



Workshop report: Biomarkers, Biostatistics & Novel Clinical Trial Design

Meeting summary

- 100 delegates from a variety of specialties attended this one-day workshop in London, organised by the NCRI Biomarkers & Imaging CSG and supported by Imperial Cancer Research UK Centre.
- Chaired by Professor Bob Brown (Imperial College London), the workshop provided an overview of the challenges and opportunities associated with biomarkers, biostatistics and clinical trial design.
- Key points from the talks and breakout groups are summarised below. Slides are available at http://ncrndev.org.uk/index.php?option=com_content&task=view&id=134&Itemid=272.
- Biomarker development and clinical trial design should operate hand-in-hand.
- Model-based approaches, such as the Continual Reassessment Method, should be considered for determining the recommended dose in future phase I trials.
- Adaptive clinical trial design should consider allowing for tumour stratification and testing of targeted agents on the basis of developing – but not yet fully validated – biomarker data.
- While the development process for a biomarker will differ depending on the type, a valid biomarker should have practical utility/clinical significance, quantifiable variables and agreed levels of validity.
- The choice of trial design used in the phase II setting depends on the strength of evidence for the current biomarker and the disease setting.
- Quality assurance and standard operating procedures (SOPs) are critical, with further development of guidelines necessary for all trial phases.

On Thursday 27th September 2012, the National Cancer Research Institute (NCRI) Biomarkers and Imaging Clinical Studies Group (BI CSG), supported by the Imperial Cancer Research UK Centre, hosted a workshop entitled 'Biomarkers, Biostatistics and Novel Clinical Trial Design' at the W12 Conference Centre in London. The workshop was attended by 100 members of the research community who were interested in learning more about the challenges and opportunities associated with biomarkers, biostatistics and clinical trial design.

Introduction to the workshop

Professor Bob Brown (Imperial College London) opened the meeting, welcomed attendees to the workshop and explained aims and objectives for the day. Professor Brown gave a brief introduction to the BI CSG and explained the group's remit and four workstreams. Workstream 4 has a focus on

education and public engagement and has led to the introduction of the BI CSG running open educational workshops 2-3 times per year. Professor Brown also mentioned that the BI CSG does not currently have a bioinformatics and biostatistics working group (workstream 3) and the opportunity to develop an interest group in this area may arise as an output from this workshop.

Introduction to challenges in clinical trial design incorporating biomarkers

Mr Jim Paul (Cancer Research UK Clinical Trials Unit, University of Glasgow) addressed the new era in drug development, where molecular diagnostics have allowed a more rational division of heterogeneous cancers and the selection of specific populations of patients for targeted drugs. Mr Paul cautioned that while this development has potential benefits, including reduced toxicities and improved cost-effectiveness, this is dependent on whether the correct patients are selected, stressing the importance of avoiding unnecessary or inaccurate selection. Mr Paul then reviewed lessons learned from the 'HER2 and trastuzumab' and 'EGFR and gefitinib' stories and concluded by suggesting that in the development process for a targeted agent, clinical trial and associated sample data are key to correctly defining/refining/confirming the associated biomarker; thus, the biomarker development and clinical trial design should operate hand-in-hand.

Phase I: Adaptive design of dose escalation phase I trials

Dr Adrian Mander (Medical Research Council Biostatistics Unit) gave a brief introduction to phase I trials, noting that the primary aim of these trials is to establish a maximum tolerated dose (MTD). Dr Mander moved on to describe the 3+3 design, discussing an example and pointing out that while the 3+3 is easy to implement, a maximum of only 6 patients are treated at the MTD, thus precision may be poor. The Continual Reassessment Method (CRM) was introduced as an alternative to the popular 3+3 design. The CRM is an adaptive Bayesian method which uses a dose-response model, but requires prior knowledge for dose selection. Dr Mander reviewed the CRM process, noting a few modifications that are now widely used as the original method tended to expose patients to unacceptably high doses. Extensions of the CRM were also described, including Escalation with Overdose Control (EWOC), Time-to-Event (TITE) monitoring, combination trials and efficacy and toxicity trials, all of which have advantages and disadvantages as compared to one another. Dr Mander concluded by encouraging the use of model-based approaches rather than the 3+3 design in future clinical trial design.

