Early Phase Combination Studies and Working with Industry

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Glasgow ECMC
Disclosures

- Honoraria / Consultancies / Speaker:
  - Astra Zeneca
  - Bayer
  - Bristol Myers Squibb
  - Celgene
  - Clovis
  - Eisai
  - Genentech
  - Glaxo Smith Kline
  - Jennerex / Transgene
  - Karus Therapeutics (Scientific Advisory Board)
  - Otsuka
  - Roche
Overview

• Combination Studies arising from:
  - ideas from our own laboratory or exploratory clinical studies
  - ideas from industry / academic collaborators’ laboratory or exploratory studies
  - ideas from the published literature

• Can be commercial or academic studies

• Not necessarily a CTIMP – can be biomarker studies
Principles

• The idea / proposal should be:

  based on a sound rationale - the agents, the combo, the tumour type(s), the clinical setting

  have supporting pre-clinical evidence

  must be feasible and deliverable

  must be attractive to patients, collaborators, regulators, and the funders

  have a development path / strategy
Principles

• Early phase (combination) studies

  optimal dose and schedule

  proof of concept / mechanism

  PK and PD….hitting the target,
  influencing the biology

  refine / enrich patient population

  allow stop : go decisions to reduce phase III
  attrition (and resources)
<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Studies</td>
<td>Ongoing: 10</td>
</tr>
<tr>
<td>Preclinical Studies</td>
<td>Ongoing: 10</td>
</tr>
<tr>
<td>Clinical Studies in Setup</td>
<td>4</td>
</tr>
<tr>
<td>Number of Patients Treated</td>
<td>195</td>
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<tr>
<td>Focus</td>
<td>1</td>
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<tr>
<td>Number of Clinical Studies</td>
<td>28</td>
</tr>
<tr>
<td>Number of NAC Submissions</td>
<td>27</td>
</tr>
<tr>
<td>Number of Combinations</td>
<td>6</td>
</tr>
<tr>
<td>Drugs Offered</td>
<td></td>
</tr>
<tr>
<td>Dated</td>
<td>January 2015</td>
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</table>
COMBINATION ALLIANCE - CATEGORIES

BUILD PRECLINICAL EVIDENCE
- Preclinical Grant
- NAC Application

CLINIC READY
- NAC Application

NEW DRUG REQUIRED
- CRUK CDD approach company
COMBINATIONS ALLIANCE - PROCESS

**Portfolio**
- Company provides access to a drug or portfolio of oncology agents (under MOU)
- Expressions of interest (EOI) are requested from the academic community

**Review**
- Proposals are reviewed by the company, CDD team and JSC
- Seek approval from New Agents Committee (NAC)

**Sponsor**
- ECMC will sponsor the proposed clinical study under a CTAg
- Studies are driven by the ECMC Alliance Team and overseen by a JSC

