EORTC protocol 10981-22023

**AMAROS: After mapping of the axilla: radiotherapy or surgery**

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The contents of this plan are confidential.

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PURPOSE

This document contains a description of how the final analysis for the EORTC Phase III study 10981 will be performed. All abstracts, presentations and publications for the primary results will be based on the analyses described here. This document is to be used in conjunction with the protocol which contains a detailed description of the clinical aspects of this study, the EORTC standard operating procedure (ST-005-SOP version 1.02 entitled ‘Statistical Analyses’), working instructions (ST-005-WIN-01 version 1.00 entitled ‘Statistical Inference’) and the data validation and update plan (UVP).

Note: suggested ‘rules’ in case of inconsistency for some variables result out of the cleaning work that was done together with CRP and data managers and should be seen as a last resort type of measure for those few patients with remaining inconsistencies at the time of lock.

ABBREVIATIONS

SN: sentinel node;
SNB: sentinel node biopsy;
ALND: axillary lymph node dissection;
AxSN: axillary sentinel node;
ITC: isolated tumor cells / submicrometastases;
RT: radiotherapy;
CTx: chemotherapy;
HTx: hormonal therapy
ax: axillary;
non-ax: non-axillary;
non-SN: non-sentinel node (a non-blue, non-radioactive lymph node that was collected / found during SN procedure);
adj: adjuvant;
trt: treatment

KM: Kaplan-Meier curve
HR: hazard ratio
CI: confidence interval
P: p-value

CONVENTIONS

In the analysis we will use the coding of the variables which is used on the crf (case report form) and in the clinical database unless otherwise specified.

Solid bullets (•) refer to variables that will be reported, circles (o) to categories. Variables in grey are on the crf, but will not be reported.

Three versions of the crf exist. Only variables that exist on the last version have been consistently cleaned. Variables that have been taken off the last version of the CRF (dated April 2008) will not be used for analysis.
1 Statistical considerations

1.1 Sample size and objectives (copied from protocol)

“The main objective of the trial is to show non-inferiority of the radiotherapy group as compared to the axillary lymph node dissection treatment group with respect to axillary recurrence free rate in sentinel node positive patients.

It is assumed that the axillary recurrence free rate in the axillary lymph node dissection treatment group at 5 years equals 98%, and we want to show that the axillary recurrence free rate in the radiotherapy group at 5 years is not less than 96%. With a one sided log-rank test for non-inferiority with alpha=0.05 and beta=0.2, 52 events are needed for which 1394 sentinel node positive patients need to be randomized during an accrual period of 8 years and the accrual period will be followed by a further follow up period of 3 years. Given that only 32.5% of the patient are sentinel node positive, and only 90% of the sentinel node positive patients are treated according to protocol (due to various reasons found out at surgery and pathology), the total number of sentinel node positive patients should be 1549, and another 3217 sentinel node negative patients will be registered so that in total 4766 patients will be registered in the study. The follow-up of 3 years will ensure an average follow-up of 6 to 7 years, and will ensure that we have follow-up data for all patients in the period where axillary recurrence is deemed most probable (first 2 years). If at 3 years post end of accrual, the number of axillary recurrences has not been reached, the primary analysis will nevertheless be performed, and at a later time a follow-up analysis can be performed to confirm it. This procedure ensures an expected power of 80%.

If at 3 years post end of accrual, the number of axillary recurrences has not been reached and is not achievable within a delay of 1 more year, a report will be submitted to the EORTC IDMC, documenting the status of the available information and speed at which it accumulates. The IDMC will then be asked to formulate a recommendation as regards the possible premature publication of the results.

Furthermore, we need to show equivalence for overall survival and axillary recurrence free survival. We assume that overall survival and axillary recurrence free survival in the axillary lymph node dissection treatment group equals 85%. We want to show that the overall survival and axillary recurrence free survival rate in the radiotherapy group at 5 years is not less than 81%, which corresponds to a hazard ratio of 1.3. With a one sided log-rank test for non-inferiority with alpha=0.05 and given the accrual numbers for the axillary recurrence free rate above, the power to reject the null hypothesis that the hazard ratio is larger than 1.3 equals 72%.

All the primary and secondary endpoints will be summarized separately for the group patients that received a mastectomy or a conservative breast surgery (information recorded on Form 7).

1.2 Implementation of clinical cut-off date

The clinical cut-off date for the final analysis is 31st of October 2012.

Follow-up form

’survival status’ section of the form
cleaned/included in the final analysis when the date last known to be alive or date of death ≤ clinical cut-off date.

‘disease status’ & ‘long term complications’ sections of the form

(When the examination date is unknown/missing, the date last known to be alive or date of death on the form is used instead in the below).

When the examination date > clinical cut-off date and the date of documented loco regional progression/recurrence (if reported) ≤ clinical cut-off date:
we clean/include the axillary and/or local recurrence.

When the examination date > clinical cut-off date and the date of documented distant progression/recurrence (if reported) ≤ clinical cut-off date:
We clean/include the distant metastasis and/or second primary and the corresponding site.

When the examination date ≤ clinical cut-off date and the date of documented loco regional or distant progression/recurrence (if reported) ≤ clinical cut-off date:
The entire sections are cleaned/included in the final analysis.

When the examination date ≤ clinical cut-off date and the date of documented loco regional and distant progression/recurrence (if reported) > clinical cut-off date:
Only the section on long term complications is cleaned/included in the final analysis.

Quality of life form: form included when date of the form ≤ clinical cut-off date.

Shoulder function form: form included when date of the shoulder function evaluation ≤ clinical cut-off date.

Serious Adverse Event forms: form included when the date of onset ≤ clinical cut-off date. Table provided by Pharmacovigilance.

All other forms are included.

2 Patient populations

2.1 Patient populations used in the analyses

Due to the complex nature of the trial several patient populations are considered to answer the research questions. They are described below. Each section of this statistical analysis plan will explicitly mention the applicable patient population(s).

Population 1: All enrolled patients
All patients in the study (irrespective of the eligibility, the result of the sentinel node procedure and the received treatment).

Population 2: Axillary Sentinel Node positive patients Intent To Treat (AxSN+ ITT)
The patients for whom the result of the SNB is ‘positive AxSN’ on the evaluation form.
Per protocol, the axillary treatment for these patients is the allocated treatment at randomization.
Note: the protocol asked for completion of the therapy form, adjuvant treatment form, shoulder movement & arm morbidity form and Quality of Life (QoL) form for these patients only.
**Population 3: Sentinel Node Biopsy negative patients (SNB-)**
The patients for whom the result of the SNB is ‘negative’ on the evaluation form.
Per protocol, the axillary treatment for this population is no further axillary treatment.

**Population 4: Axillary Sentinel Node positive patients Per Final Protocol (AxSN+ PFP)**
(population for primary endpoint and time to event endpoints)
As this is formally a non-inferiority study, the primary analysis should be done on the patients deemed to be sufficiently treated as stated in the protocol (as opposed to ITT analysis).
This population is a subgroup of population 2, consisting of the AxSN+ ITT patients where the following groups of patients are excluded:
1. Not eligible (evaluation form, see section 16.1 in the Appendix for details)
2. Non-compliance to the randomized treatment (evaluation form, see section 16.1 in the Appendix for details).
   (‘was the assigned treatment followed?’ is listed as ‘no, both given’ or ‘no, other treatment given’ or ‘no, further treatment was not given’ or ‘unknown’ on the evaluation form)
   Note: this criterion captures all absence of invasive cancer as well.
3. axSN with ITC only
   (Result of the SN biopsy (see section 6.2) is ‘AxSN with ITC only (< 0.2mm’)
4. distant progression and/or second primary that was diagnosed before the start of the randomized axillary treatment.

**NOTE:** in this definition the below conditions do not imply exclusion:
- Clinical multifocal tumor within one quadrant randomized before protocol amendment 4,
- Clinical tumor size > 30mm and ≤ 50mm randomized before protocol amendment 4.
- primary invasive tumor size < 5mm or > 50mm on pathology (size of the largest invasive part for multifocal tumors).
- Multifocal or multicentric tumor on pathology
- Axillary treatment delay (>12 weeks after SNB) for any reason
- AxRT over- or underdosage (see Appendix 14.1 for details).
- Breast conserving surgery not followed by adjuvant RT to the breast.
- Randomized to ALND, ALND performed, but less than 10 lymph nodes removed in total (SNB + ALND)
- Unknown (clinical) tumor size

**NOTE:** in this definition the below conditions imply exclusion:
- Both treatments given (except addition of AxRT to ALND when > 4 positive nodes)

**Population 5: Safety population for the randomized question (AxSN+ Safety)**
(population for shoulder movement & arm/shoulder morbidity)
AxSN+ ITT patients who received at least the randomized treatment. (AxRT done = ‘yes’ when randomized to AxRT and ALND done=‘yes’ when randomized to ALND, see sections 8.3 and 8.2.1).
3 Shoulder movement, arm morbidity and Quality of Life (QoL): windows for target assessment times and compliance

Definitions:

- **Date of SNB** as on form 4/41/42
- **Time on study** (for QoL)
  - If the patient is last known alive or lost to follow up: time from SNB till clinical cut-off date.
  - If the patient died: time from SNB till date of death.
- **Time on study with one affected side** (for the shoulder movement and arm morbidity)
  - If the patient has a bilateral tumor: 0
  - Otherwise, if the patient has a contralateral second primary (progression): time from SNB till date of contralateral second primary (see section 11.1).
  - Otherwise, if the patient is last known alive or lost to follow up: time from SNB till clinical cut-off date.
  - Otherwise, if the patient died: time from SNB till date of death.

Three compliance tables will be produced one for QoL, one for shoulder movement and one for arm morbidity. For each of these three, compliance for a group of patients at a certain time point is defined as the number of valid forms at that time point divided by the number of expected forms at that time point.

