UNICANCER Group Tumor: UNITRAD

Protocol n°UC-0107/1604

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Multicenter randomized phase III trial comparing hypo-fractioned versus standard radiotherapy in breast cancer with an indication for regional lymph node irradiation in terms of lymphedema occurrence

Abbreviated title: **HYPOG-01**

Version n°7.0 – December 19th, 2022

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Trial Title: HYPOG-01

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PROTOCOL N°: **UC-0107/1604**

Amendment 6 – Protocol v7.0 December 19th, 2022

Study title: Multicenter randomized phase III trial comparing hypo-fractioned versus standard radiotherapy in breast cancer with an indication for regional lymph node irradiation in terms of lymphedema occurrence – HYPOG-01

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SYNOPSIS – PROTOCOL N° UC-0107/1604

A) TRIAL IDENTIFICATION

SPONSOR – PROTOCOL CODE NUMBER: UC-0107/1604

VERSION (NR & DATE): 7.0, DECEMBER 19TH, 2022

TRIAL TITLE: Multicenter randomized phase III trial comparing hypo-fractioned versus standard radiotherapy in breast cancer with an indication for regional lymph node irradiation in terms of lymphedema occurrence

ABBREVIATED TITLE: HYPOG-01

COORDINATING INVESTIGATOR: Dr. Sofia RIVERA

NUMBER OF PARTICIPATING CENTERS (ESTIMATE): 40	NUMBER OF PATIENTS: 1265

B) SPONSOR IDENTIFICATION

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C) TRIAL GENERAL INFORMATION

INDICATION: early breast cancer pT1-3 or initially cT1-3, cN0-N3, M0 with an indication of loco regional irradiation

METHODOLOGY: Non inferiority phase III open-label randomized controlled multicentric trial

PRIMARY OBJECTIVE:

To show that hypofractionated locoregional radiotherapy is non-inferior to normofractioned radiotherapy in early breast cancer with an indication for irradiation of regional lymph node levels in terms of lymphedema of the arm on the side treated for breast cancer.

SECONDARY OBJECTIVE(S):

- to assess loco-regional events: acute and late toxicities (arm motion and function, cosmetic result, lung and cardiac events)
- to assess cancer related-events: locoregional relapse-free survival, distant disease-free survival, overall survival, causes of death,
- to assess and compare health related quality of life between arms
- to conduct a cost-utility analysis

DIAGNOSIS AND INCLUSION CRITERIA:

- Woman ≥ 18 years who had radical surgery for invasive breast cancer pT1-3 or initially cT1-3, cN0-N3, M0 with either mastectomy or breast conservation. The patient can be included no matter the status of oestrogen receptor, progesterone receptor, malignancy grade, HER2 status.
- ECOG 0-2
- Axillary lymph node dissection of the axilla where the findings give indication for regional nodes radiation therapy to levels +/- I +/- II +/- III +/- IV +/- interpectoral nodes (Rotter) and +/- the IMN.
- Sentinel node biopsy documenting limited nodal disease without an indication for axillary lymph node dissection according to institutional, national or other trial guidelines are accepted.
- The patient may be a candidate for boost to the tumour bed.
- Adjuvant systemic therapy with chemotherapy, endocrine therapy and anti-HER2 treatment is accepted.
- Neoadjuvant chemotherapy for downstaging according to institutional or national guidelines is accepted if there is not an indication for a boost in the area of regional nodes after surgery.
- Primary systemic therapy of an operable breast cancer is accepted.
- If the patient is not treated with chemotherapy, she must be randomized within 8 weeks from last surgery. If she has received adjuvant chemotherapy, she must be randomized within 4 weeks after the last series of adjuvant chemotherapy or within 42 days from last surgery in case of surgery after neoajduvant or adjuvant chemotherapy.Breast implants are accepted.
- Connective tissue disease is allowed if the treating radiation oncologist finds radiotherapy indicated
- Postoperative infection and/or seroma giving indication for drainage during RT is accepted
- Women of childbearing potential must agree to use adequate contraception for the duration of study participation and up to 3 months following completion of therapy
- Signed informed consent
- Affiliated to the Social Security System.

NON INCLUSION CRITERIA:

- Previous breast cancer or DCIS of the breast.
- Bilateral breast cancer
- Patient with previous non-breast malignancy with the exception of cancer in complete remission for over 5 years and low risk of recurrence. Patients with the following diseases can be accepted despite less than 5 years disease free interval: carcinoma in situ of the cervix, melanoma in situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin
- The patient has an indication for boost to 1 or more regional nodes
- Patient enrolled in another therapeutic trial. Observational cohorts are accepted if the collection of data does not interfere with the current trial
- Previous radiation therapy to the chest region
- Pregnant or lactating
- Conditions indicating that the patient cannot go through the radiation therapy or follow up, or a condition where the treating radiation oncologist thinks the patient should not participate in the trial for example due to language problems.

PRIMARY ENDPOINT:

The primary endpoint of this trial is the occurrence of arm lymphedema on the treated side at 3 years after adjuvant radiotherapy. The definition of arm lymphedema is at least≥ 10% increased arm circumference measured 15 cm proximal and/or 10 cm distal of the olecranon of the treated side from baseline, compare to the contralateral side

SECONDARY ENDPOINT(S):

non-cancer related loco-regional events:

-Range of motion of the shoulder (flexion/abduction of the upper arm) will be assessed.

-Fibrosis will be evaluated according the LENT-SOMA scoring scale, and evaluation of the lumpectomy/mastectomy scar will be made according to the scale by Aaronson *et al*; the global cosmetic result will based on Harris' 4-point scale.

-Patient satisfaction will be evaluated based on the Body Image Score (BIS) where we will use as the DBCG two additional questions regarding clothing habits and satisfaction with the appearance of the treated breast with and without comparison to the opposite breast. In addition, we will ask if the patient add reconstructive surgery and lipo-feeling injection during follow-up.

-Cosmesis will be evaluated according to the BCCT.core project score and an artificial intelligence tool based on medical photographs.

-Acute/ late toxicity will be assessed according to the flowchart and performed based on CTCAE V4 and Toxicity Criteria of RTOG/EORTC

- *Cardiac and lung assessment*
The lung and heart doses (mean, median, DVH) must be recorded as well as the LVEF (performed in standard of care) before and after radiotherapy as well as during the follow-up period for every patient. This information must be reported in the CRF.
In addition, all radiotherapy data will be uploaded into a shared platform.

Cancer related
Locoregional relapse free survival, invasive disease-free survival, distant disease-free survival, breast-cancer specific survival, causes of death, overall survival will be collected.

Quality of Life
Patients' quality of life will be assessed using self-administered questionnaires (EORTC QLQ-C30, BR23 and Euroqol EQ-5D5D) according to the flowchart. (See section 10 of the protocol).

Cost-utility
A cost-utility analysis comparing radiotherapy regimens will be performed (See section 10 of the protocol).

ANCILLARY STUDIES

- Ceramide, a pro-apoptotic sphingolipid, has been defined as early biomarker of highly hypofractionated radiotherapy using SBRT efficacy in colon and lung metastases. Ceramide and its Sphingolipid metabolites will be analyzed in INSERM 898 in Nantes in order to determine whether they are also potential biomarkers of long-term toxicity of moderately hypofractionated radiotherapy.

- Telomeres are found at the very ends of chromosomal DNA and are involved in the maintenance of genome stability. Telomere shortening in peripheral blood lymphocytes has been linked to cardiovascular-related morbidity and mortality in the general population.
The predictive value of mean telomere length and chromosome aberrations in circulating lymphocytes in post-irradiation cardiovascular effects in patients with breast cancer will be evaluated in this clinical trial.
A follow-up of the occurrence of chromosome aberrations will be performed in order to determine if they are potential biomarkers of long term toxicity

- First results have shown that radiation-induced fibrosis severity is associated with a specific transcriptomic signature. In order to identify novel biomarkers of the radiation-induced fibrosis, transcriptome expression and multiomics profiles will be assessed at different time points on plasma and whole blood and correlated with the severity of radiation-induced fibrosis (UMR 7365 IMoPA and LIH - Bioinformatics platform).

- For the NTCP modeling, functional data analysis will be run on the processing of Dose volume histograms (DVHs) of the 50 first patients from Gustave Roussy as a training set then DICOM data and DVHs from other centers will be collected to serve as an independent validation data set. For comparison, the widely used Lyman-Kutcher-Burman NTCP model will be also considered.

- A prospective meta-analyses between the Danish DBCG HYPO II trial and the current French HypoG-01 trial will be performed

- Sarco-HypoG: In breast cancer, sarcopenia is known to be a predictive factor for toxicity and survival in metastatic patients. The data in localized patients remain unknown. For all patients, sarcopenia will be calculated on planning CT scan at the L3 level.
All data will be collected on a dedicated server and evaluated in Rouen
The aim is to define whether sarcopenia is a predictive criteria of lymphedema or locoregional relapse free survival, invasive disease-free survival, distant disease-free survival, breast-cancer specific survival, causes of death, overall survival.

D) THERAPEUTIC REGIMENS

At Inclusion, patients will be randomized to:

- **Arm A**: 40 Gy / 15 fractions, 2.67 Gy per fraction, 5 fractions per week (experimental hypofractionated regimen)

- **Arm B:** 50 Gy / 25 fractions, 2.0 Gy per fraction, 5 fractions per week (standard normofractionated regimen)

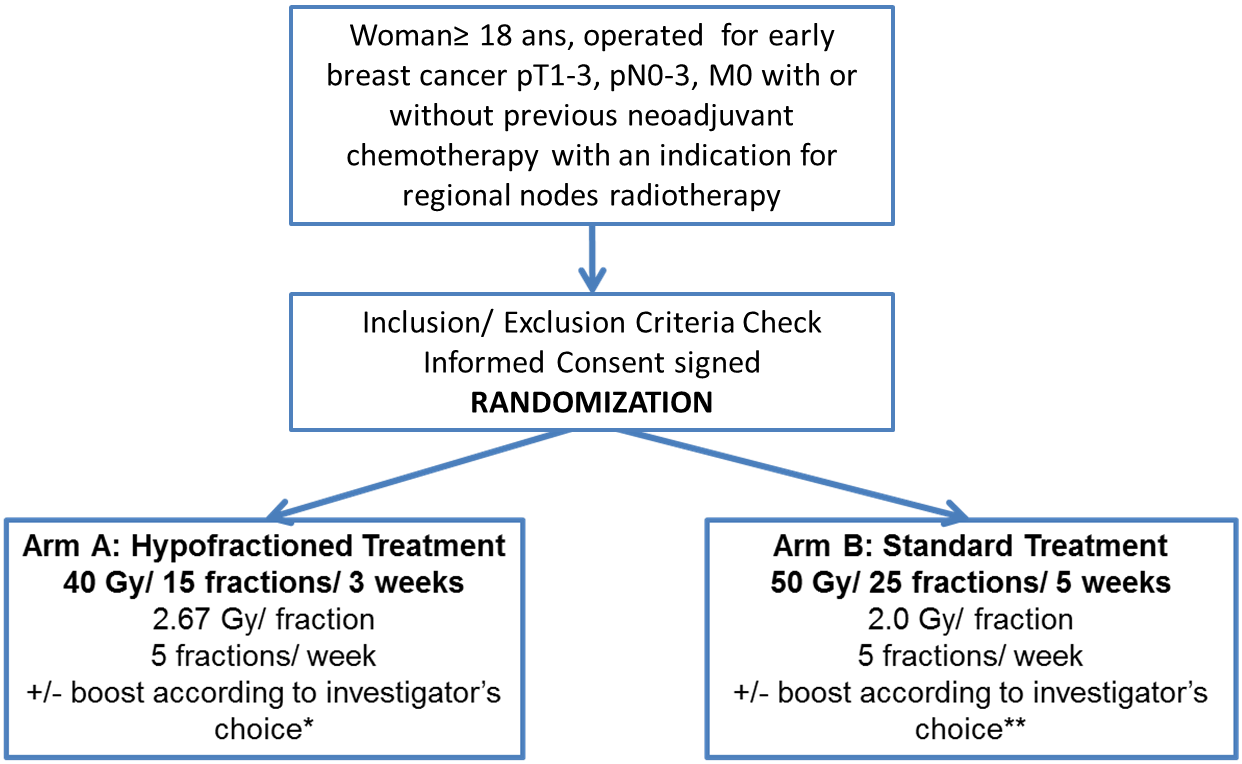
If the patient is candidate for a boost it will be provided as follows according to is randomization arm:

- **Arm A**:
  - sequential boost with 40 Gy to CTV breast in 15 fractions and 16 Gy to CTV boost in 8 fractions
  - or simultaneous integrated boost (SIB) with 42.3 Gy on CTV breast and 52.2 Gy on CTV boost in 18 fractions
- **Arm B**:
  - sequential boost with 50 Gy to CTV breast in 25 fractions and 16 Gy to CTV boost in 8 fractions

- or simultaneous integrated boost (SIB) with 51.52 Gy on CTV breast and 63 Gy on CTV boost in 28 fractions

The randomization will be performed using minimization and stratification according to:

- Surgical type: mastectomy versus lumpectomy
- Center
- Number of involved lymph nodes: 0, 1-3, 4+
- Body mass index (BMI): BMI <=25 vs, from 25 to <=30, >30
- Axillary lymph node dissection: yes/no



*Either :
sequential boost with 40 Gy to CTV breast in 15 fractions and 16 Gy to CTV boost in 8 fractions
or simultaneous integrated boost (SIB) with 42.3 Gy on CTV breast and 52.2 Gy on CTV boost in 18 fractions

**Either :
sequential boost with 50 Gy to CTV breast in 25 fractions and 16 Gy to CTV boost in 8 fractions
or simultaneous integrated boost (SIB) with 51.52 Gy on CTV breast and 63 Gy on CTV boost in 28 fractions

E) STATISTICAL ANALYSIS PLAN

REQUIRED NUMBER OF PATIENTS TO BE SCREENED / INCLUDED:
We estimated that among patients treated with axillary lymph node dissection, 50 Gy regional nodes radiotherapy and taxane-based systemic therapy, 10% will have an arm lymphedema 3 years after radiation therapy. Further assumptions are the acceptance of up to a 5% increase in arm lymphedema (thus accept of 15% of the patients having arm lymphedema ≤ 10% of the upper and/or lower arm with hypofractioned radiation therapy, non-inferiority limit HR=1.545), 80% power, 5% significance level, 1-sided test. Based on these assumptions this requires 131 events. A total of 1012 patients, 506 patients in each randomization arm will be included over 3 years in the per-protocol population (primary analysis). If we assume up to 20% of included patients will be excluded from the per-protocol population, a total of 1265 patients will need to be included.

STATISTICAL ANALYSIS:
The null hypothesis is that the hazard rate of the experimental hypofractionated arm A is worse than the standard arm B. The alternative hypothesis is that the hazard rate of arm A is not worse than arm B. The primary analysis will be performed using a one-sided logrank test at 0.05 significance level stratified for the factors used to stratify the randomization, according to the per-protocol population.
A sensitivity analysis will be performed using the intention-to-treat population (also with stratification for the same factors). In addition, a Cox regression model will be used to compare treatment differences when taking the stratification factors into account and adjusting for other prognostic factors for lymphedema such as type of radiotherapy (3D-CRT vs IMRT) and irradiated node levels according to the ESTRO guidelines. Both unadjusted and adjusted hazard ratios and their 95% confidence intervals will be computed.

Standard statistical methods as Kaplan-Meier analyses, Cox proportional cause-specific hazards regression will be used to compare the time-to-event variables between the 2 treatment arms and estimate hazard ratios adjusted for the stratification factors (using DATECAN definitions of breast-cancer related endpoints) at a one-sided 0.05 significance level. A multivariate model will also be constructed using relevant prognostic variables on the different time-to-event endpoints. A competing risk cumulative incidence approach will also be applied.

Statistical data will be expressed in the form of:
1. percentages (qualitative variables),
2. mean and standard deviation or median and range (quantitative variables),
3. survival curve estimates calculated with the Kaplan Meier method or cumulative incidence approach (survival data).

Different statistical methods will be used to compare data:
1. qualitative variables with the $\chi 2$ or Fisher test,
2. quantitative variables with the Student t test or with a non-parametric test (Wilcoxon),
3. survival data with a Logrank test or Cox model.

F) SAMPLES COLLECTED FOR TRANSLATIONAL RESEARCH

SAMPLE TYPES:
CERAMIDE ASSESSMENT: blood sample in a 3.5 ml Sodium Citrate Coagulation/CTDA (0.109mol/L) tube
TELOMERE AND CHROMOSOME ABERRATIONS ASSESSMENT: blood sample in a 7-ml Heparin-lithium tube
TRANSCRIPTOMIC SIGNATURE: blood sample in a PAXGene tube.
MULTIOMICS PROFILES: blood sample in a 4 ml EDTA tube.

SAMPLE QUANTITIES:
CERAMIDE ASSESSMENT: Three samples from each patient before, during and after Radiotherapy
TELOMERE AND CHROMOSOME ABERRATIONS ASSESSMENT: Six samples from each patient before radiotherapy, after 9th fraction of radiotherapy for patient from arm A, after 12th fraction of radiotherapy for patient from arm B, after the last fraction of radiotherapy, at 18 months and 5 years
TRANSCRIPTOMIC SIGNATURE: One sample (whole blood) from each patient at 4 or 5 years of follow-up.
MULTIOMICS PROFILES: Four samples (plasma) from each patient before, during, at the end of Radiotherapy (same samples as those collected for the ceramide analysis) then at 4 or 5 years of follow-up.

G) TRIAL DURATIONS

INCLUSION PERIOD : 3.5 YEARS

TREATMENT PERIOD: 3-7 WEEKS

FOLLOW-UP: 10 YEARS

DURATION UNTIL PRIMARY ENDPOINT EVALUATION:
ESTIMATED TIME OF PRIMARY ANALYSIS: 4.8 YEARS AFTER INCLUSION OF FIRST PATIENT

OVERALL TRIAL DURATION (INCLUDING FOLLOW-UP): 13.5 YEARS

H) TRIAL FLOW-CHART

	Before randomization	Weekly Follow-up during treatment[8]							End of Treatment[7]	Follow-up[9]						
TREATMENT[1]		W1	W2	W3	W4	W5	W6	W7		M6	Y1	Y2	Y3	Y4	Y5	Y10
Arm B : normofractioned +/- boost																
Arm A : Hypofractioned +/- boost																
Inclusion / non-inclusion criteria	X															
Signed informed consent form	X[2]															
PHYSICAL EXAMINATION																
Breast Cup Size	X[2]															
BMI, PS (WHO),BP	X[2]	X	X	X	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X	X	X	X
Medical history/ Treatment history	X[2]															
Possible Hospitalization		**Any hospitalization related to breast cancer or RT toxicity during RT and any hospitalization for RT toxicity during irradiation and follow-up**														
Concomitant Treatments	X[2]	X	X	X	X[4]	X[4]	X[4]	X[4]	X							
Toxicity/ AE assessment	X[2]	X	X	X	X[4]	X[4]	X[4]	X[4]	X	X	X	X	X	X	X	X
Arm lymphedema	X[2]			X[6]					X	X	X	X	X	X	X	X
Functional assessment (ROM+ patient form)	X[2]			X[6]					X	X	X	X	X	X	X	X
Aesthetic assessment (picture of both breasts + BIS score)	X[2]			X[6]					X	X	X	X	X	X	X	X
Sarcopenia Assessment	X[12]															
Pregnancy Test	X[2,10]															
PARACLINICAL EXAMINATION																
Bilateral Mammography	X[3]															
Breast Echography	X[3]															
Breast MRI (if indicated)	X[3]															
Bone Scintigraphy + TAP CT Scan **or** PET	X[3]															
LEVF	X[3,10]															
Histological confirmation (biopsy and surgery)	X[3]															
QoL (QLQ-C30, BR23, EQ-5D)	X			X[6]					X	X	X	X	X	X	X	X
BIOLOGICAL STUDIES																
CERAMIDE test blood sample	X[13]		X[5]	X[5]	X[5]				X							
TELOMERE and chromosome aberrations test blood Sample	X[13]	X[11]	X[14]	X[14]					X		X[15]				X	
TRANSCRIPTOMIC SIGNATURE test blood sample														X[16]	X[16]	
MULTIOMICS PROFILES test blood sample	X[17]			X[17]					X[17]					X[16]	X[16]	
Transports and sick leaves Questionnaire									X							

1. Treatment duration will depend on randomization and if a boost is needed or not
2. Within 15 days before randomization
3. Within 2 months before initiating any breast cancer treatment (surgery, chemotherapy...)
4. Only if patients are still on treatment
5. Without boost: at W2 for arm A and W3 for Arm B. With boost, at W3 for arm A and W4 for arm B.
6. During the third week of treatment
7. One month after the last fraction received
8. The treatment must begin within two weeks after randomization
9. Starting date = randomization
10. If relevant
11. After the first Fraction
12. Before Treatment
13. Pre-or post-randomization but before radiotherapy treatment.
14. After 9th fraction for patient in arm A and after fraction 12th fraction for patient in arm B
15. at 18 months
16. at 4-year or 5-year follow-up
17. Same samples as those collected for the ceramide analysis.

