Pancreatic Cancer: Light at the End of the (Very Long) Tunnel

Daniel Renouf, MD, MPH, FRCPC
Medical Oncologist, BC Cancer Agency
University of British Columbia
In compliance with accreditation, we require the following disclosures to the session audience:

<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Novartis; Bayer</td>
</tr>
<tr>
<td>Employee</td>
<td>N/A</td>
</tr>
<tr>
<td>Consultant</td>
<td>N/A</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>N/A</td>
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<tr>
<td>Speakers Bureau</td>
<td>N/A</td>
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<tr>
<td>Honoraria</td>
<td>Celgene</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>Celgene, Shire</td>
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</tbody>
</table>
Do you think we will make significant strides in the treatment of pancreatic cancer in next 10 years?

A) No
B) Yes improve overall survival by 5-10%
C) Yes improve overall survival by 10-20%
D) Yes improve overall survival by over 20%
Optimism Disclosure

• I am very optimistic of the future of pancreatic cancer treatment

• But...I am a very optimistic person!

  – I’m a medical oncologist
  – I specialize in pancreatic cancer
  – I still think “holidays” will be “relaxing” despite having a 5 year old and 2 year old twins!
Objectives

1. Discuss recent updates in systemic therapy options in the metastatic setting
2. Discuss the role of palliative radiation
3. Review genetic issues
4. Review adjuvant systemic and radiation therapy
5. Future directions
Pancreatic cancer incidence and deaths are rising

Pancreatic cancer will become 2nd most lethal cancer in the US by 2030

Pancreatic cancer rates will double in Canada by 2030

Based on annual reports from the Canadian Cancer Society and Statistics Canada.

Rahib et al., Cancer Res (2014) 74:2913-2921
Gemcitabine vs. 5-FU

Burris et al, JCO, 1997
Molecularly targeted therapy

- Preclinical studies have demonstrated several molecular pathways that may be important in pancreatic tumorigenesis

Jones et al, Science, 2008
1 year survival improved from 17-23% ($p=0.023$)

Moore et al, JCO, 2007
Studies with biological therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine versus gemcitabine and erlotinib</td>
<td>5.9 vs 6.2 (p = 0.038)</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine and cetuximab</td>
<td>6 vs 6.5 (p = NS)</td>
</tr>
<tr>
<td>Gemcitabine and cisplatin versus gemcitabine, cisplatin and cetuximab</td>
<td>7.5 vs 7.8 (p = NS)</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine and bevacizumab</td>
<td>5.7 vs 6 (p = NS)</td>
</tr>
<tr>
<td>Gemcitabine, bevacizumab and erlotinib versus gemcitabine, bevacizumab</td>
<td>7.2 vs 7.8 (p = NS)</td>
</tr>
<tr>
<td>Gemcitabine and erlotinib versus gemcitabine, erlotinib and bevacizumab</td>
<td>6 vs 7.1 (p = NS)</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine and tipifarnib</td>
<td>6.1 vs 6.4 (p = NS)</td>
</tr>
<tr>
<td>Gemcitabine versus gemcitabine and marimastat</td>
<td>5.5 vs 5.5 (p = NS)</td>
</tr>
<tr>
<td>Gemcitabine versus BAY 12-9566</td>
<td>6.7 vs 3.7 (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

Renouf and Moore, Expert Rev. Anticancer Ther. 2010
What are we doing wrong?

- Need for more active chemotherapy/combinations
- Need for improved pre-clinical models
- Need for agents that target the microenvironment

Philip et al, JCO, 2009
New Chemotherapy Combinations:

**PRODIGE 4/ACCORD 11 Trial**

Patients with metastatic pancreatic cancer

(N = 342)

- **FOLFIRINOX** (n = 171)
- **Gemcitabine** (n = 171)

for both arms:
- CT scans: obtained every 2 mos
- 6 mos of chemotherapy recommended

Stratified by

- Center
- Performance score 0 vs 1
- Location of the tumor: head vs other location of the primary

Conroy T, NEJM, 2011
PRODIGE 4/ACCORD 11: Overall Survival

Median OS, Mos
- FOLFIRINOX: 11.1
- Gemcitabine: 6.8

HR: 0.57 (95% CI: 0.45-0.73)
Stratified log rank test $P < .0001$

Patients at Risk, n
- 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

RR 31.6 vs. 9.4%

Time to definitive QoL degradation

Kaplan-Meier estimation for TUDD of Global health status/QoL (MCID 10 points)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>Folfirinox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>157</td>
<td>163</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

p = .001
**MPACT: Randomized Phase III Study**

**Planned N = 842**
- Stage IV
- No prior treatment for metastatic disease
- KPS ≥ 70
- Measurable disease
- Total bilirubin ≤ ULN

