NATIONAL CANCER INSTITUTE OF CANADA
CLINICAL TRIALS GROUP (NCIC CTG)

EFFECT OF RE-IRRADIATION FOR BONE PAIN
ON URINARY MARKERS OF OSTEOCLAST ACTIVITY

NCIC CTG Protocol Number: SC.20U

A Companion Study of SC.20
(A PHASE III INTERNATIONAL RANDOMIZED TRIAL OF SINGLE VERSUS
MULTIPLE FRACTIONS FOR RE-IRRADIATION OF PAINFUL BONE METASTASES)

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# TABLE OF CONTENTS

1.0 OBJECTIVES ......................................................................................................................................... 1
1.1 Study Population................................................................................................................................... 1
1.2 Primary Objective ........................................................................... ............................................................ 1
1.3 Secondary Objectives................................................................................................................................ 1

2.0 BACKGROUND INFORMATION AND RATIONALE ............................................................................ 2

3.0 TRIAL DESIGN ..................................................................................................................................... 4

4.0 STUDY POPULATION ............................................................................................................................ 5
4.1 Eligibility Criteria................................................................................................................................... 5

5.0 PRE-TREATMENT EVALUATION ......................................................................................................... 6

6.0 ENTRY PROCEDURES ......................................................................................................................... 7

7.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS ................................................................. 8
7.1 Definitions .............................................................................................................................................. 9
7.2 Response Duration................................................................................................................................. 9
7.3 Stable Disease Duration........................................................................................................................ 9

8.0 SERIOUS ADVERSE EVENT REPORTING ......................................................................................... 10

9.0 STATISTICAL CONSIDERATIONS ...................................................................................................... 11
9.1 Sample Size and Analysis.................................................................................................................... 11

10.0 PUBLICATION POLICY .................................................................................................................... 12
10.1 Authorship of Papers, Meeting Abstracts, Etc.................................................................................. 12
10.2 Responsibility for Publication ............................................................................................................. 12
10.3 Submission of Material for Presentation or Publication ................................................................ 12

11.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES................................................................ 13
11.1 Institution Eligibility for Participation............................................................................................... 13
11.2 Investigator Qualifications................................................................................................................ 13
11.3 REB (Research Ethics Board) Approval for Protocols ..................................................................... 13

12.0 REFERENCES ....................................................................................................................................... 14

APPENDIX I - DOCUMENTATION FOR STUDY .................................................................................... 15
APPENDIX II - EFFECT OF RADIOTHERAPY ON URINARY MARKERS OF OSTEOCLAST ACTIVITY RELATED TO PAIN RESPONSE ........................................................................ 16
APPENDIX III - HOW TO COLLECT AND SEND URINE SAMPLES TO THE STUDY ......................... 17
APPENDIX IV - PATIENT EVALUATION FLOW SHEET ........................................................................ 20
APPENDIX V - SAMPLE CONSENT FORMS ............................................................................................ 21
    ENGLISH Sample Consent Form ........................................................................................................ 21
    Exemple de formulaire de consentement en FRANÇAIS ................................................................... 26

LIST OF “CONTACTS” ............................................................................................................................... Final Page
1.0 OBJECTIVES

1.1 Study Population

Patients randomized to SC.20 in selected centres in Canada and the U.K.

1.2 Primary Objective

To correlate the response of re-irradiation to the change of urinary markers of osteoclast activity.

1.3 Secondary Objectives

1. To correlate the change of urinary markers of osteoclast activity to frequent responders to radiotherapy (response to both initial radiation and re-irradiation).

2. To correlate the change of urinary markers of osteoclast activity to eventual responders to radiotherapy (no response to initial radiation but response to re-irradiation).

3. To correlate the change of urinary markers of osteoclast activity to absolute non-responders (no response to both initial radiotherapy and re-irradiation).

4. To examine if pre-re-irradiation urinary marker levels predict for response.

5. To examine if a change in pre-re-irradiation urinary marker levels predict for early versus late response to re-irradiation.

6. To investigate if the urinary marker levels predict for duration of response.

Randomization to SC.20 → Baseline Sample (1st day of RT) → Re-irradiation Treatment → multiple → 1 Month Sample (2nd urination in morning)

Planned Sample Size: 163
2.0 BACKGROUND INFORMATION AND RATIONALE

Palliative radiotherapy is well established for the treatment of symptomatic bone metastases. The exact mechanism of its action is still uncertain, although tumour cell kill may be an important reason. However, the absence of a dose-response relation, rapid responses, and poor correlation of efficacy with radiosensitivity suggest that an effect on host mechanisms of pain could also be important.

Markers of bone remodeling have been shown to be suppressed by anti-resorptive therapy, and the response of these bone markers have been applied to monitoring therapy for bone metastases.

A myriad of new markers of bone metabolism assayed from either serum or urine specimens of patients with bone metastases are currently available for clinical investigation. Among the novel markers used to assess bone resorption are products of bone collagen breakdown that include: (1) the pyridinium cross-links: pyridinoline (PYD) and deoxypyridinoline (DPD), (2) N-telopeptide (NTX), and (3) C-telopeptide (CTX). These bone resorption markers have largely replaced urinary hydroxyproline as the preferred biochemical markers of bone turnover in the clinical laboratory.

