Multiple Biopsies Forum Discussion Notes
Wednesday 25th February 2015 4:00-7:00pm

Basement Lecture Theatre, ICR Chester Beatty Laboratories,
237 Fulham Road, London SW3 6JB

Attendees:

Patient Advocate Groups (PAG):

Independent Cancer Patients Voice (ICPV) & Cancer Partnership Research Group (CPRG):

Garry Bisshopp	Helen Bulbeck	Helen Edwards	Chris Finch
Jacqui Gath	Mairead MacKenzie	Melody McLaren	Ian McLaren
Adrienne Morgan	Hilary Stobart	Anna Wallace	Maggie Wilcox
Sophie Gasson			

The Patients and Carers Research review Panel based at the Royal Marsden Hospital:

Jonathan Powell	Anita Gray	Kathy Grant

ICR/RM Staff:

Judith Bliss, Director, ICR-CTSU
Claire Snowdon, Deputy Director & Operations Director, ICR-CTSU
Laura Stevenson, Senior Trials Manager, ICR-CTSU
Sophie Perry, Senior Trials Manager, ICR-CTSU
Leona Batten, Trial Manager, ICR-CTSU
Maggie Cheang, Translational Scientist/Biomarker Analyst, ICR-CTSU
Nick Turner, Senior Lecturer & Consultant Medical Oncologist, ICR/RM
Andrew Tutt, Consultant Medical Oncologist & Director of the Breakthrough Breast Cancer Unit, ICR
Alistair Ring, Consultant Medical Oncologist, RM
Peter Barry, Consultant Oncoplastic Breast Surgeon, RM
Mitch Dowsett, Head of the Academic Department of Biochemistry and Head of the Centre for Molecular Pathology RM, Professor of Biochemical Endocrinology and Professor of Translational Research at Breakthrough Breast Cancer Centre, ICR
Stephen Johnston, Consultant Medical Oncologist, RM
Belinda Yeo, Clinical Research Fellow, RM
Laura Sparks, Assistant Research Practitioner, Breast Cancer, RM
Diane Mackie, Research Practitioner, Breast Cancer, RM

1. Mitch Dowsett Presentation: Why do we need multiple biopsies?

MD discussed what is meant by the term 'multiple biopsies', the requirement for multiple biopsies in research and how they have been used effectively in previous clinical trials.

PAG Question: How can you be sure when taking a biopsy that you are not seeding cancer cells? And are core cut biopsies a risk?

PB – Some tumours have evidence of seeding but clinically this doesn't seem to be an issue.

AR – Chemotherapy is given prior to and after surgery to reduce the size of the tumour prior to surgery and kill any remaining cancer cells following surgery.
- Blood samples have shown shedding of cancer cells into the blood but long term there is no evidence of poor prognosis
- Conclusion: may need to have lots of cells to cause seeding.

JB – POETIC trial collected long term follow up of patients and the trial will look at those patients with high rate of relapse and investigate the factors which may have caused this relapse.

PAG Question: How do you approach multiple tumours and differences within tumours (heterogeneity)?

MD - Mutations do vary across samples, still need to work out how important this is.
- Different markers can be picked up in different areas of the tumour and tumours change and evolve over time.

PB – multiple biopsies required as the tumour changes over time, can better characterise the tumour by performing more biopsies at different time points – heralds the need for more than one biopsy at different time points/sites.

PAG Question: What is shedding?

PB – cancer cells detected in the bloodstream at time of operation, quite common but no long term significance in most women.
- Biopsy has less risk of shedding, surgery more risk of shedding as the tumour is being manipulated.

2. Nick Turner Presentation: Clinical trials based on minimal residual disease detection in early breast cancer.

NT discussed potential use of circulating tumour DNA (ctDNA) in the blood as a marker to predict relapse months before relapse is visible on a CT scan.

PAG Question: Does the presence of ctDNA directly correlate to risk of relapse?

NT – current evidence suggests ctDNA in the blood is 90% predictive value for relapse i.e. detectable ctDNA = relapse.

PAG Question: If patients will always go on to relapse would you act on presence of ctDNA in the blood?

NT – ctDNA is currently still an experimental marker for relapse and so not standard practice at the moment. Trials are planned to assess this technique for the prediction of relapse further and these could lead to a change in standard practice in the future.

PAG Question: How much does this test cost?

NT – Still experimental at the moment so costs are high but the consumables required to perform the test equate to approximately £100.

PAG Question: Do you screen for one mutation at a time or multiple mutations at the same time?

NT – Technology is still experimental but is advancing rapidly and it is possible to screen for multiple genes at the same time as per next generation sequencing.

