Reply to M. Dowsett et al

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Dowsett et al[1] provided thoughtful commentary to our article,[2] in which we assessed the validity of their CTS5 calculator to predict late distant breast cancer recurrences.[3]

Accurate estimation of cancer prognosis remains a relevant topic of research and various efforts have been made to accurately determine the prognosis of patients with breast cancer. One of those is the CTS5 calculator which, as opposed to genetic profiling tests, is a free and easy-to-use tool and is, therefore, readily available in clinical practice.[3] Dowsett et al[1] indicate that the calculator has been accessed more than 88,000 times, which underlines the importance of its risk estimations being validated in independent cohorts to ensure the reliability.

Since breast cancer is typically a disease that is characterized by late recurrences and the CTS5 specifically predicts recurrences between 5 and 10 years after diagnosis, validation cohorts need to have at least 10 years of adequate follow-up. On the other hand, treatment guidelines have been and still are subject to change, with the emergence of anti-HER2 medication, CDK4/6 inhibitors, bisphosphonates, and more. Therefore, patients who are diagnosed with breast cancer today are treated differently from the patients in the ATAC and BIG1-98 trials on which the CTS5 was built.[4–6] Indeed, it is challenging to balance the requirements of adequate follow-up and the incorporation of contemporary treatment regimes.

Dowsett et al[1] argue that the patient populations of the TEAM and IDEAL trials that were used for our analyses are not suitable to validate the CTS5 because of the use of extended endocrine therapy (ET), although the CTS5 was developed in the absence of extended ET. Patients in the IDEAL trial were indeed treated with extended ET, but we feel the TEAM trial is particularly fitting as a validation cohort since the baseline characteristics and treatment regimens are comparable, it is a more contemporary population with enough follow-up, and only a very small subset of patients received extended ET.[7] Furthermore, the overall observed late distant recurrence rate in the TEAM cohort was 8.7%, comparable but even slightly higher than the ATAC (7.0%) and BIG1-98 (5.5%) trials. The effect of extended ET in the TEAM cohort and its influence on our analyses will therefore be negligible.

In the IDEAL trial, it is true that all patients received extended ET. However, we do not agree that this discredits our findings, nor fully accounts for the difference in observed and expected late recurrences.

Dowsett et al[1] state that in the IDEAL trial, 70% patients had been treated with 2 to 5 years of tamoxifen, before switching to extended therapy with an aromatase inhibitor (AI), and cite the MA17 trial that shows a relative benefit of 43% for extended ET after 5 years of tamoxifen. However, the results of the MA17 trial are not fully applicable in this situation, because in the IDEAL trial only 11% of patients received this regimen of 5 years of tamoxifen monotherapy. On the contrary, the vast majority of patients (89%) received a regimen containing an AI, for which the DATA, NSABP B-42, and ABCSG-16 trials have shown that extended therapy does not yield significant benefit.[8–10] The patient-level meta-analysis of the Early Breast Cancer Trialists' Collaborative Group presented at San Antonio in 2018 showed an estimated relative benefit of only 16% for patients who were initially treated with an AI. We concur that our finding of a relative difference of 40% between observed and expected recurrence rates is to some extent influenced by extended therapy, but this meta-analysis shows that it only explains a minority fraction of this difference, leaving a substantial difference unexplained.

In conclusion, we feel that TEAM and IDEAL patients were treated more in resemblance with contemporary treatment regimens and therefore offer a better reflection of daily clinical practice.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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