ECMC

Experimental Cancer Medicine Centres

Annual Report

2013-14

CANCER RESEARCH UK

HSC

NISCHR

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NHS National Institute for Health Research

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Contents

Executive summary

This report highlights some of the groundbreaking studies conducted through the ECMC network in 2013/14. The breadth and innovation of the studies is a clear demonstration of the quality of the work that is supported by the network. The diversity of expertise that exists across the UK is reflected in the variety of treatment modalities that are currently under investigation. This includes radiotherapy, surgery, photodynamic therapy, gene therapy, and viral therapeutics, demonstrating that the network's capabilities extend well beyond development of novel drugs.

Through the dedication of the CRUK Centre for Drug Development, the ECMC Combinations Alliance has now delivered 15 trials of combination therapies, recruiting through the ECMC Network and using drugs supplied by four industry partners. This is an incredible achievement, both for the Combinations Alliance Team and the network as a whole.

There have also been some fantastic examples of collaboration between ECMC Centres. The CRUK Stratified Medicine 2 programme will by next year collect samples and consent patients through all 18 ECMCs, making the National Lung-Matrix trial possible and providing a host of new treatment options for lung cancer patients.

This year has seen substantial changes in the clinical research environment in the UK. The creation of 15 new Clinical Research Networks in England has been a momentous change. In Scotland we are awaiting the outcome of the CSO consultation on their Health Research Strategy, and Wales have recently completed a review of their clinical infrastructure. Once the impact of these changes is fully understood we will need to revisit how the ECMCs should work alongside and coordinate with other relevant infrastructure.

We are at the mid-point in the current quinquennium of funding for the ECMC initiative. Now is the time to start thinking about how we can build upon the progress made to date to create an unparalleled environment for the development and delivery of experimental cancer medicine studies. In the coming year the Secretariat will be working with funders, industry, clinical leads and other staff in the network to create an ambitious vision for the future. We want to hear your ideas for what the network should focus on, how it should be structured and how it should operate. We would encourage you to be bold and creative in your thinking and if you have any ideas do not hesitate to contact the Secretariat to discuss.

There have been exciting advances in the understanding of cancer, such as the increasing appreciation of the challenges posed by tumour heterogeneity and enhanced insight into the interaction between cancer and the immune system., These, combined with our improving ability to deliver challenging studies to time and target, represent a real opportunity for the network to become world renowned for the design and delivery of innovative early phase trials and associated translational research. We look forward to working with you to help bring this vision to life.

Jo Reynolds
Director of ECMCs

Introduction

This report has three main objectives

- To give an overview of the progress with the ECMC Networking Strategy
- To highlight some of the exciting research supported by the ECMC Network
- To provide an overview of the trials supported by the ECMC Network

This report is not comprehensive, the highlights presented here represent a fraction of the important scientific and clinical achievements delivered by the ECMC Network over the past year and only a portion of the activities of the ECMC Secretariat.

Progress on delivery of the ECMC Networking Strategy 2013/14

In June 2011, the ECMC Quinquennial Review (QQR) Panel agreed that if ECMCs successfully "worked together as a network they would become internationally renowned" and recommended that funding should be dedicated to support greater collaboration. The ECMC funding partners agreed to jointly invest up to £1.8M over 5 years for this purpose. This section highlights areas where substantial progress has been made towards achieving these goals, and also highlights areas where further efforts are needed.

Networking Strategy Objective: Faster set up and delivery times for multicentre studies

ECMC Trial Harmonisation programme

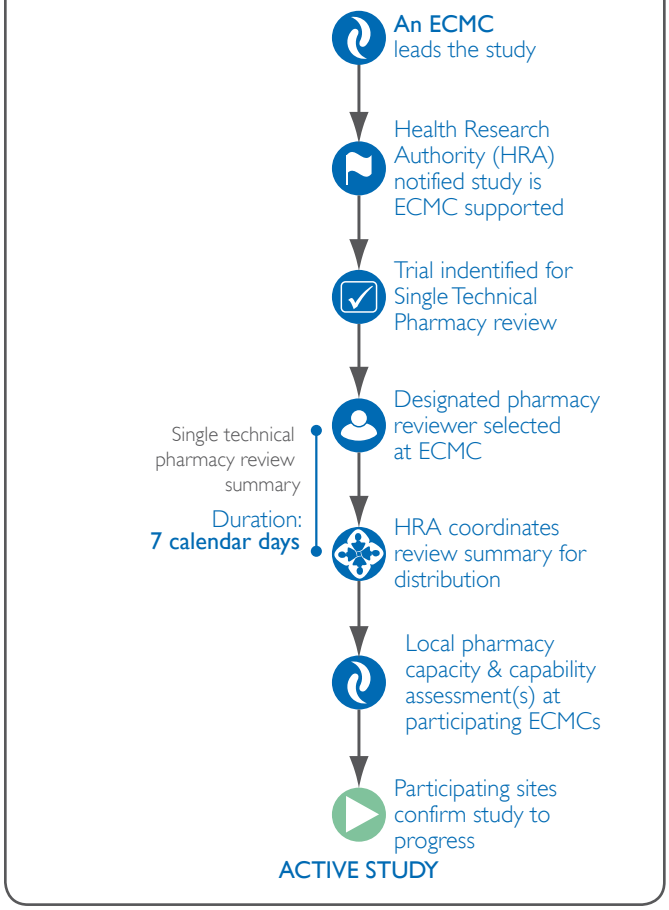
For the UK to retain and enhance our reputation in early phase clinical cancer research, efficient delivery of trials to time and target is essential. In April this year the government announced funding for the Health Research Authority (HRA) to design a single, streamlined approval process for all heath research studies. HRA Approval will provide a single approval for research in the NHS, that will incorporate assessments by NHS staff employed by the HRA alongside the independent Research Ethics Committee opinion. This will allow decisions at local sites about participation to be made on local capacity and capability alone. The process will be coordinated with those in the devolved administrations and with other regulatory approvals to unify the approval process for research in the UK.

The ECMC Secretariat has been working in partnership with the HRA to develop some of the new processes that will form part of the single assessment, and we have now established the ECMC Network as an important testing ground. This work will be critical in delivering faster set up and delivery times for multi-site trials. This year has seen some exciting progress.

