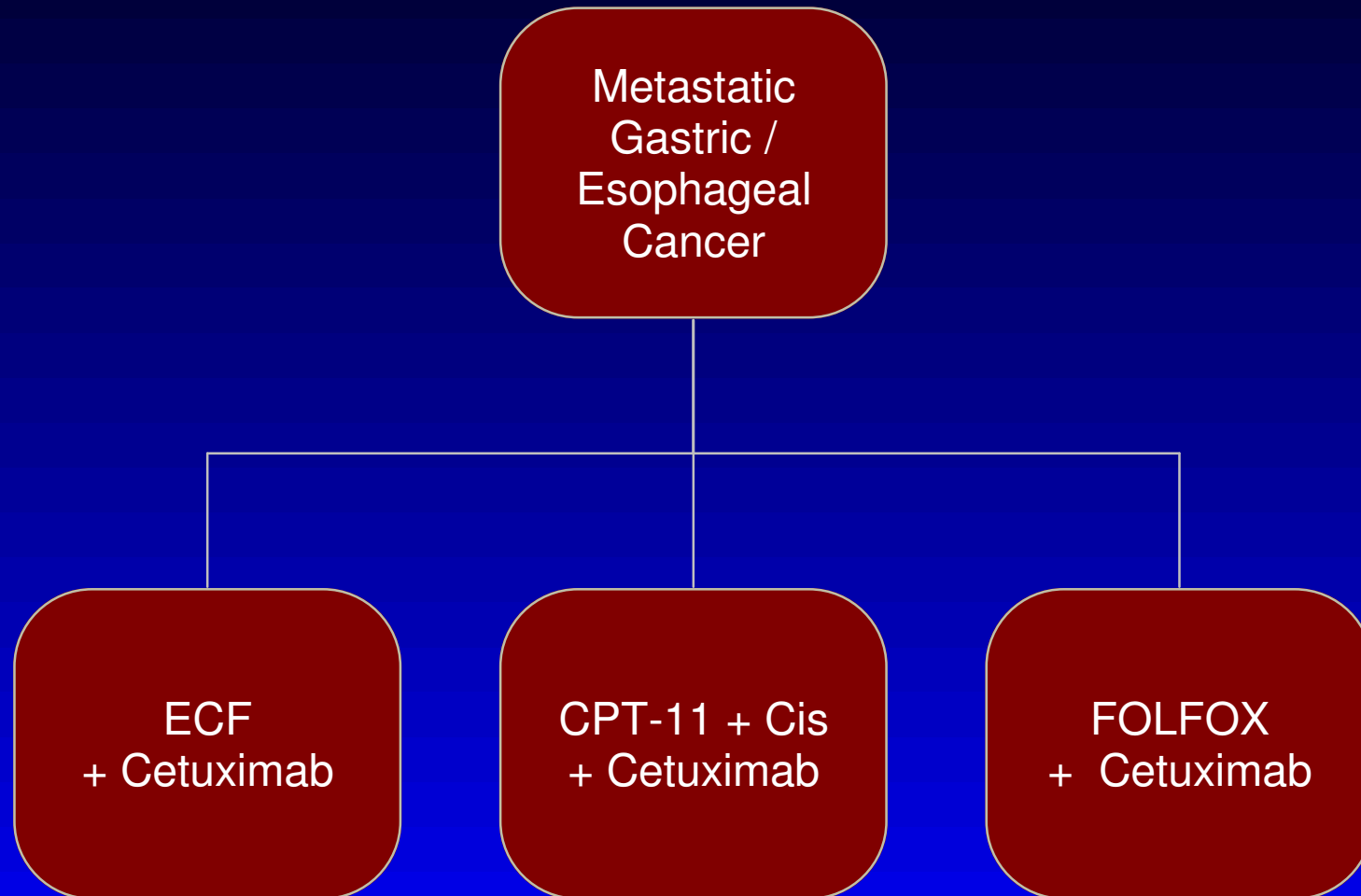
* multi-institution

Future Directions: Targeted Agents

- Growth factor receptor inhibitors:
 - VEGFr/ VEGF
 - MoAb VEGF ligand: Avastin (Bevacizumab)
 - EGFr:
 - TKI's: ZD1839, OSI-774
 - Moab C-225: Erbitux (Cetuximab)
 - Panitumimab
 - Matuzimab

CALGB / ECOG: Gastric/Esophageal Ca

Randomized Phase II



SWOG: Single Agent Cetuximab, Phase II (no responses)

EGFr Tyrosine Kinase Inhibitors: Phase II

	Number Patients	% Response
Gefitinib		
Doi (Gastric)	75	1%
Janmaat (GE Jxn)	26	0%
Erlotinib		
Tew (GE Jxn)	17	0%
Dragovich (Gastric, GE Jxn)	78	0% (25 Gastric) 9% (43 GE Jxn)

Advanced Gastric Cancer: Targeted Agents - First Line

Phase II Study	Regimen	N	Response (%)
Shah et al. 2006 ¹	Bevacizumab + Cisplatin + Irinotecan	34	65%
Di Fabio et al. 2006 ²	Cetuximab + FOLFIRI	27	52%
Pinto et al. 2006 ³	Cetuximab + FOLFIRI	25	56%
Lordick et al. 2006 ⁴	Cetuximab + FUFOX	28	64%
Bang et al 2007 ⁵	Sunitinib	42	5%
REAL 3	ECX + / - Panitumimab	Phase III	

1. Shah et al. *J Clin Oncol.* 2006;24:5201; 2. Di Fabio et al. ESMO, 2006. Abstract 1077PD; 3. Pinto et al. ASCO, 2006. Abstract 4031; 4. Lordick et al. ESMO, 2006. Abstract 1076PD. 5. Bang et al ASCO 2007.

Future Directions: Targeted Agents

- **Molecular Targeted Therapies**
 - VEGF, EGFr pathways
 - Tyrosine kinase inhibitors of downstream pathways
 - Phase II + III development with chemo, chemoRT
- **DNA Array**
 - Spectrum of genes in tumor
 - Prognostic of survival
 - Predictive of response to therapy

Future Directions: Tailoring of Therapy

- **Chemotherapy targets (TS, ERCC-1) in tumors**
 - Pharmacogenetics
 - Germ line variation in tumor target polymorphisms
 - Immunohistochemistry target expression
 - Impact on tumor response
- **Pharmacogenomics**
 - Patient drug catabolism, toxicity, activity