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16TH WORLD CONGRESS ON Gastrointestinal CANCER

What is the reference cytotoxic regimen in advanced gastric cancer?

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Germany

UNIVERSITÄT LEIPZIG

UCCL UNIVERSITÄRES KREBSZENTRUM

What we know from clinical research….

- Chemotherapy prolongs survival
- Chemotherapy improves symptom control
- Combinations are more active than monotherapy

Wagner AD *et al.* J Clin Oncol 2006;24(18):2903-2909. Review
Koizumi W et al. Lancet Oncol 2008; 9:215-21. SPIRITS trial

Established standard 1st-line: Platinum-fluoropyrimidine-combination

- Elderly (>70 years age) benefit equally

Trumper M *et al*. Eur J Cancer 2006; 42(7): 827-834

- Second-line chemotherapy is effective

Thuss P *et al.* Eur J Cancer 2011
Kang et al J Clin Oncol 2012
Ford et al. Lancet 2014

What we know from clinical research….

- Oxaliplatin can substitute for cisplatin

Al-Batran SE *et al*. J Clin Oncol 2008;26(9):1435-1442;
Cunningham D *et al.* N Engl J Med 2008;358(1):36-46

- Oral fluoropyrimidines can substitute for i.v. 5-FU

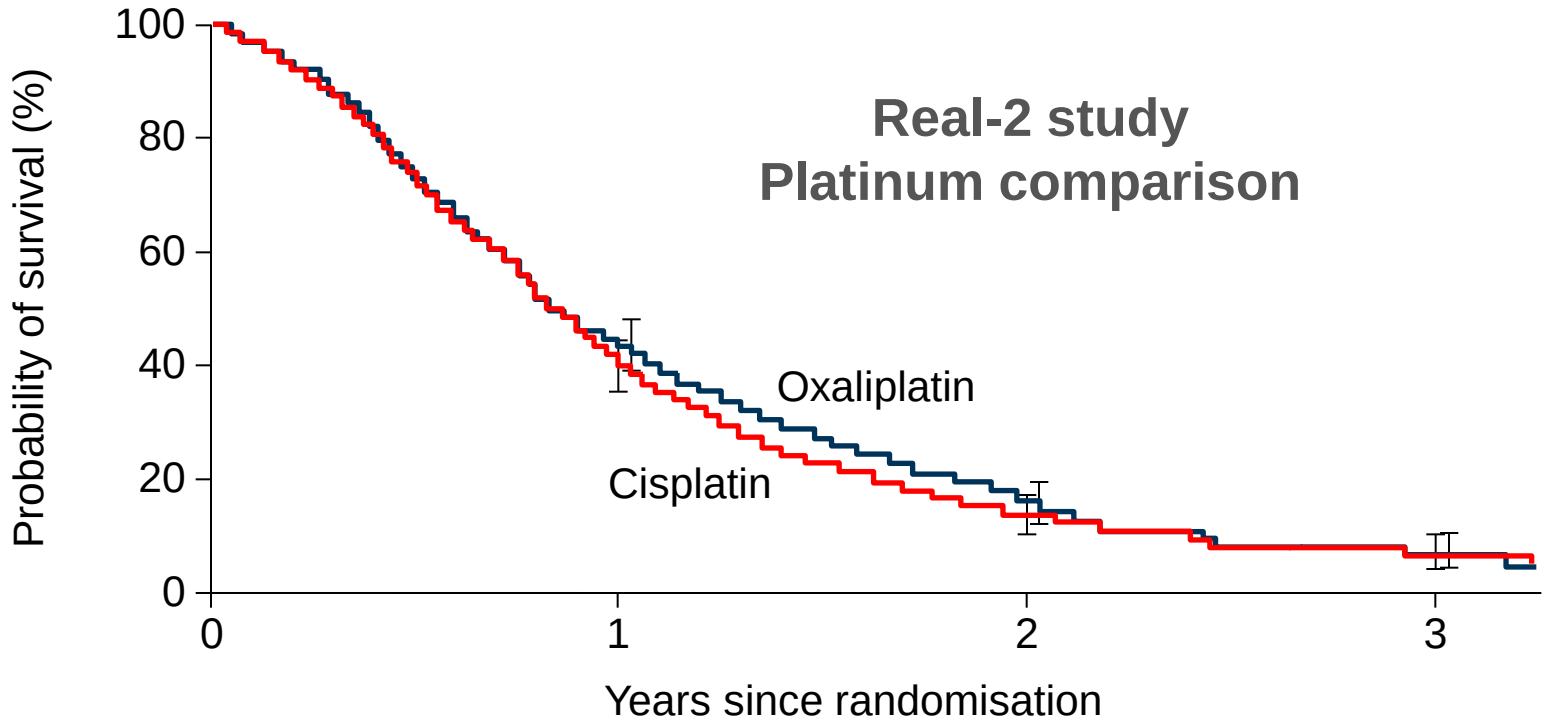
Kang YK *et al*. Ann Oncol 2009;20(4):666-673;
Cunningham D *et al.* N Engl J Med 2008;358(1):36-46;
Ajani JA *et al*. J Clin Oncol 2010;28(9):1547-1553

- A 3rd drug makes CTx more effective but is more toxic

Van Cutsem E *et al.* J Clin Oncol 2006;24(31):4991-4997;
Wagner AD *et al.* J Clin Oncol 2006;24(18):2903-2909. Review

Oxaliplatin versus cisplatin

- Can oxaliplatin substitute for cisplatin?