Progress to date:

- The variety of trial set-up processes across the Network were mapped and key bottlenecks in trial set-up and delivery were identified, including pharmacy and medical exposure reviews
- An R&D workshop was held to prioritise key areas to streamline study set-up in the Network.
- The ECMC Secretariat entered into a formal partnership with the HRA, establishing the ECMC Network as a test ground for rolling out the new processes that will come together to form the single assessment
- Working with pharmacists from across the Network, a new process for completing technical pharmacy reviews was agreed, and is now being tested in the Network.

Figure 1 ECMC Trial Harmonisation programme



Plans for the future:

- The impact of the new technical pharmacy review process on trial setup times will be monitored and reported to the HRA
- With assistance from Clinical Radiation Experts, Medical Physics Experts and R&D staff, processes to streamline assessment of medical exposure will be designed and will be ready for testing in the Network in Spring 2015
- These processes, along with other elements, will be incorporated into an operational guideline for the ECMC initiative which will be ready for locations to sign by Spring 2015

Networking Strategy Objective: More Centres are conducting studies of the highest quality due to improved staff training

Success of the Junior Investigators Network Group

To ensure that the UK remains an internationally recognised centre of excellence for experimental cancer medicine, we must ensure that our junior investigators are well supported. The Junior Investigator Network Group (JING) supports the development of young investigators across clinical and translational research in a number of ways.

Progress to date:

- A very successful two-day training event was hosted in January 2014, which brought together 66 junior investigators to develop their skills and knowledge in early phase and translational study design through presentations and interactive sessions
- The training was facilitated by 33 senior investigators who shared their experience and expertise with the trainees. The training event received positive feedback from both faculty and attendees with all sessions being ranked as either good or excellent

Plans for the future:

- Due to its popularity, the two-day Junior Investigator training course (Training the Next Generation) will be held as an annual event, open to the most promising junior investigators in the ECMC Network. The next event is in January 2015
- Provision of new training events in bioinformatics, statistics and trial design was suggested by JING. After reviewing availability of relevant courses bursaries will now be offered to JING members to attend existing courses
- FLIMS is a highly prestigious clinical research workshop run by ESMO. The Secretariat will offer one funded place to FLIMS for a candidate who has successfully applied and is strongly supported by their clinical lead
- Funding will be provided for up to 15 junior investigators to attend NCRI Clinical Study Group meetings. This will provide a fantastic opportunity for juniors to build collaborative networks and to potentially even develop their own ideas in a supportive environment

ECMC Cross-Centre Training

Skill-sharing across the ECMC Network was identified as a need at the beginning of this quinquennium. In response to this, the Secretariat launched a fund to assist any personnel at ECMC locations to travel to another ECMC to learn new techniques and practices.

Progress to date:

- Pilot call for proposals for cross centre training was launched in March 2013
- 24 placements have been awarded in a number of areas including biobanking, patient involvement and quality assurance
- The latest call for placements allows not only ECMC staff, but also UKCRF staff to participate in the cross-centre training

Plans for the future:

- Fund placements between ECMCs and UKCRFs
- Evaluate the impact of the placements to date, assess overall value and make any changes needed to the scheme
- Potentially extend the scheme to allow ECMC staff to travel to non-ECMC locations

Networking Strategy Objective: Efficient delivery of high impact research, through the sharing of resources and personnel

Pathology & biobanking

With the increasing use of molecular diagnostics and the greater demand for tissue to be used in research, pathology expertise and capacity along with biobanking have been identified as critical to the success of the ECMC Network. Both these areas have complex needs. Tackling them effectively will require a long-term strategic approach, co-ordinated with other stakeholders such as the NCRI, the Confederation of Cancer Biobanks (CCB) and the Medical Research Council (MRC). The Secretariat will seek to concentrate on areas that are most relevant to the early phase community and where we can add most value.

Progress to date:

- Professor Bridget Wilkins (GKT) was appointed as Pathology Lead to champion pathology and biobanking within the Network, help us engage with the community and to chair and develop a workplan for the Cellular and Molecular Pathology Network Group
- Following a successful workshop with pathologists from all ECMCs in January 2014 the Cellular & Molecular Pathology Network Group has been set up with four workstreams to address:
  - Training the next generation of pathologists (including providing training to encourage more NHS pathologists to become research active)
  - Optimising pathology sample quality for molecular analysis
  - Supporting greater use of digital pathology
  - Protecting research time for cellular and molecular pathologists
- This work has now been subsumed into a larger piece of work led by the NCRI.

Plans for the future:

- Assist the NCRI in developing a proposal for the NCRI Board in March 2015, aimed to reinvigorate academic pathology in the UK over a period of time
- Hold a consensus meeting for cell-free DNA (cfDNA) with the NCRI Biomarkers and Imaging Clinical Study Group. Hosted by Leicester ECMC, this meeting will aim to bring together predominant cfDNA research groups in the ECMCs to gain consensus on quality standards, analysis and techniques for this emerging technology

Capability Map

There is a large breadth and depth of expertise across the ECMC Network, however Centres can find it difficult to know where particular expertise can be found and we currently have no way of show-casing the overall capability of the Network to potential partners, such as industry.

Progress to date:

- The first phase of building the Capability Map has been completed and went live on the ECMC website in September 2013. This focuses on promoting the key capabilities of each ECMC and signposting expertise across the Network
- The pilot for the second phase of building the Capability Map has been completed in collaboration with Belfast, King's and Manchester ECMCs and input from the ABPI Cancer Working Group
- We have developed capability leaflets for four ECMC locations and after very positive feedback will develop leaflets for all ECMC locations

Plans for the future:

- Data from all ECMCs for the second phase of building the capability map will be collated
- Capability information will be included in the new ECMC website to be launched in Spring 2015 and will be more readily searchable. We will assess the demand for a capability tool that will allow rapid identification of required capabilities across the Network

Networking Strategy Objective: New partnerships are established with industry and other research organisations

One of the success criteria of the ECMC Network is engagement with industry and other relevant research organisations. The number of industry sponsored trials supported by the network is high, currently standing at 61% of all studies new to the portfolio in 2013/14. Whilst this demonstrates that industry values the Network, discussion with ABPI suggest that there is more the Secretariat could be doing to facilitate entry to the Network, assist sponsors in finding suitable investigators and study sites and in supporting on-going partnerships. This is an area where new ways of working will be explored and implemented in 2015.

