Strategies to improve the outcome of locally advanced pancreatic cancer patients

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Disclosures C. Louvet

Celgene
Roche
Nucana
Background

Role of radiation therapy in locally advanced pancreatic cancer highly debated

• **Local control** remains an important issue
  → chemoradiation (CRT)

• High rate of **distant metastasis**
  → chemotherapy
Frontline CRT versus chemotherapy in LAPC

Contradictory results


→ Contradictory results
Induction CT followed by CRT in LAPC

CRT after 3 months of induction chemotherapy

Huguet F et al, J Clin Oncol 2007

→ Promising strategy
<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>N pts</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>1-year survival (%)</th>
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<tbody>
<tr>
<td>Huguet</td>
<td>CT</td>
<td>181</td>
<td>7.4</td>
<td>11.7</td>
<td>47.5</td>
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<tr>
<td>(retrosp)</td>
<td>CT then CRT</td>
<td></td>
<td>10.8</td>
<td>15</td>
<td>65.3</td>
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<tr>
<td>Krishnan</td>
<td>CRT</td>
<td>323</td>
<td>4.2</td>
<td>8.5</td>
<td></td>
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<tr>
<td>(retrosp)</td>
<td>CT then CRT</td>
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<td>6.4</td>
<td>11.9</td>
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</tr>
<tr>
<td>Brunner</td>
<td>CRT</td>
<td>172</td>
<td></td>
<td>7.6</td>
<td>21</td>
</tr>
<tr>
<td>(retrosp)</td>
<td>CRT then CT</td>
<td></td>
<td></td>
<td>13.5</td>
<td>65</td>
</tr>
<tr>
<td>Ko</td>
<td>CT then CRT</td>
<td>25</td>
<td>10.5</td>
<td>13.5</td>
<td>62</td>
</tr>
<tr>
<td>(phase 2)</td>
<td>(32% PD after CT)</td>
<td></td>
<td>(12.7)</td>
<td>(17)</td>
<td></td>
</tr>
<tr>
<td>Schneider</td>
<td>CT - CRT - CT</td>
<td>18</td>
<td></td>
<td>12.8</td>
<td></td>
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<tr>
<td>(phase 2)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
Concurrent chemotherapy?

SCALOP (phase 2)

74 pts  
Gem-Cap x 3  
R  

- CRT 50.4 Gy with capecitabine  
  15.2 months  
- CRT 50.4 Gy with gemcitabine  
  13.4 months  

$p = 0.01$

Mukherjee S et al. Lancet Oncol 2013
LAP07 study

EVALUATION: non progressive

1 month = Gemcitabine (1000 mg/m²)/wk×3

Erlotinib: 100 mg/d with gem 150 mg/d as single agent

Secondary surgery allowed at any time

Capecitabine plus radiation
Quality assurance

R1

R2

Cape XRT

Until progression
Objectives of LAP07 study

• **Primary objective**: to assess whether administering CRT increases overall survival in patients whose tumor is controlled after 4 months of induction chemotherapy

• **Secondary objectives:**
  - Role of erlotinib
  - Progression free survival (PFS)
  - Tolerance
  - Impact of Radiation Therapy Quality Assessment (RTQA)
  - Predictive molecular markers, circulating tumor cells

Assessed for eligibility (n = 449)

1st Randomization
Intent-to-treat principle (n = 442)

Gemcitabine (n = 223)

Gemcitabine + erlotinib (n = 219)

Excluded (n = 7)

Excluded (39.1%) (n = 173)
111 progressive disease
15 toxicity
11 delay
11 patients’ will
16 investigator decision
6 intercurrent disease
3 surgery

2nd Randomization
Intent-to-treat principle (n = 269)

Chemotherapy (n = 136)

Chemoradiotherapy (n = 133)
Site of progression

- **R2 patients:**
  - 236/269 patients (88%) with tumor progression
    - 93 with local progression only (39.4%)
    - 122 with metastatic (± local) progression (51.7%)
    - 21 unknown (8.9%)