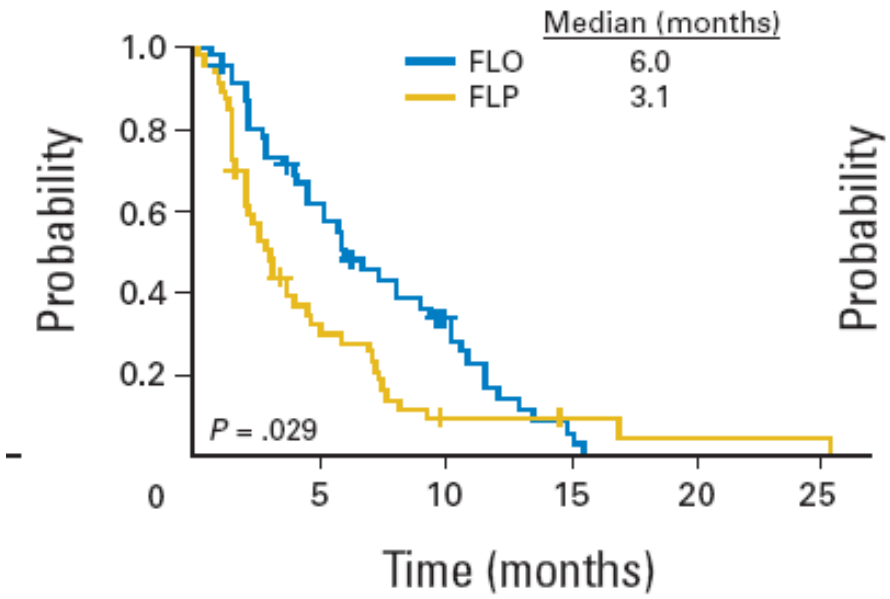
No. at risk				
Cisplatin	490	187	41	10
Oxaliplatin	474	198	48	10

Redrawn from **Cunningham D** *et al.* N Engl J Med 2008;358(1):36-46

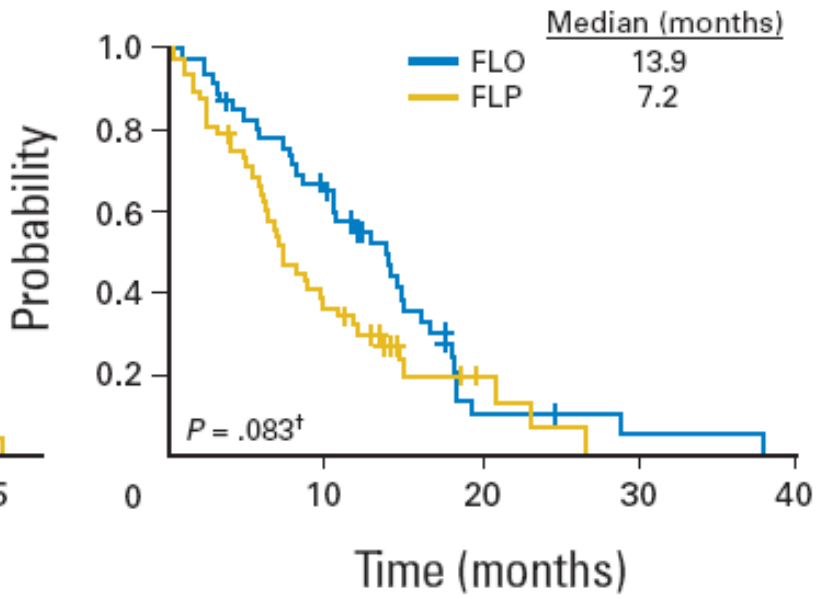
Oxaliplatin versus cisplatin

AIO study: FLO versus FLP
Elderly patients (≥65 years)

PFS: p = 0.029



OS: p = n. s.



Al-Batran SE *et al*. J Clin Oncol 2008;26(9):1435-1442

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Platinum compounds

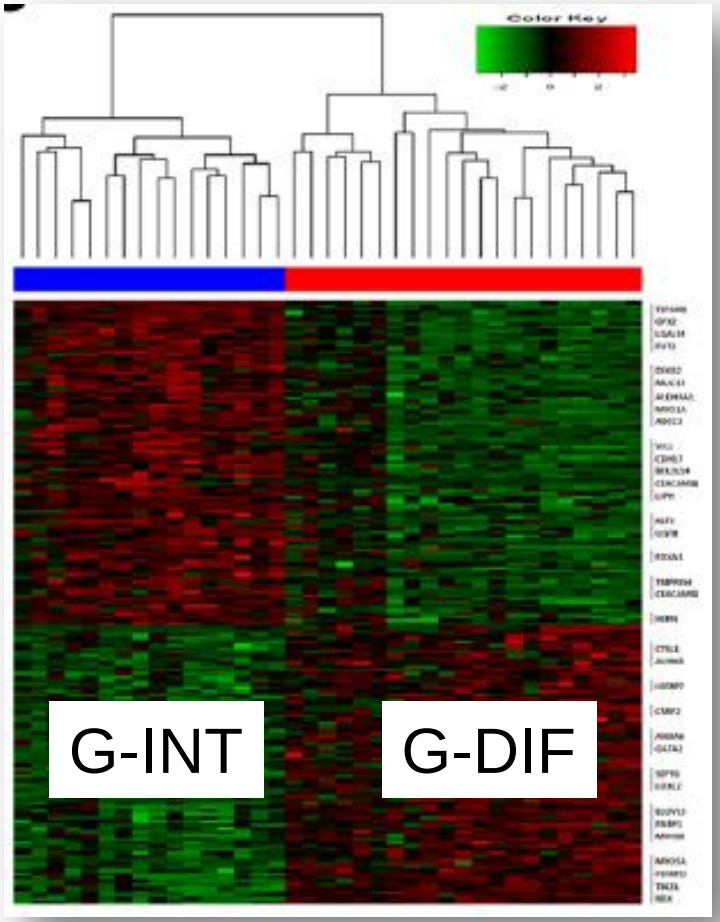
- Can oxaliplatin substitute for cisplatin?