We have made great progress in deepening our relationship with other organisations. Our trial harmonisation projects conducted jointly with the HRA are a great example of how working in partnership can deliver tangible benefits in short timeframes.

Progress to date:

- During discussions with the ABPI Cancer Working Group, they endorsed the ECMC trial harmonisation project and highlighted what more we could be doing to assist industry
- The ECMC/HRA Single Technical Pharmacy Review Project is now in test throughout the Network

Plans for the future:

- Options for extending the partnership with the HRA are currently under consideration
- Efforts will be made to increase understanding of what industry wants from the Network and how the Secretariat can facilitate this
- We are working with NOCRI to share best practice and ensure coordination of activities

Network Strategy Objective: Raising the profile of the ECMC initiative

One of the challenges in promoting the ECMC Network is establishing a clear and differentiated identity in what is a busy research landscape. This has been addressed through a number of routes, but there is more to do to establish and promote the ECMC Network with relevant stakeholders.

ECMC communications

To enhance the profile of the ECMC initiative multiple communication channels have been employed to increase engagement with our stakeholders.

Progress to date:

- The digital communications portfolio has expanded into social media by establishing a Twitter profile with ECMC branding which has already achieved an active following of over 400
- ECMC now has a presence on LinkedIn to allow for online discussion forums and to promote collaboration
- A bimonthly e-bulletin, ECMC Connect, is now circulated to over 800 people, including all ECMC staff and key stakeholders. After six months it is clear that the bulletin is performing well above the average for this form of communication

ECMC connect

- A new suite of communications materials was launched at the NCRI Conference. This included a new introductory booklet, four pilot capability leaflets and ECMC branded merchandise, which helped the ECMCs become one of the top ten tweeted items at the conference

Plans for for the future:

- The new ECMC website will be launched in Spring 2015 with a fresher look and feel, but also to potentially provide new capability, such as a platform to support peer to peer communications, an interactive capability map and enhanced member areas. Development of new capabilities will be driven by needs identified from within the ECMC research community
- Capability leaflets will be created for all ECMC locations

ECMC 2014 Annual Network Meeting

The fifth ECMC Annual Network meeting took place in May in London. This was an opportunity for staff from all ECMCs to come together to learn more about the current activities within the Network and meet with their peers. The theme of the meeting was "Collaboration in practice and patient engagement in research". There were 199 attendees and 96% of the respondents to the feedback survey felt that the meeting was successful (43% response rate). The patient focus was particularly welcomed, in particular the talk from Lyn Barrington, a lung cancer patient who told her story of her missed diagnosis, through to her participation in an early phase trial of an immunotherapy agent.

Activity in the Network

Innovation and quality

The ECMC Network and the people within it are central to the delivery of exciting innovative research. There are many hallmarks of quality and innovation in research, this section provides just a sample of the trials and studies supported by the initiative that are demonstrating hallmarks of quality. The status of these studies is as of April 2014.

First in class / First in man studies

Early phase trials in cancer are unique. Unlike most other indications, these studies take place in patients not in healthy volunteers. The expertise that resides in the Network ensures that trials that involve putting new treatments into patients for the first time can be done safely and ethically. The following are just a few recent examples of such studies.

Newcastle ECMC has opened a first in class Phase I trial, using a sphingomyelin synthase (SMS) activator. SMS is a novel anti-tumour target, and activation is thought to induce tumour cell death by increasing cellular levels of ceramide and diacylglycerol. This study is being conducted in collaboration with **ICR** ECMC, and will also involve intensive PK and PD sampling.

Southampton continues to demonstrate their expertise in immunotherapy and have opened a CRUK Centre for Drug Development (CDD) sponsored first in man Phase I study of a novel CD19 antibody for B cell disease. This study will recruit in four ECMC locations and will involve study of multiple surrogate tumour biomarkers.

The recent rapid advances in the understanding and treatment of melanoma continue. Sponsored by Millenium Pharmaceuticals, **Oxford** ECMC is participating in an international dose escalation and expansion study of a new oral RAF-kinase inhibitor (MLN2480). The study will recruit in five ECMC locations and patient eligibility will be based on their BRAF and NRAS status.

The **Belfast** ECMC is setting up a trial that will investigate a new anti-angiogenic agent discovered at the Queen's School of Pharmacy. The ALM201 study is a first in man in up to 60 patients with ovarian cancer.

UCL ECMC has moved into set-up with a phase I study of MOv18, a first in class chimaeric IgE antibody against folate receptor-a, in patients with advanced solid tumours. IgE antibodies, have a higher affinity for their effector cell receptors than IgG antibodies and a longer tissue half-life. It is hoped these characteristics will improve efficacy.

In an extensive partnership, **ICR** ECMC has established multiple first in man trials with GSK, including a Phase I/IIa dose escalation study in advanced solid tumours using a novel PI3K inhibitor in patients with known PTEN deficiency.

ICR have built on promising results of a first in man phase I trial to launch phase II trials of the HSP90 inhibitor AUY922 as a single agent and in combination with other drugs. Trials are in set up for patients with HER2-positive breast, gastric, and non-small cell lung cancers.

Novel combinations

Investigation of combinations of therapies has become an increasingly important strategy for combating cancer to help overcome resistance to therapy. The Network is now supporting a substantial and varied portfolio of combination studies. The ECMC Combinations Alliance has been a key driver in this.

ICR ECMC has been leading on a number of trials combining novel agents with other novel agents, or with standard therapy, many of which are part of the ECMC Combinations Alliance. This includes TAX-TORC a multi-centre Phase I trial of the combination of AZD2014 (a dual TORC1/TORC2 inhibitor) with weekly doses of the chemotherapy drug paclitaxel. The study was set up to address the perceived limited benefits of treating platinum-resistant ovarian cancer and is showing that the combination of AZD2014 and paclitaxel has exciting potential as a experimental treatment.

