Neoadjuvant treatment in potentially resectable Pancreatic Cancer

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Beatson West of Scotland Cancer
Pancreatic Cancer

- Estimated to become the leading cause of cancer death this year
- 5% alive at 5 years
- Average survival ~6 months
- 90% die within a year
- Surgery only cure (~20%)
- Mortality unchanged for 50 years
- Chemotherapy modestly effective –significant responses in undefined subgroups
Pancreas cancer projected outlook

Projected cancer deaths (Thousands)

Year

2017 2020 2030 2040

Lung and bronchus
Pancreas
Colon and rectum
Breast
Prostate

Adapted from Rahib L et al. 2014 Cancer Res 74:2913 and NCI SEER 2017
1 Year survival
5 Year survival (cure)
Reasons

• High rate of metastatic disease at presentation
• High rates of early metastatic disease.
• Often these present within weeks of surgery
• Even with localised disease there is a 80% chance of having positive margin at time of surgery. In these cases average survival is approx 24 months
Good news in pancreatic cancer!

- ESPAC 3
- Median Survival - Just under 2 years

"I have good news and bad news. The good news, you're not a hypochondriac..."
Even better news!

- ESPAC 4 ¹ (Gem vs Gem/Cap)
- Median survival 28 months
- BUT
- The majority of the benefit was in R0 patients getting doublet
- R1 rates = 60% (National averages may be up to 80%!!)

¹ Lancet 2017. Neoptolemos et al
Hazard ratio for death: 0.82 (95% CI, 0.68–0.98); stratified log-rank p=0.012

Number at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>366</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine</td>
<td>364</td>
</tr>
<tr>
<td>Gemcitabine-positive</td>
<td>279</td>
</tr>
<tr>
<td>Gemcitabine-negative</td>
<td>147</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine-positive</td>
<td>221</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine-negative</td>
<td>343</td>
</tr>
</tbody>
</table>

Time from randomisation (months)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival time (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>25.5 months (22.7–27.9)</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine</td>
<td>28.0 months (23.5–31.5)</td>
</tr>
<tr>
<td>Gemcitabine-positive</td>
<td>23.0 months (21.6–26.2)</td>
</tr>
<tr>
<td>Gemcitabine-negative</td>
<td>27.9 months (25.8–34.5)</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine-positive</td>
<td>23.7 months (20.7–27.5)</td>
</tr>
<tr>
<td>Gemcitabine plus capcitabine-negative</td>
<td>39.5 months (32.0–58.0)</td>
</tr>
</tbody>
</table>

X² (1) trend-14.83, p=0.0001

n = 217


Median survival
26.5 mths R0
16.5 mths R1

P < 0.0001
INSANITY:
doing the same thing over and over again and expecting different results.

~ Albert Einstein
Neoadjuvant (before definitive treatment) approach

• Staging:
  – MRI of liver identifies low volume metastatic disease in approx 20% of patients preventing futile surgery.

• Treatment:
  – By using treatment to potentially kill off microscopic mets (chemo) and to improve chance of clear margins (radiotherapy)
  – Historical experience “MAGIC” + Rectal ca. Neoadj much more deliverable
Glasgow approach (last 3 years)

- 3/12 neoadjuvant chemo either Folfirinox or Gemcitibine / Capecitibine
- If no progression
- Then either chemoRT or SABR (SPARC trial)
Stage dependent survival, including patients not undergoing resection. (p=0.001)

Grose et al. Jrnl Gastro Intestinal Onc. 2017

<table>
<thead>
<tr>
<th>Baseline resection category</th>
<th>number</th>
<th>Median Survival months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline resectable</td>
<td>45</td>
<td>22.2 (18.8 – 25.5)</td>
</tr>
<tr>
<td>(microscopic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline Resectable</td>
<td>19</td>
<td>18.5 (9.3 – 27.7)</td>
</tr>
<tr>
<td>(macroscopic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>19</td>
<td>9.0 (6.9-11.0)</td>
</tr>
<tr>
<td>Multi-visceral</td>
<td>2</td>
<td>10.6 (-)</td>
</tr>
</tbody>
</table>
Stage-dependent survival for those undergoing radical resection (p<0.001)

<table>
<thead>
<tr>
<th>Baseline resection category</th>
<th>Number</th>
<th>Median Survival months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline Resectable (microscopic)</td>
<td>30</td>
<td>37.0 (18.2 – 55.7)</td>
</tr>
<tr>
<td>Borderline Resectable (macroscopic)</td>
<td>3</td>
<td>11.5 (8.8 – 14.2)</td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Multi-visceral</td>
<td>1</td>
<td>6.9 (-)</td>
</tr>
</tbody>
</table>
Results
Resected patients only

Neoadjuvant cohort  38.0mths (95%CI: 35.1 – 40.8)
Primary Resection cohort  21.0mths (95%CI: 13.5 - 28.5)
Results

