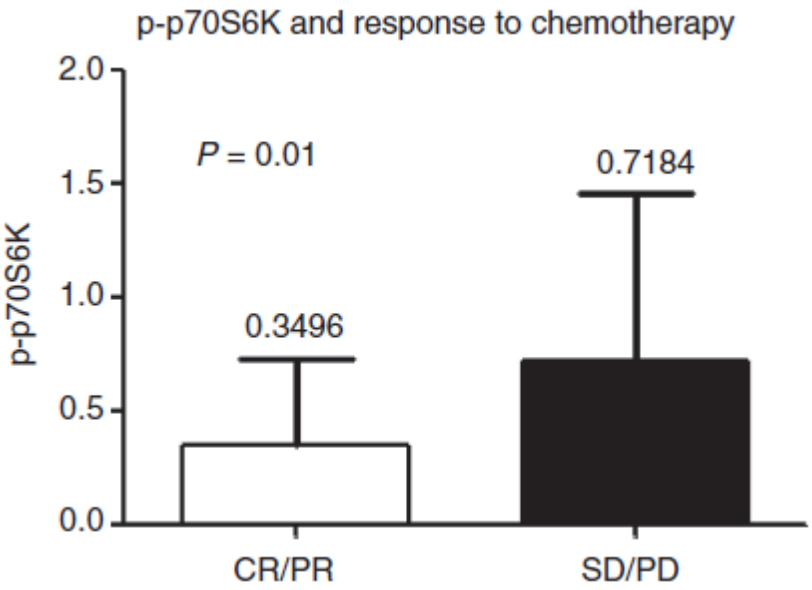
TAX-TORC: an ECMC story

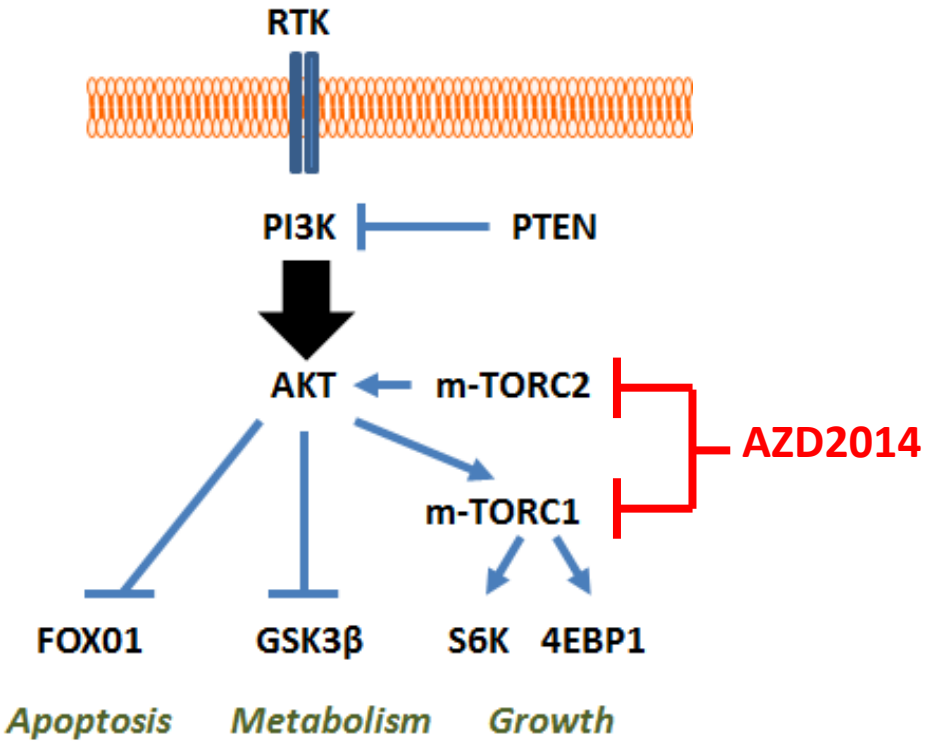
Udai Banerji, Mona Parmar, Bristi Basu, Matthew Krebs, Johann de Bono

10th Annual ECMC meeting

10th May 2017

Background



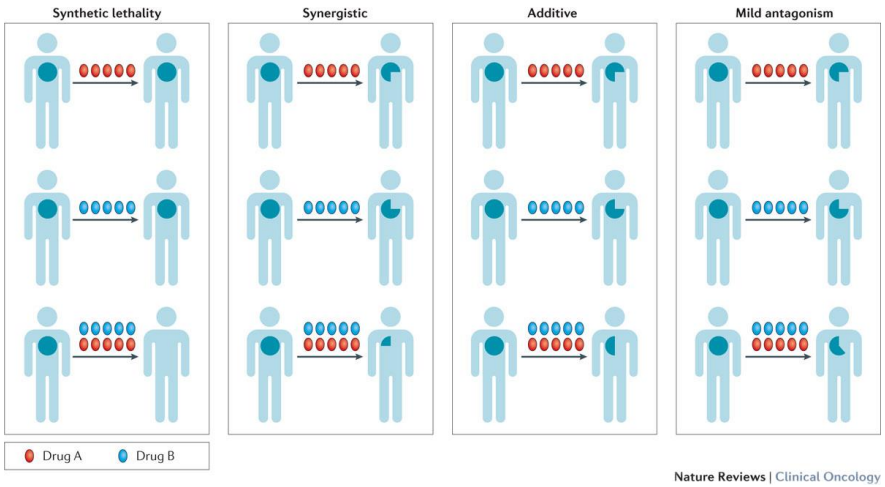


- Elevated p-S6K in cancer cells derived from ascites in patients with ovarian cancer is associated with resistance to future chemotherapy

- AZD2014 is a dual m-TORC1/2 inhibitor and targets signalling upstream of S6K

Caren C, Banerji U Mol Cancer Ther 2012, 11:1609-17 *Basu B, Banerji U Clin Cancer Res 2015, 21:3412-9*

Combination therapy



PERSPECTIVES

OPINION

Combine and conquer: challenges for targeted therapy combinations in early phase trials

Juanita S. Lopez and Udai Banerji

has been successfully overcome by a combination therapy approach, either with chemotherapy (for example, by combining rituximab with chemotherapy as therapy for diffuse large-B-cell lymphoma)[9,10], or with other targeted treatments (such as everolimus and letrozole in the treatment of hormone-receptor-positive breast cancer)[11]. In addition, a large number of mechanisms of acquired resistance have been discovered in tumour-cell clones that have evolved and

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JOURNAL OF CLINICAL ONCOLOGY | BIOLOGY OF NEOPLASIA

Development of Therapeutic Combinations Targeting Major Cancer Signaling Pathways