Yes, with some advantages for oxaliplatin in the elderly

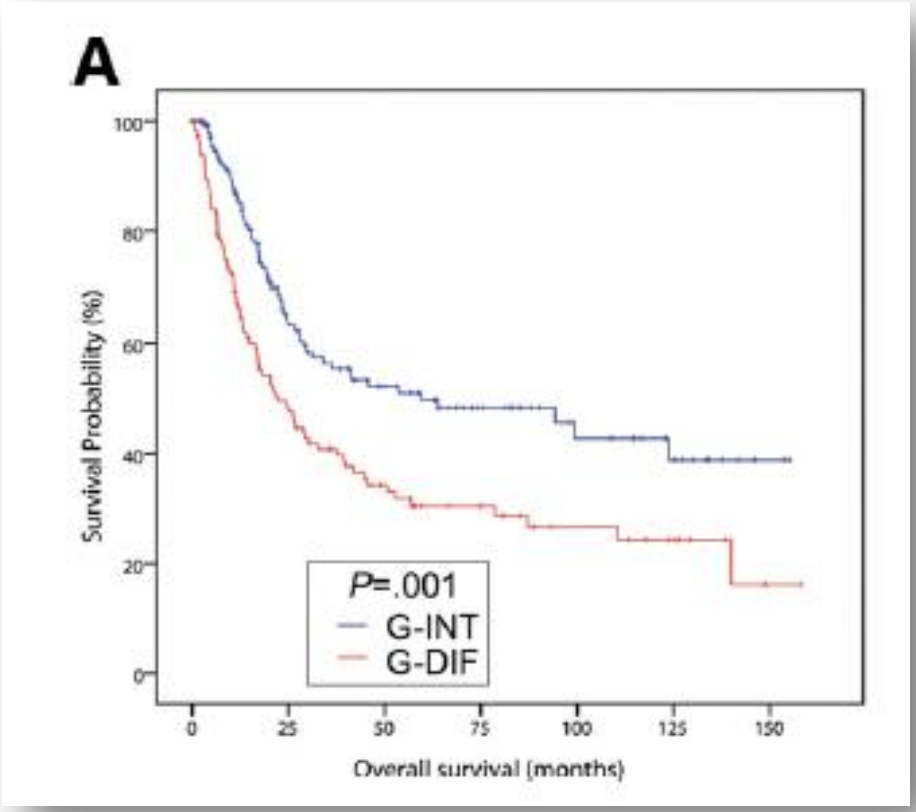
Can we predict which platinum compound works better?

Platinum compounds

Genetic heatmaps from
37 cell lines (gene expression)



Validation in patients
who received adjuvant 5-FU



Tan et al. *Gastroenterology* 2011;141:476-485

Platinum compounds

Chemosensitivity in cell lines G-INT vs. G-DIF

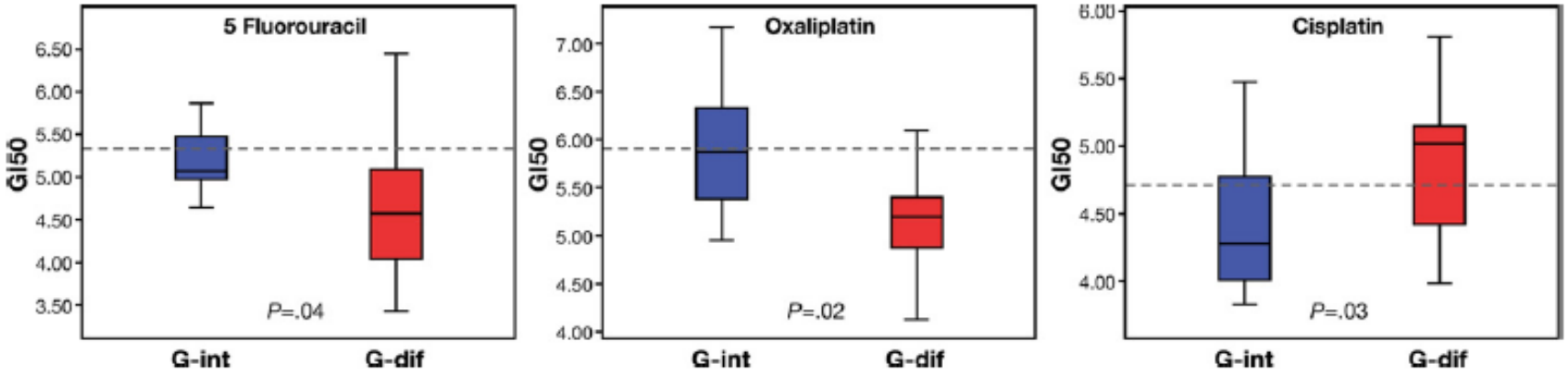
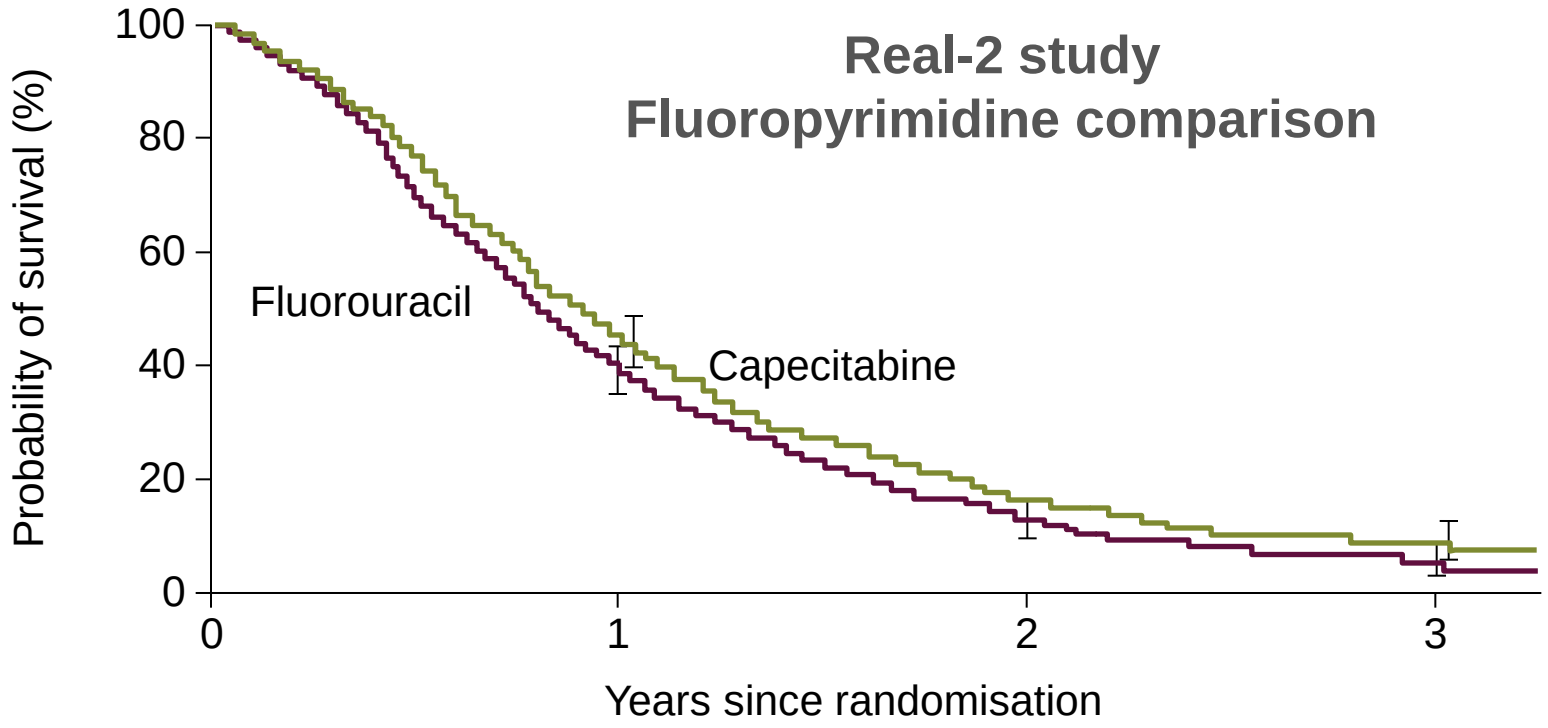


