TAX-TORC: an ECMC story

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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
Combination therapy

- 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

Yap T, de Bono J JCO 2013, 31:1592-605
Study Design

MTDs of 2 selected schedules

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
- 3/7 or 2/7 AZD2014 schedule
- Paclitaxel 80 mg/m²/week + Vistusertib 6 weeks out of 7

Expansion cohorts
- High grade serous ovarian cancer n= 25
- Squamous NSCLC n= 40
Results – expansions

Ovarian cancer 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

Squamous NSCLC expansion

- 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

2013-2014 dose escalation

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
ECMC administration
Pharma team
Public, Patient interaction

CA125 Response % change from baseline

Ongoing patients
IIT team: Sponsor-level management

ICR Labs
- External CRO's

Drug Development Unit
- Sequencing
- PK analysis
- PD assays
- Regulatory submissions
- Project management
- Trial Manager

ICR Clinical Trials and Statistics Unit
- Monitoring visits
- CRA
- Database development
- Data Analyst
- Drug Supply
- SAE processing
- PV Officer

CDMS
Infermed® MACRO
Pharmacovigilance system
SAFIRE®

Investigator sites
TAX-TORC major changes

**Initial Plan**

**MAY 2013**
- ESC 22 (2 schedules) / EXP 10 + 10 Ovarian
- 3 Centres
- 2 IIT staff

**Am 03 APR 2014**
- EXP 10 Ovarian + 15 Lung (+15 optional)
- 4th Centre added
- 3 IIT staff

**Am 04 OCT 2014**
- EXP 10 Ovarian + 40 Lung (+15 optional)
- 5 more Centres added
- 5 IIT staff

**Am 06 JUL 2015**
- EXP 25 Ovarian + 40 Lung (+15 optional)
- 6 IIT staff

**Recruitment completed**
- Ovarian LPI JUNE 2016
- Lung LPI DEC 2016
- 11 IIT staff

**LPI exp. Dec 2016**

- **FPI May 2013**
- **LPI exp. May 2015**

**• 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

LPI May 15
LPI Dec 15
Lung LPI Apr 16

Lung LPI Dec 16
Checkmate study impact
- recruitment target adjusted

15 lung patients
40 lung patients & ctDNA sampling

15 ovarian patients
Ovarian LPI Jun 16
**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.
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 disease
  - 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/m² + 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
Ovarian cancer expansion

Best radiological response 24%
Stable Disease

27.2.15
14.9.15
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

**Maintenance Olaparib stent**
Stable disease
PD and toxicity

<table>
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<tr>
<th>(CEDAR trial control arm)</th>
<th>Gemcitabine/carboplatin</th>
<th>Maintenance Olaparib</th>
<th>break</th>
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**Presentation**

**Post 1st line maintenance**
TAX-TORC TRIAL

Partial response 34%
Partial response 41%
Partial response 52%
Ongoing PR

Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 7

Combination therapy – paclitaxel/vistusertib
Monotherapy vistusertib

Baseline
Post cycle 1
Post cycle 4
TOXICITY AND QUALITY OF LIFE

• 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 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!