Timothy A. Yap, Aurelius Omlin, and Johann S. de Bono

nature biotechnology

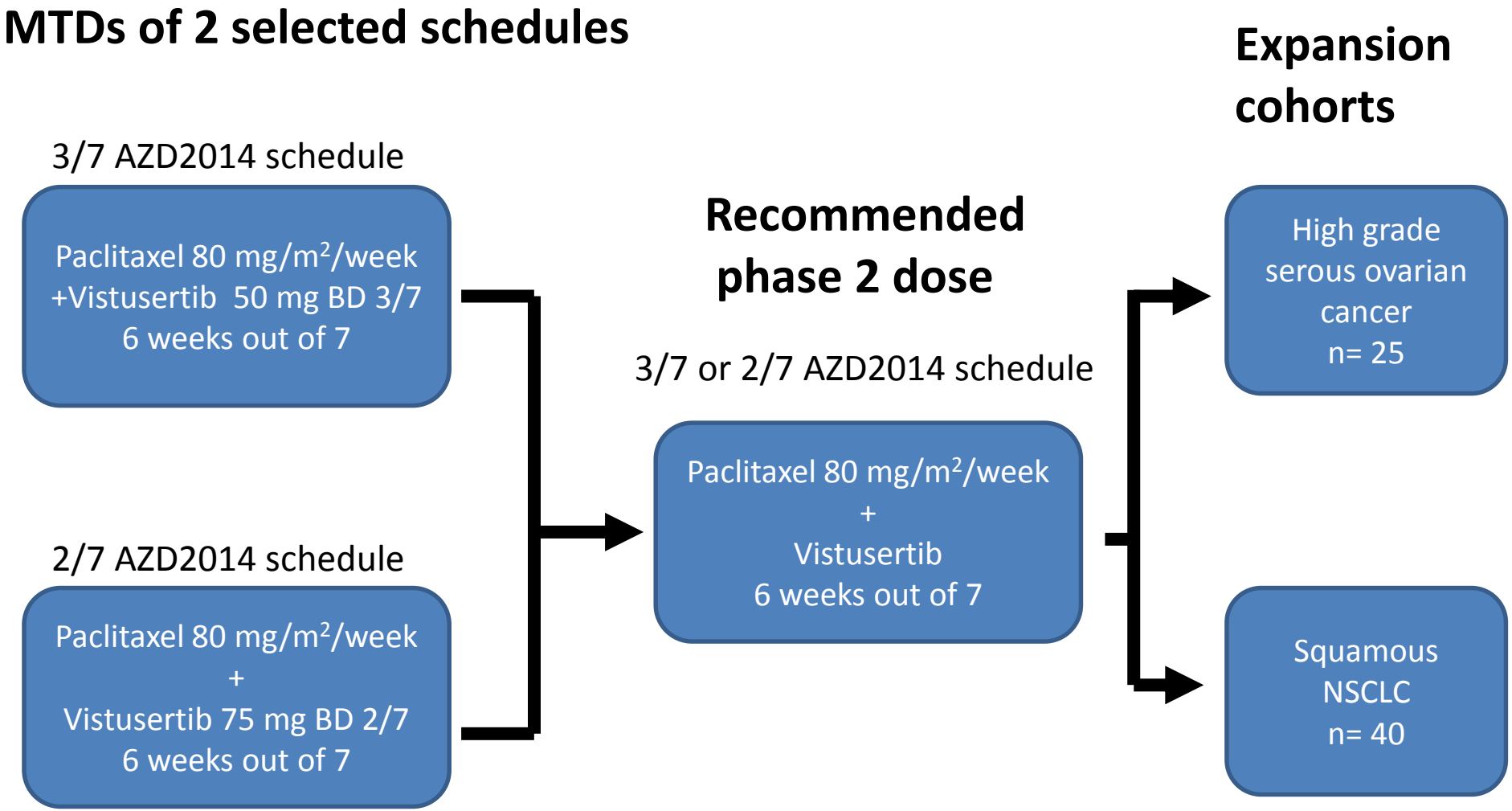
Combinatorial drug therapy for cancer in the post-genomic era

Bissan Al-Lazikani[1], Udai Banerji[1–3] & Paul Workman[1]

- Multiple signalling inhibitors are developed in combination
- Critical to have sound hypothesis
- High rates of toxicity and attention to scheduling, PK and PD critical to trial design

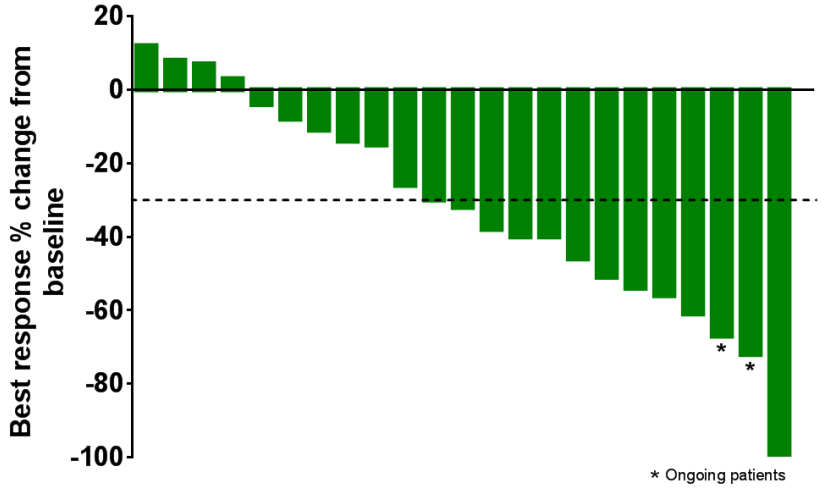
Lopez J, Banerji U Nature Rev Clin Oncol 2017, 14:57-66
Yap T, de Bono J JCO 2013, 31:1592-605
Al-Lazikani B, Banerji U Workman P Nat Biotechnology 2012, 30:679-92

Study Design

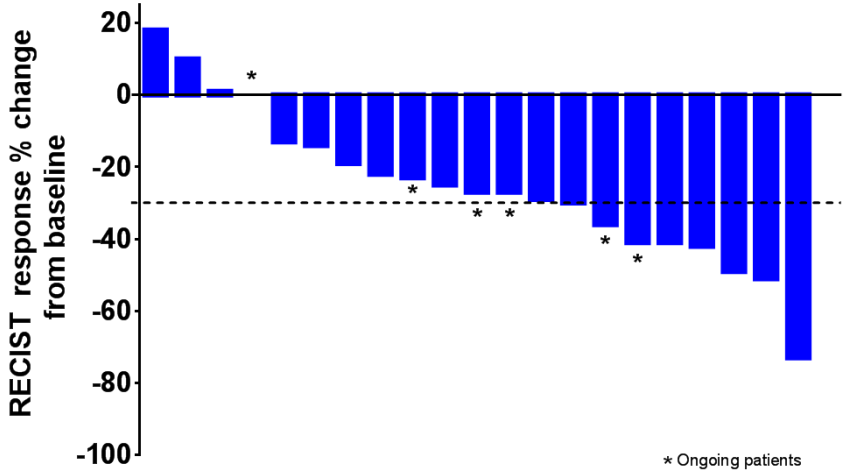


Results – expansions

Ovarian cancer expansion



Squamous NSCLC expansion

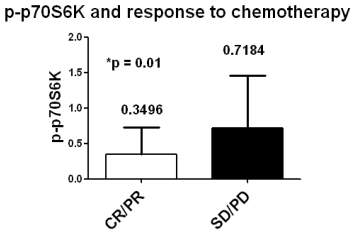


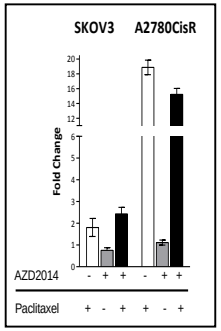
- 52% RECIST and 60% GCIG CA125 response rate in high grade serous ovarian cancer
- Results led to randomized phase 2 study OCTOPUS study of paclitaxel vs paclitaxel + vistusertib under the auspices of the NIHR
- 43% RECIST response rate in squamous NSCLC
- Biomarker data to further enrich populations likely to respond in squamous NSCLC ongoing

Banerji U # 362 PD ESMO 2016
Banerji U # O3.2 TAT 2017

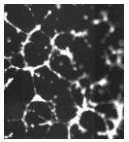
ECMC network a conduit for rapid translation of scientific ideas

