



NCRI
Cancer
Conference



Programme

2015

1-4 November
Liverpool, UK

SUNDAY



Programme at a glance

Workshops

11.00 - 15.15 Cancer data and its analysis workshop
Room 3A Hosted by **Ontario Institute for Cancer Research**, Toronto, Canada



11.00 - 15.00 How to get the job you really want - CV and interview workshop - £50
Room 12 **Martin Clarke**, Inspire Change, UK

Welcome address

15.20 - 15.30 Introduction from the Director of the NCRI and the Chair of the 2015
Hall 1A Scientific Committee
Karen Kennedy, Director of the National Cancer Research Institute
and **Charles Swanton**, Chair of the 2015 Scientific Committee

Plenary lecture

Chaired by **Charles Swanton**, The Francis Crick Institute & University College London Cancer Institute, UK

15.30 - 16.10 Hormone therapy for prostate cancer
Hall 1A **Charles Sawyers**, Memorial Sloan Kettering Cancer Center,
New York, USA



Networking and refreshment break

16.10 - 16.40 Registration area and Galleria

Plenary lectures

Chaired by **Charles Swanton**, The Francis Crick Institute & University College London Cancer Institute, UK

16.40 - 17.20 Epigenetic targets in cancer
Hall 1A **Kristian Helin**, University of Copenhagen, Denmark



17.20 - 18.00 Is late diagnosis of cancer real and if so what can we do about it?
Hall 1A **Harpal Kumar**, Cancer Research UK, London, UK



Workshop

18.00 - 19.30 This house believes we should stop focussing on the causes of breast
Room 3A cancer and get on with strategies to prevent the disease'
Hosted by Breast Cancer Now



Opening reception, networking and exhibition viewing

18.00 - 20.00 *Light supper and refreshments will be served*
Hall 2

Plenary abstracts

● Hormone therapy for prostate cancer

15.30 – 16.10

Hall 1A

Charles Sawyers,
Memorial Sloan
Kettering Cancer Center,
New York, USA



Resistance to molecularly targeted cancer therapies often occurs through mutations or genomic alterations that restore signalling downstream of the targeted pathway. Using prostate cancer as an example, I will review recent evidence that more potent inhibitors, which can clearly deliver superior clinical efficacy, can lead to more diverse mechanisms of escape. Prostate cancers treated with the novel anti-androgen enzalutamide can develop resistance through mutations in the androgen receptor, through bypass of androgen receptor blockade by signalling through the glucocorticoid receptor or by lineage plasticity, whereby androgen-dependent luminal epithelial cells undergo an identity change to more basal-like epithelial cells. The molecular basis for these resistance mechanisms includes genetic as well as epigenetic changes which point to new strategies to overcome resistance. These findings reveal the complexity underlying adaptive responses to targeted therapy and reinforce the importance of combination therapy to achieve long term clinical benefit.

● Epigenetic targets in cancer

16.40 – 17.20

Hall 1A

Kristian Helin,
University of
Copenhagen, Denmark



Cell fate decisions are regulated by an intricate interplay between the cellular environment, growth factors and intracellular signaling pathways. The balance of stability versus plasticity in stem cells is a regulatory challenge, and extensive studies in recent years have focused on understanding the contribution of transcription factors and epigenetic enzymes in the regulation of cellular identity and differentiation pathways. Disruption of epigenetic control is a frequent event in disease, and the first epigenetic-based therapies for cancer treatment have been approved. A generation of new classes of potent and specific inhibitors for several chromatin-associated proteins has shown promise in pre-clinical trials. Although the biology of epigenetic regulation is complex, these and other new inhibitors will hopefully be of clinical use in the coming years.

Our research is focused on understanding the role of epigenetic regulators in maintaining cellular identity and how their deregulation leads to cancer. At the conference, I will review the progress that has been made on the development of new epigenetic inhibitors and discuss some of our recent results on the understanding of the biological function of chromatin-associated proteins and how they contribute to cancer.

Plenary abstracts *(continued)*

● Is late diagnosis of cancer real and if so what can we do about it?

17.20 - 18.00

Hall 1A

Harpal Kumar,
Cancer Research UK,
London, UK



The National Awareness and Early Diagnosis Initiative (NAEDI) was established in 2007, following publication of England's Cancer Reform Strategy that year, to develop a better understanding of the contribution of late diagnosis to the UK's relatively poor cancer survival rates and to develop strategies to address this. A key component of the work of NAEDI over the last eight years has been to undertake new research, examine international comparisons in finer detail and establish an evidence base for future action. A growing national and international research community, as well as new funding streams, have facilitated and enabled this. This session will explore what has been learnt over the last eight years, and how this is being translated into action in the new cancer strategy for England. The session will also challenge the research community to think about the many questions which remain unanswered.

Workshops

● Cancer data and its analysis workshop

11.00 – 15.15

Room 3A

Hosted by **Ontario Institute for Cancer Research**,
Toronto, Canada

Cancer research has rapidly incorporated high-throughput technologies. As a result, large amounts of cancer genome data are becoming publically available through various portals particularly the ICGC Data Portal. This workshop will focus on how to access cancer genome data, where the resources are and how to visualise and evaluate cancer genomic data sets. Participants will gain hands-on training on the databases, visualisation and pathway analysis tools necessary to evaluate cancer genome data.

11.00 – 11.45 Welcome

Module 1: Cancer Genomic Databases – **Francis Ouellette**

- The Databases: The International Cancer Genome Consortium, The Cancer Genome Atlas, and COSMIC Database
- Data storage and access: security and privacy issues, public vs. private data

11.45 – 12.30 Module 2: ICGC Data Portal Demo – **Junjun Zhang**

12.30 – 13.15 Module 3: Pathway & Network Analysis – **Irina Kalatskaya**

- Introduction to pathway and network analysis in cancer genomics
- Sources of pathway and network information: GO biological process, network databases, pathway databases
- Overview of enrichment analysis to find over-represented pathways
- Pathway analysis of largescale cancer genomics data sets

13.15 – 13.45 Lunch

13.45 – 14.30 Module 4: Lab Practical: Accessing and Using ICGC Data Portal – **Phuong-My Do**

- A hands-on exercise on how to find, retrieve and download and visualize cancer data within ICGC

14.30 – 15.15 Module 5: Lab Practical: ICGC Data Portal and Pathway Tools – **Phuong-My Do**

- A hands-on exercise on how to do view your mutation data on pathway maps in ICGC



● How to get the job you really want – CV and interview skills workshop – £50

11.00 – 15.00

Room 12

Hosted by **Martin Clarke**,
Inspire Change, UK

To get promoted and improve your career, whether that be in research or the NHS in a clinical role, you will be assessed not just on your clinical, research and surgical skills, but also your management and soft skills. In this fun, fast moving half day workshop, you will learn how to construct a winning CV and application form, how to get yourself known and noticed and how to answer those tough interview questions.

In addition, delegates who have pre-arranged this, will receive one-to-one feedback on their CV.

Workshops *(continued)*

11.00 - 11.10	Welcome and introductions with tea and coffee
11.10 - 11.55	Working on your CV and application form – and why you need both
11.55 - 12.10	Why do interview panels choose the people they do?
12.10 - 12.45	Great answers to tough interview questions
12.45 - 13.15	Lunch
13.15 - 14.15	When to visit units and what to ask and who to see
14.15 - 14.45	Improving your Management section, Audits, Grants and Research
14.45 - 15.00	Feedback forms and next steps
15.00 - 17.00	One-to-one feedback for attendees on CVs (to be booked in advance)

● **‘This house believes we should stop focussing on the causes of breast cancer and get on with strategies to prevent the disease’**

18.00 - 19.30

Room 3A

Chaired by **Robert Coleman**, University of Sheffield, UK

Advances in our understanding of breast cancer and the development of targeted, life extending treatments mean that breast cancer patients are surviving for longer. However, the increasing cost of these treatments along with the desire to avoid personal and familial suffering caused by breast cancer, makes prevention of the disease in the first place an increasingly attractive option.

Research into breast cancer prevention involves research into the causes of breast cancer along with research into intervention strategies that can reduce breast cancer risk. Over the past decade, substantial investment has gone into identifying breast cancer risk factors, leading to a dramatic increase in our knowledge of genetic and lifestyle causes of the disease. However, very little investment has gone into identifying and developing intervention strategies to reduce risk for women at moderate and high risk of developing breast cancer.

At a time where the quantity of data generated is ever increasing we ask: is it time to stop focussing on the causes of breast cancer and get on with strategies to prevent the disease?

Causes side:

Douglas Easton, University of Cambridge, UK

Tim Key, University of Oxford, UK

Intervention side:

Annie Anderson, University of Dundee, UK

Gareth Evans, University of Manchester, UK



Join the debate ahead of time using Twitter: **#NCRIbcdeb**

MONDAY



Programme at a glance

Workshops

- 08.00 - 08.45** Room 11 BACR educational workshop: Genomics England 100,000 genomes project and cancer programme & GeCIP update
Hosted by **Clare Turnbull**, The Institute of Cancer Research, London, UK
- 08.00 - 08.45** Room 3B De-mystifying today's science
Hosted by **Elaine Vickers**, Science Communicated, Sheffield, UK



Introduction to the programme

- 08.50 - 09.00** Hall 1A Message from the Chair of the Scientific Committee
Charles Swanton, The Francis Crick Institute & University College London Cancer Institute, UK

Plenary lectures

Chaired by **Alastair Thompson**, MD Anderson Cancer Center, Houston, USA

- 09.00 - 09.40** Hall 1A Genomic tests to personalised therapy of patients with metastatic breast cancer
Fabrice André, Institut Gustave Roussy, Villejuif, France
- 09.40 - 10.20** Hall 1A Big data and patient reported outcome measures (PROMs)
Amy Abernethy, Flatiron Health, New York, USA

Networking, exhibition viewing, poster viewing and refreshment break

- 10.20 - 10.50**
Hall 2

Symposia

- 10.50 - 12.20** Room 11 Big data
Hosted by **Nicholas Luscombe**, The Francis Crick Institute, London, UK
- 10.50 - 12.20** Hall 1B Chromatin, epigenetics and cancer
Hosted by **Tony Kouzarides**, The Gurdon Institute, University of Cambridge, UK
- 10.50 - 12.20** Hall 1A Immunotherapy
Hosted by **Adrian Hayday**, King's College London & The Francis Crick Institute, London, UK
- 10.50 - 12.20** Room 3B Molecular testing for early cancer diagnosis: ready for prime time
Hosted by **Rebecca Fitzgerald**, University of Cambridge, UK



Workshop

- 10.50 - 12.20** Hall 1C Molecular pathology
Hosted by **Manuel Salto-Tellez**, Queen's University Belfast, UK

● Networking, exhibition viewing, poster viewing and lunch

12.20 - 14.10

Hall 2

● Dragon's Den workshop

12.20 - 14.00

Room 12

Hosted by **NCRI Consumer Forum**



● Scientific symposium

12.45 - 14.00

Room 3A

Immuno-oncology: where next?

Hosted by **Bristol-Myers Squibb**



● Workshop

13.00 - 14.00

Room 4B

Influencing

Martin Clarke, Inspire Change, UK

● Plenary lectures

Chaired by **Caroline Dive**, Cancer Research UK Manchester Institute, UK

14.10 - 14.40

Hall 1A

BACR Tom Connors Lecture: Probing the transcriptional consequences of Ras and Rho activation

Richard Treisman, The Francis Crick Institute, London, UK



14.40 - 15.10

Hall 1A

Heterogeneity, drug resistance and clonal evolution of colorectal cancers

Alberto Bardelli, University of Torino, Turin, Italy

● Networking, exhibition viewing, poster viewing and refreshment break

15.10 - 15.40

Hall 2

● Parallel sessions

15.40 - 17.40

Room 12

E-cigarettes and policy

Hosted by **Linda Bauld**, University of Stirling, UK and **Alison Cox**, Cancer Research UK, London, UK

15.40 - 17.40

Room 3B

Everybody's responsibility: systematic assessment of patient and carer needs in the oncology clinics and GP surgery

Hosted by **Miriam Johnson**, University of Hull, UK

15.40 - 17.40

Room 3A

Genome instability: bench to bedside

Hosted by **Thomas Helleday**, Karolinska Institute, Stockholm, Sweden

15.40 - 17.40

Hall 1A

Immune checkpoints and cancer

Hosted by **Sergio Quezada**, University College London Cancer Institute, UK

Programme at a glance *(continued)*

15.40 – 17.40 Liquid biopsies with a twist: circulating cells and DNA
Room 11 Hosted by **Nitzan Rosenfeld**, Cancer Research UK Cambridge Institute, UK

15.40 – 17.40 Physical activity – the panacea?
Room 4 Hosted by **Robert Thomas**, Bedford & Addenbrooke's Cambridge University Hospitals & Cranfield University, UK

15.40 – 17.40 Screening and epidemiology of ovarian cancer
Hall 1C Hosted by **Iain McNeish**, University of Glasgow, UK

15.40 – 17.40 Understanding the genomic landscape of brain cancer
Hall 1B Hosted by **Colin Watts**, University of Cambridge, UK



● Networking and break

17.40 – 18.00
Hall 2

● Cancer Research UK prize ceremony

18.00 – 18.20 Presented by **Nic Jones**, Chair of the Cancer Research UK Prizes Selection Panel
Hall 1A



● Plenary lecture

Chaired by **Nic Jones**, Chair of the Cancer Research UK Prizes Selection Panel

18.20 – 19.00 Cancer Research UK Lifetime Achievement Award Winner:
Hall 1A Evolutionary tales in leukaemia
Mel Greaves, The Institute of Cancer Research, London, UK



● Drinks reception, networking and exhibition viewing

19.00 – 20.45 *Canapés and drinks will be provided*
Hall 2

● Chairs' evening *(by invitation)*

Hosted by **Dame Delyth Morgan**, Chair of Trustees, National Cancer Research Institute and **Charles Swanton**, Chair of the 2015 Scientific Committee

20.00 – 22.00
Room 3A

Plenary abstracts

● Genomic tests to personalised therapy of patients with metastatic breast cancer

09.00 – 09.40

Hall 1A

Fabrice André,
Institut Gustave
Roussy, Villejuif,
France



Development of high throughput genomic analyses allow deciphering of the molecular mechanisms involved in cancer progression in individuals. Genomic tests could be used to identify oncogenic drivers, mechanisms of resistance to targeted therapies, DNA repair defects and mechanisms of immune suppression. Several genomic alterations have been suggested to be relevant in breast cancer, including PIK3CA, AKT1, ERBB2, ESR1, BRCA1, BRCA2 mutations, and ERBB2, FGFR1 amplifications. The use of whole exome sequencing could be interesting to quantify mutational load and identify mutational processes.

Several trials are evaluating the clinical utility of using high throughput technologies. Data are suggesting that response rates are low. Nevertheless, these trials were done using non-specific drugs and first generation algorithms for target identification. Current trials are using more selective and bioactive drugs and stratifying patients based on the relevance of the targets.

New technologies are being developed to better characterise molecular alterations for clinical practice. This includes circulating tumour DNA, phosphoprotein assays, and RNA-seq.

● Big data and patient reported outcome measures (PROMs)

09.40 – 10.20

Hall 1A

Amy Abernethy,
Flatiron Health,
New York, USA



Leveraging the emerging wealth of ‘big data’ from diverse healthcare sources is critical to developing the evidence base that informs decisions made by patients, providers, and policy makers. While healthcare today is generating a vast volume of data, there are certain ingredients to which the entire industry must commit in order for the data to be facile and meaningful. Solutions are needed to pull out key data points that are fundamental to cancer-focused analyses from unstructured documents (e.g., case notes, biomarker reports) at scale. Even the structured data that are routinely available in clinical datasets are messy, requiring normalisation and harmonisation, such that all data points are merged into a common analysable format. And, continuous amalgamation of longitudinal data is necessary to depict the full healthcare story.

The increasingly central role of the electronic health record (EHR), coupled with a renewed focus on the importance of the voice and experience of the patient, creates a clear opportunity to generate meaningful patient-centric data that contribute to the big data vision. Patient reported outcome measure (PROM) data include everything from personal reporting of demographic characteristics to personal reflections on satisfaction with healthcare and assessments of symptoms and quality of life. Collection of complete, high quality PROM data at scale is most practical when real-time collection of PROMs is useful by clinicians at point of care, then these data are stored in the EHR and available for a variety of secondary analytic purposes. Today, there are many PROM efforts occurring at the institutional level; these efforts are demonstrating the value of engaging with patients to generate key components of a clinical data set, which facilitates patient-centered and individualised care, leading to improved outcomes for society as a whole.

Competing interests
Employee of Flatiron Health.

Plenary abstracts *(continued)*

● BACR Tom Connors Lecture: Probing the transcriptional consequences of Ras and Rho activation

14.10 - 14.40

Hall 1A

Richard Treisman,
The Francis Crick
Institute, London, UK



Signalling by small GTPases of the Ras and Rho families controls proliferation, adhesion and invasion of both normal and transformed cells. We study how signalling from these regulators interfaces with transcriptional programmes. An initial focus on the response to acute mitogenic signals such as serum and growth factors led to the discovery of the transcriptional regulator SRF, which works in partnership with two families of signal-regulated cofactors: the TCFs, which are regulated by Ras-MAP kinase signalling, and the MRTFs, which respond to Rho GTPase-mediated alterations in cytoskeletal dynamics. The MRTFs share a novel G-actin binding element, the RPEL motif, with other protein families involved in cytoskeletal control, and represent a new paradigm for signal transduction, in which G-actin acts as a signalling molecule.

Recent studies of two aspects of this system will be discussed. The first area concerns to what extent the SRF network, and particularly TCF-SRF signalling, directs the initial transcription response to MAP kinase activation, and how this system can be used to establish a functional hierarchy between transcription factor activity, chromatin modifications and transcription. The second area concerns molecular mechanisms and transcriptional targets for the MRTF-SRF pathway. Genomic studies indicate that MRTF-SRF signalling controls the transcription of scores of genes involved in invasion, metastasis and mechanosensing.

● Heterogeneity, drug resistance and clonal evolution of colorectal cancers

14.40 - 15.10

Hall 1A

Alberto Bardelli,
University of Torino,
Turin, Italy



Colorectal cancers evolve by a reiterative process of genetic diversification and clonal evolution. Tissue and liquid biopsies can be used to define CRC molecular subtypes and to monitor clonal evolution during therapy. Using these approaches, CRC patients were found to respond selectively to targeted agents interfering with oncogenic nodes of the EGFR signaling pathway. Notably, the patient-specific responses can be recapitulated and paralleled in cellular and mouse clinical proxies (CRC-avatars). The inevitable development of acquired resistance to inhibitors of the EGFR signaling axis presently limits further clinical advances. Strategies to prevent or overcome resistance are therefore essential to design the next generation of molecularly-driven clinical trials for CRC patients.

● Cancer Research UK Lifetime Achievement Award winner: Evolutionary tales in leukaemia

18.20 - 19.00

Hall 1A

Mel Greaves,
The Institute of
Cancer Research,
London, UK



Distilling complexity down to underlying principles and coherent explanations is the challenge, and attraction, of all science. Understanding causation of disease is problematic in this respect as we tend to focus our attention on what are, in reality, individual components of a multi-factorial network of causative mechanisms.

I have spent most of my scientific career on a journey trying to understand why and how children develop leukaemia. In so far as this research has been guided by an underlying philosophy, it has been that the answer to the question posed will reside in the basic biology of the disease and be informed by the 'natural experiments' provided by patients themselves. And that an evolutionary biology perspective should help provide coherence of explanation. In retrospect, I see this choice of direction and mode of travel as being forged by a few key influences, both academic and personal, early on in my career.

The current picture I will outline was initiated ~30 years ago with minimal clues spawning a speculative hypothesis but then constructed, piecemeal, with cellular, genetic and epidemiological studies, all of them collaborative. The outcome, or proffered explanation of causality, posits childhood acute lymphoblastic leukaemia as an evolutionary dilemma and a paradox of progress. And a potentially preventable cancer.

Symposia

● Big data

Hosted by **Nicholas Luscombe**, The Francis Crick Institute, London, UK

- 10.50 - 10.55** Introduction by the host
Room 11
- 10.55 - 11.20** Benchmarking and biomarkers: the molecular and technical heterogeneity of prostate cancer
Room 11
Paul Boutros, Ontario Institute for Cancer Research, Toronto, Canada
- 11.20 - 11.45** Molecular archaeology of cancer
Room 11
Peter Van Loo, The Francis Crick Institute, London, UK & University of Leuven, Belgium
- 11.45 - 12.10** Understanding genome organisation: using HiC data to interpret gene regulation and non-coding mutations
Room 11
Nicholas Luscombe, The Francis Crick Institute, London, UK
- 12.10 - 12.20** Discussion

● Chromatin, epigenetics and cancer

Hosted by **Tony Kouzarides**, The Gurdon Institute, University of Cambridge, UK

- 10.50 - 10.55** Introduction by the host
Hall 1B
- 10.55 - 11.20** Epigenetic targets for cancer drug discovery: bromodomains and beyond
Hall 1B
Mark Bunnage, Pfizer, Cambridge, USA
- 11.20 - 11.45** Epigenetic reprogramming in mammalian development
Hall 1B
Wolf Reik, Babraham Institute, University of Cambridge & Wellcome Trust Sanger Institute, Cambridge, UK
- 11.45 - 12.10** Epigenetics impacts copy number heterogeneity and drug resistant gene selection
Hall 1B
Johnathan Whetstone, Harvard Medical School & Massachusetts General Hospital Cancer Center, Boston, USA
- 12.10 - 12.20** Discussion

● Immunotherapy

Hosted by **Adrian Hayday**, The Francis Crick Institute, Cancer Research UK & King's College London, UK

- 10.50 - 10.55** Introduction by the host
Hall 1A
- 10.55 - 11.20** Gut microbiota and anti-cancer immune responses
Hall 1A
Laurence Zitvogel, Institut Gustave Roussy and INSERM, Villejuif, France
- 11.20 - 11.45** The mechanistic basis of cancer immunotherapy
Hall 1A
Ira Mellman, Genentech, San Francisco, USA



11.45 - 12.10 T cells and the immunogenicity of immunotherapy
Hall 1A **Adrian Hayday**, King's College London & The Francis Crick Institute,
London, UK

12.10 - 12.20 Discussion

● **Molecular testing for early cancer diagnosis: ready for prime time**

Hosted by **Rebecca Fitzgerald**, University of Cambridge, UK

10.50 - 10.55 Introduction by the host
Room 3B



10.55 - 11.20 Working together in the genomics era: lessons from the Genetic
Testing in Epithelial Ovarian Cancer (GTEOC) study
Room 3B **Marc Tischkowitz**, University of Cambridge, UK

11.20 - 11.45 Molecular biomarkers: are they so much better than traditional risk
Room 3B factors and simple biomarkers?
Peter Sasieni, Queen Mary University of London, UK

11.45 - 12.10 Devising the ideal test for early diagnosis of cancer: lessons from
Room 3B the oesophagus
Rebecca Fitzgerald, University of Cambridge, UK

12.10 - 12.20 Discussion

Symposia abstracts

● Big data

MONDAY

10.50 - 10.55

Room 11

Nicholas Luscombe,
The Francis Crick
Institute, London, UK

Introduction

TUESDAY

10.55 - 11.20

Room 11

Paul Boutros,
Ontario Institute for
Cancer Research,
Toronto, Canada

Benchmarking and biomarkers: the molecular and technical heterogeneity of prostate cancer

Prostate cancer is the leading non-skin malignancy in men, affecting 1 in 7 men over their lifetime. Today the vast majority of new diagnoses are of localised disease, and these patients have their treatment determined using the clinical/pathological factors of pre-treatment serum PSA levels, T-category and the Gleason Score. These clinical metrics are used to stratify men into low-, intermediate- and high-risk groups. My presentation will describe results from the Canadian Prostate Cancer Genome Network (CPC-GENE), the world's largest prostate cancer genomics project. CPC-GENE is sequencing the somatic and germline genomes of 500 intermediate-risk prostate cancers, along with epigenetic, transcriptomic and proteomic profiles. I will first discuss the intra-tumoural heterogeneity of these tumours, which shows profound genomic and micro-environmental heterogeneity. I will then link this variability directly to patient outcome, demonstrating the benefit of linking tumour hypoxia and somatic mutation profiles to robustly predict patient survival. Finally, I will discuss the challenges in translating sequencing-based assays into clinical practice. The ICGC-TCGA DREAM Somatic Mutation Calling Challenge provides the first rigorous investigation of the error profiles of sequencing studies, and I will discuss the startling degree of heterogeneity introduced by variability in analysis. Challenge-style benchmarking evaluations are increasingly critical, and I close by discussing how moving these into the cloud provides a framework for robust, rapid and reproducible comparison and optimisation of algorithms for computational cancer biology.

WEDNESDAY

11.20 - 11.45

Room 11

Peter Van Loo,
The Francis Crick
Institute, London,
UK & University of
Leuven, Belgium

Molecular archaeology of cancer

The cancer genome carries within it an archaeological record of the tumour's past. We developed several 'molecular archaeology' algorithms to disentangle the subclonal architecture and life history of cancer from whole-genome sequencing data of the tumour bulk. We are constructing life histories of thousands of tumours from their genome sequences, using both driver and passenger mutations. By obtaining detailed timelines of many cancers' evolutionary histories that include driver mutations, copy number changes, rearrangements and mutational processes, we will identify the initiating events of cancer development, and the events that are selected for later in a cancer's lifetime, including those that drive late clonal expansions and that may play a role in tumour malignancy. In addition, these analyses will allow blueprints of the subclonal architecture across cancer types in unprecedented detail and on an unprecedented number of cases, allowing a glimpse into a tumour's future.

Complementary to this, we are performing smaller-scale collaborative studies of tumour bulk sequencing, in combination with single-cell and multi-sample sequencing of primary tumours, metastases, and circulating and disseminated tumour cells, aiming to gain insight into tumour evolution and metastasis. By profiling the genomes of single cells, tumour

evolution and subclonal architecture can in theory be dissected in minute detail, allowing unprecedented insights into tumour evolution.

In this talk, I will discuss several ongoing molecular archaeology approaches applied to a single cell and bulk sequencing data to explore intratumour heterogeneity in primary tumours, as well as the evolutionary history of disseminated tumour cells in the bone marrow.

11.45 - 12.10

Room 11

Nicholas Luscombe,
The Francis Crick
Institute, London, UK

Understanding genome organisation: using HiC data to interpret gene regulation and non-coding mutations

Transcriptional control in large genomes often requires looping interactions between distal DNA elements, such as enhancers and target promoters. Current chromosome conformation capture techniques do not offer sufficiently high resolution to interrogate these regulatory interactions on a genomic scale. Here we use Capture Hi-C (CHi-C), an adapted genome conformation assay, to examine the long-range interactions of almost 22,000 promoters in two human blood cell types. We identify over 1.6 million shared and cell type-restricted interactions spanning hundreds of kilobases between promoters and distal loci. Transcriptionally active genes contact enhancer-like elements, whereas transcriptionally inactive genes interact with previously uncharacterised elements marked by repressive features that may act as long-range silencers. Finally, we show that interacting loci are enriched for disease-associated SNPs, suggesting how distal mutations may disrupt the regulation of relevant genes. This study provides new insights and accessible tools to dissect the regulatory interactions that underlie normal and aberrant gene regulation.

12.10 - 12.20

Discussion

● **Chromatin, epigenetics and cancer**

10.50 - 10.55

Hall 1B

Tony Kouzarides,
The Gurdon Institute,
University of
Cambridge, UK

Introduction

Small chemical modifications of DNA and histones, mediate epigenetic signalling that can modulate many biological processes. The enzymes that mediate these modifications and the proteins that recognise them are proving to be good targets for therapeutic intervention, with several inhibitors currently in clinical trials. During the first talk of the session, Mark Bunnage will provide examples of targeted drug discovery directed against a class of protein that recognise acetylated histones. Two talks will follow that provide insights into the mechanism of action of DNA and histone methylation. First, Wolf Reik will describe the involvement of DNA methylation in early development and its connection to reprogramming; John Whetstone will then describe how copy number heterogeneity can be regulated by histone methylation and in particular by an enzyme KDM4A, that acts to remove methyl groups.

Symposia abstracts *(continued)*

10.55 - 11.20

Hall 1B

Mark Bunnage

Pfizer, Cambridge, USA

Epigenetic targets for cancer drug discovery: bromodomains and beyond

Epigenetics can be defined as heritable or acquired changes in gene expression that occur without a change in the underlying DNA sequence. In addition to its genome, each human cell also contains epigenetic information that is encoded through chemical modifications to the DNA itself and also the histone proteins around which DNA winds to package it in chromatin. This epigenetic signature plays a key role in modulating chromatin structure and genome function, thus helping regulate the protein expression profile in the cell. Since a hallmark of cancer is aberrant gene expression, research into epigenetics has great promise to enable future cancer drug discovery.

Chemical modifications of histones that influence epigenetic regulation include changes such as methylation of lysine/arginine residues and acetylation of lysine residues. A number of enzymes have now been identified that either introduce these epigenetic marks ('writers') or remove them ('erasers'). In addition, regulatory proteins have been discovered that directly recognise histone modification status ('readers') and drive the localisation of complexes that control gene expression.

This presentation will provide a perspective on small molecule drug discovery for epigenetic targets in cancer, with a particular focus on the bromodomain class of 'reader' proteins.

11.20 - 11.45

Hall 1B

Wolf Reik, Babraham Institute, University of Cambridge & Wellcome Trust Sanger Institute, Cambridge, UK

Epigenetic reprogramming in mammalian development

Epigenetic information is relatively stable in somatic cells but is reprogrammed on a genome-wide level in germ cells and early embryos. Epigenetic reprogramming appears to be conserved in mammals including humans. This reprogramming is essential for imprinting, and important for the return to pluripotency including the generation of iPS cells, the erasure of epimutations, and perhaps for the control of transposons in the genome. Following reprogramming, epigenetic marking occurs during lineage commitment in the embryo in order to ensure the stability of the differentiated state in adult tissues. Signalling and cell interactions that occur during these sensitive periods in development may have an impact on the epigenome with potentially long lasting effects.

A key component of reprogramming is the erasure of DNA methylation which probably involves an intricate combination of passive (DNA replication without maintaining methylation) and active mechanisms. We have identified signalling events which regulate DNA methylation dynamics during early development, and which connect reprogramming firmly with naïve pluripotency. This is probably important in order to disable epigenetic memory in pluripotent cells. Altered reprogramming may also result in transgenerational epigenetic inheritance. A recently developed method for single cell whole genome bisulfite sequencing (scBS-seq) reveals extensive heterogeneity of DNA methylation especially in enhancers at the exit of pluripotency. It is possible that such epigenetic heterogeneity could help with key cell fate decisions during gastrulation.

Full authorship

Wolf Reik^{1,2,4}, Heather Lee^{1,4}, Ines Milagre¹, Solenn Patalano¹, Christel Krueger¹, Mario Iurlaro¹, Ferdinand von Meyenn¹, Rebecca Berrens¹, Michelle King¹, Stephen Clark¹, Tamir Chandra^{1,4}, Felix Krueger³, Simon Andrews³, Fatima Santos¹ & Wendy Dean¹

¹ Epigenetics Programme, Babraham Institute, Cambridge, UK

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³ Bioinformatics Group, Babraham Institute, Cambridge, UK

⁴ Wellcome Trust Sanger Institute, Cambridge, UK

11.45 - 12.10

Hall 1B

Johnathan Whetstone,
Harvard Medical School
& Massachusetts
General Hospital
Cancer Center,
Boston, USA

Epigenetics impacts copy number heterogeneity and drug resistant gene selection

Acquired somatic copy number alterations are frequently associated with the selection of drug resistant oncogenes. However, precise mechanisms driving selection of distinct regions within the genome remains unclear. In recent years, we have established that chromatin states and lysine demethylases play critical roles in modulating copy gains of drug resistant regions of the genome. Specifically, we have identified the histone tri-demethylase KDM4A as the first enzyme capable of promoting site-specific copy number changes. KDM4A overexpression promotes localised copy gain without global chromosome instability. Tumours with increased KDM4A levels are enriched in copy gains for cytobands observed in cell culture models. We further demonstrate that these events are the result of replication. KDM4A alters heterochromatin and increases the amount of replication machinery at target loci. These copy gains occur during S phase and are removed as cells are exiting S phase. The cytoband gains are affiliated with drug resistant tumours; therefore, we asked whether targeting the copy gains through chemical inhibition of KDM4A was possible and whether a chemical screen could demonstrate that an active process is associated with elimination of copy gained regions. Our most recent data demonstrates the druggability of these processes. In fact, we have now identified small molecules that impact KDM4A and copy gain as well as the ability to remove gains during cell cycle progression. Lastly, a screen for environmental and chemical agents has uncovered input signals that are responsible for generating site-specific gains through altering the chromatin environment. Taken together, we have identified genetic, epigenetic and environmental factors promoting copy number heterogeneity in tumours and established that these events are targetable through inhibition of chromatin regulators.

- Copy gains are a regulated process
- Copy gains are regulated by KDM4A and histone methylation
- Copy gains are druggable
- Identify input pathways modulating copy gain

12.10 - 12.20**Discussion**● **Immunotherapy****10.50 - 10.55**

Hall 1A

Adrian Hayday,
Kings' College London
& The Francis Crick
Institute, London, UK

Introduction

Symposia abstracts *(continued)*

10.55 - 11.20

Hall 1A

Laurence Zitvogel,
Institut Gustave
Roussy & INSERM,
Villejuif, France

Gut microbiota and anti-cancer immune responses

The clinical management of cancer patients compromises the delicate symbiosis between the gut microbiota and the host. Mucositis, a major oncological problem caused by anticancer chemotherapeutic agents, is worsened by neutropenia and antibiotics. Our group has reported the crucial role of gut microbiota in eliciting innate and adaptive immune responses beneficial for the host in the context of effective therapies against cancer. By compromising intestinal integrity, chemotherapeutic agents enhance gut permeability and favour the selective translocation of Gram⁺ bacteria (*L. Johnsonii* + *E. Hirae*) into secondary lymphoid organs. There, anti-commensal pathogenic TH17 (pTh17) T cell responses are primed, facilitating the intratumoral accumulation of tumour-specific TH1 T cells that is associated with tumour regression after chemotherapy with cyclophosphamide (CTX) (Viaud et al Science Nov 2013). To demonstrate a causal relationship between gut microbiota and systemic pTh17 responses induced by CTX, we treated animals that had been previously sterilised by means of antibiotics with a cocktail of Gram⁺ bacteria (*L. Johnsonii* + *E. Hirae*) and found that this cocktail (but not *L. Reuteri* or *L. Plantarum*) could induce pTh17 in the spleen of CTX (but not vehicle)-treated animals and restored the CTX-anti-cancer effects lost in antibiotic-treated mice (Daillère, unpublished data). Importantly, the redox equilibrium of myeloid cells contained in the tumour microenvironment is also influenced by the intestinal microflora, contributing to tumour responses (Iida, Science Nov 2013). Moreover, we just extended these findings to immune checkpoint blockade by anti-CTLA4 Ab and identified other microbial species responsible for the efficacy of the product in mice and potentially in humans (Vétizou, submitted). These data will be presented at the meeting. Hence, the anticancer efficacy of alkylating agents, platinum salts and immunomodulators could be compromised in patients presenting a dysbiosis or cotreated with antibiotics. These findings represent a paradigm shift in our understanding of the mode of action of conventional chemotherapeutics.

11.20 - 11.45

Hall 1A

Ira Mellman,
Genentech, San
Francisco, USA

The mechanistic basis of cancer immunotherapy

The rapid advance of cancer immunotherapy is changing fundamentally the way we think about cancer care and cancer biology. To a significant degree, recent progress in the clinic was made possible by the understanding that the immunosuppressive mechanisms deployed by tumours to subvert T cell attack represented a key rate-limiting step in many patients. Interestingly, these mechanisms are not tumour-specific specialisations but rather manifestations of the normal regulatory mechanisms used by all cells and tissues to maintain immune homeostasis. The best validated of these is the interaction between the negative regulator of T cells PD-1 with its ligand PD-L1 expressed by tumour cells or tumour infiltrating immune cells in response to IFN γ release. Antibodies that block this interaction, and the interaction of PD-L1 with a second T cell negative regulator CD80, have proved to be highly effective in the clinic over a wide array of solid and hematologic tumour indications. Yet, in important tumour types such as non-small cell lung cancer, only a fraction of patients respond clinically: ~20% overall, with responses enriched 2-3 fold in patients whose tumours express PD-L1 at baseline. To improve and extend the benefit of this therapy, it has now become critical to understand the use of biomarkers to aid patient selection and also to devise combinations of anti-PDL1/PD-1 with other immunological, oncogene-targeted, or standard of care chemotherapies.

Progress in the clinic has been so rapid, however, that our understanding of how the PD-L1/PD-1 axis works at the mechanistic level has lagged considerably. Mechanistic understanding is not only a scientifically compelling problem but also will be invaluable to therapeutic efforts. We have, therefore, engaged a series of investigations guided by results of our clinical studies, particularly by the detailed biomarker analysis to discover the immune correlates of

“response” and “lack of response” in large patient cohorts. Our analysis to date has revealed a number of fundamental insights into the mechanism of action of PD-1, which in turn has informed strategies for undertaking combination therapies in the clinic.

11.45 - 12.10

Hall 1A

Adrian Hayday,
King's College London
& The Francis Crick
Institute, London, UK

T cells and the immunogenicity of immunotherapy

Some extraordinary clinical successes of immunotherapy have had game-changing effects on the way we view cancer biology and the interaction of the immune system with our tissues. In particular, the tissues where solid tumours form are commonly replete with resident T cells. $\gamma\delta$ T cells are prominent tissue-resident T cells in all vertebrates examined. We have shown that they make rapid innate-like responses to molecular markers of tissue perturbation, killing dysregulated cells, producing selective cytokines, and presenting antigen to CD8 T cells. Thus, these T cells can facilitate the immunogenicity of growing tumours. In seeking a better understanding of how tissue-resident $\gamma\delta$ T cells are regulated in situ in health and disease, we have identified organ-specific B7-like molecules that constitute de facto local checkpoints.

Although most studies of tissue-resident T cells have, for obvious reasons been conducted on mice, we have undertaken a characterisation of human tissue-resident T cells from healthy and tumour tissue in over 100 donors. Those studies emphasise the relatedness of Tumour Infiltrating Lymphocytes (TILs) with local T cells. With this knowledge, we are developing a programme of human $\gamma\delta$ T cell immunotherapy that may be particularly suited to adenocarcinomas of low mutation load or with high rates of tumour evolution.

12.10 - 12.20

Discussion

● Molecular testing for early cancer diagnosis: ready for prime time

10.50 - 10.55

Room 3B

Rebecca Fitzgerald,
University of
Cambridge, UK

Introduction

Early detection of cancer dramatically improves cancer outcomes but depending on the technology used and its implementation, there can be substantial problems with over and under-diagnosis. Hence, some established screening programmes have come under critical scrutiny because of the precarious balance of risks and benefits for the individual and for society. Most traditional screening tests do not use molecular information. The question arises as to whether, in an era of huge technological advances in molecular diagnostics, we can transform this field of medicine and overcome some of the obstacles which give screening a bad press. Dr. Marc Tischkowitz will discuss genetic testing for pre-disposition syndromes and use the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) Study as a specific example, since it explores a new way of offering BRCA1/2 testing in mainstream oncological practice. This study explored the psychological impact of mutation testing as well as the diagnostic yield. Professor Peter Sasieni will discuss the role of molecular biomarkers at the level of the tissue and whether these are so much better than traditional risk factor and simple biomarkers. Finally, Rebecca Fitzgerald will provide a specific case study for the potential of molecular biomarkers to radically alter a clinical care pathway. Specifically she will discuss the data from clinical studies in which molecular biomarkers were applied to a non-endoscopic cell collection device (Cytosponge) to diagnose Barrett's oesophagus and associated dysplasia/carcinoma in situ with applicability to the primary care setting.

