NICE National Institute for Health and Care Excellence

The Intrabeam Radiotherapy System for the adjuvant treatment of early breast cancer - MTA

3rd Committee meeting
26 August 2015

Slides for projector

ACD Preliminary recommendations (June 2014)

- Intrabeam is recommended as an option for the adjuvant treatment of early invasive breast cancer during breast conserving surgical removal of the tumour, only if clinicians:
  - fully explain the treatment options available to patients, including their associated risks and benefits, so that patients can make an informed choice about their treatment. Clinicians should ensure that patients understand that less is known about the long-term outcomes of treatment with the Intrabeam Radiotherapy System than with conventional external beam radiotherapy and that the rate of local recurrence with Intrabeam could be higher than with external beam radiotherapy **and**
  - enter details about all patients having treatment with the Intrabeam Radiotherapy System for adjuvant treatment of early invasive breast cancer on to a national register. They should audit, review and document clinical outcomes locally and consider the relationship between outcomes and patients' characteristics.

Intrabeam radiotherapy system

- CE mark in 1999 for use in radiotherapy
- Can be used to deliver intra-operative radiotherapy in a standard operating theatre at the time of surgery
- Administered to the tumour bed after wide local excision using reusable spherical applicator, low energy x-rays to cavity (20Gy), spares other tissues
- On average adds 20 – 45 minutes to operative time, wound then closed
- If, based on the pathology results after surgery, the patient is considered at high risk of recurrence, additional external beam radiotherapy (EBRT) may be recommended.

Clinical evidence

- TARGIT-A trial compared Intrabeam with conventional whole breast EBRT
  - International multicentre non-inferiority RCT – 33 centres (6 UK)
  - Pre-stated non-inferiority margin – absolute difference of 2.5% in local recurrence, non-inferiority margin based on estimated local recurrence rate with EBRT of 6%
  - Patients randomised in 2 strata:
    - Pre-pathology i.e. Intrabeam at time of first cancer operation. EBRT then offered to patients at high risk of recurrence
    - Post-pathology i.e. Intrabeam at second operation once pathology results were known. Randomised within 30 days of initial wide local excision. Could also have EBRT if high risk of recurrence
  - EBRT according to local policy (40–56 Gy) +/- boost (typically 10–16 Gy)
- EBRT standard practice in the UK: 40 gy in 15 fractions, typically over 3 weeks
- Ongoing trial (FAST-Forward) investigating the potential to provide a shorter course of treatment with EBRT (5 fractions)

TARGIT-A – local recurrence results (median follow-up 2.5 years) (1)

Local recurrence events: Events/N; 5-year cumulative risk %; (95% CI)	Intrabeam	EBRT	Absolute difference in **Kaplan-Meier estimate** at 5 years; p-value
Pre-pathology Stratum (n=2234)	**2.1%** (1.1 – 4.2) 10/1107	**1.1%** (0.5 – 2.5) 6/1127	**1%** p=0.31 4
Whole Cohort (n=3375)	**3.3%** (2.1 – 5.1) 23/1679	**1.3%** (0.7 – 2.5) 11/1696	**2.0%** p=0.042 12

Kaplan-Meier estimates of 5-year risk:

Source: AG report, page 44

- are cumulative estimates over the whole 5 year period, taking into account numbers at risk, numbers of events and numbers with no more follow-up (censoring) **at every time point** up to 5 years.

TARGIT-A protocol: "*We will use Kaplan-Meier curves ... to account for time-to event and censoring of the data.*"

- Statistical significance set at p<0.01 for local recurrence
- Pre-specified non-inferiority margin was 2.5%

TARGIT-A – local recurrence results (2)

