

## **Xeloda** **A blockbuster in the making**

*Jonathan Dickinson, LCL Xeloda*

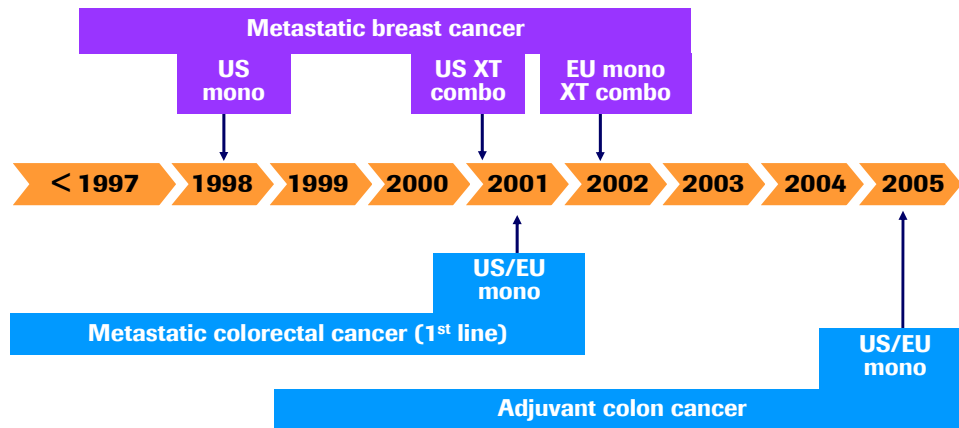


## **Xeloda – unique tumor-activated mechanism** *Delivering more cancer-killing agent straight into cancer*

- **Highly effective**
  - comparable efficacy to taxanes, anthracyclines or 5-FU single agent
- **Low toxicity**
  - minimal hair loss and minimal myelosuppression
- **Convenience (oral treatment)**
  - strong patient preference

**1 million patients treated up to date**

## Xeloda – development history



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## Xeloda today



### • Breast cancer

- Monotherapy for patients who have failed anthracycline and taxane regimens
- Combination therapy with docetaxel after patients have failed an anthracycline containing regimen

### • Colorectal cancer

- Monotherapy for 1<sup>st</sup> line treatment of metastatic colorectal cancer
- Monotherapy for the adjuvant treatment of Dukes' C (stage III) colon cancer following surgery

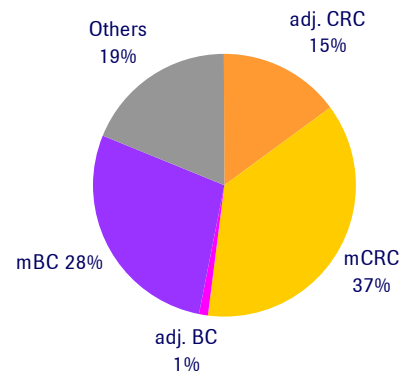
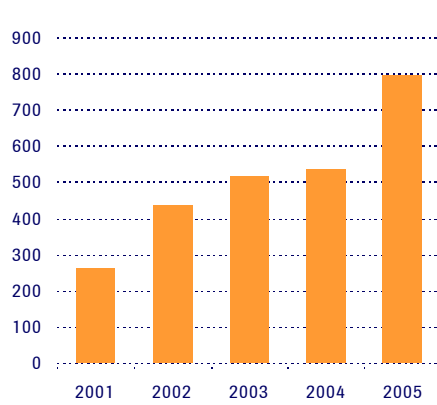
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## Current sales distribution

*Majority in breast and colorectal cancer*

### Group sales (CHF bn)



**Xeloda sales (2005) = CHF 796 m**

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### Xeloda in colorectal cancer

