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CORRESPONDENCE

Response to Letter to the Editor Re: Impact of the Prosigna assay on neoadjuvant treatment decision making in patients with early-stage HR-positive/HER2-negative breast cancer: a single-center prospective observational study

We thank Dr. Wei and colleagues for their interest in our study on the impact of the Prosigna assay on neoadjuvant treatment decision making in patients with early-stage hormone receptor (HR)-positive/human epidermal growth factor receptor (HER2)-negative breast cancer (BC).[1]

STUDY DESIGN AND LIMITATIONS

Our investigation was a feasibility decision-impact analysis, rather than a validation of predictive ability. We acknowledged that Prosigna is Food and Drug Administration-cleared only for post-operative specimens[1]; however, prior work has demonstrated its technical feasibility on biopsy material.[2] The sample size and single-center design are limitations, but the target enrollment of 60 patients was statistically justified. Importantly, most HR-positive BCs typically undergo upfront surgery, making neoadjuvant accrual challenging. None the less, emerging data on neoadjuvant immunotherapy in HR-positive disease[3] may broaden the role of preoperative trials, increasing the relevance of biopsy-based genomic assays. While prognostic assays have been supported by large adjuvant trials, neoadjuvant studies remain largely limited to small phase II or observational efforts, including ours.[4]

ROLE OF KI67 AND IMMUNOHISTOCHEMISTRY (IHC) SURROGATES

Although Ki67 and IHC-based surrogate intrinsic subtyping remain widely used, Ki67 is not routinely carried out in many United States laboratories due to reproducibility concerns.[5] Our study was designed to evaluate the feasibility and decision impact of Prosigna, not to compare against IHC surrogates. We agree that randomized studies incorporating both methods would further clarify Prosigna's added value.

CONCURRENT ONCOTYPE DX TESTING

Thirty patients (55.5%) also underwent Oncotype DX, with only one major discordance. In 23% ($n = 7$), Oncotype DX was carried out on surgical rather than biopsy specimens, and all but one of these patients underwent upfront surgery, minimizing the biological impact of systemic treatment on the assay results. Therefore, although we acknowledge the limitation of concurrent testing, we believe its impact on the primary endpoint is limited.

ASSOCIATION WITH RESIDUAL CANCER BURDEN (RCB)

The lack of association between risk of recurrence (ROR) groups and RCB ($P = 0.21$) may reflect the very small subset treated with neoadjuvant chemotherapy. As the study was not powered to test predictive ability, no conclusions can be drawn regarding treatment sensitivity. Dedicated clinical trials are needed to clarify whether assay-directed neoadjuvant decisions translate into improved outcomes.

RISK OF OVERTREATMENT

Importantly, only patients already considered candidates for neoadjuvant therapy were included. ROR-low tumors accounted for 18.5% ($n = 10$), and nearly all of these patients were managed without chemotherapy, arguing against overtreatment. None the less, given the potential for treatment changes driven by assay results and the absence of long-term outcomes, findings must be interpreted with caution. To assess the assay's impact on outcomes, one would need to examine survival data once they mature, then compare the results with historical controls where Prosigna was not used for decision making.

In conclusion, we agree that Prosigna's role in the neoadjuvant setting remains exploratory. Our study provides feasibility evidence and underscores the potential of genomic assays to refine preoperative treatment discussions. Future randomized trials with long-term outcomes will be essential to define their clinical utility.

C. Corti[1,2,3,4,5] & S. M. Tolaney[1,2,3]*

[1]*Medical Oncology, Dana-Farber Cancer Institute, Boston;* [2]*Breast Oncology Program, Dana-Farber Cancer Institute, Boston;* [3]*Harvard Medical School, Boston, USA;* [4]*Division of New Drugs and Early Drug Development, European Institute of Oncology, IRCCS, Milan;* [5]*Department of Oncology and Hematology-Oncology (DIPO), University of Milan, Milan, Italy*

(*E-mail: sara_tolaney@dfci.harvard.edu).

@stolaney1

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