Risk assessment tools and adjuvant therapy for breast cancer

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Chapter 4

BREAST CANCER INDEX (BCI) PREDICTS EXTENDED ENDOCRINE BENEFIT TO INDIVIDUALIZE SELECTION OF PATIENTS WITH HR+ EARLY-STAGE BREAST CANCER FOR 10 YEARS OF ENDOCRINE THERAPY

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ABSTRACT

Purpose

Individualized selection of patients with early-stage hormone receptor–positive (HR+) breast cancer for extended endocrine therapy (EET) is required to balance modest gains in outcome with toxicity of prolonged use. This study examined the Breast Cancer Index (BCI; HOXB13/IL17BR ratio [H/I]) as a predictive biomarker of EET benefit in patients from the Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL) trial.

Experimental design

BCI was tested in primary tumor specimens from 908 patients randomized to receive 2.5 versus 5 years of extended letrozole. The primary endpoint was recurrence-free interval. Cox regression models and likelihood ratios tested the interaction between EET and BCI [H/I].

Results

BCI [H/I]-high significantly predicted benefit from extended letrozole in the overall cohort (hazard ratio [HR] 0.42, 95% CI 0.21 – 0.84; P = 0.011) and in the any aromatase inhibitor (AI) subset (HR 0.34, 95% CI 0.16 – 0.73; P = 0.004), whereas BCI [H/I]-low patients did not derive significant benefit (HR 0.95, 95% CI 0.58 – 1.56; P = 0.84 and HR 0.90, 95% CI 0.53 – 1.55; P = 0.71, respectively). Treatment to biomarker interaction was significant (P = 0.045 in the overall cohort, P = 0.025 in the any AI subset). BCI [H/I] identified approximately 50% of patients with clinically high-risk disease that did not benefit, and with clinically low-risk disease that derived significant benefit from an additional 2.5 years of EET.

Conclusions

BCI [H/I] predicted preferential benefit from 5 versus 2.5 years of EET and identified patients with improved outcome from completing 10 years of adjuvant endocrine therapy. These findings expand the clinical utility of BCI [H/I] to a broader range of patients and beyond prognostic risk factors as a predictive endocrine response biomarker for early-stage HR+ breast cancer.

INTRODUCTION

Whereas the role of primary adjuvant endocrine therapy for women diagnosed with early-stage hormone receptor–positive (HR+) breast cancer is well established, decisions regarding the optimal composition and duration of endocrine therapy in the extended setting have become increasingly complex. Large randomized trials have demonstrated that extension of endocrine therapy reduces the risk of late distant recurrence that persists in HR+ breast cancer for more than a decade after the initial five years of adjuvant endocrine therapy.[1-13] Results to date have been mixed, with modest benefits in disease-free survival (DFS) that were most apparent in patients who have received at least 5 years of tamoxifen prior to an aromatase inhibitor (AI).[4,7-10,14,15]

Antiestrogen therapy with AIs is the standard of care for postmenopausal patients; however, the treatment effects of extending AI therapy for early-stage breast cancer are inconclusive, particularly in patients treated with adjuvant AI monotherapy.[3,8,9,15,16] Notably, the modest absolute benefits ranging from approximately 1% to 4% observed with extending AI therapy for longer durations are accompanied by increased cardiovascular toxicity, bone fractures, and side effects that impair quality of life and compliance, underscoring a critical need to individualize patient selection.[1,5,8,9,17]

Current clinical practice recommendations favor up to ten years of an AI for postmenopausal women with moderate to high risk based on clinicopathologic features and prognostic biomarkers.[18] However, predictive biomarkers that stratify underlying patterns of tumor biology related to endocrine response to identify patients who are likely or unlikely to benefit from endocrine therapy would have a critical impact on patient selection for extended treatment.

The Breast Cancer Index (BCI) is a gene expression–based signature that consists of two functional biomarker panels, the HOXB13/IL17BR (H/I) ratio and the molecular grade index (MGI), that interrogate important estrogen signaling and proliferation pathways in breast cancer. The BCI prognostic score is an algorithmic combination of the H/I ratio and MGI and reports individualized risk of overall and late distant recurrence.[19-21] The predictive component of BCI (BCI [H/I]) is based on the H/I ratio and provides a categorical prediction of high versus low likelihood of benefit from extended endocrine therapy that is reported separately from the prognostic results.[19,21,22]

Previous clinical validation studies for prediction of extended endocrine benefit and outcome have demonstrated significant interaction between BCI [H/I] and extended endocrine therapy with letrozole or tamoxifen following initial tamoxifen treatment.[19,22] A key question regarding BCI [H/I] clinical utility is the biomarker effect in postmenopausal patients treated with a contemporary standard of care that includes an AI component as part of primary adjuvant treatment. In this study, the BCI [H/I] predictive performance was examined in patients treated in the IDEAL (Investigation on the Duration of Extended Letrozole) study, a randomized controlled trial designed to directly examine the potential benefit of extended durations of AI therapy.[1,16]

METHODS

Study design and patients

The IDEAL (BOOG 2006-05) trial is a prospective phase III study that randomized 1,824 patients with HR+ early-stage postmenopausal breast cancer to receive either 2.5 or 5 years of letrozole after completing five years of adjuvant therapy with either tamoxifen monotherapy, tamoxifen followed by an AI, or AI monotherapy.[1] While the study design allowed for completion of the initial five years of adjuvant endocrine therapy up to two years prior to randomization, 89% of patients were randomized within six months of completing primary adjuvant treatment.

This study is a prospective–retrospective translational study of patients enrolled in the IDEAL trial that specifically examined the predictive component of the BCI assay, the H/I ratio. Because both treatment arms were on therapy during the first 2.5 years, BCI study criteria included patients that were recurrence free from 2.5 years post-randomization, which was a secondary analysis in the parent IDEAL trial.[1] All patients with available tumor specimens were eligible and BCI [H/I] testing was conducted blinded to clinical outcome. Exclusion criteria included lack of invasive tumor, incorrect tumor specimen, insufficient or poor RNA signal, and patients with a follow-up time or had recurred less than 2.5 years after randomization. The translational study was based on an updated clinical database with a median FU of 9.3 years after randomization.