AT – exciting prospect which is very doable and very affordable if shown to improve outcomes and treatment of cancer.

PAG Question: False negatives – in the study presented why did 3 patients without ctDNA detected in the blood relapse?

NT – these 3 patients all had metastases in the brain, ctDNA wasn't detectable in the blood due to the blood brain barrier.

3. Nick Turner presented the ctDNA Screening Trial Design

NT presented the ctDNA screening trial design which will include patients who have already completed curative treatment. Routine follow up in this group of patients is to perform annual mammograms (not by CT scan). The patient's tumour tissue will be screened for the presence of a target mutation as a marker to track ctDNA in the blood. Those with the target mutation will commence ctDNA screening. If ctDNA is detected in the blood, staging investigations will be performed to confirm whether local recurrence or metastases are visible on a CT scan, if so the patient will be treated for progression off trial. If not, the patient will be randomised between a treatment arm and an observational control arm. Patients allocated to the treatment arm would commence targeted treatment for 1 year and continue to be screened for the presence of ctDNA. The observational arm would not receive trial treatment but would continue to be screened to monitor the presence of ctDNA in the blood.

Key question the trial aims to answer: can we clear ctDNA with treatment?

Challenges: Need to confirm that ctDNA clearance does not occur by chance.

This is an initial phase II study which will try to address the questions that need to be answered to inform the design of a follow on phase III study.

So far the evidence suggests that ctDNA is not cleared by chance but could not assume this is the case for the high patient numbers required to run a phase III study.

Propose that the control arm will be blinded to ctDNA screening results. Patients would consent to randomisation in advance and if they had a positive ctDNA result and were randomised to the control arm they would not be informed of this but they would continue with ctDNA screening and be none the wiser.

PAG – *Could be that the intervention arm is worse off with side effects from the trial treatment and no outcome and so this trial is not just as simple as benefit vs no benefit for participants.*

- Whole purpose is to see how the patients benefit if at all.

- You are comparing the experimental arm with best available treatment so far (e.g. standard practice for this group of patients is no further intervention and annual

mammograms) so the design of this trial is ethically acceptable.

PAG Question: Why can't the patients in the control arm be informed of the positive ctDNA result?

NT – It could be difficult to tell a patient they are positive for ctDNA but that we don't yet fully understand what this means for them.

PAG *– most patients would want to be involved and want to know.*

PB – could you offer a cross over and therefore if a patient has a positive ctDNA they could have targeted treatment?

AR – everyone could be given treatment for a fixed period of time then stopped in stages.

NT – want to look for relapse and a crossover design would blur the trial outcome.

JB – need to get this trial into clinic asap and need it to be as efficient as possible to allow the trial to move quickly to a phase III design and have the potential to change practice.

PAG *- Should give all information to the patient and ethically should explain the design, the potential risks and benefits of participating in the trial in the patient information sheet and it should be up to the patient to decide if this is a trial they would like to participate in based on all the information.*

- e.g. the OPTIMA trial where the patient provides their tissue sample but may or may not be on the experimental arm. The patient isn't told whether they are receiving chemotherapy as part of the control arm or part of the experimental arm. As an individual it was ok to not know as the trial may see benefit for the NHS.

SJ – suggested a placebo controlled double blind trial design but recognised this would increase the cost.

NT – confirmed that randomisation would be 3:1 treatment to control arm.

AT – ctDNA use as a marker for relapse is not yet validated, question whether we should be giving this information to the patients as we aren't sure of the meaning yet.

NT – options: placebo-controlled but increases cost dramatically with use of placebo or could tell patients of the positive ctDNA result but offer regular CT scans within both arms of the trial e.g. every 3 months for early relapse detection.

