DESCARTES study: De-ESCAlating RadioTherapy in patients with pathologic complete response to neoadjuvant systemic therapy (September 2024)

PROTOCOL TITLE *"DESCARTES study: De-ESCAlating RadioTherapy in patients with pathologic complete response to neoadjuvant systemic therapy"*

Protocol ID	
Short title	**DESCARTES study**
Version	**9.0**
Date	**September 2nd 2024**
Coordinating investigator/project leader	***F.H. van Duijnhoven, M.D, Ph.D., surgical oncologist*** NKI-AVL Plesmanlaan 121, 1066 CX Amsterdam T: +31(0)20 5126170 f.v.duijnhoven@nki.nl
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	***L.J. Boersma, MD, PhD, radiation oncologist*** Maastro Dr. Tanslaan 12, 6229 ET Maastricht Liesbeth.boersma@maastro.nl T: +31(0)88 4455600 ***J. H. Maduro. MD, PhD, radiation oncologist*** UMCG Hanzeplein 1, 9713 GZ Groningen j.h.maduro@umcg.nl T: +31 (0)50 3613665 ***N. Russell, MD, PhD, radiation oncologist*** NKI-AVL Plesmanlaan 121, 1066 CX Amsterdam n. russell@nki.nl T: +31(0)20 5122134

	E.J.Th. Rutgers, MD, PhD, surgical oncologist NKI-AVL Plesmanlaan 121, 1066 CX Amsterdam e.rutgers@nki.nl T: +31(0)20 5122561 ***J. Tol, MD, PhD, medical oncologist*** Jeroen Bosch Ziekenhuis Henri Dunantstraat 1, 5223 GZ 's-Hertogenbosch J.Tol@jbz.nl T: +31 (0)73 553 200 ***M. Vrancken Peeters, MD, PhD, surgical oncologist*** NKI-AVL Plesmanlaan 121, 1066 CX Amsterdam m.vrancken@nki.nl T: +31 (0)512 2978
Sponsor (in Dutch: verrichter/opdrachtgever)	***Antoni van Leeuwenhoek*** Plesmanlaan 121, 1066 CX Amsterdam
Subsidising party	***Not applicable***
Independent expert	***W. van Houdt, MD, PhD*** NKI-AVL w.v.houdt@nki.nl T +31 (0)20-5126978

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: Prof.dr. M.W.J.M. Wouters (Head of Division Surgical Oncology)		
Coordinating Investigator/Project leader/Principal Investigator ***F.H. van Duijnhoven, M.D, Ph.D., surgical oncologist***		
Local Principal Investigator		

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
ALND	**Axillary Lymph Node Dissection**
BCS	**Breast Conserving Surgery**
BCT	**Breast Conserving Therapy**
AR	**Adverse Reaction**
CA	**Competent Authority**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring**
DFS	**Disease free survival**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medische ethische toetsing commissie (METC)**
NAC	**Neoadjuvant chemotherapy**
NCI	**Netherlands Cancer Institute**
NST	**Neoadjuvant systemic therapy**
pCR	**Pathologic complete response**
rCR	**Radiologic complete response**
(S)AE	**(Serious) adverse event**
Sponsor	**The sponsor is the party that commissions the organization of performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WMA	**World Medical Association**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

SUMMARY

Rationale:

Over 60% of the women who are diagnosed with breast cancer in the Netherlands are treated with systemic treatment, which may be administered before (neoadjuvant systemic therapy, NST) or after (adjuvant) locoregional treatment. Depending on the subtype, 10-75% of patients will have a pathologic complete response (pCR) after NST. In this patient group, risk of local recurrence is extremely low. The administration of adjuvant radiotherapy in these patients is not expected to contribute significantly to overall survival, but may cause considerable morbidity.

Objective:

Primary aim: to assess whether local recurrence is acceptable when radiotherapy is omitted after breast conserving surgery in patients treated with NST who achieve a pathologic complete response.

Secondary aim: to assess quality of life and cancer worry after omitting radiotherapy.

Study design:

DESCARTES is a national, multicentre, non-randomized, single-arm prospective cohort study.

Study population:

Patients >18 years with cT1-2, N0 HR+HER2-, HER2+(HR+/-) or TN breast cancer who are treated with breast conserving surgery and achieve pathologic complete response.

Intervention:

Omitting radiotherapy following breast-conserving surgery.

Main study parameters/endpoints:

The primary endpoint is the local recurrence rate (LRR) at 5 years. Secondary determinants are local non-salvageable recurrence free survival, quality of life, regional recurrence rate, distant recurrence free survival, disease-specific survival and overall survival.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The immediate impact for participants is to be spared intensive radiotherapy and subsequent risk of side effects (such as pain, fatigue, possible lung damage). An expected 4% will develop a local recurrence within 5 years, about half of which would not have happened with standard radiotherapy. The majority of these local recurrences can however effectively be treated with salvage breast-conserving or ablative surgery and previous studies indicated that patient survival will not be affected.