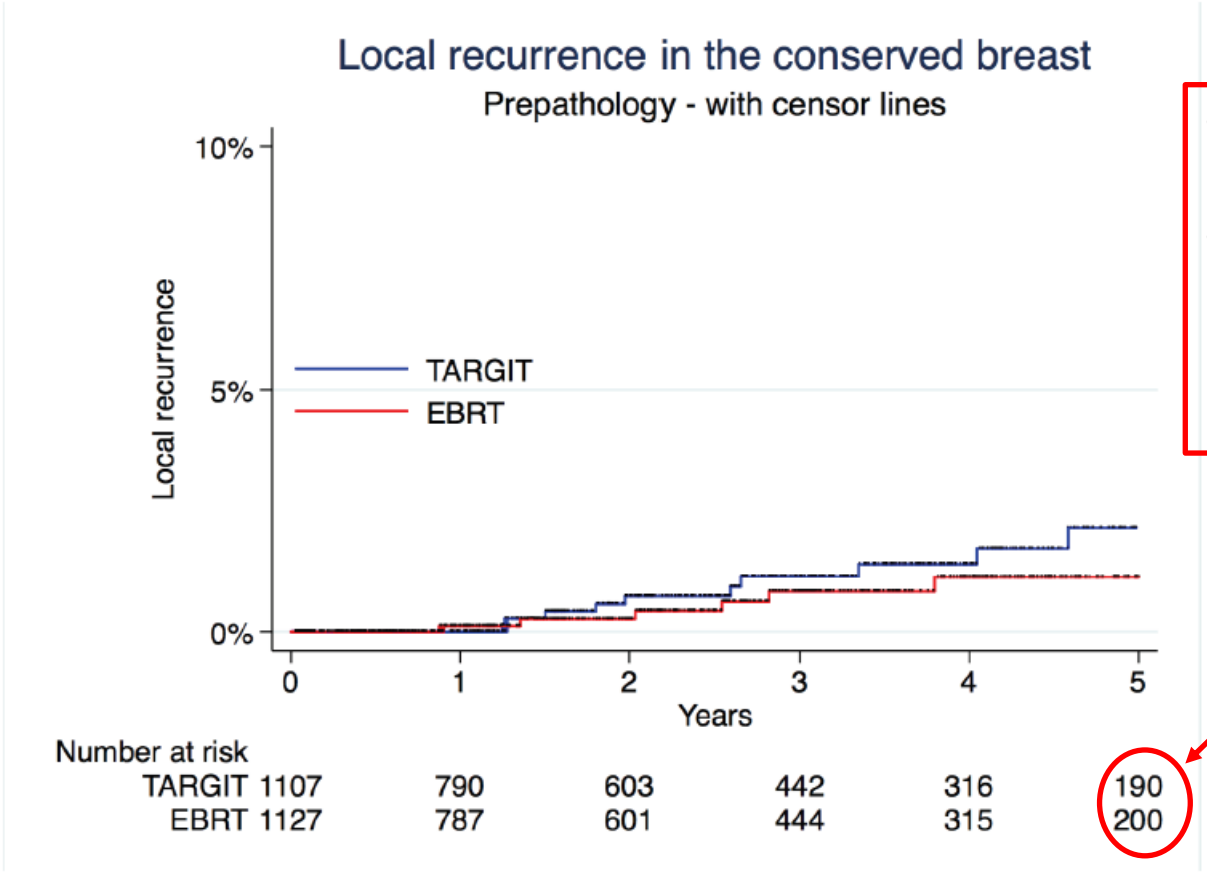
Local Recurrence	Median Follow up	Events (n)	Absolute difference (90%CI) in the **binomial proportions** (Intrabeam vs EBRT)	P non-inferiority
All patients	2 years 5 months	34	0.72% (0.2 – 1.3)	**<0.0001**
Mature Cohort	3 years 7 months	32	1.13% (0.3 – 2.0)	**0.0040**
Earliest Cohort	5 years	23	1.14% (-0.1 – 2.4)	**0.0400**

Source: AG report, pages 161 - 162

Binomial proportions at 5 years:

- include **all** people who started the trial (pre-pathology, Intrabeam: 1107, EBRT: 1127).
- assume the ~80% people who have not yet been followed for 5 years **do not have** the event (local recurrence).
- will **underestimate** the 5-year risk of local recurrence if any further people have an event before they reach 5 years of follow-up.

Estimating 5-year risk when follow-up is incomplete



- 390 people "at risk" at 5 years.
- Approx. 80% of the pre-pathology stratum had not reached 5 years follow-up at time of analysis.

