As users of the TARGIT IORT technique, as well as concerned individuals, we would like to make the following suggestions for the proposed ASTRO Clinical Practice Guideline relating to Partial Breast Irradiation (PBI) using Intra Operative RadioTherapy (IORT).

Summary of our responses:

1. Data from the TARGIT-A trial (TARGIT-IORT) should not be bundled with the data from the ELIOT trial (IOERT). One is photon radiation (TARGIT-IORT) and the other is Electron radiation (ELIOT-IOERT).
2. There is long term durable data from the TARGIT-A trial, a prospective, international Randomized Controlled Trial (RCT) with thousands of patients.
3. There are many advantages of TARGIT-IORT that no other form of PBI has reported.
4. Please keep TARGIT-IORT as an option since it has been an option for over a decade in the USA and it is data driven and due to the risk adaptive nature of it, it has shared decision making with the patient. It is in line with ASTRO’s current Strategic Plan.

**Box 1: Global Comments or Global Suggestions on the Entire document**

Appendix E1 (page 26). Peer Reviewers and Disclosures (Comprehensive) is empty. There is no list of reviewers or any of their conflicts of interest.

We would like to emphasize to the Members that 50 kvp (photon) IORT and IOE (electron) RT are two different types of radiation. They should not be bundled together in the PBI evaluation as they have different physical and biological effects.

The TARGIT-A (50 kvp IORT or TARGIT-IORT) and ELIOT (IOERT) trials differ considerably in their inclusion criteria, and most importantly, have entirely different surgical and radiotherapeutic techniques, and so are not comparable.

50 kvp IORT is intracavitary PBI in which a spherical applicator is inserted into a cavity that may be conformed to the applicator surface using purse string sutures. No tissue mobilization is required. No internal radiation barrier is needed. Ultrasound (US) is used in vivo to confirm conformance of the surgical margins to the applicator surface.

To the contrary, IOERT is a collimator-based method of IORT that requires wide mobilization (generally >10 cm diameter) of the breast gland flaps from the overlying skin and underlying chest muscle to enable placement of a radiation barrier disc on the chest muscle and to permit suture approximation of the breast gland in front of the radiation barrier and the collimator. This may result in tissue ischemia and also increases the risk of fat necrosis. Furthermore, once the collimator has been positioned, only visual assessment of the collimator to the surgical margins is possible. No in vivo US or CT assessment is possible.

Both these types of radiation have been compared exclusively to Whole Breast Irradiation (WBI) in Randomized Controlled Trials (RCTs) with very different results. 50 kvp IORT was tested in the TARGIT-A trial and IOERT was tested in the ELIOT trial. Different doses were given (20 Gy to the surface of the applicator for the TARGIT-A Trial vs 21 Gy prescribed to the 90% depth for the ELIOT Trial). The energy source for IORT and the technique used for delivery is different for TARGIT-A vs ELIOT.

Electron applicators also have cold spots in the field periphery.

Brachytherapy is similar. There is multi-catheter brachytherapy and single-entry (balloon) catheter brachytherapy. They were not bundled in the Guidelines and in fact have a different strength of recommendation under Table 4 on page 14 and 15. It is especially concerning that none of the single-entry applicators have been exclusively compared to WBI in an RCT (in your report on page 15, line 382) yet single-entry brachytherapy remains in the guidelines as “conditionally recommended.” (Table 4, page 15, #5).

The IORT recommendation was not separated for 50 kvp IORT vs IOERT. We would appreciate that they be analyzed separately.

**Box 2: Introduction/Methods/Scope**

On page 7, lines 187-192. A data search to June 30, 2022 was performed and only RCTs were included. Yet for the single-entry catheter brachytherapy, only a Registry was used since none of the single-entry applicators have been exclusively compared to WBI in an RCT.

What is the highest level of medical evidence?

National Comprehensive Cancer Network (NCCN) has categories of evidence and consensus. Category I is high level of evidence with uniform consensus. All NCCN recommendations are category 2A (lower level of evidence with uniform consensus) unless otherwise indicated. This underscores the urgent need to expand evidence base in oncology. The NCCN believes that the best management for any patient with cancer is in a clinical trial. NCCN categories of Preference Preferred intervention are interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

The TARGIT-A international, multi-center (33 centers), prospective, randomized phase III trial is a well conducted Randomized Clinical Trial (RCT) with long term results published. There were 3,451 women randomized. The international setting and broad inclusion criteria mean that the results are generalizable across relatively broad eligibility criteria and across various continents.