Compliance figures will be reported by means of absolute numbers of forms expected, absolute numbers of forms received and the percentage reflecting the ratio.

Compliance for a group of patients at a certain time point $T_i$ is defined as:

$$\text{Compliance}(T_i) = \frac{\text{Valid QoL/Shoulder movement/Arm morbidity forms within } [L_i, U_i]}{\text{QoL/Shoulder movement/Arm morbidity forms expected at } T_i}$$

Where $L_i$ and $U_i$ are the lower and upper bound of the time windows associated with $T_i$.

<table>
<thead>
<tr>
<th>Year</th>
<th>$T_i$</th>
<th>$L_i$</th>
<th>$U_i$</th>
<th>Window length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Date of randomization</td>
<td>Date of randomization–2 months</td>
<td>Date of sentinel node biopsy</td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>SNB + 12 months</td>
<td>SNB + 8 months</td>
<td>SNB + 16 months</td>
<td>8 months</td>
</tr>
<tr>
<td></td>
<td>(QoL only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>SNB + 24 months</td>
<td>SNB + 20 months</td>
<td>SNB + 28 months</td>
<td>8 months</td>
</tr>
<tr>
<td>Year 3</td>
<td>SNB + 36 months</td>
<td>SNB + 30 months</td>
<td>SNB + 42 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Year 5</td>
<td>SNB + 60 months</td>
<td>SNB + 48 months</td>
<td>SNB + 84 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Year 10</td>
<td>SNB + 120 months</td>
<td>SNB + 96 months</td>
<td>SNB + 156 months</td>
<td>60 months</td>
</tr>
</tbody>
</table>

* SNB = date of sentinel node biopsy.
Forms are considered as invalid if:
- the completion date is unknown or it cannot be assigned to a single assessment time point
- Completion date outside of time windows.
- Already a form received during the time window. In the latter case, the form closest to the intended assessment time will be kept.
- For Shoulder movement only:
  At least one of anteversion, retroversion, abduction and adduction measurements missing on one or both sides or not all within the following ranges for both sides:
  - Anteversion: \(0 \leq \cdot \leq 190\)
  - Retroversion: \(0 \leq \cdot \leq 90\)
  - Abduction: \(0 \leq \cdot \leq 190\)
  - Adduction: \(0 \leq \cdot \leq 90\).

Forms are expected at \(T_i\) for each patient that was within the assessment window. I.e. if at least one of the following conditions is met.

- (valid) form received within \(L_i\) and \(U_i\)
- For QoL:
  - Time on study > time from SNB till \(T_i\)
- For shoulder movement and arm morbidity:
  - Time on study with one affected side > time from SNB till \(T_i\)

Characteristics of patients with and without valid data will be compared.

For HRQoL:

- Item compliance (the proportion of cases where the answers could be successfully converted into scales according to the scoring procedure) will be summarized as well.
- Trends over time per dropout pattern will be investigated. Model building will be used in order to investigate whether the compliance mechanism is linked to selected prognostic variables.
- In case overall compliance is deemed too low (<50%), only an exploratory analysis will be performed in lieu of the main analysis.

**Note:** The compliance figures will be discussed with the writing committee prior to proceeding to the analysis. Time points with unacceptable low compliance in either absolute or relative numbers can modified (in terms of time windows), be merged with other assessment times or excluded altogether from the analysis.

### 4 Frequently used tabulations

**All enrolled patients by result of the sentinel node biopsy**

The result of the sentinel node biopsy as defined in section 6.2 in which:
- categories 4-5-7-8 (‘non-Ax SN+’ and ‘non-sentinel node + (non-SN+)’, ‘No SNB result (SNB attempted, SN not identified)’ and ‘No SNB result (other)’) will be merged into the column ‘other’.
The format of these tables is then as follows:

### ALL ENROLLED PATIENTS

<table>
<thead>
<tr>
<th>Result of the Sentinel Node Biopsy</th>
<th>AxSN + macro-metastases (≥ 2mm)</th>
<th>AxSN + micro-metastases (0.2mm ≤ . &lt; 2mm)</th>
<th>AxSN+ ITC Only (&lt; 0.2mm)</th>
<th>SNB -</th>
<th>Other</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Axillary sentinel node positive patients intent to treat (AxSN+ ITT) by randomized treatment**

<table>
<thead>
<tr>
<th>Axillary sentinel node positive patients intent to treat (AxSN+ ITT)</th>
<th>Randomized treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALND</td>
</tr>
<tr>
<td>Variable 1</td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

**Axillary sentinel node positive patients per final protocol (AxSN+ PFP) by treatment received**

<table>
<thead>
<tr>
<th>Axillary sentinel node positive patients per final protocol (AxSN+ PFP)</th>
<th>Treatment received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALND</td>
</tr>
<tr>
<td>Variable 1</td>
<td></td>
</tr>
<tr>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

### 5 Patient Availability

#### 5.1 Accrual

For all enrolled patients the following will be reported:

- A table with accrual, percentage eligible (evaluation form) and percentage ‘Positive AxSN (≥ 0.2mm)’ (see section 6.2) by year.
- A table with the number of patients & eligible patients by institution in descending order of accrual.
5.2 **Follow-up**

Follow-up duration will be estimated by the inverse Kaplan-Meier method (deaths are censored) and will be plotted in three figures:
- For all enrolled patients (one curve).
- For the AxSN+ PFP patients (two curves, one for each treatment arm).
- For all enrolled patients (two curves, one for the AxSN+ ITT patients and one for the other patients) (only follow-up up to 5 years requested for the latter).

Additionally a table will be shown which documents, for those patients last known to be alive, the date of last follow-up form received (compared to the clinical cut-off date), in the AxSN+ PFP population by treatment arm.

5.3 **Eligibility**

Will be reported in two separate tables, for two different populations:
- all enrolled patients by the result of the sentinel node biopsy
- AxSN+ ITT patients by randomized treatment

Eligibility as assessed on the evaluation form (see section 16.1 in the Appendix for details).

- The eligibility status
  - For the ineligible patients:
    - The reason(s) of ineligibility
      - When an ‘other’ reason was included:
        - A listing of the specification of the reason
    - Other important information (only available after SNB, but before start of axillary treatment)

6 **Baseline characteristics**

6.1 **Patient and tumor characteristics**

All variables listed below will be reported in three separate tables, for three different populations:
- all enrolled patients by the result of the sentinel node biopsy
- AxSN+ ITT patients by randomized treatment (Appendix)
- AxSN+ PFP patients by treatment received

- Year of accrual
- Age at accrual
  - o $\leq 40$
  - o $40 < . \leq 50$
  - o $50 < . \leq 65$
  - o $65 < . \leq 75$
  - o $> 75$

And will also be reported as median and range.
- Menopausal status
- Method of diagnosis
  - all combinations will be reported as additional categories.

For the remaining cases reported in the category ‘other’:
- A listing of the other methods of diagnosis
• Side of the tumor
• Tumor location
  o Tumor location includes axillary tail and/or upper outer quadrant
  o Other
  o missing
• Tumor size
  When available form1 (randomization checklist) will be used, otherwise form 2 (on study form).
  o \( \leq 0.5 \) cm
  o \( 0.5 < . \leq 1 \) cm (cT1b)
  o \( 1 < . \leq 2 \) cm (cT1c)
  o \( 2 < . \leq 5 \) cm (cT2)
  o > 5 cm (cT3)
  o missing (cTx)
• Breast examination method
• Ultrasound of the axilla
  The following categories will be reported:
  o not done
  o normal
  o abnormal, metastases
  o abnormal, other
  o missing
  When a result of the axillary ultrasound is specified on the crf, the patients is classified accordingly.
  Otherwise, (re)-classified as ‘missing’ when a date for the axilla ultrasound examination is reported but no result.
  Otherwise, classified as ‘not done’ when it is reported that no ultrasound was done.
  Otherwise, the variable is classified as ‘missing.’
For the cases reported as ‘abnormal other’:
  • A listing of the abnormalities
• Examination performed to exclude metastatic disease
• Tumor on dominant site of patient (yes/no/bilateral/missing)
  We will use the first-reported non-missing value for dominant side on form 6.
  Classified as ‘bilateral’ when side of tumor = ‘bilateral’.
  Classified as ‘yes’, when the side of the tumor = the dominant side of the patient.
  Classified as ‘no’, when the side of the tumor is the other side than the dominant side of the patient.
  Otherwise, classified as ‘missing’.

6.2 Sentinel Node procedure and corresponding pathology
Will be reported for all enrolled patients:
• The result of the sentinel node procedure
  o AxSN macrometastases (\( \geq 2 \)mm)
  o AxSN micrometastases (0.2mm \( \leq . < 2 \)mm)
  o AxSN with ITC only (\( < 0.2 \)mm)
  o Positive non-Ax SN only
Positive non-sentinel node only
Negative
No SNB result (SNB attempted, but SN not identified)
No SNB result (other)

Category 1 ‘AxSN macrometastases ($\geq 2$mm)’ are the patients classified as ‘positive AxSN’ on the evaluation form excluding the following patients:
- Sentinel nodes with ‘ITC only’ or ‘Micro (no macro)’ (see the ‘Type of sentinel node metastases’ variable in section 6.2.3.1)

Category 2 ‘AxSN micrometastases (no macro) (0.2mm $\leq$ $<$ 2mm)’ are the patients classified as ‘positive AxSN’ on the evaluation form excluding the following patients:
- Sentinel nodes with ‘ITC only’ or ‘Macro’ (see the ‘Type of sentinel node metastases’ variable in section 6.2.3.1)

Category 3 ‘AxSN with ITC only ($<$ 0.2mm)’ are the patients classified as ‘positive ITC only’ on the evaluation form and the patients classified as ‘positive AxSN’ on the evaluation form with Sentinel nodes with ‘ITC only’ (see the ‘Type of sentinel node metastases’ variable in section 6.2.3.1)

Categories 4 ‘Positive non-Ax SN’, 5 ‘Positive non-sentinel node’ and 6 ‘Negative’ are the corresponding categories on the evaluation form.

