Determine whether administering celecoxib during radiotherapy can reduce the risk of recurrence of triple-negative breast cancer. Pilot study

Trial acronym: Triple negative breast cancer and celecoxib

Protocol number: TNBC2025-5681

Version: July 2025

Investigational Product Name: Celecoxib (MAR-CELECOXIB)

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Clinical phase: 2

Short title: Triple negative breast cancer and celecoxib

Drug manufacturer name and address: Marcan Pharmaceuticals Inc.
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The trial will be conducted in accordance with Good Clinical Practice and applicable regulatory requirements of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH E6(R2))

PROTOCOL SUMMARY

1.1 Protocol Synopsis

1.1.1 Primary and Secondary Objectives and Estimantes

Relapses occur in 20 to 30% of patients with early-stage triple-negative breast cancer (**TNBC**), which is characterized by the absence of three receptors: the estrogen receptor (**ER**), progesterone receptor (**PR**) and human epidermal growth factor receptor 2 (**HER-2**). Radiotherapy (**RT**) can increase or decrease, depending on the patient, the level of cytokines that promote metastasis development. To help prevent the development of metastasis, the cyclooxygenase-2 (**COX-2**) inhibitor celecoxib will be administered during RT. This treatment aims to prevent RT-induced cytokine increases and, ultimately, improve patient prognosis.

The primary objective of this pilot study is to assess the feasibility of recruiting participants and implementing the study steps, with the intention of conducting a large-scale study in the future. The secondary objective is to evaluate celecoxib ability to inhibit the RT-induced stimulation of cytokines associated with metastasis development. This will be assessed by comparing the levels of these cytokines in plasma samples collected before, during, and after RT. In the exploratory objective, TNBC cells will be incubated *in vitro* with these plasma samples to determine whether administering celecoxib during RT can prevent increased cancer cell invasion and metastasis formation in mice.

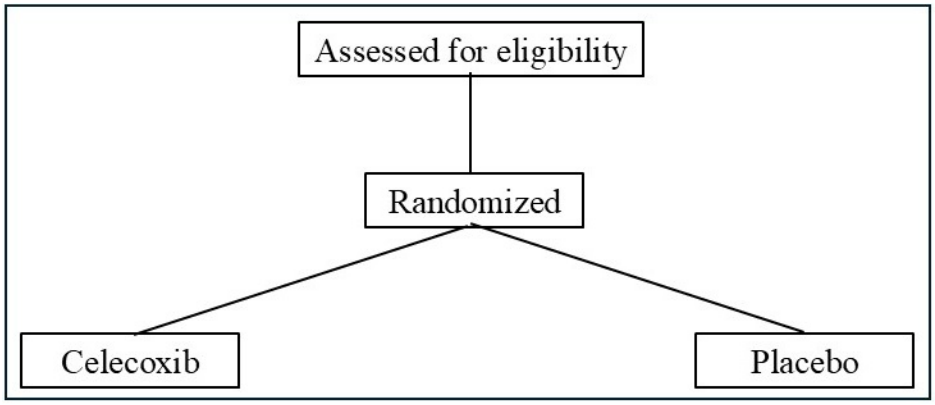
1.1.2 Overall Design

Intervention: Celecoxib (MAR-CELECOXIB) Control number: 270498	**Population Type:** Women with early-stage TNBC
Intervention Model: One capsule of 100 mg celecoxib or placebo will be taken after breakfast and one after supper, starting 7 days before RT and ending 14 days after RT.	**Population Diagnosis or Condition:** Participants with pathology-confirmed TNBC status, primary tumor removed by breast-conserving surgery and negative margins, regional lymph node of pN0 to pN3, and no evidence of distant metastasis at diagnosis. Participants will receive neoadjuvant chemotherapy. RT will be given after surgery. Immunotherapy (Pembrolizumab) will be administrated according to the clinical standard.
Control Type: Double-blind randomized clinical study	**Population Age:** 18 years and older
Control Description: Control participants will take a placebo instead of celecoxib.	**Site Distribution and Geographic Scope:** Centre intégré universitaire de santé et de services sociaux (**CIUSSS**) de l'Estrie – Centre hospitalier universitaire de Sherbrooke, Québec, Canada

Intervention Assignment Method: Participants will be recruited and followed at our facility, CIUSSS de l'Estrie CHUS Sherbrooke, by Dr. Sawyna Provencher (radiation oncologist), Dr. Isabelle Gauthier (radiation oncologist) and Dr. Michel Pavic (oncologist). Research assistant Hélène Therriault will give the participants the celecoxib or placebo bottle, explain the dosage to follow, and give them the follow-up logbook in which they will record the celecoxib or placebo intake, and any discomfort experienced, such as rashes, headaches, or dizziness. She will coordinate blood sampling with the research nurse based on administering celecoxib or placebo and radiotherapy sessions.	**Master Protocol:** Determine if celecoxib taken during RT reduces cancer relapse. The primary objective of this pilot study is to assess the feasibility of recruiting participants and implementing the study steps.
Drug/Device Combination Product Indicator: Chemotherapy and Pembrolizumab treatments will be administered according to clinical standards. The tumor will be removed by conservative surgery 4 to 8 weeks after the end of chemotherapy. RT will begin 8 to 12 weeks after surgery, which will allow the chemotherapy agents to be eliminated from the participants before taking celecoxib.	**Adaptive Trial Design:** Participants who experience discomfort or an adverse effect as mentioned in section 4.3 will be withdrawn from the clinic trial. Participants withdrawn from the trial will continue their treatment as planned.