**Study**
- Investigator led trial opens within 12 months
- Multiple centres within 1 protocol
# Study portfolio

<table>
<thead>
<tr>
<th>Study</th>
<th>CI</th>
<th>Sponsor</th>
<th>Combination</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORCA2</td>
<td>Forster</td>
<td>UCL</td>
<td>PARP inhibitor + Cisplatin + RT</td>
<td>HNSCC</td>
</tr>
<tr>
<td>PIONEER</td>
<td>Evans</td>
<td>Glasgow</td>
<td>PARP inhibitor + Capecitabine + RT</td>
<td>Pancreatic</td>
</tr>
<tr>
<td>TORCMEK</td>
<td>Schmid+Middleton</td>
<td>Barts</td>
<td>MTOR inhibitor + MEK inhibitor</td>
<td>NSCLC</td>
</tr>
<tr>
<td>TBA</td>
<td>Glasspool</td>
<td>Glasgow</td>
<td>Hedgehog inhibitor + Paclitaxel</td>
<td>Ovarian</td>
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<tr>
<td>FACING</td>
<td>Evans</td>
<td>Glasgow</td>
<td>FGFR inhibitor + Cisplatin/Capecitabine</td>
<td>Oesophogastric</td>
</tr>
<tr>
<td>DEBIOC</td>
<td>Thomas</td>
<td>Oxford</td>
<td>mixed Erb Inhibitor + Oxiplatin/Capecitabine</td>
<td>Oesophogastric</td>
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<tr>
<td>RADICAL</td>
<td>Seckl</td>
<td>Imperial</td>
<td>FGFR inhibitor + Anastrozole + Letrozole</td>
<td>Breast</td>
</tr>
<tr>
<td>FIESTA</td>
<td>Chester</td>
<td>Leeds</td>
<td>FGFR inhibitor + Gemcitabine / Cisplatin</td>
<td>Bladder</td>
</tr>
<tr>
<td>VANSEL</td>
<td>Talbot</td>
<td>Oxford</td>
<td>MEK inhibitor + RET, EGFR, VEGF inhibitor</td>
<td>NSCLC</td>
</tr>
<tr>
<td>TAX-TORC</td>
<td>Banerji</td>
<td>ICR</td>
<td>mTOR inhibitor + Taxane</td>
<td>Ovarian / Fallopian</td>
</tr>
<tr>
<td>ComPAKT</td>
<td>Yap</td>
<td>ICR</td>
<td>AKT inhibitor + PARP inhibitor</td>
<td>Solid tumours</td>
</tr>
<tr>
<td>PATRIOT</td>
<td>Harrington</td>
<td>RMH/ICR</td>
<td>ATR inhibitor + RT</td>
<td>H&amp;N/Abdo/pelvic/thorax</td>
</tr>
<tr>
<td>PANTHER</td>
<td>Hochhauser</td>
<td>UCL</td>
<td>EGFR inhibitor +FOLFIRI</td>
<td>CRC</td>
</tr>
<tr>
<td>VIBRANT</td>
<td>Thirlwell+Sarker</td>
<td>UCL</td>
<td>RET, EGFR, VEGF inhibitor + Iodine-131 MIBG</td>
<td>Pheos and PG</td>
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<tr>
<td>DREAM</td>
<td>Saunders</td>
<td>Manchester</td>
<td>MEK inhibitor + VEGFR inhibitor</td>
<td>CRC</td>
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FUTURE OF COMBINATIONS ALLIANCE

- Expand Portfolio
  - Double the number of studies recruiting by 2016
  - Increase number partners
    - Currently 6
    - Portfolios to single project
    - Big Pharma to biotech
  - Drive more novel: novel combinations

![Diagram showing portfolio by study status per year as at Jan, 2015](image-url)
Example 1

• 2006: publish biomarkers of Src Kinase inhibition by dasatinib
• 2009: publish Phase I trial of dasatinib (previous ASCO presentations)
• 2007: CR-UK funding: anti-invasive therapies in mouse model of PDAC
• 2010: publish in vitro / in vivo studies
• 2012: “Trials in Progress” poster, ASCO
• 2014: Randomised Phase II ESMO – World GI
Dasatinib - Introduction

- Potent, orally active inhibitor of several oncogenic protein tyrosine kinases, including the SRC family kinases, and BCR-ABL
- In vitro and in vivo activity

<table>
<thead>
<tr>
<th>Tyrosine kinase</th>
<th>IC$_{50}$ (nM)</th>
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<tbody>
<tr>
<td>FYN</td>
<td>0.2</td>
</tr>
<tr>
<td>c-SRC</td>
<td>0.55</td>
</tr>
<tr>
<td>YES</td>
<td>0.41</td>
</tr>
<tr>
<td>LCK</td>
<td>1.1</td>
</tr>
<tr>
<td>c-KIT</td>
<td>22</td>
</tr>
<tr>
<td>PDGF-Rβ</td>
<td>28</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>3.0</td>
</tr>
<tr>
<td>EPHA2</td>
<td>17</td>
</tr>
</tbody>
</table>
Weaning Pan (1)
Primary Tumour (2)
Metastasis (3)

Weekly imaging

Experiment Plan

4-6 wks
10 wks
20 wks
A. Dasatinib inhibits mouse PDAC cell migration (wound assay)

