Single Agent Gemcitabine vs doublet vs FOLFIRINOX

Jordan D. Berlin, M.D.
Ingram Professor of Cancer Research
Co-director, GI Oncology
Director, Phase I Research
Vanderbilt-Ingram Cancer Center
Disclosures

- Advisory Boards here and there in last year
  - Genentech/Roche
  - Karyopharm
  - Amgen
  - Astra Zeneca
  - BMS
  - Lilly/Imclone
  - Symphogen
  - Celgene

- Current Research Support
  - Amgen, Lilly/Imclone, Pfizer, Novartis, Abbvie, Immunomedics, Otsuka, Merrimack
Positives for gem
- Met primary endpoint of clinical benefit response
- Had a small but statistically significant OS benefit
- Had a larger proportion surviving 1 year

We are critical of what we want to critique. This study:
- Used suboptimal FU
- Was small (n =126)
- Was company sponsored
- Should have been repeated
Median PFS(t) = 14.1 months (95% CI: 12.5, 15.3)
Median PFS(t) = 14.3 months (95% CI: 13.5, 15.7)

χ² LR = 0.59, p = 0.44, HR GEM VS 5FU/FA = 0.95 (95% CI: 0.83, 1.09)
But we needed something so we did this instead

Gemcitabine Alone

Gemcitabine + Your Drug Here
Your Drug = chemo du jour
some nibs
Some mabs
anything that blocked VEGF

And for over 2 decades, gemcitabine remained a SOC option, and still is for PS = 2 patients
List of Your drug here

- 5FU x 2
- Capecitabine x 3
- Cisplatin x 3
- Oxaliplatin x 2
- Irinotecan
- Exatecan
- Rubitecan
- Marimastat
- Masitinib
- FTIs
- Cetuximab
- Bevacizumab
- Aflibercept
- Axitinib
- Sunitinib (phase II only)
- Sorafenib
- Docetaxel (ph II only)
- Ganitumumab

Red = negative phase 2, but still went to phase III
Yellow = such a horrible phase II it should never have been published
Blue = why even bother with phase I? When you have a bad idea start at phase III
NCIC Study PA3: Overall Survival for All Patients

HR = 0.81*
95% CI (0.67, 0.97)
P = 0.025

Gemcitabine + Erlotinib
Median = 6.37 months
1 Year Survival = 24%

Gemcitabine + Placebo
Median = 5.91 months
1 Year Survival = 17%

* Adjusted for PS, pain and disease extent at randomization
Lies we tell ourselves

- Gemcitabine couplets in general
  - “Meta-analysis” of 4,697 patients showed a “survival benefit”
    - HR was 0.91 (CI up to 0.97!!!)
    - Didn’t give a p-value (likely barely less than 0.05)
    - Included the original gem-cape data from UK when that trial was positive so update of data used would be worse
- Gemcitabine-platinum
  - HR was 0.85 (CI up to 0.96)
  - Gemcitabine and platinum probably benefits patients with BRCA2/Fanconi and the rest are just being tortured for our pleasure)

Gemcitabine vs couplets with negative phase III

- Masitinib, erlotinib
  - Masitinib may have a predictive biomarker
  - Erlotinib needs one (maybe RTOG 0848 will find this)

- Capecitabine/ 5FU
  - Except for infusional 5FU, these studies were borderline
  - Better PS (0 or 1) patients may derive benefit

- Cisplatin/oxaliplatin
  - Fanconi anemia/BRCA2/PALB2 pts likely benefit
  - Better PS (0 or 1) patients may derive benefit
nab-Paclitaxel + Gemcitabine in Pancreatic Cancer

• Preclinical models\(^1,2\)
  – *nab*-Paclitaxel (*nab*-P) active as single agent
  – Synergizes with gemcitabine (Gem)

• 67 highly selected patient phase I/II trial\(^1\)
  – MTD: *nab*-P 125 mg/m\(^2\) + Gem 1000 mg/m\(^2\) days 1, 8, and 15 every 28 days
  – Promising activity at MTD
    • ORR: 48%
    • Median PFS: 7.9 months
    • Median OS: 12.2 months

MTD, maximum tolerated dose.

CA046

Randomized Phase III Study of Weekly nab®-Paclitaxel Plus Gemcitabine vs Gemcitabine Alone in Patients With Metastatic Adenocarcinoma of the Pancreas (MPACT)

DD Von Hoff, T Ervin, FP Arena, EG Chiorean, J Infante, M Moore, T Seay, SA Tjulandin, W Ma, MN Saleh, M Harris, M Reni, RK Ramanathan, J Tabernero, M Hidalgo, E Van Cutsem, D Goldstein, X Wei, J Iglesias, MF Renschler

® nab is a registered trademark of Celgene Corporation.
Study Design

Planned N = 842

- Stage IV
- No prior treatment for metastatic disease
- Karnofsky PS ≥70
- Measurable disease
- Total bilirubin ≤ULN

nab-Paclitaxel
125 mg/m² IV qw 3/4 weeks
+ Gemcitabine
1000 mg/m² IV qw 3/4 weeks

