Neoadjuvant Therapy for Localized Pancreatic Cancer

Douglas B. Evans
Department of Surgery
Medical College of Wisconsin
devans@mcw.edu
Disclosures: none

Reminder: November is Pancreatic Cancer Awareness month
Pancreatic Cancer - #2 in cancer deaths in WI.
Team Work Makes the Dream Work
MCW Pancreatic Cancer Program

Pancreatic Cancer Group
• Callisia Clarke, MD
• Kulwinder Dua, MD
• Beth Erickson, MD
• Douglas Evans, MD
• Kathleen Christians, MD
• Jennifer Geurts, CGC
• Ben George, MD
• Tamara Giorgadze, MD, PhD
• Michael Griffin, MD, PhD
• Katherine Hagen, MD
• William Hall, MD
• Christopher Hartley, MD
• Brian Hunt, MD
• Abdul Khan, MD
• Naveen Kulkarni, MD
• Gwen Lomberk, PhD
• Stacy, O’Connor, MD
• Matthew Riese, MD, PhD
• Paul Ritch, MD
• James Thomas, MD, PhD
• Parag Tolat, MD
• Catherine Hagan, MD
• Parag Tolat, MD
• Susan Tsai, MD, MHS
• Raul Urrutia, MD

Clinical Staff
• Elizabeth Krzywda, APNP
• Dayna Dodson, APNP
• Lisa Graber, APNP
• Melissa Mena, BA
• Sarah Misustin, PA-C
• Gabby Pyptiuk, APNP
• Tanya Radke, RN, MSN, APNP
• Bente Smith, MPAS, PA-C
• Kara Sonntag, RD
• Chelsea Lyga, RD
• Gail Laschen
• Alexandra Rokvic

Research Core
• Jenny Grewal, MS
• Krissa Packard, MS
• Poojitha Sitaram, PhD

Pancreas Outcomes Research
• Mohammed Aldakkak, MD
• Idayat Akinola, MD
• Chad Barnes, MD
• Ashley Krepline, MD

Collaborators
• Guan Chen, MD, PhD
• Mike Dwinell, PhD
• Steven Gallinger, MD
• Jill Gershan, PhD
• Ajay Goel, PhD
• Elena Gostjeva, PhD
• Bryon Johnson, PhD
• William Thilly, ScD
• Lily Wang, PhD

Funding
• Advancing Healthier Wisconsin
• Ronald Burklund Eich PC Research Fund
• WeCare Fund
• American Cancer Society Pilot Grant
• Dept of Veterans Affairs
• NIH/NCI
• Batterman Foundation
• Lockton Fund
• WeCare Fund

Website: MCW Pancreatic Cancer Program
Facebook: MCWSurgery
Twitter: @MCWSurgery
YouTube: #MCWmedicalmoments
Mrs. A..... is 53 years old and referred here with newly diagnosed biliary obstruction.
Her bilirubin is 1.9 and her CA19-9 is 362 with a CEA of 2.9.
CT: 14mm tumor in panc head
Biliary brushings nondiagnostic

Pre-referral rec: surgery

MCW rec: EUS-FNA, metal stent, PET and clinical trial of adaptive neoadjuvant therapy
Resectable

Borderline Resectable

Locally Advanced
### Vascular Structures Which Determine the Stage of Disease for Localized Pancreatic Cancer

<table>
<thead>
<tr>
<th>Tumor-Artery Anatomy</th>
<th>SMA (usually pertains to a tumor of the head or uncinate process)</th>
<th>Celiac artery (usually pertains to a tumor of the pancreatic body)</th>
<th>Hepatic Artery (HA) (usually pertains to a tumor of the pancreatic neck/head)</th>
<th>SMV-PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>No radiographic evidence of abutment or encasement</td>
<td>No radiographic evidence of abutment or encasement</td>
<td>Short segment abutment/encasement without extension to celiac artery or HA bifurcation</td>
<td>≤50% narrowing of SMV, PV, SMV-PV</td>
</tr>
<tr>
<td>Borderline Resectable</td>
<td>≤180 degrees (abutment)</td>
<td>≤180 degrees (abutment)</td>
<td>&gt;180 degrees of encasement with extension to celiac artery and amenable to vascular reconstruction</td>
<td>&gt;50% narrowing of SMV, PV, SMV-PV with a distal and proximal target for reconstruction</td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>&gt;180 degrees of (encasement) but &lt;270 degrees</td>
<td>&gt;180 degrees of encasement but does not extend to the aorta and amenable to celiac resection (with or without reconstruction)</td>
<td>&gt;180 degrees and abutment/encasement of the aorta</td>
<td>Occlusion without obvious option for reconstruction</td>
</tr>
</tbody>
</table>