2012 pre clinical studies

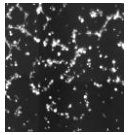




Control



Pacliaxel + AZD2014



2013-2014 dose escalation

3/7 AZD2014 schedule

Paclitaxel 80 mg/m²/week
+Vistusertib 50 mg BD 3/7
6 weeks out of 7

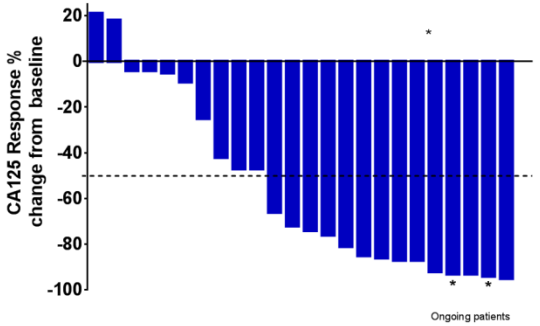
2/7 AZD2014 schedule

Paclitaxel 80 mg/m²/week
+
Vistusertib 75 mg BD 2/7
6 weeks out of 7

Recommended phase 2 dose

Paclitaxel 80 mg/m²/week
+
Vistusertib
6 weeks out of 7

2014-2015 dose expansion



2015 Randomized phase 2

NIHR study

Clinical trials are team work

Site study team

Doctor

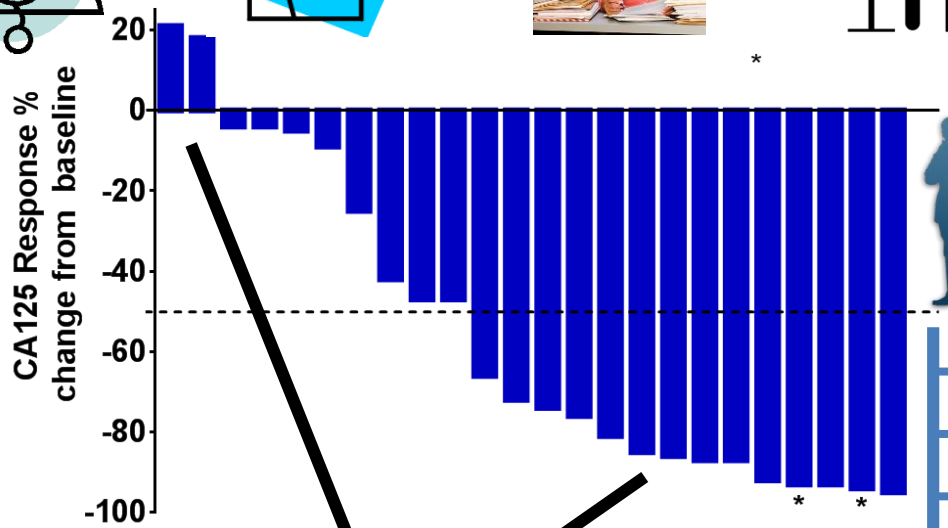
Nurse

Trial coordinator

Data manager

Central translational research team

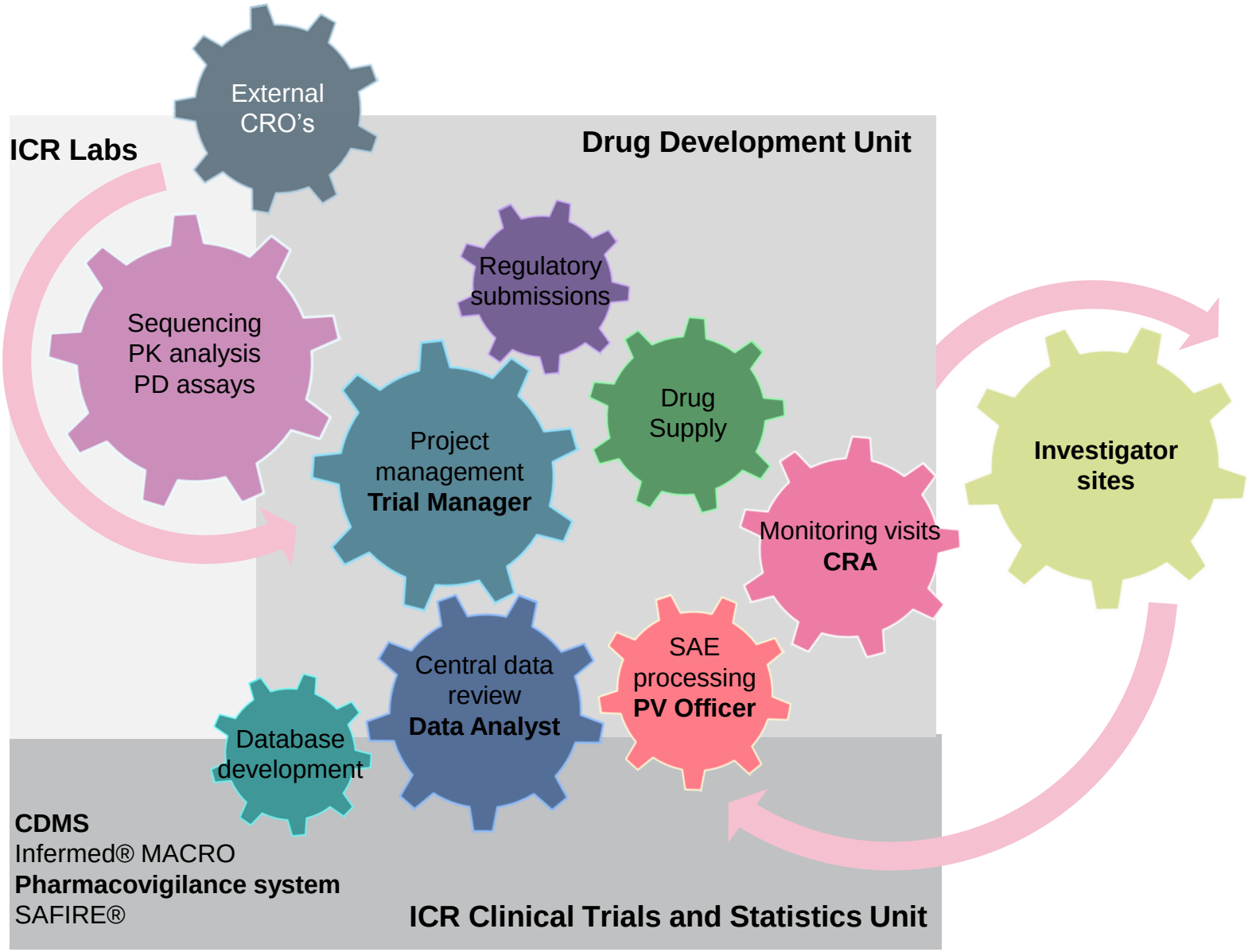
- Pharmacokinetics
- Pharmacodynamics
- Predictive biomarkers



Sponsor study team

- Regulatory
- Monitor
- Study manager
- Pharmacovigilance
- Data base
- Statistics
- IDMC
- Public, Patient interaction
- ECMC administration
- Pharma team