TARGIT-A – overall survival results

Mortality: Events/N; **5-year cumulative risk %** **(95% CI)**	**Intrabeam**	**EBRT**	**Absolute difference;** **p-value**
Overall mortality			
Pre-pathology stratum (n=2298)	**4.6%** (1.8 to 6.0) 29/1140	**6.9%** (4.3 to 9.6) 42/1158	**-2.3%;** p=NR -13
All patients (n=3451)	**3.9%** (2.7 to 5.8) 37/1721	**5.3%** (3.9 to 7.3) 51/1730	**-1.4%;** p=0.099 -14

Source: AG report, page 47

TARGIT-A – breast cancer mortality results

Mortality: Events/N; **5-year cumulative risk % (95% CI)**	**Intrabeam**	**EBRT**	**Absolute difference; p-value**
Breast cancer mortality:			
Pre-pathology stratum (n=2298)	**3.3%** (1.9 to 5.8) 17/1140	**2.7%** (1.5 to 4.6) 15/1158	p=0.72
All patients (n=3451)	**2.6%** (1.5 to 4.3) 20/1721	**1.9%** (1.1 to 3.2) 16/1730	p=0.56

Source: AG report, page 47

TARGIT-A – non-breast cancer mortality results (1)

Mortality: Events/N; **5-year cumulative risk % (95% CI)**	**Intrabeam**	**EBRT**	**Absolute difference; p-value**
Non-breast cancer mortality:			
Pre-pathology stratum (n=2298)	**1.3%** (0.7 to 2.8) 12/1140	**4.4%** (2.8 to 6.9) 27/1158	**p=0.016**
All patients (n=3451)	**1.4%** (0.8 to 2.5) 17/1721	**3.5%** (2.3 to 5.2) 35/1730	**p=0.0086**

Source: AG report, page 47

TARGIT-A – non-breast cancer mortality results (2)

Non-breast cancer mortality, causes of death (n=3451)	Intrabeam n=1721	EBRT n=1730
Other cancers	8	16
Cardiovascular causes		
Cardiac[d]	2	8
Stroke	0	2
Ischemic bowel	0	1
Other[e]	7	8
Total	17	35

Note: [d] Included one "sudden death at home" in the EBRT group. [e] Targit: 2 diabetes, 1 renal failure, 1 liver failure, 1 sepsis, 1 Alzheimer's disease, 1 unknown; EBRT: 1 myelopathy, 1 perforated bowel, 1 pneumonia, 1 old age, 4 unknown.

Source: AG report, page 163

Committee's considerations (1)

- Reasonable to consider treatment with Intrabeam only at the time of primary surgical removal of the tumour. Plausible reasons for it being less effective if delayed and given at re-operation
- The Committee heard that if there is local recurrence after treatment with Intrabeam (this does not mean an increased risk of metastatic disease), further breast-conserving surgery and EBRT still remained an option
- Doubts about generalisability of TARGIT-A to NHS clinical practice:
  - EBRT 23 fractions (NHS established practice 15)
  - Radiation dose from 40–56 Gy (NHS – usually 40 Gy)
  - EBRT quality control not reported in some centres
- Length of follow-up in the trial: clinical evidence immature and associated with considerable uncertainty and Intrabeam had not been proven to be non inferior to EBRT as the criterion for non-inferiority was not appropriately defined and the trial was therefore underpowered
- Not possible to draw any conclusions from TARGIT-A in terms of an overall survival benefit with Intrabeam compared with EBRT .

Committee's considerations (2)

- Some patients willing to accept a treatment that might have a higher risk of local recurrence as long as the absolute risk remains low and the treatment had other benefits which they consider important
- There were several benefits highlighted by the patient expert and clinical specialists in terms of improving patients' quality of life, which could not be captured in the QALY calculation
- Individual patient preference is important but patients should be fully informed of the evidence and treatment options available, the lack of information about long-term outcomes with Intrabeam and the risks and benefits associated with this technology

Committee's considerations (3)