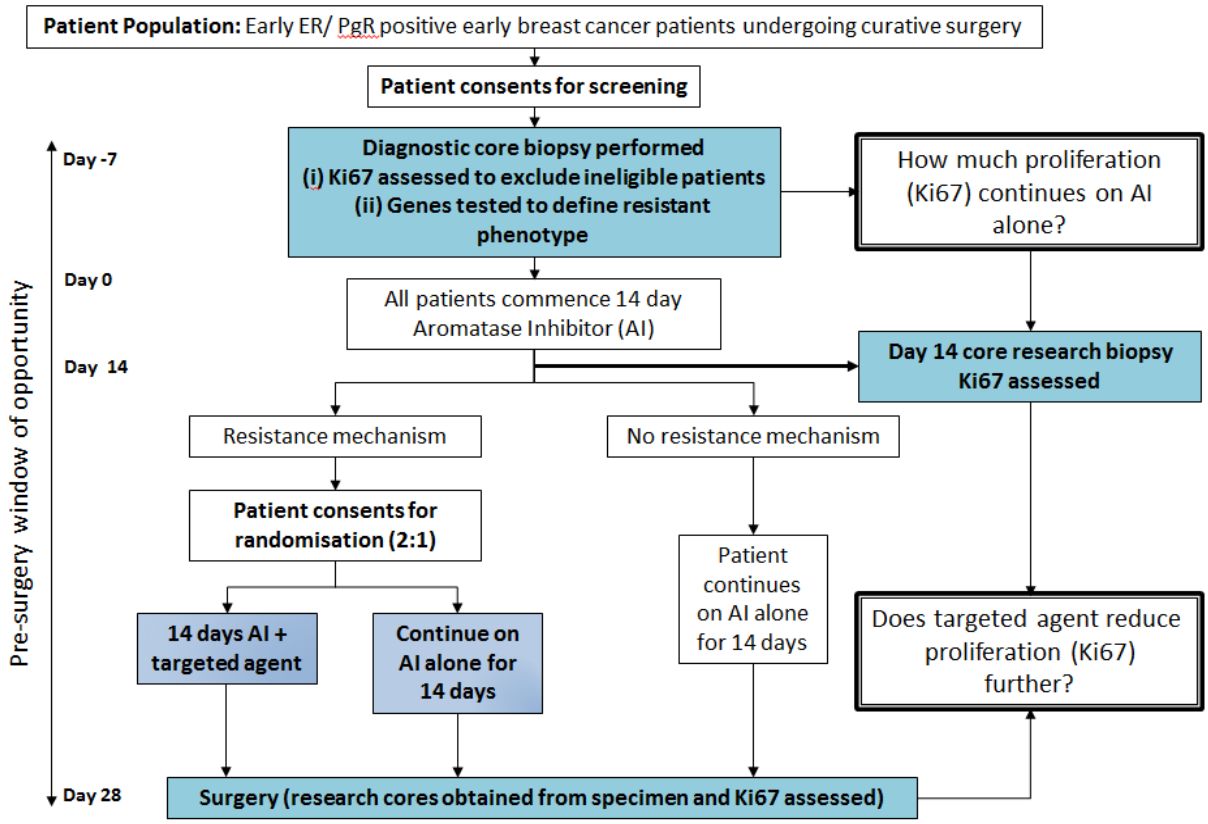
PAG *– Some patients don't want treatment and so could be happier with allocation to an observational arm.*

NT – commented the trial will also be testing patient acceptance of the design for a potential future follow on phase III design.

PAG Question: What are the technicalities of taking and processing the blood samples for ctDNA screening?

NT – currently the bloods would need to be processed and frozen within 2 hours of collection and shipped on dry ice to a central lab for testing. In the future it may be that the bloods can be taken and shipped in blood boxes in standard post.

4. Mitch Dowsett presented the POETIC-2 Trial Design



MD presented the POETIC-2 trial design shown above which will be performed in the pre-surgery window of opportunity.

