Management of advanced pancreatic cancer: treatments and outcomes

Dr Naureen Starling
Consultant Medical Oncologist
Royal Marsden, London
Clinical Challenge: Pancreatic Ductal Adenocarcinoma (PDAC)

Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, UK 2013-2015

http://info.cancerresearchuk.org/cancerstats
Clinical Challenge: Age-Standardised Five-Year Net Survival (Aged 15-99), England and Wales, 2010-2011

http://info.cancerresearchuk.org/cancerstats
Clinical Challenges and Treatment

All Pancreatic Cancer (PDAC)

Localised ~40%
- Resectable
  - Surgery + adjuvant chemotherapy
- Borderline Resectable
  - Neo-adjuvant therapy

Unresectable
- Oligometastatic Disease
  - ? Optimum strategy
    - ? Any role for downsizing, surgery, RFA, radiotherapy
- Disseminated Disease
  - Palliative Chemotherapy or BSC
First-line Treatment of Metastatic PDAC

- **Gemcitabine** 6m, Response rate (RR) 8%
- **Gemcitabine + erlotinib** 6m, RR 8%
- **Gemcitabine + capecitabine** 7m, RR 19%
- **Gemcitabine + nab-paclitaxel** 8m, RR 23%
- **FOLFIRINOX** 11m, RR 31%

Median overall survival (Months)
Second and subsequent line treatment

Historically limited utilisation but ~40-50% patients fit for 2\textsuperscript{nd} line treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Agents</th>
<th>No. pts</th>
<th>mOS (months)</th>
<th>PFS (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONKO-01</td>
<td>OFF vs. BSC</td>
<td>46</td>
<td>9.09 vs. 7.90 (p=0.03)</td>
<td>Unknown</td>
<td>Terminated early</td>
</tr>
<tr>
<td>(Pelzer et al. 2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONKO-003</td>
<td>FF vs. OFF</td>
<td>168</td>
<td>5.9 vs. 3.3 (p=0.01)</td>
<td>2.9 vs 2 (p=0.019)</td>
<td>Safety similar PN</td>
</tr>
<tr>
<td>(Oettle et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANCREOX</td>
<td>mFOLFOX6 vs. 5-FU + FA</td>
<td>108</td>
<td>6.1 vs. 9.9 (p=0.02)</td>
<td>2.9 vs 3.1 (p=0.99)</td>
<td>BUT unequal PDT and Rx discontinuation</td>
</tr>
<tr>
<td>(Gill et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAPOLI-1</td>
<td>MM398+5FU + FA vs MM398</td>
<td>417</td>
<td>6.1 vs. 4.2 (p=0.012)</td>
<td>3.1 vs 1.5 (p=0.0001)</td>
<td>Not NICE approved</td>
</tr>
<tr>
<td>(Von Hoff et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Suggested treatment approach

Metastatic PDAC

- Poor PS
  - BSC
  - Single Agent Gemcitabine

- Good PS
  - FOLFIRINOX
  - Gem-Nab-Paclitaxel
  - Gemcitabine combination

Clinical trial
The HPB Multi-disciplinary Team

- Medical Oncologist
- Specialist Surgeon
- Clinical Oncologist
- Radiologist
- Interventional Radiologist
- Nuclear Medicine
- Histo-pathologist
- Hepatologist
- Gastro-enterologist
- Dietician
- Clinical Nurse Specialist
- Active Symptom Control

The Patient

Driving Innovation
Adopting Innovation
Evidence-based practice
Patient Centered Care
Clinical Challenges and Treatment

All Pancreatic Cancer (PDAC)

Localised ~40%
- Resectable
  - Surgery + adjuvant chemotherapy
- Borderline Resectable
  - Neo-adjuvant therapy
- Unresectable
  - ? Optimum strategy
  - ? Any role for downsizing, surgery, RFA, radiotherapy

Metastatic ~60%
- Oligometastatic Disease
- Disseminated Disease
  - Palliative Chemotherapy or BSC