The team has also been combining multiple targeted therapies. The CRUK New Agents Committee has recently funded a Phase I study which will combine an AKT inhibitor with a PARP inhibitor. Used as monotherapy the clinical response from both agents has been modest and/or non-durable. Preclinical studies suggest that inhibition of both pathways will have a synergistic effect. The phase I trial will determine the optimal dose of both agents, followed by a dose expansion study with patients stratified by BRCA1/2 status.

Belfast ECMC is leading on the pan European MErCuRIC project involving 13 partners from eight different European countries. MErCuRIC is a multicentre phase Ib/II clinical trial which will assess combination of a MEK inhibitor (PD-0325901) with a MET inhibitor (PF-02341066) to combat metastasis, improve survival and change current clinical practice for colorectal cancer patients with KRAS mutant & wild type tumours. The consortium will use next generation sequencing and 'xenopatients' to identify patient subgroups that will maximally benefit from this novel treatment strategy. The study has been submitted for ethical and regulatory review.

Inhibition of MEK has become an increasingly common therapeutic strategy for a number of cancers, but it is now thought that MEK inhibition on its own is unlikely to have lasting therapeutic benefit for many patients. **Sheffield** ECMC is leading on a Phase I/II trial of a MEK inhibitor combined with an anti-retroviral treatment in patients with AIDS-associated Kaposi's sarcoma. This trial is currently recruiting in four ECMC locations.

The team in **Cambridge** are in set up for a study designed to tackle brain mets from breast and lung cancer. This proof of principle trial will look at the penetration of afatinib penetration into cerebral metastases for patients undergoing neurosurgical resection, both with and without prior low dose, targeted radiotherapy.

Glasgow ECMC is leading on a large multi-site trial for patients with stomach and oesophageal cancer. This is an academic Phase I/IIa trial, which combines standard platinum therapy with a targeted FGFR inhibitor (AZD4547). The recommended dose of AZD4547 has been determined and the study has now progressed into the randomised Phase IIa stage.

The team in **Glasgow** have also progressed the SAPROCAN study, a combination trial of a saracatinib (an aromatase inhibitor) and docetaxel, in metastatic, castrate-refectory prostate cancer. The phase I of this study has been completed, with the PK studies performed by the ECMC funded Analytical Services Unit. Recruitment to the randomised phase II trial has commenced in four ECMC locations.

Oxford ECMC is leading recruitment to a CRUK phase I study that will determine the maximum tolerated dose of the Oral Src/Abl Inhibitor AZD0424. The anti-cancer activity of AZD0424 is thought to be mediated primarily by anti-migratory and anti-invasive signalling and, as such, it is expected that in the late stage cancer setting strong signals of efficacy with this compound used as monotherapy are unlikely. Later stages of this trial will combine AZD0424 with other agents in up to three combination arms.

Kings ECMC is leading on a Novartis trial combining docetaxel with a pan PI3 Kinase inhibitor, buparlisip in patients with advanced non-small cell lung cancer. This is an international trial with recruitment taking place at 56 sites. In the UK both Kings and **Cambridge** are in set up.

Staff from **Leicester** ECMC set up a meeting at ASCO with two new companies, to push forward combinations in mesothelioma which, if successful will be offered to the Network as an expression of interest call in due course.

On behalf of RadCom **Glasgow** has also been engaging companies to promote combinations with radiotherapy, ensuring high quality preclinical data is delivered efficiently for novel phase I radiotherapy studies.

Other novel therapeutics

As well as providing the infrastructure to support hundreds of small molecule drug development studies, the ECMC Network also hosts trials investigating various other novel types of therapeutics.

ICR ECMC completed a phase I trial in patients with castration-resistant prostate cancer, using an antisense oligonucleotide to androgen receptor mRNA. This study demonstrated that the activity of the agent was minimal at the doses and schedules explored and was also associated with liver toxicity. As a result, investigations were terminated at the earliest opportunity.

Leicester ECMC is supporting a trial examining if addition of the plant extract curcumin to the FOLFOX chemotherapy regimen for metastatic colorectal cancer improves efficacy or reduces sides effects. This work progressed from Phase I to randomised Phase II in a year and is currently recruiting patients.

Birmingham ECMC has opened the AdUP trial to recruitment, in patients with locally relapsed hormone-refractory prostate cancer. This is an academic led single site study combining a genetically modified adenovirus injected straight into the prostate, followed by treatment with Pro-Drug CB1954. The virus is modified to produce the enzyme nitroreductase, which then acts locally to activate the pro-drug.

Manchester ECMC at the Christie is leading on a phase II trial of adoptive T cell therapy using the patient's own T cells, genetically engineered to target the tumour associated antigen NY-ESO-1 (New York oesophageal squamous cell carcinoma 1) in advanced oesophogastric cancer.

Leeds ECMC has opened the REO 13 trial, looking at pre-operative administration of reovirus in patients due to undergo surgery for high grade glioma or brain metastases. This is the first trial of its kind in the world.

In partnership with Viralytics, **Leeds** has also opened a Phase I, dose-finding study of the safety and efficacy of CAVATAK™ (Coxsackievirus A21, CVA21) in patients with late stage solid tumours . CAVATAK is an oncolytic version of the common cold virus. A phase II study in melanoma using this agent has completed recruitment.

A new generation of photodynamic therapy is being trialled on patients with renal cancer at **Oxford** ECMC. Patients will be treated with a light activated vascular occluding agent, followed by surgical resection. The effect of the photodymanic therapy will be assessed histologically. The aim is to demonstrate whether this modality has potential for a clinical role in the treatment of oncological kidney disease, either as an alternative to surgery, or where surgery is not feasible

Surgery and radiotherapy

Whilst the majority of studies in the Network are drug studies there are also a number of innovative surgery and radiotherapy trials.

The Network is not only involved in novel combinations of drugs. **Southampton** ECMC is recruiting to a trial led by the Christie, combining the PARP inhibitor olaparib with standard radiotherapy in patients with carcinoma of the oesophagus. This trial will assess the maximum tolerated dose of olaparib.

