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SHTAC response to Consultee comments and comments submitted on behalf of the TARGIT-A Trialists' Group on the assessment report "The clinical and cost effectiveness of the INTRABEAM® Photon Radiotherapy System for the adjuvant treatment of early breast cancer"

18th June 2014

SHTAC have considered all comments on the assessment report (AR) submitted by Consultees and authors of the key papers for the TARGIT-A trial. The comments that we believe require a response have been grouped into key themes which are presented as far as possible in a sequence that follows the ordering of the assessment report. We have provided a response for each of these themes.

1) Objective and scope of the assessment

The trial authors questioned the inclusion of data from the whole trial population and the post-pathology stratum in the AR and appear to be under a misapprehension that the SHTAC economic model includes data from the post-pathology stratum. As stated on AR p34 the timing of INTRABEAM delivery was not specified in the scope and therefore, after consulting with NICE, these data were included in the clinical effectiveness review. However, as stated on AR p87 the patient population included in the SHTAC economic model reflects the pre-pathology stratum of the TARGIT-A trial because the TARGIT-A study recommended INTRABEAM concurrent with lumpectomy but did not recommend the use of postoperative INTRABEAM as an alternative to EBRT. The SHTAC approach to economic modelling was consistent with the manufacturer's economic model.

2) Methods - perspective of analysis

The NICE Guide to the methods of technology appraisal 2013[1] sets out the methods that SHTAC have adhered to in conducting this assessment. The methods guide stipulates that the perspective for costs should be that of the NHS and PSS. It was therefore beyond our remit to include expenses incurred by patients attending for a course of EBRT within the analysis. These expenses could include travel, parking, loss of earning and potentially accommodation and other costs. These issues are discussed in section 6 "Assessment of factors relevant to the NHS and other parties".

3) Error identified in the systematic review of clinical effectiveness

The trial authors have clarified that the p-value cut off for the non-inferiority statistic was set at the conventional 0.05 level, and not at the 0.01 level as stated by SHTAC on p44. SHTAC will correct the text on this page to show that non-inferiority was established for the whole trial earliest cohort with a median follow-up of 5 years.

4) Clinical endpoints and model outputs

The clinical endpoints from the TARGIT-A trial are presented in AR Chapter 4 (p31-55). The SHTAC independent economic model is not replicating the TARGIT-A trial. The model aims to estimate the costs, benefits (in terms of QALYs) and cost-effectiveness of INTRABEAM compared to EBRT for early operable breast cancer in the context of the UK NHS. Therefore it is not inconsistent that the clinical endpoints from the TARGIT-A trial presented in Chapter 4 demonstrate that INTRABEAM is non-inferior to EBRT but the base case results from the SHTAC economic model are that INTRABEAM is cheaper but less effective than EBRT in terms of QALYs (Tables 34 and 35, p108). Furthermore SHTAC acknowledge that the base case result is subject to a degree of uncertainty - for four model parameters the difference in the upper and lower values causes a switch in which treatment option is considered cost-effective at a willingness to pay of £20,000 per QALY.

5) SHTAC independent model: Extrapolation of trial data on local recurrence

The NICE reference case set out in the Guide to the methods of technology appraisal 2013[1] states that the time horizon should be sufficiently long to reflect all important differences in costs or outcomes. For technologies such as EBRT and INTRABEAM which have impacts over a patient's lifetime and may lead to differences in survival, a lifetime time horizon is appropriate. Therefore in the health economic model an assumption has to be made about local recurrence beyond the follow-up period reported for the TARGIT-A trial. For early breast cancer patients, in patients randomised to the pre-pathology stratum (which informs the economic model), there were few local recurrences in the conserved breast in both the INTRABEAM and EBRT groups (INTRABEAM 10/1107; EBRT 6/1127) during the follow-up period (median follow-up 2 years 4 months). The low event rate and 2 year 4 month median follow-up period leads to uncertainty about what the local recurrence data will look like in the future. The trialists' view is that the peak hazard of recurrence is 2-3 years after surgery and radiotherapy protects against recurrences only during the first 5 years of follow-up. In contrast, other studies[2;3] and clinical advice to SHTAC is that the risk of local recurrence continues throughout life and is relatively linear over time. SHTAC have extrapolated the local recurrence data from the TARGIT-A trial data such that local recurrences continue to occur throughout the time horizon of the model. To extrapolate local recurrence beyond the reported trial data the lognormal curve was adopted which is described by three parameters: the constant, sigma and the beta coefficient. The constant (which essentially gives the overall mean survival associated with the comparator treatment) and sigma (which gives the variation in mean survival on a log scale) together influence the shape of the curve and its associated mean survival. The beta coefficient (the treatment effect of INTRABEAM) is then added to this curve to obtain the survival curve for the intervention. The lognormal curve parameters in the base case are presented in AR Table 23. Ideally these parameters should be varied together because they are correlated, however for simplification SHTAC did not do this for deterministic sensitivity analyses but it was done in probabilistic sensitivity analyses. Deterministic sensitivity analysis identified time to local recurrence associated with INTRABEAM as one of the top four most influential parameters in the model and one that caused a switch in which treatment is considered cost-effective at a willingness to pay threshold of £20,000. At low values of the beta coefficient for the INTRABEAM arm EBRT is cost-effective compared to