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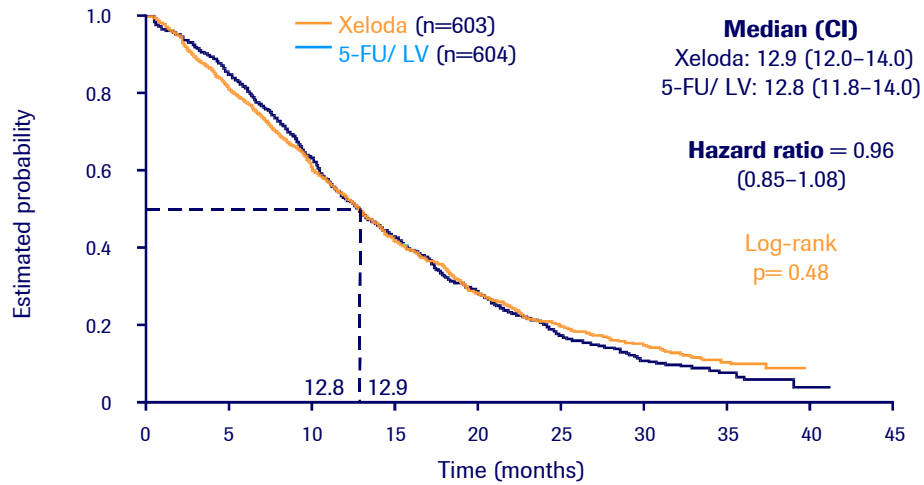
### Xeloda in breast cancer

### Xeloda in other cancers

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## Pivotal monotherapy study results in 1<sup>st</sup> line mCRC

*Similar overall survival*



Hoff PM. Ann Oncol 2000;11(Suppl. 4):60 (Abst 263)

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## Superior response rates

$X \geq 5\text{-FU/LV}$

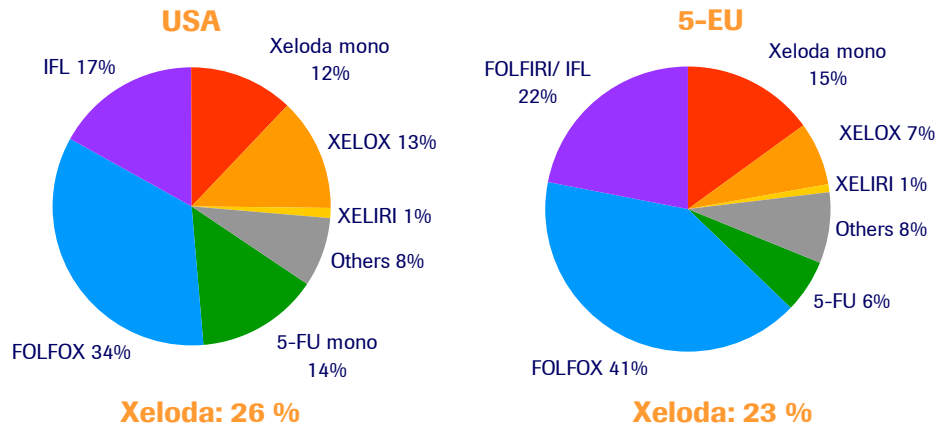


	<b>Xeloda (n=603)</b>	<b>5-FU/ LV (n=604)</b>	
PR + CR (%)	25.7	16.7	p<0.0002
Stable disease (%)	47.8	52.2	

PR = partial response; CR = complete response  
 Hoff PM. Ann Oncol 2000;11(Suppl. 4):60 (Abst 263)

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## Large future opportunity in 5-FU combinations *1<sup>st</sup> line mCRC market*

