Predictive Effect of IGFBP-3 on Low-Dose Tamoxifen Efficacy in Noninvasive Breast Cancer in the Phase III Tam-01 Trial

Harriet Johansson[1], Debora Macis[1], Martino Oliva[2], Matteo Puntoni[3], Eva Blondeaux[4], Aliana Guerrieri-Gonzaga[1], Valentina Aristarco[1], Irene Maria Briata[2], Tania Buttiron-Webber[2], Luca Boni[4], Matteo Lazzeroni[1], Davide Serrano[1], Livia Giordano[5], Maria Digennaro[6], Laura Cortesi[7], Francesco Millo[8], Katia Cagossi[9], Giuseppe Aprile[10], Fabio Falcini[11], Elisa Gallerani[12], Bernardo Bonanni[1], and Andrea DeCensi[2]

ABSTRACT

Purpose: Low-dose tamoxifen 5 mg/day (babytam) for 3 years can decrease the incidence of new breast cancer events in women with breast intraepithelial neoplasia by 42% with limited toxicity, which provides a new treatment option for these disorders. However, predictive biomarkers of babytam efficacy are lacking. We studied whether baseline levels of insulin-like growth factor-1 (IGF-I), IGF-binding protein-3 (IGFBP-3), estradiol, and sex hormone–binding globulin (SHBG) and their ratios predict babytam efficacy on breast cancer events in a preplanned secondary analysis.

Patients and Methods: Within a 1:1 placebo-controlled, multicenter randomized trial of babytam or placebo administered for 3 years after surgery in women with hormone-sensitive or unknown breast intraepithelial neoplasia, including atypical ductal hyperplasia and lobular or ductal carcinoma *in situ*, 406 of 500 participants consented to blood sampling at baseline and at 1 and 3 years. Serum IGF-I, IGFBP-3, estradiol, and SHBG levels and their ratios were measured using chemiluminescent immunoassays. Biomarker changes were estimated using mixed-effects models, and incidence rate ratios were calculated after 10 years of follow-up with Poisson regression. Subgroup analyses were performed using an interaction test and subpopulation treatment effect pattern plot.

Results: Baseline levels of IGFBP-3 in the three top quartiles (≥3.44 μg/mL), but not in the lower quartile, predicted greater babytam efficacy compared with placebo ($P_{interaction} = 0.006$). Baseline IGF-I, estradiol, or SHBG levels were not predictive of babytam efficacy, whereas the IGF-I/IGFBP-3 ratio was borderline significant ($P_{interaction} = 0.067$).

Conclusions: High baseline levels of IGFBP-3 (≥3.44 μg/mL) predicted babytam efficacy and may help differentiate which women benefit most from this treatment.

Introduction

Low-dose tamoxifen (5 mg/day for 3 years, babytam) decreased subsequent breast cancer events by 42% compared with placebo after 10 years in women with ductal carcinoma *in situ* (DCIS) or high-risk lesions (atypical ductal hyperplasia or lobular carcinoma *in situ*), without exceeding serious adverse events and patient-reported outcomes (1, 2), supporting its wide uptake in the medical community (3, 4) and National Comprehensive Cancer Network (NCCN) guideline inclusion (5). A biomarker trial also showed a noninferior reduction in mammographic density and less pronounced adverse events than 20 mg/day with lower doses of tamoxifen in premenopausal women only (6). The mechanisms behind the preventive effects of babytam remain therefore a subject of active investigation.

In addition to its antagonistic effects on estrogen receptor (ER)–dependent breast tissue proliferation, tamoxifen affects circulating biomarkers of breast cancer risk that might carry predictive significance. Specifically, insulin-like growth factor I (IGF-I), its main binding protein IGF-binding protein-3 (IGFBP-3), and their ratio, together with the estradiol/sex hormone–binding globulin (SHBG) ratio, have garnered attention for their putative predictive effect. Increased risk has been associated with higher levels of IGF-I and IGFBP-3 in healthy women (7), and higher recurrence rates have been associated with IGFBP-3 levels in patients with breast cancer (8, 9). Prospective studies demonstrated a higher risk of increased estradiol levels and decreased SHBG levels in pre- (10) and postmenopausal women (11). In premenopausal women, endogenous estradiol levels tend to synergize with IGF-I. Women with serum estradiol levels in the upper quartile benefitted most from raloxifene therapy (12), and the risk reduction by anastrozole was highest in

[1]IEO, European Institute of Oncology IRCCS, Milan, Italy. [2]EO Ospedali Galliera, Genoa, Italy. [3]Clinical & Epidemiological Research Unit, University Hospital of Parma, Parma, Italy. [4]IRCCS Ospedale Policlinico San Martino, Genoa, Italy. [5]Azienda Ospedaliera-Universitaria Città della Salute e della Scienza, Torino, Italy. [6]IRCCS, Istituto Tumori "Giovanni Paolo II," Bari, Italy. [7]Azienda Ospedaliera-Universitaria Policlinico di Modena, Modena, Italy. [8]Ospedali Riuniti ASL AL—Ospedale SS. Antonio e Margherita, Tortona, Italy. [9]Division of Medical Oncology, "B. Ramazzini" Hospital, Carpi, Italy. [10]Department of Oncology, San Bortolo General Hospital, ULSS8 Berica, Vicenza, Italy. [11]IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori"—IRST S.r.l., Meldola, Italy. [12]Aziende Socio Sanitarie Territoriale dei Sette Laghi, Varese, Italy.

