The UK NCRI CUP-One Trial:

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

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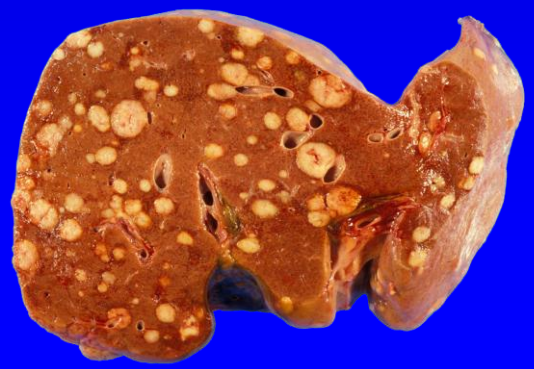

Cancer of Unknown Primary (CUP) Conference April 2012

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

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What matters
is improving outcomes
Not diagnosis?

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mary 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’?

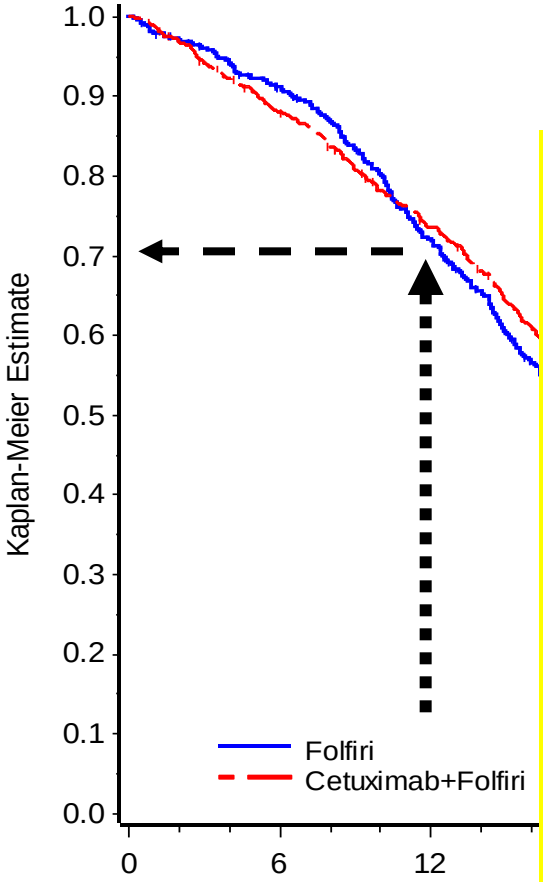
2004-2009 Survival of advanced Metastatic Cancer:

Site Of Origin	Population Incidence / Rank Global	Chemotherapy Backbone	Median Survival Months Untreated	Median Survival Months treated
Lung	Top 3	Platinum	7-9	8-12
Pancreas	Top 7	Gemcitabine	3-6	5-8
Gastro-oesophageal	Top 7	Platinum + FP	4-6	8-11
Bladder	Top 7	Platinum	7-9	10-12
HCC	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
Breast	Top 3	? taxane	?	18 -24
Colon	Top 3	Oxaliplatinum + FP	6-9	18 -24
Prostate (Hormone refractory)	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"??

Overall Survival Time (months)

At Risk											
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

Cancer of Unknown Primary (CUP): Chemoth… Summary

Type (years)	…	…	…	Survival …
… Platin… 198…				8
… Platinum based 2000-200…			…50)	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?

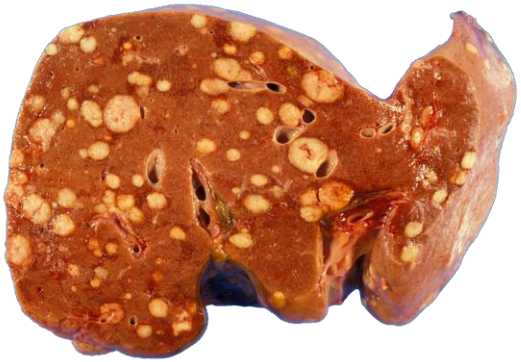
*…….maybe **no**….. but :*

- 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
  - 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