1. INTRODUCTION AND RATIONALE

NST is increasingly used in breast cancer treatment(1), resulting in tumour downsizing and increase in breast conserving surgery(BCS) rates without compromising local recurrence or overall survival.(2-6) The extent of tumour downsizing is largely dependent on breast cancer molecular subtypes with highest pCR rates in triple negative(TN) and HER2+ subtypes (40-88%) and pCR rates of 10-15% in HR+/HER2- breast cancer.(7-14)

De-escalating locoregional treatment following NST cannot be achieved by omitting surgery, since biopsies or MRI do not accurately assess pCR. (15-17). Adjuvant whole breast irradiation however may be de-escalated in pCR patients who do not have an indication for regional irradiation.(18)

In this patient group, risk of distant and local failure is low. Mamounas first reported retrospectively on cT1-3N0-2 patients treated with NST in two major clinical trials conducted from 1988 to 1993 and from 1995 to 2000. Only 10-year results on local recurrence were reported. In 225 clinically node-negative patients with pCR, local recurrence was 5.2 and 6.9% for patients >50 and <50 years respectively.(19) Notably, pCR definition included patients with residual in situ disease and axillary lymph node status was defined by palpation only. As the large majority of local recurrences occur within 5 years from treatment, especially in Her2 positive and triple-negative breast cancer, the reported 10-year recurrences will have included new primary cancers.(20) However, this overview confirmed that the absence of pCR was the most important predictor for locoregional recurrence with a hazard ratio of 2.77.(19)

Recent studies including up-to-date systemic treatments and pre-NST staging with MRI and axillary ultrasound report considerably lower 5 year recurrence rates, as shown in Table 1. All studies include patients with stage I-III disease and include residual DCIS in pCR definition. Samples sizes for pCR patients vary between 157 and 426, with **local** recurrence rates between 1.0-3.5%, with isolated tumour cells considered pCR in the highest reported recurrence. **Locoregional** recurrence rates in pCR patients range from 0.0%-3.2%.(21-23) Swisher et al report recurrence rates per molecular subtype, with lowest rates in hormone receptor positive breast cancer.(22) Notably, 61% of patients in this cohort presented with node-positive disease, but LRR was not specified for cN0 versus cN+ patients.(22)

Even more recent studies investigating risk factors for DFS and OS in patients achieving a pCR, have reported poorer outcomes for patients with ypTis compared to ypT0, cN+ compared to cN0 and cT3/4 compared to cT1/2. (24-25) Although ypTis is considered a risk factor for poorer outcomes, it is expected that not all patients with DCIS in pre-NST biopsy have the same prognosis. A study by Groen et al. demonstrated that DCIS can

respond well to NST and reported several risk factors associated with response of DCIS to NST; calcifications on mammography prior to NST, treatment with dual HER2+ blockade and absence of calcifications or Ki67>20% in pre-NST biopsy. (26)

Author	Year	cTNM	Molecular subtype	Sample size	Treatment	pCR	5-year in-breast recurrence	5-year locoregional recurrence
Chen et al.(10)	1987-2000	T1-4N0-1*	not specified	157	BCT + RT	Unknown**	1%	3%
Vila et al.(11)	1997-2005	T0-4N0-3	not specified	656	BCT + RT	Unknown	2.9%	5.5%
Vila et al. (11)	1997-2005	T0-4N0-3	not specified	250	BCT + RT or Mx +/- RT	Yes, pTis included	-	3.2%
Swisher et al.(12)	2005-2012	T0-4N0-3	All	243	BCT + RT	Yes, pTis included	-	1.0%
			HR+/HER2-	*61*	*BCT + RT*	*Yes, pTis included*		*0%*
			HR+/HER2+	*48*	*BCT + RT*	*Yes, pTis included*		*0%*
			HR-/HER2+	*42*	*BCT + RT*	*Yes, pTis included*		*2.6%*
			HR-/HER2-	*92*	*BCT + RT*	*Yes, pTis included*		*1.4%*
Gillon et al.(13)	2001-2006	T1-4N0-3	All	1553	*mastectomy / BCT + RT*	Unknown	1.9%	4.9%
				283	*mastectomy / BCT + RT*	*Yes, pTis and pTitc included*	*3.5%*	
				426	*mastectomy / BCT + RT*	*Yes, pCR of lymph nodes*		*2.3%*

Table 1. Local and locoregional recurrence rates following NST; *patients with non-inflammatory breast cancer excluded and ** no LVI, pCR or solitary residual invasive tumour of <2 cm

A recent study reports on locoregional recurrence following NST when radiotherapy is omitted. In this series, 197 cT1-4N0-3 patients with pCR following NST and treated with BCS were included, 110 of which did not receive adjuvant radiotherapy.(27) Notably, 57% of patients included in the study presented with node-positive disease and patients with residual in situ disease were considered as pCR. Five year local recurrence rates **without radiotherapy** are 0% for luminal and HER2 subtype, 3.1% for TNBC and 3.2% for luminal HER2+ breast cancer (Table 2.(27) (results obtained via personal communication with author)

		BCS followed by RT		BCS without RT	
Molecular subtype		Total (N)	5-year LR (%)	Total (N)	5-year LR (%)
All		87	1.1%	110	1.8%
	Luminal	8	0 (0%)	16	0 (0%)
	LuminalHER2+	19	0 (0%)	31	1 (3.2%)
	HER2+	18	0 (0%)	31	0 (0%)
	TNBC	42	1 (2.4%)	32	1 (3.1%)

Table 2. Local recurrence rates for pCR patients treated with NST and breast conserving surgery. For pCR definition, ypTis was included.

The effect of omitting radiotherapy on survival was investigated by Mandish et al. in 5383 patients with cT0-4, N0-3 breast cancer treated with NST and breast conserving surgery who showed pCR of both breast and lymph nodes. Of these patients, 364 did not receive adjuvant radiotherapy. This did not compromise survival, as 5-year OS rates did not significantly differ (93.6% with RT and 93% without RT, adjusted hazard ratio 1.33, 95% CI 0.76-2.31, p=0.3181).(28)

Radiotherapy of the breast is associated with both short-term and long-term morbidity in up to 50% of patients(29-32. Radiotherapy negatively influences quality of life by long-term morbidity consisting of secondary lung cancer, cardiac mortality, painful fibrosis of the breast and impaired cosmetics.(29-34) De-escalating local therapy by partial breast and hypofractionated radiotherapy was shown to positively impact quality of life by reducing fibrosis and breast deformation.(35-37) Omitting radiotherapy altogether in patients with extremely low risk of local recurrence is already implemented for a group of older patients with low risk of recurrence following primary surgical treatment (*NCT03375801)*(*TOP-1*). This results in increased local recurrence rates without compromising survival.(28,38, 39)

As the relation between radiotherapy and long-term side effects of breast conserving treatment is thus well established, omitting radiotherapy altogether can be assumed to further improve breast-specific quality of life. We therefore propose a single-arm study in which radiotherapy is omitted in eligible patients.