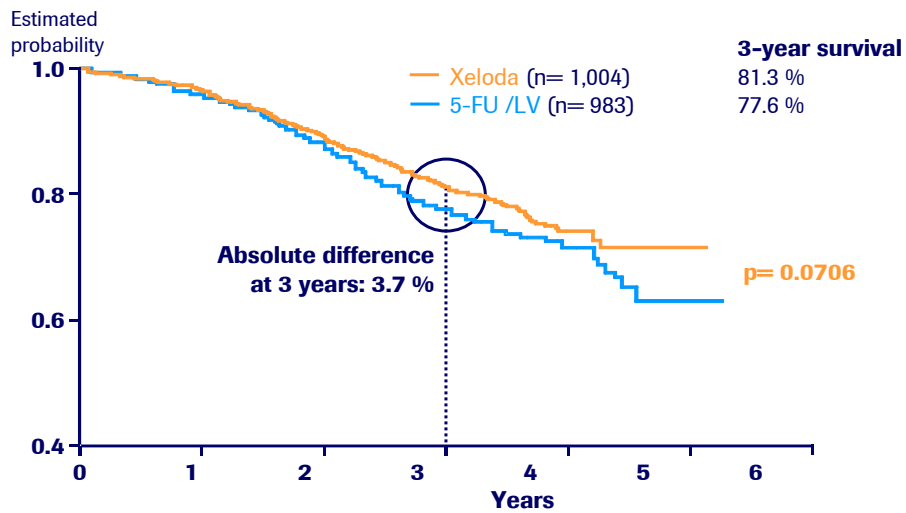


**Additional filing planned based on NO 16966 in 2006**

Tandem Q4 2005; Genactis Q4 2005

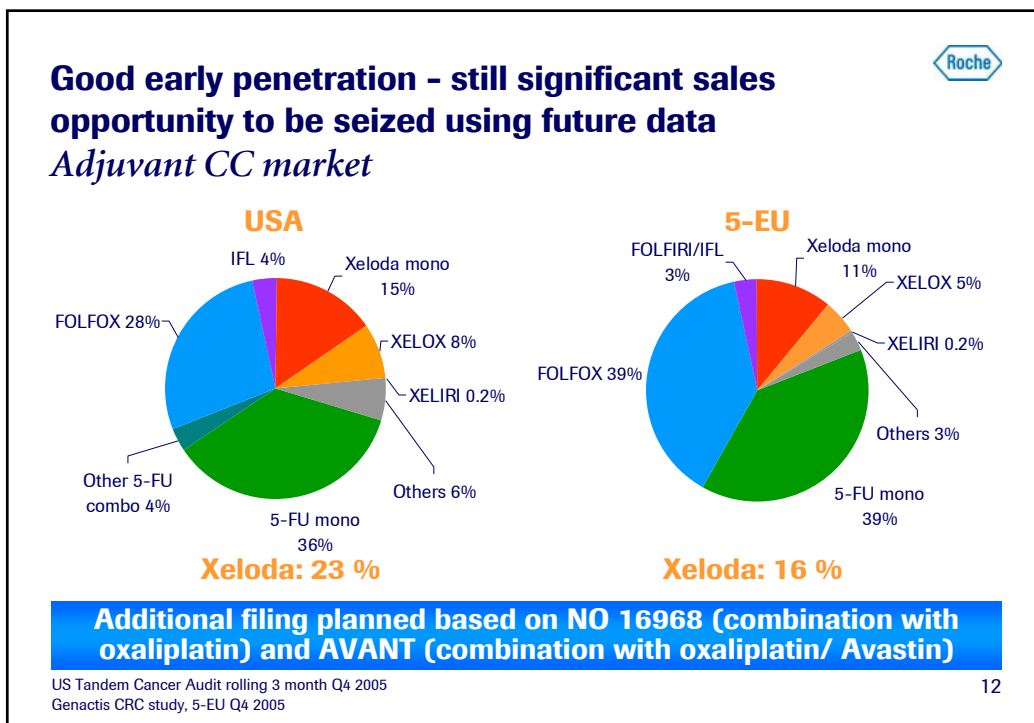