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LIST of ABBREVIATIONS

AAA	Analytical Anisotropic Algorithm
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALND	Axillary Lymph Node Dissection
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
BED	Biological Equivalent Dose
BIM	Body Mass Index
BIS	Body Image Score
BP	Blood Pressure
BRC	Biological Resource Center
CA	Competent Authority
CAD	Coronary Artery Disease
CPP	Comité de Protection des Personnes
CR	Complete Response
CRF	Case Report Form
CRA	Clinical Research Assistant
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DCIS	Ductal Carcinoma In Situ
DP	Disease Progression
DSMB	Data and Safety Monitoring Board
DSUR	Development safety update report
DBCG	Danish Breast Cancer Cooperative Group
EC	Ethic Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
ESTRO	European SocieTy for Radiotherapy & Oncology
EQ	EuroQol
FACS	Fluorescence-Activated Cell Sorting
FFMI	Fat Free Mass Index
FITC	Fluorescein IsoThioCyanate
FMI	Fat Mass Index
FMR	total Fat to Muscle Ratio
Fr	Fraction
GCP	Good Clinical Practice
Gy	Gray
HR	Hazard Ratio
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
IDMC	Independent Data Monitoring Committee

IMATI	IntraMuscular Adipose Tissue Index
IMN	Internal Mammary Nodes
IMRT	Intensity-Modulated Radiation Therapy
IP	Investigational Products
ITT	Intent-To-Treat
LADCoronary	Left Anterior Descending Coronary
LENT-SOMA	Late Effects Normal Tissue -Subjective, Objective, Management, Analytic
LC-MS	Liquid Chromatography-Mass Spectrometry
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NTCP	Normal Tissue Complication Probability
OAR	Organ At Risk
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PR	Partial Response
PRO	Patient-Reported-Outcomes
PTV	Planned Target Volume
QA	Quality Assurance
QALYS	Quality-Adjusted Life YearS
QLQ-XXX	Quality of Life Questionnaire
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors
ROM	Range Of Motion
RT	RadioTherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SBRT	Stereotactic Body RadioTherapy
SD	Stable Disease
SIB	Simultaneous Integrated Boost
SMA	Skeletal Muscle Attenuation
SMI	Skeletal Muscle Index
TDM	Tumor Diameter Measurement
uSAE	Unexpected Serious Adverse Event
UK	United Kingdom
3D-CRT	3D Conformal Radiation Therapy

1. INTRODUCTION AND RATIONALE OF THE TRIAL

1.1 Introduction

Early Breast cancer patients, after mastectomy or breast conserving surgery, are treated with standard radiotherapy (50 Gy in 25 fractions, 5 weeks). Loco-regional radiotherapy including drainage lymph nodes areas irradiation depends on the specific disease extension and characteristics. In addition, patients may receive a radiotherapy boost to the tumor bed.

1.1.1 Standard Loco-regional Radiotherapy

The standard radiotherapy for patients with early breast cancer after mastectomy or breast-conserving surgery with one or more macrometastases in the regional nodes consists in 50 Gy delivered in 25 fractions over five weeks (REMAGUS guidelines). These recommendations are based on the Danish Breast Cancer Cooperative Group 82b and 82c trials, which showed a benefit for post mastectomy patients with pT3 or at minimum pN1 disease (1, 2). Similarly, the same group investigated this standard radiotherapy (50 Gy in 25 fractions) and its effects after breast-conserving surgery and found this to be beneficial (10-12). These data have been confirmed by the 2 EBCTCG meta-analysis (71, 72)
The effects of radiotherapy both regarding recurrences and toxicities have been extensively investigated in these patient cohorts, as also the risks of radiation-induced heart disease and second cancer (3-9). The benefits/risk balance is in favour of delivering radiotherapy to such patients.

1.1.2 Hypofractionation

Recently, by delivering breast radiotherapy in a shorter overall time (3 vs 5 weeks) than in standard regimens, large interest has been shown in hypofractionated radiotherapy changing the standard practice.

1.1.2.1 Whole Breast

The START B Trial randomized 2015 patients to either receive the standard radiotherapy, 50 Gy in 25 fractions over five weeks, or the hypofractionated radiotherapy, 40 Gy in 15 fractions over three weeks. No significant difference in terms of recurrence between the groups was observed, and the risk of radiation-induced morbidities tended to be lower for the hypofractionated radiotherapy group (16). Similarly, a Canadian clinical trial concluded that hypofractionated whole-breast irradiation (42.5 Gy in 16 fractions over 22 days) was not inferior, in terms of risk of local recurrence, to the standard 50 Gy in 25 fractions over 35 days after breast-conserving surgery (17).
Following these results, the hypofractionated regimen (40 Gy in 15 fractions or 42.5 Gy in 16 fractions) has become standard for breast radiotherapy in many European countries, including France.

1.1.2.2 Regional Nodes

Only 7% of the patients in the START Trial B were treated with loco-regional radiation therapy, and the details of the morbidities have not been reported separately for this patient group. For example, it is not known what the absolute risk of arm lymphedema was in the START Trial B, except there was no difference in development of oedema between the two schemes reported in a forest plot. In addition, in the Netherlands virtually all breast cancer patients (irrespective of regional nodes radiotherapy) are now treated with 42.5 Gy / 16 fractions based on results from the hypofractionated Canadian trial, even though no regional radiotherapy was prescribed in the Canadian trial (17). Furthermore, the Dutch Breast Radiotherapy group is also considering reducing the 42.5 Gy in 16 fractions to 40 Gy in 15 fractions and thus aligning with the standard practice in the United Kingdom.

However, given the limited available evidence, many experts in breast radiotherapy are reluctant to initiate hypofractionated radiotherapy in case of indication of regional node irradiation outside trials.

1.1.3 Boost

1.1.3.1 Definition

Patients with an increased risk of local recurrence after breast-conserving surgery are administered a radiotherapy boost to the tumor bed.

The REMAGUS guidelines recommend a boost of 16 Gy in 8 fractions for patients less than 60 years old operated with breast conservation. These recommendations are based on the results of the "boost versus no boost trial" where it has been showed that after breast conserving surgery radiotherapy reduces the risk of local recurrence in all age categories, however, the absolute risk reduction is largest in young patients specially in those less than 60 years old (22).

This boost therapy is seldom recommended after a mastectomy. Although, it may be administered after mastectomy or axillary lymph node dissection for example when the mastectomy was not radical or in cases where the pathological lymph nodes in the axilla (any level) were not removed during surgery.
Special caution regarding boost in the area of regional nodes is needed, and patients treated with a regional nodes boost are NOT candidates for this trial.

1.1.3.2 Sequential or Simultaneous Integrated boost (SIB)

No data from randomized trials investigating Simultaneous Integrated boost (SIB) is available. The British IMPORT HIGH Trial, a three-armed phase III randomized trial evaluating SIB is currently accruing patients: Arm 1 is 40 Gy in 15 fractions and a sequential boost of 16 Gy in 8 fractions (thus a 23fractions in total)/ Arm 2 is 53 Gy / 40 Gy / 36 Gy in 15 fractions. Arm 3 is 48 Gy / 40 Gy / 36 Gy in 15 fractions.
The biological equivalent dose (BED) of the 53 Gy in 15 fractions compared to 40 Gy and sequential boost of 16 Gy (Arm 1) are 146.6 Gy versus 125.4 Gy (α/β 2Gy) and 90.45 Gy versus 83.76 Gy (α/β 5Gy). The trial is expected to accrue 2568.

Furthermore, a prospective 2-armed, multi-center randomized phase III trial is currently including patients in Germany (23). This trial, with accrual of 502 patients, investigates in the first arm the 64.4 Gy / 50.4 Gy / 28 fractions (2.3 Gy per fraction to boost volume) and in the second arm 50.4 Gy in 28 fractions followed by sequential boost of 16 Gy in 8 fractions (BED values based on an α/β of 2Gy and 5Gy is 138.46 Gy and 94.02 Gy respectively in the test arm).

The SIB has routinely been used in Groningen (since 2005) and Eindhoven (since 2007), in the Netherlands. Based on retrospective data from these two centers, SIB is now routinely used in most Dutch radiation departments (24). In 752 consecutively treated patients from a single institution in Groningen a SIB was provided with doses of 67.2 Gy / 50.4 Gy / 28 fractions if focally positive margins (2.4 Gy / fraction in the boost volume), and 64.4 Gy / 50.4 Gy / 28 fraction (2.3 Gy / fraction in the boost volume) if other indications for boost.

Using an α/β of 2 Gy, these boost doses correspond to 147.84 Gy and 138.46 Gy, respectively (Appendix 13). Based on these BED calculations sequential boost (16 Gy in 8 fractions) or SIB (52.2 Gy in 18 fractions in arm A or 63 Gy in 28 fractions in arm B) are authorized in the current HypoG-01 trial

The addition of a boost either sequential or SIB to standard or hypofractionated radiotherapy is not expected to increase the risk of radiation-induced late morbidity in terms of lymphedema because the fractionation regimens are based on identical biological effective doses and the boost will not affect lymph node areas.

1.1.4 Arm Lymphedema

There is an increased risk of arm lymphedema and impaired range of motion of the shoulder (12), change in sensibility and pain following mastectomy (28), breast conserving surgery (29) and adjuvant radiotherapy for early breast cancer (3; 10; 30; 31).
Morbidity is more frequent following mastectomy than breast conservative surgery (12) and axillary lymph node dissection than sentinel node biopsy (32). Morbidity increases with higher number of removed axillary lymph nodes (10; 33; 34). Regional nodes radiotherapy increases the risk of impaired shoulder motion (3).

Recently a systematic review and meta-analysis on the incidence of unilateral lymphedema after breast cancer was published (35).
Based on 72 studies reporting on lymphedema, 38 (53%) of the studies reported oedema based on arm circumference, which was by far the most frequent technique of measurement.
A pooled estimate of lymphedema in the 72 studies showed an incidence of oedema of 16.6%, however, this was based on studies with a wide range of study designs, different timing from surgery and different methods of assessment.
In the review, it was concluded that the incidence of lymphedema increased at least up to 2 years after diagnosis/surgery, and thereafter the incidence appeared to be more stable.
It was also seen in studies reporting on patients treated with axillary lymph node dissection that the incidence of lymphedema was 14.8% (95% CI, 11.4-19.0).
In 29 studies included in the systematic review risk factors for developing lymphedema were investigated, and there was a strong level of evidence (consistent finding in at least 75% of studies) that receipt of axillary lymph node dissection, having a mastectomy, a greater number of nodes dissected, and a high body-mass index increased the likelihood of developing a lymphedema.
Moderate level of evidence for risk of developing lymphedema was found in patients with node-positive disease, receipt of chemotherapy or radiotherapy, and not participating in regular physical activity. In the recently published EORTC 22922 trial lymphedema rate was 12% in the nodal irradiation arm and 6% in the AMAROS trial for patients operated with sentinel node biopsy but not ALND.

In the START B Trial, only 161 patients (7%) had lymphatic radiation. The absolute risk of arm lymphedema was not reported, but there was no difference in lymphedema development between the two schemes (16). Although only a small percentage of patients received lymphatic radiotherapy no increase in arm and shoulder toxicity with the hypofractionated radiotherapy was found (16).

Therefore with modern techniques of radiotherapy in HypoG-01 we will assume that 10% will have an arm lymphedema 3 years after radiation therapy.

1.2 Trial rationale

In summary, there is evidence that hypofractionated radiotherapy, with or without boost for women operated with early breast cancer is safe and effective. However, information concerning the subgroup of patients who in addition require regional nodes radiotherapy is limited, specifically regarding the risk of radiation-induced late morbidity including lymphedema.

Our hypothesis is that women operated for early breast cancer who require regional nodes radiotherapy with or without a boost to the tumor bed may be administered hypofractionated loco-regional radiotherapy (40 Gy in 15 fractions over 3 weeks), instead of standard radiation therapy (50 Gy in 25 fractions over 5 weeks), without an increased risk of radiation-induced late morbidity.

If by this trial we manage to demonstrate the non-inferiority of the hypofractionated arm compared to the current standard, the hypofractionated treatment will certainly become the new standard for patients with an indication of regional nodes irradiation and change the practices

1.3 Patient Benefits and foreseeable risks

The expected benefit for the patients in the experimental arm is a shorter (3 vs 5 weeks) and more convenient treatment.
The foreseeable risk(s) are the possible side-effects of radiotherapy (see section 9.4 of the protocol). However, the risk of increased late toxicity in the hypofractioned arm seems very limited based on the data described under the 1.1.2 section of this protocol.

1.4 Trial population

The trial population is composed of women, aged ≥ 18, who had radical operation for invasive breast cancer pT1-3 or initially cT1-3, cN0-N3, M0with either mastectomy or breast conservation no matter the status of estrogen receptor, progesterone receptor, malignancy grade, HER2 status with an indication for regional nodes radiotherapy to levels +/-I, +/- II, +/-III, +/-IV, +/-interpectoral nodes (Rötter) and +/-the IMN.

2. TRIAL OBJECTIVES

2.1 Primary objective

The primary objective of this phase III randomized trial is to show that moderately hypofractionated loco-regional radiotherapy is non-inferior to normofractionated radiotherapy in early breast cancer with an indication for irradiation of regional lymph node levels in terms of lymphedema of the arm on the side treated for breast cancer.

2.2 Secondary objective(s)

The Secondary objectives are:

- to assess non-cancer related loco-regional events: acute and late toxicities (arm motion and function, cosmetic result, lung and cardiac events)
- to assess cancer related-events: locoregional relapse-free survival, distant disease-free survival, overall survival, causes of death,
- to assess and compare health related quality of life between arms
- to conduct a cost-utility analysis

3. TRIAL DESIGN

3.1 Evaluation criteria

3.1.1 Primary endpoint

The primary endpoint of the trial is the occurrence radiation-induced late morbidity measured as lymphedema of the arm on the treated side after radiotherapy.
Since there is no consensus on how to measure lymphedema it was decided to use the circumference measurement method and define lymphedema as a difference in arm circumference ≥10% on the upper and/or lower arm from baseline, compared to the opposite arm. (Appendix 8)
This method was also used in the AMAROS trial. It is inexpensive (little equipment needed, although it requires staff time), reliable when used by trained assessors (Appendix 8), and might be the most appropriate method in the long term because it detects size change and inter-limb size differences irrespective of tissue composition of the lymphedema.
However, it has little sensitivity to detect preclinical lymphedema, and since it is based on an absolute difference, it does not take into account the body composition of the patient.

Self-report methods are also inexpensive and may have the potential to detect preclinical lymphedema; however, used on their own, self-report methods lack specificity, because many of the symptoms of lymphedema may also be common in many breast cancer patients without lymphedema.

3.1.2 Secondary endpoint(s)

Non-cancer related loco-regional events

Functional Assessment
The range of motion (ROM) of the arms (flexion/abduction) will be reported by the radiation oncologist and the patient according to procedure described in Appendix 9.

Aesthetics Assessment:
The global cosmetic result after breast conservation will be based on Harris´ 4-point scale (43, appendix 12). A modification of the questionnaire designed, validated and used by Rune Gärtner *et al* will also be used in order to report on pain, swellings, discomfort and daily function (28) (Appendix 6/7).

The patient evaluates her satisfaction on The Body Image Score (BIS) (44, Appendix 6), where has been added an extra question regarding clothing habits and furthermore based on the study by Lyngholm *et al* also 2 more questions regarding her satisfaction with the appearance of the treated breast after breast conservation with and without comparison to the opposite breast (11) as done in the DBCG HYPOII trial. In addition, we ask if the patient treated with breast conservation has had lipo-feeling injection in her breast during follow up.

Fibrosis as tissue induration, telangiectasia, oedema of the breast/chest wall and dyspigmentation will be evaluated according the LENT-SOMA scoring scale (Appendix 11). Evaluation of the lumpectomy/mastectomy scar will be made according to a scale presented by Aaronson et al (42).

Cosmesis will be assessed according to the BCCT.core project score and an artificial intelligence tool as well based on medical photographs (Appendix 10).

Cardiac and lung assessment
The lung and heart doses (mean, median, DVH) must be recorded as well as the LVEF (performed in standard of care) before and after radiotherapy as well as during the follow-up period for every patient. This information must be reported in the CRF.
In addition, all radiotherapy data will be uploaded into a shared platform.

Toxicity Assessment:
Acute and late toxicities (as described in section 9.4) will be evaluated according to CTCAE v.4.0 (45, appendix 4), and the Toxicity criteria of the RTOG and EORTC (46, appendix 11).

All evaluations are made according to the flow chart

Cancer related
Cancer related endpoints are secondary endpoints in this trial, and they are locoregional relapse free survival, invasive disease-free survival, distant disease-free survival, breast-cancer specific survival, causes of death, overall survival as defined per DATECAN guidelines (50). Ipsilateral local recurrence is defined as any tumour in the breast or skin over the breast or chest wall. A detailed reporting on the localisation of the local recurrence will be provided in the eCRF. Cause of death will be monitored and reported as well.
All time to cancer related endpoints are defined as starting from the date of randomization until the event.

Quality of Life
Patients' quality of life will be assessed using self-administered questionnaires (EORTC QLQ-C30, BR23 and Euroqol EQ-5D5D) according to the flowchart (see section 10 of the protocol).

Cost-utility
A cost-utility analysis comparing radiotherapy regimens will be performed based on QALYs (see section 10 of the protocol).