Trial Registration: ClinicalTrials.gov number NCT01357772; EudraCT number 2007-007740-10

Corresponding Author: Andrea DeCensi, Division of Medical Oncology, Department of Medicine, Ente Ospedaliero Ospedali Galliera, Mura delle Cappuccine 14, Genoa 16128, Italy. E-mail: andrea.decensi@galliera.it

Clin Cancer Res 2025;31:1841–6

doi: 10.1158/1078-0432.CCR-24-2987

Translational Relevance

Low-dose tamoxifen (babytam, 5 mg/day for 3 years) is an important treatment option after breast preinvasive disease, given its long-term efficacy and safety. However, predictive biomarkers of babytam efficacy are lacking. Tamoxifen affects circulating biomarkers of breast cancer risk, and the use of predictive biomarkers could help increase precision preventive intervention by selecting patients who respond better. Our phase III trial of babytam after surgery for ductal carcinoma *in situ* or high-risk lesions included the measurement of the breast cancer risk biomarkers insulin-like growth factor I (IGF-I), its main binding protein IGF-binding protein-3 (IGFBP-3), and their ratio, together with estradiol and sex hormone–binding globulin and their ratio, to assess their predictive role. After 10-year follow-up, baseline IGFBP-3 in the upper quartile predicted greater efficacy of babytam compared with placebo ($P_{interaction} = 0.006$). The IGF-I/IGFBP-3 ratio was borderline significant ($P_{interaction} = 0.067$). Our findings provide a potential option for selecting women who benefit most from babytam.

women with estradiol/SHBG ratios in quartiles 2 to 4, but not in the lowest quartile, in a nested case–control study of the IBIS-II trial (13).

To improve the therapeutic prevention precision of babytam, we investigated the role of serum levels of IGF-I, IGFBP-3, estradiol, and SHBG and their molar ratios in predicting the efficacy of breast cancer events after 10 years of follow-up.

Patients and Methods

The study details and key clinical findings have been previously reported (1, 2). The study (Tam-01) was conducted in accordance with recognized ethical guidelines (Declaration of Helsinki) and was approved by the ethics committees of the sponsor (Galliera Hospital, Genoa, Italy) and participating sites. All women signed a written informed consent. In summary, we conducted a multicenter phase III trial comparing 5 mg/day tamoxifen with a placebo over 3 years in 500 women, ages 75 or younger, with an Eastern Cooperative Oncology Group performance status of 1 or less and hormone-sensitive (ER or progesterone receptor ≥1%) or unknown DCIS (69%) or breast intraepithelial neoplasia (atypical ductal hyperplasia, 20% or lobular carcinoma *in situ*, 11%). Women with high-grade or comedo/necrotic DCIS were treated with adjuvant radiotherapy at 50 Gy in 25 fractions. Participants were followed up every 6 months, undergoing annual mammography and transvaginal ultrasound for 3 years of treatment and then being seen annually for 7 years of follow-up. All breast-related events during the trial were centrally adjudicated by an expert committee. The primary endpoint was the incidence of invasive breast cancer or DCIS. Biomarker studies included circulating IGF-I, IGFBP-3, estradiol, SHBG, C-reactive protein, CYP2D6 SNPs, tamoxifen, and metabolite blood levels.

The mean (SD) age at treatment initiation was 54 (9) years, with 58% being postmenopausal. After a median follow-up of 9.7 years (IQR, 8.3–10.9 years), 66 breast cancers were diagnosed (15 *in situ* and 51 invasive): 25 in the tamoxifen group and 41 in the placebo group (annual rate per 1,000 person-years: 11.3 with tamoxifen vs. 19.5 with placebo; HR, 0.58; 95% confidence interval, 0.35–0.95; *P* value = 0.03). The majority of recurrences were invasive (77%) and ipsilateral (59%). For contralateral breast cancer incidence, there were six events in the tamoxifen group and 16 in the placebo group (HR, 0.36; 95% confidence interval, 0.14–0.92; *P* value = 0.025). No differences were observed between the groups in terms of patient-reported outcomes (menopausal symptoms) or serious adverse events during the extended follow-up period.