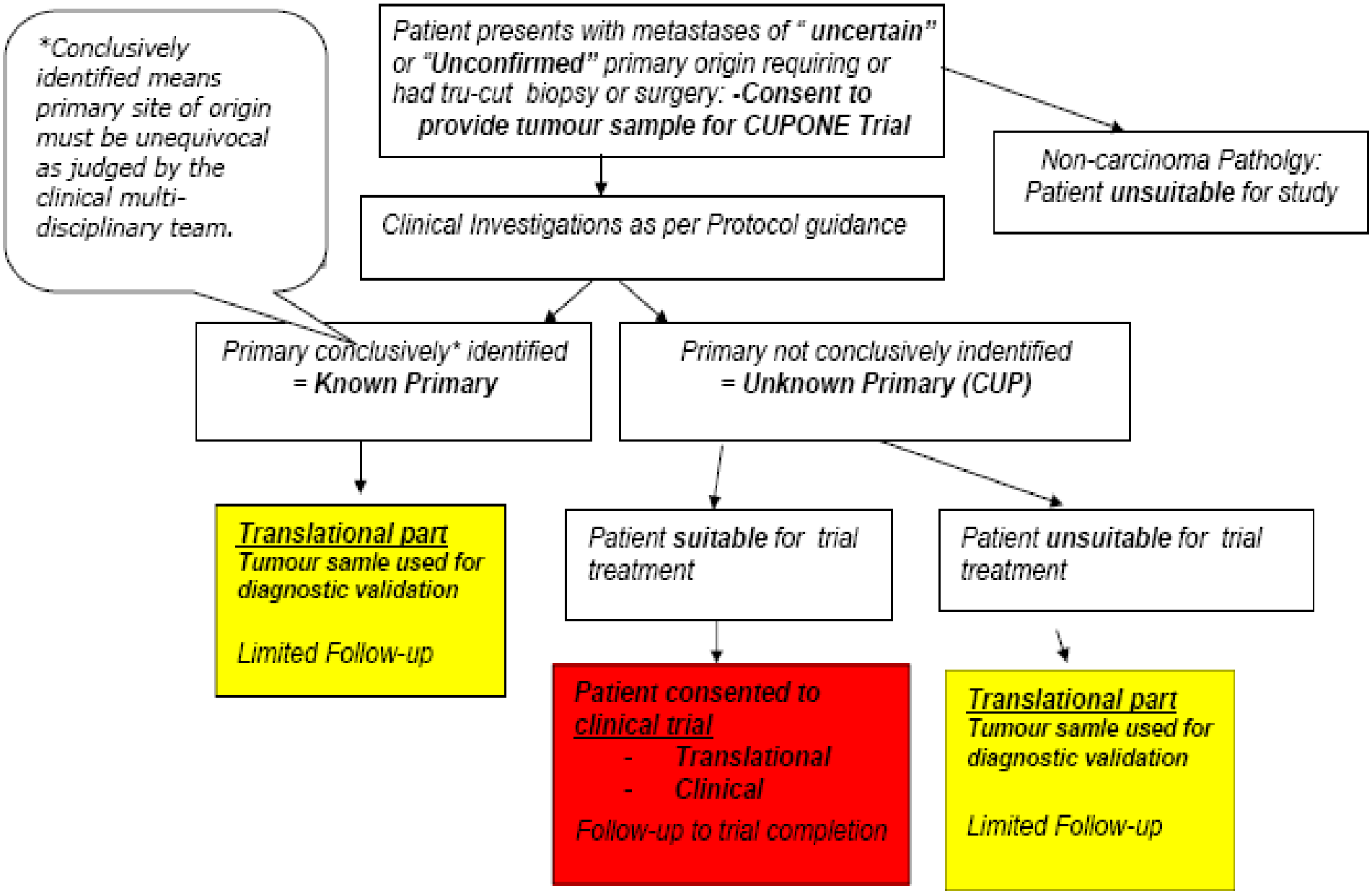
CUP ONE: UPDATE

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



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

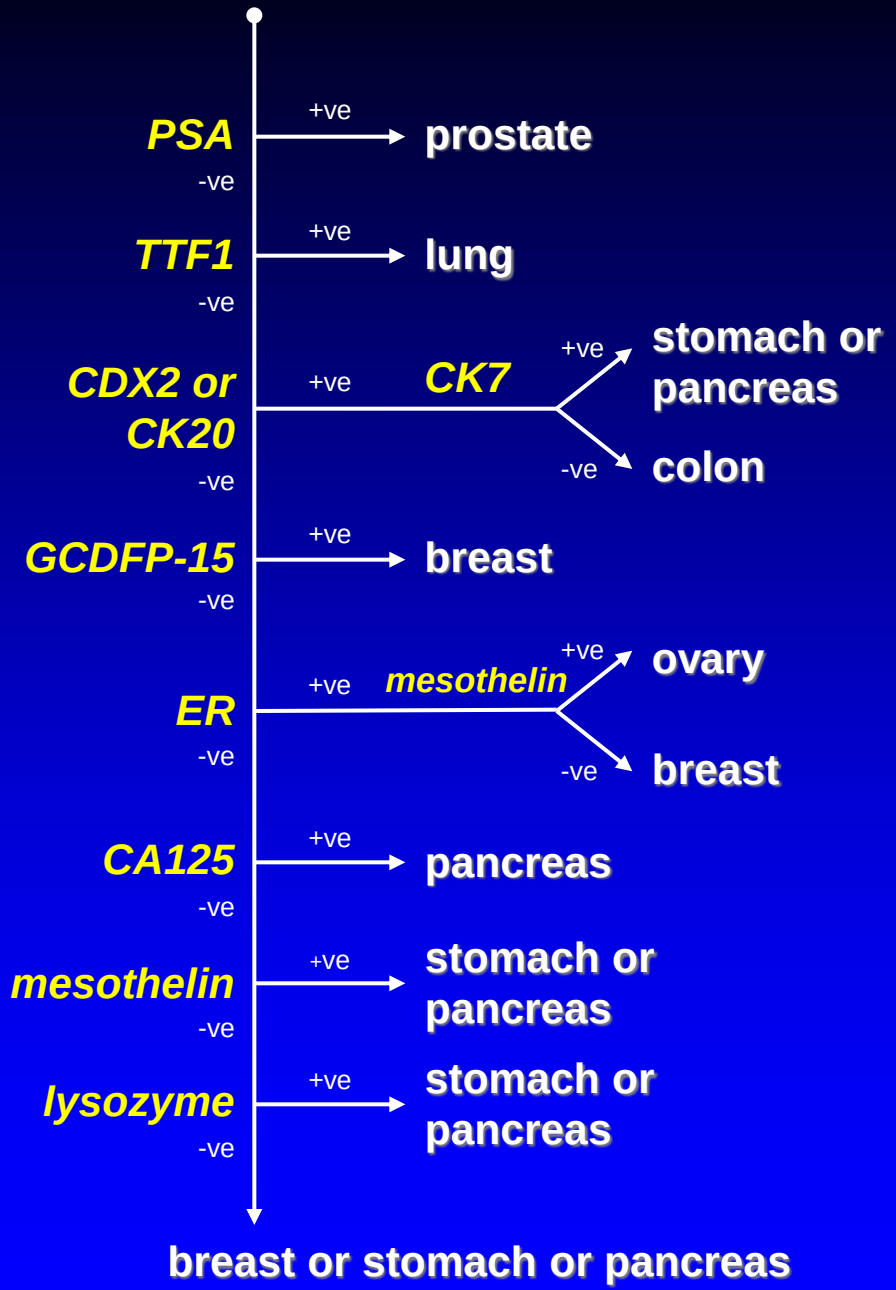
	% Positivity of each marker									
Primary site	**PSA**	**TTF1**	**GCD FP15**	**CDX2**	**CK20**	**CK7**	**ER**	**Meso thelin**	**CA 125**	**Lyso zyme**
Breast	0	0	54	0	0	83	77	3	6	14
Colon	0	0	9	83	68	4	2	2	0	53
Lung	0	91	4	2	2	91	9	39	39	43
Ovary serous	0	0	6	0	0	89	83	94	89	0
Pancreas	0	2	2	**0**	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.**