Statistical considerations

The primary objective of the study was to determine whether BCI [H/I]-high versus -low is predictive of extended endocrine benefit comparing an additional 2.5 years (7.5 years total endocrine therapy) versus 5 years (10 years total endocrine therapy) of letrozole treatment in patients that have completed five years of endocrine therapy. The key secondary objective was to determine the predictive performance of BCI [H/I] in the patient subset that received prior endocrine therapy that included an AI (primary AI subset). The IDEAL translational cohort (N = 908) showed a 4.9% absolute benefit in the reduction of 10-year risk of recurrence-free interval (RFI) events with 10 years versus 7.5 years of endocrine therapy (HR 0.69; 95%CI 0.47 – 1.03; P = 0.07). Powering assumptions included a 5% sample testing failure rate and that 40% of patients would be classified as BCI [H/I]-high based on previous studies.[19,22] At 80% power, it was estimated that a total of 768 patients would be required to detect the benefit in BCI [H/I]-high patients at the 5% significance level.

The primary endpoint was RFI, defined as the time from 2.5 years after randomization to first local, regional, or distant recurrence. Deaths before recurrence were considered as censoring events while new breast primaries (ipsilateral and contralateral disease) and other secondary cancers were not considered either as events or as censoring events. Secondary endpoints were disease-free interval (DFI) and DFS. DFI is defined as the time from 2.5 years after the random assignment to first local, regional, distant recurrence or new breast primary. DFS is defined as the time from 2.5 years after the random assignment

to first local, regional, distant recurrence, new primary breast tumor, or death from any cause as the first event.

Kaplan–Meier survival analysis and log-rank test were used to compare the two survival outcomes of the two treatment arms for all unselected patients and for patients in each of the BCI [H/I]-low and BCI [H/I]-high groups. The risk of RFI events at year 10 since randomization and 95% CIs were calculated to estimate the magnitude of absolute benefit between 10 and 7.5 years of endocrine therapy in each of the BCI [H/I] groups. Unadjusted HRs and 95% CIs were calculated from a Cox proportional hazards model to estimate the relative benefits within each BCI [H/I] group. The treatment to biomarker interaction was assessed using a likelihood ratio test based on comparing the full versus reduced Cox models, adjusting for age, tumor stage, grade, nodal stage, prior endocrine therapy, and prior chemotherapy. Analyses were prespecified in a statistical analysis plan prior to unblinding.

BCI molecular testing

BCI gene expression analysis by rt-PCR was performed using RNA extracted from formalin-fixed paraffin embedded (FFPE) tumor samples blinded to clinical outcome as described previously.[21] In addition to the five MGI genes, HOXB13, and IL17BR, gene expression analysis of ER, PR, andHER2 was also performed.[23] Briefly, manual macro-dissection was carried out on FFPE sections to enrich tumor content prior to RNA extraction. Total RNA was reverse transcribed, and the resulting cDNA was pre-amplified by PCR using the preamp Master Mix Kit (Thermo Fisher Scientific) and then subjected to TaqMan PCR analysis. Calculation of BCI was conducted utilizing a prespecified and validated assay cut-point to categorize patients as either BCI [H/I]-high or BCI [H/I]-low.[24]

Role of the funding source

This translational study was funded by Biotheranostics Inc. Novartis funded centralized biospecimen collection as part of the parent IDEAL trial. Tumor tissue processing, pathology review, and data collection were conducted by Leiden University Medical Center (LUMC, Leiden, the Netherlands). BCI assays were performed by Biotheranostics in a blinded manner, without knowledge of treatment assignment or clinical outcome. Study unblinding was led and conducted by LUMC. BCI data were merged with patient data at LUMC and access to merged data was limited to the study biostatisticians. The report was drafted in its entirety by the authors without benefit of paid assistance. Content of the final report was not subject to approval from the corporate sponsor. The corresponding author (G.J. Liefers) had final responsibility for the data submission for publication.

RESULTS

Patient characteristics

Of the 1,824 patients that participated in the IDEAL parent trial, archival tumor specimens were available for 1,047 patients (**figure 1**). Following pathology review, BCI testing was completed for 972 patients. Exclusion of 51 patients that were not recurrence-free for at least 2.5 years post-randomization resulted in a final translational cohort of 908 patients

comprising approximately 50% of the original study population with 454 patients in each arm. Patient tumors were 73% lymph node positive, 45% tumor stage 1, 48% tumor stage 2, 43% grade 2, 34% grade 3, and 9% HER2+. Regarding primary adjuvant endocrine treatment, 13% received five years of tamoxifen monotherapy, 27% received five years of AI monotherapy, 60% received sequenced therapy with tamoxifen followed by an AI, and 87% received primary adjuvant treatment with an AI (**table 1**). No statistical differences in clinicopathologic and treatment variables were observed between the translational cohort and the remaining patients not included in the study.

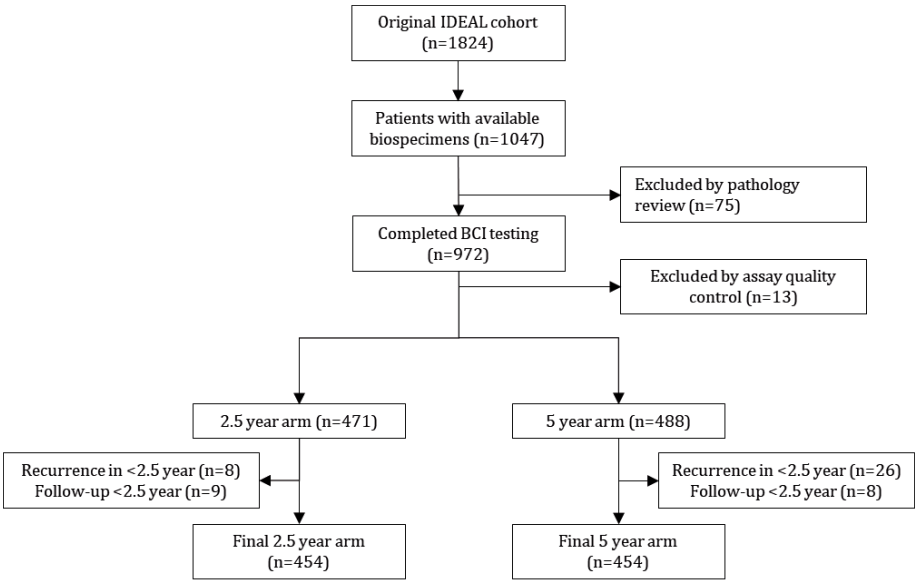

Figure 1: Modified REMARK diagram. The diagram shows biospecimen availability, biospecimen processing, and molecular testing, leading to a final analyzable cohort of 908 patients.