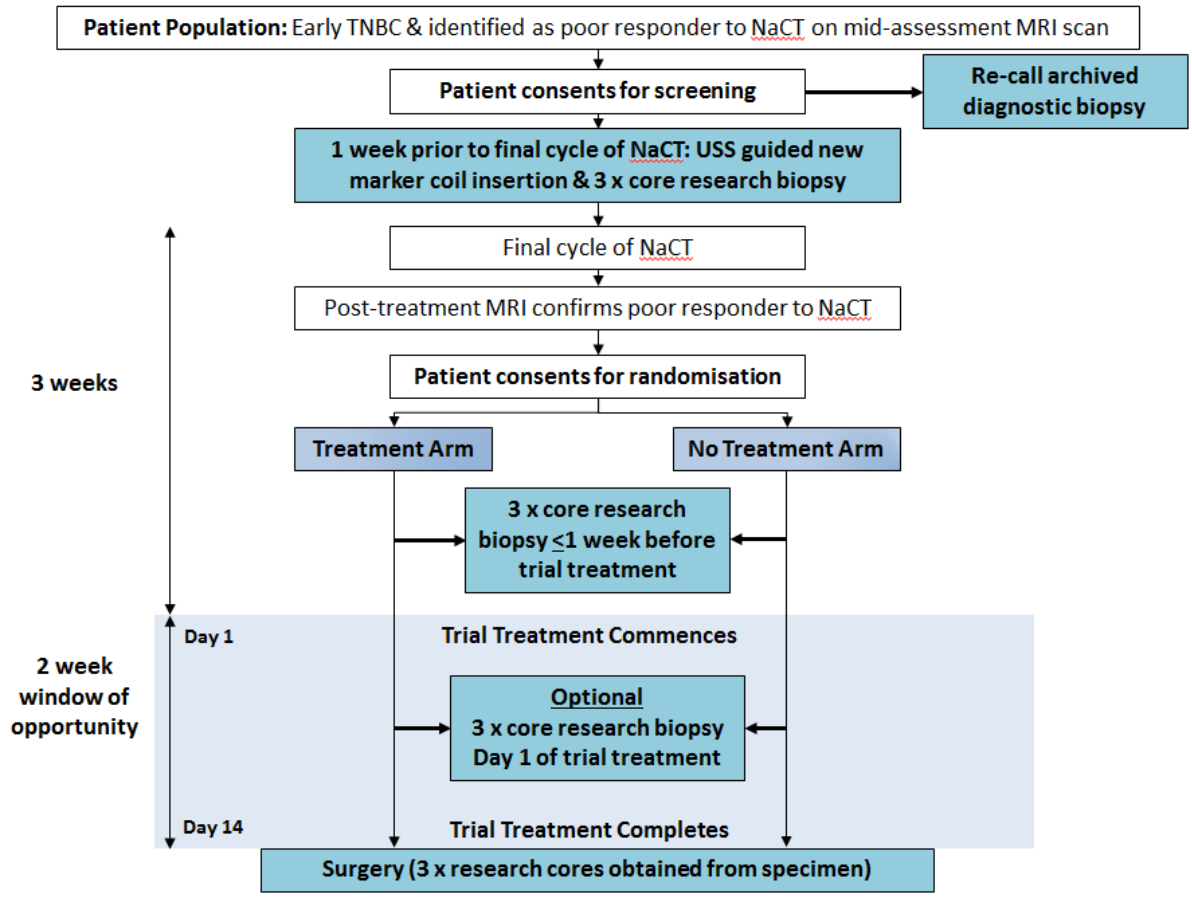
Challenge: need to reassure the patient that a potential delay to surgery is ok.

PAG *– evidence delaying surgery does not make a difference to outcome and would be able to reassure the patient that they are on active treatment already.*

PAG Question: If a patient was found to be resistant to AI as shown in the trial schema what would you do continue to treat for 5 years with AI?

MD – perhaps resistance is the wrong word and it should be insensitive in that the patient may still be benefiting from AI treatment but has the opportunity to do better and so they could be randomised to receive an additional targeted treatment.

5. Andrew Tutt presented the PHOENIX Trial Design



AT presented the PHOENIX trial design shown above which plans to use the 4-5 weeks between a patients chemotherapy and surgery to accelerate drug development and test drug combinations. Patients will have a metal clip 'marker coil' inserted one week prior to the final cycle of pre-surgery chemotherapy to mark where the tumour was and so future biopsies can be taken from the same location.

Challenges: Time in between trial biopsies acceptability to the patient (i.e. bruising or risk associated with biopsy) and logistics of obtaining biopsies.

PAG *- Ok to have optional biopsy if this will be performed on the day of treatment to avoid patients having to organise additional travel.*
- will depend on patient's prior experience of biopsy, need to ensure patients are looked after and handled carefully. Also need to make sure aftercare is good.
- could use finer needles which would be less invasive.
- need to ensure 2 weeks to recover from chemotherapy.

PAG Question: Could you perform the biopsies at the GP surgery or patient's home?
AT – need to be able to process the tissue quickly and accurately biopsy the same part of the tumour. Often image guided/quality control biopsies so need to be performed in an experienced setting i.e. hospital.

PAG Question: Is 14 days a long enough time period to show a difference between the arms?

AT – it depends on the timing of the biopsy and the drug being tested e.g. Ki67 shows very quickly.

PAG Question: Will there be side effects of the trial treatment?