Category 7 ‘No SNB result (SNB attempted, SN not identified)’ corresponds to ‘SNB was attempted, but SN could not be identified’ on the evaluation form.

Category 8 ‘No SNB result (other)’ corresponds to ‘SNB not done/result unknown for other reason’ on the evaluation form.

For the non-axillary sentinel node positive patients (non-Ax SN+):
- A listing of the locations of the non-axillary sentinel node(s)

For patients with no SNB result unknown for another reason:
- A listing of the reasons

When the result of the sentinel nodes biopsy is used to report other variables (in cross-tabulation), categories 3-4 and 6-7 will be merged (see section 4).

All variables of sections 6.2.1, 6.2.2 and 6.2.3 will be reported for all enrolled patients (unless specified otherwise) by the result of the sentinel node biopsy.

6.2.1 Lymphoscintigraphy of the SNB

- Lymphoscintigraphy done or attempted (yes/no or unknown). (calculated variable)
  Classified as ‘yes’ when at least one of the non-textbox variables of the lymphoscintigraphy section of the last version of form4 (apart from the date) is not
missing/unknown OR when for one of the four sentinel nodes on form 4 method of detections = ‘radioactive’ or ‘both’. Otherwise, classified as ‘no or unknown’.

The following variables will only be reported for patients classified as ‘yes’:

- Injection site (of radioactive tracer)
  all combinations will be reported as additional categories.
  The remaining cases reported in the category ‘combination’ will be reported as ‘other’, and for these cases:
  - A listing of the other injection sites

- Number of possible sentinel nodes
  o 0
  o 1-3
  o 4-6
  o >6
  o Missing

- Number of hot spots
  o 0
  o 1-3
  o 4-6
  o >6
  o Missing

- Location of hot spots
  all combinations will be reported as additional categories.
  The remaining cases reported in the category ‘combination’ will be reported as ‘other’, and for these cases:
  - A listing of the other locations

6.2.2 Surgical procedure of the SNB

- SNB (surgical procedure) done (yes/no or unknown). (calculated variable)
  Classified as ‘yes’ when at least one of the non-textbox variables of the surgical procedure section of the last version of form 4 (apart from the date) is not missing/unknown OR when the result of the sentinel nodes biopsy is different from ‘SNB not done/result unknown for other reason’ on the evaluation form. Otherwise, classified as ‘no/unknown’.

The following variables will only be reported for patients classified as ‘yes’:

- Use of blue dye
  Re-classified as ‘yes’ when the use of blue dye is missing or ‘no’, but type of blue dye or the location/injection site is specified.

When blue dye is used:
  - Type of blue dye, volume of blue dye and type of probe
    no longer requested on the last version of the crf and will not be reported.
• Injection site (of blue dye)
  all combinations will be reported as additional categories.
  The remaining cases reported in the category ‘combination’ will be reported
  as ‘other’, and for these cases:
  • A listing of the other injection sites

• Number of sentinel nodes removed
  o 0
  o 1-3
  o 4-6
  o >6
  o Missing

• Method and location for each removed sentinel nodes
  will not be reported. The location is summarized in the calculated variable
  below.

• Location of the removed sentinel nodes
  o Axillary only and/or missing/unknown location(s)
  o At least one extra-axillar, including at least one IMC node
  o At least one extra-axillar and not including any IMC nodes

• Number of non-radioactive and non-blue lymph nodes removed
  o 0
  o 1-3
  o 4-6
  o >6
  o Missing

6.2.3 Pathology of the SNB

The variables in section 6.2.3 will only be reported for patients for whom the surgical part
of the SNB procedure was done (see section 6.2.2)

6.2.3.1 Sentinel nodes

• Number of sentinel nodes examined
  o 0
  o 1-3
  o 4-6
  o >6
  o Missing

• Number of sentinel nodes with macrometastases
  o 0
  o 1-3
  o 4-6
  o >6
  o Missing
Classified as ‘missing’ when form 5 is missing or the number of examined sentinel nodes is missing/unknown. Otherwise, the variable counts the number of sentinel nodes positive by frozen section or H&E or IHC, and for which micrometastases is different from ‘yes’ and for which ITC is different from ‘cluster’ and ‘single cells’.

- Number of sentinel nodes with micrometastases
  - 0
  - 1-3
  - 4-6
  - >6
  - Missing

Classified as ‘missing’ when form 5 is missing or the number of examined sentinel nodes is missing/unknown. Otherwise, the variable counts the number of sentinel nodes positive by frozen section or H&E or IHC, and for which micrometastases equals ‘yes’.

- Number of sentinel nodes with ITC only
  - 0
  - 1-3
  - 4-6
  - >6
  - Missing

Classified as ‘missing’ when form 5 is missing or the number of examined sentinel nodes is missing/unknown. Otherwise, the variable counts the number of sentinel nodes positive by frozen section or H&E or IHC, and for which micrometastases is different from ‘yes’ and for which ITC equals ‘cluster’ or ‘single cells’.

- Number of positive sentinel nodes (excl. ITC only):
  - 0
  - 1-3
  - 4-6
  - >6
  - Missing

Sum of the number of sentinel nodes with macrometastases and micrometastases.

- Number of positive sentinel nodes (incl. ITC only):
  - 0
  - 1-3
  - 4-6
  - >6
  - Missing

Sum of the number of sentinel nodes with macrometastases, micrometastases and ITC only.

- Type of sentinel node metastases
  - Macro
  - Micro (no macro)
  - ITC only (no macro, no micro)
- No positive sentinel nodes
- Missing

Classified as ‘macro’ when at least one SN with macrometastases
Classified as ‘micro (no macro)’ when no SN with macrometastases but at least one SN with micrometastases
Classified as ‘ITC only (no macro, no micro)’ when no SN with macro- or micrometastases but at least one SN with ITC.
Classified as ‘no positive sentinel nodes’, when number of positive sentinel nodes (incl. ITC only) = 0.
Otherwise, classified as ‘missing’.

6.2.3.2 Non-Sentinel nodes

- Number of non-blue and non-radioactive nodes removed
  - 0
  - 1-3
  - 4-6
  - >6
  - Missing

- Number of tumor positive non blue and non-radioactive nodes
  - 0
  - 1-3
  - 4-6
  - >6
  - Missing

6.2.3.3 Calculated variables

- Number of nodes removed during SN biopsy:
  - 0
  - 1-3
  - 4-6
  - >6
  - missing

Sum of the Number of non-blue and non-radioactive nodes removed and the Number of sentinel nodes examined. When one of the summed variables is ‘missing’, the sum of the non-missing variables is taken.

- Number nodes removed during SNB that are tumor positive (excl. ITC only)
  - 0
  - 1-3
  - 4-6
  - >6
  - Missing

Sum of the Number of sentinel nodes with macrometastases, the Number of sentinel nodes with micrometastases and the Number of positive non blue and non-radioactive nodes. When one/some of the summed variables is/are missing/unknown, the sum of the non-missing variables is taken.
• Method SNB
  o Lymphoscintigraphy + blue dye
  o Only Lymphoscintigraphy
  o Only Blue dye
  o Unknown
  Unknown when either blue dye or lymphoscintigraphy or both is/are ‘no or unknown’.

7 Compliance to the protocol

7.1 Compliance to treatment allocation

For AxSN+ ITT patients by randomized treatment:
  • Was the assigned treatment followed? (as per evaluation form)
    For whom the assigned treatment was not followed:
      • Reason for non-compliance
        all combinations will be reported as additional categories.
        For the remaining cases reported as ‘other’:
          • A listing of the other reasons

For SNB- patients:
  • Further axillary treatment given to SNB- patients
    o None
    o Yes, (at least) ALND done
    o Yes, (at least) AxRT done
    o Yes, both done
    o Missing

Based on ALND done (see section 8.2.1) and AxRT done (see section 8.3). Classified as ‘missing’ when ALND or AxRT is missing and the other is not done or also missing.
Classified as ‘Yes, (at least) xxxx done’, when ALND or AxRT is missing or not done and the other is done.
Classified as ‘No’ when both ALND and AxRT not done. Classified as ‘Yes, both done’ when both ALND and AxRT done.
Note that the therapy form (form7) is not due for these patients, thus missing data are to be expected.

7.2 Other protocol treatment violation

All variables of section 7.2 will be reported in two separate tables, for two different populations:
  - AxSN+ ITT patients by randomized treatment (Appendix)
  - AxSN+ PFP patients by treatment received

For whom the assigned treatment was followed (see section 7.1):
  • Other severe protocol violation concerning axillary treatment? (evaluation form)
    all combinations will be reported as additional categories.
    For the remaining cases reported as ‘other’
7.3 Other

All variables of section 7.3 will be reported in three separate tables, for three different populations:
- all enrolled patients by the result of the sentinel node biopsy
- AxSN+ ITT patients by randomized treatment (in Appendix)
- AxSN+ PFP patients by treatment received

- SNB done before enrollment but result unknown at enrollment (evaluation form)
- Undertreatment of primary tumor: breast-sparing procedure without radiotherapy to the breast
  - Yes
  - No
  - Missing
Based on the type of primary tumor surgery (see section 8.1.1), RT to the breast/chest wall (see section 8.4.1) and absence of invasive cancer on pathology (evaluation form).
  Classified as ‘No’ when absence of invasive cancer on pathology.
  Otherwise, classified as ‘Missing’ when type of primary tumor surgery or RT to the breast/chest wall is missing.
  Otherwise, classified as ‘yes’ when a breast-conserving procedure and no RT to the breast/chest wall. Otherwise, classified as ‘No’.

Note that the therapy form (form7) and adjuvant treatment form (form8) only due for AxSN+ ITT patients, thus missing data are to be expected.

