The UK NCRI CUP-One Trial:

Will the CUP pathway eventually be applicable to most metastatic disease?

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Cancer of Unknown Primary (CUP): Evolution of CUP-ONE

• **Diagnostic Clinical Algorithms**
  - To select subsets of patients with better prognoses
    - Midline poorly differentiated tumours (EGGCS); Head & Neck SCC; Breast; Peritoneal papillary; prostate
  - Utility of investigations for searching for primary
    - £10,000-£20,000+

• **Treatment / Chemotherapy Trials**…small Phase II’s
  - To improve outcomes

• **Biology**
  - Molecular studies inconsistent
    - Role of EGFR and VEGF (IHC) in cancer generally
  - Newer biological molecular diagnostic criteria based on expression patterns
Many Metastatic Cancers are ‘Unknown Primary’ at presentation. But many remain of Uncertain Primary Origin! (‘MUO’)

Most Treated as ‘Known Primary’s...
...the rest classified as CUP?

What matters is improving outcomes, Not diagnosis?
Evolution of the CUP-ONE Trial:
Many Metastatic Cancers are ‘Uncertain Primary’

How Certain are when we ‘call’ a primary?
- Important for trial design but ....
  - Difficult to quantify / QA – MDT
    - Known’s
    - Unknown’s

...We don’t really have a gold-standard....?
Many Metastatic Cancers are ‘Unknown Primary’ at presentation

Real experience constantly leaves me uncertain..........

1) CT mass seen in ascending colon: CT liver + peritoneal + bone mets, G3 adenocarcinoma, sCEA-120, Anemia, Colonoscopy (adequate) negative (twice)

2) IHC: G3-NET IHC? Biliary origin; Bone mets++, sCA19.9-N sCA-125 >1800
   - Rx as PD-NET or ABC/CCA??

3) Liver lesions only- IHC G3-HCC, sAFP-30, sCEA>40, sCA19.9> 2000, sCA-125-N no cirrhosis....?? Sorafenib

Progress in Treating Common Metastatic Cancers Hit a ‘ceiling’?
### 2004-2009 Survival of advanced Metastatic Cancer:

<table>
<thead>
<tr>
<th>Site Of Origin</th>
<th>Population Incidence / Rank Global</th>
<th>Chemotherapy Backbone</th>
<th>Median Survival Months Untreated</th>
<th>Median Survival Months treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Top 3</td>
<td>Platinum</td>
<td>7-9</td>
<td>8-12</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Top 7</td>
<td>Gemcitabine</td>
<td>3-6</td>
<td>5-8</td>
</tr>
<tr>
<td>Gastro-oesophageal</td>
<td>Top 7</td>
<td>Platinum + FP</td>
<td>4-6</td>
<td>8-11</td>
</tr>
<tr>
<td>Bladder</td>
<td>Top 7</td>
<td>Platinum</td>
<td>7-9</td>
<td>10-12</td>
</tr>
<tr>
<td>HCC</td>
<td>Top 5</td>
<td>Cytotoxic resistant (Sorafenib)</td>
<td>3-7</td>
<td>4-10</td>
</tr>
</tbody>
</table>
### 2009 Survival of advanced Metastatic Cancer: Good prognosis ‘Knowns’ Stage IV

<table>
<thead>
<tr>
<th>Site Of Origin</th>
<th>Population Incidence / Rank Global</th>
<th>Chemotherapy Backbone</th>
<th>Median Survival Months Untreated</th>
<th>Median Survival Months treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Top 3</td>
<td>? taxane</td>
<td>?</td>
<td>18 - 24</td>
</tr>
<tr>
<td>Colon</td>
<td>Top 3</td>
<td>Oxaliplatinum + FP</td>
<td>6-9</td>
<td>18 - 24</td>
</tr>
<tr>
<td>Prostate (Hormone refractory)</td>
<td>Top 3</td>
<td>taxane</td>
<td>?</td>
<td>16-19</td>
</tr>
</tbody>
</table>
CRYSTAL Trial metastatic CRC: OS in ITT Population

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

For a common cancer this represents a significant population burden

Are these subsets not really “Conventional Response colorectal cancer”??

