Microarray Identifies Best Cancer Type Markers

79 genes

qRT-PCR

Tothill et al 2005 CancerRes.65:10
My Disclosures in respect of this talk (CUP)

bioTheranostics, (BioMerieux / Pasteur Foundation):
- Advisory Board (uncompensated)
- Research funding within CUP-ONE Trial

Topotargets A.S:
- Advisory Board (uncompensated)

Astra Zeneca:
- Advisory Board (uncompensated)

Jo's Foundation (CUP charitable trust):
- Medical Advisor (uncompensated)
- Research funding

NICE CUP Guidelines CG104
- Medical input to advisors (uncompensated)

CRUK:
Research funding

Merck KGA:
Research funding (COIN-B), biomarker development and advisory boards
UK UPDATE CUP RESEARCH

- **UK CRUK NCRI CUP-ONE Trial**
  - ‘Best’ Tissue based test for site-of-origin
  - Patient Outcomes (OS, predictive Biomarkers)
    - Untreated
    - Treated as site-specific
    - Treated as CUP

- **Other Research & Trials (proposed)**
  - Audits from CUP/MUO MDT’s
  - NHSE GECIP 100K Genome

- **Dynamic cancer models**:
  - Lessons from treating solid cancers
Cancer of Unknown Primary: Paradigm for future as model for treatment direction of all metastatic disease?

• Molecular Heterogeneity has major clinical implications for treatment (more than site of origin)

Breast Cancer:
- Triple –ve
- Her2+

Gastric Cancer:
- Her2+
- Longer survival + Traztuzumab

• Phase II study promise ....

...Phase III failure phenomenon
Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. Gerlinger et al. NEJM 2012

101 nonsynonymous point mutations and 32 indels
133 significant (?) changes in 10 biopsies

“Intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development”

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing. Gerlinger et al. NEJM 2012
Emerging Molecular Taxonomy by “Site of Origin” - Traditional

Potentially many low prevalence phenotypes

RESPONSE prediction to Biomarker?

uncommon

- HER2 amplified
- 5-FU responsive
- FA/BRCA defective
- EGFR inhibitor responsive
- nab-paclitaxel responsive
- Gemcitabine responsive
Challenges

CUP Patient 45y male PS-2:

- liver + peritoneal + bone metastases
- Liver Bx G3 adenocarcinoma, sCEA-120, Anemia, CT mass ?? in ascending colon:
  Colonoscopy (adequate X2) negative …
  MDT – Path consistent with lower GI origin
  Bio-T SOO Expression Profile – prob CRC

*No response to first line*

FOLFOX-Bevacizumab (RAS-mut)
Where is this patient on the curve?

CRYSTAL Trial metastatic CRC: OS in ITT Population: where would a MUO ~ CRC fit?

30% of the population are not surviving beyond a year!

A common cancer this represents a significant population burden

**?? CUP-”CRC”**

Overlap

-in good (‘wished’) or bad part (++) of curve (or both)
Molecular Taxonomy – Cancer “Biotypes”

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genes/Prototypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Dependent</td>
<td>BREAST, CML, GIST, RCC</td>
</tr>
<tr>
<td>Abl-like Kinase Dependant</td>
<td>LUNG, COLON, SCCHN</td>
</tr>
<tr>
<td>EGFR dependent</td>
<td>BREAST, GASTRIC</td>
</tr>
<tr>
<td>HER2 Amplified</td>
<td>NSCLC, NHL, NB</td>
</tr>
<tr>
<td>ALK</td>
<td>BREAST, OVARY, Pa</td>
</tr>
<tr>
<td>Homologous Recombination Defective</td>
<td>MELANOMA</td>
</tr>
<tr>
<td>BRAF mutant</td>
<td></td>
</tr>
<tr>
<td>NOVEL mutant</td>
<td></td>
</tr>
</tbody>
</table>

Unraveling recent developments in translational research
CUP ONE TRIAL:

A multi-centre phase II trial to assess
- the efficacy of epirubicin, cisplatin and capecitabine in carcinomas of unknown primary (CUP):
  - incorporating the prospective validation of molecular classifiers in diagnosis and classification and exploratory metabonomics
UK CUP-ONE: evolution of Clinical & research Framework

- NCRN Upper GI /HPB group 2004 +
- CTAAC full application / Glasgow CTU
  - Randomised clinical study *not* supported due to accrual concerns
- TRICC application: Awarded Jan 2007
- **Planned start was Nov’09 - actual Feb 2010**
  - 16+ Centres with expression of interest
  - Drug Funding – AZ collaboration ?Vandetanib
- NICE UK CUP Clinical Guidance 2010
  - Acute Oncology service review
- **Trial accrued Target 400 2014**
CUP ONE Trial evolution.....