- Company and AG estimated that the costs of Intrabeam were lower than EBRT – the size of the cost savings was uncertain
- Cost savings would be greater if the capital cost of EBRT included
- Based on the high degree of uncertainty, not possible to state a most plausible ICER for Intrabeam compared with EBRT, but concluded that Intrabeam was associated with slightly lower costs and fewer QALYs than EBRT
- There are 6 Intrabeam devices in the UK, which were used as part of TARGIT-A: given these existing resources, which include staff trained in the use of Intrabeam, it would be reasonable to use these resources first

Consultation on ACD (1)

Several comments from consultation expressed concerns on TARGIT-A data and Committee's preliminary recommendations including:

- given the short median follow up of TARGIT-A, the evidence is too immature to allow informed discussion of the long term efficacy and safety of Intrabeam
- Intrabeam cannot be considered to be non-inferior to EBRT
- 5-year local recurrence rates in TARGIT- A are misleading and almost certainly under-represent the real risk at 5 years
- excess risk of local breast cancer relapse can be observed in women treated with Intrabeam over the next 10 years
- methodological flaws of TARGIT A: follow up, pre-specified non-inferiority margin, statistical analyses, errors in the analysis in terms of attributing causes of excess non-breast cancer mortality
- important that patients are aware of the current lack of data so they are able to make an informed choice
- funding of Intrabeam should include dedicated staff for commissioning and initial installation: in the short term extra medical physics staff will be needed to establish the service

Consultation on ACD (2)

Several comments from consultation expressed concerns on TARGIT-A data and Committee's preliminary recommendations including:

- *"Patients would rather avoid extra visits for radiotherapy but if the alternative is a potential doubling their risk of mastectomy, is this a successful strategy?"*
- *"Patient choice is paramount, but this must be informed and based on high quality trials with adequate follow up: Given the short median follow up of TARGIT-A, the evidence reported is too premature to allow informed discussion regarding the long term efficacy and safety of Intrabeam"*
- *"Treatment with a combination of Intrabeam and EBRT causes greater side effects (e.g. high levels of late normal tissue fibrosis)"*
- *"Lack of appropriate research governance for the TARGIT trial"*
- *"INTRABEAM should not be used outside well designed clinical trials"*
- *"Due to limitations in the current evidence base breast surgeons across the UK are not in a position to satisfactorily counsel patients that intra-operative radiotherapy is currently a proven, safe alternative to EBRT. Offering informed choice is established practice in the UK but it is not possible to offer as a therapeutic option a procedure that has insufficient reliable background information".*

Consultation on ACD (3)

Several comments from consultation supported TARGIT-A data and use of Intrabeam in the NHS including:

- overall survival may be better with TARGIT
- the number of patients who might benefit is grossly underestimated
- difference in local recurrence unlikely to increase: TARGIT-A already has 1222 patients with a median follow-up of 5 years, would not expect a larger difference in local recurrence than that is already seen (currently 1%, p=0.31)
- results were obtained from an analysis of a pre-specified stratum, classified by the timing of randomisation in relation to lumpectomy (pre-pathology), without restricting the analysis to any particular age group or biological subtype
- side effects were fewer, quality of life and cosmesis improved
- denying many patients the opportunity for safe breast conservation with the convenience of a single dose radiotherapy during lumpectomy with lower toxicity is unreasonable. It is up to individual clinicians and multi-disciplinary teams to take responsibility to choose the correct treatment for an individual patient.

Consultation on ACD (4)

Comments were also received on the availability of other IORT technologies including:

- in the UK and other countries IORT is already being delivered using alternative equipment based on the evidence of the TARGIT and other trials
- disappointed and surprised to learn that only a single vendor of IORT technology had been specified.
- We suggest that the reimbursement should be offered for similar IORT technologies such as Xoft Axxent System which is currently used for breast IORT in 4 hospitals in the UK.

Committee's conclusion after 2nd Committee meeting

- The Committee based its preliminary recommendations on the 1% difference in local recurrence rate between Intrabeam and EBRT in the pre-pathology group in TARGIT-A
- After reviewing the comments from consultation on its preliminary recommendations and the discussion at the 2nd Committee meeting, it questioned the reliability of the data presented and noted that definitive statements were being made about the 5-year risk of local recurrence based on immature data (median follow up 2.5 years)
- The Committee (and commentators) noted that the conclusion about non-inferiority was based on a 90% CI around the difference in binomial proportions, rather than a 95% CI around the difference in Kaplan-Meier estimates of local recurrence (which had not been provided)
- The level of uncertainty around this difference would help the Committee to make a more informed judgment about whether Intrabeam is likely to be non-inferior compared with EBRT once further follow-up data have accumulated.