In this preplanned biomarker study, 406 of 500 women consented to blood sampling at baseline and at 1 and 3 years. Serum levels of IGF-I, IGFBP-3, estradiol, and SHBG and their molar ratios were quantified by chemiluminescent assay. The units used were (nmol/L)/(nmol/L) for the IGF-I/IGFBP-3 molar ratio and (pmol/L)/(nmol/L) for the estradiol/SHBG molar ratio. We subdivided the hormone and protein values by the median, quartiles, and treatment arms. Biomarker changes were estimated using mixed-effects models for repeated measures, including treatment per time interaction, age and body mass index (BMI) as fixed effects, and a random intercept for patient ID to account for intrasubject variability. Ten-year incidence rate ratios of the primary endpoint (invasive breast cancer or DCIS) were calculated using Poisson regression. The predictive effect of the biomarkers was assessed using an interaction test. The subpopulation treatment effect pattern plot methodology (ref. 14) explored the 10-year cumulative incidence rate along the continuous scale of IGF-I, IGFBP-3, and their ratio. A sliding window pattern was adopted, including 100 subjects in each subpopulation, with 50 subjects overlapping between consecutive subpopulations. The analysis implemented 100,000 permutations of biomarker covariates, adjusting for age and baseline BMI. The issue of multiplicity was addressed by adopting the Benjamini–Hochberg methods for FDR correction (15). Statistical analyses were performed using Stata software (StataCorp. 2023, Release-18, RRID: SCR_012763). See Supplementary Table S1 for representativeness of study participants.

Data availability

Individual participant data are not publicly available because this requirement was not anticipated in the study protocol.

The deidentified data underlying this article may be shared upon request to the corresponding author. A specific purpose for data request is required for approval by the institutional authorities.

Results

There was no difference in the event rates between women with blood samples ($n = 406$) and those without ($n = 94$, not shown). The participant flow diagram is illustrated in Supplementary Fig. S1, and the main subject characteristics at baseline are presented in Supplementary Table S2. The direct effects of babytam on biomarker levels at 1 and 3 years are illustrated in Supplementary Figs. S2–S4. Compared with placebo, the IGF-I level and IGF-I/IGFBP-3 ratio decreased significantly, with a slight increase in IGFBP-3 by babytam irrespective of menopausal status (Supplementary Fig. S2). The effects on estradiol differed by menopausal status, with an increase observed in premenopausal women, whereas SHBG increased in both pre- and postmenopausal women (Supplementary Figs. S3 and S4).

The predictive effects of these biomarkers are shown in **Table 1** and further stratified by menopausal status in Supplementary Tables S3 and S4. Baseline levels of IGFBP-3 in the three top quartiles (≥3.44 μg/mL),

Table 1. Mean event rate (per 1,000 person-years) stratified by treatment arm and baseline IGF-I, IGFBP-3, E2, and SHBG and IGF-I/IGFBP-3 and E2/SHBG ratios at 10 years of follow-up.

10-year follow-up	Babytam	Placebo	IRR (95% CI)
IGF-I[a], ng/mL			
≤Median (127.3)	11.8 (6.3–21.9)	20.9 (13.2–33.2)	0.49 (0.22–1.11)
>Median	11.0 (5.9–20.5)	21.5 (13.5–34.0)	0.52 (0.23–1.15)
IRR (95% CI)	0.90 (0.35–2.31)	1.09 (0.53–2.22)	$P_{interaction} = 0.967$
IGFBP-3[a], μg/mL			
Q1 (≤3.43)	10.6 (4.0–28.3)	8.8 (3.3–23.4)	1.24 (0.33–4.66)
Q2 (3.44–4.21)	21.4 (11.5–39.8)	25.5 (13.3–49.0)	0.75 (0.30–1.85)
Q3 (4.22–4.91)	11.6 (4.8–27.8)	20.6 (10.3–41.3)	0.59 (0.18–1.98)
Q4 (≥4.92)	2.2 (0.3–15.9)	30.7 (18.2–51.8)	0.07 (0.01–0.52)**
IRR (95% CI)	0.71 (0.50–1.01)	1.36 (1.02–1.82)*	$P_{interaction} = 0.006$***
IGF-I/IGFBP-3[a]			
≤Median (0.167)	7.7 (3.7–16.2)	26.3 (17.2–40.4)	0.29 (0.13–0.69)**
>Median	15.9 (9.2–27.4)	16.4 (9.7–27.7)	0.89 (0.41–1.94)
IRR (95% CI)	1.72 (0.67–4.40)	0.60 (0.30–1.20)	$P_{interaction} = 0.067$
E2[a], pg/mL			
≤Median (15.8)	7.9 (3.7–16.5)	21.1 (13.3–33.5)	0.38 (0.16–0.91)*
>Median	15.0 (8.7–25.8)	21.3 (13.4–33.8)	0.62 (0.29–1.34)
IRR (95% CI)	1.47 (0.54–3.96)	0.90 (0.39–2.11)	$P_{interaction} = 0.390$
SHBG[a], nmol/L			
≤Median (60.2)	13.2 (7.3–23.8)	25.2 (16.4–36.8)	0.50 (0.24–1.05)
>Median	9.7 (5.1–18.7)	17.3 (10.5–28.8)	0.54 (0.23–1.30)
IRR (95% CI)	0.67 (0.24–1.90)	0.77 (0.32–1.85)	$P_{interaction} = 0.801$
E2/SHBG[a]			
≤Median (1.37)	9.4 (4.7–18.9)	19.3 (12.0–31.1)	0.49 (0.21–1.16)
>Median	13.2 (7.5–23.2)	23.2 (14.8–36.4)	0.52 (0.24–1.10)
IRR (95% CI)	0.91 (0.33–2.50)	1.09 (0.51–2.35)	$P_{interaction} = 0.977$