3.2 Trial methodology

The randomisation is between 50 Gy / 25 fractions *versus* 40 Gy / 15 fractions as follows:

- **Arm A**: 40 Gy / 15 fractions, 2.67 Gy per fraction, 5 fractions per week
- **Arm B**: 50 Gy / 25 fractions, 2.0 Gy per fraction, 5 fractions per week

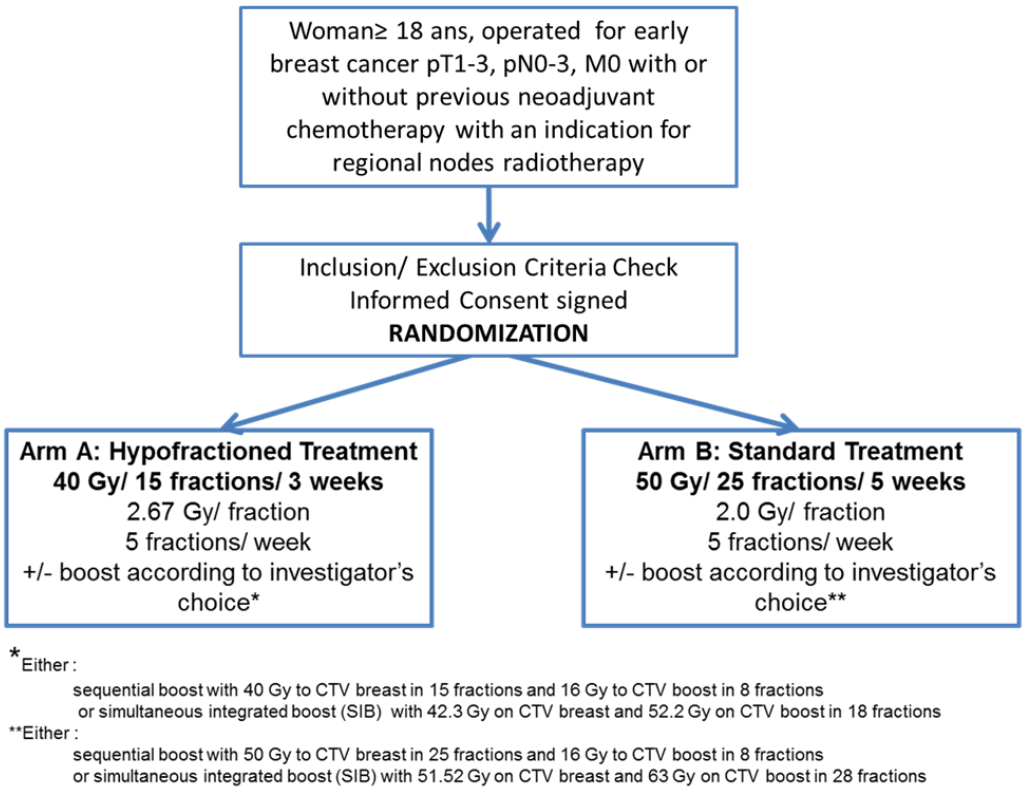
If the patient is candidate for a boost it will be provided as follows:

- Either:
  - sequential boost with 40 Gy to CTV breast in 15 fractions and 16 Gy to CTV boost in 8 fractions
  - or simultaneous integrated boost (SIB) with 42.3 Gy on CTV breast and 52.2 Gy on CTV boost in 18 fractions
- Either:
  - sequential boost with 50 Gy to CTV breast in 25 fractions and 16 Gy to CTV boost in 8 fractions
  - or simultaneous integrated boost (SIB) with 51.52 Gy on CTV breast and 63 Gy on CTV boost in 28 fractions

The randomization will be minimized on the following factors:

- Surgical type: mastectomy versus lumpectomy
- Center
- Number of involved lymph nodes : 0, 1-3, 4+
- Body mass index (BMI) : BMI <=25 vs, from 25 to <=30, >30
- Axillary lymph node dissection yes/no

Figure 1: protocol flow sheet



3.3 Progress of the trial

Patients participating in the trial will comply with the protocol for a total number of 10 years after they are included, including 3 to 6.5 weeks of treatment and 10 years of follow-up.

The investigation/examination schedule is defined by the trial flow-chart provided in section H of the protocol synopsis.

3.4 Inclusion and/or randomization procedure(s)

After inclusion and non-inclusion criteria have been fulfilled and the patient consent has been obtained, the patient will be randomized in the trial within 2 weeks.

To randomize their patient, the site will have to connect to a specific web site using the login and password given during the site initiation visit.

A user guide explaining precisely how to connect to the web server and proceed to a patient's randomization will be handed out to the clinical investigators every time the trial is set up in a new center. Access to the website will be secured with an individual password required for each user.

Once the study investigator performs the randomization, notification will be automatically sent by e-mail to:
- the investigator,
- the sponsor (UNICANCER)

4. PATIENT SELECTION

4.1 Diagnosis and inclusion criteria

- Woman ≥ 18 years who had radical surgery for invasive breast cancer pT1-3 or initially cT1 T1-3, cN0-N3, M0 with either mastectomy or breast conservation. The patient can be included no matter the status of oestrogen receptor, progesterone receptor, malignancy grade, HER2 status.
- ECOG 0-2
- Axillary lymph node dissection of the axilla where the findings give indication for regional nodes radiotherapy to levels +/-I, +/- II, +/-III, +/-IV, +/-interpectoral nodes (Rötter) and +/-the IMN.
- Sentinel node biopsy documenting limited nodal disease without an indication for axillary lymph node dissection according to institutional, national or other trial guidelines are accepted.
- The patient may be a candidate for a boost to the tumour bed.
- Adjuvant systemic therapy with chemotherapy, endocrine therapy and anti-HER2 treatment is accepted.
- Neoadjuvant chemotherapy for downstaging according to institutional or national guidelines is accepted if there is ***not*** an indication for a boost in the area of regional nodes after surgery.
- Primary systemic therapy of an operable breast cancer is accepted.
- If the patient is not treated with chemotherapy, she must be randomized within 8 weeks from last surgery. If she has received adjuvant chemotherapy, she must be randomized within 4 weeks after the last series of adjuvant chemotherapy or within 42 days from last surgery in case of surgery after neoajduvant or adjuvant chemotherapy. Breast implants are accepted.
- Connective tissue disease is allowed if the treating radiation oncologist finds radiotherapy indicated
- Postoperative infection and/or seroma giving indication for drainage during RT is accepted
- Women of childbearing potential must agree to use adequate contraception for the duration of study participation and up to 3 months following completion of therapy
- Signed informed consent
- Affiliated to the Social Security system

4.2 Non-inclusion criteria

- Previous breast cancer or DCIS of the breast.
- Bilateral breast cancer
- Patient with previous non-breast malignancy with the exception of cancer in complete remission for over 5 years and low risk of recurrence. Patients with the following diseases can be accepted despite less than 5 years disease free interval: carcinoma in situ of the cervix, melanoma in situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin
- The patient has an indication for boost to 1 or more regional nodes
- Previous radiotherapy to the chest region
- Patient enrolled in another therapeutic trial. Observational cohorts are accepted if the collection of data does not interfere with the current trial
- Pregnant or lactating
- Conditions indicating that the patient cannot go through the radiation therapy or follow up, or a condition where the treating radiation oncologist thinks the patient should not participate in the trial for example due to language problems.

5. TRIAL TREATMENTS

5.1 Radiotherapy

The patients will be randomized to:

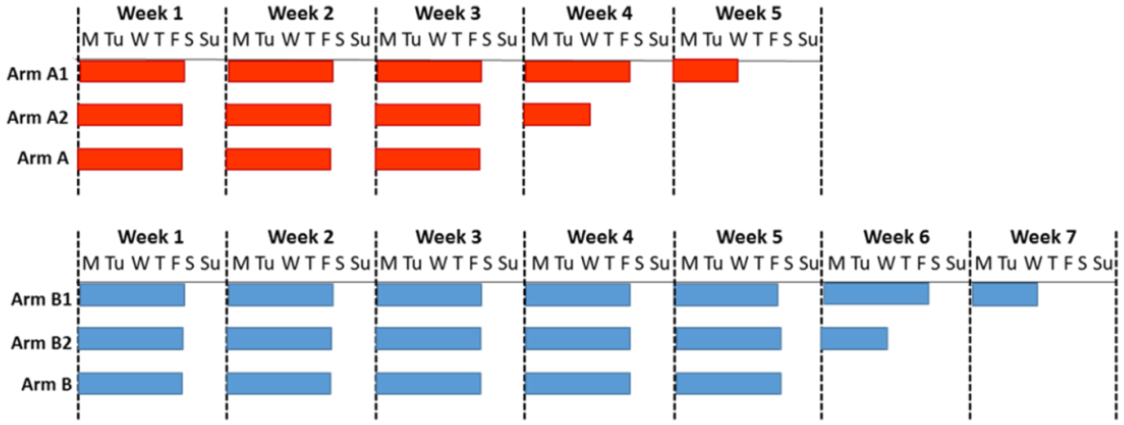
- **Arm A**: 40 Gy in 15 fractions, 3 weeks, (experimental therapy).
- **Arm B**: 50 Gy in 25 fractions, 5 weeks, (standard therapy)

If the patient is also a candidate for boost this will be provided as a sequential or simultaneous integrated boost (SIB) according to the investigator's choice without any randomisation of the boost, provided the boost is not to regional nodes.
Boost provided sequentially will be 16 Gy in 8 fractions in both arms depending on individual risk factors. The simultaneous integrated boost therapy will be provided in a way that the overall treatment time is reduced by 5 treatment days compared to standard therapy with 63 Gy / 28 fractions or 52.2 Gy / 18 fractions. This corresponds to 2.25 Gy per fraction in the simultaneous boost volume, and 1.84 Gy per fraction to the non-boost volumes in the standard arm. In the hypofractionated arm the integrated boost will correspond to 2.9 Gy per fraction in the boost volume, and 2.35 Gy per fraction to the non-boost volumes. All treatments are based on 5 fractions per week.
The proposed fractionation schemes are presented in Figure 1.

To sum up:

- experimental therapy will deliver either:
    - **Arm A1:** sequential boost with 40 Gy to CTV breast in 15 fractions and 16 Gy to CTV boost in 8 fractions
    - **Arm A2:** simultaneous integrated boost (SIB) with 42.3 Gy on CTV breast and 52.2 Gy on CTV boost in 18 fractions
- standard therapy will deliver either:
    - **Arm B1**: sequential boost with 50 Gy to CTV breast in 25 fractions and 16 Gy to CTV boost in 8 fractions
    - **Arm B2**: simultaneous integrated boost (SIB) with 51.52 Gy on CTV breast and 63 Gy on CTV boost in 28 fractions

Figure 2 : Treatment schedules



5.2 Planning CT Scan and Target

5.2.1 Planning CT scan

The patient is scanned in supine treatment position preferably with both arms up. The head is positioned straight with the chin slightly upwards or a little tilted to the contralateral side, avoiding skin folds at the level of the lower neck. Fixation is done according to the guidelines of the treating department, and a daily set up reproducibility of approximately 5 mm must be achieved. The scanned volume is neck and breast region including both lungs and abdomen to L5 for Sarco-HYPOG. The slice thickness is max 3mm. Respiratory gated techniques should ideally be used.

5.2.2 Delineation

For consistency, each site must use the following structure names following ESTRO contouring guidelines as resumed in table 1

Table 1: List of nomenclature to be used in this trial

Target volumes	Name to use in HYPOG01*
Breast	CTVp_breast
Boost	CTVp_tumourbed
Breast minus Boost	Breast-tbed**
Chest Wall	CTVp_thoracicw
Rotter or interpectoral nodes	CTVn_interpec
Internal mammary chain	CTVn_IMN
Lymph node level 1	CTVn_L1
Lymph node level 2	CTVn_L2
Lymph node level 3	CTVn_L3
Lymph node level 4	CTVn_L4
Total Lymph Node***	CTVn_Ltot

** Breast-tbed= CTVp_breast- CTVp_tumourbed
***+/- level 1+/- level 2+/- level 3+/- Level 4+/- Rotter

PTVs will be called accordingly to CTVs for each volume, ex: PTVp_breast.

Organs At Risk (OAR)	Name to use in HYPOG01*
Heart	Heart
Left anterior descending coronary artery	A_LADCoronary
Ipsilateral Lung	Lung_ipsilat
Contralateral Lung	Lung_contra
Both lungs	Lungs
Humeral head	HumeralHead
Humeral head +1 cm margin	HumHead_PRV
Contralateral breast	Breast_contra
Body	External
Breast Implant	Implant
Spinal cord	Spinal_cord
Thyroid	Thyroid
Brachial plexus	BrachialPlexus

*Names of the volumes must strictly be respected (small, capital letters and underscore matters) when delineating each patient CT scan

ESTRO consensus guidelines on target volume delineation to be followed for HYPOG-01 are available at http://www.sciencedirect.com.gate2.inist.fr/science/article/pii/S0167814014005246

5.2.2.1 Breast CTV and Lymph Node Targets

The CTV lymph node targets are delineated according to the ESTRO consensus guideline, and the structure names must follow the nomenclature of the ESTRO consensus. A delineated example following ESTRO guidelines with properly named structures is available at

http://www.sciencedirect.com.gate2.inist.fr/science/article/pii/S0167814014005246

It is not acceptable to delineate all the CTVn´s as one large volume. Regarding dose coverage of the CTVn_IMN, it is recommended to include intercostal levels 1, 2, 3 in all patients. In patients with a tumour localization in the lower-inner quadrant of the breast the IMN intercostal level 4 is also recommended included in the target. This may cause high doses to the heart for left-sided patients, and respiratory gated techniques should be used to lower the dose to this organ. It has been estimated that the number needed to treat to save one breast cancer death is significantly lower than the “number needed to harm” with ischaemic heart death when evaluating dose coverage of the IMN and the heart (14).
Controlateral breast is recommended to be delineated in cases where dose planning is based on intensity modulated technique.

5.2.2.2 BOOST: CTVp_tumourbed

Tumour bed should be delineated based on all available information from pre-operative imaging, surgical report, pathology report and the localization of the surgical clips. The clips must be positioned according to a protocol, and the radiation oncologist must be aware of this protocol. If oncoplastic surgery has been carried out, a close collaboration between the surgeon and the oncologist is particularly important if the patient is a candidate for a boost. The CTVp_tumourbed is generated by adding a 5 mm margin to the tumour bed inside the CTVp_breast.

5.2.2.3 Planning Target Volume (PTV)

PTV is generated by adding a margin around the CTV to account for set up errors during therapy. For the lymph nodes target volumes, a PTVn including all the CTVn´s is defined. Correspondingly a PTVp_breast/ PTVp_thoracicwall is generated from CTVp_breast / CTVp_thoracicwall. In general PTV should be cropped to

5 mm beneath the skin. A typical CTV to PTV margin is 5 mm in all directions. However the actual setup error depends on immobilisation of the patient and on the image guidance strategy, and therefore varies among departments. Each department should perform measurements to determine their CTV to PTV margin. The PTV_tumourbed is typically defined as the CTV_tumourbed + 5 mm margin in all directions, without exceeding the PTVp_breast/ PTVp_thoracicwall (39).

5.2.2.4 Organs at risk (OAR)

Delineation of Lung_ipsilat, Lung_controlat, Lungs, Thyroid, Spinal_cord is performed according to DBCG guidelines (38).
For heart and Left anterior descending coronary artery (LADCA) Feng et al guidelines are recommended (48) where heart is defined by the heart muscle including the complete pericardia from the lower part of the pulmonic trunk to the apex where pericardia disappears close to liver. For LADCA: from aorta including the left main artery to the cardiac apex cordis. It is often difficult to visualise the caudal part of the LADCA as we do not recommend IV contrast in this protocol but here a surrogate is the interventricular gap.
For brachial plexus Kong et al guidelines are recommended (49).

5.3 Dosimetry and OAR dose constraints

5.3.1 Dose Planning

Dose planning is based on the ICRU 50, 62 and 83 recommendations (40). Dose is prescribed to the CTV. For 3D-CRT planning it is recommended to use a technique based on a single isocenter with tangential fields with parallel posterior field edges to cover PTVp_breast / PTVp_thoracicwall. A 25 mm skin flash is applied (when applicable) to account for potential swelling of the breast/thoracic wall. In case of boost, fields are added to cover the PTVp_tumourbed. For regional nodes radiotherapy an anterior periclavicular field is used, and an opposing posterior field may be added to ensure homogeneous dose in the target when relevant. Wedges may be used to obtain dose homogeneity. It is accepted to use intensity-modulated RT techniques including VMAT and Tomotherapy. A bolus on the lumpectomy scar is not accepted as routine, but may be indicated in special cases, although a bolus on the mastectomy scar in general is accepted when relevant.

CTVp_breast / CTVp_thoracicwall is to be covered with doses of 95-107% of prescribed dose if radiotherapy is normofractionated, and 95-105% of prescribed dose if radiotherapy is hypofractionated. The volume of CTVp_breast / CTVp_thoracicwall receiving 110% of prescribed dose (normofractionated) or 108% of prescribed dose (hypofractionated) must be ≤ 2%. The overdosage should preferably be distributed over several areas.
CTVn's are to be covered with doses 90-107% of prescribed dose with $D_{2\%}$ ≤ 108% of prescribed dose (normofractionated therapy) and 90-105% of prescribed dose with $D_{2\%}$ ≤ 106% of prescribed dose (hypofractionated therapy). No volume of CTVp_breast or CTVp_thoracicwall except in the build-up zones must in principle receive dose < 95% of prescribed dose. No part of the nodal volumes except in build-up zones must in principle receive < 90% of prescribed dose (see table 2).
The maximum dose to the treated volume should be kept below 110% (normofractionated therapy)/ 108% (hypofractionated therapy). Photon energy is chosen to fulfil 95% dose 5 mm under the skin surface. Multi-leaf collimation is used to minimise the risk of dose to organs at risk.

Table n° 2 - Overview of target volumes dose constraints according to randomization arm.

	Recommended dose for normofractionated	Recommended dose for hypofractionated	$D_{2\%}$ for normofractionated	$D_{2\%}$ for hypofractionated
CTVp_breast/ CTVp_thoracicwall	95-107% of prescribed dose	95-105% of prescribed dose	$D_{2\%}$ ≤ 110%	$D_{2\%}$ ≤ 108%

CTVn_Ltot	90-107% of prescribed dose	90-105% of prescribed dose	$D_{2\%} \leq 108\%$	$D_{2\%} \leq 106\%$
CTVn_IMN	90-107% of prescribed dose	90-105% of prescribed dose	$D_{2\%} \leq 108\%$	$D_{2\%} \leq 106\%$
CTVp_tumourbed	95-107% of prescribed dose to the boost	95-107% of prescribed dose to the boost	$D_{2\%} \leq 110\%$	$D_{2\%} \leq 108\%$

The highest priority is given to the tumour bed irrespective of breast conservation or mastectomy. Thereafter priority should be given to the internal mammary nodes based on recent data from the DBCG IMN study. Dosimetry planning should be designed to lower the dose to heart and lung, and therefore compromises may be accepted on CTVp_breast or CTVp_thoracicwall. Lower priority is given to PTV provided that the compromise is distant from the tumor bed, and finally contralateral breast has priority.

In slim patients, the chest wall may be so thin that the CTVp_thoracicwall disappears when cropping the volume 5 mm beneath the skin. In such cases, a 5mm bolus may be applied and the CTVp_thoracic wall should be extended up to the level of the skin surface or the cropping of the volume can be reduced to 3 mm beneath the skin instead of 5 mm.

Dose calculation is recommended on modern dose algorithms (Monte Carlo, AAA, Collapsed Cone or similar) with inhomogeneity correction. Nevertheless, other dose algorithms are tolerated.

5.3.2 Doses

If the patient is a candidate for boost it will be provided as a sequential normofractionated boost or a simultaneous integrated boost according to the investigator choice.