- Timing of primary tumor surgery.
  - ≤ 2 months after diagnosis
  - > 2 months after diagnosis, but ≤ 2 months after enrollment
  - > 2 months after diagnosis & enrollment, without neoadjuvant s.t.
  - > 2 months after diagnosis & enrollment, but neoadjuvant systemic therapy
  - missing
Based on the difference in the date of histologic and/or cytological diagnosis (form2) and date of surgery of primary tumor (form7).
  Classified as ‘missing’ when one of the two dates is missing. Neoadjuvant systemic therapy will be implemented as neoadjuvant CTx, hormonal or other anticancer treatment received (see section 8.4).
  Note that the therapy form (form7) is only due for AxSN+ ITT patients, thus missing data are to be expected.

- More than 5 nodes removed during SNB.
  Based on ‘Number of nodes removed during SN biopsy’ (section 6.2.3.36.2.3.1)

8 Exposure to treatment

All variables of section 8 will be reported in three separate tables, for three different populations:
- all enrolled patients by the result of the sentinel node biopsy *
- AxSN+ ITT patients by randomized treatment (Appendix)
- AxSN+ PFP patients by treatment received

* Form7 (therapy form) and 8 (adjuvant treatment form) were only requested for the axSN+ ITT patients. For ≈ 40% of patients for whom these forms were not due, they were received nevertheless. Therefore this table will include
only those non-(axSN+ ITT) patients for whom the corresponding form is received. All axSN+ITT patients are included regardless of whether we received the form or not.

8.1 Surgery to the Primary Tumor and corresponding pathology

8.1.1 Surgery to the Primary Tumor

- Type of surgery to the primary tumor
  - Mastectomy
  - Breast-conserving procedure
  - Other
  - Missing

Classified as ‘breast-conserving procedure’ when a tumorectomy, wide local excision, quadrectomy or a combination involving only the latter is specified.
Classified as ‘mastectomy’ when a mastectomy or a combination with a mastectomy was specified.
Otherwise, classified in the ‘breast-conserving procedure’ when another type of breast conserving procedure was identified by the study monitor (see UVP).

For the remaining cases reported as ‘other’:
  - a listing of the types

- Reconstruction of the breast
  Was no longer requested on the last form of the crf and will not be reported.

8.1.2 Pathology of the Primary Tumor

- Multifocality

- Size of the largest invasive part (maximal diameter) will be classified as follows:
  - Absence of invasive cancer on pathology
  - $\leq 0.5$ cm
  - $0.5 < . \leq 1$ cm (pT1b)
  - $1 < . \leq 2$ cm (pT1c)
  - $2 < . \leq 5$ cm (pT2)
  - $> 5$ cm (pT3)
  - missing (pT$x$)

Classified as ‘absence of invasive cancer on pathology’, when listed as such on the evaluation form.
Otherwise, for the first version of the crf only:
  Size of the largest invasive part was requested in an additional variable (box55) for multifocal tumors. If there is a multifocal tumor, box55 is used. If it missing, box46 (size of the invasive part) is taken.

- Surgical margins/minimal distance between tumor and margin
  No longer requested in last version of the crf and will not be reported.

- Histological type
  - invasive ductal
  - invasive lobular
  - other
o absence of invasive cancer on pathology
o missing
‘absence of invasive cancer on pathology’ as on the evaluation form.

For the first version of the crf only:
Two additional categories were included (‘medular’ and ‘tubular’). These patients will be re-classified into ‘other’ and ‘medular’ and ‘tubular’ will be put in the listing of the other type.

For the cases classified as ‘other’:
• A listing of the other histological types

For the cases classified as ‘absence of invasive cancer’:
• A listing of the histological types

• B&R grade
• Clear margins
No longer requested in the last version of the crf and will not be reported.
• ER/PgR staining
No longer requested in the last version of the crf and will not be reported.

8.2 Axillary lymph node dissection

8.2.1 Treatment received and pathology

• ALND done (yes/no/Missing)
  Classified as ‘yes’ when the type of ALND (form7) is either ‘level I+II’ or ‘level I+II+III’.
  Otherwise, classified as ‘no’ when the type of ALND is ‘SN biopsy only’.
  Otherwise, classified as ‘yes’ when ALND reported as done on form 5.
  Otherwise, classified as ‘no’ when ALND reported as not done on form 5.
  Otherwise, classified as ‘no’ when compliance to randomized treatment=‘no further treatment’ on evaluation form.
  Otherwise, classified as ‘missing.’
Note that sometimes level I ALND was communicated. These have been classified as ‘SN biopsy only’ on form7 during the cleaning (see also UVP).

For those patients who had an ALND:
• Type of ALND
  o Level I+II
  o Level I+II+III
  o ALND done, level unknown
  Classified as ‘ALND done, level unknown’ when type (form7) does not equal ‘level I+II’ or ‘level I+II+III’ or form7 is not received.
• Whether or not a drain was used, for how many days and the total production was no longer requested in the last version of the crf and will not be reported.
• Number of nodes in ALND specimen (pathology)
  o 0 nodes
  o 1-3 nodes
  o 4-9 nodes
• Number of positive nodes in ALND specimen (pathology)
  o No further nodal involvement (0)
  o 1-3 nodes
  o 4-9 nodes
  o > 9 nodes
  o Missing

• Number of positive non-sentinel nodes (ALND specimen + SNB) (pathology)
  o No further nodal involvement (0)
  o 1-3 nodes
  o 4-9 nodes
  o > 9 nodes
  o Missing

Sum of the Number of positive nodes in ALND specimen and Number of tumor positive non-blue and non-radioactive nodes (see section 6.2.3.2). Classified as ‘Missing’ when one of the two variables or both is/are missing.

8.2.2 Cross tables & calculated variables

For those patients who had an ALND:

• Total number of nodes removed (SNB+ALND) (pathology)
  o 0
  o 1-3 nodes
  o 4-9 nodes
  o > 9 nodes
  o Missing

Sum of the number of nodes in ALND specimen and the number of nodes removed during SN biopsy (see section 6.2.3.3). Classified as ‘missing’ when one of the summed variables is missing.

• Total number of positive nodes (SNB+ALND) (pathology) (Excl. ITC only)
  o 0
  o 1-3 nodes
  o 4-9 nodes
  o > 9 nodes
  o Missing

Sum of the Number of positive nodes in ALND specimen (see section 8.2.1) and the number of nodes removed during SN biopsy that are tumor positive (excl. ITC only) (see section 6.2.3.3). Classified as ‘missing’ when one of the summed variables is missing.

- Cross table: Number of positive nodes (in ALND specimen) (see section 8.2.1) versus the type of sentinel node metastases (see section 6.2.3.1).

8.3 Axillary Radiotherapy

• Axillary Radiotherapy done (yes/no/missing)
  Classified as ‘yes’ when the start date or end date or number of fractions or dose per fractions is specified. Classified as ‘yes’ for patient 2497 (it was communicated by the investigator that
received AxRT, however no info was provided on form 7). Otherwise, classified as ‘no’ if form 7 is received or compliance to randomized treatment = ‘no further treatment received’ on the evaluation form. Otherwise, classified as missing.

For those patients who had an AxRT:

- Number of fractions & dose per fraction
  all specified combinations are reported
- Total dose received
- Duration of Axillary RT

8.4 (neo-)Adjuvant treatment (other than therapy to the axilla)

8.4.1 Adjuvant radiotherapy (other than RT to the axilla)

- Adjuvant radiotherapy to the breast/chest wall, combined with type of surgery
  - Mastectomy
  - Breast conserving procedure + RT
    - + boost
    - no boost
  - Mastectomy +RT
    - + boost
    - no boost
  - Breast conserving procedure
  - Missing

Classified as ‘missing’ when type of surgery to the primary tumor (see section 8.1.1) is missing. Otherwise,
- RT = ‘yes’ when the radiotherapy field equals ‘breast’, ‘chest wall’ or ‘boost’ or the field equals ‘other’ and ‘chest wall’ or ‘breast’ specified in a combination.
  Otherwise, RT = ‘no’ when the radiotherapy field equals ‘other’, or any adjuvant treatment or adjuvant radiotherapy is listed as ‘no’.
- Boost = ‘yes’ when the radiotherapy field equals ‘boost’ or field equals ‘other’ and ‘boost’ specified in a combination.
  Otherwise, boost = ‘no’ when the radiotherapy field equals ‘other’, or any adjuvant treatment or adjuvant radiotherapy is listed as ‘no’.

Combinations with type of surgery are formed accordingly. Otherwise or if form8 is missing, classified as ‘missing’.

- Adjuvant radiotherapy to the internal mammary chain
- Adjuvant supraclavicular radiotherapy (apart from protocol RT to the axilla)
  Supraclavicular RT is part of protocol RT to the axilla. In case the patient received RT to the axilla (see section 8.3), this variable is re-classified as ‘no’, irrespective of what was reported on form8.
- Adjuvant radiotherapy to another field (Yes/No/missing)
Classified as ‘yes’ when the radiotherapy field equals ‘other’ and another field (different from the ones above) is specified (see UVP).
Otherwise, classified as ‘no’ when the radiotherapy field is specified.
Otherwise, classified as ‘no’ when any adjuvant treatment or adjuvant radiotherapy is listed as ‘no’.
Otherwise or if form8 is missing, classified as ‘missing’.
When adjuvant RT to another field:

- A listing of the fields

- Any adjuvant radiotherapy (apart from axilla RT) (Yes/No/missing)
  Classified as ‘yes’ if at least one of the first 5 variables of this section equals ‘yes’.
  Classified as ‘no’ if all five equal ‘no’.
  Otherwise, classified as ‘missing’.

When any adjuvant radiotherapy:

- Radiation quality

  For the cases classified as ‘other’

  - A listing of the other radiation quality

  - Total number of fractions and dose per fraction

  Will not be reported since it is not clear from the crf to which field these variables correspond. Has also not been cleaned.

