

**Embargoed for Release:** 3:15 p.m. CT, Dec. 12, 2019

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## **MINDACT Trial Data Reveal Certain Women With Luminal Breast Cancer May Be Undertreated With Tamoxifen Alone**

SAN ANTONIO — Among women with hormone receptor (HR)-positive, HER2-negative breast cancer with a high clinical risk (determined by tumor size and histologic grade) and low genomic risk (determined by MammaPrint), those 40 to 50 years old had a greater benefit from chemotherapy than those older than 50, according to data from an unplanned subgroup analysis of the [MINDACT trial](#) presented at the [2019 San Antonio Breast Cancer Symposium](#), held Dec. 10–14.

“Younger women with breast cancer are underrepresented in clinical trials, and treatment decisions are often based on data obtained in older, postmenopausal women,” said Fatima Cardoso, MD, director of the Breast Unit at the Champalimaud Clinical Center/Champalimaud Foundation in Lisbon, Portugal. “It is important to examine how age impacts treatment efficacy and disease recurrence in patients with breast cancer to determine the best treatment option for each patient.”

While most patients with HR-positive breast cancer are treated with endocrine therapy, the selection of patients that will derive clinical benefit from the addition of chemotherapy is an area of current research, explained Cardoso.

The goal of the MINDACT trial is to compare the utility of the 70-gene signature commercial diagnostic test [MammaPrint](#) with common clinical-pathological criteria (determined by modified [Adjuvant!Online](#)) to select breast cancer patients with zero to three positive nodes for adjuvant chemotherapy. A recent [analysis](#) of the [TAILORx trial](#) revealed that patients who were 50 years old or younger had an estimated chemotherapy benefit in reducing distant recurrence at nine years if they had an [Oncotype DX recurrence score \(RS\)](#) of 16-20 with high clinical risk, or if they had RS of 21-25, irrespective of clinical risk.

“We conducted this unplanned analysis of the MINDACT trial to determine if the addition of chemotherapy had an age-dependent impact on distant metastasis-free survival (DMFS) among certain breast cancer patients, as was seen recently in an analysis of the TAILORx trial,” said Cardoso.

Cardoso and colleagues evaluated five-year DMFS among HR-positive, HER2-negative breast cancer patients enrolled in the MINDACT trial who had a low genomic risk and a high clinical risk and were randomized to receive chemotherapy based on either clinical or genomic risk. Because there were only two DMFS events in patients under 40 years old, the researchers restricted their analysis to patients older than 40, resulting in a total population of 1,264 patients. Among this group, 399 patients were aged 40 to 50, and 865 patients were older than 50.

Among patients older than 50, the estimated five-year DMFS was similar between patients who received and who did not receive chemotherapy (95.2 percent versus 95.4 percent, respectively). However, among patients 40 to 50 years old, the estimated five-year DMFS for patients who received chemotherapy was 96.2 percent versus 92.6 percent for those who did not receive chemotherapy.

“Similar to the TAILORx trial, we found that women classified as high risk of recurrence by traditional clinical-pathological factors but low risk by MammaPrint had a worse outcome if treated with tamoxifen alone, and that the benefit of chemotherapy may eventually be higher in this group,” said Cardoso.

“In both of these trials, the vast majority of women received tamoxifen alone (without ovarian suppression) as adjuvant chemotherapy,” noted Cardoso. “Therefore, we are unable to determine if the results seen in younger women are due to the direct effect of chemotherapy or through chemotherapy-induced ovarian suppression.

“These findings, while hypothesis-generating, are not yet practice-changing as they require confirmation,” continued Cardoso. “However, our results and the TAILORx trial results seem to indicate that younger women with high clinical risk and low genomic risk (per MammaPrint) or with an intermediate RS (per Oncotype DX) may benefit from additional treatment.”

This specific study represents a subset analysis of the MINDACT trial and is therefore only exploratory, representing a limitation of the study, noted Cardoso.

The MINDACT trial was supported by grants from the European Commission Sixth Framework Program, the Breast Cancer Research Foundation, Novartis, F. Hoffmann–La Roche, Sanofi-Aventis, Eli Lilly, Veridex, the National Cancer Institute (U.S.), the European Breast Cancer Council–Breast Cancer Working Group, the Jacqueline Seroussi Memorial Foundation for Cancer Research, Prix Mois du Cancer du Sein, Susan G. Komen for the Cure, Fondation Belge contre le Cancer, Dutch Cancer Society (KWF), the Netherlands Genomics Initiative–Cancer Genomics Center, Association le Cancer du Sein, Parlons-en!, the Brussels Breast Cancer Walk-Run and the American Women’s Club of Brussels, NIF Trust, German Cancer Aid, the Grant Simpson Trust and Cancer Research UK, Ligue Nationale contre le Cancer, and the EORTC Cancer Research Fund. Whole-genome analysis was provided by Agendia without cost.