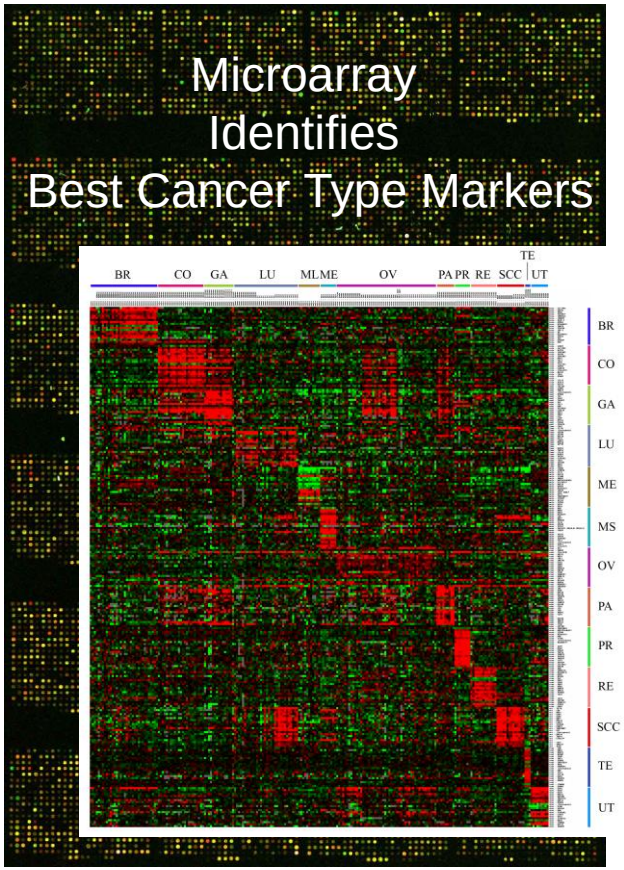
Decision Tree



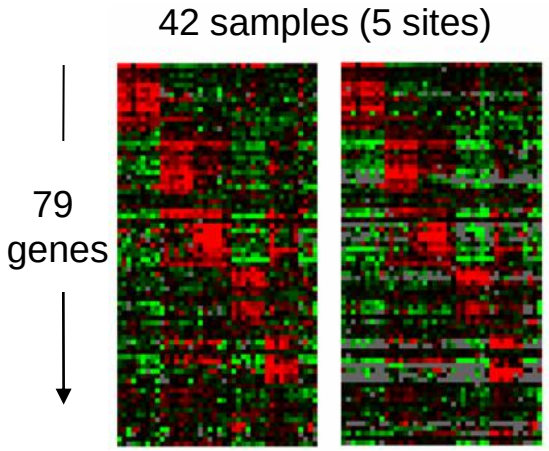
Dennis, J.L., et al…karen Oien Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm. Clin Cancer Res, 2005. 11(10): p. 3766-72