2. OBJECTIVES

Primary Objective:

To show that omitting radiotherapy in patients with a pathologic complete response to NST results in a 5-year local control rate of >94%.

Secondary Objective:

To show that omitting radiotherapy in patients with a pathologic complete response to NST results in good quality of life without compromising cancer worry levels.

To assess the 5- and 10-year local control rate, distant- and regional metastasis free survival and local non salvageable recurrence free survival.

3. STUDY DESIGN

The DESCARTES trial is a prospective single arm study investigating the effects on local control and quality of life of omitting radiotherapy after NST in cT1-2N0 patients who achieve breast and axillary pCR after NST. Eligibility of patients will be assessed at multi-disciplinary meetings.

Women with any type of invasive breast cancer are eligible for inclusion. Patients with a history of breast cancer, DCIS or LCIS are excluded. Concurrent DCIS in pre-NST biopsy is allowed if there is no suspicion of an extensive component; patients are excluded if they have the combination of concurrent DCIS in pre-NST biopsy and calcifications on pre-NST mammography and/or non-mass enhancement on pre-NST MRI, contrast-enhanced mammography or breast-specific gamma imaging. Concurrent LCIS of any type in pre-NST biopsy is not allowed. A marker should be placed in the center of the tumour before start of NST. Contrast- enhanced breast MRI, a contrast-enhanced mammography or breast-specific gamma imaging is conducted pre-NST for reliable assessment of unifocal disease. Axillary status is evaluated by ultrasound. In case of suspicious axillary lymph node(s), fine needle aspiration is performed for cytology analysis to confirm node-negative disease.
Following NST, breast conserving surgery is performed. A post-NST sentinel node biopsy procedure (if not performed pre-NST) is performed using single or dual-tracer technique. The surgical specimen will be assessed by a specialized breast pathologist according to national guidelines. A pathologic complete response is defined as ypT0N0 (i.e. absence of invasive carcinoma and in-situ carcinoma in breast and axilla). In case One-Step Nucleid Acid Amplification (OSNA) is used to determine status of sentinel node, only negative OSNA results will be accepted as N0.

If pCR of breast and lymph nodes is present (ypT0N0), patients may be entered into the single-arm study, in which radiotherapy of the breast is omitted. Adjuvant systemic therapy is administered according to national breast cancer guidelines.

Patients will be followed yearly for a period of 5 years and at 10 years to assess local-regional recurrence. Quality of life (QOL) is measured using the Patient Reported Outcome Measures (PROMs), which are integrated in standard care in the Antoni van Leeuwenhoek and other centers, and additional questionnaires containing measure not included in the standard PROMS set. The PROMs include the EORTC-QLQ-C30 and EORTC-QLQ-BR23. The 8-item Cancer Worry Scale will be used to measure if worry related to omission of radiotherapy may affect QOL. Two demographic variables (education level and tolerance for uncertainty) will be measured at baseline as these patient characteristics could be associated with quality of life and level

of experienced cancer worry and need to be considered in the analyses. The additional QOL questionnaires are provided simultaneously with the PROMs: the first are provided for baseline measurement, and the following are provided at 1 year and 4 years after surgery. See table 3 for an overview of the QOL measurements.

All recurrences should be confirmed with pathology analysis. All lesions suspect for disease recurrence are discussed at multidisciplinary meetings, according to clinical practice guidelines.

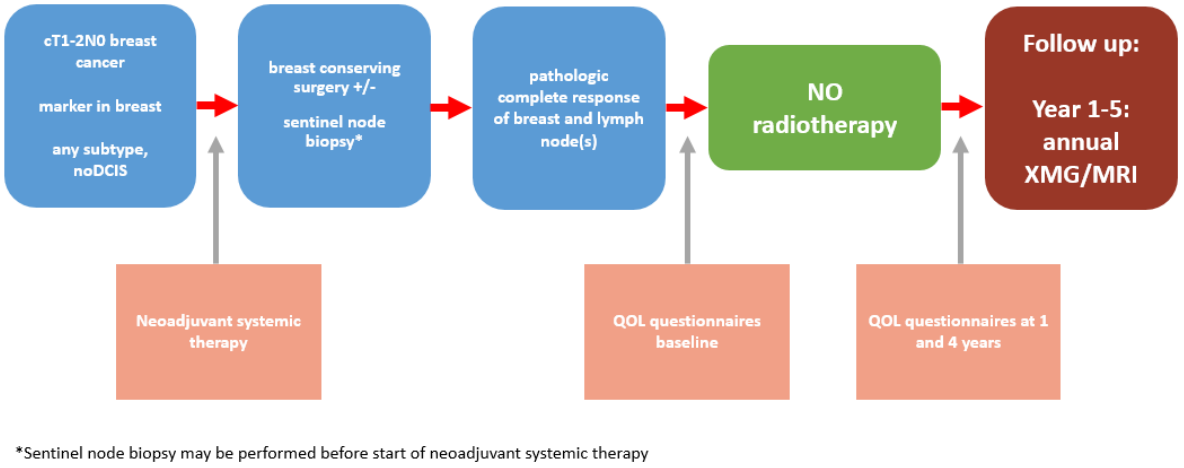

Figure 1. Descartes trial study design

	PROMs	Additional QOL questionnaires
Baseline	EORTC-QLQ-C30, EORTC-QLQ-BR23	Education level, 12-item Intolerance of uncertainty scale, Cancer Worry Scale
1 year after surgery	EORTC-QLQ-C30, EORTC-QLQ-BR23	Cancer Worry Scale
4 years after surgery	EORTC QLQ-C30	Cancer Worry Scale, EORTC-QLQ-BR23