Vinholes et al in a double-blind, placebo-controlled study evaluated the efficacy of pamidronate on pain relief from bone metastases. Patients with a persistent elevation of urinary NTX level had poor pain relief [Vinholes 1997a].

Lipton et al studied 21 patients placed on pamidronate therapy [Lipton 1998]. Over the course of 4 to 6 months, NTX concentrations in 12 of the patients decreased to levels within the normal reference range of pre-menopausal women, whereas in the remaining 9 patients the marker did not reach normality. Those with normalization of NTX levels had a lower bone fracture rate (5/12 – 42%) than the other cohort with elevated bone markers (8/9 – 89%). Furthermore, in the patients in whom the marker normalized, there was progression of disease in bone in only 25% (3/12) of the patients compared with 78% (7/9) of patients in whom the NTX remained elevated.

Vinholes et al in another study evaluated 37 patients with newly diagnosed bone metastases from breast cancer randomized to oral pamidronate or placebo in addition to anticancer therapy for assessment of response and identification of progression [Vinholes 1997b, Vinholes 1998]. An increase of NTX of 30% predicted progression of disease. In a similar prospective study of 97 patients, of whom 53 were breast cancer patients, with metastatic bone disease, Costa et al again observed that a 50% increase in NTX correlated significantly with radiograph diagnosis of bone metastases progression [Costa 2002]. Serial measurements of the newer markers of bone resorption hold promise in helping the clinician to more rapidly assess which patients are responding to systemic therapy than do traditional radiograph techniques.

In the recent UK Bone Pain Radiotherapy Trial [Bone Pain Trial Working Party 1999], 22 patients were entered into a supplementary study to establish the effects of local radiotherapy for metastatic bone pain on markers of osteoclast activity, particularly the pyridinium crosslinks pyridinoline and deoxypyridinoline, the latter being specific for bone turnover [Hoskin 2000, Abbiati 1993]. Urine samples were collected before and one month after radiotherapy. Patients were treated with either a single 8 Gy or 20 Gy in 5 daily fractions. Pain response was scored with validated pain charts completed by patients.
Urinary pyridinium concentrations were compared with pain response (Appendix II). In the non-responding patients, baseline concentrations of both pyridinoline and deoxypyridinoline were higher than responders, and rose further after treatment, whereas in responders, the mean values remained unchanged. This resulted in significant differences between responders and non-responders for both indices after treatment ($p = 0.027$). The authors conclude that radiotherapy-mediated inhibition of bone resorption, and thus osteoclastic activity, could be a predictor for pain response. They also propose that tumour cell killing reduces the production of osteoclast activating factors, or there is a direct effect upon osteoclasts within the radiation volume, distant from tumour shrinkage. Their study supports the results from randomized trials that high dose radiotherapy is not necessary for pain relief, and that single low-doses of treatment are more than adequate for most patients.

However, their study is limited by a small sample size. Moreover, there is evidence in the literature demonstrating the effectiveness of re-irradiation after initial non-response to palliative radiotherapy for symptomatic bone metastases. Mithal et al reported 6 of 8 (75%) non-responders to previous radiotherapy responded to re-irradiation [Mithal 1994]. Jeremic et al reported in 26 patients that initially did not respond to a previous single fraction radiotherapy, there were 12 (46%) responses following a single fraction of 4 Gy given for retreatment of bone metastases [Jeremic 1999]. The authors concluded that lack of response to initial radiotherapy should not deter repeat irradiation. The same group further reported the efficacy of second single 4 Gy re-irradiation for painful bone metastases following the previous two single fractions, 4 of the 6 non-responders (67%) to the 2 prior single fractions responded to the third radiotherapy [Jeremic 2002]. There is evidence that a proportion of non-responders would respond to a re-irradiation. However, there remains a small group of patients who appear to be non-responsive to any amount of palliative radiotherapy. The examination of urinary markers may provide an explanation for this observation.
3.0 TRIAL DESIGN

Randomization to SC.20, registration to the companion SC.20U substudy.

Methods and Materials

Patients enrolled in the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) SC-20 study: *A Phase III International Randomized Trial of Single Versus Multiple Fractions for Re-Irradiation of Painful Bone Metastases* at selected centres will be approached for this substudy. They will be asked to submit a urine specimen before and 1 month after re-irradiation (Appendix III). The urine specimen before radiotherapy can be collected any time of the day in the clinic. The urine specimen 1 month after re-irradiation should be the second morning specimen. Urine samples will be analyzed after extraction by use of high performance liquid chromatography with fluorescence detection for total pyridinoline, deoxypyridinoline (Metra Labs Inc, CA), and N-telopeptide (Ostex, Seattle, WA), and the results normalized relative to urinary creatinine concentration. In addition, urinary calcium, phosphate, and magnesium will also be measured in each urine sample for normalization purposes. Pain response is scored with the Brief Pain Inventory (see SC.20 protocol) and the response at 1 and 2 months after re-irradiation is compared with baseline scores. The patient’s response to initial radiation will be recorded.
4.0 STUDY POPULATION

Patients enrolled in the SC.20 study.