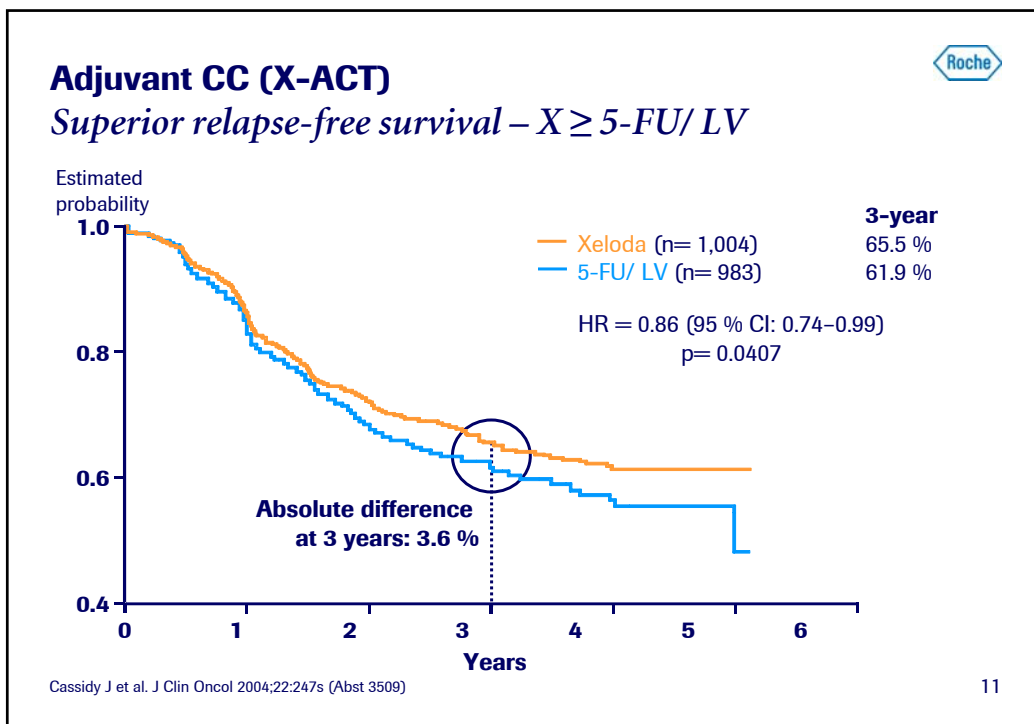
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## Adjuvant CC (X-ACT) *Trend to improved overall survival*