### Tumor-Vein Anatomy

| SMV-PV |
|----------------------|---------------------------------------------------------------|
| ≤50% narrowing of SMV, PV, SMV-PV |
| >50% narrowing of SMV, PV, SMV-PV with a distal and proximal target for reconstruction |
| Occlusion without obvious option for reconstruction |

### Traditionally Considered for Resection After Neoadjuvant Therapy

| Yes | Yes | No | No |

SMA, superior mesenteric artery; SMV, superior mesenteric vein; PV, portal vein; SMV-PV, superior mesenteric-portal vein


TABLE 2 The importance of pre-treatment staging for the development of goals of therapy; specifically, the likelihood of completing all planned neoadjuvant therapy and surgical resection of the primary pancreatic cancer

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Potential for completion of all intended neoadjuvant therapy and surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>90</td>
</tr>
<tr>
<td>Borderline Resectable</td>
<td>75</td>
</tr>
<tr>
<td>Locally Advanced A</td>
<td>60</td>
</tr>
<tr>
<td>Locally Advanced B</td>
<td>25</td>
</tr>
</tbody>
</table>

Data generated from the following manuscripts: Refs 10,12,18,19
<table>
<thead>
<tr>
<th>Neoadjuvant Therapy – then Surgery</th>
<th>Surgery First – Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult metastatic disease 80-90% (what is seen on CT does not kill the patient)</td>
<td><em>Radiographic</em> CR achieved in one day All doctors and patients love CRs</td>
</tr>
<tr>
<td>Nonsurgical therapies delivered to 100% of operated patients</td>
<td>Handoffs straight forward</td>
</tr>
<tr>
<td><strong>Assessment of treatment response is possible (patients do not receive 6 mo of ineffective systemic therapy)</strong></td>
<td></td>
</tr>
<tr>
<td>Surgery avoided in those who progress during Neoadjuvant Rx</td>
<td>Surgery is an effective form of Darwinian selection for medical oncology referrals</td>
</tr>
<tr>
<td>Surgery is immunosuppressive – there may be a biologic/oncologic advantage to Neoadjuvant sequencing</td>
<td>Some patients may struggle to tolerate multiple treatments in series esp when surgery is last</td>
</tr>
<tr>
<td>Adjuvant therapy only gets to 50-75% of operated patients</td>
<td></td>
</tr>
<tr>
<td>R0 (margin negative) resections more likely – local control improved (esp with the addition of XRT)</td>
<td></td>
</tr>
</tbody>
</table>

**All patients with operable pancreatic cancer should be on a clinical trial**
FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgoü-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akou, M.D., Boua, S.V. Neve, M.D., Galerne-Bulliard, M.D., Eric Assenat, M.D., Ph.D., Christine Montserrat, M.D., for the Groupe Turner. PFS

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOLFIRINOX (N=171)</th>
<th>Gemcitabine (N=171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (0.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>53 (31.0)</td>
<td>16 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>66 (38.6)</td>
<td>71 (41.5)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>26 (15.2)</td>
<td>59 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>25 (14.6)</td>
<td>25 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Rate of objective response†</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. (%)</td>
<td>54 (31.6)</td>
<td>16 (9.4)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Objective Responses in the Intention-to-Treat Population.†

Figure 1. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival, According to Treatment Group.