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (n= 125)</th>
<th>Chemoradiation (n= 111)</th>
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<tbody>
<tr>
<td>LA</td>
<td>58 (46%)</td>
<td>35 (32%)</td>
</tr>
<tr>
<td>M+</td>
<td>55 (44%)</td>
<td>67 (60%)</td>
</tr>
<tr>
<td>unknown</td>
<td>12 (10%)</td>
<td>9 (8%)</td>
</tr>
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</table>

$p=0.035$
Progression Free Survival

Chemotherapy: n=136  n.events=125  median time=8.4
Chemoradiotherapy: n=133  n.events=122  median time=9.9
Log-rank p=0.055
HR - 95%CI: 0.78 [0.61-1.01]
Treatment Free Survival

Chemotherapy: n=136 n.events=121 median time=3.7
Chemoradiotherapy: n=133 n.events=112 median time=6.1
Log-rank p=0.017
LAP07 Conclusions

• LAP07 prospectively confirmed the value of frontline chemotherapy in LAPC patients

• Overall survival in CRT arm is not superior to chemotherapy arm in LAPC patients with tumor controlled after 4 months of chemotherapy

• However, trend for PFS in favor of CRT

• In the CRT arm, patients had a significantly less local tumor progression and a longer period without chemotherapy
Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy
**FOLFIRINOX**

**Overall Survival**

Stratified Log-rank test, $p<0.0001$

HR = 0.57 : 95%CI [0.45-0.73]

Number at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Gemcitabine</th>
<th>Folfirinox</th>
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<tbody>
<tr>
<td>0</td>
<td>171</td>
<td>171</td>
</tr>
<tr>
<td>3</td>
<td>134</td>
<td>146</td>
</tr>
<tr>
<td>6</td>
<td>89</td>
<td>116</td>
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<td>9</td>
<td>48</td>
<td>81</td>
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<td>12</td>
<td>28</td>
<td>62</td>
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<tr>
<td>15</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td>18</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>21</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>24</td>
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<td>9</td>
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<td>27</td>
<td>3</td>
<td>5</td>
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<tr>
<td>30</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>33</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Months

- **Gemcitabine**
- **Folfirinox**
**Nab-P + Gem**  **Overall Survival**

**OS, months**

<table>
<thead>
<tr>
<th>Events/N (%)</th>
<th>Median (95% CI)</th>
<th>75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>333/431 (77)</td>
<td>8.5 (7.89–9.53)</td>
<td>14.8</td>
</tr>
<tr>
<td>359/430 (83)</td>
<td>6.7 (6.01–7.23)</td>
<td>11.4</td>
</tr>
</tbody>
</table>

**HR = 0.72**

95% CI (0.617–0.835)

**P = 0.000015**

**Pts at Risk**

| nab-P + Gem: | 431  | 357  | 269  | 169  | 108  | 67   | 40   | 27   | 16   | 9    | 4    | 1    | 1    | 1    | 0    |
|--------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Gem:         | 430  | 340  | 220  | 124  | 69   | 40   | 26   | 15   | 7    | 3    | 1    | 0    | 0    | 0    |

Von Hoff et al., ASCO GI 2013 LBA148
Nab-Paclitacel + FOLFOX

Phase I study (Saffran, ASCO 2014)

Very promising results
Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine
Strategies to improve the outcome of LAPC patients

1- Improvement of systemic chemotherapy

2- Personalized medicine
   - Prognostic factor analysis from LAP07
   - Biomarkers and targeted drugs
Gemcitabine: mechanisms of action

- Intracellular uptake
  - hENT1
  - hCNT 3

- Activation
  - dCK
    - Nucleoside Phosphate Kinase

- Inactivation
  - CDA
  - DCTD
  - 5’-NT

- Action
  - Inhibition DNA synthesis
hENT1

« Positive » trials

RTOG
(adjuvant, retrospective)

French-Belgium series
(adjuvant, retrospective)

ESPAC 1&3
(adjuvant, retrospective)

Negative trials

Clovis C01-101
(metastatic, prospective)

ECOG
(metastatic, retrospective)