INTRABEAM, but at the highest values considered INTRABEAM becomes slightly more cost-effective than EBRT.

6) <u>SHTAC independent model: modelling the general underlying risk of mortality</u>

The population included in the economic model may either die from breast cancer or from another cause (non-breast cancer) as shown in AR Figure 5 (p88). As described in the AR p94-96 the general underlying risk of mortality (non-breast cancer death) was modelled using 2010-2012 ONS female interim life table data for England. As described on AR p96 SHTAC has compared the annual probabilities of death on the EBRT arm with annual all-cause mortality probabilities obtained from ONS data and found that they are similar. A chart for comparison of these data was not presented in the report but is provided below (Figure A). SHTAC does not therefore consider that there is an excess of deaths on the EBRT arm, but rather a shortfall of deaths on the INTRABEAM arm. Furthermore survival was a secondary outcome for the trial and the non-breast cancer death rates observed in the TARGIT-A trial are based on a small number of events (INTRABEAM n=12, and EBRT n=27 non-breast cancer deaths). SHTAC is aware that there is a currently an ongoing debate amongst the clinical community about the possible reasons for the difference in non-breast cancer deaths between the EBRT and INTRABEAM study arms[4-6] with age mentioned secondarily as only one of what may be many potential factors. Overall SHTAC considers that the ONS data are more robust than the TARGIT-A trial data for this parameter and hence used these data to model the underlying risk of mortality. Nevertheless SHTAC have conducted a scenario analysis using the trial observed mortality data where INTRABEAM dominates EBRT (AR p117-118).