Number of Arms: 2

Trial Blind Schema:



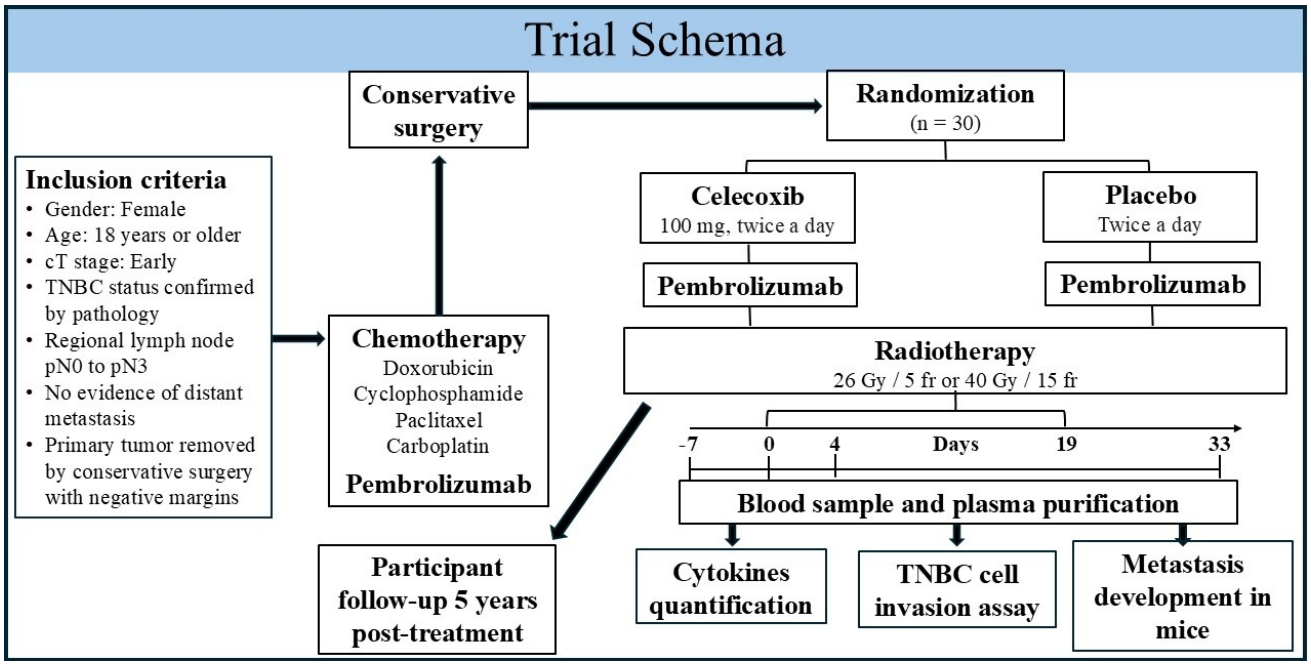
Blinded Roles: The promoter, Pr Benoit Paquette, will perform randomization and inform his research assistant, Hélène Therriault. If any adverse effects occur, clinicians Dr. Sawyna Provencher (radiation oncologist), Dr. Isabelle Gauthier (radiation oncologist) and Dr. Michel Pavic (oncologist) will be informed if the participant has taken celecoxib.

Number of Participants: Two groups containing 15 participants each. Total: 30

Duration: Total planned duration of trial intervention for each participant**.**
Participant recruitment will end in June 2027, with a 5-year follow-up period until 2032.

Committees: The Research Ethics Committee of the CIUSSS de l'Estrie - CHUS is responsible for auditing the research project.

1.2 Trial Schema



1.3 Schedule of Activities

Schedule of Activities															
Activities	Months														
	-4	-1	1	2	6	8	10	12	14	16	18	20	22	24	82
Chemotherapy and immunotherapy															
Conservative surgery															
Recruitment and randomization															
Radiotherapy and immunotherapy															
Plasma collection															
Cytokines quantification															
TNBC cell invasion assay *in vitro*															
Metastasis development assay in mice															
Participant follow-up															

2 INTRODUCTION

2.1 Purpose of Trial

Breast cancer is a heterogeneous disease, encompassing a number of distinct biological entities associated with specific morphological and clinical behavior. TNBC is a subgroup that accounts for 10–20% of all breast carcinomas, which is characterized by the absence of ER, PR and HER-2.[1] Hormone receptor-positive and HER2-positive breast cancers generally respond well to chemotherapy and targeted therapies for ER or HER2. In contrast, TNBC shows mixed results, and it does not benefit from targeted therapies.

For some non-metastatic patients with TNBC, the prognosis is less favorable compared to other breast cancer subtypes, with recurrence occurring on average 2.6 years after treatment.[2,3] However, five years after diagnosis, in patients whose cancer has not recurred early, the probability of recurrence is not significantly different from that of non-TNBC patients.[2,4] Therefore, TNBC patients can be divided into two groups: those who respond well to treatment and those for whom early recurrence is observed.[2]

Microfoci of cancer cells are often scattered in the breast and may be present up to a few centimeters from the edge of the primary tumor.[5] Conservative surgery removes the primary tumor, while microfoci of cancer cells are targeted with RT. The treated area frequently covers the entire breast and the axillary and subclavian lymph nodes. Unfortunately, the radiation dose used clinically does not always eliminate all cancer cells spread throughout the breast, as it is intended to optimize long-term results with minimal adverse effects. Nevertheless, many cancer cells are effectively eliminated, since RT reduces the likelihood of local recurrence and distant metastases.[3]

RT induces inflammation of varying intensity in all patients. Significant skin inflammation resembling sunburn (dermatitis) may be observed in some women in the treated area. Rarely is this dermatitis accompanied by severe pain, requiring treatment to be stopped.

A growing body of research suggests that radiation-induced inflammatory cytokines may stimulate the development of new metastases.[6-13] In support of clinical observations, it has been demonstrated in a murine model that pre-irradiation of the mammary gland before implantation of TNBC D2A1 cells stimulated their migration, increased the number of circulating tumor cells, and promoted the

development of lung metastases.[6] A similar stimulation of metastasis development was also observed after irradiation of a D2A1 tumor implanted in the mouse mammary gland.[14] The inflammatory pathways involved remain to be studied in detail. However, these adverse effects of radiation have been associated with cytokines, including interleukin-6 (**IL-6**) and the inflammatory enzyme COX-2.

Our team is currently conducting a study in TNBC patients with the aim of developing a test based on an RT-induced cytokine signature to identify participants at high risk of recurrence (Project Title: Prediction of Radiotherapy Efficacy in Patients with Triple-Negative Breast Cancer. Project Number: 14-205). The preliminary results support our research hypothesis. In 23% of participants, plasma isolated during RT increased the invasive capacity of TNBC cells and the formation of lung metastases in a mouse model. This percentage corresponds to that of patients whose cancer recurred. The addition of a COX-2 inhibitor, celecoxib, completely blocked these adverse effects of RT.

