November 2001

MA.17/JMA.17 TRIAL NEWS

A PHASE III RANDOMIZED DOUBLE-BLIND STUDY OF LETROZOLE VERSUS PLACEBO IN WOMEN WITH PRIMARY BREAST CANCER COMPLETING FIVE OR MORE YEARS OF ADJUVANT TAMOXIFEN (NCIC CTG MA.17, U.S. JMA.17, BIG 97-01)

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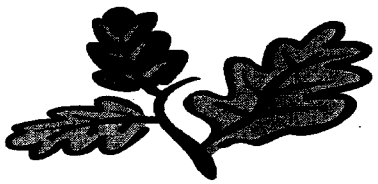

MA.17 - Central Office Team

Physician Coordinator:
Dr. Lois Shepherd

Study Coordinators:
Michael Palmer, M.Sc.
Catherine Elliott, M.Sc.

Research Associates:
Christine Bishop, CCHRA (A)
Shari Leeson, RPN
Curtis McMahon

Clinical Trials Assistants:
Gina Howard
Sue Flindall

Data Entry Clerks:
Brent Cameron, B.A.
Mary Anne Kidson

Since our last issue of the MA.17 Newsletter, we have had more changes to the MA.17 Team. As the trial grows in size, so do we.

Amy Carkner, formerly a Clinical Trials Assistant with the team, accepted another position in Ottawa. We miss Amy but congratulate her and wish her the very best.

Gina Howard, formerly a conscientious Health Care Worker, joined us in January of this year, is new to NCIC CTG and has quickly become an important asset to the team.

Shari Leeson was promoted from Clinical Trials Assistant to Research Associate this past Spring. Her RPN and oncology clinic experience have proven very valuable, in a number of ways, to the work of the team.

Sue Flindall transferred to us from another NCIC CTG team and is enjoying the fast pace and many challenges of MA.17. She is also an excellent public speaker!

Brent Cameron and wife, Jodi now have a beautiful and active son, Ethan.

We welcome two new members to the team: Curtis McMahon, as a Research Associate and Mary Anne Kidson as our new data entry clerk.
Curtis comes to us from the London Regional Cancer Centre where he has had seventeen years of experience, four of which he worked in the Clinical Trials Unit. Curtis brings to us his experience as a Multicentre Project Coordinator, where he coordinated and collected data from countries such as Canada, Mexico and Argentina.

Mary Anne has been working at Kingston Imaging Services as a Radiology Dictatranscriptionist.

We all continue to learn from your questions, appreciate your comments and look forward to reaching our target sample size in the coming year.

A word from the Chair

- Dr. Paul Goss

MA17 continues to be an extremely successful study. Accrual has been steady and exceeds our monthly projections. Letrozole has been approved as first line therapy for metastatic disease in the past year and the ODAC/FDA has recognized the superiority of its data over other inhibitors.

A second neoadjuvant study has confirmed its superiority to tamoxifen. MA17 will be the first trial in the world to report placebo controlled toxicity data for a third generation inhibitor. It will also give us the best companion data about effects in women coming off

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5 years of tamoxifen. This will make its contribution to the literature unique.

The lipid companion study is accruing very successfully but we are still having trouble with the bone mineral density companion study. SWOG will join this and we would ask that as many investigators within Canada help with this important companion. It is easy to conduct for the patient and your centre. Thank you all and the NCIC CTG head office staff for your contribution and hard work.

MA17 Local Activation of New Centres in North America

Please take note that as of **Monday, December 10, 2001**, we will not be activating any more new centres for MA17 in Canada or the US. Any Local Activation Record received prior to December 10, 2001 will be processed in the usual timely manner. We anticipate reaching our sample size by June 2002.

