Title

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Journal

npj Breast Cancer, 10(1)

ISSN

2374-4677

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Publication Date

2024-11-02

DOI

10.1038/s41523-024-00670-2

Peer reviewed

npj | breast cancer

Article

Published in partnership with the Breast Cancer Research Foundation

https://doi.org/10.1038/s41523-024-00670-2

Benefit of systemic therapy in MINDACT patients with small, ER-positive, HER2-negative breast cancers

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Small, hormone receptor-positive (HR+), HER2-negative (HER2-), lymph node-negative breast cancers are associated with relatively low rates of disease recurrence and have therefore been underrepresented in clinical trials assessing the effects of systemic therapy. Consequently, it remains uncertain if this patient population derives benefit from these treatments. For this exploratory analysis, we selected MINDACT (NCT00433589) patients with a HR+, HER2-, T1ab (≤1 cm) tumor and negative lymph nodes. Patients with discordant clinical risk and MammaPrint genomic risk classification were randmomized to receive chemotherapy based on either the clinical or the genomic risk assessment. Endocrine therapy treatment was based on local guidelines. 715/6693 (10.7%) MINDACT patients had HR+, HER2-, T1abN0 breast cancer and were included in this analysis. All were clinically low-risk, 124/715 (17.3%) were genomic high-risk. For genomic high-risk tumors, 8-year distant metastasis-free survival (DMFS) was 92.9% (95% CI 86.2–96.4%) compared to 95.0% (95% CI 92.8–96.6%) for genomic low-risk tumors. For genomic high-risk tumors treated with or without chemotherapy, 8-year DMFS was 89.2% (95% CI 73.6–95.8%) and 94.1% (95% CI 82.9–98.1%), respectively. For genomic low-risk tumors, the 8-year DMFS and disease-free survival (DFS) were 96.1% (95% CI 93.4–97.6%) and 89.3% (95% CI 85.5–92.2%) when treated with endocrine therapy and 92.9% (95% CI 87.9–95.9%) and 79.4% (95% CI 72.5–84.8%) without. In conclusion, although the number of randomized patients is small, patients with small, genomic high-risk breast cancer did not seem to derive benefit from chemotherapy. Endocrine therapy was associated with improved outcomes even in genomic low-risk breast cancers.

In early breast cancer, tumor size is a well-established prognostic factor. Patients with a small (≤1 cm), hormone receptor-positive (HR+), HER2-negative (HER2-) tumor and negative lymph nodes are generally considered at low risk of disease recurrence. Nonetheless, current clinical guidelines suggest that even for small, node-negative cancers chemotherapy can be considered if high risk pathological or molecular features are present[1,2]. There is, however, no conclusive data showing that patients with a small, ER+, HER2- tumor and negative lymph nodes derive clinically meaningful benefit to justify the added toxicity of chemotherapy. Even the role of endocrine therapy in this patient population has been questioned by some. Given that since the introduction of screening almost 1 in 4 invasive breast cancers is ≤1 cm at

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diagnosis, it is important to establish the optimal treatment strategy in this subgroup[3].

Results from previous studies assessing chemotherapy benefit in small, HR+, HER2-, node-negative breast cancers have been limited. This patient population has been underrepresented in randomized clinical trials. Although one study pooling data from several chemotherapy trials concluded there was benefit from chemotherapy for ≤1 cm tumors, this study did not take into account HER2 overexpression[4]. Other, non-randomized, studies concluded that there was no or very limited benefit from chemotherapy, but had a relatively short median follow-up of at most 6.5 years[5–7]. As the risk of disease recurrence for HR+ breast cancer persists for at least two decades after initial diagnosis, long-term follow-up is crucial[8]. Similarly, only a small number of studies with short follow-up have assessed endocrine therapy benefit in this group of tumors[9,10].

The MINDACT phase III clinical trial randomized patients with T1-3 breast cancer and up to 3 positive lymph nodes to receive chemotherapy or not if their clinical risk and genomic risk were discordant[11]. Here, we present the results of an exploratory analysis for the subgroup of patients with T1ab (≤1 cm), node-negative, HR+, HER2- breast cancer. After a median follow-up of 8.8 years, we examine the effect of chemotherapy on disease-free survival (DFS), distant metastasis-free survival (DMFS) and overall survival (OS) in the randomized patients. In addition, we assess these outcomes in patients who based on shared decision making (i.e. no randomization) did or did not receive endocrine therapy.