Figure 4. In vitro chemosensitivity of G-INT and G-DIF cell lines. GI-50 values of 11 G-INT and 17 G-DIF cell lines upon treatment with 5-FU, oxaliplatin, and cisplatin. GI-50 refers to the drug concentration at which 50% growth inhibition is achieved (y-axis: GI-50 enumerated in negative $\log_{10}$). The *horizontal gray lines* represent the therapeutic concentration patients are exposed to based on pharmacokinetic data.[25–27] Mean GI-50 concentrations for G-INT and G-DIF cell lines were as follows, respectively: 5-FU, 5.20 μmol/L and 23.22 μmol/L; cisplatin, 38.61 μmol/L and 13.35 μmol/L; oxaliplatin, 1.33 μmol/L and 5.49 μmol/L.

Tan et al. *Gastroenterology* 2011;141:476-485

Oral fluoropyridines - capecitabine

Can oral fluoropyrimidines substitute for i.v. 5-FU?

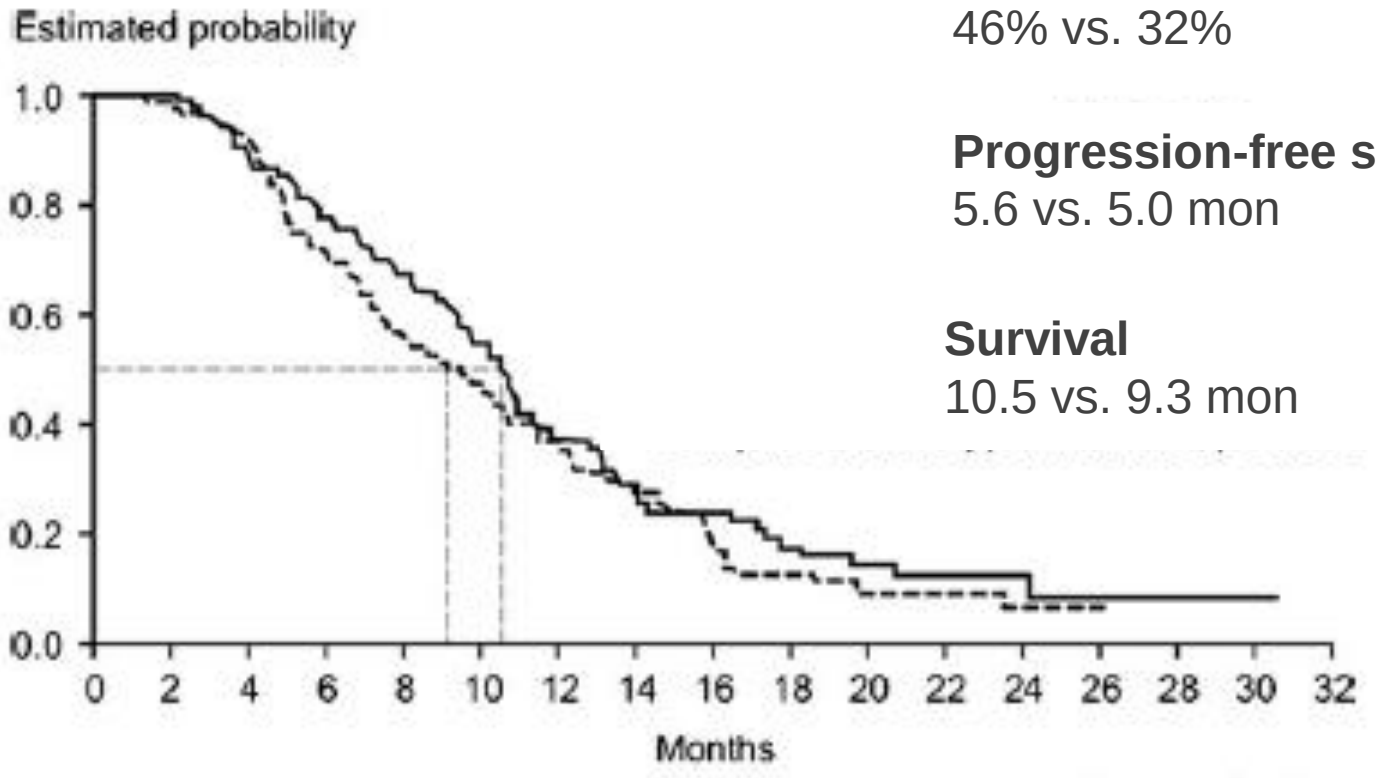


No. at risk				
Fluorouracil	484	178	37	8
Capecitabine	480	206	52	12