Two of the twenty TNBC participants recruited so far took a COX-2 inhibitor, including celecoxib, during their RT treatment for another medical indication. Unlike the other TNBC participants, the levels of almost all cytokines in their plasma collected during RT were decreased. Their plasma collected during RT did not increase the invasiveness of TNBC cells *in vitro*, nor the formation of metastasis in mice, and the cancer of these participants did not recur. This fortuitous observation suggests that administering celecoxib during RT could reduce the risk of recurrence in TNBC patients. This hypothesis will be tested in the current clinical study.

2.2 Assessment of Risks and Benefits

2.2.1 Risk Summary and Mitigation Strategy

Celecoxib can lead to gastric toxicity when administered concomitantly with chemotherapy.[15] For this reason, it is not typically prescribed to cancer patients. Our study addresses this issue by implementing a treatment plan that begins with chemotherapy, followed by tumor removal through surgery 4 to 8 weeks later. RT is then administered 3 to 8 weeks after the surgery. This approach allows for the clearance of chemotherapy agents from the body before starting celecoxib, thereby reducing the risk of gastric toxicity.

The risk of serious adverse effects (myocardial infarction and stroke) will be minimized since celecoxib will be administered for a short period (26 to 40 days according to the radiotherapy plan) and at a dose not exceeding 200 mg/day. Nevertheless, attention will be paid to the possible serious adverse effects.

2.2.2 Benefit Summary

A meta-analysis showed that administration of aspirin, a cyclooxygenase (**COX)** inhibitor, was associated with a 23% reduction in the risk of breast cancer,[16] a reduction that depended on the frequency of administration.[17-19] On the other hand, it is also suggested that the lack of association between aspirin use and breast cancer risk, reported in other studies, may be due to too low a dose and too short a duration of use.[20] Better protection against breast cancer risk may be achieved with selective COX-2 inhibitors such as celecoxib, when used regularly.[21-23]

Similar benefits were observed regardless of ER, PR, and HER-2 expression when aspirin was used throughout adult life.[24] A 41% risk reduction was observed for luminal A breast cancer and a similar 48% risk reduction for TNBC.[24] These results are consistent with most studies, except for a few.[25,26]

In standard neoadjuvant therapy, celecoxib may improve the objective response rate, but not the pathological complete response;[27,28] while its combination with adjuvant therapy may prolong overall survival.[29] One study demonstrated that celecoxib used as maintenance therapy in patients with non- metastatic TNBC after adjuvant therapy prolonged disease-free survival (**DFS**). A 4-year DFS rate of 66% was measured for patients who received celecoxib compared to 41.9% for those who did not.[30] It should be noted that this protective effect of celecoxib was not observed in hormone receptor-positive breast cancers, which already have a better prognosis than TNBC.[29] A statistically significant reduction in breast cancer recurrence was also associated with regular ibuprofen use, but not with aspirin use.[31] This reduction may be attributed to the suppression of the inflammatory process that can trigger the development of metastases.[32] Nonsteroidal anti-inflammatory drug (**NSAID**) use has also been shown to reduce the incidence of gynecological cancer secondary to breast cancer treatments.[33] Although encouraging, these benefits of using an NSAID or a specific COX-2 inhibitor need to be further validated by additional studies.

Regarding combining celecoxib with RT, animal models have demonstrated that this combination leads to better control of tumor growth.[34] In clinical settings, few studies have been conducted.[35] A phase I study showed that this combination is well tolerated and reduces itching and pain during RT.[36]

2.2.3 Overall Risk-Benefit Assessment

The risk of severe adverse effects is considered very low because celecoxib will be administered at a daily dose of 200 mg for only 26 to 40 days according to the radiotherapy plan. On the other hand, treating participants with this COX-2 inhibitor could help reduce the relapse rate of TNBC by preventing RT stimulation of cytokines associated with the development of metastases.

3 TRIAL OBJECTIVES AND ASSOCIATED ESTIMANDS

3.1 Primary Objective and Associated Estimands

3.1.1 Primary Objective

The primary objective of this pilot study is to assess the feasibility of recruiting participants and implementing the study steps, with the intention of conducting a large-scale study in the future.

Estimand Characteristic	**Description**
Population	
Non-metastatic TNBC participants	• Gender: Female • Age: 18 years or older • cT stage: Early • TNBC status confirmed by pathology • Regional lymph node pN0 to pN3 • No evidence of distant metastasis • Primary tumor removed by conservative surgery with negative margins
Treatment	
Celecoxib or placebo administration	Capsules of 100 mg celecoxib or placebo will take per

	os one after breakfast and one after supper starting 7 days before RT and end 14 days after RT. Chemotherapy according to the clinical standard (Doxorubicin, Cyclophosphamide, Paclitaxel, Carboplatin) Immunotherapy with Pembrolizumab will be administered during chemotherapy and radiotherapy if the tumor diameter exceeds 2 cm or if lymph nodes are positive. RT will consist of 26 Gy in 5 fractions or 40 Gy in 15 fractions if participants are under 50 years old with lymph node positivity.
Endpoint	
Feasibility of recruiting participants and implementing the study steps	Confirm the ability to recruit all participants. Access to data sources to obtain clinical data related to the diagnosis, treatment, and follow-up of TNBC. Coordinate blood sampling by research nurses with radiotherapy treatment, as well as with the CRCHUS pharmacy to obtain vials of celecoxib or placebo. Establish effective communication between clinicians and the sponsor to facilitate participant recruitment and monitor adverse events. Confirm that all forms are completed and signed (information and consent form, confirmation that participants meet the inclusion and exclusion criteria, confirmation of each blood draw).

3.2 Secondary Objective and Associated Estimands

3.2.1 Secondary Objective

The secondary objective is to determine whether taking celecoxib will prevent the increase in cytokines induced by RT, some of which are known to stimulate the invasion capacity of cancer cells and the formation of metastases.