Tumor Regression: Implications

Patients categorized into 3 subgroups:
- Complete or near complete response
- Moderate response
- Minimal response

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete or near complete response</td>
<td>15</td>
<td>31%</td>
</tr>
<tr>
<td>Moderate response</td>
<td>10</td>
<td>21%</td>
</tr>
<tr>
<td>Minimal response</td>
<td>23</td>
<td>48%</td>
</tr>
</tbody>
</table>

**Cumulative Survival Analysis**

- Complete Response: 15 months (31%)
- Moderate Response: 10 months (21%)
- Minimal Response: 23 months (48%)

**P-values**
- Complete vs. Minimal: P = 0.03
- Complete vs. Moderate: P = 0.011
• How do we target/identify this group of good responders

• 90% FFX
• 85% CRT
• All but 1 R0…. 
Whole genomes redefine the mutational landscape of pancreatic cancer

Waddell et al. Nature 2015
Molecular classes and transcriptional networks defining PDAC

- 4 classes identified
  - Squamous
  - Aberrantly differentiated endocrine exocrine (ADEX)
  - Pancreatic progenitor
  - Immunogenic

- ADEX tumors display upregulation of genes that regulate networks involved in KRAS activation
- Targeting of KRAS has not been successful to date

Driver Gene Analysis

Genomic analyses identify molecular subtypes of pancreatic cancer

- N = 457
- MutSigCV2
- Oncodriver FM
- HOTNET2
- 32 recurrently mutated genes
- 10 molecular mechanisms

BRCA/FA defective: sensitive to DNA damaging agents & radiation

Platinum Exceptional Responder

Exceptional Responder

ICGC_0006
UNSTABLE / SOMATIC BRCA2 Biallelic
BRCA signature Rank 14
Complete radiological & CA19.9 response

Waddell et al. Nature 2015
Platinum responders are enriched by high BRCA signature ranking with overlapping unstable genomes and mutations in BRCA DNA maintenance pathway genes. 

Waddell et al. Nature 2015
A Dynamic Platform for Precision Oncology
Therapeutic Development
For Pancreatic Cancer

Molecular Pathology
“Knowledge Bank”

Deep interrogation of
Biospecimens to define
Mechanisms of response
and resistance

Education & Training
Forward and Backward Translation

Prioritised Target
Vulnerabilities

Master Protocol:
“Find the Trial for the Patient”

Molecular Mechanisms
of Disease
PRIMUS 002

A Precision-Panc Study

An umbrella phase II study examining two neo-adjuvant regimens.

(FOLFOX-A and AG) in resectable and borderline resectable PDAC

Focusing on biomarker and liquid biopsy development
PRIMUS-002 (Parallel FOLFOX-A and AG)

- Key Clinical Question:
  Are DDR defective tumours less likely to progress during platinum-containing neoadjuvant therapeutic regimen in resectable and borderline resectable PDAC

- Key Objectives:
  1. Define and refine biomarker of therapeutic responsiveness in FOLFOX-A
  2. Exploratory analyses of biomarkers of therapeutic responsiveness in AG
  3. Tumour clonal evolution analysis using serial biopsies
  4. Study of resistance mechanisms
  5. Feasibility of liquid biopsies
TRIAL OBJECTIVES

- To define and refine biomarker of therapeutic responsiveness in FOLFOX-A
- To perform exploratory analysis of biomarkers of therapeutic responsiveness to *nab*-paclitaxel and gemcitabine (AG)
- Survival
- Safety of multimodality therapy in localised pancreatic cancer
- To study resistance mechanisms
- To define the feasibility of liquid biopsies
Trial Population

- In the initial stage 89 patients will be registered to the study to obtain 62 patients on FOLFOX-A (assuming 70% of patients recruited are eligible for this arm as per historical data from Glasgow Royal Infirmary).

- This will increase to 178 in the expansion phase to obtain 124 patients on FOLFOX-A.

- Initially West of Scotland with the Christie opening in future (also potential for further centres pending success in feasibility)
Trial Schema

PRIMUS-002

An umbrella phase II study examining two neo-adjuvant regimens (FOLFOX-A and AG) in resectable and borderline resectable Pancreatic Ductal AdenoCarcinoma (PDAC), focusing on biomarker and liquid biopsy development.

Phase 1
- Safety
  - YES: Chemo + Chemorad
  - NO: Chemotherapy Alone

Phase 2
- IMRT
- Surgery
- NGS Characterisation
  - Cancer gene panel +/− WGS
  - CT
  - MRI
  - PET
  - CA 19.9
  - EUS + Biopsy

Baseline:
- CT
- MRI
- EUS + Biopsy
- PET
- CA 19.9
- Liquid biopsy

Resectable & Borderline Resectable PC
- PS 0, Age ≤ 75
- PS 1, Age ≤ 70

FOLFOX-Abraxane

Abraxane-Gemcitabine
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