GEM-CAP et NALIRI :
Nouveaux standards dans le cancer du pancréas ?

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Institut Mutualiste Montsouris, Paris
ESPAC-1 :

Démonstration du bénéfice d'une chimiothérapie adjuvante (5FU / AF)

Neoptolemos et al, NEJM 2004; 350:1200-10
CONKO 01: gemcitabine vs observation

**Gemcitabine**
Median: 22.8 months (IC 95%: 18.5-27.2)

**Observation**
Median: 20.2 months (IC 95%: 17.7-22.8)

Log Rank p=0.005

Survival

Months

ESPAC-3: 5FU / AF vs Gemcitabine

Median $S(t) = 23.0$ m (95% CI: 21.1, 25.0)
Median $S(t) = 23.6$ m (95% CI: 21.4, 26.4)

χ² LR = 0.74, p = 0.39, HRGEM VS 5FU/FA = 0.94 (95% CI: 0.81, 1.08)

Neoptolemos et al., ASCO2009
ESPAC - 4

722 patients pancreatic ductal adenocarcinoma ‘curative’ resection <12 wks

RANDOMISATION at Liverpool Cancer Trials Unit

GEMCITABINE
1000mg/m² - Days 1, 8, and 15 for 6 cycles

GEMCITABINE
1000mg/m² - Days 1, 8, and 15 for 6 cycles

CAPECITABINE
1660mg/m²/day – 21/28d i.e. 24 weeks

3-MONTHLY FOLLOW UP FROM RANDOMISATION TO DEATH

Stratified log-rank test with 5% 2-sided α, for a 10% difference in 2 year survival, 90% power = 480 events = 722 patients, 361 in @ arm

Target number of patients | 722
Start date | 13/01/08
Number of sites opened | 106
Planned close date | 01/11/14
Target achieved | 31/07/14

Cumulative Rand
Cumulative Target
722 Target
Survival by Treatment

HR = 0.82 (95% CI, 0.68-0.98)
\[ \chi^2 (1) = 4.61, \ p = 0.032 \]

Median \( S(t) = 25.5 \) months (95% CI: 22.7-27.9)
Median \( S(t) = 28.0 \) months (95% CI: 23.5-31.5)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Gem</th>
<th>GemCap</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>366</td>
<td>364</td>
</tr>
<tr>
<td></td>
<td>302</td>
<td>328</td>
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<td>207</td>
<td>219</td>
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<td>109</td>
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<td>27</td>
<td>50</td>
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<td>9</td>
<td>19</td>
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LCTU
Liverpool Clinical Trials Unit

NCRI
National Cancer Research Institute

UKCRC
Registered Clinical Trials Units

NHS
National Institute for Health Research

CANCER RESEARCH UK
Conclusions

- Median survival for patients treated with GEMCAP was significantly better than GEM: 28.0 (95% CI, 23.5 -31.5) vs 25.5 (22.7-27.9) months
- The estimated 5 years survival rate was superior with GEMCAP than GEM: 28.8 (22.9-35.2)% vs 16.3 (10.2-23.7)%
- As expected there was slightly more toxicity in the GEMCAP arm but overall this was manageable and not significant: 154 SAEs in 86 (24%) GEMCAP patients vs 151 SAEs in 94 (26%) GEM patients
- The 5 year survival rate with GEMCAP=28.8 (22.9-35.2)% was superior to previous ESPAC trial arms including no chemotherapy=8.0 (3.8-14.1)%, chemoradiotherapy=10.8 (6.1-17.0)%, 5FU/FA=15.9 (12.7-19.4)%
- Marginal benefit of active agents in advanced pancreatic cancer can translate into a much bigger effect in the adjuvant setting
- All patients with pancreatic cancer should be offered entry into randomised trials: biomarkers must be evaluated (hENT1, etc)
- Adjuvant GEMCAP is the new standard of care for resected pancreatic cancer
Survival by Treatment

HR = 0.82 (95% CI, 0.68-0.98)
\[ \chi^2 (1) = 4.61, p = 0.032 \]

Median S(t) = 25.5 months (95% CI: 22.7-27.9)
Median S(t) = 28.0 months (95% CI: 23.5-31.5)