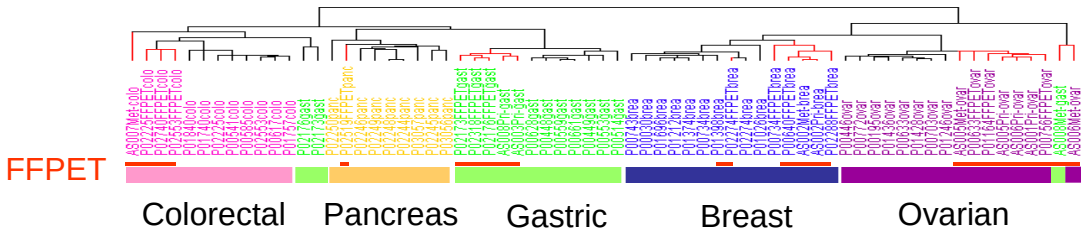
Cancer Site of Origin Diagnostic

Peter MacCallum Cancer Centre, Melbourne, Australia



Translate test to qRT-PCR



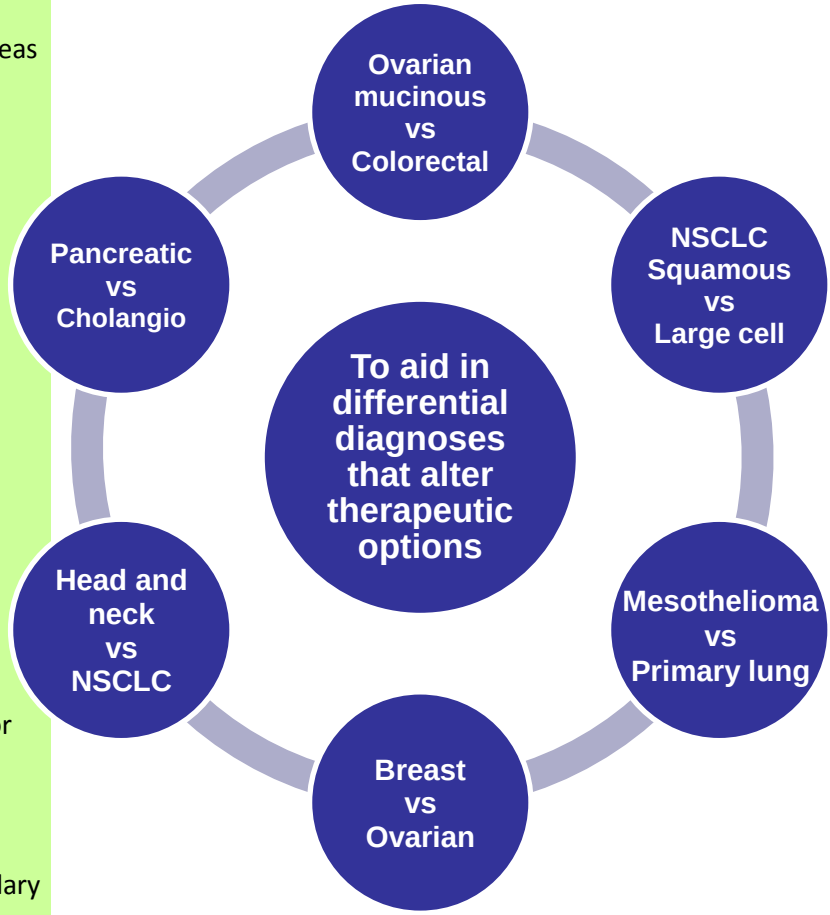


Tothill *et al 2005* *CancerRes.65:10*

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

CancerTYPE ID Classifies 54 Histological Subtypes

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



Reference database contains >2000 tumor specimens

CUP-ONE Trial has two parts: clinical and translational

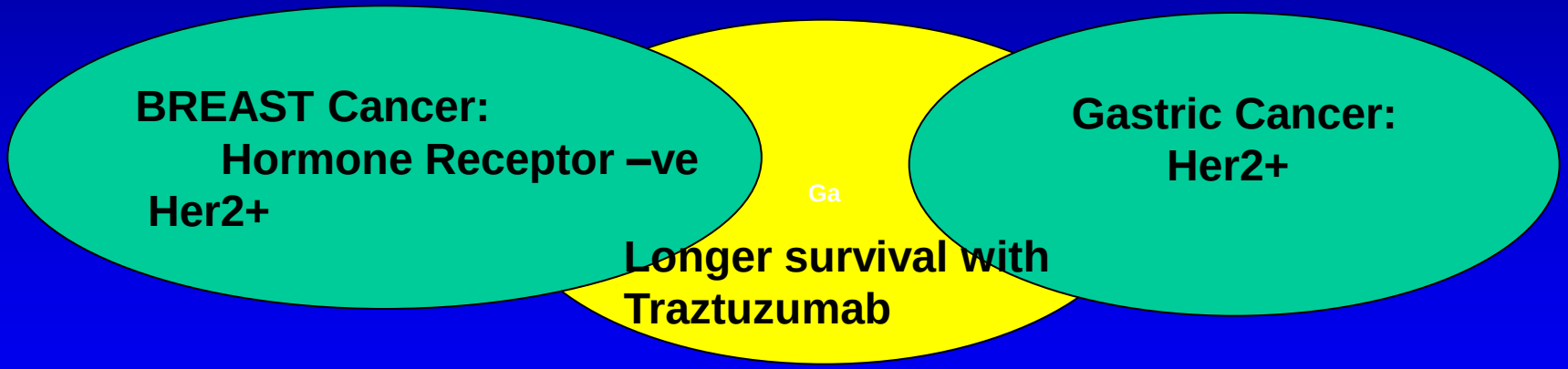
- Clinical part of trial
  - CUP by exclusion of known primary
  - Phase II epirubicin, cisplatin, capecitabine
    - 20 patients : Futility / safety analysis
    - 56 patients : efficacy analysis
    - ? randomised Phase II –
      - Vandetanib maintenance (AZ-NCRN)