	Parent cohort (N = 1718)	Translational cohort (N = 908)	Remaining cohort (N = 810)	P-value
Age at surgery				0.877
> 50	564 (33)	296 (33)	264 (33)	
≥ 50	1154 (67)	612 (67)	541 (67)	
Tumor stage				0.198
pT1	802 (47)	406 (45)	396 (49)	
pT2	774 (45)	433 (48)	341 (42)	
pT3	89 (5)	49 (5)	40 (5)	
pT4	37 (2)	19 (2)	18 (2)	
Unknown	16 (1)	1 (0)	15 (2)	

Table 1: Clinicopathologic characteristics for patients who were recurrence free at 2.5 years after randomization in the parent trial, translational cohort, and those remaining patients not included in the study. All values are N (%).

P-values comparing the translational cohort versus the remaining patients not included in the study were calculated using Fisher exact tests.

	Parent cohort (N = 1718)	Translational cohort (N = 908)	Remaining cohort (N = 810)	P-value
Grade				0.077
1	268 (16)	135 (15)	133 (16)	
2	735 (43)	390 (43)	345 (43)	
3	536 (31)	311 (34)	225 (28)	
Unknown	179 (10)	72 (8)	107 (13)	
Nodal stage				0.544
pN0	461 (27)	241 (27)	220 (27)	
pN1	941 (55)	499 (55)	442 (55)	
pN2	234 (14)	131 (14)	103 (13)	
pN3	73 (4)	34 (4)	39 (5)	
Unknown	9 (1)	3 (0)	6 (1)	
Tumor type				0.447
Ductal	1340 (78)	720 (79)	620 (77)	
Mucinous	15 (1)	7 (1)	8 (1)	
Medullar	7 (0)	3 (0)	4 (0)	
Lobular	273 (16)	142 (16)	131 (16)	
Other	82 (5)	36 (4)	46 (6)	
Unknown	1 (0)	0 (0)	1 (0)	
Estrogen receptor				0.769
Positive	1670 (97)	881 (97)	789 (97)	
Negative	47 (3)	26 (3)	21 (3)	
Unknown	1 (0)	1 (0)	0 (0)	
Progesterone receptor				0.454
Positive	1333 (78)	720 (79)	613 (76)	
Negative	320 (19)	165 (18)	155 (19)	
Unknown	65 (4)	23 (3)	42 (5)	
HER2				0.659
Positive	163 (9)	79 (9)	84 (10)	
Negative	595 (35)	302 (33)	293 (36)	
Unknown	960 (56)	527 (58)	433 (54)	
Prior endocrine therapy				0.560
5 years TAM	211 (12)	114 (13)	97 (12)	
5 years AI	492 (29)	250 (27)	242 (30)	
TAM followed by AI	1015 (59)	544 (60)	471 (58)	
Prior chemotherapy				0.795
Yes	1176 (68)	619 (68)	557 (69)	
No	542 (32)	289 (32)	253 (31)	
Breast cancer events				0.783
Local recurrence	28 (12)	17 (14)	11 (10)	
Distant recurrence	150 (65)	79 (64)	71 (66)	
New breast primary	53 (23)	28 (22)	25 (23)	

Table 1 continued

HER = human epidermal growth factor receptor. TAM = tamoxifen. AI = aromatase inhibitor.

Within the translational cohort, the same number of patients (N = 454) received 5 years and 2.5 years of extended letrozole with 10.6% (95% CI 7.1 – 14.0) and 15.5% (95% CI 11.5 – 19.3) of patients having recurrences in the 5-year and 2.5-year arms, respectively. Overall, 75% of patients in the translational cohort completed 80% of their allocated treatment duration. Treatment arms of the translational cohort were also balanced,

recapitulating features of the parent trial, and confirming the translational cohort is essentially unbiased.

BCI [H/I] status predicts benefit from extended endocrine therapy

Analysis of the overall cohort (N = 908) showed that significant differences in outcome from randomized treatment of 2.5 years versus 5 years of letrozole were dependent on classification by BCI [H/I]. Significant benefit from 5 years of extended letrozole was demonstrated in the 47% (N = 429) of patients classified as BCI [H/I]-high (HR 0.42; 95% CI 0.21 – 0.84). The risk of recurrence was 5.9% (95% CI 2.3 – 9.3) and 15.7% (95% CI 9.5 – 21.5) for patients treated with 5 and 2.5 years of letrozole, respectively, demonstrating an absolute benefit of 9.8% for reduction of the risk of recurrence (P = 0.011; **figure 2A**, **figure 3**). In contrast, no statistically significant benefit from5 years versus 2.5 years of letrozole was observed in the 53% (N = 479) of patients classified as BCI [H/I]-low (HR 0.95; 95% CI 0.58 – 1.56). The risk of recurrence was 14.9% (95% CI 9.1 – 20.3) and 15.4% (95% CI 10.1 – 20.4) for patients treated with 5 and 2.5 years of letrozole, respectively (P = 0.835; **figure 2A**, **figure 3**). BCI [H/I] effects on extended endocrine benefit and outcome were consistent across recurrence endpoints of RFI and DFI as well as mortality based on DFS.

BCI [H/I]-status also significantly predicted benefit from extended letrozole in patients treated with primary adjuvant endocrine therapy that included an aromatase inhibitor (primary AI subset, N = 794). In a combined analysis of patients treated with either AI monotherapy or sequenced tamoxifen-AI, BCI [H/I]-high patients experienced a significant absolute benefit from 5 years versus 2.5 years of extended letrozole treatment of 11.8% (P = 0.004; HR 0.34; 95% CI 0.16 – 0.73) whereas BCI [H/I]-low patients had no statistically significant benefit (P = 0.712; HR 0.90; 95% CI 0.53 – 1.55; **figure 2B**). Importantly, treatment to biomarker interaction was significant in both the overall (P = 0.045) and primary AI (P = 0.025) cohorts, adjusting for age, tumor stage, grade, nodal stage, prior endocrine therapy, and prior chemotherapy.