Committee's request for further data

The Committee requested further information to the TARGIT-A investigators. It requested the following results and analyses using the most up-to-date data (without requirement for data unblinding):

- absolute number of local recurrence and mortality events
- Kaplan-Meier analyses including all patients using the most up-to-date follow-up data from TARGIT-A for each treatment group showing the cumulative risk of local recurrence and mortality over time using the latest available follow-up data
- the absolute difference in the Kaplan-Meier estimate of the 5-year risks of local recurrence and mortality between treatment groups and the 95% confidence interval around that difference
- the full patient-level dataset so that these analyses can be critically appraised independently.

TARGIT-A investigators response (1)

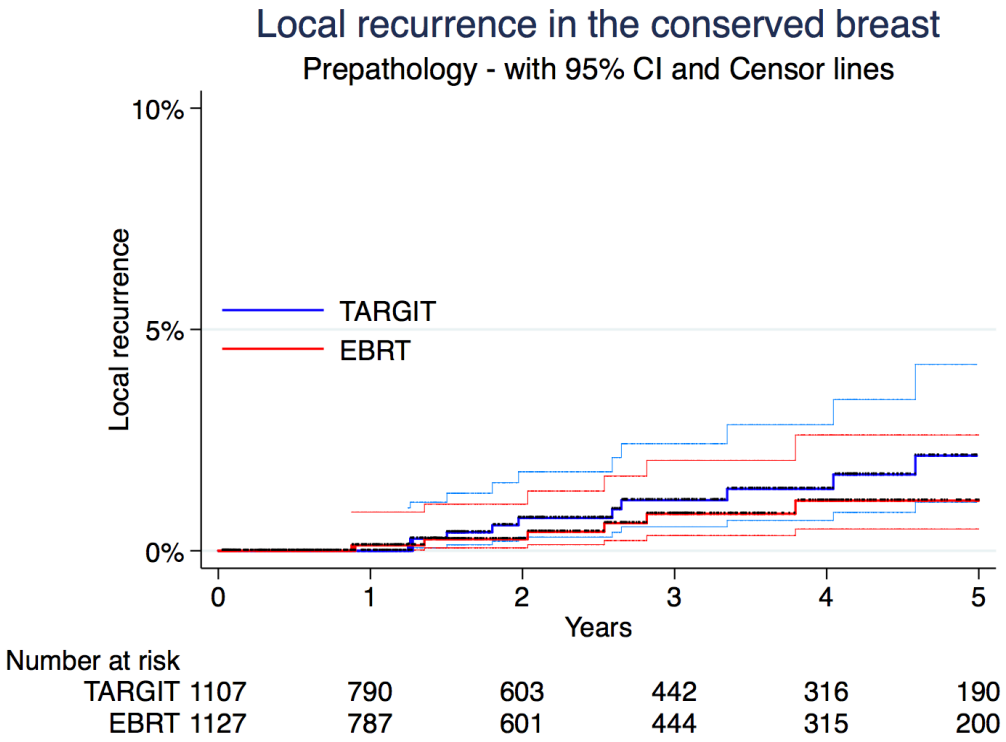
In response to the request the investigators noted that :

- The appropriate method of calculating the difference between Kaplan-Meier curves is by using the integrated difference of the 2 survival functions
- In the presence of censoring, the Kaplan-Meier estimate at a particular time point is not a simple binomial proportion and it is inappropriate to apply the simple formula used to calculate the SE and CI
- When looking at Kaplan-Meier curves, the right hand of the curve has the most uncertainty and with the widest CI. These values, i.e. 5-year point estimates, should not be used to calculate the CI of the difference or for testing non-inferiority.
- Currently the median follow up is 4 years: 1725 patients have at least 4 years of followed up or longer
- They were willing to supply raw data as long as all the governance, consent, custody, data access and security issues are looked after appropriately.

