

# 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

.....*Oct 2004!*

- 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

Most T  
'Know  
..the  
as CU

**What matters  
is improving outcomes  
Not diagnosis?**

...ain of  
Primary Origin!  
("MUO")

# 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

# **Evolution of the CUP-ONE Trial: 2004-2007**

**Progress in Treating  
Common Metastatic Cancers  
Hit a 'ceiling'?**

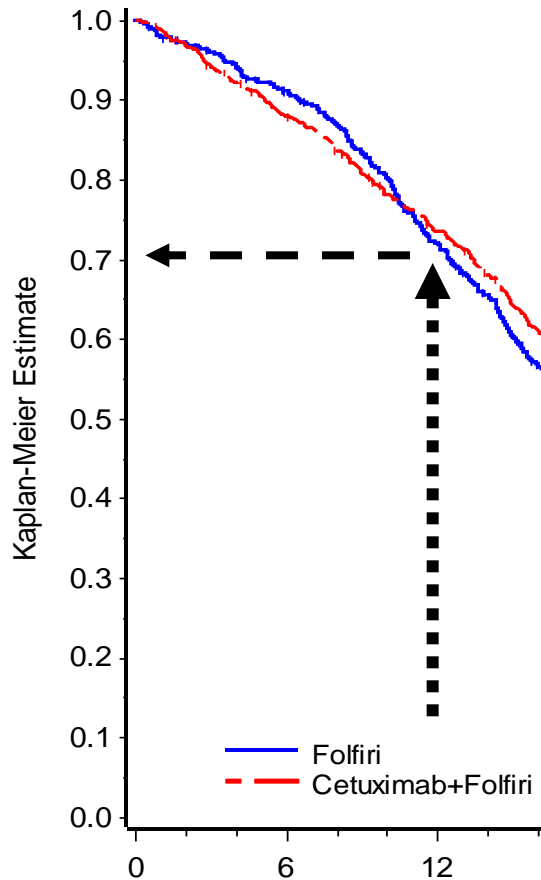
# 2004-2009 Survival of advanced Metastatic Cancer:

Site Of Origin	Population Incidence / Rank Global	Chemotherapy Backbone	Median Survival Months Untreated	Median Survival Months treated
<b>Lung</b>	Top 3	Platinum	7-9	8-12
<b>Pancreas</b>	Top 7	Gemcitabine	3-6	5-8
<b>Gastro-oesophageal</b>	Top 7	Platinum + FP	4-6	8-11
<b>Bladder</b>	Top 7	Platinum	7-9	10-12
<b>HCC</b>	Top 5	Cytotoxic resistant (Sorafenib)	3-7	4-10

# 2009 Survival of advanced Metastatic Cancer: ? Good prognosis 'Knowns' Stage IV

Site Of Origin	Population Incidence / Rank Global	Chemotherapy Backbone	Median Survival Months Untreated	Median Survival Months treated
<b>Breast</b>	Top 3	? taxane	?	18 -24
<b>Colon</b>	Top 3	Oxaliplatinum + FP	6-9	18 -24
<b>Prostate (Hormone refractory)</b>	Top 3	taxane	?	16-19

# 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” ??***

At Risk

	0	6	12	18	24	30	36	42	48	54	60
Folfiri	599	534	414	283	197	138	97	67	20	3	0
Cet+FIRI	599	520	427	319	220	160	125	97	33	6	0

Overall Survival Time (months)

# Cancer of Unknown Primary (CUP): Chemotherapy Summary

Type (years)	Survival months
Platinum 1980s	8
Platinum based 2000-200	8

**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
    - Health 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 multi-disciplinary 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*

*Non-carcinoma Pathology: Patient unsuitable for study*

*Clinical Investigations as per Protocol guidance*

*Primary conclusively\* identified = Known Primary*

*Primary not conclusively identified = Unknown Primary (CUP)*

*Translational part  
Tumour sample used for diagnostic validation*

*Limited Follow-up*

*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

- Erlander, M.G., et al., *Molecular classification of carcinoma of unknown primary by gene expression profiling from formalin-fixed paraffin-embedded tissues*. J Clin Oncol, 2004. **22**(14S): p. 9545.
- Tothill, R.W., et al., *An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin*. Cancer Res, 2005. **65**(10): p. 4031-40
- Dennis, J.L., et al., *Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm*. Clin Cancer Res, 2005. **11**(10): p. 3766-72.

