Oncological treatment of pancreatic cancer

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Denmark
Danmark
Cancerregisteret
1991-95

US
Gem-treated patients
1995-96

<table>
<thead>
<tr>
<th>1 year survival rate</th>
<th>5 year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Storm & Engholm: www.cancer.dk

Storinolo et al., Cancer 1998
<table>
<thead>
<tr>
<th>Disease stage</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>15.2</td>
</tr>
<tr>
<td>Regional</td>
<td>6.8</td>
</tr>
<tr>
<td>Distant</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Resectable disease

- Adjuvant or neoadjuvant chemotherapy
- Adjuvant or neoadjuvant chemoradiotherapy (CRT)
# Adjuvant chemotherapy vs. observation

## Table 1. Randomized trials comparing adjuvant chemotherapy with observation

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Treatment arms</th>
<th>Duration of treatment (months)</th>
<th>Median OS (months)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakkevold [12]</td>
<td>1993</td>
<td>30</td>
<td>AFM regimen every 3 weeks for 6 cycles</td>
<td>4.5</td>
<td>23b</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31</td>
<td>Observation</td>
<td></td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Takada [14]</td>
<td>2002</td>
<td>81</td>
<td>Mitomycin C + 5-FU → oral 5-FU</td>
<td>0.75a</td>
<td>NA</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>77</td>
<td>Observation</td>
<td></td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>Kosuge [13]</td>
<td>2006</td>
<td>45</td>
<td>5-FU + cisplatin every 4–8 weeks for two cycles</td>
<td>2–4</td>
<td>12.5</td>
<td>26.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44</td>
<td>Observation</td>
<td></td>
<td>15.8</td>
<td>14.9</td>
</tr>
<tr>
<td>ESPAC-1 [15]</td>
<td>2004</td>
<td>147</td>
<td>5-FU/FA</td>
<td>6</td>
<td>20.1</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>142</td>
<td>No chemotherapy</td>
<td></td>
<td>15.5c</td>
<td>8</td>
</tr>
<tr>
<td>CONKO-001 [16]</td>
<td>2007</td>
<td>179</td>
<td>Gemcitabine weekly $\times$3 every 4 weeks for six cycles</td>
<td>6</td>
<td>22.8d</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>177</td>
<td>Observation</td>
<td></td>
<td>20.2</td>
<td>9</td>
</tr>
</tbody>
</table>

AFM, doxorubicin + 5-fluorouracil + mitomycin C; FA, folinic acid; 5-FU, 5-fluorouracil; NA, data not available; OS, overall survival.

*Intravenous therapy only.

b $P = 0.02$.

c $P = 0.009$.

d $P = 0.005$. 
Meta-analysis, effect on median survival

Fig. 2. Differences in median survival time between chemotherapy and control groups and CI among the 4 studies included in the meta-analysis. Studies are ordered by length of CI (uncertainty in estimates).

Boeck et al., Oncology 2007
CONKO-001, Gem vs observation

Significant increase in DFS from 7 to 13 months
Significant increase in median survival from 20 to 23 months
Increase in est. 5-year survival rate from 9% to 21%
Beneficial effect in all subgroups

Neuhaus et al., ASCO 2008    Oettle et al., JAMA 2007
### Table 2. Randomized trials investigating adjuvant chemoradiation

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Treatment arm</th>
<th>OS (months)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG [20]</td>
<td>1985</td>
<td>21</td>
<td>aCRT/5-FU → 5-FU maintenance for 2 years</td>
<td>20.0*</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>1985</td>
<td>22</td>
<td>Observation</td>
<td>10.9</td>
<td>5</td>
</tr>
<tr>
<td>EORTC [21]</td>
<td>1999</td>
<td>60</td>
<td>bCRT/ 5-FU (no maintenance)</td>
<td>17.1</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>54</td>
<td>Observation</td>
<td>12.6</td>
<td>10</td>
</tr>
<tr>
<td>ESPAC-1 [15]</td>
<td>2004</td>
<td>145</td>
<td>aCRT/5-FU ± 5-FU/FA bolus ×6 cycles</td>
<td>15.9</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>144</td>
<td>No chemoradiation</td>
<td>17.9</td>
<td>20</td>
</tr>
<tr>
<td>RTOG 9704 [22]</td>
<td>2006</td>
<td>187</td>
<td>Gem 3 weeks → CRT/5-FU → Gem 3 months</td>
<td>20.5**</td>
<td>31 (3-year OS)</td>
</tr>
<tr>
<td>Pancreatic head only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 9704 [22]</td>
<td>2006</td>
<td>194</td>
<td>5-FU 3 weeks → CRT/5-FU → 5-FU 3 months</td>
<td>16.9</td>
<td>22 (3-year OS)</td>
</tr>
<tr>
<td>All patients</td>
<td>2006</td>
<td>221</td>
<td>Gem 3 weeks → CRT/5-FU → Gem 3 months</td>
<td>18.8</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>2006</td>
<td>221</td>
<td>5-FU 3 weeks → CRT/5-FU → 5-FU 3 months</td>
<td>16.9</td>
<td>NA</td>
</tr>
</tbody>
</table>