Panel A shows overall survival; the median was 11.1 months in the group receiving FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin). Panel B shows progression-free survival; the median was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group.
62 man with locally advanced type A panc CA

<table>
<thead>
<tr>
<th>Component</th>
<th>Latest Ref Rng &amp; Units</th>
<th>8/13/2018</th>
<th>10/8/2018</th>
<th>1/7/2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARCINOEMBRYONIC ANTIGEN</td>
<td>&lt;=4.7 ng/mL</td>
<td>11.0 (H)</td>
<td>10.8 (H)</td>
<td>3.4</td>
</tr>
<tr>
<td>CA199</td>
<td>&lt;=35.0 unit/mL</td>
<td>964.3 (H)</td>
<td>764.0 (H)</td>
<td>33.5</td>
</tr>
</tbody>
</table>

FOLFIRINOX no response Gem-nab

Aug, 2018 Oct, 2018 Jan, 2019
Dynamic changes during the treatment of pancreatic cancer

Robert A. Wolff1,*, Andrea Wang-Gillam2,*, Hector Alvarez8,*, Hervé Tiriac3,*, Dannielle Engle3,*, Shurong Hou4,*, Abigail F. Groff6,*, Anthony San Lucas9, Vincent Bernard10, Kelvin Allenson11, Jonathan Castillo8, Dong Kim8, Feven Mulu8, Jonathan Huang8, Bret Stephens8, Ignacio I. Wistuba9, Matthew Katz11, Gauri Varadhachary1, YoungKyu Park3, James Hicks3, Arul Chinnaiyan5, Louis Scampavia4, Timothy Spicer4, Chiara Gerhardinger6, Anirban Maitra8, David Tuveson3, John Rinn6,13, Gregory Lizee12, Cassian Yee12 and Arnold J. Levine7

[Image: Diagram of anatomical structures, including SMV, PV, stomach, divided pancreas, left adrenal, aorta, celiac, SMA, gastroepiploic vein, left gastric artery stump, portion of left celiac ganglion.]
Dynamic changes during the treatment of pancreatic cancer

Robert A. Wolff¹,*, Andrea Wang-Gillam²,*, Hector Alvarez⁸,*, Hervé Tiriac³,*, Dannielle Engle³,*, Shurong Hou⁴,*, Abigail F. Groff⁶,*, Anthony San Lucas⁹, Vincent Bernard¹⁰, Kelvin Allenson¹¹, Jonathan Castillo⁸, Dong Kim⁸, Feven Mulu⁸, Jonathan Huang⁸, Bret Stephens⁸, Ignacio I. Wistuba⁹, Matthew Katz¹¹, Gauri Varadhachary¹, YoungKyu Park³, James Hicks³, Arul Chinnaiyan⁵, Louis Scampavia⁴, Timothy Spicer⁴, Chiara Gerhardinger⁶, Anirban Maitra⁸, David Tuveson³, John Rinn⁶,¹³, Gregory Lizee¹², Cassian Yee¹² and Arnold J. Levine⁷
Follow-up CT scan 6 months after an uncomplicated Whipple procedure

Our initial reason for neoadjuvant therapy

Two ways to think about this:
- We did the best we could
- We should not have operated on this patient
Initial experience with multimodality/neoadjuvant therapy for pancreatic cancer

Presented at the SSO, Spring 1992

Preoperative Chemoradiation and Pancreaticoduodenectomy for Adenocarcinoma of the Pancreas

Douglas B. Evans, MD; Tyvin A. Rich, MD; David R. Byrd, MD; Karen R. Cleary, MD; John H. Connelly, MD; Bernard Levin, MD; Chusilp Charnsangavej, MD; Claudia J. Fenoglio, RN; Frederick C. Ames, MD

Arch Surg—Vol 127, November 1992
Surgery-first approach to localized pancreatic cancer

OR

1-2 wks

6-10 wks

Adj Therapy

Recovery from surgery

CT

Diagnosis, staging and preparation for surgery

**Point 1:**
Every operated patient will **NOT** receive adjuvant therapy

**Point 2:**
Surgery changes the platform of Rx – host becomes immunosuppressed or never receives treatment or if receives treatment has a reduced ability to respond
**Not Staged but Borderline Resectable after 2 mo of chemotherapy**

60 yo man from Michigan: referred in **Feb, 2018** as a sequencing dilemma. His CA19-9 was 40 at diagnosis and after 4 cycles of FOLFIRINOX it was 42. His CEA was 2.0 in Feb, not checked at dx.