4.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of registration. Questions about eligibility criteria should be addressed PRIOR to calling for registration.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

4.1.1 Any patient at participating centres who meets the eligibility criteria for SC.20 (section 4.0 of SC.20 protocol) is eligible for SC.20U.

4.1.2 Patient consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the NCIC CTG Study Coordinator that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, a standard consent form for the trial will not be provided but a sample form is given in Appendix V. A copy of the initial REB approval and approved consent form must be sent to the central office. The patient must sign the consent form prior to registration. Please note that the consent form for this study must contain a statement which gives permission for the NCIC CTG and monitoring agencies to review and receive patient records.

4.1.3 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.
5.0  PRE-TREATMENT EVALUATION
(Also see Appendix III)

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Collection</td>
<td>1st day of RT <em>(any time of day before RT begins)</em></td>
<td>Clinic</td>
</tr>
</tbody>
</table>
6.0 ENTRY PROCEDURES

All eligible patients enrolled on the study by a participating treatment centre will be entered into a patient registration log provided by the NCIC CTG. The serial number assigned to patients participating on SC.20 will also be used on all documentation and correspondence with the NCIC CTG for SC.20U.

**Canadian centres**
All registrations will be done centrally by the NCIC CTG and will be obtained by calling the NCIC CTG Clinical Trials Assistant at (613) 533-6430 or by faxing the eligibility checklist to (613) 533-2941. At the time of entry, a copy of the completed eligibility checklist must be available.

**UK centres**
All enrolment registry will be done centrally by the Cancer Research UK and UCL Cancer Trials Centre trial coordinator who will review the eligibility with the caller and will register the patient using a web-based system provided by NCIC CTG.

**Note:** The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient’s data be withdrawn prior to final analysis, except on disclosure of initial ineligibility.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting registration.
7.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT
(Also see Appendix III)

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Timing</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Collection</td>
<td>One month after first day of re-irradiation (second urination in the morning)</td>
<td>Patient’s home (or clinic)</td>
</tr>
</tbody>
</table>
8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

Please see Section 9.0 of the SC.20 protocol for appropriate definitions.

If a patient only submits the baseline urine sample, this sample will be analyzed for study endpoints related to pre-re-irradiation urinary markers only. If a patient has submitted both samples, the samples will be analyzed for all study endpoints.
9.0 SERIOUS ADVERSE EVENT REPORTING

No Serious Adverse Events will be collected as this is only an observational study. SAEs that occur as a result of the re-irradiation treatment should be reported as outlined in Section 10.0 of the SC.20 protocol.
10.0 STATISTICAL CONSIDERATIONS

This is an observational study.

10.1 Sample Size and Analysis

The level of the selected urinary markers will be measured as the primary outcome. The increase / decrease (in both absolute and percentage scales) of the level from baseline will be used in the analysis to account for differences in baseline values. Response to radiotherapy will be categorized into two groups (responders vs non-responders). ANOVA with the GLM procedure will be used to analyze the difference between the two groups. Stratification of treatment regimens (single and multiple fractions) will be included.

The analysis of the secondary objectives will be conducted as follows. The response to both, either or none of the initial and re-irradiation will be classified into categories and the level of the urinary markers will be compared with multiple comparison method within GLM (Dunnett comparison to fixed reference). Odds ratio in logistic regression will be used to analyze the predictive relationship between the pre-irradiation level and change of the urinary markers and the response. The relationship between the urinary marker level and response duration will be analyzed with the Pearson correlation.

Because this companion study will include only a subset of the patients in the main study (SC 20), and, thus, the maximum sample size is fixed, deltas have been calculated under the conditions of $\alpha=0.05$ and power=80% if different proportions of study patients enter this sub-study. The means and SDs of Pyridinoline (PYD) and Deoxypyridinoline (DPD) were derived from a previous study. The baseline mean value of PYD is 165 n mol/m mol creatinine and its SDs are 15 and 170 for responders and non-responders, respectively; while the corresponding numbers for DPD are: baseline mean 46 n mol/m mol creatinine, SDs 8 and 65 respectively [Hoskin 2000]. The equation for calculating deltas is denoted from the sample size equation of Chow and Liu [Chow 1998]:

$$\Delta = \sqrt{\frac{(\delta_1^2 + \delta_2^2)(Z_{\alpha/2} + Z_\beta)^2}{N}}$$

The proportion of the difference over baseline mean tells the expected relative change. We hypothesize the difference between responders and non-responders may be as large as 50% from baseline, the sample size would be 35 and 65 per group for PYD and DPD respectively. The required sample size for this companion study is therefore 130 patients. Assuming 20% of the patients do not submit the 1-month urine specimen, we need to recruit 163 patients. We anticipate half of these patients will be recruited in UK. The anticipated accrual will be 3 years.
11.0 PUBLICATION POLICY

11.1 Authorship of Papers, Meeting Abstracts, Etc

11.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.

- A limited number of the members of the NCIC Clinical Trials Group may be credited as authors depending upon their level of involvement in the study.

- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

11.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

“A study coordinated by the Clinical Trials Group of the National Cancer Institute of Canada. Participating investigators included: (a list of the individuals who have contributed patients and their institutions).”