BCI [H/I] prediction of extended endocrine benefit in clinical subsets

In patients with node-positive disease, the 46% (N = 307) that were classified as BCI [H/I]-high demonstrated a statistically significant benefit from 5 years versus 2.5 years of letrozole with a HR of 0.30 (95% CI 0.12 – 0.77) and absolute benefit of 10.8% (P = 0.008), whereas the 54% of node-positive patients (N = 357) classified as BCI [H/I]-low showed no significant benefit (HR 0.88; 95% CI 0.50 – 1.53; P = 0.644; **figure 4A**). Similar findings were observed in the node-negative subset (N = 241; **figure 4B**). Although statistical significance was not reached, possibly due to a limited sample size, a consistent trend in endocrine response was noted in the 50% of node-negative patients (N = 120) classified as BCI [H/I]-high demonstrating a HR of 0.74 (95% CI 0.25 – 2.13) and absolute benefit of 7.4% (P = 0.569). The 50% of node-negative patients (N = 121) classified as BCI [H/I]-low did not show benefit (HR 1.32; 95% CI 0.43 – 4.11; absolute benefit 4.2%; P = 0.626). In addition, a three-way test for statistical interaction evaluating the impact of nodal status on BCI biomarker effect did not show significance (P = 0.624), indicating BCI predictive activity is not dependent on nodal status.

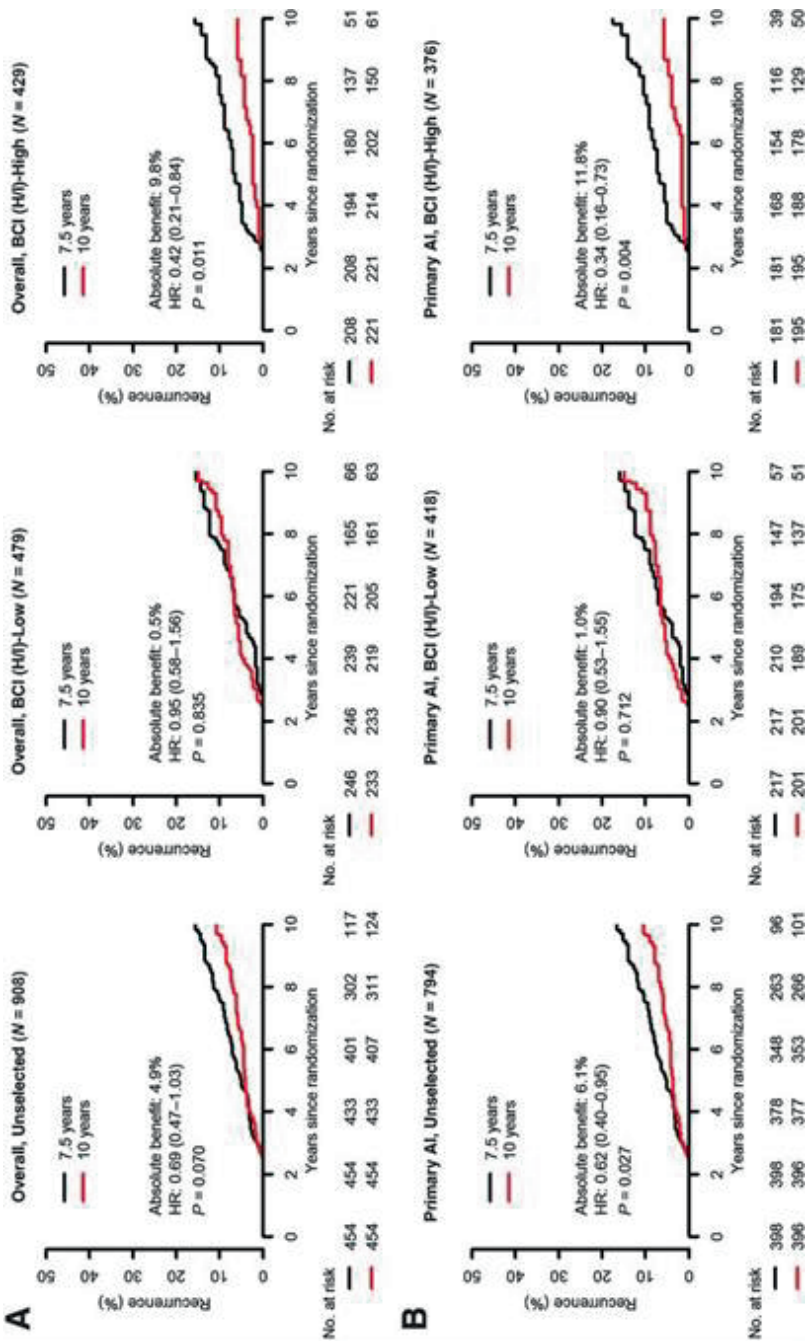

Figure 2: Kaplan-Meier analysis of risk of recurrence comparing 10 years versus 7.5 years of ET by BCI [H/I] groups in the overall cohort (A) and in the primary AI subset (B).

AI = aromatase inhibitor.

