Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alastair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists' group

Summary

Background The TARGIT-A trial compared risk-adapted radiotherapy using single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated external beam radiotherapy (EBRT) for breast cancer. We report 5-year results for local recurrence and the first analysis of overall survival.

Methods TARGIT-A was a randomised, non-inferiority trial. Women aged 45 years and older with invasive ductal carcinoma were enrolled and randomly assigned in a 1:1 ratio to receive TARGIT or whole-breast EBRT, with blocks stratified by centre and by timing of delivery of targeted intraoperative radiotherapy: randomisation occurred either before lumpectomy (prepathology stratum, TARGIT concurrent with lumpectomy) or after lumpectomy (postpathology stratum, TARGIT given subsequently by reopening the wound). Patients in the TARGIT group received supplemental EBRT (excluding a boost) if unforeseen adverse features were detected on final pathology, thus radiotherapy was risk-adapted. The primary outcome was absolute difference in local recurrence in the conserved breast, with a prespecified non-inferiority margin of 2·5% at 5 years; prespecified analyses included outcomes as per timing of randomisation in relation to lumpectomy. Secondary outcomes included complications and mortality. This study is registered with ClinicalTrials.gov, number NCT00983684.

Findings Patients were enrolled at 33 centres in 11 countries, between March 24, 2000, and June 25, 2012. 1721 patients were randomised to TARGIT and 1730 to EBRT. Supplemental EBRT after TARGIT was necessary in 15·2% [239 of 1571] of patients who received TARGIT (21·6% prepathology, 3·6% postpathology). 3451 patients had a median follow-up of 2 years and 5 months (IQR 12–52 months), 2020 of 4 years, and 1222 of 5 years. The 5-year risk for local recurrence in the conserved breast was 3·3% (95% CI 2·1–5·1) for TARGIT versus 1·3% (0·7–2·5) for EBRT (p=0·042). TARGIT concurrently with lumpectomy (prepathology, n=2298) had much the same results as EBRT: 2·1% (1·1–4·2) versus 1·1% (0·5–2·5; p=0·31). With delayed TARGIT (postpathology, n=1153) the between-group difference was larger than 2·5% (TARGIT 5·4% [3·0–9·7] vs EBRT 1·7% [0·6–4·9]; p=0·069). Overall, breast cancer mortality was much the same between groups (2·6% [1·5–4·3] for TARGIT vs 1·9% [1·1–3·2] for EBRT; p=0·56) but there were significantly fewer non-breast-cancer deaths with TARGIT (1·4% [0·8–2·5] vs 3·5% [2·3–5·2]; p=0·0086), attributable to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3·9% (2·7–5·8) for TARGIT versus 5·3% (3·9–7·3) for EBRT (p=0·099). Wound-related complications were much the same between groups but grade 3 or 4 skin complications were significantly reduced with TARGIT (four of 1720 vs 13 of 1731, p=0·029).

Interpretation TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected as per the TARGIT-A trial protocol, as an alternative to postoperative EBRT.

Funding University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre, UCLH Charities, National Institute for Health Research Health Technology Assessment programme, Ninewells Cancer Campaign, National Health and Medical Research Council, and German Federal Ministry of Education and Research.

Introduction

Adjuvant whole-breast external beam radiotherapy (EBRT) is deemed mandatory after lumpectomy for breast cancer on the basis of the reduction of local recurrence in the conserved breast and of breast cancer mortality.[1] Even in highly selected patients, omission of radiotherapy increases the risk of local recurrence.[2–5]

To develop a more refined and personalised approach to adjuvant radiotherapy, we designed the TARGIT-A (TARGeted Intraoperative radioTherapy Alone) trial.[6] The

Denmark (H L Flyger MD,
H M R Holtveg MD); Department
of Surgery (S Massarut MD), and
Department of Radiation
Oncology (M Roncadin MD),
Centro di Riferimento
Oncologia, Aviano, Italy; School
of Surgery, University of
Western Australia, Perth, WA,
Australia (Prof C Saunders);
Department of Surgery,
University of California,
San Francisco, CA, USA
(M Alvarado MD,
Prof L Esserman MD);
Department of Gynecology and
Obstetrics, Red Cross Hospital,
Munich, Germany
(Prof W Eiermann MD);
Department of Radiation
Oncology (Prof J A Dewar FRCR),
and Department of Surgery
(D Brown FRCS,
Prof A Thompson FRCS),
Ninewells Hospital, Dundee,
UK; Department of Radiation
Oncology, Technical University
of Munich, Munich, Germany
(S Pigorsch MD); Department of
Radiation Oncology, East
Carolina University Brody
School of Medicine, Greenville,
NC, USA (E Harris MD);
Psychosocial Oncology Clinical
Studies Group, National Cancer
Research Institute, London, UK
(A Matthews BSc); and
Independent Cancer Patients'
Voice, London, UK (A Matthews)

Correspondence to:
Prof Jayant S Vaidya, Department
of Surgery, Clinical Trials Group,
Division of Surgery and
Interventional Science,
University College London,
London W1W 7EJ, UK
jayant.vaidya@ucl.ac.uk

See Online for appendix

For a summary of the TARGIT-A
protocol see http://www.
thelancet.com/protocol-
reviews/99PRT-47

For the full TARGIT-A protocol
see http://www.hta.ac.uk/
project/1981.asp

For details of the TARGIT
technique see http://www.
targit.org.uk

experimental intervention (risk-adapted radiotherapy) consisted of one dose of radiation to the tumour bed using targeted intraoperative radiotherapy (also known as TARGIT), supplemented when necessary by EBRT in patients in whom unforeseen risk factors were discovered on the final pathology report. The control intervention was standard treatment, consisting of several weeks of whole-breast EBRT.

The TARGIT-A trial was originally conceived[7–9] as a response to a clinical dilemma and a clinicopathological paradox. The clinical dilemma is faced by many patients with limited access to radiotherapy. Many such patients, presenting with breast cancer suitable for breast-conserving surgery but unable to attend daily for up to 6 weeks for postoperative radiotherapy, will face mastectomy. Even in the USA, women living far from a radiotherapy centre do not receive optimum breast-conserving therapy.[10] Where access is easy, the prolonged course can be stressful and inconvenient. If a one-off radiation treatment at the time of surgery could be shown to be non-inferior to EBRT, then many women worldwide might avoid the protracted course of EBRT and many might be spared an unnecessary mastectomy. At the very least, one-off radiation treatment would significantly shorten treatment time and improve patient experience.

The clinicopathological paradox that led to the idea of focusing radiation to the tumour bed was motivated by the repeated observation that although two-thirds of specimens of mastectomies undertaken for small breast cancers harbor occult cancer foci distributed throughout the breast,[7–9,11] most local recurrences in the conserved breast appear in the original tumour bed.[7–9]

This investigator-initiated trial was launched in March, 2000, and reached the original accrual goal of 2232 participants in April, 2010. In July, 2010, when we reported the initial results for local control and early complications,[6] the 4-year Kaplan-Meier estimate of local recurrence in the conserved breast was 1·20% (95% CI 0·53–2·71) for those randomised to TARGIT and 0·95% (0·39–2·31) for those randomised to EBRT. A second analysis was planned after a further 2 years of follow-up. We continued randomisation until June, 2012, to allow accrual in sub-protocols while the data matured further, and closed the trial after accruing the planned 1200 additional patients (1219 accured, total n=3451). In the present report, we provide updated analyses and 5-year estimates for local control and the first analysis of overall survival. Additionally, we investigated whether the timing of TARGIT in relation to lumpectomy made a difference to the outcome.

Methods
Procedures

As previously described,[6] women with early breast cancer were eligible if they were aged 45 years or older and suitable for wide local excision for invasive ductal carcinoma that was unifocal on conventional examination and imaging. MRI was not required and only 5·6% (192) of patients in the trial had an MRI performed. Patients gave written informed consent to join the trial. The protocol was approved by the appropriate regulatory and ethics authorities for each centre before enrolment could begin.

Patients were randomly assigned in a 1:1 ratio to receive a risk-adapted approach using single-dose TARGIT or EBRT as per standard schedules over several weeks, with randomisation blocks stratified by centre and by proposed timing of delivery of TARGIT (prepathology and post-pathology strata; appendix); details have been described previously.[6] A risk-adapted approach meant that if the final pathology report showed unpredicted prespecified adverse features, then EBRT was to be added to TARGIT, in which case TARGIT served as the tumour-bed boost. The core protocol defined three such features when EBRT was recommended to supplement TARGIT within the experimental group: tumour-free margin smaller than 1 mm, extensive in-situ component, or unexpected invasive lobular carcinoma. Pragmatically, individual centres could prespecify more than these core factors, such as close margins (eg, 1–10 mm) or other adverse prognostic factors (eg, several positive nodes, extensive lymphovascular invasion) in a treatment policy document before they started recruitment. Therefore, the trial was a comparison of two policies—so called one-size-fits-all whole-breast radiotherapy versus individualised risk-adapted therapy—in which a proportion of patients who received TARGIT were also given EBRT if they were shown to have adverse tumour factors. This situation was expected in 15% of cases and was incorporated into the power calculations. Sample size calculations have been described previously.[6] All analyses were by intention to treat. A summary of the protocol and the full protocol are available online.

The concept and the TARGIT technique, which was pioneered by investigators at University College London,[12–14] allows the patient to receive all required radiation in one fraction before she awakes from surgery (appendix).[12–21] The Intrabeam device (Carl Zeiss Meditec, Oberkochen, Germany) provides a point source of 50 kV energy x-rays at the centre of a spherical applicator. The appropriately sized (1·5–5·0 cm diameter) applicator is placed in the tumour bed using a meticulous surgical technique, including a carefully inserted purse-string suture that ensures that breast tissues at risk of local recurrence receive the prescribed dose while skin and deeper structures are protected. Radiation is delivered over 20–45 min to the tumour bed. The surface of the tumour bed typically receives 20 Gy that attenuates to 5–7 Gy at 1 cm depth.

In the initial trial design, randomisation to TARGIT or EBRT group was done before lumpectomy (pre-pathology). However, the trial was also firmly rooted on the principles of pragmatism to test a new approach (single dose targeted intraoperative radiotherapy to the tumour bed followed by EBRT in patients with

unforeseen adverse factors). Therefore, when some of the centres planning to join the trial requested us to allow them to give intraoperative radiotherapy as a second procedure by reopening the wound, we permitted it: this decision facilitated more stringent selection of patients (tumour pathology was available—hence postpathology) and was logistically easier, allowing enrolment of patients from neighbouring centres who had already had the lumpectomy. We therefore made a protocol amendment on Sept 22, 2004, obtained ethics approval, and added this postpathology stratum to the trial, along with a completely separate randomisation table for such patients.

We specified that postpathology patients should be randomised within 30 days after lumpectomy. If allocated to TARGIT, patients in the prepathology stratum received it concurrently, immediately after surgical excision under the same anaesthesia; patients in the postpathology stratum received it as a subsequent procedure. We planned a separate analysis of the two strata (prepathology vs postpathology). The rationale for stratification according to the scheduling of radiotherapy was that randomisation to the trial after full pathology had become available might theoretically allow better case selection. Conversely, treatment given at the time of initial lumpectomy could have a greater effectiveness because of its immediacy. Furthermore, the degree of accuracy of placement of the radiotherapy applicator for giving TARGIT by reopening the cavity might be quite different from that achieved at the time of original lumpectomy.

The primary outcome measure was the absolute difference in local recurrence in the conserved breast in patients who had received breast-conserving therapy. Power calculations were based on this outcome measure for an absolute non-inferiority margin of 2·5% (as detailed in section 9 of the protocol) and the original recruitment goal was 2232 patients in total. The secondary outcomes were toxicity and overall survival, including breast-cancer deaths and non-breast-cancer deaths. An independent senior clinician, masked to randomisation, reviewed the available data and ascertained the cause of death in all cases. If breast cancer was present at the time of death, the death was presumed to be from breast cancer. We prespecified a formal analysis for deaths from cardiovascular causes and deaths from other cancers.

