The Christie NHS
NHS Foundation Trust

Experimental Cancer Medicine Service

Operational Structure

The Experimental Cancer Medicine Team (ECMT) provides opportunities for patients to participate in clinical trials of new experimental cancer drugs, delivered by a specialist team in a dedicated world class facility. The early phase clinical trials remit includes first-in-human and first-in-combination trials where the focus is assessing tolerability and pharmacokinetics and thus defining a recommended dose and schedule for further clinical research. We also conduct clinical pharmacology trials which seek to characterise the impact of food, organ impairment, concomitant medication and formulation changes upon drug exposure. Our precision medicine capabilities are rapidly expanding enabling the classification of cancer tumours according to their genetic make-up using tumour and surrogate biomarkers, and selection of a therapy to target specific individual tumour molecular changes. All new and follow-up patients are reviewed and treated in our state-of-the-art Clinical Trials Unit which can accommodate inpatient and outpatient trials.

Referrals

We accept oncology referrals from within The Christie, across Greater Manchester and nationwide.

Experimental Cancer Medicine Team

Direct Tel: 0161 918 7672

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Personnel

Strategic Director	Prof Andrew Hughes
Consultants	Dr Emma Dean Dr Matthew Krebs Dr Saeed Rafii (to be replaced by Dr. Natalie Cook)
Advanced Nurse Practitioners	Andrea Burgess Lorraine Turner Michelle Davies (trainee)
Research Nurses	Debra Jowle Alison White Helen Shekelton Anisah Mehmood
Senior Clinical Trials Co-ordinator	Sukhwinder Thandi
Clinical Trials Co-ordinators	Heather Driscoll Claire Davies Hannah Gornall

Translational Research Technician	Carla Siswick
Secretarial Support	Angela White

Activity

Approximately 150 new patients and 1000 follow-up appointments were conducted by the ECMT in 2013-2014. The Experimental Cancer Medicine Team is rapidly expanding and activity has tripled in the last quarter of 2014. Since 2007, 170 new Investigational Medicinal Products with distinct mechanisms of action have been administered in clinical trials.

Service Development 2013/14

Our aspiration is to be a top 5 Experimental Cancer Medicine Unit by 2020, providing patients access to the latest novel therapies. Our ambitious growth plan is underpinned by the delivery of high quality patient centric care and clinical trial data, recognising that our trials require a high number of study visits and maintaining expert caregiver continuity. Support for our strategic growth is highlighted by the recent recruitment of Clinical Senior Lecturers as part of the MCRC Academic Investment Plan. With proposed recruitment of a clinical chair in 2014/15 we will pursue additional capital investment through MCRC partners and notably funding through the CRUK Major Centre award, Manchester Experimental Cancer Medicine Centre and through new strategic partnerships with pharmaceutical companies and contract research organisations. We are working towards treating more patients on more trials with a re-structuring of our team to deliver our strategic goals.

All new patients are initially reviewed in our new patient clinic to assess suitability for early phase clinical trials and to discuss possible alternative options. If a patient chooses to participate, they are allocated to a clinical trial during our patient allocation meeting. All patients receive detailed written information about taking part in a clinical trial, have opportunity to review this information and ask questions to their physician and nursing team. Patients are closely monitored during the clinical trial and we carefully record symptoms, laboratory parameters, morbidity and mortality to examine potential relationships to treatment. As many patients have limited treatment options available, we are strengthening collaborations with Palliative Care to pursue a bespoke supportive care service alongside anti-cancer treatment.

Our Clinical Trials Unit comprises exceptional facilities including 31 beds and treatment chairs, 5 outpatient suites, trials pharmacy, a large sample collection and pre-analytical laboratory, and an administrative floor for safety monitoring. We can accommodate

inpatient and outpatient trials for a range of mechanistically distinct treatments including small molecule inhibitors, genetically modified and immunotherapy products, and radiolabelled compounds. For each trial, we identify a named single point of contact to liaise with the trial sponsor and operate as an extended clinical trial team. We prioritise investigator time to attend safety review meetings, review protocols and meet with sponsors to assist with the programme strategy. Each trial participant has a personalised workbook to facilitate monitoring and adherence with the protocol and we provide dedicated monitoring space within the Clinical Trials Unit.

The Experimental Cancer Medicine Team has an international reputation for clinical research. The team is based within the Christie NHS Foundation Trust which, along with The University of Manchester and Cancer Research UK Manchester Institute comprises the Manchester Cancer Research Centre (MCRC). The Christie NHS Foundation Trust is a dedicated cancer hospital treating all major tumour types with a broad catchment area (14,000 new cancer patients and 40,000 treatments per annum) and top recruiter into clinical trials. It is the largest single centre cancer hospital in Europe and a founding member of the Organisation of European Cancer Institutes (OECI). The MCRC is one of only 6 Academic Health Science Centres in the UK and one of two awarded Proton Beam Therapy Centres in the UK. The ECMT is ideally located next to the cancer discovery and translational laboratories including the clinical and experimental pharmacology (CEP) laboratories (world leading in cancer blood-borne biomarkers), MCRC biobank to support molecular diagnostics and genomic profiling and the Wolfson Molecular Imaging Centre. Planned delivery of an Integrated Procedures Unit from 2016 will augment the ability to deliver translational clinical studies.