TARGIT-A investigators response (2)

Pre-pathology: local recurrence

Pre-pathology group	Intrabeam	EBRT
Number of local recurrence events	10	6



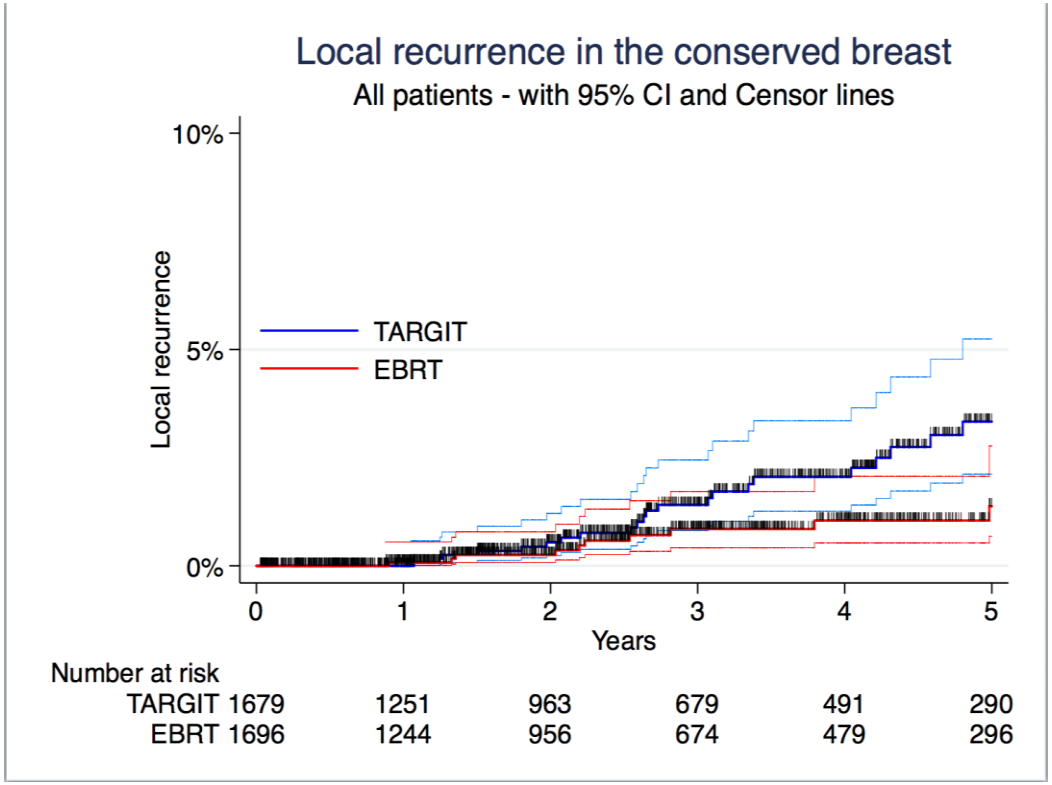
- The absolute difference (95%CI) in the Kaplan-Meier estimate of the 5-year risk of local recurrence between treatment groups:
  1% (-0.68% to 2.68%)

- Difference (95%CI) between Kaplan-Meier curves from 0 to 5 years using the integrated difference:
  0.3% (-0.4% to 1.03%)

TARGIT-A investigators response (3)

