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

- Metastatic breast cancer
  - US mono
  - US XT combo
  - EU mono XT combo
- Metastatic colorectal cancer (1st line)
- Adjuvant colon cancer

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 1st line treatment of metastatic colorectal cancer
  - Monotherapy for the adjuvant treatment of Dukes’ C (stage III) colon cancer following surgery
Current sales distribution
Majority in breast and colorectal cancer

Group sales (CHF bn)

Xeloda sales (2005) = CHF 796 m

Xeloda in colorectal cancer

Xeloda in breast cancer

Xeloda in other cancers
Pivotal monotherapy study results in 1st line mCRC

**Similar overall survival**

Median (CI)
- Xeloda: 12.9 (12.0–14.0)
- 5-FU/ LV: 12.8 (11.8–14.0)

Hazard ratio = 0.96
(0.85–1.08)

Log-rank
p = 0.48

PR = partial response; CR = complete response

Hoff PM. Ann Oncol 2000;11(Suppl. 4):60 (Abst 263)
Large future opportunity in 5-FU combinations

1st line mCRC market

USA

IFL 17%

Xeloda mono 12%

XELIRI 1%

Others 8%

FOLFOX 34%

5-FU mono 14%

5-EU

Xeloda mono 15%

XELIRI 1%

Others 8%

FOLFOX 41%

5-FU 6%

Xeloda: 26 %

Xeloda: 23 %

Additional filing planned based on NO 16966 in 2006

Tandem Q4 2005; Genactis Q4 2005

Adjuvant CC (X-ACT)

Trend to improved overall survival

3-year survival

Xeloda (n=1,004) 81.3 %

5-FU/LV (n=983) 77.6 %

Absolute difference at 3 years: 3.7 %

p=0.0706

**Adjuvant CC (X-ACT)**

Superior relapse-free survival – \( X \geq 5\text{-FU} / \text{LV} \)

Estimated probability

- **Xeloda** (n= 1,004)
  - 3-year: 65.5%
- **5-FU/ LV** (n= 983)
  - 3-year: 61.9%

HR = 0.86 (95 % CI: 0.74–0.99)

\[ p= 0.0407 \]

**Additional filing planned based on NO 16968 (combination with oxaliplatin) and AVANT (combination with oxaliplatin/ Avastin)**

**Good early penetration - still significant sales opportunity to be seized using future data**

**Adjuvant CC market**

- **USA**
  - 5-FU mono: 36%
  - FOLFOX: 28%
  - Other 5-FU combo: 4%
  - Xeloda mono: 15%
  - XELOX: 8%
  - XELIRI: 0.2%
  - Others: 6%

- **5-EU**
  - FOLFOX: 39%
  - Other: 3%
  - Xeloda mono: 11%
  - XELOX: 3%
  - XELIRI: 0.2%
  - Others: 2%

**Xeloda: 23 %**

**Xeloda: 16 %**

Additional filing planned based on NO 16968 (combination with oxaliplatin) and AVANT (combination with oxaliplatin/ Avastin)

US Tandem Cancer Audit rolling 3 month Q4 2005
Genacris CRC study, 5-EU Q4 2005
Xeloda in colorectal cancer

Xeloda in breast cancer

Xeloda in other cancers

Xeloda prolongs survival beyond Taxotere
3 months overall survival benefit in 1st line mBC

Good uptake - significant sales opportunity
1st line mBC HER2-negative market

Future strategy in breast cancer
Move up to 1st line and adjuvant

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

*Greatest market potential*

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

**Patients with node +ve or high risk node -ve breast cancer (n=2,610)**

**Primary endpoint:** DFS

- Recruitment completed January 2006
- Filing planned in 2009

---

Xeloda in colorectal cancer

Xeloda in breast cancer

**Xeloda in other cancers**
ML17032: Xeloda in 1st line gastric Ca
At least as effective as current standard of care

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

Filing planned in 2006

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
<th>Median survival</th>
<th>Response rate</th>
<th>Clinic visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin + 5-FU iv</td>
<td>5.0 m</td>
<td>9.3 m</td>
<td>29 %</td>
<td>5 days / 3 weeks</td>
</tr>
<tr>
<td>Cisplatin + Xeloda</td>
<td>5.6 m</td>
<td>10.5 m</td>
<td>41 %</td>
<td>1 day / 3 weeks</td>
</tr>
</tbody>
</table>

- HR=0.81, P=0.008 for superiority
- HR=0.85, P>0.001 for 80 % reduction

Xeloda - current and future filings

- Adjuvant BC (AC-XT)
- Metastatic 1st line CRC (XELOX + Avastin)
- Metastatic 2nd line CRC (XELOX)
- Adjuvant CC (XELOX)
- Adjuvant CC (XELOX + Avastin)
- 1st line gastric cancer (XP)