Abbreviations: CI, confidence interval; E2, estradiol; IRR, incidence rate ratio.
*, $P < 0.05$; **, $P < 0.01$. ***Statistically significant even after Benjamini–Hochberg FDR correction.
P values were calculated using Poisson regression adjusted for age and BMI at baseline.
[a]All women.

but not in the lowest quartile, predicted increasingly greater babytam efficacy compared with placebo (*p* interaction = 0.006 by Poisson, **Fig. 1**). Similar results observed on breast cancer cumulative incidence curves by IGFBP-3 quartiles and treatment arms are shown in **Fig. 2**. The subpopulation treatment effect pattern plot technique confirmed the effect modification of baseline IGFBP-3 and, to a lesser extent, of the IGF-I/IGFBP-3 ratio on babytam efficacy (supremum test *P* value = 0.051 and 0.056, **Fig. 3**). Baseline IGF-I, estradiol, or SHBG did not seem to predict babytam efficacy on cumulative incidence Kaplan–Meier curves, whereas the IGF-I/IGFBP-3 ratio was borderline significant ($P_{interaction} = 0.067$; Supplementary Figs. S5A and S5B).

Discussion

The identification of predictive biomarkers is crucial for selecting patients who may benefit most from a specific therapy without experiencing unwanted toxicity. This is particularly important in preventive therapy to increase precision and limit adverse events. A biomarker is predictive when the treatment effect differs according to its presence or level.

The direct modulation of the IGF-I/IGFBP-3 ratio following babytam administration confirms the role of this drug in modulating the IGF axis (16). More importantly, our results show the predictive effect of IGFBP-3 and IGF-I/IGFBP-3 ratio on babytam efficacy. Baseline levels of IGFBP-3 in the three top quartiles (≥3.44 μg/mL), but not in the lowest quartile, predicted greater babytam efficacy compared with placebo. Findings in the placebo arm indicate that high IGFBP-3 levels are a significant risk factor for new breast cancer events, in line with prior studies in healthy women (7) and patients with breast cancer (8, 9). In a case–cohort study within the Melbourne Collaborative Cohort Study, IGF-I and IGFBP-3 were positively associated with breast cancer risk in older women (17). Likewise, the Nurses' Health Study II found that IGFBP-3 was associated with increased risk in postmenopausal women (18). A large prospective case–control study nested within the European Prospective Investigation into Cancer and Nutrition cohort confirmed previous findings for an association of serum IGF-I and IGFBP-3 concentrations with breast cancer risk, particularly for women with a later diagnosis of cancer (19).

The decline in IGFBP-3 over 3 years on placebo supports the known effect of aging on this biomarker. However, the interaction between babytam and IGFBP-3 on breast events was adjusted for age and BMI, thus attenuating their respective effect. IGFBP-3 may exert modulatory effects related to its role in regulating IGF bioavailability via sequestration in circulating ternary complexes (20). The IGFBP-3 ternary complex, being unable to cross the vascular endothelium, prolongs IGF half-life in circulation and maintains an IGF reservoir (21). It inhibits the mitogenic and antiapoptotic effects of free IGF-I until the complex is broken down. Conversely, IGFBP-3 can directly modulate IGF actions in tissues, for example, interacting with the