We did exploratory analyses for regional recurrence (axilla plus supraclavicular), loco-regional recurrence (local plus regional), distant recurrence, any other recurrence (regional, contralateral breast, and distant recurrence), and all recurrence (local recurrence in the conserved breast and any other recurrence).

Early complications were published previously[6] and for this report, we analysed complications arising 6 months after randomisation. This trial is registered with ClinicalTrials.gov, number NCT00983684.

Statistical analysis

We analysed the non-inferiority statistic by calculating the difference in binomial proportions of local recurrences in the conserved breast between the two randomised groups (TARGIT vs EBRT). To assess stability over time, we also calculated this statistic for the mature cohort (n=2232), reported in 2010, and for the earliest cohort (excluding the last 4 years of enrolment; n=1222) who had a median follow up of 5 years. We calculated the Z score and $p_{non-inferiority}$ using established methods[22–24] for the whole cohort and the two prespecified strata—prepathology and postpathology.

To address the issue of follow-up, we charted the absolute differences in the 5-year Kaplan-Meier estimates of local recurrence in the conserved breast and overall mortality for patients with prepathology randomisation in the whole trial along with the mature cohort reported in 2010, which has a longer follow up (median 3 years 8 months, maximum 12 years), and the earliest cohort.

A patient was deemed to have adequate follow-up if they had at least 5 years of follow-up or if they were seen within the year before database lock. Patients were censored when they were last seen or withdrawn from the trial. The database (customised Microsoft Access) as validated on June 29, 2012, was used for this analysis, with June 1, 2012, as a reference date. SAS System (version 9.3), Excel 2011, STATA (version 12.0), and SPSS (version 20.0) were used for data compilation, validation, and analysis. Kaplan-Meier graphs were displayed as recommended by Pocock and colleagues,[25] and a log-rank test was used to compare the difference between survival function and to obtain p values (significance level set at p<0·01 for local recurrence and p<0·05 for survival).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and the trial statistician had full access to all the data in the study; all authors were responsible for the decision to submit for publication.

Results

The trial recruited 3451 patients from 33 centres in 11 countries from March 24, 2000, to June 25, 2012; 1721 patients were randomly allocated to TARGIT and 1730 to EBRT. Two thirds of patients (n=2298) were randomised before lumpectomy (prepathology) and a third (n=1153) were randomised after lumpectomy (postpathology). As per protocol, of those who received TARGIT, 15·2% (239 of 1571) received both TARGIT and EBRT (21·6% [219 of 1012] in the prepathology stratum and 3·6% [20 of 559] in the postpathology stratum).

Since the 2010 analysis, the number of primary events has increased from 13 to 34. There have been 88 deaths, 36 from breast cancer and 52 from causes other than breast cancer.

The patient and tumour characteristics and trial profile are in the appendix. The risk-adapted design is shown in the trial profile—eg, of the 1140 patients allocated TARGIT in the prepathology stratum, 219 received TARGIT and EBRT as per protocol, because they were shown to have characteristics of high-risk disease postoperatively (appendix). There was no significant difference between prepathology and postpathology in the timing of delivery of EBRT (p=0·58). Most cancers were small and of good prognosis (87% [2685 of 3082] were up to 2 cm, 85% [2573 of 3032] grades 1 or 2, 84% [2610 of 3112] node negative, 93% [2874 of 3093] oestrogen-receptor positive and 82% [2462 of 3016] progesterone-receptor positive) and detected by screening 69% [2102 of 3063]. The appendix shows tumour characteristics and main results as per treatment received.

93·7% [3234 of 3451] of patients were seen within the year before datalock or had at least 5 years of follow-up (appendix). The whole cohort of 3451 patients had a median follow-up of 2 years and 5 months (IRQ 12–52 months), 2020 patients had a median follow-up of 4 years, and 1222 patients had a median follow-up of 5 years. The mature cohort of 2232 patients, which was originally reported in 2010, had a median follow up of 3 years and 7 months (IRQ 30–61 months).

Table 1 shows detailed results for the local recurrence in the conserved breast (primary outcome), any other recurrence (exploratory outcome), and death (secondary outcome).

The 5-year risks for local recurrence in the conserved breast for TARGIT versus EBRT were 3·3% (95% CI 2·1–5·1) versus 1·3% (0·7–2·5; p=0·042). Breast cancer mortality was much the same in the two groups: 2·6% (1·5–4·3) for TARGIT versus 1·9% (1·1–3·2) for EBRT (p=0·56), but there were significantly fewer non-breast-cancer deaths in the TARGIT group than the EBRT group (1·4%, 0·8–2·5 vs 3·5%, 2·3–5·2; p=0·0086), attributable to fewer deaths from cardiovascular causes and other cancers (figure 1, table 2). Overall mortality for TARGIT was 3·9% (2·7–5·8) versus 5·3% (3·9–7·3) for EBRT (p=0·099). Overall, in absolute terms, there were 12 additional local recurrences but 14 fewer deaths in the TARGIT group (figures 1, 2).

Despite the poor prognostic factors for survival in the group selected to receive TARGIT plus EBRT, as shown by the increased breast cancer mortality (8·0%, 95% CI 3·5–17·5), local recurrence was low in that group (0·9%, 0·1–6·1), and did not differ from those who received TARGIT alone (appendix).

In the prepathology stratum—ie, when TARGIT was delivered during the initial lumpectomy, 2298 patients—the risk of local recurrence in the conserved breast was much the same for TARGIT as for EBRT: TARGIT 2·1% (95% CI 1·1–4·2) versus EBRT 1·1% (0·5–2·5; p=0·31). Breast-cancer mortality was 17 patients for TARGIT

| | Events; 5-year cumulative risk (95%CI) | | Absolute difference* |
	TARGIT	EBRT	
All patients			
Local recurrence (n=3375)	23; 3·3% (2·1–5·1)	11; 1·3% (0·7–2·5)	12 (2·0%)
Any other recurrence (n=3375)	46; 4·9% (3·5–6·9)	37; 4·4% (3·0–6·4)	9 (0·5%)
Death (n=3451)	37; 3·9% (2·7–5·8)	51; 5·3% (3·9–7·3)	–14 (–1·4%)
Prepathology†			
Local recurrence (n=2234)	10; 2·1% (1·1–4·2)	6; 1·1% (0·5–2·5)	4 (1·0%)
Any other recurrence (n=2234)	29; 4·8% (3·1–7·3)	25; 4·7% (3·0–7·4)	4 (0·1%)
Death (n=2298)	29; 4·6% (1·8–6·0)	42; 6·9% (4·3–9·6)	–13 (–2·3%)
Postpathology‡			
Local recurrence (n=1141)	13; 5·4% (3·0–9·7)	5; 1·7% (0·6–4·9)	8 (3·7%)
Any other recurrence (n=1141)	17; 5·2% (3·0–8·8)	12; 3·7% (1·9–7·0)	5 (1·5%)
Death (n=1153)	8; 2·8% (1·3–5·9)	9; 2·3% (1·0–5·2)	–1 (0·5%)

TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. *In Kaplan-Meier point estimate at 5 years (TARGIT minus EBRT). †TARGIT given at same time as lumpectomy. ‡TARGIT given after lumpectomy, as separate procedure.

Table 1: Results of primary (local recurrence in the conserved breast), secondary (death), and exploratory (any other recurrence) outcomes for all patients and the two strata as per timing of randomisation and delivery of TARGIT
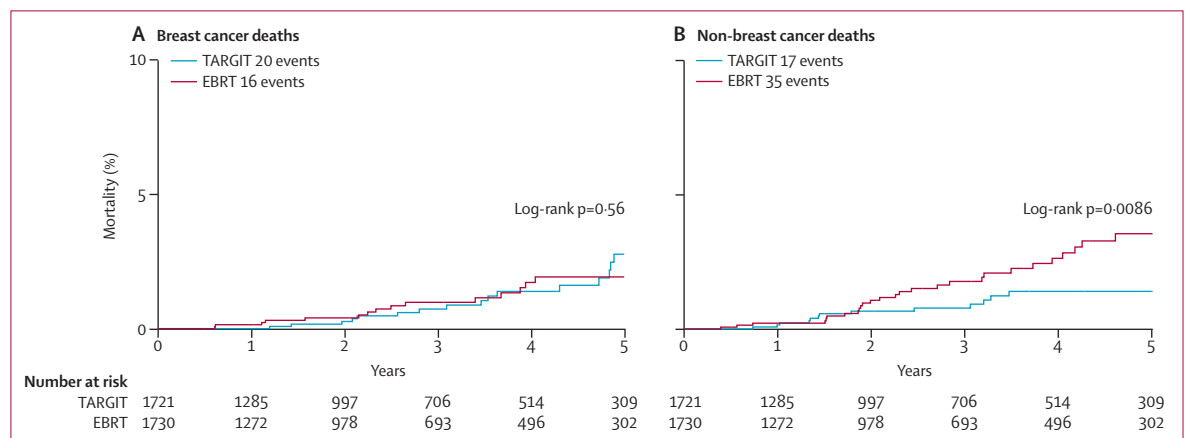

Figure 1: Kaplan-Meier analysis of breast cancer deaths and non-breast-cancer deaths
(A) Breast cancer. (B) Non-breast-cancer. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy.

versus 15 patients for EBRT (3·3%, 1·9–5·8 vs 2·7%, 1·5–4·6; p=0·72), non-breast-cancer mortality was 12 patients for TARGIT versus 27 patients for EBRT (1·3%, 0·7–2·8% vs 4·4%, 2·8–6·9; p=0·016). Thus, in absolute terms, there were four additional local recurrences but 13 fewer deaths in the prepathology TARGIT stratum (figure 3; appendix).

In the postpathology stratum—ie, when TARGIT was delivered as a delayed procedure by reopening the lumpectomy cavity, 1153 patients—the difference in local recurrence in the conserved breast between the two groups was larger than 2·5%: TARGIT 5·4% (95% CI 3·0–9·7) vs EBRT 1·7% (0·6–4·9; p=0·069). Breast-cancer mortality was three patients for TARGIT versus one patient for EBRT (1·2%, 0·4–4·2 vs 0·5%, 0·1–3·5; p=0·35), and non-breast-cancer mortality was five patients for TARGIT versus eight patients for EBRT (1·58%, 0·62–3·97 vs 1·76%, 0·7–4·4; p=0·32). Thus, in absolute terms, there were eight additional local recurrences and one less death in the postpathology TARGIT stratum (figure 3).

The results of a comparison[26] of cumulative incidence for local recurrence in the presence of competing risks (death and withdrawal from trial) were no different from Kaplan-Meier estimates, showing that these risks did not bias the main results (data not shown).

Analysis limited to the mature cohort, first reported in 2010 (n=2232, median follow-up now 3 years 7 months), in which most events had occurred (32 of 34 local recurrences and 85 of 88 deaths), yielded much the same results (data not shown).

Table 3 shows the Z score and $p_{non-inferiority}$ for the primary outcome of local recurrence in the conserved breast, for the whole cohort, the mature cohort, and the earliest cohort. Non-inferiority is established for the whole cohort and for prepathology patients but not for post-pathology patients.

Figure 4 shows the primary (local recurrence in the conserved breast) and secondary outcomes (deaths) for the prepathology stratum. It shows the differences in 5-year estimates for these outcomes for the whole cohort,

the mature cohort, and the earliest cohort. It demonstrates the stability of the results with longer follow-up and the trade-offs between the two outcomes.

For the secondary outcome of complications 6 months after randomisation, we noted no significant difference in any protocol-defined wound-related complication. There were fewer grade 3 or 4 radiotherapy-related skin complications with TARGIT than with EBRT (four of 1721 vs 13 of 1730, p=0·029).