FA, folinic acid; 5-FU, 5-fluorouracil; OS, overall survival; Gem, gemcitabine; NA, data not available.

*aCRT: 20 Gy + 5-FU bolus days 1–3 ×2.

*bCRT: 20 Gy + 5-FU continuous infusion ×2

*P = 0.035; **P = 0.09.
Neoadjuvant chemotherapy, Gem vs. Gem + cisplatin, a randomized phase II study

Resection rate improved from 38% to 70%
1-year survival improved from 46% to 61%

TABLE 3. Patient outcome data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gem (n = 24)</th>
<th>Gem + Cis (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic resection</td>
<td>9 (38%)</td>
<td>18 (70%)</td>
</tr>
<tr>
<td>Bypass</td>
<td>14 (58%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>No surgery</td>
<td>1 (4%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Tumor type (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No evidence of malignancy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No histology</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Posterior resection margins$^a$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2 (25%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Negative</td>
<td>6 (75%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Lymph nodes$^a$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease positive</td>
<td>6 (75%)</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Disease negative</td>
<td>2 (25%)</td>
<td>7 (44%)</td>
</tr>
</tbody>
</table>

Neoadjuvant CRT,
Gem-based CRT, a phase II-study

Evans et al., JCO 2008
Conclusions, adjuvant and neoadjuvant treatment

• **Adjuvant Gem** is a standard of care
  - Relative effect of 5FU?
    • ESPAC-3: 5FU/FA vs Gem
  - Combination chemotherapy and molecular therapy?
  - Treatment of R1-resected pts?

• **Adjuvant CRT** is another standard, but evidence is debatable
  • EORTC-trial: Gem vs Gem-based CRT

• **Neoadjuvant chemotherapy** or CRT is experimental
Locally advanced disease

- Chemotherapy
  - Gem
  - Gem in combinations
- Chemoradiotherapy
Overall survival on Gem

![Kaplan-Meier curve survival by disease stage.](image)

**FIGURE 4.** Kaplan-Meier curve survival by disease stage.

Storinolo et al., Cancer 1998
Effect of Combination Chemotherapy in LAPC

No benefit from GemOx in LAPC patients

Louvet JCO 2005
CRT in locally advanced disease
- studies are heterogeneous and difficult to compare

- Prolongation of survival vs. “down sizing”
- Lack of randomized studies using modern treatment
- Lack of clear definition of locally advanced disease
- Indications for operation after CRT are not standardized

Massucco et al., Ann. Surg. Oncol. 2005
Chauffert et al.,
Phase III study of Gem +/- 5FU/cisplatin-based CRT

Chemoradiotherapy vs Chemotherapy
in locally advanced pancreatic cancer

Radiochemotherapy
2 Gy x 30
FUFA /Cisplatin

Chemotherapy
Gemcitabine
1000 mg/m² wk x 7

Stratification
Centre
WHO-PS 0-1 vs 2
Expl. surgery vs not

Recruitment
planned: 176 pts
stop after: 119 pts

Chauffert et al. ASCO 2006
LOCALLY ADVANCED DISEASE

RCT (5-FU/Cisplatin) → Gemcitabine versus Gemcitabine

109 patients included, median follow-up: 16 months [1 – 60]

Overall Survival according to treatment arm

Median survival
CRT (5-FU/Cis): 8 mo  
Gemcitabine: 14 mo

1-yr-survival:
CRT (5-FU/Cis): 24%  
Gemcitabine: 51%

Chauffert. ASCO 2006, # 4008
Chauffert et al.,
Phase III-study of Gem +/- 5FU/cisplatin-based CRT

Locally Advanced Disease

RCT (5-FU/Cisplatin) → Gemcitabine versus Gemcitabine
Analysis of Grade 3-4 Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Initial CHRT</th>
<th>Initial Gem</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=59</td>
<td>n=60</td>
<td></td>
</tr>
<tr>
<td>Overall toxicities</td>
<td>31 (53%)</td>
<td>16 (25%)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Hematologic toxicities</td>
<td>28 (47%)</td>
<td>11 (18%)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (24%)</td>
<td>5 (8%)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (27%)</td>
<td>2 (3%)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (12%)</td>
<td>6 (10%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Cumulative dose of gemcitabine