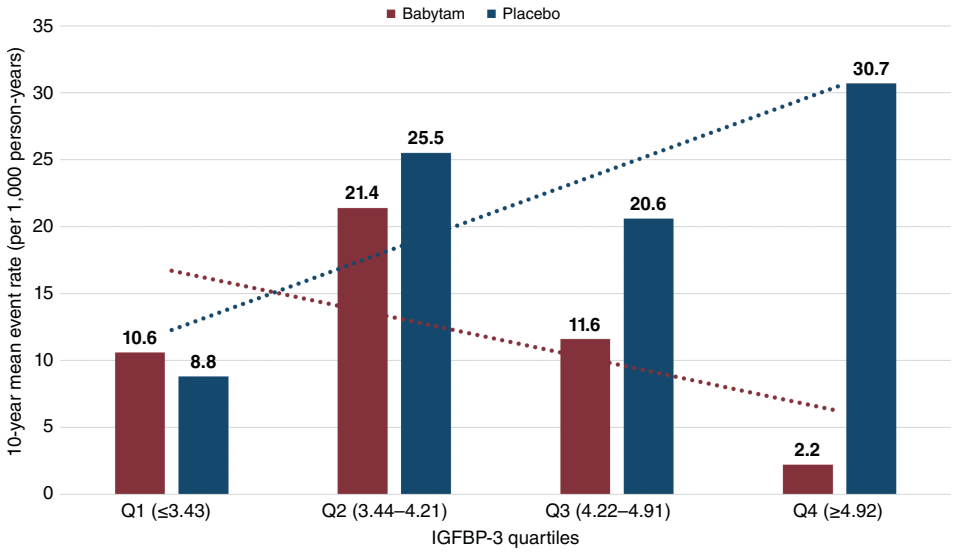
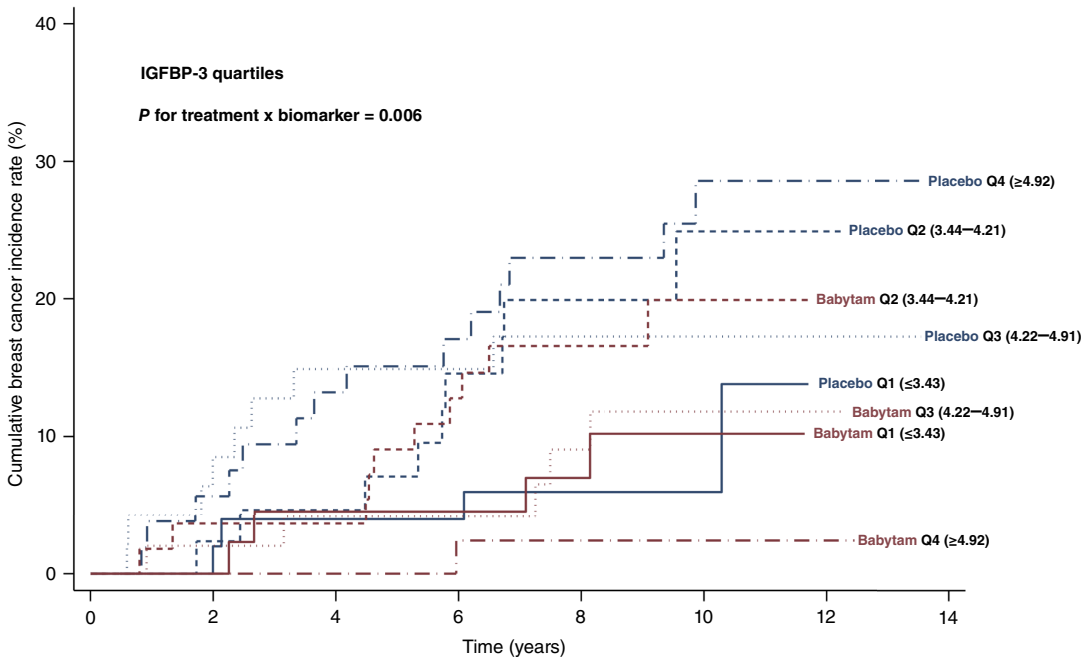


Figure 1.
Ten-year cumulative mean event rate (per 1,000 person-years) according to baseline IGFBP-3 quartiles (Q1–Q4) and treatment arm. $P_{interaction} = 0.006$ by Poisson adjustment for age and BMI.

extracellular matrix (21), undergoing cellular uptake and nuclear importation binding to nuclear receptors, thereby regulating gene transcription independently (22). Notably, IGFBP-3 has been shown to increase cancer risk and proliferation of breast cancer cells (23). The blockade of ER function by babytam at the mammary gland might be particularly effective in subjects in the higher IGFBP-3 quartiles, reducing the likelihood of cross-talk between insulin-like growth factor receptor and ER, thus



Number at risk:

Placebo Q1 (≤3.43)	52	(1)	50	(1)	49	(0)	47	(1)	41	(0)	18	(1)	0	(0)	0
Placebo Q2 (3.44–4.21)	43	(1)	42	(1)	39	(4)	34	(2)	26	(1)	14	(0)	1	(0)	0
Placebo Q3 (4.22–4.91)	48	(4)	43	(3)	40	(0)	37	(1)	28	(0)	14	(0)	5	(0)	0
Placebo Q4 (≥4.92)	53	(3)	50	(4)	46	(2)	42	(3)	37	(2)	23	(0)	1	(0)	0
Babytam Q1 (≤3.43)	47	(0)	44	(2)	41	(0)	40	(1)	31	(1)	13	(0)	0	(0)	0
Babytam Q2 (3.44–4.21)	56	(2)	53	(0)	53	(5)	47	(2)	39	(1)	18	(0)	0	(0)	0
Babytam Q3 (4.22–4.91)	51	(1)	49	(1)	44	(0)	42	(2)	33	(1)	18	(0)	3	(0)	0
Babytam Q4 (≥4.92)	46	(0)	45	(0)	45	(1)	41	(0)	37	(0)	28	(0)	3	(0)	0

Figure 2.
Ten-year cumulative breast cancer incidence rate (%) according to IGFBP-3 quartiles (Q1–Q4) and treatment arm. $P_{interaction} = 0.006$ by Poisson adjustment for age and BMI.