11.2 Responsibility for Publication

It will be the responsibility of the study chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

11.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the NCIC CTG physician and study coordinator, and approval of the study chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.
12.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

12.1 Institution Eligibility for Participation

All member centres in good standing of the NCIC CTG and participating in SC.20 are eligible to participate in this study. Institutions which are not NCIC CTG members can either make application for membership or submit a single study agreement document.

12.2 Investigator Qualifications

- All investigators (principal investigators and co-investigators) must have on file with the NCIC CTG a current curriculum vitae.
- For Canadian centres: documentation indicating completion of training in the protection of human research participants (e.g. NCI U.S. Completion Certificate), if not already on file with NCIC CTG.
- For centres participating through a cooperative group: all applicable regulations pertaining to investigator qualifications must be adhered to.

12.3 REB (Research Ethics Board) Approval for Protocols

*This section applies to Canadian centres only. All centres participating through cooperative groups must adhere to the appropriate regulations established by those groups and/or the appropriate national regulations.*

Each participating centre will have on file with the NCIC CTG central office, as part of its membership/agreement documents, a description of its ethics review process and composition of its REB.

Initial Approval

Member centres wishing to participate in a trial are required to obtain ethics approval of the protocol and consent form by the appropriate REB. Expedited approval is acceptable provided full board approval for the SC.20 protocol has been received and this does not contravene local policy. A completed NCIC CTG Confirmation of Initial Ethical Approval form must be submitted to document the REB was properly constituted and there were no conflicts of interest in the REB approval process.

For information re REB approval and annual re-approvals, amendments, and informed consents, please see section 15.3 of the SC.20 protocol.
13.0 REFERENCES


APPENDIX I - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of registration and will apply to all eligible patients.

<table>
<thead>
<tr>
<th>Form</th>
<th>To be Completed</th>
<th>Due in Central Office</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC.20U Consent Form</td>
<td>prior to registration to SC.20U</td>
<td>with SC.20 Form 1 (Canadian patients only)</td>
</tr>
<tr>
<td>USSR Urine Sample Submission Report</td>
<td>1) after the baseline sample is sent</td>
<td>within 24hrs of courier package being sent</td>
</tr>
<tr>
<td></td>
<td>2) after the 1 month post RT sample is sent</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX II - EFFECT OF RADIOTHERAPY ON URINARY MARKERS OF OSTEOCLAST ACTIVITY RELATED TO PAIN RESPONSE

A. Pyridinoline; B. Deoxypyridinoline

Total: 22 patients, 8 with breast cancer and 14 with prostate cancer; 5 patients showed no response, 9 a partial response and 8 a complete response
APPENDIX III - HOW TO COLLECT AND SEND URINE SAMPLES TO THE STUDY

1. Urine Collection Instructions and Kits:

A. For Canadian Centres:

Once each participating centre has obtained local REB approval for SC.20U and is activated, urine collection kits will be sent to the centre. Please contact the NCIC Clinical Trials Group when more urine collection kits are required.

**Baseline Sample Collection**

A urine sample should be collected on the 1st day of radiotherapy (RT) (any time of day before radiotherapy begins) and placed in the provided collection tube.

- Have the patient collect a urine sample in the collection bottle that has been labelled with the NCIC CTG patient ID, the patient’s initials, and the date.
- Complete the tube label with the following information:
  - NCIC CTG patient ID
  - patient initials
  - the fact that it is a baseline sample (circle “B” on the label)
  - sample collection date
- Affix the label to the tube and transfer part of the urine sample to the tube using the disposable squeeze dropper until the tube is approximately half full.
- Screw the cap onto the sample tube and place it in the smaller zip-lock pouch.
- Seal the pouch, put it in the box and then put the box into the large courier package.
- Dispose of the collection bottle and the dropper in an appropriate manner.
- Have the sample shipped in the self-addressed courier package to the Queen’s University Pathology Department in Kingston, Ontario. Samples can be refrigerated prior to shipping.
- Once the package has been sent, a Urine Sample Submission Report (USSR) must be faxed to the NCIC Clinical Trials Group.

**One-Month Post-Radiotherapy Sample Collection**

During a clinic visit (either at baseline or during treatment) please ensure that the patient is given a urine collection kit to take home for the 1-month post-radiotherapy sample. The label should be filled out by the CRA before being sent with the patient.

- Complete the tube label with the following information:
  - NCIC CTG patient ID
  - patient initials
  - the fact that it is a 1-month sample (circle “1M RT” on the label)
  - the sample collection date should be left blank
- Affix the label to the tube.
- Partially complete the Sample Collection Date form included in the kit with the NCIC CTG patient ID and the patient’s initials. **Leave the sample collection date blank.**
- Instruct the patient to complete the Sample Collection Date form after they have collected the 1-month sample and to include this form in the box with the sample when they send it to the lab. **If the Sample Collection Date form is not present in the kit, please ask the patient to note the date the sample was collected on the kit box.**
• Please fill in the sender information on the courier waybill for the package. In the sender’s name portion, please put “SC.20U” and the patient’s NCIC CTG patient serial number to help maintain patient confidentiality. The address portion should be completed with the address where the sample will be collected. Please note that the person sending the package will have to sign the waybill.
• It may be helpful for the CRA to demonstrate what is required in collecting and packaging the sample.