HR (95%):   0.88 [0.77 - 1.00]
p-Value:      0.04 (log-rank)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Events</th>
<th>Median OS</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folfiri</td>
<td>502</td>
<td>18.6</td>
<td>[16.7-19.8]</td>
</tr>
<tr>
<td>Cetuximab+Folfiri</td>
<td>487</td>
<td>19.9</td>
<td>[18.5-21.3]</td>
</tr>
</tbody>
</table>

At Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk</th>
<th>Overall Survival Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folfiri</td>
<td>599</td>
<td>599 534 414 283 197 138 97 67 20 3 0</td>
</tr>
<tr>
<td>Cetuximab+Folfiri</td>
<td>599</td>
<td>599 520 427 319 220 160 125 97 33 6 0</td>
</tr>
</tbody>
</table>
Cancer of Unknown Primary (CUP): Chemotherapy Trials Summary

<table>
<thead>
<tr>
<th>Type</th>
<th>Start Year</th>
<th>End Year</th>
<th>Study No.</th>
<th>Patients</th>
<th>RR (%)</th>
<th>Survival Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxane/Platinum based</td>
<td>2000</td>
<td>2002</td>
<td>8</td>
<td>455</td>
<td>26</td>
<td>(7 - 50)</td>
</tr>
</tbody>
</table>

Outcomes similar to most advanced common tumours - exceptions?
Evolution of the CUP-ONE Trial: Is it always an Orphan or a separate disease?

- Pragmatic approach to develop structure and organisation in UK for CUP

- Is there value in ‘hunting’ the primary in highly metastatic carcinoma?
  - Exclude subsets of patients with better prognoses
  - Does it change outcomes?
    - **ASSUMPTION**: Patient management and prognosis are linked to the tumour site of origin
Evolution of the CUP-ONE Trial: Is there value in ‘hunting’ the primary in highly metastatic carcinoma?

.........maybe no..... but :

• Patients (and clinicians!) find it easier to cope with “certainty”
• Molecular Profiling, not site of origin, to direct treatment
• Diagnosis of more favourable subsets
• Lymphoma, breast & ? Colorectal support ‘genetic taxonomy’ approach (prognostic & predictive)

• Rapid Diagnosis of first presentation of any cancer
  • Provide clues where to look first
  • Heath economics benefit
CUP-ONE : Trial evolution

- NCRN Upper GI group
- CTAAC full application / Glasgow CTU
- TRICC application: Awarded Jan 2007
- Planned start was Nov’09 - actual Feb 2010
- 16+ Centres with expression of interest
- Australian GISG clinical involvement being considered
- Drug Funding – AZ collaboration Vandetanib
CUP ONE: UPDATE

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

data as presented to NCRI UGI Annual meeting as of Dec 2011
CUP ONE: Study Schema

*Conclusively identified means primary site of origin must be unequivocal as judged by the clinical multidisciplinary team.

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

Non-carcinoma Pathology: Patient unsuitable for study

Primary conclusively* identified = Known Primary

Translational part
Tumour sample used for diagnostic validation
Limited Follow-up

Primary not conclusively identified = Unknown Primary (CUP)

Patient suitable for trial treatment

Patient consented to clinical trial
- Translational
- Clinical
Follow-up to trial completion

Patient unsuitable for trial treatment

Translational part
Tumour sample used for diagnostic validation
Limited Follow-up
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 V Peter MacCallum Cancer Center

- up to 400 patients
### Table of Immunohistochemistry Results: Diagnostic Algorithm

<table>
<thead>
<tr>
<th>Primary site</th>
<th>PSA</th>
<th>TTF1</th>
<th>GCD</th>
<th>CDX2</th>
<th>CK20</th>
<th>CK7</th>
<th>ER</th>
<th>Meso</th>
<th>CA 125</th>
<th>Lysozyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>83</td>
<td>77</td>
<td>3</td>
</tr>
<tr>
<td>Colon</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>83</td>
<td>68</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>91</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>91</td>
<td>9</td>
<td>39</td>
</tr>
<tr>
<td>Ovary serous</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>89</td>
<td>83</td>
<td>94</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>19</td>
<td>96</td>
<td>0</td>
<td>47</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Prostate</td>
<td>100</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stomach</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>18</td>
<td>18</td>
<td>35</td>
<td>0</td>
<td>21</td>
<td>9</td>
<td>85</td>
</tr>
</tbody>
</table>

Dennis, J.L., et al...karen Oien

Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm.