Cunningham D *et al.* N Engl J Med 2008;358(1):36-46

Oral fluoropyridines - capecitabine

ML 17032 Study
XP versus 5-FU/Cisplatin



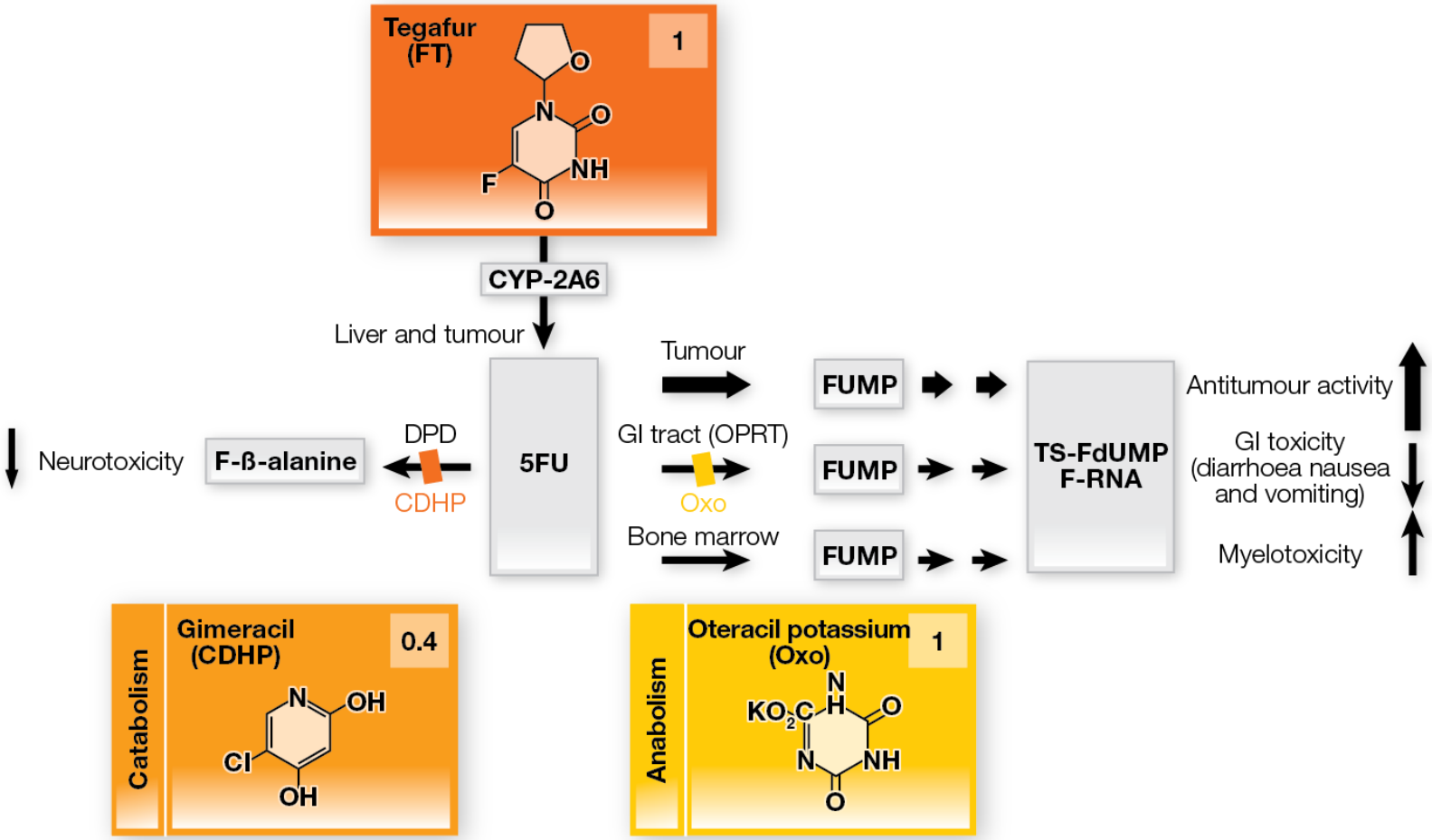
Response rate
46% vs. 32% p=0.02

Progression-free survival
5.6 vs. 5.0 mon p≤0.001 (non-inferior)

Survival
10.5 vs. 9.3 mon p=0.008 (non-inferior)

Kang YK *et al.* Ann Oncol 2009; 20: 666-673

Oral fluoropyridines – S1



Lamont EB and Schilsky RL. *Clin Cancer Res* 1999;5:2289–96

Oral fluoropyridines – S1

- **Japan – Spirits study**
  Addition of cisplatin to S-1 improves survival

Koizumi W *et al*. *Lancet Oncol* 2008; 9: 215–21

- **West – Flags study**
  S-1/cisplatin = i.v. 5-FU/cisplatin (5-day reg) equally effective but less side effects

Ajani JA *et al*. *J Clin Oncol* 2010;28(9):1547-1553

MATEO International Study by AIO Young Investigators

Young Medical Oncologists (YMO)