IIT team: Sponsor-level management

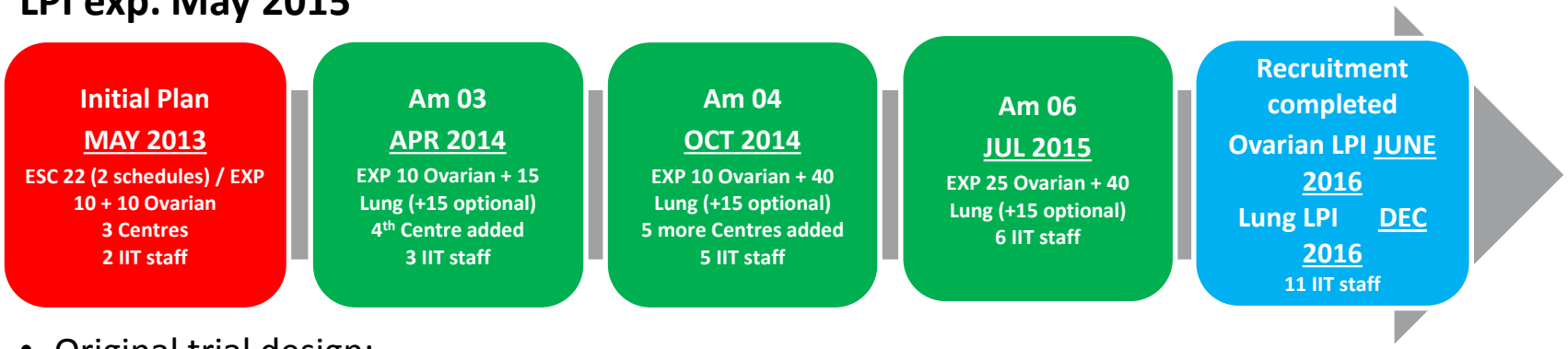


TAX-TORC major changes

FPI May 2013

LPI exp. May 2015

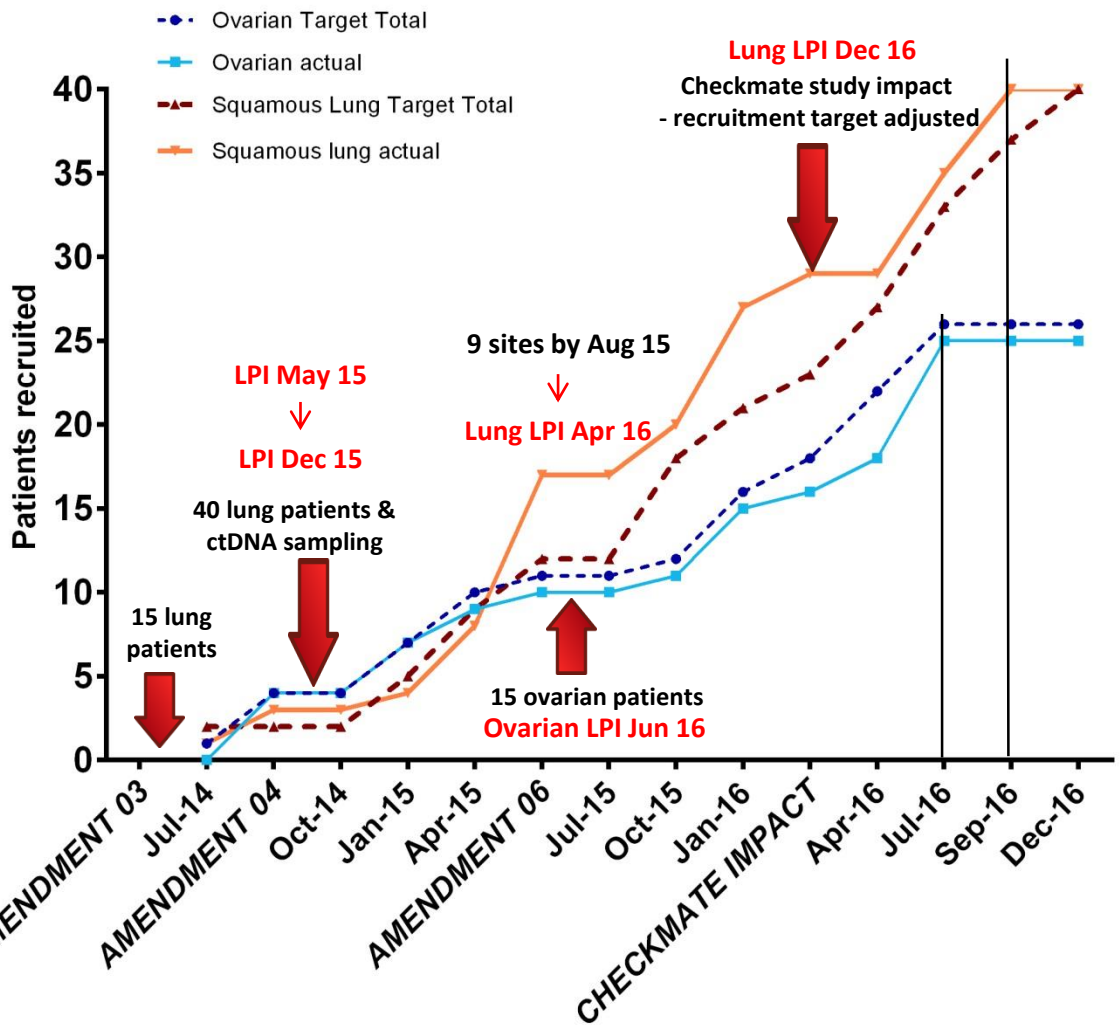
LPI exp. Dec 2016



- Original trial design:
  - sequential dose escalation of 3/7 days and 2/7 days schedules
  - 2 expansion cohorts - 10 patients with ovarian cancer per schedule
  - **Total 42** patients
- Amendments to expand 3/7 schedule (whilst 2/7 schedule ongoing) adding:
  - 15 patients with squamous cell lung cancer (SqCLC) (Am 03 Apr-2014)
  - 40 patients with SqCLC (Am 04 Oct-2014)
  - 15 additional patients with ovarian cancer (Am 06 Jul-2015)
- Final design:
  - 40 patients with SqCLC
  - 25 patients with ovarian cancer
  - **Total 87** patients

TAX-TORC challenges: recruitment

- 40 SqCLC patients - decreasing population, co-morbidities, high drop out rate
- 3 sites to 9 – set up and SIV's took 6 months: all open by August 2015
- Monitoring resource increased
- Re-forecasted accrual rates at 3 main points in the study
  - Frequent contact CI to PI's
  - TAX-TORC newsletters
- Data cleaning for 87 patients and 9 close out visits
- Final timelines:
  - LPI: 21-Sept-2016
  - Data cut off: 21-Mar-2017
  - Clean data: 21-June-2017
  - Final report: by 21-Sept-2017