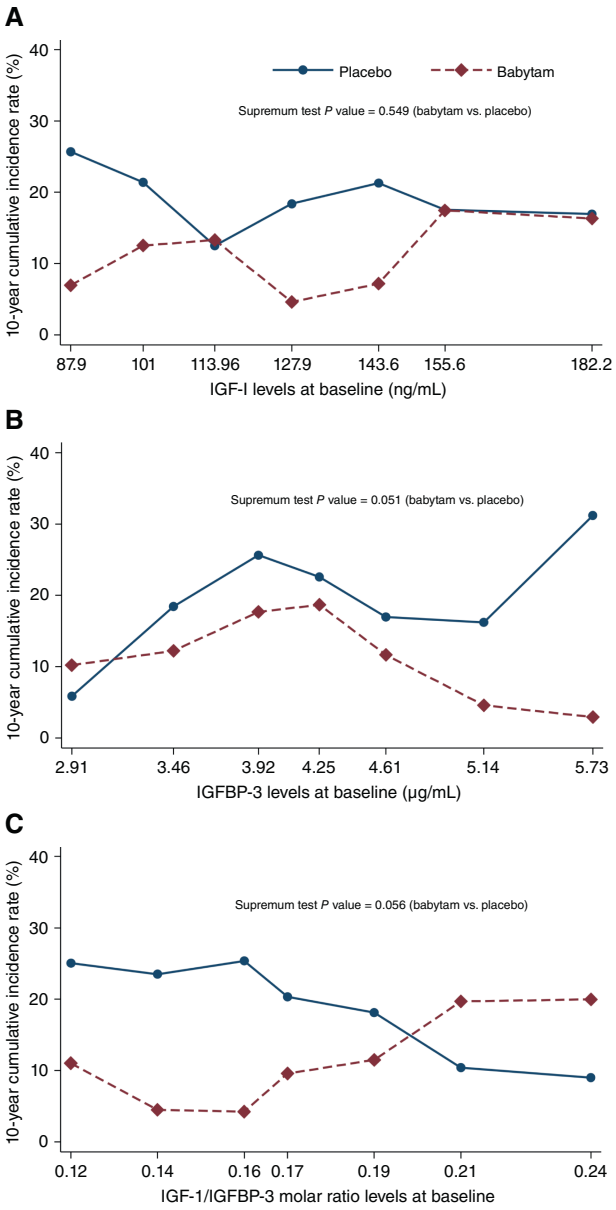


Figure 3.

Subpopulation treatment effect pattern plot (STEPP) of the 10-year cumulative incidence by baseline IGF-I (top), IGFBP-3 (middle), and IGF-I/IGFBP-3 molar ratio (bottom) and treatment arm. The plot was drawn by adopting the sliding window pattern, including 100 subjects in each subpopulation and 50 subjects in common among consecutive subpopulations, implementing 100,000 permutations of the covariate of biomarkers, adjusting for age and BMI at baseline. (**A**) IGF-I levels at baseline (ng/mL); (**B**) IGFBP-3 levels at baseline (µg/mL); and (**C**) IGF-I/IGFBP-3 molar ratio levels at baseline are shown.

counteracting the IGF-mediated enhancement of cell proliferation and cell adhesion (21, 24, 25).

Although systematic reviews have reported increased risk with higher levels of IGF-I and IGFBP-3 (7–9), the direct role of IGFBP-3 in breast carcinogenesis is complex. The IGFBP-3 activity may be modulated through several proteolytic enzymes, which could, to some extent, affect the analytic results of serum concentrations, depending on the assay methodology applied (19). However, we can exclude any significant postsampling proteolysis interference as the serum was separated and stored in aliquots at −80°C until IGFBP-3 measurement. Additionally, women were free of cancer at blood draws.

We did not observe any significant interaction between estradiol and estradiol/SHBG on tamoxifen response at 10-year follow-up, indicating no predictive role of these biomarkers. In a previous analysis with fewer events at 5-year follow-up, we showed a non-significant trend to a greater benefit in postmenopausal women or women with estradiol levels below the median of 15.8 pg/mL. However, the interaction test was again not significant at 10 years ($P = 0.13$ and $P = 0.42$ for menopausal status and estradiol levels, respectively), indicating no predictive effect of both variables. It is important to underline that these subgroup analyses are underpowered for the low number of events in premenopausal women so that any firm conclusion about a lower benefit in premenopausal women is premature. Moreover, we were unable to synchronize blood drawing and menstrual cycle phase in some premenopausal women.

