ARTemis: Avastin® Randomised Trial with neo-adjuvant chemotherapy for patients with early breast cancer

ARTemis Newsletter
Issue 7
June 2011

Welcome to this seventh edition which will tell you about some interesting ASCO results, the outcome of our first DSMC meeting and will give you an update on recruitment, site setup, AE's of special interest, data and sample collection, the Warwick Trial Team and finally back to ASCO results.

ASCO and DSMC Results - Good News for ARTemis!

NSABP-B40 reported on the primary endpoint of pathological complete response (their definition no invasive cancer in the Breast and Axilla, but DCIS allowed), shows a statistically significant advantage for the addition of bevacizumab in the overall population (28.4 vs. 34.5%, p=0.027), which was driven predominantly by **improvements in the ER+ve population**. The pathCR in ER+ve patients was 15.2% increasing to 23.3% with bevacizumab (p=0.008) and in ER–ve patients is 47.3% increasing to 51.3% with bevacizumab (p=0.44).

GEPARQUINTO reported a significant **increase of pathological complete response rate but only for the TNT population** having received neo-adjuvant chemotherapy with bevacizumab. Their definition of pathCR does not allow DCIS (although they included an analysis using the B-40 definitions). This group confirmed an advantage for ER–ve patients with 27.8% increasing to 36.4% with bevacizumab (p=0.02).

Neither NSABP-B40 nor GEPARQUINTO reported any new safety issues.

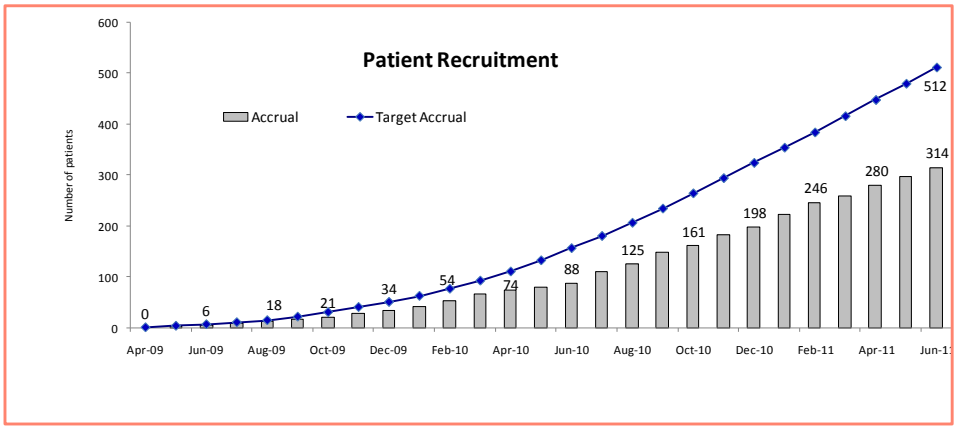
Our Data and Safety Monitoring Committee (DSMC) validated on the 10 June 2011 no new safety concerns in the ARTemis trial. Also, they confirmed that ARTemis has every reason to push to complete recruitment, to add data for both the ER+ve and the ER-ve cohorts, without bias.

Of the three trials, **ARTemis will be the only trial** to analyse the pathology response to treatment through a central review of the surgery slides by experienced pathologists. Also ARTemis will be the first of these trials to look for a definition of a signature of response to bevacizumab by collection and analysis of linked translational material (fixed tissue, fresh tissue and blood).

ARTemis is therefore in a strong position to explain the different outcomes of the NSABP-40 and GEPARQUINTO trials. **It is therefore important that we complete recruitment as soon as possible.** For further information, see page 4.

PATIENT RECRUITMENT: Number of Patients Recruited: 314

(as of 23 June 2011)



Recruitment is still below target (30-35 patients a month) with current accrual averaging 19 patients per month. We need your support, please **keep screening actively. Every patient counts.**

Note: The protocol recommends that patients are randomised within 28 days of diagnostic biopsy as part of best practice. However, if the Principal Investigator feels it is clinically acceptable to wait more than 28 days, the protocol is flexible enough to allow patients to be recruited up to 8 weeks.

Well done to Nottingham City Hospital for recruiting our 300th patient. Congratulations to new site Leicester Royal Infirmary, who opened on 24 May and randomised their first patient on 31 May, and also to Royal Bournemouth and Addenbrookes who have recruited 4 patients since May.

We hope to achieve our 50% recruitment target at the end of the summer.

SITE SET UP

We currently have **50 sites open**. Welcome to Ysbyty Gwynedd, Weston Park and Blackpool Victoria Hospitals and Leicester Royal Infirmary who opened recently. 10 sites are in set up and pending initiation.

More new sites are very welcome to take part.

ADVERSE EVENTS OF SPECIAL INTEREST

Following the analysis of safety data for the first 200 patients, the Trial Management Group has ended the requirement for reporting of AEs of Specials Interest as per protocol pages 24-25.