Twelves C et al. N Engl J Med 2005;352:2696-704

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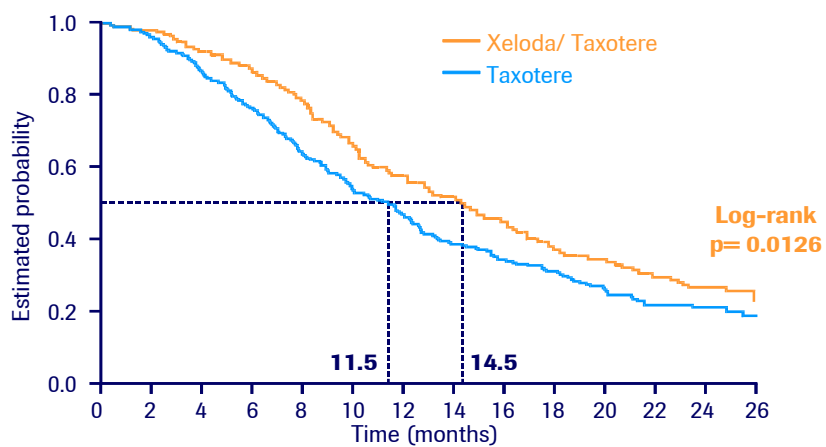


**Xeloda in colorectal cancer**

**Xeloda in breast cancer**

**Xeloda in other cancers**

**Xeloda prolongs survival beyond Taxotere**  
*3 months overall survival benefit in 1<sup>st</sup> line mBC*



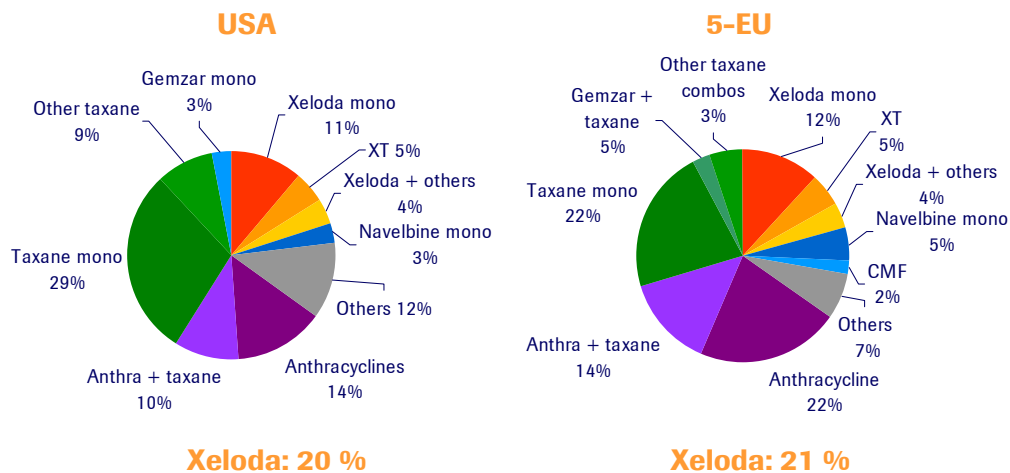
**Superior response rate → superior TTP → superior survival**

O'Shaughnessy J et al. J Clin Oncol 2002;20(12):2812-23



## Good uptake - significant sales opportunity

*1<sup>st</sup> line mBC HER2-negative market*



Tandem Q4 2005; Genactis Q4 2005

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## Future strategy in breast cancer

*Move up to 1<sup>st</sup> line and adjuvant*

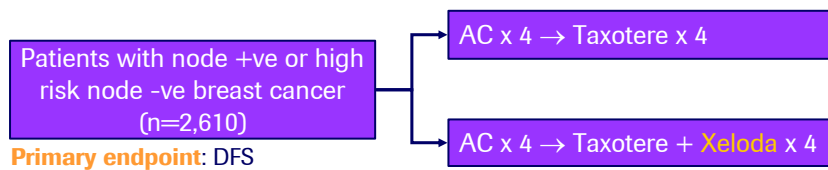
- **Develop Xeloda**
  - as 1<sup>st</sup> line and adjuvant treatment
  - as single agent and in combination
  - combination partners include commonly used or novel BC agents
    - taxanes
    - anthracyclines
    - Herceptin
    - Avastin

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## Xeloda in adjuvant BC

*Greatest market potential*

- Adjuvant market three times the size of metastatic
- Current standard of care: anthracyclines or anthracyclines + taxanes



- Recruitment completed January 2006
- Filing planned in 2009

## Xeloda in colorectal cancer

### Xeloda in breast cancer

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### Xeloda in other cancers

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## ML17032: Xeloda in 1<sup>st</sup> line gastric Ca

*At least as effective as current standard of care*

	Median PFS	Median survival	Response rate	Clinic visits
1 <sup>st</sup> line gastric ca (n=316) → Cisplatin + 5-FU iv	5.0 m	9.3 m	29 %	5 days / 3 weeks
1 <sup>st</sup> line gastric ca (n=316) → Cisplatin + Xeloda	5.6 m	10.5 m	41 %	1 day / 3 weeks
	HR=0.81 P>0.001	HR=0.85 P=0.008	P=0.03 for superiority	80 % reduction