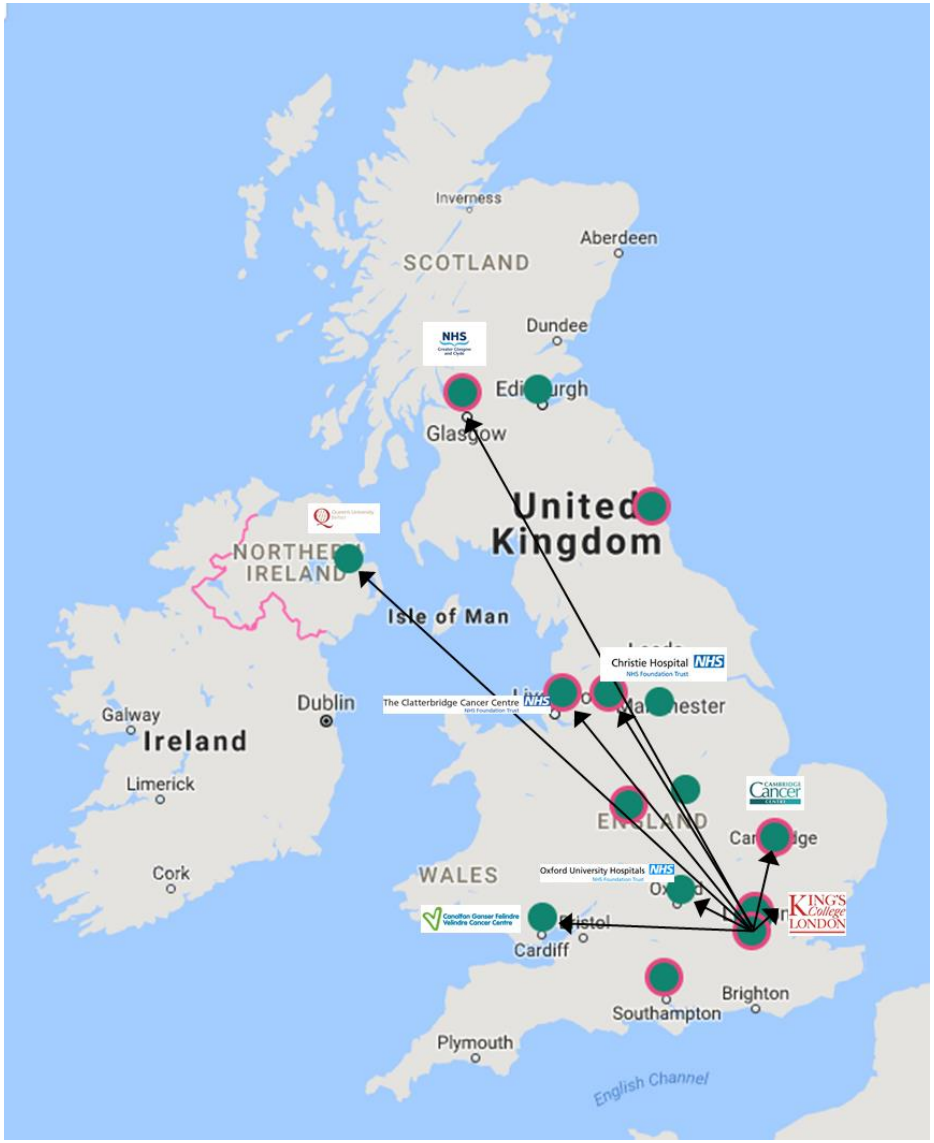


TAX-TORC challenges: samples

- Archival Tumour → 87 patients
  → DNA extracted → Sequenced ~ 70 genes including PI3K mutations and oncogenes
- Pharmacokinetics
  » Blood plasma → 704 samples
- Pharmacodynamics
  - Blood → Platelet rich plasma (PRP) → 396 samples
  - Blood Serum → 176 samples
  - Fresh biopsies → 9 samples
- Buccal swabs → 65 patients
  → baseline comparator sequencing
- Serial bloods → 780
  → 6 time points: baseline, C1D1, C1D43, PR, PD, EOS
  → DNA extracted → Sequenced ~ 70 genes including PI3K mutations and oncogenes

All shipped/posted from 8 sites around the UK to the ICR to be logged, stored and analysed. Analysis completed by 1 May-2017.

TAX-TORC Successes



Recruitment completed early**:**

LPI 21-Sept-2016

Follow-on: national, randomized Phase II trial in progress (Octopus).

Recruitment target exceeded thanks to our ECMC investigators:

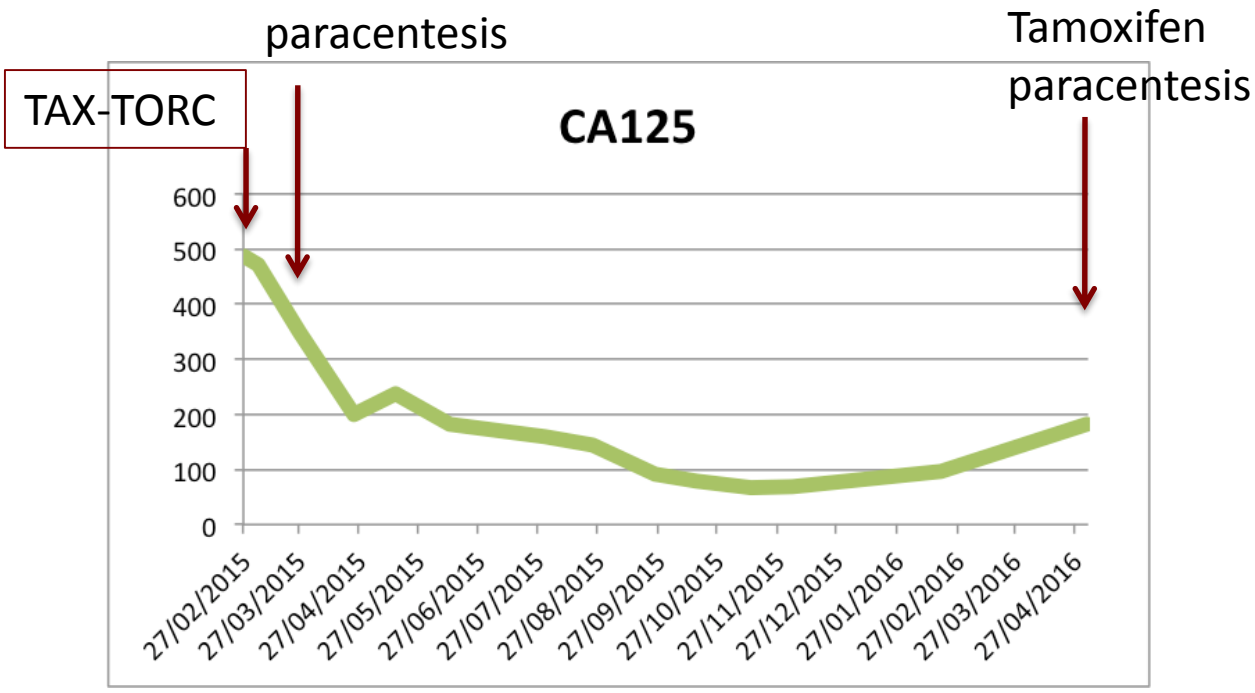
- Addenbrooke's (PI: Dr Bristi Basu)
- Belfast (PI: Prof. Richard Wilson)
- Guys Hospital (PI: Dr. James Spicer)
- Cardiff (PI: Dr Rob Jones)
- Manchester (PI: Dr Matt Krebs)
- Clatterbridge (PI: Prof. Mike Brada)
- Oxford (PI: Dr Dennis Talbot)
- Glasgow (PI: Dr Nicola Steele)

Patient in high grade serous ovarian cancer expansion cohort

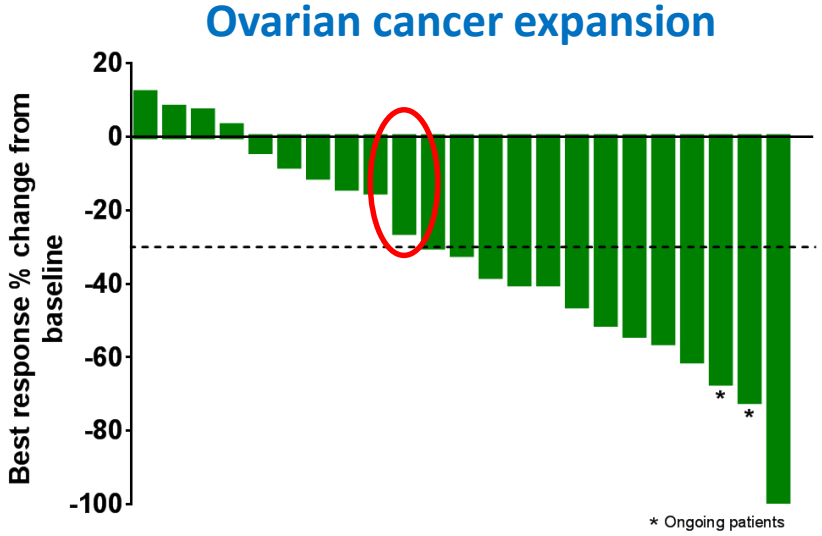
Platinum and paclitaxel refractory disease