Table 3. Overview of quality of life questionnaires

4. STUDY POPULATION

4.1 Population (base)

Eligible patients are women with cT1-2, N0 HR+HER2-, HER2+(HR+/-) or TN breast cancer who achieve pathologic complete response after NST. Concurrent DCIS in pre-NST biopsy is allowed if there is no suspicion of an extensive component; patients are excluded if they have the combination of concurrent DCIS in pre-NST biopsy and calcifications on pre-NST mammography and/or non-mass enhancement on pre-NST MRI, contrast-enhanced mammography or breast-specific gamma imaging. Concurrent LCIS of any type in pre-NST biopsy is not allowed. Patients are clinically node negative in the absence of suspect nodes on ultrasound and/or FDG-PET/CT, or the absence of tumour cells at cyto-/histopathology in patients with suspect nodes on ultrasound and/or FDG-PET/CT pre-NST. A marker should be placed in the tumour before start of NST and adequate position should be confirmed by mammography or ultrasound. In case of suspicious axillary lymph node(s), fine needle aspiration is performed for cytology analysis.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Women, aged ≥ 18 years
- Invasive HR positive/Her2 negative, Her2+ (ER/PR +/-) or TN breast cancer
- Concurrent DCIS in pre-NST biopsy is allowed if there is no suspicion of extensive component i.e. absence of non-mass enhancement on pre-NST MRI, contrast-enhanced mammography or breast-specific gamma imaging and/or absence of calcifications on pre-NST mammography
- Primary tumour (T) clinical stage cT1-2
- Unifocal disease; confirmed by pre-NST MRI, contrast-enhanced mammography or breast-specific gamma imaging
- Clinical nodal stage 0; absence of lymph node metastases should be confirmed by ultrasound or FDG-PET/CT
- Neoadjuvant systemic treatment (NST)
- Marker placed in breast tumour prior to NST
- Breast conserving surgery performed, i.e. no mastectomy
- Sentinel node biopsy performed before or after NST
- Pathologic complete response in breast and lymph nodes, i.e. no residual tumour cells, DCIS or LCIS detected
- Written informed consent within 16 weeks following the date of surgery

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Primary tumour (T) clinical stage cT3-4
- Pre- or post-NST diagnosis of nodal disease including isolated tumour cells
- Concurrent LCIS of any type in either pre-NST biopsy or surgical specimen
- Patients without axillary ultrasound or FDG-PET/CT pre-NST
- History of breast cancer, DCIS or LCIS
- Synchronous contralateral breast cancer, DCIS or LCIS
- Synchronous M1 disease
- Carrier of gene mutation associated with increased risk of breast cancer, i.e. BRCA1, BRCA2, CHEK2, TP53 or PALB-2

4.4 Sample size calculation

Reported 5 year local and locoregional recurrence rates for patients with stage 2 and 3 disease (cT1-4N0-3) treated with NST, breast conserving surgery and radiotherapy who achieve pCR range from 0 to 3.5%, in which patients with DCIS (all reports) and even isolated tumour cells (one report, with highest reported LR of 3.5%(23)) were included in the pCR group.

As radiotherapy in primary breast cancer reduces recurrence with at least a factor 2.5, local recurrence at 5 year without radiotherapy could be in the range of 0-8.75% for pCR patients.(28)

Recently, 5-year local recurrence rates in NST patients treated with breast conserving surgery without radiotherapy were reported in a relatively large group of 110 pCR patients, with a very low recurrence rate of 1.8%. Notably, this concerned a group of cT1-4N0-3 patients, with >60% of patients being node-positive. Also, residual DCIS was included in the pCR group.(27)

As we will include only node negative patients with tumours <5 cm AND will exclude patients with residual DCIS, we may expect the recurrence rate to be on the lower side of the hypothesized range of 0-8.75%. For our statistical analysis, we have therefore used an **expected rate of local recurrence of 4%.**

A 5 year **local recurrence rate of less than 6% is deemed acceptable**, as studies have shown that the effect of RT on local recurrence is mainly achieved in the first 5 years following treatment(40), especially in TN and Her2 positive subtypes which will constitute the majority of our population.

Simulations were performed to calculate the sample size of a two stage single arm trial (including an interim analysis of futility), using the one sample log rank test. Assuming a 5 year follow up and a 5 year uniform accrual, assuming as well an exponential distribution for survival, we calculated that the expected number of events when 325 patients are included should be at most 6, under the null hypothesis. If less or equal events are observed at that time, the trial continues and **595 patients** in total are needed to achieve a power of >80% (an one-side alpha of 0.05). The expected number of events during the study are 35 to exclude a local recurrence risk at 5 years of 6% or more, if the actual local recurrence rate is 4%.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Not applicable

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

The primary endpoint of the DESCARTES study is the local recurrence rate after 5 years.

6.1.2 Secondary study parameters/endpoints

- Local non-salvageable recurrence free survival (i.e. an in-breast recurrence that cannot be adequately cured with breast conserving surgery with RTx) after 5 years
- Quality of life at baseline and after 1 and 4 years after surgery
- Cancer worry at baseline and after 1 and 4 years after surgery
- Regional recurrence after 5 years
- Distant RFS after 5 and 10 years
- Disease-specific survival after 5 and 10 years
- OS after 5 and 10 years

6.2 Randomisation, blinding and treatment allocation

This is a prospective non-randomized clinical trial.