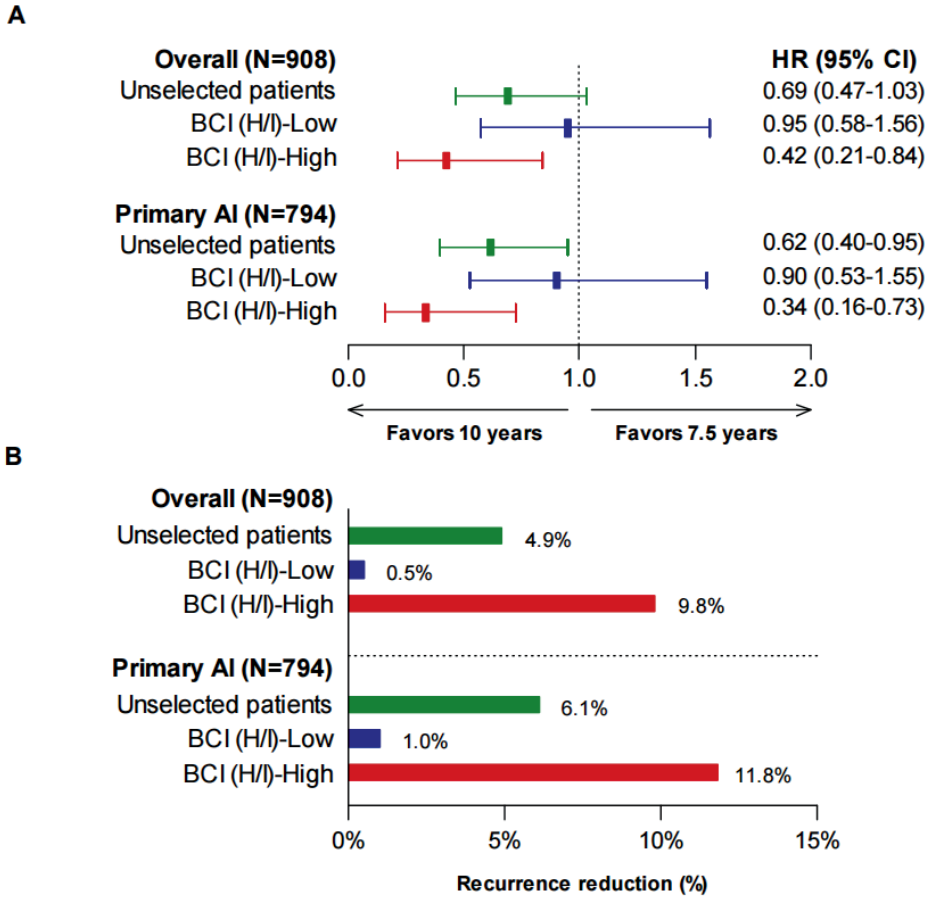

Figure 3: Forest plot of unadjusted hazard ratios of treatment effect (A) and bar graph of absolute recurrence risk reduction (B) by BCI [H/I] group in the overall cohort and the primary AI subset.

Analysis of HR point estimates for patients classified as BCI [H/I]-high were similar across all other clinical subsets by age, tumor stage, grade, prior endocrine therapy, and prior chemotherapy treatment, favoring 10 years of endocrine therapy, whereas those for BCI [H/I]-low patients were generally close to 1 (**figure 5**). One exception was observed in the subset of patients that did not receive prior chemotherapy. Of note, subset analysis of patients treated with primary adjuvant tamoxifen monotherapy was not calculated because of an imbalance in the number of node-positive patients across the two treatment arms, resulting in harm from longer treatment with endocrine therapy in the unselected patients. Overall, the predictive performance of BCI [H/I] was consistent across clinical subsets examined.

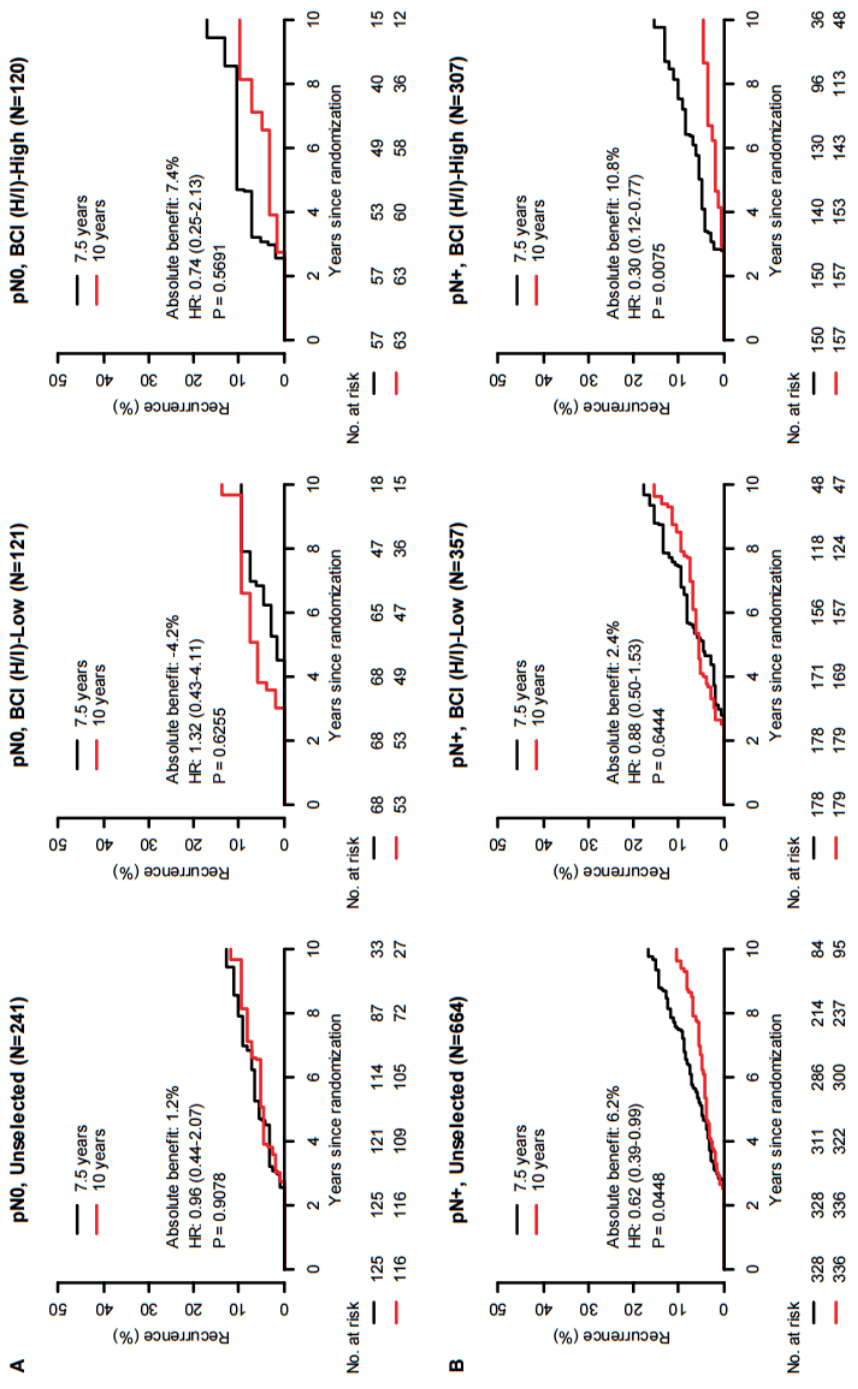

Figure 4: Kaplan-Meier analysis of risk of recurrence comparing 10 years versus 7.5 years of ET by BCI [H/I] group in node-negative (A) and node-positive (B) patients.