8.4.2 (neo-) Adjuvant chemotherapy

- (Neo-) adjuvant chemotherapy
  o Yes, adjuvant
  o Yes, neoadjuvant
  o No
  o missing

Classified as ‘yes, neoadjuvant’ when the start date, end date or CTx regimen is specified and the start date < date of surgery to the primary tumor. Or when neoadjuvant systemic treatment is reported on the evaluation form and ‘chemo’ noted in the other reason for eligibility textbox.
Otherwise, classified as ‘yes, adjuvant’ when the start date, end date or CTx regimen is specified. Otherwise, classified as ‘no’ when any adjuvant treatment or adjuvant chemotherapy is listed as ‘no’. Otherwise, classified as ‘missing’.

When (neo-) adjuvant chemo was given:

- Duration of chemotherapy

- Type of chemotherapy
  o CMF (6x)
  o AC (4x or 6x or 2x)
  o FEC (6x or 5x)
  o CAF (6x or 5x)
  o EPI (4x) + CMF (4x)
  o EC
  o Docetaxel based
8.4.3  
(neo-) Adjuvant hormonotherapy

- (Neo-) adjuvant hormonotherapy
  - Yes, adjuvant
  - Yes, neoadjuvant
  - No
  - Missing

Classified as ‘yes, neoadjuvant’ when the start date or type of HTx is specified and the start date < date of surgery to the primary tumor. Or when neoadjuvant systemic treatment is reported on the evaluation form and ‘hormono’ noted in the other reason for eligibility textbox.

Otherwise, classified as ‘yes, adjuvant’ when the start date or type of HTx therapy is specified. Otherwise, classified as ‘no’ when any adjuvant treatment or adjuvant HTx is listed as ‘no’. Otherwise, classified as ‘missing’

When (neo-)adjuvant hormonotherapy was given:

- Type of hormonotherapy
  - tamoxifen
  - castration
  - aromatase inhibitor (AI)
  - tamoxifen + castration
  - tamoxifen + AI
  - castration + AI
  - tamoxifen + castration + AI
  - unknown

( DM box created based on CRP review, see UVP)

8.4.4  
(neo-) Adjuvant other anticancer regimens

- (Neo-) adjuvant anti HER2 therapy
  - Yes, adjuvant
  - Yes, neoadjuvant
  - No
  - Missing

Classified as ‘yes, neoadjuvant’ when the patient received anti-HER2 therapy (DM box created based on CRP review, see UVP) and the start date < date of surgery to the primary tumor. Otherwise, classified as ‘yes, adjuvant’ when the patient received adjuvant anti-HER2 therapy.
Otherwise, classified as ‘no’ when adjuvant other anticancer therapy is listed as ‘yes’ and the type is specified.
Otherwise, classified as ‘no’ when any adjuvant treatment or adjuvant other anticancer therapy is listed as ‘no’.
Otherwise, classified as ‘missing’.

- Other anti-cancer therapy
  - Yes
  - No
  - Missing

(�M box created based on CRP review, see UVP)
If ‘yes’:
  - A listing of the type

9 Safety evaluations

9.1 Surgery (SNB and/or primary tumor and/or axilla)
The variables in section 9.1 will be reported for all enrolled patients. If the below complication is reported at least once, the variable is coded ‘yes’. Otherwise, coded as ‘no’.

- Post-operative hemorrhage requiring re-operation or drainage
- Post-operative local wound infection requiring antibiotics
- Post-operative wound infection requiring drainage
- Persistent seroma formation
- Early lymph edema of the arm (within 3 months)
- Post-operative death
- Other complication
  If ‘yes’:
    - A listing of the other complications

9.2 Axillary Radiotherapy
The variables in section 9.2 will be reported for AxSN+ Safety patients randomized to AxRT.

- Was radiotherapy interrupted for more than 1 week?
  If ‘Yes, other’:
    - a listing of the other reasons why it was interrupted
- Was radiotherapy definitely stopped before its expected completion?
  If ‘Yes, other’:
    - a listing of the other reasons why it was stopped

9.3 Adjuvant therapy

9.3.1 Radiotherapy toxicity
Will be reported for all enrolled patients who received adjuvant RT (other than axilla RT) (see section 8.4.1)
• Intended treatment completely given?
  If ‘No, other’:
  • a listing of the other reasons why it was not completely given
• Any complications related to the radiotherapy (incl. mild side effects)
  If ‘yes’:
  • a listing of the complication
Note that this variable also includes some complications related to axillary RT (since no such variable on form 7), but this is likely partial information.

9.3.2 Chemotherapy toxicity
Will be reported for all enrolled patients who received adjuvant chemotherapy (see section 8.4.2)
• Intended treatment completely given?
  If ‘No, other’:
  • a listing of the other reasons why it was not completely given

9.4 Arm/shoulder morbidity
The variables in section 9.4 will be reported for AxSN+ safety patients by treatment received. Patients who received both treatments are reported by the randomized treatment. The tumor side on form2 is used to determine which of the reported variables (left/right) corresponds to the side of the primary tumor.

9.4.1 Lymphedema and edema therapies
If the below complication is reported at least once, the variable is coded ‘yes’. Otherwise, coded as ‘no’. Forms dating before the lower boundary of the time window for the 1 year assessment time (see section 3) are excluded.
• Any sign of lymphedema
  The variable on form6 combined with the one on form9.
  (Note that this can include e.g. edema on breast (on form 6, the variable asks for any edema))
• Lymph drainage physiotherapy (yes/no)
  • If yes, the side (operated/’untreated’/both/unknown)
• Compression therapy (yes/no)
  • If yes, the side (operated/’untreated’/both/unknown)
• Elastic stockings (yes/no)
  • If yes, the side (operated/’untreated’/both/unknown)
• Any edema treatment (yes/no)
  (lymph drainage and/or compression and/or elastic stockings)
  • If yes, the side (operated/’untreated’/both/unknown)
• Edema treatment or any sign of edema
  Any sign of lymphedema and/or any edema treatment

These variables will be reported a second and third time, but now for target assessment times 1 year, and 5 years using the time windows as in section 3. In this setting, the variables
are only reported for those patients for whom we have a valid form (see section 3) for that
target assessment time.

9.4.2 Scapula alata

If the below complication is reported at least once, the variable is coded ‘yes’. Otherwise,
coded as ‘no’. Forms dating before the lower boundary of the time window for the 1 year
assessment time (see section 3) are excluded.
- Scapula alata on operated arm
- Scapula alata on other (‘untreated’) arm

9.4.3 Arm circumference

The variables in section 9.4.3 will be reported for assessment times 1 year and 5 years using
the time windows as in section 3. The variables are only reported for those patients for
whom we have a valid form (see section 3). If more than one valid form, the form which
dates the closest to the target is used.

- Relative upper arm circumference of operated vs. ‘untreated’ arm
  - $\leq 0.50$
  - $0.50 < \leq 0.75$
  - $0.75 < \leq 0.90$
  - $0.90 < \leq 1.11$
  - $1.11 < \leq 1.33$
  - $1.33 < \leq 2$
  - $> 2$
  - missing
  (calculated as circumference of upper treated arm divided by that of the upper
  ‘untreated’ arm)
- Relative lower arm circumference of operated vs. ‘untreated’ arm (same categories).
  - Figure (2 curves), showing the average of the log* of the relative circumference (and
    CI) for the upper arm at the 4 target assessment times. One curve for each treatment
    arm.
  - Same figure for the relative circumference of the lower arm.

In the Appendix:
- Figure (2 curves), showing the average circumference (and CI) for the upper operated
  arm at the 4 target assessment times. One curve for each treatment arm.
- Same figure for the lower operated, upper untreated and lower untreated arm.

*The log transform creates an appropriate scale for the average because the data are ratios.

9.5 Shoulder movement

Note: Internal and external rotation will not be reported/used in the analysis. They were deemed
unreliable due the high number (≈50%) of out of range measurements for internal rotation.

The variables in section 9.4 will be reported for AxAxSN+ safety patients by treatment received*
Patients who received both treatments are reported by the randomized treatment. The variables are only reported for those patients for whom a we have a valid form (see section 3). If more than one valid form6 within the window, the form which dates the closest to the target is used. The tumor side on form2 is used to determine which of the reported variables (left/right) corresponds to the side of the primary tumor.

Considering the problems encountered with out of range measurement and suspected variability of in-between rater, it is opted to compare the measurements of the treated arm with the measurements of the ‘reference’ (untreated) arm on the same form (measurements conducted by the same physician/study nurse), rather than to compare with the baseline measurement of the same arm. These relative measurements are included in the main part of the report. The ‘raw’ data summaries (not relative to the untreated arm) are reported in the appendix.

Measurements of 0 are set to 1 for numerical reasons (division by 0)

- **Relative anteversion** of operated vs. untreated side
  - $0 \leq 0.50$ (severe morbidity)
  - $0.50 < \cdot \leq 0.75$ (moderate morbidity)
  - $0.75 < \cdot \leq 0.90$ (mild morbidity)
  - $0.90 < \cdot \leq 1.11$ (not affected)
  - $1.11 < \cdot \leq 1.33$
  - $1.33 < \cdot \leq 2$
  - $> 2$
  (Calculated as anteversion untreated arm divided by anteversion of operated arm)

- **Relative retroversion** of operated vs. untreated side (same categories)

- **Relative abduction** of operated vs. untreated side

- **Relative adduction** of operated vs. untreated side

- Figure (with 2 curves), showing the average (and CI) of the log* of the relative anteversion at the 4 target assessment times. One curve for each treatment arm.

- Same figure for relative retroversion, abduction and adduction

In the Appendix:

- Figure (with 2 curves), showing the average anteversion for the operated arm at the 4 target assessment times. One curve for each treatment arm.