6.3 Study procedures

- Neoadjuvant systemic therapy

Patients included in the DESCARTES trial will receive neoadjuvant chemotherapy +/- antiHER2 therapy according to national and local breast cancer guidelines.

- Surgery of breast and axilla

Breast conserving surgery should be performed. If studies show post-NST biopsies to be equally reliable in assessing pCR, these may substitute surgery following protocol amendment. Axillary surgery will consist of SLNB.

- Pathology examination

Breast and lymph node tissue will be assessed according to standard clinical practice. Pathologic complete response is defined by the absence of any residual tumour or DCIS cells, including isolated tumour cells. In case One-Step Nucleid Acid Amplification (OSNA) is used to determine status of sentinel node, only negative OSNA results will be accepted as N0.

- Inclusion and follow-up

Patients are not randomized. Patients will be followed for 10 years and assessed for local disease recurrence with yearly mammography and physical examination in the first 5 years. After five years the patient may be referred back to the breast cancer screening program. At 10 years, data on recurrence will be retrieved for all patients. If deemed necessary by the medical specialist assessing the patient, additional imaging and/or histopathology analysis may be performed. Axillary recurrences should be confirmed with pathology analysis. All lesions suspect for disease recurrence are discussed at multidisciplinary meetings, according to clinical practice guidelines. QoL will be evaluated with the PROMs including the EORTC QLQ-C30 and BR23. Additionally the Cancer Worry Scale, education level and 12-item Intolerance of uncertainty scale will be used to measure if anxiety is related to omission of radiotherapy may affect QoL.

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

6.5 Replacement of individual subjects after withdrawal

Not applicable.

6.6 Follow-up of subjects withdrawn from treatment

Not applicable.

6.7 Premature termination of the study

If the interim analysis for futility shows a higher than acceptable local recurrence rate, the study will be terminated. See statistics for detailed information.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

All serious adverse events that occur within 90 days of omission of radiotherapyconsidered by the investigator to be related to study treatment , must be medically well documented and reported to the NKI Data Center within 24 hours or, at the latest, on the following working day.

The report must be sent by **email (drugsafety@nki.nl)** to the **Antoni van Leeuwenhoek Data Centre.** The Data Centre can also be contacted by **telephone (+316205129047)** between 09.00 and 17.00 hours (GM+1) Monday to Friday.

The sponsor will not report the SAEs through the web portal ToetsingOnline. All SAEs will be reported to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

7.5 Safety Committee

A data safety committee will be established to monitor the number and nature of any recurrences that may occur. The data safety committee will consist of a surgical oncologist, radiation oncologist, pathologist and statistician.

8. STATISTICAL ANALYSIS

8.1 Primary study parameter(s)

The primary endpoint of the study is the local recurrence rate, defined as recurrence in the ipsilateral breast. Any LR is considered as an event and is included in the analysis. Time to LR will be estimated by the Kaplan-Meier method and compared to the acceptable rate of 6% at 5 years by the one sample log rank test. Additionally an estimation of cumulative incidence of LR using death as a competing risk will be computed.

8.2 Secondary study parameter(s)

Rates of distant metastasis free survival, overall survival and disease specific free survival and local non-salvageable recurrence free survival after 5 and 10 years are calculated by the method of Kaplan-Meier and comparisons are made by log-rank test.

8.3 Other study parameters

Characteristics of the cohort will be described in detail using mean and standard deviation for continuous variables, and count and percentage for categorical variables. To compare distribution of clinical factors among subgroups (molecular subtypes), the Chi square test are used for categorical factors and Kruskal-Wallis test for continuous factors.

8.4 Interim analysis

An analysis of futility will be performed after inclusion of 325 patients and a minimum median follow up time of 16.2 months. Assuming a 5 year follow up and a 5 year uniform accrual, assuming as well an exponential distribution for survival, we calculated that the expected number of events when 325 patients are included should be at most 6, under the null hypothesis. If less or equal events are observed at that time, the trial continues and 595 patients in total needed to achieve power of >80% (an one-side alpha of 0.5). The expected number of events during the study are 35 to exclude a local recurrence risk at 5 years of 6% or more.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

9.2 Recruitment and consent

Patients eligible for the study will be contacted during the pre-operative outpatient clinical appointment by a specialist. Patients will receive oral information and a patient information letter as well as the informed consent form (see attachment). Patients will be given enough time to consider the provided information and ask questions about it. Every patient will receive a copy of the signed informed consent form. The informed consent form must be signed within 16 weeks following the date of surgery.

9.3 Objection by minors or incapacitated subjects

Not applicable.

9.4 Benefits and risks assessment, group relatedness

Patients participating in this study will be spared side-effects associated with radiotherapy. Patients in which radiotherapy is omitted may have a higher risk of developing a local recurrence. The majority of local recurrences can be treated with breast conserving therapy and radiotherapy. Extra burden during the study are additional questionnaires according quality of life which will be provided simultaneously with the PROMs, which are integrated in standard care in the Antoni van Leeuwenhoek and other centers.

9.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.6 Incentives

Not applicable.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

The central data management will be performed by the Netherlands Cancer Institute-Antoni van Leeuwenhoek. Registration will be done after the written informed consent is obtained and after verification of eligibility. After the written informed consent is obtained, patients will be assigned to a registration number.
Registration will be performed using ALEA® registration package run by the NKI Data Center.