Multiple publications on the TARGIT-A results have been published including in 2021 and 2022. We noticed the following paper from the TARGIT-A Trial was not on the Reference List on pages 28 and 29 and it was published before the cutoff date of June 30, 2022:

Vaidya JS, Bulsara M, Baum M, Wenz F, Massarut S, Pigorsch S, et al. New clinical and biological insights from the international TARGIT-A randomised trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer. Br J Cancer 2021; 125(3):380-89.

Also, two other papers concerning TARGIT-A were not included and have updated results that are critical. They were not included since they were published <2 months after the deadline:

Vaidya JS, Bulsara M, Wenz F, Sperk E, Massarut S, Alvarado M, et al. The TARGIT-A randomised trial -TARGIT-IORT vs whole breast radiotherapy: long term local control and survival. Int J Radiat Oncol Biol Phys 2022. Published in 8/2022.

Vaidya JS, Vaidya UJ, Baum M, Bulsara M, Joseph D, Tobias JS, et al. Global adoption of single-shot targeted intraoperative radiotherapy (TARGIT-IORT) to improve breast cancer treatment – better for patients, better for health care systems. Frontiers in Oncology 2022; 12:786515. Published 8/11/2022.

Under 2.4 Scope of the guideline, Table 2, KQ 2 and KQ4 (pages 8 and 9) lists IOERT separately from kv IORT yet in the majority of the paper, they are bundled which is inappropriate since they are very different radiation methods with different outcomes. Please keep these PBI treatment options separate, as you do for brachytherapy.

**Box 3: KQ1 (Indications for PBI as an alternative to WBI)**

Line 329 states that surgical margin positivity represented an exclusion criterion for most of the RCTs examined, with the only exception being PBI trials of IORT. TARGIT-IORT is a pre-pathology treatment and thus no surgery has been performed yet and thus margins are unknown until after the kv IORT has been performed. It is a risk adapted trial and one the pre-prescribed high-risk criteria is a positive margin. These patients go on to have a re-excision and afterwards were recommended to receive WBI. This is still the recommendation for patients who receive TARGIT-IORT who have a positive margin after the lumpectomy and TARGIT-IORT.

**Box 4: KQ2 (Appropriate PBI techniques with respect to IBR)**

In Table 4 on page 15, #5, IORT is not recommended despite the Quality of evidence being Moderate, as is the Quality of Evidence for 4/5 for other various PBI techniques, including single-entry catheter brachytherapy when none of the single-entry applicators have been exclusively compared to WBI in an RCT. Also, again, TARGIT-IORT has been bundled with ELIOT-IOERT which is not appropriate due to their different physical and radiobiological attributes.

In general, we are puzzled by the unbalanced levels of evidence used for the recommendations in the current draft of the guidance. The recommendations for various approaches of partial breast irradiation do not appear to have any correlation with the level of supporting evidence, or the lack of it.

Lines 117-122: We have concerns that some members of the Committee may not understand the radiation nuances of TARGIT-IORT to make a proper consensus decision using the 5-point Likert scale, esp since TARGIT-IORT is bundled with the ELIOT- IOERT data, which, again, is a completely different type of radiation.

Page 16, lines 405-427: Again, TARGIT-IORT is bundled with ELIOT-IORT, which masks the advantages and benefits of TARGIT-IORT.

1. Line 407-408: TARGIT-IORT has “incomplete pathologic information at the time of treatment” because it is performed up front at the time of the initial lumpectomy (partial mastectomy) for appropriate patients. The only pathology available is from the core biopsy. TARGIT - A is risk adapted for that exact reason. If there are poor prognostic indicators on the final path not realized at the initial core biopsy, then IORT becomes the boost and the patient is offered WBI. The hypothesis behind TARGIT-A was always Risk Adapted Therapy. There never was an arm for TARGIT alone regardless of risk profile before or after surgery. Even lumpectomy itself is risk adapted therapy vs. Mastectomy.