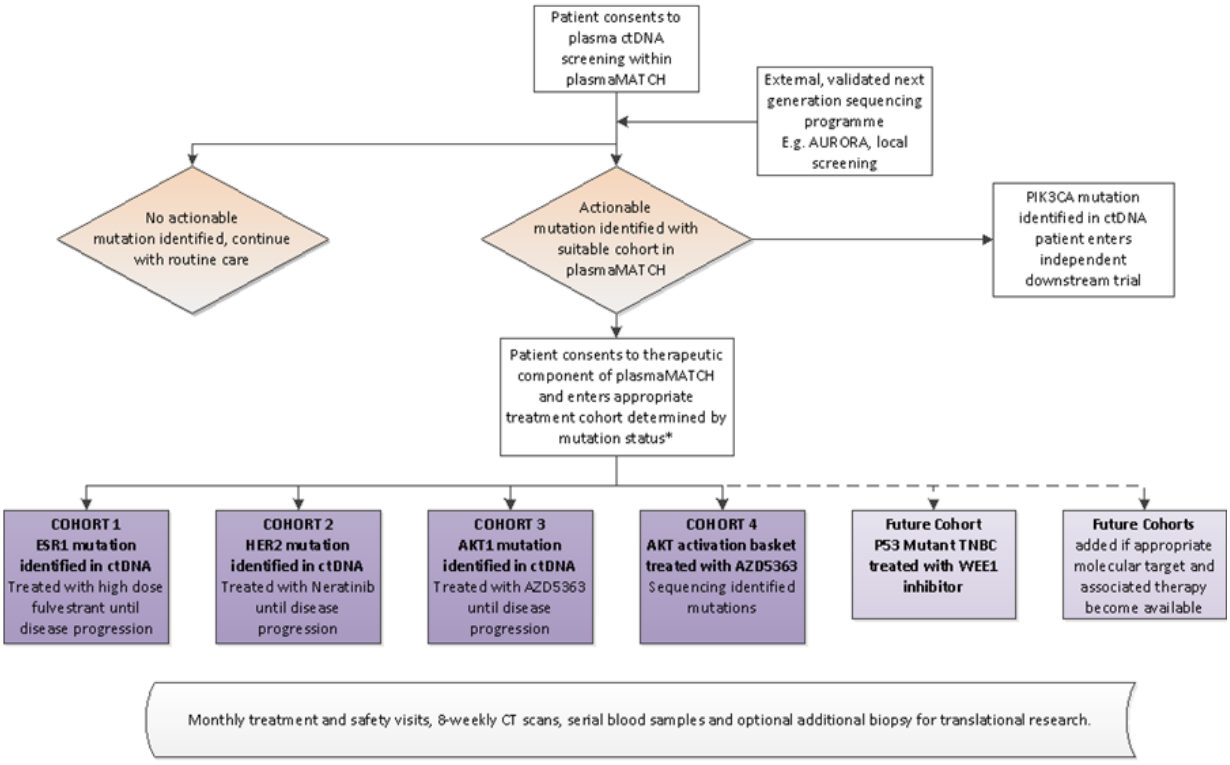
AT – drugs would be earlier in development and so less is known about them. The drugs used would be chosen carefully and patients fully informed of the potential risks and side effects. Short exposure to treatment should mean that there is less risk of side effects which tend to be seen as toxicities accumulate over time with a number of doses/cycles. With this in mind would not want surgery to be delayed.
- confirmed that the trial design would not use drugs that decrease blood count or increase the risk of wound healing complications or cardiovascular events. Therefore elect for some important filters when selecting potential drugs to test using this design.

***PAG** – General problem of the clinician protecting the patient by not asking the patient to participate in a trial.*
- Need to be consistent with the NIHR "OK to Ask" Campaign.

PAG Question: Is consent for trials and additional biopsies verbal, written or assumed?

AT – always formal written informed consent for these type of trials.

6. Alistair Ring presented the plasmaMATCH Trial Design



AR presented the plasmaMATCH trial design shown above explaining that metastatic biopsy of the lymph nodes, bone, liver, lung etc. are very different procedures to the breast biopsy and can be very uncomfortable for the patient. The plasmaMATCH trial aims to assess whether patients can be screened for the presence of rare target mutations in their metastatic cancer with the use of ctDNA screening of a blood sample. Therefore avoiding the requirement for unnecessary metastatic biopsies e.g. in rare subtypes over 100 patients may be required to undergo biopsy in order to identify 2 or 3 patients who may benefit from treatment. Also the plasmaMATCH trial design provides an efficient method of testing several drugs at the same time for rare mutations which would not be viable in individual trials. It is routine care to biopsy metastatic disease in 50% of sites nationally.

PAG *- Need ensure patient expectations are managed, that only a small number of patients will have the rare mutations identified and will have the opportunity to enter a treatment arm.*

PAG Question: How many tests can you perform from a biopsy?
AR –DNA is extracted from the sample so several different analyses can be performed, but following the analysis relatively little will be left over.

PAG Question: How do you tell patients the results of trials they have participated in?
AR – The plasmaMATCH phase II trial outcome will tell us whether the treatment is active or not. However this will need to be confirmed in a phase III trial.

JB – The ICR-CTSU website contains link to the Cancer Help UK webpages for the specific trials and any results would be published here. The problem is that you can't assume consent for the patient to be notified of the study outcome in 5 years time and so put the onus on the patient to find out once published. A written lay summary of any results published would be provided to the hospitals to distribute to participants as applicable.