Microarray Identifies Best Cancer Type Markers

Translate test to qRT-PCR

42 samples (5 sites)

79 genes

cDNA qRT-PCR

FFPET

Colorectal Pancreas Gastric Breast Ovarian

Tothill et al 2005 CancerRes.65:10

2006 New Version qRT-PCR Test
20 sites of origin
31 Histological Subtypes
**CancerTYPE ID Classifies 54 Histological Subtypes**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Histological Subtype</th>
<th>Reference database contains &gt;2000 tumor specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td>Adrenal-cortical</td>
<td>Mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Adrenal-pheo</td>
<td>Neuroendocrine-lung</td>
</tr>
<tr>
<td>Brain</td>
<td>Brain</td>
<td>Neuroendocrine-pancreas</td>
</tr>
<tr>
<td>Breast</td>
<td>Breast</td>
<td>Neuroendocrine-skin</td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervix-adeno</td>
<td>Carcinoid-GI</td>
</tr>
<tr>
<td></td>
<td>Cervix-squamous</td>
<td>Carcinoid-Lung</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Cholangiocarcinoma</td>
<td>Ovary-clear-cell</td>
</tr>
<tr>
<td>Endometrium</td>
<td>Endometrium</td>
<td>Ovary-endometrioid</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophagus-squamous</td>
<td>Ovary-mucinous</td>
</tr>
<tr>
<td>GIST</td>
<td>GIST</td>
<td>Ovary-serous</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Gallbladder</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Gastroesophageal</td>
<td>GE-adeno</td>
<td>Prostate</td>
</tr>
<tr>
<td>Germ-cell</td>
<td>GC-germinomatous</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>GC-nongerminomatous</td>
<td>MFH</td>
</tr>
<tr>
<td>HeadNeck</td>
<td>HeadNeck-salivary</td>
<td>PNET</td>
</tr>
<tr>
<td></td>
<td>HeadNeck-squamous</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Intestine</td>
<td>Intestine-large</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td></td>
<td>Intestine-small</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Kidney</td>
<td>Kidney-clear-cell</td>
<td>Synovial</td>
</tr>
<tr>
<td></td>
<td>Kidney-oncroytoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kidney-papillary</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Lung-adeno-large-cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung-squamous</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td>Meningioma</td>
<td>Meningioma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To aid in differential diagnoses that alter therapeutic options:

- Ovarian mucinous vs Colorectal
- Pancreatic vs Cholangio
- NSCLC Squamous vs Large cell
- Head and neck vs NSCLC
- Breast vs Ovarian
- Mesothelioma vs Primary lung
- Urinary Bladder vs NSCLC
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
  - ? randomised Phase II –
    - Vandetanib maintenance (AZ-NCRN)
What next?
Cancer of Unknown Primary: paradigm for future as model for highly metastatic disease?

- Molecular Heterogeneity has major clinical implications (not site of origin)

BREAST Cancer: Hormone Receptor –ve
Her2+

Gastric Cancer: Her2+

Longer survival with Traztuzumab

- R-Phase II study? ECX (3-4 cycles)
- Vandetanib maintenance
- Molecularly stratified trial
CUP NCRN framework
Carcinoma Unknown Primary

Principles:
- Adaptive design with constant control arm
- Variable phase 1b/2/3
- Central tissue collection

Platinum/5FU
(control arm defined by clinician survey)

CUP-02 -rapid diagnostic site-of-origin directed Therapy

CUP-03 (Molecular analysis)
CUP Global randomised trials
Carcinoma Unknown Primary

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 therapies
CUP-ONE Study Team

• CR-UK CTU (Glasgow)
  – Chief Investigator: Harpreet Wasan Harpreet.wasan@cancer.org.uk
  – 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;
THANK YOU!

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