- Same figure for retroversion, abduction and adduction of operated arm and all 4 movements for untreated arm.

*The log transform creates an appropriate scale for the average because the data are ratios.

### 9.6 Safety (secondary) endpoints & inference

#### 9.6.1 Lymph edema (short & long term)

Two Fisher exact tests are performed to test for a difference between the two treatment arms for the variable ‘Edema treatment during last 12 months or any sign of edema?’: one for the
1-year post-SNB target and one for the 5-year post-SNB target (see section 9.4.1). A significance level of 5% is used for each.

9.6.2 Shoulder movement (short & long term)

Omnibus test
For the shoulder movement two composite endpoints are considered, one at the 1 year (short term), and one at the 5 year post-SNB mark (long term):

- Relative shoulder movement to reference 1-year post SNB (RSMref-1)
- Relative shoulder movement to reference 5-year post SNB (RSMref-5)

These endpoints (RSMref-1 resp. RSMref-5) are defined as the (multivariate) vector of the log transform of the following 4 variables (see section 9.5):

- Relative anteversion of operated vs. untreated side at 1 year resp. 5 years
- Relative retroversion of operated vs. untreated side at 1 year resp. 5 years
- Relative abduction of operated vs. untreated side at 1 year resp. 5 years
- Relative adduction of operated vs. untreated side at 1 year resp. 5 years

A multivariate analysis of variance (MANOVA) is performed on these multivariate vectors, where we test for a difference in multivariate mean between the two randomized treatment groups. We perform Hotelling’s $T^2$ test for both composite endpoints at the 5% significance level. Hotelling’s $T^2$ is calculated with proc glm with manova statement in SAS 9.3.

Motivation:
As anticipated, pooled data exploration revealed that at each target timepoint the within patient variation of the 4 different type of movements was small compared to the across patient variation for each type of movement. Therefore the four movements will be combined in a single (multivariate) variable. Such a multivariate analysis avoids multiple testing and takes into account the correlation between the 4 movements.

Note: Based on exploration of the pooled data at baseline and after 1 year, the data will likely not follow a (multivariate) normal distribution within each treatment arm. There is a large percentage of patients with log relative movement of 0 (no difference), and possible skewness. Simulation studies showed that the sample size is sufficient for the (asymptotic) central limit theorem to be reliable for such a distribution (in the univariate case), and therefore Hotelling’s $T^2$ test is still reliable in absence of normality of the data.

Univariate testing
When the multivariate test is significant, univariate t-tests are performed for each of the 4 (log transformed) relative movements (at the 5% significance level).

9.7 Long term complications
The variables in section 9.1 will be reported for all enrolled. And AxSN+ safety patients by received treatment. Patients who received both treatments are reported by the randomized treatment.
If the below complication is reported at least once, the variable is coded ‘yes’. Otherwise, coded as ‘no’.

- Neuropathy breast on the operated side (yes/no)
- Neuropathy axilla area on the operated side (yes/no)
- Neuropathy arm on the operated side (yes/no)
- Neuropathy shoulder area on the operated side (yes/no)
- Neuropathy other site on the operated side (yes/no)

If ‘yes’:
- A listing of the other site
- Any neuropathy breast/axilla/arm/shoulder area on the operated side
- Radiation pneumonitis
- Other long term complications
  If ‘yes’:
  - A listing of the other type of complication

10 Reasons for stopping randomized treatment

Will be reported for AxSN+ ITT patients by randomized treatment

When RT to the axilla was done (see section 8.3):
- Radiotherapy to the axilla stopped before expected completion?
  If ‘yes’:
  - Reason for stopping axillary radiotherapy (toxicity/progression/other).
  If ‘other’:
  - A listing of the other reasons.

11 Time to event endpoint definitions (primary and secondary)

Note: All inconsistencies and text boxes on the follow-up form (form9) have been reviewed by the CRP and study monitor (see also UVP). The way the events and endpoint are defined and reported is in accordance with this review.

Summary of the review:
Whenever in the disease status section, a type of recurrence (or the textbox ‘combination’), a site of distant metastasis (or the textbox ‘mixed’), a date of locoregional progression, a date of distant progression or a type of second primary was specified, this has been checked and/or reviewed (by the study monitor and CRP) to make sure the first event of each type was correctly specified in box08 (type of progression). Also when evidence of first progression/recurrence (box07) was reported as ‘yes’ and no progression was reported before or on that form, this has been queried/reviewed. When distant metastases were reported at the same time or after a second primary, they have been reviewed (by the study monitor and CRP) to make sure (to the extent possible) they were not distant metastases of the second primary.

11.1 Type of events and dates
- Date last known alive: last date (pertaining to the patient) reported on any case report form.
- Death: Survival status is ‘dead’ on dead on form9 or post-operative death on form7.
- Date of death: reported death date.
- Axillary recurrence:
  Type of recurrence reported as (a combination with) axillary recurrence on form9.
- Local recurrence:
  Type of recurrence reported as (a combination with) local recurrence on form9.
Note: includes ipsilateral DCIS

- **Loco-regional recurrence:**
  Type of recurrence reported as (a combination with) axillary recurrence or local recurrence on form9.

- **Distant metastasis (of primary breast cancer)**
  Type of recurrence reported as (a combination with) distant metastasis on form9.

- **Second primary**
  Type of recurrence reported as (a combination with) second primary on form9.
  Note: excludes basal cell carcinoma and carcinoma in situ of the cervix
  Note: includes Contralateral DCIS

- **Contralateral breast cancer**
  Type of recurrence reported as (a combination with) second primary and site of second primary is contralateral BC on form9.
  Note: includes Contralateral DCIS

- **Date of axillary/local/locoregional recurrence:**
  In case an axillary/local/locoregional recurrence is reported (missing otherwise):
  Date of documented locoregional progression/recurrence
  If the latter is unknown/missing: date of examination
  When axillary/local/locoregional recurrence reported on more than one follow-up form, the earliest date is taken.

- **Date of distant metastases/second primary/contralateral:**
  In case distant metastases/second primary/contralateral is reported (missing otherwise):
  Date of documented distant progression/recurrence
  If the latter is unknown/missing: date of examination
  When distant metastases/second primary reported on more than one follow-up form, the earliest date is taken.

### 11.2 Time to event endpoints

11.2.1 **Axillary recurrence rate – primary endpoint**

Events for this endpoint: axillary recurrence
Competing risks: death (for cumulative incidence curves)
Time to axillary recurrence will be defined as time from enrollment till date of axillary recurrence or date last known alive (if no axillary recurrence). Patients without event are censored at the date last known alive.

11.2.2 **Axillary recurrence free survival (AxRFS) – secondary endpoint**

Events for this endpoint: axillary recurrence and death.
Duration of AxRFS will be defined as time from enrollment till date of first event (if any) or date last known alive (if no axillary recurrence). Patients without event are censored at the date last known alive.

11.2.3 **Relapse free survival (RFS) – secondary endpoint**

Events for this endpoint: locoregional recurrence, distant metastases (of primary breast cancer) and death.
Duration of RFS will be defined as time from enrollment till date of first event (if any) or date last known alive (if no event). Patients without event are censored at the date last known alive.

11.2.4 **Disease free survival (DFS) – secondary endpoint**

Events for this endpoint: locoregional recurrence, distant metastasis (of primary breast cancer), second primary and death.

Duration of DFS will be defined as time from enrollment till date of first event (if any) or date last known alive (if no event). Patients without event are censored at the date last known alive.

11.2.5 **Overall survival (OS) – secondary endpoint**

Events for this endpoint: death.

Duration of OS will be defined as time from enrollment till date of event (if any) or date last known alive (if no event). Patients without event are censored at the date last known alive.

11.2.6 **Time to second primary - exploratory**

Events for this endpoint: second primary

Competing risks: death (for cumulative incidence curves)

Time to second primary will be defined as time from enrollment till date of second primary or date last known alive (if no second primary). Patients without event are censored at date last known alive.

12 **Disease status**

All variables of section 12 will be reported in three separate tables, for three different populations:
- all enrolled patients by the result of the sentinel node biopsy
- AxSN+ ITT patients by randomized treatment (Appendix)
- AxSN+ PFP patients by randomized treatment

12.1 **Frequency of events**

- Axillary recurrence (yes/no)
- Local recurrence (yes/no)
- Distant metastasis (yes/no)

  For patients who had (a) distant metastasis(es):
  - The site (soft tissue/bone/visceral/combinations)
    Brain metastases were classified under soft tissue (medical review) (see also UVP)

- Second primary (yes/no)

  For patients who had a second primary:
  - The site (contralateral/other neoplasm)

- Death (yes/no)

  For patients that died:
  - Main cause of death
    In case cause of death is ‘other malignancy’:
    - A listing of the type of malignancy will be provided
    In case cause of death is ‘other’:
• A listing of the causes

12.2 Sequence of events

• First type of event in disease free survival
  o No event
  o (combination with) Axillary recurrence
  o (combination with) Local recurrence (no axillary recurrence)
  o (combination with) Distant metastasis (no locoregional recurrence)
  o Second Primary (no distant or locoregional recurrence)
  o Death as first event
  If the difference between the dates of two types of events < 1 month, they are considered a combination for this variable.

• First type event of relapse free survival
  o No event
  o (combination with) Axillary recurrence
  o (combination with) Local recurrence (no axillary recurrence)
  o (combination with) Distant metastasis (no locoregional recurrence)
  o Death as first event
  If the difference between the dates of two types of events < 1 month, they are considered a combination for this variable.

12.3 Case report of patients with axillary recurrence
Section to be provided by the CRP.

13 Efficacy analysis

13.1 Per protocol endpoints
See section 11.2: Axillary recurrence rate, AxRFS, RFS, DFS, OS.

13.2 Analyses for the comparison of the two treatment groups
All the analyses described in section 13.2 are performed in the AxSN+ PFP population (apart from the sensitivity analyses described below). Additional to the endpoint-specific analyses listed in each subsection, common analyses include: KM’s, median time to event and 5 year event free rates, all by treatment arm.