CLINICAL & TRANSLATIONAL RESEARCH
Novel therapeutic targets in pancreatic cancer
PRECISION PANC: A Dynamic Platform for Therapeutic Development

**DISCOVERY**

Well-annotated, deeply molecularly characterised patient cohorts to define:

- Novel Pathophysiology;
- Therapeutic Targets; Clinical Features; Actionable Segments;
- Biomarker Discovery; Resistance Mechanisms; Clonal Evolution; Predisposition;
- Molecular Taxonomy

Enabling Data Access and Analysis for Researchers from all backgrounds

**CLINICAL DEVELOPMENT**

**Primus**

Pancreatic Cancer Individualised Multi-arm Umbrella Study

“Master Protocol” for Clinical Testing of Molecular Driven Therapeutic Selection and Biomarker Discovery/Development

**PRE-CLINICAL DEVELOPMENT**

Next-Generation Model Systems
- Biology and Mechanism
- Novel Targets
- Therapeutic Testing
- Biomarker Development

**PredICT™**

A platform for capturing, assembling, combining, analysing and visualising data

Pre-clinical Platform of Evidence

Slide courtesy of Andrew Biankin
RM/ICR NIHR BRC Clinical & Translational Research Themes

**Genotypes, Phenotypes and Cancer Evolution**  Prof Nicholas Turner

*Pull through from Novel Cancer Therapeutics to specific tumour types*

- Novel Cancer Therapeutics  Prof de Bono
- Breast Cancer  Prof Dowsett
- GI Cancers  Prof Cunningham
- Prostate Cancer  Professor Eels
- Uncommon Cancers  Dr Larkin
- Targeted Physical Therapies  Prof Harrington

*Pull through from Targeted Physical Therapies to specific tumour types*

**Digital: Capability, Informatics, Big Data, e-Health**  Prof Winette van der Graaf
New pre-clinical models to study pancreatic cancer and novel treatments:
3D cultures and co-cultures for Pancreatic Desmoplasia
(Muge Sarper, Amine Sadok, Ilona Nowak and Raj Chopra, ICR)

- Predictive validity of the disease model: Capturing the biology of the tumour

**Strengths**

1. Heterogenous cell population similar to cells of tumour that are in different phases of cell cycle including proliferating, hypoxic and necrotic cells

2. Robust, amenable to high throughput screening (384well format)

3. Multiple end points, compatible with most reagents (Cell titre Glo, Pi staining, Cell brighter Glo, Alamar blue...)

4. Possibility to incorporate stromal cells (co-culture with CAFs, immune cells)

5. Bridges the gap between in vitro and in vivo: higher predictive validity
Personalized treatment in advanced pancreatic cancer

**In vitro approach**
- High throughput technologies
- To explore mediators of drug resistance

**Clinical relevance**
- Human tissues
- To confirm clinical relevance

**Mechanistic insights**
- Patients cell lines and organoids
- To understand biology

**Novel biomarkers**
- Liquid biopsy
- To validate predictive value of response
- To validate early diagnostic potential in symptomatic patients

---

Early diagnosis in pancreatic cancer

**Basic findings**
- Deregulation of long ncRNAs is associated with malignant transformation

**PDAC specificity**
- Long ncRNA expression in early PDAC and pre-neoplastic lesions

---

In integrating pre-clinical models with human samples and patient derived disease models to identify novel biomarkers in pancreatic cancer.

Slide courtesy of Dr Chiara Braconi, RM/ICR
Patient-derived organoids model treatment response of metastatic gastrointestinal cancers

Conclusions

• Understanding the biology of pancreatic cancer and developing completely novel approaches is critical to advancing future treatment and outcomes

• Translational research utilising patient biospecimens (tissue, blood, urine etc) is essential so that we can learn as much as we can from patients themselves

• Integration of clinical care and clinical/translational research as routine practice in pancreatic cancer is important leveraging nationally distributed research infrastructure and collaboration

• The multi-disciplinary team approach is key with a holisitic approach to patient care with critical roles for the clinical nurse specialist, the dietician, palliative care team and counsellors