Feb 2018

---

HS 10917504
After 4 cycles of FOLFIRINOX
HA lymph node got larger (? Significance)
CA19-9: low level elevation, did not go down
(young man, with expectation that he would see the OR)

- Change systemic therapy
- Transition to chemoradiation

Path:
T: 3.3 cm
N: 4/24
Postoperative Complications and Overall Survival After Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma

AMUDHAN PUGALENTHI, MD,1 MLADJAN PROTIC, MD,2 MITHAT GONEN, PhD,3 T. PETER KINGHAM, MD,1 MICHAEL J.D’. ANGELICA, MD,1 RONALD P. DEMATTEO, MD,1 YUMAN FONG, MD,1 WILLIAM R. IARNAGIN. MD,1 AND PETER I. ALLEN. MD1*

Journal of Surgical Oncology 2016;113:188–193

Fig. 3. Survival curve for patients who had no high grade complications (n = 481, black curve) and high grade complications (n = 90) (dotted gray curve).
Surgery First


![Graph showing survival rates and statistical significance levels.](image-url)

**Cum Survival vs. Months after surgery**

- **NoComplication/Adjuvant**: 319.5, 139.0, 62.5, 39.0, 29.0, 19.5
- **NoComplication/No Adjuvant**: 257.5, 83.5, 47.5, 33.5, 19.5, 14.0
- **Complication/Adjuvant**: 296.0, 109.5, 42.5, 19.0, 10.5, 7.5
- **Complication/No Adjuvant**: 260.0, 55.0, 19.0, 14.5, 12.0, 8.5

*Note: The graph illustrates survival rates over months after surgery, with significance levels indicated for different groups.*
Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial


www.thelancet.com Vol 389 March 11, 2017

CT staged

To OR

Recovered

Enrolled

Median CA19-9: 18.7
9% missing values
68% < 37

28 mo

26 mo

Hazard ratio for death: 0.82
stratified log-rank p=0.032

Overall survival (%)

Number at risk

Gemcitabine 366

Gemcitabine plus capecitabine 364

Gemcitabine 302

Gemcitabine plus capecitabine 219

Median survival time = 25.5 months (95% CI 22.7-27.9)

Median survival time = 28.0 months (95% CI 23.5-31.5)
Surgery a bit later (Neoadjuvant-Medical College of Wisconsin)

Aldakkak, *HPB*

Miura, *Surgery*

Christians, *Surgery*

Barnes, *J Gastrointes Surg*

Barnes, *Surgery*

46 months if preop 19-9 NL

37 months

45 mo (resectable)

39 months

31 mo (borderline resectable)
A Phase II Clinical Trial of Molecular Profiled Neoadjuvant Therapy for Localized Pancreatic Ductal Adenocarcinoma

Susan Tsai, MD, MHS,* Kathleen K. Christians, MD,* Ben George, MD,† Paul S. Ritch, MD,† Kulwinder Dua, MD,‡ Abdul Khan, MD,‡ A. Craig Mackinnon, MD, PhD,§ Parag Tolat, MD,¶ Syed A. Ahmad, MD,|| William A. Hall, MD,** Beth A. Erickson, MD,** and Douglas B. Evans, MD*
PRODIGE 24/CCTG PA.6, an Unicancer GI trial: a multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas.