If the patient is candidate for a boost it will be provided as follows:

- Arm A:
  - **Arm A1:** sequential boost with 40 Gy to CTV breast in 15 fractions and 16 Gy to CTV boost in 8 fractions
  - **Arm A2:** simultaneous integrated boost (SIB) with 42.3 Gy on CTV breast and 52.2 Gy on CTV boost in 18 fractions

- Arm B:
  - **Arm B1**: sequential boost with 50 Gy to CTV breast in 25 fractions and 16 Gy to CTV boost in 8 fractions
  - **Arm B2**: simultaneous integrated boost (SIB) with 51.52 Gy on CTV breast and 63 Gy on CTV boost in 28 fractions

Table n°3 – Prescribed doses summary

	Treatment with Sequential Boost	Boost Dose / fraction	Breast/chest wall dose	Non-boost dose/fraction	Fraction
Normofractionated	50Gy+16Gy	2 Gy	50 Gy	2 Gy	33
Hypofractionated	40Gy+16 Gy	2 Gy	40 Gy	2.67Gy	23
	Treatment with SIB	Boost dose / fraction	Breast/chest wall dose	Non-boost dose/fraction	Fraction
Normofractionated	63 Gy	2.25 Gy	51.52 Gy	1.84 Gy	28
Hypofractionated	52.2 Gy	2.90 Gy	42.3 Gy	2.35 Gy	18

5.3.3 Organs at Risk

Organs at risk are the Heart, A_LADCoronary, Lung_ipsilat, Lung_controlat, Lungs, Thyroid, Spinal_cord, HumeralHead, BrachialPlexus_ipsilat and Breast_contralat.
The A_LADCoronary should be delineated and the max dose reported (as point dose). In the current DBCG guidelines (May 2015) the dose to A_LADCoronary should be maximum 17 Gy (hypofractionated) and 20 Gy (normofractionated), however, new data indicates a higher gain from irradiating the CTVn_IMN than we previously thought.
Dose constraints to the heart are: V20 < 10% and V40 < 5% (normofractionated). Mean dose to the heart will be reported but no dose constraint is fixed but it should be kept as low as possible.
Contralateral breast mean dose of 1 Gy resulted in <0.5% risk of cancer (73) In the import High trial a maximum contralateral breast mean dose of 2 Gy is recommended (74). Contralateral breast should receive as little dose as possible and a Dmean<2 Gy.
A V20 Gy <22% for total lungs gave no risk of pneumonitis in a non–small-cell lung cancer study (75) and lung V20 Gy <30% for ipsilateral lung resulted in few cases of pneumonitis in breast radiotherapy study (76) so we use this dose constraints as in the import High trial.
The risk of radiation induced brachial plexopathy is closely related to dose per fraction and total dose (41). The incidence of brachial plexopathy is today < 1-2% in patients receiving plexus total doses <55 Gy in 2 Gy/fraction. The DBCG guideline recommends a maximum dose in the brachial plexus of 54 Gy (2 Gy/fraction). Using an α/β 2 Gy, this corresponds to a BED of 108 Gy, so if therapy was based on 2.67 Gy/fraction a max dose of 46.25 Gy has the same BED (=108 Gy). Thus a dose of 40 Gy/15 fractions is expected to be acceptable.
The shoulder joint and the connective tissues around it should receive as low a dose as possible, and preferably less than 50% dose.
Heart and Thyroid mean dose constraints should respect local guidelines of each investigating center according to the technique used, no major deviation has been predefined but these mean doses will have to be reported in the eCRF.
Other OAR should comply with the standard constraints of each investigating center.

Table n°4 Overview of OAR dose constraints according to randomization arm.

OAR	V17Gy (hypo)	V20Gy (normo)	V35Gy (hypo)	V40Gy (normo)	Dose (hypo)	Dose (normo)
Heart	10%	10%	5%	5%	-	-
Lung_ipsilat	30%	30%	-	-	D_{mean}< 16 Gy	D_{mean} < 18 Gy
Lungs	22%	22%	-	-	-	-
BrachialPlexus_ipsilat	-	-	-	-	D_{max} < 46.25 Gy	D_{max}< 54 Gy
Spinal_cord	-	-	-	-	D_{max} < 38.54 Gy	D_{max} < 45 Gy
Breast_contralat	-	-	-	-	D_{mean} < 2 Gy	D_{mean} < 2 Gy

At any time it is important to strive to achieve as low doses in the organs at risk whilst assuring sufficient doses to the targets.

It is not the intention that patients where these constraints cannot be met are withdrawn from the trial. If the treating radiation oncologist finds that the patient is going to be treated, the approved dose plan is considered the best solution in that case unless specified otherwise by the QA committee which can be contacted by the investigator in case of dosimetry not meeting the constraints. Notice that an automatic check of dose constraints not met will be performed in the eCRF and that these non-compliant dosimetries can be asked and reviewed by the QA committee.

It will be part of the quality control to investigate in how many patients the constraints are met.

5.4 Quality assurance of the Radiation Therapy

Before inclusion of the first patient a contouring workshop for all participating departments will be held to assure as little variation in delineation.

A dummy patient will have to be delineated by each center willing to participate to the protocol. The dummy run will be then evaluated by the QA committee. If the dummy run is validated, the participating center will be allowed to include patient in the protocol.

All PIs will be trained before entering the study during a training workshop. Each PI will be responsible of the training of his/her co-investigators.
In case of change of PI, a new training session with dummy run submission will be necessary unless if the new PI is an already trained former Co-investigator.

Within the first 3 months after initiation of the protocol, each participating center will have to send 1 randomly selected approved and delivered treatment plan. This treatment plan will be evaluated for quality assurance by the QA committee according to the protocol recommendations in terms of delineation, dose constraints and treatment workflow.
Once a year, at least 5 randomly selected approved and delivered treatment plans among all the participating centres will be evaluated for quality assurance by the QA committee, according to the protocol recommendations.

5.5 Treatment Interruption

Treatment interruption may occur during the study and the reasons can be, but not limited to:
- Holidays
- Technical reasons: Maintenance, Machine break down
- Patient related reason: Choice of the patient, intercurrent disease that don't allow the patient to come for the radiotherapy treatment, patient unable to comply with radiotherapy
- Investigator related reasons;
- Toxicity grade III or more justifying treatment interruption (notice that not all Grade III toxicity justify treatment interruption and that interruptions are left at the discretion of the investigator)

If the sum total of radiotherapy interruptions exceeds 3 normally scheduled treatment days in Arm A or 5 normally scheduled treatment days in Arm B or 3 consecutive normally scheduled treatment days in both Arms, this will be considered as an unacceptable deviation from the protocol**.** This should be reported to the sponsor and the patient will be considered unevaluable on final data analysis.

The investigator can make the decision to compensate for interruption according to local practice and the follow-up will continue in compliance with the protocol.

5.6 Treatment Discontinuation

The physician-investigator may also decide an early interruption of the treatment for any reason that would be beneficial for the patient, even in case of intercurrent disease or occurrence of AE.

These reasons can be, but not limited to:
- toxicity which in the opinion of the investigator indicates that continued treatment with study therapy is not in the best interests of the patient,
- patient’s refusal to continue the treatment or incapacity to pursue the treatment
- major protocol violation*
- patient lost to follow-up,

*Major protocol violation are:

- Violation of inclusion and exclusion criteria
- Treatment interruption: the sum total length of radiotherapy interruptions exceeds 3 normally scheduled treatment days in Arm A or 5 normally scheduled treatment days in Arm B or 3 consecutive normally scheduled treatment days in both Arms.
- Any deviation defined as Major by the Steering Committee or QA Committee (including unacceptable dose constraints violations…).

At any stage of the treatment, the physician-investigator must document in the eCRF and in the medical chart the reasons of a premature treatment stop as exhaustively as possible.

Any participant who stops prematurely the treatment due to an adverse event will be followed until the undesirable event is reversed.

In case of treatment discontinuation, the patient is still participating in the trial. Follow-up will continue in compliance with the protocol and follow-up data will be collected until the end of the trial, unless the patient has withdrawn their consent for participation in the trial.
In case of consent withdrawal by the patient, please refer to section 16.4.

5.7 Concomitant treatments

All medications and therapies taken by the patients or administered to the patients at the onset of trial and all medication given during radiotherapy are considered as concomitant medications.

5.7.1 Authorized concomitant treatments

Concomitant treatments should be reported in the medical data of the patient at each visit. Concomitant treatments and namely treatments in case of toxicity are to the choice of the investigator according to local guidelines.

5.7.2 Prohibited concomitant treatments

Radio-sensitizing drugs are not authorized during radiotherapy and their respective wash out period.

6. EVALUATION OF TREATMENT EFFICACY AND SAFETY

6.1 Efficacy evaluation

Treatment efficacy will be evaluated by the follow up as secondary objectives including assessment of locoregional control, distant disease-free survival, overall survival, causes of death.

6.2 Safety evaluation

Treatment safety evaluation will be based on adverse event (AE) occurrence, the use of concomitant treatments, changes occurring in the course of treatment, observed during physical examination, and clinical examinations. Safety criteria will be determined according to the Toxicity Criteria (NCI-CTCAE) v4.0 (see Appendix 5).

In case of emergency, the patient, a patient relative or the patient's general practitioner will have to inform by phone the investigator about the occurrence of an AE. The possible treatment interruption or dose adaptation

(decrease) for the investigational treatment will be considered as well as adequate concomitant treatment if necessary.

7. DESCRIPTION OF VISITS AND INVESTIGATIONS

7.1 Screening

Eligible patients with signed informed consent form will have an initial assessment at baseline, within 15- days prior.
However, some examinations (e.g. tumor extent evaluation) performed before trial participation may be used for inclusion provided that all evaluations are performed within 2 months prior to initial treatment start (either chemotherapy if neoadjuvant chemotherapy or surgery).

7.2 Baseline assessment

- **Baseline demographic evaluations**
  - Prior treatment history: adjuvant or neoadjuvant chemotherapy received (agent(s), date of last dose), surgery,
  - Relevant medical history other than studied disease.

- **Paraclinical examination (within 2 months before initiating any breast cancer treatment)**
  - Bilateral Mammography
  - Breast Echography,
  - Breast MRI (if indicated)
  - TAP CT scan+bone scintigraphy or PET
  - LEVF assessment (if relevant)

- **Clinical examination (≤ 15 days before randomization):**
  - Physical examination including the patient's Body Mass Index (BMI), breast cup size and blood pressure (BP)
  - Performance status: ECOG (see Appendix 1),
  - Wound healing and aspect of the scar
  - Record all medication(s) and significant non-drug therapies taken within 2 weeks prior to randomization and note if the medication is continuing.
  - Pregnancy test if doubt with possible pregnancy or non-menopausal patient

- **Histological confirmation (biopsy and surgery reports)**

- **Arm Lymphedema Assessment:**

  - Arm lymphedema on both sides will be reported by the physician or a trained collaborator (i.e. trained nurse) according to appendix 8.

- **Questionnaire on quality of life (≤ 15days before randomization):**
  - QLQ - C30, BR23, EQ-5D. (appendix 5)

- **Functional Assessment ≤ 15 days before randomization)**
  - Range of motion (ROM) of the arm on the treated side (flexion/abduction) will be reported by the physician or a trained collaborator (i.e. trained nurse) and the patient according to the scale given in appendix 9 and patient form in appendix 7

- **Aesthetic Assessment (≤ 15 days before randomization)**
  - Documentary photographs of both breasts (digital and in color) according to appendix 10 Aesthetic assessment by the physician and the patient according to the scale given in appendix 6/7

- **Sarcopenia Assessment (appendix 15)**

- **Biological Ancillary studies (cf. section 11 of the protocol)**

7.3 Assessment during treatment period

During the treatment period, patients will have a weekly consultation visit. However, depending on treatment tolerance, additional consultation visit may be scheduled. At every visit, patients will be assessed as follows:

Every week,

- **Physical examination**
  - Physical examination including the patient's BMI, BP
  - Performance status: ECOG
  - Collect information on concomitant treatment

- **Toxicity and Adverse Event (AE) Assessment**
  - Collect information on safety, toxicity in the time interval between two treatment visits (appendix 4/6)

At 3 weeks of treatment,

- **Arm Lymphedema Assessment**
- **Questionnaire on quality of life** (QLQ - C30, BR23, EQ-5D.)
- **Functional Assessment (ROM+ patient form)**
- **Aesthetic Assessment (picture + score)**
- **Biological Ancillary studies (cf. section 11 of the protocol)**

7.4 End-of-treatment

After the last fraction of treatment, patients will have a consultation/visit. The following examination and tests will have to be performed **1 month after the last fraction of treatment**

- **Physical examination**
  - Physical examination including the patient's BMI, BP
  - Performance status: ECOG
  - Collect information on significant concomitant treatment
  - Collect information on any hospitalization related to breast cancer or RT toxicity during the treatment

- **Toxicity and Adverse Event (AE) Assessment**
- **Arm Lymphedema Assessment**
- **Questionnaire on quality of life** (QLQ - C30, BR23, EQ-5D.)
- **Transport and sick leaves questionnaire (see appendix 14)**
- **Functional Assessment (ROM+ patient form)**
- **Aesthetic Assessment (picture + score)**
- **Biological Ancillary studies (cf. section 11 of the protocol)**

7.5 Follow-up

Follow-up assessment will be performed at **6 months, then 1, 2, 3, 4, 5 and 10 years after randomization**

- **Physical examination**
  - Physical examination including the patient's BMI, BP
  - Performance status: ECOG
  - Collect information on any hospitalization for RT toxicity during the follow-up
  - Collect information on any cancer related events (local relapse, metastasis etc…)

- **Toxicity and Adverse Event (AE) Assessment**
- **Arm Lymphedema Assessment**
- **Questionnaire on quality of life** (QLQ - C30, BR23, EQ-5D.)
- **Functional Assessment (ROM+ patient form)**
- **Aesthetic Assessment (picture + score)**
- **Biological Ancillary studies (cf. section 11 of the protocol)**

8. TRIAL TERMINATION CRITERIA

The trial will be considered as terminated once the last visit of the last patient will be recorded in the eCRF. The trial can be suspended or stopped by the sponsor in consultation with the principal investigator or at the request of the competent authority if:

- Unacceptable toxicity,
- Insufficient patient recruitment,
- Poor quality of data collection.

9. SAFETY EVALUATION

9.1 Adverse event : general definition

An adverse event (AE) is defined as any untoward medical occurrence, in a patient or clinical trial subject treated by a medicinal treatment and which does not necessarily have a causal relationship with this treatment.

9.2 Serious adverse event: general definition

- **A serious adverse event (SAE) is defined as any untoward medical occurrence or effect that at any dose:**
  - results in death,
  - is life-threatening,
  - requires hospitalization or prolongation of existing hospitalization,
  - results in persistent or significant disability or incapacity,
  - is a congenital anomaly or birth effect,
  - or is medically relevant in the context of the pathology and the clinical trial.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

The terms disability and incapacity correspond to any clinically relevant physical or psychic handicap, transient or permanent, with impacts on the physical condition/activity and/or the quality of life of the patient.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above (for example: overdose, second cancer…).

The following are not considered to be serious adverse events (SAE):

- Hospitalization:
  - for care, procedures, tests or all investigations performed on an outpatient basis without any seriousness criteria associated,
  - *or* already scheduled before the start of the trial,
  - *or* which is part of the protocol,
  - *or* occurring in the context of tumor progression of disease under trial,
- Progression of disease under trial*;
- Any events related to progression of disease under trial are not to be reported as SAE.

The assessment of whether there is a reasonable causal relationship is made by the investigator. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

A Suspected Unexpected Serious Adverse Reaction is defined as any serious adverse reaction, the nature, severity or outcome is not consistent with the treatment information, practiced acts or methods used in the research

The assessment of expected / unexpected character is the responsibility of the sponsor.

- **New event**: is defined as any new event relating to the conduct of the trial or the development of the product used, practiced acts or methods where that new event is likely to affect the safety of the subjects.

- **Severity criterion**: the severity criterion must not be confused with the seriousness criterion which is the guide for defining the reporting requirements.

The intensity (severity) of events will be estimated using the extract of CTCAE v4.0 classification (see Appendix 5). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- **Grade 1**: **Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: **Moderate**, minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- **Grade 3**: **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4**: Life-threatening consequences; urgent intervention indicated.
- **Grade 5**: **Death** related to the event.

9.3 Measures to be taken in case of a serious adverse event

The investigator ensures that adequate medical care is provided to the patient.

The investigator must immediately and no later than 24 hours following knowledge of the event, notify the R&D UNICANCER pharmacovigilance unit of any SAE or any new event defined here above, whether or not related to the research, which occurs during the 'trial reporting period'. This reporting period:

- Starts at the date of the signature of the informed consent form,
- covers the entire period during which the patient is receiving the radiotherapy or is subject to specific procedures related to the trial,
- covers a period of 90 days after the last administration of the last fraction of radiotherapy.

Any later SAE, i.e. occurring after a period of 90 days, which is considered to be related to the radiotherapy or to the research (other treatment used, diagnostic procedures and examinations carried out during the research) must be reported without any limitation in terms of deadline.

Notification must be carried out immediately by fax to the R&D UNICANCER pharmacovigilance unit by sending the form "notification of a SAE", located in the Investigator Master File, completed as precisely as possible, dated and signed by the physician-investigator:

Notification must be carried out immediately by fax to the R&D UNICANCER pharmacovigilance unit:

R&D UNICANCER
Pharmacovigilance unit, France
Phone: +33 (0)1 44 23 04 16 – Fax: +33 (0)1 44 23 55 70
e-mail: fax-pv@unicancer.fr

For any other communication:
Email: pv-rd@unicancer.fr / Phone: +33 (0)1 44 23 04 16

Abnormal laboratory results should be reported as SAE if they possibly put at risk the patient or they require medical intervention to prevent an outcome corresponding to one of the severity criteria.

Second cancer, whether or not related to the research, must be reported to the R&D UNICANCER pharmacovigilance unit without any limitation in terms of deadline.

The investigator **shall send additional information to the R&D UNICANCER pharmacovigilance unit** using a SAE declaration form (by ticking the Follow-up X box to specify that it is a follow-up and not an initial report) as soon as he is aware of the event. He shall also submit the last follow-up at the resolution or stabilization of the SAE.

The investigator is responsible for appropriate medical follow-up of patients until the resolution or stabilization of the event or until the death of the patient. This can sometimes mean that the follow-up continues after the patient has left the trial.

The investigator must keep the documents concerning the suspected SAE in order to supplement the information previously submitted if necessary.

Requests for clarification and / or additional information may be sent to the investigator by the R&D UNICANCER pharmacovigilance unit or CRA sponsor of the trial to document and treat the case.

The physician-investigator should also attach to the form « notification of a SAE », whenever possible:

- ✓ a copy of the hospital report or extended hospitalization report,
- ✓ a copy of all results of additional investigations carried out, including also relevant negative results, and enclosing the normal laboratory values,
- ✓ a copy of the autopsy report if necessary,
- ✓ any other document deemed to be useful and pertinent.

All these documents must be anonymised.

The pregnancies:
The occurrence of pregnancy is not considered as an SAE. However, any pregnancy must be reported with the same modalities as an SAE, using a Pregnancy Notification Form. Pregnancy will be subject to special follow-up until their end. While pregnancy itself is not considered to be an SAE, any anomaly detected in the foetus or child, any elective termination of a pregnancy for medical reasons or spontaneous abortion will be reported as an SAE as well, using the same procedure as an SAE.

9.4 Adverse events of special interest (AESI)

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the procedure safety profile and require close monitoring and rapid communication by the Investigator. AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the treatment procedure.

If AESI respond to a seriousness criteria, they must be reported by using the SAE report form and with the same reporting modalities.

If AESI do not respond to a seriousness criteria, they will only be recorded in the eCRF.

AESIs will comprise the following:

Arm lymphedema, our primary endpoint, is a potential risk in patients treated with axillary lymph node dissection, taxan-based chemotherapy and loco-regional radiation therapy. With modern techniques of radiotherapy in HypoG-01 we will assume that 10% will have an arm lymphedema 3 years after radiation therapy. **Treatment will be left at the investigator choice according to symptoms, severity and local guidelines.**

Brachial plexopathy is a potential but seldom risk in patients treated with axillary lymph node dissection, taxan-based chemotherapy and loco-regional radiation therapy. It is however very difficult to distinguish between brachial plexopathy and the classical side effects from chemotherapy and surgical traumas (e.g. paresthesia). In this trial brachial plexopathy is therefore present if diagnosed by a neurologist. Thus if the patient has ipsilateral symptoms indicating plexopathy, she is recommended referred to a neurologist.

Pneumonitis is a potential but rare risk in patients treated with thoracic radiotherapy if dose constraints to Lungs are met. In case of pneumonitis radiation induced or not diagnosis and treatment will be left at the investigator choice according to symptoms and severity.

Dyspnea is a potential but rare risk in patients treated with thoracic radiotherapy if dose constraints to Lungs and heart are met. In case of dyspnea radiation induced or not diagnosis and treatment will be left at the investigator choice according to symptoms and severity.

Cardiac events such as coronary events, myocardial infraction, pericardic effusion are potential but seldom risks in patients treated with radiotherapy on breast/chest wall and drainage lymph node areas. Diagnosis and treatment will be left at the investigator choice according to symptoms and severity. Thus if the patient has cardiac symptoms, she is recommended referred to a cardiologist

Hypothyroidism is a potential but seldom risks in patients treated with thoracic radiotherapy specially when irradiating levels 3, 4 and the IMN. Diagnosis and treatment will be left at the investigator choice according to symptoms and severity.

Dysphagia is a potential but rare risk in patients treated with thoracic radiotherapy specially when irradiating levels 3, 4 and the IMN. Diagnosis and treatment will be left at the investigator choice according to symptoms and severity.

