Treatment of Advanced and Metastatic Gastric Cancer

Semenisty V. MD

Gastric cancer is a significant global health problem.

Recent data indicate that 1.4 million new cases of gastroesophageal and gastric cancer are diagnosed annually, and 1.1 million deaths are attributed to this disease

Advanced disease- aim of treatment

- Prolong survival/progression free survival
- Palliation/symptom control
- Improve/preserve quality of life (QoL)

Single Agents Active in Gastric Cancer

5-fluorouracil (UFT,Capecitabine)
S1
Cisplatin
Doxorubicin/Epirubicin
Paclitaxel
Docetaxel
Irinotecan

Van De Velde, Kelsen D…Gastric cancer.2008

Agents	RR (%)
5-FU	21
UFT	28
S1	49
Xeloda	26
Doxorub	17
Epirub	19
Taxol	17
Taxotere	19
CPT11	23
cisplatin	19

Combination Regimens vs. Best Supportive Care

- Small studies
- 4 trials showing improved survival of 4-8 months with combined chemotherapy

Scheithauer et al. 1995 ELF vs. BSC

Pyrhonen et al. 1995 FEMTX vs. BSC

Glimelius et al. 1997 ELF vs. BSC

Murad et al. 1999 FAMTX vs. BSC

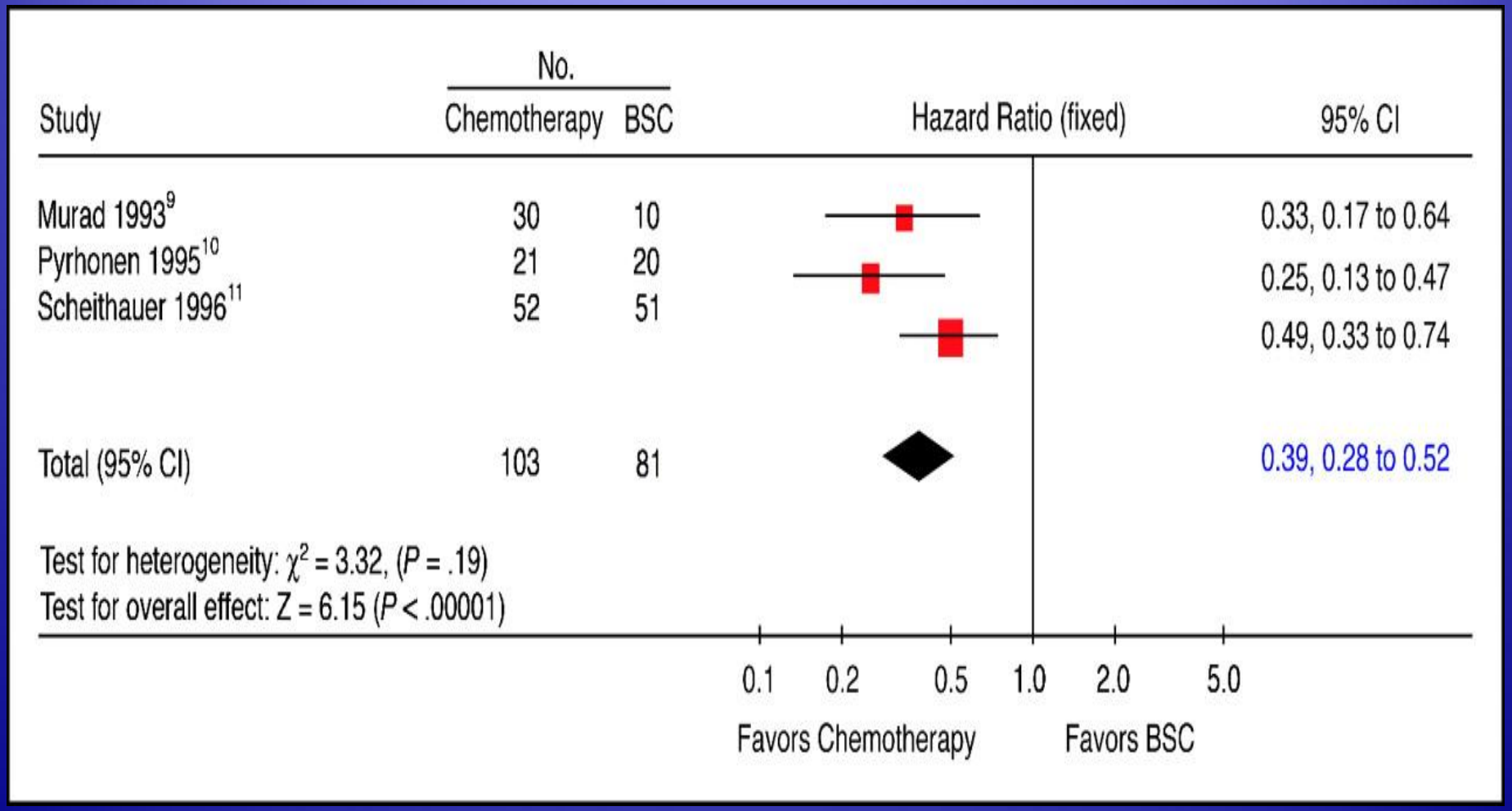
QOL reported to be better

Chemotherapy in Advanced Gastric Cancer: A Systematic Review and Meta-Analysis Based on Aggregate Data