Standard SAEs (death, hospitalisation, life-threatening experience and disability) should continue to be reported to the Cambridge Trial Office within 24 hours of first knowledge of the event.

CRF COMPLETION

A **big thank you** to everyone who sent in CRFs prior to our first DSMC meeting! We had a fantastic response and, between us, achieved a really high percentage return rate. Currently we are running at a 95% return rate for full sets of Treatment Forms and Surgery Forms!

Watch this space … we are amending the Guidelines to help you complete the CRFs and thereby reduce the number of queries.

On the Treatment Form, the hypertension management data should relate to the patient's blood pressure at the end of the current cycle, prior to the next one.

We've picked up some **recurrent protocol deviations**, and so wish to highlight the following as mandatory:

- LVEF measurement is mandatory at the end of cycle 4.
- All patients on Arm B (Avastin) must have protein urinalysis and PT/PTT taken prior to treatment cycles 1 – 4.
- Blood pressure must be taken and recorded prior to every cycle; and taken and reviewed at the end of each infusion.
- Radiological measurements must be done by ultrasound.

WITHDRAWALS

If your patient withdraws from trial treatment, please telephone the ARTemis trial office in Warwick immediately. The team will provide you with specific instructions on CRF completion depending on the reason and timing of withdrawal. A new version of the Withdrawal Form requesting details of any further neo-adjuvant treatment will be issued to all sites shortly.

For patients who switch to the FEC regimen earlier than cycle 4 (e.g. following an allergy to Docetaxel or suffering from toxicity due to the bevacizumab); as well as completing a Withdrawal Form, sites should also complete and return all the usual CRFs e.g. Treatment Forms, Radiology Forms, the Surgery Form and QoL Questionnaires.

Centres open:
sorted by date of activation

Addenbrooke's Hospital	61
Western General Hospital	28
Peterborough District Hospital	16
Royal Surrey County Hospital	15
St Bartholomew's Hospital	9
Guy's Hospital	1
Charing Cross Hospital	14
St Mary's London	8
Torbay District General Hospital	8
St James's University Hospital	12
Queen's Hospital Burton	3
Newham Hospital	3
West Middlesex Hospital	19
Christie Hospital	7
Southampton General Hospital	2
Essex County Hospital	3
Aberdeen Royal Infirmary	9
Royal Hampshire County	3
Maidstone Hospital	6
Bedford Hospital	3
Glan Clwyd Hospital	3
City Hospital (Sandwell)	6
Clatterbridge Centre for Oncology	0
St John's Hospital	1
Royal Liverpool & Broadgreen	1
Royal Glamorgan Hospital	1
Southport Hospital	0
Newcastle Upon Tyne	0
UCLH (London)	6
UHCW	6
New Cross Hospital	7
North Middlesex Hospital	1
Royal Bournemouth Hospital	14
Warrington & Halton Hospitals	1
Dorset County Hospital	1
King's College Hospital	3
Nottingham University Hospital	10
Southend University	6
Cheltenham General Hospital	3
Gloucestershire Royal Hospital	0
Macclesfield District Hospital	2
Royal Gwent Hospital	0
Poole Hospital	4
St Helen's Hospital	7
Sandwell Hospital	0
Worcestershire Royal	0
Leicester Royal Infirmary	1
Ysbyty Gwynedd	0
Weston Park Hospital	0
Blackpool Victoria Hospital	0

Centres to be open soon

Barking, Havering & Redbridge Hospital
Basingstoke & North Hampshire Hospital
Kidderminster
Medway Maritime Hospital
Prince Charles Hospital
Queen Elizabeth Hospital, Birmingham
Royal Derby Hospital
Royal Free Hospital
Stafford Hospital
Velindre Hospital

Thank you to all centres for your continued efforts on setting up sites.

MANDATORY BLOOD SAMPLE

Samples are arriving slowly: we have 155 blood samples to date which is half the number of recruited patients, so please do remember to add this one-off sample (2x9ml EDTA bottles) to your patient's list at any blood collection time, even during follow-up. If you require a list of patient trial numbers for the outstanding samples from your site, please contact Louise at Cambridge.

FRESH TISSUE AND SEQUENTIAL BLOODS SUB-STUDIES

Please keep asking your patients to consent to donate their tissue and / or their blood for these important sub-studies. As we said in the first part of the Newsletter, we are looking for a signature of response to bevacizumab and to do so we need as many samples as possible.

If you are interested in setting-up one of these sub-studies at your site, please contact Louise for assistance.

QUALITY OF LIFE SUB-STUDY

196 baseline questionnaires have been received from 265 patients who have consented to the QOL sub-study to date. Please check that you have sent in all completed baseline forms. The subsequent time-points are post cycles 3 and 6, on completion of surgery/radiotherapy, 12 and 24 months post surgery.