Skin toxicities (itching, radiation dermatitis, telangiectasia, fibrosis), breast swelling, discomfort or breast pain are frequent to rare events. Acute skin reactions are most often transient symptoms. Treatment will be left at the investigator choice according to symptoms, severity and local guidelines.

10. QUALITY OF LIFE ,ECONOMIC STUDIES, CARDIAC AND LUNG ASSESSEMENT

10.1 Quality of life

By delivering Breast Radiotherapy in a shorter overall time (3 *vs* 5 weeks) than in standard regimens, hypofractionated RT is susceptible to impact the quality of life of patients in two opposite ways. First, the reduction of the period of treatment may impact on fatigue and anxiety of patients, patients undergoing a hypofractionated regimen recovering more rapidly their baseline QoL (before RT). In a RCT comparing hypofractionated irradiation and conventional irradiation, patients reported significantly less acute effects, less fatigue and less trouble meeting family needs 6 months after RT (53). But, hypofractionated irradiation by delivering a higher dose per session may induce more fatigue during the treatment phase. Likewise, hypofractionated irradiation may be associated with more acute and late toxicities translating in a poorer quality of life. Indeed, patients experiencing lymphedema may have lower quality of life scores on the social and role functioning dimensions at short and long term (54,55,56) However, until now, there have been few quality of life studies in the field of RT (57) and even less studies focusing on hypofractionated regimens in breast cancer (36,58). The analysis of quality of life (n=2,208) in the START trials did not found difference between RT regimens neither for symptoms (breast symptoms and arm symptoms) nor for body image (36). Other dimensions of QLQ-C30 were not reported.

Our trial will investigate the HRQoL of patients using two types of validated patient-reported outcomes (PROs) measures: the EORTC QCLQ-C30 (cancer specific; 51) and QLQ-BR23 questionnaires (breast cancer specific; 52) and the Euroqol EQ-5D-3L questionnaire (generic measure; Euroqol Group 1990).

The EORTC QLQ-C30 consists of 30 items related to patients' global QoL, physical symptoms, and physical, role, social and emotional functioning. The breast cancer module (EORTC BR23) consists of 23 items specific to breast cancer including two functional scales (body image and sexuality) and three symptom scales (arm symptoms, breast symptoms, and systemic therapy side effects).

The EQ-5D is a two-part self-assessment questionnaire that takes approximately 5 minutes to complete. The first part consists of 5 items covering 5 dimensions including: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added. The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20-cm 10-point interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale, and best imaginable health state is scored as 100 at the top. Both the 5-item index score and the VAS score are transformed into a utility score between 0 —Worst health stateǁ and 1 —Best health state.ǁ

PROs (EORTC QLQ-C30, BR23 and Euroqol EQ-5D) will be administered with the same schedule in the two arms: at baseline (before randomization), 3 weeks of treatment, within 1 month after the end of treatment, 6 months after randomization, at 1, 2, 3, 5 years and 10 years after randomization.

PRO	Before RT	At 3 weeks of treatment	End of treatment (1 month after last fraction)	Follow Up after randomization						
				M6	Y1	Y2	Y3	Y4	Y5	Y10
QLQ-C 30	X	X	X	X	X	X	X	X	X	X
BR 23	X	X	X	X	X	X	X	X	X	X
EQ-5D-3L	X	X	X	X	X	X	X	X	X	X

Based on literature, our primary QOL comparisons between treatment arms consist of fatigue and social functioning for QLQ-C30 and arm and shoulder symptoms for QLQ-BR23 as in the START trials (36), and also item 6 “Were you limited in doing either your work or other daily activities?” pf qlq-C30.
Analysis will take into account repeated measures (mixed models or generalized estimating equations). To better understand the consequence of lymphedema on HRQoL, we will compare PROs in patients with and without breast cancer related lymphedema.

10.2 Cost-Utility Analysis

A cost-utility analysis alongside the HypoG01 trial will be performed to determine which regimen is the most cost-effective. We will compare costs and outcomes between the two arms of the trial based on the intent-to-treat principle.

Costs

Previous cost studies showed that hypofractionation is associated with a cost reduction of 20 to 30 % (59,60,61,62,63). However, cost data in the French context are not available. Moreover, some of these studies did not take into account travel expenses and sick leaves which may be important cost drivers for RT.

We will assess direct (medical and non-medical) and indirect costs from the French national health insurance perspective. For resource use, data collection will focus on high-cost resources and on resources that are expected to differ between the treatment arms. For each patient, we will collect the type of dosimetry, the characteristics of irradiation (technique, dedicated machine, etc..) and the number of fractions, transportation and sick leaves during RT (patient questionnaire administered at the visit within a month after treatment). Any hospitalization related to the breast cancer during RT will be collected. During follow-up, we will only collect possible hospitalizations for toxicity. To value resources, we will use cost weights (reimbursement tariffs for medical services and average compensation per day for sick leaves) from the French national health insurance at the date of the analysis. However, the payment per case for RT is under experimentation in France and may replace the current payment per fraction. To calculate the cost of irradiation, we will use the tariff per fraction before the payment reform. In France, tariff paid to hospitals for a fraction depends on the technique used (IMRT, 3D or 2D), patient positioning control and whether or not the equipment is dedicated in case of complex irradiation. We will use the accurate tariffs from the French national insurance for each patient enrolled in the trial. To do so, items will be added to the case report form (technique, characteristic of equipment and number of fractions received by the patient) and diagnosis related groups for treatment preparation and for each fraction will be collected from the Department of Medical Information in each centre (in charge of coding medical information for the national hospital episode statistics database). Likewise, for possible hospitalizations, the date of admission, the date of discharge, the diagnosis related group (*code GHS*) and the total lump sum for the stay (*recettes T2A*) will be provided by the Department of Medical Information in each centre.

Costs will be compared between the two arms using a t-test. Mean costs in each arm, cost difference and 95% confidence intervals will be computed.

Quality-adjusted life years
To compute QALYs in the two arms, survival estimates for patients in each trial arm will be combined with utility weights in the French context (64) at each evaluation. Mean QALYs in each arm, difference in QALYs and 95% confidence interval will be computed under the normality assumption or using the bootstrap method in case of non-normality of the distribution of QALYs. QALYs will be compared between the two arms using either a t-test or a Wilcoxon test in case of non-normality.

Cost-utility analysis
Cost-utility will be analyzed at two time points: at the time of analysis of primary endpoint and at 10 years follow-up to consider late toxicities.
Cost-utility will be measured as cost per QALY. For these two time horizons, estimates for cumulative costs and QALYs will be computed in each treatment arm. Both costs and QALYs will be discounted to their present value according French guidelines at the time of analysis. Mean cost difference and mean difference in QALYs from boostrap replicates will be represented in the cost-effectiveness plane. The cost-effectiveness

acceptability curve will be computed using the net monetary benefit approach. A sensitivity analysis will be performed to quantify parameter uncertainty (eg: RT tariffs and discount rate).

10.3 Cardiac and lung assessment

It was shown radiotherapy can cause late cardiac toxicities that can be correlated to the heart dose (Darby et al, NEJM 2013). These published results are very approximated and directly related to old irradiation techniques and theoretical estimates of dose received by the coronaries. In the era of modern radiotherapy, there is a need of objective analysis of cardiac doses using objective criteria as the dose volume histograms (DVH) of lung and heart, central lung distance (CLD), median heart distance (MHD) and dose per fraction. There is an urgent need to prepare the guidelines with the doses related to the hypofractionated radiotherapy. This is the first study asking this question and can add an important information to the meta analyses of old and not always adapted data (Taylor et al, IJROBP 2013, Aznar et al, 2016, in preparation)
In practice, the lung and heart doses (mean, median, DVH) must be recorded as well as the LVEF (performed in standard of care) before the radiotherapy as well as after, and during the follow-up period for every patient. This information must be reported in the CRF.
In addition, all radiotherapy data will be uploaded into a shared platform.

11. ANCILLARY STUDIES

11.1 Biological ancillary study

Only apply to patient whom had consented to do these biological studies.

11.1.1 Ceramide Assessment

Ceramide, a pro-apoptotic sphingolipid, has been defined as early biomarker of highly hypofractionated radiotherapy using Stereotactic Body RadioTherapy (SBRT) efficacy in colon and lung metastases *(Dubois and al, in press*).
Ceramide and its Sphingolipid metabolites (sphingomyelin, sphingosine, sphingosine 1-phosphate, glucosyl-ceramide, lactosyl-ceramide, ceramide 1-phosphate) will be analyzed for this clinical trial in order to determine whether they are also potential biomarkers of long-term toxicity of radiation therapy.

To perform this study, 3 blood samples (3.5 ml in a Sodium Citrate Coagulation/CTDA (0.109mol/L) tube) will be collected before the beginning of radiotherapy, at mid-treatment and at the end of treatment (1 month after the last fraction).

After centrifugation, plasmas (1 ml at least) must be stored at -80 °C before sphingolipidomic analysis.

All samples will be shipped and centralized at Centre des Ressources Biologiques d'UNICANCER, (CRB-CLB), under the responsibility of Severine Tabone-Eglinger, located at the following address: Centre Léon Berard, 28 rue Laënnec – 69373 Lyon cedex 08, Bâtiment CHENEY B Rez de Chaussée – CRB échantillons biologiques) – France.

The dosage of sphingolipids species will be done by Liquid chromatography–mass spectrometry (LC-MS / MS) at The Laboratoire de Biologie des Cancers et de Théranostic (LaBCT)/ Inserm 892 in Nantes.

The ratio between the Sphingolipids concentration at each time will be correlated to the occurrence of side effects throughout the patient follow-up.

11.1.2 Telomere and Chromosomes Aberration Assessment

Telomeres are found at the very ends of chromosomal DNA and are involved in the maintenance of genome stability (77,78). Mean telomere length is considered to be a marker for biological age with shorter telomeres

indicative of greater biological age (79). Telomere shortening in peripheral blood lymphocytes has been linked to cardiovascular-related morbidity and mortality in the general population (80, 81,82)

The potential correlation of conventional risk factors, radiation dose and telomere shortening with the development of coronary artery disease (CAD) following radiation therapy was investigated in a large cohort of Hodgkin lymphoma (HL) patients (83,84). Multivariate analysis demonstrated that hypertension and telomere length were the only independent risk factors.
This was the first study in a large cohort of patients that demonstrates significant telomere shortening in patients treated by radiation therapy who developed cardiovascular disease. Telomere length appears to be an independent prognostic factor that could help determine patients at high risk of developing CAD after exposure in order to implement early detection and prevention.

A feasibility study will be conducted in this clinical trial to evaluate the predictive value of mean telomere length and chromosome aberrations in circulating lymphocytes in post-irradiation cardiovascular effects in patients with breast cancer. A follow-up of the occurrence of chromosome aberrations will be performed in order to determine if they are potential biomarkers of long term toxicity

Cytogenetic analysis will be conducted on metaphase and PCC (Premature Condensed Chromosomes) to:
- Estimate biological dose at each stage of treatment.
- Quantify the mean telomere length and its post-processing modulation.

To perform this study, a blood sample (6 ml in a heparin-lithium tube) will be collected before the beginning of radiotherapy, after the first fraction , after 9th fraction of radiotherapy for patient from arm A, after 12th fraction of radiotherapy for patient from arm B , after the last fraction of radiotherapy, at 18 months and 5 years.

All samples must be stored at room temperature before shipping to:
PROCyTox CEA - DRF/FAR/UP2S - Bât. 5
18 Route du Panorama -BP6
92265 FONTENAY-AUX-ROSES CEDEX

A first study on 10 patients in the normofractioned and hypofractioned arms from Gustave Roussy will estimate the feasibility of biological analysis on samples pre-and post-radiotherapy as well as variability in interindividual Pre- and post –treatment responses.

If the feasibility is inconclusive after a first serie of 10 patients, 10 more would be recruited. If the initial results are informative, this study will be extended within the normofractioned arm and to hypofractioned arm and more centers.

11.1.3 Longitudinal multiomics analysis

Radiation-induced fibrosis (RIF) is a long-term side effect for breast cancer patients treated by radiotherapy and which occurs more than 90 days after the last RT fraction delivered. This complication significantly impacts patient's quality of life.

The tolerance of radiotherapy is patient-specific and is defined by the concept of individual radiosensitivity (IRS).

In order to prevent the radiation-induced fibrosis and adapt radiation doses, biomarkers able to predict the occurrence of this toxicity are investigated.
UMR 7365 CNRS-UL IMoPA – Nancy laboratory highlighted a transcriptomic signature associated to radiation-induced fibrosis occurrence on a developmental cohort (patent). To validate externally the prognostic value of the signature and investigate new biomarkers, transcriptome expression profiles will be assessed at 4 or 5 years of follow-up. To perform this analysis, the following additional blood samples will be collected at 4-year or 5-year follow-up: 2.5ml in a PAX Gene tube.
Immediately after blood collection, the PAXGene tubes (whole blood) will be gently invert 8-10 times and store upright at room temperature (18−25˚C) for a minimum of 2 hours and a maximum of 72 hours before transferring to -80°C. These tubes will be shipped and processed at IMoPA laboratory – Nancy by Dr Isabelle

Behm-Ansmant: total RNA will be extracted and the transcriptome-level expression will be analyzed with Clariom D Assays.The transcriptomic profiles identified with these analyses will be correlated with the severity of radiation-induced fibrosis.

LIH Bioinformatics platform – Luxembourg will investigate novel plasmatic/circulating multiomic (proteomic, metabolomic, lipidomic) biomarkers of IRS. To perform this analysis, the following plasma samples will be transferred to this platform:

- ≥500 µL plasma tubes stored at -80 °C corresponding to plasma collected before the beginning of radiotherapy, at mid-treatment and at the end of treatment (1 month after the last fraction).
- Additional 4 ml in an EDTA tube collected at 4 or 5 years of follow-up.

These samples will be shipped to LIH - Luxembourg where extraction, preanalytic conditioning, high-resolution mass spectrometry and bioinformatic analysis will be performed. The multiomic profiles identified with these analyses will be correlated with the severity of radiation-induced fibrosis.

11.2 NCTP modeling

For the NTCP modeling, functional data analysis will be run on the processing of Dose volume histograms (DVHs) of the 50 first patients from Gustave Roussy as a training set then DICOM data and DVHs from other centers will be collected to serve as an independent validation data set. For comparison, the widely used Lyman-Kutcher-Burman NTCP model will be also considered.

11.3 Prospective meta-analysis of the DBCG HYPOII trial and the current French HYPOG 01 trial

The individual patient data of the 2 trials will be merged and analyzed in a prospective meta-analysis for which a specific meta-analysis protocol will be developed. A combined number of 316 events between HypoG01 and DBCG-HYPOII will trigger the prospective meta-analysis and will allow to show non-inferiority for a 3% increase in lymphedema (HR=1.32) at 80% power, 5% significance level, 1-sided logrank test.

11.4 Sarco-HYPOG

In breast cancer, sarcopenia is known to be a predictive factor for toxicity and survival in metastatic patients (85). The data in localized patients remain unknown. For all patients, sarcopenia will be evaluated at the L3 level on planning CT scan.

All datas will be collected, pseudonymised and centralized on a dedicated server and evaluated in Rouen by Quantif Group (EA 4108 S Thureau and R Modzelewski)

Sarcopenia assessment will be assessed with 6 indexes (Appendix 15): SMI (cm2/m2): Squeletal Muscle Index, FMI: Fat Mass Index (kg/m2), FMR: total Fat to muscle ratio, FFMI: Fat Free Mass Index (kg/m2), SMA: Skeletal Muscle attenuation (HU), IMATI: IntraMuscular Adipose tissue Index (cm2/m2)
The size of the patient must be noticed in the eCRF.

The aim is to define whether sarcopenia is a predictive criteria of lymphedema or locoregional relapse free survival, invasive disease-free survival, distant disease-free survival, breast-cancer specific survival, causes of death, overall survival.

12. STATISTICAL ANALYSIS PLAN (SAP)

12.1 Required number of patients

We estimated that among patients treated with axillary lymph node dissection, 50 Gy regional nodes radiotherapy and taxane-based systemic therapy 10% will have an arm lymphedema 3 years after radiation therapy. Further assumptions are the acceptance of up to a 5% increase in arm lymphedema (thus accept of 15% of the patients having arm lymphedema ≤ 10% of the upper and/or Lower arm with hypofractioned radiation therapy, corresponding to a non-inferiority limit HR=1.545), 80% power, 5% significance level, 1-sided test. Based on these assumptions this requires 131 events. A total of 1012 patients, 506 patients in each randomization arm will be included over 3 years in the per-protocol population (primary analysis). If we assume up to 20% of included patients will be excluded from the per-protocol population, a total of 1265 patients will need to be included.
The projected time of analysis (based on the expected number of events) is at 4.8 years after inclusion of the first patient. The final analysis will be triggered by the number of events.

12.2 Planned statistical analysis

12.2.1 Primary Analysis

The null hypothesis is that the hazard rate of the experimental hypofractionated arm A is worse than the standard arm B. The alternative hypothesis is that the hazard rate of arm A is not worse than arm B. The primary analysis will be performed using a one-sided logrank test at 0.05 significance level stratified for the factors used to stratify the randomization, according to the per-protocol population.
A sensitivity analysis will be performed using the intention-to-treat population (also with stratification for the same factors). In addition, a Cox regression model will be used to compare treatment differences when taking the stratification factors into account and adjusting for other prognostic factors for lymphedema such as type of radiotherapy (3D-CRT vs IMRT) and irradiated node levels according to the ESTRO guidelines. Both unadjusted and adjusted hazard ratios and their 95% confidence intervals will be computed.

Standard statistical methods as Kaplan-Meier analyses, Cox proportional cause-specific hazards regression will be used to compare the time-to-event variables between the 2 treatment arms and estimate hazard ratios adjusted for the stratification factors (using DATECAN definitions of breast-cancer related endpoints) at a one-sided 0.05 significance level. A multivariate model will also be constructed using relevant prognostic variables on the different time-to-event endpoints. A competing risk cumulative incidence approach will also be applied.

Statistical data will be expressed in the form of:
1. percentages (qualitative variables),
2. mean and standard deviation or median and range (quantitative variables),
3. survival curve estimates calculated with the Kaplan Meier method or cumulative incidence approach (survival data).

Different statistical methods will be used to compare data:
1. qualitative variables with the χ^2 or Fisher test,
2. quantitative variables with the Student t test or with a non-parametric test (Wilcoxon),
3. survival data with a Logrank test or Cox model.

12.2.2 QoL Analysis

All of the dimensions of QoL questionnaires will be described by median and interquartile range in both arms and longitudinally.
An overall measure of QoL missingness is defined as:
missingness = 100*{1-(No. assessments completed / No. assessments expected to be completed)}
The overall measure of QOL missingness will be summarized by treatment arm using the mean, standard deviation, and median.
Based on the literature, our primary QOL comparisons between treatment arms consist of fatigue and social functioning for QLQ-C30 and arm and shoulder symptoms for QLQ-BR23 as in the START trials (36) , and also item 6 “Were you limited in doing either your work or other daily activities?” pf qlq-C30.
A total of 840 patients with complete QoL data will allow to detect a standardized effect size as small as 0.25 between the treatment arms with 85% at a two-sided significance level of 0.01 (to allow for multiple testing). The effect size is defined as the difference between arms in the mean changes from baseline divided by the

pooled standard deviation of the changes, and according to a meta-analysis an effect size of 0.25 is small for the Subscales of EORTC QLQ-C30 (70).
Mean changes over time in QoL scores will be compared between treatment arms using a restricted maximum likelihood-based repeated measures linear mixed model under the missing at random (MAR) assumption. The model will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, the fixed, continuous covariates of baseline HRQoL score and baseline score-by-visit interaction, as well as the randomization stratification factors. Generalized estimating equations will be used for binary or ordinal data.
In order to better understand the consequence of lymphedema on HRQoL, we will compare PROs in patients with and without breast cancer related lymphedema.

Data will be analyzed with the SAS software.