All data that are relevant for the study will be collected on eCRFs developed by the NKI data Center. The system can be accessed via internet to include data directly in the Data Centre Servers. The AVL Datacenter will supply accounts to the local data manager to enter data into the system. Checks will be incorporated into the eCRF system to prompt queries at the moment that data is entered facilitating the work of the local data manager who could quickly correct errors. Additional checks will be programmed using statistical programs with the goal of obtaining a clean file.
The time between the patient's visit and completion of eCRF pages should be kept to a reasonable minimum allowing answering the questions posed by the study. In all cases it remains the responsibility of the investigator to check and validate the data after verifying that they are completed and filled out correctly. If information is not known, this must be clearly indicated.
The investigator will retain all pertinent information for a period of at least 15 years from study completion.

10.2 Monitoring and Quality Assurance

The study will be monitored according to ICH GCP, either on site or remote. This study will be considered as a low risk study.
A monitoring plan specific to the study and describing the nature and frequency of the monitoring will be written by the appointed monitor and approved by the Principal Investigator and the Head of the Data Centre.
Data from all patients will also be centrally checked at the Data Centre. Through central monitoring of the data collected, the Data Centre will be able to detect outliers or apparently spurious data. When persistent irregularities or protocol violations are detected, the Data Centre will inform the local investigator (and Principal Investigators) and queries will be sent to the local Data Manager

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave

a favourable opinion.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

The data will be published by the project leader and investigators mentioned in this protocol.

11. STRUCTURED RISK ANALYSIS

Not applicable.

12. REFERENCES

1. Murphy, B. L., and Boughey, J. C. (2018) ASO Author Reflections: Changes in Use of Neoadjuvant Chemotherapy Over Time-Highest Rates of Use Now in Triple-Negative and HER2+ Disease. *Ann Surg Oncol* **25**, 695-696
2. Straver, M. E., Rutgers, E. J., Rodenhuis, S., Linn, S. C., Loo, C. E., Wesseling, J., Russell, N. S., Oldenburg, H. S., Antonini, N., and Vrancken Peeters, M. T. (2010) The relevance of breast cancer subtypes in the outcome of neoadjuvant chemotherapy. *Ann Surg Oncol* **17**, 2411-2418
3. Mieog, J. S., van der Hage, J. A., and van de Velde, C. J. (2007) Neoadjuvant chemotherapy for operable breast cancer. *Br J Surg* **94**, 1189-1200
4. Shin, H. C., Han, W., Moon, H. G., Im, S. A., Moon, W. K., Park, I. A., Park, S. J., and Noh, D. Y. (2013) Breast-conserving surgery after tumor downstaging by neoadjuvant chemotherapy is oncologically safe for stage III breast cancer patients. *Ann Surg Oncol* **20**, 2582-2589
5. Kummel, S., Holtschmidt, J., and Loibl, S. (2014) Surgical treatment of primary breast cancer in the neoadjuvant setting. *Br J Surg* **101**, 912-924
6. von Minckwitz, G., Blohmer, J. U., Costa, S. D., Denkert, C., Eidtmann, H., Eiermann, W., Gerber, B., Hanusch, C., Hilfrich, J., Huober, J., Jackisch, C., Kaufmann, M., Kummel, S., Paepke, S., Schneeweiss, A., Untch, M., Zahm, D. M., Mehta, K., and Loibl, S. (2013) Response-guided neoadjuvant chemotherapy for breast cancer. *J Clin Oncol* **31**, 3623-3630
7. von Minckwitz, G., Rezai, M., Loibl, S., Fasching, P. A., Huober, J., Tesch, H., Bauerfeind, I., Hilfrich, J., Eidtmann, H., Gerber, B., Hanusch, C., Kuhn, T., du Bois, A., Blohmer, J. U., Thomssen, C., Dan Costa, S., Jackisch, C., Kaufmann, M., Mehta, K., and Untch, M. (2010) Capecitabine in addition to anthracycline- and taxane-based neoadjuvant treatment in patients with primary breast cancer: phase III GeparQuattro study. *J Clin Oncol* **28**, 2015-2023
8. Schneeweiss, A., Chia, S., Hickish, T., Harvey, V., Eniu, A., Hegg, R., Tausch, C., Seo, J. H., Tsai, Y. F., Ratnayake, J., McNally, V., Ross, G., and Cortes, J. (2013) Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* **24**, 2278-2284
9. von Minckwitz, G., Eidtmann, H., Rezai, M., Fasching, P. A., Tesch, H., Eggemann, H., Schrader, I., Kittel, K., Hanusch, C., Kreienberg, R., Solbach, C., Gerber, B., Jackisch, C., Kunz, G., Blohmer, J. U., Huober, J., Hauschild, M., Fehm, T., Muller, B. M., Denkert, C., Loibl, S., Nekljudova, V., Untch, M., German Breast, G., and

Arbeitsgemeinschaft Gynakologische Onkologie-Breast Study, G. (2012) Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med* **366**, 299-309