Georg Martin Haag
Heidelberg
Study PI

Gertraud Stocker
Leipzig
Translational Research

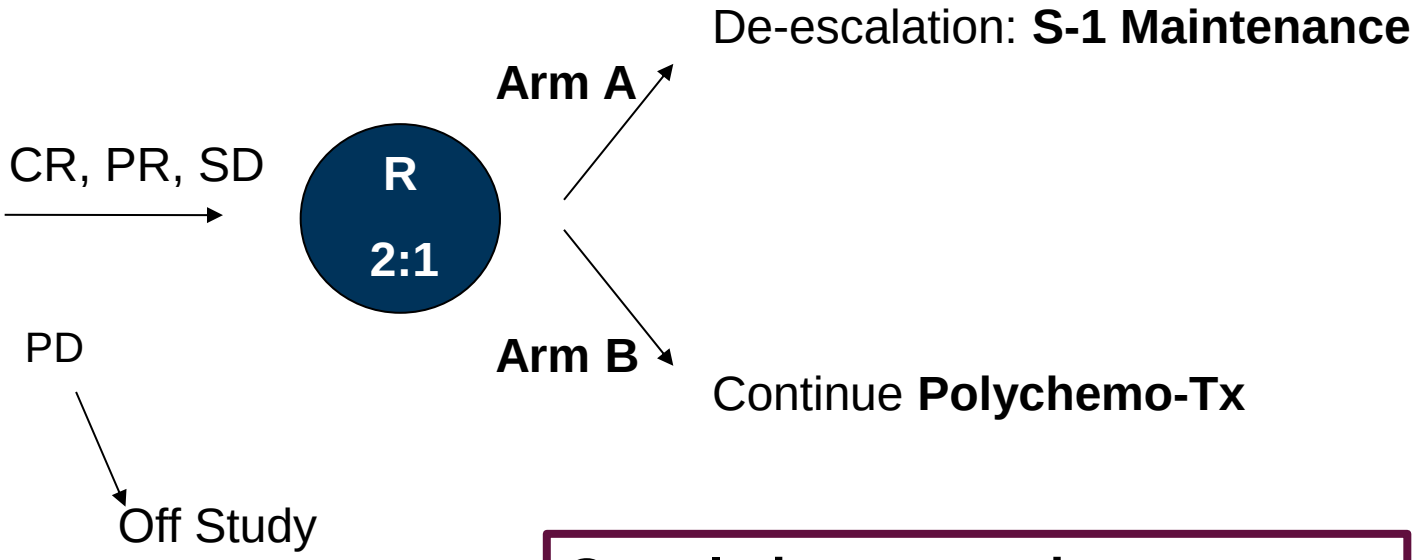
Julia Quidde
Hamburg
QoL Research

MATEO International Study
De-escalation and S-1 maintenance

3 months Induction Polychemo-tx

Investigator´s choice:

mod. Folfox
Cisplatin/S-1
FLOT
EOX/EOF



Correlative research
Polymorphisms, Target expression
Gene expression….

Primary Endpoint: Overall survival
297 patients will be randomized in 50 centers in Europe.

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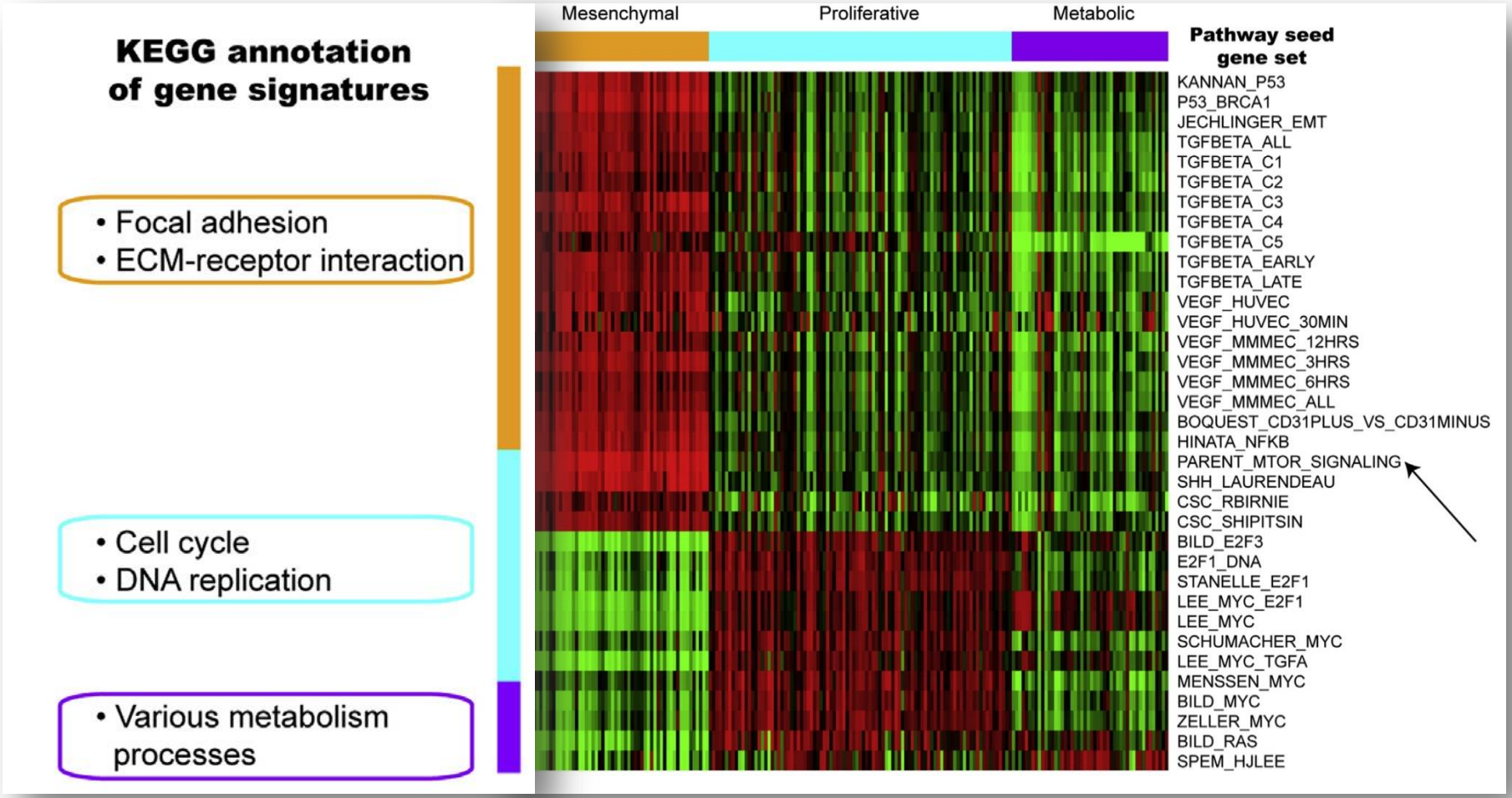
Does gene expression matter?