<table>
<thead>
<tr>
<th></th>
<th>RCT→Gem</th>
<th>initial Gem</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative dose of gemcitabine</td>
<td>3500 mg/m²</td>
<td>6900 mg/m²</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of infusions</td>
<td>4 (0-33)</td>
<td>9 (0-44)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

No data on resection rate
Loehrer et al.,
Phase III-study of Gem +/- Gem-based CRT

E4201 Study: Phase III in LAPC

- Radiation 50.4 Gy
  Gemcitabine 600 wkly

- Gemcitabine 5 cycles

primary endpoint
overall survival

- Gemcitabine wkly x 6

- Gemcitabine 5 cycles

3D conformal radiation
central review of treatment dose volume

recruitment
planned: 316 pts
stop after: 74 pts

Loehrer et al. ASCO 2008, #4506,
Loehrer et al.,
Phase III study of Gem +/- Gem-based CRT

LOCALLY ADVANCED DISEASE

Overall Survival

- GEM: Median Survival 9.2 Months (95% CI [7.8, 11.4])
- GEM + Radiation: Median Survival 11.0 Months (95% CI [8.4, 15.5])

p-value = 0.034
Two-Sided, stratified Log rank

Loehrer et al. ASCO 2008, #4506.
Conclusions,
Oncological treatment of locally advanced disease

• Current evidence that CRT prolongs overall median survival compared to Gem is scarce
  – Negative effect of Cis-5FU-based CRT followed by Gem
  – Effect of Gem-based CRT, but study underpowered

• Phase II-studies indicate that CRT may induce down sizing and R0-resection in some patients
  – Selection of candidates
  – Detrimental effect in unresectable patients?
Treatment Algorithm in LAPC

LAPC

chemotherapy
re-evaluation after 3 months

progression

alternative chemotherapy

SD, PR, CR

option of CRT

Surgery

Surgery

Herrmann 2008
Advanced disease

- Median survival 3-4 months
- Primary goals of treatment
  - Prolongation of survival
  - Improvement in QoL

FIGURE 4. Kaplan-Meier curve survival by disease stage.

Storinolo et al., Cancer 1998
## Gem vs. 5-FU

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>5-FU</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit response*</td>
<td>24%</td>
<td>5%</td>
<td>0.002</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>5.7</td>
<td>4.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to progression (months)</td>
<td>2.1</td>
<td>0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>6-month survival</td>
<td>46%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>1-year survival</td>
<td>18%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>5.4%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>39.3%</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

*Composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight

Survival of Gem-treated patients according to performance status

**FIGURE 3.** Kaplan–Meier curve survival by baseline Kamofsky performance status.

Storinolo et al., Cancer 1998
Case,
Fatal interstitial pneumonitis due to Gem

One day before death
One week before
One month before
Negative phase III 1st-line Gem combination chemotherapy trials

- Gemcitabine vs gemcitabine + 5-FU (n=316)

- Gemcitabine vs gemcitabine + irinotecan (n=360)

- Gemcitabine vs gemcitabine + oxaliplatin (n=326)

- Gemcitabine vs gemcitabine + pemetrexed (n=565)

- Gemcitabine vs gemcitabine + exatecan (n=349)

- Gemcitabine vs gemcitabine + cisplatin + epirubicin + 5-FU (n=104)
UK NCRI

Gem-capecitabine vs Gem phase III study

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

12-month survival
GEMCAP (n=267) 26%
Gemcitabine (n=266) 19%

Cunningham D et al. Eur J Cancer Suppl 2005
SAKK
Gem-capecitabine versus Gem phase III study

Patients surviving (%)

GEMCAP (n=160)
Gemcitabine (n=159)

p=0.234

Herrmann R et al. Eur J Cancer Suppl 2005
**Combination chemotherapy and effect according to performance status**

Review: GEM vs. GEM+X in advanced pancreas cancer (X = cytotoxic)
Comparison: 01 GEM vs. GEM+X
Outcome: 02 Survival by Performance Status