<table>
<thead>
<tr>
<th>Time from randomisation (months)</th>
<th>No. at Risk</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>366 364</td>
</tr>
<tr>
<td>10</td>
<td>302 328</td>
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<td>20</td>
<td>207 219</td>
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<tr>
<td>30</td>
<td>109 139</td>
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<td>40</td>
<td>61 83</td>
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<tr>
<td>50</td>
<td>27 50</td>
</tr>
<tr>
<td>60</td>
<td>9 19</td>
</tr>
</tbody>
</table>

Gemcitabine
Gemcitabine-Capecitabine
Gemcitabine: mechanisms of action

- Intracellular uptake
  - hENT1
  - hCNT 3

- Activation
  - dCK
    - Nucleoside Phosphate Kinase

- Inactivation
  - CDA
  - DCTD
  - 5’-NT

- Action
  - Inhibition DNA synthesis
Expérience Franco-Belge

Population « gemcitabine »

Population « non gemcitabine »

Marechal R, Bachet JB, Mackey J et al
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)
Follow-up trop court

Données de DFS ?

Traitements métastatiques ?

hENT1 ?
Overall Survival (JASPAC study)

<table>
<thead>
<tr>
<th></th>
<th>2-year OS (95% CI)</th>
<th>median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-1</td>
<td>70% (63-76)</td>
<td>Not matured</td>
</tr>
<tr>
<td>GEM</td>
<td>53% (46-60)</td>
<td>25.9 months</td>
</tr>
</tbody>
</table>

HR 0.54 (99.8% CI, 0.35-0.83)

Based on the final data (219 events)
Vivement les résultats de PRODIGE 24 ! ....
Nal-IRI in pancreatic cancer
The MTD of nal-IRI was determined as 120 mg/m²

- This will be the recommended dose for future studies

Nal-IRI has modified PK parameters, compared to what is known about free-form irinotecan

- Characterised by slow clearance, small volume of distribution and prolonged terminal half-life

Two patients (pancreatic and cervical cancer) had an objective tumor response

- At the MTD, 20% (1 of 5) patients responded to treatment and 60% (3 of 5) demonstrated disease control


MTD, maximum tolerated dose

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Study met primary endpoint of 3-month survival rate of 75% (30 out of 40) in metastatic pancreatic cancer patients who had previously failed gemcitabine therapy.

Significant tumor shrinkage and reduction of CA19-9 responses and sustained clinical benefit* noted in 30 evaluable patients treated with Nal-IRI.

Grade 3/4 toxicities were primarily haematologic in nature, with gastrointestinal toxicities, fatigue and abdominal pain also commonly experienced.

The results of this clinical trial provided the support to move forward with the international, randomised phase III trial, NAPOLI-1.


5-FU, 5-fluorouracil; AE, adverse events; GI, gastrointestinal; LU, leucovorin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PP, per protocol

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NAPOLI-1 trial
Study design

- Study endpoints: OS (1°); PFS, time to treatment failure and ORR (2°); other endpoints CA19-9 (tumor marker) response and safety
- Stratification factors: serum albumin levels, KPS, ethnicity

*The study was amended to add the nal-IRI + 5-FU/LV arm once safety data on the combination treatment became available;

5-FU, 5-fluorouracil; KPS, Karnofsky performance status; LU, leucovorin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

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NAPOLI-1 trial
PFS (ITT population)

**nal-IRI+5-FU/LV combination therapy vs. 5-FU/LV**

- **nal-IRI+5-FU/LV**
  - Median, mo (95% CI): 3.1 (2.7–4.2)
  - HR: 0.56 (0.41–0.75)
  - P: 0.0001

- **5-FU/LV**
  - Median, mo (95% CI): 1.5 (1.4–1.8)

**nal-IRI monotherapy vs. 5-FU/LV**

- **nal-IRI**
  - Median, mo (95% CI): 2.7 (2.1–2.9)
  - HR: 0.81 (0.63–1.04)
  - P: 0.1001

- **5-FU/LV**
  - Median, mo (95% CI): 1.6 (1.4–1.8)