Cardoso has advisory roles with Amgen, Astellas Pharma/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai Inc., GE Oncology, Genentech, GlaxoSmithKline, MacroGenics, Medscape, Merck-Sharp, Merus, Mylan, Mundipharma, Novartis, Pfizer, Pierre Fabre, prIME Oncology, Roche, Sanofi, Seattle Genetics, and Teva Pharmaceutical Industries Ltd.

**ABSTRACT**

**Publication Number:** GS4-05

Should age be integrated together with clinical and genomic risk for adjuvant chemotherapy decision in early luminal breast cancer? MINDACT results compared to those of TAILOR-X

# MINDACT Trial Data Reveal Certain Women With Luminal Breast Cancer May Be Undertreated With Tamoxifen Alone

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## Background:

A secondary analysis of the TAILOR-X trial, based on the integration of a “clinical risk” - as defined in the MINDACT trial – on top of the Oncotype Recurrence Score (RS) revealed that women aged 40 to 50 years with either a RS between 16 and 20 and a high clinical risk (cH) or a RS between 21 and 25, independently from clinical risk, derive non negligible benefits from the addition of chemotherapy to endocrine therapy, in terms of distant recurrence rate at 9 years (J.A. Sparano et al., N Engl J. Med 2019; 380).

## Methods:

We decided to run a similar (unplanned) analysis of the MINDACT “cH” patients with “luminal” breast cancers (hormone receptor-positive, HER2-negative by local pathology) classified as “low” genomic risk (gL) using the 70 gene signature Mammaprint™ (F. Cardoso, N. Engl. J. Med. 2016; 375). Analysis is done as per treatment arm allocated (chemotherapy or no chemotherapy) by randomization. MINDACT primary endpoint was used (5-year distant metastases free survival, DMFS). Of note, the comparison of outcomes with or without chemotherapy was a secondary objective in MINDACT.

## Results:

Among 6693 enrolled patients, 5402 (81.7%) had luminal breast cancers. Within luminal breast cancers, 1358 (25.1%) had cH/gL risk and were aged <40 (n= 53), 40-50 years old (n= 411), >50 (n = 894). There were too few DMFS events (n = 2) in the <40 year old group to display further results. The analysis population included patients randomized to receive chemotherapy or not (399 patients aged 40-50 and 865 patients >50 years old). Median tumor size was 2.2 cm in both age groups (40-50 years old group: 35.9%/58.4% patients had T1/T2 tumors, respectively; >50 years old: T1/T2: 41.2%/55.5%). Half of the patients had negative nodal status (40-50 year old: 50.9%; >50 years old: 51.8%). Majority of patients had grade 2 or grade 3 tumors (40-50 years old: 63.9% grade 2 and 26.6% grade 3; >50 year old: 66.6% grade 2 and 26.9% grade 3).

	Luminal cH/gL, 40-50y old patients N = 399		Luminal cH/gL > 50y old patients N = 865	
	Events/total	5-year Kaplan Meier DMFS estimate (95% CI)	Events/total	5-year Kaplan Meier DMFS estimate (95% CI)
No chemotherapy	16/196	92.6% (87.7 ; 95.7)	23/440	95.4% (92.8 ; 97.1)
Chemotherapy	8/203	96.2% (91.5 ; 98.3)	23/425	95.2% (92.4 ; 97.0)

## Conclusions:

While postmenopausal patients primarily received aromatase inhibitors, adjuvant endocrine therapy consisted mostly in tamoxifen in younger women with only 7.0% of them also receiving an LHRH analog.

This unplanned analysis, limited by a small number of events and large confidence intervals, nevertheless shows the same «trend» as seen in Tailor-X and also suggests that women aged 40 to 50, classified cH / gL risk and presumably premenopausal, might be undertreated with tamoxifen alone. It is probable but not proven that this age-dependent chemotherapy effect is due to ovarian function suppression (OFS). The added value of chemotherapy in case of optimal endocrine therapy (i.e. OFS + tamoxifen or aromatase inhibitor) cannot be evaluated in MINDACT nor in TailorX and should be further studied. Possibly, optimal endocrine therapy, e.g. ovarian ablation in addition to tamoxifen in the 40-50y age group cH could be adequate. This reinforced message is important for practicing oncologists and patients.

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