10. Baselga, J., Bradbury, I., Eidtmann, H., Di Cosimo, S., de Azambuja, E., Aura, C., Gomez, H., Dinh, P., Fauria, K., Van Dooren, V., Aktan, G., Goldhirsch, A., Chang, T. W., Horvath, Z., Coccia-Portugal, M., Domont, J., Tseng, L. M., Kunz, G., Sohn, J. H., Semiglazov, V., Lerzo, G., Palacova, M., Probachai, V., Pusztai, L., Untch, M., Gelber, R. D., Piccart-Gebhart, M., and Neo, A. S. T. (2012) Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet* **379**, 633-640
11. Gianni, L., Pienkowski, T., Im, Y. H., Roman, L., Tseng, L. M., Liu, M. C., Lluch, A., Staroslawska, E., de la Haba-Rodriguez, J., Im, S. A., Pedrini, J. L., Poirier, B., Morandi, P., Semiglazov, V., Srimuninnimit, V., Bianchi, G., Szado, T., Ratnayake, J., Ross, G., and Valagussa, P. (2012) Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* **13**, 25-32
12. Untch, M., Rezai, M., Loibl, S., Fasching, P. A., Huober, J., Tesch, H., Bauerfeind, I., Hilfrich, J., Eidtmann, H., Gerber, B., Hanusch, C., Kuhn, T., du Bois, A., Blohmer, J. U., Thomssen, C., Dan Costa, S., Jackisch, C., Kaufmann, M., Mehta, K., and von Minckwitz, G. (2010) Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol* **28**, 2024-2031
13. Untch, M., Fasching, P. A., Konecny, G. E., Hasmuller, S., Lebeau, A., Kreienberg, R., Camara, O., Muller, V., du Bois, A., Kuhn, T., Stickeler, E., Harbeck, N., Hoss, C., Kahlert, S., Beck, T., Fett, W., Mehta, K. M., von Minckwitz, G., and Loibl, S. (2011) Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol* **29**, 3351-3357
14. van Ramshorst, M. S., van der Voort, A., van Werkhoven, E. D., Mandjes, I. A., Kemper, I., Dezentje, V. O., Oving, I. M., Honkoop, A. H., Tick, L. W., van de Wouw, A. J., Mandigers, C. M., van Warmerdam, L. J., Wesseling, J., Vrancken Peeters, M. T., Linn, S. C., Sonke, G. S., and Dutch Breast Cancer Research, G. (2018) Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* **19**, 1630-1640

15. Basik, M., Costantino, J. P., Santos, J. F. D. L., and al., e. (2018) NRG Oncology BR005: Phase II trial assessing accuracy of tumor bed biopsies (Bx) in predicting pathologic response in patients (Pts) with clinical/radiological complete response (CR) after neoadjuvant chemotherapy (NCT) in order to explore the feasibility of breast-conserving treatment (BCT) without surgery. *J Clin Oncol* **36**, TPS604-TPS604

16. Teoh, V., Dumitru, D., Tasoulis, M. K., and Macneill, F. (2019) P088. Breast cancer patients with no surgery in the breast after an exceptional response to neoadjuvant chemotherapy: a case series. *Eur J Surg Oncol* **45**, 908

17. Heil, J., Sinn, P., Richter, H., Pfob, A., Schaefgen, B., Hennigs, A., Riedel, F., Thomas, B., Thill, M., Hahn, M., Blohmer, J. U., Kuemmel, S., Karsten, M. M., Reinisch, M., Hackmann, J., Reimer, T., Rauch, G., and Golatta, M. (2018) RESPONDER - diagnosis of pathological complete response by vacuum-assisted biopsy after neoadjuvant chemotherapy in breast Cancer - a multicenter, confirmative, one-armed, intra-individually-controlled, open, diagnostic trial. *BMC Cancer* **18**, 851

18. Morrow, M., and Winer, E. P. (2020) De-escalating Breast Cancer Surgery-Where Is the Tipping Point? *JAMA Oncol* **6**, 183-184

19. Mamounas, E. P., Anderson, S. J., Dignam, J. J., Bear, H. D., Julian, T. B., Geyer, C. E., Jr., Taghian, A., Wickerham, D. L., and Wolmark, N. (2012) Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. *J Clin Oncol* **30**, 3960-3966

20. van Maaren, M. C., de Munck, L., Strobbe, L. J. A., Sonke, G. S., Westenend, P. J., Smidt, M. L., Poortmans, P. M. P., and Siesling, S. (2019) Ten-year recurrence rates for breast cancer subtypes in the Netherlands: A large population-based study. *Int J Cancer* **144**, 263-272

21. Vila, J., Teshome, M., Tucker, S. L., Woodward, W. A., Chavez-MacGregor, M., Hunt, K. K., and Mittendorf, E. A. (2017) Combining Clinical and Pathologic Staging Variables Has Prognostic Value in Predicting Local-regional Recurrence Following Neoadjuvant Chemotherapy for Breast Cancer. *Ann Surg* **265**, 574-580

22. Swisher, S. K., Vila, J., Tucker, S. L., Bedrosian, I., Shaitelman, S. F., Litton, J. K., Smith, B. D., Caudle, A. S., Kuerer, H. M., and Mittendorf, E. A. (2016) Locoregional Control According to Breast Cancer Subtype and Response to Neoadjuvant Chemotherapy in Breast Cancer Patients Undergoing Breast-conserving Therapy. *Ann Surg Oncol* **23**, 749-756

23. Gillon, P., Touati, N., Breton-Callu, C., Slaets, L., Cameron, D., and Bonnefoi, H. (2017) Factors predictive of locoregional recurrence following neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancer: An analysis of the EORTC 10994/BIG 1-00 study. *Eur J Cancer* **79**, 226-234

24. Huober J, van Mackelenbergh M, Schneeweiss A, Seither F, Blohmer JU, Denkert C, et al. Identifying breast cancer patients at risk of relapse despite pathological complete response after neoadjuvant therapy. NPJ Breast Cancer. 2023;9(1):23.

25. van Mackelenbergh MT, Loibl S, Untch M, Buyse M, Geyer CE, Jr., Gianni L, et al. Pathologic Complete Response and Individual Patient Prognosis After Neoadjuvant Chemotherapy Plus Anti-Human Epidermal Growth Factor Receptor 2 Therapy of Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer. J Clin Oncol. 2023;41(16):2998-3008.