# Table of Immunohistochemistry Results: Diagnostic Algorithm

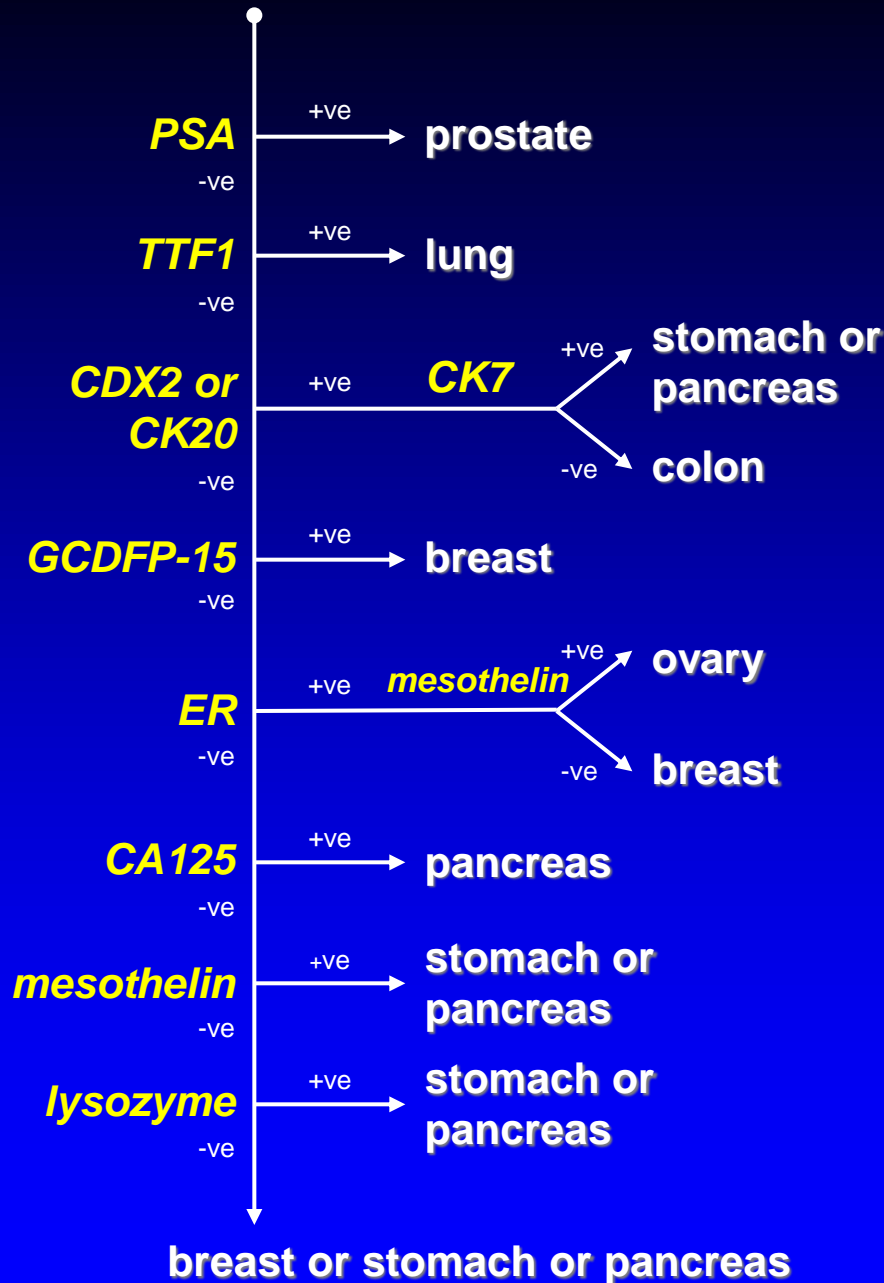
Primary site	% Positivity of each marker									
	PSA	TTF1	GCD FP15	CDX2	CK20	CK7	ER	Meso thelin	CA 125	Lyso zyme
Breast	0	0	54	0	0	83	77	3	6	14
Colon	0	0	9	83	68	4	2	2	0	53
Lung	0	91	4	2	2	91	9	39	39	43
Ovary serous	0	0	6	0	0	89	83	94	89	0
Pancreas	0	2	2	0	19	96	0	47	53	51
Prostate	100	11	0	0	0	0	11	0	0	6
Stomach	3	3	0	18	18	35	0	21	9	85

– Dennis, J.L., et al...karen Oien

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

–Clin Cancer Res, 2005. 11(10): p. 3766-72.