Our findings of a greater response to babytam in women with high IGFBP-3 levels offer an additional clue over and above the mild estradiol increase to explain why babytam might be less effective in young, premenopausal women (26).

The increase in the estradiol/SHBG molar ratio observed in premenopausal women versus the mild decrease in postmenopausal women underscores the complex interplay between tamoxifen and endogenous estrogen levels, which may influence drug efficacy. However, the estradiol/SHBG ratio did not exhibit a predictive role for babytam efficacy in postmenopausal women, at variance with a previous study on raloxifene (12).

Given their low cost, serum IGF-I and IGFBP-3 might be measured routinely and integrated into risk management decisions to distinguish which women will benefit most from babytam. However, a limitation is that the study was not specifically powered to assess the prognostic and predictive effects of biomarkers, although these were preplanned secondary objectives of the trial. The finding needs further validation in an independent cohort investigating this biomarker in a similar setting before it can be introduced into clinical practice.

In conclusion, this study unveils the potential of serum biomarkers, specifically IGFBP-3 and IGF-I/IGFBP-3 ratios, as predictive factors of babytam efficacy among individuals with DCIS or high-risk lesions. These findings hold significant implications in clinical practice, offering a means to discern patients who may derive maximal benefits from babytam.

Authors' Disclosures

E. Blondeaux reports personal fees from Eli Lilly and Company and grants from Gilead Sciences outside the submitted work. L. Boni reports personal fees from Pfizer outside the submitted work. L. Cortesi reports personal fees from AstraZeneca, MSD, Pfizer, Novartis, Gilead Sciences, Roche, and Daichii Sankyo outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

H. Johansson: Conceptualization, data curation, supervision, methodology, writing–original draft, writing–review and editing. **D. Macis:** Resources, data curation, writing–review and editing. **M. Oliva:** Software, formal analysis, methodology, writing–original draft, writing–review and editing. **M. Puntoni:** Conceptualization, data curation, software, formal analysis, supervision, methodology, writing–original draft, writing–review and editing. **E. Blondeaux:** Software, formal analysis, writing–review and editing. **A. Guerrieri-Gonzaga:** Data curation, project administration, writing–review and editing. **V. Aristarco:** Resources, data curation, writing–review and editing. **I.M. Briata:** Data curation, project administration, writing–review and editing. **T. Buttiron-Webber:**

Project administration, writing–review and editing. **L. Boni:** Software, formal analysis, writing–review and editing. **M. Lazzeroni:** Resources, data curation, writing–review and editing. **D. Serrano:** Resources, data curation, writing–review and editing. **L. Giordano:** Resources, data curation, writing–review and editing. **M. Digennaro:** Resources, data curation, writing–review and editing. **L. Cortesi:** Resources, data curation, writing–review and editing. **F. Millo:** Resources, data curation, writing–review and editing. **K. Cagossi:** Resources, data curation, writing–review and editing. **G. Aprile:** Resources, data curation, writing–review and editing. **F. Falcini:** Resources, data curation, writing–review and editing. **E. Gallerani:** Resources, data curation, writing–review and editing. **B. Bonanni:** Conceptualization, resources, data curation, writing–review and editing. **A. DeCensi:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, methodology, writing–original draft, project administration, writing–review and editing.

Acknowledgments

This work was partially supported by the Italian Ministry of Health with "Ricerca Corrente" and 5 × mille funds and Galliera Hospital (Sper 22 to A. DeCensi). The authors thank Chiara Accornero, Research Nurse at the European Institute on Oncology, Milan, Italy, and Marianna Fava for providing patient care and data management during the trial. The authors are deeply grateful to the study participants and their families for their altruistic and careful contribution to the research project. This work was supported by the Italian Ministry of Health (RFPS-2006-1-339898 to A. DeCensi), Breast Cancer Research Foundation (Grant no. PPI-23-002 to A. DeCensi), Associazione Italiana per la Ricerca sul Cancro (IG 2008 Grant no. 5611 to A. DeCensi), and Italian League Against Cancer (LILT 7-08 to A. DeCensi).

Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received September 17, 2024; revised November 26, 2024; accepted March 11, 2025; posted first April 28, 2025.