Results

Patients and tumor characteristics

Between February 2007 and July 2011, 6693 patients were enrolled in the MINDACT study. Out of these patients, 715 (10.7%) had a HR+, HER2- tumor of ≤1 cm (T1a $n = 34$, T1b $n = 681$) with negative lymph nodes (Supplementary Figure 1). All 715 T1ab, HR+, HER-tumors were classified as clinical low-risk, according to MINDACT criteria. The MammaPrint assay classified 591 (82.7%) of these as genomic low-risk and 124 (17.3%) as genomic high-risk (Table 1). Genomic high-risk tumors were more often grade 3 (34.1% vs. 5.4%), progesterone receptor-negative (18.9% vs. 11.7%), and Ki67 ≥ 30% (22.2% vs. 1.2%) compared to genomic low-risk tumors. Regardless of genomic risk, the large majority of tumors (96.8% and 98.8% for high- and low-risk, respectively) were luminal according to BluePrint. Patients with a genomic high-risk tumor were less likely to receive breast conserving surgery (83.1% vs. 91.7%) and radiotherapy (83.3% vs. 92.2%) compared to patients with a genomic low-risk tumor. As patients with a clinical low-risk/genomic high-risk tumor were randomized to receive chemotherapy or not (1:1), while patients with a clinical low-risk/genomic low-risk tumor would according to the protocol not receive chemotherapy, there was also a substantial difference in chemotherapy use between the genomic risk groups (42.3% vs. 2.2%). Endocrine therapy was given or not following local guidelines and shared decision making. Patients with genomic high-risk tumors more often received endocrine therapy (86.7% vs. 65.0%) compared to patients with genomic low-risk tumors.

Outcome by genomic risk in patients with small tumors

In the subgroup of patients with T1ab, HR+, HER- tumors, the median follow-up was 8.8 years. For DMFS, the curves for the two genomic risk groups started diverging after approximately 4 years, resulting in an 8-year DMFS of 92.9% (95% CI 86.2–96.4%) for high-risk tumors and 95.0% (95% CI 92.8-96.6%) for low-risk tumors (Fig. 1, Supplementary Table 1). The 8-year DFS, however, was very similar with 87.3% (95% CI 79.4–92.3%) and 86.0% (95% CI 82.7-88.7%) for patients with genomic high-risk and low-risk tumors, respectively. The 8-year survival estimates for OS were 92.3% (95% CI 85.1–96.1%) for genomic high-risk tumors and 96.2% (95% CI 94.2–97.5%) for low-risk tumors.

Chemotherapy benefits in patients with small genomic high-risk tumors

Among the 124 patients with a genomic high-risk tumor, 4 opted out of randomization, while 59 and 61 were randomized to receive adjuvant chemotherapy and no adjuvant chemotherapy, respectively (Supplementary table 2). The baseline characteristics were mostly well-balanced, although there was a slight difference in the distribution of tumors by grade. While in the no chemotherapy arm, 16 (26.2%) tumors were grade 1, this was the case only for 6 (10.2%) of tumors in the chemotherapy arm. Of note, 15 patients (25.9%) in the chemotherapy arm, in the end, did not receive chemotherapy. Patients in The Netherlands and patients aged ≥50 were more likely to not receive chemotherapy (Supplementary table 2). Conversely, there were 5 patients (8.2%) in the no chemotherapy arm who were treated with chemotherapy. Patients aged <50 and those with a grade 3 tumor were more likely to receive chemotherapy treatment regardless of randomization to the no chemotherapy arm. Endocrine therapy use was also different between the per-protocol groups, with 41 (100%) and 42 (79.2%) of patients receiving endocrine therapy in the chemotherapy and no chemotherapy group, respectively.

At 8 years follow-up, in the intention to treat population, DMFS, DFS, and OS were 92.1% (95% CI 80.2–97.0%), 88.3% (95% CI 75.7–94.6%) and 91.7% (95% CI 79.4–96.8%) in the chemotherapy arm, respectively (Supplementary Figure 2). Outcomes in the no chemotherapy arm were very similar, with 93.1% (95% CI 82.5–97.3%), 85.6% (95% CI 73.1–92.6%), and 92.3 (95% CI 80.6–97.0%) for DMFS, DFS, and OS. As non-adherence to the assigned treatment would result in a dilution of the effect of chemotherapy, outcomes were also assessed in the per-protocol population (Fig. 2, Supplementary table 3). Again, no improved outcome was observed in the patients treated with chemotherapy, with an 8-year DMFS of 89.2% (95% CI 73.6–95.8%) compared to 94.1% (95% CI 82.9–98.1%) in those who did not receive chemotherapy (HR 2.25, 95% CI 0.54–9.43). DFS and OS were 84.0% (95% CI 67.7–92.5%) and 88.6% (95% CI 72.4–95.6%) in patients treated with chemotherapy and 87.7% (95% CI 74.4–94.3%) and 93.3% (95% CI 80.5–97.8%) for the patients who had not received chemotherapy. We did not observe a subgroup of patients in which a clear benefit from chemotherapy was shown, although these analyses were underpowered due to the low number of events (Supplementary table 4).