Phase II: Review of novel clinical trial designs using biomarkers in phase II trials

Mr Roger A'Hern (Institute of Cancer Research) began his talk by briefly describing the differences between phase IIa and phase IIb trials. Mr A'Hern then reviewed a number of the pitfalls that can arise, such as those due to multiple testing. It was noted that in a phase II trial, both marker-positive and marker-negative patients should be enrolled. Mr A'Hern reviewed a number of phase II trials with novel designs, including FOCUS-4 in colorectal cancer, which used a multi-arm, multi-stage (MAMS) design, I-SPY2 in breast cancer, which employed a Bayesian design, BATTLE in non-small cell lung cancer, which utilised a Bayesian design with an adaptive randomisation and finally, TOPARP in prostate cancer which aimed to assess multiple predictive biomarkers. Mr A'Hern suggested that the best biomarkers of response to 'X' may be better detected after a short exposure to 'X', describing examples of trials involving Ki67 as a marker of tumour proliferation and introducing tumour size as a novel continuous variable, briefly describing a trial in advanced pancreatic cancer.

Phase III: A new comprehensive, molecularly stratified trial design for a common cancer: the FOCUS4 trial programme for colorectal cancer

Professor Rick Kaplan (Medical Research Council Clinical Trials Unit) opened with a list of reasons why new trial designs are necessary and why conventional designs are unsatisfactory, particularly noting the lengthy time it takes to confirm clinical benefit of a new agent and to validate a meaningful biomarker. Professor Kaplan reviewed a number of lessons learned from the COIN and FOCUS3 trials, including that colorectal cancer has clearly defined molecular subtypes that appear to segregate the population and that biomarker characterisation is possible in a multicentre trial taking place across the NHS. With those in mind, FOCUS4 was designed as a phase II/potential phase III trial with an aim to rationally test selected targeted drugs for single-agent or combined-agent activity. Professor Kaplan described the FOCUS4 design in detail, emphasizing both its and MAMS's main advantages, notably, an adaptive nature, which allows for efficient incorporation of new information or drugs into the trial. Professor Kaplan finished by outlining the funding structure behind FOCUS4 that has made a trial of this design possible. His overall conclusion was that this design, and others to be developed, should allow for stratifying tumours and initiating testing of targeted agents on the basis of developing – but not yet validated – biomarker data.

Breakout Session 1: Biostatistical challenges: How to define validation

The first breakout session, chaired by Professor Jorge Reis-Filho (Institute of Cancer Research) and Mr Matt Sydes (Medical Research Council Clinical Trials Unit), began with the definition of a biomarker, where it was noted that a biomarker might be diagnostic, prognostic, predictive, metabolic and/or pharmacogenetic amongst other characteristics. Professor Reis-Filho and Mr Sydes then outlined the general process of biomarker development, suggesting that because clinical assay development and retrospective validation require significant efforts and receive little recognition or reward, it's often difficult to progress past this point of the development path. While the process of development may differ depending on the type of biomarker, generally, 3 stages of development should be proven: analytical validity, clinical validity and clinical utility (per Evaluation of Genomic Applications in Practice and Prevention guidelines). Professor Reis-Filho and Mr Sydes then reviewed the issue of validity, at which time a question from the group arose asking if it's necessary to understand the biology of a biomarker if you know it works. General consensus revealed that in order to deem a biomarker 'valid', it should have practical utility/clinical significance, quantifiable variables and agreed levels of validity. The session continued with a discussion of the many challenges of biomarker validation including, but not limited to, potential for subjectivity, lack of Level I evidence, lack of reward and high risk of failure. The group concluded by indentifying of number of key factors to achieve successful biomarker validation, most notably the important of a reliable and tolerant assay that can be used on 'real-life' samples.