This is very similar to other specialties in breast cancer where we do not know the final pathologic result until after the initial treatment, ie neoadjuvant chemotherapy. We then adjust our treatment plan once we have the final pathology. This is even true after a partial mastectomy, sentinel lymph node biopsy or mastectomy.

The risk-adapted nature of TARGIT-A is comparable to all randomized controlled surgical trials. Patients are randomized based on information available prior to surgery and then adapted/modified based on information obtained after surgery. This was the principle behind every landmark breast conservation trial, in which information obtained from surgery permitted conversion to mastectomy. The same principle applies to radiation trials where a tumor bed boost or Regional Nodal Irradiation are added based on surgical pathology findings. The fact that some lumpectomy patients require mastectomy or some PBI patients require WBI does not mean that lumpectomy or PBI are ineffective for suitable patients.

However, if it is felt by the Committee that since the pre-pathology group in TARGIT-A is a risk adapted group and no other form of PBI is risk adapted, perhaps pre-path TARGIT-IORT should be removed from the PBI Guidelines altogether since it is not like the other forms of PBI. If the Committee won’t consider a risk adapted approach for PBI, please consider removing pre-path TARGIT-A from this guideline and allow physicians to continue to offer it as a treatment option for appropriate women with early stage breast cancer per the TARGIT-A eligibility criteria.

TARGIT-IORT can be considered a form of PBI even it is risk adapted since ~80% of the TARGIT-A patients had it as their sole radiation. There is always a discussion with the patient before surgery at which time the risks, benefits and potential side effects are reviewed and there is shared decision making with the patient.

2. Line 408: “Lack of Image-Guided Quality Assurance of Dose Distribution”

It is not true that the in-vivo dose with KV- IORT is uncertain or not known, since the TARGIT applicators have well-defined and reproducible depth dose rates. Also, real-time intra-operative ultra-sound measurements can show doses at depths in the tissue.

When performing TARGIT-IORT, there are a number of procedures/protocols in place that are used to validate accuracy and uniformity of the TARGIT-IORT dose:

(a) The physics of low kV photons is well understood in relation to dose fall off and delivered dose.

(b) For a given lumpectomy cavity, the appropriately sized largest diameter spherical applicator is used to reduce the likelihood of air gaps and ensure uniform target dose. (This is similar to single catheter brachytherapy applicator mentioned by the Task force, where the balloon is inflated to ensure conformality).

(c) Ultrasound imaging is performed to assure target conformality and to ensure low skin dose.

(d) All IORT dosimetry and treatment times undergo stringent QA prior to patient treatment.

(e) A redundant (independent) check of treatments is performed by a Qualified Medical Physicist prior to initiating IORT.

(f) A Monte Carlo based 3D treatment planning system (including effects of tissue heterogeneities) is now available to evaluate IORT dose distributions (isodoses, DVH, etc).

Additionally, although the Task force points out superior (lower) recurrence rates of IORT (kV photons) compared to IOERT (delivered with electrons), they have grouped both techniques into one IORT recommendation. We believe, as mentioned several times in this reply, that it is important to keep them separate. Based on the physics of these two treatment modalities, the techniques are quite different for the following reasons:

(a)Compared to IOERT (electrons), TARGIT-IORT given with low energy photons is more conformal and presents uniform dose to the target.

(b) TARGIT- IORT with photons also has a rapid dose fall off away from intended target region leading to lower toxicity.

(c) IOERT given with electrons on the other hand can lead to inhomogeneous dose distribution. This is due to electrons undergoing multiple coulomb scattering leading to non-uniform (sub optimal) dose in the presence of any tissue heterogeneities (clips, air gaps etc). Unfortunately, these variations can be rather large (>10%).

(d) If a higher electron energy is used to overcome (c), this may lead to unwanted normal tissue toxicity.

We therefore feel that TARGIT-IORT with kV photons should be considered separately from IOERT with electrons. We strongly believe that TARGIT-IORT with low energy kV X-rays is convenient, safe, and effective treatment modality for PBI with low risk of recurrence.

