A UK Perspective on the CUPISCO Trial
The Agony and the Efficacy

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Disclosures

**Remuneration reasons:** attendance at advisory boards; chairing educational meetings; giving invited lectures; travel, accommodation and registration at national/international meetings, consultancy

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Amgen, BMS, BTG, Guardant Health, Merck Group, MSD, Roche, Sirtex, Servier

**Funding for UCLH trials and research:**
Amgen, BMS, Guardant Health, Merck Group, MSD, Roche
Focus on 3 main strategies for CUP patients

**STRATEGY**

1) Find the molecular primary

2) Find the therapeutic target

3) Access a clinical trial

**HYPOTHESIS**

1. **Primary-specific therapies will be more effective**
   - IHC
   - MIRNA
   - METHYLATION

2. **Targeted therapy is feasible, safe and efficacious**
   - IHC
   - MRNA
   - ACTIONABLE MUTATIONS/ALTERATIONS
     - (WHOLE GENOME MUTATION)
     - (EXOME SEQUENCE)
UCLH CUP MDT 2013-2017: cCUP patients who embark on therapy (n= 48/61)

Mean Performance Status 1.5 (0-4)
Median OS 9.5 months, 1 year survival 40%
On a trial? 1 in first 4 years, now 4 in last 6 months

(Hessey, Mcvinnie, Shiu – Poster)
The CITA IMDC* Platform

DNA
- Next Gen sequencing
- Genetic alterations, ITH

RNA
- RNAseq/TCR Seq
- Transcriptional profiles

Protein
- Mass spectrometry
- Proteomic signatures
- NanoString

Tumour and immune cells
- Sciomics protein profiling
- Phenotypic characterisation

Tissue sections
- Flow and mass cytometry
- Key regulatory components
- Immunohistochemistry
- Topology of TME

Bioinformatic multi-level data integration with clinical response data

Identification of mechanisms and biomarkers of response, resistance, and toxicity

*Imune Monitoring and Discovery Core

CANCER IMMUNOTHERAPY NETWORK ACCELERATOR
Is TMB a good immunotherapy biomarker?

…it can’t be as simple as that...
And blood TMB is coming…..
Mutation Burden (Guardant360) Predicts IO Outcomes

**Six or more Variants**
Higher SD $\geq$ 6 mos/PR/CR  
(P=0.025)

**More than three VUS’s**
Higher SD $\geq$ 6 mos/PR/CR  
(P=0.014)

Disease Control Rate $\geq$ 6 Months

* VUS = Variant of Unknown Significance

Khagi (Kurzrock) et al. 2017 Clinical Cancer Research
The median turnaround time (TAT) from sample collection to report was 10 days (range 6-15).

Seventeen patients had potentially actionable mutations (17/25 = 68%)

4 patients had no mutations detected which might be explained by: 1 patient had post resection; 2 patients were responding to chemotherapy; 1 patient was sampled prior to commencing chemotherapy.

Significant actionable targets included: 2 BRAF\textsuperscript{V600E}; 5 KRAS mutations; FGFR; MYC amplifications; KIT; PIK3CA; \textit{ERRB2}.

Three or more somatic mutations (including variants of uncertain significance (VUS)) were found in 12 patients; six or more mutations were found in 6 patients.
Future Value of IO therapy?

63 year old man: poorly differentiated carcinoma, CK7 focally +ve, all other markers -ve

Good response to 6 cycles of Cisplatin-Capecitabine

Taxane?

Irinotecan?

Immunotherapy?
Trunk and branch clonal diversity (& clinical outcome)

Palm  ❖  Chestnut  ❖  Baobab Tree  ❖  Dying Muhly Bush

Successful Predictive Biomarkers and Drug Targets
HER2/EGFR/KRAS/ALK/BRAF

Aim – gently push or big kick?

Swanton NEJM 2012
Roylance et al 2011
Birkbak et al 2011
The PEACE (Posthumous Evaluation of Advanced Cancer Environment) consortium
A national post-mortem programme and consortium

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National prospective observational study intended to facilitate tissue donation, in metastatic cancer, from multiple tumour sites in the post-mortem setting
Funded by a Cancer Research UK Centre Network Accelerator Award
Aim: establish a national PM protocol and a resource of tissue & blood in highly clinically annotated patient cohorts (500 PMs over 5 years) leveraging investment in CRUK-funded clinical studies
Timelines of cancer development

Colorectal cancer

Ovarian cancer
Perspectives for CUP

- **Molecular archaeology of cancer**: massively parallel sequencing and bioinformatics algorithms can **disentangle the subclonal architecture and life history of tumours**
- **Post-mortem sampling** allows **tracking evolution** of clones and subclones over time and space
- Could answer key questions in CUP:
  - Evolutionary history of CUP: track the **pattern of spread** and the **site of origin**
  - Are **common aetiologies/drivers/pathways** underlying early metastatic dissemination?
  - Can we **identify early events** and develop **early diagnosis approaches**?

NCRI CUP Day March 2018. Van Loo, Francis Crick
Biobank all pCUP/cCUP

STRATEGY

1) Find the primary using molecular profiling
   - MUO/pCUP
   - TIMELY
   - APPROPRIATE MANAGEMENT
   - QOL/PROM/PREMS

2) Find the therapeutic target
   - SMDTs
   - Genomic Boards
   - Trials for Good
   - Prognosis cCUP
   - Poor PS subgroups
   - QOL/PROM/PREMS

3) Access a clinical trial

CONVERSION

STUDY/TRIAL/ARENA

Primary-specific therapies will be more effective

Targeted therapy is feasible, safe and efficacious

The optimal way to test a treatment strategy
Thank you

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