Gemcitabine
1000 mg/m² IV qw for 7 weeks then qw 3/4 weeks

Overall Survival

<table>
<thead>
<tr>
<th>Pts at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab-P + Gem: 431</td>
<td>39</td>
</tr>
<tr>
<td>Gem: 430</td>
<td>39</td>
</tr>
</tbody>
</table>

HR = 0.72
95% CI (0.617 - 0.835)
P = 0.000015
## IMPACT: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>nab-Pacli + GEM</th>
<th>GEM</th>
<th>Hazard ratio p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med OS, mos</td>
<td>8.5</td>
<td>6.7</td>
<td>0.72/0.000015</td>
</tr>
<tr>
<td>Med PFS, mos</td>
<td>5.5</td>
<td>3.7</td>
<td>0.69/0.000024</td>
</tr>
<tr>
<td>12-mon alive, %</td>
<td>35</td>
<td>22</td>
<td>0.00002</td>
</tr>
<tr>
<td>RR, %</td>
<td>23</td>
<td>7</td>
<td>1.1x10^{-10}</td>
</tr>
</tbody>
</table>

Response Rate is 29% for gemcitabine + nab-paclitaxel by investigator review
### Safety

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>nab-P + Gem n = 421</th>
<th>Gem n = 402</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 AE leading to death, %</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Grade ≥ 3 hematologic AEs,(^a) %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td><strong>Patients who received growth factors, %</strong></td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td><strong>Febrile neutropenia,(^b) %</strong></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Grade ≥ 3 nonhematologic AEs(^b) in &gt; 5% of patients, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Peripheral neuropathy(^c)</td>
<td>17</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Grade ≥ 3 neuropathy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to onset in days, median</td>
<td>140</td>
<td>113</td>
</tr>
<tr>
<td>Time to improvement by ≥ 1 grade in days, median</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Time to improvement to grade ≤ 1 in days, median</td>
<td>29</td>
<td>--</td>
</tr>
<tr>
<td>Patients who resumed nab-P, %</td>
<td>44</td>
<td>--</td>
</tr>
</tbody>
</table>

\(^a\) Based on lab values. \(^b\) Based on investigator assessment of treatment-related events. \(^c\) Grouped term.

AE, adverse event. Gem, gemcitabine; nab-P, nab-paclitaxel.

Gemcitabine + nab-paclitaxel

- HR for OS was 0.72 which is better than erlotinib or any of the “meta-analysis” results
- No clear biomarkers yet, but analyses are pending
  - SPARRC, a protein found in the tumor tissue and binds nab-paclitaxel in the tissue is a putative marker
- For gemcitabine couplets, this is likely the regimen of choice
  - Still unclear in BRCA2/Fanconi/PALB2 (DNA repair deficient tumors) if platins could be better here
FOLFIRINOX

• A phase II-III randomized study comparing Folfirinox regimen to gemcitabine alone was launched
  – Please note: Robust randomized phase II with strong signal for going forward
  – This is the best-supported go-forward in pancreas cancer history

• Results of phase II randomized study step (n=88) were presented during ASCO 2007:
  – 31.8% RR in the Folfirinox arm vs
  – 11.4% in the gemcitabine arm

• Due to these encouraging interim results, the trial continued as a phase III study

Ychou M et al. J Clin Oncol 2007;25
<table>
<thead>
<tr>
<th>Objective Response Rate</th>
<th>Folfirinox (N=171)</th>
<th>Gemcitabine (N=171)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0.6%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>31%</td>
<td>9.4%</td>
<td>0.0001</td>
</tr>
<tr>
<td>CR/PR 95% CI</td>
<td>[24.7-39.1]</td>
<td>[5.9-15.4]</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>38.6%</td>
<td>41.5%</td>
<td></td>
</tr>
<tr>
<td>Disease control</td>
<td>70.2%</td>
<td>50.9%</td>
<td>0.0003</td>
</tr>
<tr>
<td>CR+PR+SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>15.2%</td>
<td>34.5%</td>
<td></td>
</tr>
<tr>
<td>Not assessed</td>
<td>14.6%</td>
<td>14.6%</td>
<td></td>
</tr>
<tr>
<td>Median duration of response</td>
<td>5.9 mo.</td>
<td>4 mo.</td>
<td>ns</td>
</tr>
</tbody>
</table>

**Objective Response Rate**
Progression-Free Survival

Median PFS Folfirinox: 6.4 mo.  Median PFS Gemcitabine: 3.3 mo.