3. Line 411-427: Risk-adapted approach is essential with TARGIT-A IORT. The 2,298 patients written about on line 413 were in the PRE-pathology group when IORT is given immediately after the lumpectomy. This number of patients were not treated post pathology. This is the group that has favorable non-inferior 5-year IBR outcomes of 2.1% with TARGIT-IORT vs 1.1% with EBRT.

4. Line 420-427:

In the 2020 BMJ publication of long-term outcomes, Figure 3 shows the Kaplan-Meier curves and figure 4 shows magnified Kaplan-Meier curves. The Kaplan-Meier curves illustrate the long term results up to 12 years. These data confirm the comparable effectiveness of TARGIT-IORT versus EBRT in terms of cancer control, with no difference in local recurrence-free survival, invasive local recurrence-free survival, mastectomy-free survival, or distant disease-free survival. These results are consistent with the previously published data and a meta-analysis of randomized trials.

Furthermore, the Kaplan-Meier curve for overall survival for TARGIT-IORT always remains above EBRT, with the curves continuing to separate further well beyond 10 years.

In the 2021 BJC publication, new clinical and biological insights from the TARGIT-A Trial were revealed. Figure 4 on page 386 are Kaplan-Meier estimates of cumulative incidences. There are significantly fewer deaths in patients randomized to TARGIT-IORT.

Importantly, there is a definite Overall Survival benefit of using TARGIT-IORT in patients with grade 1 or 2 cancers with a 28% reduction in overall mortality.

In this same publication, the impact of the rare local recurrence is much worse if it occurs after EBRT with a hazard of death of about 40% at 12 years. On the other hand, the patients who have local recurrence after TARGIT-IORT have the same prognosis as those who have no local recurrence.

NICE reviewed the TARGIT-A data from 2013 and recommended that NHS patients should be offered TARGIT-IORT at centers where the equipment and expertise is available. Since this analysis, the long term TARGIT-A data has been published.

Line 426-427: “Given the above uncertainties and the higher IBR seen on the ELIOT trial, IORT is not recommended.

AGAIN, TARGIT-A IORT should not be lumped with ELIOT-IOERT for the many reasons cited above.

**BOX 5: KQ3**

TARGIT-IORT was not discussed in this Key Question. The appropriate dose fractionation, target volume and planning parameters are all outlined in the TARGIT-A Trial.

**BOX 6: KQ4 Toxicity and Cosmesis:**

Line 516: “A central hypothesis of PBI is that the reduced target volume should result in a favourable toxicity profile (both acute and late) and improved long-term cosmesis relative to WBI.” This is what TARGIT-IORT accomplishes.

Outlined are the many shortcomings of the PBI trials in reporting these outcomes. Again, TARGIT-IORT is bundled with IOERT, which is not appropriate since they are two very different forms of radiation treatment.

The 2014 publication of the TARGIT-A trial published in the Lancet reported wound-related complications were much the same between TARGIT-IORT and WBI, but there were significantly fewer grade 3 or 4 radiotherapy-related skin complications with TARGIT-IORT than with WBI (p=0.029).

**Box 7: Conclusions ad Future Directions:**

We find it astonishing that line 635-636 states “preoperative PBI offers an opportunity to better understand the biology of radiotherapeutic effects, like that seen with delivery of neoadjuvant systemic therapy” yet the recommendation is to remove TARGIT-IORT from the PBI guidelines.

TARGIT-IORT does exactly that. It is preoperative PBI with long term results of statistically significant improved Overall Survival and also improved outcome if a recurrence occurs after IORT compared to if a recurrence occurs after WBI.

With the increased prevalence of treatment de-escalation in oncology, TARGIT-IORT is positioned to be a superb initial treatment option for women with early-stage breast cancer. “Less is More” is happening in oncology: Less surgery, Less chemo and Less Radiation with less morbidity and equal or better Overall Survival and significantly improved Quality of Life.

Is local control the appropriate endpoint for radiation oncology when we are offering some breast cancer patients no radiation since their Overall Survival is not effected despite a significantly higher IBR? Shouldn’t we be using a technique that improves Overall Survival for early-stage breast cancer that also has a very low IBR?

The proposed PBI guideline with the removal of IORT may also deny access to patients for BCS as written on line 649-651.