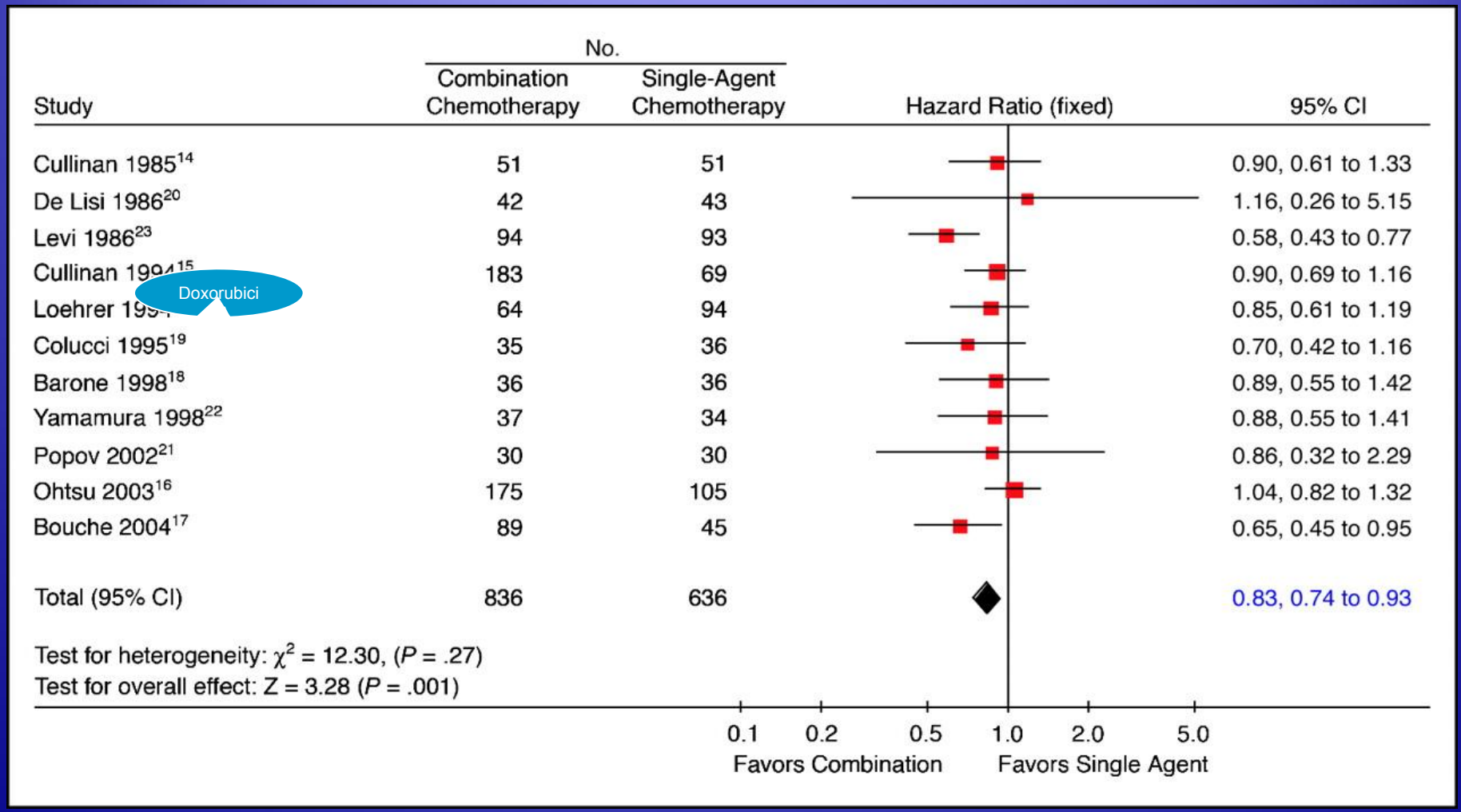
Anna D. Wagner, Wilfried Grothe, Johannes Haerting, Gerhard Kleber, Axel Grothey, Wolfgang E. Fleig

Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2903-2909

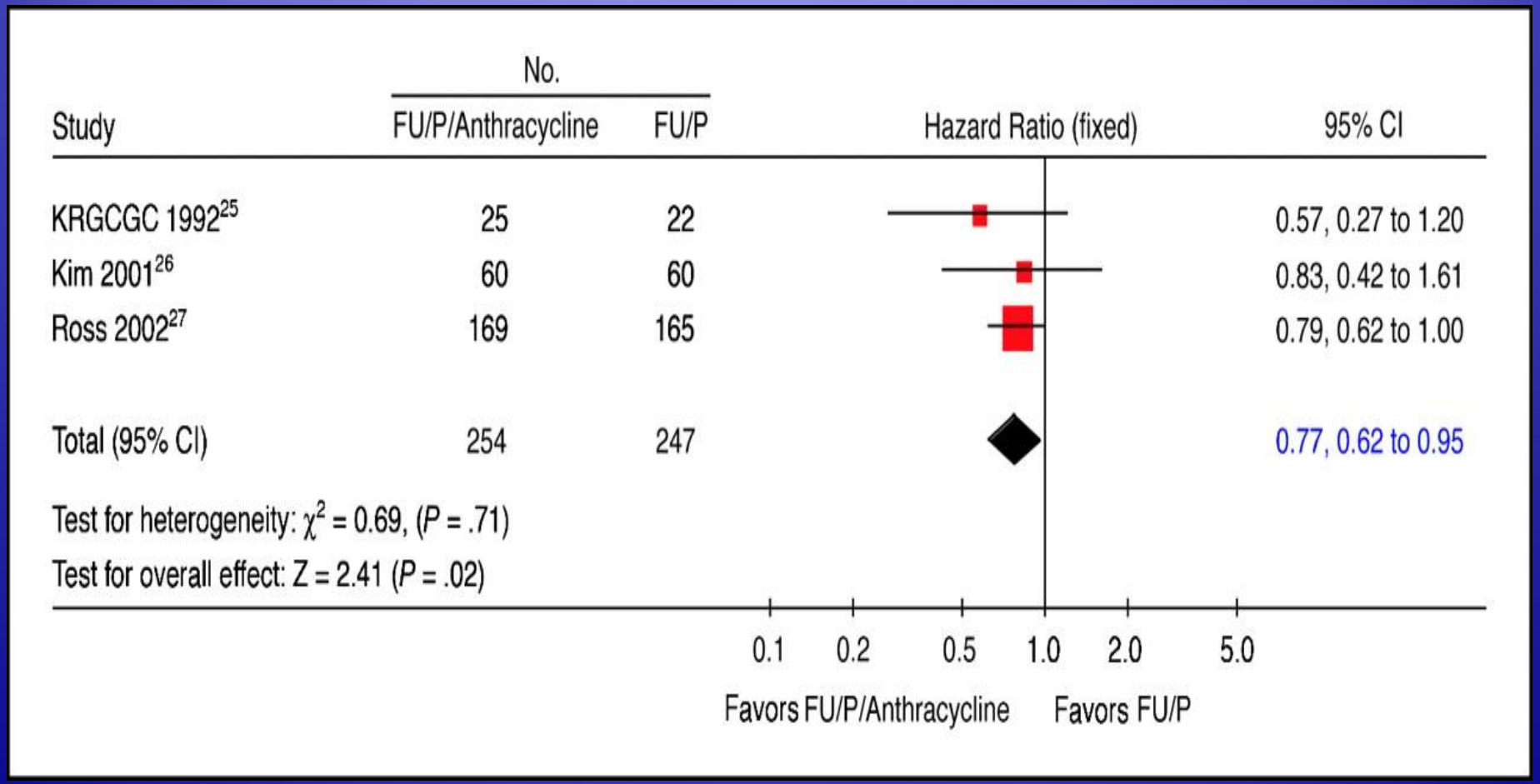
Effect of chemotherapy versus best supportive care (BSC) on overall survival