Serious Adverse Event reporting:

Because the toxicity profile of our study drug is, as yet, young, the toxicity data emerging from MA.17 will be an important contribution to the overall body of knowledge. Section 11 of the protocol outlines the criteria for reporting *serious* adverse events. While we hope to collect all adverse events reported by patients or noted by their physicians on the case report forms, only those events which are thought to be **serious** (grade 4 / grade 5 / unplanned hospitalization or prolongation of hospitalization), **unexpected** (not anticipated according to baseline medical history or the Investigator Brochure) and **thought to be related to study treatment** (relation code 3, 4 or 5) should be reported in an expedited fashion on the Serious Adverse Event Report Form. Please note that **second malignancies** (not breast recurrences or contralateral breast carcinoma) and **myeloid dysplasias** are considered serious adverse events and require expedited reporting. If in doubt about whether or not an event qualifies as a serious adverse event, please contact the central office and we will sort it out together. Thank you for your conscientiousness in this regard thus far.

COMPANION STUDIES

MA17B - Bone Mineral Density Companion Study

MA17B has been centrally activated since July 2000, but seems to be off to a slow start. As of September 30, 2001, 74 patients were registered with one ineligible. 19 Canadian centres are locally activated, as well as 13 NCCTG centres in the United States. Some centres, however, have not registered patients as yet.

If there are barriers to accrual at your centre, we would like to know. It is important that we enroll any qualified patients interested in participating in this study.

Please note that the lab reports received from SI Laboratories **do not** need to be sent to the central office, as we receive copies directly from SI Laboratories. Please keep your copies for your patient charts.

As per discussions with the Physician Coordinator at central office, patients with "controlled thyroid disease" **are eligible** for the study. Patients with "uncontrolled" thyroid disease are not.

Thank you for your contributions to this very important companion study. Let's work together to meet our accrual goal of 200 patients!

MA17L-Lipid Companion Study

The goal of this study is to enroll 300 eligible patients to examine the effect of Letrozole/Placebo on serum lipid profiles and the cardiovascular health of post-menopausal women. With the hard work of all the participating Canadian centres, and the addition of NCCTG sites, as of October 5th, 2001, we have 244 patients enrolled. Of those, however, we have 24 ineligible patients. Continued effort is still needed to reach the accrual goal and complete this study.

The majority of those deemed ineligible are patients whose baseline lipid results were found to be elevated and outside of the eligibility parameters. Since these patients met all of the other eligibility criteria, patient funding was provided ($50) and no further lipid samples were required. Full funding for eligible patients is $200.

FYI. As a reminder, we are unable to confirm eligibility or fund until we have received the Lipid On-Study Forms, as well as all baseline documentation for the core MA17 study. This information is crucial, as patients deemed ineligible for the core protocol are automatically ineligible for the Lipid Study.

MA17 – Patient Accrual by Co-operative Group as of September 30, 2001

Group	Jul.98 / Sep.'99	Oct./ Dec.'99	Jan./ Mar.'00	Apr./ Jun.'00	Jul./ Sep.'00	Oct./ Dec.'00	Jan./ Mar.'01	Apr./ Jun.'01	Jul./ Sep.01	TOTAL
CALGB	42	45	46	56	52	69	92	99	97	598
ECOG	99	57	65	66	80	87	91	96	103	744
EORTC	0	0	0	0	0	1	7	11	12	31
IBCSG	0	0	0	0	0	0	0	0	0	0
NCCTG	62	20	13	25	19	17	24	41	43	264
NCIC CTG	294	86	94	104	72	118	109	118	92	1087
SWOG	100	55	64	68	73	91	100	105	112	768
TOTAL	597	263	282	319	296	383	423	470	459	3492

Accrual

Over 420 sites participate on this study. Accrual has been impressive, with approximately 150 patients per month. The European Organization for Research and Treatment of Cancer recruited their first patient in November, 2000. The International Breast Cancer Study Group recently activated their first site, and we expect the first IBCSG patient to be entered on study.

New Treatment Reassignments:

Patients will be re-assigned a new treatment box approximately 11 months after randomization (and yearly after that...). We fax a "re-supply" letter identifying the NCIC CTG patient serial number and the new treatment box number to be dispensed. We will fax this letter to the Pharmacist and PCRA identified as contacts when your centre was locally activated. If these names and/or numbers have changed, please let us know!! Should you need an "early patient re-supply", call us with the NCIC CTG patient serial number as well as the last treatment box number the patient received. We will be happy to process your request!

One final note: Please **DO NOT** forget to fax us page 2 of Form 1 (or page 1 of Form 5 on follow-up) with the treatment box label affixed. It is imperative that we are able to confirm treatment dispensation.