In post-hoc exploratory analyses, we noted no significant difference in 5-year risk of regional recurrence
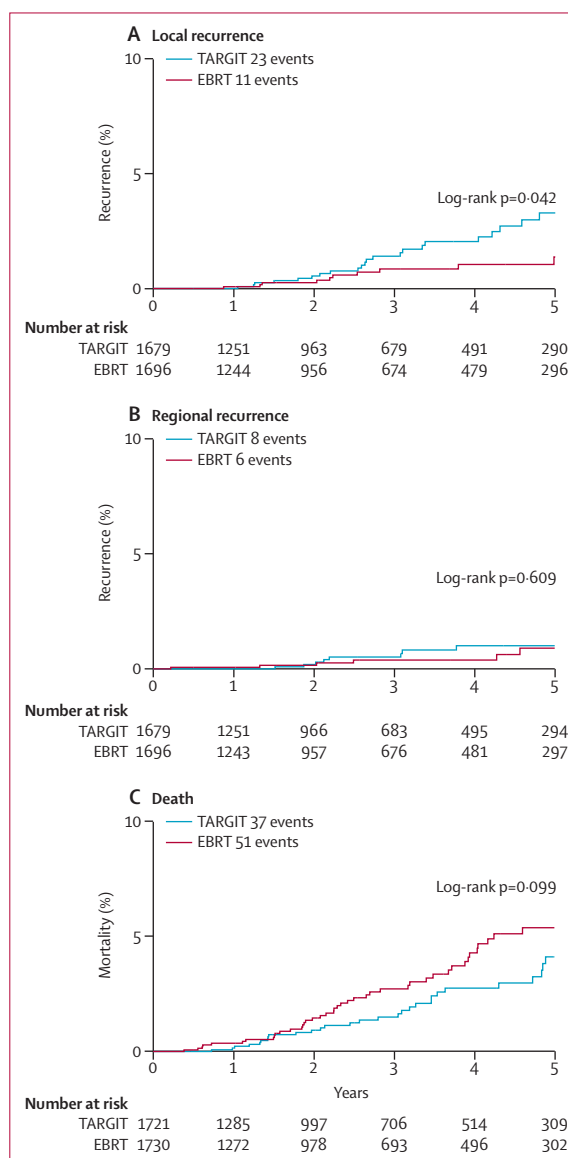

Figure 2: Kaplan-Meier analysis of local recurrence in the conserved breast, regional recurrence (axillary and supraclavicular), and deaths
Local recurrence was the primary outcome, death was a secondary outcome, regional recurrence was an exploratory outcome. Three of the 14 regional recurrences had breast recurrence as well (one TARGIT and two EBRT). (A) Local recurrence in the conserved breast. (B) Regional recurrence. (C) Death. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy.

	TARGIT	EBRT
Other cancers	8	16
Cardiovascular causes		
Cardiac*	2	8
Stroke	0	2
Ischaemic bowel	0	1
Other†	7	8
Total	17	35

5-year risk 1·4% for TARGIT versus 3·5% for EBRT; log-rank p=0·0086.
TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy.
*Included one "sudden death at home" in EBRT group. †TARGIT: two diabetes, one renal failure, one liver failure, one sepsis, one Alzheimer's disease, one unknown; EBRT: one myelopathy, one perforated bowel, one pneumonia, one old age, four unknown.

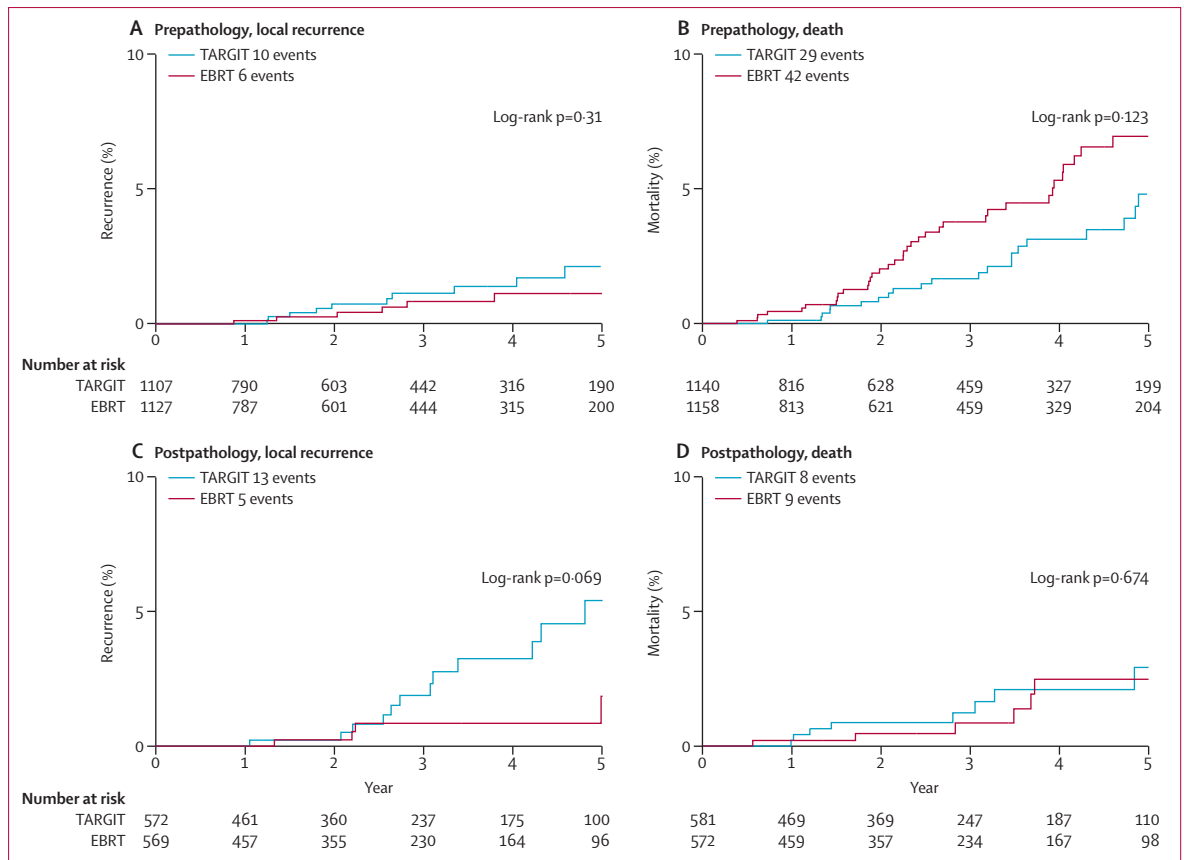*Table 2:* **Causes of death other than breast cancer in all patients**

Figure 3: **Kaplan-Meier analysis of local recurrence in the conserved breast and death for the two strata as per timing of randomisation and delivery of TARGIT (prepathology *vs* postpathology)**

Local recurrence was the primary outcome, death was a secondary outcome. Prepathology (n=2298), randomised before lumpectomy and TARGIT given concurrently with lumpectomy. Postpathology (n=1153), randomised after lumpectomy and TARGIT given by reopening the wound. (A) Local recurrence in prepathology stratum. (B) Deaths in prepathology stratum. (C) Local recurrence in postpathology stratum. (D) Deaths in postpathology stratum. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy.

(1·1%, 95% CI 0·5–2·1 for TARGIT *vs* 0·9%, 0·4–2·2 for EBRT), distant recurrence (3·9%, 2·7–5·6 *vs* 3·2%, 2·1–4·9), any other recurrence (4·9%, 3·5–6·9 *vs* 4·4%, 3·0–6·4), or all recurrence (8·2%, 6·3–10·6 *vs* 5·7%, 4·1–7·8). The difference in all recurrence, which was driven by local recurrence in the conserved breast, was smaller in the prepathology stratum (6·9%, 4·8–9·8 *vs* 5·8%, 3·9–8·5) than in the postpathology stratum (10·4%, 7·0–15·2 *vs* 5·4, 3·1–0·2). Similarly, the difference in loco-regional recurrence 4·2% (2·8–6·1) for TARGIT versus EBRT 2·0% (1·1–3·5) was smaller in the prepathology stratum (3·1%, 1·8–5·2 *vs* 2·0%, 1·0–4·0) than the the postpathology stratum (6·2%, 3·6–10·6 *vs* 2·0%, 0·8–5·2).

Discussion

At 5 year follow-up, risk of local recurrence with TARGIT was non-inferior to EBRT when all patients were analysed together. Analysis of the two strata according to timing of delivery of TARGIT confirmed non-inferiority when TARGIT was delivered concurrently with lumpectomy

(prepathology stratum) but not in the postpathology stratum, in which TARGIT was given as a second procedure after reopening the wound. Overall, breast-cancer mortality was much the same for TARGIT and EBRT, but significantly fewer non-breast-cancer deaths occurred in the TARGIT group than the EBRT group, attributable to fewer deaths from cardiovascular causes and other cancers. Wound-related complications were much the same between the groups, but there were significantly fewer grade 3 or 4 radiotherapy-related complications with TARGIT than with EBRT. The main outcomes remained stable in cohorts of patients with increasing median follow-up periods (figure 4).

We emphasise that this trial is of a risk-adapted design: it is a trial of two policies, not of TARGIT versus EBRT. The aim in the experimental group was to complete therapy with one radiation treatment delivered at the time of surgery in most patients, but if subsequent pathology suggested adverse histological features then it was mandatory to complete treatment to the whole breast (but omitting a tumour-bed radiation boost). This

	Median follow-up	Number of events	Absolute difference (90% CI) in the binomial proportions of local recurrence* in the conserved breast (TARGIT minus EBRT)	Z score	$p_{non-inferiority}$
Whole trial					
All patients (n=3451)	2 years 5 months	34	0·72% (0·2 to 1·3)	–5·168	<0·0001
Mature cohort (n=2232)	3 years 7 months	32	1·13% (0·3 to 2·0)	–2·652	0·0040
Earliest cohort (n=1222)	5 years	23	1·14% (–0·1 to 2·4)	–1·750	0·0400
Prepathology†					
All patients (n=2298)	2 years 4 months	16	0·37% (–0·2 to 1·0)	–5·954	<0·0001
Mature cohort (n=1450)	3 years 8 months	14	0·6% (–0·3 to 1·5)	–3·552	0·0002
Earliest cohort (n=817)	5 years	9	0·76% (–0·4 to 2·0)	–2·360	0·0091
Postpathology‡					
All patients (n=1153)	2 years 4 months	18	1·39% (0·2 to 2·6)	–1·503	0·0664
Mature cohort (n=782)	3 years 7 months	18	2·04% (0·3 to 3·8)	–0·429	0·3339
Earliest cohort (n=405)	5 years	14	1·8% (–1·2 to 4·8)	–0·382	0·3511

The prespecified non-inferiority margin was 2·5%. Mature cohort consisted of 2232 patients for whom data was previously reported in 2010. Earliest cohort excluded patients enrolled in the last 4 years of the study. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. *Binomial proportion=number of recurrences/number of patients. †TARGIT given at same time as lumpectomy. ‡TARGIT given after lumpectomy, as separate procedure.

Table 3: Calculation of $p_{non-inferiority}$ for the whole cohort, the mature cohort, and the earliest cohort

scenario occurred in 15% of cases as per our original estimate. Because the allocation of treatment was randomised, about the same percentage of patients with adverse pathology would be included in the TARGIT and EBRT groups. This trial therefore has a true pragmatic design, reflecting practice in the real world, while maintaining statistical validity. The addition of EBRT in the TARGIT group is not a crossover or a protocol deviation but was prospectively required in the protocol.