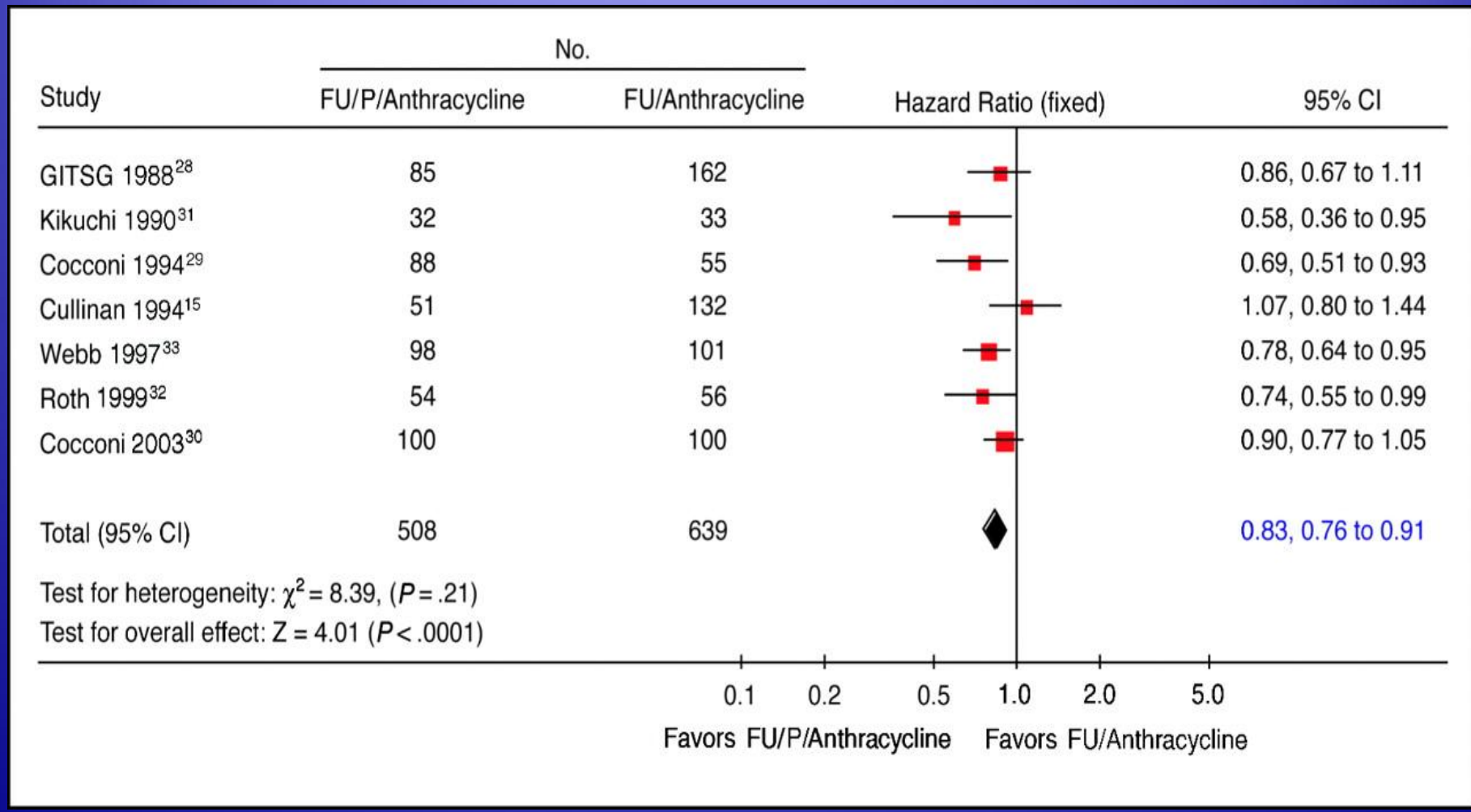
Effect of combination versus single-agent chemotherapy on overall survival



Effect of fluorouracil (FU)/cisplatin (P)/anthracycline combinations versus FU/cisplatin combinations (without anthracyclines)



Effect of fluorouracil (FU)/cisplatin (P)/anthracycline combinations versus FU/anthracycline combinations (without cisplatin)



Toxicity

- PELF; 184 patients :
  cisplatin, epirubicin, leucovorin, and FU bolus
- ECF; 327 patients:
  epirubicin, cisplatin, and FU cont.
  The rate of treatment-related deaths was 3.3% for PELF versus 0.6% for ECF (OR = 5.36; 95% CI, 1.1 to 27.4; Fisher's exact test,
  P = .02834

Quality of life was analyzed in two studies evaluating **ECF** compared with **FU, doxorubicin**, and **methotrexate and mitomycin, cisplatin, and FU** and was **superior** in patients treated with **ECF**.

Outcomes From Phase III Trials

	Response Rate	Median Survival
FAM	25-40%	6.9 months
FAMTX	20-30%	7.7 months
EAP	20%	6.1 months
ELF	21%	7.0 months
ECF	45%	8.9 months