Endocrine therapy benefit in patients with small genomic low-risk tumors

Among the 585 patients with a clinical low-risk and genomic low-risk tumor, 205 (35.0%) did not receive endocrine therapy (Supplementary table 5). The majority of these patients, were enrolled in the Netherlands where guidelines at the time did not recommend endocrine therapy for most tumors ≤1 cm. Patients who received no endocrine therapy were also more likely to have a grade 1 (120/205 [58.8%] vs. 349/380 [44.1%]) or progesterone receptor-negative (39/205 [19.0%] vs. 30/380 [7.9%]) tumor. The 8-year DMFS and OS were 96.1% (95% CI 93.4–97.6%) and 96.6% (95% CI 94.0–98.0%) compared to 92.9% (95% CI 87.9–95.9%) and 95.5% (95% CI 91.2–97.7) for patients treated with and without endocrine therapy respectively (Fig. 3). The difference in 8-year DFS was larger, with 89.3% (95% CI 85.5–92.2%) for patients treated with endocrine therapy and 79.4% (95% CI 72.5–84.8%) for patients without endocrine treatment (Fig. 3, Supplementary table 6). The number of patients with second primary breast cancer as their first DFS event was 4 (1.1%) in the endocrine therapy-treated patients and 13 (6.3%) in patients treated without endocrine therapy. Endometrial cancer, which has been associated with tamoxifen treatment[12], was reported as a first DFS event in 1 (0.5%) patient who did not receive endocrine therapy, and 2 (0.5%) patients who did.

Discussion

In this exploratory analysis of the MINDACT study, we observed no clear differences in survival outcomes at 8 years for patients with T1ab, HR+, HER2-, genomic high-risk tumors compared to those with genomic low-risk tumors. Patients with small genomic high-risk tumors who received chemotherapy did not appear to have a better outcome compared to those who did not receive chemotherapy with 89.2% vs. 94.1% DMFS respectively,

Table 1 | Patients and tumor characteristics by genomic risk

	Genomic low-risk *n* (%)	Genomic high-risk *n* (%)
Total	591 (100)	124 (100)
Tumor size		
T1a (≤5 mm)	26 (4.4)	8 (6.5)
T1b (>5–10 mm)	565 (95.6)	116 (93.5)
Age		
<40	30 (5.1)	9 (7.3)
40- < 50	125 (21.2)	28 (22.6)
50- < 60	216 (36.5)	37 (29.8)
≥ 60	220 (37.2)	50 (40.3)
Menopausal status		
Premenopausal	193 (33.7)	38 (31.4)
Postmenopausal	379 (66.3)	83 (68.6)
Missing	19	3
Histology		
NST	493 (83.6)	113 (91.1)
Lobular	52 (8.8)	7 (5.6)
Other	45 (7.6)	4 (3.2)
Missing	1	0
ER		
Positive	588 (99.5)	124 (100)
Negative	3 (0.5)	0 (0)
PR		
Positive	521 (88.3)	99 (81.1)
Negative	69 (11.7)	23 (18.9)
Missing	1	2
Grade		
1	289 (49.1)	22 (17.9)
2	268 (45.5)	59 (48.0)
3	32 (5.4)	42 (34.1)
Missing	2	1
Ki67		
≤5%	85 (16.6)	1 (1.0)
>5 - <30%	420 (82.2)	83 (76.9)
≥30%	6 (1.2)	24 (22.2)
Missing	80	16
BluePrint		
Luminal	584 (98.8)	120 (96.8)
Basal	4 (0.7)	3 (2.4)
ERBB2	3 (0.5)	1 (0.8)
Surgery		
Breast conserving	542 (91.7)	103 (83.1)
Mastectomy	49 (8.3)	21 (16.9)
Radiotherapy		
Yes	540 (92.2)	100 (83.3)
No	46 (7.8)	20 (16.7)
Missing	5	4
Endocrine therapy		
Yes	380 (65.0)	104 (86.7)
No	205 (35.0)	16 (13.3)
Missing	6	4
Chemotherapy		
Yes	13 (2.2)	52 (42.3)
No	577 (97.8)	71 (57.7)
Missing	1	1

Ki67 was assessed centrally, all other pathological variables are reported as assessed locally.

at 8 years. For the patients with low-risk tumors, we observed better 8-year DFS outcomes in those treated with endocrine therapy (89.3%) compared to those treated without endocrine therapy (79.4%).