Outcomes

The purpose of a Phase I clinical trial is to characterise the safety, tolerability and pharmacokinetics of a new anti-cancer drug whilst seeking evidence of preliminary activity (pharmacodynamic and/or clinical) in patients with different types of cancer. As the trials treat small numbers of patient, it may not be possible to provide accurate information about the effectiveness of these drugs against an individual cancer. Across all tumour types, there is only a small chance that the cancer will respond. It is estimated that, for every 100 patients who are treated in a Phase I clinical trial, between 5 and 10 patients may have some benefit. However, with development of our precision medicine agenda we hope to match relevant experimental drugs with individual patient genetic aberrations with the potential to improve outcomes on our early phase trials.

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Research

Every Phase I study achieved the NIHR 70-day set-up target (valid research application to open trial) and all of our open trials have met or exceeded the recruitment target provided at feasibility. Our median time from protocol receipt to first subject recruited is 76 days, ethics approval to NHS permission median 6 working days, NHS permission to first consented patient median 8 working days, average date entry time 2 working days.

Trials Available

An open-label, randomised, Phase I study to determine the effect of food on the pharmacokinetics of single oral doses of AZD9291 in patients with EGFRm positive NSCLC whose disease has progressed on an EGFR TKI

A Phase I, open-label, non-randomised study to assess the effect of itraconazole (a CYP3A4 inhibitor) on the pharmacokinetics of a single oral dose of AD9291 in patients with EGFRm positive NSCLC whose disease has progressed on an EGFR TKI

A Phase I, open-label, non-randomised, multicentre study to assess the effect of rifampicin (a CYP3A4 inducer) on the pharmacokinetics of AZD9291 in patients with EGFRm positive Non-small Cell Lung Cancer (NSCLC) whose disease has progressed on an EGFR TKI

A Phase Ib/II, multicentre, open label, randomised study of BI 836845 in combination with enzalutamide versus enzalutamide alone, in metastatic castration-resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy and abiraterone

A Phase I, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of ascending doses of AZD6738 in combination with cytotoxic chemotherapy and/or DNA damage repair / novel anti-cancer agents in patients with advanced solid malignancies

An open-label, non-randomised, parallel group, multicentre, Phase I study to assess the safety and the effect of olaparib at steady state on the pharmacokinetics of the anti-hormonal agents anastrazole, letrozole and tamoxifen at steady state, and the effect of the anti-hormonal agents on olaparib, following administration in patients with advanced solid cancer

A Phase I, open-label, multicentre study to compare two dosage formulations of AZD5363

and to establish the effect of food on the pharmacokinetic exposure, safety and tolerability of AZD5363 in patients with advanced solid malignancies (OAK)

A Phase I, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of ascending doses of AZD5363 under adaptable dosing schedules in patients with advanced solid malignancies

An open-label, multicentre, multiple dose, Phase I study to establish the maximum tolerated dose of E7389 liposomal formulation in patients with solid tumours

An open-label, first-in-human study of the safety tolerability, and pharmacokinetics of VX-970 in combination with cytotoxic chemotherapy in subjects with advanced solid tumours

A Phase I, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of selumetinib (AZD6244; ARRY – 142886) in combination with first line chemotherapy regimens in patients with non-small cell lung cancer (NSCLC).

Peer Reviewed Publications 2013/14

A Phase I, Dose-Escalation Study of the Multi-Targeted Receptor Tyrosine Kinase Inhibitor, Golvatinib, in Patients with Advanced Solid Tumors Molife LR, **Dean E**, Blanco Codesido M, **Krebs MG**, Brunetto A, Greystoke AP, Daniele G, Lee L, Kuznetsov G, Myint KT, de Las Heras B, Wood K, Ranson MR. Clin Cancer Res. 2014 Oct 2. pii: clincanres.0409.2014. [Epub ahead of print]

Tracking Genomic Cancer Evolution for Precision Medicine: The Lung TRACERx Study. TRACERx Consortium members. *PLOS Biology*. Epub July 2014 doi:10.1371/journal.pbio.1001906

Molecular analysis of circulating tumour cells – biology and biomarkers. **Krebs M**, Metcalf R, Carter L, Brady G, Blackhall FH, Dive C. *Nature Reviews Clinical Oncology* 11(3):129-44*,* 2014

1242P - A Phase I study of the MEK1/2 inhibitor selumetinib in combination with first-line chemotherapy regimens for NSCLC.**E. Dean**, N. Steele, H. Arkenau, F.H. Blackhall, N.M. Haris, C. Lindsay, M. Saggese, R. Califano, A. Greystoke, M. Voskoboynik, D. Ghiorghiu, A. Dymond, I. Smith, R. Plummer. Annals of Oncology (2014) 25 (suppl_4): iv426-iv470. 10.1093/annonc/mdu349