Data available
Filing
Xeloda product strategy

In summary

• Target 1st 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

Appendix
## Product profile

**Xeloda**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Metastatic breast cancer, metastatic colorectal cancer, adjuvant colon cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusions</td>
<td>Severe renal impairment and DPD insufficiency</td>
</tr>
<tr>
<td>Dosing</td>
<td>1250mg/m² b.i.d</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>Hand-and-foot syndrome</td>
</tr>
<tr>
<td>Incidence mCRC; adjCC</td>
<td>~42 000 (US), ~60 000 (5-EU); ~217 000 (US), ~192 000 (5-EU)</td>
</tr>
<tr>
<td>Incidence mBC; adjBC</td>
<td>~29 000 (US), ~95 000 (5-EU); ~74 000 (US), ~90 000 (5-EU)</td>
</tr>
<tr>
<td>Current sales (2005)</td>
<td>CHF 796m</td>
</tr>
<tr>
<td>Further development</td>
<td>mCRC/adjuvant CC: combinations with Avastin and oxaliplatin; adjuvant BC, mBC with Avastin, Gastric Ca, Pancreatic Ca</td>
</tr>
</tbody>
</table>

## 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/m² 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.
**Approval status**

**Xeloda in colorectal cancer**

**EU**

Xeloda is indicated for **first line monotherapy** of metastatic colorectal cancer

**US**

The use of Xeloda is indicated as **1st line treatment** of patients with metastatic colorectal 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.

Xeloda is indicated for the **adjuvant treatment** of patients following surgery of stage III (Dukes’ stage C) colon cancer

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

**Xeloda in 1st line mCRC**

<table>
<thead>
<tr>
<th></th>
<th>Xeloda (n=603)</th>
<th>Bolus 5-FU/ LV (n=604)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (%)</td>
<td>26</td>
<td>17</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>TPP (months)</td>
<td>4.6</td>
<td>4.7</td>
<td>0.9535</td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td>12.9</td>
<td>12.8</td>
<td>0.48</td>
</tr>
</tbody>
</table>

The efficacy of Xeloda versus bolus 5-FU/ LV was similar to infusional 5-FU/ LV versus bolus 5-FU/ LV
**Gastric cancer (1)**

*Comparable overall survival*

<table>
<thead>
<tr>
<th></th>
<th>Estimated probability</th>
<th>Median OS months (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XP (n=139)</strong></td>
<td>1.0</td>
<td>10.5 (9.3–11.2)</td>
</tr>
<tr>
<td><strong>FP (n=137)</strong></td>
<td>0.85</td>
<td>9.3 (7.4–10.6)</td>
</tr>
</tbody>
</table>

HR= 0.85 (95 % CI: 0.64–1.13) Compared to HR upper limit 1.25, p< 0.008

**Per protocol analysis**

---

**Gastric cancer (2)**

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

<table>
<thead>
<tr>
<th></th>
<th>Estimated probability</th>
<th>Median PFS months (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>XP (n=160)</strong></td>
<td>1.0</td>
<td>5.6 (4.8–6.9)</td>
</tr>
<tr>
<td><strong>FP (n=156)</strong></td>
<td>0.80</td>
<td>5.0 (3.9–5.7)</td>
</tr>
</tbody>
</table>

HR=0.80 (95 % CI: 0.63–1.03)

Test for superiority p= 0.0801

**Intent-to-treat analysis**
Gastric cancer (REAL2)
Survival by Regimen (ITT)

<table>
<thead>
<tr>
<th>Arm</th>
<th>OS (m)</th>
<th>1 year survival (95% CI)</th>
<th>p-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF</td>
<td>9.9</td>
<td>37.7 (31.5-43.6)</td>
<td>1.0</td>
<td>1.00</td>
</tr>
<tr>
<td>EOF</td>
<td>9.3</td>
<td>40.4 (34.2-46.5)</td>
<td>0.612</td>
<td>0.96 (0.79-1.15)</td>
</tr>
<tr>
<td>ECX</td>
<td>9.9</td>
<td>40.8 (34.7-46.9)</td>
<td>0.389</td>
<td>0.92 (0.76-1.11)</td>
</tr>
<tr>
<td>EOX</td>
<td>11.2</td>
<td>46.8 (40.4-52.9)</td>
<td>0.020</td>
<td>0.80 (0.66-0.97)</td>
</tr>
</tbody>
</table>

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

Pancreatic cancer
Significantly improved overall survival with GEMCAP

Proportion of patients

12-month survival
- GEMCAP: 26%
- Gemcitabine: 19%

Hazard ratio: 0.80
95% CI: 0.65–0.98
Log rank p = 0.026

Metastatic breast cancer
Xeloda can replace epirubicin (anthracycline) in 1st line

Median, months (95% CI)
- XP: 25.6 (20.1–28.0)
- EP: 24.0 (18.0–30.1)

p=ns

Estimated probability

Median follow-up: 9.9 months