Patients with small (≤1 cm) node negative tumors have often been excluded from chemotherapy trials due to their relatively good prognosis. It has therefore long been uncertain if this population derives significant benefit from these treatments. Recently, two large analyses of the Surveillance, Epidemiology, and End Results (SEER) database showed that for T1abN0 HER2-positive and triple negative breast cancers absolute difference in 5-year breast cancer-specific survival between patients treated with and without chemotherapy was very small (for T1b: TNBC 96.6% vs. 95.8% [$n = 2175$], HER2+/HR + 99.3% vs. 97% [$n = 2439$] and HER2+/HR- 98.9% vs. 98.6% [$n = 712$]). No statistically significant benefit of chemotherapy was found when correcting for potential confounding factors[13,14]. In our study, after 8 years follow-up and with a very small number of events, we found no indication that chemotherapy improves outcome in genomic high-risk T1abN0 HR+, HER2- breast cancer. This echoes the overall results of the MINDACT study, in which the group of patients with clinical low-risk/genomic high-risk tumors seemed to derive no benefit from chemotherapy (8-year DMFS 92.3% vs. 90.8% for chemotherapy and no chemotherapy respectively). These results are also in line with the results of several registry-based cohort studies in T1abN0 HR+, HER2- breast cancer, which all reported no statistically significant difference in outcome for patients treated with or without chemotherapy[5–7]. A study combining data from 5 NSABP trials, did report an 8-year recurrence-free survival (RFS) of 93% in T1ab, HR+ breast cancers treated with tamoxifen alone compared to 95% in those treated with tamoxifen and chemotherapy although this difference was not statistically significant and the HER2-status of these cancers was unknown. Further research is needed to determine if there is a subgroup of patients with T1ab, HR+, HER2-, genomic high-risk tumors that might benefit from other treatment strategies, such as extended endocrine therapy or treatment with a CDK4/6 inhibitor.

Although endocrine therapy is associated with substantially less toxicity compared to chemotherapy, it is associated with a small increased risk of endometrial cancer and thromboembolic disease. Moreover, its common side effects can impact quality of life[15]. It has therefore been suggested that for some patients with small, low-risk, HR+, HER2- breast cancers the benefits of endocrine therapy might not outweigh the side effects. In our exploratory analysis of patients with genomic low-risk, T1ab, HR+, HER2- breast cancers, we observed an absolute difference of 9.9% in DFS at 8 year (89.3% vs. 79.4%) for patients treated with endocrine therapy compared to those treated without. The majority of this effect was due to a difference in the development of second primary breast cancers (1.1% vs. 6.3%). For the 8-year DMFS a more modest difference was observed, with 96.1% vs. 92.9% (3.1% absolute benefit with overlapping confidence intervals) for endocrine therapy treated compared to systemically untreated patients, respectively. These results are similar to those observed in the meta-analysis of 5 NSABP trials, where the 8-year RFS was 86% for patients with T1ab, HR+ breast cancers treated with surgery alone and 93% for those who received tamoxifen[4]. More recently, Adachi and colleagues reported the results from an institution-based cohort (T1ab $n = 662$) where the 5-year DFS was 96% for endocrine therapy treated patients compared to 93% for those who did not receive tamoxifen, although this difference was not statistically significant[9]. Together these results suggest that even in small, low-risk breast