References

1. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, Caviglia S, Avino F, Cortesi L, et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. J Clin Oncol 2019;37:1629–37.
2. Lazzeroni M, Puntoni M, Guerrieri-Gonzaga A, Serrano D, Boni L, Buttiron Webber T, et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent recurrence in breast noninvasive neoplasia: a 10-year follow-up of TAM-01 study. J Clin Oncol 2023;41:3116–21.
3. Bychkovsky B, Laws A, Katlin F, Hans M, Knust Graichen M, Pace LE, et al. Initiation and tolerance of chemoprevention among women with high-risk breast lesions: the potential of low-dose tamoxifen. Breast Cancer Res Treat 2022;193:417–27.
4. Laws A, Punglia RS. Endocrine therapy for primary and secondary prevention after diagnosis of high-risk breast lesions or preinvasive breast cancer. J Clin Oncol 2023;41:3092–9.
5. Gradishar WJ, Moran MS, Abraham J, Abramson V, Aft R, Agnese D, et al NCCN guidelines version 1. 2025. Breast cancer; 2025. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
6. Eriksson M, Eklund M, Borgquist S, Hellgren R, Margolin S, Thoren L, et al. Low-dose tamoxifen for mammographic density reduction: a randomized controlled trial. J Clin Oncol 2021;39:1899–908.
7. Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, Reeves GK, Roddam AW. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol 2010;11:530–42.
8. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Hartwick W, et al. Insulin-like growth factor binding proteins 1 and 3 and breast cancer outcomes. Breast Cancer Res Treat 2002;74:65–76.
9. Rosendahl AH, Björner S, Ygland Rödström M, Jirström, K, Borgquist, S, Ingvar, C, et al. Pre- and postoperative circulating IGF-I, IGFBP-3, and IGFBP-7 levels in relation to endocrine treatment and breast cancer recurrence: a nested case-control study. Front Oncol 2021;11:626058.
10. Key TJ, Appleby PN, Reeves GK, Travis RC, Alberg AJ, Barricarte A, et al; Endogenous Hormones and Breast Cancer Collaborative Group. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncol 2013;14:1009–19.
11. Endogenous Hormones and Breast Cancer Collaborative Group. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer 2011;105:709–22.
12. Cummings SR, Duong T, Kenyon E, Cauley JA, Whitehead M, Krueger KA, et al. Serum estradiol level and risk of breast cancer during treatment with raloxifene. JAMA 2002;287:216–20.
13. Cuzick J, Chu K, Keevil B, Brentnall AR, Howell A, Zdenkowski N, et al. Effect of baseline oestradiol serum concentration on the efficacy of anastrozole for preventing breast cancer in postmenopausal women at high risk: a case-control study of the IBIS-II prevention trial. Lancet Oncol 2024;25:108–16.
14. Bonetti M, Gelber RD. Patterns of treatment effects in subsets of patients in clinical trials. Biostatistics 2004;5:465–81.
15. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289–300.
16. Decensi A, Bonanni B, Guerrieri-Gonzaga A, Gandini S, Robertson C, Johansson H, et al. Biologic activity of tamoxifen at low doses in healthy women. J Natl Cancer Inst 1998;90:1461–7.
17. Baglietto L, English DR, Hopper JL, Morris HA, Tilley WD, Giles GG. Circulating insulin-like growth factor-I and binding protein-3 and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2007;16:763–8.
18. Schernhammer ES, Holly JM, Hunter DJ, Pollak MN, Hankinson SE. Insulin-like growth factor-I, its binding proteins (IGFBP-1 and IGFBP-3), and growth hormone and breast cancer risk in The Nurses Health Study II. Endocr Relat Cancer 2006;13:583–92.
19. Rinaldi S, Peeters PHM, Berrino F, Dossus L, Biessy C, Olsen A, et al. IGF-I, IGFBP-3 and breast cancer risk in women: the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer 2006;13:593–605.
20. Renehan AG, Harvie M, Howell A. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and breast cancer risk: eight years on. Endocr Relat Cancer 2006;13:273–8.
21. LeRoith D, Holly JMP, Forbes BE. Insulin-like growth factors: ligands, binding proteins, and receptors. Mol Metab 2021;52:101245.
22. Baxter RC. Nuclear actions of insulin-like growth factor binding protein-3. Gene 2015;569:7–13.
23. McIntosh J, Dennison G, Holly JMP, Jarrett C, Frankow A, Foulstone EJ, et al. IGFBP-3 can either inhibit or enhance EGF-mediated growth of breast epithelial cells dependent upon the presence of fibronectin. J Biol Chem 2010;285:38788–800.
24. Yee D, Lee AV. Crosstalk between the insulin-like growth factors and estrogens in breast cancer. J Mammary Gland Biol Neoplasia 2000;5:107–15.
25. Voudouri K, Nikitovic D, Berdiaki A, Kletsas D, Karamanos NK, Tzanakakis GN. IGF-I/EGF and E2 signaling crosstalk through IGF-IR conduit point affects breast cancer cell adhesion. Matrix Biol 2016;56:95–113.
26. DeCensi A, Puntoni M, Johansson H, Guerrieri-Gonzaga A, Caviglia S, Avino F, et al. Effect modifiers of low-dose tamoxifen in a randomized trial in breast noninvasive disease. Clin Cancer Res 2021;27:3576–83.