Key Inclusion Criteria
- Histologically confirmed resected pancreatic ductal adenocarcinoma
- Macroscopically complete resection (R0 or R1 resection)
- Patients able to receive chemotherapy within 12 weeks after resection

Key Exclusion Criteria
- Metastatic disease, or macroscopic incomplete tumor removal (R2 resection)
- Postoperative CA 19-9 ≥ 180 U/mL assessed within 21 days of randomization
- Symptomatology
- Major comorbidities
- Inflammatory bowel disease or severe comorbidities
- Concomitant malignancy

PRODIGE 24/CCTG PA.6 trial: study design

NCT01526135
- R0 or R1 resected pancreatic cancer
- postoperative CT-scan mandatory
- CA19-9 level < 180 U/mL within 12 weeks after surgery

Stratification:
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

Randomize
1:1

mFolfirinox
Oxaliplatin 85 mg/m², Leucovorin 400 mg/m², Irinotecan 180 mg/m²*, all at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
Every 2 weeks; 12 cycles
*Reduced to 150 mg/m² after patient 162

Gemcitabine
1000 mg/m², qw 3/4 weeks; 6 cycles

for both arms:
- 6 months of chemotherapy
- CT scans: every 3 months
Recruitment and Analysis

- **Recruitment:** April 2012-October 2016
- **Final accrual:** 493 patients in 77 French and Canadian centres

493/77 = 6.4/center in 4.5 years

Patients baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>mFolfirinox N=247</th>
<th>Gemcitabine N=246</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs)[range]</td>
<td>63 [30-79]</td>
<td>64 [30-81]</td>
<td>0.09</td>
</tr>
<tr>
<td>Gender male</td>
<td>57.5 %</td>
<td>55.6 %</td>
<td>0.67</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>49.8 %</td>
<td>52.5 %</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25.3 %</td>
<td>26.6 %</td>
<td>0.44</td>
</tr>
</tbody>
</table>
FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

Within 12 weeks of surgery

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>21.6</td>
<td>12.8</td>
</tr>
<tr>
<td>OS</td>
<td>54.4</td>
<td>35</td>
</tr>
</tbody>
</table>

**CT** 19-9

**postop** 100% < 180

93% < 90
Adjuvant Chemotherapy With Gemcitabine vs Observation in Patients Undergoing Curative-Intent Resection of Pancreatic Cancer

A Randomized Controlled Trial

CONKO-001

Figure 2. Disease-Free and Overall Survival (Intent-to-Treat Analysis)

JAMA, January 17, 2007—Vol 297, No. 3

Rx started within 6 weeks if possible

<table>
<thead>
<tr>
<th></th>
<th>Gem</th>
<th>Obs</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>13.4</td>
<td>6.9</td>
<td>19-9</td>
</tr>
<tr>
<td>OS</td>
<td>22.1</td>
<td>20.2</td>
<td>Prior to enrollment</td>
</tr>
</tbody>
</table>
Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial


<table>
<thead>
<tr>
<th></th>
<th>G/C</th>
<th>Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>13.9</td>
<td>13.1</td>
</tr>
<tr>
<td>OS</td>
<td>28</td>
<td>25.5</td>
</tr>
<tr>
<td>CT</td>
<td>19-9</td>
<td></td>
</tr>
<tr>
<td>within 3 mo</td>
<td>83%</td>
<td>92.5</td>
</tr>
<tr>
<td></td>
<td>68%</td>
<td>37</td>
</tr>
</tbody>
</table>
Table S6. Treatments after Relapse of Pancreatic Cancer.*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mFOLFIRINOX (N = 127)</th>
<th>Gemcitabine (N = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy†</td>
<td>80 (63.0)</td>
<td>128 (75.7)</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>9 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>38 (47.5)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Gemcitabine + nab-paclitaxel</td>
<td>23 (28.7)</td>
<td>7 (5.5)</td>
</tr>
<tr>
<td>Other gemcitabine-based</td>
<td>2 (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>FOLFOX/XELOX</td>
<td>2 (2.5)</td>
<td>16 (12.5)</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>4 (5.0)</td>
<td>0</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1 (1.2)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>LV5FU2</td>
<td>1 (1.2)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>(Chemo)radiotherapy</td>
<td>16 (12.6)</td>
<td>10 (5.9)</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (4.7)</td>
<td>8 (4.7)</td>
</tr>
<tr>
<td>No treatment</td>
<td>13 (10.2)</td>
<td>10 (5.9)</td>
</tr>
<tr>
<td>Missing data</td>
<td>12 (9.5)</td>
<td>13 (7.7)</td>
</tr>
</tbody>
</table>

* Only the first treatment administered after relapse (excluding second cancers and deaths as first event) was taken into account.