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>GEM N</th>
<th>GEM+X N</th>
<th>log[Hazard ratio] (SE)</th>
<th>Hazard ratio (fixed)</th>
<th>Weight %</th>
<th>Hazard ratio (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Good performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 Louvet</td>
<td>127</td>
<td>131</td>
<td>0.2460 (0.1380)</td>
<td>15.13</td>
<td>0.78</td>
<td>0.60, 1.02</td>
</tr>
<tr>
<td>02 Heinemann</td>
<td>40</td>
<td>44</td>
<td>0.4850 (0.2401)</td>
<td>5.00</td>
<td>0.62</td>
<td>0.38, 0.99</td>
</tr>
<tr>
<td>06 Riesch</td>
<td>86</td>
<td>80</td>
<td>0.2150 (0.1577)</td>
<td>11.58</td>
<td>0.81</td>
<td>0.59, 1.10</td>
</tr>
<tr>
<td>09 Cunningham</td>
<td>217</td>
<td>215</td>
<td>0.2130 (0.1143)</td>
<td>22.05</td>
<td>0.81</td>
<td>0.65, 1.01</td>
</tr>
<tr>
<td>10 Herrmann</td>
<td>84</td>
<td>84</td>
<td>0.3710 (0.1663)</td>
<td>10.42</td>
<td>0.69</td>
<td>0.50, 0.96</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>554</td>
<td>554</td>
<td></td>
<td>64.18</td>
<td>0.76</td>
<td>0.67, 0.87</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 1.57, df = 4 (P = 0.81), P = 0%
Test for overall effect Z = 4.00 (P < 0.0001)

<table>
<thead>
<tr>
<th>02 Poor performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Louvet</td>
</tr>
<tr>
<td>02 Heinemann</td>
</tr>
<tr>
<td>06 Riesch</td>
</tr>
<tr>
<td>09 Cunningham</td>
</tr>
<tr>
<td>10 Herrmann</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 2.72, df = 4 (P = 0.61), P = 0%
Test for overall effect Z = 0.84 (P = 0.40)

Total (95% CI) 842  840
Test for heterogeneity: Chi² = 13.72, df = 9 (P = 0.13), P = 34.4%
Test for overall effect Z = 2.70 (P = 0.007)

Figure 2
Meta-analysis for combination chemotherapy in advanced pancreatic cancer – overall survival with regard to performance status.
Negative phase III trials of Gem vs. Gem + biological agents

Ras-farnesyltransferase inhibitors

- Gemcitabine vs gemcitabine + tipifarnib

Matrix metalloproteinase inhibitors

- Gemcitabine vs gemcitabine + marimastat
- Gemcitabine vs BAY 12-9566

Vaccines

- Gemcitabine vs gemcitabine + G17DT
  - Aphton Corporation press release
- Gemcitabine vs GW1001 + Gemcitabine at PD
  - Pharmexa press release, 2008
Negative phase III trials of Gem vs. Gem + biologic agents, cont.

Angiogenesis inhibitors

• Gemcitabine vs gemcitabine + bevacizumab
  – Kindler, ASCO 2007

• Gemcitabine + erlotinib vs gemcitabine + erlotinib + bevacizumab
  – Vervenne, ASCO 2008

Epidermal Growth Factor Receptor inhibitors

• Gemcitabine vs gemcitabine + cetuximab
  – Philip, ASCO 2007
EGFR-mediated signal transduction

- Cetuximab
- Panitumumab
- Gefitinib
- Lapatinib
- Erlotinib
- PI-3K
- PTEN
- Akt
- Ras
- MEK
- Erk
- mTOR

Survival pathway

Proliferative pathway

TKI

EGFR MoAB

Multitarget-TKI

Sorafenib
Sunitinib

mTOR-Inhibitors

Rapamycin
Temsirolimus
Everolimus (RAD 001)

Camp et al, Clin Cancer Res 2005
PA.3 study,
Gem + erlotinib vs Gem + placebo

HR=0.79* (95% CI, 0.66-0.95), P=0.011
(*adjusted for PS and extent of disease at randomization)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (months)</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarceva™/gemcitabine (n=285)</td>
<td>6.37</td>
<td>24%</td>
</tr>
<tr>
<td>Placebo/gemcitabine (n=284)</td>
<td>5.91</td>
<td>17%</td>
</tr>
</tbody>
</table>