Shortly before this sample is scheduled to be collected 1 month after the first day of re-irradiation to the SC.20 study site (based on the planned protocol treatment start date provided with the eligibility checklist at the time of randomization to SC.20), an email reminder will be sent to the CRA. The CRA should then call the patient and remind him or her that:
• the second urine sample of the day should be collected on the day corresponding to one month after the patient’s SC.20 re-irradiation treatment was actually started;
• the date the sample was taken should be noted on the Sample Collection Date form or the kit box; and
• the sample should be refrigerated until it is couriered.

After the expected date of sample collection, the CRA should call the patient again to confirm that the sample has been collected and couriered. Once this is confirmed, a Urine Sample Submission Report should be faxed by the CRA to the NCIC Clinical Trials Group. If the patient did not collect the sample, the CRA should ask the patient to collect it on the following day and repeat the process for verification and reporting of sample shipment. If the patient no longer wishes to collect the sample, please notify the NCIC CTG Study Coordinator. Please do not send in the USSR if the patient did not submit the 1-month post-RT sample.

All samples will be stored in Kingston until the end of the study, at which point they will be shipped to the Pathology Department at Mount Sinai Hospital in Toronto, Ontario and analyzed for osteoclast activity under the direction of Dr. Reinhold Vieth. Following analysis, the urine samples will be destroyed by an NCIC Clinical Trials Group designate.

B. For U.K. Centres:

Urine samples:
The urine samples are collected in a sterile universal container and then posted directly to the Marie Curie Research Wing at Mount Vernon Hospital. They will then be anonymised and transferred to the Gray Laboratory for storage at -20°C and later transported to Toronto for analysis of markers of osteoclastic activity.

One month post-radiotherapy (patient collection):
A urine bottle and packaging approved for use in the UK postal system will be given to the patient. ONE sample of some urine from the second time the patient goes to the washroom, after waking in the morning is collected. When the urine has been collected into the bottle please ensure the lid is tightly sealed and place it in the packaging; it can then be posted in a standard post box for return.

Note: Please do NOT forward Urine Sample to NCIC CTG.
For Canadian Centres:

**NCIC CTG SC.20U: How to collect and send sample.**

This kit makes it possible to take part in this research without the need for a special trip to the hospital or laboratory.

☆ ☆ **Please do not take a calcium supplement during the 8 hours before taking a urine sample.** ☆ ☆

We need ONE sample of some urine from the second time you go to the washroom, after waking in the morning.

Your kit contains:
- one bottle with orange cap to collect the urine
- one disposable squeeze dropper
- one tube with screw-on cap
- one zip-lock pouch with tissue to absorb possible leaks.

1. After you collect a sample in the bottle, take one good squeeze of it using the dropper, and transfer the sample into the tube, filling about half way.

   Please throw the dropper and the bottle with orange cap into the garbage.

2. Screw the cap onto the sample tube, and put it into the smaller zip-lock pouch.

3. Seal the pouch and put it in the box.

4. Write today’s date on the Sample Collection Date Form and put it in the box.

5. Put the box in the large courier package.

6. Call the courier number on the package and it will be picked up from your home.

   **Note:** Keep the urine sample cold by placing it in the refrigerator until you ship it. You can store the urine for up to three days before it must be couriered.
APPENDIX IV - PATIENT EVALUATION FLOW SHEET

<table>
<thead>
<tr>
<th>Required Investigations</th>
<th>1st Day of RT (any time of day before RT begins)</th>
<th>1 Month after first day of re-irradiation (2nd urination in the morning)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Collection</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Please Note: After each sample is sent, an Urine Sample Submission Report (USSR) must be faxed to the NCIC CTG.
APPENDIX V - SAMPLE CONSENT FORMS

ENGLISH Sample Consent Form

Please note that this sample language does not preempt or replace local REB review and approval. Investigators are required to provide the local REB with a copy of its sample language along with the language intended for local use. Local REBs are required to weigh the unique risks, constraints, and population considerations as a condition of any approval.

EFFECT OF RE-IRRADIATION FOR BONE PAIN
ON URINARY MARKERS OF OSTEOCLAST ACTIVITY

SC.20U

A Companion Study of SC.20:
(A PHASE III INTERNATIONAL RANDOMIZED TRIAL OF SINGLE VERSUS
MULTIPLE FRACTIONS FOR RE-IRRADIATION OF PAINFUL BONE METASTASES)

You have agreed to participate in a randomized trial to look at the effects on your bone pain of additional radiation treatments.

You are now being asked if you would also like to take part in a companion study. Radiation treatment can be effective in relieving bone pain; however, how it works has not been fully determined. We are interested in looking at changes in urine taken before and after radiation treatment.

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this companion study is to compare the response to radiation treatment to the biochemical changes in urine. It will help researchers to understand how pain relief works with radiation treatment. Also, it may help to predict the response to radiation treatment.