Estimand Characteristic	**Description**
Population	
Non-metastatic TNBC participants	• Gender: Female • Age: 18 years or older • cT stage: Early • TNBC status confirmed by pathology • Regional lymph node pN0 to pN3 • No evidence of distant metastasis • Primary tumor removed by conservative surgery with negative margins

Treatment	
Celecoxib administration	Capsules of 100 mg celecoxib or placebo will take per os one after breakfast and one after supper starting 7 days before RT and end 14 days after RT. Chemotherapy according to the clinical standard (Doxorubicin, Cyclophosphamide, Paclitaxel, Carboplatin) Immunotherapy with Pembrolizumab will be administered if the tumor diameter exceeds 2 cm or if lymph nodes are positive.
Endpoint	
Quantification of cytokines in plasmas collected from TNBC participants	Quantify and compare the level of 48 cytokines in plasma samples collected from 30 participants at 4 times: 1) The day before the start of taking celecoxib or placebo, which corresponds to 7 days before starting RT, 2) the day of the start of RT and just before administering the 1st fraction of radiation, 3) after the 4th fraction of radiation, and 4) 14 days after the end of RT and stopping taking celecoxib or placebo.

3.3 Exploratory Objectives

3.3.1 Exploratory Objectives

As determined in preclinical models, RT can enhance the level of cytokines known to increase cancer cell invasion and the development of metastases. The exploratory objective will determine whether these adverse effects would be prevented by the administration of celecoxib during RT.

Estimand Characteristic	Description
Population	
Non-metastatic TNBC participants	• Gender: Female • Age: 18 years or older • cT stage: Early • TNBC status confirmed by pathology • Regional lymph node pN0 to pN3 • No evidence of distant metastasis • Primary tumor removed by conservative surgery with negative margins

Treatment

Celecoxib administration	Capsules of 100 mg celecoxib or placebo will take per os one after breakfast and one after supper starting 7 days before RT and end 14 days after RT
	Chemotherapy according to the clinical standard (Doxorubicin, Cyclophosphamide, Paclitaxel, Carboplatin)
	Immunotherapy with Pembrolizumab will be administered if the tumor diameter exceeds 2 cm or if lymph nodes are positive

Endpoint

Determine whether administration of celecoxib during RT reduces radiation-stimulation of cancer cell invasion and metastasis development in mice	Plasma samples will be collected from 30 participants at 4 times: 1) The day before the start of taking celecoxib or placebo, which corresponds to 7 days before starting RT, 2) the day of the start of RT and just before administering the 1st fraction of radiation, 3) after the 4th fraction of radiation, and 4) 14 days after the end of RT and stopping taking celecoxib or placebo.
	Comparison of the four plasma samples collected from each participant.
	Three TNBC cell lines will be incubated with the plasma collected from the participants.
	Following this incubation, the invasive capacity of the TNBC cells will be measured *in vitro* using invasion chambers.
	These cells will also be injected intravenously into the tail of immunocompetent mice, and the number of lung metastases will be determined 28 days later.

4 TRIAL DESIGN

4.1 Description of Trial Design

Non-metastatic TNBC participants will be recruited. The overall aim is to determine whether administering celecoxib during RT could reduce the risk of cancer recurrence. The hypothesis is that celecoxib will block the increase in cytokines, induced by RT, that are known to promote cancer cell invasion and metastasis. The primary objective of this pilot study is to assess the feasibility of recruiting participants and implementing the study steps, with the intention of conducting a large-scale study in the future.

Thirty participants will be recruited and randomized: fifteen will receive celecoxib, and fifteen will receive a placebo. Participants who take a COX-2 inhibitor for other medical indications or medications such as ibuprofen will be excluded. A limitation of this study will be the use of anti-inflammatory drugs in the years after treatment.

After chemotherapy and removal of the tumor by partial mastectomy, participants will be recruited by their treating physician, either the hemato-oncologist or the radiation oncologist. The pharmacy department of CIUSSS de l'Estrie CHUS, Sherbrooke, Quebec will prepare bottles containing 100 capsules of 100 mg celecoxib. Bottles of placebo will be supplied by GALENOVA INC, Saint-Hyacinthe, Quebec, Canada. Participants will take one capsule after breakfast and one after supper starting 7 days before RT and end 14 days after RT. RT will consist of 26 Gy in 5 fractions or 40 Gy in 15 fractions if participants are under 50 years old with lymph node positivity. According to the RT plan, celecoxib will be taken for no longer than 40 days. In a logbook, participants will report when celecoxib was taken and if they experience discomfort such as skin rashes, headache, or dizziness. See section 7 for details regarding the criteria to withdraw participants from the study. Participant follow-up will last 5 years after treatment and will be carried out according to clinical guidelines, which consist of a clinical examination and a mammogram every year. If breast density is categorized as D (extremely dense), an MRI will be performed in alternating years with the mammogram. A CT or PET scan will be conducted if symptoms such as bone pain are present. The date corresponding to the detection of a local or distant recurrence will be recorded in the participant file to determine whether taking celecoxib could reduce the risk of regional or distant recurrence.

The secondary objective is to determine whether taking celecoxib will prevent the increase in cytokines induced by RT, some of which are known to stimulate the invasion capacity of cancer cells and the formation of metastases. This will be determined by collecting plasma samples at four time points: **1**) the day before the start of taking celecoxib or placebo, which corresponds to 7 days before starting RT, **2**) the day of the start of RT and just before administering the 1st fraction of radiation, **3**) after the 4^{th} fraction of radiation, and **4**) 14 days after the end of RT and stopping taking celecoxib or placebo. During the blood draw, participants will be questioned by the research nurse to ensure that celecoxib is well tolerated. The impact of celecoxib on changes in 48 cytokines will be determined by Eve Technologies (Calgary) using laser bead multiplexing.

The beneficial effect of celecoxib in preventing RT-induced cytokine elevations on cancer cell invasion capacity and metastasis development will be evaluated in preclinical models. This exploratory objective will be assessed by comparing the four plasma samples collected from each participant. Three TNBC cell lines will be incubated with these plasma samples. Using invasion chambers, the correlation between celecoxib-induced cytokine reduction and inhibition of RT-induced cancer cell invasion stimulation will be determined. These cells will also be injected intravenously into the tail of immunocompetent mice, and 28 days later, the reduction in the number of lung metastases with plasma

collected from participants treated with celecoxib compared to those taking placebo will be determined.

4.2 Overall Rationale for Trial Design

The relapse rate of patients with TNBC ranges between 20 and 30%. The primary objective of this pilot study is to assess the feasibility of recruiting participants and implementing the study steps, with the intention of conducting a large-scale study in the future.