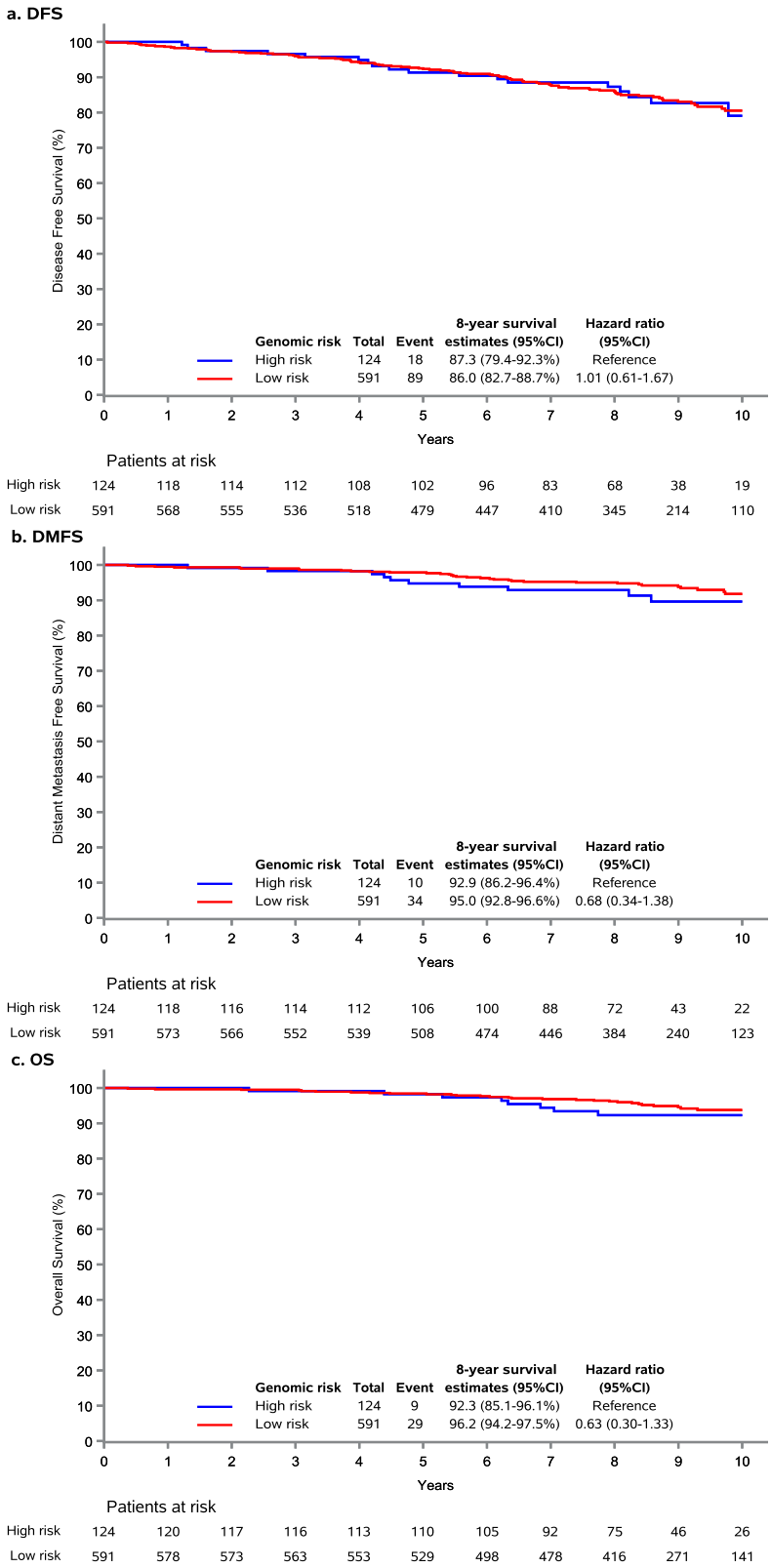

Fig. 1 | Outcome by genomic risk. Outcome by genomic risk classification for **a** disease-free survival (DFS), **b** distant metastasis-free survival (DMFS) and **c** overall survival (OS). CI confidence interval.

tumors endocrine therapy can prevent a substantial number of disease recurrences. A recent study assessing the outcomes for patients with a tumor classified as ultralow risk by MammaPrint, reported a 8-year DMFI of 97.8% for systemically untreated patients and 97.4% for patients treated with endocrine therapy, regardless of tumor size[16]. Eventough this suggests that patients with ultralow-risk tumors might be better candidates to forgo endocrine therapy, it should be noted that the characteristics of a first primary breast cancer likely do not affect the benefit of endocrine therapy in terms of prevention of second primary breast cancers.

Our current study has a number of limitations. First of all, due to the general good prognosis of patients with small, HR+, HER2- breast tumors, we observed a low number of events. This means that our study is