Symposia abstracts *(continued)*

10.55 - 11.20

Room 3B

Marc Tischkowitz,
University of
Cambridge, UK

Working together in the genomics era: lessons from the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) study

The introduction of next generation sequencing over the last five years has resulted in cheaper and faster genetic testing for hereditary cancers. The challenge we now face is how best to incorporate these advances into routine oncological practice, while at the same time maintaining the necessary support and counselling for affected individuals and their families. In this presentation I will use results from the Genetic Testing in Epithelial Ovarian Cancer (GTEOC) Study to highlight how such integration might be achieved. From 1st July 2013 to 30th June 2015, women newly diagnosed with EOC were recruited through six sites in East Anglia for BRCA1/2 testing. Eligibility was irrespective of patient age and family history of cancer. Consent for genetic testing was obtained by the research team after participants reviewed the study information sheet. The psychosocial arm of the study utilised quantitative questionnaires and qualitative interviews. 233 women were recruited and testing has now been completed in 186. The mean age at diagnosis was 65 years (range 30-90). 13 mutations were detected (9 in BRCA1, 4 in BRCA2) giving a yield of 7%. The mutation yield was 10.5% in unselected women <70 (11/105) and 2.5% in unselected women 70+ (2/81). Preliminary analysis of the first 81 completed questionnaire responses showed that IES and DASS scores in response to genetic testing were significantly lower than equivalent scores of IES and DASS in response to cancer diagnosis ($p < .001$). Based on these results it seems that population-based genetic testing is acceptable to newly diagnosed patients with cancer and is less resource-intensive than current standard practice where all patients have a full assessment by the genetics team prior to testing. The study necessitated a close working relationship between cancer genetics and oncology and is feasible within existing NHS resources and infrastructure.

11.20 - 11.45

Room 3B

Peter Sasieni,
Queen Mary University
of London, UK

Molecular biomarkers: are they so much better than traditional risk factors and simple biomarkers?

Molecular technology holds enormous promise for screening and early detection but has so far been rather disappointing. The three NHS cancer screening programmes are based on old technologies and adoption of molecular testing has provided only modest improvements. Early diagnosis relies on symptom recognition and for the most part imaging. There is much talk of using genetic profiling to better target cancer screening, but such an approach is counter to the principles of population screening and raises important questions about data confidentiality.

There has been a huge reduction in cardiovascular disease through recognition of the risk factors of high cholesterol and blood pressure, but the advances have come from treating these risk factors rather than simply identifying high-risk individuals. There is a danger that by testing for genetic predisposition to cancer we will label millions of people as being at high risk of a particular cancer and fail to offer any intervention to the majority of people who will develop cancer. Currently individuals identified as being at high risk age 40 are less likely to develop cancer in the next 5 years than the average 70 year old!

Using examples from cervical screening and breast cancer risk prediction, I shall consider what molecular biomarkers have delivered so far. By analogy to cardiovascular disease prevention and early diagnosis, I shall consider what we should require from a new molecular biomarker for early diagnosis of cancer.

11.45 - 12.10

Room 3B

Rebecca Fitzgerald,
University of
Cambridge, UK

Devising the ideal test for early diagnosis of cancer: lessons from the oesophagus

Oesophageal adenocarcinoma (OAC) is the most prevalent form of oesophageal cancer in the western world. OAC develops gradually from the benign metaplastic lesion Barrett's oesophagus. Due to the increased risk of developing adenocarcinoma and its exceptionally poor prognosis, regular endoscopy (surveillance) is recommended for patients with Barrett's. The current endoscopic surveillance regimes are confounded by sampling bias and a subjective diagnosis of dysplasia.

One clinical approach to earlier diagnosis would be more systematic screening for Barrett's oesophagus and to couple this with molecular risk stratification. We have made progress in this area by developing a non-endoscopic cell collection tool called the Cytosponge coupled with a diagnostic biomarker specific to Barrett's oesophagus called Trefoil Factor 3 (TFF3). Additional biomarkers can then be applied to the same Cytosponge sample to stratify patients according to their likelihood for progression to adenocarcinoma and this information can be used to inform the requirement for surveillance or endoscopic therapy.

As part of the International Cancer Genome Consortium we are performing genomic analyses on unique sample cohorts of OAC and Barrett's oesophagus to precisely determine the order of mutational events in the evolution of the disease. To date WGS data has demonstrated that the OAC and Barrett's genomes are highly mutated with a unique mutational pattern which may reflect specific environmental exposures including the reflux of acid and bile. Furthermore, there are few recurrent driver gene mutations observed and the disease seems to be dominated by chromosomal rearrangements possibly as a result of catastrophes acquired during punctuated evolution. TP53 is the only truly recurrent mutation and this occurs at the stage of high grade dysplasia. As cancer develops the copy number increases markedly, including genome doubling events. These findings inform emerging molecular diagnostic strategies to distinguish between patients at low and high risk.

Competing interests

The Cytosponge and associated assays have been licensed to Medtronic and Rebecca Fitzgerald is a named inventor on related patents.

12.10 - 12.20**Discussion**

Parallel sessions

● E-cigarettes and policy

Hosted by **Linda Bauld**, University of Stirling, UK and **Alison Cox**, Cancer Research UK, London, UK

15.40 - 15.55 Introduction by the host
Room 12 **Linda Bauld**, University of Stirling, UK and **Alison Cox**, Cancer Research UK, London, UK

15.55 - 16.25 Trends in electronic cigarette use in England
Room 12 **Robert West**, University College London, UK

16.25 - 16.55 Electronic cigarettes: are they safe?
Room 12 **Maciej Goniewicz**, Roswell Park Cancer Institute, Buffalo, USA

16.55 - 17.25 E-cigarettes: an evidence update
Room 12 **Ann McNeill**, King's College London, UK

17.25 - 17.40 Discussion

● Everybody's responsibility: systematic assessment of patient and carer needs in the oncology clinic and GP surgery

Hosted by **Miriam Johnson**, University of Hull, UK

15.40 - 15.45 Introduction by the host
Room 3B

15.45 - 16.10 Using the Patient care Outcome Scale (POS) in palliative care and oncology: international experiences from research, clinical practice and education
Room 3B **Irene Higginson**, King's College London, UK

16.10 - 16.25 Proffered paper: Palliative care referrals by general practitioners in the United Kingdom: an observational study of cancer patients who died in 2000-2008
Room 3B **Wei Gao**, King's College London, UK

16.25 - 16.50 Identification and triage of patient and carer needs: a clinician-rated tool for the clinic or surgery
Room 3B **Miriam Johnson**, University of Hull, UK

16.50 - 17.05 Proffered paper: Symptoms and quality of life in multiple myeloma – a longitudinal study of predictive factors
Room 3B **Christina Remsenthaler**, Cicely Saunders Institute, King's College London, UK

17.05 - 17.30 Operationalising needs-based assessment
Room 3B **David Currow**, Flinders University, Adelaide, Australia

17.30 - 17.40 Discussion

● Genome instability: bench to bedside

Hosted by **Thomas Helleday**, Karolinska Institute, Stockholm, Sweden

- 15.40 – 15.45** Introduction by the host
Room 3A
- 15.45 – 16.10** Therapeutic implications of DNA repair defects in metastatic prostate cancer
Room 3A
Johann de Bono, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, London, UK
- 16.10 – 16.25** BACR/AstraZeneca Young Scientist Frank Rose Award: Polyubiquitylation drives replisome disassembly at the termination of eukaryotic DNA replication
Room 3A
Agnieszka Gambus, University of Birmingham, UK
- 16.25 – 16.50** Targeting DNA repair in cancer treatment
Room 3A
Thomas Helleday, Karolinska Institute, Stockholm, Sweden
- 16.50 – 17.05** Proffered paper: Exploiting synthetic lethality to kill H3K36me3-deficient cancers by WEE1 inhibition
Room 3A
Timothy Humphrey, Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, UK
- 17.05 – 17.30** Cell cycle checkpoint rewiring after p53 loss blocks G1/S and G2/M progression through kinase control of a single RNA-binding protein
Room 3A
Michael B. Yaffe, Koch Institute for Integrative Cancer Research at MIT, Cambridge, USA
- 17.30 – 17.40** Discussion

● Immune checkpoints and cancer

Hosted by **Sergio Quezada**, University College London Cancer Institute, UK

- 15.40 – 15.45** Introduction by the host
Hall 1A
- 15.45 – 16.10** Innate immune modulation unlocks curative anti-tumour combination therapies
Hall 1A
Holbrook Kohrt, Stanford University, California, USA
- 16.10 – 16.25** Proffered paper: PD-L1 blockade improves response of pancreatic adenocarcinoma to radiotherapy
Hall 1A
Emmanouil Fokas, Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, UK
- 16.25 – 16.50** Title to be confirmed
Hall 1A
Martin Pule, Autolus, UK
- 16.50 – 17.05** Proffered paper: Clinical response, PFS and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) versus IPI monotherapy in CheckMate 069 study
Hall 1A
Michael Postow, Memorial Sloan Kettering Cancer Center & Weill Cornell Medical College, New York, USA

Parallel sessions *(continued)*

17.05 – 17.30 Fc-mediated depletion of Tregs via ipilimumab-dependent ADCC
Hall 1A
in advanced melanoma patients
Emanuela Romano, Department of Oncology, Institut Curie,
Paris, France

17.30 – 17.40 Discussion

● **Liquid biopsies with a twist: circulating cells and DNA**

Hosted by **Nitzan Rosenfeld**, Cancer Research UK Cambridge Institute, UK

15.40 – 15.45 Introduction by the host
Room 11

15.45 – 16.15 Title to be confirmed
Room 11
Luis Diaz, John Hopkins Sidney Kimmel Cancer Center, Baltimore, USA

16.15 – 16.45 Liquid biopsy in breast cancer: what can we learn from ctDNA
Room 11
and CTCs?
Jacqui Shaw, University of Leicester, UK

16.45 – 17.00 BACR Translational Award winner: Implementing personalised
Room 11
medicine in melanoma patients
Maria Romina Girotti, Cancer Research UK Manchester Institute, UK

17.00 – 17.30 Genomic analysis of circulating tumour DNA: pushing the limits
Room 11
for cancer application
Nitzan Rosenfeld, Cancer Research UK Cambridge Institute & Inivata
Ltd., Cambridge, UK

17.30 – 17.40 Discussion

● **Physical activity – the panacea?**

Hosted by **Robert Thomas**, Bedford & Addenbrooke's Cambridge University Hospitals & Cranfield University, UK

15.40 – 15.45 Introduction by the host
Room 4

15.45 – 16.10 Reducing prostate cancer progression and mortality: what you can
Room 4
do to reduce your risk
Stacy Kenfield, University of California, San Francisco & Harvard
School of Public Health, Boston, USA

16.10 – 16.35 Physical activity reduces late effects and improves outcomes: the
Room 4
clinical evidence and biological mechanisms of action
Robert Thomas, Bedford & Addenbrooke's Cambridge University
Hospitals & Cranfield University, UK

16.35 – 16.50 Proffered paper: Physical activity levels and barriers to exercise
Room 4
referral among patients with cancer
Dorothy Yang, University of Cambridge, UK

- 16.50 – 17.05**
Room 4
Proffered paper: Trajectories of quality of life, health status and personal wellbeing in the two years following curative intent treatment for colorectal cancer: results from the UK ColoREctal Wellbeing (CREW) cohort study
Joanne Haviland, University of Southampton, UK
- 17.05 – 17.30**
Room 4
Promoting physical activity among people living with advanced cancer
Matthew Maddocks, King's College London, UK
- 17.30 – 17.40**
Discussion

● Screening and epidemiology of ovarian cancer

Hosted by **Iain McNeish**, University of Glasgow, UK

- 15.40 – 15.45**
Hall 1C
Introduction by the host
- 15.45 – 16.10**
Hall 1C
Population-based approach(es) to genetic testing for ovarian cancer prevention
Ranjit Manchanda, Barts Cancer Institute, Queen Mary University of London & Bartshealth NHS Trust, London, UK
- 16.10 – 16.25**
Hall 1C
Proffered paper: Childbearing patterns and ovarian cancer in the Million Women Study: variation by histological subtype
Kezia Gaitskell, University of Oxford, UK
- 16.25 – 16.50**
Hall 1C
Title to be confirmed
Valerie Beral, University of Oxford, UK
- 16.50 – 17.05**
Hall 1C
Proffered paper: The Salt Inducible Kinase 2 (SIK2) links lipid metabolism to survival of ovarian cancer metastasis
Fabrizio Miranda, Weatherall Institute of Molecular Medicine, University of Oxford & John Radcliffe Hospital, Oxford, UK
- 17.05 – 17.30**
Hall 1C
Opportunistic salpingectomy: development and implementation of an Ovarian Cancer Prevention Campaign
Jessica McAlpine, University of British Columbia, Canada
- 17.30 – 17.40**
Discussion

● Understanding the genomic landscape of brain cancer

Hosted by **Colin Watts**, University of Cambridge, UK

- 15.40 – 15.45**
Hall 1B
Introduction by the host
- 15.45 – 16.10**
Hall 1B
Title to be confirmed
David Jones, Heidelberg University, Germany
- 16.10 – 16.25**
Hall 1B
Proffered paper: Detection of brain tumours using translational molecularly targeted magnetic resonance imaging
Sébastien Serres, Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, UK

Parallel sessions *(continued)*

- 16.25 - 16.50**
Hall 1B Title to be confirmed
Cameron Brennan, Memorial Sloan Kettering Cancer Center,
New York, USA
- 16.50 - 17.05**
Hall 1B Proffered paper: Radiation responses of 2D and 3D glioblastoma
cells: a novel, 3D-specific radioprotective role for VEGF activation
through NHEJ
Natividad Gomez-Roman, University of Glasgow, UK
- 17.05 - 17.30**
Hall 1B Investigating the genomic landscape of brain tumours using
metabolic imaging
Kevin Brindle, University of Cambridge, UK
- 17.30 - 17.40**
Discussion

Parallel session abstracts

● E-cigarettes and policy

15.40 - 15.55

Room 12

Linda Bauld,
University of Stirling,
UK and **Alison Cox**,
Cancer Research UK,
London, UK

Introduction

This symposium focuses on electronic cigarettes and potential benefits and challenges they pose for efforts to reduce preventable cancers caused by smoking. E-cigarettes, or nicotine vapourisers, are currently the most popular aid to stopping smoking in the UK, involved in one in three quit attempts in England for example. However, evidence regarding their effectiveness for smoking cessation is still limited and there are concerns about some elements of the products and potential use by children. This session will outline CRUK's contribution to supporting research that aims to address important unanswered questions on e-cigarettes as well as build networks to provide evidence to inform policy on these issues. The three speakers in the session will outline findings from the latest research and also provide an international perspective on this issue.

15.55 - 16.25

Room 12

Robert West,
University College
London, UK

Trends in electronic cigarette use in England

England is a country with a relatively strong tobacco control climate that regulates electronic cigarettes as consumer products but with marketing restrictions and a ban on sale to those under 18 years of age. Understanding trends in e-cigarette use in such a country can be informative in assessing appropriate policies in relation to these products internationally. The Smoking Toolkit Study (STS www.smokinginengland.info) involves monthly national household surveys of representative samples of the population aged 16+ years and focuses on key performance indicators on smoking and smoking cessation. It has been running since November 2006. Key findings to date are: 1) after an initial rapid growth, prevalence of e-cigarettes plateaued in late 2013; 2) daily use account for about 2/3rds of use; 3) there is continued growth in use of e-cigarettes to aid attempts to stop smoking; 4) e-cigarettes used without health professional involvement appear similarly effective to stop-smoking medicines obtained on prescription with limited behavioural support and more effective than use of no aid or licensed nicotine products bought from a shop; 5) use of e-cigarettes by never smokers remains negligible (0.2%) and similar to licensed nicotine products; 6) use of e-cigarettes by long-term ex-smokers remains low (3.5%) and similar to licensed nicotine products; 7) population rates of attempts to stop smoking do not appear to have been affected by the growth in e-cigarette use; 8) increased use of e-cigarettes may have increased the population rates of success at stopping smoking among those who try, leading to an estimated additional 17,000 ex-smokers in 2014; 9) there is a growing belief among smokers that e-cigarettes are at least as harmful as tobacco cigarettes.

Competing interests

RW has undertaken research and consultancy for companies that manufacture smoking cessation medication (Pfizer, J&J, GSK). He is a trustee of QUIT. He is unpaid advisor to the UK's National Centre for Smoking cessation and Training. His salary is funded by CRUK. He has no financial or other links with manufacturers of e-cigarettes.

16.25 - 16.55

Room 12

Maciej Goniewicz,
Roswell Park Cancer
Institute, Buffalo, USA

Electronic cigarettes: are they safe?

Electronic cigarettes, also known as e-cigarettes, are devices designed to imitate regular cigarettes and deliver nicotine via inhalation without combusting tobacco. They are purported to deliver nicotine without other toxicants and to be safer alternative to regular cigarettes. Distributors of e-cigarettes promote the product as completely free of harmful substances. However, nicotine solutions used in e-cigarettes vary with respect to concentrations of

toxicants, and the quality control in e-cigarette manufacturing is questionable. Although a number of toxicants have been identified in e-cigarette vapours, the levels of these toxicants are orders of magnitude lower than those found in cigarette smoke, but higher than those found in nicotine replacement therapy (NRT) products. Some studies suggest that vapour from e-cigarette is significantly less cytotoxic compared to tobacco smoke. One study found that after switching from tobacco to electronic cigarettes nicotine exposure is unchanged while exposure to selected toxicants is substantially reduced. Although it cannot be said that currently marketed e-cigarettes are safe, e-cigarette vapour is likely to be much less toxic than cigarette smoke. The devices likely pose less direct hazard to the individual smoker than tobacco cigarettes and might help smokers quit smoking or reduce harm by smoking fewer cigarettes. The use of e-cigarettes as a harm reduction strategy among cigarette smokers who are unable to quit, warrants further studies. Further research is needed to evaluate long term effects of switching, including the health effects of continued use of e-cigarettes.

Competing interests

I received research funding from Pfizer, a manufacturer of stop smoking medications.

16.55 - 17.25

Room 12

Ann McNeill,
King's College
London, UK

E-cigarettes: an evidence update

In August 2015 we published an evidence update on electronic cigarettes covering a variety of issues: usage by adults and adolescents, health beliefs and attitudes, international use and an update of safety scares: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457102/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf. This talk will focus on those areas in the report not covered by the other two speakers in the session. In particular, evidence on the use of electronic cigarettes when used in a quit attempt will be presented, covering a Cochrane review published November 2014 and recent studies. In addition, evidence on the impact of electronic cigarettes when used alongside smoking (referred to as 'dual use') will be discussed, with implications for smokers using electronic cigarettes in this way. Another key concern is uptake of electronic cigarettes by young people and whether this leads to smoking – recent evidence on this issue will be presented. Finally, the impending changes to the regulatory system for electronic cigarettes, through the European Union Tobacco Products Directive and the medicinal licensing system, will be discussed.

17.25 - 17.40

Discussion

● **Everybody's responsibility: systematic assessment of patient and carer needs in the oncology clinical and GP surgery**

15.40 - 15.45

Room 3B

Miriam Johnson,
University of Hull, UK

Introduction

All people with cancer, and their family and friends, have a variety of concerns directly or indirectly related to the cancer. These range from physical and psychosocial symptoms through to legal, financial and work related matters and combine to affect quality of life running alongside the need for tailored and timely information. These needs, affecting all domains of life, are present from around the time of diagnosis through to death, and, for bereaved family and friends, beyond. In addition, the ability to care, and wellbeing of,

Parallel session abstracts *(continued)*

informal caregivers such as family members is a crucial part of successful management of the patient themselves.

In the busy oncology clinic, or primary care consultation, needs may not be volunteered by the patient themselves and go unrecognised unless these are assessed for systematically. Most needs, if identified, could be managed within primary care or oncology teams, but some patients with persistent or complex issues require referral to specialist palliative care services. This group are important to identify in the light of published phase 3 randomised controlled trials which show the benefit of early involvement of specialist palliative care.

This session is for any clinician who cares for people with cancer and will cover clinician assessment of need as part of routine care, patient-reported need, and the role of needs-based care in service delivery.

15.45 - 16.10

Room 3B

Irene Higginson,
King's College
London, UK

Using the Patient care Outcome Scale (POS) in palliative care and oncology: international experiences from research, clinical practice and education

Assessment of patient centred outcomes is increasingly recognised as vital by multiple agencies involved in cancer care and research. Outcomes centred on patients and their families concerns are extensively recognised the most valid way to understand people's needs, monitor change and determine the results of treatment and care.¹

The Palliative (or Patient) care Outcome Scales (POS) are a family of patient centred outcomes to measure patients' physical symptoms, psychological, emotional and spiritual, and information and support needs. They are validated instruments that can be used in clinical treatment, care, audit, research and training, and are freely available for download: www.pos-pal.org.

The POS measures are specifically developed for use among people severely affected by diseases who may face multiple problems or complex symptoms. Thus, they are intentionally brief; the original POS had 10 questions and could be completed in around 5 minutes. The POS measures are widely used globally including in Europe, Australia, Asia, Africa and America, and are available in 11 languages, with more validation in other languages underway.

The Integrated Patient care Outcome Scale (IPOS) integrates the best of several POS modules. A version specifically for use in myeloma, with more myeloma questions, has been developed. This session will discuss some of the latest developments in the validation of these measures, their use for screening² and aid assessment in clinical practice,³ in research trials,⁴ and next steps for development in the international literature.⁵

References

- 1 Osborne TR, et al What issues matter most Eur J Haematol. 2012.
- 2 Antunes B, et al Screening for depression J Pain Symptom Manage. 2015;49(2):277-288.
- 3 Antunes B, et al Implementing patient-reported outcome .. Palliat Med. 2014;28(2):158-175.
- 4 Bajwah S, et al Thorax. 2015.
- 5 Bausewein C, et al EAPC White Paper on outcome measurement : Palliat Med. 2015.

Competing interests

I am one of the individuals who developed and validated the Palliative care Outcome Scale. I have no financial interests in its use, and make no money from its use. I believe measures should be free and used to improve care, treatment and practice.

16.10 – 16.25

Room 3B

Wei Gao,
King's College
London, UK**Proffered paper: Palliative care referrals by general practitioners in the United Kingdom: an observational study of cancer patients who died in 2000-2008***Background*

Enabling more people access to palliative care (PC) service needs professional inputs from general practitioners (GP). However, it is poorly understood about when and how British GPs refer patients for specialist PC. This study aims to describe the trend of PC referrals and the associated factors.

Method

The data was extracted from the Clinical Practice Research Datalink (CPRD). Patients with a common cancer diagnosis (lung, head & neck, colorectal, breast, prostate), and died in between 2000 and 2008 were included. We reviewed the referral records of the cancer patients, covering a 100 year period dated back to 1909. Data were described using count and proportion. Factors associated with early PC referral (more than one year survival) were evaluated using adjusted odds ratio (AOR) derived from multiple logistic regression modeling.

Results

In a total of 356,822 referral records for 27,814 (93%) out of 29,810 cancer patients who died in 2000-2008, PC referrals accounted for 0.34% (95% Confidence Interval(CI): 0.32-0.35%). PC referrals first appeared in the system from 1996 (0.01%; 95%CI: 0.00-0.02%), thereafter increased at a slow rate to 3.2% (95%CI: 2.5-3.9%) in 2008. 81.0% (95%CI: 78.7-83.2%) and 19.1% (95%CI: 16.8-21.7%) of the PC referrals occurred in the last year and beyond last year, respectively. Those who are aged under 50 (AOR vs 80+ 2.66, 95%CI: 1.25-5.65), with a diagnosis of breast or prostate cancer (AORs vs lung cancer: 3.94 (95%CI: 2.20-7.05) and 3.71 (95%CI: 2.06-6.71)), living in the most deprived area(AOR vs least deprived 0.29, 95%CI: 0.13-0.62), or registered with a GP in Scotland or Wales (AORs vs Southern Cluster: 3.61 (95%CI: 1.55-8.41) and 2.10 (95%CI: 1.09-4.03) were more likely to have early PC referral.

Conclusion

PC referral by GPs increased over time but is still rather low; old age, cancer site in lung, colorectal or in head and neck, people living in deprived areas or registered with a practice in England are disadvantaged for early PC referral. Future studies need to understand the underlying reasons to inform end of life improvement.

16.25 – 16.50

Room 3B

Miriam Johnson,
University of Hull, UK**Identification and triage of patient and carer needs: a clinician-rated tool for the clinic or surgery**

Cancer affects every aspect of a person's life and the lives of their family and friends from diagnosis through to living with advanced disease, dying and bereavement. The multi-disciplinary team across primary and secondary care is thus a vital cornerstone of management. However, in the busy clinic or GP surgery, it can be difficult to systematically assess, identify patient and carer needs, and ensure these needs are addressed by the appropriate team members.

This talk will outline the variation in cancer needs assessment and present the Needs Assessment Tool: Progressive Disease – Cancer (NAT:-PD) as a clinician-rated tool in daily practice. Such a tool could help: i) standardise assessment and triage of patient and carer concerns by the oncology or primary care teams; ii) use limited services such as specialist

Parallel session abstracts *(continued)*

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palliative care in an appropriate and timely manner; iii) identify basic supportive and palliative care training needs in the oncology and primary care teams; and, iv) identify service resource gaps.

16.50 - 17.05

Room 3B

Christina

Remsenthaler,

Cicely Saunders

Institute, King's

College London, UK

Proffered paper: Symptoms and quality of life in multiple myeloma – a longitudinal study of predictive factors

Background

Multiple myeloma remains an incurable cancer with evidence that patients suffer more symptoms than in other haematological conditions. Palliative care services are rarely involved. We aimed to determine how symptom prevalence, severity and quality of life as well as cost/health care utilisation change over time, and what demographic, clinical and social factors predict changes.

Method

We recruited patients into a 14-site multicentre, longitudinal observational study, consenting patients at various stages of their illness (newly diagnosed, stable and progressive/relapsed disease). At baseline and then on up to four occasions over eight months, patients completed self reported demographic, clinical, symptom, palliative, quality of life and service use questionnaires. Clinical details were abstracted from medical records. We used myeloma-specific and generic, validated scales, including the Myeloma Patient Outcome Scale (MyPOS), a quality-of-life questionnaire specifically developed for multiple myeloma. We tested for predictors using multivariable analysis, adjusting for confounders.

Results

257 patients with multiple myeloma with a median age of 69 years (range: 34-92) and on average 2.5 years post-diagnosis participated. 18.2% were newly diagnosed, 47.9% had stable disease and 32.7% had relapsed disease or were in the advanced, palliative phase of illness. Patients reported a mean of 7.1 (SD=3.4) symptoms. Over 70% had pain, 88.7% fatigue and 61.1% breathlessness. The most burdensome symptoms in the advanced stages were fatigue, poor mobility, pain, and tingling in the hand/feet. Over the eight months, patients showed distinct trajectories according to whether they were in an early or advanced treatment-interval or in an early or advanced treatment-free interval. Trajectories of physical functioning did not follow other domains of quality of life. The strongest predictors of higher levels of symptoms and health care service use at the end of follow-up were initial scores on MyPOS, type of myeloma, performance status and co-morbid conditions.

Conclusion

Burden of symptoms in multiple myeloma is high and symptoms are not resolved even during the treatment-free intervals. Those with a high symptom burden and with light chain disease are at increased risk for poor HRQOL, should be monitored and could potentially be considered for early referral to palliative care services.

Acknowledgements

This work was supported by grants from Myeloma UK, St Christopher's Hospice London, UK, and the National Institute of Health Research (NIHR) UK (Professor Irene Higginson holds a Senior Investigator Award).

17.05 - 17.30

Room 3B

David Currow,
Flinders University,
Adelaide, Australia

Operationalising needs-based assessment

Needs-based care is crucial to ensuring that the people who have the most complex needs are identified early and systematically in order to ensure that as much as possible is done to address their needs. This is crucial in a complex health system where demands will always outstrip supply, and where those demands may not reflect the genuine underlying need of every person making them.

A systematic approach is required. The assessment is the responsibility of every health professional. This lies with primary care, tertiary services and in every health setting.

There are a number of tools that are available for such processes. The principles of such tools include the needs for them to be brief, easily learned, excellent inter-rater reliability and significant face validity.

These tools, in order to address the complexities of people with advancing cancers, requires a patient aspect dealing with all of the domains of personhood (physical, social, sexual, existential, emotional, financial), the well-being of caregivers as well as their willingness to provide that care and any professional issues that may also impinge on the ability to provide care.

Importantly, available data to date suggests that such tools do not make clinical consultations longer (and may actually shorten them) while at the same time improving patient satisfaction because the consultation has better met with his/her needs.

Ultimately, at a systems level, systematic approaches need to identify the changing and evolving needs of patients and their caregivers over the course of advancing cancer.

17.30 - 17.40**Discussion**

● **Genome instability: bench to bedside**

15.40 - 15.45

Room 3A

Thomas Helleday,
Karolinska Institute,
Stockholm, Sweden

Introduction**15.45 - 16.10**

Room 3A

Johann de Bono,
The Institute of
Cancer Research &
The Royal Marsden
NHS Foundation
Trust, London, UK

Therapeutic implications of DNA repair defects in metastatic prostate cancer

Metastatic prostate cancer is a highly heterogeneous disease. Donald Gleason captured this heterogeneity in his pathological grading system, recognising both intra-patient and inter-patient heterogeneity. Despite this, our treatment for this disease has not to date pursued any molecular stratification. We hypothesised that a subset of poor prognosis prostate cancers had DNA repair defects and that these would sensitise to PARP inhibition. Preliminary data indicate that BRCA mutation carriers who suffered prostate cancers have poorer prognosis disease and are sensitive to PARP inhibition. We have also published that PARP inhibitors have some anti-tumour activity in this disease, with previous studies indicating that platinum including

Parallel session abstracts *(continued)*

satraplatin also resulting in a 20-30% response rate. We therefore conducted an investigator initiated, adaptive, multi-step Phase II trial (TOPARP) of olaparib in patients with advanced prostate cancer. TOPARP-A is now completed and has demonstrated anti-tumour activity in heavily pre-treated patients with metastatic castration resistant prostate cancer (CRPC) with responses being associated with molecular aberrations in DNA repair genes including BRCA2, ATM, PALB2 and other genes critical to DNA repair. These data indicate that this inter-patient genomic divergence may lead to phenotypic convergence. The response data, and predictive biomarker qualification data will be presented. These data may support for the first time molecular stratified treatment for this common cancer.

16.10 – 16.25

Room 3A

Agnieszka Gambus,
University of
Birmingham, UK

BACR/AstraZeneca Young Scientist Frank Rose Award: Polyubiquitylation drives replisome disassembly at the termination of eukaryotic DNA replication

To ensure duplication of the whole genome, DNA replication initiates from thousands of replication origins. The replication forks move through the chromatin until they encounter forks from the neighbouring origins. During the termination of replication forks the replisomes disassemble by an unknown mechanism and topoisomerase II resolves the daughter DNA molecules. If not resolved properly, the terminating forks are at high risk of stalling and fork reversal, leading to DNA damage and genomic instability.

Using the *X.laevis* egg extract system, we have shown that blocking polyubiquitylation results in the prolonged association of the active helicase with replicating chromatin and replication termination defect. It has lead us to propose that it is the disassembly of the active helicase at the termination of replication forks that is defective upon polyubiquitylation inhibitor. The Mcm7 protein is the only component of the active helicase that we find polyubiquitylated during S-phase and this ubiquitylation is blocked when forks cannot terminate. Once ubiquitylated, the disassembly of the helicase is dependent on p97/VCP/Cdc48 segregase.

Altogether, our data provides first insight into the mechanism of replisome disassembly during eukaryotic DNA replication termination and sheds light onto the way the terminating replication forks are resolved efficiently to maintain a stable genome.

16.25 – 16.50

Room 3A

Thomas Helleday,
Karolinska Institute,
Stockholm, Sweden

Targeting DNA repair in cancer treatment

DNA damaging agents, i.e., radio- and chemotherapy, constitute the backbone for treatment of a wide variety of cancers and may result in complete cure from the disease. Here, I will give an overview on how DNA repair can be targeted using PARP and completely novel inhibitors and more specifically how cancer cells may require a specific DNA repair pathway to mediate survival to the high load of endogenous DNA damage. Cancers have deregulated levels of reactive oxygen species (ROS), damaging both DNA and free dNTPs. The MTH1 protein sanitises oxidised dNTP pools, converting 8-oxo-dGTP to 8-oxo-dGMP, to prevent incorporation of damaged bases during DNA replication. MTH1 overexpression reverses the mutator phenotype caused by mismatch repair defects and prevents Ras-induced senescence by suppressing the overall level of DNA damage. These data suggest that a majority of damage in cancer cells occur on the free dNTP pool and that this need sanitation for cancer cell survival. Here we show that cancer cells are dependent on MTH1 activity for survival, due to the effects of MTH1 in preventing incorporation of oxidised dNTPs into DNA to avoid ATM and p53 mediated apoptosis. As MTH1^{-/-} mice are viable and MTH1 is not required for survival of non-transformed cells, targeting MTH1 may selectively cause DNA damage to cancer cells. We validate MTH1 as an anti-cancer target in vivo and describe small molecules, TH287 and TH588 that potently and selectively inhibit MTH1. Protein

co-crystal structures demonstrate that the compounds bind as inhibitors in the enzymatic pocket of MTH1. These first-in-class inhibitors of the Nudix hydrolase family cause increased incorporation of oxidized dNTPs in cells subject to high ROS levels, causing DNA damage and cytotoxicity to cancer cells. This study exemplifies a new general therapeutic approach to convert oxidative stress to cytotoxic DNA damage and cancer cell death.

References

Gad et al 2014 Nature. 508(7495):215-21.

16.50 - 17.05

Room 3A

Timothy Humphrey,
Cancer Research UK
and Medical Research
Council Oxford Institute
for Radiation Oncology,
UK

Proffered paper: Exploiting synthetic lethality to kill H3K36me3-deficient cancers by WEE1 inhibition

Background

Loss of the histone mark H3K36 trimethylation (H3K36me3) is found in multiple cancer types and is associated with poor patient prognosis, making it a potential therapeutic target. However, there are currently no therapies targeting H3K36me3-deficient cancers. Here we show that these cancers are killed by inhibiting the checkpoint kinase WEE1, and provide insights into the molecular mechanisms.

Method

H3K36me3-deficient isogenic cancer cell lines were generated by three methods: CRISPR knockout of SETD2 trimethyltransferase; overexpression of KDM4A demethylase; or expression of histone H3.3K36M. DNA replication was analysed by DNA fibre assay and iPOND. Deoxynucleotide (dNTP) pools were measured by polymerase-catalysed incorporation of radioactive dNTP.

Results

We have identified a synthetic lethal interaction between loss of both H3K36me3 and WEE1. Accordingly, cancer cells exhibiting reduced or depleted H3K36me3 levels displayed a striking sensitivity to the WEE1 inhibitor AZD1775 compared to wild type. Sensitivity was associated with DNA replication fork arrest, high levels of MUS81-dependent DNA damage, and apoptosis. Consistent with these findings, we found that WEE1 inhibition or H3K36me3 depletion resulted in significantly reduced dNTP levels, which were further critically reduced following treatment of H3K36me3-deficient cells. Xenograft experiments showed oral treatment with AZD1775 induced a robust regression in H3K36me3-deficient tumours (tumour size on day 12 = 50mm³ vs. 291mm³, $p < 0.0001$) with no effect on H3K36me3-proficient tumours.

Conclusion

We show that WEE1 inhibition selectively kills H3K36me3-deficient cells by replication stress and suggest that patients with H3K36me3-deficient cancers could benefit from treatment with WEE1 inhibitors.

Acknowledgements

We thank OCRC, MRC, CRUK and Clarendon for funding.

Parallel session abstracts *(continued)*

17.05 – 17.30

Room 3A

Michael B. Yaffe,
Koch Institute for
Integrative Cancer
Research at MIT,
Cambridge, USA

Cell cycle checkpoint rewiring after p53 loss blocks G1/S and G2/M progression through kinase control of a single RNA-binding protein

In response to genotoxic stress and chemotherapy-induced DNA damage, cells activate p53 to arrest cell cycle progression, allowing time for repair. In irreparable damaged cells, p53 subsequently initiates programmed cell death. In tumour cells, however, the p53 pathway is dysfunctional, resulting in inappropriate cell survival, and re-wiring of cell cycle checkpoints by recruiting the p38MAPK/MK2 kinase pathway to control cell cycle machinery. Here we show that the RNA binding protein hnRNPA0 is the “successor” to p53 for checkpoint control. Like p53, hnRNPA0 is activated by a checkpoint kinase (MK2) and simultaneously controls both the G1/S and G2/M cell cycle checkpoints through induction of distinct target mRNAs. Unlike p53, which controls p21 gene transcription, MK2 and hnRNPA0 regulate the post-transcriptional stabilization of p27Kip1 and Gadd45 α mRNAs. This MK2/hnRNPA0 pathway drives cisplatin resistance in lung cancer, demonstrating the importance of post-transcriptional RNA control in the clinical response to anti-cancer chemotherapy. Furthermore, in the presence of a functional p53 response, this MK2/hnRNPA0 successor pathway is actively repressed through down-regulation of hnRNPA0 mRNA levels.

17.30 – 17.40

Discussion

● Immune checkpoints and cancer

15.40 – 15.45

Hall 1A

Sergio Quezada,
University College
London Cancer
Institute, UK

Introduction

15.45 – 16.10

Hall 1A

Holbrook Kohrt,
Stanford University,
California, USA

Innate immune modulation unlocks curative anti-tumour combination therapies

Abstract not received.

16.10 – 16.25

Hall 1A

Emmanouil Fokas,
Cancer Research UK
and Medical Research
Council Oxford
Institute for Radiation
Oncology, UK

Proffered paper: PD-L1 blockade improves response of pancreatic adenocarcinoma to radiotherapy

Background

The programmed death ligand 1 (PD-L1) plays a key role in tumour progression and metastasis of pancreatic ductal adenocarcinoma (PDAC). Although recent preclinical studies have explored the radiosensitising potential of PD-1/PD-L1 inhibitors, the effect of PD-L1 blockade on the response of PDAC to radiotherapy remains unexplored.

Method

Herein, we investigated the influence of an anti-PD-L1 mAb on the tumour response to single dose and fractionated radiotherapy, and chemotherapy with gemcitabine and capecitabine.