Oncology History

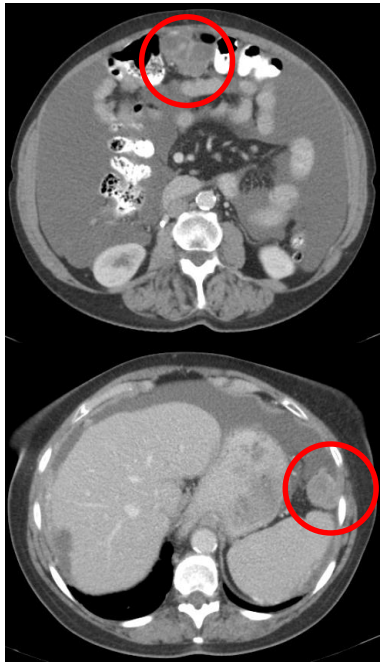
- Oct 2006 - Initial stage IV HGSOC (malignant pleural effusion)
  - platinum-based therapy with good partial response
- May 2008 – relapse: ascites, diffuse peritoneal disease
  - carboplatin + paclitaxel
  - Oct 2008 - TAH, BSO, omentectomy: **HGSOC ER + residual disease**
    - adjuvant carboplatin + paclitaxel then maintenance letrozole
- Oct 2010 – progressive disease with ascites, hydronephrosis and peritoneal disease
  - Oct 2010 – Apr 2011 carboplatin + caelyx
- Nov 2011 – progression of ascites and intra-abdominal disease
  - Nov 2011 – Mar 2012 carboplatin + paclitaxel followed by maintenance exemestane
- Feb 2013 – Disease progression
  - Feb 2013 – Apr 2013 – **3 cycles of weekly paclitaxel**
- Apr 2013 – Increase in intra-abdominal disease, ascites and CA125
  - May 2013 – Oct 2013 Carboplatin + caelyx
- July 2014 Progressive diseae
  - July 2014 – Sep 2014 Gemcitabine + carboplatin x 3 cycles
- Oct 2014 – Progressing disease
  - Oct-2014 – Dec 2014 **Carboplatin** + caelyx
- Jan 2015 Progressive peritoneal disease, large volume ascites, hydronephrosis
  - **Feb 2015 – Dec 2016 - TAX-TORC trial: weekly paclitaxel 80mg/m^2 + AZD2014 50 mg bd 3/7 x 6 cycles**
  - **Best response stable disease by RECIST 1.1, GCIG CA125 response**
- May 2016 – progression of ascites



Best radiological response 24%
Stable Disease



27.2.15



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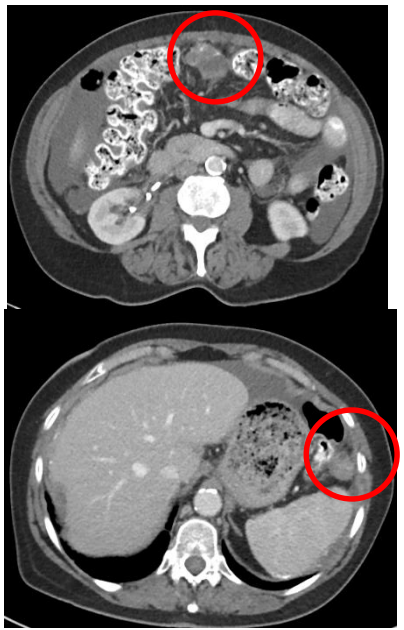
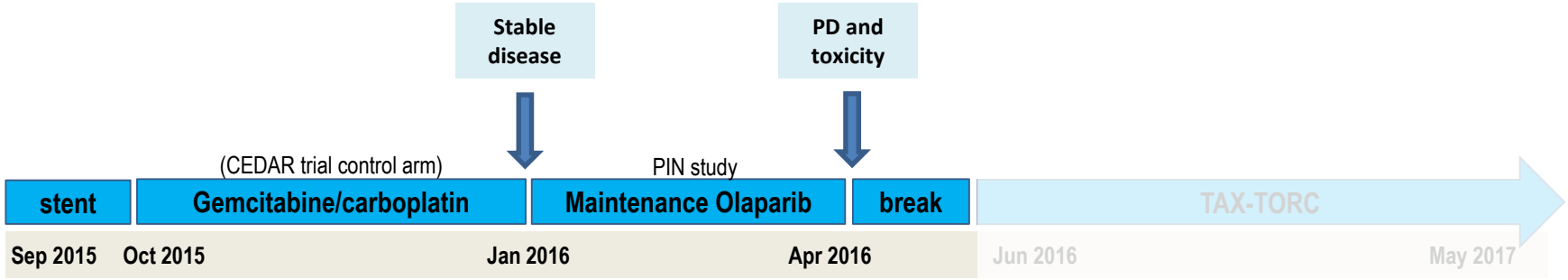
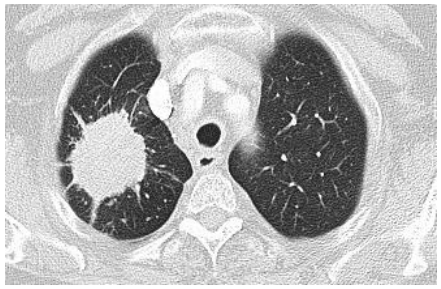


Case study – Squamous Cell Lung Cancer

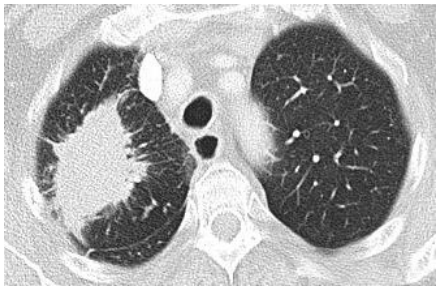
- 71 year old female
- Hospital Chaplain (local hospital)
- Ex smoker – 53 pack-years
- Diagnosed Sep 2015: Stage IV Squamous cell carcinoma of right lung – T2BN3M1a (small pericardial effusion). Extensive mediastinal LN, displacement trachea and partial obstruction right main bronchus at presentation