The prepathology and postpathology divisions were not subgroups based on patient or tumour characteristics; they were two distinct strata, as per the timing of randomisation (either before or after lumpectomy), and therefore delivery of TARGIT (either concurrently with the initial lumpectomy under the same anaesthetic or as a second separate procedure). They had different methods of case selection, separate randomisation tables, and different methods of giving the experimental treatment (fresh wound *vs* reopened wound). Individual separate analysis of each of these two strata was prespecified, and the two could be considered as parallel trials.

Length of follow-up did not differ between the prepathology and postpathology strata, because although the postpathology randomisation started a few years later than the prepathology stratum, accrual was slow in the first few years and only about 5% of all patients were recruited before postpathology randomisation was started; hence the difference in median follow-up was only 1 month.

The original mature cohort of 2232 patients,[6] included within this analysis, has a median follow up of close to 4 years (and 1222 of these patients have a median follow up of 5 years), thus covering the period of the peak hazard for breast cancer local recurrent events that seem
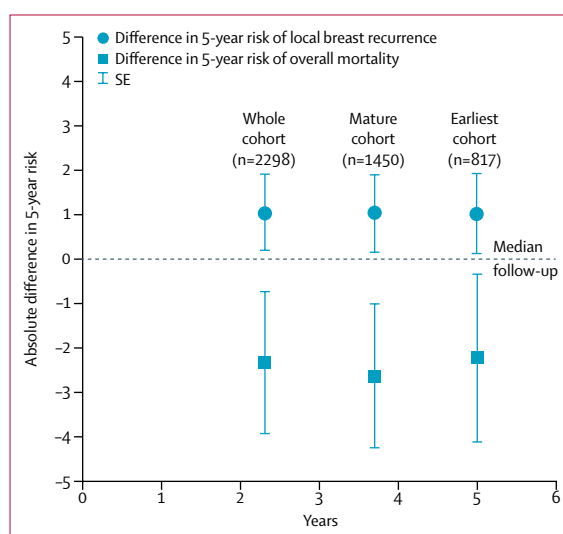

Figure 4: Absolute differences in 5-year Kaplan-Meier estimate of local recurrence in the conserved breast and overall mortality (TARGIT minus EBRT) for the prepathology stratum in the whole cohort, the mature cohort and the earliest cohort
All patients in the earlier cohorts are included in later cohorts. Median follow-up for whole cohort was 2 years 4 months. Median follow-up for mature cohort was 3 years 8 months. Median follow-up for earliest cohort was 5 years.
TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy.

to cluster around 2–3 years.[27] Furthermore, since the first report,[6] the number of primary events has increased from 13 to 34.

Although the original power calculations needed 2232 patients for the trial, we have previously explained how with a background recurrence rate of 1·5% a trial testing for a non-inferiority margin of 2·5% with 80% power and 95% confidence needs a sample size of only

585.[6] We have 2298 patients in the prepathology stratum and 1153 patients in the postpathology stratum and we have 1222 patients with a median follow-up of 5 years.

We can be assured that there is no increased toxicity with TARGIT, and radiotherapy-related local toxic effects are slightly reduced. The low incidence of grade 3 or grade 4 radiotherapy-related toxic effects and local recurrences is also indicative of the high-quality radiotherapy being given in the EBRT group. Previous studies from individual centres have suggested a better cosmetic outcome,[28] lower short-term and long-term skin toxicity, and better quality of life with TARGIT.[29,30] In a separate comparison no difference was shown between the toxicity of TARGIT plus EBRT versus EBRT with EBRT boost.[30]

We had not planned a statistical test comparing the EBRT groups in the two strata with each other, since this would have been a non-randomised comparison. Nevertheless, the apparent difference in non-breast-cancer deaths between the EBRT groups in the two prepathology and postpathology strata is not statistically significant (p=0·17).

Cause-specific mortality was much the same in the two groups but there were significantly fewer non-breast-cancer deaths in the TARGIT group (p=0·0086). This difference was mainly attributable to fewer (two vs 11) deaths from cardiovascular causes and new non-breast cancers (eight vs 16; figure 1, table 2). Although an increase in cardiovascular deaths related to radiotherapy[1] has not previously become apparent for 7–10 years[31] a large study that included patients treated until 2001, has shown that significant radiotherapy-related cardiac toxicity is apparent within the first 4 years.[32] Importantly, in the TARGIT-A trial, 1222 patients have a median follow up of 5 years, and the statistical probability that the difference we have identified has arisen by pure chance is low (p=0·0086). Data for comorbidities were not collected at the time of randomisation. However, we believe that with such a large trial size (n=3451) it is improbable that there was a substantial imbalance in baseline comorbidities between the two randomised groups of the trial. We shall continue monitoring for deaths, because longer follow-up would allow further validation of the mortality findings.

Several different approaches for partial breast irradiation or accelerated partial breast irradiation are currently in clinical practice or in clinical studies and have been reviewed elsewhere.[33] All partial breast irradiation techniques share the concept of restriction of the radiation to the tumour bed, but only the TARGIT-A trial has studied the addition of EBRT if adverse risk factors are present. Radiobiological studies suggest that one or a few fractions of larger doses, delivered to a small volume in a shorter overall treatment time, increases the biologically equivalent dose, and this notion is supported by clinical data.[16,34,35] Furthermore, studies suggest that the relative biological effectiveness of TARGIT is 1·2–1·4 at 8 mm depth.[35]

The only other randomised trial testing intraoperative partial breast radiotherapy is the ELIOT (intraoperative radiotherapy with electrons) trial,[36] but the techniques are fundamentally different. Whereas TARGIT delivers radiation from within the undisturbed tumour bed, for ELIOT, the mammary gland is mobilised, a prepectoral lead shield is inserted, the edges of the tumour bed are apposed, and radiation is delivered from without. TARGIT uses 50 kV x-rays delivering 20 Gy to the tumour bed surface and 5–7 Gy at 1 cm depth, in 20–45 min (set up time 10 min). ELIOT uses electrons at 4–12 MeV delivering 21 Gy in 3–5 min (set up time 20 min).

Several factors might have played a part in achieving the low recurrence rates that we have identified in the stratum randomised to receive TARGIT immediately after lumpectomy. These factors include immediate delivery of radiation to well vascularised tissues at the right time and delivery of an optimum dose to the minimum required volume of target tissue at a dose rate that would allow normal tissue to repair, as well as addition of EBRT when high-risk factors were identified postoperatively. In the postpathology stratum this advantage of immediate placement of the radiotherapy applicator directly in the fresh tumour bed seems to be lost (median time between primary surgery and post-pathology TARGIT treatment was 37 days), along with its beneficial effects on the tumour microenvironment,[37,38] and this difference might have contributed to the higher recurrence rate in that stratum. It could be argued that the patients in the prepathology stratum might have done just as well without radiotherapy; however, this study provides its own internal control: the patients in the postpathology stratum were highly selected for favourable pathological entry criteria yet they showed a significant difference of 3·7% (5·4% vs 1·7%) in local recurrence, much the same as for patients in studies with a non-irradiated experimental group.[39,40] In the pre-pathology stratum the difference was only 1·0%, suggesting that TARGIT is effective in reducing local recurrence when given concurrently with lumpectomy.

When TARGIT was given concurrently with lumpectomy, the (non-significant) absolute difference in local recurrence between the two randomised groups remains within the prespecified non-inferiority margin, and this approach would be our preferred option. We emphasise that this result is obtained from an analysis of a prespecified stratum, classified by the timing of randomisation in relation to lumpectomy (prepathology), without restricting the analysis to any particular age group or biological subtype. Studies examining patient preference confirm that this level of difference will also be acceptable to most patients.[41,42] The satisfactory local control rate shown in the prepathology stratum is obtained using a pragmatic protocol in which about one in five women had EBRT in addition to TARGIT. While the need for supplemental EBRT might have been disappointing for these individual women, most women in the

prepathology stratum (about 80%) avoided having to attend for several weeks of EBRT.

Although it is possible that with longer follow-up the postpathology stratum might eventually do as well as the larger prepathology stratum, in view of the present results we wish to exercise caution and only support the use of TARGIT concurrent with lumpectomy, for which there is no significant difference between the randomised groups (n=2298) in respect of local recurrence.

In practice, individual women should be allowed to make the choice between treatment options when presented with robust evidence and the relevant trade-offs. To facilitate this decision making, and to show the stability of the results, we charted the main results for the prepathology stratum in figure 4, which gives the absolute differences in the 5-year risks of local recurrence in the conserved breast and overall mortality for whole cohort, the mature cohort[6] with longer median follow-up close to 4 years, and the earliest cohort with a median follow-up of 5 years. First, this figure suggests that any difference between TARGIT and EBRT for local recurrence and overall mortality remains stable with longer follow-up. Second, it shows the trade-off between these two important outcomes, and could facilitate counselling patients about TARGIT. When TARGIT is given concurrently with lumpectomy, there is a 1% increase in local recurrence (from 99% to 98% chance of being free of local recurrence) along with a potential 2·3% decrease in overall mortality (from 93·1% to 95·4% chance of being alive) at 5 years.

Omission of radiotherapy in a low-risk group of patients already receiving endocrine therapy might not increase breast cancer mortality, but it does increase local recurrence by a small but significant amount: an absolute increase of about 7% at 5 years overall,[3,43] and about 8% at 10 years, even in patients older than 70 years.[5] Therefore, achieving local control (local recurrence down to 2% at 5 years) while minimising the cost and reducing toxicity (local toxicity and non-breast-cancer mortality) that is noted with conventional radiotherapy[32] by use of TARGIT concurrently with lumpectomy would seem a worthwhile goal. Since these results give confidence about the applicability of TARGIT to patients who fulfil the eligibility criteria of the TARGIT-A trial, there should be little hesitation in offering this treatment to selected patients with a good prognosis (eg, those deemed suitable by the European Society for Radiotherapy and Oncology[44] or American Society for Radiation Oncology[45] criteria).

The projected cost-saving with TARGIT has previously been estimated to be in the region of several million pounds in the UK[46] and substantially more in the USA,[47] even without including time-savings and cost-savings to the patient.

The most important benefit of TARGIT for a woman with breast cancer is that it allows her to complete her entire local treatment at the time of her operation, with lower toxicity. If these results are to be applied to everyday

practice, we wish to emphasise that the selection of patients must adhere to the eligibility criteria in the trial, and we would favour the prepathology (concurrent) approach over the delayed approach (panel). Importantly, the risk-adapted design of the TARGIT group must be followed—ie, when higher risk factors are found postoperatively, EBRT should be added. Ultimately, we believe that these data should allow patients and their clinicians to make a more informed choice about individualising their treatment.

Panel: Research in context

Systematic review

We searched PubMed on July 21, 2013, with no restriction of date or language, using the terms "randomised", "breast", "cancer", "intraoperative", and "radiation" or "radiotherapy" to identify randomised trials comparing postoperative whole-breast irradiation with intraoperative radiotherapy after breast conserving surgery for breast cancer. Although in the past 15 years there has been much interest in this treatment, as shown by the large number of phase 1 and 2 trials, we identified only two techniques in phase 3 trials: TARGIT and ELIOT (intraoperative radiotherapy with electrons). We did not include other methods of giving partial breast irradiation.

We are awaiting publication of the results of the ELIOT trial (n=1300) in which intraoperative radiotherapy was given with a mobile linear accelerator (NOVAC-7) delivering 21 Gy by placing a cylindrical applicator onto a reconstructed tumour bed.

With the TARGIT technique, one dose of 20 Gy to the tumour bed is delivered by placing a spherical applicator within it. This technique could be done either immediately after the lumpectomy during the same anaesthetic (prepathology) or as a second procedure (with randomisation done after pathological examination of the specimen leading to tighter case selection—postpathology) by reopening the wound. The two types of delivery were two separate strata within the TARGIT-A trial.

The first results of the TARGIT-A trial[6] (n=2232) showed that local recurrence with TARGIT was non-inferior to EBRT.

