There is a reply to this letter by Sasieni, P. D. & Sawyer, E. J. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-021-00472-6 (2020).

Jayant S. Vaidya[1] ✉, *Max Bulsara*[1,2], *Michael Baum*[1], *Michael Alvarado*[3], *Marcelle Bernstein*[4], *Samuele Massarut*[5], *Christobel Saunders*[6], *Elena Sperk*[7], *Frederik Wenz*[8], *Jeffrey S. Tobias*[9] *and the TARGIT-A investigators**

[1]*Division of Surgery and Interventional Science, University College London, London, UK.*
[2]*Department of Biostatistics, University of Notre Dame, Fremantle, WA, Australia.*
[3]*Department of Surgery, University of California, San Francisco, CA, USA.* [4]*London, UK.*
[5]*Department of Surgery, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy.*
[6]*School of Surgery, University of Western Australia, Perth, WA, Australia.*
[7]*University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany.*
[8]*University Medical Center Freiburg, Freiburg, Germany.*
[9]*Department of Clinical Oncology, University College London Hospitals, London, UK.*
**A list of authors and their affiliations appears at the end of the paper.*
✉*e-mail: jayantvaidya@gmail.com*

https://doi.org/10.1038/s41571-021-00471-7

1. Sasieni, P. D. & Sawyer, E. J. Intraoperative radiotherapy for early breast cancer — insufficient evidence to change practice. *Nat. Rev. Clin. Oncol.* **17**, 723–724 (2020).
2. Vaidya, J. S. et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. *BMJ* **370**, m2836 (2020).
3. Coombs, N. J. et al. Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. *BMJ Open* **6**, e010703 (2016).
4. Taylor, C. et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J. Clin. Oncol.* **35**, 1641–1649 (2017).
5. Darby, S. C. et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N. Engl. J. Med.* **368**, 987–998 (2013).
6. Grantzau, T. & Overgaard, J. Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. *Radiother. Oncol.* **114**, 56–65 (2015).
7. Vaidya, J. S. et al. Reduced mortality with partial-breast irradiation for early breast cancer: a meta-analysis of randomized trials. *Int. J. Radiat. Oncol. Biol. Phys.* **96**, 259–265 (2016).
8. Aziz, M. H. et al. Can the risk of secondary cancer induction after breast conserving therapy be reduced using intraoperative radiotherapy (IORT) with low-energy x-rays? *Radiat. Oncol.* **6**, 174 (2011).
9. Gourgou-Bourgade, S. et al. Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). *Ann. Oncol.* **26**, 873–879 (2015).
10. Hudis, C. A. et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J. Clin. Oncol.* **25**, 2127–2132 (2007).

Acknowledgements
Funding for the TARGIT-A trial was mainly provided by the National Institute for Health Research (NIHR) Health Technology Assessment programme (HTA 07/60/49). J.S.V. and J.S.T. received funding from the UK HTA, NIHR, and Department of Health for some activities related to the TARGIT trials.

Competing interests
J.S.V. has received research funding and honoraria from Photoelectron Corp and Carl Zeiss and has received travel support from Carl Zeiss. M. Bulsara has received travel support from Carl Zeiss. M. Baum has served on the scientific advisory board, has acted as a consultant of and received travel support from Carl Zeiss. M.A. has received travel support from Carl Zeiss. M. Bernstein has received travel support from Carl Zeiss. S. M. has received travel support from Carl Zeiss. C.S. has received travel support from Carl Zeiss. E.S. has received honoraria and travel support from Carl Zeiss. F.W. has received research funding and travel support from Carl Zeiss. J.S.T. has received travel support from Carl Zeiss.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41571-021-00471-7.

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National and International Guidelines include TARGIT-IORT for breast cancer: https://www.targit.org.uk/targit-iort-in-guidelines

The TARGIT-A investigators

Jayant S. Vaidya[1], *Max Bulsara*[1,2], *Michael Baum*[1], *Michael Alvarado*[3], *Marcelle Bernstein*[4], *Samuele Massarut*[5], *Christobel Saunders*[6], *Elena Sperk*[7], *Frederik Wenz*[8] *and Jeffrey S. Tobias*[9]

A full list of consortium members and their affiliations appears in the supplementary information.

Reply to 'Intraoperative radiotherapy for breast cancer: powerful evidence to change practice'

Peter D. Sasieni and Elinor J. Sawyer

The TARGIT-A investigators claim in their Correspondence (Vaidya, J. S. et al. Intraoperative radiotherapy for breast cancer: powerful evidence to change practice. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-021-00471-7 (2020))[1] that our article (Sasieni, P. D. & Sawyer, E. J. Intraoperative radiotherapy for early breast cancer — insufficient evidence to change practice. *Nat. Rev. Clin. Oncol.* **17**, 723–724 (2020))[2] contains several factual and logical errors but we are unclear as to what these are. We stand by our assertion that the treatment that they recommend has not been shown to have any effect against local recurrence and suggest that, were radiotherapy held to the same regulatory standards as chemotherapy, this particular usage would not be licensed.

