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Commentary on the manuscript "Accelerated Partial Breast Irradiation Consensus Statement: Update of an ASTRO Evidence-Based Consensus Statement" for Practical Radiation Oncology

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Commentary on the manuscript "Accelerated Partial Breast Irradiation Consensus Statement: Update of an ASTRO Evidence-Based Consensus Statement" for Practical Radiation Oncology.

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Shortened Running Title: Commentary on ASTRO APBI Guidelines

Conflict of Interest Notification:

Roberto Diaz has received personal fees from Carl Zeiss for US TARGIT Academy Faculty outside the submitted work.

Stephen Grobmyer has received grants and non-financial support from Carl Zeiss outside the submitted work.

Dennis Holmes has received grants and personal fees from Carl Zeiss related to the submitted work.

Christine Laronga has received royalties from Up-To-Date and speech honoraria from Genomic Health outside the submitted work.

Andrea McKee has received speech honoraria from Carl Zeiss outside the submitted work.

William Small, Jr. has received honoraria for talk and travel expenses and a grant for the TARGIT US Registry Trial from Carl Zeiss both related to and outside the submitted work.

Jeffrey Tobias has received honoraria for speeches and travel support for International Steering Committee meetings and conferences where TARGIT data is being presented from Carl Zeiss both related to and outside the submitted work.

Jayant Vaidya has received honoraria for speeches and travel support for International Steering Committee meetings and conferences where TARGIT data is being presented from Carl Zeiss, both related to and outside the submitted work, and a grant from Photoelectron Corporation from 1996-1999 related to the submitted work.

Frederik Wenz has received grants and personal fees from Carl Zeiss and Elekta related to the submitted work, personal fees from Celgene and Ipsen outside the submitted work, and two issued patents with no financial or commercial aspects.

While the new ASTRO consensus statement on accelerated partial breast irradiation (APBI) reflects many important changes relative to case selection and inclusion criteria for ABPI, we would like address our concerns specifically regarding the recommendations on the use of low-energy X-ray intraoperative radiation therapy (IORT). The consensus should include the fact that TARGIT IORT achieves local control similar to EBRT with a potential for a survival benefit[1-4].

Although the panel correctly recognized that the local recurrence rate in pre-pathology (TARGIT given simultaneously during lumpectomy) *stratum* was NOT significantly different than the WBI arm (2.1% vs 1.1%, p=0.31), the panel gave 'greater weight' to the local recurrence rate of the entire IORT cohort [pre-pathology and post-pathology (TARGIT given following lumpectomy as a second procedure by reopening the wound at a median of 37 days after the initial excision) strata combined]. Sometimes the devil is in the details. The TARGIT-A trial specified stratification between pre- and post-pathology *before randomization* to accommodate different practices in the participating sites[5]. As the two strata were randomized separately, there is little bias that could explain the differing results. Instead, the superior result in the pre-pathology group is likely explained by avoidance of spatial and temporal miss as well as by data suggesting that biologically IORT inhibits local chemokines that promote local recurrence[6]. Thus, the panel's recommendations regarding IORT should have acknowledged the results for the pre-specified analysis for the primary end-point of IORT treatment in the whole trial (n=3451, a difference of 2 % p=0.04), as well the pre-pathology stratum (n=2298, a difference of 1% p=0.31) [1-3]. Results of pre-pathology TARGIT IORT were clinically and statistically *not* significantly different from EBRT.