.......... Japan Vs South Africa !
UK CUP-ONE: evolution of Clinical & research Framework

- **Trial accrual Target 400 2014**
- **Trial accrual Target increased 2014**
  - Part 1 ECX clinical Phase II completed 2013
  - Tissue QA guidance : IDMC 2014
  - **Extend Recruitment**
  - **624 final recruitment – Closed Dec 2014**
    - some larger centres e.g. Manchester not open until 2014
CUP-ONE Trial has two parts: clinical and translational

- **Translational part of trial**
  - Uncertainty (at any-time of patient Pathway)
  - Bx available- ‘split into 3’
  - compares (double-blinded) –
    - best currently available IHC tools at the highest standard
    - vs
  - Modern molecular diagnostics
    - Biotheranostics CancerTypeID
    - V Healthscope CUPGuide Peter MacCallum Cancer Center
  - up to 400 patients assessable

CUP-ONE Trial has two parts: **clinical** and translational

- **Clinical** part of trial
  - CUP by exclusion of known primary
  - Phase II epirubicin, cisplatin, capecitabine
    - 20 patients: Futility / safety analysis
    - 56 patients: efficacy analysis

- **off-trial** Chemotherapy regimens & survival data
  - up to 400 patients assessable
  - Clinical – molecular predictive & prognostic correlates

- ? randomised Phase II –
  - Vandetanib maintenance (AZ-NCRN) never happened
**CUP ONE: Study Schema**

1. **Patient presents with metastases of “uncertain” or “Unconfirmed” primary origin requiring or had tru-cut biopsy or surgery:**
   - Consent to provide tumour sample for CUPONE Trial
   - Clinical Investigations as per Protocol guidance

2. **Primary conclusively* identified**
   - Known Primary
   - **Translational part**
     - Tumour sample used for diagnostic validation
     - Limited Follow-up
   - **Patient suitable for trial treatment**

3. **Primary not conclusively identified**
   - Unknown Primary (CUP)
   - **Patient unsuitable for trial treatment**

4. **Non-carcinoma Pathology:**
   - Patient unsuitable for study

*Conclusively identified means primary site of origin must be unequivocal as judged by the clinical multi-disciplinary team.
CUP-ONE Study Objectives

• **Primary objective:**
  - For *translational* part primary objective is to select the molecular classifier with the highest diagnostic accuracy *(expecting at least 50%% knowns)*
  - For the *clinical* trial the primary objective is to estimate the response rate with ECX (+/- biological)

• **Secondary objective: Both parts of Trial**
  - Progression-free survival (clinical)
  - Overall survival
  - Quality of life
  - Cost utility comparison of diagnostic molecular classifiers with average clinical diagnostic work-up
  - Correlation of molecular profiles with patient outcome
  - To assess utility, relevance and necessity of clinical investigations in CUP, in comparison to molecular classifiers
CUP ONE: Clinical Trial Recruitment

Clinical Trial/Translational Study Overlap

- Clinical Trial Only: 68.10%
- Clinical Trial and Translational Study: 29.40%
- Translational Study Only: 2.50%
CUP ONE: Trial Recruitment
Q4 2014

Recruitment
> 600+ (Oct’14)
➢ 8-12 patients / month

Clinical
Translational

Temp stopped futility analysis

Figure 2.1-1: Clinical Trial Recruitment
CUP-ONE combines a multicentre phase II trial of an ongoing translational study [Part 1] incorporating blinded prospective validation of 3 diagnostic molecular classifiers, and treatment with epirubicin, cisplatin and capecitabine (ECX) [Part 2].

**Recruitment:** Since February 2010, CUP-ONE has recruited 592 patients to the Part 1 translational study (ongoing) and 59 to the clinical trial Part 2 (54 assessable in both parts). Part 2 closed to recruitment in February 2013. Results are presented for 58 eligible patients.

**Study population:**
- Male 47%, female 53%
- ECOG PS 0: 38%, 1: 62%
- Median age: 63 (range 29-78)
- 93% Stage IV, 5% Stage III
- 81% adenocarcinoma, 5% squamous carcinoma, 50% poorly/undifferentiated pathology

**Treatment response (RECIST 1.1):**
- The best overall response rate was 35% (90% confidence interval 26%-46%), which rejects the null hypothesis of 20% (p=0.006).
- The second evaluation demonstrates that additional continued responses are seen beyond 12 weeks in up to a quarter of patients.