In a first of its kind, the team at **Manchester** has completed and published an international, multi-centre phase II trial (FIZZ) to evaluate the efficacy and toxicity of fractionated 90Y-ibritumomab tiuxetan as initial therapy of follicular lymphoma (FL). The overall response rate was 94.4% and complete response rate was 69.4% and the therapy was well tolerated.

Oxford is also combining targeted therapies with standard radiotherapy, in a CRUK phase I dose escalation study of a pan PI3K inhibitor (BKM120) in patients with non-small cell lung cancer (NSCLC) receiving thoracic radiotherapy.

Sheffield ECMC is participating in an exploratory study of MTL-005 in patients with advanced carcinoma of the head and neck. This is an agent that is designed to sensitise cancer to the effects of radiotherapy, hopefully decreasing the dose needed for therapeutic effect.

Three ECMC sites have been selected to participate in a phase I trial of pre-operative stereotactic body radiation therapy for previously untreated borderline resectable pancreatic cancer, led by **Oxford** ECMC. The aim is to try and increase the number of patients eligible for surgery through pre-treatment with radiotherapy.

Imperial ECMC will be initiating a first-in-man evaluation of i-knife technology for intra-operative cancer margin assessment in colorectal cancer. The i-knife burns through tissue and the resulting smoke is analysed in real time by mass spectrometry indicating where the cancer margins are.

Imaging

Focusing on patients with sarcoma, **Manchester** ECMC at the Christie is setting up an imaging study to help determine the best MRI imaging technique for assessing early response to radiotherapy.

In another study, the team at **Manchester** is recruiting to a feasibility study to determine if PET scans using the FLT tracer can provide more information about advanced pancreatic cancer, and to assess how patients are responding to treatment with gemcitabine.

Kings ECMC has completed recruitment to the MELAMag trial, an international study testing the efficacy of a new tracer containing magnetic nanoparticles in detecting cancer in sentinel node scans of patients with melanoma. It is hoped this will enable surgeons to identify and remove all nodes containing cancerous cells, whilst preserving those that do not.

A study led by **Imperial** ECMC has completed recruiting women to a trial investigating the effects of a new hormone treatment for breast cancer called Irosustat, a steroid inhibitor. Response to treatment was assessed through PET-CT, using the FLT PET tracer.

Translational research

Circulating tumour cells are being extensively investigated in the Network as a potential route to monitor response to treatment and the development of resistance (see "Working with industry" section for more details). Recently published in Nature Medicine, **Manchester** ECMC has developed a unique approach to study small cell lung cancer using patient derived circulating tumour cell explants mouse models (CDX). Circulating tumour cell samples taken at patient presentation and again at relapse will shed light on the mechanisms of drug resistance, facilitate novel drug target identification and be used to test novel agents.

The team at **Manchester** has also developed a 26 gene signature for hypoxia, that is hoped will predict the patients most likely to benefit from hypoxia modifying treatment. This will be tested in the NIMRAD study in advanced head and neck cancer.

Patients with bladder cancer stand to benefit from studies in **Oxford** that have identified a biomarker that may help select those patients most likely to benefit from radiotherapy. With direct funding from CRUK, the marker assay is now being developed to appropriate standards and the relationship of the biomarker to clinical outcome is being further defined.

In **Cambridge** plans are being made for a study of ctDNA as a molecular monitoring tool in metastatic breast cancer across the ECMC Network. In addition they have been funded by AstraZeneca to deliver a liquid biopsy and tumour profiling study for patients on early phase trials (CALIBRATE study).

Following a successful ECMC Cross-Centre Placement application **Cardiff** ECMC has set up a network for sharing SOPs and best practice for organoid models in colorectal cancer. If successful these models could have applications in pre-clinical and translational work within the ECMCs.

The ECMC at **Imperial** has been investigating epigenetic markers in susceptibility and patient stratification in ovarian cancer in phase II & III studies. In an international study, the team at Imperial helped demonstrate how DNA methylation patterns are notably distinct between subtypes of ovarian cancer, and have also indentified the first clear-cell ovarian cancer-susceptibility gene.

The team in **Cambridge** made a major breakthrough in understanding myeloid malignancies and their relationship to normal haematopoiesis, published in the New England Journal of Medicine. Using massively parallel sequencing the team described the genomic landscape of 151 patients with myeloproliferative neoplasms (MPNs) and identified CALR as a new cancer gene mutated in the majority of MPN patients with non-mutated JAK2.

The BriTROC1 sample collection study, led by **Glasgow** ECMC, is collecting samples from patients with ovarian cancer previously treated with platinum agents. Developing resistance is a major issue for these patients and this study will try to identify the factors that cause resistance. This is currently recruiting patients through eight ECMCs.

The **Leeds** ECMC, through its NIHR-funded biomarker programme has been leading the UK effort in the CAGEKID consortium, which aims to identify biomarkers for the most common form of clear-cell renal carcinoma. Another seven ECMC locations are now involved in the validation phase of the programme recruiting over 2000 patients with renal cancer.

Research conducted at **Barts/Brighton** ECMC has revealed that high levels of integrin $\alpha v\beta 6$ in breast tumours from HER-2 positive patients identifies those at high risk of developing secondary tumours (and poor

survival) and has also shown that targeting $\alpha v\beta 6$ with blocking antibody therapy (264RAD) could be effective against some of the most aggressive types of breast cancer - tumours were even eliminated in their combination therapy model. Further studies are on-going.

The effect of vitamin D on cancer has long been debated. The team at **Belfast** ECMC has initiated a study looking at the effect of the levels of vitamin D on surrogate biomarkers for colorectal cancer.

Published early this year, staff at the **Belfast** ECMC have also validated an assay to predict response to anthracycline and cyclophosphamide–based chemotherapy in the clinic. The investigators are currently exploring how the assay can be qualified in further prospective studies.

The **Edinburgh/Dundee** ECMC has been working on building a predictive model for progression in breast cancer. This was presented at the 9th European Breast cancer Conference and has been submitted for patent protection.

Working with industry

ECMC locations have forged multiple new links with industry during the year. 125 different companies conducted trials in the ECMC Network in 2013/14. This excludes the partnerships that have been created around technologies and biomarkers. This section will highlight some of the partnerships that ECMCs are forming with companies.

