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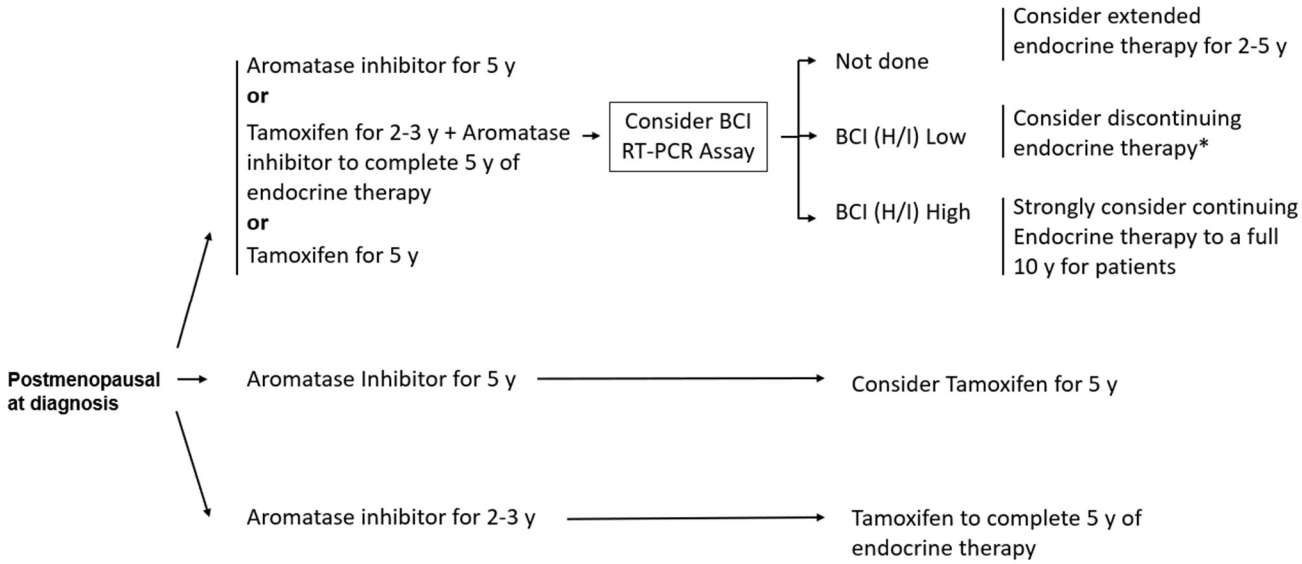
NCCN Guidelines Panel: Breast Cancer

On behalf of Biotheranostics Inc., I respectfully request the **NCCN Breast Cancer Panel** to update the NCCN Guidelines based on the enclosed data for the **Breast Cancer Index (BCI)** in the evaluation of patients with hormone receptor-positive (HR+), HER2-negative early stage breast cancer to identify patients with endocrine-responsive tumor biology who are likely to benefit from extended endocrine therapy, and to stratify patients for risk of late (post-5 years from diagnosis) distant recurrence.

Specific Changes (one sentence): Amendment of BINV-K[4] (sample schema below) is requested to include BCI as a tool to stratify postmenopausal women with HR+, T1-T3, N0/N1 breast cancer treated with primary adjuvant endocrine therapy into those who are likely to benefit and prevent recurrence from extending endocrine therapy for a total of 10 years, versus those that are unlikely to benefit from extending endocrine therapy with either tamoxifen or an aromatase inhibitor (AI).



* Patients with a low BCI (H/I) do not demonstrate significant RFI benefit from longer duration endocrine therapy across multiple studies.

Regulatory Status: BCI testing is conducted, and the results are generated, at the Biotheranostics clinical laboratory in San Diego, California. The Biotheranostics clinical laboratory is Clinical Laboratory Improvement Amendments (CLIA)- certified, College of American Pathologists (CAP)-accredited, and licensed in all 50 states.

Rationale (one sentence): The collective evidence which includes newly reported data from the BCI IDEAL study[3] of 908 patients (87% treated with primary adjuvant AI or sequenced tamoxifen to AI), in conjunction with previous findings from the MA.17[1] and Trans-aTTom[2] cohorts (Tables below), consistently demonstrates that BCI (HoxB13/IL17BR, H/I) significantly stratifies ~50% of early stage HR+ patients into endocrine-responsive (BCI (H/I)-High) vs non-responsive (BCI (H/I)-Low) tumor biology in a manner that is agnostic to anti-estrogen therapy with tamoxifen or AI, and predicts which patients are likely to experience improved outcomes (Recurrence Free Interval, Breast Cancer Specific Survival) from completing 10 years of extended endocrine therapy.

Recurrence Free Interval benefit by BCI (H/I):

Study Cohort	Relative Risk Reduction		Absolute Benefit (RFI; in H/I High)	Interaction P-Value
	BCI (H/I) High	BCI (H/I) Low		
Treatment: Extended AI vs Placebo after adjuvant TAM				
MA.17[1] (n=249)	OR: 0.35 (0.16-0.75); p=0.007	OR: 0.68 (0.31-1.52); p=0.350	**16.5%**	0.030
Treatment: Extended TAM vs Stop after adjuvant TAM				
Trans-aTTom[2] (n=583)	HR: 0.35 (0.15-0.86); p=0.027	HR: 1.07 (0.69-1.65); p=0.768	**10.2%**	0.012
Treatment: 5y vs 2.5y Extended AI after adjuvant TAM, AI, or TAM/AI sequence				
IDEAL[3] (n=908) Overall	HR: 0.42 (0.21–0.84); p=0.011	HR: 0.95 (0.58-1.56); p=0.835	**9.8%**	0.045
(n=794) Any AI subset	HR: 0.34 (0.16–0.73); p=0.004	HR: 0.9 (0.53-1.55); p=0.712	**11.8%**	0.025

Breast Cancer Specific Survival benefit by BCI (H/I):

Study Cohort	Relative Risk Reduction		Absolute Benefit (BCCS; in H/I High)	Interaction P-Value
	BCI (H/I) High	BCI (H/I) Low		
Treatment: Extended TAM vs Stop after adjuvant TAM				
Trans-aTTom (n=789)	HR: 0.48 (0.24-0.99); p=0.047	HR: 1.07 (0.74-1.55); p=0.716	**8.8%**	0.025

References

1. Sgroi DC, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. J Natl Cancer Inst 2013;105:1036-42.
2. Bartlett JM, et al. Trans-aTTom: Breast Cancer Index for prediction of endocrine benefit and late distant recurrence (DR) in patients with HR+ breast cancer treated in the adjuvant tamoxifen—To offer more? (aTTom) trial. Annals of Oncol 2019 doi:10.1093/annonc/mdz289
3. Liefers GJ, et al Breast Cancer Index (BCI) Predicts Benefit of 2.5 vs. 5 Years of Extended Endocrine Therapy in HR+ Breast Cancer Patients Treated in the IDEAL Trial. J Clin Onc. 38, no. 15_suppl (May 20, 2020) 512-512.
4. National Comprehensive Cancer Network. Breast Cancer (Version 5.2020). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 2, 2020.

We appreciate the opportunity to provide this information for consideration by the NCCN Breast Cancer Guideline Panel. If you have any questions or require additional information, please do not hesitate to contact me directly.

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