12.3 Managing the missing and/or non-valid data

Patients lost to follow-up before the evaluation of primary criterion will be considered either as to be censored, and taken into account in the statistical analysis (assuming censoring and evaluation criteria time periods are independent variables), or considered as treatment failures for secondary time-to-event endpoints when relevant. In the QOL sub-study the primary analysis will assume a Missing At Random Mechanism for missing data.

12.4 Selection of patients to be included in the statistical analysis

Different populations of patients are defined for the analysis:

- Intent To Treat (ITT)

  All randomized patients will be included in the ITT population, whether or not any treatment was administered after randomization, and regardless of the eligibility status. As far as statistical inferences are concerned, patients are analyzed in the treatment group to which they were assigned by the randomization.

- Per-protocol :

  Eligible patients are patients with no major violations/ deviations as defined by the protocol:
  - Inclusion and exclusion criteria
  - Treatment interruption: the sum total of radiotherapy interruptions exceeds 3 normally scheduled treatment days in Arm A or 5 normally scheduled treatment days in Arm B or 3 consecutive normally scheduled treatment days in both Arms.
  - Any deviation defined as Major by the Steering Committee or Quality Assurance Procedures (including dose constraints violations…).

The primary analysis will be conducted on the per-protocol population, and a sensitivity analysis will be conducted on the intention-to-treat analysis.

12.5 Modifications of SAP and initial statistical analysis strategy

Any modification/change made to the initial statistical analysis plan (SAP) will be described in details, well-argued and commented in an updated version of the SAP. These modifications may be complementary/exploratory analyses not envisaged initially.

13. OVERSIGHT COMMITTEES

13.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee, with expertise and experience in the pathology, in radiotherapy or in biostatistics, and without direct involvement in the conduct of the trial, will be set up specifically to

guarantee effective protection of patients, insure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial.

The IDMC will meet once 2.5 years after the first recruited patient and will be composed of 3 members.

Data presented to IDMC are strictly confidential. Interim analyses will be presented to the IDMC

Management of the unblinded data by the Committee should be detailed, with provisions set up in order to maintain the Sponsor team blinded.

The IDMC is responsible for monitoring the safety of the trial participants, for ensuring that the trial is being conducted with the highest ethical and scientific standards, and making appropriate recommendations based on the safety data seen. This committee's main responsibilities are as follows:

- Reviewing reports relevant to conduct of the study, safety variables and safety outcomes, and making recommendations that may be required to ensure patient safety and preserve trial integrity.
- Reviewing serious adverse event (SAE) listings, i.e. line listings from Pharmacovigilance and listings from the clinical database.
- To make safety-driven recommendations concerning the continuation, the modification, the early, partial or complete, suspension or termination of the trial with regard to the risk-benefit ratio, changes in inclusion/exclusion criteria, frequency of visits or safety monitoring.

The IDMC has only a consultative role; it will inform the sponsor who will decide whether the IDMC recommendation will be followed.

An IDMC charter must be available upon submission of the trial (initial protocol) to the respective Competent authority.

13.2 Steering Executive Committee

A steering executive committee has been implemented for this trial. The Steering executive committee will meet physically (or at least through a teleconference) on a quarterly basis. Additional meetings may be set, as required.

The Steering executive committee is composed by:

- The Coordinating investigator
- The study physicist
- UNICANCER project manager
- The study statistician
- The study economist
- The biological coordinators
- Some investigators involved in the study

The Steering executive committee will be responsible for:

- approving the protocol and any amendments thereof
- maintaining the scientific integrity of the Study, according to the protocol
- ensuring the trial is conducted in an ethical manner
- reviewing recommendations of the IDMC and determining actions to be taken as applicable in order to ensure the safety of the participants
- reviewing and deciding on the publications and presentations of the Study Data.

The Steering executive committee will assist UNICANCER in resolving issues and/or questions encountered during the conduct of the trial and will consider with UNICANCER changes to the protocol as necessary.

13.3 Quality assurance committee (QA committee)

A Quality Assurance Committee for radiotherapy has been implemented for this trial. The QA committee will meet physically (and through web-conference) on a regular basis.

The QA committee is composed by:
- The Coordinating investigator
- The study physicist
- UNICANCER project manager
- An independent Radiation oncologist
- An independent medical physicist

The Q/A committee will be responsible for:
- The teaching workshop on contouring guidelines and radiotherapy procedures that the investigator will have to attend prior entering the trial
- Creating, validating, reviewing the dummy run
- Validating the dummy run done by each investigating center prior entering the trial
- Reviewing randomly selected treatment plan, contours and treatment delivery of at least 1 case per center within the first three months after initiation of the protocol
- Reviewing randomly selected treatment plan, contours and treatment delivery of at least 5 cases per year.
- Review and report on protocol deviations (ex: when dose constraints are not met)
- Provide support and advices to the investigators when dose constraints are not met
- Analyze and report on protocol deviations

14. ACCESS TO DATA

It is the responsibility of the sponsor to obtain the agreement from all parties involved in the research in order to guarantee that the sponsor has direct access to all investigator sites, original records, source data/document and reports to allow quality control and auditing by the sponsor or on behalf of the sponsor.

Investigators will make available to the authorized persons the documents and the patients' individual data that are essential to monitor the trial on an ongoing basis, to perform quality control and audit of this research in accordance with national regulatory requirements.

15. QUALITY ASSURANCE OF THE TRIAL

15.1 Data collection

All data necessary to the research must be entered timeliness into the trial electronic case report forms (eCRFs). eCRFs will be completed by the investigator and other designated members duly designated from his/her staff.

During the trial, Data clarification forms (DCFs) may be sent for data consistency validation, by the UNICANCER Central Data Center (CDC), under the responsibility of Mrs. Sophie Gourgou, located at the following address:
Institut régional du Cancer Montpellier (ICM) / Val d'Aurelle,
208 rue des Apothicaires – Parc Euromédecine –
34298 Montpellier cedex 5 - France.

Corrections addressed by these queries should be made by persons authorized to complete the eCRF.

When using electronic CRF, traceability of access and changes is traced by the software (audit trial).

15.2 Trial monitoring

To ensure the authenticity and credibility of data in accordance with the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006", the sponsor establishes a system of quality assurance that consists in:

- The management and the monitoring of the trial according to UNICANCER procedures;
- The quality control data of the investigational centers by the monitor involves:
  - verifying that the protocol, as well as the current guidelines ICH-GCP, the national regulatory requirements, are accurately followed,
  - verifying the informed consent and the eligibility of each patient participating in another research,
  - verifying that the eCRF data is consistent and in agreement with the source documents,
  - verifying the notification of each SAE,
  - verifying the treatment traceability
  - verifying *(if applicable)* that patients are not already participating in another research trial which may exclude their inclusion in this protocol. The monitor also verifies that patients have not participate in another trial following which an exclusion period if applicable before they can participate in another protocol,
- The audit of the participating investigational centers when deemed necessary;

The monitors and CRAs in charge of trial monitoring will be mandated by the sponsor. They must have access to all patient data as necessary for their duty in accordance with the national regulatory requirements. The monitors and CRAs are bound by professional secrecy under the national regulatory requirements. Written reports must be issued to ensure monitoring visit traceability.

In order to ensure the optimal research quality control, the investigator commits to provide the monitor with direct access to all patient files.

15.3 Audits and Inspection

As part of its audit program, the sponsor may need to audit some investigational centers. The center and the investigator agree that audits are carried out by Sponsor or any person duly authorized for at least fifteen years after the trial

More generally, the investigator center and the investigator undertake to devote the time necessary to audit procedures, control and additional information requested by the sponsor or by a Concerned Competent Authority.

A Competent Authority may also wish to conduct an inspection (during the trial or after its completion). If a Competent Authority requests an inspection, the investigator must inform the sponsor immediately that this request has been made. The investigator must provide a direct access to source documents.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1 General requirements

The trial must be conducted in accordance with the French national regulatory requirements, including but not limited to:

- The principles of ethics as stated in the last version of the Declaration of Helsinki,
- Loi n°2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine as modified in 2016
- Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
- Amended Loi Informatique et Libertés n° 78-17 du 6 janvier 1978, relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel,
- Amended Loi n° 2004-800 du 6 août 2004, relative à la bioéthique,
- The relevant principles of Décision du 24 novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur des médicaments à usage humain

16.2 Clinical Trial Authorization

Prior to the start of the trial, the sponsor will submit the trial protocol, patient information sheet(s), informed consent form(s), and other trial-related documents as required by French national regulatory requirements, to the ANSM for authorization and to the CPP for their written approval.

The sponsor will inform ANSM and the CPP, according to French national regulatory requirements, about protocol amendments including any substantial modification that require an ethical/regulatory reconsideration of the trial protocol.

Data recorded during this trial are subject to a computerized treatment by the UNICANCER Central Data Center in compliance with Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) and Amended Loi Informatique et Libertés n° 78-17 du 6 janvier 1978, relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel,the “Loi Informatique et Libertés n° 78-17, 6 January 1978 modified”.

The collection of biological samples implemented within the framework of the trial was declared to ANSM in the same time that the request of Clinical Trial Authorization. After the trial, and in case of storage, the storage of the collection of biological samples will be notified to the Minister of Research (and submitted to the CPP to notice if change of purpose of Research).

16.3 Patient identification

Patient will be identified by a numeric code, the first three letters of the last name, and the first two letters of the first name and the date of birth in case of namesake.

All patients will receive a unique patient identification number when signing the informed consent form by the patient and before any trial procedure is performed. This number will be used to identify the patient throughout the trial and must be used on all trial documentation related to this patient. The patient identification number must remain constant throughout the entire trial; it must not be changed.

16.4 Patient information and consent

16.4.1 Generalities

Patient information and informed consent from the patient must be handled in accordance with the “French regulation, especially article L.1122-1 and subsequent articles.

Prior to the participation of a patient in the trial, this patient will be informed both verbally and in writing about the objectives of the trial, its methods, anticipated benefits and potential risks and the discomfort to which they may be exposed. All items must be explained by the investigator in a language and in terms that are easy to comprehend by the patient. Patients will also be informed that the participation is voluntary and that they have the right to withdraw from participation in the trial at any time without giving the reasons and without any disadvantages for their subsequent care.

The patients must be given enough time to decide about their participation in the trial.

They will confirm their consent in writing prior to trial start and any trial-related procedure. The informed consent form must be personally dated and signed by the patient and investigator in two originals. An original copy will be filed in the Trial Master File (IMF). Patients must be provided with an original of the patient information sheet and the signed informed consent.

In case of substantial changes in the written patient information sheet or informed consent form, the investigator ensures that all patients still participating in the trial receive the updated patient information in a timely manner and are asked for written consent to the changes.

Such amendments may only be implemented after written approval of the Ethics Committee has been obtained and compliance with the local regulatory requirements, with the exception of an amendment required to eliminate an immediate risk to the study participants.

16.4.2 Patient consent withdrawal

In some cases, the patient may wish to stop their participation to the trial. A consent withdrawal causes the end of the participation in the trial, including administration of the investigational treatment and follow-up.

Please note that this is a different situation from a treatment discontinuation for other reasons as referred in Section 5.6 Treatment discontinuation.

The patient may withdraw his/her consent to participate in the ancillary study involving the use of biological samples independently from his/her participation in the main study. If the patient withdraws his/her consent to participate in the ancillary study, his/her samples will be destroyed

The patient does not have an obligation to give reason(s) for withdrawing their consent. The consent can be withdrawn in oral or written form. However, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the patient's rights and must document the date of the withdrawal.

<u>At the investigator's initiative</u>
The patient may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons.
Prior to the withdrawal, the investigator must complete as fully as possible the study report with the patient's status, clinical information and reasons for withdrawal.

<u>Follow-up</u>
When the patient is withdrawn from the study, the consent stops and no further data can legally be collected, therefore follow-up within the study is not possible.
However, SAEs and new events are to be reported according to Section 9. Safety evaluation, in accordance with Article L1123-10 of the French "Code de la santé publique".

16.5 Changes to protocol

The trial will be conducted in strict compliance with this protocol. Changes will be included in an amended version of the trial protocol. The list and tracking of modifications and rationales will be provided in the

amended version of the trial protocol. Amended trial protocols with substantial modifications have to be submitted to the ANSM and to the CPP by the sponsor, according to the French regulation.

Amendments with substantial modifications to the protocol should be implemented only after approval by the ANSM and the CPP.

16.6 Sponsor responsibilities

UNICANCER, the sponsor of the trial, who has initiated this trial and is therefore accountable for the trial management and for verifying that the financing schedule covers the anticipated expenses.

The main sponsor responsibilities are:

- The protocol writing and amendments, as well as trial-related documents;
- The subscription of a civil-responsibility insurance;
- The obtaining of an ID-RCB identification number;
- The request according to the French regulation the opinion of the CPP, and authorization from the ANSM on the initial protocol and possible amendments;
- The notification of any suspected unexpected serious adverse reactions according to the French regulation, to the ANSM, and the notification of this information to the CPP and the physician-investigators of the trial;
- The information on the trial to the investigational centers' heads, pharmacists and physician-investigators, according to local regulatory requirements;
- The information of any new event to the ANSM, and the measures taken, and the notification to the CPP in the same time, according to the local requirements;
- The recording of the trial in database research accessible to the public
- Also the recording of the trial in the international database ClinicalTrials.gov and the "Register of French cancer clinical trials" of the INCA, before the enrollment of the first patient;
- The permanent assessment of ongoing safety of the investigational drug and therefore the safety of patients;
- The transmission of the Development Safety Update Reports (DSUR) to the ANSM and to the CPP according to the French regulation;
- The notification of the beginning and the end of the trial to the ANSM and to the responsible CPP, according to the French regulation;
- The final report writing on the trial and its communication, according to the French regulation, to the ANSM;
- The information on the trial's results, according to the French regulation, to the ANSM, to the CPP. The trial's results may also be communicated to the research participant, at their request, by the physician-investigator;
- The archiving of the trial's essential documents for a minimal duration of 15 years after the research has ended

16.7 Insurance compensation

UNICANCER, the sponsor of the trial certifies that it has taken out a Civil Liability insurance policy covering its civil liability for this clinical trial under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the sponsor does not exempt the investigator and its team from maintaining their own liability insurance policy.

16.8 Investigator responsibilities

The principal investigator of each investigator site participating in the trial commits to conduct the trial as specified in this protocol and in accordance with the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006".

It is the responsibility of the principal investigator to:

- Provide to the sponsor with her/his own *curriculum vitae* (CV) and those of his/her collaborators, and evidence that the center will be able to conduct the trial. CV must be dated and signed;
- Identify the members of his/her team who participate in the trial and to define their individual responsibilities;
- Start recruiting patients after approval of the sponsor;
- Be available for monitoring visits, audits and investigator meetings.

It is the responsibility of each principal investigator and of each investigator team member to:

- Ensure the confidentiality of all data recorded during the trial;
- Collect the informed consent, written, dated and signed personally by each individual research participant before any specific selection procedure to the trial;
- Regularly complete the case report form (CRF) for each of the patients included in the trial and allow the clinical research assistant (CRA) mandated by the sponsor to have direct access to the source documents in order to validated the data collected in the CRF;
- Declare to the sponsor as soon as he aware, any serious adverse event occurring during the trial according to provisions of this protocol;
- Accept regular visits by the CRA and possibly those of auditors as mandated by the sponsor or the inspectors of the respective regulatory authorities;
- Date, correct and sign the corrections made in the CRF and the requests of the data correction forms (DCF) for each patient included in the trial.

16.9 Federation of the Patient Committees for Clinical Research in Cancerology

The dedicated task of the Committee is to review clinical trial protocols in oncology. The French patient committees' federation is coordinated by the "Ligue Nationale Contre le Cancer" and the French NCI (INCa). The Committee reviews the trial protocol and documentation to suggest improvements in the quality of information given to the patients, the delivery of trial treatment and monitoring plan, to maximize the convenience and comfort of the patients.

16.10 Human biological samples collection

Biological studies are necessary to improve the knowledge of diseases as they allow the development of new and more effective treatments. These studies use human biological samples (blood) than can be collected from patients either while they receive medical care (examination, surgery) or specifically for the research purpose.

The objectives of this research are to study:

- Patient's radiosensitivity by using Radiation Induced Lymphocyte Apoptosis Test
- Ceramide and its Sphingolipid metabolites as potential biomarkers of long-term toxicity of radiation therapy.
-Predictive value of mean telomere length and chromosome aberrations in post-irradiation cardiovascular effects

- Compare the global profiles of splicing and expression of coding and non-coding RNAs in blood as well as longitudinal multiomic plasmatic profiles according to the severity of the observed toxicity, which will make it possible to search for blood/plasma markers associated with radiation-induced fibrosis and to validate a blood transcriptomic signature of individual radiosensitivity.

To perform this research, 11 additional blood sample(s), will be collected during the treatment as follow:

	Before RT	After 1st Fraction	Mid-treatment	End of Treatment	18 months	4 years	5 years
CERAMIDE Test (5ml)	X		X	X			
Telomere and chromosome aberrations Test (6ml)	X	X	X[1]	X	X		X
Transcriptome Assessment (2,5 ml)						X[3]	X[3]
Multiomics profiles (4ml ml[4])	X[2]		X[2]	X[2]		X[3]	X[3]

1. after 9th fraction for patient in arm A and after 12th fraction for patient in arm B
2. Same samples as those collected for the ceramide analysis
3. At 4-year or 5-year follow-up
4. Volumes applicable for the blood samples collected at 4-year or 5-year follow-up.

These biological samples will be prepared, stored and used for the purpose of the research.

These additional samples are subject to written consent from the patient. Consent, different consent for participation in the clinical trial, is revocable at any time. Similarly, at any time of the research, the patient has the opportunity to request the destruction of these samples.

17. DATA PROCESSING AND CONSERVATION OF DOCUMENTS AND DATA OF THE RESEARCH

17.1 Data processing

17.1.1 Under the responsibility of the sponsor

The statistical data analysis will be transferred to the biostatistical unit of Gustave Roussy under the responsibility of Stefan Michiels. All data from the trial remain the property of UNICANCER, the research sponsor.

The software Ennov Clinical® will be used for data entry, management and archiving of data. The statistical analysis will be performed using the SAS software.

17.1.2 In the investigational center, when computerized medical records are used

If the case that computerized patient records are used in a participating center to process or store data related to the trial, the center must:

a) Verify and document that the computer system used to process the data is in conformity with the requirements in terms of data completeness, accuracy and reliability with respect to the expected performances (quality validation);

b) Define and follow the standardized procedures related to these systems;

c) Ensure that these systems allow modifications of the collected data, that each modification is automatically authentified, and that the data cannot be removed (i.e. any change or modification of the data must be traceable);

d) Set up and maintain a security control to prevent unauthorized access to the data;

e) Establish and regularly update the list of persons authorized to have access and modify the data;

f) Carry out appropriate backups of the data;

g) Ensure confidentiality, whenever it is applicable (e.g. during data input);

h) Ensure that the computerized patient individual Data are processed in accordance with the "Loi Informatique et Libertés n° 78-17, 6 January 1978 modified".

If data are transformed while being processed, it should always be possible to compare them with the original observations/records.

The computerized system used to identify the patients participating in the trial must not be ambiguous and should allow the identification of all data collected for each patient while preserving their confidentiality in accordance with the "Loi Informatique et Libertés n° 78-17, 6 January 1978 modified".

17.2 Retention of documents by investigator sites

The investigator must maintain source documents for each trial patient.

All information in case report forms must be traceable and consistent with source documents, which are generally maintained in the patient's file. The source documents should contain all demographic and medical information, laboratory data, radiology, electrocardiograms, etc…, including a copy of the patient information sheet and signed informed consent form.

The investigator must retain essential documents as listed below, as described below. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- Approvals from the CPP for the trial protocol and all amendments
- Authorizations from the ANSM for the trial protocol and all amendments;
- All source documents and laboratory records;
- CRF copies;
- Patients' informed consent forms;
- Investigator master file (IMF) and Investigator master file-pharmacy (IMF-P);
- Any other pertinent trial document.