Whole study population: local recurrence

Whole study population	Intrabeam	EBRT
Number of local recurrence events	23	11



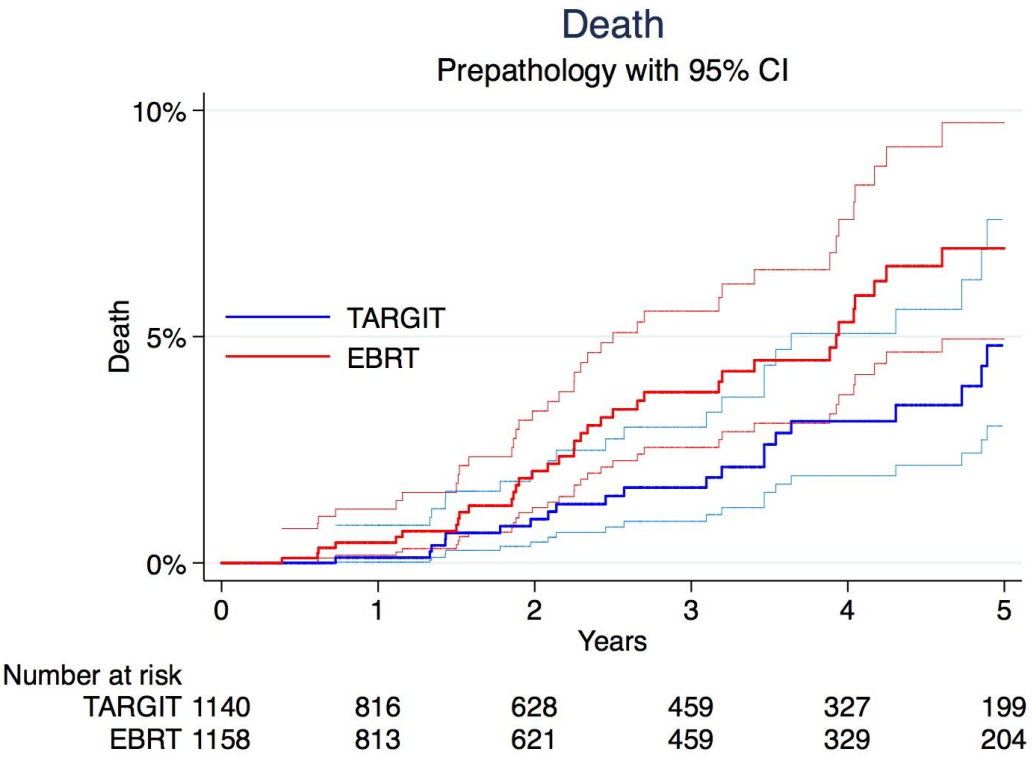
- The absolute difference (95%CI) in the Kaplan-Meier estimate of the 5-year risk of local recurrence between treatment groups:
  2% (-0.14% to 4.14%)

- Difference (95%CI) between Kaplan-Meier curves from 0 to 5 years using the integrated difference:
  0.62% (0.007% to 1.24%)

TARGIT-A investigators response (4)

Pre-pathology group: overall mortality

Pre-pathology group	Intrabeam	EBRT
Number of deaths	29	42



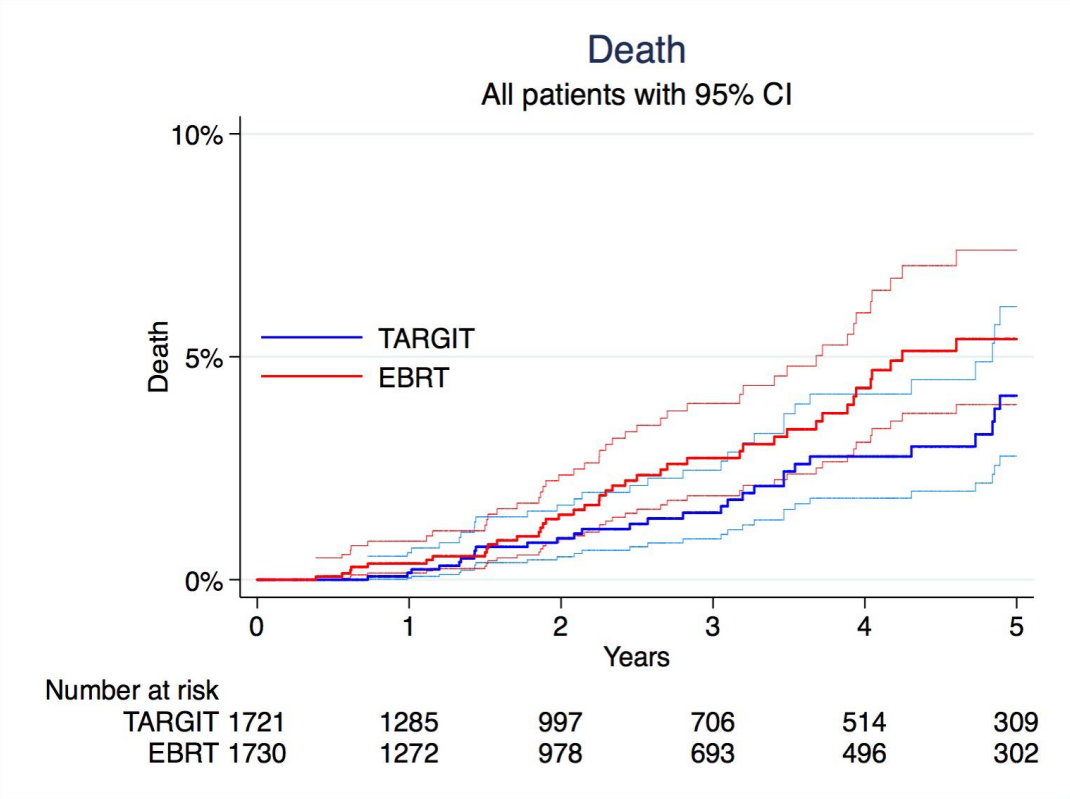
- The absolute difference (95%CI) in the Kaplan-Meier estimate of the 5-year risk of overall mortality between treatment groups:
  -2.33% (-5.48% to 0.82%)