Presentation

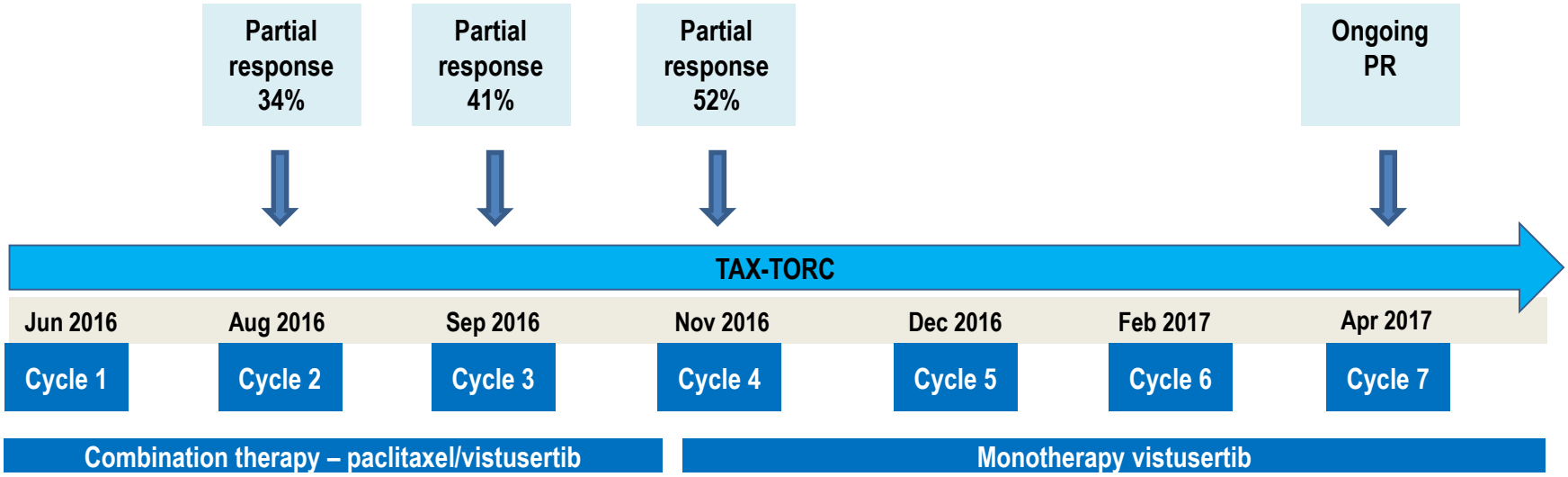


Post 1st line maintenance

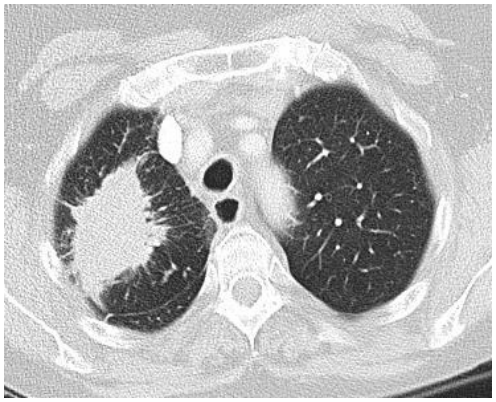


TAX-TORC TRIAL

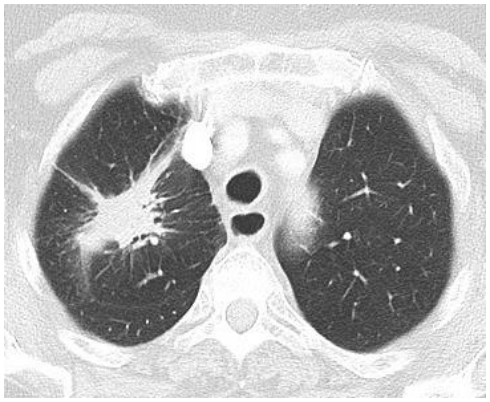
The Christie
TOWARDS A FUTURE WITHOUT CANCER



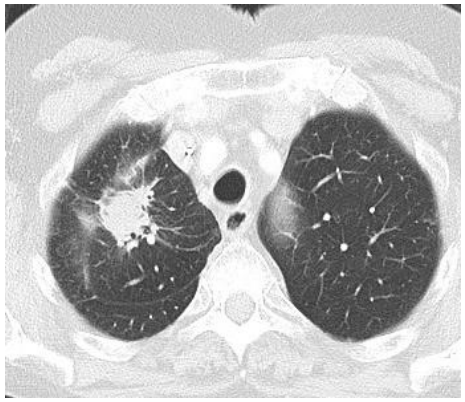
Baseline



Post cycle 1



Post cycle 4



TOXICITY AND QUALITY OF LIFE

The Christie
TOWARDS A FUTURE WITHOUT CANCER

- Remained largely asymptomatic
- Continued to work part-time throughout and attend weekly hospital visits
- Excellent QOL
- Almost 1 year on treatment
- Series of G1/2 toxicities during C1 and C2 – diarrhoea, nausea, anorexia, fatigue, anaemia
- G2 neutropenia and anaemia during cycle 3 with 1-2 doses deferred
- Tolerated step-down monotherapy well

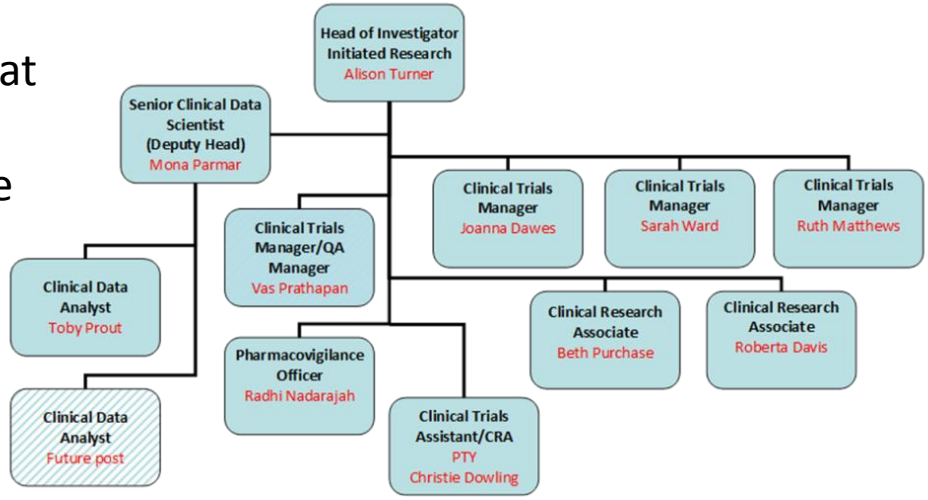
Promising combination therapy for SqCC lung cancer with manageable toxicity profile

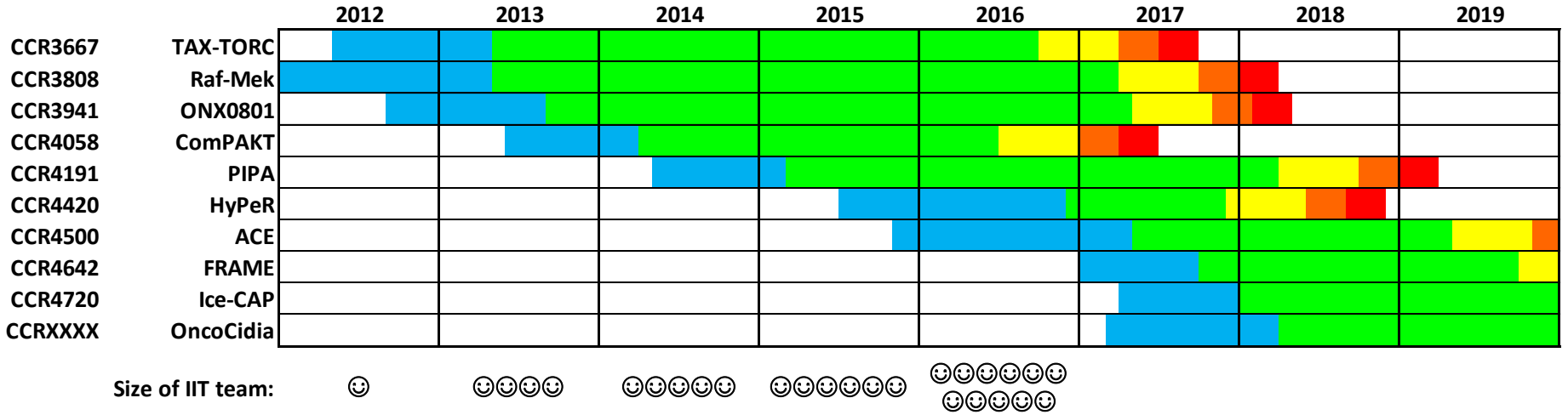
The ICR/RM ECMC

- This ECMC Combinations Alliance trial is one of several investigator-initiated trials sponsored by our Phase I group at The Institute of Cancer Research.
- The ECMC has been key to our serving men and women suffering from cancer to try and impart benefit from early phase clinical trials.
- We are running our investigator-initiated trials across the whole ECMC network collaborating with almost all the ECMC sites.