The increase in cytokines known to promote cancer cell invasion and metastasis by RT suggests that preventing this stimulation may improve the prognosis of patients with TNBC. This working hypothesis will be tested by determining whether celecoxib administration can block the increase of cytokines in plasma, compared to plasma collected from participants taking a placebo. Furthermore, identifying the cytokines whose levels do not increase when treating with celecoxib treatment could be utilized in future studies to evaluate the response of TNBC patients to celecoxib.

Assays using *in vitro* invasion chambers and the development of lung metastases in mice will contribute to demonstrating that blocking RT-stimulation of protumor cytokines can attenuate two critical steps in cancer progression: the invasiveness of cancer cells and their ability to metastasize.

4.3 Trial Stopping Rules

Participants who experience discomfort, such as rashes, headaches, or dizziness while taking celecoxib, should inform the research assistant or research nurse assigned to the clinical trial. They will then notify the promoter, Benoit Paquette, within 24 hours, who will discuss the reported event with co-investigators Dr Michel Pavic (chemotherapy), Dr Sawyna Provencher (RT) and Isabelle Gauthier (RT). Based on the severity of the adverse effects, they will decide whether or not to withdraw the participant from the trial.

In the event of withdrawal from the trial, the adverse effects and their severity will be compiled, and the serious unexpected adverse drug reactions will be reported to the Canadian Minister of Health and included in the scientific publications documenting the trial results.

Participants withdrawn from the trial will continue their RT as planned.

Annual medical follow-ups of participants will be conducted over the five years following treatment.

4.4 Start of Trial and End of Trial

The trial will start when the first participant signs the consent form (expected in August 2025) and end after the last participant 5-year follow-up.

5 TRIAL POPULATION

5.1 Description of Trial Population and Rationale

Women aged over 18 years with pathologically confirmed TNBC breast cancer.

5.2 Inclusion Criteria

- Gender: Female
- Age: 18 years or older
- pT stage: Early
- TNBC status confirmed by pathology
- Regional lymph node pN0 to pN3
- No evidence of distant metastasis
- Primary tumor removed by conservative surgery with negative margins

5.3 Exclusion Criteria

Participants will be excluded if they have experienced any of the following conditions in the last six months:

- Stomach ulcer
- Kidney disease: Glomerular filtration rate (**GFR**) lower than 50 mL/min
- Liver disease: AST/ALT - 3 times the upper limit of normal, Bilirubine - 2 times the upper limit of normal, INR - 1.3 times the upper limit of normal, Cirrhose Child-Pugh B or more
- Congestive heart failure: Left ventricular ejection fraction (**LVEF**) lower than 50%

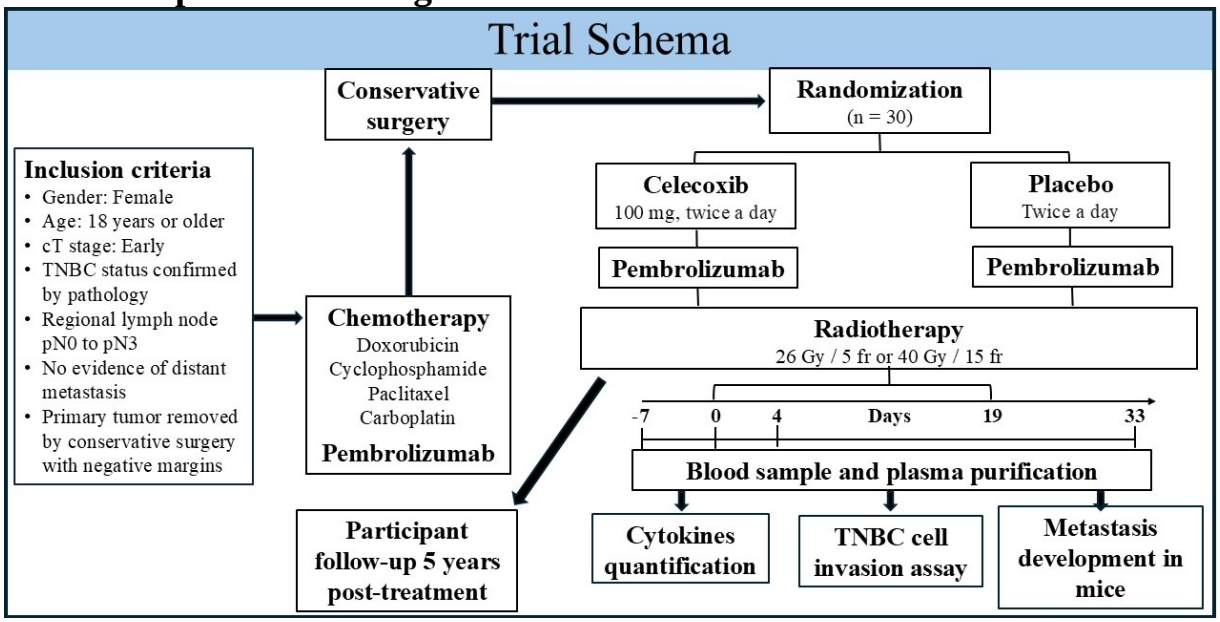
Participants taking an NSAID for another medical condition or as needed before starting their radiotherapy treatment

Participants who have demonstrated:

- Hypersensitivity to celecoxib
- A history of allergic reactions to sulfonamides
- A history of asthma attacks, urticaria, or allergic reactions after taking acetylsalicylic acid (**ASA**) or another nonsteroidal anti-inflammatory drug
- The presence of inflammatory bowel disease
- Proven hyperkalemia

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Description of Investigational Trial Intervention



6.2 Rationale for Investigational Trial Intervention Dose and Regimen

One capsule of 100 mg celecoxib or placebo will be taken after breakfast and one after supper, starting 7 days before RT and ending 14 days after RT. The risk of serious side effects (myocardial infarction and stroke) will be minimized since celecoxib will be administered for a short period (40 days or less) and at a dose not exceeding 200 mg/day.

6.3 Investigational Trial Intervention Administration

One capsule of 100 mg celecoxib or placebo will be taken after breakfast and one after supper, starting 7 days before RT and ending 14 days after RT.

6.4 Investigational Trial Intervention Dose Modification

No change in celecoxib dosage

6.5 Management of Investigational Trial Intervention Overdose

The research assistant will give the participants the celecoxib or placebo bottle, explain the dosage to follow, and give them the follow-up logbook in which they will record the celecoxib or placebo intake, and any discomfort experienced, such as rashes, headaches, or dizziness. During the four participant visits corresponding to the blood sampling, the research assistant will confirm with participants that the intake of celecoxib or placebo is respected.