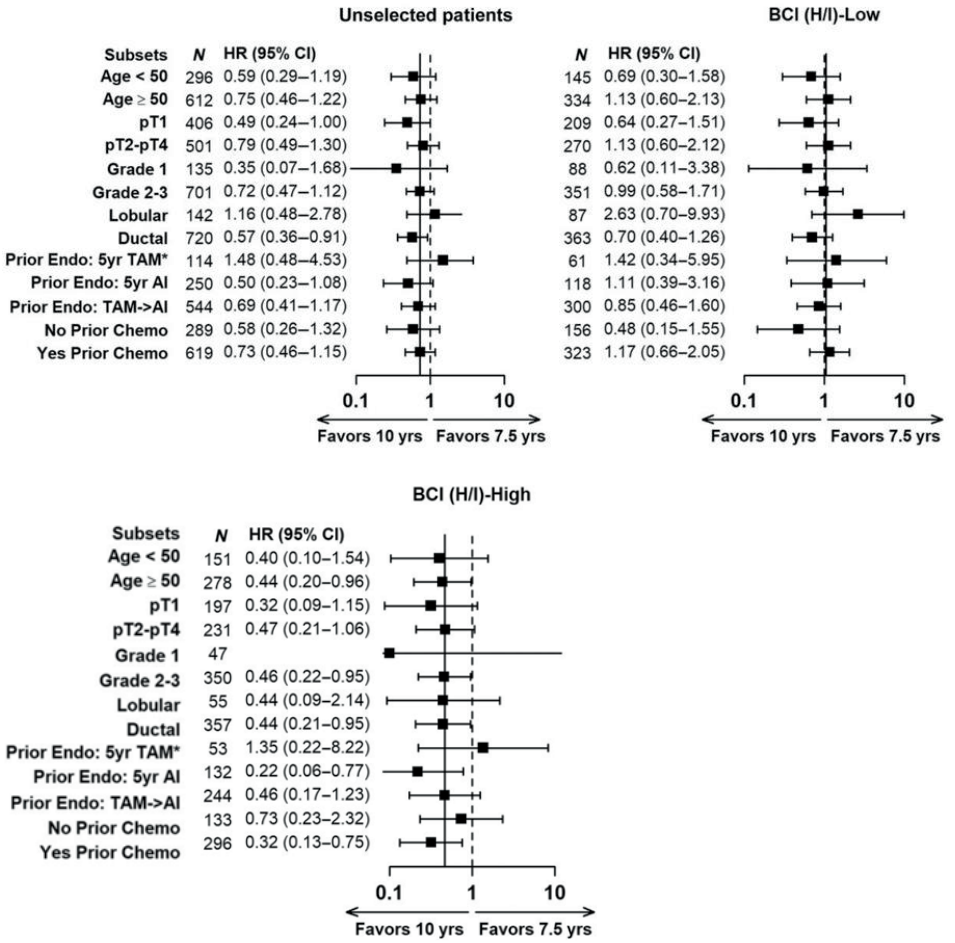

Figure 5: Forest plot of hazard ratios for comparing 10 years versus 7.5 years of ET by BCI [H/I] groups based on RFI in relevant clinical subsets.

BCI [H/I] prediction of extended endocrine benefit beyond clinicopathologic factors

In patients with clinically high-risk features (node-positive and tumor stage 2 or higher), the 46% (N = 162) that were classified as BCI [H/I]-high experienced a statistically significant benefit from 5 years versus 2.5 years of letrozole (HR 0.32; 95% CI 0.10 – 0.98; absolute benefit 12.5%; P = 0.035), whereas the 54% of clinically high-risk patients classified as BCI [H/I]-low (N = 191) did not show significant benefit (P = 0.742; HR 1.13; 95% CI 0.55 – 2.31; **figure 6A**).

Conversely, the 48% of patients (N = 220) in a clinically low-risk subset (tumor stage 1 or grade 1) that were classified as BCI [H/I]-high demonstrated a statistically significant benefit from 5 years versus 2.5 years of letrozole (HR 0.23; 95% CI 0.07 – 0.81) and absolute benefit of 11.9% (P = 0.013), whereas the 52% of clinically low-risk patients

(N = 239) classified as BCI [H/I]-low did not show significant benefit (HR 0.62; 95% CI 0.27 – 1.38; P = 0.235; **figure 6B**).

Distribution of BCI [H/I]-levels in relation to molecular ER, PR, and HER2 expression in the different primary endocrine treatment groups did not demonstrate any strong correlations. Weak negative correlations were observed between BCI [H/I] levels and ER and PR and weak positive correlations between BCI [H/I] and HER2.

DISCUSSION

Clinical trials evaluating extended endocrine therapy to reduce the ongoing residual risk of recurrence that is characteristic of HR+ disease have demonstrated modest benefits with increased morbidity, requiring patient selection to become highly individualized because of diverse prognosis, disease heterogeneity, biological characteristics of the tumor, and patient tolerability.[1-13] To date, the net benefit of extended endocrine therapy based on tumor biology has incorporated individualized assessment of risk but has lacked individualized assessment of endocrine responsiveness to predict the likelihood to benefit from longer durations of endocrine treatment.