Interpretation

Randomisation in the TARGIT-A trial was continued while the data matured and the trial was closed after 3451 patients were accrued. This preplanned analysis provides more mature data than previously reported: the number of local recurrences increased from 13 to 34 and there were 88 deaths.

This is the first analysis of deaths and of the two strata as per timing of delivery of TARGIT. We showed that in comparison with several weeks of conventional whole breast radiotherapy, all breast cancer outcomes are much the same when single-dose TARGIT is delivered concurrently with lumpectomy (n=2298). However, when TARGIT is delivered as a second procedure by reopening the wound, despite tighter case selection (n=1143), the local recurrence rate was higher than with EBRT. We also showed that in the TARGIT group, there was a significant reduction in deaths from causes other than breast cancer (17 vs 35), attributable to fewer deaths from cardiovascular causes or other cancers.

TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected as per the TARGIT-A trial protocol, as an alternative to postoperative external beam breast radiotherapy.

References

1 Darby S, McGale P, Correa C, et al, and the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Lancet* 2011; **378:** 1707–16.

2 Fisher B, Bryant J, Dignam JJ, et al, and the National Surgical Adjuvant Breast and Bowel Project. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimetre or less. *J Clin Oncol* 2002; **20:** 4141–49.

3 Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004; **351:** 963–70.

4 Pötter R, Gnant M, Kwasny W, et al, and the Austrian Breast and Colorectal Cancer Study Group. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. *Int J Radiat Oncol Biol Phys* 2007; **68:** 334–40.

5 Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013; **31:** 2382–87.

6 Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010; **376:** 91–102.

7 Vaidya JS, Vyas JJ, Mittra I, Chinoy RF. Multicentricity and its influence on conservative breast cancer treatment strategy. Hong Kong International Cancer Congress; Hong Kong; Nov 17–19, 1995. Abstract 44.4.

8 Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* 1996; **74:** 820–24.

9 Baum M, Vaidya JS, Mittra I. Multicentricity and recurrence of breast cancer. *Lancet* 1997; **349:** 208.

10 Athas WF, Adams-Cameron M, Hunt WC, Amir-Fazli A, Key CR. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst* 2000; **92:** 269–71.

11 Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985; **56:** 979–90.

12 Vaidya JS, Baum M, Tobias JS, et al. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Ann Oncol* 2001; **12:** 1075–80.

13 Vaidya JS, Baum M, Tobias JS, Morgan S, D'Souza D. The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. *Eur J Surg Oncol* 2002; **28:** 447–54.

14 Vaidya JS. A novel approach for local treatment of early breast cancer. *PhD Thesis, University of London* 2002 http://www.ucl.ac.uk/~rmhkjsv/papers/thesis.htm.

15 Tobias JS, Vaidya JS, Keshtgar M, D'Souza DP, Baum M. Reducing radiotherapy dose in early breast cancer: the concept of conformal intraoperative brachytherapy. *Br J Radiol* 2004; **77:** 279–84.

16 Herskind C, Steil V, Kraus-Tiefenbacher U, Wenz F. Radiobiological aspects of intraoperative radiotherapy (IORT) with isotropic low-energy X rays for early-stage breast cancer. *Radiat Res* 2005; **163:** 208–15.

17 Vaidya JS. Partial breast irradiation using targeted intraoperative radiotherapy (Targit). *Nat Clin Pract Oncol* 2007; **4:** 384–85.

18 Enderling H, Chaplain MA, Anderson AR, Vaidya JS. A mathematical model of breast cancer development, local treatment and recurrence. *J Theor Biol* 2007; **246:** 245–59.

19 Herskind C, Griebel J, Kraus-Tiefenbacher U, Wenz F. Sphere of equivalence—a novel target volume concept for intraoperative radiotherapy using low-energy X rays. *Int J Radiat Oncol Biol Phys* 2008; **72:** 1575–81.

20 Herskind C, Wenz F. Radiobiological comparison of hypofractionated accelerated partial-breast irradiation (APBI) and single-dose intraoperative radiotherapy (IORT) with 50-kV X-rays. *Strahlenther Onkol* 2010; **186:** 444–51.

21 Vaidya JS, Baum M, Tobias JS, et al. Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2011; **81:** 1091–97.

22 Laster LL, Johnson MF, Kotler ML. Non-inferiority trials: the 'at least as good as' criterion with dichotomous data. *Stat Med* 2006; **25:** 1115–30.

23 Tunes da Silva G, Logan BR, Klein JP. Methods for equivalence and noninferiority testing. *Biol Blood Marrow Transplant* 2009; **15** (suppl): 120–27.

24 Smits PC, Hofma S, Togni M, et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. *Lancet* 2013; **381:** 651–60.

25 Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet* 2002; **359:** 1686–89.

26 Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res* 2007; **13:** 559–65.

27 Baum M, Chaplain MA, Anderson AR, Douek M, Vaidya JS. Does breast cancer exist in a state of chaos? *Eur J Cancer* 1999; **35:** 886–91.

28 Keshtgar MR, Williams N, Corica T, Saunders C, Joseph D. Significantly better cosmetic outcome after intraoperative radiotherapy compared with external beam radiotherapy for early breast cancer: objective assessment of patients from a randomized controlled trial. *Ann Surg Oncol* 2011; S171.

29 Sperk E, Welzel G, Keller A, et al. Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: results from the randomized phase III trial TARGIT A. *Breast Cancer Res Treat* 2012; **135:** 253–60.

30 Welzel G, Boch A, Sperk E, et al. Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A. *Radiat Oncol* 2013; **8:** 9.

31 Cuzick J, Stewart H, Peto R, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. *Cancer Treat Rep* 1987; **71:** 15–29.

32 Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; **368:** 987–98.

33 Offersen BV, Overgaard M, Kroman N, Overgaard J. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: a systematic review. *Radiother Oncol* 2009; **90:** 1–13.

34 Kraus-Tiefenbacher U, Bauer L, Scheda A, et al. Long-term toxicity of an intraoperative radiotherapy boost using low energy X-rays during breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2006; **66:** 377–81.

35 Liu Q, Schneider F, Ma L, Wenz F, Herskind C. Relative Biologic Effectiveness (RBE) of 50 kV X-rays measured in a phantom for intraoperative tumor-bed irradiation. *Int J Radiat Oncol Biol Phys* 2013; **85:** 1127–33.

36 Veronesi U, Orecchia R, Luini A, et al. Full dose intraoperative radiotherapy with electrons (ELIOT) during breast conserving surgery: experience with 1246 cases. *Ecancermedicalscience* 2008; **2:** 65.

37 Belletti B, Vaidya JS, D'Andrea S, et al. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. *Clin Cancer Res* 2008; **14:** 1325–32.

38 Vaidya JS, Baldassarre G, Massarut S. Beneficial effects of intraoperative radiotherapy on tumor microenvironment could improve outcomes. *Int J Radiat Oncol Biol Phys* 2009; **74:** 976.

39 Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; **355:** 1757–70.

40 Clarke M, Collins R, Darby S, et al, and the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **366:** 2087–106.

41 Alvarado M, Connolly J, Oboite M, Moore D, Park C, Esserman L. Patient preference for choosing intra-operative or external-beam radiotherapy following breast conservation. *Eur J Cancer* 2010; **8** (suppl): 2.

42 Corica T, Nowak A, Saunders C, Bulsara M, Joseph D. Patient preferences for adjuvant radiotherapy in early breast cancer— an Australian sub-study of the International TARGIT Trial. *Eur J Cancer* 2012; **48** (suppl 1): S187.

43 Blamey RW, Bates T, Chetty U, et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. *Eur J Cancer* 2013; **49:** 2294–302.

44 Polgár C, Van Limbergen E, Pötter R, et al, and the GEC-ESTRO breast cancer working group. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol* 2010; **94:** 264–73.

45 Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009; **74:** 987–1001.

46 Vaidya JS, Tobias JS, Baum M, et al. Intraoperative radiotherapy for breast cancer. *Lancet Oncol* 2004; **5:** 165–73.

47 Alvarado M, Ozanne E, Mohan A, Esserman L. Cost-effectiveness of intraoperative radiation therapy for breast conservation. *J Clin Oncol* 2011; **29** (suppl): 6081 (abstr).

THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Web –appendix

Risk-adapted targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alastair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists' group

e-table 1: Patient and tumour characteristics The denominator for unknown percentages is the total number randomised (1721 and 1730) and the denominator for each category is the total number of known cases. Most of the unknown data is from the 342 patients randomised in the last 6 months before data lock. The bar chart (bottom) gives a summary of the data. Totals of percentages of known may not add up to 100 due to rounding.

	TARGIT (1721)		EBRT (1730)		
Age (years)					p=0.274
<=50	150	9%	122	7%	
51-60	527	31%	548	32%	
61-70	781	45%	807	47%	
>70	263	15%	253	15%	
Pathological tumour size					p=0.273
<=1cm	611	39%	597	39%	
1.1-2cm	751	48%	726	48%	
>2cm	190	12%	207	14%	
Unknown	169	10 %	200	12 %	
Grade					p=0.394
1	528	35%	558	37%	
2	757	50%	720	48%	
3	232	15%	227	15%	
Unknown	194	11%	225	13%	
Lymphovascular invasion					p=0.224
Absent	1348	87%	1343	88%	
Present	194	13%	178	12%	
Unknown	179	10%	209	12%	
Nodes involved					p=0.091
0	1307	83%	1303	85%	
1-3	219	14%	211	14%	
>3	43	3%	29	2%	
Unknown	152	9%	187	11%	
ER status					p=0.090
ER +ve	1441	92%	1433	94%	
ER -ve	120	8%	99	7%	
ER Unknown	160	9%	198	12%	
PgR status					p=0.179
PgR +ve	1232	81 %	1230	82%	
PgR -ve	289	19 %	265	18%	
PgR Unknown	200	12%	235	14%	
HER 2 receptor					p=0.585
Positive	170	11%	178	12%	
Negative	1329	89%	1309	88%	
Unknown	222	13%	243	14%	
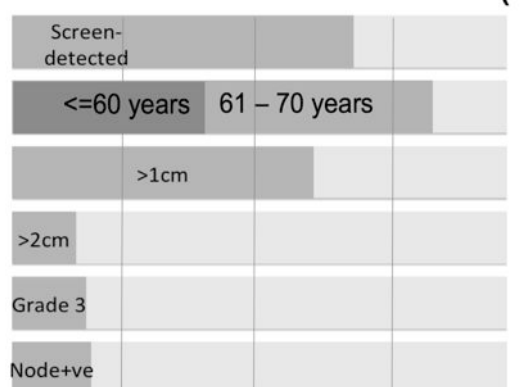
e-table 2: Unplanned post-hoc exploratory non-randomised comparison of tumour characteristics and primary and secondary outcomes as per treatment received amongst those who were randomised to TARGIT and received the allocated treatment. Percentages are of the known values.