All documents of the trial must be kept in a locked and secured place and considered to be confidential material.

Data will be archived under the responsibility of the principal investigator of each participating center according to the "Décision portant sur les Bonnes Pratiques Cliniques, 24 November 2006". The archives will be kept as well as a list of patient identifications for a minimum period of 15 years after the end of the trial. UNICANCER will inform the investigational centers when the trial-related records are no longer required.

The investigational center may destroy the data only after the sponsor has given its written authorization.

18. DATA OWNERSHIP AND CONFIDENTIALITY

By signing the protocol, the investigator agrees to keep all information provided by UNICANCER in strict confidence and to request similar confidentiality from his/her staff. This obligation does not cover information to be provided to the patients nor information already publicly available.

Trial documents provided by UNICANCER (protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by UNICANCER to the physician-investigator may not be disclosed to others without direct written authorization from UNICANCER.

The physician-investigator commits not to publish, not to spread or use in any manner, directly or indirectly, the scientific and technical information and results related to the trial.

19. PUBLICATION RULES

All information resulting from this trial is considered confidential, at least until appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the trial.

Any publication, abstract or oral presentations including results of the trial must be submitted to the sponsor (UNICANCER) for approval.

Additionally, all communications, manuscripts or oral presentations must include a section mentioning UNICANCER as well as any institution, physician-investigators, collaborative research group, scientific society that has contributed to the trial, including organizations that have provided financial support.

For the main publication, the first author and writer of the publication will be the study coordinator and the statistician will be the last author. The study coordinator may however designate another person to co-write the publication.
The other investigators or contributors will appear in the list of co-authors in decreasing order, according to the number of recruited patients or the importance of their contribution (e.g.: pathologists) regardless of the importance of the cooperating group they belong to, followed by a person representing each cooperating group among the investigation centers that have the highest rates of recruitment. The sponsor representative is co-author as well.

It is desirable to include the contributors from weakly recruiting centers and who have not been mentioned in the first article in the later publications.

Similarly, the list of authors of ancillary study (biological study) publications will include the name of the person(s) who carried it out as well as the name of the study coordinator and of any other person who was involved in it and a sponsor representative.
Inclusion in subsequent publications of representatives of sites with a lower accrual in the list of co-authors will be taken into account.

Any conflict regarding author's name appearance will be submitted to the UNICANCER R&D executive management decision.

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21. APPENDIX

- Appendix 1: Performance status evaluation – WHO scale
- Appendix 2: World Medical Association/ Declaration of Helsinki
- Appendix 3: ICH Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP)
- Appendix 4: Toxicity criteria (NCI-CTCAE)
- Appendix 5: Quality of Life Questionnaires (QLCQ-C30, BR23, EUROQOL EQ-5D)
- Appendix 6 : Morbidity & Body Image Score Form
- Appendix 7: Patient Form-Questionnaire
- Appendix 8: Guide for measurement of arm lymphedema
- Appendix 9 : Range of motion of the arms assessment
- Appendix 10: Guide for documentary Photos of both breasts for cosmetic assessment
- Appendix 11 : LENT SOMA Scale
- Appendix 12: Harris 4-point Scale
- Appendix 13: BED according to different radiotherapy Regimens and alpha/beta Ratios
- Appendix 14: Transport & Sick leaves Questionnaire
- Appendix 15 : Sarcopenia Assessment

Appendix 1: Performance status evaluation – WHO scale

Performance status ECOG-ZUBROD/ OMS	value
Fully active, able to carry on all pre-disease performance without Restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	4

Appendix 2: World Medical Association- Declaration of Helsinki

The current Declaration of Helsinki can be found on the World Medical Association web page via the link provided below:

http://www.wma.net/

Appendix 3: ICH Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP)

The current ICH-GCP can be found on the European Mediciny Agency web page via the link provided below:

http://www.ema.europa.eu/

Appendix 4: Toxicity criteria (NCI-CTCAE)

In the present trial, adverse events will be recorded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE), *(Publish Date October 1, 2009)*

Toxicity evaluation scale provided separately in attached documents or download it from the NCI website



http://ctep.cancer.gov/

Appendix 5: Quality of Life Questionnaires (QLQ-C30, BR23 et EQ-5D)

N° CENTRE	N° PATIENT	INITIALES
|___|___|___|	|___|___|___|___|	Nom |___|___|___| Prénom |___|___|

Questionnaires remis à :

☐ **à l'inclusion** ☐ **à 3 semaines de traitement** ☐ **à 1 mois après la fin de traitement**

☐ **à 6 mois après randomisation** ☐ **à 1 an après randomisation** ☐ **à 2 ans après randomisation**

☐ **à 3 ans après randomisation** ☐ **à 4 ans après randomisation** ☐ **à 5 ans après randomisation**

☐ **à 10 ans après randomisation**

Madame, Mademoiselle,

Vous avez accepté de participer à l'essai : afin de mieux connaitre votre qualité de vie pendant votre traitement et votre suivi, et de comprendre vos attentes, nous vous remercions par avance de répondre aux questions suivantes en Pour cela, merci de cocher la réponse qui correspond le mieux à votre situation. Il n'y a pas de « bonne » ou de « mauvaise » réponse.

Dans la mesure du possible, il est très important que vous répondiez à toutes les questions pour l'interprétation des résultats.
Ces informations sont strictement confidentielles.

Si vous avez des questions, n'hésitez pas à contacter votre médecin.

Merci

DATE DE NAISSANCE (jour/mois/année) |__|__|/|__|__|/|__|__|__|__|

DATE DE REMPLISSAGE (jour/mois/année) |__|__|/|__|__|/|__|__|__|__|

1. EORCT-QLQ-version 3



EORTC QLQ-C30 (version 3)

Nous nous intéressons à vous et à votre santé. Répondez vous-même à toutes les questions en entourant le chiffre qui correspond le mieux à votre situation. Il n'y a pas de "bonne" ou de "mauvaise" réponse. Ces informations sont strictement confidentielles.

Merci de préciser:

Vos initiales: _____

Date de naissance (jour/mois/année): _____

La date d'aujourd'hui (jour/mois/année): 31 _____

		Pas du tout	Un peu	Assez	Beaucoup
1.	Avez-vous des difficultés à faire certains efforts physiques pénibles comme porter un sac à provisions chargé ou une valise?	1	2	3	4
2.	Avez-vous des difficultés à faire une longue promenade?	1	2	3	4
3.	Avez-vous des difficultés à faire un petit tour dehors?	1	2	3	4
4.	Etes-vous obligée de rester au lit ou dans un fauteuil pendant la journée?	1	2	3	4
5.	Avez-vous besoin d'aide pour manger, vous habiller, faire votre toilette ou aller aux toilettes?	1	2	3	4

Au cours de la semaine passée:		**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
6.	Avez-vous été gênée pour faire votre travail ou vos activités de tous les jours?	1	2	3	4
7.	Avez-vous été gênée dans vos activités de loisirs?	1	2	3	4
8.	Avez-vous eu le souffle court?	1	2	3	4
9.	Avez-vous ressenti de la douleur?	1	2	3	4
10.	Avez-vous eu besoin de repos?	1	2	3	4
11.	Avez-vous eu des difficultés pour dormir?	1	2	3	4
12.	Vous êtes-vous sentie faible?	1	2	3	4
13.	Avez-vous manqué d'appétit?	1	2	3	4
14.	Avez-vous eu des nausées (mal au coeur)?	1	2	3	4
15.	Avez-vous vomi?	1	2	3	4

Passez à la page suivante S.V.P.

Au cours de la semaine passée:	Pas du tout	Un peu	Assez	Beaucoup
16. Avez-vous été constipée?	1	2	3	4
17. Avez-vous eu de la diarrhée?	1	2	3	4
18. Etiez-vous fatiguée?	1	2	3	4
19. Des douleurs ont-elles perturbé vos activités quotidiennes?	1	2	3	4
20. Avez-vous eu des difficultés à vous concentrer sur certaines choses par exemple pour lire le journal ou regarder la télévision?	1	2	3	4
21. Vous êtes-vous sentie tendue?	1	2	3	4
22. Vous êtes-vous fait du souci?	1	2	3	4
23. Vous êtes-vous sentie irritable?	1	2	3	4
24. Vous êtes-vous sentie déprimée?	1	2	3	4
25. Avez-vous eu des difficultés pour vous souvenir de certaines choses?	1	2	3	4
26. Votre état physique ou votre traitement médical vous ont-ils gênée dans votre vie familiale?	1	2	3	4
27. Votre état physique ou votre traitement médical vous ont-ils gênée dans vos activités sociales (par exemple, sortir avec des amis, aller au cinéma...)?	1	2	3	4
28. Votre état physique ou votre traitement médical vous ont-ils causé des problèmes financiers?	1	2	3	4

Pour les questions suivantes, veuillez répondre en entourant le chiffre entre 1 et 7 qui s'applique le mieux à votre situation

29. Comment évalueriez-vous votre état de santé au cours de la semaine passée?

1	2	3	4	5	6	7
Très mauvais						Excellent

30. Comment évalueriez-vous l'ensemble de votre qualité de vie au cours de la semaine passée?

1	2	3	4	5	6	7
Très mauvais						Excellent

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2. EORTC-BR23- version 1



EORTC QLQ - BR23

Les patientes rapportent parfois les symptômes ou problèmes suivants. Pourriez-vous indiquer, s'il vous plaît, si, durant la semaine passée, vous avez été affectée par l'un de ces symptômes ou problèmes. Entourez, s'il vous plaît, le chiffre qui correspond le mieux à votre situation.

Au cours de la semaine passée:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
31. Avez-vous eu la bouche sèche?	1	2	3	4
32. La nourriture et la boisson avaient-elles un goût inhabituel?	1	2	3	4
33. Est-ce que vos yeux étaient irrités, larmoyants ou douloureux?	1	2	3	4
34. Avez-vous perdu des cheveux?	1	2	3	4
35. Répondez à cette question uniquement si vous avez perdu des cheveux : La perte de vos cheveux vous a-t-elle contrariée?	1	2	3	4
36. Vous êtes-vous sentie malade ou souffrante?	1	2	3	4
37. Avez-vous eu des bouffées de chaleur?	1	2	3	4
38. Avez-vous eu mal à la tête?	1	2	3	4
39. Vous êtes-vous sentie moins attirante du fait de votre maladie ou de votre traitement?	1	2	3	4
40. Vous êtes vous sentie moins féminine du fait de votre maladie ou de votre traitement?	1	2	3	4
41. Avez-vous trouvé difficile de vous regarder nue?	1	2	3	4
42. Votre corps vous a-t-il déplu?	1	2	3	4
43. Vous êtes vous inquiétée de votre santé pour l'avenir?	1	2	3	4

Au cours des quatre dernières semaines:	**Pas du tout**	**Un peu**	**Assez**	**Beaucoup**
44. Dans quelle mesure vous êtes-vous intéressée à la sexualité?	1	2	3	4
45. Avez-vous eu une activité sexuelle quelconque (avec ou sans rapport)?	1	2	3	4
46. Répondez à cette question uniquement si vous avez eu une activité sexuelle: Dans quelle mesure l'activité sexuelle vous a-t-elle procuré du plaisir?	1	2	3	4

Passez à la page suivante S.V.P.

Au cours de la semaine passée:	Pas du tout	Un peu	Assez	Beaucoup
47. Avez-vous eu mal au bras ou à l'épaule?	1	2	3	4
48. Avez-vous eu la main ou le bras enflé?	1	2	3	4
49. Avez-vous eu du mal à lever le bras devant vous ou sur le côté?	1	2	3	4
50. Avez-vous ressenti des douleurs dans la région du sein traité?	1	2	3	4
51. La région de votre sein traité était-elle enflée?	1	2	3	4
52. La région de votre sein traité était-elle particulièrement sensible?	1	2	3	4
53. Avez-vous eu des problèmes de peau dans la région de votre sein traité (démangeaisons, peau qui pèle, peau sèche)?	1	2	3	4

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3. EuroQol Group EQ-5D-3L

Veuillez indiquer, pour chacune des rubriques suivantes, l'affirmation qui décrit le mieux votre état de santé aujourd'hui, en cochant la case appropriée.

Mobilité

Je n'ai aucun problème pour me déplacer à pied ❑

J'ai des problèmes pour me déplacer à pied ❑

Je suis obligé(e) de rester alité(e) ❑

Autonomie de la personne

Je n'ai aucun problème pour prendre soin de moi ❑

J'ai des problèmes pour me laver ou m'habiller tout(e) seul(e) ❑

Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

Activités courantes *(exemples: travail, études, travaux domestiques, activités familiales ou loisirs)*

Je n'ai aucun problème pour accomplir mes activités courantes ❑

J'ai des problèmes pour accomplir mes activités courantes ❑

Je suis incapable d'accomplir mes activités courantes ❑

Douleurs / gêne

Je n'ai ni douleur ni gêne ❑

J'ai des douleurs ou une gêne modérée(s) ❑

J'ai des douleurs ou une gêne extrême(s) ❑

Anxiété / Dépression

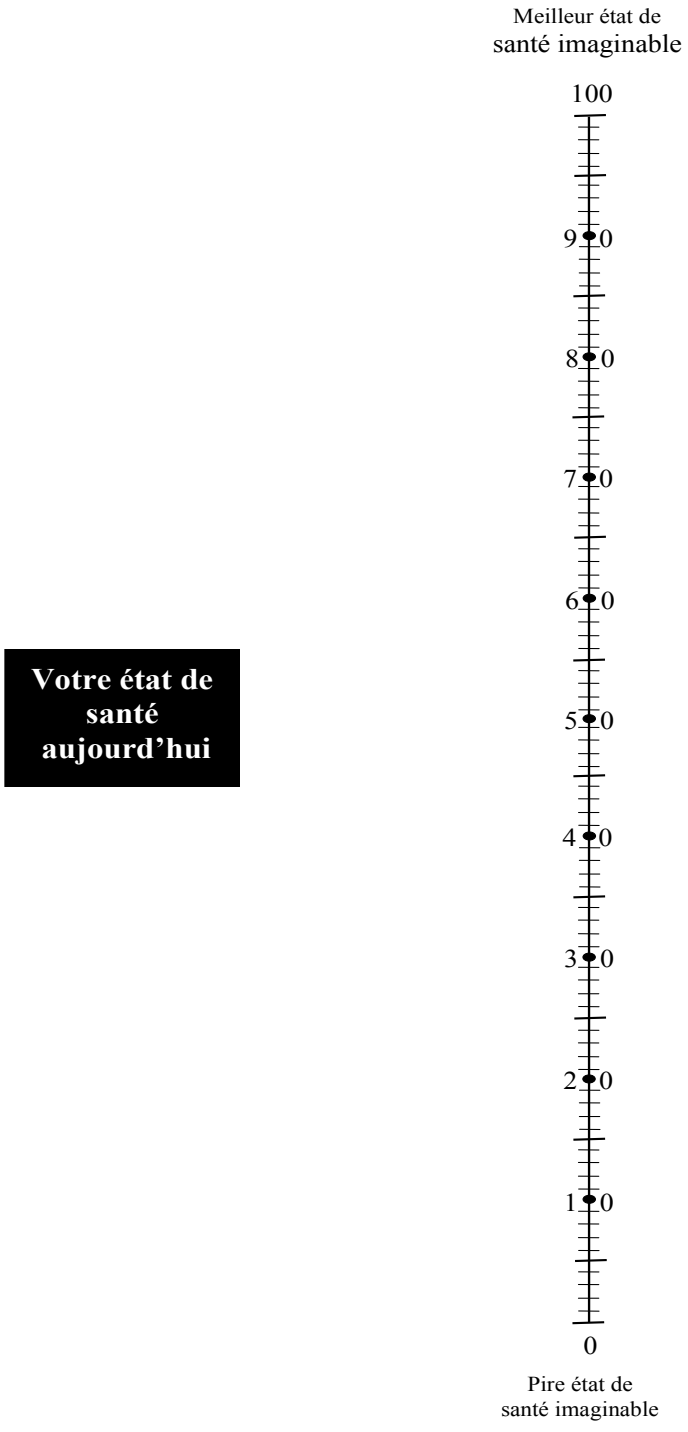
Je ne suis ni anxieux(se) ni déprimé(e) ❑

Je suis modérément anxieux(se) ou déprimé(e) ❑

Je suis extrêmement anxieux(se) ou déprimé(e) ❑

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Pour vous aider à indiquer dans quelle mesure tel ou tel état de santé est bon ou mauvais, nous avons tracé une échelle graduée (comme celle d'un thermomètre) sur laquelle 100 correspond au meilleur état de santé que vous puissiez imaginer et 0 au pire état de santé que vous puissiez imaginer.
Nous aimerions que vous indiquiez sur cette échelle où vous situez votre état de santé aujourd'hui. Pour cela, veuillez tracer une ligne allant de l'encadré ci-dessous à l'endroit qui, sur l'échelle, correspond à votre état de santé aujourd'hui Nous aimerions que vous indiquiez sur cette échelle où vous situez votre état de santé aujourd'hui. Pour cela, veuillez tracer une ligne allant de l'encadré ci-dessous à l'endroit qui, sur l'échelle, correspond à votre état de santé aujourd'hui



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Appendix 6: Morbidity and Body Image Score Form

Name – Patient ID	Hospital
__ - __ - __ - ____ (Day - Month - Year - No.)	
Years after RT __ __ __ __ __ __ __ (0 1 2 3 4 5 10)	Date __ __ __ __ __ __ (ddmmyy)

Patient reported morbidity

	None	Sometimes	Often	Always
Pain, breast / chest wall				

	None	Sometimes, mild	Often, mild	Opiod need
Analgesics because of pain in breast / chest wall				

	None	Slight	Moderate	Severe
Sensibility changes, breast / chest wall				

	High confidence	Feels less confidence, less feminine	Lack of confidence, avoids mirrors	Ashamed of body
Body image				

	No	Yes
Dresses differently, e.g. prefers looser fitting clothing		

Body Image Scale

	Not at all	A little	Quite a bit	Very much
Have you been feeling self-conscious about your appearance?				
Have you felt less physically attractive as a result of your disease or treatment?				
Have you been dissatisfied with your appearance when dressed?				
Have you been feeling less feminine/masculine as a result of your disease or treatment?				
Did you find it difficult to look at yourself naked?				
Have you been feeling less sexually attractive as a result of your disease or treatment?				
Did you avoid people because of the way you felt about your appearance?				
Have you been feeling the treatment has left your body less whole?				
Have you felt dissatisfied with your body?				
Have you been dissatisfied with the appearance of your scar?				

	Poor	Fair	Good	Excellent
How satisfied are you with the overall result of your treated breast?				
How satisfied are you with the overall result of your treated breast compared to the other breast? (Only relevant after breast conserving surgery.)				

	No	Yes
Have you had lipo injection in your treated breast / chest wall since last follow up visit?		
Have you had lipo injection in your opposite breast since last follow up visit?		

Appendix 7: Patient Form-Questionnaire

Name – Patient ID	Hospital
__ - __ - __ - ____ (Day - Month - Year - No.)	
Years after RT: 0 1 2 3 4 5 10	Date: _____ ddmmyy

	Right-handed	Left-handed
1. Are you right-handed or left-handed?		

Questions regarding pain

In this questionnaire we define "breast area" as either the operated breast or the area from which the breast was removed.

	No	Yes
2. Do you have pain in the area of the breast, armpit, side of the body or the arm on the side where you had surgery? If "No", please proceed to question 12 (next page).		
3. If "Yes", where do you have pain? (Please, tick yes or no for each area)		
Area of the breast		
The side of the body		
Armpit		
Arm		

	0	1	2	3	4	5	6	7	8	9	10
4. If you have pain in the **area of the breast**, how strong on average is the pain? (0 is no pain and 10 is the worst pain imaginable)											

	(Almost) every day	1-3 days a week	More rarely
5. If you have pain in the area of the breast, how often do you have this pain?			

	0	1	2	3	4	5	6	7	8	9	10
6. If you have pain on the **side of the body**, how strong on average is the pain?											