**Primary endpoint:**
- OS

**Secondary endpoints:**
- PFS and ORR by independent review (RECIST)

**Safety and tolerability**
- by NCI CTCAE v3.0

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

1:1, stratified by KPS, region, liver metastasis

**Gemcitabine**
- 1000 mg/m² IV qw for 7/8 weeks then qw 3/4 weeks

- With 608 events, 90% power to detect OS
- HR = 0.769 (2-sided $\alpha = 0.049$)
- One interim analysis for futility
- Treat until progression
- CT scans every 8 weeks

Gemcitabine and Nab-paclitaxel

**OS, months**

<table>
<thead>
<tr>
<th>Events/n</th>
<th>Median (95% CI)</th>
<th>75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>380/431</td>
<td>8.7 (7.89 - 9.69)</td>
<td>14.8</td>
</tr>
<tr>
<td>394/430</td>
<td>6.6 (6.01 - 7.20)</td>
<td>11.1</td>
</tr>
</tbody>
</table>

HR 0.72
95% CI, 0.620 - 0.825
P < 0.0001

**Patients at Risk**

- **nab-P + Gem:** 431 357 284 208 144 84 48 34 25 16 10 6 5 2 1 0
- **Gem:** 430 340 231 149 90 47 27 19 14 8 4 2 0 0 0 0
## Gemcitabine + nab-Paclitaxel vs. FOLFIRINOX

<table>
<thead>
<tr>
<th></th>
<th>FOLFIRINOX</th>
<th>nab-P + Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>342</td>
<td>861</td>
</tr>
<tr>
<td>Sites of accrual</td>
<td>France</td>
<td>International</td>
</tr>
<tr>
<td>PS included</td>
<td>ECOG 0,1</td>
<td>KPS 70-100</td>
</tr>
<tr>
<td>Survival in Gem arm</td>
<td>6.8 mos</td>
<td>6.7 mos</td>
</tr>
<tr>
<td>Survival in experimental arm</td>
<td>11.1 mos</td>
<td>8.5 mos</td>
</tr>
<tr>
<td>HR for OS</td>
<td>0.57</td>
<td>0.72</td>
</tr>
<tr>
<td>HR for PFS</td>
<td>0.47</td>
<td>0.69</td>
</tr>
<tr>
<td>RR</td>
<td>31.6</td>
<td>23</td>
</tr>
</tbody>
</table>
Recent Updates:
Any New Options?
Immune Checkpoint

Postow et al, JCO, 2015
Hypothesis

- Mutations have been shown to encode proteins that can be recognized and targeted by the immune system.

- Average tumor has dozens of somatic mutations; Mismatch repair deficient tumors harbor thousands of mutations.

- Immune augmentation with PD-1 blockade may be highly effective in mismatch repair deficient tumors.
Mutations per tumor

Mismatch-repair proficient colon cancers

Mismatch-repair deficient colon cancers

Mutations per tumor

Presented By Dung Le at 2015 ASCO Annual Meeting
PD-1 Blockade in Mismatch Repair Deficient Non-Colorectal Gastrointestinal Cancers


The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
Ohio State University Comprehensive Cancer Center, Columbus, OH
Providence Cancer Center, Portland, OR
Stanford University School of Medicine, Stanford, CA
University of Pittsburgh, Pittsburgh, PA
National Cancer Institute, Bethesda, MD
Merck & Co., Inc., Kenilworth, NJ

Presented By Dung Le at TBD
Study Design

Colorectal Cancers

- Cohort A: Deficient in Mismatch Repair (n=25)
- Cohort B: Proficient in Mismatch Repair (n=25)

Non-Colorectal Cancers

- Cohort C: Deficient in Mismatch Repair (n=21)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks
- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MMR-deficient Gl non-CRC n=17 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age – years</td>
<td>60 (34-92)</td>
</tr>
<tr>
<td>Gender-female</td>
<td>5 (29)</td>
</tr>
<tr>
<td>ECOG PS-zero</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Tumor Type</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>4 (23)</td>
</tr>
<tr>
<td>Ampullary</td>
<td>4 (23)</td>
</tr>
<tr>
<td>Biliary</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Gastric</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Liver Mets</td>
<td>11 (65)</td>
</tr>
<tr>
<td>Median Prior Regimens</td>
<td>2</td>
</tr>
</tbody>
</table>

Presented By Dung Le at TBD
# Objective Responses

<table>
<thead>
<tr>
<th>Type of Response-no (%)</th>
<th>MMR-deficient GI non-CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Stable Disease (Week 12)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

**Objective Response Rate (%)**

- **95% CI**
  - 23-72

**Disease Control Rate (%)**

- **95% CI**
  - 50-93

**Median Follow Up (mos)**

- 5.3

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1 Patients were considered not evaluable if they did not undergo a 12 week scan due to clinical progression.