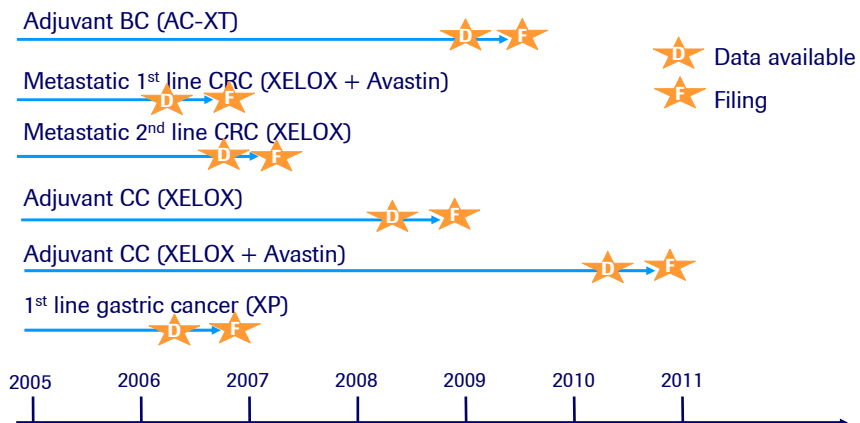
- Phase III, randomised, open-label
- **Primary endpoint:** PFS non-inferiority
- **Secondary endpoints:** RR, OS

**Filing planned in 2006**

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## Xeloda - current and future filings



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## **Xeloda product strategy**

### *In summary*

- Target 1<sup>st</sup> line metastatic and adjuvant setting in CRC and BC
- Focus on efficacy
- Replace 5-FU in CRC
- Replace anthracyclines and taxanes or add onto taxanes in BC
- Use portfolio synergies with Avastin and Herceptin

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## **Appendix**



## Product profile

### *Xeloda*

<b>Indication</b>	Metastatic breast cancer, metastatic colorectal cancer, adjuvant colon cancer
<b>Exclusions</b>	Severe renal impairment and DPD insufficiency
<b>Dosing</b>	1250mg/m <sup>2</sup> b.i.d
<b>Adverse reactions</b>	Hand-and-foot syndrome
<b>Incidence mBC; adjBC</b>	~42 000 (US), ~60 000 (5-EU); ~217 000 (US), ~192 000 (5-EU)
<b>Incidence mCRC; adjCC</b>	~29 000 (US), ~95 000 (5-EU); ~74 000 (US), ~90 000 (5-EU)
<b>Current sales (2005)</b>	CHF 796m
<b>Further development</b>	mCRC/adjuvant CC: combinations with Avastin and oxaliplatin; adjuvant BC, mBC with Avastin, Gastric Ca, Pancreatic Ca

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## Approval status

### *Xeloda in breast cancer*

#### EU

Xeloda in **combination** with docetaxel is indicated for the treatment of patients with **locally advanced or metastatic** breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline

Xeloda is also indicated as **monotherapy** for the treatment of patients with **locally advanced or metastatic** breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated

#### US

XELODA in **combination** with docetaxel is indicated for the treatment of patients with **metastatic breast cancer** after failure of prior anthracycline-containing chemotherapy

XELODA **monotherapy** is also indicated for the treatment of patients with **metastatic breast cancer** resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated, eg, patients who have received cumulative doses of 400 mg/m<sup>2</sup> of doxorubicin or doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen

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## Approval status

### *Xeloda in colorectal cancer*

#### EU

#### US

<p>Xeloda is indicated for <b>first line monotherapy</b> of metastatic colorectal cancer</p>	<p>The use of Xeloda is indicated as <b>1<sup>st</sup> line treatment</b> of patients with metastatic colo-rectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination therapy has shown a survival benefit compared to 5FU/LV alone. A survival benefit over 5FU/LV has not been demonstrated with Xeloda monotherapy. Use of Xeloda instead of 5FU/LV in combination has not been adequately studied to assure safety or preservation of the survival advantage</p>
<p>Xeloda is indicated for the <b>adjuvant treatment</b> of patients following surgery of stage III (Dukes' stage C) colon cancer</p>	<p>XELODA is indicated as a single agent for <b>adjuvant treatment</b> in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. XELODA was non-inferior to 5-fluorouracil and leucovorin (5-FU/LV) for disease-free survival (DFS). Although neither XELODA nor combination chemotherapy prolongs overall survival (OS), combination chemotherapy has been demonstrated to improve disease-free survival compared to 5-FU/LV. Physicians should consider these results when prescribing single-agent XELODA in the adjuvant treatment of Dukes' C colon cancer</p>

