correspondence

Calibration of CTS5 in Women With Early Estrogen Receptor–Positive Breast Cancer

Noordhoek et al[1] have expressed interest in assessing the validity of the Clinical Treatment Score post-5 years (CTS5), but unfortunately we disagree that their data reliably support their key conclusion that the CTS5 overestimates risk in high-risk patients with estrogen receptor–positive breast cancer who remain free of distant recurrence after 5 years of endocrine therapy.

The CTS5 online calculator has been accessed more than 88,000 times and therefore seems to be widely used in patient care. As such, it is important that risk estimates that affect care should be as accurate as we can make them. We pointed out in our original paper that improvements in patient care may in fact have led to the CTS5 not accurately estimating the risk in contemporary patients.[2] This is a concern with all prognostic tools that depend on substantial follow-up for their development and validation. We therefore agree that further study of more contemporary populations is an important objective but regret to conclude that the work by Noordhoek et al[1] cannot provide a reliable improvement in calibration.

We developed the CTS5 as a prognostic tool to aid in making the decision on whether to extend adjuvant endocrine therapy beyond 5 years if a patient remained free of distant recurrence (DR) at that time.[2] It estimates the risk of recurrence in the *absence* of extended therapy to allow decisions to be made on the potential benefit from extending therapy. Development and validation of this tool can be reliably conducted only in patients who have not received such extended therapy. The ATAC and BIG1-98 trials finished their recruitment in 2000 and 2003, respectively.[3,4] Given that data first emerged on the benefits of endocrine treatment beyond 5 years with the publication in late 2003 of the MA17 trial on the impact of letrozole following 5 years of tamoxifen,[5] we estimated that $< 1\%$ and $< 5\%$ of patients, respectively, would have received extended therapy. Noordhoek et al[1] assessed the CTS5 in the IDEAL and TEAM trials.[6,7] In the former, all patients received extended therapy. In the latter, recruitment completed in 2006 and although the proportion of patients receiving extended therapy in TEAM was not known or estimated, it would undoubtedly be greater than that in the ATAC and BIG1-98 populations.

Noordhoek et al[1] note the possibility that the extension of endocrine therapy in their studies may have led to a slight reduction in late DR rates, reflecting that this is unlikely to explain the 16% risk difference seen in their analysis. This 16% difference appears to be that seen between the observed versus the expected number of events in the 10% of patients at the highest risk in the IDEAL trial and is therefore at the very extreme of the high-risk population. Their data in Table 2 and Figure 3B indicate that the difference in risk between observed and expected distant recurrence rates is largely proportional across the population; our estimate from this is that the relative difference is approximately 40% in the IDEAL trial. Such a proportional effect is consistent with all the patients in IDEAL receiving extended therapy irrespective of risk. It is also notable that 70% of the IDEAL patients had received 2.5 or 5 years of tamoxifen before the random assignment to an aromatase inhibitor at 5 years. The MA17 study reported a hazard ratio for disease-free survival of 0.57 (95% CI, 0.43 to 0.75), that is, an estimated 43% reduction, for patients receiving letrozole after 5 years of tamoxifen.[5]

Although the IDEAL study showed proportional reductions in observed versus predicted risk in all risk categories, the TEAM study found this in only the high-risk patients, where the relative reduction of observed versus expected events was approximately 25%. This high-risk group is likely to be the most affected by clinicians recommending extended therapy to patients on the basis of a conventional consideration of the clinicopathologic factors that constitute the CTS5.

Although concerned that we differ in the interpretation of the report by Noordhoek et al,[1] we agree that accurate estimates of risk are important across the risk spectrum. We are reassured that their report affects only those patients predicted to be above the intermediate–high risk cutoff, and these are the ones who would be strong candidates for extended endocrine therapy irrespective of their absolute risk estimate.

Mitch Dowsett, PhD
Ralph Lauren Centre for Breast Cancer Research, Royal Marden Hospital, London, UK

Ivana Sestak, PhD and Jack Cuzick, PhD
Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.02551.

REFERENCES

1. Noordhoek I, Blok EJ, Kranenbarg EMK, et al: Overestimation of late distant recurrences in high-risk patients with ER-positivie breast cancer: Validity and accuracy of the CTS5 risk score in the TEAM and IDEAL trials. J Clin Oncol 38:3273-3281, 2020
2. Dowsett M, Sestak I, Regan MM, et al: Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen-receptor positive breast cancer treated with 5 years of endocrine therapy: CTS5. J Clin Oncol 36:1941-1948, 2018

Corresponding author: Mitch Dowsett, PhD, Ralph Lauren Centre for Breast Cancer Research, Royal Marden Hospital, London SW3 6JJ, UK; e-mail: Mitchell.dowsett@icr.ac.uk.

3. Baum M, Buzdar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomized trial. Lancet 359:2131-2139, 2002
4. Breast International Group (BIG) 1-98 Collaborative Group: A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 353:2747-2757, 2005
5. Goss PE, Ingle JN, Martino S, et al: A randomized trial of letrozole in postmenopausal women after 5 years of tamoxifen therapy for early breast cancer. N Engl J Med 349:1793-1802, 2003
6. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al: Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL trial (BOOG 2006-05). J Natl Cancer Inst 110:40-48, 2018
7. van de Velde CJH, Rea D, Seynaeve C, et al: Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): A randomised phase 3 trial. Lancet 377:321-331, 2011

DOI: https://doi.org/10.1200/JCO.20.02551; Published at ascopubs.org/journal/jco on December 16, 2020.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Calibration of CTS5 in Women With Early Estrogen Receptor–Positive Breast Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Mitch Dowsett
Honoraria: Myriad Genetics, NanoString Technologies, Lilly, BCN Sciences
Consulting or Advisory Role: GTx, Radius Health, Orion Pharma GmbH, G1 Therapeutics, Abbvie, H3 Biomedicine, Zentalis
Research Funding: Pfizer, Radius Health, Lilly
Travel, Accommodations, Expenses: Pfizer, Myriad Genetics
Other Relationship: Institute of Cancer Research

Ivana Sestak
Honoraria: Myriad Genetics, NanoString Technologies, Pfizer
Consulting or Advisory Role: Myriad Genetics

No other potential conflicts of interest were reported.