B. Dasatinib inhibits mouse PDAC cell invasion
Nonparametric Survival Plot for Dasatinib-Treated Mice
Kaplan-Meier Method

Table of Statistics
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib 6 weeks</td>
<td>155.789</td>
<td>130</td>
<td>79</td>
</tr>
<tr>
<td>Vehicle 6 weeks</td>
<td>114.867</td>
<td>94</td>
<td>69</td>
</tr>
<tr>
<td>Dasatinib 10 weeks</td>
<td>137.846</td>
<td>127</td>
<td>49</td>
</tr>
<tr>
<td>Vehicle 10 weeks</td>
<td>172.889</td>
<td>147</td>
<td>71</td>
</tr>
</tbody>
</table>
Incidence of Metastasis in Dasatinib-Treated $Pdx1$-Cre $Kras^{G12D/+}$ $Trp53^{R172H/+}$ Mice

Vehicle

- Metastatic: 65%
- Non-metastatic: 35%

Dasatinib (10mg/kg)

- Metastatic: 30%
- Non-metastatic: 70%

$P = 0.0010$
Locally Advanced Pancreatic Cancer
N = 200 randomized

Stratification factors:
• Site intent to provide radiotherapy (Y or N)
• ECOG PS (0 or 1)

1:1 Randomization

Primary Endpoint:
■ Overall survival

Secondary Endpoints:
■ Progression-Free Survival (PFS)
■ Safety

Exploratory Endpoints:
■ Freedom from Distant Metastasis (FFDM)
■ Pain, Fatigue
■ CA19-9 Response
■ Objective Response Rate

Gemcitabine 1000mg/M^2
Q week x3 of 4 week cycle + Dasatinib
orally 100mg QD
(n = 100)

Gemcitabine 1000mg/M^2
Q week x3 of 4 week cycle + Placebo Pill
QD
(n = 100)

Statistics:
• OS: median 10 to 13.3 mos; 79% power
  • 1-sided $\alpha = 0.2$ (HR = 0.75)
• PFS: median 5 to 7 mos; 88% power
  • 1-sided $\alpha = 0.15$ (HR = 0.714)
**Stage 1**

Advanced Pancreatic Cancer
PS 0 OR 1
Informed Consent 1
Biopsy

**Molecular Phenotyping**

Molecular MDT Review of Actionability
Allocation to Specific Sub-protocol

**Stage 2**

**Actionable Phenotype** (Biomarker Testing)

- Trial
  - Strong Predictor (Randomised Phase 2)
  - Exploratory Target (Randomised Phase 2)
  - Exploratory Target (Randomised Phase 2)
  - External Trials

**Non-Actionable Phenotype** (Biomarker Discovery/Validation)

- Trial
- Non-Trial

**Informed Consent 2**

- PARP inhibitor
- mTOR inhibitor
- EGFR inhibitor
- PanHER inhibitor
- MET inhibitor
- CCR2 inhibitor

- A
- B
- C
- D
- E
- F
- etc

**External Consent**

- SEIGE
- SCALP
- Open to Investigator

- FOLFRINOX
- Gem / nab-Paclitaxel
- Gem / Capecitabine
- Gemcabine
Example 2

- Data on FGFR polysomy and amplification in OG adenocarcinoma
- AZD4547 made available through AZ – ECMC Combinations Alliance
- Work with AZ – existing data on AZD4547 in OG *in vitro / in vivo*
- Study proposal selected by Steering Committee, funded by NAC
- Lessons learned from this........
FGFR Inhibitor and Chemotherapy IN Gastric Cancer

A Phase I/IIa Trial of AZD4547 in combination with Cisplatin and Capecitabine (CX)

EudraCT Number: 2011-000642-37
Lessons Learned

• **Challenges**
  - Emerging toxicity data
  - Additional NHS resources
  - Working with external vendors

• **Advantages**
  - Supportive sponsors
  - Work with a recognised CTU
  - Relationships with funders, industry, ECMC network
A Phase I study of olaparib in combination with chemo-radiation in locally advanced pancreatic cancer

Jeff Evans on behalf of the Glasgow ECMC and Glasgow Pancreatic Cancer Research Group

Will Steward and the Leicester ECMC

Martin Eatock and the Belfast ECMC

Olaparib + Chemo-Radiation (LAPC)
**PIONEER: A Phase I study of olaparib in combination with chemo-radiation in locally advanced pancreatic cancer**

The unmet medical need

- Capecitabine (radiation–sensitizer)/chemo-radiation is used to treat patients with present with locally advanced, un-resectable, non-metastatic disease
- Median survival of only ~15 months
  - Most patients ultimately develop local disease progression and / or distant metastases.