Predictive factors of survival for patients with bladder cancer in phase I clinical trials. Michalarea V, **Rafii S**, Kumar R, Kaye SB, de Bono JS, Banerji U, Molife LR., Annals of Oncology (2014) 25 (suppl_4): iv280-iv304. 10.1093/annonc/mdu337

A study of risk of infection with drugs targeting the PI3 kinase (PI3K), AKT, and mTOR pathway**. Rafii S**, Geuna E, Roda D, Jimenez B, Rihawi K, Capelan M, Yap TA, Molife LR, Kaye SB, de Bono JS, Banerji U., J Clin Oncol 32:5s, 2014 (suppl; abstr 2608)

Safety and antitumor activity of the PARP inhibitor BMN673 in a phase 1 trial recruiting metastatic small-cell lung cancer (SCLC) and germline BRCA-mutation carrier cancer patients. Wainberg Z, **Rafii S**, Ramanathan R, Mina L, Byers L, Chugh R, Goldman J, Sachdev J, Matei D, Wheler J, Henshaw JW, Zhang C, Gallant G, De Bono JS., J Clin Oncol 32:5s, 2014 (suppl; abstr 7522)

Complications of hyperglycaemia in phase 1 trials targeting the PI3K-akt-mTOR (PAM) pathwayGeuna E, Roda D, **Rafii S**, Jimenez B, Rihawi K, Capelan M, Yap TA, Molife LR, Kaye SB, de Bono JS, Banerji U. J Clin Oncol 32:5s, 2014 (suppl; abstr 2612)

TAX-TORC: A phase I trial of the combination of AZD2014 (dual mTORC1/mTORC2 inhibitor) and weekly paclitaxel in patients with solid tumours. Roda D, Wong H, Geuna E, **Rafii S,** et al., J Clin Oncol 32:5s, 2014 (suppl; abstr 26What factors influence advanced ovarian cancer patients outcomes to phase I trial treatments? Yap T, George A, Michie C, Wong M, Bowen R, **Rafii S**, et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 5560

Clinical utility of circulating tumour cell detection in non-small cell lung cancer. Fusi A, Metcalf R, **Krebs M**, Dive C, Blackhall F. *Current Treatment Options in Oncology* 14(4):610-22, 2013

Method validation of circulating tumour cell enumeration at low cell counts. Cummings J, Morris K, Zhou C, Sloane R, Lancashire M, Morris D, Bramley S, **Krebs M**, Khoja L, Dive C. *BMC Cancer* 13(1):415, 2013

Neuroendocrine and epithelial phenotypes in small-cell lung cancer: implications for metastasis and survival in patients.Stovold R, Meredith SL, Bryant JL, Babur M, Williams KJ, **Dean EJ**, Dive C, Blackhall FH and White A. Br J Cancer. 108: 1704-1711; 30 Apr 2013 doi:10.1038/bjc.2013.112

Results of two Phase 1 multicenter trials of AZD5363, an inhibitor of AKT1, 2 and 3: biomarker and early clinical evaluation in Western and Japanese patients with advanced solid tumors. Udai Banerji, Malcolm Ranson, Jan HM Schellens, Taito Esaki, **Emma Dean**, Andrea Zivi, Ruud Van der Noll, Paul K. Stockman, Marcelo Marotti, Michelle D. Garrett, Barry R. Davies, Paul Elvin, Andrew Hastie, Peter Lawrence, SY Amy Cheung, Christine Stephens, Kenji Tamura. Abstract LB-66 AACR 2013.

Results of a phase I study of AZD4547, an inhibitor of fibroblast growth factor receptor (FGFR), in patients with advanced solid tumors.Fabrice Andre, Malcolm Ranson, **Emma Dean**, Andrea Varga, Ruud Van der Noll, Paul K. Stockman, Dana Ghiorghiu, Elaine Kilgour, Paul D. Smith, Merran Macpherson, Peter Lawrence, Andrew Hastie, Jan HM Schellens. Abstract LB-145 AACR 2013.

Is Uterine Serous Carcinoma a part of Hereditary Breast Cancer Syndrome?**Rafii S**, Dawson P, Williams S, Pascoe J, Nevin J, Sundar S., J Clin Oncol 31, 2013 (suppl; abstr 5587)

Clinical Audit Activity

Audit of the patient referral pathway to early phase research

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Educational, Teaching and Training Activity

The Experimental Cancer Medicine Team delivers top quality education and training in experimental therapeutics. We offer undergraduate and postgraduate degree training and secondments in experimental cancer medicine. We have funding approved to establish an MRes/MSc in Experimental Therapeutics accredited by The University of Manchester in Sept 2015. We also offer a Clinical Fellows Training Scheme and clinical placements for specialty registrars. We have an established in-house training programme to train our Clinical Trial Coordinators and clinical research nurses in all aspects of Good Clinical Practice and quality systems.