Results

In vitro, radiation and chemotherapy resulted in PD-L1 upregulation in both human (PSN-1) and murine (KPC-derived, Pan02) PDAC cells, although variability was observed. Exposure to conditioned media from pre-treated cells did not alter PD-L1 expression. In vivo, PD-L1 was also upregulated in the tumour microenvironment after radiation and chemotherapy in the KPC-derived and Pan02 syngeneic mouse models. Similarly, chemotherapy induced PD-L1 upregulation in the KPC (Pdx1Cre, KRASG12D/+, P53R172H/+), a genetically-engineered mouse model of pancreatic cancer. In vitro, PD-L1 blockade failed to radio- or chemosensitise PDAC cells. The anti-PD-L1 mAb significantly improved tumour response after irradiation in the KPC and Pan02 syngeneic mouse models. This effect was mediated by a cytotoxic T cell-dependent mechanism, whereas blockade of CD8+ cells attenuated the radiosensitising potential of anti-PD-L1. The effect of scheduling of anti-PD-L1 mAb with radiotherapy (concomitant vs. sequential) was also investigated. Finally, we assessed the intratumoural and systemic expression of several immune markers (CD45+: CD8, CD4, CD19, NK1.1, CD11b Gr1, Ly6G, CXCR2, FOXP3, IFN- γ) after the different treatments.

Conclusion

Altogether, our findings support PD-L1 inhibition in combination with radiation as a promising approach in the treatment of PDAC.

Acknowledgements

We would like to thank Dr Sally Hill, Dr Ana Da Silva Gomes and Dr Mick Woodcock for the technical assistance.

16.25 - 16.50

Hall 1A

Martin Pule,
Autolus, UK

Title to be confirmed*Abstract not received.***16.50 - 17.05**

Hall 1A

Michael Postow,
Memorial Sloan
Kettering Cancer
Center & Weill Cornell
Medical College, New
York, USA

Proffered paper: Clinical response, PFS and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) versus IPI monotherapy in CheckMate 069 study

Background

Combined blockade of T-cell checkpoints by NIVO and IPI demonstrated a high objective response rate (ORR), promising overall survival and a manageable safety profile in pts with advanced MEL. We report efficacy and safety of NIVO + IPI versus IPI alone in treatment-naïve pts with advanced MEL in a phase II study.

Method

Pts (N=142) with metastatic or unresectable MEL were randomized 2:1 to receive IPI 3 mg/kg combined with either NIVO 1 mg/kg or placebo Q3W \times 4, followed by NIVO 3 mg/kg or placebo Q2W until disease progression or unacceptable toxicity. The primary endpoint was

Parallel session abstracts *(continued)*

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ORR in BRAF wild-type (WT) pts. Secondary and exploratory objectives included PFS in BRAF WT pts, ORR and PFS in BRAF V600 mutation-positive (MT) pts, and safety.

Results

In BRAF WT pts (n=109) ORR was 60% (43/72) for NIVO + IPI; 11% (4/37) for IPI alone (P<0.0001); complete responses were reported in 12 (17%) and 0 pts, respectively; median PFS was 8.9 vs 4.7 months, respectively (P=0.0012). Higher ORR was observed for NIVO + IPI versus IPI in poor prognostic pt subgroups: elevated baseline LDH (53% vs 0%); M1c stage disease (62% vs 25%). Similar ORR and PFS were observed in 33 BRAF MT pts. Grade 3-4 drug-related adverse events (AEs) were reported in 51% of pts receiving NIVO + IPI vs 20% for IPI alone. The safety profile of NIVO + IPI was similar across pt subgroups and generally manageable.

Conclusion

NIVO + IPI significantly improved ORR and PFS compared with IPI alone, had a manageable safety profile across pt subgroups, and provided a favorable risk-benefit ratio in treatment-naïve pts with advanced MEL.

Acknowledgements

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17.05 – 17.30

Hall 1A

Emanuela Romano,
Department of
Oncology, Institut
Curie, Paris, France

Fc-mediated depletion of Tregs via ipilimumab-dependent ADCC in advanced melanoma patients

Enhancing immune responses with immune-modulatory monoclonal antibodies (mAbs) directed to inhibitory immune-receptors is a promising modality in cancer therapy. Clinical efficacy has been demonstrated with antibodies blocking inhibitory immune checkpoints such as CTLA-4 or PD-1/PD-L1. Treatment with ipilimumab, a fully human CTLA-4 specific mAb, showed durable clinical efficacy and improved overall survival in metastatic melanoma; its mechanism/s of action, however, are only partially understood. Recent studies in melanoma mouse models revealed that the anti-tumour activity of CTLA-4 blockade is mediated by FcγRIV-expressing macrophages in the tumour microenvironment (TME) via in-trans depletion of tumour-infiltrating Tregs. We speculated that a similar mechanism might operate in melanoma patients responding to ipilimumab. To investigate this hypothesis, we interrogated peripheral blood mononuclear cells (PBMCs) and matched melanoma metastases from 15 patients responding (R) and 14 non-responding (NR) to ipilimumab. Our findings show, for the first time, that ipilimumab leads to the depletion in vitro of regulatory T cells (Tregs) via an antibody-dependent-cellular-cytotoxicity (ADCC) mechanism, selectively mediated by FcγRIIIA (CD16)-expressing, non-classical monocytes. In contrast, classical monocytes, lacking the FcγRIIIA expression, are unable to deplete Tregs in an ADCC assay. Interestingly, patients responding to ipilimumab displayed significantly higher baseline peripheral frequencies of non-classical monocytes than non-responder patients. Evaluation of matched melanoma metastases from pre- and post-ipilimumab time-points by IHC revealed that, in the TME, responders had the highest CD68⁺/CD163⁺ macrophage ratios at baseline, and showed decreased infiltration of Tregs after treatment. Notably, baseline Treg infiltration was comparable between the two groups. Our results provide novel mechanistic insight into the clinical activity of ipilimumab, highlighting the contribution of the tumour stroma into the final outcome of antibody-based immunomodulatory therapies and suggest non-classical monocytes as a potential biomarker of response.

17.30 – 17.40

Discussion

● Liquid biopsies with a twist: circulating cells and DNA

15.40 – 15.45

Room 11

Nitzan Rosenfeld,
Cancer Research UK
Cambridge Institute,
UK

Introduction

The improving ability to extract and identify rare tumour cells and DNA makes it possible to develop new approaches to biomarker research. Possible applications span a range of uses in clinical diagnostics as well as new noninvasive tools for cancer genomics research. Recent reports demonstrated proofs of concept that have used CTCs and ctDNA to aid in cancer detection and prognostication, to suggest therapy and monitor response, to dissect mechanisms of resistance and to explore tumour heterogeneity. This session will present and discuss recent advances and topical challenges in the field.

15.45 – 16.15

Room 11

Luis Diaz, John
Hopkins Sidney
Kimmel Cancer Center,
Baltimore, USA

Title to be confirmed

Abstract not received.

16.15 – 16.45

Room 11

Jacqui Shaw,
University of
Leicester, UK

Liquid biopsy in breast cancer: what can we learn from ctDNA and CTCs

Abstract not received.

16.45 – 17.00

Room 11

Maria Romina Girotti,
Cancer Research UK
Manchester Institute,
UK

BACR Translational Award winner: Implementing personalised medicine in melanoma patients

Background

Metastatic melanoma that progresses after first line therapy represents a significant clinical challenge, because there are no clear rationales for selecting second line therapies and no biomarkers to guide this decision. BRAF is mutated in about half of human melanomas and treatment with BRAF and MEK inhibitors have resulted in increased progression-free and overall survival in melanoma patients. However, the majority of patients relapse after a relatively short period of disease control. To address this, early detection of relapse and timely elucidation of resistance mechanisms are essential to guide clinical care and personalise treatment decisions for individual patients. In addition, tools to identify targeted treatment options for the 50% of patients who are BRAF wild type are lacking.

Methods

We have combined the use of whole exome sequencing (WES), patient derived xenografts

Parallel session abstracts *(continued)*

(PDXs) and circulating tumour DNA (ctDNA) in the development of a platform for personalised medicine in melanoma.

Results

We present three patient cases where we show that genome analysis can be used to monitor development of resistance and to develop novel hypothesis-driven therapeutic strategies for patients, and we show that these treatments can be validated in the patients' PDXs. Moreover, we demonstrate the use of circulating tumour DNA (ctDNA) as a predictive biomarker of response to therapy and as a powerful approach to reveal and then monitor mechanisms of resistance.

Conclusions

Tumour exome sequencing allowed identification of new therapeutic targets that we validated in xenografts established from patient tumours. Sequencing of circulating tumour DNA allowed us to monitor responses and the emergence of resistance. Thus, our data shows that we are able to implement a powerful combination of techniques for personalised medicine to improve clinical management of BRAF wild type and BRAF mutant melanoma patients.

17.00 - 17.30

Room 11

Nitzan Rosenfeld,
Cancer Research UK
Cambridge Institute
& Inivata Ltd.,
Cambridge, UK

Genomic analysis of circulating tumour DNA: pushing the limits for cancer applications

Cancer is driven by genomic alterations, and can evolve in response to selective pressures. Sampling of tumour material however is a limiting factor for both diagnostics and research. Circulating tumour DNA can be found in plasma and other body fluids, and with advanced genomic techniques it can be used as an effective source of information for oncology. On one hand, sensitive detection of mutations, rearrangements and copy number changes can be used for genomic characterisation of cancer using non-invasive sampling. Targeted molecular profiling tests of 'liquid biopsies' in blood plasma are now entering clinical use, and are emerging as an informative clinical research tool to track response to treatment, cancer progression and emergence of resistance to therapy. Wider-scale analysis can be used to study new drivers and mechanisms of resistance. In parallel, the specificity of genomic alterations makes these excellent markers to quantify cancer dynamics and disease burden. Improved methods and strategies can allow us to stretch the boundaries of analysis to detect smaller amounts of tumour DNA and to obtain more information from limited samples. These can be used to support an expanding range of applications for both earlier and later stage cancers.

17.30 - 17.40

Discussion

● Physical activity – the panacea?

15.40 - 15.45

Room 4

Robert Thomas,
Bedford &
Addenbrooke's
Cambridge University
Hospitals & Cranfield
University, UK

Introduction

15.45 - 16.10

Room 4

Stacey Kenfield,
University of California,
San Francisco &
Harvard School of
Public Health, Boston,
USA

Reducing prostate cancer progression and mortality: what you can do to reduce your risk

Prostate cancer is the most common cancer in men in the US and UK. Most patients are diagnosed with clinically indolent tumours without lethal potential. Substantial evidence suggests that risk factors for lethal prostate cancer differ from those for indolent disease. Growing, but still limited, scientific evidence suggests that exercise and other lifestyle practices after prostate cancer diagnosis may affect prostate cancer specific and overall mortality. Our team at the University of California, San Francisco (UCSF) has collectively built a translational portfolio of research to grow the evidence base through rigorous observational and interventional studies; identify biological mechanisms underlying associations of lifestyle and cancer; and disseminate information to patients via tested methods to improve clinical and psychological outcomes. Factors associated with a possible higher risk of aggressive prostate cancer include body fatness, smoking, and intake of processed meat, saturated fat, selenium supplements, or high-fat dairy; while factors associated with possible lower risk include vigorous physical activity and consumption of vegetable fats, cruciferous vegetables, fish, or cooked tomato products/lycopene. We have initiated several randomised controlled lifestyle-focused trials at UCSF and with external US collaborators and international partners to test whether select factors affect prostate cancer biology and improve patient outcomes, and whether web and text-based approaches can change behaviors. In the future, personalised lifestyle programmes may be provided to patients as adjunctive therapy to standard management options to improve cancer survivorship.

16.10 - 16.35

Room 4

Robert Thomas,
Bedford &
Addenbrooke's
Cambridge University
Hospitals & Cranfield
University, UK

Physical activity reduces late effects and improves outcomes: the clinical evidence and biological mechanisms of action

Through a combination of earlier detection and enhanced multidisciplinary management, the chances of surviving cancer are significantly improving. As a result, the number of individuals who have undergone the trauma of cancer is growing by 3 per annum, which means by 2030, there will be over 3 million people in UK society, including a quarter of people over 65 years. Unfortunately, many suffer acute and long-term physical and psychological adverse effects which can affect their quality of life and require medical intervention in primary and secondary care.

Fortunately, a physically active lifestyle and particularly supervised exercise rehabilitation programmes improve many of these adverse effects, particularly cancer-related fatigue, weight gain, arthralgia, hot flushes, muscle power, peripheral neuropathy, overall quality

Parallel session abstracts *(continued)*

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of life, mood, anxiety and depression. What's more, the benefits of physical activity span across several common cancer types involving range of treatments, including surgery, radiotherapy, chemotherapy, hormonal and biological therapies. This talk provides an up to date summary of the principal randomised controlled trials, which provide the most robust evidence for the symptomatic benefits of physical activity.

This talk also focuses on the biological changes which occur after physical activity which have potential anti-cancer attributes. These could explain the strong links between higher physical activity (PA), relapse and over survival seen in numerous large prospective cohort studies which are also summarised along with updates of other ongoing studies and UK projects.

16.35 - 16.50

Room 4

Dorothy Yang,
University of
Cambridge, UK

Proffered paper: Physical activity levels and barriers to exercise referral among patients with cancer

Background

Physical activity after cancer is linked to a lower rate of adverse effects and better survival.

Method

The purpose of this study was to record the current physical activity levels of People Living With and Beyond Cancer (PLWBC) attending a typical UK community hospital, and assess their barriers to supervised exercise referral.

Results

Of the entire cohort of patients attending our unit over a 2 month period, only 12 of 114 (11%) were classed as active according to the General Practice Physical Activity Questionnaire (GPPAQ). 68% were overweight or obese, but only 7% smoked. Despite receiving written and verbal explanations about the benefits of exercise, 47% of eligible patients declined formal exercise referral, with health safety concerns, time pressures, and the perception that they were already adequately exercising, being stated as the three most common reasons. Overall, 82% met one or more of the current indications for the National Exercise Referral Scheme, so even in regions where the inclusion criteria have not been broadened to include cancer, this is a practical option for most.

Conclusion

Unfortunately, it is clear from this data that we are failing to motivate patients into healthier lifestyles after cancer. Furthermore, physical activity levels have not improved since a similar previous evaluation¹. This study suggests that further research should evaluate whether information materials should be changed to emphasise the safety of exercise, what level is appropriate, and how to incorporate it into a busy lifestyle.

References

Thomas et al. (2013) Lifestyle factors correlate with the risk of late pelvic symptoms after prostatic radiotherapy. *Clinical Oncology* 25(4), 246-251.

16.50 – 17.05

Room 4

Joanne Haviland,
University of
Southampton, UK

Proffered paper: Trajectories of quality of life, health status and personal wellbeing in the two years following curative intent treatment for colorectal cancer: results from the UK ColoREctal Wellbeing (CREW) cohort study

Background

Cancer survivorship is a growing global concern and the current aftercare system does not sufficiently meet patients' needs. It is important to understand patterns of recovery in order to tailor aftercare appropriately. We examine trajectories of quality of life (QoL), health status and personal wellbeing in the first two years following colorectal surgery.

Methods

Prospective cohort study of 872 UK colorectal cancer patients who consented to follow-up. Questionnaires at baseline (pre-surgery), 3, 9, 15, 24 months. QoL (Quality of Life in Adult Cancer Survivors, QLACS), health status (EQ-5D), personal wellbeing (Personal Wellbeing Index), physical symptoms, anxiety, depression, self-efficacy, social support, socio-demographic and clinical/treatment characteristics were examined. Longitudinal analyses assessed change in QoL, health and wellbeing over time and predictors of trajectories.

Results

Four distinct trajectories (groups) were identified for each outcome measure. Group 1: consistently good QoL (31.3%), mild and improving health problems (20.9%), consistently good wellbeing (44.9%). Groups 2 and 3 displayed intermediate and changing levels of QoL, health status and personal wellbeing. Group 4: consistently poor QoL (5.3%) and health status (7.4%), very poor/declining wellbeing (4.2%). 11.5% were in Group 4 for at least one of the outcome measures. Factors statistically significantly associated with poorer trajectories: higher deprivation, more comorbidities, stoma, worse physical and psychological symptoms, lower self-efficacy to self-manage and less social support.

Conclusion

Results from this large representative study show that distinct recovery trajectories following surgery for colorectal cancer can be identified with risk factors. Different approaches to follow-up care are warranted and these results provide robust data regarding who is likely to need more intensive support, which will inform the development of risk-stratified follow-up management tailored to an individual's need. This provides NHS commissioners with cost-effective, comprehensive packages of care for this patient group.

Acknowledgements

CREW is funded by Macmillan Cancer Support.

17.05 – 17.30

Room 4

Matthew Maddocks,
King's College
London, UK

Promoting physical activity among people living with advanced cancer

Strong evidence supports physical activity and/or exercise as a safe and effective treatment among patients with early stage cancer during or following treatment for their illness. The potential for benefit is increasingly recognised among those living with advanced cancer. In this group the emphasis is on proactive intervention to maintain or slow down the decline in function. This role for physical activity will become ever more important as with improved treatments the number of survivors living with cancer will increase. This presentation will provide an overview of the rationale, efficacy and practical implementation of physical activity programmes for people living with advanced cancer.

Parallel session abstracts *(continued)*

Physical activity and exercise may attenuate the adverse effects of cancer and its treatment via modulating metabolism, body composition and levels of inflammation. By targeting skeletal muscle function and cardiorespiratory fitness, exercise may impact favourably on meaningful patient outcomes such as the ability to exercise, levels of physical activity and functional dependency. Programmes offered alongside cancer treatment have led to favourable changes in patients' symptoms, function and quality of life. Nonetheless, most studies are small and provide limited data to understand which patients respond best to which type of programme. Further, there are practical challenges in offering exercise and intensive programmes are not acceptable to all patients, particularly those with a poor performance status. In this group a focus on specific transfers and basic activities of daily living may be most relevant. Strategies to make physical activity more widely accessible could also include offering programmes earlier in the course of illness, at lower intensities, or in home or local community settings.

17.30 - 17.40

Discussion

● Screening and epidemiology of ovarian cancer

15.40 - 15.45

Hall 1C

Iain McNeish,
University of
Glasgow, UK

Introduction

15.45 - 16.10

Hall 1C

Ranjit Manchanda,
Barts Cancer
Institute, Queen Mary
University of London
& Bartshealth NHS
Trust, London, UK

Population-based approach(es) to genetic testing for ovarian cancer prevention

The landscape in cancer genetics is changing. The traditional family history (FH) based approach to genetic testing implemented through cancer genetic clinics following intensive face-to-face genetic counselling misses >50% mutation carriers and is being replaced by population-based approaches. A randomised trial (GCaPPS; ISRCTN73338115) of BRCA1/2 testing in the Ashkenazi-Jewish (AJ) population comparing population screening (PS) with standard FH-based testing found no difference in psychological/quality of life consequences between the two approaches. Additionally 60% mutations would be missed by FH-criteria alone. A cost-effectiveness analysis suggests that population screening for BRCA1/BRCA2 mutations in AJ women >30years reduces breast/ovarian cancer(OC) incidence by 0.34%/0.62%, saves 0.101 quality-adjusted-life-years (QALYs) leading to 33 days gain in life-expectancy and is extremely cost-effective with a discounted incremental cost-effectiveness ratio (ICER) of '-£2079/QALY'. 94% of simulations on probabilistic-sensitivity analysis reconfirm population screening is highly cost-effective at £20,000/QALY threshold. This supports a call to change the clinical paradigm in the AJ population.

Efficient, acceptable and more cost-effective ways of counselling/delivering genetic risk information on a population basis are necessary for population testing. A cluster-randomised non-inferiority trial shows that DVD-based approach is an effective, acceptable, non-inferior, time saving and cost-efficient alternative to traditional face-to-face genetic counselling in

population testing. Telephone counselling is non-inferior in high-risk women. Alternate models like mainstreaming/use of dedicated nurse specialists are being explored in affected individuals.

A population-based case series approach for BRCA1/2 testing is recommended for OC. However, implementation is prevented by lack of funding and awareness. Emergence of improved/sophisticated OC-risk models and validated estimates for new moderate penetrance genes (RAD51C/RAD51D/BRIP1) provides opportunity for population risk stratification and will lead to panel testing. The OC-risk threshold for effective surgical prevention is changing and will facilitate a clinical prevention strategy for moderate-risk women. Advances in high-throughput genetic testing technology, computational analytics and systems medicine approach, provides increasing potential for population testing, risk stratification and cancer prevention. Implementation studies assessing acceptability, clinical validity and cost-effectiveness are needed.

Competing interests

Investigator on the GCaPPS trial on population based testing Research funding from The Eve Appeal for research into population based testing.

16.10 - 16.25

Hall 1C

Kezia Gaitskell,

Univeristy of Oxford,
UK

Proffered paper: Childbearing patterns and ovarian cancer in the Million Women Study: variation by histological subtype

Background

A reduced risk of ovarian cancer amongst parous women has been reported by many investigators; reports of associations with breastfeeding have been varied. Histopathological and molecular evidence suggests the different ovarian cancer subtypes have distinct origins, but few epidemiological studies have sufficient cases to explore variation in risk by histological subtype.

Method

We examined associations between ovarian cancer and childbearing patterns in the Million Women Study, a prospective cohort of UK women. Using Cox regression models, we estimated adjusted relative risks (RR) of ovarian cancer in women with different childbearing patterns, using competing risks to explore heterogeneity by histological subtype.

Results

After excluding women with previous cancer, bilateral oophorectomy, and unknown parity, the study population included 1,146,985 women, aged 56 years on average at recruitment. 7570 incident cases of ovarian cancer accrued, after an average of 13.0 years of follow-up. Overall, parous women had a 26% lower risk of ovarian cancer than nulliparous women (RR: 0.74, 95%CI: 0.69-0.79), with significant heterogeneity by histological subtype ($p\text{-het}<0.00001$). Amongst parous women, each additional birth was associated with a 7% reduction in relative risk of ovarian cancer (RR-per-birth: 0.93, 95%CI: 0.90-0.96), with heterogeneity by tumour subtype ($p\text{-het} = 0.04$). We found little evidence of a trend with increasing age at first or last birth. Overall, breastfeeding (ever vs never) was not associated with ovarian cancer (RR: 0.94, 95%CI: 0.89-1.00, $p=0.07$), and no variation was seen by histological subtype ($p\text{-het}=0.4$). However, there was a reduced risk of ovarian cancer with longer durations of breastfeeding (per 6-month increase in average breastfeeding duration per child - RR: 0.88, 95%CI: 0.83-0.93, $p<0.001$).

Parallel session abstracts *(continued)*

Conclusion

In this largest prospective study of ovarian cancer to date, our results provide new reliable evidence that associations with reproductive factors vary between different subtypes of ovarian cancer, consistent with hypotheses of different aetiologies.

Acknowledgements

The Million Women Study was funded by the Medical Research Council and Cancer Research UK. This work was supported by Cancer Research UK (CR-UK) grant number C38302/A17318, through a Clinical Research Training Fellowship for KG from the CRUK Oxford Centre.

References

Some of these results were previously presented at meetings of the American Association of Cancer Research and the Society for Social Medicine.

16.25 - 16.50

Hall 1C

Valerie Beral,
University of Oxford, UK

Title to be confirmed

Abstract not received.

16.50 - 17.05

Hall 1C

Fabrizio Miranda,
Weatherall Institute
of Molecular Medicine,
University of Oxford
& John Radcliffe
Hospital, Oxford, UK

Proffered paper: The Salt Inducible Kinase 2 (SIK2) links lipid metabolism to survival of ovarian cancer metastasis

Background

High Grade Serous Ovarian Cancer (HGSOC) metastatic disease is strongly dependent on the adipocyte-rich microenvironment of the omentum. Although previous work has shown that adipocytes are required for driving cancer metastasis to fat-rich environments, the mechanisms involved in the process of linking metabolism to cancer cell survival at this niche have remained poorly understood and this has, therefore, hindered therapeutic exploitation. We have previously shown that the expression of the Salt Inducible Kinase 2 (SIK2) is important for ovarian cancer cell survival and that it correlates with poor patient survival. In this work we present a previously unrecognised role for SIK2 in driving cancer cell metabolism and proliferation at the omental metastatic niche

Method

We established a system for the co-culture of cancer cells with adipocytes obtained from freshly excised normal omentum from women undergoing surgical staging. This system was used in combination with a chemical biology approach utilizing cells expressing gate-keeper mutants of SIK2 and a type I kinase inhibitor to test the specificity of observed phenotypic effects. Our results were validated using immunohistochemistry of a panel of ovarian cancers and a xenograft model of ovarian cancer metastasis

Results

SIK2 was significantly overexpressed in omental metastases of ovarian tumours compared to paired ovarian cancer primary lesions from the same patients. In a xenograft model of ovarian cancer metastasis SIK2-overexpressing cells implanted orthotopically at the ovarian bursa formed significantly larger omental metastases compared to cells with endogenous levels of SIK2. We first observed that co-culture of ovarian cancer cells with adipocytes resulted in an increased SIK2 autophosphorylation and activation which, in turn stimulated

cancer cell proliferation. Next, we showed that PLC-dependent activation of calcium release was required for adipocyte-induced SIK2 autophosphorylation in ovarian cancer cells. Surprisingly, we identified a role for adipocyte-activated SIK2 in stimulating cancer cell metabolism through augmenting AMPK-induced phosphorylation of ACC and activation of carnitine palmitoyltransferase 1 (CPT1) transcription. Concurrently, SIK2 was required to activate the PI3K complex through direct p85 α -S154 phosphorylation

Conclusion

Our results suggested that SIK2 phosphorylation and activation were required to establish ovarian cancer lesions at the adipocyte-rich omental environment. Therefore we suggest a therapeutic role for targeting SIK2 in preventing ovarian cancer metastases.

17.05 – 17.30

Hall 1C

Jessica McAlpine,
University of British
Columbia, Canada

Opportunistic salpingectomy: development and implementation of an ovarian cancer prevention campaign

Frustrations with the low impact of ovarian cancer screening strategies, and a plateau in overall survival statistics, highlight the urgent need for novel methods to control this disease. In September of 2010, British Columbia announced a prevention campaign aimed at women at low risk/general population risk for developing ovarian cancer. Five years later we look back at the rationale, uptake, and safety data pertaining to opportunistic salpingectomy in British Columbia and beyond, and share data on the health economics and cancer outcomes (historic and projected) associated with this surgical intervention.

17.30 – 17.40

Discussion

● **Understanding the genomic landscape of brain cancer**

15.40 – 15.45

Hall 1B

Colin Watts,
University of
Cambridge, UK

Introduction

15.45 – 16.10

Hall 1B

David Jones,
Heidelberg University,
Germany

Title to be confirmed

Abstract not received.

Parallel session abstracts *(continued)*

16.10 - 16.25

Hall 1B

Sébastien Serres,
Cancer Research UK
and Medical Research
Council Oxford
Institute for Radiation
Oncology, UK

Proffered paper: Detection of brain tumours using translational molecularly targeted magnetic resonance imaging

Background

Recent advances in molecularly-targeted magnetic resonance imaging (MRI) offer a number of advantages over conventional methodologies, including identification of specific molecular processes, such as upregulation of vascular cell adhesion molecule 1 (VCAM-1), that may be particularly active in the invasive margins of brain tumour. The aim of this study was to determine whether VCAM-1-targeted MRI could facilitate improved spatial delineation of tumour margins and more accurate assessment of tumour activity in brain tumour.

Method

Three cohorts of nude rats were injected intracerebrally with either a metastatic human breast carcinoma cell line, a multiform glioblastoma cell line, or with a desmoplastic medulloblastoma cell line. All animals underwent clinical T1- and T2-weighted to assess tumour growth and blood-brain barrier (BBB) integrity. For VCAM-1-targeted MRI, animals underwent T2* gradient echo 3D MRI after injection of microparticles of iron oxide (MPIO) functionalised with either an anti-VCAM-1 antibody (VCAM-MPIO) or a control IgG antibody (IgG-MPIO). Immunohistochemical assessment was also performed post-mortem.

Results

In all cases, brain tumours exhibited a compromised BBB using post-gadolinium T1-weighted imaging. Additionally, marked hypointensities were evident on T2*-weighted MRI following intravenous injection of VCAM-MPIO, but not IgG-MPIO, and this was particularly evident at the margins of the tumours. VCAM-1 upregulation detected immunohistochemically was significantly greater on blood vessels associated with the tumour margins than the tumour core, and co-localised with proliferative regions of the tumour. Spatial comparison of VCAM-MPIO binding and gadolinium-enhanced signal, using a 3D composite analysis method, indicated clearer delineation of tumour margins with the molecularly-targeted approach.

Conclusion

These findings suggest that VCAM-1-targeted MRI may enable improved detection of tumour margins, as compared to the current clinical gadolinium-enhanced MRI, for both primary and secondary tumours in the brain and, thus, provide a sensitive biomarker for effective surgical resection and/or radiotherapy in brain tumour patients.

16.25 - 16.50

Hall 1B

Cameron Brennan,
Memorial Sloan
Kettering Cancer
Center, New York, USA

Title to be confirmed

Abstract not received.

16.50 – 17.05

Hall 1B

Natividad Gomez-Roman, University of Glasgow, UK

Proffered paper: Radiation responses of 2D and 3D glioblastoma cells: a novel, 3D-specific radioprotective role for VEGF activation through NHEJ

Background

Glioblastoma (GBM) is the most common primary brain tumour with dismal prognosis. Tumours exhibit inherent resistance to radiation and chemotherapy which has been attributed to a subpopulation of cancer cells termed ‘GBM stem-like cells’ (GSC) characterised by multipotentiality and potent tumorigenic capacity. The use of established cancer cell lines in simplified two-dimensional (2D) in vitro cultures might explain the observed discrepancy between pre-clinical and clinical responses to cytotoxic treatments.

Method

We developed a customised, 3D GSC culture system using a polystyrene scaffold (Alvetex®) that recapitulates key histological features of GBM including high cellularity and sparse extracellular matrix (ECM) and compared it to conventional 2D GSC cultures.

Results

2D and 3D cultures of three different primary GSC lines exhibited similar radiation sensitivities as measured by clonogenic survival. Previous studies have demonstrated radiopotentiating efficacy of the EGFR inhibitor erlotinib against GBM cell lines in 2D cultures; however it failed in GBM clinical trials. Thus we evaluated the radiation modifying effects of erlotinib on 2D and 3D GSC cultures. Erlotinib enhanced radiosensitivity of 2D GSC cultures but had no effect on radiation responses of 3D GSC or in neurosphere formation assays, where cells grow in 3D conditions devoid of a scaffold or extrinsic ECM. We next examined VEGF inhibition, since anti-VEGF therapy in combination with standard radio-chemotherapy increases progression-free survival of GBM patients. VEGF deprivation was associated with significant radiosensitisation of 3D GSC cultures but had no effect on 2D GSC. Erlotinib treatment of VEGF-deprived 3D cultures increased the radiation resistance of 3D cells to the same extent as VEGF addition, indicating epistasis. EGFR has been shown to regulate repair of radiation-induced double-strand breaks by activating the non-homologous end-joining (NHEJ) repair protein DNA-PKcs. A correlation between radiosensitivity, increased gammaH2AX foci and phospho-DNA-PK nuclear foci after radiation treatment was observed. In contrast, increased numbers of foci of the homologous recombination (HR) repair protein Rad51 were observed in radioresistant populations.

Conclusion

Our results show that EGFR inhibition and/or VEGF signalling induce a switch from ineffective NHEJ to more accurate HR repair leading to radiation protection. These 3D effects recapitulate data from clinical trials, strongly supporting the clinical relevance of this 3D model and its potential value in preclinical studies.

17.05 – 17.30

Hall 1B

Kevin Brindle, University of Cambridge, UK

Investigating the genomic landscape of brain tumours using metabolic imaging

Nuclear spin hyperpolarisation can increase sensitivity in the magnetic resonance imaging experiment by >10,000-fold¹. This has allowed imaging of injected hyperpolarised ¹³C labelled cell substrates in vivo and, more importantly, their metabolic conversion into other cell metabolites. We have been using this technique both to detect treatment response^{2,3} and to investigate the tumour microenvironment^{4,5} (reviewed in [6-8]). The technique has transferred to the clinic recently with a study in prostate cancer⁹ and we expect to start patient studies in Cambridge later this year.

Parallel session abstracts *(continued)*

In this talk I will discuss recent work in which we have used hyperpolarised [1-13C]pyruvate to investigate glycolytic metabolism in patient derived xenograft (PDX) models of glioblastoma. These measurements have shown significant heterogeneity between tumours derived from different patients, which we believe is related to underlying oncogenic mutations.

References

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- ² Day, S.E., et al. Nature Med 13, 1382-1387 (2007).
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- ⁴ Gallagher, F., et al. Nature 453, 940-943 (2008).
- ⁵ Bohndiek, S.E., et al. J Am Chem Soc 133, 11795-11801 (2011).
- ⁶ Brindle, K.M., et al. Magn Reson Med 66, 505-519 (2011).
- ⁷ Brindle, K. Brit. J. Radiol. 85, 697-708 (2012).
- ⁸ Brindle, K.M. Journal of the American Chemical Society 137, 6418-6427 (2015).
- ⁹ Nelson, S.J., et al. Science Translational Medicine 5, 198ra108 (2013).

Competing interests

We have a research agreement with GE Healthcare and hold patents with them on metabolic imaging using hyperpolarised 13C-labelled cell substrates.

17.30 - 17.40

Discussion

Bristol-Myers Squibb Scientific Symposium

● Immuno-oncology: where next?

12.45 - 14.00

Room 3A

Hosted by

Bristol-Myers Squibb

Since it was first proposed that targeting key immunomodulatory pathways may result in an effective anti-tumour immune response, the field of immuno-oncology has progressed substantially. Today immuno-oncology agents are approved for two solid tumours, and a wealth of clinical trials is ongoing across a range of tumour types, evaluating a variety of treatment targets.

At this symposium, Dr Sergio Quezada (University College London) will consider the future of immuno-oncology, discussing the potential of targeting new inhibitory and activatory molecules. Dr Paul Nathan (Mount Vernon Cancer Centre) will then review the rationale and data for combining immuno-oncology agents with each other and with other treatment modalities. He will discuss whether a combinatorial or sequential approach could improve patient outcomes. Finally, Professor John Gosney (Royal Liverpool University Hospital) will discuss the parameters under evaluation in lung cancer that may help to select patients most likely to benefit from treatment. We hope you will join us in Liverpool for this exciting event.



Workshops

● BACR educational workshop: Genomics England 100,000 genomes project and cancer programme & GeCIP update

08.00 - 08.45

Room 11

Hosted by **Clare Turnbull**, The Institute of Cancer Research, London, UK

The Genomics England 100,000 Genomes Project Cancer programme has been launched through Genomic Medicine Centres across England, with sample collection underway via the Initiation Implementation Phase. Through this programme, whole genome sequencing will be undertaken on tens of thousands of patients with cancer recruited within the NHS. As well as delivering clinical results back to individual patients, this programme will generate enormous data and sample resources to be made available for research via GeCIP (Genomics England Clinical Interpretation Partnership). Furthermore, through implementation of this programme via the Genomics Medicine Centres, in conjunction with NHSE, innovative changes in sample handling and molecular pathology are being rolled out, as well as delivery of more systematic structures for clinical data capture, interpretation, validation and clinical reporting.

Dr Clare Turnbull, Clinical Lead of the Genomics England 100,000 Genomes Project Cancer programme will give an overview of the programme and progress made, and discuss the challenges and opportunities ahead. Professor Louise Jones, Clinical Lead for Pathology will present findings from the pilot work and molecular pathology experimental group underpinning the development of working protocols for molecular pathology. Professor Charles Swanton, Professor Johann de Bono, Professor Josef Vormoor and Dr James Larkin will give insights into the development of the GeCIP domains for cancer.

● De-mystifying today's science

08.00 - 08.45

Room 3B

Elaine Vickers,
Science
Communicated,
Sheffield, UK

Do words like signal transduction, epigenetics, genomics and biomarkers bring a puzzled frown to your face?

Do you plan to attend today's plenary lectures whilst fearing that you won't understand a word?

Well never fear!

Elaine will explain many of the words, concepts and ideas behind today's plenary lectures, including:

- An introduction to biomarkers and how they are relevant to the concept of personalised medicine
- The core ideas of epigenetics
- Cancer metabolism
- The ideas behind cancer immunotherapy

Similar to previous years' workshops, Elaine will use diagrams and illustrations to provide clear, easy-to-understand explanations of complicated biological concepts.

The workshop is geared towards non-scientists, such as doctors, nurses, trials staff and patients who'd like to get the most out of this year's conference.

Workshops *(continued)*

● Molecular pathology

10.50 - 12.30

Hall 1C

Manuel Salto-Tellez,
Queen's University
Belfast, UK

2015 has been a good year for cancer Molecular Pathology in the UK. These excellent new developments include substantial funding from MRC Molecular Pathology Nodes and CRUK Accelerator Award; plans for molecular pathology development within the Precision Medicine Catapult; the continuation of the CRUK Stratified Medicine Initiative; the CM-Path initiative within the ECMC umbrella; and the creation of the Molecular Pathology schemes within the Genomics England initiative, among others.

The purpose of this Workshop is to present to the cancer research community the scientific programmes behind some of these initiatives, with the aim of encouraging maximum use of these platforms by scientists and industrial partners across the UK.

This meeting will be a prelude of a broader UK Stratified Medicine Conference in December 2015, coordinated by the Stratified Medicine Innovation Platform Programme Coordination Group.

10.50 - 11.00

Introduction - Molecular Pathology in 2015

Manuel Salto-Tellez, Queen's University Belfast, UK

11.00 - 11.20

Molecular Pathology: the Edinburgh-St Andrews MRC Node

Tim Aitman, University of Edinburgh, UK

11.20 - 11.40

MRC Mole Path Node - The Newcastle Proximity Laboratory

Philip Sloan, University of Newcastle, UK

11.40 - 12.00

The Glasgow MRC Mol Path Node

Karen Oien and **Iain McNeish**, University of Glasgow, UK

12.00 - 12.20

CRUK Accelerator in Digital Pathology "Digital Pathology and cancer immunology"

Peter Hamilton, Queens University Belfast, UK and **Gareth Thomas**, University of Southampton, UK

12.20 - 12.30

Discussion

● Dragon's Den workshop

12.20 - 14.00

Room 12

Hosted by **NCRI
Consumer Forum**

The NCRI Consumer Forum is once again hosting a Dragon's Den session. This session offers researchers the opportunity to meet with small groups of knowledgeable consumers who are already involved in research, as well as other consumers (patients or carers) who are attending the conference. Researchers are welcome to present new ideas, to discuss problems with studies already running, to seek endorsements for funding, to disseminate findings to patients or to talk about how to create effective consumer involvement in their work.

This session offers practical on-the-spot advice for those who want to engage some consumers to offer long-term support, or just want to talk through an idea at the back of their mind.

Lunch and refreshments will be available. Please arrive on time; Dragon's Den is always one of the Conference's most popular events.

Who are the friendly dragons?

Patients and carers who are experienced in cancer research, including NCRI Consumer Forum members who sit on Clinical Studies Groups and other NCRI initiatives, members of the Independent Cancer Patients' Voice (ICPV), consumers who sit on funding committees, consumers funded by Cancer Research UK, Macmillan, Tenovus or other charities, or those who work with CTUs or other institutions. The session is also open any conference attendee who wishes to take part, for example, researchers who may have someone in their family affected by cancer, or who simply wish to see some consumer involvement in action.

What will happen during this session?

Researchers who submitted their ideas prior to the Conference will pitch it at a table of friendly Dragons. There will be several tables in the room and presenters will be allocated to one. Dragons will review the proposal or discuss the idea, offer feedback and address any specific problems or questions they or the presenter may have. All discussions happen in small groups in an informal setting and presenters are encouraged to arrange for follow-up contacts if they wish. NCRI Consumers are encouraged to join Trial Management or Steering Groups as part of their roles as NCRI Consumers.