- Difference (95%CI) between Kaplan-Meier curves from 0 to 5 years using the integrated difference:
  -1.43% (-2.66% to -0.2%)

TARGIT-A investigators response (5)

Whole study population: overall mortality

Whole study population	Intrabeam	EBRT
Number of deaths	37	51



- The absolute difference (95%CI) in the Kaplan-Meier estimate of the 5-year risk of overall mortality between treatment groups: **-1.38% (-3.67% to 0.91%)**
- Difference (95%CI) between Kaplan-Meier curves from 0 to 5 years using the integrated difference: **-0.85% (-1.75% to 0.04%)**

TARGIT-A investigators response (6) – new data on local recurrence

- Since the data lock in June 2012, there were 15 new local recurrences in the pre-pathology group (in addition to the 16 already reported in the Lancet publication). Remaining blind to randomisation, the investigators presented 2 hypothetical scenarios:

Local Recurrence scenarios	Events on Intrabeam	Events on EBRT	Absolute difference in the binomial proportions (Intrabeam vs EBRT) (90%CI) (95% CI)	P non-inferiority
Worst-case scenario	12	3	1.19% (0.4% to 2.0%)(0.2% to 2.2%)	**<0.0041**
Less extreme scenario	10	5	0.83% (0.0% to 1.6%)(-0.1% to 1.8%)	**0.00038**

TARGIT-A investigators response (7) – new data on overall survival

- There were 28 new death events since data lock in June 2012 – these would need to have occurred in a ratio of 20 in TARGIT vs. 8 in EBRT in order to equalise the total number of deaths between the 2 treatments. As the initial observation was 29 deaths in TARGIT vs. 42 in EBRT, probability of such drastic reversal is low (p=0.008), so the difference in deaths is likely to remain in favour of TARGIT.

Key issues for consideration

- Does the Committee consider that its request has been responded to by the TARGIT-A group in an appropriate, clear and robust manner?
- What are the Committee's view on the uncertainty of the presented data?
- To what extent should patient choice be taken into account, and how is that informed?
- Are there major implications for service delivery?
- Taking into account the comments from consultation, discussion at the 2nd ACM, and responses from the TARGIT-A investigators, does the Committee consider that its preliminary recommendations on Intrabeam are suitable basis for guidance to the NHS?

Considerations options

- The evidence on Intrabeam is uncertain and the results of TARGIT-A are not mature:
  - Should Intrabeam be 'not recommended' in the guidance and considered for review when the final data are available?
- Intrabeam *could* be less clinically effective than EBRT:
  - Does this mean it should not be recommended?
  - Should it only be recommended for people who cannot have or are unwilling to have EBRT?
  - Is it reasonable to recommend it as an option provided that patients are fully informed about the evidence and choose it based on their own preferences?
    - How could patients be supported to make this decision when the professionals cannot agree on the interpretation of the evidence?
    - Should Intrabeam only be recommended with appropriate long-term data collection on the use of Intrabeam in the NHS (e.g. registry)?