26. Groen EJ, van der Noordaa MEM, Schaapveld M, Sonke GS, Mann RM, van Ramshorst MS, et al. Pathologic response of ductal carcinoma in situ to neoadjuvant systemic treatment in HER2-positive breast cancer. Breast Cancer Res Treat. 2021;189(1):213-24.

27. Asaoka, M., Narui, K., Suganuma, N., Chishima, T., Yamada, A., Sugae, S., Kawai, S., Uenaka, N., Teraoka, S., Miyahara, K., Kawate, T., Sato, E., Nagao, T., Matsubara, Y., Gandhi, S., Takabe, K., and Ishikawa, T. (2019) Clinical and pathological predictors of recurrence in breast cancer patients achieving pathological complete response to neoadjuvant chemotherapy. *Eur J Surg Oncol* **45**, 2289-2294

28. Mandish, S. F., Gaskins, J. T., Yusuf, M. B., Amer, Y. M., and Eldredge-Hindy, H. (2020) The effect of omission of adjuvant radiotherapy after neoadjuvant chemotherapy and breast conserving surgery with a pathologic complete response. *Acta Oncol* **59**, 1210-1217

29. Hill-Kayser, C. E., Vachani, C., Hampshire, M. K., Di Lullo, G. A., and Metz, J. M. (2012) Cosmetic outcomes and complications reported by patients having undergone breast-conserving treatment. *Int J Radiat Oncol Biol Phys* **83**, 839-844

30. Meretoja, T. J., Leidenius, M. H. K., Tasmuth, T., Sipila, R., and Kalso, E. (2014) Pain at 12 months after surgery for breast cancer. *JAMA* **311**, 90-92

31. Lilla, C., Ambrosone, C. B., Kropp, S., Helmbold, I., Schmezer, P., von Fournier, D., Haase, W., Sautter-Bihl, M. L., Wenz, F., and Chang-Claude, J. (2007) Predictive factors for late normal tissue complications following radiotherapy for breast cancer. *Breast Cancer Res Treat* **106**, 143-150

32. Prescott, R. J., Kunkler, I. H., Williams, L. J., King, C. C., Jack, W., van der Pol, M., Goh, T. T., Lindley, R., and Cairns, J. (2007) A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. *Health Technol Assess* **11**, 1-149, iii-iv

33. Taylor, C., Correa, C., Duane, F. K., Aznar, M. C., Anderson, S. J., Bergh, J., Dodwell, D., Ewertz, M., Gray, R., Jagsi, R., Pierce, L., Pritchard, K. I., Swain, S., Wang, Z., Wang, Y., Whelan, T., Peto, R., McGale, P., and Early Breast Cancer Trialists' Collaborative, G. (2017) Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. *J Clin Oncol* **35**, 1641-1649

34. Jagsi, R., Griffith, K. A., Vicini, F., Boike, T., Burmeister, J., Dominello, M. M., Grills, I., Hayman, J. A., Moran, J. M., Paximadis, P., Radawski, J. D., Walker, E. M., Pierce, L. J., and Michigan Radiation Oncology Quality, C. (2020) Toward Improving Patients' Experiences of Acute Toxicity From Breast Radiotherapy: Insights From the Analysis

of Patient-Reported Outcomes in a Large Multicenter Cohort. *J Clin Oncol* **38**, 4019-4029

35. Coles, C. E., Griffin, C. L., Kirby, A. M., Titley, J., Agrawal, R. K., Alhasso, A., Bhattacharya, I. S., Brunt, A. M., Ciurlionis, L., Chan, C., Donovan, E. M., Emson, M. A., Harnett, A. N., Haviland, J. S., Hopwood, P., Jefford, M. L., Kaggwa, R., Sawyer, E. J., Syndikus, I., Tsang, Y. M., Wheatley, D. A., Wilcox, M., Yarnold, J. R., Bliss, J. M., and Trialists, I. (2017) Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* **390**, 1048-1060
36. Schafer, R., Strnad, V., Polgar, C., Uter, W., Hildebrandt, G., Ott, O. J., Kauer-Dorner, D., Knauerhase, H., Major, T., Lyczek, J., Guinot, J. L., Dunst, J., Miguelez, C. G., Slampa, P., Allgauer, M., Lossl, K., Kovacs, G., Fischedick, A. R., Fietkau, R., Resch, A., Kulik, A., Arribas, L., Niehoff, P., Guedea, F., Schlamann, A., Gall, C., Polat, B., Groupe Europeen de Curietherapie of European Society for, R., and Oncology. (2018) Quality-of-life results for accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. *Lancet Oncol* **19**, 834-844
37. Hopwood, P., Haviland, J. S., Sumo, G., Mills, J., Bliss, J. M., Yarnold, J. R., and Group, S. T. M. (2010) Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol* **11**, 231-240
38. Kunkler, I. H., Williams, L. J., Jack, W. J., Cameron, D. A., Dixon, J. M., and investigators, P. I. (2015) Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* **16**, 266-273
39. Wickberg, A., Holmberg, L., Adami, H. O., Magnuson, A., Villman, K., and Liljegren, G. (2014) Sector resection with or without postoperative radiotherapy for stage I breast cancer: 20-year results of a randomized trial. *J Clin Oncol* **32**, 791-797
40. Sjostrom, M., Lundstedt, D., Hartman, L., Holmberg, E., Killander, F., Kovacs, A., Malmstrom, P., Nimeus, E., Werner Ronnerman, E., Ferno, M., and Karlsson, P. (2017) Response to Radiotherapy After Breast-Conserving Surgery in Different Breast Cancer Subtypes in the Swedish Breast Cancer Group 91 Radiotherapy Randomized Clinical Trial. *J Clin Oncol* **35**, 3222-322