Reference protocol

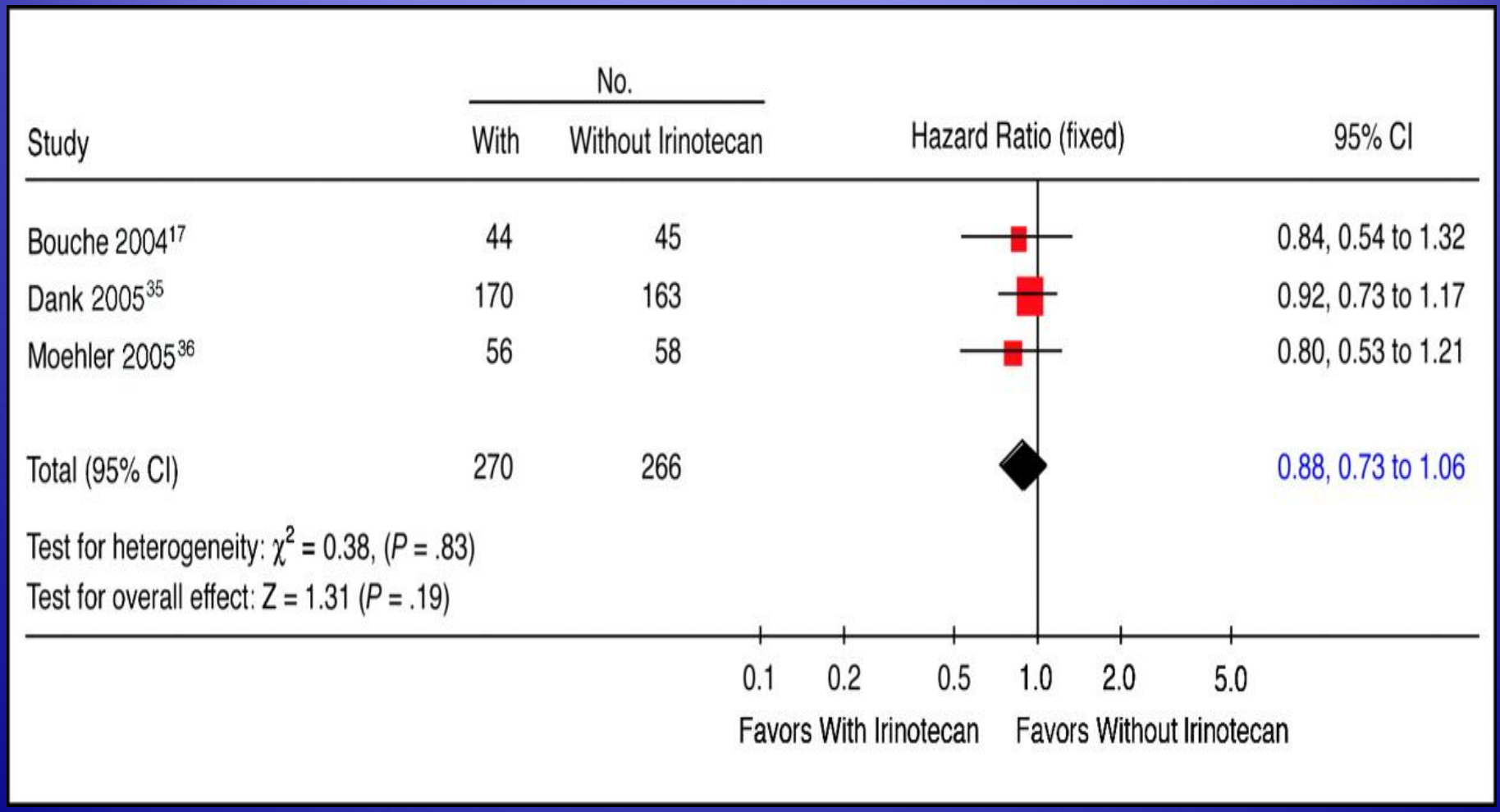
- ECF
- CF

	ECF	CF
TTP	7.4	3.7
OS	8.9	8.6
RR	45%	25%

Cisplatin/5-FU (CF) and ECF (epirubicin plus CF) regimens have been investigated

widely in clinical studies and were until recently presented as the reference regimens.

Effect of irinotecan-containing versus nonirinotecan-containing regimens



Effect of irinotecan-containing versus nonirinotecan-containing regimens

- Bouché O, Raoul JL, Bonnetain F, et al: **Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: A Fédération Francophone de Cancérologie Digestive Group study-FFCD** 9803. J Clin Oncol 22:4319-4328, 2004
- Moehler M, Eimermacher A, Siebler J, et al: **Randomized phase II evaluation of irinotecan plus high-dose 5-fluorouracil and leucovorin (ILF) versus 5-fluorouracil, leucovorin, and etoposide (ELF) in untreated metastatic gastric cancer**. Br J Cancer 92:2122-2128, 2005
- Dank M, Zaluski J, Valvere V, et al: **Randomized phase III trial of irinotecan (CPT 11) + 5-FU/folinic acid (FA) vs CDDP + 5-FU in first line advanced gastric cancer patients.** J Clin Oncol 23:308s, 2005 (suppl 16, abstr 4003)

Irinotecan-containing regimens exhibit a benefit in survival of approximately 1 month and a lower rate of treatment-related deaths over the reference regimen, which was FU and cisplatin in two of three studies.

CPT-11 plus Cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma

Results of a Phase II study

A. Ajani, M.D., Jackie Baker, R.N, …

65 mg/m2 CPT-11 plus 30 mg/m2 cisplatin, both administered intravenously 1 day per week for 4 consecutive weeks

Median TTP - 24 weeks

Median survival - 9 months (range, 1-23+ months).