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Presented By Dung Le at TBD
Durability of Response
Progression-Free and Overall Survival

PFS = Non-estimable (NE)

OS = 21 Mos
Second Line Therapy: NAPOLI Trial

- Phase III trial of nanoliposomal irinotecan (MM-398/Onivide) alone vs. 5-fluorouracil alone vs. combination

Median OS
6.1 vs. 4.2 months

Radiation Therapy in Advanced Disease (LAP07 Trial)

JAMA, 2016
Early Stage and Locally Advanced PDAC

- A number of trials ongoing
  - Resectable
    - Neoadjuvant FOLFIRINOX vs. Gem/Nab-Paclitaxel
    - Adjuvant FOLFIRINOX
    - Adjuvant Gem/Nab-Paclitaxel
  - Borderline Resectable
    - FOLFIRINOX +/- SBRT
  - Locally Advanced
    - Role of high dose radiation
- Multidisciplinary assessment is key
ESPAC-4: A multicenter, international, open label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP), versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma


NCRI Pancreatic Cancer Sub-Group
CRUK Liverpool Cancer Trials Unit

EudraCT#: 2007-004299-38
ISRCTN#: 43482138
CRUK#: C245/A8968/A20830

ASCO, Chicago 06/06/2016 8:00 AM - 11:00 AM LBA4006

Presented By John Neoptolemos at 2016 ASCO Annual Meeting
ESPAC-1, N=289, NEJM 2004: Benefit for Chemotherapy

2x2 Factorial: Survival by Adjuvant Chemotherapy

Survival rates 2-year 5-year
No CT: 30.0% 8.4%
CT: 39.7% 21.1%
HR=0.71 (0.55, 0.92), p=0.009

Presented By John Neoptolemos at 2016 ASCO Annual Meeting
CONKO-001: FINAL RESULTS

Overall Survival

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

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

Log Rank p = .005

5-year survival
20.7% vs. 10.4%

Oettle et al, JAMA, 2007
ESPAC-3, N=1,088: Gemcitabine not better than 5-FU/FA

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

$\chi^2_{LR} = 0.74$, $p = 0.39$, $HR_{GEM \text{ vs } 5FU/FA} = 0.94$ (95%CI: 0.81, 1.08)

Neoptolemos et al JAMA 2010; 304: 1073-81
Presented at the 2016 ASCO Annual Meeting by John Neoptolemos.

**ESPAC - 4**

- **722 patients**
- Pancreatic ductal adenocarcinoma
- ‘Curative’ resection ≤ 12 weeks

**RANDOMISATION at Liverpool Cancer Trials Unit**

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

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

Previous Phase III trial by same group in advanced setting demonstrated improvement in PFS but not significant for OS (7.1 vs. 6.2 months, p=0.08)
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)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Gem</th>
<th>366</th>
<th>302</th>
<th>207</th>
<th>109</th>
<th>61</th>
<th>27</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>GemCap</td>
<td>364</td>
<td>328</td>
<td>219</td>
<td>139</td>
<td>83</td>
<td>50</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>
## ESPAC Trials: 5 Year Overall Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>No. of pts (N=2092)</th>
<th>5-Year OS (95% CI)</th>
<th>Stratified Log-Rank $X^2$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESPAC-1</td>
<td>5FU/FA</td>
<td>149</td>
<td>21 (14.6 – 28.5) %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No chemotherapy</td>
<td>143</td>
<td>8.0 (3.8 – 14.1) %</td>
<td>7.03</td>
<td>0.030*</td>
</tr>
<tr>
<td></td>
<td>Chemoradiotherapy (5FU/Rad)</td>
<td>145</td>
<td>10.8 (6.1 – 17.0) %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPAC-3</td>
<td>GEM</td>
<td>539</td>
<td>17.5 (14.0 – 21.2) %</td>
<td>0.74</td>
<td>0.390*</td>
</tr>
<tr>
<td></td>
<td>5FU/FA</td>
<td>551</td>
<td>15.9 (12.7 – 19.4) %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPAC-4</td>
<td>GEM</td>
<td>366</td>
<td>16.3 (10.2 – 23.7) %</td>
<td>4.61</td>
<td>0.032†</td>
</tr>
<tr>
<td></td>
<td>GEMCAP</td>
<td>364</td>
<td>28.8 (22.9 – 35.2) %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stratification factor: resection margin status; †stratification factors: resection margin status and country
Adjuvant therapy for PDAC

- GEMCAP is now an option for resected PDAC

- Results of APACT and PA.6 will be eagerly awaited

- Role of neoadjuvant chemotherapy is being explored
Exciting time in Oncology

● Entering a new era
  – Chemotherapy for all (Up until 10 years ago)
  – Targeted therapy, basic molecular markers (KRAS) (10 years ago to present)
  – Mix of chemotherapy, targeted therapy, and immunotherapy

● How can we get there in pancreatic cancer?
Critical focus areas in pancreatic cancer

- Inter-tumoral heterogeneity
- Clinically relevant biomarkers
- New treatment modalities
Pancreatic cancer subtypes (or lack thereof...)

