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Re: NCCN Guidelines® Panel: Breast Cancer

On behalf of NanoString Technologies, I respectfully request the NCCN Breast Cancer Guideline Panel to consider the referenced clinical data as Level 1 evidence to support inclusion of Prosigna® Breast Cancer Gene Signature Assay in the decision tree/treatment algorithm on *BINV-6*.

Specific Changes:

I.   On page <u>BINV-6</u>, we request to modify the decision tree/treatment algorithm by including the PAM50 gene signature assay in assessing the risk of recurrence and selection of adjuvant therapy, or alternatively, recommend only a footnote "*ee*" without highlighting specific assay(s) in the decision tree/treatment algorithm.
II. On page <u>MS-29</u> to include information on the 510K FDA clearance of the PAM50 assay.
III. On page <u>MS-29</u>, we request to update the information to uniformly identify the 50-gene assay as a PAM50 gene signature assay.

Rationale: In the past 12 months, major breast cancer treatment guidelines (AGO, SEOM, St. Gallen, ESMO, Japanese Breast Cancer Society, and ASCO) included Prosigna (PAM50) for its prognostic and predictive value. Additional data was published confirming the prognostic ability of Prosigna (PAM50)-based intrinsic subtypes independent of clinical factors.[1] These updates underscore the significant body of evidence demonstrating Prosigna's clinical validity and clinical utility, and further strengthen the case for a corresponding update in the next version of the 2017 NCCN guidelines.

ASCO Breast Cancer Guidelines Update (2016)[2]

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines provide evidence-based recommendations and recommend Prosigna (PAM50) to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer with known hormone receptor and HER2 status.[2] Specifically, it states that "chemotherapy should be considered in the PAM50 high-risk group."[2]

The currently available assays have all been validated for risk of distant recurrence and not for prediction of chemotherapy benefit. The ASCO guidelines included a subtle but powerful critique of the "prediction studies" that have historically been the foundation of the privileged positioning of the OncotypeDX (21-gene assay) within treatment guidelines. For example, in the section "Recommendation 1.2", the ASCO Committee states: "However, the B20 data are confounded by the data set originally used to generate the 21-gene RS algorithm. The results from SWOG S8814 must be considered hypothesis generating because the number of samples analyzed in each RS subgroup was small, there was no additional prediction beyond 5 years, and the risks of systemic recurrence continues to be high for patients with node-positive disease." On page 19 of the Data Supplement, the ASCO Committee characterized the conclusion that the B20 study showed chemoprediction as "highly speculative." OncotypeDx recurrence score was shown as not predictive for anthracycline benefit based on the recent WSG PlanB trial results.[3]

The Prosigna (PAM50) gene signature assay received a "high" rating of evidence quality together with a "strong" recommendation, making the evidence quality and strength of recommendation the highest among all genomic assays reviewed and equal to that of OncotypeDx (21-gene assay).[2] We believe that above-mentioned argues strongly for eliminating any distinction between the ways that these assays are represented in the decision tree/treatment algorithm on *BINV-6*.

Newly Presented Data from SABCS 2016

<u>Prosigna provides the highest differentiation between low- and high-risk patients of the four multigene expression profiles tested, measured by the Likelihood Ratio (LR).</u>[4]

A comparison of prognostic signatures (clinical treatment score (CTS), Prosigna, Oncotype Dx, EndoPredict and Breast Cancer Index) for prognostication of early ER-positive breast cancer treated with endocrine therapy in TransATAC was presented (800 samples) demonstrating that:[4]

- Prosigna provided the most prognostic value for late distant relapse in node-negative patients, significantly improving prognostication over CTS alone (ΔLR-χ^2=18.4) for both 10-year DR (74.5% improvement) as well as late recurrence (111% improvement).
- In women with node-negative disease (N=591), Prosigna's ROR score provided most independent (in addition to CTS) prognostic information for distant recurrence in years 0-10 (ΔLR-χ^2=23.7) and years 5-10 (ΔLR-χ^2=18.4).

Conclusion

In summary, the data presented from TransATAC at SABCS further validated the prognostic ability of Prosigna compared to other commercially available assays. It also added to the body of evidence which includes ABCSG8 and the Danish Breast Cancer Group cohort nationwide cohort analyzes of 2,700 patients[5-8], all demonstrating the clinical utility of Prosigna for use in early breast cancer. In parallel, Prosigna (PAM50) has been incorporated into international treatment guidelines, at the highest levels of evidence awarded for any assay and strengths of recommendation that match that of OncotypeDX (21-gene assay. Based on these factors, we believe that Prosigna (PAM50) should be included in the NCCN guidelines, positioned on par with other assay(s) at the highest levels of evidence for clinical validity or utility. We welcome any questions or clarifications that you may have.

References:

1. Liu MC, et al. Npj Breast Cancer 2016;2:15023.
2. Harris LN, et al. J Clin Oncol 2016 Feb.
3. Harbeck N, et al. J Clin Oncol 35, 2017 (suppl; abstr 504).
4. Sestak I, et al. Abstract S6-05. Cancer Res 2017;77:S6-05-S6.
5. Gnant M, et al. Ann Oncol. 2015 Aug;26(8):1685-91.
6. Lænkholm A, Jensen M, Eriksen J, et al. J Clin Oncol 33, 2015 (suppl; abstr 546). 2015.
7. Ejlertsen B, et al. J Clin Oncol 33, 2015 (suppl; abstr 513). 2015.
8. Lænkholm A, et al. J Clin Oncol 33, 2015 (suppl; abstr 544). 2015.