Lei et al., *Gastroenterology* 2013; 145: 554-6

Gene expression and chemosensitivity

	Mesenchymal	Proliferative	Metabolic
CTx-sensitivity in cell lines	**PI3K-AKT-mTOR inhibitors**	-	**5-FU**
Pathway activation	EMT, TGF-B, VEGF, NFKB, mTOR, SHH	E2F, MYC, RAS	SPEM
Lauren diffuse	58.2%	73.6%	40.6%
Genetic diffuse (Tan et al. 2011)	92.5%	28.8%	15.7%

Lei et al., *Gastroenterology* 2013; 145: 554-6

Triplet drug combinations

- What is the role of triplets, and especially docetaxel?

TAX325

Stage IV GC
n=445

RANDOM

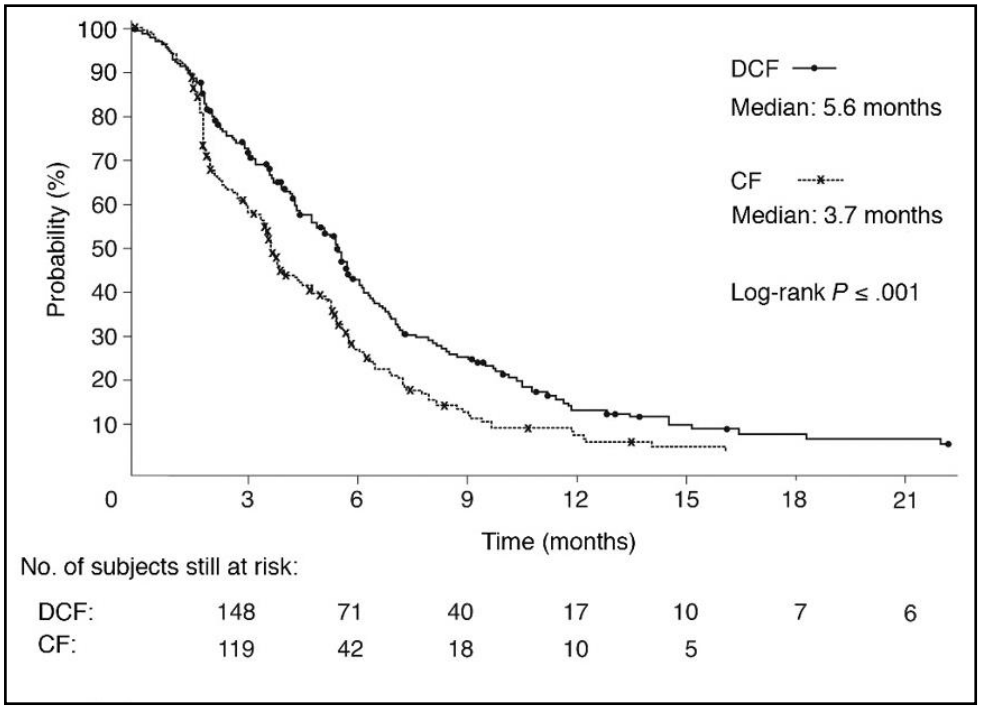
Docetaxel 75 mg/m² d1
Cisplatin 75 mg/m² d1
5-FU 750 mg/m² d1-5
q3w

Primary endpoint: Time to progression (TTP)

Cisplatin 100 mg/m² d1
5-FU 1000 mg/m² d1-5
q4w

Van Cutsem E *et al.* J Clin Oncol 2006;24(31):4991-4997

More efficacious treatment – Tax-325 study. Role of docetaxel



Kaplan-Meier curve: Time to progression

Response rate
37% vs. 25% p=0.01

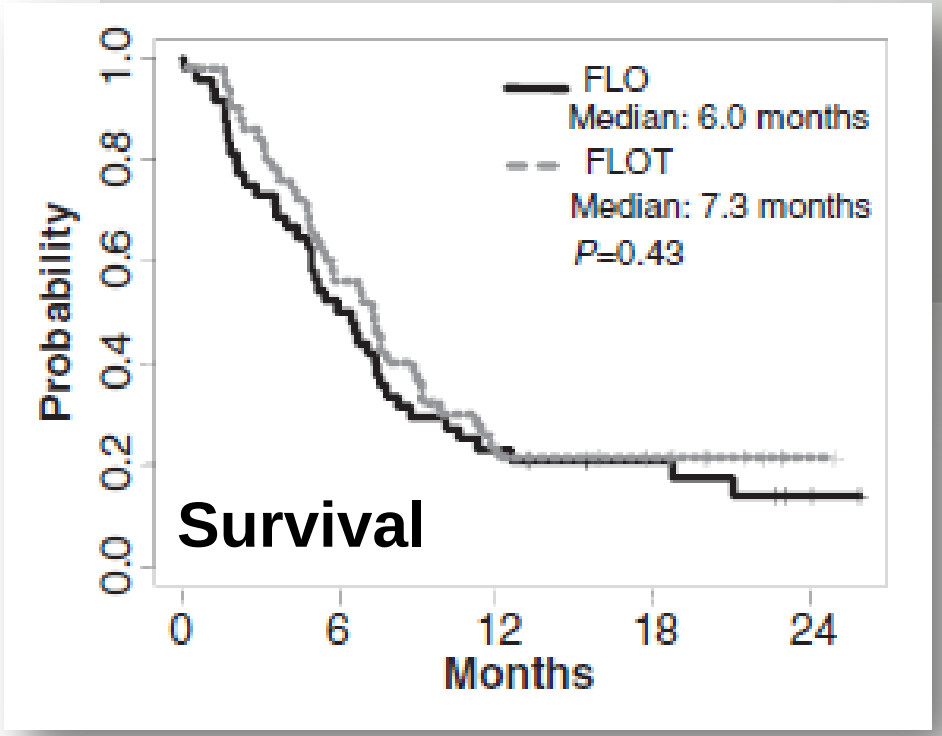
Time to progression
5.6 vs. 3.7 months p≤0.01