NEW! TIMEPOINTS REMINDER

A reminder of important time points such as LVEFs and sub-studies, specific for your newly randomised patient, will be faxed through to site post randomisation. The reminder should be placed where you can easily access it for each of your patient's visits.

WARWICK TEAM

Welcome to Asha Chauhan who last month joined ARTemis as our Administrator. Asha will be dealing with data management and day to day administration but also issuing site files and CRF booklets – a.chauhan@warwick.ac.uk

Photograph Left to Right of the Warwick Team:
Caroline Jevons Recruitment Facilitator, Clare Blenkinsop Trial Coordinator
Asha Chauhan Trial Administrator

Please be aware that **neo-adjuvant HER-2+** patients can be entered into *PERSEPHONE*.
Herceptin® can be administered either concomitantly or sequentially for 6 or 12 months in conjunction with chemotherapy. For more details, please contact anne-laure.vallier@addenbrookes.nhs.uk

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Dear Principal Investigator

As you might be aware the NSABP-B40 study and an update from the GEPARQUINTO study were presented at ASCO earlier this month. (The presentations have been posted to your PI for full information.)

Both studies use bevacizumab with chemotherapy in neoadjuvant breast cancer and are therefore highly relevant in the context of the ARTemis trial.

NSABP-B40 reports on the primary endpoint of pathological complete response (their definition: no invasive cancer in the Breast and Axilla, but DCIS allowed), shows a statistically significant advantage for the addition of bevacizumab in the overall population (28.4 vs. 34.5%, p=0.027), which was driven predominantly by **improvements in the ER+ve population**. The pathCR in ER +ve patients was 15.2% increasing to 23.3% with bevacizumab (p=0.008) and in ER–ve patients is 47.3% increasing to 51.3% with bevacizumab (p=0.44).

In San Antonio in December 2010, and more recently at ASCO, GEPARQUINTO group reported a statistically significant **increase of** pathological complete response **rate but only for the TNT population having received neo-adjuvant chemotherapy with bevacizumab**. Their definition of pathCR does not allow DCIS (although they included an analysis using the B-40 definitions). This group confirmed an advantage for ER–ve patients with 27.8% increasing to 36.4% with bevacizumab (p=0.02).

Each trial shows a positive advantage for the addition of bevacizumab. The improvement in pathCR for the TNT group in each study is slightly different, but the confidence intervals for the estimates overlap, and so are compatible with one another. During the discussion at the ASCO 2011 session, it appears that the GEPARQUINTO study has potentially introduced significant bias to their results in respect of the ER+ group, which are known to respond more slowly to chemotherapy. In their trial after 4 cycles of chemotherapy +/- bevacizumab, an ultrasound (US) assessment was made and all patients not achieving a partial response(PR) (i.e. reduction in size by 50% on US) were removed from the study as non-responders and given weekly paclitaxel x 12 weeks with a novel RAD001 inhibitor. These patients, many of whom were ER+ve, were, for the purposes of the ITT analysis, designated as no-pathCR for the primary endpoint.

Our Data and Safety Monitoring Committee validated on the 10th June 2011 that there are no new safety concerns in the ARTemis trial. Also, they confirmed that ARTemis has every reason to complete recruitment, which will add data for both the ER+ve and the ER-ve cohorts, without bias.

In keeping with the observations reported in a number of UK audits for standard therapy with FEC-Docetaxel outwith trials, there is as expected a significant rate of febrile neutropenia with this regime. The use of primary or secondary prophylaxis with growth factors to reduce this rate is at the discretion of local investigators, but we are aware this is a strategy used increasingly in many centres outwith trials in the United Kingdom, and we would recommend local PIs consider this option for ARTemis too.

Of the three trials, we will be the first and only trial to analyse the pathology response to treatment through a central review of the surgery slides by experienced pathologists.

Finally, it is important to stress that a central aim of ARTemis from the outset has been the definition of a signature of response to bevacizumab by collection and analysis of linked translational material. All participants provide fixed tissue for translational studies, and additionally optional substudies collecting fresh tumour tissue and blood are recruiting well. It is clear from the results in breast cancer and in other diseases that the optimal use of anti-angiogenic drugs will require the identification of a response signature, and the neoadjuvant setting, and the ARTemis trial in particular, provide the best means of achieving this. ARTemis is therefore in a strong position to explain the different outcomes of the NSABP-40 and GEPARQUINTO trials.

Recruitment into ARTemis has been a bit slower than expected (20 patients a month versus 30 expected) but we hope that these recent data will reinforce the interest of the British community for the ARTemis trial and boost recruitment.

Please do not hesitate to contact our team (artemis@warwick.ac.uk) should you need any further help to run the study at your site.

Dr Helena Earl and Dr Larry Hayward, Co-Chief Investigators for ARTemis