†P=0.16 between groups.

FOLFIRI denotes fluorouracil, leucovorin and irinotecan; LV5FU2 denotes fluorouracil and leucovorin; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; FOLFOX, fluorouracil, leucovorin and oxaliplatin; XELOX, capecitabine and oxaliplatin; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan and oxaliplatin.
FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akouz, M.D., P. Ariès, M.D., Catherine Belibaldo, M.D., Eric Assenat, M.D., Ph.D., Christine Montrey, M.D., Ph.D., for the Groupe Turn.

F 
Gem

PFS 6.4 3.3
OS 11.1 6.8

Table 2. Objective Responses in the Intention-to-Treat Population.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>FOLFIRINOX (N=171)</th>
<th>Gemcitabine (N=171)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (0.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>53 (31.0)</td>
<td>16 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>66 (38.6)</td>
<td>71 (41.5)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>26 (15.2)</td>
<td>59 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Could not be evaluated</td>
<td>25 (14.6)</td>
<td>25 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Rate of objective response†</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. (%)</td>
<td>54 (31.6)</td>
<td>16 (9.4)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival, According to Treatment Group.

Panel A shows overall survival; the median was 11.1 months in the group receiving FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin). Panel B shows progression-free survival; the median was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group.
Table S3. Disease-free Survival Events in the Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Event</th>
<th>mFOLFIRINOX</th>
<th>Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival event — no. (%)</td>
<td>134 (54.2)</td>
<td>180 (73.2)</td>
</tr>
<tr>
<td>First event occurred — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>70 (28.3)</td>
<td>82 (33.2)</td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>33 (13.4)</td>
<td>44 (17.9)</td>
</tr>
<tr>
<td>Locoregional plus distant recurrence</td>
<td>24 (9.7)</td>
<td>42 (17.1)</td>
</tr>
<tr>
<td>Second cancer</td>
<td>2 (0.8)</td>
<td>7 (2.8)</td>
</tr>
<tr>
<td>Second cancer and metastatic disease</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Death as first event</td>
<td>5 (2.0)*</td>
<td>4 (1.6)†</td>
</tr>
</tbody>
</table>

* Including three deaths from intercurrent disease and two deaths from pancreatic cancer.

† Including one toxic death, one death from intercurrent disease, one death from unknown cause and one death from pancreatic cancer.

mFOLFIRINOX denotes modified fluorouracil, leucovorin, irinotecan and oxaliplatin.
Hopkins
Pattern of Recurrence
N = 692
2000-2010
Resectable
Surgery-first
R2 excluded
Periop deaths excluded

LR > 40%

Have to be alive to have a LR
Figure 1. Patterns of any disease recurrence following neoadjuvant therapy (to include XRT) and surgery (n=306)

- No Recurrence (n=120, 39%)
- Local Recurrence (LR) (n=29, 9%)
- Regional Recurrence (RR) (n=19, 6%)
- Distant Recurrence (DR) (n=108, 35%)
- LR + RR (n=6, 2%)
- LR + DR (n=10, 3%)
- RR + DR (n=8, 3%)
Figure 3. Kaplan Meier estimates of overall survival by the site of first disease recurrence (n=306). Abbreviation: SS = single site
Why Radiation Therapy is important

Fig. 5. The growth pattern of a cancer determines the minimum clearance on which the diagnosis of microscopic margin involvement (R1) is to be based. The red dots represent the tumor cells in cancers with a compact (upper part) and a more dispersed growth pattern (lower part). The yellow line indicates the surgical resection margin. The dotted white line indicates a clearance of 1 mm. Although for both tumors the minimum clearance is the same
Why Radiation Therapy is important

Stuff in between that can ruin the day
Will this come off or will it not??