# Decision Tree



*Dennis, J.L., et al...karen Oien  
Markers of adenocarcinoma  
characteristic of the site of origin:  
development of a diagnostic algorithm.  
Clin Cancer Res, 2005. 11(10): p. 3766-72*



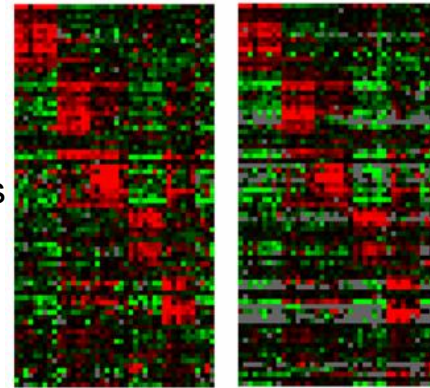
# Cancer Site of Origin Diagnostic

Peter MacCallum Cancer Centre, Melbourne, Australia

Translate test to qRT-PCR

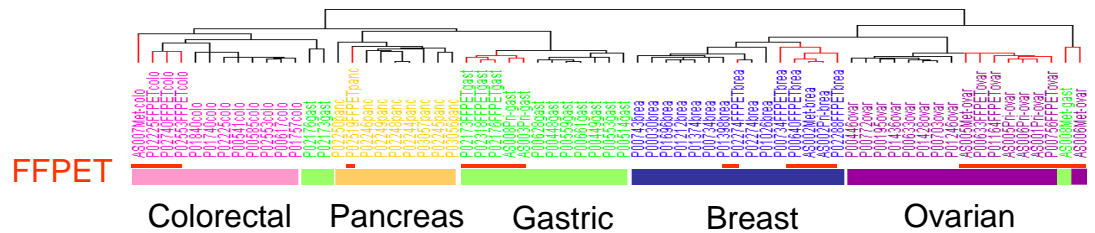
42 samples (5 sites)

79 genes



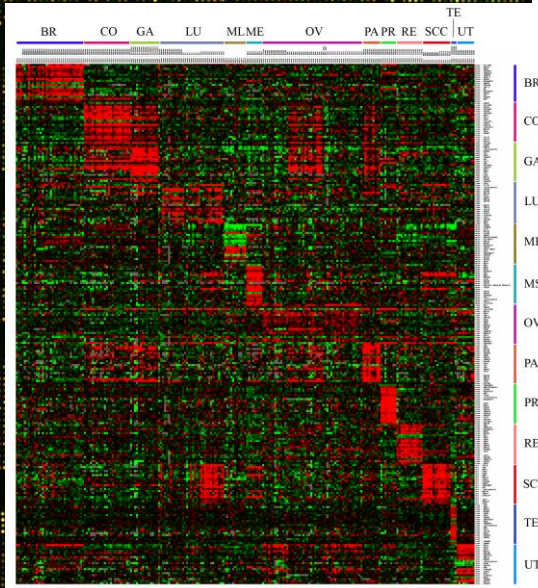
cDNA

qRT-PCR



Tothill *et al* 2005 *CancerRes*.65:10

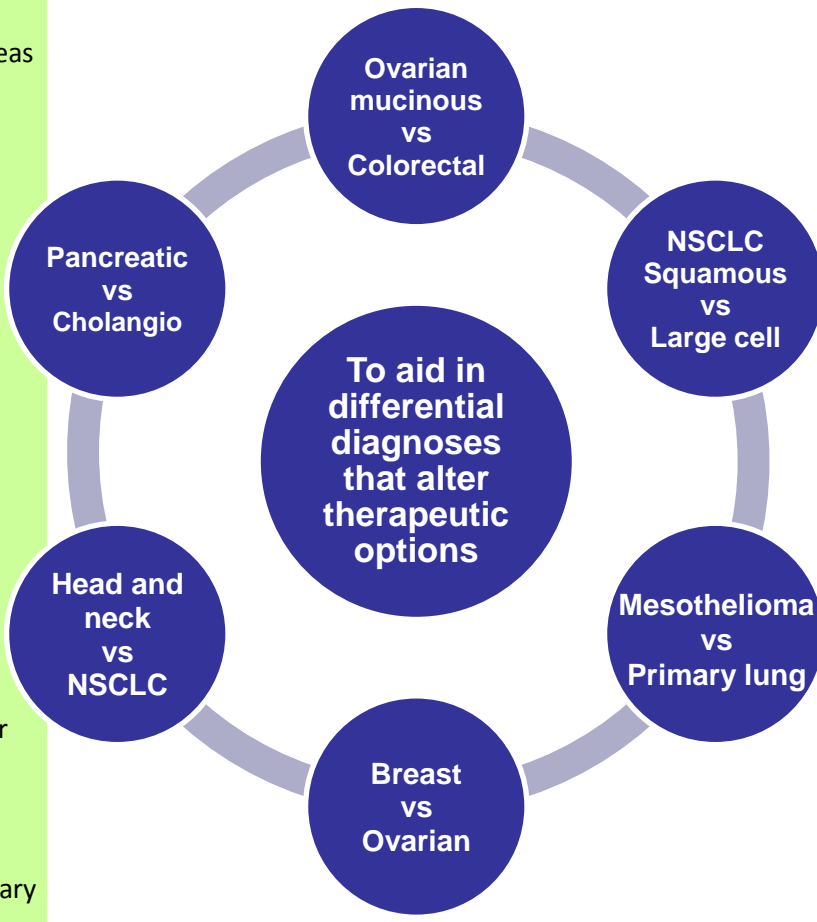
Microarray  
Identifies  
Best Cancer Type Markers