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## Significantly superior response rate vs. bolus 5-FU/ LV

### *Xeloda in 1<sup>st</sup> line mCRC*

	<b>Xeloda (n=603)</b>	<b>Bolus 5-FU/ LV (n=604)</b>	<b>p value</b>
Response rate (%)	26	17	< 0.0002
TPP (months)	4.6	4.7	0.9535
Overall survival (months)	12.9	12.8	0.48

**The efficacy of Xeloda versus bolus 5-FU/ LV was similar to infusional 5-FU/ LV versus bolus 5-FU/ LV**

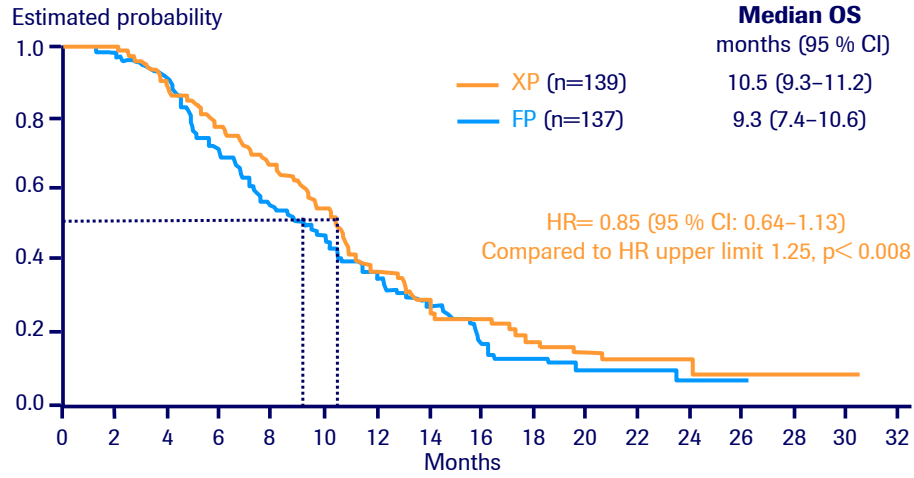
TTP = time to progression  
Van Cutsem E et al. Br J Cancer 2004;90:1190-7

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## Gastric cancer (1)

*Comparable overall survival*

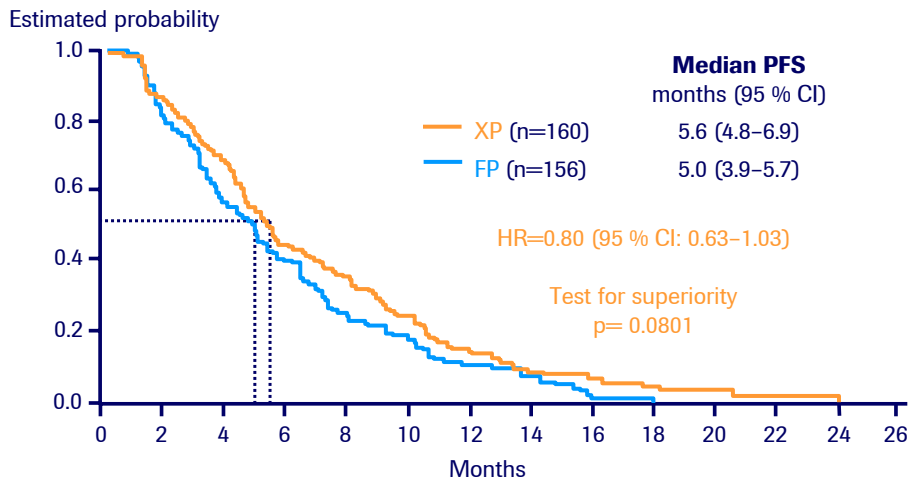


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## Gastric cancer (2)