Autonomic nerve tissue enveloping the artery
Autonomic nerve tissue enveloping the artery

Why Radiation Therapy is important
A Randomized, Phase II Clinical Trial of Stereotactic Body Radiation Therapy or Conventionally Fractionated Concurrent Chemotherapy and Radiation Therapy Preoperatively for Resectable or Borderline Resectable Pancreatic Adenocarcinoma "SOFT Pre-Op Trial"

Bill Hall
Beth Erickson
A Phase II Clinical Trial of Molecular Profiled Neoadjuvant Therapy for Localized Pancreatic Ductal Adenocarcinoma

Susan Tsai, MD, MHS,* Kathleen K. Christians, MD,* Ben George, MD,† Paul S. Ritch, MD,† Kulwinder Dua, MD,‡ Abdul Khan, MD,‡ A. Craig Mackinnon, MD, PhD,§ Parag Tolat, MD,¶ Syed A. Ahmad, MD,‖ William A. Hall, MD,** Beth A. Erickson, MD,** and Douglas B. Evans, MD*  

Overall Survival by Clinical Stage

FIGURE 3. Overall survival by clinical stage (n = 130). Median follow-up of all 130 patients was 25 months; 28 months for the 61 patients with resectable PDAC and 21 months for the 69 patients with BLR disease. The median overall survival of all 130 patients was 38 months; 41 months among the 61 patients with resectable PDAC and 33 months for the 69 patients with BLR disease (P = 0.99).
Molecular Profiling

<table>
<thead>
<tr>
<th>SPARC-p</th>
<th>Topo1</th>
<th>RRM1</th>
<th>ENT1</th>
<th>ERCC1</th>
<th>TYMS</th>
</tr>
</thead>
</table>

Neither Gem or 5-FU

Profile Not Predictive: Chemo/XRT

5-FU Based

ERCC

SPARC

Cap/nab

TOPO

FOLFIRINOX

Gem/nab

Gem/Platin

TOPO

Gem/Irino

Gem/XRT

Either Gem or 5-FU

ERCC

SPARC

FOLFIRINOX

Gem/nab

TOPO

FOLFIRI vs. Gem/Irino

Gem/Cap
A Phase II Clinical Trial of Molecular Profiled Neoadjuvant Therapy for Localized Pancreatic Ductal Adenocarcinoma

Susan Tsai, MD, MHS,* Kathleen K. Christians, MD,* Ben George, MD,† Paul S. Ritch, MD,† Kulwinder Dua, MD,‡ Abdul Khan, MD,‡ A. Craig Mackinnon, MD, PhD,§ Parag Tolat, MD,‖ Syed A. Ahmad, MD,‖ William A. Hall, MD,** Beth A. Erickson, MD,** and Douglas B. Evans, MD*  


FIGURE 4. Overall survival by completion of all neoadjuvant therapy and surgery (n = 130). Median follow-up of all 130 patients was 25 months; 28 months for the 107 patients who completed all intended therapy and surgery and 11 months for the 23 patients who were not resected. The median overall survival of all 130 patients was 38 months; 45 months among the patients who completed all neoadjuvant therapy and surgery and 11 months for the 23 patients who were not resected (P < 0.001).
Min F/U of all living patients = 12 mon

<table>
<thead>
<tr>
<th>Adj F</th>
<th>Adj G</th>
<th>Tsai 130</th>
<th>Tsai 107</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>21.6</td>
<td>12.8</td>
<td>20</td>
</tr>
<tr>
<td>OS</td>
<td>54.4</td>
<td>35</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L/R %</th>
<th>Dist %</th>
</tr>
</thead>
<tbody>
<tr>
<td>mFOLFIRINOX</td>
<td>23</td>
</tr>
<tr>
<td>Gem</td>
<td>35</td>
</tr>
</tbody>
</table>

Site of 1st Failure

<table>
<thead>
<tr>
<th>Site</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>7</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>16</td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
</tr>
<tr>
<td>Local</td>
<td>4</td>
</tr>
<tr>
<td>Multisite</td>
<td>15</td>
</tr>
<tr>
<td>All local (total)</td>
<td>16</td>
</tr>
</tbody>
</table>
# Goals of Treatment Sequencing for Localized Pancreatic Cancer