IF vs. CF

phase III, 337 pts

Dank et. al, Ann Oncol. 2008

Arm A

Irinotecan (80mg/m2) D1

LV (500mg/m2) D1

5**F**U (2,000mg/m2) CIVI 22hrs

Cycle weekly for 6/7 weeks

Arm B

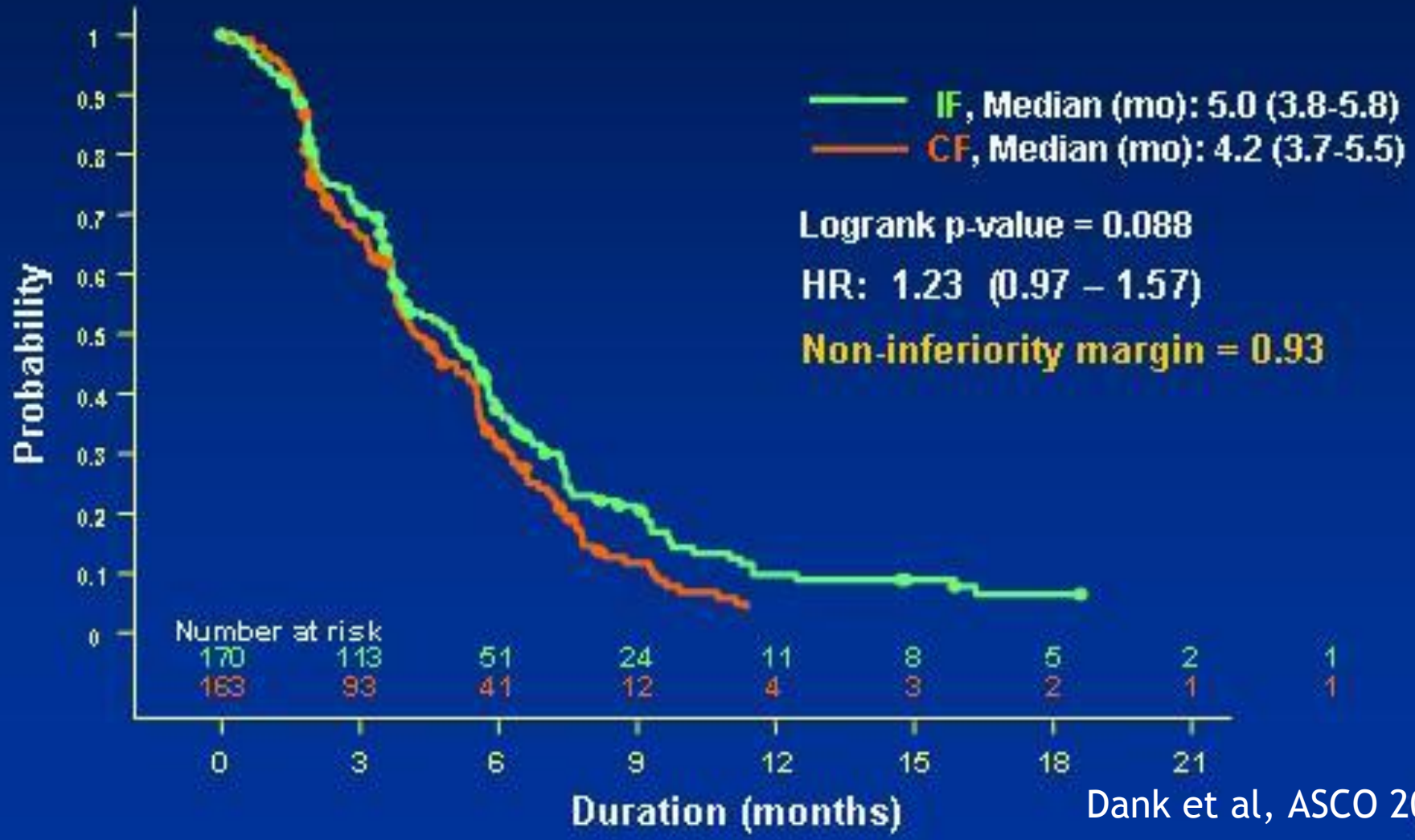
Cisplatin (100mg/m2) D1

5**F**U (1000mg/m2) CIVI D1-5

cycle q28 days

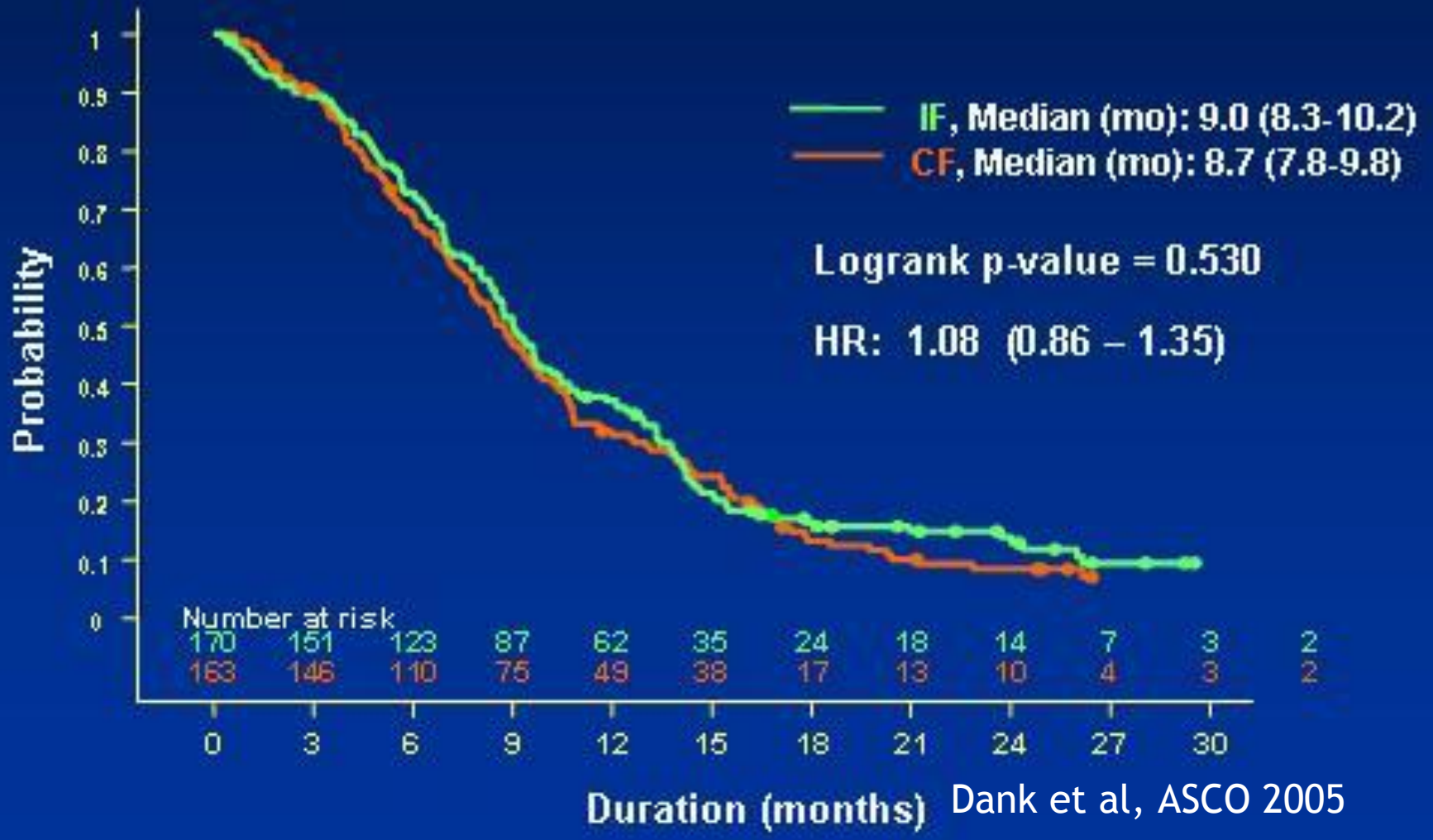
- 97% metastatic
- No palliative/prior treatment within 12 months
- Baseline characteristics with slightly worse PS in IF arm

Time to Tumor Progression



Dank et al, ASCO 2005

Overall Survival



Dank et al, ASCO 2005

IF vs. CF

- Potential alternative therapy

Taxotere

Final results of a randomized controlled phase III trial (TAX 325) comparing docetaxel (T) combined with cisplatin (C) and 5-fluorouracil (F) to CF in patients (pts) with metastatic gastric adenocarcinoma (MGC).

Moiseyenko VM, Ajani J, Tjulandin SA, et al.

J Clin Oncol 23:308s, 2005 (suppl 16, abstr 4002)

TAX 325

Arm A

D 75mg/m2 D1

C 75mg/m2 D1

F 750mg/m2 CIVI D1-5

cycles q21 days

Arm B

C 100mg/m2 D1

F 1000mg/m2 CIVI D105

cycles q28 days

- International Phase III
- 457 chemotherapy-naive patients
- Median age 55
- 97% had metastatic disease
- Patient characteristics well balanced

TAX 325

Median survival, **9.2** *v* **8.6** month

The small survival advantage for DCF compared with cisplatin and FU observed in this randomized phase III study, although statistically significant (median survival, **9.2** *v* **8.6** months, respectively $P = .02$), seems to be of questionable clinical relevance in the light of a considerably increased toxicity, especially in patients older than 65 years of age.

original article

Annals of Oncology 18: 1673–1679, 2007
doi:10.1093/annonc/mdm269
Published online 28 July 2007

Split-dose docetaxel, cisplatin and leucovorin/ fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial

S. Lorenzen[1], M. Hentrich[2], C. Haberl[3], V. Heinemann[4], T. Schuster[5], T. Seroneit[6],

- **Initially:**

  Docetaxel - 50 mg/m2 Cisplatin 50 mg/m2 on days 1, 15 and 29

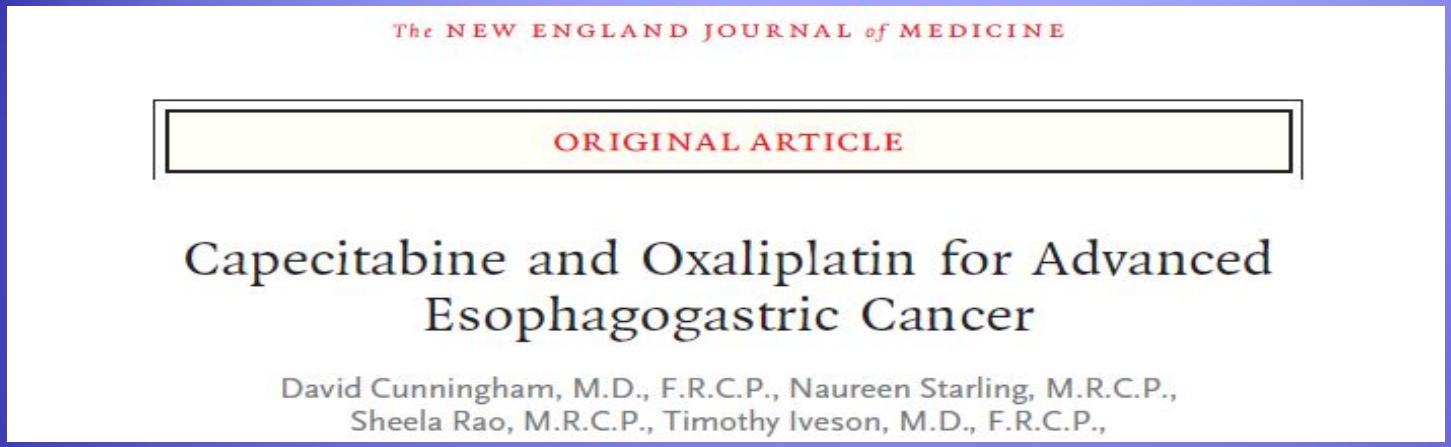
  Leucovorin 500 mg/m2 and Fluorouracil 2000 mg/m2 on days 1, 8, 15, 22, 29 and 36, every 8 weeks (1 cycle)