In **Sheffield**, colleagues from the departments of Chemistry, Dentistry and Oncology are working in collaboration with a biotechnology company called Argenta to carry out preclinical work on a class of novel microtubule agents, which have been developed in Sheffield.

At **Southampton**, the ECMC facility leveraged additional investment in translational medicine and moved to a purpose built clinical trial evaluation laboratory that incorporates immune monitoring, nutritional endpoints and NGS/informatics capacity. The £1.4m Wessex Investigational Sciences Hub Laboratory hosted both the CRUK Centre for Drug Development and ECMC teams last year.

Southampton ECMC has also formed a partnership with Huntington Life Sciences (UK) for the development of assays to predict cytokine storm in the development of novel immunostimulatory antibodies. As these therapies become more prevalent, predicting this potentially deadly side-effect is of vital importance.

A few of our ECMCs have the capability to manufacture investigational products. **Kings** has entered into a partnership with Northwest Biotech/Cognate for the GMP production of tumour lysate-pulsed dendritic cells for a Phase III vaccine trial for glioblastoma.

Developing partnerships can provide a view of the expertise residing within the Network. A number of new partnerships have been created around circulating tumour cells (CTCs) and cell free DNA (cfDNA). **Manchester** ECMC has entered into a £700k partnership with Silicon Biosystems, involving DEPArray™ technology to isolate and molecularly profile individual circulating tumour cells to explore CTC genomic heterogeneity and drug resistance signatures.

Imperial has partnered with AZ Pharma and Roche Diagnostics to fund evaluation of cfDNA to diagnose EGFR mutant lung cancer in patients who are either unfit for or have declined biopsy but are willing to swallow tablets (gefitinib) for liquid biopsy diagnosed EGFR mutant positive lung cancer.

UCL has established a partnership with Gilupi to develop the CellCollector, a device for increasing the yield of circulating tumour cells by sampling the circulating blood volume. Gilupi have provided 1000 devices at no cost to UCL as part of the development partnership (total value of £350,000). Working on circulating cells in neuroendocrine tumours (NETs), UCL are collaborating on a clinical trial with IPSEN which will explore the role of CTCs as response markers in patients with functional mid-gut NETS following therapy with somatostatin analogues. The CTC analysis will be undertaken at the UCL GCLP lab.

Leicester, in collaboration with Synta Pharmaceuticals, will be conducting cfDNA and genome wide copy number variation analysis to support the Galaxy trial.

Barts/Brighton ECMC has formed a partnership around a new trial. ATLANTIS is a personalised therapy study in bladder cancer. In partnership with Exelixis and Astellas, Barts ECMC will run the translational oncology biomarker part of the study supported by a grant of £550,000.

Belfast has entered into a long-term partnership with ALMAC to create an integrated ALMAC/Queens University Belfast Drug Discovery Unit, with additional support from Invest Northern Ireland, the total value of the partnership is £5.5m.

Demonstrating the power of the Network

Previous sections of this report amply demonstrates the exciting activity happening in all ECMC locations. This section will highlight a few of the activities that have allowed ECMC locations to come together and truly function as a network. Going forward, we will need to examine if the Network and the Secretariat are doing all that can be done to ensure that these exciting trials deliver their potential.

Supporting complex trials – Lung Matrix Trial and the Stratified Medicine Programme

In 2011, the CRUK Stratified Medicine Programme (SMP1) set out to work in collaboration with eight of the ECMCs, a network of 26 hospitals and three diagnostics labs, to tackle the challenges in delivering large scale, molecular testing in cancer within the NHS. By July 2013, over 9,000 patients had had their tumour samples tested for genetic defects that could be related to their cancer, proving that national screening of tumour biomarkers is not only feasible but also widely accepted by patients. Now, the programme is embarking on the next step, SMP2.

SMP2 will set up processes and infrastructure in NHS hospitals and laboratories so that every patient in the UK with a specific type of lung cancer will have their tumour tested and potentially be given access to the new drugs most likely to specifically target the defects in their tumour. SMP2 has been divided in two operational areas:

- Building on SMP1 to develop a collaborative national pre-screening network through the ECMC initiative
- Setting up and delivering a national clinical trial with a matrix structure (the National Lung Matrix Trial).

The targets for the pre-screening are ambitious at 2,000 non-small cell lung cancer patients per year. Using a new technology, their samples will be tested for a wide range of molecular defects and in a clinically relevant turnaround time, to enable the identification of patients eligible for the National Lung Matrix Trial. Running alongside this will be the collection of valuable patient data that will help future research into personalised medicines. The National Lung Matrix Trial will be run by the CRUK Clinical Trials Unit in **Birmingham** with Professor Gary Middleton leading as Chief Investigator.

The ECMC Network, with its strong emphasis on collaboration, is the perfect back drop to a programme like SMP. As well as the infrastructure, the ECMCs have a wealth of knowledge and experience to offer. In the coming year, CRUK will look to expand the pre-screening programme to all of the 18 centres in the Network to deliver a study that has the potential to truly change the landscape for delivery of stratified medicine in the UK.

Update from the Combinations Alliance 2013/14

As demonstrated in "Novel combinations" section, trials that combine therapies are becoming increasingly prevalent in the ECMC Network. The ECMC Combinations Alliance has been a key part in driving this activity, and now the first generation of ECMC Combination Alliance trials have started reporting promising results. Dr Udai Banjeri (**ICR** ECMC) presented exciting TAX-TORC data (delivered in collaboration with Cambridge) at a poster session at ASCO 2014, where the Combinations Alliance also featured on a stand with the NIHR CRN. MedImmune has now offered two of its angiogenesis antibodies (MEDI0639, an anti-DLL4 antibody and MEDI3617, an anti-ANG2 antibody) and will join the scheduled joint Combination Alliance ECMC/NIHR CRN: Cancer workshop in November 2014. Lilly also showed interest in broadening their involvement to additional projects. Astex are pleased with delivery so far and have received a good scientific response to their first Expression of Interest call.