Douglas B. Evans, MD, Mandana Kamgar, MD, MPH, and Susan Tsai, MD, MHS

1Pancreatic Cancer Program, Department of Surgery, The Medical College of Wisconsin, Milwaukee, WI; 2Pancreatic Cancer Program, Department of Medicine, The Medical College of Wisconsin, Milwaukee, WI

## TABLE 2
The importance of pre-treatment staging for the development of goals of therapy; specifically, the likelihood of completing all planned neoadjuvant therapy and surgical resection of the primary pancreatic cancer

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Potential for completion of all intended neoadjuvant therapy and surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>90</td>
</tr>
<tr>
<td>Borderline Resectable</td>
<td>75</td>
</tr>
<tr>
<td>Locally Advanced A</td>
<td>60</td>
</tr>
<tr>
<td>Locally Advanced B</td>
<td>25</td>
</tr>
</tbody>
</table>

Data generated from the following manuscripts: Refs. 10, 12, 18, 19
Neoadjuvant Therapy & Surgery for Pancreatic Cancer

Guiding Principles:

- Patient selection
  Do not operate on a high risk patient, who needs a high risk operation (high degree of difficulty), who also has a high risk oncologic profile (inc. CA19-9, for example)

- Survival duration is the primary end point
- Quality of life is the co-primary endpoint

- Survival duration < 1 yr: surgery provided no clinical benefit
- Survival duration 1-2 yrs: surgery may have done something
- Survival duration > 2 yrs: surgery-associated clinical benefit assumed

- Commitment to multimodality therapy
- Field is moving to a surgery last approach (after chemo and chemoradiation)
62 man with locally advanced (type A) panc CA (celiac encasement) 
Healthy missionary minister

<table>
<thead>
<tr>
<th>Component</th>
<th>Latest Ref Rng &amp; Units</th>
<th>8/13/2018</th>
<th>10/8/2018</th>
<th>1/7/2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARCINOEMBRYONIC ANTIGEN</td>
<td>&lt;=4.7 ng/mL</td>
<td>11.0 (H)</td>
<td>10.8 (H)</td>
<td>3.4</td>
</tr>
<tr>
<td>CA199</td>
<td>&lt;=35.0 unit/mL</td>
<td>964.3 (H)</td>
<td>764.0 (H)</td>
<td>33.5</td>
</tr>
</tbody>
</table>

FOLFIRINOX → no response → Gem-nab

Aug, 2018

Oct, 2018

Jan, 2019


Decision made here that the tumor was operable – transition to chemoXRT with preoperative intent
62 man with locally advanced type A panc CA – restaged after chemoXRT; prior to surgery

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CARCINOEMBRYONIC ANTIGEN</td>
<td>&lt;=4.7 ng/mL</td>
<td>11.0 (H)</td>
<td>10.8 (H)</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>CA199</td>
<td>&lt;=35.0 unit/mL</td>
<td>964.3 (H)</td>
<td>764.0 (H)</td>
<td>33.5</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Be careful of the phrenic artery

Distal common hepatic artery looks good

Left gastric artery has significance
Encased in this patient

Origin of the GDA looks good
Surgery March 18, 2019
Path:
Mod diff adeno
Nodes: 2/26
Margins neg

Ligated left gastric artery

Saph vein graft from celiac origin to CHA
- Please always consider a clinical trial: our current focus combines adaptive neoadjuvant therapy with PM.

- Field is moving to a surgery last sequencing schema.

- Local control will become more significant as survival duration continues to increase.

(by 2022: responding disease will be viewed as different than stable disease; preop chemoXRT will no longer be debated)
Neoadjuvant Therapy:
- the best platform for the study of anti-cancer Rx
- the only platform for window of opportunity trials
- Roger was treated on a novel anti-stem cell WOOT at MCW (Dr. Susan Tsai)

NED: October 30, 2018