TARGIT-IORT as the sole, one shot treatment at the time of initial lumpectomy is achievable in ~80% of eligible patients per TARGIT-A. It also has the following unique abilities:

1. Bridges the health care disparity gap. TARGIT-IORT is Inclusive.

2. Can be used for women with ipsilateral pacemakers. The pacemaker does not need to be moved if it is >= 3 cm from the applicator

3. It is "Green" with a lower carbon footprint: less travel, less pollution, less cost

4. Saves patients time and money:

a) No extra time off from work

b) No childcare issues

c) No daily transportation issues

5. Less risk of getting Covid or other air-born infections

6. Decreases the concern patients have for cardiovascular issues after radiation with left sided breast cancer, which is often stated as a reason for declining breast conservation.

7. Less radiation dose to the skin, lungs and heart (collateral damage).

There are minimal skin side effects with TARGIT-IORT.

8. Less chance of inducing a lung cancer in patients with breast cancer who continue to smoke during their WBI.

9. No table top weight limits in the Radiation Oncology Department so one can easily treat obese and morbidity obese patients. Significantly less skin damage for these patients also.

10. Easier for patients with "challenging" conditions that make coming in for Simulation and any external radiation a hardship:

a) Physically challenged (ie Parkinson's, Multiple Sclerosis, W/C bound, etc)

b) Emotionally challenged

c) Spiritually challenged

d) Psychologically challenged (Anxiety, Depression, Claustrophobia, etc)

e) Chromosomally challenged (ie Autism, Down's, etc)

11. Gives options to patients in rural communities (distances patients have to travel is critical. Pts chose no radiation or mastectomy when they have lengthy travel times for their radiation-even if it is just 6 days (sim and 5 treatment days).

12. Better Quality of Life for the Patient:

a) Less Pain

b) Cosmetically superior with less risk of breast shrinkage compared to WBI

c) No time spent driving for daily radiation treatments

d) Save the patient money

13. Fewer non-breast cancer deaths with TARGIT-IORT

14. Improved Overall Survival for patients with Grade 1 or 2 breast cancers.

15. Statistically significant better outcome if a local recurrence occurs after TARGIT-IORT vs EBRT.

16. Gives marginalized patients options besides a mastectomy (Equitable):

a) Non-English-speaking patients

b) Homeless

c) Incarcerated

17. In addition, it can be used successfully to:

a) Treat an ipsilateral 2nd breast cancer or recurrence after whole breast external radiation

b) Can be used on augmented breasts with no harm to the Si or saline implant

c) Can be used at the time of concurrent breast reduction and/or with oncoplastic techniques

TARGIT-A Trial is not a Registry and not Retrospective. It has excellent long-term follow-up. It is also not a speculative article that "estimates" data. TARGIT-IORT is approved and now standard of care in many countries. It is included in several national and international guidelines (https://www.targit.org.uk/targit-iort-in-guidelines) and available with long term effects observed and tens of thousands of patients treated in 260 centers in 38 countries. There are now over 200 papers describing the safe and effective use of TARGIT-IORT (http://bit.ly/TARGIT-IORT-Bibliography)

TARGIT-IORT is in line with ASTRO’s Mission, Vision and Goals and Objectives.

As the then Editor-in-Chief of the Red Journal, Anthony Zeitman, MD, FACS wrote in his Editorial in May 2015:

“After decades of careful and progressive investigation into fractionated radiation therapy, women have been moved from a dark past of radical mastectomies into the modern era of breast conservation. TARGIT-A applauds that outcome but suggests there may be another way to achieve it. Many careers have been built around fractionated radiation therapy for breast cancer, and it comprises a substantial proportion of the practice of the average contemporary radiation oncologist. **Depending on your perspective, intraoperative radiation therapy is thus either a very serious threat or a quantum leap forward.** Data will ultimately resolve this debate as TARGIT-A matures.”

The TARGIT-A data is now mature and the results are superior compared to WBI in this phase III prospective, randomized, international trial.

TARGIT-IORT is performed in over 80 centers in the USA. It is already an approved treatment option for early stage breast cancer in the USA. MediCare compensates TARGIT-IORT as well as most insurance companies. Taking a treatment option away from patients with early stage breast cancer is not in line with ASTRO’s mission, vision, goals and objectives.