**Number at risk**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>nal-IRI+5-FU/LV</strong></td>
<td>117</td>
<td>50</td>
<td>22</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>5-FU/LV</strong></td>
<td>119</td>
<td>23</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Therapy</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>nal-IRI</strong></td>
<td>151</td>
<td>49</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>5-FU/LV</strong></td>
<td>149</td>
<td>31</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>


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5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LU, leucovorin; PFS, progression-free survival
**NAPOLI-1 trial**

**Key efficacy data: OS (ITT population)**

- **OS (ITT population)**: Protocol defined primary analysis data cut-off (14 February, 2014, after 305 events);
  - **Un-stratified HR = 0.67 (0.49–0.92), P = 0.0122**;
  - **Un-stratified HR = 0.99 (0.77–1.28), P = 0.9416**;


Chen LT, Von Hoff D, Li CP, et al. ASCO GI (abstract 234) 2015;

Clinicaltrials.gov - NCT01494506

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**Survival probability (%)**

1. **nal-IRI+5-FU/LV combination therapy vs. 5-FU/LV**
   - **Median, mo (95% CI)**:
     - nal-IRI+5-FU/LV: 6.1 (4.8–8.9)
     - 5-FU/LV: 4.2 (3.3–5.3)
   - **Stratified HR**:
     - nal-IRI+5-FU/LV vs. 5-FU/LV: 0.57 (0.41–0.80), P = 0.0009

2. **nal-IRI monotherapy vs. 5-FU/LV**
   - **Median, mo (95% CI)**:
     - nal-IRI+5-FU/LV: 6.1 (4.8–8.9)
     - 5-FU/LV: 4.2 (3.3–5.3)
   - **Stratified HR**:
     - nal-IRI vs. 5-FU/LV: 0.57 (0.41–0.80), P = 0.0009

---

**Number at risk**

1. **nal-IRI+5-FU/LV**
   - 117
   - 97
   - 51
   - 20
   - 8
   - 0

2. **5-FU/LV**
   - 119
   - 68
   - 34
   - 11
   - 6
   - 1

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5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; LU, leucovorin; mo, months; OS, overall survival

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### NAPOLI-1 trial

**Safety: AEs (safety population*)**

<table>
<thead>
<tr>
<th></th>
<th>nal-IRI + 5-FU/LV (n = 117)</th>
<th>nal-IRI (n = 147)</th>
<th>5-FU/LV (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade ≥3 non-haematological AEs in &gt;5% patients, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td><strong>Grade ≥3 haematological AEs based on laboratory values, %</strong>,***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patients with at least 1 AE leading to death (all causes), %</td>
<td>2</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

The safety profile in the nal-IRI + 5-FU/LV combination group demonstrated that the most frequent grade ≥3 AEs included neutropenia, fatigue and GI-related effects.

*Patients receiving at least one dose of study drug; **Per CTCAE version 4; ***Includes only one patient who had at least one baseline assessment; [Von Hoff D, Li CP, Wang-Gillam A, et al. Ann Oncol 2014; 25(Suppl 2): 105-6](abstract O-0003); [Chen LT, Von Hoff D, Li CP, et al. ASCO GI (abstract 234) 2015; Clinicaltrials.gov - NCT01494506](#)
NAPOLI-1 trial Summary

In the NAPOLI-1 trial, nal-IRI +5-FU/LV combination treatment extended OS in patients with mPC after gemcitabine-based therapies vs. 5-FU/LV alone.

The primary endpoint for improvement of overall survival with the combination therapy group vs 5-FU/LV alone was met: median OS 6.1 months vs. 4.2 months (stratified HR = 0.57, P = 0.0009).

PFS, ORR and CA19-9 (tumor marker) responses were also increased.

Treatment with nal-IRI monotherapy was comparable to 5FU/LV alone on OS and PFS.

The most frequent grade ≥3 AEs associated with nal-IRI + 5-FU/LV treatment included neutropenia, fatigue and GI-related effects.


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Méthodologie « pure »

Pas de comparaison avec 5FU - CPT11
Pas de comparaison avec 5FU - Oxali

Disponibilité et coût du produit

Population concernée ?
GEM-CAP et NALIRI :

Nouveaux standards dans le cancer du pancréas ?

GEM-CAP : Non (pour l’instant)

NALIRI : Oui, mais …
NE JAMAIS ABANDONNER !