The panel neglecting to recognize the identical results of TARGIT IORT vs EBRT in PR positive patients of the pre-pathology stratum is surprising in light of their decision to use a subgroup analysis from the ELIOT trial to validate the use of electron beam IORT (ELIOT)[7,8]. A post hoc analysis of a small subgroup of 294 patients meeting the 2009 ASTRO "suitable" criteria[9] in the ELIOT trial (n=1301) were used to support the panel's recommendations in favor of electron beam IORT. The consensus should therefore also include the outcome of the much larger group of 2298 pre-specified subjects in the TARGIT pre-pathology stratum in which comparable local control was achieved. Furthermore, the 5-year local recurrence rate in the large subgroup of 1625 PR positive patients, pre-specified before unblinding of the data, was 1.4 % in the TARGIT and 1.2 % in the WBI arm with a significant improvement in overall survival in the TARGIT patients (Figures 1and 2)[1]. Comparing the 636 TARGIT-A patients with a median 5 year follow-up to the whole and mature cohorts of the trial notes no evidence of delayed recurrences. These 636 TARGIT-A patients' results (LRR of 1.4%) compare

well with the post-hoc ELIOT good risk sub-group analysis of the 294 ELIOT patients with LRR rate of 1.5%, both with a median follow up of 5 years.

While looking at follow up, one must remember that the effect of radiotherapy on local recurrence is generally in the first 2-3 years and disappears after 5 years. The follow-up for the entire TARGIT-A trial dataset included 3451 patients with a median follow-up of 2 years and 5 months. Moreover, the earliest cohort of 1222 patients had a median of 5 years follow up. The analysis of the number of events in all patients and this earliest cohort found that the absolute difference (90% CI) in the binomial proportions of local recurrence in the conserved breast was 0.72% (0.2- 1.3) and 1.14% (-0.1 to 2.4) with a highly significant p value confirming non-inferiority[2]. The ELIOT trial[7] included 1305 patients with a median follow up of 5 years which is comparable in number to the earliest cohort of patients (n=1222) in the TARGIT-A trial. More recently, results of the GEC-ESTRO phase 3 trial of APBI utilizing interstitial multicatheter brachytherapy[10] used a non-inferiority margin of 3%, similar to the 2.5% used in the TARGIT-A trial. Both trials showed no significant difference in local recurrence between the two randomized groups as well as lower non-breast-cancer mortality[11]. Furthermore, patient-reported quality of life results recently reported that patients treated with IORT have similar self-reported cosmetic outcomes with better breast-related quality of life than patients treated with external beam therapy[12]. We must also recognise the savings to the healthcare system by using TARGIT which have been estimated to be at least $1.2 billion in the United States over 5 years[13].

One cannot ignore that the available evidence has prompted clinicians and patients to use TARGIT IORT in over 300 major hospitals in 35 countries including the USA (61 centers – including Loyola Univ, Cornell Univ, Georgetown Univ, UCSF, Columbia Univ, Cleveland Clinic, Northwestern, William Beaumont, USC, etc.) Canada, UK, France, Germany (60 centers,) Italy, Scandinavia, Switzerland, China, Australia (government funded), and New Zealand. Over 20,000 women have been treated successfully worldwide (Figure 3).

An objective consensus statement requires the collaboration and intellectual analysis of all specialty physicians involved in patient's care. Excellent examples of this approach are the recently reported margin consensus guidelines for DCIS and invasive cancer; which included representation from the American Society of Radiation Oncology, Society of Surgical Oncology, American Society of Breast Surgeons and the American Society of Clinical Oncology. This APBI "consensus" statement was created in isolation despite calls from the leadership of national surgical societies to participate in the data analysis and consensus statement preparation.[14,15]

In summary, we have numerous concerns regarding the selection and interpretation of the data presented and request reconsideration of the entirety of available data and a more balanced interpretation, in order that all breast cancer patients can benefit from the best available options. The ASTRO statement should include the high-quality evidence that indicates that low-energy IORT is an excellent option for suitable patients.