**Trial Hypothesis: Inhibition of Poly (ADP-ribose) polymerases (PARP) by Olaparib may potentiate the effects of the combined modality therapy.**

- In preclinical assays, PARP-1 inhibition potentiates the cytotoxicity of DNA-damaging agents, including radiation.
- Olaparib (AZD2281) is a potent inhibitor of PARP-1
TRIAL DESIGN (1) - Phase I

<table>
<thead>
<tr>
<th>Proposed trial design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose escalation model?</strong></td>
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</tbody>
</table>
| **Dosing regimen?** | **Induction chemotherapy**  
  Weeks 1 – 12  
  **Chemo-Radiation**  
  **Capecitabine:** 830 mg / m2 po (Monday – Friday) with RT  
  **RT:** 50.4 Gy in 28 fractions (Monday – Friday)  
  **Olaparib:** start 3 days prior to chemo-radiation then Monday – Friday with RT  
  100 mgs bid; 150 mgs bid; 200 mgs bid; 250 mgs bid; 300 mgs bid (tablet formulation); |
# TRIAL DESIGN (2)-Phase I

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>Dose ESCALATION (complete as applicable)</th>
<th>Dose EXPANSION (complete as applicable)</th>
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</thead>
<tbody>
<tr>
<td>Patient Population</td>
<td>Locally advanced inoperable (anatomical; MDT) PDAC</td>
<td>“Borderline” resectable PDAC (anatomical; MDT)</td>
</tr>
<tr>
<td>No. Patients</td>
<td>12 - 18</td>
<td>12</td>
</tr>
<tr>
<td>All comers?</td>
<td>LAPC suitable for chemo-radiation</td>
<td>Suitable for neo-adjuvant chemo-radiation</td>
</tr>
<tr>
<td>Specific tumour group?</td>
<td>LAPC suitable for chemo-radiation</td>
<td>Borderline resectable for neo-adjuvant chemo-RT</td>
</tr>
<tr>
<td>Stratified patient group?</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>By Genotype?</td>
<td>No – not restricted to BRCA or DDR (n)</td>
<td>No – not restricted to BRCA or DDR (n)</td>
</tr>
<tr>
<td>By biomarker profile?</td>
<td>No – not restricted to BRCA or DDR deficiency</td>
<td>No – not restricted to BRCA or DDR deficiency</td>
</tr>
</tbody>
</table>
PIioneer: Phase I Study

• **Primary Endpoint:**
  - Optimal dose of olaparib in combination with capecitabine-based chemo-radiation based on clinical and laboratory toxicity

• **Secondary Endpoints:**
  - Safety and tolerability of olaparib in combination with capecitabine-based chemo-radiation

• **Research (tertiary) endpoints**
  - Pharmacokinetic profile of olaparib in the combination regimen
  - Pharmacodynamic effects of the combination in blood (apoptosis/PARP inhibition) and hair follicles (DNA damage)
PIONEER Biomarkers
Establishing PK/PD relationships and predicting response

**Target Engagement**
Does olaparib block PARP activity?

**Pathway Biomarker**
How does combination therapy alter the DNA damage response/cell viability?

**PK Biomarker**
At what dose of olaparib do I observe these effects?

**Predictive Biomarker**
Can I predict response to treatment based on sequence data?

- **PARP ELISA (PBMCs)**
- **DNA Damage Marker (Hair Follicles)**
- **Cell Death Marker (Serum)**
- **Olaparib LC-MS (Plasma)**
- **NGS analysis (Tumor/Plasma)**