- **The doses were amended to**:

  Docetaxel 40 mg/m2, Cisplatin 40 mg/m2, LCV 200 mg/m2, and Fluorouracil 2000 mg/m2 after treatment of the first 15 patients.

Toxicity G3-4	**TAX 325** phase III	**Split** phase II
Neutropenia	85%	13%
Febrile neutropenia	29%	3%

Efficacy		
TTP	5.6	9.4
OS	9.2	15.1
RR	37%	47%



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer

David Cunningham, M.D., F.R.C.P., Naureen Starling, M.R.C.P., Sheela Rao, M.R.C.P., Timothy Iveson, M.D., F.R.C.P.,

- 2x2 randomized study comparing ECF to alternative regimens substituting Oxaliplatin for Cisplatin Capecitabine for 5-fluorouracil.

ECF (E 50mg/m2); (C 60mg/m2); (FU 200mg/m2)

EOF (E 50mg/m2); (O 130mg/m2); (FU 200mg/m2)

ECX (E 50mg/m2); (C 60mg/m2); (X 1000/1250mg/m2)

EOX (E 50mg/m2); (O 130mg/m2); (X 1000/1250mg/m2)

Cycles q21 days

REAL-2

- The 2x2 comparisons primarily compared the fluoropyridine-containing arms (ECF + EOF versus ECX + EOX) and platinum-containing arms (ECF + ECX versus EOF + EOX).

REAL-2

For the fluoropyrimidine comparison of **5-FU** versus **capecitabine**:

1 y OS - **39.4%** (median **OS** 9.6 months)
versus **44.6%** (median **OS** 10.9 months)

(HR:0.86 (95% CI:0.75-0.99))

REAL-2

For the platinum comparison of **cisplatin** versus **oxaliplatin**:

1 y OS - **40.1%** (median **OS** 10.0 months)
versus **43.9%** (median **OS** 10.4 months)

(HR:0.92 (95% CI: 0.80-1.05

REAL-2

conclusion

- capecitabine is not inferior to 5-FU and oxaliplatin is not inferior to cisplatin in the first-line treatment of oesophago-gastric cancers.

- In a comparison of survival by regimen, the median overall survival for ECF, EOF, ECX and EOX was 9.9, 9.3, 9.9 and 11.2 months respectively.
- EOX was associated with a significantly better median OS compared to ECF (p=0.02).

Capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin,respectively,

Table 2. Analysis of Efficacy (Intention-to-Treat Population).*

Variable	ECF (N=263)	ECX (N=250)	EOF (N=245)	EOX (N=244)
Death				
No. of patients	225	213	213	199
Hazard ratio (95% CI)		0.92 (0.76–1.11)	0.96 (0.79–1.15)	0.80 (0.66–0.97)
P value		0.39	0.61	0.02
Overall survival				
Median — mo	9.9	9.9	9.3	11.2
At 1 yr — % (95% CI)	37.7 (31.8–43.6)	40.8 (34.7–46.9)	40.4 (34.2–46.5)	46.8 (40.4–52.9)
Progression-free survival				
Median — mo	6.2	6.7	6.5	7.0
Patients who had progression or died	237	231	221	213
Hazard ratio (95% CI)		0.98 (0.82–1.17)	0.97 (0.81–1.17)	0.85 (0.70–1.02)
P value		0.80	0.77	0.07
Response				
Overall — % (95% CI)†	40.7 (34.5–46.8)	46.4 (40.0–52.8)	42.4 (36.1–48.8)	47.9 (41.5–54.3)
Complete — %	4.1	4.2	2.6	3.9
Partial — %	36.6	42.2	39.8	44.0
P value		0.20	0.69	0.11

n engl j med 358;1 www.nejm.38 org january 3, 2008

Metastatic disease ongoing phase III trials:

United States:

cisplatin/S-1 vs. cisplatin/5FU

- 28 day cycles
- S-1 given daily 21/28 days

Japanese: Trials with S-1,RAD001

German: Irinotecan vs. BSC

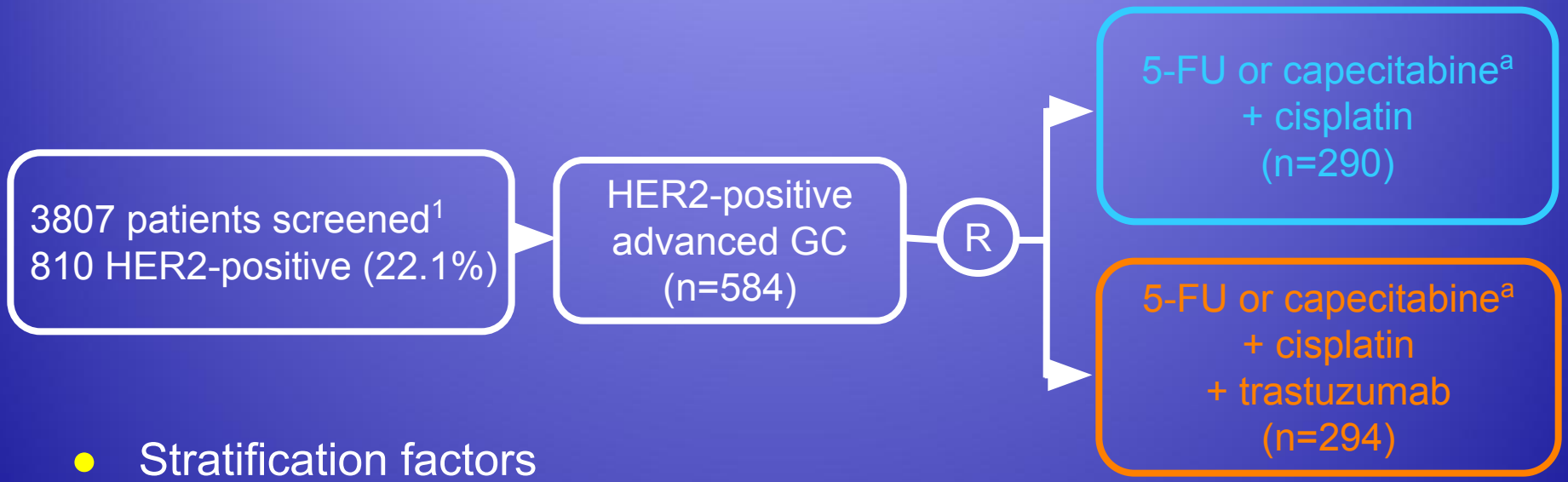
HER2 positive gastric cancer:

ToGA trial is an ongoing Phase III, randomised, open-label, multicentre study evaluating the efficacy and safety of Herceptin in combination with a fluoropyrimidine (Xeloda or 5-fluorouracil at the investigator's discretion) and cisplatin versus chemotherapy alone as first-line therapy in patients with HER2-positive advanced gastric cancer.