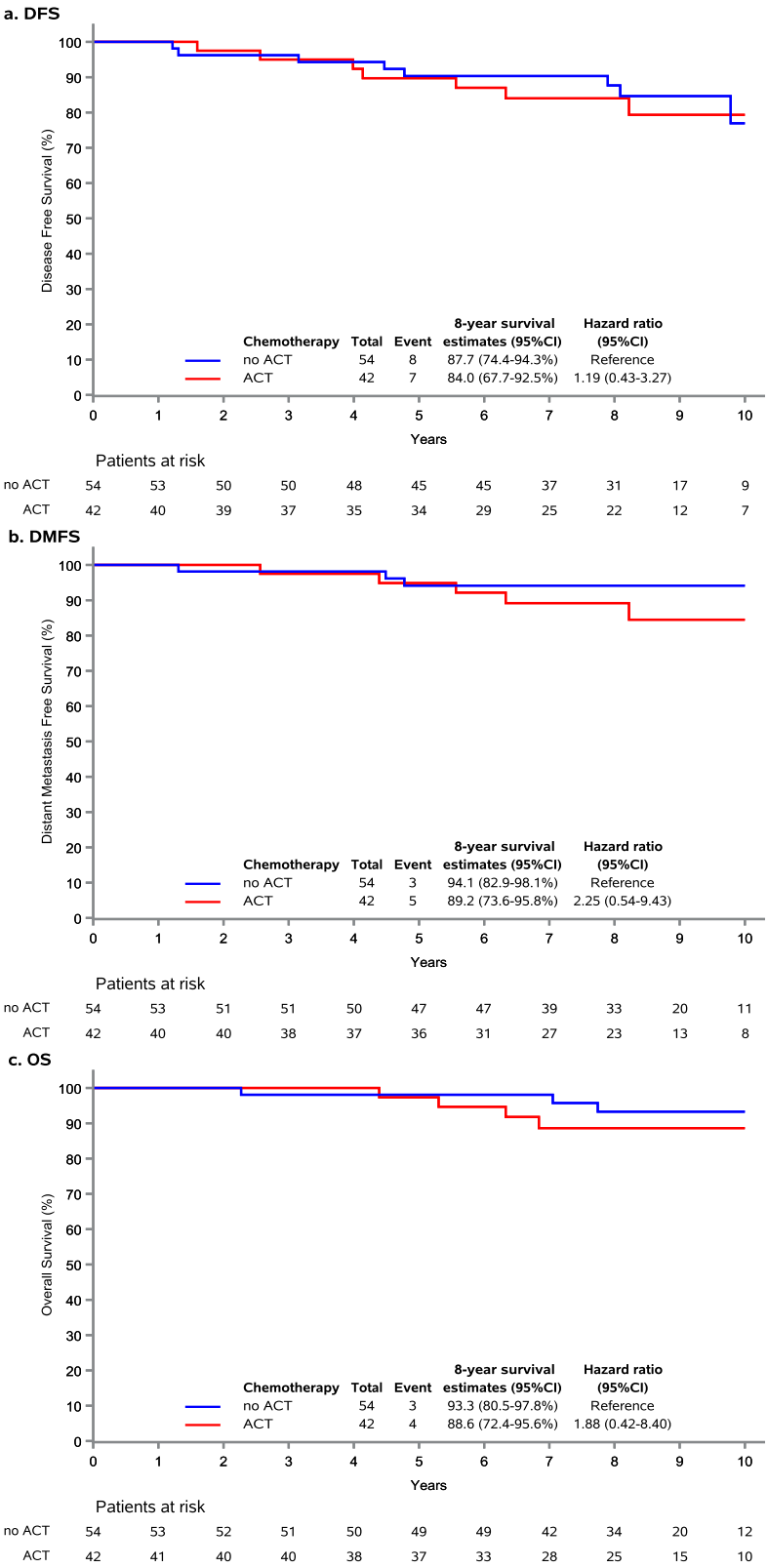

Fig. 2 | Outcome for the per-protocol population of the chemotherapy randomization in patients with genomic high-risk tumors. Outcome for the per-protocol population of the chemotherapy randomization in patients with genomic high-risk tumors for **a** disease-free survival (DFS), **b** distant metastasis-free survival (DMFS), and **c** overall survival (OS). ACT adjuvant chemotherapy; CI confidence interval.

underpowered to detect smaller treatment effects and that it is not possible to look at outcomes for T1a tumors ($n = 34$) separately. Similarly, we do not have the power to assess chemotherapy benefit in pre-menopausal women separately. Results from the MINDACT overall population and TailorX have suggested that some pre-menopausal women with discordant risk classification might benefit from chemotherapy, although it is uncertain whether this is due to the cytotoxic or menopause-inducing effects of chemotherapy[11,17]. We can also not exclude that other prognostic gene expression signatures would be able to identify a subgroup of patients with T1ab tumors who benefit from chemotherapy treatment. Secondly, even with a median follow-up of 8.8 years we do not capture all disease recurrences in this patient population, as it has been shown that patients with HR