Note to centre: If an REB approved French consent is not used at your institution you should remove the above statement.
HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 163 people from Canada and the UK will take part in this companion study. The study should take about 3 years to complete and the results should be known in 4 years.

WHAT IS INVOLVED IN THE STUDY?

Only two urine specimens will be required for this companion study.

One urine sample will be collected before your radiation treatment, at the clinic.

You will then be given a home collection urine kit with instructions. You will also be given a pre-paid courier return envelope.

One month after your radiation treatment you will use the kit to collect the urine sample at home. You will use the courier envelope to return the sample to Queen’s University. This will make it possible for you to take part in this study without making a special trip to the clinic.

HOW LONG WILL I BE IN THE STUDY?

This companion study will require two urine samples, one before your radiation treatment and one again 1 month after your radiation treatment. The samples will be stored until the study is complete, then they will be tested for biochemical changes related to your radiation treatment. When the tests are complete, any remaining urine will be destroyed.

You can choose not to take part in this study or stop taking part at any time and your doctor will continue to treat you with the best means available. If you decide to stop participating in the study, we encourage you to talk to your doctor first.

Please note you can refuse to participate in the companion study but may continue to participate in the main protocol.

WHAT ARE THE RISKS OF THE STUDY?

There are no risks to your health in this companion study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you other than the potential pain relief from re-irradiation. We hope the information learned from this study will help other patients with painful bone metastases in the future.
WHAT ABOUT CONFIDENTIALITY?

Every effort will be made to keep your personal information confidential.

Qualified representatives of the following organizations may inspect your medical/study records and receive information from your medical/study records for quality assurance and data analysis:

- National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), the research group coordinating this study
- The research ethics committee who oversees the ethical conduct of this study in your hospital/clinic
- Cancer Research UK and UCL Cancer Trials Centre

This information may include test results and questionnaires.

The organizations listed above will keep information about you confidential, to the extent permitted by applicable laws, in the following manner:

- your name will not be used in any reports about the study
- your date of birth, if required to confirm your age, will not be used in any reports about the study
- you will be identified only by a trial code, a patient serial number, and initials as well as a hospital/clinic number (if permitted by the local REB)
- identifying information will be kept behind locked doors

WHAT ARE THE COSTS?

You will not be paid for taking part in this study. Taking part in this study may result in added costs to you.

In the case of research-related side effects or injury, medical care will be provided by your doctor or you will be referred for appropriate medical care. Although no funds have been set aside to compensate you in the event of injury or illness related to the study treatment or procedures, you do not waive any of your legal rights for compensation by signing this form.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Deciding not to take part or deciding to leave the study later will not result in any penalty or any loss of benefits to which you are entitled. Your doctor will discuss further treatments with you and continue to treat your cancer with the best means available.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

You will be given a copy of this signed and dated consent form.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have questions about taking part in this study or if you suffer a research-related injury you can talk to your doctor. Or, you can meet with the doctor who is in charge of the study at this institution. That person is:

______________________________  _________________________
Name                              Telephone

If you would like advice regarding your rights as a patient, you can talk to someone who is not involved in the study at all. That person is:

______________________________  _________________________
Name                              Telephone
SIGNATURES

My signature on this consent form means the following:

- The study has been fully explained to me and all of my questions have been answered,
- I understand the requirements and the risks of the study,
- I authorize access to my medical records as explained in this consent form, and
- I agree to take part in this study.

_________________________________ ________________
Signature of Patient Date

Note to centres: The following signature blocks may be added to your sample consent if required by your centre. If they are included in the REB approved sample consent form the signatures and dates must be completed for each consent form signed by a patient.

_________________________________ ________________
Signature of Person Conducting the Consent Discussion Date

________________________________ ________________
Signature of Doctor Date

_________________________________ ________________
Signature of Witness Date

Was the patient consented in a language other than that on this written form with the assistance of a translator? Please indicate in the checkbox below:

☐ Yes, the assistance of a translator was used for the consent process.
☐ No, the assistance of a translator was not used for the consent process.

Please note:
More information regarding the use of a translator should be noted in the medical record for the patient if applicable.
Exemple de formulaire de consentement en FRANÇAIS

Veuillez noter que cet exemple de formulation n’annule ni ne remplace l’examen par le CER local et son approbation. Les chercheurs sont tenus de communiquer au CER local une copie dans la présente langue et dans la langue locale prévue. Les CER locaux doivent évaluer les risques et les contraintes spécifiques, ainsi que des considérations démographiques, comme condition de toute approbation.

EFFET D’UNE NOUVELLE IRRADIATION CONTRE LES DOULEURS OSSEUSES SUR LES MARQUEURS URINAIRES DE L’ACTIVITÉ DES OSTÉOCLASTES

SC.20U

Étude d’accompagnement de l’étude SC.20
(ÉTUDE RANDOMISÉE INTERNATIONALE DE LA PHASE III PORTANT SUR L’UTILISATION DE FRACTIONS SIMPLES OU MULTIPLES POUR UNE NOUVELLE IRRADIATION DE MÉTASTASES OSSEUSES DOULOUREUSES)

An English version of this consent form is available upon request.

Note : Si votre établissement n’utilise PAS le formulaire de consentement en français approuvé par le CER, il faut biffer cette phrase.