Moore et al., JCO 2007
PA.3 study,
Hazard ratios for survival

<table>
<thead>
<tr>
<th>Factors</th>
<th>HR</th>
<th>95% CI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarceva:placebo</td>
<td>0.82</td>
<td>0.7-1.0</td>
<td>569</td>
</tr>
<tr>
<td>Performance status 0-1</td>
<td>0.87</td>
<td>0.7-1.1</td>
<td>463</td>
</tr>
<tr>
<td>Performance status 2</td>
<td>0.56</td>
<td>0.4-0.8</td>
<td>106</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>0.94</td>
<td>0.6-1.4</td>
<td>138</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0.78</td>
<td>0.6-0.9</td>
<td>431</td>
</tr>
<tr>
<td>Pain ≤20</td>
<td>0.70</td>
<td>0.5-0.9</td>
<td>258</td>
</tr>
<tr>
<td>Pain &gt;20</td>
<td>0.98</td>
<td>0.8-1.3</td>
<td>296</td>
</tr>
<tr>
<td>Male</td>
<td>0.74</td>
<td>0.6-0.9</td>
<td>298</td>
</tr>
<tr>
<td>Female</td>
<td>0.96</td>
<td>0.7-1.3</td>
<td>271</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>0.74</td>
<td>0.6-1.0</td>
<td>301</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>0.93</td>
<td>0.7-1.2</td>
<td>268</td>
</tr>
<tr>
<td>United States</td>
<td>0.71</td>
<td>0.5-0.9</td>
<td>211</td>
</tr>
<tr>
<td>Canada</td>
<td>0.79</td>
<td>0.5-1.2</td>
<td>117</td>
</tr>
<tr>
<td>Rest of World</td>
<td>0.96</td>
<td>0.7-1.3</td>
<td>241</td>
</tr>
<tr>
<td>HER1/EGFR positive</td>
<td>0.73</td>
<td>0.4-1.2</td>
<td>74</td>
</tr>
<tr>
<td>HER1/EGFR negative</td>
<td>0.77</td>
<td>0.5-1.3</td>
<td>71</td>
</tr>
<tr>
<td>HER1/EGFR unknown</td>
<td>0.86</td>
<td>0.7-1.1</td>
<td>424</td>
</tr>
</tbody>
</table>

Moore et al., JCO 2007
# PA.3 study, Adverse events

![Table showing adverse events and their grades for Tarceva and Placebo groups.](image)

<table>
<thead>
<tr>
<th>Events</th>
<th>Tarceva (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Grade 3,4</td>
</tr>
<tr>
<td>Rash</td>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Infection</td>
<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>23</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>89</td>
<td>15</td>
</tr>
</tbody>
</table>

Moore et al., JCO 2007
PA.3 study, Rash vs survival

HR [Rash] = 0.71
p < 0.0001

Moore et al., JCO 2007
Further studies to identify subset of pts who benefit from erlotinib or to increase effect

Can dose escalation of erlotinib improve outcome?

- Primary endpoint: OS
- Mandatory tissue collection
- Secondary endpoints: PFS, disease control, safety, correlation of EGFR-related biomarkers with outcome (EGFR, EGF, TGFα, K-ras, pAKT, pMAPK)
## 2nd-line treatment?

### 2nd-Line After Failure of Gemcitabine

<table>
<thead>
<tr>
<th>Agent</th>
<th>n</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>52</td>
<td>1.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>39</td>
<td>2.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Capecitabine + Oxaliplatin</td>
<td>39</td>
<td>na</td>
<td>5.8</td>
</tr>
<tr>
<td>5-FU/FA + Oxaliplatin</td>
<td>30</td>
<td>5.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Gemcitabine + Oxaliplatin</td>
<td>33</td>
<td>4.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Gemcitabine + Cisplatin</td>
<td>24</td>
<td>na</td>
<td>4.0</td>
</tr>
<tr>
<td>Capecitabine + Erlotinib</td>
<td>30</td>
<td>3.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Irinotecan + Oxaliplatin</td>
<td>30</td>
<td>4.1</td>
<td>5.9</td>
</tr>
</tbody>
</table>

**PFS** 1.6 – 5.1 months  
**OS** 4.7 – 7.6 months

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Boeck S, Heinemann V, Future Oncology 2008
CONKO-003,
Phase III study of oxaliplatin-5FU vs. 5FU

Pelzer et al., ASCO 2008
CONKO-003, Phase III - study of oxaliplatin-5FU vs. 5FU

CONKO-003 Results - 2nd line OS

Survival from start of sec. line

- **OFF**: median: 26 weeks (95% CI: 19.5; 32.41)
- **FF**: median: 13 weeks (95% CI: 10.01; 15.99)

Log Rank: p = 0.014

Pelzer et al., ASCO 2008
Current acceptable choices of palliative treatment of advanced disease

1st-line

- Gem alone or combined with either erlotinib, capecitabine or oxaliplatin/cisplatin for good PS patients
- Gem or Gem + erlotinib for intermediate PS patients
- BSC for poor PS patients
- Protocols

2nd-line

- BSC
- Treatment preferably in protocols
- Oxaliplatin-5FU should be considered for fit patients, especially those with long TTP on 1st-line