	Prepathology patients who received TARGIT Alone N=793	Prepathology patients who received TARGIT+EBRT N=219	Postpathology patients who received TARGIT Alone N=539
T size			
<=1cm	36% (256/703)	24% (47/199)	52% (269/515)
1-2 cm	52% (366/703)	49% (98/199)	43% (223/515)
>2cm	12% (81/703)	27% (54/199)	5% (23/515)
Grade			
Grade 1	27%(188/707)	19% (38/200)	59% (285/486)
Grade 2	54%(380/707)	60.5% (121/200)	38% (182/486)
Grade 3	20%(139/707)	20.5% (41/200)	4% (19/486)
Lymph node positivity			
Node negative	85% (604/712)	63% (126/201)	95% (492/519)
1-3 nodes involved	13% (94/712)	29% (59/201)	5% (27/519)
>3 nodes involved	2% (14/712)	8% (16/201)	0 (0/519)
5-year Local recurrence in the conserved breast (95%CI)	2.7 (1.3-5.5)	0.9 (0.1-6.1)	5.9 (3.3-10.5)
5-year risk of Breast cancer death (95%CI)	1.8 (0.7-4.6)	8.0 (3.5-17.5)	0.6 (0.2-2.5)
5-year risk of Deaths from other causes (95%CI)	1.9 (0.9-4.0)	0	1.5 (0.6-4.3)

N.B. Only 20 postpathology patients received TARGIT+EBRT and therefore their data is not given.

e-table 3 Complications 6 months after randomisation

	TARGIT	EBRT
Wound related complications		
Haematoma / Seroma requiring more than 3 aspirations or surgery	4	2
Wound infection requiring intravenous antibiotics or surgery	12	9
Skin breakdown / Delayed wound healing	3	5
Total	19 (1.1%)	16 (0.9%)
	p=0.599	
Radiotherapy related complications		
Radiation Therapy Oncology Group (RTOG) Grade 3 or 4 radiotherapy toxicity	4 (0.2%)	13 (0.8%)
	p=0.029	

eFigure 1 Trial summary: Schema for the TARGIT-A randomised trial comparing risk-adapted radiotherapy with conventional whole breast radiotherapy.

Eligibility:

Age >=45 years

Unifocal invasive ductal carcinoma preferably <3.5cm

(MRI not required)

Suitable for breast conserving surgery

Stratification prior to randomisation

S T R A T I F Y

Diagnosis established by needle biopsy and the patient has NOT had excision of cancer

Prepathology stratum

-- If randomised to TARGIT

TARGIT given concurrently with lumpectomy

-- If randomised to EBRT

EBRT given as usual after lumpectomy

n=2298

Diagnosis is established and the patient has already had excision of cancer

Postpathology stratum

-- If randomised to TARGIT

TARGIT given as a delayed procedure

by re-opening the wound

-- If randomised to EBRT

EBRT given as usual after lumpectomy

n=1153

R A N D O M I S E

Risk-adapted radiotherapy

TARGeted Intraoperative radioTherapy (TARGIT)

focussed to the tumour bed and delivered in a single dose with Intrabeam

If high risk factors are found on final pathology, EBRT should be added

n= 1140

One-size fits all radiotherapy

Standard fractionated whole breast

Exteral Beam RadioTherapy (EBRT)

n=1158

R A N D O M I S E

Risk-adapted radiotherapy

TARGeted Intraoperative radioTherapy (TARGIT)

focussed to the tumour bed and delivered in a single dose with Intrabeam

If high risk factors are found on final pathology, EBRT should be added

n=581

One-size fits all radiotherapy

Standard fractionated whole breast

Exteral Beam RadioTherapy (EBRT)

n=572

eFigure 2 The TARGIT technique The Intrabeam device (top left) and a schematic diagram showing how the spherical applicator fits into the tumour bed (top right). Intraoperative radiotherapy being delivered in the operation theatre (bottom left) and a close up of the spherical applicator in the tumour bed (bottom right)
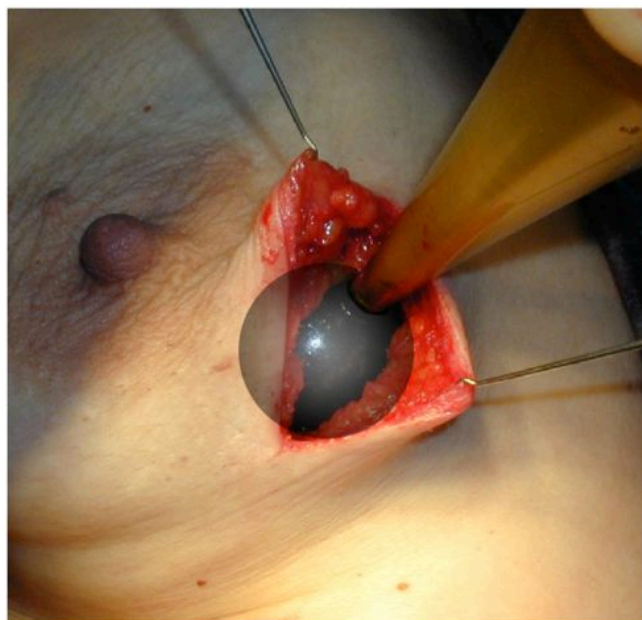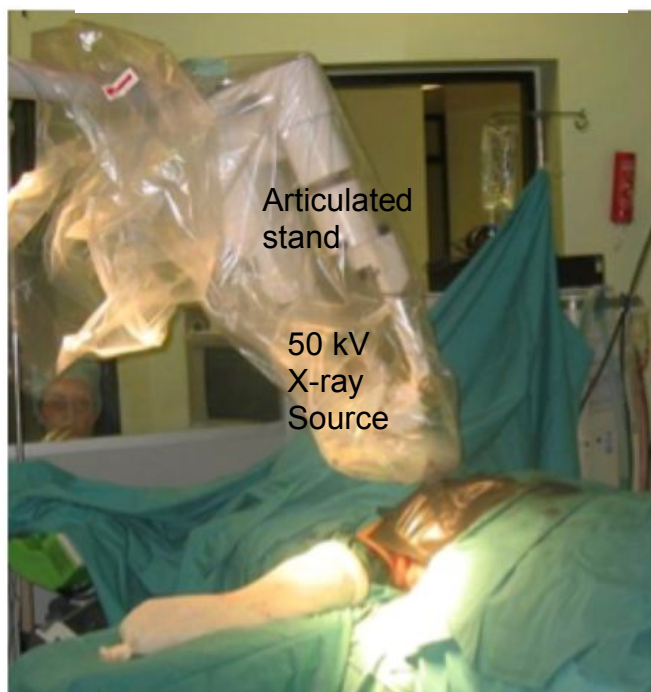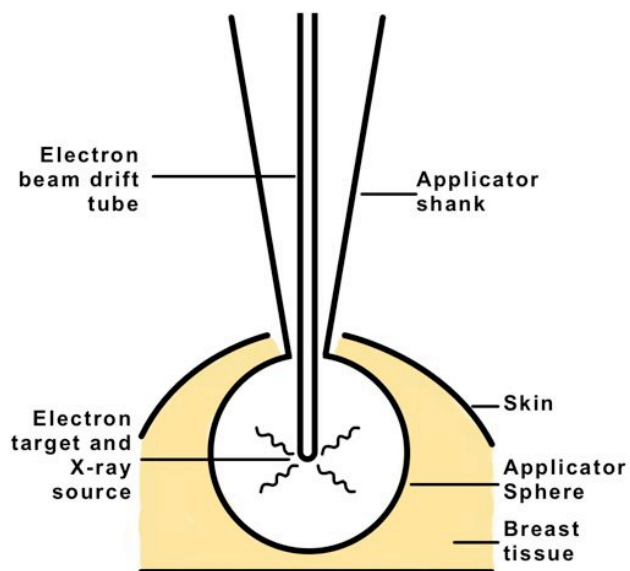
eFigure 3: Consort diagram (top) and completeness of follow up (bottom) showing the observed and expected follow up for the whole trial cohort.

```
                        ┌─────────────────────────────────────────┐
                        │  3451 patients enrolled and randomised   │
                        └─────────────────────────────────────────┘
```

1721 Allocated to TARGIT with or without EBRT	**1730** Allocated to EBRT

9 withdrawn	**27 withdrawn**

141 did not receive allocated treatment	**113 did not receive allocated treatment**
78 received EBRT*	12 received TARGIT*
42 had a mastectomy	14 received TARGIT and EBRT
21 did not receive TARGIT or EBRT	34 had a mastectomy
	53 did not receive TARGIT or EBRT

1571 received allocated treatment	**1590 received allocated treatment**
1332 received TARGIT	
239 received TARGIT and EBRT**	

1679 included in analysis of breast recurrence	1696 included in analyis of breast recurrence
(42 had a mastectomy)	(34 had a mastectomy)
1721 included in analysis of death	1730 included in analysis of death

* **protocol deviations:** 78/1721 (4.5%) patients allocated TARGIT received EBRT and 12/1730 (0.7%) allocated EBRT received TARGIT

** 239/1721 (13.8%) patients allocated TARGIT received EBRT after TARGIT **as per protocol** and 239/1571 (15.2%) **as per treatment received**

9491 women-years of follow up

Actual FU
Expected FU
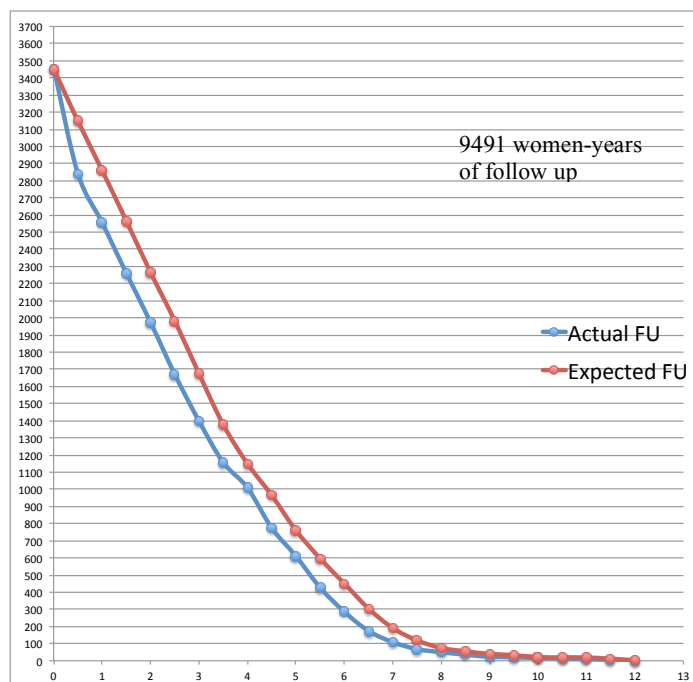
eFigure 4: Consort diagram for the prepathology (top) and postpathology (bottom) strata

Prepathology: 2298 patients enrolled and randomised before excision of cancer

1140 Allocated to TARGIT with or without EBRT

1158 Allocated to EBRT

8 withdrawn

120 did not receive allocated treatment
67 received EBRT*
33 had a mastectomy
20 did not receive TARGIT or EBRT

1012 received allocated treatment
793 received TARGIT
219 received TARGIT and EBRT**

1107 included in analysis of breast recurrence
  (33 had a mastectomy)
1140 included in analysis of death

21 withdrawn

98 did not receive allocated treatment
10 received TARGIT*
8 received TARGIT and EBRT
31 had a mastectomy
49 did not receive TARGIT or EBRT

1039 received allocated treatment

1127 included in analyis of breast recurrence
  (31 had a mastectomy)
1158 included in analysis of death