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

2011	2012	2013	2014	2015	…

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

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

CUP-03
(Molecular analysis)

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 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

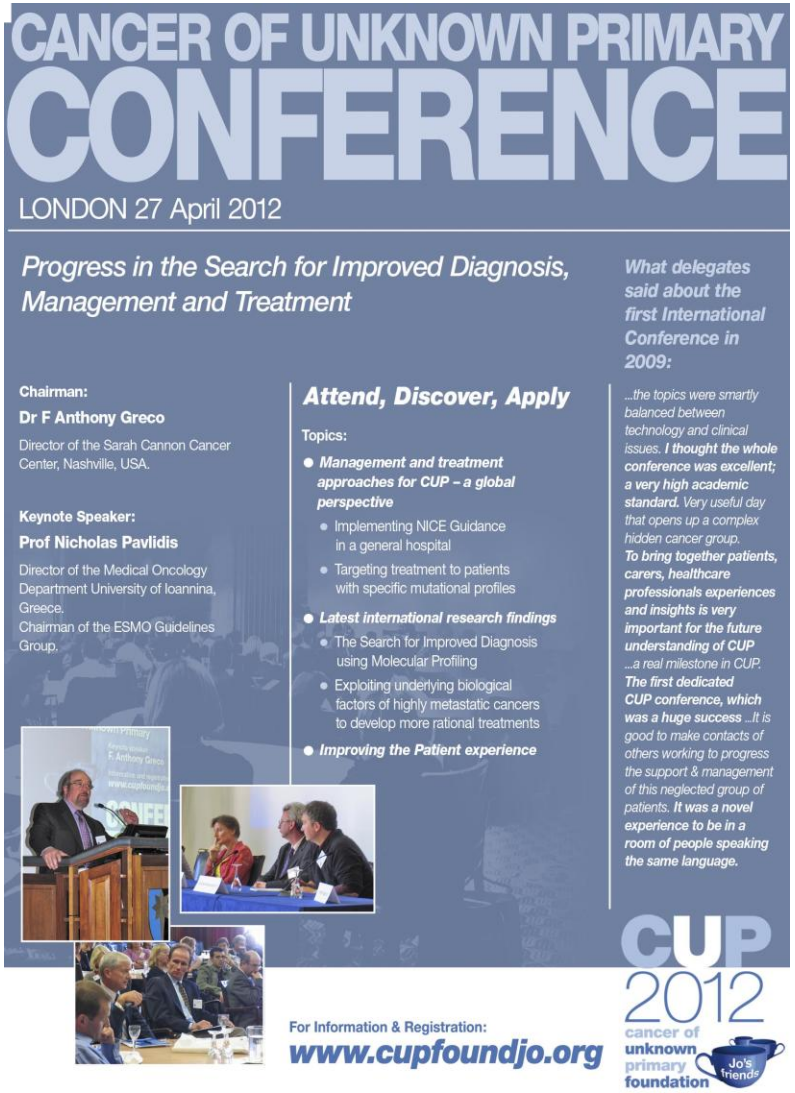
CUP-ONE Study Team

- **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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