Findings from this study further establish the predictive ability of BCI by H/I status to classify patients who demonstrate a high or low degree of endocrine responsiveness with categorical differences in outcome from extended endocrine therapy.

Similar relative improvements in outcome based on RFI by BCI [H/I] category were generally observed in all clinical and pathologic factors examined. One notable exception was observed in the subset analyzed that did not receive prior chemotherapy wherein patients classified as BCI [H/I]-low showed a response to extended endocrine therapy, and the relative response in BCI [H/I]-high patients was less pronounced. The basis of this inconsistency compared with the overall study findings is unclear and may be arbitrary in nature. Consistent with previous data BCI [H/I] expression did not show a strong correlation with canonical endocrine biomarkers, ER and PR.[22,25,26] In addition, multiple translational studies in the ATAC, BIG 1-98, and TEAM trials have reproducibly demonstrated that quantitative ER and PR expression levels in patients with HR+ breast cancer do not predict benefit from endocrine therapy, suggesting that BCI [H/I] predictive effects are predicated on distinct biological mechanisms that are not directly coupled to ER/PR expression levels.[27-29]

Whereas previous studies have established the ability of BCI [H/I] to predict endocrine response in patients treated with tamoxifen in the first five years, the novel finding from this study is the direct validation of BCI [H/I] in patients treated with an AI in the primary adjuvant setting. Importantly, these data align BCI [H/I] to the standard of care for antiestrogen therapy in patients with HR+ early-stage breast cancer that are post-menopausal at diagnosis, which comprise the majority of patients.[30] BCI validation studies consistently evaluated a total of ten years of endocrine therapy; however, the IDEAL study design differed in that it compared a treatment differential of an additional 2.5 years of

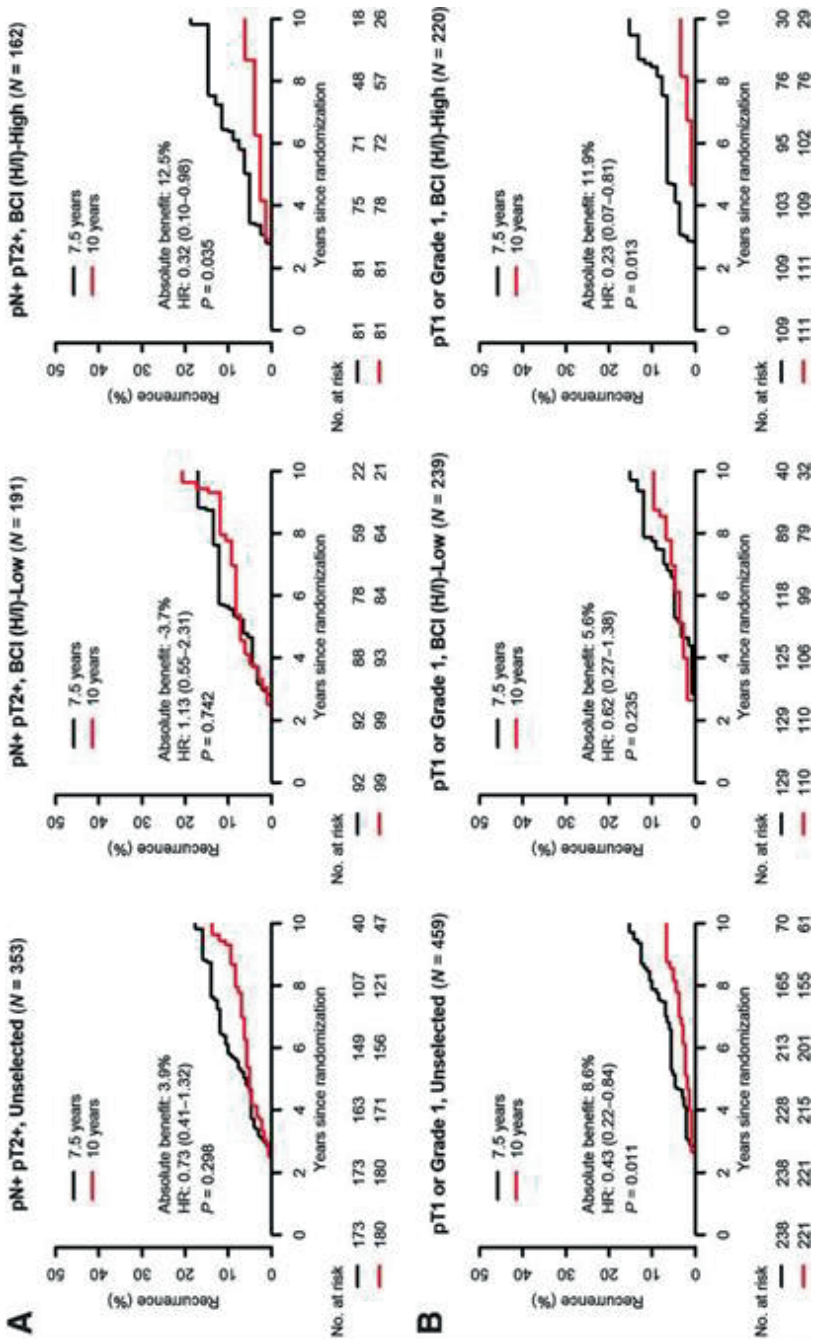

Figure 6: Kaplan-Meier analysis of risk of recurrence comparing 10 years versus 7.5 years of ET by BCI [H/I] group in clinically high risk (A) and clinically low risk (B) patients.

endocrine therapy versus an additional 5 years of endocrine therapy as was investigated in both the MA.17 and aTTom trials.[1,4,6] In comparison with the MA.17 cohort, the patient population evaluated in this study contained a relatively higher proportion of patients with node-positive and grade 3 tumors, whereas the Trans-aTTom study reported on node-positive patients only. BCI biomarker effects across these studies were associated with an approximately two- to threefold improvement in outcome based on the absolute benefit observed in BCI [H/I]-high disease relative to that observed in unselected patients. An important point to note is that results determined from population-based approaches (Trans-aTTom, IDEAL) versus case-controlled methods (MA.17) are regarded as a more accurate estimation of the BCI [H/I] biomarker effect on absolute benefit.[19,22]

Another interesting observation from this analysis is that unlike previous BCI [H/I] results from studies comparing five years versus ten years of therapy, BCI [H/I]-high and -low patients in the 2.5-year arm displayed relatively similar rates of recurrence (approximately 15%) due to the effect of the initial 2.5 years of therapy in the BCI [H/I]-high group. Overall, the data presented herein add to the growing body of evidence demonstrating significant treatment to biomarker interaction between BCI [H/I] and endocrine therapy in a variety of treatment scenarios, and in a manner that is agnostic to antiestrogen approach whether through prevention of ER action or estrogen synthesis. The underlying tumor biology interrogated by BCI [H/I] expression levels may distinguish tumors predominantly driven by estrogen signaling from those with reduced hormone receptor dependence and therefore less responsive to antiestrogen approaches.