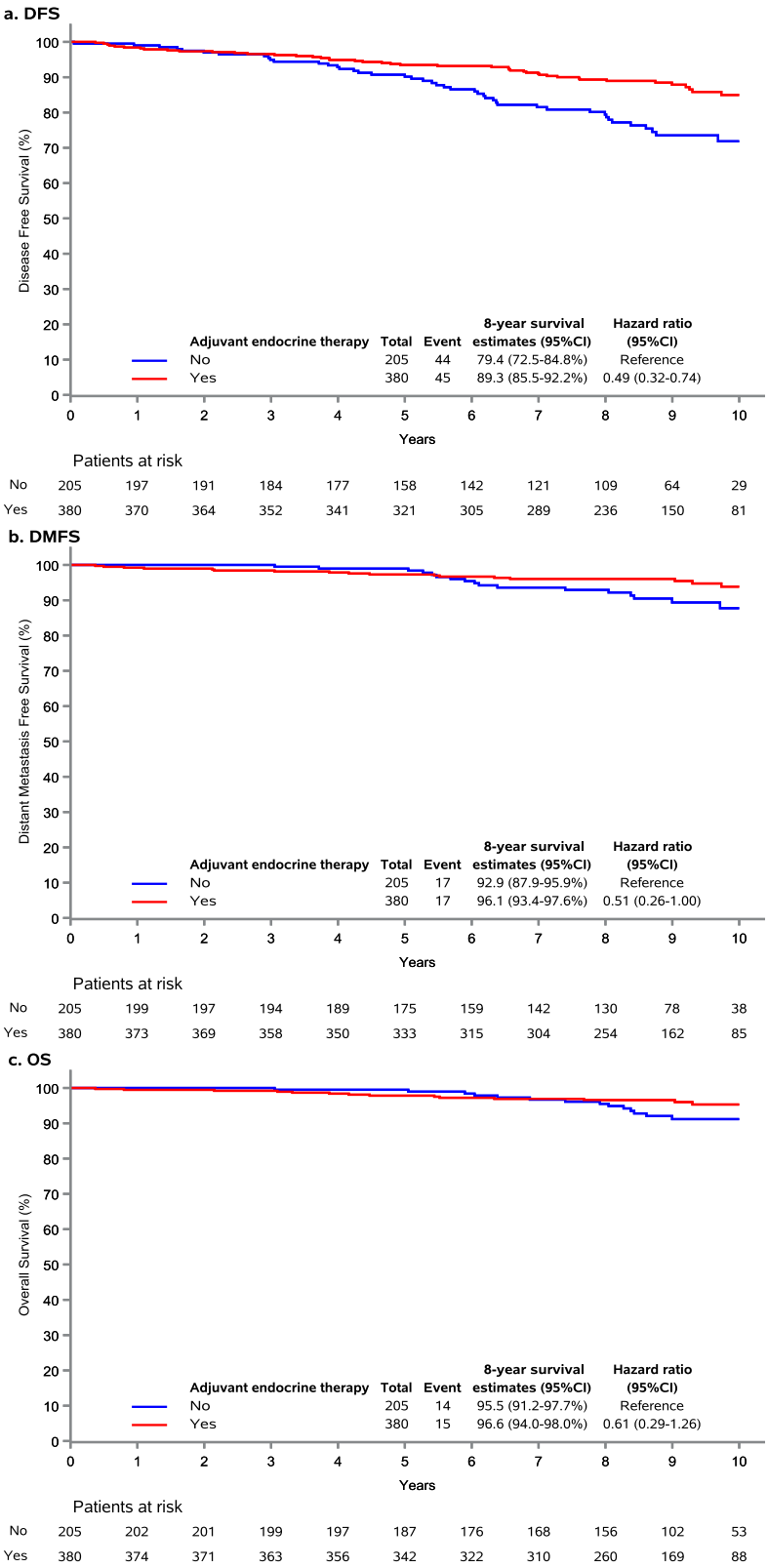

Fig. 3 | Outcome by endocrine therapy use in patients with genomic low-risk tumors. Outcome by endocrine therapy use in patients with genomic low-risk tumors for **a** disease-free survival (DFS), **b** distant metastasis-free survival (DMFS) and **c** overall survival (OS). CI confidence interval.

+ breast cancer can experience disease recurrences up to at least 20 years after initial diagnosis[8]. Endocrine therapy has been shown to have a carry-over effect and affect the risk of disease recurrence up to 10 years after diagnosis[18,19]. We can not therefore exclude that the difference between endocrine therapy treated and untreated patients will further increase with longer follow-up. Also for some chemotherapy regimens, effects on recurrence risk at 5–9 years after diagnosis have been shown[20]. However, it seems unlikely that in the absence of chemotherapy benefits in the first 8 years after diagnosis, a treatment effect will arise in later years. Lastly, there was no randomization determining whether or not a patient received endocrine therapy in our study. While the chemotherapy treatment in the patients with genomic high-risk patients was randomized, non-adherence

to the randomized treatment might have introduced a bias. Our results are therefore potentially affected by confounding by indication since systemic therapy might be more likely omitted for cancers with low-risk features. As confounding by indication is likely to decrease the difference in outcome between patients treated with and without systemic therapy, the true therapy benefit is possibly slightly larger than what we have observed.

In conclusion, long-term outcome for MINDACT patients with a genomic high-risk, HR+, HER2-, T1abN0 tumor was similar to that patients with a genomic low-risk tumor. Although the number of randomized patients was relatively small, chemotherapy treatment did not seem to improve survival in the genomic high-risk population. Endocrine therapy was associated with improved outcome even in patients with genomic low-risk HR+, HER2-, T1abN0 breast cancer, although this effect was largely driven by the prevention of second primary tumors.

Methods

Study design and population

The design of the MINDACT study (NCT00433589, EudraCT2005-002625-31) has been previously described[11,21]. The study included women aged 18 to 70 years with T1, T2, or operable T3 unilateral invasive breast cancer and up to 3 positive axillary lymph nodes. For all patients, a frozen tumor sample taken at the time of enrollment was available for genomic risk assessment by MammaPrint. A modified version of Adjuvant! Online (version 8.0 with HER2-status) was used for clinical risk assessment (Supplementary table 7). Low clinical risk was defined as the 10-year probability of breast cancer-specific survival (BCSS) without systemic therapy of more than 88% among women with HR+ tumors. Patients classified as high-risk by both assessment methods were assigned to adjuvant chemotherapy administration, while those classified as low-risk by both methods were assigned not to receive adjuvant chemotherapy. Those with discordant results were randomly (1:1) assigned to have their treatment decision based on either the clinical or the genomic result. For this substudy, patients were selected if they were node-negative, and their tumor was T1a (≤5 mm) or T1b (>5 and ≤10 mm) and considered HR+ (estrogen receptor and/or progesterone receptor positive) and HER2-negative according to the local pathology assessment. The protocol review committee of the European Organization for Research and Treatment of Cancer (EORTC) and the ethics committees at each participating center (see list of participating centers in Supplementary table 8) approved the protocol and all participating patients provided written informed consent. Trial conduct and reporting was compliant with Good Clinical Practice guidelines, the Declaration of Helsinki, and the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Endpoints