HR=0.47 : 95%CI [0.37-0.59]  p<0.0001

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>Folfirinox</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>171</td>
<td>171</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>121</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Overall Survival

Med Survival: 11.1 vs 6.8 months

Stratified Log-rank test, p<0.0001

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

Number at risk

Gemcitabine 171 134 89 48 28 14 7 6 3 3 2 2 2
Folfirinox 171 146 116 81 62 34 20 13 9 5 3 2 2 2

Months

0 3 6 9 12 15 18 21 24 27 30 33 36

0.00 0.25 0.50 0.75 1.00
## Safety: hematological AEs

<table>
<thead>
<tr>
<th>AE, % per patient</th>
<th>Folfirinox N=167</th>
<th></th>
<th>Gemcitabine N=169</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
<td>All</td>
<td>Grade 3/4</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>79.9</td>
<td>45.7</td>
<td>54.8</td>
<td>18.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>7.2</td>
<td>5.4</td>
<td>2.4</td>
<td>0.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Anemia</td>
<td>90.4</td>
<td>7.8</td>
<td>94.6</td>
<td>5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75.2</td>
<td>9.1</td>
<td>54.8</td>
<td>2.4</td>
<td>0.008</td>
</tr>
</tbody>
</table>

42.5% of the pts received G-CSF in the F arm vs 5.3% in the G arm.
One toxic death occurred in each arm.

AE, adverse event
# Safety: main non-hematological AEs

### Table: Non-hematological AEs

<table>
<thead>
<tr>
<th>AE, % per patient</th>
<th>Folfirinox N=167</th>
<th>Gemcitabine N=169</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
<td>All</td>
</tr>
<tr>
<td>Infection without neutropenia</td>
<td>6</td>
<td>1.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>70.5</td>
<td>9</td>
<td>0.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>61.4</td>
<td>14.5</td>
<td>43.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>87.3</td>
<td>23.2</td>
<td>78.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>73.3</td>
<td>12.7</td>
<td>30.8</td>
</tr>
<tr>
<td>Alopecia (grade 2)</td>
<td>32.5</td>
<td>(11.4)</td>
<td>3.0</td>
</tr>
<tr>
<td>ALT</td>
<td>64.8</td>
<td>7.3</td>
<td>83.8</td>
</tr>
</tbody>
</table>

**FOLFIRINOX Conclusions**

- Clearly the most robust phase III results in metastatic pancreatic cancer
- Limited patient subset
  - PS 0 or 1 only
  - Age <76
- Trade-off was side effect profile
- Includes a platinum to decrease question about BRCA2/Fanconi/PALB2 subset
- Largely being used in modified form
  - Most common modification is dropping the bolus 5FU
FOLFIRINOX vs Gem-nab-paclitaxel

- **Similarities in population**
  - Median age
  - Gender
  - 100% stage IV
  - Site of primary
  - % with liver involvement

- **Differences in population**
  - MPACT allowed PS 2 (KPS 70%) patients though <10% of population
  - MPACT was worldwide, PRODIGE in France only
  - Age >75 allowed on MPACT though only 5%
  - Median # of sites of mets
    - 3 in MPACT
    - 2 in PRODIGE
### Tolerability: Select Grade 3+ Toxicities, %

<table>
<thead>
<tr>
<th>Condition</th>
<th>nab-pacli + GEM</th>
<th>FOLFIRINOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>23.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>12.7</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38</td>
<td>45.7</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>3</td>
<td>5.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Neuropathy appears to resolve faster with nab-paclitaxel

Von Hoff, et al GI ASCO 2013 and ASCO 2013
Differences in efficacy

• OS for FOLFIRINOX was 11.1 months vs 8.7 months for gemcitabine + nab-paclitaxel
  – Comparison is limited by differences in study design/population, etc
  – However control arm was the same gemcitabine for both (FOLFIRINOX 6.8 months and Gem-nab-paclitxel 6.7 months)
    • The most difficult thing to get around is that we are now looking at hazard ratios, not medians so comparable medians does not guarantee that the curves are superimposable

• Response Rate
  – Really similar: By investigator assessment
    • 29% for gem-nab-paclitaxel vs 31.6% for FOLFIRINOX
Stratified Log-rank test, \( p < 0.0001 \)

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

But Bill Gates invented PowerPoint and look at this
Impact vs Prodigie

• Comparing across trials is not really possible
• Key eligibility of PS and age differs in the two studies
  – Prodigie had max age of 75
  – IMPACT allowed KPS of 70%
    • This is a PS of 2
• Despite this, the gemcitabine control arms in both trials had nearly identical survivals
• BOTTOM LINE: Both are options—we don’t know if one is better, but survivals appear to favor FOLFIRINOX
However,

– Gemcitabine + nab-paclitaxel appears to be a better regimen for adding more drugs at least on the surface
– We are using FOLFIRINOX largely in different doses than used on the trial
– While the makers of nab-paclitaxel will be submitting this for regulatory approval, nobody will be submitting FOLFIRINOX

And the result?
The new era of mindless clinical trial design

Randomize

Gemcitabine + nab-paclitaxel

Gemcitabine + nab-paclitaxel + Your Drug Here

Your Drug = blocked some new nibs mabs pibs and despite our better awareness, probably something that blocks VEGF
Slides Provided By

• Thierry Conroy
• Malcolm Moore
• Philip Philip
• Dan Von Hoff