● Influencing

13.00 – 14.00

Room 4B

Martin Clarke,
Inspire Change, UK

In this session influencing expert Martin Clarke (Inspire Change, UK) will cover how people make decisions, the research behind how these (sometimes surprising) things really work and why a 'one size fits all' approach will not work. The workshop will help delegates learn how to influence colleagues and will give them something to use when other approaches have failed. This session will also cover:

- How to ask for more funding and increase your chances of getting it
- Six muses of influence: authority, consistency, liking, scarcity and social proof
- Better ways of asking for money, change in behaviour and increasing patient compliance

TUESDAY



Programme at a glance

Workshops

08.00 - 08.45 BACR educational workshop: Patient-derived xenograft models: current future and state-of-the-art
Room 11
Hosted by **Robert Clarke**, The University of Manchester, UK and **Anna Grabowska**, The University of Nottingham, UK



08.00 - 08.45 De-mystifying today's science
Room 3B
Hosted by **Elaine Vickers**, Science Communicated, Sheffield, UK

Clinical Trials Showcase part 1

Hosted by **Matt Seymour**, NIHR Clinical Research Network: Cancer, Leeds, UK

09.00 - 09.20 PET-NECK: A multi-centre, randomised, phase III, controlled trial (RCT) comparing PETCT guided active surveillance with planned neck dissection (ND) for locally advanced (N2/N3) nodal metastases (LANM) in patients with head and neck squamous cell cancer (HNSCC) treated with primary radical chemoradiotherapy (CRT)
Hall 1A
Hisham Mehanna, InHANSE University of Birmingham, UK



09.20 - 09.40 CheckMate 067: a phase III randomised double-blind study of nivolumab (NIVO) monotherapy or NIVO combined with ipilimumab (IPI) versus IPI monotherapy treatment-naïve patients (pts) with advanced melanoma (MEL)
Hall 1A
James Larkin, The Royal Marsden Hospital, London, UK

Plenary lecture

Chaired by **Ricky Sharma**, Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, UK

09.40 - 10.20 Technical developments in radiotherapy
Hall 1A
Uwe Oelfke, The Institute of Cancer Research, London, UK



Networking, exhibition viewing, poster viewing and refreshment break

10.20 - 10.50
Hall 2

Symposia

10.50 - 12.20 DNA repair and cancer
Room 11
Hosted by **Keith Caldecott**, University of Sussex, UK

10.50 - 12.20 Genomics and cancer evolution
Hall 1A
Hosted by **Marco Gerlinger**, The Institute of Cancer Research, London, UK



10.50 - 12.20 Lifestyle behaviour and prevention
Room 3B
Hosted by **Eileen Kaner** and **Linda Sharp**, Newcastle University, UK

- 10.50 – 12.20** Molecular imaging and radionuclide therapy
Room 3A Hosted by **Nandita deSouza**, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, London, UK



● **Networking, exhibition viewing, poster viewing and lunch**

- 12.20 – 14.10**
Hall 2

● **The Royal College of Radiologists proffered paper session**

- 12.30 – 13.40** One of the presentations in this session will be awarded an RCR Ross Prize for the best oral presentation, as judged by an RCR judging panel.
Hall 1C



● **Workshops**

- 12.45 – 14.00** Involving patients in the use of their data
Room 12 Hosted by **National Cancer Intelligence Network**, UK

- 12.45 – 14.00** Cancer Research UK Grand Challenge drop in session
Room 11



● **Plenary lectures**

Chaired by **Caroline Dive**, Cancer Research UK Manchester Institute, UK

- 14.10 – 14.40** Title to be confirmed
Hall 1A **Tim Hunt**, The Francis Crick Institute, London, UK

- 14.40 – 15.10** Title to be confirmed
Hall 1A **Dennis Slamon**, UCLA Jonsson Comprehensive Cancer Center, Los Angeles, USA

● **Networking, exhibition, poster viewing and refreshment break**

- 15.10 – 15.40**
Hall 2

● **Parallel sessions**

- 15.40 – 17.40** Cardiovascular toxicity in paediatric cancer treatment
Room 4 Hosted by **Chris Plummer**, Freeman Hospital, Newcastle upon Tyne, UK

- 15.40 – 17.40** Integration of germline genetic information can improve cancer diagnosis, treatment and prevention
Room 12 Hosted by **Nazneen Rahman**, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, London, UK

- 15.40 – 17.40** Largescale genomics trials
Room 11 Hosted by **Gary Middleton**, University of Birmingham, UK

- 15.40 – 17.40** Pancreatic and hepatobiliary cancers
Room 3A Hosted by **Roger Taylor**, University of Swansea & The Royal College of Radiologists, UK



Programme at a glance *(continued)*

15.40 – 17.40 'Prevention is better than cure': cancer chemoprevention in 2015
Room 3B Hosted by **Jack Cuzick**, Queen Mary University of London, UK

15.40 – 17.40 Single cell analysis: clinically useful or research tool?
Hall 1B Hosted by **Thierry Voet**, Wellcome Trust Sanger Institute, Cambridge, UK

15.40 – 17.40 The future role of primary care in cancer control
Hall 1C Hosted by **Greg Rubin**, University of Durham, UK



THE LANCET Oncology

15.40 – 17.40 Tumour:stroma interactions
Hall 1A Hosted by **Erik Sahai**, The Francis Crick Institute, London, UK

● Networking and break

17.40 – 18.00
Hall 2

● Clinical Trials Showcase part 2

Hosted by **Matt Seymour**, NIHR Clinical Research Network: Cancer, Leeds, UK

18.00 – 18.20 Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer:
Hall 1A first overall survival results from STAMPEDE(NCT00268476)
Nicholas D. James, University of Warwick & Queen Elizabeth Hospital,
Birmingham, UK



18.20 – 18.40 A phase II/III randomised trial comparing maintenance lapatinib vs
Hall 1A placebo after first line chemotherapy in HER1/2 positive metastatic
bladder cancer
Simon Chowdhury, Guy's and St Thomas' Hospital NHS Trust,
London, UK

● Plenary lecture

Chaired by **Caroline Dive**, Cancer Research UK Manchester Institute, UK

18.40 – 19.20 'Rethinking cancer' as a complex adaptive system
Hall 1A **Anna Barker**, Arizona State University, USA

● Conference dinner and party *(ticketed event)*

20.00 onwards Limited tickets are available for this event. Please go to the onsite
The Echo Arena, BT payment desk to reserve your place no later than noon, Tuesday 3
Convention Centre November. Only ticket holders will be admitted.

Plenary abstracts

● Technological developments in radiotherapy

09.40 – 10.20

Hall 1A

Uwe Oelfke,
The Institute of
Cancer Research,
London, UK



Technological innovations have been the driving force behind step changes in radiation therapy practice in recent decades. The introduction of intensity-modulated radiation therapy (IMRT) with high energy photon beams led to fascinating new opportunities conforming doses tightly, even to concave radiation targets encompassing organs-at-risk. The exploitation of this improved dose-shaping potential critically required an accurate knowledge of the patient's anatomy at the time of treatment and led to the development of image guided radiotherapy (IGRT) technologies.

IGRT was introduced as a hybrid technology integrating an X-ray source and a flat-panel imager with state of the art dose delivery equipment. This technology has been available for more than a decade and is increasingly viewed as a means of facilitating therapy adaptation for a substantial proportion of RT patients. However, despite its success, the day to day practice of IGRT revealed severe limitations inherent to this approach.

First, its poor soft tissue contrast makes it impossible to discriminate between tumour targets and adjacent healthy tissues for most clinical indications. Second, the detection and monitoring of intra-fraction organ motion is difficult. A solution to these shortcomings is the integration of magnetic resonance imaging (MRI) within modern RT treatment machines. Currently, there are five different types of systems either under development or in clinical practice worldwide. A comprehensive overview of their basic features will be presented.

Parallel to these developments in radiation therapy with photon beams the technology for the practice of proton radiation therapy advanced considerably. The design of intensity modulated proton therapy (IMPT) concepts with scanning pencil beams allows the design of improved dose patterns reducing integral doses in healthy tissues by a factor of 2-3 when compared to photon RT. Other recent technological innovations that will be discussed are the development of compact single room proton therapy delivery systems and proton specific IGRT solutions.

Competing interests

Member of the MR-Linac Consortium Elekta.

● Title to be confirmed

14.10 – 14.40

Hall 1A

Tim Hunt,
The Francis Crick
Institute, London, UK



Abstract not received.

Plenary abstracts *(continued)*

● Title to be confirmed

14.40 – 15.10

Hall 1A

Dennis Slamon,
UCLA Jonsson
Comprehensive
Cancer Center,
Los Angeles, USA



Abstract not received.

● ‘Rethinking’ ‘cancer as a complex adaptive system

18.40 – 19.20

Hall 1A

Anna Barker,
Arizona State
University, USA



Progress in cancer genomic sequencing technologies (with its associated ‘big data’) now offers hope that cancer’s seemingly unyielding complexity can now be deconvoluted to identify real targets for cancer treatment, detection and prevention. Cancer genomic alterations, and increasingly their prescribed clinical interventions, are now the central focus across virtually all aspects of cancer biomedicine. This ‘revolution’ has unquestionably been enabled by largescale genome sequencing projects such as The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC); as largescale sequencing projects have endeavoured to profile the genomics alterations in nearly all of the major cancers. Interestingly, data from these comprehensive efforts are beginning to offer a great deal more insight into cancer’s complexity than simply providing an ‘atlas’ of these changes. While the ‘holy grail’ of drug development in oncology is the ‘driver’ mutation, increasingly we are learning that although some of these so-called ‘actionable’ alterations may be present to a greater or lesser extent in selected cancers, overall they are relatively rare. Instead, in TCGA and similar efforts, we observed an extraordinarily complex ‘long tail’ of genomic alterations which generally remain unexplored. This landscape of genomic heterogeneity is reflected in cancer’s heterogeneity (and the clonal heterogeneity) of most tumours – which makes the reality of achieving cures elusive.

Despite an enormous amount of effort by myriad investigators, we are still early in our attempts to functionalise the complex array of inter-related changes that generally comprise the dysfunctional signalling pathways for the range of complex diseases we label as cancer. Recent largescale genomics projects, combined with decades of cancer research, indicate that cancer is not simply a ‘disease of the genes’, and in fact, should more appropriately be viewed and studied as an emergent and evolving complex adaptive system (CAS) (within the tumour and within the individual patient). Employing CAS approaches and models to understand cancer at a more fundamental level will require research that considers macro- and microenvironments across scales ranging from the molecular level to the patient. Of equal or even greater importance, understanding the emergent properties (hallmarks of complex systems) that are characteristic of cancer will require analysis of the coherent whole vs. the component parts.

Approaching the investigation of cancer as a complex adaptive system represents an opportunity to achieve a deeper level of comprehension of the biological, temporal and spatial aspects of this extraordinarily complex disease. Such a conceptual shift will provide new strategies for knowledge-based diagnostic, therapeutic and preventive cancer interventions. For example, the heterogeneity of cancer provides it with redundancy which renders the system 'robust' and all too often this 'robustness' renders it resistant to even the most 'targeted' of therapies. Understanding the evolution of these robust cancer phenotypes (states) both in carcinogenesis per se, and following therapeutic intervention, through appropriate data driven CAS models is becoming increasingly feasible. Predictably altering the 'state' of complex, hierarchically organised, systems such as cancer requires embracing new ideas, disciplines and models – all of which will require significant change. However, all indications are that achieving a future where stable disease (effectively rendering cancer a chronic, treatable condition) and/or cure are achieved for most cancers will require that the cancer research communities embrace complexity. Although viewing and ultimately pursuing cancer through the lens of CAS research is currently a road less travelled – it may in fact ultimately be the road to precision medicine.

Clinical Trials Showcase

- **PET-NECK: A multi-centre, randomised, phase III, controlled trial (RCT) comparing PETCT guided active surveillance with planned neck dissection (ND) for locally advanced (N2/N3) nodal metastases (LANM) in patients with head and neck squamous cell cancer (HNSCC) treated with primary radical chemoradiotherapy (CRT)**

09.00 – 09.20

Hall 1A

Hisham Mehanna,
InHANSE, University
of Birmingham, UK

Background

Planned ND after radical CRT for LANM remains controversial. 30% of ND specimens show histological evidence of tumour, albeit tumour viability cannot be confirmed. Consequently, many clinicians still practice planned ND. In mainly retrospective single-institution studies, FDG-PETCT demonstrated high negative predictive values for persistent nodal disease, providing a possible alternative paradigm to ND. This study aimed to determine the efficacy and cost-effectiveness of PETCT guided surveillance, compared to planned ND, in a multicentre randomised setting.

Method

Eligibility: Patients with LANM of oro-, hypo-pharynx, larynx, oral or occult HNSCC receiving CRT and fit for ND. **Randomisation (1:1):** to planned ND before or after CRT (control), or CRT followed by FDG-PETCT 10-12 weeks post CRT with ND only if PETCT showed incomplete or equivocal response of nodal disease (intervention). **Balanced by centre, planned ND timing, CRT schedule, disease site, T / N stage.** **Primary outcome:** Overall Survival (OS), minimum follow-up 2 years. **Analysis:** 560 patients needed to detect non-inferior OS in the intervention arm with 80% power, Type I error 5%, defining non-inferiority as having a hazard ratio (HR) no higher than 1.50. Intention to treat analysis was performed by Cox proportional hazards model.

Results

564 patients recruited (282 ND arm, 282 surveillance arm; 17% N2a, 61% N2b, 18% N2c, 3% N3). 84% had oropharyngeal cancer. 75% of tested cases were p16+ve. Median follow-up 36 months. The HR for OS was 0.92 (95% CI: 0.65, 1.32) indicating non-inferiority. HR margin of 1.50 lies at the 99.6 percentile of this estimate, $p = 0.004$. There were no differences by p16 status. There were 54 NDs performed in the surveillance arm with 22 surgical complications; 221 NDs in the ND arm with 85 complications.

PETCT surveillance was cost effective compared to planned neck dissection with a £1,415 per person saving and an additional gain of 0.07 QALY.

Conclusion

PETNECK is the largest surgical head neck trial to be done in the UK, and one of the largest in the world. PETCT guided active surveillance showed similar survival outcomes to ND arm, but resulted in considerably fewer NDs, and fewer complications, and is more cost-effective, supporting its use in routine practice.

Acknowledgements

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Robinson⁹, Elizabeth Junor¹⁰, Claire Hulme¹¹, Alison F Smith¹¹, Peter Hall¹², Bal Sanghera², Janet A Dunn³

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● **CheckMate 067: a phase III randomised double-blind study of nivolumab (NIVO) monotherapy or NIVO combined with ipilimumab (IPI) versus IPI monotherapy treatment-naïve patients (pts) with advanced melanoma (MEL)**

09.20 – 09.40

Hall 1A

James Larkin,
The Royal Marsden
Hospital, London, UK

Background

Results from a phase I study in MEL pts suggested complementary clinical activity between NIVO (a programmed death-1 [PD-1] immune checkpoint inhibitor) and IPI (a cytotoxic T lymphocyte antigen-4 [CTLA-4] checkpoint inhibitor). This phase III, double-blind study evaluated the efficacy and safety of NIVO alone or NIVO plus IPI versus IPI alone in MEL.

Method

Treatment-naïve pts (N=945) with MEL were randomized 1:1:1 to receive NIVO 3 mg/kg every 2 weeks (Q2W) + IPI placebo Q3W, or NIVO 1 mg/kg Q2W combined with IPI 3 mg/kg Q3W for 4 doses followed by NIVO 3 mg/kg Q2W, or IPI 3 mg/kg Q3W + NIVO placebo Q2W for 4 total doses followed by NIVO placebo Q2W until progression or unacceptable toxicity. Pts were stratified by PD ligand-1 (PD-L1) status, BRAF status and M-stage. Co-primary endpoints were progression-free survival (PFS) and overall survival. Pts continue to be followed for overall survival.

Results

PFS was 11.5, 6.9, and 2.9 months for NIVO + IPI, NIVO, and IPI, respectively. In PD-L1-positive pts, PFS was the same for NIVO and NIVO + IPI. In PD-L1-negative pts, however, PFS was numerically higher with NIVO + IPI. Objective response rate was significantly higher with NIVO and NIVO + IPI than IPI alone. Grade 3-4 treatment-related adverse events occurred in 16.3%, 55.0%, and 27.3% in the NIVO, NIVO + IPI, and IPI groups, with 1, 0, and 1 treatment-related deaths, respectively.

Conclusion

NIVO alone or in combination with IPI significantly improved PFS versus IPI alone in treatment-naïve MEL pts, particularly for those with PD-L1-negative tumours, with no new safety signals or drug-related deaths in the combination group.

Acknowledgements

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Clinical Trials Showcase *(continued)*

Arvin Yang¹⁶, Linda Rollin¹⁷, Christine Horak¹⁶, James Larkin¹⁸, Stephen Hodi¹⁹

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● Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First overall survival results from STAMPEDE(NCT00268476)

18.00 – 18.20

Hall 1A

Nicholas D James,
University of Warwick
& Queen Elizabeth
Hospital, Birmingham,
UK

Background

STAMPEDE is a randomised controlled trial using a novel multi-arm multi-stage design. It recruits men (pts) with high-risk locally advanced or metastatic prostate cancer (PCa) starting long-term hormone therapy (HT) for the first time. The trial initially assessed adding 1 or 2 of 3 treatment approaches to standard of care (SOC). We report primary survival results for 3 research comparisons that recruited through all their intermediate analyses: docetaxel (D), zoledronic acid (ZA) & the combination (D+ZA).

Method

SOC was hormone therapy for ≥ 3 yrs; RT was encouraged for NOMO pts up to Nov-2011, then mandated; RT was optional for N+MO pts. Stratified randomisation allocated pts 2:1:1:1 to SOC (control), SOC+D, SOC+ZA or SOC+D+ZA. 4mg ZA was given for six 3-weekly cycles then 4-weekly until 2yrs. D was given as 75mg/m² for six 3-weekly cycles with prednisolone 10mg daily. The primary outcome measure was survival (time from randomisation to death from any cause). Pairwise comparisons to control on survival for each research arm had 90% power at 2.5% 1-sided alpha for a hazard ratio of 0.75 requiring ~400 control arm deaths, accounting for 3 intermediate lack of benefit analyses on failure-free survival. Analyses used the Cox model of the logrank test, adjusted for stratification factors.

Results

From Oct-2005 to Mar-2013, 2,962 pts were randomised to the 4 arms. The groups were balanced with median age 65yrs; 61% metastatic, 14% N+/XMO, 22% NOMO; 93% diagnosed within 6m of randomisation; median PSA 65ng/ml. Median follow-up was 42m. Grade 3-5 toxicity was reported for 31% SOC, 50% SOC+D, 32% SOC+ZA and 52% SOC+D+ZA. There were 405 deaths on the control arm (84% from PCa). The hazard ratio was 0.76 (95% CI 0.63, 0.91; $p = 0.003$) for SOC+D vs SOC; 0.93 (95% CI 0.79, 1.11; $p = 0.437$) for SOC+ZA vs SOC; and 0.81 (95% CI 0.68, 0.97; $p = 0.020$) for SOC+D+ZA vs SOC. Median survival was increased by 1yr from 67m on SOC to 77m on SOC+D. Results in M0 and M1 disease will be shown.

Conclusion

Survival data from STAMPEDE show a clinically and statistically significant improvement in survival from adding docetaxel but not from adding zoledronic acid in men starting long-term

hormone therapy for the first time.

Nicholas D James^{1,13}, Matthew R Sydes², Malcolm D Mason³, Noel W Clarke¹⁴, David P Dearnaley⁴, Melissa R Spears², Robin Millman¹⁵, Christopher C Parker⁸, Alastair W S Ritchie², J Martin Russell⁵, John Staffurth¹¹, Robert J Jones⁵, Shaun P Tolan⁶, John Wagstaff⁷, Andrew Protheroe⁸, Rajaguru Srinivasan⁹, Alison J Birtle¹⁰, Joe M O'Sullivan¹¹, Richard Cathomas¹², Mahesh K B Parmar²

¹University of Warwick, Coventry, UK, ²MRC Clinical Trials Unit at UCL, London, UK, ³Velindre Hospital, Cardiff, UK, ⁴The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK, ⁵Beatson West of Scotland Cancer Centre, Glasgow, UK, ⁶Clatterbridge Cancer Centre, Wirral, UK, ⁷South West Wales Cancer Institute, Swansea, UK, ⁸University of Oxford Medical Oncology Department, Oxford, UK, ⁹Royal Devon and Exeter NHS Foundation Trust, Exeter, UK, ¹⁰Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK, ¹¹Belfast City Hospital, Belfast, UK, ¹²Kantonsspital Chur, Chur, Switzerland, ¹³Queen Elizabeth Hospital, Birmingham, UK, ¹⁴The Christie and Salford Royal Hospitals, Manchester, UK, ¹⁵Prostate Cancer Support Group, Middlesbrough, UK

● A phase II/III randomised trial comparing maintenance lapatinib vs placebo after first line chemotherapy in HER1/2 positive metastatic bladder cancer

18.20 - 18.40

Hall 1A

Simon Chowdhury,
Guy's and St Thomas'
Hospital NHS Trust,
London, UK

Background

First-line chemotherapy for metastatic transitional cell carcinoma (TCC) is associated with clinical benefit. Further therapies are largely ineffective. The purpose of this trial was to establish if maintenance lapatinib after first-line chemotherapy was associated with clinical benefit in HER1/HER2 positive TCC patients.

Method

During first-line chemotherapy, patients were screened for their HER1/HER2 status by centralised immunohistochemistry (IHC). HER1/2 positive patients with advanced/metastatic TCC who achieved clinical benefit after completing first-line chemotherapy (4-8 cycles) were potentially eligible for randomisation (1:1). The primary endpoint was to compare progression free survival (PFS). Secondary endpoints included adverse events (AE), overall survival (OS) and subset analysis for HER status.

Results

Between 2007-2013, 455 patients were screened and 232 HER 1 or 2 positive patients were randomised to lapatinib (L) (n = 116) or placebo (P) (n = 116). 72.5% had visceral metastasis. 60.8% received cisplatin based chemotherapy. The median number of chemotherapy cycles was 6. The progression free survival for L and P was 4.6 months (95% CI: 2.8 - 5.4) and 5.3 months (95% CI: 3.0 - 5.8) respectively [HR: 1.1 (95% CI: 0.79 - 1.39) p = 0.77]. The overall survival for L and P was 12.6 months (95% CI: 9 - 16.2) and 11.9 months (95% CI: 10.6 - 15.8) respectively [HR = 0.96 (95% CI: 0.71 - 1.31) p = 0.79]. The best response rate for L and P was 13.8% vs 7.8% (p = 0.14). The rate of grade 3-4 AEs for L and P was 24.3% vs. 15.5% (p = 0.09). Subset analysis of i) HER1/HER2 3+ positive patients on IHC ii) HER1 positive patients iii) HER2 positive patients showed no significant benefit in PFS (HR 0.94, 0.99 and 1.19 respectively: p > 0.05 for each) or OS (HR 0.76, 0.92 and 1.03 respectively: p > 0.05 for each) for lapatinib. A model predicting outcomes was constructed.

Conclusion

This is the first personalised randomised trial in metastatic TCC. It shows maintenance lapatinib does not improve outcomes in HER1 or HER2 positive individuals.

Simon Chowdhury², Tony Elliot³, Robert Jones⁴, Syed Hussain⁵, Simon Crabb⁶, Charlotte Ackerman¹, Satinder Jagdev⁷, John Chester⁷, Serena Hilman⁸, Mark Beresford⁸, Graham Macdonald⁹, Sundar Santhanam¹⁰, John Frew¹¹, Andrew Stockdale¹², Shah-Jalal Sarker¹, Dan Berney¹, Thomas Powles¹, Robert Huddart¹³

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Symposia

● DNA repair and cancer

Hosted by **Keith Caldecott**, University of Sussex, UK

- 10.50 - 10.55** Introduction by the host
Room 11
- 10.55 - 11.20** Protective packaging for DNA: the role of the PBAF and INO80 chromatin remodelling complexes in maintaining genome instability
Room 11
Jessica Downs, University of Sussex, UK
- 11.20 - 11.45** Role of the BRCA-1:BARD1 ubiquitin ligase activity in DNA repair
Room 11
Jo Morris, University of Birmingham, UK
- 11.45 - 12.10** Genetic dissection of tumour development, therapy response and resistance in mouse models of BRCA1-deficient breast cancer
Room 11
Jos Jonkers, The Netherlands Cancer Institute, Amsterdam, The Netherlands
- 12.10 - 12.20** Discussion

● Genomics and cancer evolution

Hosted by **Marco Gerlinger**, The Institute of Cancer Research, London, UK

- 10.50 - 10.55** Introduction by the host
Hall 1A
- 10.55 - 11.20** Phylogenetic analysis reveals divergent modes of clonal spread and intraperitoneal mixing in high grade serous ovarian cancer
Hall 1A
Sohrab Shah, BC Cancer Agency Research Centre, British Columbia, Canada
- 11.20 - 11.45** Evolution and drug resistance in cancer
Hall 1A
Ultan McDermott, Wellcome Trust Sanger Institute, Cambridge, UK
- 11.45 - 12.10** Tracking tumour evolution with clonal assays - mutation order matters
Hall 1A
David Kent, University of Cambridge, UK
- 12.10 - 12.20** Discussion



● Lifestyle behaviour and cancer prevention

Hosted by **Eileen Kaner** and **Linda Sharp**, Newcastle University, UK

- 10.50 - 10.55** Introduction by the hosts
Room 3B
- 10.55 - 11.20** How many cancers can we prevent through dietary modifications?
Room 3B
Paolo Boffetta, Icahn Medical Institute at Mount Sinai, New York, USA
- 11.20 - 11.45** Reducing exposure to alcohol to reduce cancer risk
Room 3B
Peter Anderson, Newcastle University, UK

Symposia *(continued)*

11.45 - 12.10 Physical activity, obesity and cancer
 Room 3B **Martin Wiseman**, World Cancer Research Fund International, London,
 UK & University of Southampton, UK

12.10 - 12.20 Discussion

● Molecular imaging and radionuclide therapy

Hosted by **Nandita deSouza**, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust,
 London, UK

10.50 - 10.55 Introduction by the host
 Room 3A

10.55 - 11.20 Molecularly targeted radiation therapy: towards individualised
 treatment
 Room 3A

Katherine Vallis, Cancer Research UK and Medical Research Council
 Oxford Institute for Radiation Oncology, UK

11.20 - 11.45 Translating novel diagnostic and therapeutic radiopharmaceuticals
 into the clinic
 Room 3A

Wim Oyen, The Institute of Cancer Research & The Royal Marsden
 NHS Foundation Trust, London, UK

11.45 - 12.10 Radium-223 for prostate cancer bone metastases: how research
 can change clinical practice
 Room 3A

Joe O'Sullivan, Queen's University Belfast & Northern Ireland Cancer
 Centre, UK

12.10 - 12.20 Discussion



Symposia abstracts

● DNA repair and cancer

10.50 – 10.55

Room 11

Keith Caldecott,
University of
Sussex, UK

Introduction

10.55 – 11.20

Room 11

Jessica Downs,
University of
Sussex, UK

Protective packaging for DNA: the role of the PBAF and INO80 chromatin remodelling complexes in maintaining genome stability

In eukaryotes, genomic DNA is packaged into the nucleus primarily by association with histone proteins to form chromatin. This structure, while necessary for compaction and chromosome segregation, is inhibitory to most processes that require access to DNA, such as transcription, replication and repair. For this reason, cells have two powerful mechanisms for manipulating the structure of chromatin; covalent modification of histones and ATP-dependent chromatin remodelling activities. Multiple chromatin modifying activities are involved in preventing genome instability by functioning to signal and repair damaged DNA, as well as to promote faithful chromosome segregation. Our recent work has focused on two complexes: PBAF (also called SWI/SNF-B) and INO80. Both of these complexes contribute to cellular functions that promote and maintain genome stability, but by different mechanisms. Our aim is to investigate the molecular mechanisms underpinning these activities and to explore the potential interplay between these complexes in the cell. These approaches will yield insights into how chromatin remodelling activities contribute to genome stability and prevent tumourigenesis.

11.20 – 11.45

Room 11

Jo Morris, University
of Birmingham, UK

Role of the BRCA1:BARD1 ubiquitin ligase activity in DNA repair

The breast and ovarian cancer predisposition protein BRCA1 and its partner, BARD1, have enzymatic activity as a ubiquitin ligase. However whether this has relevance to DNA repair and thus to treatment choice and potentially to cancer predisposition has been unclear. Here we identify a novel element required for activity in a structural subset of dimeric RING ubiquitin ligases including BRCA1:BARD1. Using mutants to separate the role of the heterodimer from that of its activity we demonstrate the role of the activity in DNA repair. Our data indicates substrates of the activity and indicate the mechanistic influence of both mimics of modified substrates and of the ligase activity. Our data support the notion that the enzymatic function of BRCA1 has a role in DNA repair and is likely to be relevant to treatment choice and to cancer predisposition.

11.45 – 12.10

Room 11

Jos Jonkers, The
Netherlands Cancer
Institute, Amsterdam,
The Netherlands

Genetic dissection of tumour development, therapy response and resistance in mouse models of BRCA1-deficient breast cancer

Advancing cancer medicine through development of individualised cancer treatment requires detailed knowledge of the mechanisms underlying therapy response and acquired resistance. Mouse models of human cancer provide powerful tools to study these aspects in a realistic in vivo setting.

We have established several genetically engineered mouse models (GEMMs) and patient-derived tumour xenograft (PDX) models for BRCA1-deficient breast cancer. These mice develop mammary tumours that are characterised by genomic instability and hypersensitivity

Symposia abstracts *(continued)*

to DNA-damaging agents, including platinum drugs and PARP inhibitors. We have used these mammary tumour models for preclinical evaluation of therapy response and elucidation of mechanisms of acquired drug resistance. Using functional genetic screens, reverse genetics and genomic analysis of therapy-resistant tumours, we found that therapy response and resistance of BRCA1-deficient mammary tumours to cisplatin and the clinical PARP inhibitor olaparib is affected by several factors, including drug efflux transporter activity, type of BRCA1 founder mutation and 53BP1 or REV7 status. Also BRCA1 re-activation via genetic or epigenetic mechanisms contributes to acquired therapy resistance in PDX models of BRCA1-deficient breast cancer.

12.10 - 12.20

Discussion

● Genomics and cancer evolution

10.50 - 10.55

Hall 1A

Marco Gerlinger, The
Institute of Cancer
Research, London, UK

Introduction

10.55 - 11.20

Hall 1A

Sohrab Shah,
BC Cancer Agency
Research Centre,
British Columbia,
Canada

Phylogenetic analysis reveals divergent modes of clonal spread and intraperitoneal mixing in high grade serous ovarian cancer

To study the properties of intraperitoneal spreading patterns in high grade serous ovarian cancers, we performed phylogenetic analysis of the evolutionary histories of individual clones across multiple intraperitoneal sites. Tumour specimens were synchronously obtained at the time of primary debulking surgery, including 68 primary ovarian and intraperitoneal foci from seven patients. Whole genome sequencing and targeted deep sequencing from bulk tissues combined with single nucleus sequencing of >1500 cells was performed to compute phylogenetic clonal reconstructions from somatic genomic aberrations and establish clonal mixtures present in each sample. I will discuss at least two divergent modes of intraperitoneal metastasis, highlighting the interplay between genomically diverse clones and their migratory potential prior to therapeutic intervention in high grade serous ovarian cancers.

11.20 - 11.45

Hall 1A

Ultan McDermott,
Wellcome Trust
Sanger Institute,
Cambridge, UK

Evolution and drug resistance in cancer

Despite an increasing array of new cancer therapies, drug resistance is an almost universal phenomenon that can be traced to the presence of rare subclonal populations that act as a reservoir for the emergence of drug resistance. The emergence of drug resistance ultimately proves fatal for the majority of patients, and therefore the early detection of resistance and the identification of novel strategies to overcome the underlying mechanisms is a subject of intense activity worldwide.

For these reasons, there is renewed interest in the use of screens capable of deliberately engineering into the cancer genome random mutational events that can then be tested for

their ability to cause drug resistance in an unbiased fashion. Such screens, if sufficiently unbiased, could in theory capture the entire breadth of genetic resistance effectors for any drug. Recent studies have demonstrated the power of both genome-wide gain-of-function (GoF) and loss-of-function (LoF) screens using CRISPR and lentiviral shRNA technologies to identify clinically relevant drug resistance mechanisms in cancer. Here we will discuss the potential role for these in systematically defining the complete repertoire of genetic mechanisms of resistance for cancer drugs.

Competing interests

Founder and consultant, 14M Genomics.

11.45 - 12.10

Hall 1A

David Kent,
University of
Cambridge, UK

Tracking tumour evolution with clonal assays: mutation order matters

Cancers result from the accumulation of somatic mutations and their properties are thought to reflect the sum of these mutations. However, virtually nothing is known about whether or not the order in which these mutations are accrued has an impact on disease pathogenesis. Numerous important studies have discussed 'mutational order' as the stepwise accumulation of key mutations during tumourigenesis, with some mutations driving genetic instability (e.g. p53) and others priming specific subsequent mutations (e.g. genetic canalisation). We have recently demonstrated in human malignancies that the evolution of a tumour is also influenced by the order in which its mutations are acquired. Specifically, clinical presentation, risk of thrombosis, and clonal evolution are distinct in patients with myeloproliferative neoplasms who acquire JAK2V617F mutations prior to TET2 mutations compared to those that acquire TET2 mutations before JAK2V617F. We have now used clonal stem and progenitor cell assays to show that the impact of a given mutation is dependent on whether it is acquired in a wildtype or a single mutant cell, meaning that the consequences of each mutation are shaped by the effects of the preceding mutation. This new model is not only biologically compelling but also of significant clinical importance as knowledge of mutation order could predict stage of disease or treatment response based on the evolution of the stem cell compartment.

12.10 - 12.20

Discussion

● **Lifestyle behaviour and cancer prevention**

10.50 - 10.55

Room 3B

Eileen Kaner and
Linda Sharp, Newcastle
University, UK

Introduction

The session will outline current epidemiological and behavioural evidence on the relationship between different lifestyle behaviours and the development of a wide range of cancers in adults. We will also describe behaviour change interventions which can help to reduce cancer risk in patients and strategies which encourage lifestyle screening by practitioners to support the preventive agenda. To date, most focus has been on tobacco smoking and cancer development. This session will address increasing concern about other lifestyle risk factors such as heavy alcohol consumption, poor diet and low physical activity.

Symposia abstracts *(continued)*

10.55 - 11.20

Room 3B

Paolo Boffetta,

Icahn Medical Institute
at Mount Sinai, New
York, USA

How many cancers can we prevent through dietary modifications?

A recent review concluded that about 9% of all cancers in the UK are attributable to four dietary factors: low intake of fruits and vegetables, any consumption of meat, low intake of fibres, and high intake of salt. Other authors have reached different conclusions, from less than 1% to over 30%. Such a wide range reflects the uncertainties in the understanding of the relationship between dietary factors and human cancer, and the variability in the methods used to derive the estimates (e.g. choice of counterfactual, 'optimal' exposure distribution). A review of the evidence linking low fruit and vegetable intake to stomach cancer illustrates how differences in the criteria used by review panels have led to different conclusions on the causal nature of the association and its strength. Aspects such as opportunity for bias, exposure misclassification, residual confounding, biologically relevant timing, and statistical power are at the core of the interpretation of the evidence from observational studies. Furthermore, the association between diet and cancer, and its implications for cancer prevention, can be addressed at multiple levels, from micro- and macro-nutrients, to food and food group, to dietary patterns.

Competing interests

The author has consulted with the American Meat Institute Foundation (2011-2012) and the Quaker Oats Company (2013-2014).

11.20 - 11.45

Room 3B

Peter Anderson,

Newcastle University,
UK

Reducing exposure to alcohol to reduce cancer risk

Alcohol is a carcinogen, increasing the risk of cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colon, rectum, and female breast with dose response relationships varying from linear to exponential. Gram for gram, there is no evidence that risk is related to beverage type. Amongst 15-64 year old Europeans, 1 in 5 of all alcohol-related deaths are due to cancer; 8% of all male and 6% of all female cancer deaths are due to alcohol. At 14 grams of alcohol per day, the margin of exposure (MOE, which measures the ratio of the benchmark dose [lowest dose which is 95% certain to cause no more than a 10% cancer incidence in animals] to exposure) is 3.1 and at 54 grams a day is 0.8. The European Food Standards Authority considers an MOE based on animal studies for low risk to public health to be 10,000. For a voluntarily consumed produce such as ethanol, this can be dropped to 1,000. For Europeans, this would mean a consumption of about 50 mg ethanol a day, compared with an average consumption of 30 grams a day. It is unrealistic for a 600-fold reduction in alcohol consumption by Europeans, but progress can be made in reducing exposure by reducing the alcohol concentration of beverages, by introducing a minimum price per gram of alcohol consumed, and by reducing heavy drinking through primary health care driven advice and treatment programmes. All beverages should include a warning label stating that alcohol causes cancer.

11.45 - 12.10

Room 3B

Martin Wiseman,

World Cancer
Research Fund
International, London,
UK & University of
Southampton, UK

Physical activity, obesity and cancer

Prospective epidemiological observations consistently show a positive association between increasing Body Mass Index (BMI) and several cancers. This is interpreted by the World Cancer Research Fund (WCRF) Continuous Update Project (CUP) independent expert panel as reflecting an effect of increasing adiposity. Though curvilinear the relation is seen throughout the range of BMI reflecting a healthy weight, and beyond to overweight and obesity. The WCRF CUP has concluded that there is strong evidence that increasing adiposity is a contributory cause to 10 different cancers (postmenopausal breast, colorectum, advanced prostate, kidney, endometrium, gallbladder, oesophageal adenocarcinoma, pancreas, liver and ovary). Increasing physical activity reduces the likelihood of excess

adiposity, and so contributes indirectly to reducing risk of these cancers. There is mounting evidence that physical activity also has a direct protective effect in addition to its impact on adiposity against cancers of the breast (postmenopause), endometrium and colon. There is evidence that obesity promotes insulin resistance and increases exposure to growth factors, as well as generating a low grade systemic inflammatory response, both of which have tumour promoting potential. In addition, postmenopausal obesity promotes oestrogen production through the action of aromatase, which fosters tumour growth in hormone-sensitive tissues. Increasing physical activity also reduces inflammation and modulates metabolism of growth factors and their binding proteins to reduce cancer risk. In patients already diagnosed with breast cancer, obesity and low levels of physical activity are markers of adverse outcome, though it remains unclear whether or not these are causal factors in this context. Within England NIHR has established a Cancer and Nutrition infrastructure collaboration to help promote a coherent approach to translational research in nutritional aspects of cancer, from prevention through to management and palliation.

12.10 - 12.20

Discussion

● Molecular imaging and radionuclide therapy

10.50 - 10.55

Room 3A

Nandita deSouza,
The Institute of
Cancer Research &
The Royal Marsden
NHS Foundation Trust,
London, UK

Introduction

10.55 - 11.20

Room 3A

Katherine Vallis,
Cancer Research UK
and Medical Research
Council Oxford
Institute for Radiation
Oncology, UK

Molecularly targeted radiation therapy: towards individualised treatment

Molecularly targeted radiation therapy combines the cytotoxicity of ionising radiation with the targeting potential of molecular therapeutics and so enables individualised treatment. Recent clinically important advances in the field include the introduction of Ra-223 for the treatment of metastatic prostate cancer and the emergence of selective internal radiation therapy (SIRT) as an effective treatment for hepatic metastases.