Patient Eligibility – Bilateral Mastectomies

We review every patient's baseline documentation to ensure each patient meets the eligibility criteria.

Sometimes we receive baseline documentation (Form 1, page 4, section 3) indicating that the patient has had bilateral mastectomies, but no information is provided about one of these two mastectomies. Immediately, we would ask as we review this, does the timing and treatment given for another possible breast malignancy make this patient ineligible?
If two independent breast primaries were diagnosed at the same time, surgically removed and treated with adjuvant Tamoxifen, there is no eligibility issue. Similarly, a patient who chooses to have the contralateral breast removed prophylactically at the time of surgery for her single breast malignancy presents no eligibility problem. If two independent breast primaries are diagnosed at different times (*e.g.* 10 years ago and then 5 years ago): the patient is eligible if the treatment for the first primary did not include Tamoxifen and there has been no recurrence of either primary.

Patients are deemed ineligible under the following circumstances: those who develop a contralateral breast primary during, or after, any Tamoxifen treatment; as well as those with a *recurrence* of breast disease at any time prior to randomization.
We hope this information helps you in decisions about your patients' eligibility for MA.17 / JMA.17. By ensuring the details of both mastectomies are present on page 6 of the Form 1, you will be helping us to confirm patient eligibility as well.

Form 5 Follow-up Reports

NCIC CTG Form 5 is the case report form we use to document patient follow-up. The protocol requires that it be submitted, while the patient is on treatment, at 6 months, 12 months and yearly thereafter. One final Form 5 is

requested when the patient ceases treatment so that date and reason can be accurately recorded.

We have been receiving "extra" Form 5 reports from some sites at the request of their own cooperative group. While we appreciate your conscientiousness these extra forms present two problems for us:

1. with a study as large as this one, it creates a lot of unnecessary work for the central office (not to mention the extra work it requires from the site to submit them);
2. we have come to learn that some of these "extra" Form 5's do not, in fact, represent patient assessments by the physician but only a telephone contact. It is difficult to imagine that recurrent disease could be detected over the telephone and a completed Form 5 implies to us that the patient has been assessed by the Investigator for signs of recurrent disease.

We have always intended that this important study be easy for your Investigator, your patients and your site. In the interest of all of us who work so hard to make this research a success, please consult your protocol for the timing of follow-up reports and call us if you have any questions.

Off Treatment Management

While a patient is actively taking the study drug), their follow-up should be recorded on the Form 5 – Follow-Up Report. (Please complete all required investigations according to the protocol, ensuring that we have accurate data for the endpoints of this study).

When a patient goes off-treatment, we require that a full Form 5 be completed, including all of the final investigations and documentation for the reason off treatment. The Form 5 is the only place in the database where we can indicate that a patient is off-treatment and thus stop the generation of new treatment box numbers for that patient.

Once the full form 5 has been received the patient needs only to be followed annually, from treatment discontinuation (not randomization), with a Form 5S (Short Follow-Up Report).

Thanks everyone for all your hard work on this study!!

Did you know...

Since the beginning of the MA17 Study, our fax machine has:

**** sent out 18,008 messages***
**** received over 9,300 messages***
**** printed roughly 38,000 pages***

Forms Completion

As we approach our accrual target, we would like to express our appreciation for the hard work and careful attention of everyone involved. In order to better ensure the accuracy of our database, as well as reduce the need for query letters, we would request that the following be checked when completing forms:

1. Please ensure that there are no blanks left on the forms, and that all questions are completed. Where information is unknown, please fill out the section as such.
2. When reporting values under the **Haematology and Biochemistry** section, please include values for Normal Range UNL.
3. Ensure that all pages of the completed forms are submitted together.

Your help will ensure the accuracy of our data, and the value of our collective work – as well as a reduction of the queries that we send to our participating centres.

A Quick Reminder...

Please ensure that central office has your correct fax number. Incorrect or outdated information could lead to delays in treatment re-supply information.

Drug Supply

Covance Pharmaceutical Packaging Services has a new name – *Fisher Clinical Services.*

The warehouses in Allentown, PA and Horsham, UK will still continue to supply participating centres, but please note the new name.

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