CONKO-01
(adjuvant, retrospective)
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Prognostic</th>
<th>Predictive</th>
<th>Current clinical impact</th>
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<tbody>
<tr>
<td>CA 19.9</td>
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<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CTC / cDNA</td>
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<td>No</td>
<td>No</td>
</tr>
<tr>
<td>miRNAs</td>
<td>Yes</td>
<td>No</td>
<td>? (Anti-sens)</td>
</tr>
<tr>
<td>Proteomic / LAMC</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Genomic profiles</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>hENT1</td>
<td>No</td>
<td>Yes (Gem)</td>
<td>Likely (Gem)</td>
</tr>
<tr>
<td>dCK</td>
<td>No</td>
<td>Yes (Gem)</td>
<td>Likely (Gem)</td>
</tr>
<tr>
<td>CDA</td>
<td>No</td>
<td>Yes (Gem toxicity)</td>
<td>Likely (Gem)</td>
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<tr>
<td>SPARC</td>
<td>Yes</td>
<td>?</td>
<td>? (Abraxane)</td>
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<td>Histone modifications</td>
<td>Yes</td>
<td>?</td>
<td>? (5FU)</td>
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<td>?</td>
<td>? (HH inhibitors)</td>
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<tr>
<td>CXCR4</td>
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<td>?</td>
<td>? (CXCR4 inhibitors)</td>
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<td>HGF / c-Met</td>
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<td>?</td>
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<td>SMAD4</td>
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<td>?</td>
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<tr>
<td>HER2</td>
<td>?</td>
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<td>? (HER2 inhibitors)</td>
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<td>EGFR</td>
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<td>VEGFR</td>
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<tr>
<td>IGFR</td>
<td>? (No)</td>
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Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation
Strategies to improve the outcome of LAPC patients

1– Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation

   Dose radiation
   Target volume
   IMRT, gating
   concurrent radiosenziter
Strategies to improve the outcome of LAPC patients

1- Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation

4- Improvement in strategy and techniques
Strategies to improve the outcome of LAPC patients

1- Improvement of systemic chemotherapy

2- Personalized medicine

3- Improvement of chemoradiation

4- Improvement in strategy and techniques
   - Increased time of systemic CT before CTRT ?
   - Place of secondary surgery after systemic CT and CTRT ?
   - Place of HIFU ?
RTOG 1201 will help address the question of whether more effective chemotherapy impacts the role of radiation in locally advanced disease.

Locally advanced PDAC

Stratify:
SMAD4 status (predicts patterns of local vs distant disease progression)

Gemcitabine/nab-paclitaxel
x 3 months

- 3D-CRT + cape
  50.4 Gy
- IMRT + cape
  63 Gy
- Continue chemotherapy

(P.I.: Christopher Crane, MD Anderson)
Phase III SCALOP 2 design

LAPC patients, PS 0-1
255 pts

GEM/Nab-Pacltaxel ou GEMCAP x 3 cycles

Randomise if eligible for CRT (65%) 1:1:1:1:1 between arms A-E
Then GEM/Nab-Pacltaxel x 1 cycle whilst RT is planned

<table>
<thead>
<tr>
<th>Arm A</th>
<th>- Nelfinavir n=66</th>
<th>+ Nelfinavir n=66</th>
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<tbody>
<tr>
<td>n=33</td>
<td>50.4 Gy n=66</td>
<td>Arm B n=33</td>
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<tr>
<td></td>
<td>CAPE 50.4Gy/28F</td>
<td>Arm C n=33</td>
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<tr>
<td></td>
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<td>CAPE 50.4Gy/28F</td>
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<td></td>
<td>+Nelfinavir</td>
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<tr>
<td>60 Gy</td>
<td>Arm D n=33</td>
<td>Arm E n=33</td>
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<tr>
<td>n=66</td>
<td>CAPE 60Gy/30F</td>
<td>CAPE 60Gy/30F</td>
</tr>
<tr>
<td></td>
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<td>+Nelfinavir</td>
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</table>
Methodological and medico-economic issues

Systematic QoL studies?

Composite endpoints?

Amount of requested material for genomic issues?

Place of « liquid biopsies »?

Cost of new drugs and of CTRT?
Strategies to improve the outcome of LAPC patients

1. Improvement of systemic chemotherapy
2. Personalized medicine
3. Improvement of chemoradiation
4. Improvement in strategy and techniques
5. Methodological and medico-economic issues
Never give up!