References

1. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare targeted intra-operative radiotherapy (TARGIT) with conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer (The TARGIT-A trial). *Health technology assessment.* 2016;20(73).
2. Vaidya JS, Bulsara M, Wenz F, et al. Pride, Prejudice, or Science – attitudes towards the results of the TARGIT-A trial of targeted intraoperative radiotherapy for breast cancer. *International Journal of Radiation Oncology*Biology*Physics.* 2015;92(3):494-500.
3. Vaidya JS, Wenz F, Bulsara M, et al. 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. *Lancet.* 2014;383(9917):603-613.
4. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph D, Baum M. Radiotherapy for breast cancer, the TARGIT-A trial - Authors' reply. *Lancet.* 2014;383(9930):1719-1720.
5. Vaidya JS, Tobias JS, Baum M. *THe TARGIT-A trial protocol.* 1999;https://njl-admin.nihr.ac.uk/document/download/2006598.
6. 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. *Human Cancer Biology.* 2008; 14(5): 1325-1332.
7. Leonardi MC, Maisonneuve P, Mastropasqua MG, 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. *International journal of radiation oncology, biology, physics.* 2012;83(3):806-813.
8. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *The lancet oncology.* 2013;14(13):1269-1277.
9. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *International journal of radiation oncology, biology, physics.* 2009;74(4):987-1001.
10. Strnad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet.* 2015.
11. Vaidya JS, Bulsara M, Wenz F, Tobias JS, Joseph D, Baum M. Partial breast irradiation and the GEC-ESTRO trial. *Lancet.* 2016;387(10029):1717.
12. Corica T, Nowak AK, Saunders C, et al. Cosmesis and Breast-Related Quality of Life Outcomes After Intraoperative Radiation Therapy for Early Breast Cancer: A Substudy of the TARGIT-A Trial. *International journal of radiation oncology, biology, physics.* 2016;96(1):55-64.
13. Alvarado MD, Mohan AJ, Esserman LJ, et al. Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. *Annals of surgical oncology.* 2013;20(9):2873-2880.
14. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ. *Practical radiation oncology.* 2016;6(5):287-295.
15. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *International journal of radiation oncology, biology, physics.* 2014;88(3):553-564.

Figure Legend

Figure 1: Local Recurrence and Overall Mortality for PR positive patients in the pre-pathology TARGIT-A trial.[1] Reproduced with permission from NIHR Journals Library.

Figure 2: Local Recurrence, Death from Cancer and Death from Other Causes in the pre-pathology TARGIT-A trial. [1] Reproduced with permission from NIHR Journals Library.

Figure 3: Countries Offering TARGIT IORT for Breast Cancer. Reproduced and modified with permission from Carl Zeiss Meditech.