Vous avez consenti à participer à une étude randomisée qui vise à analyser les effets qu’auront sur vos douleurs osseuses des traitements supplémentaires de radiothérapie.

Nous vous demandons maintenant si vous voulez participer aussi à une étude d’accompagnement. La radiothérapie peut réussir à soulager les douleurs osseuses. On n’a toutefois pas déterminé complètement son mode d’action. Nous souhaitons étudier les changements dans l’urine prélevée avant et après le traitement.

Cette étude est une étude clinique (type d’étude de recherche). Les études cliniques portent seulement sur les patients qui choisissent d’y participer. Veuillez prendre le temps nécessaire pour vous décider. Discutez-en avec vos amis et les membres de votre famille.

POURQUOI EFFECTUER CETTE ÉTUDE?

Cette étude d’accompagnement vise à analyser et comparer la réponse à la radiothérapie aux changements biochimiques dans l’urine. Cette recherche aidera les chercheurs à comprendre comment la radiothérapie soulage la douleur. Elle pourra aussi aider à prédire la réponse à la radiothérapie.
COMBIEN DE PERSONNES PARTICIPERONT À L’ÉTUDE?

Quelque 163 personnes du Canada et du R.-U. participeront à cette étude d’accompagnement. L’étude devrait prendre environ trois ans et les résultats devraient être connus dans quatre ans.

QU’EST-CE QUE COMPREND L’ÉTUDE?

Il faudra présenter deux échantillons d’urine pour cette étude d’accompagnement.

On en prélèvera un avant votre radiothérapie, à la clinique.

On vous remettra alors une trousse de collecte d’urine à la maison, des instructions et une enveloppe préaffranchie de retour par messager.

Un mois après votre radiothérapie, vous utiliserez la trousse pour recueillir l’échantillon d’urine à domicile. Vous utiliserez l’enveloppe du service de messagerie pour renvoyer l’échantillon à l’Université Queen’s. Vous pouvez ainsi participer à cette étude d’accompagnement sans avoir à vous rendre à la clinique.

PENDANT COMBIEN DE TEMPS PARTICIPERAI-JE À L’ÉTUDE?

Pour cette étude d’accompagnement, il faudra présenter deux échantillons d’urine, un avant votre radiothérapie et l’autre, un mois après le traitement. On gardera les échantillons jusqu’à ce que l’étude soit terminée et on les analysera ensuite pour déterminer s’ils ont subi des changements biochimiques reliés à votre radiothérapie. Lorsque les tests seront terminés, on détruira toute urine qui restera.

Vous pouvez décider de ne pas participer à l’étude ou cesser d’y participer n’importe quand et votre médecin continuera de vous traiter par les meilleurs moyens disponibles. Si vous décidez de cesser de participer à l’étude, nous vous encourageons à en parler d’abord à votre médecin.

Veuillez noter que vous pouvez refuser de participer à l’étude d’accompagnement tout en continuant quand même à participer à l’étude principale.

QUELS SONT LES RISQUES?

Cette étude d’accompagnement ne pose aucun risque pour votre état de santé.

Y A-T-IL DES AVANTAGES À PARTICIPER À L’ÉTUDE?

Si vous consentez à participer à l’étude, vous pourrez en tirer ou non des avantages directs autres que le soulagement possible de la douleur par la nouvelle radiothérapie. Nous espérons que les renseignements tirés de cette étude aideront un jour d’autres patients qui ont des métastases osseuses douloureuses.
ET LE CARACTÈRE CONFIDENTIEL DES RENSEIGNEMENTS?

On fera tous les efforts possibles pour que vos renseignements personnels demeurent confidentiels.

Des représentants qualifiés des organisations suivantes peuvent inspecter vos dossiers médicaux ou ceux de l’étude et recevoir des renseignements qui en sont tirés pour des fins d’assurance de la qualité et d’analyse des données :

- le Groupe des essais cliniques de l’Institut national du cancer du Canada (GEC INCC), groupe de recherche qui coordonne l’étude;
- le comité d’éthique en recherche qui supervise la conduite éthique de cette étude dans votre hôpital/clinique;
- le Cancer Research UK and UCL Cancer Trials Centre;

Ces renseignements peuvent inclure des résultats d’examen et des questionnaires.

Les organisations mentionnées maintiendront le caractère confidentiel des renseignements à votre sujet, dans la mesure où les lois pertinentes le permettent, de la façon suivante :

- votre nom ne servira dans aucun rapport sur l’étude;
- votre date de naissance, si elle est nécessaire pour confirmer votre âge, ne servira dans aucun rapport sur l’étude;
- on vous identifiera seulement par un code d’étude, un numéro de patient, vos initiales et le numéro de l’hôpital ou de la clinique (si votre comité local d’éthique en recherche le permet);
- on gardera sous clé les renseignements permettant de vous identifier.

QU’EST-CE QU’IL EN COÛTE?

Vous ne toucherez aucun paiement pour participer à l’étude. La participation peut entraîner des frais supplémentaires pour vous.