- Pancreatic ductal adenocarcinoma (PDAC) 95%
- Pancreatic neuroendocrine tumour (PNET) 5%
Inter-tumoral heterogeneity of pancreatic cancer: genetic mutations

**Sporadic PDAC**
- KRAS (95%)
- p16/CDKN2A (95%)
- p53 (75%)
- SMAD4 (50%)
- BRAF, MYB, AKT2, EGFR, MAP2K4, STK11, TGFBR1, TGFBR2, ACVR1B, ACVR2A, FBXW7, EP300 (<20%)

**Familial PDAC**
- BRC1A2
- PALB2
- CDKN2A
- STK11/LKB1
- PRSS1
Critical focus areas in pancreatic cancer

- Inter-tumoral heterogeneity
- Clinically relevant biomarkers
- New treatment modalities
Recently Proposed Subtypes

Bailey et al, 
Unstables as Exceptional Responders

“Unstable” subtype (>200 structural variation events) is associated with BRCA mutation signature

Patients with “unstable” PDAC subtype responded well to therapy

BCCA Personalized Oncogenomics

WEEK 0
ONCOLOGY CONSULT AND CONSENT
SAMPLE ACQUISITION
PATHOLOGY ASSESSMENT
LIBRARY CONSTRUCTION
QUALITY CONTROL

WEEK 2
SOMATIC MUTATIONS
PANEL SEQUENCING
WGS/WTS SEQUENCING

WEEK 3
SEQUENCING RESULTS

WEEK 4-6
GENERATION OF GENOMICS REPORT
MULTIDISCIPLINARY CLINICAL GENOMICS TUMOR BOARD
ONCOLOGIST DISCUSSES RESULTS WITH PATIENT
PanGen study schema

**Recruit 120 patients**

**Baseline**
- CT Scan
- Core Biopsy
  1. Clinical
  2. WGS
  3. WTS
  4. Metab.
  5. Bank/PDX
- Plasma, serum
  Ca19-9
  Metabolomics
- Whole blood
  WTS
  (germline DNA)

**Prospective clinical data collection**

**First line therapy**
- FOLFIRINOX or Gemcitabine/nab-paclitaxel based regimes

**Analysis**
- Biopsy cohort
  N = 70
- WGS
- WTS
- Proteogenomics
- Metabolomics

**Plasma, serum**
- Ca19-9
- Metabolomics

**CT Scan**
- every 8 weeks until progression

**Plasma, serum every 4 weeks until progression**
- Ca19-9
- Metabolomics

**Progression**

**Outcome data**

**Targeted Analysis**
- Archival cohort
  N = 50

**EPPIC Knowledge Bank and Biorepository**
- Genomic
- Transcriptomic
- Proteogenomic
- Metabolomic

**Clinical outcome data**

**Biobank data (ATM system)**

**Metastatic PDAC patients eligible for biopsy**

Registration
Critical focus areas in pancreatic cancer

- Inter-tumoral heterogeneity
- Clinically relevant biomarkers
- New treatment modalities
New Targets

Chemotherapy combined with Immunotherapy

- Limited activity of single agent PD-L1 inhibition in PDAC (MMR proficient)
- Mechanism of resistance may be related to cancer associated fibroblasts (CAF)
  - Depletion may induce sensitivity to PD-1/PD-L1 inhibition (Feig, C. et al. 2013)
- Nab-paclitaxel depletes CAFs
- Chemotherapy may induced neo-antigen release
CCTG PA.7 study schema

Baseline
CT Scan
Diagnostic biopsy
Serum Ca19.9

1. Gemcitabine + nab-paclitaxel + Durvalumab + Tremelimumab

CT Scan every 8 weeks until progression

Plasma, serum every 4 weeks until progression
Ca19-9

Primary Endpoint: OS

Metastatic PDAC patients eligible for biopsy (treatment naïve)
Multidisciplinary Team
Summary

- Evolving biomarkers and therapeutic options for pancreatic cancer
- Entering era of increasing molecular sub-stratification (BRCA, MMR)
- Multidisciplinary assessment key
- Reason for Optimism!
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McGill University
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