The ionizing emissions from radionuclides used in cancer treatment include short-range electrons such as Auger and internal conversion electrons, beta electrons and alpha particles as well as gamma photons. Many factors contribute to the extent and pattern of radiation dose deposition following administration of radionuclide-based treatments. These include the physical properties of the radionuclide itself as well as the pharmacokinetics and the biodistribution at the whole body and organ level of the carrier molecule to which the radionuclide is conjugated. In some cases the extent of cellular uptake and intracellular distribution of radioactivity also determines the fate of targeted cancer cells. These complexities have hampered progress towards individualized treatment plans and rendered the development of rationale protocols for combining radionuclide therapy with external

Symposia abstracts *(continued)*

beam radiation therapy challenging. Many new radiopharmaceuticals are designed as theranostic agents, with dual imaging and therapeutic roles. A detailed understanding of the biodistribution and biological consequences of administration of radionuclides used in PET and SPECT probes is therefore also important.

We have developed new autoradiographic methods for detection of radionuclides in individual cells and 3D multicellular models at the nanometer to micrometer scale and have used Monte Carlo simulation to illuminate the biological consequences of differences in distribution. In this session the application of these methods to peptide-, antibody, and nano- and micro-particle based radiopharmaceuticals will be discussed.

11.20 - 11.45

Room 3A

Wim Oyen, The
Institute of Cancer
Research & The
Royal Marsden NHS
Foundation Trust,
London, UK

Translating novel diagnostic and therapeutic radiopharmaceuticals into the clinic

There is a continuous flow of novel radiopharmaceuticals originating from preclinical research which hold promise for human applications. Translation to the clinic may prove challenging and development into procedures used in routine patient care is demanding.

As most radiopharmaceuticals are used in subpharmacological doses, toxicity is a minor issue. Nevertheless, rules and regulations are highly similar to those applicable to non-radioactive drugs that aim at a pharmacological effects. This results in time-consuming development, requiring significant resources that hamper introduction of novel radiopharmaceuticals in clinical research.

Nevertheless, there are several examples of successful development of new radiolabelled agents. Somatostatin analogues can be considered the role model. After approval of the indium-111 labeled octreotide for somatostatin subtype receptor 2 imaging, a wealth of derivatives for imaging (first for SPECT and later for PET) as well as peptide receptor radionuclide therapy with Y-90 and Lu-177 labeled peptides were developed. It took many years to arrive at a registration trial for the therapeutic Lu-177 octreotate, which has been completed recently. A more recent example is the development of highly promising radiolabeled PSMA-ligands for imaging and treatment of prostate cancer.

Radiolabelled antibodies are another class of radiopharmaceuticals used for experimental cancer imaging and therapy. For-human-use antibody production with the sole purpose of nuclear medicine applications rarely occurs. The widespread use of unlabelled antibodies for treatment of many cancer types opened the door for molecular imaging with radiolabelled antibodies, mainly for translational research. The possibility to actually depict the receptor status and the targeting potential of these drugs is a very attractive concept to study heterogeneity of receptor expression and tumour penetration of the antibodies in vivo.

In conclusion, despite the non-trivial hurdles in bringing radiopharmaceuticals to the clinic, they are great assets for molecular imaging of cancer for characterisation of tumours, staging and therapy response prediction.

11.45 - 12.10

Room 3A

Joe O'Sullivan,
Queen's University
Belfast & Northern
Ireland Cancer
Centre, UK

Radium-223 for prostate cancer bone metastases: how research can change clinical practice

More than 90% of men with metastatic castrate resistant prostate cancer (mCRPC) have bone metastases, often as the only significant metastatic site. Bone metastases in prostate cancer can result in pain, pathological fracture, metastatic spinal cord compression and are the leading cause of prostate cancer mortality.

Bone targeted therapy in prostate cancer has included bone-seeking radionuclides for nearly 30 years. The beta-emitting bone-seeking radionuclides Strontium-89 and Samarium-153 EDTMP as well as Rhenium-186 HEDP and Rhenium-188 HEDP have been used to palliate pain in advanced cancer metastatic to bone for many years. Despite clear evidence of benefit in palliation, these agents have never been shown to result in a survival benefit for patients.

Radium-223 is the first in class alpha-emitting radionuclide which began clinical testing nearly 10 years ago and has recently been licenced for the treatment of symptomatic castration resistant prostate cancer (CRPC) metastatic to bone. In an international prospective randomised clinical trial, Radium-223 (50kBq/kg, for 6 cycles at 4 weekly intervals) + best standard of care (BOS) was shown to improve overall survival compared to placebo + BOS in men with symptomatic, metastatic CRPC. Radium-223 also resulted in significant improvement in time to symptomatic progression. Radium-223 was very well tolerated with very few serious toxicities recorded.

The rationale for using bone-targeted radionuclide therapy in CRPC will be discussed along with postulation on the likelihood of combination therapies using Radium-223. Because Radium-223 will be widely used in a very common cancer, there are opportunities for the development of the field of radionuclide therapy including the use of dosimetry-led prescribing of radionuclide.

Competing interests

Advisory board and Speaker's bureau: Astellas, Bayer, Janssen, Sanofi.

12.10 - 12.20**Discussion**

The Royal College of Radiologists proffered paper session

● The Royal College of Radiologists proffered paper session

12.30 - 12.35 Introduction
Hall 1C

12.35 - 12.50 DNA excision repair mediates adaptive response to low doses of ionising radiation in C57BL/6J mice
Hall 1C
Youssef Ismail, Canadian Nuclear Laboratories, Ontario, Canada

12.50 - 13.05 Biodistribution and radiation dosimetry of a novel ¹⁸F-fluoroethyl triazole [Tyr³] octreotate analogue for PET imaging in patients with advanced neuroendocrine tumours
Hall 1C
Suraiya Dubash, Imperial College, London, UK

13.05 - 13.20 Correlation of clinico-pathological outcomes with changes in IHC4 status after neo-adjuvant chemotherapy (NACT) for locally advanced breast cancers: do pre NACT ER/PR status act as better prognosticators?
Hall 1C
Animesh Saha, Tata Medical Center, Kolkata, India

13.20 - 13.35 Gain-of-function screens as a discovery tool for regulators of response to ionising radiation and novel drug targets
Hall 1C
Crispin Hiley, The Francis Crick Institute, London, UK

13.35 - 13.40 Discussion and winner announcement



The Royal College of Radiologists proffered paper session abstracts

12.30 - 12.35

Hall 1C

Introduction

● DNA excision repair mediates adaptive response to low doses of ionising radiation in C57BL/6J mice

12.35 - 12.50

Hall 1C

Youssef Ismail,
Canadian Nuclear
Laboratories, Ontario,
Canada

Background

Our previous studies showed that exposure to low dose gamma-radiation can increase life span and latency times for tumour formation in C57BL/6J mice. In this study, we examined whether this systemic radioadaptive response can be mediated by activated DNA repair mechanisms.

Method

For this study, we conducted in vivo mice experiments of damage stemming from external gamma radiation exposure. Repair of DNA double strand breaks was determined by measuring gamma-H2AX levels in splenic lymphocytes by flow cytometry and western blot. DNA excision repair including base (BER) and nucleotide (NER) excision repair were determined in spleen by: (1) DNA excision and synthesis repair functional assay, (2) gene expression quantitative PCR analysis, and (3) western blot analyses

Results

The results of our study indicate that exposure of mice to 20 or 100 mGy of gamma-radiation 24 h prior to a 2 Gy challenging dose did not result in enhanced repair of DNA double-strand breaks in splenic lymphocytes, measured as gamma-H2AX formation and loss by flow cytometry and western blot. In contrast, base (BER) and nucleotide excision repair (NER) rates, measured by the DNA excision and synthesis repair functional assay, were significantly higher in cells from low dose irradiated compared to non-irradiated mice. In quantitative RT-PCR experiments we measured expression levels of 84 key genes involved in various DNA repair pathways. We showed that only DNA excision repair genes were modulated by low dose radiation. Using western blot, we validated these results for Ddb1, Xpd, Rad51, Apex2 and Brca2 genes. Altogether, our data provide strong evidence that DNA excision repair is activated in response to low dose radiation in vivo.

Conclusion

Given our previous results showing increased tumour latency times following exposure to low dose radiation in the same experimental mouse model, our results suggest the role of BER and NER in increased genome stability and anti-tumour effects triggered by low dose radiation.

The Royal College of Radiologists proffered paper session abstracts *(continued)*

● Biodistribution and radiation dosimetry of a novel ^{18}F -fluoroethyl triazole [Tyr³] octreotate analogue for PET imaging in patients with advanced neuroendocrine tumours

12.50 - 13.05

Hall 1C

Suraiya Dubash,
Imperial College,
London, UK

Background

Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms. Despite advances, detection and quantification of NET activity by imaging remains a challenge, with no universally accepted imaging standard. We present the first in-man study of ^{18}F -fluoroethyl triazole [Tyr³] octreotate (^{18}F -FET- β AG TOCA) in NET patients to evaluate biodistribution, dosimetry, and safety.

Method

^{18}F -FET- β AG TOCA was synthesised via the click reaction (Iddon L et al, 2011). Nine patients (6 female, 3 male) were enrolled into study. Eight patients with sporadic NET and 1 MEN1 syndrome. Mean age 56 yr (range 35-73 yr) and weight 75.2kg (91.2-66.3 kg). Safety data was collected during and 24 hours post tracer administration. Patients underwent whole body PET-CT multi-bed scanning over 4 hours and venous blood samples taken at specific intervals to measure ^{18}F radioactivity concentration in blood and plasma. Regions of interest were drawn, to derive individual and mean organ residence times; effective dose (ED) was calculated with OLINDA 1.1.

Results

All patients tolerated ^{18}F -FET- β AG TOCA with no adverse events. Over 60% parent tracer was present in plasma at 60 minutes. High tracer uptake was observed in tumours (primary and metastases). Physiological uptake was seen in pituitary, salivary, thyroid and spleen, with low background uptake in liver, an organ where metastases commonly occur. The organs receiving highest absorbed dose were gallbladder, spleen, stomach, liver, kidneys and bladder. The calculated ED over all subjects was 0.029mSv/MBq (SD \pm 0.004).

Conclusion

We present the first in-man study of ^{18}F -FET- β AG-TOCA. The favourable safety, imaging and dosimetric profile makes it a valuable candidate in staging and management of NETs. Clinical studies in an expanded cohort are ongoing to clinically qualify this agent.

References

Synthesis and in vitro evaluation of [^{18}F]fluoroethyl triazole labelled [Tyr³]octreotate analogues using click chemistry. Iddon L, Leyton J, Indrevoll B, Glaser M, Robins EG, George AJ, Cuthbertson A, Luthra SK, Aboagye EO. *Bioorg Med Chem Lett.* 2011 May 15;21(10):3122-7.

● **Correlation of clinico-pathological outcomes with changes in IHC4 status after neo-adjuvant chemotherapy (NACT) for locally advanced breast cancers: Do pre NACT ER/PR status act as better prognosticators?**

13.05 - 13.20

Hall 1C

Animesh Saha,
Tata Medical Center,
Kolkata, India

Background

Differential expression of 4 immunohistochemical markers (IHC-4) i.e, oestrogen receptor (ER), progesterone receptor (PR), Her-2 receptor and Ki-67 in breast cancer is used as surrogate to molecular classification. The correlation of changes in IHC-4 following neoadjuvant chemotherapy (NACT) , to tumour pathological response rates (pCR) and disease relapse rates could lead to better understanding of tumour behaviour.

Method

Pre and post NACT IHC 4 status was analysed in 156 breast cancer patients. Response to chemotherapy was reported as per CAP recommendations 2009. Associations between IHC-4 before and after NACT were evaluated by using the McNemar test for ER, PR, HER-2 and a paired Student t-test for the Ki-67. Associations between the pCR to other categorical variables were assessed by using the chi-square tests or Fisher exact tests. Associations between pCR and the Ki-67 index were performed using the independent Student t-test. Kaplan-Myer plots were analysed to obtain relapse free survival (RFS).

Results

The median age was 48years. 25.3 % patients had pCR . Grade 3 tumours had a higher pCR (27.4%). ER and PR both positive tumours had the lowest (14.3%) pCR compared to tumours with both ER and PR negative (29%) or those with either ER or PR positive (38.6%). PR positivity was significantly associated with less likelihood of pCR (15% vs 34%). The pCR rate was lowest for LA subtype (13.68%) compared to 24.36%, 26.31%, 33.33% for LB, HE and TN subtypes respectively. There were significant reduction in expression of ER receptors and Ki-67 index post NACT. RFS of patients in whom the hormonal status changed from positive to negative was better compared to those who changed from negative to positive.

Conclusion

Changes in IHC 4 occur post NACT. pCR rates are lower in PR positive tumours and pre, not post, NACT HR status seemed to prognosticate RFS better.

Acknowledgements

The authors acknowledge the Department of Pathology and cCytogenetics for their immense support for this project.

References

- Barton S, Zabaglo L, A'Hern R, Turner N, Ferguson T, O'Neill S, Hills M, Smith I, Dowsett M (2012) Assessment of the contribution of the IHC4+C score to decision making in clinical practice in early breast cancer. *Br J Cancer* 106(11):1760-1765.
- Lee HC, Ko H, Seol H, Noh DY, Han W, Kim TY, Im SA, Park IA (2013) Expression of Immunohistochemical Markers before and after Neoadjuvant Chemotherapy in Breast Carcinoma, and Their Use as Predictors of Response . *J Breast Cancer* 16(4): 395-403. doi: 10.4048/jbc.2013.16.4.395.

The Royal College of Radiologists proffered paper session abstracts *(continued)*

● Gain-of-function screens as a discovery tool for regulators of response to ionising radiation and novel drug targets

13.20 - 13.35

Hall 1C

Crispin Hiley,
The Francis Crick
Institute, London, UK

Background

Radiotherapy, given with concurrent chemotherapy, remains the standard of care for patients with unresectable non-small cell lung cancer (NSCLC). Previous efforts to sensitise tumour cells to ionising radiation and improve the tumour control probability have focused predominantly on modulation of the DNA damage response.

Method

The primary objective of this study is to use a transposon based system for unbiased gain-of-function screens in NSCLC cell lines for discovery of genes involved radiation resistance. Transposons are mobile DNA elements that allow functional genomic screens. Using a piggyBac transposon system, which is highly efficient in mammalian cell lines, we have developed a system to switch on expression of genes located downstream of the transposable element. Identification of transposon integration sites can be determined with Sanger or Next Generation Sequencing following Splinkerette PCR. We are able to directly validate transposon-mediated activation of genes with RT-PCR using a unique sequence tag in transcripts expressed from the transposon promoter. The current workflow permits collection of surviving colonies following ionising radiation, enabling a resource for subsequent molecular studies on radio-resistance mechanisms. A panel of NSCLC are currently being screened to generate recurrent overlapping hits.

Results

Results from a pilot screen in the A549 cell lines have generated initial hits:

- RNF168 which ubiquitinates K13-15 on H2A/H2AX to drive DNA damage signalling
- SCM1 which has E3 Ubiquitin ligase activity for Histone H2A and for Geminin which is a regulator of DNA replication and mitotic progression via the APC/C
- KIAA0195 an uncharacterised transmembrane protein

Conclusion

Further data from genome wide screen coverage in multiple cell lines will be presented. Using the results from the TRACERx – Tracking Lung Cancer Evolution Through Therapy (NCT01888601) observational study we will assess the frequency of activating mutations and copy number gains in screen hits and their spatial heterogeneity to assess in-vivo relevance.

13.35 - 13.40

Discussion and winner announcement

Parallel sessions

● Cardiovascular toxicity in paediatric cancer treatment

Hosted by **Chris Plummer**, Freeman Hospital, Newcastle upon Tyne, UK

- 15.40 – 15.45** Introduction by the host
Room 4
- 15.45 – 16.10** Monitoring: How should we monitor our patients for cardiovascular toxicity? Serum biomarkers, imaging or both?
Room 4
Charlotte Manisty, University College London, University College London Hospital & Barts Heart Centre, London, UK
- 16.10 – 16.25** Proffered paper: Multiregion copy number analysis reveals Wilms' tumour genetic heterogeneity
Room 4
George Cresswell, The Francis Crick Institute, London, UK
- 16.25 – 16.50** Treatment: How should we treat our patients who develop cardiovascular toxicity? How could we have prevented it?
Room 4
Chris Plummer, Freeman Hospital, Newcastle upon Tyne, UK
- 16.50 – 17.05** Children's Cancer and Leukaemia Group (CCLG) McElwain Award winner: Adamantinomatous craniopharyngioma contains senescent cells with tumour-inducing potential
Room 4
Juan Pedro Martinez-Barbera, University College London, UK
- 17.05 – 17.30** Cardiovascular toxicity in paediatric cancer treatment
Room 4
Steven Lipschutz, Children's Hospital of Michigan & Wayne State University, Detroit, USA
- 17.30 – 17.40** Discussion

● Integration of germline genetic information can improve cancer diagnosis, treatment and prevention

Hosted by **Nazneen Rahman**, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, London, UK

- 15.40 – 15.45** Introduction by the host
Room 12
- 15.45 – 16.10** Integration of germline genetic information can improve cancer diagnosis, treatment and prevention
Room 12
Nazneen Rahman, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, London, UK
- 16.10 – 16.25** Proffered paper: Young patients with HER2+ breast cancer rarely have a germline mutation in a known cancer predisposition gene
Room 12
Diana Eccles, University of Southampton, UK
- 16.25 – 16.50** Interventional genetics
Room 12
John Burn, Newcastle University, UK
- 16.50 – 17.05** Proffered paper: Mutations in the transcriptional repressor REST predispose to Wilms tumour
Room 12
Shazia Mahamdallie, The Institute of Cancer Research, London, UK

Parallel sessions *(continued)*

17.05 – 17.30 Germline genomics and predisposition to serious adverse drug reactions with anti-cancer drugs
Room 12
Munir Pirmohamed, University of Liverpool, UK

17.30 – 17.40 Discussion

● **Largescale genomics trials**

Hosted by **Gary Middleton**, University of Birmingham, UK

15.40 – 15.45 Introduction by the host
Room 11

15.45 – 16.15 Master Protocols in lung cancer
Room 11
Fred Hirsch, University of Colorado Cancer Center, USA

16.15 – 16.30 Proffered paper: A national platform for molecular diagnostics: results from Phase I of the Cancer Research UK Stratified Medicine Programme
Room 11
Colin R. Lindsay, Cancer Research UK, London, UK

16.30 – 17.00 Lung cancer profiling: the end of the beginning
Room 11
Fabrice Barlesi, Aix Marseille University, Assistance Publique Hôpitaux de Marseille, France

17.00 – 17.30 Title to be confirmed
Room 11
Speaker to be confirmed

17.30 – 17.40 Discussion

● **Pancreatic and hepatobiliary cancers**

Hosted by **Roger Taylor**, University of Swansea & The Royal College of Radiologists, UK

15.40 – 15.45 Introduction by the host
Room 3A

15.45 – 16.20 Selective internal radiotherapy: microdosimetry, clinical research and patient advocacy
Room 3A
Ricky Sharma, University of Oxford & Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, UK

16.20 – 16.55 George Edelystyn Lecture: The future of radiation therapy for pancreatic and liver malignancies
Room 3A
Theodore S. Lawrence, University of Michigan, USA

16.55 – 17.30 Title to be confirmed
Room 3A
David Chan, University of Glasgow, UK

17.30 – 17.40 Discussion

● ‘Prevention is better than cure’: cancer chemoprevention in 2015

Hosted by **Jack Cuzick**, Queen Mary University of London, UK

- 15.40 – 15.45** Introduction by the host
Room 3B
- 15.45 – 16.10** Molecular risk stratification for aspirin chemoprevention
Room 3B
Andrew Chan, Massachusetts General Hospital, Boston, USA
- 16.10 – 16.25** Proffered paper: Signatures of ionising radiation in second malignancies
Room 3B
Sam Behjati, Wellcome Trust Sanger Institute, Cambridge, UK
- 16.25 – 16.50** Title to be confirmed
Room 3B
Dario Alessi, University of Dundee, UK
- 16.50 – 17.05** Proffered paper: A randomised trial of interventions to increase uptake of screening 25 year old non-attenders; final results of the STRATEGIC trial
Room 3B
Henry Kitchener, Institute of Cancer Sciences, University of Manchester, UK
- 17.05 – 17.30** Benefits and harms of preventive therapy for cancer
Room 3B
Jack Cuzick, Queen Mary University of London, UK
- 17.30 – 17.40** Discussion

● Single cell analysis: clinically useful or research tool?

Hosted by **Thierry Voet**, Wellcome Trust Sanger Institute, Cambridge, UK

- 15.40 – 15.45** Introduction by the host
Hall 1B
- 15.45 – 16.10** Circulating tumour cells and plasma DNA for non-invasive monitoring of cancers during their treatment
Hall 1B
Michael Speicher, Medical University of Graz, Austria
- 16.10 – 16.25** Proffered paper: Longitudinal single cell clonal analysis reveals evolutionary stasis and predetermined malignant potential in non-dysplastic Barrett’s Oesophagus
Hall 1B
Pierre Martinez, Barts Cancer Institute, Queen Mary University of London, UK
- 16.25 – 16.50** Title to be confirmed
Hall 1B
Ged Brady, Cancer Research UK Manchester Institute, UK
- 16.50 – 17.05** Proffered paper: Targeted next-generation sequencing: cell-free DNA profiles mirror the heterogeneity of single CTCs
Hall 1B
David Guttery, Department of Cancer Studies and Cancer Research UK Leicester Centre, UK
- 17.05 – 17.30** Title to be confirmed
Hall 1B
James Hicks, Cold Spring Harbour Laboratory, USA
- 17.30 – 17.40** Discussion

Parallel sessions *(continued)*

● The future role of primary care in cancer control

Hosted by **Greg Rubin**, University of Durham, UK



THE LANCET Oncology

15.40 – 15.50 Introduction by the host
Hall 1C

15.50 – 16.15 Primary prevention, symptomatic diagnosis and screening: roles for general practice and primary care
Hall 1C
David Weller, University of Edinburgh, UK

16.15 – 16.30 Proffered paper: Variations in GPs' decisions to investigate suspected lung cancer: a factorial experiment using multimedia vignettes
Hall 1C
Jessica Sheringham, University College London, UK

16.30 – 16.55 The future role of primary care in cancer control – survivorship care
Hall 1C
Annette Berendsen, University of Groningen, The Netherlands

16.55 – 17.20 It takes a team: the importance of integration between primary care and cancer specialist care
Hall 1C
Eva Grunfeld, Ontario Institute for Cancer Research, Toronto, Canada

17.20 – 17.40 Discussion

● Tumour:stroma interactions

Hosted by **Erik Sahai**, The Francis Crick Institute, London, UK

15.40 – 15.45 Introduction by the host
Hall 1A

15.45 – 16.10 Title to be confirmed
Hall 1A
Kairbaan Hodivala-Dilke, Queen Mary University of London, UK

16.10 – 16.25 Proffered paper: E-cadherin deficiency a novel determinant of ROS1 inhibitor sensitivity
Hall 1A
Ilijana Bajrami, The Institute of Cancer Research, London, UK

16.25 – 16.50 Targeting tumour angiogenesis by targeting Angiopoietin/Tie signalling: from vascular regression over vascular normalisation to stromal reprogramming therapies
Hall 1A
Hellmut G. Augustin, Vascular Oncology and Metastasis, German Cancer Research Center, Heidelberg (DKFZ-ZMBH Alliance), Vascular Biology and Tumor Angiogenesis, Medical Faculty Mannheim (CBTM), Heidelberg University & German Cancer Consortium (DKTK), Heidelberg, Germany

16.50 – 17.05 Proffered paper: CTEN (C-terminal Tensin-like) regulates head and neck cancer invasion and survival
Hall 1A
Jason Fleming, University of Southampton, UK

17.05 – 17.30 Intravital imaging reveals how stroma dictates heterogeneous responses to targeted therapy
Hall 1A
Erik Sahai, The Francis Crick Institute, London, UK

17.30 – 17.40 Discussion

Parallel session abstracts

● Cardiovascular toxicity in paediatric cancer treatment

15.40 – 15.45

Room 4

Chris Plummer,
Freeman Hospital,
Newcastle upon
Tyne, UK

Introduction

15.45 – 16.10

Room 4

Charlotte Manisty,
University College
London, University
College London
Hospital & Barts Heart
Centre, London, UK

Monitoring: How should we monitor our patients for cardiovascular toxicity? Serum biomarkers, imaging or both?

Survival rates from childhood cancers are now greater than 80%, and there is increasing recognition of the high incidence of late cardiotoxic effects even with modern cancer treatment regimens. Oncologists and cardiologists therefore have a responsibility to collaborate to improve the prevention, early detection and treatment of cardiotoxic effects during and following cancer treatment.

Although it is acknowledged that baseline cardiac investigations should be performed prior to starting potentially cardiotoxic treatment and that early detection and treatment is essential to prevent long term cardiac dysfunction, there is currently no evidence-based consensus for screening during cancer treatment, and the long-term cardiac follow-up of childhood cancer survivors is highly variable.

The current mainstay of cardiac monitoring involves echocardiography and measurement of serum cardiac biomarkers, most notably NT-proBNP and troponin. Conventional echocardiography however has significant limitations in that it has poor reproducibility and is unable to detect early subtle cardiac deterioration. This presentation will focus on current recommendations for monitoring during treatment and will present the recently-published international harmonised guidelines for screening for late cardiotoxic effects in childhood cancer survivors. It will also introduce novel imaging biomarkers for improving the early detection of subclinical cardiotoxicity, including LV strain measurements and cardiac MRI.

16.10 – 16.25

Room 4

George Cresswell,
The Francis Crick
Institute, London, UK

Proffered paper: Multiregion copy number analysis reveals Wilms' tumour genetic heterogeneity

Background

Understanding genetic heterogeneity in cancers, as well as their clonal evolution, allows us to understand biomarkers in the context of cancer development. Copy number variations (CNVs) can be used to track evolutionary events in cancers. We investigated genetic heterogeneity in the paediatric cancer Wilms' tumour by obtaining copy number profiles from multiple tumour regions. By comparing these profiles we were able to infer tumour evolution.

Method

Multiple snap-frozen samples were obtained from consecutive post-chemotherapy Wilms' tumour nephrectomy specimens at Great Ormond Street Hospital, May 2011-June 2013. The extracted DNA was analysed using Illumina CytoSNP-12 arrays for CNV and allelic imbalance. We used R and Bioconductor packages to estimate aberrant cell fraction, segment

Parallel session abstracts *(continued)*

the genome into regions of CNV across samples and to calculate allele specific copy numbers per region. MEDICC was used to perform intra-patient phylogenetic analysis of tumours.

Results

102 arrays from 21 Wilms' tumours were analysed in this study. We developed a robust analysis pipeline to identify comparable copy number changes across multiple tumour samples and assess phylogenetic relationships in our dataset. We found that all prospective Wilms' tumour biomarkers are variably heterogeneous. Furthermore, inferring clonal evolution highlights some well-characterised copy number changes as consistent early events in Wilms' tumourigenesis. Finally, Wilms' tumour phylogenetics potentially explain spatially different treatment response and histological heterogeneity.

Conclusion

Using a curated bioinformatics analysis we describe the genetic heterogeneity and evolutionary patterns of 21 Wilms' tumours. Overall, Wilms' tumours show a large variation in general patterns of genetic heterogeneity that may provide insight into future patient stratification. As well as describing these patterns, we also categorise important copy number alterations as early or late events in Wilms' tumourigenesis. This has implications for both understanding Wilms' tumourigenesis and choosing the appropriate strategy for genetic characterisation of this cancer in future clinical trials.

16.25 - 16.50

Room 4

Chris Plummer,
Freeman Hospital,
Newcastle upon
Tyne, UK

Treatment: How should we treat our patients who develop cardiovascular toxicity? How could we have prevented it?

The wide range of cancer treatments used in modern oncology practice result in a wide range of cardiovascular effects. These include changes in myocyte repolarisation, endothelial function, myocyte contractility and apoptosis. The incidence and mechanisms of these effects are incompletely understood. Although there are clearly marked differences in susceptibility between individuals, suggesting a genetic susceptibility, we are not yet able to predict who will be affected.

In many cases, toxicity can be managed by discontinuing the causative agent or treating the physiological effects to prevent complications. Anthracycline cardiovascular toxicity poses unique problems associated with late detection because, in routine clinical practice, myocyte damage is likely to be complete before signs and symptoms are evident. When the treatment regimen is already complete, it cannot be adjusted to reduce cardiovascular damage.

The randomised controlled trial evidence base for the prevention and treatment of cardiovascular toxicity from cancer treatment in children or adults is limited, but there are excellent data on the management of myocardial dysfunction and other toxicities caused by other disease processes. The presentation will review the evidence for the available treatments and potential preventative strategies. It will highlight areas of uncertainty and suggest future research to improve the understanding and management of these important iatrogenic toxicities.

16.50 – 17.05

Room 4

Juan Pedro Martinez-Barbera, University College London, UK**Children's Cancer and Leukaemia Group (CCLG) McElwain Award winner – Adamantinomatous craniopharyngioma contains senescent cells with tumour-inducing potential***Background*

Adamantinomatous craniopharyngioma (ACP) is a paediatric pituitary tumour that is associated with high morbidity due to the tendency of the tumour to infiltrate locally into surrounding brain structures such as the hypothalamus and visual tracts. We have developed and validated two mouse models for human ACP, which have provided original insights into the aetiology and pathogenesis of human ACP (1-3). Recently, we revealed a novel and intriguing mechanism by which Sox2+ve pituitary stem cells contribute to oncogenesis, which is fundamentally different to the classical cancer stem cell paradigm. When targeted to express oncogenic beta-catenin, mutant Sox2+ve stem cells do not give rise to the progeny populating the tumour, instead these oncogenic stem cells induce tumorigenesis in a paracrine manner (3). Our current research aims to dissect the molecular and cellular mechanisms underlying this paracrine involvement for stem cells in tumorigenesis.

Method

We use a multidisciplinary approach combining state-of-the-art mouse genetics with histological, molecular and stem cell biology methods. We use our ACP mouse models to investigate basic mechanisms, which are subsequently validated in human samples of ACP available to us through the GOSH hospital.

Results

Our research indicates that senescence and the senescence-associated secretory phenotype are critical players for tumour initiation. Specifically, we show that following a short burst of proliferation, oncogenic Sox2+ve cells stop dividing to form beta-catenin-accumulating cell clusters that become senescent. These clusters show senescence-associated beta-galactosidase activity, p53 pathway activation and up-regulate the expression of the cell cycle inhibitors p21 and p16. Additionally, cluster cells show elevated expression of lysosomal components and activate the autophagy pathway. Oncogenic beta-catenin also causes DNA damage as evidenced by an increase in H2A.X phosphorylation, triggering the DNA damage response. As a consequence, NF-kB signalling is elevated resulting in the expression of activation a Senescence-Associated Secretory Phenotype (SASP) with expression of multiple secreted factors including pro-inflammatory cytokines such as IL1, IL6 and IL8. Of translational significance, we show that this mechanism is relevant in human ACP tumorigenesis. Beta-catenin-accumulating cell clusters in human ACP express several senescence markers such as p21, p16 and lysosomal enzymes, exhibit DNA damage and activate P53, NF-kB and autophagy pathways, resulting in SASP activation.

Conclusion

Together, the mouse and human data suggest that senescence and SASP are likely to modify the tumour microenvironment resulting in cell transformation and tumour growth.

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Parallel session abstracts *(continued)*

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17.05 - 17.30

Room 4

Steven Lipshultz,
Children's Hospital
of Michigan & Wayne
State University,
Detroit, USA

Cardiovascular toxicity in paediatric cancer treatment

Children with cancer are now living longer due to advances in cancer treatments, but not without consequences. Anthracyclines, chemotherapy agents commonly used to treat solid and haematologic tumours, are associated with persistent and progressive cardiotoxicity. Collaborative efforts between oncologists and cardiologists are currently taking place to balance oncologic efficacy with the risks of cardiotoxicity to maximise the quality of life and survival for long-term survivors of childhood cancer. This presentation describes the epidemiology of cardiotoxicity in childhood cancer survivors, provides the latest evidence in prevention and surveillance, and suggests areas of future research.

17.30 - 17.40

Discussion

● **Integration of germline genetic information can improve cancer diagnosis, treatment and prevention**

15.40 - 15.45

Room 12

Nazneen Rahman,
The Institute of
Cancer Research &
The Royal Marsden
NHS Foundation Trust,
London, UK

Introduction

15.45 - 16.10

Room 12

Nazneen Rahman,
The Institute of
Cancer Research &
The Royal Marsden
NHS Foundation
Trust, London, UK

Integration of germline genetic information can improve cancer diagnosis, treatment and prevention

Genes in which germline mutations confer substantial increased risks of cancer are called cancer predisposition genes (CPG). To date CPG testing and characterisation of CPG cancers has been relatively limited. In particular, tumour sequencing studies have typically used the germline data generated merely as an exclusion filter to remove non-somatic variants, and have not exploited opportunities to research the germline contribution to oncogenesis. Using data from >5000 individuals with cancer tested for a panel of cancer predisposition genes and >7000 tumours analysed by exome sequencing I will demonstrate how integration of information can improve cancer diagnosis, treatment and prevention.

16.10 – 16.25

Room 12

Diana Eccles,
University of
Southampton

Proffered paper: Young patients with HER2+ breast cancer rarely have a germline mutation in a known cancer predisposition gene

Introduction

Young age at diagnosis for breast cancer raises the question of genetic susceptibility. We explored breast cancer susceptibility genes testing amongst patients with HER2 amplified invasive breast cancer aged 40 years or younger.

Methods

Patients from selected from the POSH study (1) were aged ≤ 40 at diagnosis with confirmed HER2 amplified breast cancer. The probability of finding a BRCA gene mutation was calculated based on family history. Genetic testing was either clinical testing for BRCA1 and BRCA2 with a subset also tested for TP53 mutations, or research based testing using a typical panel comprising 17 breast cancer susceptibility genes (CSGs) including BRCA1, BRCA2 and TP53.

Results

There were 591 eligible patients. Clinical testing results were available for 133 cases, an additional 263 cases had panel testing. BRCA testing across 396 cases found 8 BRCA2 (2.0%) and 5 BRCA1 (1.2%) pathogenic mutations. Of 290 tested for TP53 mutations overall 9/290 (3.1%) had deleterious TP53 mutations.

Of 396 patients, 101 (25.5%) met clinical criteria for BRCA testing ($\geq 10\%$ probability), amongst whom BRCA testing yielded 11% with pathogenic BRCA mutations (6 BRCA2, 5 BRCA1), where probability was $< 10\%$, only 4/295 (1.32%) had BRCA mutations. Amongst the 59 patients meeting the 10% threshold who had TP53 testing, there were 7 mutations (12.5%). Likely functionally deleterious mutations were present in 12/263 (4.56%) of 14 lower penetrance CSGs in the panel.

Conclusions

Patients under 41 at diagnosis with HER2+ breast cancer and no family history of breast cancer can be reassured that they have a low chance of being a high risk gene carrier. If there is a strong family history, not only BRCA but also TP53 gene testing should be considered. The clinical utility of testing lower penetrance CSGs remains unclear.

References

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16.25 – 16.50

Room 12

John Burn, Newcastle
University, UK

Interventional genetics

The advance of genomics into clinical genetics and oncology is exposing the need to adapt clinical practice. Clinical genetics has tended to focus on diagnosis and prognosis, leaving therapeutic intervention to others. The strengthening evidence of major cancer prevention with aspirin in those at high genetic risk demands a shift towards prescription alongside prediction.

Hereditary tumours are an ideal target for interventional trials given the specificity of the molecular mechanism and enthusiasm of patients. Trk inhibitors can be tested in cylindromatosis patients by comparing tumours in the same patient exposed to placebo and active agent.

Parallel session abstracts *(continued)*

“All cancer is genetic” yet tumour and germline DNA collection in routine oncology practice remains the exception rather than the rule. The pivotal role of genomics in future cancer management demands a system change in our approach to the organisation of laboratory services and the care of patients. A novel method of extracting DNA quickly and cheaply at the clinical interface will be presented as a contribution to making interventional genetics a routine reality.

16.50 - 17.05

Room 12

Shazia Mahamdallie,
The Institute of Cancer
Research, London, UK

Mutations in the transcriptional repressor REST predispose to Wilms tumour

Background

Wilms tumour is the most common childhood renal cancer, affecting 1 in 10,000 children. Whilst Wilms tumour is primarily a non-familial condition, about 2% of cases have one or more relatives that have also had Wilms tumour. Only a small proportion of familial cases are due to WT1 mutations, epigenetic 11p15 defects, or autosomal recessive conditions that include Wilms tumour. In addition, rare germline DICER1 mutations have been identified in Wilms tumours of pleiotropic tumour syndromes, and mutations in CTR9 were recently identified as a rare cause of familial Wilms tumour. Furthermore, two familial Wilms tumour loci have been mapped by genome-wide linkage analysis to chromosomes 17q12-q21 and 19q13, but the causative genes remain elusive. Therefore, additional genetic causes of Wilms tumour remain to be discovered.

Method

To identify genes that predispose to Wilms tumour we conducted exome and Sanger sequencing studies.

Results

We identified 11 different inactivating mutations, in the RE1 Silencing Transcription factor, REST, in four familial Wilms tumour pedigrees and nine non-familial cases. Notably, no similar mutations were identified in the ICR1000 UK control series (13/558 vs 0/993; $P < 0.0001$), nor the ExAC series (13/558 vs 0/61312; $P < 0.0001$). A second mutational event was identified in two tumours, suggesting REST may act as a tumour suppressor gene in Wilms tumour pathogenesis. REST is a zinc finger transcription factor that functions in cellular differentiation and embryonic development. 10 of 11 mutations clustered within the DNA binding domain of REST and functional analyses revealed that they compromise REST transcriptional repression.

Conclusion

We demonstrate that germline REST mutations account for ~8% familial (4/52) and ~2% non-familial (9/519) Wilms tumour, the largest contribution to familial Wilms tumour known to date and are equivalent in contribution to non-familial Wilms tumour to WT1. This study will allow clinical genetic testing and targeted screening to at-risk children.