ToGA trial design

Phase III, randomized, open-label, international, multicenter study

HER2 over expression – 6-35% (20%)



- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

[1]Bang et al; Abstract 4556, ASCO 2009

Treatment regimens

- Capecitabine
  1000 mg/m^2 bid d1-14 q3w x 6
- 5-fluorouracil
  800 mg/m^2/day continuous iv infusion d1-5 q3w x 6
- Cisplatin
  80 mg/m^2 q3w x 6
- Trastuzumab
  8 mg/kg loading dose followed by 6 mg/kg q3w until PD

ToGA

Endpoints:

Primary: overall survival

Secondary: progression-free survival PFS

overall response rate ORR

clinical benefit rate

duration of response

safety profile

quality of life

pharmacokinetics of Herceptin

Results

Median OS was significantly improved with **H+CT** compared to **CT** alone

13.8 vs. **11.1** mo

p=0.0048; HR 0.74; 95% CI 0.60, 0.91

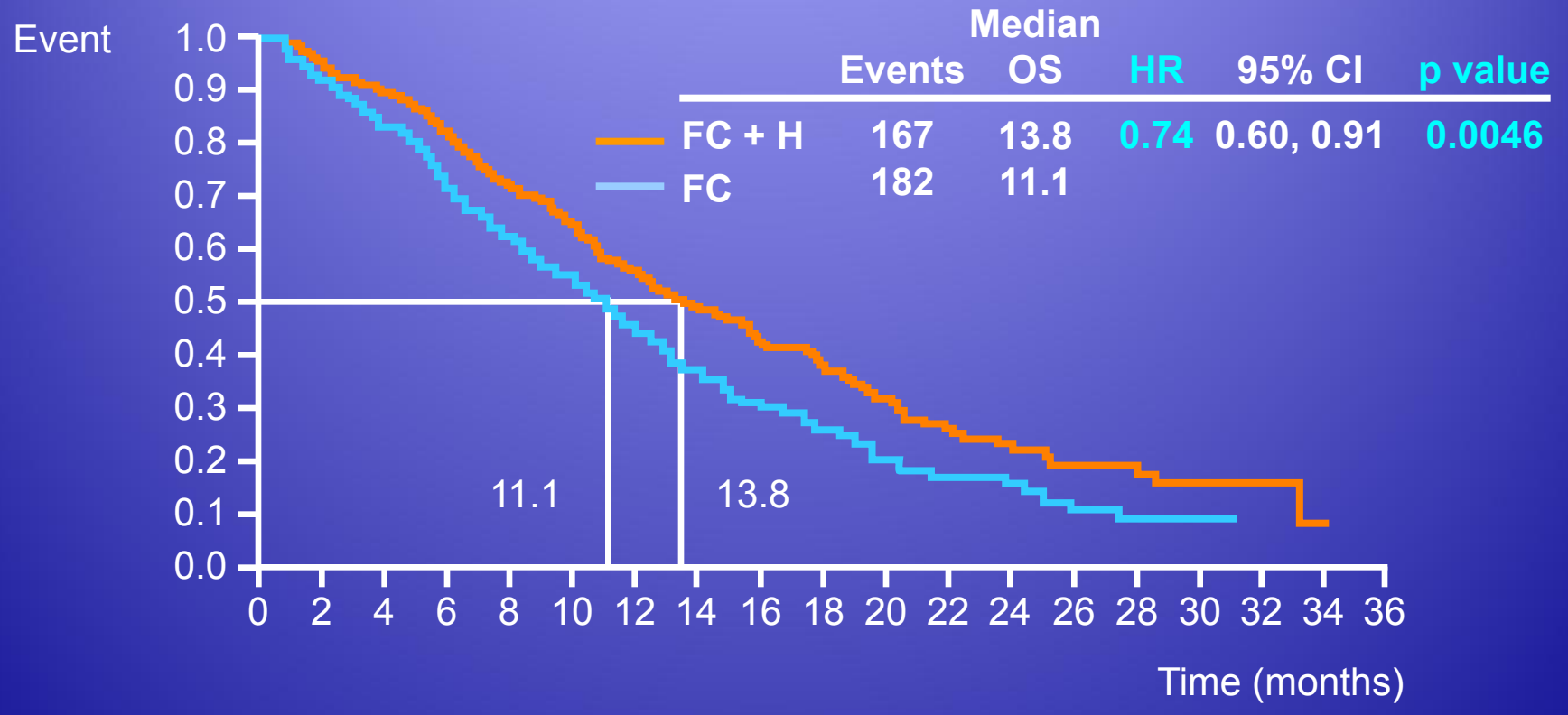
ORR - **47.3%** in the H+CT arm

34.5% in the CT arm p=0.0017

There was no difference in symptomatic congestive heart failure between arms.

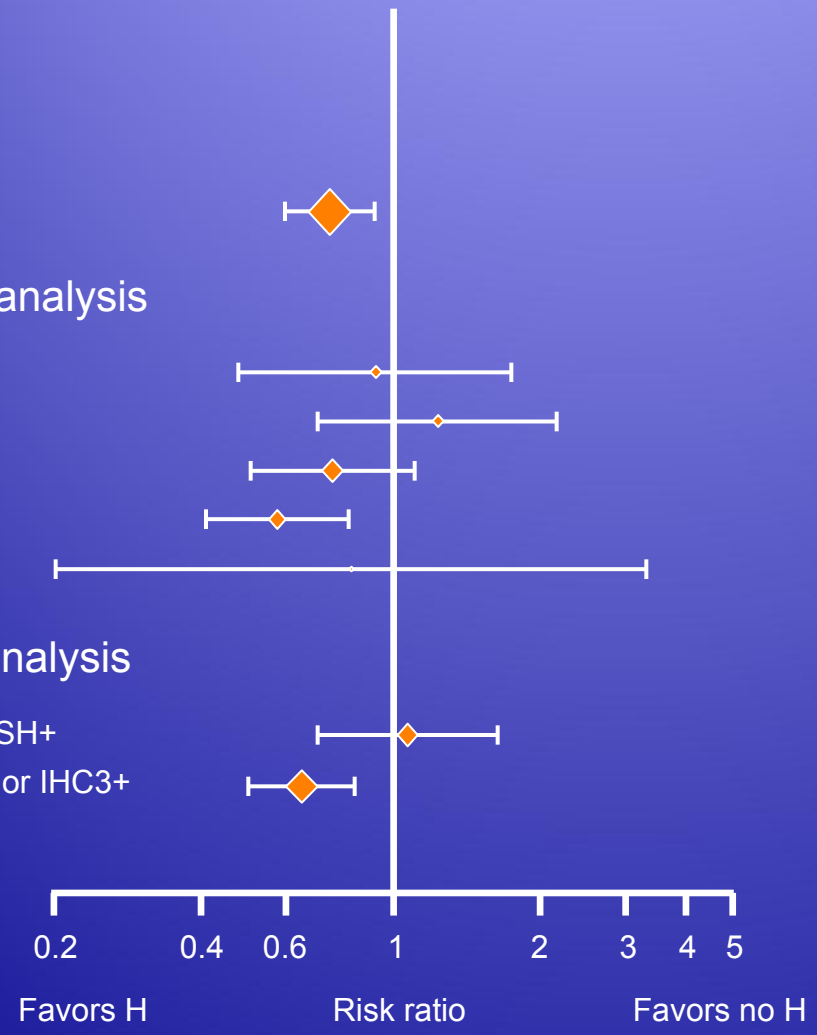
Asymptomatic left ventricular ejection fraction decreases were reported in 4.6% of pts in the H+CT arm and 1.1% in the CT arm.