* protocol deviations': 67/1140 (5.9%) patients allocated TARGIT received EBRT and 10/1158 (0.9%) allocated EBRT received TARGIT .
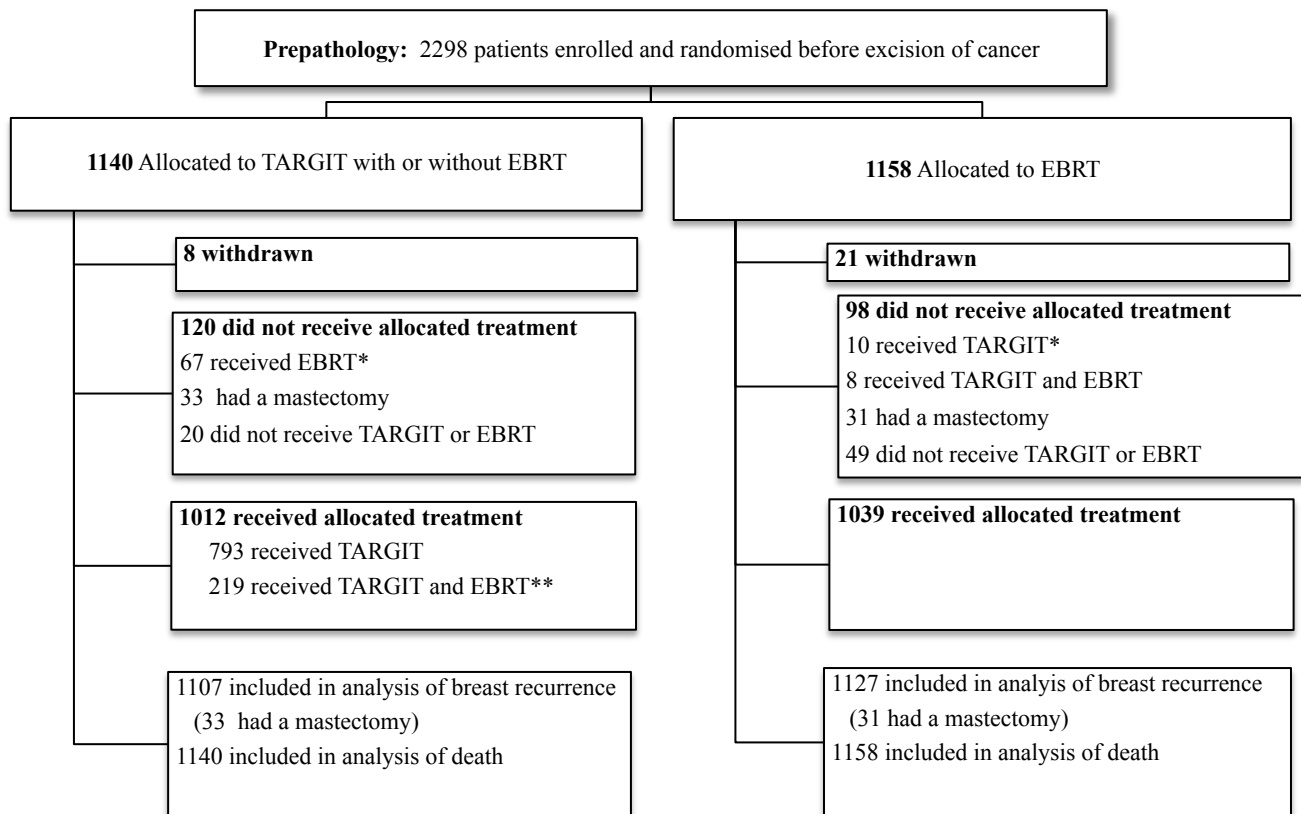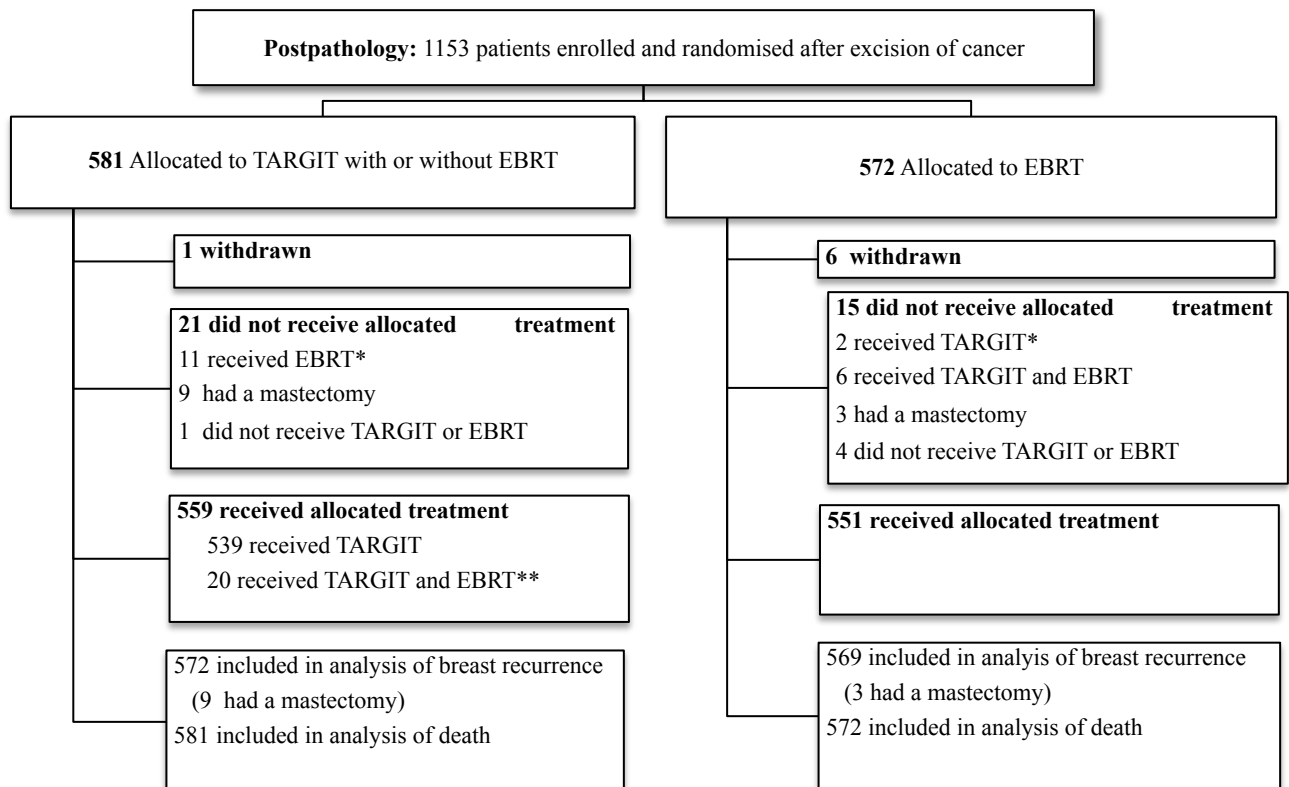****** 219/1140 (19.2%) patients allocated TARGIT received EBRT after TARGIT **as per protocol,** and 219/1012 (21.6%) **as per treatment received**

Postpathology: 1153 patients enrolled and randomised after excision of cancer

581 Allocated to TARGIT with or without EBRT

572 Allocated to EBRT

1 withdrawn

21 did not receive allocated   treatment
11 received EBRT*
9 had a mastectomy
1 did not receive TARGIT or EBRT

559 received allocated treatment
539 received TARGIT
20 received TARGIT and EBRT**

572 included in analysis of breast recurrence
  (9 had a mastectomy)
581 included in analysis of death

6 withdrawn

15 did not receive allocated   treatment
2 received TARGIT*
6 received TARGIT and EBRT
3 had a mastectomy
4 did not receive TARGIT or EBRT

551 received allocated treatment

569 included in analyis of breast recurrence
  (3 had a mastectomy)
572 included in analysis of death

* 'protocol deviations': 11/581 (1.9%) patients allocated TARGIT received EBRT and 2/572 (0.3%) allocated EBRT received TARGIT
** 20/581 (3.4%) patients allocated TARGIT received EBRT after TARGIT **as per protocol**, and 20/559 (3.6%) **as per treatment received**

eFigure 5: Primary and secondary outcomes for the Prepathology stratum (n=2298, randomised before lumpectomy and TARGIT given concurrently with lumpectomy): Kaplan-Meier plots for local recurrence in the conserved breast (top) in patients who had breast conserving surgery, for breast cancer deaths and non-breast-cancer deaths in all patients(middle and bottom) Blue: TARGIT and Red: EBRT. The top graph is the same as in figure 3A – reproduced here for context.
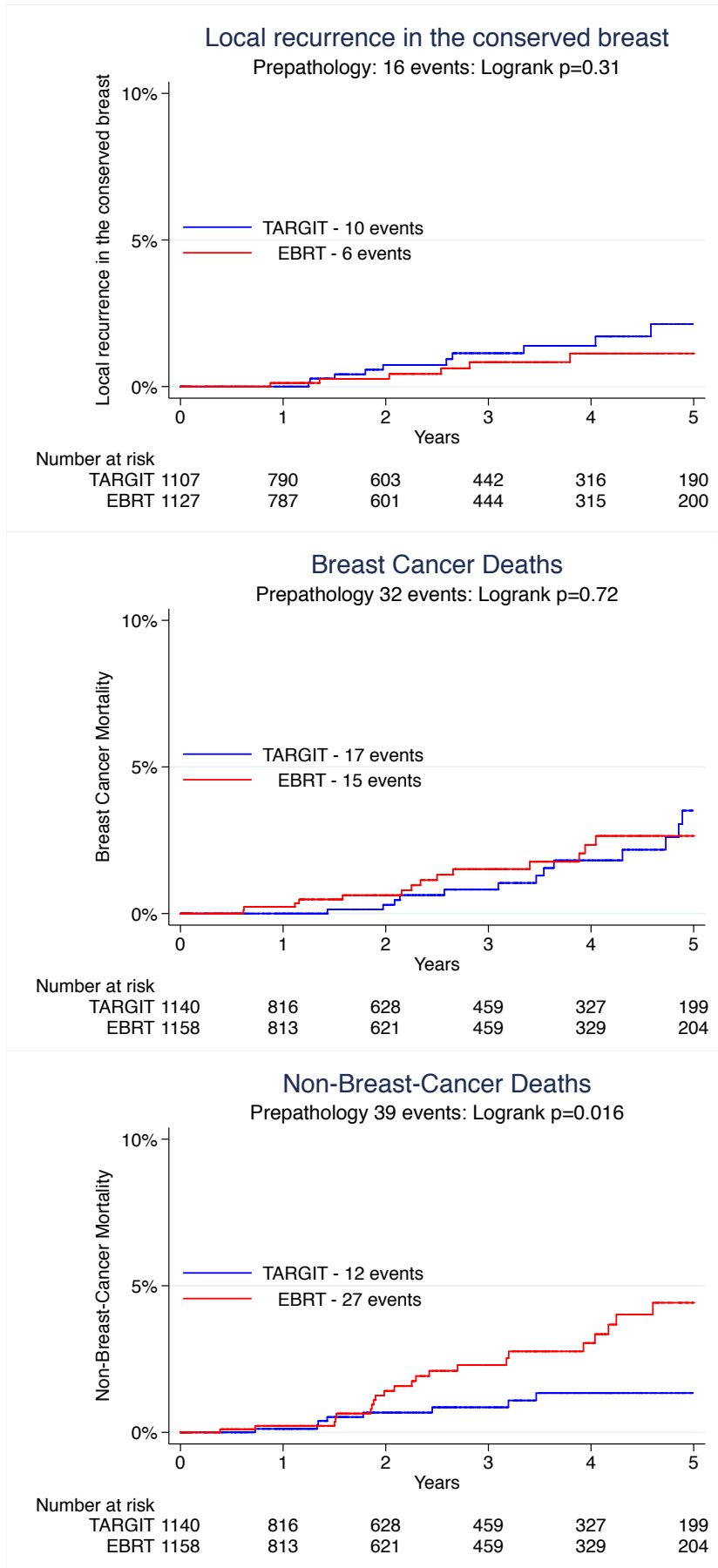
TARGIT-A team

Trial Operations Staff: London, UK: Michael Baum (director), Jayant S Vaidya (Scientific Director), Norman R Williams, Ingrid Potyka, Chris Brew-Graves, Cindy Li, Cinzia Baldini, Mortez Ali, Past: Joan Houghton, Christina Lennon, Olive Murphy, Alexandra Sherley; *Mannheim, Germany:* Anke Keller; *Perth, WA, Australia:* Tammy Corica, Celsete Lopez, Eva Vosikova.