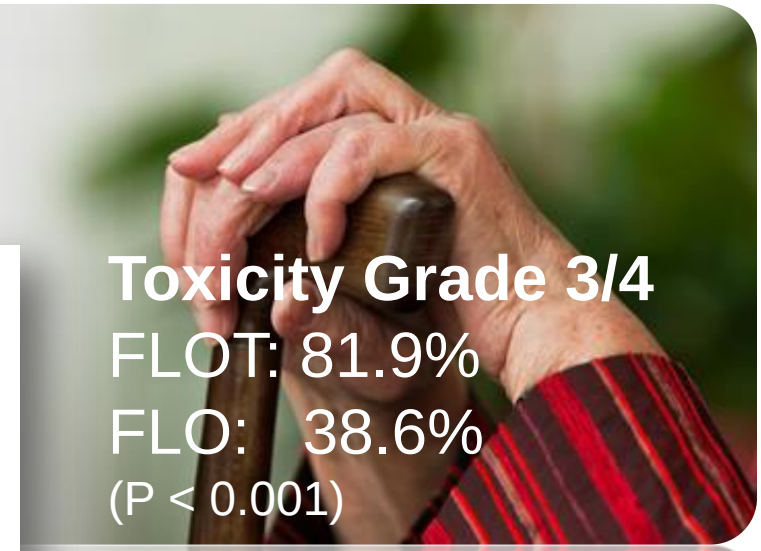
Survival
9.2 vs. 8.6 months p=0.02

Increased efficacy at the price of increased toxicity

Van Cutsem E *et al.* J Clin Oncol 2006;24(31):4991-4997

Docetaxel-triplet in older patients with mGC





Toxicity Grade 3/4
FLOT: 81.9%
FLO: 38.6%
(P < 0.001)

Impairment of EORTC Global Health
Scale ≥ 10 points
FLOT: 47.5%
FLO: 20.5%
(P < 0.01)

Al-Batran et al., *Eur J Cancer.* 2013; 49: 2823-2831

Second-line treatment of gastric cancer

NEWS & VIEWS

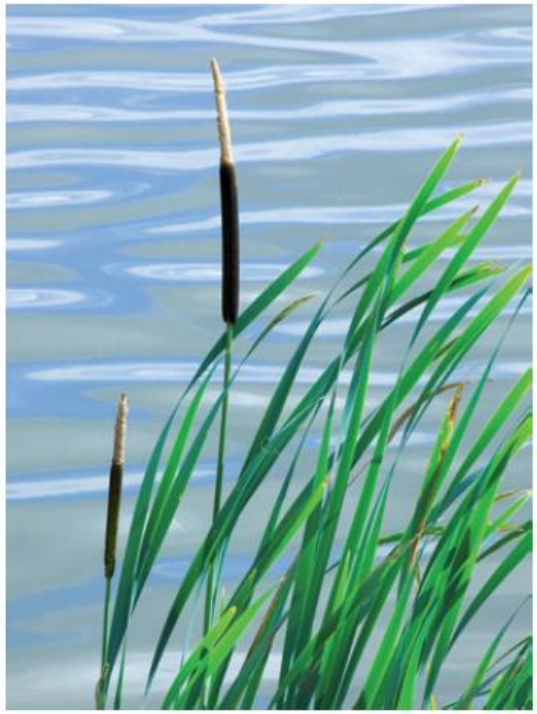
GASTROINTESTINAL CANCER

Salvage chemotherapy in gastric cancer—more than a straw?

Florian Lordick

The benefit of salvage chemotherapy in gastric cancer refractory to first-line platinum and fluoropyrimidine therapy was previously unknown. A randomized multicentre study has shown that irinotecan or docetaxel administered as single agents improved survival compared with best supportive care alone. Hence, salvage chemotherapy is now a proven option in pretreated gastric cancer.

Lordick, F. *Nat. Rev. Clin. Oncol.* 9, 312–313 (2012); published online 1 May 2012;
doi:10.1038/nrclinonc.2012.76



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Gastric cancer is one of the most common and fatal malignancies. Despite a decreasing incidence in Western civilisations,[1] gastric cancer accounts for approximately 700,000 deaths every year worldwide.[2] Cure can

(hazard ratio = 0.657; 95% CI 0.485–0.891; one-sided $P = 0.007$). Overall survival benefit for salvage chemotherapy was consistent in most of the prospectively defined subgroups that included age, perfor-

administered in the majority of patients. For example, in a Japanese study that com-

Lordick F et al. *Nat Reviews Clin Oncol* 2012;9(6):312-313

Second-line chemotherapy of gastric cancer: Randomised studies

Study	Protocol	Survival	Symptom control
2011 Thuss-Patience (n=40)	**Irinotecan** vs. BSC	4.0 mon vs. 2.4 mon (p=0.012)	44% improvement vs. 5% improvement
2012 Kang (n=202)	**Irinotecan or Docetaxel** vs. BSC	5.3 mon vs. 3.8 mon (p=0.007)	No data
2014 Ford (n=168)	**Docetaxel** vs. BSC	5.2 mon vs. 3.6 mon (p=0.001)	Global QoL unchanged but better symptom control
2013 Hironaka (n=219)	**Paclitaxel vs. Irinotecan**	9.5 mon vs. 8.4 mon (p=0.38)	No data
2014 Higuchi (n=130)	**Iri + Cisplatin vs. Irinotecan**	10.7 mon vs. 10.1 mon (p=0.9823)	No data

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Summary

- Optimal 1st line Tx prolongs survival and can maintain Quality of Life
  - There is not ONE universally accepted regimen
  - **Platin-fluoropyrimidine doublets are standard**
  - UK-NL: addition of epirubicine is popular and well established
- Less toxic regimens and drugs should be used
  - **Oxaliplatin** can replace cisplatin
  - **S-1 or capecitabine** can replace 5-day i.v. 5-FU
  - **Modified docetaxel triplets** can be used **in selected patients**
- Second-line Tx (cytotoxic monotherapy) can prolong survival and lead to better symptom control
  - **Taxanes or irinotecan mono** are equally effective options

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Unresolved issues in advanced GC

- Surgical and local Tx in oligometastatic disease (peritoneum, liver)
- Continous treatment vs. de-escalation vs.chemotherapy breaks
- Integration of molecularly targeted drugs beyond anti-HER2
- Integration of best supportive and palliative care