Advances in adjuvant endocrine therapy for postmenopausal women include more widespread use of AIs in the adjuvant setting; however, data on the safety and efficacy of AI durations beyond five years of therapy are inconclusive.[3,5,8,9,15,16] Of particular concern are women who have received adjuvant AI monotherapy because longer treatment is associated with additional toxicity including adverse effects on cardiovascular and bone health. Risk stratification by clinicopathologic factors and prognostic biomarkers has been recommended in clinical practice guidelines to help guide patient selection.[18] The American Society of Clinical Oncology guidelines recommend AI treatment for up to a total of ten years for higher risk, node-negative patients, including women with tumor stage 2 or 3 and tumor stage 1c tumors with higher risk prognostic factors, and five years of adjuvant endocrine therapy in total including an AI as sufficient for women with tumor stage 1a and 1b or tumor stage 1c tumors with lower risk prognostic factors. Recommendations also include extending AI-based therapy for up to a total of ten years of adjuvant endocrine treatment for all women with node-positive breast cancer.[18]

However, not all patients with elevated intrinsic risk of recurrence such as those with larger tumors and nodal involvement will benefit equally from extended endocrine therapy. Indeed, findings from this study clearly show that BCI [H/I] identifies 54% of clinically high-risk patients with limited benefit from extended endocrine therapy. Conversely, patient selection based on risk assessment would also assume that improvements in outcome are proportional to level of risk, and that patients with lower risk clinicopathologic features would derive less benefit from extended endocrine therapy.

However, subset analysis of patients with tumor stage 1 or grade 1 tumors demonstrates a similar magnitude in extended endocrine benefit by BCI [H/I] classification as observed in higher risk patients. Moreover, a meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated that HR+ patients across all clinical stages, including those with stage 1 disease, have a significant ongoing risk of late distant recurrence, indicating that risk factors alone are inadequate to individualize patient selection for extended endocrine therapy.[12] These data highlight the distinct clinical utility of BCI [H/I] to provide increased resolution beyond prognostic factors to better individualize the risk-benefit considerations for extended therapy by providing insight into endocrine-responsive biology.

Aside from BCI, several genomic classifiers have been used in clinical practice. The 21-gene recurrence score is predictive for adjuvant chemotherapy benefit, as was more recently demonstrated in the TAILORx trial, but is not predictive of endocrine therapy benefit.[31] In a head-to-head comparison in the Trans-ATAC cohort, BCI, EPclin and ROR each had significant ability to prognosticate late (>5 years) distant recurrence.[32] In addition, the Clinical Treatment Score post-5 years (CTS5), which integrates clinicopathologic factors, was also shown to prognosticate late distant recurrence risk.[33] In a direct comparison between CTS5 and BCI prognostic scores, BCI was able to further stratify those with the intermediate CTS5 risk category into separate risk groups with clinically distinct rates of distant recurrences (12.5% for BCI-high vs. 0% for BCI-low; P = 0.140) indicating that BCI risk stratification provided improved prognostic resolution beyond CTS5.[34] However, these are all prognostic biomarkers. Among currently available genomic signatures, BCI [H/I] is the only assay validated to predict the likelihood of benefit from endocrine therapy. Notably, in a recent analysis of the TEAM and IDEAL clinical study cohorts, CTS5 showed no predictive ability in determining benefit from extended endocrine therapy, including patients that were classified as high-risk (P for interaction = 0.5).[35]

Recently completed studies have concluded that 7 to 7.5 years endocrine therapy in total may be sufficient for many HR+ patients.[1,3,13] However, a critical finding of this study is that BCI [H/I] identified approximately 50% of postmenopausal patients that derived a significant benefit from completing ten years of endocrine therapy (five years of extended AI therapy) versus stopping at 7.5 years (2.5 years of extended letrozole). The clinical implications of these results are that there is a substantial number of women who may derive additional benefit from longer durations of endocrine treatment based on BCI [H/I] status, and that BCI could serve a critical role in the identification of patients who are likely to experience a significant reduction in risk and improved outcomes from prolonging AI treatment to ten years.

Limitations of the study include its retrospective nature and that it was conducted in a parent trial with an open-label design. The study also examined a relatively high-risk early-stage breast cancer population of 73% node-positive patients, with a majority having received chemotherapy. Although BCI [H/I] prediction of endocrine response in node-negative disease has been validated in patients treated with primary adjuvant therapy, additional studies with adequate power to assess BCI [H/I] predictive ability in the

extended endocrine setting are of interest.[21] Strengths of the study include that the translational analysis was prospectively defined in a randomized study with an updated 9.3 years of median follow-up. In addition, the translational cohort contained approximately 50% of the parent trial population, which represents a larger proportion of patients than in previous BCI validation studies.

CONCLUSION

Findings from this study demonstrate significant prediction of extended endocrine benefit based on BCI [H/I] classification in patients treated with contemporary standards of care for primary adjuvant endocrine therapy. In conjunction with previous data from MA.17[19] and Trans-aTTom[22], BCI predictive performance is established across a comprehensive range of treatment scenarios involving tamoxifen and AIs. Clarifying the magnitude and level of efficacy of extended endocrine therapy with approaches that provide additive and distinct information is important to ensure that overtreatment and undertreatment do not occur. BCI may provide the rationale as a standardized molecular tool that measures preferential response and magnitude of benefit to help individualize patient selection for extending endocrine therapy to ten years.

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