Shazia Mahamdallie¹, Sandra Hanks¹, Kristen Karlin^{2,3}, Anna Zachariou¹, Elizabeth Perdeaux¹, Elise Ruark¹, Chad Shaw³, Alexander Renwick³, Emma Ramsay¹, Shawn Yost¹, Anna Elliot¹, The Wilms Tumor Susceptibility Collaboration (WTSC)¹, Michael Capra⁴, Thomas McLean⁵, Anthony Renwick¹, Sheila Seal¹, Charles Stiller⁶, Neil Sebire⁷, Thomas Westbrook^{2,3}, Nazneen Rahman^{1,8}

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17.05 - 17.30

Room 12

Munir Pirmohamed,
University of
Liverpool, UK**Germline genomics and predisposition to serious adverse drug reactions with anti-cancer drugs**

The benefit-risk profile of drugs is important in every disease area including cancer. As cancer therapy becomes more effective, it is important to understand the mechanisms behind serious adverse drug reactions associated with anti-cancer drugs in order to further improve the benefit-risk ratio, and reduce cancer survivor issues. Using the germline genome to identify predisposing factors for adverse drug reactions has seen major advances in non-cancer areas, but perhaps less so in cancer. The identification of a genetic predisposing factor for an adverse drug reaction may have several benefits: (a) a better understanding of the mechanism of toxicity, which may allow the development of interventional agents, but will also feed into future drug development; and (b) the development of predictive testing which could then be used prior to drug prescription to optimise both the choice and dose of drug. Both these scenarios require the identification and recruitment of deeply phenotyped patients, a major limitation at present. For predictive testing, a validated genetic test is required together with an appropriate interventional strategy to reduce harm (increased monitoring, alteration of dose or different drug choice). These areas will be considered in the talk focusing on anti-cancer drugs, but comparing and contrasting with non-cancer therapeutic areas.

17.30 - 17.40**Discussion**● **Largescale genomics trials****15.40 - 15.45**

Room 11

Gary Middleton,
University of
Birmingham, UK**Introduction****15.45 - 16.15**

Room 11

Fred Hirsch, University
of Colorado Cancer
Center, USA**Master protocols in lung cancer**

In order to speed up the identification of new active drugs and the approval process, the US National Cancer Institute, FDA, representatives from academic institutions and the industry met in February 2012 to discuss "How to integrate biomarkers into clinical trial designs". The conclusion from this meeting was to develop "Masterprotocols in Lung Cancer". Through unique public-private partnerships, several Masterprotocols were developed:

- LungMAP; a protocol for patients with advanced squamous lung cancer, 2. Line (SWOG 1400)
- ALCHEMIST study: an adjuvant study for early stage adenocarcinomas.
- NCI-MATCH-trial: a biomarker driven clinical study across organs.

Several other Masterprotocols are under development:

- ALK- Masterprotocol
- Small Cell Lung Cancer Masterprotocol
- The Masterprotocol concept and the individual protocols will be discussed.

Parallel session abstracts *(continued)*

16.15 - 16.30

Room 11

Colin R. Lindsay,
Cancer Research UK,
London, UK

Proffered paper: A national platform for molecular diagnostics: results from Phase I of the Cancer Research UK Stratified Medicine Programme

Background

There is an increasing demand for early analysis of multiple prognostic and predictive genetic markers in patient tumour samples. Phase I of the Cancer Research UK Stratified Medicine Programme (SMPI) was designed to develop a platform to incorporate molecular diagnostics into the normal pathway of patient care and demonstrate the applicability of a nationwide testing network, with results linked to healthcare records and held in a central database.

Method

From August 2011 to June 2013, patients with breast, colorectal, prostate, lung or ovarian cancer, or metastatic melanoma, were approached at 26 hospitals for consent to molecular testing of tumour samples in three centres. Formalin-fixed paraffin-embedded sections and peripheral blood samples were collected for analysis of a small panel of molecular aberrations in driver genes. Results were transmitted directly to participating clinical centres for inclusion in medical records. An agreed clinical dataset was obtained for all patients and stored using the English national cancer registration system. Sequence mutations were assessed by Sanger sequencing, pyrosequencing or screening methods (BRAF, DDR2, EGFR, KIT, KRAS, NRAS, PIK3CA, PTEN, TP53). Gene rearrangements were assessed by fluorescent in situ hybridisation (ALK and Tmprss2-ERG).

Results

10754 patients (98% of those approached) consented, with 9010 samples sent for analysis. Confirming a level of quality in the clinical data and corresponding genetic analysis, the results across all six cancers are consistent with what has been reported previously: examples include near-mutual exclusivity of EGFR mutation (8.3% of samples) and ALK rearrangement (1.9%) in NSCLC (1889 samples in total), and KRAS (39%), NRAS (4%) and BRAF mutation (11%) in colorectal cancer (1605 patients). We also observed significantly high levels of TP53 mutation in late stage breast (75% incidence in stage IV, 1873 patients) and colorectal cancer (64% incidence in stage IV), and high levels of BRAF mutation (39%, 52 patients) in mucinous colorectal cancer. With large patient numbers facilitating an examination of gene-gene and genetic-clinical correlations on a largely unselected population-wide level, SMP1 also offers a number of novel insights which will require future validation: a high incidence of KRAS mutation (37%) in UK lung adenocarcinoma, a significant elevation of TP53 mutation in ductal carcinoma of the breast (27%; 1425 patients) compared to lobular carcinoma of the breast (3%, $p < 0.0001$; 179 patients), and similar rates of genetic aberrations between superficial spreading and nodular melanomas. Correlations between survival and genetic modification will be presented with a minimum of 2 years follow up.

Conclusion

Here we report the first UK-wide study assessing the molecular drivers of cancer within nationalised healthcare systems. We have confirmed the feasibility of incorporating molecular diagnostics in the normal pathway of UK cancer care. SMP1 features large patient numbers and offers a unique dataset, unrepresented in other genomic studies: one that is not subject to planned selection bias and features large patient numbers.

Acknowledgements

Funding for the Stratified Medicine Programme is acknowledged from Cancer Research UK and programme founding partners AstraZeneca and Pfizer. Thanks to National Cancer

Registration Service – Eastern Office and the University of Oxford Department of Computer Science for hosting the Stratified Medicine Programme data.

16.30 – 17.00

Room 11

Fabrice Barlesi,
Aix Marseille
University, Assistance
Publique Hôpitaux de
Marseille, France

Lung cancer profiling: the end of the beginning

Lung cancer genotyping is now largely offered to advanced lung cancer patients worldwide.

Various types of genotyping programmes have been developed either by academic institutions, academic consortiums, private companies or national cancer institutes. Globally, between the half and two-thirds of the tested tumours harbour a genetic alteration that could potentially be targeted by commercially available drugs or compounds assessed in clinical trials.

Beside the molecular profile issued from these large genotyping projects, the impact of these large genotyping initiatives on patients' outcomes, and especially patients' survival, is essential. Results available to date, both in the Lung Cancer Mutation Consortium study and the Biomarkers France study, are clearly encouraging.

However, many questions remain to be solved (targets? optimal technique(s)? turnaround time? sampling? assessment of resistances? Etc.) and are currently assessed through activated or planned clinical trials worldwide, either in the adjuvant or the metastatic setting. A review of already activated and planned clinical trials will give a good view of the challenges to be faced in this new era of the management of lung cancer patients.

17.00 – 17.30

Room 11

Speaker to be
confirmed

Title to be confirmed

Abstract not received.

17.30 – 17.40

Discussion

● **Pancreatic and hepatobiliary cancers**

15.40 – 15.45

Room 3A

Roger Taylor,
University of Swansea
& The Royal College
of Radiologists, UK

Introduction

Parallel session abstracts *(continued)*

15.45 - 16.20

Room 3A

Ricky Sharma,
University of Oxford
& Cancer Research
UK and Medical
Research Council
Oxford Institute for
Radiation Oncology, UK

Selective internal radiotherapy: microdosimetry, clinical research and patient advocacy

Knowledge that liver tumours preferentially take their blood from the host's arterial blood supply rather than the portal venous system can be used for local delivery of treatment or for embolisation to cut off the blood supply to tumours. Over the past two decades, this fundamental knowledge has resulted in the development of new ways of delivering brachytherapy to tumours via their arterial blood supply using radioisotopes such as yttrium-90 and holmium-166. Selective internal radiation therapy (SIRT) of primary or secondary liver malignancies can be performed with yttrium-90 microspheres, a treatment also termed radio-embolisation. Differences in the dosimetry that can be achieved between resin and glass microspheres will be discussed in this talk. Patient advocacy has resulted in these medical devices being evaluated by the NHS via the Commissioning through Evaluation programme. Using SIRT as an example, registry-based models to accelerate the introduction of new medical technologies will be discussed. Finally, the extensive portfolio of Phase III clinical studies of SIRT in metastatic colorectal cancer and hepatocellular carcinoma will be summarised. Results from patients who have proceeded to liver surgery following SIRT confirm that the principal mechanism of action appears to be via arterially directed delivery of highly radioactive microspheres in and around the vascular tumour bed rather than by micro-arterial embolisation.

Competing interests

Professor Sharma is the Chief Investigator for the FOXFIRE clinical trial funded by Cancer Research UK and Sirtex Medical, and for the EPOCH clinical trial funded by BTG plc.

16.20 - 16.55

Room 3A

Theodore S. Lawrence,
University of Michigan,
USA

George Edelstyn Lecture: The future of radiation therapy for pancreatic and liver malignancies

Although pancreatic cancer and hepatocellular cancer (HCC) differ in their natural history, both present significant issues in local control. Only a small minority of patients can undergo resection or, in the case of HCC cancer, transplantation. Thus, a significant fraction of patients with liver cancer die of uncontrolled local disease. Even in the case of pancreatic cancer, which has a strong tendency to metastasise, up to one third of patients were found to have died of local disease at autopsy (Iacobuzio-Donahue CA, et al. J Clin Oncol. 2009;27:1806). Until recently, radiation therapy has played a limited role in the treatment of HCC because of the inability to safely deliver high doses to the tumour without producing injury to the uninvolved liver, which is often cirrhotic. Likewise, the location of the pancreas makes it difficult to deliver tumouricidal doses without injuring the intestine. Recent advances in technology, especially stereotactic body radiation therapy, now permit higher doses to be more safely administered, but treatment is still based on the average tumour and normal tissue sensitivities. We are now entering an era of precision radiation medicine, which is beginning to permit the individualisation of treatment. We have taken two approaches toward personalised radiation therapy. The first is the use of targeted drugs that selectively abrogate the radiation-induced DNA damage responsive in pancreatic and HCC cells, compared to normal cells, thus leading to cancer-selective cytotoxicity. The second approach is to adapt therapy to the individual patient response. We assess subclinical changes in global liver function after the delivery of 60% of the treatment and use this to predict the effect of the entire course. If the liver would be injured by the current course, we attenuate the latter 40% of treatment and avoid toxicity. In our newest protocol, we are evaluating changes in dynamic contrast-enhanced MRI to determine which parts of the tumour are resistant to therapy, and thus need to receive intensified dose during the latter part of treatment, and which parts of the liver are showing injury, and thus need to be spared. These predictions are improved by assessing changes in other indicators of response such as plasma cytokines and miRNAs. For

pancreatic cancer, we are evaluating whether changes in diffusion MRI and in circulating tumour cells during the course of treatment can predict the success of tumour control and reveal resistant regions of the tumour. We hope that by targeting cancer specific pathways and by adapting treatment to the individual patient response, we can help to usher in a new era of precision radiation medicine that will increase cure rates and decrease toxicity in the treatment of pancreatic cancer and HCC as well as other cancers.

16.55 - 17.30

Room 3A

David Chan, University
of Glasgow, UK

Title to be confirmed

Abstract not received.

17.30 - 17.40

Discussion

● **‘Prevention is better than cure’: cancer chemoprevention in 2015**

15.40 - 15.45

Room 3B

Jack Cuzick,
Queen Mary University
of London, UK

Introduction

15.45 - 16.10

Room 3B

Andrew Chan,
Massachusetts General
Hospital, Boston, USA

Molecular risk stratification for aspirin chemoprevention

Remarkably consistent experimental and epidemiologic evidence demonstrates that aspirin is associated with a lower risk of colorectal cancer. Five placebo-controlled randomised controlled trials (RCTs) among individuals with a history of colorectal neoplasia showed that aspirin reduced the risk of recurrent adenomas, the precursors of the vast majority of cancers. Additionally, data from long-term follow-up of a RCT of aspirin among individuals with the Lynch hereditary colorectal cancer syndrome and a RCT of aspirin among women for primary prevention of cardiovascular disease and cancer demonstrated a lower risk of colorectal cancer associated with randomised aspirin treatment. Nonetheless, current clinical guidelines recommend against the routine use of aspirin to prevent colorectal cancer in individuals at average risk largely due to concerns about its potential gastrointestinal toxicity. In concert with broader efforts to tailor prevention strategies, our group has led several studies into the mechanistic basis of aspirin’s anti-cancer effect that has led to the development of intratumoural, germline, and circulating molecular correlates of outcomes. Such biomarkers can be exploited for risk stratification to more effectively target aspirin chemoprevention for those with more favourable risk-benefit profiles. In this presentation, we will review the evidence supporting a role for aspirin in the prevention and treatment of cancer, with a focus on novel strategies for molecular risk stratification.

Competing interests

Consultant for Bayer Healthcare.

Parallel session abstracts *(continued)*

16.10 - 16.25

Room 3B

Sam Behjati,
Wellcome Trust Sanger
Institute, Cambridge,
UK

Proffered paper: Signatures of ionising radiation in second malignancies

Background

Buried within the genomes of radiation-associated second malignancies are the somatic mutations generated by ionising radiation. It is conceivable that some of these are discernible as distinct mutation signatures, which we aimed to define.

Method

We performed whole genome sequencing of 4 different types of radiation-associated second malignancies: 4 osteosarcomas; 3 breast cancers; 2 spindle cell sarcomas; 3 angiosarcomas. We defined all classes of somatic mutations using the analysis pipeline of the Cancer Genome Project, supplemented by bespoke pattern and statistical analyses. We compared our findings to 319 radiation-naïve tumours processed by the same analysis pipeline. We extended our findings to metastatic prostate tumours from 10 patients, half of whom received ionising radiation treatment prior to metastases formation.

Results

Overall the tumour genomes were diverse and displayed somatic changes specific to each tumour type. Against this backdrop of genomic diversity, we identified two mutation signatures that characterised radiation-associated second malignancies, irrespective of tumour type. We found a significant enrichment of deletions in radiation-associated malignancies ($p=1.93 \times 10^{-15}$, linear mixed effects model). Compared to radiation-naïve deletions, these were of larger size and distributed more evenly across the genome. Further, radiation-associated genomes harboured a significant excess of balanced inversions, a rare type of rearrangement ($p = 2 \times 10^{-16}$, generalised linear model). We were able to extend these findings into metastatic prostate tumours, comparing radiation-treated with radiation-naïve patients.

Conclusion

In tumours associated with ionising radiation we identified a highly significant enrichment of two mutation signatures, an excess of deletions and of balanced inversions. As these were present across tumour types, it seems likely that they represent genomic signatures of ionising radiation. A future challenge will be to explore the utility of our findings as genomic markers of radiation exposure, for example, as diagnostic adjuncts or in determining the burden of radiation-associated tumours at population level.

Acknowledgements

Wellcome Trust. Skeletal Cancer Action Trust.

16.25 - 16.50

Room 3B

Dario Alessi,
University of
Dundee, UK

Title to be confirmed

Abstract not received.

16.50 – 17.05

Room 3B

Henry Kitchener,
Institute of Cancer
Sciences, University
of Manchester, UK

A randomised trial of interventions to increase uptake of cervical screening among 25 year old non-attenders; final results of the STRATEGIC trial

Background

Cervical screening coverage amongst women has been falling in the UK and internationally, risking not only a rising incidence of cervical cancer in non-vaccinated women but also reduced engagement with cervical screening in later years.

Method

Following a pilot study, which demonstrated that self-sampling (SS) for HPV testing, timed appointments (TA), and choice between a nurse navigator (NN) or SS offered were all feasible and associated with increased uptake amongst non-attenders (6 months following their first invitation), a cluster randomised trial evaluated the effectiveness of these interventions in Greater Manchester and in Aberdeen, where HPV vaccinated teenagers have become eligible for cervical screening. General practices were randomised to one of five interventions; a) a SS sent unsolicited b) SS on request, c) NN, d) choice between the latter two or e) TA. A control group of practices had no interventions. Interventions were offered by a personalised letter from the NHS Screening Agency. The primary outcome was uplift in cervical screening 12 months following the intervention.

Results

272 general practices were randomised. SS kits were sent to 1139 women and offered to 1308. 1027 were offered a NN, 1282 a choice between NN and SS. TA's were offered to 1560, 4066 acted as a control group. The uplift for each intervention was: SS sent, 20.8%; SS offered, 19.3%; NN 17.0%; and choice, 23.6%. None of these demonstrated a significant increase in uptake compared with controls (21.3%), with odds ratios of 0.98, 0.99, 0.80, 0.95, 1.1 respectively. In the Aberdeen cohort, incompletely and completely vaccinated women had a significantly increased uptake compared with unvaccinated; OR's 2.19 ($p=0.036$) and 2.5 ($p=0.001$) respectively.

Conclusion

This large controlled study has not shown any benefit of interventions designed to increase uptake of cervical screening in young women receiving their initial invitation. Vaccinated women showed significantly greater uptake.

Acknowledgements

Funding: STRATEGIC was funded by NIHR HTA.

17.05 – 17.30

Room 3B

Jack Cuzick,
Queen Mary University
of London, UK

Benefits and harms of preventive therapy for cancer

The development of preventive therapy for cancer is still in its infancy, and much can be learned from cardiovascular medicine, where it has now become firmly established. This is due to the existence of agents with clearly proven efficacy and minimal side-effects, such as the statins for cholesterol-lowering and the anti-hypertensive agents to control blood pressure. For cancer, with the exception of vaccination against the human papillomavirus to prevent cervix cancer and hepatitis B to prevent liver cancer, currently available efficacious medicines carry a higher side-effect profile, and minimally toxic agents do not have well established efficacy profiles.

Because most effective cancer preventive agents carry a toxicity burden it becomes very important to target preventive therapy to individuals who stand to benefit most. This has two major elements: an accurate risk assessment to identify those at greatest risk of a given cancer,

Parallel session abstracts *(continued)*

and an ability to identify those at greatest risk of side-effects in order to avoid treatment or to take special precautions, such as those predisposed to gastrointestinal bleeding for aspirin.

In this talk I contrast two different cases for preventive therapy – aspirin and endocrine therapy. For aspirin the benefits are seen for a range of different cancers, making identification of high risk individuals difficult. For most individuals there are no side effects and the potential benefits outweigh the potential harms, but it is highly desirable to identify the small subset most likely to suffer side effects (gastrointestinal and cerebral bleeding) and to not offer aspirin to them.

In the case of endocrine agents such as tamoxifen or the aromatase inhibitors, the benefit is expected only for breast cancer and minor side effects are common and rare but serious side effects also exist so that the identification of high risk individuals for this cancer becomes a key priority.

Competing interests

Professor Jack Cuzick's institution received research support from AstraZeneca and Aventis.

17.30 - 17.40

Discussion

● **Single cell analysis: clinically useful or research tool?**

15.40 - 15.45

Hall 1B

Thierry Voet,
Wellcome Trust
Sanger Institute,
Cambridge, UK

Introduction

15.45 - 16.10

Hall 1B

Michael Speicher,
Medical University of
Graz, Austria

Circulating tumour cells and plasma DNA for non-invasive monitoring of cancers during their treatment

Circulating tumour cells (CTCs) and circulating tumor DNA (ctDNA) offer a unique opportunity for serially monitoring tumour genomes in a non-invasive fashion from the peripheral blood of patients with cancer, a method which is therefore frequently referred to as a “liquid biopsy”. In order to make whole-genome analysis from plasma DNA amenable to clinical routine applications, we perform whole-genome sequencing from plasma at a shallow sequencing depth to establish a genome-wide copy number profile of the tumour at low costs within 2 days. We termed this approach plasma-Seq. In parallel, we sequence a panel of high-interest genes and introns with frequent fusion breakpoints with high coverage. CTCs are subjected to whole-genome amplification (WGA) and the WGA products can be analysed by similar means. To facilitate the biological and clinical interpretability, we have developed bioinformatics tools for pathway analysis and tumour genome stratification based on liquid biopsy data. Data of our liquid biopsy analyses derived from breast (n=139 plasma samples) and prostate cancer (n=176 plasma samples) will be presented, which includes comparisons of results obtained using CTCs and ctDNA as well as novel insights about the plasticity and dynamics of clonal evolution of tumour genomes.

16.10 - 16.25

Hall 1B

Pierre Martinez,
Barts Cancer Institute,
Queen Mary University
of London, UK

Proffered paper: Longitudinal single cell clonal analysis reveals evolutionary stasis and predetermined malignant potential in non-dysplastic Barrett's Oesophagus*Background*

Endoscopic surveillance of the premalignant condition Barrett's Oesophagus provides a unique opportunity to study the evolution of a solid human neoplasm over both space and prolonged periods of time. Here we report the pattern of longitudinal clonal evolution occurring in a large cohort of 195 non-dysplastic Barrett's patients followed for a median duration of 43 (range: 11-130) months.

Method

Multicolor fluorescence in situ hybridization was used to obtain single-cell genetic profiles from at least two different time points from each patient. We calculated several genetic diversity metrics and used uni- and multivariate analyses, Kaplan-Meier survival curves and resampling analyses to assess the relevance of our findings. We estimated clone size by multiplying clonal frequencies by segment area estimates.

Results

We found that the level of genetic diversity in the population remained relatively stable over time with only one detectable clonal expansion every 36.8 patient years. These clones grew at an average of 2.1mm per year. Nevertheless, the non-dysplastic Barrett's lesions proved to be in a dynamic equilibrium whereby existing clones were continually lost and replaced by new clones. Strikingly, the baseline level of genetic diversity was a significant predictor of progression risk that outperformed all other single-marker measures.

Conclusion

Our results indicate a lack of strong selection for mutant clones within the Barrett's segment, while a high initial diversity status predicts future progression risk. These data challenge the existing stepwise model of carcinogenesis in solid tissues, and even argue against the prior model of neoplastic progression as a series of selective sweeps. Our results, consistent with other recent findings, suggest that clonal expansions are rare and slow growing, and that the malignant potential of a 'benign' Barrett's lesion is predetermined within this observational timeframe. These observations have important consequences for managing cancer risk in Barrett's patients.

16.25 - 16.50

Hall 1B

Ged Brady,
Cancer Research
UK Manchester
Institute, UK

Title to be confirmed*Abstract not received.*

Parallel session abstracts *(continued)*

16.50 - 17.05

Hall 1B

David Guttery,

Department of Cancer
Studies and Cancer
Research UK Leicester
Centre, UK

Proffered paper: Targeted next-generation sequencing: cell-free DNA profiles mirror the heterogeneity of single CTCs

Background

Cell-free DNA (cfDNA) and circulating tumour cells (CTCs) can provide a “liquid biopsy” as a surrogate for the tumour for real-time monitoring of patients with cancer. We aimed to compare single CTCs and a pool of CTCs isolated from CellSearch cassettes with matched cfDNA by targeted NGS.

Method

CTCs were enriched and enumerated by CellSearch® from 7.5 ml of blood from 2 MBC patients with >100 CTCs. For one patient, five single CTCs and 5 lymphocytes were isolated by DEPArray™, and DNA was isolated and whole genome amplified (WGA) using the Ampli1 WGA kit (Silicon Biosystems). DNA was extracted from a pool of CTCs for the other patient. Matched cfDNA was analysed for both patients. Targeted NGS was performed with 2 amplicon panels (Ampli1 and a focused, custom mutation panel (1)) using the Ion PGMTM platform.

Results

Molecular heterogeneity was observed in the 5 single CTCs. Of note, 2 CTCs had both a PIK3CA p.H1047R and an ESR1 p.E380Q mutation, which were absent from the other 3 CTCs, although 2 of these had a unique TP53 p.P72R mutation. A number of novel variants of unknown significance were also identified that were heterogeneous between CTCs. The matched cfDNA sample had all mutations found across the 5 CTCs, with no additional mutations unique to cfDNA. The other patient had the same ESR1 p.D538G mutation in DNA isolated from pooled CTCs and matched cfDNA, but also had a novel variant in exon 7 of FGFR1 in cfDNA.

Conclusion

These data confirm molecular heterogeneity of single CTCs and suggest cfDNA as a suitable biomarker for the genetic landscape of CTCs in MBC. Analysis of other patients and samples is currently ongoing.

References

(1) Guttery et al., (2015) Noninvasive Detection of Activating Estrogen Receptor 1 (ESR1) Mutations in Estrogen Receptor-Positive Metastatic Breast Cancer. *Clinical Chemistry*. pii: clinchem.2015.238717.

17.05 - 17.30

Hall 1B

James Hicks,

Cold Spring Harbour
Laboratory, USA

Title to be confirmed

Abstract not received.

17.30 - 17.40

Discussion

● The future role of primary care in cancer control

15.40 – 15.50

Hall 1C

Greg Rubin,
University of
Durham, UK

Introduction

In the UK and many other developed countries, cancer policy is being required to address several common issues; achieving earlier diagnosis of symptomatic cancer, the scale of challenge presented by survivorship and a need for efficient but safe models of care delivery. For all these, the contribution of primary care is a key consideration. A Lancet Oncology Commission (published in October 2015) has summarised the evidence and current thinking about the role of primary care at all stages in the cancer pathway, It is intended to stimulate debate about future configuration of services for cancer control, both for optimal patient outcomes and for effective health care delivery.

15.50 – 16.15

Hall 1C

David Weller,
University of
Edinburgh, UK

Primary prevention, symptomatic diagnosis and screening: roles for general practice and primary care

This section of the Lancet Oncology Commission focussed on the role of primary care in prevention, early diagnosis and screening. There is good evidence that interventions based in primary care can lead to reductions associated with alcohol and tobacco consumption. The evidence is more variable when it comes to diet and obesity and in these areas other, complementary approaches are needed. Ideally in all areas of primary prevention primary care should work alongside public health and government initiatives.

Primary care has important roles in awareness raising about cancer symptoms and these can complement other initiatives such as public awareness campaigns. There is a complex process by which patients appraise symptoms and decide whether or not to take action – interactions with primary care have an important influence on this process. It is important for primary care practitioners to understand the psychological processes which govern their patients' help-seeking behaviour in response to cancer-related symptoms.

Primary care also has key roles in cancer screening; in the case of colorectal cancer there is ample evidence that endorsement from primary care leads to higher uptake of screening tests. Primary care practitioners are seen as a credible source of advice about cancer screening decisions and it's vital, even for programmes which are largely co-ordinated outside of primary care, that GPs and other primary care practitioners engage in the screening programme and its various components – particularly recruitment, informed choice and appropriate follow up of positive screening tests.

16.15 – 16.30

Hall 1C

Jessica Sheringham,
University College
London, UK

Proffered paper: Variations in GPs' decisions to investigate suspected lung cancer: a factorial experiment using multimedia vignettes

Background

Patients with symptoms suggestive of lung cancer commonly present to primary care but diagnostic delays are well documented (1-3) and it is unclear how general practitioners (GPs) distinguish which patients require further investigation. This factorial experiment examined how patients' clinical and socio-demographic characteristics influence GPs' decisions to initiate lung cancer investigations.

Parallel session abstracts *(continued)*

Method

A multimedia interactive website simulated key features of GP consultations using actors ('patients'). A national sample of GPs made management decisions online for six 'patients' randomly selected from 36 vignettes, with clinical and socio-demographic characteristics systematically varying across three levels of cancer risk. In low-risk vignettes (positive predictive value [PPV] <1.2%) investigation by the GP (i.e. chest X-ray ordered or respiratory physician referral) was not indicated, in medium-risk (PPV=1.7-2.5%) investigation could be appropriate, in high-risk vignettes (PPV>3%) investigation was definitely indicated. Each 'patient' had two lung cancer-related symptoms; one volunteered and the other elicited if GPs specifically asked. Variations in investigation likelihood were examined by 'patient' characteristics using multilevel logistic regression.

Results

227 GPs completed 1356 vignettes of which 1348 were included in analysis. GPs investigated lung cancer in 74% (1000/1348) of cases. Investigation likelihood did not increase with cancer risk. Investigations were more likely when GPs sought information on symptoms that 'patients' had but did not volunteer (adjusted odds ratio [AOR] 3.18 95% CI 2.27-4.70) but GPs omitted to seek this information in 42% (570/1348) of cases. GPs were less likely to investigate older than younger 'patients' (AOR 0.52 95% CI 0.39-0.70) and Black 'patients' compared with White (AOR 0.68 95% CI 0.48-0.95).

Conclusion

When GPs explicitly seek relevant clinical information, most act on it appropriately, but inequalities in cancer investigation by age and ethnicity remain.

Acknowledgements

We acknowledge the support of NIHR, through the Primary Care Research Network for its recruitment of study participants. We thank the GPs and patient representatives who contributed to the design of the research instrument.

16.30 - 16.55

Hall 1C

Annette Berendsen,
University of Groningen,
The Netherlands

The future role of primary care in cancer control – survivorship care

As the number of cancer survivors is increasing rapidly, traditional models of follow-up are no longer sustainable. Internationally, there is increasing support for the idea that PCPs (and other primary care providers) should be more involved in all stages of cancer care.

The role of PCPs in the survivorship phase is not well defined, and yet with their knowledge of the patient's prior medical history, co-morbidities and family situation, and their holistic approach to care, PCPs have much to offer.

Challenges, barriers, and expectations for new models of survivorship care of PCPs, medical specialists and patients will be discussed.

16.55 - 17.20

Hall 1C

Eva Grunfeld,
Ontario Institute for
Cancer Research,
Toronto, Canada

It takes a team: the importance of integration between primary care and cancer specialist care

Projected increases in cancer incidence and prevalence herald a greater reliance on primary care along the entire cancer care pathway. Integration of services between primary care and cancer specialist care is vital to optimise quality and outcomes of care, and yet is known to be problematic. Patients often need to consult many health professionals across multiple healthcare settings. Without proper integration this can lead to care that is fragmented and

uncoordinated which, in turn, can jeopardise quality, efficiency and patient safety. Mitigating this problem brings new challenges and opportunities for both primary care and cancer systems. This presentation will give examples of the consequences of poor integration and review approaches designed to improve integration such as structuring of healthcare services, innovative models of care, and practice tools.

17.20 - 17.40

Discussion

● Tumour:stroma interactions

15.40 - 15.45

Hall 1A

Erik Sahai,
The Francis Crick
Institute, London, UK

Introduction

15.45 - 16.10

Hall 1A

**Kairbaan
Hodivala-Dilke,**
Queen Mary University
of London, UK

Title to be confirmed

Abstract not received.

16.10 - 16.25

Hall 1A

Ilirjana Bajrami,
The Institute of Cancer
Research, London, UK

Proffered paper: E-cadherin deficiency a novel determinant of ROS1 inhibitor sensitivity

Background

The E-cadherin (CDH1) tumour suppressor gene encodes a calcium-dependent cell-cell adhesion glycoprotein, which has roles in maintaining cell polarity, differentiation, cell migration and survival. E-cadherin dysfunction is a feature common to many epithelial tumours, with the highest incidence occurring in diffuse gastric cancer (50%) and lobular breast cancer (56%) and can occur via CDH1 mutation, deletion or epigenetic silencing. Although E-cadherin dysfunction is relatively common, approaches to target this pathogenic alteration do not as yet exist.

Method

We have taken an integrated functional genomics approach to identifying E-cadherin synthetic lethality effects that exploits siRNA. Using a combination of Achilles' Heel siRNA screens in histologically and genetically diverse tumour cell line panels, we have identified a compendium of genes whose disruption selectively targets E-cadherin deficient cells. Alongside the Achilles' Heel screens in tumour cell models, complementary screens siRNA and pharmacological screens in isogenic systems with Zinc-finger and CRISPR-engineered E-Cadherin defects were undertaken.

Parallel session abstracts *(continued)*

SUNDAY

MONDAY

TUESDAY

WEDNESDAY

Results

The integrated functional genomics approach identified a robust synthetic lethal interaction between the orphan receptor tyrosine kinase ROS1 and E-cadherin dysfunction. Functional and chemical inhibition of ROS1 in a variety of breast cell line models induced sensitivity in E-cadherin deficient cells. The synthetic lethal interaction between E-cadherin and ROS1 was characterized by induction of apoptosis, nuclear defects, and a G2/M cell cycle arrest.

Conclusion

This integrated genomics approach identified novel genetic determinants selective for E-cadherin deficiency, a gene that is recurrently mutated in breast cancer. This study suggests that E-cadherin deficiency could be used as candidate predictive biomarker in future clinical trials involving ROS1 inhibitors.

16.25 - 16.50

Hall 1A

Hellmut G. Augustin,
Vascular Oncology and
Metastasis, German
Cancer Research
Center, Heidelberg
(DKFZ-ZMBH Alliance),
Vascular Biology and
Tumor Angiogenesis,
Medical Faculty
Mannheim (CBTM),
Heidelberg University
& German Cancer
Consortium (DKTK),
Heidelberg, Germany

Targeting tumour angiogenesis by targeting Angiopoietin/Tie signalling: from vascular regression over vascular normalisation to stromal reprogramming therapies

Anti-angiogenesis was originally proposed to 'starve tumours to death' by driving the tumour-associated vasculature into regression. This bold ambition did not materialize, but combination therapies involving VEGF/VEGFR targeting drugs have become part of standard tumour therapy for several types of tumours. With more than 10 years into the clinic, their efficacy in terms of progression free survival (PFS) and overall survival (OS) continues to be limited. Yet, the implementation of anti-angiogenic therapy marks a fundamental change-of-paradigm as the first proof-of-principle that stromal targeting can be of therapeutic benefit. Today, it is widely recognised that the MOA of anti-angiogenic intervention in human tumours can only partially be explained by global regression of the tumour-associated vasculature. Instead, anti-VEGF/VEGFR therapies prune particularly the immature tumour vasculature thereby facilitating chemotherapy by functionally normalising the pruned tumour vascular tree. Progress in anti-angiogenic intervention can be expected from combination therapies that broaden the therapeutic window of established anti-angiogenic VEGF/VEGFR targeting therapies. Moreover, the facilitation effect on other forms of therapy, not just chemotherapy, but in the future most likely also immunotherapies, promises to substantially advance vascular targeting tumour therapies. In fact, it can be foreseen that the concepts of anti-angiogenesis and vascular normalisation may be transformed towards stromal reprogramming therapies that systematically alter the tumour microenvironment to enhance the efficacy of tumouricidal drugs. The Angiopoietin/Tie system acts in concert with VEGF/VEGFR signaling. It is high up in the hierarchy of events the control vascular responses and paracrine-acting vascular-derived growth factors. The presentation will focus on the development of Ang/Tie targeting therapies for the improvement of established anti-angiogenic therapies and for the eventual development of stromal targeting therapies.

16.50 - 17.05

Hall 1A

Jason Fleming,
University of
Southampton, UK

Proffered paper: CTEN (C-terminal Tensin-like) regulates head and neck cancer invasion and survival

Background

C-terminal tensin-like (CTEN; TNS4) is a member of the TENSIN gene family that encodes focal adhesion adaptor proteins. CTEN in particular is emerging as a prognostic marker in many cancer types but its mechanism of action and clinical relevance in head and neck cancer (HNSCC) is unknown.

Method

We investigated the functional role of CTEN in a panel of head and neck cancer cell lines. Gene knockdown of CTEN was utilised to evaluate function in integrin-dependent assays including transwell invasion assays and physiological 3D organotypic cultures. Clinical correlation was examined through tissue microarray construction and immunohistochemistry analysis of 259 consecutively treated oropharyngeal cancer (OPSCC) patients. Clonogenic assays were performed in a radiosensitive cell line (SCC25) following ionising radiation/cisplatin exposure to identify the effect of CTEN expression on radio/chemosensitivity.

Results

CTEN knockdown suppressed invasion of all tested HNSCC cell lines, both in Transwell invasion assays and 3D organotypic cultures ($P < 0.05$). Immunohistochemistry analysis of OPSCC microarray demonstrated that on univariate analysis, high CTEN protein expression predicted shortened disease-free survival ($P < 0.01$). Similarly on multivariate analysis, CTEN independently influenced disease-free survival when adjusted for age, T stage, N stage, and smoking status ($P < 0.05$). Kaplan-Meier survival analysis linked high CTEN expression with significantly reduced overall disease-specific OPSCC survival ($P < 0.001$; log-rank test). This significant correlation was maintained for both HPV-negative ($P < 0.05$) and HPV-positive disease ($P < 0.01$). Interestingly sub-group analysis demonstrated the impact of CTEN expression on survival was most significant in patients treated with chemo-radiation and clonogenic assays suggested a role for CTEN in promoting radioresistance.

Conclusion

Our results suggest that CTEN functions as an oncogene in HNSCC through its promotion of cell invasion. Furthermore, CTEN demonstrates prognostic ability in OPSCC irrelevant of viral status and this may function through a novel role in regulating radiosensitivity. These findings have important implications for head and neck cancer prognosis and targeted treatment of individual patients.

17.05 - 17.30

Hall 1A

Erik Sahai,The Francis Crick
Institute, London, UK**Intravital imaging reveals how stroma dictates heterogeneous responses to targeted therapy**

The Ras-MAPK pathway is mutated in the majority of melanoma, with BRAF mutations being most common. Tumours with BRAF mutations show an initial response to BRAF inhibitors before genetic resistance emerges. However, little is known about the spatio-temporal response to BRAF inhibitors in vivo and how this relates to the failure of targeted therapy. In this study, we have used both intravital ratiometric FRET and FLIM of an ERK/MAP kinase biosensor to investigate heterogeneity in signalling in melanoma models. We have longitudinally monitored responses to targeted therapy and identified areas that become refractory to drug action. BRAF mutant melanoma cells can rapidly become tolerant to PLX4720 in areas of high stroma. The rapid kinetics of this process indicate that it is not caused by genetic events. We demonstrate that PLX4720 has an unexpected effect on the tumour stroma leading to enhanced matrix remodelling. The remodelled matrix then provides signals that enable melanoma cells to tolerate PLX4720. We propose that this safe haven enhances the population of cancer cells from which genetically resistance emerges.

17.30 - 17.40**Discussion**

Workshops

● BACR educational workshop: Patient-derived xenograft models: current future and state-of-the-art

08.00 – 08.45

Room 11

Hosted by **Robert Clarke**, The University of Manchester, UK and **Anna Grabowska**, The University of Nottingham, UK

Recently, there has been an interest in improving cancer models through the development of patient-derived xenograft (PDX) tumours. Where these PDX have been characterised, they mostly retain the principal histologic and genetic characteristics of their donor tumour and remain stable across several passages. PDX tumour models are now available that represent many different cancer types and have been shown to undergo metastases, making them useful for biological and pre-clinical modelling of patient disease. They are thus being used for preclinical drug evaluation, biomarker identification, biologic studies, and personalised medicine strategies. At the BACR workshop, we will discuss current state of the art, including methodological issues, available collections, practical applications, challenges and future directions.

● De-mystifying today's science

08.00 – 08.45

Room 3B

Elaine Vickers, Science Communicated, Sheffield, UK

Do words like signal transduction, epigenetics, genomics and biomarkers bring a puzzled frown to your face?

Do you plan to attend today's plenary lectures whilst fearing that you won't understand a word?

Well never fear!

In this second of Elaine's workshops, she will explain many of the words, concepts and ideas behind today's plenary lectures*. Including:

- Explained: genetic instability and intra-tumoural heterogeneity
- An introduction to the cell cycle
- What we mean by 'genomics trials'
- The tumour microenvironment and the role of non-cancer cells in cancer – why they matter

Similar to previous years' workshops, Elaine will use diagrams and illustrations to provide clear, easy-to-understand explanations of complicated biological concepts.

The workshop is geared towards non-scientists, such as doctors, nurses, trials staff and patients who'd like to get the most out of this year's conference.