Individual centre teams (in order of the date of randomisation of the first patient): University College London Hospital, London, UK (J S Vaidya, JS Tobias, M Baum, M Keshtgar, G Blackman, C Brew-Graves, M Douek, D D'Souza, M Falzon, E Harrison, C Kocjan, S Lakhani, M Metaxas, P Mulvey, SV Naidu, G Petralia, R Sainsbury, C Saunders, C Stacey, I Taylor, N Williams); Universitätsmedizin Mannheim, Universität Heidelberg, Mannheim, Germany (Frederik Wenz, E Blank, M Bohrer, S Clausen, B Hermann, R Hildenbrand, Anke Keller, Uta Kraus-Tiefenbacher, B Kuepper, A Marx, F Melchert, D Neumann, F Schneider, V Steil, M Suetterlin, M Trunk); Sir Charles Gairdner Hospital, Perth, WA, Australia (Christobel Saunders, David J Joseph, Sean Bydder, Sheryl Campbell, Joe Clarke, Tammy Corica, Annette Haworth, Rosemary Hedges, Robin Kane, Peter Lanzon, Celeste Lopez, Mandy Taylor, Eva Vosikova, Claire Haworth, Katayun Mohammadi, Alberta Abreu, Nik Zeps , Diana Hastrich, David Ingram, Lee Jackson, Neill Kling, Margaret Latham, David Minchin, Annemarie Naylor, David Oliver, Rosemary Wilkinson); Centro di Riferimento Oncologico, Aviano, Italy (Samuele Massarut, M Arcicasa, E Bidoli, E Cadiani, E Capra, M Oliva, T Perin, S Reccanello, M Roncadin, G Sartor, G Tabaro, M Trovo, R Volpe Mario Mileto, Erica Piccoli, Antonella Spada); Ninewells Hospital, Dundee, UK (M Adams, DJA Adamson, K Armoogum, J Bosch, DC Brown, JA Dewar, S Edwards, J Gardner, A Gunning, M Hawkes, LB Jordan, A Lee, J Lindsay, G Little, C Mackay, AJ Munro, J Parry, CA Purdie, MM Reis, AM Thompson, JS Vaidya, V Walker, RAB Wood); University of California, San Francisco Medical Center, San Francisco, CA, USA (Laura Esserman, Michael Alvarado, Alfred Au, Alison Bevan, Jay Connolly, Cheryl Ewing, Clark Fisher, Shelley Hwang, K Lane, Christina Minami, Michelle Oboite, Cathy Park, Jean Pouliot, Theadora Sakata, Aron Mohan, Brittany Harrison, Albert Chan, Mitchell Hayes); Frauenklinik vom Roten Kreuz, Munich, Germany (Wolfgang Eiermann, Beyhan Ataseven, C Becker, B Hoegel, P Kneschaurek, A Lackermeier, M Molls, Carsten Nieder, Steffi Pigorsch, J Rauch, Barbara Röper, Sabine Schill, Brigitte Werner, Christopher Wolf); University of Southern California, Los Angeles, CA, USA (Dennis R Holmes, Melvin Astrahan, Carryl Dubois, Jacqueline Majors, Sylvia Villegas Mendez, Afshin Rashtian, Ronald Rivera, Howard Silberman, Melvin Silverstein, Rashida Soni, Oscar E Streeter Jr, Lina Wang, Heather Macdonald, Stephen Sener, America Casillas); Ospedale San Giuseppe di Empoli, Empoli, Italy (Gianmaria Fiorentini, Carli Ballola Adele, Rafaella Barca, Mauro Biancalani, Giampaolo Biti, Enrico Cellai, Antonella Compagnucci, Claudio Caponi, Vito Maria Fontanarosa, Roberta Ghezzi, Alessandro Ghirelli, Gloria Giustarini, Barbara Grilli Leonulli, Francesca Littori, Maurizio Pertici, Visna Petrina, Paola Raffaele, Francesca Righi, Serenella Russo, Michele de Simone, Gina Turrisi, Giuditta Zipoli); Sankt Gertrauden-Krankenhaus, Berlin, Germany (Jens-Uwe Blohmer, Petra Feyer, J Gross, G Jautzke, K Luebbert, Michaela Platzer, Joerg Preussler, D Puppe, Esther Wiedemann); Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (Michael Henderson, David Blakey, Boon Chua, Ram Das, Roslyn Drummond, Annette Haworth, Penny Fogg, Stephen Fox, Jodi Lynch, Jane O'Brien, Catherine Poliness, Ann-Marie Power, David Speakman, Tina Thorpe, Melanie Walker); Ludwig Maximilians Universität, Munich, Germany (Wolfgang Janni, Ulrich Andergassen, C Balka, Darius Dian, Sylvia Dondl, Klaus Friese, Julia Jueckstock, Thomas Kirchner, Klaus Krimmel, Doris Mayr, Susanne Reinhard, Dr Schaffer, Christian Schindlbeck, Harald Sommer, Justus Well); Universität Frankfurt am Main, Frankfurt, Germany (M Kaufmann, H Boettcher, J Moog, Achim Rody, Claus Rödel, S Schopohl, Christian Weiss, Inge Fraunholz, Ulla Ramm, Martin-Leo Hansmann, R Strohmeier); Herlev/Rigs Hospitals, Copenhagen, Denmark (Henrik Flyger, Eva Balslev, Niels Bentzon, Paul Geertsen, Helle Holtveg, Claus Kamby, Niels Kroman, Faisal Mahmood, Fritz Rank, Birgitte Bruun Rasmussen, Lone Gry Schäfer, Peter Michael Vestlev, Vera Timmermans Wielenga, Eva Wilken); Medical University of Lublin, Lublin, Poland (Wojciech P Polkowski, Malgorzata Jankiewicz, Andrzej Kurylcio, Maria Mazurkiewicz, Jerzy Mielko, Krzysztof Paprota, Barbara Pawlowska-Wakowicz, Urszula Radwanska, Jaroslaw Romanek, Zofia Siezieniewska, Magdalena Skorzewska, Andrzej Stanislawek, Monika Lewicka, Jadwiga Sierocinska-Sawa, Edyta Matajek, Rafael Smyk, Andrzej Bedinski, Bogumila Cislo, Bogumila Cisel); Royal Free Hospital, London, UK (Mohammed Keshtgar, Katherine Pigott, Tim Davidson, Jayant S Vaidya, Debasis Ghosh, Alison Jones, Jawad Keshtgar, Samia Shah, Katia Pasciuti, Neil Dancer, Kashmira Metha, Benjamin Earner, Stephan Duck, David Woolf); Whittington Hospital, London, UK (Jayant S Vaidya, Jeffrey S Tobias, Alan Wilson, Mohammed Keshtgar, Peng Tan, Debashis Ghosh, Glen Blackman, Renata Rowicka, Veronica Conteh, Su Ramachandra, Lucy Harbin, R Chaudhuri, Ros Crooks, Francesca Peters, Tom Connors, Alison Jones, Mulyati Mohamed, Tim Crook, Vivienne Maidens, Sylvia Grieve Lotta Jonsson, Ciara McNulty); Lafayette Surgical Clinic, Lafayette, IN, USA (Thomas L Summer, Mario Contreras, Paul M DesRosiers, Irene Gordon, Kazumi Chino, Bedatri Sinha, Cindy McDowell, Mike Ringer, Tammy Spurlock, Lisa Ramsey); Sentara Surgery Specialists, Hampton, VA, USA (Richard A Hoefer, Mary Berry, Donna Forrest, Arvind Mahatma, Michael Miller, Song Kang, Gregory J Lavalle, Deborah A Martinez, Sandra Piggee); Uniklinikum des Saarlandes, Homburg, Germany (Erich Solomayer, K Abel, S Baum, Rainer Allgayer, R M Bohle, Mustafa Deryal, J Fleckenstein, R Grobholz, Jeanett Koehn, Anja Martin-Riedheimer, Marcus Niewald, Markus Promnik, Christian Ruebe, W Schmidt); Princess Margaret Cancer Centre, Toronto, ON, Canada (David McCready, Akbar Beiki-Ardakani, John Cho, Susan Done, Jamie Escallon, Anthony W Fyles, Wilfred Levin, Alex Vitkin, Marie Vranic); Royal Hampshire County Hospital, Winchester, UK (Dick Rainsbury, Claire Birch, Lyn Booth, Caroline Cross, Alan Gately, Virginia Hall, Kevin Harris, Siobhan Laws, Sanjay Raj, Balvinder Shoker, Virginia Straker, Jennifer Wilson); Brust Zentrum Seefeld, Zurich, Switzerland (Christopher Rageth, Uwe Gneveckow, Elisabeth Grob, Guenther Gruber, Baerbel Papassotiropoulos, Barbara Tausch, C Tausch, Zsuszanna Varga, Iris Vergin); Universitäts Spital Zurich, Zurich, Switzerland (Claudia Hutzli, Yvonne Burgstaller, Rosemary Caduff, Daniel Fink, Guntram Kunz, Claudia Linsenmeier, Yousef Najafi, Natalie Gabriel, Cornelia Betschart, Eleftherios

Samartzis, Ana-Maria Schmidt, Tino Streller, Z Varga, Madeleine Wick, Cornelia Leo, Zsuzsanna Varga, Leila Kocan); St Olav's Hospital, Trondheim, Norway (Steinar Lundgren, Anne Brit Abusland, Marianne Brekke, Dagrun Danielsen, Hans E Fjosne, Jomar Frengen, Kristen Helset, Jarle Karlsen, Petter Osthus, Hanne-Brit Grong Smethurst, Trond Strickert); University of Nebraska Medical Center, Omaha, NE, USA (James Edney, Aaron Sasson, Debra Spence, Robert Thompson, William W West, Sumin Zhou); Guy's and St Thomas' Hospital, London, UK (Michael Douek, Sarah Aldridge, Ashutosh Kothari, Nick Beechey-Newman, Charles Deehan, Ian Fentiman, Hisham Hamed, Sarah Harris, Hardeep Johal, Sarah Pinder, Arnie Purushotham, Vernie Ramalingam, Chris Stacey); Vassar Brothers Medical Center, Poughkeepsie, NY, USA (Angela Keleher, Eileen Abate, Nicole Cappillino, Laszlo Csury, Edward Farhangi, Anne Kim, Sutini Ngadiman, Dimitrios Papadopoulos, Dan Pavord, P Hank Schmidt, Camilo Torres, Erika Mednick); Ashikari Clinic, New York Medical College, New York, NY, USA (P Kelemen, Andrew Ashikari, Ulrich Hermato, Helen Li, Demetrious Makrides, Mike Malamed, Wanda Rivera, Yadita Samnarain, Alfred Tinger, Raphael Yankelevich, Yasmin Yusuf). Medizinische Hochschule Hannover, Germany (Tjoung-Won Park-Simon, Peter Hillemans, Ursula Hille, Michael Bremer, Frank Bruns, Frank Rudolf, Hans Grudtke, Jorg Fruhauf, H. H. Kreipe, Florian Laenger, Adelheid Klein), Centre Rene Gauducheau, Nantes, France (Magali Le Blanc-Onfroy, Maud Aumont, Francois Dravet, Magali Dejode, Albert Lisbona, Delphine Loussouarn, Christine Sagan, Nicolas Rougé, Stephanie Gaudaine-Josset), Instituto Oncologico Veneto (Michele Pignataro, Fernando Bozza, Raffaello Grigoletto, Silvia Michieletto, Stefano Valente, Tania Saibene, Franco Berti, Ornella Lora, Marta Paiusco, Sonia Reccanello, Davide Canonico, Enrico Orvieto, Marcello Lo Mele, Liliana Spangaro), Hospital of St John and St Elizabeth, London, UK (Katharine Pigott, Punita Vyas, Catherine O'Connor, Donna Gibbs, Simon Stevens, Ashley Richmond, Tabasom Ghaus, Thomas Ashford, Deborah Waters, Mohammed Keshtgar), Institut Bergonie, Bordeaux, France (Marion Fournier, Christine Tunon De Lara, Christelle Breton-Callu, Philippe Lagarde, Sarah Belhomme, Gaetan MacGrogan, Beatrice Gonzalves, Mickael Antoine)