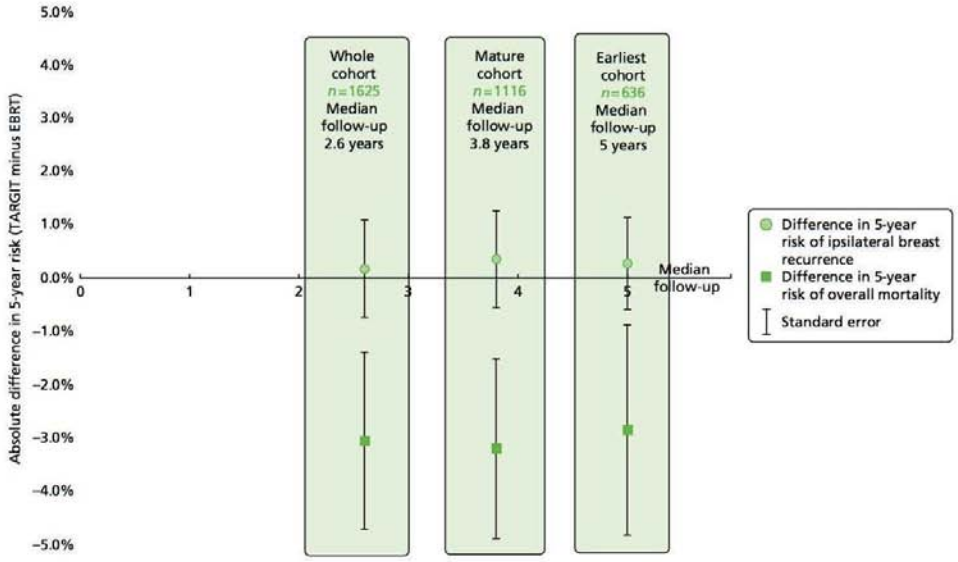

Fig. 1

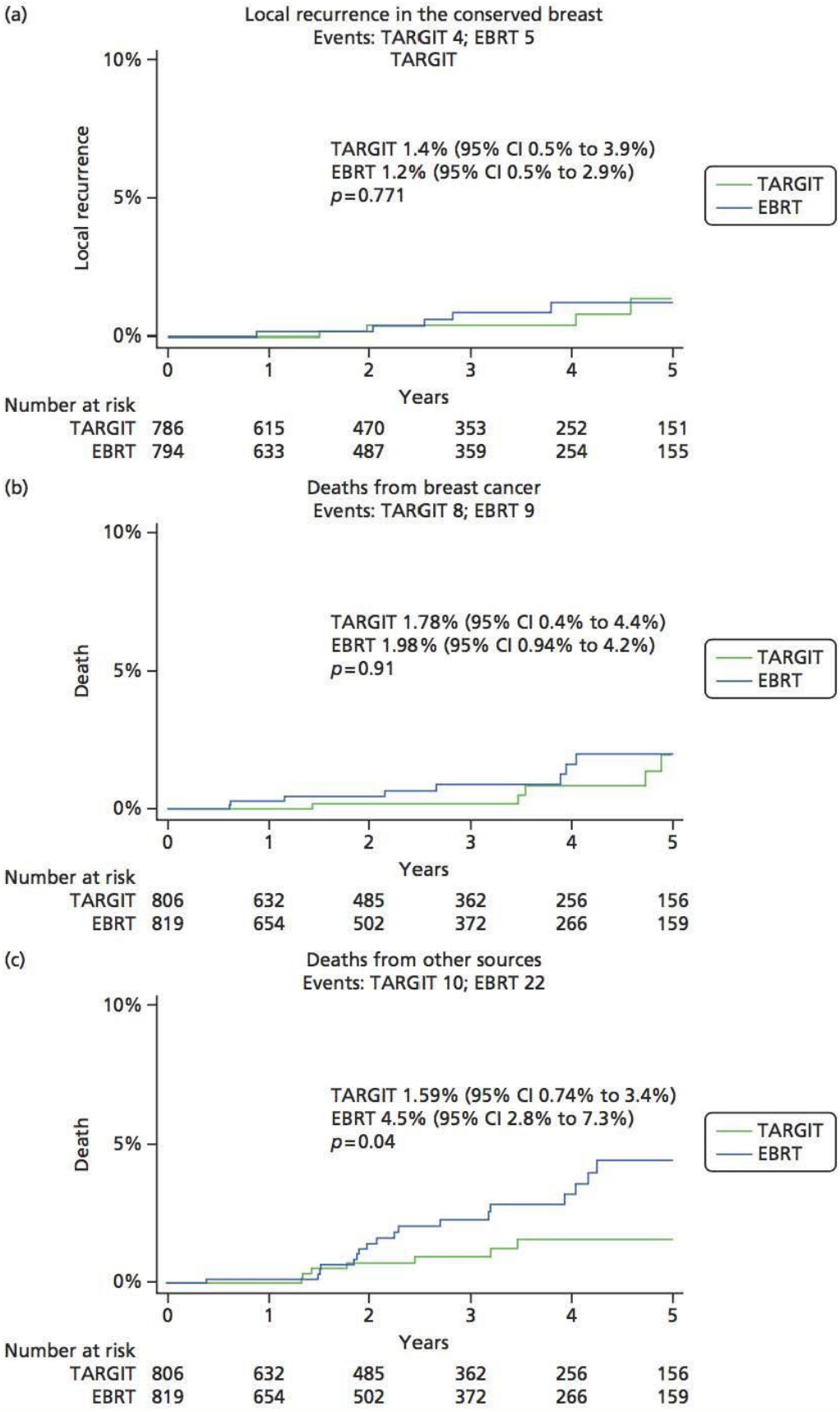

Fig. 2

Fig. 3