For all the endpoints in section 13.2, the analyses are supplemented by two types of sensitivity analyses:
- AxSN+ ITT population instead of AxSN+ PFP population
- Analyses by type or primary tumor surgery (mastectomy/breast conserving procedure). Patients where the type of surgery is missing are excluded.

The sensitivity analyses concerns the HR and its CI. For the non-inferiority tests (AxRFS and OS) the 1-sided 95% confidence interval is reported.

13.2.1 Axillary recurrence rate - primary endpoint
- Cumulative incidence curves (with death as a competing risk).
cumulative incidence at 5 years
- HR with a one-sided 95% confidence interval (Cox PH model, Wald). Per protocol, non-inferiority corresponds to an upper bound of the confidence interval $\leq 2$.
  The a posteriori power of this test based on the number of observed events in the database will be calculated. (80% was anticipated in the protocol)

13.2.2 **Axillary recurrence free survival (AxRFS) - secondary endpoint**
HR with a one-sided 95% confidence interval (Cox PH model, Wald). Per protocol, non-inferiority corresponds to an upper bound of the confidence interval $\leq 1.3$.
  The a posteriori power of this test based on the number of observed events in the database will be calculated (72% was anticipated in the protocol).

13.2.3 **Relapse free survival (RFS) - secondary endpoint**
HR, CI, P (Cox PH model, Wald)

13.2.4 **Disease free survival (DFS) - secondary endpoint**
HR, CI, P (Cox PH model, Wald)

13.2.5 **Overall survival (OS) - secondary endpoint**
HR with a one-sided 95% confidence interval (Cox PH model, Wald). Per protocol, non-inferiority corresponds to an upper bound of the confidence interval $\leq 1.3$.
  The a posteriori power of this test based on the number of observed events in the database will be calculated (72% was anticipated in the protocol).

14 **Exploratory analyses**

14.1 **Multivariate analyses for DFS and OS**

AxSN+ PFP population
A Cox proportional hazards model will be fitted for DFS and OS (not for AxRFS because of the low event count). The following covariates are considered for inclusion in the model:

- Tumor size on pathology (T1, T2, T3, Tx/absence of invasive)
- Age ($\leq 50$, $50 < \ldots \leq 65$, $> 65$)
- Menopausal status (presence, absence, unknown)
- Histological type (ductal, lobular, other)
- Hormonal therapy received ((Neo-) adjuvant setting or for progression*)
  (surrogate for HR status, which was not collected)
- (Neo-) adjuvant Chemo therapy
- anti-HER2 therapy received ((Neo-) adjuvant setting or for progression*)
  (surrogate for HER-2 status, which was not collected)
- Type of primary tumor surgery in combination with RT
- Treatment arm
- Type of ALND? (level I+II, level III, unknown)
- Location of primary tumor
- Interaction location of tumor with treatment arm
- Interaction location of tumor with tumor size (T3 vs. other)
- Type of SN metastases (macro, micro, ITC only)
- Interaction type of SN metastases (ITC only vs. other) with treatment arm
• Year of accrual (< 2003, ≥ 2003)

Of the above variables, only those variables that are significant at the 20% level in the single predictor model are included in the extended model. A backwards selection procedure will be performed on the latter (5% critical p-value). Variables with more than 5% missing data will receive a separate unknown category for the missing data to avoid excessive data loss. When an interaction term is significant, the main effects are also kept in the model. The stability of the resulting model and its effects is assessed by bootstrap resampling.

* Two DM boxes were created on the follow-up form to indicate whether a hormonal or Anti-HER2 treatment was given for progression (see UVP).

14.2 Subgroup analyses (forest plots)

AxSN+ PFP population

Forest plots (Cox model, Wald CI for HR) of the randomized treatment comparison for DFS and OS will be made for the following variables:

- Tumor size on pathology (T1, T2, T3, Tx/absence of invasive)
- Age (≤ 50, 50 < ≤ 65, > 65)
- Menopausal status (presence/absence/unknown)
- (Neo-) adjuvant Hormonal therapy (surrogate for HR status) (yes vs. no/unknown)
- (Neo-) adjuvant anti-HER2 therapy (surrogate for HER2 status) (yes vs. no/unknown)
- Tumor location (2 categories: tumor location includes upper outer quadrant and/or axillary tail vs. other)
- Interation tumor location * tumor size (tumor size: T3 vs other)
- Type of SN metastases (macro, micro, ITC only)

Patients for whom the variable is missing are excluded for that subgroup analysis.

14.3 DFS & OS by result of the Sentinel Node Biopsy & randomized treatment

All patients for which the result of the sentinel node biopsy (see section 6.2) is one of the following: ‘AxSN macrometastases (≥ 2mm)’, ‘AxSN micrometastases (0.2mm ≤ < 2mm)’. ‘AxSN with ITC only (< 0.2mm)’, ‘Negative’.

The following subgroups are considered:

- macro ALND: ‘AxSN macrometastases’ and randomized to ALND
- macro AxRT: ‘AxSN macrometastases’ and randomized to AxRT
- micro ALND: ‘AxSN micrometastases’ and randomized to ALND
- micro AxRT: ‘AxSN micrometastases’ and randomized to AxRT
- ITC only ALND: ‘AxSN with ITC only’ and randomized to ALND
- ITC only AxRT: ‘AxSN with ITC only’ and randomized to AxRT
- ITC only (not randomized): ‘AxSN with ITC only (< 0.2mm)’ and enrolled after April 2nd 2008
- AxSN - : ‘Negative’

Kaplan-Meier OS and DFS curves will be plotted for each cohort including HR (AxSN- as reference) and CI (Cox model, Wald) median DFS/OS and 5 year DFS/OS rates.
14.4 Time to second primary

AxSN+ PFP population
- Cumulative incidence curves (with death as a competing risk.
  Cumulative incidence at 5 years.
- HR, CI, P (Cox PH model: Wald)

14.5 Multivariate analysis for Relative Shoulder Movements at 1 year

Same population as described in section 9.6.2.
Linear regression model fitted separately for the log transform of each of the four relative movements (4 models).
The following variables are considered for inclusion in the model:
• Tumor size on pathology (T1, T2, T3, Tx/absence of invasive)
• Age (≤ 50, 50 < . ≤ 65, > 65)
• Menopausal status (presence/absence/unknown)
• Location of tumor (2 categories: tumor location includes upper outer quadrant and/or axillary tail, other)
• Treatment arm
• Interaction location of tumor with treatment arm
• Interaction location of tumor with treatment arm and tumor size on pathology (only 2 categories for tumor size: T3 versus other)
• Supraclavicular RT
• Type of ALND
• Type of surgery to primary tumor combined with RT to breast/Chest wall
• Interaction location of tumor with Type of surgery to primary tumor combined with RT to breast/Chest wall

Of the above variables, only those variables that are significant at the 20% level in the single predictor model are included in the extended model. A backwards selection procedure will be performed on the latter (5% critical p-value). Variables with more than 5% missing data will receive a separate unknown category for the missing data to avoid excessive data loss. When an interaction term is significant, the main effects are also kept in the model.

14.6 Impact of shoulder movement measurements on (patient reported) QoL

Rationale of these models: link ‘objectively’ measured shouldered movement problems with patient reported shoulder movement problems. Are the potentially significant effects we find, relevant for the patient?

14.6.1 Impact on shoulder movement problems

AxSN+ ITT population
A proportional odds model (ordinal logistic regression) will be fitted to question 49 of the Quality of Life questionnaire (‘Was it difficult to raise your arm or to move it sideways’) for the 1-year post-enrollment assessment time. This response variable has 4 categories (Not at all/a little/quite a bit/very much).
Only patients for whom we have a valid QoL form in the window for the 1-year time point are included. If more than 1 such form, the form dated closest to the 1 year target is taken.
The following variables are considered for inclusion in the model:

- Tumor on dominant side of patient*
- Log of absolute value of Relative Anteversion (linear & quadratic)
- Log of absolute value of Relative Retroversion (linear & quadratic)
- Log of absolute value of Relative Abduction (linear & quadratic)
- Log of absolute value of Relative Adduction (linear & quadratic)
- Interaction tumor on dominant side of patient with the above four relative movements (linear only)
- Age (≤ 50, 50 < . ≤ 65, > 65)

Of the above variables, only those variables that are significant at the 20% level in the single predictor model are included in the extended model. A backwards selection procedure will be performed on the latter (5% critical p-value). Variables with more than 5% missing data will receive a separate unknown category for the missing data to avoid excessive data loss. When an interaction term is significant, the main effects are also kept in the model.

* the first reported dominant side is used.

14.6.2 **Impact on daily activities**

Same as section 14.6.1, but for questions 6 and 7 as response.

(‘Were you limited in doing either your work or other daily activities’, ‘Were you limited in pursuing your hobbies or other leisure activities’). The questions will be scored according to the scoring manual.

14.6.3 **Impact on family and social life**

Same as section 14.6.1, but for questions 26 and 27 as response.

(‘Has your physical condition or medical treatment interfered with your family life’, ‘Has your physical condition or medical treatment interfered with your social activities’). The questions will be scored according to the scoring manual.

15 **Quality of Life analysis**

15.1 **Quality of Life instrument**

QoL is measured using the EORTC QLQ-C30 questionnaire and the BR23 breast module questionnaire.

**QLQ-C30**

The EORTC QLQ-C30 is a 30-item, self-administered, multi-dimensional, cancer-specific QoL questionnaire that measures the following: global health status (2 items), functional scales (15 total items within 5 domains), and symptom scales (13 items). For questions under the functional and symptom scales, subjects respond to each item on a 4-point Likert-type scale ranging from 1 (Not at all) to 4 (Very much). For questions under global health status, subjects respond to each item on a 7 point Likert-type scale ranging from 1 (Very poor) to 7 (Excellent).