● Involving patients in the use of their data

12.45 – 14.00

Room 12

Hosted by **National Cancer Intelligence Network**, UK

The recently published 'Achieving world-class cancer outcomes: a strategy for England 2015-2020' states:

"An inability to link data sets and make these available to providers, commissioners and researchers sustains the provision of sub-standard care. There is extensive evidence that cancer patients want their data to be used for research and to improve care. We must

harness their support, ensuring cancer patients are placed at the heart of strengthening our cancer data intelligence.”

The National Cancer Intelligence Network (NCIN), together with the NCRI and charity partners, are running a workshop for patients, to describe and help plan a wider programme of activities aimed at education, involvement and support from patients for the usage of data to save lives.

Speakers

Michael Chapman, Head of Cancer Intelligence & Impact, Cancer Research UK

Margaret Grayson, NCRI Consumer & Chair, NI Cancer Research Consumer Forum

Richard Stephens, Chair, NCRI Consumer Forum

● Cancer Research UK Grand Challenge drop in session

12.45 – 14.00

Room 11

Grand Challenge is Cancer Research UK’s boldest, most innovative funding scheme and the biggest cancer grant in the world. We are planning to make an award of up to £20m to the multinational, interdisciplinary team that can convince us they have what it takes to tackle the toughest questions in cancer research. Grand Challenge will emphasise collaboration, free exchange of ideas and enable the winning team to work close to the edge of possibility.

In this session aimed at researchers, CRUK will host a free lunch with:

- The chance to hear from, and ask questions to, a high profile panel from Cancer Research UK who have been close to the development of the Grand Challenge questions.
- The chance to get advice about your application and network with other potential applicants.



WEDNESDAY



Programme at a glance

● Prize winners announcement

09.00 - 09.10 **Charles Swanton**, Chair of the 2015 Scientific Committee
Hall 1A

● Plenary lecture

Chaired by **Sergio Quezada**, University College London Cancer Institute, UK

09.10 - 09.50 Immune checkpoint blockade in cancer therapy: new insights and opportunities and prospects for cures
Hall 1A
James P. Allison, MD Anderson Cancer Center, Houston, USA



● Drug Discovery and Development Course part 1

09.50 - 12.00
Room 4

● Workshop

09.50 - 13.00 Prognostic modelling and evaluation of diagnostic tests - £75
Room 14 **Abdel Douiri**, King's College London, UK

● Parallel sessions

10.00 - 12.00 Advances in surgical oncology
Hall 1B Hosted by **Richard Shaw**, NIHR Clinical Research Network: Cancer and University of Liverpool, UK

10.00 - 12.00 Early diagnosis
Hall 1C Hosted by **Max Parmar**, University College London, UK

10.00 - 12.00 Economic impact of cancer
Room 11 Hosted by **Robert Peston**, BBC Economics Editor, London, UK and **Tito Fojo**, Columbia University Medical Center, New York, USA

10.00 - 12.00 Late breaking proffered papers
Room 12

10.00 - 12.00 MicroRNA and non-coding RNA
Hall 1A Hosted by **Nicola Valeri**, The Institute of Cancer Research, London, UK

10.00 - 12.00 Rare tumours
Room 3B Hosted by **Matt Seymour**, NIHR Clinical Research Network: Cancer, Leeds, UK

10.00 - 12.00 Selecting rational combinations for cancer and delivering early phase clinical trials in the UK
Room 3A Hosted by **Hazel Jones**, Cancer Research UK, London, UK and **Udai Banerji**, The Institute of Cancer Research, London, UK

● Networking and refreshment break

12.00 - 12.20 Registration area and Galleria

● Plenary lecture

Chaired by **Charles Swanton**, The Francis Crick Institute & University College London Cancer Institute, UK

12.20 - 13.00 Engineering T cells for cancer therapy: progress and challenges
Hall 1A **Carl June**, Perelman School of Medicine, University of Pennsylvania,
USA



● Closing remarks

13.00 - 13.10 **Caroline Dive**, Cancer Research UK Manchester Institute, UK
Hall 1A & Chair of 2016 Scientific Committee

● Networking and lunch (*available to take away*)

13.10 - 13.30 Registration area and Galleria

● Drug Discovery and Development Course part 2

13.15 - 16.00
Room 4

Plenary abstracts

● Immune checkpoint blockade in cancer therapy: new insights and opportunities, and prospects for cures

09.10 - 09.50

Hall 1A

James P. Allison,
MD Anderson
Cancer Center,
Houston, USA



The existence of multiple non-redundant inhibitory pathways that limit T cell responses offers novel strategies for mobilising the immune system to attack cancer cells. The best characterised of these immune checkpoints is CTLA-4, which inhibits T cell proliferation by interfering with the interaction of the costimulatory molecule CD28 with its ligands B7-1 and B7-2 on the surface of antigen presenting cells. Antibodies to CTLA-4 have proven effective against multiple tumour types in both pre-clinical and clinical studies. Ipilimumab, an antibody to human CTLA-4, showed long term (>4 years) survival benefit in about 20% of patients in a randomised, placebo-controlled trial in late stage melanoma. In 2011 it was approved by the FDA for treatment of late stage melanoma and is now a standard of care for that disease.

The mechanism(s) of action of anti-CTLA-4 are still being elucidated. We and others have shown that CTLA-4 limits T cell proliferation by a cell intrinsic mechanism. However, there is also evidence that anti-CTLA-4 has to engage the target on both effector (Teff) and regulatory (Treg) T cells. Thus anti-CTLA-4 exerts its anti-tumour effects by multiple mechanisms.

PD-1, another checkpoint, recruits a phosphatase and seems to interfere with T cell antigen receptor mediated signalling. It has two ligands, PD-L1 and PD-L2, which are both expressed on dendritic cells. However, many tumour cells also express PD-L1. Antibodies to PD-1 and PD-L1 have both shown objective responses against several tumour types in clinical trials with response rates of about 25%. A recent phase II trial of a combination of anti-PD-1 and anti-CTLA-4 in melanoma showed objective responses in about 50% of late stage melanoma patients.

Emerging data suggest that T cell responses are largely directed toward neoantigens arising as a result of mutational events associated with the carcinogenesis. While all tumours with antigens recognisable by the immune system should be targets for checkpoint blockade, it is becoming clear that certain types of tumours with lower burdens of mutations (e.g. prostate, breast, and kidney cancer) present special challenges for immune therapy. Strategies for effective treatment of such tumours will be discussed.

● Engineering T cells for cancer therapy: progress and challenges

12.20 - 13.00

Hall 1A

Carl June,
Perelman School of
Medicine, University
of Pennsylvania, USA



It is now well established that the immune system can control and eliminate cancer cells. Adoptive T cell transfer has the potential to overcome the significant limitations associated with vaccine-based strategies in patients who are often immune compromised. Application of the emerging discipline of synthetic biology to cancer, which combines elements of genetic engineering and molecular biology to create new biological structures with enhanced functionalities, is the subject of this presentation. Various chimeric antigen receptor designs, manufacturing processes and study populations, among other variables, have been tested and reported in recent clinical trials.

Many questions remain in the field of engineered T cells, but the encouraging response rates pave a wide road for future investigation into many, if not all, forms of cancer.

Parallel sessions

● Advances in surgical oncology

Hosted by **Richard Shaw**, NIHR Clinical Research Network: Cancer & University of Liverpool, UK

- 10.00 - 10.05** Introduction by the host
Hall 1B
- 10.05 - 10.30** 'Comic opera' is dead... surgical research is alive and well
Hall 1B
Freddie C. Hamdy, University of Oxford, UK
- 10.30 - 10.45** Proffered paper: Real-time diagnosis of ovarian cancer with the surgical intelligent knife (iKnife)
Hall 1B
David Phelps, Imperial College London, UK
- 10.45 - 11.10** Pitfalls in surgical trials
Hall 1B
Emiel Rutgers, The Netherlands Cancer Institute, Amsterdam, The Netherlands
- 11.10 - 11.35** CReST trial: addressing surgical management of emergency oncology admissions and the role of randomised trials
Hall 1B
James Hill, Manchester Royal Infirmary, UK
- 11.35 - 11.50** NCRI and NIHR initiatives in surgical oncology
Hall 1B
Presentation of 2015 CREST award (Cancer Research Excellence in Surgical Trials)
Richard Shaw, NIHR Clinical Research Network: Cancer & University of Liverpool, UK
- 11.50 - 12.00** Discussion

● Early diagnosis

Hosted by **Max Parmar**, University College London, UK

- 10.00 - 10.05** Introduction by the host
Hall 1C
- 10.05 - 10.30** What can observational studies tell us about early diagnosis of symptomatic cancer?
Hall 1C
Willie Hamilton, University of Exeter, UK
- 10.30 - 10.45** Proffered paper: Public understanding of the purpose of cancer screening – a population-based survey
Hall 1C
Jo Waller, University College London, UK
- 10.45 - 11.10** Ovarian cancer screening – update from UK trials
Hall 1C
Usha Menon, University College London, UK
- 11.10 - 11.35** Proffered paper: MAMMO-50: The results of the pre-planned internal 2 year feasibility study for mammographic surveillance in early breast cancer patients over 50 years of age at diagnosis
Hall 1C
Janet A. Dunn, Warwick Clinical Trials Unit, Coventry, UK

Parallel sessions *(continued)*

11.35 - 11.50 Can we do randomised controlled trials (RCTs) of interventions to expedite the diagnosis of symptomatic cancer? And should we?
Hall 1C
Richard Neal, Bangor University, UK

11.50 - 12.00 Discussion

● Economic impact of cancer

Hosted by **Robert Peston**, BBC Economics Editor, London, UK and **Tito Fojo**, Columbia University Medical Center, New York, USA

10.00 - 10.05 Introduction by the hosts
Room 11

10.05 - 10.40 Clash of cultures: the economic sustainability of cancer care and research across Europe
Room 11
Richard Sullivan, King's College London, UK

10.40 - 11.15 How do health economists value personalised medicine in oncology?
Room 11
Maarten IJzerman, University of Twente, Enschede, The Netherlands

11.15 - 11.50 The cost of cancer drugs in the US: why we must look beyond published data
Room 11
Tito Fojo, Columbia University Medical Center, New York, USA

11.50 - 12.00 Discussion

● Late breaking proffered papers

Host to be confirmed

10.00 - 10.05 Introduction
Room 12

10.05 - 10.25 Effect of pre-diagnostic NSAID use on ovarian cancer survival
Room 12
Chris Brown, National Cancer Registry, Cork, Ireland

10.25 - 10.45 5 year outcomes of a phase III randomised trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer [CRUK/06/016]: report from the CHHiP Trial Management Group
Room 12
David Dearnaley, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, London, UK

10.45 - 11.05 Expanded analyses of NAPOLI-1: Phase 3 study of nal-IRI (MM-398), with or without 5-fluorouracil (5FU) and leucovorin (LV), versus 5-fluorouracil and leucovorin (5FU/LV), in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy
Room 12
Richard Hubner, The Christie Hospital NHS Foundation Trust, Manchester, UK

11.05 - 11.25 CheckMate 025: a randomized, open-label, phase III study of nivolumab versus everolimus in advanced renal cell carcinoma (RCC)
Room 12
John Wagstaff, Swansea University, UK

11.25 – 11.45 Can WBRT be omitted in NSCLC patients with brain metastases not suitable for stereotactic radiosurgery or surgical resection? Results from the UK Medical Research Council QUARTZ randomised clinical trial
 Room 12
Paula Mulvenna, Northern Centre for Cancer Care, Newcastle upon Tyne, UK

11.45 – 12.00 Discussion

● **MicroRNA and non-coding RNA**

Hosted by **Nicola Valeri**, The Institute of Cancer Research, London, UK

10.00 – 10.05 Introduction by the host
 Hall 1A

10.05 – 10.30 MicroRNA mechanism and its involvement in DNA damage response pathway
 Hall 1A
Martin Bushell, Medical Research Council Toxicology Unit, Leicester, UK

10.30 – 10.45 Proffered paper: The splicing inhibitor Spliceostatin A down-modulates Mcl-1 expression and induces a potent apoptotic response in Chronic Lymphocytic Leukaemia cells
 Hall 1A
Marta Larrayoz, University of Southampton, UK

10.45 – 11.10 miRNA as biomarkers for early lung cancer detection
 Hall 1A
Gabriella Sozzi, National Cancer Institute, Milan, Italy

11.10 – 11.25 Proffered paper: Key role of AGO2 and the 8q24 complicon in the regulation of microRNA biogenesis in cancer
 Hall 1A
Simon Wigfield, Weatherall Institute of Molecular Medicine, University of Oxford, UK

11.25 – 11.50 The miRNA landscape of breast cancer
 Hall 1A
Carlos Caldas, Cancer Research UK Cambridge Institute, UK

11.50 – 12.00 Discussion

● **Rare tumours**

Hosted by **Matt Seymour**, NIHR Clinical Research Network: Cancer, Leeds, UK

10.00 – 10.05 Introduction by the host
 Room 3B

10.05 – 10.30 Methodology to influence clinical practice in rare cancers
 Room 3B
Lucinda Billingham, Cancer Research UK Clinical Trials Unit, School of Cancer Sciences and University of Birmingham, UK

10.30 – 10.45 Proffered paper: Adamantinomatous craniopharyngioma contains senescent cells with tumour-inducing potential
 Room 3B
Juan Pedro Martinez-Barbera, University College London, UK

10.45 – 11.10 The value of genomics in rare cancers
 Room 3B
Ultan McDermott, Wellcome Trust Sanger Institute, Cambridge, UK

Parallel sessions *(continued)*

11.10 - 11.25 Proffered paper: EURAMOS-1: an international collaboration for osteosarcoma
Room 3B

Jeremy S. Whelan, University College Hospital, London, UK

11.25 - 11.50 Changing the paradigm for therapeutic progress for rare tumours: SPECTArare “Optimising molecular profiling technologies through partnerships”
Room 3B

Denis Lacombe, EORTC, Brussels, Belgium

11.50 - 12.00 Discussion

● **Selecting rational combinations for cancer and delivering early phase clinical trials in the UK**

Hosted by **Hazel Jones**, Cancer Research UK, London, UK and **Udai Banerji**, The Institute of Cancer Research, London, UK

10.00 - 10.10 Introduction by the hosts
Room 3A

10.10 - 10.35 DEBIOC: A Combinations Alliance Study of AZD8931 in combination with Oxaliplatin and Capecitabine chemotherapy in patients with Oesophago-gastric adenocarcinoma
Room 3A
Anne Thomas, University of Leicester, UK

10.35 - 11.00 Combinations Alliance from an industry perspective
Room 3A
Susan Galbraith, AstraZeneca Oncology Innovative Medicines, Cambridge, UK

11.00 - 11.25 Progressing radiotherapy-drug combinations towards early phase clinical trials
Room 3A
Anthony Chalmers, University of Glasgow, UK

11.25 - 11.50 Novel inpatient dose escalation phase I trial of two schedules of the combinations of the PARP inhibitor olaparib and AKT inhibitor AZD5363 in BRCA1/2 and non-BRCA1/2 mutation patients with advanced cancers
Room 3A
Timothy Yap, The Institute of Cancer Research & The Royal Marsden NHS Foundation Trust, London, UK

11.50 - 12.00 Discussion

Parallel session abstracts

● Advances in surgical oncology

10.00 – 10.05

Hall 1B

Richard Shaw,
NIHR Clinical
Research Network:
Cancer & University
of Liverpool, UK

Introduction

Surgery constitutes at least 50% of the cure of cancer patients but the involvement of surgeons in national cancer structures has notably lagged behind chemotherapy and radiotherapy. There are a number of funded trials and new initiatives from College, NCRI and the NIHR in the field of surgical oncology trials that we will seek to highlight in this session.

10.05 – 10.30

Hall 1B

Freddie C. Hamdy,
University of Oxford, UK

'Comic opera' is dead...surgical research is alive and well

It is a well-known conception, popularised in the mid-nineties, that surgical research in the UK was no more than a 'comic opera', with few exceptions. Regrettably, much of this carried truth. 'Many questions were being asked, but few answers were given.'¹

Root causes were multifactorial, including the complexity of conducting high quality research by craft specialties, the lack of protected academic time, ill-designed career structures, and expectations of competitive outputs by Higher Education Institutions, particularly through the Research Excellence Framework. A further hindrance to high quality surgical research has been the antiquated 'silo' culture entertained by many surgeons, and lack of multidisciplinary research approaches to unmet needs in surgical practice.

Many of these issues have been addressed and resolved over the past two decades. From new, structured surgeon scientist careers to well-funded high impact clinical trials, innovation and testing of interventional technologies, surgical research is now thriving in the UK, and can be redefined as follows:

"Where conventional and/or minimally invasive surgical interventions can be tested, compared and evaluated, including the precise delivery of ablative energy. Where surgical techniques, used alone or in combination with other treatment options (physical or systemic) can be investigated to improve outcomes and cure, enhanced by functional imaging, whilst reducing adverse events from individual treatment options. And where surgical interventional procedures can be improved by targeting the right patient through novel and experimental genetic, epigenetic or biochemical markers."

1. Horton R. Surgical research or comic opera: questions, but few answers. *Lancet*. 1996 Apr 13;347(9007):984-5.

10.30 – 10.45

Hall 1B

David Phelps, Imperial
College London, UK

Proffered paper: Real-time diagnosis of ovarian cancer with the surgical intelligent knife (iKnife)

Background

Women have a 2% lifetime risk of developing ovarian cancer. Five year survival for stage III or IV disease is 19% and 3% respectively(1). Standard treatment is surgical debulking followed by chemotherapy. Some centres give neo-adjuvant chemotherapy followed by delayed debulking, which renders tumour deposits difficult to identify during surgery. Debulking to zero residual disease improves prognosis for stage IV to 54.6 months compared to 23.9 months with >10mm residual disease(2).

Parallel session abstracts *(continued)*

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Surgeons rely on frozen tissue sections for histopathological diagnosis during surgery which is time-consuming and expensive. The inability to accurately identify non-descript lesions can lead to more radical, perhaps unnecessary surgery.

Method

A Xevo Q-TOF mass spectrometer was used with a modified handheld diathermy. The technology analyses the diathermy smoke for ionic species. The spectra and histopathological diagnoses were used to populate a library with background subtracted and lock mass corrected spectra in the phospholipid range. Principal component (PCA) and linear discriminant analysis (LDA) were used to find the variance in spectral signatures between chosen tissue groups.

Results

486 sampling points were obtained from 144 fresh frozen tissues (normal ovary n=15, fallopian tube n=15, peritoneum n=15, benign tumours n=14, borderline n=15, malignant n=70). The iKnife differentiated tissue types using unique phospholipid spectral signatures as fingerprints. The leave-one out patient cross-validation showed 100% sensitivity and specificity in the separation of normal ovary and malignant ovary sampling points (n=189). Sensitivity and specificity remained 100% when including normal fallopian tube and peritoneum in the model (n=291). Overall the correct tissue classification rate was 92.7%, reduced from 100% due to some spectral crossover within the normal tissue groups.

Conclusion

The iKnife accurately separates different gynaecological tissues. In surgical gynae-oncology the iKnife has the potential to reduce operating times, improve margin status and identify lesions. Enhanced on-table decision making may result in reduced morbidity and improved survival.

References

- (1) CRUK. Ovarian cancer survival statistics - Figure 3.1: Ovarian Cancer (C56, C57.0-C57.7), Five-Year Relative Survival Rates by Age, England 2005-2009 2012 [updated June 20]. Available from: www.cancerresearchuk.org/cancer-info/cancerstats/types/ovary/survival/ovarian-cancer-survival-statistics
- (2) Wimberger P. Influence of Residual Tumor on Outcome in Ovarian Cancer Patients With FIGO Stage IV Disease. *Annals of Surgical Oncology*. 2010;964-9

10.45 - 11.10

Hall 1B

Emiel Rutgers, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Pitfalls in surgical trials

Since the polemic editorial "Surgical research a comic opera: questions but few answers" by R. Horton (*Lancet* 1996), the debate on what good and "relevant" surgical research constitutes, is fierce and ever ongoing. I prefer to see it from another - more positive - angle: how to learn from the past and to design optimal surgical trials leading to practice changing outcomes? Because the only way to advance cancer surgery is by careful and thoughtful implementation of innovations. Are these innovations really worthwhile? What is the clinical benefit? Is the outcome of the patients really improved by these innovations?

First, what are the most relevant possible outcome measures?

- Is there any survival benefit
- Can we improve local and regional control of the solid cancers
- Can we diminish the side effects
- Can we improve quality of life
- Can we manage/reduce the ever increasing costs

Survival and local-regional control are the only real objective outcome measures. Side effects, quality of life and costs are subject to interpretation biases and may in general only

serve as secondary endpoints. Small or even a real differences in these subjective outcomes will rarely be strong enough to be practice changing.

What are to me the most important pitfalls or difficulties in executing surgical trials?

- Surgical trials are by nature usually non blinded. For the surgical act this is quite logical. However for those who are gathering the data and prepare the data for analysis, should be (as much as possible) be blinded for the type of intervention.
- Non inferiority design: this takes many (frequently too many) patients to really proof that a certain intervention is non inferior to the standard practice (for instance to proof that a less extensive intervention is associated with equal loco regional control; e.g. limited lymph node dissection in melanoma, head and neck cancer, thyroid cancer, or organ sparing surgeries).
- The non-standardisation of surgical procedures
- No quality control of surgery
- Poor outcomes in the standard arm
- Much lower than expected event rates – jeopardising the accrual and primary end point
- Slow accrual due to lack of interest
- Poor funding since surgical trial are usual ‘academic’

What are the ingredients for a surgical clinical trial that is able to advance clinical care and in the end results in practice changing outcomes.

- There has to be an unmet clinical need: e.g. can loco or regional control be improved, is standard treatment associated with considerable side effects which should be reduced, can cost be reduced by more simple interventions. Simply is there something to gain? “Me too” trials are generally bound to fail.
- Surgery or interventions (like radiotherapy and systemic therapy) should be standardized as well in the standard arm as in the experimental arm of the study.
- Standardization of procedures should be secured in clear SOP’s and monitored by site visits or proctoring (depending of the complexity of the interventions)
- Statistics must be sound and realistic. Try to circumvent non inferiority designs. Find alternative ways to conduct a trial, e.g. sometimes a prospective registration study with predefined end points where a new intervention is tested, can be an acceptable approach.
- Procedures should be executed by experienced teams so standard procedures reflect optimal standard of care.
- Funding must be secured: this is a challenge since surgical trials are generally non-sponsored academic endeavors.

Data management should be (as much as possible) blinded for the intervention. The statistical analysis plan should be available before final analysis. Missing values should be diminished as much as possible. Statistical analysis should be performed in an independent way.

- No competing trials in the same population.
- Broad consensus on trial design by trial participants (and patients): the clinical unmet need should be well described, the hypothesis should be realistic as well as the statistics, the number of patients, the quality of participating teams, the protocol of the intervention, the monitoring and or proctoring of the interventions.

In my presentation I will discuss a number of successful surgical trials.

Surgical trials: a comic opera? Now, twenty years later, we have learned a lot. It is still a challenge to perform a clinical trial but it is possible and in the end it is for the well being of our patients.

Parallel session abstracts *(continued)*

11.10 - 11.35

Hall 1B

James Hill,
Manchester Royal
Infirmary, UK

CReST trial: addressing surgical management of emergency oncology admissions and the role of randomised trials

Changes in the provision of both elective cancer surgery and emergency laparotomy care (being pioneered as part of the Healthier Together initiative in Greater Manchester) should provide more speciality specific care for emergency oncology admissions.

A significant proportion of patients with colorectal cancer present as an emergency with large bowel obstruction and require emergency surgery. This is associated with increased mortality rate, prolonged stay in hospital, increased need for stoma formation and greatly reduced patient quality of life. This surgery should be provided by specialist colorectal surgeons.

Colonic stenting is an alternative to surgery for malignant large bowel obstruction as it allows relief of the obstruction while avoiding stoma formation in palliative cases. It can also facilitate bowel decompression (acting as a 'bridge to surgery') for those with resectable disease, avoiding the need for emergency surgery.

Previously published studies have reported small numbers with conflicting results and stenting in the potentially curative setting is still not recommended. Recent NICE guidance on this topic considered only evidence from randomised clinical trials. Significant challenges to completion of the CReST study included quality assurance and randomisation in the emergency setting.

Stent design will be the subject of a further randomised study. The potential complications associated with stenting include perforation, stent obstruction and stent migration. A recent systematic review concluded that tumour ingrowth was more common with uncovered stents, but that late migration occurred more frequently with covered stents, and expulsion causes significant morbidity. The evidence relating to stent design is very limited and further large scale randomised controlled trials are recommended to compare covered and uncovered stents to assess their clinical and cost-effectiveness.

Competing interests

I am chief investigator for the CReST trial which has now completed recruitment and for a planned trial of stent design (CReST 2). I have no financial conflict of interest.

11.35 - 11.50

Hall 1B

Richard Shaw, NIHR
Clinical Research
Network: Cancer
& University of
Liverpool, UK

NCRI and NIHR initiatives in surgical oncology Presentation of 2015 CREST award (Cancer Research Excellence in Surgical Trials)

The newly appointed national specialty lead for surgical oncology will present an update on initiatives in the network including:

- Tomorrow's leaders: training workshop for surgical registrars.
- CREST: recognition of excellence in the networks and the 2015 award announcement.
- Details of the surgical oncology portfolio – areas of strength and weakness.
- NCRI initiatives including the future of surgery workshop series and plans for NCRI in 2016.

11.50 - 12.00

Discussion

● Early diagnosis

10.00 – 10.05

Hall 1C

Max Parmar,
University College
London, UK

Introduction

This session will cover some recent developments in early diagnosis, including progress and reports from a number of ongoing and completed studies in this area.

10.05 – 10.30

Hall 1C

Willie Hamilton,
University of Exeter, UK

What can observational studies tell us about early diagnosis of symptomatic cancer?

It is axiomatic that early diagnosis of cancer is beneficial. However, the key clinical question is not the value of early diagnosis, but of expedited diagnosis. That matters, as interventions to expedite diagnosis act to bring forward diagnosis – which may (or may not) yield benefits. This talk will draw on the extensive observational studies in this field to try and answer four inter-related questions:

- a) Is expedited diagnosis useful?
- b) If so, by how much?
- c) If so, how can we offer expedited diagnosis to our patients?
- d) If so, can we estimate the health-economics of the subject to aim for cost-effectiveness as well as clinical effectiveness?

Observational studies have been conducted in many cancer sites, with breast and colorectal receiving most attention. What will be key is the level of reliance policymakers can have for such studies, given the relatively few randomised controlled trials in this field.

10.30 – 10.45

Hall 1C

Jo Waller, University
College London, UK

Proffered paper: Public understanding of the purpose of cancer screening – a population-based survey

Background

Cancer screening tests vary in whether their primary aim is to prevent cancer (through treatment of pre-cancerous lesions) or to detect cancer before symptoms emerge. Fear about what a screening test might find is often cited as barrier to participation, suggesting that if the public were aware that two tests (cervical screening and flexible sigmoidoscopy) were primarily preventive, this might reduce fear and increase uptake.

Method

We carried out a population based, face-to-face interview survey with 1,464 adults in or close to the screening age range (50-70 years) across Great Britain. They were asked whether they thought the primary aim of cervical, breast, faecal occult blood test (FOBT), and flexible sigmoidoscopy (FS) screening was to prevent cancer or detect it early.

Results

There was no sign that people were aware of the differences between the screening tests. Among women, 78% thought breast cancer aimed to detect cancer early, and the figure was only slightly lower at 72% for cervical cancer (only 19% knew it aims to prevent cancer). For colorectal screening (in men and women), 72% knew that FOBT aims to detect cancer early,

Parallel session abstracts *(continued)*

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but 70% also (incorrectly) thought that FS is primarily for early detection. Among 519 women aged 50-64 (i.e. eligible for cervical screening, a long-standing NHS programme), awareness of the preventive aims of the test was not associated with age, social class, or previous screening participation, suggesting knowledge is low across the board.

Conclusion

Greater efforts may be needed to communicate the potential preventive role of cervical and FS screening, and give the public a more nuanced understanding of the differences between different cancer screening tests.

10.45 - 11.10

Hall 1C

Usha Menon,
University College
London, UK

Ovarian cancer screening – update from UK trials

In the UK large ovarian cancer screening trials have been undertaken in both the general (United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and high-risk (UK Familial Ovarian Cancer Screening Study – [UKFOCSS] population. The 13 centre UKCTOCS is one of the largest individual randomised controlled trials. Between 2001-5, over 1.2 million women aged 50-74 were invited. 202,638 were randomised 2:1:1 to control (101,359), multimodal screening with serum CA125 interpreted using the Risk of Ovarian Cancer Algorithm (ROCA) with repeat CA125 and transvaginal ultrasound as second line tests (50,640) and ultrasound screening alone (50,639). Women underwent a median of 7 annual screens till December 2011. They were followed using data linkage to national registries and postal questionnaires. 346,990 annual screens (50,708 women) were undertaken in the multimodal arm. Sensitivity (89% prevalence, 85% incidence) and specificity (99.8% prevalence, 99.8% incidence) for detection of invasive epithelial ovarian/fallopian tube cancer (iEOC) was encouraging. The use of ROCA appeared to double the number of screen-detected iEOC detected during incidence screening compared to a fixed cut off used previously. 328,894 annual screens (46,237 women) were undertaken in the ultrasound arm. Sensitivity (75% prevalence, 62% incidence) and specificity (98.2% prevalence, 99.7% incidence) were lower. About 40% of all screen detected iEOC in both arms were stage I/II.

In the high-risk population, the multimodal strategy with a shorter screening interval of four months was investigated in UKFOCSS Phase II. 4,531 women underwent 14,263 women years of screening between 2007-2012. Such intensive screening led to women recalled for abnormal results experiencing transient cancer-specific distress but there was no significant effect on general anxiety/depression or overall reassurance. The strategy had high sensitivity and specificity. 42% of screen-detected iEOC were stage I/II.

The key issue is impact on ovarian cancer mortality, which will be available from UKCTOCS in December 2015.

Competing interests

Stock ownership in Abcodia Ltd, a UCL spin-off company with an interest in ovarian cancer screening.

11.10 - 11.35

Hall 1C

Janet A. Dunn,
Warwick Clinical Trials
Unit, Coventry, UK

Proffered paper: MAMMO-50: The results of the pre-planned internal 2 year feasibility study for mammographic surveillance in early breast cancer patients over 50 years of age at diagnosis*Background*

There is no clear evidence or consensus amongst surgeons on the optimum frequency or duration of follow-up and mammographic surveillance for early breast cancer patients who are 50 years and older at diagnosis. Mammo-50 aims to investigate frequency and duration questions whilst exploring alternative follow-up strategies. A pre-planned internal 2 year feasibility study has assessed acceptability of the trial and user perspectives. Quality of life (QoL) and patient reported outcome measures (PROMs) were also collected with the aim of identifying which questions to collect in the main trial.

Method

Mammo-50 is a multicentre, randomised controlled, phase III trial of annual mammography versus 2 yearly for conservation surgery and 3 yearly for mastectomy patients. There is also a linked observational cohort study of those eligible patients for whom the surgeon or patient opts for continued mammographic surveillance as per local practice. Patients are randomised 3 years after surgery.

Results

To date (31st May 2015) 843 patients (69%) have been randomised between the two arms and 371 patients (31%) have entered the cohort study. 82 sites are open to recruitment with an additional 17 in set-up, which indicates the target of 100 centres will be met. Of patients randomised, 74% have undergone conservation surgery, 89% have invasive disease, 82% aged 55-75 years, 83% ER +ve and 73% undergoing hormone therapy. Focus groups were undertaken, exploring experiences and perceptions of the trial and follow-up options (e.g. telephone, written or internet contact). Altruism was a common reason for entering the trial. Preliminary analysis of the QoL and PROM data indicate that 29% patients have raised level of distress with fatigue, sleep, memory/concentration, pain and itchy/dry skin reported as the more common problems.

Conclusion

Mammo-50 is an acceptable trial to patients and clinical teams. The findings from the feasibility phase demonstrate patients are willing to be entered into the study. The PROMs and QoL gathered within the feasibility phase demonstrate that 29% of early breast cancer patients 3 years post-surgery report distress.

Acknowledgements

Project funded by NIHR HTA programme (11/25/03). Views expressed are those of the authors and not those of the HTA programme, NIHR, NHS or the Department of Health.

Parallel session abstracts *(continued)*

11.35 - 11.50

Hall 1C

Richard Neal,
Bangor University, UK

Can we do randomised controlled trials of interventions to expedite the diagnosis of symptomatic cancer? And should we?

Interventions to expedite cancer diagnosis are hard to design and implement. This is because the 'solution' to expediting diagnosis is probably multi-factorial and involves change across a number of systems. These include patient awareness and help-seeking behaviour, GP education and clinical practice, GP's access to – and speed of – diagnostic investigations and specialist opinion, plus secondary care diagnostics. Hence, there are probably only a few simple interventions that may be amenable to trialling; additionally complex interventions are time-consuming and expensive.

We know that patients value investigations for potential cancer even at low risk, but we don't know whether patients find randomisation to the control arms of diagnostic trials acceptable. In recent years, there have been a small number of primary care trials of expediting cancer diagnosis. These have focused on, for example, lowering GPs' thresholds for diagnostic investigation, development and evaluation of educational interventions for GPs, and the use of computerised decision support tools. The findings – and design – of these trials will be presented, in order to address a number of questions:

- a) What type of interventions are amenable to be trialled – and which are not?
- b) How could /should we identify potential interventions for a trial?
- c) What are the best designs for such trials (individual, cluster, stepped/wedge)?
- d) Are participants willing to accept randomisation to control group if they are at risk of having a currently undiagnosed cancer?
- e) Does the time/effort/resource needed to undertake such trials outweigh the benefit of a higher level of evidence over observational studies?

11.50 - 12.00

Discussion

● **Economic impact of cancer**

10.00 - 10.05

Room 11

Robert Peston,
BBC Economics Editor,
London, UK and
Tito Fojo, Columbia
University Medical
Center, New York, USA

Introduction

10.05 – 10.40

Room 11

Richard Sullivan,
King's College
London, UK

Clash of cultures: the economic sustainability of cancer care and research across Europe

Cancer has a major economic impact across all European member states, estimated now to be over 185 billion euros every year, both in terms of direct costs of care, informal costs and productivity losses due to premature mortality and morbidity. Socio-demographic, particularly increasing inequality and social exclusion, political and fiscal factors are having significant negative effects on the sustainability of cancer costs, yet there has been little critical examination of public policy around national models of care and research. Our analysis of the European research landscape demonstrates significant disconnection and contradiction from a policy agenda that could deliver affordable, equitable cancer care. Furthermore macroeconomic projections suggest that many member states in Europe will never achieve affordable care, instead becoming increasingly unequal in their delivery of cancer services without radical re-structuring. The impact for Europe with its free movement of people is significant, and data will be presented to show projections to 2025.

10.40 – 11.15

Room 11

Maarten IJzerman,
University of Twente,
Enschede, The
Netherlands

How do health economists value personalised medicine in oncology?

Several clinical institutes and collaborative networks have implemented whole genome sequencing. Clinical and basic scientists expect genome sequencing may change current thinking in healthcare and management of patients, as it allows careful assessment of the molecular basis for targeted treatment. Also, developments in nanomedicine providing high-sensitive detection technologies such as technologies for detection of hypermethylated DNA, cell-free DNA in body fluids, or circulating tumour cells in blood. These markers may have added value for public health screening and for early detection of malignancies.

This presentation introduces the health economic considerations relevant for personalised medicine in general, and more specifically in relation to the added value of genome sequencing.

11.15 – 11.50

Room 11

Tito Fojo,
Columbia University
Medical Center,
New York, USA

The cost of cancer drugs in the US: why we must look beyond published data

Viewed by many as the system to emulate, our approach to cancer patients in the US is, like that of any other country, far from perfect. Many argue that the system is not sustainable and it is increasingly obvious that this is so. Included amongst the reasons for this problem is the high cost of pharmaceuticals, including those developed to treat cancer. A majority of approved cancer drugs are available to a majority of patients with cancer – often “off-label” – and one can say with confidence this will not change appreciably as it represents “the American way”. It is therefore incumbent on oncologists to ensure our decisions are evidence-based and that the evidence is sound. In this regard I would argue we have to consider several factors: [1] Clinical trial results are the best one can possibly achieve. Numerous examples have shown that once a drug has been approved outcomes in the community are inferior. This is often attributed to the use of agents in patient populations who are less fit and in patients who have already had multiple lines of therapy. The inferior outcomes obtained after drug approval makes estimates of cost/benefit somewhat misleading, given that such calculations are a best-case estimate and fail to account for results obtained once drugs enter the community setting. [2] Clinical trial results apply only to the setting in which they were conducted. One cannot extrapolate to other settings. Particularly, clinical trial results cannot be expected to be the same or even similar with more advanced disease or after other therapies have been received. [3] Increasingly marginal results that achieve statistical significance with large numbers of patients are of concern. The push to accept endpoints other than overall survival is problematic because outcomes such as progression-free survival can be greatly influenced by the extent of censoring, emerging

Parallel session abstracts *(continued)*

as an increasing problem in oncology trials. [4] In a clinical trial not everyone achieves the median benefit. Especially with marginal results, only a small percentage of patients achieve meaningful benefit and others are actually harmed. One can expect that the more marginal the results the greater the fraction of patients that are harmed. [5] Harm from a therapy can take many forms but most often is manifested as physical toxicity. In the era of targeted therapy, such toxicity can be a major problem because these agents are administered daily. This assumes special importance because such toxicity is usually managed by dose reductions and this invariably means reduced efficacy.

While cancer patients looking for hope in a therapy often voice the sentiment that nothing can be worse than the death they feel is a certainty, seasoned oncologists know there is something far worse – death from cancer complicated by the toxicity of a treatment that brought no benefit. The US system is unlikely to change or adapt a rational approach such as that employed by NICE. Its hope lies in oncologists, especially academic oncologists, ensuring our therapies bring more than marginal benefits, are based on studies applicable in the community and are as free of toxicity as possible.

11.50 - 12.00

Discussion

● Late breaking proffered papers

10.00 - 10.05

Room 12

Introduction

10.05 - 10.25

Room 12

Chris Brown,
National Cancer
Registry, Cork, Ireland

Effect of pre-diagnostic NSAID use on ovarian cancer survival

Background

There is some evidence in breast, colorectal and prostate cancer that patients who use nonsteroidal anti-inflammatory (NSAID) drugs have better survival. There is conflicting evidence of benefit in ovarian tumours. Our objective was to determine the association of pre-diagnostic NSAID use with survival in ovarian cancer patients in Ireland.

Method

Women diagnosed with invasive ovarian cancer (ICD-10 code C56) between 2001-2011 were identified in a retrospective cohort study from the National Cancer Registry. Those with continuous eligibility for a (means-tested) medical card in the year immediately prior to diagnosis were identified and linked to community prescription records. Any NSAID prescription in the year prior to diagnosis was determined. Date and cause of death was sourced from linked death-certificates. Association between exposure and cause-specific survival (end of follow-up: 31/12/2012) was estimated using Cox regression (adjusted for: age, smoking, marital status, year of diagnosis, urban/rural, local area deprivation, ovarian cancer stage and grade, surgery at diagnosis). Secondary analysis accounting for competing risks was conducted. Analysis by type of NSAID (aspirin/other) was pre-planned.