Understanding tumour heterogeneity – TracerX

One of the biggest challenges in understanding the most effective strategies to beat cancer is the substantial genetic heterogeneity that can exist within a single tumour. TRACERx, which stands for Tracking Cancer Evolution through Therapy (Rx), will look at the spatial and temporal evolution of the most common form of lung cancer, non-small cell lung cancer (NSCLC), between primary and metastatic sites, and the dynamics of intratumour heterogeneity over time.

It is the largest study of its kind in the world and uniquely possible in the UK because of the strength of our early phase clinical trial infrastructure. The new £14m study was funded by CRUK with additional support from the UCL NIHR Biomedical Research Centre and the Rosetrees Trust.

The majority of the trial will be run though five ECMCs, specifically **UCL, Birmingham**, **Leicester, Manchester** and **Cardiff,** in collaboration with Cancer Research UK's Manchester Institute, LRI and Aberdeen Centre. Each ECMC is bringing a unique area of expertise to the project. Cardiff ECMC has established access to a significant lung cancer patient population, while UCL has world-class analytical services. Birmingham will contribute immunobiology expertise to study the heterogeneity of tumour immune cell infiltrates and neo-antigens. Leicester and Manchester are providing circulating free DNA and tumour cell expertise respectively, which will potentiate the development of minimally invasive technologies for tracking disease progression in the future. In collaboration, the participating ECMCs are able to provide the operational, scientific and clinical support for a project of this size.

Over nine years, researchers will recruit 850 NSCLC patients from across the UK, taking samples of their tumour before and following surgery, and subsequently if the disease recurs. Biopsies from different parts of the patient's tumour(s) will be analysed with the latest sequencing technology to give a more comprehensive genetic profile. The TRACERx study is now open, patients are being consented, samples are being collected and analysed (as of Sep 2014).

How do we continue to support nationally important studies?

Adaptive multi-arm umbrella studies such as FOCUS-4 and Lung-Matrix pose great challenges for the investigators, and also to the Network. Dealing with the need to adapt to new drugs as they arrive, supporting the demand for increasingly sophisticated molecular pathology and coping with the sheer volume of data generated are all real and substantial challenges. As these studies are relatively new to the portfolio, and are likely to increase in number, we must now ask if the ECMC Network is well positioned to assist investigators, and if not, what change is needed.

The ECMC portfolio

Every year the ECMC Secretariat collects data from the ECMCs to help us understand the totality of activity across the Network and how this has shifted over time. This year the data provided to us by ECMC locations has been validated through independent data sets such as clinicaltrials.gov. It should be noted that 87% of newly reported trials are on public clinical trial registers.

Overall trial activity supported by ECMC funding

The **figure 2** shows that over the last five years of ECMC funding, there has been a slight decrease in the number of trials newly reported each year. The reasons for this are unclear, but it should be noted that there is one less ECMC in the new quinquennium (2012/13 onwards), and data from this quinquennium has been validated to a greater extent than previously. In 2013/14, 124 studies were reported for the first time. The median number of new studies opened per centre was 10, with a range of 1-53. (The median for Tier 1 funded Centres was 13, the median for Tier 3&4 was 3).

In total, 760 new and continuing studies were reported in 2013/14, an increase in total activity of 20% from 2012/13. 50% (363) studies were open to recruitment, with 80 in set-up and another 167 in active follow up. A further 150 were completed, withdrawn or suspended in year. Together these trials recruited over 2,200 patients in year, a 10% increase from 2012/13.

Figure 3 demonstrates that the Network is supporting a large number of studies across a variety of cancers.

Figure 2 New trials reported as using ECMC support

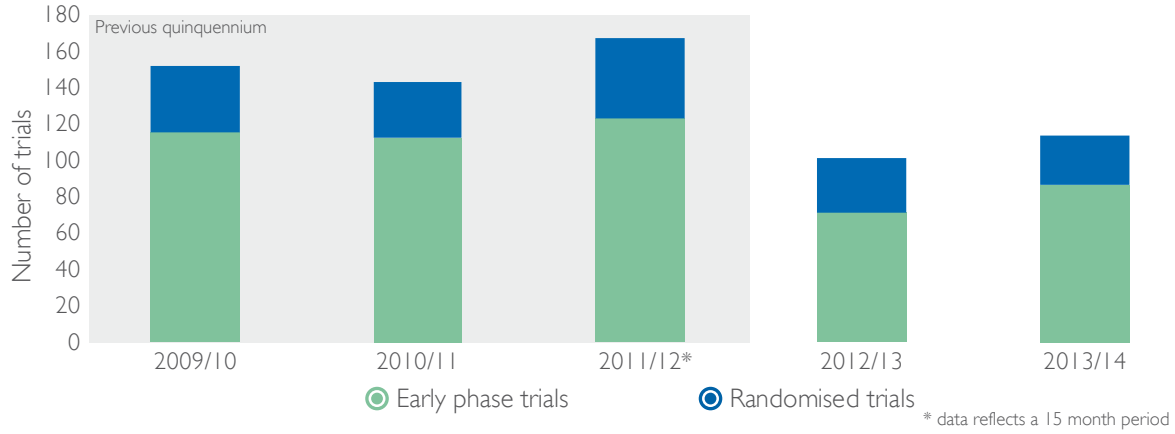
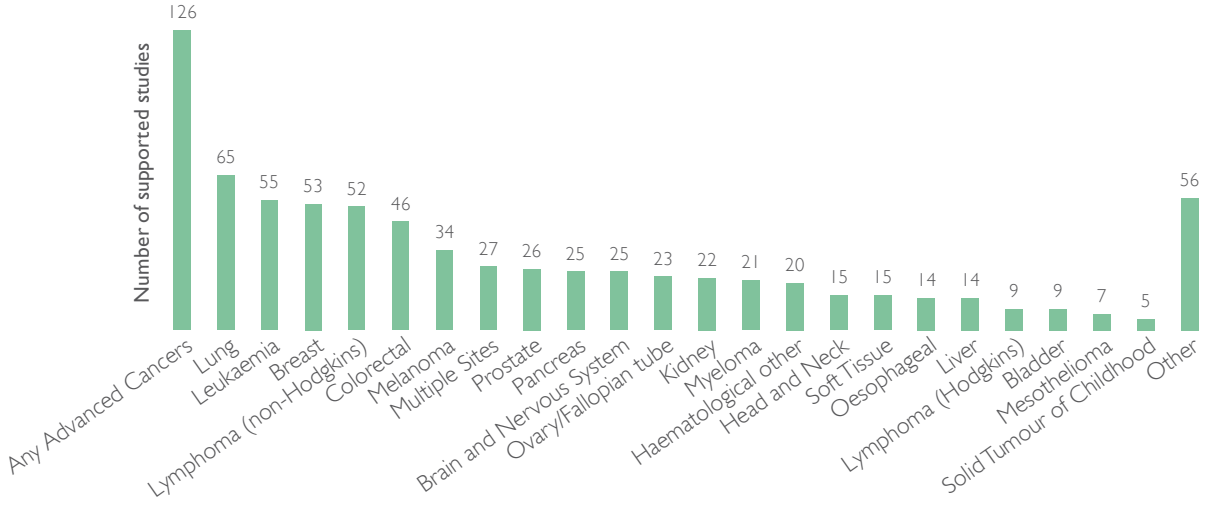