It seems that we failed to convey our central argument in that Vaidya et al.[1] complain that we overlooked the long-term positive findings and the patient perspective. We accept that targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) is more convenient than conventional whole-breast external beam radiotherapy (WBRT). However, a new treatment needs to have been shown (at least indirectly) to be superior to no treatment[3], and TARGIT-IORT fails in this regard. We know of no convincing argument that TARGIT-IORT might reduce non-breast cancer mortality relative to no radiotherapy, therefore, the question as to whether TARGIT-IORT results in fewer non-breast cancer deaths than WBRT is only relevant if TARGIT-IORT is shown to reduce breast cancer recurrence.

In their analysis of indirect evidence of superiority to no radiotherapy, the authors make an error — they focus on the wrong end of the confidence interval (CI). In Prime-II[4] the 95% CI for the additional risk of ipsilateral recurrence at 5 years comparing no radiotherapy with WBRT was 1.1–4.8%. TARGIT-A has not shown the difference in local recurrence at 5-years comparing TARGIT-IORT to WBRT to be <1.1% (and may therefore be no better than no radiotherapy). Vaidya et al. make the point that patients enrolled in PRIME-II had a generally lower risk of recurrence, but 5-year local recurrence in women assigned WBRT was in fact higher in PRIME-II (1.3%) than in TARGIT-A (1.0%).

Rather than using the 95% CI from a single trial, we would suggest using meta-analysis[5]: we calculate the 95% CI for the risk ratio as 0.26–0.38 (Supplementary information). Thus, to show that TARGIT-IORT is superior to no radiotherapy, one would have to set a non-inferiority margin on the relative risk of 1/0.38 = 2.6, and require that the upper limit of the 95% CI comparing TARGIT-IORT with WBRT is at most 2.6. Based on the number of local recurrences by 5 years in the per-protocol analysis, the 95% CI for the risk ratio in TARGIT-A is 1.14–4.99 (REF.[6]) (Supplementary information). By contrast, in FAST-Forward[7], the upper limit of the 95% CI for the hazard ratio comparing 26 Gy in 5 fractions (over 1 week) to 40 Gy in 15 fractions (over 3 weeks) was 1.16: well below the margin required to infer superiority to no radiotherapy.

TARGIT-IORT is inferior to WBRT in terms of local recurrence: in all four analyses, the 95% CI for the excess local recurrence at 5 years with TARGIT-IORT does not include 0 (REF.[6]); and at a median follow-up duration of

8.6 years, the excess is 3.2% (95% CI 1.7–4.7%) (Supplementary information). Compared with WBRT, TARGIT-IORT (with WBRT added for the 20% of patients at greatest risk of recurrence) leads to at least an additional 1.7% having local recurrence. The authors emphasize that there was no significant difference in recurrence-free survival in women randomized pre-surgery; however, that was a post-hoc sub-group analysis. Combining with data from the post-surgery sub-group[8] yields a hazard ratio for recurrence-free survival of 1.20 (95% CI 1.01–1.43) (Supplementary information).

We agree that "patient choice, informed by clearly presented evidence"[1] is important. When presenting the benefits of TARGIT-IORT to patients it is essential to also make clear that it is somewhat inferior to standard treatment and might be no better than no treatment.

Peter D. Sasieni ✉ *and Elinor J. Sawyer*
School of Cancer & Pharmaceutical Sciences, King's College London, London, UK.
✉*e-mail: peter.sasieni@kcl.ac.uk*

https://doi.org/10.1038/s41571-021-00472-6

1. Vaidya, J. S. et al. Intraoperative radiotherapy for breast cancer: powerful evidence to change practice. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-021-00471-7 (2020).
2. Sasieni, P. D. & Sawyer, E. J. Intraoperative radiotherapy for early breast cancer — insufficient evidence to change practice. *Nat. Rev. Clin. Oncol.* **17**, 723–724 (2020).
3. FDA. Non-Inferiority Clinical Trials to Establish Effectiveness, Guidance for Industry. https://www.fda.gov/media/78504/download (2016).
4. Kunkler, I. H. et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol.* **16**, 266–273 (2015).
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). et al. 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* **378**, 1707–1716 (2011).
6. Vaidya, J. S. et al. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. *BMJ* **370**, m2836 (2020).
7. Murray Brunt, A. et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* **395**, 1613–1626 (2020).
8. Vaidya, J. S. et al. Effect of delayed targeted intraoperative radiotherapy vs whole-breast radiotherapy on local recurrence and survival: long-term results from the TARGIT-A randomized clinical trial in early breast cancer. *JAMA Oncol.* **6**, e200249 (2020).

Competing interests
The authors declare no competing interests.

Supplementary information
The online version contains supplementary material available at https://doi.org/10.1038/s41571-021-00472-6.