Breakout Session 2: Design challenges: How to incorporate biomarkers into phase II clinical trials

The second breakout session, chaired by Mr Jim Paul, Mr Roger A'Hern and Dr Robert Jones (Beatson Oncology Centre, University of Glasgow), addressed how biomarkers could be incorporated into phase II clinical trials using two studies as examples. Dr Jones began with an overview of a phase Ib/IIa study of AZD2014 in combination with gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma (PDAC Study). The study's design was presented by Mr Paul, who outlined the pros and cons of the three different study designs considered in its development (restricted to

‘target’; partially enriched - gateway testing; partially enriched - fall back testing). A fourth alternative design based on a recently published paper (Randomized Phase II Trial Designs With Biomarkers Boris Freidlin, Lisa M. McShane, Mei-Yin C. Polley, and Edward L. Korn J Clin Oncol 30:3304-3309) was also discussed. Dr Jones followed by presenting the rationale for the second trial, TO-PARP, a study to determine whether a PARP-inhibitor is effective in patients with metastatic, castration-resistant prostate cancer. Mr A’Hern discussed the possible alternative designs to the funded protocol, concluding they were not feasible. The presentations sparked discussions surrounding the difficulty with getting fresh samples for biomarker analysis and problems with the reliable/consistent assessment of samples in the lab. The group debated ethical concerns of study designs where experimental treatments are given to non-target groups and whether these concerns might be addressed through the patient information sheet. The session concluded the trial design used in phase II rests crucially on the strength of evidence for the current biomarker and the disease setting. While there is not a one size fits all approach, it may often be necessary to include patients from the “non-target” group in order to demonstrate/refine the clinical utility of the proposed biomarker.

Breakout Session 3: Bioinformatic challenges: How to integrate complex data sets using different molecular endpoints

The third breakout session, chaired by Professor Yike Guo (Imperial College London) and Dr Ed Curry (Imperial College London), focused on the logistical issues surrounding bioinformatics and the challenges of data analysis. Professor Guo began with a detailed overview of an integrated informatics system called eTRIKS (European Translational Research Information and Knowledge Management Services), a new informatics platform for collaborative translational research whose development is being led by Imperial College London. eTRIKS is based on a previous system called U-BIOPRED (Unbiased Biomarkers for Predicting Respiratory Disease Outcomes), which was an earlier integrated informatics system that resulted from a collaboration between 10 pharmaceutical companies and 30 academic medical centres. Professor Guo reviewed example of how U-BIOPRED has been used for integrated data analysis and how the system was extended to create eTRIKS, outlining the objectives, architecture, curation process and timeline for eTRIKS. Professor Guo finished by noting that eTRIKS will serve projects associated with the Innovative Medicine Initiative and that Imperial College London is interested in potential collaboration with translational research groups during development of the platform. Dr Curry then gave a talk on the logistical issues of data integration and subsequent data analysis. Analysis of integrated data sets can provide more powerful and robust results, a more complete picture of biological mechanisms and contextual interpretation of results. Dr Curry focused on the issues surrounding integration of datasets with multiple molecular endpoints, aptly suggesting that some problems may not have solutions and the key to appropriate analysis is to consider the biological or clinical question at hand. Potential methods to integrate copy number alteration and gene expression were explained and Dr Curry stressed that interpretation of any results requires a detailed understanding of the method of analysis used. There was a sense that appropriate training and sharing of expertise will be key if the ultimate goal is to empower people to analyse their own data. It was suggested that perhaps bioinformatics standards should be adopted to make interpretation of data easier. However, this is likely not feasible as there isn’t a gold standard for analysis; appropriate data analysis should follow a ‘fit for purpose’ approach.

General discussion

Following the breakout sessions, the breakout session chairs gave brief summaries of the discussions that took place in their respective sessions and the floor was then opened to general discussion, chaired by Professor Bob Brown. Data quality was an early theme; the concept of 'bad data in, bad data out' was echoed throughout the group and quality assurance and standard operating procedures (SOPs) were deemed critical. Wide implementation of SOPs to ensure data quality was identified as the main challenge and it was suggested that clear guidelines might be necessary. Professor Brown noted that this was an issue to raise at a higher level, highlighting the important role of NCRI Pathology Leads. The meeting was then brought to a close and delegates thanked for their attendance and valuable input.

Mrs Jenny Lewandowski, Dr Katy Coxon, Miss Laura Chambers, Professor Bob Brown - October 2012