Figure 3 Trials by disease site



It is interesting to note, that of the trials that are site specific, lung cancer trials are the most prevalent. This is encouraging news for this difficult to treat cancer.

As shown in **figure 4**, centres use ECMC funding in a variety of ways to support trials. The most prevalent activities are recruiting patients and administering drugs. Both these activities depend heavily on the expertise of research nurses. Of all the staff supported by ECMC funding, 26% are research nurses. We recognise that research nurses working in early phase oncology trials have a specific and valuable skill set, and we continue to work with them through the Research Nurse Network Group.

Sponsorship of trials supported by ECMC funding

In 2013/14, 76 out of the 124 studies opened in the network were sponsored by industry representing 61% of the total portfolio. An additional 16% are funded by industry but academically sponsored, meaning that over three quarters of trials on the portfolio have industry involvement. A total of 125 different companies conducted trials in the Network.

The remaining, roughly 25%, of new trials are academically sponsored and funded. We hope this represents a relatively balanced portfolio, and demonstrates that the Network is supporting studies from both industry and academia.

Figure 4 How ECMC funding is used to support trials

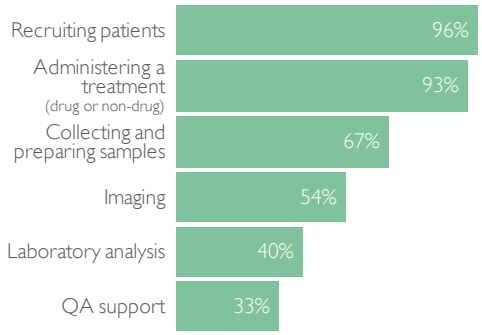


Figure 5 Balance of funding and sponsorship for studies new to the portfolio in 2013/14

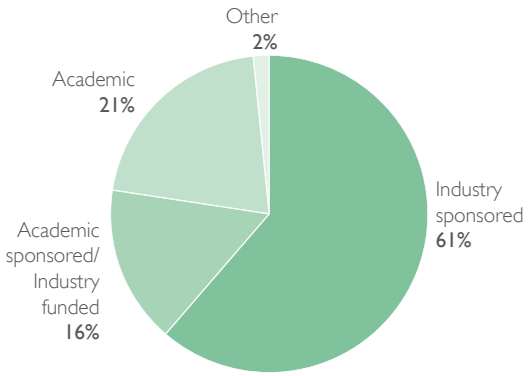
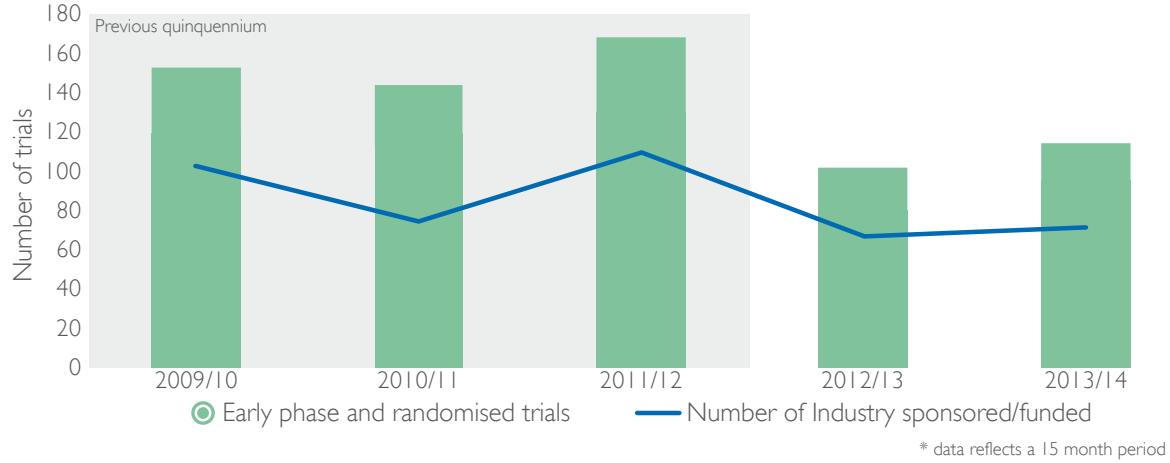


Figure 6 Industry sponsored trials compared to new ECMC supported studies



What next for portfolio analysis?

Going forward we will validate and further enhance the data we receive from ECMCs by adding information sourced from other resources such as clinical trial registers, databases such as Global Data, and bespoke analysis. This will increase the confidence in the data, and will provide additional views such as the number and type of combination studies, the number of first-in-class/ first-in-man studies and the number of studies particular ECMCs are leading on. This will add to our understanding of the activity carried out with-in the ECMC Network. Figures will be available in 2015.

Experimental Cancer Medicine Centres (ECMC) Network
A: Angel Building, 407 St John Street, London, EC1V 4AD
T: 020 3469 5381
E: ecmcadmin@cancer.org.uk
W: ecmcnetwork.org.uk
: ECMC_UK