6.6 Preparation, Storage, Handling and Accountability of Investigational Trial Intervention

6.6.1 Preparation of Investigational Trial Intervention

The pharmacy department of CIUSSS de l'Estrie CHUS, Sherbrooke, Quebec will prepare bottles containing 100 capsules of 100 mg celecoxib. Bottles of placebo will be supplied by GALENOVA INC, Saint-Hyacinthe, Quebec, Canada.

6.6.2 Storage and Handling of Investigational Trial Intervention

The pharmacy department of CIUSSS de l'Estrie CHUS, Sherbrooke, Quebec, will store and handle the bottles of celecoxib. The research assistant will handle the placebo bottles and store them in a locked cabinet in the laboratory of the promoter, Pr Benoit Paquette.

6.6.3 Accountability of Investigational Trial Intervention

Dr. Sawyna Provencher (radiation oncologist), Dr. Isabelle Gauthier (radiation oncologist) and Dr. Michel Pavic (oncologist) will recruit participants. They will fill a request form addressed to Julie Leblond of the pharmacy department of CIUSSS de l'Estrie CHUS, asking to prepare a bottle of celecoxib or placebo capsules. The bottle will be identified with a code associated with each participant. The unused capsules of celecoxib or placebo will be brought back to the pharmacy department. The promoter, Pr Benoit Paquette, will randomize the participants in the arm of celecoxib or placebo, and inform Julie Leblond, who is responsible for the pharmacy department.

6.7 Investigational Trial Intervention Assignment, Randomisation and Blinding

6.7.1 Participant Assignment to Investigational Trial Intervention

Dr. Sawyna Provencher (radiation oncologist), Dr. Isabelle Gauthier (radiation oncologist) and Dr. Michel Pavic (oncologist) will recruit participants and validate the inclusion and exclusion criteria. Participants will be divided into two arms: 1) celecoxib, and 2) placebo. For this pilot study, 15 participants per arm will be enrolled. The promoter, Pr Benoit Paquette, will randomize the participants. The research assistant will register the participants in an Excel file that will include participant characteristics (age, tumor diameter, stage, chemotherapeutic agents, chronology of the treatment plan – chemotherapy, surgery, RT plan – , cancer staging and grading, conservative surgery, pembrolizumab, Ki67, BRCA1 and 2 statuses, radiodermatitis, date of relapse). The researcher assistant will assign each participant a unique code beginning with "C" followed by a number indicating the chronological order of enrollment in the study. Only the research assistant and the promoter will know the link between the code and the patient identity.

6.7.2 Randomization

The first participant recruited will be included in the first arm, the second participant in the second arm, and so on. The process will begin again with the fifth and subsequent participants recruited.

6.7.3 Measures to Maintain Blinding

The promoter, Pr Benoit Paquette, will randomize the participants. Only him and the research assistant will know the link between participants and their identification code.

6.7.4 Emergency Unblinding at the Site

Participants who experience discomfort, such as rashes, headaches, or dizziness while taking celecoxib, should inform the research assistant or research nurse assigned to the clinical trial. They will then notify the promoter, Benoit Paquette, within 24 hours, who will discuss the reported event with co-investigators Dr Michel Pavic, Dr Sawyna Provencher and Dr Isabelle Gauthier. The promoter will inform them of the meaning of the participant identification code to ensure appropriate clinical follow-up. Based on the severity of the adverse effect, they will decide whether or not to withdraw the participant from the trial.

6.8 Investigational Trial Intervention Adherence

During the four visits of the participants corresponding to the blood sampling, the research assistant will confirm with them that the taking of celecoxib or placebo is respected, and that the follow-up book is correctly completed.

6.9 Description of Noninvestigational Trial Intervention

Chemotherapy: Doxorubicine, Cyclophosphamide, Paclitaxel, Carboplatin

Conservative surgery

Immunotherapy with Pembrolizumab will be prescribed if the tumor diameter exceeds 2 cm or if lymph nodes are positive.

RT will consist of 26 Gy in 5 fractions or 40 Gy in 15 fractions if participants are under 50 years old with lymph node positivity.

6.10 Concomitant Therapy

One capsule of 100 mg celecoxib or placebo will be taken after breakfast and one after supper, starting 7 days before RT and ending 14 days after RT.

7 PARTICIPANT DISCONTINUATION OF TRIAL INTERVENTION AND DISCONTINUATION OR WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Trial Intervention for Individual Participants

7.1.1 Permanent Discontinuation of Trial Intervention

Participants who experience discomfort, such as rashes, headaches, or dizziness while taking celecoxib, should inform the research assistant or research nurse assigned to the clinical trial. They will then notify the promoter, who will discuss the situation with co-investigators Dr Michel Pavic, Dr Sawyna Provencher and Dr Isabelle Gauthier. The promoter will inform them of the meaning of the participant identification code to ensure appropriate clinical follow-up. Based on the severity of the adverse effect, they will decide whether or not to withdraw the participant from the trial. Participants withdrawn from the trial will continue their RT as planned.

7.2 Participant Discontinuation or Withdrawal from the Trial

Participants who no longer consent to participate in the trial will be withdrawn. See also section 7.1.1

7.3 Management of Loss to Follow-Up

Participant follow-up will last 5 years after treatment and will be carried out according to clinical guidelines, which consist of a clinical examination and a mammogram every year. No loss of follow-up is expected for any participant.

8 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Trial Assessments and Procedures Considerations

This pilot study is to assess the feasibility of recruiting participants and implementing the study steps, with the intention of conducting a large-scale study in the future. Participants who experience discomfort, such as rashes, headaches, or dizziness while taking celecoxib, should inform the research assistant or research nurse assigned to the clinical trial. They will then notify the promoter, who will discuss the situation with co-investigators Dr Michel Pavic, Dr Sawyna Provencher and Dr Isabelle Gauthier. The promoter will inform them of the meaning of the participant identification code to ensure appropriate clinical follow-up. Based on the severity of the symptoms, they will decide whether or not to withdraw the participant from the trial. Participants withdrawn from the trial will continue their RT as planned.