All time-to-event endpoints are considered from the date of reception of a patient's frozen tumor sample. The primary endpoint was DMFS at 8-years, defined as the time until first distant metastatic recurrence or death from any cause. Contralateral breast cancer and secondary cancers were not considered as events. Secondary endpoints were DFS, including locoregional or distant relapses, invasive contralateral or ipsilateral BC, ductal carcinoma in situ or a second primary cancer or death from any cause. If the patient was alive without an event of DMFS or DFS, the censoring date was the last examination date. Two patients who died more than 2 years after their last examination date were censored at the last examination date as per the censoring rules applied in the main MINDACT study. OS was defined as the time until death from any cause. The date the patient was last known to be alive was used as censoring date.

Statistical analysis

Descriptive statistics were used to compare the characteristics of the genomic risk and treatment-based subgroups. Non-parametric Kaplan-Meier method was used to estimate the distributions of DMFS, DFS, and OS over time and the corresponding 8-year estimates of DMFS, DFS, and OS rates. The 95% CIs were calculated based on the asymptotic normality of log-log transformed survival estimates. All analyses were carried out with SAS software (SAS Institute 9.4).

Data availability

The MINDACT dataset with patient characteristics and clinical outcomes is available through the EORTC (https://www.eortc.org/data-sharing/). Following a successful data request procedure, the EORTC can share all or a selection of the clinical-pathological or full-transcriptome data for translational research.

Received: 15 January 2024; Accepted: 9 July 2024;
Published online: 02 November 2024

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Acknowledgements

The MINDACT trial has received grants from the European Commission Framework Programme VI (FP6-LSHCCT- 2004-503426), the Breast Cancer Research Foundation, Novartis, F. Hoffman La Roche, Sanofi-Aventis, Eli Lilly, Veridex, the EBCC Breast Cancer Working Group (BCWG grant for the MINDACT biobank), the Jacqueline Seroussi Memorial Foundation for Cancer Research (2006 JSMF award), Prix Mois du Cancer du Sein (2004 award), Susan G. Komen for the Cure (SG05-0922-02), Fondation Belge Contre le Cancer (SCIE 2005-27), Dutch Cancer Society (KWF), the Netherlands Genomic Initiative- Cancer Genomics Center (2008-2012), Association Le Cancer du Sein, Parlons-en!, the Brussels Breast Cancer Walk- Run and the American Women's Club of Brussels, NIF Trust, Deutsche Krebshilfe, the Grant Simpson Trust and Cancer Research UK, Ligue Nationale contre le Cancer and the EORTC Cancer Research Fund. Whole genome analysis was provided in kind by Agendia. We are grateful to all patients participating in this study; all the investigators, surgeons, pathologists, and research nurses; the National Coordinating Centers/BIG Groups (BOOG, GOIRC, NCRI-BCG, SOLTI, UNICANCER, WSG); BIG headquarters; EORTC headquarters; Europa Donna – the European Breast Cancer Coalition. The authors acknowledge the crucial contribution of all MINDACT investigators and their teams, without whom this research would not be possible.

Author contributions

KT, CP, LvtV, and FC conceived and designed the exploratory project. CP, KT, GV, SD, JYP, EGCB, ITR, AMT, EJTR, MJP, LvtV, and FC data acquisition and conduct of the trial. FSH, KT, CP, LvtV, and FC were responsible for the methodology, data analysis, and interpretation of the results. FSH and KT drafted the manuscript. All authors reviewed, edited, and approved the final manuscript. FC and LvtV supervised this exploratory analysis and contributed equally to this work.

Competing interests

LV reports personal fees and is stock-holder of Agendia NV. FC reports personal fees for consultancy role for: Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, Gilead, GlaxoSmithKline, Iqvia, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seagen, Teva, Touchime, none in relation with this work. GV reports personal fees for consultancy roles from Roche, AstraZeneca, Daiichi Sankyo, Gilead, Pfizer, MSD Oncology, and Agilent, none in relation to this work. MP is a scientific board member for Oncolytics and reports personal fees for consultancy roles for: AstraZeneca, Gilead, Lilly, Menarini, MSD, Novartis, Pfizer, Roche-Genentech, Seattle Genetics, Seagen, NBE Therapeutics, Frame Therapeutics; as well as institutional research grants from: AstraZeneca, Lilly, Menarini, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, Synthon, Gilead, none in relation with this work. KT is currently an employee of Merck. All other authors report no conflicts of interest.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41523-024-00670-2.

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