**BR23**
The breast cancer module is meant for use among patients varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy and hormonal treatment) (Sprangers et al., 1996). The module comprises 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy and hormonal treatment), body image, sexual functioning and future perspective. The breast cancer module incorporates five multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning. In addition, single items assess sexual enjoyment, hair loss and future perspective.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where:

- A high score for a symptom scale or item represents a high level of symptoms or problems.
- A high score for a functional scale represents a high or healthy level of functioning.
- A high score for the global health status/QoL represents high QoL.

### 15.2 Quality of Life Compliance

See section 3.

### 15.3 Quality of Life primary analysis.

The hypothesis to be tested is: after treatment, there will be a difference between patients undergoing the ALND and the AxRT with a better HRQOL seen in the AxRT group and (axillary) sentinel node tumour positive group. The HRQoL domains that are considered relevant for this study are:

- arm swelling scale (BR23) primary.
- pain scale (QLQ-C30) secondary.
- body image scale (BR23) secondary.

The other available scales will only be analyzed on an exploratory basis.

A difference of 10 points on the 100-point QLQ-C30 scale between the two arms will be considered as clinically relevant. The standard deviation of this scale is approximately 20 points. With the 2-sided alpha set at 5% and a power of 80% to detect a difference of 10 points (effect size of 0.5), a minimum of 128 patients (64 per treatment arm) is required. For an effect size of 0.75 (difference of 15 points), 56 patients (28 per treatment arm) are required. Therefore, this study should be sufficiently powered to detect differences in HRQoL (pending adequate compliance).

Changes in HRQoL scores over time will be evaluated with a repeated measurement modeling using linear mixed effects modeling on the AxSN+ ITT population (population 4). A linear mixed model with treatment, a time effect, a time-treatment interaction and possibly other baseline covariates as fixed effects and a patient specific random effect will be fitted. Prior to reducing the model, the most suitable covariance structure should be determined on the basis of Akaike’s
Information Criterion (AIC). Covariates other than the treatment and the time indicator may be dropped from the model based on a 5% significance level for the Type III fixed effect test. The main test will be obtained by contrasting the scores in the two treatment arms over all post-baseline time-points (F-test). The repeated measures analysis will be supplemented by a cross-sectional analysis. Graphs will display the mean score by treatment group with their 99% confidence intervals.

15.4 Quality of Life sensitivity analysis.

In case of non-trivial missing data (>10% or related to prognostic factors), the main analysis may be repeated using sensitivity techniques. These sensitivity techniques will depend on the nature of the missing data but may include using summary scales or imputational techniques.

The main analysis will be repeated on the AxSN+ per-final-protocol population (population 5).

An investigation of informative drop-out will be done by modeling the probability of missing a QoL assessment through logistic regression on age, stratification factors, WHO performance score, and time. For the primary HRQOL scale, explicit regression imputation will be used in which imputed values were predicted from a linear regression model that included time, treatment group, age, WHO performance score, and any stratification factor found to be statistically significant related to the missingness probability.

Finally a summary statistic will be constructed where patients will be divided into responder categories according to the difference observed between their baseline assessment and the lowest score reported after end of protocol treatment (regardless of timing) for each of the three selected scales. Following the guidelines as reported by Osoba et al (1998), the categories will be:

- Strongly improved   > +10
- Improved:            <= +10 and > +5
- Stable:              <= +5 and >= -5
- Worsened            < -5 and >= -10
- Severely worsened   < -10

Only patients who have a baseline QoL assessment and one additional assessment will be included. Categories may be merged depending on available numbers. Groups will be compared using a proportional odds logistic model.

16 Appendix

16.1 Evaluation form

This section provides detailed information on how the evaluation was done:

Reason(s) for ineligibility and other important events:

The categories listed under ‘disease status’, ‘patient status’, ‘treatment status’ and ‘other’ are based on the information that was known at the time of randomization or in the period between
randomization and the sentinel node biopsy. These patients are ineligible (and are reported on the evaluation form as such: eligible yes/no? = no). The ineligibility reasons reported under ‘other’ on the evaluation form are: ‘Start axillary treatment before randomization’ only.

The categories listed under ‘other important events after SNB (not implying ineligibility)’ are based on the information that became available in the period between the sentinel node biopsy and start of axillary treatment. These patients are considered eligible (and are reported on the evaluation form as such: eligible yes/no? = yes).

The patients in the category listed under ‘other important events before SNB (not implying ineligibility)’ are considered eligible (and are reported on the evaluation form as: eligible yes/no? = yes), but will be reported in section 7.3 (protocol non-compliance).

**Result of the sentinel node procedure**

Clarification of some of the categories:

- **Positive axillary sentinel node (AxSN+):**
  - At least one tumor positive **axillary** sentinel node.
  - Both macrometastases and/or micrometastases are considered positive.
  - For ITC only, a different rule was implemented on the evaluation form before and after the 2\(^{nd}\) of April 2008. Before this date, ITC only are evaluated as positive, but after this date they are classified separately (in ‘axSN ITC only’).

  *The cut-off is motivated by the following:*  
  *After the protocol 4\(^{th}\) amendment (PRC approved on 22\(^{nd}\) of February 2008) patients who have axillary sentinel nodes with ITC only were no longer considered to be sentinel nodes positive. The Netherlands was the first country where the amendment was approved (on the 2\(^{nd}\) of April 2008). This date (2/04/2012) is used as a cut-off date to implement the amendment.*

- **Axillary sentinel node with isolated tumor cells only (axSN ITC only):**
  - Patient randomized after the 2\(^{nd}\) of April 2008. No axillary sentinel node with macrometastases and/or micrometastases, but at least one axillary sentinel node with ITC only.

- **Positive non-axillary sentinel node (non-axSN+):**
  - No tumor positive axillary sentinel node (no macro-, micrometastases nor ITC only), but at least one positive non-axillary sentinel node. Both macrometastases and/or micrometastases and/or ITC only are considered positive.

- **Positive non-sentinel node (non-SN+):**
  - At least one sentinel node examined and none tumor positive (no macro-, micrometastases nor ITC only), but at least one positive non-sentinel node (a non-blue, non-radioactive lymph node that was collected / found during SN procedure). Both macrometastases and/or micrometastases are considered positive.

- **Negative (SNB-):**
  - At least one sentinel node examined and none tumor positive (no macro-, micrometastases nor ITC only). Additionally, these patients did not have a positive non-sentinel node (removed during SNB).

- **SNB after lymphoscintigraphy was attempted but SN could not be identified**
  - SNB attempted, but SN not identified. (will be merged with the category below)

- **SNB not done because not hot spot(s) were identified at lymphoscintigraphy**
SNB attempted, but SN not identified. (will be merged with the category above)
The distinction between the two can often not be made based on the information we have.

**Axillary Treatment compliance for AxSN+ patients:**

- **Was the assigned treatment followed?**
  
  Clarification of some of the categories:
  
  o **No, both given**
    
    Patient randomized to ALND, axRT added, but not ≥ 4 positive nodes at surgery (SNB + ALND). OR, patient randomized to axRT, AxRT started but stopped before completion and ALND given.
  
  o **Yes, but both given because > 4 positive nodes after ALND**
    
    Patient randomized to ALND. RT was added after ALND and ≥ 4 positive nodes at surgery (SNB + ALND). ITC only is not considered positive. There could still be a protocol violation with respect to the ALND for these patients (and if so, the type of violation is specified).
    
    *Note: this category also includes one special case of a patient receiving both treatments for another reason (but which is also not considered as treatment non-compliance): patient randomized to ALND, ALND started, during surgery extensive involvement of fat tissue observed. ALND stopped and AxRT given.*
  
  o **No, other given**
    
    Patient randomized to AxRT, but ALND given (afterwards AxRT might also be added). OR patient randomized to ALND, but no ALND given and AxRT received.
  
  o **No, further treatment was not given**
    
    No ALND nor AxRT received
  
  o **Yes, but with a severe violation**
    
    Only the randomized treatment was given, but with a severe violation regarding the administration.

- **Reason for deviation randomized treatment:**
  
  Specified when the assigned treatment is not followed (‘no, both given’, ‘no, other treatment given’, ‘no further treatment not given’ or ‘unknown’).
  
  Clarification of some of the categories:
  
  o **Radiotherapy added because more than 4 positive nodes at surgery**
    
    Patients randomized to AxRT, who had an ALND instead, but where afterwards AxRT was still added because > 4 positive nodes at surgery. (this reason can only apply to category ‘No, other given’)
  
  o **SN contains ITC only (before 4th amendment)**
    
    Patient enrolled before cut-off of the 4th amendment, but investigator decision not to follow randomized treatment because ITC only.
  
  o **AxRT was added because no adequate ALND was performed**
    
    Patients randomized to ALND, who received an ALND, but where the ALND specimen contained less than 10 lymph nodes. AxRT was then added. (this reason can only apply to category ‘No, both given’)

- **Reason for other severe violation:**
Specified when the assigned treatment was followed, but with a severe protocol violation regarding the execution.

Clarification of some of the categories:

- **Axillary treatment delay too long**
  > 12 weeks between SNB and start axillary treatment. (Except for RT at ALMANAC centers).

- **Overdosage for AxRT**
  Higher total dose than the following regimens:
  15 x 2.7Gy, 24 x 2.0 Gy, 23 x 2.1 Gy, 26 x 2.0 Gy, 16 x 2.7 Gy, 28 x 1.8 Gy, 25 x 2.0 Gy

- **Underdosage for AxRT**
  lower total dose than the following regimens:
  15 x 2.7Gy, 24 x 2.0 Gy, 23 x 2.1 Gy, 26 x 2.0 Gy, 16 x 2.7 Gy, 28 x 1.8 Gy, 25 x 2.0 Gy