9 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, PRODUCT COMPLAINTS, PREGNANCY AND POSTPARTUM INFORMATION, AND SPECIAL SAFETY SITUATIONS

9.1 Definitions

9.1.1 Definitions of Adverse Events

Participants who experience discomfort - such as rashes, headaches, or dizziness - while taking celecoxib.

9.1.2 Definitions of Serious Adverse Events

Serious adverse events include life-threatening event where the participant is at risk of death at the time of the event and required hospitalization. Serious adverse events may also include persistent or significant disability leading to a substantial disruption of the person's ability to conduct normal life functions.

Previous clinical trials reported a low increase of serious adverse events when celecoxib is taken for 6 months and more at a dose above 200 mg daily (see monograph of MAR-CELECOXIB). These low but significant increases in severe adverse events were associated with:

- Incidence of borderline-normal liver function test elevations (ALT, AST, alkaline phosphatase) of 6% for participants taking celecoxib capsules and 5% for placebo.
- Increased risk of serious cardiovascular complications (such as myocardial infarction, stroke, or thrombotic events) was reported in participants presenting ischemic heart disease, cerebrovascular disease, heart failure (NYHA Class II-IV), or cardiovascular risk factors.
- Cases of severe renal failure, some requiring dialysis and others resulting in death, have been reported in patients with renal impairment.
- Stomach or intestinal problems such as ulcers, inflammation, bleeding, holes/perforation, blockage, or pain.

In our trial, the risk of severe adverse events is expected to be very low because celecoxib will be administered at a daily dose of 200 mg for no longer than 40 days. In addition, participants will be excluded from the trial if they have experienced any of the following conditions in the last six months:

- Stomach ulcer
- Kidney disease: Glomerular filtration rate (**GFR**) lower than 50 mL/min
- Liver disease: AST/ALT - 3 times the upper limit of normal; Bilirubine - 2 times the upper limit of normal; INR - 1.3 times the upper limit of normal; Cirrhose Child-Pugh B or more
- Congestive heart failure: Left ventricular ejection fraction (**LVEF**) lower than 50%

Will also be excluded participants demonstrating:

- Hypersensitivity to celecoxib
- History of allergic reactions to sulfonamides
- History of asthma attacks, urticaria, or allergic reactions after taking acetylsalicylic acid (**ASA**) or another nonsteroidal anti-inflammatory drug
- Presence of inflammatory bowel disease
- Proven hyperkalemia

9.2 Timing and Procedures for Collection and Reporting

During the four visits of the participants corresponding to blood sampling, the research assistant will confirm with them that the taking of celecoxib or placebo is respected, and that the follow-up book

is correctly completed, and any experience discomforts are collected by the participants. Participants will be questioned by the research nurse to ensure that celecoxib is well tolerated. Participants who experience discomfort, such as rashes, headaches, or dizziness while taking celecoxib, should inform the research nurse or the research assistant. They will notify the promoter, Benoit Paquette, within 24 hours, who will discuss the reported event with co-investigators Dr Michel Pavic, responsible for chemotherapy, and Drs Sawyna Provencher and Isabelle Gauthier, who will plan the RT. The clinicians will be notified about whether the participant received celecoxib or the placebo. They will evaluate the severity of the adverse effect and their possible relationship with the administration of celecoxib. The research staff will receive this report immediately.

The promoter will compile the type, frequency, duration, and intensity of adverse effects on the CIOMS form and in the database file that collects all adverse effects. Unexpected serious adverse events associated with the drug but not fatal or life-threatening will be reported within 15 calendar days to the Canadian Minister of Health and the research staff. Unexpected serious adverse events associated with the drug and fatal or life-threatening events will be reported as soon as possible, but within 7 calendar days by phone, followed by a written report within 8 calendar days.

In the event of participant withdrawal from the trial, adverse events (serious or not) and their severity will be included in the scientific publications documenting the trial results.

10 STATISTICAL CONSIDERATIONS

10.1 General Considerations

For this pilot trial, the analysis will include all eligible participant data at trial completion.

10.2 Analysis Sets

Participants will be divided into two arms: 1) celecoxib, and 2) placebo. For this pilot study, 15 participants per arm will be enrolled.

The primary objective of this pilot study is to assess the feasibility of recruiting participants and implementing the study steps, with the intention of conducting a large-scale study in the future. The secondary objective is to determine whether taking celecoxib will prevent the increase in cytokines induced by RT, some of which are known to stimulate the invasion capacity of cancer cells and the formation of metastases. This will be determined by collecting plasma samples at four time points: 1) the day before the start of taking celecoxib or placebo, which corresponds to 7 days before starting RT, 2) the day of the start of RT and just before administering the 1st fraction of radiation, 3) after the 4th fraction of radiation, and 4) 14 days after the end of RT and stopping taking celecoxib or placebo. The impact of celecoxib on changes in 48 cytokines will be determined by Eve Technologies (Calgary) using laser bead multiplexing.

The exploratory objective will determine whether preventing elevation induced by RT of cytokines by celecoxib will block the enhancement of cancer cell invasion and metastasis. This will be evaluated in preclinical models. The four plasma samples collected from each participant will be compared. Three TNBC cell lines will be incubated with these plasma samples. Using invasion chambers, the correlation between celecoxib-induced cytokine reduction and inhibition of RT-induced cancer cell invasion stimulation will be determined. These cells will also be injected intravenously into the tail of immunocompetent mice, and 28 days later, the reduction in the number of lung metastases with plasma collected from participants treated with celecoxib compared to those taking placebo will be determined.

10.3 Analyses of Demographics and Other Baseline Variables

10.4 Analyses Associated with the Primary Objective

10.4.1 Primary Objective

The primary objective of this pilot study is to assess the feasibility of recruiting participants and implementing the study steps, with the intention of conducting a large-scale study in the future.10.4.1.1 Statistical Analysis Method

When the large-scale study will be conducted, a Kaplan–Meier analysis will be used to perform univariate survival analysis and log-rank test to calculate the hazard ratio and compare two survival curves. For multivariate survival analysis, the multivariate Cox proportional hazards regression model was used to test the impact of celecoxib. All statistical analyses were performed with GraphPad Prism. A *P* value < 0.05 will be considered statistically significant.