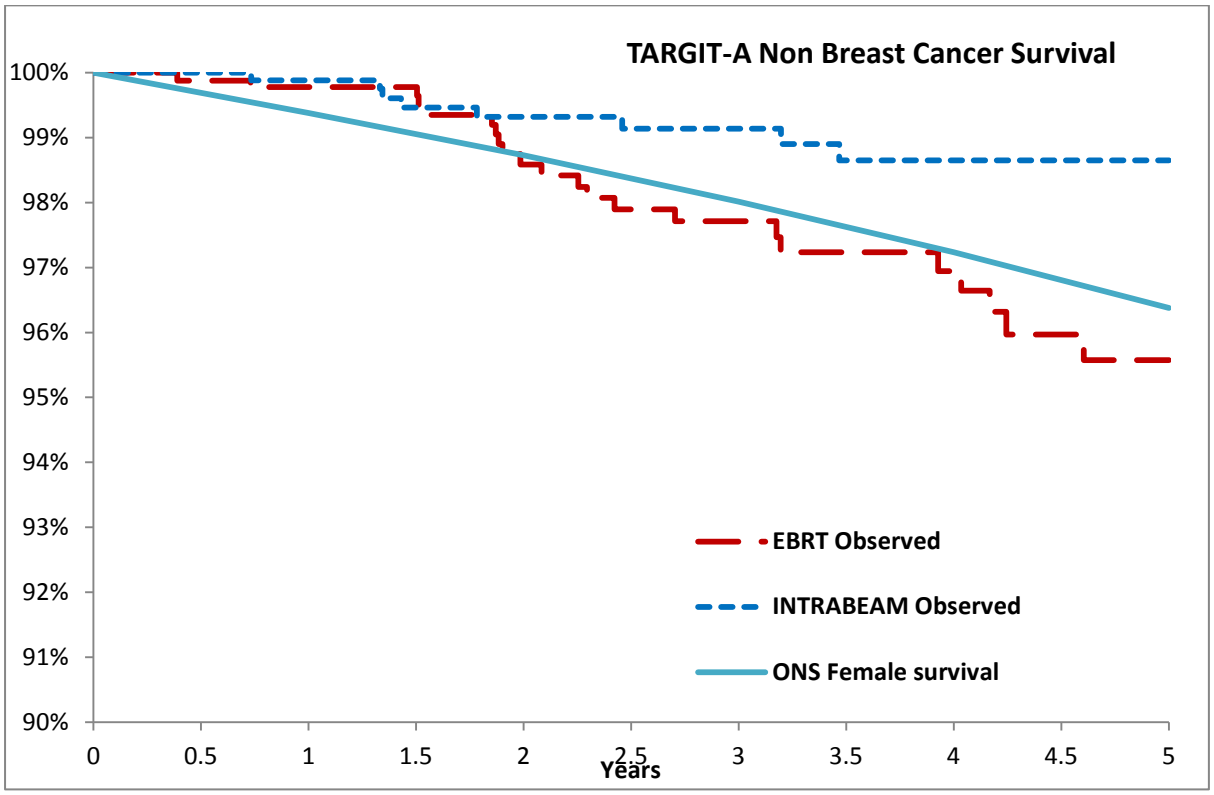

Figure A: Comparison of the annual probabilities of death observed in the trial arms with annual all-cause mortality probabilities obtained from ONS data

7) SHTAC independent model: Proportions of patients receiving mastectomy at local recurrence and proportion of patients having reconstruction after mastectomy

Clinical advice to the SHTAC assessment group was that the most common and evidence-based approach in the UK is to offer mastectomy at local recurrence and that approximately 70-80% of UK patients opt for mastectomy. At local recurrence the SHTAC base case model assumes that 80% of INTRABEAM patients have mastectomy (AR p98). The trial authors state that 50% of INTRABEAM patients had mastectomy at recurrence (information that was not available to the assessment group from the published papers or the manufacturer's submission) and state that this is the value that should be used, although SHTAC note that this would likely reflect international practice (rather than UK practice) given that the TARGIT-A trial was an international trial. SHTAC have examined alterations to the proportion having mastectomy in deterministic sensitivity analysis taking 2.5th and 97.5th percentiles of the assumed distribution (p109). Varying this parameter had very little impact on the outcome (an excerpt from AR Appendix 11 is reproduced in Table 1 below).

The proportion of patients who opt for reconstruction when receiving a mastectomy was based on figures from the National Mastectomy and Breast Reconstruction Audit (AR p99) which showed that in 2011 only around 31% of those undergoing mastectomy choose to have a reconstruction. Varying this parameter also had very little impact on the outcome (excerpts from AR Appendix 11 are reproduced in Table 1).

Table 1: Deterministic sensitivity analysis for proportion of patients receiving mastectomy at local recurrence and proportion of patients having reconstruction after mastectomy

Variable description	Low value	High value	Low value incremental NMB (£)	High value incremental NMB (£)	Range (£)
Proportion of INTRABEAM patients having mastectomy at local recurrence	0.618	0.933	-1,611	-1,625	14
Proportion having reconstruction after mastectomy	0.304	0.318	-1,620	-1,620	0

(Excerpts reproduced from AR Appendix 11. Complete set of results from deterministic sensitivity analysis, IORT vs EBRT. WTP set to £20,000 per QALY.)

8) SHTAC independent model: estimates of staff resources required

Comments received from the Society and College of Radiographers indicate that the staffing grades for non surgical staff seem appropriate but it was considered that SHTAC should have included costs for a therapeutic radiographer who should be involved in the pathway of care and delivery of treatment. This would increase costs for INTRABEAM but SHTAC believe the impact on the ICER would be minimal.

The manufacturer comments that the time requirement is not as high as SHTAC have estimated. In this case costs for INTRABEAM would decrease but again SHTAC believe that the impact on the ICER would be minimal.