	(Almost) every day	1-3 days a week	More rarely
7. If you have pain on the side of the body, how often do you have this pain?			

	0	1	2	3	4	5	6	7	8	9	10
8. If you have pain in the **armpit**, how strong on average is the pain?											

	(Almost) every day	1-3 days a week	More rarely
9. If you have pain in the armpit, how often do you have this pain?			

	0	1	2	3	4	5	6	7	8	9	10
10. If you have pain in the **arm**, how strong on average is the pain?											

	(Almost) every day	1-3 days a week	More rarely
11. If you have pain in the arm, how often do you have this pain?			

PATIENT FORM – QUESTIONNAIRE, page 2

Patient ID	Day	Month	Year	No.

Questions regarding sensory disturbances or discomfort

	No	Yes
12. Do you have sensory disturbances or discomfort in the area of the breast, armpit, side of the body or the arm on the side where you had surgery? If "No", please proceed to question 14.		
13. If "Yes", where do you have sensory disturbances or discomfort?		
Area of the breast		
The side of the body		
Armpit		
Arm		

Questions regarding swelling and heaviness (lymphedema)

	No	Yes
14. Does the armpit, the arm or the back of the hand, on the side where you had surgery, sometimes or always feel swollen or heavy? If "No", please proceed to question 19.		
15. If "Yes", where do you feel the armpit, arm or back of the hand is swollen or heavy?		
Back of the hand		
Forearm		
Upper arm		
Armpit		

	0	1	2	3	4	5	6	7	8	9	10
16. How severe are the swellings/sensation of heaviness of your armpit and/or upper arm? (0 is no swellings/sensation of heaviness and 10 is the worst imaginable swellings/sensation of heaviness)											
17. How severe are the swellings/sensation of heaviness of your forearm and/or back of your hand?											

	(Almost) every day	1-3 days a week	More rarely
18. How often does the swellings/sensation of heaviness occur?			

Questions regarding restriction of function

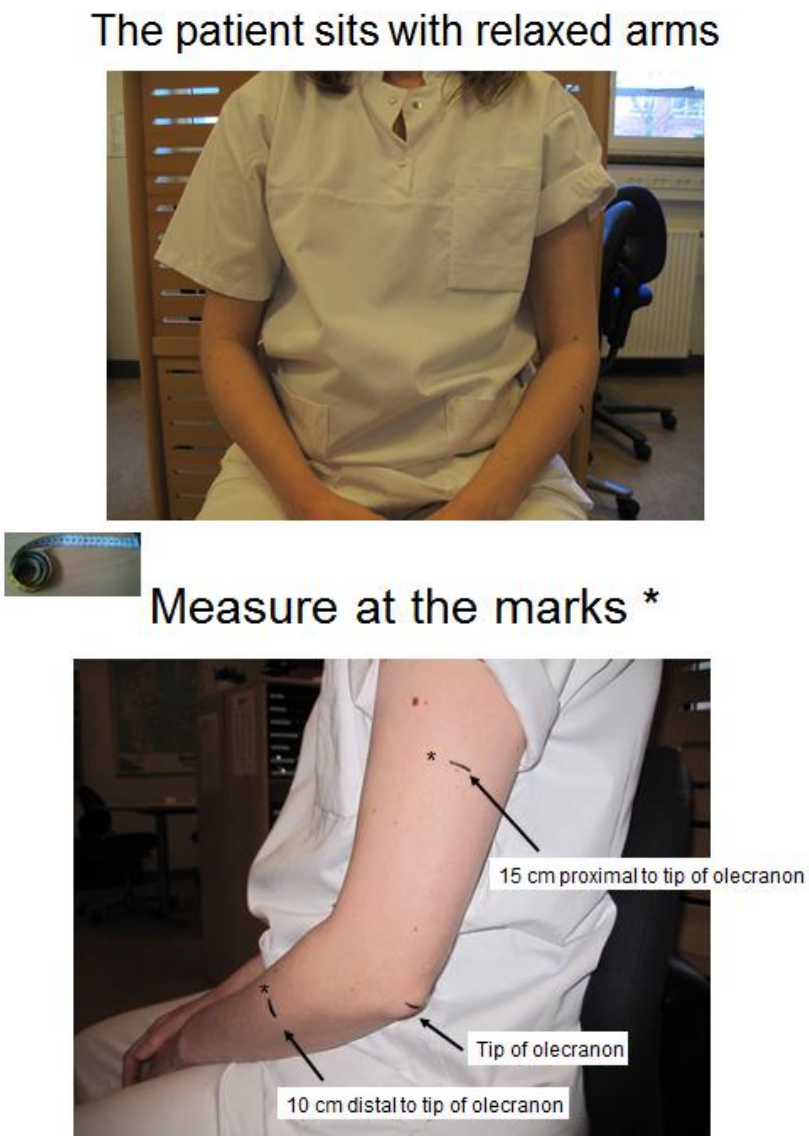
How do you manage the following activities compared with before your treatment for breast cancer?
(Select "Not relevant" for activities you do not perform.)

	The same way as before	The same way as before, but with difficulties/slower and/or more tired afterwards	The same way as before, but with more pain afterwards	In another way than before, for example using the other arm/both hands	Not relevant
19. Washing hair					
20. Brushing teeth					
21. Taking a bra off/on					
22. Carrying shopping bags					
23. Lifting above the height of shoulders					
24. Cleaning floors					

Appendix 8: Guide for measurement of arm lymphedema

Definition of arm lymphedema:
Edema is present if there is minimum 10% increased circumference on the arm measured 15 cm proximal and/or 10 cm distal of the olecranon on the operated side from baseline, compared to the contralateral side. The absolute measure-ments on the arms are reported (i.e. no subtraction is done in reporting of data).





All PIs will be trained before entering the study during a training workshop.

Each of them will responsible of the training of his team.

In case of PI change, new training workshop will be proposed except if he/she is already trained.

Appendix 9: Guide for Range of Shoulder Motion Assessment

Definition of ROM: Range of shoulder motion is measured at active abduction and active flexion bilaterally. An imaginary line in the middle of the upper arm is projected on the circular scale, and the number of degrees is reported. Absolute values are reported separately for each arm. A difference -25 grades defines decreased ROM (Oslo).

Photo of scale



Wall paper scale will be provided by Unicancer to each investigating center



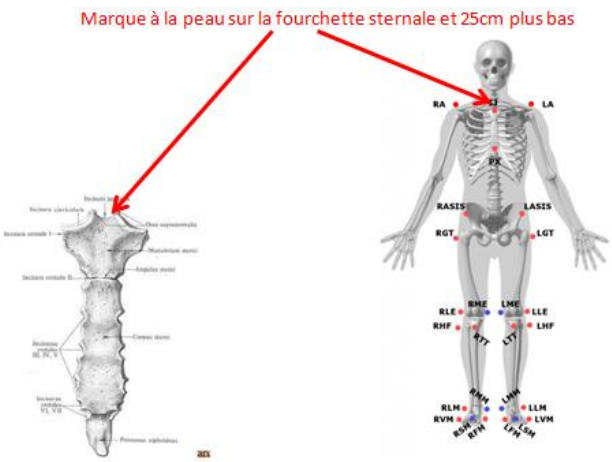
Abduction: lift of the arm laterally up to the ears



Flexion: lift of the arm anteriorly up to the ears

Appendix 10: Guide for documentary Photos of both breasts for cosmetic assessment

The identification of the patient must be legible on the photograph (center number, randomization number, initials) and the date of shooting.



The identification tag must be white to be used for color balance for the software BCCT.Core.

Two marks must be made on the patient, one at the suprasternal notch, one at 25 cm lower. It will be used as benchmark by the software

The face of the patient will not appear on the photograph.

The pictures must be taken as follow:
- Bare-chested.
- Standing in front of uniform backdrop (wall for example).
- Frontal view with arms down (M1)
- Frontal view with arms up (M2)
- Lateral view treated side with arms up (M3)







All pictures will be saved on a dedicated platform.

Appendix 11: Late Radiation Morbidity Scoring according to the RTOG/EORTC and LENT-SOMA

A. Acute radiation dermatitis

	Common terminology criteria for radiation dermatitis
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
3	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion
4	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site
5	Death

B. Late toxicity scoring according to the RTOG/EORTC and LENT/SOMA*

	Grade 1	Grade 2	Grade 3	Grade 4
RTOG/EORTC				
Skin	Slight atrophy, pigmentation change, some hair loss	Patchy atrophy, moderate telangiectasia, total hair loss	Marked atrophy, gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis), and loss of subcutaneous fat	Moderate fibrosis, but asymptomatic; slight field contracture, ≤10% linear reduction	Severe induration and loss of subcutaneous tissue, field contracture, ≥10% linear reduction	Necrosis
LENT/SOMA – BREAST SUBJECTIVE				
Pain	Occasional and minimal hypersensation, pruritus	Intermittent and tolerable	Persistent and intense	Refractory, excruciating
LENT/SOMA – BREAST OBJECTIVE				
Telangiectasia	$<1\ cm^2$	$1–4\ cm^2$	$>4\ cm^2$	
Fibrosis	Barely palpable, increased density	Definite increased intensity and firmness	Very marked density, retraction, and fixation	
Edema	Asymptomatic	Symptomatic	Secondary dysfunction	
Retraction, atrophy	10–25%	>25–40%	>40–75%	Whole breast
LENT/SOMA – SKIN				
Pigmentation change	Transitory, slight	Permanent, marked	–	–

RTOG, Radiation Therapy Oncology Group; EORT, European Organization for Research and Treatment of Cancer; LENT/SOMA, late effects of normal tissue task force; SOMA, subjective, objective, management and analytic.

**Hoeller et al. (2003).*

RTOG/EORTC Late Radiation Morbidity Scoring Schema

ORGAN TISSUE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
SKIN	None	Slight atrophy /Pigmentation change/Some hair loss	Patch atrophy/ Moderate telangiectasia/ Total hair loss	Marked atrophy/ Gross telangiectasia	Ulceration
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture; >10% linear measurement	Necrosis
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia
LARYNX	None	Hoarseness/Slight arytenoid edema	Moderate arytenoid edema/Chondritis	Severe edema/ Severe Chondritis	Necrosis
LUNG	None	Asymptomatic or mild symptoms (dry cough)/Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough)/ Low Grade Fever/Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis/Dense radiographic changes	Severe respiratory insufficiency/ Continuous O2/ Assisted ventilation
HEART	None	Asymptomatic or mild symptoms/Transient T wave inversion & ST changes/Sinus tachycardia >110 (at rest)	Moderate angina on effort/Mild pericarditis/Normal heart size/Persistent abnormal T wave and ST changes/Low ORS	Severe angina/Pericardial effusion/Constrictive pericarditis/Moderate heart failure/Cardiac enlargement/EKG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis
ESOPHAGUS	None	Mild fibrosis/Slight difficulty in swallowing solids/No pain on swallowing	Unable to take solid food normally/Swallowing semi-solid food/Dilatation may be indicated	Severe fibrosis/Able to swallow only liquids/May have pain on swallowing/Dilation required	Necrosis/ Perforation/Fistula
BONE	None	Asymptomatic/No growth retardation/Reduced bone density	Moderate pain or tenderness/Growth retardation/Irregular bone sclerosis	Severe pain or tenderness/Complete arrest of bone growth/Dense bone sclerosis	Necrosis/ Spontaneous fracture
JOINT	None	Mild joint stiffness/Slight limitation of movement	Moderate stiffness/Intermittent or moderate joint pain/Moderate limitation of movement	Severe joint stiffness/Pain with severe limitation of movement	Necrosis/ Complete fixation

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Appendix 12: Harris 4-point Scale

Score	Criteria
Excellent	Treated breast nearly identical to untreated breast
Good	Treated breast slightly different from untreated breast
Fair	Treated breast clearly different from untreated breast but not seriously distorted
Poor	Treated breast seriously distorted

Score	Critères
Excellent	aucune différence avec le sein controlatéral.
Satisfaisant	légères différences
Médiocre	différences marquées.
Mauvais	déformation importante du sein traité.

Référence : Harris JR, Levene MB, Svensson G, Hellman S. Analysis of cosmetic results following primary radiation therapy for Stages I and II carcinoma of the breast. Int J Radiat Oncol Biol Phys 5:257-261, 1979

Appendix 13: BED according to different radiotherapy Regimens and alpha/beta Ratios

Standard boost	α/β 2	α/β 3	α/β 4	α/β 5
50/25	100	83,33	75	70
40/15	93,4	75,6	66,7	61,36
66/33	132	110	99	92,4
40/15+16/8	93,4+32=125,4	75,6+26,67=102,27	66,7+24=90,7	61,36+22,4=83,76

All calculations are based on Biological Equivalent Dose, BED. All values are in Gray (Gy).
Formula: BED= D (1 + d/(α/β))

Randomization arm 50Gy / 25 fractions combined with boost

Regime SIB	α/β 2	α/β 3	α/β 4	α/β 5
16 Gy boost				
66/33	132	110	99	92,4
58,8/28 (2,1)	120,54	99,96	89,67	83,50
61,6/28 (2,2)	129,36	106,77	95,48	88,70
63/28 (2,25)	133,88	110,25	98,44	91,35
50/25	100	83,33	75	70
50,96/28 (1,82)	97,33	81,88	74,15	69,51
51,24/28 (1,83)	98,12	82,50	74,68	69,99
51,52/28 (1,84)	98,92	83,12	75,22	70,48

All calculations are based on Biological Equivalent Dose, BED. All values are in Gray (Gy).
Formula: BED= D (1 + d/(α/β))
In green, the standard regime, in red, the regime with BED closest to the standard regime

Randomization arm 40Gy / 15 fractions combined with boost

RegimeSIB	α/β 2	α/β 3	α/β 4	α/β 5
16Gyboost				
40/15+16/8	93,4+32=125,4	75,6+26,67=102,27	66,7+24=90,7	61,36+22,4=83,76
50,4/18(2,8)	120,96	97,44	85,68	78,62
51,3/18 (2,85)	124,4	100,04	87,85	80,54
52,2/18(2,9)	127,89	102,66	90,05	82,48
43,2/18(2,4)	95,04	77,76	69,12	63,94
41,4/18(2,3)	89,01	73,14	65,21	60,44
42,3/18 (2,35)	92,0	75,43	67,15	62,18

All calculations are based on Biological Equivalent Dose, BED. All values are in Gray (Gy).
Formula: BED= D (1 + d/(α/β))
In green, the standard regime, in red, the regime with BED closest to the standard regime

Appendix 14: Transport and Sick Leaves Questionnaire

ETUDE HYPOG-01 – QUESTIONNAIRE PATIENTE

A remplir dans le mois qui suit la fin de la radiothérapie

A remplir par l'attaché de recherche clinique

Numéro centre |___|___| Numéro patient |___|___|___| Nom |___|___|___| Prénom |___|___|

Date de remise du questionnaire |___|___| |___|___| |___|___|___|___|

Vos modes de transport au cours de la radiothérapie

Les informations suivantes portent sur les modes de transport que vous avez utilisés pour vous rendre à l'hôpital dans lequel vous avez fait votre radiothérapie pour votre cancer du sein.

Quel mode de transport avez-vous utilisé, le plus souvent, pour venir en radiothérapie :

☐ Ambulance
☐ VSL
☐ Taxi
☐ Véhicule personnel
☐ Train
☐ Transport en commun (Bus, tram, métro, RER), Préciser : ……..

Merci d'indiquer le code postal de la commune de votre résidence : |__|__| |__|__|__|

Merci d'indiquer le code postal de la commune de l'hôpital : |__|__| |__|__|__|

Avez-vous demandé un remboursement par la sécurité sociale pour vos frais transports pour venir en radiothérapie ? Oui ☐ non ☐

Votre situation professionnelle

Quelle est votre situation vis-à-vis de l'emploi actuellement ?

☐ En activité et occupant un emploi rémunéré,

profession

☐ En activité et actuellement demandeur d'emploi,

profession

☐ A la retraite

☐ Sans activité professionnelle (mère au foyer, invalidité…)

☐ Etudiant

☐ Autre,

précisez :

Etiez-vous en arrêt de travail pour votre cancer du sein pendant la radiothérapie ?

Oui ☐ Non ☐

Si oui, préciser les dates d'arrêt et de reprise du travail pour vos différents arrêts de travail depuis le début de la radiothérapie :

	Date de début de l'arrêt de travail	Date de reprise du travail
Arrêt 1	|__|__| |__|__| |__|__|__|__|	|__|__| |__|__| |__|__|__|__| Toujours en arrêt ☐
Arrêt 2	|__|__| |__|__| |__|__|__|__|	|__|__| |__|__| |__|__|__|__| Toujours en arrêt ☐
Arrêt 3	|__|__| |__|__| |__|__|__|__|	|__|__| |__|__| |__|__|__|__|

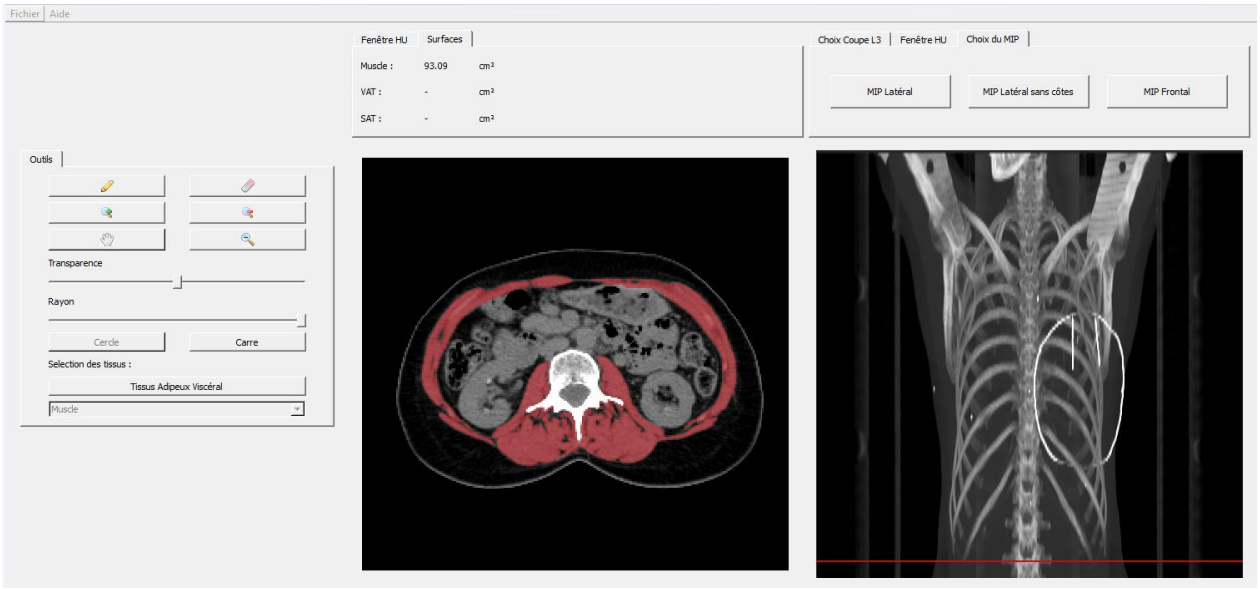
		Toujours en arrêt ☐

Appendix 15: Sarcopenia Assessment

The Sarcopenia assessment will be evaluated with a home made software developed by LITIS-QUANTIF group. An expert reader will localize the L3 CT slice and segment the squeletal muscle tissue, abdominal visceral adipose tissue, subcutaneous tissue, intramuscular adipose tissue. The size of the patient has to be entered manually in the software.

As a result, the software will compute some indexes characterizing sarcopenia:

- SMI (cm^2/m^2): Skeletal Muscle Index expressed as the surface of skletal muscle tissue (cm^2) normalized to stature (size of patient)^2 (in m^2)
- FMI: Fat Mass Index (kg/m2)
- FMR: total Fat to muscle ratio
- FFMI: Fat Free Mass Index (kg/m2)
- SMA: Skeletal Muscle attenuation (HU)
- IMATI: IntraMuscular Adipose tissue Index (cm2/m2)



Example of SMI assessment