Primary end point: OS



CI, confidence interval; H, trastuzumab

Efficacy: OS by HER2 status



Subgroup	N	Median OS (months)	Hazard ratio	95% CI
All	584	11.1 vs 13.8	0.74	0.60, 0.91
Pre-planned analysis				
IHC0/FISH+	61	7.2 vs 10.6	0.92	0.48, 1.76
IHC1+/FISH+	70	10.2 vs 8.7	1.24	0.70, 2.20
IHC2+/FISH+	159	10.8 vs 12.3	0.75	0.51, 1.11
IHC3+/FISH+	256	12.3 vs 17.9	0.58	0.41, 0.81
IHC3+/FISH-	15	17.7 vs 17.5	0.83	0.20, 3.38
Exploratory analysis				
IHC0 or 1+/FISH+	131	8.7 vs 10.0	1.07	0.70, 1.62
IHC2+/FISH+ or IHC3+	446	11.8 vs 16.0	0.65	0.51, 0.83

Conclusions

- Trastuzumab is the first biological agent to show a survival benefit in gastric cancer
- Trastuzumab in combination with chemotherapy is a new treatment option for patients with HER2-positive gastric adenocarcinoma

Avastin…

Multicenter Phase II Study of Irinotecan, Cisplatin, and Bevacizumab in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Manish A. Shah, Ramesh K. Ramanathan, David H. Ilson, Alissa Levnor, David D'Adamo, Eileen O'Reilly, Archie Tse, Robin Trocola, Lawrence Schwartz, Marinela Capanu, Gary K. Schwartz, David P. Kelsen

Journal of Clinical Oncology, Vol 24, No 33 (November 20), 2006: pp. 5201-5206

47 patients with metastatic or unresectable gastric/GEJ adenocarcinoma were treated with bevacizumab 15 mg/kg on day 1, irinotecan 65 mg/m2, and cisplatin 30 mg/m2 on days 1 and 8, every 21 days.

The primary end point was to demonstrate a 50% improvement in time to progression over historical values. Secondary end points included safety, response, and survival.

- **Median TTP was 8.3 months** (95% CI, 5.5 to 9.9 months
- **Median overall survival was 12.3 months** (95%CI, 11.3 to 17.2 months

Cetuximab …

- **Phase II study of c**etuximab **in c**ombi**n**ation with FOLFIRI **in** patients with untreated advan**c**ed gastri**c** or gastroesophageal jun**c**tion adeno**c**ar**cin**oma (FOL**C**ETUX **study**). Pinto C… Annals **of** On**c**ology Advan**c**e A**cc**ess De**c**ember 12, 2006
- ORR - 44.1%
- mTTP - 8 months (95% **C**I 7–9).
- OS - 16 months (95% **C**I 9–23).

- The **c**ombi**n**ation **of c**etuximab and FOLFIRI is a**c**tive **in** gastri**c** and GEJ adeno**c**ar**cin**oma. The higher toxi**c**ity appears to be limited to neutropenia(41%)

Cetuximab …

- Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study) Pinto C…***British Journal of Cancer*** (October 2009)
- cetuximab – 400mg/m2 - initial dose i.v., followed by weekly doses of 250m2,
- cisplatin 75mg/m2 i.v. on day 1,

docetaxel 75mg/m2 i.v. on day 1, every 3 weeks, for a maximum of 6 cycles, and then cetuximab maintenance treatment was allowed in patients with a complete response, partial response, or stable disease.

mTTP – 5mo
mOS – 9mo
ORR – 41.2%

Not improve the TTP and OS.

The toxicity of cisplatin/docetaxel chemotherapy was not affected by the addition of cetuximab.

Cetuximab …

- **EXPAND**
  (Phase III)

- Cetuximab (Erbitux) in combination with capecitabine (Xeloda, X) and cisplatin (P) versus XP alone

Second line therapy

- **Second-line chemotherapy with FOLFIRI in patients with metastatic gastric cancer (MGC) not previously treated with fluoropyrimidines.**

  L. Di Lauro, S. I. Fattoruso, L. Giacinti …J Clin Oncol 27:15s, 2009

  First-line therapy : epirubicin, docetaxel and cisplatin or oxaliplatin
  Second line: irinotecan 180 mg/mq (150 mg/mq in pts >70 ys old) day 1; leucovorin 100 mg/mq/day , bolus fluorouracil (FU) 400 mg/mq and a 22-h infusion of FU 600 mg/mq day 1-2, every 2 weeks for a maximum of 12 cycles or until disease progression, unacceptable toxicity or patients refusal.
  Endpoints : response rate (RR), time to progression (TTP), overall survival (OS) and safety.

- Median TTP - 4.0 months (95% CI, 2.9-5.1)
- Median OS - 6.2 months (95% CI, 4.7-7.7).

- FOLFIRI is an active and well tolerated second-line regimen for MGC pts not previously treated with fluoropyrimidines.

Second-line chemotherapy for patients with advanced gastric cancer: who may benefit?

V Catalano, F Graziano . . . *British Journal of Cancer* (2008)

- **Median survival for the whole group was 6.1 months**
- **1-year OS - 20.5% (95% CI, 14.4–26.6**
- **Overall response rate of 16.0% (95% CI, 10.6–21.4**
- No statistically significative difference was found between each regimen used as second-line chemotherapy.

	No. of patients
First-line chemotherapy	
5-FU-based	13
5FU/cisplatin-based	141
5-FU/oxaliplatin-based	21
TTP	6 m
Second-line chemotherapy	
5-FU-based	47
5-FU/CDDP	21
5-FU/irinotecan-based	51
5-FU/taxane	25
5-FU/oxaliplatin-based3	31

Conclusion

- No dramatic improvement with new studies.
- DCF with slight improvement, but increased toxicity
- IF possible alternative for those unable to tolerate a platinum agent
- REAL-trial results with provide role for oxaliplatin and capecitabine

Thank you!