2006 New Version qRT-PCR Test  
20 sites of origin  
31 Histological Subtypes

# CancerTYPE ID Classifies 54 Histological Subtypes

<b>Adrenal</b>	Adrenal-cortical Adrenal-pheo	<b>Mesothelioma</b>	Mesothelioma
<b>Brain</b>	Brain	<b>Neuroendocrine</b>	Neuroendocrine-lung Neuroendocrine-pancreas Neuroendocrine-skin
<b>Breast</b>	Breast	<b>Carcinoid-GI</b>	Carcinoid-GI
<b>Cervix</b>	Cervix-adeno Cervix-squamous	<b>Carcinoid-Lung</b>	Carcinoid-Lung
<b>Cholangiocarcinoma</b>	Cholangiocarcinoma	<b>Ovary</b>	Ovary-clear-cell Ovary-endometrioid Ovary-mucinous Ovary-serous
<b>Endometrium</b>	Endometrium	<b>Pancreas</b>	Pancreas
<b>Esophagus</b>	Esophagus-squamous	<b>Prostate</b>	Prostate
<b>GIST</b>	GIST	<b>Sarcoma</b>	MFH PNET Leiomyosarcoma Liposarcoma Osteosarcoma Synovial
<b>Gallbladder</b>	Gallbladder	<b>Sex-cord-stromal-tumor</b>	Sex-cord-stromal-tumor
<b>Gastroesophageal</b>	GE-adeno	<b>Skin</b>	Skin-basal-cell Skin-squamous
<b>Germ-cell</b>	GC-germinomatous GC-nongerminomatous	<b>Thymus</b>	Thymus
<b>HeadNeck</b>	HeadNeck-salivary HeadNeck-squamous	<b>Thyroid</b>	Thyroid-follicular-papillary Thyroid-medullary
<b>Intestine</b>	Intestine-large Intestine-small	<b>UrinaryBladder</b>	UBladder-TCC UBladder-adeno UBladder-squamous
<b>Kidney</b>	Kidney-clear-cell Kidney-oncoytoma Kidney-papillary		
<b>Liver</b>	Liver		
<b>Lung</b>	Lung-adeno-large-cell Lung-squamous		
<b>Lymphoma</b>	Lymphoma		
<b>Melanoma</b>	Melanoma		
<b>Meningioma</b>	Meningioma		



**Reference database contains >2000 tumor specimens**





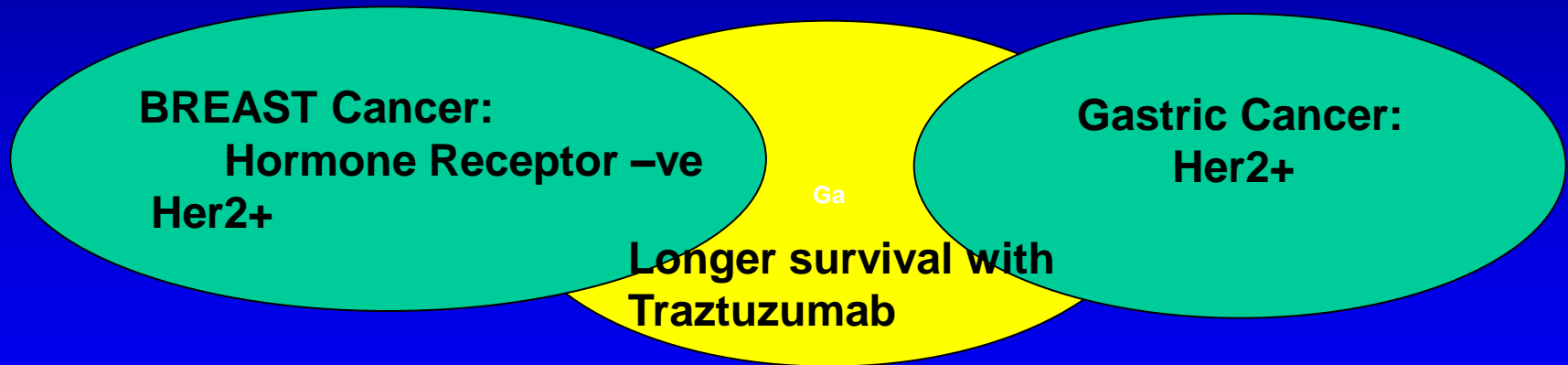
# CUP-ONE Trial has two parts: **clinical** and translational