En cas d’effets secondaires ou de traumatisme reliés à la recherche, les soins médicaux vous seront dispensés par votre médecin, ou l’on vous enverra recevoir les soins médicaux nécessaires. Même si l’on n’a pas réservé de fonds pour vous indemniser en cas de traumatisme ou de maladie découlant du traitement donné ou des interventions pratiquées dans le cadre de l’étude, vous ne renoncez à aucun de vos droits légaux à une indemnisation en signant ce formulaire.

QUELS SONT MES DROITS EN TANT QUE PARTICIPANT(E)?

La participation à l’étude est volontaire. Vous pouvez décider de ne pas y participer, ou cesser d’y participer n’importe quand. En décidant de ne pas y participer ou de quitter l’étude par la suite, vous ne vous exposez à aucune pénalité et ne risquez nullement de perdre des avantages auxquels vous avez droit. Votre médecin discutera plus à fond des traitements avec vous et continuera de traiter votre cancer par les meilleurs moyens disponibles.
Nous vous communiquerons les nouveaux renseignements qui peuvent avoir un effet sur votre santé, votre mieux-être ou votre volonté de continuer de participer à l’étude.

Vous recevrez une copie de ce formulaire de consentement portant votre signature et la date.

QUI APPELER SI J’AI DES QUESTIONS OU DES PROBLÈMES?

Si vous avez des questions au sujet de votre participation à cette étude ou si vous subissez un traumatisme relié à la recherche, vous pouvez en parler avec votre médecin. Vous pouvez aussi rencontrer le médecin responsable de l’étude ici. Il s’agit de :

___________________________  _________________________
Nom                         Téléphone

Si vous cherchez des conseils au sujet de vos droits de patient(e), vous pouvez en parler à quelqu’un qui n’a aucun lien avec l’étude. Il s’agit de :

___________________________  _________________________
Nom                         Téléphone
SIGNATURES

Ma signature apposée sur ce formulaire de consentement signifie ce qui suit :

- L’étude m’a été expliquée au complet et l’on a répondu à toutes mes questions.
- Je comprends les exigences de l’étude et les risques qu’elle comporte.
- Je permets qu’on ait accès à mes dossiers médicaux de la façon expliquée dans ce formulaire de consentement.
- Je consens à participer à cette étude.

_________________________________ ________________
Signature du(de la) patient(e) Date

Note aux centres : Vous pouvez ajouter les blocs de signature qui suivent si votre centre l’exige. S’ils sont inclus dans votre échantillon de formulaire de consentement approuvé par le CER, il faut les remplir sur chaque formulaire de consentement signé par le(la) patient(e).

_________________________________ ________________
Signature de la personne chargée de la discussion sur le consentement éclairé Date

________________________________ ________________
Signature du médecin Date

_________________________________ ________________
Signature du témoin Date

A-t-on obtenu le consentement du(de la) patient(e) dans une langue autre que celle du présent formulaire, avec l’aide d’un(e) interprète. Veuillez l’indiquer dans la case ci-dessous :
(langue) _______________

☐ Oui, on a eu recours à l’aide d’un(e) interprète pour obtenir le consentement.
☐ Non, on n’a pas eu recours à l’aide d’un(e) interprète pour obtenir le consentement.

Veuillez noter :
Il faut consigner dans le dossier médical du(de la) patient(e), le cas échéant, d’autres renseignements sur le recours à un(e) interprète.
## LIST OF “CONTACTS”

<table>
<thead>
<tr>
<th>Contact</th>
<th>Tel. #</th>
<th>Fax #</th>
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<td><strong>ELIGIBILITY CHECKLIST</strong></td>
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<tr>
<td>Must be completed prior to the telephone call to request an allocation.</td>
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</tr>
<tr>
<td>Amy Hawkins</td>
<td>Clinical Trials Assistant</td>
<td>NCIC CTG</td>
</tr>
<tr>
<td>E-Mail:</td>
<td><a href="mailto:ahawkins@ctg.queensu.ca">ahawkins@ctg.queensu.ca</a></td>
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<td><strong>STUDY SUPPLIES</strong></td>
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<td>Forms, Protocols</td>
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<tr>
<td>Carolyn Wilson</td>
<td>SC.20U Study Coordinator</td>
<td>NCIC CTG</td>
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<tr>
<td>E-Mail:</td>
<td><a href="mailto:cwilson@ctg.queensu.ca">cwilson@ctg.queensu.ca</a></td>
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<tr>
<td>or: Dr. Joseph Pater</td>
<td>Physician Coordinator</td>
<td>NCIC CTG</td>
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<tr>
<td>E-Mail:</td>
<td><a href="mailto:jpayer@ctg.queensu.ca">jpayer@ctg.queensu.ca</a></td>
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<tr>
<td>or: Dr. Edward Chow</td>
<td>Study Chair</td>
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<tr>
<td>E-Mail:</td>
<td><a href="mailto:Edward.Chow@sw.on.ca">Edward.Chow@sw.on.ca</a></td>
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<td>Dr. Peter Hoskin</td>
<td>Gray Laboratory</td>
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<tr>
<td>E-Mail:</td>
<td><a href="mailto:peterhoskin@nhs.net">peterhoskin@nhs.net</a></td>
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<td><strong>UK Centres (UCL CTU)</strong></td>
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