10.5 Analyses Associated with the Secondary Objective

10.5.1 Secondary Objective

The secondary objective is to determine whether taking celecoxib will prevent the increase in cytokines induced by RT, some of which are known to stimulate the invasion capacity of cancer cells and the formation of metastases.

10.5.1.1 Statistical Analysis Method

Identification of cytokines that differentiate patients who experience a relapse from those who do not will be done using Python programming leveraging machine-learning packages (e.g. Scikit-learn). These data will be scrutinized through various methods to establish correlations (positive or negative) using a correlation matrix and heatmap for both patient and cytokines. Principal Component Analysis (**PCA**) on standardized (mean removal and variance scaling) data will also be employed to reduce the dimensionality of the data, thereby allowing us to identify the most significant variables. Cytokine clusters will be determined using a Gaussian-Mixture-based unsupervised clustering algorithm (e.g. Variation Bayesian Gaussian Mixture). The thresholds for increases and decreases in the levels of these cytokines linked to relapse will then be determined.

10.6 Analyses Associated with the Exploratory Objective

The exploratory objective will determine whether preventing elevation induced by RT of cytokines by celecoxib will block the enhancement of cancer cell invasion and metastasis.

The invasion assays will be performed 3 times in triplicate. For the metastasis formation assay, each group will include 8 mice. An Anova assay will be done using GraphPad Prism. A *P* value < 0.05 will be considered statistically significant.

10.7 Safety Analyses

Celecoxib is currently indicated for the relief of symptoms associated with: osteoarthritis, rheumatoid, arthritis in adults and ankylosing spondylitis. It is also indicated in adults for the short-term relief (≤ 7 days) of acute moderate to severe pain caused by: soft tissue and musculoskeletal trauma -

including sprains, orthopedic surgery, tooth extraction.

The risk of serious side effects will be minimized since celecoxib will be administered for a short period (40 days or less) and at a dose not exceeding 200 mg/day.

11 TRIAL OVERSIGHT AND OTHER GENERAL CONSIDERATIONS

11.1 Regulatory and Ethical Considerations

Pending approval from Health Canada, this clinical trial was approved by the ethics and scientific committees of the Clinical Research Center of the CIUSSS de l'Estrie CHUS. Protocol number: TNBC2025-5681

This trial will be conducted in accordance with the protocol and with the following:

- Ethical principles that have their origin in the Declaration of Helsinki for medical research involving human subjects
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the Council for International Organisations of Medical Sciences (**CIOMS**) International Ethical Guidelines
- ICH Good Clinical Practice (**GCP**) Guidelines
- Applicable laws and regulations

11.2 Trial Oversight

Promoter : Benoit Paquette, Ph.D.
Department of Medical Imaging and Radiation Sciences
Faculty of Medicine and of Health Sciences Université de Sherbrooke
3001, 12th Avenue North, Sherbrooke, Québec, Canada J1H 5N4

11.3 Informed Consent Process

Participants will be recruited and followed at our facility, CIUSSS de l'Estrie CHUS Sherbrooke, by Dr Sawyna Provencher (radiation oncologist), Dr Isabelle Gauthier (radiation oncologist) and Dr Michel Pavic (oncologist).

The consent form will be presented to the participants by the treating radiation oncologist, the research nurse or the research assistant.

11.4 Committees

Not applicable.

11.5 Insurance and Indemnity

Not applicable.

11.6 Risk-Based Quality Management

Not applicable.

11.7 Data Governance

Blood samples collected as part of this trial will be identified with a specific code. The patient names will not be identified on the samples, but a code will be used to link them. Decoding can only be performed by the promoter, Pr Benoit Paquette, or a person designated by him.

The study data will be archived on the computer of the promoter and his research assistant.

The blood samples will be stored for 10 years in a -20°C freezer in Pr Paquette laboratory, or until exhaustion.

11.8 Data Protection

The trial data will be archived on the computer of the promoter and his research assistant.

All participant-related forms, such as the signed consent form, blood sampling certificates, and logbook filled by participants, will be kept in a locked file by the promoter.

Trial records will be kept for 15 years after completion or discontinuation of the study.

11.9 Source Data

Participant source data, such as tumor size, lymph node status, chemotherapy type, RT plan, and administration or not of pembrolizumab, will be obtained by the research assistant from the CIUSSS de l'Estrie CHUS Sherbrooke computer registry using a secure internet line.

11.10 Protocol Deviations

Research assistant will give the participants the celecoxib or placebo bottle, explain the dosage to follow, and give them the follow-up logbook in which they will record the celecoxib or placebo intake, and any discomfort experienced, such as rashes, headaches, or dizziness. During the four participant visits corresponding to blood sampling, the research assistant will confirm with participants that the intake of celecoxib or placebo is respected. Participants who will not respect the protocol for celecoxib or placebo intake will be excluded from the trial.

11.11 Early Site Closure

The promoter already works on another trial with clinicians who recruit the participants and perform the 5-years follow-up. Early site closure is not expected.

11.12 Data Dissemination

As with other studies conducted by their team, Pr Paquette will publish the results of this trial in a peer-reviewed scientific journal, such as the International Journal of Radiation Biology & Related Studies in Physics, Chemistry & Medicine. These results will also be presented at the annual conference of Canadian Association of Radiation Oncology and at specialized conferences on breast cancer.

12 APPENDIX: SUPPORTING DETAILS

12.1 Clinical Laboratory Tests

Clinical laboratory tests usually used in TNBC patients treated with chemotherapy, pembrolizumab, and RT will be performed. Eve Technology (Calgary) will identify and quantify cytokines in plasma collected from the participants.

12.2 Country/Region-Specific Differences

Not applicable

12.3 Prior Protocol Amendment

Not applicable

13 APPENDIX: GLOSSARY OF TERMS AND ABBREVIATIONS

ASA, acetylsalicylic acid
CIOMS, Council for International Organisations of Medical Sciences
CIUSSS, Centre intégré universitaire de santé et de services sociaux
COX-2, cyclooxygenase-2
DFS, disease-free survival
ER, estrogen receptor
GCP, Good Clinical Practice
GFR, Glomerular filtration rate
HER-2, human epidermal growth factor receptor 2
IL-6, interleukin-6
LVEF, Congestive heart failure: Left ventricular ejection fraction
NSAID, nonsteroidal anti-inflammatory drug
PCA, Principal Component Analysis
PR, progesterone receptor
RT, radiotherapy

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