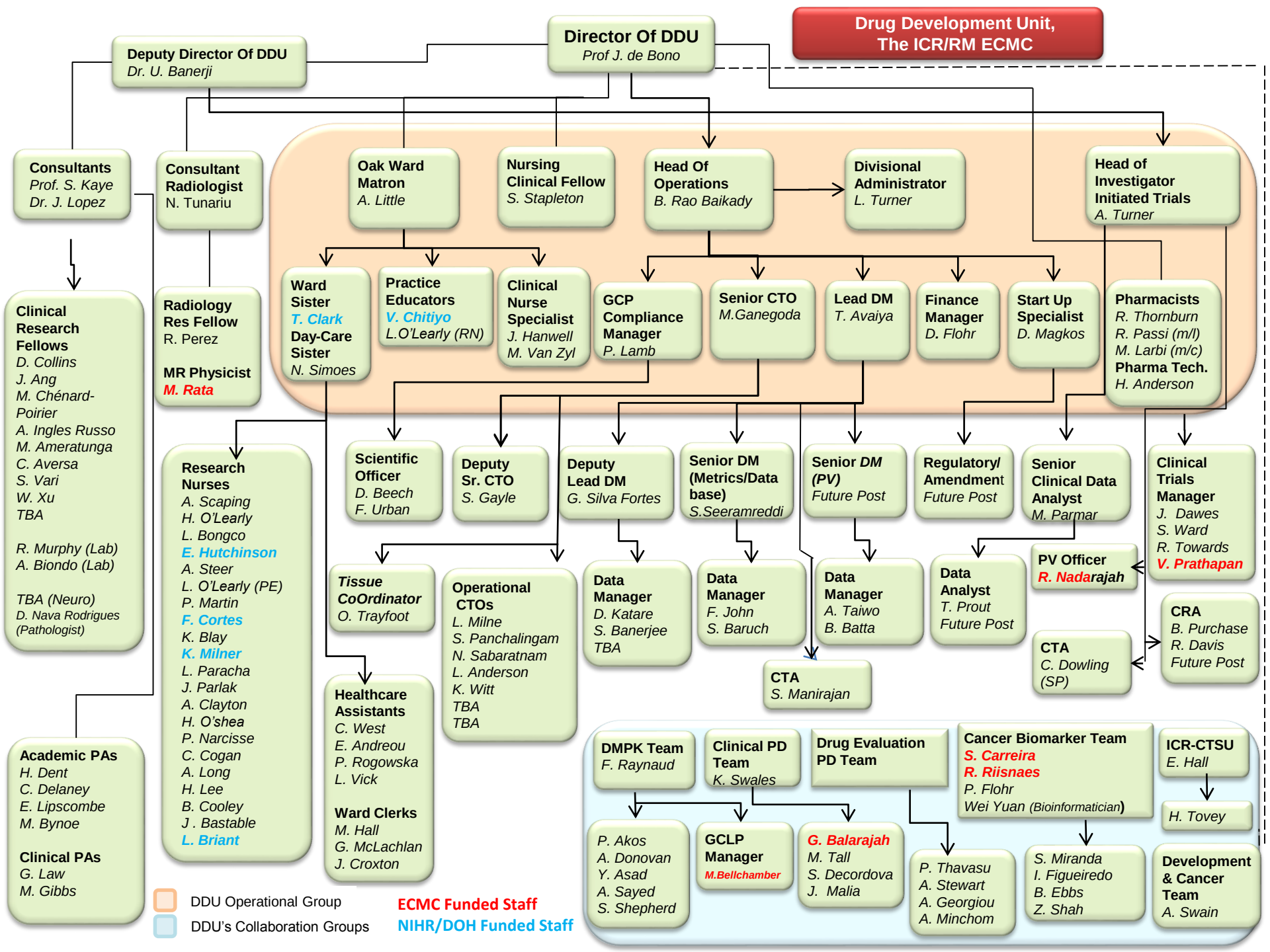
Our Investigator-initiated trials (2017)

- To deliver these trials we set up **a 'sponsor' team** for our Phase I portfolio, aiming to treat 25-30% of our Phase I patients on IIT's
- Our IIT team has expanded to accommodate a growing portfolio of IMP trials and is affiliated with The ICR CTSU
- We work with sites across ECMC network, opening trials rapidly (eg COMPAKT trial)





A Team Effort!


Drug Development Unit,
The ICR/RM ECMC
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Prof J. de Bono
Deputy Director Of DDU
Dr. U. Banerji
Consultants
Prof. S. Kaye
Dr. J. Lopez
Consultant Radiologist
N. Tunariu
Oak Ward Matron
A. Little
Nursing Clinical Fellow
S. Stapleton
Head Of Operations
B. Rao Baikady
Divisional Administrator
L. Turner
Head of Investigator Initiated Trials
A. Turner
Ward Sister
T. Clark
Day-Care Sister
N. Simoes
Practice Educators
V. Chitiyo
L.O'Learly (RN)
Clinical Nurse Specialist
J. Hanwell
M. Van Zyl
GCP Compliance Manager
P. Lamb
Senior CTO
M.Ganegoda
Lead DM
T. Avaiya
Finance Manager
D. Flohr
Start Up Specialist
D. Magkos
Pharmacists
R. Thornburn
R. Passi (m/l)
M. Larbi (m/c)
Pharma Tech.
H. Anderson
Clinical Research Fellows
D. Collins
J. Ang
M. Chénard-Poirier
A. Ingles Russo
M. Ameratunga
C. Aversa
S. Vari
W. Xu
TBA
R. Murphy (Lab)
A. Biondo (Lab)
TBA (Neuro)
D. Nava Rodrigues (Pathologist)
Radiology Res Fellow
R. Perez
MR Physicist
M. Rata
Research Nurses
A. Scaping
H. O'Learly
L. Bongco
E. Hutchinson
A. Steer
L. O'Learly (PE)
P. Martin
F. Cortes
K. Blay
K. Milner
L. Paracha
J. Parlak
A. Clayton
H. O'shea
P. Narcisse
C. Cogan
A. Long
H. Lee
B. Cooley
J . Bastable
L. Briant
Scientific Officer
D. Beech
F. Urban
Deputy Sr. CTO
S. Gayle
Deputy Lead DM
G. Silva Fortes
Senior DM (Metrics/Data base)
S.Seeramreddi
Senior DM (PV)
Future Post
Regulatory/ Amendment
Future Post
Senior Clinical Data Analyst
M. Parmar
Clinical Trials Manager
J. Dawes
S. Ward
R. Towards
V. Prathapan
Tissue CoOrdinator
O. Trayfoot
Operational CTOs
L. Milne
S. Panchalingam
N. Sabaratnam
L. Anderson
K. Witt
TBA
TBA
Data Manager
D. Katare
S. Banerjee
TBA
Data Manager
F. John
S. Baruch
Data Manager
A. Taiwo
B. Batta
Data Analyst
T. Prout
Future Post
PV Officer
R. Nadarajah
CRA
B. Purchase
R. Davis
Future Post
CTA
S. Manirajan
CTA
C. Dowling (SP)
Healthcare Assistants
C. West
E. Andreou
P. Rogowska
L. Vick
Ward Clerks
M. Hall
G. McLachlan
J. Croxton
Academic PAs
H. Dent
C. Delaney
E. Lipscombe
M. Bynoe
Clinical PAs
G. Law
M. Gibbs
DMPK Team
F. Raynaud
Clinical PD Team
K. Swales
Drug Evaluation PD Team
Cancer Biomarker Team
S. Carreira
R. Riisnaes
P. Flohr
Wei Yuan (Bioinformatician)
ICR-CTSU
E. Hall
H. Tovey
P. Akos
A. Donovan
Y. Asad
A. Sayed
S. Shepherd
GCLP Manager
M.Bellchamber
G. Balarajah
M. Tall
S. Decordova
J. Malia
P. Thavasu
A. Stewart
A. Georgiou
A. Minchom
S. Miranda
I. Figueiredo
B. Ebbs
Z. Shah
Development & Cancer Team
A. Swain
DDU Operational Group
DDU's Collaboration Groups
ECMC Funded Staff
NIHR/DOH Funded Staff

A Big Thank You

- To the ECMC Secretariat
- To the whole ECMC Network
- To Cancer Research UK and the NCRI/DOH
- To our multidisciplinary team
- To our patients and families
- Many many others

Cancer research is a team effort!