**Progression-free survival and overall survival**
- Median PFS is 30 weeks, 80% CI: (25 and 33 weeks)
- Median OS is 44 weeks, 80% CI: (30 and 48 weeks)
The CUP-ONE trial and translational study - 592 patients in total and 59 Part 2 (clinical) patients.

The following data about site of CUP biopsy are from 24 of the 59 tissue samples so far sectioned and despatched to investigators for molecular analyses.

<table>
<thead>
<tr>
<th>Biopsy Site</th>
<th>Number</th>
<th>% of total (205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other(s)</td>
<td>9</td>
<td>38%</td>
</tr>
<tr>
<td>Liver</td>
<td>7</td>
<td>29%</td>
</tr>
<tr>
<td>Bone</td>
<td>4</td>
<td>17%</td>
</tr>
<tr>
<td>Peritoneum/Omentum/Ascites</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>Neck Nodes/Mass</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Abdominal Nodes</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Mediastinal Nodes</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Inguinal/Pelvic Nodes</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Pleural Effusions</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Brain</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 1: Biopsy site using common categories (from CRF)

<table>
<thead>
<tr>
<th>Biopsy Site</th>
<th>Number</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper gastro-intestinal tract</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td>Pancreatico-biliary tract</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>Chest Wall or Abdomen</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Lower gastro-intestinal tract</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Axillary Nodes</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>38%</td>
</tr>
</tbody>
</table>

Table 2: Biopsy site categorised under “Other” (from CRF)
Efficacy & Response (RR 35%): CUP ONE Clinical Trial

**Progression-free Survival**
- Median PFS: 30 weeks
- 80% CI: (25 weeks, 33 weeks)

**Overall Survival**
- Median OS: 44 weeks
- 80% CI: (36 weeks, 48 weeks)
Cancer of Unknown Primary (CUP):

UK Planned research development
Developing the UK CUP NCRN framework

Carcinoma Unknown Primary

<table>
<thead>
<tr>
<th>Year</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>…</th>
</tr>
</thead>
</table>

CUP-01 - Platinum/5FU (FOLFOX) (control arm defined by clinician survey)

2013-14
CUP-02 – NOT approved by CRUK
CUP-T – NOT approved by CRUK
NHSE 100K – Initial Pilot planned - on hold

Principles:
• Adaptive design with constant control arm
• Variable phase 1b/2/3
• Central tissue collection
CUP ONE Trial evolution.....

I think I can, I think I can, I think I can, I think I can...
CUP Global randomised trials
Future is international collaboration

<table>
<thead>
<tr>
<th>Year</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>…</td>
<td></td>
</tr>
</tbody>
</table>

GEFCAPI-04 site-of-origin directed Therapy rII
Pr Karim Fizazi, Head of the Department of Cancer Medicine
Institut Gustave Roussy, University of Paris

SUPER
PeterMac / AGITG
detailed NG Molecular analysis leading to available targeted therapiess

Original discussion in 2004
CUP-ONE!
CUP ONE TRIAL may define which classification(s) for treatment
- predictives and prognostics
- how to refine the population for a treatment hypothesis

(NGS….NHSE 100k genome project ?)
CUP: Molecular Biotype Taxonomy in 2020

- Current system organ based – assumption that cancers are more related to their organ of origin than other cancers

- “Biotype” Classification of Cancer
  TNM will become ... a personal signature

CK20+, CEA+, CK7-, TTF1- ...... Site of origin
RAS13D; RAF+, MSI EGFR-amphi++ Significant Molecular aberrations

...........TxS-PLR-GemS Hierarchical Treatment

.....which also be dynamic
CUP-ONE Study Team

• CR-UK CTU (Glasgow)
  – Chief Investigator: Harpreet Wasan
  – Translational Pathology lead: Karin Oien
  – Trial Statistician: Jim Paul
  – Project Management: Lynn McMahon;
  – Pharmacovigilance: Lindsey Connery; Katie Nocher
  – Quality Assurance: Lindsey Connery
  – Trial Co-ordinators: Pamela Fergusson; Robina Ullah;
    Linda Stevens; Elaine McCartney;
    Elizabeth Douglas; Eileen Smillie;
    Samantha Carmichael; Deepthi Beeravelli

• TMG Marianne Nicolson; David Bowtell; Mark Erlander; Jeff Evans;
  Hani Gabra, Jayson Wang
Cancer of Unknown Primary (CUP):

Thank you : Panel discussion
(+ 2 jobs for post-CST fellows in AOS/CUP research)

Dr. Harpreet S. Wasan
Department of Cancer Medicine
Hammersmith Hospital / Imperial College London
wasan@cancer.org.uk

OCT 2009