A comment by the trialists indicates a misunderstanding on their part regarding staff in theatre during delivery of the INTRABEAM dose. Table 28 of the AR (p101) indicates one surgical consultant only and this is the anaesthetist. No surgeon time is included during INTRABEAM delivery.

9) SHTAC independent model: estimates of EBRT cost

Comments received from the consultees suggested that costs for replacement and additional linear accelerators should have been included in EBRT costs. As described in the AR p102 costs for planning and delivery of EBRT were obtained as weighted averages from NHS Reference Costs 2012-1013. The NHS reference costs capture all the running costs of providing the service. Each cost therefore includes direct costs, indirect costs and overhead costs.[7]

The effect of uncertainty in estimates contributing to the overall cost of EBRT was explored in deterministic sensitivity analysis (excerpts from AR Appendix 11 are reproduced in Table 2).

Table 2: Deterministic sensitivity analysis for costs contributing to the cost of EBRT

Variable description	Low value	High value	Low value incremental NMB (£)	High value incremental NMB (£)	Range (£)
Number of EBRT deliveries required to complete a course of treatment	5	23	-2,604	-832	1,772
Cost of delivering one fraction EBRT	71	178	-2,211	-877	1,334
EBRT planning cost	90	704	-1,813	-1,303	510

(Excerpts reproduced from AR Appendix 11. Complete set of results from deterministic sensitivity analysis, IORT vs EBRT. WTP set to £20,000 per QALY.)

Newer radiotherapy techniques such as intensity modulated radiotherapy (IMRT) were not included in the NICE scope for this MTA. SHTAC acknowledge that some newer techniques may involve increased cost but on the other hand there are shorter courses of EBRT being investigated by the Fast-Forward trial which would be associated with lower costs.

10) SHTAC independent model: demand for INTRABEAM

The estimated proportion of incident breast cancer cases which are early breast cancer and suitable for INTRABEAM was based on both expert opinion (two estimates one of 10-20%, one of 50%) and a published study by Leonardi and colleagues.[8] AR Table 32 suggests in error that Leonardi and colleagues was the only source of information and this will be corrected. In addition to the base case

assumption of 16%, the range of suggested values (10% to 50%) was examined in deterministic sensitivity analysis (Table 3 below). Although this parameter was more influential than some others examined, INTRABEAM was not cost-effective at either value and therefore SHTAC do not believe that this parameter contributes to decision uncertainty.

Table 3: Deterministic sensitivity analysis proportion of cases suitable for INTRABEAM

Variable description	Low value	High value	Low value incremental NMB (£)	High value incremental NMB (£)	Range (£)
Proportion of incident cases which are early BC and suitable for INTRABEAM	0.1	0.5	-2,064	-1,128	936

(Excerpt reproduced from AR Appendix 11. Complete set of results from deterministic sensitivity analysis, IORT vs EBRT. WTP set to £20,000 per QALY.)

Reference List

(1) National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. *NICE, London* 2013.

(2) Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013; 14(13):1269-1277.

(3) Kreike B, Hart AA, van d, V, Borger J, Peterse H, Rutgers E et al. Continuing risk of ipsilateral breast relapse after breast-conserving therapy at long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; 71(4):1014-1021.

(4) Mackenzie P, Fyles A, Chung C. Radiotherapy for breast cancer, the TARGIT-A trial. *Lancet* 2014; 383(9930):1717-6736.

(5) Yarnold J, Offersen BV, Olivotto I, Poortmans P, Sarin R. Radiotherapy for breast cancer, the TARGIT-A trial. *Lancet* 2014; 383(9930):1717-1718.

(6) Harness JK, Silverstein MJ, Wazer DE, Riker AI. Radiotherapy for breast cancer, the TARGIT-A trial. *Lancet* 2014; 383(9930):1718-1719.

(7) Department of Health. Reference costs 2012-13. 2013.

(8) Leonardi MC, Maisonneuve P, Mastropasqua MG, Morra A, Lazzari R, Rotmensz N et al. How do the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation fit intraoperative radiotherapy? A retrospective analysis of patients treated at the European Institute of Oncology. *Int J Radiat Oncol Biol Phys* 2012; 83(3):806-813.