Results

Of 3097 invasive ovarian cancers diagnosed 2001-2011, 1823 (59%) had had a medical card history for at least one year prior to diagnosis and, of these, 1123 (62%) had some exposure to NSAIDs in that year. 78% of women in the cohort had died by 31/12/2012 (median follow-up=5.8years). Pre-diagnostic NSAID use was associated with improved ovarian cancer-specific survival (AHR=0.84, 95%CI 0.74, 0.96) as well as other causes (AHR=0.62, 95%CI 0.42, 0.93). Adjusting for competing risks, NSAID use was no longer significant (cancer-specific: 0.90 (0.78, 1.05), other causes: 0.75, (0.5, 1.11)). Effects were similar for aspirin and other NSAIDs.

Conclusion

In this, the largest ever study of NSAID use in ovarian cancer, we observed an association between pre-diagnostic NSAID use and cancer specific survival. The association was no longer observed after adjusting for competing risks.

Acknowledgements

Project funding, Health Research Board Ireland; Registry funding, Department of Health Ireland.

Chris Brown¹, Thomas Ian Barron², Kathleen Bennett², Linda Sharp^{1,3}

¹ National Cancer Registry Ireland, Cork, Ireland, ² Trinity College Dublin, Dublin, Ireland, ³ Newcastle University, Newcastle, UK

10.25 - 10.45

Room 12

David Dearnaley,
The Institute of
Cancer Research &
The Royal Marsden
NHS Foundation Trust,
London, UK

5 year outcomes of a phase III randomised trial of conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer [CRUK/06/016]: report from the CHHiP Trial Management Group

Background

CHHiP is a non-inferiority trial to determine efficacy and safety of hypofractionated radiotherapy (hRT) using intensity modulated radiotherapy.

Method

Patients with node negative T1b-T3a localised prostate cancer (PCa) were randomised (1:1:1 ratio) to 74 Gray(Gy)/37 fractions(f) (control), 60Gy/20f or 57Gy/19f. The primary endpoint was PCa progression, defined as freedom from biochemical failure (Phoenix consensus guidelines) or PCa recurrence. 3213 patients were needed to rule out 5% inferiority (80% power, one-sided alpha 5%) assuming 70% event-free in the control arm (critical hazard ratio (HR): 1.208). Toxicity was assessed to week 18 post start of RT and late side effects 6 monthly to 2 years (yr) and yearly to 5yr by RTOG, LENT-SOM and patient reported outcomes (PROs).

Results

3216 patients were randomised between 2002 and 2011. Baseline characteristics were well balanced: median age 69yr; PSA 10.1ng/ml; NCCN risk group 15% low, 73% intermediate, 12% high. With median follow up of 62 months, 5yr progression-free rate (95%CI) was 74Gy: 88.3% (86.0%, 90.2%); 60Gy: 90.6% (88.5%, 92.3%), 57Gy: 85.9 (83.4, 88.0); HR60: 0.83, 90%CI (0.68, 1.03), HR57: 1.20, 90%CI (0.99, 1.45). Acute RTOG grade 2+ (G2+) bowel toxicity was higher in patients receiving hRT, with no significant difference in G2+ bladder toxicity. Late toxicity profile was favourable with significantly less RTOG G2+ bowel toxicity observed with 57Gy compared to 74Gy at 2yr, but no significant difference at 5yr. G2+ bladder toxicity showed no significant difference between control and experimental groups at 2yr or 5yr. Analysis of LENT-SOM and PROs supported these results.

Parallel session abstracts *(continued)*

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Conclusion

After 5yr follow up, 60Gy/20f is non-inferior to control for PCa progression and is not associated with significant differences in late toxicity. 57Gy/19f has not been shown to be non-inferior. hRT using 60Gy/20f appears effective and safe and may be recommended as a new standard of care.

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10.45 – 11.05

Room 12

Richard Hubner,
The Christie Hospital
NHS Foundation Trust,
Manchester, UK

Expanded analyses of NAPOLI-1: Phase 3 study of nal-IRI (MM-398), with or without 5-fluorouracil (5FU) and leucovorin (LV), versus 5-fluorouracil and leucovorin (5FU/LV), in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy

Background

Nal-IRI is a nanoliposomal encapsulation of irinotecan. OS in the ITT-population was significantly longer with nal-IRI+5FU/LV over 5FU/LV alone (median OS for nal-IRI+5FU/LV was 6.1m (95%CI=4.8-8.9m; N=117) vs 4.2m (95%CI=3.3-5.3m; N=119) for 5FU/LV (unstratified HR=0.67; 95%CI=0.49-0.92; log-rank test p=0.012). Most frequent grade 3+ AEs included neutropenia, fatigue, and GI-effects (diarrhoea and vomiting).¹ Expanded, pre-specified analyses of the Phase-3 study have been presented.²

Method

Patients with mPAC (n=417) previously treated with gemcitabine-based therapy, were randomized 1:1:1 in an open-label study to receive: (A) Nal-IRI (120mg/m² IV over 90min) q3w; (B) 5FU (2,000mg/m² over 24h) plus racemic LV (200mg/m² over 30min) x4w followed by 2w rest; or (C) combination of nal-IRI (80mg/m² IV over 90min) prior to 5FU (2,400mg/m² over 46h) and racemic LV (400mg/m² over 30min) q2w. The primary endpoint was OS. The Intent to Treat (ITT)-population included all randomized patients; the Per Protocol (PP)-population included patients who received at least 80% of the target dose in the first 6 weeks and did not violate any inclusion/exclusion criteria.

Results

Analysis of the PP-populations confirmed the favourable OS, which was also reflected by the PFS, ORR and CA19-9 levels, of the combination nal-IRI+5FU/LV over the control 5FU/LV arm. Median OS in the PP-population for nal-IRI+5FU/LV-arm was 8.9m (95%CI=6.4-10.5m; N=66) vs 5.1m (95%CI=4.0-7.2m; N=71) for 5FU/LV (unstratified HR=0.57; 95%CI=0.37-0.88; log-rank test p=0.011). The nal-IRI-monotherapy arm did not show a statistically significant improvement in OS compared with the control arm. Analysis of subgroups, based on pretreatment characteristics including stage at diagnosis, time since initial histological diagnosis, prior lines of therapy, time since last prior therapy, and CA19-9, consistently favoured OS for the nal-IRI+5FU/LV arm over the 5FU/LV arm.

Conclusion

Expanded analysis of the PP-population and sensitivity analyses support the favourability of nal-IRI+5FU/LV over 5FU/LV, with a manageable safety profile. Clinical trial information: NCT01494506.³

References

1 Ann Oncol (2014) 25 (suppl 2): ii105-ii1062. J Clin Oncol 33, 2015 (suppl 3; abstr 234)3. Clinical trial information: <https://clinicaltrials.gov/show/NCT01494506>

Richard Hubner¹, Li-Tzong Chen^{2,3}, Daniel D. Von Hoff^{4,5}, Chung-Pin Li^{6,7}, Andrea Wang-Gillam⁸, György Bodoky⁹, Andrew Dean¹⁰, Yan-Shen Shan^{2,3}, Gayle Jameson^{5,11}, Teresa Macarulla^{12,13}, Kyung-Hun Lee¹⁴, Jean-Frédéric Blanc¹⁵, Chang-Fang Chiu¹⁶, Gilberto Schwartzmann¹⁷, Jens T. Siveke¹⁸, Fadi S. Braiteh¹⁹, Victor M. Moyo²⁰, Bruce Belanger²⁰, Eliel Bayever²⁰, David Cunningham²¹

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11.05 - 11.02

Room 12

John Wagstaff,
Swansea University,
UK

CheckMate 025: a randomized, open-label, phase III study of nivolumab versus everolimus in advanced renal cell carcinoma (RCC)

Background

Treatments for advanced or metastatic RCC (mRCC) are associated with limited overall survival (OS) in previously treated patients.

Method

Adults with advanced or metastatic clear-cell RCC, 1–2 prior anti-angiogenic therapies (≤ 3 prior systemic), measurable disease (RECIST v1.1), and Karnofsky performance status $\geq 70\%$ were randomized (1:1) to nivolumab 3 mg/kg intravenously every 2 weeks or everolimus 10 mg orally once daily (NCT01668784). Treatment continued to progression/unacceptable toxicity; treatment post-progression allowed based on investigator-assessed benefit. Primary endpoint: OS. Results are from a planned interim analysis.

Results

Patients (white, 88%; male, 75%; median age, 62 years; 1 [72%] versus 2 [28%] prior anti-angiogenic therapies for advanced RCC) were randomized to nivolumab (n=410) or everolimus (n=411). Minimum follow-up: 15 months. Median (95% confidence interval [CI]) OS: 25.0 months (21.8–not estimable [NE], nivolumab) vs 19.6 months (17.6–23.1, everolimus; hazard ratio [HR], 0.73; 98.5% CI, 0.57–0.93; P=0.0018). Objective response rate: 25% (102/410, nivolumab) versus 5% (22/411, everolimus; odds ratio, 6.05; 95% CI, 3.69–9.91; P<0.0001). Median (95% CI) progression-free survival: 4.6 mo (3.7–5.4) for nivolumab vs 4.4 mo (3.7–5.5) for everolimus (HR, 0.88; 95% CI, 0.75–1.03; P=0.1135). 370/410 (90%; nivolumab) and 386/411 (94%; everolimus) were evaluable for programmed death-ligand 1 (PD-L1) expression. Median OS (95% CI): 21.8 months (16.5–28.1; nivolumab)

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and 18.8 months (11.9–19.9, everolimus) in patients with $\geq 1\%$ PD-L1 expression (25%, nivolumab; 23%, everolimus); and 27.4 months (21.4–NE, nivolumab) and 21.2 months (17.7–26.2, everolimus) in patients with $< 1\%$ PD-L1 expression (75%, nivolumab; 77% everolimus). Treatment-related adverse events (TRAEs): 79% (nivolumab) and 88% (everolimus) of patients; grade 3 or 4: 19% and 37%, respectively.

Conclusion

Primary endpoint was reached; treatment-experienced patients with advanced RCC lived longer with nivolumab than with everolimus, regardless of PD-L1 expression. TRAEs were less frequent with nivolumab than with everolimus.

Padmanee Sharma¹, Bernard Escudier², David F. McDermott³, Saby George⁴, Hans J. Hammers⁵, Sandhya Srinivas⁶, Scott S. Tykodi⁷, Jeffrey A. Sosman⁸, Giuseppe Procopio⁹, Elizabeth R. Plimack¹⁰, Daniel Castellano¹¹, Howard Gurney¹², Frede Donskov¹³, Petri Bono¹⁴, John Wagstaff¹⁵, Thomas C. Gauler¹⁶, Takeshi Ueda¹⁷, Li-An Xu¹⁸, Ian M. Waxman¹⁹, Robert J. Motzer²⁰

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11.25 - 11.45

Room 12

Paula Mulvenna,
Northern Centre
for Cancer Care,
Newcastle upon
Tyne, UK

Can WBRT be omitted in NSCLC patients with brain metastases not suitable for stereotactic radiosurgery or surgical resection? Results from the UK Medical Research Council QUARTZ randomised clinical trial.

Background

Brain metastases affect up to 40% of patients with non-small cell lung cancer (NSCLC), and for inoperable cases, whole brain radiotherapy (WBRT) and dexamethasone is standard treatment. However there are no randomised clinical trials to show whether WBRT improves either quality of life or survival.

Method

A phase III randomised non-inferiority trial with a primary outcome measure of quality adjusted life years (QALYs). Patients with inoperable brain metastases from NSCLC, were randomly allocated to either optimal supportive care (OSC), including dexamethasone, plus WBRT 20 Gy/5f (OSC+WBRT) or OSC alone. The trial sought to exclude more than a one week detriment in QALYs in the OSC alone arm.

Results

From 2007-2014, 538 patients were recruited from 69 UK and 3 Australian centres. Baseline characteristics were well balanced: 58% male; median age 66 years (range 38 – 85); 38% Karnofsky performance status (KPS) < 70 ; 54% extracranial metastases; 30% solitary brain metastasis.

Median survival was 66 days (OSC+WBRT) vs 57 days (OSC), hazard ratio 1.10 (95% CI 0.93 – 1.30). The mean QALY was 45.4 days (OSC+WBRT) vs 41.2 days (OSC), difference

-4.2 days (90% CI -13.5 - +4.7).

In subgroup analyses, younger age, higher KPS, metastases confined to the brain, controlled primary tumour, and lower recursive partitioning analysis (RPA) or graded prognostic assessment (GPA) class were all prognostic of improved QALYs and overall survival.

Younger patients (<60) appeared to derive more benefit from WBRT in terms of both QALYs and overall survival than older patients (≥70).

Conclusion

This is the only large randomised trial evaluating WBRT in NSCLC. Although the results include the pre-specified non-inferiority margin of one week, the estimate of the difference in QALYs is small, questioning the widespread use of WBRT. RPA and GPA class, whilst prognostic of improved QALYs and survival, were not predictive of benefit from WBRT.

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11.45 - 12.00

Discussion

● MicroRNA and non-coding RNA

10.00 - 10.05

Hall 1A

Nicola Valeri,
The Institute of
Cancer Research,
London, UK

Introduction

10.05 - 10.30

Hall 1A

Martin Bushell,
Medical Research
Council Toxicology Unit,
Leicester, UK

MicroRNA mechanism and its involvement in DNA damage response pathway

The discovery of microRNAs (miRNAs) has revolutionised the way in which we view gene expression. In human's there are approximately 1000 miRNAs in the genome, each on average targeting ~200 different mRNAs, with estimates suggesting that at least 60% of all protein encoding mRNAs are controlled by miRNAs. Intensive analysis of tissues from a large diverse set of human diseases has shown dramatic alterations in the miRNAs profiles following disease onset. Moreover, global changes in miRNA function either by alterations in the miRNA biogenesis pathways or changes in the target miRNA's 3'UTR length have been observed in many disease setting. Regardless of the dysregulation mechanisms, miRNAs have been shown

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to be sufficient and required for the development of a number of diseases, particularly cancer. These small non-coding RNA molecules inhibit gene expression by binding to complementary regions within target mRNAs. It is well known that following engagement with the target mRNA, miRNAs induce both the translation repression and cause mRNA destabilisation of the targeted mRNA. However, the exact mechanism by which these small RNA molecules control gene expression has remained elusive. Here I will discuss our investigations into how miRNAs control gene expression and show how the miRNA biogenesis enzymes appear to have a second pivotal cellular function, moonlighting in the DNA repair pathway.

10.30 - 10.45

Hall 1A

Marta Larrayoz,
University of
Southampton, UK

Proffered paper: The splicing inhibitor Spliceostatin A down-modulates Mcl-1 expression and induces a potent apoptotic response in Chronic Lymphocytic Leukaemia cells

Background

The pro-survival Bcl-2 family member Mcl-1 is expressed in chronic lymphocytic leukaemia (CLL), with high protein expression correlated with progressive disease. Nonetheless, Mcl-1 antagonists have shown limited effects. The SF3B1 inhibitor spliceostatin A (SSA), is known to regulate Mcl-1, so we assessed the ability of SSA to elicit apoptosis in CLL.

Method

Primary CLL cells, normal lymphocytes and Ramos cells were exposed to increasing concentrations of SSA and apoptosis and downstream signalling evaluated by flow cytometry and immunoblotting, respectively. Next, we explored whether Bcl-xL expression was a resistance mechanism for SSA by inducing the protein with IL-4/CD40L and whether the combination of SSA with the Bcl-2/Bcl-xL inhibitor ABT-263 presented any additive/synergistic effects within the CLL cells.

Results

SSA induced apoptosis of CLL cells at low nanomolar concentrations in a dose-, time- and caspase-dependent manner, but independently of SF3B1 mutational status and progressive disease markers. However, normal B and T cells were significantly more resistant to SSA treatment than CLL samples ($P=0.002$). SSA-induced apoptosis was proceeded via an increase in MCL-1 gene splicing from the MCL-1L isoform into the MCL-1S isoform which resulted in a subsequent decrease in Mcl-1L protein expression ($P\leq 0.001$). The role of Mcl-1 in regulating SSA-induced apoptosis was also observed in Ramos cells where over-expression of non-spliceable Mcl-1L, significantly protected them from SSA-induced apoptosis. SSA-induced apoptosis of CLL cells treated with CD40L and IL-4, factors known to induce Mcl-1 and prosurvival Bcl-xL, was significantly reduced. Therefore, to explore possible strategies for overcoming this resistance, we investigated combining SSA with ABT-263 and showed that dual exposure to both inhibitors significantly increased apoptosis, overcoming the protective effects of IL-4/CD40L.

Conclusion

SSA has a potent apoptotic effect on CLL cells through Mcl-1 inhibition. SSA alone or in combination with Bcl-2/Bcl-xL antagonists may have therapeutic utility for this incurable leukaemia.

10.45 - 11.10

Hall 1A

Gabriella Sozzi,
National Cancer
Institute, Milan, Italy

miRNA as biomarkers for early lung cancer detection

Detection of lung cancer at an early stage offers the real potential to reduce mortality with new chances of cure. Although low-dose CT screening (LDCT) is currently the standard of care for early lung cancer detection, it results in a general over diagnosis of indolent nodules, thus increasing unnecessary confirmatory diagnostic procedures. Circulating microRNAs (miRNAs), represent promising complementary biomarkers since they act as extracellular messengers of biological signals derived from the cross-talk between the tumor and its surrounding microenvironment. We developed a miRNA signature classifier (MSC) containing 24 miRNAs and tested its performance in an enlarged validation set composed of 85 patients and 1000 controls belonging to the MILD trial [1,2]. The results of this study showed that the combination of MSC and LDCT reduced LDCT false-positive rate from 19.4% to 3.7% and that the MSC risk groups were significantly associated with survival. The diagnostic characteristic of MSC that showed high sensitivity (87%) and specificity (81%) coupled with an NPV of 99% indicates that MSC is a clinically useful screening test. Importantly, the diagnostic performance of MSC as a predictor of lung cancer development was confirmed by the time dependency analysis given the availability of pre-disease plasma samples. More recently, taking advantage of results obtained in two screening programs with a total follow up of 23,967 person-years and a median time follow-up of 5.9 years, we proved the prognostic value and the disease-monitoring capacity of MSC in lung cancer patients identified in LDCT screening programs (unpublished data). The results presented highlight the clinical usefulness of circulating miRNAs as predictive, diagnostic, prognostic and monitoring tool in lung cancer.

11.10 - 11.25

Hall 1A

Simon Wigfield,
University of
Oxford, UK

Key role of AGO2 and the 8q24 amplicon in regulation of microRNA biogenesis in cancer*Background*

MicroRNA (miRNA) biogenesis requires a range of enzymes, processing, stabilising and transportation factors to produce a functional miRNA. Disruption of component factors can occur by changes at the genomic level including DNA copy number aberrations. Cancer genomes accumulate such genomic changes to promote cancer progression.

Method

Using a comprehensive list of processing machinery genes we explore the effect of genomic amplification on miRNA biogenesis in multiple cancer types with a focus on three integrated genomic datasets from Breast Cancer patients. We compared expression and amplification profiles for the genes to find the most disrupted candidates with a prognostic impact.

Results

AGO2 was identified as frequently amplified (> 26%) as well as exhibiting prognostic relevance (Cox p-value = 0.01424, HR = 1.4). It is the central component of the miRNA silencing complex and is responsible for recruiting the mature miRNA to target and thereby silence the mRNA. It is co-amplified with PABPC1 ($p < 2.2e-16$), another component of the RISC. Both are located in the 8q24 region and co-expressed with multiple relevant driver genes including MYC. Interestingly, AGO2 mRNA has a poor prognostic effect independent of MYC (Cox p-value = 2.21e-05, HR = 3.3).

Conclusion

This study has highlighted the disruption of an important player in the miRNA biogenesis pathway. Using independent patient sets we show AGO2's role and validate these findings in vitro.

Parallel session abstracts *(continued)*

11.25 - 11.50

Hall 1A

Carlos Caldas,
Cancer Research
UK Cambridge
Institute, UK

The miRNA landscape of breast cancer

Abstract not received.

11.50 - 12.00

Discussion

● **Rare tumours**

10.00 - 10.05

Room 3B

Matt Seymour,
NIHR Clinical
Research Network:
Cancer, Leeds, UK

Introduction

Rare cancers collectively account for over 20% of new cancer diagnoses: more than any individual common cancer. However, while expansion in cancer clinical and translational research are establishing a robust evidence base and improving outcomes for most common cancers, many rare cancers have been left behind. In this session, we explore the challenges of rare cancer research. These include translational approaches, novel clinical trial methods to maximise information when a large sample size is not possible, initiatives for international collaboration and the potential for genomics-based precision medicine approaches in rare cancer.

10.05 - 10.30

Room 3B

Lucinda Billingham,
Cancer Research
UK Clinical Trials
Unit, School of
Cancer Sciences
and University of
Birmingham, UK

Methodology to influence clinical practice in rare cancers

Methods for investigating interventions to influence clinical practice are dominated by large phase III randomised controlled trials comparing experimental treatments with standard of care. Regulatory bodies and research funders acknowledge that trials in rare diseases are challenging and indicate that less conventional methodological approaches may be acceptable. Strategies that maximise recruitment, minimise sample size or maximise the utility of the evidence may enable the application of conventional clinical trial design to rare cancer populations. Alternative designs that address specific challenges for rare cancers with the aim to potentially influence clinical practice include Bayesian designs, uncontrolled n-of-1 trials and umbrella and basket trials. Rare cancers fall on a sliding scale of rarity and different methods may be appropriate at different points on the scale. This presentation will review the methods, illustrated with real world examples and highlight approaches that have been implemented by the International Rare Cancers Initiative.

10.30 - 10.45

Room 3B

**Juan Pedro Martinez-
Barbera,** University
College London, UK

Proffered paper: Adamantinomatous craniopharyngioma contains senescent cells with tumour-inducing potential

Background

Adamantinomatous craniopharyngioma (ACP) is a paediatric pituitary tumour that is associated with high morbidity due to the tendency of the tumour to infiltrate locally into surrounding brain structures such as the hypothalamus and visual tracts. We have developed and validated two mouse models for human ACP, which have provided original insights into the aetiology and pathogenesis of human ACP (1-3). Recently, we revealed a novel and

intriguing mechanism by which Sox2+ve pituitary stem cells contribute to oncogenesis, which is fundamentally different to the classical cancer stem cell paradigm. When targeted to express oncogenic beta-catenin, mutant Sox2+ve stem cells do not give rise to the progeny populating the tumour, instead these oncogenic stem cells induce tumorigenesis in a paracrine manner (3). Our current research aims to dissect the molecular and cellular mechanisms underlying this paracrine involvement for stem cells in tumorigenesis.

Method

We use a multidisciplinary approach combining state-of-the-art mouse genetics with histological, molecular and stem cell biology methods. We use our ACP mouse models to investigate basic mechanisms, which are subsequently validated in human samples of ACP available to us through the GOSH hospital.

Results

Our research indicates that senescence and the senescence-associated secretory phenotype are critical players for tumour initiation. Specifically, we show that following a short burst of proliferation, oncogenic Sox2+ve cells stop dividing to form beta-catenin-accumulating cell clusters that become senescent. These clusters show senescence-associated beta-galactosidase activity, p53 pathway activation and up-regulate the expression of the cell cycle inhibitors p21 and p16. Additionally, cluster cells show elevated expression of lysosomal components and activate the autophagy pathway. Oncogenic beta-catenin also causes DNA damage as evidenced by an increase in H2A.X phosphorylation, triggering the DNA damage response. As a consequence, NF- κ B signalling is elevated resulting in the expression of activation a Senescence-Associated Secretory Phenotype (SASP) with expression of multiple secreted factors including pro-inflammatory cytokines such as IL1, IL6 and IL8. Of translational significance, we show that this mechanism is relevant in human ACP tumorigenesis. Beta-catenin-accumulating cell clusters in human ACP express several senescence markers such as p21, p16 and lysosomal enzymes, exhibit DNA damage and activate P53, NF- κ B and autophagy pathways, resulting in SASP activation.

Conclusion

Together, the mouse and human data suggest that senescence and SASP are likely to modify the tumour microenvironment resulting in cell transformation and tumour growth.

10.45 - 11.10

Room 3B

Ultan McDermott,
Wellcome Trust
Sanger Institute,
Cambridge, UK

The value of genomics in rare cancers

The sequencing of rare cancers has lagged behind that of the more common tumour types. This has been largely a consequence of their rarity and the realisation that in more common tumours the degree of genomic heterogeneity is only captured by sequencing many hundreds of patients. However, there is increasing evidence that the genomic landscape of some of these more obscure tumours can be simpler than that of their more prevalent counterparts and thus be amenable to definition, using in some cases a handful of samples. These less complex mutational landscapes offer the opportunity for a more focussed look at oncogenic processes and provide fundamental insights into cancer biology. We can therefore make a compelling case for the systematic characterisation of the entire compendium of rare tumours and that this would be best achieved through focussed international consortiums, such as the International Rare Cancers Initiative and the EORTC SPECTArare programs.

Competing interests

Founder and consultant, 14M Genomics.

Parallel session abstracts *(continued)*

11.10 - 11.25

Room 3B

Jeremy S. Whelan,
University College
Hospital, London, UK

Proffered paper: EURAMOS-1: an international collaboration for osteosarcoma

Background

Osteosarcoma treatment involves surgery of the primary tumor and metastases plus pre- and postoperative chemotherapy; high-dose methotrexate, adriamycin (doxorubicin), and cisplatin (MAP) is an international standard. Histologic response to pre-operative chemotherapy is prognostic for survival. The European and American Osteosarcoma Study trial, EURAMOS-1, assessed alternatives. We reflect on the findings and the challenges.

Method

Patients were registered before MAP chemotherapy and were assessed for response at surgery. "Poor responders" were randomized postoperatively to continue MAP (to week 29) or to augment MAP with high-dose ifosfamide and etoposide (to week 40; MAPIE). "Good responders" were randomised to continue MAP then have 18 months maintenance pegylated Interferon- α -2b or not. The primary outcome measure was event-free survival.

Results

2,260 patients from 17 countries joined EURAMOS-1. 716/1,041 "good responders" were randomised. There was no evidence of improved EFS with interferon (HR=0.83, 95%CI 0.61-1.12), complicated by one quarter not starting their allocated interferon. 618/1,059 "poor responders" were randomised. There was no evidence MAPIE improved EFS (HR=0.99, 95%CI 0.79 to 1.24) but was associated with more severe acute toxicities, poorer treatment compliance and increased secondary acute leukaemias. In the full cohort, 3-yr and 5-yr estimates of EFS from biopsy were 60% (95%CI 57 to 62) and 54% (95%CI 52 to 57) and survivals at 3-yr and 5-yr from biopsy were 79 (95%CI 78 to 81) and 71% (95%CI 69 to 73).

Conclusion

Data from the trial do not support a change away from MAP in post-operative treatment for patients with a good response nor those with a poor response. The EURAMOS investigators surmounted considerable practical challenges in undertaking this trial. The consortium will initiate further front-line trials in an expanded collaboration when agents suitable for testing are identified. Current efforts focus on finding genomic and immunologic targets.

11.25 - 11.50

Room 3B

Denis Lacombe,
EORTC, Brussels,
Belgium

Changing the paradigm for therapeutic progress for rare tumours: SPECTA rare "Optimising molecular profiling technologies through partnerships"

Building on the pan European EORTC SPECTA (Screening Patients for Efficient Clinical Trial Access) already up and running in frequent tumours, the program is being customised for rare tumours. Molecular profiling technologies able to detect multiple gene alterations convey promises to develop new treatments based on robust biological information for unknown and scarce tumour types. Well-structured prospective programs based on high quality data collection can not only help structuring for systematic collection of rare cases, but also allow for the evolution of new system development for research. There is an absolute necessity to improve the quality of diagnostic, treatment and care for rare diseases. A current challenge is to bring latest and fast developing technologies to the patients ensuring therapeutic progress based on knowledge development platform. Integrating research and care is an even greater need for rare tumours as few therapeutic options are sound, at a time when expertise is still scattered across centres, health care providers and researchers. New forms of platforms such as screening models allow optimal access to new treatments.

SPECTARare is a unique pan European standardised quality assured molecular screening platform for tumour characterisation. It allows long term patient follow up and enables continued acquisition of clinical, biological and imaging data after all lines of treatment as part of routine clinical care to understand patterns of resistance and relapses. Access to new treatments is subject to revisited development methods currently being addressed by regulators and the pharmaceutical industry sector. For instance adaptive licensing may evolve alongside new forms of clinical studies such as pre-approval bench marking studies and post approval observational studies for clinical situations where the classical drug development models are no longer applicable. Therefore, new methodological advances are needed and can be best developed through multi-stakeholder partnerships and collaboration through molecular screening platforms.

11.50 - 12.00

Discussion

● **Selecting rational combinations for cancer and delivering early phase clinical trials in the UK**

10.00 - 10.10

Room 3A

Hazel Jones, Cancer Research UK, London, UK and **Udai Banerji**, The Institute of Cancer Research, London, UK

Introduction

Combination strategies must be investigated earlier in the drug development pipeline to maximise opportunities. This session will provide an overview of current models and collaborative ways of working to support investigator led combination clinical trials, involving UK academia, biotech and pharma. The Experimental Cancer Medicine Centres (ECMC) Combinations Alliance (<http://www.ecmcnetwork.org.uk/ca>) will be presented along with novel preclinical and clinical data describing lessons learnt from the different collaborative experiences. A focus will also be given to radiotherapy-drug consortium (RaDCom) and indications not typically followed by industry. The ECMC Combinations Alliance has grown considerably over the last 12 months and new initiatives are currently being considered.

Even with their significant resources, drug companies can only explore a fraction of all possible treatment combinations. So frameworks for different combination strategies allows investigation of safety and preliminary efficacy, whilst encompassing novel biomarkers to ensure combination therapies are tailored to the patient's disease. Successful delivery is essential in today's competitive environment and Combinations Team in CRUK Centre for Drug Development adds robust process and efficiencies to drive these studies forwards. In addition, the ECMC Combinations Alliance Joint Steering Committee shapes future strategy, triages the broad range of ideas submitted and identifies proposals that require additional preclinical rationale.

There is huge opportunity to maximize the effective use of targeted therapies in combination with other targeted therapies or conventional agents such as chemotherapy or radiotherapy. The introduction will cover important questions that need to be answered in order for these strategies to succeed clinically, with examples from drugs targeting the PI3 kinase pathway.

Parallel session abstracts *(continued)*

10.10 - 10.35

Room 3A

Anne Thomas,
University of
Leicester, UK

DEBIOC: a Combinations Alliance Study of AZD8931 in combination with oxaliplatin and capecitabine chemotherapy in patients with oesophago-gastric adenocarcinoma

Treatment options for patients with oesophago-gastric cancer remain poor. AZD8931 is a novel small-molecule inhibitor which has equipotent activity against signalling by three members of the erbB family: EGFR, erbB2(HER-2), and erbB3. Our hypothesis is that combining AZD8931 with chemotherapy will be effective not just in patients who overexpress high levels of HER-2, but those with low HER-2 expression as well. This study seeks to establish the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of AZD8931 with oxaliplatin and capecitabine (XELOX) in patients with oesophagogastric cancer (OGC).

In protocol design, special attention was paid to potential overlapping toxicity from AZD8931 and XELOX. Moreover, in line with Combination Alliance studies a two phase approach was required: escalation and a randomised expansion including a control arm. To maximise recruitment rates the dose-escalation phase was planned in chemo-naïve all-comers with OGC although we wished to expand the study in patients receiving neoadjuvant chemotherapy; this would facilitate a translational substudy. We recognised the importance of planned dose delivery in the neoadjuvant setting and therefore in addition to classical Dose Limiting Toxicity (DLT) definitions, another DLT definition was utilised: failure to deliver 100% of the planned dose of XELOX due to toxicity attributable to AZD8931 or the AZD8931/XELOX combination.

For the dose escalation a rolling 6 method was used and patients received oxaliplatin (130 mg/m² day(d) 1 every 21 days (q21) and capecitabine (X) (1250mg/m²/d) d1-21, for a maximum of 8 cycles. AZD8931 dosing was planned for 3 cohorts (20mg bd, 40 mg bd, 60 mg bd continuously). In the expansion phase, 20 operable patients were planned to receive 2 cycles of the RP2D combination and 10 patients XELOX alone pre oesophagectomy.

In this talk, demographic, safety, PK and early results from the expansion phase will be presented.

10.35 - 11.00

Room 3A

Susan Galbraith,
AstraZeneca Oncology
Innovative Medicines,
Cambridge, UK

Combinations alliance from an industry perspective

Recent drug development successes have led to launches of targeted therapies with high response rates to monotherapy treatment for example EGFR inhibitors in the treatment of patients whose tumours have an activating EGFR mutation. However, emergence of resistance mechanisms and reactivation of pathway signalling in the targeted pathway limit the extent of cancer cell kill which can be achieved by monotherapy, so combinations are critical to further improve outcomes. Indeed, the history of cancer drug development shows substantial improvements in long-term patient outcomes have more frequently been built via combination regimens.

Thus early investment in understanding the potential for rational combinations with both currently available standard of care therapies and for novel-novel combinations is important. Access to the Combinations Alliance has enabled the more rapid assessment of such combinations in parallel with the initial development plan for Phase I and II stage development compounds. Examples include trials of AZD2014 (a dual TORC1/2 inhibitor) with weekly paclitaxel in the TAX-TORC study, which has tested different combination schedules and delivered early proof of principle in lung and ovarian cancer settings. Another example is the combination of AZD5363 (an AKT inhibitor) with olaparib (PARP inhibitor). Both examples illustrate the need for consideration of dose and schedule to optimise the safety and potential for efficacy by understanding the PK/PD relationship and the links to triggering cell death.

These examples will be discussed in the context of the value of such trials to broaden and enrich early development programmes.

Competing interests

I am a full time employee of AstraZeneca.

11.00 - 11.25

Room 3A

Anthony Chalmers,
University of
Glasgow, UK

Progressing radiotherapy-drug combinations towards early phase clinical trials

The Radiotherapy-Drug Combinations consortium (RaDCom) was established in 2013 by the NCRI Clinical and Translational Radiotherapy working group (CTRad) and Cancer Research UK's Centre for Drug Development (CDD), in response to a clear requirement for high quality preclinical data to support the development of radiotherapy (RT) combination trials. RaDCom is a collaborative network of UK-based laboratories working in partnership with industry, Cancer Research UK and other funding bodies; it seeks to work with UK-based investigators to develop and deliver preclinical projects evaluating specific RT-drug combinations. The Cancer Research UK New Agents Committee Preclinical Combination Grant scheme provides one of the funding options for these studies, with the potential to feed into early phase clinical trials via the ECMC Combinations Alliance. RaDCom members have been working closely with industrial partners to design and deliver studies to evaluate novel agents which may provide a better therapeutic ratio for cancer patients receiving radiotherapy as part of their treatment. We facilitate the coordination of industry interactions, triage new proposals, monitor active projects, and engage with the RT community to promote collaboration and networking (via a capability map). RaDCom also supports CTRad initiatives to overcome other barriers to RT-drug combination advances including working to improve preclinical quality assurance and identifying a route to registration for RT-drug treatments. These activities will place the UK at the forefront of radiotherapy-drug preclinical research and provide a significant incentive for pharmaceutical companies to invest in this area and utilise the RaDCom network.

11.25 - 11.50

Room 3A

Timothy Yap,
The Institute of
Cancer Research &
The Royal Marsden
NHS Foundation Trust,
London, UK

Novel inpatient dose escalation phase I trial of two schedules of the combination of the PARP inhibitor olaparib and AKT inhibitor AZD5363 in BRCA1/2 and non-BRCA1/2 mutation patients with advanced cancers

In vivo synergy between PARP and phosphatidylinositol 3-kinase pathway inhibition was seen in BRCA1-related and sporadic cancers, providing rationale for this study. A novel inpatient dose escalation trial design was used to optimise drug exposures and accelerate drug development (Yap et al, JCO 2013).

Two-stage investigator-initiated ECMC Combinations Alliance phase I trial: a) inpatient dose escalation; b) recommended Phase II combination dose (RP2CD) expansion. Advanced cancer patients received escalating doses of AZD5363 BD in 2 parallel arms (4-days-on 3-days-off [4/7 arm]; 2-days-on, 5-days-off [2/7 arm]) with olaparib at 300mg BD 3-weekly. Pharmacokinetics and pharmacodynamics were assessed. Next generation sequencing of tumour and plasma DNA was undertaken in all patients. The first patient's first treatment was achieved <6 months after CR-UK NAC approval. Dose escalation was completed in 7.5 months in 20 patients in 1 centre. 30 advanced cancer patients (15 with BRCA1/2 mutations) were enrolled. Common G1-2 toxicities were gastrointestinal symptoms, fatigue and anaemia. A DLT of G3 rash was seen at 480mg BD 4/7 AZD5363 + 300mg BD olaparib. Non-DLT G3 anaemia (n=2), diarrhoea (n=2), fatigue (n=1) and vomiting (n=1) were seen in 4/7 arm (n=10), while G3 hyperglycemia, transaminitis, anaemia, diarrhoea

Parallel session abstracts *(continued)*

(all n=1), rash (n=2) and fatigue (n=3) in 2/7 arm (n=20). No obvious PK drug-drug interactions were observed. pSer9 GSK3 β decreased on therapy in platelet-rich plasma at all dose levels. Multiple responses were seen in BRCA1/2 and non-BRCA1/2 mutation tumours, including 4 confirmed RECIST partial responses. A BRCA1 mutation prostate cancer patient has MRI and PSA responses for 11m+. A peritoneal mesothelioma patient (prior PI3K/mTOR inhibitor) has RECIST stable disease for 12m+ with CA125 response.

This novel trial design led to rapid completion of dose escalation. RP2CD expansion is ongoing in: a) germline BRCA1/2 mut cancers; b) sporadic cancers with relevant somatic mutations.

Competing interests

Research funding from AstraZeneca.

11.50 - 12.00

Discussion

Workshops

● Prognostic modelling and evaluation of diagnostic tests – £75

09.50 – 13.00

Room 14

Abdel Douiri,
King's College
London, UK

This is an introductory course for anyone interested in finding out more about statistical tools related to the assessment of the effectiveness of new diagnostic tests and mathematical tools related to the development and validation of prognostic models in clinical practice. This course will suit researchers, clinicians and non-clinicians who have an interest in optimising diagnostic test and prognostic systems, and might need to present their work for publication.

Visit the on-site registration desk to book your place.

Drug Discovery and Development Course

This course, designed primarily for PhD students and Post Docs, offers a day of interactive learning and development in small groups with experts in drug discovery from industry and academia.

09.50 - 10.10 Register
Room 4

10.10 - 12.00 What makes a good oncology drug target: building a case for working on a new target
Steve Wedge, Northern Institute for Cancer Research, Newcastle University, UK
David Blakey, Oncology IMED, AstraZeneca, UK
Susan Critchlow, Oncology IMED, AstraZeneca, UK

12.00 - 13.15 Break
Attend the plenary lecture by **Carl June**, University of Pennsylvania, USA (12.20 - 13.00, Hall 1A), get some lunch and take the opportunity for career discussions with speakers/mentors.

13.15 - 14.10 Generation of chemical leads to a target: approaches and challenges
Allan Jordan, Cancer Research UK Manchester Institute, UK

14.10 - 14.20 Break

14.20 - 15.30 Translational science and early clinical development
Paul S. Jones, Cancer Research UK Centre for Drug Development, London, UK

15.30 - 16.00 Roundtable Q and A
Lead by **Nigel Brooks**, Cancer Research UK Manchester Centre, UK