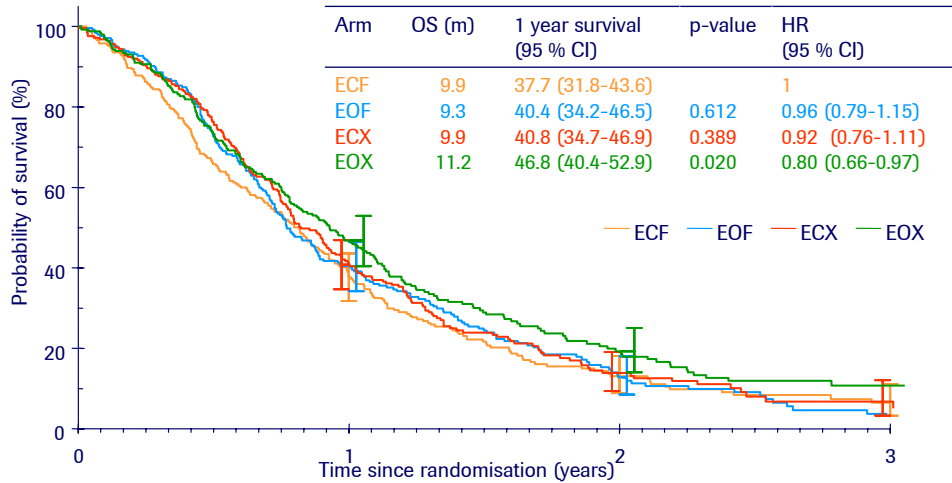
*Trend to superior progression-free survival with XP vs. FP*



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## Gastric cancer (REAL2)

### Survival by Regimen (ITT)

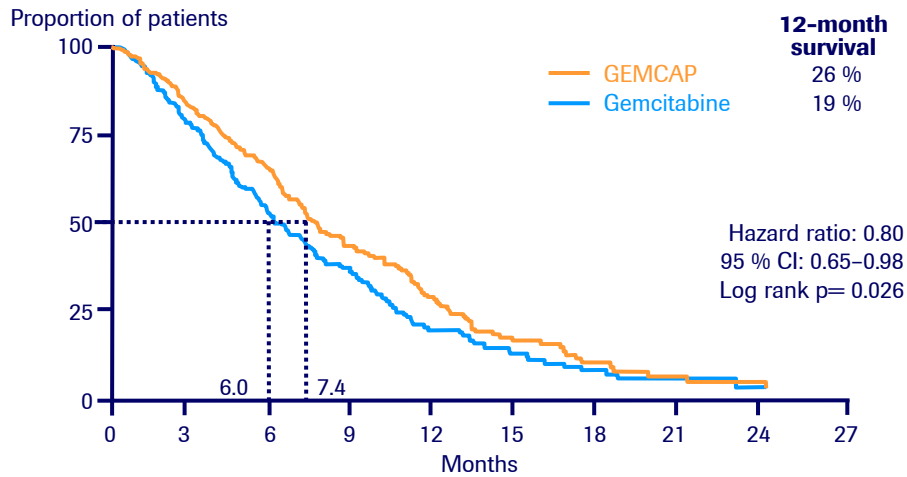


E: Epirubicin; C: Cisplatin; F: PVI 5-FU; O: Oxaliplatin; X: Xeloda

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## Pancreatic cancer

### Significantly improved overall survival with GEMCAP



Cunningham D et al. Eur J Cancer Suppl 2005;3:4 (Abst PS11)

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## Metastatic breast cancer

*Xeloda can replace epirubicin (anthracycline) in 1<sup>st</sup> line*