- **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?

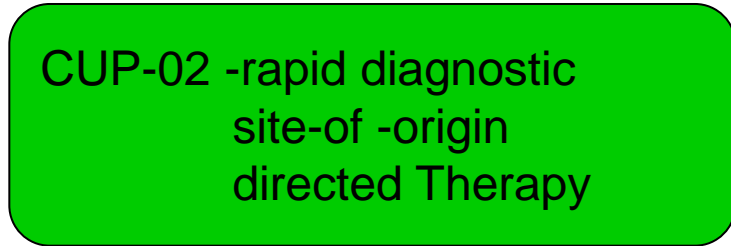
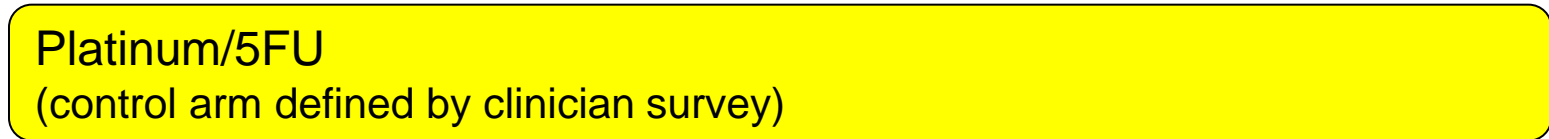
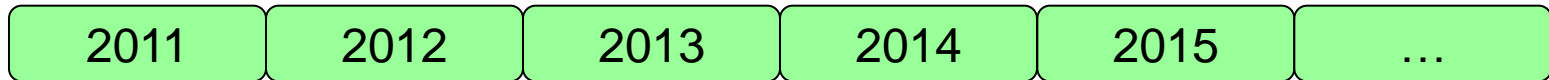
- Molecular Heterogeneity has major clinical implications (?not site of origin)



- 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

# CUP Global randomised trials

## Carcinoma Unknown Primary

2011

2012

2013

2014

2015

...

GEFCAPI-04      site-of -origin  
directed Therapy rll

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](mailto: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 !

## CANCER OF UNKNOWN PRIMARY CONFERENCE

LONDON 27 April 2012

*Progress in the Search for Improved Diagnosis,  
Management and Treatment*

**Chairman:**

**Dr F Anthony Greco**

Director of the Sarah Cannon Cancer  
Center, Nashville, USA.

**Keynote Speaker:**

**Prof Nicholas Pavlidis**

Director of the Medical Oncology  
Department University of Ioannina,  
Greece.  
Chairman of the ESMO Guidelines  
Group.

**Attend, Discover, Apply**

**Topics:**

- **Management and treatment approaches for CUP – a global perspective**
  - Implementing NICE Guidance in a general hospital
  - Targeting treatment to patients with specific mutational profiles
- **Latest international research findings**
  - The Search for Improved Diagnosis using Molecular Profiling
  - Exploiting underlying biological factors of highly metastatic cancers to develop more rational treatments
- **Improving the Patient experience**


*What delegates said about the first International Conference in 2009:*

*...the topics were smartly balanced between technology and clinical issues. I thought the whole conference was excellent; a very high academic standard. Very useful day that opens up a complex hidden cancer group. To bring together patients, carers, healthcare professionals experiences and insights is very important for the future understanding of CUP ...a real milestone in CUP. The first dedicated CUP conference, which was a huge success ...It is good to make contacts of others working to progress the support & management of this neglected group of patients. It was a novel experience to be in a room of people speaking the same language.*



For Information & Registration:

[www.cupfoundjo.org](http://www.cupfoundjo.org)

**CUP**  
**2012**  
cancer of  
unknown  
primary  
foundation  


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